Supporting Information

Total Synthesis of Gelsenicine via a Catalyzed Cycloisomerization Strategy

Eric T. Newcomb, Phil C. Knutson, Blaine A. Pedersen, and Eric M. Ferreira*

Department of Chemistry, University of Georgia, Athens, GA 30602 USA

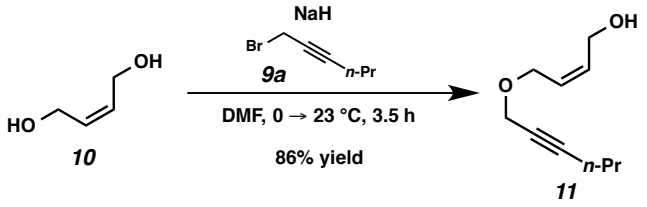
emferr@uga.edu

Table of Contents

Materials and Methods

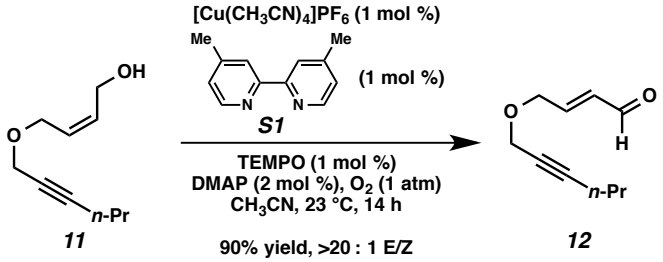
Reactions were performed under an argon atmosphere unless otherwise noted. Tetrahydrofuran, diethyl ether, dichloromethane, acetonitrile, and toluene were purified by passing through activated alumina columns. All other solvents and reagents were used as received unless otherwise noted. Commercially available chemicals were purchased from Alfa Aesar (Ward Hill, MA), Sigma-Aldrich (St. Louis, MO), Oakwood Products (West Columbia, SC), Strem (Newburyport, MA), and TCI America (Portland, OR). Qualitative TLC analysis was performed on 250 mm thick, 60 Å, glass backed, F254 silica (SiliCycle, Quebec City, Canada). Visualization was accomplished with UV light and exposure to iodine, exposure to *p*-anisaldehyde solution followed by heating, or exposure to $KMnO_4$ solution followed by heating. Flash chromatography was performed using SiliCycle silica gel (230-400 mesh). ^{1}H NMR spectra were acquired on a Varian Mercury 300 (at 300 MHz), a Varian 400 (at 400 MHz), or an Agilent Inova 500 (at 500 MHz) and are reported relative to $SiMe_4$ (δ 0.00). ^{13}C NMR spectra were acquired on a Varian 400 MR (at 100 MHz) or an Agilent Inova 500 (at 125 MHz) and are reported relative to $SiMe_4$ (δ 0.0). All IR spectra were obtained on an ATR-ZnSe as thin films with a Nicolet iS-50 FT-IR or Shimadzu IRPrestige-21 FT-IR spectrometer and are reported in wavenumbers (ν). High resolution mass spectrometry (HRMS) data were acquired by the Colorado State University Central Instrument Facility on an Agilent 6210 TOF LC/MS or Proteomics and Mass Spectrometry Facility at the University of Georgia on a Thermo Orbitrap Elite.

Experimental Section



To a solution of *cis*-2-butene-1,4-diol (**10**, 6.30 mL, 76.7 mmol, 2.50 equiv) in anhydrous DMF (82.5 mL, 0.9 M) at 0 °C was added NaH (1.23 g, 60% dispersion in mineral oil, 30.7 mmol, 1.00 equiv) in two portions. The ice water bath was removed, and the resulting mixture was stirred until the effervescence ceased (*ca.* 30 min). To this mixture was added bromide **9a**[1] (4.94 g, 30.7 mmol), as a solution in anhydrous THF (10 mL), dropwise over 10 min, and the reaction mixture was stirred at 23 °C for 2 h. The reaction was quenched with H_2O (100 mL) and poured into EtOAc (100 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed successively with 10% aqueous LiCl solution (2 x 50 mL) and brine (50 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified via flash chromatography (2:1 hexanes/EtOAc eluent), affording allylic alcohol **11** (4.44 g, 86% yield).

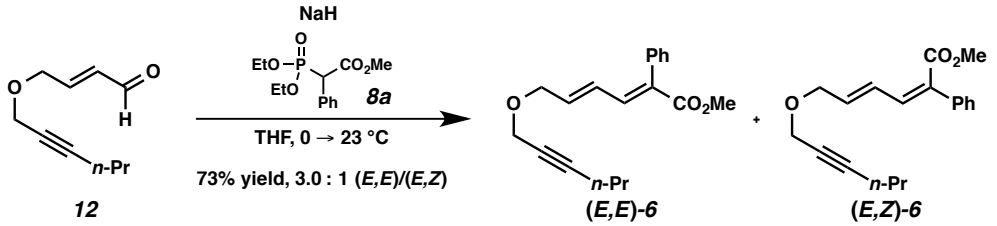
Alcohol 11:
Physical State: colorless oil.
R_f: 0.32 (2:1 hexanes/EtOAc, $KMnO_4$).
IR (film): 3415 (br), 2965, 2224, 1243, 1069, 1032 cm^{-1}.
HRMS (APCI+): *m/z* calc. for $(M + H)^+$ $[C_{10}H_{16}O_2 + H]^+$: 169.1223, found 169.1228.
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.84 (dtt, *J* = 11.3, 6.4, 1.4 Hz, 1H), 5.70 (dtt, *J* = 11.3, 6.4, 1.4 Hz, 1H), 4.23 (app. d, *J* = 6.1 Hz, 2H), 4.15-4.13 (comp. m, 4H), 2.20 (tt, *J* = 7.1, 2.2 Hz, 2H), 1.74 (br s, 1H), 1.54 (app. sextet, *J* = 7.2 Hz, 2H), 0.99 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 132.9, 128.1, 87.5, 75.8, 64.8, 58.9, 58.0, 22.2, 20.9, 13.6.



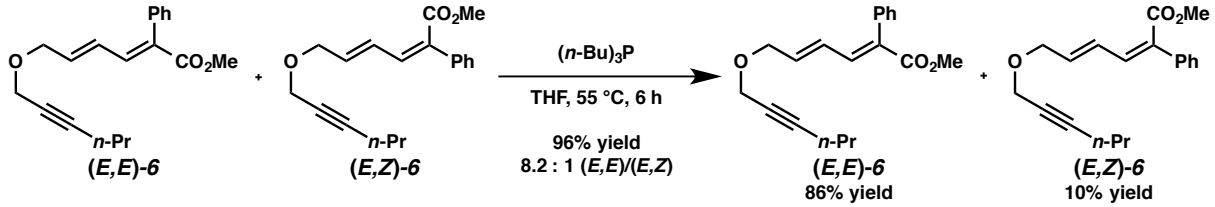
To a solution of allylic alcohol **11** (2.00 g, 11.9 mmol) in CH_3CN (60.0 mL, 0.2 M) was added tetrakis(acetonitrile)copper (I) hexafluorophosphate (44.3 mg, 0.120 mmol, 1.00 mol %), 4,4'-dimethyl-2,2'-bipyridine (**S1**, 21.9 mg, 0.120 mmol, 1.00 mol %), 2,2,6,6-tetramethyl-1-piperidinyloxy (18.6 mg, 0.210 mmol, 1.00 mol %) and 4-(dimethylamino)pyridine (30.0 mg, 0.240 mmol, 2.00 mol %). The reaction vessel was then purged with an O_2 balloon (bubbling through the solution) for 10 min and placed under 1 atm of O_2 via a balloon (replaced as needed throughout the reaction). The resulting mixture was stirred at 23 °C for 15 h. The reaction mixture was then diluted with H_2O (400 mL) and poured into pentane (350 mL). The layers were separated, and the aqueous layer was extracted with pentane (2 x 350 mL). The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$, filtered, and

concentrated under reduced pressure. The resulting residue was purified by flash chromatography (9:1 → 4:1 hexanes/EtOAc eluent), affording enal **12** (1.77 g, 90% yield, >20:1 *E/Z*).

Enal 12:
Physical State: colorless oil.
R_f: 0.38 (4:1 hexanes/EtOAc, $KMnO_4$).
IR (film): 2964, 2224, 1690, 1357, 1134, 1106 cm^{-1}.
HRMS (ESI+): *m/z* calc. for $(M + H)^+$ $[C_{10}H_{14}O_2 + H]^+$: 167.1067, found 167.1072.
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.58 (d, *J* = 7.9 Hz, 1H), 6.84 (dt, *J* = 15.8, 4.3 Hz, 1H), 6.36 (ddt, *J* = 15.8, 7.9, 1.9 Hz, 1H), 4.33 (dd, *J* = 4.3, 1.9 Hz, 2H), 4.21 (t, *J* = 2.2 Hz, 2H), 2.20 (app. tt, *J* = 7.1, 2.2 Hz, 2H), 1.57 (app. sextet, *J* = 7.3 Hz, 2H), 0.98 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 193.0, 152.4, 131.8, 87.7, 75.0, 67.7, 58.6, 21.8, 20.6, 13.3.



To a solution of phosphonate ester **8a**[2] (3.20 g, 11.2 mmol, 1.10 equiv) in anhydrous THF (12.5 mL, 0.9 M) under argon at 0 °C was added NaH (407 mg, 60% dispersion in mineral oil, 10.2 mmol, 1.00 equiv) in two portions. The ice water bath was removed, and the resulting mixture was stirred until the effervescence ceased (*ca.* 25 min). The reaction mixture was then cooled back to 0 °C, and a solution of enal **12** (1.69 g, 10.2 mmol) in THF (2.0 mL) was added dropwise over 2 min. After the addition, the ice water bath was removed, and the mixture was stirred at 23 °C for 4 h. The mixture was filtered through a long plug of silica (10 x 3 cm, 4:1 hexanes/EtOAc), and the solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent), affording a 3.0:1 mixture of dienynes **(*E,E*)-6** and **(*E,Z*)-6** (2.22 g, 73% yield).

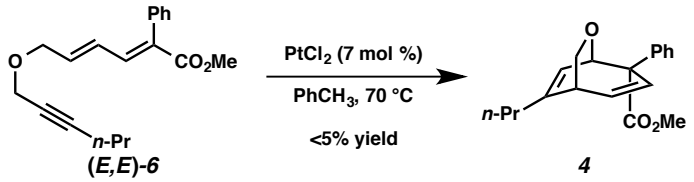


To the mixture of isomers **(*E,E*)-6** and **(*E,Z*)-6** (104 mg, 0.349 mmol, 1.0 equiv) in anhydrous THF (1.40 mL, 0.25 M) under argon at 55 °C was added (n-Bu)$_3$P (174 μL, 0.697 mmol, 2.0 equiv). The reaction mixture was stirred for 6 h at 55 °C. The reaction mixture was then diluted with hexanes (5.0 mL) and filtered through a plug of silica (4 x 2.5 cm, 2:1 hexanes/EtOAc). The solution was concentrated under reduced pressure. The crude ^{1}H NMR indicated an 8.2:1 isomeric mixture of the (*E,E*) and (*E,Z*)-dienynes. This material was purified by flash chromatography (19:1 → 9:1 hexanes/EtOAc eluent), affording pure dienyne **(*E,E*)-6** (89.1 mg, 86% yield). Dienyne **(*E,Z*)-6** could also be isolated (10.2 mg, 10% yield).

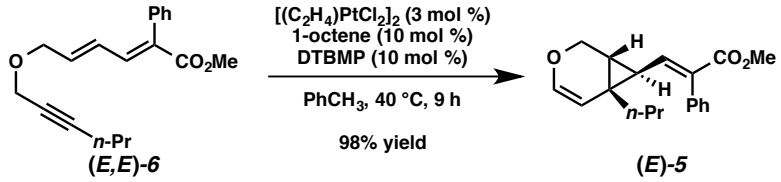
Dienyne (*E,E*)-6:
Physical State: colorless oil.

R_f: 0.36 (9:1 hexanes/EtOAc, anisaldehyde).
IR (film): 3056, 2961, 2223, 1710, 1639, 1592, 1433 cm^{-1}.
HRMS (ESI+): *m/z* calc. for $(M + Na)^+$ $[C_{19}H_{22}O_3 + Na]^+$: 321.1461, found 321.1473.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 10.8 Hz, 1H), 7.40-7.31 (comp. m, 3H), 7.23-7.19 (comp. m, 2H), 6.30 (ddt, *J* = 15.3, 10.8, 1.1 Hz, 1H), 6.21 (dt, *J* = 15.3, 5.5 Hz, 1H), 4.10-4.07 (comp. m, 4H), 3.76 (s, 3H), 2.16 (tt, *J* = 7.1, 2.2 Hz, 2H), 1.50 (app. sextet, *J* = 7.2 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 137.8, 136.9, 136.7, 133.5, 129.3, 128.5, 128.1, 127.7, 87.4, 75.9, 69.6, 58.2, 52.1, 22.2, 20.9, 13.7.

Dienyne (*E,Z*)-6:
Physical State: colorless oil.
R_f: 0.38 (9:1 hexanes/EtOAc, anisaldehyde).
IR (film): 3057, 2961, 2282, 1710, 1638, 1594, 1433 cm^{-1}.
HRMS (ESI+): *m/z* calc. for $(M + Na)^+$ $[C_{19}H_{22}O_3 + Na]^+$: 321.1461, found 321.1467.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.29 (comp. m, 5H), 7.01 (ddt, *J* = 15.2, 11.3, 1.5 Hz, 1H), 6.69 (d, *J* = 11.3 Hz, 1H), 6.10 (dt, *J* = 15.2, 6.0, 1H), 4.20 (dd, *J* = 6.0, 1.5 Hz, 2H), 4.17 (t, *J* = 2.2 Hz, 2H), 3.83 (s, 3H), 2.21 (tt, *J* = 7.1, 2.2 Hz, 2H), 1.60-1.51 (comp. m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 139.8, 138.6, 135.0, 133.0, 130.3, 128.6, 128.1, 127.9, 87.5, 75.7, 69.4, 58.2, 52.4, 22.2, 20.9, 13.6.

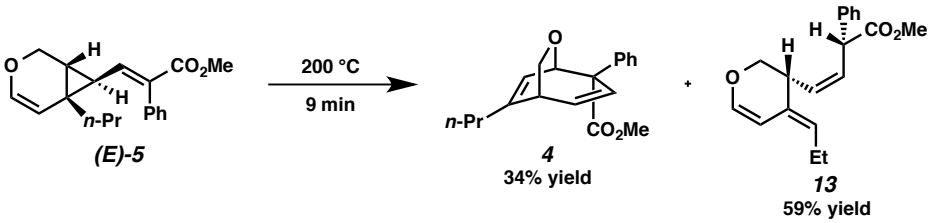


To a solution of dienyne **(*E,E*)-6** (20.0 mg, 67.0 μmol, 1.0 equiv) in anhydrous toluene (2.23 mL, 0.03 M) under argon was added platinum(II) chloride (1.2 mg, 4.69 μmol, 7.00 mol %). This mixture was sealed and heated to 70 °C. After stirring for 3.25 h, the reaction mixture was cooled to 23 °C, and triethylamine (1 drop) was added. The resulting mixture was passed through a short pad of silica (4 x 5 cm, 1:1 hexanes/EtOAc), and the solvent was removed under reduced pressure. Analysis of ^{1}H NMR of the crude reaction mixture indicated <5% of desired bicycle **4**.



To a solution of dienyne **(*E,E*)-6** (362 mg, 1.21 mmol, 1.0 equiv) in anhydrous toluene (24.2 mL, 0.03 M) under argon was added 1-octene (18.9 μL, 0.121 mmol, 10.0 mol %), 2,6-di-*tert*-butyl-4-methylpyridine (24.8 mg, 0.121 mmol, 10.0 mol %), and Zeise's dimer (21.0 mg, 0.0360 mmol, 3.00 mol %). This mixture was stirred at ambient temperature until all the solids were dissolved (*ca*. 20 min) then heated to 40 °C. After stirring for 9 h, the reaction mixture was cooled to 23 °C, and triethylamine (150 μL) was added. The mixture was concentrated under reduced pressure to *ca*. 5 mL and purified by flash chromatography (15:1 hexanes/EtOAc with 2% Et_3N eluent), affording divinylcyclopropane **(*E*)-5** (354 mg, 98% yield).

Divinylcyclopropane (*E*)-5:
Physical State: colorless oil.
R_f: 0.38 (9:1 hexanes/EtOAc, $KMnO_4$).
IR (film): 2955, 1711, 1620, 1435, 1244, 1198 cm^{-1}.
HRMS (DART+): *m/z* calc. for $(M + H)^+$ $[C_{19}H_{22}O_3 + H]^+$: 299.1642, found 299.1645.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.28 (comp. m, 3H), 7.25-7.23 (comp. m, 2H), 6.78 (d, *J* = 10.8 Hz, 1H), 6.06 (d, *J* = 6.0 Hz, 1H), 5.02 (d, *J* = 6.0 Hz, 1H), 4.05 (d, *J* = 10.7 Hz, 1H), 3.81 (dd, *J* = 10.7, 2.3 Hz, 1H), 3.74 (s, 3H), 1.82 (dd, *J* = 10.8, 5.2 Hz, 1H), 1.67-1.40 (comp. m, 6H), 0.96 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 144.0, 142.0, 135.2, 133.1, 130.3, 128.1, 127.6, 107.8, 61.4, 52.2, 35.7, 34.4, 32.7, 26.8, 20.7, 14.3.

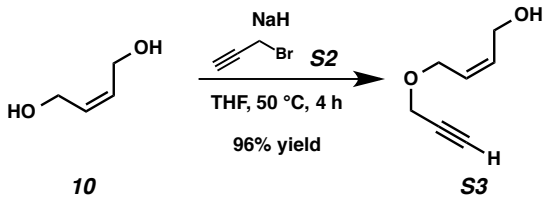


To a flame dried vial under argon was charged divinylcyclopropane **(*E*)-5** (340 mg, 1.14 mmol) neat. The vessel was capped and placed on an aluminum heating block preheated to 200 °C and stirred at this temperature neat for 9 min, at which time the vial was cooled to 23 °C. The crude material was purified by flash chromatography (100% hexanes → 9:1 hexanes/EtOAc eluent), affording desired bicycle **4** (114 mg, 34% yield) and triene **13** (200 mg, 59% yield).
Note: Extended reaction times reduced the yield of triene **13** but did not increase the conversion or yield of bicycle **4**.

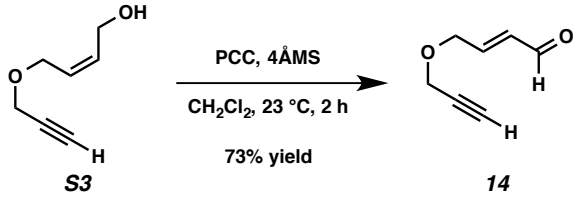
Bicycle 4:
Physical State: colorless oil.
R_f: 0.39 (9:1 hexanes/EtOAc, $KMnO_4$).
IR (film): 2955, 1726, 1433, 1252, 1223, 955 cm^{-1}.
HRMS (APCI+): *m/z* calc. for $(M + H)^+$ $[C_{19}H_{22}O_3 + H]^+$: 299.1642, found 299.1649.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 7.3 Hz, 2H), 7.37-7.33 (comp. m, 2H), 7.29 (app. dt, *J* = 7.1, 1.7 Hz, 1H), 6.37 (dd, *J* = 11.1, 8.6 Hz, 1H), 5.94 (dd, *J* = 6.1, 1.5 Hz, 1H), 5.81 (dd, *J* = 11.1, 2.3 Hz, 1H), 4.88 (dd, *J* = 6.1, 2.3 Hz, 1H), 4.06 (dd, *J* = 8.1, 1.1 Hz, 1H), 3.66 (s, 3H), 3.59 (dd, *J* = 8.1, 2.5 Hz, 1H), 2.65 (dd, *J* = 8.6, 1.5 Hz, 1H), 2.14 (t, *J* = 7.5 Hz, 2H), 1.53-1.46 (comp. m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 151.0, 141.6, 132.6, 130.2, 128.5, 127.5, 126.9, 122.2, 69.4, 61.4, 52.2, 38.5, 37.9, 20.3, 13.7.

Triene 13:
Note: ^{1}H NMR contains 5-10% of bicycle **4**
Physical State: yellow oil.
R_f: 0.48 (9:1 hexanes/EtOAc, $KMnO_4$).
IR (film): 2960, 1811, 1736, 1488, 1225, 1048, 926 cm^{-1}.
HRMS (DART+): *m/z* calc. for $(M + NH_4)^+$ $[C_{19}H_{22}O_3 + NH_4]^+$: 316.1907, found 316.1913.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.31 (comp. m, 4H), 7.30-7.24 (m, 1H), 6.47 (dd, *J* = 6.2, 1.3 Hz, 1H), 6.16 (app. t, *J* = 10.3 Hz, 1H), 5.56 (dd, *J* = 6.2, 0.8 Hz, 1H), 5.45 (app. t, *J* = 10.3 Hz, 1H), 5.00 (td,

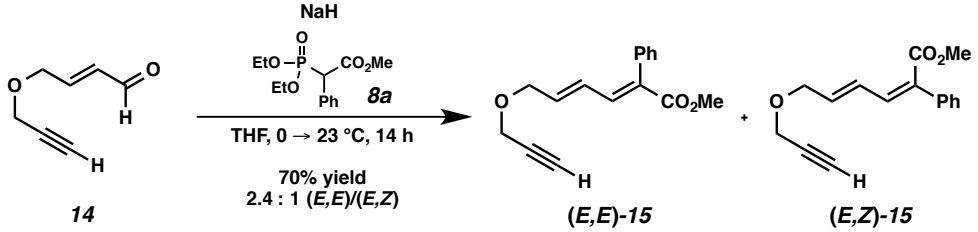
J = 7.3, 0.8 Hz, 1H), 4.63 (d, *J* = 9.8 Hz, 1H), 3.80 (dd, *J* = 10.3, 4.1 Hz, 1H), 3.68 (s, 3H), 3.59 (app. t, *J* = 9.8 Hz, 1H), 3.44-3.37 (comp. m, 1H), 2.19-2.04 (comp. m, 2H), 0.98 (t, *J* = 7.5 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 145.3, 139.1, 129.6, 129.5, 129.0, 128.7, 127.8, 127.5, 124.7, 101.2, 69.8, 52.4, 50.0, 38.3, 20.5, 14.4.



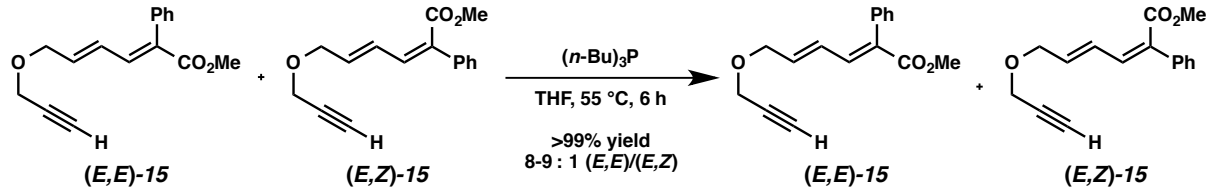
To a solution of *cis*-2-butene-1,4-diol (**10**, 20.6 mL, 250 mmol, 2.50 equiv) in anhydrous THF (200 mL, 0.50 M) under argon at 0 °C was added NaH (4.00 g, 60% dispersion in mineral oil, 100 mmol, 1.00 equiv) in four portions over 20 min. The ice bath was removed and the resulting mixture was stirred until the effervescence ceased (*ca.* 30 min). To this mixture was added propargyl bromide (**S2**, 11.1 mL, 100 mmol) dropwise over 5 min, and the reaction mixture was heated to 50 °C and stirred 4 h. After completion, the reaction was cooled to room temperature and subsequently quenched with H_2O (300 mL) and poured into EtOAc (300 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 300 mL). The combined organic layers were washed successively with H_2O (2 x 150 mL) and brine (2 x 150 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified via flash chromatography (4:1 hexanes/EtOAc eluent), affording allylic alcohol **S3** (11.9 g, 96% yield) as a light yellow oil. The spectroscopic data for alcohol **S3** matched the reported data.[3]



To a flame dried flask, PCC (12.8 g, 59.4 mmol, 1.50 equiv) was added to a mixture of activated 4ÅMS (2.00 g, 50.0 mg/mmol of substrate) in anhydrous CH_2Cl_2 (400 mL, 0.10 M) under argon at 23 °C. Once the PCC was fully dissolved, a solution of allylic alcohol **S3** (5.00 g, 39.6 mmol, 1.00 equiv) in anhydrous THF (10.0 mL) was added, and the reaction was stirred for 2 h at 23 °C. Upon completion, the reaction mixture was passed through a plug of silica (6 x 5 cm, 4:1 hexanes/EtOAc eluent), and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent), affording aldehyde **14** as a yellow oil (3.59 g, 73% yield). The spectroscopic data for aldehyde **14** matched the reported data.[4]



In a flame-dried flask, a solution of phosphonate ester **8a** (3.68 g, 12.8 mmol, 1.10 equiv) in anhydrous THF (15.0 mL, 0.80 M) under argon at 0 °C was added NaH (467 mg, 60% dispersion in mineral oil, 11.7 mmol, 1.00 equiv) in four portions over 20 min. The ice bath was removed, and the resulting mixture was stirred until the effervescence ceased (*ca.* 30 min). The reaction mixture was then cooled back to 0 °C, and a solution of enal **14** (1.45 g, 11.7 mmol) in THF (3.0 mL) was added dropwise over 2 min. After the addition, the ice bath was removed and the mixture was stirred at 23 °C for 4 h. The mixture was filtered through a long plug of silica (4 x 5 cm, 4:1 hexanes/EtOAc), and the solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography (9:1 → 3:1 hexanes/EtOAc eluent), affording a 2.4:1 mixture of dienynes **(*E,E*)-15** and **(*E,Z*)-15**, respectively (2.10 g, 70% yield) as a colorless oil.

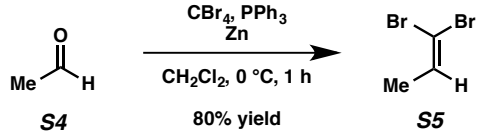


To a solution of the mixture of isomers **(*E,E*)-15** and **(*E,Z*)-15** (1.40 g, 5.46 mmol, 1 equiv) in anhydrous THF (22.0 mL, 0.25 M) under argon was added (n-Bu)$_3$P (2.79 mL, 10.9 mmol, 2.00 equiv). The reaction mixture was stirred for 6 h at 55 °C. The reaction mixture was then concentrated under reduced pressure, and then promptly loaded onto a column for purification via flash chromatography (9:1 → 4:1 hexanes/EtOAc eluent), resulting in an enriched mixture of dienynes **(*E,E*)-15** and **(*E,Z*)-15** (1.39 g, 99% yield). Isomeric ratios were consistently within the range of 8-9:1, favoring **(*E,E*)-15**.

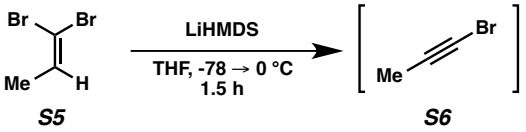
Dienyne (*E,E*)-15:
Physical State: colorless oil.
R_f: 0.44 (9:1 hexanes/EtOAc, anisaldehyde).
IR (film): 3287, 3024, 2847, 2114, 1713, 1227, 1111 cm^{-1}.
HRMS (ESI+): *m/z* calc. for $(M + H)^+$ $[C_{16}H_{16}O_3 + H]^+$: 257.1172, found 257.1174.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, J = 11.1 Hz, 1H), 7.40-7.32 (comp. m, 3H), 7.21 (d, J = 6.4 Hz, 2H), 6.31 (dd, J = 15.4, 11.1 Hz, 1H), 6.20 (dt, J = 15.4, 5.7 Hz, 1H), 4.12-4.07 (comp. m, 4H), 3.76 (s, 3H), 2.46 (s, 1H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 139.5, 137.9, 134.8, 133.0, 130.1, 128.6, 128.0, 127.8, 79.3, 74.8, 69.5, 57.5, 52.2.

Because the isomeric mixture of dienynes was inseparable, the signals for dienyne **(*E,Z*)-15** were elucidated by analysis of the 2.4:1 mixture of dienynes in comparison to the enriched dienyne **(*E,E*)-15**.

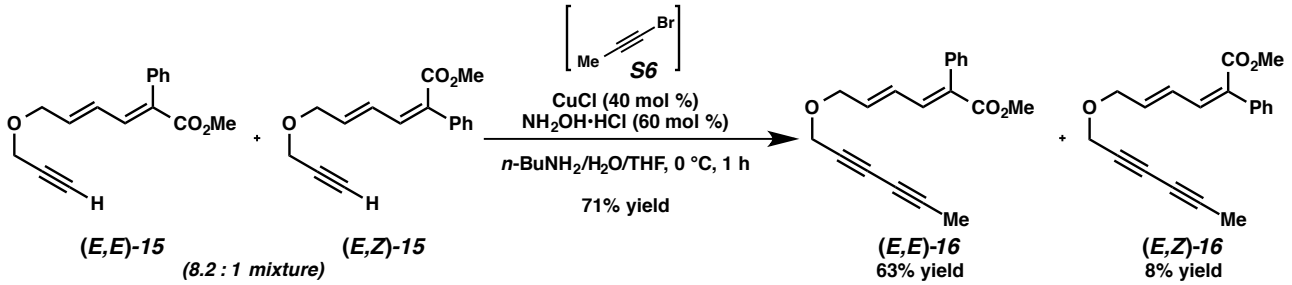
Dienyne (*E,Z*)-15:
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.32 (comp. m, 3H), 7.21 (d, J = 7.4 Hz, 2H), 7.02 (dd, J = 15.3, 11.0 Hz, 1H), 6.69 (d, J = 11.0 Hz, 1H), 6.12-6.05 (dt, J = 15.3, 5.5 Hz 1H), 4.22 (d, J = 5.5 Hz, 2H) 4.19 (s, 2H), 3.84 (s, 3H), 2.41 (s, 1H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 137.9, 137.6, 136.4, 136.2, 133.0, 129.4, 128.3, 127.5, 79.4, 74.7, 69.6, 57.4, 52.0.



To a mixture of CBr_4 (3.32 g, 10.0 mmol, 2.0 equiv) and zinc dust (2.62 g, 40.0 mmol, 8.0 equiv) in anhydrous CH_2Cl_2 (25.0 mL, 0.20 M) under argon at 23 °C was added a solution of PPh_3 (2.67 g, 10.0 mmol, 2.00 equiv) in CH_2Cl_2 (10.0 mL). After 30 min of stirring at 23 °C, the reaction mixture was cooled to 0 °C. Acetaldehyde (**S4**, 280 μL, 5.00 mmol, 1.00 equiv) was added, and the reaction mixture was stirred at 0 °C for 30 min. Upon completion, the mixture was filtered through a plug of silica (6 x 8 cm, CH_2Cl_2 eluent) and concentrated under reduced pressure. (Caution! Dibromopropene **S5** is volatile, and care should be taken during concentration.) The excess PPh_3O was removed by washing with cold Et_2O (3 x 100 mL) and filtering off the white solid. The filtrate was concentrated in vacuo, affording dibromopropene **S5** (810 mg, 80% yield) as a light yellow liquid. The product was used in the subsequent reaction without further purification. The spectroscopic data for alkene **S5** matched the reported data.[5]



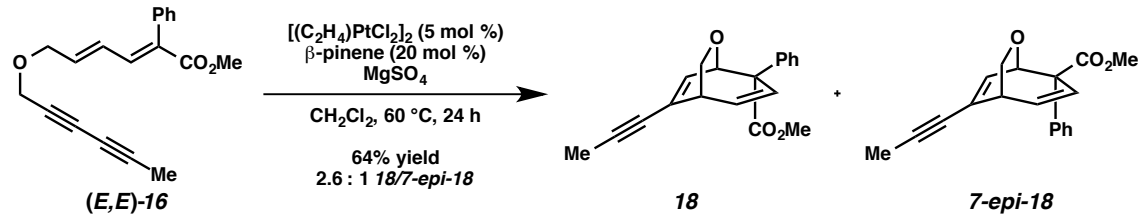
To a mixture of freshly distilled HMDS (2.57 mL, 6.76 mmol, 1.56 equiv) in anhydrous THF (4.45 mL, 1.45 M) under argon at -78 °C, *n*-BuLi (2.57 mL, 2.5 M in hexanes, 6.44 mmol, 1.50 equivalents) was added dropwise. The LiHMDS was generated over 30 min stirring at -78 °C. In a separate flask, dibromopropene **S5** (1.29 g, 6.44 mL, 1.50 equiv) was dissolved in anhydrous THF (4.45 mL, 1.45 M) under argon, and the solution was cooled to -78 °C. To this solution, the generated LiHMDS solution was added dropwise. The reaction mixture was stirred for 30 min at -78 °C, and then it was warmed to 0 °C and stirred for an additional 1 h to allow the elimination to fully occur. The resulting solution of 1-bromopropyne (**S6**) was carried immediately to the next reaction.



While the elimination was ongoing, in a separate flask, CuCl (170 mg, 1.72 mmol, 0.400 equiv) was added to a stirred solution of *n*-$BuNH_4$ (9.00 mL, 85.8 mmol, 20.0 equiv) and H_2O (14.3 mL, 0.30 M) under argon at 0 °C, resulting in a deep blue solution. NH_2OH•HCl (179 mg, 2.58 mmol, 0.600 equiv) was added, returning the mixture to a colorless solution. A solution of terminal alkyne isomers ***(E,E)*-15** and ***(E,Z)*-15** (1.10 g, 8.2:1 (*E,E*), 4.29 mmol, 1.00 equiv) in THF (2.0 mL) was added to the reaction mixture, resulting in a bright yellow solution. After 5 min, the solution of 1-bromopropyne (**S6**, held at 0 °C) was then added to the reaction mixture via syringe, and the resulting mixture was allowed to stir at 0 °C for 1 h. The dark brown mixture was then poured into EtOAc (100 mL), the phases were separated, and the aqueous layer was extracted with EtOAc (2 x 60 mL). The organic layers were combined, washed with brine (50 mL), and dried over $MgSO_4$. Purification by flash chromatography (19:1 → 9:1

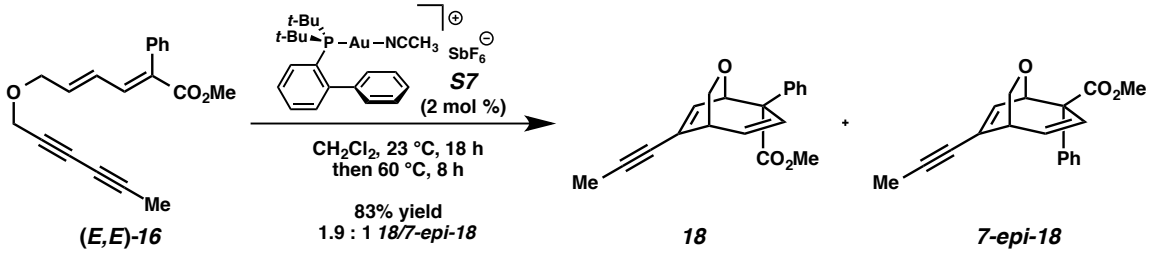
hexanes/EtOAc eluent) afforded dienediyne **(*E,E*)-16** (870 mg, 63% yield). Dienediyne **(*E,Z*)-16** could also be isolated (106 mg, 8% yield).

Dienediyne (*E,E*)-16:
Physical State: colorless oil.
R_f: 0.44 (9:1 hexanes/EtOAc, anisaldehyde).
IR (film): 3024, 2847, 2261, 1713, 1227, 1103 cm^{-1}.
HRMS (ESI+): *m/z* calc. for $(M + H)^+$ $[C_{19}H_{18}O_3 + H]^+$: 295.1329, found 295.1328.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, *J* = 11.0 Hz, 1H), 7.39-7.34 (comp. m, 3H), 7.21 (d, *J* = 7.2 Hz, 2H), 6.30 (dd, *J* = 15.3, 11.0 Hz, 1H), 6.19 (dt, *J* = 15.3, 5.5 Hz, 1H), 4.15 (s, 2H), 4.08 (d, *J* = 5.5 Hz, 2H), 3.76 (s, 3H), 1.93 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 139.5, 137.8, 134.7, 133.0, 130.1, 128.6, 128.0, 127.8, 71.7, 70.6, 69.5, 63.6, 58.1, 52.2, 4.3.



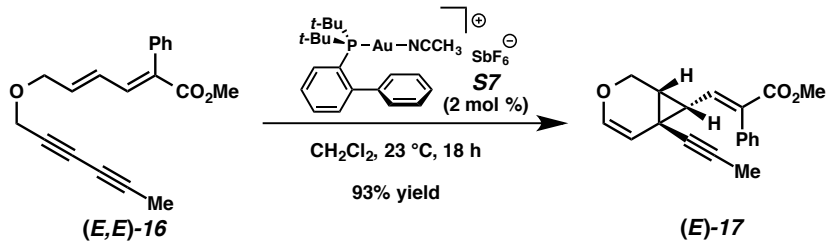
(*E,E*)-16 — *18* — *7-epi-18*

To a solution of dienediyne **(*E,E*)-16** (10.0 mg, 0.0340 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (1.13 mL, 0.03 M) under argon, β-pinene (0.9 mg, 0.00679 mmol, 20 mol %), $MgSO_4$ (20.4 mg, 0.170 mmol, 5.00 equiv) and Zeise's dimer (1.0 mg, 0.00170 mmol, 5 mol %) were added at room temperature. Once all solids were dissolved, the reaction mixture was heated to 60 °C. After stirring for 24 h the reaction was put through a plug (2 x 1 cm, 2:1 hexanes/EtOAc). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (9:1 hexanes:EtOAc eluent), affording bicycle **18** (4.6 mg, 46% yield) and bicycle **7-*epi*-18** (1.8 mg, 18% yield).



(*E,E*)-16 — *18* — *7-epi-18*

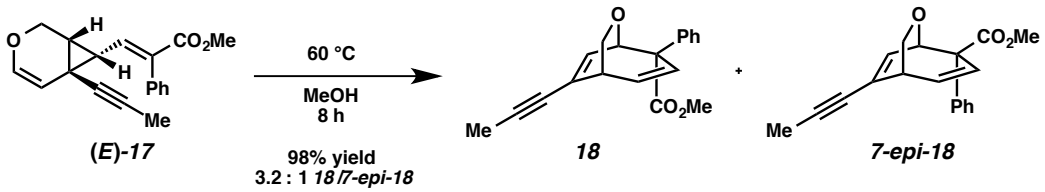
A flame-dried flask was charged with (acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate (**S7**, 0.5 mg, 0.000679 mmol, 2 mol %) in a glovebox. The flask was removed, and the gold catalyst was dissolved in CH_2Cl_2 (0.260 mL, 0.060 M) at 23 °C under argon. To this solution was added a solution of dienediyne **(*E,E*)-16** (10.0 mg, 0.0340 mmol, 1.0 equiv) in CH_2Cl_2 (0.300 mL), and the resulting reaction mixture was stirred at 23 °C for 18 h. After completion of the cycloisomerization was determined by TLC, the reaction was heated to 60 °C and stirred for 8 h. The mixture was then filtered through a plug of silica (2 x 1 cm, 2:1 hexanes/EtOAc eluent). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (9:1 hexanes:EtOAc eluent), affording bicycle **18** (5.4 mg, 54% yield) and bicycle **7-*epi*-18** (2.9 mg, 29% yield).



A flame-dried flask was charged with (acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate (**S7**, 21.0 mg, 0.0272 mmol, 0.0200 equiv) in a glovebox. The flask was removed, and the gold catalyst was dissolved in CH_2Cl_2 (23.0 mL, 0.060 M) at 23 °C under argon. To this solution was added a solution of dienediyne **(*E,E*)-16** (400 mg, 1.35 mmol, 1.0 equiv) in CH_2Cl_2 (5.00 mL), and the resulting reaction mixture was stirred at 23 °C for 18 h. The mixture was then filtered through a plug of silica (3 x 1 cm, 2:1 hexanes/EtOAc eluent), and the filtrate was concentrated in vacuo. Purification of the resulting residue by flash chromatography (9:1 hexanes/EtOAc eluent) afforded divinylcyclopropane **(*E*)-17** (381 mg, 93% yield).

Note: Compound **(*E*)-17** was isolated in 93% purity, with the remaining material presumably the alkene geometrical isomer. Thus, this process contributes in small part to the diastereomeric erosion that was observed after the Cope rearrangement.

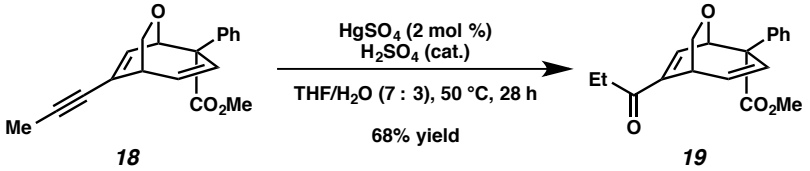
Divinylcyclopropane (*E*)-17:
Physical State: colorless oil.
R_f: 0.48 (9:1 hexanes/EtOAc, anisaldehyde).
IR (film): 3029, 2954, 2253, 1709, 1638, 1237, 1055 cm^{-1}.
HRMS (ESI+): *m/z* calc. for $(M + H)^+$ $[C_{19}H_{18}O_3 + H]^+$: 295.1329, found 295.1329.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (t, *J* = 7.3 Hz, 2H), 7.36-7.34 (m, 1H), 7.32-7.30 (comp. m, 2H), 6.90 (d, *J* = 10.3 Hz, 1H), 6.04 (d, *J* = 6.0 Hz, 1H), 5.17 (d, *J* = 6.0 Hz, 1H), 4.08 (d, *J* = 11.0 Hz, 1H), 3.87 (dd, *J* = 11.0, 2.0 Hz, 1H), 3.78 (s, 3H), 2.06 (dd, *J* = 10.3, 5.8 Hz, 1H), 2.01 (d, *J* = 5.8 Hz, 1H), 1.90 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5, 142.9, 141.3, 134.9, 133.7, 130.1, 128.0, 127.6, 78.8, 75.8, 60.2, 52.1, 36.1, 34.2, 32.5, 18.0, 3.7.



A solution of divinylcyclopropane **(*E*)-17** (250 mg, 0.849 mmol, 1.0 equiv) in MeOH (14.2 mL, 0.060 M) under argon was heated to 60 °C and stirred for 8 h. The reaction was concentrated in vacuo, affording a 3.2:1 mixture of bicycle **18** and bicycle **7-*epi*-18**. The isomers were separated by flash chromatography (9:1 hexanes:EtOAc eluent), affording bicycle **18** (189 mg, 75% yield) and bicycle **7-*epi*-18** (59 mg, 23% yield).

Bicycle 18:
Physical State: light yellow oil.
R_f: 0.60 (9:1 hexanes/EtOAc, anisaldehyde).

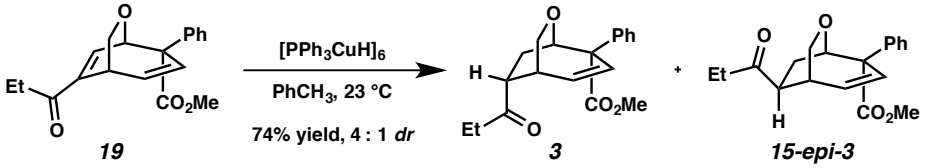
IR (film): 3034, 2951, 2249, 1726, 1226, 1100 cm^{-1}.
HRMS (ESI+): *m/z* calc. for $(M + H)^+$ $[C_{19}H_{18}O_3 + H]^+$: 295.1329, found 295.1328;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 1H), 6.50 (d, *J* = 6.3 Hz, 1H), 6.48 (dd, *J* = 11.1, 8.6 Hz, 1H), 5.89 (dd, *J* = 11.1, 2.3 Hz, 1H), 4.94 (dd, *J* = 6.3, 2.3 Hz, 1H), 4.08 (dd, *J* = 8.4, 1.5 Hz, 1H), 3.73 (dd, *J* = 8.4, 2.7 Hz, 1H), 3.69 (s, 3H), 2.92-2.88 (m, 1H), 2.03 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 140.9, 133.0, 132.6, 132.3, 130.2, 128.5, 127.5, 126.6, 89.9, 78.0, 76.5, 69.1, 61.4, 52.3, 39.4, 4.5.



18 *19*

A flask under argon at 23 °C was charged with bicycle **18** (28.0 mg, 0.0951 mmol, 1.0 equiv). A 30% mixture of H_2O in THF (950 μL, 0.10 M) was added to this flask followed by a drop of conc. H_2SO_4. Finally, $HgSO_4$ (0.6 mg, 0.00190 mmol, 2 mol %) was added and the reaction mixture heated to 50 °C and allowed to stir for 28 h. Once complete, the reaction was poured into EtOAc (8 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 8 mL). Then, the combined organic layers were washed once with brine (35 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified via flash chromatography (9:1 hexanes/EtOAc eluent), affording enone **19** (20.3 mg, 68% yield) as a light yellow oil.

Enone 19:
Physical State: colorless oil.
R_f: 0.40 (4:1 hexanes/EtOAc, $KMnO_4$).
IR (film): 2953, 1723, 1672, 1377, 1254, 1224, 1195 cm^{-1}.
HRMS (ESI+): *m/z* calc. for $(M + H)^+$ $[C_{19}H_{20}O_4 + H]^+$: 313.1434, found 313.1433.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.30 (comp. m, 6H), 6.45 (dd, *J* = 11.1, 8.7 Hz, 1H), 5.80 (dd, *J* = 11.1, 2.1 Hz, 1H), 5.06 (dd, *J* = 6.3, 2.1 Hz, 1H), 4.17 (dd, *J* = 8.4, 1.0 Hz, 1H), 3.67 (s, 3H), 3.64 (d, *J* = 8.7, 1H), 3.58 (dd, *J* = 8.4, 2.8 Hz, 1H), 2.84-2.68 (comp. m, 2H), 1.15 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 198.0, 172.2, 147.4, 140.6, 138.8, 134.0, 129.3, 128.6, 127.8, 126.6, 76.4, 69.7, 61.3, 52.4, 31.0, 29.9, 8.3.

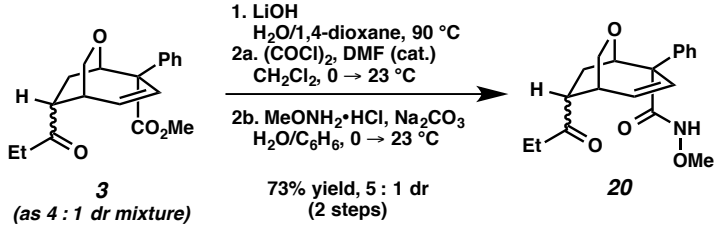


19 *3* *15-epi-3*

In an N_2-filled glovebox, enone **19** (189 mg, 0.605 mmol) and Stryker's Reagent (356 mg, 0.182 mmol, 0.300 equiv) were dissolved in toluene (6.72 mL, 0.09 M), sealed with a rubber septum and electrical tape, and removed from the glovebox. The resulting mixture was stirred sealed for 1 h. The septum was removed, and after stirring open to air for *ca*. 30 min, the mixture was filtered through silica (0.5 x 3 cm, 2:1 hexanes/EtOAc). The solvent was removed under reduced pressure, and the crude material was purified by flash chromatography (9:1 → 4:1 hexanes/EtOAc eluent), affording ketones **3** (115.8 mg, 61% yield) and **15-*epi*-3** (24.4 mg, 13% yield) as separable diastereomers.

Enone 3:
Note: The ^{1}H and ^{13}C NMR spectra have a minor impurity of triphenylphosphine. ^{1}H NMR: δ 7.36 (s, 15H); ^{13}C NMR: δ 137.4, 133.7, 128.6, 128.5.
Physical State: colorless oil.
R_f: 0.47 (2:1 hexanes/EtOAc, $KMnO_4$).
IR (film): 3054, 2936, 1725, 1434, 1223 cm^{-1}.
HRMS (APCI+): *m/z* calc. for $(M + H)^+$ $[C_{19}H_{22}O_4 + H]^+$: 315.1591, found 315.1595.
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.39 (comp. m, 2H), 7.34-7.26 (comp. m, 3H), 6.30 (dd, *J* = 10.9, 7.8 Hz, 1H), 6.22 (ddd, *J* = 10.9, 1.9, 1.0 Hz, 1H), 4.91 (dd, *J* = 8.4, 1.7 Hz, 1H), 3.73 (app. t, *J* = 2.8 Hz, 2H), 3.64 (s, 3H), 2.90 (app. td, *J* = 9.3, 2.8 Hz, 1H), 2.80-2.75 (comp. m, 1H), 2.63-2.52 (comp. m, 1H), 2.51-2.43 (comp. m, 2H), 2.11-2.03 (m, 1H), 1.07 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 210.9, 173.1, 134.0, 129.7, 129.1, 127.6, 126.5, 74.1, 70.0, 64.7, 52.7, 47.6, 33.4, 33.2, 27.1, 7.9.

Enone 15-*epi*-3:
Note: The ^{1}H and ^{13}C NMR spectra have a minor impurity of triphenylphosphine. ^{1}H NMR: δ 7.36 (s, 15 H); ^{13}C NMR: δ 137.4, 133.7, 128.6, 128.5.
Physical State: colorless oil.
R_f: 0.57 (2:1 hexanes/EtOAc, $KMnO_4$).
IR (film): 3053, 2935, 2874, 1724, 1434, 1222 cm^{-1}.
HRMS (DART+): *m/z* calc. for $(M + NH_4)^+$ $[C_{19}H_{22}O_4 + NH_4]^+$: 332.1856, found 332.1865.
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44-7.40 (comp. m, 2H), 7.34-7.28 (comp. m, 3H), 6.40 (dd, *J* = 10.9, 8.8 Hz, 1H), 6.11 (dd, *J* = 10.9, 1.9 Hz, 1H), 4.67 (app. d, *J* = 6.2 Hz, 1H), 3.84 (dd, *J* = 10.1, 2.8 Hz, 1H), 3.74-3.71 (m, 1H), 3.70 (s, 3H), 2.96 (app. dd, *J* = 10.1, 7.7 Hz, 1H), 2.71 (app. d, *J* = 8.2 Hz, 1H), 2.63-2.43 (comp. m, 3H), 2.34 (dd, *J* = 13.4, 10.4 Hz, 1H), 1.08 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 211.0, 173.3, 141.8, 134.0, 131.7, 127.4, 126.8, 74.2, 65.2, 64.2, 52.5, 47.1, 33.8, 32.8, 25.9, 8.2.

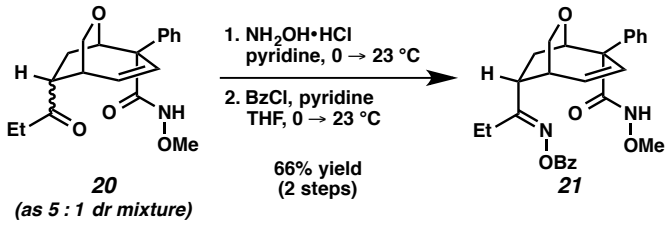


To a solution of 4:1 enone diastereomers **3** and **15-*epi*-3** (80.1 mg, 0.255 mmol) in 1,4-dioxane (2.55 mL, 0.1 M) and H_2O (2.00 mL, 0.128 M) at 23 °C was added lithium hydroxide (611 mg, 25.5 mmol, 100 equiv). This mixture was heated to 90 °C and stirred at this temperature for 2.5 h. The mixture was cooled with an ice water bath, and 1 M aq. HCl was added dropwise until the pH was *ca.* 3. This mixture was then poured into EtOAc (20 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine (20 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was azeotroped with toluene (3 x 1 mL) and taken on crude (100 mg).
Crude acid R_f: 0.09 (1:1 hexanes/Et_2O, $KMnO_4$).

A solution of crude carboxylic acid in anhydrous CH_2Cl_2 (3.19 mL, 0.0800 M to **3**) under argon was cooled to 0 °C, and oxalyl chloride (43.7 μL, 0.510 mmol, 2.00 equiv to **3**) was added. Dimethylformamide (*ca*. 2 μL, catalytic) was then added to the solution, and the resulting mixture was stirred at 0 °C for 15 min, at which time the ice water bath was removed. After stirring at 23 °C for 2 h, the volatile materials were removed under reduced pressure. The resultant residue was azeotroped with toluene (3 x 1.5 mL) to provide crude acid chloride (112 mg), which was carried immediately on.
Crude acid chlorides R_f: 0.38 (major) and 0.56 (minor) (1:1 hexanes/Et_2O, $KMnO_4$).

To a solution of *O*-methylhydroxylamine hydrochloride (31.9 mg, 0.383 mmol, 1.50 equiv to **3**) in benzene (1.19 mL, 0.21 M to **3**) and H_2O (2.00 mL, 0.13 M to **3**) stirring vigorously at *ca.* 0 °C was added sodium carbonate (108 mg, 1.02 mmol, 4.00 equiv to **3**). This was stirred for 10 min at 23 °C, and then a solution of the crude acid chloride in benzene (2.00 mL, 0.13 M to **3**) was added. The resulting biphasic mixture was stirred at 23 °C for 40 min, poured into aqueous HCl (25 mL, 0.05 M) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (1 x 20 mL), dried over $MgSO_4$, and filtered. After removal of the solvent under reduced pressure, the crude material was purified by flash chromatography (4:1 → 1:1 hexanes/EtOAc eluent), affording amide **20** (61.1 mg, 73% yield) as a 5:1 mixture of diastereomers.

Amide 20:
Physical State: colorless film.
R_f: 0.33 (1:1 hexanes/EtOAc, $KMnO_4$).
IR (film): 3159 (br), 2926, 1708, 1670, 1438, 1118 cm^{-1}.
HRMS (DART+): *m/z* calc. for $(M + H)^+$ $[C_{19}H_{23}NO_4 + H]^+$: 330.1700, found 330.1703.
^{1}H NMR (400 MHz, $CDCl_3$) major reported: δ 8.12 (br s, 1H), 7.52 (d, *J* = 7.4 Hz, 2H), 7.36 (app. t, *J* = 7.5 Hz, 2H), 7.31-7.28 (m, 1H), 6.32 (dd, *J* = 10.6, 8.4 Hz, 1H), 5.86 (d, *J* = 10.6 Hz, 1H), 4.83 (dd, *J* = 8.2, 2.0 Hz, 1H), 3.77-3.72 (comp. m, 2H), 3.68 (br s, 3H), 2.95 (td, *J* = 9.2, 3.1 Hz, 1H), 2.80-2.75 (m, 1H), 2.63-2.43 (comp. m, 3H), 2.33 (dd, *J* = 14.5, 8.7 Hz, 1H), 1.08 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) major reported: δ 211.5, 141.0, 134.8, 128.9, 128.8, 127.7, 127.1, 74.4, 69.5, 64.2, 63.5, 47.9, 33.53, 33.45, 27.0, 7.9.

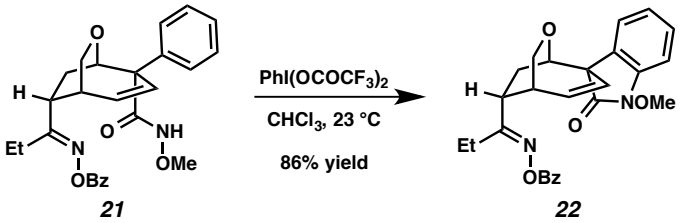


To a solution of amide **20** (42.5 mg, 0.129 mmol) in pyridine (1.29 mL, 0.1 M) at 0 °C was added hydroxylamine hydrochloride (17.9 mg, 0.258 mmol, 2.00 equiv). The reaction mixture was stirred at 23 °C for 3.5 h, at which point it was poured into 1 M aq. HCl saturated with NaCl (10 mL) and EtOAc (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and filtered. The solution was concentrated in vacuo, and the crude material (59.2 mg) was taken on immediately to the next reaction.

To a solution of crude oxime and pyridine (22.9 μL, 0.248 mmol, 2.2 equiv to **20**) in THF (1.29 mL, 0.1 M to **20**) at 0 °C was added benzoyl chloride (16.5 μL, 0.142 mmol, 1.1 equiv to **20**). After stirring for 3 h

at 23 °C, 1 M aq. HCl (5.0 mL) was added. This mixture was diluted with EtOAc (15 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and filtered. The solution was concentrated in vacuo, and the crude residue was purified by flash chromatography (4:1 → 1:1 hexanes/EtOAc eluent), affording benzoate **21** (38.1 mg, 66% yield over two steps) as a single diastereomer.

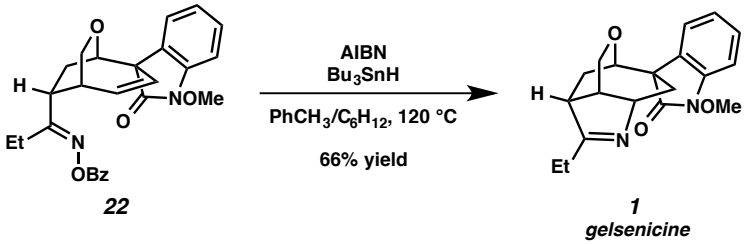
Benzoate 21:
Physical State: white powder.
R_f: 0.33 (1:1 hexanes/EtOAc, $KMnO_4$).
IR (film): 3254 (br), 2936, 2876, 1741, 1662, 1246 cm^{-1}.
HRMS (APCI+): *m/z* calc. for $(M + Na)^+$ $[C_{26}H_{28}N_2O_5 + Na]^+$: 471.1890, found 471.1882.
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.96 (br s, 1H), 8.07 (d, *J* = 7.2 Hz, 2H), 7.63-7.58 (comp. m, 3H), 7.50 (app. t, *J* = 7.7 Hz, 2H), 7.36 (app. t, *J* = 7.6 Hz, 2H), 7.30-7.26 (comp. m, 2H), 6.38 (dd, *J* = 10.9, 8.5 Hz, 1H), 6.03 (dd, *J* = 10.9, 1.8 Hz, 1H), 4.86 (dd, *J* = 8.1, 1.8 Hz, 1H), 3.86 (app. d, *J* = 9.4 Hz, 1H), 3.82 (app. dd, *J* = 9.7, 3.9 Hz, 1H), 3.67 (s, 3H), 3.05 (app. ddd, *J* = 9.6, 8.1, 3.0 Hz, 1H), 2.82-2.78 (m, 1H), 2.68-2.59 (m, 1H), 2.51 (app. q, *J* = 7.5 Hz, 2H), 2.37 (dd, *J* = 14.7, 8.1 Hz, 1H), 1.25 (t, *J* = 7.6 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 171.9, 164.4, 141.2, 134.8, 133.5, 129.7, 129.2, 128.9, 128.8, 128.6, 127.5, 127.4, 74.8, 69.9, 63.9, 63.7, 41.1, 34.3, 28.3, 23.0, 11.1.



21 *22*

To a solution of oxime **21** (5.0 mg, 0.011 mmol) in chloroform (140 μL, 0.08 M) under argon at 23 °C was added bis(trifluoroacetoxy)iodobenzene (5.8 mg, 0.013 mmol, 1.2 equiv). After stirring at ambient temperature for 3 h, solid $NaHCO_3$ (*ca.* 50 mg, excess) was added. This mixture was stirred for 5 min and filtered through a short silica plug (0.5 x 5 cm, 1:1 hexanes/EtOAc eluent). The solvent was removed under reduced pressure, and the resulting residue was purified by flash chromatography (3:1 → 2:1 hexanes/EtOAc eluent), affording oxindole **22** (4.2 mg, 86% yield).

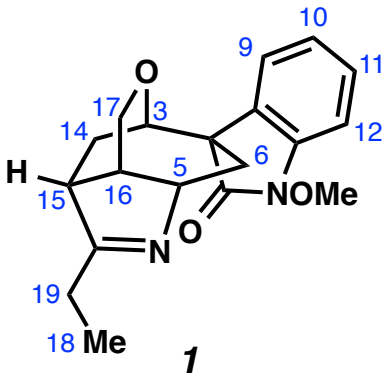
Oxindole 22:
Physical State: white solid.
R_f: 0.24 (2:1 hexanes/EtOAc, $KMnO_4$).
IR (film): 2939, 2877, 1724, 1616, 1464, 1246, 1064 cm^{-1}.
HRMS (DART+): *m/z* calc. for $(M + H)^+$ $[C_{26}H_{26}N_2O_5 + H]^+$: 447.1914, found 447.1917.
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09-8.07 (comp. m, 2H), 7.60 (app. t, *J* = 7.5 Hz, 1H), 7.49 (app. t, *J* = 7.6 Hz, 2H), 7.36-7.31 (comp. m, 2H), 7.13 (app. t, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 7.6 Hz, 1H), 6.49 (dd, *J* = 10.6, 8.4 Hz, 1H), 5.33 (dd, *J* = 10.6, 2.0 Hz, 1H), 4.34 (d, *J* = 9.4 Hz, 1H), 4.17 (dd, *J* = 9.4, 4.3 Hz, 1H), 4.01 (s, 3H), 3.83 (dd, *J* = 8.5, 2.0 Hz, 1H), 3.25 (td, *J* = 9.6, 2.7 Hz, 1H), 3.07 (dd, *J* = 14.1, 9.6 Hz, 1H), 3.00 (dt, *J* = 8.0, 3.8 Hz, 1H), 2.77 (dq, *J* = 13.1, 7.6 Hz, 1H), 2.57 (dq, *J* = 13.1, 7.6 Hz, 1H), 2.44 (dt, *J* = 14.1, 9.1 Hz, 1H), 1.30 (t, *J* = 7.6 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 171.7, 164.0, 138.9, 136.3, 133.3, 129.7, 129.5, 128.9, 128.7, 127.21, 127.19, 126.5, 123.6, 107.4, 73.5, 72.4, 63.6, 60.7, 40.7, 34.2, 25.0, 21.8, 11.2.



To a degassed solution of benzoyl oxime **22** (2.5 mg, 5.6 μmol) in toluene (400 μL, 0.014 M) under argon at 120 °C was added a degassed solution of azobisisobutyronitrile (1.0 mg, 5.6 μmol, 1.0 equiv) and tributyltin hydride (1.5 μL, 5.6 μmol, 1.0 equiv) in cyclohexane (100 μL) via syringe pump over 45 min. The reaction mixture was stirred for an additional 15 min at 120 °C, removed from the heat, and allowed to cool to ambient temperature. The solvent was removed under reduced pressure, and the crude residue was purified by flash chromatography (6:4:3 petroleum ether/Et_2O/MeOH → 6:4:4 petroleum ether/Et_2O/MeOH eluent), affording gelsenicine (**1**, 1.2 mg, 66% yield).

Gelsenicine (1):
Physical State: white solid.
R_f: 0.10 (3:1:1 petroleum ether/Et_2O/MeOH, I_2 → $KMnO_4$).
IR (film): 2922, 2852, 1726, 1645, 1616, 1465, 1111 cm^{-1}.
HRMS (APCI+): *m/z* calc. for $(M + H)^+$ $[C_{19}H_{22}N_2O_3 + H]^+$: 327.1703, found 327.1695.
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 (d, *J* = 7.2 Hz, 1H), 7.25 (hidden under $CHCl_3$, 1H), 7.07 (app. td, *J* = 7.6, 1.0 Hz, 1H), 6.88 (d, *J* = 7.9 Hz, 1H), 4.44-4.39 (m, 1H), 4.30 (dd, *J* = 11.0, 3.1 Hz, 1H), 4.27 (dd, J = 11.0, 1.6 Hz, 1H), 3.94 (s, 3H), 3.73 (dd, *J* = 4.5, 1.8 Hz, 1H), 2.86 (t, *J* = 9.3 Hz, 1H), 2.71 (dq, *J* = 16.5, 8.0 Hz, 1H), 2.57 (app. t, *J* = 8.2 Hz, 1H), 2.41 (comp. m, 1H), 2.40 (dd, *J* = 15.3, 5.0 Hz, 1H), 2.37 (dd, *J* = 14.9, 2.0 Hz, 1H), 2.29 (dd, *J* = 15.3, 2.0 Hz, 1H), 2.13 (ddd, *J* = 14.9, 10.1, 4.8 Hz, 1H), 1.29 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): 128.0, 124.7, 123.3, 106.5, 74.9, 72.6, 63.3, 62.1, 42.5, 39.8, 37.7, 27.0, 25.7, 10.0.

Comparison of ^{1}H Spectra for Synthetic Gelsenicine with Semisynthesis Report



1

gelsenicine

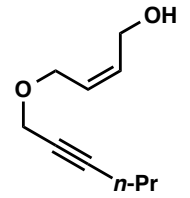
Assignment	Semisynthesis[6]	This Synthesis
H-9	7.53 (d, J = 7.0 Hz, 1H)	7.54 (d, J = 7.2 Hz, 1H)
H-11	7.25 (td, J = 7.5, 1.3 Hz, 1H)	7.25 (hidden under $CHCl_3$, 1H)
H-10	7.07 (td, J = 7.6, 1.0 Hz, 1H)	7.07 (app. td, J = 7.6, 1.0 Hz, 1H)
H-12	6.87 (d, J = 7.9 Hz, 1H)	6.88 (d, J = 7.9 Hz, 1H)
H-5	4.40 (m, 1H)	4.44-4.39 (m, 1H)
H-17	4.30 (dd, J = 11.0, 3.9 Hz, 1H)	4.30 (dd, J = 11.0, 3.1 Hz, 1H)
H-17	4.27 (dd, J = 11.0, 1.7 Hz, 1H)	4.27 (dd, J = 11.0, 1.6 Hz, 1H)
OCH_3	3.95 (s, 3H)	3.94 (s, 3H)
H-3	3.74 (dd, J = 4.7, 2.0 Hz, 1H)	3.73 (dd, J = 4.5, 1.8 Hz, 1H)
H-15	2.86 (t, J = 9.3 Hz, 1H)	2.86 (t, J = 9.3 Hz, 1H)
H-19	2.71 (dq, J = 17.1, 7.3 Hz, 1H)	2.71 (dq, J = 16.5, 8.0 Hz, 1H)
H-16	2.57 (m, 1H)	2.57 (app. t, J = 8.2 Hz, 1H)
H-19	2.41 (dq, J = 17.1, 7.3 Hz, 1H)	2.41 (comp. m, 1H)
H-6	2.40 (dd, J = 15.6, 5.0 Hz, 1H)	2.40 (dd, J = 15.3, 5.0 Hz, 1H)
H-14	2.39 (dd, J = 14.9, 2.2 Hz, 1H)	2.37 (dd, J = 14.9, 2.0 Hz, 1H)
H-6	2.29 (dd, J = 15.6, 2.2 Hz, 1H)	2.29 (dd, J = 15.3, 2.0 Hz, 1H)
H-14	2.13 (ddd, J = 14.9, 10.3, 4.6 Hz, 1H)	2.13 (ddd, J = 14.9, 10.1, 4.8 Hz, 1H)
H-18	1.29 (t, J = 7.3 Hz, 3H)	1.29 (t, J = 7.4 Hz, 3H)

References

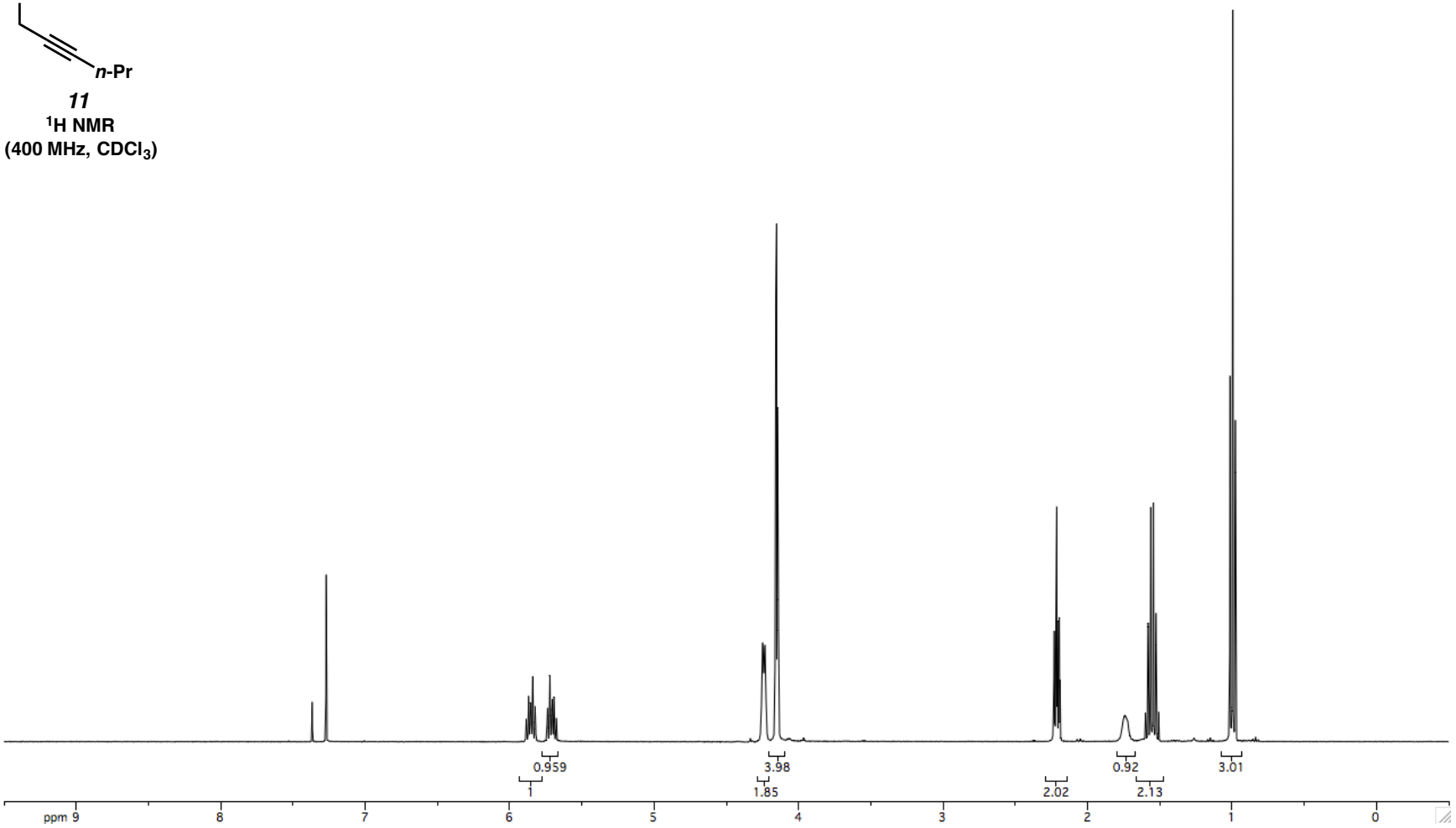
[1] Zhao, L.; Lu, X.; Xu, W. *J. Org. Chem.* **2005**, *70*, 4059–4063.
[2] Geirsson, J. K. F.; Njardarson, J. T. *Tetrahedron Lett.* **1994**, *35*, 9071-9072.
[3] Iafe, R. G.; Kuo, J. L.; Hochstatter, D. G.; Saga, T.; Turner, J. W.; Merlic, C. A. *Org. Lett*. **2013**, *15*, 582-585.
[4] Shu, X.-Z.; Li, X.; Shu, D.; Huang, S.; Schienebeck, C. M.; Zhou, X.; Robichaux, P. J.; Tang, W. *J. Am. Chem. Soc.* **2012**, *134*, 5211−5221.
[5] Perriot, P.; Normant, J. F.; Villieras, J. *C. R. Acad. Sci. Ser. C Chim.* **1979**, *289*, 259-262.
[6] Takayama, H.; Tominaga, Y.; Kitajima, M.; Aimi, N.; Sakai, S. *J. Org. Chem.* **1994**, *59*, 4381-4385.

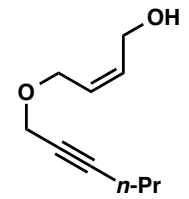
Supporting Information: Spectra Compilation

Total Synthesis of Gelsenicine via a Catalyzed Cycloisomerization Strategy



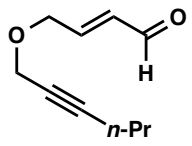
11
^{1}H NMR
(400 MHz, $CDCl_3$)





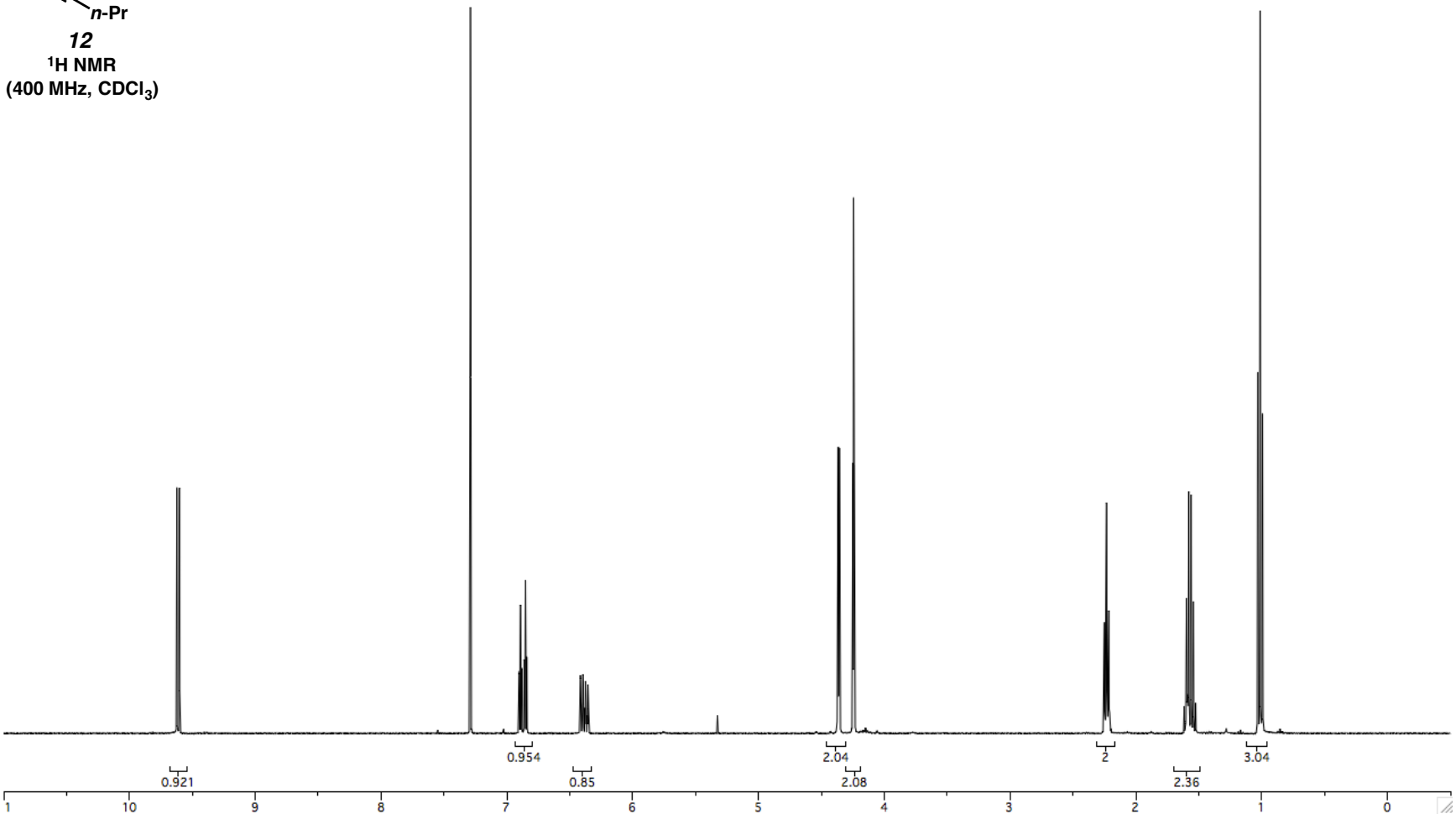
11

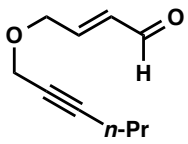
^{13}C NMR
(100 MHz, $CDCl_3$)



12

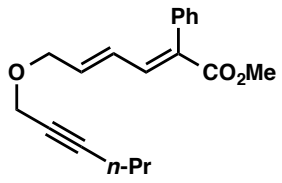
^{1}H NMR
(400 MHz, $CDCl_3$)



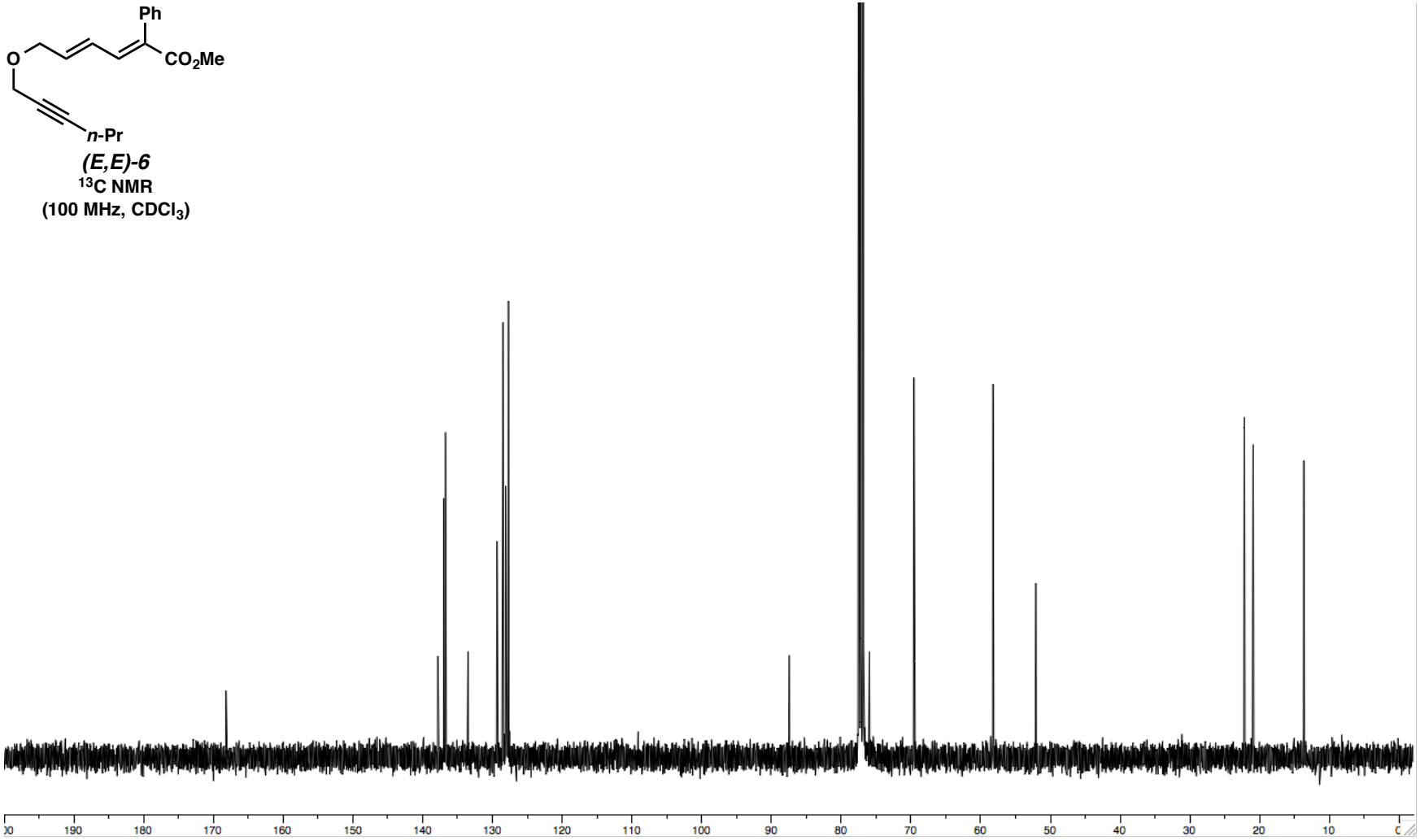


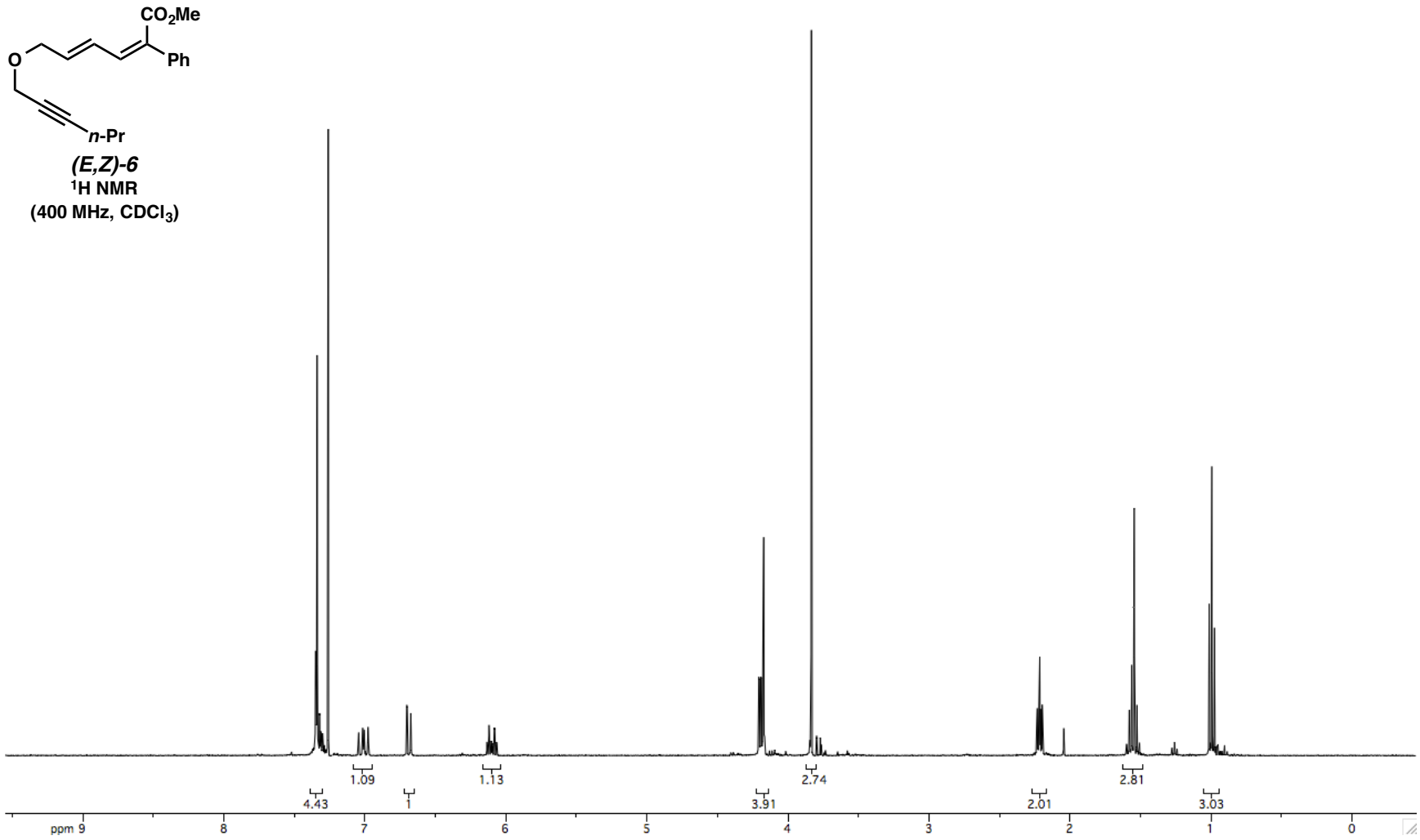
12

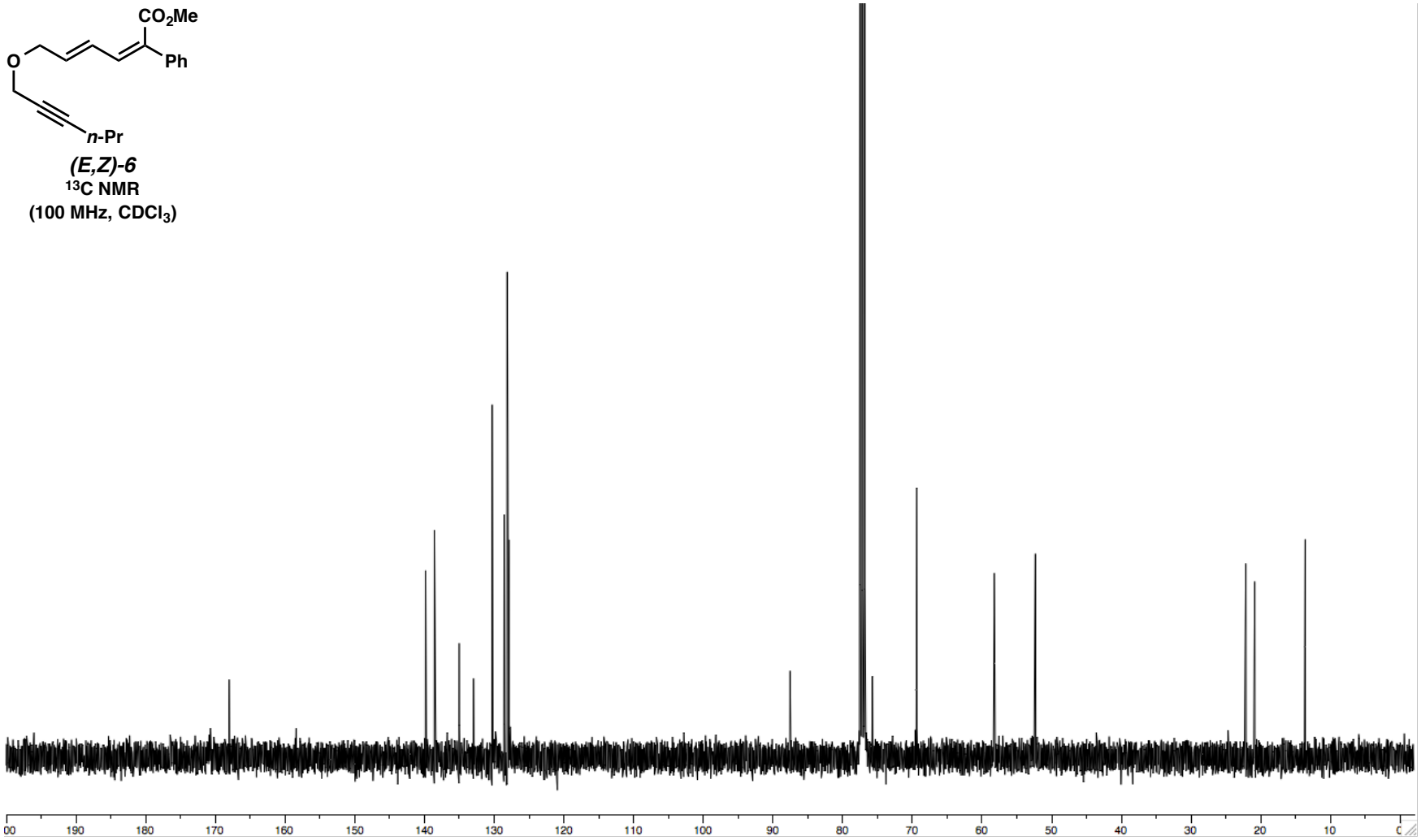
^{13}C NMR
(100 MHz, $CDCl_3$)

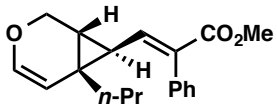


(E,E)-6
^{1}H NMR
(400 MHz, $CDCl_3$)

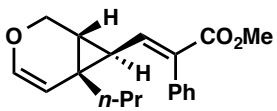

Ph
O
CO2Me
n-Pr
(E,E)-6
13C NMR
(100 MHz, CDCl3)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


CO2Me
Ph
O
n-Pr
(E,Z)-6
1H NMR
(400 MHz, CDCl3)
4.43
1.09
1
1.13
3.91
2.74
2.01
2.81
3.03
ppm 9
8
7
6
5
4
3
2
1
0

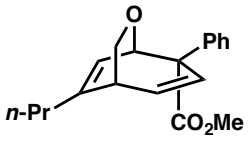

CO2Me
O
Ph
n-Pr
(E,Z)-6
13C NMR
(100 MHz, CDCl3)
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0



(E)-5
^{1}H NMR
(400 MHz, $CDCl_3$)

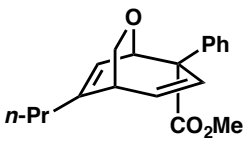


(E)-5
^{13}C NMR
(100 MHz, $CDCl_3$)



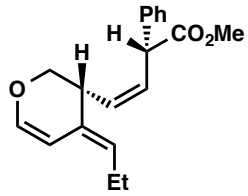
4

^{1}H NMR
(400 MHz, $CDCl_3$)



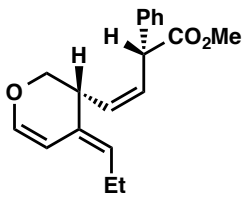
4

^{13}C NMR
(100 MHz, $CDCl_3$)



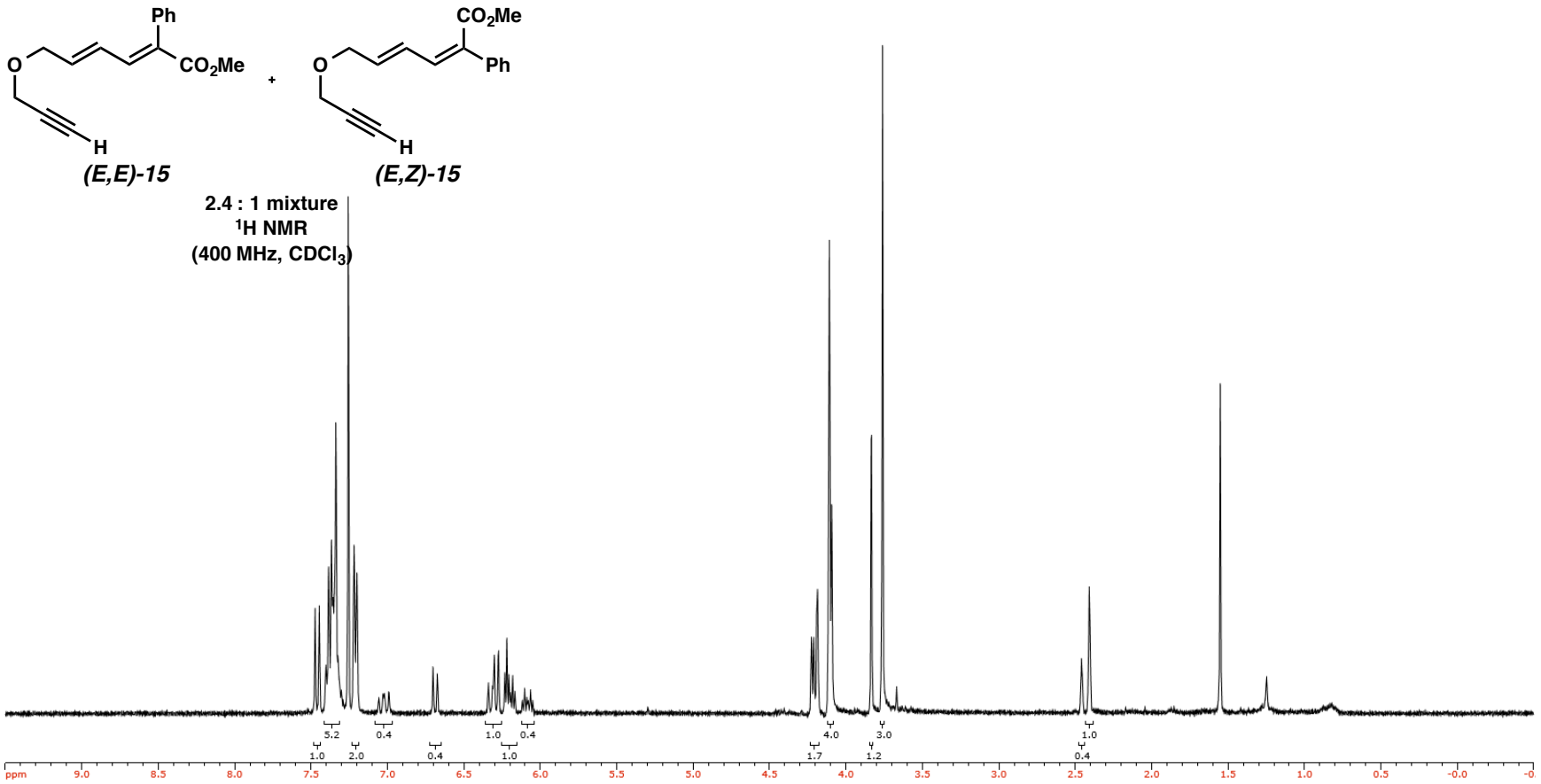
13

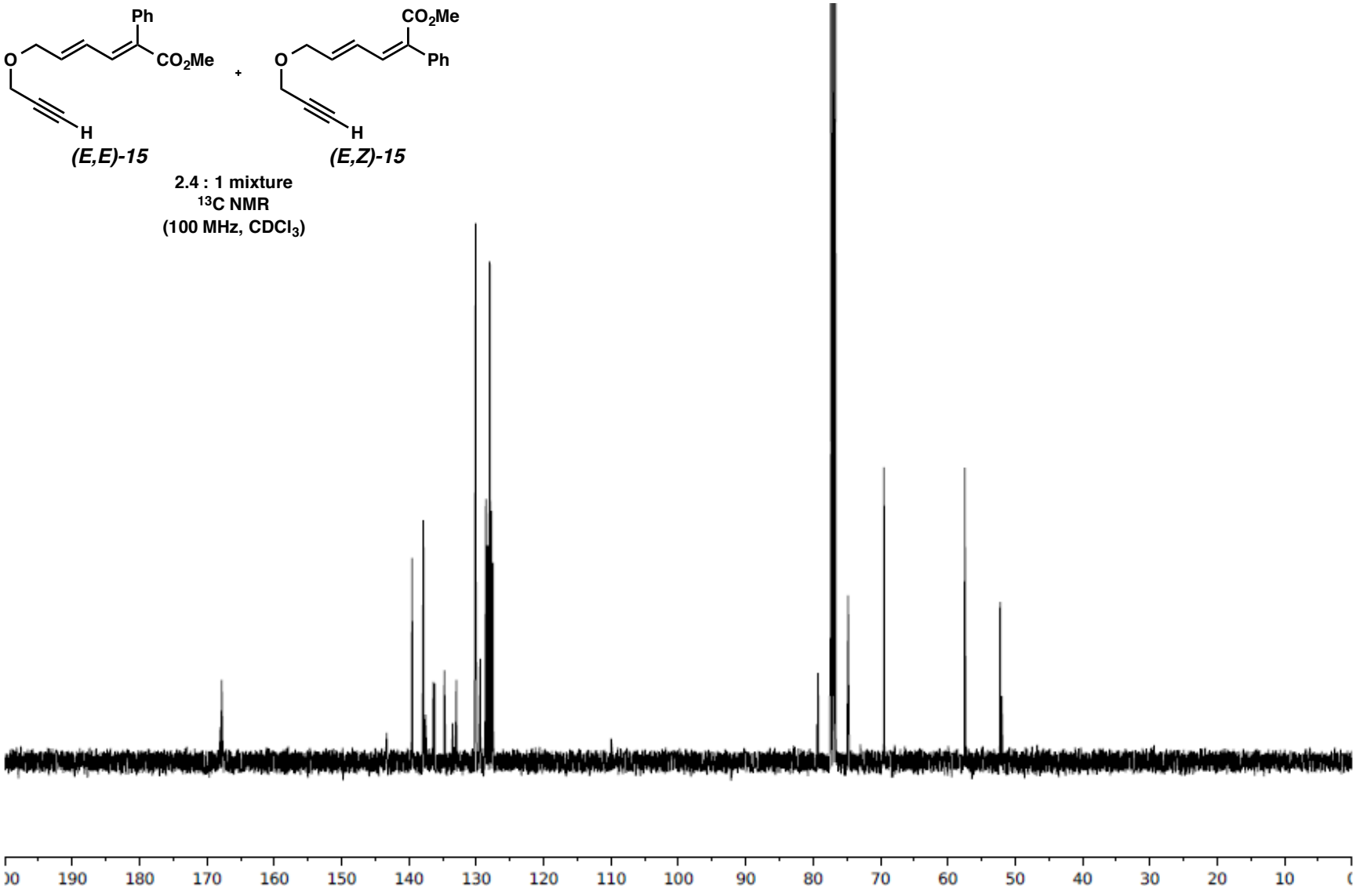
^{1}H NMR
(400 MHz, $CDCl_3$)

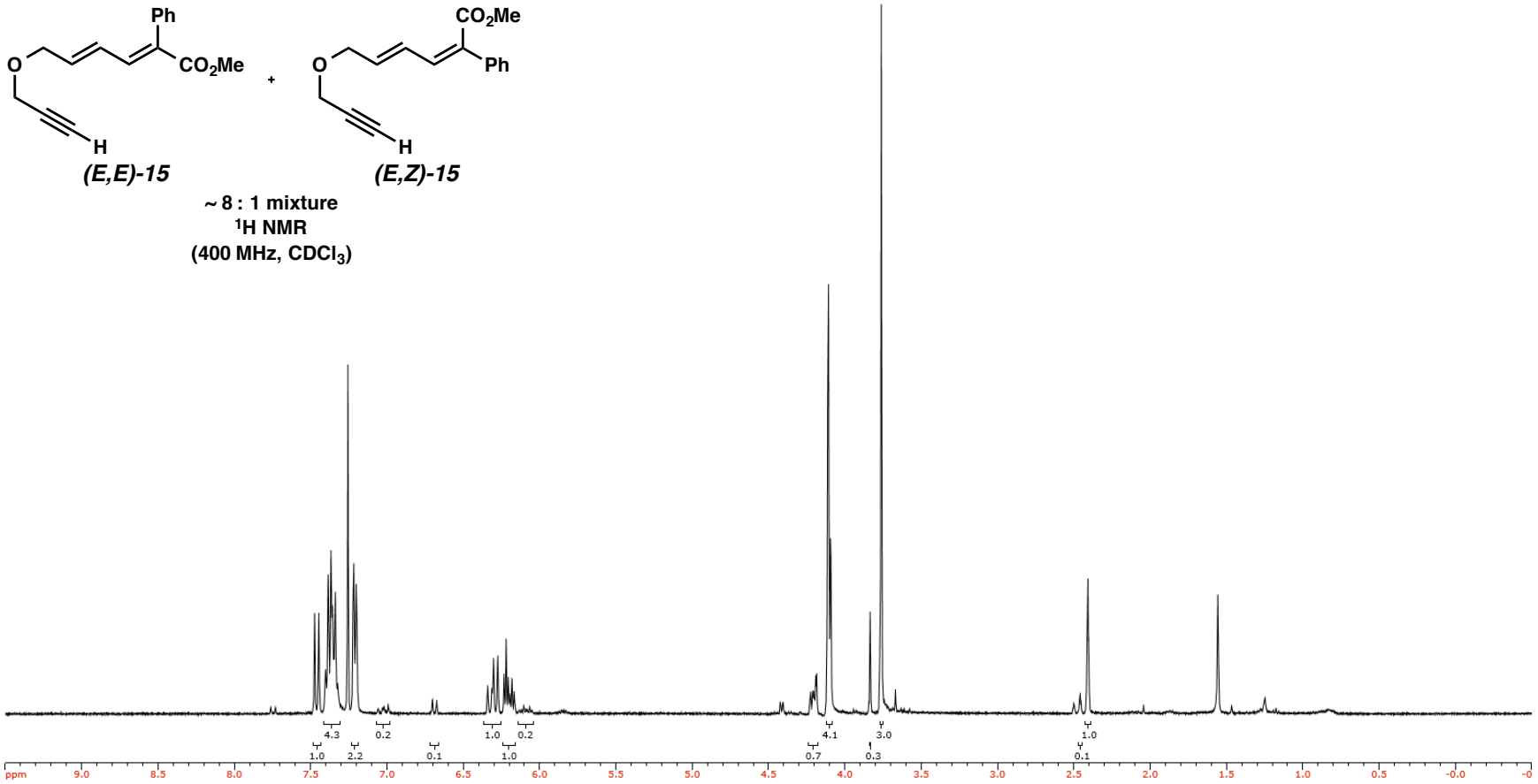


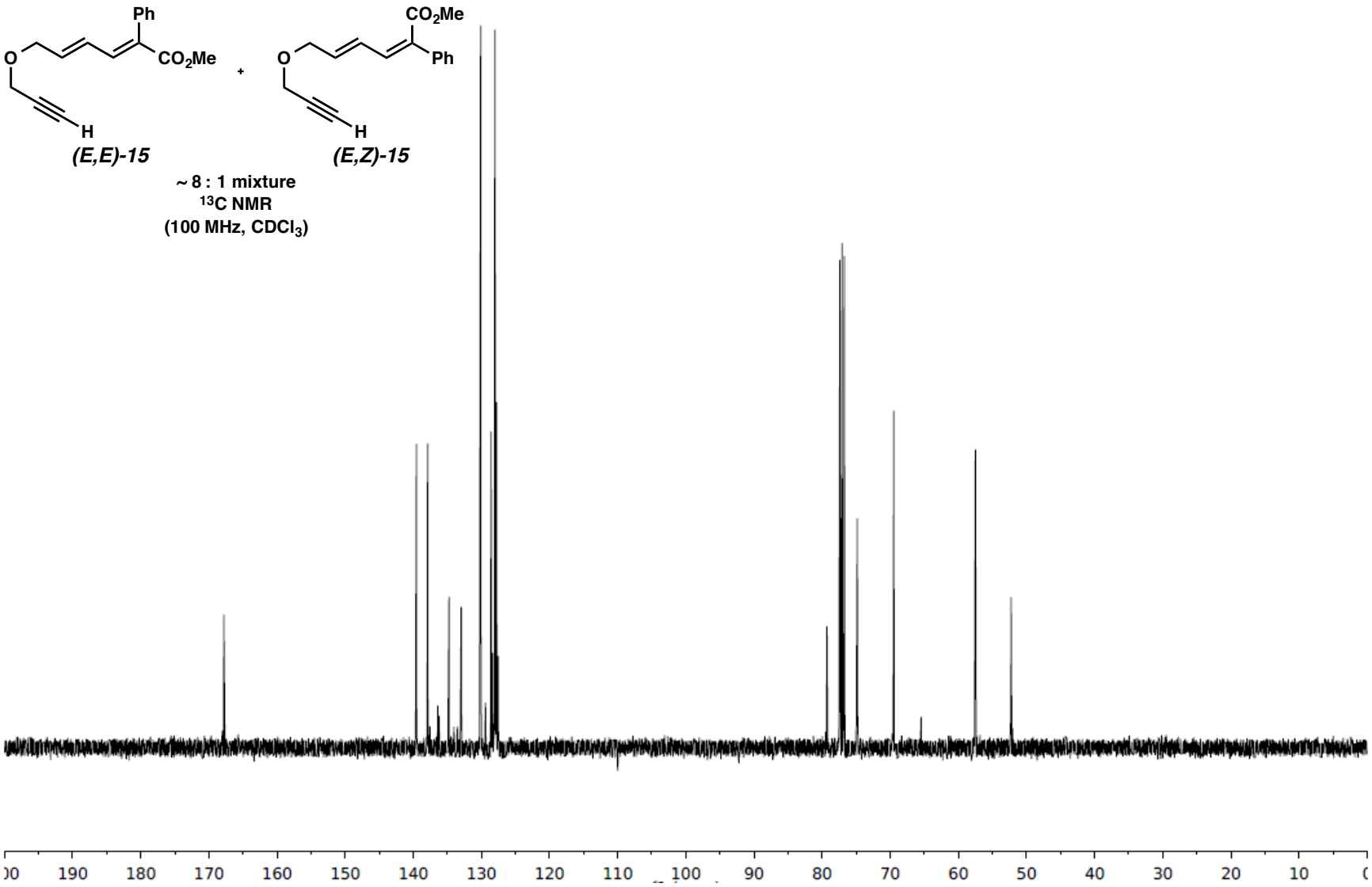
13

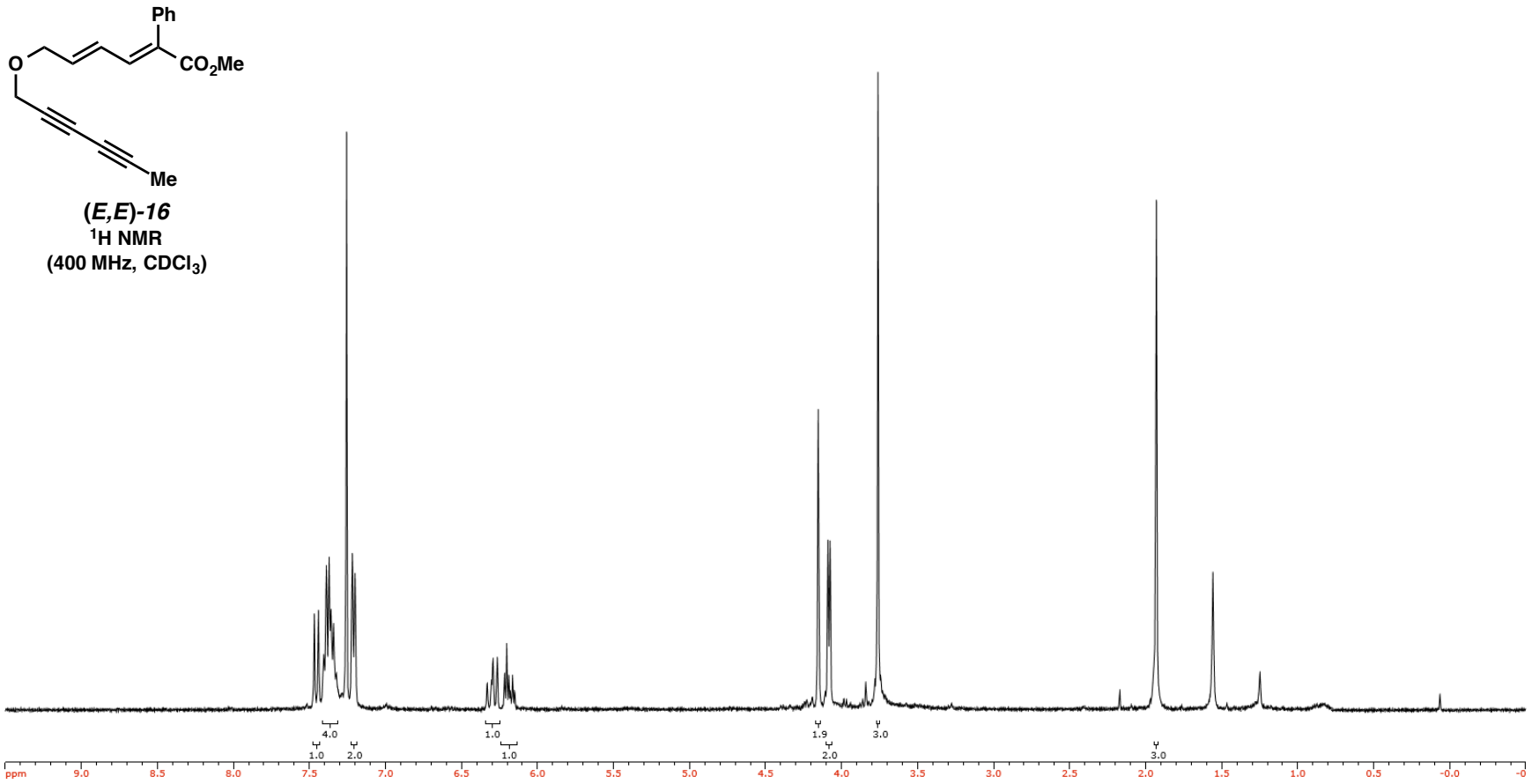
^{13}C NMR
(100 MHz, $CDCl_3$)

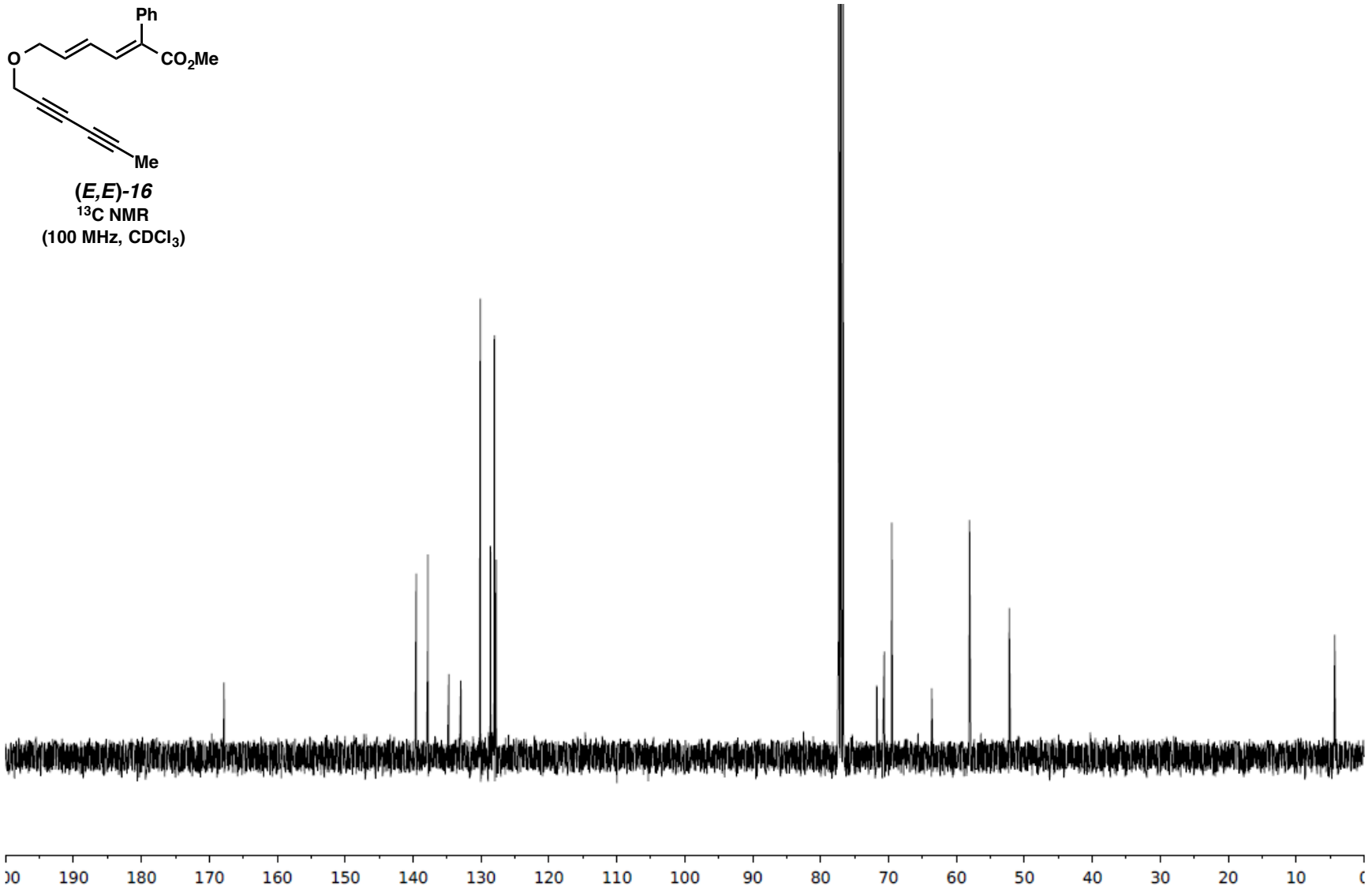

Ph
CO2Me
O
H
(E,E)-15
+
CO2Me
Ph
O
H
(E,Z)-15
2.4 : 1 mixture
1H NMR
(400 MHz, CDCl3)
5.2
0.4
1.0
0.4
4.0
3.0
1.0
1.0
2.0
0.4
1.0
1.7
1.2
0.4
ppm
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
-0.0

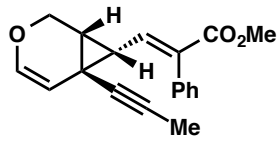

Ph
CO2Me
O
H
(E,E)-15
+
CO2Me
Ph
O
H
(E,Z)-15
2.4 : 1 mixture
13C NMR
(100 MHz, CDCl3)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


Ph
CO2Me
O
H
(E,E)-15
+
CO2Me
Ph
O
H
(E,Z)-15
~ 8 : 1 mixture
1H NMR
(400 MHz, CDCl3)
4.3
0.2
1.0
0.2
4.1
3.0
1.0
1.0
2.2
0.1
1.0
0.7
0.3
0.1
ppm
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

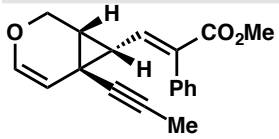

Ph
CO2Me
O
H
(E,E)-15
+
CO2Me
Ph
O
H
(E,Z)-15
~ 8 : 1 mixture
13C NMR
(100 MHz, CDCl3)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


Ph
O
CO2Me
Me
(E,E)-16
1H NMR
(400 MHz, CDCl3)
4.0
1.0
2.0
1.0
1.0
1.9
2.0
3.0
3.0
ppm
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
-0

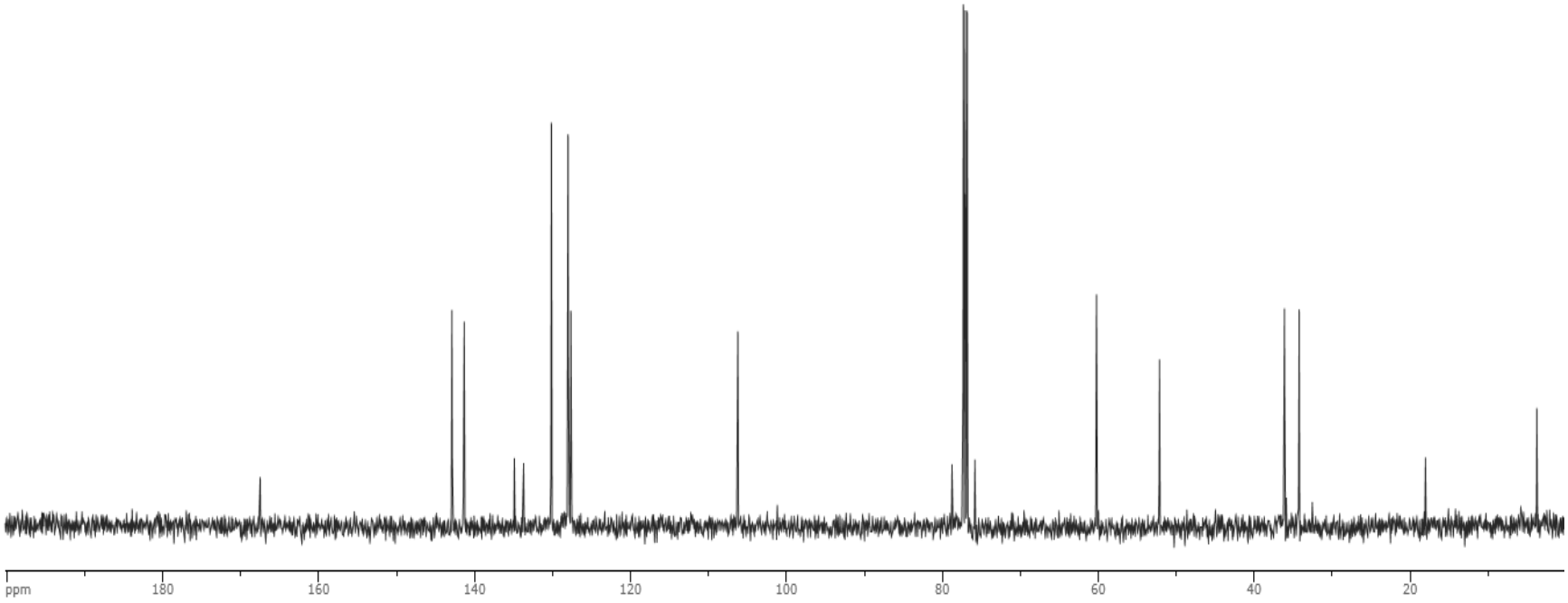

Ph
O
CO2Me
Me
(E,E)-16
13C NMR
(100 MHz, CDCl3)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

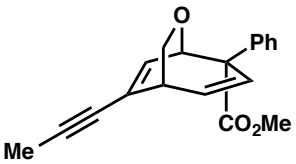


(E)-17
^{1}H NMR
(400 MHz, $CDCl_3$)



(*E*)-*17*
^{13}C NMR
(100 MHz, $CDCl_3$)

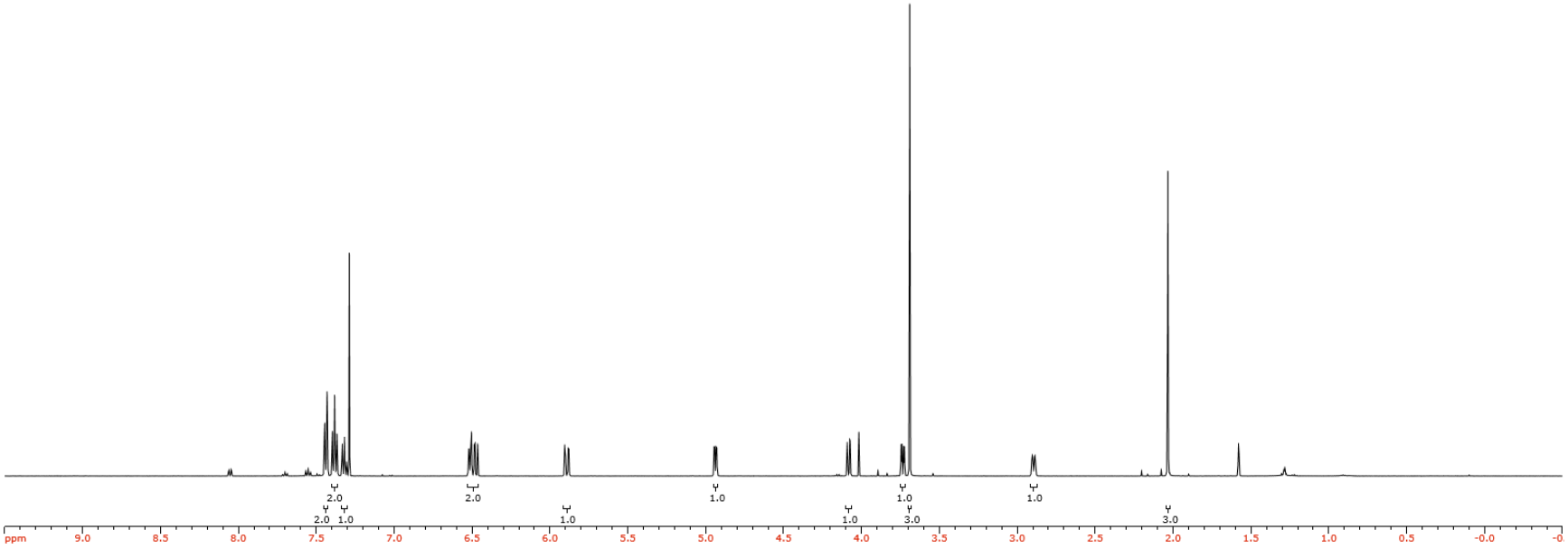


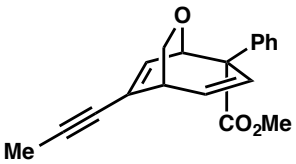


18

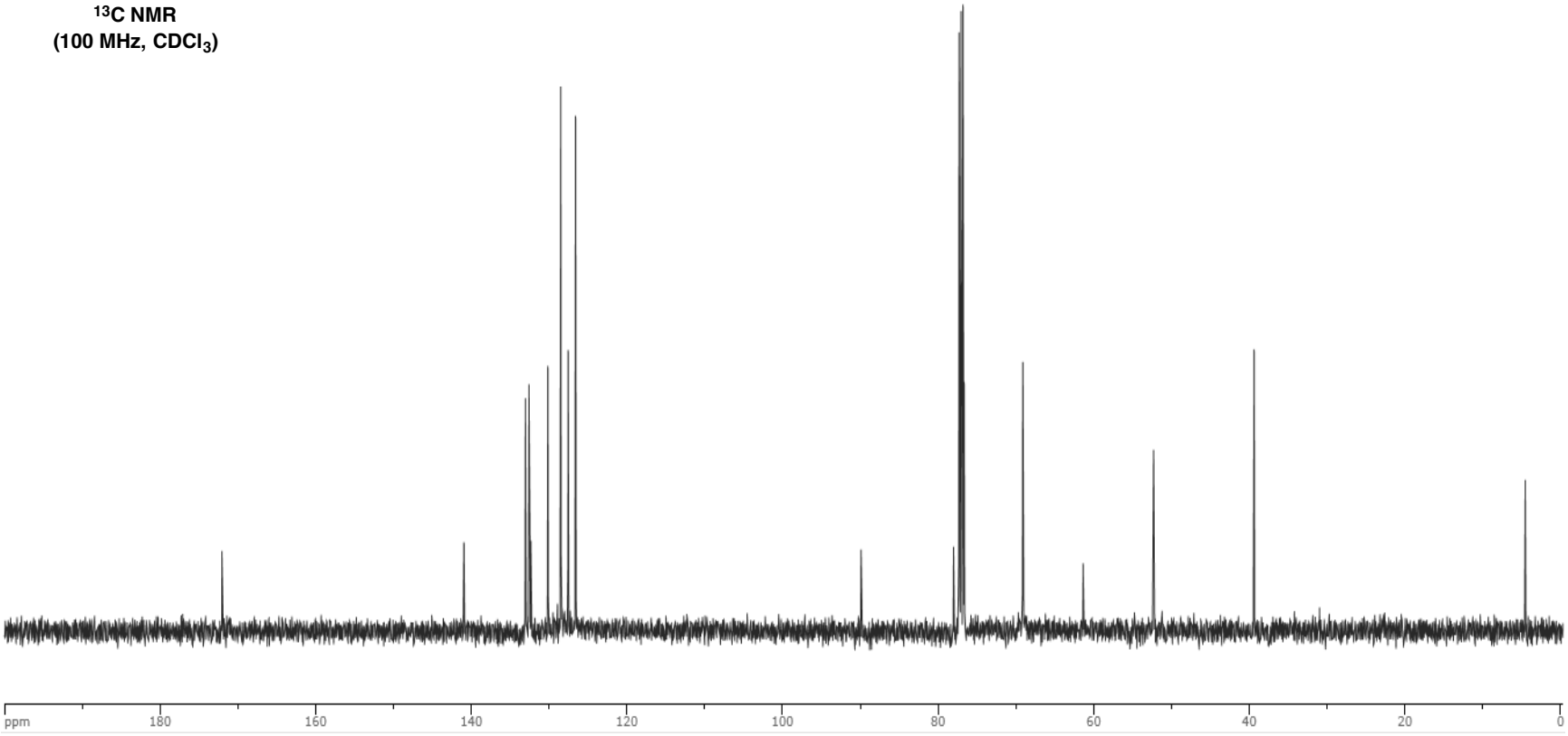
^{1}H NMR

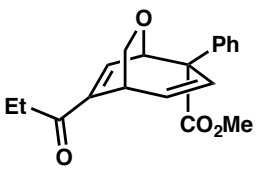
(400 MHz, $CDCl_3$)





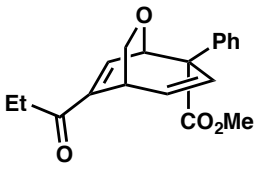
18
^{13}C NMR
(100 MHz, $CDCl_3$)





19

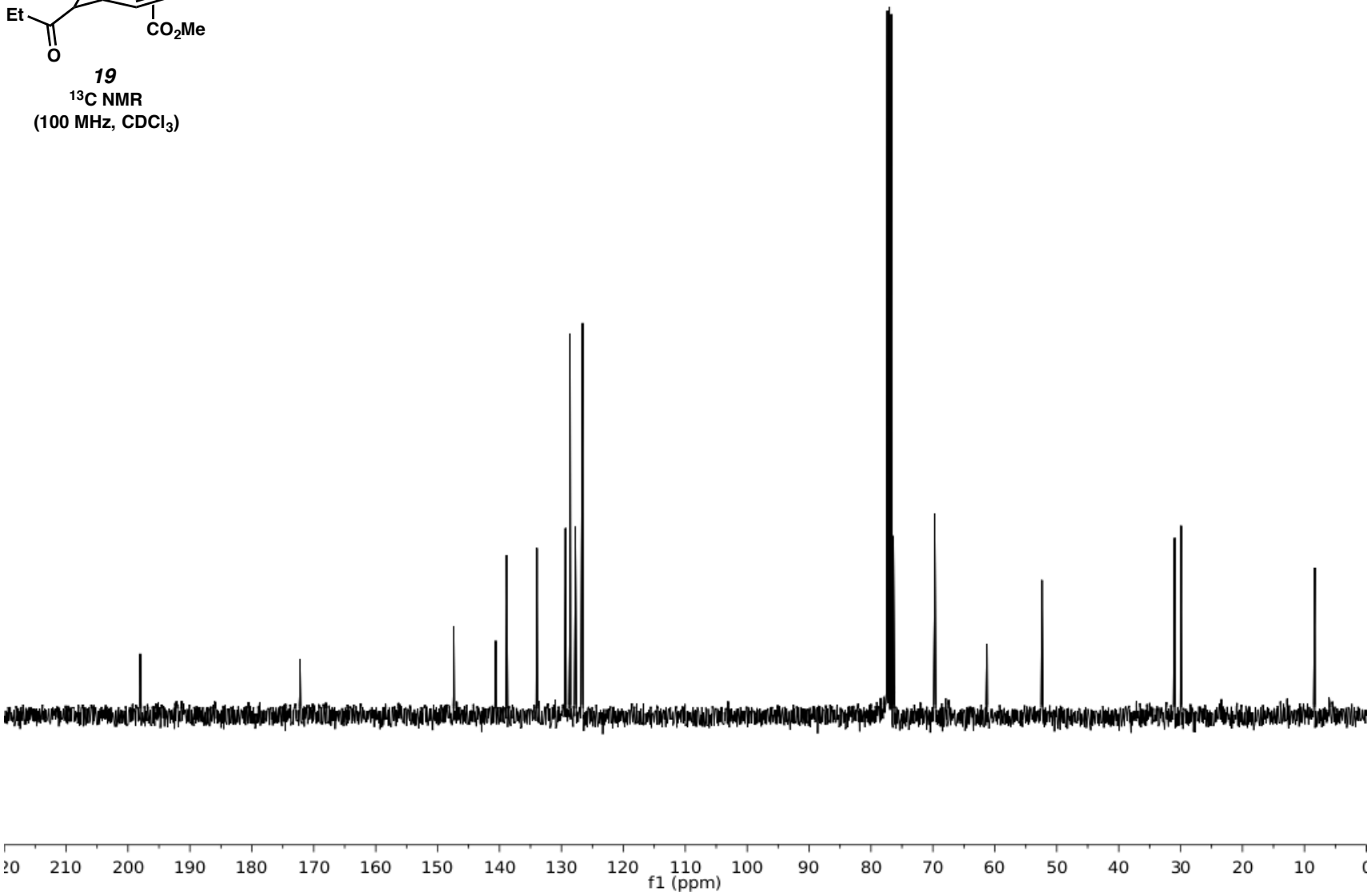
^{1}H NMR
(400 MHz, $CDCl_3$)

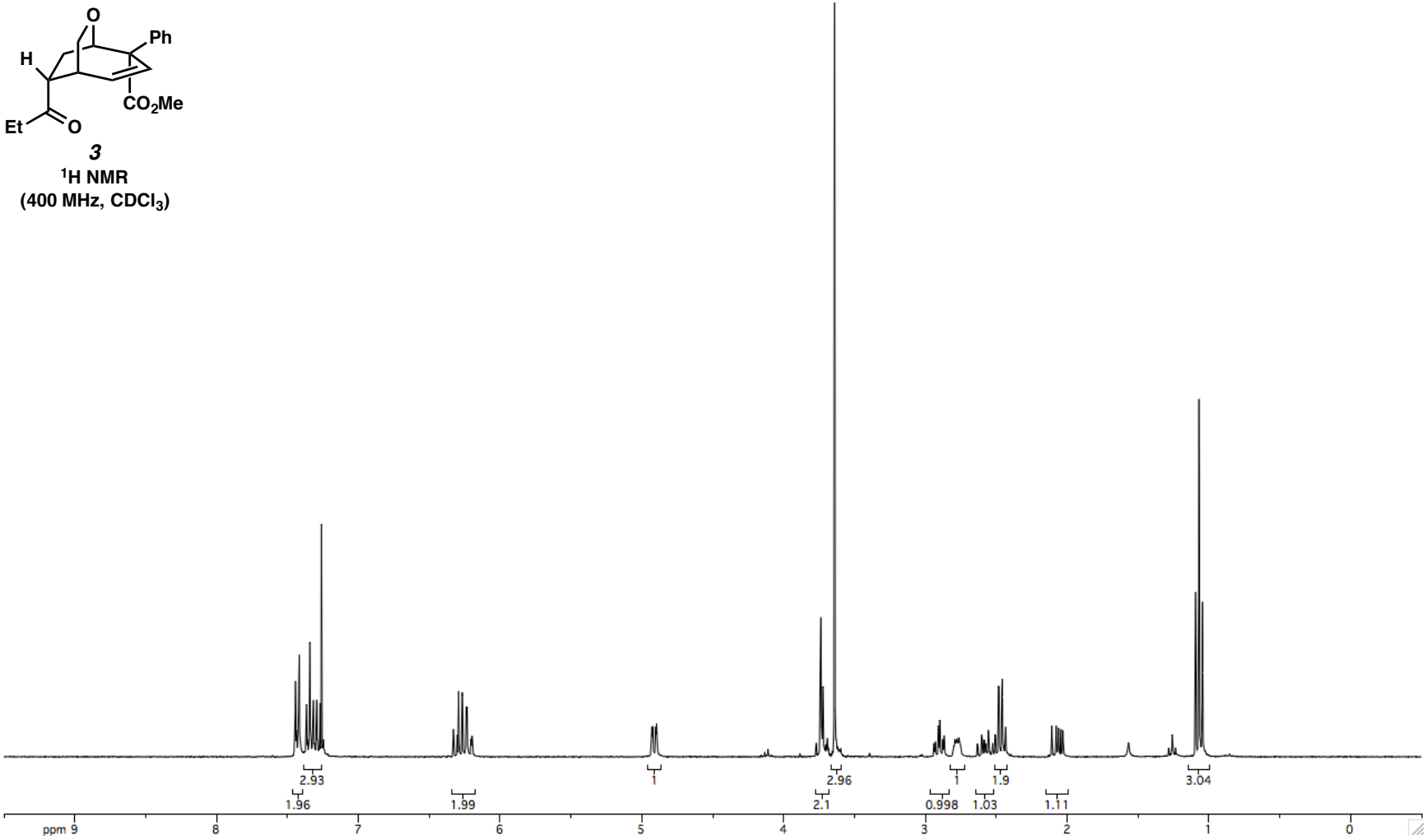


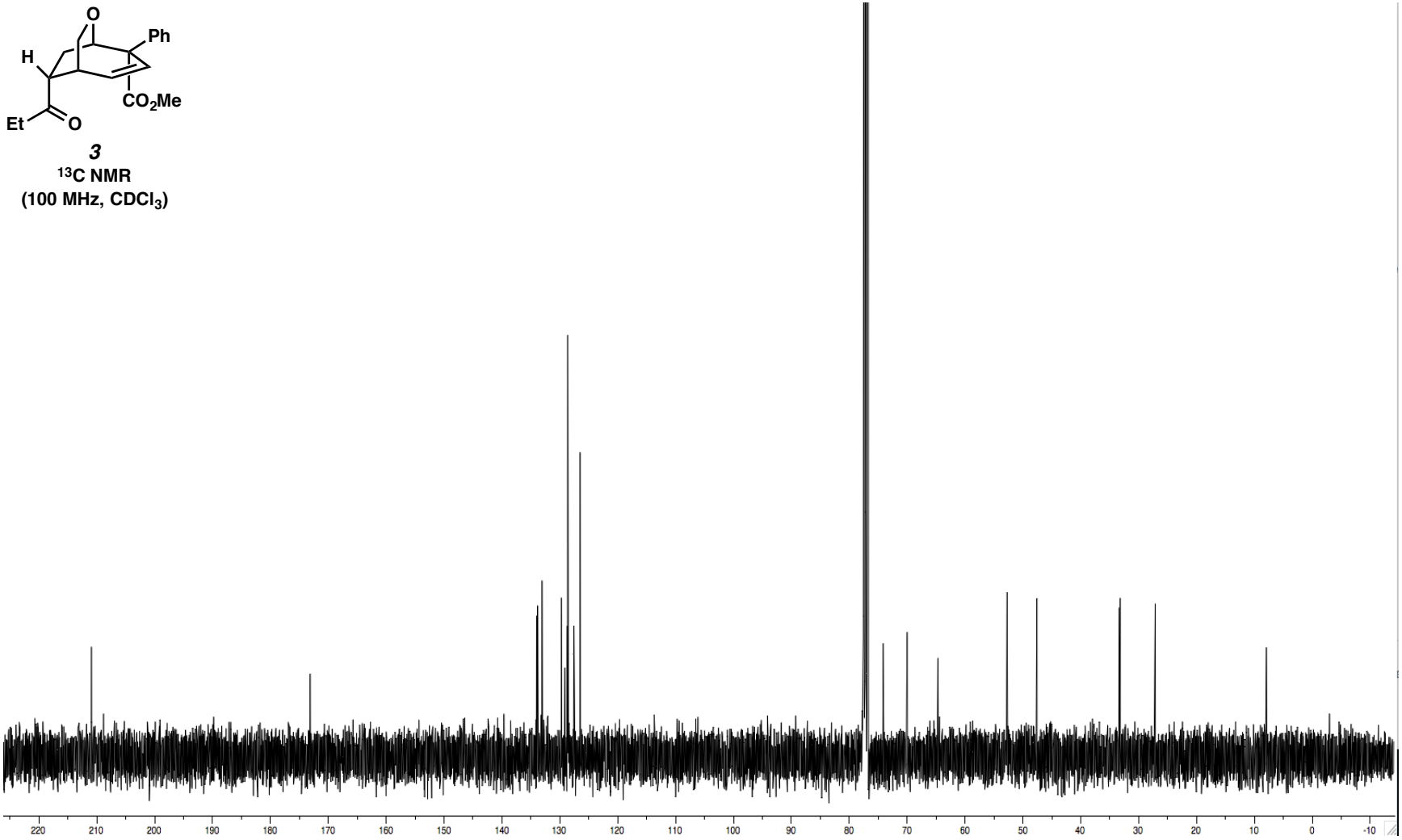
19

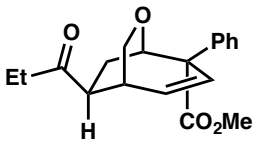
^{13}C NMR

(100 MHz, $CDCl_3$)




O
Ph
H
CO2Me
Et
O
3
1H NMR
(400 MHz, CDCl3)
2.93
1.96
1.99
1
2.96
2.1
1
0.998
1.9
1.03
1.11
3.04
ppm 9
8
7
6
5
4
3
2
1
0

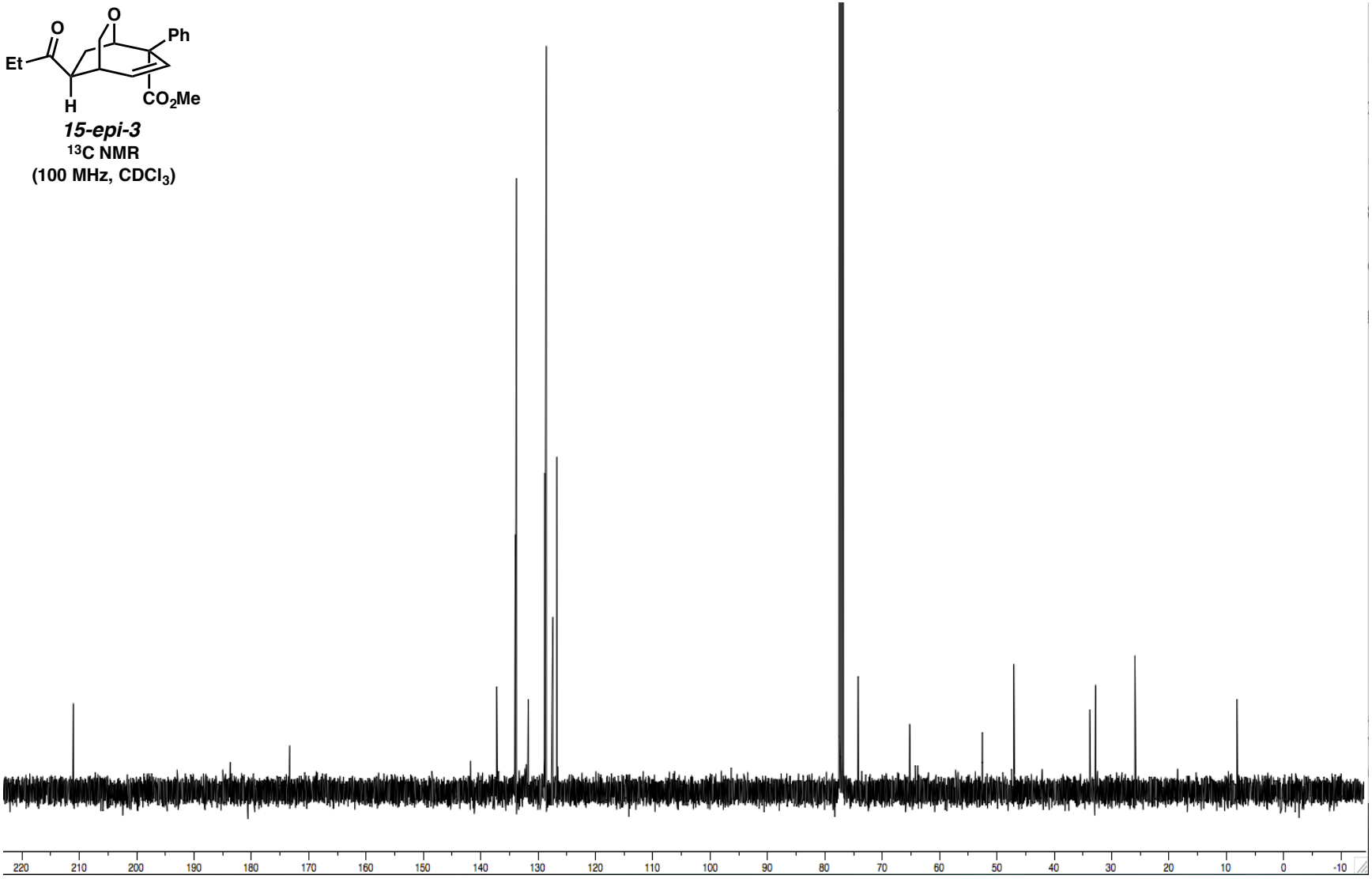

O
Ph
H
CO2Me
Et
O
3
13C NMR
(100 MHz, CDCl3)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

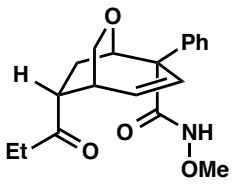


15-epi-3

^{1}H NMR

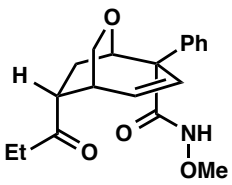
(400 MHz, $CDCl_3$)


O
O
Ph
Et
H
CO2Me
15-epi-3
13C NMR
(100 MHz, CDCl3)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10



20

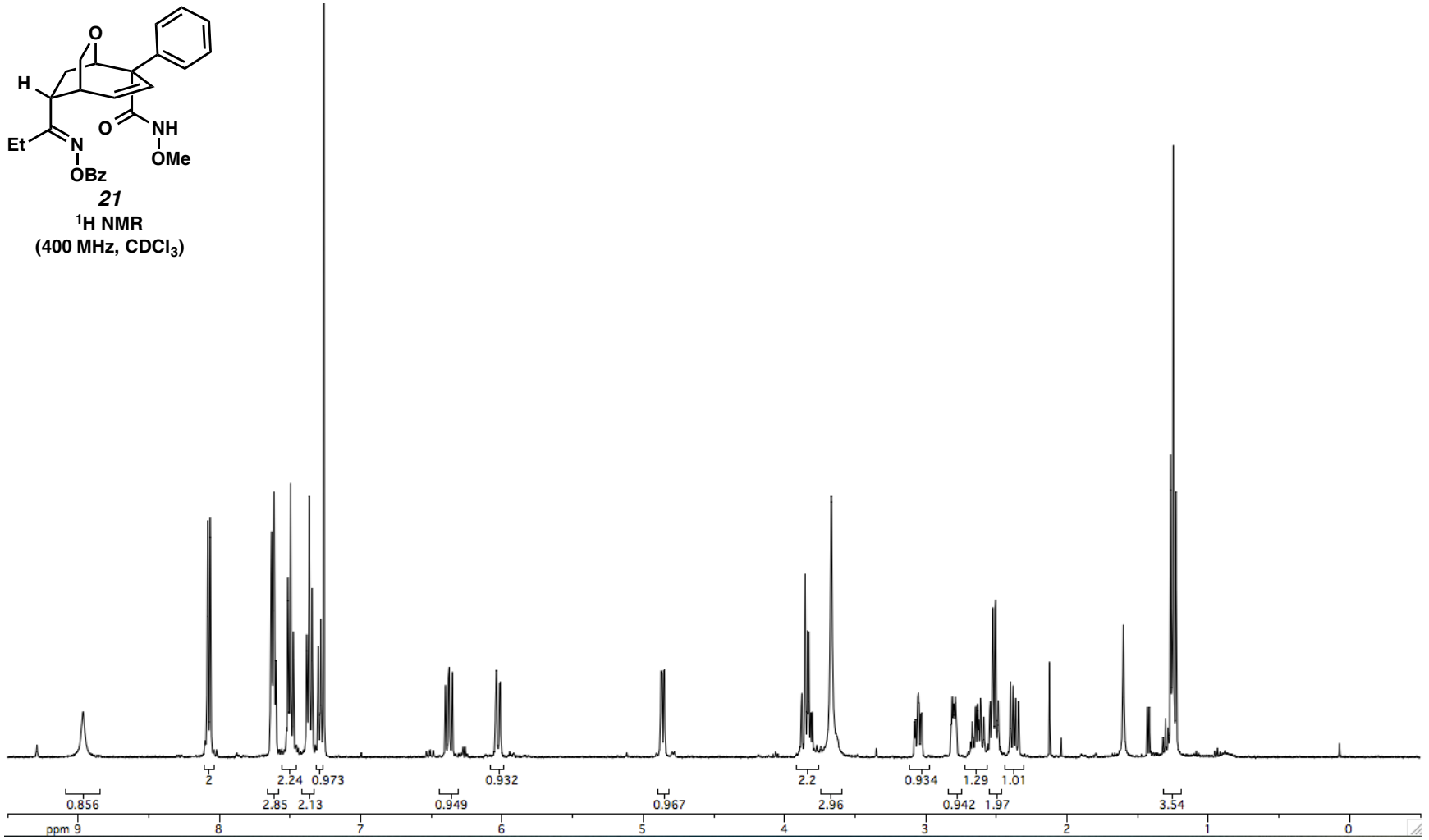
^{1}H NMR
(400 MHz, $CDCl_3$)

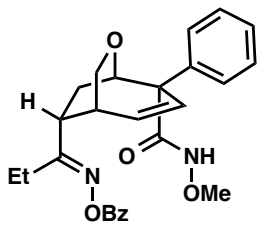


20

^{13}C NMR

(100 MHz, $CDCl_3$)

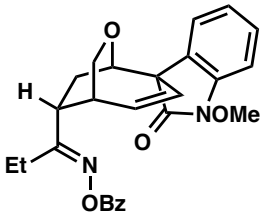

O
H
Et
N
OBz
O
NH
OMe
21
1H NMR
(400 MHz, CDCl3)
2
2.24
0.973
0.932
2.2
0.934
1.29
1.01
0.856
2.85
2.13
0.949
0.967
2.96
0.942
1.97
3.54
ppm 9
8
7
6
5
4
3
2
1
0



21

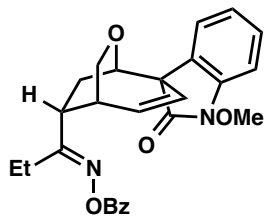
^{13}C NMR

(100 MHz, $CDCl_3$)



22

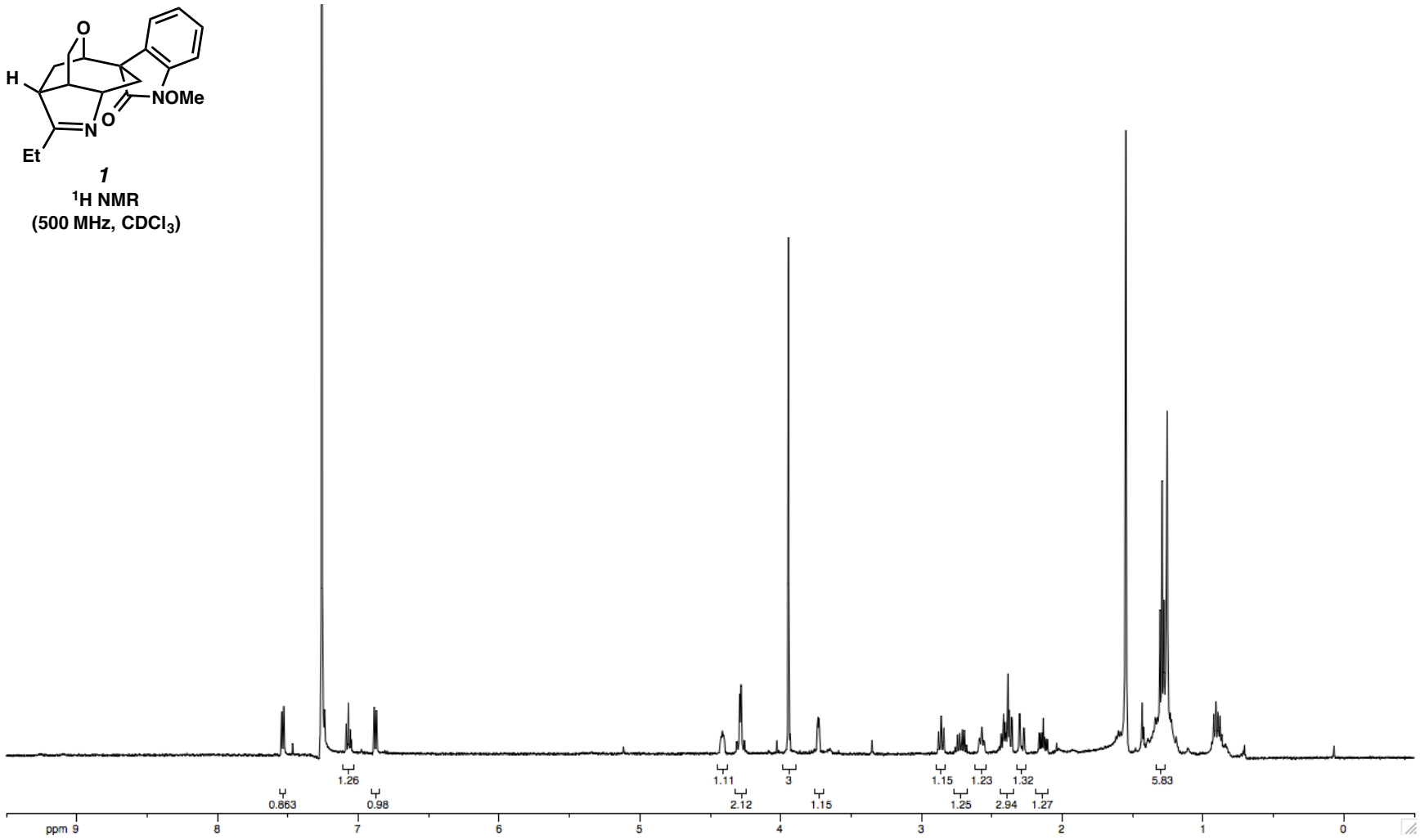
^{1}H NMR
(400 MHz, $CDCl_3$)



22

^{13}C NMR

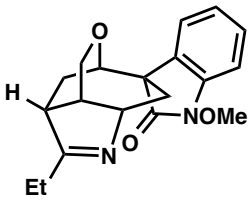
(100 MHz, $CDCl_3$)



1

^{1}H NMR

(500 MHz, $CDCl_3$)



1

^{13}C NMR

(125 MHz, $CDCl_3$)