Indolizinones as Useful Scaffolds: Fundamental Reactivity and the Relay of Stereochemical Information

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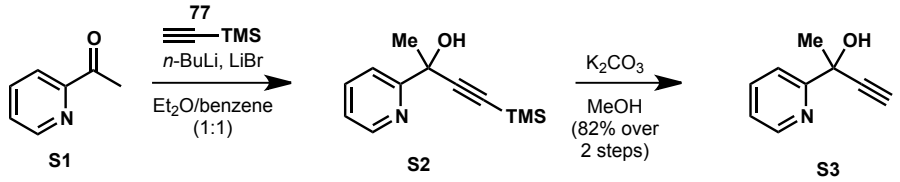
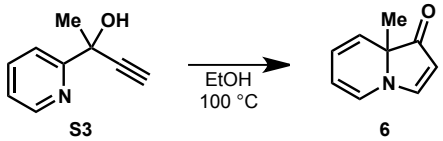
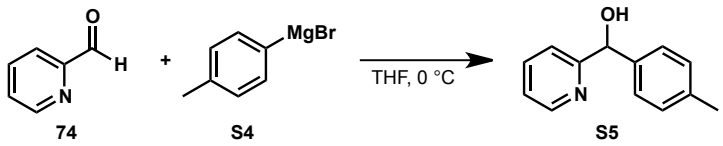
Unless otherwise stated, reactions were performed in flame-dried glassware fitted with rubber septa under a nitrogen atmosphere and were stirred with Telflon-coated magnetic stirring bars. Liquid reagents and solvents were transferred via syringe using standard Schlenk techniques. Tetrahydrofuran (THF), diethyl ether, benzene, toluene, and triethylamine were dried over alumina under a nitrogen atmosphere in a GlassContour solvent system. Dichloromethane (DCM) was distilled over calcium hydride. All other solvents and reagents were used as received unless otherwise noted. Reaction temperatures above 23 °C refer to oil or sand bath temperatures, which were controlled by an OptiCHEM temperature modulator. Thin layer chromatography was performed using SiliCycle silica gel 60 F-254 precoated plates (0.25 mm) and visualized by UV irradiation and anisaldehyde or potassium permanganate stain. SiliCycle Silica-P silica gel (particle size 40-63 μm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AVB-400, DRX-500, AV-500 and AV-600 MHz spectrometers with ^{13}C operating frequencies of 100, 125, 125, and 150 MHz, respectively. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal ($CDCl_3$; δ = 7.26 for ^{1}H NMR and δ = 77.0 for ^{13}C NMR; C_6D_6; δ = 7.15 for ^{1}H NMR and δ = 128.39 for ^{13}C NMR). Data for ^{1}H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants, number of hydrogens). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), m (multiplet), br (broad). IR spectra were recorded on a Nicolet MAGNA-IR 850 spectrometer and are reported in frequency of absorption (cm^{-1}). Only selected IR absorbencies are reported. High resolution mass spectral data were obtained from the Mass Spectral Facility at the University of California, Berkeley.



Tertiary alcohol S3: *n*-Butyllithium (5.60 mL, 14.0 mmol, 2.5 M in hexanes) was added dropwise to trimethylsilylacetylene (2.14 mL, 15.0 mmol) in Et_2O (10.0 mL) at 0 °C, and the resulting mixture was stirred for 30 min at this temperature. The lithium acetylide solution was added dropwise to a vigorously stirred mixture of 2-acetylpyridine (**S1**) (1.12 mL, 10.0 mmol) and lithium bromide (2.60 g, 30.0 mmol) in a 1:1 mixture of Et_2O and benzene (total volume = 60.0 mL). The reaction mixture was stirred at ambient temperature for 12 h at which point a saturated $NH_4Cl_{(aq)}$ solution (30 mL) was added to quench the reaction. The aqueous layer was extracted with EtOAc (3 x 40 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to afford the trimethylsilyl alkyne (**S2**), which was used without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.74 (s, 1H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.26 (s, 1H), 5.49 (s, 1H), 1.75 (s, 3H), 0.16 (s, 9H). Potassium carbonate (3.00 g, 21.7 mmol) was added to crude trimethylsilyl alkyne **S2** in MeOH (100 mL), and the mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated and the residue was taken up in water (30 mL) and EtOAc (30 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to afford tertiary alcohol **S3** in 82% yield over 2 steps (1.21 g, 8.23 mmol). **R_f** (3:1 hexanes/EtOAc) 0.29; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.50 – 8.40 (m, 1H), 7.69 (td, *J* = 7.8, 1.7 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.24 – 7.15 (m, 1H), 5.53 (s, 1H), 2.51 (s, 1H), 1.73 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.2, 147.3, 137.3, 122.7, 119.7, 86.9, 71.8, 68.3, 31.7; **HRMS** (EI+) calcd for [C_9H_9NO]: *m/z* 147.0684, found 147.0684.

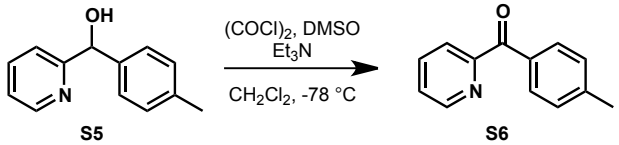


Methyl indolizinone 6: A solution of tertiary alcohol **S3** (77.0 mg, 0.523 mmol) in EtOH (500 µL) was sparged with N_2 for 5 min. The reaction vessel, a 4 mL vial, was equipped with a green Teflon-lined cap and Telfon tape and heated at 100 °C for 4 h. The reaction mixture was cooled to room temperature and concentrated to provide indolizinone **6** in 97% yield (75.0 mg, 0.507 mmol). $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.31; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.75 (d, J = 3.6 Hz, 1H), 6.36 (d, J = 7.0 Hz, 1H), 5.86 (dt, J = 23.6, 7.3 Hz, 2H), 5.40 (t, J = 6.2 Hz, 1H), 5.05 (d, J = 3.6 Hz, 1H), 1.31 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 204.5, 159.3, 124.5, 123.0, 122.0, 108.2, 97.6, 66.8, 24.3; **HRMS** (ESI+) calcd for $[C_9H_{10}ON]^+$ $(M-H)^+$: *m/z* 148.0757, found 148.0757.



74 **S4** **S5**

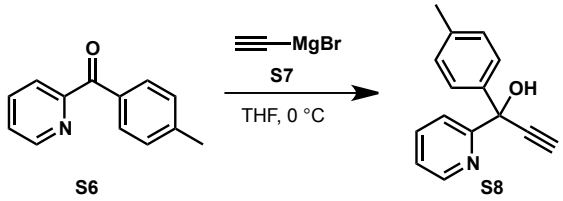
Secondary alcohol S5: *p*-tolylmagnesium bromide (5.50 mL, 5.50 mmol, 1.0 M) was added to pyridine-2-carboxaldehyde (**74**, 478 µL, 5.00 mmol) in THF (50 mL) at 0 °C. After 1 h, the reaction was quenched by the addition of a saturated $NH_4Cl_{(aq)}$ solution (30 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to afford secondary alcohol **S5** in 86% yield (862 mg, 4.33 mmol). **S5** was taken on without further purification. $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.29; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.09 (d, J = 0.7 Hz, 1H), 8.56 (d, J = 4.9 Hz, 1H), 7.62 (td, J = 7.7, 1.5 Hz, 1H), 7.29 – 7.24 (m, 2H), 7.19 (dd, J = 7.2, 5.1 Hz, 1H), 7.15 (t, J = 7.8 Hz, 3H), 5.74 (s, 1H), 2.32 (s, 3H); **HRMS** (ESI+) calcd for $[C_{13}H_{14}ON]^+$ $(M-H)^+$: *m/z* 200.1070, found 200.1068.



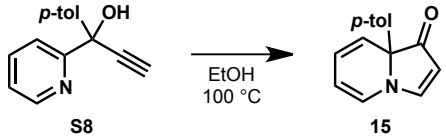
S5 **S6**

Ketone S6: DMSO (1.23 mL, 17.3 mmol) was added dropwise to oxalyl chloride (755 µL, 8.66 mmol) in CH_2Cl_2 (25 mL) at -78 °C. After 30 min, alcohol **S5** (862 mg, 4.33 mmol) in CH_2Cl_2 (5.0 mL) was added dropwise at -78 °C. The reaction mixture was stirred for 30 min at this

temperature. Et_3N (4.80 mL, 34.6 mmol) was added at -78 °C. The cold bath was allowed to gradually expire as the reaction mixture was stirred for 4 h. The reaction was quenched with water (30 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layer was washed with water, dried over $MgSO_4$ and concentrated to afford a brown oil. The crude oil was purified via flash chromatography (4:1 hexanes/EtOAc) to provide **S6** as a yellow oil in 58% yield (493 mg, 2.49 mmol). **R_f** (3:1 hexanes/EtOAc) 0.53; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.70 (d, *J* = 4.7 Hz, 1H), 7.98 (dd, *J* = 13.7, 8.0 Hz, 3H), 7.88 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.48 – 7.43 (m, 1H), 7.26 (t, *J* = 6.1 Hz, 2H), 2.41 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 193.5, 155.4, 148.4, 143.8, 137.0, 133.6, 131.2, 128.8, 125.9, 124.5, 21.7; **HRMS** (ESI+) calcd for $[C_{13}H_{12}ON]^+$ $(M-H)^+$: *m/z* 198.0913, found 198.0913.

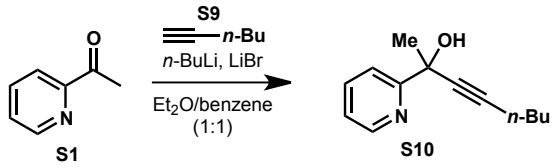


Tertiary alcohol S8: Ethynylmagnesium bromide (**S7**, 5.20 mL, 2.62 mmol, 2.5 M in THF) was added dropwise to ketone **S6** (470 mg, 2.38 mmol) in THF (20.0 mL) at 0 °C. The reaction mixture was stirred for 1.5 h at which point the reaction was quenched by the addition of a saturated $NH_4Cl_{(aq)}$ solution (30 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to afford tertiary alcohol **S8** in 94% yield (498 mg, 2.23 mmol). **HRMS** (ESI+) calcd for $[C_{15}H_{14}ON]^+$ $(M-H)^+$: *m/z* 224.1070, found 224.1068. Crude **S8** was taken on without further purification.

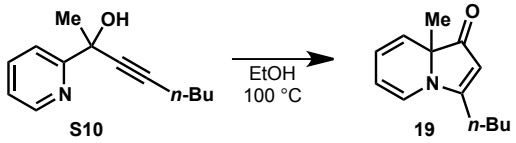


***p*-tolyl indolizinone 15:** A solution of tertiary alcohol **S8** (75.5 mg, 0.339 mmol) in EtOH (500 μL) was sparged with N_2 for 5 min. The reaction vessel, a 4 mL vial, was equipped with a green Teflon-lined cap and Teflon tape and heated at 100 °C for 4 h. The reaction mixture was cooled

to room temperature and concentrated to provide indolizinone **15** in 98% yield (74.0 mg, 0.332 mmol). **R_f** (3:1 hexanes/EtOAc) 0.38; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 3.7 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 2H), 7.13 (d, *J* = 8.2 Hz, 2H), 6.51 (d, *J* = 7.0 Hz, 1H), 6.24 (d, *J* = 9.3 Hz, 1H), 6.00 (dd, *J* = 9.3, 5.5 Hz, 1H), 5.40 (s, 1H), 5.07 (d, *J* = 3.7 Hz, 1H), 2.30 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.6, 161.1, 137.7, 136.5, 129.3, 125.6, 124.3, 122.9, 122.2, 109.2, 98.3, 70.4, 21.0; **HRMS** (ESI+) calcd for $[C_{15}H_{14}ON]^+$ $(M-H)^+$: *m/z* 224.1070, found 224.1070.

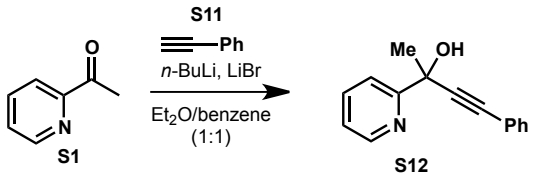


Internal alkyne S10: *n*-Butyllithium (5.60 mL, 14.0 mmol, 2.5 M in hexanes) was added dropwise to 1-hexyne (1.12 mL, 15.0 mmol) in Et_2O (10.0 mL) at 0 °C, and the resulting mixture was stirred for 30 min at this temperature. The lithium acetylide solution was added dropwise to a vigorously stirred mixture of 2-acetylpyridine (**S1**) (1.12 mL, 10.0 mmol) and lithium bromide (2.60 g, 30.0 mmol) in a 1:1 mixture of Et_2O and benzene (total volume = 60.0 mL). The reaction mixture was stirred at ambient temperature for 12 h at which point a saturated $NH_4Cl_{(aq)}$ solution (30 mL) was added to quench the reaction. The aqueous layer was extracted with EtOAc (3 x 40 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to afford alkyne **S10** [**R_f** (3:1 hexanes/EtOAc) 0.43] in 83% yield (1.68 g, 8.28 mmol), which was used without further purification.

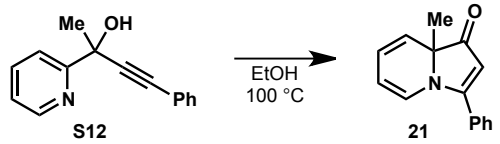


***n*-Butyl indolizinone 19:** A solution of the tertiary alcohol (200 mg, 0.984 mmol) in EtOH (9.0 mL) was sparged with N_2 for 5 min. The reaction vessel, a 20 mL vial, was equipped with a green Teflon-lined cap and Teflon tape and heated at 100 °C for 4 h. The reaction mixture was cooled to room temperature and concentrated to provide indolizinone **19** in 98% yield (196 mg, 0.964 mmol). **R_f** (3:1 hexanes/EtOAc) 0.46; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.43 (d, *J* = 7.1 Hz,

1H), 5.89 (d, J = 4.2 Hz, 2H), 5.45 (s, 1H), 4.93 (s, 1H), 2.50 – 2.45 (m, 2H), 1.64 (s, 2H), 1.43 (d, J = 7.5 Hz, 2H), 1.30 (s, 3H), 0.96 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 203.1, 175.2, 124.3, 121.8, 121.5, 108.9, 96.6, 67.7, 28.6, 26.8, 24.2, 22.4, 13.6; **HRMS** (EI+) calcd for [$C_{13}H_{17}NO$]: *m/z* 203.1310, found 203.1310.

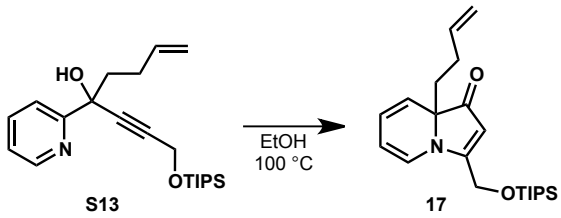


Tertiary alcohol S12: *n*-Butyllithium (5.60 mL, 14.0 mmol, 2.5 M in hexanes) was added dropwise to phenylacetylene **(S11**, 1.65 mL, 15.0 mmol) in Et_2O (10.0 mL) at 0 °C, and the resulting mixture was stirred for 30 min at this temperature. The lithium acetylide solution was added dropwise to a vigorously stirred mixture of 2-acetylpyridine (**S1**, 1.12 mL, 10.0 mmol) and lithium bromide (2.60 g, 30.0 mmol) in a 1:1 mixture of Et_2O and benzene (total volume = 60.0 mL). The reaction mixture was stirred at ambient temperature for 12 h at which point a saturated $NH_4Cl_{(aq)}$ solution (30 mL) was added to quench the reaction. The aqueous layer was extracted with EtOAc (3 x 40 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to afford alkyne **S12** [**R_f** (3:1 hexanes/EtOAc) 0.40] in 98% yield (2.20 g, 9.82 mmol), which was used without further purification.



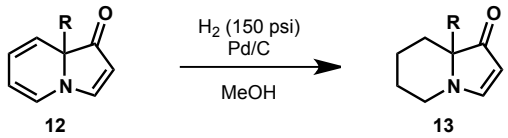
Phenyl indolizinone 21: A solution of tertiary alcohol **S12** (200 mg, 0.896 mmol) in EtOH (9.0 mL) was sparged with N_2 for 5 min. The reaction vessel, a 20 mL vial, was equipped with a green Teflon-lined cap and Teflon tape and heated at 100 °C for 4 h. The reaction mixture was cooled to room temperature and concentrated to provide indolizinone **21** in 98% yield (196 mg, 0.878 mmol). **R_f** (3:1 hexanes/EtOAc) 0.53; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.51 (s, 6H), 6.53 (d, J = 7.3 Hz, 1H), 5.97 – 5.89 (m, 2H), 5.38 (s, 1H), 5.18 (s, 1H), 1.45 (s, 3H); **^{13}C NMR** (151

MHz, $CDCl_3$) δ 202.9, 172.4, 130.9, 129.6, 129.0, 128.0, 123.8, 123.1, 121.8, 108.7, 98.8, 68.5, 24.9; **HRMS** (ESI+) calcd for $[C_{15}H_{14}ON]^+$ $(M-H)^+$: *m/z* 224.1070, found 224.1070.

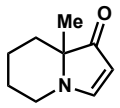


Indolizinone 17: A solution of tertiary alcohol **S13** (300 mg, 0.803 mmol) in EtOH (5.0 mL) was sparged with N_2 for 5 min. The reaction vessel, a 20 mL vial, was equipped with a green Teflon-lined cap and Telfon tape and heated at 100 °C for 4 h. The reaction mixture was cooled to room temperature and concentrated to provide indolizinone **17** in 99% yield (298 mg, 0.800 mmol). $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.83; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 6.48 (d, *J* = 7.2 Hz, 1H), 5.87 (dd, *J* = 17.9, 7.3 Hz, 2H), 5.69 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.40 (s, 1H), 5.14 (s, 1H), 4.95 (dd, *J* = 17.1, 1.7 Hz, 1H), 4.90 (dd, *J* = 10.2, 1.6 Hz, 1H), 4.65 (d, *J* = 0.5 Hz, 2H), 2.04 (m, 4H), 1.80 (d, *J* = 5.7 Hz, 2H), 1.15 (dd, *J* = 14.3, 6.7 Hz, 3H), 1.08 (d, *J* = 6.2 Hz, 18H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 202.7, 137.7, 124.0, 123.0, 122.2, 114.8, 109.5, 97.7, 71.0, 58.6, 37.6, 26.5, 17.9, 11.9; **IR** (film) υ_{max} 2943, 2866, 1677, 1572, 1457, 1131 cm^{-1}; **HRMS** (ESI+) calcd for $[C_{22}H_{36}O_2NSi]^+$ $(M-H)^+$: *m/z* 374.2510, found 374.2513.

Representative procedure for the partial hydrogenation of indolizinones:

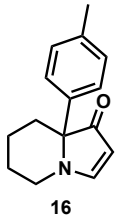


Palladium (10 wt %) on activated carbon was added to a solution of indolizinone **12** (10.0 mg, 0.0679 mmol) in methanol (600 μL). The mixture was stirred vigorously under an atmosphere are hydrogen (200 psi) in a Parr bomb for 12 h. The reaction mixture was filtered through a plug of celite and concentrated to provide **13**.



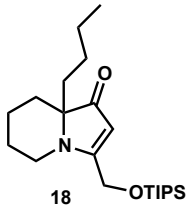
14

Vinylogous amide 14: The standard hydrogenation protocol afforded **14** in 98% yield. $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.20; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.71 (d, *J* = 3.0 Hz, 1H), 5.04 (d, *J* = 3.1 Hz, 1H), 3.55 (dd, *J* = 13.4, 5.0 Hz, 1H), 3.37 (td, *J* = 13.2, 3.2 Hz, 1H), 1.82 (d, *J* = 13.6 Hz, 1H), 1.79 – 1.71 (m, 3H), 1.65 (dd, *J* = 13.4, 3.2 Hz, 2H), 1.40 – 1.29 (m, 3H), 1.26 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 207.44, 161.65, 94.60, 65.43, 46.47, 32.64, 27.95, 19.81, 17.15; **HRMS** (ESI+) calcd for $[C_9H_{14}ON]^+$ $(M-H)^+$: *m/z* 152.1070, found 152.1071.



16

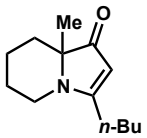
Vinylogous amide 16: The standard hydrogenation protocol afforded **16** in 94% yield. $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.35; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.96 (d, *J* = 3.2 Hz, 1H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 8.3 Hz, 2H), 5.01 (d, *J* = 3.2 Hz, 1H), 3.64 (dd, *J* = 13.4, 4.9 Hz, 1H), 3.40 – 3.34 (m, 1H), 2.66 (d, *J* = 14.2 Hz, 1H), 2.32 (s, 3H), 1.71 (t, *J* = 15.0 Hz, 3H), 1.62 – 1.56 (m, 1H), 1.49 (s, 1H), 1.46 – 1.39 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 204.9, 163.4, 137.2, 131.8, 129.8, 125.9, 94.0, 71.4, 47.0, 32.5, 28.1, 21.0, 20.3; **HRMS** (ESI+) calcd for $[C_{15}H_{18}ON]^+$ $(M-H)^+$: *m/z* 228.1383, found 228.1383.



18

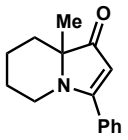
Vinylogous amide 18: The standard hydrogenation protocol afforded **18** in 78% yield. $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.81; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.14 (s, 1H), 4.56 (s, 2H), 3.89 (s, 1H),

3.79 (d, *J* = 12.0 Hz, 1H), 3.46 (s, 2H), 3.07 (s, 1H), 1.91 – 1.76 (m, 4H), 1.76 – 1.59 (m, 6H), 1.38 (d, *J* = 4.1 Hz, 4H), 1.22 (dd, *J* = 15.7, 7.7 Hz, 3H), 1.13 (dd, *J* = 14.3, 7.1 Hz, 3H), 1.10 – 0.99 (m, 18H), 0.90 (d, *J* = 6.5 Hz, 2H), 0.81 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 205.5, 174.7, 96.2, 70.5, 59.0, 42.0, 33.3, 31.0, 27.8, 24.8, 22.8, 19.8, 17.8, 13.9, 11.8; **HRMS** (ESI+) calcd for $[C_{22}H_{42}O_2NSi]^+$ $(M-H)^+$: *m/z* 380.2979, found 380.2993.



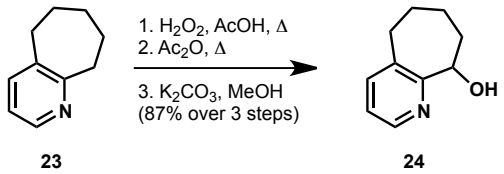
20

Vinylogous amide 20: The standard hydrogenation protocol afforded **20** in 93% yield. **R_f** (3:1 hexanes/EtOAc) 0.43; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.95 (s, 1H), 3.74 (dd, *J* = 13.8, 4.4 Hz, 1H), 3.14 (d, *J* = 2.9 Hz, 1H), 2.39 (td, *J* = 7.5, 2.8 Hz, 2H), 1.83 (d, *J* = 13.6 Hz, 1H), 1.78 – 1.68 (m, 2H), 1.66 (d, *J* = 13.3 Hz, 1H), 1.56 (dd, *J* = 15.1, 7.2 Hz, 2H), 1.40 (dd, *J* = 14.9, 7.4 Hz, 2H), 1.36 – 1.29 (m, 2H), 1.25 (s, 3H), 0.94 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 205.2, 175.7, 94.8, 66.5, 40.8, 32.9, 29.2, 27.7, 27.4, 22.4, 19.7, 17.6, 13.7; **HRMS** (ESI+) calcd for $[C_{13}H_{22}ON]^+$ $(M-H)^+$: *m/z* 208.1696, found 208.1696.



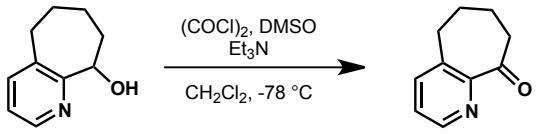
22

Vinylogous amide 22: The standard hydrogenation protocol afforded **22** in 99% yield. **R_f** (3:1 hexanes/EtOAc) 0.51; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 4.0 Hz, 3H), 7.41 (d, *J* = 3.9 Hz, 2H), 5.17 (s, 1H), 3.84 (dd, *J* = 13.6, 4.1 Hz, 1H), 3.22 (d, *J* = 2.8 Hz, 1H), 1.93 (d, *J* = 13.4 Hz, 1H), 1.72 (dd, *J* = 20.4, 7.5 Hz, 2H), 1.64 (d, *J* = 14.3 Hz, 1H), 1.52 (dd, *J* = 13.0, 4.3 Hz, 1H), 1.39 (s, 4H), 1.24 (dt, *J* = 9.7, 4.4 Hz, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 205.4, 173.7, 130.9, 130.3, 128.8, 127.9, 97.1, 66.8, 42.3, 33.1, 27.8, 19.8, 18.0; **HRMS** (ESI+) calcd for $[C_{15}H_{18}ON]^+$ $(M-H)^+$: *m/z* 228.1383, found 228.1386.



23 **24**

Alcohol 24: H_2O_2 (959 µL, 30% in H_2O) was added dropwise to pyridine **23** (700 mg, 4.75 mmol) in AcOH (2.66 mL). The reaction mixture was heated to 70 °C for 12 h before it was cooled and concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (4.5 mL) and sodium carbonate (2.8 g) was added slowly in portions. The mixture was stirred for 2 h at room temperature. The solids were removed via filtration, and the organic layer was concentrated under reduced pressure to afford the *N*-oxide. The *N*-oxide was taken up in Ac_2O (5.0 mL). The mixture was stirred at 90 °C for 36 h before being cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in water (13 mL) and potassium carbonate (1.33 g) was added in portions over 10 min. Next, MeOH (3.0 mL) was added and the reaction mixture was stirred at 70 °C. After 24 h, the reaction mixture was cooled to room temperature and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were concentrated to provide alcohol **24** in 87% yield over 3 steps (675 mg, 4.13 mmol), which was used without further purification. $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.48; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 4.9, 1.1 Hz, 1H), 7.44 (d, *J* = 7.3 Hz, 1H), 7.12 (dd, *J* = 7.4, 4.9 Hz, 1H), 4.76 (dd, *J* = 11.2, 2.0 Hz, 1H), 2.82 (s, 1H), 2.77 – 2.69 (m, 2H), 2.51 (d, *J* = 4.8 Hz, 1H), 2.26 – 2.20 (m, 1H), 2.07 (dd, *J* = 10.8, 7.7 Hz, 1H), 2.02 – 1.94 (m, 2H), 1.91 – 1.78 (m, 2H), 1.76 – 1.65 (m, 1H), 1.47 – 1.35 (m, 1H), 1.22 (dd, *J* = 13.1, 2.4 Hz, 1H). [1]

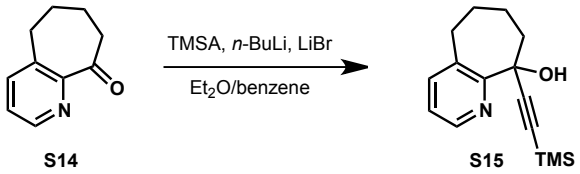


24 **S14**

Ketone S14: Oxalyl chloride (217 µL, 2.48 mmol) was added dropwise to DMSO (354 µL, 4.97 mmol) in CH_2Cl_2 (18 mL) at -78 °C. The mixture was stirred at this temperature for 15 min, then

[1] Gudmundsson, K.; Boggs, S. D. U.S. Patent Appl. 11/574,583, **2007**.

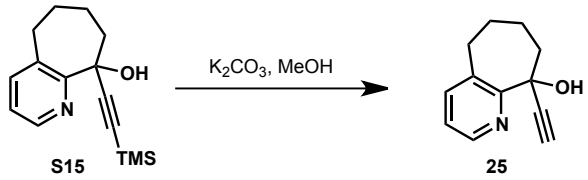
a solution of alcohol **24** (338 mg, 2.07 mmol) in CH_2Cl_2 (2.0 mL) was added dropwise. The reaction mixture was stirred for 30 min at -78 °C. Et_3N (1.38 mL, 9.94 mmol) was added at -78 °C, and the reaction mixture was stirred as the cold bath was allowed to gradually expire. The reaction was quenched with water (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layer was washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford ketone **S14** in quantitative yield. The crude ketone was used without further purification. $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.52; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.64 (d, *J* = 4.7 Hz, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.34 (d, *J* = 4.7 Hz, 1H), 3.10 (dd, *J* = 7.3, 4.9 Hz, 2H), 2.94 – 2.89 (m, 2H), 2.83 – 2.78 (m, 2H), 1.95 – 1.86 (m, 2H). [2]



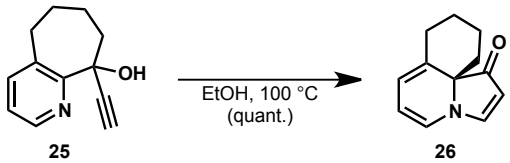
Propargylic alcohol S15: *n*-Butyllithium (1.27 mL, 3.18 mmol, 2.5 M in hexanes) was added dropwise to trimethylsilylacetylene (604 μL, 4.24 mmol) in Et_2O (3.0 mL) at 0 °C and stirred at this temperature for 30 min. The lithium acetylide solution was added dropwise to a vigorously stirred mixture of ketone **S14** (342 mg, 2.12 mmol) and flame-dried lithium bromide (552 mg, 6.36 mmol) in a 1:1 mixture of benzene and Et_2O (total volume = 20 mL). The mixture was stirred for 36 h at ambient temperature. The reaction was quenched with a saturated ammonium chloride solution (20 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine (40 mL), dried over $MgSO_4$ and concentrated under reduced pressure to provide tertiary alcohol **S15** in 53% yield (354 mg, 1.12 mmol), which was used without further purification. $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.46; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.32 (d, *J* = 4.8 Hz, 1H), 7.48 (d, *J* = 7.4 Hz, 1H), 7.17 (dd, *J* = 7.4, 4.8 Hz, 1H), 3.29 (s, 1H), 2.70 (d, *J* = 6.0 Hz, 1H), 2.28 – 2.22 (m, 2H), 2.01 – 1.95 (m, 2H), 1.87 (s, 2H), 1.71 – 1.62 (m, 1H), 1.56 (d, *J* = 2.6 Hz, 1H), 0.16 – 0.13 (m, 10H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 158.7, 143.8, 138.9, 136.5, 123.1, 105.9, 90.5, 71.4, 40.5, 34.2, 27.5, 27.5, -0.1; **IR** (film) υ_{max}

[2] Gudmundsson, K.; Boggs, S. D. U.S. Patent Appl. 11/574,583, **2007**.

3350, 2930, 2175, 1398, 843 cm^{-1}; **HRMS** (ESI+) calcd for $[C_{15}H_{22}ONSi]^+$ $(M-H)^+$: *m/z* 260.1465, found 260.1463.

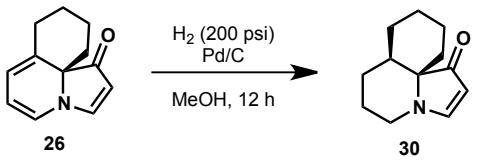


Tertiary alcohol 25: Potassium carbonate (288 mg, 2.08 mmol) was added to a solution of trimethylsilyl alkyne **S15** (270 mg, 1.04 mmol) in MeOH (10 mL). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated and diluted with water (20 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with bring, dried over $MgSO_4$ and concentrated under reduced pressure to afford propargylic alcohol **25** in 80% yield (147 mg, 0.785 mmol). $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.37; ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 8.34 (d, *J* = 4.9 Hz, 1H), 7.50 (d, *J* = 7.4 Hz, 1H), 7.19 (dd, *J* = 7.4, 4.9 Hz, 1H), 3.30 (t, *J* = 13.7 Hz, 1H), 2.72 (dd, *J* = 14.6, 6.1 Hz, 1H), 2.58 (s, 1H), 2.29 (dd, *J* = 19.8, 17.0 Hz, 2H), 2.07 – 1.98 (m, 3H), 1.62 (dd, *J* = 13.5, 2.5 Hz, 1H), 1.31 – 1.23 (m, 1H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 146.6, 143.8, 139.0, 136.4, 123.2, 84.6, 73.7, 71.0, 40.3, 34.3, 27.3, 27.3; **IR** (film) υ_{max} 3418, 2950, 1647, 1047 cm^{-1}; **HRMS** (ESI+) calcd for $[C_{12}H_{14}ON]^+$ $(M-H)^+$: *m/z* 188.1070, found 188.1068.



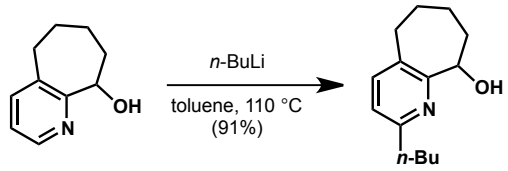
Indolizinone 26: A solution of tertiary alcohol **25** (73.5 mg, 0.393 mmol) in EtOH (2.0 mL) was sparged with N_2 for 5 min, then heated to 100 °C. After 4 h, the reaction mixture was cooled to room temperature and concentrated to provide a crude yellow oil. The oil was purified via flash chromatography (9:1 hexanes/EtOAc) to afford indolizinone **26** in 95% yield (70.1 mg, 0.374 mmol). $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.47; ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 7.65 (d, *J* = 3.6 Hz, 1H), 6.18 (d, *J* = 7.1 Hz, 1H), 5.43 (d, *J* = 5.7 Hz, 1H), 5.14 (t, *J* = 6.5 Hz, 1H), 4.93 (d, *J* = 3.6 Hz,

1H), 3.24 (d, *J* = 4.2 Hz, 1H), 2.32 (d, *J* = 13.5 Hz, 1H), 2.23 (dd, *J* = 11.9, 3.4 Hz, 1H), 2.08 – 1.94 (m, 3H), 1.57 (dd, *J* = 16.0, 6.9 Hz, 2H), 1.45 (d, *J* = 12.8 Hz, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 205.1, 158.9, 140.5, 124.0, 114.1, 107.2, 95.7, 72.0, 36.8, 31.2, 30.7, 19.3; **IR** (film) υ_{max} 3467, 2076, 1640 cm^{-1}; **HRMS** (ESI+) calcd for $[C_{12}H_{13}NO]^+$ (M-H)$^+$: *m/z* 188.1070, found 188.1069.



26 **30**

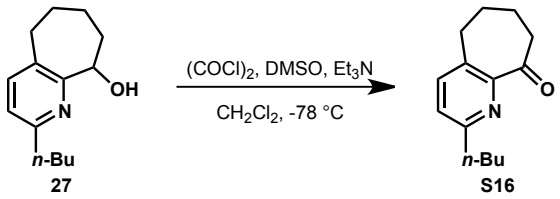
Tricycle 30: Palladium (4.0 mg, 10 wt %) on activated carbon was added to a solution of indolizinone **2** (64.7 mg, 0.0251 mmol) in methanol (400 µL). The mixture was stirred vigorously under an atmosphere are hydrogen (200 psi) in a Parr bomb for 12 h. The reaction mixture was filtered through a plug of celite and concentrated to provide **30** as a light yellow oil in 94% yield (4.5 mg, 0.0235 mmol). **R_f** (3:1 hexanes/EtOAc) 0.32; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.66 (d, *J* = 3.2 Hz, 1H), 4.98 (d, *J* = 3.1 Hz, 1H), 3.46 (d, *J* = 4.9 Hz, 1H), 3.29 – 3.24 (m, 1H), 2.50 (s, 2H), 2.35 (d, *J* = 13.4 Hz, 1H), 1.87 (ddd, *J* = 17.5, 13.2, 3.8 Hz, 1H), 1.75 (d, *J* = 12.9 Hz, 1H), 1.65 (d, *J* = 13.0 Hz, 1H), 1.62 – 1.51 (m, 2H), 1.48 – 1.42 (m, 2H), 1.38 (ddd, *J* = 18.6, 10.5, 6.3 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 207.7, 161.3, 95.1, 66.7, 46.0, 36.3, 27.0, 26.0, 25.5, 24.5, 19.6, 19.4; **IR** (film) υ_{max} 2926, 2854, 1540, 1445 cm^{-1}; **HRMS** (ESI+) calcd for $[C_{12}H_{18}ON]^+$ (M-H)$^+$: *m/z* 192.1383, found 192.1383.



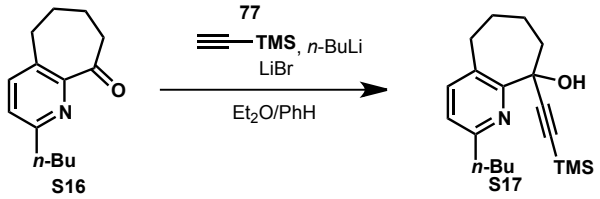
24 **27**

Trisubstituted pyridine 27: *n*-Butyllithium (2.51 mL, 6.27 mmol, 2.5 M in hexanes) was added dropwise to pyridine **24** (500 mg, 3.06 mmol) in toluene (30 mL). The Schlenk flask was sealed and heated to 110 °C. After 18 h, the reaction mixture was cooled to room temperature. The reaction was quenched by the addition of MeOH (2.0 mL) followed by a saturated $NH_4Cl_{(aq)}$

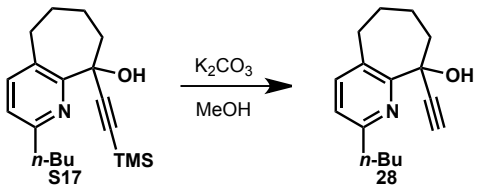
solution (20 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure to provide **27** in 91% yield (611 mg, 2.78 mmol) as a brown oil that was used without further purification. $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.29; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.23 (s, 1H), 4.70 (dd, *J* = 11.2, 2.2 Hz, 1H), 2.79 – 2.71 (m, 2H), 2.69 (dd, *J* = 11.6, 8.3 Hz, 2H), 2.25 – 2.17 (m, 1H), 2.04 (s, 1H), 1.95 (ddd, *J* = 9.7, 4.7, 1.9 Hz, 1H), 1.82 (dt, *J* = 12.8, 2.6 Hz, 1H), 1.74 – 1.66 (m, 2H), 1.42 – 1.32 (m, 3H), 1.27 – 1.17 (m, 1H), 0.93 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.9, 157.1, 137.6, 132.4, 120.7, 72.0, 37.1, 36.4, 33.9, 31.6, 29.1, 27.2, 22.4, 13.9; **IR** (film) υ_{max} 3353, 2927, 2854, 1594, 1470, 1064 cm^{-1}; **HRMS** (ESI+) calcd for $[C_{14}H_{22}ON]^+$ $(M-H)^+$: *m/z* 220.1696, found 220.1695.



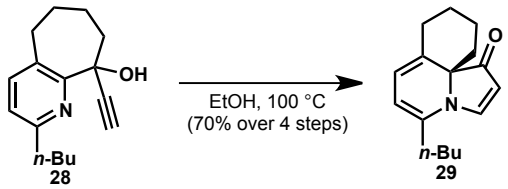
Ketone S16: Oxalyl chloride (836 μL, 9.58 mmol) was added dropwise to DMSO (1.37 mL, 19.2 mmol) in CH_2Cl_2 (40 mL) at -78 °C. The mixture was stirred at this temperature for 15 min, then, alcohol **27** (1.05 g, 4.79 mmol) in CH_2Cl_2 (5.0 mL) was added dropwise. The reaction mixture was stirred for 30 min at -78 °C. Et_3N (5.30 mL, 38.3 mmol) was added at -78 °C, and the reaction mixture was stirred as the cold bath was allowed to gradually expire. The reaction was quenched with water (40 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layer was washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford ketone **S16**. The crude ketone was used without further purification. $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.39; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 1H), 2.84 (dd, *J* = 13.8, 5.9 Hz, 4H), 2.79 – 2.73 (m, 2H), 1.90 – 1.82 (m, 4H), 1.68 (ddd, *J* = 12.7, 6.7, 4.0 Hz, 2H), 1.38 (dd, *J* = 14.9, 7.4 Hz, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 205.4, 161.3, 154.4, 138.2, 133.1, 124.7, 40.5, 37.8, 32.1, 30.6, 25.1, 22.6, 21.5, 13.9; **IR** (film) υ_{max} 2931, 2860, 1698, 1590, 1461 cm^{-1}; **HRMS** (ESI+) calcd for $[C_{14}H_{20}ON]^+$ $(M-H)^+$: *m/z* 218.1539, found 218.1538.



Alkyne S17: *n*-Butyllithium (948 μL, 2.37 mmol, 2.5 M in hexanes) was added dropwise to trimethylsilylacetylene (**77**, 451 μL, 3.17 mmol) in Et_2O (3.0 mL) at 0 °C and stirred at this temperature for 30 min. The lithium acetylide solution was added dropwise to a vigorously stirred mixture of ketone **S16** (344 mg, 1.58 mmol) and lithium bromide (412 mg, 4.74 mmol) in a 1:1 mixture of benzene and Et_2O (total volume = 20 mL). The mixture was stirred for 36 h and ambient temperature. The reaction was quenched with a saturated $NH_4Cl_{(aq)}$ solution (20 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine (40 mL), dried over $MgSO_4$ and concentrated under reduced pressure to provide tertiary alcohol **S17**, which was used without further purification. $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.79; ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.6 Hz, 1H), 7.00 (d, *J* = 7.5 Hz, 1H), 3.23 (t, *J* = 13.6 Hz, 1H), 2.80 – 2.72 (m, 3H), 2.66 (dd, *J* = 14.7, 5.6 Hz, 1H), 2.24 (d, *J* = 12.4 Hz, 2H), 2.00 (s, 2H), 1.70 (dd, *J* = 15.4, 7.7 Hz, 4H), 1.57 (d, *J* = 13.3 Hz, 3H), 1.38 (dd, *J* = 14.9, 7.4 Hz, 3H), 0.94 (d, *J* = 7.4 Hz, 3H), 0.16 (s, 9H); **IR** (film) υ_{max} 3423, 2929, 2857, 2156, 1387, 843 cm^{-1}; **HRMS** (ESI+) calcd for $[C_{19}H_{30}ONSi]^+$ $(M-H)^+$: *m/z* 316.2091, found 316.2088.

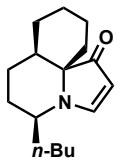


Tertiary alcohol 28: Potassium carbonate (281 mg, 2.03 mmol) was added to a solution of trimethylsilyl alkyne **S17** (320 mg, 1.02 mmol) in MeOH (10 mL). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated and diluted with water (20 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with bring, dried over $MgSO_4$ and concentrated under reduced pressure to afford propargylic alcohol **28**, which was used without further purification. $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.69; ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 7.6 Hz, 1H), 3.23 (s, 1H), 2.75 (dd, *J* = 13.8, 5.9 Hz, 3H), 2.28 (s, 2H), 2.04 – 1.97 (m, 2H), 1.70 (dd, *J* = 15.3, 7.8 Hz, 2H), 1.59 (d, *J* = 2.1 Hz, 1H), 1.37 (dd, *J* = 14.9, 7.4 Hz, 2H), 1.26 (d, *J* = 12.9 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H); ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 157.2, 156.8, 139.5, 133.2, 122.0, 84.9, 73.5, 70.8, 40.4, 36.9, 33.8, 31.4, 27.5, 27.4, 22.4, 13.9; **IR** (film) υ_{max} 3286, 2929, 2857, 1595, 1468, 1054 cm^{-1}; **HRMS** (ESI+) calcd for $[C_{16}H_{22}ON]^+$ $(M\text{-}H)^+$: *m/z* 244.1696, found 244.1693.



Indolizinone 29: A solution of tertiary alcohol **28** (53.0 mg, 0.218 mmol) in EtOH (1.0 mL) was sparged with N_2 for 5 min, then heated to 100 °C. After 4 h, the reaction mixture was cooled to room temperature and concentrated to provide a crude yellow oil. The oil was purified via flash chromatography (9:1 hexanes/EtOAc) to afford indolizinone **29** in 70% yield over 4 steps (from alcohol **27**). $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.65; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 3.7 Hz, 1H), 5.41 (d, *J* = 5.9 Hz, 1H), 5.04 (d, *J* = 5.9 Hz, 1H), 4.95 (d, *J* = 3.7 Hz, 1H), 3.71 (d, *J* =

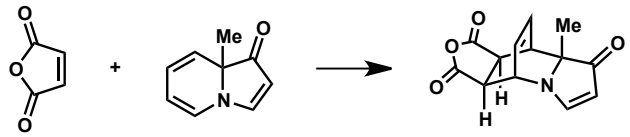
7.0 Hz, 1H), 3.28 (d, *J* = 4.5 Hz, 1H), 3.03 – 2.97 (m, 1H), 2.70 (s, 1H), 2.34 (d, *J* = 8.8 Hz, 2H), 2.21 (s, 1H), 2.16 – 2.10 (m, 1H), 2.08 (d, *J* = 3.6 Hz, 1H), 2.01 (s, 3H), 1.89 – 1.82 (m, 1H), 1.71 – 1.60 (m, 2H), 1.54 (dd, *J* = 15.5, 5.8 Hz, 3H), 1.47 (s, 3H), 1.39 (d, *J* = 12.5 Hz, 4H), 0.93 (dd, *J* = 9.2, 5.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 205.1, 155.9, 139.1, 134.6, 114.5, 106.0, 95.7, 72.9, 36.5, 31.3, 30.3, 29.9, 28.7, 22.1, 19.3, 13.8; **HRMS** (ESI+) calcd for $[C_{16}H_{22}ON]^+$ $(M\text{-}H)^+$: *m/z* 244.1696, found 244.1693.



31

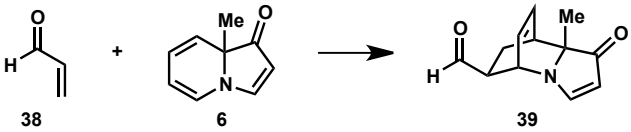
Tricycle 31: Palladium (10 wt %) on activated carbon was added to a solution of indolizinone **29** (10.0 mg, 0.0411 mmol) in methanol (400 μL). The mixture was stirred vigorously under an atmosphere are hydrogen (200 psi) in a Parr bomb for 12 h. The reaction mixture was filtered through a plug of celite and concentrated to provide **31** as a light yellow oil in 93% yield (9.4 mg, 0.038 mmol). **R_f** (3:1 hexanes/EtOAc) 0.54; **^{1}H NMR** (600 MHz, C_6D_6) δ 7.10 (d, *J* = 3.6 Hz, 1H), 5.20 (d, *J* = 3.6 Hz, 1H), 4.46 (s, 1H), 2.98 (tt, *J* = 13.4, 4.4 Hz, 1H), 2.71 – 2.63 (m, 1H), 2.09 (dd, *J* = 18.3, 11.1 Hz, 1H), 1.90 – 1.83 (m, 2H), 1.73 (dd, *J* = 14.9, 7.6 Hz, 2H), 1.53 (ddd, *J* = 11.2, 8.8, 5.2 Hz, 5H), 1.32 (s, 5H), 1.24 – 1.21 (m, 2H), 1.15 (dd, *J* = 7.1, 4.7 Hz, 4H), 0.82 (d, *J* = 7.3 Hz, 3H); **^{13}C NMR** (151 MHz, C_6D_6) δ 204.8, 154.8, 104.6, 100.6, 65.8, 50.8, 32.8, 31.2, 29.7, 26.8, 25.1, 24.9, 22.8, 19.9, 19.8, 14.6; **HRMS** (ESI+) calcd for $[C_{16}H_{26}ON]^+$ $(M\text{-}H)^+$: *m/z* 248.2009, found 248.2012.

Diels-Alder cycloaddition of methyl indolizinone with various dienophiles:



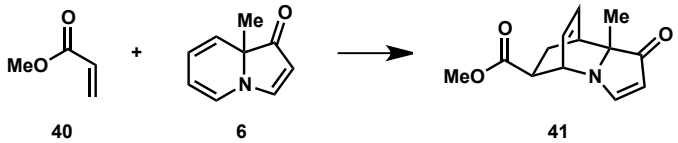
36 6 37

Anhydride 37: A solution of methylindolizinone **6** (5.0 mg, 0.034 mmol) and maleic anhydride (**36**, 4.0 mg, 0.041 mmol) in benzene (400 µL) was heated to 80 °C for 12 h in a 4 mL vial equipped with a green Teflon-lined cap and Teflon tape. The reaction mixture was cooled and concentrated to provide a light yellow oil, **37** (8.0 mg, 0.033 mmol) in 96% yield. $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.29; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 3.5 Hz, 1H), 6.61 – 6.53 (m, 2H), 5.66 (d, *J* = 3.6 Hz, 1H), 4.80 (d, *J* = 2.8 Hz, 1H), 3.59 – 3.53 (m, 1H), 3.29 (dd, *J* = 8.6, 4.4 Hz, 1H), 3.10 (dd, *J* = 8.6, 3.1 Hz, 1H), 1.16 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 206.6, 170.2, 169.8, 167.1, 133.6, 130.2, 112.3, 68.8, 52.9, 44.4, 39.6, 38.6, 22.8; **HRMS** (EI) calcd for $[C_{13}H_{11}O_4N]$ (M): *m/z* 245.0688, found 245.0691.



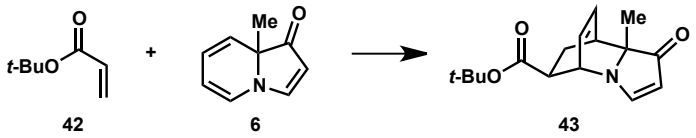
38 6 39

Aldehyde 39: A solution of methylindolizinone **6** (50.0 mg, 0.267 mmol) and acrolein (**38**, 179 µL, 2.67 mmol) in benzene (2.00 mL) was heated to 80 °C for 12 h in a 4 mL vial equipped with a green Teflon-lined cap and Teflon tape. The reaction mixture was cooled and concentrated to provide a yellow oil, **39** (45.8 mg, 0.224 mmol) in 84% yield. $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.13; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.35 (s, 1H), 7.84 (d, *J* = 3.4 Hz, 1H), 6.56 – 6.51 (m, 1H), 6.34 (dd, *J* = 7.9, 6.3 Hz, 1H), 5.59 (dd, *J* = 3.5, 1.6 Hz, 1H), 4.68 – 4.63 (m, 1H), 3.08 (s, 1H), 2.78 (d, *J* = 9.4 Hz, 1H), 1.80 – 1.65 (m, 3H), 1.10 (t, *J* = 2.6 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 209.0, 201.4, 168.3, 135.8, 128.4, 110.8, 71.2, 53.4, 51.3, 38.3, 23.1, 19.8; **HRMS** (ESI+) calcd for $[C_{12}H_{14}O_2N]^+$ $(M\text{-}H)^+$: *m/z* 204.1019, found 204.1020.



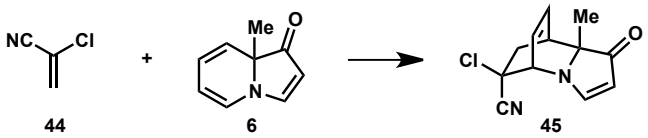
40 6 41

Methyl ester 41: A solution of methylindolizinone **6** (20.0 mg, 0.136 mmol) and methyl acrylate (**40**, 122 µL, 1.36 mmol) in benzene (1.00 mL) was heated to 80 °C for 12 h in a 4 mL vial equipped with a green Teflon-lined cap and Teflon tape. The reaction mixture was cooled and concentrated to provide a yellow oil, **41** (30.0 mg, 0.128 mmol) in 94% yield. $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.25; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.84 (d, *J* = 3.4 Hz, 1H), 6.52 (t, *J* = 7.3 Hz, 1H), 6.34 – 6.29 (m, 1H), 5.56 (d, *J* = 3.4 Hz, 1H), 4.64 (dd, *J* = 5.6, 4.1 Hz, 1H), 3.64 (s, 3H), 3.05 – 2.99 (m, 1H), 2.82 – 2.77 (m, 1H), 1.78 (dd, *J* = 10.7, 6.9 Hz, 1H), 1.64 – 1.59 (m, 1H), 1.09 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 209.1, 172.8, 168.3, 135.7, 128.0, 110.6, 70.9, 54.6, 52.1, 43.6, 38.5, 23.0, 21.8; **HRMS** (ESI+) calcd for $[C_{13}H_{16}O_3N]^+$ $(M-H)^+$: *m/z* 234.1125, found 234.1126.



42 6 43

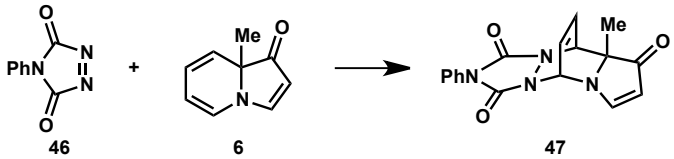
***t*-Butyl ester 43:** A solution of methylindolizinone **6** (20.0 mg, 0.136 mmol) and *tert*-butyl acrylate (**42**, 118 µL, 0.816 mmol) in benzene (1.00 mL) was heated to 80 °C for 12 h in a 4 mL vial equipped with a green Teflon-lined cap and Teflon tape. The reaction mixture was cooled and concentrated to provide a yellow oil, **43** (34.2 mg, 0.124 mmol) in 91% yield. $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.32; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.86 (d, *J* = 3.4 Hz, 1H), 6.51 (t, *J* = 7.3 Hz, 1H), 6.35 – 6.28 (m, 1H), 5.54 (d, *J* = 3.4 Hz, 1H), 4.62 – 4.57 (m, 1H), 3.00 (d, *J* = 2.3 Hz, 1H), 2.73 – 2.68 (m, 1H), 1.78 – 1.72 (m, 1H), 1.55 (dd, *J* = 7.8, 5.9 Hz, 1H), 1.40 (s, 9H), 1.08 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 209.3, 171.4, 168.5, 135.5, 127.9, 110.2, 81.0, 71.0, 54.9, 44.6, 38.7, 28.0, 23.0, 21.7; **HRMS** (ESI+) calcd for $[C_{16}H_{22}O_3N]^+$ $(M-H)^+$: *m/z* 276.1594, found 276.1596.



44 6 45

[2.2.2]azabicycle 45: A solution of methylindolizinone **6** (20.0 mg, 0.136 mmol) and **44** (65.0 µL, 0.816 mmol) in benzene (1.00 mL) was heated to 80 °C for 12 h in a 4 mL vial equipped

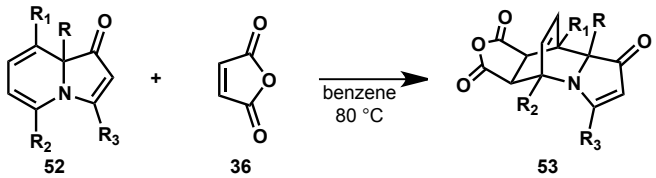
with a green Teflon-lined cap and Teflon tape. The reaction mixture was cooled and concentrated to provide **45** (29.7 mg, 0.126 mmol) in 93% yield. $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.30; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.11 (d, *J* = 3.6 Hz, 1H), 6.63 (s, 1H), 6.46 (s, 1H), 5.58 (d, *J* = 3.6 Hz, 1H), 4.66 (d, *J* = 6.1 Hz, 1H), 3.13 (s, 1H), 2.29 (dd, *J* = 15.5, 1.6 Hz, 1H), 2.07 (dd, *J* = 15.5, 4.0 Hz, 1H), 1.15 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 206.8, 166.8, 134.5, 127.8, 119.7, 116.1, 110.3, 69.7, 59.6, 53.8, 37.2, 22.9; **HRMS** (ESI+) calcd for $[C_{12}H_{12}ON_2Cl]^+$ $(M-H)^+$: *m/z* 235.0633, found 235.0637.



46 6 47

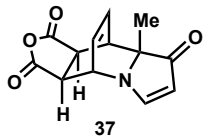
[2.2.2]triazabicycle 47: PTAD (**46**, 23.8 mg, 0.136 mmol) was added to methylindolizinone (**6**, 20.0 mg, 0.136 mmol) in CH_2Cl_2 (1.00 mL) at 0 °C. The reaction mixture was stirred for 2 min at 0 °C. The solvent was removed under reduced pressure to afford **47** (32.0 mg, 0.0993 mmol) in 73% yield. $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.05; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 3.3 Hz, 1H), 7.41 – 7.33 (m, 5H), 6.26 (d, *J* = 2.6 Hz, 1H), 6.01 (s, 1H), 5.27 (s, 1H), 5.00 (s, 1H), 4.80 (d, *J* = 5.8 Hz, 1H), 1.48 (s, 3H); **^{13}C NMR** (151 MHz, MeOD) δ 173.8, 166.8, 155.6, 132.2, 131.0, 130.9, 130.3, 128.6, 126.2, 99.0, 67.6, 62.4, 33.6, 24.5, 15.3; **HRMS** (EI) calcd for $[C_{17}H_{14}O_3N_4]$ (M): *m/z* 322.1066, found 322.1063.

Representative procedure for the Diels-Alder cycloaddition of indolizinones with maleic anhydride:



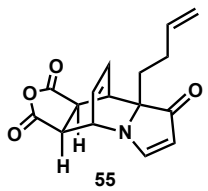
52 36 53

A solution of indolizinone **52** (0.0340 mmol) and maleic anhydride (**36**, 0.0408 mmol) in benzene (400 μL) was heated to 80 °C for 12 h in a 4 mL vial equipped with a green Teflon-lined cap and Teflon tape. The reaction mixture was cooled and concentrated to provide **53**.



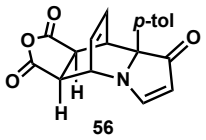
37

[2.2.2]bicycle 37: The standard Diels-Alder protocol afforded **37** in 96% yield. $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.29; **^{1}H NMR** (600 MHz, C_6D_6) δ 7.71 (d, *J* = 3.5 Hz, 1H), 6.46 (dd, *J* = 5.0, 2.5 Hz, 2H), 5.56 (d, *J* = 3.6 Hz, 1H), 4.70 (d, *J* = 2.2 Hz, 1H), 3.46 (d, *J* = 2.5 Hz, 1H), 3.19 (dd, *J* = 8.6, 4.4 Hz, 1H), 3.02 – 2.98 (m, 1H), 1.06 (s, 3H); **^{13}C NMR** (151 MHz, C_6D_6) δ 206.6, 170.2, 169.8, 133.6, 130.2, 128.3, 112.3, 68.9, 52.9, 44.4, 39.6, 38.6 22.9; **HRMS** (ESI+) calcd for $[C_{13}H_{12}O_4N]^+$ $(M\text{-}H)^+$: *m/z* 246.0761, found 246.0763.



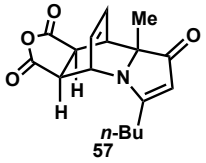
55

[2.2.2]bicycle 55: The standard Diels-Alder protocol afforded **55** in 67% yield. $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.55; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 3.5 Hz, 1H), 6.55 (dd, *J* = 4.8, 2.5 Hz, 2H), 5.71 (d, *J* = 3.6 Hz, 1H), 5.63 (d, *J* = 6.7 Hz, 1H), 4.92 (dd, *J* = 20.9, 5.3 Hz, 2H), 4.80 (d, *J* = 2.4 Hz, 1H), 3.60 – 3.55 (m, 1H), 3.31 (dd, *J* = 8.6, 4.4 Hz, 1H), 3.10 (dd, *J* = 8.6, 3.1 Hz, 1H), 1.95 – 1.86 (m, 1H), 1.73 (d, *J* = 8.3 Hz, 2H), 1.58 (td, *J* = 12.8, 4.3 Hz, 1H); **HRMS** (ESI+) calcd for $[C_{16}H_{15}O_4N]^+$ $(M\text{-}H)^+$: *m/z* 285.1001, found 285.1003. For X-ray crystal structure see **35**.



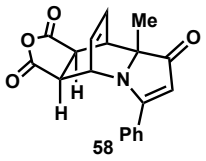
56

[2.2.2]bicycle 56: The standard Diels-Alder protocol afforded **56** in 89% yield. $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.45; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.98 (d, *J* = 3.5 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 2H), 6.45 (d, *J* = 7.5 Hz, 1H), 6.16 (t, *J* = 7.1 Hz, 1H), 5.56 (d, *J* = 3.6 Hz, 1H), 4.95 (t, *J* = 5.2 Hz, 1H), 4.13 (d, *J* = 3.6 Hz, 1H), 3.47 (dd, *J* = 8.6, 4.4 Hz, 1H), 3.33 (dd, *J* = 8.6, 2.9 Hz, 1H), 2.29 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 203.8, 167.4, 164.1, 136.5, 133.4, 129.8, 129.3, 128.3, 125.6, 111.9, 72.4, 52.7, 45.2, 41.4, 38.6, 21.0; **HRMS** (ESI+) calcd for $[C_{19}H_{16}O_4N]^+$ $(M\text{-}H)^+$: *m/z* 322.1074, found 322.1073.



57

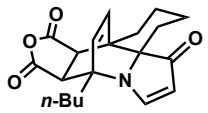
[2.2.2]bicycle 57: The standard Diels-Alder protocol afforded **57** in 93% yield. $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.47; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.57 (d, *J* = 6.8 Hz, 1H), 6.53 (d, *J* = 6.3 Hz, 1H), 5.50 (s, 1H), 4.86 – 4.82 (m, 1H), 3.53 – 3.49 (m, 1H), 3.14 (dd, *J* = 16.8, 3.5 Hz, 2H), 2.52 (d, *J* = 7.9 Hz, 1H), 2.46 (d, *J* = 7.8 Hz, 1H), 1.69 – 1.62 (m, 2H), 1.44 (dd, *J* = 7.4, 3.2 Hz, 2H), 1.13 (s, 3H), 0.97 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 205.7, 170.4, 170.0, 134.1, 129.7, 128.3, 111.2, 69.8, 50.6, 42.8, 38.8, 38.7, 29.5, 29.2, 23.5, 22.4, 13.7; **HRMS** (ESI+) calcd for $[C_{17}H_{19}O_4N]^+$ $(M\text{-}H)^+$: *m/z* 301.1314, found 301.1312.



58

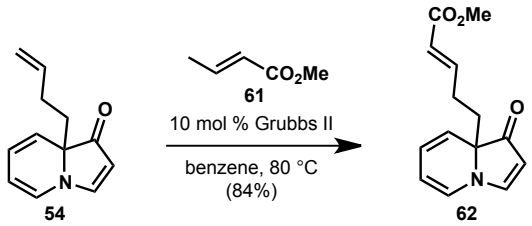
[2.2.2]bicycle 58: The standard Diels-Alder protocol afforded **58** in 91% yield. $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.49; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.66 – 7.62 (m, 2H), 7.61 (d, *J* = 7.3 Hz,

1H), 7.56 (t, *J* = 7.4 Hz, 2H), 6.61 (d, *J* = 6.8 Hz, 1H), 6.56 (d, *J* = 6.3 Hz, 1H), 5.85 (s, 1H), 4.86 – 4.82 (m, 1H), 3.62 – 3.58 (m, 1H), 3.26 (dd, *J* = 8.6, 3.1 Hz, 1H), 3.11 (dd, *J* = 8.6, 4.2 Hz, 1H), 1.27 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 205.6, 170.4, 169.9, 133.9, 132.6, 130.2, 130.2, 129.6, 128.3, 127.9, 111.3, 70.5, 52.1, 42.2, 39.2, 38.6, 23.8; **HRMS** (ESI+) calcd for $[C_{19}H_{15}O_4N]^+$ $(M\text{-}H)^+$: *m/z* 321.1001, found 321.1004.



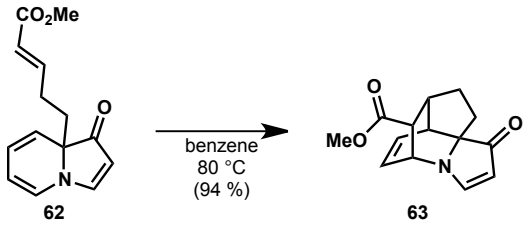
59

[2.2.2]bicycle 59: The standard Diels-Alder protocol afforded **59** in 88% yield. **R_f** (3:1 hexanes/EtOAc) 0.46; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.80 (d, *J* = 3.7 Hz, 1H), 6.26 (t, *J* = 5.9 Hz, 2H), 5.53 (d, *J* = 3.7 Hz, 1H), 3.01 – 2.96 (m, 2H), 2.64 (dd, *J* = 13.6, 4.1 Hz, 1H), 2.47 – 2.39 (m, 1H), 2.19 (d, *J* = 13.7 Hz, 1H), 2.13 – 2.05 (m, 1H), 2.05 – 1.97 (m, 2H), 1.85 (d, *J* = 13.2 Hz, 1H), 1.59 (ddd, *J* = 13.2, 10.6, 3.9 Hz, 2H), 1.54 – 1.41 (m, 5H), 1.39 (d, *J* = 15.0 Hz, 1H), 0.99 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 207.2, 169.7, 168.8, 162.5, 137.2, 132.0, 111.9, 70.9, 61.3, 51.7, 45.2, 45.0, 30.7, 30.7, 25.6, 25.1, 22.9, 21.2, 17.2, 14.0; **HRMS** (ESI+) calcd for $[C_{20}H_{24}O_4N]^+$ $(M\text{-}H)^+$: *m/z* 342.1700, found 342.1696.



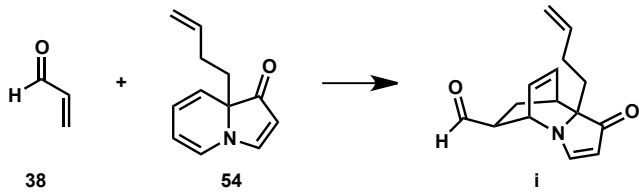
Ester 62: A solution of indolizinone **54** (100 mg, 0.534 mg), methyl crotonate (**61**, 283 μL, 2.67 mmol) and Grubbs 2nd generation catalyst (45.0 mg, 0.0534) in CH_2Cl_2 (5.0 mL) was stirred at room temperature for 20 h. The reaction mixture was concentrated under reduced pressure and purified via flash chromatography to afford ester **62** in 84% yield (69.4 mg, 0.283 mmol). **R_f** (3:1 hexanes/EtOAc) 0.29; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.81 (d, *J* = 3.7 Hz, 1H), 6.85 (d, *J* = 15.6 Hz, 1H), 6.37 (d, *J* = 7.0 Hz, 1H), 5.95 (dd, *J* = 9.3, 5.5 Hz, 1H), 5.80 – 5.74 (m, 2H), 5.41 (dd, *J*

= 9.2, 3.3 Hz, 1H), 5.11 (d, *J* = 3.7 Hz, 1H), 3.70 (s, 3H), 2.30 – 2.23 (m, 1H), 2.21 – 2.13 (m, 1H), 1.89 (ddd, *J* = 13.5, 11.1, 5.3 Hz, 1H), 1.79 (ddd, *J* = 13.5, 11.2, 5.1 Hz, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 203.5, 166.8, 161.0, 148.0, 125.3, 122.9, 122.1, 121.3, 109.0, 99.2, 69.2, 51.4, 36.3, 24.8; **HRMS** (ESI+) calcd for $[C_{14}H_{16}O_3N]^+$ $(M\text{-}H)^+$: *m/z* 246.1125, found 246.1126.



62 63

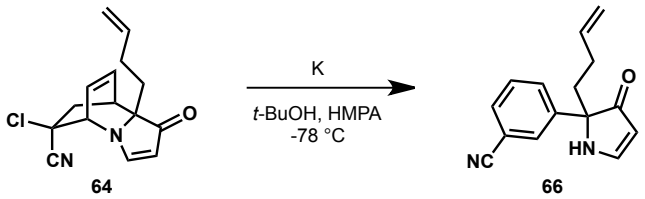
Caged polycycle 63: A solution of indolizinone **62** (25.3 mg, 0.103 mmol) in xylenes (1.0 mL) was heated to 150 °C for 20 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure to afford polycycle **63** in a 99% yield (25.0 mg, 0.102 mmol). **R_f** (3:1 hexanes/EtOAc) 0.24; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.65 (d, *J* = 3.5 Hz, 1H), 6.14 – 6.10 (m, 1H), 6.07 – 6.02 (m, 1H), 5.49 (d, *J* = 3.5 Hz, 1H), 4.43 – 4.39 (m, 1H), 3.67 (s, 3H), 2.98 – 2.93 (m, 1H), 2.81 – 2.77 (m, 1H), 2.63 (s, 1H), 2.24 (dd, *J* = 13.5, 3.4 Hz, 1H), 2.16 – 2.08 (m, 1H), 1.89 – 1.83 (m, 1H), 1.74 – 1.68 (m, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 205.3, 172.2, 167.2, 129.1, 128.3, 111.3, 75.5, 53.2, 52.7, 52.1, 47.4, 40.3, 33.8, 30.0; **HRMS** (ESI+) calcd for $[C_{14}H_{16}O_3N]^+$ $(M\text{-}H)^+$: *m/z* 246.1125, found 246.1123.



38 54 i

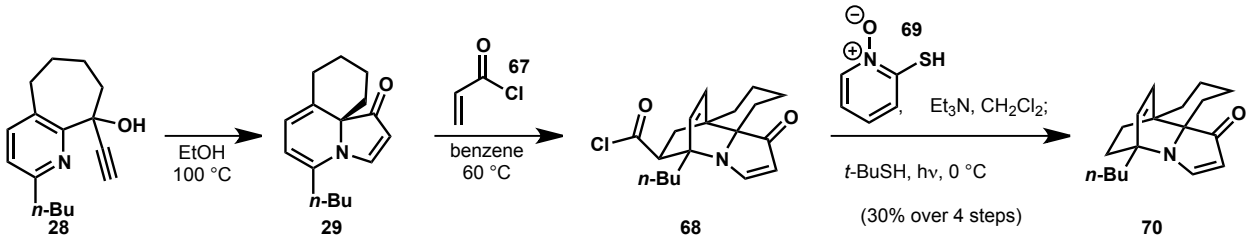
Aldehyde i: A solution of indolizinone **54** (50.0 mg, 0.267 mmol) and acrolein (**38**, 179 μL, 2.67 mmol) in benzene (2.00 mL) was heated to 80 °C for 12 h in a 4 mL vial equipped with a green Teflon-lined cap and Teflon tape. The reaction mixture was cooled and concentrated to provide a yellow oil, **i** (47.6 mg, 0.195 mmol) in 73% yield. **R_f** (3:1 hexanes/EtOAc) 0.24; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.37 (s, 1H), 7.93 (d, *J* = 3.5 Hz, 1H), 6.57 – 6.50 (m, 1H), 6.35 (s, 1H), 5.70 – 5.59 (m, 2H), 4.93 (dd, *J* = 17.1, 1.6 Hz, 1H), 4.88 (d, *J* = 10.2 Hz, 1H), 4.66 (dd, *J* = 5.8, 3.8

Hz, 1H), 3.14 – 3.07 (m, 1H), 2.81 (d, *J* = 9.2 Hz, 1H), 1.92 – 1.84 (m, 1H), 1.79 – 1.66 (m, 5H), 1.61 (dd, *J* = 12.5, 4.3 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 208.6, 201.5, 170.0, 137.9, 135.8, 128.4, 114.7, 113.0, 74.0, 53.6, 51.8, 38.6, 36.2, 26.6, 19.7; **HRMS** (ESI+) calcd for $[C_{15}H_{18}O_2N]^+$ $(M-H)^+$: *m/z* 244.1332, found 244.1333.



64 66

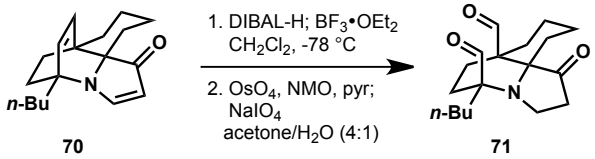
Arene 66: Potassium metal (26.9 mg, 0.688 mmol) was added in portions to **64** (18.9 mg, 0.0688 mmol) in HMPA/*t*-BuOH (1:1, total volume = 600 μL) at -78 °C. The reaction mixture was stirred warming to ambient temperature for 30 min. The reaction was quenched with by addition of a saturated solution of ammonium chloride (2.0 mL). The mixture was extracted with CH_2Cl_2 (3 x 2.0 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure to give a crude oil, which after flash chromatography afforded **66** (10.7 mg, 0.0447 mmol) in 65% yield. **R_f** (3:1 hexanes/EtOAc) 0.21; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.17 (t, *J* = 3.7 Hz, 1H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.75 (s, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.49 (d, *J* = 7.9 Hz, 1H), 5.86 (s, 1H), 5.79 (d, *J* = 6.1 Hz, 1H), 5.18 (d, *J* = 3.5 Hz, 1H), 5.03 – 4.96 (m, 2H), 3.65 (s, 1H), 2.21 (s, 1H), 2.14 – 2.07 (m, 2H), 1.99 (d, *J* = 8.4 Hz, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 201.6, 163.4, 139.8, 137.3, 131.2, 130.3, 129.6, 129.1, 116.2, 112.8, 110.6, 98.8, 70.6, 37.0, 28.4; **HRMS** (ESI+) calcd for $[C_{15}H_{15}ON_2]^+$ $(M-H)^+$: *m/z* 239.1179, found 239.1177.



28 29 68 70

[2.2.2]azabicycle 70: A solution of tertiary alcohol **28** (155 mg, 0.637 mmol) in EtOH (5.0 mL) was sparged with N_2 for 3 min, then heated at 100 °C. After 2 h, the reaction mixture was cooled

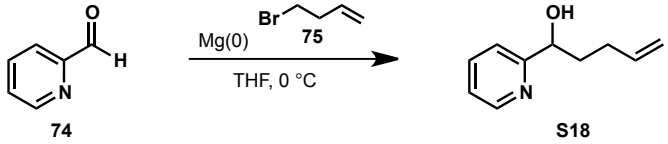
to room temperature and concentrated to afford **29**, which was taken on without purification. A solution of indolizinone **29** (entire crude) and acryloyl chloride (**67**, 518 µL, 6.37 mmol) in benzene (5.0 mL) was heated to 60 °C for 2 h. The reaction mixture was cooled to room temperature, concentrated under reduced pressure and dried under high vac for 2 h. Next, the acid chloride (**68**) was dissolved in CH_2Cl_2 (5.0 mL) and a solution of 2-mercaptopyridine *N*-oxide (**69**, 122 mg, 0.956 mmol) and Et_3N (178 µL, 1.27 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise over 1 h in the dark. The reaction mixture was stirred for 12 h at ambient temperature. The reaction mixture was cooled to 0 °C and *tert*-butylthiol (718 µL, 6.37 mmol) was added dropwise over 1 min. The mixture was irradiated with a tungsten lamp for 2.5 h, while the temperature was maintained at 0 °C. The reaction mixture was diluted with water (5.0 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 5.0 mL). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to afford a brown oil. The crude product was purified via flash chromatography (9:1 hexanes/EtOAc) to provide [2.2.2]azabicycle **70** in 30% yield over 4 steps (51.0 mg, 0.188 mmol). $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.66; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.79 (d, *J* = 3.5 Hz, 1H), 6.16 (d, *J* = 8.0 Hz, 2H), 5.38 (d, *J* = 3.5 Hz, 1H), 2.44 (d, *J* = 4.2 Hz, 1H), 2.14 (d, *J* = 14.2 Hz, 1H), 1.87 – 1.80 (m, 1H), 1.72 (s, 1H), 1.68 – 1.63 (m, 2H), 1.63 – 1.57 (m, 4H), 1.53 – 1.48 (m, 3H), 1.45 – 1.39 (m, 5H), 1.36 – 1.30 (m, 4H), 1.27 (ddd, *J* = 11.4, 8.5, 4.6 Hz, 2H), 1.12 – 1.08 (m, 1H), 0.96 (t, *J* = 7.1 Hz, 4H), 0.88 (t, *J* = 7.2 Hz, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 210.0, 164.2, 138.2, 131.8, 109.4, 73.7, 61.0, 43.3, 35.6, 33.6, 30.9, 28.7, 28.2, 26.2, 23.2, 21.6, 17.5, 14.0; **HRMS** (ESI+) calcd for $[C_{18}H_{26}ON]^+$ $(M-H)^+$: *m/z* 272.2009, found 272.2015.



70 71

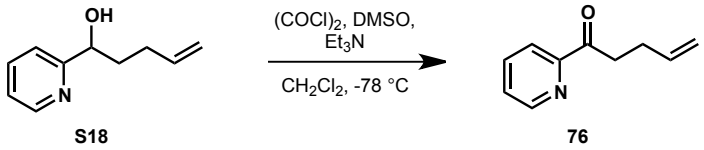
Dialdehyde 71: DIBAL-H (13 µL, 0.074 mmol) followed by BF_3OEt_2 (6.0 µL, 0.44 mmol) was added to a solution of vinylogous amide **70** (10.0 mg, 0.0368 mmol) in CH_2Cl_2 (400 µL) at -78 °C. The reaction mixture was stirred for 1 h at -78 °C and was then quenched by addition of a saturated solution of sodium bicarbonate (2.0 mL). The mixture was extracted with CH_2Cl_2 (3 x

2.0 mL). The organic layers were combined, washed with brine (100 mL) and concentrated to give a yellow oil. The oil was dissolved in acetone/water (4:1, total volume = 500 μL) and osmium tetroxide (1 drop, 2.5 wt % in *tert*-butanol) and NMO (7.8 mg, 0.067 mmol) were added. The reaction mixture was stirred at ambient temperature for 1 d. $NaOI_4$ (36 mg, 0.17 mmol) was added and the reaction mixture was stirred for 1 d. The reaction was quenched by addition of a saturated solution of sodium bicarbonate (2.0 mL). The mixture was extracted with CH_2Cl_2 (3 x 2.0 mL). The organic layers were combined, washed with brine (100 mL) and concentrated to give **71** as a mixture with its hydrate forms. **HRMS** (ESI+) calcd for $[C_{18}H_{28}O_3N]^+$ $(M\text{-}H)^+$: *m/z* 306.2064, found 306.2060.

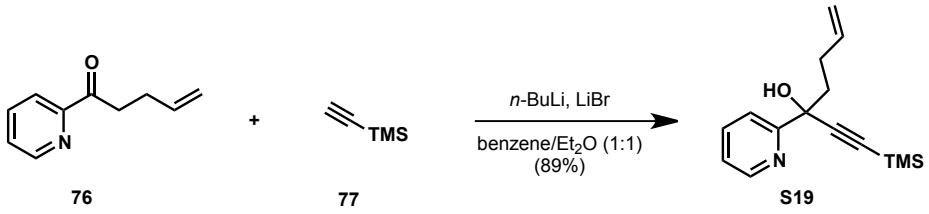


74 S18

Alcohol S18: 1-Bromo-4-butene (**75**, 7.61 mL, 75.0 mmol) was added dropwise to Mg(0) in THF (10 mL). Following initiation of the Grignard formation, which was marked by vigorous bubbling, an additional 10 mL of THF was added. The round bottom flask was equipped with a reflux condenser and heated to reflux (oil bath temperature = 70 °C) for 1 h. The Grignard solution was removed from the oil bath and cooled to room temperature, then further cooled to 0 °C in an ice bath. The Grignard solution was diluted with THF (80 mL) and pyridine-2-carboxaldehyde (**74**, 4.76 mL, 50 mmol) in THF (20 mL) was added dropwise over 10 min. The reaction mixture was stirred while the ice bath expired. The reaction was quenched by addition of a saturated solution of ammonium chloride (30 mL). The mixture was extracted with EtOAc (3 x 50 mL). the organic layers were combined, washed with brine (100 mL), dried over $MgSO_4$, and concentrated to give a brown oil. Flash chromatography (1:1 hexanes/EtOAc) provided the alcohol **S18** in 97% yield. $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.36; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 3.4 Hz, 2H), 7.66 (td, *J* = 7.7, 1.4 Hz, 1H), 7.28 – 7.24 (m, 2H), 7.17 (dd, *J* = 7.2, 5.1 Hz, 2H), 5.82 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.01 (dt, *J* = 8.8, 4.4 Hz, 1H), 4.94 (dd, *J* = 10.2, 0.9 Hz, 1H), 4.77 – 4.72 (m, 2H), 2.23 – 2.12 (m, 2H), 1.90 (dddd, *J* = 13.5, 9.2, 6.9, 4.3 Hz, 1H), 1.81 – 1.71 (m, 1H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 162.1, 148.1, 136.6, 122.2, 120.3, 114.8, 72.2, 64.2, 37.6, 29.5; **IR** (film) υ_{max} 3363, 3080, 2918, 1641, 1595, 1071 cm^{-1}; **HRMS** (ESI+) calcd for $[C_{10}H_{14}ON]^+$ $(M\text{-}H)^+$: *m/z* 164.1070, found 164.1069.

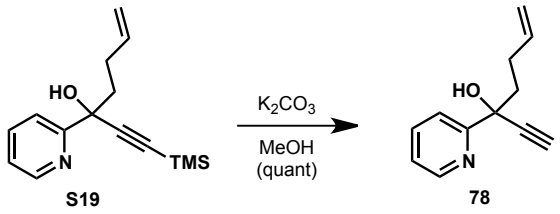


Ketone 76: DMSO (6.10 mL, 85.6 mmol) was added dropwise to oxalyl chloride in CH_2Cl_2 (80 mL) at -78 °C. After 30 min, alcohol **S18** (3.50 g, 21.4 mmol) in CH_2Cl_2 (20 mL) was added dropwise at -78 °C. The reaction mixture was stirred for 30 min at this temperature. Et_3N (24.0 mL, 171 mmol) was added at -78 °C. The cold bath was allowed to gradually expire as the reaction mixture was stirred for 4 h. The reaction was quenched with water (100 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layer was washed with water, dried over $MgSO_4$ and concentrated to afford **76** as a brown oil in 98% yield (3.39 g, 21.0 mmol) that was used without further purification. $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.51; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.68 (d, J = 4.7 Hz, 1H), 8.03 (d, J = 7.9 Hz, 1H), 7.83 (d, J = 1.6 Hz, 1H), 7.49 – 7.44 (m, 1H), 5.91 (d, J = 6.6 Hz, 1H), 5.09 (dd, J = 17.1, 1.6 Hz, 1H), 4.99 (dd, J = 10.2, 1.2 Hz, 1H), 3.33 (t, J = 7.4 Hz, 2H), 2.50 (d, J = 7.2 Hz, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 200.8, 153.0, 148.6, 137.2, 136.8, 126.9, 121.5, 114.8, 36.6, 27.7; **IR** (film) υ_{max} 3381, 3077, 2979, 2600, 1698, 1437, 995 cm^{-1}; **HRMS** (ESI+) calcd for $[C_{10}H_{12}ON]^+$ $(M\text{-}H)^+$: *m/z* 162.0913, found 162.1310.

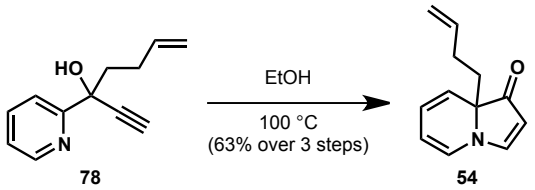


Propargylic alcohol S19: *n*-Butyllithium (6.95 mL, 17.4 mmol, 2.5 M in hexanes) was added dropwise to trimethylsilylacetylene (**77**, 2.82 mL, 19.8 mmol) in Et_2O (20 mL) at 0 °C. After 30 min, the lithium acetylide solution was added dropwise to a mixture of ketone **76** (2.00 g, 12.4 mmol) and lithium bromide (3.20 g, 37.2 mmol) in a 1:1 mixture of Et_2O and benzene (total volume = 120 mL) at ambient temperature. The reaction mixture was stirred vigorously for 18 h. The reaction was quenched with the addition of a saturated $NH_4Cl_{(aq)}$ solution (60 mL). The

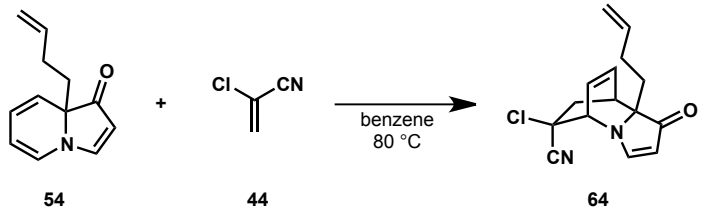
aqueous phase was extracted with EtOAc (3 x 80 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to provide propargylic alcohol **S19** as a brown oil in 80% yield (2.00 g, 4.69 mmol). $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.64; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.51 (d, *J* = 4.9 Hz, 1H), 7.74 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.26 (q, *J* = 4.7 Hz, 1H), 5.80 (d, *J* = 6.6 Hz, 1H), 5.47 (s, 1H), 4.98 (dd, *J* = 17.1, 1.6 Hz, 1H), 4.91 (d, *J* = 10.3 Hz, 1H), 2.33 – 2.25 (m, 1H), 2.17 – 2.10 (m, 1H), 2.10 – 2.03 (m, 1H), 1.94 – 1.87 (m, 1H), 0.20 – 0.15 (m, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.8, 147.2, 138.1, 137.2, 122.8, 120.6, 114.5, 107.2, 89.3, 71.6, 44.2, 28.5, -0.2; **IR** (film) υ_{max} 3363, 3077, 2959, 2078, 1593, 844 cm^{-1}; **HRMS** (ESI+) calcd for $[C_{15}H_{22}ONSi]^+$ $(M-H)^+$: *m/z* 260.1465, found 260.1464.



Propargylic alcohol 78: Potassium carbonate (2.02 g, 14.6 mmol) was added to trimethylsilyl alkyne **S19** (1.90 g, 7.32 mmol) in MeOH (70 mL). The reaction mixture was stirred for 2 h at ambient temperature. The reaction mixture was concentrated under reduced pressure. The residue was taken up in water (100 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to provide **78** as a brown oil in 97% yield (1.33 g, 7.10 mmol). $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.44; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 4.9 Hz, 1H), 7.74 (td, *J* = 7.7, 1.7 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.28 – 7.22 (m, 1H), 5.77 (d, *J* = 6.4 Hz, 1H), 5.48 (s, 1H), 4.97 (dd, *J* = 17.1, 1.5 Hz, 1H), 4.90 (d, *J* = 10.2 Hz, 1H), 2.56 (s, 1H), 2.29 (s, 1H), 2.17 – 2.09 (m, 2H), 1.93 (dd, *J* = 11.7, 8.4 Hz, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 160.4, 147.3, 137.8, 137.3, 122.9, 120.4, 114.6, 85.9, 72.7, 71.2, 43.6, 28.2; **IR** (film) υ_{max} 3299, 3150, 1641, 1593, 1435, 1079 cm^{-1}; **HRMS** (ESI+) calcd for $[C_{12}H_{14}ON]^+$ $(M-H)^+$: *m/z* 188.1070, found 188.1069.

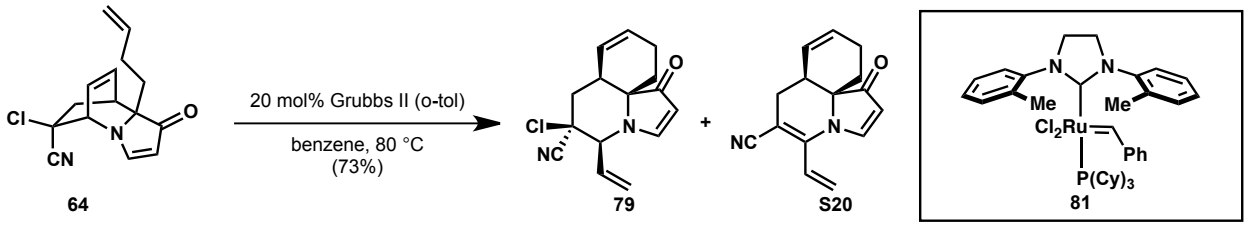


Homoallyl indolizinone 54: A solution of tertiary alcohol **78** (600 mg, 3.20 mmol) in EtOH (6.0 mL) was sparged with N_2 for 5 min. The reaction vessel, a 20 mL vial, was equipped with a green Teflon-lined cap and Telfon tape and heated at 100 °C for 4 h. The reaction mixture was cooled to room temperature and concentrated to provide indolizinone **54** in 99% yield (594 mg, 3.17 mmol). $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.44; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 3.7 Hz, 1H), 6.36 (d, *J* = 7.0 Hz, 1H), 5.89 (d, *J* = 5.5 Hz, 1H), 5.76 (d, *J* = 9.3 Hz, 1H), 5.67 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.37 (s, 1H), 5.07 (d, *J* = 3.7 Hz, 1H), 4.94 (dd, *J* = 17.1, 1.6 Hz, 1H), 4.89 (dd, *J* = 10.2, 1.2 Hz, 1H), 2.06 (s, 1H), 1.98 (s, 1H), 1.86 – 1.68 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 204.0, 160.9, 137.4, 125.2, 122.5, 122.4, 114.9, 108.8, 99.0, 69.6, 37.6, 26.2; **HRMS** (ESI+) calcd for $[C_{12}H_{14}ON]^+$ $(M\text{-}H)^+$: *m/z* 188.1070, found 188.1069.

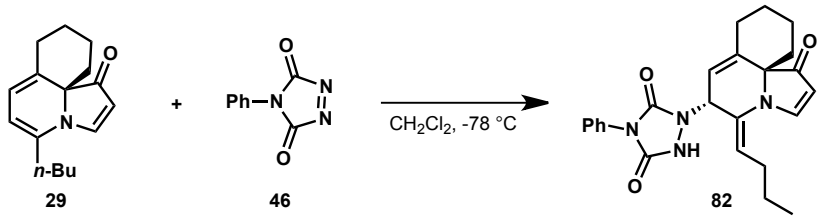


[2.2.2]azabicycle 64: A solution of indolizinone **54** (250 mg, 1.34 mmol) and 2-chloroacrylonitrile (**44**, 535 µL, 6.70 mmol) were heated in benzene (6.0 mL) at 80 °C for 24 h. The reaction mixture was cooled to room temperature and concentrated to afford a brown oil. The crude product was purified via flash chromatography (gradient 4:1 hexanes/EtOAc, then 2:1 hexanes/EtOAc) to afford **64** as a yellow oil in 71% yield (259 mg, 0.951 mmol). $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.51; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.35 (d, *J* = 0.8 Hz, 1H), 7.92 (d, *J* = 3.4 Hz, 1H), 6.51 (t, *J* = 7.3 Hz, 1H), 6.35 – 6.30 (m, 1H), 5.69 – 5.59 (m, 2H), 4.91 (dd, *J* = 17.2, 1.7 Hz, 1H), 4.87 (dd, *J* = 10.2, 1.7 Hz, 1H), 4.65 (dd, *J* = 5.7, 3.8 Hz, 1H), 3.09 (dd, *J* = 5.5, 2.4 Hz, 1H), 2.82 – 2.76 (m, 1H), 1.92 – 1.81 (m, 2H), 1.78 – 1.54 (m, 8H); **^{13}C NMR** (151 MHz,

C_6D_6) δ 205.8, 168.8, 138.5, 134.8, 120.5, 115.6, 112.8, 109.8, 72.4, 59.8, 55.3, 37.5, 37.2, 36.7, 27.5; **HRMS** (ESI+) calcd for $[C_{15}H_{16}ON_2Cl]^+$ $(M-H)^+$: *m/z* 275.0946, found 275.0951.

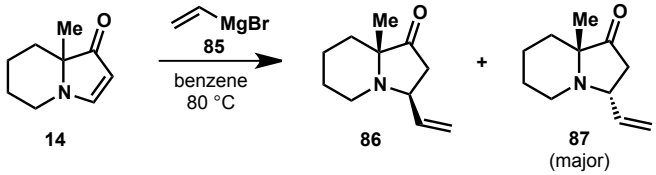


Tricycle 79: A solution of **64** (10 mg, 0.036 mmol) and **81** (3.1 mg, 0.0036 mmol) in benzene (3.6 mL) was sparged with ethylene for 5 min. The 20 mL vial was equipped with a Teflon cap and heated to 80 °C. After 12 h, the reaction mixture was cooled to room temperature and concentrated under reduced pressure to give a brown oil. The crude oil was purified via flash chromatography to afford **79** and **S20**. Relative amounts of these products varied depending on the scale of the reaction. In this case, **79** was obtained in 73% yield. $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.27; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 3.6 Hz, 1H), 6.23 – 6.12 (m, 1H), 5.94 (dd, *J* = 9.9, 5.1 Hz, 1H), 5.57 – 5.50 (m, 3H), 5.19 (d, *J* = 3.6 Hz, 1H), 4.53 (dd, *J* = 7.1, 1.4 Hz, 1H), 2.77 (d, *J* = 2.4 Hz, 1H), 2.60 (d, *J* = 12.9 Hz, 1H), 2.47 (ddd, *J* = 14.1, 4.0, 1.6 Hz, 1H), 2.11 (ddd, *J* = 19.3, 15.9, 9.2 Hz, 2H), 2.02 – 1.96 (m, 1H), 1.61 (dd, *J* = 13.7, 5.6 Hz, 1H); **^{13}C NMR** (151 MHz, C_6D_6) δ 202.4, 167.4, 138.0, 129.5, 119.6, 115.9, 110.0, 99.1, 72.6, 66.5, 59.8, 52.8, 40.2, 38.7, 27.2; **HRMS** (ESI+) calcd for $[C_{15}H_{16}ON_2Cl]^+$ $(M-H)^+$: *m/z* 275.0946, found 275.0950.

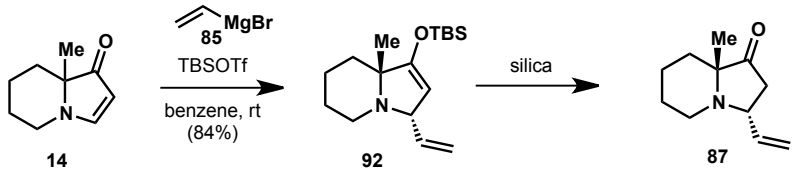


Ene adduct 82: PTAD (**46**, 13.9 mg, 0.0793 mmol) was added to indolizinone **29** (20.3 mg, 0.0834 mmol) in CH_2Cl_2 (800 µL) at 0 °C. The reaction mixture was stirred for 2 min at 0 °C. The solvent was removed under reduced pressure to afford **82** (23.8 mg, 0.0567 mmol) in 68%

yield. **R_f** (3:1 hexanes/EtOAc) 0.08; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.17 (d, *J* = 3.4 Hz, 1H), 7.41 – 7.35 (m, 5H), 6.76 (d, *J* = 9.9 Hz, 1H), 5.66 (d, *J* = 9.9 Hz, 1H), 5.37 (s, 1H), 5.26 (d, *J* = 3.2 Hz, 1H), 3.05 (d, *J* = 3.4 Hz, 1H), 2.23 (dd, *J* = 19.3, 7.7 Hz, 3H), 1.86 (m, 1H), 1.65 – 1.59 (m, 2H), 1.57 – 1.50 (m, 2H), 1.50 – 1.42 (m, 2H), 1.40 (d, *J* = 13.8 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 204.1, 157.8, 152.5, 151.1, 131.1, 130.0, 128.9, 128.0, 125.9, 125.5, 125.0, 117.0, 100.0, 98.3, 68.3, 63.4, 53.4, 31.9, 30.0, 28.4, 23.2, 21.5, 18.5, 13.6; **HRMS** (ESI+) calcd for $[C_{24}H_{27}O_3N_4]^+$ $(M\text{-}H)^+$: *m/z* 419.2078, found 419.2126.



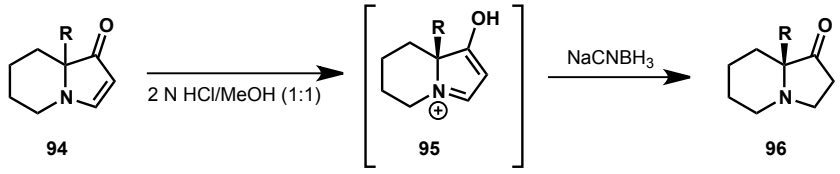
Tertiary amines 86 and 87: Vinylmagnesium bromide (**85**, 142 µL, 0.0992 mmol, 0.7 M in hexanes) was added dropwise to **14** (10.0 mg, 0.0661 mmol) in benzene (600 µL). The reaction mixture was heated to 80 °C for 2 h. The mixture was cooled to room temperature and quench by the addition of water (1.0 mL). The product was extracted with CH_2Cl_2 (3 x 2.0 mL) from 1 M $NaOH_{(aq)}$. The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure to afford a 3:1 mixture of **87** to **86** in 64% yield. **R_f** (3:1 hexanes/EtOAc) 0.15; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.68 – 5.59 (m, 1H), 5.31 – 5.23 (m, 1H), 5.21 (dd, *J* = 10.0, 1.5 Hz, 1H), 3.83 (d, *J* = 6.4 Hz, 1H), 3.04 – 2.97 (m, 1H), 2.88 (d, *J* = 2.2 Hz, 1H), 2.61 (dd, *J* = 18.5, 6.4 Hz, 1H), 2.19 (dd, *J* = 18.5, 9.7 Hz, 1H), 1.72 – 1.56 (m, 4H), 1.29 (s, 3H), 1.23 – 1.12 (m, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 216.8, 139.7, 118.3, 63.2, 57.4, 42.2, 40.7, 24.5, 20.0, 19.2, 18.2; **HRMS** (ESI+) calcd for $[C_{11}H_{18}ON]^+$ $(M\text{-}H)^+$: *m/z* 180.1383, found 180.1386.



Tertiary amine 87: TBSOTf (141 µL, 0.615 mmol) was added to **14** (31.0 mg, 0.205 mmol) in benzene (2.0 mL) at ambient temperature. Vinylmagnesium bromide (**85**, 586 µL, 0.410 mmol)

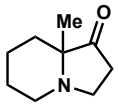
was added dropwise to the reaction mixture. The mixture was stirred for 1 h then quenched by the addition of water (1.0 mL). The product was extracted with CH_2Cl_2 (3 x 2.0 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure to afford crude **92**. Flash chromatography afforded ketone **87** in 84% yield as a single diastereomer.

Representative procedure for the reduction of vinylogous amides with sodium cyanoborohydride:



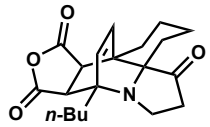
94 **95** **96**

2 N $HCl_{(aq)}$ (300 µL) was added dropwise to vinylogous amide **94** (0.150 mmol) in MeOH (700 µL). $NaCNBH_3$ (0.375 mmol, 2.50 equiv) was added slowly to the reaction mixture. After 6 h, a saturated $NaHCO_{3(aq)}$ (1.0 mL) was added dropwise. The reaction mixture was extracted with CH_2Cl_2 (3 x 2.0 mL). The combined organic layers were concentrated under reduced pressure to afford tertiary amine (**96**).



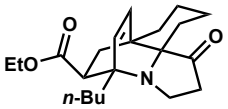
93
(87%)

Tertiary amine 93: The standard reduction protocol afforded **93** as the HCl salt in 87% yield. **R_f** (3:1 hexanes/EtOAc) 0.05; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 11.00 (s, 1H), 4.48 (s, 1H), 4.10 (d, J = 6.3 Hz, 1H), 3.76 (s, 1H), 3.49 (d, J = 56.9 Hz, 1H), 3.27 (d, J = 40.5 Hz, 1H), 3.07 (s, 1H), 2.87 (s, 1H), 2.49 (d, J = 13.0 Hz, 1H), 2.17 (s, 3H), 1.85 (s, 3H), 1.64 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 192.5, 69.9, 48.5, 46.1, 30.4, 28.6, 22.5, 17.8, 15.0.



97
(83%)

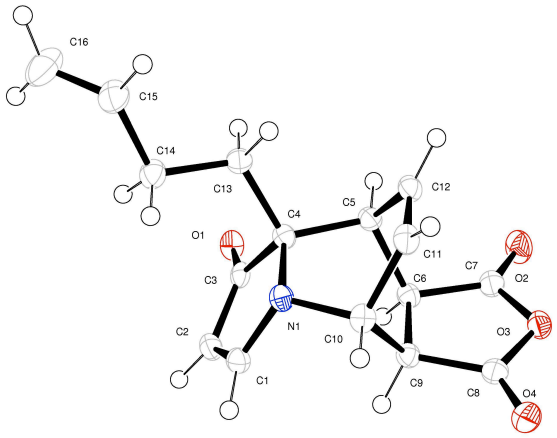
Tertiary amine 97: The standard reduction protocol afforded **97** in 83% yield. $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.11; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.71 (d, *J* = 10.0 Hz, 1H), 5.58 (d, *J* = 10.4 Hz, 1H), 4.70 (s, 1H), 3.66 (s, 1H), 3.63 – 3.59 (m, 1H), 3.35 (s, 1H), 3.23 (s, 1H), 3.17 (m, 1H), 2.76 (d, *J* = 7.4 Hz, 1H), 2.71 (d, *J* = 7.8 Hz, 2H), 2.63 (d, *J* = 7.2 Hz, 2H), 2.50 (m, 4H), 2.41 (d, *J* = 8.7 Hz, 2H), 2.36 (s, 3H), 1.41 (m, 1H), 0.97 – 0.91 (t, 3H).



98
(76%)

Tertiary amine 98: The standard reduction protocol afforded **98** in 76% yield. $\mathbf{R_f}$ (3:1 hexanes/EtOAc) 0.09; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.11 (d, *J* = 8.2 Hz, 1H), 6.07 (d, *J* = 8.2 Hz, 1H), 4.10 – 4.01 (m, 2H), 3.18 (t, *J* = 8.2 Hz, 2H), 2.74 (dd, *J* = 9.1, 5.8 Hz, 2H), 2.51 (dd, *J* = 16.2, 8.1 Hz, 2H), 2.14 (d, *J* = 3.9 Hz, 1H), 1.74 – 1.59 (m, 6H), 1.56 – 1.49 (m, 3H), 1.49 – 1.41 (m, 7H), 1.33 (dt, *J* = 11.5, 10.2 Hz, 8H), 1.24 (dt, *J* = 14.3, 5.1 Hz, 9H), 0.92 (dd, *J* = 9.2, 4.8 Hz, 3H).

X-Ray Structure of 55:



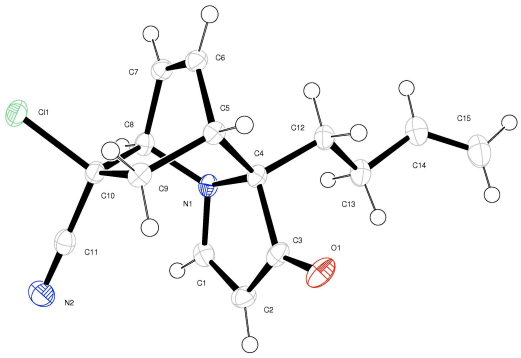
X-Ray Experimental Details: A colorless rod 0.12 x 0.08 x 0.06 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of 1.0°. Data collection was 97.8% complete to 67.00° in θ. A total of 2466 reflections were collected covering the indices, -26<=*h*<=24, 0<=*k*<=15, 0<=*l*<=12. 2466 reflections were found to be symmetry independent, with an R_{int} of 0.0188. Indexing and unit cell refinement indicated a twinned, C-centered monoclinic lattice. The space group was found to be C2/c (No. 15). The data were integrated using the Bruker SAINT software program and scaled using the TWINABS software program. Solution by direct methods (SIR-2008) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-97). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-97.

X-Ray Data:

X-ray ID	sarpong18	
Sample/notebook ID	ARN-IX-173B	
Empirical formula	C16 H15 N O4	
Formula weight	285.29	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 22.2396(13) Å	α= 90°.
	b = 12.8939(7) Å	β= 110.568(3)°.
	c = 10.3090(6) Å	γ = 90°.

Volume	2767.7(3) $Å^3$
Z	8
Density (calculated)	1.369 Mg/m^3
Absorption coefficient	0.820 mm^{-1}
F(000)	1200
Crystal size	0.12 x 0.08 x 0.06 mm^3
Crystal color/habit	colorless rod
Theta range for data collection	4.03 to 68.18°.
Index ranges	-26<=h<=24, 0<=k<=15, 0<=l<=12
Reflections collected	2466
Independent reflections	2466 [R(int) = 0.0188]
Completeness to theta = 67.00°	97.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9524 and 0.9080
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2466 / 0 / 191
Goodness-of-fit on F^2	1.070
Final R indices [I>2sigma(I)]	R1 = 0.0465, wR2 = 0.1257
R indices (all data)	R1 = 0.0479, wR2 = 0.1274
Largest diff. peak and hole	2.113 and -0.188 $e.Å^{-3}$

X-Ray Structure of 64:

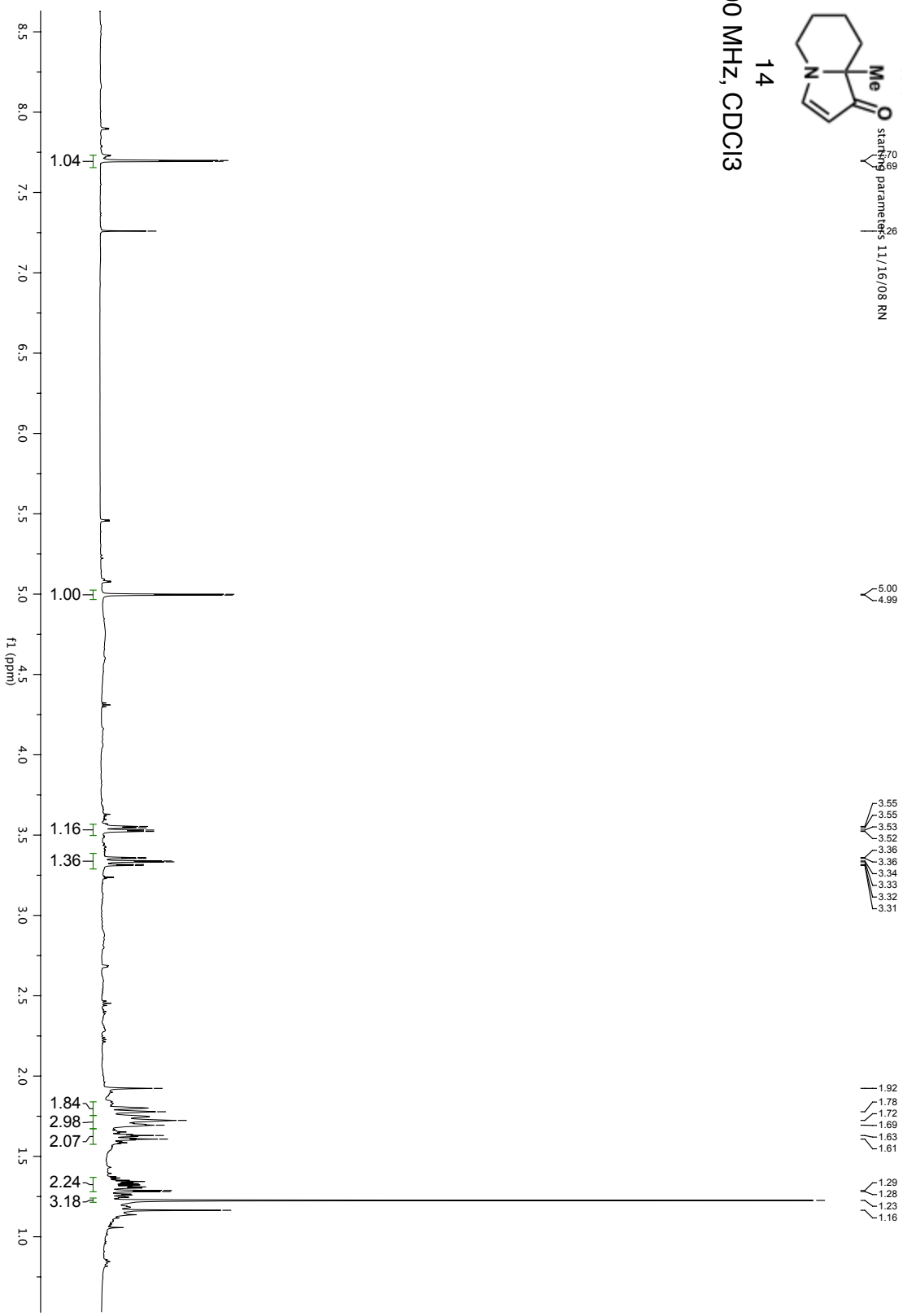


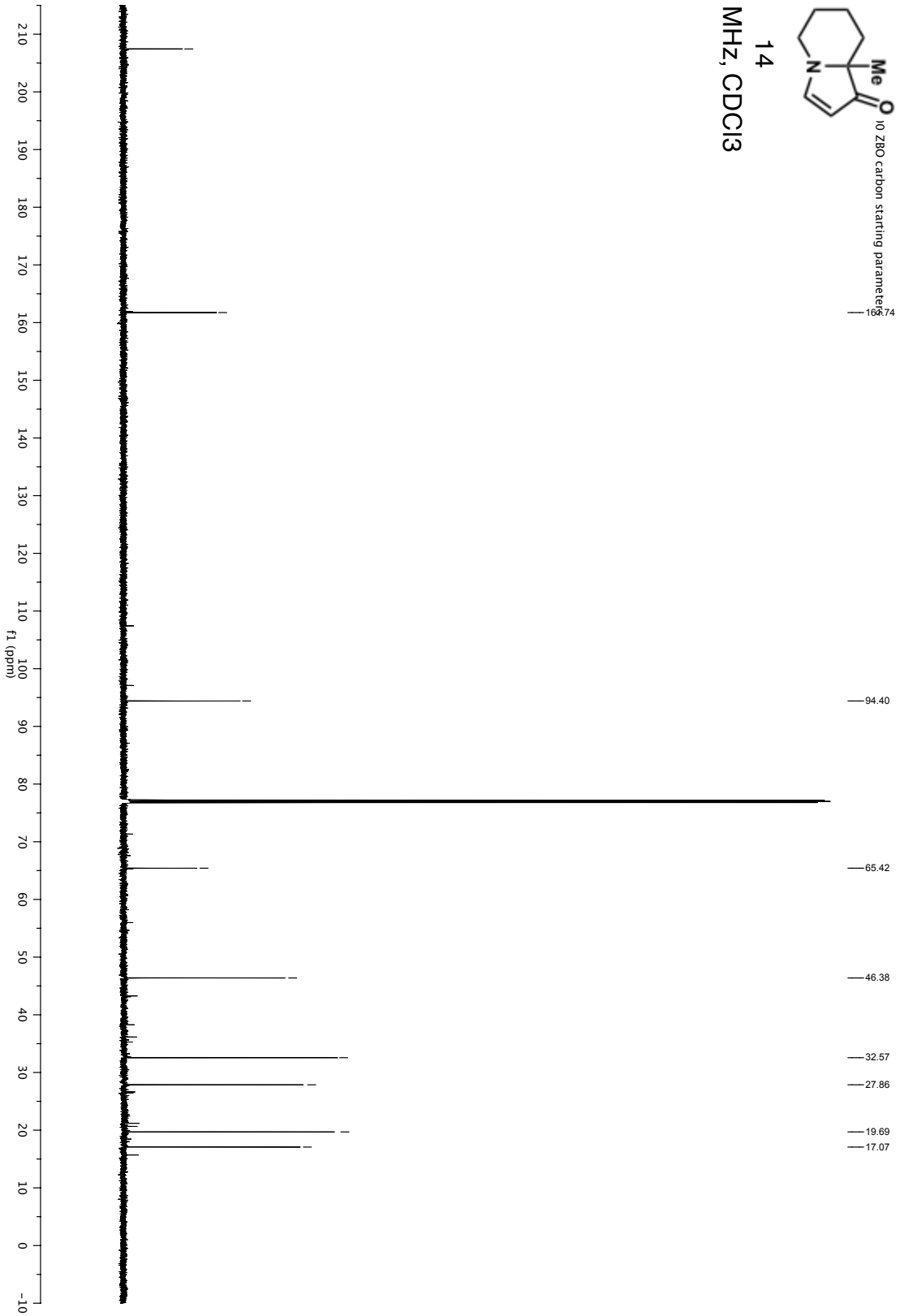
X-Ray Experimental Details: A colorless plate 0.12 x 0.10 x 0.06 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of 1.0°. Data collection was 99.8% complete to 67.00° in θ. A total of 14245 reflections were collected covering the indices, -10<=*h*<=10, -7<=*k*<=8, -26<=*l*<=26. 2476 reflections were found to be symmetry independent, with an R_{int} of 0.0123. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P2(1)/n (No. 14). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SIR-2004) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-97). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-97.

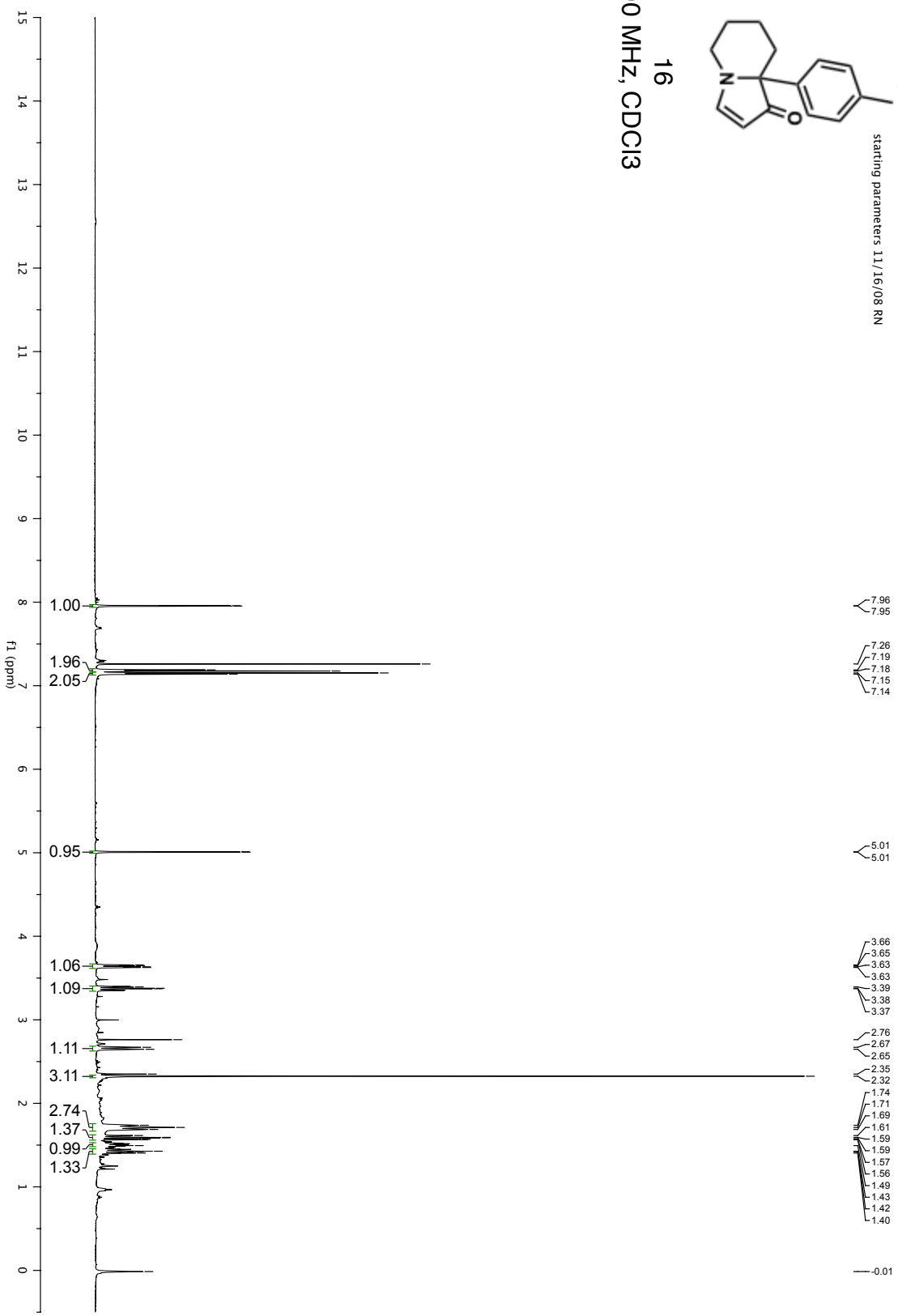
X-Ray Data:

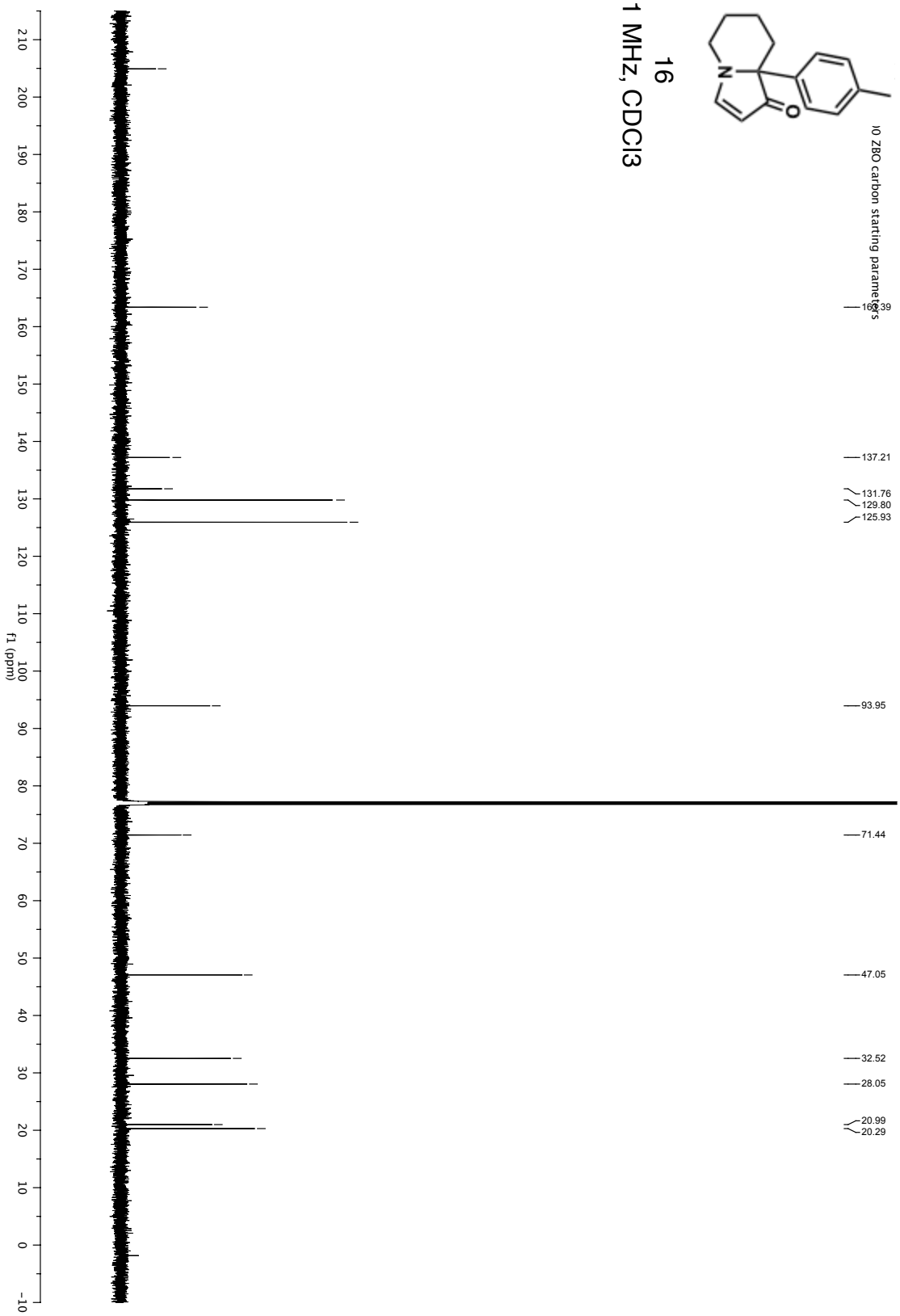
Empirical formula	C15 H15 Cl N2 O	
Formula weight	274.74	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 8.4660(3) Å	a= 90°.
	b = 7.2644(2) Å	b= 95.0810(10)°.
	c = 22.2712(7) Å	g = 90°.
Volume	1364.31(7) $Å^3$	
Z	4	
Density (calculated)	1.338 Mg/m^3	
Absorption coefficient	2.418 mm^{-1}	

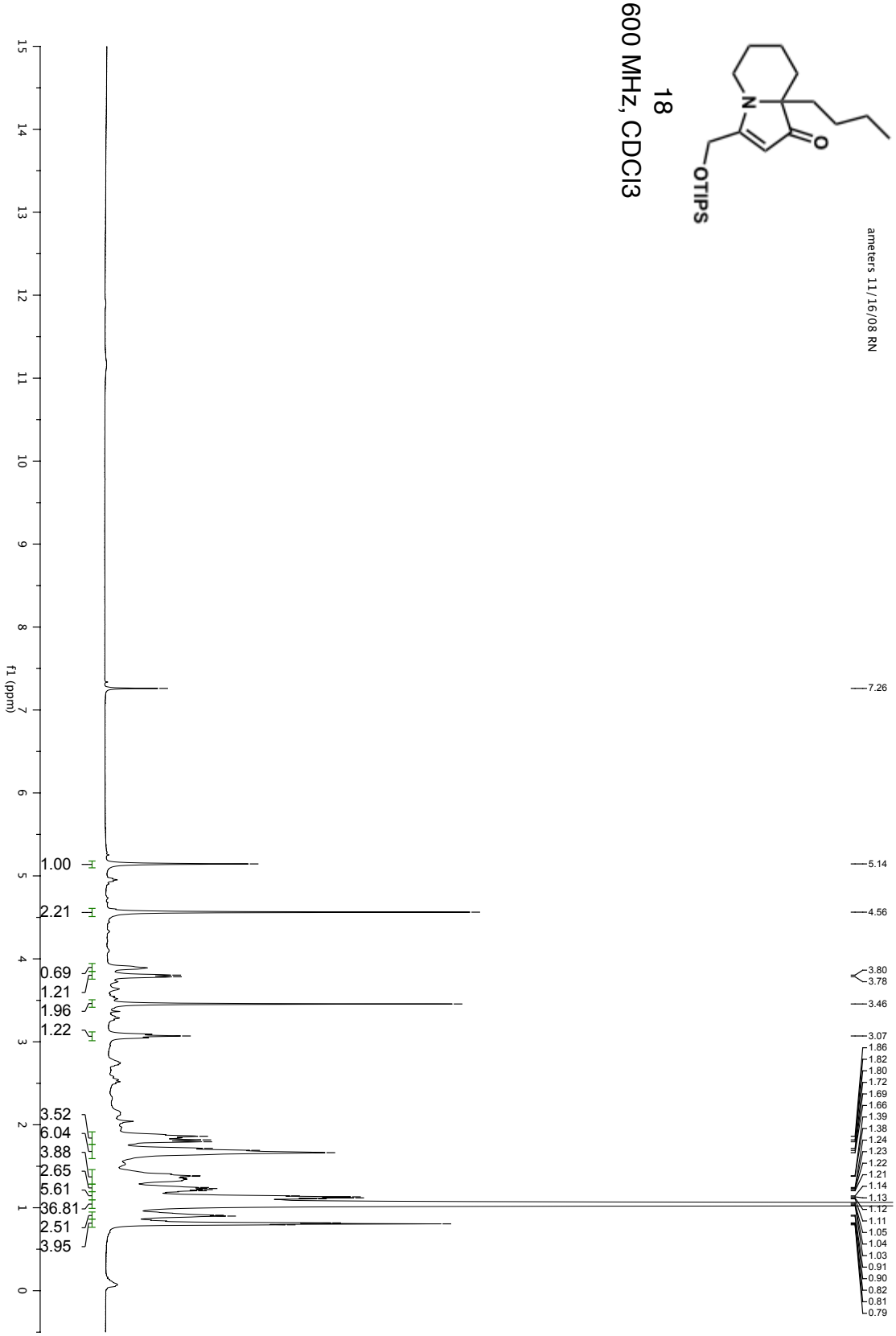
F(000)	576
Crystal size	0.12 x 0.10 x 0.06 mm^3
Crystal color/habit	colorless plate
Theta range for data collection	3.99 to 68.08°.
Index ranges	-10<=h<=10, -7<=k<=8, -26<=l<=26
Reflections collected	14245
Independent reflections	2476 [R(int) = 0.0123]
Completeness to theta = 67.00°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.8685 and 0.7601
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2476 / 0 / 172
Goodness-of-fit on F^2	1.057
Final R indices [I>2sigma(I)]	R1 = 0.0353, wR2 = 0.0949
R indices (all data)	R1 = 0.0361, wR2 = 0.0956
Largest diff. peak and hole	0.357 and -0.326 e.$Å^{-3}$

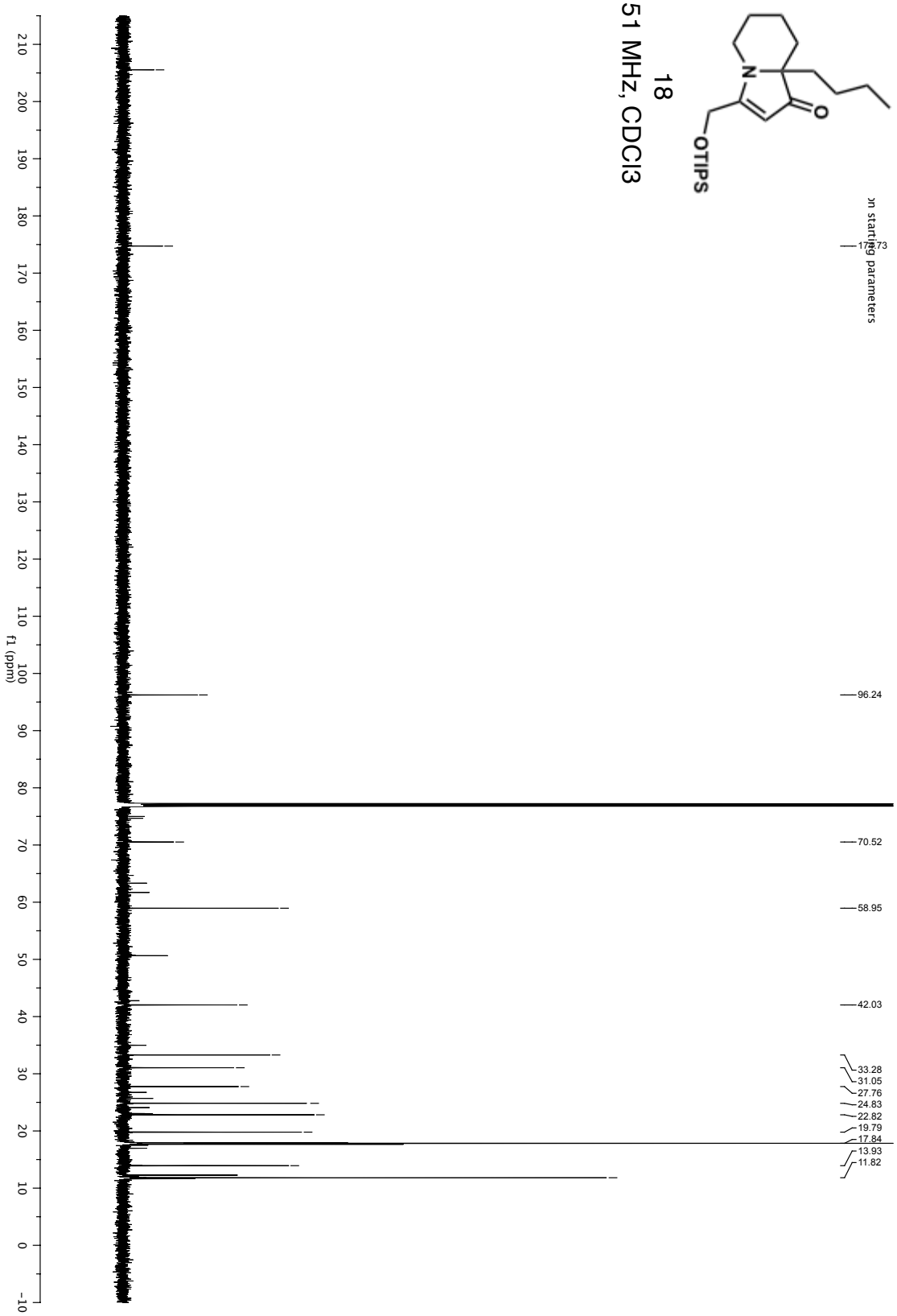


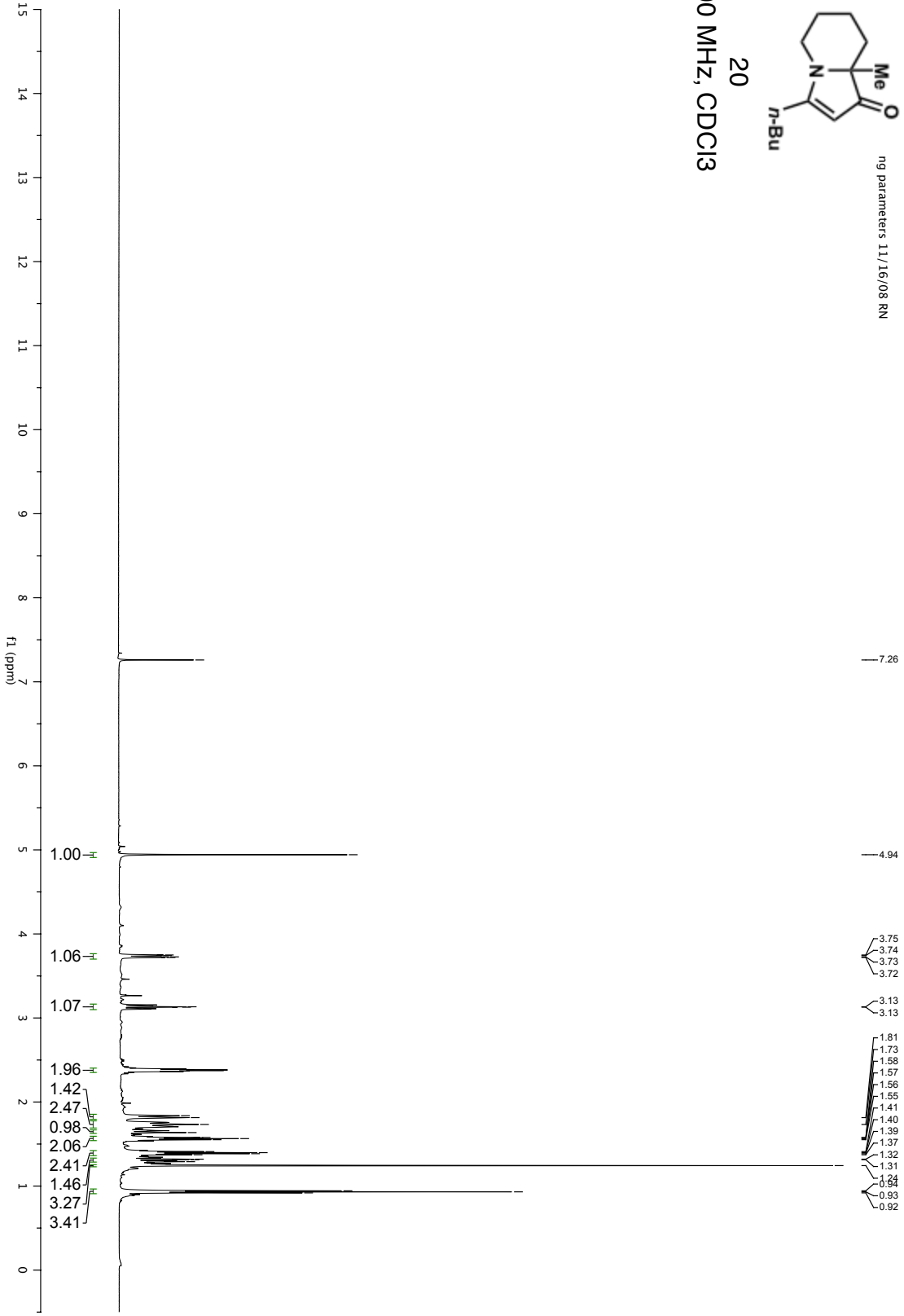


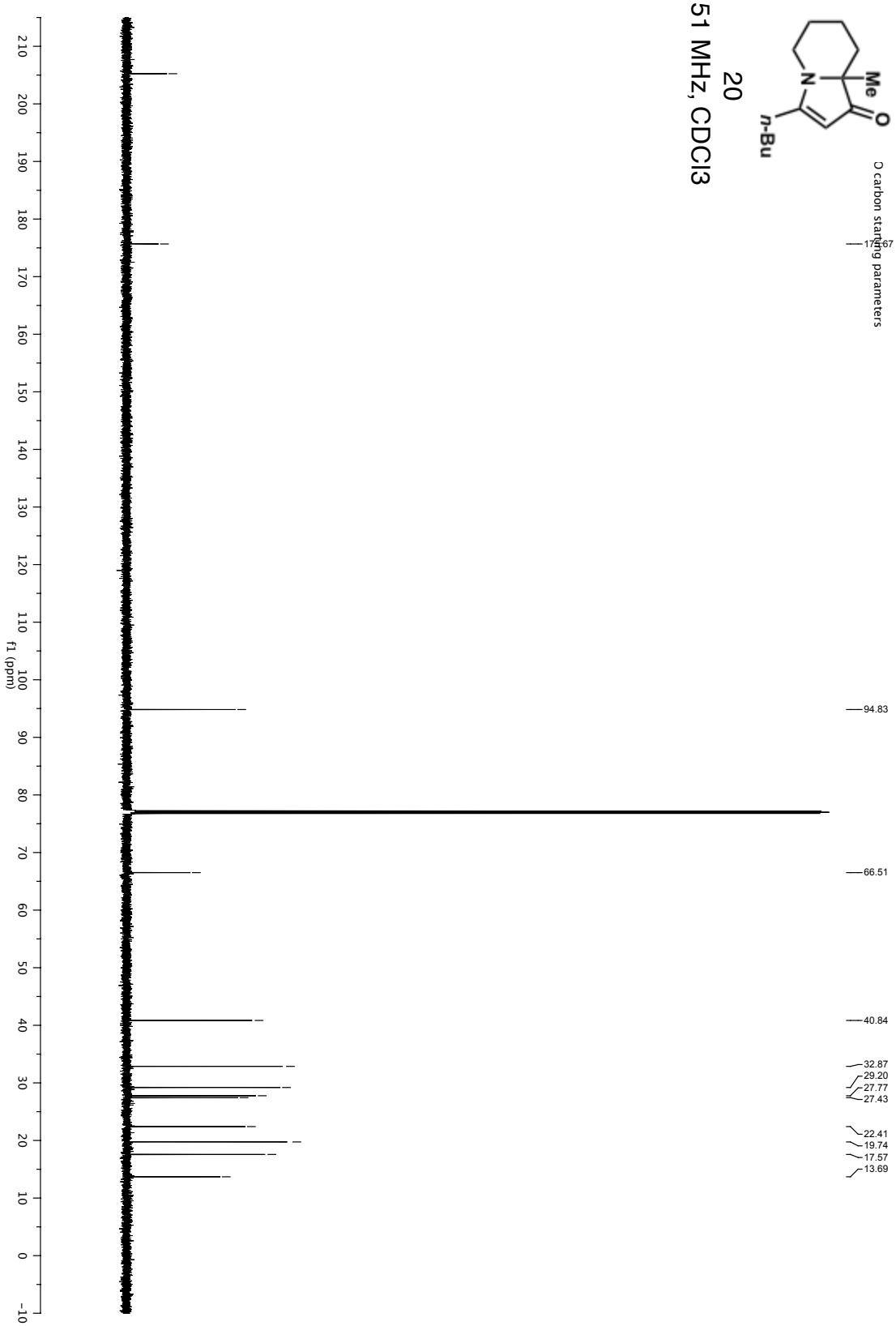


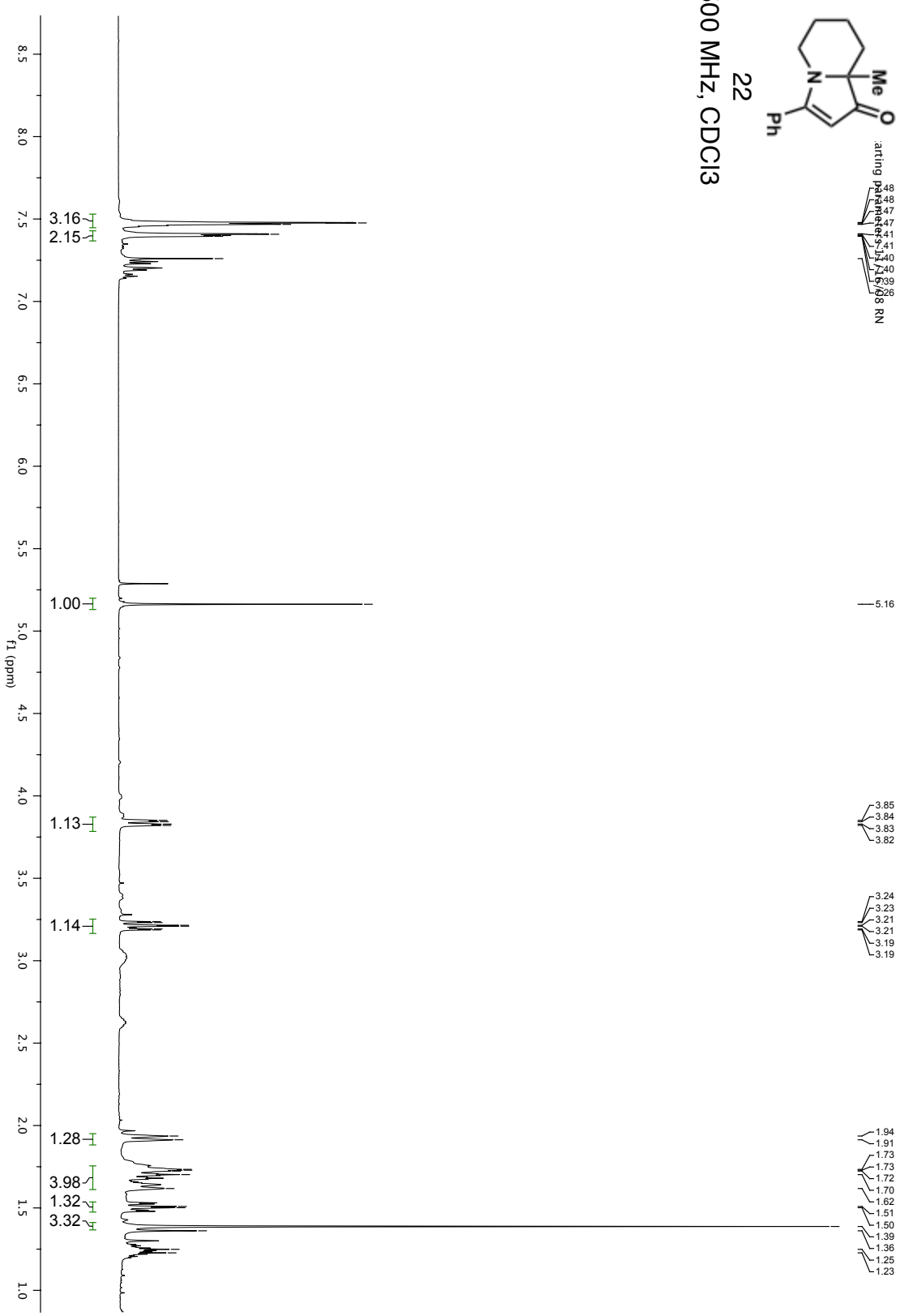


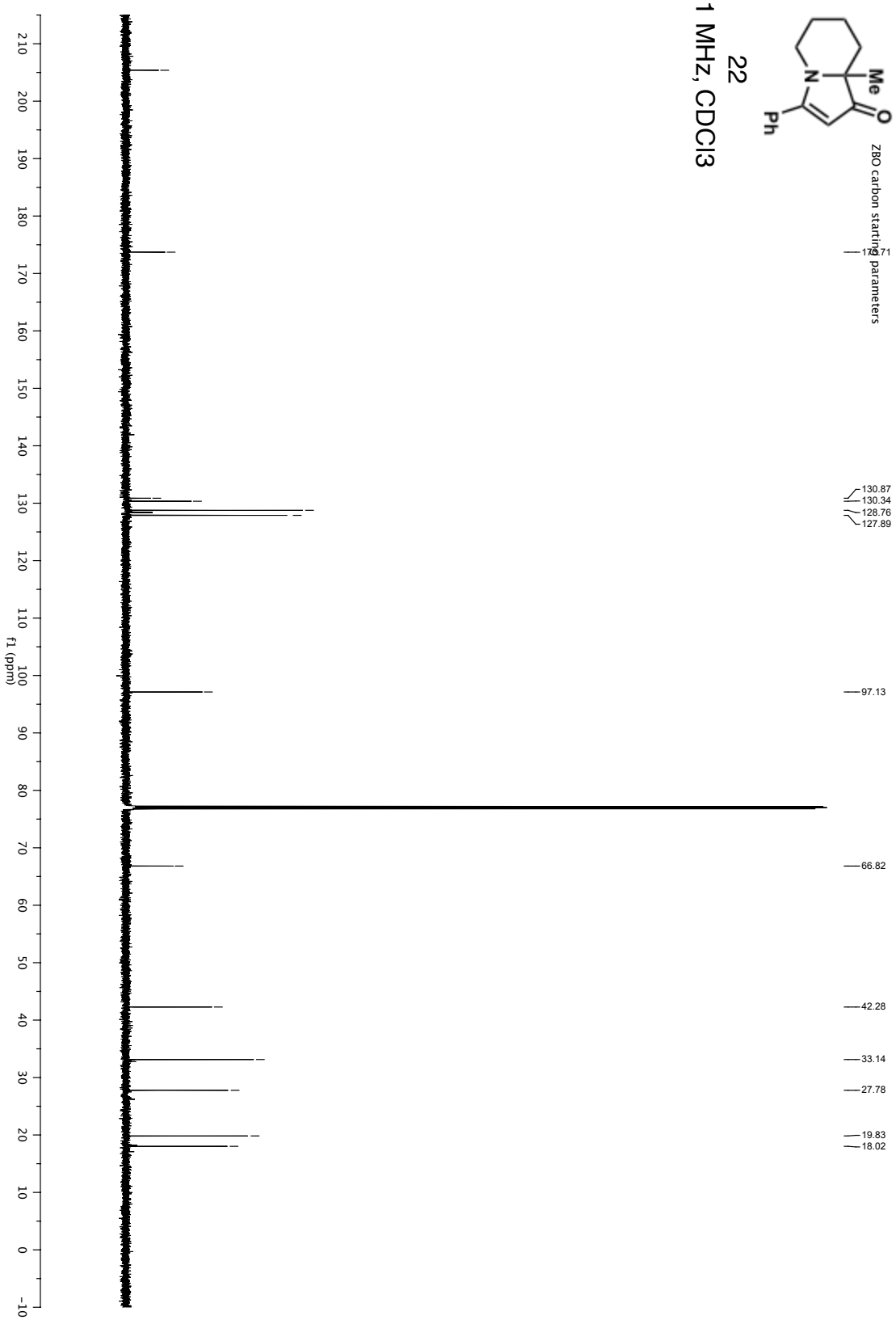


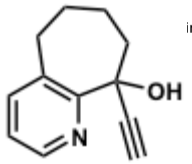












ing parameters 11/16/08 RN

8.34
8.34
7.50
7.49
7.27
7.20
7.19
7.19
7.18
3.32
3.30
3.28
2.81
2.79
2.58
2.29
2.04
2.03
2.03
2.02
2.01
1.61
1.61
1.50
1.27
1.25

25 (crude)
600 MHz, CDCl3