Three-Component Coupling Sequence for the Regiospecific Synthesis of Substituted Pyridines

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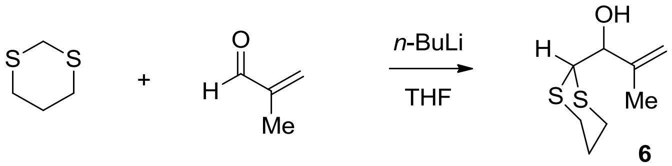
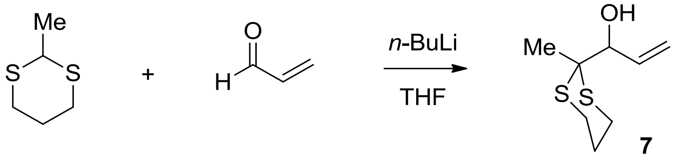
Supporting Information

Experimental Procedures and Spectral Data

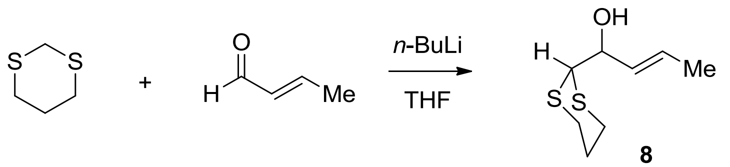
General. All reactions were conducted in flame-dried glassware under an argon atmosphere with anhydrous solvents, unless otherwise noted. Anhydrous diethyl ether (Et_2O) and tetrahydrofuran (THF) were obtained by passing HPLC grade solvents through activated alumina columns. Isobutyraldehyde, heptanal and benzaldehyde were distillated prior to use. Titanium(IV) tetraisopropoxide ($Ti(Oi\text{-}Pr)_4$) was purified prior to use by distillation at 250 millitorr. *c*-C_5H_9MgCl and *n*-BuLi were titrated using 1,10-phenanthroline/*sec*-butanol.[1] (*E*)-2-phenylbut-2-enal[2], cyclopent-1-enecarbaldehyde[3], cyclohept-1-enecarbaldehyde[4], and 2-(methoxymethyl)acrylaldehyde[5] were synthesized according to the literature procedures. 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, ^{13}C NMR and ^{19}F NMR data were recorded at 400 MHz, 100 MHz and 376 MHz, respectively. ^{1}H NMR chemical shifts were 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 Perkin Elmer Spectrum One 2000 FT-IR spectrometer. Low-resolution mass spectrometry was performed using electrospray ionization.


6

Synthesis of 1-(1,3-dithian-2-yl)-2-methylprop-2-en-1-ol (6). To a solution of 1,3-dithiane (601 mg, 5.0 mmol) in THF (50 mL) at –20 ºC was added dropwise *n*-BuLi (2.2 mL, 5.5 mmol, 2.5 M in hexanes). The resultant clear solution was stirred at the same temperature for 1 h. After cooling down to –78 ºC, methacrolein (412 μL, 350 mg, 5.0 mmol) was added dropwise via a syringe. The reaction was stirred for 30 min, then quenched with saturated aqueous NH_4Cl (5 mL) and warmed to ambient temperature. The reaction mixture was further diluted with H_2O (10 mL) and extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by flash column chromatography on silica gel (10→20% EtOAc/hexanes) to afford allylic alcohol **6** (904 mg, 95%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.06 (s, 1H), 4.97 (s, 1H), 4.25 (dd, *J* = 7.8, 3.0 Hz, 1H), 3.97 (d, *J* = 7.8 Hz, 1H), 2.95-2.82 (m, 2H), 2.77-2.66 (m, 3H), 2.09-1.98 (m, 1H), 1.96-1.84 (m, 1H), 1.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 115.0, 76.4, 49.6, 28.6, 28.0, 25.6, 17.2; IR (thin film, NaCl) ν_{max} 3437 (br), 3075, 2900, 2239, 1813, 1652, 1424, 1373, 909, 749 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_8H_{14}OS_2Na$ [M + Na] 213.1, found 213.1.

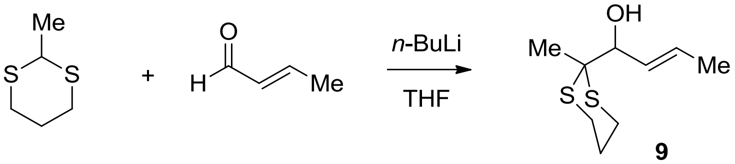

7

Synthesis of 1-(2-methyl-1,3-dithian-2-yl)prop-2-en-1-ol (7). To a solution of 2-methyl-1,3-dithiane (1.44 mL, 1.61 g, 12 mmol) in THF (100 mL) at –20 ºC was added dropwise *n*-BuLi (4.80 mL, 12 mmol, 2.5 M in hexanes). The resultant clear solution was stirred at the same temperature for 1 h. After cooling down to –78 ºC, acrolein (668 μL, 561 mg, 10 mmol) was added dropwise via a syringe. The reaction was stirred for 30 min, then quenched with saturated aqueous NH_4Cl (10 mL) and warmed to ambient temperature. The reaction mixture was further diluted with H_2O (20 mL) and extracted with Et_2O (3 x 40 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by flash column chromatography on silica gel (5→15% EtOAc/hexanes) to afford allylic alcohol **7** (1.70 g, 90%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 6.05 (ddd, *J* = 17.7, 11.1, 5.2 Hz, 1H), 5.42 (d, *J* = 17.7 Hz, 1H), 5.27 (d, *J* = 11.1 Hz, 1H), 4.47 (d, *J* = 5.2 Hz, 1H), 3.07-2.92 (m, 2H), 2.83 (s, 1H), 2.65-2.57 (m, 2H), 2.11-2.02 (m, 1H), 1.90-1.77 (m, 1H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.2, 117.9, 72.3, 52.9, 26.2, 25.9, 24.3, 22.2; IR (thin film, NaCl) ν_{max} 3460 (br), 2908, 1638, 1415, 1369, 1276, 1239, 1068, 990, 758 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_8H_{14}OS_2Na$ [M + Na] 213.1, found 213.2.



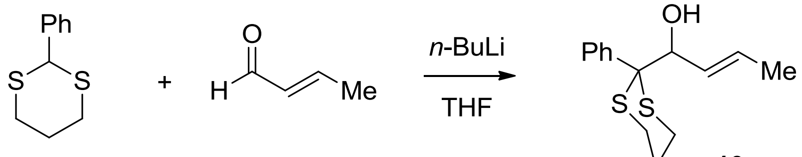
8

Synthesis of (*E*)-1-(1,3-dithian-2-yl)but-2-en-1-ol (8). To a solution of 1,3-dithiane (1.44 g, 12 mmol) in THF (100 mL) at –20 ºC was added dropwise *n*-BuLi (4.80 mL, 12 mmol, 2.5 M in hexanes). The resultant clear solution was stirred at the same temperature for 1 h. After cooling down to –78 ºC, (*E*)-crotonaldehyde (828 μL, 701 mg, 10 mmol) was added dropwise via a syringe. The reaction was stirred for 30 min, then quenched with saturated aqueous NH_4Cl (10 mL) and warmed to ambient temperature. The reaction mixture was further diluted with H_2O (20 mL) and extracted with Et_2O (3 x 40 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by flash column chromatography on silica gel (5→15% EtOAc/hexanes) to afford allylic alcohol **8** (1.71 g, 90%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 5.80 (dq, *J* = 15.2, 6.5 Hz, 1H), 5.56 (dd, *J* = 15.2, 7.0 Hz, 1H), 4.27 (appd t, *J* = 7.0 Hz, 1H), 3.93 (d, *J* = 7.0 Hz, 1H), 2.94-2.84 (m, 2H), 2.79-2.69 (m, 2H), 2.54 (s, 1H), 2.11-2.00 (m, 1H), 1.98-1.86 (m, 1H), 1.72 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.1, 129.8, 73.7, 52.5, 28.7, 28.4, 25.8, 17.9; IR (thin film, NaCl) ν_{max} 3430 (br), 2900, 1673, 1423, 1277, 1034, 964, 805 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_8H_{14}OS_2Na$ [M + Na] 213.1, found 213.1.



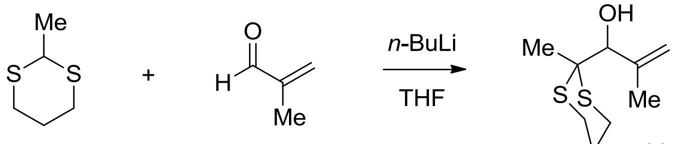
9

Synthesis of (*E*)-1-(2-methyl-1,3-dithian-2-yl)but-2-en-1-ol (9). To a solution of 2-methyl-1,3-dithiane (1.44 mL, 1.61 g, 12 mmol) in THF (100 mL) at –20 ºC was added dropwise *n*-BuLi (4.80 mL, 12 mmol, 2.5 M in hexanes). The resultant clear solution was stirred at the same temperature for 1 h. After cooling down to –78 ºC, (*E*)-crotonaldehyde (828 μL, 701 mg, 10 mmol) was added dropwise via a syringe. The reaction was stirred for 30 min, then quenched with saturated aqueous NH_4Cl (10 mL) and warmed to ambient temperature. The reaction mixture was further diluted with H_2O (20 mL) and extracted with Et_2O (3 x 40 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by flash column chromatography on silica gel (5→15% EtOAc/hexanes) to afford allylic alcohol **9** (1.86 g, 91%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (dq, *J* = 15.3, 6.5 Hz, 1H), 5.64 (dd, *J* = 15.3, 6.3 Hz, 1H), 4.39 (d, *J* = 6.3 Hz, 1H), 3.06-2.93 (m, 2H), 2.74 (s, 1H), 2.70-2.56 (m, 2H), 2.13-1.99 (m, 1H), 1.95-1.79 (m, 1H), 1.71 (d, *J* = 6.5 Hz, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.0, 127.1, 73.1, 53.4, 26.3, 26.0, 24.5, 22.5, 18.1; IR (thin film, NaCl) ν_{max} 3467 (br), 2914, 1672, 1448, 1376, 1277, 1070, 969, 758 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_9H_{16}OS_2Na$ [M + Na] 227.1, found 227.2.



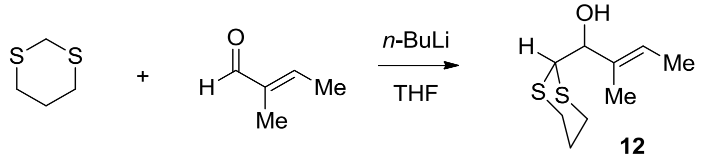
10

Synthesis of (*E*)-1-(2-phenyl-1,3-dithian-2-yl)but-2-en-1-ol (10). To a solution of 2-phenyl-1,3-dithiane (1.47 g, 7.5 mmol) in THF (50 mL) at –20 ºC was added dropwise *n*-BuLi (3.0 mL, 7.5 mmol, 2.5 M in hexanes). The resultant clear solution was stirred at the same temperature for 1 h. After cooling down to –78 ºC, (*E*)-crotonaldehyde (414 μL, 350 mg, 5.0 mmol) was added dropwise via a syringe. The reaction was stirred for 30 min, then quenched with saturated aqueous NH_4Cl (5 mL) and warmed to ambient temperature. The reaction mixture was further diluted with H_2O (10 mL) and extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by flash column chromatography on silica gel (10% EtOAc/hexanes) to afford allylic alcohol **10** (900 mg, 68%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.4 Hz, 2H), 7.47-7.37 (m, 2H), 7.35-7.25 (m, 1H), 5.66 (dq, *J* = 15.2, 6.5 Hz, 1H), 5.38 (dd, *J* = 15.2, 5.3 Hz, 1H), 4.31 (appd t, *J* = 5.3 Hz, 1H), 2.78-2.62 (m, 4H), 2.20 (d, *J* = 5.3 Hz, 1H), 1.98-1.90 (m, 2H), 1.66 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 130.8, 130.2, 128.5, 127.4, 127.4, 79.5, 65.3, 27.1, 27.0, 25.0, 17.8; IR (thin film, NaCl) ν_{max} 3464 (br), 3055, 2906, 2854, 2244, 1671, 1486, 1442, 1277, 907 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{14}H_{18}OS_2Na$ [M + Na] 289.1, found 289.1.



11

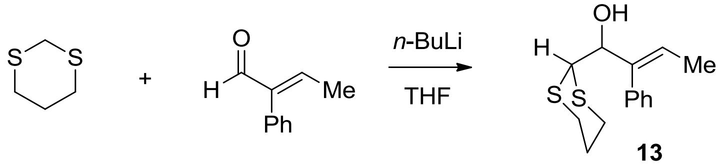
Synthesis of 2-methyl-1-(2-methyl-1,3-dithian-2-yl)prop-2-en-1-ol (11). To a solution of 2-methyl-1,3-dithiane (599 μL, 671 mg, 5.0 mmol) in THF (50 mL) at –20 ºC was added dropwise *n*-BuLi (2.20 mL, 5.5 mmol, 2.5 M in hexanes). The resultant clear solution was stirred at the same temperature for 1 h. After cooling down to –78 ºC, methacrolein (618 μL, 526 mg, 7.5 mmol) was added dropwise via a syringe. The reaction was stirred for 30 min, then quenched with saturated aqueous NH_4Cl (5 mL) and warmed to ambient temperature. The reaction mixture was further diluted with H_2O (10 mL) and extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (10% EtOAc/hexanes) to afford allylic alcohol **11** (733 mg, 72%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13 (s, 1H), 5.11 (s, 1H), 4.47 (s, 1H), 3.09-2.96 (m, 2H), 2.89 (s, 1H), 2.72-2.63 (m, 2H), 2.14-2.04 (m, 1H), 2.06 (s, 3H), 2.06-1.82 (m, 1H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 116.2, 75.0, 53.6, 26.8, 26.2, 24.5, 23.2, 21.9; IR (thin film, NaCl) ν_{max} 3460 (br), 3076, 2911, 1646, 1424, 1372, 1276, 1047, 908, 752 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_9H_{16}OS_2Na$ [M + Na] 227.1, found 227.2.



12

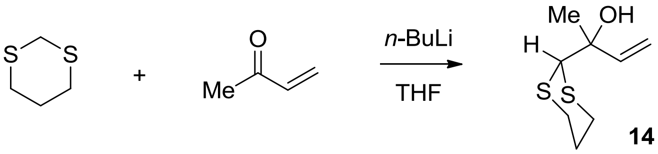
Synthesis of (*E*)-1-(1,3-dithian-2-yl)-2-methylbut-2-en-1-ol (12). To a solution of 1,3-dithiane (1.20 g, 10 mmol) in THF (100 mL) at –20 ºC was added dropwise *n*-BuLi (4.40

mL, 11 mmol, 2.5 M in hexanes). The resultant clear solution was stirred at the same temperature for 1 h. After cooling down to –78 ºC, (*E*)-2-methylbut-2-enal (1.45 mL, 1.26 g, 15 mmol) was added dropwise via a syringe. The reaction was stirred for 30 min, then quenched with saturated aqueous NH_4Cl (10 mL) and warmed to ambient temperature. The reaction mixture was further diluted with H_2O (20 mL) and extracted with Et_2O (3 x 40 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by flash column chromatography on silica gel (10→20% EtOAc/hexanes) to afford allylic alcohol **12** (1.92 g, 94%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 5.59 (q, *J* = 6.3 Hz, 1H), 4.17 (d, *J* = 8.4 Hz, 1H), 3.98 (d, *J* = 8.4 Hz, 1H), 2.99-2.79 (m, 2H), 2.79-2.65 (m, 2H), 2.54 (s, 1H), 2.12-1.97 (m, 1H), 1.97-1.83 (m, 1H), 1.64 (d, *J* = 6.3 Hz, 3H), 1.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.8, 125.0, 78.3, 49.8, 28.6, 28.0, 25.7, 13.3, 10.8; IR (thin film, NaCl) ν_{max} 3437 (br), 2900, 1671, 1423, 1379, 1277, 1016, 909, 828, 730 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_9H_{16}OS_2Na$ [M + Na] 227.1, found 227.1.

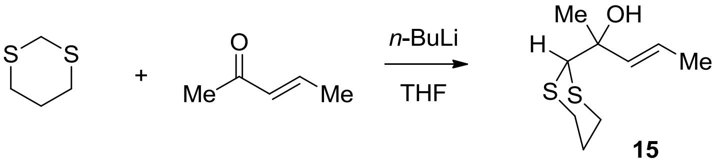


13

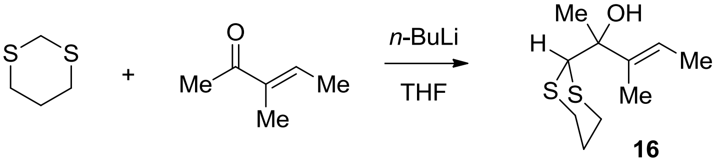
Synthesis of (*E*)-1-(1,3-dithian-2-yl)-2-phenylbut-2-en-1-ol (13). To a solution of 1,3-dithiane (877 mg, 7.29 mmol) in THF (50 mL) at –20 ºC was added dropwise *n*-BuLi (2.92 mL, 7.29 mmol, 2.5 M in hexanes). The resultant clear solution was stirred at the same temperature for 1 h. After cooling down to –78 ºC, (*E*)-2-phenylbut-2-enal (710 mg, 4.86 mmol) was added dropwise via a syringe. The reaction was stirred for 30 min, then quenched with saturated aqueous NH_4Cl (5 mL) and warmed to ambient temperature. The reaction mixture was further diluted with H_2O (10 mL) and extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by flash column chromatography on silica gel (10% EtOAc/hexanes) to afford allylic alcohol **13** (1.20 g, 93%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.24 (m, 5H), 5.95 (q, *J* = 6.8 Hz, 1H), 4.54 (dd, *J* = 7.9, 3.4 Hz, 1H), 3.67 (d, *J* = 7.9 Hz, 1H), 2.95-2.81 (m, 2H), 2.68 (d, *J* = 3.4 Hz, 1H), 2.68-2.57 (m, 2H), 2.07-1.87 (m, 2H), 1.58 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 137.1, 130.0, 128.2, 127.3, 127.3, 77.2, 49.7, 28.2, 27.5, 25.6, 14.6; IR (thin film, NaCl) ν_{max} 3445 (br), 3053, 2903, 2241, 1599, 1493, 1423, 1277, 1082, 704 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{14}H_{18}OS_2Na$ [M + Na] 289.1, found 289.1.



Synthesis of 2-(1,3-dithian-2-yl)but-3-en-2-ol (14). To a solution of 1,3-dithiane (1.44 g, 12 mmol) in THF (100 mL) at –20 ºC was added dropwise *n*-BuLi (4.80 mL, 12 mmol, 2.5 M in hexanes). The resultant clear solution was stirred at the same temperature for 1 h. After cooling down to –78 ºC, but-3-en-2-one (820 μL, 700 mg, 10 mmol) was added dropwise via a syringe. The reaction was stirred for 30 min, then quenched with saturated aqueous NH_4Cl (10 mL) and warmed to ambient temperature. The reaction mixture was further diluted with H_2O (20 mL) and extracted with Et_2O (3 x 40 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (10→15% EtOAc/hexanes) to afford allylic alcohol **14** (1.18 g, 62%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (dd, *J* = 17.1, 10.7 Hz, 1H), 5.35 (d, *J* = 17.1 Hz, 1H), 5.14 (d, *J* = 10.7 Hz, 1H), 4.11 (s, 1H), 2.95-2.68 (m, 4H), 2.56 (s, 1H), 2.09-1.96 (m, 1H), 1.88-1.73 (m, 1H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 114.2, 75.3, 59.0, 30.5, 30.2, 25.8, 25.6; IR (thin film, NaCl) ν_{max} 3468 (br), 3088, 2900, 1857, 1714, 1642, 1417, 1278, 925, 796 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_8H_{14}OS_2Na$ [M + Na] 213.1, found 213.2.

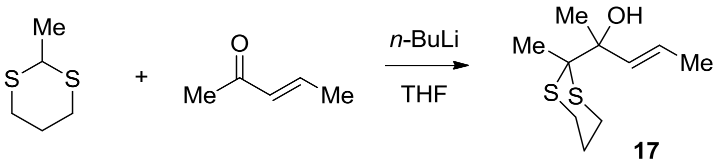


Synthesis of (*E*)-2-(1,3-dithian-2-yl)pent-3-en-2-ol (15). To a solution of 1,3-dithiane (1.44 g, 12 mmol) in THF (100 mL) at –20 ºC was added dropwise *n*-BuLi (4.80 mL, 12 mmol, 2.5 M in hexanes). The resultant clear solution was stirred at the same temperature for 1 h. After cooling down to –78 ºC, (*E*)-pent-3-en-2-one (976 μL, 841 mg, 10 mmol) was added dropwise via a syringe. The reaction was stirred for 30 min, then quenched with saturated aqueous NH_4Cl (10 mL) and warmed to ambient temperature. The reaction mixture was further diluted with H_2O (20 mL) and extracted with Et_2O (3 x 40 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by flash column chromatography on silica gel (10→20% EtOAc/hexanes) to afford allylic alcohol **15** (1.54 g, 75%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (dq, *J* = 15.4, 6.4 Hz, 1H), 5.63 (d, *J* = 15.4 Hz, 1H), 4.11 (s, 1H), 2.94-2.72 (m, 4H), 2.48 (s, 1H), 2.10-1.98 (m, 1H), 1.90-1.75 (m, 1H), 1.70 (d, *J* = 6.4 Hz, 3H), 1.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.5, 125.3, 74.9, 59.9, 30.7, 30.4, 26.1, 25.8, 17.8; IR (thin film, NaCl) ν_{max} 3460 (br), 2933, 1671, 1423, 1374, 1337, 1277, 1146, 966, 750 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_9H_{16}OS_2Na$ [M + Na] 227.1, found 227.2.



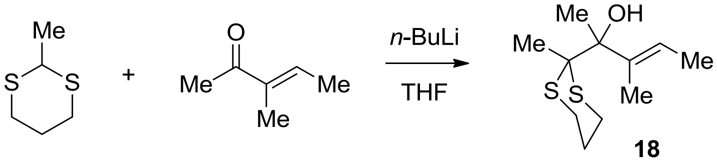
16

Synthesis of (*E*)-2-(1,3-dithian-2-yl)-3-methylpent-3-en-2-ol (16). To a solution of 1,3-dithiane (721 mg, 6.0 mmol) in THF (40 mL) at –20 °C was added dropwise *n*-BuLi (2.40 mL, 6.0 mmol, 2.5 M in hexanes). The resultant clear solution was stirred at the same temperature for 1 h. After cooling down to –78 °C, (*E*)-3-methylpent-3-en-2-one (329 mg, 4.0 mmol) was added dropwise via a syringe. The reaction was stirred for 30 min, then quenched with saturated aqueous NH_4Cl (5 mL) and warmed to ambient temperature. The reaction mixture was further diluted with H_2O (10 mL) and extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by flash column chromatography on silica gel (5→7% EtOAc/hexanes) to afford allylic alcohol **16** (799 mg, 91%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (q, *J* = 6.7 Hz, 1H), 4.36 (s, 1H), 2.95-2.76 (m, 4H), 2.28 (s, 1H), 2.10-1.98 (m, 1H), 1.87-1.71 (m, 1H), 1.64 (s, 3H), 1.63 (d, *J* = 6.7 Hz, 3H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 120.2, 77.7, 58.0, 31.0, 30.8, 25.9, 24.9, 13.4, 12.8; IR (thin film, NaCl) ν_{max} 3468 (br), 2982, 2899, 1664, 1423, 1372, 1278, 1078, 839, 617 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{10}H_{18}OS_2Na$ [M + Na] 241.1, found 241.1.



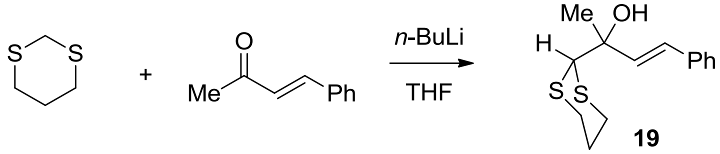
17

Synthesis of (*E*)-2-(2-methyl-1,3-dithian-2-yl)pent-3-en-2-ol (17). To a solution of 2-methyl-1,3-dithiane (1.44 mL, 1.61 g, 12 mmol) in THF (100 mL) at –20 ºC was added dropwise *n*-BuLi (4.80 mL, 12 mmol, 2.5 M in hexanes). The resultant clear solution was stirred at the same temperature for 1 h. After cooling down to –78 ºC, (*E*)-pent-3-en-2-one (976 µL, 841 mg, 10 mmol) was added dropwise via a syringe. The reaction was stirred for 30 min, then quenched with saturated aqueous NH_4Cl (10 mL) and warmed to ambient temperature. The reaction mixture was further diluted with H_2O (20 mL) and extracted with Et_2O (3 x 40 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by flash column chromatography on silica gel (5→10% EtOAc/hexanes) to afford allylic alcohol **17** (1.48 g, 68%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87-5.71 (m, 2H), 2.96-2.77 (m, 4H), 2.59 (s, 1H), 2.05-1.92 (m, 1H), 1.92-179 (m, 1H), 1.74 (s, 3H), 1.73 (d, *J* = 4.9 Hz, 3H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.8, 125.6, 78.5, 59.7, 27.1, 27.0, 25.2, 24.9, 23.7, 18.0; IR (thin film, NaCl) ν_{max} 3481 (br), 2979, 2932, 1713, 1670, 1449, 1369, 1277, 1069, 970 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{10}H_{18}OS_2$ Na [M + Na] 241.1, found 241.1.



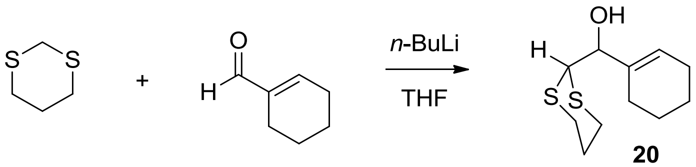
18

Synthesis of (*E*)-3-methyl-2-(2-methyl-1,3-dithian-2-yl)pent-3-en-2-ol (18). To a solution of 2-methyl-1,3-dithiane (898 µL, 1.01 g, 7.5 mmol) in THF (50 mL) at –20 ºC was added dropwise *n*-BuLi (3.0 mL, 7.5 mmol, 2.5 M in hexanes). The resultant clear solution was stirred at the same temperature for 1 h. After cooling down to –78 ºC, (*E*)-3-methylpent-3-en-2-one (490 mg, 5.0 mmol) was added dropwise via a syringe. The reaction was stirred for 30 min, then quenched with saturated aqueous NH_4Cl (5 mL) and warmed to ambient temperature. The reaction mixture was further diluted with H_2O (10 mL) and extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by flash column chromatography on silica gel (5→10% EtOAc/hexanes) to afford allylic alcohol **18** (857g, 74%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 5.76 (q, *J* = 6.7 Hz, 1H), 2.97-2.76 (m, 4H), 2.73 (s, 1H), 2.07-1.94 (m, 1H), 1.91-1.78 (m, 1H), 1.78 (s, 3H), 1.77 (s, 3H), 1.64 (d, *J* = 6.7 Hz, 3H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 123.3, 80.7, 60.9, 27.2, 27.1, 25.6, 25.0, 24.6, 15.4, 13.9; IR (thin film, NaCl) ν_{max} 3481 (br), 2980, 2930, 1449, 1369, 1277, 1146, 1068, 911, 751 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{11}H_{20}OS_2Na$ [M + Na] 255.1, found 255.2.



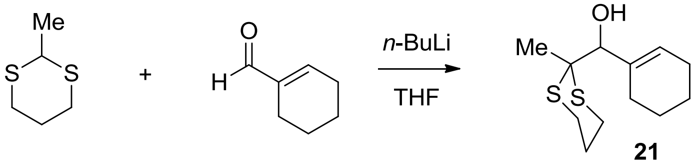
19

Synthesis of (*E*)-2-(1,3-dithian-2-yl)-4-phenylbut-3-en-2-ol (19). To a solution of 1,3-dithiane (902 mg, 7.5 mmol) in THF (50 mL) at –20 ºC was added dropwise *n*-BuLi (3.0 mL, 7.5 mmol, 2.5 M in hexanes). The resultant clear solution was stirred at the same temperature for 1 h. After cooling down to –78 ºC, (*E*)-4-phenylbut-3-en-2-one (730 mg, 5.0 mmol) was added dropwise via a syringe. The reaction was stirred for 30 min, then quenched with saturated aqueous NH_4Cl (5 mL) and warmed to ambient temperature. The reaction mixture was further diluted with H_2O (10 mL) and extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by flash column chromatography on silica gel (10→20% EtOAc/hexanes) to afford allylic alcohol **19** (1.16 g, 87%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.1 Hz, 2H), 7.31 (appd t, *J* = 7.1 Hz, 2H), 7.23 (t, *J* = 7.1 Hz, 1H), 6.76 (d, *J* = 15.9 Hz, 1H), 6.41 (d, *J* = 15.9 Hz, 1H), 4.22 (s, 3H), 2.95-2.78 (m, 4H), 2.76 (s, 1H), 2.10-2.00 (m, 1H), 1.93-1.80 (m, 1H), 1.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 133.2, 129.0, 128.7, 127.8, 126.8, 75.5, 59.4, 30.4, 30.1, 26.4, 25.6; IR (thin film, NaCl) ν_{max} 3444 (br), 3025, 2900, 2247, 1599, 1494, 1421, 1273, 967, 904 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{14}H_{18}OS_2Na$ [M + Na] 289.1, found 289.1.



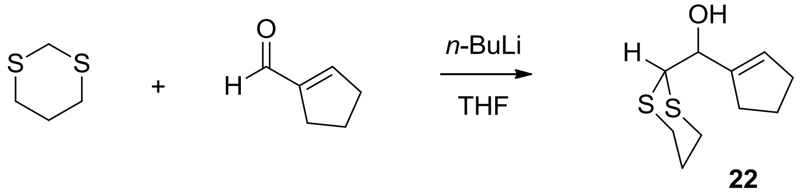
20

Synthesis of cyclohex-1-en-1-yl(1,3-dithian-2-yl)methanol (20). To a solution of 1,3-dithiane (1.80 g, 15 mmol) in THF (100 mL) at –20 ºC was added dropwise *n*-BuLi (6.0 mL, 15 mmol, 2.5 M in hexanes). The resultant clear solution was stirred at the same temperature for 1 h. After cooling down to –78 ºC, cyclohex-1-enecarbaldehyde (1.14 mL, 1.10 g, 10 mmol) was added dropwise via a syringe. The reaction was stirred for 30 min, then quenched with saturated aqueous NH_4Cl (10 mL) and warmed to ambient temperature. The reaction mixture was further diluted with H_2O (20 mL) and extracted with Et_2O (3 x 40 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by flash column chromatography on silica gel (10→20% EtOAc/hexanes) to afford allylic alcohol **20** (2.18 g, 95%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (s, 1H), 4.13 (d, *J* = 8.7 Hz, 1H), 3.99 (d, *J* = 8.7 Hz, 1H), 2.99-2.79 (m, 2H), 2.79-2.67 (m, 2H), 2.48 (s, 1H), 2.17-1.99 (m, 4H), 1.99-1.82 (m, 2H), 1.74-1.47 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 127.3, 77.2, 49.9, 28.6, 28.0, 25.7, 25.2, 23.2, 22.6, 22.5; IR (thin film, NaCl) ν_{max} 3437 (br), 2928, 1668, 1422, 1276, 1139, 1015, 920, 803, 736 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{11}H_{18}OS_2Na$ [M + Na] 253.1, found 253.2.



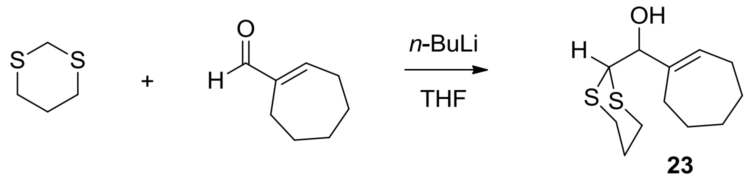
21

Synthesis of cyclohex-1-en-1-yl(2-methyl-1,3-dithian-2-yl)methanol (21). To a solution of 2-methyl-1,3-dithiane (1.80 mL, 2.01 g, 15 mmol) in THF (100 mL) at –20 ºC was added dropwise *n*-BuLi (6.0 mL, 15 mmol, 2.5 M in hexanes). The resultant clear solution was stirred at the same temperature for 1 h. After cooling down to –78 ºC, cyclohex-1-enecarbaldehyde (1.14 mL, 1.10 g, 10 mmol) was added dropwise via a syringe. The reaction was stirred for 30 min, then quenched with saturated aqueous NH_4Cl (10 mL) and warmed to ambient temperature. The reaction mixture was further diluted with H_2O (20 mL) and extracted with Et_2O (3 x 40 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by flash column chromatography on silica gel (10→20% EtOAc/hexanes) to afford allylic alcohol **21** (2.31 g, 95%) as a colorless crystalline solid. ^1H NMR (400 MHz, $CDCl_3$) δ 5.79 (s, 1H), 4.30 (s, 1H), 3.03-3.90 (m, 2H), 2.77 (s, 1H), 2.72-2.60 (m, 2H), 2.41-2.29 (m, 1H), 2.11-1.95 (m, 4H), 1.95-1.79 (m, 1H), 1.66-1.49 (m, 4H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.1, 127.4, 76.3, 54.1, 27.8, 26.8, 26.1, 25.3, 24.6, 23.4, 23.0, 22.6; IR (thin film, NaCl) ν_{max} 3461 (br), 2929, 2666, 1661, 1424, 1368, 1242, 1140, 1027, 921 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{12}H_{20}OS_2Na$ [M + Na] 267.1, found 267.2.



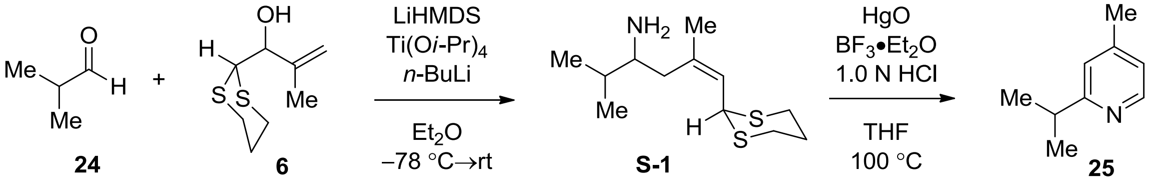
22

Synthesis of cyclopent-1-en-1-yl(1,3-dithian-2-yl)methanol (22). To a solution of 1,3-dithiane (902 mg, 7.5 mmol) in THF (50 mL) at –20 ºC was added dropwise *n*-BuLi (3.0 mL, 7.5 mmol, 2.5 M in hexanes). The resultant clear solution was stirred at the same temperature for 1 h. After cooling down to –78 ºC, cyclopent-1-enecarbaldehyde (481 mg, 5.0 mmol) was added dropwise via a syringe. The reaction was stirred for 30 min, then quenched with saturated aqueous NH_4Cl (5 mL) and warmed to ambient temperature. The reaction mixture was further diluted with H_2O (10 mL) and extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by flash column chromatography on silica gel (10% EtOAc/hexanes) to afford allylic alcohol **22** (1.03 g, 95%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 5.81-5.78 (m, 1H), 4.52 (dd, *J* = 7.4, 3.5 Hz, 1H), 4.02 (d, *J* = 7.4 Hz, 1H), 2.98-2.85 (m, 2H), 2.81-2.69 (m, 2H), 2.50 (d, *J* = 3.5 Hz, 1H), 2.48-2.22 (m, 4H), 2.13-2.01 (m, 1H), 2.00-1.85 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 129.8, 72.0, 50.5, 32.2, 30.8, 28.6, 28.0, 25.6, 23.3; IR (thin film, NaCl) ν_{max} 3433 (br), 2894, 2844, 1421, 1274, 1042, 1009, 908, 794, 673 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{10}H_{16}OS_2Na$ [M + Na] 239.1, found 239.1.



23

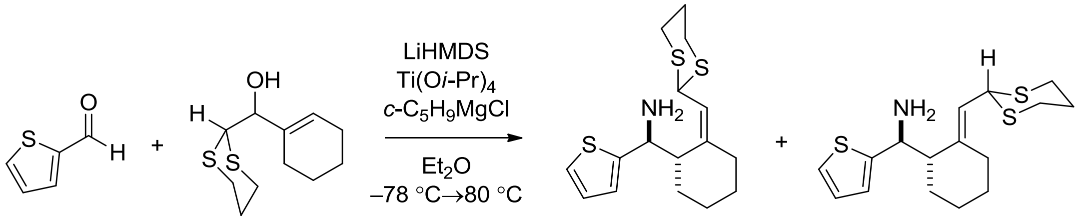
Synthesis of cyclohept-1-en-1-yl(1,3-dithian-2-yl)methanol (23). To a solution of 1,3-dithiane (902 mg, 7.5 mmol) in THF (50 mL) at –20 ºC was added dropwise *n*-BuLi (3.0 mL, 7.5 mmol, 2.5 M in hexanes). The resultant clear solution was stirred at the same temperature for 1 h. After cooling down to –78 ºC, cyclohept-1-enecarbaldehyde (621 mg, 5.0 mmol) was added dropwise via a syringe. The reaction was stirred for 30 min, then quenched with saturated aqueous NH_4Cl (5 mL) and warmed to ambient temperature. The reaction mixture was further diluted with H_2O (10 mL) and extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by flash column chromatography on silica gel (10% EtOAc/hexanes) to afford allylic alcohol **23** (1.15 g, 96%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (t, *J* = 6.4 Hz, 1H), 4.16 (d, *J* = 8.5 Hz, 1H), 3.95 (d, *J* = 8.5 Hz, 1H), 2.97-2.80 (m, 2H), 2.77-2.65 (m, 2H), 2.50 (m, 1H), 2.22-2.00 (m, 5H), 1.97-1.94 (m, 1H), 1.79-1.39 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 132.0, 78.4, 49.8, 32.4, 28.5, 28.4, 27.9, 27.4, 26.8, 26.6, 25.6; IR (thin film, NaCl) ν_{max} 3428 (br), 2917, 2846, 1446, 1275, 1242, 1026, 908, 849, 785 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{12}H_{20}OS_2Na$ [M + Na] 267.1, found 267.2.



Synthesis of 2-isopropyl-4-methylpyridine (25). To a solution of Ti(O*i*-Pr)$_4$ (296 µL, 284 mg, 1.0 mmol) in Et_2O (4.0 mL) at –78 ºC was added dropwise *n*-BuLi (800 µL, 2.0 mmol, 2.5 M in hexanes). The resultant orange solution was allowed to warm to –50 ºC over 20 min. Meanwhile, *N*-TMS imine was prepared by slowly adding LiHMDS (1.0 mL, 1.0 mmol, 1.0 M in THF) to a solution of isobutyraldehyde (91.3 µL, 72.1 mg, 1.0 mmol) in THF (2.0 mL) at –78 ºC followed by stirring for 10 min. The newly prepared imine was cannulated rapidly to the Ti-solution. The resultant mixture was warmed to 0 ºC over 1 h as it turned from orange color to wine red, and then re-cooled down to –78 ºC.

A solution of the lithium alkoxide, generated *in situ* via deprotonation of alcohol **6** (95.2 mg, 0.50 mmol) in THF (1.0 mL) with *n*-BuLi (220 μL, 0.55 mmol, 2.5 M in hexanes) at –78 °C followed by warming to 0 °C over 10 min, was cannulated dropwise to the Ti-imine complex. The resultant mixture was allowed to warm to ambient temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (1.0 mL), stirred rapidly for 10 min, filtered through a pad of Celite, and concentrated *in vacuo* to afford crude **S-1** as a yellow oil.

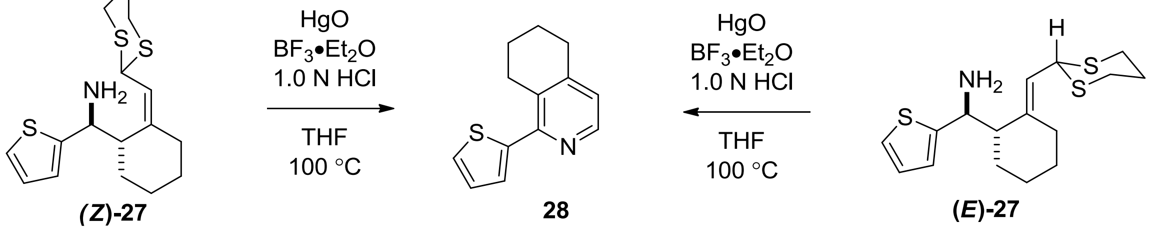
The crude product was then dissolved in THF (11 mL) and added to a stirred orange suspension of HgO (325 mg, 1.5 mmol) and $BF_3 \cdot Et_2O$ (188 μL, 213 mg, 1.5 mmol) in THF (10 mL); then 1.0 N HCl (4.0 mL) was added, and the reaction was heated in a sealed tube at 100 °C overnight. After cooling down to ambient temperature, saturated aqueous K_2CO_3 (10 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (2→5% EtOAc/hexanes with 1% Et_3N) to afford pyridine **25** (36.1 mg, 53%) as a colorless oil. The spectral data acquired for **25** correspond to those reported in the literature.[6]



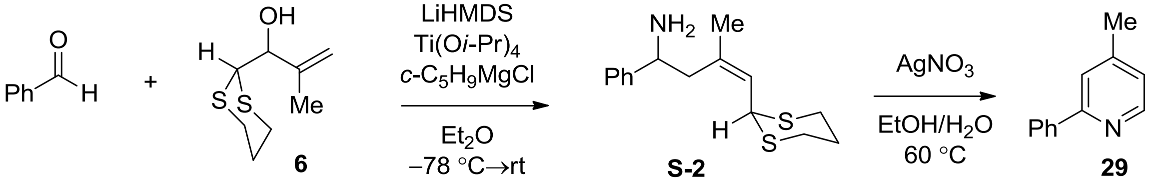
26 **17** ***(Z)*-27** ***(E)*-27**

Z:*E* = 4.5:1.0

Synthesis of (S)-((S)-2-((1,3-dithian-2-yl)methylene)cyclohexyl)(thiophen-2-yl)methanamine (27). To a solution of thiophene-2-carbaldehyde (93.5 μL, 112 mg, 1.0 mmol) in Et_2O (6.0 mL) at 0 °C in a sealed tube was added slowly LiHMDS (1.0 mL, 1.0 mmol, 1.0 M in THF). The reaction was stirred for 10 min, then cooled down to –78 °C. Ti(O*i*-Pr)$_4$ (444 μL, 426 mg, 1.5 mmol) was added followed by dropwise addition of *c*-C_5H_9MgCl (1.5 mL, 3.0 mmol, 2.0 M in Et_2O) via a syringe. The resultant yellow solution was allowed to warm to –30 °C over 1.5 h as it turned dark brown. A solution of the lithium alkoxide, generated *in situ* via deprotonation of alcohol **17** (115 mg, 0.50 mmol) in THF (1.0 mL) with *n*-BuLi (220 μL, 0.55 mmol, 2.5 M in hexanes) at –78 °C followed by warming to 0 °C over 10 min, was cannulated dropwise to the Ti-imine complex. The resultant mixture was allowed to warm to ambient temperature, and then heated at 80 ºC for 24 h. After cooling down to ambient temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ (1.2 mL), stirred rapidly for 10 min, filtered through a pad of Celite, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel ($10\rightarrow50\%$ EtOAc/hexanes with 1% Et_3N) to afford homoallylic amines ***(Z)*-27** (94.0 mg, 58%) and ***(E)*-27** (20.0 mg, 12%) as a pale yellow oil (*Z:E* = 4.5 :1.0, combined yield 70%). *Spectroscopic data of **(Z)-27***: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 5.3 Hz, 1H), 6.99-6.91 (m, 2H), 5.36 (d, *J* = 10.1 Hz, 1H), 5.12 (d, *J* = 10.1 Hz, 1H), 3.05-2.90 (m, 2H), 2.83-2.71 (m, 3H), 2.31-2.20 (m, 1H), 2.14-2.03 (m, 2H), 1.89-1.78 (m, 2H), 1.67-1.25 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.4, 145.1, 126.2, 124.3, 124.1, 122.5, 50.8, 46.6, 43.4, 33.0, 30.6, 30.4, 29.4, 28.4, 24.9, 21.4; IR (thin film, NaCl) ν_{max} 3005, 2931, 2857, 2318, 1650, 1447, 1422, 1275, 896, 701 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{16}H_{24}NS_3$ $[M + H]^+$ 326.1, found 326.1. *Spectroscopic data of **(E)-27***: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 5.1 Hz, 1H), 6.96-6.91 (m, 2H), 5.42 (d, *J* = 9.3 Hz, 1H), 4.97 (d, *J* = 9.3 Hz, 1H), 4.47 (d, *J* = 11.0 Hz, 1H), 3.00-2.88 (m, 2H), 2.86-2.76 (m, 2H), 2.62-2.53 (m, 1H), 2.24-2.16 (m, 1H), 2.14-2.00 (m, 2H), 1.91-1.79 (m, 2H), 1.69-1.31 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 145.1, 126.1, 124.3, 124.1, 121.8, 53.9, 50.7, 43.6, 30.6, 30.5, 29.8, 28.1, 26.3, 24.9, 22.0; IR (thin film, NaCl) ν_{max} 3005, 2928, 2856, 1735, 1641, 1446, 1372, 1275, 908, 696 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{16}H_{24}NS_3$ $[M + H]^+$ 326.1, found 326.1.

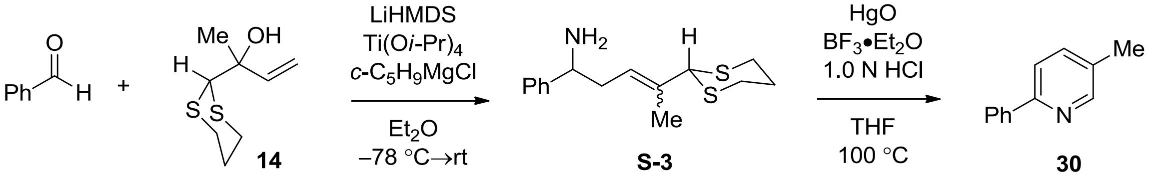


Synthesis of 1-(thiophen-2-yl)-5,6,7,8-tetrahydroisoquinoline (28). A solution of **(*Z*)-27** or **(*E*)-27** (23.0 mg, 0.071 mmol) in THF (1.0 mL) was added to a stirred orange suspension of HgO (45.9 mg, 0.212 mmol) and $BF_3{\cdot}Et_2O$ (26.6 µL, 30.1 mg, 0.212 mmol) in THF (1.8 mL); then 1.0 N HCl (0.7 mL) was added, and the reaction was heated in a sealed tube at 100 °C overnight. After cooling down to ambient temperature, saturated aqueous K_2CO_3 (5.0 mL) was added and the mixture was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (3% EtOAc/hexanes with 1% Et_3N) to afford pyridine **28** (13.2 mg, 88% and 11.2 mg, 75%, respectively) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 4.9 Hz, 7.42-7.38 (m, 2H), 7.10 (dd, J = 5.3, 3.7 Hz, 1H), 6.90 (d, J = 4.9 Hz, 1H), 2.97-2.90 (m, 2H), 2.84-2.77 (m, 2H), 1.89-1.76 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 147.2, 145.7, 144.9, 130.1, 127.3, 127.1, 127.0, 122.9, 29.6, 28.1, 23.2, 21.9; IR (thin film, NaCl) ν_{max} 3046, 2935, 2861, 1661, 1577, 1436, 1403, 1272, 824, 705 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{13}H_{14}NS$ $[M + H]^+$ 216.1, found 216.1.



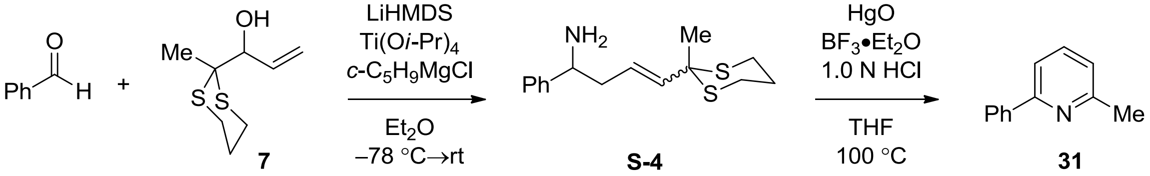
Synthesis of 4-methyl-2-phenylpyridine (29). To a solution of benzaldehyde (101 μL, 106 mg, 1.0 mmol) in Et_2O (6.0 mL) at 0 ºC was added slowly LiHMDS (1.0 mL, 1.0 mmol, 1.0 M in THF). The reaction was stirred for 10 min, then cooled down to –78 ºC. $Ti(O\textit{i}\text{-}Pr)_4$ (444 μL, 426 mg, 1.5 mmol) was added followed by dropwise addition of *c*-C_5H_9MgCl (1.5 mL, 3.0 mmol, 2.0 M in Et_2O) via a syringe. The resultant yellow solution was allowed to warm to –30 ºC over 1.5 h as it turned dark brown. A solution of the lithium alkoxide, generated *in situ* via deprotonation of alcohol **6** (95 mg, 0.50 mmol) in THF (1.0 mL) with *n*-BuLi (220 μL, 0.55 mmol, 2.5 M in hexanes) at –78 °C followed by warming to 0 °C over 10 min, was cannulated dropwise to the Ti-imine complex. The resultant mixture was allowed to warm to ambient temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (1.2 mL), stirred rapidly for 10 min, filtered through a pad of Celite, and concentrated *in vacuo* to afford crude **S-2** (*Z:E* ≥ 20:1 based on ^{1}H NMR of the crude) as a yellow oil.

The crude was taken up in EtOH (6.0 mL) and added to a stirred solution of $AgNO_3$ (255 mg, 1.5 mmol) in EtOH (6.0 mL) and H_2O (3.0 mL). The reaction was heated in a sealed tube at 60 °C overnight. After cooling down to ambient temperature, pyrrolidine (1.2 mL) was added and the reaction was stirred for 30 min. The reaction was then filtered through a pad of Celite. The filtrate was treated with saturated aqueous K_2CO_3 (10 mL) and extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (2→5% EtOAc/hexanes with 1% Et_3N) to afford pyridine **29** (68.4 mg, 80%) as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 5.8 Hz, 1H), 8.00-7.95 (m, 2H), 7.55 (s, 1H), 7.50-7.37 (m, 3H), 7.06 (d, *J* = 5.8 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 149.5, 147.7, 139.6, 128.8, 128.7, 126.9, 123.1, 121.5, 21.2; IR (thin film, NaCl) ν_{max} 3059, 2956, 1604, 1582, 1557, 1446, 1073, 827, 776, 694 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{12}H_{12}N$ $[M + H]^+$ 170.1, found 170.2.



Synthesis of 5-methyl-2-phenylpyridine (30). To a solution of benzaldehyde (101 μL, 106 mg, 1.0 mmol) in Et_2O (6.0 mL) at 0 °C was added slowly LiHMDS (1.0 mL, 1.0 mmol, 1.0 M in THF). The reaction was stirred for 10 min, then cooled down to –78 °C. $Ti(Oi\text{-}Pr)_4$ (444 μL, 426 mg, 1.5 mmol) was added followed by dropwise addition of *c*-C_5H_9MgCl (1.5 mL, 3.0 mmol, 2.0 M in Et_2O) via a syringe. The resultant yellow solution was allowed to warm to –30 °C over 1.5 h as it turned dark brown. A solution of the lithium alkoxide, generated *in situ* via deprotonation of alcohol **14** (95.2 mg, 0.50 mmol) in THF (1.0 mL) with *n*-BuLi (220 μL, 0.55 mmol, 2.5 M in hexanes) at –78 °C followed by warming to 0 °C over 10 min, was cannulated dropwise to the Ti-imine complex. The resultant mixture was allowed to warm to ambient temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (1.2 mL), stirred rapidly for 10 min, filtered through a pad of Celite, and concentrated *in vacuo* to afford crude **S-3** (as a mixture of olefin isomers based on ^1H NMR of the crude) as a yellow oil.

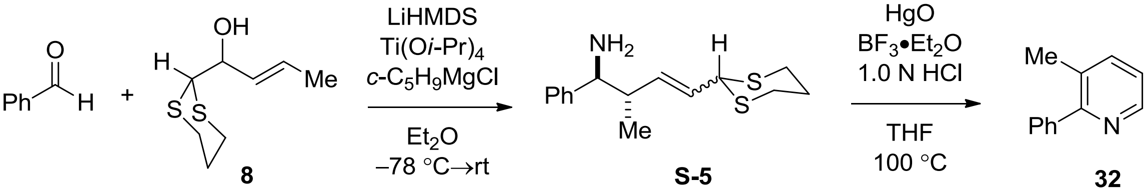
The crude was taken up in THF (11 mL) and added to a stirred orange suspension of HgO (325 mg, 1.5 mmol) and $BF_3{\cdot}Et_2O$ (188 μL, 213 mg, 1.5 mmol) in THF (10 mL); then 1.0 N HCl (4.0 mL) was added, and the reaction was heated in a sealed tube at 100 °C overnight. After cooling down to ambient temperature, saturated aqueous K_2CO_3 (10 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (2→5% EtOAc/hexanes with 1% Et_3N) to afford pyridine **30** (57.7 mg, 68%) as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.98 (m, 2H), 7.62 (d, J = 8.2 Hz, 1H), 7.54 (d, J = 8.2 Hz, 1H), 7.49-7.43 (m, 2H), 7.42-7.36 (m, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 150.1, 139.5, 137.3, 131.6, 128.7, 128.6, 126.7, 120.3, 18.2; IR (thin film, NaCl) ν_{max} 3033, 3003, 2924, 2216, 1599, 1562, 1477, 1379, 905, 692 cm^{-1}; LRMS (EI, H) m/z calc'd for $C_{12}H_{12}N$ $[M + H]^+$ 170.1, found 170.3.



Synthesis of 2-methyl-6-phenylpyridine (31). To a solution of benzaldehyde (101 μL, 106 mg, 1.0 mmol) in Et_2O (6.0 mL) at 0 ºC was added slowly LiHMDS (1.0 mL, 1.0 mmol, 1.0 M in THF). The reaction was stirred for 10 min, then cooled down to –78 ºC. Ti(O*i*-Pr)$_4$ (444 μL, 426 mg, 1.5 mmol) was added followed by dropwise addition of *c*-C_5H_9MgCl (1.5 mL, 3.0 mmol, 2.0 M in Et_2O) via a syringe. The resultant yellow solution was allowed to warm to –30 ºC over 1.5 h as it turned dark brown. A solution of the lithium alkoxide, generated *in situ* via deprotonation of alcohol **7** (95.2 mg, 0.50 mmol) in THF (1.0 mL) with *n*-BuLi (220 μL, 0.55 mmol, 2.5 M in hexanes) at –78 °C followed by warming to 0 °C over 10 min, was cannulated dropwise to the Ti-imine complex. The resultant mixture was allowed to warm to ambient temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (1.2 mL), stirred rapidly for 10 min, filtered through a pad of Celite, and concentrated *in vacuo* to afford crude **S-4** (as a mixture of olefin isomers based on ^1H NMR of the crude) as a yellow oil.

The crude was taken up in THF (11 mL) and added to a stirred orange suspension of HgO (325 mg, 1.5 mmol) and $BF_3 \cdot Et_2O$ (188 μL, 213 mg, 1.5 mmol) in THF (10 mL); then 1.0 N HCl (4.0 mL) was added, and the reaction was heated in a sealed tube at 100 °C overnight. After cooling down to ambient temperature, saturated aqueous K_2CO_3 (10 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*.

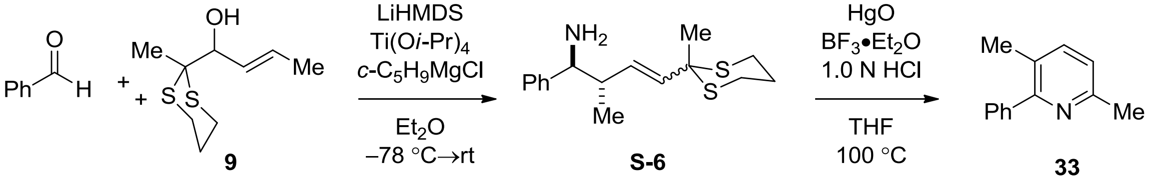
The crude product was purified by flash column chromatography on silica gel (2→5% EtOAc/hexanes with 1% Et_3N) to afford pyridine **31** (48.0 mg, 57%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99-7.95 (m, 2H), 7.62 (appd t, J = 7.8 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.49-7.42 (m, 2H), 7.42-7.35 (m, 1H), 7.08 (d, J = 7.8 Hz, 1H), 2.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 157.0, 139.8, 136.9, 128.7, 128.7, 127.0, 121.6, 117.6, 24.8; IR (thin film, NaCl) ν_{max} 3062, 2924, 1592, 1574, 1459, 1448, 1234, 1161, 1029, 758 cm^{-1}; LRMS (EI, H) m/z calc'd for $C_{12}H_{12}N$ $[M + H]^+$ 170.1, found 170.2.



Synthesis of 3-methyl-2-phenylpyridine (32). To a solution of benzaldehyde (101 μL, 106 mg, 1.0 mmol) in Et_2O (6.0 mL) at 0 ºC was added slowly LiHMDS (1.0 mL, 1.0 mmol, 1.0 M in THF). The reaction was stirred for 10 min, then cooled down to –78 ºC. Ti(O*i*-Pr)$_4$ (444 μL, 426 mg, 1.5 mmol) was added followed by dropwise addition of *c*-C_5H_9MgCl (1.5 mL, 3.0 mmol, 2.0 M in Et_2O) via a syringe. The resultant yellow solution was allowed to warm to –30 ºC over 1.5 h as it turned dark brown. A solution of the lithium alkoxide, generated *in situ* via deprotonation of alcohol **8** (95.2 mg, 0.50 mmol) in THF (1.0 mL) with *n*-BuLi (220 μL, 0.55 mmol, 2.5 M in hexanes) at –78 ^{o}C followed by warming to 0 ^{o}C over 10 min, was cannulated dropwise to the Ti-imine complex. The resultant mixture was allowed to warm to ambient temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (1.2 mL), stirred rapidly for 10 min, filtered through a pad of Celite, and concentrated *in vacuo* to afford crude **S-5** (as a mixture of olefin isomers based on ^{1}H NMR of the crude) as a yellow oil.

The crude was taken up in THF (11 mL) and added to a stirred orange suspension of HgO (325 mg, 1.5 mmol) and $BF_3 \cdot Et_2O$ (188 μL, 213 mg, 1.5 mmol) in THF (10 mL); then 1.0 N HCl (4.0 mL) was added, and the reaction was heated in a sealed tube at 100 ^{o}C overnight. After cooling down to ambient temperature, saturated aqueous K_2CO_3 (10 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*.

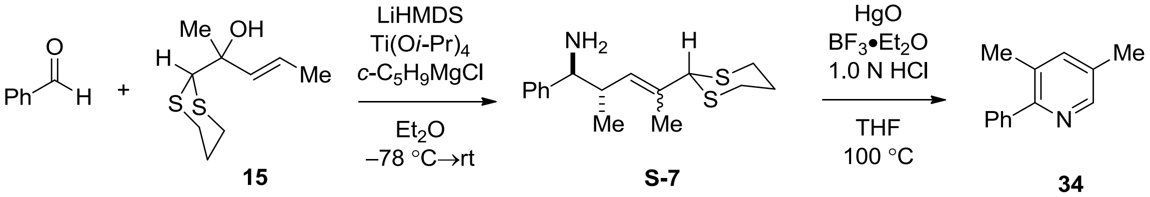
The crude product was purified by flash column chromatography on silica gel (2→5% EtOAc/hexanes with 1% Et_3N) to afford pyridine **32** (36.0 mg, 43%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 4.8 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.55-7.49 (m, 2H), 7.48-7.35 (m, 3H), 7.17 (dd, *J* = 8.0, 4.8 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 147.0, 140.7, 138.5, 130.8, 128.9, 128.2, 127.9, 122.6, 20.1; IR (thin film, NaCl) ν_{max} 3056, 2955, 1581, 1565, 1424, 1119, 1020, 785, 748, 701 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{12}H_{12}N$ $[M + H]^+$ 170.1, found 170.3.



Synthesis of 3,6-dimethyl-2-phenylpyridine (33). To a solution of benzaldehyde (101 μL, 106 mg, 1.0 mmol) in Et_2O (6.0 mL) at 0 °C was added slowly LiHMDS (1.0 mL, 1.0 mmol, 1.0 M in THF). The reaction was stirred for 10 min, then cooled down to –78 °C. Ti(O*i*-Pr)$_4$ (444 μL, 426 mg, 1.5 mmol) was added followed by dropwise addition of *c*-C_5H_9MgCl (1.5 mL, 3.0 mmol, 2.0 M in Et_2O) via a syringe. The resultant yellow solution was allowed to warm to –30 °C over 1.5 h as it turned dark brown. A solution of the lithium alkoxide, generated *in situ* via deprotonation of alcohol **9** (102 mg, 0.50 mmol) in THF (1.0 mL) with *n*-BuLi (220 μL, 0.55 mmol, 2.5 M in hexanes) at –78 °C followed by warming to 0 °C over 10 min, was cannulated dropwise to the Ti-imine complex. The resultant mixture was allowed to warm to ambient temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (1.2 mL), stirred rapidly for 10 min, filtered through a pad of Celite, and concentrated *in vacuo* to afford crude **S-6** (as a mixture of olefin isomers based on ^{1}H NMR of the crude) as a yellow oil.

The crude was taken up in THF (11 mL) and added to a stirred orange suspension of HgO (325 mg, 1.5 mmol) and $BF_3{\cdot}Et_2O$ (188 μL, 213 mg, 1.5 mmol) in THF (10 mL); then 1.0 N HCl (4.0 mL) was added, and the reaction was heated in a sealed tube at 100 °C overnight. After cooling down to ambient temperature, saturated aqueous K_2CO_3 (10 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (1→2%

EtOAc/hexanes with 1% Et_3N) to afford pyridine **33** (74.0 mg, 81%) as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.52-7.34 (m, 6H), 7.04 (d, *J* = 7.7 Hz, 1H), 2.56 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 155.4, 141.0, 138.7, 129.0, 128.2, 127.7, 127.4, 121.7, 24.2, 19.6; IR (thin film, NaCl) ν_{max} 2924, 1593, 1570, 1374, 1252, 1128, 1062, 1028, 736, 700 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{13}H_{14}N$ $[M + H]^+$ 184.1, found 184.2.

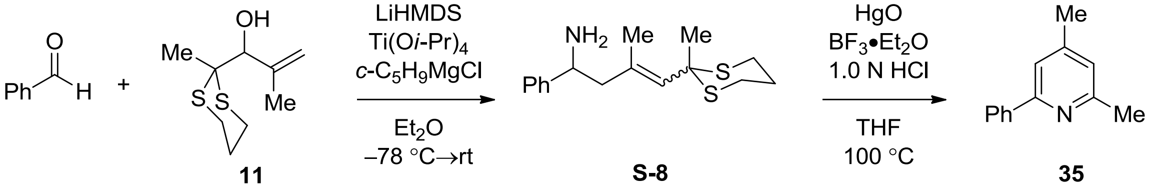


15 **S-7** **34**

Synthesis of 3,5-dimethyl-2-phenylpyridine (34). To a solution of benzaldehyde (101 μL, 106 mg, 1.0 mmol) in Et_2O (6.0 mL) at 0 ºC was added slowly LiHMDS (1.0 mL, 1.0 mmol, 1.0 M in THF). The reaction was stirred for 10 min, then cooled down to –78 ºC. Ti(O*i*-Pr)$_4$ (444 μL, 426 mg, 1.5 mmol) was added followed by dropwise addition of *c*-C_5H_9MgCl (1.5 mL, 3.0 mmol, 2.0 M in Et_2O) via a syringe. The resultant yellow solution was allowed to warm to –30 ºC over 1.5 h as it turned dark brown. A solution of the lithium alkoxide, generated *in situ* via deprotonation of alcohol **15** (102 mg, 0.50 mmol) in THF (1.0 mL) with *n*-BuLi (220 μL, 0.55 mmol, 2.5 M in hexanes) at –78 °C followed by warming to 0 °C over 10 min, was cannulated dropwise to the Ti-imine complex. The resultant mixture was allowed to warm to ambient temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (1.2 mL), stirred rapidly for 10 min, filtered through a pad of Celite, and concentrated *in vacuo* to afford crude **S-7** (as a mixture of olefin isomers based on ^1H NMR of the crude) as a yellow oil.

The crude was taken up in THF (11 mL) and added to a stirred orange suspension of HgO (325 mg, 1.5 mmol) and $BF_3 \cdot Et_2O$ (188 μL, 213 mg, 1.5 mmol) in THF (10 mL); then 1.0 N HCl (4.0 mL) was added, and the reaction was heated in a sealed tube at 100 °C overnight. After cooling down to ambient temperature, saturated aqueous K_2CO_3 (10 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (1→2% EtOAc/hexanes with 1% Et_3N) to afford pyridine **34** (71.0 mg, 78%) as a pale yellow oil.

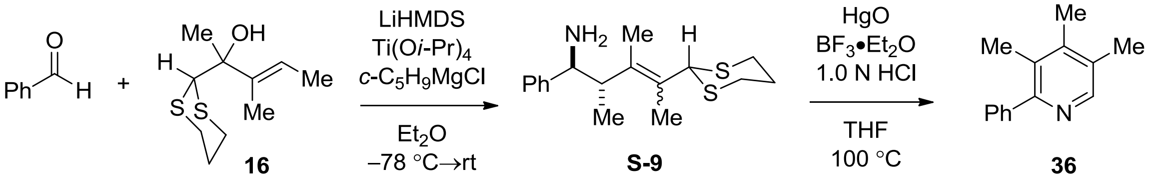
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.34 (s, 1H), 7.55-7.30 (m, 6H), 2.33 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 156.0, 147.4, 140.6, 139.1, 131.4, 130.1, 129.0, 128.1, 127.7, 19.9, 18.0; IR (thin film, NaCl) ν_{max} 2923, 1558, 1464, 1399, 1204, 1151, 1074, 1021, 884, 701 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{13}H_{14}N$ [M + H]$^+$ 184.1, found 184.2.



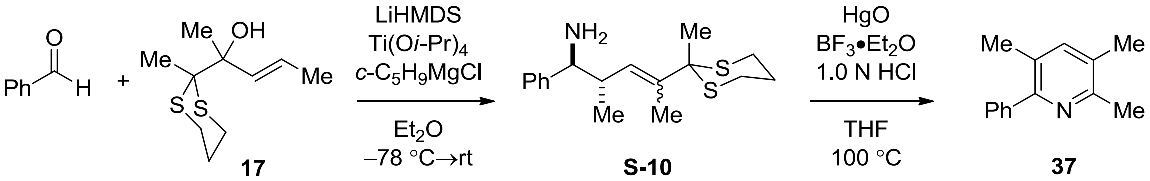
Synthesis of 2,4-dimethyl-6-phenylpyridine (35). To a solution of benzaldehyde (101 μL, 106 mg, 1.0 mmol) in Et$_2$O (6.0 mL) at 0 ºC was added slowly LiHMDS (1.0 mL, 1.0 mmol, 1.0 M in THF). The reaction was stirred for 10 min, then cooled down to –78 ºC. Ti(O*i*-Pr)$_4$ (444 μL, 426 mg, 1.5 mmol) was added followed by dropwise addition of *c*-C$_5$H$_9$MgCl (1.5 mL, 3.0 mmol, 2.0 M in Et$_2$O) via a syringe. The resultant yellow solution was allowed to warm to –30 ºC over 1.5 h as it turned dark brown. A solution of the lithium alkoxide, generated *in situ* via deprotonation of alcohol **11** (102 mg, 0.50 mmol) in THF (1.0 mL) with *n*-BuLi (220 μL, 0.55 mmol, 2.5 M in hexanes) at –78 ºC followed by warming to 0 ºC over 10 min, was cannulated dropwise to the Ti-imine complex. The resultant mixture was allowed to warm to ambient temperature overnight. The reaction was quenched with saturated aqueous NaHCO$_3$ (1.2 mL), stirred rapidly for 10 min, filtered through a pad of Celite, and concentrated *in vacuo* to afford crude **S-8** (as a mixture of olefin isomers based on ^{1}H NMR of the crude) as a yellow oil.

The crude was taken up in THF (11 mL) and added to a stirred orange suspension of HgO (325 mg, 1.5 mmol) and BF$_3$·Et$_2$O (188 μL, 213 mg, 1.5 mmol) in THF (10 mL); then 1.0 N HCl (4.0 mL) was added, and the reaction was heated in a sealed tube at 100 ºC overnight. After cooling down to ambient temperature, saturated aqueous K$_2$CO$_3$ (10 mL) was added and the mixture was extracted with Et$_2$O (3 x 20 mL). The combined organic extracts were washed with brine, dried over MgSO$_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (1→5% EtOAc/hexanes with 1% Et$_3$N) to afford pyridine **35** (73.2 mg, 80%) as a pale yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.97 (d, *J* = 7.2 Hz, 2H), 7.48 (appd t, *J* = 7.2 Hz, 2H), 7.44-7.38 (m, 1H), 7.37 (s, 1H), 6.94 (s, 1H), 2.60 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100

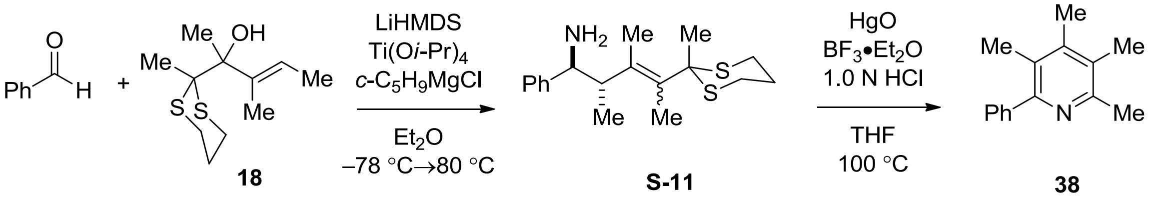
MHz, $CDCl_3$) δ 158.1, 157.0, 147.7, 140.0, 128.6, 128.5, 127.0, 122.6, 118.8, 24.6, 21.1; IR (thin film, NaCl) ν_{max} 2922, 1608, 1556, 1450, 1230, 1031, 848, 756, 733, 695 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{13}H_{14}N$ $[M + H]^+$ 184.1, found 184.2.



Synthesis of 3,4,5-trimethyl-2-phenylpyridine (36). To a solution of benzaldehyde (101 μL, 106 mg, 1.0 mmol) in Et_2O (6.0 mL) at 0 ºC was added slowly LiHMDS (1.0 mL, 1.0 mmol, 1.0 M in THF). The reaction was stirred for 10 min, then cooled down to –78 ºC. $Ti(O\textit{i}\text{-}Pr)_4$ (444 μL, 426 mg, 1.5 mmol) was added followed by dropwise addition of *c*-C_5H_9MgCl (1.5 mL, 3.0 mmol, 2.0 M in Et_2O) via a syringe. The resultant yellow solution was allowed to warm to –30 ºC over 1.5 h as it turned dark brown. A solution of the lithium alkoxide, generated *in situ* via deprotonation of alcohol **16** (109 mg, 0.50 mmol) in THF (1.0 mL) with *n*-BuLi (220 μL, 0.55 mmol, 2.5 M in hexanes) at –78 °C followed by warming to 0 °C over 10 min, was cannulated dropwise to the Ti-imine complex. The resultant mixture was allowed to warm to ambient temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (1.2 mL), stirred rapidly for 10 min, filtered through a pad of Celite, and concentrated *in vacuo* to afford crude **S-9** (as a mixture of olefin isomers based on ^1H NMR of the crude) as a yellow oil. The crude was taken up in THF (11 mL) and added to a stirred orange suspension of HgO (325 mg, 1.5 mmol) and $BF_3{\cdot}Et_2O$ (188 μL, 213 mg, 1.5 mmol) in THF (10 mL); then 1.0 N HCl (4.0 mL) was added, and the reaction was heated in a sealed tube at 100 °C overnight. After cooling down to ambient temperature, saturated aqueous K_2CO_3 (10 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (1→5% EtOAc/hexanes with 1% Et_3N) to afford pyridine **36** (81.0 mg, 82%) as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.49-7.29 (m, 5H), 2.30 (s, 3H), 2.26 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 147.5, 145.4, 141.9, 130.6, 129.5, 129.3, 128.3, 127.8, 17.5, 17.1, 16.0; IR (thin film, NaCl) ν_{max} 2949, 1583, 1463, 1388, 1199, 1128, 1074, 1007, 750, 701 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{14}H_{16}N$ [M + H]$^+$ 198.1, found 198.2.

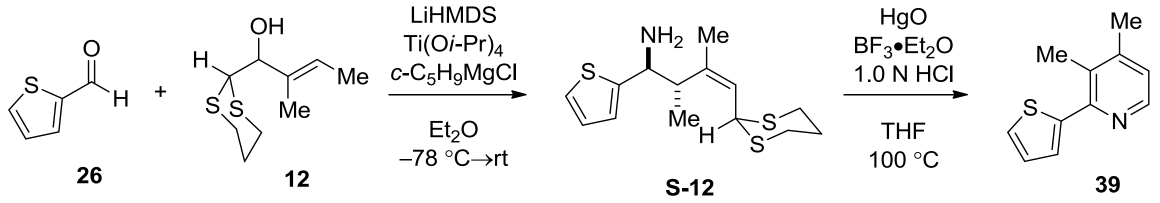


Synthesis of 2,3,5-trimethyl-6-phenylpyridine (37). To a solution of benzaldehyde (101 μL, 106 mg, 1.0 mmol) in Et_2O (6.0 mL) at 0 ºC was added slowly LiHMDS (1.0 mL, 1.0 mmol, 1.0 M in THF). The reaction was stirred for 10 min, then cooled down to –78 ºC. Ti(O*i*-Pr)$_4$ (444 μL, 426 mg, 1.5 mmol) was added followed by dropwise addition of *c*-C_5H_9MgCl (1.5 mL, 3.0 mmol, 2.0 M in Et_2O) via a syringe. The resultant yellow solution was allowed to warm to –30 ºC over 1.5 h as it turned dark brown. A solution of the lithium alkoxide, generated *in situ* via deprotonation of alcohol **17** (109 mg, 0.50 mmol) in THF (1.0 mL) with *n*-BuLi (220 μL, 0.55 mmol, 2.5 M in hexanes) at –78 ^{o}C followed by warming to 0 ^{o}C over 10 min, was cannulated dropwise to the Ti-imine complex. The resultant mixture was allowed to warm to ambient temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (1.2 mL), stirred rapidly for 10 min, filtered through a pad of Celite, and concentrated *in vacuo* to afford crude **S-10** (as a mixture of olefin isomers based on ^{1}H NMR of the crude) as a yellow oil. The crude was taken up in THF (11 mL) and added to a stirred orange suspension of HgO (325 mg, 1.5 mmol) and $BF_3{\cdot}Et_2O$ (188 μL, 213 mg, 1.5 mmol) in THF (10 mL); then 1.0 N HCl (4.0 mL) was added, and the reaction was heated in a sealed tube at 100 ^{o}C overnight. After cooling down to ambient temperature, saturated aqueous K_2CO_3 (10 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (1→5% EtOAc/hexanes with 1% Et_3N) to afford pyridine **37** (44.3 mg, 45%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.47 (m, 2H), 7.45-7.39 (m, 2H), 7.38-7.32 (m, 1H), 7.30 (s, 1H), 2.52 (s, 3H), 2.29 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 154.3, 141.2, 140.0, 130.0, 129.3, 128.4, 128.1, 127.8, 22.5, 19.6, 19.0; IR (thin film, NaCl) ν_{max} 2922, 1603, 1559, 1496, 1461, 1240, 1028, 965, 743, 701 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{14}H_{16}N$ [M + H]$^+$ 198.1, found 198.2.



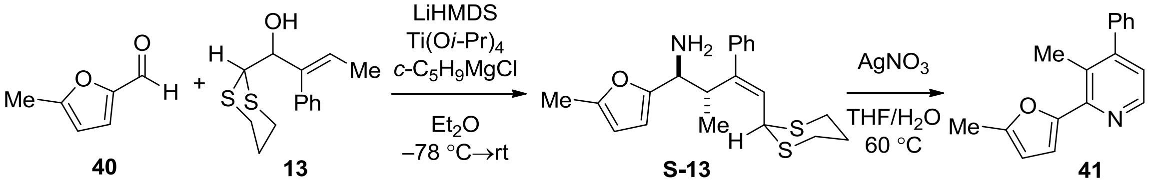
Synthesis of 2,3,4,5-tetramethyl-6-phenylpyridine (38). To a solution of benzaldehyde (101 μL, 106 mg, 1.0 mmol) in Et_2O (6.0 mL) at 0 ºC was added slowly LiHMDS (1.0 mL, 1.0 mmol, 1.0 M in THF). The reaction was stirred for 10 min, then cooled down to –78 ºC. Ti(O*i*-Pr)$_4$ (444 μL, 426 mg, 1.5 mmol) was added followed by dropwise addition of *c*-C_5H_9MgCl (1.5 mL, 3.0 mmol, 2.0 M in Et_2O) via a syringe. The resultant yellow solution was allowed to warm to –30 ºC over 1.5 h as it turned dark brown. A solution of the lithium alkoxide, generated *in situ* via deprotonation of alcohol **18** (116 mg, 0.50 mmol) in THF (1.0 mL) with *n*-BuLi (220 μL, 0.55 mmol, 2.5 M in hexanes) at –78 °C followed by warming to 0 °C over 10 min, was cannulated dropwise to the Ti-imine complex. The resultant mixture was allowed to warm to ambient temperature, and then heated at 80 °C for 24 h. After cooling down to ambient temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ (1.2 mL), stirred rapidly for 10 min, filtered through a pad of Celite, and concentrated *in vacuo* to afford crude **S-11** (as a mixture of olefin isomers based on ^{1}H NMR of the crude) as a yellow oil.

The crude was taken up in THF (11 mL) and added to a stirred orange suspension of HgO (325 mg, 1.5 mmol) and $BF_3 \cdot Et_2O$ (188 μL, 213 mg, 1.5 mmol) in THF (10 mL); then 1.0 N HCl (4.0 mL) was added, and the reaction was heated in a sealed tube at 100 °C overnight. After cooling down to ambient temperature, saturated aqueous K_2CO_3 (10 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (2% EtOAc/hexanes with 1% Et_3N) to afford pyridine **38** (37.0 mg, 35%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.32 (m, 5H), 2.54 (s, 3H), 2.64 (s, 6H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 153.1, 144.8, 141.9, 129.2, 128.4, 128.1, 127.3, 126.8, 23.5, 16.9, 16.1, 15.5; IR (thin film, NaCl) ν_{max} 2930, 1684, 1563, 1448, 1407, 1218, 1075, 1021, 747, 701 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{15}H_{18}N$ [M + H]$^+$ 212.1, found 212.2.



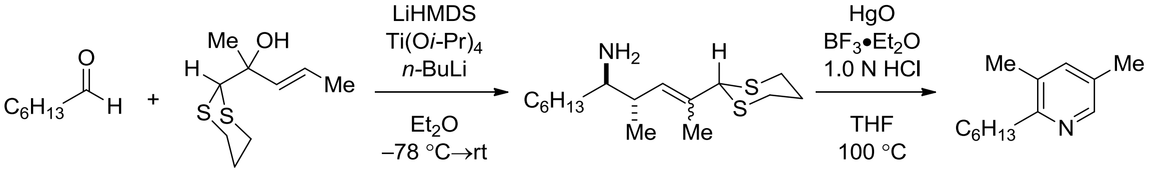
Synthesis of 3,4-dimethyl-2-(thiophen-2-yl)pyridine (39). To a solution of thiophene-2-carbaldehyde (93.5 µL, 112 mg, 1.0 mmol) in Et_2O (6.0 mL) at 0 ºC was added slowly LiHMDS (1.0 mL, 1.0 mmol, 1.0 M in THF). The reaction was stirred for 10 min, then cooled down to –78 ºC. Ti(O*i*-Pr)$_4$ (444 µL, 426 mg, 1.5 mmol) was added followed by dropwise addition of *c*-C_5H_9MgCl (1.5 mL, 3.0 mmol, 2.0 M in Et_2O) via a syringe. The resultant yellow solution was allowed to warm to –30 ºC over 1.5 h as it turned dark brown. A solution of the lithium alkoxide, generated *in situ* via deprotonation of alcohol **12** (102 mg, 0.50 mmol) in THF (1.0 mL) with *n*-BuLi (220 µL, 0.55 mmol, 2.5 M in hexanes) at –78 ^{o}C followed by warming to 0 ^{o}C over 10 min, was cannulated dropwise to the Ti-imine complex. The resultant mixture was allowed to warm to ambient temperature and stirred for 24 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (1.2 mL), stirred rapidly for 10 min, filtered through a pad of Celite, and concentrated *in vacuo* to afford crude **S-12** (*Z:E* ≥ 20:1 based on ^{1}H NMR of the crude) as a yellow oil.

The crude was taken up in THF (11 mL) and added to a stirred orange suspension of HgO (325 mg, 1.5 mmol) and $BF_3 \cdot Et_2O$ (188 µL, 213 mg, 1.5 mmol) in THF (10 mL); then 1.0 N HCl (4.0 mL) was added, and the reaction was heated in a sealed tube at 100 ^{o}C overnight. After cooling down to ambient temperature, saturated aqueous K_2CO_3 (10 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (2→5% EtOAc/hexanes with 1% Et_3N) to afford pyridine **39** (60.2 mg, 64%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 5.0 Hz, 1H), 7.40 (d, *J* = 5.2 Hz, 1H), 7.34 (d, *J* = 3.6 Hz, 1H), 7.10 (dd, *J* = 5.2, 3.6 Hz, 1H), 7.00 (d, *J* = 5.0 Hz, 1H), 2.45 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 147.0, 146.4, 144.8, 129.3, 127.2, 127.2, 126.9, 123.7, 20.4, 16.4; IR (thin film, NaCl) ν_{max} 2923, 1581, 1560, 1439, 1397, 1275, 1090, 974, 826, 705 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{11}H_{12}NS$ [M + H]$^+$ 190.1, found 190.2.



Synthesis of 3-methyl-2-(5-methylfuran-2-yl)-4-phenylpyridine (41). To a solution of 5-methylfuran-2-carbaldehyde (100 µL, 110 mg, 1.0 mmol) in Et_2O (6.0 mL) at 0 ºC was added slowly LiHMDS (1.0 mL, 1.0 mmol, 1.0 M in THF). The reaction was stirred for 10 min, then cooled down to –78 ºC. Ti(O*i*-Pr)$_4$ (444 µL, 426 mg, 1.5 mmol) was added followed by dropwise addition of *c*-C_5H_9MgCl (1.5 mL, 3.0 mmol, 2.0 M in Et_2O) via a syringe. The resultant yellow solution was allowed to warm to –30 ºC over 1.5 h as it turned dark brown. A solution of the lithium alkoxide, generated *in situ* via deprotonation of alcohol **13** (133 mg, 0.50 mmol) in THF (1.0 mL) with *n*-BuLi (220 µL, 0.55 mmol, 2.5 M in hexanes) at –78 °C followed by warming to 0 °C over 10 min, was cannulated dropwise to the Ti-imine complex. The resultant mixture was allowed to warm to ambient temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (1.2 mL), stirred rapidly for 10 min, filtered through a pad of Celite, and concentrated *in vacuo* to afford crude **S-13** (*Z:E* ≥ 20:1 based on ^1H NMR of the crude) as a yellow oil.

The crude was taken up in THF (6.0 mL) and added to a stirred solution of $AgNO_3$ (255 mg, 1.5 mmol) in THF (6.0 mL) and H_2O (3.0 mL). The reaction was heated in a sealed tube at 60 °C overnight. After cooling down to ambient temperature, pyrrolidine (1.2 mL) was added and the reaction was stirred for 30 min. The reaction was then filtered through a pad of Celite. The filtrate was treated with saturated aqueous K_2CO_3 (10 mL) and extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (2→5% EtOAc/hexanes with 1% Et_3N) to afford pyridine **41** (63.0 mg, 51%) as a viscous yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.9 Hz, 1H), 7.48-7.36 (m, 3H), 7.34-7.29 (m, 2H), 7.03 (d, *J* = 4.9 Hz, 1H), 6.80 (d, *J* = 3.3 Hz, 1H), 6.15 (d, *J* = 3.3 Hz, 1H), 2.43 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 151.8, 151.3, 149.2, 146.7, 140.0, 129.0, 128.5, 128.0, 127.4, 122.7, 113.3, 107.9, 17.9, 14.1; IR (thin film, NaCl) ν_{max} 3057, 2925, 1575, 1539, 1463, 1387, 1201, 1006, 763, 703 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{17}H_{16}NO$ $[M + H]^+$ 250.1, found 250.3.

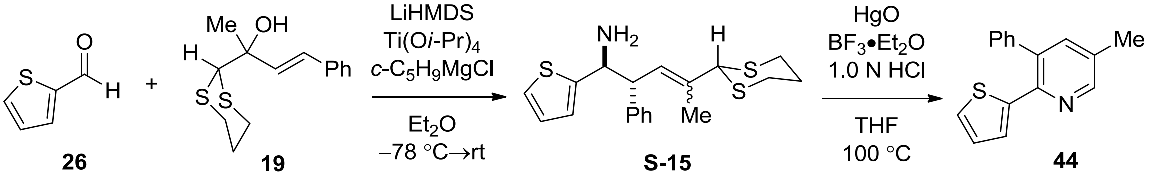


42 **15** **S-14** **43**

Synthesis of 2-hexyl-3,5-dimethylpyridine (43). To a solution of Ti(O*i*-Pr)$_4$ (296 μL, 284 mg, 1.0 mmol) in Et_2O (4.0 mL) at –78 ºC was added dropwise *n*-BuLi (800 μL, 2.0 mmol, 2.5 M in hexanes). The resultant orange solution was allowed to warm to –50 ºC over 20 min. Meanwhile, *N*-TMS imine was prepared by slowly adding LiHMDS (1.0 mL, 1.0 mmol, 1.0 M in THF) to a solution of heptanal (140 μL, 114 mg, 1.0 mmol) in THF (2.0 mL) at –78 ºC followed by stirring for 10 min. The newly prepared imine was then rapidly transferred to the Ti-solution by cannula. The resultant mixture was warmed to 0 ºC over 1 h as it turned from orange color to wine red, and then re-cooled down to –78 ºC. A solution of the lithium alkoxide, generated *in situ* via deprotonation of alcohol **15** (133 mg, 0.50 mmol) in THF (1.0 mL) with *n*-BuLi (220 μL, 0.55 mmol, 2.5 M in hexanes) at –78 ^{o}C followed by warming to 0 ^{o}C over 10 min, was cannulated dropwise to the Ti-imine complex. The resultant mixture was allowed to warm to ambient temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (1.0 mL), stirred rapidly for 10 min, filtered through a pad of Celite, and concentrated *in vacuo* to afford crude **S-14** (as a mixture of olefin isomers based on ^{1}H NMR of the crude) as a yellow oil.

The crude was taken up in THF (11 mL) and added to a stirred orange suspension of HgO (325 mg, 1.5 mmol) and $BF_3 \cdot Et_2O$ (188 μL, 213 mg, 1.5 mmol) in THF (10 mL); then 1.0 N HCl (4.0 mL) was added, and the reaction was heated in a sealed tube at 100 ^{o}C overnight. After cooling down to ambient temperature, saturated aqueous K_2CO_3 (10 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*.

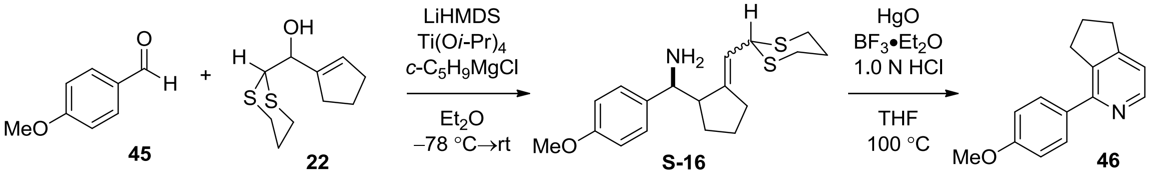
The crude product was purified by flash column chromatography on silica gel (2→5% EtOAc/hexanes with 1% Et_3N) to afford pyridine **43** (56.0 mg, 58%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.18 (s, 1H), 2.71 (t, J = 7.0 Hz, 2H), 2.25 (s, 3H), 2.23 (s, 3H), 1.69-1.59 (m, 2H), 1.42-1.22 (m, 6H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 146.9, 138.3, 130.1, 130.0, 35.2, 31.8, 29.5, 29.0, 22.6, 18.6, 17.8, 14.1; IR (thin film, NaCl) ν_{max} 2956, 2926, 2857, 1568, 1470,1403, 1261, 1135, 882, 750 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{13}H_{22}N$ $[M + H]^+$ 192.2, found 192.3.



Synthesis of 5-methyl-3-phenyl-2-(thiophen-2-yl)pyridine (44). To a solution of thiophene-2-carbaldehyde (93.5 μL, 112 mg, 1.0 mmol) in Et_2O (6.0 mL) at 0 ºC was added slowly LiHMDS (1.0 mL, 1.0 mmol, 1.0 M in THF). The reaction was stirred for 10 min, then cooled down to –78 ºC. Ti(O*i*-Pr)$_4$ (444 μL, 426 mg, 1.5 mmol) was added followed by dropwise addition of *c*-C_5H_9MgCl (1.5 mL, 3.0 mmol, 2.0 M in Et_2O) via a syringe. The resultant yellow solution was allowed to warm to –30 ºC over 1.5 h as it turned dark brown. A solution of the lithium alkoxide, generated *in situ* via deprotonation of alcohol **19** (133 mg, 0.50 mmol) in THF (1.0 mL) with *n*-BuLi (220 μL, 0.55 mmol, 2.5 M in hexanes) at –78 ^oC followed by warming to 0 ^oC over 10 min, was cannulated dropwise to the Ti-imine complex. The resultant mixture was allowed to warm to ambient temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (1.2 mL), stirred rapidly for 10 min, filtered through a pad of Celite, and concentrated *in vacuo* to afford crude **S-15** (as a mixture of olefin isomers based on ^1H NMR of the crude) as a yellow oil.

The crude was taken up in THF (11 mL) and added to a stirred orange suspension of HgO (325 mg, 1.5 mmol) and $BF_3{\cdot}Et_2O$ (188 μL, 213 mg, 1.5 mmol) in THF (10 mL); then 1.0 N HCl (4.0 mL) was added, and the reaction was heated in a sealed tube at 100 ^oC overnight. After cooling down to ambient temperature, saturated aqueous K_2CO_3 (10 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*.

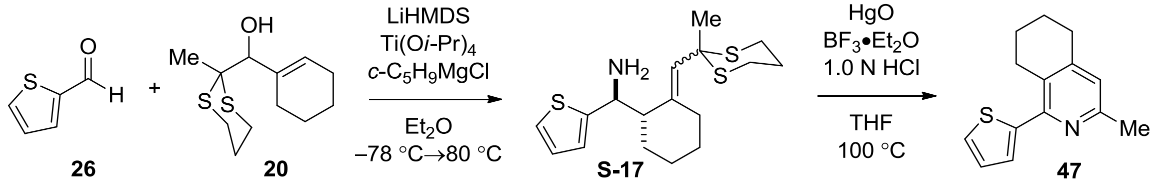
The crude product was purified by flash column chromatography on silica gel (2→5% EtOAc/hexanes with 1% Et_3N) to afford pyridine **44** (64.9 mg, 52%) as an orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.36-7.29 (m, 4H), 7.27-7.22 (m, 2H), 7.16 (d, *J* = 5.1 Hz, 1H), 6.70 (dd, *J* = 5.1, 3.8 Hz, 1H), 6.41 (d, *J* = 3.8 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 147.7, 144.4, 140.1, 139.3, 134.2, 131.0, 129.2, 128.7, 127.8, 127.4, 127.3, 126.8, 18.0; IR (thin film, NaCl) ν_{max} 3026, 2921, 2851, 2252, 1553, 1438, 1268, 1053, 905, 779 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{16}H_{14}NS$ $[M + H]^+$ 252.1, found 252.2.



Synthesis of 1-(4-methoxyphenyl)-6,7-dihydro-5*H*-cyclopenta[c]pyridine (46). To a solution of 4-methoxybenzaldehyde (121 μL, 136 mg, 1.0 mmol) in Et_2O (6.0 mL) at 0 ºC was added slowly LiHMDS (1.0 mL, 1.0 mmol, 1.0 M in THF). The reaction was stirred for 10 min, then cooled down to –78 ºC. Ti(O*i*-Pr)$_4$ (444 μL, 426 mg, 1.5 mmol) was added followed by dropwise addition of *c*-C_5H_9MgCl (1.5 mL, 3.0 mmol, 2.0 M in Et_2O) via a syringe. The resultant yellow solution was allowed to warm to –30 ºC over 1.5 h as it turned dark brown. A solution of the lithium alkoxide, generated *in situ* via deprotonation of alcohol **22** (108 mg, 0.50 mmol) in THF (1.0 mL) with *n*-BuLi (220 μL, 0.55 mmol, 2.5 M in hexanes) at –78 ^{o}C followed by warming to 0 ^{o}C over 10 min, was cannulated dropwise to the Ti-imine complex. The resultant mixture was allowed to warm to ambient temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (1.2 mL), stirred rapidly for 10 min, filtered through a pad of Celite, and concentrated *in vacuo* to afford crude **S-16** (as a mixture of olefin isomers based on ^{1}H NMR of the crude) as a yellow oil.

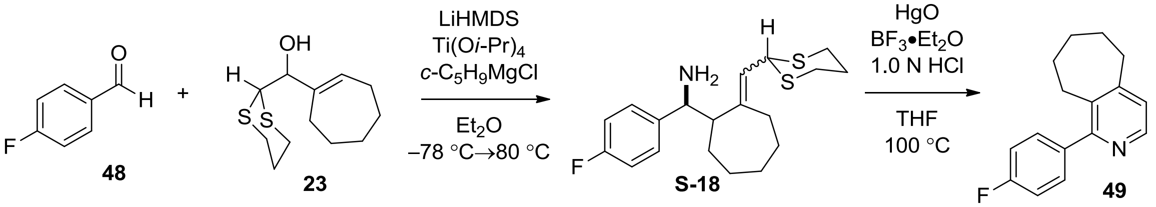
The crude was taken up in THF (11 mL) and added to a stirred orange suspension of HgO (325 mg, 1.5 mmol) and $BF_3 \cdot Et_2O$ (188 μL, 213 mg, 1.5 mmol) in THF (10 mL); then 1.0 N HCl (4.0 mL) was added, and the reaction was heated in a sealed tube at 100 ^{o}C overnight. After cooling down to ambient temperature, saturated aqueous K_2CO_3 (10 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*.

The crude product was purified by flash column chromatography on silica gel (10% EtOAc/hexanes with 1% Et_3N) to afford pyridine **46** (71.2 mg, 63%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 4.9 Hz, 1H), 7.72 (d, *J* = 8.9 Hz, 1H), 7.10 (d, *J* = 4.9 Hz, 1H), 6.98 (d, *J* = 8.9 Hz, 1H), 3.85 (s, 3H), 3.09 (t, *J* = 7.3 Hz, 2H), 2.95 (t, *J* = 7.4 Hz, 2H), 2.12-2.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 154.8, 153.9, 147.3, 136.9, 132.8, 129.7, 118.3, 113.6, 55.3, 33.0, 32.8, 25.3; IR (thin film, NaCl) ν_{max} 2951, 2836, 1608, 1568, 1510, 1421, 1171, 1029, 833, 762 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{15}H_{16}NO$ $[M + H]^+$ 226.1, found 226.2.



Synthesis of 3-methyl-1-(thiophen-2-yl)-5,6,7,8-tetrahydroisoquinoline (47). To a solution of thiophene-2-carbaldehyde (93.5 μL, 112 mg, 1.0 mmol) in Et_2O (6.0 mL) at 0 ºC in a sealed tube was added slowly LiHMDS (1.0 mL, 1.0 mmol, 1.0 M in THF). The reaction was stirred for 10 min, then cooled down to –78 ºC. Ti(O*i*-Pr)$_4$ (444 μL, 426 mg, 1.5 mmol) was added followed by dropwise addition of *c*-C_5H_9MgCl (1.5 mL, 3.0 mmol, 2.0 M in Et_2O) via a syringe. The resultant yellow solution was allowed to warm to –30 ºC over 1.5 h as it turned dark brown. A solution of the lithium alkoxide, generated *in situ* via deprotonation of alcohol **20** (122 mg, 0.50 mmol) in THF (1.0 mL) with *n*-BuLi (220 μL, 0.55 mmol, 2.5 M in hexanes) at –78 °C followed by warming to 0 °C over 10 min, was cannulated dropwise to the Ti-imine complex. The resultant mixture was allowed to warm to ambient temperature, and then heated at 80 ºC for 24 h. After cooling down to ambient temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ (1.2 mL), stirred rapidly for 10 min, filtered through a pad of Celite, and concentrated *in vacuo* to afford crude **S-17** (as a mixture of olefin isomers based on ^{1}H NMR of the crude) as a yellow oil.

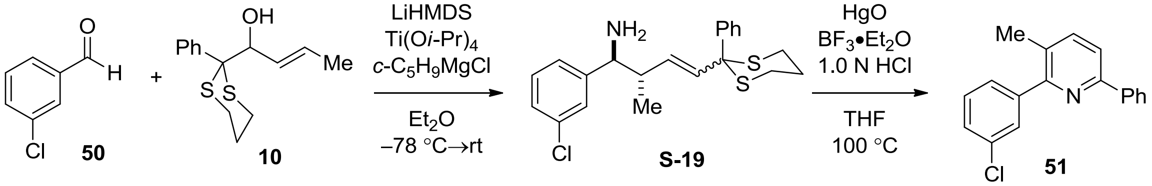
The crude was taken up in THF (11 mL) and added to a stirred orange suspension of HgO (325 mg, 1.5 mmol) and $BF_3{\cdot}Et_2O$ (188 μL, 213 mg, 1.5 mmol) in THF (10 mL); then 1.0 N HCl (4.0 mL) was added, and the reaction was heated in a sealed tube at 100 °C overnight. After cooling down to ambient temperature, saturated aqueous K_2CO_3 (10 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (2→5% EtOAc/hexanes with 1% Et_3N) to afford pyridine **47** (75.0 mg, 65%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.35 (m, 2H), 7.08 (dd, J = 4.9, 3.9 Hz, 1H), 6.79 (s, 1H), 2.93-2.83 (m, 2H), 2.83-2.70 (m, 2H), 2.49 (s, 3H), 1.87-1.72 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 150.9, 147.3, 144.9, 127.2, 127.0, 126.9, 126.8, 122.4, 30.4, 29.6, 27.7, 23.9, 23.4, 22.1; IR (thin film, NaCl) ν_{max} 2931, 1662, 1591, 1557, 1437, 1314, 1232, 858, 795, 701 cm^{-1}; LRMS (EI, H) m/z calc'd for $C_{14}H_{16}NS$ $[M + H]^+$ 230.1, found 230.2.



Synthesis of 1-(4-fluorophenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[c]pyridine (49). To a solution of 4-fluorobenzaldehyde (106 μL, 124 mg, 1.0 mmol) in Et_2O (6.0 mL) at 0 ºC in a sealed tube was added slowly LiHMDS (1.0 mL, 1.0 mmol, 1.0 M in THF). The reaction was stirred for 10 min, then cooled down to –78 ºC. Ti(O*i*-Pr)$_4$ (444 μL, 426 mg, 1.5 mmol) was added followed by dropwise addition of *c*-C_5H_9MgCl (1.5 mL, 3.0 mmol, 2.0 M in Et_2O) via a syringe. The resultant yellow solution was allowed to warm to –30 ºC over 1.5 h as it turned dark brown. A solution of the lithium alkoxide, generated *in situ* via deprotonation of alcohol **23** (122 mg, 0.50 mmol) in THF (1.0 mL) with *n*-BuLi (220 μL, 0.55 mmol, 2.5 M in hexanes) at –78 °C followed by warming to 0 °C over 10 min, was cannulated dropwise to the Ti-imine complex. The resultant mixture was allowed to warm to ambient temperature, and then heated at 80 ºC for 24 h. After cooling down to ambient temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ (1.2 mL), stirred rapidly for 10 min, filtered through a pad of Celite, and concentrated *in vacuo* to afford crude **S-18** (as a mixture of olefin isomers based on ^1H NMR of the crude) as a yellow oil.

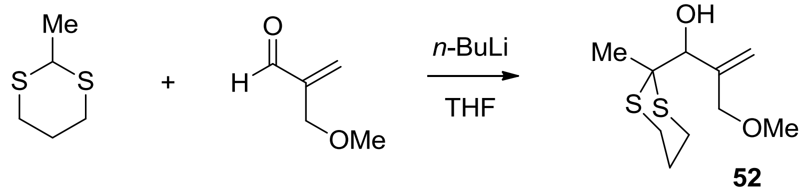
The crude was taken up in THF (11 mL) and added to a stirred orange suspension of HgO (325 mg, 1.5 mmol) and $BF_3 \cdot Et_2O$ (188 μL, 213 mg, 1.5 mmol) in THF (10 mL); then 1.0

N HCl (4.0 mL) was added, and the reaction was heated in a sealed tube at 100 °C overnight. After cooling down to ambient temperature, saturated aqueous K_2CO_3 (10 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (2→5% EtOAc/hexanes with 1% Et_3N) to afford pyridine **49** (88.6 mg, 73%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 4.8 Hz, 1H), 7.44-7.37 (m, 2H), 7.14-7.06 (m, 2H), 7.00 (d, J = 4.8 Hz, 1H), 2.87-2.74 (m, 4H), 1.90-1.81 (m, 2H), 1.74-1.57 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4 (d, J_F = 246 Hz), 157.1, 153.5, 146.7, 137.4 (d, J_F = 3.4 Hz), 136.4, 130.8 (d, J_F = 8.1 Hz), 123.2, 114.9 (d, J_F = 21.5 Hz), 36.2, 32.3, 30.6, 27.6, 27.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ –114.8; IR (thin film, NaCl) ν_{max} 3046, 2922, 2851, 1604, 1414, 1220, 1156, 839, 823, 806 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{16}H_{17}FN$ $[M + H]^+$ 242.1, found 242.2.



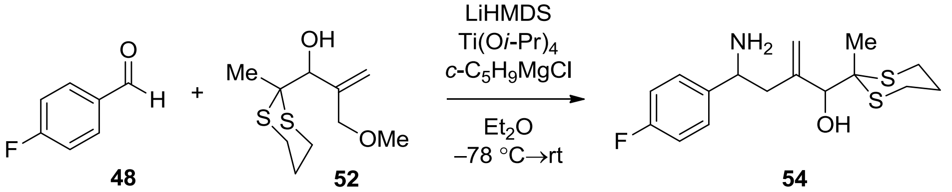
Synthesis of 2-(3-chlorophenyl)-3-methyl-6-phenylpyridine (51). To a solution of 3-chlorobenzaldehyde (114 μL, 141 mg, 1.0 mmol) in Et_2O (6.0 mL) at 0 ºC was added slowly LiHMDS (1.0 mL, 1.0 mmol, 1.0 M in THF). The reaction was stirred for 10 min, then cooled down to –78 ºC. Ti(O*i*-Pr)$_4$ (444 μL, 426 mg, 1.5 mmol) was added followed by dropwise addition of *c*-C_5H_9MgCl (1.5 mL, 3.0 mmol, 2.0 M in Et_2O) via a syringe. The resultant yellow solution was allowed to warm to –30 ºC over 1.5 h as it turned dark brown. A solution of the lithium alkoxide, generated *in situ* via deprotonation of alcohol **10** (133 mg, 0.50 mmol) in THF (1.0 mL) with *n*-BuLi (220 μL, 0.55 mmol, 2.5 M in hexanes) at –78 °C followed by warming to 0 °C over 10 min, was cannulated dropwise to the Ti-imine complex. The resultant mixture was allowed to warm to ambient temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (1.2 mL), stirred rapidly for 10 min, filtered through a pad of Celite, and concentrated *in vacuo* to afford crude **S-19** (as a mixture of olefin isomers based on ^{1}H NMR of the crude) as a yellow oil.

The crude was taken up in THF (11 mL) and added to a stirred orange suspension of HgO (325 mg, 1.5 mmol) and $BF_3 \cdot Et_2O$ (188 µL, 213 mg, 1.5 mmol) in THF (10 mL); then 1.0 N HCl (4.0 mL) was added, and the reaction was heated in a sealed tube at 100 °C overnight. After cooling down to ambient temperature, saturated aqueous K_2CO_3 (10 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (1% EtOAc/hexanes with 1% Et_3N) to afford pyridine **51** (76.7 mg, 55%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.7 Hz, 2H), 7.69-7.64 (m, 3H), 7.56-7.37 (m, 6h), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 154.7, 142.7, 139.6, 139.2, 134.1, 129.5, 129.3, 129.3, 128.8, 128.7, 128.0, 127.5, 126.8, 119.1, 19.8; IR (thin film, NaCl) ν_{max} 3064, 2956, 2926, 2248, 1701, 1585, 1563, 1455, 1077, 905 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{18}H_{15}ClN$ $[M + H]^+$ 280.1, found 280.4.

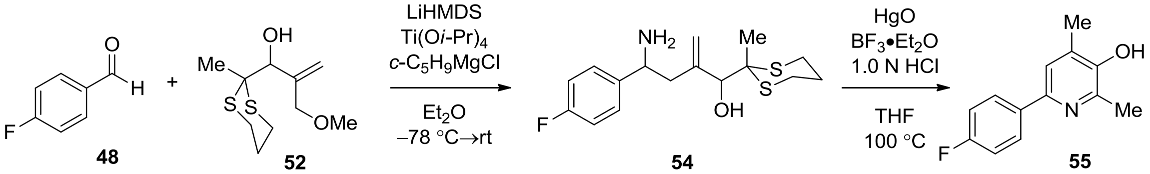


52

Synthesis of 2-(methoxymethyl)-1-(2-methyl-1,3-dithian-2-yl)prop-2-en-1-ol (52). To a solution of 2-methyl-1,3-dithiane (719 µL, 805 mg, 6.0 mmol) in THF (50 mL) at –20 ºC was added dropwise *n*-BuLi (2.4 mL, 6.0 mmol, 2.5 M in hexanes). The resultant clear solution was stirred at the same temperature for 1 h. After cooling down to –78 ºC, 2-(methoxymethyl)acrylaldehyde (500 mg, 5.0 mmol) was added dropwise via a syringe. The reaction was stirred for 30 min, then quenched with saturated aqueous NH_4Cl (5 mL) and warmed to ambient temperature. The reaction mixture was further diluted with H_2O (10 mL) and extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by flash column chromatography on silica gel (10→30% EtOAc/hexanes) to afford allylic alcohol **52** (960 mg, 82%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 5.38 (s, 1H), 5.34 (s, 1H), 4.66 (s, 1H), 4.29 (d, *J* = 12.4 Hz, 1H), 4.08 (d, *J* = 12.4 Hz, 1H), 3.33 (s, 3H), 3.18-3.00 (m, 3H), 2.69-2.60 (m, 2H), 2.13-2.03 (m, 1H), 1.92-1.80 (m, 1H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 117.6, 76.1, 71.6, 57.8, 52.8, 26.6, 26.1, 24.2, 22.5; IR (thin film, NaCl) ν_{max} 3452 (br), 2924, 2820, 1645, 1448, 1422, 1276, 1189, 908, 754 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{10}H_{18}O_2S_2Na$ [M + Na] 257.1, found 257.2.



Synthesis of 4-amino-4-(4-fluorophenyl)-1-(2-methyl-1,3-dithian-2-yl)-2-methylenebutan-1-ol (54). To a solution of 4-fluorobenzaldehyde (106 µL, 124 mg, 1.0 mmol) in Et_2O (6.0 mL) at 0 ºC was added slowly LiHMDS (1.0 mL, 1.0 mmol, 1.0 M in THF). The reaction was stirred for 10 min, then cooled down to –78 ºC. Ti(O*i*-Pr)$_4$ (444 µL, 426 mg, 1.5 mmol) was added followed by dropwise addition of *c*-C_5H_9MgCl (1.5 mL, 3.0 mmol, 2.0 M in Et_2O) via a syringe. The resultant yellow solution was allowed to warm to –30 ºC over 1.5 h as it turned dark brown. A solution of the lithium alkoxide, generated *in situ* via deprotonation of alcohol **52** (117 mg, 0.50 mmol) in THF (1.0 mL) with *n*-BuLi (220 µL, 0.55 mmol, 2.5 M in hexanes) at –78 ^{o}C followed by warming to 0 ^{o}C over 10 min, was cannulated dropwise to the Ti-imine complex. The resultant mixture was allowed to warm to ambient temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (1.2 mL), stirred rapidly for 10 min, filtered through a pad of Celite, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (2→5% MeOH/DCM with 1% aqueous NH_4OH) to afford aminoalcohol **54** (as a 1.2:1.0 inseparable mixture of diastereomers based on ^{1}H NMR, 131 mg, 80%) as a pale yellow oil. *Spectroscopic data of the major isomer*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.28 (m, 2H), 7.09-6.94 (m, 2H), 5.21 (s, 1H), 4.89 (s, 1H), 4.41 (s, 1H), 4.36 (dd, *J* = 7.5, 4.7 Hz, 1H), 3.10-2.92 (m, 4H), 2.88-2.71 (m, 2H), 2.38 (dd, *J* = 13.5, 7.5 Hz, 2H), 2.10-1.89 (m, 3H), 1.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8 (d, J_F = 246 Hz), 143.1, 140.8 (d, J_F = 3.1 Hz), 127.9 (d, J_F = 7.9 Hz), 119.6, 115.1 (d, J_F = 21.2 Hz), 78.7, 54.1, 53.7, 44.5, 26.9, 26.3, 24.6, 24.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ –115.4. *Spectroscopic data of the minor isomer*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.28 (m, 2H), 7.09-6.94 (m, 2H), 5.30 (s, 1H), 5.21 (s, 1H), 4.41 (s, 1H), 3.94 (dd, *J* = 10.5, 3.6 Hz, 1H), 3.10-2.92 (m, 2H), 2.88-2.71 (m, 4H), 2.54 (dd, *J* = 13.5, 3.6 Hz, 2H), 2.10-1.89 (m, 3H), 1.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9 (d, J_F = 246 Hz), 145.7, 142.0 (d, J_F = 3.1 Hz), 127.4 (d, J_F = 7.9 Hz), 118.9, 115.4 (d, J_F = 21.2 Hz), 78.9, 56.7, 53.6, 43.9, 27.0, 26.4, 24.8, 24.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ –115.9. *Spectroscopic data of the mixture*: IR (thin film, NaCl) ν_{max} 3070, 2917, 1602, 1507, 1421, 1218, 908, 868, 751, 677 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{16}H_{23}FNOS_2$ [M + H]$^+$ 328.1, found 328.3.



Synthesis of 6-(4-fluorophenyl)-2,4-dimethylpyridin-3-ol (55). To a solution of 4-fluorobenzaldehyde (106 µL, 124 mg, 1.0 mmol) in Et_2O (6.0 mL) at 0 ºC was added slowly LiHMDS (1.0 mL, 1.0 mmol, 1.0 M in THF). The reaction was stirred for 10 min, then cooled down to –78 ºC. Ti(O*i*-Pr)$_4$ (444 µL, 426 mg, 1.5 mmol) was added followed by dropwise addition of *c*-C_5H_9MgCl (1.5 mL, 3.0 mmol, 2.0 M in Et_2O) via a syringe. The resultant yellow solution was allowed to warm to –30 ºC over 1.5 h as it turned dark brown. A solution of the lithium alkoxide, generated *in situ* via deprotonation of alcohol **52** (117 mg, 0.50 mmol) in THF (1.0 mL) with *n*-BuLi (220 µL, 0.55 mmol, 2.5 M in hexanes) at –78 °C followed by warming to 0 °C over 10 min, was cannulated dropwise to the Ti-imine complex. The resultant mixture was allowed to warm to ambient temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (1.2 mL), stirred rapidly for 10 min, filtered through a pad of Celite, and concentrated *in vacuo* to afford crude **54** (as a mixture of diastereomers based on ^{1}H NMR of the crude) as a yellow oil.

The crude was taken up in THF (11 mL) and added to a stirred orange suspension of HgO (325 mg, 1.5 mmol) and $BF_3 \cdot Et_2O$ (188 µL, 213 mg, 1.5 mmol) in THF (10 mL); then 1.0 N HCl (4.0 mL) was added, and the reaction was heated in a sealed tube at 100 °C overnight. After cooling down to ambient temperature, saturated aqueous K_2CO_3 (10 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (10→40% EtOAc/hexanes with 1% Et_3N) to afford pyridine **55** (55.0 mg, 51%) as a yellow solid. ^{1}H

NMR (400 MHz, $CDCl_3$) δ 7.83-7.76 (m, 2H), 7.27 (d, J = 14.4 Hz, 1H), 7.08 (appd t, J = 8.7 Hz, 2H), 2.54 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9 (d, J_F = 247 Hz), 148.3, 148.1, 144.6, 135.8 (d, J_F = 3.0 Hz), 132.5, 128.1 (d, J_F = 8.1 Hz), 120.8, 115.4 (d, J_F = 21.5 Hz), 19.2, 15.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ –115.1; IR (thin film, NaCl) ν_{max} 3675, 3053, 2987, 1605, 1512, 1468, 1421, 1220, 1066, 837 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{13}H_{12}FNO$ $[M + H]^+$ 218.1, found 218.2.

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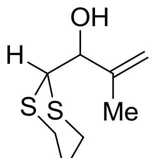

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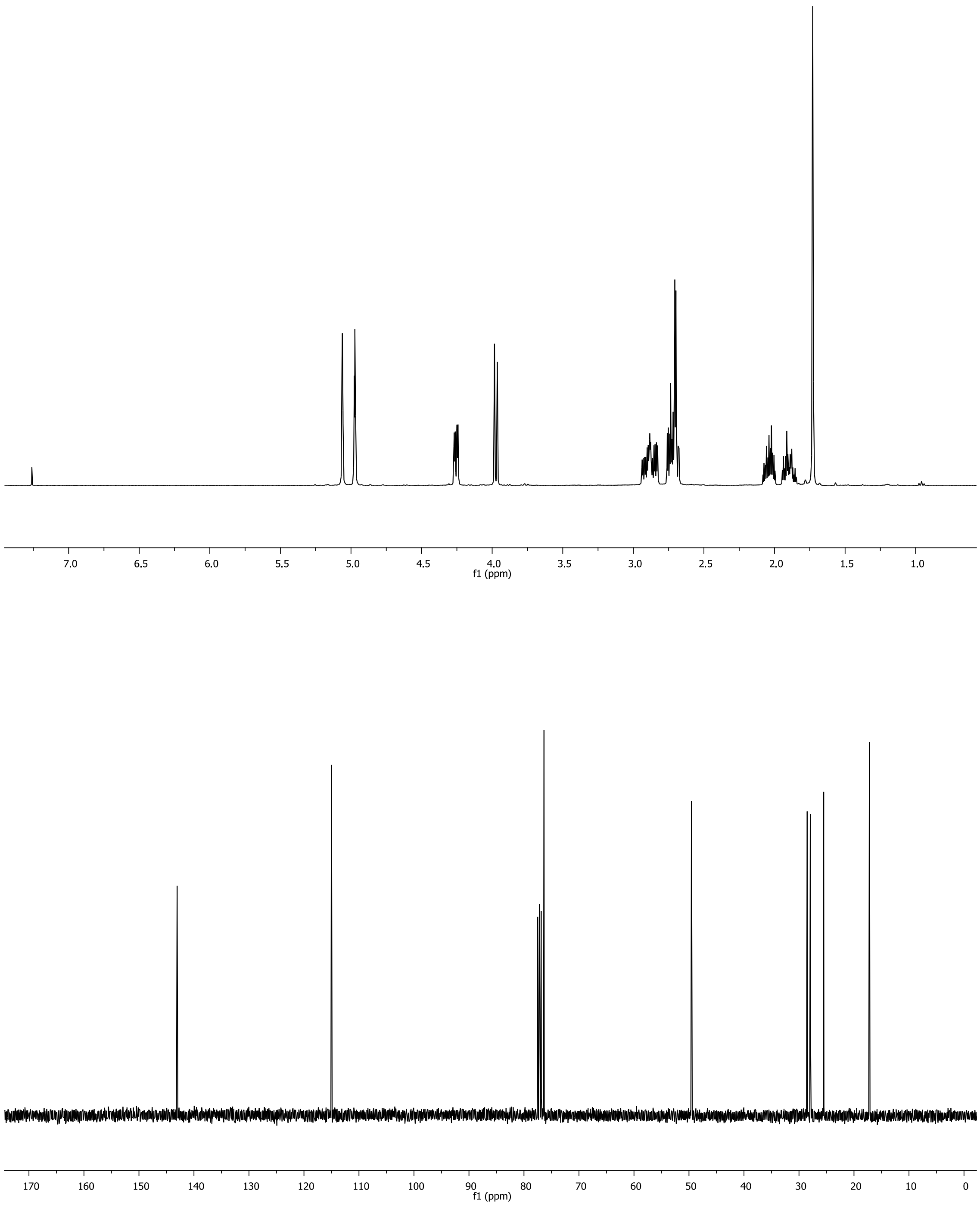
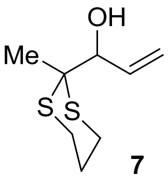


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **6**



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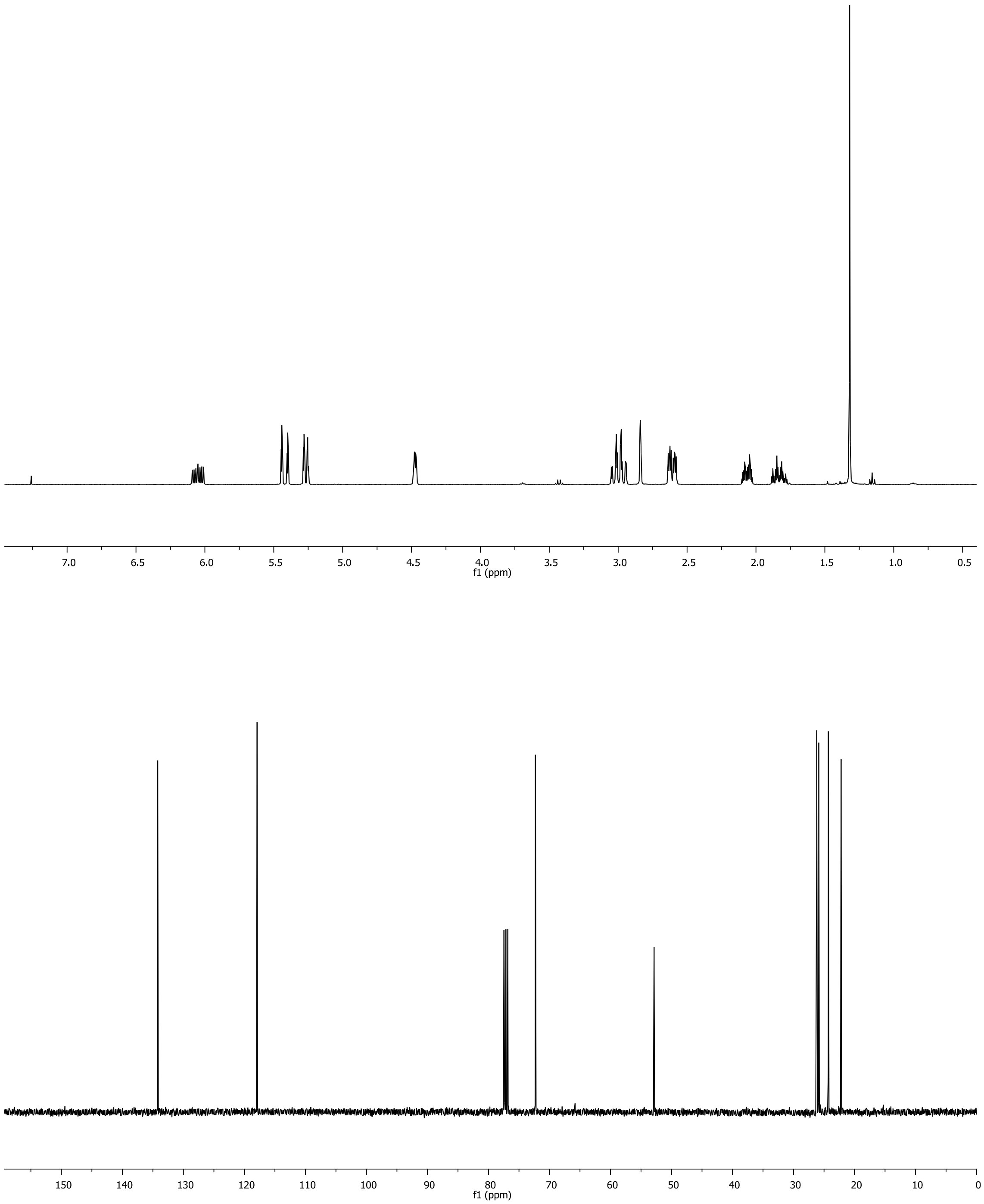
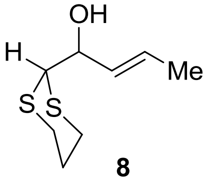


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **7**



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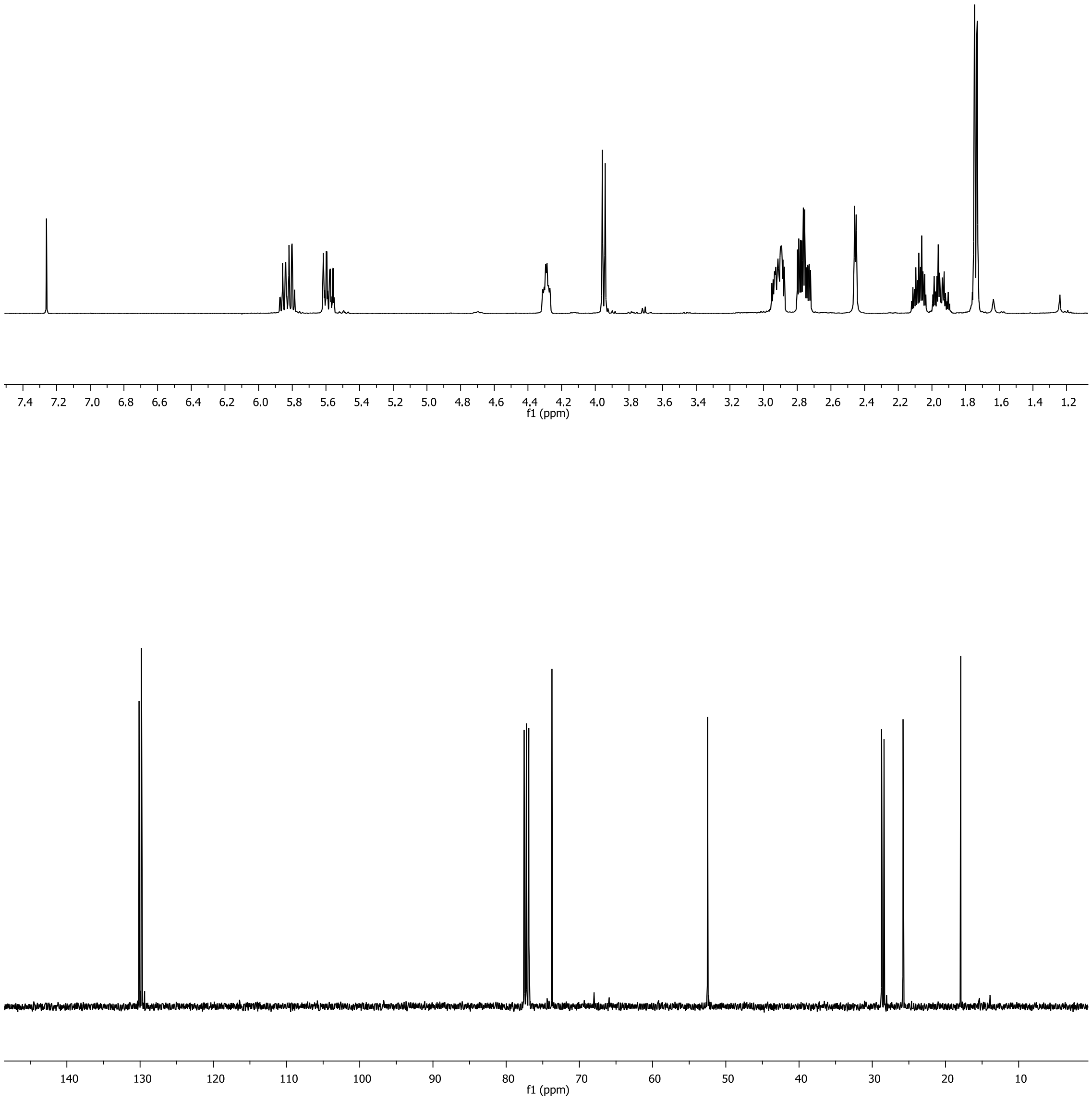
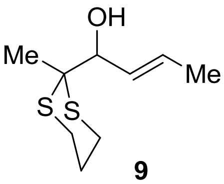
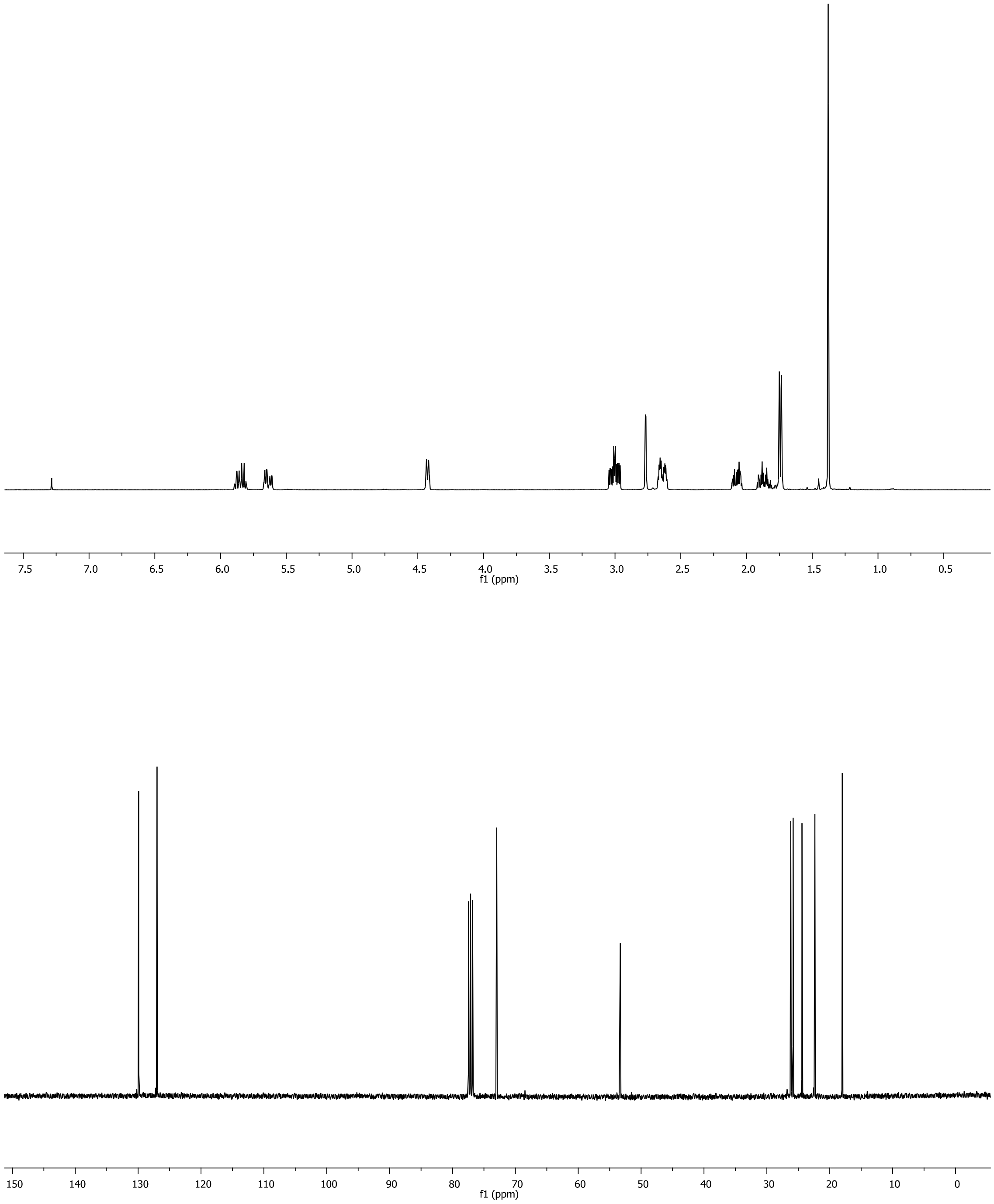


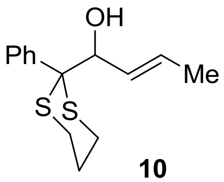
^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **8**



9



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



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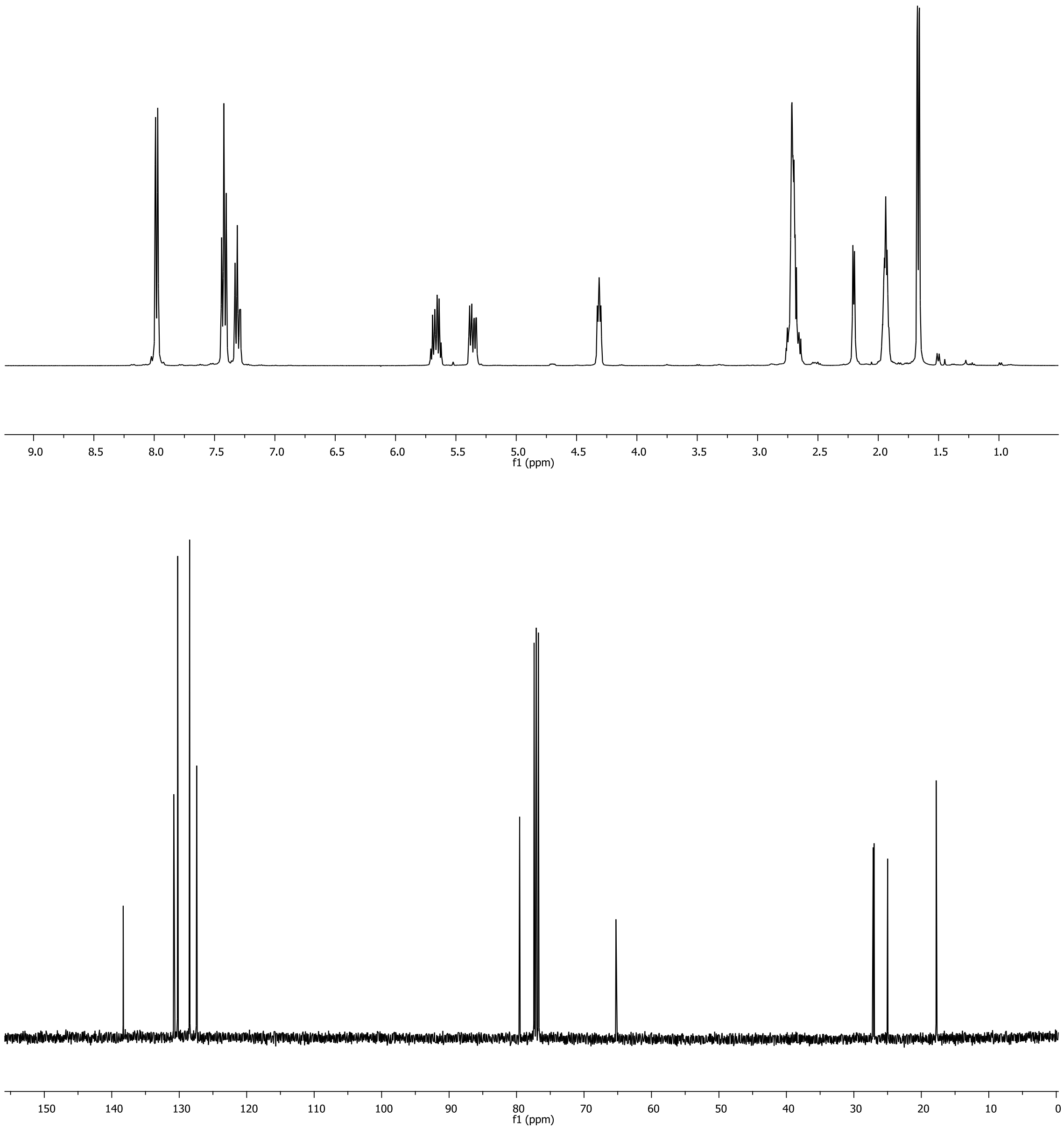
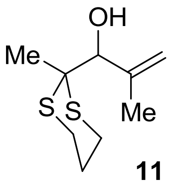


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **10**



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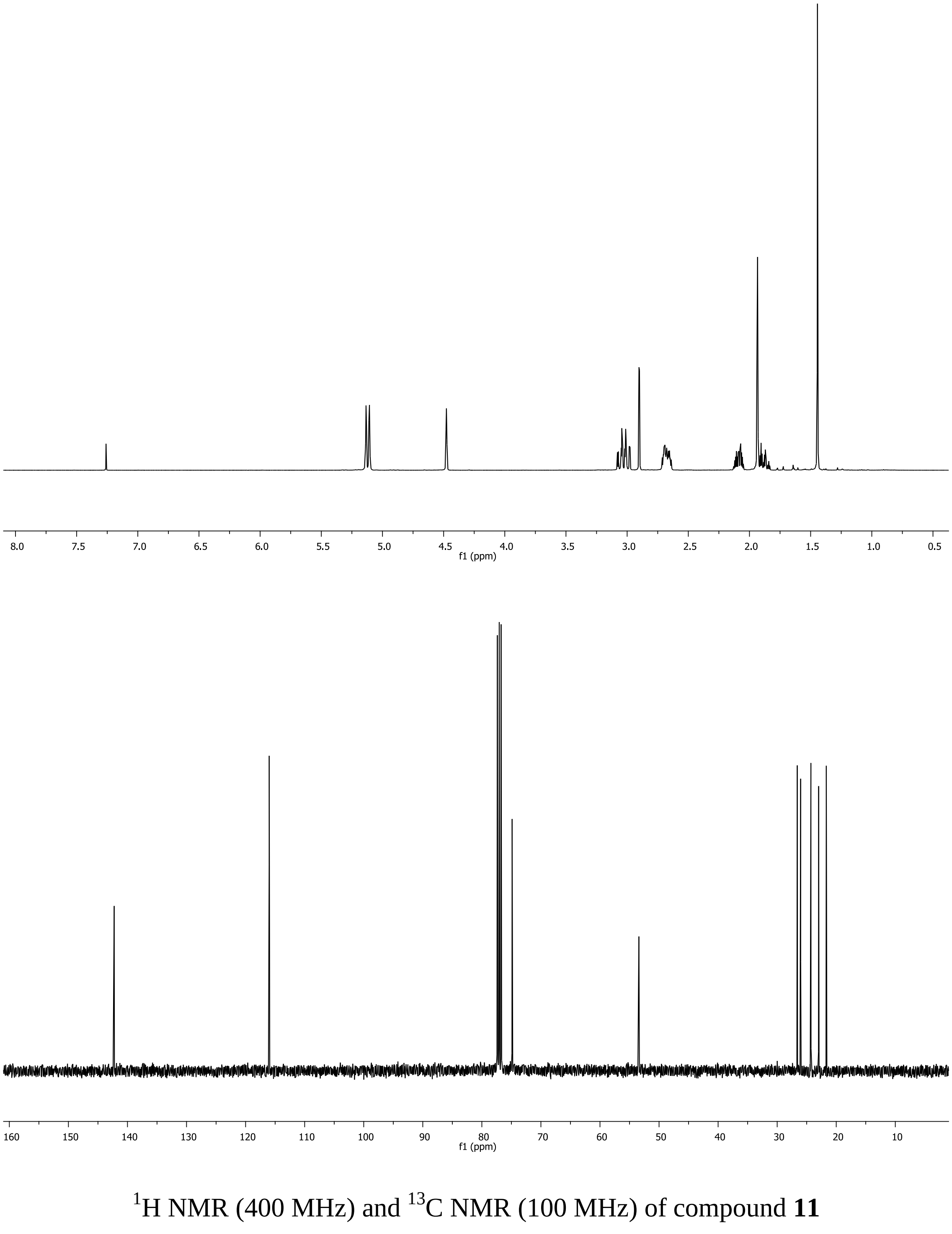
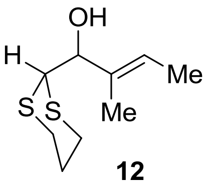


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **11**



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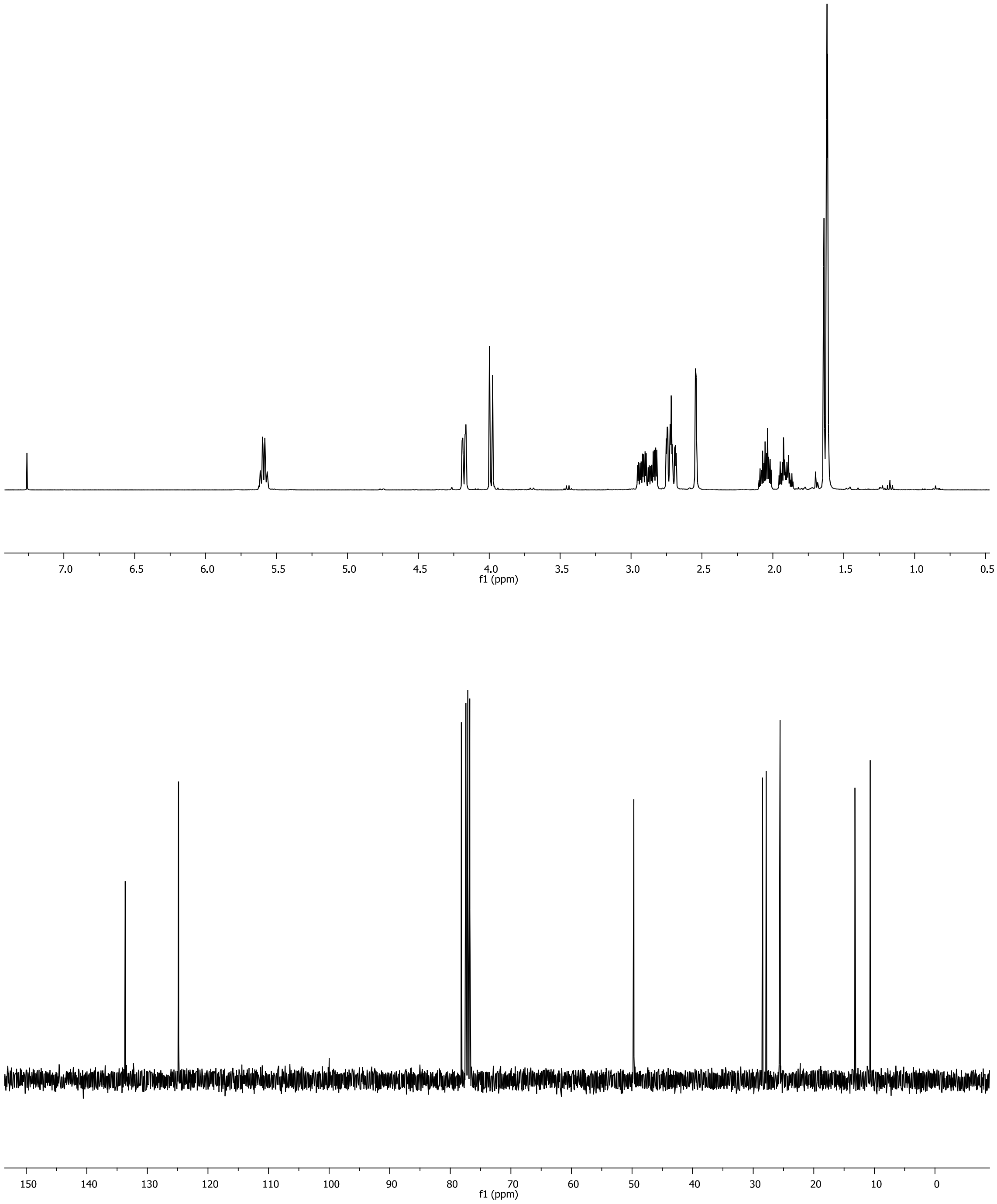
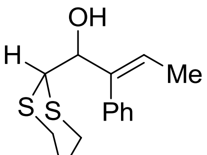


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **12**



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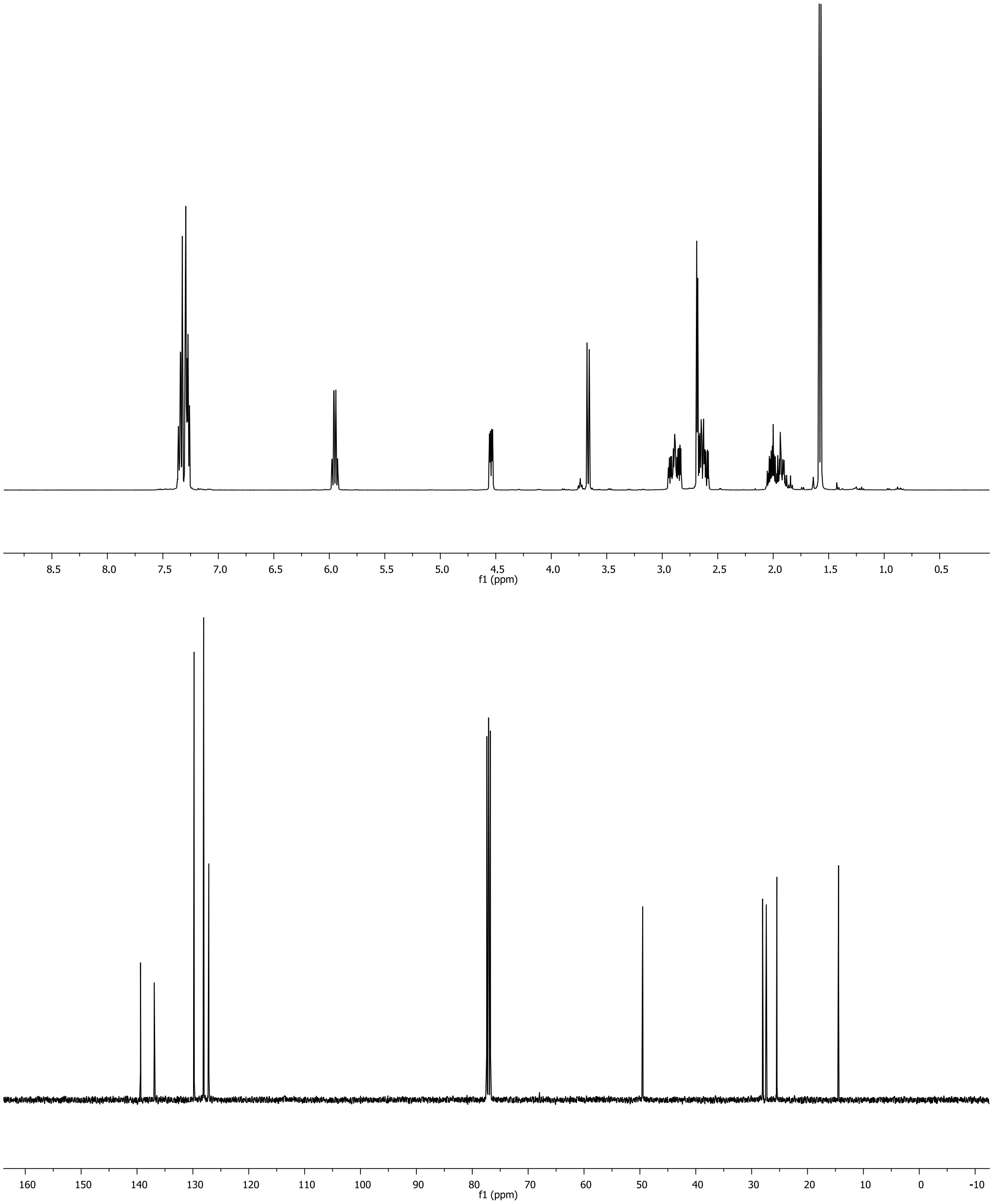
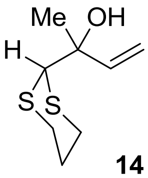


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **13**



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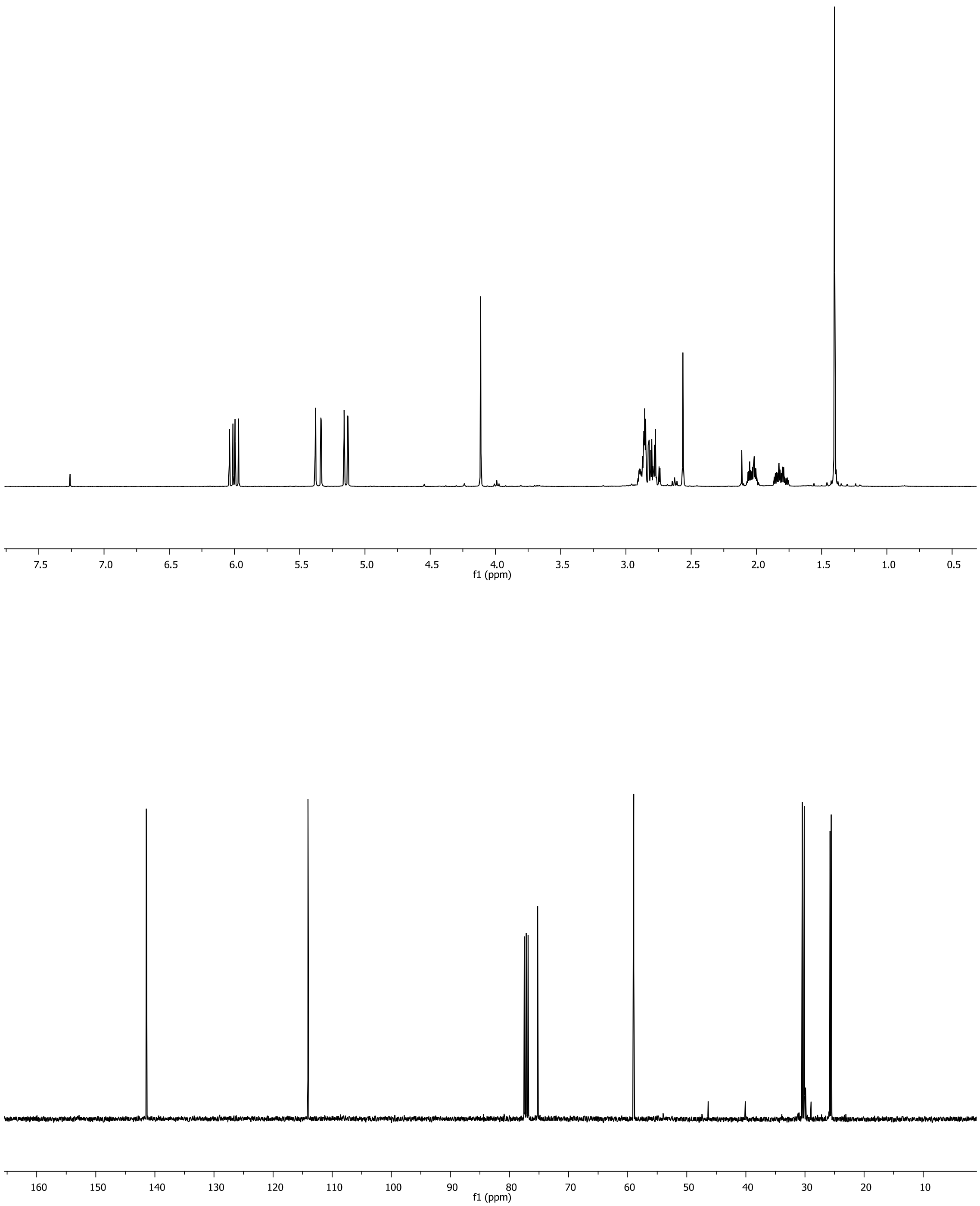
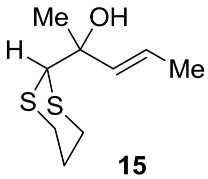


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **14**



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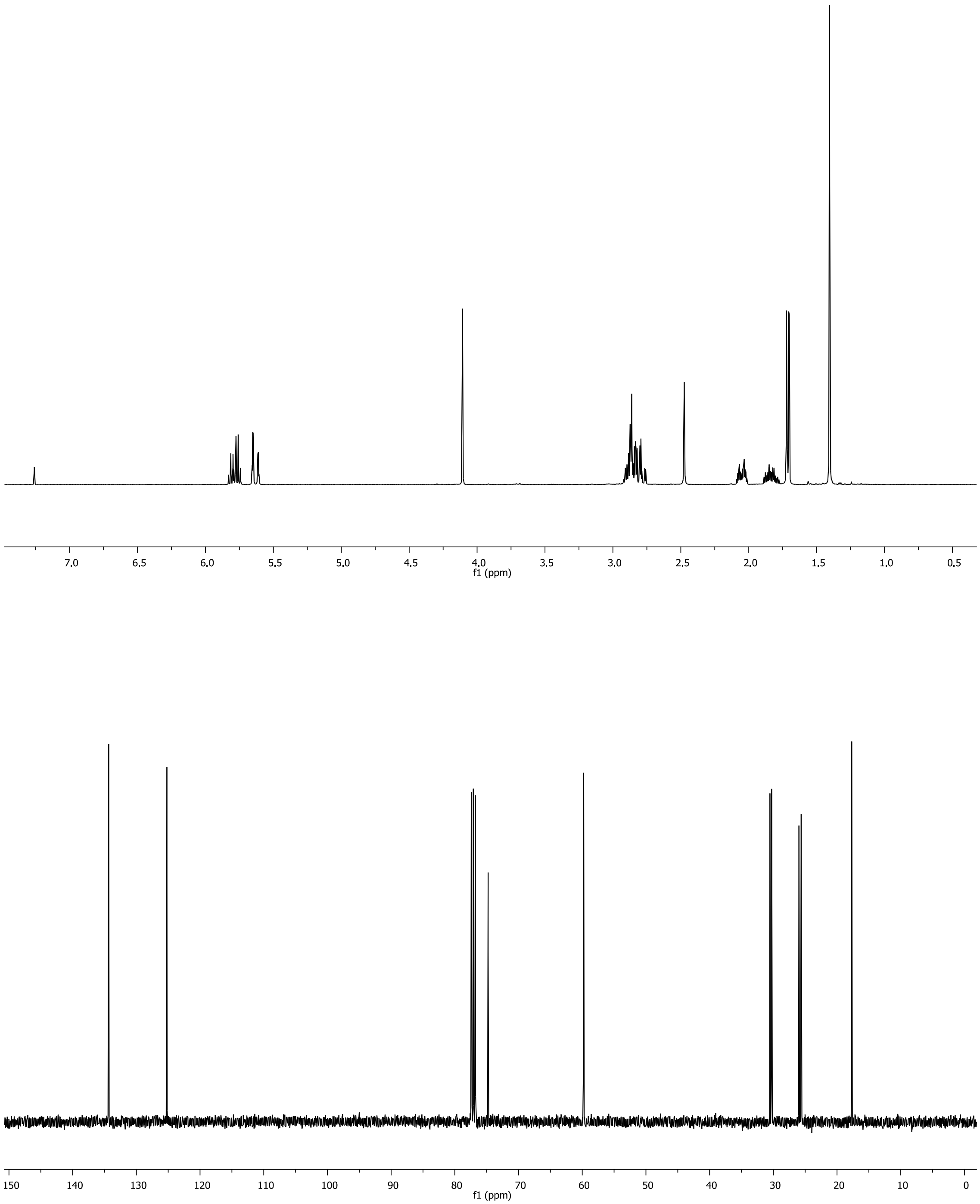
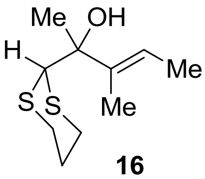


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **15**



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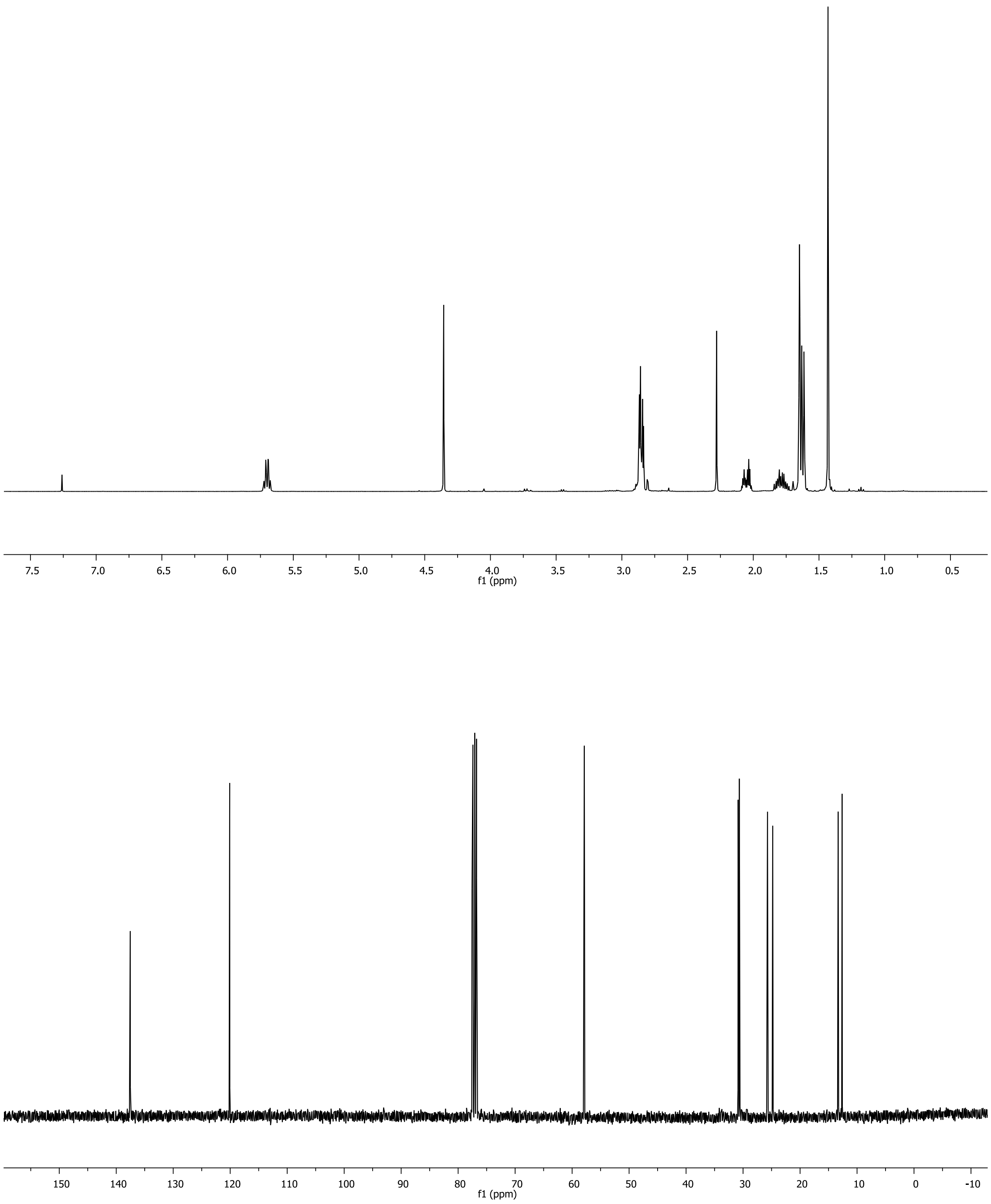
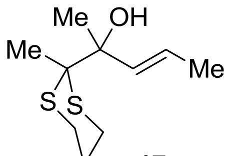


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **16**



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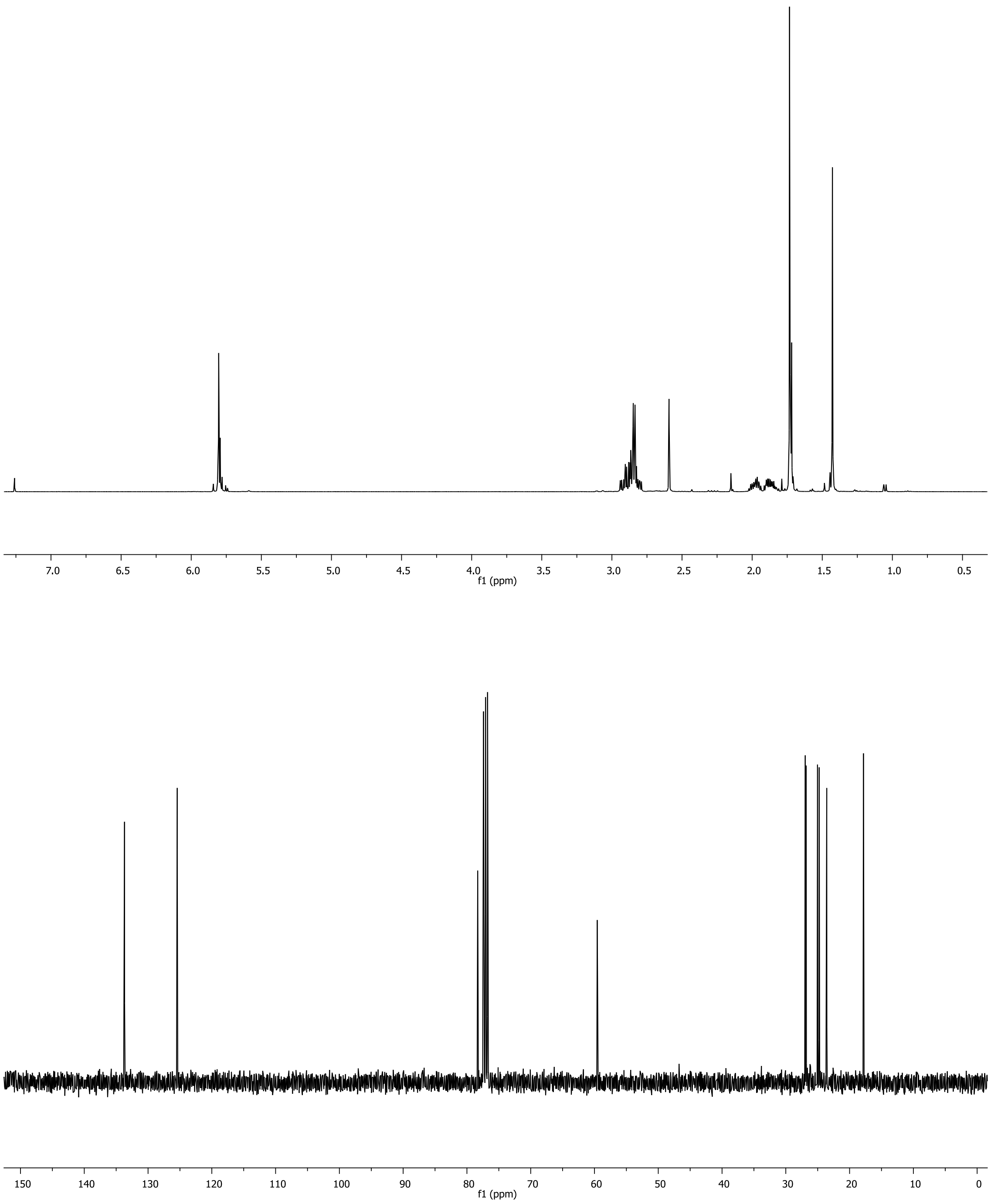
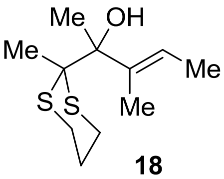


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **17**



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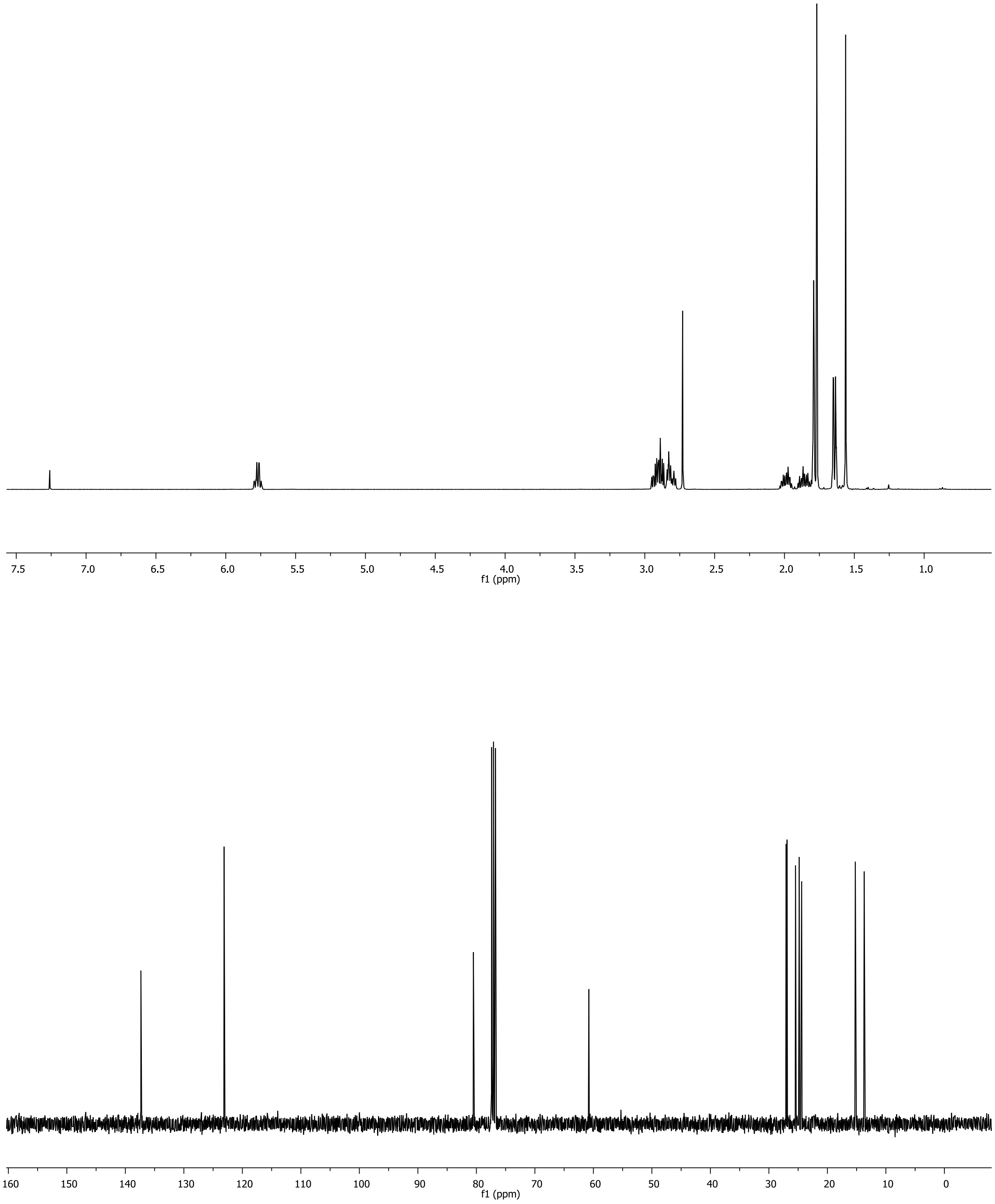
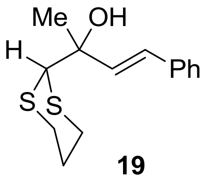


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **18**



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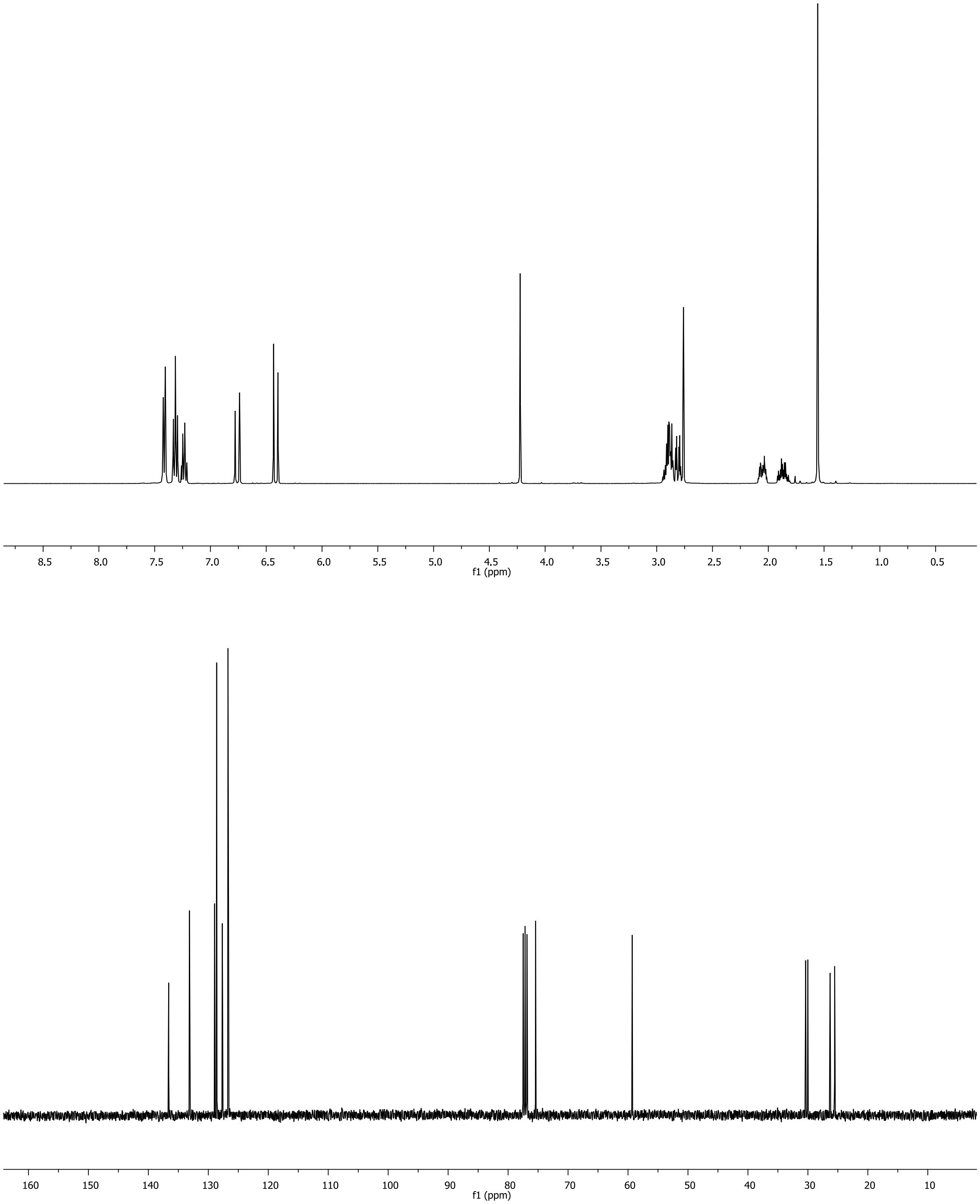
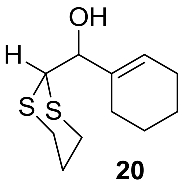


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **19**



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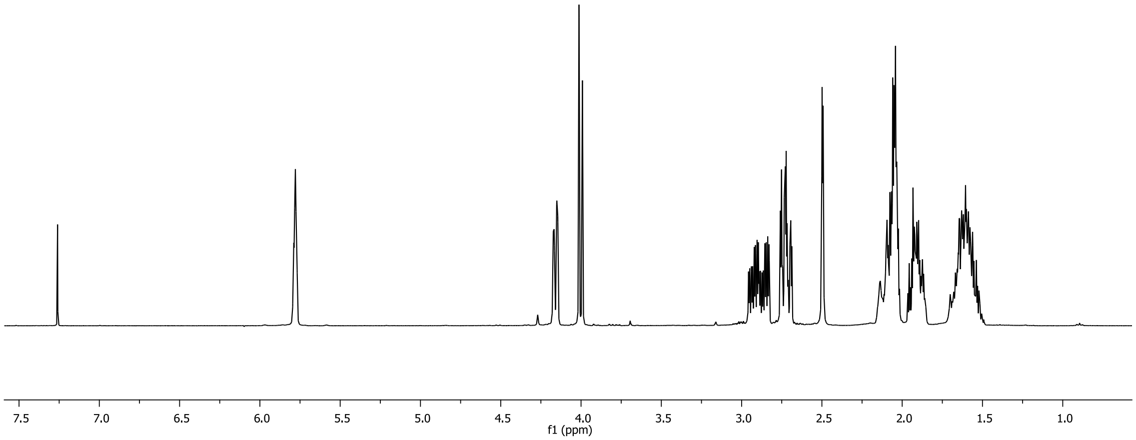
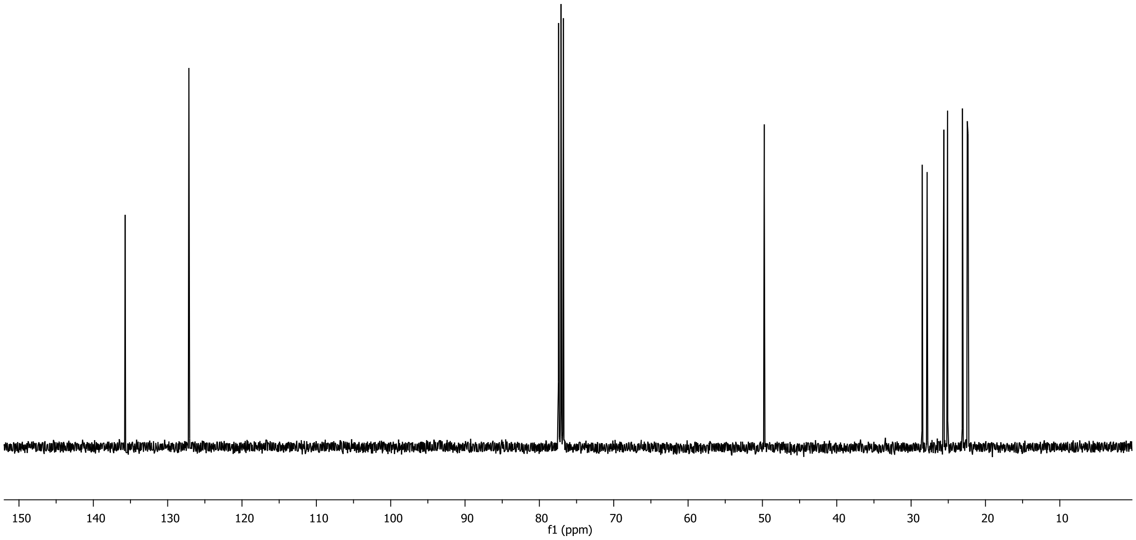
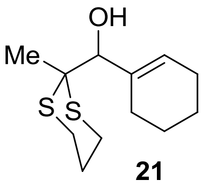




^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **20**



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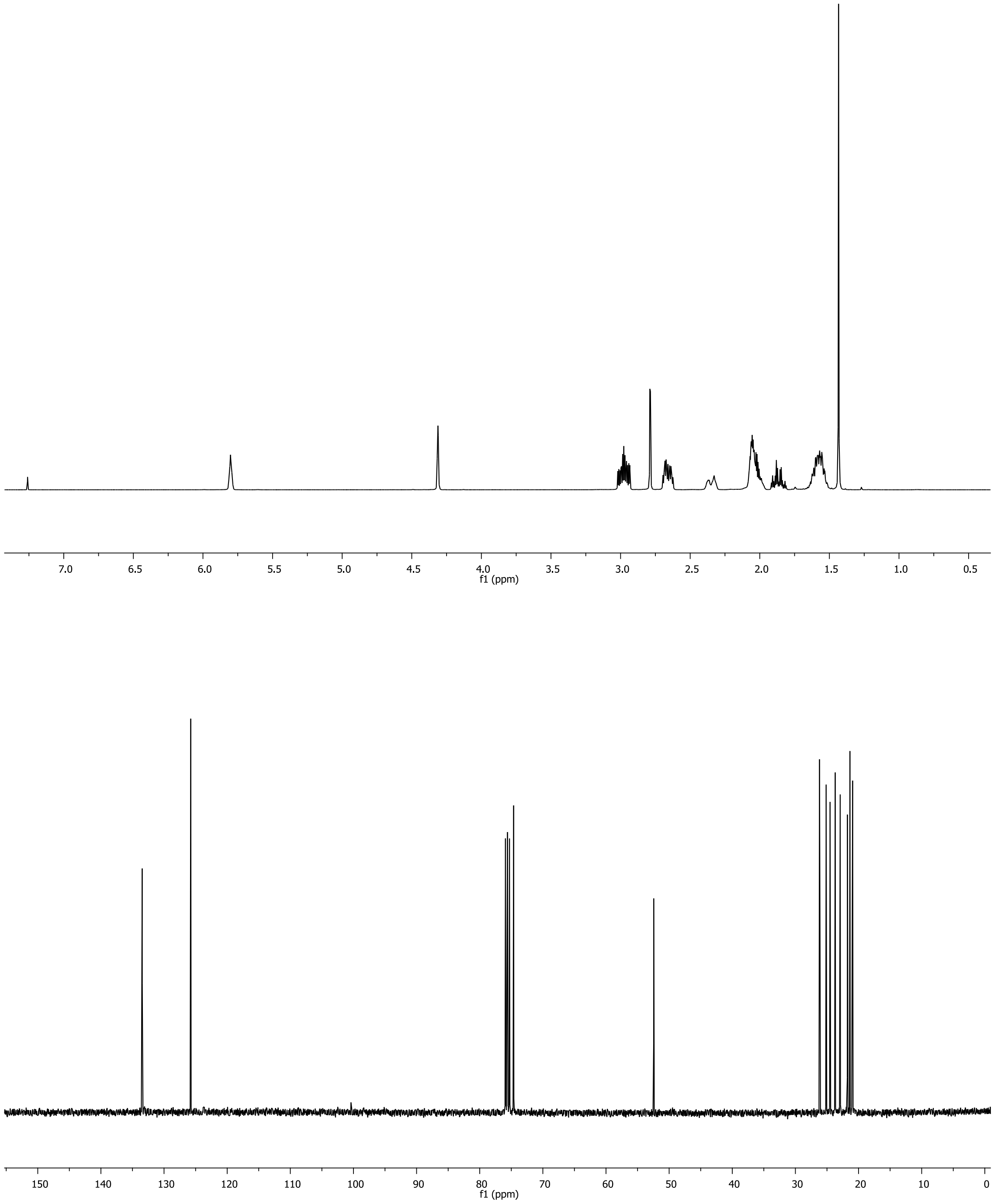
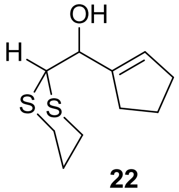


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **21**



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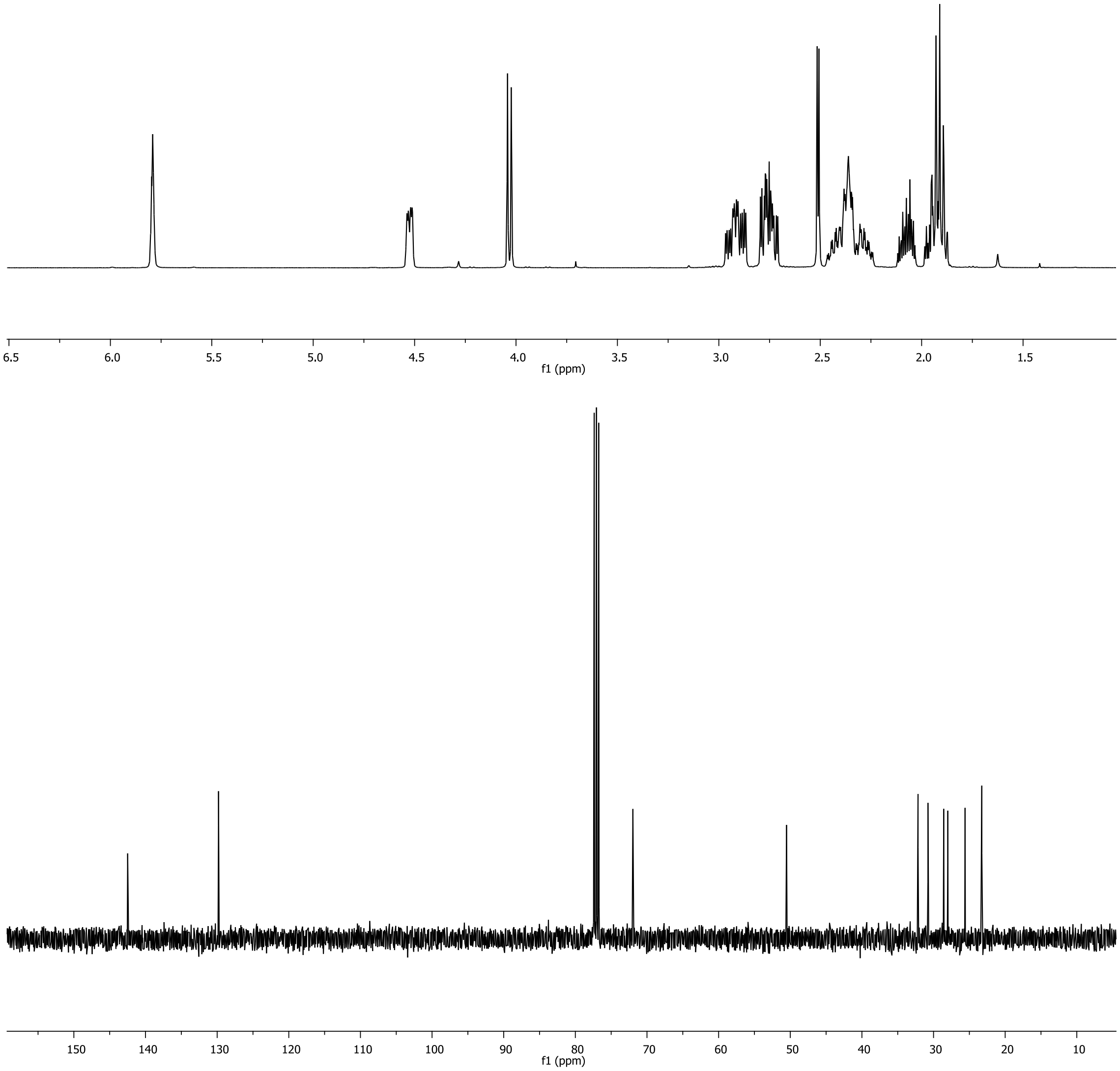
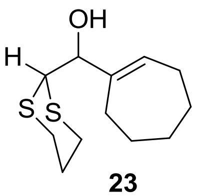


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **22**



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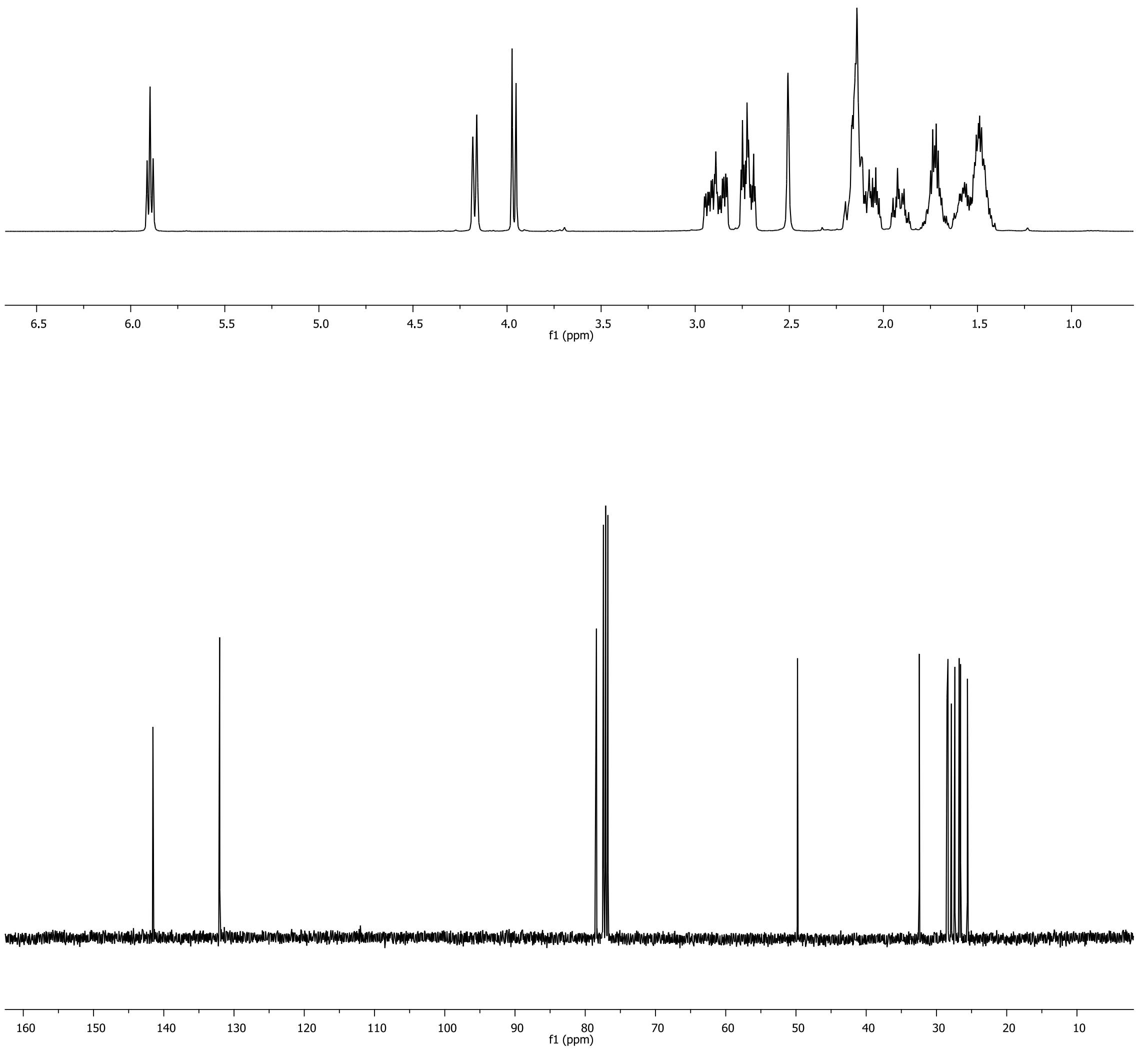
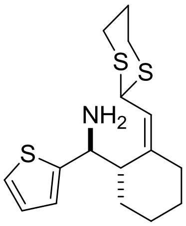
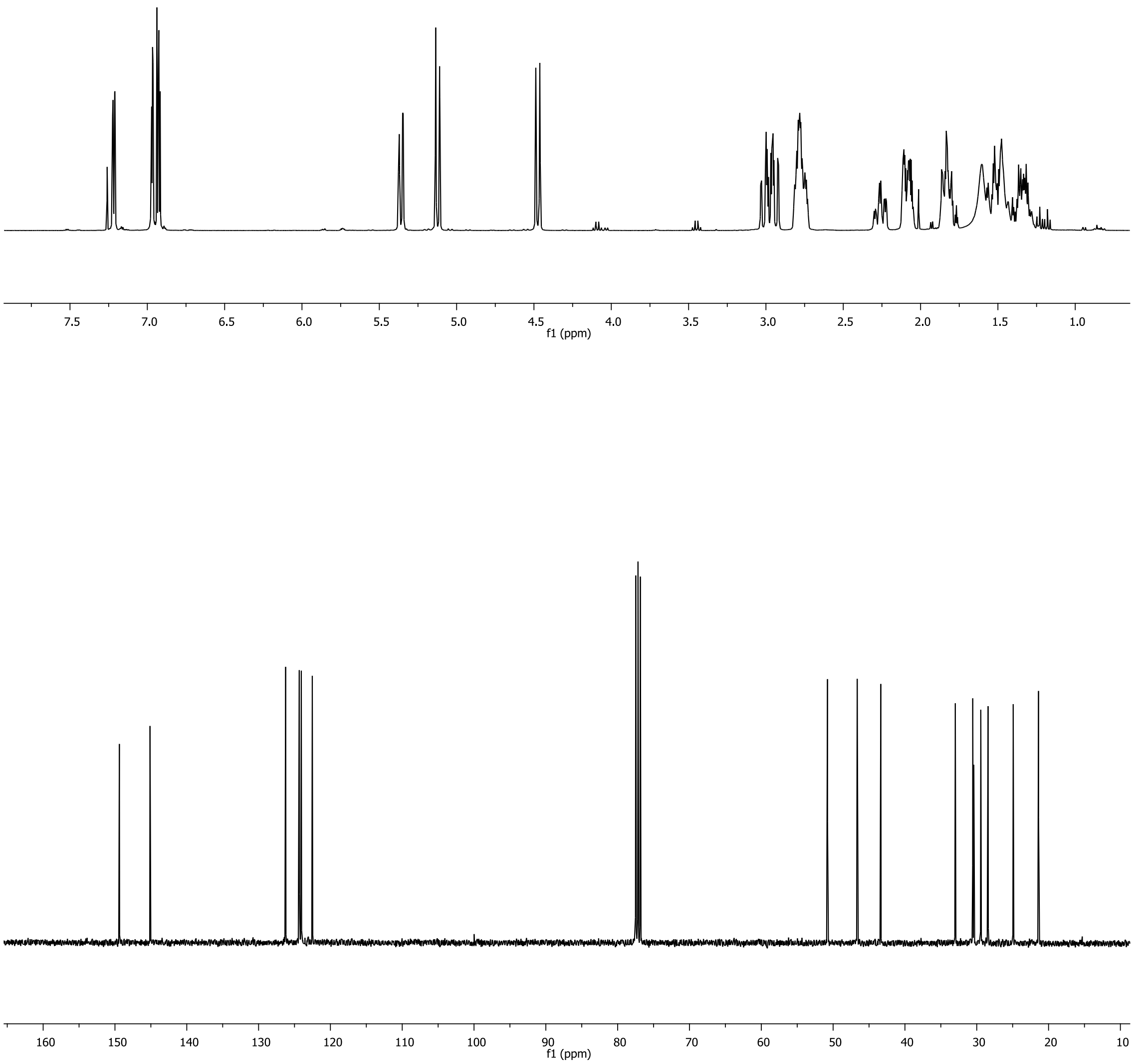


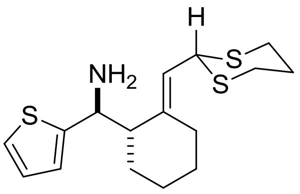
^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **23**



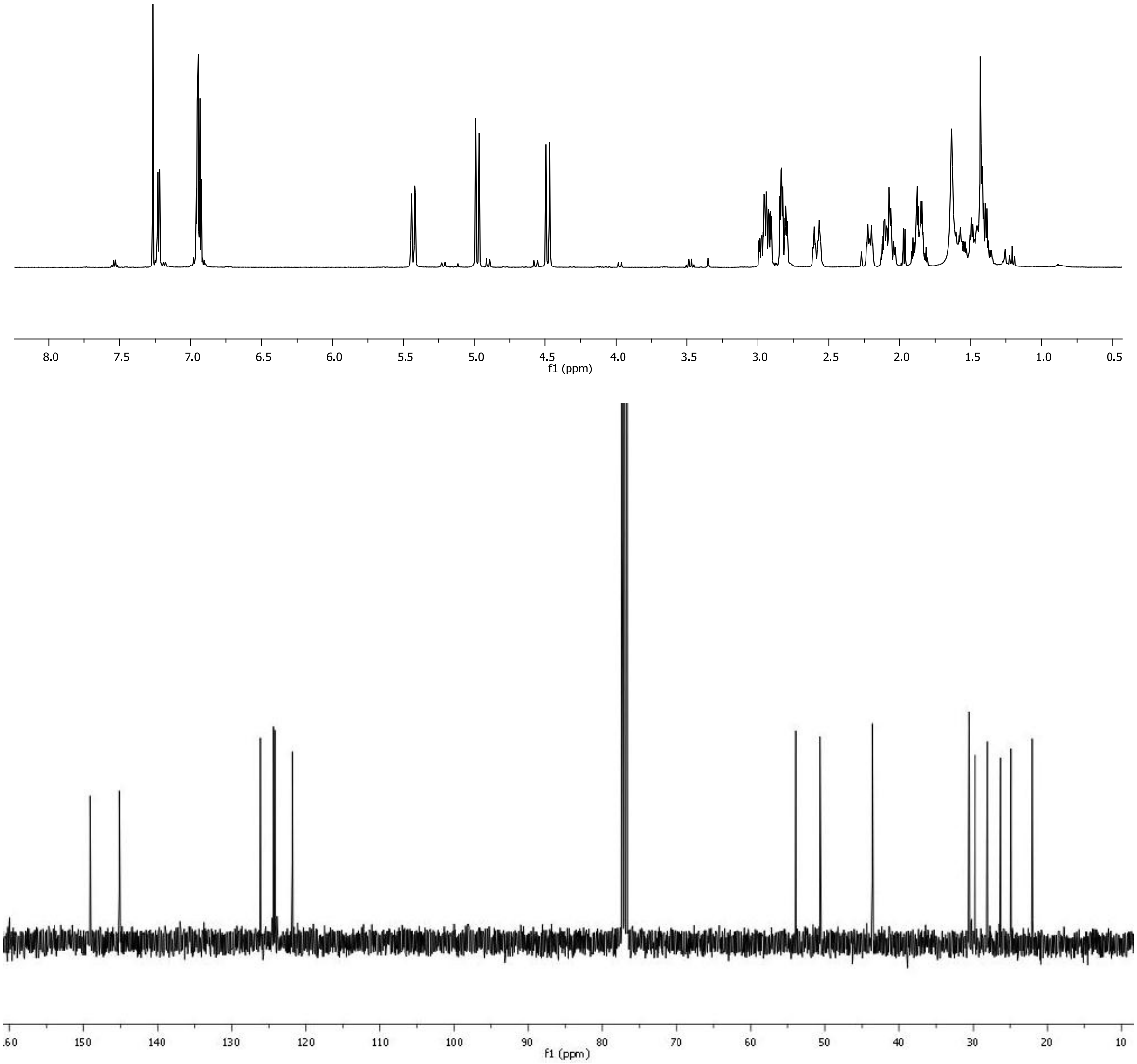
(*Z*)-27



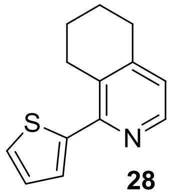
^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **(*Z*)-27**



(*E*)-27



^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **(*E*)-27**



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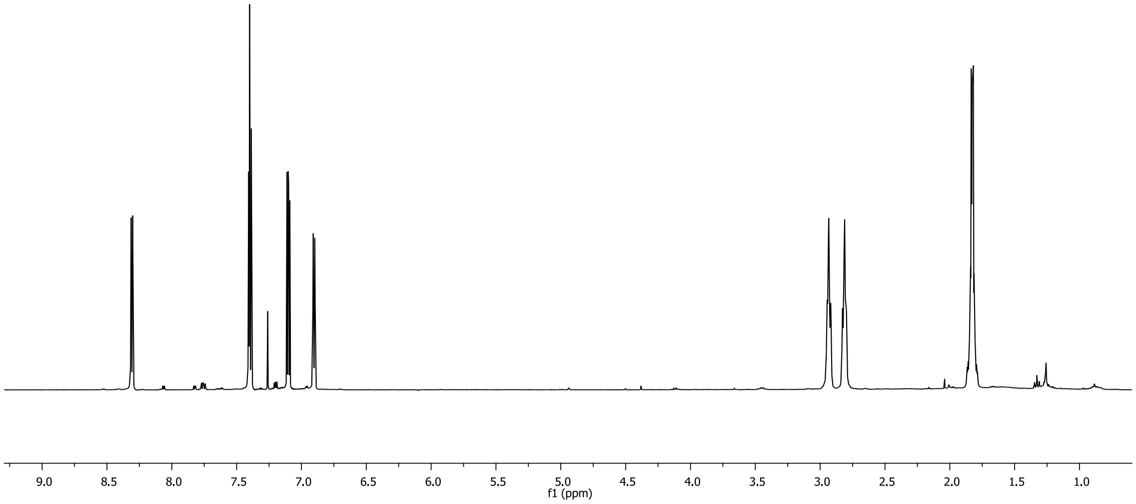
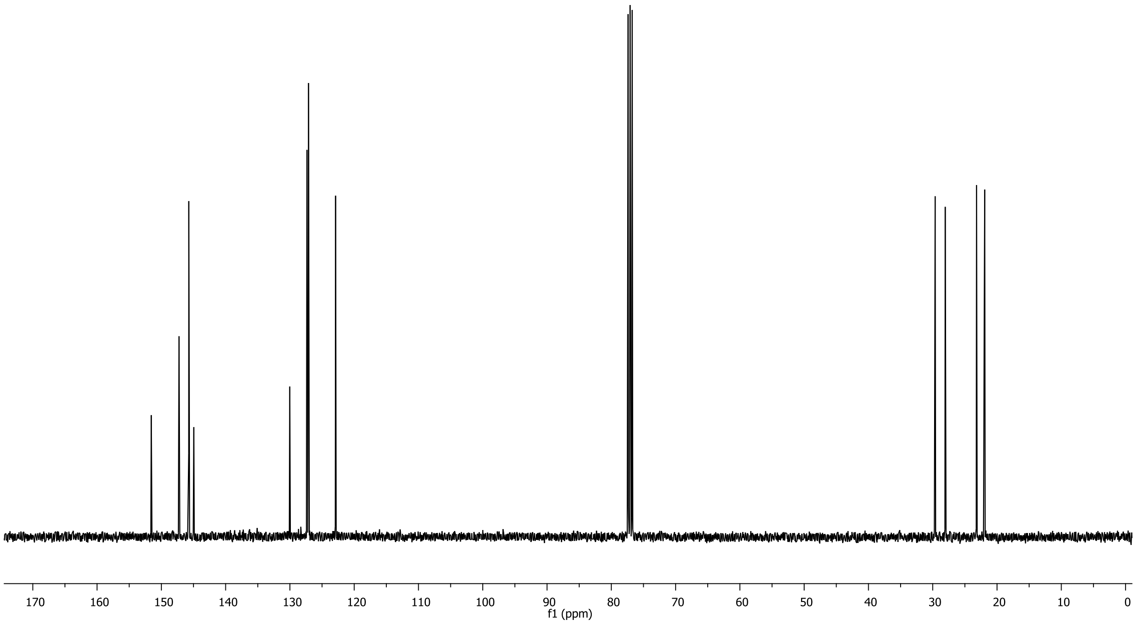
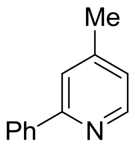




^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **28**



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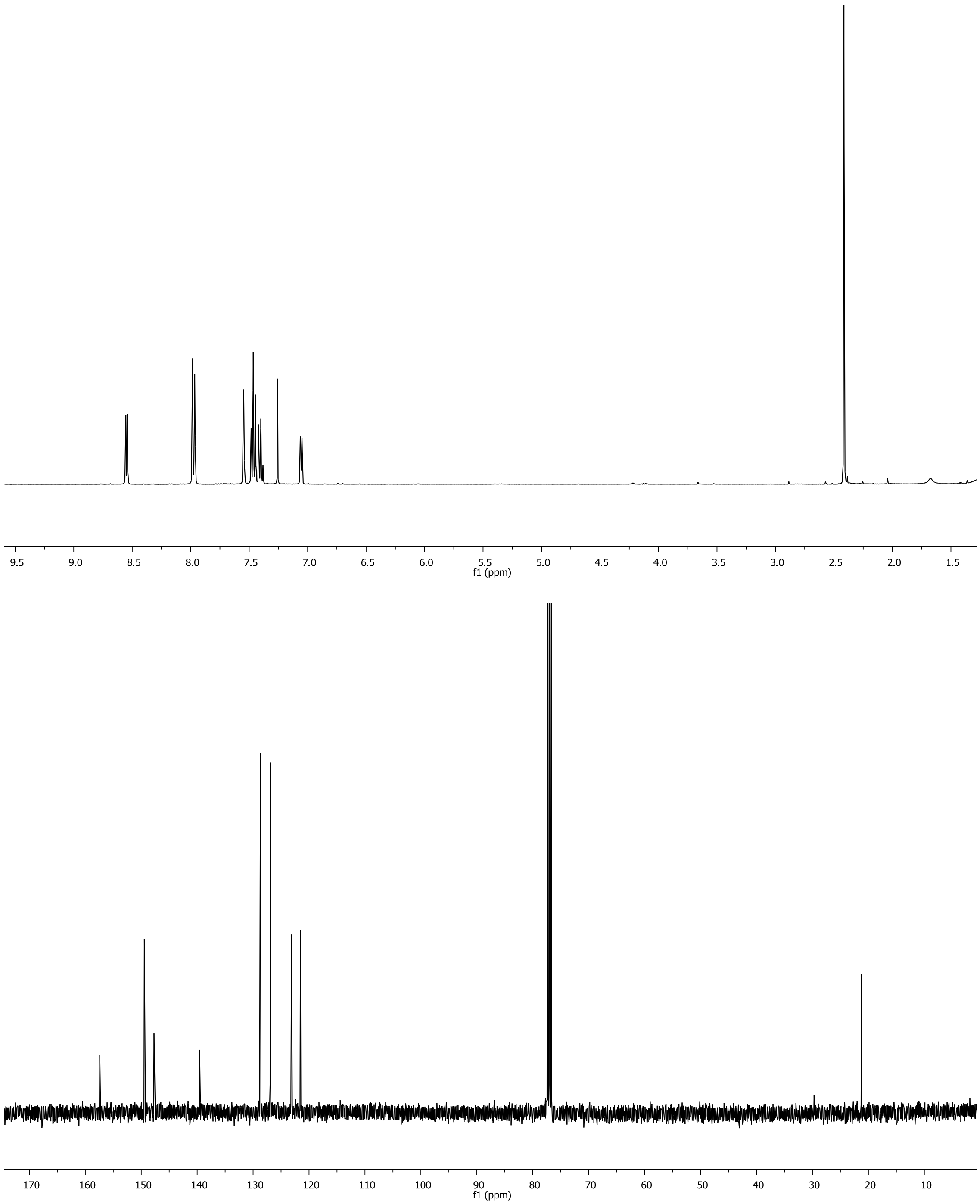
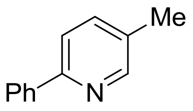


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **29**



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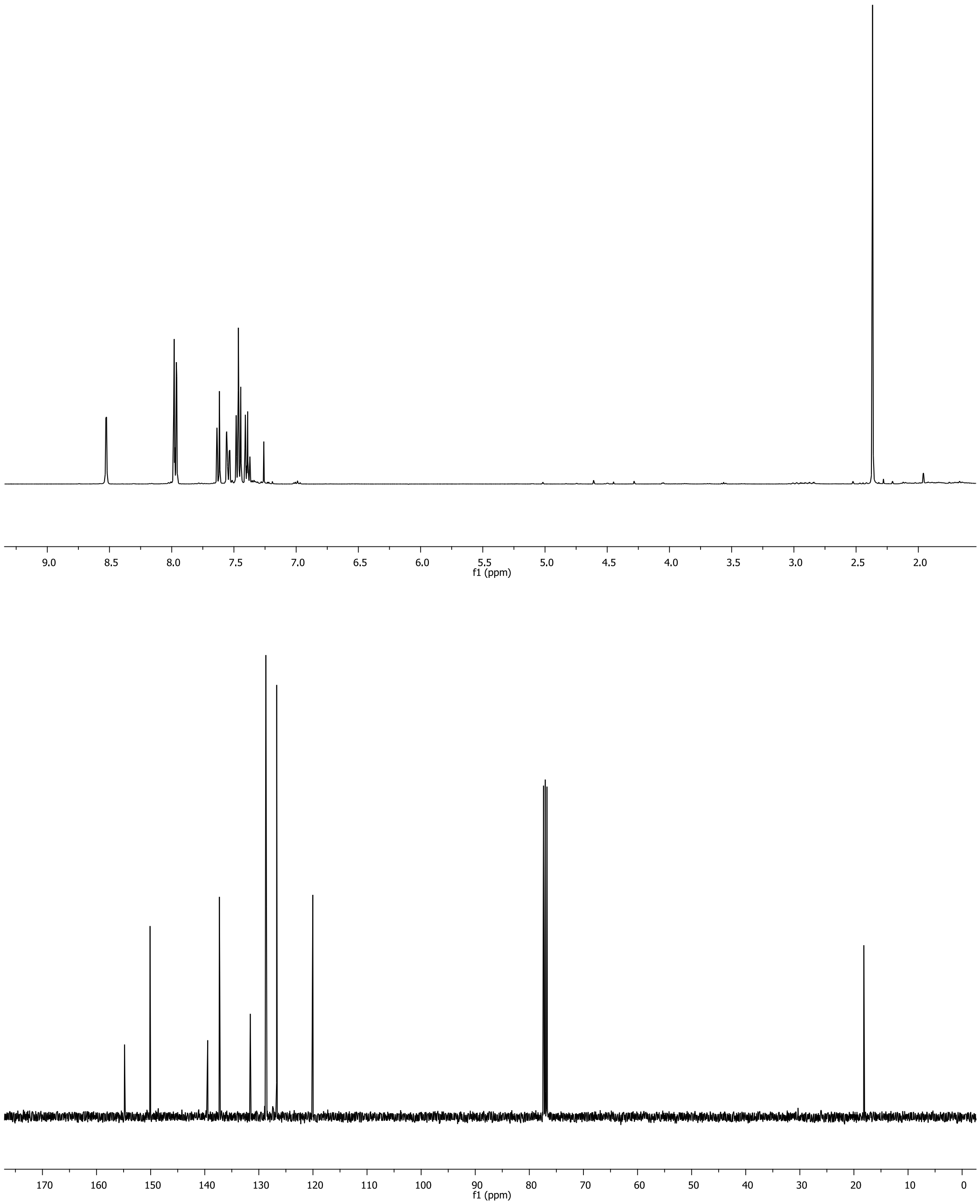

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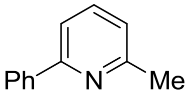

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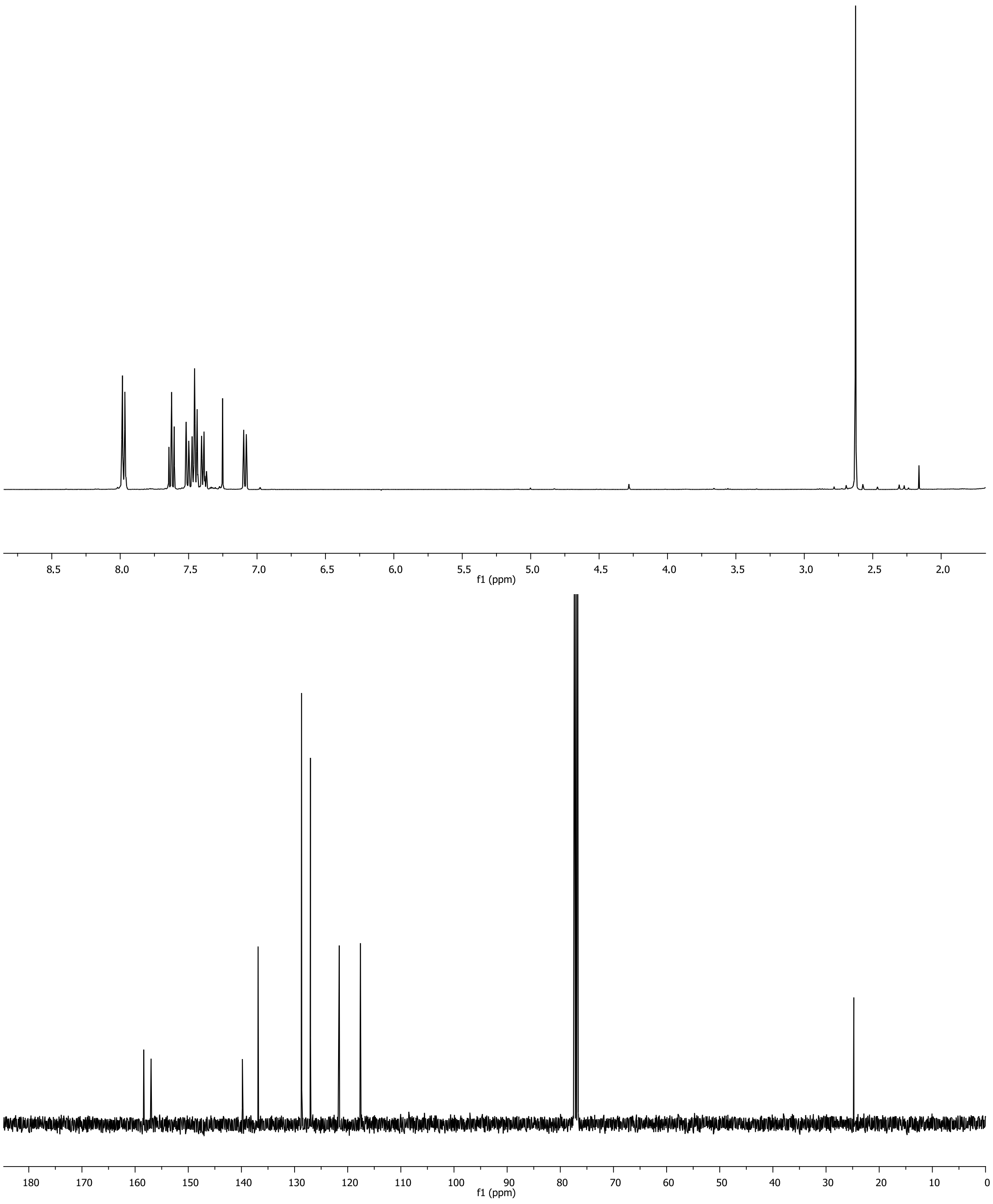
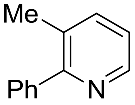


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **31**



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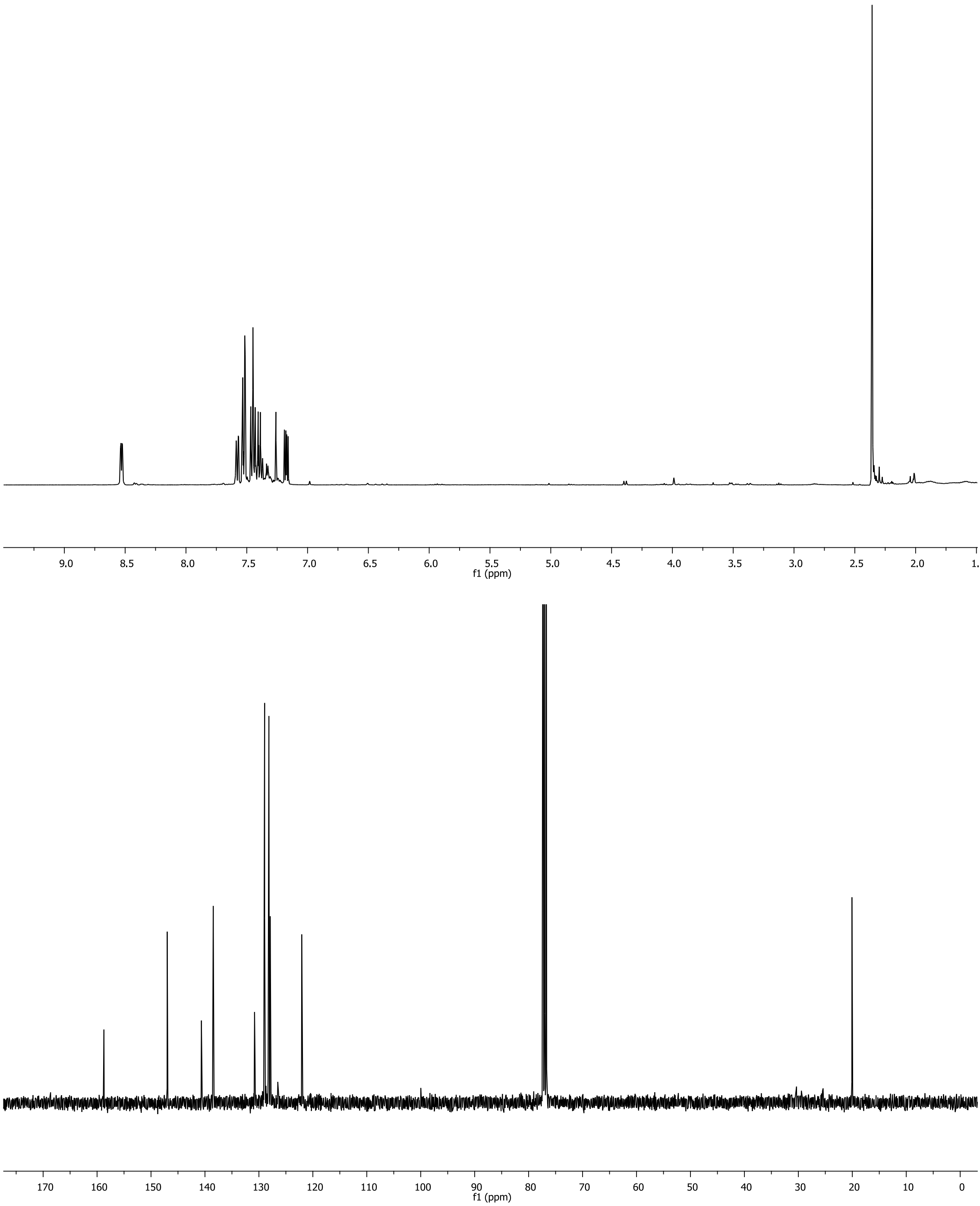
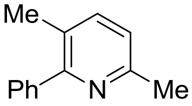


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **32**



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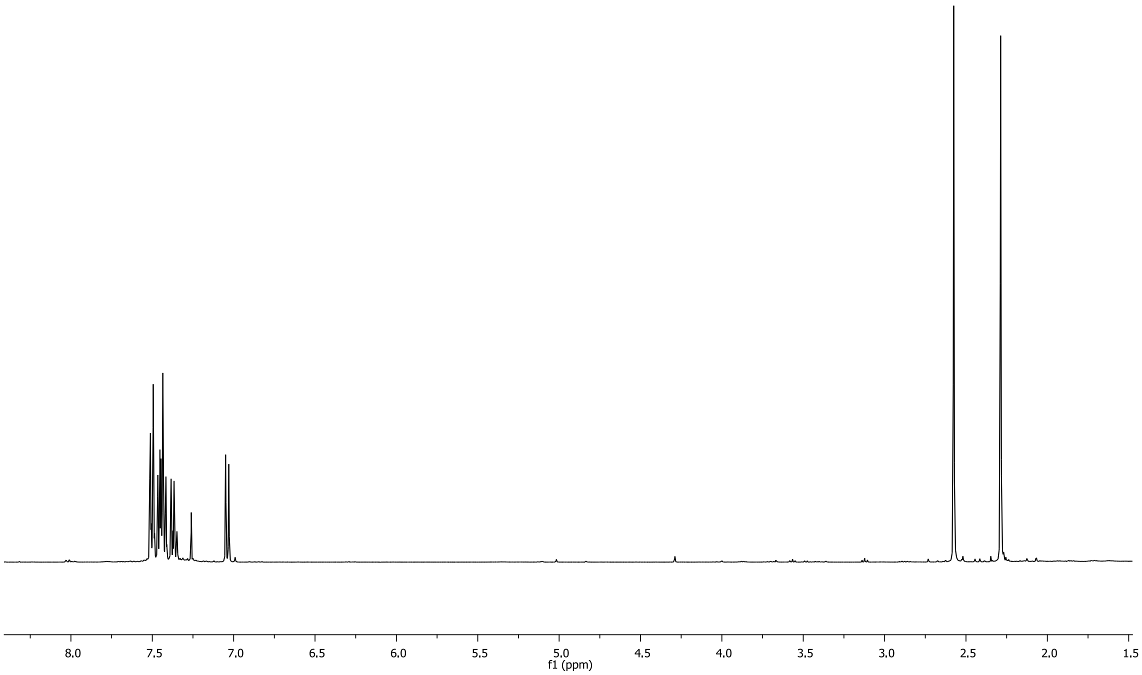
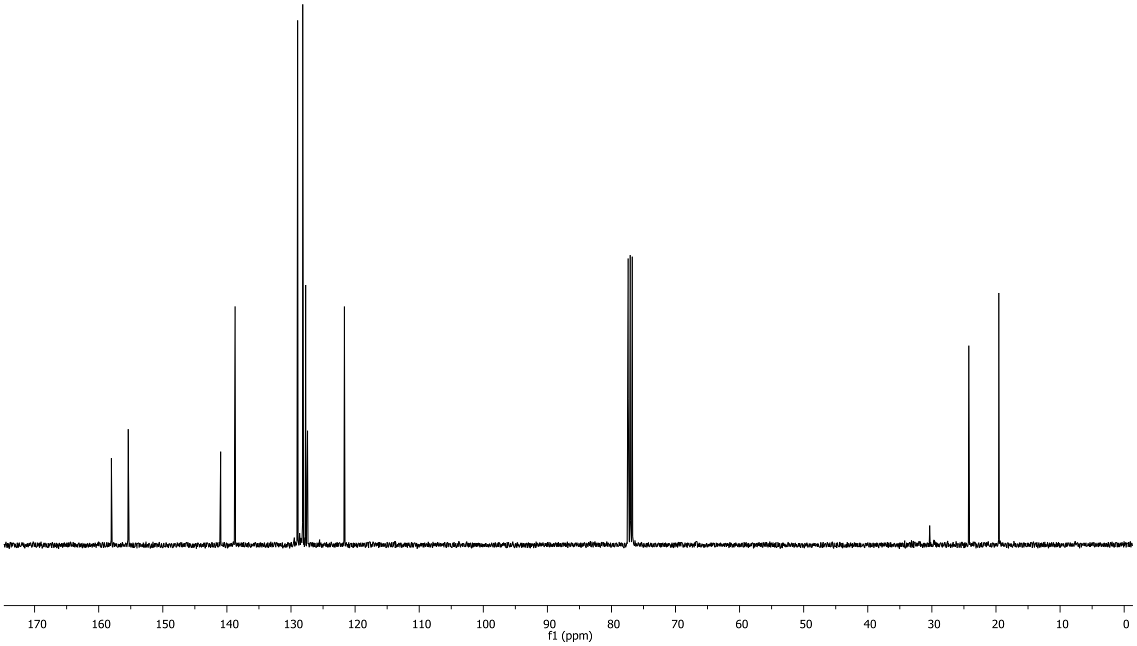
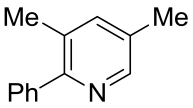




^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **33**



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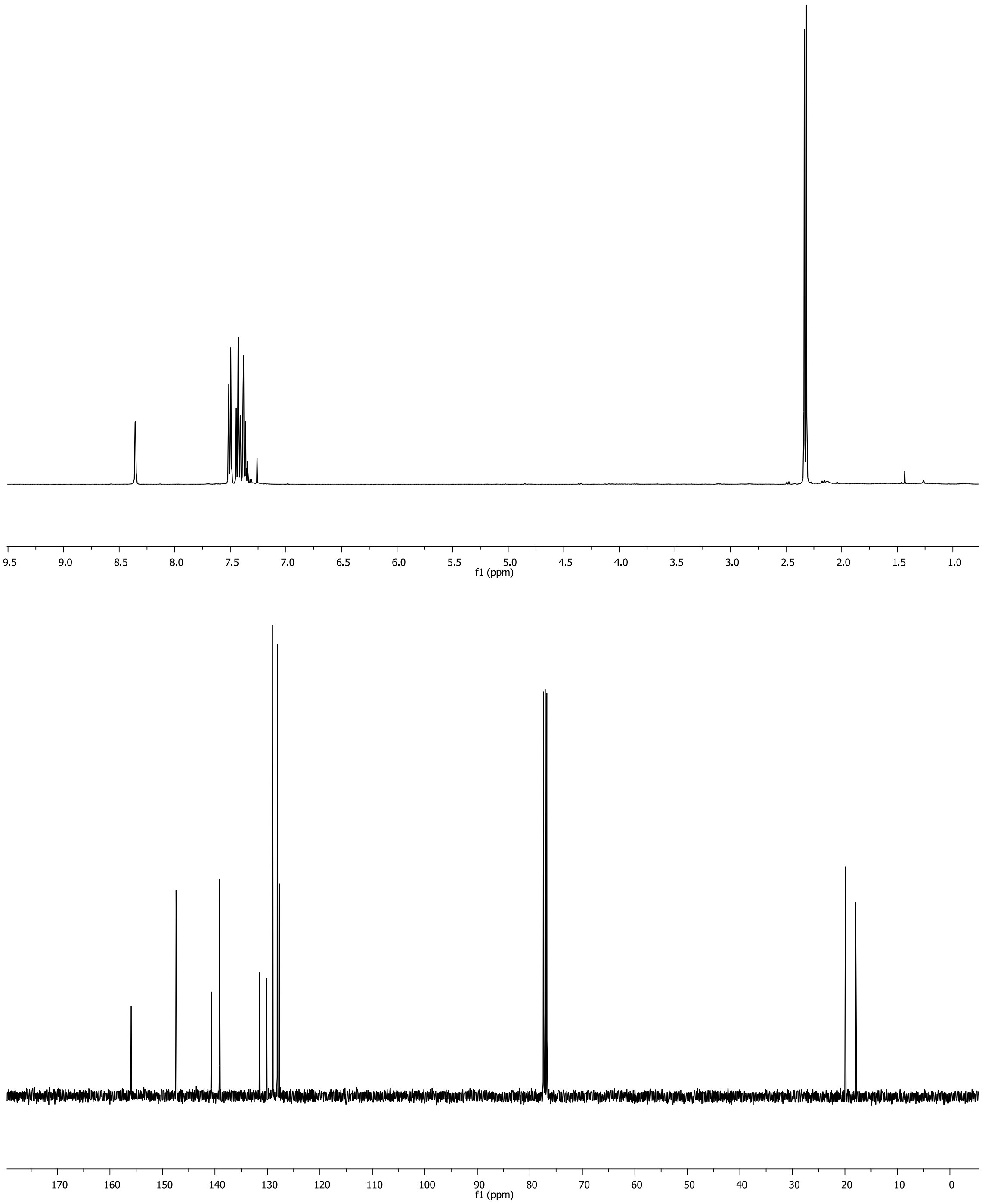
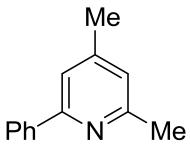


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **34**



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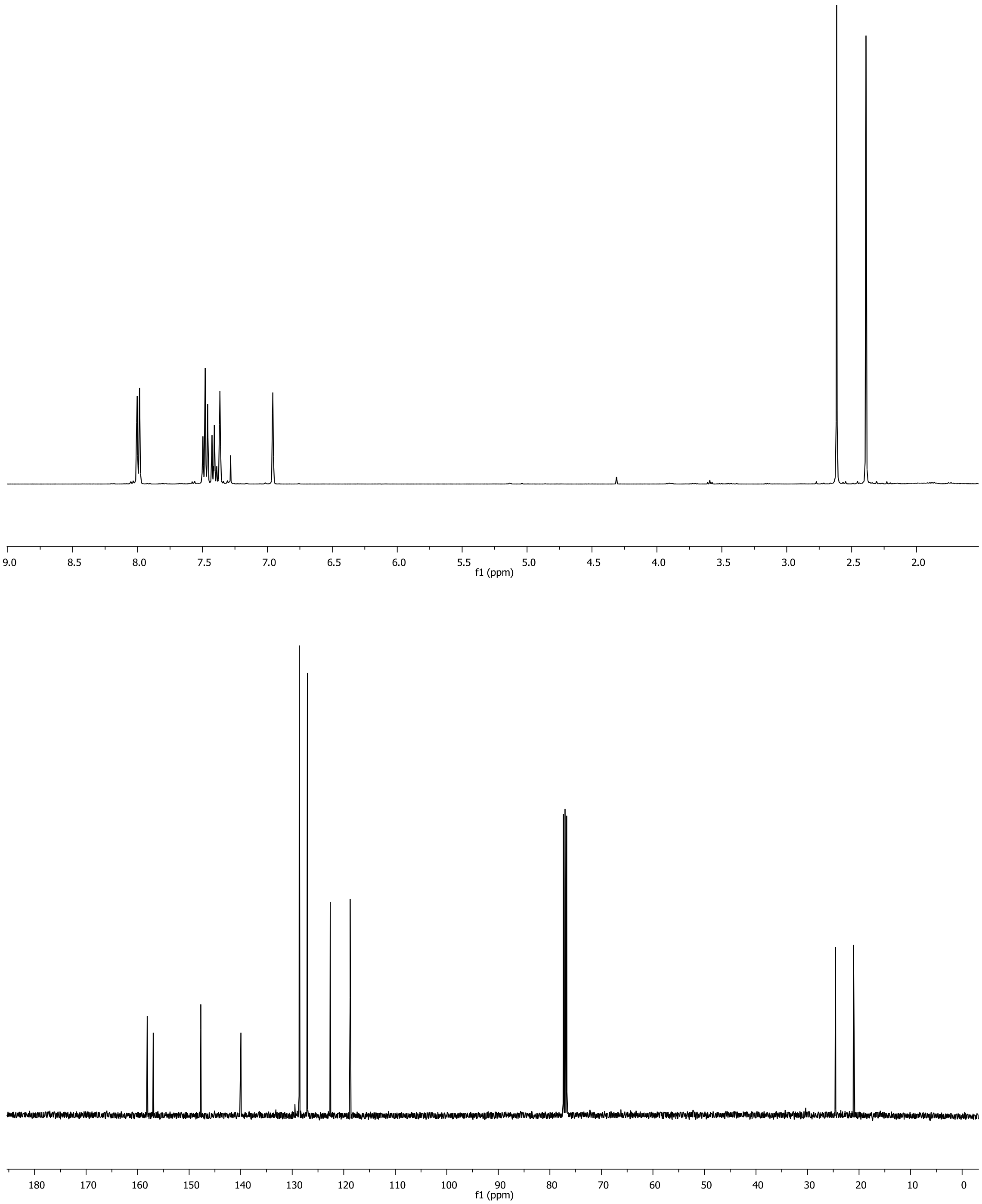
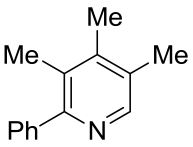


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **35**



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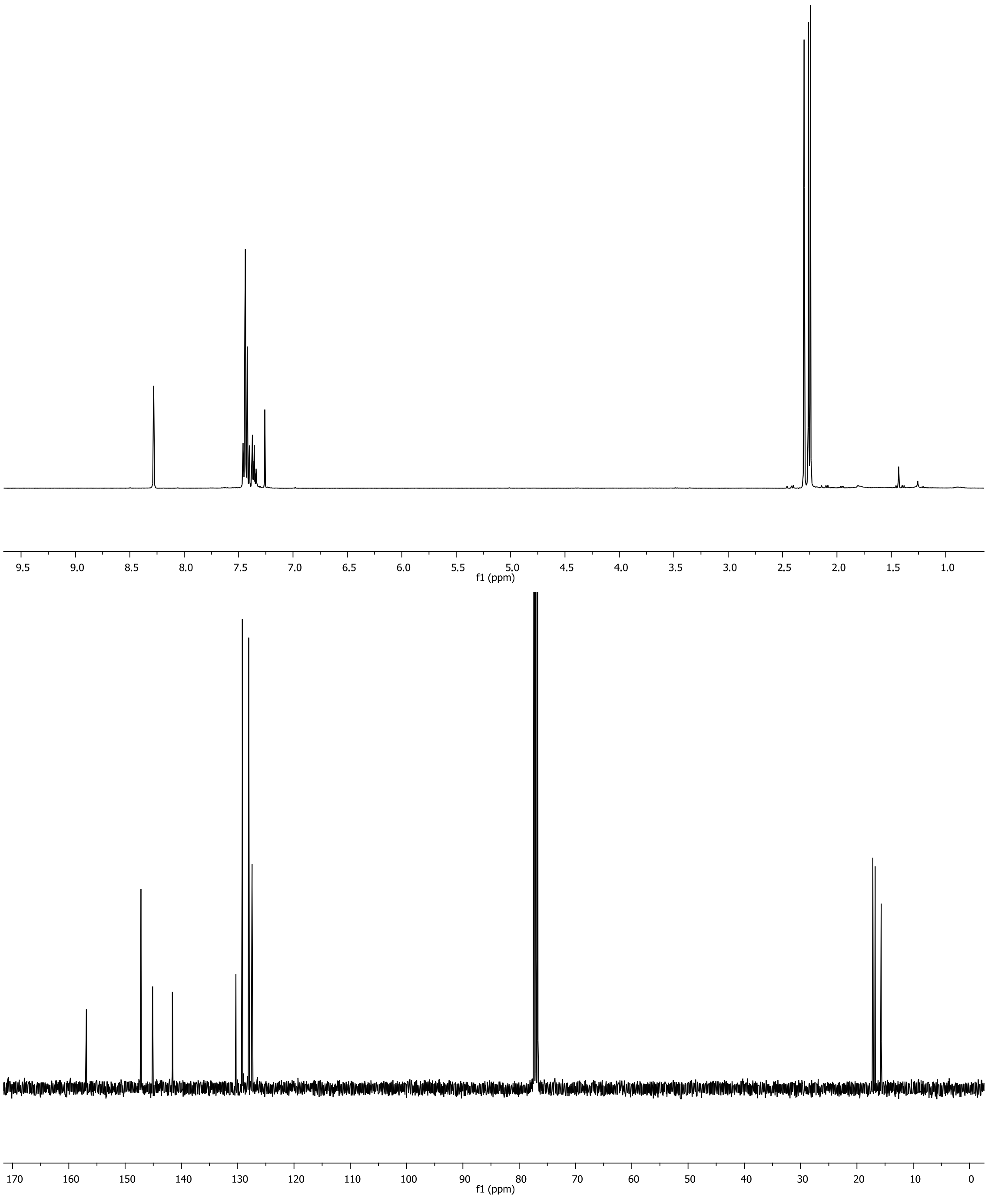
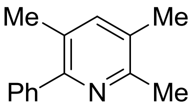


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **36**



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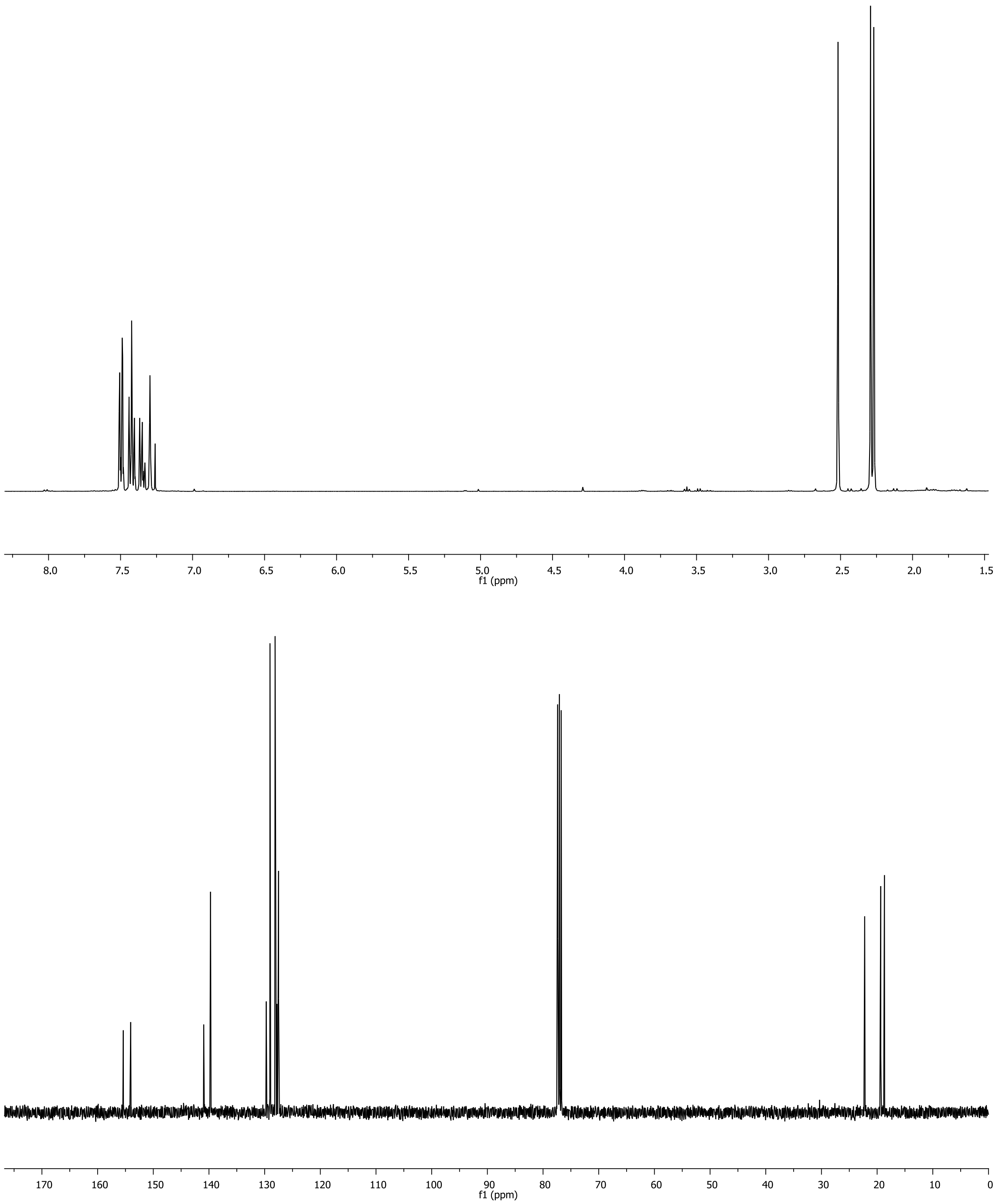

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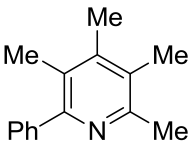

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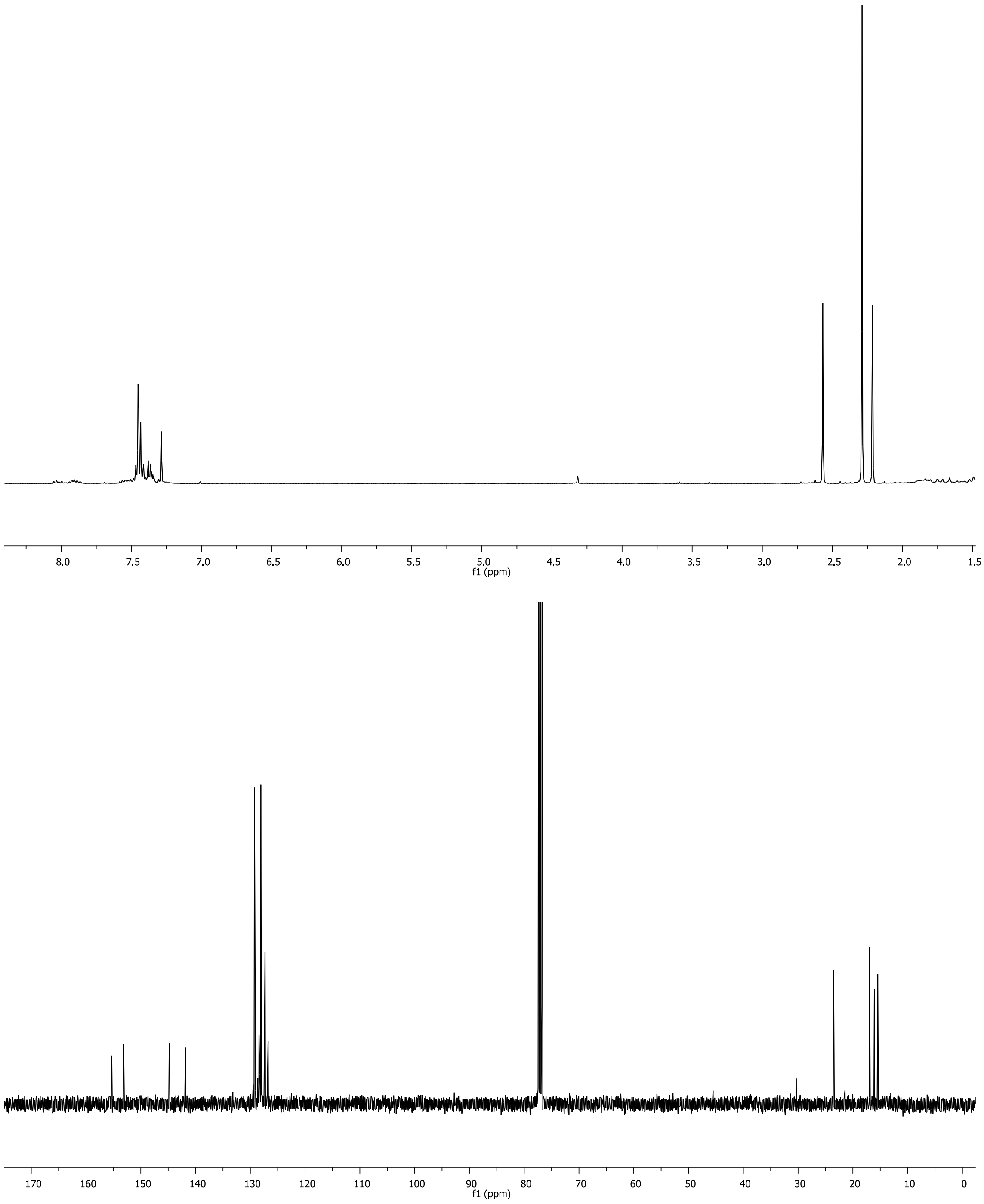
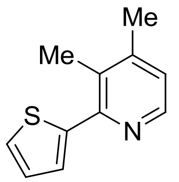


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **38**



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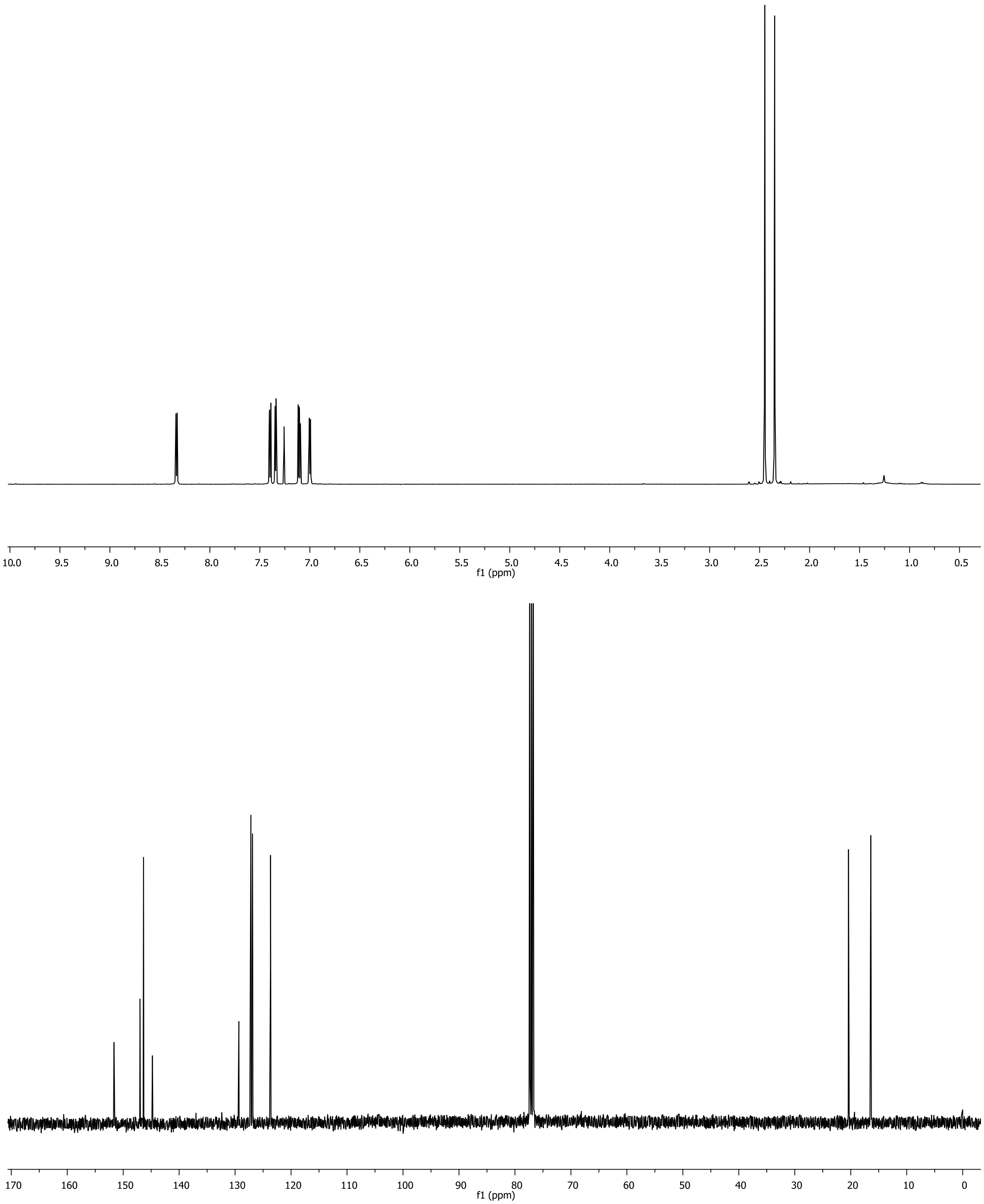
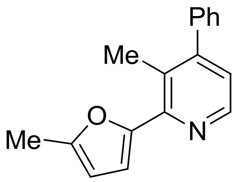


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **39**



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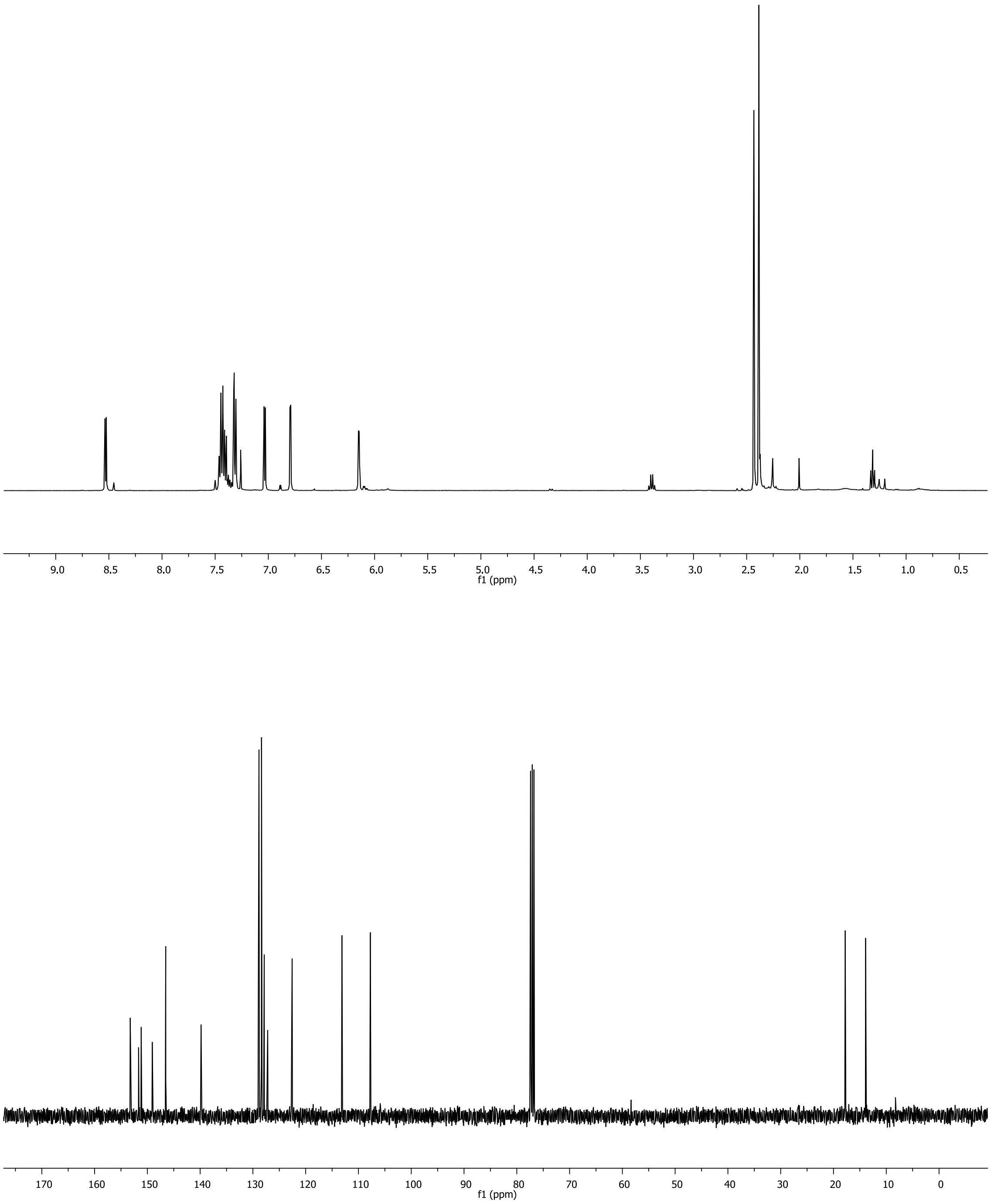
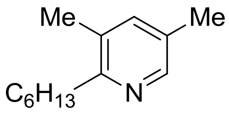


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **41**



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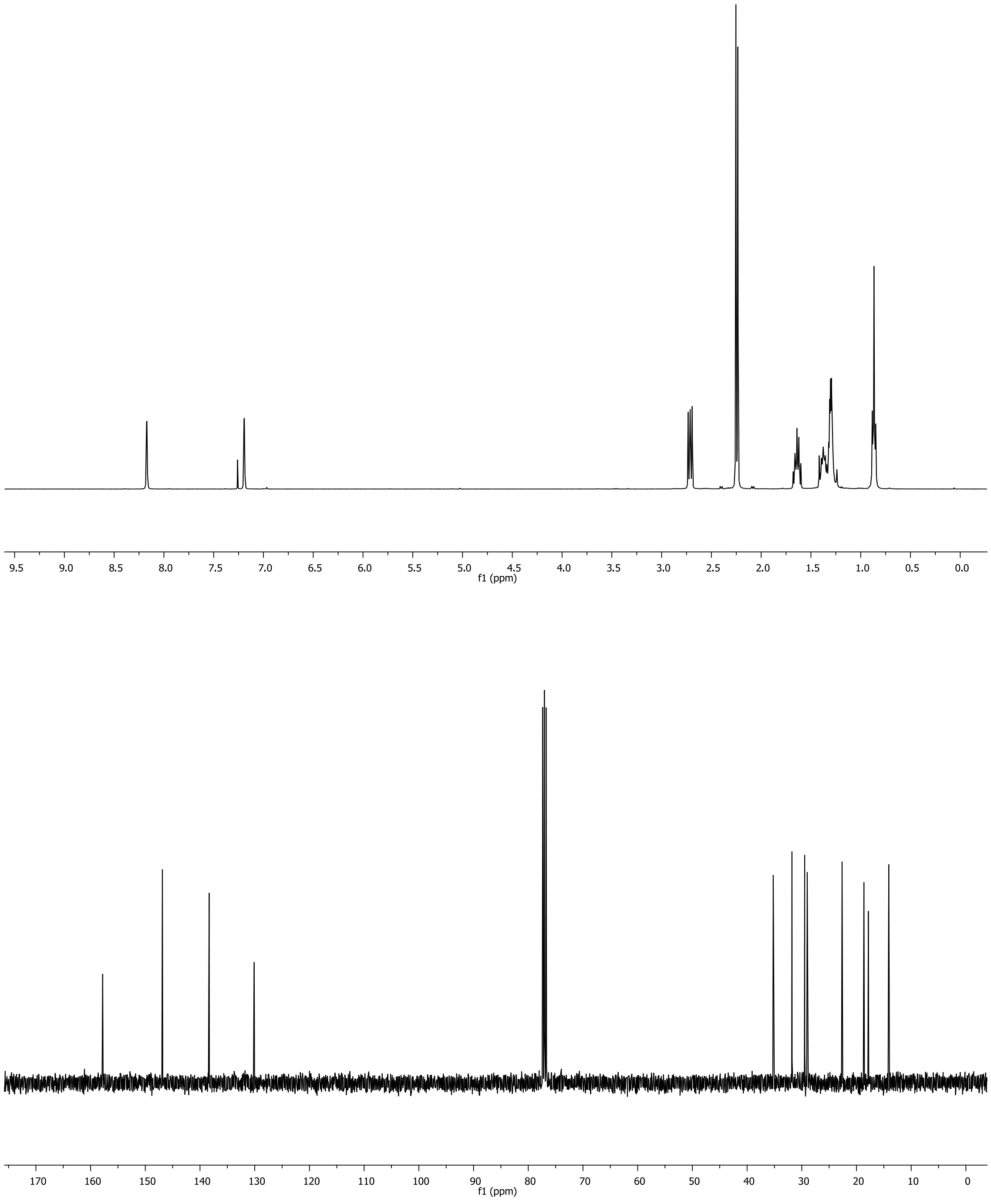
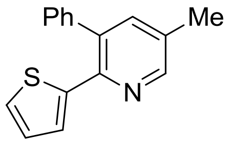


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **43**



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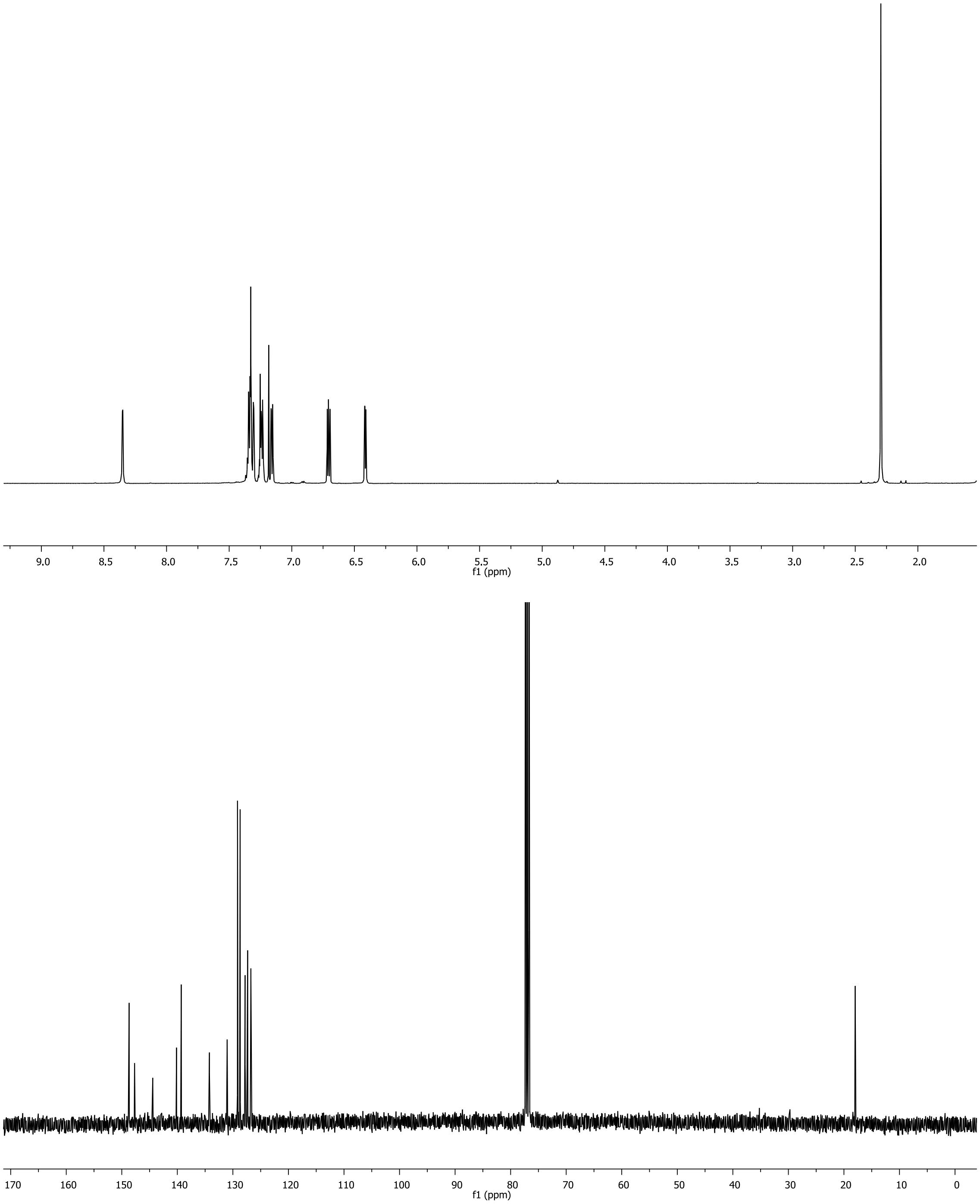
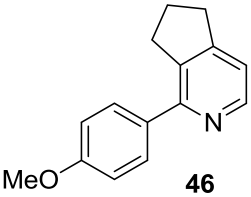


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **44**



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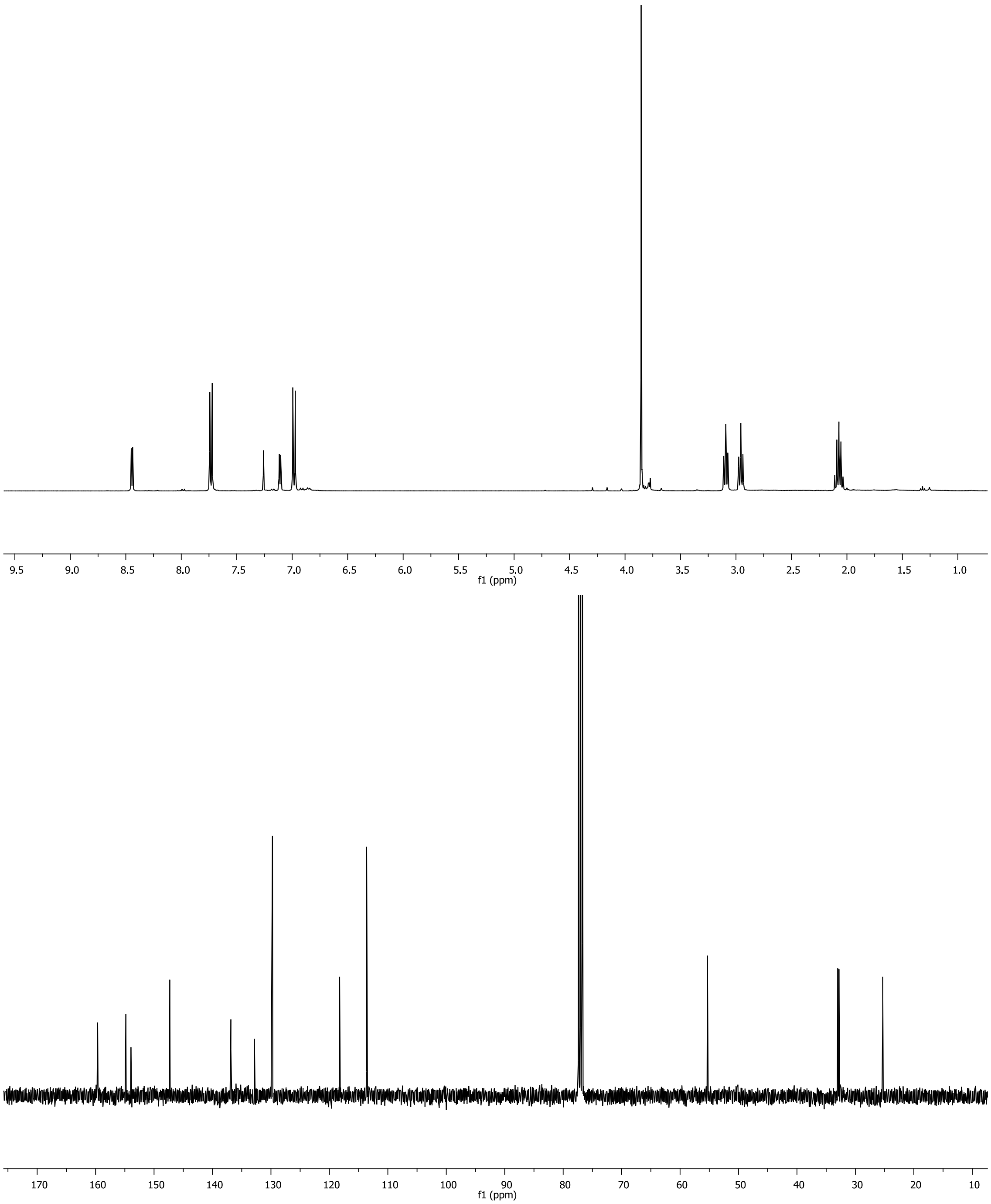
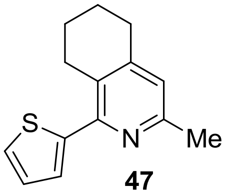


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **46**



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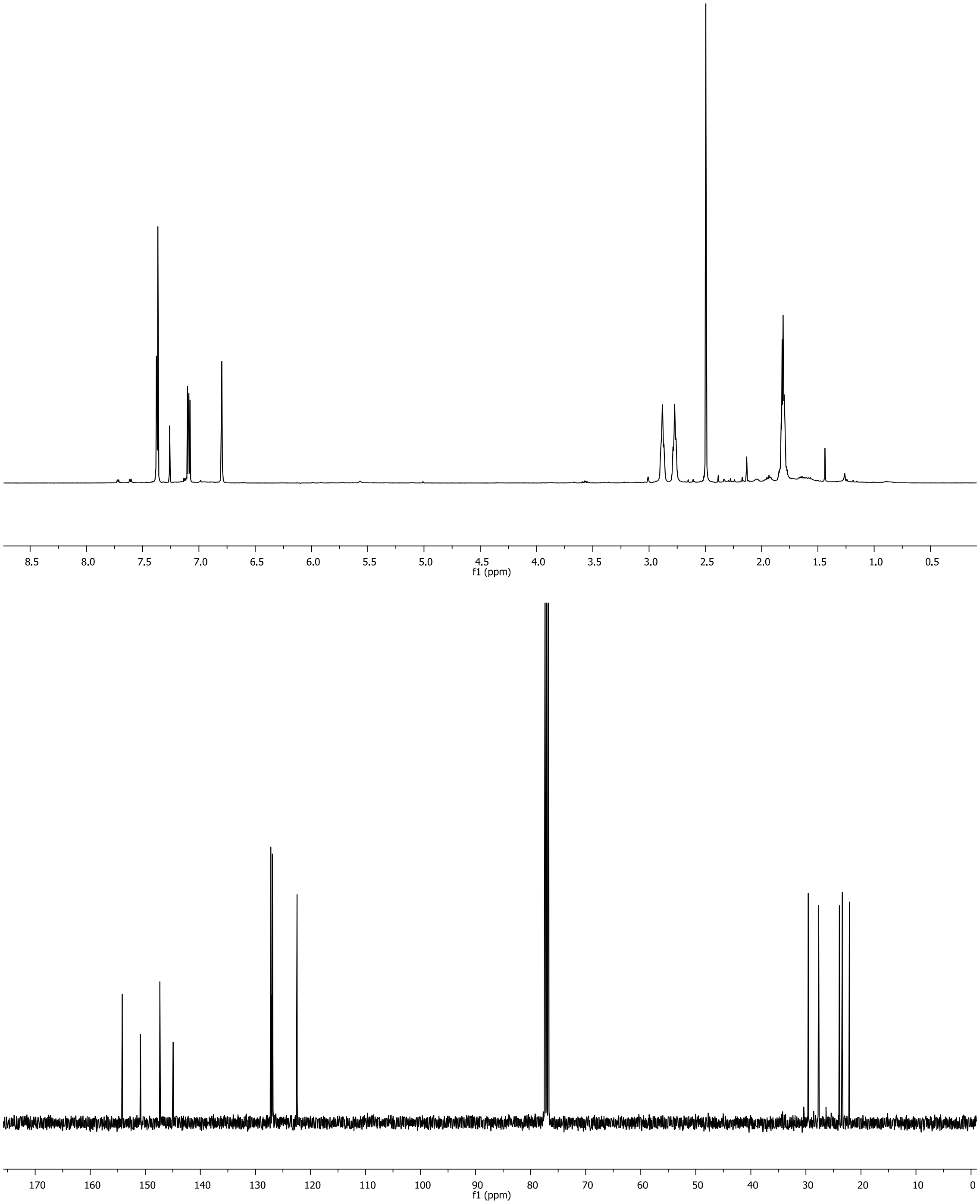
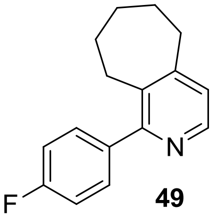


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **47**



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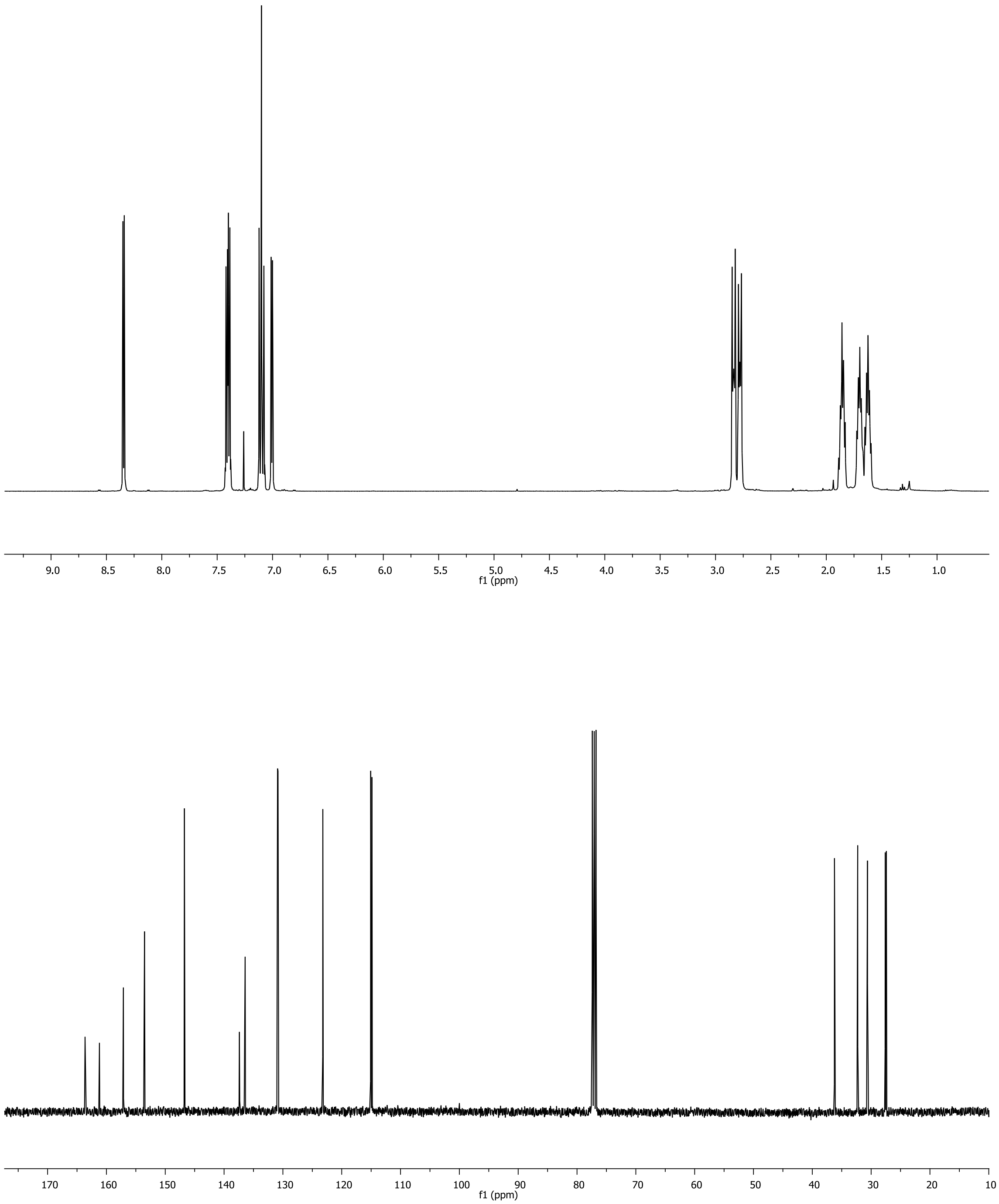
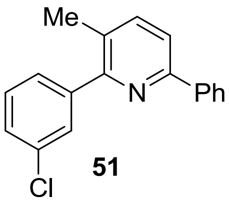


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **49**



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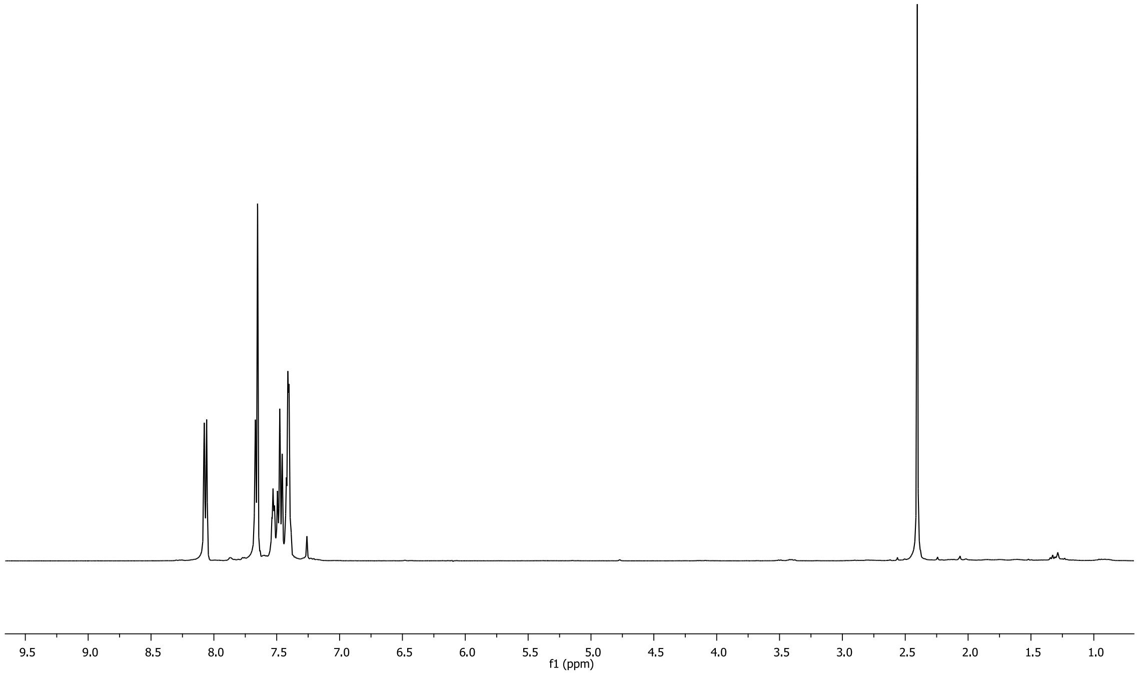

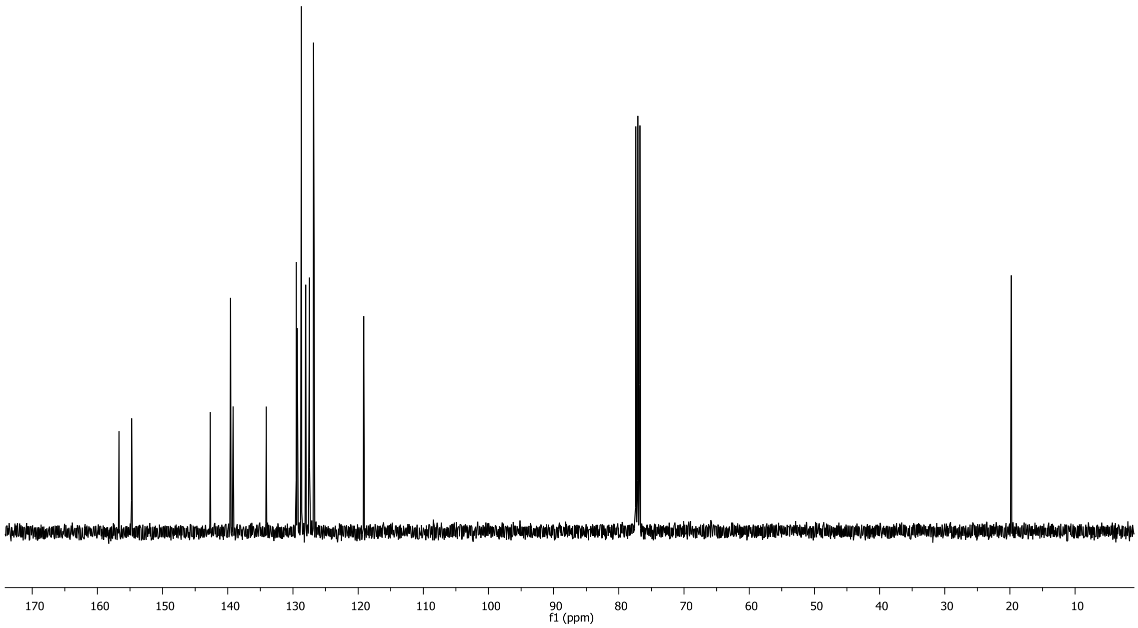

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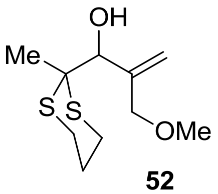
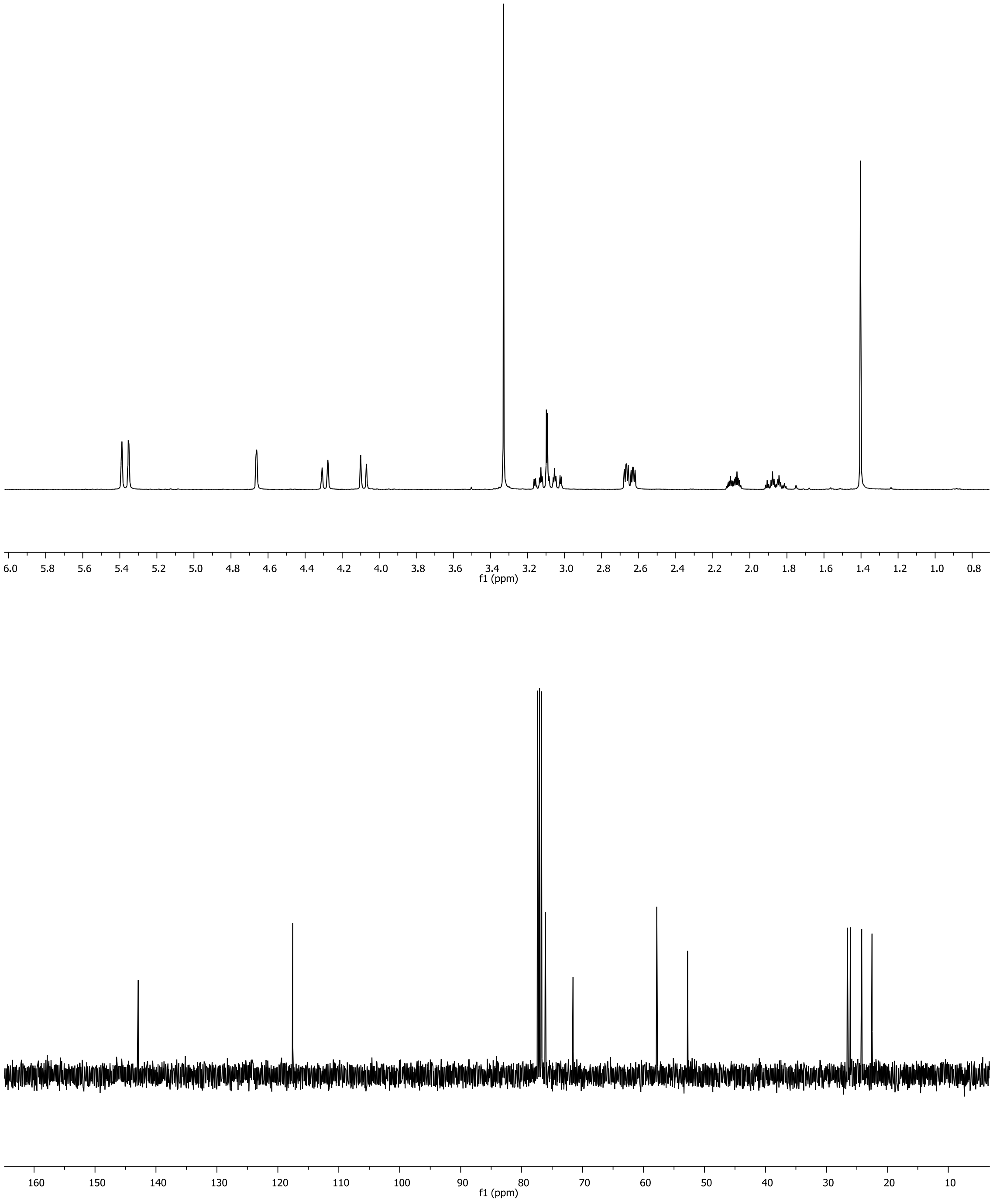
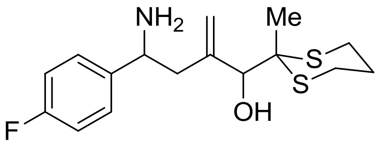


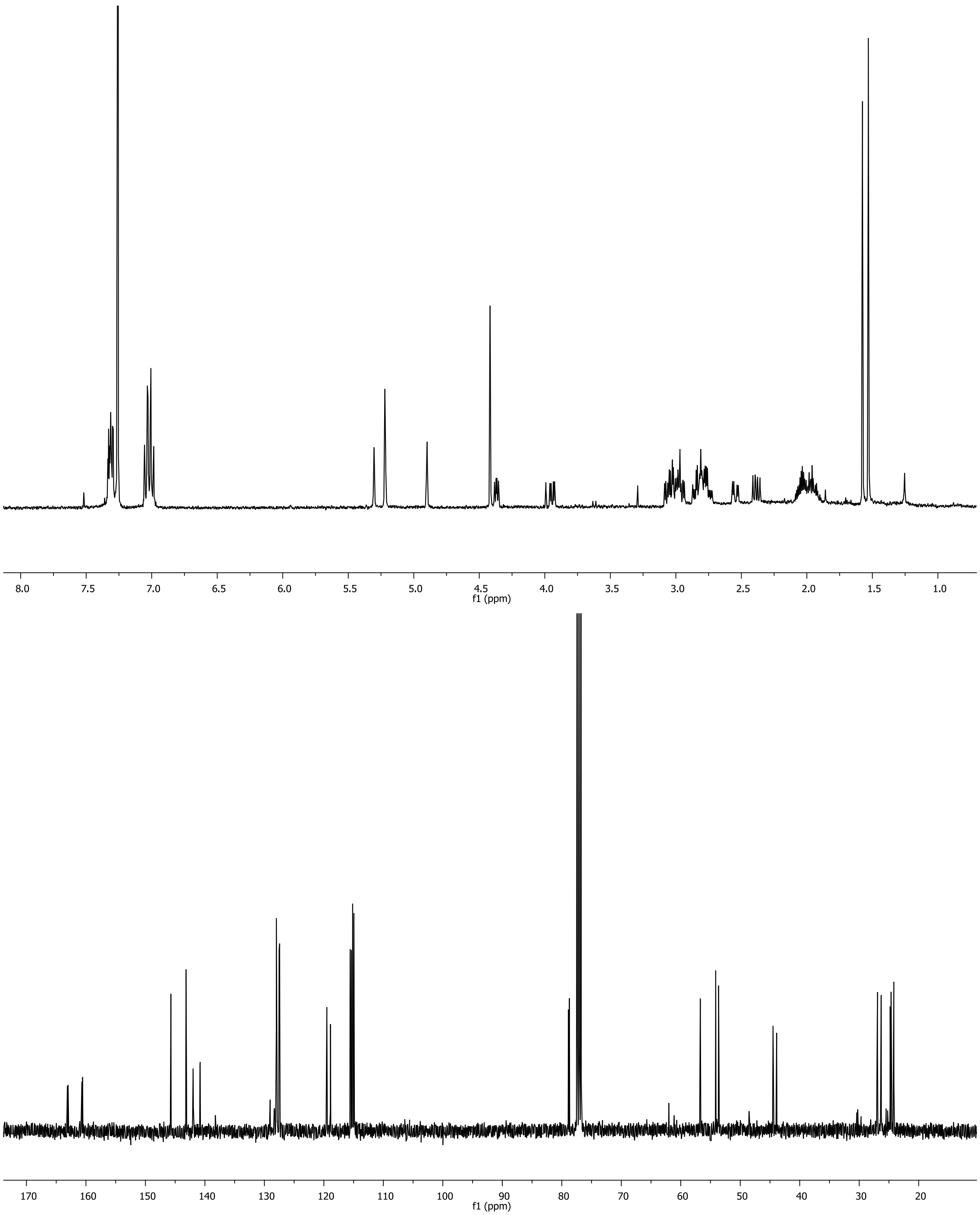
52



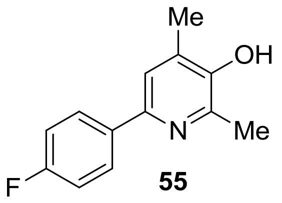
^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **52**



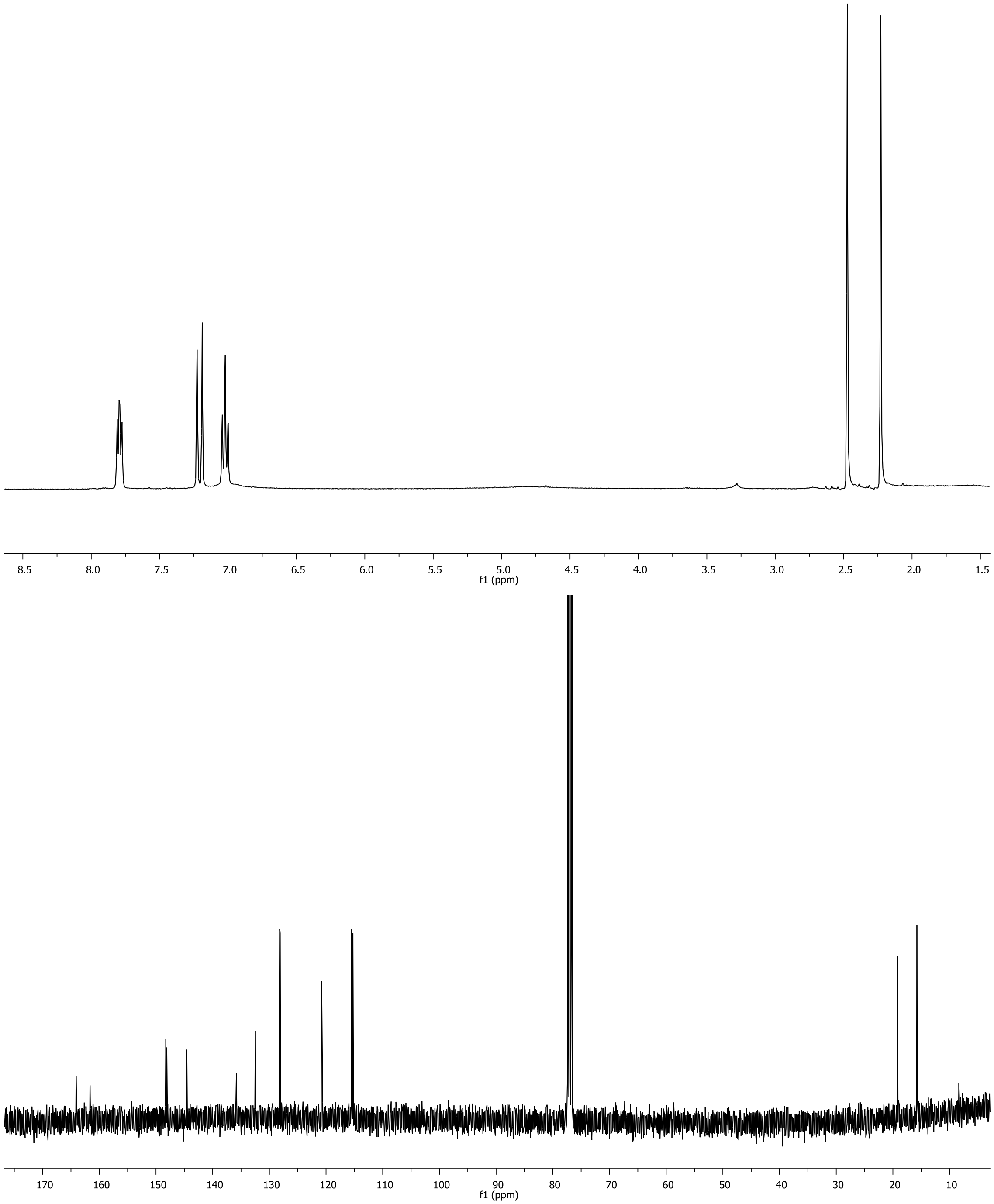
54



^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **54** (inseparable mixture of two diastereomers)



55



^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **55**