Supplemental material for:

Application of In Situ Generated Rh-bound Trimethylenemethane Variants to the Synthesis of 3,4-Fused Pyrroles

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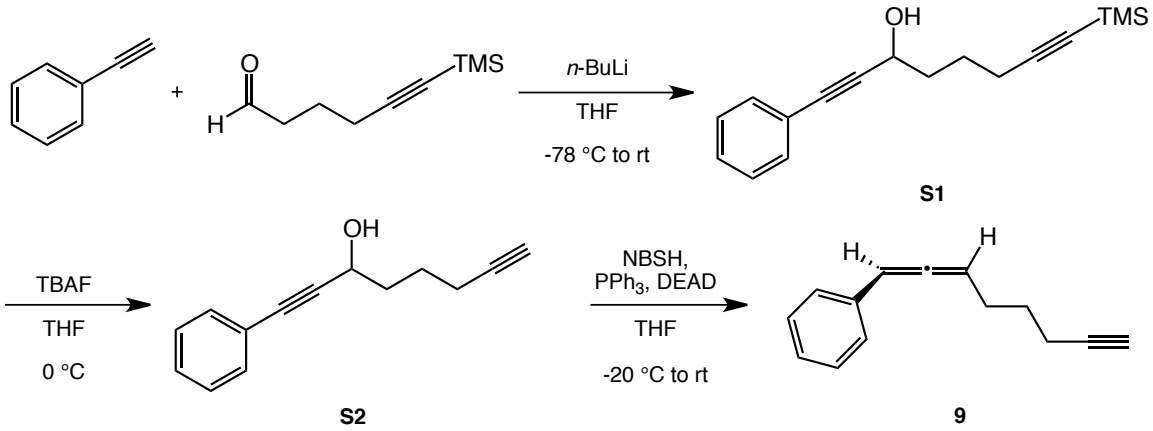
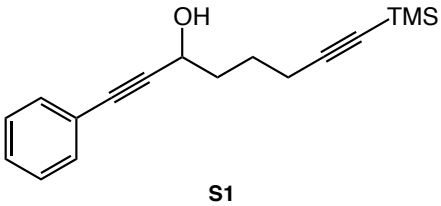
Table of Contents

Materials and Methods.

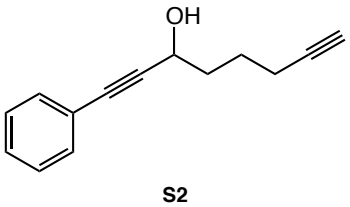
Unless stated otherwise, reactions were performed in oven-dried glassware sealed with rubber septa under a nitrogen atmosphere and were stirred with Teflon-coated magnetic stir bars. Liquid reagents and solvents were transferred via syringe using standard Schlenk techniques. Tetrahydrofuran (THF), toluene, acetonitrile (MeCN), and methanol (MeOH) were dried by passage over a column of activated alumina; dichloromethane was distilled over calcium hydride. Anhydrous chloroform was obtained in a Sure/Seal bottle from Aldrich. All other solvents and reagents were used as received unless otherwise noted. Thin layer chromatography was performed using SiliCycle silica gel 60 F-254 precoated plates (0.25 mm) and visualized by UV irradiation and anisaldehyde, CAM, potassium permanganate, or iodine stain. Sorbent silica gel (particle size 40-63 μm) was used for flash chromatography. NMR experiments were performed on Bruker spectrometers operating at 300, 400, 500 or 600 MHz for ^{1}H and 75, 101, 126, or 151 MHz for ^{13}C experiments. ^{1}H and ^{13}C chemical shifts (δ) are reported relative to the residual solvent signal. Data are reported as follows: chemical shift (multiplicity, coupling constants where applicable, number of hydrogens). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), dt (doublet of triplet), p (pentet), hept (heptet), m (multiplet), bs (broad singlet). Only select ^{1}H and ^{13}C spectra are reported. IR spectra were recorded on a Nicolet MAGNA-IR 850 spectrometer as thin films on NaCl plates and are reported in frequency of absorption (cm-1). Only selected IR absorbencies are reported. Low and high-resolution mass spectral data were obtained from the University of California; Berkeley Mass Spectral Facility, on a VG 70-Se Micromass spectrometer for FAB, and a VG Prospec Micromass spectrometer for EI. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The microwave-assisted reactions were conducted using a Biotage Initiator 2.5 reactor.

Representative procedure for allene substrate synthesis.





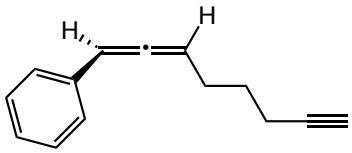
Propargylic alcohol (S1). To a solution of phenyl acetylene (0.30 mL, 2.7 mmol, 1.0 equiv) in THF (9 mL, 0.3 M) at -78 °C was added *n*-BuLi (1.1 mL of a 2.5 M solution in hexanes, 2.9 mmol, 1.1 equiv) dropwise over 20 minutes. After holding at this temperature for 15 min, the dry ice/acetone bath was replaced with a 0 °C ice bath and the reaction mixture was held at 0 °C for 20 min before being cooled to -78 °C. The reaction flask was charged with TMS-protected hex-5-ynal,[1] which was added dropwise via syringe over 20 minutes. The reaction mixture was stirred for 15 min at -78 °C, then 1 h at ambient temperature, at which time TLC indicated complete consumption of the starting material, and the reaction mixture was quenched by the slow addition of saturated aqueous ammonium chloride (10 mL). The biphasic mixture was stirred for 15 min, then diluted with ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to give **S1** (690 mg, 95%) as a colorless oil, which was used without further purification.



Terminal alkyne (S2). A solution of TBAF (3.1 mL of a 1.0 M solution in THF, 3.1 mmol, 1.2 equiv) was added dropwise to a solution of propargylic alcohol **S1** (690 mg, 2.6 mmol, 1.0 equiv) in THF (13 mL, 0.2 M) at 0 °C. The reaction mixture was allowed to stir at 0 °C for 30 min at which time TLC analysis indicated complete consumption of the starting material. The reaction mixture was

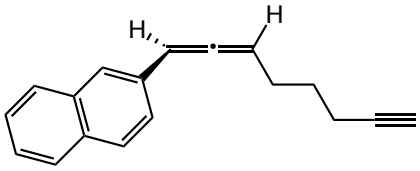
[1] Harris, G. D.; Herr, R. J.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 5452.

quenched by the addition of saturated aqueous ammonium chloride (15 mL) and diluted with diethyl ether (10 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to give **S2** (510 mg, 99%) as a colorless oil, which was used without further purification.



9

Octa-1,2-dien-7-yn-1-yl benzene (9).[2] To a solution of triphenylphosphine (1.0 g, 3.9 mmol, 1.5 equiv) in THF (5.2 mL, 0.75 M) at -20 °C (dry ice/brine bath) was added diethyl azodicarboxylate (0.61 mL, 1.5 equiv) dropwise over 1 min. The reaction mixture was stirred at -20 °C for an additional 10 min, then charged with **S2** (510 mg, 2.6 mmol, 1.0 equiv) as a solution in THF (4.3 mL, 0.5 M) added dropwise over 10 min. After 30 minutes, 2-nitrobenxylsulfonylhydrazine (NBSH)[3] (850 mg, 3.9 mmol, 1.5 equiv) as a solution in THF (5.2 mL, 0.75 M) was added dropwise over 10 min. The reaction mixture was held at -20 °C for an additional 2 h then allowed to warm to ambient temperature and stirred for 10 h. After this time, the reaction mixture was diluted with dichloromethane (10 mL), the stirbar was removed and silica gel (2 g) was added to the reaction flask and the mixture was concentrated *in vacuo* and filtered through a short silica plug eluting with pentanes to give **9** (320 mg, 67%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.29 - 7.25 (m, 4H), 7.16 (tt, *J* = 5.8, 2.9 Hz, 1H), 6.13 (dt, *J* = 6.4, 3.1 Hz, 1H), 5.56 (q, *J* = 6.6 Hz, 1H), 2.28 - 2.21 (m, 1H), 1.93 (t, *J* = 2.6 Hz, 1H), 1.75-1.85 (m, 2H). Spectra were consistent with those reported previously.[4]

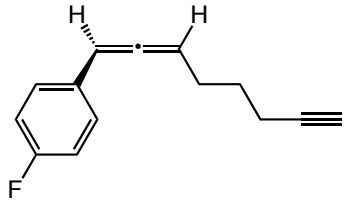


S3

2-(octa-1,2-dien-7-yn-1-yl)naphthalene (S3). Prepared from 2-ethynylnaphthalene using the representative procedure. **IR** (film): 3230, 3055, 2920, 2849, 1947, 1598, 1510, 1433, 1128, 895, 857, 820, 749. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.83 - 7.72 (m, 3H), 7.65 (s, 1H), 7.49 (d, *J* = 8.5 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.3 Hz, 1H), 6.34 (dt, *J* = 6.3, 3.1 Hz, 1H), 5.66 (q, *J* = 6.6 Hz, 1H), 2.33 - 2.27 (m, 4H), 1.97 (t, *J* = 2.7 Hz, 1H), 1.80 - 1.72 (m, 2H). **^{13}C NMR** (150 MHz, $CDCl_3$) d 205.8, 133.7, 132.5, 132.3, 128.2,

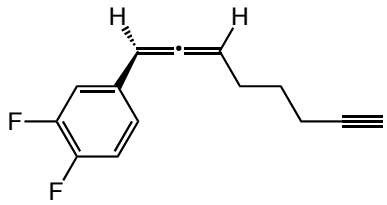
[2] Modified procedure adapted from Myers' synthesis of allenes. Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492.
[3] Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62*, 7507.
[4] Brummond, K. M.; Wan, H.; Kent, J. L. *J. Org. Chem.* **1998**, *63*, 6535.

127.7, 127.6, 126.1, 125.5, 125.3, 124.6, 95.4, 94.3, 84.0, 68.6, 27.7, 27.6, 17.9. **HRMS** (*m/z*): M^+ calcd for $C_{18}H_{16}$, 232.1252; found, 232.1253.



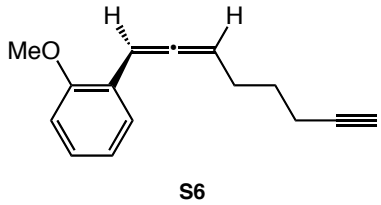
S4

1-fluoro-4-(octa-1,2-dien-7-yn-1-yl)benzene (S4). Prepared from 1-ethynyl-4-fluorobenzene using the representative procedure. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 8.5, 5.4 Hz, 2H), 7.00 (t, *J* = 8.5 Hz, 2H), 6.13 (dt, *J* = 6.4, 3.1 Hz, 1H), 5.58 (q, *J* = 6.6 Hz, 1H), 2.32 - 2.21 (m, 4H), 1.97 (t, *J* = 2.8 Hz, 1H), 1.78 - 1.67 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 205.0, 162.6, 161.0, 130.7, 130.7, 128.0, 127.9, 115.5, 115.4, 94.3, 94.0, 84.0, 68.6, 27.7, 27.6, 17.9. **HRMS** (*m/z*): M^+ calcd for $C_{18}H_{16}$, 232.1252; found, 232.1253. **HRMS** (*m/z*): M^+ calcd for $C_{14}H_{13}F$, 200.1001; found, 200.1003.



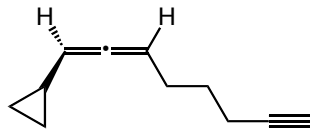
S5

1,2-Difluoro-4-(octa-1,2-dien-7-yn-1-yl)benzene (S5). Prepared from 1-ethynyl-3,4-difluorobenzene using the representative procedure. **IR** (film): 3309, 2927, 2855, 2119, 1951, 1606, 1516, 1455, 1410, 1228, 1206, 1150, 1116, 960, 882, 785, 741, 631.**^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.15 - 7.03 (m, 2H), 7.00 - 6.93 (m, 1H), 6.07 (dt, *J* = 6.4, 3.1 Hz, 1H), 5.61 (q, *J* = 6.6 Hz, 1H), 2.31 - 2.24 (m, 4H), 1.97 (t, *J* = 2.9 Hz, 1H), 1.78 - 1.65 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 205.3, 205.3, 151.4, 151.3, 150.1, 150.0, 149.7, 149.7, 148.4, 148.4, 132.1, 132.1, 132.1, 132.0, 122.4, 122.4, 122.4, 122.4, 117.3, 117.2, 115.0, 114.9, 94.9, 93.7, 93.7, 93.6, 83.8, 68.7, 27.6, 27.4, 17.9. **HRMS** (*m/z*): M^+ calcd for $C_{14}H_{12}F_2$, 218.0907; found, 218.0905.



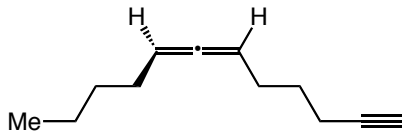
S6

1-Methoxy-2-(octa-1,2-dien-7-yn-1-yl)benzene (S6). Prepared from 1-ethynyl-4-methoxybenzene using the representative procedure. **IR** (film): 3230, 2938, 2836, 2117, 1948, 1727, 1596, 1493, 1464, 1288, 1246, 1099, 1049, 1029, 885, 752, 629. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.5 Hz, 1H), 7.17 (t, *J* = 7.8 Hz, 1H), 6.92 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.56 (dt, *J* = 6.3, 3.1 Hz, 1H), 5.54 (q, *J* = 6.6 Hz, 1H), 3.85 (s, 3H), 2.32 - 2.20 (m, 4H), 1.96 (t, *J* = 2.6 Hz, 1H), 1.77 - 1.68 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 205.6, 155.9, 127.8, 127.5, 123.2, 120.7, 110.9, 93.2, 88.8, 84.1, 68.5, 55.5, 27.8, 27.7, 17.9. **HRMS** (*m/z*): M^+ calcd for $C_{15}H_{16}O$, 212.1201; found, 212.1219.



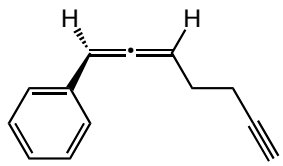
S7

Octa-1,2-dien-7-yn-1-ylcyclopropane (S7). Prepared from ethynylcyclopropane using the representative procedure. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.16 (qd, *J* = 6.5, 1.3 Hz, 1H), 4.98 (tt, *J* = 6.2, 2.9 Hz, 1H), 2.23 (td, *J* = 7.2, 2.7 Hz, 2H), 2.12 - 2.05 (m, 2H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.63 (p, *J* = 7.3 Hz, 2H), 1.26 - 1.16 (m, 1H), 0.70 - 0.64 (m, 2H), 0.37 - 0.29 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 203.3, 95.6, 91.7, 84.2, 68.3, 28.0, 27.8, 17.8, 9.5, 6.7, 6.5. **HRMS** (*m/z*): M^+ calcd for $C_{11}H_{14}$, 146.1096; found, 146.1095.



S8

Dodeca-6,7-dien-1-yne (S8). Prepared from 1-hexyne using the representative procedure. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.13 - 5.02 (m, 2H), 2.23 (td, *J* = 7.2, 2.7 Hz, 2H), 2.09 (qd, *J* = 7.0, 3.1 Hz, 2H), 2.02 - 1.95 (m, 2H), 1.94 (t, *J* = 2.7 Hz, 1H), 1.64 (p, *J* = 7.3 Hz, 2H), 1.42 - 1.30 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 204.0, 91.4, 89.7, 84.3, 68.2, 31.3, 28.6, 27.9, 27.8, 22.1, 17.8, 13.9. **HRMS** (*m/z*): M^+ calcd for $C_{12}H_{18}$, 162.1409; found, 162.1410.

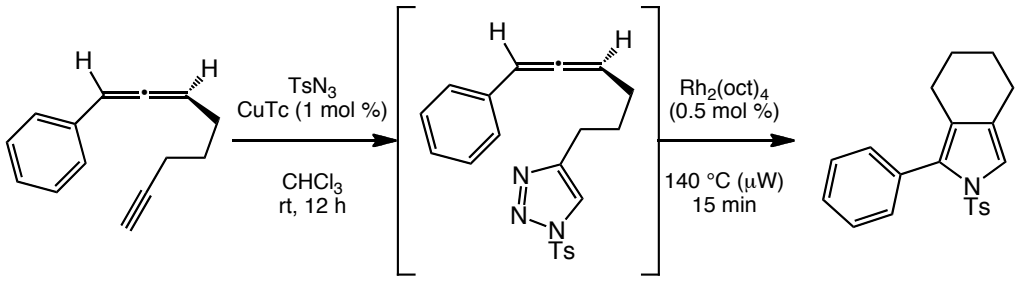


S9

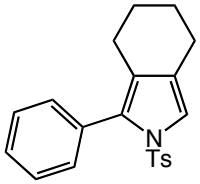
Hepta-1,2-dien-6-yn-1-ylbenzene (S9). Prepared from phenyl acetylene and TMS-protected pent-4-ynal[5] using the representative procedure. **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.34 - 7.28 (m, 4H), 7.22 - 7.17 (m, 1H), 6.22 - 6.17 (m, 1H), 5.68 - 5.62 (m, 1H), 2.41 - 2.33 (m, 4H), 1.99 (t, *J* = 2.3 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 205.2, 134.5, 128.5, 126.8, 126.7, 95.6, 93.4, 83.7, 68.9, 28.0, 18.3. **HRMS** (*m/z*): M^+ calcd for $C_{13}H_{12}$, 168.0939; found, 168.0942.

[5] Cruciani, P.; Stammler, R.; Aubert, C.; Malacria, M. *J. Org. Chem.* **1996**, *61*, 2699.

Representative procedure for pyrrole synthesis.

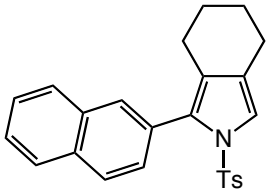


9 **10** **11**



11

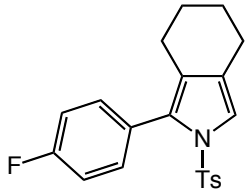
1-Phenyl-2-tosyl-4,5,6,7-tetrahydro-2*H*-isoindole (11). To a flame-dried microwave vial was added copper (I) thiophene carboxylate (CuTc, 1.0 mg, 5 mol %). The vial was sealed, and evacuated and backfilled with N_2 (3x), then allene **9** (100 mg, 0.54 mmol, 1.0 equiv) in chloroform (2.7 mL, 0.2 M) was added, followed by tosyl azide (84 μL, 0.54 mmol, 1.0 equiv). The reaction mixture was allowed to stir at ambient temperature for 12 h at which time TLC analysis indicated complete consumption of the starting material, and formation of triazole **10**. The reaction flask was then charged with $Rh_2(oct)_4$ (2.1 mg, 0.5 mol %) dissolved in chloroform (0.2 mL, 0.015 M) via syringe. The resulting mixture was heated to 140 °C under microwave irradiation for 15 min. After cooling to ambient temperature, silica gel was added to the reaction mixture and the solvent was removed *in vacuo.* The resulting residue was purified by column chromatography eluting with 6:1 hexanes:ethyl acetate to give **11** (146 mg, 77%) as a colorless oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.34 - 7.29 (m, 3H), 7.26 - 7.22 (m, 2H), 7.18 - 7.13 (m, 2H), 7.13 - 7.08 (m, 3H), 2.56 (t, *J* = 6.6 Hz, 2H), 2.36 (s, 3H), 2.26 (t, *J* = 6.3 Hz, 2H), 1.70 - 1.63 (m, 2H), 1.63 - 1.55 (m, 2H). **HRMS** (*m/z*): M^+ calcd for $C_{21}H_{21}NO_2S$, 351.1293; found, 351.1294.



S10

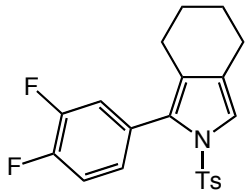
1-(naphthalen-2-yl)-2-tosyl-4,5,6,7-tetrahydro-isoindole (S10). Prepared from **S3** using the representative procedure. **IR** (film): 2928, 2856, 1726, 1596, 1369, 1248, 1166, 1056, 817, 742, 672. **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.87 (dd, *J* = 7.4, 1.9 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.75 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.53 - 7.48 (m, 3H), 7.38 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.25 - 7.23 (m, 2H), 7.15 (s, 1H), 7.05 (d, *J* = 8.0 Hz, 2H), 2.59 (t, *J* = 6.5, 2H), 2.35 (s, 3H), 2.31 (t, *J* = 6.3 Hz, 2H), 1.73 - 1.65 (m, 2H), 1.64 - 1.55 (m, 2H).**^{13}C NMR** (151 MHz, $CDCl_3$) δ 144.1, 136.0, 132.7, 132.6, 130.1, 129.5, 129.3, 129.2, 128.8, 128.0, 127.7, 127.1, 127.0, 126.6,

126.2, 126.2, 125.9, 124.3, 118.4, 23.2, 23.2, 22.2, 22.0, 21.5. **HRMS** (*m/z*): M^+ calcd for $C_{25}H_{23}NO_2S$, 401.1449; found, 401.1454.



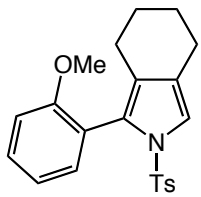
S11

1-(4-fluorophenyl)-2-tosyl-4,5,6,7-tetrahydro-2*H*-isoindole (S11). Prepared from **S4** using the representative procedure. **IR** (film): 2930, 2857, 1596, 1495, 1369, 1222, 1173, 1101, 671. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.26 1 7.22 (m, 2H), 7.15 - 7.07 (m, 5H), 7.04 - 6.96 (m, 2H), 2.55 (td, *J* = 6.4, 1.4 Hz, 2H), 2.37 (s, 3H), 2.22 (t, *J* = 6.2 Hz, 2H), 1.70 - 1.56 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.6, 161.2, 144.3, 135.9, 133.1, 133.0, 129.3, 128.3, 127.0, 127.0, 126.9, 125.8, 124.0, 118.2, 114.4, 114.2, 23.1, 22.1, 21.8, 21.6. **HRMS** (*m/z*): M^+ calcd for $C_{21}H_{20}FNO_2S$, 369.1199; found, 369.1195.



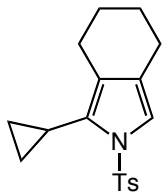
S12

1-(3,4-difluorophenyl)-2-tosyl-4,5,6,7-tetrahydro-2*H*-isoindole (S12). Prepared from **S5** using the representative procedure.**^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.28 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.14 - 7.07 (m, 2H), 6.94 - 6.87 (m, 2H), 2.55 (t, *J* = 6.3 Hz, 2H), 2.38 (s, 3H), 2.23 (t, *J* = 6.2 Hz, 2H), 1.71 - 1.57 (m, 4H).**^{13}C NMR** (151 MHz, $CDCl_3$) δ 149.2, 149.2, 148.5, 148.4, 144.0, 135.9, 129.4, 127.7, 127.7, 127.6, 127.2, 127.0, 126.4, 124.1, 120.2, 120.1, 118.6, 116.2, 116.1, 23.1, 22.0, 21.8, 21.5. **HRMS** (*m/z*): M^+ calcd for $C_{21}H_{19}F_2NO_2S$, 387.1105; found, 387.1104.



12

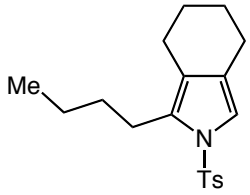
1-(2-methoxyphenyl)-2-tosyl-4,5,6,7-tetrahydro-2*H*-isoindole (12). Prepared from **S6** using the representative procedure. **IR** (film): 2931, 2856, 1737, 1596, 1434, 1367, 1246, 1171, 1098, 670. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.52 - 7.28 (m, 3H), 7.26 - 7.11 (m, 3H), 7.09 - 6.99 (m, 1H), 6.99 - 6.93 (m, 1H), 6.91 - 6.81 (m, 1H), 3.62 (s, 3H), 2.71 - 2.56 (m, 2H), 2.40 (s, 3H), 2.31 - 2.17 (m, 2H), 1.80 - 1.56 (m, 4H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.5, 143.8, 136.5, 133.4, 129.9, 129.1, 127.3, 125.8, 125.5, 123.8, 120.0, 119.4, 117.6, 110.3, 55.2, 23.3, 23.1, 22.0, 21.8, 21.6. **HRMS** (*m/z*): M^+ calcd for $C_{22}H_{23}NO_3S$, 381.1399; found, 381.1403.



S13

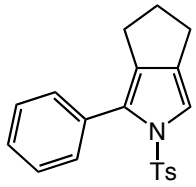
1-cyclopropyl-2-tosyl-4,5,6,7-tetrahydro-2*H*-isoindole (S13). Prepared from **S7** using the representative procedure. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.04 (s, 1H), 2.52 (t, *J* = 5.1 Hz, 2H), 2.45 (t, *J* = 6.2 Hz, 1H), 2.42 (s, 3H), 1.78 - 1.69 (m, 1H), 1.68 - 1.59 (m, 4H), 0.72 - 0.70 (m, *J* = 4.2 Hz, 2H), 0.46 - 0.39 (m, 2H).**^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.0, 137.0, 129.5, 129.0, 127.0, 123.3, 122.5, 117.0, 23.4, 23.0,

22.8, 21.9, 21.5, 6.9, 6.4. **HRMS** (*m/z*): M^+ calcd for $C_{18}H_{21}NO_2S$, 315.1293; found, 315.1293.



S14

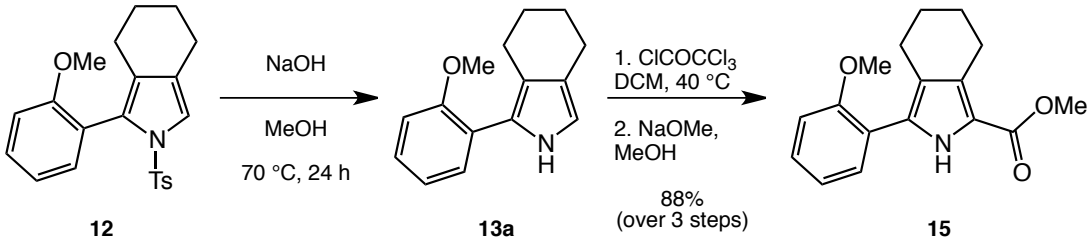
1-butyl-2-tosyl-4,5,6,7-tetrahydro-2*H*-isoindole (S14). Prepared from **S8** using the representative procedure. **IR** (film): 2930, 2858, 1597, 1440, 1365, 1249, 1187, 1174, 1100, 1066, 668, 587. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.62 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H), 6.92 (s, 1H), 2.61 - 2.52 (m, 2H), 2.49 (td, *J* = 5.7, 4.9, 1.9 Hz, 2H), 2.39 (s, 3H), 2.38 - 2.32 (m, 2H), 1.70 - 1.59 (m, 4H), 1.45 - 1.34 (m, 2H), 1.33 - 1.21 (m, 2H), 0.85 (t, *J* = 7.2 Hz, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.1, 137.2, 129.9, 129.8, 126.6, 123.6, 123.0, 116.5, 32.1, 25.2, 23.4, 23.3, 22.7, 21.9, 21.7, 21.6, 13.9. **HRMS** (*m/z*): M^+ calcd for $C_{19}H_{25}NO_2S$, 331.1606; found, 331.1602.



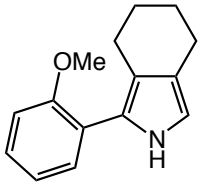
S15

1-phenyl-2-tosyl-2,4,5,6-tetrahydrocyclopenta[*c*]pyrrole (S15). Prepared from **S9** using the representative procedure. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.36 - 7.30 (m, 3H), 7.29 - 7.23 (m, 4H), 7.10 (d, *J* = 7.9 Hz, 2H), 7.01 (s, 1H), 2.59 (t, *J* = 7.2 Hz, 2H), 2.44 (t, *J* = 7.2 Hz, 2H), 2.35 (s, 3H), 2.21 (p, *J* = 7.2 Hz, 2H).**^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.5, 138.7, 136.2, 135.5, 132.1, 130.9, 129.6, 128.0, 127.8, 127.6, 127.4, 115.5, 31.2, 25.3, 25.2, 22.0. **HRMS** (*m/z*): M^+ calcd for $C_{20}H_{19}NO_2S$, 337.1136; found, 337.1137.

Further functionalization of pyrrole 12.

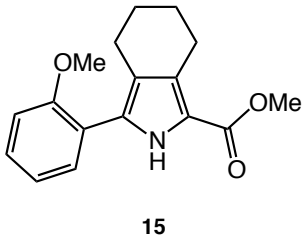


12 **13a** **15**



13a

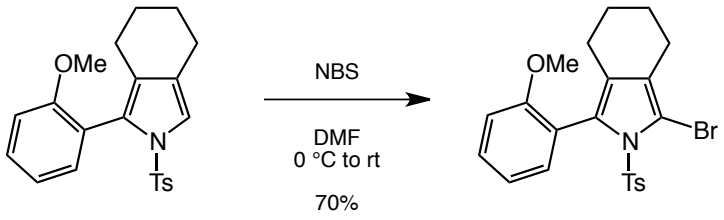
Deprotected pyrrole (13a). To a degassed solution of **12** (38 mg, 0.10 mmol, 1.0 equiv) in methanol (1 mL, 0.1 M), was added finely powdered NaOH (60 mg, 1.5 mmol, 15 equiv) under a stream of N_2. The reaction mixture was heated to 70 °C and held at this temperature for an additional 24 h. After this time, the reaction mixture was cooled to ambient temperature and quenched by the addition of saturated ammonium chloride (2 mL) and diluted with dichloromethane (2 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 2 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give **13a** as a purple film, which was used immediately without further purification. **IR** (film): 3315, 2934, 2857, 2360, 1693, 1489, 1463, 1437, 1245, 1047, 1023, 754, 679. **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.35 - 7.30 (m, 1H), 7.18 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.02 - 6.94 (m, 2H), 6.43 (s, 1H), 3.93 (s, 3H), 2.48 - 2.38 (m, 2H), 2.18 - 2.11 (m, 2H), 1.74 - 1.62 (m, 4H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.8, 157.0, 156.8, 132.1, 129.8, 127.4, 126.5, 121.4, 111.4, 88.6, 55.7, 22.0, 22.0, 21.7, 19.8.



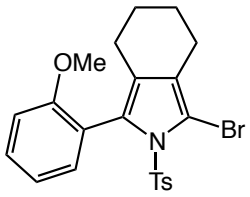
15

Pyrrole methyl ester (15). Dichloromethane (0.5 mL, 0.2 M) was added to a vial containing pyrrole **13a** (0.10 mmol, 1.0 equiv) and imidazole (11 mg, 0.16 mmol, 1.6 equiv). To this solution was added 2,2,2-trichloroacetyl chloride (17 μL, 0.15 mmol, 1.5 equiv). The resulting solution was heated to 40 °C and held at this temperature for 2 h. Upon cooling to ambient temperature, the reaction mixture was quenched by the addition of saturated aqueous sodium bicarbonate (1 mL). The layers were separated the aqueous layer was extracted with dichloromethane (2 x 2 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo.* To this residue was added a stirbar and NaOMe (2 mL as a freshly prepared 0.05 M solution in methanol, 0.10 mmol, 1.0 equiv). After stirring at ambient temperature for 2 h, the reaction mixture was quenched by the addition of saturated ammonium chloride (1 mL). The methanol was then removed *in vacuo* and the

resulting residue was diluted with water (2 mL) and ethyl acetate (2 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 2 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to give **15** (24.5 mg, 88% over 3 steps) as a colorless film. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 9.82 (bs, 1H), 7.53 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.30 - 7.24 (m, 1H), 7.06 - 6.98 (m, 2H), 3.93 (s, 3H), 3.86 (s, 3H), 2.87 (t, *J* = 6.1 Hz, 2H), 2.71 (t, *J* = 5.9 Hz, 2H), 1.84 - 1.72 (m, 4H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.2, 156.1, 129.2, 129.0, 128.6, 128.3, 121.0, 120.7, 120.6, 116.7, 111.4, 55.8, 51.2, 24.5, 23.9, 23.5, 23.1.



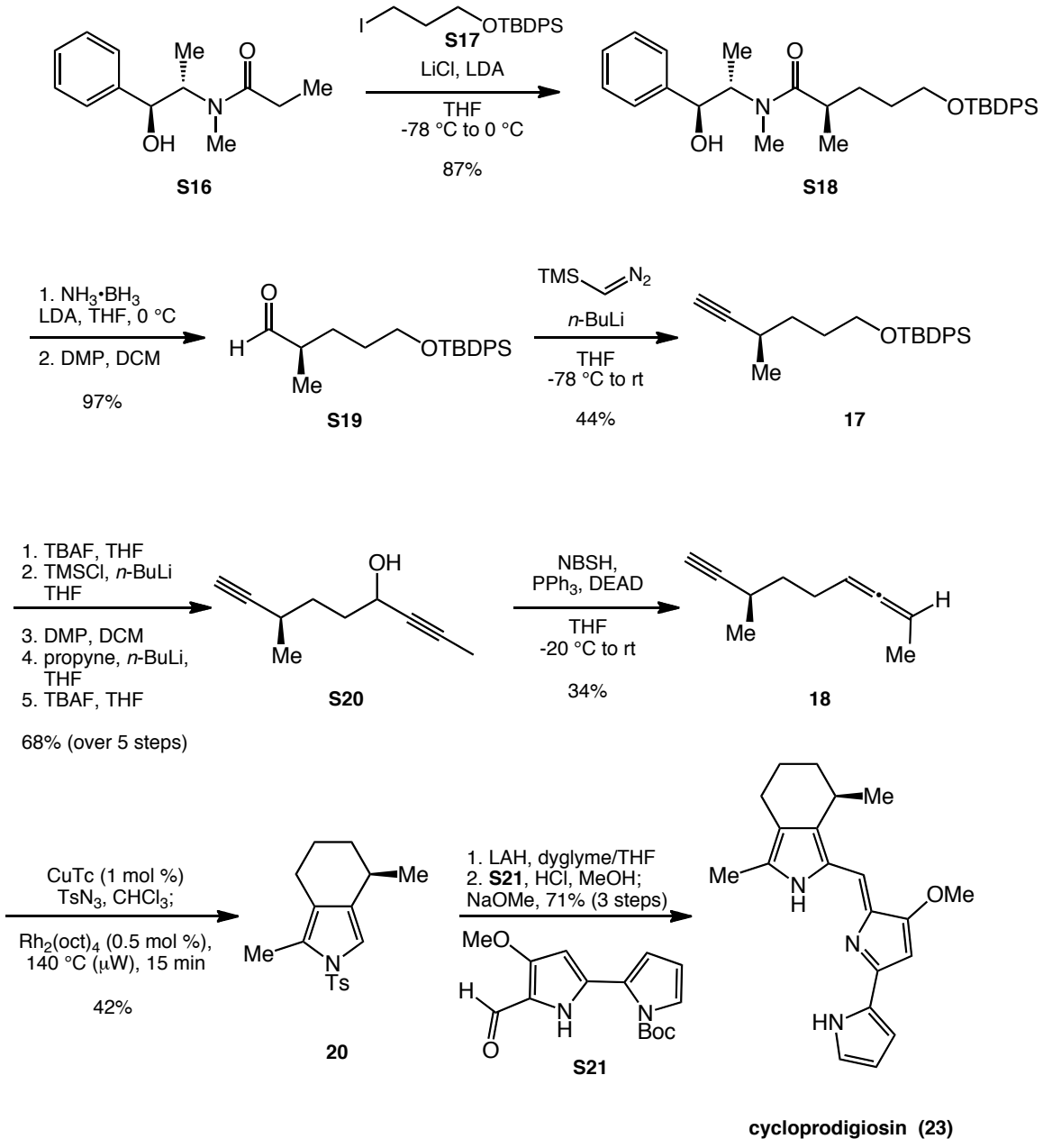
12 **16**

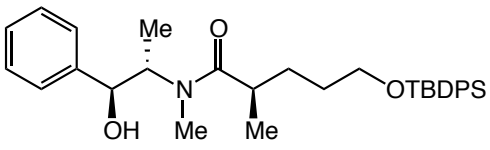


16

Bromopyrrole (16). To a degassed solution of **12** (27 mg, 0.071 mmol, 1.0 equiv) in DMF (0.7 mL, 0.1 M) cooled to 0 °C, was added NBS (14 mg, 0.078 mmol, 1.1 equiv) portionwise under a stream of N_2. The reaction mixture was allowed to warm to ambient temperature over 1 h, then quenched by the addition of saturated aqueous sodium thiosulfate (1 mL), and diluted with dichloromethane (2 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 2 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give **16** (22 mg, 70%) as a colorless oil. **IR** (film): 2932, 2857, 1595, 1486, 1378, 1180, 1028, 667. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.59 (d, *J* = 8.1 Hz, 2H), 7.36 (td, *J* = 7.7, 1.7 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.16 - 7.11 (m, 1H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.93 (d, *J* = 8.3 Hz, 1H), 3.80 (s, 3H), 2.39 (s, 3H), 2.34 (t, *J* = 6.5 Hz, 2H), 2.26 - 2.12 (m, 2H), 1.74 - 1.57 (m, 4H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.2, 144.3, 136.3, 132.2, 129.9, 129.7, 129.3, 127.6, 127.5, 125.9, 121.7, 119.7, 110.6, 99.3, 55.4, 23.1, 22.8, 22.7, 22.1, 21.7, 14.2. **HRMS** (*m/z*): M^+ calcd for $C_{22}H_{22}BrNO_3S$, 459.0504; found, 459.0504.

Synthesis of Cycloprodigiosin.

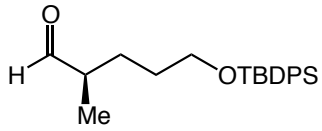




S18

Pseudophedrine alkylation product (S18). Flame-dried LiCl (8.43 g, 221 mmol, 6.0 equiv) was placed in a 250 mL round-bottom flask. The reaction flask was charged with THF (34 mL, 6.0M), and diisopropyl amine (10.8 mL, 77.0 mmol, 2.3 equiv). The reaction mixture was cooled to -78 °C, then *n*-BuLi (28.1 mL of a 2.5 M solution in hexanes, 70.3 mmol, 2.1 equiv) was added. The solution was stirred a -78 °C for 15 min, then warmed to 0 °C. After

holding at this temperature for 15 min, the reaction mixture was re-cooled to -78 °C, and **S16** (7.40 g, 33.5 mmol, 1.0 equiv) was added via cannula as a solution in THF (67 mL, 0.5 M). The reaction mixture was stirred for an additional hour at -78 °C, then warmed to 0 °C for 15 min, then to ambient temperature for 5 min. The reaction mixture was then re-cooled to 0 °C and **S17** (28.4 g, 67.0 mmol, 2.0 equiv) as a solution in THF (17 mL, 4.0 M) was added via cannula. The reaction mixture was held at 0 °C for 12 h then quenched by slow addition of aqueous ammonium chloride. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 200 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* and purified by column chromatography (1:1 hexanes:ethyl acetate) to give **S18** (15.0 g, 87%) as a colorless viscous oil. **IR** (film): 3385, 3070, 2932, 2858, 2739, 1960, 1890, 1824, 1739, 1620, 1472, 1428, 1110, 939, 912, 823, 741, 701, 613. **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.70 - 7.62 (m, 4H), 7.45 - 7.28 (m, 10H), 7.23 (t, *J* = 7.3 Hz, 1H), 4.60 (d, *J* = 6.7 Hz, 1H), 4.39 (bs, 1H), 3.61 (tt, *J* = 10.5, 5.3 Hz, 2H), 2.79 (s, 3H), 2.58 (q, *J* = 6.7 Hz, 1H), 1.77 - 1.62 (m, 2H), 1.53 - 1.40 (m, 3H), 1.12 (d, *J* = 7.0 Hz, 3H), 1.08 (d, *J* = 6.7 Hz, 3H), 1.05 (s, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 142.6, 135.5, 135.5, 133.9, 129.5, 128.3, 127.6, 127.5, 126.2, 76.5, 67.9, 63.6, 36.2, 30.2, 30.1, 26.8, 25.6, 19.2, 17.2, 14.4. **HRMS** (m/z): **[**M-*t*Bu]$^+$ calcd for $C_{28}H_{34}O_3SiN$, 460.2308, found 460.2287.



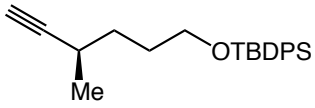
S19

Aldehyde (S19). To a cooled a solution of diisopropyl amine (11.5 mL, 81.6 mmol, 4.2 equiv) in THF (72 mL) at -78 °C was added *n*-BuLi (36.2 mL of a 2.2 M solution in hexanes, 79.7 mmol, 4.1 equiv) dropwise over 20 min, and the reaction mixture was warmed to 0 °C. After 15 min, ammonia borane (2.40 g, 77.7 mmol, 4.0 equiv) was added portionwise. After an additional 15 min at 0 °C, the reaction mixture was warmed to ambient temperature for 15 min, then re-cooled to 0 °C and **S18** (10.0 g, 19.4 mmol, 1.0 equiv) was added. The reaction mixture was allowed to stir for an additional 2 h at 0 °C, then was quenched by its addition via cannula into a pre-cooled solution of saturated aqueous ammonium chloride (70 mL), methanol (35 mL), and diethyl ether (35 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 x 200 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* and purified by column chromatography (10:1 hexanes:ethyl acetate) to give the resulting primary alcohol (6.7 g, 97%) as a colorless oil. Spectra were consistent with those reported previously.[6]

The alcohol (18.8 mmol, 1.0 equiv) was dissolved in dichloromethane (70 mL, 0.25 M), and to this solution was added Dess-Martin periodinane (10.3 g, 24.4

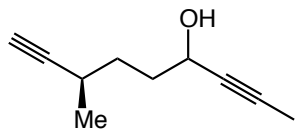
[6] Oikawa, M.; Ueno , T.; Oikawa, H.; Ichihara, A. *J. Org. Chem.*, 1995, *60*, 5048.

mmol, 1.3 equiv). The reaction mixture was allowed to stir at ambient temperature for 90 min, then was quenched by the addition of saturated sodium bicarbonate (100 mL) and sodium thiosulfate (100 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (100 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* and purified by column chromatography (4:1 hexanes:ethyl acetate) to give **S19** as a colorless oil which was used immediately in the next reaction. Spectra were consistent with those reported previously.[7]



17

Terminal alkyne (17).[8] A solution of TMS-diazomethane (9.34 mL of a 2.0 M solution in diethyl ether, 20.6 mmol, 1.2 equiv) in THF (60 mL, 0.3 M) was cooled to -78 °C under a N_2 atmosphere. The reaction flask was charged with *n*-BuLi (9.34 mL of a 2.2 M solution in hexanes, 20.5 mmol, 1.2 equiv). After 45 min, **S19** (18.8 mmol, 1.0 equiv) in THF (18 mL, 1.0 M) was added dropwise over 20 min. After the reaction mixture was stirred at -78 °C for an hour, it was warmed to 0 °C for 30 min, and finally ambient temperature for 1 h. The reaction mixture was quenched by the addition of saturated aqueous ammonium chloride (200 mL) and diluted with diethyl ether (200 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 x 200 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* and purified by column chromatography (50:1 hexanes:ethyl acetate) to give **17** (2.8 g, 43% over 3 steps) as a colorless oil. **IR** (film): 308, 3071, 3050, 2932, 2858, 2113, 1959, 1889, 1824, 1589, 1473, 1390, 1112, 999, 938, 823, 741, 702, 614. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.75 (dt, *J* = 6.5, 1.7 Hz, 4H), 7.50 - 7.41 (m, 6H), 3.76 (t, *J* = 6.3 Hz, 2H), 2.56 - 2.42 (m, 1H), 2.07 (d, *J* = 2.4 Hz, 1H), 1.90 -1.79 (m, 1H), 1.79 - 1.68 (m, 1H), 1.68 - 1.54 (m, 2H), 1.24 (d, *J* = 6.9 Hz, 3H), 1.13 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 135.7, 134.1, 134.1, 129.6, 127.7, 89.0, 68.4, 63.7, 33.1, 30.3, 27.0, 25.5, 21.1, 19.3. **HRMS** (*m/z*): **[**M-*t*Bu]$^+$ calcd for $C_{19}H_{21}OSi$, 293.1362; found, 293.1366. $[\alpha]^{23}_D$ – 13.2 (c 1.1, CH_2Cl_2) lit. for (*S*)-**17** $[\alpha]^{20}_D$ + 12.3 (c 1.1, CH_2Cl_2).



S20

Propargylic alcohol (S20). A solution of TBAF (10.7 mL of a 1.0 M solution in THF, 10.7 mmol, 2.0 equiv) was added dropwise to a solution of **17** (1.87 g, 5.44 mmol, 1.0 equiv) in THF (10 mL, 0.5 M) at 0 °C. The reaction mixture was allowed to warm to ambient temperature and stir for 5 h at which time TLC analysis indicated complete consumption of the starting material. The reaction mixture was quenched by the addition of saturated aqueous ammonium chloride (20 mL) and diluted with diethyl ether (20

[7] See ref. 6.

[8] Adapted from the synthesis of the (*S*)-**17**: Magauer, T., Martin, Harry J. and Mulzer, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 6032.

mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered, concentrated *in vacuo* and passed through a short silica plug eluting with hexanes then 6:1 (hexanes:ethyl acetate) to give the deprotected primary alcohol (590 mg, quant.) after concentrating as a colorless oil, which was used without further purification.

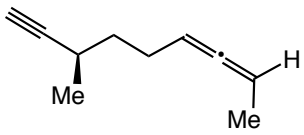
The alcohol (590 mg, 5.44 mmol, 1.0 equiv) was dissolved in THF (16 mL, 0.33 M) and the resulting solution was cooled to -78 °C. The flask was charged with *n*-BuLi (7.28 mL of a 2.2 M solution in hexanes, 16.0 mmol, 3.0 equiv). After the reaction mixture was stirred at -78 °C for 1 h, trimethylsilyl chloride (2.36 mL, 18.7 mmol, 3.5 equiv) was added dropwise. The reaction mixture was then allowed to warm to ambient temperature and stir for 1 h before being quenched by the addition of water (20 mL) and 1N HCl (5 mL). The resulting biphasic mixture was stirred vigorously for 30 min, then diluted with ether (30 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* and passed through a short silica plug eluting with hexanes then 6:1 hexanes:ethyl acetate to give the TMS-protected alkyne as a colorless oil (980 mg, quant.), which was used without further purification.

The TMS-protected alkyne (980 mg, 5.44 mmol, 1.0 equiv) was dissolved in dichloromethane (27 mL, 0.2 M), and to this solution was added Dess-Martin periodinane (2.94 g, 6.94 mmol, 1.3 equiv). The reaction mixture was allowed to stir at ambient temperature for 90 min, then was quenched by the addition of saturated sodium bicarbonate (50 mL) and sodium thiosulfate (50 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, concentrated *in vacuo* and purified by column chromatography (8:1 hexanes:ethyl acetate) to give the resulting unstable aldehyde (691 mg, 71%) as a colorless oil which was used immediately in the next reaction.

Condensed propyne (> 1.3 mL, > 6.0 equiv) at -78 °C, was diluted with THF (20 mL, 0.25 M). The flask was charged with *n*-BuLi (5.0 mL of a 2.2 M solution in hexanes, 11.4 mmol, 3.0 equiv). After the reaction mixture was stirred at -78 °C for 2 h, the aldehyde (690 mg, 3.79 mmol, 1.0 equiv) in THF (10 mL, 0.4 M) was introduced by dropwise addition via syringe. The reaction mixture was held at -78 °C for an additional 4 h then allowed to warm to ambient temperature and stir for 8 h. The reaction mixture was quenched by the addition of saturated aqueous ammonium chloride (20 mL) and diluted with diethyl ether (20 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* and passed through a short

silica plug eluting with 4:1 hexanes:ethyl acetate to give the propargylic alcohol (807 mg, 96%) which was used immediately in the next step.

A solution of TBAF (7.58 mL of a 1.0 M solution in THF, 7.58 mmol, 2.0 equiv) was added dropwise to a solution of the propargylic alcohol (840 mg, 3.79 mmol, 1.0 equiv) in THF (20 mL, 0.2 M) at 0 °C. The reaction mixture was allowed to stir at 0 °C for 30 min at which time TLC analysis indicated complete consumption of the starting material. The reaction mixture was quenched by the addition of saturated aqueous ammonium chloride (15 mL) and diluted with diethyl ether (10 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered, concentrated *in vacuo* and purified by column chromatography (10:1 hexanes:ethyl acetate) to yield **S20** (387 mg, 3.70 mmol, 68% over 5 steps) as a colorless oil. **IR** (film): 3298, 2951, 2922, 2873, 1455, 1377, 1331, 1018, 630. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 4.38 - 4.32 (m, 1H), 2.53 - 2.39 (m, 1H), 2.04 (dd, *J* = 2.4, 1.3 Hz, 1H), 2.00 - 1.93 (bs, 1H), 1.89 - 1.84 (m, 1H), 1.83 (d, *J* = 2.2 Hz, 3H), 1.80 - 1.70 (m, 1H), 1.65 - 1.51 (m, 2H), 1.19 (dd, *J* = 7.1, 1.0 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 88.6, 88.6, 81.2, 81.2, 80.2, 80.2, 68.7, 68.7, 62.5, 62.3, 35.8, 35.7, 32.2, 32.1, 25.5, 25.4, 21.0, 21.0, 3.6, 3.6. **HRMS** (*m/z*): **[**M+H]$^+$ calcd for $C_{10}H_{15}O$, 151.1123; found, 151.1117.

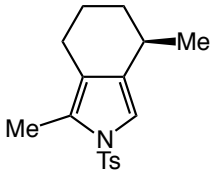


18

(3*R*)-3-methylnona-6,7-dien-1-yne (18). To a solution of triphenylphosphine (1.0 g, 3.9 mmol, 1.5 equiv) in THF (5.2 mL, 0.75 M) at -20 °C (dry ice/brine bath) was added diethyl azodicarboxylate (0.61 mL, 1.5 equiv) dropwise over 1 min. The reaction mixture was stirred at -20 °C for an additional 10 min, then charged with **S20** (390 mg, 2.6 mmol, 1.0 equiv) as a solution in THF (4.3 mL, 0.5 M) dropwise over 10 min. After 30 minutes, 2-nitrobenxylsulfonylhydrazine (NBSH)[9] (850 mg, 3.9 mmol, 1.5 equiv) as a solution in THF (5.2 mL, 0.75 M) was added dropwise over 10 min. The reaction mixture was held at -20 °C for an additional 2 h then allowed to warm to ambient temperature and stirred for 10 h. After this time, the reaction mixture was diluted with dichloromethane (10 mL), the stirbar was removed and silica gel (2 g) was added to the reaction flask and the mixture was concentrated *in vacuo* and filtered through a short silica plug eluting with pentanes to give **18** (121 mg, 34%) as a very volatile colorless liquid. **IR** (film): 3067, 2999, 2918, 2349, 1964, 1475, 1306, 1202, 1179, 1087, 1026, 742, 694. **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 5.11 - 5.00 (m, 2H), 2.53 - 2.46 (m, 2H), 2.22 - 2.12 (m, 2H), 2.12 - 2.05 (m, 1H), 2.05- 2.03 (m, 1H), 1.64 (dt, *J* = 6.6, 3.3 Hz, 3H), 1.61 - 1.48 (m, 2H), 1.19 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 204.7, 204.7, 89.6, 89.6, 88.8, 88.8,

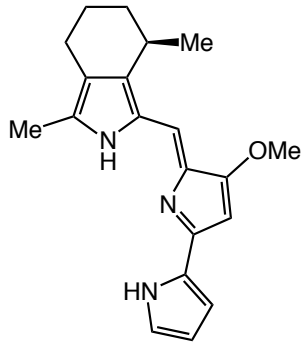
[9] Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62*, 7507.

85.9, 85.8, 68.3, 35.9, 35.9, 26.5, 26.4, 25.0, 25.0, 20.8, 20.8, 14.5, 14.5.



20

(*R*)-1,4-dimethyl-2-tosyl-4,5,6,7-tetrahydro-2*H*-isoindole (20). To a flame-dried microwave vial, was added copper (II) thiophene carboxylate (CuTc, 1.7 mg, 5 mol %). The vial was sealed and evacuated and backfilled with N_2 (3x), then allene **18** (121 mg, 0.91 mmol, 1.0 equiv) in chloroform (4.6 mL, 0.2 M) was added, followed by tosyl azide (140 μL, 0.91 mmol, 1.0 equiv). The reaction mixture was allowed to stir at ambient temperature for 12 h at which time TLC analysis indicated complete consumption of the starting material. The reaction flask was then charged with $Rh_2(oct)_4$ (3.5 mg, 0.5 mol %) dissolved in chloroform (0.2 mL, 0.023 M) via syringe. The resulting mixture was heated to 140 °C under microwave irradiation for 15 min. After cooling to ambient temperature, silica gel was added to the reaction mixture and the solvent was removed *in vacuo.* The resulting residue was purified by column chromatography eluting with 6:1 hexanes:ethyl acetate to give **20** (114 mg, 42%) as a colorless oil. **IR** (film): 2954, 2925, 2855, 1365, 1262, 1187, 1104, 671. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.01 (d, *J* = 1.6 Hz, 1H), 2.63 - 2.54 (m, 1H), 2.40 (s, 3H), 2.39 - 2.36 (m, 1H), 2.26 - 2.18 (m, 2H), 2.15 (s, 3H), 1.90 - 1.77 (m, 2H), 1.54 - 1.46 (m, 1H), 1.18 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 144.2, 136.9, 129.8, 129.8, 126.8, 124.3, 122.5, 115.9, 32.5, 28.5, 22.7, 21.6, 21.5, 21.3, 11.0. **HRMS** (*m/z*): **[**M+H]$^+$ calcd for $C_{17}H_{22}NO_2S$, 304.1371; found, 304.1368. $[\alpha]^{23}_D$ – 36.4 (c 0.3, $CDCl_3$).

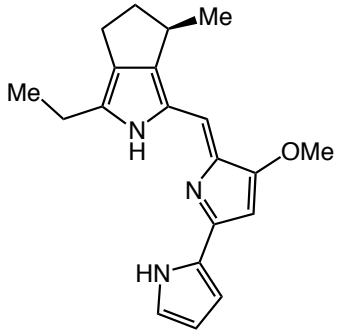


cycloprodigiosin (23)

Cycloprodigiosin (23). To a degassed solution of **20** (55 mg, 0.18 mmol, 1.0 equiv) in THF (1.0 mL, 0.18 M) and diglyme (0.4 mL, 0.45 M) in a Schlenck tube was added lithium aluminum hydride (138 mg, 3.62 mmol, 20.0 equiv). After sealing the Schlenk tube, the reaction mixture was heated to 100 °C. After stirring at 100 °C for 20 h, the reaction mixture was cooled to 0 °C and quenched by the sequential addition of water (0.14 mL), 15% aqueous sodium hydroxide (0.14 mL), and again water (0.43 mL). After 1 h at 0 °C, the resulting slurry was diluted with diethyl ether (4 mL) and filtered through celite and washed with diethyl ether (10 x 2 mL). The filtrate was then transferred to a separatory funnel and the layers were separated. The organic layer was washed with water (10 x 5 mL), brine (5 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo.* The deprotected pyrrole (**21**) was used immediately without purification.

To a flask containing pyrrole **21** (0.18 mmol, 1.0 equiv) and aldehyde **S12**[10] (62 mg, 0.22 mmol, 1.2 equiv) was added methanol (3 mL, 0.06 M). The flask was placed into an ambient temperature water bath, and then charged with anhydrous HCl (0.18 mL of a freshly prepared 1.0 M solution of acetyl chloride in methanol, 0.18 mmol, 1.0 equiv). The reaction mixture was allowed to stir at ambient temperature for 75 min at which time TLC analysis indicated complete consumption of the starting material. The reaction flask was then charged with sodium methoxide (47 mg, 1.8 mmol, 10 equiv). After an additional 45 min, the reaction mixture was diluted with diethyl ether (5 mL) and water (5 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over sodium sulfate, filtered, concentrated *in vacuo* and purified by column chromatography (eluting with 99:1 to 98:2 chloroform:methanol) to afford cycloprodigiosin (**23**) (46mg, 71% over 3 steps) as the HCl salt, which is a purple-black microcrystalline solid (m.p. > 220 °C, decomposes at > 220 °C). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 12.61 (s, 2H), 12.48 (s, 1H), 7.19 (s, 1H), 7.01 (s, 1H), 6.87 (s, 1H), 6.36 - 6.31 (m, 1H), 6.08 (s, 1H), 4.00 (s, 3H), 3.19 - 3.07 (m, 1H), 2.50 (s, 3H), 2.48 - 2.42 (m, 1H), 2.30 (dt, *J* = 15.8, 7.8 Hz, 1H), 1.84 - 1.57 (m, 4H), 1.29 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.0, 147.3, 146.3, 145.8, 126.2, 123.9, 123.1, 122.6, 119.2, 115.9, 113.1, 111.5, 92.6, 76.9, 58.7, 30.5, 26.3, 24.0, 20.9, 18.4, 12.4. **HRMS** (*m/z*): **[**M+H]$^+$ calcd for $C_{20}H_{24}N_3O$, 322.1919; found, 322.1923. Spectra were consistent with those reported previously.[11]

Minor isomer:



***ii*·HCl**

^{1}H NMR (500 MHz, Chloroform-*d*) δ 12.70 (s, 1H), 12.28 (s, 1H), 7.20 (s, 1H), 6.96 (s, 1H), 6.89 (s, 1H), 6.32 (s, 1H), 6.08 (s, 1H), 4.00 (s, 3H), 2.95 (q, *J* = 7.7 Hz, 1H), 2.74 - 2.54 (m, 3H), 1.70 – 1.68 (m, 1H), 1.36 - 1.31 (m, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.4, 156.5, 147.1, 133.2, 126.6, 122.5, 119.8, 119.6, 116.5, 114.4, 111.6, 92.8, 58.8, 39.8, 34.4, 24.1, 21.6, 12.8.

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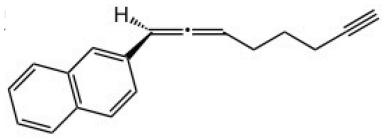
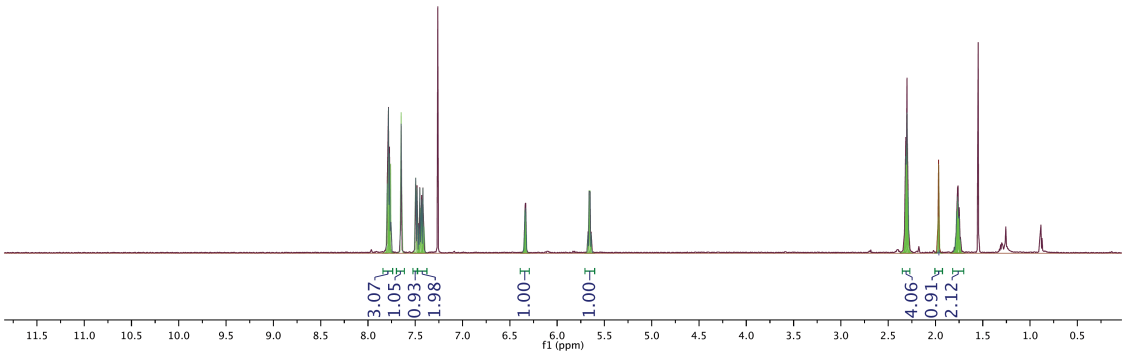
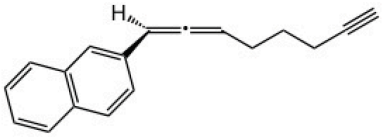
[10] Aldrich, L. N.; Dawsen, E. S.; Linsley, C. W. *Org. Lett.* **2010**, *12*, 1048.

[11] Gerber, N. N.; Gauthier, M. J. *Appl. Environ. Microbiol.* **1979**, *37*, 1176.; Gerber, N. N.*Tetrahedron Lett.* **1983**, *22*, 2197.



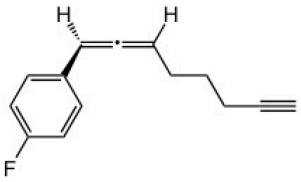
S3


3.07
1.05
0.93
1.98
1.00
1.00
4.06
0.91
2.12
f1 (ppm)

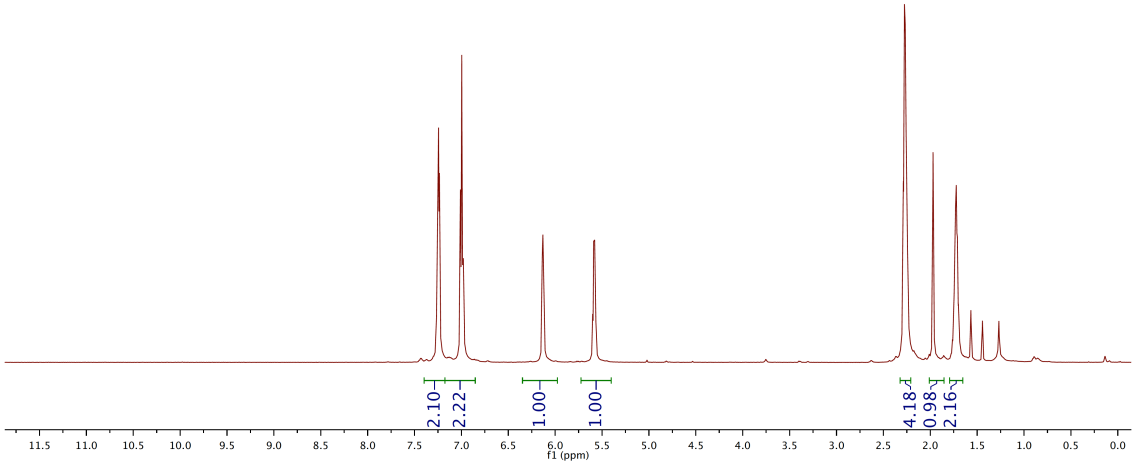


S3

205.81
133.67
132.54
132.30
128.15
127.66
127.61
125.54
125.49
125.28
124.55
95.39
84.31
84.01
68.59
27.73
27.63
17.89
f1 (ppm)


H
H
F

S4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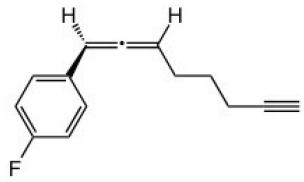
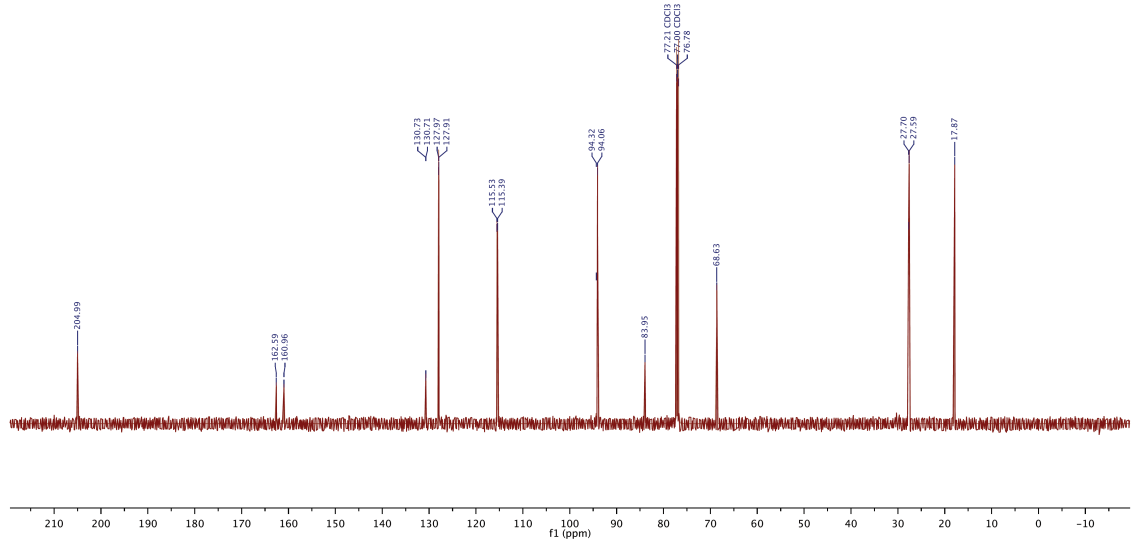
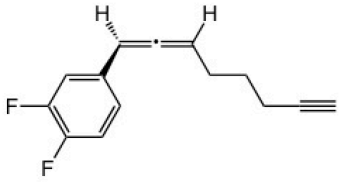
1.00
1.00
4.18
0.98
2.16
f1 (ppm)

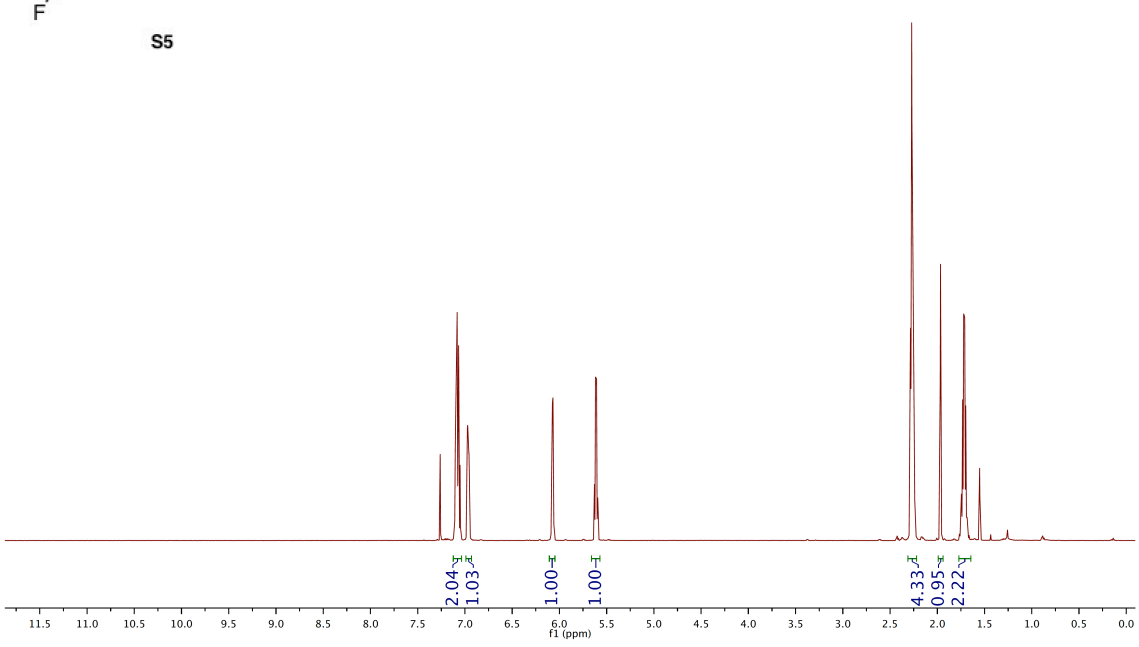

H
H
F

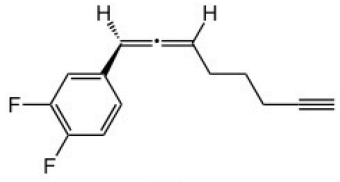
S4


204.99
162.59
160.96
130.73
130.71
127.97
127.91
115.53
115.39
94.32
94.06
83.95
77.21 CDCl3
77.00 CDCl3
76.78
68.63
27.70
27.59
17.87
f1 (ppm)


H
H
F
F

S5


2.04
1.03
1.00
1.00
4.33
0.95
2.22
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


H
H
F
F

S5

205.26
205.25
151.38
151.30
150.08
149.99
149.74
149.66
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148.35
132.09
132.07
132.05
132.03
122.42
122.40
122.38
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94.66
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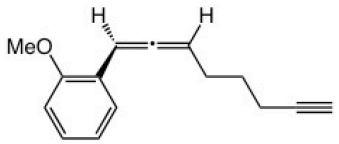
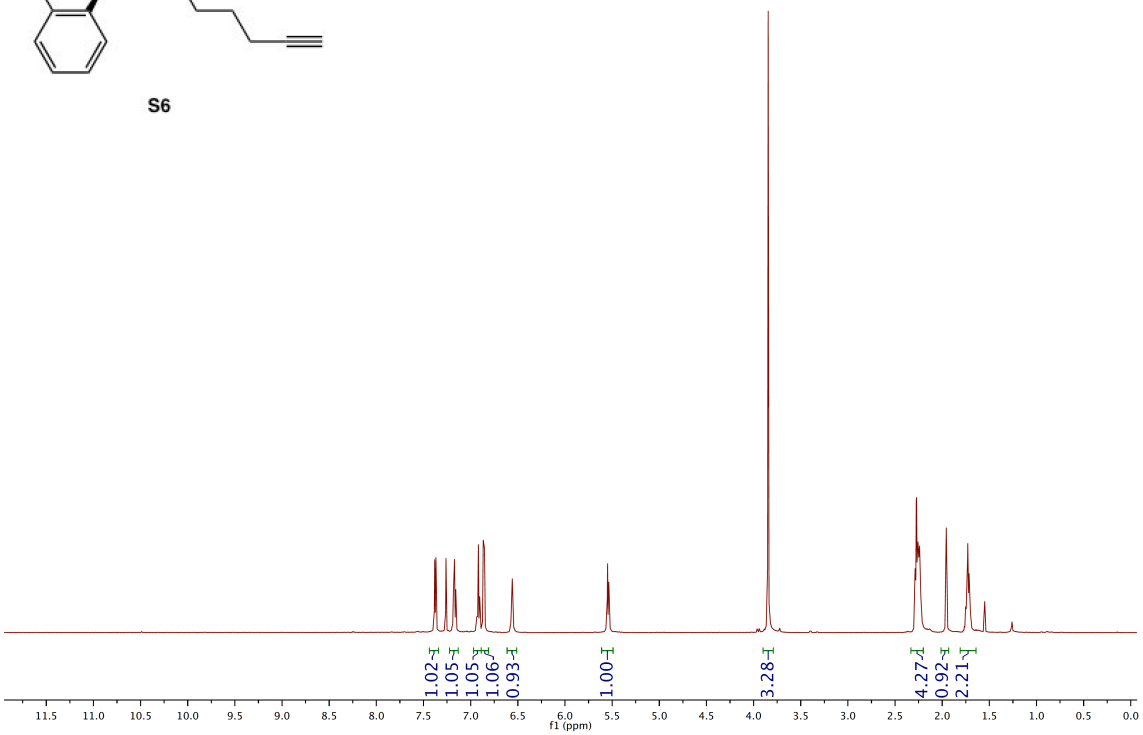
f1 (ppm)


H
H
MeO

S6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1.00
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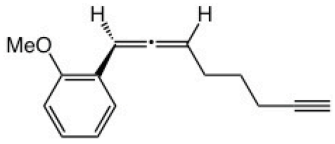
4.27
0.92
2.21
f1 (ppm)


H
H
MeO

S6

205.60
155.89
127.75
127.53
123.19
120.70
110.91
93.24
88.82
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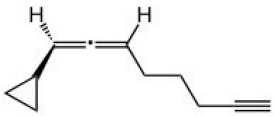
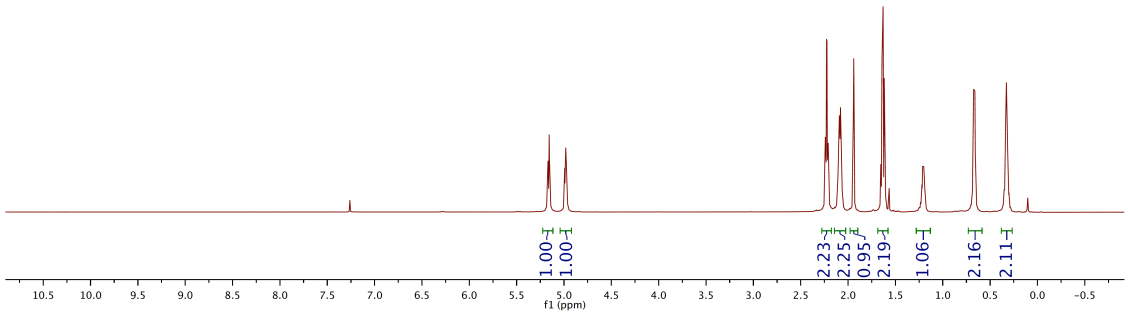
55.52
27.84
27.67
17.88
f1 (ppm)



S7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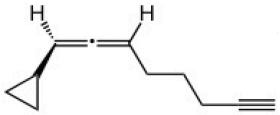
2.19
1.06
2.16
2.11
f1 (ppm)



S7

203.32
95.63
91.71
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68.32
27.96
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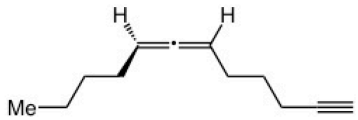
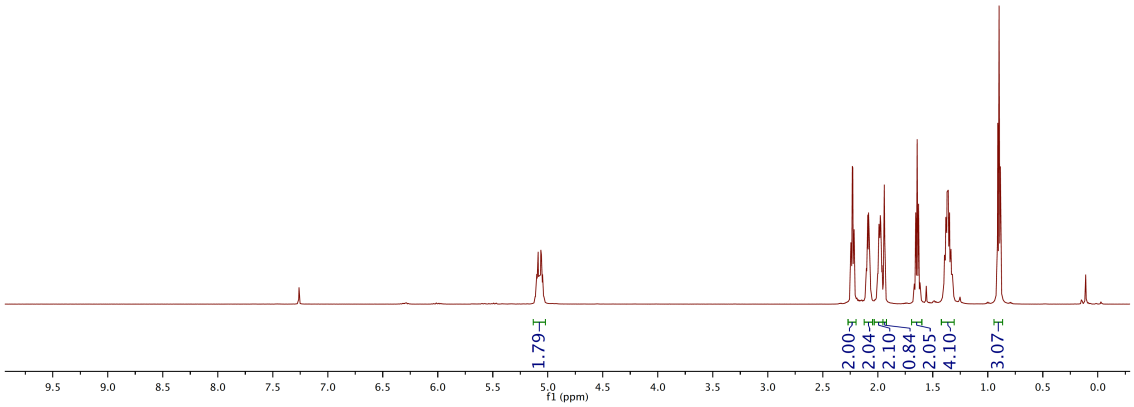
17.75
9.50
6.70
6.54
f1 (ppm)


H
H
Me

S8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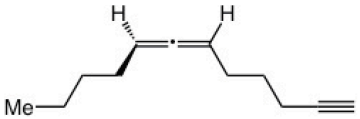
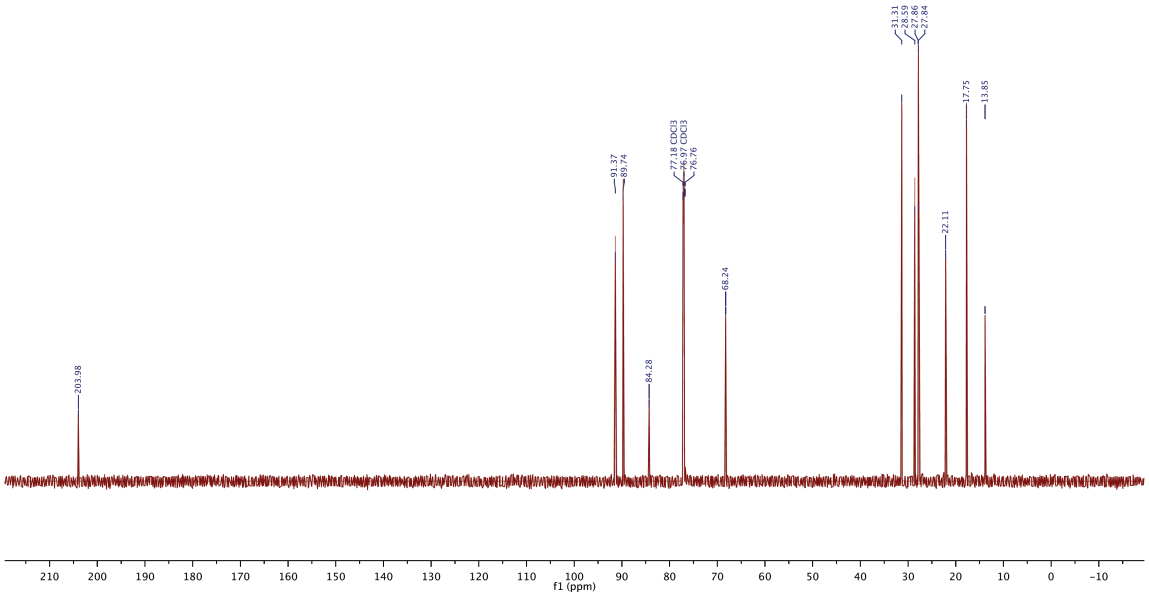
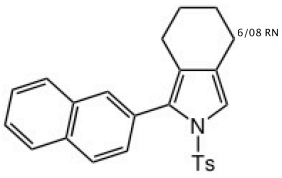
2.05
4.10
3.07
f1 (ppm)

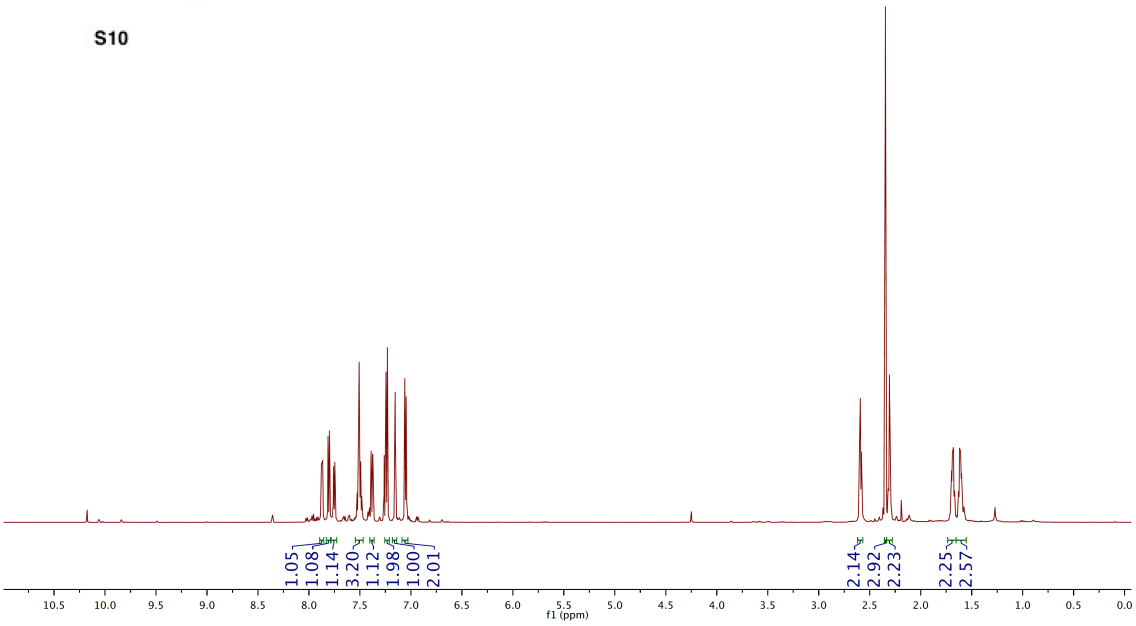

H
H
Me

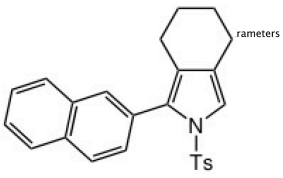
S8


203.98
91.37
89.74
84.28
77.18 CDCl3
76.97 CDCl3
76.76
68.24
31.31
28.59
27.86
27.84
22.11
17.75
13.85
f1 (ppm)

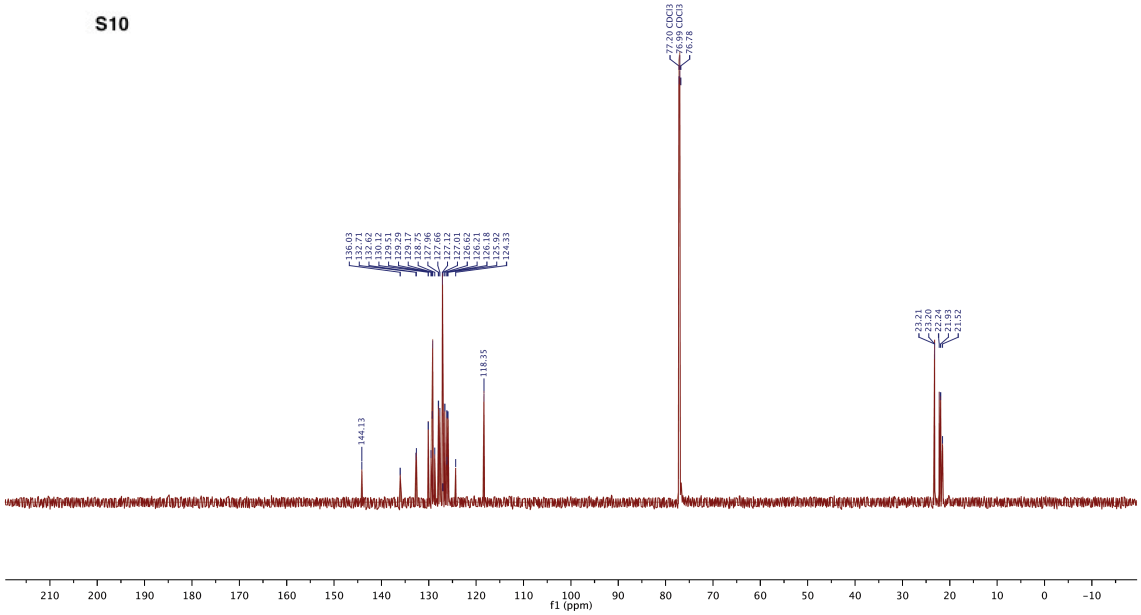

6/08 RN
N
Ts

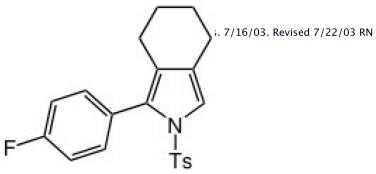
S10


1.05
1.08
1.14
3.20
1.12
1.98
1.00
2.01
2.14
2.92
2.23
2.25
2.57
f1 (ppm)


rameters
N
Ts

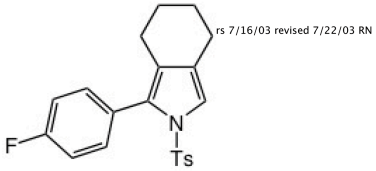
S10


77.20 CDCl3
76.99 CDCl3
76.78
136.03
132.71
132.62
130.24
129.51
129.29
128.77
128.75
127.96
127.76
127.12
127.01
126.62
126.21
126.18
125.92
124.33
118.35
144.13
23.21
23.20
22.94
21.93
21.52
f1 (ppm)


F
N
Ts

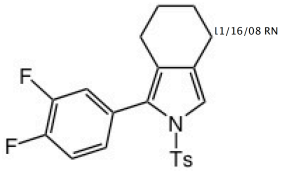
S11

1.95
4.95
2.00
2.02
3.03
1.96
4.68
f1 (ppm)


F
N
Ts

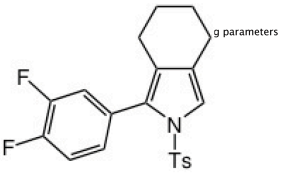
S11

135.04
133.08
130.00
129.27
128.33
127.00
126.95
126.92
125.23
124.02
118.17
114.44
114.23
144.25
163.61
161.15
23.14
22.05
21.83
21.56
f1 (ppm)


l1/16/08 RN
F
F
N
Ts

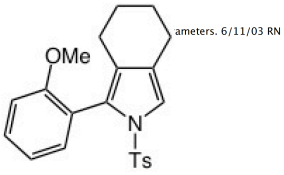
S12

2.53
2.00
1.94
1.79
1.81
3.00
1.94
4.10
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

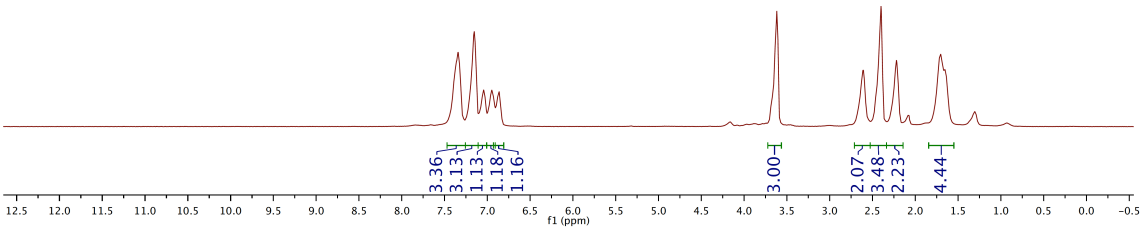

g parameters
F
F
N
Ts

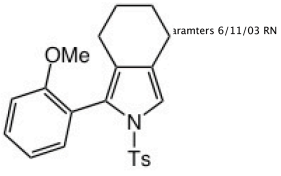
S12

129.36
127.70
127.68
127.66
127.20
126.95
126.77
124.12
120.19
120.07
118.62
116.21
116.10
149.20
149.17
148.49
148.42
144.50
135.87
23.05
22.02
21.77
21.54
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

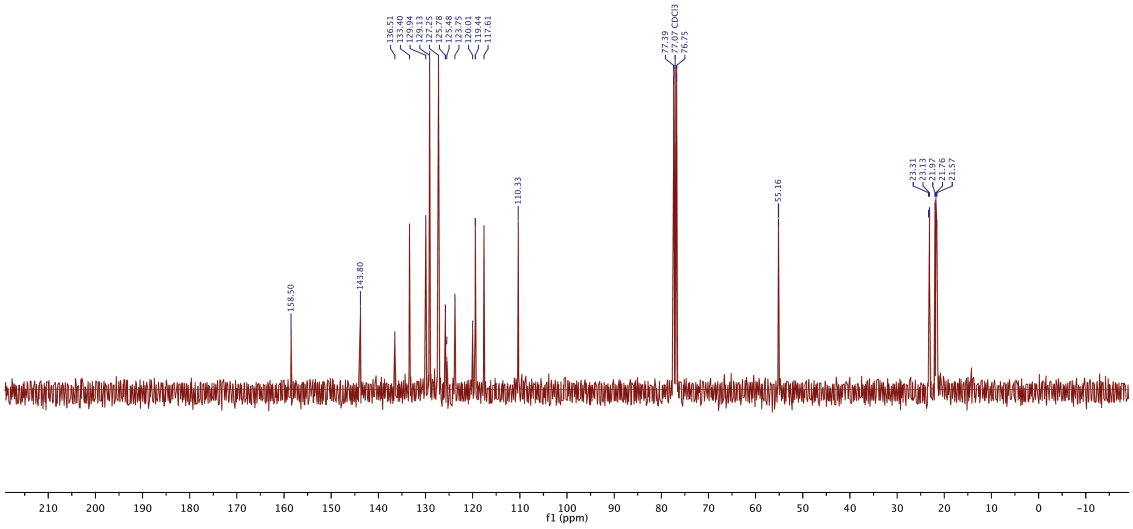

ameters. 6/11/03 RN
OMe
N
Ts

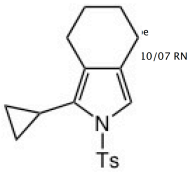
12


3.36
3.13
1.13
1.18
1.16
3.00
2.07
3.48
2.23
4.44
f1 (ppm)

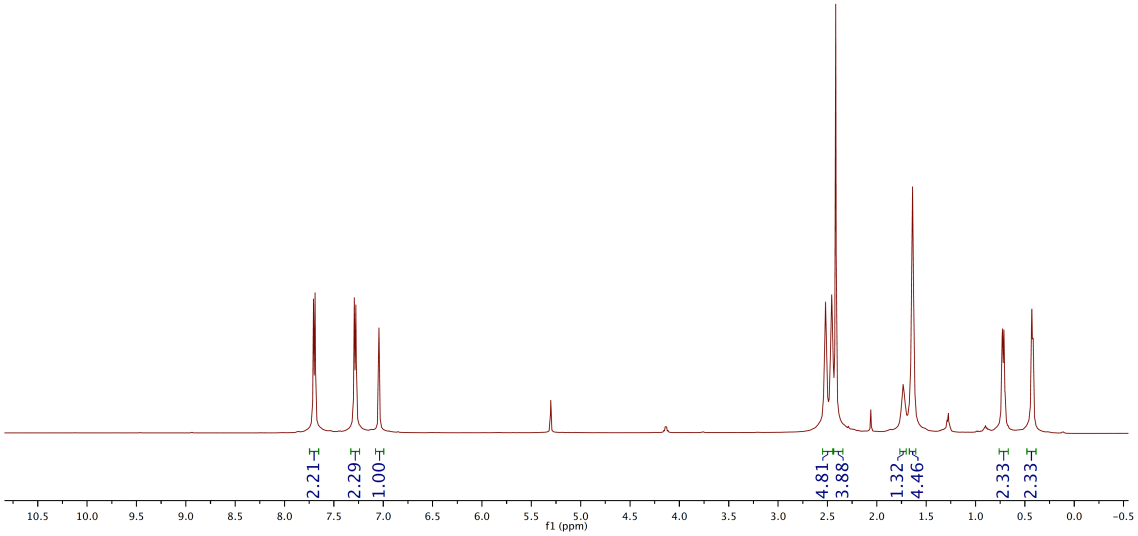

aramters 6/11/03 RN
OMe
N
Ts

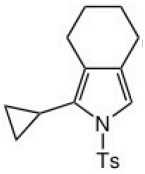
12


136.51
133.60
129.94
129.13
127.35
125.78
125.48
123.05
120.01
119.44
117.61
158.50
143.80
110.33
77.39
77.07 CDCl3
76.75
55.16
23.31
23.13
21.89
21.76
21.57
f1 (ppm)

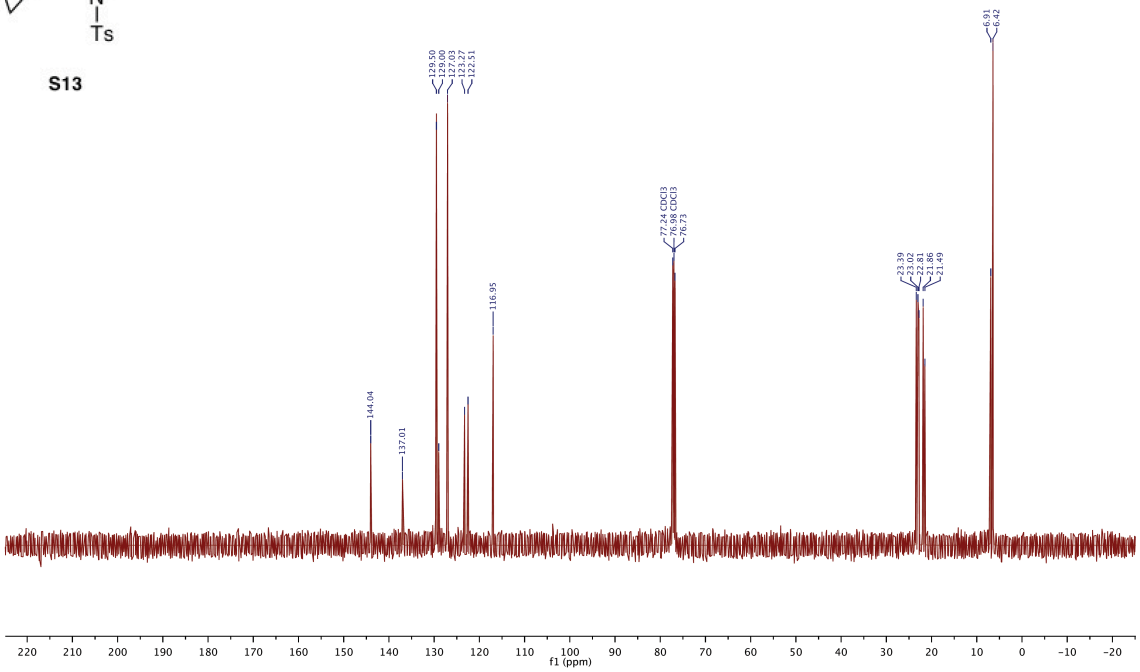

10/07 RN
N
Ts

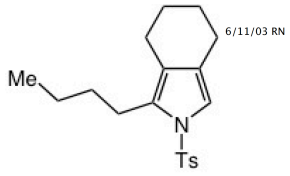
S13


2.21
2.29
1.00
4.81
3.88
1.32
4.46
2.33
2.33
f1 (ppm)

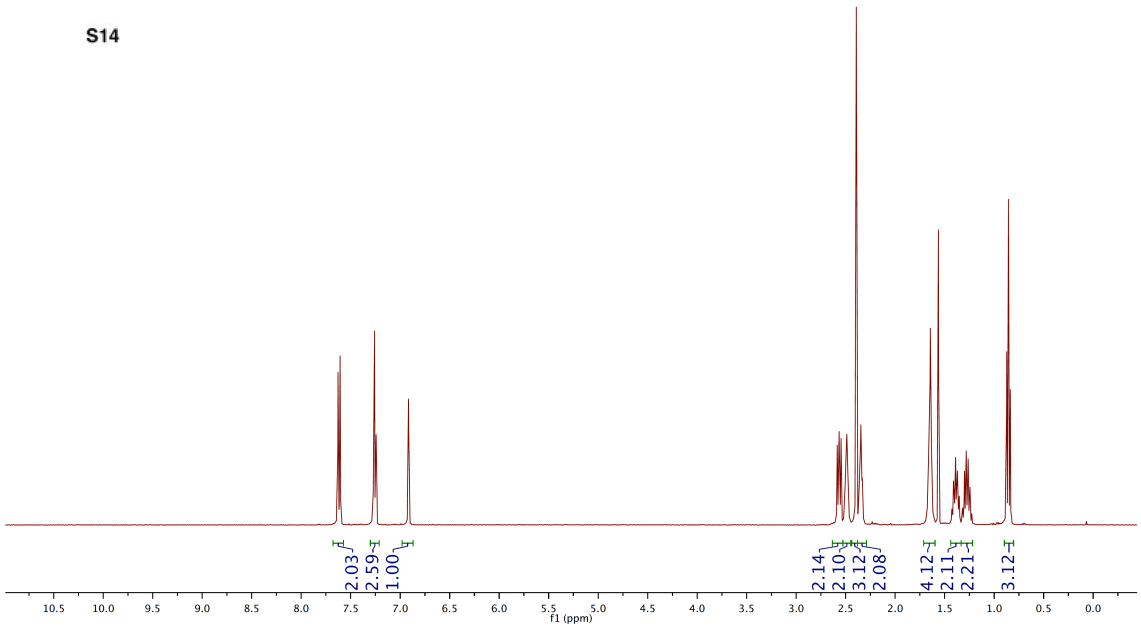

N
Ts

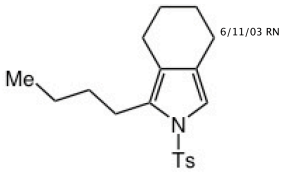
S13


129.50
129.00
127.03
122.27
122.51
116.95
144.04
137.01
77.24 CDCl3
76.99 CDCl3
76.73
22.39
23.02
22.52
22.81
21.86
21.49
6.91
6.42
f1 (ppm)


6/11/03 RN
Me
N
Ts

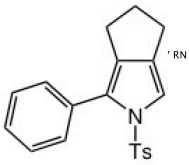
S14


2.03
2.59
1.00
2.14
2.10
3.12
2.08
4.12
2.11
2.21
3.12
f1 (ppm)


6/11/03 RN
Me
N
Ts

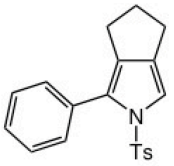
S14

144.13
137.22
129.92
129.76
126.60
123.62
123.00
116.51
77.32
32.13
23.36
23.33
22.65
21.91
21.69
13.87
f1 (ppm)


RN
N
Ts

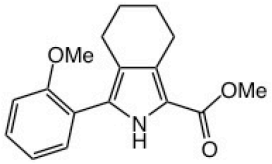
S15

3.14
4.23
2.22
1.00
2.22
2.34
3.29
2.43
f1 (ppm)

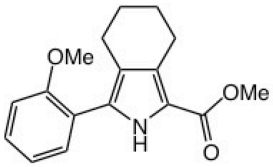

N
Ts

S15

138.66
136.23
135.50
132.11
130.87
129.62
127.96
127.81
127.64
127.41
144.49
115.54
31.24
25.26
21.77
22.02
f1 (ppm)

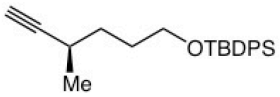


15

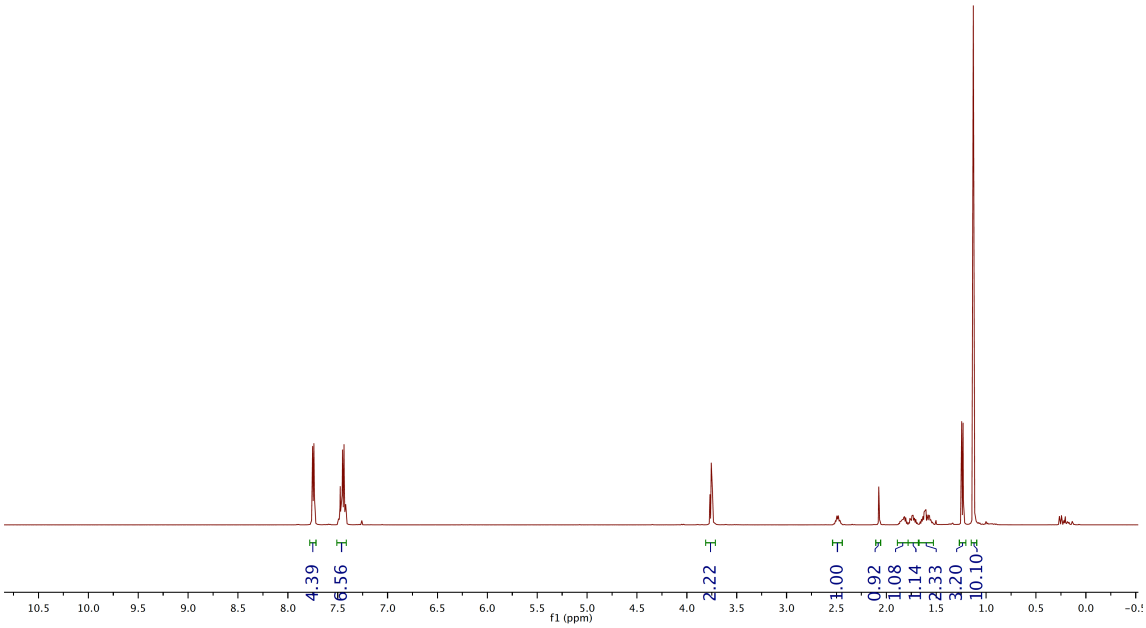


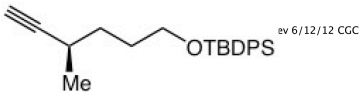
15

Rev 3/2/12 CGC



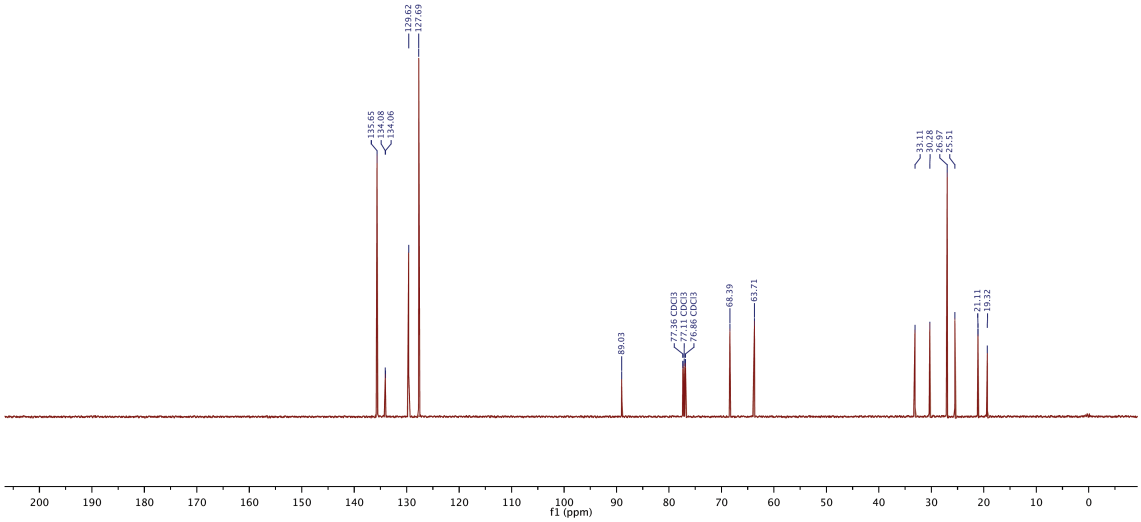
17

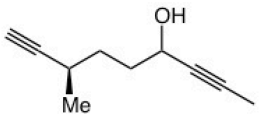




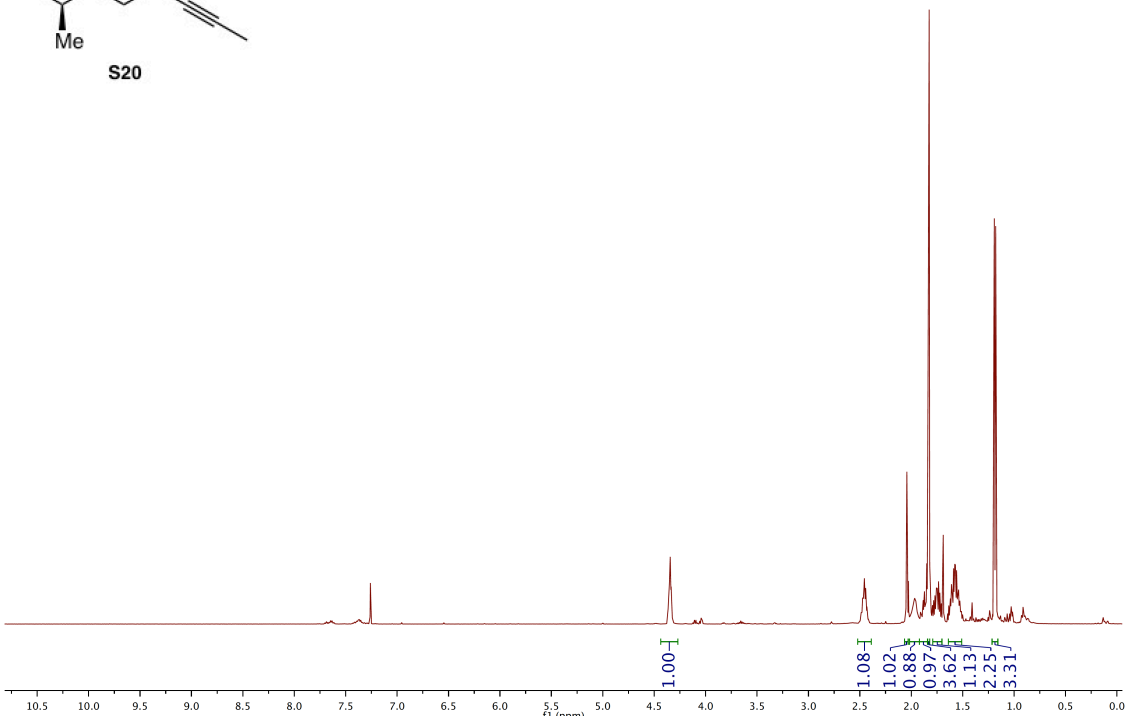
ev 6/12/12 CGC

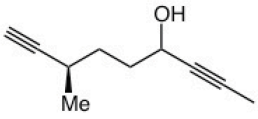
17





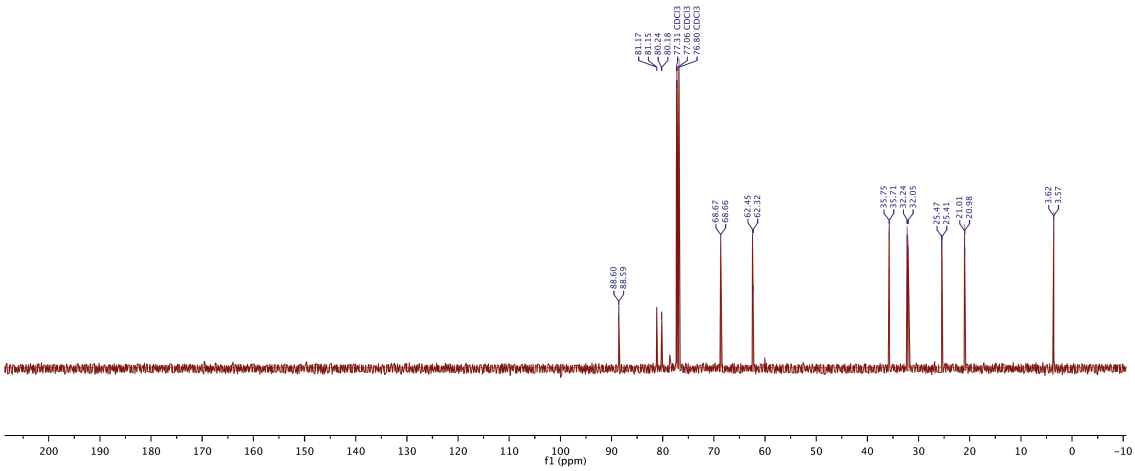
S20

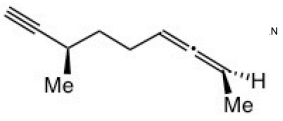




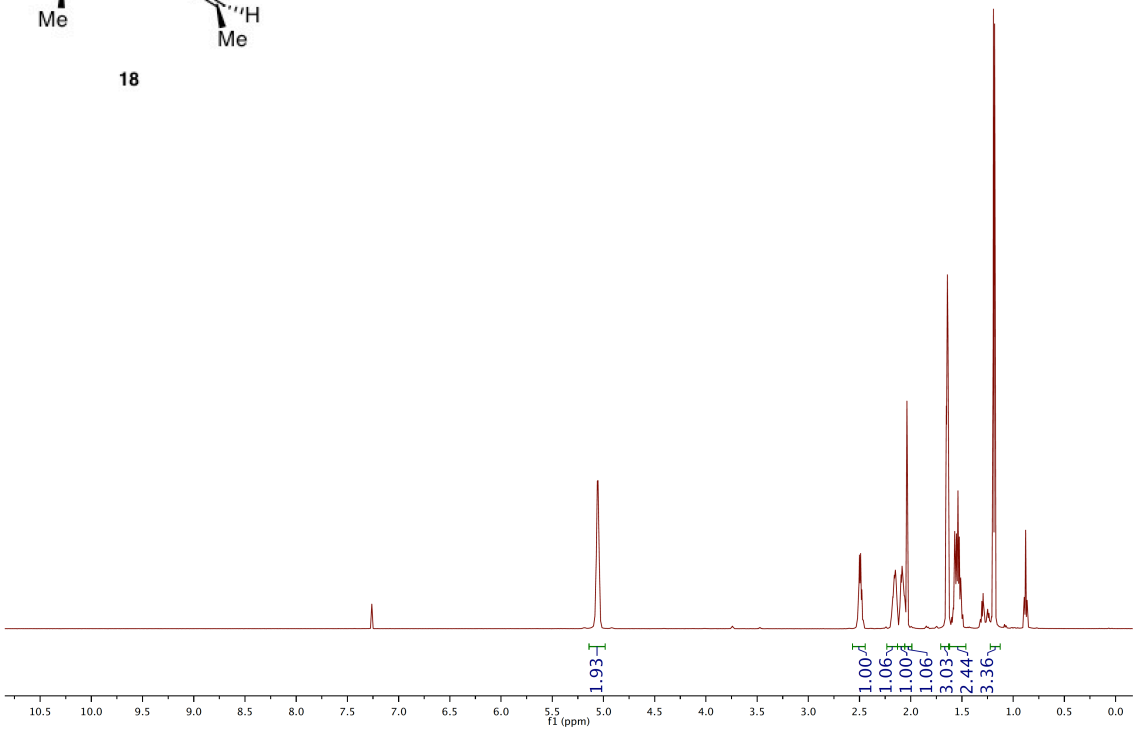
S20

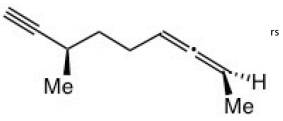
;. Rev 6/12/12 CGC



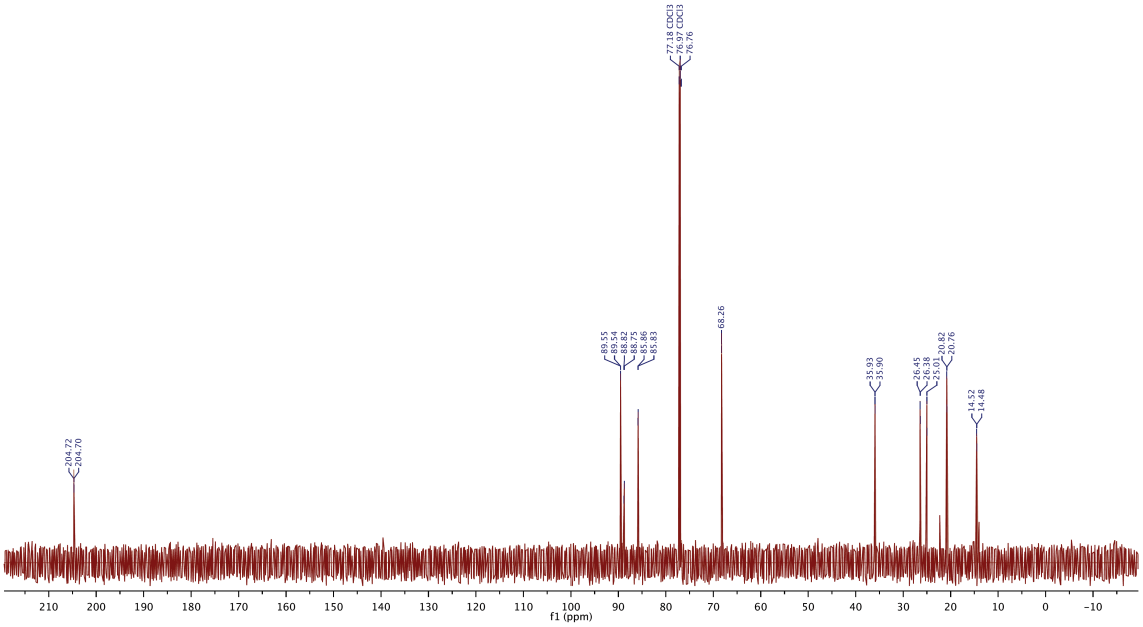

N
Me
H
Me

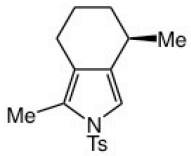
18


1.93
1.00
1.06
1.00
1.06
3.03
2.44
3.36
f1 (ppm)


rs
Me
H
Me

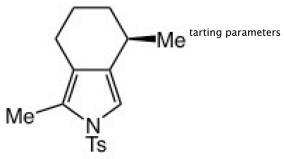
18


77.18 CDCl3
76.97 CDCl3
76.76
89.55
89.54
88.82
88.75
85.86
85.83
68.26
35.93
35.90
26.45
26.38
25.01
20.82
20.76
14.52
14.48
204.72
204.70
f1 (ppm)


Me
Me
N
Ts

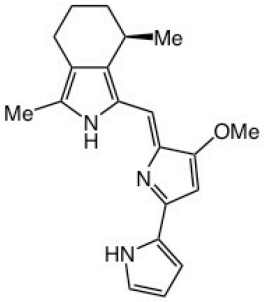
20

2.14
2.17
1.00
1.15
3.51
0.93
1.82
2.98
2.36
1.07
3.71
f1 (ppm)

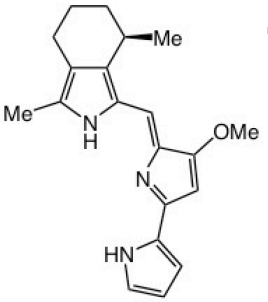

Me
tarting parameters
Me
N
Ts

20

144.21
136.85
129.82
129.81
128.77
124.33
122.48
115.89
32.52
28.50
22.65
21.49
21.25
11.04
f1 (ppm)



cycloprodigiosin (23)



Rev 6/12/12 CGC

cycloprodigiosin (23)