Pharmacophore-Directed Retrosynthesis Applied to Ophiobolin A: Simplified Bicyclic Derivatives Displaying Anticancer Activity

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Supporting Information

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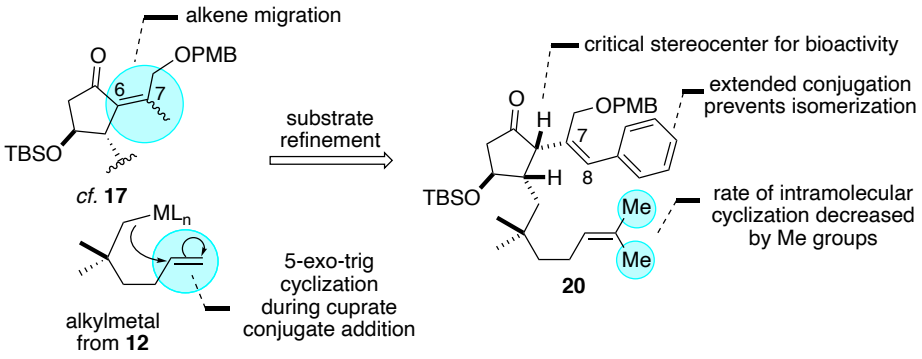
General

All non-aqueous reactions were performed under a nitrogen atmosphere in oven-dried glassware. Dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), toluene, and diethyl ether (Et_2O) were dried by passing through activated molecular sieves or alumina (solvent purification system). Other solvents and reagents were used as received from commercially available sources. Alkylithium reagents (n-BuLi, t-BuLi, MeLi) were used as received (no larger than 100 mL bottles) were used without titration and often consumed within 1 month of initial opening. Alkylithium reagents were added through leur-lock plastic syringe and metal needle. *i*-Pr_2NH and TMSCl were freshly distilled from CaH_2. Deuterated solvents were purchased from either Aldrich or Cambridge Isotopes and used as received. All heated reactions used heating mantle as the heat source. ^{1}H NMR spectra were measured at 600 MHz, 500 MHz, and 400 MHz, referenced relative to residual chloroform (7.26 ppm), and were reported in parts per million. Coupling constants (*J*) were reported in Hertz (Hz), with multiplicity reported following the usual convention: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dddd, doublet of doublet of doublet of doublets; dt, doublet of triplets; dq, doublet of quartets; ABq, AB quartet; m, multiplet; bs, broad singlet (prefix app indicates 'apparent'). ^{13}C NMR spectra were measured at 150 MHz, 100 MHz and 75 MHz, referenced relative to residual chloroform (77.23 ppm) or benzene (128.06 ppm), and were reported in parts per million (ppm). Flash column chromatography was performed with 60Å Silica Gel (230-400 mesh) as stationary phase using a gradient solvent system or on an automated Flash column chromatography system (EtOAc/hexanes as eluent unless indicated otherwise). High resolution mass spectra (ESI) were obtained through the Baylor University Mass Spectrometry Center. High resolution mass (HRMS) analysis involved electro-spray ionization (ESI) and mass analysis by ion trap. Thin Layer Chromatography (TLC) was performed using glass-backed silica gel F254 (Silicycle, 250 μm thickness). Visualization of developed plates was performed by fluorescence quenching or by staining with phosphomolybdic acid (PMA), potassium permanganate ($KMnO_4$), *p*-anisaldehyde or cerium sulfate. Fourier Transform Infrared (FTIR) spectra were recorded as thin films on NaCl plates.

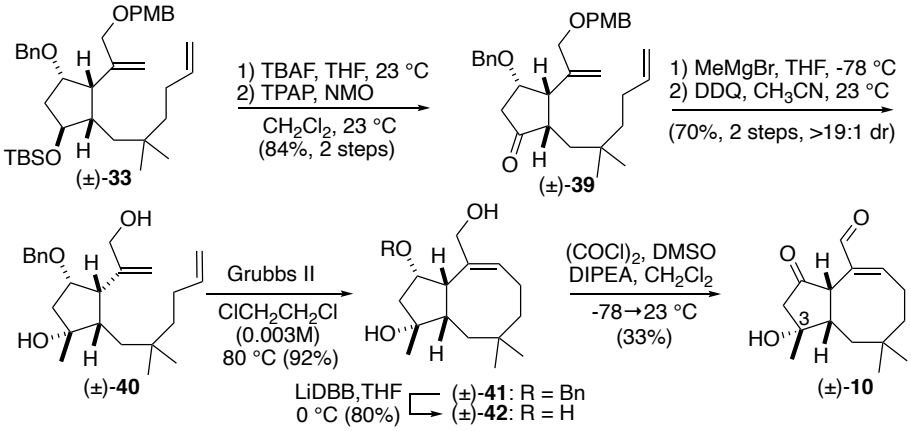
Defensive Synthetic Strategy Taken to Avoid Competing Intramolecular Cyclizations and Alkene Isomerizations. As previously implemented to avoid intramolecular cyclization of the alkylmetal intermediate **13** during conjugate addition, we decided to again employ a defensive strategy by refining the structure of the substrates without altering the overall synthetic plan and these two strategies are summarized in Scheme S1. After extensive exploration, we settled on introduction of a phenyl ring and thus targeted adduct **(±)-20** to minimize the tendency of C7-C8 olefin isomerization during installation of the critical C6 stereocenter required for biological potency.

Scheme S1. A Defensive Synthetic Strategy to Avoid Competing Intramolecular Cyclizations and Alkene Isomerizations Leading to Design of Targeted Cyclopentanone 20

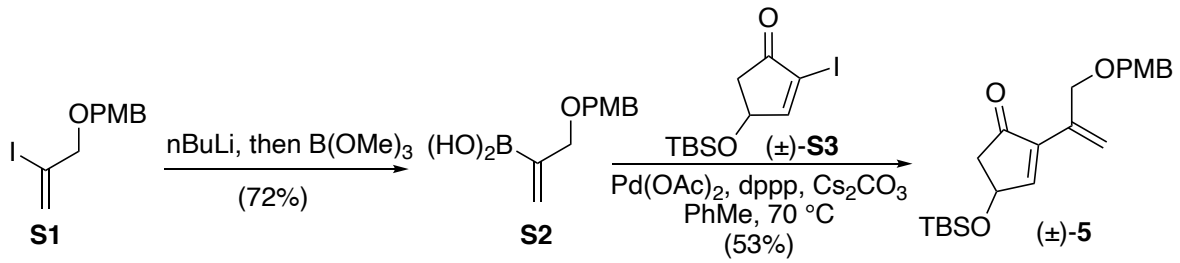


Detailed Synthetic Sequence Toward Bicyclic Derivative (±)-10. Synthesis of bicyclic derivative (±)-**10** bearing a tertiary alcohol at C3 began with alcohol (±)-**33** and followed a similar sequence as described for bicyclic derivative (±)-**38** (Scheme S2). Deprotection of the TBS ether followed by Ley oxidation[1] gave ketone (±)-**39** in 84% yield over the two steps. Methyl Grignard addition proceeded diastereoselectively (dr > 20:1) to deliver the tertiary alcohol. After PMB ether deprotection, allylic alcohol (±)-**40** underwent RCM with Grubbs 2nd generation catalyst[2] to yield tertiary alcohol (±)-**41**. Deprotection of the benzyl ether proceeded uneventfully to provide triol (±)-**42**. However, final oxidation to the ketoaldehyde was found to be quite challenging as the reaction was plagued by C6-epimerization or C3-dehydration through b-elimination under a variety of oxidative conditions screened. After thorough exploration, we found that Hünig's base in lieu of the more commonly employed triethylamine was key to a clean Swern bis-oxidation of triol (±)-**42**. However, it must be noted that the resulting ketoaldehyde (±)-**10**, while stable once purified, is quite sensitive to most separation methods studied. Silica gel including deactivation with Et_3N, basic alumina, and Fluorosil® all resulted in extensive decomposition. Use of reversed-phase semi-prep HPLC was unique in enabling purification of OpA derivative (±)-**10**. This is in stark contrast to the C3-secondary alcohol bearing OpA derivative (±)-**38** which was found to be much more stable and points to the importance of the C3-substitution pattern for stability of OpA derivatives. While OpA itself is more stable compared to both OpA derivatives (±)-**38** and (±)-**10** tolerating silica gel separation, it is also prone to C6 epimerization and C3 dehydration under acidic or basic conditions leading to significant loss in bioactivity.[3]

Scheme S2. Detailed Synthetic Sequence Leading to Bicyclic Derivative (±)-10



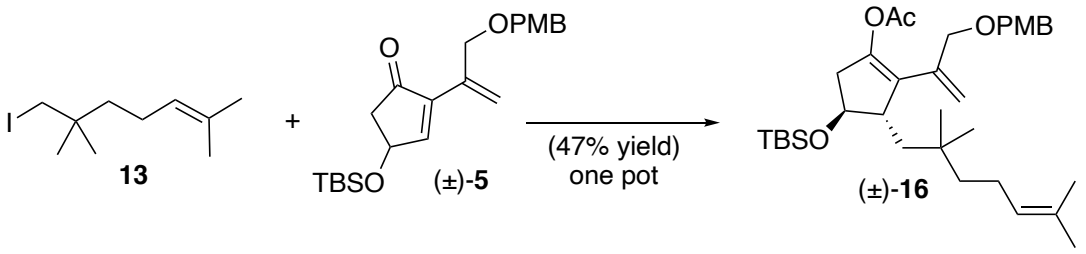
Synthetic Procedures



Enone (±)-5:

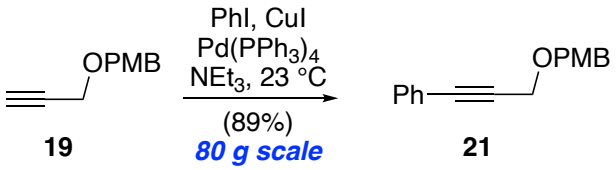
To an oven dried, 250 mL round-bottomed flask equipped with a stir bar was added known iodide **S1**[4] (5.6 g, 18.4 mmol, 1.0 equiv) and 90 mL anhydrous Et_2O under a nitrogen atmosphere. The flask was then cooled to -78 ºC (acetone-dry ice bath) and *n*-BuLi (8.9 mL of 2.5 M solution in hexanes, 22.1 mmol, 1.2 equiv) was carefully added slowly dropwise using a 12 mL leur-lock plastic syringe and metal needle and then stirred for 20 min. $B(OMe)_3$ (2.9 mL, 25.8 mmol, 1.4 equiv) was added dropwise and the reaction was stirred at -78 ºC for 30 min, then allowed to warm to ambient temperature (23 ºC) over 2 h. The reaction was carefully quenched with 50 mL HCl (1 N) (added slowly initially) and stirred at 23 ºC for 10 min. The mixture was then extracted with Et_2O (3 × 80 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. Flash column chromatography (SiO2, gradient elution, 0 → 60% EtOAc/hexanes) afforded the boronic acid **S2** (2.9 g, 72%) as a pale-yellow oil: TLC (EtOAc: hexanes, 1:1 v/v): R_f = 0.3. This intermediate showed a complex NMR upon concentration, possibly due to polymerization through dehydration, and was used immediately in the following step without further characterization.

To an 250 mL oven dried, round-bottomed flask equipped with a stir bar was added boronic acid **S2** (3.9 g, 17.8 mmol, 1.2 equiv), iodoenone **(±)-S3**[5] (5.0 g, 14.8 mmol, 1.0 equiv), and 80 mL anhydrous toluene under a nitrogen atmosphere. Cs_2CO_3 (9.6 g, 29.6 mmol, 2.0 equiv), bis-1,3(diphenylphosphino)propane (dppp, 0.24 g, 0.577 mmol, 0.04 equiv), and $Pd(OAc)_2$ (66 mg, 29.5 mmol, 0.02 equiv) were successively added to the reaction under a stream of nitrogen. The reaction was then stirred at 70 ºC for 2 h. After cooling to 23 ºC, the mixture was filtered through a pad of Celite, then concentrated. Flash column chromatography (SiO2, gradient elution, 0 → 20% EtOAc/hexanes) afforded the diene (±)-**5** (3.0 g, 53%) as a pale yellow oil: TLC (EtOAc: hexanes, 1:4 v/v): R_f = 0.5; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (d, *J* = 2.5 Hz, 1H), 7.23 – 7.19 (m, 2H), 6.85 – 6.80 (m, 2H), 6.24 (d, *J* = 1.8 Hz, 1H), 5.46 (d, *J* = 1.8 Hz, 1H), 4.85 (dt, *J* = 5.6, 2.5 Hz, 1H), 4.38 (s, 2H), 4.14 (d, *J* = 12.2 Hz, 1H), 4.10 (d, *J* = 12.1 Hz, 1H), 3.76 (s, 3H), 2.76 (dd, *J* = 18.1, 6.1 Hz, 1H), 2.31 (dd, *J* = 18.1, 2.4 Hz, 1H), 0.87 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 204.4, 159.3, 157.7, 140.4, 134.8, 130.1, 129.5 (2), 120.8, 113.8 (2), 72.2, 71.4, 68.2, 55.3, 46.5, 25.8 (3), 18.1, -4.7, -4.6; IR (thin film): 2957, 2361, 1720, 1615 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{22}H_{32}O_4NaSi^+$ $[M+Na]^+$: 411.1962, found: 411.1957.



Enol acetate (±)-16:

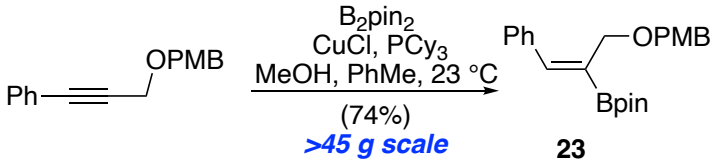
To an oven dried, 25 mL round-bottomed flask equipped with a stir bar was added iodide **13**[6] (175 mg, 0.66 mmol, 1.0 equiv), 0.7 mL anhydrous Et_2O, and 1.5 mL anhydrous pentane under a nitrogen atmosphere. The flask was then cooled to -78 ºC with an acetone-dry ice bath and *t*-BuLi (0.81 mL of 1.7 M solution in pentanes, 1.4 mmol, 2.1 equiv) was added dropwise and then stirred for 2.5 h at -78 ºC. (Th)Cu(CN)Li (2.8 mL of 0.25 M solution in THF, 0.70 mmol, 1.05 equiv) was added dropwise to the reaction mixture down the flask wall to ensure sufficient cooling prior to mixing. In the process of addition, a slurry formed at the bottom of the flask which disrupted stirring. No special measure was taken as the slurry dissolved again and stirring went back to normal after about 70% of the solution was added. After addition was complete, the mixture was stirred for another 15 min at -78 ºC. In a separate dry 6-dram vial, enone **(±)-5** (305 mg, 0.66 mmol, 1.0 equiv) was dissolved in 1 mL anhydrous THF and then mixed with freshly distilled TMSCl (0.25 mL, 2.0 mmol, 3.0 equiv). This mixture was then added dropwise by syringe to the reaction flask containing the cuprate reagent generated from iodide **13**. The reaction mixture was stirred at -78 ºC for 1 h until TLC indicated consumption of the enone **(±)-5**.When complete, 0.5 mL dry HMPA was then added, followed by MeLi (1.6 mL of 1.6 M solution in Et_2O, 2.6 mmol, 4.0 equiv) and the reaction was moved to an ice-water bath and stirred at 0 ºC for 1 h. The reaction was then cooled back to -78 ºC and Ac_2O was added (0.5 mL, 5.3 mmol, 8.0 equiv). The reaction was allowed to warm to 0 ºC over 4 h and then poured into a cold saturated $NaHCO_3$ solution (20 mL, cooled in an ice water bath). The combined organic layers following extraction with Et_2O (3 × 20 mL) were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. Flash column chromatography (SiO2, gradient elution, 0 → 10% EtOAc/hexanes) afforded the enol acetate **(±)-16** (200 mg, 47%, >20:1 dr) as a pale yellow oil: TLC (EtOAc: hexanes, 1:8 v/v): R_f = 0.6; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 – 7.24 (m, 2H), 6.89 – 6.84 (m, 2H), 5.34 (d, *J* = 1.8 Hz, 1H), 5.12 (d, *J* = 1.7 Hz, 1H), 5.08 (dd, *J* = 8.5, 5.8 Hz, 1H), 4.45 (d, *J* = 11.5 Hz, 1H), 4.41 (d, *J* = 11.5 Hz, 1H), 4.19 (dt, *J* = 13.3, 1.3 Hz, 1H), 4.13 (d, *J* = 13.2 Hz, 1H), 4.10 (d, *J* = 5.3 Hz, 1H), 3.80 (s, 3H), 3.15 (dd, *J* = 17.1, 5.2 Hz, 1H), 2.73 (d, *J* = 10.2 Hz, 1H), 2.24 (d, *J* = 17.1 Hz, 1H), 2.06 (s, 3H), 1.91 (q, *J* = 7.4 Hz, 2H), 1.67 (d, *J* = 1.5 Hz, 3H), 1.60 – 1.58 (m, 3H), 1.30 – 1.22 (m, 3H), 1.17 (dd, *J* = 14.7, 10.3 Hz, 1H), 0.94 (s, 3H), 0.93 (s, 3H), 0.87 (s, 9H), 0.055 (s, 3H), 0.048 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.4, 159.1, 143.9, 138.5, 131.0, 130.6, 129.3 (2), 126.3, 125.1, 115.0, 113.7 (2), 74.6, 71.5, 71.1, 55.3, 49.9, 43.0, 42.2, 41.5, 33.6, 27.2, 27.0, 25.9 (3), 25.7, 22.8, 21.0, 17.9, 17.6, -4.0, -4.5; IR (thin film): 2855, 1759, 1613 cm^{-1} ; HRMS (ESI+) *m/z* calcd for $C_{34}H_{54}O_5NaSi^+$ $[M+Na]^+$: 593.3633, found: 593.3638.



19 **21**

alkyne 21:

To an oven dried, 1 L round-bottomed flask equipped with a stir bar was added alkyne **20**[7] (34 g, 0.19 mol, 1.0 equiv), phenyl iodide (47 g, 0.23 mol, 1.2 equiv), and about 500 mL triethylamine (ACS grade, not dried). The reaction flask was evacuated with high vacumn briefly (~5 sec) and back-filled with N_2 (3X). CuI (3.6 g, 0.019 mol, 0.10 equiv) and $Pd(PPh_3)_4$ (2.2 g, 1.9 mmol, 0.010 equiv) was then added to the flask under a stream of nitrogen. The reaction mixture was then stirred at ambient temperature (23 ºC) for 12 h. The mixture was then filtered through a plug of silica gel with dichloromethane and concentrated. Flash column chromatography (gradient, SiO_2, 0 → 10% EtOAc/hexanes) afforded phenyl alkyne **21** (43 g, 89%) as a pale yellow oil: TLC (EtOAc: hexanes, 1:8 v/v): R_f = 0.3; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55 – 7.46 (m, 2H), 7.39 – 7.33 (m, 5H), 6.98 – 6.87 (m, 2H), 4.65 (s, 2H), 4.40 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.4, 131.8 (2), 129.9 (2), 129.6, 128.4, 128.3 (2), 122.7, 113.9 (2), 86.4, 85.2, 71.3, 57.5, 55.3; IR (thin film): 2839, 2240, 1613, 1515 cm^{-1} ; HRMS (ESI+) *m/z* calcd for $C_{17}H_{16}O_2Na^+$ $[M+Na]^+$: 275.1043, found: 275.1044.

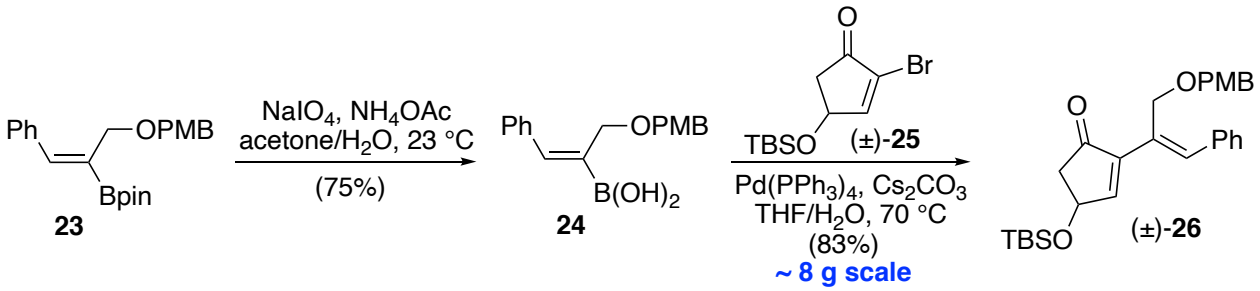


23

Vinyl borane 23:

To an oven dried,1 L round-bottomed flask equipped with a stir bar was added B_2pin_2 (56.8 g, 223 mmol, 1.3 equiv), PCy_3 (6.27 g, 22.3 mmol, 0.12 equiv), NaO^tBu (2.68 g, 27.9 mmol, 0.15 equiv), in 500 mL anhydrous toluene. The entire mixture was degassed by two freeze-pump-thaw cycles using liquid nitrogen and then backfilled with N_2. Neat phenyl alkyne **22** (47.0 g, 186 mmol, 1.0 equiv) was added to the mixture via syringe. CuCl (1.85 g, 18.7 mmol, 0.10 equiv) (relatively newly opened bottle, measured out in open air) was then added to the mixture under a stream of N_2. The flask was evacuated and backfilled with N_2. After the reaction mixture was stirred at 23 ºC for 15 min, anhydrous methanol (15.0 mL, 446 mmol, 2.0 equiv) was added. The reaction was stirred at 23 ºC for 16 h. The crude reaction mixture was then directly filtered through a pad of Celite, concentrated and dry-loaded onto silica gel. Flash column chromatography (gradient, SiO_2, 0 → 10% EtOAc/hexanes) afforded tri-substituted alkene **23** (52.0 g, 74%) as a pale yellow oil: TLC (EtOAc: hexanes, 1:8 v/v): R_f = 0.25; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.47 – 7.41 (m, 2H), 7.37 – 7.27 (m, 5H), 6.92 – 6.84 (m, 2H), 4.53 (s, 2H), 4.29 (d, *J* = 0.8 Hz, 2H), 3.83 (s, 3H), 1.36 (s, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.0, 146.7, 136.8, 130.9, 129.5(2), 129.5(2), 128.1(2), 127.9, 113.6(2), 83.6(2), 71.9, 66.7, 55.3,

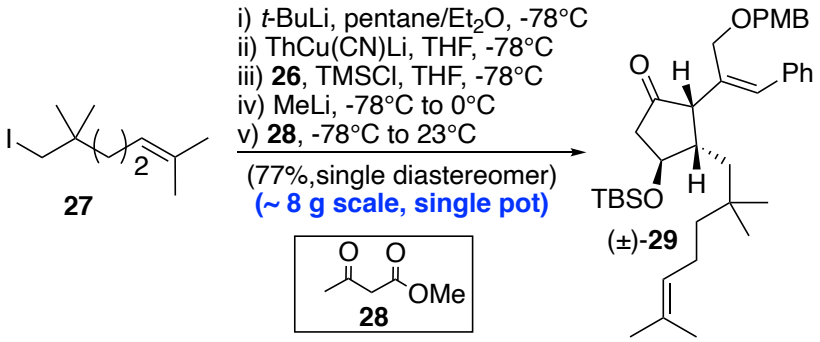
24.9 (4) (the carbon directly attached to boron does not appear in carbon NMR); IR (thin film): 2932, 2364, 1616, 1515 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{23}H_{29}BO_4Na^+$ $[M+Na]^+$: 403.2051, found: 403.2050.



diene (±)-26:

To a 1 L round-bottomed flask carbon directly attached to boron does not appear in carbon NMR due to was added tri-substituted alkene **23** (15.3 g, 40.2 mmol, 1 equiv), 300 mL acetone (ACS grade), 300 mL deionized water, $NaIO_4$ (42.9 g, 200 mmol, 5.0 equiv), and NH_4OAc (15.4 g, 200 mmol, 5.0 equiv). The mixture was vigorously stirred at 23 ºC for 30 h, then concentrated to remove most of the acetone. The mixture was then extracted with ethyl acetate (3 × 200 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. Flash column chromatography (SiO_2, gradient elution, 0 → 60% EtOAc/hexanes) afforded the boronic acid **24** (9.0 g, 75%) as a colorless oil: TLC (EtOAc: hexanes, 1:1 v/v): R_f = 0.28. This intermediate showed a complex NMR upon concentration, possibly due to polymerization, and was used directly in the following step without further characterization.

To a 500 mL round-bottomed flask equipped with a stir bar was added boronic acid **24** (11 g, 36.9 mmol, 1.3 equiv), bromo enone **25** (8.2 g, 28.2 mmol, 1.0 equiv) and diluted by addition of 200 mL THF and 20 mL deionized water. The entire mixture was degassed by freeze-pump-thaw cycles (2X) using liquid nitrogen and then backfilled with N_2. Cs_2CO_3 (27.6 g, 84.6 mmol, 3.0 equiv), $Pd(PPh_3)_4$ (845 mg, 0.846 mmol, 0.03 equiv) were successively added to the reaction mixture under a stream of nitrogen. The reaction was then stirred at 70 ºC for 4 h. After cooling to 23 ºC, the mixture was extracted with Et_2O (3 × 150 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. Flash column chromatography (SiO_2, gradient elution, 0 → 15% EtOAc/hexanes) afforded diene **26** (8.7 g, 81%) as a pale yellow oil: TLC (EtOAc: hexanes, 1:8 v/v): R_f = 0.6; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.38 (d, *J* = 2.6 Hz, 1H), 7.31 – 7.25 (m, 5H), 7.25 – 7.23 (m, 2H), 6.87 – 6.84 (m, 2H), 4.91 (dt, *J* = 5.6, 2.5 Hz, 1H), 4.45 (d, *J* = 1.7 Hz, 2H), 4.25 (s, 2H), 3.80 (s, 3H), 2.84 (dd, *J* = 18.1, 6.1 Hz, 1H), 2.41 (dd, *J* = 18.1, 2.4 Hz, 1H), 0.92 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 204.6, 159.4, 157.9, 142.2, 136.5, 136.5, 129.9 (2), 129.9, 129.2 (2), 128.5, 128.2 (2), 127.6, 113.8 (2), 72.2, 68.0, 66.5, 55.3, 47.0, 25.8 (3), 18.2, -4.6 (2); IR (thin film): 2954, 2856, 1716, 1513 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{28}H_{36}O_4SiNa^+$ $[M+Na]^+$: 487.2275, found: 487.2274.

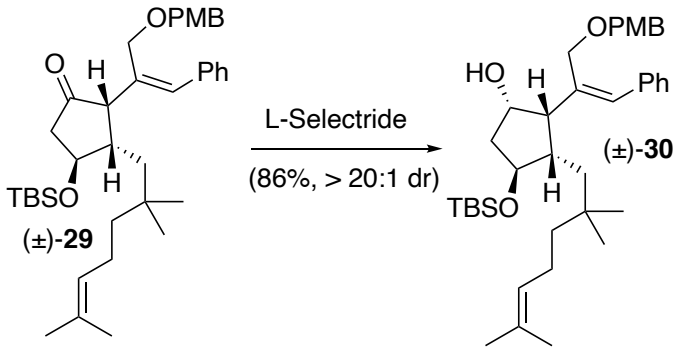


Ketone (±)-29:

To an oven dried, 250 mL round-bottomed flask equipped with a stir bar was added iodide **27** (4.94 g, 18.6 mmol, 1.0 equiv), 12 mL anhydrous Et_2O, and 20 mL anhydrous pentane under nitrogen atmosphere. The flask was then cooled to -78 ºC with an acetone-dry ice bath and *t*-BuLi (22.9 mL of 1.7 M solution in pentanes, 39.0 mmol, 2.1 equiv) was added dropwise by syringe and then stirred for 2.5 h at -78 ºC. (Th)Cu(CN)Li (81.8 mL of 0.25 M solution in THF, 20.5 mmol, 1.1 equiv) was then added by syringe dropwise (over 20 min) to the reaction mixture down the side of the flask wall to improve cooling prior to mixing with the reaction. In the process of addition, a slurry formed at the bottom of the flask which disrupted stirring. No special measure was taken as the slurry became homogenous after about 70% of the solution was added. After the addition was complete, the mixture was stirred for another 15 min. In a separate 25 mL dry flask, enone **26** (8.62 g, 18.6 mmol, 1.0 equiv) was dissolved in 12 mL anhydrous THF and then mixed with freshly distilled TMSCl (3.54 mL, 27.9 mmol, 1.5 equiv). This mixture was then added dropwise via syringe to the reaction flask containing the cuprate reagent. The mixture was stirred at -78 ºC for 1 h until TLC indicated consumption of the enone starting material. MeLi (16.0 mL of 2.9 M solution in DME, 46.5 mmol, 2.5 equiv) was then added via syringe, and the reaction was moved to an ice-water bath and stirred at 0 ºC for 2 h. The reaction was then recooled to -78 ºC, and cannulated rapidly into a 500 mL round-bottomed flask containing methylacetoacetate (**28**, 19.6 mL, 186 mmol, 10 equiv, previously dried over 4 Å molecular sieves) in 200 mL anhydrous THF at -78 ºC. The reaction mixture was then allowed to warm to 0 ºC over 4 h (left in the cooling bath, let the dry ice melt). (*Note*: ensure the temperature reaches 0 ºC or even slightly above before the next operation, otherwise the protonation is not complete, and quenching with AcOH leads to lower diastereoselectivity. The undesired diastereomer has a slightly lower Rf thus enolate protonation can be monitored by TLC.) Neat AcOH (2.23 mL, 37.2 mmol, 2.0 equiv) was added to the reaction and stirred at 23 ºC for 3 min. The entire mixture was then poured into 400 mL of cold saturated $NaHCO_3$ solution in a 1 L separation funnel and extracted with Et_2O (3 × 200 mL), and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. (*Note*: for best results, perform the chromatographic purification immediately; leaving the crude reaction mixture over $MgSO_4$ for prolonged time results in olefin isomerization). Flash column chromatography (SiO_2, gradient elution, 0 → 10% EtOAc/hexanes) afforded ketone **29** (8.65 g, 77%, single diastereomer) as a colorless oil: TLC (EtOAc: hexanes, 1:8 v/v): R_f = 0.5; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 8.2, 6.8 Hz, 2H), 7.26 – 7.22 (m, 1H), 7.18 – 7.15 (m, 2H), 7.15 – 7.12 (m, 2H), 6.83 – 6.77 (m, 2H), 6.57 (s, 1H), 5.08 – 5.03 (m, 1H), 4.28 – 4.23 (m, 3H), 4.11 (dd, *J* = 3.8, 1.1 Hz, 2H), 3.78 (s, 3H), 3.64 (d, *J* = 9.0 Hz, 1H),

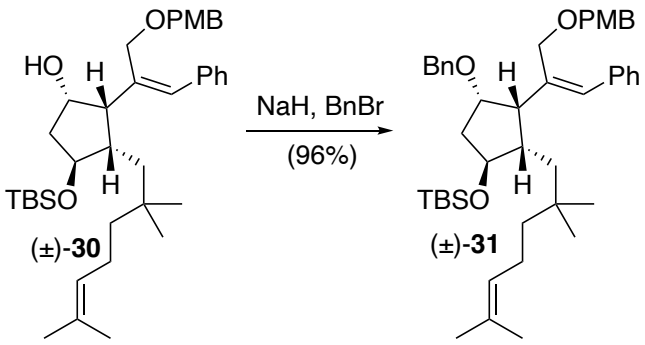
2.52 (dd, J = 18.2, 6.0 Hz, 1H), 2.40 (dq, J = 10.3, 5.3 Hz, 1H), 2.14 (dd, J = 18.2, 4.7 Hz, 1H), 1.88 (app tt, J = 14.4, 7.3 Hz, 2H), 1.66 (d, J = 1.5 Hz, 3H), 1.55 (d, J = 1.3 Hz, 3H), 1.47 (dd, J = 14.2, 5.1 Hz, 1H), 1.21 (ddd, J = 9.9, 7.8, 4.3 Hz, 2H), 1.15 (dd, J = 14.3, 5.3 Hz, 1H), 0.881 (s, 3H), 0.876 (s, 9H), 0.85 (s, 3H), 0.06 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 215.5, 159.1, 136.8, 135.2, 134.7, 131.01, 130.0, 129.4 (2), 129.0 (2), 128.1 (2), 127.0, 125.0, 113.7 (2), 73.9, 71.8, 67.78, 57.5, 55.3, 47.1, 45.9, 43.1, 39.1, 33.5, 27.0, 26.9, 25.8 (3), 25.7, 22.8, 17.9, 17.6, -4.5, -4.6; IR (thin film): 2956, 2858, 1738, 1613, 1470 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{38}H_{56}NaO_4Si^+$ $[M+Na]^+$: 627.3840, found: 627.3844.

Note: Although compound **29** is stable, we recommend performing the next step (reduction) right away to avoid any epimerization or isomerization problems.



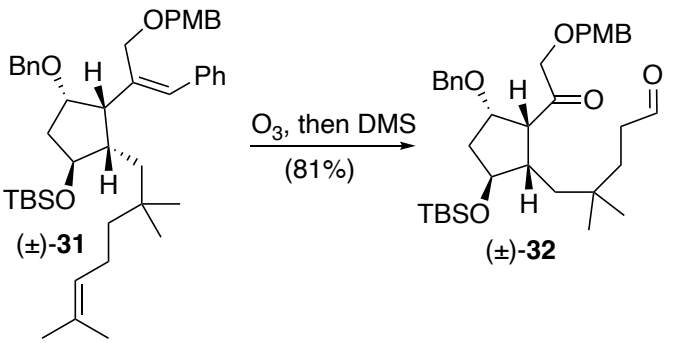
Alcohol (±)-30:

To an oven dried, 250 mL round-bottomed flask equipped with a stir bar was added ketone **29** (8.60 g, 14.2 mmol, 1.0 equiv), and 70 mL anhydrous THF under a N_2 atmosphere. The flask was then cooled to -78 ºC with an acetone-dry ice bath and L-Selectride (18.5 mL of 1 M solution in THF, 18.5 mmol, 1.3 equiv) was added dropwise and then stirred at -78 ºC for 2 h. The reaction was then allowed to slowly warm to 23 ºC by letting the dry ice melt over 6 h and then 50 mL of 3% H_2O_2 was added to the mixture and vigorously stirred for 2 h. The mixture was extracted with Et_2O (3 × 50 mL) and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. Flash column chromatography (SiO_2, gradient elution, 0 → 20% EtOAc/hexanes) afforded the alcohol **30** (7.41 g, 86%, >20:1 dr) as a very pale yellow oil: TLC (EtOAc: hexanes, 1:4 v/v): R_f = 0.6; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 7H), 6.90 – 6.87 (m, 2H), 6.61 (s, 1H), 5.10 – 5.04 (m, 1H), 4.52 (dt, J = 8.4, 8.0 Hz, 1H), 4.49 (s, 2H), 4.07 – 4.03 (m, 1H), 4.02 (d, J = 9.6 Hz, 1H), 3.85 (d, J = 9.5 Hz, 1H), 3.81 (s, 3H), 3.67 (d, J = 7.7 Hz, 1H), 3.19 (t, J = 7.0 Hz, 1H), 2.09 (dq, J = 7.0, 3.8 Hz, 1H), 2.00 – 1.97 (m, 2H), 1.89 (hept, J = 6.9 Hz, 2H), 1.67 (d, J = 1.5 Hz, 3H), 1.57 (d, J = 1.3 Hz, 3H), 1.45 (dd, J = 14.2, 7.0 Hz, 1H), 1.28 – 1.24 (m, 1H), 1.22 – 1.18 (m, 2H), 0.89 (s, 9H), 0.88 (s, 3H), 0.87 (s, 3H), 0.039 (s, 3H), 0.036 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.5, 137.8, 136.9, 134.5, 130.8, 130.0 (2), 128.8, 128.7 (2), 128.1 (2), 127.0, 125.2, 113.9 (2), 78.0, 73.2, 72.8, 68.5, 56.5, 55.2, 46.9, 43.0, 43.0, 40.6, 33.5, 27.1, 27.0, 25.8 (3), 25.6, 22.7, 17.9, 17.6, -4.3, -4.7; IR (thin film): 2957, 2364, 2336, 1515cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{38}H_{58}NaO_4Si$ $[M+Na]^+$: 629.3997, found: 629.3991.



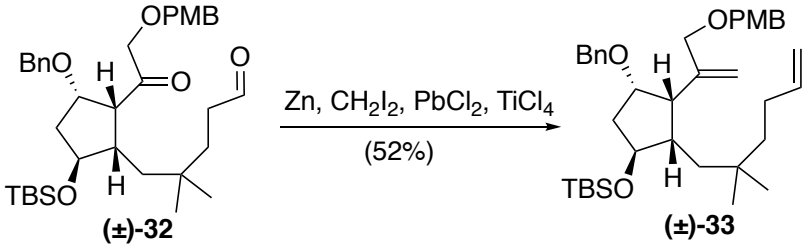
Benzyl ether (±)-31:

To an oven dried, 250 mL round-bottomed flask equipped with a stir bar was added alcohol **30** (7.41 g, 12.2 mmol, 1.0 equiv), and 100 mL anhydrous THF under a N_2 atmosphere. The flask was then cooled to 0 ºC with a water-ice bath and NaH (weighed out in open air) (0.980 g of 60% suspension in parafilm, 24.4 mmol, 2.0 equiv) was added slowly and carefully (gas evolution) and the mixture was stirred at 0 ºC for 30 min. To the mixture was then added TBAI (450 mg, 1.22 mmol, 0.10 equiv), BnBr (2.3 mL, 18.3 mmol, 1.5 equiv) and stirred at 50 ºC for 8 h. The reaction was then cooled to 0 ºC and quenched by careful addition of 50 mL saturated NH_4Cl solution and then further diluted with 150 mL water and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. Flash column chromatography (SiO_2, gradient elution, 0 → 10% EtOAc/hexanes) afforded benzyl ether **31** (8.20 g, 96%) as a colorless oil: TLC (EtOAc: hexanes, 1:8 v/v): R_f = 0.8; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 6H), 7.25 – 7.20 (m, 6H), 6.85 – 6.81 (m, 2H), 6.71 (s, 1H), 5.09 – 5.04 (m, 1H), 4.48 (d, *J* = 11.8 Hz, 1H), 4.44 (d, *J* = 11.8 Hz, 1H), 4.41 – 4.35 (m, 2H), 4.32 (dt, *J* = 8.3, 5.7 Hz, 1H), 4.20 (ddd, *J* = 8.2, 6.1, 3.9 Hz, 1H), 4.11 (d, *J* = 10.4 Hz, 1H), 3.98 (d, *J* = 10.3 Hz, 1H), 3.80 (s, 3H), 3.35 (t, *J* = 6.6 Hz, 1H), 2.21 (ddd, *J* = 14.1, 8.4, 5.4 Hz, 1H), 2.04 (m, 1H), 1.95 – 1.84 (m, 3H), 1.71 (dd, *J* = 14.6, 5.7 Hz, 1H), 1.66 (d, *J* = 1.4 Hz, 3H), 1.55 (s, 3H), 1.28 – 1.17 (m, 3H), 0.88 (s, 9H), 0.87 (s, 3H), 0.84 (s, 3H), 0.01 (s, 3H), -0.00 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.0, 138.9, 137.6, 136.5, 134.6, 130.7, 130.6, 129.2 (2), 128.9 (2), 128.2 (2), 128.0(2), 127.3 (2), 127.2, 126.6, 125.4, 113.6 (2), 80.4, 72.1, 72.0, 70.8, 68.6, 55.2, 51.4, 46.8, 43.4, 41.2, 40.1, 33.4, 27.0, 26.9, 25.9 (3), 25.7, 22.8, 17.9, 17.5, -4.3, -4.7; IR (thin film): 2925, 2849, 2361, 1252, 1089 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{45}H_{64}NaO_4Si^+$ $[M+Na]^+$: 719.4466, found: 719.4462.



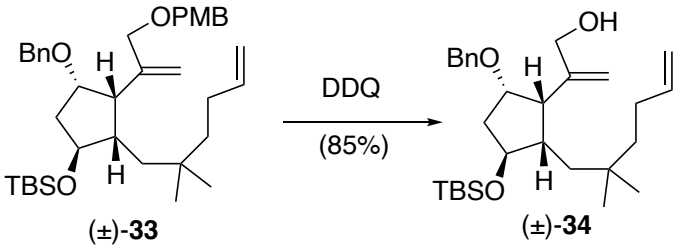
Ketoaldehyde (±)-32:

To an oven dried, 250 mL round-bottomed flask equipped with a stir bar was added benzyl ether **31** (6.19 g, 8.89 mmol, 1.0 equiv), 80 mL anhydrous dichloromethane, and 80 mL anhydrous methanol. The flask was then cooled to -78 ºC with an acetone-dry ice bath and ozone was purged into the solution. After about 25 min, the solution turns light grey to faint blue, indicating the completion of reaction. Ozone was stopped and oxygen was purged into the solution for about 5 min until the gray or blue color disappeared. Dimethyl sulfide (26 mL, 356 mmol, 40 equiv) was added. The reaction was stirred at -78 ºC under nitrogen atmosphere and was allowed to warm up to 23 ºC over night (~ 12 h). The mixture was then concentrated. Flash column chromatography (SiO2, gradient elution, 0 → 25% EtOAc/hexanes) afforded the ketoaldehyde **32** (4.30 g, 81%) as a pale yellow oil: TLC (EtOAc: hexanes, 1:4 v/v): R_f = 0.3; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.74 (t, *J* = 1.6 Hz, 1H), 7.33 – 7.27 (m, 3H), 7.25 – 7.23 (m, 2H), 7.21 – 7.19 (m, 2H), 6.84 – 6.80 (m, 2H), 4.50 (dd, *J* = 11.7, 7.6 Hz, 2H), 4.42 (ddd, *J* = 9.1, 7.9, 3.5 Hz, 1H), 4.38 (d, *J* = 11.9 Hz, 1H), 4.36 – 4.30 (m, 2H), 4.15 (d, *J* = 17.5 Hz, 1H), 3.99 (d, *J* = 17.5 Hz, 1H), 3.78 (s, 3H), 3.58 (t, *J* = 6.5 Hz, 1H), 2.39 (dddd, *J* = 16.5, 10.9, 5.6, 1.6 Hz, 1H), 2.32 (dddd, *J* = 17.0, 10.6, 5.6, 1.7 Hz, 1H), 2.07 (ddd, *J* = 13.6, 9.3, 8.0 Hz, 1H), 1.85 (ddd, *J* = 13.5, 8.6, 3.5 Hz, 1H), 1.79 (dq, *J* = 7.9, 6.1 Hz, 1H), 1.51 – 1.40 (m, 2H), 1.38 (d, *J* = 6.1 Hz, 2H), 0.88 (s, 9H), 0.82 (s, 3H), 0.80 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.0, 202.7, 159.3, 138.0, 129.7, 129.5 (2), 128.4 (2), 127.6, 127.5 (2), 113.7 (2), 79.6, 77.0, 76.4, 72.7, 71.6, 55.3, 53.1, 45.5, 39.5, 39.2, 38.5, 33.7, 32.3, 27.4, 27.3, 25.9 (3), 17.9, -4.4, -4.7; IR (thin film): 2925, 2354, 1723, 1699, 1515 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{35}H_{52}O_6NaSi^+$ $[M+Na]^+$: 619.3425, found: 619.3422.



Bis-olefin (±)-33:

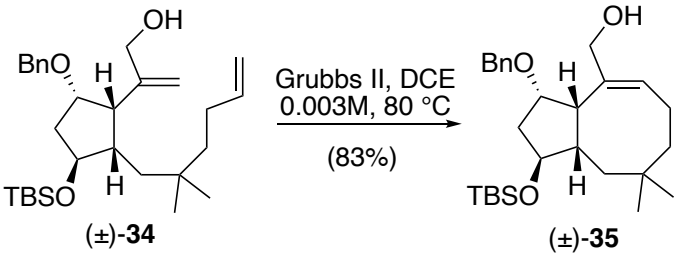
To an oven dried, 100 mL round-bottomed flask was added zinc powder (3.92 g, 60.3 mmol, 18 equiv), and $PbCl_2$ (75.0 mg, 0.270 mmol, 0.08 equiv). The solid mixture was dried under vacuum using a heating gun for 5 min. After cooling to 23 ºC under nitrogen atmosphere, a stir bar and 15 mL anhydrous THF were added. CH_2I_2 (2.70 mL, 33.5 mmol, 10 equiv) was added dropwise to the reaction mixture with vigorous stirring. (*Note*: After the first 0.3 mL of CH_2I_2 was added, the reaction was stirred for 5 min for initiation. When an exothermic process started, the flask was immersed in a room temperature water bath. Then the rest volume of CH_2I_2 was added.) After addition of CH_2I_2, the reaction was stirred at 23 ºC for 30 min to give a grey mixture. It was then cooled to 0 ºC and $TiCl_4$ (8.40 mL of 1 M solution in dichloromethane, 8.40 mmol, 2.5 equiv) was added dropwise via syringe to the mixture with vigorous stirring. (*Note*: The needle tip has to be inside the solvent of the mixture to avoid smoke formation inside the flask.) After addition, the mixture was stirred at 23 ºC for 30 min to give a greyish green mixture. A THF (5 mL) solution of the starting ketoaldehyde **32** (2.02 g, 3.39 mmol, 1.0 equiv) was then added to the above mixture slowly via syringe and then stirred at 23 ºC for 30 min. Silica gel was carefully added portion-wise to the mixture to quench the reaction until there was no bubble. The mixture was then filtered through a pad of silica gel, washed with dichloromethane, and concentrated. Flash column chromatography (SiO2, gradient elution, 0 → 10% EtOAc/hexanes) afforded the olefin **33** (1.06 g, 52%) as a colorless oil: TLC (EtOAc: hexanes, 1:8 v/v): R_f = 0.7; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 7H), 6.87 – 6.83 (m, 2H), 5.80 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.42 (m, 1H), 5.01 – 4.96 (m, 2H), 4.90 (dd, *J* = 10.2, 2.3 Hz, 1H), 4.49 – 4.40 (m, 4H), 4.23 (dt, *J* = 8.6, 6.7 Hz, 1H), 4.01 – 3.96 (m, 2H), 3.91 (dt, *J* = 13.3, 1.3 Hz, 1H), 3.80 (s, 3H), 3.06 (t, *J* = 6.6 Hz, 1H), 2.05 (ddd, *J* = 14.3, 8.8, 6.9 Hz, 1H), 2.02 – 1.91 (m, 3H), 1.88 (ddd, *J* = 14.2, 8.6, 3.6 Hz, 1H), 1.52 (dd, *J* = 14.3, 6.9 Hz, 1H), 1.27 – 1.23 (m, 2H), 1.20 (dd, *J* = 14.4, 3.7 Hz, 1H), 0.87 (s, 9H), 0.84 (s, 3H), 0.83 (s, 3H), 0.02 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.1, 142.9, 139.9, 138.8, 130.7, 129.2 (2), 128.3 (2), 127.4 (2), 127.3, 115.3, 113.7 (2), 113.7, 80.0, 77.4, 73.3, 72.0, 71.1, 55.3, 49.8, 46.3, 42.2, 40.4, 39.9, 33.2, 28.6, 27.2, 27.0, 25.9 (3), 18.0, -4.4, -4.6; IR (thin film): 2929, 2853, 2354, 1512 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{37}H_{56}NaO_4Si$ $[M+Na]^+$: 615.3840, found: 615.3838.



(±)-**33** (±)-**34**

Allylic alcohol (±)-34:

To a 25 mL round-bottomed flask equipped with a stir bar was added PMB ether **33** (300 mg, 0.507 mmol, 1.0 equiv), and 5 mL dichloromethane/methanol (9:1 v/v). DDQ (138 mg, 0.608 mmol, 1.3 equiv) was added and the mixture was stirred at 23 ºC for 6 h until TLC indicates the full consumption of starting material. Since the resulting 4-methoxybenzaldehyde has a similar Rf as the alcohol product **34**, $NaBH_4$ (38.5 mg, 1.01 mmol, 2 equiv) was added to the mixture and stirred at 23 ºC for 30 min to reduce the 4-*p*-methoxybenzaldehyde to the corresponding alcohol, which has a vastly different Rf. The mixture was then concentrated. It was then diluted with 20 mL water and then extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. Flash column chromatography (SiO2, gradient elution, 0 → 20% EtOAc/hexanes) afforded the alcohol **34** (203 mg, 85%) as a colorless oil: TLC (EtOAc: hexanes, 1:4 v/v): R_f = 0.7; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 – 7.26 (m, 5H), 5.80 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.37 (m, 1H), 4.99 (d, *J* = 17.1 Hz, 1H), 4.91 (dd, *J* = 10.2, 2.3 Hz, 1H), 4.87 (d, *J* = 1.5 Hz, 1H), 4.52 (d, *J* = 11.6 Hz, 1H), 4.49 (d, *J* = 11.7 Hz, 1H), 4.31 (q, *J* = 7.9 Hz, 1H), 4.06 (dt, *J* = 8.7, 3.7 Hz, 1H), 4.02 – 3.99 (m, 2H), 3.19 (t, *J* = 7.0 Hz, 1H), 3.09 (t, *J* = 5.3 Hz, 1H), 2.10 (ddd, *J* = 14.1, 9.2, 7.9 Hz, 1H), 2.03 – 1.88 (m, 4H), 1.48 (dd, *J* = 14.1, 8.5 Hz, 1H), 1.29 – 1.21 (m, 3H), 0.88 (s, 9H), 0.84 (s, 3H), 0.83 (s, 3H), 0.04 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.3, 139.8, 137.7, 128.5 (2), 127.8, 127.7 (2), 118.0, 113.7, 79.9, 77.2, 71.6, 67.4, 51.4, 46.5, 41.9, 39.8, 39.3, 33.2, 28.5, 27.3, 27.1, 25.9 (3), 18.0, -4.4, -4.7; IR (thin film): 2925, 2856, 2361, 1470 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{29}H_{48}NaO_3Si^+$ $[M+Na]^+$: 495.3265, found: 495.3262.

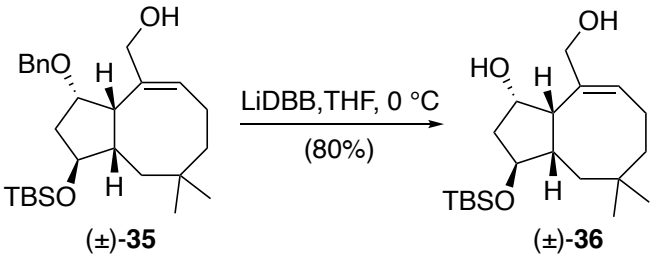


(±)-**34** (±)-**35**

Olefin (±)-35:

To an oven dried, nitrogen flushed, 100 mL round-bottomed flask equipped with a stir bar was added alcohol **34** (57 mg, 0.12 mmol, 1.0 equiv), Grubbs II catalyst (31 mg, 0.036 mmol, 0.3 equiv). The flask was evacuated and backfilled with nitrogen three times. Anhydrous dichloroethane (40 mL, 0.003M) was then added. The reaction was stirred at 80 ºC for 6 h until TLC indicates the full consumption of starting material. The reaction mixture was then concentrated. Flash

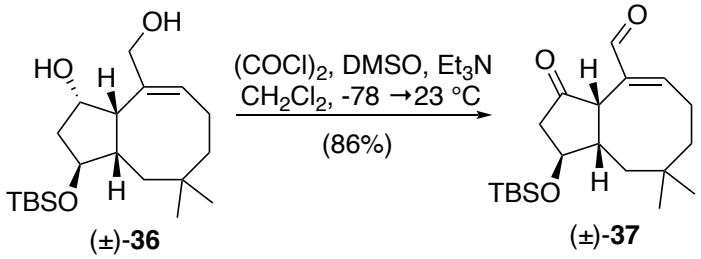
column chromatography (SiO2, gradient elution, 0 → 20% EtOAc/hexanes) afforded the olefin **35** (46 mg, 83%) as a colorless oil: TLC (EtOAc: hexanes, 1:4 v/v): R_f = 0.65; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 5H), 5.93 (t, *J* = 8.0 Hz, 1H), 4.56 (d, *J* = 11.5 Hz, 1H), 4.53 (d, *J* = 11.5 Hz, 1H), 4.43 – 4.38 (m, 1H), 4.07 – 4.02 (m, 2H), 3.88 (dd, *J* = 12.1, 10.7 Hz, 1H), 3.73 (dt, *J* = 9.5, 4.7 Hz, 1H), 3.53 (t, *J* = 6.9 Hz, 1H), 2.25 – 2.15 (m, 2H), 1.98 (m, 3H), 1.49 (dd, *J* = 13.9, 7.8 Hz, 1H), 1.39 (dd, *J* = 14.2, 3.5 Hz, 1H), 1.26 – 1.16 (m, 2H), 0.90 (s, 3H), 0.88 (s, 3H), 0.87 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.1, 136.5, 135.9, 128.6 (2), 128.1 (2), 128.0, 79.6, 76.1, 72.2, 67.2, 50.0, 44.7, 42.6, 39.8, 39.5, 35.2, 33.9, 25.9(3), 25.0, 24.4, 18.1, -4.4, -4.8; IR (thin film): 2957, 2364, 1640 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{27}H_{44}NaO_3Si^+$ $[M+Na]^+$: 467.2952, found: 467.2951.



(±)-**35** (±)-**36**

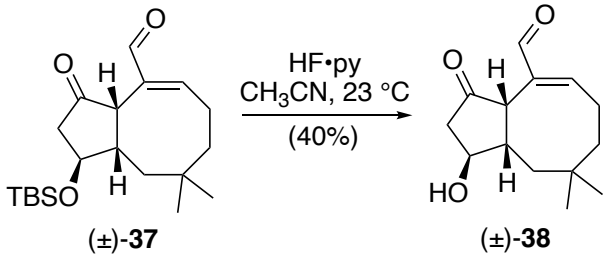
Alcohol (±)-36:

To an oven dried, 10 mL round-bottomed flask equipped with a stir bar was added benzyl ether **35** (43 mg, 0.097 mmol, 1.0 equiv), and 1 mL anhydrous THF. The flask was cooled to 0 ºC by an ice-water bath. Freshly prepared Freeman's reagent (0.58 mL of 0.5 M solution in THF, 0.290 mmol, 3.0 equiv) was added dropwise to the reaction. With every drop, the solution turned green and instantly went back to colorless or pale yellow. The completion of addition was dictated by a persisting dark green color of the reaction mixture. Slightly more Freeman's reagent was added if the dark green color is not reached. The reaction was then stirred for another 5 min and quenched by adding 5 mL saturated NH_4Cl solution. It was further diluted with 5 mL water and then extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. Flash column chromatography (SiO2, gradient elution, 0 → 30% EtOAc/hexanes) afforded the diol **36** (27 mg, 80%) as a colorless oil: TLC (EtOAc: hexanes, 1:2 v/v): R_f = 0.3; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.93 (t, *J* = 8.0 Hz, 1H), 4.64 (ddd, *J* = 9.2, 7.8, 6.2 Hz, 1H), 4.06 (app s, 2H), 3.78 (dt, *J* = 8.6, 4.8 Hz, 1H), 3.42 (t, *J* = 6.8 Hz, 1H), 2.24 (dddd, *J* = 13.9, 11.9, 8.6, 1.7 Hz, 1H), 2.12 – 2.03 (m, 2H), 2.02 – 1.91 (m, 2H), 1.52 – 1.47 (m, 1H), 1.36 (ddd, *J* = 14.2, 3.4, 1.4 Hz, 1H), 1.32 – 1.24 (m, 2H), 1.19 (ddd, *J* = 13.9, 11.7, 1.9 Hz, 1H), 0.93 (s, 3H), 0.88 (s, 9H), 0.88 (s, 3H), 0.027 (s, 3H), 0.026 (s, 3H)(Note: one alcohol proton is not observed); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.5, 136.2, 77.7, 73.2, 68.2, 49.7, 47.5, 42.6, 42.3, 40.6, 34.9, 33.8, 25.9 (3), 25.1, 24.1, 18.1, -4.4, -4.8; IR (thin film): 2922, 2364, 1463cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{20}H_{38}O_3NaSi^+$ $[M+Na]^+$: 377.2482, found: 377.2490.



Ketoaldehyde (±)-37:

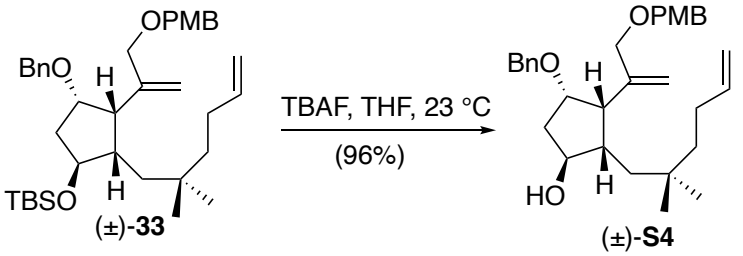
To an oven dried, 5 mL round-bottomed flask equipped with a stir bar was added $(COCl)_2$ (0.17 mL of 2 M solution in DCM, 0.339 mmol, 10 equiv), 1 mL anhydrous dichloromethane. The flask was cooled to -78 ºC by a dry ice-acetone bath. A solution of anhydrous DMSO (36 µL, 0.509 mmol, 15 equiv, a new sure-seal bottle from Sigma) in 0.5 mL anhydrous dichloromethane was then added dropwise to the reaction flask and then stirred for 30 min. A solution of diol **36** (12 mg, 0.034 mmol, 1.0 equiv) in 0.5 mL anhydrous dichloromethane was added dropwise and stirred at -78 ºC for 1 h. Freshly distilled triethylamine (0.14 mL, 1.02 mmol, 30 equiv) was added dropwise. The reaction was then allowed to warm to 23 ºC over 3 h. 5 mL water was added to quench the reaction, and then extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. Flash column chromatography (SiO2, gradient elution, 0 → 50% EtOAc/hexanes) afforded the ketoaldehyde **37** (10 mg, 86%) as a colorless oil: TLC (EtOAc: hexanes, 1:2 v/v): R_f = 0.6; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.23 (s, 1H), 7.02 – 6.94 (m, 1H), 3.78 (dt, *J* = 9.6, 7.1 Hz, 1H), 3.50 (d, *J* = 10.0 Hz, 1H), 2.97 (dd, *J* = 18.0, 7.2 Hz, 1H), 2.56 – 2.39 (m, 2H), 2.29 (dd, *J* = 12.3, 9.9 Hz, 1H), 2.15 (ddd, *J* = 18.0, 9.3, 1.9 Hz, 1H), 1.83 (ddd, *J* = 14.2, 10.6, 2.9 Hz, 1H), 1.63 (dd, *J* = 14.4, 2.5 Hz, 1H), 1.32 (ddd, *J* = 14.7, 8.0, 3.1 Hz, 1H), 1.12 (dd, *J* = 14.4, 12.0 Hz, 1H), 0.98 (s, 3H), 0.95 (s, 3H), 0.88 (s, 9H), 0.034 (s, 3H), 0.029 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 215.6, 193.2, 159.1, 141.6, 73.8, 50.0, 48.4, 39.3, 38.7, 34.4, 32.1, 27.6, 26.4, 25.8 (3), 18.0 (2), -4.4, -4.9; IR (thin film): 2956, 2361, 1744, 1681cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{20}H_{34}O_3NaSi^+$ $[M+Na]^+$: 373.2169, found: 373.2168.



Ketoaldehyde (±)-38:

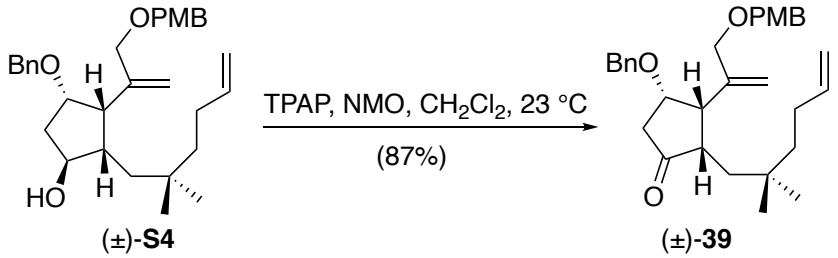
The TBS ether **37** (10 mg, 0.029 mmol, 1.0 equiv) was dissolved in 0.5 mL anhydrous CH_3CN and transferred into a 1-dram plastic vial equipped with a stir bar. HF·py (12 µL, 0.087 mmol, 3.0 equiv) was added and the vial was capped. The reaction was stirred at 23 ºC over night (~16h) and then concentrated. Flash column chromatography (gradient

fluorosil, 50 → 100% EtOAc/hexanes) afforded the ketoaldehyde **38** (2.7 mg, 40%) as a colorless residue: TLC (EtOAc: hexanes, 1:1 v/v): R_f = 0.2; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.23 (s, 1H), 7.00 (t, *J* = 6.6 Hz, 1H), 3.94 – 3.86 (m, 1H), 3.55 (d, *J* = 9.9 Hz, 1H), 3.10 (dd, *J* = 18.0, 7.3 Hz, 1H), 2.57 – 2.42 (m, 2H), 2.29 (dd, *J* = 12.4, 10.0 Hz, 1H), 2.21 (ddd, *J* = 18.0, 9.5, 1.9 Hz, 1H), 1.88 – 1.80 (m, 2H), 1.68 (dd, *J* = 14.5, 2.6 Hz, 1H), 1.34 (ddd, *J* = 14.8, 8.0, 3.1 Hz, 1H), 1.22 (dd, *J* = 14.5, 12.0 Hz, 1H), 1.01 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 214.8, 193.2, 159.4, 141.4, 73.7, 50.5, 47.9, 39.4, 38.5, 34.5, 32.1, 29.7, 27.5, 26.4; IR (thin film): 2918, 2364, 1727, 1678cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{14}H_{20}O_3Na^+$ $[M+Na]^+$: 259.1305, found: 259.1304.



Alcohol (±)-S4:

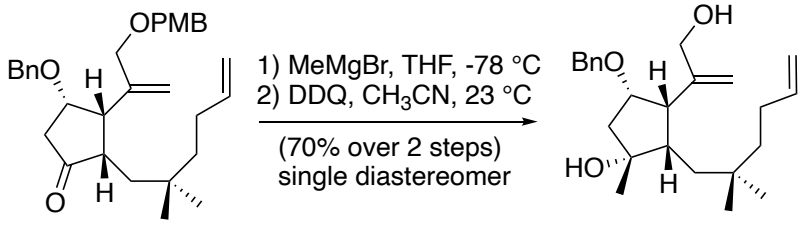
To an oven dried, 50 mL round-bottomed flask equipped with a stir bar was added the TBS ether **33** (1.40 g, 2.36 mmol, 1.0 equiv), and 15 mL anhydrous THF. TBAF (4.73 mL of 1 M solution in THF, 4.73 mmol, 2.0 equiv) was then added. The reaction was stirred at 23 ºC over night (~16h) under nitrogen atmosphere. The reaction was then quenched by adding 20 mL saturated NH_4Cl solution. It was further diluted with 20 mL water and then extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. Flash column chromatography (SiO2, gradient elution, 0 → 30% EtOAc/hexanes) afforded the alcohol **S4** (1.09 g, 96%) as a colorless oil: TLC (EtOAc: hexanes, 1:4 v/v): R_f = 0.2; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 – 7.25 (m, 7H), 6.92 – 6.86 (m, 2H), 5.83 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.42 (q, *J* = 1.6 Hz, 1H), 5.09 (dd, *J* = 2.1, 1.1 Hz, 1H), 5.04 – 4.98 (m, 1H), 4.93 (dd, *J* = 10.1, 2.3 Hz, 1H), 4.49 – 4.47 (m, 2H), 4.46 (s, 2H), 4.25 (dt, *J* = 7.5, 6.0 Hz, 1H), 4.18 – 4.14 (m, 1H), 4.00 (dt, *J* = 13.0, 1.2 Hz, 1H), 3.94 (d, *J* = 12.8 Hz, 1H), 3.83 (s, 3H), 3.08 (t, *J* = 6.5 Hz, 1H), 2.25 (ddd, *J* = 14.7, 8.6, 6.1 Hz, 1H), 2.04 – 1.98 (m, 2H), 1.96 (dq, *J* = 7.0, 5.5 Hz, 1H), 1.89 (ddd, *J* = 14.6, 7.5, 3.3 Hz, 1H), 1.60 – 1.54 (m, 2H), 1.32 – 1.27 (m, 3H), 0.90 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.1, 142.7, 139.8, 138.7, 130.6, 129.3 (2), 128.3 (2), 127.3, 127.3 (2), 115.5, 113.8, 113.7 (2), 80.4, 77.7, 73.4, 71.9, 71.0, 55.3, 49.9, 46.0, 41.9, 40.7, 40.2, 33.2, 28.6, 27.1, 27.1; IR (thin film): 2936, 2853, 2361, 1512cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{31}H_{42}O_4Na^+$ $[M+Na]^+$: 501.2975, found: 501.2972.



(±)-**S4** (±)-**39**

Ketone (±)-39:

To an oven dried, 25 mL round-bottomed flask equipped with a stir bar was added the alcohol **S4** (1.08 g, 2.26 mmol, 1.0 equiv), and 12 mL anhydrous dichloromethane. TPAP (40 mg, 0.113 mmol, 0.05 equiv), and NMO (396 mg, 3.39 mmol, 1.5 equiv) were added and the reaction was stirred at 23 ºC for 4 h under nitrogen atmosphere. The reaction mixture was then concentrated. Flash column chromatography (SiO2, gradient elution, 0 → 20% EtOAc/hexanes) afforded the ketone **39** (870 mg, 87%) as a colorless oil: TLC (EtOAc: hexanes, 1:4 v/v): R_f = 0.2; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 – 7.19 (m, 7H), 6.87 – 6.82 (m, 2H), 5.77 (m, 1H), 5.38 (d, *J* = 1.4 Hz, 1H), 4.97 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.89 (dd, *J* = 10.2, 2.2 Hz, 1H), 4.72 (s, 1H), 4.57 (d, *J* = 11.9 Hz, 1H), 4.50 (d, *J* = 11.9 Hz, 1H), 4.45 (d, *J* = 11.6 Hz, 1H), 4.32 (d, *J* = 11.8 Hz, 1H), 4.31 – 4.25 (m, 1H), 4.02 (dt, *J* = 13.0, 1.2 Hz, 1H), 3.91 – 3.86 (m, 1H), 3.78 (s, 3H), 3.39 (t, *J* = 7.2 Hz, 1H), 2.60 (br dd, *J* = 18.9, 8.2 Hz, 1H), 2.33 (dd, *J* = 18.9, 9.7 Hz, 1H), 2.14 (dt, *J* = 8.2, 2.9 Hz, 1H), 2.04 – 1.91 (m, 2H), 1.85 (dd, *J* = 14.5, 3.0 Hz, 1H), 1.31 (dd, *J* = 14.5, 5.8 Hz, 1H), 1.22 (m, 2H), 0.82 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.8, 159.1, 142.0, 139.5, 138.0, 130.3, 129.2 (2), 128.4 (2), 127.7,127.5 (2), 115.9, 113.8, 113.7 (2), 76.3, 73.2, 71.9, 71.6, 55.2, 50.7, 48.4, 41.2, 40.8, 35.3, 32.9, 28.5, 27.0, 26.9; IR (thin film): 2917, 2355, 1747, 1511cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{31}H_{40}O_4Na^+$ $[M+Na]^+$: 499.2819, found: 499.2827.

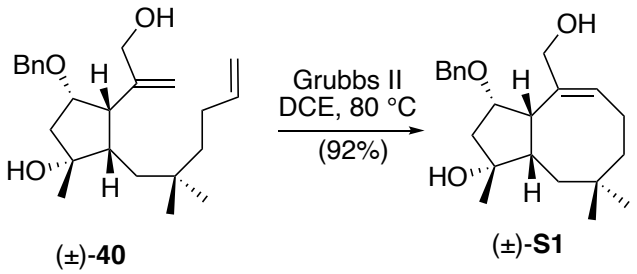


(±)-**39** (±)-**40**

Alcohol (±)-40:

To an oven dried, 25 mL round-bottomed flask equipped with a stir bar was added the ketone **39** (870 mg, 1.83 mmol, 1.0 equiv), and 10 mL anhydrous THF. (*Note*: Using Et_2O instead of THF gives inferior results.) The reaction was cooled to -40 ºC by an dry ice-acetonitrile bath. MeMgBr (1.50 mL of 3 M solution in Et_2O, 4.56 mmol, 2.5 equiv) was added dropwise via syringe through the flask wall and the reaction was then allowed to warm up to 23 ºC over 6 h. The reaction was then quenched by adding 15 mL saturated NH_4Cl solution. It was further diluted with 15 mL water and then extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and

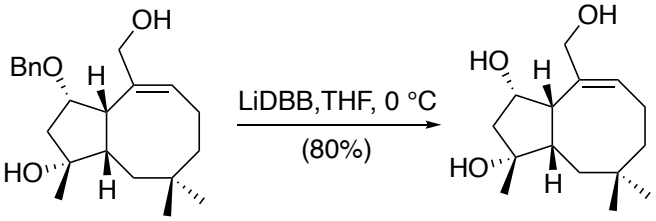
concentrated. The crude material was dissolved in 5 mL dichloromethane and DDQ (830 mg, 3.66 mmol, 2.0 equiv) was added. 5 mL pH = 7 buffer was then added. The reaction was stirred at 23 ºC over night. The mixture was then poured to 30 mL saturated $NaHCO_3$ solution and then extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. Flash column chromatography (SiO2, gradient elution, 0 → 40% EtOAc/hexanes) afforded the alcohol **40** (480 mg, 70% over two steps, single diastereomer) as a white solid: TLC (EtOAc: hexanes, 1:4 v/v): R_f = 0.3; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 5.83 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.36 (d, *J* = 1.8 Hz, 1H), 5.18 (d, *J* = 2.0 Hz, 1H), 5.02 (d, *J* = 17.1 Hz, 1H), 4.94 (dd, *J* = 10.2, 2.4 Hz, 1H), 4.59 (d, *J* = 11.6 Hz, 1H), 4.53 (d, *J* = 11.7 Hz, 1H), 4.23 (d, *J* = 12.8 Hz, 1H), 4.21 (d, *J* = 12.8 Hz, 1H), 4.15 (dt, *J* = 8.6, 7.3 Hz, 1H), 3.78 (br s, 2H), 3.33 (t, *J* = 8.4 Hz, 1H), 2.30 (dd, *J* = 14.7, 8.7 Hz, 1H), 2.12 (dd, *J* = 14.8, 7.1 Hz, 1H), 2.03 (m, 2H), 1.78 (ddd, *J* = 9.7, 8.2, 1.9 Hz, 1H), 1.47 (dd, *J* = 14.8, 1.9 Hz, 1H), 1.41 (dd, *J* = 14.8, 8.0 Hz, 1H), 1.30 – 1.28 (m, 2H), 1.26 (s, 3H), 0.87 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.5, 139.7, 137.6, 128.5 (2), 127.9, 127.7 (2), 121.0, 113.8, 79.9, 77.8, 72.0, 67.1, 53.8, 47.3, 47.3, 41.9, 36.2, 32.8, 29.3, 28.6, 27.1, 26.9; IR (thin film): 2958, 2357, 1639, 1454 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{24}H_{36}O_3Na^+$ $[M+Na]^+$: 395.2557, found: 395.2556.



(±)-**40** (±)-**S1**

Olefin (±)-S1:

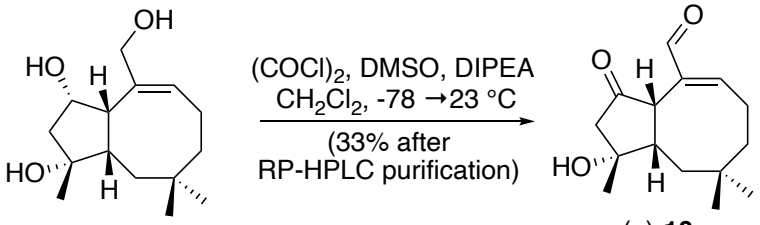
To an oven dried, nitrogen flushed, 500 mL round-bottomed flask equipped with a stir bar was added alcohol **40** (300 mg, 0.806 mmol, 1.0 equiv), Grubbs II catalyst (210 mg, 0.242 mmol, 0.3 equiv). The flask was evacuated and backfilled with nitrogen three times. Anhydrous dichloroethane (250 mL, 0.003M) was then added. The reaction was stirred at 80 ºC for 4 h until TLC indicates the full consumption of starting material. The reaction mixture was then concentrated. Flash column chromatography (SiO2, gradient elution, 0 → 20% EtOAc/hexanes) afforded the olefin **(±)-S1** (255 mg, 92%) as an off-white foam: TLC (EtOAc: hexanes, 1:2 v/v): R_f = 0.2; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 5H), 5.93 (t, *J* = 7.4 Hz, 1H), 4.59 (d, *J* = 11.6 Hz, 1H), 4.52 (s, 2H), 4.19 – 4.12 (m, 2H), 3.46 (t, *J* = 7.5 Hz, 1H), 3.10 (br s, 1H), 2.35 (dd, *J* = 14.3, 8.5 Hz, 1H), 2.24 – 2.11 (m, 2H), 2.01 (dd, *J* = 16.0, 8.5 Hz, 1H), 1.85 (ddd, *J* = 11.4, 8.2, 2.7 Hz, 1H), 1.60 – 1.49 (m, 5H), 1.25 (s, 3H), 0.94 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.9, 137.0, 136.9, 128.5 (2), 127.8 (2), 127.8, 80.0, 77.8, 72.0, 66.7, 50.2, 47.5, 44.5, 42.1, 35.4, 34.9, 33.5, 29.7, 25.6, 24.5; IR (thin film): 2929, 2357, 1449cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{22}H_{32}O_3Na^+$ $[M+Na]^+$: 367.2244, found: 367.2256.



(±)-**S1** (±)-**S2**

Triol (±)-S2:

To an oven dried, 25 mL round-bottomed flask equipped with a stir bar was added benzyl ether **(±)-S1** (255 mg, 0.741 mmol, 1.0 equiv), and 5 mL anhydrous THF. The flask was cooled to 0 ºC by an ice-water bath. Freshly prepared Freeman's reagent (4.44 mL of 0.5 M solution in THF, 2.22 mmol, 3.0 equiv) was added dropwise to the reaction. With every drop, the solution turned green and instantly went back to colorless or pale yellow. The completion of addition was dictated by a persisting dark green color of the reaction mixture. Slightly more Freeman's reagent should be added if the dark green color is not reached. The reaction was then stirred for another 5 min and quenched by adding 15 mL saturated NH_4Cl solution. It was further diluted with 10 mL water and then extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. Flash column chromatography (SiO_2, gradient elution, 20 → 60% EtOAc/hexanes) afforded the triol **(±)-S2** (150 mg, 80%) as a white solid: TLC (EtOAc: hexanes, 1:1 v/v): R_f = 0.15; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.84 (ddd, *J* = 9.0, 7.2, 1.9 Hz, 1H), 4.48 (app q, *J* = 5.7 Hz,1H), 4.31 (d, *J* = 12 Hz, 1H), 4.28 (d, *J* = 12 Hz, 1H), 3.30 (br dd, *J* = 9.9, 5.1 Hz, 1H), 2.15 – 1.99 (m, 4H), 1.92 (m, 1H), 1.55 – 1.45 (m, 2H), 1.35 (dt, *J* = 14.6, 1.8 Hz, 1H), 1.28 (s, 3H), 1.26 – 1.19 (m, 1H), 0.95 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.7, 136.5, 80.1, 74.5, 68.0, 49.4, 48.7, 48.6, 41.3, 35.7, 34.6, 33.4, 28.7, 26.0, 24.0; IR (thin film): 2950, 2350, 1453 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{15}H_{26}O_3Na^+$ $[M+Na]^+$: 277.1774, found: 277.1773.



(±)-**S2** (±)-**10**

Ketoaldehyde (±)-10:

To an oven dried, 10 mL round-bottomed flask equipped with a stir bar was added $(COCl)_2$ (0.47 mL of 2 M solution in DCM, 0.940 mmol, 10 equiv), 2 mL anhydrous dichloromethane. The flask was cooled to -78 ºC by a dry ice-acetone bath. A solution of anhydrous DMSO (0.10 mL, 1.410 mmol, 15 equiv, a new sure-seal bottle from Sigma) in 0.5 mL anhydrous dichloromethane was then added dropwise to the reaction flask and then stirred for 30 min. A solution of triol

(±)-S2 (24 mg, 0.094 mmol, 1.0 equiv) in 0.5 mL anhydrous THF (triol **(±)-S2** does not dissolve well in dichloromethane) was added dropwise and stirred at -78 ºC for 1 h. Freshly distilled DIPEA (0.50 mL, 2.82 mmol, 30 equiv) was added dropwise. The reaction was then allowed to warm to 0 ºC over 3 h. 10 mL pH = 7 buffer was added to quench the reaction, and then extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to dryness. Semi-preparative reverse-phase HPLC (100 x 21.20 mm, 5 µm; linear gradient, 5% CH_3CN/H_2O to 95% CH_3CN/H_2O over 20 min, 23 mL/min, collect peak at 8.3 min) afforded the ketoaldehyde **10** (8 mg, 33%) as a white solid: TLC (DCM: Et_2O, 6:1 v/v): R_f = 0.5; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.22 (s, 1H), 7.05 (dt, *J* = 6.0, 1.3 Hz, 1H), 3.56 (d, *J* = 10.8 Hz, 1H), 3.05 (s, 1H), 2.76 (dd, *J* = 19.1, 1.0 Hz, 1H), 2.57 – 2.52 (m, 2H), 2.49 (dd, *J* = 19.1, 1.2 Hz, 1H), 2.33 (dt, *J* = 10.6, 3.3 Hz, 1H), 1.87 (ddd, *J* = 15.0, 9.4, 5.7 Hz, 1H), 1.46 – 1.38 (m, 2H), 1.36 (s, 3H), 1.35 – 1.29 (m, 1H), 0.98 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 217.6, 195.8, 160.4, 141.5, 77.1, 54.6, 50.1, 48.7, 38.3, 35.6, 33.9, 30.9, 28.8, 27.0, 25.5; IR (thin film): 2922, 1364, 1747, 1668 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{15}H_{22}O_3Na^+$ $[M+Na]^+$: 273.1461, found: 273.1463.

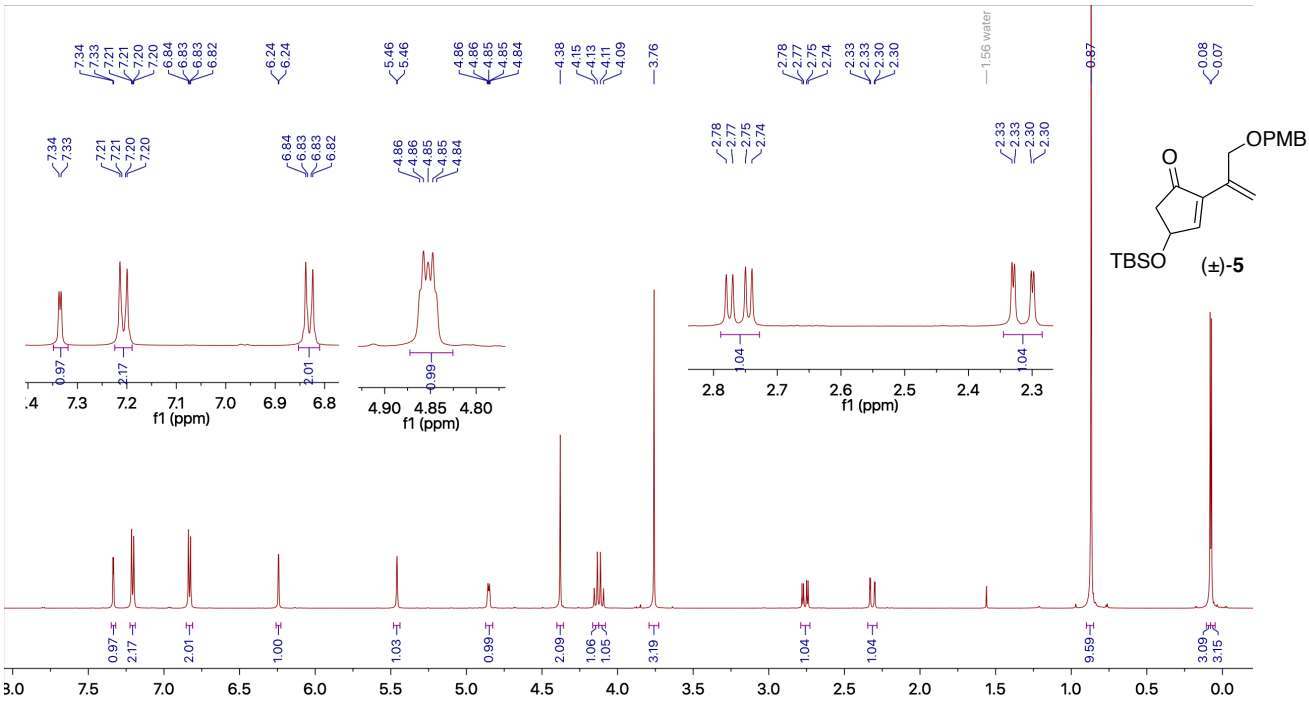
Source of Ophiobolin A and Congeners

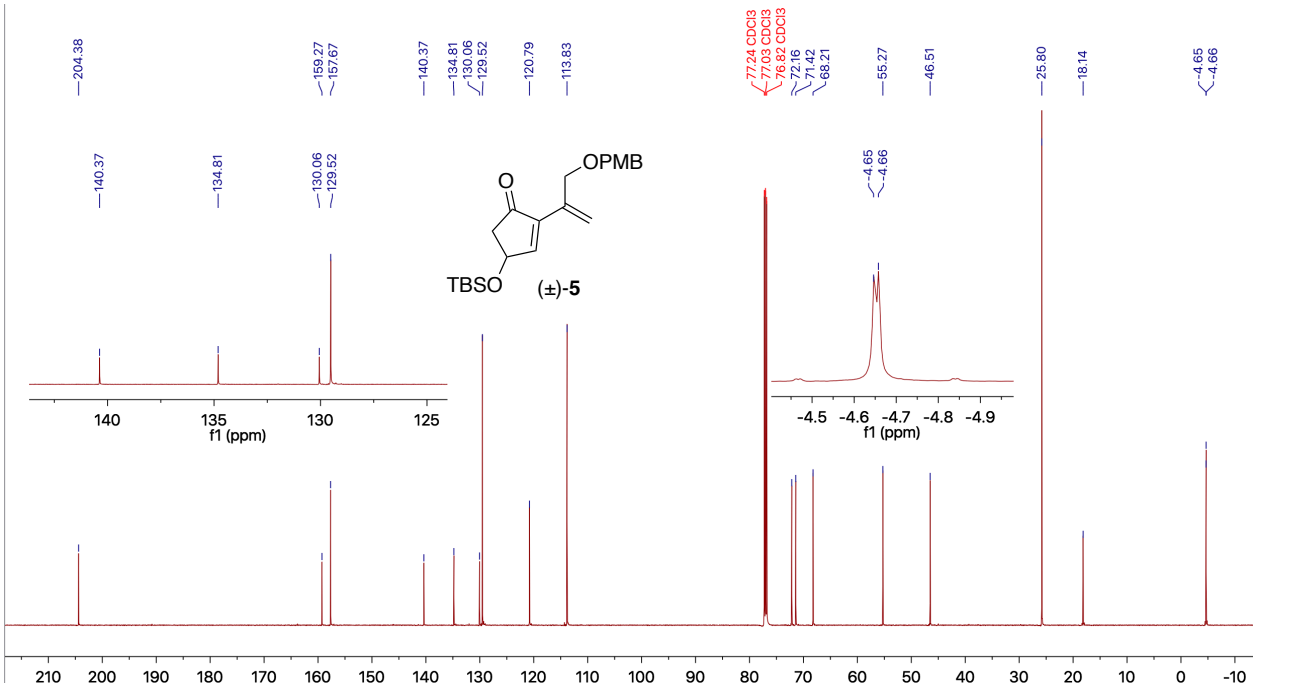
Ophiobolins A, 6-*epi*-ophiobolin A, 3-anhydro-6-*epi*-ophiobolin A and ophiobolin I were obtained from the organic extract of *Drechslera gigantea* culture filtrates as previously reported.[8] Their purity (>99 %) was ascertained by ^{1}H NMR and HPLC analyses.

Cytotoxicity Assays

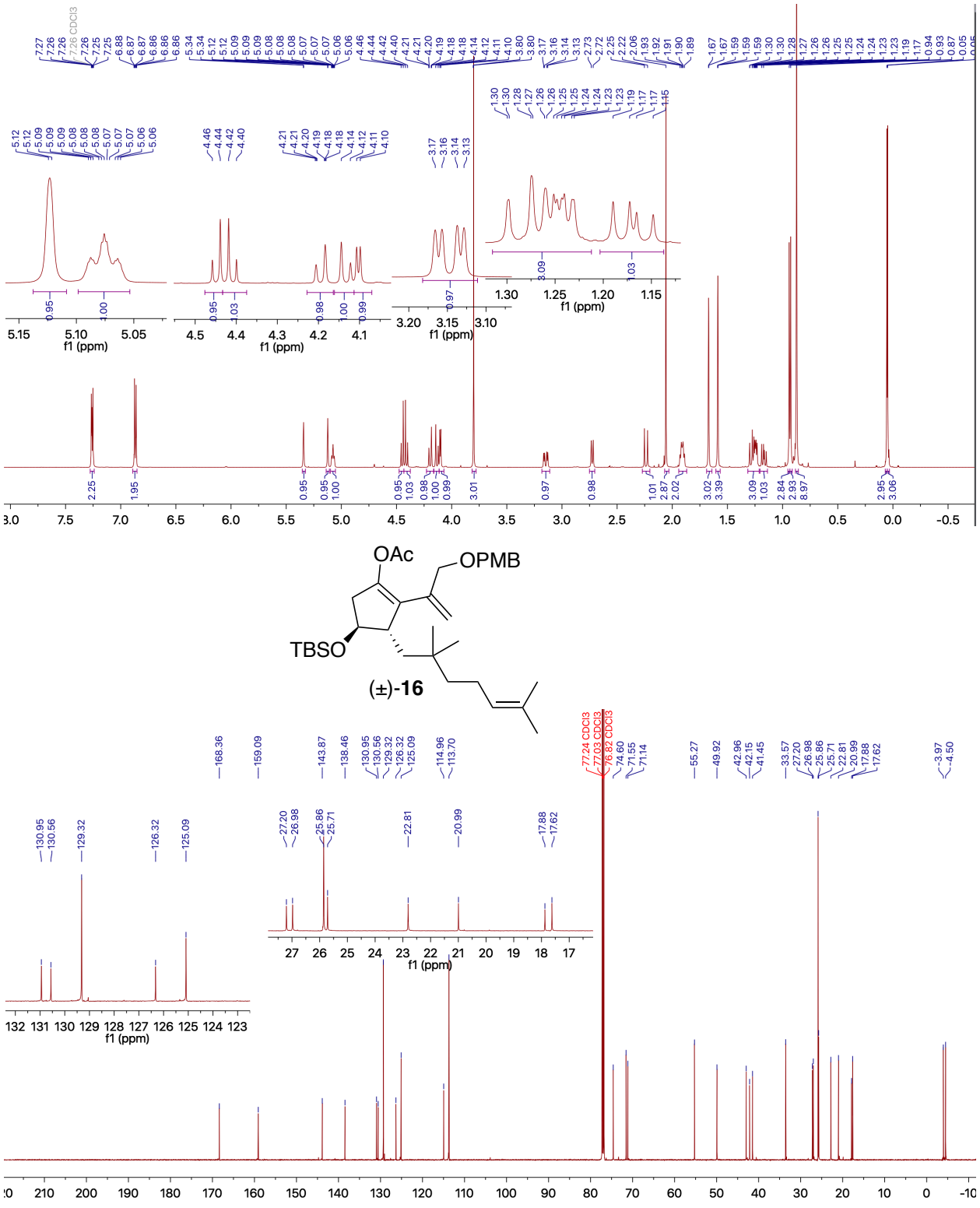
Simplified ophiobolin A derivatives ((±)-**10**, (±)-**11**, and (±)-**38**) and congeners to be assayed, as solids or oils, were dissolved in DMSO, by vortexing to ensure complete dissolution. Quantities of compounds and DMSO were used to achieve a final concentration of 25 mM and aliquots were stored at -80ºC for no longer than 3 months or in the case of the unstable compound, a freshly prepared sample was used. Cells were plated in triplicate on 96-well plates with 2,000 cells per well in DMEM media with 10% FBS. Following cell attachment to the floor of the wells, the dissolved compounds were added to the wells and incubated for 72 hours at 37ºC, 5% CO_2. Relative cell metabolic activity was assessed by incubation with MTS assay reagent for up to 3 hours (CellTiter 96 Aqueous One Solution Cell Proliferation Assay, Promega) according to the manufacturer's protocol. Background absorbance (media only) was subtracted from all other wells and absorbance was then normalized to DMSO treatment at matching concentrations. The normalized relative viability values were graphed against the drug dosage and IC_{50} (drug concentration eliciting 50% of the maximum inhibition) values were calculated for each tested cell line using the "log(inhibitor) vs. response -- Variable slope" function in Prism6 (Graphpad). The experiments were repeated again at an additional two time points.

Note: Monocyclic ketoaldehyde (±)-**11** was unstable in DMSO and thus a freshly prepared sample was required to preclude inconsistencies observed when using stored DMSO stock solutions.

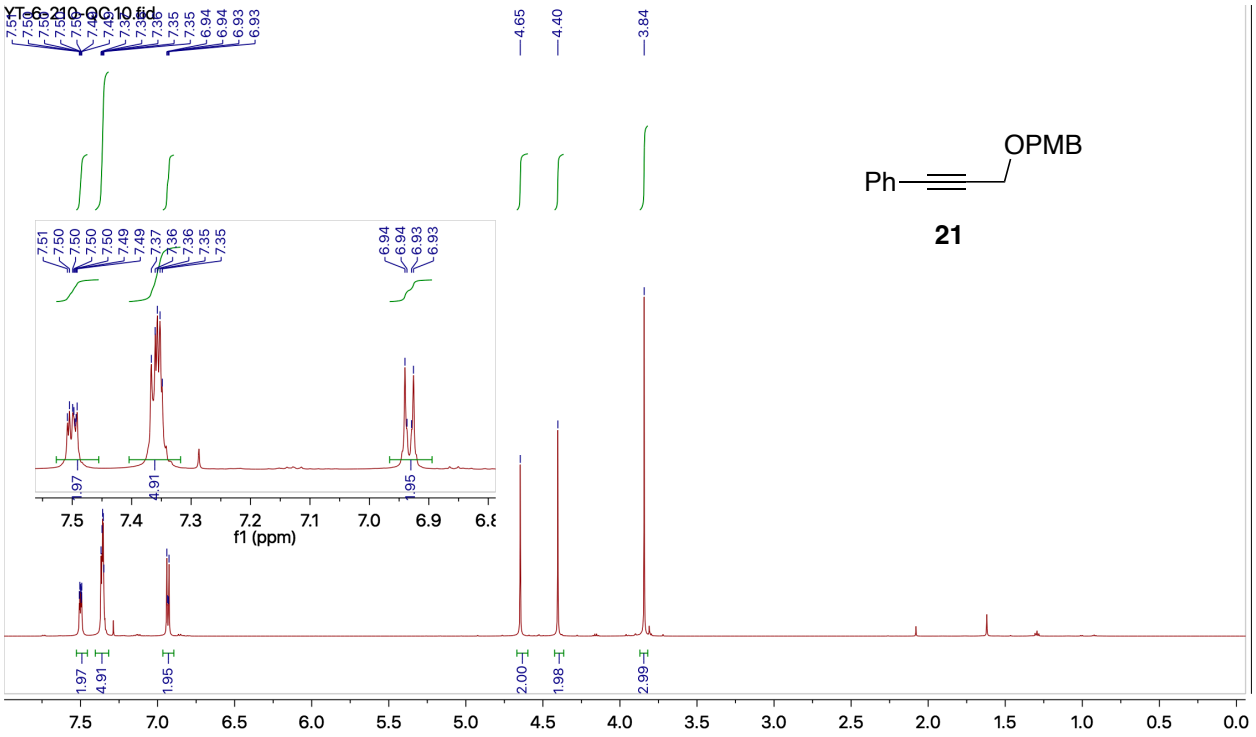


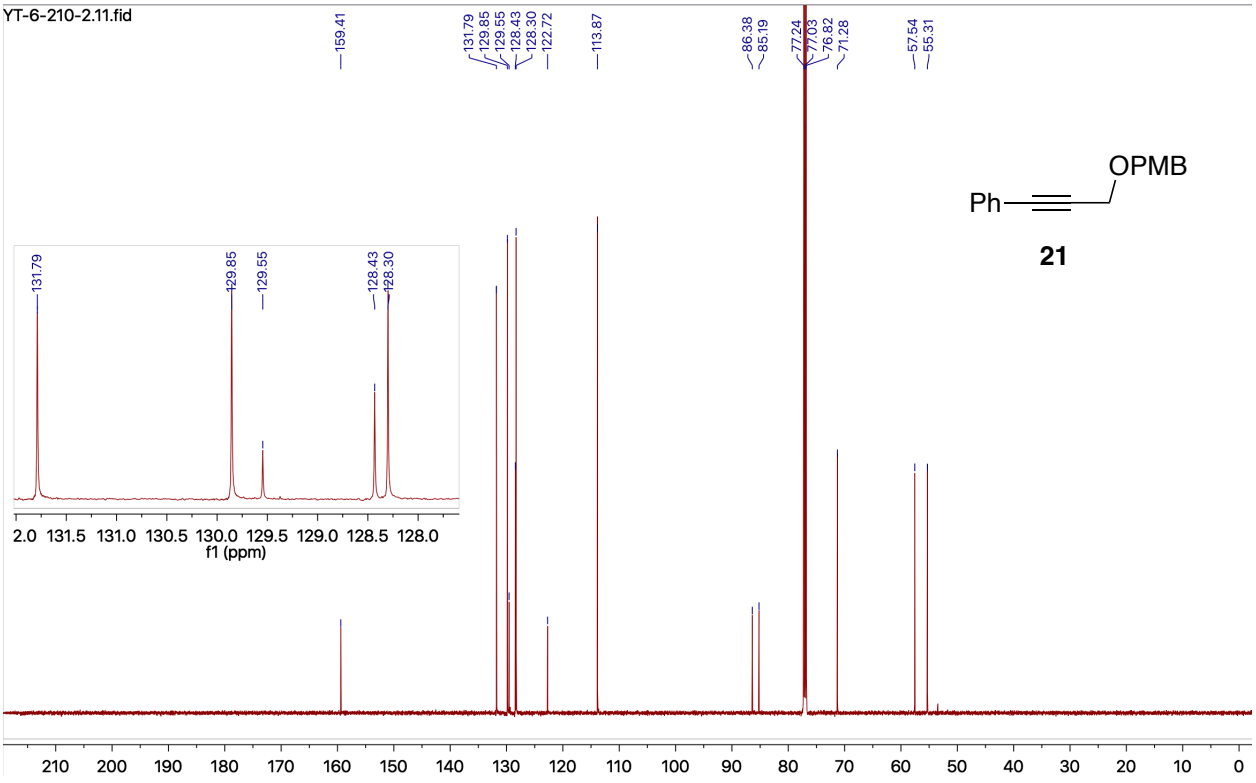


^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of diene (±)-**5**

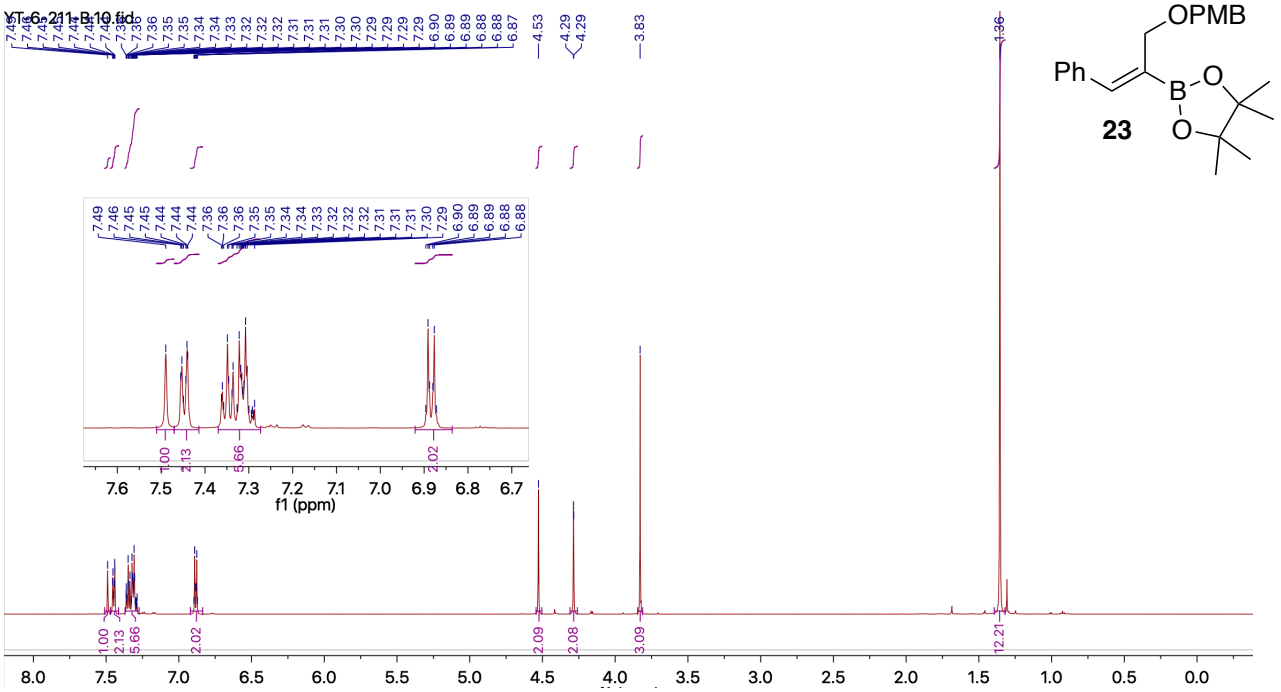


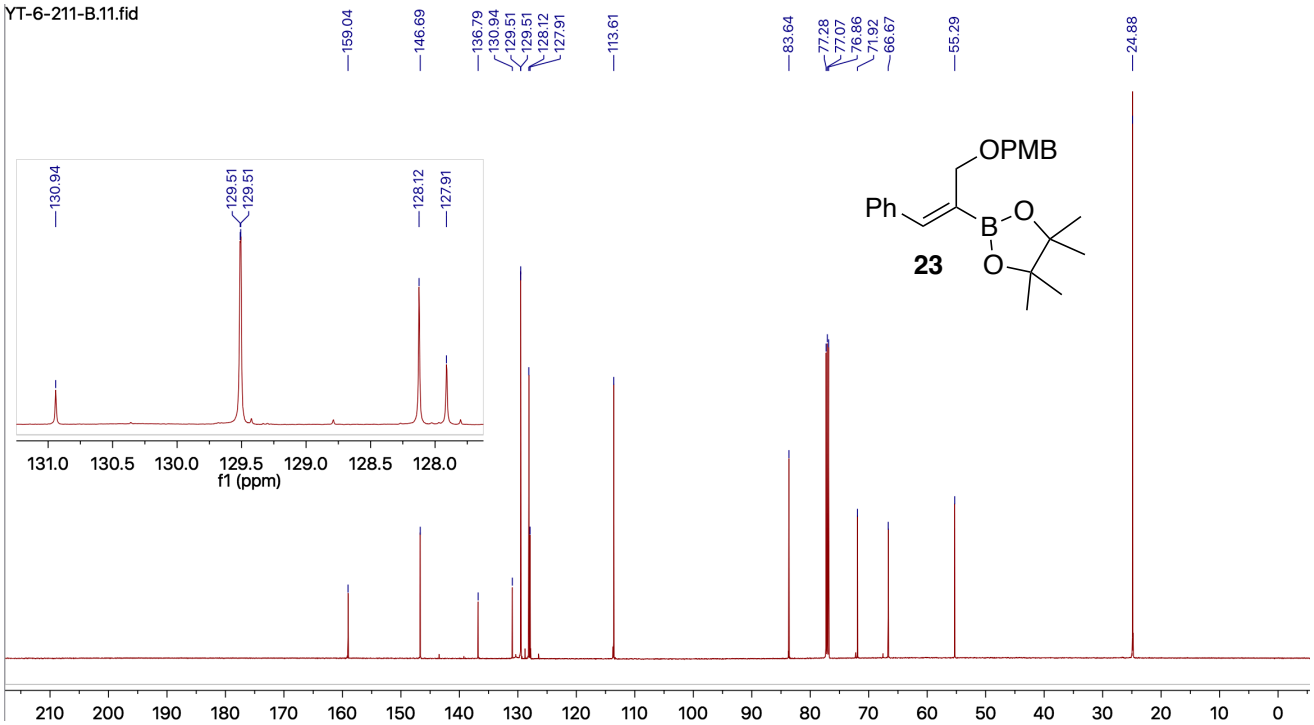
^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of enol acetate (±)-**16**



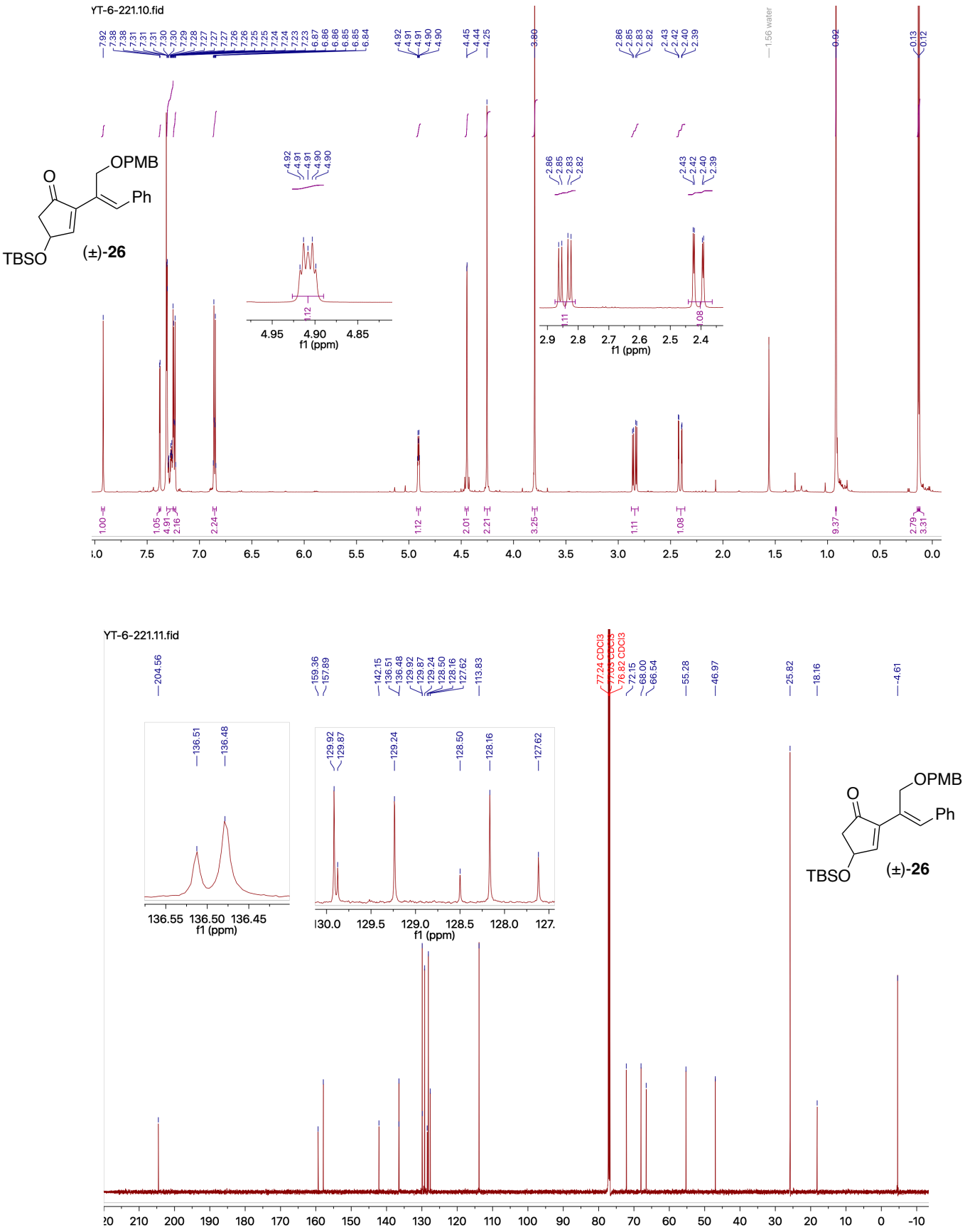


^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of alkyne **21**

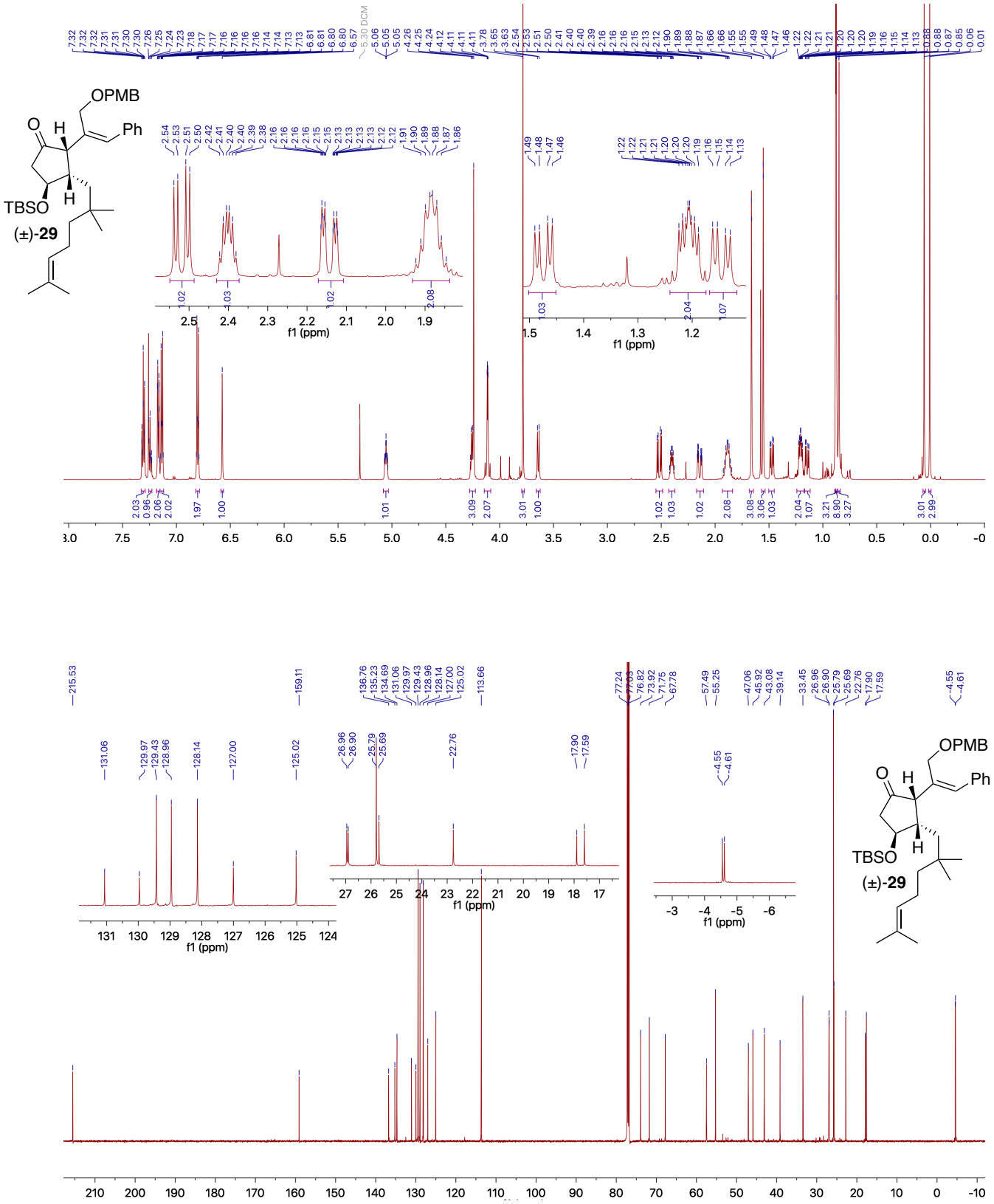




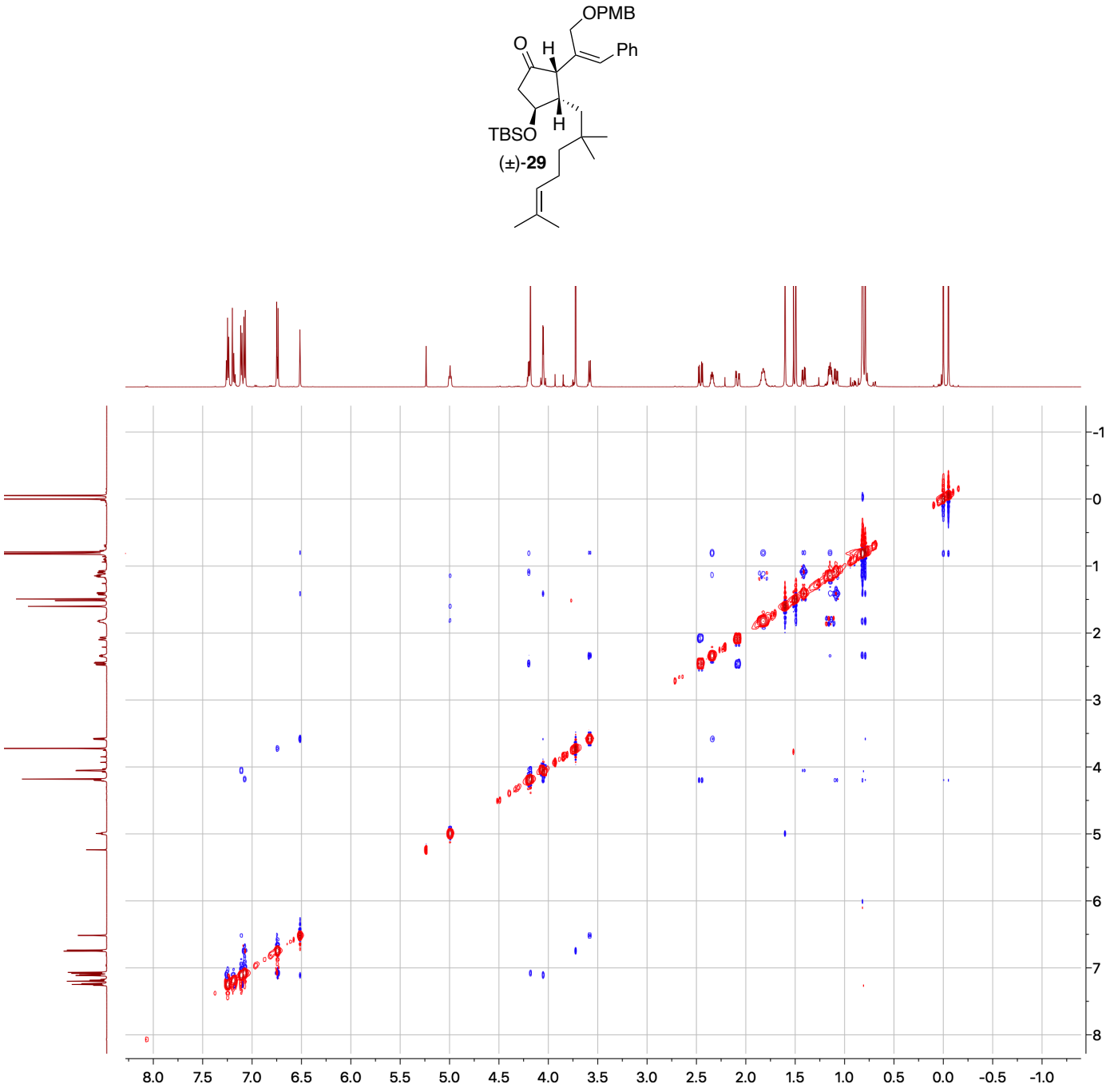
^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of alkene **23**



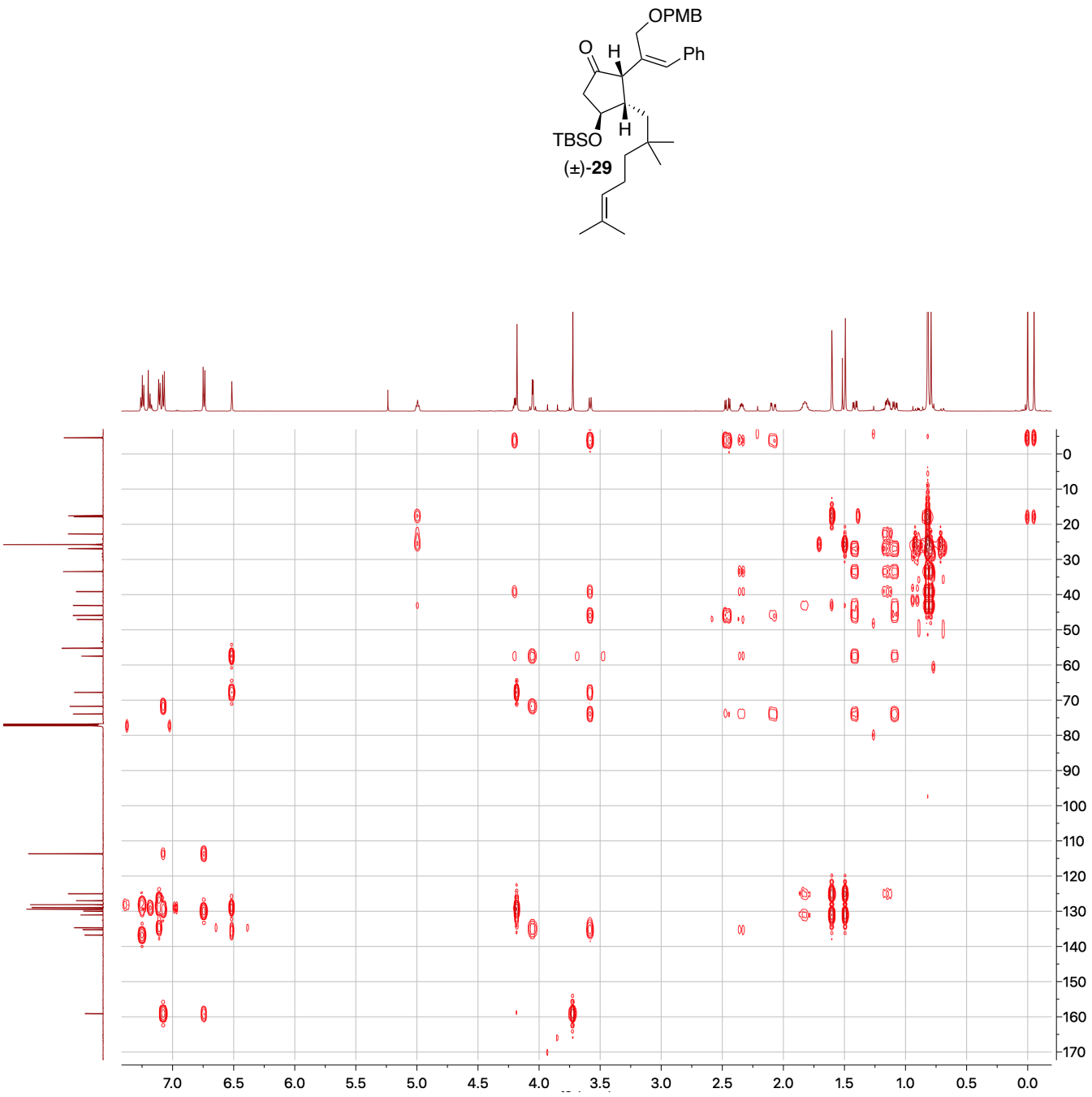
^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of (±)-**26**



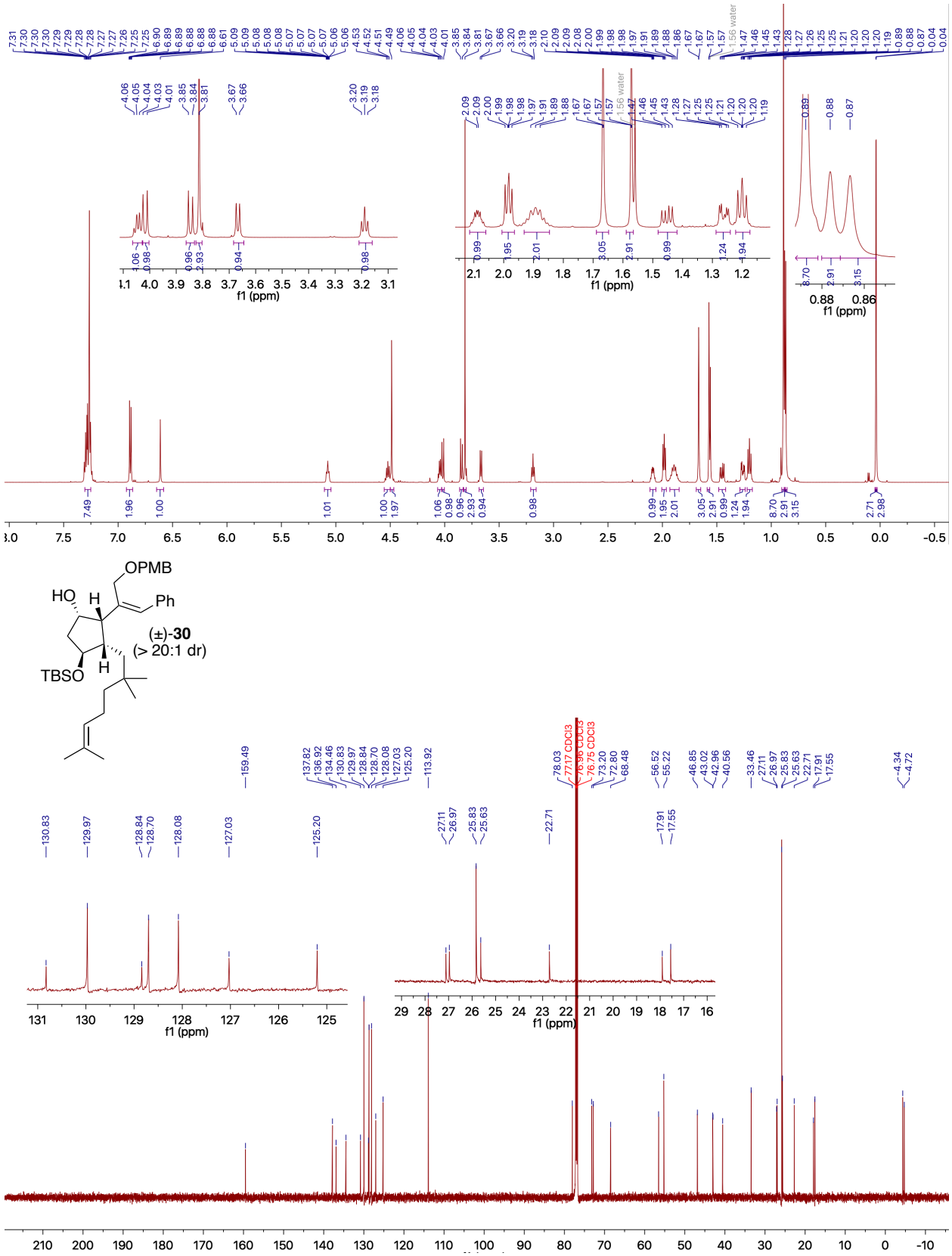
^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of (±)-**29**



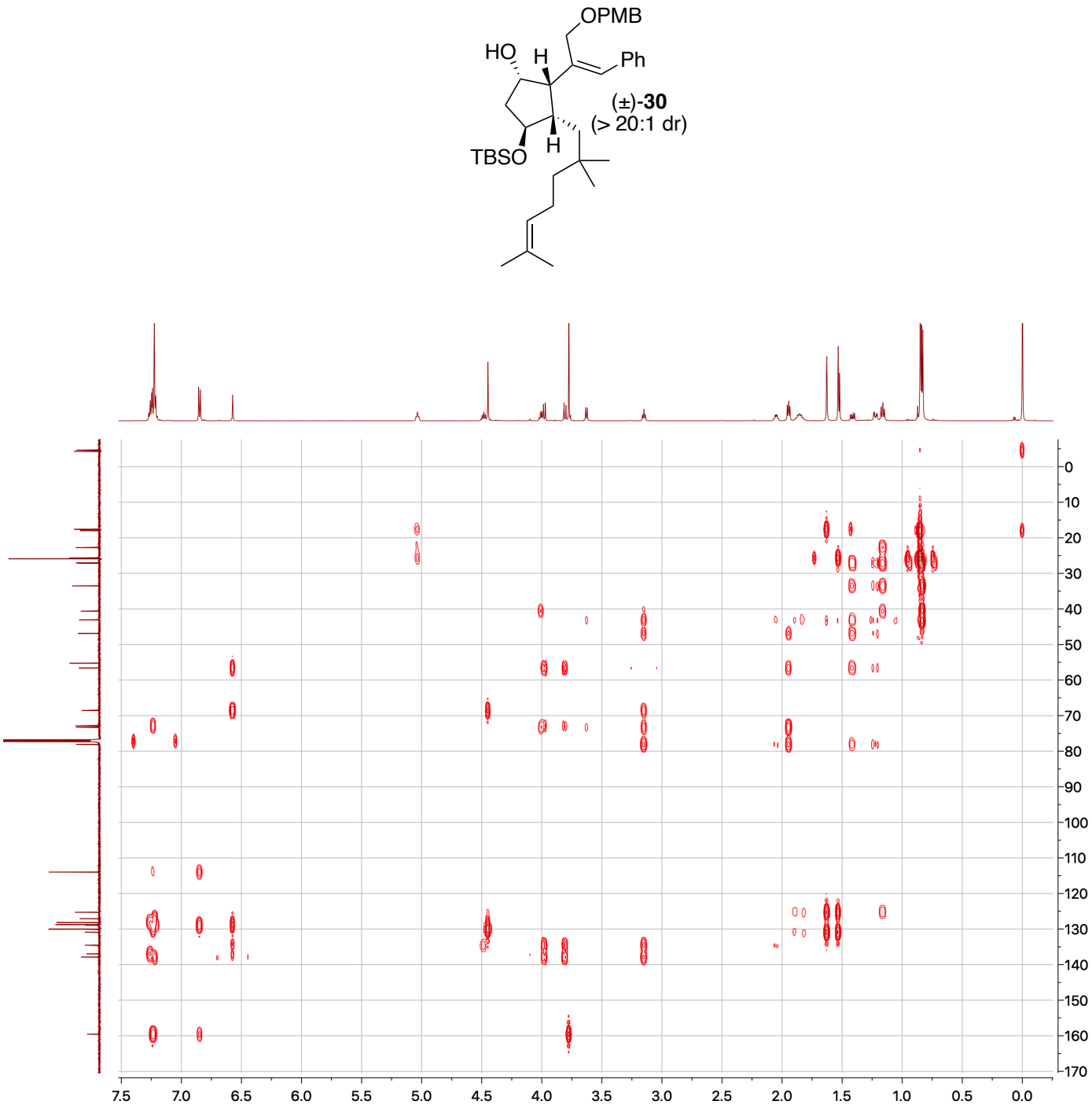
NOESY (600 MHz, $CDCl_3$) of (±)-**29**



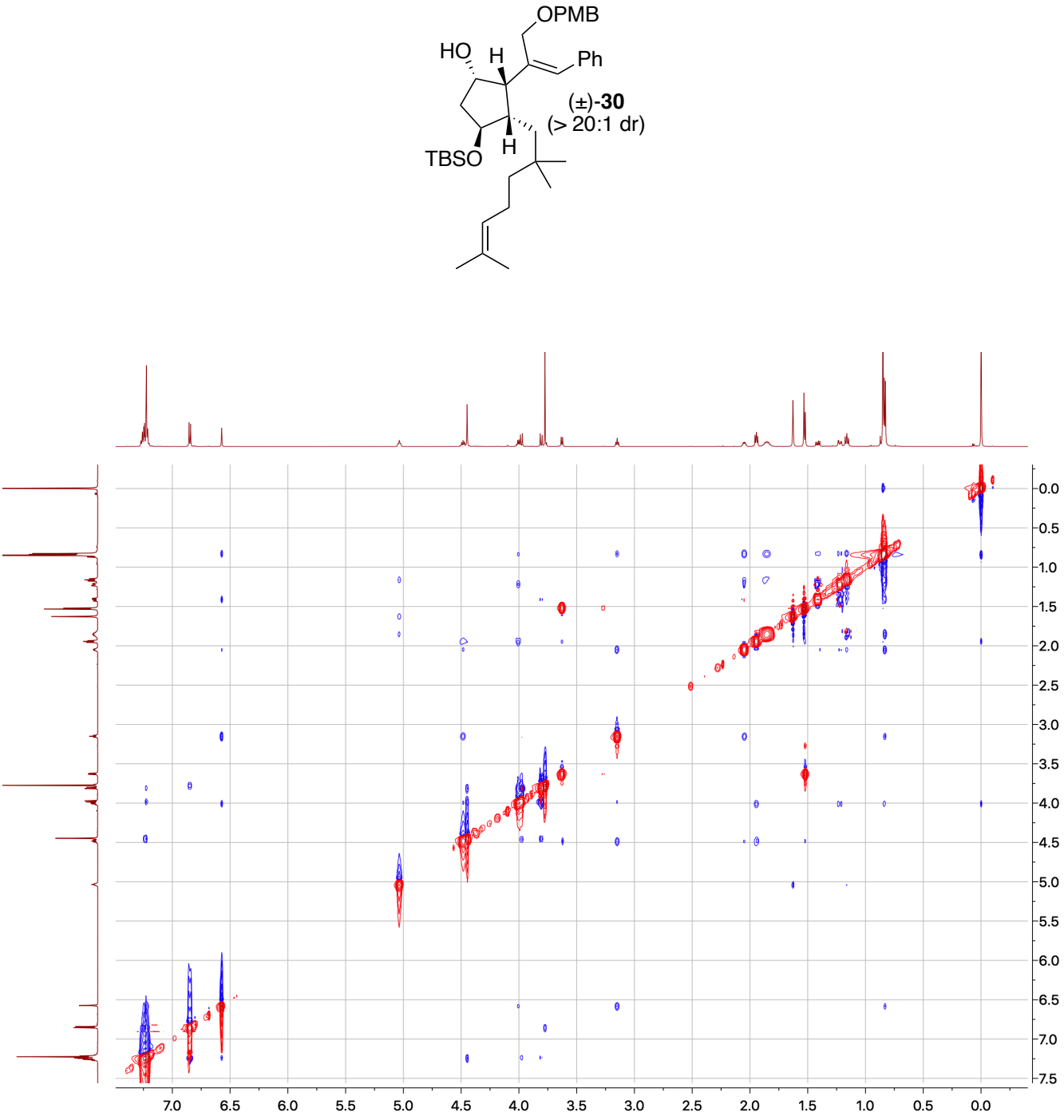
HMBC (600 MHz, $CDCl_3$) of (±)-**29**



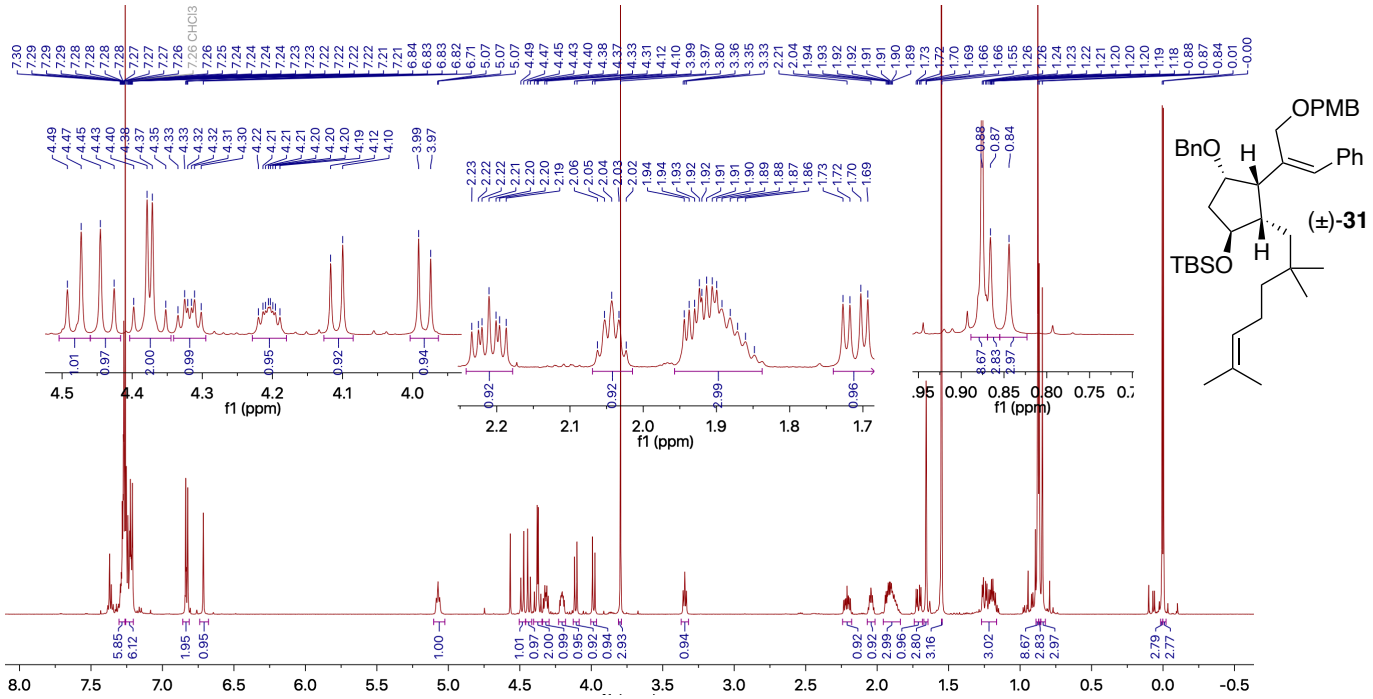
^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of (±)-**30**

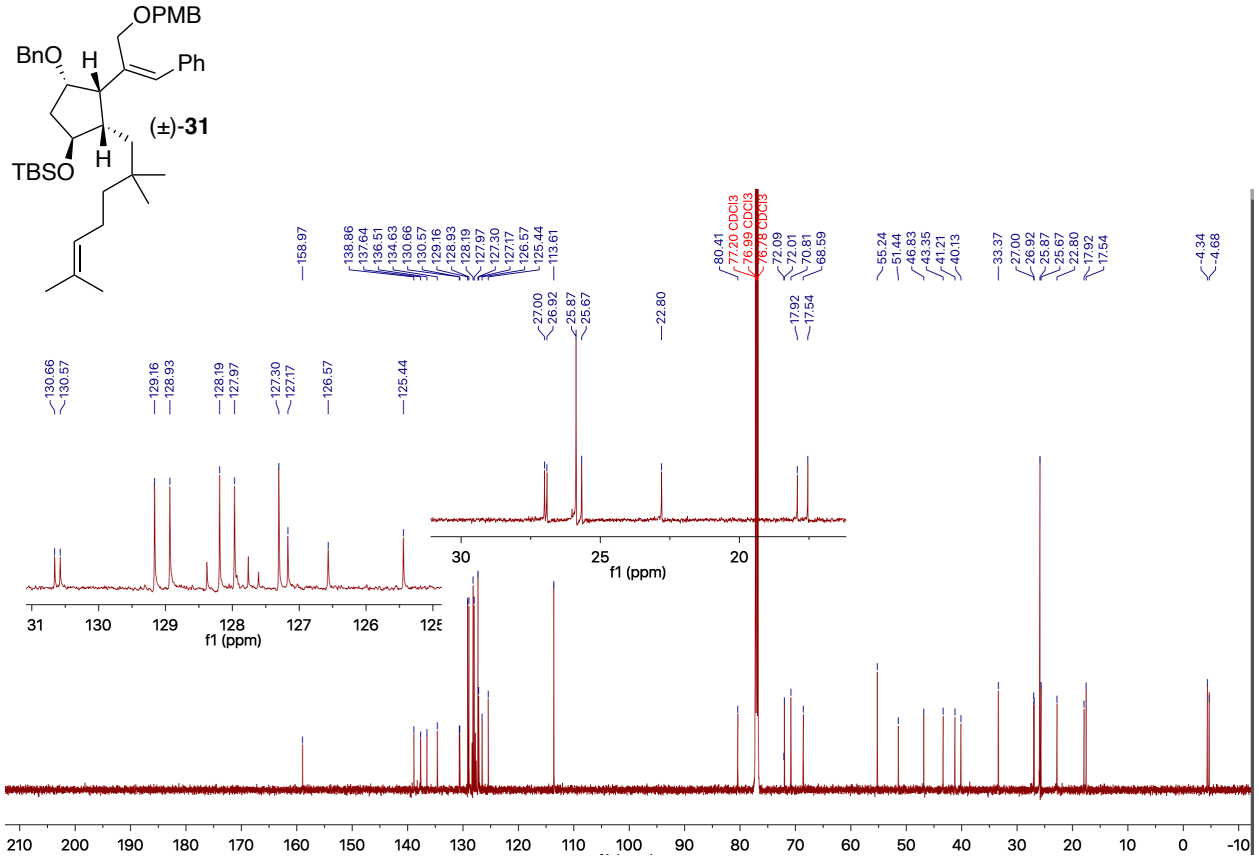


HMBC (600 MHz, $CDCl_3$) of (±)-**30**

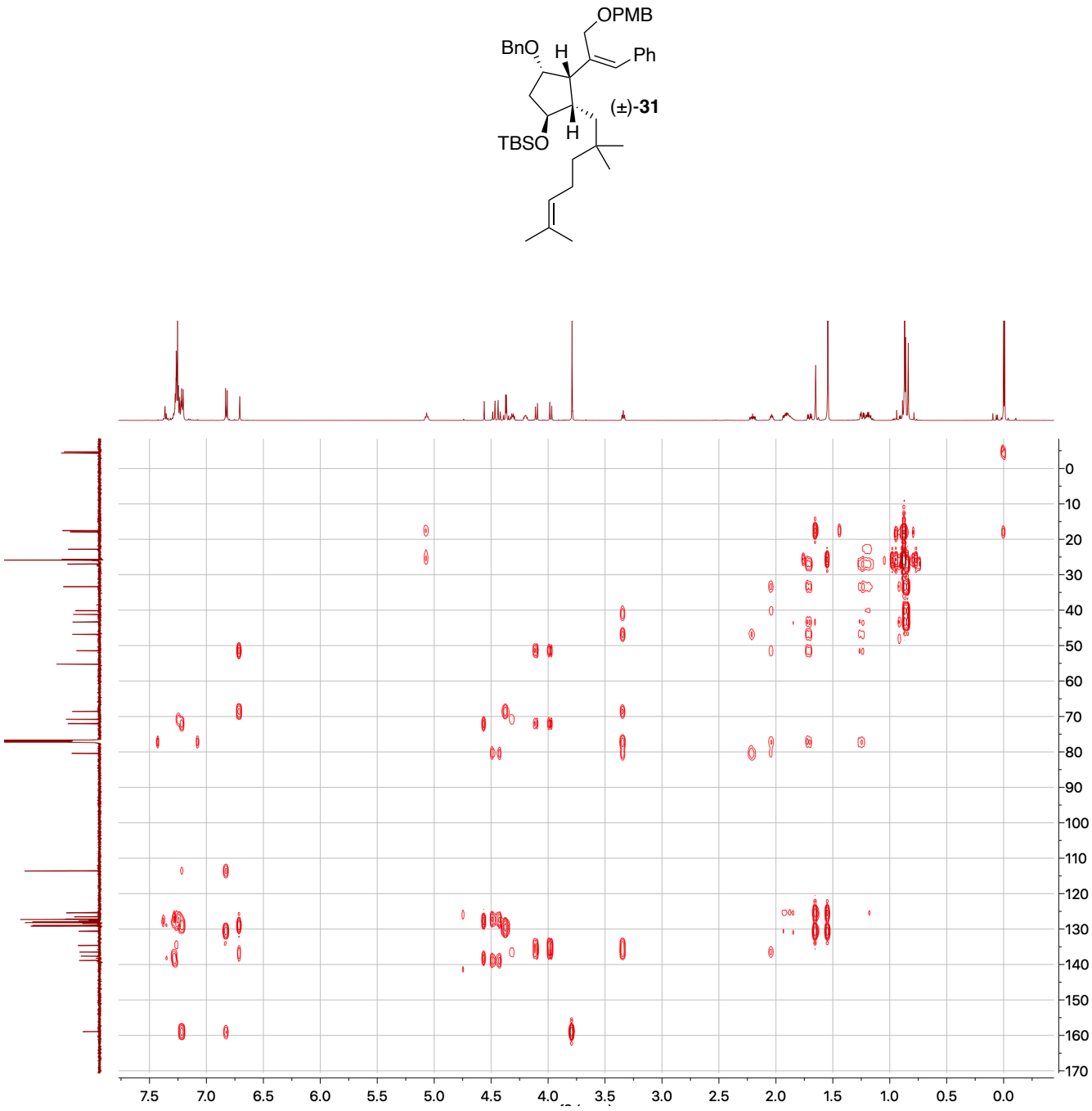


NOESY (600 MHz, $CDCl_3$) of (±)-**30**

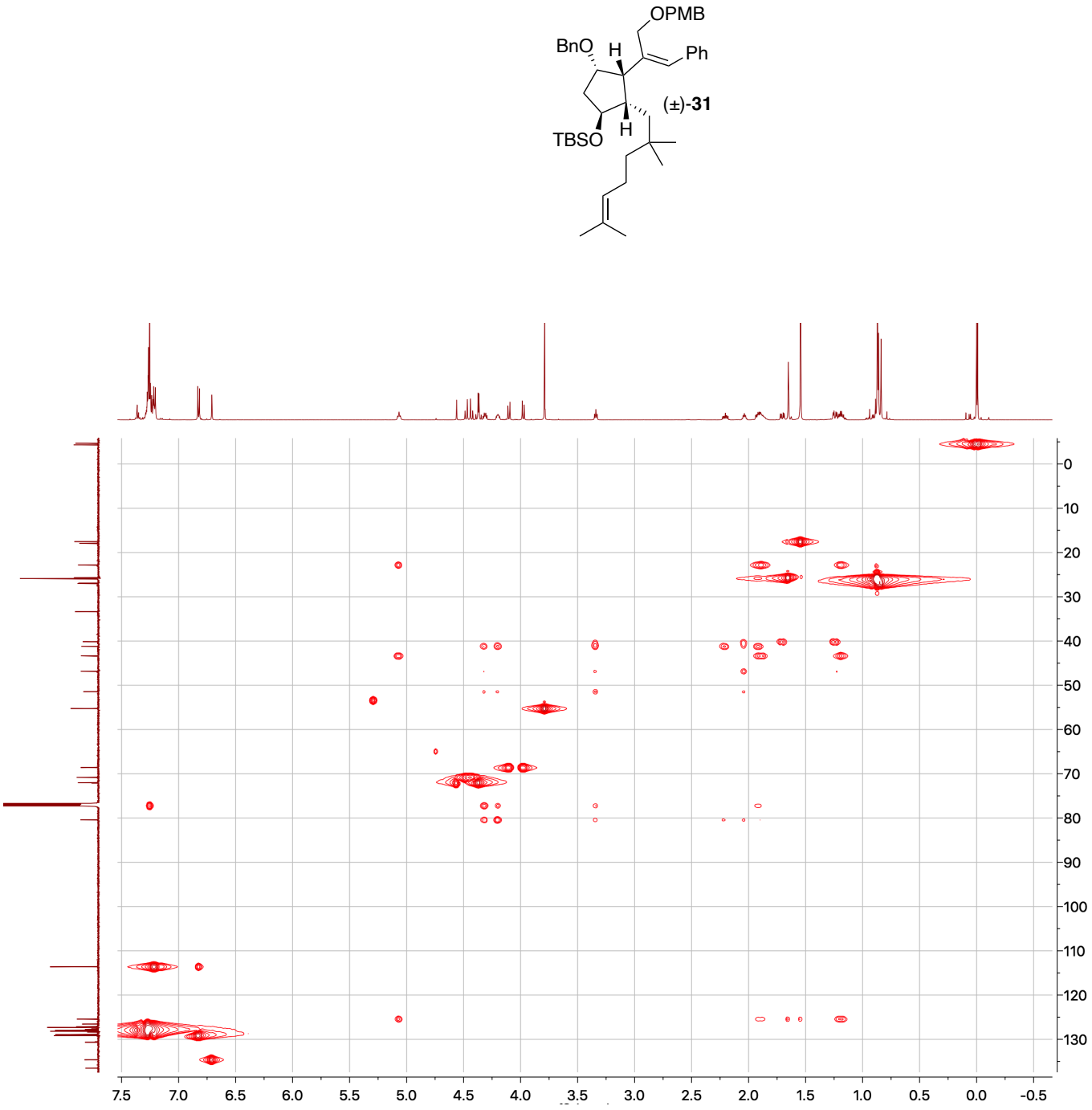




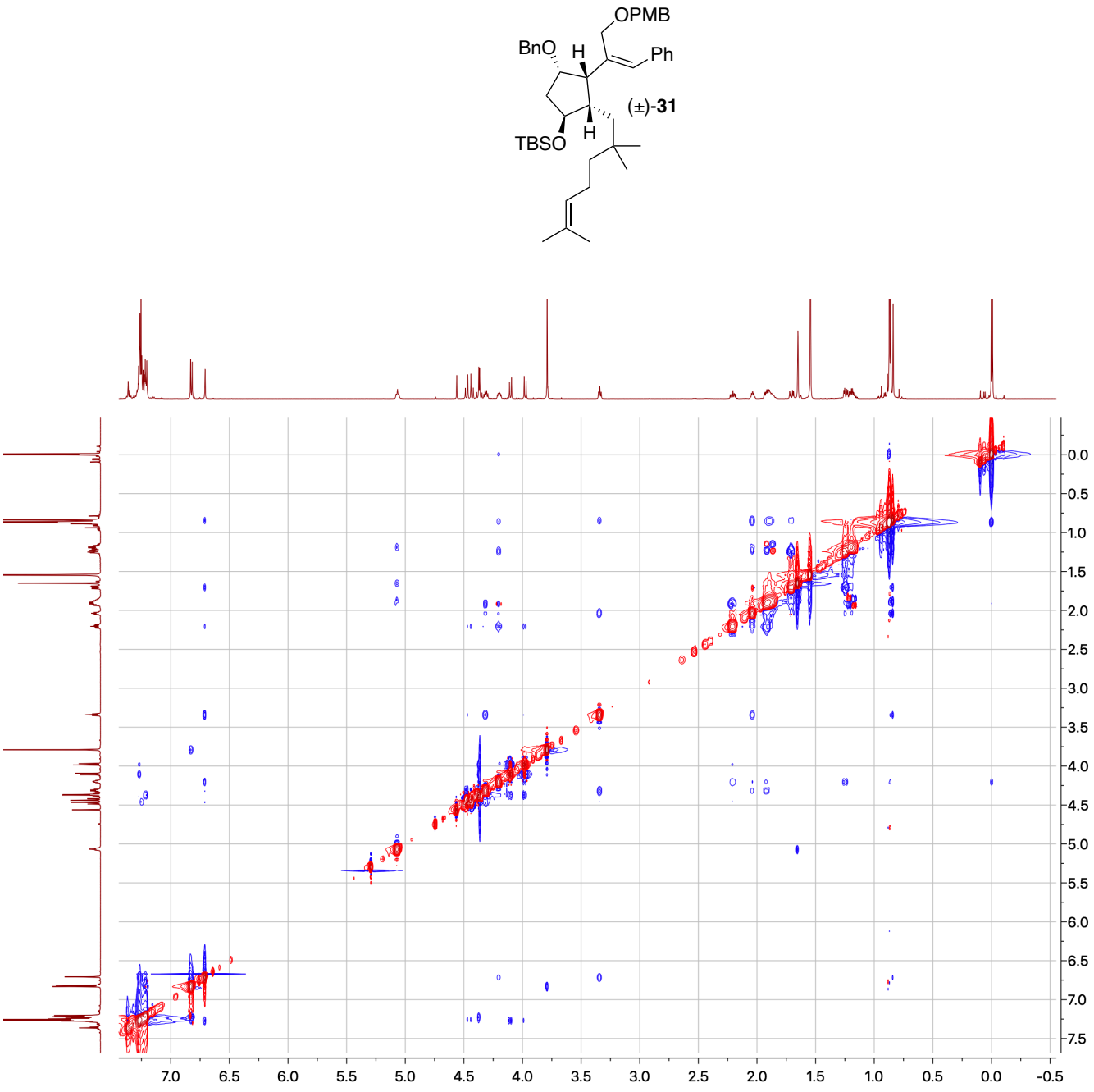
^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of (±)-**31**



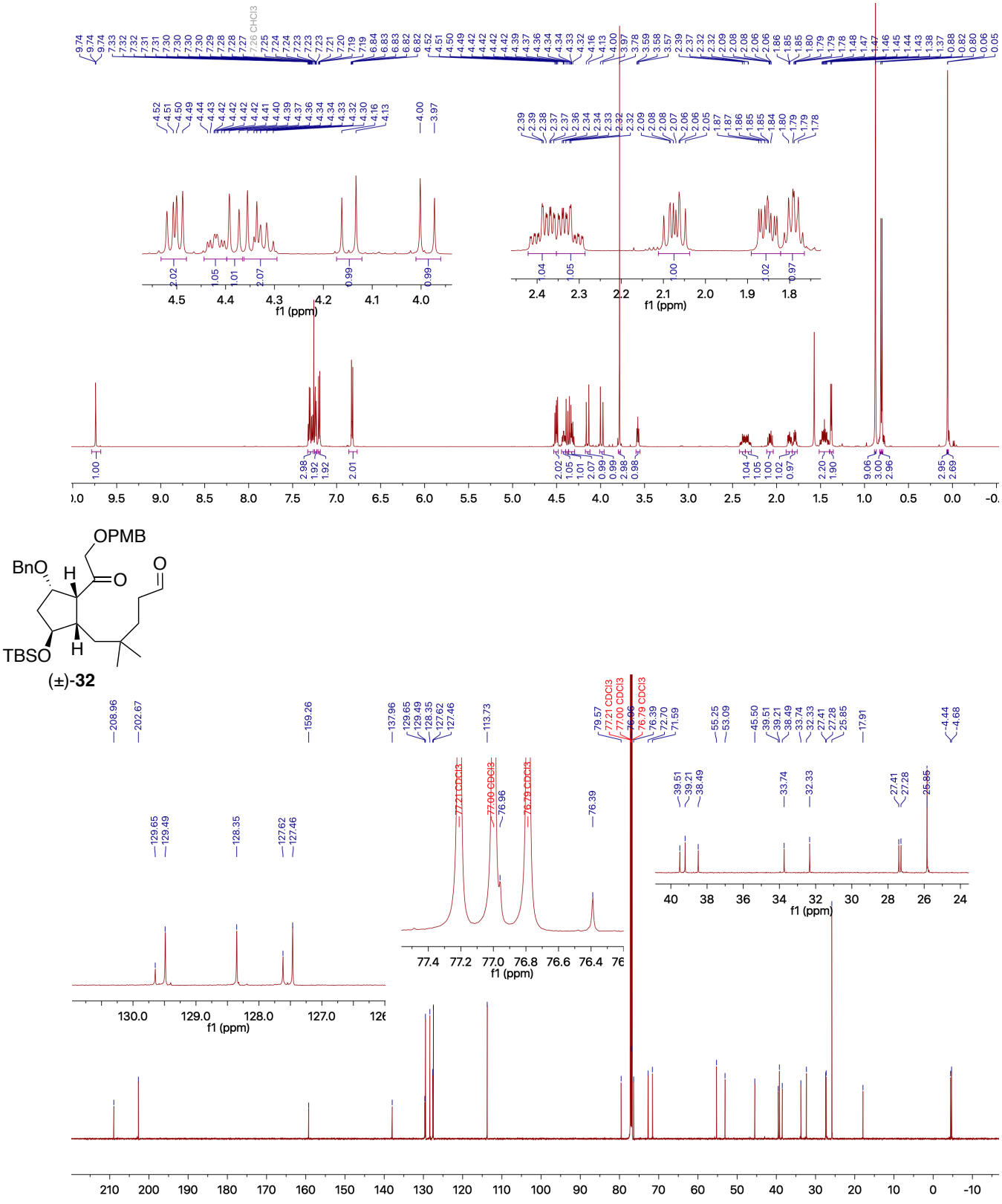
HMBC (600 MHz, $CDCl_3$) of (±)-**31**



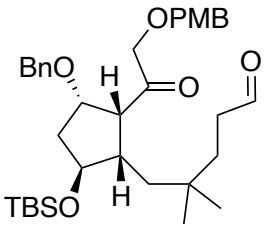
HSQC (600 MHz, $CDCl_3$) of (±)-**31**



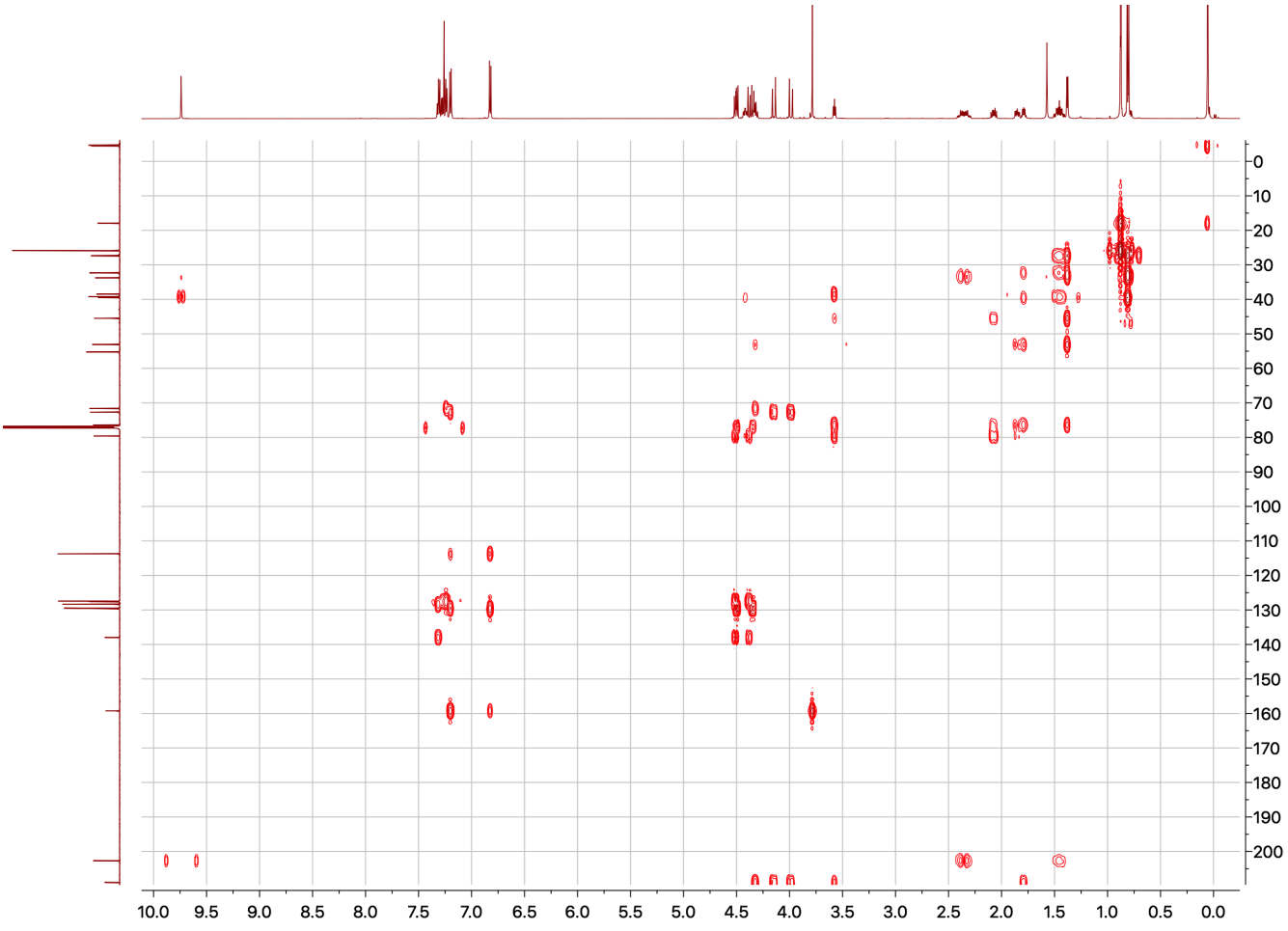
NOESY (600 MHz, $CDCl_3$) of (±)-**31**



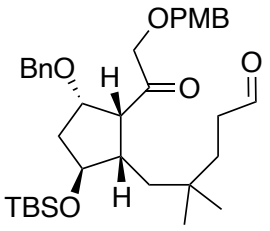
^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of (±)-**32**



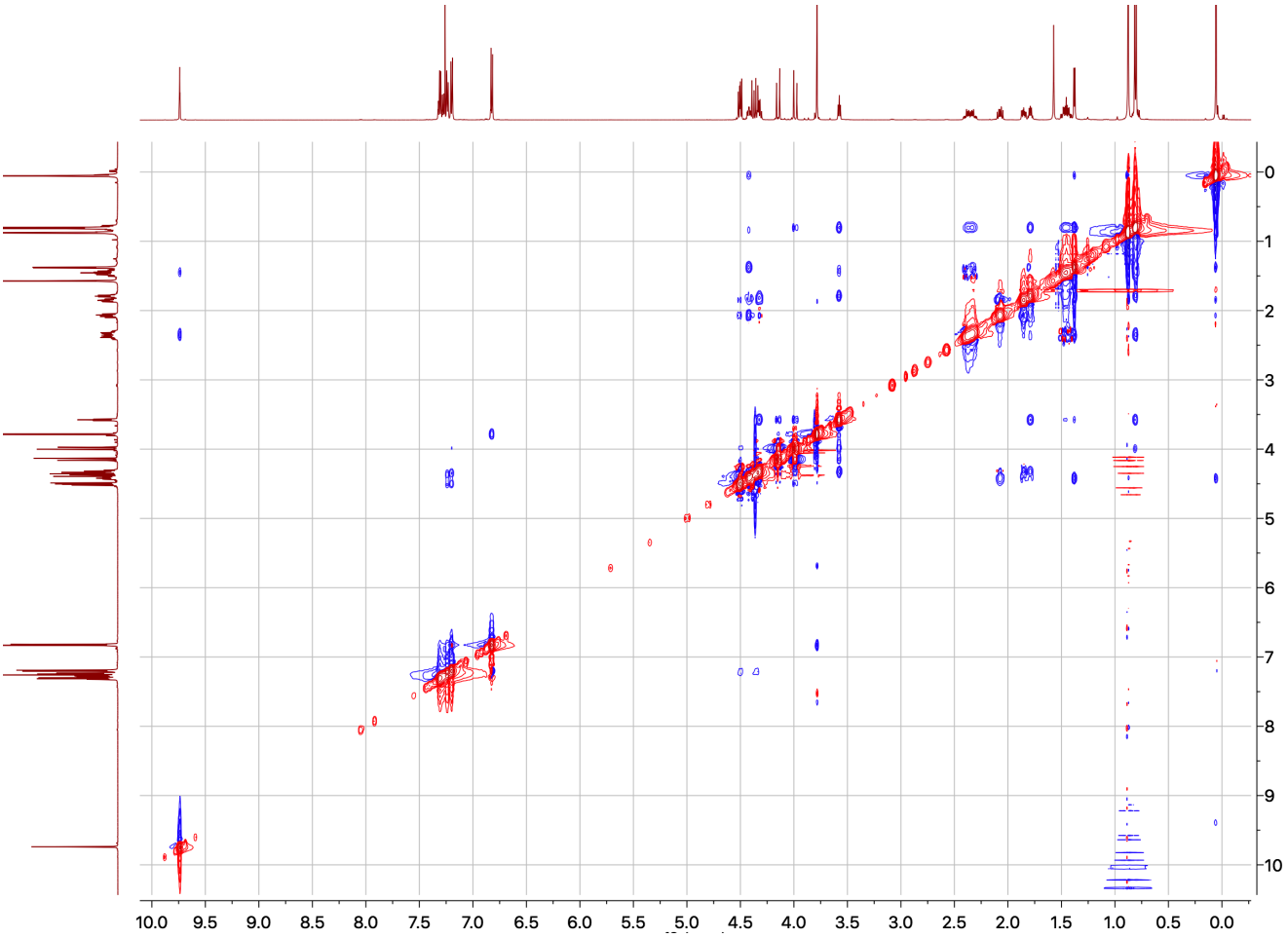
(±)-**32**



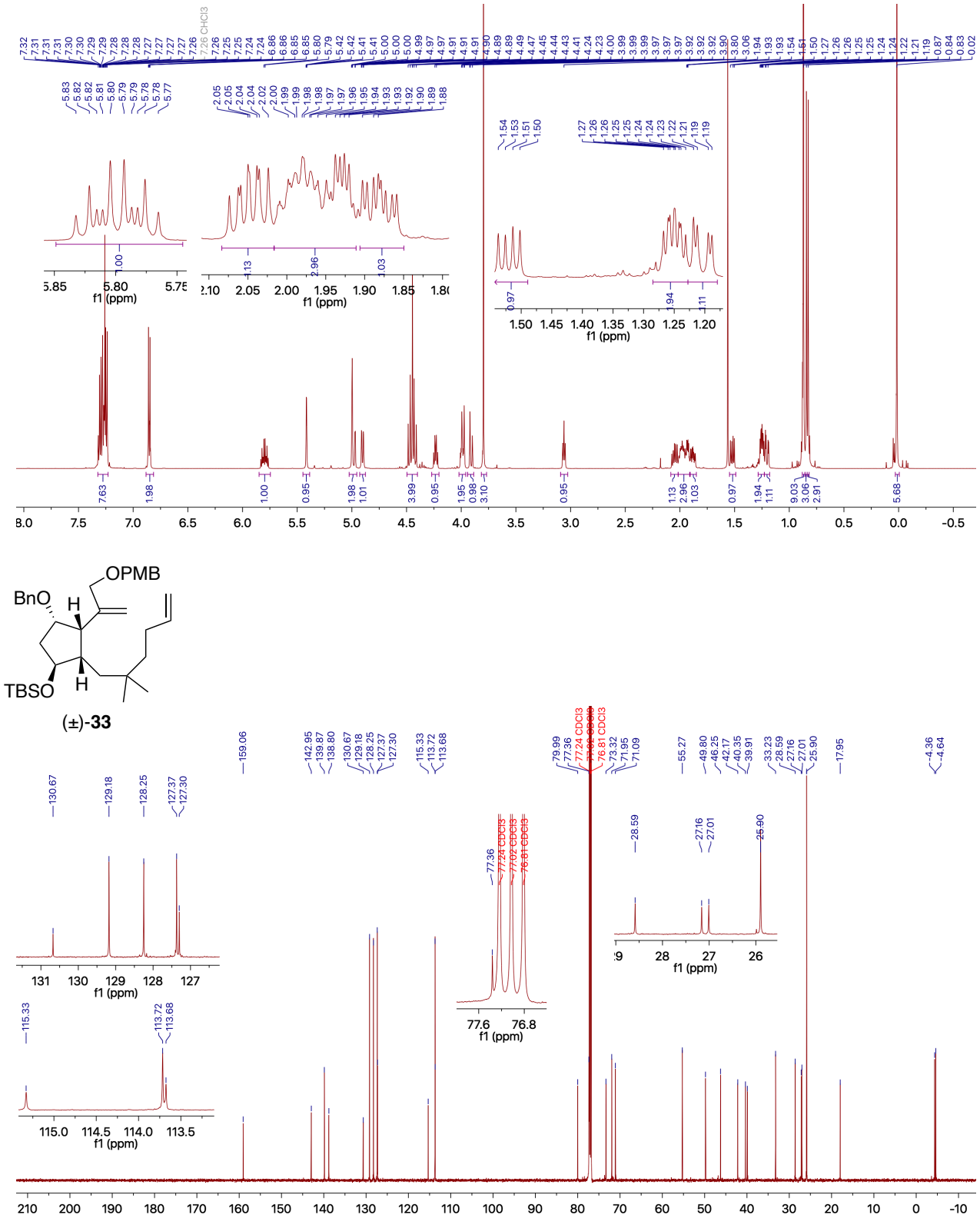
HMBC (600 MHz, $CDCl_3$) of (±)-**32**



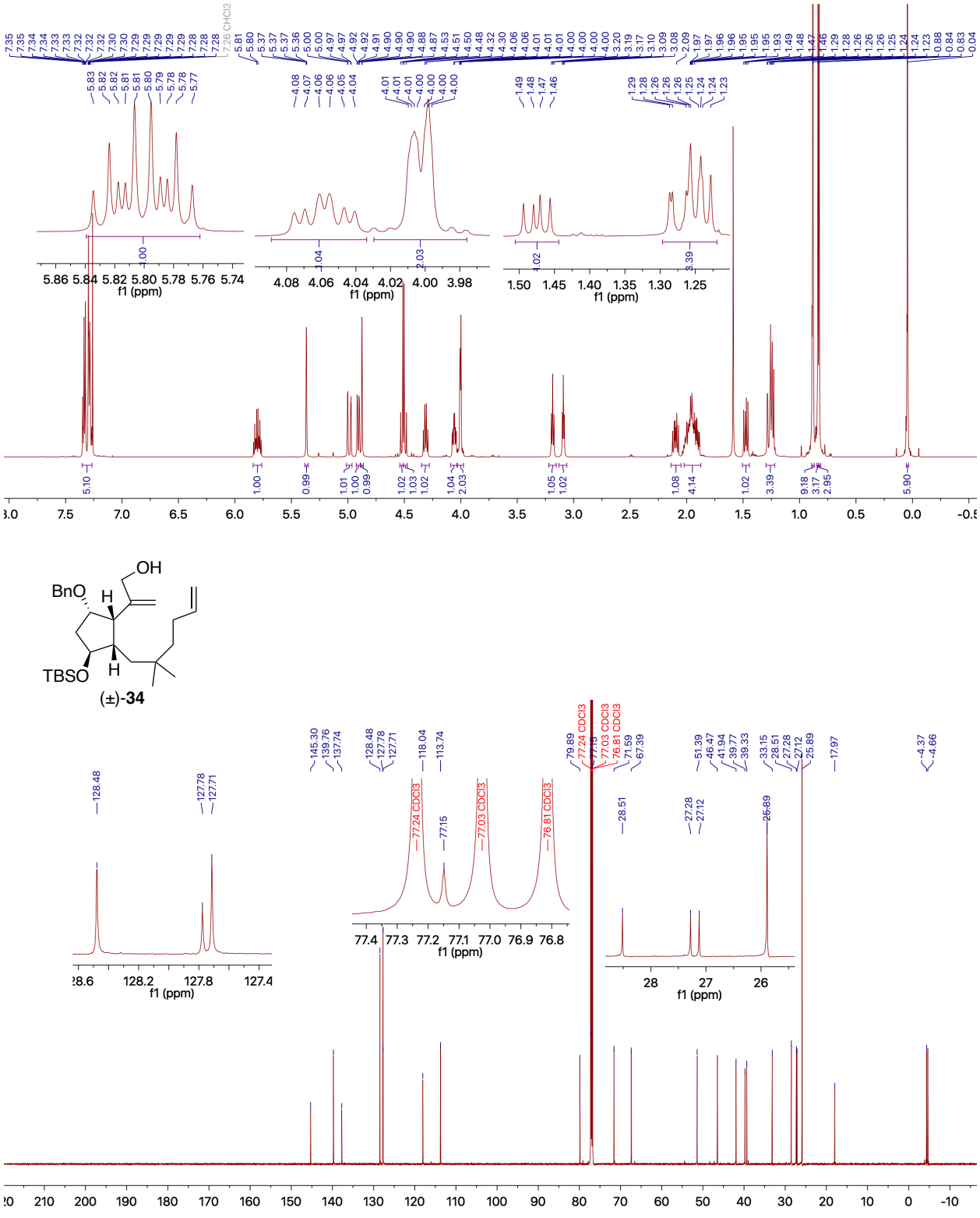
(±)-**32**



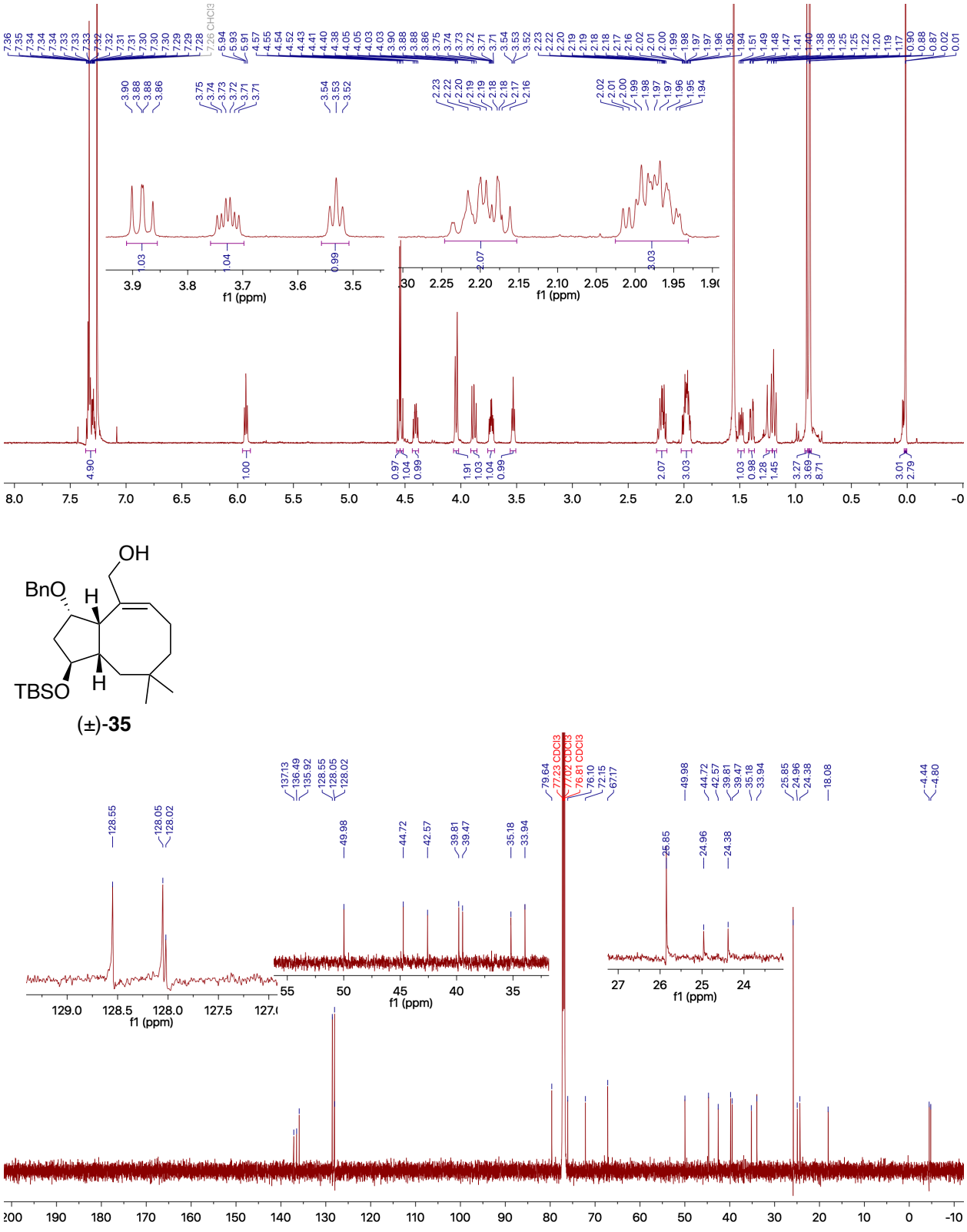
NOESY (600 MHz, $CDCl_3$) of (±)-**32**



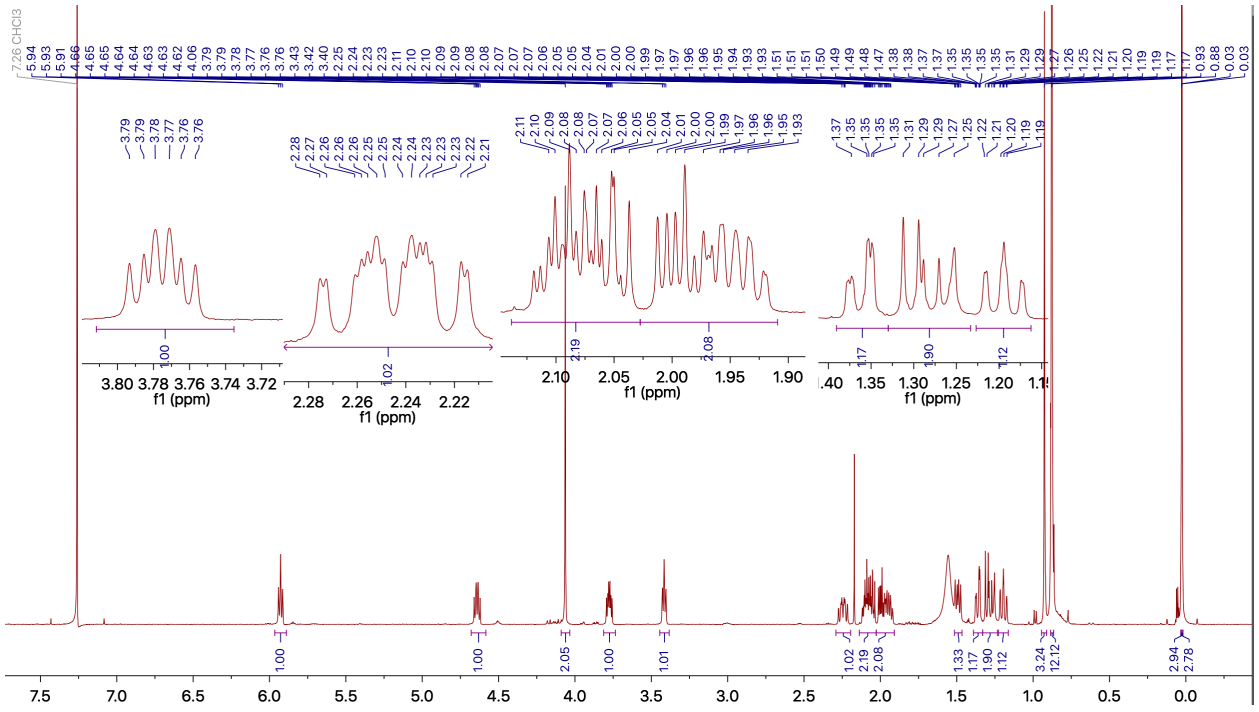
^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of (±)-**33**

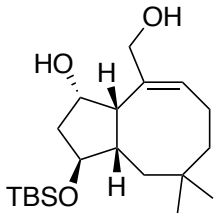


^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of (±)-**34**

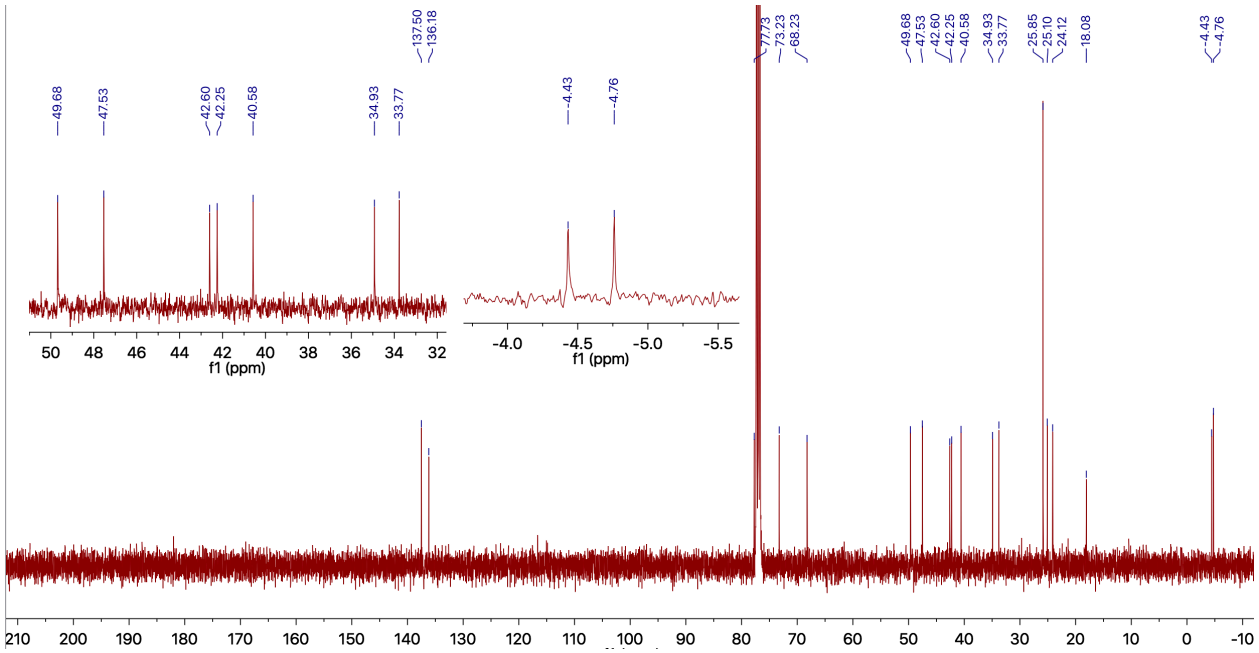


^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of (±)-**35**

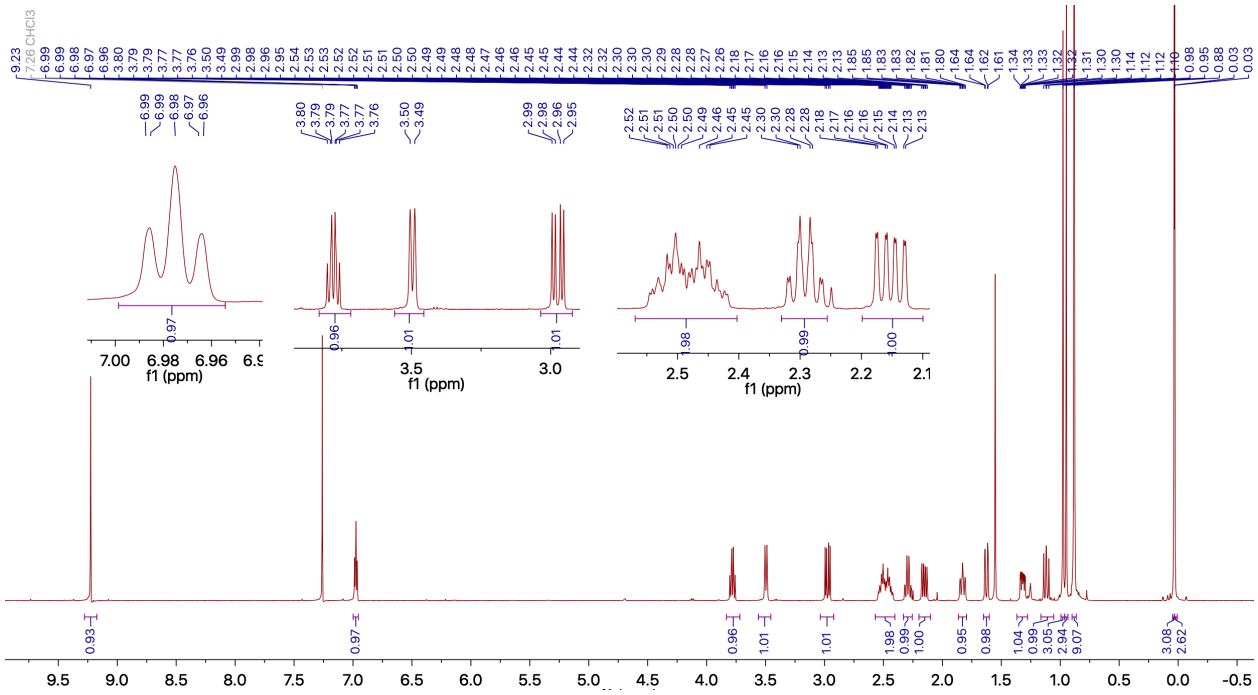


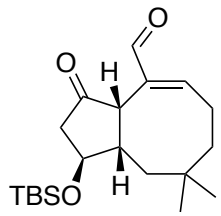


(±)-**36**

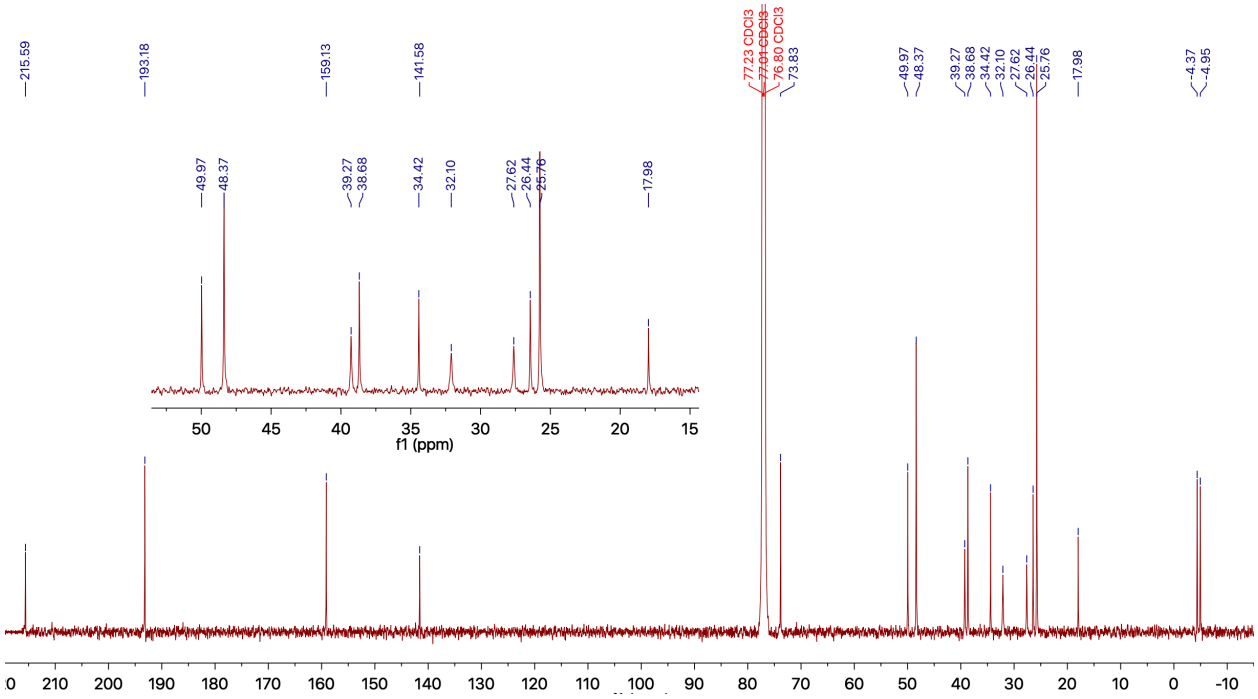


^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of (±)-**36**

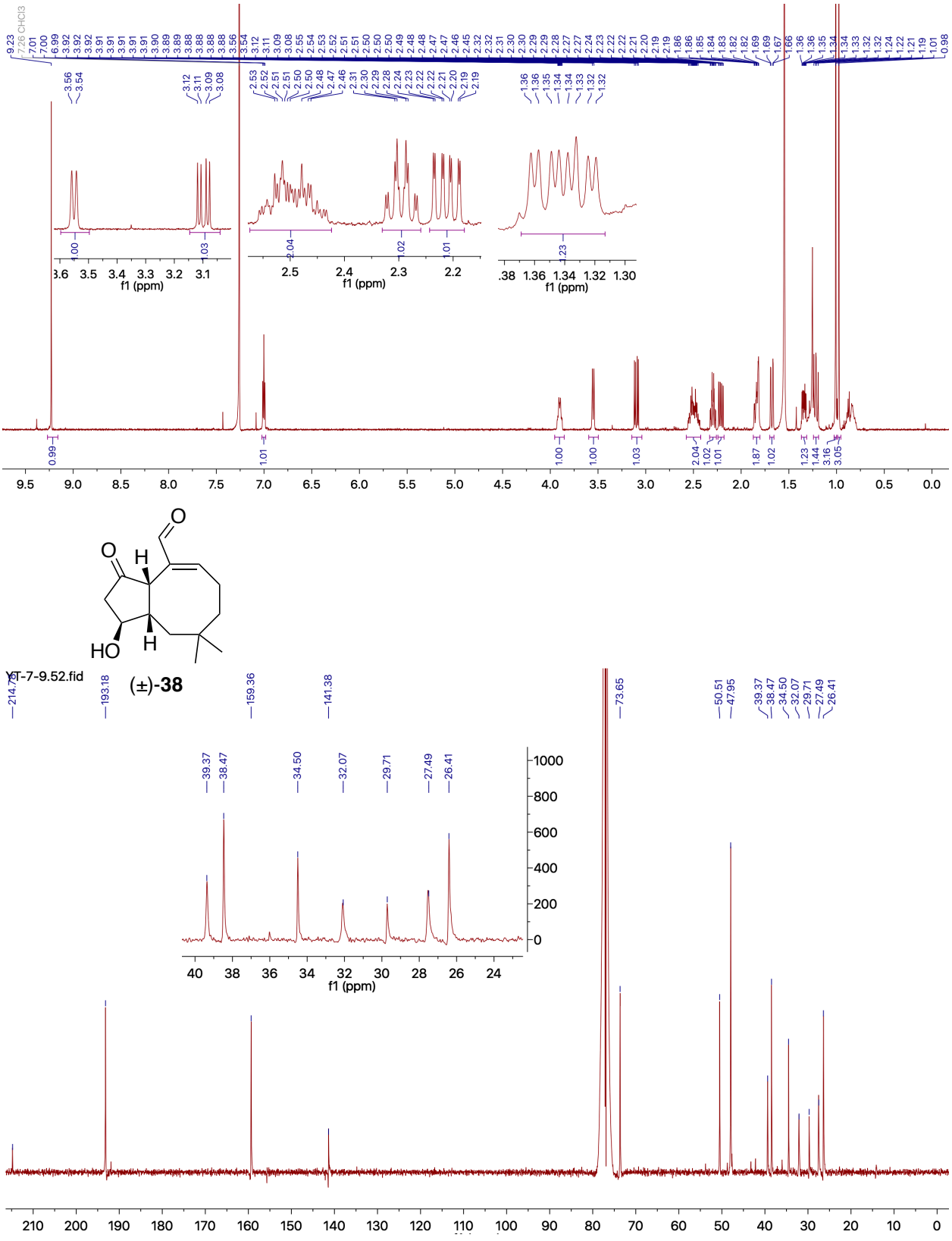




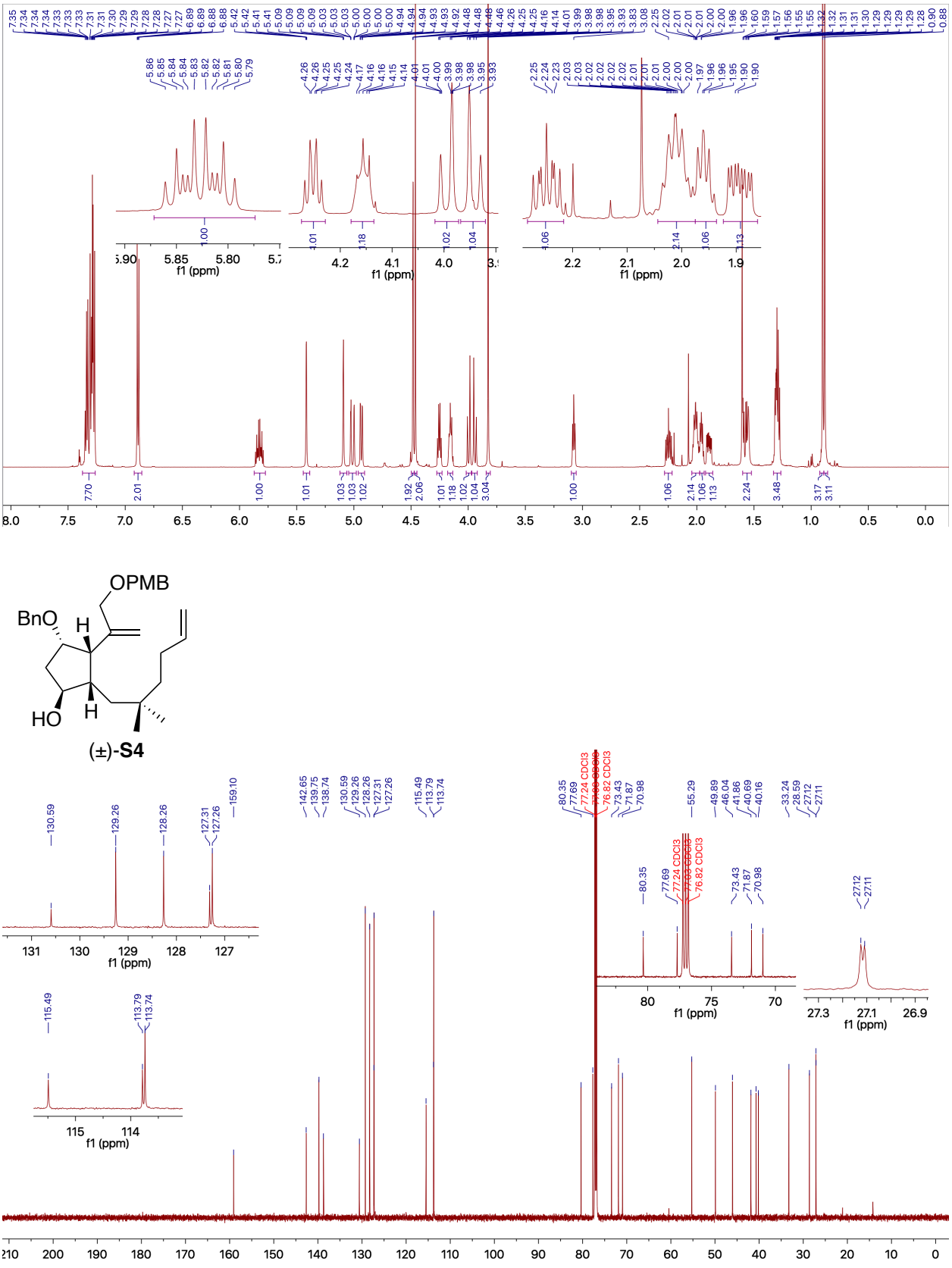
(±)-**37**



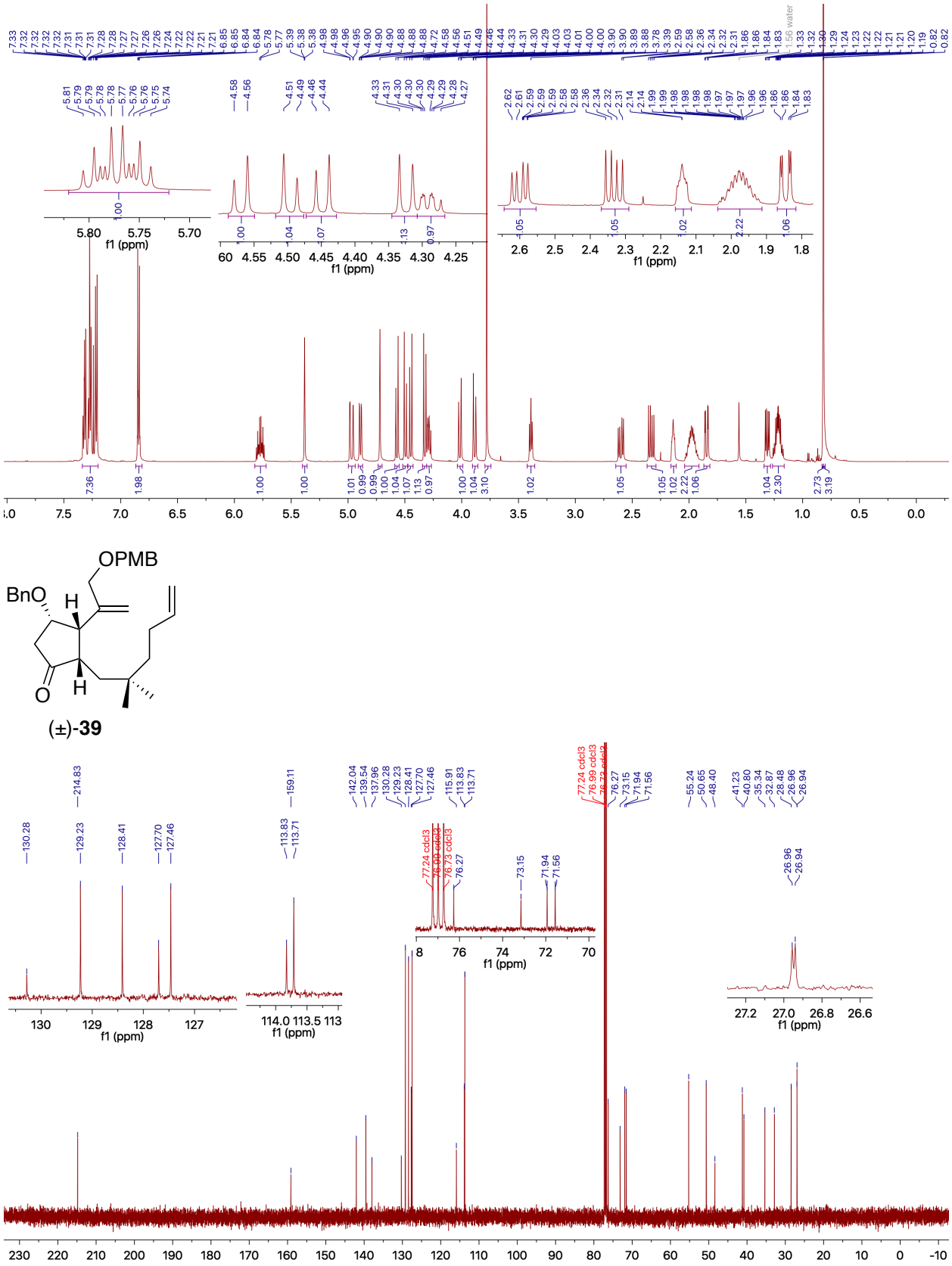
^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of (±)-**37**



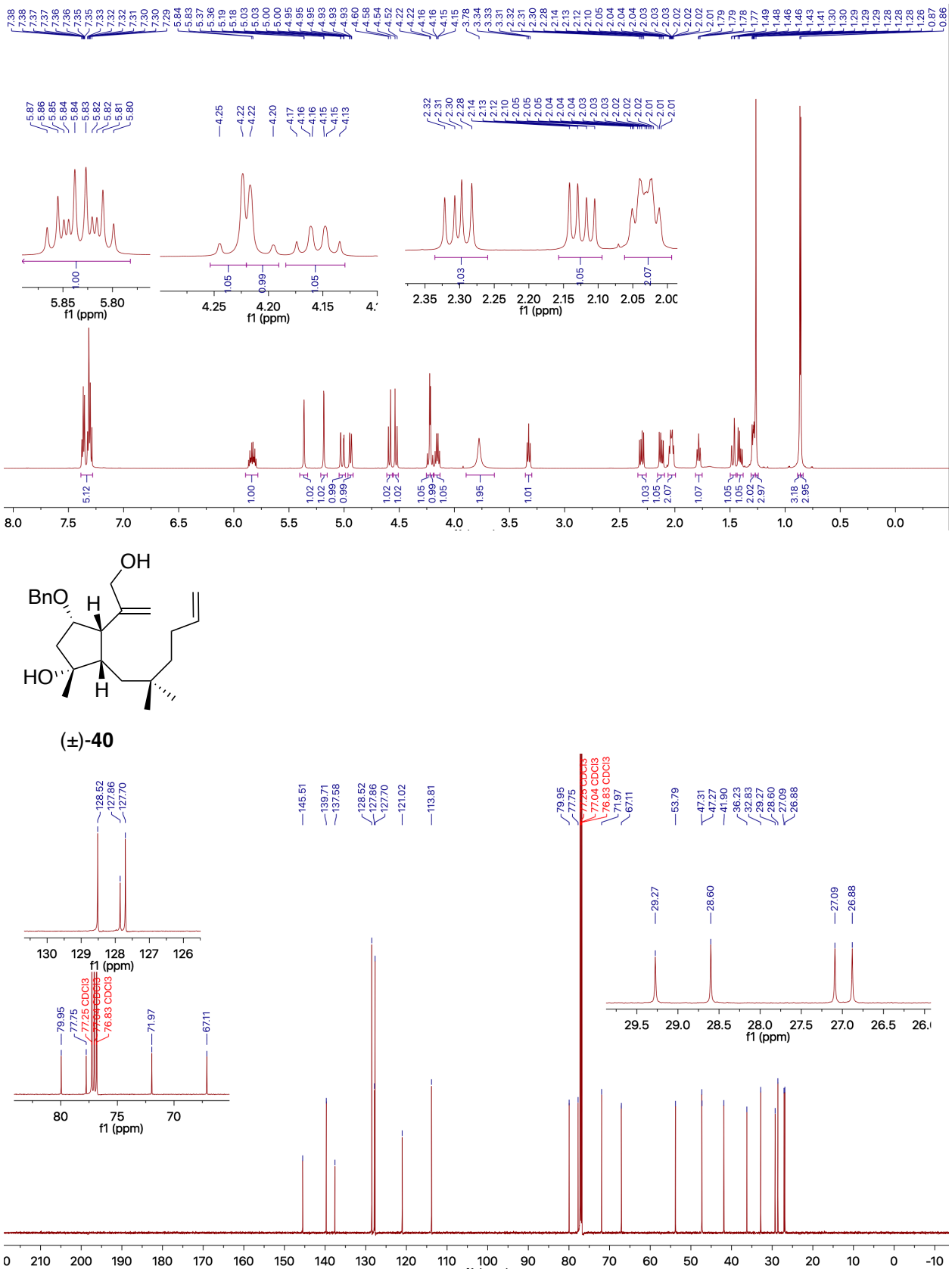
^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of (±)-**38**



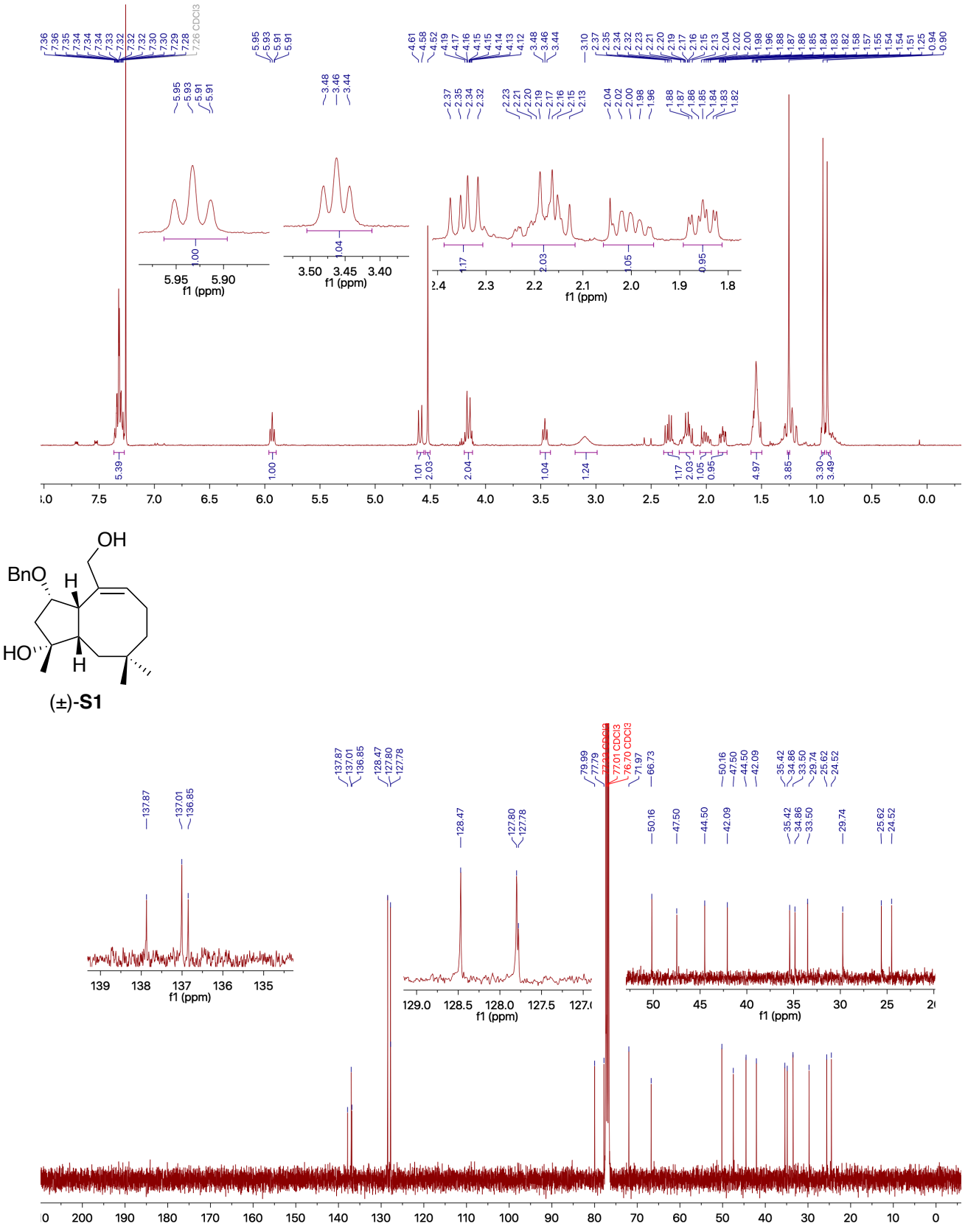
^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of (±)-**S4**



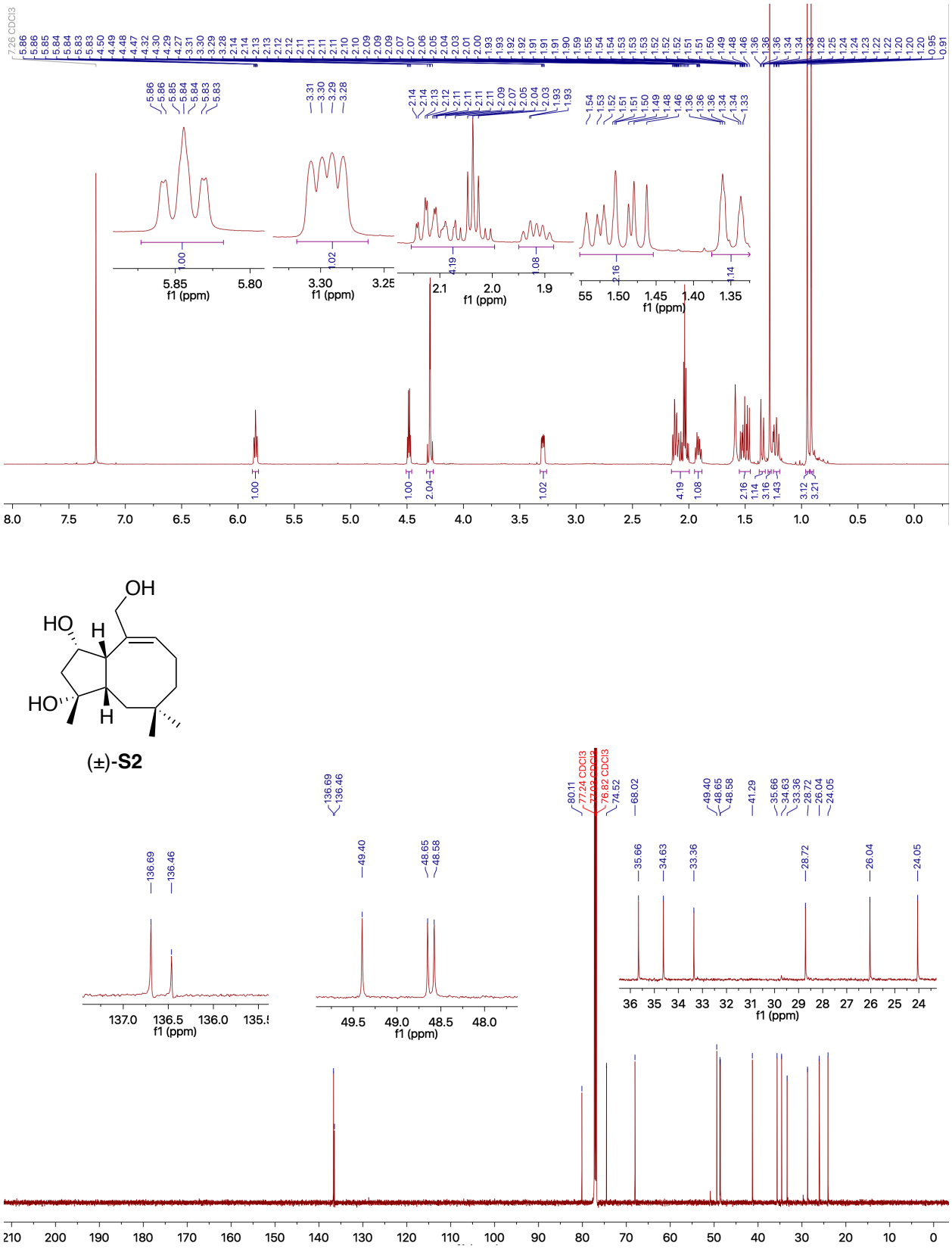
^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of (±)-**39**



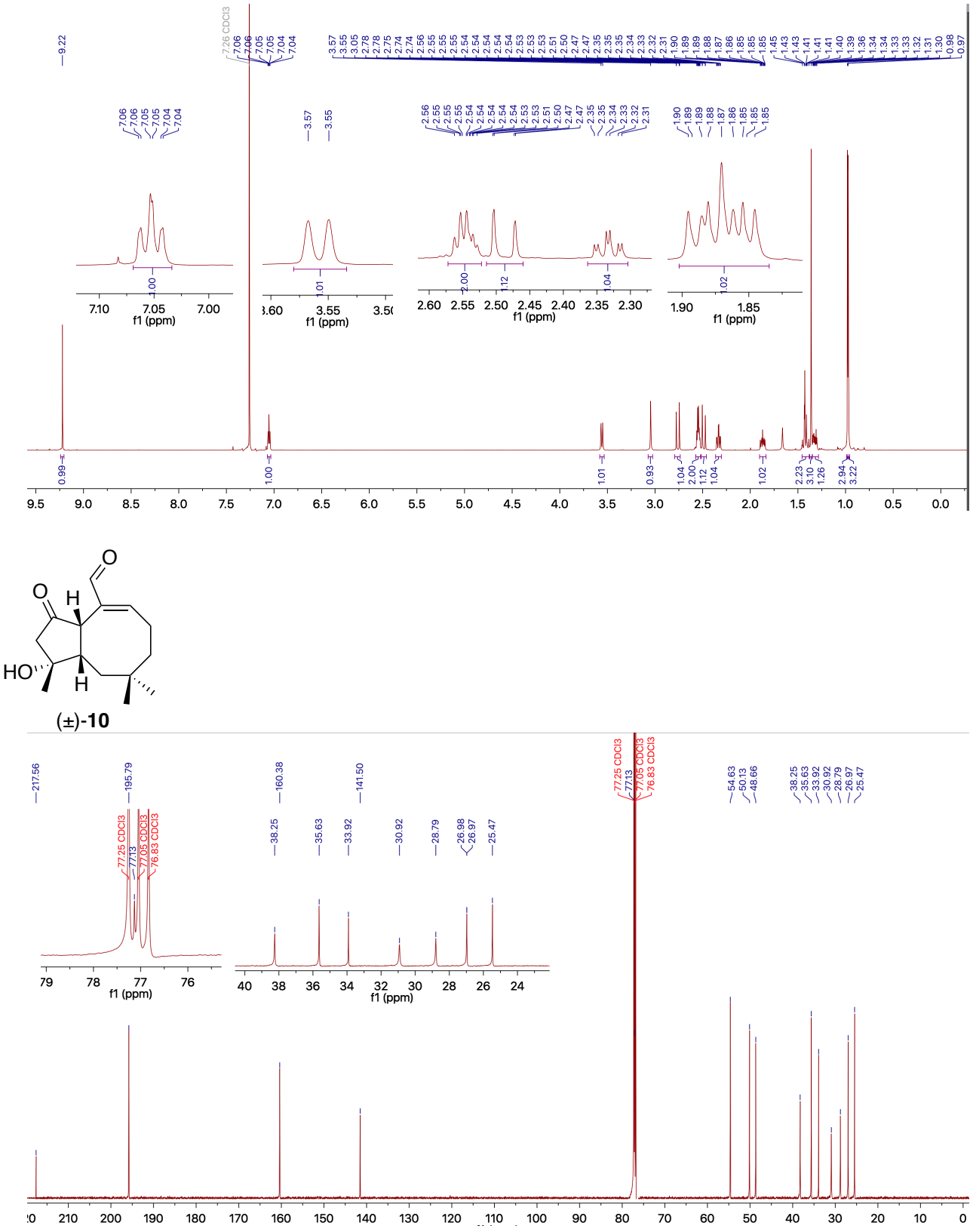
^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of (±)-**40**



^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of (±)-**41**



^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of (±)-**42**



(±)-**10**

^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (150 MHz, $CDCl_3$) of (±)-**10**

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