Supporting Information

Platinum-Catalyzed α,β-Unsaturated Carbene Formation in the Formal Syntheses of Frondosin B and Liphagal

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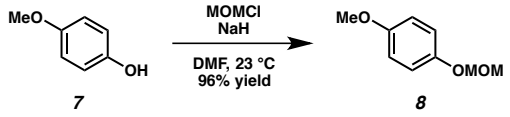
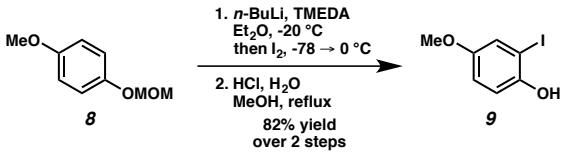
Materials and Methods

Reactions were performed under an argon atmosphere unless otherwise noted. Tetrahydrofuran, ether, dichloromethane and toluene were purified by passing through activated alumina columns. 1,4-dioxane was distilled over sodium/benzophenone. All other solvents used were ACS grade. Ethyl diazoacetate was distilled prior to use, and all other reagents were used as received, unless otherwise noted. Zeise's Dimer ($[(C_2H_4)PtCl_2]_2$) was purchased from Strem Chemical Company. All other commercially available chemicals were purchased from Alfa Aesar (Ward Hill, MA), Sigma-Aldrich (St. Louis, MO), Oakwood Products, (West Columbia, SC), Strem (Newburport, MA) and TCI America (Portland, OR). Qualitative TLC analysis was performed on 250 mm thick, 60 Å, glass backed, F254 silica (Silicycle, Quebec City, Canada). Visualization was accomplished with UV light and exposure to $KMnO_4$ stain solution followed by heating. Flash chromatography was performed using Silicycle silica gel (230-400 mesh). ^{1}H NMR spectra were acquired on a Varian 400 MR (at 400 MHz), a Varian Mercury Plus (at 400 MHz), or a Varian Unity Inova (at 500 MHz) and are reported in ppm relative to $SiMe_4$ (δ 0.00). ^{13}C NMR spectra were acquired on a Varian 400 MR (at 101 MHz), a Varian Mercury Plus (at 100 MHz), or a Varian Unity Inova (at 125 MHz) and are reported in ppm relative to $SiMe_4$ (δ 0.00). IR spectra were obtained on NaCl plates (film) with a Shimadzu IRPrestige 21 FT-IR. High resolution mass spectrometry data were acquired by the Proteomics and Mass Spectrometry Core Facility at University of Georgia on a Thermo Scientific Orbitrap Elite Hybrid Ion Trap-Orbitrap MS.

Synthesis of Frondosin B

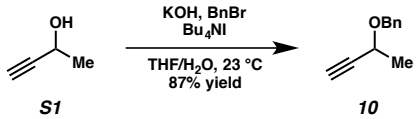


Methoxymethyl Ether 8. To a solution of 4-methoxyphenol (**7**, 12.4 g, 100 mmol) in DMF (100 mL) at 23 °C (with an external water bath) was added NaH (6.00 g, 60% dispersion in mineral oil, 150 mmol) portionwise at such a rate as to control H_2 evolution. Once the addition was complete, MOMCl (9.11 mL, 120 mmol) was added via additional funnel at a rate of 1 drop/s, taking a total of approx. 10 min. Once the addition was complete, the reaction mixture was stirred an additional 1 h, at which point TLC indicated consumption of starting material. The reaction mixture was then poured into H_2O (300 mL) and extracted with pentane (3 x 75 mL). The combined organic extracts were washed sequentially with H_2O (100 mL) and brine (100 mL), dried with Na_2SO_4, and concentrated. The crude residue was purified by flash column chromatography (hexanes → 4:1 hexanes/Et_2O eluent) to give methoxymethyl ether **8** as a colorless liquid (16.1 g, 96% yield, R_f = 0.62 in 7:3 hexanes/EtOAc). The spectroscopic data for methoxymethyl ether **8** matched those presented in the literature.[1]

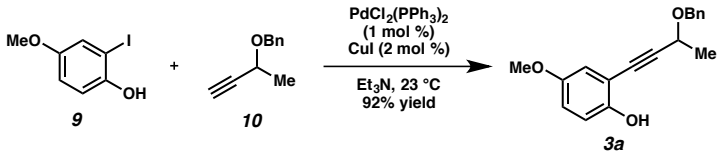


Phenol 9. To a 500 mL round bottom flask charged with a large stir bar and a solution of methoxymethyl ether **8** (16.8 g, 100 mmol) and TMEDA (18.0 mL, 120 mmol) in Et_2O (100 mL) at -78 °C was added *n*-BuLi (48.0 mL, 2.5 M in hexanes, 120 mmol) over 60 s. The reaction mixture was stirred at this temperature for 5 min and then allowed to warm to -20 °C and stir for an additional 30 min. The reaction mixture was then cooled to -78 °C and a solution of I_2 (33.0 g, 130 mmol) in Et_2O (200 mL) was added via cannula over 10 min. During this addition, the reaction mixture became a thick slurry, and manual swirling was necessary to ensure full mixing. When the addition was complete, the reaction mixture was swirled an additional 5 min at -78 °C and then allowed to warm to ambient temperature with occasional swirling. Once the reaction mixture had reached ambient temperature, it was poured into a mixture of 1 M aq. $NaHCO_3$ (100 mL) and sat. aq. $Na_2S_2O_3$ (100 mL). The organic layer was separated and washed sequentially with 1 M aq. HCl (100 mL), 1 M aq. NaOH (100 mL) and brine (100 mL). The organic extract was dried with $MgSO_4$ and concentrated to give the aryl iodide (R_f = 0.89 in 9:1 hexanes/EtOAc) as a yellow oil that was used immediately without further purification.

To a solution of the crude aryl iodide (assume 100 mmol) in MeOH (100 mL) at 23 °C was added 10% aq. HCl (30 mL, 100 mmol). The reaction mixture was heated to reflux for 20 min, at which point TLC indicated consumption of the iodide starting material. The reaction mixture was allowed to cool to ambient temperature and was then concentrated to remove MeOH. The resulting residue was partitioned between EtOAc (100 mL) and brine (100 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (50 mL). The combined organic extracts were washed with brine (100 mL), dried with $MgSO_4$, and concentrated. The crude residue was purified by flash column chromatography (19:1 hexanes/EtOAc eluent) to give phenol **9** as a colorless solid (20.4 g, 82% yield over 2 steps, R_f = 0.27 in 3:1 hexanes/EtOAc). The spectroscopic data for phenol **9** matched those presented in the literature.[2]

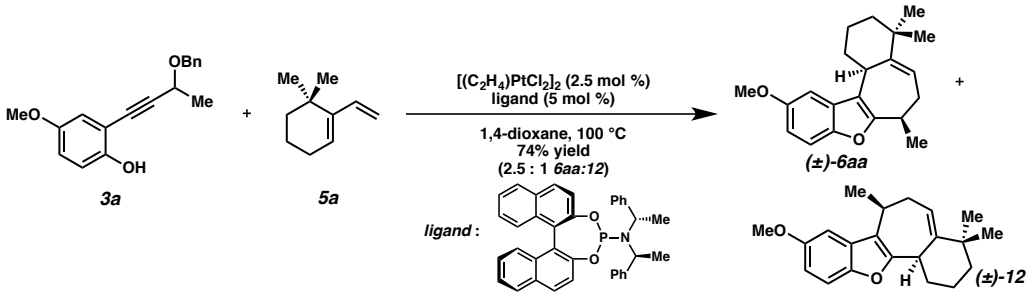


Benzyl Ether 10. To alcohol **S1** (13.5 g, 55% w/w in H_2O, 106 mmol) was added KOH pellets (85%, 14.0 g, 212 mmol). The solution was stirred until it partially solidified, at which point THF (20 mL) was added, followed by *n*-Bu_4NI (1.96 g, 5.30 mmol). A thermometer was placed directly into the reaction mixture, and BnBr (12.6 mL, 106 mmol) was added with vigorous stirring. When the reaction mixture reached 40 °C, the flask was submerged in an ice bath until the internal temperature reached 23 °C. The reaction was stirred an additional 1 h, then partitioned between pentane (150 mL) and H_2O (100 mL). The organic layer was washed sequentially with 1 M aq. HCl (50 mL), H_2O (50 mL), and brine (50 mL). The organic extract was dried with Na_2SO_4 and concentrated. The resulting pale yellow residue was purified by flash column chromatography (19:1 hexanes/EtOAc eluent) to give benzyl ether **10** (14.7 g, 87% yield, R_f = 0.36 in 19:1 hexanes/EtOAc) as a colorless liquid. The spectroscopic data for ether **10** matched those previously reported.[3]



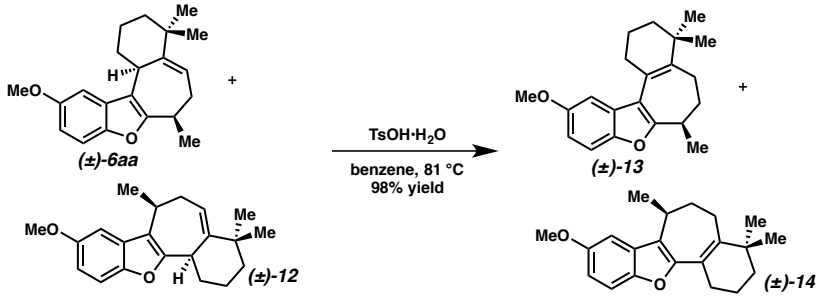
Alkyne 3a. A mixture of aryl iodide **9** (5.01 g, 20.0 mmol), $PdCl_2(PPh_3)_2$ (140 mg, 0.200 mmol), and CuI (76.2 mg, 0.400 mmol) were stirred dry under vacuum until a fine powder resulted. The resulting powder was suspended/dissolved in Et_3N (40 mL) at 23 °C, and alkyne **10** (3.54 g, 22.0 mmol) was added neat via tared syringe. The reaction mixture became black and was stirred for 3 h at ambient temperature, at which point TLC indicated consumption of iodide **9**. Then H_2O (20 mL) was added and Et_3N was removed in vacuo. The resulting residue was suspended in 1 M aq. HCl (100 mL) and extracted with Et_2O (3 x 50 mL). The organic extracts were then stirred with 0.2 M aq. Na_3EDTA (100 mL) for 30 min, separated, washed with brine (100 mL), dried with $MgSO_4$, and concentrated. The crude residue was purified by flash column chromatography (9:1 hexanes/EtOAc eluent) and concentrated. This product was then allowed to stand 16 h at -10 °C to further precipitate Pd residue. This material was dissolved in Et_2O (20 mL) and filtered through a plug of SiO_2, rinsing with Et_2O (100 mL) to give alkyne **3a** (5.22 g, 92% yield, R_f = 0.18 in 9:1 hexanes/EtOAc) as an orange oil.

Data for alkyne 3a.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.27 (comp. m, 5H), 6.89-6.82 (comp. m, 3H), 5.41 (s, 1H), 4.83 (d, *J* = 11.7 Hz, 1H), 4.59 (d, *J* = 11.7 Hz, 1H), 4.49 (q, *J* = 6.3 Hz, 1H), 3.76 (s, 3H), 1.59 (d, *J* = 6.3 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2, 151.3, 137.9, 128.7, 128.2, 128.1, 117.8, 115.82, 115.76, 109.1, 96.4, 79.7, 71.1, 65.2, 56.1, 22.5.
IR (film): 3383 (br), 2985, 2935, 2865, 2834, 1494, 1275, 1204, 1167, 1090, 1035, 814 cm^{-1}.
MS (DART): m/z calc'd for $(M + NH_4)^+$ $[C_{18}H_{18}O_3 + NH_4]^+$: 300.1594, found 300.1605.



Benzofuran (±)-6aa. To a solution of phosphoramidite ligand (3.3 mg, 0.00561 mmol) in 1,4-dioxane (0.50 mL, 0.2 M) at 23 °C under argon was added $[(C_2H_4)PtCl_2]_2$ (1.6 mg, 0.00272 mmol, 2.5 mol %), and the resulting solution was stirred for 10 min. A solution of phenol **3a** (29.7 mg, 0.105 mmol) in 1,4-dioxane (0.50

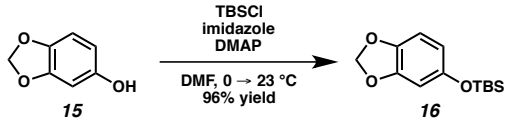
mL, 0.2 M) was then added to the catalyst mixture. Diene 5a (29.1 mg, 0.214 mmol) was subsequently added, and the resulting mixture was heated to 100 °C and stirred for 15 h. The reaction mixture was then cooled to room temperature and filtered through a plug of SiO_2, eluting with EtOAc (3 mL). The filtrate was concentrated in vacuo, and the resulting residue was purified by flash column chromatography (9:1 hexanes/EtOAc eluent) to afford an inseparable 2.5:1 mixture of benzofuran **(±)-6aa** and benzofuran **(±)-12** (24.0 mg, 74% yield, R_f = 0.45 in 9:1 hexanes/EtOAc) as a pale yellow oil. The spectroscopic data for compound **(±)-6aa** matched those reported in the literature.[4] The diastereomer drawn for compound **(±)-6aa** is consistent with the assignment of Xue and Li.[4]



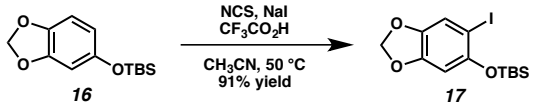
Benzofurans (±)-13 and (±)-14. To a solution of cycloadducts **(±)-6aa** and **(±)-12** (17.4 mg, 0.0560 mmol) in benzene (1.0 mL, 0.056 M) was added TsOH•H_2O (4.2 mg, 0.0221 mmol). The reaction mixture was heated to reflux and stirred for 15 h. The mixture was cooled to room temperature, and the solvent was removed by rotary evaporation. The crude residue was purified by flash column chromatography (9:1 hexanes/EtOAc eluent) to afford a mixture of benzofurans **(±)-13 (±)-14** (17.0 mg, 98% yield) as a pale yellow oil. The mixture could be further separated by column chromatography (39:1 hexanes/EtOAc eluent) to provide benzofuran **(±)-13** (R_f = 0.18 in 39:1 hexanes/EtOAc) and benzofuran **(±)-14** (R_f = 0.15 in 39:1 hexanes/EtOAc) as colorless oils. The spectroscopic data for benzofuran **(±)-13** (an approx. 2.5:1 mixture of conjugated alkene isomers) was consistent with those reported for this compound.[2,5] These alkene isomers have been separated after demethylation to afford frondosin B.[2,5a]

Data for benzofuran (±)-14.
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.8 Hz, 1H), 6.95 (d, *J* = 2.6 Hz, 1H), 6.82 (dd, *J* = 8.8, 2.6 Hz, 1H), 3.86 (s, 3H), 3.24 - 3.18 (m, 1H), 2.64 - 2.56 (m, 1H), 2.51 - 2.45 (m, 1H), 2.32 (dd, *J* = 14.9, 9.7 Hz, 1H), 2.19 - 2.10 (m, 1H), 2.09 - 2.00 (m, 2H), 1.74 - 1.67 (m, 2H), 1.65 - 1.59 (m, 1H), 1.56 - 1.51 (m, 2H), 1.34 (d, *J* = 6.9 Hz, 3H), 1.11 (s, 3H), 1.07 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ 155.4, 153.1, 148.5, 148.4, 130.9, 123.3, 120.5, 111.7, 111.2, 103.0, 56.2, 39.4, 36.1, 36.0, 31.1, 28.0, 27.9, 27.3, 26.2, 21.9, 19.5.
IR (film): 2964, 1612, 1595, 1475, 1263, 1215, 1171, 1139, 1071, 1034, 1022, 833, 791 cm^{-1}.
MS (ESI^+): m/z calc'd for $(M + NH_4)^+$ $[C_{21}H_{26}O_2]^+$: 310.1927, found 310.1927.

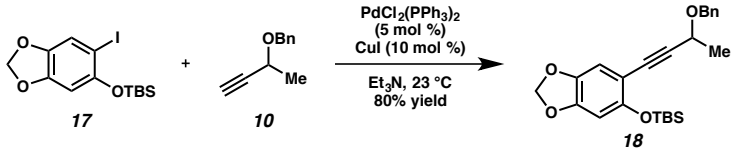
Synthesis of Liphagal



Silyl ether 16. To a solution of sesamol (**15**, 3.00 g, 21.7 mmol) in DMF (43.5 mL, 0.5 M) at 0 °C under argon was added TBSCl (3.95 g, 26.2 mmol), DMAP (33.1 mg, 0.271 mmol), and imidazole (1.75 g, 25.7 mmol) sequentially. The reaction mixture was allowed to warm to 23 ºC and stirred for 4 h. The reaction mixture was diluted with H_2O (150 mL) and extracted with Et_2O (3 x 75 mL). The combined organic layers were washed with H_2O (100 mL), then brine (75 mL), and dried over $MgSO_4$. The solvent was removed by rotary evaporation, and the residue was purified by flash column chromatography (20:1 hexanes/EtOAc eluent) to afford *tert*-butyl silyl ether **16** (5.28 g, 96% yield, R_f = 0.46 in 20:1 hexanes/EtOAc) as a colorless oil. The spectroscopic data for silyl ether **16** matched those previously reported.[6]



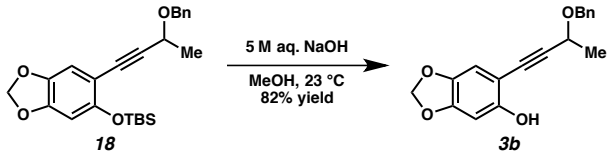
Iodide 17. Iodide **17** was synthesized according to the procedure described by Poli and coworkers.[6] To a solution of *N*-chlorosuccinimide (0.600 g, 4.49 mmol) in CH_3CN (8.00 mL, 0.56 M) at 23 °C under argon was added NaI (0.654 g, 4.36 mmol). The mixture was stirred for 30 min. A solution of silyl ether **16** (0.980 g, 3.88 mmol) in CH_3CN (8.00 mL, 0.49 M) was then added to the mixture, followed by addition of TFA (44.0 μL, 0.000575 mmol). The reaction mixture was stirred at 50 ºC for 2 h, and then it was diluted with EtOAc (100 mL). The solution was washed with sat. aq. $Na_2S_2O_3$ (50 mL), then brine (50 mL), and dried over $MgSO_4$. The solvent was removed by rotary evaporation, and the residue was purified by flash column chromatography (20:1 hexanes/EtOAc eluent) to afford iodide **17** (1.34 g, 91% yield, R_f = 0.50 in 20:1 hexanes/EtOAc) as a yellow oil. The spectroscopic data for iodide **17** matched those previously reported.[6]



Alkyne 18. To a solution of iodide **17** (4.99 g, 13.2 mmol) in Et_3N (26 mL, 0.5 M) at 23 °C under argon was added CuI (0.257 g, 1.35 mmol) and $PdCl_2(PPh_3)_2$ (0.466 g, 0.664 mmol). The mixture was stirred for 10 min. Benzyl ether **10** (2.33 g, 14.5 mmol) was then added dropwise, and the resulting mixture was stirred overnight at 23 ºC. The reaction mixture was diluted with 1.0 M aq. HCl (120 mL) and extracted with Et_2O (3 x 60 mL). The combined organic layers were washed with brine (60 mL) and dried over $MgSO_4$. The solvent was removed by rotary evaporation, and the residue was purified by flash column chromatography (20:1 hexanes/EtOAc eluent) to afford alkyne **18** (4.32 g, 80% yield, R_f = 0.25 in 20:1 hexanes/EtOAc) as a colorless oil.

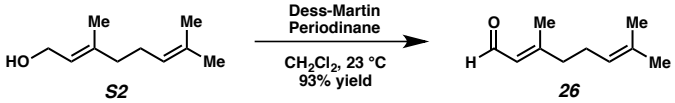
Data for alkyne 18.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.27 (m, 5H), 6.80 (s, 1H), 6.36 (s, 1H), 5.92 (s, 2H), 4.83 (d, *J* = 11.7 Hz, 1H), 4.53 (d, *J* = 11.7 Hz, 1H), 4.42 (q, *J* = 6.6 Hz, 1H), 1.53 (d, *J* = 6.6 Hz, 3H), 1.01 (s, 9H), 0.22 (s, 6H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 152.4, 148.5, 141.5, 138.2, 128.3, 128.0, 127.6, 111.7, 106.7, 101.8, 101.5, 91.1, 82.7, 70.5, 65.2, 25.7, 22.3, 18.2, -4.3.

IR (film): 2929, 2858, 2220, 1479, 1425, 1325, 1174, 1087, 1037, 837, 781, 734, 696 cm^{-1}.
HRMS (ESI^+) *m/z* calc'd for $(M + Na)^+$ $[C_{24}H_{30}O_4Si + Na]^+$: 433.1805, found 433.1806.

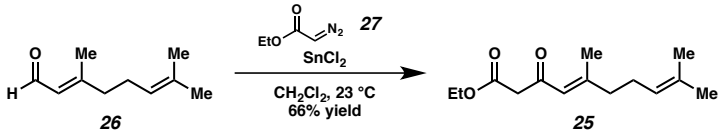


Phenol 3b. To a solution of alkyne **18** (3.81 g, 9.23 mmol) in MeOH (93 mL, 0.1 M) at 23 °C was added 5 M aq. NaOH (5.00 mL). The mixture was stirred for 2 h. The solution was slowly quenched with 1 M aq. HCl (100 mL), and it was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (50 mL) and dried over $MgSO_4$. The solvent was removed by rotary evaporation, and the residue was purified by flash column chromatography (5:1 hexanes/EtOAc eluent) to afford phenol **3b** (2.04 g, 82% yield, R_f = 0.22 in 5:1 hexanes/EtOAc) as a colorless oil.

Data for phenol 3b.
^{1}H NMR (500 MHz, C_6D_6): δ 7.30 (d, *J* = 4.2 , 2H), 7.18 – 7.13 (m, 2H), 7.09 (t, *J* = 7.3 , 1H), 6.73 (s, 1H), 5.73 (s, 1H), 5.12 (s, 2H), 4.70 (d, *J* = 11.9 Hz, 1H), 4.37 (d, *J* = 11.9 Hz, 1H), 4.15 (q, *J* = 6.6 Hz, 1H), 1.36 (d, *J* = 6.6 Hz, 3H).
^{13}C NMR (125 MHz, C_6D_6): δ 154.6, 150.5, 142.0, 138.9, 129.0, 128.5, 110.3, 101.8, 100.7, 97.9, 96.3, 80.5, 71.2, 65.6, 22.8.
IR (film): 3506, 2985, 2893, 2358, 2212, 1618, 1479, 1311, 1224, 1178, 1078, 1037, 935 cm^{-1}.
HRMS (ESI^+) *m/z* calc'd for $(M + Na)^+$ $[C_{18}H_{15}O_4Si + Na]^+$: 319.0940, found 319.0941.



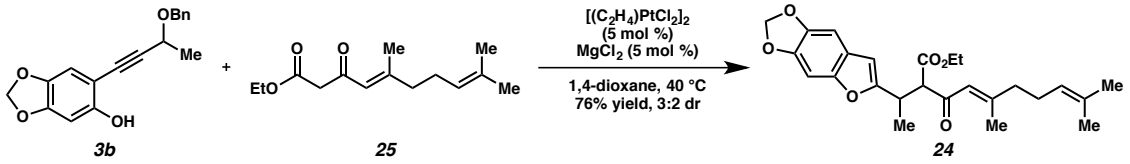
Aldehyde 26. To a solution of alcohol **S2** (2.20 mL, 12.5 mmol) in CH_2Cl_2 (100 mL, 0.13 M) at 23 °C under argon was added Dess-Martin Periodinane (6.98 g, 16.5 mmol). The resulting solution was stirred for 2 h. The reaction mixture was then quenched with a mixture of 10% aq. Na_2SO_3 (75 mL) and sat. aq. $NaHCO_3$ (75 mL), and the mixture was stirred for 2 h. The mixture was partitioned, and the aqueous layer was extracted with CH_2Cl_2 (100 mL). The organic layers were combined, washed with brine (100 mL), and dried over $MgSO_4$. The solvent was removed by rotary evaporation, and the residue was purified by flash column chromatography (4:1 hexanes/EtOAc eluent) to afford aldehyde **26** (1.76 g, 93% yield, R_f = 0.48 in 4:1 hexanes/EtOAc) as a colorless oil. The spectroscopic data for aldehyde **26** agreed with those previously reported.[7]



β-Ketoester 25. In an argon filled glove box, anhydrous $SnCl_2$ (0.211 g, 1.11 mmol) was added to a solution of aldehyde **26** (0.170 g, 1.11 mmol) in CH_2Cl_2 (3.70 mL, 0.3 M) at 23 °C. Ethyl diazoacetate (0.350 mL, 3.35 mmol) was added to the reaction mixture via syringe pump over a period of 30 min. The reaction mixture was stirred for an additional 2 h at 23 °C. The reaction mixture was diluted with 1 M aq. HCl (20 mL) and vigorously stirred for 2 h. The layers were then partitioned, and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (20 mL), then brine (20 mL), and

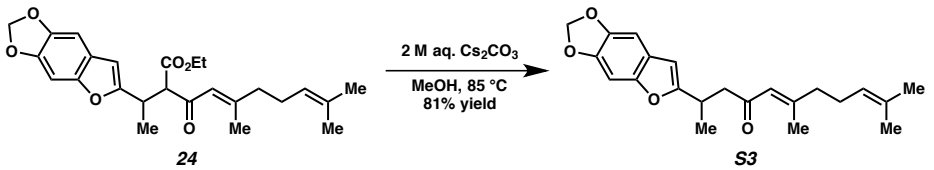
dried over $MgSO_4$. The solvent was removed by rotary evaporation, and the residue was purified by flash column chromatography (10:1 hexanes/EtOAc eluent, using neutralized silica gel that was previously washed with 50:1 hexanes/Et_3N) to afford β-ketoester **25** (0.177 g, 66% yield, R_f = 0.45 in 10:1 hexanes/EtOAc) as a yellow oil.

Data for β-Ketoester 25.
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.09 (s, 1H), 5.10 – 5.02 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.46 (s, 2H), 2.19 – 2.13 (comp. m, 7H), 1.69 (s, 3H), 1.60 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ 192.0, 167.8, 161.9, 132.7, 122.8, 122.0, 61.2, 50.8, 41.4, 26.1, 25.7, 19.8, 17.7, 14.2.
IR (film): 2974, 2922, 2362, 1737, 1683, 1614, 1307, 1265, 1157, 1091, 1029 cm^{-1}.
HRMS (ESI^+) *m/z* calc'd for $(M + Na)^+$ $[C_{14}H_{22}O_3 + Na]^+$: 261.1461, found 261.1461.



β-Ketoester 24. To a mixture of β-ketoester **25** (0.671 g, 2.81 mmol), anhydrous $MgCl_2$ (13.4 mg, 0.141 mmol, 5 mol %) and $[(C_2H_4)PtCl_2]_2$ (83.1 mg, 0.142 mmol, 5 mol %) in 1,4-dioxane (11 mL) at 40 °C was added a solution of phenol **3b** (1.00 g, 3.37 mmol) in 1,4-dioxane (17 mL) over 4 h via syringe pump. After stirring for an additional 1 h, the reaction mixture was passed through a plug of SiO_2, eluting with EtOAc (60 mL). The filtrate was concentrated by rotary evaporation, and the residue was purified by flash column chromatography (10:1 hexanes/EtOAc eluent) to afford benzofuran **24** (0.918 g, 76% yield, R_f = 0.27 in 10:1 hexanes/EtOAc) as a colorless oil.

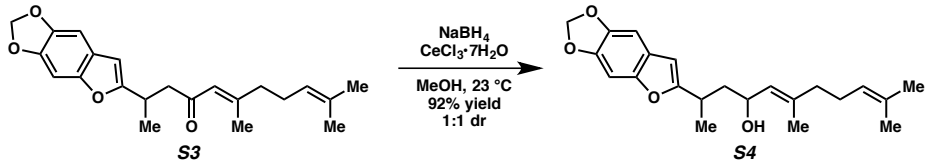
Data for benzofuran 24. (Isolated as a 3:2 diastereomeric mixture)
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.91 (s, 0.4H), 6.88 (s, 0.6H), 6.84 (s, 0.4H), 6.81 (s, 0.6H), 6.31 (s, 0.4H), 6.26 (s, 0.6H), 6.17 (s, 0.4H), 5.98 (s, 0.6H), 5.94 (s, 1. 2H), 5.92 (s, 0.8H) 5.03 (app. s, 0.4H), 4.96 (app. s, 0.6H), 4.20 (q, *J* = 7.1 Hz, 1.2H), 4.02 (q, *J* = 7.1 Hz, 0.8H), 3.89 – 3.81 (m, 1H), 3.79 – 3.70 (comp. m, 1H), 2.17 (s, 1.8H), 2.15 (s, 1.2H), 1.98 (s, 4H), 1.68 (s, 1.2H), 1.65 (s, 1.8H), 1.59 (s, 1.2H), 1.55 (s, 1.8H), 1.36 (d, *J* = 6.9 Hz, 2H), 1.30 – 1.22 (comp. m, 3H), 1.05 (t, *J* = 7.1 Hz, 1H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 193.3, 192.8, 168.67, 168.65, 162.6, 161.7, 159.3, 158.8, 149.6, 149.5, 145.4, 144.2, 132.7, 132.5, 122.8, 122.1, 121.9, 121.5, 102.9, 102.6, 101.1, 99.2, 93.3, 64.7, 64.3, 61.3, 61.2, 41.4, 41.1, 33.8, 33.7, 26.0, 25.6, 20.0, 19.7, 17.7, 17.6, 17.5, 17.2, 14.1, 13.9;
IR (film): 2972, 2910, 1735, 1681, 1612, 1460, 1369, 1317, 1161, 1035, 943, 846 cm^{-1}.
HRMS (ESI^+) *m/z* calc'd for $(M + Na)^+$ $[C_{25}H_{30}O_6 + Na]^+$: 449.1934, found 449.1935.



Ketone S3. To a solution of ethyl ester **24** (1.64 g, 3.84 mmol) in MeOH (39 mL) at 23 °C was slowly added 2 M aq. Cs_2CO_3 (10.0 mL, 20.0 mmol). The mixture was stirred at 85 ºC for 4 h. The solution was cooled to 23 ºC, quenched with sat. aq. NH_4Cl (100 mL), and extracted with CH_2Cl_2 (3 x 60 mL). The combined organic layers were washed with brine (60 mL) and dried over $MgSO_4$. The solvent was removed by rotary evaporation,

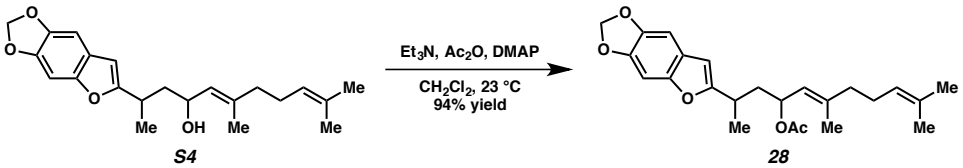
and the residue was purified by flash column chromatography (10:1 hexanes/EtOAc eluent) to afford benzofuranyl ketone **S3** (1.10 g, 81% yield, R_f = 0.40 in 10:1 hexanes/EtOAc) as a colorless oil.

Data for ketone S3.
^{1}H NMR (500 MHz, C_6D_6): δ 6.93 (s, 1H), 6.80 (s, 1H), 5.99 (s, 1H), 5.82 (s, 1H), 5.34 (s, 2H), 5.07 – 5.01 (comp. m, 1H), 3.63 – 3.53 (m, 1H), 2.75 (dd, *J* =16.3, 5.4 Hz, 1H), 2.36 (dd, *J* =16.3, 8.3 Hz, 1H), 2.15 (s, 3H), 2.03 – 1.95 (comp. m, 2H), 1.90 – 1.84 (comp. m, 2H), 1.63 (s, 3H), 1.48 (s, 3H), 1.25 (d, *J* = 7.0 Hz, 3H).
^{13}C NMR (125 MHz, C_6D_6): δ 198.0, 162.7, 158.1, 150.5, 146.3, 145.2, 132.6, 124.0, 123.9, 122.8, 102.1, 101.5, 99.9, 94.0, 50.1, 41.6, 30.3, 26.8, 26.1, 19.7, 19.3, 18.0.
IR (film): 2968, 2910, 1687, 1616, 1460, 1373, 1317, 1159, 1037, 941, 846 cm^{-1}.
HRMS (ESI$^+$) *m/z* calc'd for $(M + H)^+$ $[C_{22}H_{26}O_4 + H]^+$: 355.1903, found 355.1905.



Alcohol S4. To a solution of benzofuranyl ketone **S3** (1.10 g, 3.11 mmol) in MeOH (50 mL, 0.06 M) at 23 °C under argon was added $CeCl_3 \cdot 7H_2O$ (2.34 g, 6.28 mmol) and $NaBH_4$ (0.200 g, 5.29 mmol) sequentially. The reaction mixture was stirred for 3 h, then diluted with Et_2O (50 mL), and the mixture was slowly quenched with H_2O (100 mL). The layers were partitioned, and the aqueous layer was extracted with Et_2O (2 x 50 mL). The combined organic layers were washed with brine (30 mL) and dried over $MgSO_4$. The solvent was removed by rotary evaporation, and the residue was purified by flash column chromatography (4:1 hexanes/EtOAc eluent) to afford benzofuranyl alcohol **S4** (1.02 g, 92% yield, R_f = 0.35 in 4:1 hexanes/EtOAc) as a colorless oil.

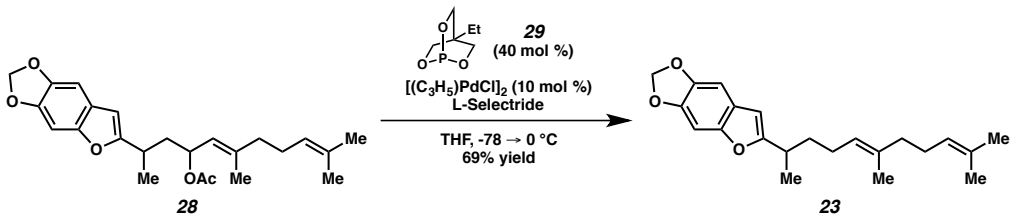
Data for alcohol S4. (Isolated as a ~1:1 diastereomeric mixture)
^{1}H NMR (500 MHz, C_6D_6): δ 6.94 (s, 0.5H), 6.93 (s, 0.5H), 6.84 (s, 0.5H), 6.83 (s, 0.5H), 6.07 (s, 0.5H), 6.01 (s, 0.5H), 5.34 (s, 1H), 5.33 (s, 1H), 5.23 – 5.12 (comp. m, 2H), 4.41 – 4.34 (m, 0.5H), 4.33 – 4.28 (m, 0.5H), 3.20 – 3.12 (m, 0.5H), 3.11 – 3.04 (m, 0.5H), 2.19 – 2.02 (comp. m, 2H), 2.01 – 1.87 (comp. m, 3H), 1.80 – 1.72 (comp. m, 0.5H), 1.68 (s, 1.5H), 1.66 (s, 1.5H), 1.64 – 1.57 (comp. m, 0.5H), 1.55 (s, 1.5H), 1.53 (s, 1.5H), 1.46 (s, 1.5H), 14.1 (s, 1.5H) 1.25 (d, *J* = 7.0 Hz, 1.5H), 1.23 (d, *J* = 7.0 Hz, 1.5H).
^{13}C NMR (125 MHz, C_6D_6): δ 163.8, 163.3, 150.5, 146.2, 145.2, 138.2, 137.7, 131.9, 131.8, 129.5, 129.4, 124.89, 124.87, 122.80, 102.3, 101.4, 99.9, 99.8, 94.04, 94.01, 67.1, 66.6, 44.3, 44.0, 40.3, 40.2, 31.3, 27.14, 27.13, 26.21, 26.18, 20.5, 19.8, 18.12, 18.09, 16.9, 16.8.
IR (film): 3371, 2966, 2914, 1460, 1315, 1159, 1037, 941, 845 cm^{-1}.
HRMS (ESI$^+$) *m/z* calc'd for $(M)^+$ $[C_{22}H_{28}O_4]^+$: 356.1981, found 356.1982.



Acetate 28. To a solution of benzofuran alcohol **S4** (1.01 g, 2.84 mmol) in CH_2Cl_2 (25 mL, 0.11 M) at 0 °C under argon was added Et_3N (0.900 mL, 6.44 mmol), acetic anhydride (0.320 mL, 3.28 mmol) and DMAP (6.0 mg, 0.0491 mmol) sequentially. The solution was slowly warmed to 23 ºC and stirred overnight. The reaction mixture was diluted with H_2O (120 mL) and extracted with CH_2Cl_2 (3 x 60 mL). The combined organic layers were washed with brine (60 mL) and dried over $MgSO_4$. The solvent was removed by rotary evaporation, and

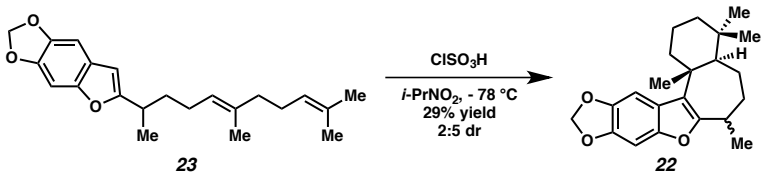
the residue was purified by flash column chromatography (4:1 hexanes/EtOAc eluent) to afford benzofuranyl acetate **28** (1.11 g, 94% yield, R_f = 0.55 in 4:1 hexanes/EtOAc) as a colorless oil.

Data for acetate 28. (Isolated as a ~1:1 diastereomeric mixture)
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.91 (s, 1H), 6.85 (s, 1H), 6.31 (app. s, 0.5H), 6.24 (app. s, 0.5H), 5.94 (s, 2H), 5.71 – 5.56 (comp. m, 1H), 5.14 – 4.92 (comp. m, 2H), 2.98 – 2.84 (m, 1H), 2.26 –2.13 (comp. m, 1.5H), 2.11 – 2.03 (comp. m, 1.5H), 2.02 – 1.95 (m, 1.5H), 1.97 – 1.91 (comp. m, 3.5H), 1.91 – 1.84 (comp. m, 1H), 1.74 – 1.51 (comp. m, 9H), 1.31 (d, J = 7.0 Hz, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 170.5, 162.4, 162.3, 149.7, 145.4, 144.3, 141.3, 131.97, 131.95, 124.2, 124.04, 124.00, 123.5, 123.4, 122.0, 101.4, 101.2, 99.3, 93.5, 70.2, 70.0, 40.6, 39.74, 39.69, 30.6, 26.43, 26.40, 25.93, 25.89, 21.5, 20.0, 17.93, 17.91, 17.04, 17.00.
IR (film): 2966, 2912, 1732, 1460, 1371, 1315, 1240, 1161, 1037, 943, 846 cm^{-1}.
HRMS (ESI$^+$) *m/z* calc'd for $(M + Na)^+$ $[C_{24}H_{30}O_5 + Na]^+$: 421.1981, found 421.1985.



Benzofuran 23. The allylic acetate reduction procedure was performed according to the protocol described by Parker and coworkers.[8] To a solution of benzofuranyl acetate **28** (0.419 g, 1.05 mmol) in THF (53 mL) at 23 ºC under argon was added phosphite **29**[9] (71.5 mg, 0.423 mmol) and $[(C_3H_5)PdCl]_2$ (37.8 mg, 0.106 mmol). The solution was cooled to -78 ºC, and L-Selectride (0.210 mL, 1.0 M in THF, 0.210 mmol) was added. The reaction mixture was slowly warmed to 0 ºC over a 3 h period. Upon completion, the solution was quenched with sat. aq. NH_4Cl (125 mL) and extracted with CH_2Cl_2 (3 x 60 mL). The combined organic layers were washed with brine (60 mL) and dried over $MgSO_4$. The solvent was removed by rotary evaporation, and the residue was purified by flash column chromatography (20:1 hexanes/EtOAc eluent) to afford benzofuran **23** (0.263 g, 69% yield, R_f = 0.47 in 20:1 hexanes/EtOAc) as a colorless oil.

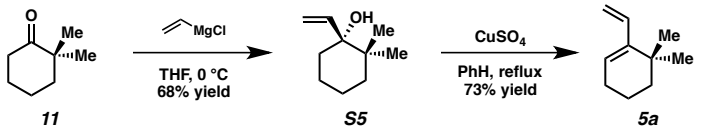
Data for benzofuran 23.
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.93 (s, 1H), 6.86 (s, 1H), 6.24 (s, 1H), 5.94 (s, 2H), 5.15 – 5.04 (comp. m, 2H), 2.93 – 2.83 (m, 1H), 2.09 – 1.92 (comp. m, 6H), 1.84 – 1.75 (m, 1H), 1.67 (app. s, 4H), 1.60 (s, 2H), 1.55 (s, 3H), 1.29 (d, J = 6.9 Hz, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ 163.5, 149.6, 145.2, 144.2, 135.7, 124.9, 124.5, 124.2, 122.1, 101.2, 99.2, 93.6, 39.9, 35.7, 33.3, 32.2, 26.9, 25.9, 25.7, 19.3, 16.2.
IR (film): 2964, 2914, 2362, 2337, 1460, 1375, 1317, 1159, 1039, 947, 844 cm^{-1}.
HRMS (ESI$^+$) *m/z* calc'd for $(M + H)^+$ $[C_{22}H_{28}O_3 + H]^+$: 341.2110, found 341.2111.



Pentacycle 22. The polycyclization was performed according to the protocol described by Andersen and coworkers.[10] To a solution of benzofuran **23** (0.263 g, 0.773 mmol) in 2-nitropropane (8.00 mL, 0.1 M) at -78 °C was added chlorosulfonic acid (0.210 mL, 3.10 mmol) at -78 ºC under argon. The resulting mixture was

stirred for 1 h at -78 ºC. The solution was quenched with sat. aq. NH_4Cl (40 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (25 mL) and dried over $MgSO_4$. The solvent was removed by rotary evaporation, and the residue was purified by flash column chromatography (20:1 hexanes/EtOAc eluent) to afford pentacyclic compound **22** (77.0 mg, 29% yield, R_f = 0.62 in 9:1 hexanes/EtOAc) as a 2:5 mixture of diastereomers as a colorless oil. The spectroscopic data for compound **22** matched those previously reported in the literature.[11]

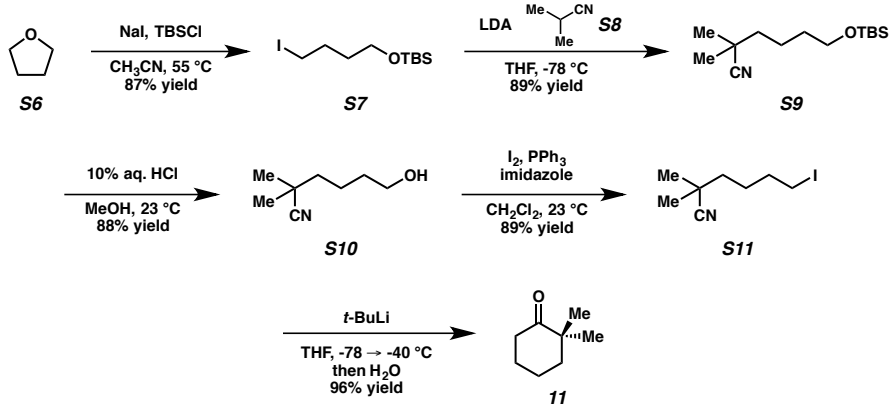
Other Compound Syntheses



11 *S5* *5a*

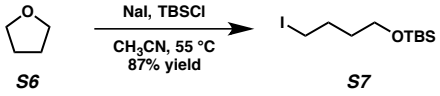
Vinylcyclohexanol S5. According to the reported literature procedure,[12] to a solution of cyclohexanone **11** (0.915 g, 7.25 mmol) in anhydrous THF (18 mL, 0.4 M) cooled to 0 °C was added vinylmagnesium chloride (5.89 mL, 1.6 M in THF, 1.3 equiv) dropwise, and the resulting mixture was allowed to warm to 23 °C and stirred for 2 h. Saturated aq. NH_4Cl (5 mL) was then added dropwise to quench the reaction, and the solvent was removed by rotary evaporation. The crude residue was then dissolved in Et_2O (50 mL), washed with brine (30 mL), dried over $MgSO_4$ and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography (9:1 hexanes/EtOAc eluent) to afford vinylcyclohexanol **S5** (0.757 g, 68% yield, R_f = 0.70 in 4:1 hexanes/EtOAc) as a pale yellow oil. This alcohol was taken directly to the subsequent transformation.

Diene 5a. To a solution of vinylcyclohexanol **S5** (0.105 g, 0.681 mmol) in benzene (3.00 mL, 0.25 M) was added anhydrous $CuSO_4$ (0.250 g, 1.56 mmol, 2.30 equiv) at 23 °C. The reaction vessel was then equipped with a Dean-Stark apparatus, and the resulting suspension was heated to reflux (bath temp. 90 °C) and stirred for 24 h. The system was then cooled to 23 °C, vacuum filtered to remove insoluble materials, and concentrated by rotary evaporation. The residue was purified using flash column chromatography (1:1 pentane/Et_2O eluent) to afford diene **5a** (0.0672 g, 73% yield, R_f = 0.80 in 1:1 pentane/Et_2O) as a volatile colorless oil. The spectroscopic data for diene **5a** matched those previously reported.[12]



S6 *S7* *S9* *S10* *S11* *11*

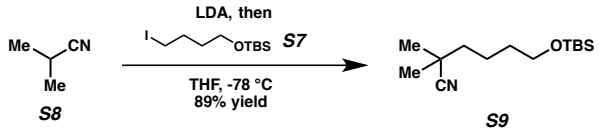
Note: Cyclohexanone **11** is commercially available, but we found the high-yielding sequence above to be preferable for accessing large quantities of the compound.



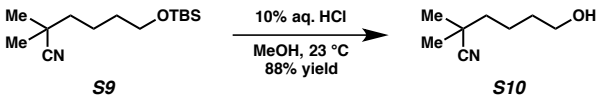
S6 *S7*

Alkyl iodide S7. Alkyl iodide **S7** was synthesized according to the procedure described by Waldmann and coworkers.[13] To a solution of TBSCl (3.02 g, 20.0 mmol, 1.0 equiv) and NaI (6.00 g, 40.0 mmol, 2.0 equiv) in anhydrous CH_3CN (100 mL, 0.2 M in TBSCl) was added anhydrous tetrahydrofuran (4.06 mL, 50.0 mmol, 2.5 equiv) at 23 °C. The resulting mixture was heated to 55 °C and stirred for 12 h. The solution was then cooled to 23 °C, diluted with water (50 mL) and extracted into diethyl ether (3 x 100 mL). The combined organic layers were washed with saturated aq. sodium thiosulfate (50 mL), then brine (50 mL) and dried over $MgSO_4$. The solvent was removed by rotary evaporation, and the residue was purified by flash column chromatography

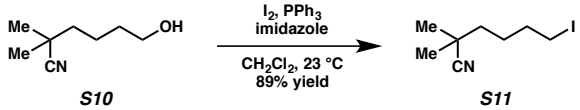
(19:1 hexanes/EtOAc eluent) to afford alkyl iodide **S7** (13.7 g, 87% yield, R_f = 0.50 in 9:1 hexanes/EtOAc) as a light-sensitive colorless oil. The spectroscopic data for iodide **S7** were consistent with those reported.[13]
Iodide S7: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.63 (t, *J* = 6.2 Hz, 2H), 3.22 (t, *J* = 7.0 Hz, 2H), 1.90 (app. quintet, *J* = 7.0 Hz, 2H), 1.66 - 1.56 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H).



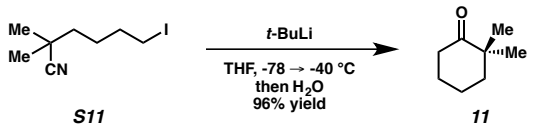
Nitrile S9. Nitrile **S9** was synthesized according to the procedure described by Frontier and coworkers.[14] LDA was prepared *in situ* by addition of *n*-BuLi (3.60 mL, 2.48 M in hexanes, 8.91 mmol) to a solution of *i*-Pr_2NH (1.78 mL, 12.7 mmol) in anhydrous THF (22.3 mL) at 0 °C. The solution of LDA (1.4 equiv, 0.40 M in THF) was then cooled to -78 °C, isobutyronitrile (0.800 mL, 8.91 mmol, 1.4 equiv) was added dropwise, and the resulting mixture was stirred for 1 h. A solution of alkyl iodide **S7** (2.00 g, 6.36 mmol) in anhydrous tetrahydrofuran (1.27 mL, 5.0 M) was then added dropwise, and the mixture was allowed to stir for an additional 2 h at -78 °C. After warming to 23 °C, the solution was diluted with water (20 mL) and extracted into CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (50 mL) and dried over $MgSO_4$. The solvent was removed by rotary evaporation, and the crude residue was purified by flash column chromatography (9:1 hexanes/EtOAc eluent) to afford nitrile **S9** (1.45 g, 89% yield, R_f = 0.58 in 9:1 hexanes/EtOAc) as a pale yellow oil. The spectroscopic data were consistent with those reported.[14]
Nitrile S9: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.66 - 3.59 (m, 2H), 1.58 - 1.52 (m, 6H), 1.34 (s, 6H), 0.89 (s, 9H), 0.05 (s, 6H).



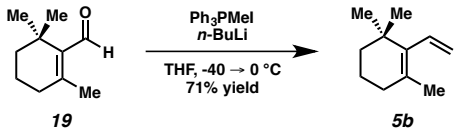
Alcohol S10. Silyl ether **S9** (1.00 g, 3.91 mmol) was dissolved in a mixture of methanol (19.6 mL, 0.2 M) and 10% aq. hydrochloric acid (9.78 mL, 0.4 M) at 23 °C, and the solution was allowed to stir for 30 min. Saturated aq. $NaHCO_3$ (50 mL) was then added to neutralize the mixture, and the solvent was removed by rotary evaporation. The crude residue was then dissolved in CH_2Cl_2 (20 mL) and washed with water (20 mL), then brine (20 mL), dried over $MgSO_4$ and concentrated by rotary evaporation. The crude residue was then purified by flash column chromatography (1:1 hexanes/EtOAc eluent) to afford alcohol **S10** (0.483 g, 88% yield, R_f = 0.38 in 1:1 hexanes/EtOAc) as a colorless oil.
Alcohol S10: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.68 (t, J = 7.9 Hz, 2H), 1.65 - 1.50 (m, 6H), 1.35 (s, 6H).



Iodonitrile S11. To a foil-wrapped flask containing a solution of triphenylphosphine (0.876 g, 3.34 mmol, 1.2 equiv) in CH_2Cl_2 (4.1 mL, 0.82 M) was added imidazole (0.284 g, 4.73 mmol, 1.5 equiv) and iodine (0.954 g, 3.76 mmol, 1.4 equiv). To this mixture, a solution of alcohol **S10** (0.393 g, 2.78 mmol) in CH_2Cl_2 (1.0 mL, 2.7 M) was added dropwise, and the reaction mixture was stirred at 23 °C for 1 h. The solvent was then removed by rotary evaporation, and the crude reaction mixture was purified by flash column chromatography (9:1 hexanes/EtOAc eluent) to afford pure iodonitrile **S11** (0.621 g, 89% yield, R_f = 0.36 in 9:1 hexanes/EtOAc) as an extremely light-sensitive colorless oil.
Iodonitrile S11: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.21 (t, *J* = 6.9 Hz, 2H), 1.87 (app. quintet, *J* = 6.9 Hz, 2H), 1.68 - 1.49 (m, 6H), 1.36 (s, 6H).



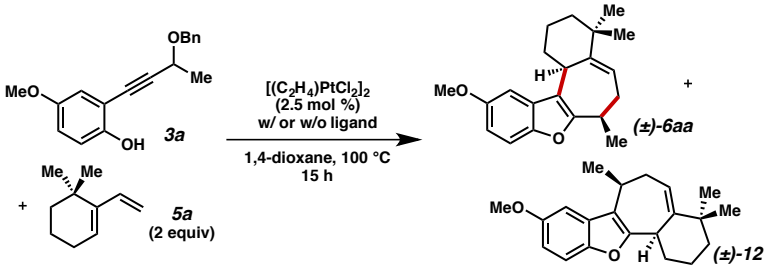
Cyclohexanone 11. To a solution of iodonitrile **S11** (2.27 g, 9.02 mmol) in anhydrous THF (18 mL, 0.50 M) cooled to -78 °C was added *tert*-butyllithium (11.8 mL, 1.6 M in pentane, 2.1 equiv) dropwise. The resulting mixture was allowed to warm to -40 °C and stirred for 10 min, and then the reaction was diluted with saturated aq. NH_4Cl (10 mL). Water (20 mL) was then added, and the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography (9:1 hexanes/EtOAc eluent), affording cyclohexanone **11** (1.10 g, 96% yield, R_f = 0.47 in 9:1 hexanes/EtOac) as a volatile colorless oil. The spectroscopic data matched those reported in the literature.[15]
Cyclohexanone 11: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.39 (t, *J* = 6.7 Hz, 2H), 1.88 - 1.63 (m, 6H), 1.11 (s, 6H).

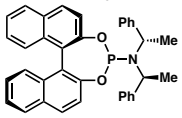


Diene 5b. Diene **5b** was synthesized according to the previously reported procedure.[4] To a well stirred suspension of $Ph_3PCH_3^+I^-$ (24.3 g, 60.0 mmol) in THF (120 mL) at -40 °C was added *n*-BuLi (23.7 mL, 2.53 M in hexanes, 60.0 mmol) over 2 min. The solution became orange and was allowed to warm to ambient temperature and stir for 30 min. The resulting solution was then recooled to -40 °C, and aldehyde **19** (6.46 mL, 40.0 mmol) was added over 5 min. The reaction mixture was stirred at -40 °C for 10 min, then allowed to warm to ambient temperature and stirred an additional 30 min, at which point TLC indicated consumption of aldehyde **19**. The reaction mixture was quenched by adding 20 mL sat. aq. NH_4Cl, and most of the THF was removed in vacuo. The resulting residue was diluted with 100 mL H_2O and 100 mL pentane and filtered, rinsing with pentane. The organic layer was separated and washed with brine (50 mL), dried with Na_2SO_4, and concentrated. The crude product was purified by flash column chromatography (pentane eluent) to give diene **5b** (4.28 g, 71% yield, R_f = 0.81 in 99:1 hexanes/EtOAc) as a clear colorless liquid. The spectroscopic data for diene **5b** matched those presented in the literature.[4]

Other Pt-Catalyzed Reactions

Optimization of Pt-catalyzed cycloaddition toward frondosin B.



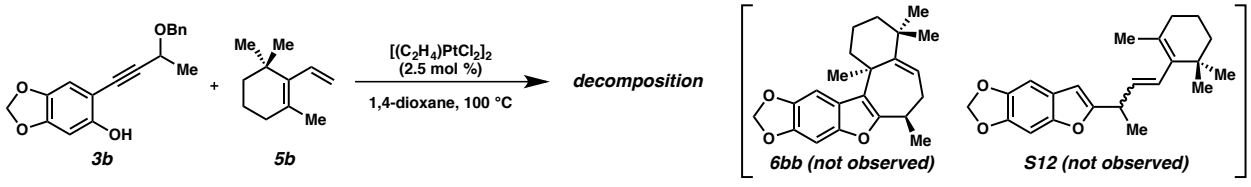
ligand (5 mol %)	combined yield (%)*	*6aa : 12**
none	40	1 : 1.07
$P(C_6F_5)_3$	45	1.2 : 1
PPh_3	56	1.5 : 1
	74% (isolated)	2.5 : 1

* determined by ^{1}H NMR

No ligand added: In a vial, to a solution of alkyne **3a** (10.0 mg, 0.0354 mmol) and diene **5a** (1, 2, or 4 equiv) in 1,4-dioxane (0.350 mL, 0.1 M) at 23 °C was added $[(C_2H_4)PtCl_2]_2$ (0.5 mg, 0.000885 mmol). The reaction vessel was sealed, and it was heated to 100 °C and stirred. Upon completion as determined by TLC, the reaction mixture was cooled to room temperature and filtered through a plug of SiO_2 (0.5 x 2 cm), washing with 1:1 hexanes/EtOAc (~ 2 mL). The filtrate was concentrated by rotary evaporation, and the crude mixture was analyzed by ^{1}H NMR, using vanillin as a standard. The ratio of **(±)-6aa** to **(±)-12** was determined by 1H NMR integration of the benzylic methyl substituents of the respective isomers.

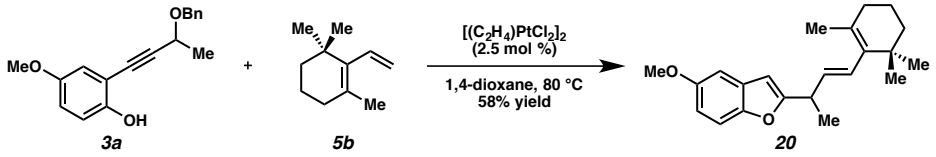
With ligand added: In a vial, to a solution of ligand (0.00177 mmol, 5 mol %) in 1,4-dioxane (0.200 mL, 0.18M) at 23 °C was added $[(C_2H_4)PtCl_2]_2$ (2.5 mol %), and the resulting solution was stirred for 15 min. In a separate vial, a solution of alkyne **3a** (10.0 mg, 0.0354 mmol) and diene **5a** (9.7 mg, 0.0708mmol) in 1,4-dioxane (0.150 mL, 0.24 M) was prepared, and this solution was added to the catalyst mixture. The resulting mixture was sealed in the vial, and it was heated to 100 °C and stirred. Upon completion as determined by TLC, the reaction mixture was cooled to room temperature and filtered through a plug of SiO_2 (0.5 x 2 cm), washing with 1:1 hexanes/EtOAc (~ 2 mL). The filtrate was concentrated by rotary evaporation, and the crude mixture was analyzed by ^{1}H NMR, using vanillin as a standard.

Evaluation of cycloadditions using other alkyne/diene combinations.



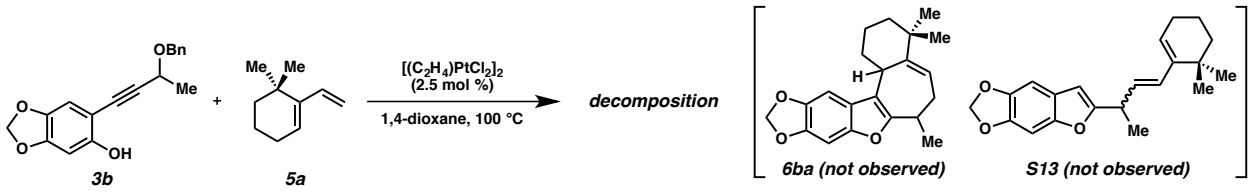
To a solution of alkyne **3b** (38.1 mg, 0.129 mmol) and diene **5b** (58.0 mg, 0.386 mmol) in 1,4-dioxane (1.29 mL) at ambient temperature was added $[(C_2H_4)PtCl_2]_2$ (1.9 mg, 0.00323 mmol). The resulting solution was stirred for 10 min and then heated to 100 °C in a preheated aluminum block. The reaction mixture was stirred at this temperature for 3 h, at which point TLC indicated consumption of alkyne **5b**. The reaction mixture was

cooled, diluted with hexanes (5 mL), and filtered through a plug of SiO_2, rinsing with 9:1 hexanes/EtOAc. The filtrate was concentrated and analyzed by ^{1}H NMR. Only decomposition was observed.



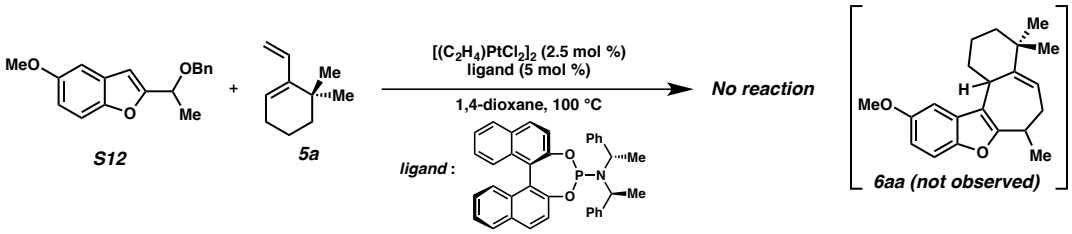
To a solution of alkyne **3a** (142 mg, 0.504 mmol) and diene **5b** (152 mg, 1.01 mmol) in 1,4-dioxane (5.0 mL) at ambient temperature was added $[(C_2H_4)PtCl_2]_2$ (7.4 mg, 0.0126 mmol). The resulting solution was stirred for 10 min and then heated to 80 °C in a preheated aluminum block. The reaction mixture was stirred at this temperature for 1 h, then cooled to ambient temperature and charged with an additional portion of $[(C_2H_4)PtCl_2]_2$ (7.4 mg, 0.0126 mmol). The reaction mixture was reheated to 80 °C and stirred for 30 min, at which point TLC indicated consumption of alkyne **3a**. The reaction mixture was cooled, diluted with hexanes (10 mL), and filtered through a plug of SiO_2, rinsing with 19:1 hexanes/EtOAc. The filtrate was concentrated, and the resulting residue was purified by flash column chromatography (1:1 toluene/pentane eluent) to give benzofuran **20** (114 mg, 58% yield, R_f = 0.26 in 19:1 hexanes/EtOAc) as a colorless liquid.

Data for benzofuran 20.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, *J* = 8.9 Hz, 1H), 6.97 (d, *J* = 2.4 Hz, 1H), 6.81 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.34 (s, 1H), 6.01 (d, *J* = 16.0 Hz, 1H), 5.53 (dd, *J* = 16.0, 7.6 Hz, 1H), 3.83 (s, 3H), 3.74-3.62 (m, 1H), 1.97 (t, *J* = 6.3 Hz, 2H), 1.68 (s, 3H), 1.64-1.57 (comp. m, 2H), 1.54 (s, 3H), 1.49-1.42 (comp. m, 5H), 1.00 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$): δ 163.6, 155.9, 149.9, 137.3, 134.9, 129.6, 128.61, 128.55, 111.7, 111.3, 103.5, 101.2, 56.1, 39.5, 37.7, 34.2, 32.8, 28.9, 21.5, 19.5, 19.4.
IR (film): 2961, 2927, 2864, 2832, 1478, 1450, 1205, 1179, 1033, 836 cm^{-1}.
HRMS (ESI+): m/z calc'd for $(M + H)^+$ $[C_{22}H_{28}O_2 + H]^+$: 325.2162, found 325.2155.



To a solution of alkyne **3b** (14.8 mg, 0.0499 mmol) and diene **5a** (13.4 mg, 0.0984 mmol) in 1,4-dioxane (0.500 mL) at 23 °C was added $[(C_2H_4)PtCl_2]_2$ (0.8 mg, 0.00136 mmol, 2.5 mol %). The solution was heated to 100 °C and stirred for 8 h. The reaction mixture was then cooled and filtered through a plug of SiO_2, eluting with 1:1 hexanes/EtOAc. The solvent was removed by rotary evaporation, and the resulting residue was analyzed by ^{1}H NMR. Only decomposition was observed.

Test for furanyl cation formation/cycloaddition.



Benzofuran **S12** was synthesized via benzofuranyl alcohol formation[4a] followed by standard benzyl etherification (NaH, BnBr, DMF). To a solution of phosphoramidite ligand (1.8 mg, 0.00333 mmol) in 1,4-dioxane (0.34 mL, 0.2 M) at 23 °C under argon was added $[(C_2H_4)PtCl_2]_2$ (0.9 mg, 0.00153 mmol), and the solution was stirred for 10 min. A solution of benzofuran **S12** (19.4 mg, 0.0687 mmol) in 1,4-dioxane (0.34 mL, 0.2 M) was added to the catalyst mixture. Diene **5a** (18.7 mg, 0.137 mmol) was then added, and the reaction mixture was heated to 100 °C and stirred for 15 h. The reaction mixture was passed through a plug of SiO_2, eluting with EtOAc (2 mL). The filtrate was concentrated by rotary evaporation. No reaction was observed by ^{1}H NMR.

References

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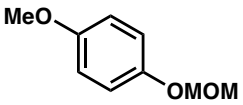
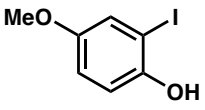
Supporting Information: Spectra Compilation

Platinum-Catalyzed α,β-Unsaturated Carbene Formation in the Formal Syntheses of Frondosin B and Liphagal



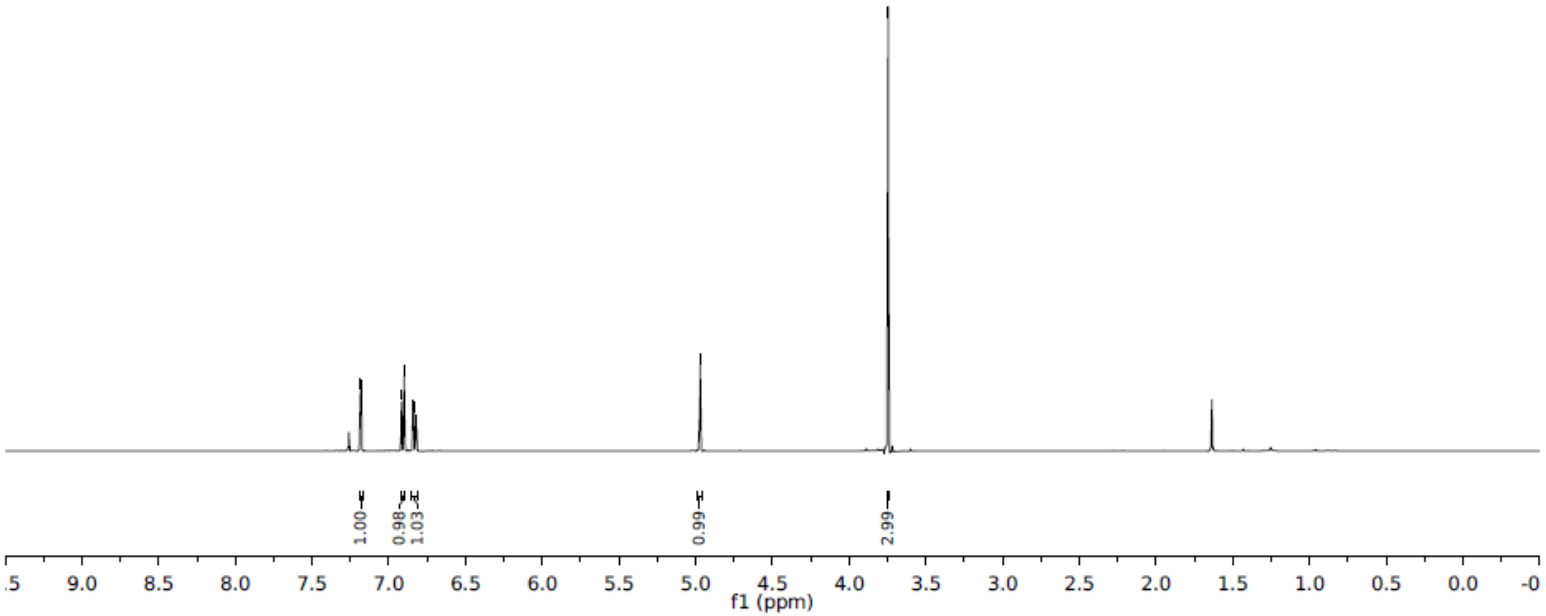
8

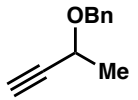
^{1}H NMR
(500 MHz, $CDCl_3$)



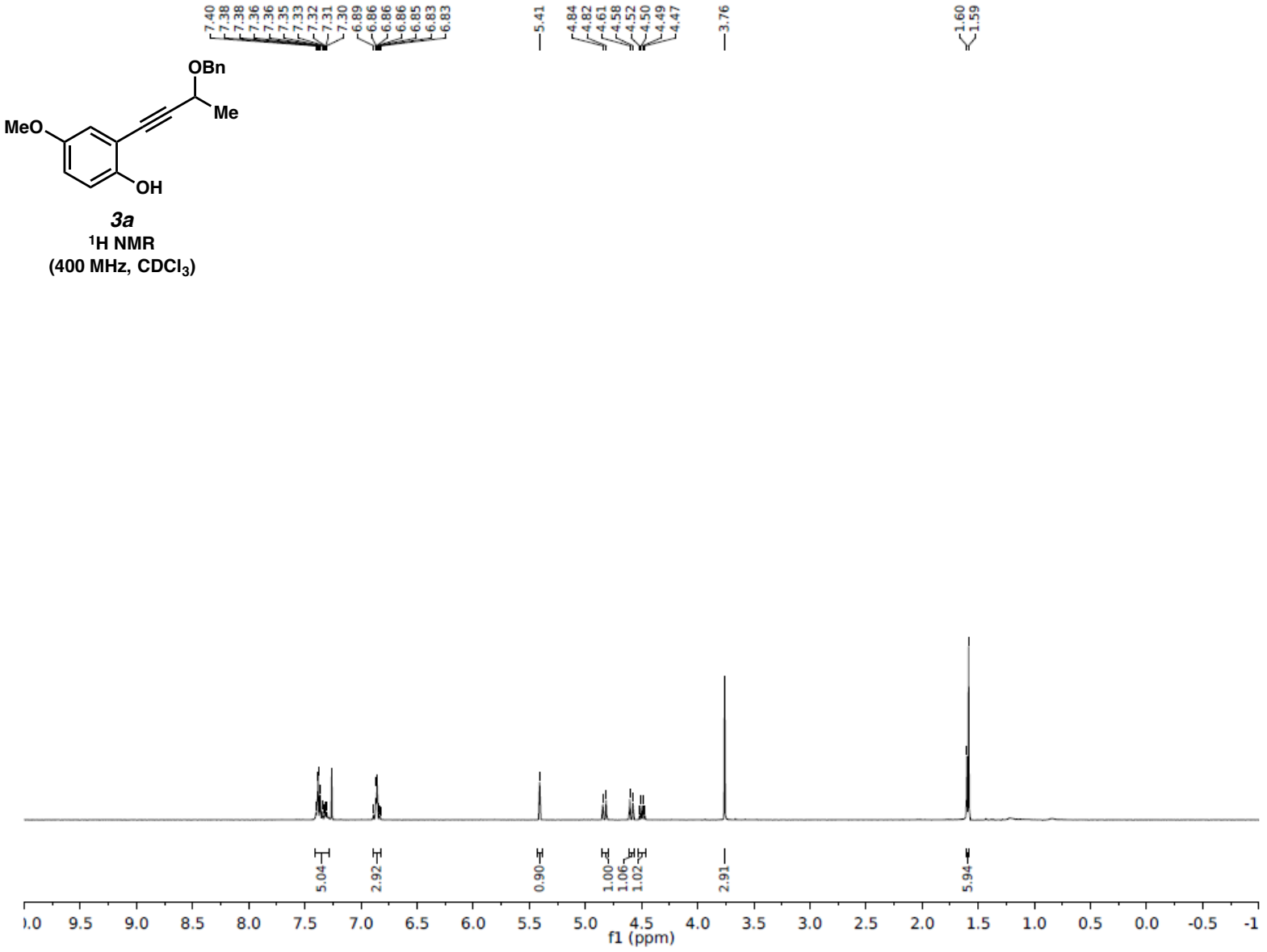
9

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

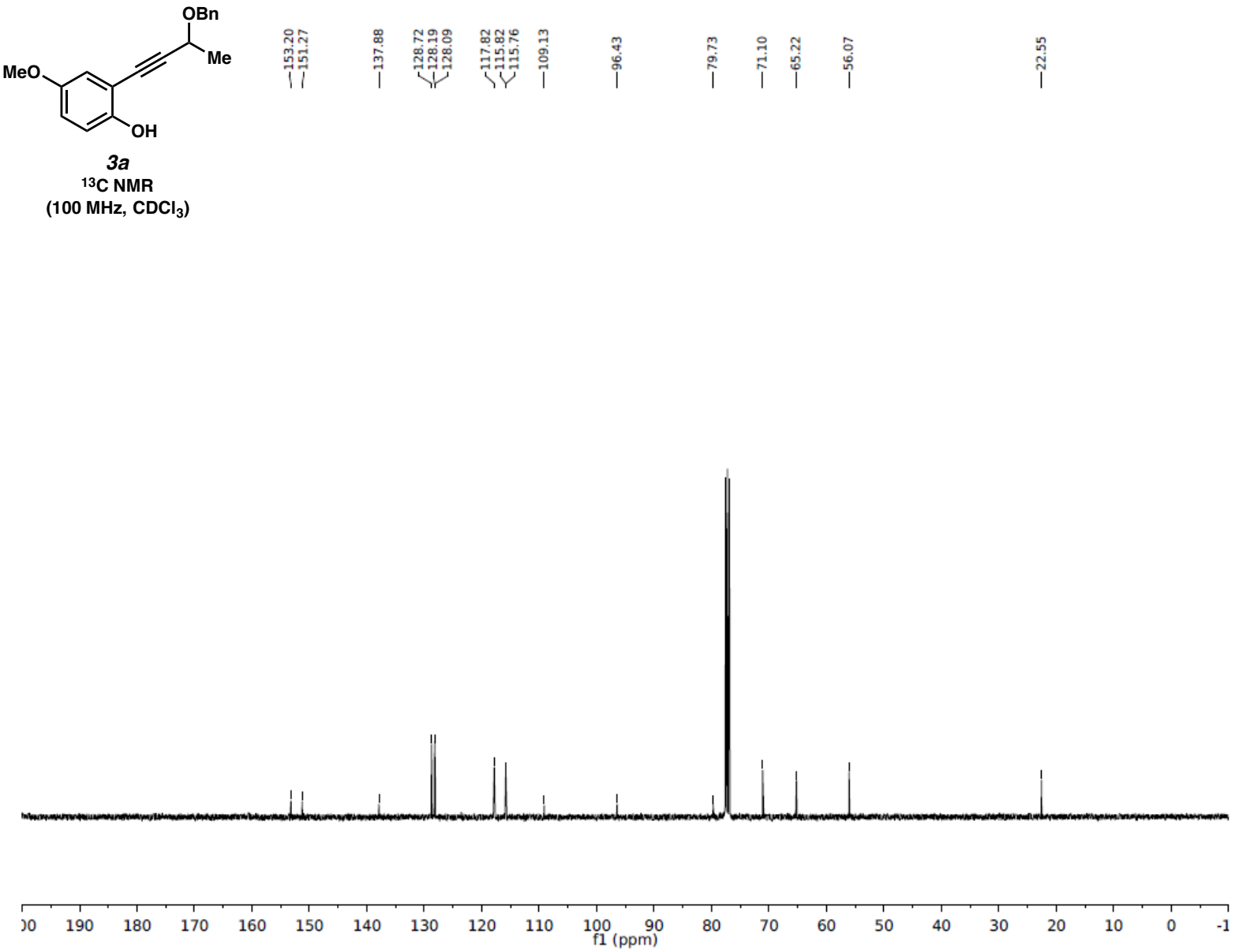




10
^{1}H NMR
(500 MHz, $CDCl_3$)



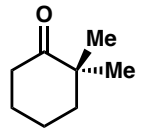
3a
^{1}H NMR
(400 MHz, $CDCl_3$)



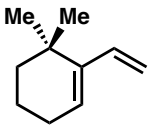
3a

^{13}C NMR

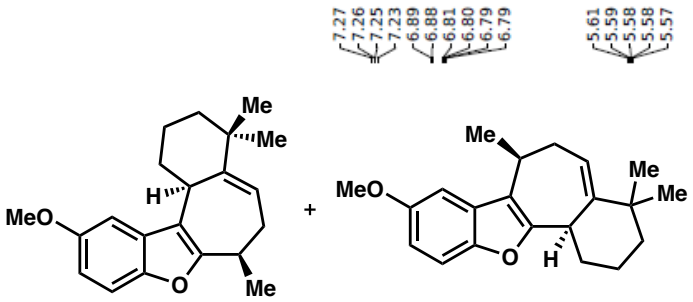
(100 MHz, $CDCl_3$)



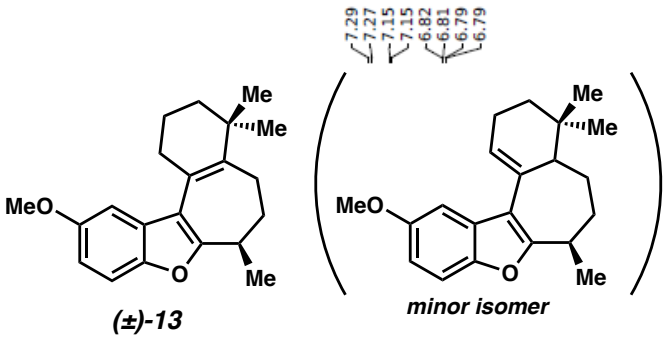
11
^{1}H NMR
(400 MHz, $CDCl_3$)



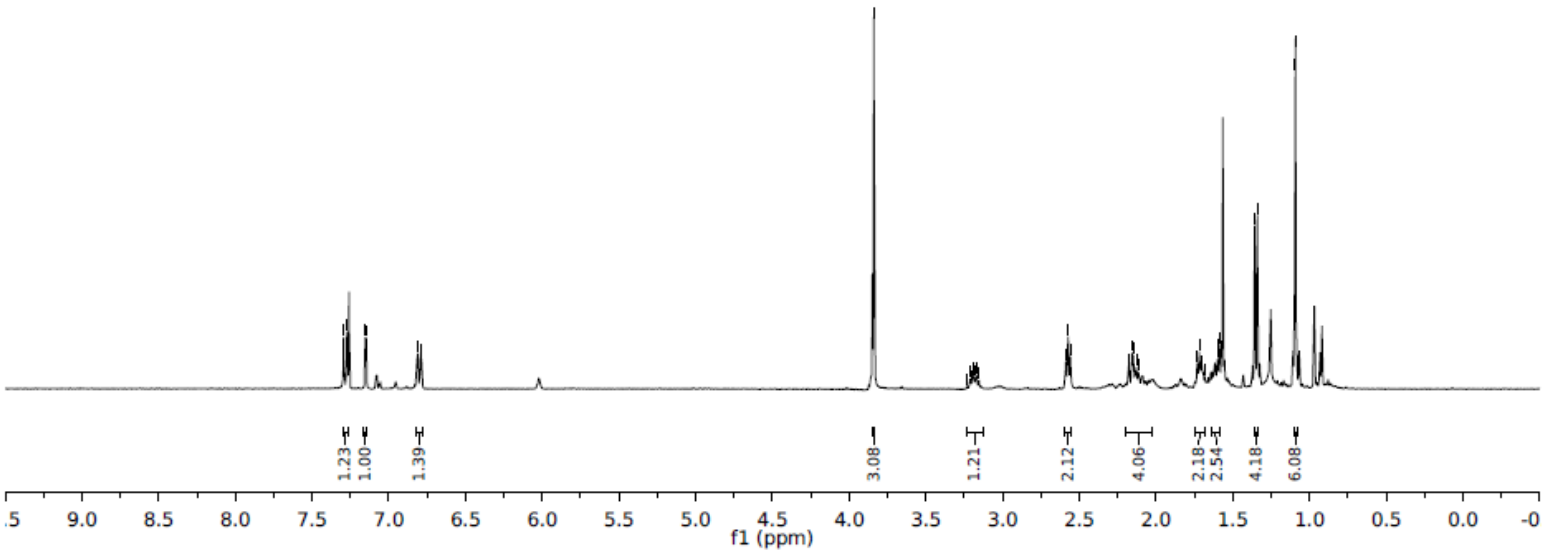
5a
^{1}H NMR
(400 MHz, $CDCl_3$)

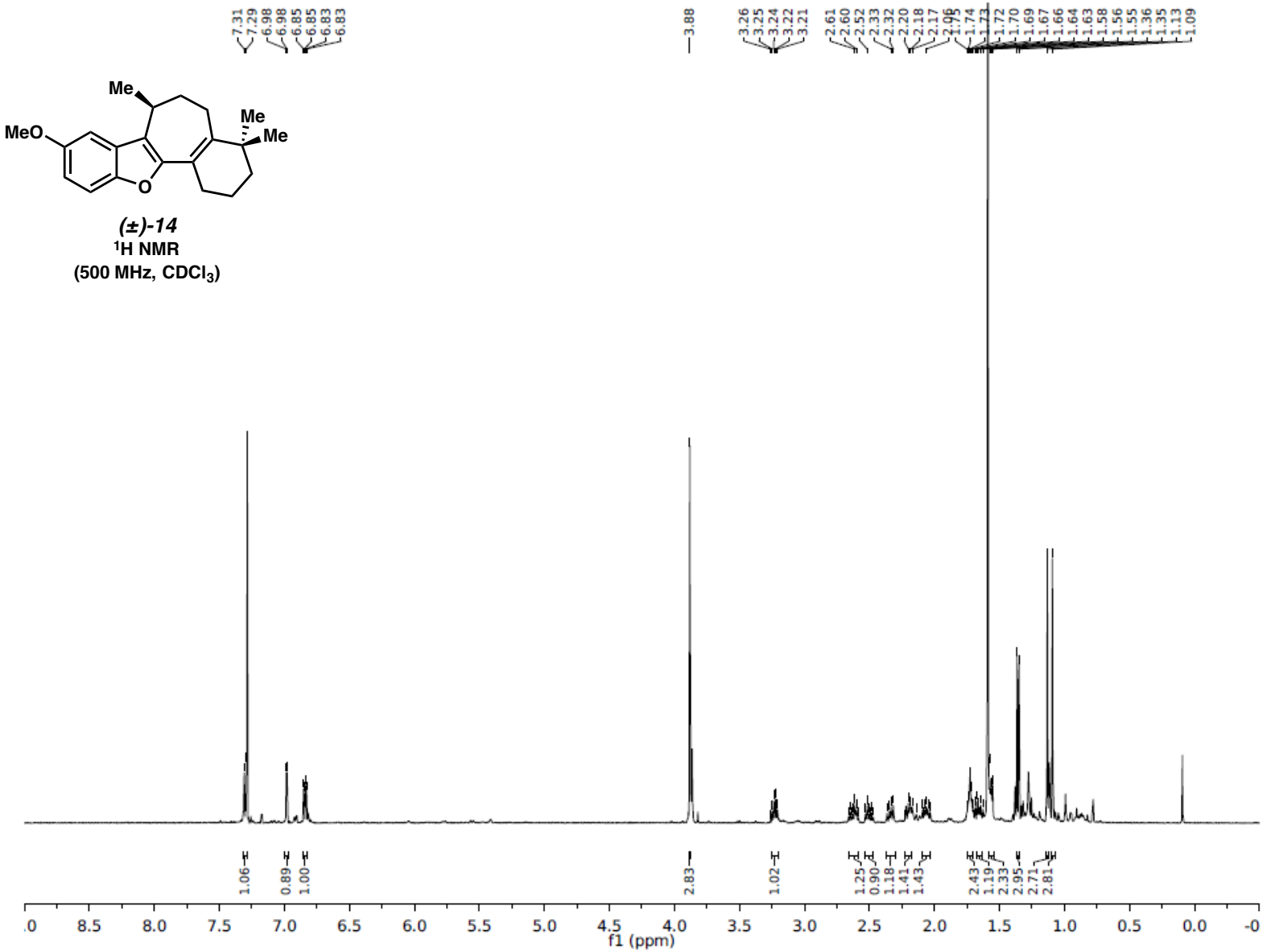


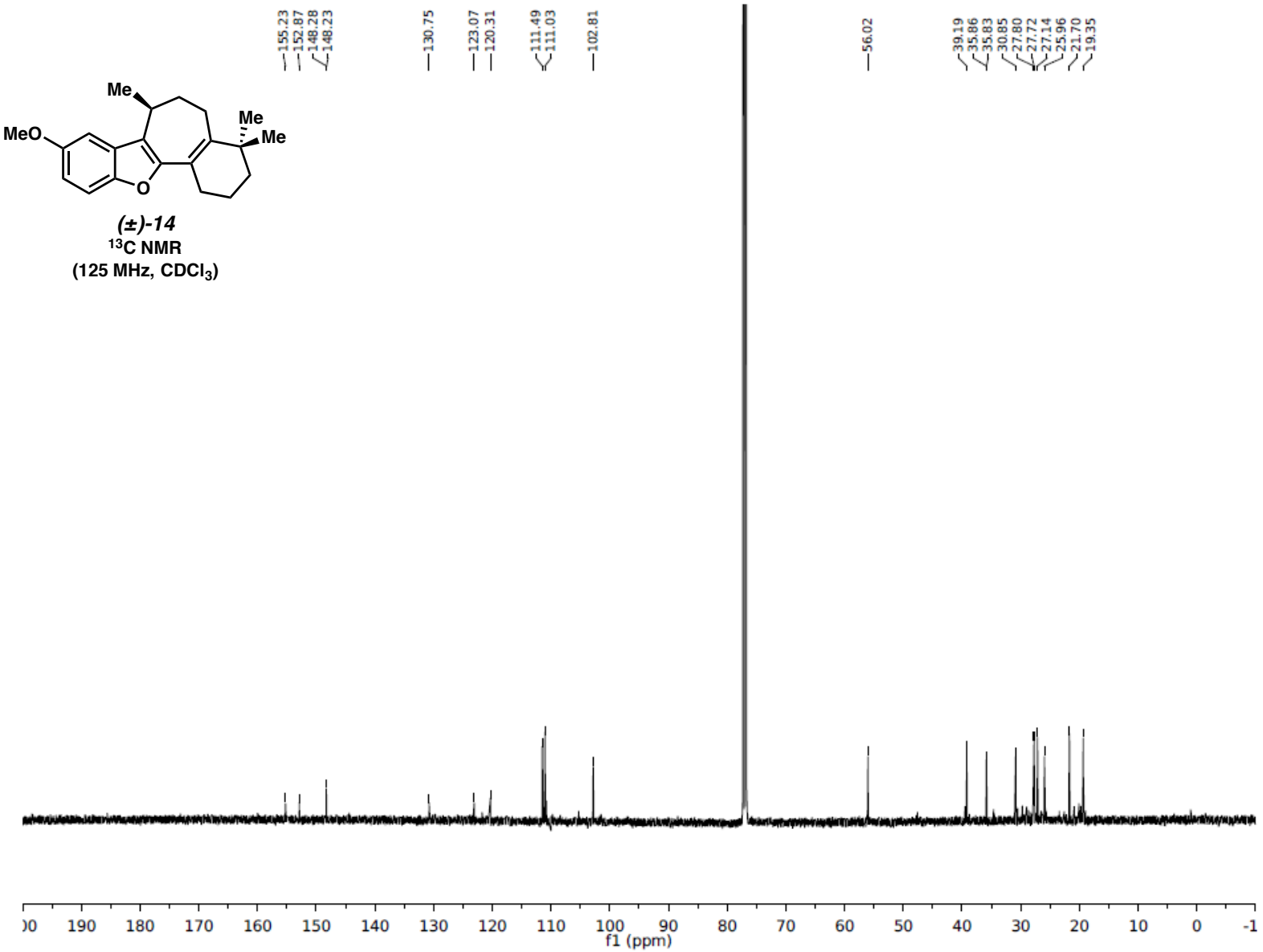
(±)-6aa /(±)-12 **(2.5 : 1 mixture)**
^{1}H NMR
(500 MHz, $CDCl_3$)



(±)-13
^{1}H NMR
(400 MHz, $CDCl_3$)



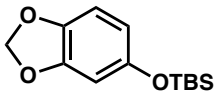

Me
MeO
Me
Me
O
(±)-14
1H NMR
(500 MHz, CDCl3)
7.31
7.29
6.98
6.98
6.85
6.85
6.83
6.83
3.88
3.26
3.25
3.24
3.22
3.21
2.61
2.60
2.52
2.33
2.32
2.20
2.18
2.17
2.06
1.74
1.73
1.72
1.70
1.69
1.67
1.66
1.64
1.63
1.58
1.56
1.55
1.36
1.35
1.13
1.09
1.06
0.89
1.00
2.83
1.02
1.25
0.90
1.18
1.41
1.43
2.43
1.19
2.33
2.95
2.71
2.81
f1 (ppm)



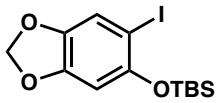
(±)-14

^{13}C NMR

(125 MHz, $CDCl_3$)

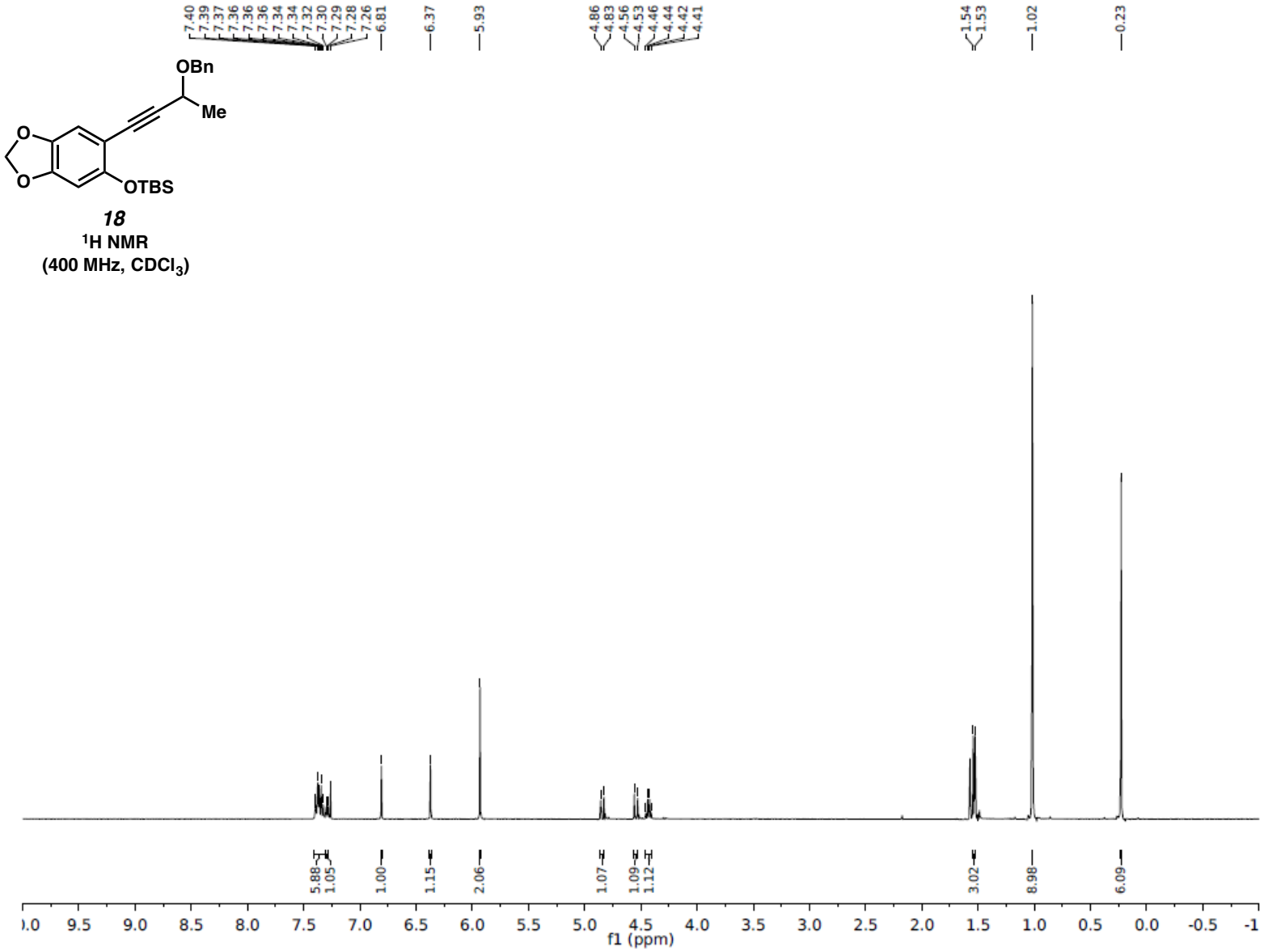


16
^{1}H NMR
(400 MHz, $CDCl_3$)



17

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


OBn
Me
O
O
OTBS
18
1H NMR
(400 MHz, CDCl3)
7.40
7.39
7.37
7.36
7.36
7.36
7.34
7.34
7.32
7.30
7.29
7.28
7.26
6.81
6.37
5.93
4.86
4.83
4.56
4.53
4.46
4.44
4.42
4.41
1.54
1.53
1.02
0.23
5.88
1.05
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1.07
1.09
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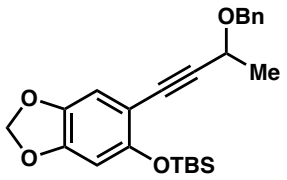
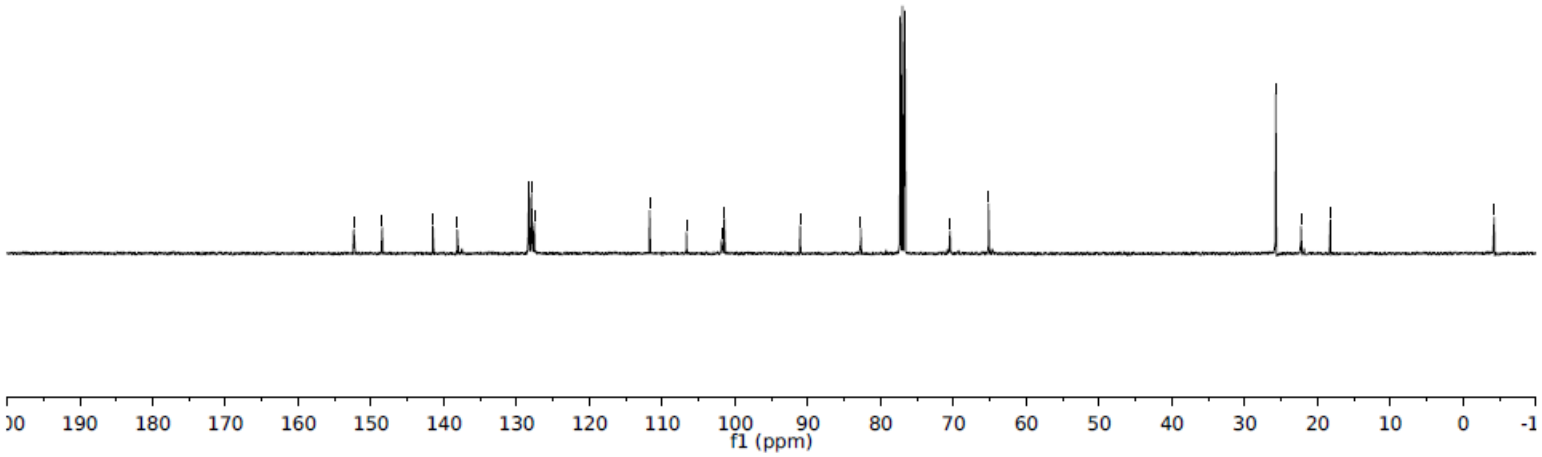
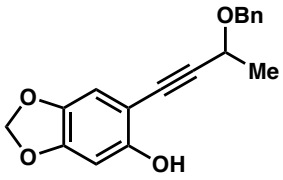
3.02
8.98
6.09
f1 (ppm)



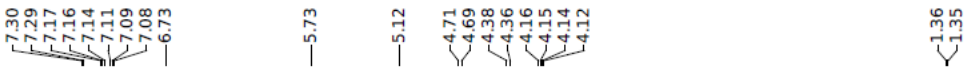
18

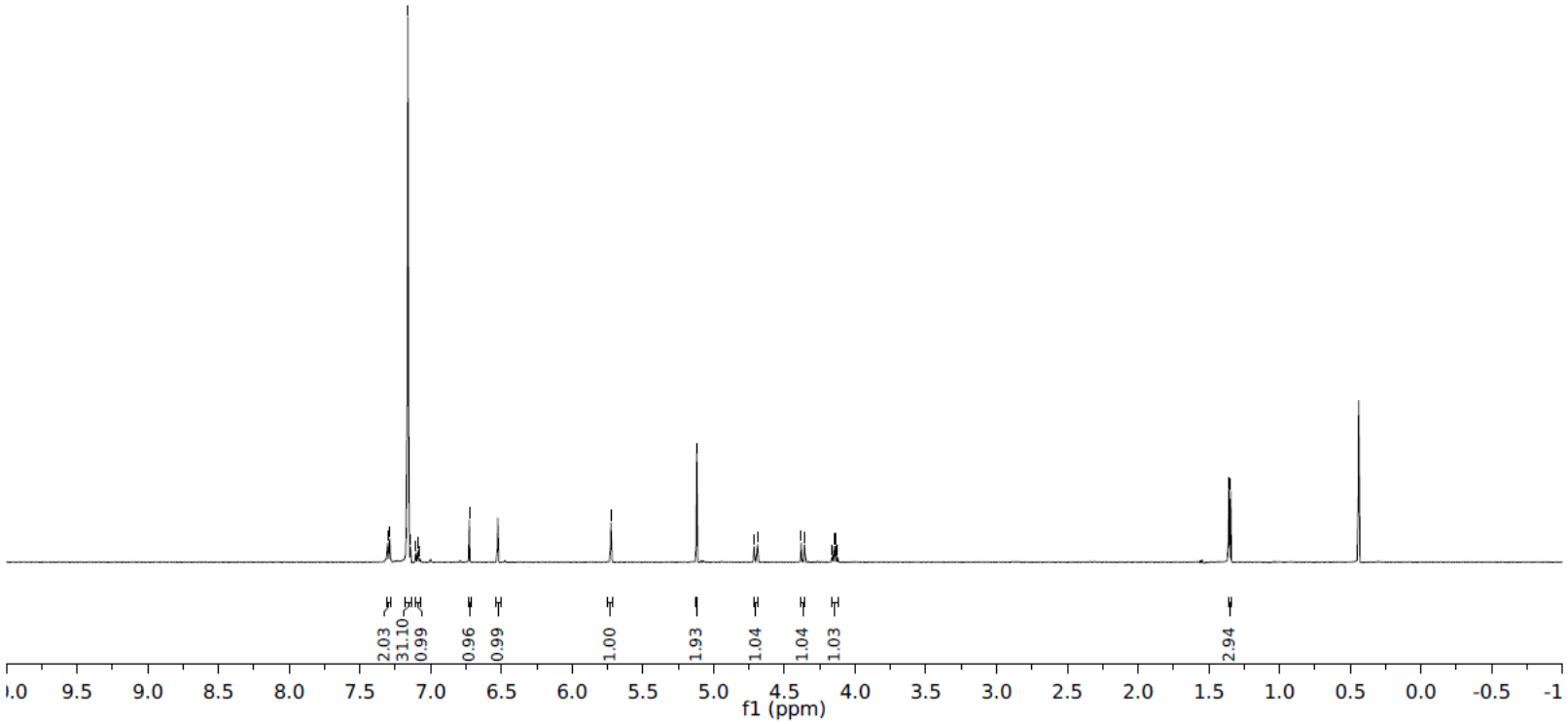
^{13}C NMR
(100 MHz, $CDCl_3$)

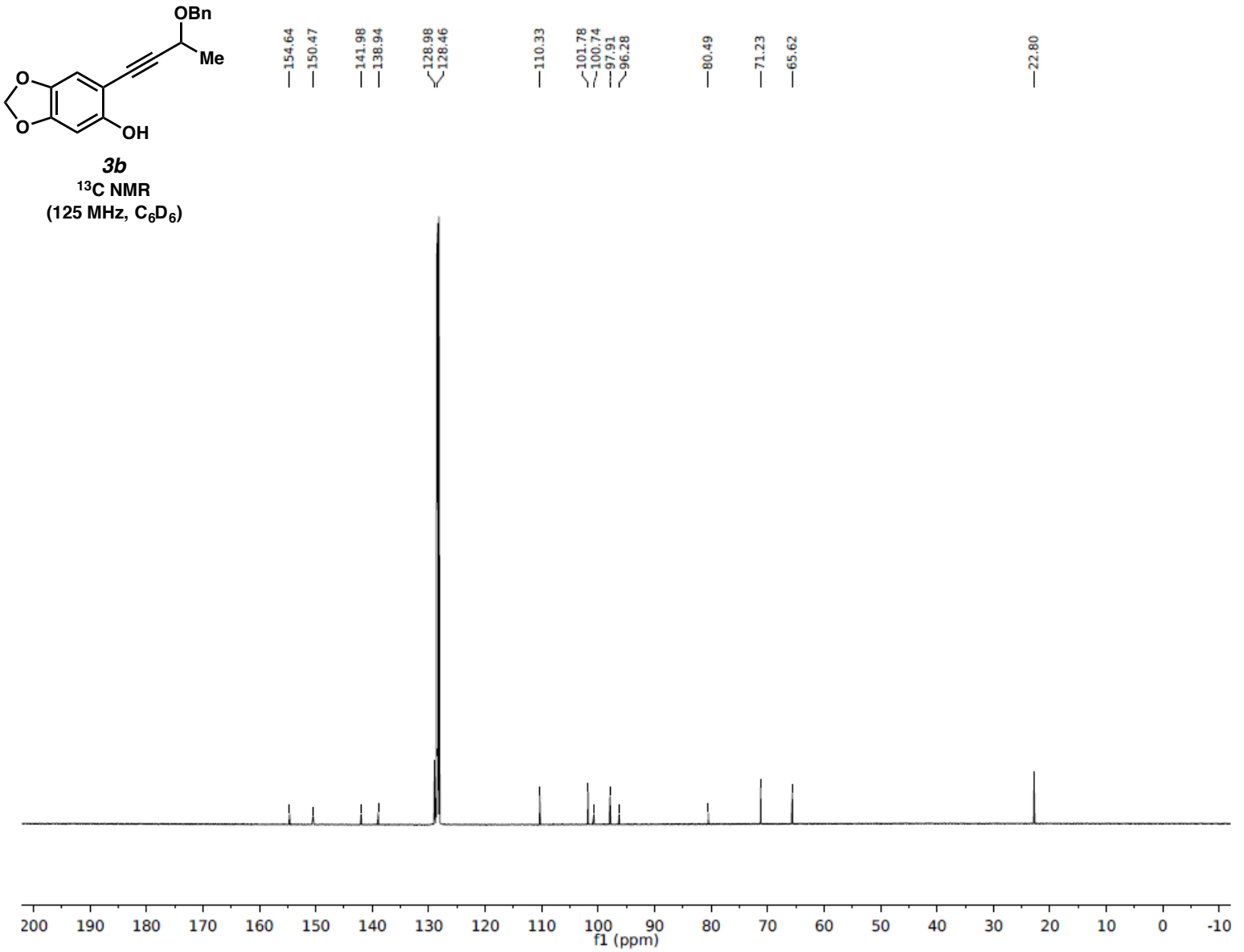




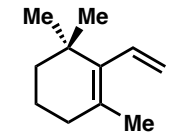
3b
^{1}H NMR
(500 MHz, C_6D_6)





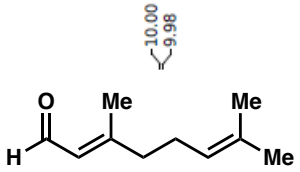


3b
^{13}C NMR
(125 MHz, C_6D_6)



5b

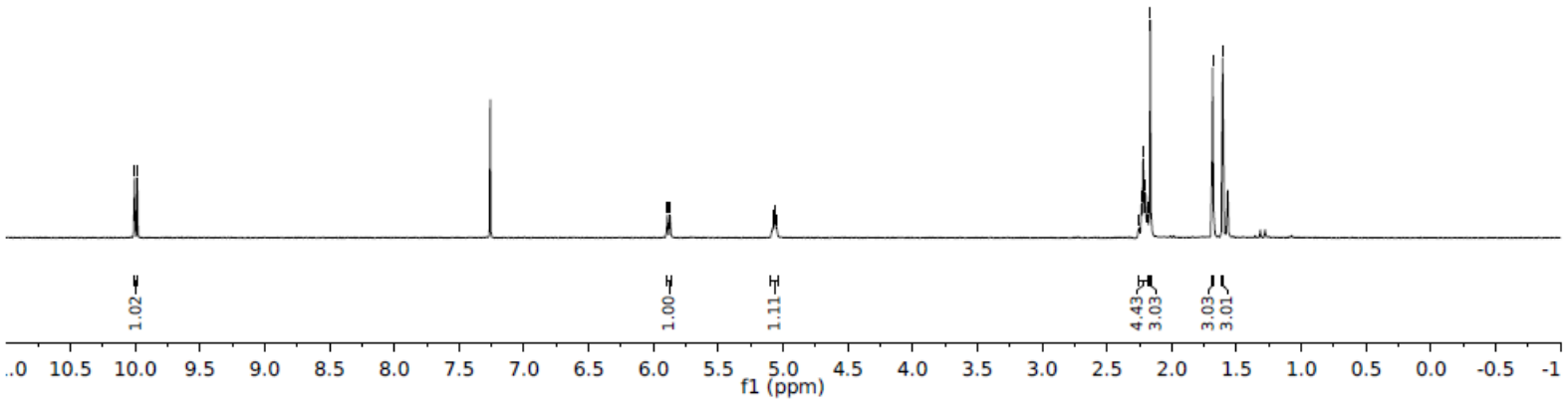
^{1}H NMR
(500 MHz, $CDCl_3$)

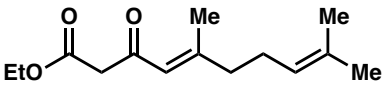


26

^{1}H NMR

(400 MHz, $CDCl_3$)

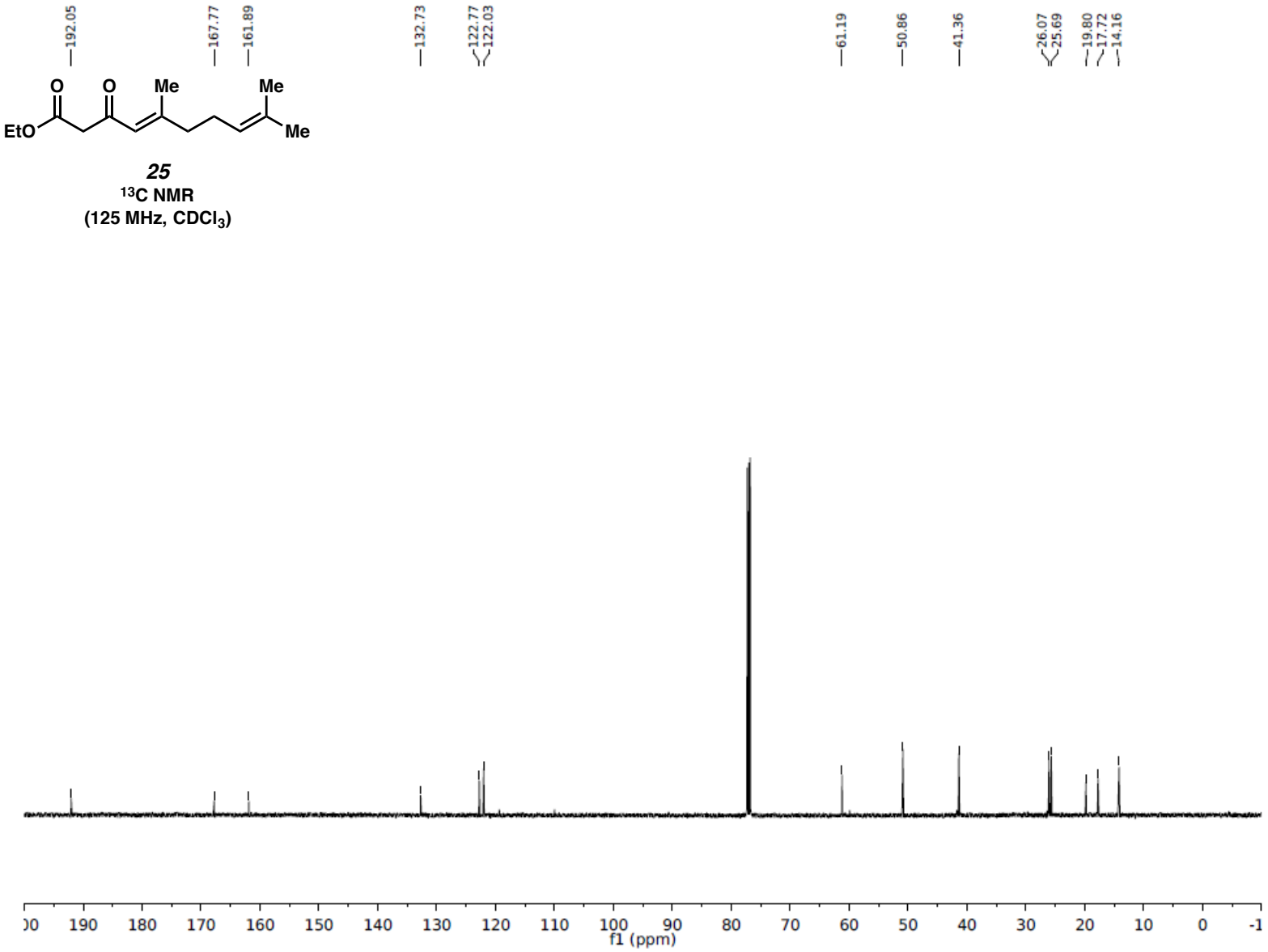




25

^{1}H NMR

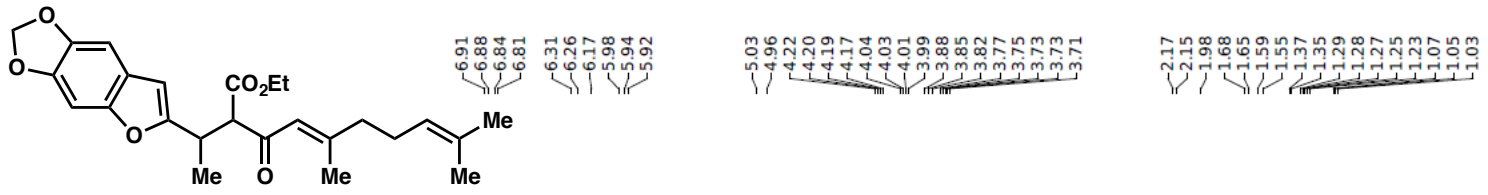
(500 MHz, $CDCl_3$)



25

^{13}C NMR

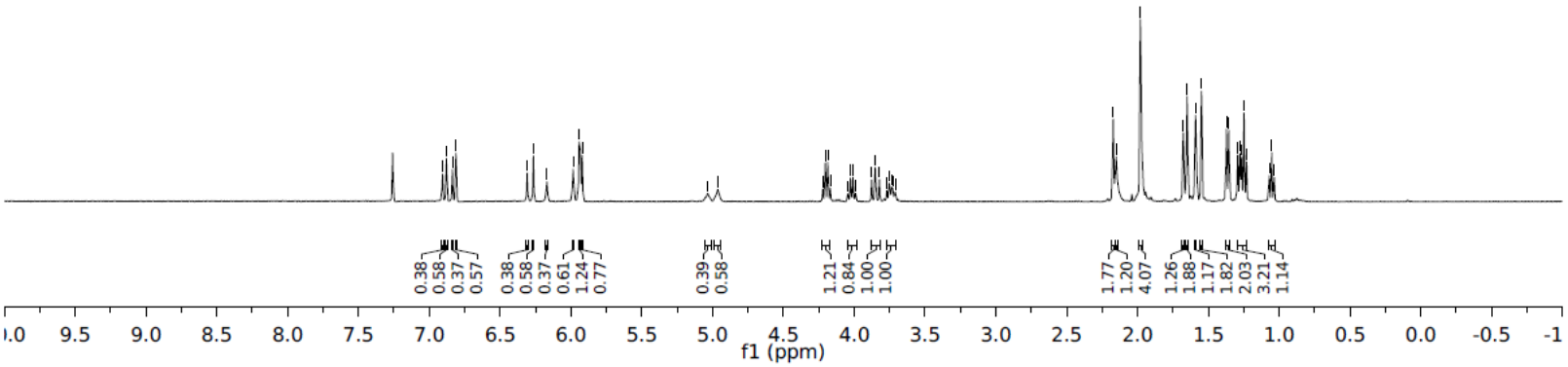
(125 MHz, $CDCl_3$)

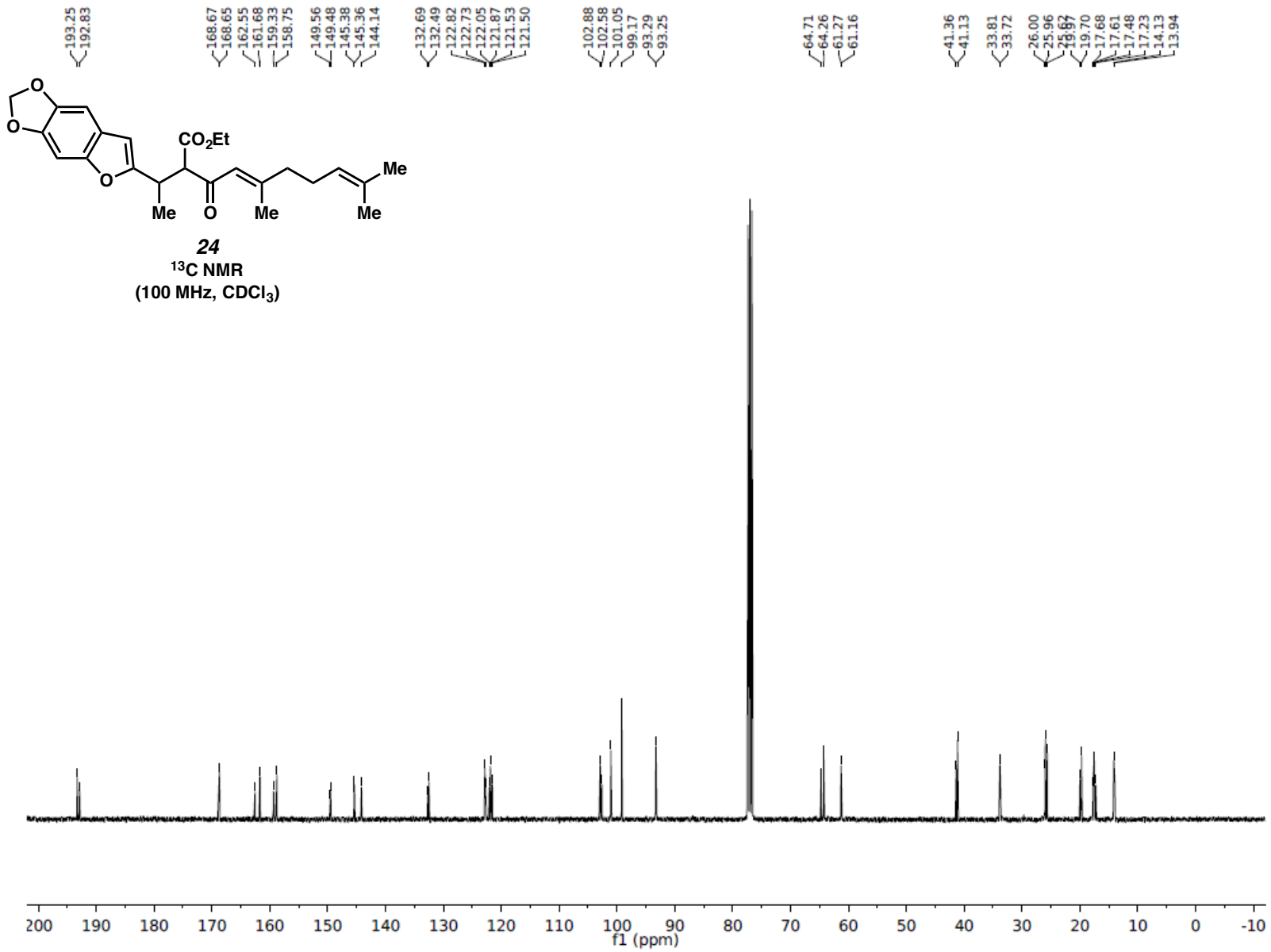


24

^{1}H NMR

(400 MHz, $CDCl_3$)

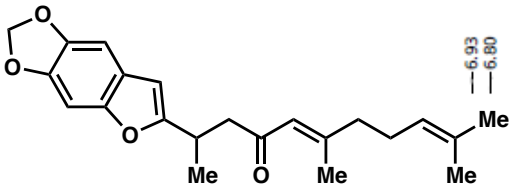




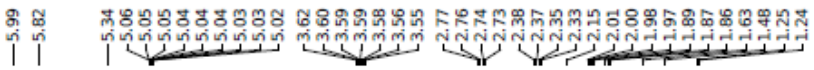
24

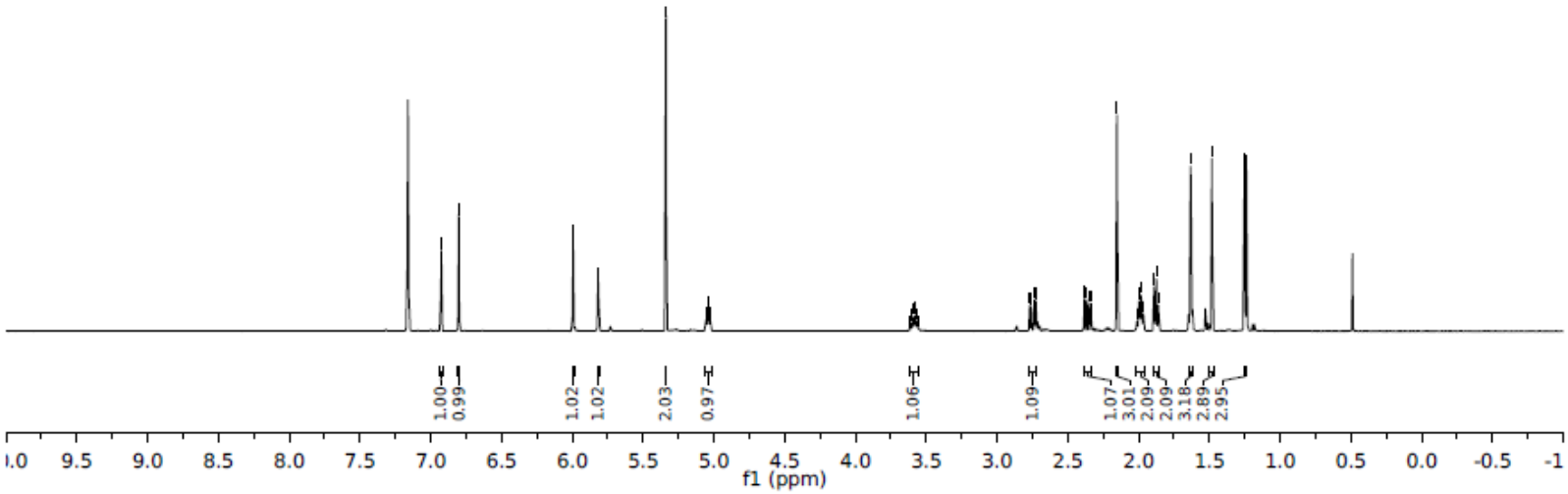
^{13}C NMR

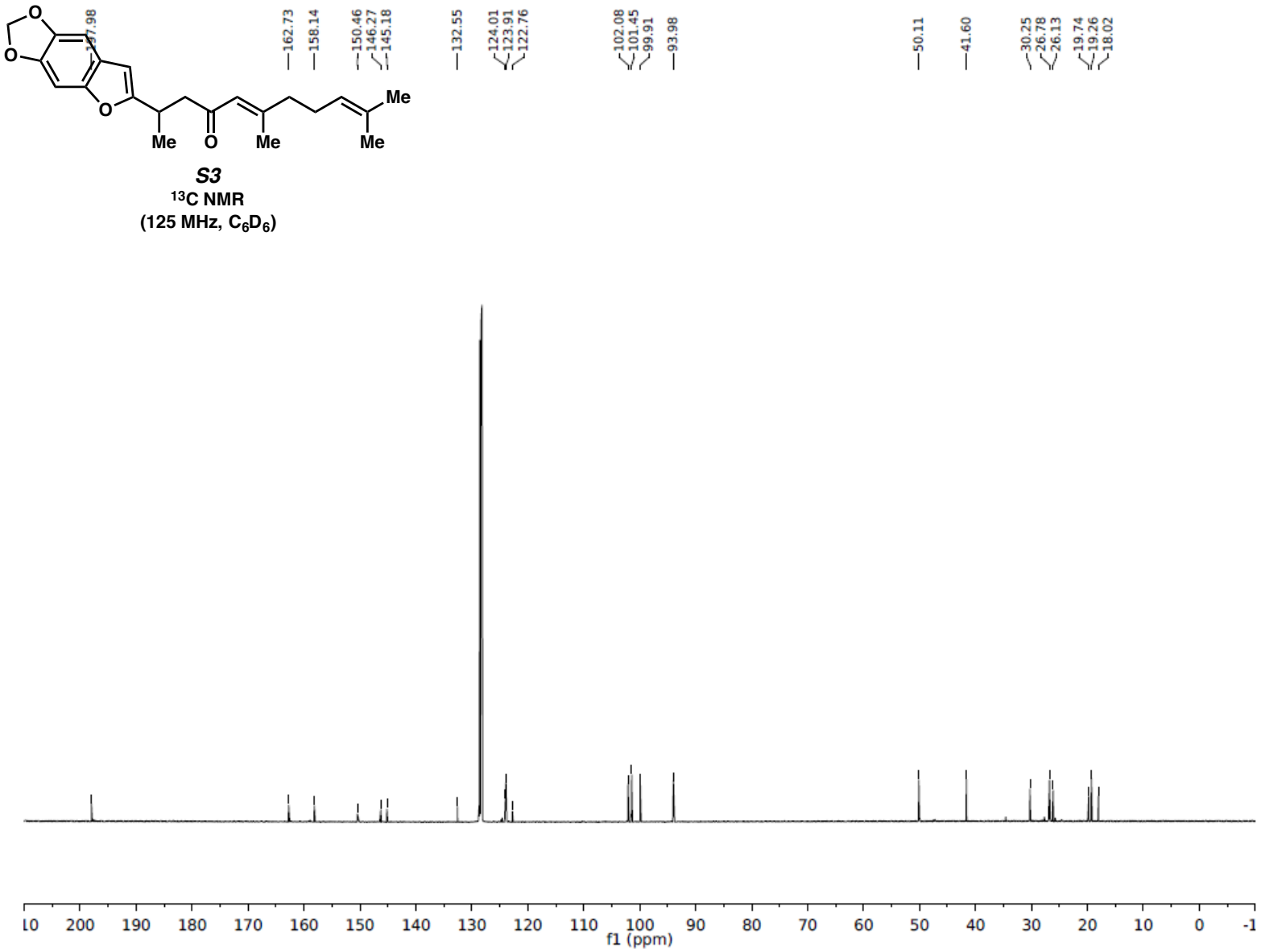
(100 MHz, $CDCl_3$)



S3
^{1}H NMR
(500 MHz, C_6D_6)



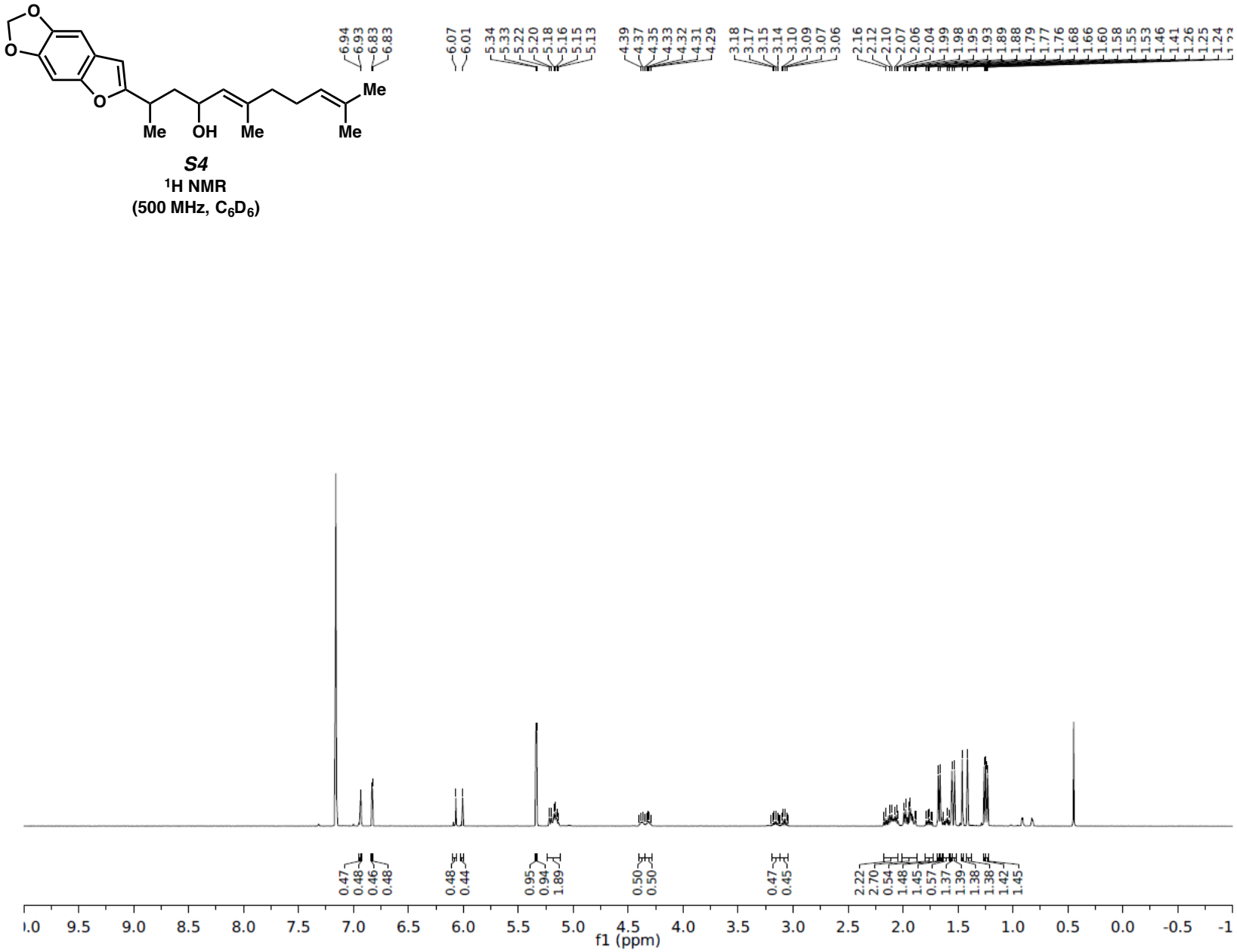




S3

^{13}C NMR

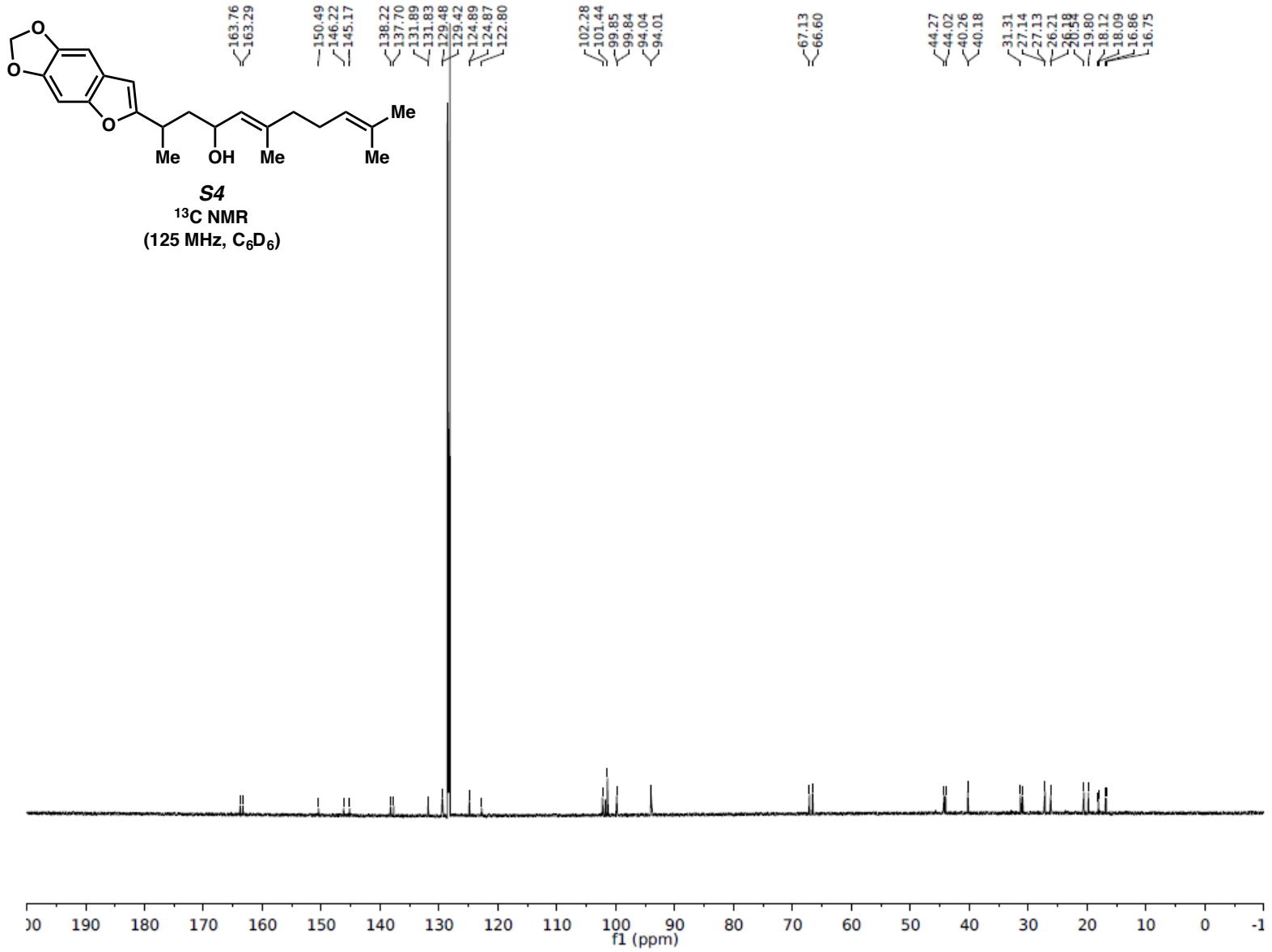
(125 MHz, C_6D_6)



S4

^{1}H NMR

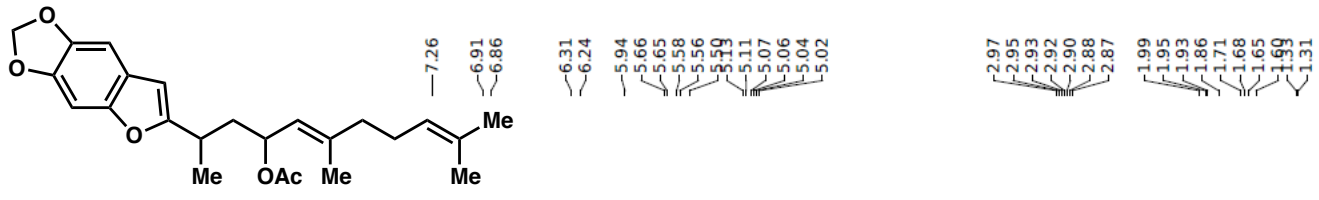
(500 MHz, C_6D_6)



S4

^{13}C NMR

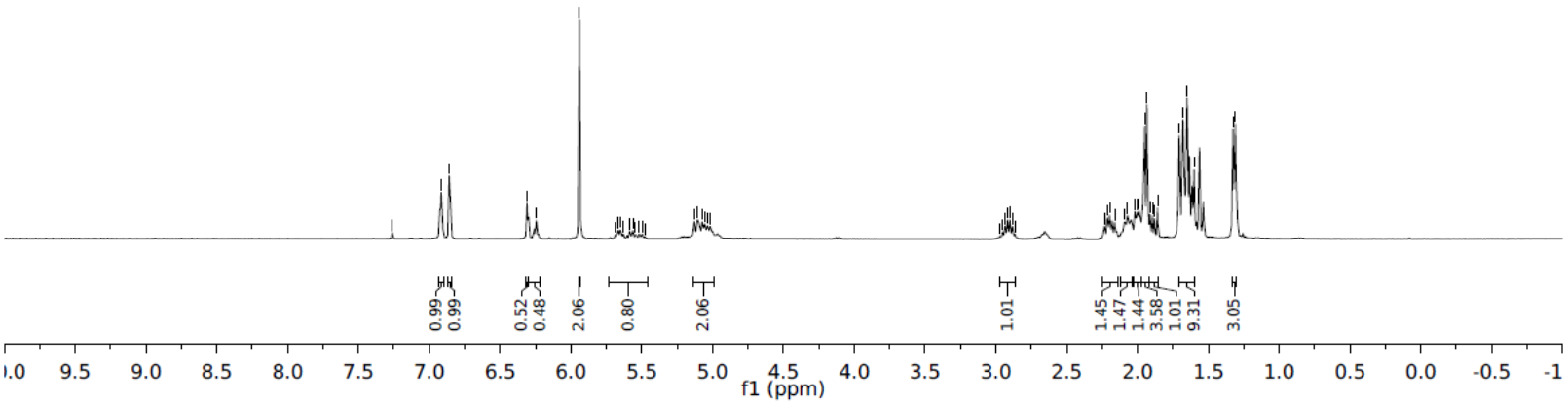
(125 MHz, C_6D_6)

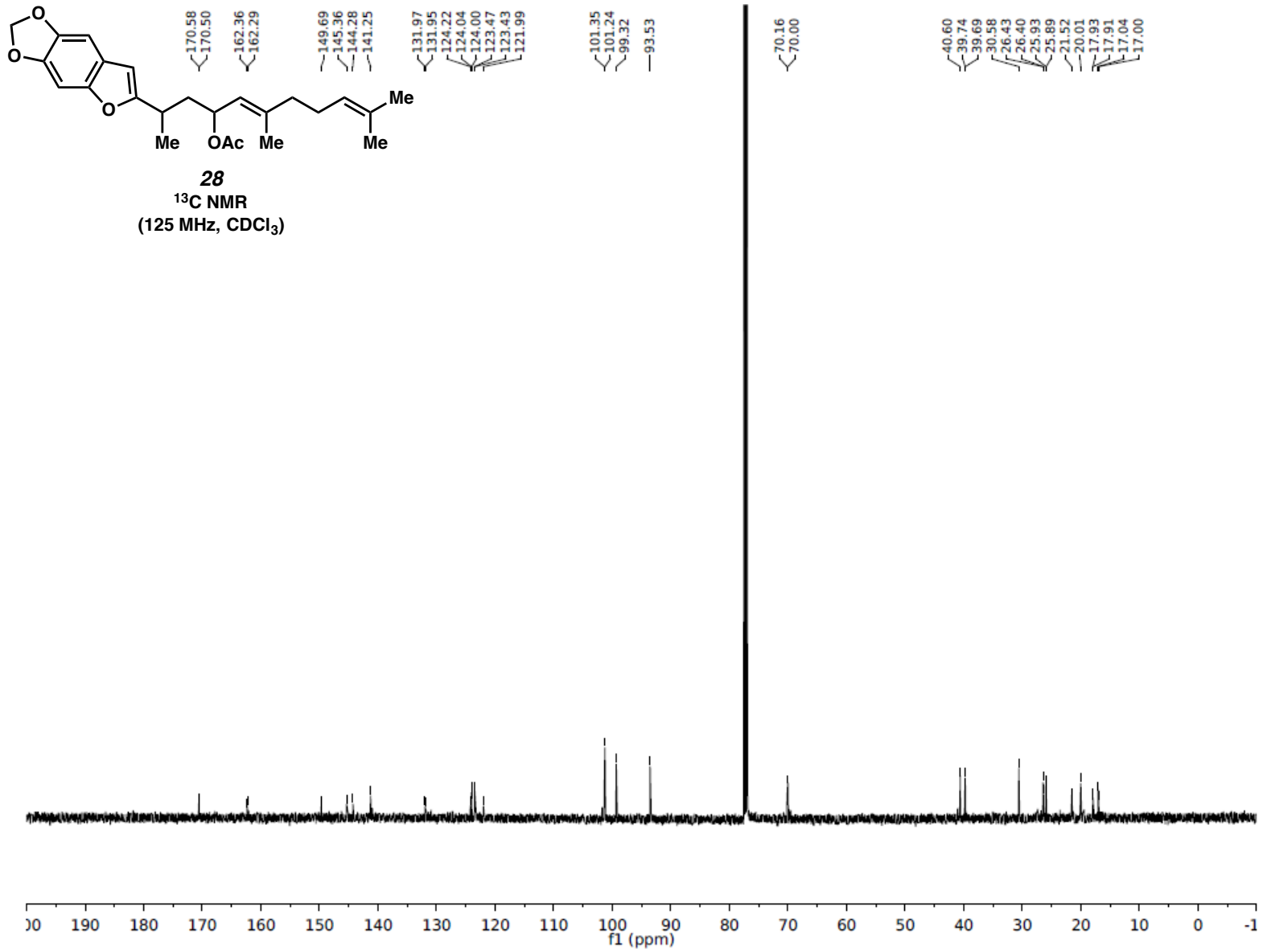


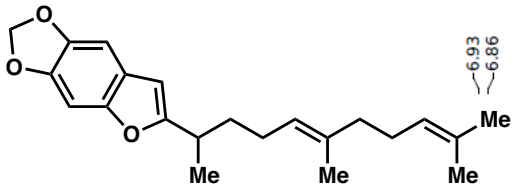
28

^{1}H NMR

(400 MHz, $CDCl_3$)



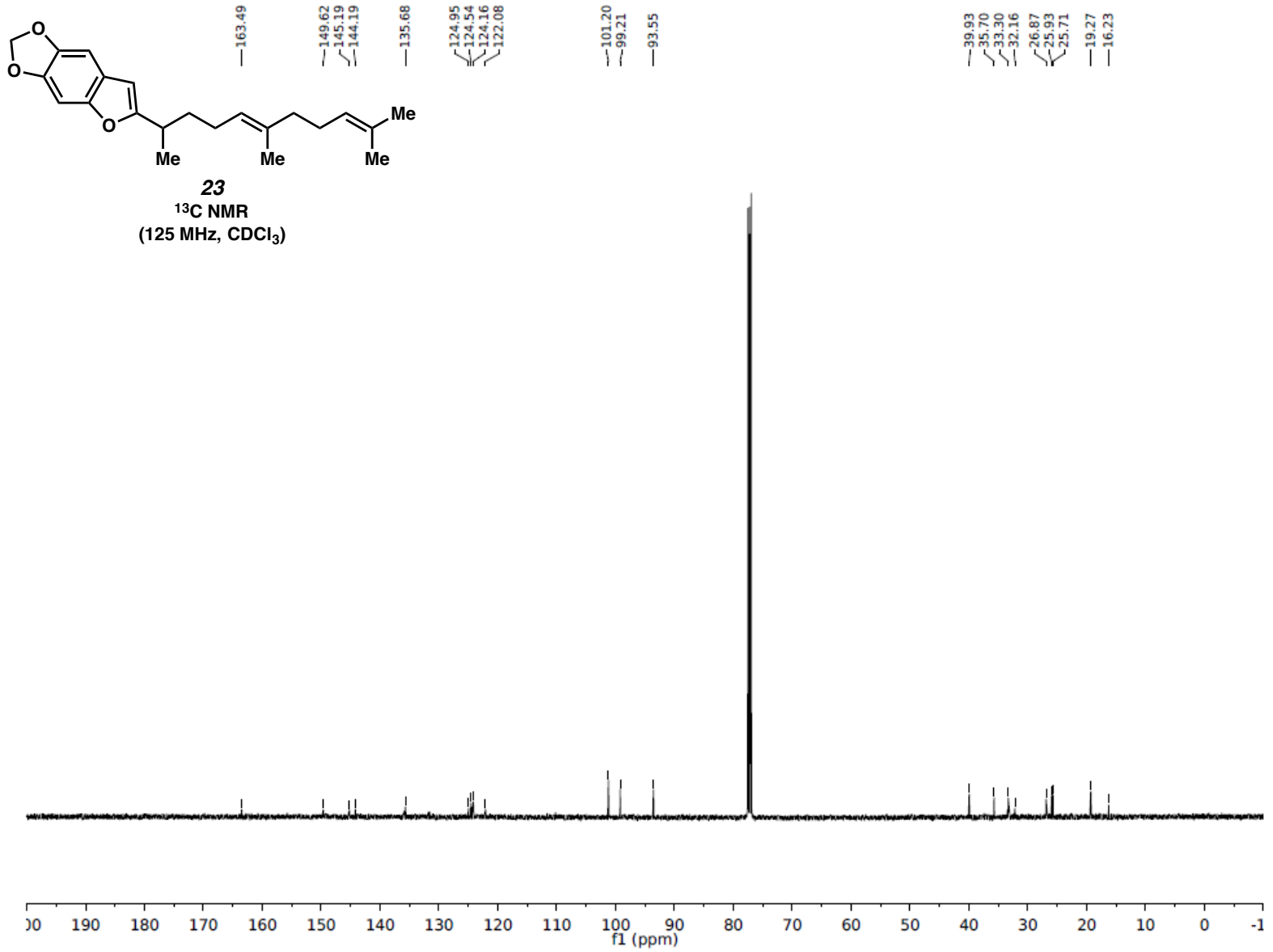

170.58
170.50
162.36
162.29
149.69
145.36
144.28
141.25
131.97
131.95
124.22
124.04
124.00
123.47
123.43
121.99
101.35
101.24
99.32
93.53
70.16
70.00
40.60
39.74
39.69
30.58
26.43
26.40
25.93
25.89
21.52
20.01
17.93
17.91
17.04
17.00
O
O
O
Me
Me
OAc
Me
Me
28
13C NMR
(125 MHz, CDCl3)
f1 (ppm)



23

^{1}H NMR

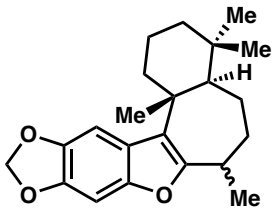
(500 MHz, $CDCl_3$)



23

^{13}C NMR

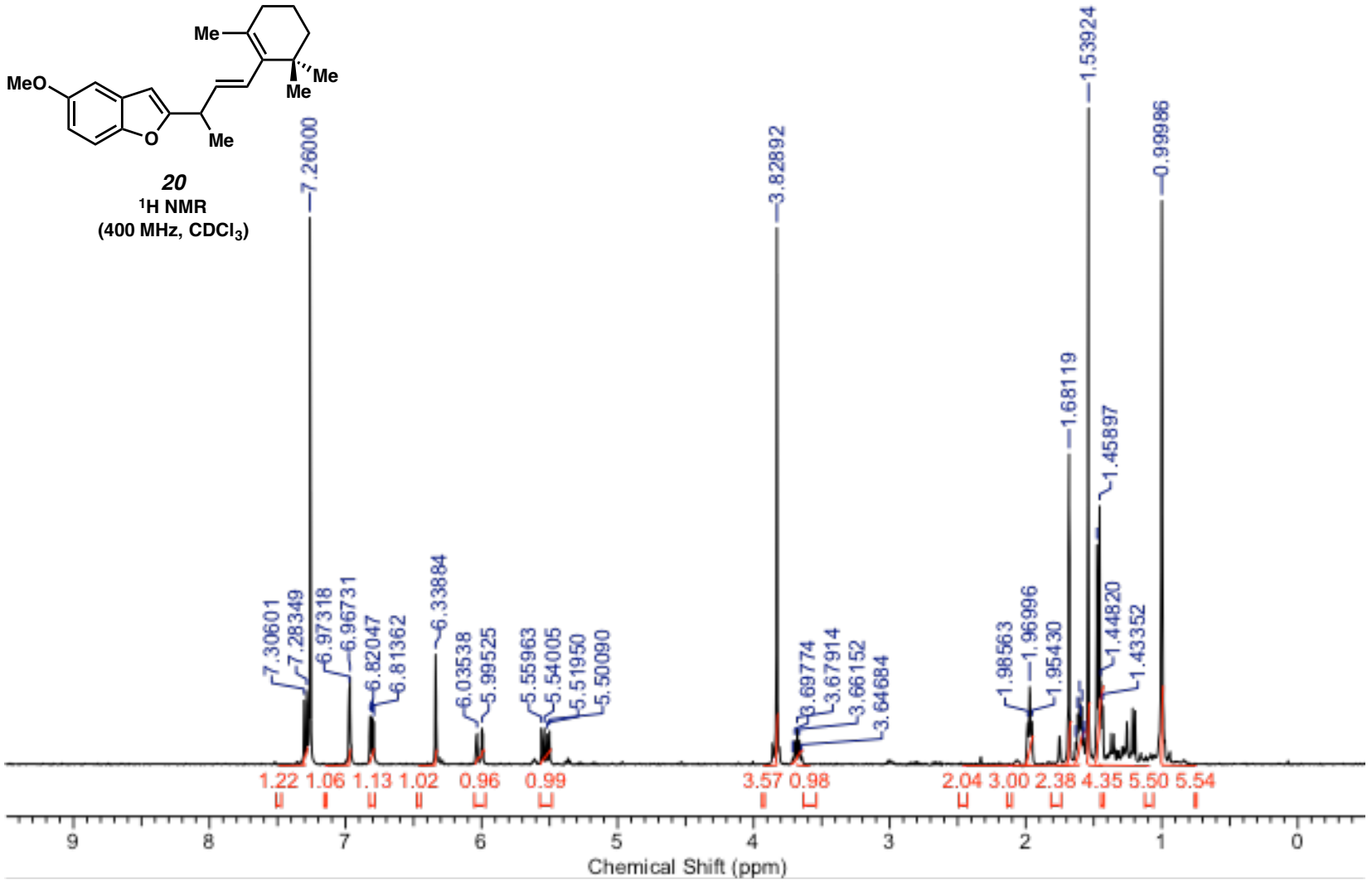
(125 MHz, $CDCl_3$)

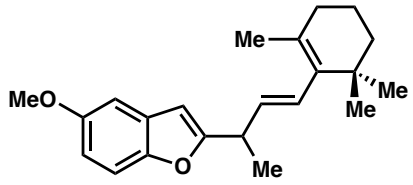


22

^{1}H NMR

(400 MHz, $CDCl_3$)


Me
MeO
Me
Me
O
Me
20
1H NMR
(400 MHz, CDCl3)
7.26000
7.30601
7.28349
6.97318
6.96731
6.82047
6.81362
6.33884
6.03538
5.99525
5.55963
5.54005
5.51950
5.50090
3.82892
3.69774
3.67914
3.66152
3.64684
1.98563
1.96996
1.95430
1.68119
1.53924
1.45897
1.44820
1.43352
0.99986
1.22 1.06 1.13 1.02 0.96 0.99 3.57 0.98 2.04 3.00 2.38 4.35 5.50 5.54
9 8 7 6 5 4 3 2 1 0
Chemical Shift (ppm)



20

^{13}C NMR

(101 MHz, $CDCl_3$)