Supporting Information for:

A Copper-catalyzed Double Coupling Enables 3-Step Entry into the Quassinoid Core Architecture

Mathew L. Condakes, Rachel Z. Rosen, Stephen J. Harwood, Thomas J. Maimone

Table of Contents:

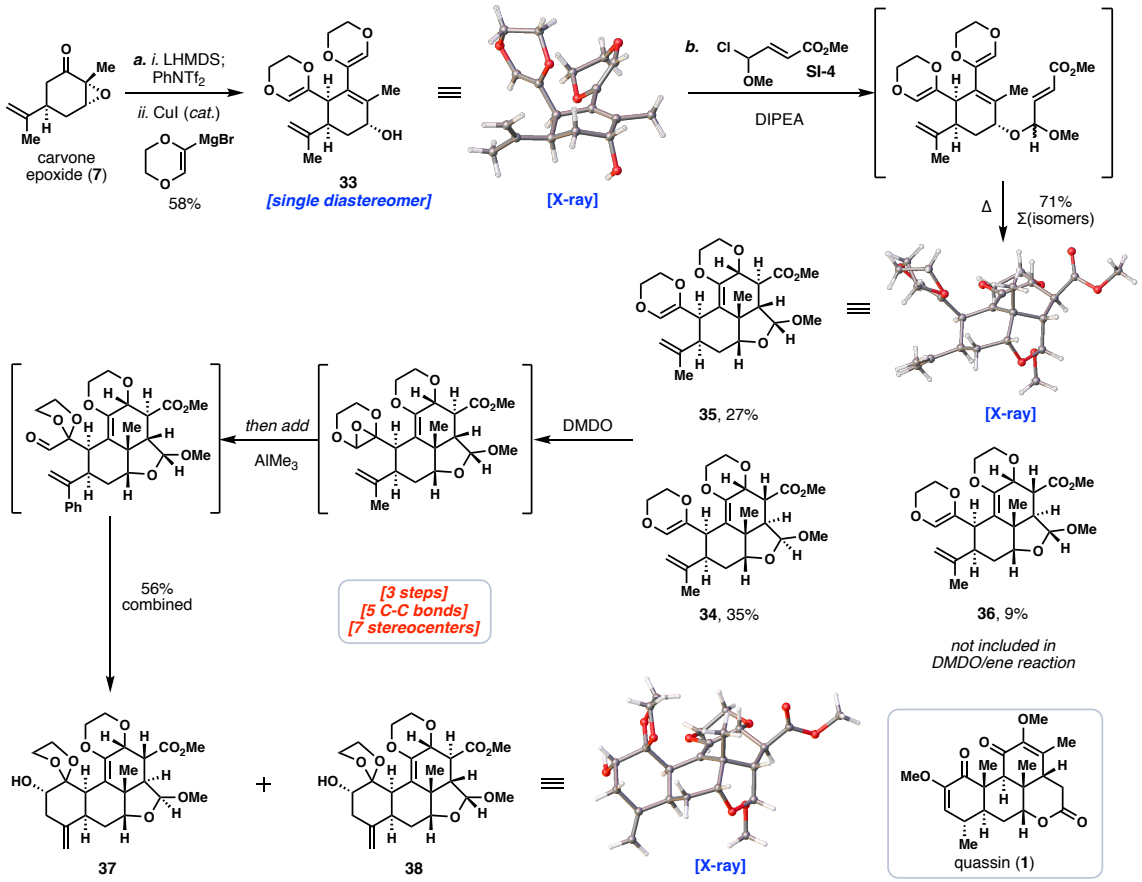
General Procedures:

All reactions were performed in flame- or oven-dried glassware under a positive pressure of nitrogen or argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe. Volatile solvents were removed under reduced pressure rotary evaporation below 35 °C. Analytical and preparative thin-layer chromatography (TLC) were performed using glass plates pre-coated with silica gel (250 μm thickness, 10 μm particle size, Millipore Sigma) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV) and then were stained by submersion in an ethanolic anisaldehyde solution, followed by brief heating on a hot plate. Flash column chromatography was performed employing silica gel purchased from Fisher (60 Å, 230-400 mesh, 40-63 μm).

Anhydrous tetrahydrofuran (THF), diethyl ether (Et_2O), toluene (PhMe), and dichloromethane (DCM) were obtained by passing these previously degassed solvents through activated alumina columns. Hexamethylphosphoramide (HMPA) was distilled over calcium hydride and stored under inert atmosphere. Though commercially available, *cis*-carvone epoxide could also be prepared according to the literature procedure.[1] Additional epoxide substrates were prepared following established literature protocols,[2] with the exception of 2,3-epoxy-2-methyl-cyclohexanone, which is uncharacterized in the literature. Dimethyldioxirane (DMDO) was prepared according to the *Organic Synthesis* procedure.[3] Lithium bis(trimethylsilyl)amide was purchased as a 1.0 M solution in THF from Millipore Sigma and used as received. N-Phenyl-bis(trifluoromethanesulfonamide) was purchased from Oakwood Chemicals and used as received. Grignard reagents were purchased from Millipore Sigma and used as received, except where otherwise indicated. $[Cu(MeCN)_4][PF_6]$ was purchased from Millipore Sigma and used as received. All other solvents and reagents, including additional copper sources, were purchased at the highest commercial grade and used as received, without additional purification.

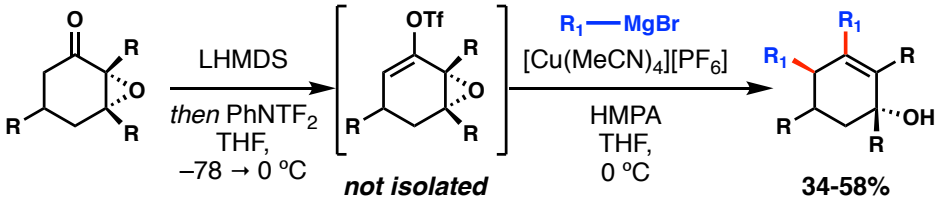
Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Bruker DRX 500 (500 MHz/126 MHz), Bruker AV 500 (500 MHz/126 MHz), Bruker AV 600 (600 MHz/151 MHz), or Bruker AV 700 (700 MHz/176 MHz) spectrometers at 23 °C. Fluorine nuclear magnetic resonance (^{1}F NMR) spectra were recorded on a Bruker AVQ 400 (376 MHz) spectrome-

ter at 23 ºC. Proton chemical shifts are expressed as parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.26, C_6D_5H: δ 7.16, CD_2HOD: δ 3.31). Carbon chemical shifts are expressed as parts per million (ppm, δ scale) and are referenced to the carbon resonance of the NMR solvent ($CDCl_3$: δ 77.16, C_6D_6: 128.06, CD_3OD: δ 49.00). Fluorine chemical shifts are expressed as parts per million (ppm, δ scale) and are not additionally referenced. Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (*J*) in Hertz (Hz), and integration. Infrared (IR) spectra were recorded on a Bruker Alpha FT-IR spectrometer as thin films and are reported in frequency of absorption (cm^{-1}). Optical rotations were recorded on a Perkin Elmer polarimeter, model 241. High-resolution mass spectra were obtained at the QB3/Chemistry Mass Spectrometry Facility at University of California, Berkeley using a Thermo LTQ-FT mass spectrometer, and at the Lawrence Berkeley National Laboratory Catalysis Center using a Perkin Elmer AxION 2 TOF mass spectrometer. X-ray diffraction data for compounds **18**, **21**, **32**, **33**, **35**, and **38** were collected at the Small Molecule X-ray Crystallography Facility (CheXray) at University of California, Berkeley using a Bruker MicroSTAR-H APEX II QUAZAR X-ray source.



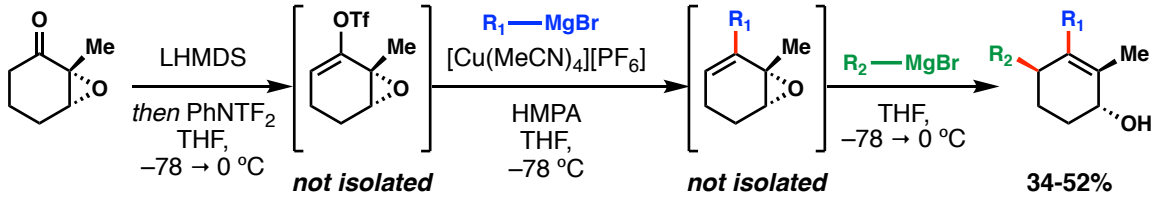
Scheme SI-1: Synthetic route to the full quassinoid core architecture.

Standard Procedure for the Cu-catalyzed double coupling reaction between epoxy ketones and Grignard reagents employing two of the same nucleophiles.



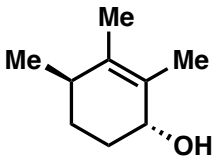
A solution of epoxy ketone (1.0 mmol, 1.0 equiv) in THF (2 mL) was cooled to –78 ºC. LHMDS (1.0 M in THF, 1.0 mL, 1.0 mmol, 1.0 equiv) was added dropwise and the resulting solution was stirred for 10 min. N-Phenyl-bis(trifluoromethanesulfonamide) (357 mg, 1.0 mmol, 1.0 equiv) was then added as a solid and the solution was warmed to 0 ºC and stirred for 10 min. In a separate flask, at 23 ºC, $[Cu(MeCN)_4][PF_6]$ (55 mg, 0.15 mmol, 0.15 equiv) was suspended in THF (1 mL). The desired Grignard reagent (typically 1.0 M in THF, 3.0 mL, 3.0 mmol, 3.0 equiv) was added dropwise to the suspension, followed by HMPA (0.87 mL, 5.0 mmol, 5.0 equiv). The mixture was stirred until homogeneous and cooled to 0 ºC. The so-prepared cuprate solution was then directly added to the vinyl triflate solution and the reaction mixture was stirred at 0 ºC until product formation was complete (typically 1-2 h). The reaction mixture was diluted with Et_2O:hexanes (1:1, 20 mL) and quenched with a 9:1 saturated aqueous ammonium chloride:saturated aqueous ammonium hydroxide solution (5 mL). The biphasic suspension was stirred vigorously until the aqueous layer had turned a deep blue. The layers were separated and the organic layer was further washed with water (2 x 10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica gel chromatography, and due to the instability of products to acid, chromatographic eluents were buffered with triethylamine (typically 27→47% Et_2O in hexanes + 3% Et_3N). Residence time of the compounds on the column was likewise minimized. Products were afforded as solid, single isomers, except where otherwise indicated.

Standard Procedure for the Cu-catalyzed double coupling reaction between epoxy ketones and Grignard reagents employing two different nucleophiles.

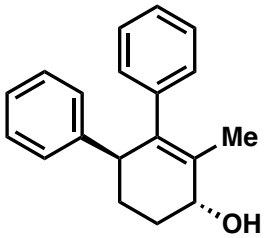


A solution of epoxy ketone (1.0 mmol, 1.0 equiv) in THF (2 mL) was cooled to –78 ºC. LHMDS (1.0 M in THF, 1.0 mL, 1.0 mmol, 1.0 equiv) was added dropwise and the resulting solution was stirred for 10 min. N-Phenyl-bis(trifluoromethanesulfonamide) (1.0 mmol, 1.0 equiv) was then added as a solid and the solution was warmed to 0 ºC and stirred for 10 min before being re-cooled to –78 ºC. In a separate flask, at 23 ºC, $[Cu(MeCN)_4][PF_6]$ (55 mg, 0.15 mmol, 0.15 equiv) was suspended in THF (1 mL). The desired Grignard reagent for cross-coupling (typically 1.0 M in THF, 2.0 mL, 2.0 mmol, 2.0 equiv) was added dropwise to the suspension, followed by HMPA (0.87 mL, 5.0 mmol, 5.0 equiv). The mixture was stirred until homogeneous, cooled briefly to 0 ºC, and then added dropwise to the vinyl triflate solution. Conversion to the cross-coupled product was carefully monitored and addition was stopped when full conversion was observed (typically when only 80-90% of the solution – or *ca*. 1.6-1.8 equiv of Grignard reagent – had been added). At the end of addition, the reaction was stirred for 1 h at –78 ºC. The desired Grignard reagent for allylic substitution (typically 1.0 M in THF, 2.0 mL, 2.0 mmol, 2.0 equiv) was then added dropwise. The solution was allowed to warm to 0 ºC and was stirred at that temperature for a further hour, or until complete conversion to product. The reaction mixture was diluted with Et_2O:hexanes (1:1, 20 mL) and quenched with a 9:1 saturated aqueous ammonium chloride:saturated aqueous ammonium hydroxide solution (5 mL). The biphasic suspension was stirred vigorously until the aqueous layer had turned a deep blue. The layers were separated and the organic layer was further washed with water (2 x 10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica gel chromatography (typically 27→47% Et_2O in hexanes + 3% Et_3N). Products were afforded as solid, single isomers, except where otherwise indicated.

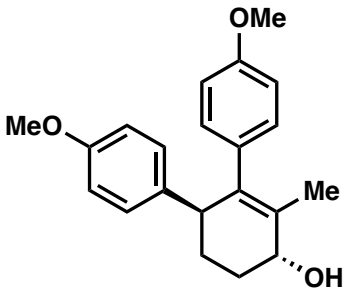
Products from coupling two of the same nucleophiles:



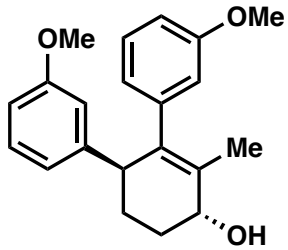
Substrate 12: The standard procedure was followed with 2,3-epoxy-2-methyl-cyclohexanone (126 mg, 1.0 mmol, 1.0 equiv) and MeMgBr (3.0 M in Et_2O diluted with THF to 1.0 M, 3.0 mL, 3.0 mmol, 3.0 equiv) to afford **12** (62 mg, 0.44 mmol, 44%) as a white solid (> 20:1 d.r.). ^{1}H NMR (700 MHz, $CDCl_3$) δ 3.89 (d, *J* = 5.5 Hz, 1H), 2.09 – 2.03 (m, 1H), 1.90 – 1.82 (m, 2H), 1.73 (s, 3H), 1.64 (s, 3H), 1.64 – 1.60 (m, 1H), 1.36 (d, *J* = 5.5 Hz, 1H), 1.35 – 1.31 (m, 1H), 0.98 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 135.6, 127.4, 69.6, 34.7, 28.2, 25.7, 18.5, 18.0, 16.9; IR (thin film) ν_{max}: 3349, 2923, 2853, 1668, 1462 cm^{-1}; HRMS (EI) calcd for $C_9H_{16}O$: 140.1201, found: 140.1203.



Substrate 13: Magnesium turnings (112 mg, 4.8 mmol, 4.8 equiv) were suspended in THF (3.0 mL) and a drop of 1,2-dibromoethane (< 10 μL) was added. Separately, bromobenzene (0.42 mL, 4.0 mmol, 4.0 equiv) was dissolved in THF (1.0 mL) and then added dropwise to the magnesium suspension. After Grignard initiation, addition was slowed so as to maintain a gentle reflux. Upon completion of addition, the resulting grey solution was stirred at room temperature for a further hour. The so-prepared phenylmagnesium bromide solution was used in the coupling step without further purification (1.0 M assumed). The standard procedure was followed with 2,3-epoxy-2-methyl-cyclohexanone (126 mg, 1.0 mmol, 1.0 equiv) and phenylmagnesium bromide (1.0 M in THF, 3.0 mL, 3.0 mmol, 3.0 equiv) to afford **13** (122 mg, 0.46 mmol, 46%) as a white solid (> 20:1 d.r.). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.20 (dd, *J* = 8.5, 7.0 Hz, 2H), 7.18 (dd, *J* = 8.5, 7.0 Hz, 2H), 7.13 (dd, *J* = 8.5, 1.3 Hz, 2H), 7.11 (tt, *J* = 7.0, 1.3 Hz, 1H), 7.10 (tt, J = 7.0, 1.3 Hz, 1H), 7.06 (dd, *J* = 8.4, 1.3 Hz, 2H), 4.25 – 4.23 (m, 1H), 3.78 (dq, *J* = 5.8, 1.5 Hz, 1H), 2.36 – 2.30 (m, 1H), 1.96 – 1.89 (m, 1H), 1.81 (d, *J* = 1.5 Hz, 3H), 1.74 – 1.69 (m, 2H), 1.67 (br s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 143.2, 142.3, 137.7, 133.4, 128.9 (4C, overlapping), 128.1 (2C), 127.9 (2C), 126.4, 126.1, 68.7, 46.9, 27.3, 27.3, 18.1; IR (thin film) ν_{max}: 3146, 2937, 1601, 619 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{20}O$: 264.1514, found: 264.1518.

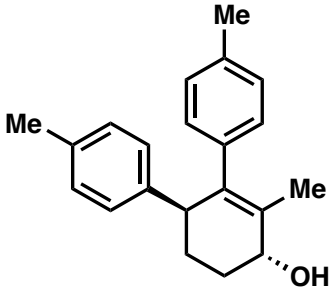


Substrate 14: The standard procedure was followed with 2,3-epoxy-2-methyl-cyclohexanone (126 mg, 1.0 mmol, 1.0 equiv) and 4-methoxyphenylmagnesium bromide (0.5 M in THF, 6.0 mL, 3.0 mmol, 3.0 equiv) to afford **14** (168 mg, 0.52 mmol, 52%) as a white solid (> 20:1 d.r.). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.03 (d, *J* = 8.1 Hz, 2H), 6.98 (d, *J* = 8.1 Hz, 2H), 6.75 (d, *J* = 8.1 Hz, 2H), 6.72 (d, *J* = 8.1 Hz, 2H), 4.20 (br s, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.72 – 3.69 (m, 1H), 2.28 (td, *J* = 13.4, 5.6 Hz, 1H), 1.88 (tdd, *J* = 13.4, 3.4, 2.9 Hz, 1H), 1.81 (s, 3H), 1.72 – 1.62 (m, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.0, 157.9, 137.5, 135.4, 134.7, 133.0, 129.9 (2C), 129.8 (2C), 113.5 (2C), 113.3 (2C), 68.7, 55.3, 55.2, 46.1, 27.3, 27.1, 18.2; IR (thin film) ν_{max}: 3352, 2930, 1607, 1508, 1240 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{24}O_3Na$ $[M+Na]^+$: 347.1623, found: 347.1628.

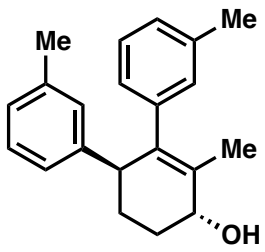


Substrate 15: Magnesium turnings (112 mg, 4.8 mmol, 4.9 equiv) were suspended in THF (3.0 mL) and a drop of 1,2-dibromoethane (< 10 μL) was added. Separately, 3-bromoanisole (0.51 mL, 4.0 mmol 4.0 equiv) was dissolved in THF (1.0 mL) and then added dropwise to the magnesium suspension. After Grignard initiation, addition was slowed so as to maintain a gentle reflux. Upon completion of addition, the resulting grey solution was stirred at room temperature for a further hour. The so-prepared 3-methoxyphenylmagnesium bromide solution was used in the coupling step without further purification (1.0 M assumed). The standard procedure was followed with 2,3-epoxy-2-methyl-cyclohexanone (126 mg, 1.0 mmol, 1.0 equiv) and 3-methoxyphenylmagnesium bromide (1.0 M in THF, 3.0 mL, 3.0 mmol, 3.0 equiv) to afford **15** (142 mg, 0.44 mmol, 44%) as a white solid (> 20:1 d.r.). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.13 (t, *J* = 7.9 Hz, 1H), 7.10 (t, *J* = 7.9 Hz, 1H), 6.74 (dt, *J* = 7.9, 1.5 Hz, 1H), 6.68 (t, *J* = 2.1 Hz, 1H), 6.66 (dd, J = 7.9, 2.1 Hz, 1H), 6.66 (dd, J = 7.9 2.1 Hz, 1H), 6.66 (ddd, J = 7.9, 2.5, 1.5 Hz, 1H), 6.61 (dd, *J* = 2.5, 1.5 Hz, 1H), 4.21 (br d, *J* = 5.8 Hz, 1H), 3.75 (s, 3H), 3.73 (br dq, J = 5.1, 1.5 Hz, 1H), 3.70 (s, 3H), 2.34 – 2.26 (m, 1H), 1.97 – 1.89 (m, 1H), 1.81 (d, *J* = 1.5 Hz, 3H), 1.73 – 1.68 (m, 2H), 1.65 (d, *J* = 5.8 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.5, 159.2, 145.0, 143.7, 137.6, 133.5, 129.0, 128.8,

121.54, 121.48, 115.2, 114.8, 111.8, 111.0, 68.7, 55.3, 55.2, 46.8, 27.3, 27.2, 18.2; IR (thin film) ν_{max}: 3247, 2938, 1604, 1575, 1480, 1048 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{24}O_3Na$ $[M+Na]^+$: 347.1618, found: 347.1615.

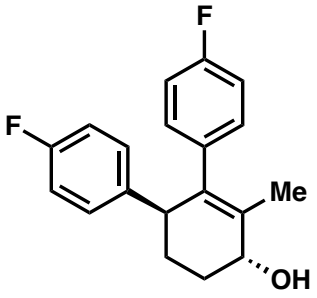


Substrate 16: Magnesium turnings (112 mg, 4.8 mmol, 4.9 equiv) were suspended in THF (3.0 mL) and a drop of 1,2-dibromoethane (< 10 μL) was added. Separately, 4-bromotoluene (0.49 mL, 4.0 mmol 4.0 equiv) was dissolved in THF (1.0 mL) and then added dropwise to the magnesium suspension. After Grignard initiation, addition was slowed so as to maintain a gentle reflux. Upon completion of addition, the resulting grey solution was stirred at room temperature for a further hour. The so-prepared 4-tolylmagnesium bromide solution was used in the coupling step without further purification (1.0 M assumed). The standard procedure was followed with 2,3-epoxy-2-methyl-cyclohexanone (126 mg, 1.0 mmol, 1.0 equiv) and 4-tolylmagnesium bromide (1.0 M in THF, 3.0 mL, 3.0 mmol, 3.0 equiv) to afford **16** (116 mg, 0.44 mmol, 44%) as a white solid (> 20:1 d.r.). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.02 (s, 4H), 6.99 (d, J = 8.0 Hz, 2H), 6.96 (d, J = 8.0 Hz, 2H), 4.20 (dd, J = 4.4, 2.4 Hz, 1H), 3.74 (dq, J = 5.7, 1.4 Hz, 1H), 2.30 (dddd, J = 15.2, 12.9, 5.7, 2.4 Hz, 1H), 2.26 (s, 3H), 2.24 (s, 3H), 1.88 (tt, J = 15.2, 13.9, 4.4 Hz, 1H), 1.81 (d, J = 1.4 Hz, 3H), 1.71 – 1.64 (m, 2H), 1.63 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 140.2, 139.4, 137.7, 135.9, 135.5, 133.0, 128.82 (2C), 128.79 (2C), 128.77 (2C), 128.6 (2C), 68.7, 46.4, 27.3, 27.1, 21.2, 21.1, 18.3; IR (thin film) ν_{max}: 3265, 2937 1511, 814 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{24}O$: 292.1827, found: 292.1823.

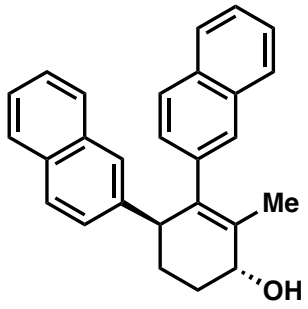


Substrate 17: Magnesium turnings (112 mg, 4.8 mmol, 4.8 equiv) were suspended in THF (3.0 mL) and a drop of 1,2-dibromoethane (< 10 μL) was added. Separately, 3-bromotoluene (0.49 mL, 4.0 mmol 4.0 equiv) was dissolved in THF (1.0 mL) and then added dropwise to the magnesium suspension. After Grignard initiation, addition was slowed so as to maintain a gentle reflux. Upon completion of addition, the resulting grey solution was stirred at room temperature for a further hour. The so-

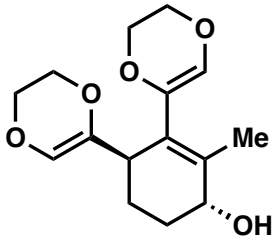
prepared 3-tolylmagnesium bromide solution was used in the coupling step without further purification (1.0 M assumed). The standard procedure was followed with 2,3-epoxy-2-methyl-cyclohexanone (126 mg, 1.0 mmol, 1.0 equiv) and 3-tolylmagnesium bromide (1.0 M in THF, 3.0 mL, 3.0 mmol, 3.0 equiv) to afford **17** (110 mg, 0.42 mmol, 42%) as a white solid (10:1 d.r., major reported). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.10 (t, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 7.7 Hz, 1H), 6.98 – 6.89 (m, 5H), 6.85 (d, *J* = 7.6 Hz, 1H), 4.22 (s, 1H), 3.74 (d, *J* = 5.6 Hz, 1H), 2.34 – 2.24 (m, 1H), 2.28 (s, 3H), 2.26 (s, 3H), 1.91 (td, *J* = 13.1, 5.6 Hz, 1H), 1.81 (s, 3H), 1.73 – 1.65 (m, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 143.1, 142.3, 137.8, 137.6, 137.3, 133.1, 129.8, 129.6, 127.8, 127.7, 127.1, 126.8, 126.0, 125.9, 68.7, 46.7, 27.2, 27.1, 21.60, 21.57, 18.2. IR (thin film) ν_{max}: 3170, 2934, 1604, 1484 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{24}ONa$ $[M+Na]^+$: 315.1719, found: 315.1720.



Substrate 18: The standard procedure was followed with 2,3-epoxy-2-methyl-cyclohexanone (126 mg, 1.0 mmol, 1.0 equiv) and 4-fluorophenylmagnesium bromide (1.0 M in THF, 3.0 mL, 3.0 mmol, 3.0 equiv) to afford **18** (128 mg, 0.43 mmol, 43%) as a white solid (> 20:1 d.r.). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (dd, *J* = 8.5, 5.6 Hz, 2H), 7.00 (dd, *J* = 8.5, 5.6 Hz, 2H), 6.88 (t, *J* = 8.5 Hz, 2H), 6.87 (t, *J* = 8.5 Hz, 2H), 4.23 (dt, *J* = 4.7, 3.0 Hz, 1H), 3.72 (tq, *J* = 3.0, 1.6 Hz, 1H), 2.31 (tdd, *J* = 13.2, 5.7, 3.0 Hz, 1H), 1.88 (dddd, *J* = 14.0, 13.2, 5.0, 3.0 Hz, 1H), 1.79 (d, *J* = 1.6 Hz, 3H), 1.76 (d, *J* = 4.7 Hz, 1H), 1.71 (ddt, *J* = 14.0, 5.7, 3.0 Hz, 1H), 1.66 (ddt, *J* = 13.2, 5.0, 3.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.42 (d, J = 245 Hz), 161.39 (d, J = 242 Hz), 138.7 (d, *J* = 3.2 Hz), 137.8 (d, *J* = 3.5 Hz), 136.6, 134.1, 130.4 (d, *J* = 7.7 Hz, 2C), 130.1 (d, *J* = 7.9 Hz, 2C), 115.0 (d, J = 21 Hz, 2C), 114.9 (d, J = 21 Hz, 2C), 68.4, 46.2, 27.22, 27.16, 18.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ –115.30 (tt, *J* = 8.5, 5.6 Hz), –116.38 (tt, *J* = 8.5, 5.6 Hz); IR (thin film) ν_{max}: 3333, 2934, 1602, 1505 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{18}OF_2$: 300.1326, found: 300.1326.

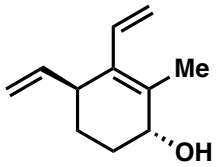


Substrate 19: Magnesium turnings (80 mg, 3.3 mmol, 1.1 equiv) were suspended in THF (3.0 mL) and a crystal of iodine (< 10 mg) was added. The magnesium suspension was heated at 65 ºC. Separately, 2-bromonaphthalene (620 mg, 3.0 mmol 1.0 equiv) was dissolved in THF (3.0 mL) and then added dropwise to the heated magnesium suspension. Upon completion of addition, the resulting brown-grey solution was heated at 65 ºC for a further hour. The so-prepared 2-naphthylmagnesium bromide solution was used in the coupling step without further purification (0.5 M assumed). The standard procedure was followed with 2,3-epoxy-2-methyl-cyclohexanone (126 mg, 1.0 mmol, 1.0 equiv) and 2-naphthylmagnesium bromide (0.5 M in THF, 6.0 mL, 3.0 mmol, 3.0 equiv) to afford **19** (147 mg, 0.40 mmol, 40%) as a white solid (> 20:1 d.r.). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.2 Hz, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.73 – 7.70 (m, 3H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.63 (s, 2H), 7.43 (t, *J* = 7.2 Hz, 1H), 7.41 – 7.34 (m, 4H), 7.31 (d, *J* = 8.2 Hz, 1H), 4.36 (dd *J* = 3.7, 3.0 Hz, 1H), 4.11 (d, *J* = 3.0 Hz, 1H), 2.48 (dddd, *J* = 13.9, 13.3, 5.7, 3.0 Hz, 1H), 2.03 (tdd, *J* = 13.9, 3.7, 3.0 Hz, 1H), 1.94 (d, *J* = 1.8 Hz, 3H), 1.86 (dq, *J* = 13.3, 3.0 Hz, 1H), 1.86 (br s, 1H), 1.79 (ddt, *J* = 13.9, 5.7, 3.0 Hz, 1H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 140.7, 139.8, 137.5, 134.2, 133.3, 133.2, 132.2, 132.1, 127.9, 127.8, 127.7, 127.61, 127.59, 127.56 (2C, overlapping), 127.5, 127.4, 127.2, 125.89, 125.87, 125.6, 125.3, 68.7, 47.0, 27.22, 27.20, 18.3; IR (thin film) ν_{max}: 3357, 2933, 1629, 1598, 745 cm^{-1}; HRMS (EI) calcd for $C_{27}H_{24}O$: 364.1827, found: 364.1829.



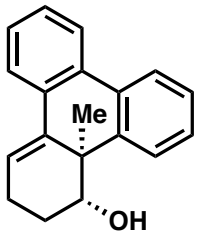
Substrate 20: Dioxene (0.65 M in THF, 5.1 mL, 3.3 mmol, 3.3 equiv) was cooled to 0 ºC. *n*BuLi (2.6 M in hexanes, 1.2 mL, 3.0 mmol, 3.0 equiv) was added and the pale yellow solution was stirred at 0 ºC for 1 h. Anhydrous $MgBr_2$ (550 mg, 3.0 mmol, 3.0 equiv) was added and the solution was allowed to warm to room temperature over 30 min. The so-prepared dioxenemagnesium bromide solution was used in the coupling step without further purification. The standard procedure was followed with 2,3-epoxy-2-methyl-cyclohexanone (126 mg, 1.0 mmol, 1.0 equiv) and dioxenemagnesium bromide (*ca.* 6.5 mL, 3.0 equiv) to afford **20** (153 mg, 0.55 mmol, 55%) as a

white solid (> 20:1 d.r.). ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.94 (s, 1H), 5.77 (s, 1H), 4.11 (ddd, *J* = 10.0, 7.5, 3.6 Hz, 1H), 4.08 – 4.01 (m, 5H), 3.99 (dt, *J* = 10.9, 3.8 Hz, 1H), 3.96 (t, *J* = 3.8 Hz, 2H), 2.84 (tq, *J* = 5.3, 1.7 Hz, 1H), 1.99 (ddt, *J* = 18.0, 10.1, 4.5 Hz, 1H), 1.94 (d, *J* = 1.7 Hz, 3H), 1.84 – 1.76 (m, 2H), 1.68 – 1.63 (m, 1H), 1.45 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.4, 137.6, 135.1, 128.5, 126.6, 123.7, 68.7, 64.8, 64.6, 64.4, 64.1, 39.3, 28.9, 22.6, 18.3; IR (thin film) ν_{max}: 3338, 2937, 1718, 1660, 1145, 919 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{20}O_5Na$ $[M+Na]^+$: 303.1203, found: 303.1201.

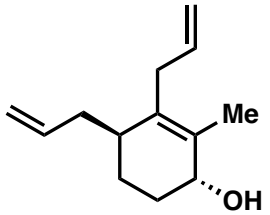


Substrate 21: The standard procedure was followed with 2,3-epoxy-2-methyl-cyclohexanone (126 mg, 1.0 mmol, 1.0 equiv) and vinylmagnesium bromide (1.0 M in THF, 3.0 mL, 3.0 mmol, 3.0 equiv) to afford **21** (56 mg, 0.35 mmol, 35%) as a white solid (> 20:1 d.r.). ^{1}H NMR (700 MHz, $CDCl_3$) δ 6.67 (dd, *J* = 17.5, 11.2 Hz, 1H), 5.78 (ddd, *J* = 17.3, 10.3, 6.2 Hz, 1H), 5.22 (dd, *J* = 17.5, 1.4 Hz, 1H), 5.13 (dd, *J* = 11.2, 1.4 Hz, 1H), 5.04 (dt, *J* = 10.3, 1.6 Hz, 1H), 4.89 (dt, *J* = 17.3, 1.6 Hz, 1H), 3.98 (t, *J* = 2.3 Hz, 1H), 3.16 (dtt, *J* = 6.1, 2.4, 1.6 Hz, 1H), 1.95 (br s, 3H), 1.90 (dddd, *J* = 14.6, 12.1, 4.8, 2.3 Hz, 1H), 1.84 (dddd, *J* = 14.3, 13.7, 4.3, 2.4 Hz, 1H), 1.69 (ddt, *J* = 13.7, 4.8, 2.3 Hz, 1H), 1.59 (br s, 1H), 1.58 (ddt, *J* = 12.1, 4.3, 2.3 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 140.5, 134.3, 133.9, 133.1, 115.5, 115.3, 69.5, 37.7, 27.0, 23.3, 17.3; IR (thin film) ν_{max}: 3161, 2924, 1636, 1418 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{16}O$: 164.1201, found: 164.1200.

Anomalous products:

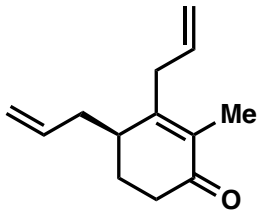


Substrate 22: This compound was prepared in a departure from the standard procedure in the following ways: copper(I) iodide was used in place of tetrakis(acetonitrile)copper(I) hexafluorophosphate, and no HMPA was added. Magnesium turnings (115 mg, 4.8 mmol, 4.8 equiv) were ground in a mortar and pestle then transferred to a 2-neck round bottom flask equipped with a reflux condenser. The apparatus was flame dried and its contents were placed under an argon atmosphere. THF (6.0 mL) was added followed by 3 drops of 1,2-dibromoethane (*ca*. 30 μL). Separately, 2,2'-dibromobiphenyl (624 mg, 2.0 mmol, 2.0 equiv) was dissolved in THF (2.0 mL) and then added dropwise to the magnesium suspension. After Grignard initiation, a vigorous reflux was maintained throughout addition. Upon completion of addition, the resulting solution was heated at 60 ºC for 4 h. The reaction mixture was cooled to room temperature and a wide-bore needle was used to transfer the resulting Grignard solution (transfer quantitated with 2 x 1.0 mL THF rinses). Special care was taken to ensure all solids (excepting small flakes of residual magnesium metal) were transferred to the copper suspension. This modified standard procedure was then followed with 2,3-epoxy-2-methyl-cyclohexanone (126 mg, 1.0 mmol, 1.0 equiv) and the presumed 2,2'-biphenyldimagnesium bromide reagent (0.25 M in THF, 10 mL, 2.0 equiv) to afford **22** (91 mg, 34 mmol, 34%) as a foamy solid (> 20:1 d.r., > 20:1 S_N2:S_N2'). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 – 8.08 (m, 1H), 7.78 – 7.70 (m, 2H), 7.41 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.34 (td, *J* = 7.6, 1.4 Hz, 1H), 7.31 – 7.26 (m, 3H), 5.99 (dd, *J* = 5.8, 2.4 Hz, 1H), 4.46 (dt, *J* = 9.8, 4.4 Hz, 1H), 2.45 – 2.37 (m, 1H), 2.33 – 2.25 (m, 1H), 1.99 – 1.91 (m, 2H), 1.64 (d, *J* = 4.4 Hz, 1H), 1.23 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 145.3, 140.5, 135.7, 132.8, 132.6, 128.5, 128.1, 128.0, 127.0, 126.6, 126.4, 124.2, 123.7, 123.1, 74.0, 43.8, 30.3, 25.3, 21.2; IR (thin film) ν_{max}: 3379, 3062, 2932, 1445, 1405, 751 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{18}O$: 262.1358, found: 262.1358.



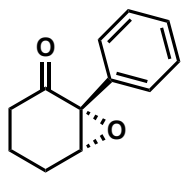
Substrate 23: This compound was prepared in a departure from the standard procedure in the following ways: copper(I) iodide was used at 35 mol% loading in place of tetrakis(acetonitrile)copper(I) hexafluorophosphate, and no HMPA was added. This modified

standard procedure was followed with 2,3-epoxy-2-methyl-cyclohexanone (126 mg, 1.0 mmol, 1.0 equiv) and allylmagnesium bromide (1.0 M in Et_2O, 3.0 mL, 3.0 mmol, 3.0 equiv) to afford **23** (107 mg, 0.56 mmol, 56%) as mixture of diastereomers (~1:1 d.r. as judged by ^1H NMR analysis). To characterize this mixture as a single compound, the crude residue was quickly passed through a plug of silica gel (eluting with 97% Et_2O + 3% Et_3N) and then immediately oxidized to ketone **SI-1**.

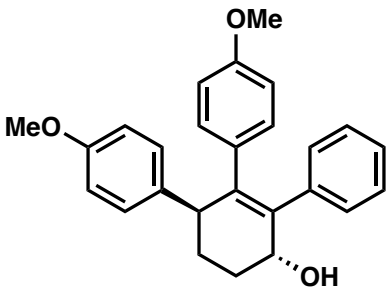


Ketone SI-1: PCC (299 mg, 1.4 mmol, 3.0 equiv) was added to **23** (~1:1 d.r., 89 mg, 0.46 mmol, 1.0 equiv) dissolved in DCM (4.6 mL) and the solution was stirred for 12 h. The reaction mixture was diluted with EtOAc (5 mL) and filtered through celite. The organic phase was quenched with saturated *aq*. $NaHCO_3$ (10 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica gel chromatography (25% Et_2O in hexanes) to afford ketone **SI-1** (84 mg, 0.44 mmol, 96%) as a single compound. ^1H NMR (600 MHz, $CDCl_3$) δ 5.82 – 5.72 (m, 2H), 5.13 – 5.05 (m, 4H), 3.15 (ddt, J = 14.9, 5.7, 1.8 Hz, 1H), 2.90 (dd, J = 14.9, 6.9 Hz, 1H), 2.52 (ddd, J = 17.5, 12.8, 5.9 Hz, 1H), 2.41 – 2.36 (m, 2H), 2.33 (dt, J = 17.5, 4.1 Hz, 1H), 2.18 (ddd, J = 14.9, 11.0, 8.0 Hz, 1H), 2.01 – 1.91 (m, 2H), 1.77 (br s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 199.2, 158.5, 136.8, 133.4, 132.2, 117.1, 116.9, 38.6, 38.0, 35.4, 33.1, 25.4, 11.0; IR (thin film) ν_{max}: 2925, 1662, 1448, 911 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{18}O$: 190.1358, found: 190.1356.

Products with an alternative epoxide starting material:

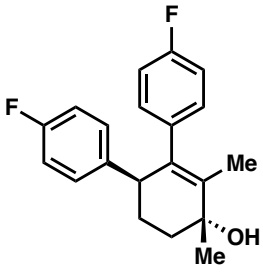


Epoxide SI-2: 2-phenyl-cyclohexanone (473 mg, 2.75 mmol, 1.0 equiv) was dissolved in EtOH (3.8 mL) at rt. Separately H_2O_2 (50wt% in H_2O, 0.11 mL, 3.9 mmol, 1.4 equiv) was diluted with H_2O (0.29 mL) and then added dropwise to the former solution. An aqueous solution of NaOH (5.0 M, 20 μL, 0.93 mmol, 0.34 equiv) was then added dropwise and the reaction mixture was stirred for 1 h. Brine (5 mL was added) followed by DCM (10 mL). The layers were separated and the aqueous layer was futher extracted with DCM (2 x 5 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by column chromatography (30% Et_2O in hexanes) to afford **SI-2** (333 mg, 1.77 mmol, 64%) as a clear, colorless oil. ^{1}H NMR (700 MHz, C_6D_6) δ 7.42 (dd, *J* = 7.7, 1.3 Hz, 2H), 7.16 (t, *J* = 7.7 Hz, 2H), 7.10 (tt, *J* = 7.7, 1.3 Hz, 1H), 2.94 (t, *J* = 2.1 Hz, 1H), 2.35 (dt, *J* = 16.6, 5.2 Hz, 1H), 1.72 (ddd, *J* = 16.6, 10.9, 5.6 Hz, 1H), 1.64 (dtd, *J* = 15.2, 4.9, 2.1 Hz, 1H), 1.55 (dddd, *J* = 13.4, 10.9, 10.2, 5.2, 4.9 Hz, 1H), 1.26 (dddd, *J* = 15.2, 10.2, 5.5, 2.1 Hz, 1H), 1.08 (ddddd, *J* = 13.4, 5.8, 5.6, 5.5, 4.9 Hz, 1H); ^{13}C NMR (176 MHz, C_6D_6) δ 202.8, 135.3, 128.3, 128.2 (2C), 127.6 (2C), 64.7, 62.5, 37.8, 23.5, 18.1; IR (thin film) ν_{max}: 2951, 1709, 1498 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{12}O_2$: 188.0837, found: 188.0837.

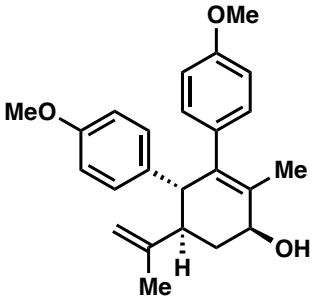


Substrate 24: The standard procedure was followed with 2,3-epoxy-2-phenyl-cyclohexanone (188 mg, 1.0 mmol, 1.0 equiv) and 4-methoxyphenylmagnesium bromide (0.5 M in THF, 6.0 mL, 3.0 mmol, 3.0 equiv) to afford **24** (154 mg, 0.40 mmol, 40%) as a white solid. ^{1}H NMR (700 MHz, C_6D_6) δ 7.18 (dd, *J* = 7.7, 0.9 Hz, 2H), 7.08 (d, *J* = 8.6 Hz, 2H), 7.03 (tt, *J* = 7.7, 0.9 Hz, 2H), 6.94 (tt, *J* = 7.7, 0.9 Hz, 1H), 6.94 (d, *J* = 8.6 Hz, 2H), 6.73 (d, *J* = 8.7 Hz, 2H), 6.43 (d, *J* = 8.8 Hz, 2H), 4.63 (t, *J* = 4.5, 3.0 Hz, 1H), 4.02 (dd, *J* = 5.8, 3.0 Hz, 1H), 3.24 (s, 3H), 3.02 (s, 3H), 2.55 (tdd, *J* = 13.2, 5.8, 3.0 Hz, 1H), 2.01 (dddd, *J* = 13.6, 13.2, 4.5, 3.1 Hz, 1H), 1.89 (ddt, *J* = 13.6, 5.4, 3.0 Hz, 1H), 1.76 (ddt, *J* = 13.2, 5.4, 3.0 Hz, 1H), 1.37 (br s, 1H); ^{13}C NMR (176 MHz, C_6D_6) δ 158.5,

158.4, 141.8, 139.9, 139.6, 135.4, 134.2, 131.1 (2C), 130.5 (2C), 130.0 (2C), 128.4 (2C), 126.7, 114.0 (2C), 113.4 (2C), 68.2, 54.7, 54.3, 46.1, 27.7, 26.9; IR (thin film) ν_{max}: 3332, 2970, 1467, 1379, 950 cm^{-1}; HRMS (EI) calcd for $C_{26}H_{26}O_3$: 386.1882, found: 386.1884.

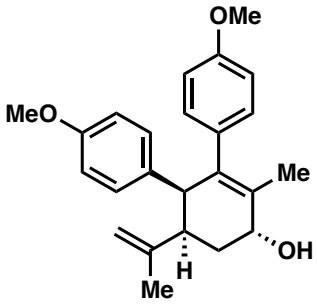


Substrate 25: The standard procedure was followed with 2,3-epoxy-2,3-dimethyl-cyclohexanone (140 mg, 1.0 mmol, 1.0 equiv) and 4-fluorophenylmagnesium bromide (1.0 M in THF, 3.0 mL, 3.0 mmol, 3.0 equiv) to afford **25**. **25** was unstable to purification by silica gel chromatography, even with buffered eluent; yield was assessed by NMR of the crude reaction mixture with 1,3,5-trimethoxybenzene as an internal standard and determined to be 54% (> 20:1 d.r.). An analytic sample could be isolated by preparatory TLC (50% Et_2O in hexanes) with minimal decomposition. ^1H NMR (700 MHz, C_6D_6) δ 6.75 – 6.72 (m, 4H), 6.69 – 6.63 (m, 4H), 3.43 (ddq, *J* = 4.1, 3.0, 1.7 Hz, 1H), 2.06 (dddd, *J* = 13.2, 11.9, 5.8, 3.0 Hz, 1H), 1.67 (ddd, *J* = 13.6, 11.9, 4.1 Hz, 1H), 1.62 (d, *J* = 1.7 Hz, 3H), 1.54 (ddd, *J* = 13.6, 5.8, 3.0 Hz, 1H), 1.48 (dddd, *J* = 13.2, 6.8, 4.1, 3.0 Hz, 1H), 1.29 (s, 3H), 1.08 (br s, 1H); ^{13}C NMR (176 MHz, C_6D_6) δ 161.79 (d, *J* = 244 Hz), 161.75 (d, *J* = 245 Hz), 139.3 (d, *J* = 3.2 Hz), 138.6 (d, *J* = 3.7 Hz), 137.7, 135.5, 130.7 (d, *J* = 7.7 Hz, 2C), 130.2 (d, *J* = 7.7 Hz, 2C), 115.1 (d, *J* = 21.5 Hz, 2C), 115.0 (d, *J* = 21.3 Hz, 2C), 69.8, 47.2, 35.3, 29.0, 28.2, 14.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ –115.08 (p, *J* = 7.0 Hz), –116.05 (p, *J* = 7.2 Hz); IR (thin film) ν_{max}: 3381, 2933, 1601, 1504, 1367 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{20}OF_2$: 314.1482, found: 314.1483.



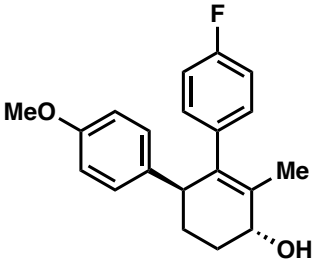
Substrate 26: The standard procedure was followed with *trans*-carvone epoxide (166 mg, 1.0 mmol, 1.0 equiv) and 4-methoxyphenylmagnesium bromide (0.5 M in THF, 6.0 mL, 3.0 mmol, 3.0 equiv) to afford **26** (189 mg, 0.52 mmol, 52%) as a white solid (> 20:1 d.r.). $[\alpha]_D^{23}$ = +143 (*c* 0.8, C_6H_6); ^1H NMR (700 MHz, $CDCl_3$) δ 6.96 (d, *J* = 8.3 Hz, 2H), 6.90 (d, *J* = 8.3 Hz, 2H), 6.71 (d, *J* = 8.3 Hz, 2H), 6.70 (d, *J* = 8.3 Hz, 2H), 4.90 (s, 1H), 4.84 (s, 1H), 4.23 (ddd, *J* = 9.4, 6.0, 4.8 Hz, 1H), 3.74 (d, *J* = 4.8 Hz, 1H), 3.73 (s, 3H), 3.72 (s,

3H), 2.42 (dt, *J* = 6.0, 4.8 Hz, 1H), 2.10 (dt, *J* = 13.7, 4.8 Hz, 1H), 2.03 (dt, *J* = 13.7, 6.0 Hz, 1H), 1.98 (d, *J* = 9.4 Hz, 1H), 1.81 (s, 3H), 1.77 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.92, 157.89, 150.1, 135.73, 135.71, 134.6, 133.5, 123.0 (2C), 129.9 (2C), 113.5 (2C), 113.3 (2C), 111.3, 70.4, 55.3, 55.2, 50.8, 47.4, 33.2, 21.9, 17.2; IR (thin film) ν_{max}: 3371, 2931, 1643, 1509, 1241 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{28}O_3Na$ $[M+Na]^+$: 387.1931, found: 387.1928.

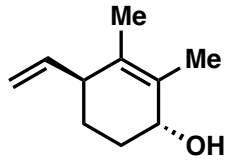


Substrate 27: This compound was prepared in a departure from the standard procedure in the following way: $[Cu(MeCN)_4][PF_6]$ was used at 30 mol% loading. This modified standard procedure was followed with *cis*-carvone epoxide (166 mg, 1.0 mmol, 1.0 equiv) and 4-methoxyphenylmagnesium bromide (0.5 M in THF, 6.0 mL, 3.0 mmol, 3.0 equiv) to afford **27** (186 mg, 0.51 mmol, 51%) as a white solid (> 20:1 d.r.). $[\alpha]_D^{23}$ = –96.3 (*c* 0.3, C_6D_6); ^{1}H NMR (700 MHz, $CDCl_3$) δ 6.93 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 6.65 (d, *J* = 8.7 Hz, 4H), 4.72 (q, *J* = 1.6 Hz, 1H), 4.68 (d, *J* = 1.1 Hz, 1H), 4.19 (t, *J* = 4.7 Hz, 1H), 3.71 (s, 6H), 3.54 (d, *J* = 7.8 Hz, 1H), 2.68 (ddd, *J* = 10.4, 7.8, 3.5 Hz, 1H), 2.00 (ddd, *J* = 13.7, 10.4, 4.7 Hz, 1H), 1.91 (dt, *J* = 13.7, 4.7, 3.5 Hz, 1H), 1.71 (d, *J* = 1.8 Hz, 3H), 1.70 (br s, 1H), 1.66 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.70, 157.67, 147.4, 138.1, 135.6, 134.2, 131.9, 130.0 (2C), 129.9 (2C), 113.3 (2C), 113.1 (2C), 111.3, 69.8, 55.19, 55.16, 51.3, 45.7, 34.9, 21.2, 18.7; IR ν_{max}: 3361, 2932, 1646, 1508 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{28}O_3Na$ $[M+Na]^+$: 387.1931, found: 387.1928.

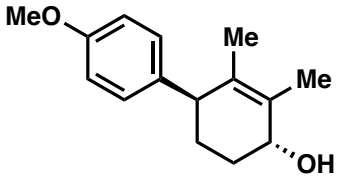
Products from coupling two different nucleophiles:



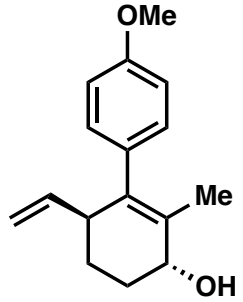
Substrate 28: The standard procedure was followed with 2,3-epoxy-2-methyl-cyclohexanone (126 mg, 1.0 mmol, 1.0 equiv) and 4-fluorophenylmagnesium bromide (1.0 M in THF, 2.0 mL, 2.0 mmol, 2.0 equiv) followed by 4-methoxyphenylmagnesium bromide (0.5 M in THF, 4.0 mL, 2.0 mmol, 2.0 equiv) to afford **28** (163 mg, 0.52 mmol, 52%) as a white foam (this product was isolated as a ~15:1 inseparable mixture with **18**). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.03 (d, *J* = 8.7 Hz, 2H), 7.02 (dd, *J* = 8.4, 5.6 Hz, 2H), 6.87 (dd, *J* = 9.4, 8.4 Hz, 2H), 6.77 (d, *J* = 8.7 Hz, 2H), 4.23 (t, *J* = 3.0 Hz, 1H), 3.74 (s, 3H), 3.69 (tq, *J* = 3.0, 2.0 Hz, 1H), 2.31 (tdd, *J* = 13.4, 5.8, 3.0 Hz, 1H), 2.06 (s, 1H), 1.93 (tdd, *J* = 13.4, 5.0, 3.0 Hz, 1H), 1.80 (d, *J* = 2.0 Hz, 3H), 1.71 (ddt, *J* = 13.4, 5.8, 3.0 Hz, 1H), 1.68 (ddt, *J* = 13.4, 5.0, 3.0 Hz, 1H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 161.3 (d, *J* = 244.9 Hz), 157.9, 138.1 (d, *J* = 3.2 Hz), 137.0, 135.0, 133.6, 130.3 (d, *J* = 7.7 Hz, 2C), 129.6 (2C), 114.7 (d, *J* = 21.1 Hz, 2C), 113.5 (2C), 68.5, 55.2, 46.1, 27.3, 27.2, 18.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ –115.63 (tt, *J* = 9.4, 5.5 Hz); IR (thin film) ν_{max}: 3355, 2934, 1602, 1582, 1442 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{21}OF$: 312.1526, found: 312.1529.



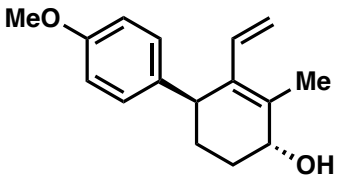
Substrate 29: The standard procedure was followed with 2,3-epoxy-2-methyl-cyclohexanone (126 mg, 1.0 mmol, 1.0 equiv) and methylmagnesium bromide (3.0 M in Et_2O diluted with THF to 1.0 M, 2.0 mL, 2.0 mmol, 2.0 equiv) followed by vinylmagnesium bromide (1.0 M in THF, 2.0 mL, 2.0 mmol, 2.0 equiv) to afford **29** (46 mg, 0.34 mmol, 34%) as a white solid (> 20:1 d.r.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (ddd, *J* = 17.0, 10.2, 7.7 Hz, 1H), 5.02 (ddd, *J* = 10.2, 2.0, 0.9 Hz, 1H), 4.94 (ddd, *J* = 17.0, 2.0, 1.2 Hz, 1H), 3.92 (br s, 1H), 2.62 (br s, 1H), 1.95 – 1.81 (m, 2H), 1.78 (s, 3H), 1.66 – 1.62 (m, 1H), 1.61 (s, 3H), 1.52 – 1.43 (m, 1H), 1.43 (br s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 140.2, 131.9, 129.4, 115.1, 69.3, 44.9, 28.0, 23.8, 18.4, 17.0; IR (thin film) ν_{max}: 3773, 2931, 1443 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{16}O$: 152.1201, found: 152.1199.



Substrate 30: The standard procedure was followed with 2,3-epoxy-2-methyl-cyclohexanone (126 mg, 1.0 mmol, 1.0 equiv) and methylmagnesium bromide (1.0 M in Et_2O diluted with THF to 1.0 M, 2.0 mL, 2.0 mmol, 2.0 equiv) followed by 4-methoxyphenylmagnesium bromide (1.0 M in THF, 2.0 mL, 2.0 mmol, 2.0 equiv) to afford **30** (111 mg, 0.48 mmol, 48%) as a white solid (> 20:1 d.r.). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.01 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 4.04 (dd, J = 3.6, 2.9 Hz, 1H), 3.79 (s, 3H), 3.26 (t, *J* = 4.3 Hz, 1H), 2.12 (tdd, *J* = 13.2, 5.9, 2.9 Hz, 1H), 1.87 (s, 3H), 1.75 (tt, *J* = 13.5, 3.6 Hz, 1H), 1.59 – 1.50 (m, 3H), 1.54 (s, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 158.0, 136.2, 132.3, 130.5, 129.5 (2C), 113.7 (2C), 69.3, 55.3, 46.0, 27.6, 27.3, 18.9, 16.9; IR (thin film) ν_{max}: 3429, 2935, 1610, 1509, 830 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{20}O$: 232.1463, found: 232.1466.



Substrate 31: The standard procedure was followed with 2,3-epoxy-2-methyl-cyclohexanone (126 mg, 1.0 mmol, 1.0 equiv) and 4-methoxyphenylmagnesium bromide (1.0 M in THF, 2.0 mL, 2.0 mmol, 2.0 equiv) followed by vinylmagnesium bromide (1.0 M in THF, 2.0 mL, 2.0 mmol, 2.0 equiv) to afford **31** (117 mg, 0.48 mmol, 48%) as a white solid (> 20:1 d.r.). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.02 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 5.65 (ddd, *J* = 17.4, 10.3, 7.3 Hz, 1H), 4.88 (dd, *J* = 10.3, 1.7 Hz, 1H), 4.80 (dt, *J* = 17.4, 1.7 Hz, 1H), 4.09 (dt, *J* = 6.4, 2.9 Hz, 1H), 3.80 (s, 3H), 3.09 – 3.04 (m, 1H), 2.07 (dddd, *J* = 13.5, 13.1, 5.5, 2.9 Hz, 1H), 1.94 (tt, *J* = 13.7, 3.3 Hz, 1H), 1.77 (ddt, *J* = 13.7, 5.5, 2.9 Hz, 1H), 1.70 (d, *J* = 1.6 Hz, 3H), 1.66 (dddd, *J* = 13.1, 5.5, 3.3, 2.9 Hz, 1H), 1.57 (d, *J* = 6.4 Hz, 1H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 158.1, 139.3, 137.7, 134.6, 131.8, 130.1 (2C), 115.3, 113.3 (2C), 68.7, 55.3, 44.4, 27.8, 23.7, 18.2; IR (thin film) ν_{max}: 3352, 2933, 1607, 1509, 1242 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{20}O_2$: 244.1463, found: 244.1460.



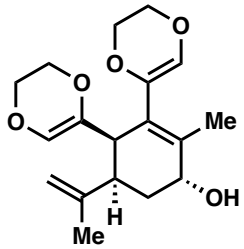
Substrate 32: The standard procedure was followed with 2,3-epoxy-2-methyl-cyclohexanone (126 mg, 1.0 mmol, 1.0 equiv) and vinylmagnesium bromide (1.0 M in THF, 2.0 mL,

2.0 mmol, 2.0 equiv) followed by 4-methoxyphenyl-magnesium bromide (1.0 M in THF, 2.0 mL, 2.0 mmol, 2.0 equiv) to afford **32** (122 mg, 0.50 mmol, 50%) as a white solid (> 20:1 d.r.). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.01 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 6.70 (dd, *J* = 17.5, 11.1 Hz, 1H), 5.01 (dd, *J* = 11.1, 1.3 Hz, 1H), 4.97 (dd, *J* = 17.5, 1.3 Hz, 1H), 4.09 (t, *J* = 5.2 Hz, 1H), 3.77 (s, 3H), 3.75 (d, *J* = 5.5 Hz, 1H), 2.18 – 2.09 (m, 1H), 2.06 (d, *J* = 1.3 Hz, 3H), 1.73 – 1.66 (m, 1H), 1.62 (br s, 1H), 1.61 – 1.57 (m, 2H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 157.9, 136.4, 135.2, 133.8, 133.2, 129.1 (2C), 116.1, 113.7 (2C), 69.6, 55.3, 39.5, 26.6, 26.5, 17.3; IR (thin film) ν_{max}: 3445, 2932, 1611, 1510, 1251 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{20}O_2$: 244.1463, found: 244.1460.

Synthetic studies on the quassinoid core architecture:

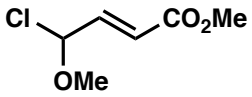
Dioxene (SI-3): Although commercially available, dioxene can also be prepared in a rapid, economical fashion from readily accessible starting materials. Described here is a modification of known literature protocols[4] to produce dioxene on large scale. Dioxane (85 mL, 1.0 mol, 1.0 equiv) was placed in a 500 mL flask and a reflux condenser was attached. In addition to the inlet tubing at the top of the condenser providing a positive pressure of nitrogen, outlet tubing to a beaker containing 4 M NaOH (1000 mL) was connected. Sulfuryl chloride (162 mL, 2.0 mol, 2.0 equiv) was added dropwise over 30 min. After this addition was completed, the cooling bath was removed and the resulting pale yellow solution was heated at 40 ºC for 16 h. The solution was then heated at 65 ºC for 4 h at which point it gradually turned colorless. The solution was cooled to room temperature and argon was sparged through to displace any trace acidic gas. The crude product was concentrated under reduced pressure and the resulting *trans*-2,3-dichloro-1,4-dioxane was used immediately in the next step without further purification. This highly sensitive intermediate gradually decomposes over time and is best used fresh for subsequent chemistry.

Magnesium metal (36 g, 1.5 mol, 1.5 equiv) was suspended in THF (250 mL). The so-prepared crude *trans*-2,3-dichloro-1,4-dioxane (1.0 mol assumed, 1.0 equiv) was added neat to that suspension dropwise. After Grignard initiation, addition was continued to maintain a steady reflux. The resulting suspension was heated at 65 ºC for 4 h. The grey suspension was cooled to room temperature and filtered through Celite. Additional THF (*ca.* 200 mL) was used to wash the filter cake and quantitate transfer. The crude solution was directly distilled (100 ºC, house vacuum) into a flask cooled to –78 ºC. Dioxene was found to readily azeotrope with THF and so purified dioxene was afforded as a solution in THF (0.65 M, 28 g, 330 mmol, 33% over two steps, as judged by ^{1}H NMR analysis).



Diene 33: The procedure for the preparation of this compound represents a significant departure from the standard conditions and thus will be described in full. Carvone epoxide (332 mg, 2.0 mmol 1.0 equiv) was dissolved in THF (4.0 mL) and cooled to –78 ºC.

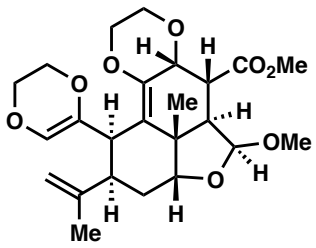
LHMDS (1.0 M in THF, 2.0 mL, 2.0 mmol, 1.0 equiv) was added dropwise and the resulting solution was briefly warmed to 0 ºC (< 5 min) before being cooled back to –78 ºC. N-Phenyl-bis(trifluoromethanesulfonamide) (750 mg, 2.1 mmol, 1.05 equiv) was added as a solid and the reaction mixture was warmed to 0 ºC. In a separate flask, dioxene (0.65 M in THF, 12.3 mL, 8.0 mmol, 4.0 equiv) was cooled to 0 ºC. *n*-BuLi (2.5 M in hexanes, 3.0 mL, 7.4 mmol, 3.7 equiv) was added and the pale yellow solution was stirred for 1 h. In another separate flask, CuI (133 mg, 0.7 mmol, 0.35 equiv) was combined with anhydrous $MgBr_2$ (1.3 g, 7.0 mmol, 3.5 equiv). To this mixture of solids was rapidly added the dioxene-lithium solution. The cloudy suspension was stirred at room temperature for 30 min before being added dropwise to the vinyl triflate at 0 ºC. A wide-bore needle was used and care was taken during this operation to ensure all solids were transferred along with the solution. The reaction mixture was allowed to warm to room temperature slowly and was stirred for 16 h. The reaction mixture was diluted with EtOAc (50 mL) and quenched with a 9:1 saturated aqueous ammonium chloride:saturated aqueous ammonium hydroxide solution (10 mL). The biphasic suspension was stirred vigorously until the aqueous layer had turned a deep blue. The layers were separated and the organic layer was further washed with water (2 x 10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica gel chromatography (27 → 37% Et_2O in hexanes + 3% Et_3N) to afford diene **33** (370 mg, 1.1 mmol, 58%) as a white solid. $[\alpha]_D^{23}$ = +176 (*c* 1.0, C_6D_6); ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.94 (s, 1H), 5.73 (s, 1H), 4.82 (br s, 1H), 4.66 (br s, 1H), 4.16 – 4.11 (m, 2H), 4.08 – 4.00 (m, 3H), 3.92 – 3.85 (m, 4H), 2.94 (dq, *J* = 5.8, 1.6 Hz, 1H), 2.46 (ddd, *J* = 13.7, 5.8, 2.4 Hz, 1H), 2.18 (td, *J* = 13.7, 4.2 Hz, 1H), 1.98 (d, *J* = 1.6 Hz, 3H), 1.78 (br s, 3H), 1.73 (dt, *J* = 13.7, 2.4 Hz, 1H), 1.58 (br s, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 147.5, 136.3, 135.7, 134.5, 129.6, 126.9, 124.4, 109.9, 69.2, 64.6, 64.5, 64.4, 64.0, 42.0, 38.3, 32.5, 22.9, 19.1; IR (thin film) ν_{max}: 3419, 3034, 1673, 1478, 1143 cm^{-1}; HRMS (ESI): calcd for $C_{18}H_{25}O_5$ $[M+H]^+$: 321.1657, found: 321.1654.



Dienophile SI-4: (*E*)-4,4-dimethoxybut-2-enoic acid methyl ester (480 mg, 3.0 mmol, 1.0 equiv)[5] and acetyl chloride (430 µL, 6.0 mmol, 2.0 equiv) were combined with a crystal of iodine (8 mg,

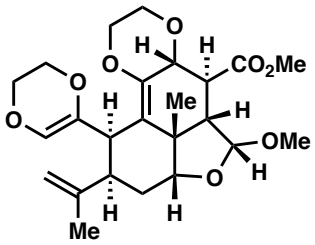
0.03 mmol, 0.01 equiv). The mixture was stirred at rt for 6 h. The crude residue was directly concentrated and then azeotroped from benzene (3 x 5 mL). The dienophile was used immediately in the next step without further purification (*ca.* 480 mg, near quantitative mass recovery). This crude product typically contained *ca.* 5% recovered starting material and *ca*. 5% (2E)-4-oxo-2-butenoic acid, along with some decomposition products; a purity of 80% was conservatively assumed by ^{1}H NMR analysis for the subsequent step. Tabulated ^{1}H and ^{13}C NMR data of this unpurified material were obtained: ^{1}H NMR (600 MHz, C_6D_6) δ 7.00 (dd, *J* = 15.6, 4.7 Hz, 1H), 6.11 (dd, *J* = 15.6, 1.3 Hz, 1H), 5.34 (ddq, *J* = 4.7, 1.3, 1.1 Hz, 1H), 3.30 (s, 3H), 2.97 (d, *J* = 1.1 Hz, 3H); ^{13}C NMR (151 MHz, C_6D_6) δ 165.6, 142.6, 122.4, 95.3, 57.2, 51.4.

Diels-Alder Reaction: Diene **33** (320 mg, 1.0 mmol, 1.0 equiv) was dissolved in PhMe (10 mL) and N,N-diisopropylethylamine (0.67 mL, 4.0 mmol, 4.0 equiv) was added at room temperature. Dienophile **SI-4** (crude from previous operation, 328 mg, 2.0 mmol, 2.0 equiv) was dissolved in PhMe (5 mL) and added dropwise to the solution. The reaction mixture was stirred at room temperature for 12 h and then diluted with further PhMe (10 mL) and HMDS (2.5 mL). A reflux condenser was attached and the solution was heated at 110 ºC for 3 d. The reaction mixture was cooled to room temperature and concentrated. The crude residue was directly purified by silica gel chromatography (7 → 47% Et_2O in hexanes + 3% Et_3N; products are very sensitive to acid) to afford the desired product as a mixture of diastereomers (~1.3:1 d.r. as judged by ^{1}H NMR analysis, 279 mg, 0.62 mmol, 62%). A small amount of additional diastereomers was isolated as well (~11:1 d.r., 40 mg, 0.09 mmol, 9%). The two major diastereomers were used in subsequent chemistry as a mixture but could be separated by very careful preparatory TLC (2% THF in DCM). The two additional diastereomers could not be separated from each other; in this case, only the primary component of that mixture is reported.

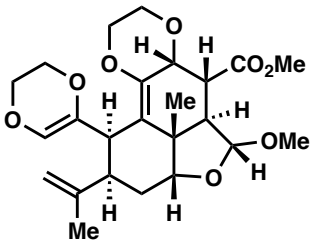


Diels-Alder Product 34: $[\alpha]_D^{23}$ = +6.7 (*c* 0.7, C_6D_6); ^{1}H NMR (600 MHz, C_6D_6) δ 6.03 (s, 1H), 5.53 (d, *J* = 4.5 Hz, 1H), 4.93 (br s, 1H), 4.89 (br s, 1H), 4.46 (dd, *J* = 8.0, 5.3 Hz, 1H), 4.38 (d, *J* = 7.7 Hz, 1H), 3.79 (dd, *J* = 13.2, 7.7 Hz, 1H), 3.71 (d, *J*

= 5.4 Hz, 1H), 3.50 (s, 3H), 3.48 – 3.30 (m, 8H), 3.28 (s, 3H), 2.83 (dd, *J* = 13.2, 4.5 Hz, 1H), 2.48 (ddd, *J* = 14.6, 9.7, 8.0 Hz, 1H), 2.35 (ddd, *J* = 9.7, 7.7, 5.4 Hz, 1H), 1.85 (ddd, *J* = 14.6, 7.7, 5.3 Hz, 1H), 1.71 (br s, 3H), 1.52 (s, 3H); ^{13}C NMR (176 MHz, C_6D_6) δ 171.1, 146.8, 143.6, 136.4, 131.0, 124.6, 111.1, 104.3, 82.2, 71.2, 68.2, 66.8, 64.0, 63.6, 55.0, 51.4, 51.1, 43.2, 42.7, 42.1, 36.9, 31.4, 26.4, 23.1; IR (thin film) νmax: 2978, 1745, 1671, 1096 cm^{-1}; HRMS (ESI): calcd for $C_{24}H_{33}O_8$ $[M+H]^+$: 449.2175, found: 449.2180.

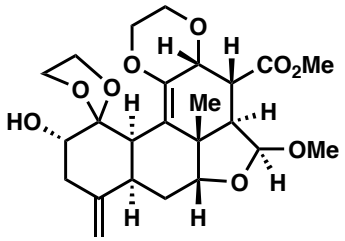


Diels-Alder Product 35: $[\alpha]_D^{23}$ = –66.4 (*c* 1.2, C_6D_6); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.88 (s, 1H), 4.84 (d, *J* = 6.1 Hz, 1H), 4.84 (br s, 1H), 4.74 (br s, 1H), 4.66 (dd, *J* = 7.3, 1.1 Hz, 1H), 3.98 – 3.84 (m, 8H), 3.80 (dt, *J* = 11.7, 2.5 Hz, 1H), 3.76 (s, 3H), 3.48 (d, *J* = 5.3 Hz, 1H), 3.34 (s, 3H), 3.16 (dd, *J* = 7.3, 3.6 Hz, 1H), 2.42 – 2.36 (m, 3H), 1.87 – 1.81 (m, 1H), 1.80 (br s, 3H), 1.15 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 175.7, 147.6, 143.2, 138.4, 123.8, 115.7, 109.9, 104.8, 83.6, 68.7, 66.0, 64.4, 64.1, 63.8, 56.0, 52.5, 51.9, 45.2, 40.8, 38.0, 35.2, 27.8, 24.1, 23.0; IR (thin film) ν_{max}: 2956, 1736, 1671, 1646, 1091 cm^{-1}; HRMS (ESI): calcd for $C_{24}H_{32}O_8Na$ $[M+Na]^+$: 471.1995, found: 471.1999.

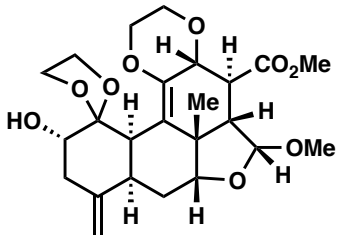


Diels-Alder Product 36: Afforded as a ~11:1 mixture of diastereomers; major reported. $[\alpha]_D^{23}$ = –17.7 (*c* 1.1, C_6D_6); ^{1}H NMR (700 MHz, C_6D_6) δ 6.02 (s, 1H), 4.94 (d, *J* = 8.1 Hz, 1H), 4.90 – 4.85 (m, 1H), 4.83 – 4.79 (m, 1H), 4.37 (d, *J* = 9.1 Hz, 1H), 4.37 (t, *J* = 8.0 Hz, 1H), 3.75 (d, *J* = 6.7 Hz, 1H), 3.59 (s, 3H), 3.53 – 3.50 (m, 1H), 3.48 (dd, *J* = 12.8, 9.1 Hz, 1H), 3.45 (s, 3H), 3.43 – 3.40 (m, 2H), 3.39 – 3.36 (m, 2H), 3.33 – 3.28 (m, 3H), 3.00 (dd, *J* = 12.8, 8.1 Hz, 1H), 2.49 (q, *J* = 9.7, 6.7 Hz, 1H), 2.41 (dt, *J* = 14.4, 8.0, 6.7 Hz, 1H), 2.02 (ddd, *J* = 14.4, 9.7, 8.0 Hz, 1H), 1.67 – 1.64 (m, 3H), 1.08 (s, 3H); ^{13}C NMR (176 MHz, C_6D_6) δ 170.1, 147.2, 142.3, 136.5, 125.7, 124.5, 111.0, 106.7, 80.9, 68.9, 66.5, 65.8, 64.0, 63.6, 55.4, 51.3, 49.8, 44.2, 43.2, 42.9, 36.3, 31.7, 23.3, 22.3; IR (thin film) ν_{max}: 2965, 1740, 1565, 1435, 1137 cm^{-1}; HRMS (ESI): calcd for $C_{24}H_{32}O_8Na$ $[M+Na]^+$: 471.1995, found: 471.2000.

Oxidation/Ene Reaction: The purified mixture of Diels-Alder products **34** and **35** (~1.3:1 d.r., 200 mg, 0.45 mmol, 1.0 equiv) was dissolved in DCM (7.5 mL) and cooled to –40 ºC. Freshly prepared and titrated DMDO (0.06 M in acetone, 7.5 mL, 0.45 mmol, 1.0 equiv) was then added dropwise. At the conclusion of the addition (< 5 min), the reaction mixture was further diluted with DCM (7.5 mL) and $AlMe_3$ (2.0 M in hexanes, 330 µL, 0.67 mmol, 1.5 equiv) was added dropwise. The resulting solution was allowed to warm to 0 ºC over 5 min before H_2O (20 µL) was added. An aqueous solution of NaOH (3 M, 20 µL) was added followed by additional H_2O (50 µL). When no further bubbling was observed, $MgSO_4$ was added and the suspension was warmed to room temperature and stirred for 15 min. The mixture was filtered through celite, the residue was concentrated, and the crude product was purified by column chromatography (47→ 97% EtOAc in hexanes + 3% Et_3N) to afford quassin architectures **37** and **38** (~1.3:1 d.r. as judged by ^{1}H NMR analysis, 116 mg, 0.25 mmol, 57%). These diastereomers could be separated by careful preparatory TLC (7% THF in DCM) and were subsequently characterized as single compounds:



Quassin Architecture 37: $[\alpha]_D^{23}$ = +79.4 (*c* 0.8, CD_3OD); ^{1}H NMR (700 MHz, CD_3OD) δ 5.00 (d, *J* = 4.4 Hz, 1H), 4.85 (t, *J* = 2.0 Hz, 1H), 4.76 (t, *J* = 2.0 Hz, 1H), 4.41 (d, *J* = 7.7 Hz, 1H), 4.07 (dd, *J* = 8.6, 2.7 Hz, 1H), 4.03 (td, *J* = 7.1, 3.4 Hz, 1H), 3.97 (td, *J* = 7.1, 3.4 Hz, 1H), 3.92 (dt, *J* = 8.2, 7.1 Hz, 1H), 3.88 – 3.81 (m, 2H), 3.79 – 3.75 (m, 1H), 3.73 (dt, *J* = 8.2, 7.1 Hz, 1H), 3.70 – 3.68 (m, 1H), 3.68 (s, 3H), 3.67 (d, *J* = 5.4 Hz, 1H), 3.67 (dd, *J* = 3.8, 3.1 Hz, 1H), 3.49 (dd, *J* = 13.4, 7.8 Hz, 1H), 3.26 (s, 3H), 2.77 (ddt, *J* = 14.6, 3.8, 2.0 Hz, 1H), 2.51 (dt, *J* = 12.0, 7.5, 5.4 Hz, 1H), 2.38 (ddd, *J* = 15.0, 12.0, 8.6 Hz, 1H), 2.31 (dd, *J* = 13.3, 4.4 Hz, 1H), 2.26 (dd, *J* = 14.6, 3.1 Hz, 1H), 1.55 (ddd, *J* = 15.0, 7.5, 2.7 Hz, 1H), 1.22 (s, 3H); ^{13}C NMR (176 MHz, CD_3OD) δ 173.3, 147.2, 147.1, 129.1, 112.3, 110.6, 105.1, 82.9, 71.7, 70.0, 69.4, 67.7, 66.3, 65.1, 55.4, 53.0, 52.1, 43.3, 42.2, 41.7, 37.0, 36.0, 32.7, 27.8; IR (thin film) ν_{max}: 3488, 2954, 1742, 1653, 1437 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{32}O_9Na$ $[M+Na]^+$: 487.1944, found: 487.1947.



Quassin Architecture 38: $[\alpha]_D^{23}$ = –41.8 (*c* 1.0, CD_3OD); ^1H NMR (700 MHz, CD_3OD) δ 4.82 (t, *J* = 2.2 Hz, 1H), 4.81 (d, *J* = 5.6 Hz, 1H), 4.73 (t, *J* = 2.2 Hz, 1H), 4.67 (dd, *J* = 7.5, 1.1 Hz, 1H), 3.98 – 3.91 (m, 3H), 3.88 – 3.82 (m, 3H), 3.79 – 3.75 (m, 2H), 3.75 (s, 3H), 3.71 – 3.67 (m, 2H), 3.61 (t, *J* = 3.1 Hz, 1H), 3.35 (s, 3H), 3.09 (dd, *J* = 7.5, 3.4 Hz, 1H), 2.71 (ddt, *J* = 14.3, 3.1, 2.2 Hz, 1H), 2.66 (ddd, *J* = 13.8, 6.1, 3.1 Hz, 1H), 2.50 (td, *J* = 13.8, 2.9 Hz, 1H), 2.39 (dd, *J* = 5.6, 3.4 Hz, 1H), 2.27 (dt, *J* = 14.3, 3.1, 1.4 Hz, 1H), 1.49 (dtd, *J* = 13.8, 3.1, 1.3 Hz, 1H), 1.16 (s, 3H); ^{13}C NMR (176 MHz, CD_3OD) δ 176.9, 148.3, 146.4, 112.8, 112.0, 111.9, 106.3, 85.3, 71.2, 69.9, 66.6, 66.0, 65.3, 64.8, 55.9, 54.0, 52.8, 46.4, 41.6, 39.0, 36.6, 36.4, 30.9, 25.5; IR (thin film) ν_{max}: 3451, 2919, 1735, 1652, 1436 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{32}O_9Na$ $[M+Na]^+$: 487.1944, found: 487.1951.

References:

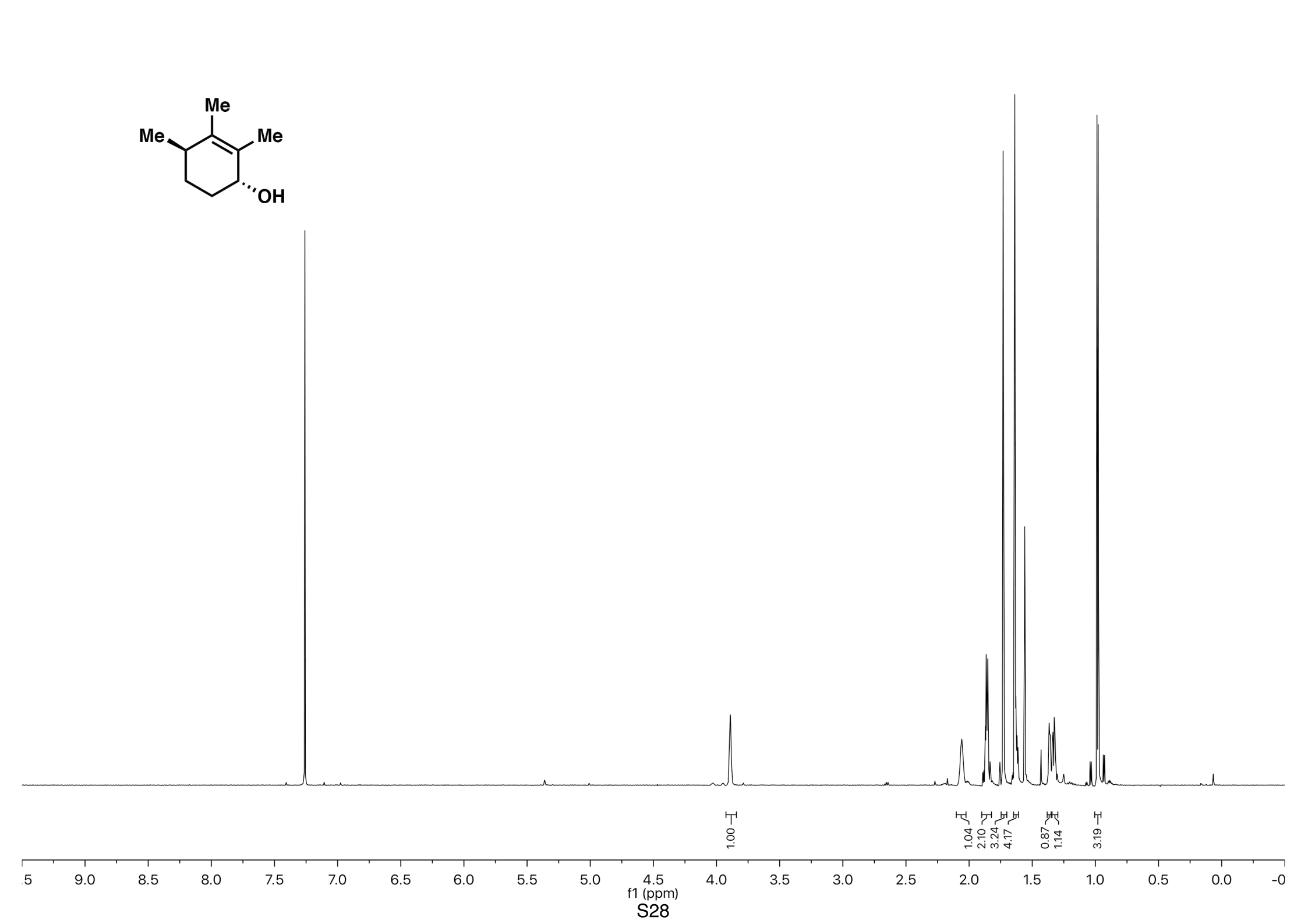
(1) L. Wang, H. Wang, Y. Li, P. Tang, *Angew. Chem. Int. Ed.* **2005**, *54*, 5732.

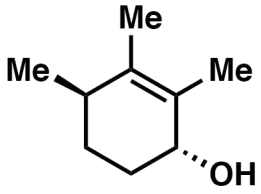
(2) (a) P. Kraft, C. Berthold, *Synthesis* **2008**, *4*, 543; (b) C. E. Harding, S. L. King, *J. Org. Chem.* **1992**, *57*, 883; (c) Q. Wang, Q. Huang, B. Chen. J. Lu, H. Wang, X. She, X. Pan, *Angew. Chem. Int. Ed.* **2006**, *45*, 3651.

(3) D. F. Taber, P. W., DeMatteo, R. A. Hassan, *Org. Synth.* **2013**, *90*, 350.

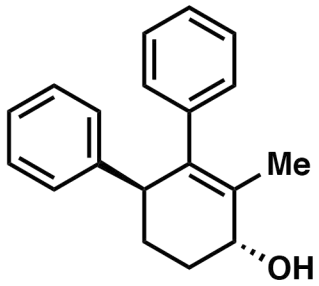
(4) R. I. Meltzer, A. D. Lewis, A. Fischman, *J. Org. Chem.* **1959**, *24*, 1763.

(5) L.-L. Shen, H.-S. Mun, J.-H. Jeong, *Eur. J. Org. Chem.* **2010**, 6895.

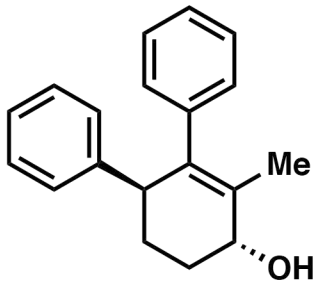

Me
Me
Me
OH
1.00
1.04
2.10
3.24
4.17
0.87
1.14
3.19
f1 (ppm)


Me
Me
Me
OH

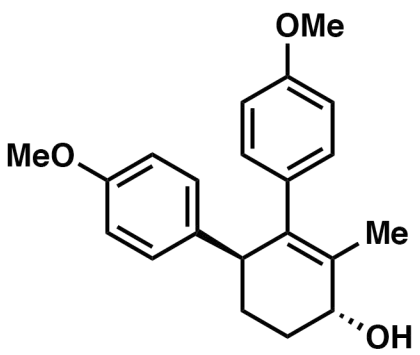
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


Me
OH

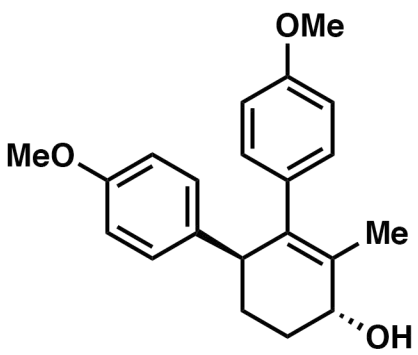
4.05
2.10
1.93
1.94
1.00
1.00
1.06
1.05
3.06
2.12
0.96
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Me
OH

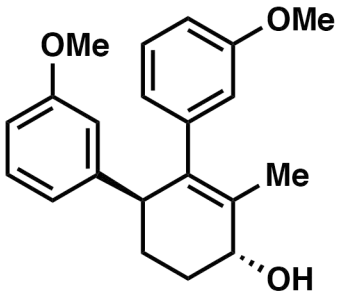
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


OMe
MeO
Me
OH

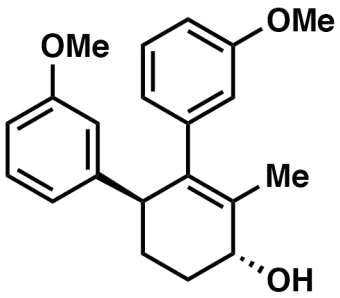
1.94
1.91
3.92
1.00
2.90
3.15
1.01
1.01
1.05
2.98
3.06
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


OMe
MeO
Me
OH

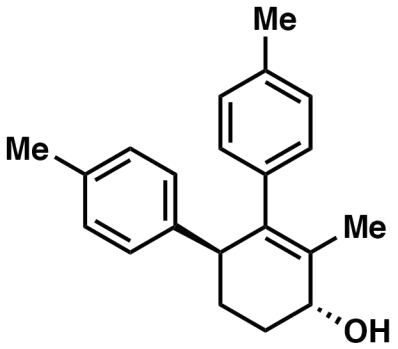
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


OMe
OMe
Me
OH

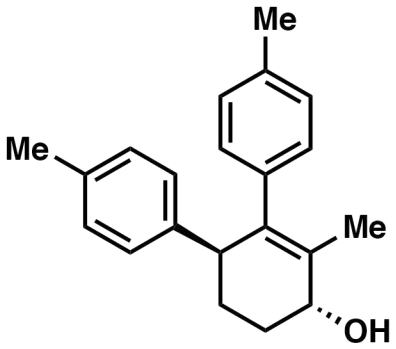
0.96
0.96
0.97
1.01
2.77
0.93
1.00
2.93
1.08
2.85
0.99
1.00
2.92
1.99
0.91
.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)


OMe
OMe
Me
OH

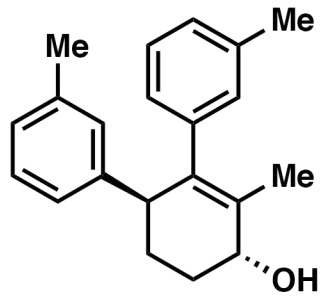
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


Me
Me
Me
OH

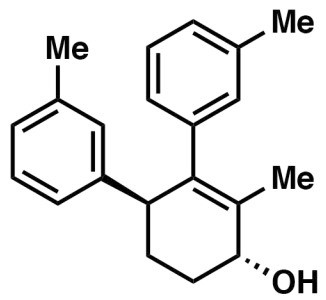
3.73
4.18
0.99
1.00
1.36
2.95
2.99
1.13
2.97
2.19
0.70
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

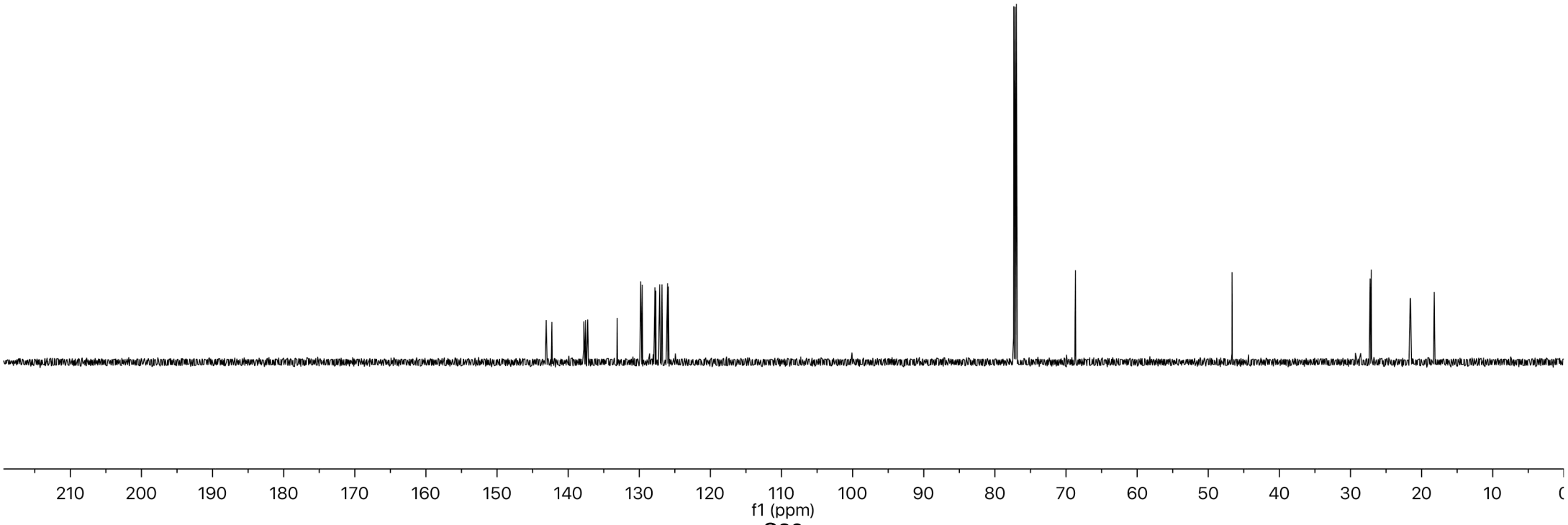

Me
Me
Me
OH

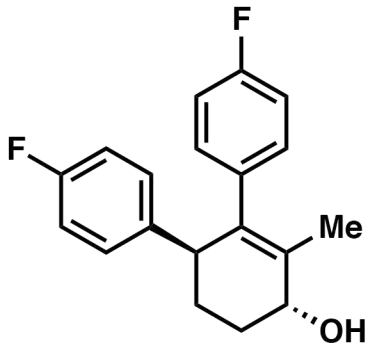
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


Me
Me
Me
OH

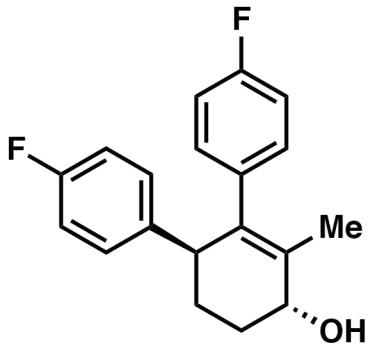
1.01
1.06
4.90
0.95
0.10
1.00
0.98
1.02
3.04
2.84
1.17
2.92
3.04
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


Me
Me
Me
OH

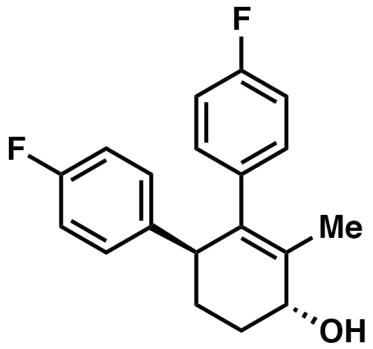

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


F
F
Me
OH

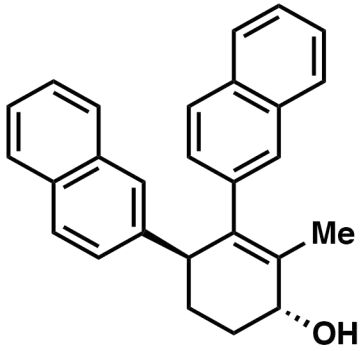
1.98
2.00
3.83
1.00
0.98
1.01
1.06
2.87
1.00
1.07
1.07
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)


F
F
Me
OH

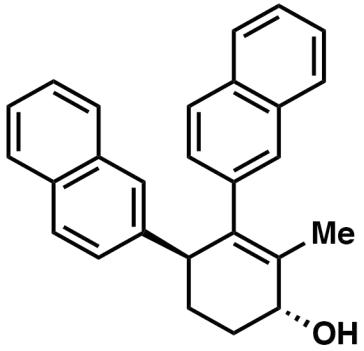
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


F
F
Me
OH

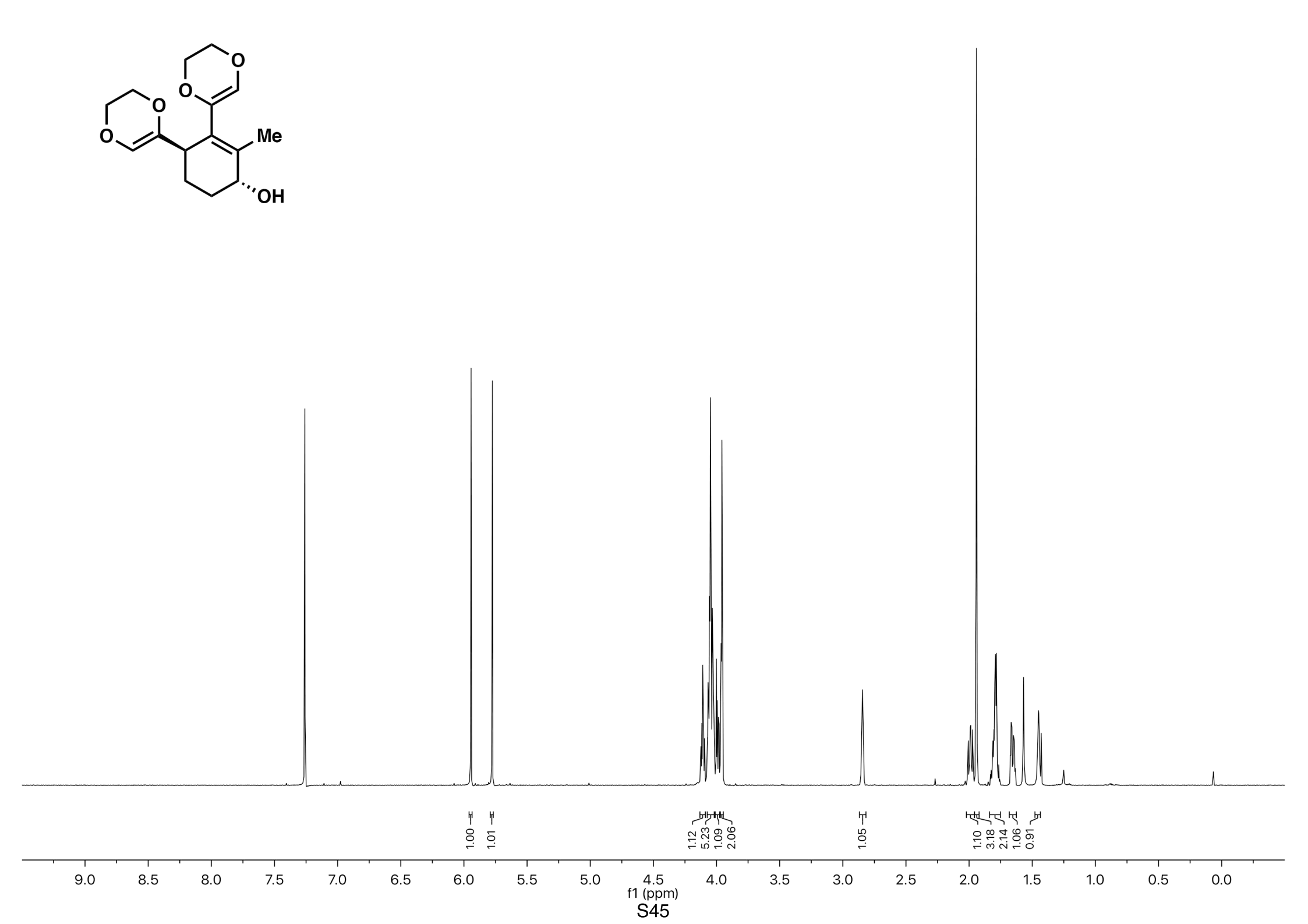
1.00
0.89
8.0
-108.5
-109.0
-109.5
-110.0
-110.5
-111.0
-111.5
-112.0
-112.5
-113.0
-113.5
-114.0
-114.5
-115.0
-115.5
-116.0
-116.5
-117.0
-117.5
f1 (ppm)

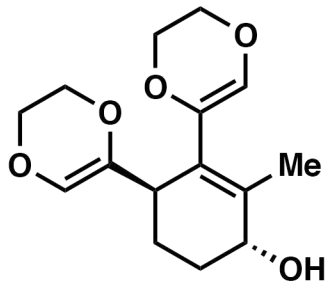

Me
OH

1.02
1.01
2.91
1.00
1.93
1.01
3.88
0.98
1.00
1.00
1.02
1.10
3.05
1.92
1.14
.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)

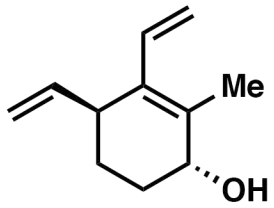

Me
OH

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

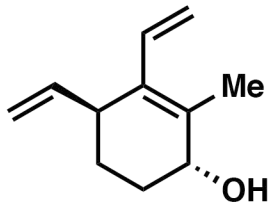

O
O
O
O
Me
OH
1.00
1.01
1.12
5.23
1.09
2.06
1.05
1.10
3.18
2.14
1.06
0.91
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
O
O
O
Me
OH

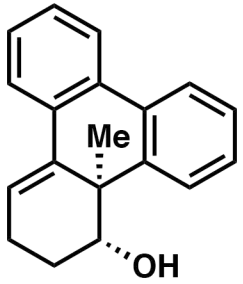
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


Me
OH

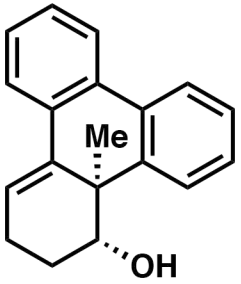
1.00
1.00
1.03
1.01
1.01
1.00
1.00
1.01
3.08
1.07
1.09
1.05
0.93
0.99
.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

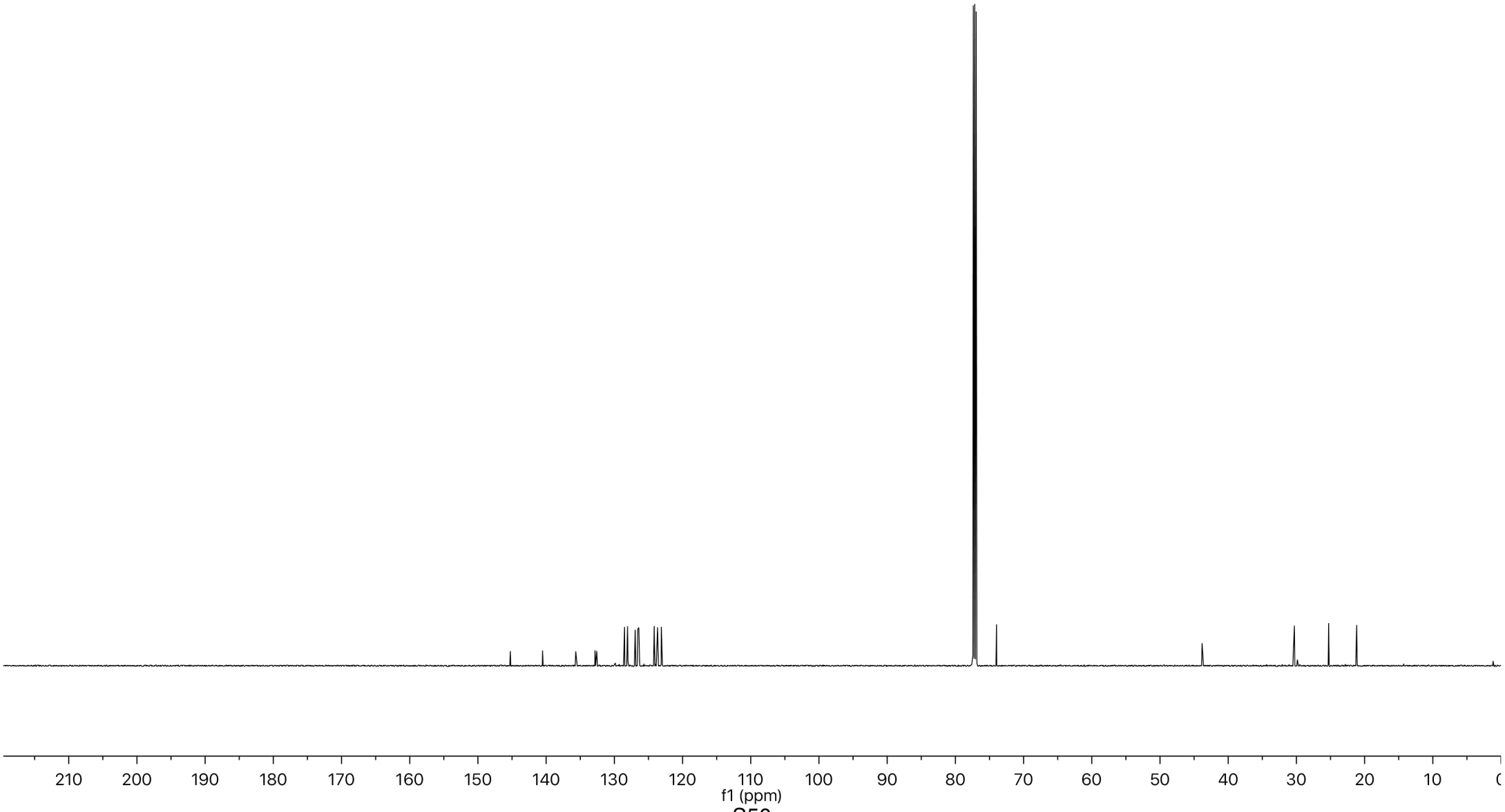

Me
OH

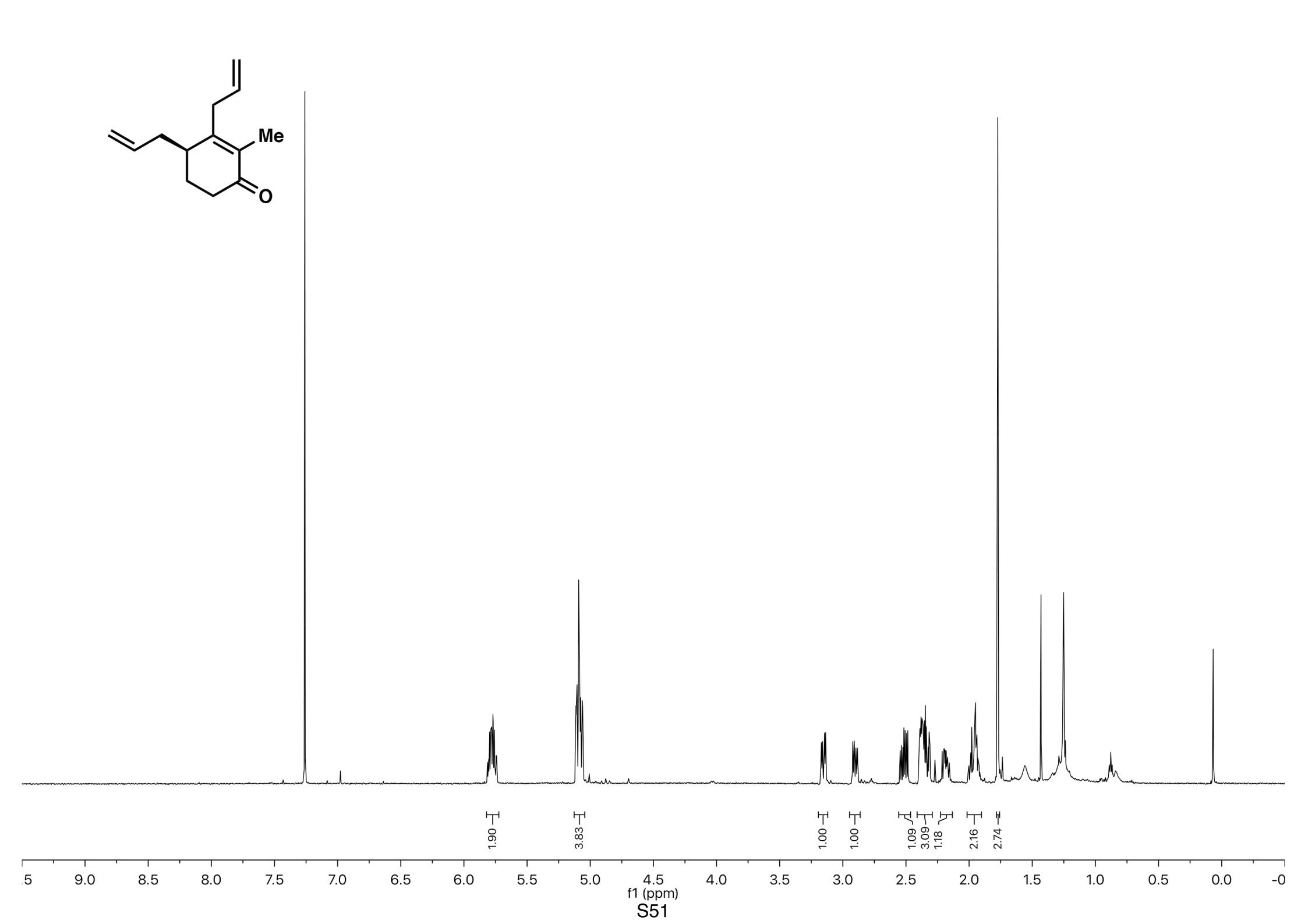
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

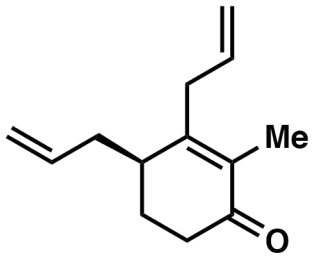

Me
OH

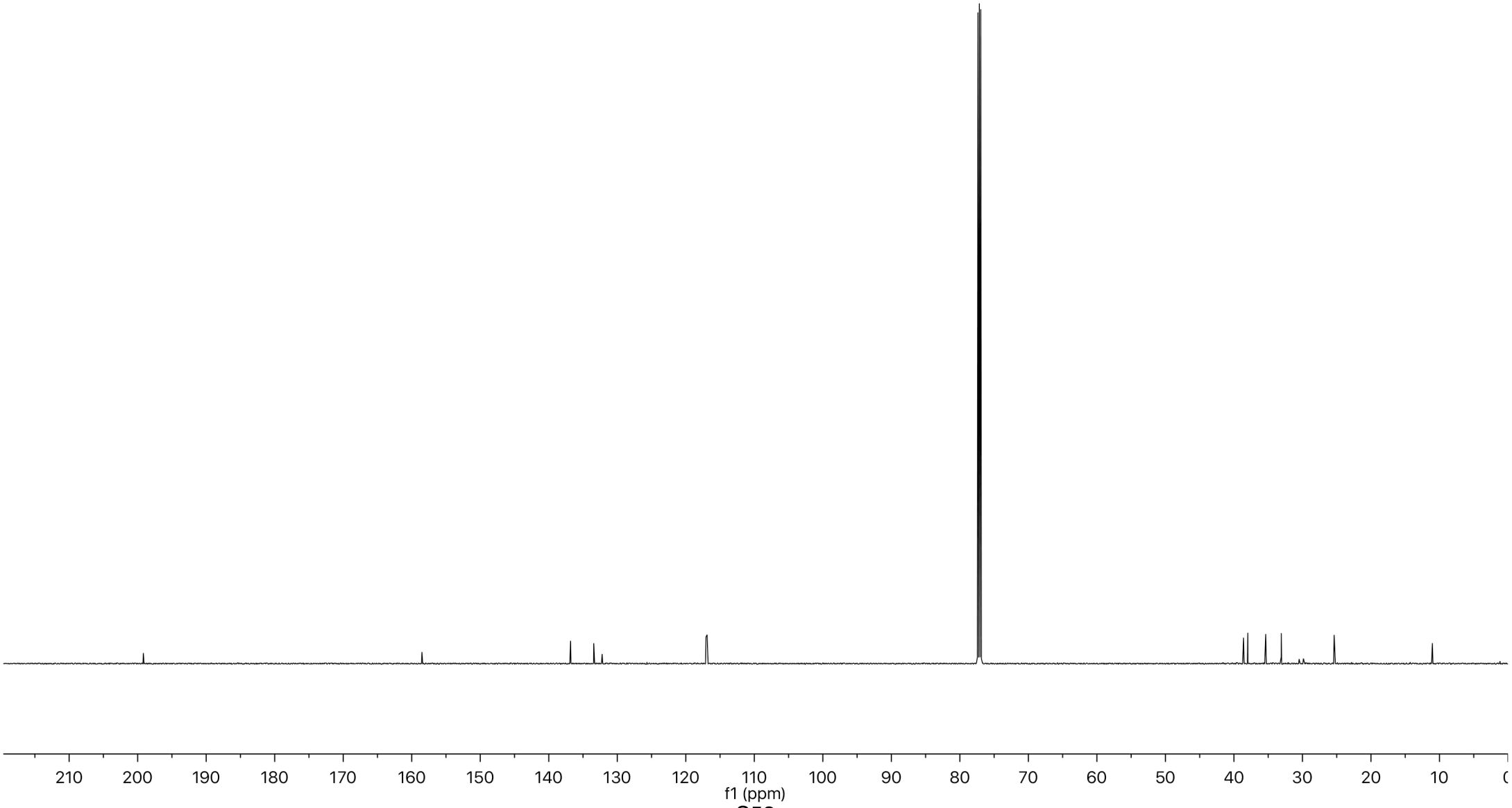
1.01
2.05
1.26
1.25
3.28
1.00
1.04
1.07
1.20
2.11
0.92
3.05
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

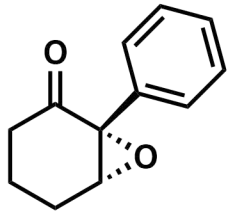

Me
OH

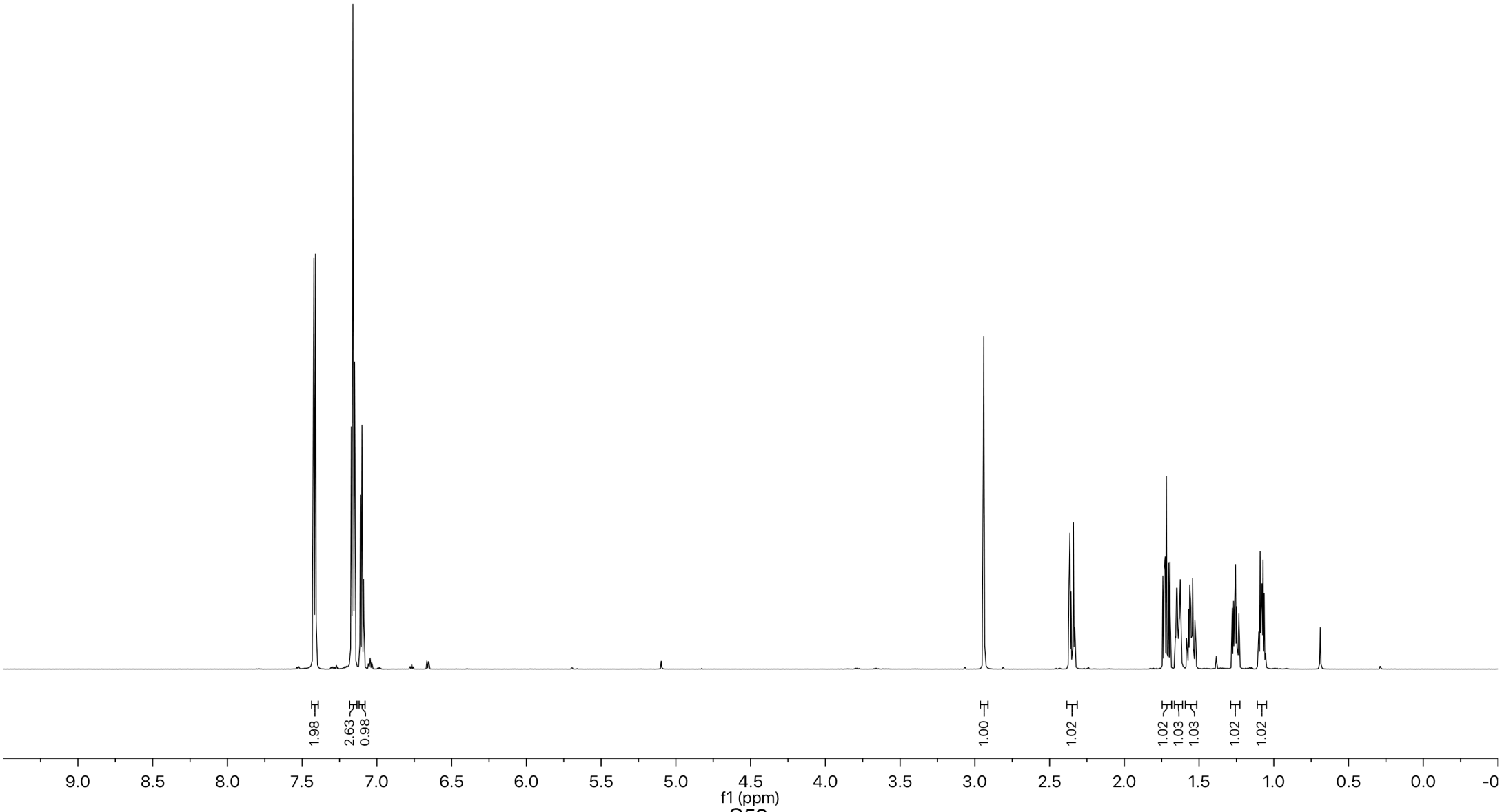

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

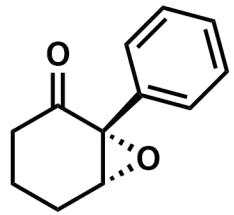

Me
O
1.90
3.83
1.00
1.00
1.09
3.09
1.18
2.16
2.74
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Me
O

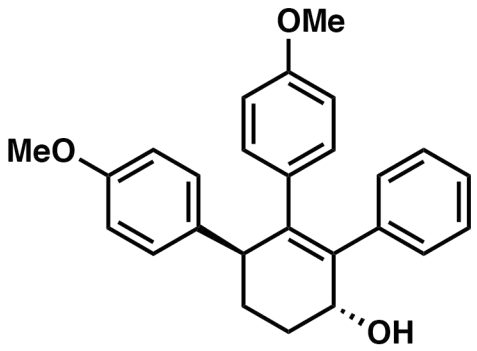

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


O
O

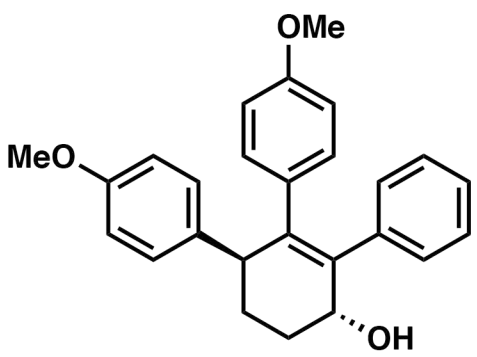

1.98
2.63
0.98
1.00
1.02
1.02
1.03
1.03
1.02
1.02
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)


O
O

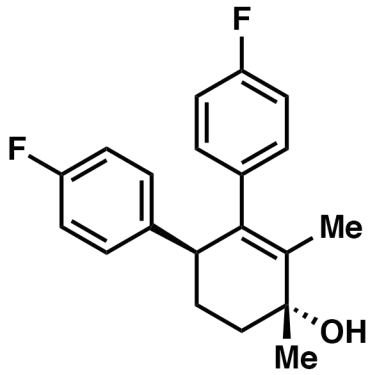
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OMe
MeO
OH

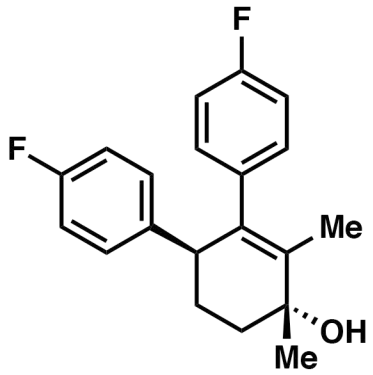
2.00
2.05
1.97
2.94
1.85
1.78
1.00
0.99
3.03
2.99
0.99
1.04
1.01
0.99
1.12
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)


OMe
MeO
OH

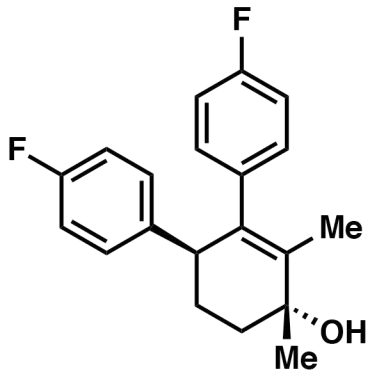
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


F
F
Me
OH
Me

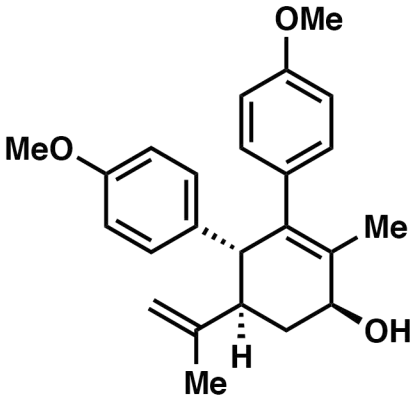
3.97
3.96
1.00
1.11
1.11
3.04
1.12
1.07
3.09
0.91
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)


F
F
Me
OH
Me

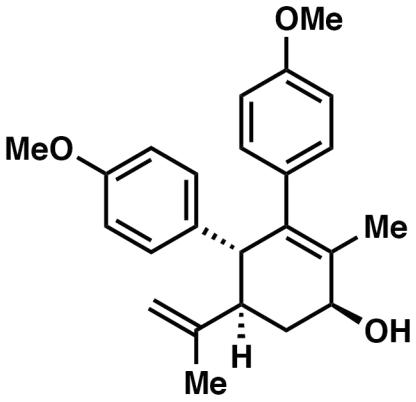
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


F
F
Me
OH
Me

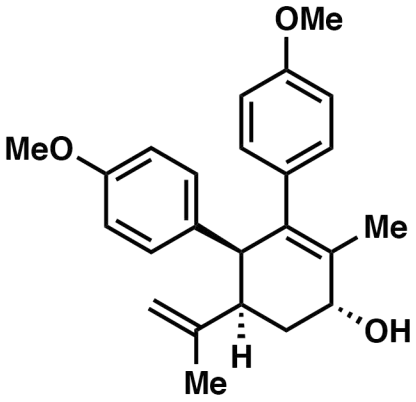
1.03
1.00
8.0
-108.5
-109.0
-109.5
-110.0
-110.5
-111.0
-111.5
-112.0
-112.5
-113.0
-113.5
-114.0
-114.5
-115.0
-115.5
-116.0
-116.5
-117.0
-117.5
f1 (ppm)


OMe
MeO
Me
OH
H
Me

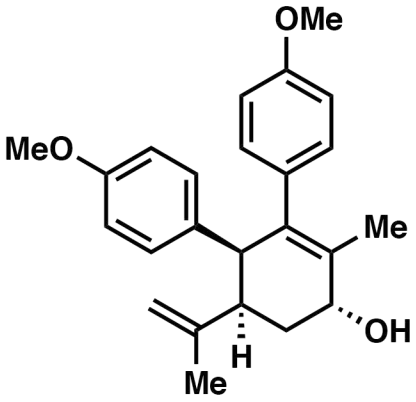
1.98
2.03
1.93
2.00
1.01
1.02
1.00
0.92
3.00
2.96
1.00
1.04
1.05
1.01
3.04
3.02
.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)


OMe
MeO
Me
OH
H
Me

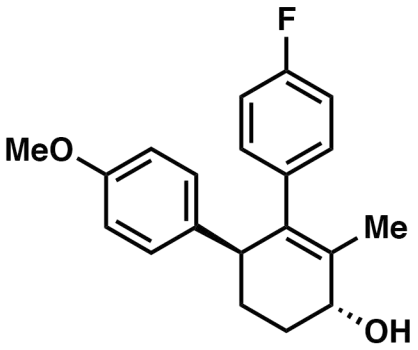
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


OMe
MeO
Me
OH
H
Me

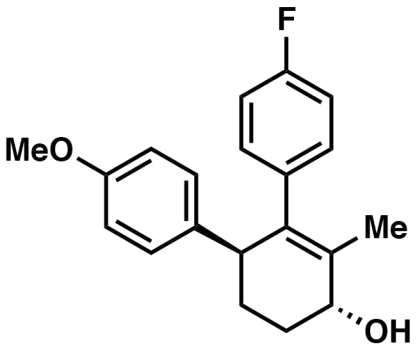
1.94
1.97
3.93
1.01
1.00
1.00
6.01
1.01
0.99
1.02
1.02
3.81
3.15
.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)

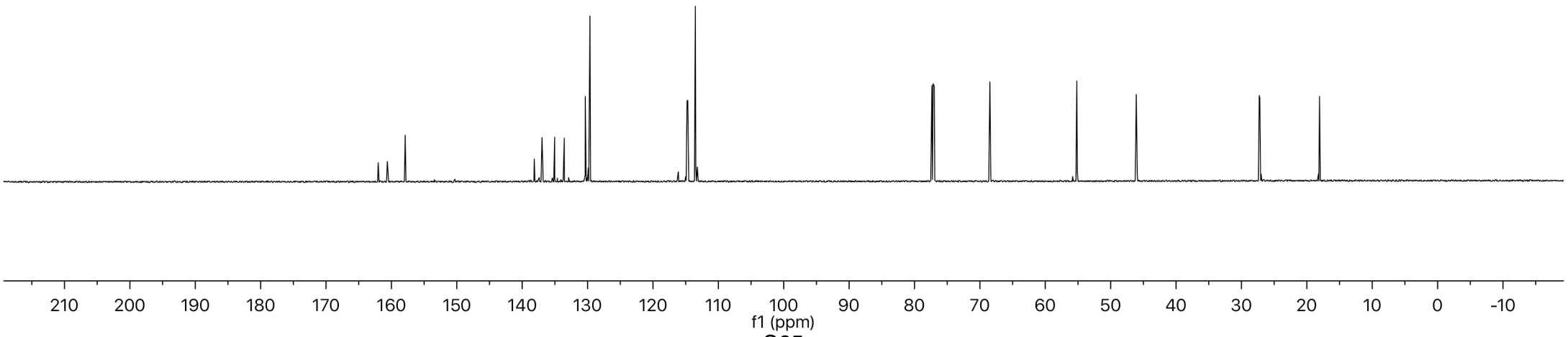

OMe
MeO
Me
OH
H
Me

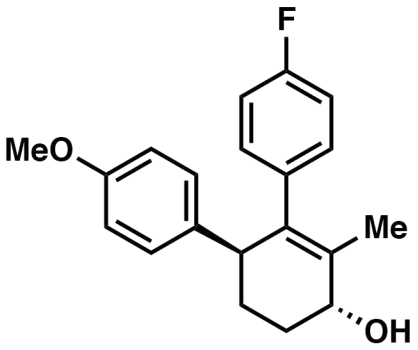
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


F
MeO
Me
OH

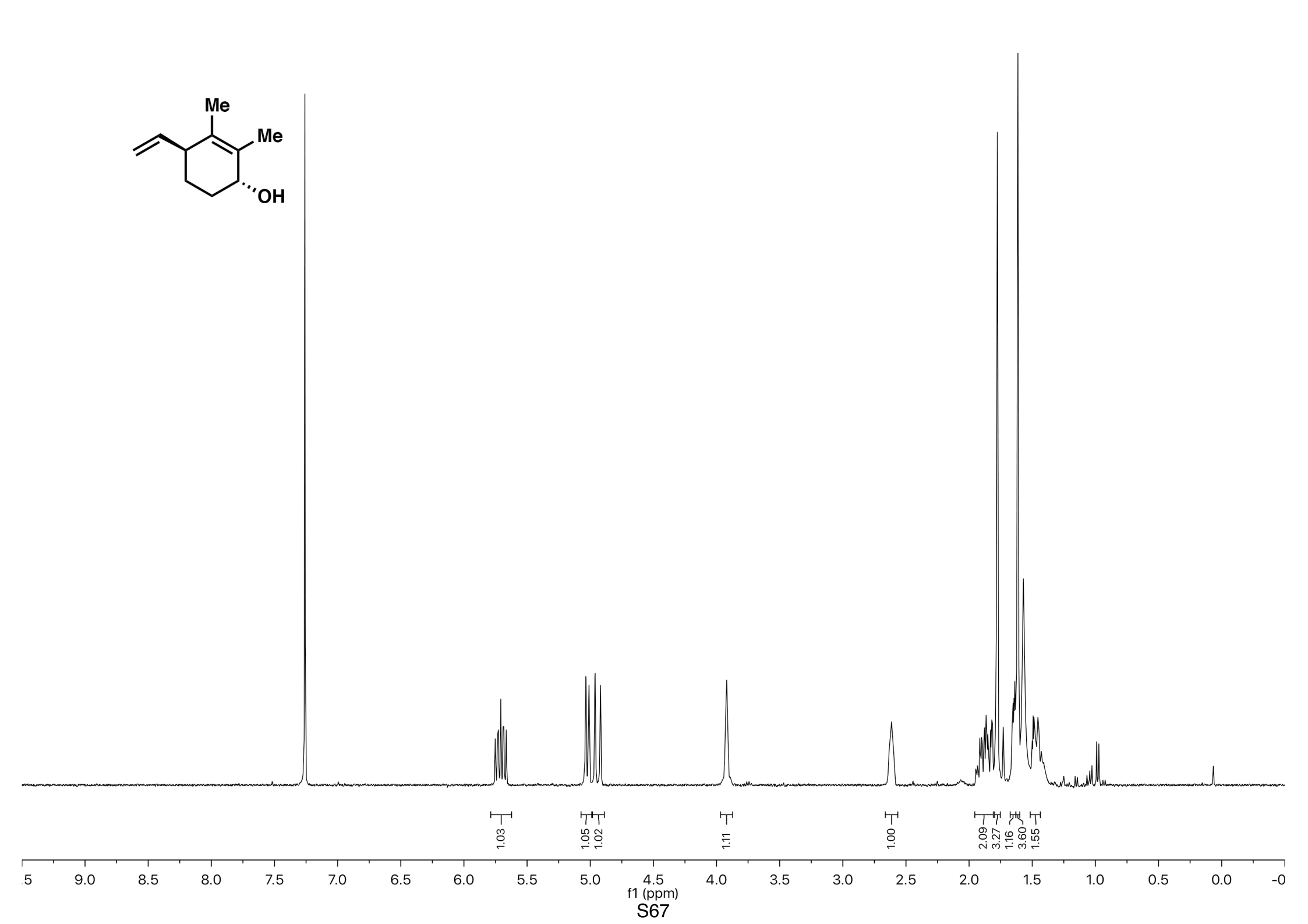
4.04
1.86
2.07
1.02
3.06
1.03
1.07
1.03
1.04
3.03
2.21
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

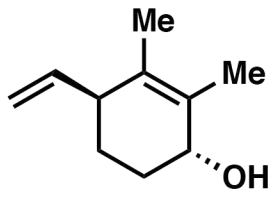

F
MeO
Me
OH


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

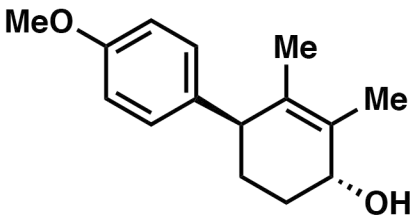

F
MeO
Me
OH

8.0
-108.5
-109.0
-109.5
-110.0
-110.5
-111.0
-111.5
-112.0
-112.5
-113.0
-113.5
-114.0
-114.5
-115.0
-115.5
-116.0
-116.5
-117.0
-117.5
f1 (ppm)

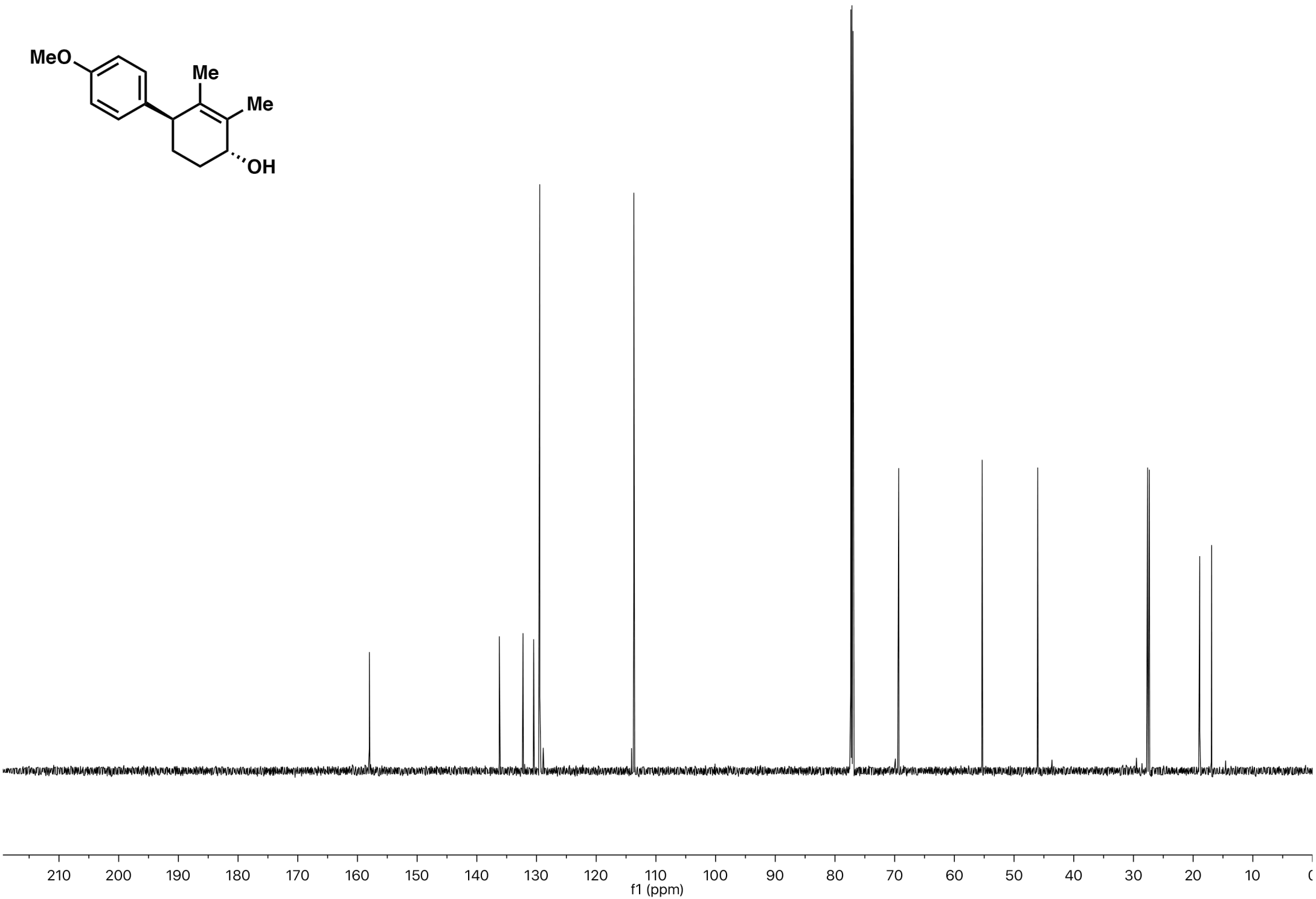

Me
Me
OH
1.03
1.05
1.02
1.11
1.00
2.09
3.27
1.16
3.60
1.55
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)

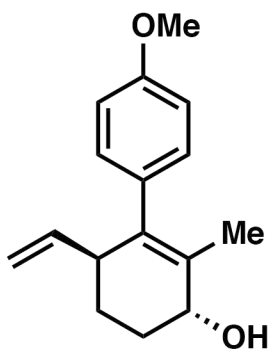

Me
Me
OH

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

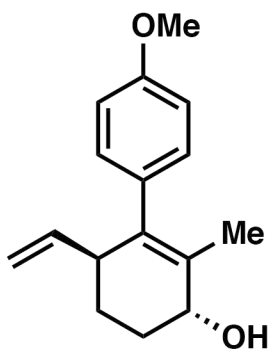

MeO
Me
Me
OH

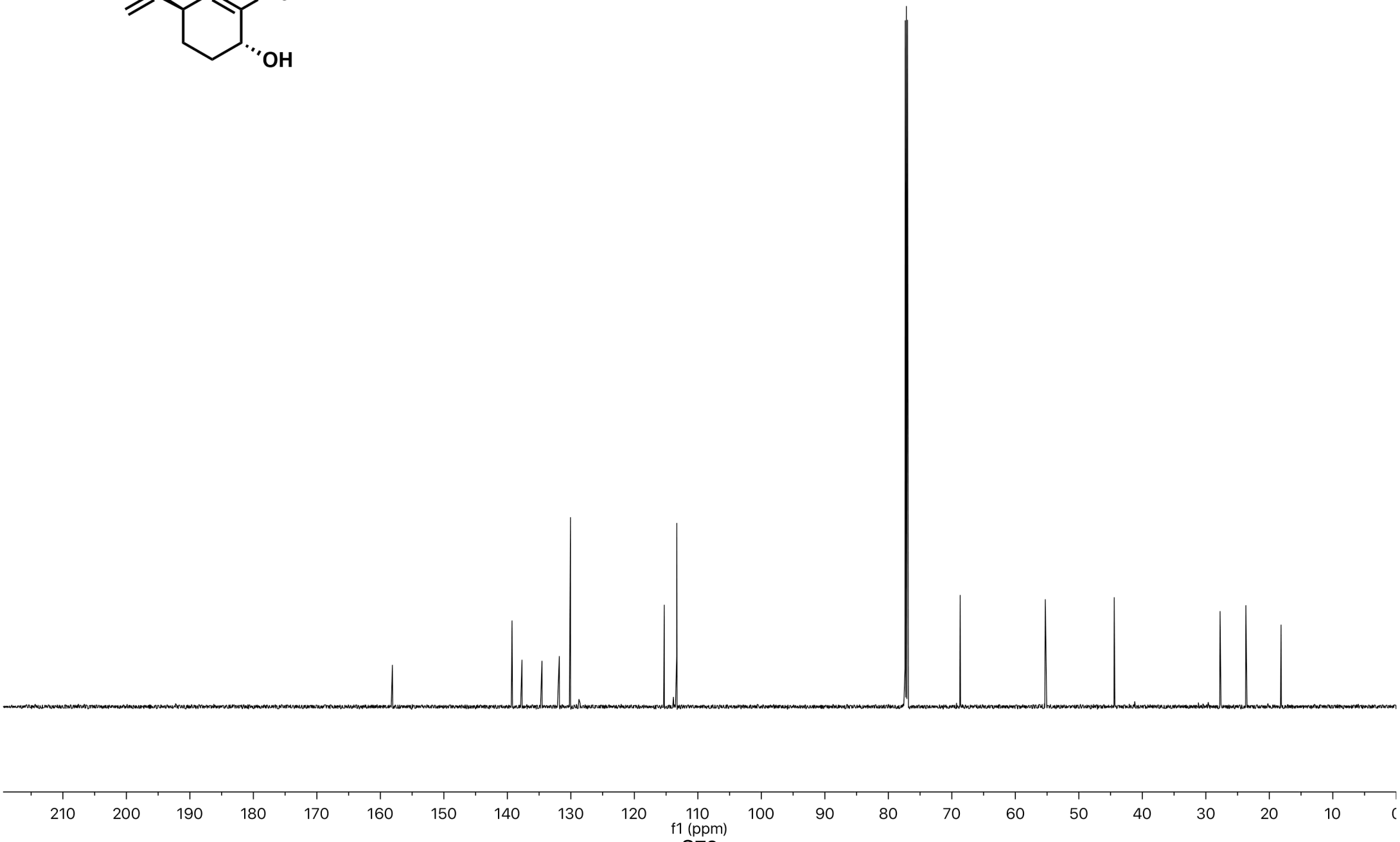
1.92
1.93
1.00
3.14
1.00
1.03
2.99
1.06
6.05
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)

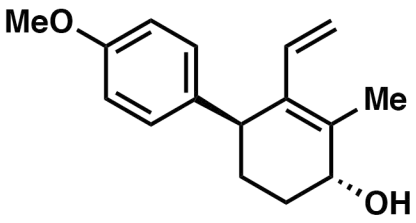

MeO
Me
Me
OH
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


OMe
Me
OH

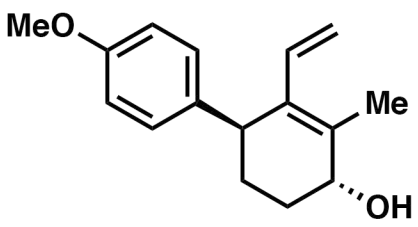
1.96
2.08
0.97
0.99
0.99
1.00
3.21
1.00
1.11
1.03
1.04
3.01
1.11
0.86
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


OMe
Me
OH

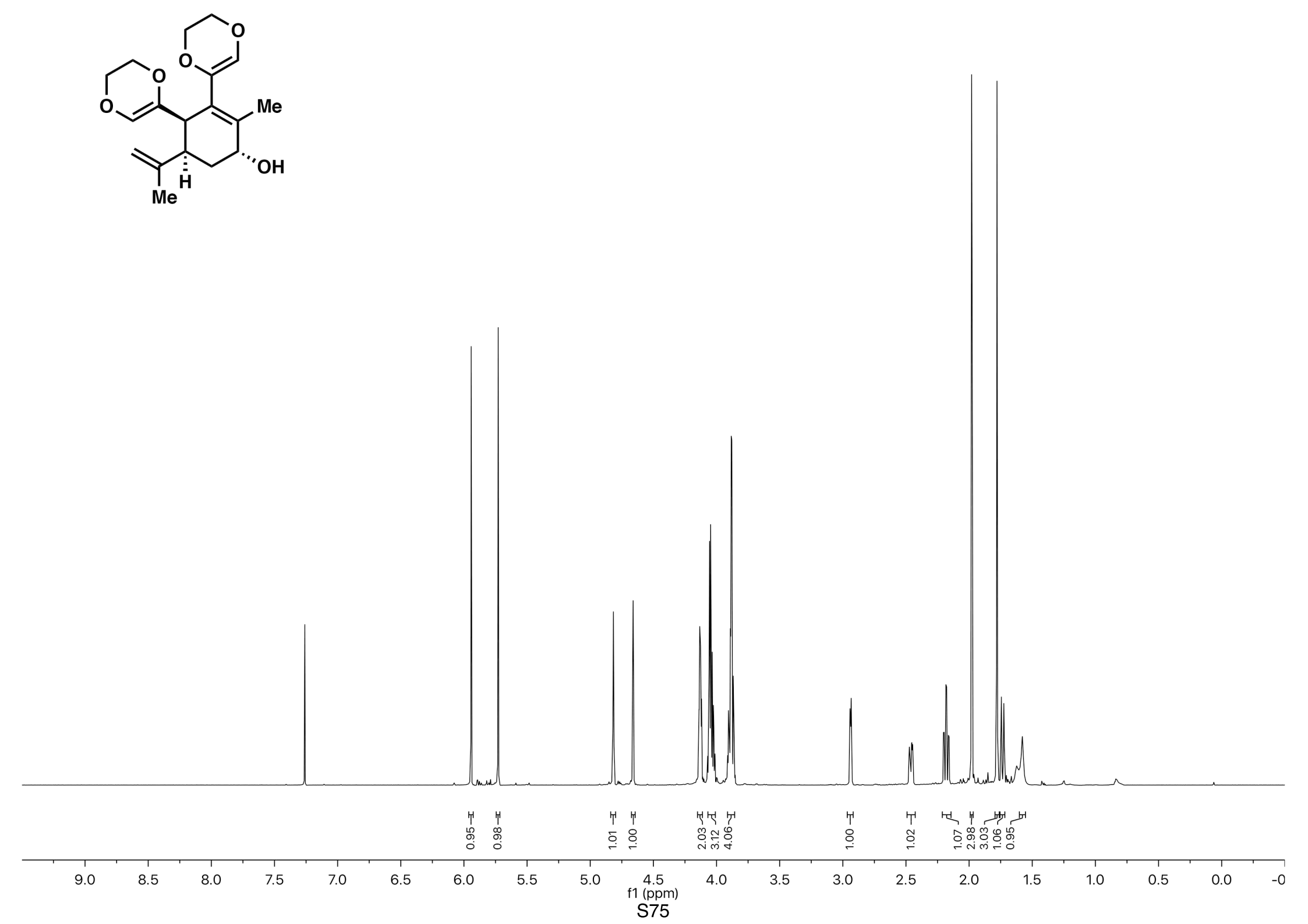

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

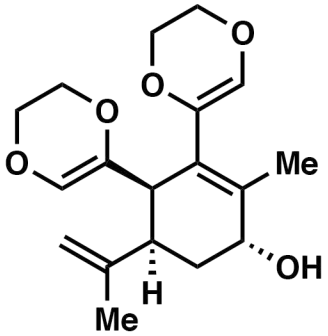

MeO
Me
OH

2.02
1.99
1.00
2.05
1.00
3.05
1.03
1.04
3.04
1.04
1.19
2.05
.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

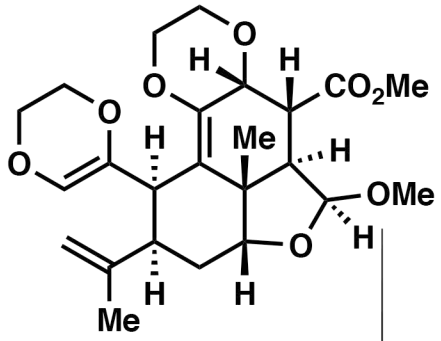

MeO
Me
OH

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

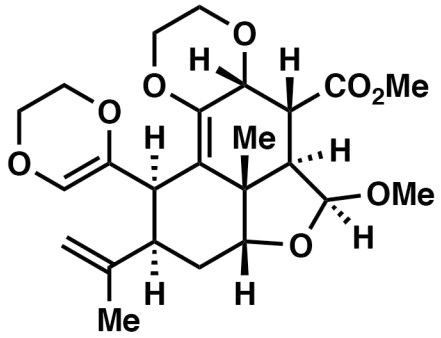

O
O
O
O
Me
OH
H
Me
0.95
0.98
1.01
1.00
2.03
3.12
4.06
1.00
1.02
1.07
2.98
3.03
1.06
0.95
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)


O
O
O
O
Me
OH
H
Me

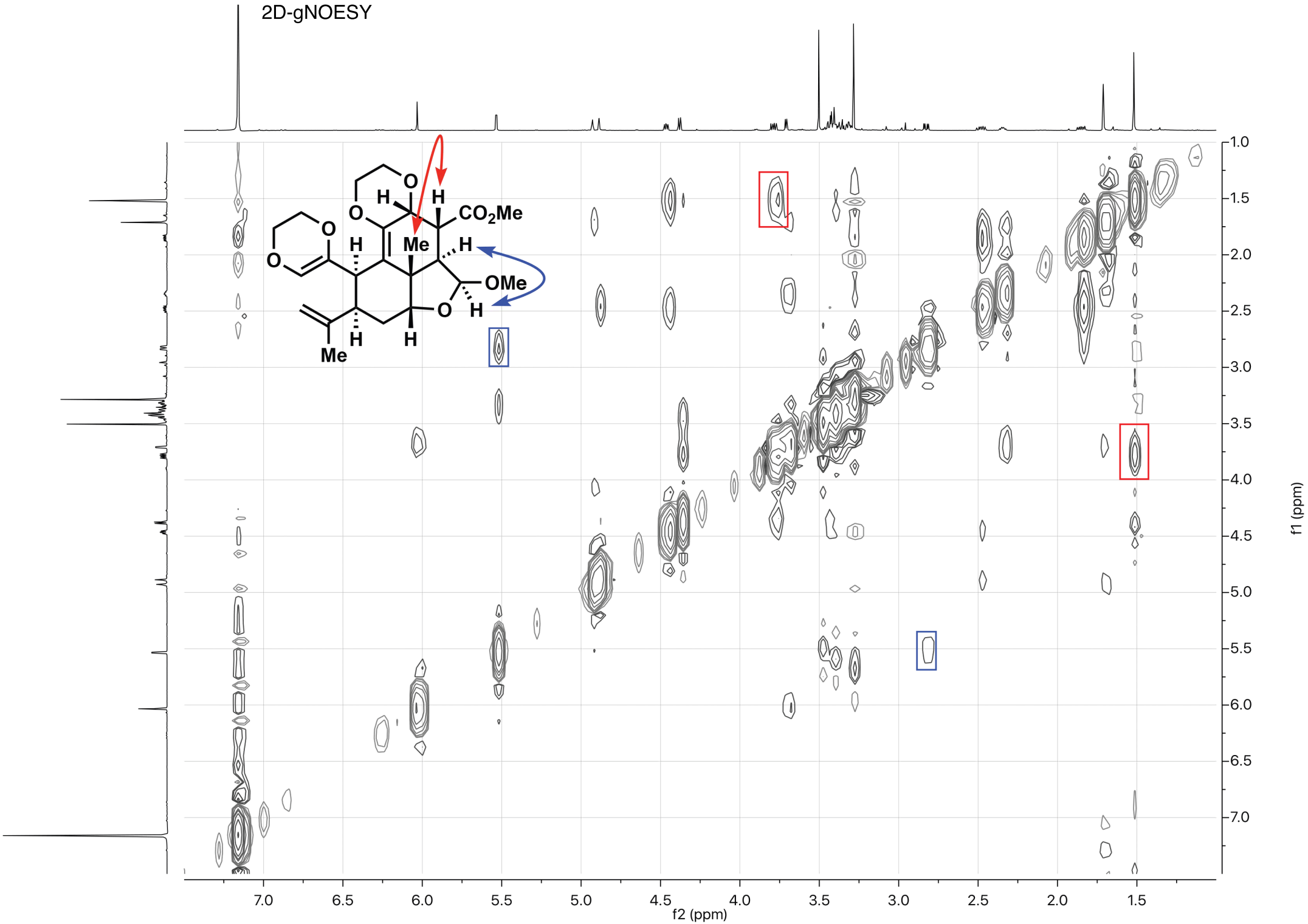
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

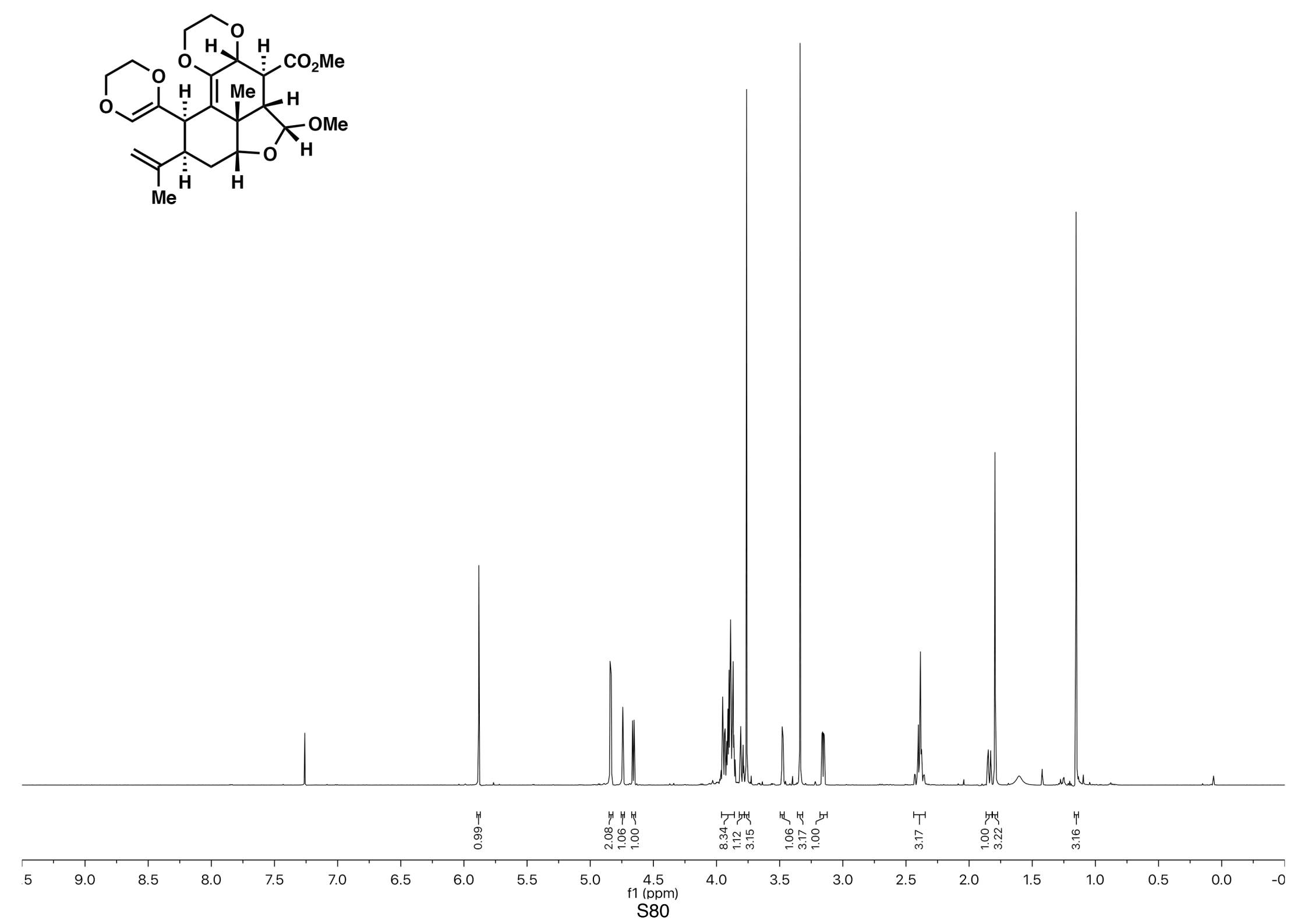

O
H
H
O
CO2Me
O
H
Me
H
O
OMe
O
H
H
H
Me

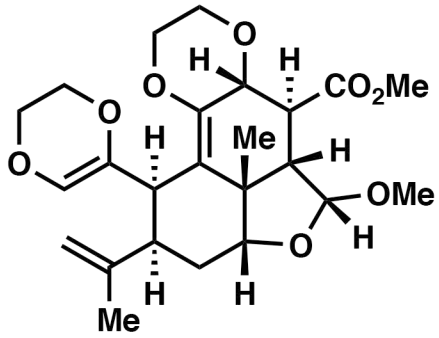
0.99
1.00
1.00
1.04
0.98
0.98
1.01
1.03
3.06
9.41
3.14
1.01
1.03
1.02
1.17
3.01
3.07
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)


O
H
H
O
CO2Me
O
H
Me
H
O
OMe
O
H
H
H
Me

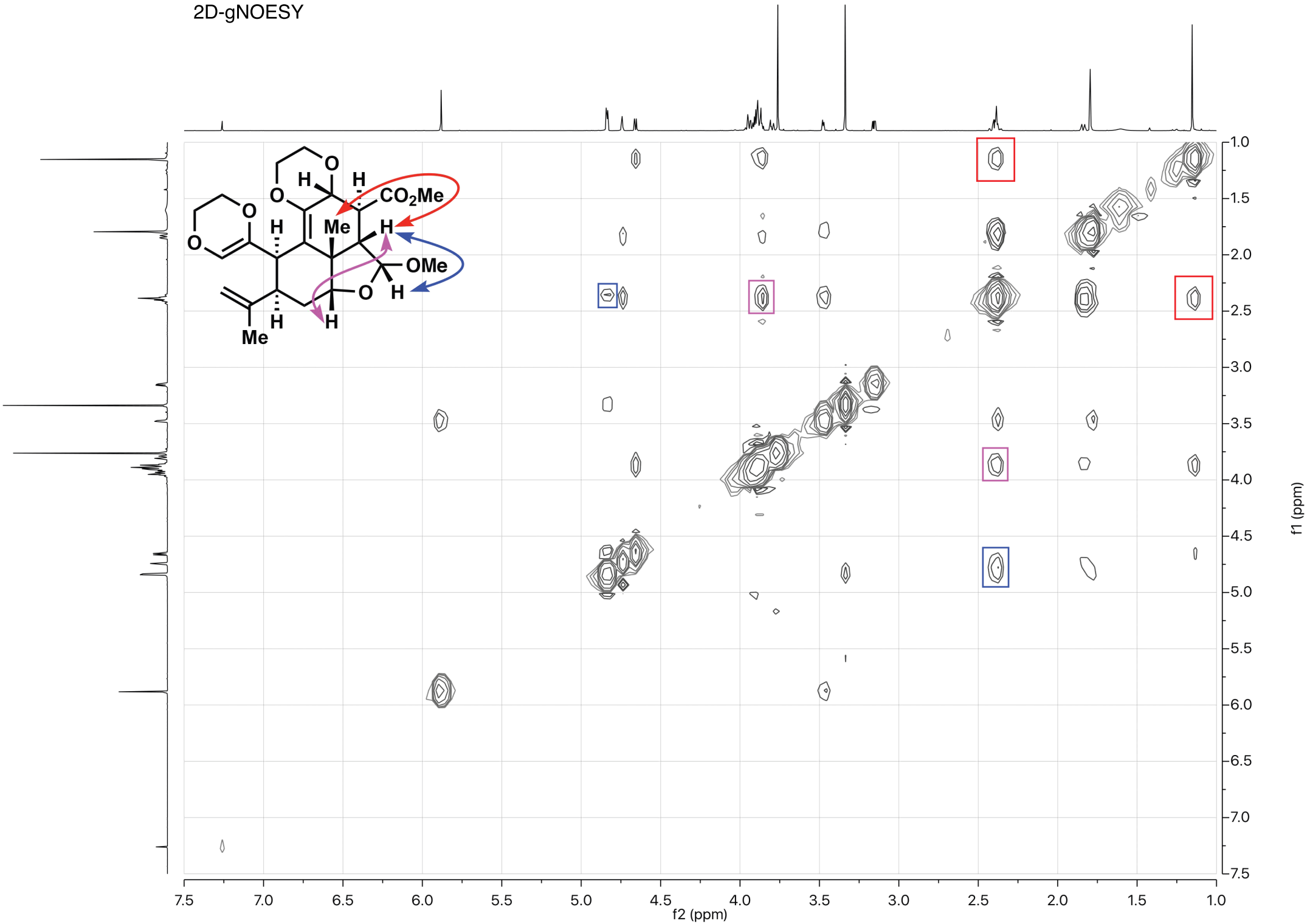
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

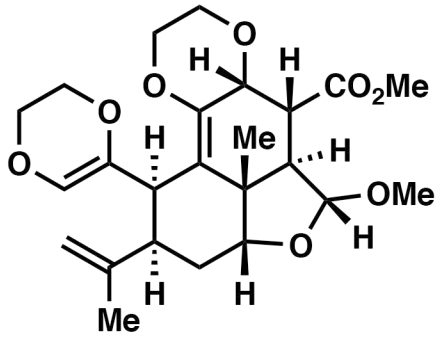

2D-gNOESY
CO2Me
OMe
Me
Me
f2 (ppm)
f1 (ppm)

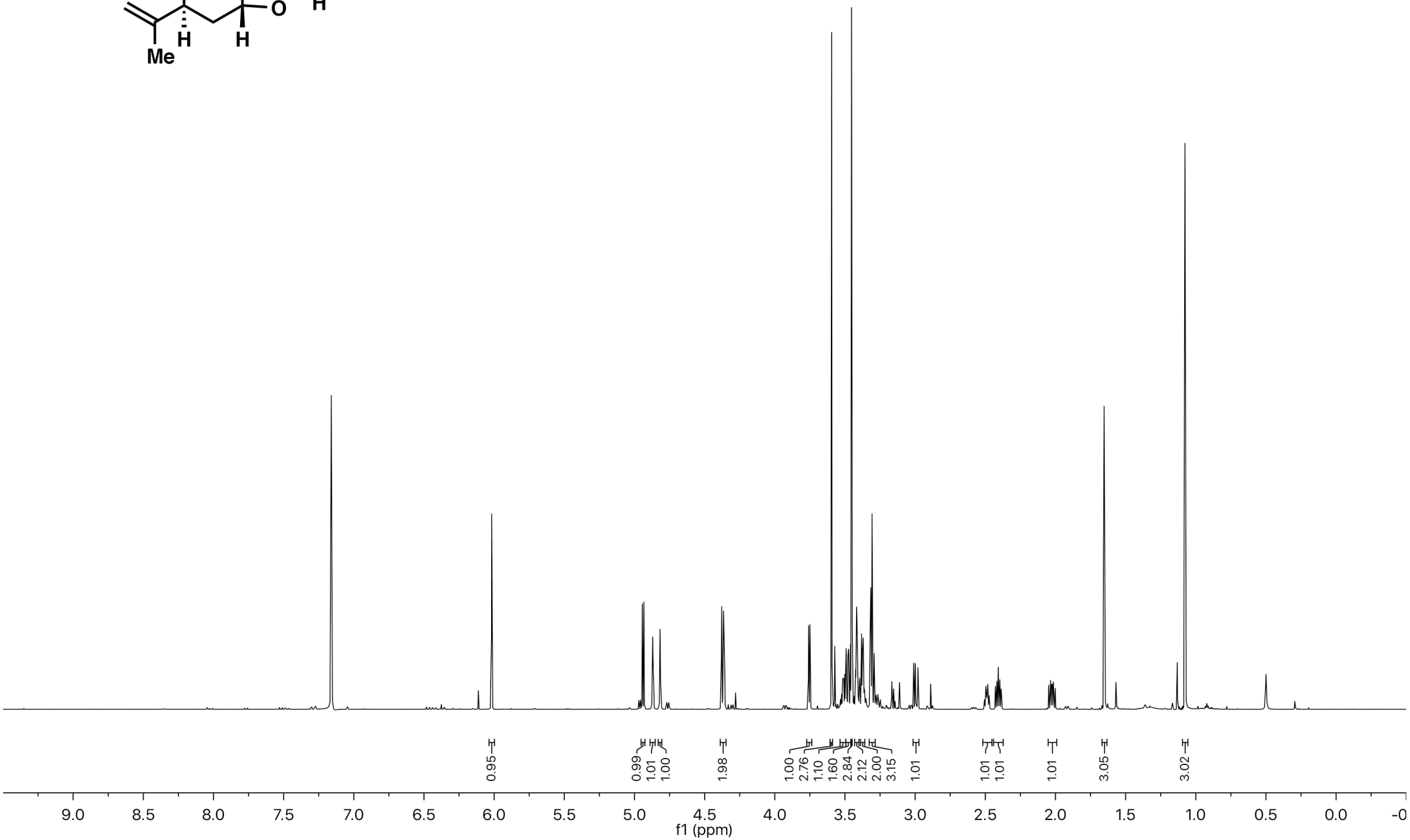

O
H
H
O
CO2Me
O
H
Me
H
O
OMe
O
H
H
H
Me
0.99
2.08
1.06
1.00
8.34
1.12
3.15
1.06
3.17
1.00
3.17
1.00
3.22
3.16
.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)

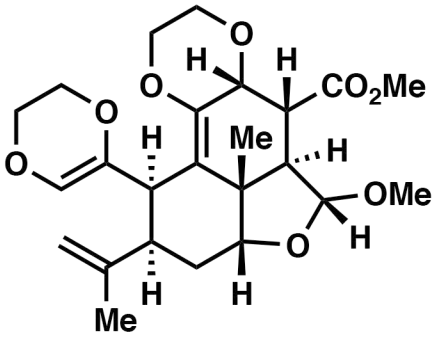

O
H
H
O
CO2Me
O
H
Me
H
O
OMe
O
H
H
H
Me

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

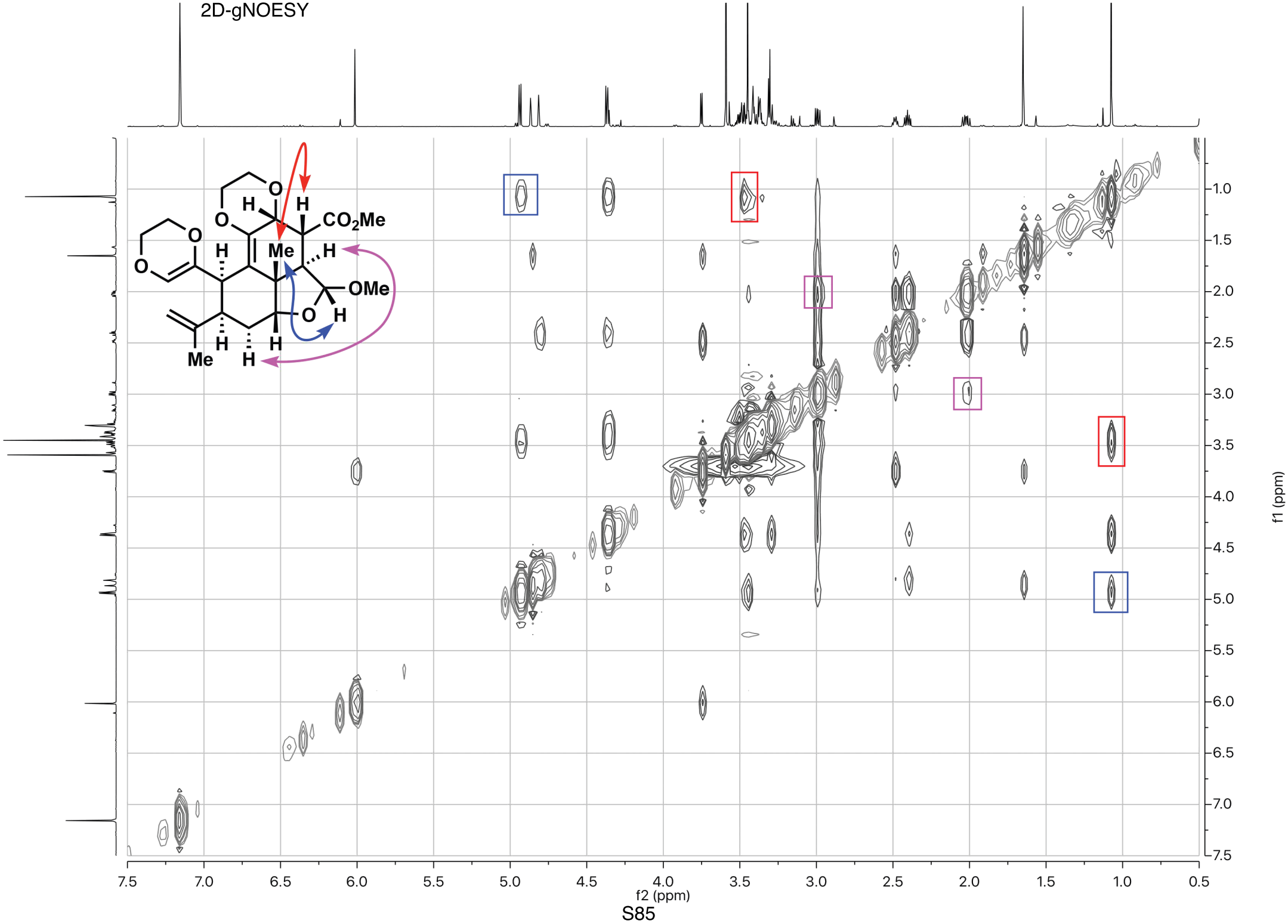

2D-gNOESY
O
H
H
O
CO2Me
O
H
Me
H
OMe
O
H
H
H
Me
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
f1 (ppm)

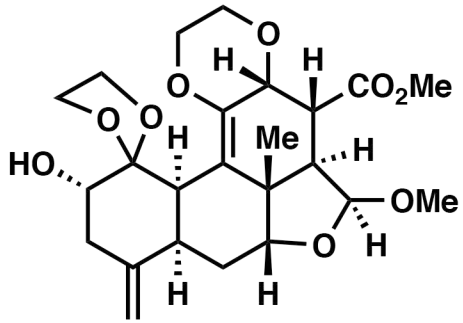

O
H
H
O
CO2Me
O
H
Me
H
O
OMe
H
O
H
H
Me


0.95
0.99
1.01
1.00
1.98
1.00
2.76
1.10
1.60
2.84
2.12
2.00
3.15
1.01
1.01
1.01
3.05
3.02
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
f1 (ppm)

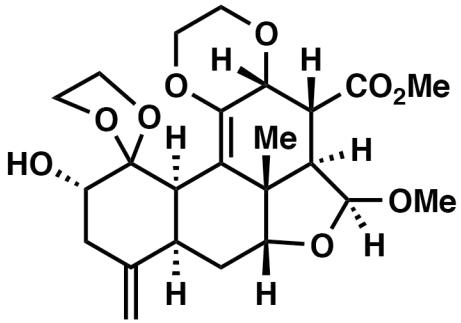

O
H
H
O
CO2Me
O
H
Me
H
O
OMe
O
H
H
H
Me

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

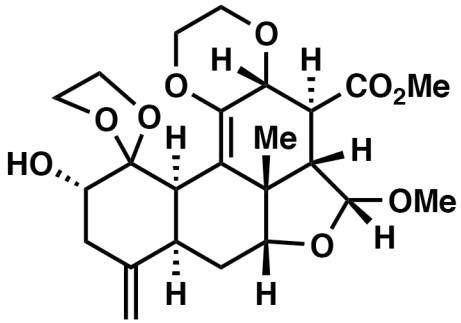

2D-gNOESY
O
H
H
CO2Me
O
O
H
Me
H
OMe
O
H
H
H
Me
H
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
f1 (ppm)


O
H
H
CO2Me
O
O
O
H
Me
H
HO
OMe
O
H
H
H

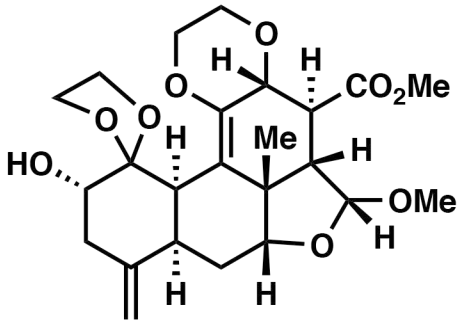
0.95
0.95
0.95
0.98
1.04
1.07
1.08
1.16
2.17
1.29
1.19
3.74
2.24
1.13
2.93
0.98
1.01
1.04
1.00
1.04
1.06
3.01
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
H
H
CO2Me
O
O
O
H
Me
H
HO
OMe
O
H
H
H

20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
H
H
CO2Me
O
O
O
H
Me
H
HO
OMe
O
H
H
H

2.00
1.01
1.00
3.43
3.35
2.25
3.06
1.97
1.04
3.07
0.95
1.01
1.04
1.03
1.01
1.11
1.07
3.14
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)


O
H
H
CO2Me
O
O
H
Me
H
HO
OMe
O
H
H
H

20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)