Supporting Information

Studies Targeting Ryanodol Result in an Annulation Reaction for the Synthesis of a Variety of Fused Carbocycles

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I. Materials and Methods

A. Stereochemical Relationships

All stereochemical relationships depicted are relative, not absolute (all chiral compounds are racemic mixtures).

B. Experimental Setups

All reactions were conducted in flame-dried glassware under an atmosphere of nitrogen and in anhydrous solvents unless otherwise indicated. All reagents and starting materials were purchased from commercial sources and used as received, unless otherwise indicated. Anhydrous dichloromethane (CH_2Cl_2), diethyl ether (Et_2O), tetrahydrofuran (THF), and toluene were obtained by passing commercially available HPLC grade solvents through a column of activated alumina using a Glass Contour Solvent Purification System by Pure Process Technology LLC. THF for the Ti-mediated annulation reaction was freshly distilled in Na/benzophenone still prior to its use. Titanium isopropoxide [Ti(O*i*-Pr)$_4$)] was distilled prior to use and stored in a foil-wrapped round bottom flask under an atmosphere of nitrogen. Said flask was stored in a desiccator when not in use. *n*-BuLi was purchased from Sigma-Aldrich as a 2.5 M solution in hexanes, and was titrated against *N*-benzylbenzamide according to a literature procedure[1] to accurately determine the titer before use. Cyclopentylmagnesium chloride (*c*-C_5H_9MgCl) was purchased from Sigma-Aldrich as 2.0 M solutions in Et_2O, and was titrated against salicylaldehyde phenylhydrazone according to a literature procedure[2] to accurately determine the titer before use. Percent yields correspond to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Flash chromatography was performed on a Biotage ® Automated Liquid Chromatography System Isolera One ® using Biotage ® SNAP KP-Sil 10–25g or Biotage ® SNAP Ultra 25 μm HP-Sphere 10–25g silica gel cartridges or performed using a forced flow of the indicated solvent system on Sorbent Technologies TM silica gel 60Å (40–63 μm particle size). Thin layer chromatography (TLC) analyses were performed on EMD TLC silica gel 60 F_{234} glass plates and the compounds were visualized by exposure to UV light (254 nm) followed by staining with *p*-anisaldehyde, cerium ammonium molybdate, or $KMnO_4$.

C. Instruments for the Characterization of the Synthesized Compounds

^{1}H NMR spectra were recorded on a Bruker Avance III 500 MHz (TBI probe) or a 600 MHz (BBFO probe) spectrometer in chloroform-*d* ($CDCl_3$) or benzene-d_6 (C_6D_6) as

indicated. All signals are reported in parts per million (ppm) and calibrated to the residual protium signal of chloroform ($CHCl_3$, 7.26 ppm) or benzene (C_6H_6, 7.15 ppm). Signals are reported as δ chemical shifts in ppm (multiplicity, coupling constants in Hz, integration). ^{13}C NMR spectra were recorded on a Bruker Avance III 600 MHz (BBFO probe) spectrometer measured at 150 MHz or a Bruker Avance III 500 MHz (TBI probe) spectrometer measured at 125 MHz. All signals are reported in ppm and are calibrated to the central line of the residual solvent signal of $CHCl_3$ (77.16 ppm). Signals are reported as δ chemical shift(s) in ppm with substitution on the carbon atom indicated as; (C), fully substituted; (CH), methine; (CH_2), methylene; or (CH_3), methyl. Two-dimensional NMR spectra, including COSY, HSQC, and NOESY were recorded on a Bruker Avance III 600 MHz spectrometer (BBFO probe), or a Bruker Avance III 500 Mhz spectrometer (TBI probe). Infrared spectra were recorded on a JASCO FT/IR-4100 Fourier Transform Infrared Spectrometer. IR absorption is reported as strong (s), medium (m), weak (w), or broad (br). High-resolution mass spectroscopy (HRMS) analyses were performed at the mass spectrometry laboratory of the University of Illinois at Urbana-Champaign. X-ray data were collected at UCSD Crystallography Facility using Bruker Single-Crystal Diffractometers.

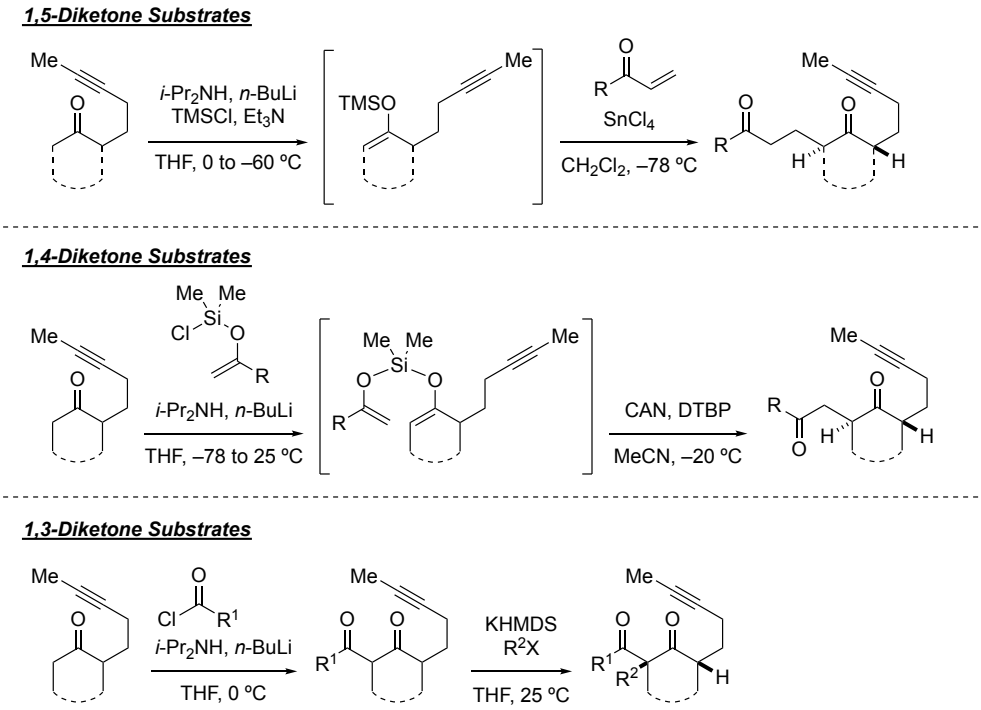
C. Characterization of the Synthesized Compounds

All the newly synthesized compounds were characterized using analyzing both 1D (^1H, ^{13}C, DEPT-135) and selected 2D NMR (HSQC, HMBC, COSY, NOESY) spectra. The result of the analysis for each compound is depicted as a picture with selected homo- or heteroatom correlation to support the stereochemistry. Structure and stereochemistry of several compounds were further confirmed by X-ray crystallography.

II. Experimental and Analytical Data

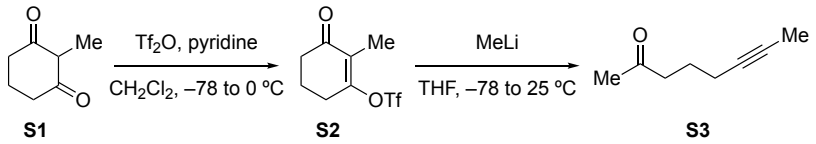
For the synthesis and characterization data of compounds **10** and **11**, see ref. 6.

A. General Scheme for the Synthesis of Substrates



B. Detailed Procedure for the Synthesis of Substrates

(1) Synthesis of Substrate 5



Preparation of S3:

Using a modified procedure,[3] to a stirred solution of 2-methylcyclohexane-1,3-dione (S1, 5.0 g, 35.67 mmol, 1.0 equiv) and pyridine (5.8 mL, 71.34 mmol, 2.0 equiv) in dry CH_2Cl_2 (90 mL) at –78 °C was slowly added Tf_2O (7.2 mL, 42.81 mmol, 1.2 equiv), and the reaction mixture was warmed to 0 °C. After complete consumption of **S1** (TLC

monitoring), 1N aq. HCl was added to the reaction mixture. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (x 2). The combined organic phase was concentrated and filtered through a pad of silica gel with 33% EtOAc in hexanes. The filtrate was concentrated to get 8.7 g **S2** (94% yield) as light brown oil, which was used in the following step without further purification.

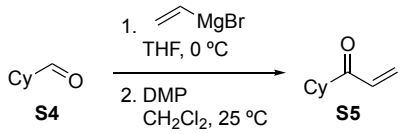
Using a modified procedure,[3] to a stirred solution of **S2** (~8.7 g, 33.69 mmol, 1.1 equiv) in dry THF (120 mL) at –78 °C was added MeLi solution (20 mL, 32.0 mmol, 1.6 M in Et_2O, 1.0 equiv) dropwise. After 15 min, the cooling bath was removed to let the reaction mixture warm to room temperature. The reaction was quenched with sat. aq. NH_4Cl. The layers were separated and the aqueous phase was extracted with Et_2O (x 2). The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure. The crude was purified on a silica gel column to obtain 1.85 g **S3** (46% yield) as colorless oil.

<u>Analytical data for compound S3:</u>

^{1}H NMR (600 MHz, $CDCl_3$): δ 2.55 (t, J = 7.2 Hz, 2H), 2.17–2.14 (m, 5H), 1.77 (t, J = 2.7 Hz, 3H), 1.76–1.71 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 208.54, 78.22, 76.34, 42.41, 30.01, 29.93, 18.11, 3.44.

HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_8H_{13}O$ 125.0966; found, 125.0962.



Preparation of S5:

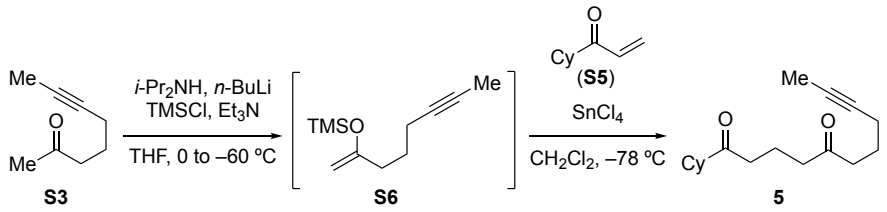
Using a modified procedure,[4] to a stirred solution of cyclohexanecarboxaldehyde (**S4**, 5.0 g, 45.5 mmol, 1.0 equiv) in dry THF (200 mL) at 0 °C was added vinyl magnesium bromide (55 mL, 55 mmol, 1 M in THF, 1.2 equiv) dropwise. After 15 min, complete consumption of **S4** was observed (by TLC) and the reaction was quenched with sat. aq. NH_4Cl solution at 0 °C and warmed to room temperature. The layers were separated and the aqueous phase was extracted with ethyl acetate (x 2). The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure. The crude oil (light yellow) was dissolved in dry CH_2Cl_2 and DMP (21 g, 50.5 mmol, 1.1 equiv) was added at 0 °C. The reaction mixture was stirred for 1 h at ambient temperature, and then filtered through a plug of silica gel. The filtrate was washed successively with water, sat. aq. $NaHCO_3$, and

brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified on a silica gel column, which furnished 4.96 g **S5** (84% yield over 2 steps) as light yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.42 (dd, J = 17.5, 10.6 Hz, 1H), 6.25 (dd, J = 17.5, 1.3 Hz, 1H), 5.74 (dd, J = 10.6, 1.4 Hz, 1H), 2.64–2.59 (m, 1H), 1.84–1.78 (m, 4H), 1.70–1.67 (m, 1H), 1.40–1.22 (m, 5H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 203.52 (C), 134.96 (CH), 127.73 (CH), 48.19 (CH), 28.54 (CH_2), 25.87 (CH_2), 25.69 (CH_2).

HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_9H_{14}O$ 138.1045; found, 138.1043.



Preparation of 5:

Using a modified procedure,[5] to a stirred solution of diisopropylamine (6.2 mL, 44.29 mmol, 5.5 equiv) in dry THF (100 mL) at 0 °C was added *n*-BuLi (16.9 mL, 40.26 mmol, 2.39 M in hexanes, 5.0 equiv). After 15 min, the prepared LDA solution was cooled to –78 °C. To the cold LDA solution was added TMSCl (10.2 mL, 80.53 mmol, 10 equiv) followed by a solution of **S3** (1.0 g, 8.05 mmol, 1.0 equiv) in 25 mL dry THF (additional 5 mL wash), and the mixture was stirred for 30 minutes at the same temperature. Triethylamine (15 mL) was added followed by a sat. aq. $NaHCO_3$ solution and the reaction mixture was allowed to warm up to room temperature. The layers were separated and the aqueous phase was extracted with pentane (x 2). The combined organic phase was dried over anhydrous K_2CO_3, filtered, and the filtrate was concentrated under reduced pressure to afford the silyl enol ether (**S6**) as colorless oil, which was used immediately without further purification. Cyclohexyl vinyl ketone (**S5**, 421 mg, 3.04 mmol, 1.0 equiv) was added to the crude **S6**. The mixture was dissolved in anhydrous benzene and dried under reduced pressure (x 3). The mixture was dissolved in 100 mL anhydrous CH_2Cl_2 and the solution was cooled to –78 °C. $SnCl_4$ (16.1 mL, 16.10 mmol, 1.0 M in CH_2Cl_2, 2.0 equiv) was added slowly and the stirring was continued for 3 h. The reaction was quenched with sat. aq. Na_2CO_3 solution at –78 °C, and the mixture was warmed up to room temperature. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (x 2). The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and the filtrate was concentrated under reduced

pressure. The crude was purified by silica gel column chromatography to afford 442 mg **5** (21% yield over 2 steps) as colorless oil.

Analytical data for compound 5:

TLC: R_f = 0.50 (20% EtOAc in hexanes).

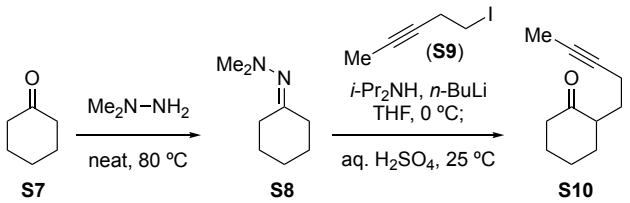
^{1}H NMR (600 MHz, $CDCl_3$): δ 2.48 (t, *J* = 7.3 Hz, 2H), 2.44 (t, *J* = 7.0 Hz, 2H), 2.41 (t, *J* = 7.1 Hz, 2H), 2.31–2.26 (m, 1H), 2.14–2.10 (m, 2H), 1.82–1.77 (m, 4H), 1.76–1.73 (m, 5H), 1.70 (quin, *J* = 7.1 Hz, 2H), 1.65–1.62 (m, 1H), 1.32–1.20 (m, 4H), 1.19–1.12(m, 1H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 213.62 (C), 210.22 (C), 78.18 (C), 76.32 (C), 50.77 (CH), 41.78 (CH_2), 41.36 (CH_2), 39.35 (CH_2), 28.45 (CH_2), 25.82 (CH_2), 25.64 (CH_2), 25.63 (CH_2), 22.86 (CH_2), 18.12 (CH_2), 17.73 (CH_2), 3.43 (CH_3).

IR (neat, cm^{-1}): 3403 (w, br), 2924 (s), 2852 (s), 1705 (s), 1448 (m), 1406 (m), 1372 (m), 1144 (m), 1092 (w), 998 (w).

HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{17}H_{27}O_2$ 263.2011; found, 263.2007.

(2) Synthesis of Substrate 7



Preparation of S10:

Using a modified procedure,[6] *N,N*-dimethylhydrazine (13.5 g, 224.2 mmol, 1.1 equiv) was slowly added to a flask containing cyclohexanone (20.0 g, 203.8 mmol, 1.0 equiv) at room temperature. The mixture was stirred at 80 °C overnight. The reaction mixture was allowed to cool down to room temperature and the formed water was carefully removed using a pipette. The reaction mixture was dried over anhydrous $MgSO_4$, filtered (washed with small amount of ethyl acetate) and concentrated under reduced pressure to get crude hydrazone **S8** (25.2 g, 88% yield) as light yellow oil. The crude was used in the next step without further purification. The analytical data matched with previous report.[3]

Using a modified procedure,[6] to a solution of diisopropylamine (4.8 mL, 34.23 mmol, 1.2 equiv) in dry THF (40 mL) at 0 °C was added *n*-BuLi (15 mL, 32.8 mmol,

2.19 M in hexanes, 1.15 equiv). After stirring for 15 min, a solution of crude hydrazone **S8** (4 g, 28.52 mmol, 1.0 equiv) in 25 mL dry THF (additional 5 mL wash) was added to the prepared LDA. After stirring for 30 min at 0 °C, 5-iodo-2-pentyne (**S9**, 6.64 g, 34.23 mmol, 1.2 equiv) was added dropwise. The reaction mixture was stirred for 1 h before pouring into an Erlenmeyer flask containing 1M aq. H_2SO_4 (100 mL) and diethyl ether (100 mL) and the biphasic mixture was stirred overnight at room temperature. The organic phase was separated, washed successively with water, aq. sat. $NaHCO_3$ solution, and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified on a silica gel column (0 to 10% EtOAc in hexane) to afford **S10** (3.95 g, 84% yield) as colorless oil.

Analytical data for compound S8:

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.46–2.44 (m, 2H), 2.37 (s, 6H), 2.19–2.17 (m, 2H), 1.66–1.62 (m, 2H), 1.61–1.54 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1 (C), 47.5 (CH_3), 35.9 (CH_2), 28.6 (CH_2), 27.4 (CH_2), 26.6 (CH_2), 26.0 (CH_2).

Analytical data for compound S10:

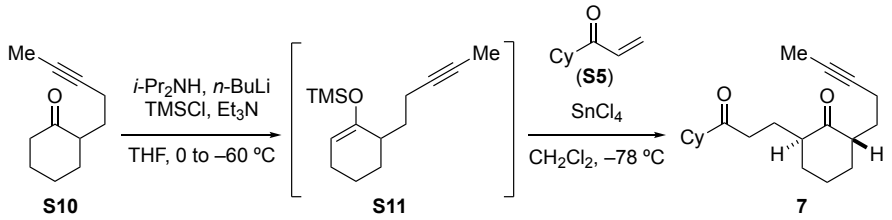
TLC: R_f = 0.37 (10% EtOAc in hexanes).

^{1}H NMR (600 MHz, $CDCl_3$): δ 2.47–2.41 (m, 1H), 2.38–2.28 (m, 2H), 2.18–2.08 (m, 3H), 2.08–2.02 (m, 1H), 1.99–1.93 (m, 1H), 1.86–1.82 (m, 1H), 1.75–1.73 (m, 3H), 1.71–1.60 (m, 2H), 1.36–1.27 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 212.91 (C), 78.66 (C), 75.80 (C), 49.24 (CH_3), 42.18 (CH_2), 33.87 (CH_2), 28.71 (CH_2), 28.07 (CH_2), 25.07 (CH_2), 16.40 (CH_2), 3.47 (CH_3).

IR (neat, cm^{-1}): 2932 (s), 2960 (s), 1709 (s), 1448 (s), 1371 (m), 1338 (m), 1312 (m), 1227 (m), 1129 (s), 1072 (m), 1042 (w), 836 (w).

HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{11}H_{17}O$ 165.1279; found, 165.1278.



Preparation of 7:

Using a modified procedure,[5] to a stirred solution of diisopropylamine (2.4 mL, 16.74 mmol, 5.5 equiv) in dry THF (40 mL) at 0 °C was added *n*-BuLi (6.5 mL, 15.22 mmol, 2.34 M in hexanes, 5.0 equiv). After 15 min, the prepared LDA solution was cooled to –60 °C. To the cold LDA solution was added TMSCl (3.8 mL, 30.22 mmol, 10 equiv) followed by a solution of **S10** (500 mg, 3.04 mmol, 1.0 equiv) in 12 mL dry THF (additional 3 mL wash), and the mixture was stirred for 15 minutes at the same temperature. Triethylamine (6 mL) was added followed by a sat. aq. $NaHCO_3$ solution and the reaction mixture was allowed to warm up to room temperature. The layers were separated and the aqueous phase was extracted with pentane (x 2). The combined organic phase was dried over anhydrous K_2CO_3, filtered, and the filtrate was concentrated under reduced pressure to afford the silyl enol ether (**S11**) as colorless oil, which was used immediately without further purification. Cyclohexyl vinyl ketone (**S5**, 421 mg, 3.04 mmol, 1.0 equiv) was added to the crude **S11**. The mixture was dissolved in anhydrous benzene and dried under reduced pressure (x 3). The mixture was dissolved in 40 mL anhydrous CH_2Cl_2 and the solution was cooled to –78 °C. $SnCl_4$ (6.1 mL, 6.1 mmol, 1.0 M in CH_2Cl_2, 2.0 equiv) was added slowly down the side of the flask and continue stirring for 3 h. The reaction was quenched with sat. aq. Na_2CO_3 solution at –78 °C, and the mixture was warmed up to room temperature. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (x 2). The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure. The crude was purified by silica gel column chromatography to afford 273 mg **7** (30% yield over 2 steps) as colorless oil.

<u>Analytical data for compound 7:</u>

TLC: R_f = 0.25 (10% EtOAc in hexanes).

^{1}H NMR (600 MHz, $CDCl_3$): δ 2.56–2.51 (m, 1H), 2.42–2.31 (m, 3H), 2.27–2.22 (m, 1H), 2.14–2.01 (m, 2H), 1.95–1.82 (m, 4H), 1.77–1.64 (m, 9H), 1.62–1.57 (m, 3H), 1.52–1.46 (m, 1H), 1.42–1.36 (m, 1H), 1.29–1.09 (m, 5H)

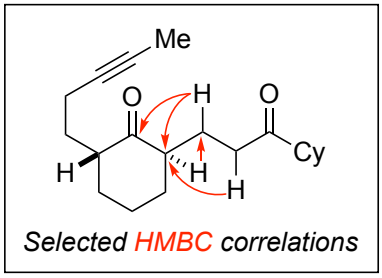
^{13}C NMR (150 MHz, $CDCl_3$): δ 215.65 (C), 213.47 (C), 78.27 (C), 76.04 (C), 50.82 (CH), 48.61 (CH), 47.22 (CH), 38.07 (CH_2), 33.37 (CH_2), 33.08 (CH_2), 29.41 (CH_2),

28.48 (CH_2), 28.41 (CH_2), 25.81 (CH_2), 25.63 (CH_2), 25.60 (CH_2), 24.53 (CH_2), 20.67 (CH_2), 16.58 (CH_2), 3.42 (CH_3).

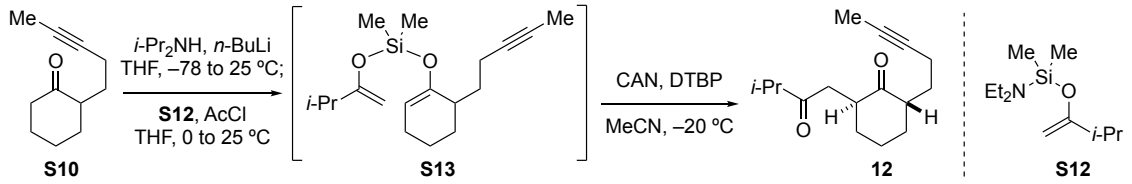
IR (neat, cm^{-1}): 2929 (s), 2855 (s), 1704 (s), 1448 (s), 1410 (w), 1374 (m), 1239 (w), 1146 (m0, 994 (m).

HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{20}H_{31}O_2$ 303.2324; found, 303.2322.

Structure Determination: The structure of **7** was determined by ^1H and ^{13}C NMR. The connectivity of the atoms were determined using HSQC and HMBC data. The relative stereochemistry was not identified at this point. However, the structure was assigned by analogy to the structure of the tricyclic products **8** and **9** (isolated after carrying out the Ti-mediated annulation reaction of **7**) whose structures were confirmed by X-ray analysis.[7]



(3) Synthesis of Substrate 12



Using a modified procedure,[8] to a stirred solution of diisopropylamine (1.6 mL, 11.2 mmol, 1.15 equiv) in dry THF (30 mL) at 0 °C was added *n*-BuLi (7.44 mL, 10.71 mmol, 1.44 M in hexanes, 1.1 equiv). After 15 min, the prepared LDA solution was cooled down to –78 °C and a solution of **S10** (1.6 g, 9.74 mmol, 1.0 equiv) in 16 mL dry THF (additional 2 mL wash x 2) was added dropwise, and continue stirring for 1 h at the same temperature. In a timely manner, **S12**[8] (2.4 g, 11.2 mmol, 1.15 equiv) was dissolved in dry THF (25 mL) at 0 °C in a separate flask and AcCl (0.78 mL, 10.91 mmol, 1.12 equiv) was added dropwise. The ice-bath was removed after 5 min and stirring was continued at ambient temperature for 15 min. This solution was transferred to the precooled (–78 °C) solution of Li-enolate prepared earlier. After 30 min, the cooling bath was removed and stirring was continued for 1.5 h. The reaction was quenched with aq.

sat. NH_4Cl solution, and extracted with pentane (x 2). The combined organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford crude **S13** as colorless oil, which was used in the following step without any purification and characterization.

Using a modified procedure,[9] 2,6-Di-*tert*-butylpyridine (9.62 mL, 42.86 mmol, 4.4 equiv) was slowly added to a flask containing CAN (11.75 g, 21.43 mmol, 2.2 equiv) in anhydrous MeCN (125 mL) at –25 °C. After 5 min, a solution of crude **S13** in 100 mL anhydrous MeCN (additional 20 mL wash) was added to the flask. The mixture was stirred for 30 h at –20 °C. The reaction mixture was poured into a separatory funnel containing sat. aq. $NaHCO_3$ solution and extracted with CH_2Cl_2 (x 3). The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified on a silica gel column to obtain 540 mg of **12** (22% yield over 2 steps) as colorless oil.

Analytical data for compound 12:

TLC: R_f = 0.26 (10% EtOAc in hexanes).

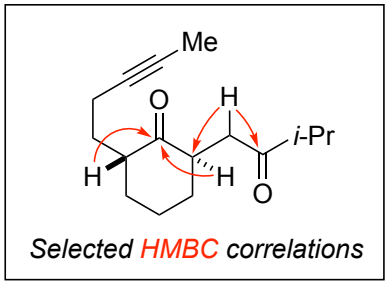
^{1}H NMR (600 MHz, $CDCl_3$): δ 3.14–3.09 (m, 1H), 2.93 (dd, *J* = 17.7, 7.5 Hz, 1H), 2.67–2.61 (m, 1H), 2.55–2.51 (m, 1H), 2.21 (dd, *J* = 17.4, 5.4 Hz, 1H), 2.14–2.08 (m, 2H), 2.03–1.97 (m, 2H), 1.89–1.84 (m, 2H), 1.83–1.79 (m, 1H), 1.78–1.73 (m, 4H), 1.72–1.63 (m, 2H), 1.41–1.35 (m, 1H), 1.12–1.09 (m, 6H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 214.38 (C), 212.95 (C), 78.14 (C), 76.08 (C), 49.48 (CH), 42.71 (CH), 41.12 (CH), 40.13 (CH_2), 33.67 (CH_2), 31.75 (CH_2), 30.68 (CH_2), 20.57 (CH_2), 18.28 (CH_3), 18.17 (CH_3), 16.75 (CH_2), 3.48 (CH_3).

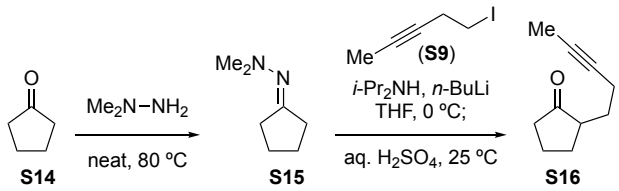
IR (neat, cm^{-1}): 2965 (s), 2933 (s), 2864 (m), 1704 (s), 1672 (w), 1449 (m), 1383 (w), 1355 (w), 1104 (w), 1038 (s).

HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{16}H_{25}O_2$ 249.1855; found, 249.1860.

Structure Determination: The structure of **12** was determined by ^{1}H and ^{13}C NMR. The connectivity of atoms was supported by HSQC, HMBC, and COSY data. The relative stereochemistry was assigned by analogy to the structure of the tricyclic product **14** (isolated after carrying out the Ti-mediated annulation reaction of **12**) whose structures were confirmed by X-ray analysis.[7]



(4) Synthesis of Substrate 15



Preparation of S16:

Using a modified procedure,[6] *N,N*-dimethylhydrazine (15.7 g, 261.5 mmol, 1.1 equiv) was slowly added to a flask containing cyclopentanone (20.0 g, 237.8 mmol, 1.0 equiv) at room temperature. The mixture was stirred at 80 °C overnight. The reaction mixture was allowed to cool down to room temperature and the formed water was carefully removed using a pipette. The reaction mixture was dried over anhydrous $MgSO_4$, filtered (washed with small amount of ethyl acetate) and concentrated under reduced pressure to get crude hydrazone **S15** (26 g, 87% yield) as light yellow oil. The crude was used in the next step without further purification.

Using a modified procedure,[6] to a solution of diisopropylamine (4.0 mL, 28.52 mmol, 1.2 equiv) in dry THF (60 mL) at 0 °C was added *n*-BuLi (12.5 mL, 27.34 mmol, 2.19 M in hexanes, 1.15 equiv). After stirring for 15 min, a solution of crude hydrazone **S15** (3.0 g, 23.77 mmol, 1.0 equiv) in 20 mL dry THF (additional 5 mL wash) was added to the prepared LDA. After stirring for 30 min at 0 °C, 5-iodo-2-pentyne (5.6 g, 28.52 mmol, 1.25 equiv) was added dropwise. The reaction mixture was stirred for 1 h before pouring into an Erlenmeyer flask containing 1 M aq. H_2SO_4 (80 mL) and diethyl ether (80 mL) and the biphasic mixture was stirred overnight at room temperature. The organic phase was separated, washed successively with water, aq. sat. $NaHCO_3$ solution, and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified on a silica gel column (0 to 10% EtOAc in hexane) to afford **S16** (2.85 g, 80% yield) as colorless oil.

Analytical data for compound S15:

TLC: R_f = 0.17 (33% EtOAc in hexanes).

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.46 (s, 6H), 2.37 (t, *J* = 7.2 Hz, 2H), 2.33 (t, *J* = 7.2, 2H), 1.78–1.70 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 175.89 (C), 47.05 (CH_3), 33.54 (CH_2), 29.34 (CH_2), 24.92 (CH_2), 24.18 (CH_2).

IR (neat, cm^{-1}): 2956 (s), 2855 (s), 2816 (s), 2771 (m), 1741 (m), 1658 (s), 1467 (s), 1451 (s), 1428 (s), 1181 (m), 1153 (m), 1021 (m), 972 (s).

HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_7H_{15}N_2$ 127.1235; found, 127.1239.

Analytical data for compound S16:

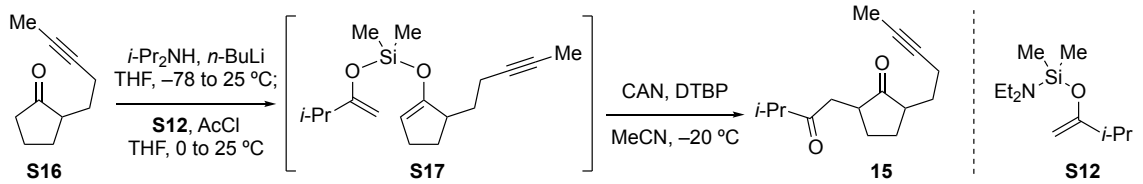
TLC: R_f = 0.34 (10% EtOAc in hexanes).

^{1}H NMR (600 MHz, $CDCl_3$): δ 2.32–2.07 (m, 6H), 2.03–1.91 (m, 2H), 1.82–1.74 (m, 4H), 1.52–1.46 (m, 1H), 1.43–1.37 (m, 1H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 221.01 (C), 78.23 (C), 76.21 (C), 48.14 (CH), 38.09 (CH_2), 29.42 (CH_2), 29.06 (CH_2), 20.70 (CH_2), 16.97 (CH_2), 3.45 (CH_3).

IR (neat, cm^{-1}): 2957 (s), 2919 (s), 2863 (s), 1737 (s), 1449 (m), 1408 (m), 1352 (m), 1327 (w), 1271 (w), 1159 (s), 1120 (w), 1006 (w), 929 (w), 820 (m).

HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{10}H_{15}O$ 151.1123; found, 151.1124.



Preparation of 15:

Following a modified procedure,[8] to a stirred solution of diisopropylamine (0.44 mL, 3.06 mmol, 1.15 equiv) in dry THF (4 mL) at 0 °C was added *n*-BuLi (1.28 mL, 2.93 mmol, 2.29 M in hexanes, 1.1 equiv). After 15 min, the prepared LDA solution was cooled down to –78 °C and a solution of **S16** (400 mg, 2.66 mmol, 1.0 equiv) in 6 mL dry THF (additional 2 mL wash x 2) was added dropwise, and continue stirring for 1 h. In a timely manner, **S12**[8] (688 mg, 3.2 mmol, 1.2 equiv) was dissolved in dry THF (12 mL) at

0 °C in a separate flask and AcCl (218 μL, 3.06 mmol, 1.15 equiv) was added dropwise. The ice-bath was removed after 5 min and stirring was continued at ambient temperature for 15 min. This solution was transferred to the precooled (–78 °C) solution of Li-enolate prepared earlier. After 30 min, the cooling bath was removed and stirring was continued for 1.5 h. The reaction was quenched with aq. sat. NH_4Cl solution, and extracted with pentane (x 2). The combined organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford crude **S17** as colorless oil, which was used in the following step without any purification and characterization.

Following a modified procedure,[9] 2,6-Di-*tert*-butylpyridine (2.64 mL, 11.72 mmol, 4.4 equiv) was slowly added to a flask containing CAN (3.22 g, 5.87 mmol, 2.2 equiv) in anhydrous MeCN (50 mL) at –25 °C. After 5 min, a solution of crude **S17** in 40 mL anhydrous MeCN (additional 10 mL wash) was added to the flask. The mixture was stirred for 30 h at –20 °C. The reaction mixture was poured into a separatory funnel containing sat. aq. $NaHCO_3$ solution and extracted with CH_2Cl_2 (x 3). The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified on a silica gel column, which furnished 275 mg of **15** (colorless oil, 44% yield over 2 steps) as an inseparable mixture of diastereomers.

Analytical data for compound 15:

TLC: R_f = 0.47 (20% EtOAc in hexanes).

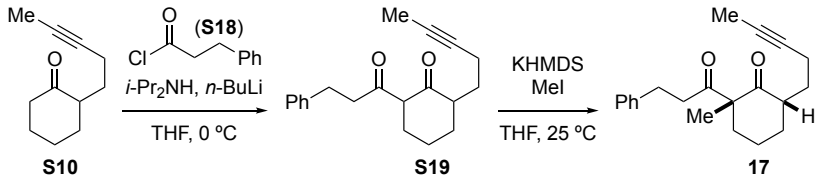
^{1}H NMR (600 MHz, $CDCl_3$): δ 2.92 (dd, *J* = 18.1, 3.7 Hz, 1H, first diastereomer), 2.86 (dd, *J* = 17.9, 3.7 Hz, 1H, second diastereomer), 2.65–2.51 (m, mixed), 2.45–2.39 (m, mixed), 2.36–2.31 (m, 1H, first diastereomer), 2.30–2.22 (m, mixed), 2.21–2.14 (m, mixed), 2.12–2.06 (m, 1H, second diastereomer), 2.01–1.96 (m, 1H, first diastereomer), 1.91–1.86 (m, 1H, second diastereomer), 1.76–1.74 (m, 3H, mixed), 1.72–1.66 (m, 1H, second diastereomer), 1.54–1.41 (m, mixed), 1.09–1.07 (m, 6H, mixed).

^{13}C NMR (150 MHz, $CDCl_3$): All discernible peaks for both diastereomers. δ 221.26 (C), 221.11 (C), 212.62 (C), 212.44 (C), 78.24 (C), 78.23 (C), 76.23 (C), 76.23 (C), 47.81 (CH), 46.39 (CH), 45.10 (CH), 43.87 (CH), 40.84 (CH), 40.82 (CH_2), 40.69 (CH_2), 40.29 (CH_2), 29.75 (CH_2), 29.64 (CH_2), 27.66 (CH_2), 27.56 (CH_2), 26.88 (CH_2), 26.33 (CH_2), 18.22 (CH_3), 18.19 (CH_3), 18.18 (CH_3), 18.17 (CH_3), 17.04 (CH_2), 16.88 (CH_2), 3.48 (CH_3).

IR (neat, cm^{-1}): 2969 (s), 2924 (s), 2874 (m), 1738 (s), 1711 (s), 1467 (m), 1452 (m), 1387 (w), 1035 (w).

HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{15}H_{23}O_2$ 235.1698; found, 235.1702.

(5) Synthesis of Substrate 17



Using a modified procedure,[6] to a stirring solution of diisopropylamine (3.3 mL, 23.44 mmol, 1.1 equiv) in dry THF (24 mL) at –78 °C, was added *n*-BuLi (10.7 mL, 23.44 mmol, 2.19 M in hexanes, 1.1 equiv). After, stirring for 45 min, a solution of **S10** (3.5 g, 21.31 mmol, 1.0 equiv) in dry THF (22 mL, additional 2 mL wash) was added dropwise. After 1 h, the generated enolate was transferred to a precooled solution of acid chloride **S18** (3.8 mL, 25.57 mmol, 1.2 equiv) in 24 mL dry THF, and the stirring was continued for 2 h. The reaction was quenched with an aqueous saturated $NaHCO_3$ solution at –78 °C and the solution was allowed to warm up to room temperature. The layers were separated. The aqueous phase was extracted with ethyl acetate (x 2). The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was purified on a silica gel column to afford 3.98 g **S19** (light yellow oil, 63% yield) as a mixture of diastereomers and enol isomer, along with 560 mg of starting ketone **S10** (colorless oil, 16%).

Using a modified procedure,[6] KHMDS (28.1 mL, 14.1 mmol, 0.5 M in PhMe, 1.05 equiv) was added dropwise to a solution of **S19** (3.97 g, 13.4 mmol, 1.0 equiv) in dry THF (60 mL) at room temperature. After 30 min, iodomethane (1.1 mL, 17.4 mmol, 1.3 equiv) was added dropwise and stirring was continued for 5 h. The reaction was quenched by addition of 20 mL aqueous saturated $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc (x 2). The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified on a silica gel column (0 to 10% EtOAc in hexanes) to obtain **17** (1.52 g, 37%) as colorless oil.

Analytical data for compound 17:

TLC: R_f = 0.37 (10% EtOAc in hexanes).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30–7.28 (m, 2H), 7.22–7.18 (m, 3H), 2.95 (t, *J* = 8.1 Hz, 2H), 2.80–2.71 (m, 3H), 2.26–2.10 (m, 4H), 1.95 (sext, *J* = 6.9 Hz, 1H), 1.89–1.80 (m, 2H), 1.78 (t, *J* = 2.7 Hz, 3H), 1.69–1.65 (m, 1H), 1.43–1.36 (m, 1H), 1.41 (s, 3H), 1.33 (sext, *J* = 6.6 Hz, 1H).

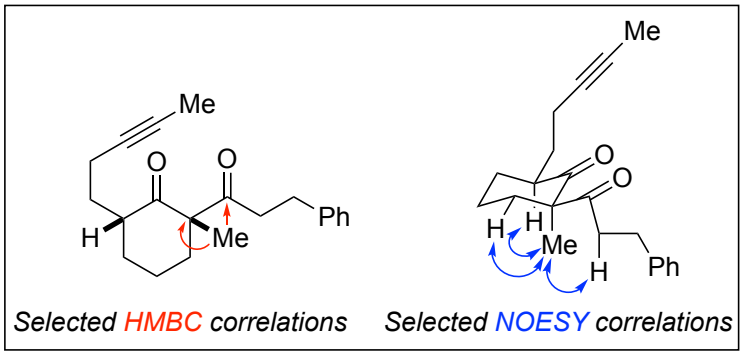
^{13}C NMR (150 MHz, $CDCl_3$): δ 213.68 (C), 209.54 (C), 141.51 (C), 128.45 (CH), 128.42 (CH), 126.00 (CH), 78.25 (C), 76.21 (C), 62.23 (C), 45.50 (CH), 41.71 (CH_2), 34.99

(CH_2), 33.04 (CH_2), 30.36 (CH_2), 28.42 (CH_2), 20.58 (CH_2), 19.85 (CH_3), 16.35 (CH_2), 3.48 (CH_3).

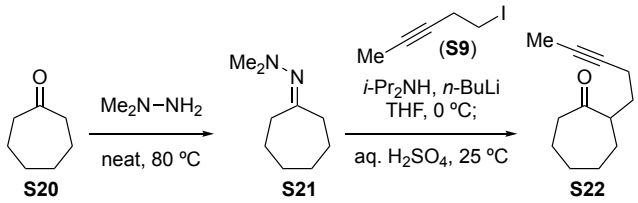
IR (neat, cm^{-1}): 3088 (w), 3061 (m), 3030 (m), 2936 (s), 2864 (s), 1713 (s), 1696 (s), 1603 (w), 1495 (m), 1453 (s), 1370 (m), 1266 (s), 1155 (w), 1077 (m), 989 (m), 739 (s), 698 (s).

HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{21}H_{27}O_2$ 311.2011; found, 311.2014.

Structure Determination: The structure of **17** was determined by ^1H and ^{13}C NMR. The relative stereochemistry was assigned based on HSQC, HMBC, COSY, and NOESY analysis.[7]



(6) Synthesis of Substrate 20



Preparation of S19:

Using a modified procedure,[6] *N,N*-dimethylhydrazine (11.79 g, 196.1 mmol, 1.1 equiv) was slowly added to a flask containing cycloheptanone (20.0 g, 178.3 mmol, 1.0 equiv) at room temperature. The mixture was stirred at 80 °C. After overnight stirring, the formed water was carefully removed using a pipette. The reaction mixture was dried over anhydrous $MgSO_4$, filtered (washed with small amount of ethyl acetate) and concentrated under reduced pressure to get crude hydrazone **S21** (26.64 g, 97% yield) as light yellow oil. The crude was used in the next step without further purification.

Using a modified procedure,[6] to a solution of diisopropylamine (2.7 mL, 19.45 mmol, 1.2 equiv) in dry THF (24 mL) at 0 °C was added *n*-BuLi (9.4 mL, 18.64 mmol, 1.98 M in hexanes, 1.15 equiv). After stirring for 15 minutes, a solution of crude hydrazone **S21** (2.5 g, 16.21 mmol, 1.0 equiv) in 10 mL dry THF (additional 1 mL wash) was added to the prepared LDA. After stirring for 30 minutes at 0 °C, 5-iodo-2-pentyne (3.8 g, 19.45 mmol, 1.2 equiv) was added dropwise. The reaction mixture was stirred for 1 h before pouring into an Erlenmeyer flask containing 1M aq. H_2SO_4 (70 mL) and diethyl ether (70 mL) and the biphasic mixture was stirred overnight at room temperature. The organic layer was separated, washed successively with water, aq. sat. $NaHCO_3$ solution, and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified on a silica gel column (0 to 10% EtOAc in hexane) to afford **S22** (2.18 g, 75% yield) as colorless oil.

Analytical Data for Compound S21:

TLC: R_f = 0.27 (33% EtOAc in hexanes).

^{1}H NMR (600 MHz, $CDCl_3$): δ 2.62–2.59 (m, 2H), 2.40–2.38 (m, 8H), 1.63–1.60 (m, 4H), 1.58–1.51 (m, 4H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 174.35 (C), 47.26 (CH_3), 37.23 (CH_2), 31.07 (CH_2), 30.62 (CH_2), 30.13 (CH_2), 27.41 (CH_2), 25.24 (CH_2).

IR (Thin Film CH_2Cl_2, cm^{-1}): 2978 (m), 2922 (s), 2850 (s), 2811 (m), 2770 (m), 1741 (m), 1616 (m), 1449 (m).

HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_9H_{19}N_2$ 155.1548; found, 155.1544.

Analytical Data for Compound S22:

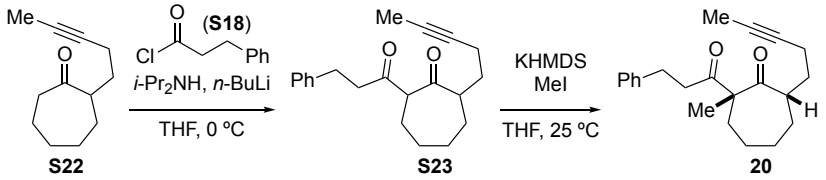
TLC: R_f = 0.46 (10% EtOAc in hexanes).

^{1}H NMR (600 MHz, $CDCl_3$): δ 2.70–2.65 (m, 1H), 2.47–2.45 (m, 2H), 2.13–2.09 (m, 2H), 1.91–1.78 (m, 5H), 1.76–1.74 (m, 3H), 1.67–1.59 (m, 1H), 1.48–1.38 (m, 2H), 1.33–1.26 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 215.94 (C), 78.70 (C), 76.29 (C), 50.87 (CH), 43.23 (CH_2), 31.41 (CH_2), 31.38 (CH_2), 29.54 (CH_2), 28.85 (CH_2), 24.50 (CH_2), 16.77 (CH_2), 3.69 (CH_3).

IR (Thin Film CH_2Cl_2, cm^{-1}): 2926 (s), 2953 (s), 1699 (s), 1453 (m).

HRMS (EI) (m/z): $[M]^+$ calcd for $C_{12}H_{18}O$ 178.1358; found, 178.1355.



Preparation of 20:

Using a modified procedure,[6] to a stirring solution of diisopropylamine (0.49 mL, 3.5 mmol, 1.25 equiv) in dry THF (4 mL) at –78 °C, was added *n*-BuLi (1.5 mL, 3.37 mmol, 2.25 M in hexanes, 1.2 equiv). After, stirring for 45 min, a solution of **S22** (500 mg, 2.80 mmol, 1.0 equiv) in dry THF (8 mL, additional 2 mL wash) was added dropwise. After 1 h, the generated enolate was transferred to a precooled solution of acid chloride **S18** (0.5 mL, 3.36 mmol, 1.2 equiv) in 10 mL dry THF, and the stirring was continued for 2 h. The reaction was quenched with an aqueous saturated $NaHCO_3$ solution at –78 °C and the solution was allowed to warm up to room temperature. The layers were separated. The aqueous phase was extracted with ethyl acetate (x 2). The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The dried crude **S23** (light yellow oil) was dissolved in dry THF (24 mL), and KMHDS (5.6 mL, 2.8 mmol, 0.5 M in PhMe, 1.0 equiv) was added dropwise at room temperature. After 30 min, iodomethane (0.23 mL, 3.69 mmol, 1.3 equiv) was added dropwise and stirring was continued for 5 h. The reaction was quenched by addition of 10 mL aqueous saturated $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc (x2). The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified on a silica gel column (0 to 10% EtOAc in hexanes) to obtain 525 mg of **20** (58% yield) as colorless oil.

<u>Analytical data for compound 20:</u>

TLC: R_f = 0.42 (10% EtOAc in hexanes).

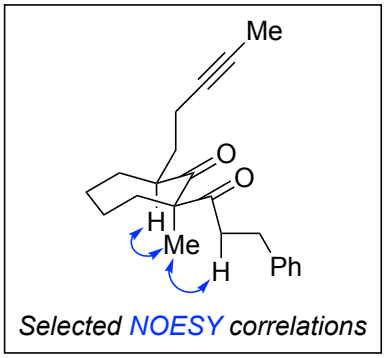
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28–7.26 (m, 2H), 7.21–7.16 (m, 3H), 3.04–3.00 (m, 1H), 2.94–2.76 (m, 4H), 2.18 (dd, *J* = 14.8, 7.8 Hz, 1H), 2.02–1.95 (m, 2H), 1.87–1.80 (m, 2H), 1.76 (t, *J* = 2.5 Hz, 3H), 1.71–1.68 (m, 1H), 1.46–1.38 (m, 3H), 1.36 (s, 3H), 1.34–1.24 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 215.39 (C), 210.35 (C), 141.59 (C), 128.46 (CH), 128.41 (CH), 125.96 (CH), 78.46 (C), 76.33 (C), 64.11 (C), 47.87 (CH), 42.79 (CH_2), 34.36 (CH_2), 33.57 (CH_2), 31.34 (CH_2), 30.23 (CH_2), 29.98 (CH_2), 25.70 (CH_2), 22.78 (CH_3), 16.78 (CH_2), 3.46 (CH_3).

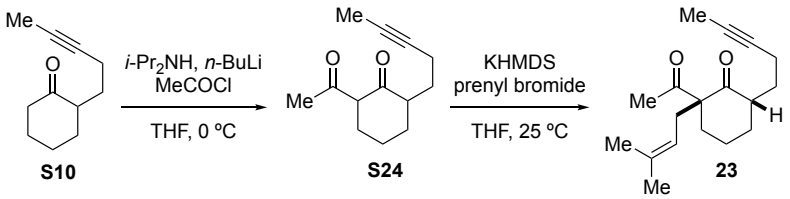
IR (neat, cm^{-1}): 3085 (w), 3061 (w), 3027 (m), 2929 (s), 2855 (s), 1737 (s), 1697 (s), 1604 (w), 1496 (m), 1454 (s), 1374 (s), 1242 (m), 1189 (w), 1047 (m), 940 (m), 750 (m), 700 (s).

HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{22}H_{29}O_2$ 325.2168; found, 325.2165.

Structure Determination: The structure of **20** was determined by ^1H and ^{13}C NMR. The relative stereochemistry was assigned based on NOESY analysis.[7]



(6) Synthesis of additional Substrate 23



Using a modified procedure,[6] to a stirring solution of diisopropylamine (535 μL, 3.8 mmol, 1.25 equiv) in dry THF (6 mL) at –78 °C, was added *n*-BuLi (1.7 mL, 3.65 mmol, 2.18 M in hexanes, 1.2 equiv). After, stirring for 45 min, a solution of **S10** (500 mg, 3.04 mmol, 1.0 equiv) in dry THF (8 mL, additional 2 mL wash) was added dropwise. After 1 h, the generated enolate was transferred to a precooled solution of acetyl chloride (282 μL, 3.96 mmol, 1.3 equiv) in 4 mL dry THF, and the stirring was continued for 2 h. The reaction was quenched with an aqueous saturated $NaHCO_3$ solution at –78 °C and the solution was allowed to warm up to room temperature. The layers were separated and the aqueous phase was extracted with ethyl acetate (x 2). The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to obtain crude **S24** as light yellow oil, which was used in the next step without further purification.

Using a modified procedure,[6] KHMDS (6.4 mL, 3.2 mmol, 0.5 M in PhMe, 1.05 equiv) was added dropwise to a solution of crude **S24** in dry THF (9 mL) at room

temperature. After 30 min, prenyl bromide (0.46 mL, 3.96 mmol, 1.3 equiv) was added dropwise and stirring was continued for 5 h. The reaction was quenched by addition of 6 mL aqueous saturated $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc (x2). The combined organic phase was washed with brine, dried over anhydrous MgSO4, filtered, and concentrated under reduced pressure. The crude material was purified on a silica gel column (0 to 10% EtOAc in hexanes) to obtain **23** (140 mg, 17% over 2 steps) as colorless oil.

Analytical data for compound 23:

TLC: R_f = 0.31 (10% EtOAc in hexanes).

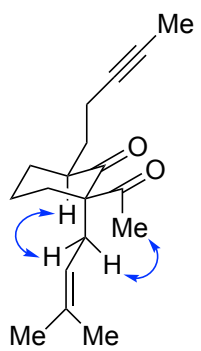
^{1}H NMR (600 MHz, C_6D_6): δ 5.00–4.98 (m, 1H), 2.58–2.44 (m, 3H), 2.20–2.08 (m, 2H), 2.04 (s, 3H), 2.02–1.94 (m, 2H), 1.59–1.55 (m, 2H), 1.55 (t, 3H, J = 2.5 Hz), 1.52 (s, 3H), 1.48 (s, 3H), 2.42–1.37 (m, 2H), 1.28–1.22 (m, 1H), 1.01–0.94 (m, 1H).

^{13}C NMR (150 MHz, C_6D_6): δ 211.49 (C), 205.68 (C), 134.33 (C), 118.65 (CH), 78.60 (C), 75.76 (C), 65.99 (C), 46.40 (CH), 32.25 (CH_2), 31.89 (CH_2), 31.26 (CH_2), 28.99 (CH_2), 27.22 (CH_3), 25.50 (CH_3), 20.22 (CH_2), 17.60 (CH_3), 16.47 (CH_2), 3.04 (CH_3).

IR (neat, cm^{-1}): 2922 (s), 2860 (m), 1712 (s), 1698 (s), 1446 (m), 1372 (w), 1353 (m), 1167 (w), 1121 (w).

HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{18}H_{27}O_2$ 275.2011; found, 275.2016.

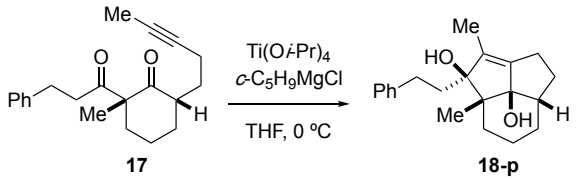
Structure Determination: The structure of **23** was determined by ^{1}H and ^{13}C NMR. The relative stereochemistry was assigned based on HSQC, COSY, and NOESY analysis.[7]



Selected NOESY correlations

C. Synthesis of Polycyclic Carbocycles by Ti-mediated Annulation Reaction

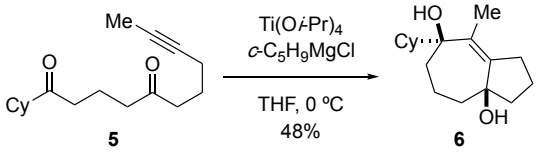
- **Representative Procedure for Alkyne–Diketone Coupling Reaction**



To a stirred solution of **17** (380 mg, 1.22 mmol, 1.0 equiv) and Ti(O*i*-Pr)$_4$ (760 μL, 2.57 mmol, 2.1 equiv) in 13 mL dry THF at 0 °C was added cyclopentylmagnesium chloride solution (2.9 mL, 5.14 mmol, 1.80 M in Et_2O, 4.2 equiv) dropwise. After complete consumption of starting material (~10 minutes), the reaction is quenched with a half-saturated aq. $NaHCO_3$ solution (15 mL) and stirred for 1 h at room temperature. The biphasic mixture was filtered through a plug of celite and the celite-cake was washed with ethyl acetate (10 mL x 2). The layers were separated and the aqueous phase was extracted with ethyl acetate (5 mL x 2). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was purified on Biotage 25G KP-Sil column to obtain 214 mg **18-p** (56% yield) as white solid.

- **Alkyne–1,5-diketone Annulation Reactions**

(1) Construction of Hydrazulene Ring System – Synthesis of 6



To a stirred solution of **5** (29.0 mg, 0.11 mmol, 1.0 equiv) in 4 mL dry THF was added Ti(O*i*-Pr)$_4$ (69 μL, 0.232 mmol, 2.1 equiv) at 0 °C. Cyclopentylmagnesium chloride (228 μL, 0.464 mmol, 1.80 M in Et_2O, 4.2 equiv) was added dropwise. After 30 min, reaction is quenched with a half-saturated aq. $NaHCO_3$ solution and stirred for an additional 30 min. The biphasic mixture was filtered through a plug of celite. The layers were separated and the aqueous phase was extracted with 2 mL ethyl acetate (x 2). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was purified on a silica gel column (Biotage SNAP Ultra 10G column) to afford 14.1 mg **6** (48% yield) as colorless oil.

Analytical data for compound 6:

TLC: R_f = 0.29 (33% EtOAc in hexanes).

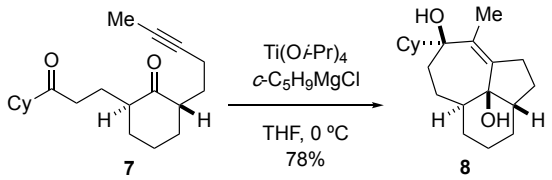
^{1}H NMR (600 MHz, C_6D_6): δ 2.75 (brs, 2H), 2.41–2.36 (m, 1H), 2.20–2.13 (m, 1H), 2.11–2.06 (m, 1H), 2.00–1.95 (m, 2H), 1.93–1.90 (m, 1H), 1.86–1.72 (m, 4H), 1.71 (s, 3H), 1.71–1.64 (m, 2H), 1.55–1.44 (m, 6H), 1.30–1.10 (m, 4H), 1.04 (ddd, J = 24.6, 12.6, 3.0 Hz, 1H).

^{13}C NMR (150 MHz, C_6D_6): δ 144.82 (C), 137.23 (C), 79.86 (C), 77.42 (C), 46.53 (CH), 45.21 (CH_2), 37.96 (CH_2), 35.14 (CH_2), 33.96 (CH_2), 29.13 (CH_2), 27.21 (CH_2), 26.95 (CH_2), 21.72 (CH_2), 19.78 (CH_2), 17.84 (CH_3).

IR (neat, cm^{-1}): 3398 (s, br), 3049 (w), 2931 (s), 2849 (s), 1641 (m), 1447 (s), 1260 (w), 1156 (w), 1031 (w), 934 (m), 891 (w), 845 (w), 830 (w), 740 (m).

HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{17}H_{28}O_2Na$ 287.1982; found, 287.1982.

(2) Construction of 6-5-7 Fused Tricycles – Synthesis of 8 and 9



Preparation of 8:

To a stirred solution of **7** (31.0 mg, 0.102 mmol, 1.0 equiv) in 4 mL dry THF was added Ti(O*i*-Pr)$_4$ (64 μL, 0.215 mmol, 2.1 equiv) at 0 °C. Cyclopentylmagnesium chloride (240 μL, 0.430 mmol, 1.80 M in Et_2O, 4.2 equiv) was added dropwise. After complete consumption of starting material (~10 minutes), reaction is quenched with a half-saturated aq. $NaHCO_3$ solution and stirred for an additional 1 h. The biphasic mixture was filtered through a plug of celite. The layers were separated and the aqueous phase was extracted with 2 mL ethyl acetate (x 2). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The spectroscopically pure crude (quantitative crude yield) was purified on a basic alumina column to afford 24.5 mg **8** (78% yield) as white solid.

Analytical data for compound 8:

TLC: R_f = 0.55 (33% EtOAc in hexanes).

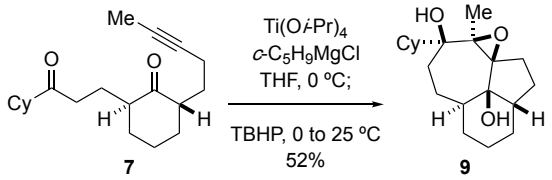
^{1}H NMR (600 MHz, C_6D_6): δ 2.45–2.34 (m, 2H), 2.27–2.25 (m, 1H), 2.20–2.12 (m, 2H), 1.95–1.90 (m, 2H), 1.87–1.77 (m, 5H), 1.73–1.71 (m, 2H), 1.59–1.57 (m, 2H), 1.49–1.38 (m, 7H), 1.35–1.24 (m, 3H), 1.22–1.13 (m, 3H), 1.03–0.95 (m, 1H).

^{13}C NMR ^{13}C NMR (150 MHz, C_6D_6): δ 148.48 (C), 136.59 (C), 79.31 (C), 76.10 (C), 48.33 (CH), 47.17 (CH), 39.93 (CH_2), 34.40 (CH_2), 32.65 (CH_2), 30.54 (CH_2), 29.72 (CH_2), 28.94 (CH_2), 27.35 (CH_2), 27.21 (CH_2), 26.88 (CH_2), 26.86 (CH_2), 26.69 (CH_2), 24.60 (CH_2), 21.49 (CH_2), 17.52 (CH_3).

IR (neat, cm^{-1}): 3411 (br), 3213 (br), 2924 (s), 2853 (s), 1445 (s), 1264 (m), 1031 (w), 923 (w), 738 (m).

HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{20}H_{32}O_2Na$ 327.2300; found, 327.2301.

Structure Determination: The structure of **8** was determined by ^{1}H and ^{13}C NMR. The structure and the relative stereochemistry were confirmed by single-crystal X-ray analysis.[7]



Preparation of 9:

To a stirred solution of **7** (20.0 mg, 0.066 mmol, 1.0 equiv) in 3 mL dry THF was added Ti(O*i*-Pr)$_4$ (41 μL, 0.139 mmol, 2.1 equiv) at 0 °C. Cyclopentylmagnesium chloride (154 μL, 0.278 mmol, 1.80 M in Et_2O, 4.2 equiv) was added dropwise. After complete consumption of starting material (10 min), TBHP (120 μL, 0.66 mmol, 5.5 M in nonane, 10 equiv) was added and the reaction mixture was warmed up to room temperature. After 1 h, the reaction is quenched with a half-saturated aq. $NaHCO_3$ solution and stirred for an additional 1 h. The biphasic mixture was filtered through a plug of celite. The layers were separated and the aqueous phase was extracted with 2 mL ethyl acetate (x 2). The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was purified on Biotage 10G SNAP Ultra to obtain 11.1 mg **9** (52% yield) as white solid.

<u>Analytical data for compound 9:</u>

TLC: R_f = 0.30 (20% EtOAc in hexanes).

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.66 (brs, 1H), 3.25 (brs, 1H), 2.33–2.29 (m, 1H), 2.22–2.18 (m, 1H), 2.06–2.04 (m, 1H), 1.83–1.75 (m, 4H), 1.74–1.56 (m, 6H), 1.51–1.44 (m, 3H), 1.43–1.38 (m, 2H), 1.37–1.31 (m, 2H), 1.30–1.24 (m, 6H), 1.22–1.14 (m, 4H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 76.53 (C), 75.54 (C), 71.82 (C), 66.31 (C), 45.76 (CH), 44.86 (CH), 38.90 (CH), 31.34 (CH_2), 30.18 (CH_2), 29.95 (CH_2), 28.17 (CH_2), 26.86 (CH_2), 26.67 (CH_2), 26.64 (CH_2), 26.44 (CH_2), 26.41 (CH_2), 23.64 (CH_2), 22.05 (CH_2), 20.24 (CH_2), 18.42 (CH_3).

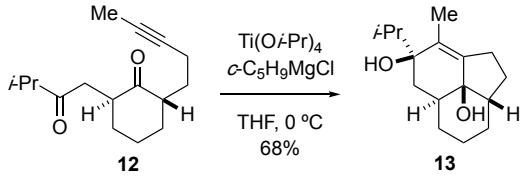
IR (neat, cm^{-1}): 3328 (br), 3230 (br), 2958 (m), 2920 (s), 2881 (m), 2850 (s), 1460 (m), 1442 (m), 1417 (m), 1271 (m), 1219 (w), 1125 (w), 846 (w), 735 (s).

HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{20}H_{33}O_3$ 321.2430; found, 321.2424.

Structure Determination: The structure of **9** was determined by ^{1}H and ^{13}C NMR. The structure and the relative stereochemistry were confirmed by single-crystal X-ray analysis.[7]

- **Alkyne–1,4-diketone Annulation Reactions**

(3) Construction of 6-5-6 Fused Tricycles – Synthesis of 13 and 14



Preparation of 13:

To a stirred solution of **12** (24.5 mg, 0.099 mmol, 1.0 equiv) in 3 mL dry THF was added Ti(O*i*-Pr)$_4$ (62 μL, 0.207 mmol, 2.1 equiv) at 0 °C. Cyclopentylmagnesium chloride (269 μL, 0.414 mmol, 1.54 M in Et_2O, 4.2 equiv) was added dropwise. After complete consumption of starting material (<15 minutes), reaction is quenched with a half-saturated aq. $NaHCO_3$ solution and stirred for an additional 1 h. The biphasic mixture was filtered through a plug of celite. The layers were separated and the aqueous phase was extracted with 2 mL ethyl acetate (x 2). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was purified on a basic alumina column to afford 16.8 mg **13** (68% yield) as colorless oil. It is important to note that compound **13** is unstable on a silica gel column. Initial attempts towards purification on a silica gel column (Biotage SNAP Ultra 10G column) led to isolation of the **13** in lower yield (38%, 41%) due to partial decomposition.

Analytical data for compound 13:

TLC: R_f = 0.22 (33% EtOAc in hexanes).

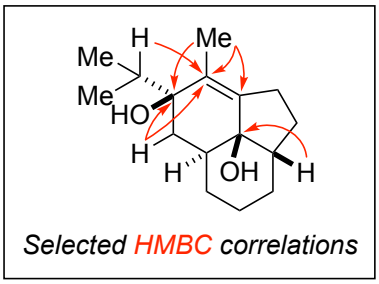
^{1}H NMR (600 MHz, $CDCl_3$): δ 2.42 (brs, 2H), 2.37–2.29 (m, 2H), 2.10–2.04 (m, 1H), 2.01–1.90 (m, 3H), 1.76–1.72 (m, 1H), 1.68 (s, 3H), 1.61–1.55 (m, 1H), 1.54–1.42 (m, 3H), 1.41–1.35 (m, 1H), 1.32–1.27 (m, 1H), 1.19–1.13 (m, 1H), 1.06–0.99 (m, 4H), 0.73 (d, J = 6.9 Hz, 3H).

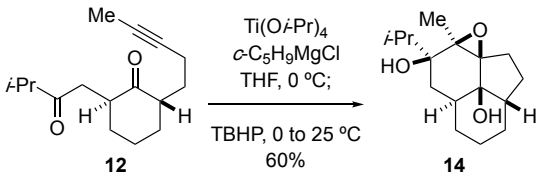
^{13}C NMR (150 MHz, $CDCl_3$): δ 147.97 (C), 129.81 (C), 76.20 (C), 75.62 (C), 47.80 (CH), 37.25 (CH), 34.19 (CH), 33.22 (CH_2), 31.68 (CH_2), 29.18 (CH_2), 26.10 (CH_2), 23.80 (CH_2), 20.50 (CH_2), 18.26 (CH_3), 15.96 (CH_3), 13.64 (CH_3).

IR (neat, cm^{-1}): 3408 (br), 2941 (s), 2857 (s), 1700 (w), 1460 (m), 1376 (m), 1201 (w), 1035 (w), 979 (m), 787 (w), 735 (w).

HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{16}H_{26}O_2Na$ 273.1830; found, 273.1832.

Structure Determination: The structure of **13** was determined by ^{1}H and ^{13}C NMR. The connectivity of atoms was supported by HSQC, HMBC, COSY, and NOESY analysis. The stereochemistry was assigned by analogy to the structure of **14** whose structure was confirmed by X-ray analysis.[7]





Preparation of 14:

To a stirred solution of **12** (16.6 mg, 0.067 mmol, 1.0 equiv) in 3 mL dry THF was added Ti(O*i*-Pr)$_4$ (42 μL, 0.140 mmol, 2.1 equiv) at 0 °C. Cyclopentylmagnesium chloride (182 μL, 0.281 mmol, 1.54 M in Et_2O, 4.2 equiv) was added dropwise. After complete consumption of starting material (7 min), TBHP (122 μL, 0.67 mmol, 5.5 M in

nonane, 10 equiv) was added and the reaction mixture was warmed up to room temperature. After 1 h, the reaction is quenched with a half-saturated aq. $NaHCO_3$ solution and stirred for an additional 1 h. The biphasic mixture was filtered through a plug of celite. The layers were separated and the aqueous phase was extracted with 2 mL ethyl acetate (x 2). The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was purified on Biotage 10G SNAP Ultra to obtain 10.7 mg **14** (60% yield) as white solid.

Analytical data for compound 14:

TLC: R_f = 0.26 (33% EtOAc in hexanes).

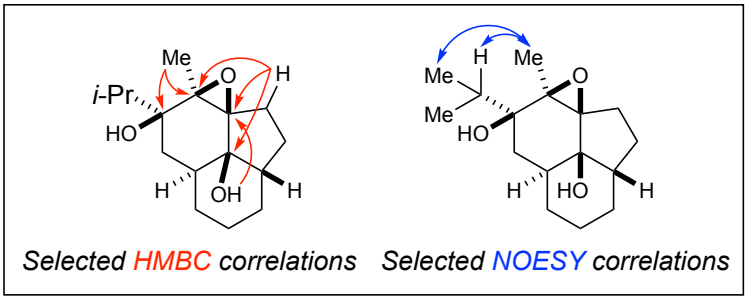
^{1}H NMR (600 MHz, C_6D_6): δ 2.43 (s, 1H), 2.02–1.96 (m, 1H), 1.82 (sept, *J* = 6.8 Hz, 1H), 1.68 (dt, *J* = 13.5, 6.7 Hz, 1H), 1.57–1.45 (m, 5H), 1.41 (dd, *J* = 13.1, 5.9 Hz, 1H), 1.36–1.32 (m, 1H), 1.29–1.21 (m, 1H), 1.08 (s, 3H), 1.07–1.00 (m, 2H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.81–0.70 (m, 2H), 0.65 (dq, *J* = 12.6, 5.9 Hz, 1H), 0.49 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (150 MHz, C_6D_6): δ 79.34 (C), 74.85 (C), 72.45 (C), 69.40 (C), 46.36 (CH), 34.42 (CH), 33.42 (CH), 30.48 (CH_2), 28.53 (CH_2), 26.53 (CH_2), 26.15 (CH_2), 22.83 (CH_2), 19.93 (CH_2), 19.14 (CH_3), 16.66 (CH_3), 15.78 (CH_3).

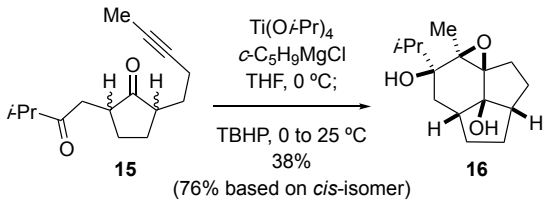
IR (neat, cm^{-1}): 3482 (br), 2944 (s), 2860 (s), 1460 (m), 1380 (w), 1309 (w), 1204 (w), 1103 (w), 1012 (m), 991 (m), 886 (w).

HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{16}H_{26}O_3Na$ 289.1780; found, 289.1779.

Structure Determination: The structure of **14** was determined by ^{1}H and ^{13}C NMR. The connectivity of atoms was supported by HSQC, HMBC, COSY, and NOESY analysis. The structure of **14** was further confirmed by X-ray analysis.[7]



(4) Construction of 5-5-6 Fused Tricycle – Synthesis of 16



Preparation of 16:

To a stirred solution of **15** (~1:1 mixture of diastereomers, 33.3 mg, 0.142 mmol, 1.0 equiv) in 5 mL dry THF was added Ti(O*i*-Pr)$_4$ (88 μL, 0.298 mmol, 2.1 equiv) at 0 °C. Cyclopentylmagnesium chloride (388 μL, 0.597 mmol, 4.2 equiv) was added dropwise. After complete consumption of starting material (<10 minutes), TBHP (0.26 mL, 1.42 mmol, 5.5 M in nonane, 10 equiv) was added and the reaction mixture was warmed up to room temperature. After 1 h, the reaction is quenched with a half-saturated aq. $NaHCO_3$ solution and stirred for an additional 1 h. The biphasic mixture was filtered through a plug of celite. The layers were separated and the aqueous phase was extracted with 2 mL ethyl acetate (x 2). The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was purified on Biotage 10G SNAP Ultra to obtain 13.8 mg **16** (38%, or ~76% from *cis*-**15**) as colorless oil which solidified when refrigerated.

<u>Analytical data for compound 16:</u>

TLC: R_f = 0.28 (33% EtOAc in hexanes).

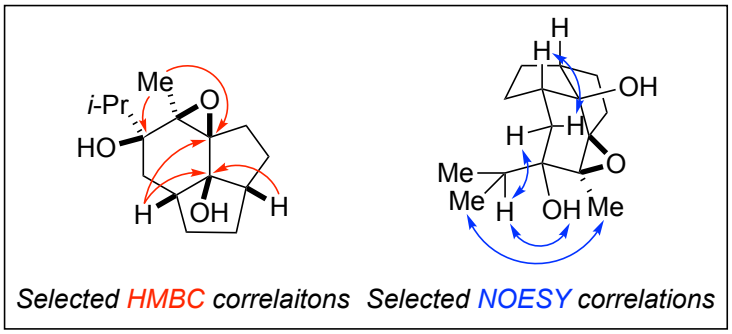
^{1}H NMR (600 MHz, $CDCl_3$): δ 2.98 (s, 1H), 2.56–2.51 (m, 1H), 2.22 (d, *J* = 13.6, 7.6 Hz, 1H), 2.18 (s, 1H), 2.11–2.02 (m, 2H), 2.00–1.96 (m, 1H), 1.95–1.88 (m, 3H), 1.87–1.81 (m, 1H), 1.43–1.38 (m, 1H), 1.37 (s, 3H), 1.29–1.24 (m, 1H), 1.20–1.13 (m, 1H), 1.03 (d, *J* = 6.5 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.80 (dd, *J* = 13.5, 9.5 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 83.79 (C), 74.47 (C), 70.37 (C), 66.81 (C), 52.60 (CH), 45.22 (CH), 36.50 (CH_2), 33.31 (CH_2), 32.86 (CH), 28.84 (CH_2), 28.77 (CH_2), 25.81 (CH_2), 17.97 (CH_3), 17.32 (CH_3), 15.88 (CH_3).

IR (neat, cm^{-1}): 3438 (br), 2954 (s), 2869 (s), 1715 (m), 1457 (m), 1380 (m), 1306 (w), 1045 (m), 1011 (m).

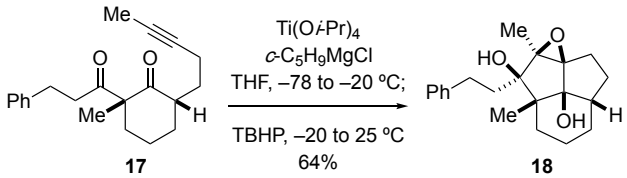
HRMS (ESI-TOF) (m/z): [M + H]+ calcd for $C_{15}H_{25}O_3$ 253.1804; found, 253.1807.

Structure Determination: The structure of **16** was determined by ^{1}H and ^{13}C NMR. The relative stereochemistry was assigned based on HSQC, HMBC, COSY, and NOESY analysis. The structure was further confirmed by single-crystal X-ray analysis.[7]



- **Alkyne–1,3-diketone Annulation Reactions**

(5) Construction of 6-5-5 Fused Tricycles – Synthesis of compounds including 18 & 19



Preparation of 18:

To a stirred solution of Ti(O*i*-Pr)$_4$ (74 μL, 0.247 mmol, 2.1 equiv) in 3 mL dry THF at –78 °C was dropwise added cyclopentylmagnesium chloride (332 μL, 0.494 mmol, 4.2 equiv). After 30 min, a solution of **17** (36.5 mg, 0.118 mmol, 1.0 equiv) in 5 mL dry THF (additional 1 mL wash) was added dropwise and the reaction mixture was warmed to –20 °C. After 90 min, TBHP (214 μL, 1.18 mmol, 5.5 M in nonane, 10 equiv) was added and the mixture was stirred for 2 h at room temperature. The reaction was quenched by addition 2 mL aq. HCl (1 M) solution at –20 °C, and stirred at room temperature for 30 min where two clear layers were observed. The layers were separated and the aqueous phase was extracted with 2 mL ethyl acetate (x 2). The combined organic phase was washed with sat. aq. $NaHCO_3$ solution followed by brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was purified on Biotage 10G SNAP Ultra to obtain 24.8 mg **18** (64% yield) as white solid.

<u>Analytical data for compound 18:</u>

TLC: R_f = 0.39 (33% EtOAc in hexanes).

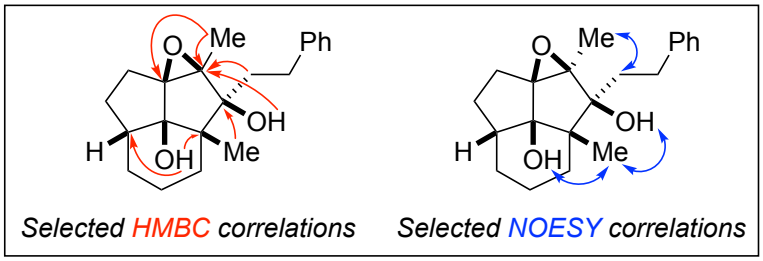
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30 – 7.28 (m, 2H), 7.22 – 7.18 (m, 3H), 2.86 – 2.75 (m, 2H), 2.80 (s, 1H), 2.30 – 2.24 (m, 1H), 2.13 (s, 1H), 2.09 – 2.00 (m, 2H), 1.93 – 1.88 (m, 1H), 1.85 – 1.77 (m, 2H), 1.74 – 1.69 (m, 1H), 1.57 – 1.46 (m, 3H), 1.48 (s, 3H), 1.44 – 1.37 (m, 1H), 1.15 – 1.09 (m, 1H), 1.04 (s, 3H), 0.98 (td, *J* = 12.9, 4.2 Hz).

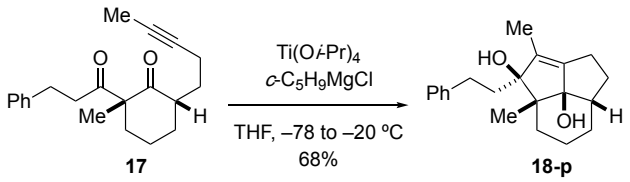
^{13}C NMR (150 MHz, $CDCl_3$): δ 142.98 (C), 128.47 (CH), 128.32 (CH), 125.84 (CH), 84.49 (C), 83.98 (C), 83.75 (C), 73.39 (C), 54.34 (C), 43.29 (CH), 35.49 (CH_2), 31.90 (CH_2), 30.98 (CH_2), 30.44 (CH_2), 26.37 (CH_2), 23.63 (CH_2), 18.18 (CH_2), 14.80 (CH_3), 14.43 (CH_3).

IR (neat, cm^{-1}): 3502 (br), 3060 (w), 3024 (m), 2937 (s), 2868 (s), 1711 (w), 1605 (w), 1495 (m), 1452 (s), 1379 (s), 1327 (m), 1115 (m), 1100 (m), 1038 (s), 899 (m), 738 (s), 700 (s).

HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{21}H_{29}O_3$ 329.2117; found, 329.2116.

Structure Determination: The structure of **18** was determined by ^{1}H and ^{13}C NMR. The relative stereochemistry was assigned based on HSQC, HMBC, and NOESY analysis. The structure was further supported by X-ray.[7]





Preparation of 18-p:

To a stirred solution of Ti(O*i*-Pr)$_4$ (105 μL, 0.352 mmol, 2.1 equiv) in 3 mL dry THF at –78 °C was dropwise added cyclopentylmagnesium chloride (419 μL, 0.704 mmol, 4.2 equiv). After 30 min, a solution of **17** (52.0 mg, 0.168 mmol, 1.0 equiv) in 5 mL dry THF (additional 1 mL wash) was added dropwise. The reaction mixture was warmed to –20 °C and stirred for 75 min. The reaction was quenched by addition of a half-saturated aq. $NaHCO_3$ solution at –20 °C, and stirred at room temperature for 1 h. The biphasic mixture was filtered through a plug of celite. The layers were separated and the aqueous phase was extracted with 2 mL ethyl acetate (x 2). The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was purified on Biotage 10G SNAP Ultra to obtain 35.4 mg **18-p** (68% yield) as colorless oil which solidifies over time. In a 1.22 mmol

scale reaction, **18-p** was isolated in 56% yield (see representative procedure for detailed procedure).

Analytical data for compound 18-p:

TLC: R_f = 0.24 (20% EtOAc in hexanes).

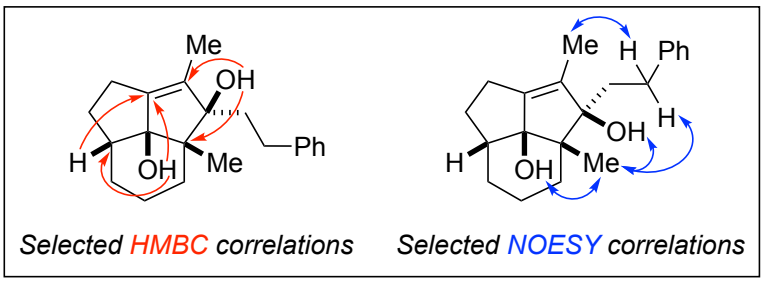
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31 – 7.28 (m, 2H), 7.23 – 7.22 (m, 2H), 7.20 – 7.18 (m, 1H), 2.89 (td, *J* = 13.2, 4.8 Hz, 1H), 2.79 (td, *J* = 12.6, 5.4 Hz, 1H), 2.51 (s, 1H), 2.43 – 2.36 (m, 1H), 2.32 – 2.27 (m, 1H), 2.22 – 2.16 (m, 1H), 2.06 (s, 1H), 1.89 (ddd, *J* = 14.2, 12.7, 5.3 Hz, 1H), 1.82 – 1.74 (m, 2H), 1.68 (t, *J* = 1.8 Hz, 3H), 1.68 – 1.60 (m, 3H), 1.46 – 1.42 (m, 1H), 1.32 (qt, *J* = 13.4, 2.6 Hz, 1H), 1.25 (s, 3H), 1.12 (td, *J* = 13.2, 2.4 Hz, 1H), 0.77 (ddd, *J* = 25.7, 13.3, 3.1 Hz, 1H).

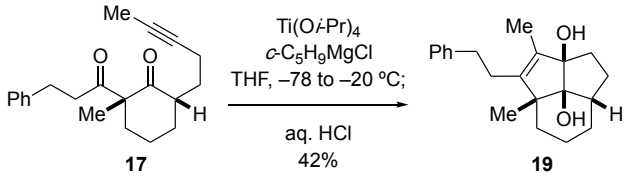
^{13}C NMR (150 MHz, $CDCl_3$): δ 148.56 (C), 143.24 (C), 136.55 (C), 128.43 (CH), 128.34 (CH), 125.76 (CH), 93.18 (C), 93.11 (C), 48.92 (C), 41.89 (CH), 35.45 (CH_2), 35.44 (CH_2), 32.94 (CH_2), 30.31 (CH_2), 29.51 (CH_2), 21.14 (CH_2), 19.91 (CH_2), 15.78 (CH_3), 11.92 (CH_3).

IR (neat, cm^{-1}): 3367 (br), 3086 (w), 3059 (w), 3024 (m), 2933 (s), 2960 (s), 1702 (m), 1604 (w), 1496 (m), 1446 (m), 1401 (m), 1376 (m), 1324 (w), 1274 (w), 1086 (m), 1015 (m), 911 (m), 841 (w), 742 (m), 701 (m).

HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{21}H_{28}O_2Na$ 335.1987; found, 335.1987.

Structure Determination: The structure of **18-p** was determined by ^{1}H and ^{13}C NMR. The relative stereochemistry was assigned based on HSQC, HMBC, and NOESY analysis.[7]





Preparation of 19:

To a stirred solution of Ti(O*i*-Pr)$_4$ (105 μL, 0.353 mmol, 2.1 equiv) in 4 mL dry THF at –78 °C was dropwise added cyclopentylmagnesium chloride (460 μL, 0.706 mmol, 4.2 equiv). After 30 min, a solution of **17** (52.1 mg, 0.168 mmol, 1.0 equiv) in 6 mL dry THF (additional 2 mL wash) was added dropwise and the reaction mixture was warmed to –20 °C. After 2 h, the reaction was quenched by addition 3.4 mL aq. HCl (1 M) solution at –20 °C, and stirred at 0 °C for 2.5 h. The TLC clearly showed the transformation of initially formed compound to a more polar compound over time. The layers were separated and the aqueous phase was extracted with 2 mL ethyl acetate (x 2). The combined organic phase was washed with water, sat. aq. $NaHCO_3$ solution, followed by brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was purified on a basic alumina column to afford 22 mg **19** (42% yield) as colorless oil. It is important to note that compound **19** is unstable on a silica gel column. Initial attempt towards purification on a silica gel column (Biotage SNAP Ultra 10G column) led to isolation of the **19** in lower yield (32%) due to partial decomposition.

<u>Analytical data for compound 19:</u>

TLC: R_f = 0.23 (33% EtOAc in hexanes).

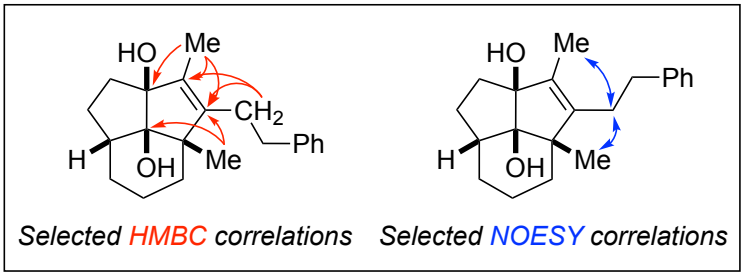
^{1}H NMR (600 MHz, C_6D_6): δ 7.19 – 7.17 (m, 2H), 7.11- 7.09 (m, 3H), 2.62 – 2.52 (m, 3H), 2.23 – 2.07 (m, 3H), 1.81 (dd, *J* = 12.0, 5.0 Hz, 1H), 1.73 – 1.67 (m, 2H), 1.55 (brs, 1H), 1.46 (s, 3H), 1.45 – 1.40 (m, 2H), 1.33 – 1.24 (m, 3H), 1.04 – 0.97 (m, 1H), 1.02 (s, 3H), 0.86 (dq, *J* = 12.6, 5.3 Hz, 1H).

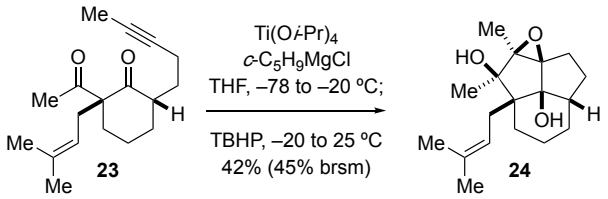
^{13}C NMR (150 MHz, C_6D_6): δ 145.98 (C), 142.35 (C), 132.43 (C), 128.43 (CH), 128.17 (CH), 125.93 (CH), 90.23 (C), 79.67 (C), 51.21 (C), 47.12 (C), 35.86 (CH_2), 33.47 (CH_2), 33.32 (CH_2), 28.05 (CH_2), 27.43 (CH_2), 27.16 (CH_2), 26.77 (CH_3), 18.65 (CH_2), 9.54 (CH_3).

IR (neat, cm^{-1}): 3404 (br), 2926 (s), 2857 (s), 1717 (w), 1651 (w), 1456 (m), 1080 (m), 1048 (w), 696 (m).

HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{21}H_{29}O_2$ 313.2168; found, 313.2161.

Structure Determination: The structure of **19** was determined by ^{1}H and ^{13}C NMR. The relative stereochemistry was assigned based on HSQC, HMBC, COSY, and NOESY analysis.[7]





Preparation of 24:

To a stirred solution of Ti(O*i*-Pr)$_4$ (63 μL, 0.210 mmol, 2.1 equiv) in 2 mL dry THF at –78 °C was dropwise added cyclopentylmagnesium chloride (283 μL, 0.494 mmol, 1.49 M in Et_2O, 4.2 equiv). After 30 min, a solution of **23** (27.5 mg, 0.1 mmol, 1.0 equiv) in 5 mL dry THF (additional 2 mL wash) was added dropwise and the reaction mixture was warmed to –20 °C. After 2 h, TBHP (200 μL, 1.0 mmol, 5.5 M in nonane, 10 equiv) was added and the mixture was stirred for 2 h at room temperature. The reaction was quenched with a half-saturated aq. $NaHCO_3$ solution and stirred overnight. The biphasic mixture was filtered through a plug of celite. The layers were separated and the aqueous phase was extracted with 2 mL ethyl acetate (x 2). The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was purified on Biotage 10G SNAP Ultra to afford 12.3 mg **24** (42% yield) as white solid along with 1.7 mg unreacted **23**.

<u>Analytical data for compound 24:</u>

TLC: R_f = 0.42 (33% EtOAc in hexanes).

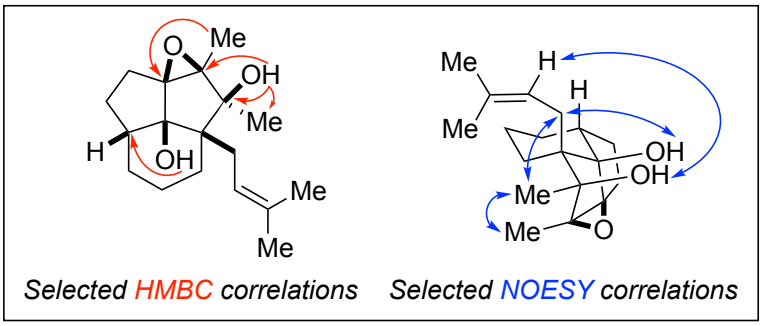
^{1}H NMR (600 MHz, $CDCl_3$): δ 5.27 – 5.24 (m, 1H), 2.64 (s, 1H), 2.55 (dd, *J* = 14.9, 8.3 Hz, 1H), 2.35 – 2.29 (m, 1H), 2.11 – 2.06 (m, 4H), 1.82 – 1.78 (m, 1H), 1.77 – 1.72 (m, 2H), 1.70 (s, 3H), 1.52 – 1.48 (m, 1H), 1.47 – 1.38 (m, 2H), 1.37 (s, 3H), 1.16 (s, 3H), 1.11 – 1.04 (m, 1H), 0.75 – 0.69 (m, 1H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 132.56 (C), 121.57 (CH), 85.21 (C), 84.14 (C), 83.48 (C), 73.88 (C), 55.64 (C), 43.50 (CH), 31.57 (CH_2), 29.89 (CH_2), 27.30 (CH_2), 26.35 (CH_2), 26.21 (CH_3), 23.30 (CH_2), 20.48 (CH_3), 18.82 (CH_2), 17.92 (CH_3), 14.15 (CH_3).

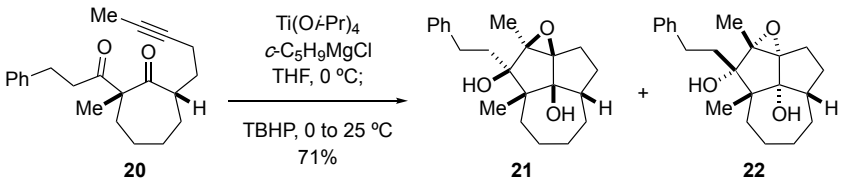
IR (neat, cm^{-1}): 3446 (br), 2931 (s), 2864 (s), 1717 (w), 1699 (w), 1653 (w), 1558 (w), 1457 (m), 1036 (m).

HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{18}H_{29}O_3$ 293.2117; found, 293.2121.

Structure Determination: The structure of **24** was determined by ^{1}H and ^{13}C NMR. The relative stereochemistry was assigned based on HSQC, HMBC, COSY, and NOESY analysis. The structure was further confirmed by X-ray crystallography.[7]



(5) Construction of 7-5-5 Fused Tricycles – Synthesis of 21 & 22



To a stirred solution of **20** (131.0 mg, 0.404 mmol, 1.0 equiv) in 15 mL dry THF was added Ti(O*i*-Pr)$_4$ (252 μL, 0.848 mmol, 2.1 equiv) at 0 °C. Cyclopentylmagnesium chloride (945 μL, 1.697 mmol, 1.80 M in Et_2O, 4.2 equiv) was added dropwise. After complete consumption of starting material (10 min), TBHP (800 μL, ~4.04 mmol, 5–6 M in decane, ~10 equiv) was added and the reaction mixture was warmed up to room temperature. After 1.5 h, the reaction is quenched with a half-saturated aq. $NaHCO_3$ solution and stirred for an additional 1 h. The biphasic mixture was filtered through a plug of celite. The layers were separated and the aqueous phase was extracted with 2 mL ethyl acetate (x 2). The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was purified on Biotage 10G SNAP Ultra to afford 54 mg **21** (white solid, 39% yield) and 44 mg **22** (white solid, 32% yield).

Analytical data for compound 21:

TLC: R_f = 0.15 (20% EtOAc in hexanes).

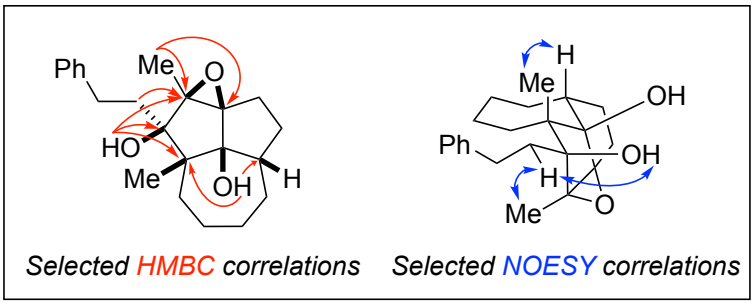
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30–7.28 (m, 2H), 7.21–7.18 (m, 3H), 3.08 (s, 1H), 2.84–2.78 (m , 1H), 2.74–2.69 (m , 1H), 2.53 (s, 1H), 2.30–2.26 (m, 1H), 2.05–1.94 (m, 2H), 1.89–1.58 (m, 10H), 1.49 (s, 3H), 1.49–1.46 (m, 1H), 1.30–1.25 (m, 1H), 1.12 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 142.85 (C), 128.48 (CH), 128.29 (CH), 125.87 (CH), 85.57 (C), 82.43 (C), 82.32 (C), 74.39 (C), 62.88 (C), 51.28 (CH), 36.20 (CH_2), 30.53 (CH_2), 30.17 (CH_2), 25.96 (CH_2), 25.78 (CH_2), 24.79 (CH_2), 23.67 (CH_2), 23.47 (CH_2), 15.23 (CH_3), 14.23 (CH_3).

IR (neat, cm^{-1}): 3446 (br), 3025 (w), 2940 (s), 2868 (s), 1603 (w), 1496 (w), 1456 (m), 1379 (m0, 1111 (m0, 1041 (m), 736 (s), 700 (s).

HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{22}H_{30}O_3Na$ 365.2093; found, 365.2088.

Structure Determination: The structure of **21** was determined by ^{1}H and ^{13}C NMR. The connectivity of the atoms was assigned based on HSQC and HMBC analysis. The structure was confirmed by single-crystal X-ray analysis.[7]



Analytical data for compound 22:

TLC: R_f = 0.36 (20% EtOAc in hexanes).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30–7.28 (m, 2H), 7.22–7.18 (m, 3H), 3.21 (s, H), 2.77 (m, 2H), 2.46 (s, 1H), 2.13–2.04 (m, 2H), 1.96–1.89 (m, 3H), 1.88–1.80 (m, 3H), 1.79–1.74 (m, 2H), 1.68–1.61 (m, 2H), 1.59–1.46 (m, 2H), 1.42 (s, 3H), 1.28–1.24 (m, 1H), 1.01 (s, 3H).

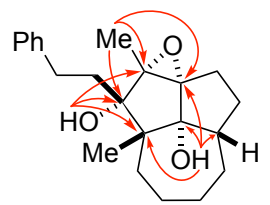
^{13}C NMR (150 MHz, $CDCl_3$): δ 142.97 (C), 128.45 (CH), 128.34 (CH), 125.81 (CH), 88.14 (C), 85.22 (C), 82.93 (C), 73.51 (C), 56.67 (C), 42.14 (CH), 37.47 (CH_2), 32.77

(CH_2), 30.37 (CH_2), 29.41 (CH_2), 27.42 (CH_2), 26.82 (CH_2), 26.10 (CH_2), 25.22 (CH_2), 23.56 (CH_3), 15.15 (CH_3).

IR (neat, cm^{-1}): 3446 (br), 3060 (w), 3026 (m), 2958 (s), 2927 (s), 2857 (s), 1699 (w), 1602 (m), 1469 (m), 1456 (s), 1380 (m), 1265 (w), 1123 (m), 1030 (w), 1001 (w), 886 (m), 738 (s).

HRMS (ESI-TOF) (m/z): $[M + Na]^+$ calcd for $C_{22}H_{30}O_3Na$ 365.2093; found, 365.2087.

Structure Determination: The structure of **22** was determined by ^1H and ^{13}C NMR. The connectivity of the atoms was assigned based on HSQC and HMBC analysis. The structure was confirmed by single-crystal X-ray analysis.[7]

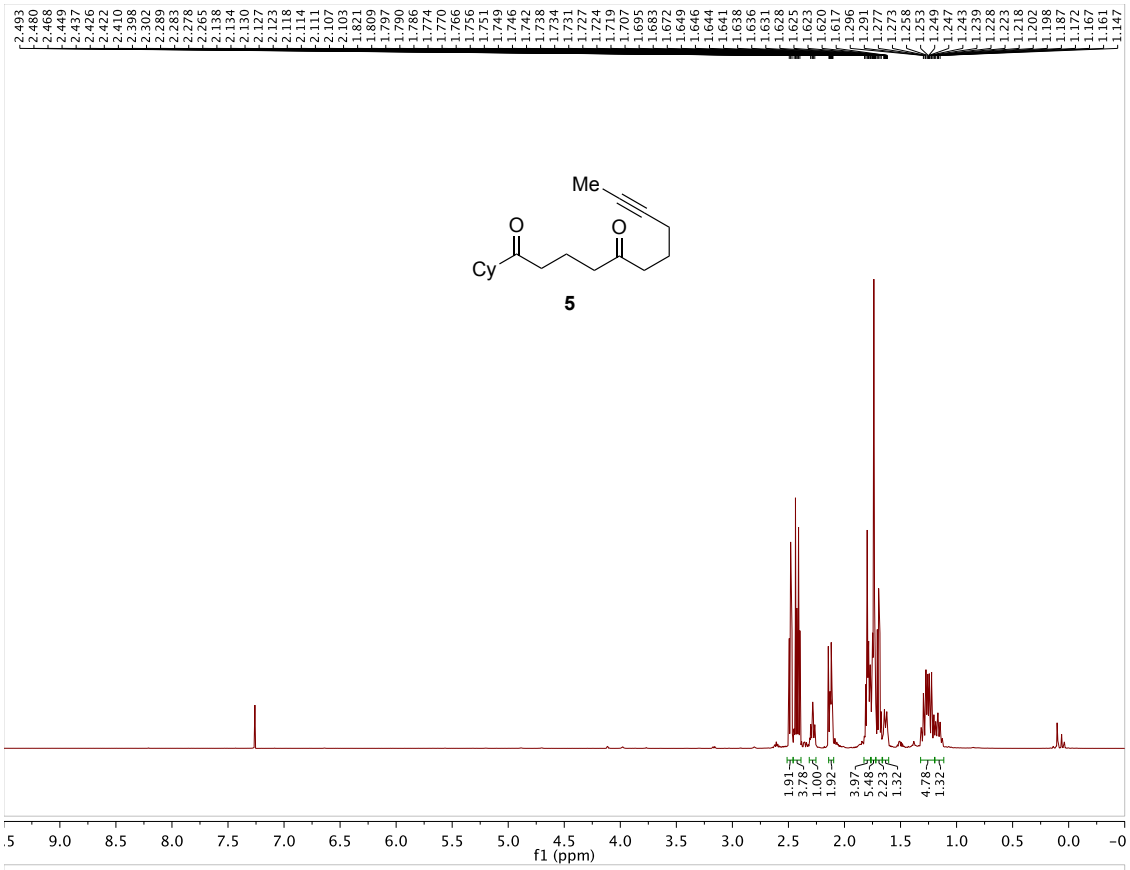


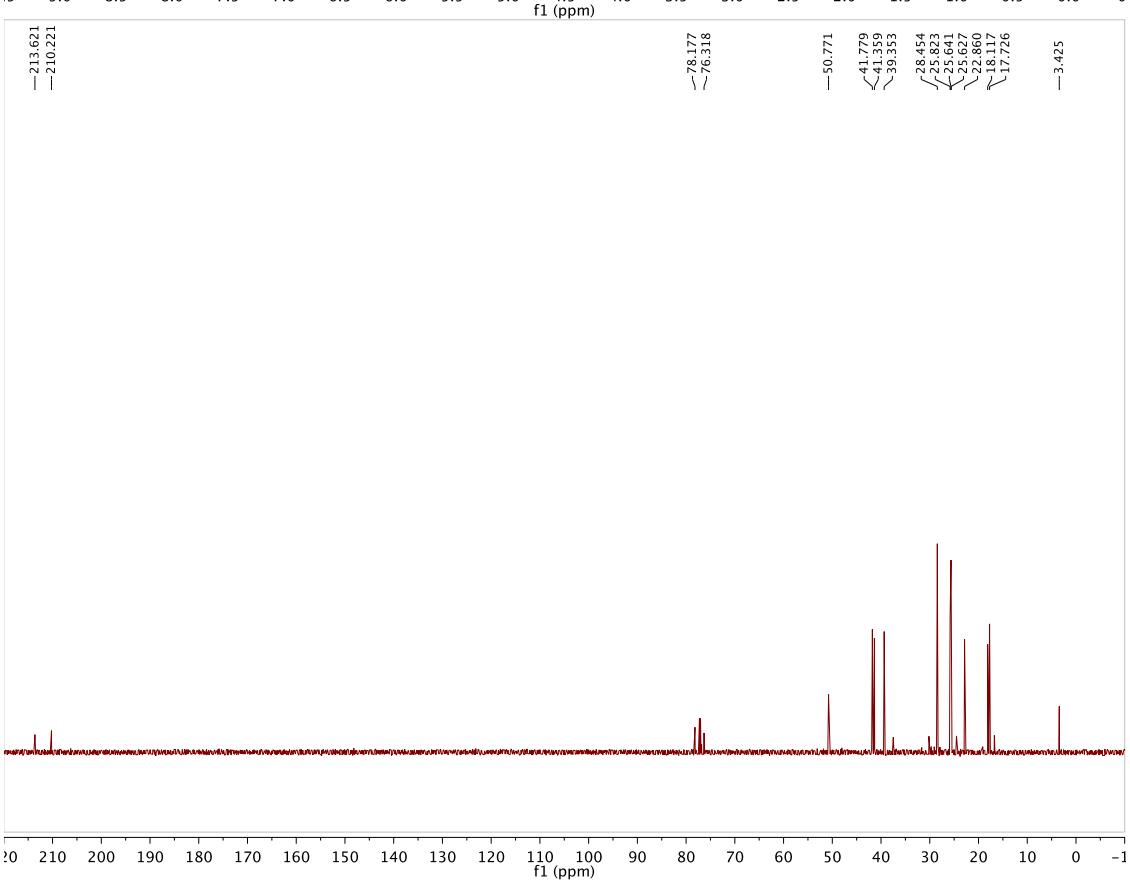
Selected HMBC correlations

[1] Burchat, A. F.; Chong, J. M.; Nielsen, N. *J. Organomet. Chem.* **1997**, *542*, 281–283.
[2] Love, B. E.; Jones, E. G. *J. Org. Chem.* **1999**, *64*, 3755–3756.
[3] Kamijo, S.; Dudley, G. B. *J. Am. Chem. Soc.* **2005**, *127*, 5028–5029.
[4] Brandt, D.; Bellosta, V.; Cossy, *J. Org. Lett.* **2012**, *14*, 5594–5597.
[5] Davidson, J. P.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 13486–13489.
[6] Kier, M. J.; Leon, R. M.; O'Rourke, N. F.; Rheingold, A. L.; Micalizio, G. C. *J. Am. Chem. Soc.* **2017**, *139*, 12374–12377.
[7] The stereochemistry depicted here is relative. The compound was made as a racemic mixture.
[8] Clift, M. D.; Taylor, C. N.; Thomson, R. J. *Org. Lett.* **2007**, *9*, 4667–4669.
[9] Clift, M. D.; Thomson, R. J. *J. Am. Chem. Soc.* **2009**, *131*, 14579–14583.

III. NMR Spectra of New Compounds

^{1}H and ^{13}C NMR spectra of all the new compounds (substrates and annulation products) are given below. For spectra of compounds **10** and **11**, see ref. 6.


Me
O
O
Cy
5
f1 (ppm)


213.621
210.221
78.177
76.318
50.771
41.779
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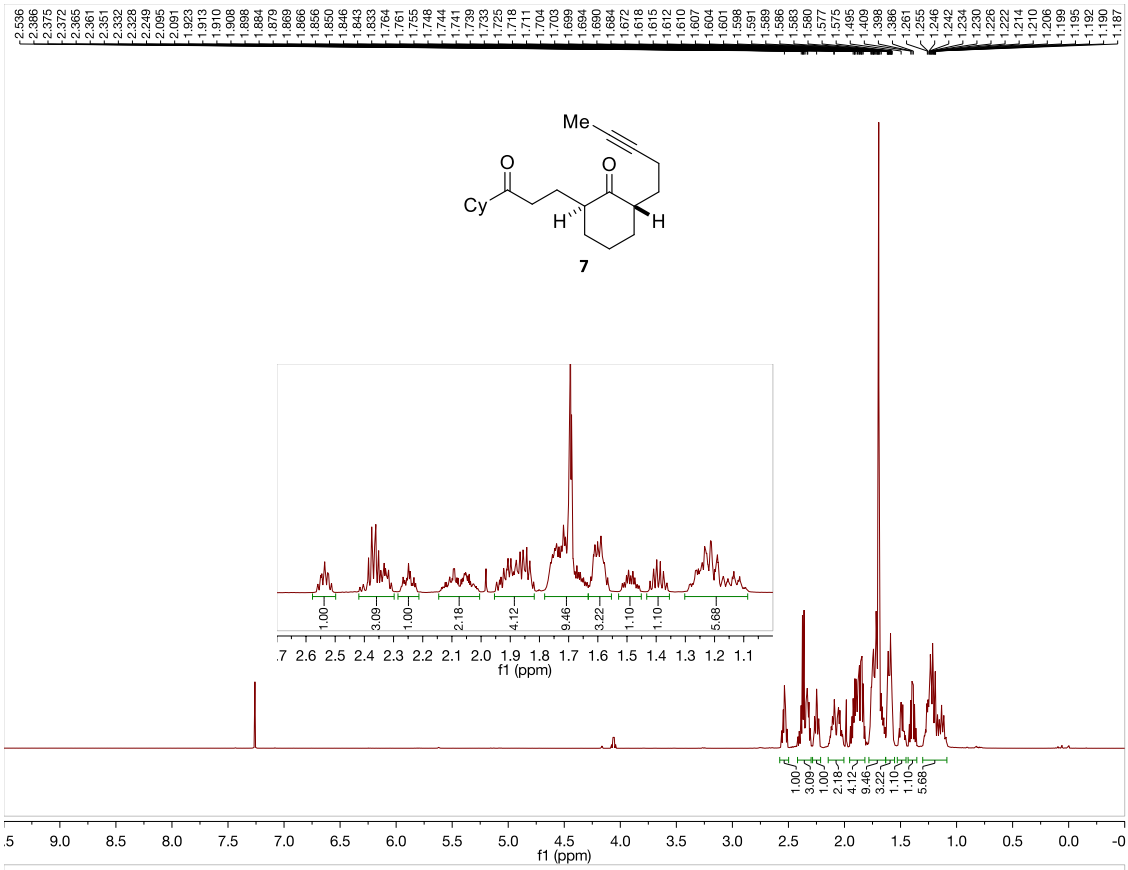
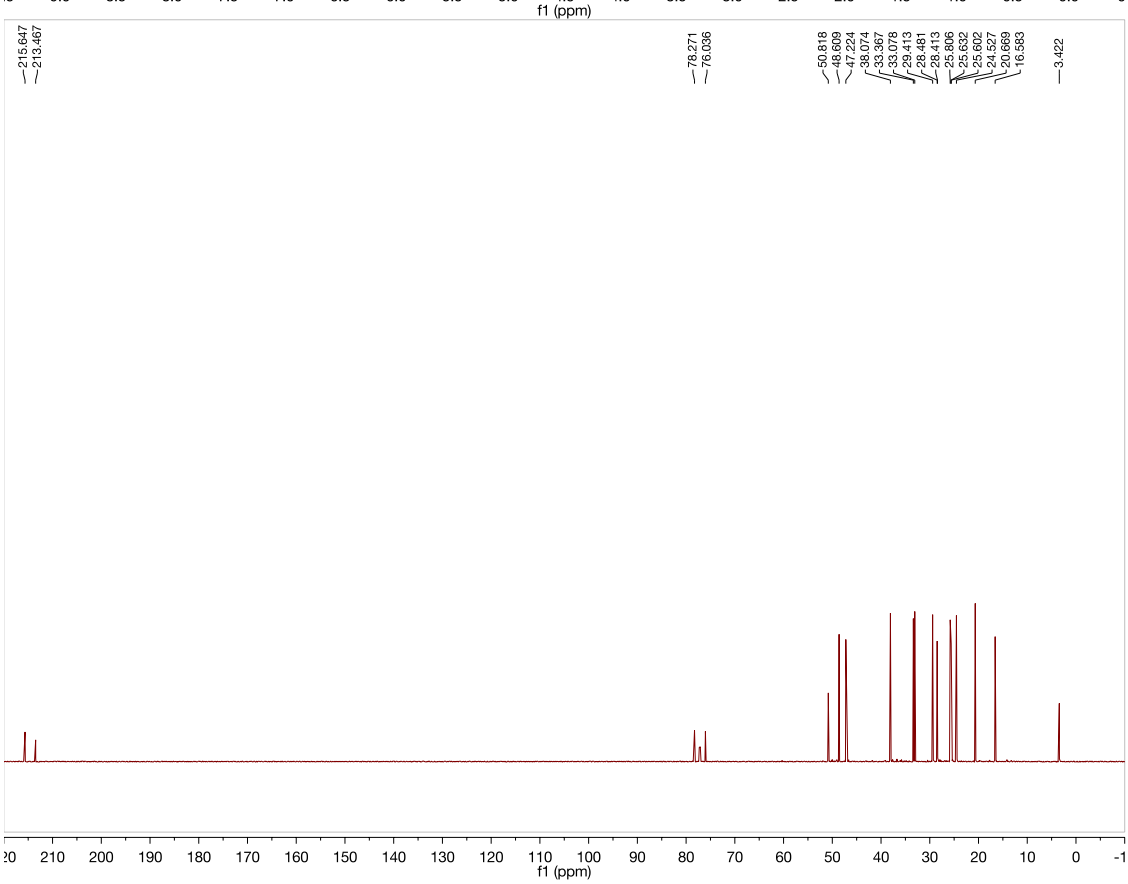
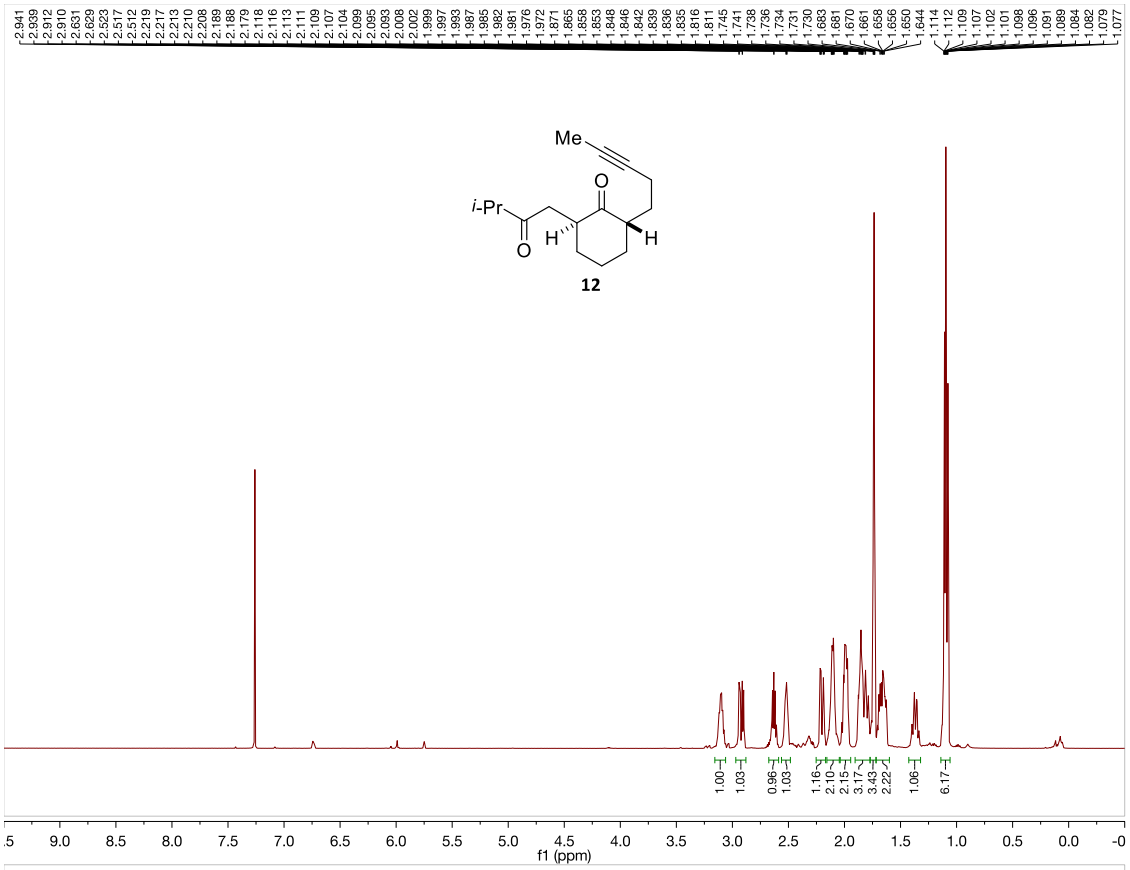
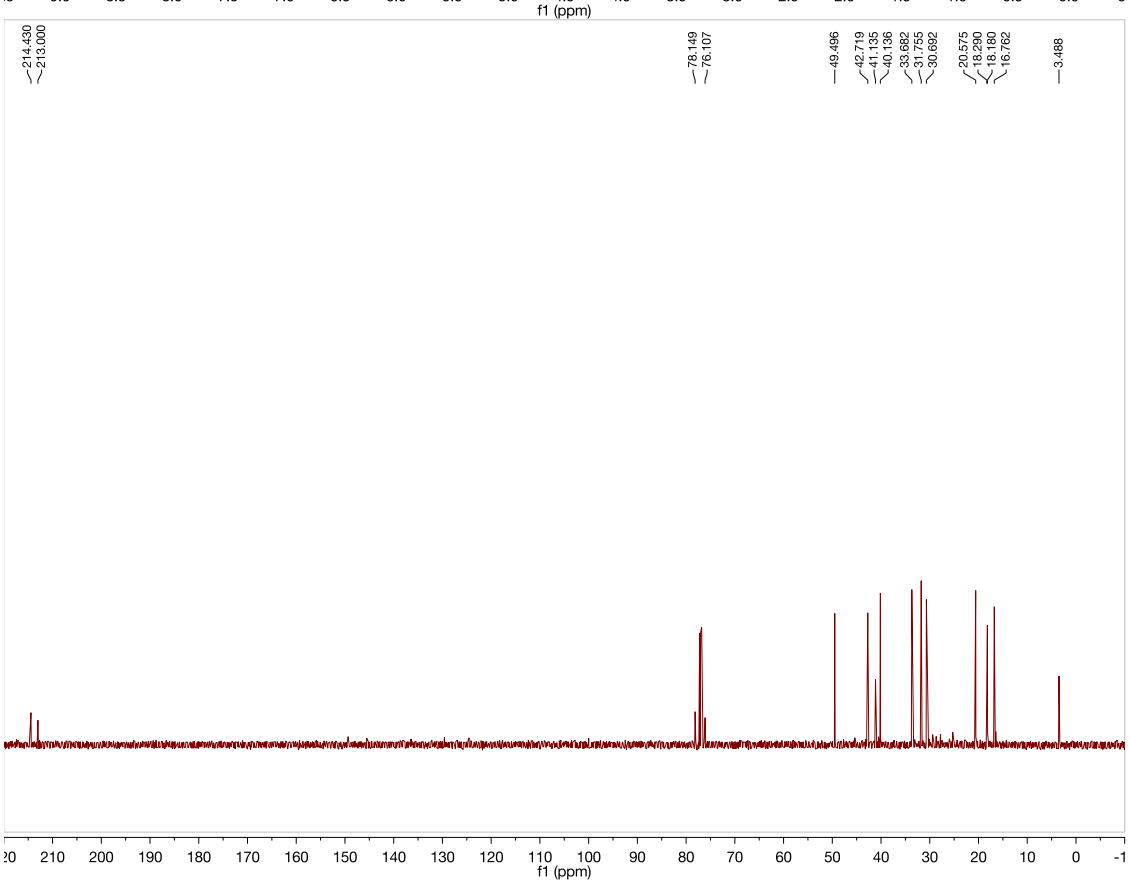
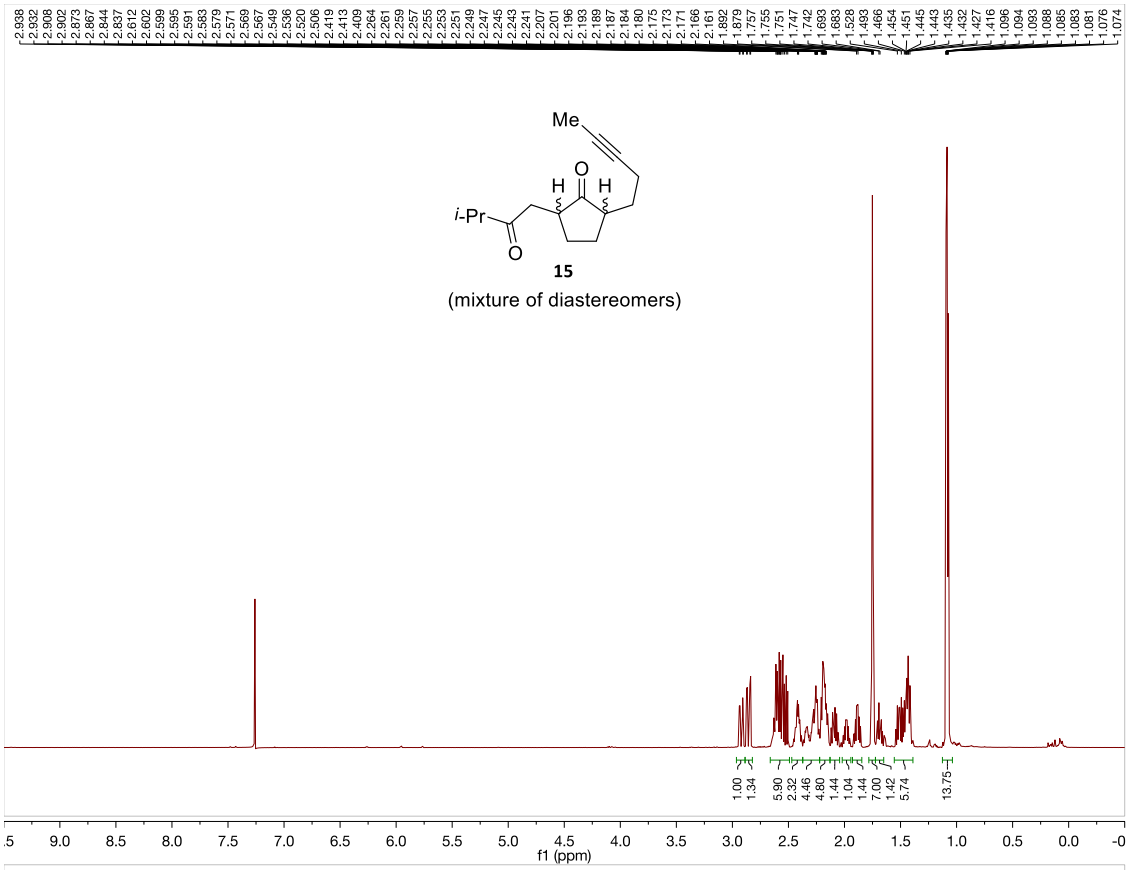
39.353
28.454
25.823
25.641
25.627
22.860
18.117
17.726
3.425
f1 (ppm)

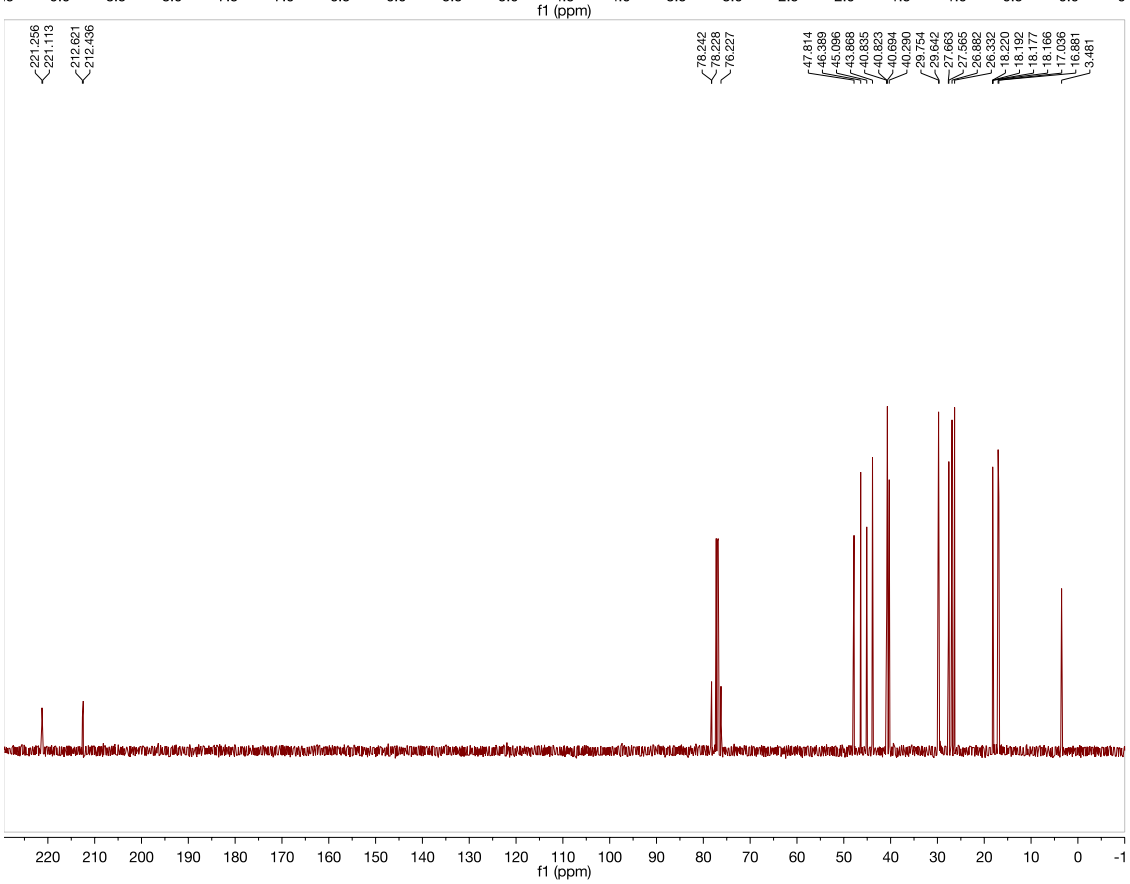

Me
O
O
Cy
H
H
7
f1 (ppm)

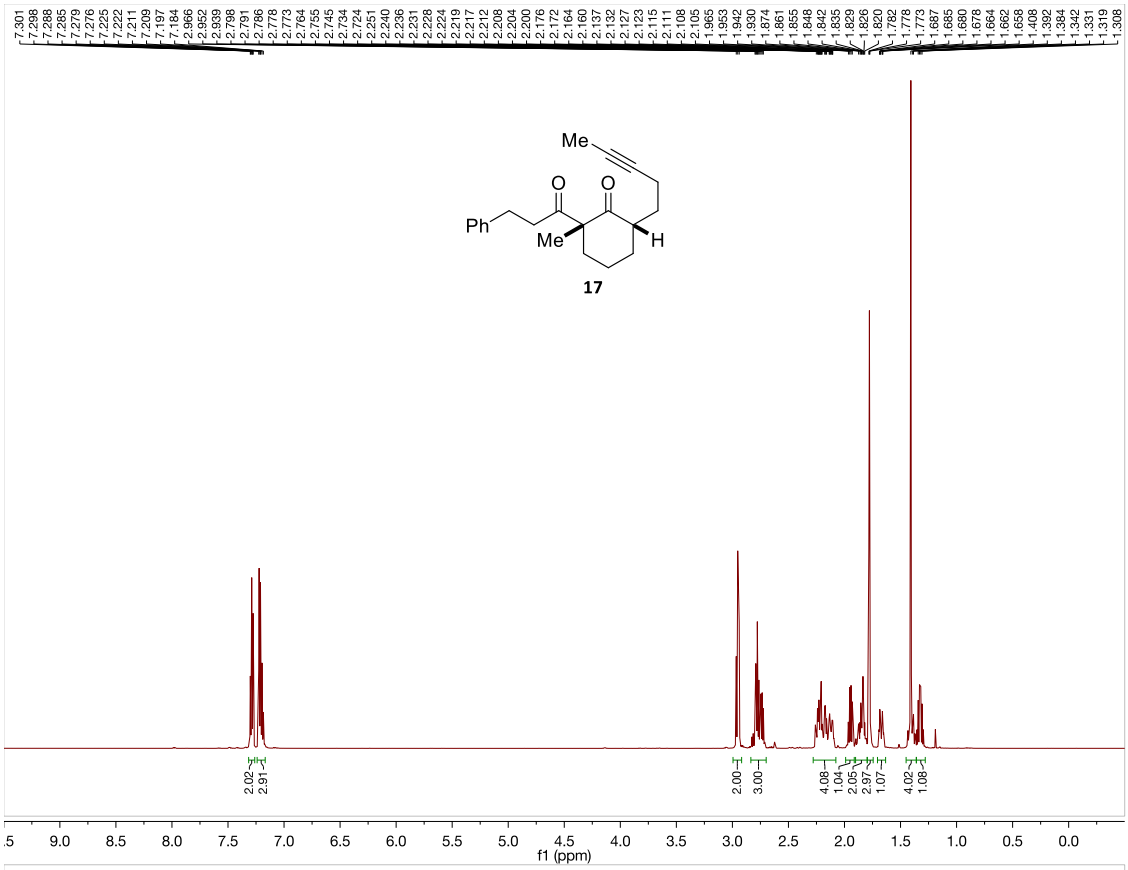

f1 (ppm)

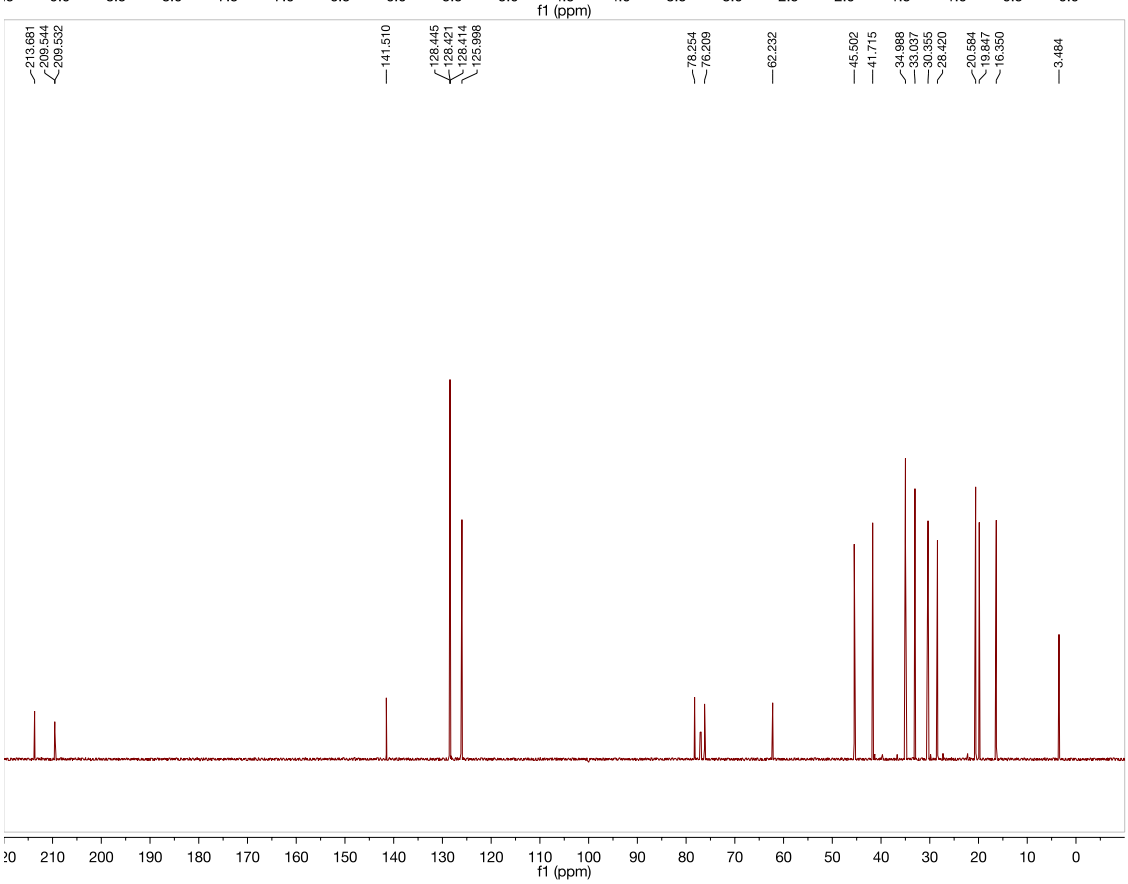

Me
O
i-Pr
H
H
O
12
f1 (ppm)

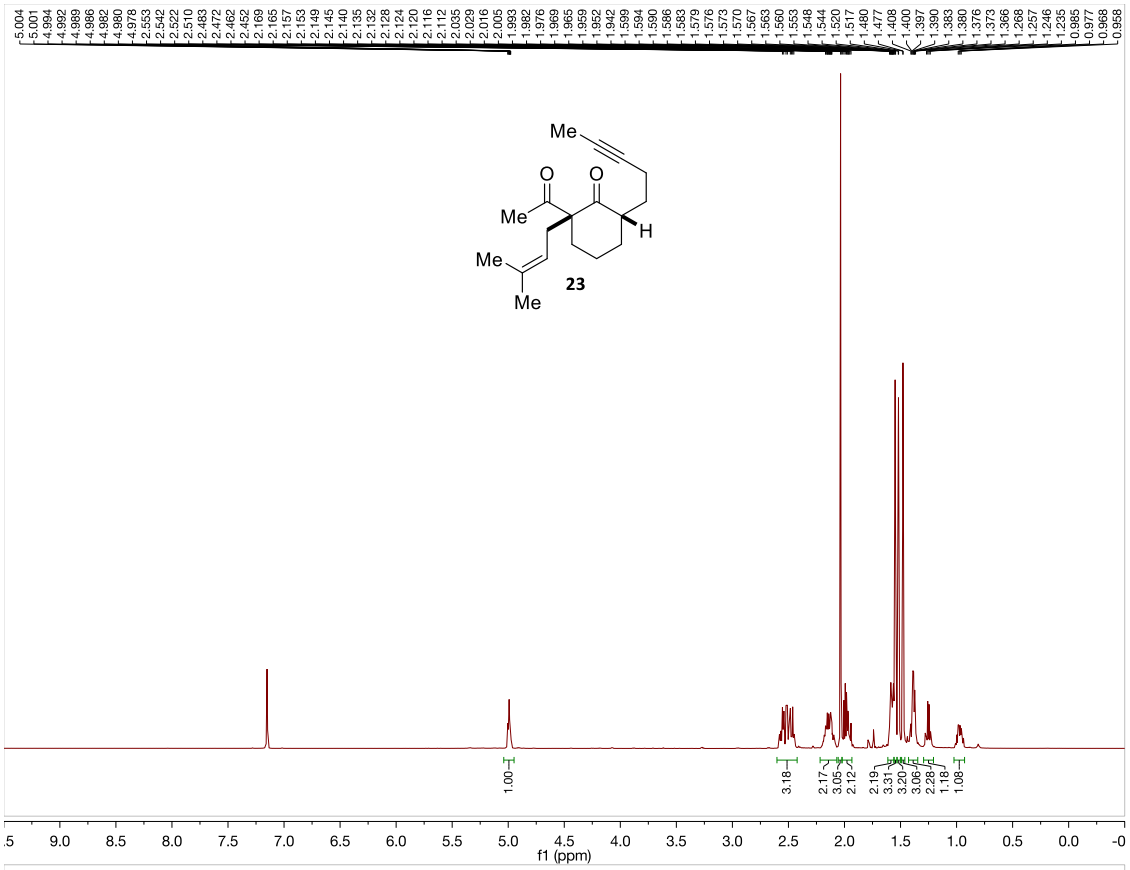

214.430
213.000
78.149
76.107
49.496
42.719
41.135
40.136
33.682
31.755
30.692
20.575
18.290
18.180
16.762
3.488
f1 (ppm)

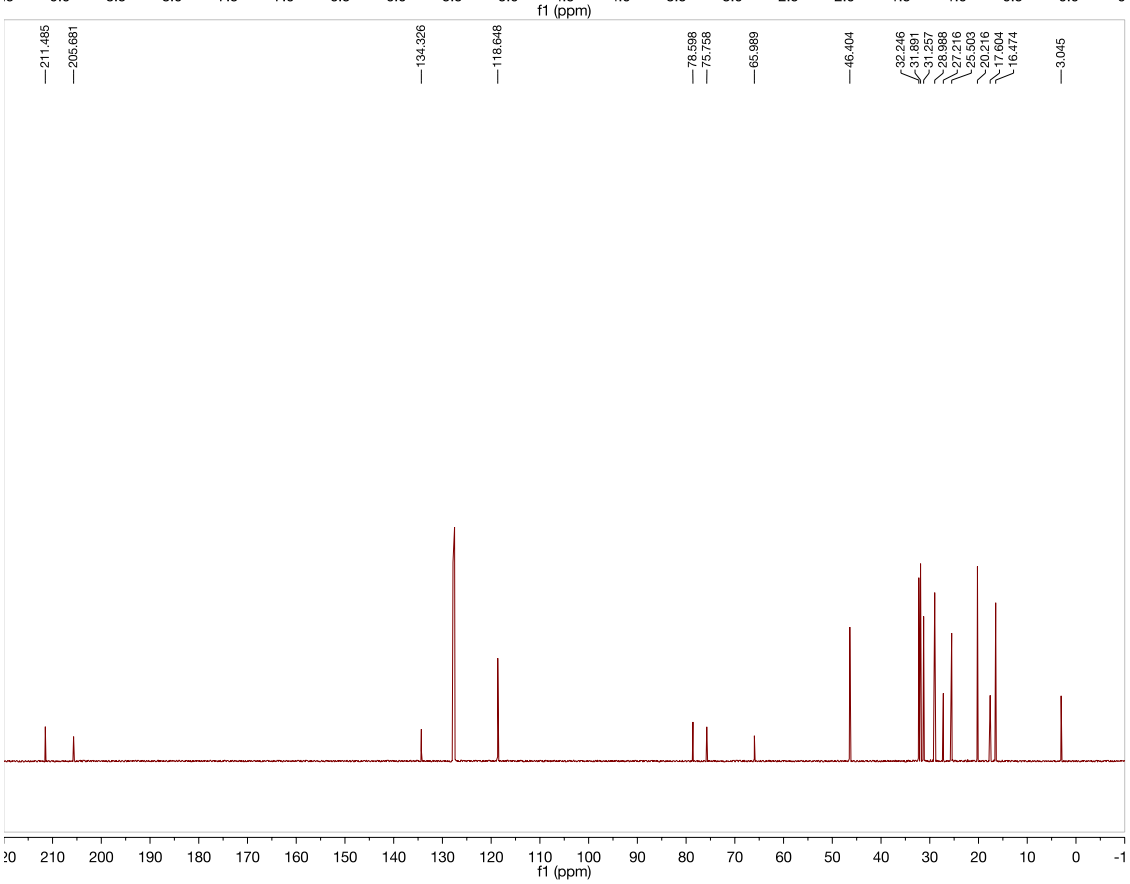

Me
O
H
H
i-Pr
O
15
(mixture of diastereomers)
f1 (ppm)


f1 (ppm)


Me
O
O
Ph
Me
H
17
f1 (ppm)


f1 (ppm)


Me
O
O
Me
H
Me
Me
23
f1 (ppm)


211.485
205.681
134.326
118.648
78.598
75.758
65.989
46.404
32.246
31.891
31.257
28.988
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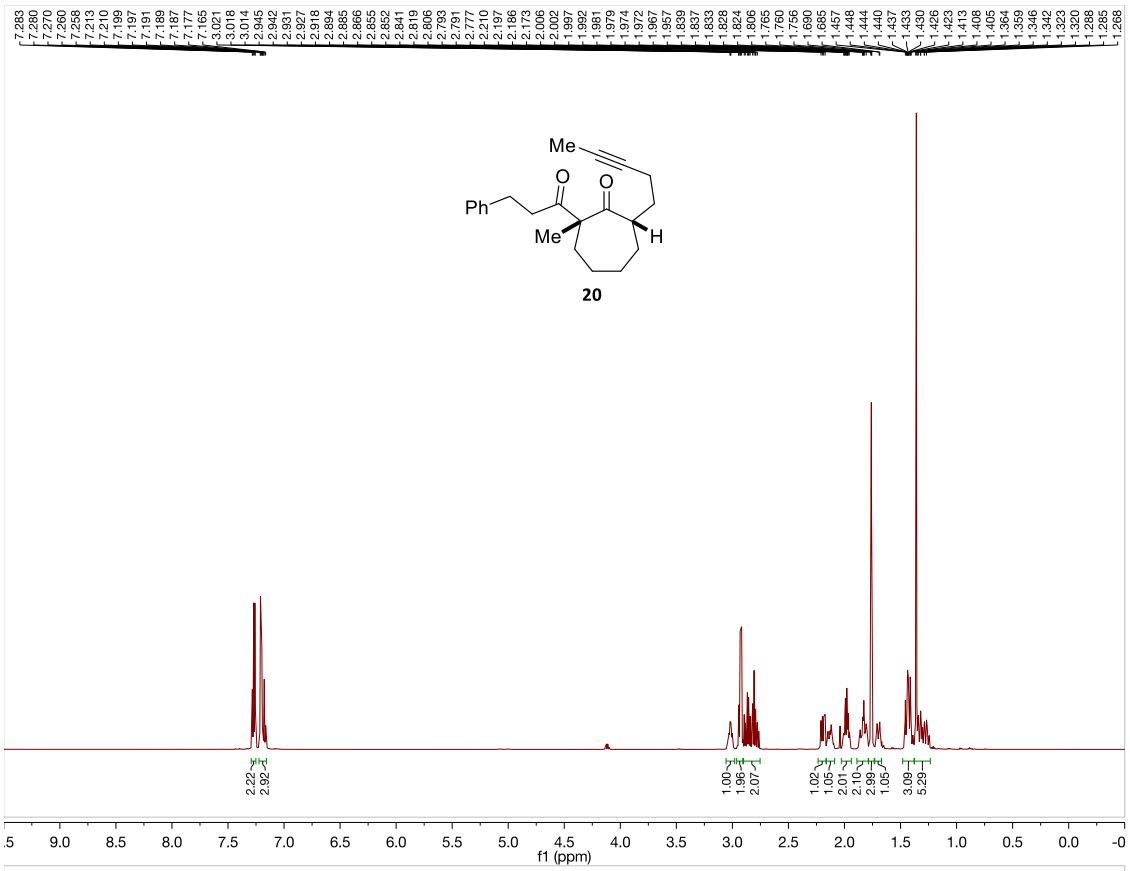
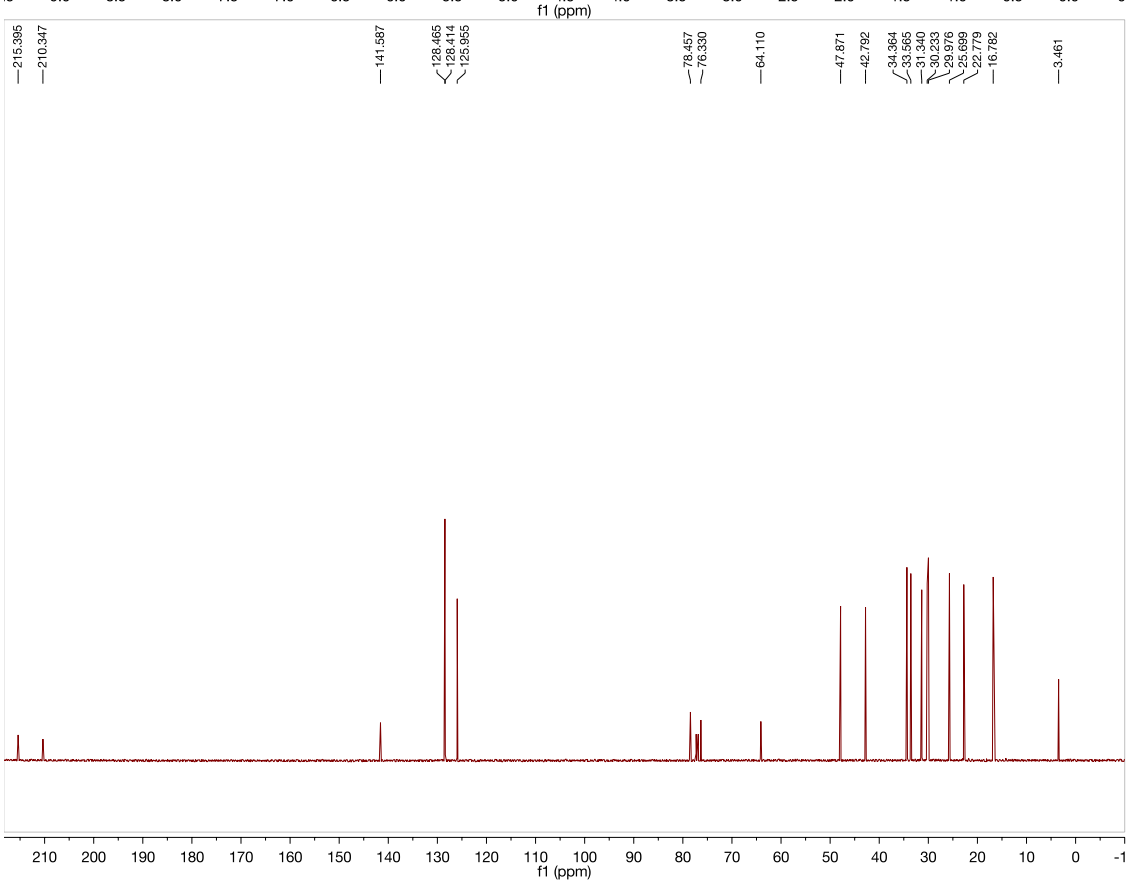
25.503
20.216
17.604
16.474
3.045
f1 (ppm)


Me
O
O
Ph
Me
H
20
f1 (ppm)


215.395
210.347
141.587
128.465
128.414
125.955
78.457
76.330
64.110
47.871
42.792
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33.565
31.340
30.233
29.976
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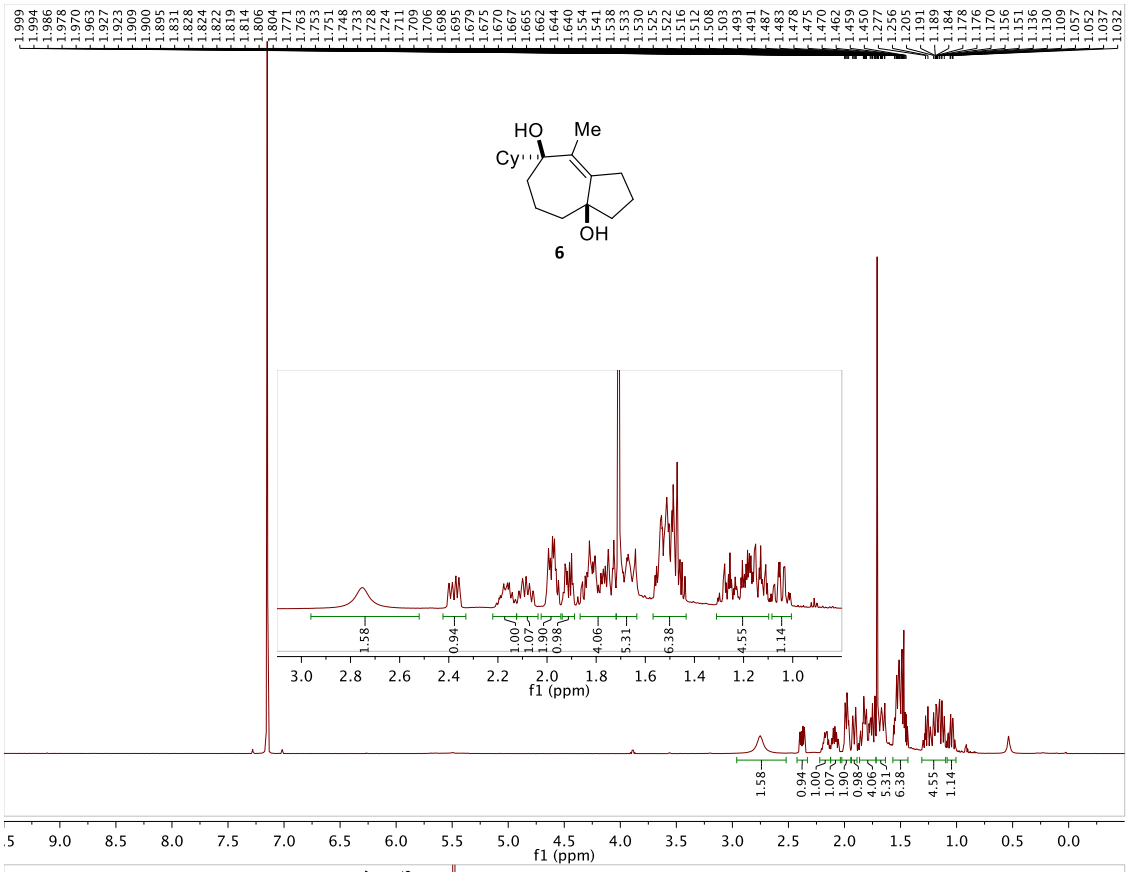
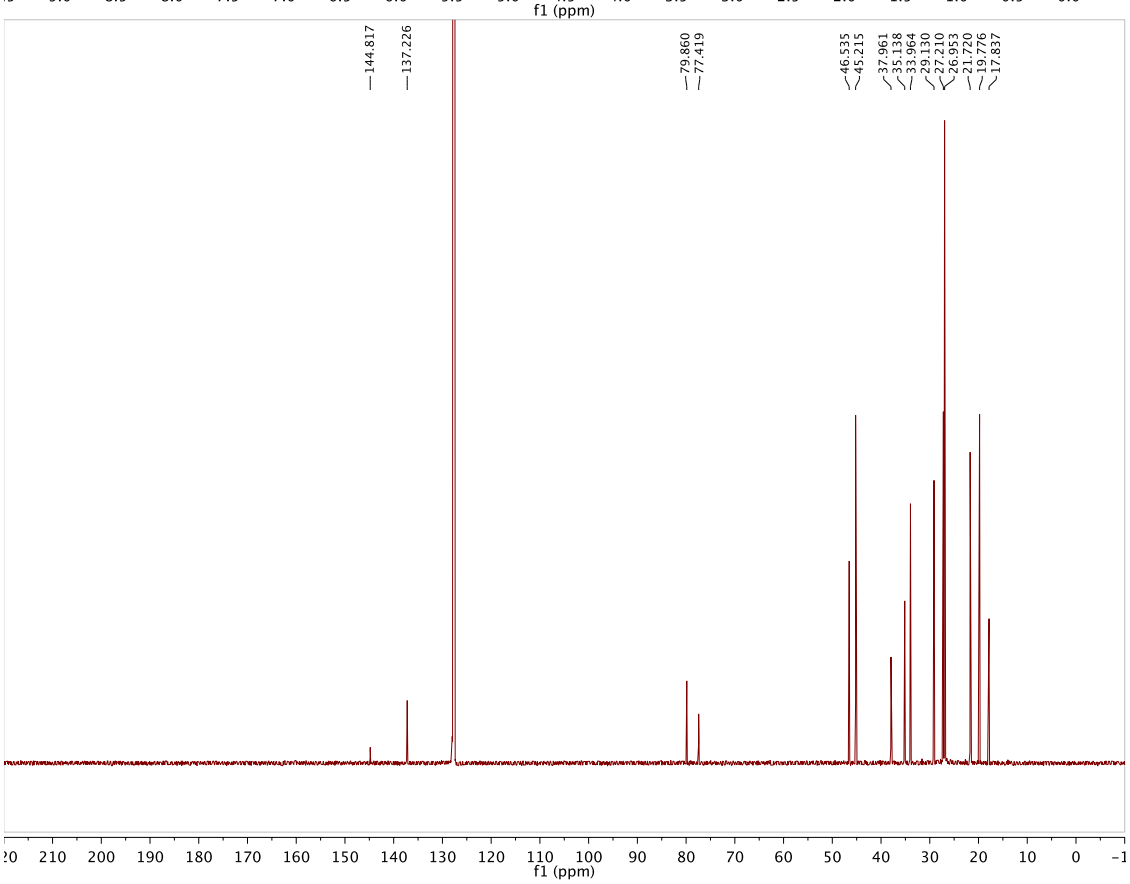
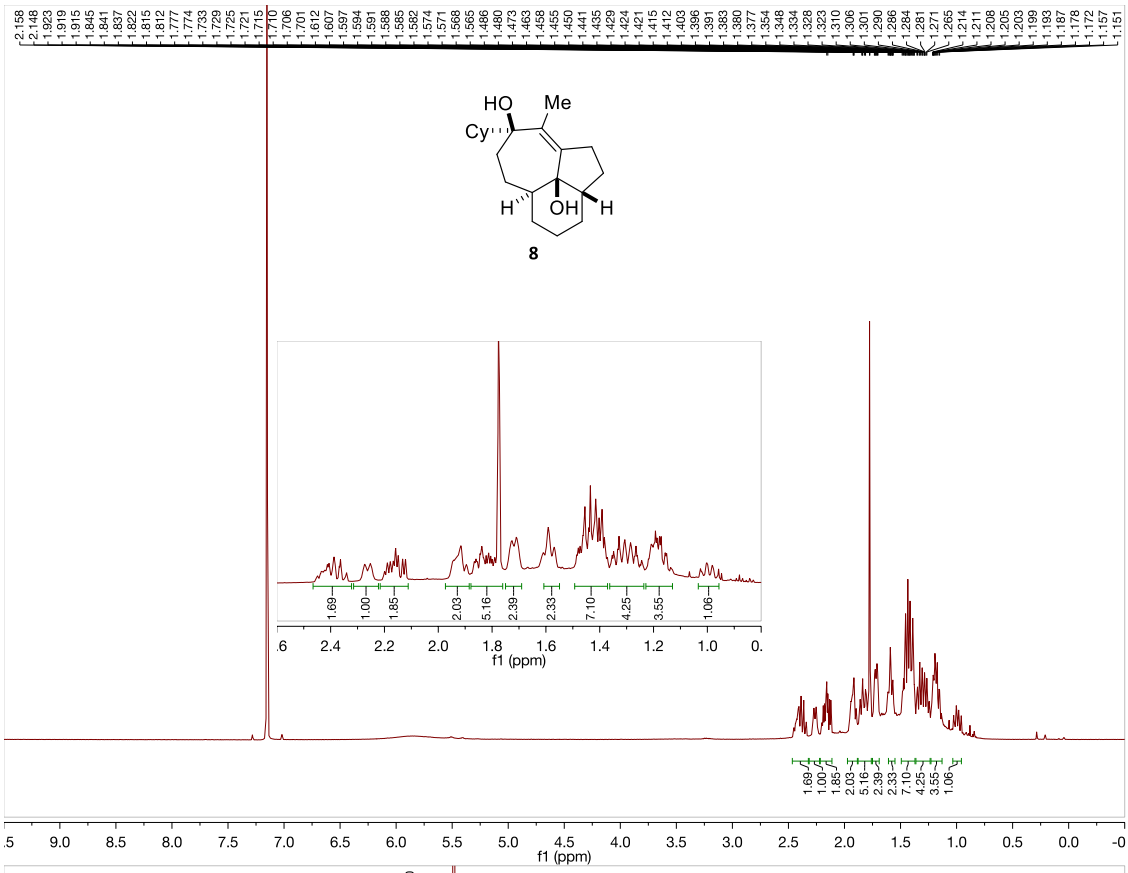
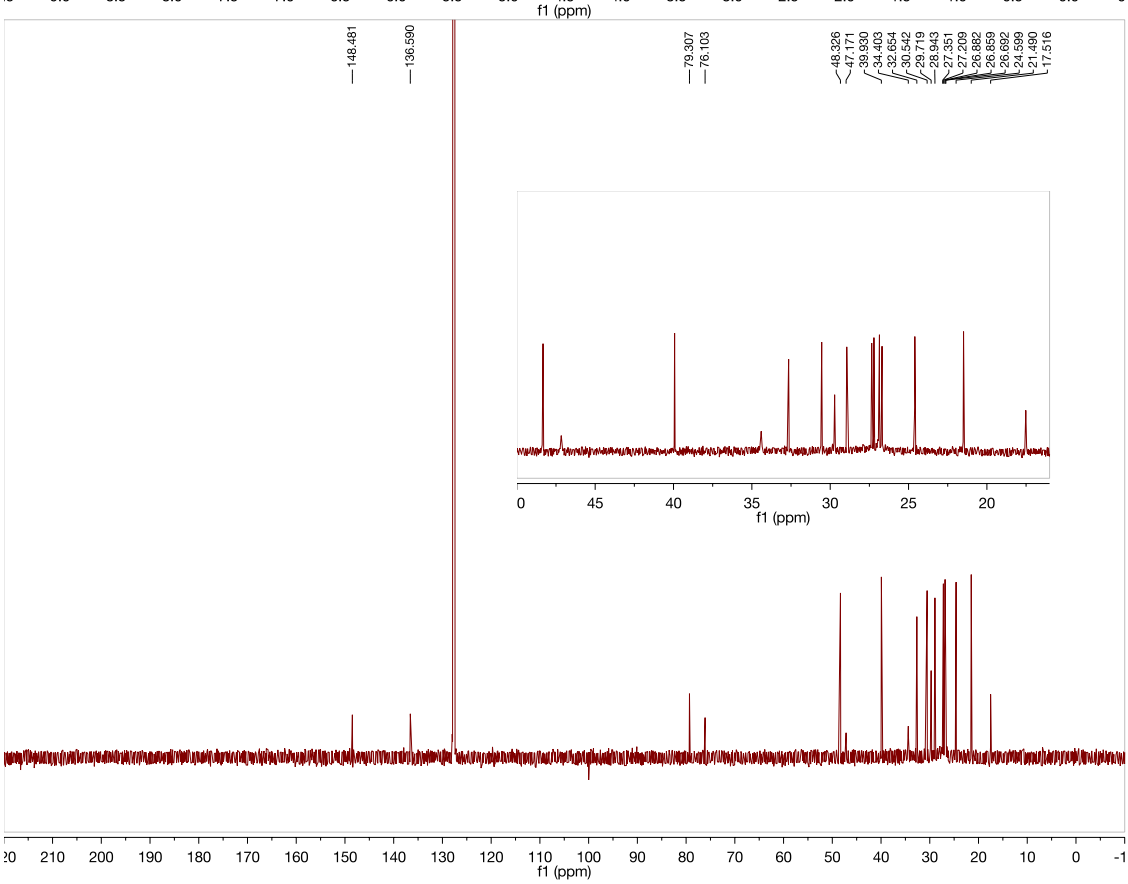
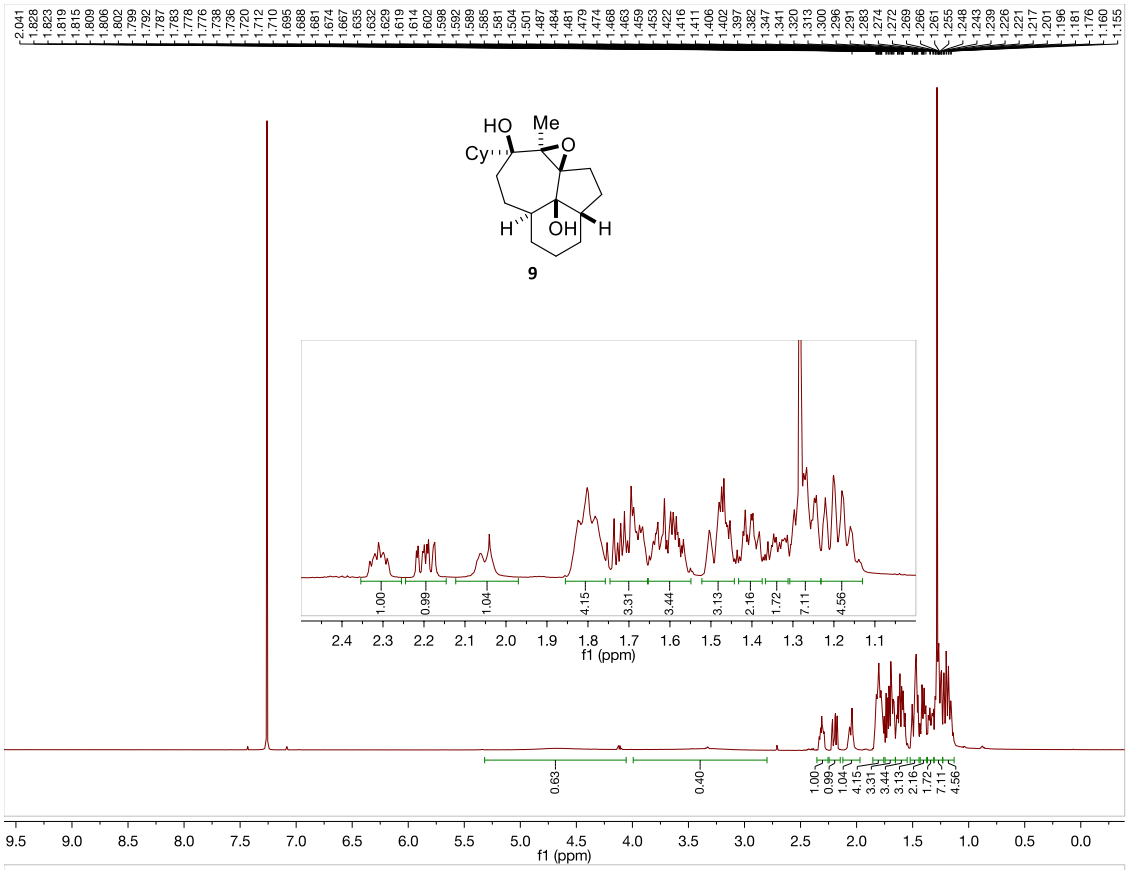
22.779
16.782
3.461
f1 (ppm)

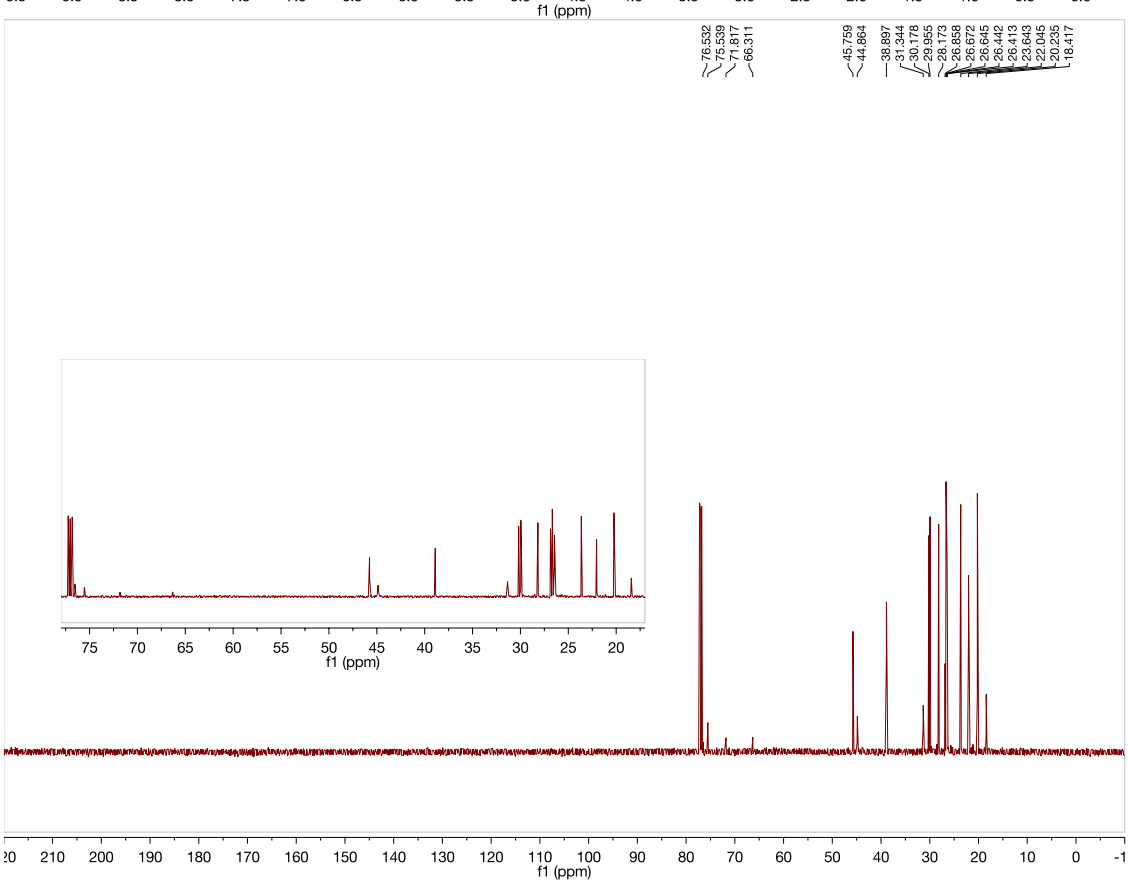

HO
Me
Cy
OH
6
f1 (ppm)

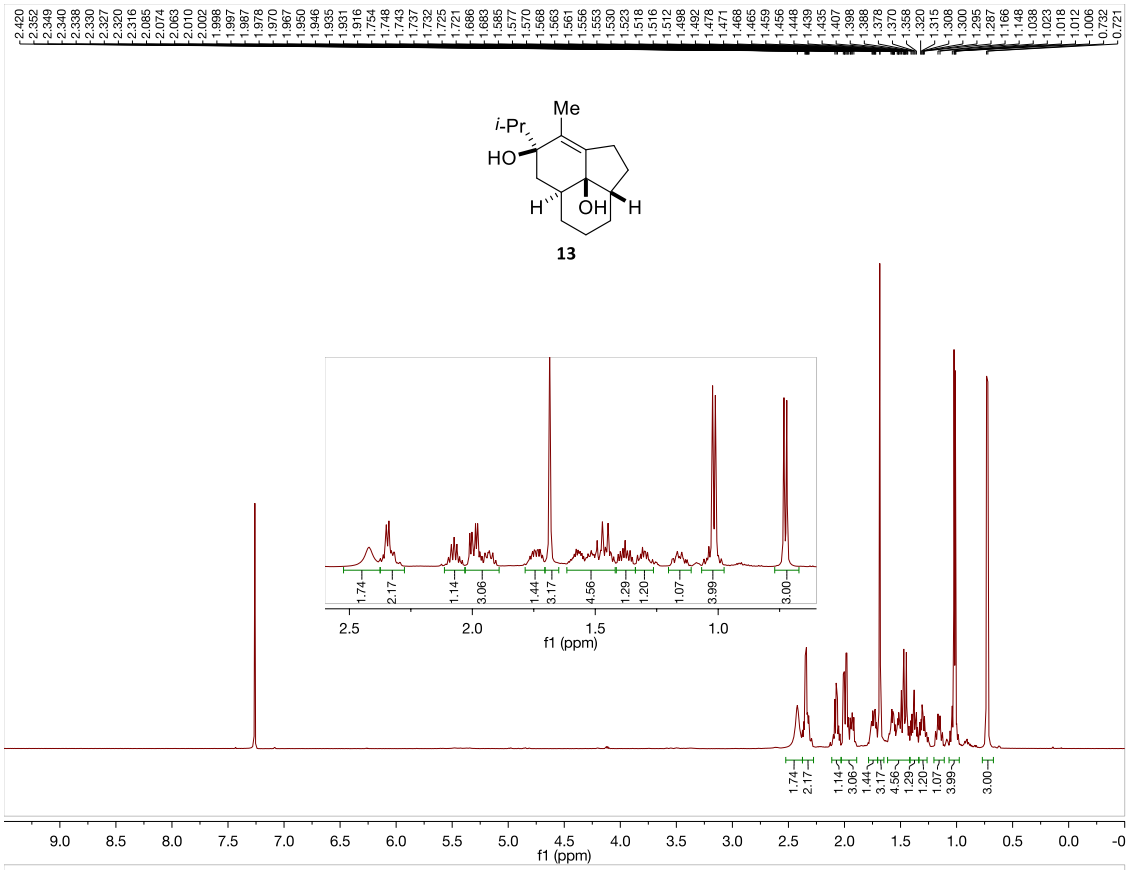

144.817
137.226
79.860
77.419
46.535
45.215
37.961
35.138
33.964
29.130
27.210
26.953
21.720
19.776
17.837
f1 (ppm)

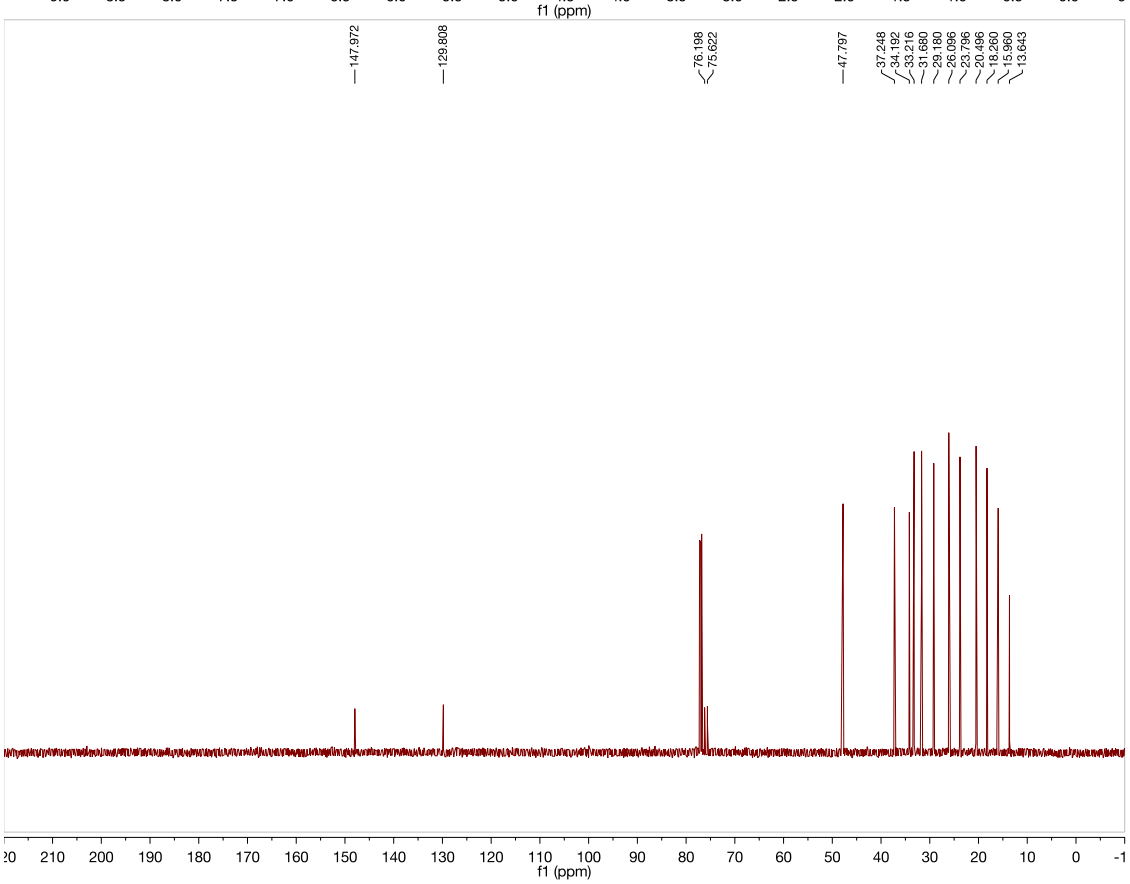

HO
Me
Cy
H
OH
H
8
f1 (ppm)

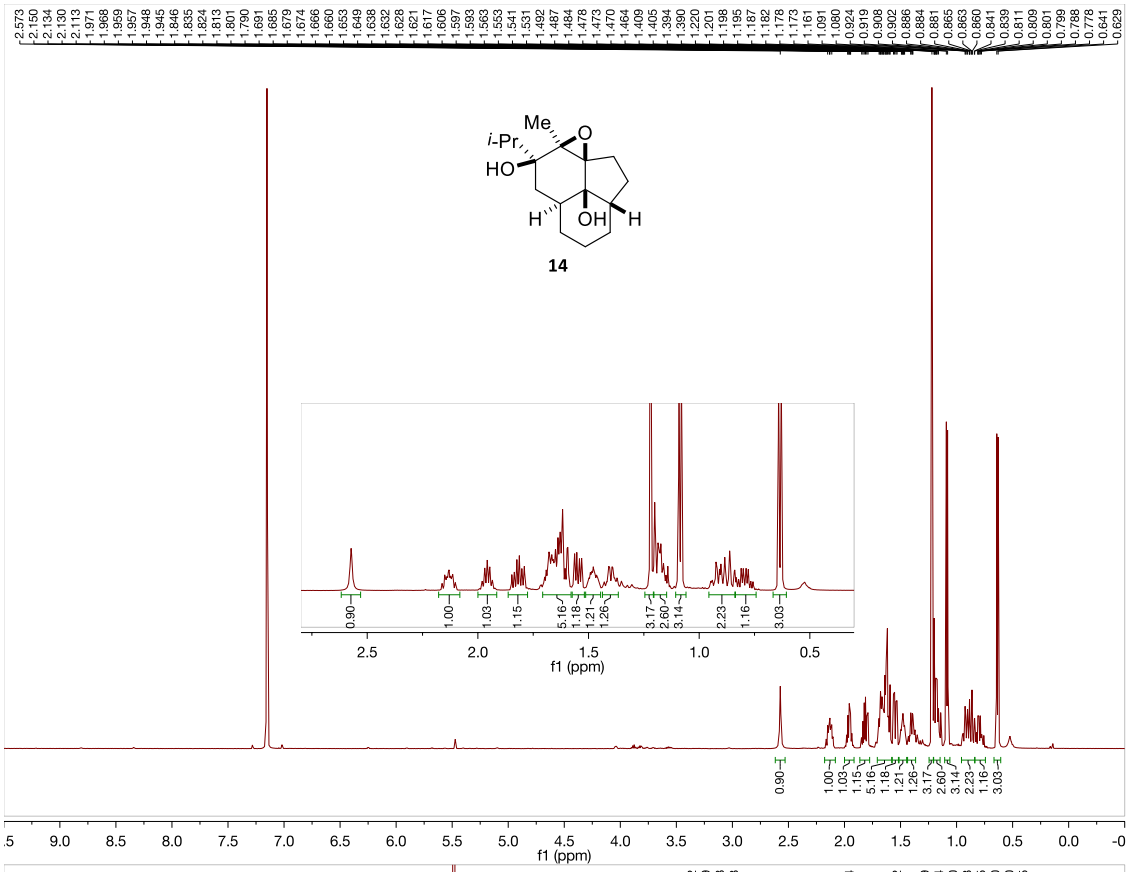

148.481
136.590
79.307
76.103
48.326
47.171
39.930
34.403
32.654
30.542
29.719
28.943
27.351
27.209
26.882
26.859
26.692
24.599
21.490
17.516
f1 (ppm)

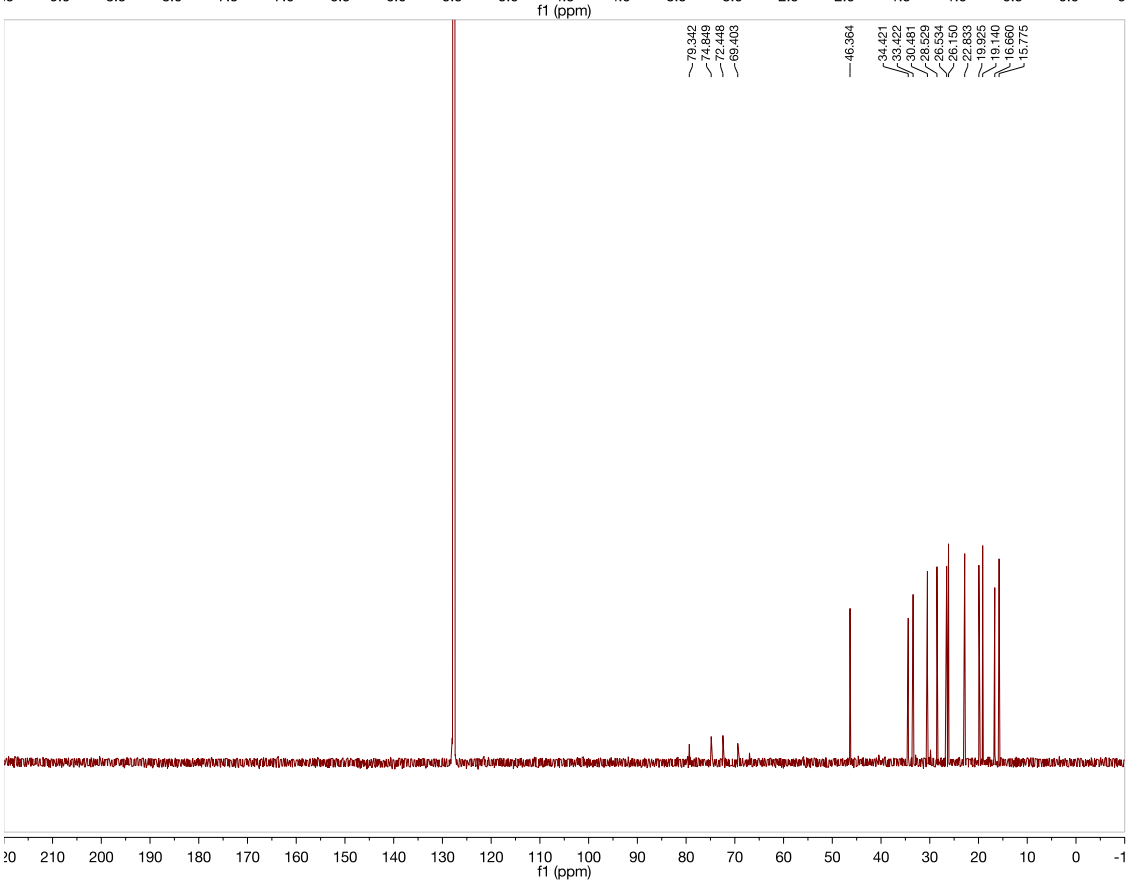

HO
Me
Cy
O
H
OH
H
9
f1 (ppm)

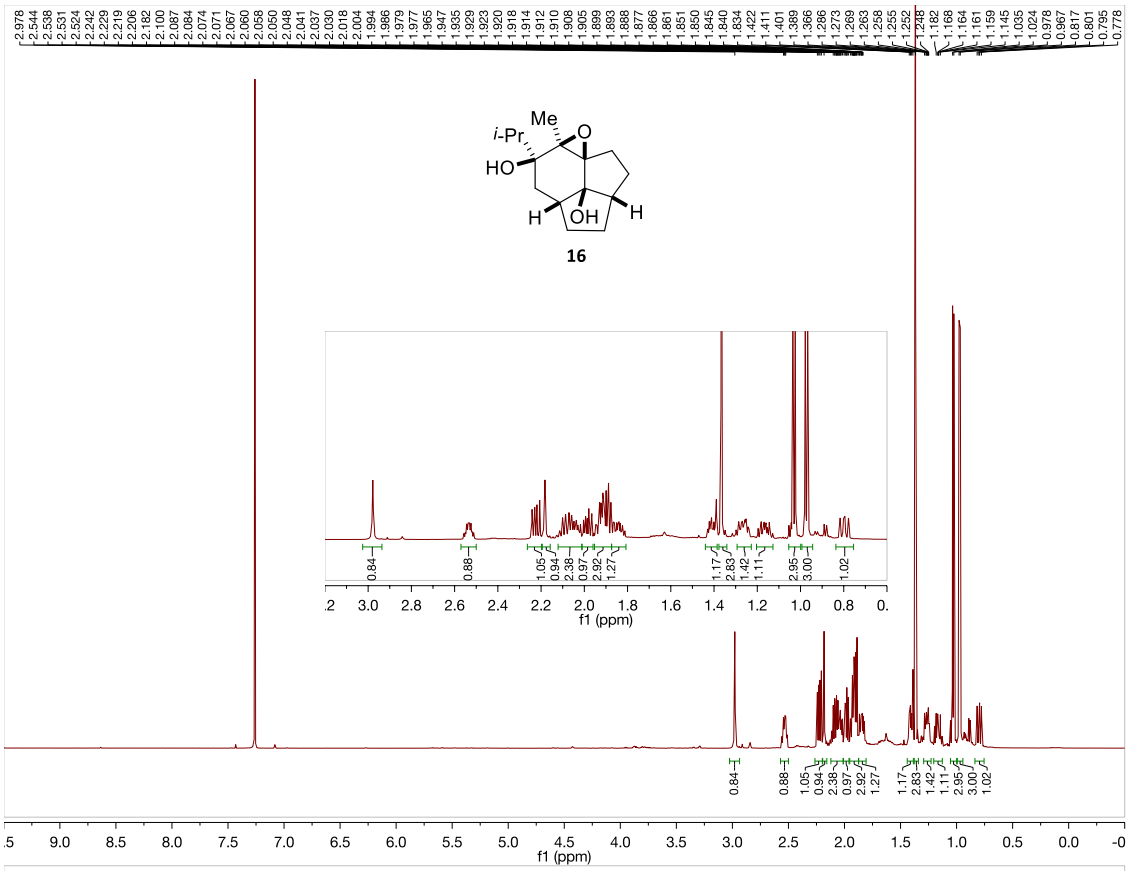

f1 (ppm)

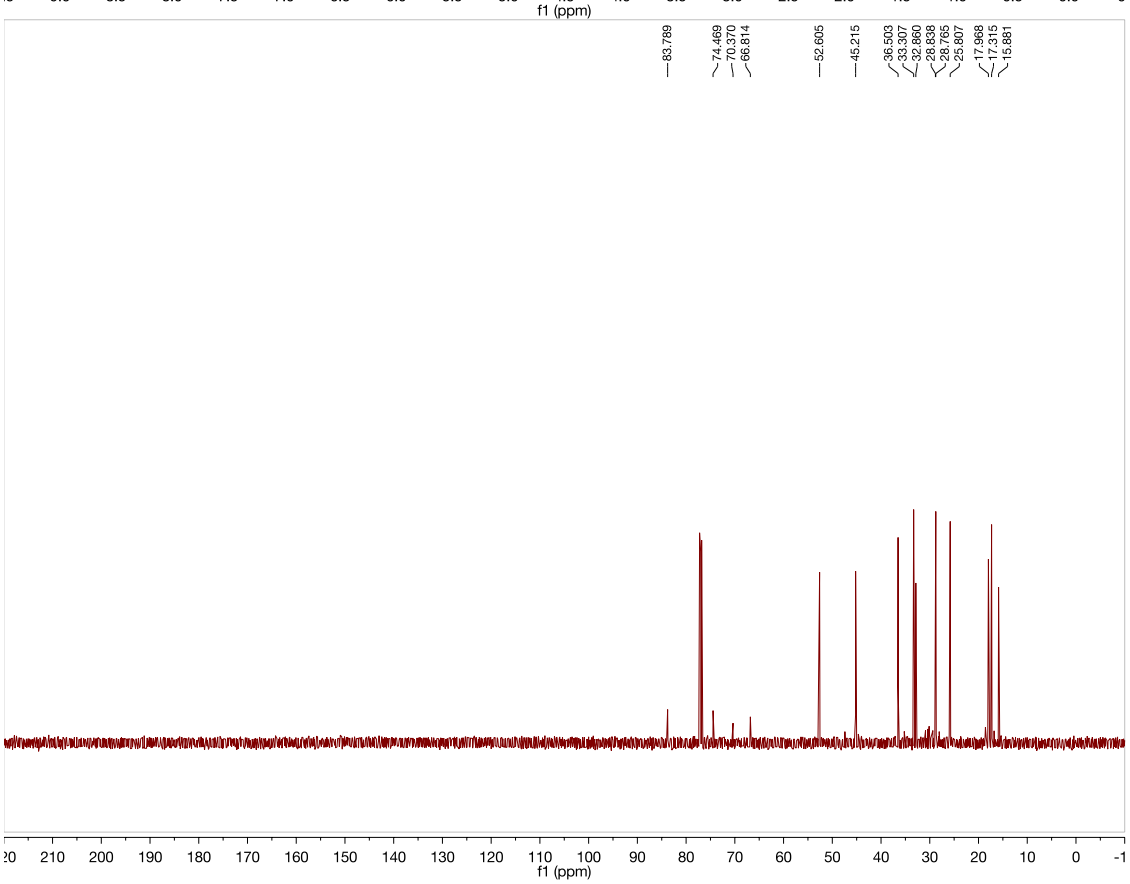

Me
i-Pr
HO
H
OH
H
13
f1 (ppm)

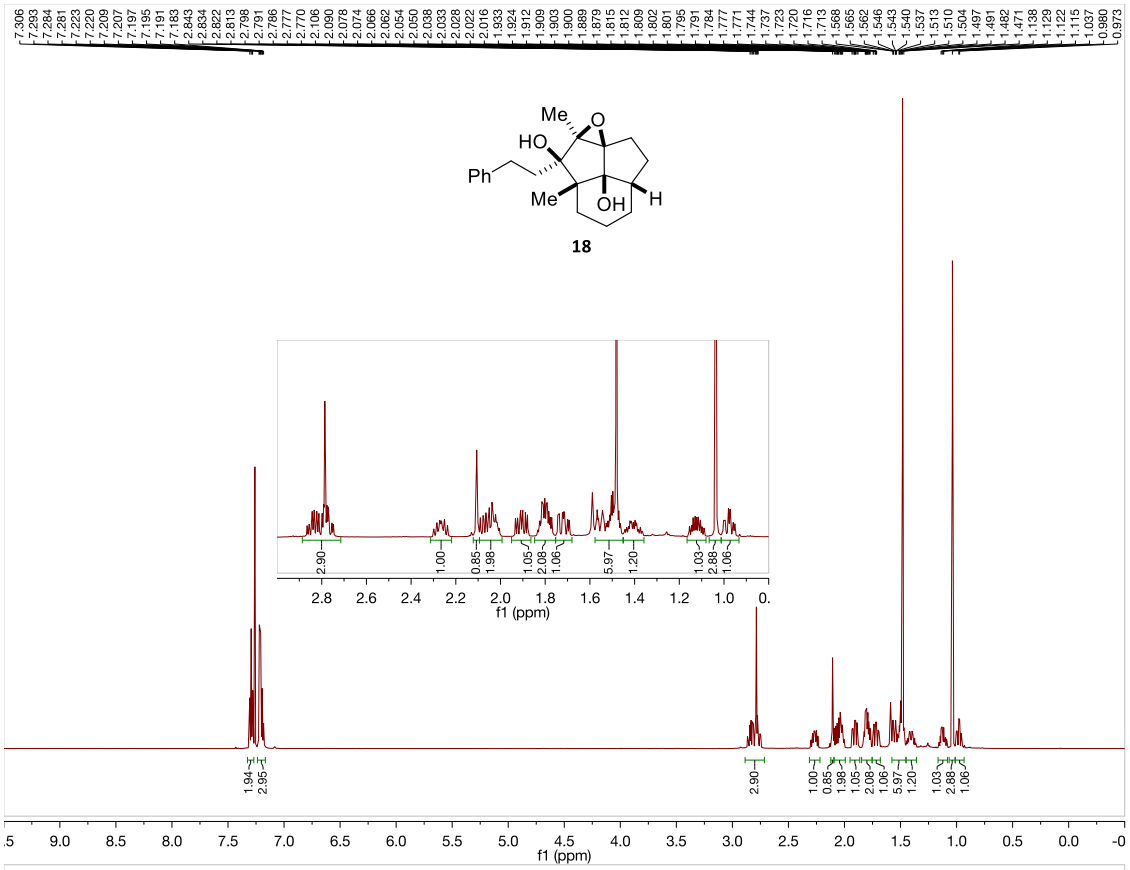

147.972
129.808
76.198
75.622
47.797
37.248
34.192
33.216
31.680
29.180
26.096
23.796
20.496
18.260
15.960
13.643
f1 (ppm)

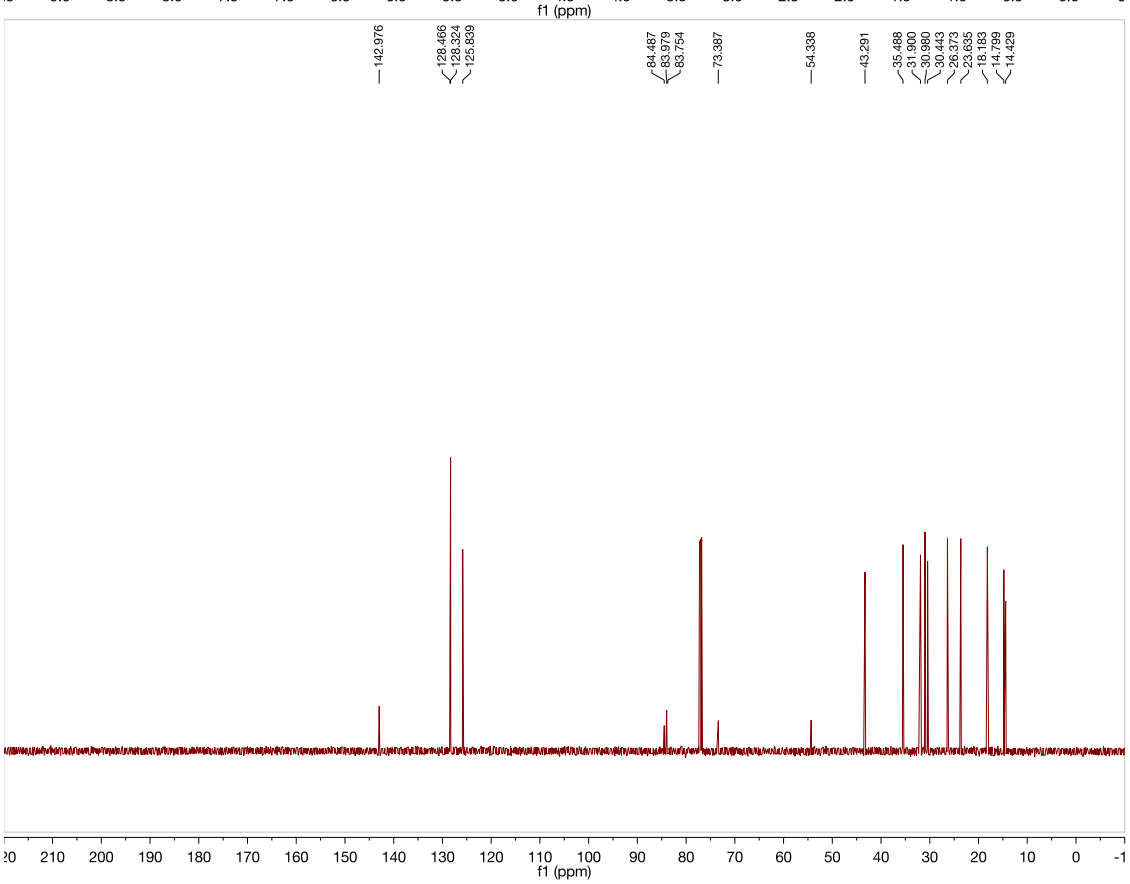

Me
i-Pr
O
HO
H
OH
H
14
f1 (ppm)

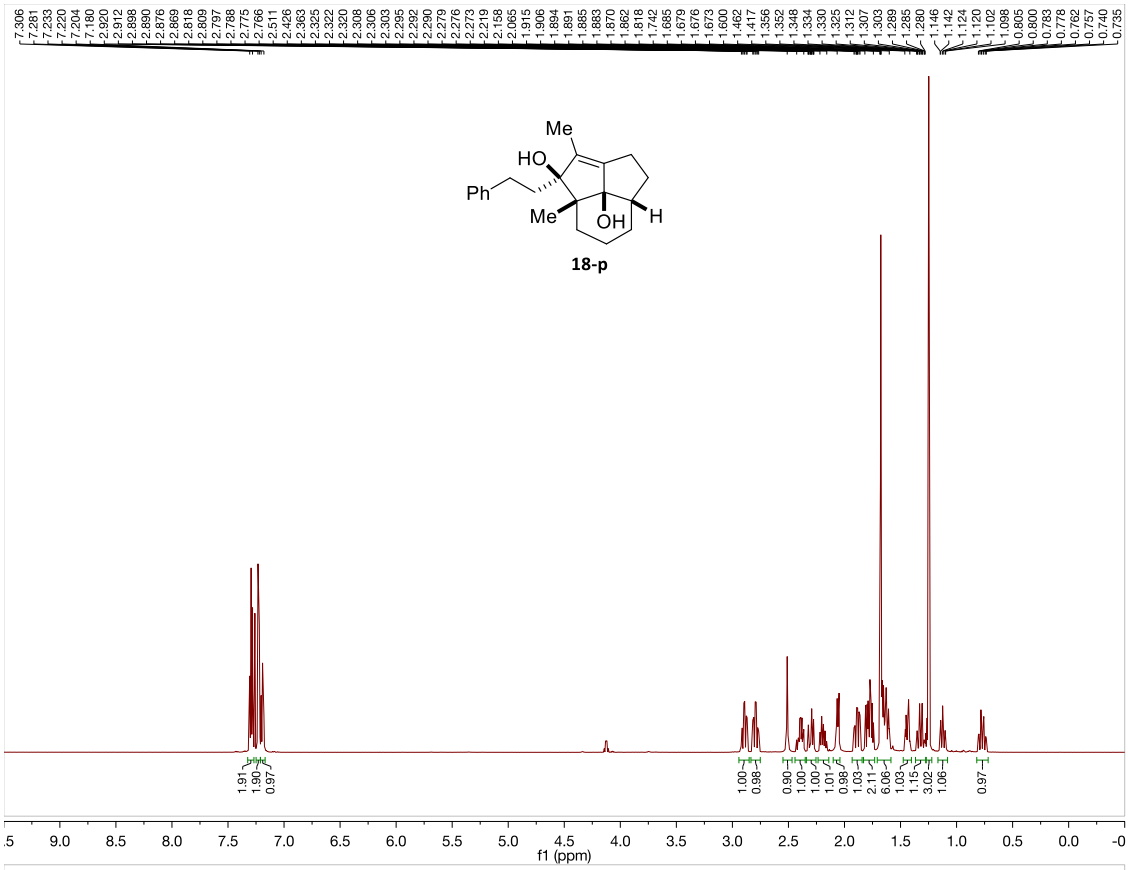

f1 (ppm)

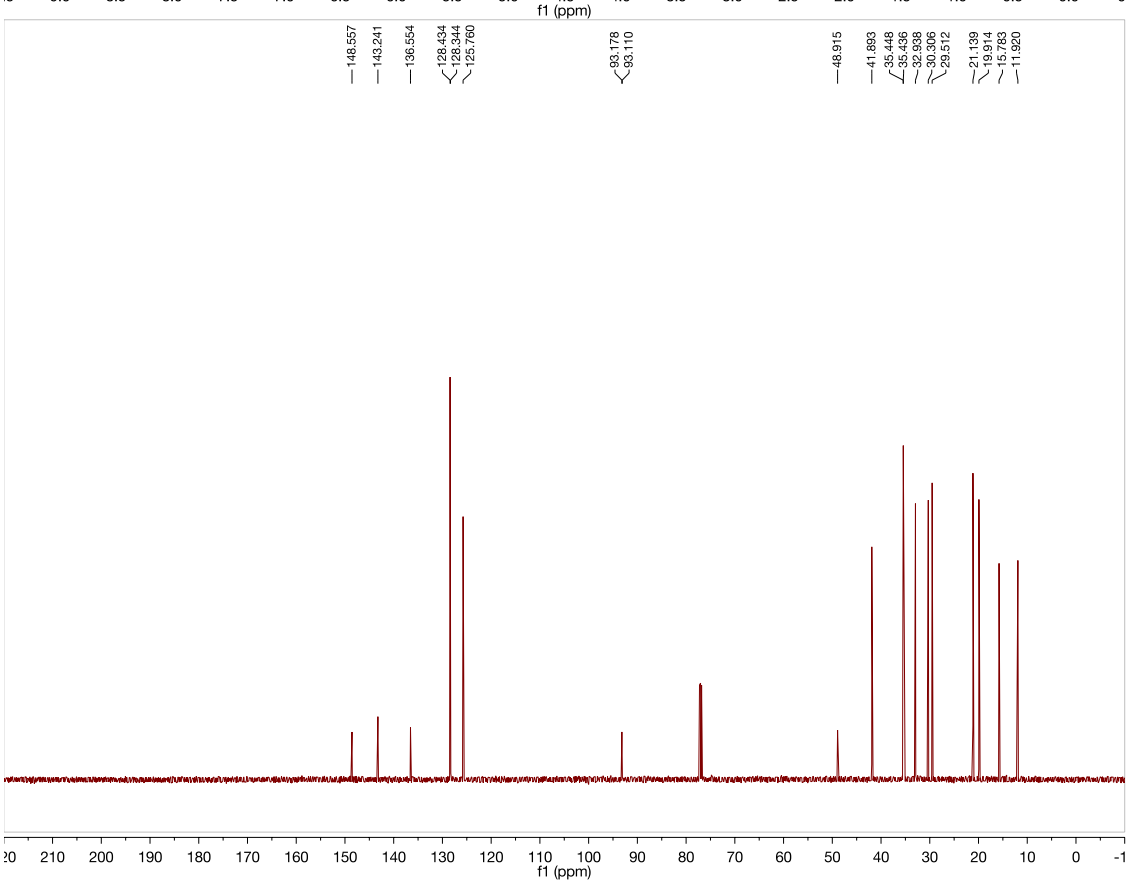

Me
i-Pr
O
HO
H
OH
H
16
f1 (ppm)

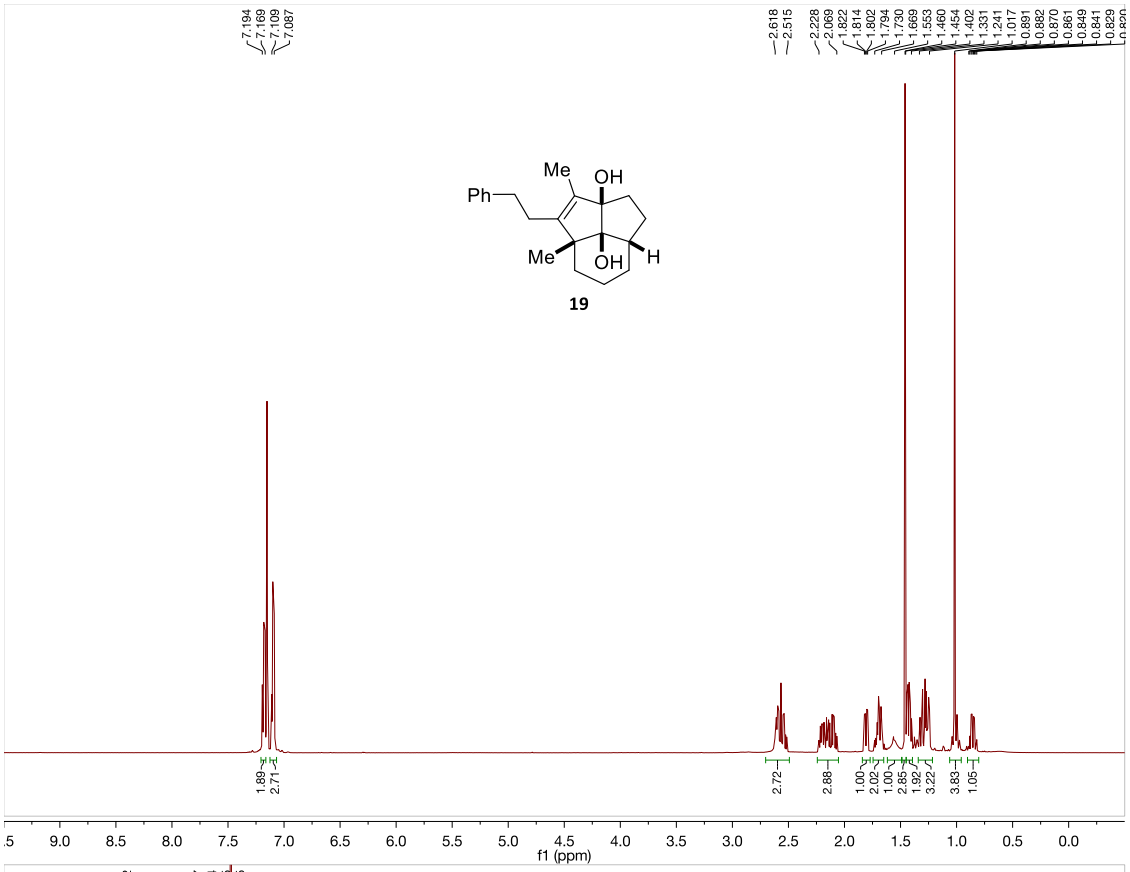

83.789
74.469
70.370
66.814
52.605
45.215
36.503
33.307
32.860
28.838
28.765
25.807
17.968
17.315
15.881
f1 (ppm)

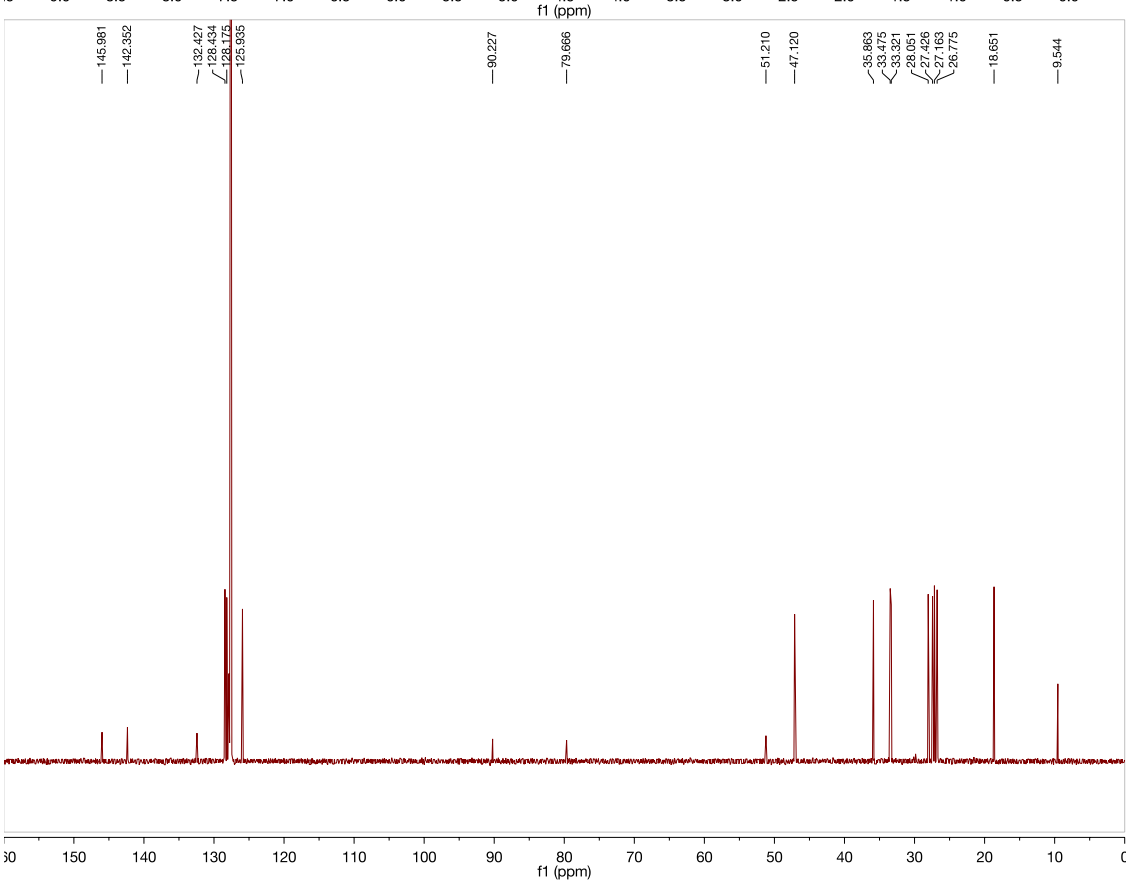

Me
O
HO
Ph
Me
OH
H
18
f1 (ppm)

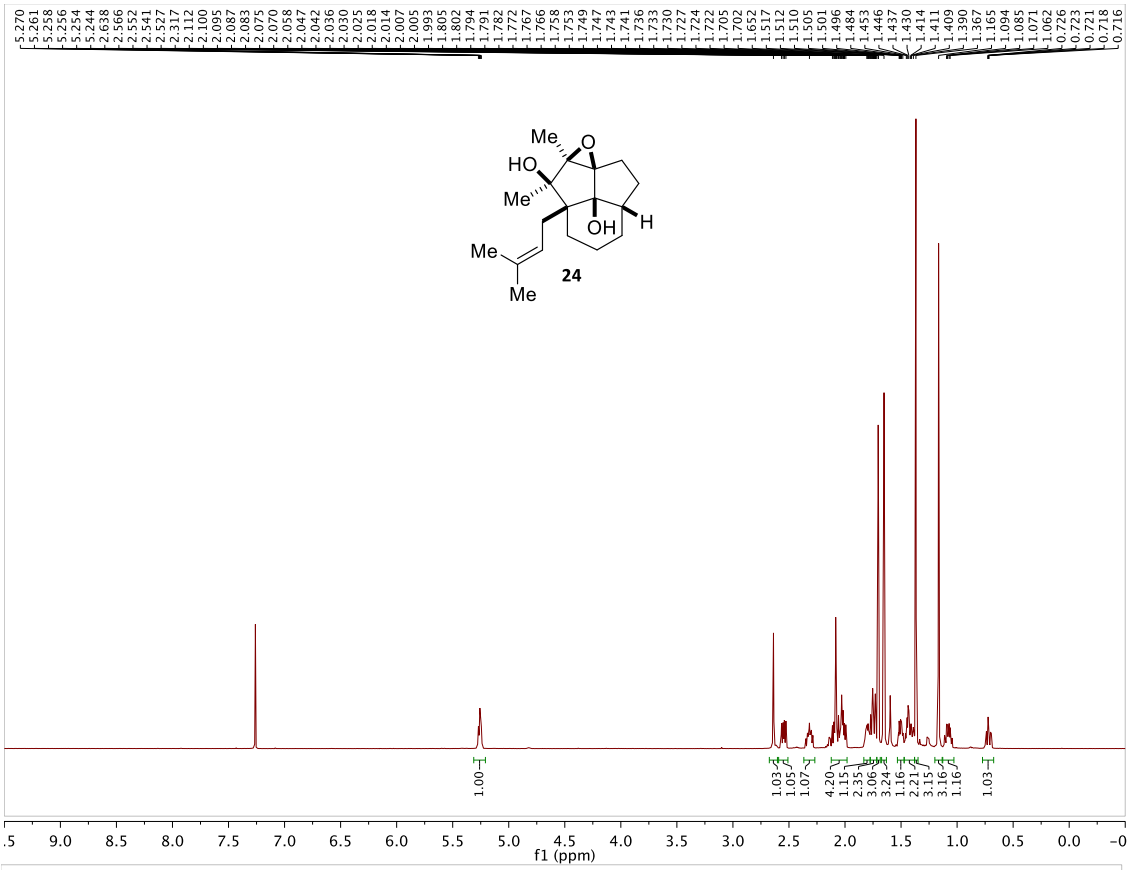

142.976
128.466
128.324
125.839
84.487
83.979
83.754
73.387
54.338
43.291
35.488
31.900
30.980
30.443
26.373
23.635
18.183
14.799
14.429
f1 (ppm)

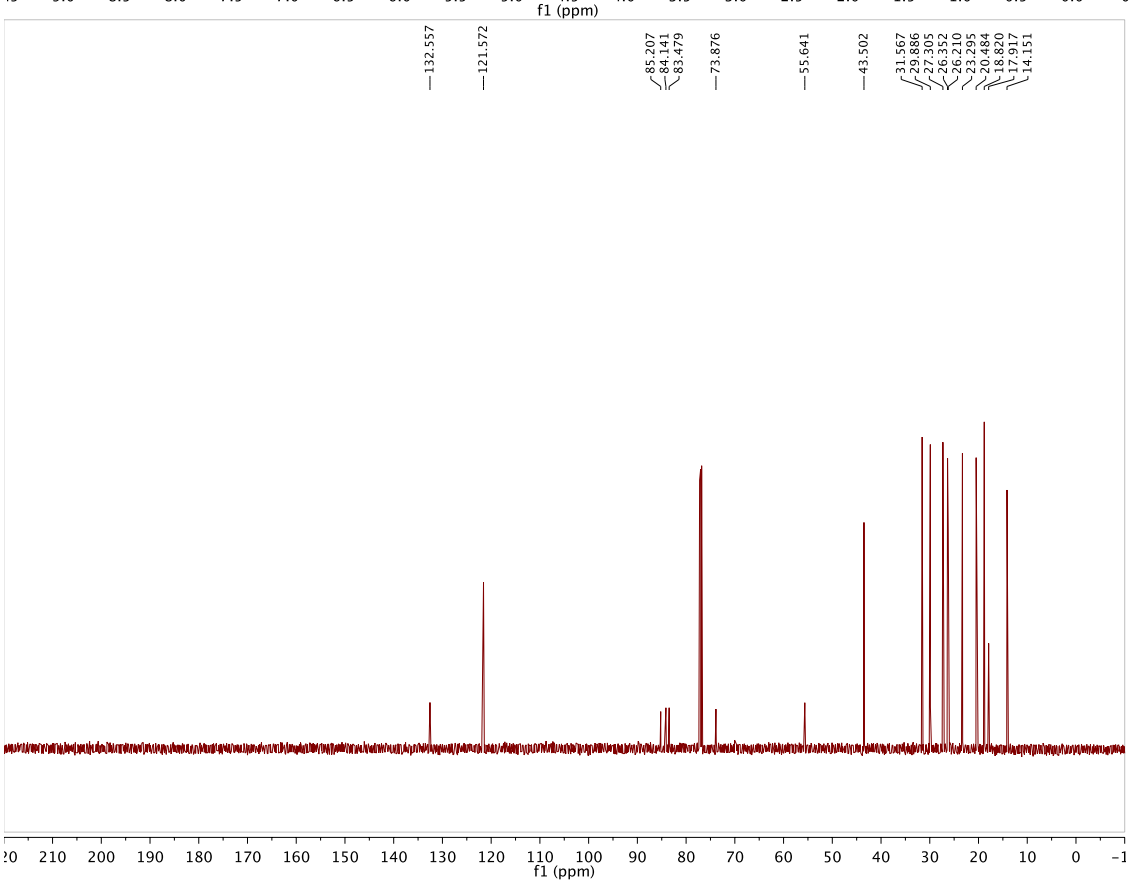

Me
HO
Ph
Me
OH
H
18-p
f1 (ppm)

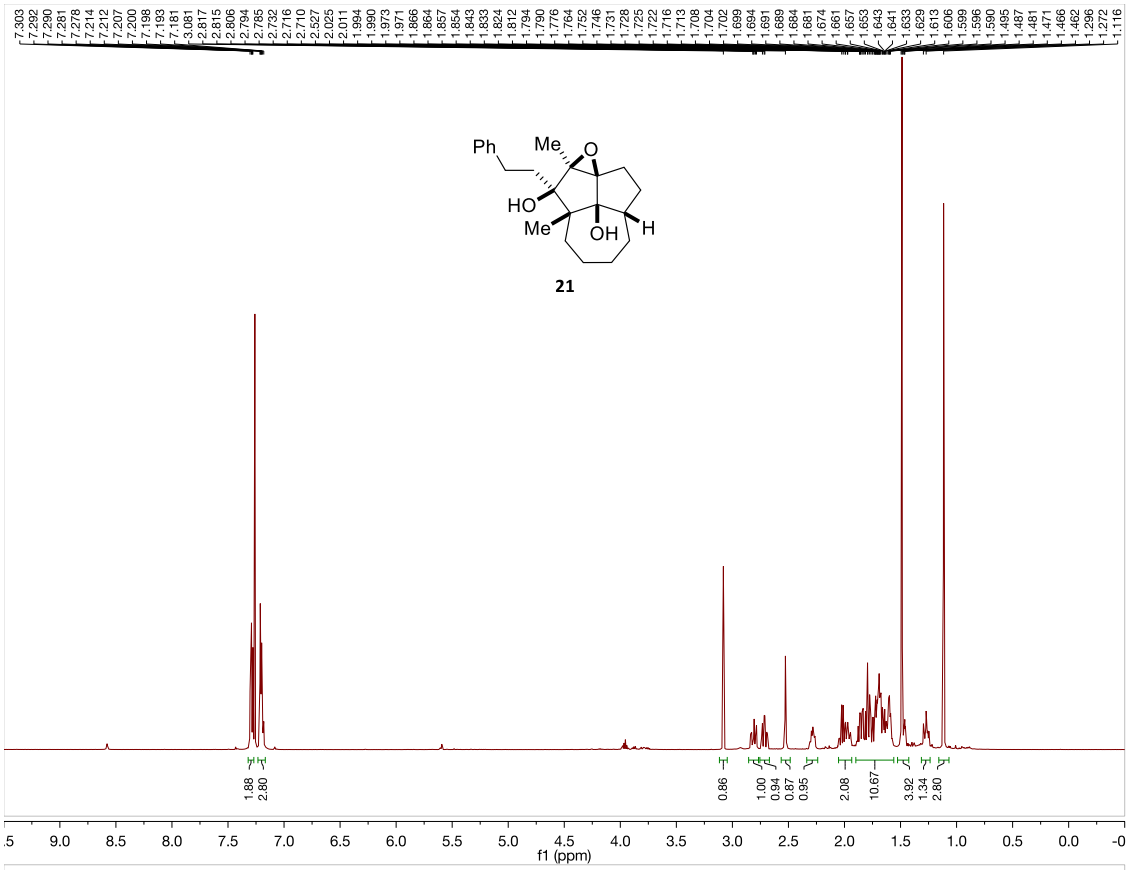

148.557
143.241
136.554
128.434
128.344
125.760
93.178
93.110
48.915
41.893
35.448
35.436
32.938
30.306
29.512
21.139
19.914
15.783
11.920
f1 (ppm)

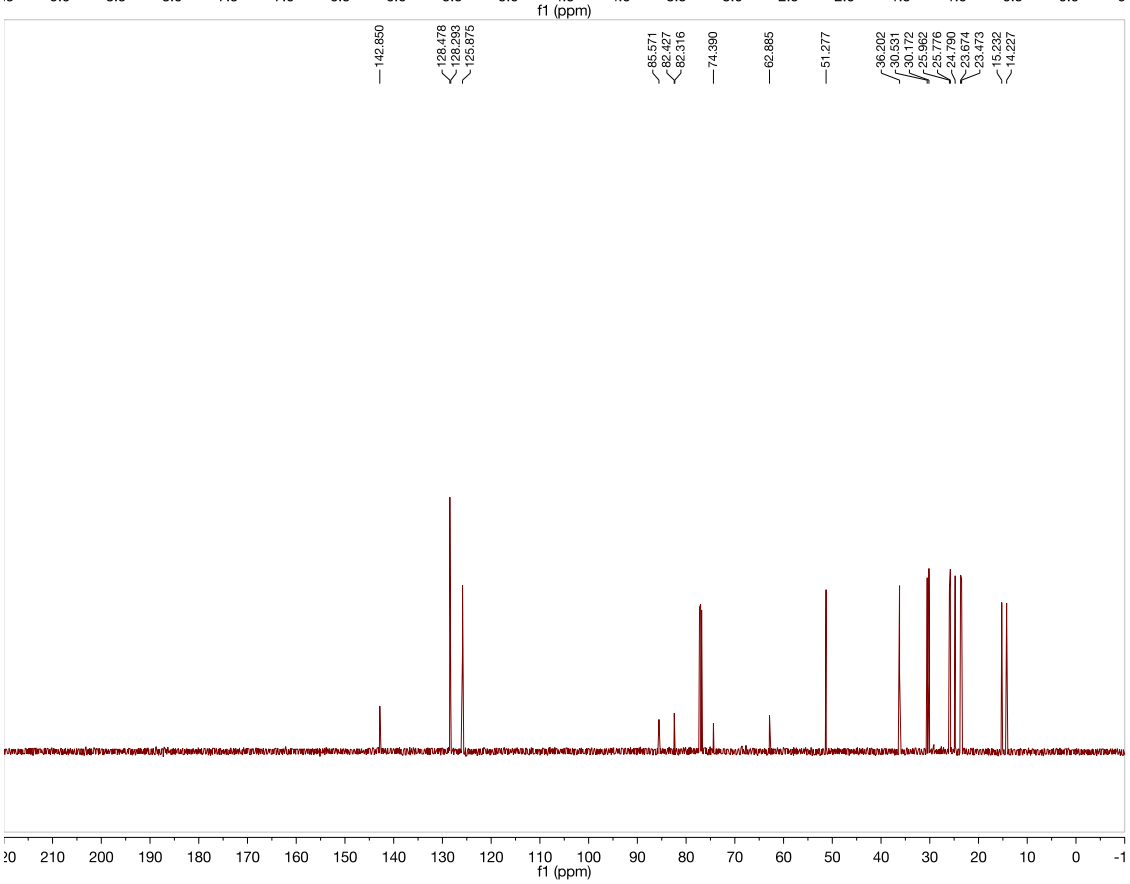

7.194
7.169
7.109
7.087
2.618
2.515
2.228
2.069
1.822
1.814
1.802
1.794
1.730
1.669
1.553
1.460
1.454
1.402
1.331
1.241
1.017
0.891
0.882
0.870
0.861
0.849
0.841
0.829
Me
OH
Ph
Me
OH
H
19
1.89
2.71
2.72
2.88
1.00
2.02
1.00
2.85
1.92
3.22
3.83
1.05
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

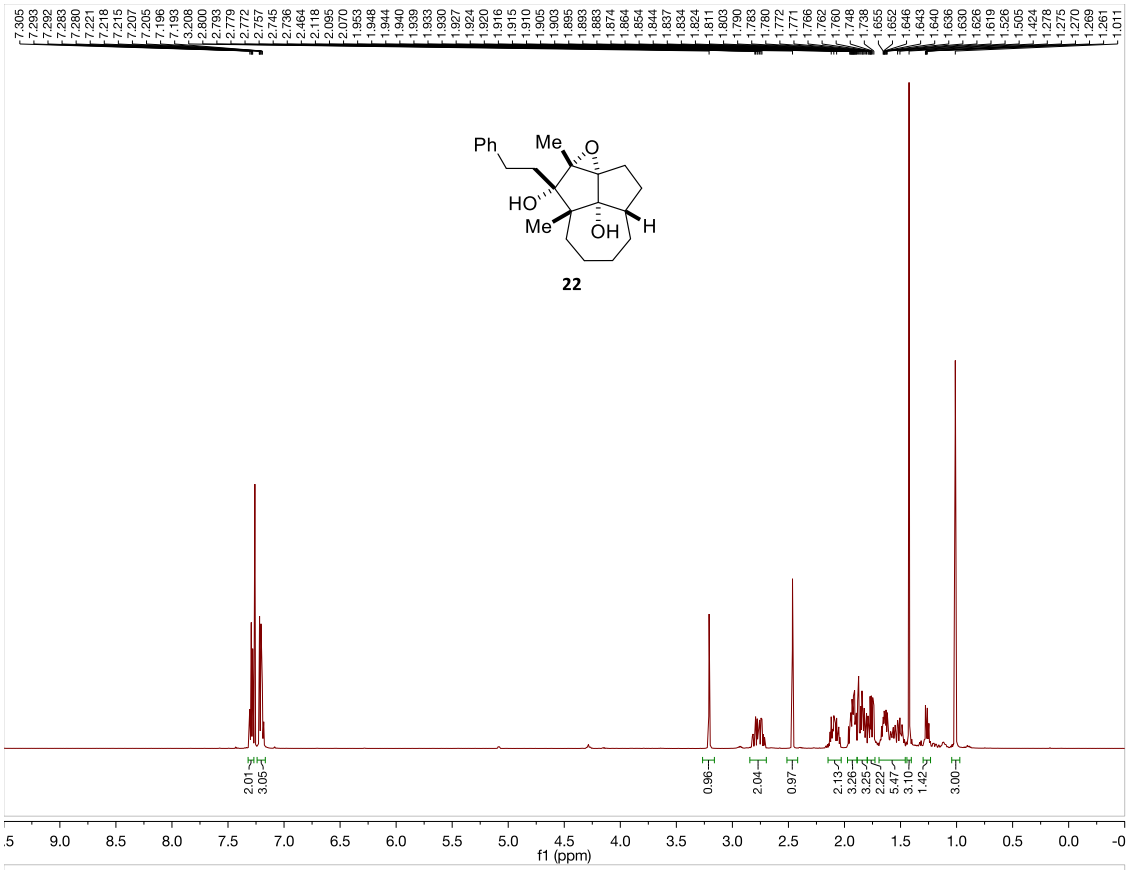

145.981
142.352
132.427
128.434
128.175
125.935
90.227
79.666
51.210
47.120
35.863
33.475
33.321
29.051
27.426
27.163
26.775
18.651
9.544
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

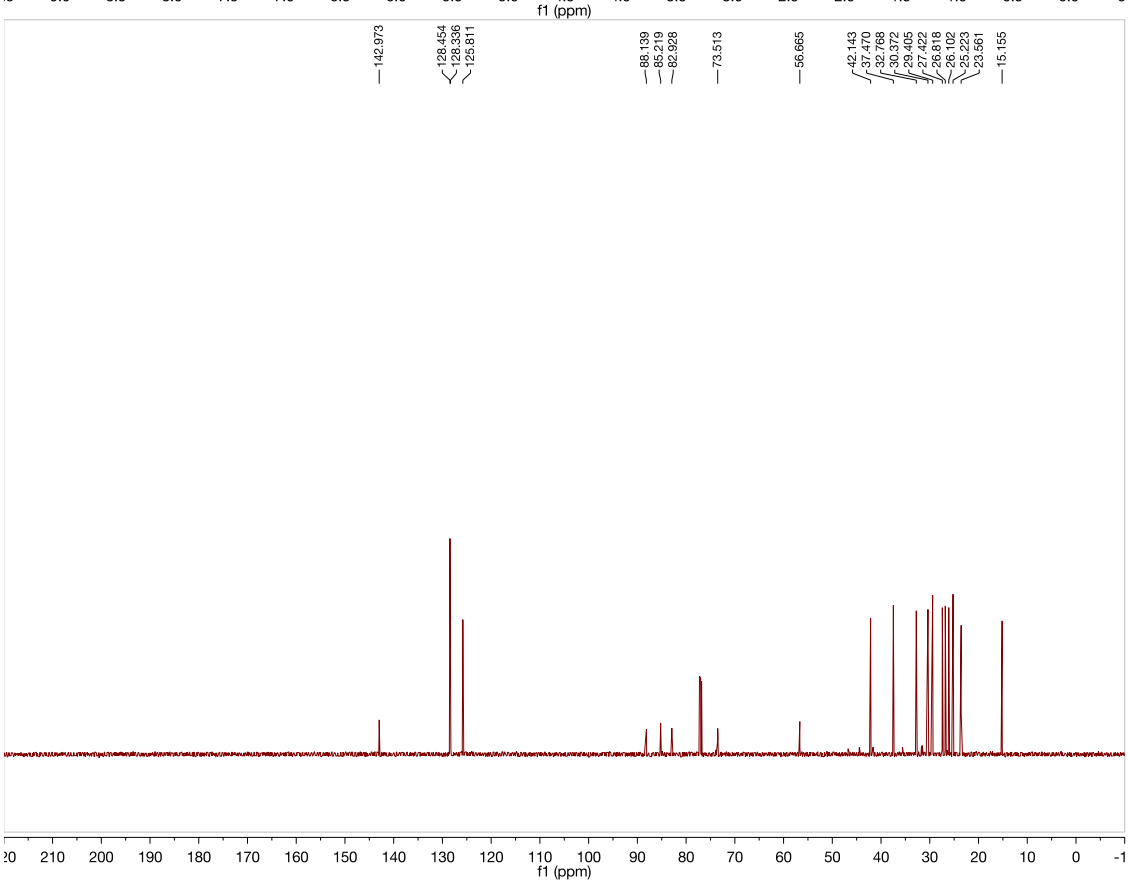

Me
O
HO
Me
OH
H
Me
Me
24
f1 (ppm)


132.557
121.572
85.207
84.141
83.479
73.876
55.641
43.502
31.567
29.886
27.305
26.352
26.210
23.295
20.484
18.820
17.917
14.151
f1 (ppm)


Ph
Me
O
HO
Me
OH
H
21
f1 (ppm)


142.850
128.478
128.293
125.875
85.571
82.427
82.316
74.390
62.885
51.277
36.202
30.531
30.172
25.962
25.776
24.790
23.674
23.473
15.232
14.227
f1 (ppm)


Ph
Me
O
HO
Me
OH
H
22
f1 (ppm)


142.973
128.454
128.336
125.811
88.139
85.219
82.928
73.513
56.665
42.143
37.470
32.768
30.372
29.405
27.422
26.818
26.102
25.223
23.561
15.155
f1 (ppm)