

Convergent Total Synthesis of (+)-Principinol D, a Rearranged Kaurane Diterpenoid

Timothy Newhouse, Aneta Turlik, Yifeng Chen, Anthony Scruse

Submitted date: 05/04/2019 • Posted date: 05/04/2019

Licence: CC BY-NC-ND 4.0

Citation information: Newhouse, Timothy; Turlik, Aneta; Chen, Yifeng; Scruse, Anthony (2019): Convergent Total Synthesis of (+)-Principinol D, a Rearranged Kaurane Diterpenoid. ChemRxiv. Preprint.

The total synthesis of principinol D, a rearranged kaurane diterpenoid, is reported. This grayanane natural product is constructed via a convergent fragment coupling approach, wherein the central 7-membered ring is synthesized at a late stage. The bicyclo[3.2.1]octane fragment is accessed by a Ni-catalyzed α -vinylation reaction. Strategic reductions include a diastereoselective SmI₂-mediated ketone reduction with PhSH and a new protocol for selective ester reduction in the presence of ketones. The convergent strategy reported herein may be an entry point to the larger class of kaurane diterpenoids.

File list (3)

Principinol D - SI.pdf (13.41 MiB)	view on ChemRxiv • download file
principinol D - ms.pdf (708.99 KiB)	view on ChemRxiv • download file
Compound 2.cif (2.63 MiB)	view on ChemRxiv • download file

Supporting Information

Convergent Total Synthesis of (+)-Principinol D, a Rearranged Kaurane Diterpenoid

Aneta Turlik, Yifeng Chen, Anthony C. Scruse, and Timothy R. Newhouse.*

Department of Chemistry, Yale University, 225 Prospect St.,
New Haven, Connecticut 06520-8107

*E-mail: timothy.newhouse@yale.edu

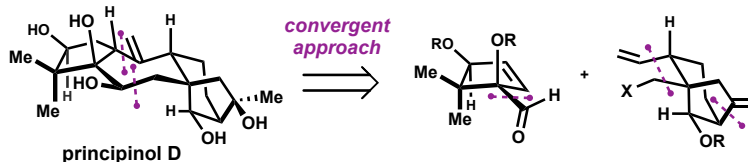


Table of Contents

General experimental	2
Synthetic route towards the 5-membered ring fragment.....	3
Synthetic route towards the bicyclo[3.2.1]octane fragment	16
Fragment coupling and completion of synthesis	40
Comparison of synthetic and natural principinol D (1)	97

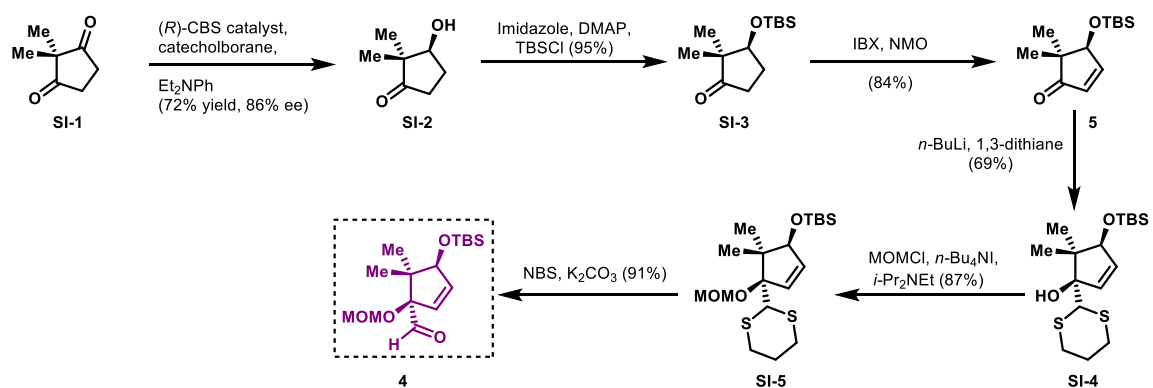
General experimental

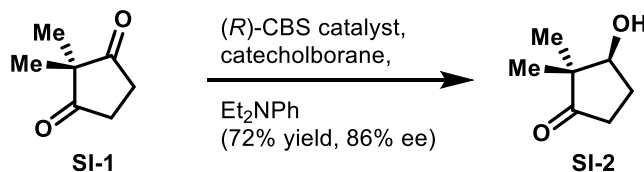
General experimental procedures: All reactions were carried out under an inert nitrogen atmosphere with dry solvents under anhydrous conditions unless otherwise stated. All reactions were capped with a rubber septum, or Teflon-coated silicon microwave cap unless otherwise stated. Stainless steel cannula or syringe were used to transfer solvent and air- and moisture-sensitive liquid reagents. Reactions were monitored by thin-layer chromatography (TLC), carried out on 0.25 mm Merck silica gel plates (60F-254) using UV light as the visualizing agent and potassium permanganate, cerium ammonium molybdate, phosphomolybdic acid, an acidic solution of *p*-anisaldehyde, and vanillin as developing agents. Flash column chromatography employed SiliaFlash® P60 (40–60 μm , 230–400 mesh) silica gel purchased from SiliCycle Inc.

Materials: All reaction solvents were purified using a Seca solvent purification system by Glass Contour, with the exception of 1,4-dioxane, ethanol, and dimethylsulfoxide, which were used as received without further purification. Methanol was distilled over magnesium. Pyridine, *N,N*-diisopropylethylamine, triethylamine, and HMPA were distilled over CaH_2 . 2,3-dibromopropene was distilled before use. NBS was crystallized from water. IBX was synthesized according to the procedure developed by Santagostino and coworkers.¹ K_2CO_3 was purchased from Acros. All other reagents were used as received without further purification, unless otherwise stated.

Instrumentation: All new compounds were characterized by means of R_f , optical rotation (where applicable), ^1H NMR, ^{13}C NMR, FT-IR (thin film), and HR-MS. Copies of the ^1H - and ^{13}C -NMR spectra can be found at the end of each experimental procedure. NMR spectra were recorded using a Varian 400 MHz NMR spectrometer, Varian 500 MHz NMR spectrometer, or Varian 600 MHz NMR spectrometer. All ^1H -NMR data are reported in δ units, parts per million (ppm), and were calibrated relative to the signals for residual chloroform (7.26 ppm) in deuteriochloroform (CDCl_3) or residual methanol (3.31 ppm) in deuteromethanol (CD_3OD). All ^{13}C -NMR data are reported in ppm relative to CDCl_3 (77.16 ppm) or CD_3OD (49.00) and were obtained with ^1H decoupling. The following abbreviations or combinations thereof were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet, and a = apparent. All IR spectra were taken on an FT-IR/Raman Thermo Nicolet 6700. High resolution mass spectra (HR-MS) were recorded on a Bruker microTOF mass spectrometer using ESI-TOF (electrospray ionization-time of flight). Optical rotation data was obtained using a Perkin-Elmer 341 polarimeter.

Synthetic route towards the 5-membered ring fragment





Keto-alcohol SI-2:

The following procedure was modified from the reported protocol.^{2,3}

2,2-dimethylcyclopentanone (10.4 g, 254 mmol) was dissolved in toluene (170 mL, 0.5 M). Et₂NPh (4.0 mL, 41.2 mmol, 0.5 equiv) and (R)-(+)-2-Butyl-CBS-oxazaborolidine solution (1 M in toluene; 8.25 mL, 8.25 mmol, 0.1 equiv) were added. The reaction mixture was cooled to –60 °C using a chloroform/dry ice bath. A solution of catecholborane (15.6 mL, 147 mmol, 1.78 equiv) in toluene (140 mL, 1.0 M) was added via addition funnel over two hours. The reaction was stirred at –60 °C for two more hours. MeOH (30 mL) was then added slowly down the side of the flask, then moved to room temperature. Et₂O was added (200 mL), followed by NaHCO₃ (100 mL) and 3 N NaOH (100 mL), upon which the reaction mixture turned brown. The reaction was stirred for one hour, then extracted with Et₂O three times (200 mL each). The organic layers were washed with water (200 mL) and brine (200 mL), dried with Na₂SO₄, and filtered. In order to remove the toluene before concentration by rotary evaporation, the compound was loaded onto a silica plug. The toluene was flushed through with pentane, then the compound was eluted with Et₂O (R_f = 0.6 in Et₂O) into a separate flask and concentrated. Subsequent purification by flash column chromatography (hexanes→50% Et₂O /hexanes) afforded product **SI-2** in 72% yield (7.52 g, 86% ee).

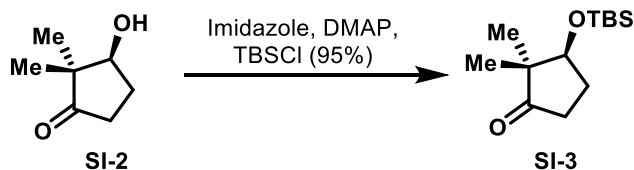
The characterization data are consistent with those reported in the literature.^{2,3}

R_f = 0.45 (40% Et₂O in CH₂Cl₂; UV-active, stains yellow in p-anisaldehyde);

[α]_D^{20.0}: +12.7° (*c* 1.0, CHCl₃) (lit = –14.9 for the enantiomer);²

¹H NMR (500 MHz, CDCl₃) δ 4.05 (m, 1H), 2.51-2.43 (m, 1H), 2.30-2.20 (m, 2H), 1.95-1.87 (m, 1H), 1.65 (d, *J* = 3.4 Hz, 1H), 1.04 (s, 6H);

¹³C NMR (151 MHz, CDCl₃) δ 221.6, 78.2, 50.2, 34.3, 27.8, 22.2, 16.9.



TBS-protected alcohol SI-3:

Keto-alcohol **SI-2** (9.9 g, 77.3 mmol, 1.0 equiv) was dissolved in DMF (50 mL, 1.5 M). Imidazole (14.3 g, 210 mmol, 2.8 equiv), DMAP (1.82 g, 120 mmol, 0.2 equiv), and TBSCl (15.56 g, 100 mmol, 1.4 equiv) were added sequentially. The reaction mixture was heated to 60 °C. After 7 hours, the reaction mixture was cooled to room temperature, then filtered through cotton and sand. Sat. aq. NaHCO₃ (200 mL) was added, and the mixture was extracted with a 1:1 solution of Et₂O in hexane (200 mL x 3), followed by hexane (100 mL x 2). The organic layers were washed with brine (4 x 100 mL), separated, dried with Na₂SO₄, filtered, and concentrated under reduced pressure. The compound was flushed through a silica plug, eluting with EtOAc. The solution was concentrated, producing a colorless oil (18.0 g, 95% yield).

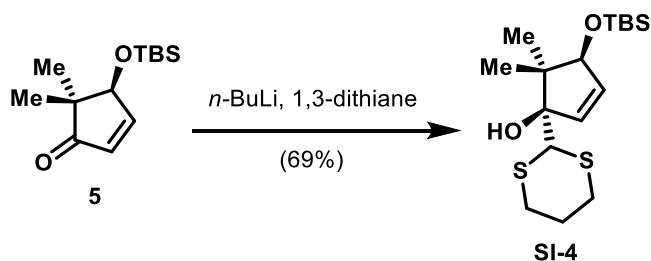
The characterization data are consistent with those reported in the literature.³



Enone 5:

Ketone **SI-3** (12.1 g, 49.6 mmol) was dissolved in DMSO (500 mL, 0.1 M). IBX (42.4 g, 149 mmol, 3.0 equiv) was added, followed by NMO (17.4, 149 mmol, 3.0 equiv). The reaction apparatus was heated to 80 °C. After 12 hours, the reaction was cooled to 0 °C and ½ sat. aq. NaHCO₃ (300 mL) was added. EtOAc was added, then the reaction mixture was filtered through a fritted funnel. The resulting filtrate was extracted with EtOAc (300 mL x 3). The combined organic layers were washed with sat. aq. NaHCO₃ (300 mL), then washed with brine (200 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure by rotary evaporation. Purification by silica plug, flushing with Et₂O, afforded enone **5** (10.0 g, 84%) as a colorless oil.

The characterization data are consistent with those reported in the literature.^{4,5}



Dithiane SI-4:

1,3-dithiane (11.5 g, 98.1 mmol, 3.0 equiv) was dissolved in THF (350 mL, 0.1 M). The solution was cooled to $-78\text{ }^{\circ}\text{C}$, then *n*-butyllithium (2.5 M in hexanes, 41 mL, 98.1 mmol, 3.0 equiv) was added. After 45 minutes of stirring at $-78\text{ }^{\circ}\text{C}$, the reaction mixture was warmed to $-40\text{ }^{\circ}\text{C}$ and stirred for 1.5 hours. The reaction mixture was cooled back to $-78\text{ }^{\circ}\text{C}$, and ketone **5** (8.0 g, 32.8 mmol, 1.0 equiv) was added as a solution in THF (10 mL). The reaction mixture was slowly warmed to $0\text{ }^{\circ}\text{C}$. After 4.5 hours, the reaction was quenched by addition of sat. aq. NH_4Cl (200 mL). The aqueous layer was extracted with EtOAc (150 mL \times 3) and the combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure by rotary evaporation. Purification by flash column chromatography on silica gel (hexanes \rightarrow 20% CH_2Cl_2 /hexanes) afforded dithiane **SI-4** (8.11 g, 69%) as a colorless oil.

$R_f = 0.54$ (75% Et_2O in hexanes; UV-active, stains brown in *p*-anisaldehyde);

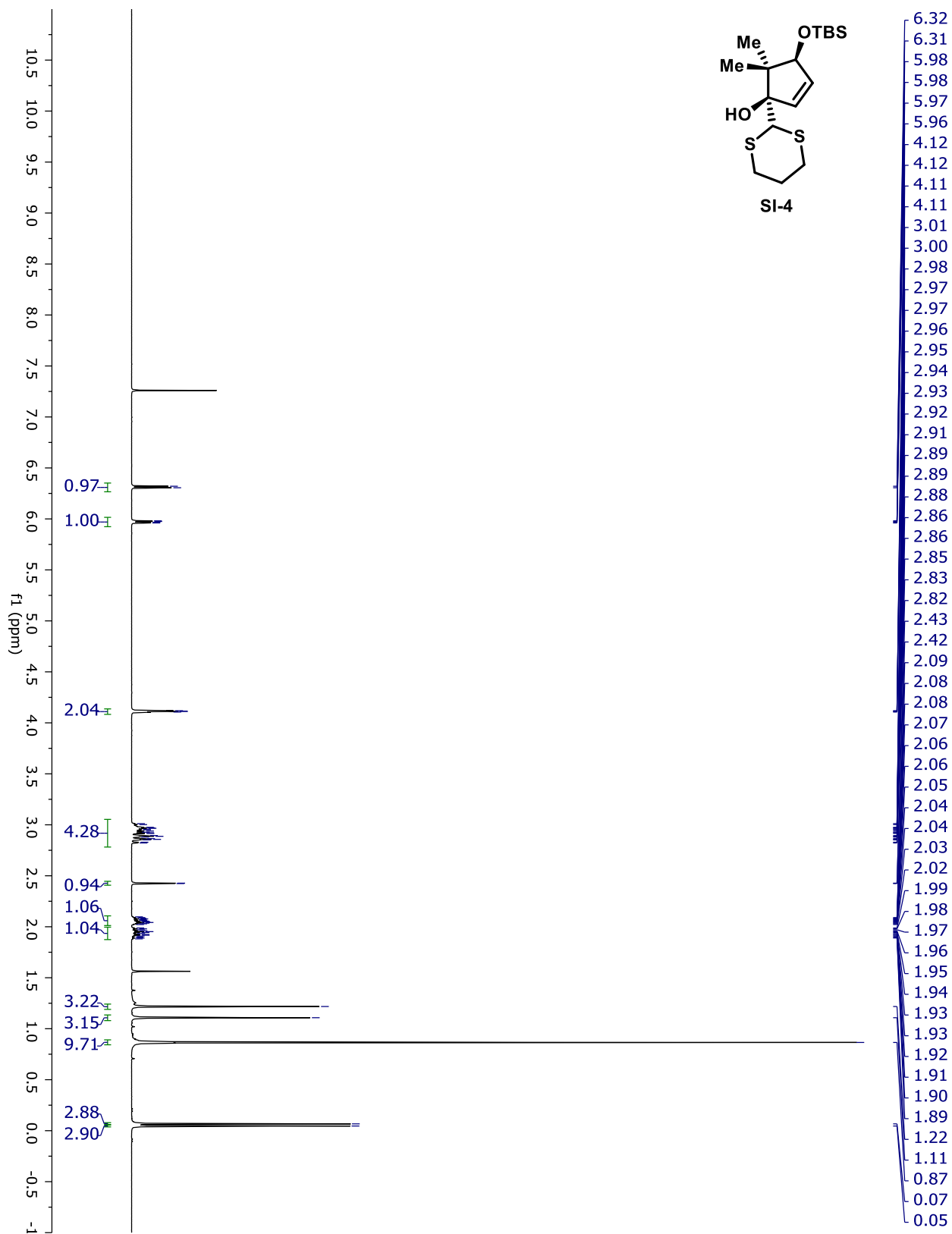
$[\alpha]_D^{25.0}$: 75.4° (*c* 1.0, CHCl_3);

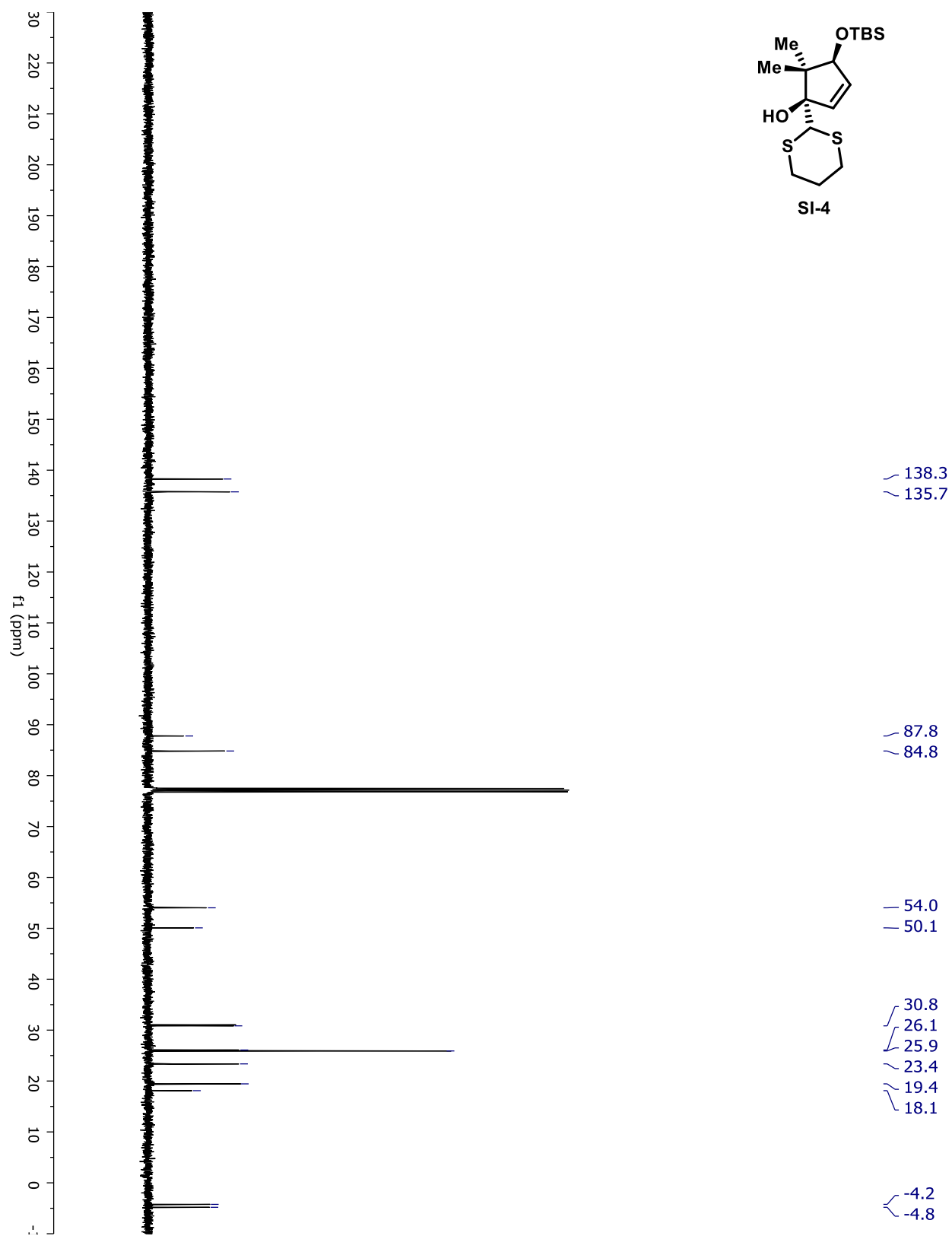
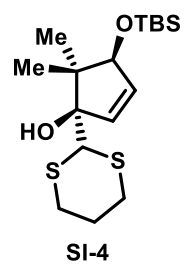
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 6.31 (d, $J = 5.9\text{ Hz}$, 1H), 5.97 (dd, $J = 5.9, 2.4\text{ Hz}$, 1H), 4.12 – 4.10 (m, 2H), 3.03 – 2.81 (m, 4H), 2.43 (d, $J = 1.5\text{ Hz}$, 1H), 1.22 (s, 1H), 1.11 (s, 1H), 0.87 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H).

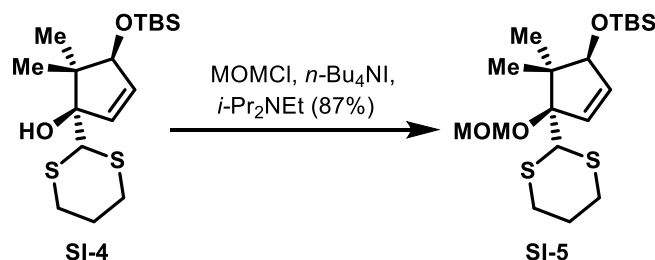
$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 138.3, 135.7, 87.8, 84.8, 54.0, 50.1, 30.8, 26.1, 25.9, 23.4, 19.4, 18.1, -4.2, -4.8.

IR (cm^{-1}): 3505, 2954, 2929, 2896, 2856, 1471, 1384, 1362, 1252, 1136, 1066, 1004, 864, 836, 776, 670;

ESI-HRMS (m/z): $[\text{M}+\text{Na}]^+$ calc'd for $\text{C}_{17}\text{H}_{32}\text{NaO}_2\text{S}_2\text{Si}^+$: 383.1505; found: 383.2195.







MOM-protected dithiane SI-5:

Dithiane **SI-4** (8.55 g, 23.7 mmol, 1.0 equiv) was dissolved in THF (120 mL, 0.2 M) in a flask equipped with a reflux condenser. *i*-Pr₂NEt (25 mL, 142 mmol, 6.0 equiv) was added, followed by *n*-Bu₄NI (5.28 g, 14.3 mmol, 0.6 equiv) and chloromethyl methyl ether (9.0 mL, 5.0 equiv). The reaction mixture was heated to 80 °C and stirred for 12 hours. The reaction mixture was then cooled to 23 °C, followed by addition of NaHCO₃ (120 mL). The aqueous layer was extracted with EtOAc (30 mL × 4) and the combined organic layers were washed with brine (200 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure by rotary evaporation. Purification by flash column chromatography on silica gel (hexanes → 20% Et₂O/hexanes) afforded MOM-protected dithiane **SI-5** (8.38 g, 87%) as a colorless oil.

R_f = 0.40 (25% Et₂O in hexanes; UV-active, stains yellow-brown in *p*-anisaldehyde);

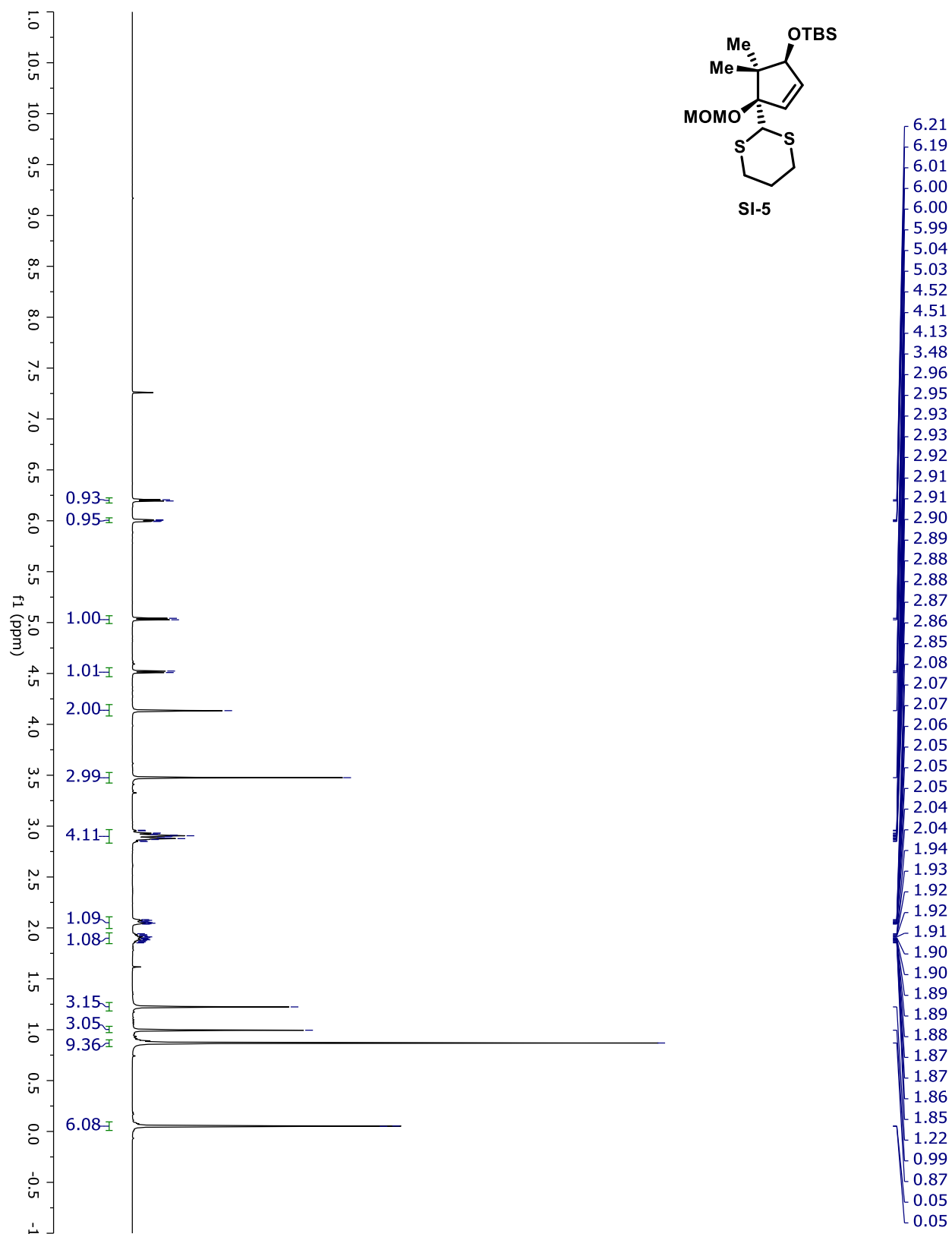
[α]_D^{20.0}: −6.9 ° (*c* 1.0, CHCl₃);

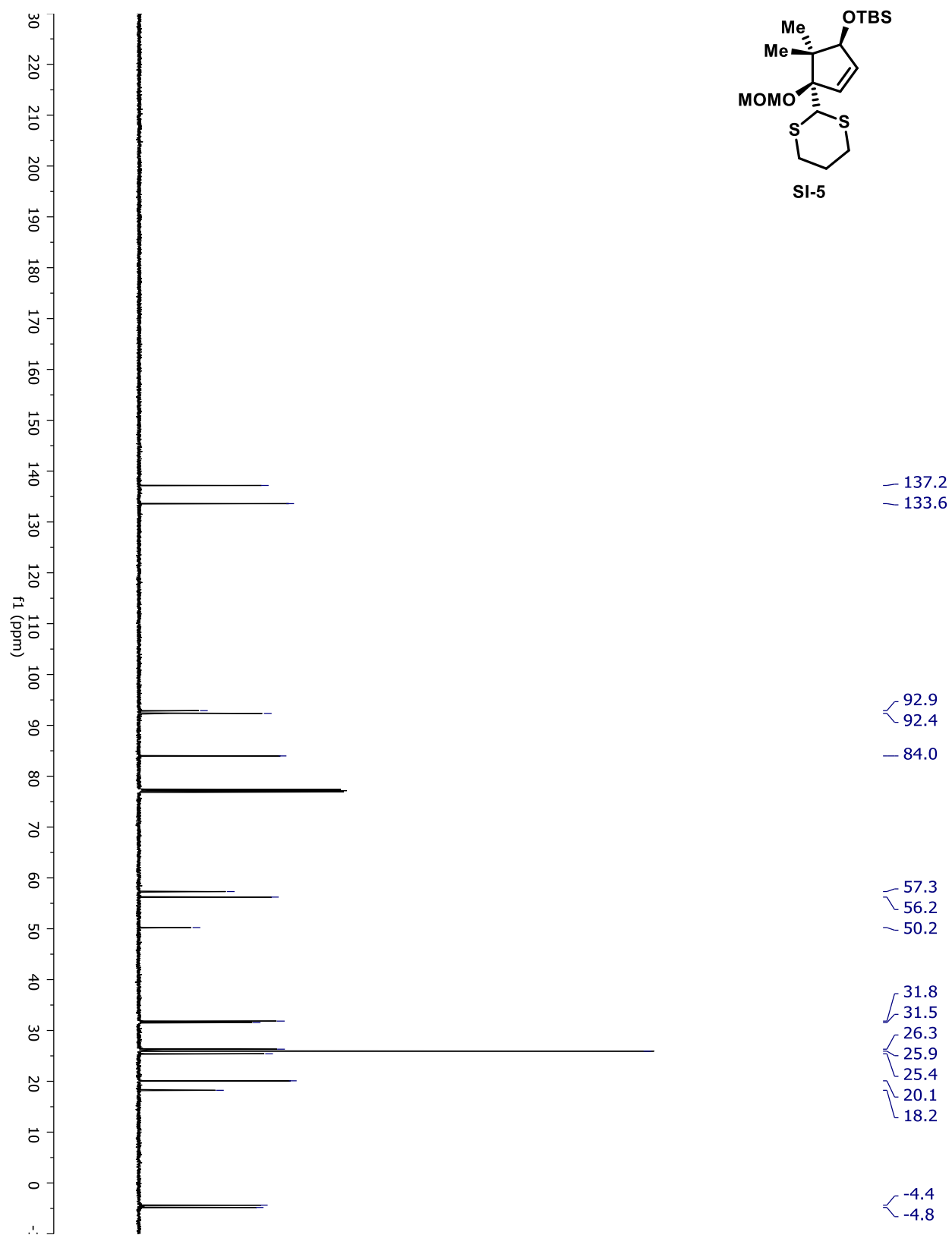
¹H NMR (500 MHz, CDCl₃) δ 6.20 (d, *J* = 6.0 Hz, 1H), 6.00 (dd, *J* = 6.0, 2.1 Hz, 1H), 5.03 (d, *J* = 7.4 Hz, 1H), 4.52 (d, *J* = 7.4 Hz, 1H), 4.13 (s, 1H), 3.48 (s, 2H), 2.98 – 2.83 (m, 3H), 2.09 – 2.03 (m, 1H), 1.95 – 1.85 (m, 1H), 1.22 (s, 3H), 0.99 (s, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.05 (s, 4H);

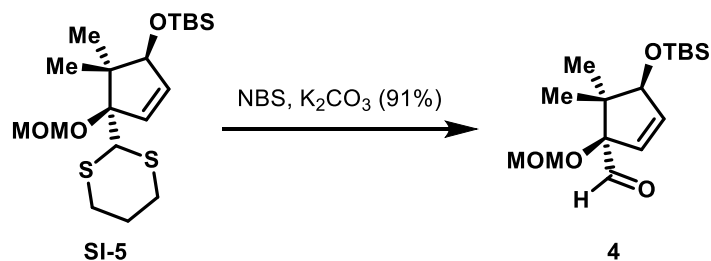
¹³C NMR (126 MHz, CDCl₃) δ 137.2, 133.6, 92.9, 92.4, 84.0, 57.3, 56.2, 50.2, 31.8, 31.5, 26.3, 25.9, 25.4, 20.1, 18.2, −4.4, −4.8;

IR (cm^{−1}): 2953, 2929, 2891, 2856, 1471, 1362, 1252, 1156, 1137, 1091, 1068, 1021, 961, 920, 872, 835, 775, 669;

ESI-HRMS (*m/z*): [M+Na]⁺ calc'd for C₁₉H₃₆NaO₃S₂Si⁺: 427.1767; found: 427.1767.







Aldehyde 4:

Freshly crystallized *N*-bromosuccinimide⁶ (4.37 g, 24.5 mmol, 6.6 equiv) was dissolved in MeCN (36 mL).⁷ A solution of K₂CO₃* (6.55 g, 47.4 mmol, 12.8 equiv) in water (11 mL) was added, and the reaction flask was cooled to −10 °C. A solution of dithiane **SI-5** (1.50 g, 3.70 mmol, 1.0 equiv) in MeCN (7 mL, 0.07 M) was added. The resulting mixture was stirred at −10 °C for 1 hour. Sat. aq. Na₂SO₃ (50 mL) was added. The aqueous layer was extracted with EtOAc (50 mL × 3) and the combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure by rotary evaporation. The resulting solid was suspended in hexanes (100 mL) and filtered through a fritted funnel. The resulting solution was concentrated under reduced pressure by rotary evaporation. The resulting oil was purified by SiO₂ plug, flushing with 20% Et₂O/hexanes to produce aldehyde **4** (1.06 g, 91% yield) as a light yellow oil.

*Complete dissolution of K₂CO₃ is necessary for the success of the reaction.

R_f = 0.51 (20% Et₂O in hexanes; not UV-active, stains pink in *p*-anisaldehyde);

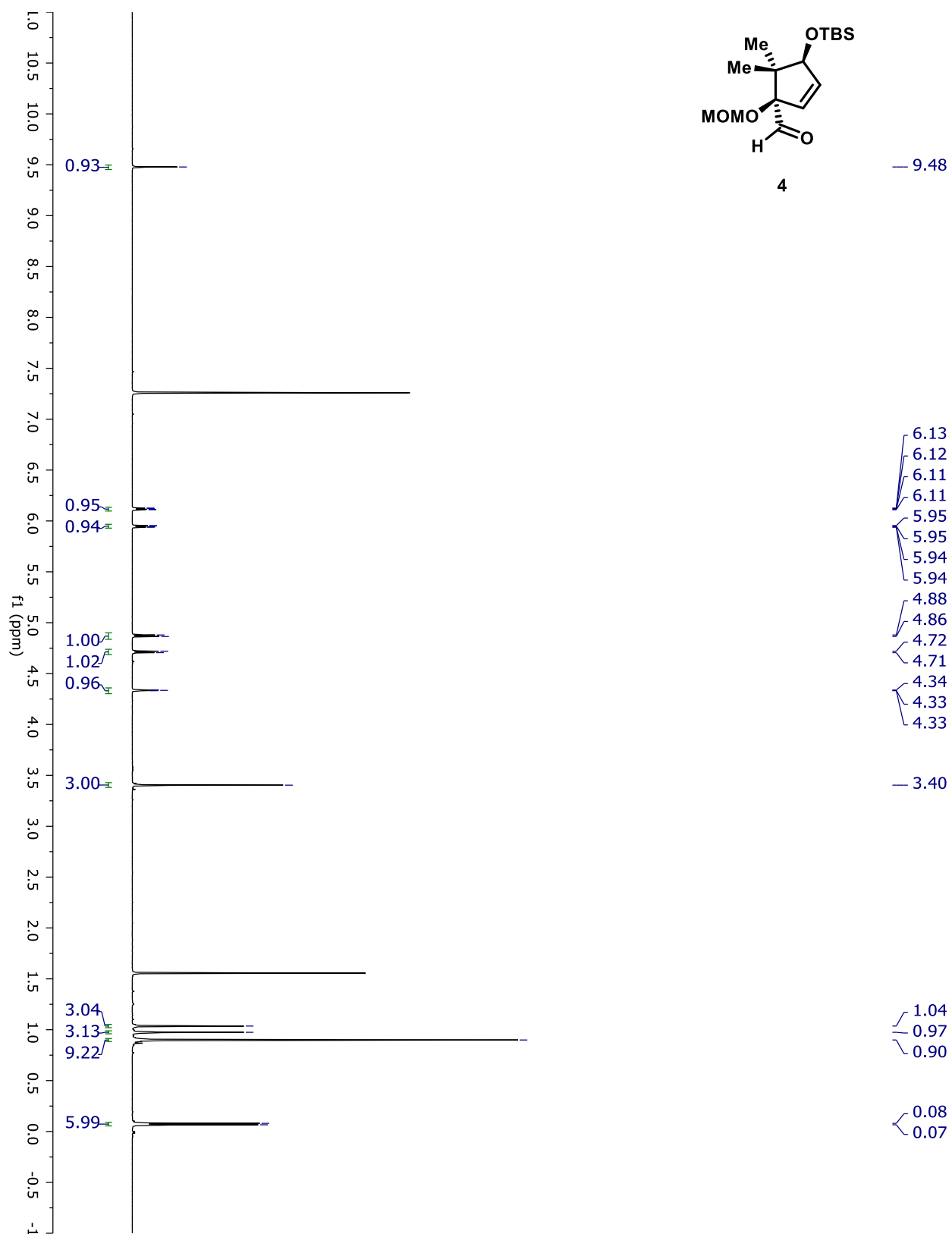
[α]_D^{20.0} : +208.7 ° (*c* 1.0, CHCl₃);

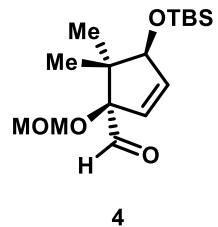
¹H NMR (500 MHz, CDCl₃) δ 9.48 (s, 1H), 6.12 (dd, *J* = 6.1, 1.7 Hz, 1H), 5.95 (dd, *J* = 6.1, 1.4 Hz, 1H), 4.87 (d, *J* = 7.4 Hz, 1H), 4.71 (d, *J* = 7.3 Hz, 1H), 4.33 (t, *J* = 1.6 Hz, 1H), 3.40 (s, 3H), 1.04 (s, 3H), 0.98 (s, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H);

¹³C NMR (151 MHz, CDCl₃) δ 201.8, 140.6, 128.1, 95.7, 93.5, 82.0, 55.8, 53.6, 25.9, 21.6, 18.7, 18.2, −4.4, −4.8;

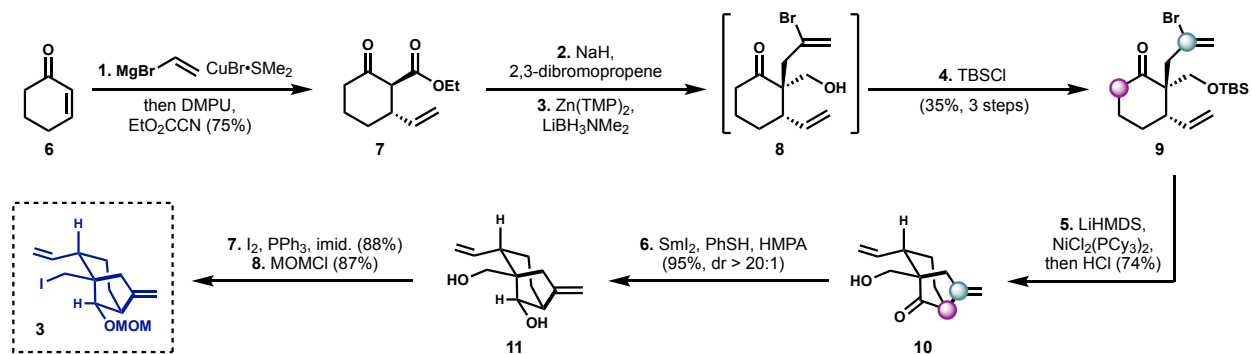
IR (cm^{−1}): 2956, 2930, 2887, 2857, 1732, 1471, 1388, 1362, 1253, 1217, 1148, 1099, 1039, 1026, 1006, 938, 920, 872, 836, 775, 727, 670;

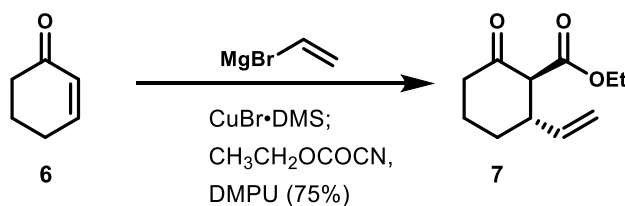
ESI-HRMS (*m/z*): [M+Na]⁺ calc'd for C₁₆H₃₀NaO₄Si⁺: 337.1806; found: 337.1775.





Synthetic route towards the bicyclo[3.2.1]octane fragment





β-keto ester 7:

In a 2-L flask, CuBr·SMe₂ (7.5 g, 36 mmol, 0.1 equiv) was suspended in THF (70 mL; 0.6 M, total) and cooled to −50 °C. Vinylmagnesium bromide solution (1.0 M in THF, 400 mL, 400 mmol, 1.1 equiv) was added to the reaction via addition funnel over 40 minutes. After 20 minutes, the reaction flask was cooled to −72 °C. Cyclohexenone (35.2 mL, 264 mmol, 1.0 equiv) was added after 10 minutes. After 2 hours of stirring, freshly distilled DMPU (112 mL, 928 mmol, 3.5 equiv) was added, followed by ethyl cyanoformate (39.5 mL, 400 mmol, 1.1 equiv). The reaction mixture was allowed to slowly warm to room temperature, and was quenched after 3 hours by addition of H₂O (300 mL). The aqueous layer was extracted with EtOAc (500 mL × 3) and the combined organic layers were washed with brine (500 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure by rotary evaporation. The compound was distilled under reduced pressure to produce product **7** as a colorless oil (53.4 g, 75% yield). The characterization data are consistent with those reported in the literature.⁷

R_f = 0.54, 0.64 (30% EtOAc in hexanes; UV-active, stain pink-purple in *p*-anisaldehyde);

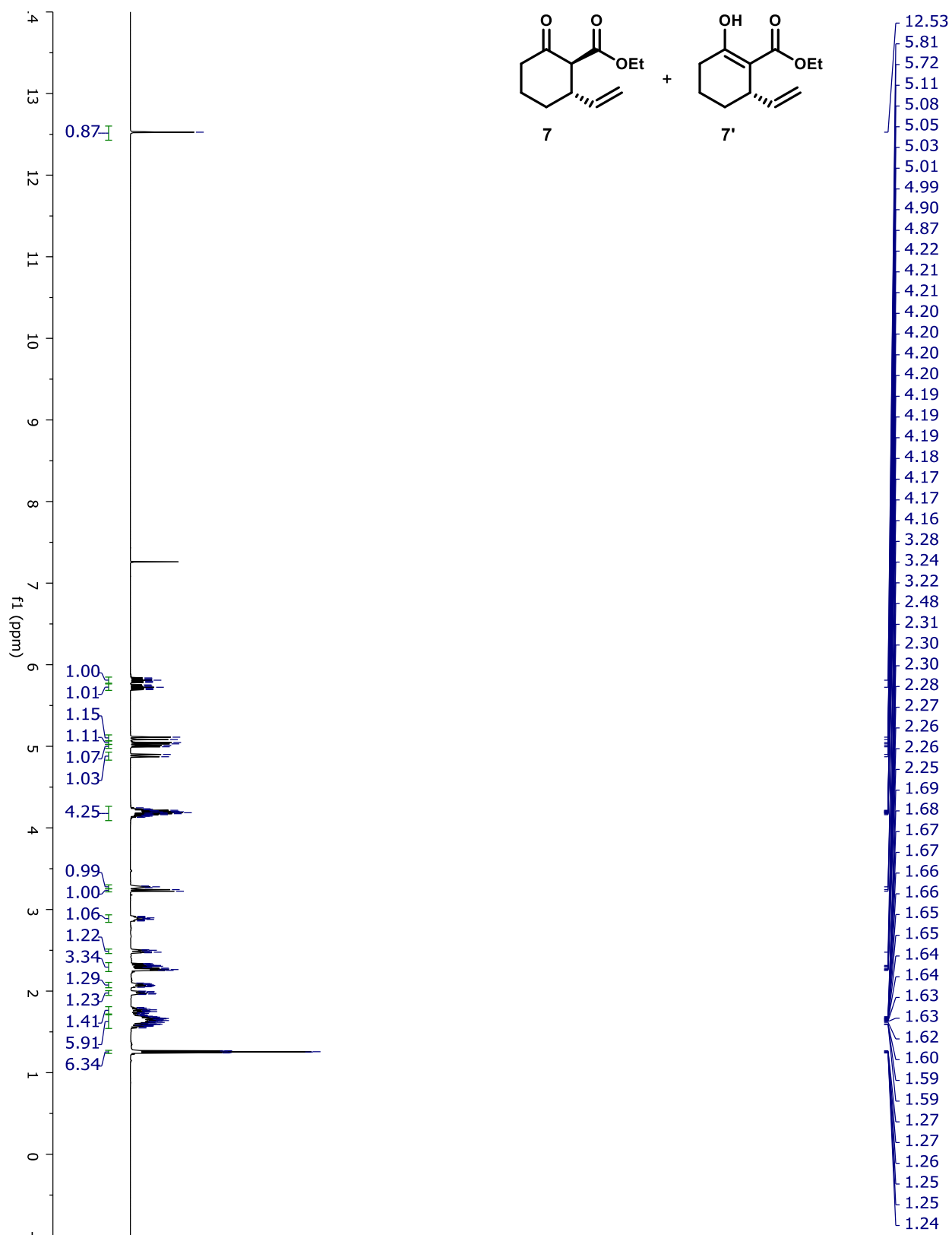
Note: The keto and enol tautomers are present in approximately a 1:1 ratio

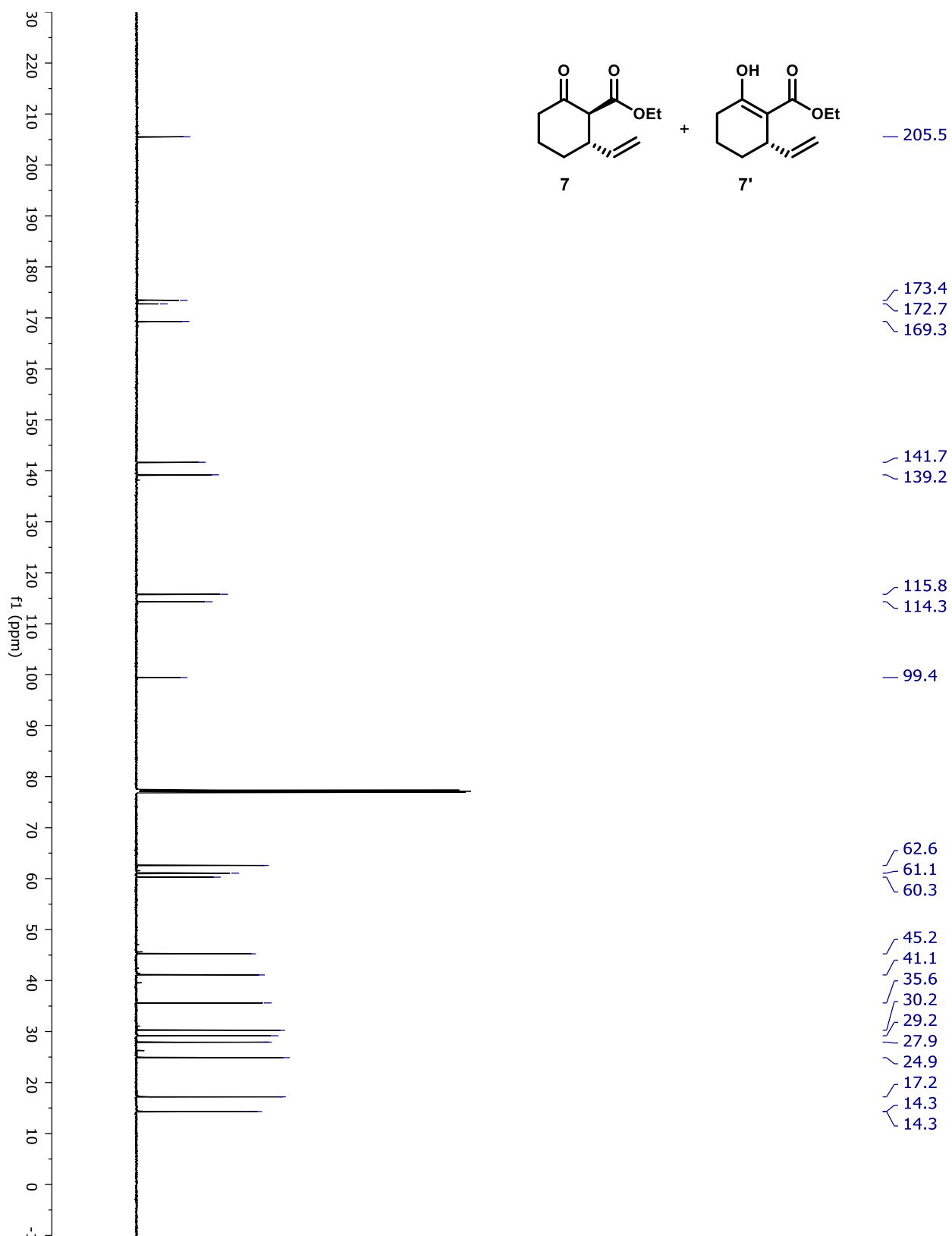
¹H NMR (600 MHz, CDCl₃) δ 12.53 (s, 1H), 5.81 (ddd, *J* = 16.6, 10.3, 6.1 Hz, 1H), 5.72 (ddd, *J* = 17.4, 10.4, 7.3 Hz, 1H), 5.10 (d, *J* = 17.2 Hz, 1H), 5.04 (d, *J* = 10.4 Hz, 1H), 5.00 (d, *J* = 10.2 Hz, 1H), 4.89 (d, *J* = 17.1 Hz, 1H), 4.26 – 4.13 (m, 4H), 3.28 (s, 1H), 3.30 – 3.26 (m, 1H), 3.23 (d, *J* = 11.3 Hz, 1H), 2.89 (tdd, *J* = 11.3, 7.3, 3.9 Hz, 1H), 2.49 (dt, *J* = 14.2, 3.8 Hz, 1H), 2.35 – 2.24 (m, 3H), 2.07 (ddt, *J* = 13.6, 7.1, 3.6 Hz, 1H), 1.98 (dq, *J* = 12.0, 3.5 Hz, 1H), 1.76 (qt, *J* = 13.0, 4.0 Hz, 1H), 1.71 – 1.54 (m, 5H), 1.27 – 1.24 (m, 8H);

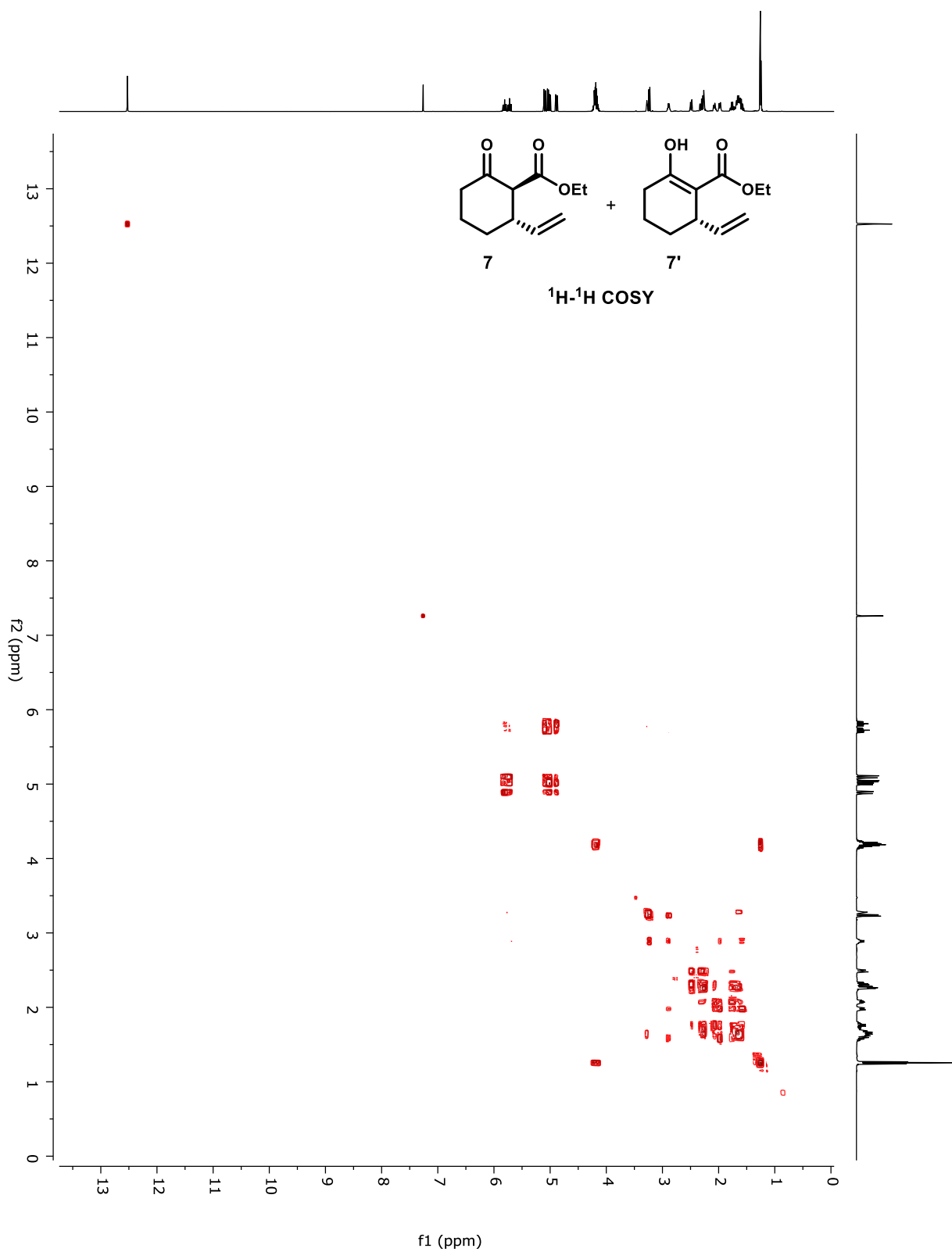
¹³C NMR (151 MHz, CDCl₃) δ 205.5, 173.4, 172.7, 169.3, 141.7, 139.2, 115.8, 114.3, 99.4, 62.6, 61.1, 60.3, 45.2, 41.1, 35.6, 30.2, 29.2, 27.9, 24.9, 17.2, 14.3, 14.3;

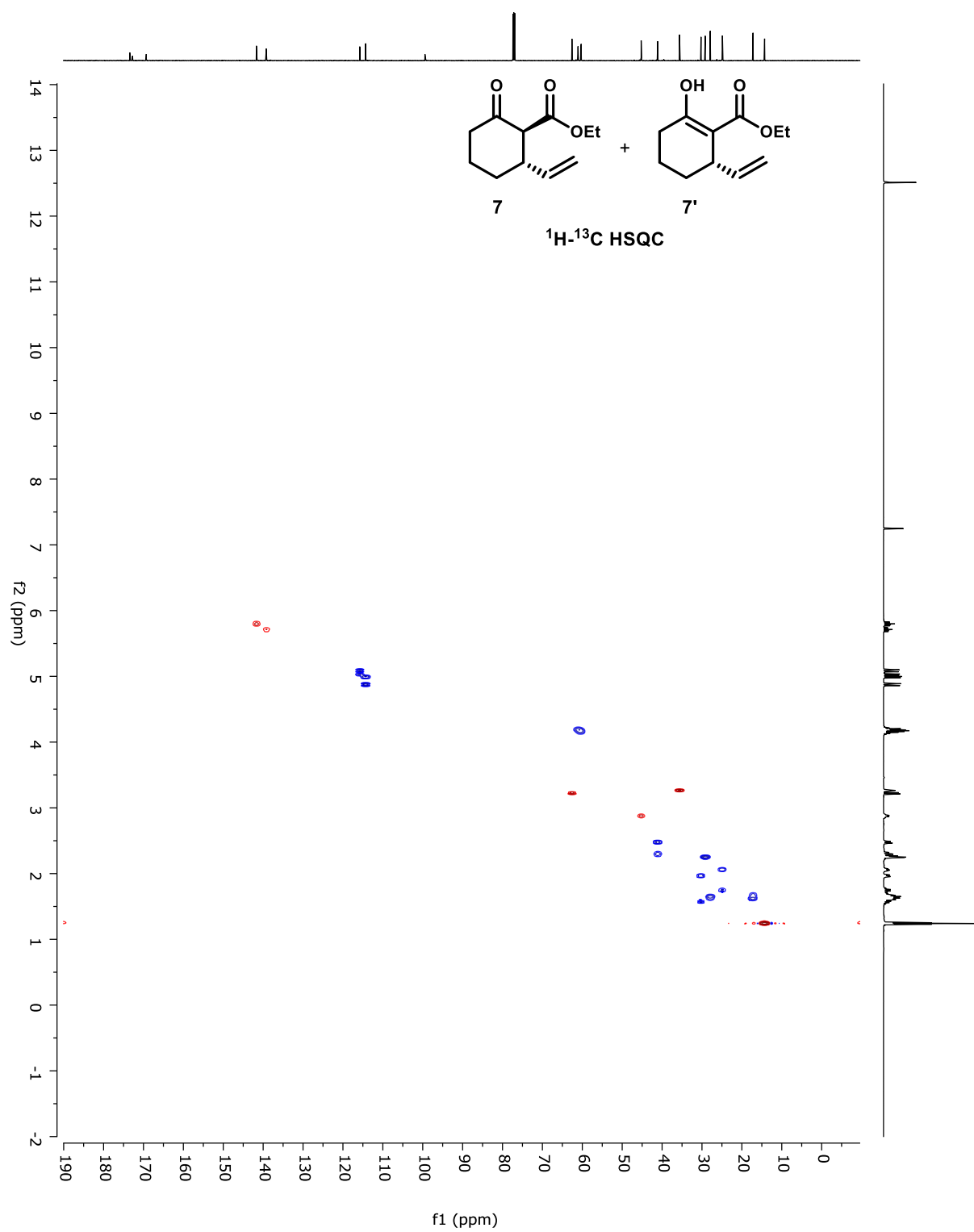
IR (cm^{−1}): 2940, 1745, 1715, 1644, 1612, 1267, 1220, 1091;

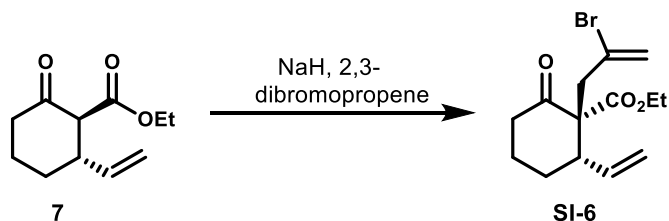
ESI-HRMS (*m/z*): [M+Na]⁺ calc'd for C₁₁H₁₆O₃Na⁺: 219.0992; found: 219.1013.











Allyl β -keto ester SI-6:

Sodium hydride (60% mineral oil dispersion, 0.51 g, 12.8 mmol, 1.3 equiv) was suspended in DMF (25 mL, 0.4 M) and cooled to 0 °C. β -keto ester **7** (2.03 g, 10.3 mmol, 1.0 equiv) was suspended in DMF (2 mL) and added slowly to the suspension of NaH. 2,3-dibromopropene (1.20 mL, 12.2 mmol, 1.2 equiv) was added after one hour. The reaction mixture was allowed to slowly warm to 23 °C over 13 hours. The mixture was then diluted with EtOAc (80 mL) and quenched at 0 °C by addition of sat. aq. NH_4Cl (30 mL). The aqueous layer was extracted with EtOAc (30 mL \times 3) and the combined organic layers were washed with water (100 mL \times 5), brine (150 mL \times 2), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure by rotary evaporation to give **SI-6** (3.14 g). The crude compound was used in the next step without further purification.

A small sample was purified for analysis using flash column chromatography on silica gel (hexanes \rightarrow 5% Et_2O /hexanes), affording allylated β -keto ester **SI-6** as a colorless oil.

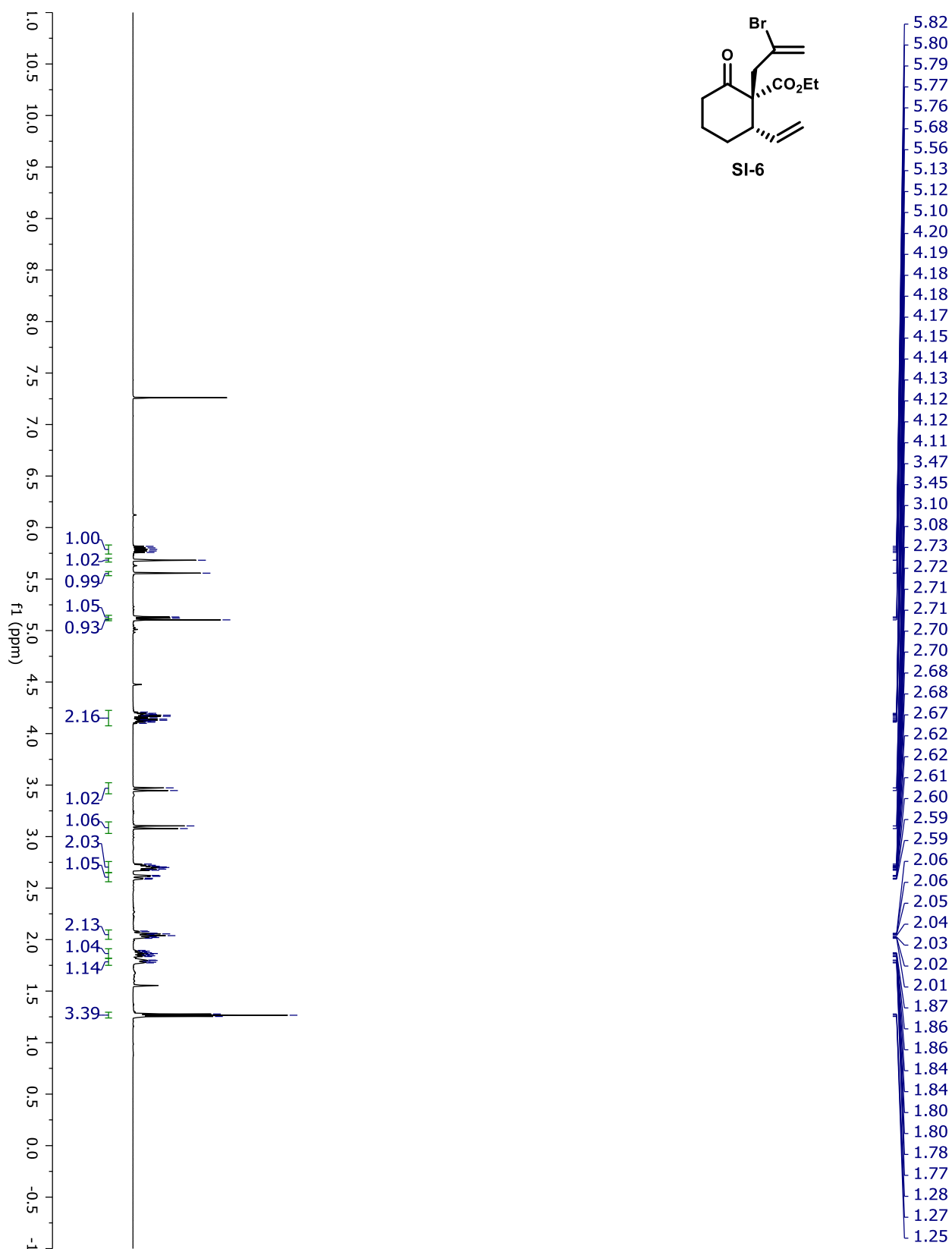
R_f = 0.19 (5% Et_2O in hexanes; UV-active, stains orange in *p*-anisaldehyde);

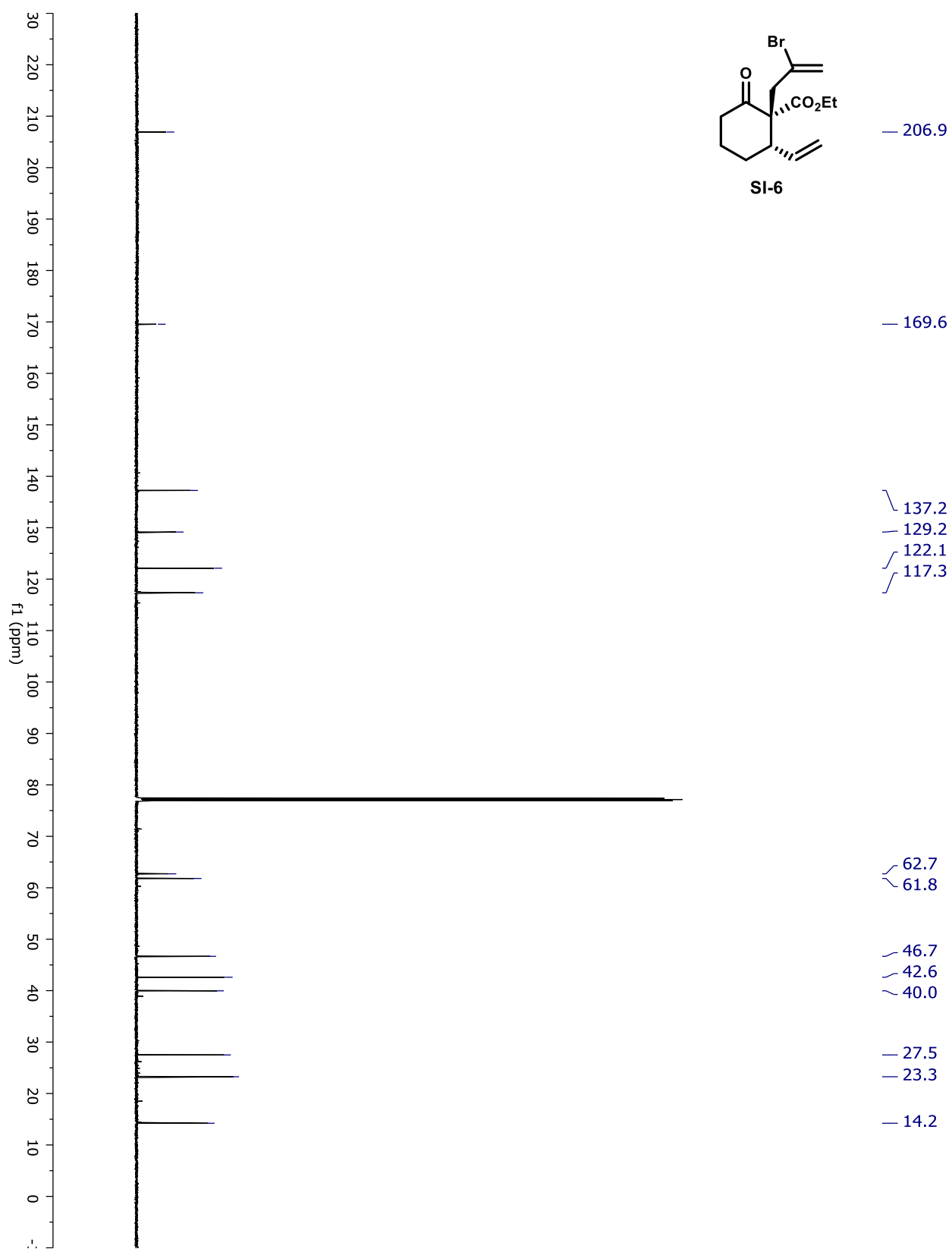
^1H NMR (600 MHz, CDCl_3) δ 5.79 (dt, J = 17.7, 8.5 Hz, 1H), 5.68 (s, 1H), 5.56 (s, 1H), 5.13 (d, J = 6.5 Hz, 1H), 5.10 (s, 1H), 4.22 – 4.09 (m, 2H), 3.46 (d, J = 15.4 Hz, 1H), 3.09 (d, J = 15.4 Hz, 1H), 2.70 (ddd, J = 15.9, 8.0, 4.6 Hz, 2H), 2.63 – 2.57 (m, 1H), 2.11 – 2.00 (m, 2H), 1.86 (ddt, J = 13.1, 8.5, 4.7 Hz, 1H), 1.82 – 1.75 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H);

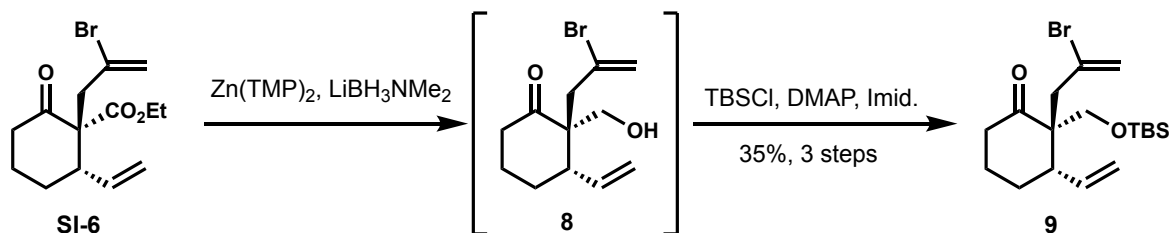
^{13}C NMR (151 MHz, CDCl_3) δ 206.9, 169.5, 137.2, 129.2, 122.1, 117.3, 62.7, 61.8, 46.7, 42.6, 40.0, 27.5, 23.3, 14.2;

IR (cm^{-1}): 2940, 1739, 1707, 1624, 1419, 1227, 1203, 1181, 1020;

ESI-HRMS (m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{14}\text{H}_{20}\text{BrO}_3$: 315.0590; found: 315.0562.







Keto-alcohol 8:

To a 0 °C solution of crude allyl β -keto ester **SI-6** (3.14 g, 9.96 mmol, 1.0 equiv) in THF (100 mL, 0.1 M) was added Zn(TMP)_2 (0.5 M in PhMe, 22 mL, 11 mmol, 1.1 equiv). The solution was allowed to stir at this temperature for 20 min, followed by the addition of $\text{LiBH}_3\text{NMe}_2$ (1.0 M in THF, 10 mL, 9.96 mmol, 1.0 equiv) over the course of 2 min. The mixture was stirred at 0 °C for 45 min and then removed from the ice-water bath and allowed to stir at room temperature for 15 min after which time the reaction was re-cooled to 0 °C using a ice-water bath. The mixture was then *slowly* quenched with sat. aq. NH_4Cl (85 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (200 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure by rotary evaporation to yield an orange oil that was used in the next reaction without purification.

Keto-alcohol **8** (2.91 g, 9.96 mmol, 1.0 equiv) was dissolved in DMF (100 mL, 0.1 M), followed by the addition of imidazole (6.79 g, 100 mmol, 10.0 equiv), DMAP (365 mg, 2.99 mmol, 0.3 equiv) and then TBSCl (7.64 g, 50.1 mmol, 5.0 equiv). The reaction was then transferred to an oil bath pre-heated to 40 °C and allowed to stir at this temperature for 16 hr. The mixture was then diluted with EtOAc (100 mL) and quenched with sat. aq. NaHCO_3 (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (4 x 30 mL). The combined organic extracts were washed with water (3 x 200 mL), brine (2 x 300 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure by rotary evaporation to yield the crude product. The material was purified by flash chromatography on silica gel (hexanes \rightarrow 1% Et_2O /hexanes) to yield ketone **9** as a yellow oil (1.39 g, 35%, 3 steps).

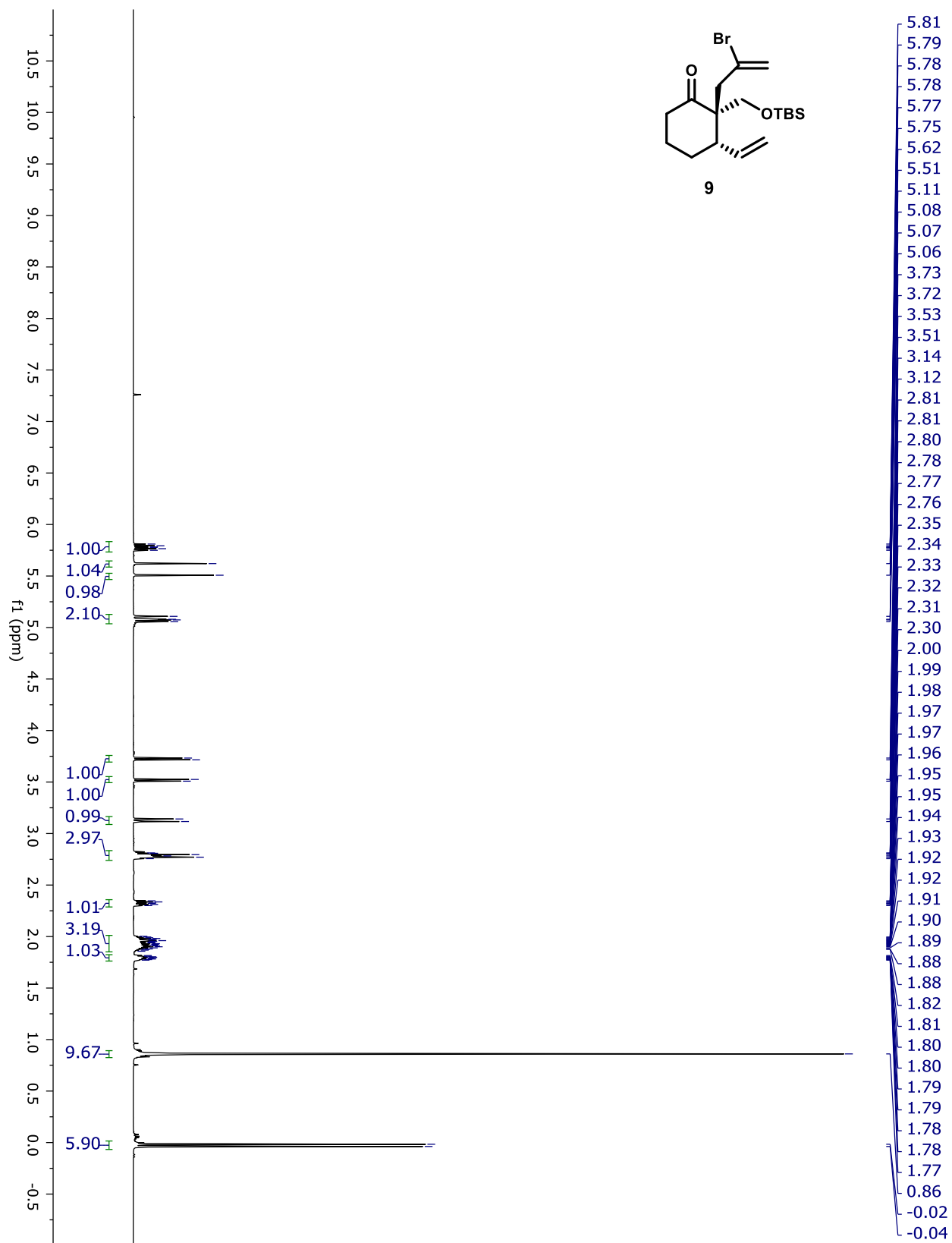
R_f = 0.57 (10% EtOAc in hexanes; not UV-active, stains brown in *p*-anisaldehyde);

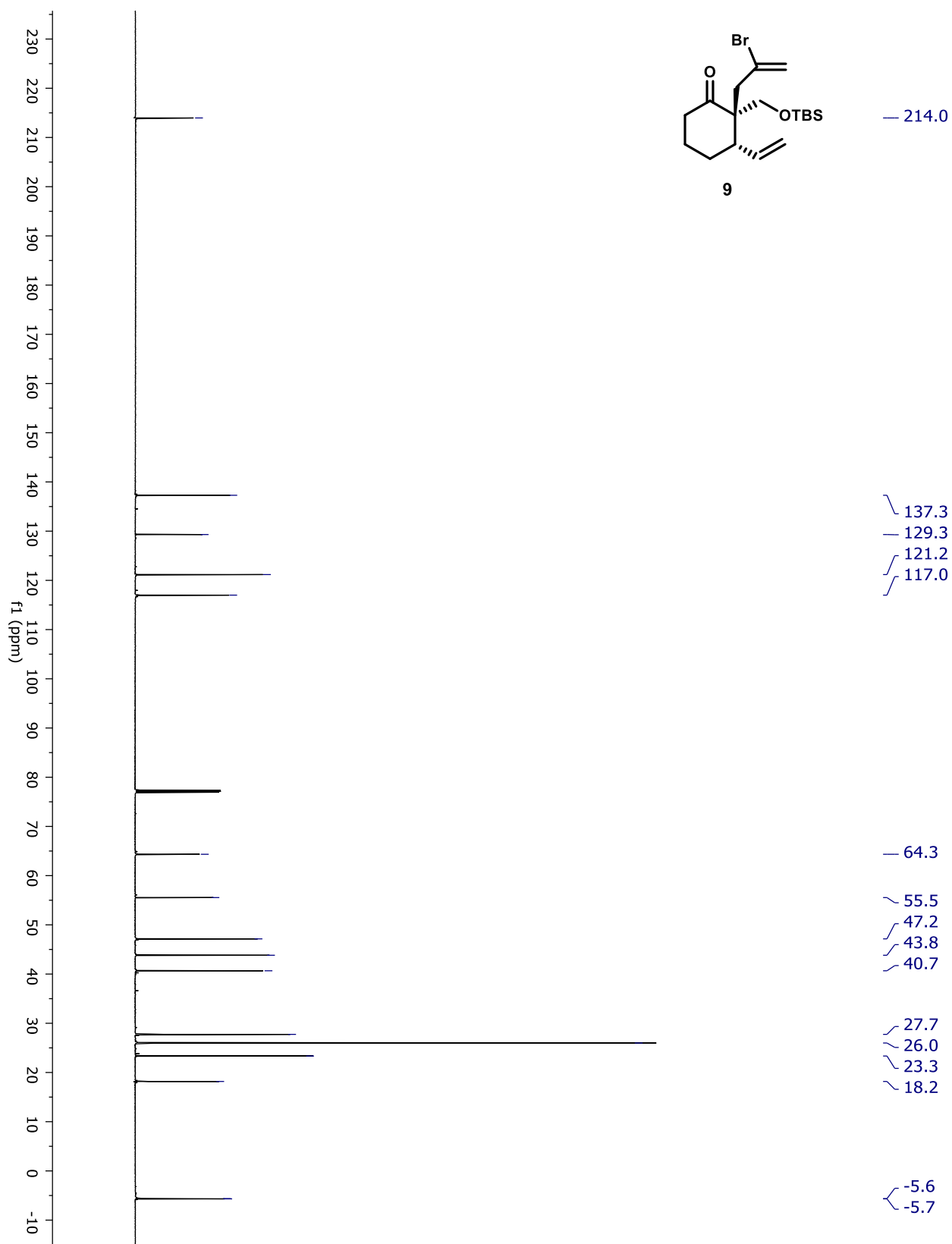
$^1\text{H NMR}$ (600 MHz, CDCl_3) δ 5.78 (dt, J = 17.0, 9.7 Hz, 1H), 5.62 (s, 1H), 5.51 (s, 1H), 5.09 (d, J = 17.0 Hz, 1H), 5.07 (d, J = 10.3 Hz, 1H), 3.72 (d, J = 10.0 Hz, 1H), 3.52 (d, J = 10.0 Hz, 1H), 3.13 (d, J = 14.8 Hz, 1H), 2.84 – 2.75 (m, 2H), 2.78 (d, J = 14.9 Hz, 1H), 2.32 (dt, J = 15.0, 6.4 Hz, 1H), 1.93 (m, 3H), 1.79 (m, 1H), 0.86 (s, 9H), -0.02 (s, 3H), -0.04 (s, 3H);

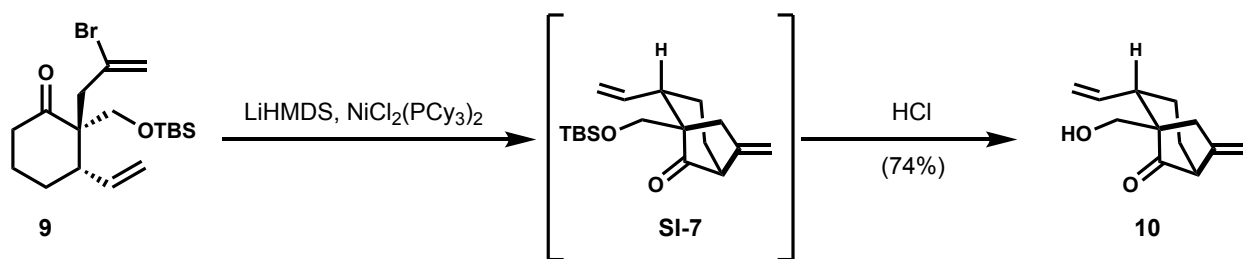
$^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 214.0, 137.3, 129.3, 121.2, 117.0, 64.3, 55.5, 47.1, 43.8, 40.7, 27.7, 26.0, 23.3, 18.2, -5.6, -5.7;

IR (cm^{-1}): 2929, 1703, 1625, 1471, 1257, 978, 1074, 836, 777;

ESI-HRMS (m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{18}\text{H}_{32}\text{BrO}_2\text{Si}^+$: 387.1349; found: 387.1372.







Bicyclo[3.2.1]octane keto-alcohol **10**:

To a $-40\text{ }^{\circ}\text{C}$ solution of **9** (2.31 g, 5.96 mmol, 1.0 equiv) in THF (30 mL, 0.2 M) was added LiHMDS (1.0 M in THF, 11.9 mL, 11.9 mmol, 2.0 equiv) and the resulting solution was stirred for 1 h. $\text{NiCl}_2(\text{PCy}_3)_2$ (1.23 g, 1.78 mmol, 0.3 equiv) was added into the resulting solution at the same temperature. After stirring for 3 min at $-40\text{ }^{\circ}\text{C}$, the mixture was placed into a preheated $50\text{ }^{\circ}\text{C}$ oil bath and stirred for 2 h. After the mixture was cooled down to room temperature, sat. aq. NH_4Cl (25 mL) was added, and the organic phase was separated. The aqueous phase was extracted with EtOAc ($3 \times 25\text{ mL}$) and the combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure by rotary evaporation. THF was added (44 mL) and cooled with an ice-water bath; 6 N HCl (88 mL) was added. The mixture was allowed to slowly warm to room temperature over 1 h, at which time it was diluted with H_2O (50 mL) and Et_2O (50 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O ($3 \times 25\text{ mL}$). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure by rotary evaporation. An identical procedure was followed using an additional batch of material of similar scale (2.82 g, 7.28 mmol) and the two batches were combined before purification by flash column chromatography on silica gel (hexanes/EtOAc = 5:1 \rightarrow 2:1) to afford alcohol **10** (1.88 g, 74%) as a colorless oil.

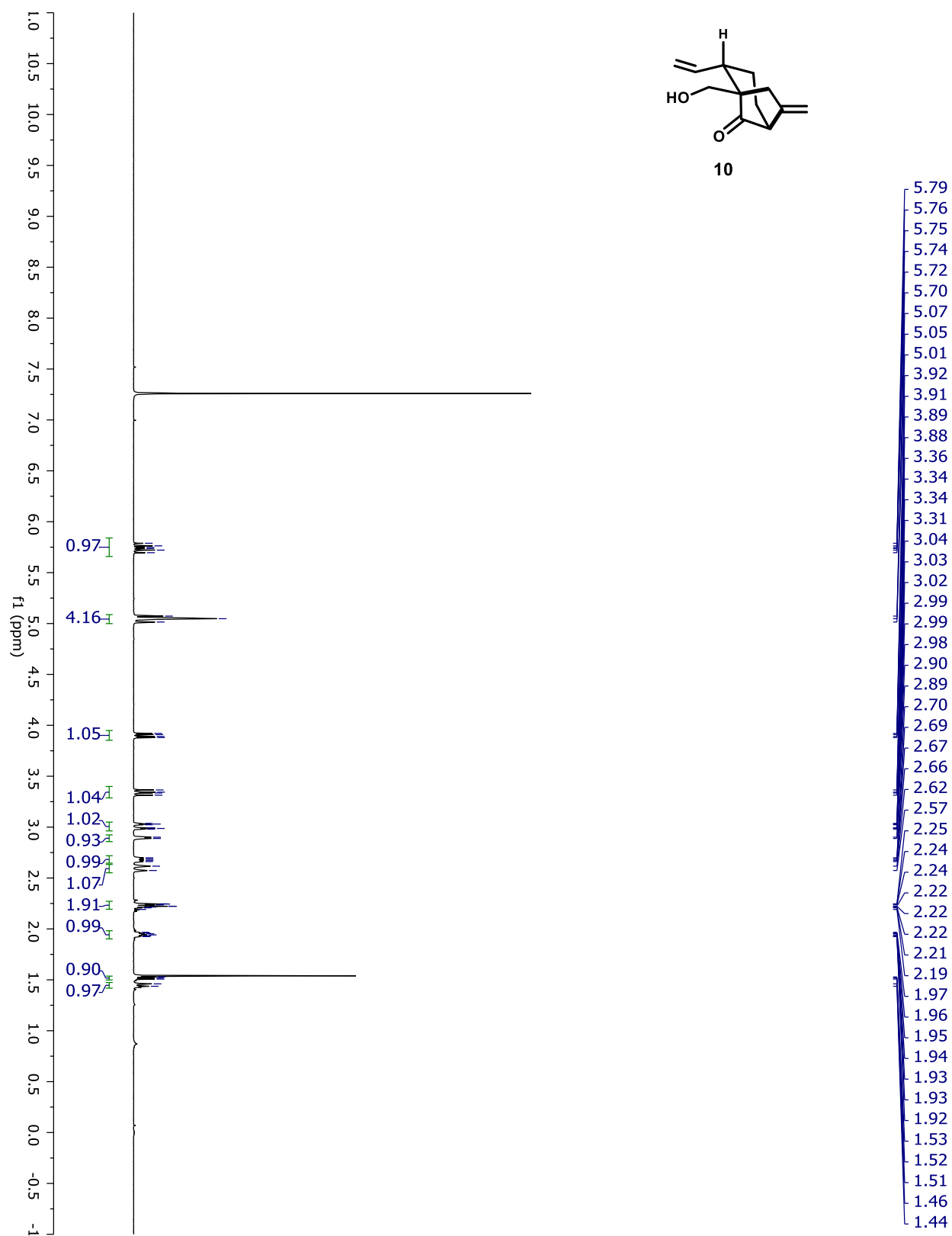
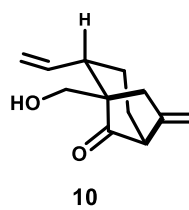
$R_f = 0.35$ (25% EtOAc in hexanes; not UV-active, stains blue in *p*-anisaldehyde);

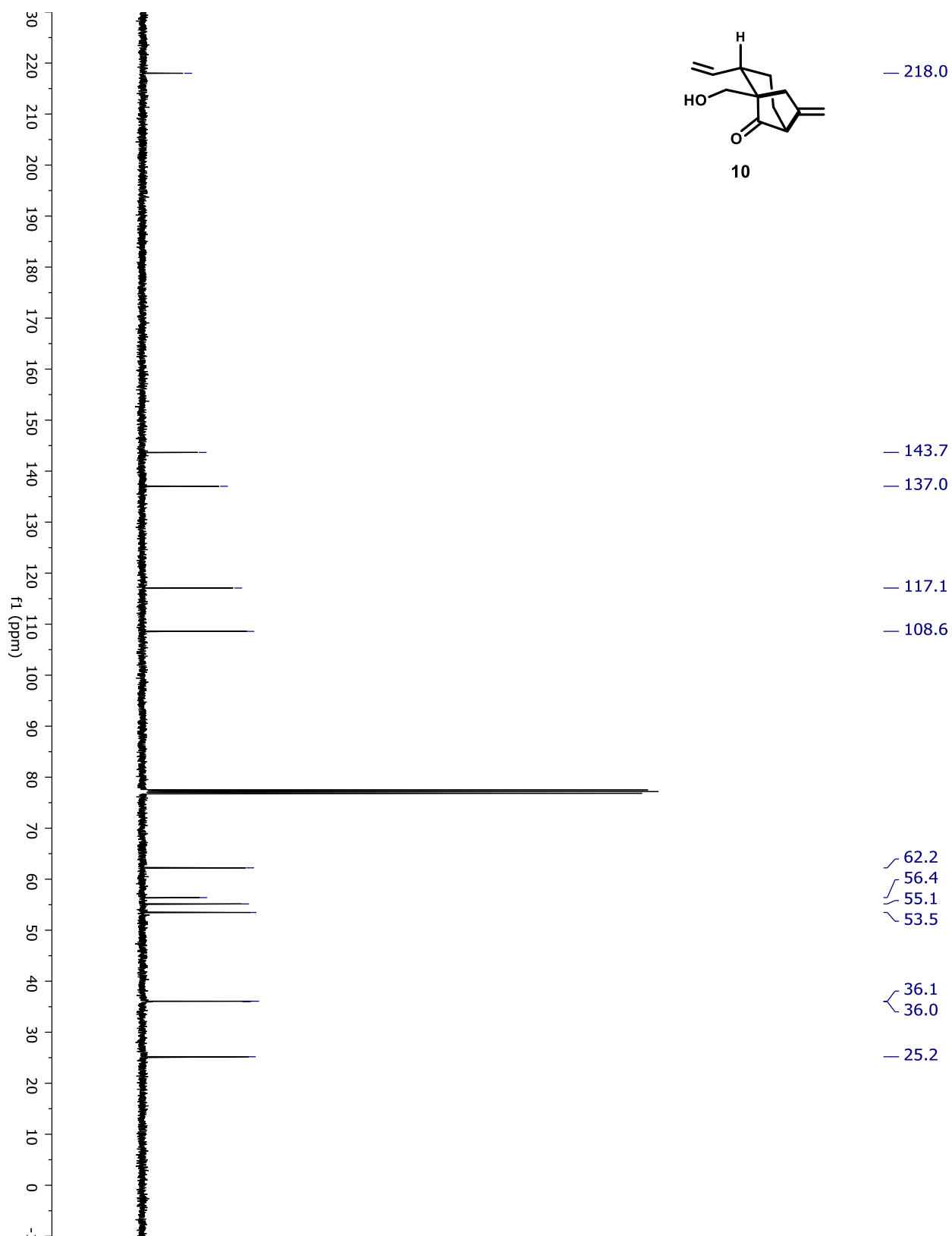
^1H NMR (400 MHz, CDCl_3) δ 5.74 (dt, $J = 16.8, 10.2\text{ Hz}$, 1H), 5.10 – 4.99 (m, 4H), 3.90 (dd, $J = 11.8, 4.4\text{ Hz}$, 1H), 3.34 (dd, $J = 11.8, 8.6\text{ Hz}$, 1H), 3.01 (dt, $J = 17.3, 2.7\text{ Hz}$, 1H), 2.90 (d, $J = 5.0\text{ Hz}$, 1H), 2.68 (dd, $J = 10.0, 4.9\text{ Hz}$, 1H), 2.60 (d, $J = 17.1\text{ Hz}$, 1H), 2.27 – 2.18 (m, 2H), 1.99 – 1.90 (m, 1H), 1.54 – 1.50 (m, 1H), 1.45 (d, $J = 9.5\text{ Hz}$, 1H);

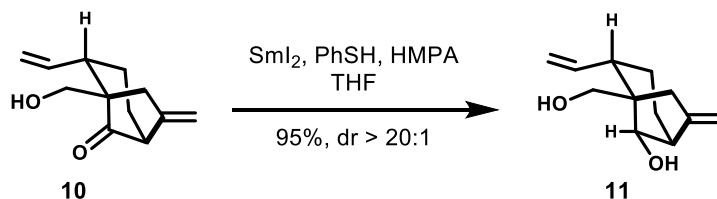
^{13}C NMR (101 MHz, CDCl_3) δ 218.0, 143.7, 137.0, 117.1, 108.6, 62.2, 56.4, 55.1, 53.5, 36.1, 36.0, 25.2;

IR (cm^{-1}): 3434, 2939, 1747, 1659, 1448, 1337, 1178, 1053, 1018, 923, 883;

ESI-HRMS (m/z): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{12}\text{H}_{17}\text{O}_2^+$: 193.1223; found: 193.1228.







Diol **11**:

To a 0 °C solution of keto alcohol **10** (3.65 g, 18.5 mmol) in THF (180 mL, 0.1 M) was subsequently added PhSH (11.4 mL, 111 mmol, 6.0 equiv), HMPA (32 mL, 185 mmol, 10.0 equiv) and SmI_2 (0.1 M in THF, 555 mL, 55.5 mmol, 3.0 equiv). The resulting solution was stirred for 1 h at the same temperature. The reaction was stopped by addition of sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ (300 mL), and diluted with EtOAc (250 mL). The resulting suspension was then filtered through a fritted funnel. The organic layers were separated. The aqueous layer was extracted with EtOAc (3 × 200 mL) and the combined organic layers were washed with brine (400 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure by rotary evaporation. Purification by flash column chromatography on silica gel (15% → 50% EtOAc/hexanes) afforded diol **11** (3.41 g, 95%) as a white solid.

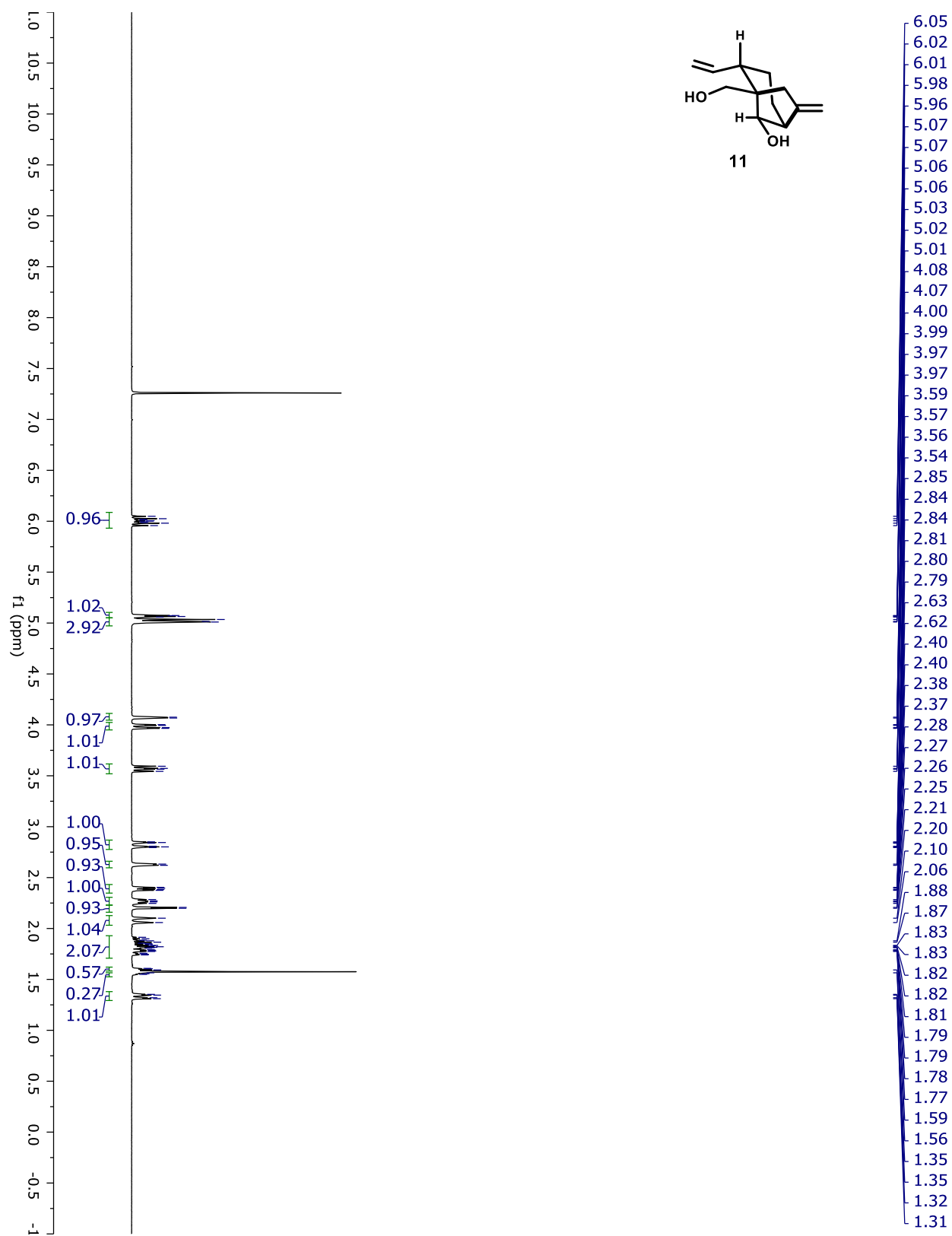
R_f = 0.26 (30% EtOAc in hexanes; not UV-active, stains blue in *p*-anisaldehyde);

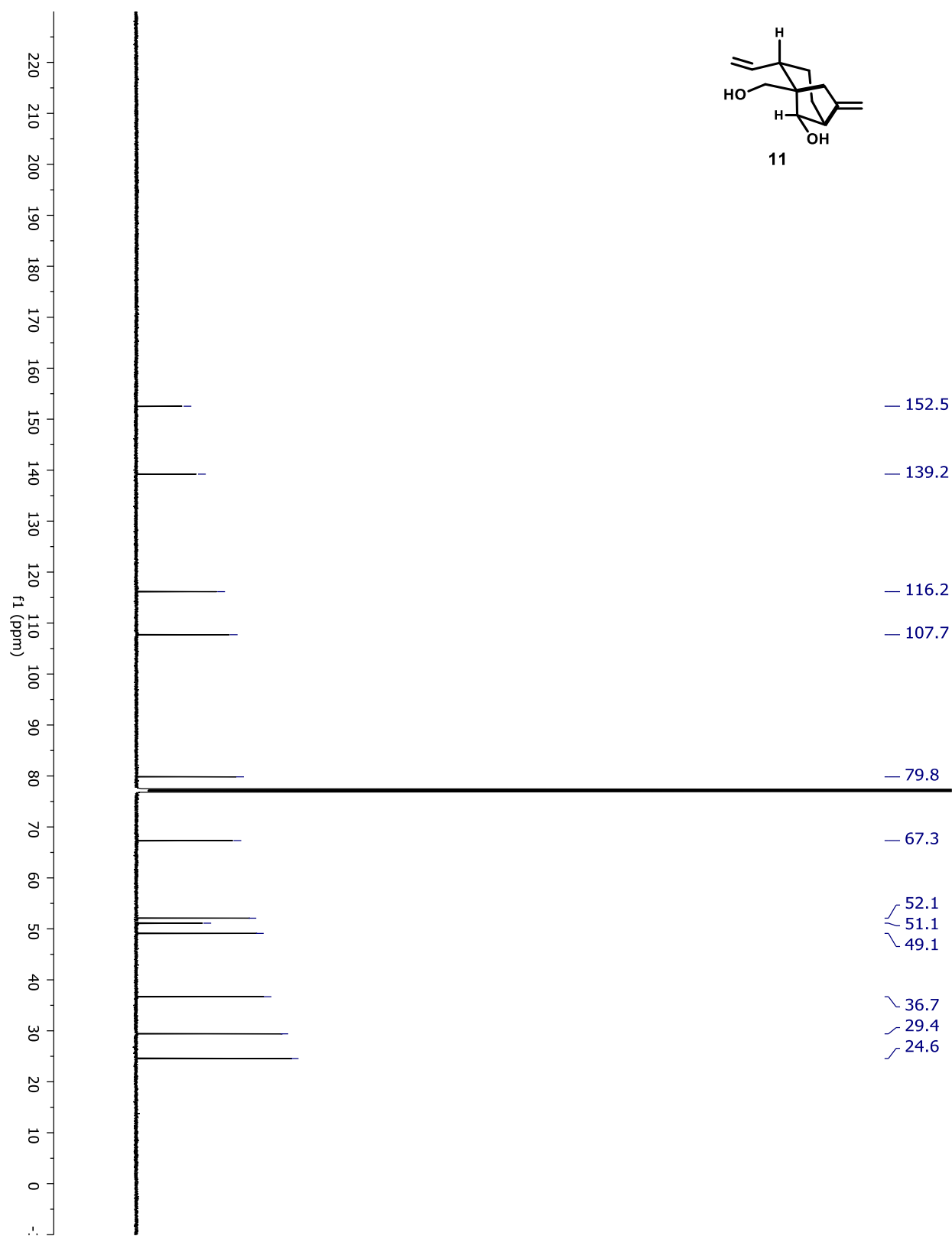
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 6.00 (dt, J = 17.6, 9.6 Hz, 1H), 5.09 – 5.05 (m, 1H), 5.05 – 4.99 (m, 3H), 4.07 (d, J = 2.9 Hz, 1H), 3.98 (dd, J = 11.6, 3.0 Hz, 1H), 3.57 (dd, J = 11.5, 8.5 Hz, 1H), 2.82 (dt, J = 17.1, 2.6 Hz, 1H), 2.63 (d, J = 4.8 Hz, 1H), 2.39 (dd, J = 8.5, 3.1 Hz, 1H), 2.27 (dd, J = 9.4, 5.5 Hz, 1H), 2.20 (d, J = 3.5 Hz, 1H), 2.08 (d, J = 17.1 Hz, 1H), 1.93 – 1.73 (m, 2H), 1.63 – 1.53 (m, 1H), 1.33 (dd, J = 13.1, 3.9 Hz, 1H);

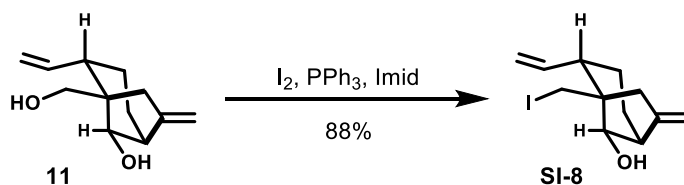
$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 152.6, 139.2, 116.1, 107.7, 79.8, 67.3, 52.1, 51.2, 49.1, 36.7, 29.4, 24.6;

IR (cm^{-1}): 3329, 3070, 2937, 2875, 1661, 1638, 1447, 1135, 1065, 1023, 995, 915, 889;

ESI-HRMS (m/z): $[\text{M}+\text{Na}]^+$ calc'd for $\text{C}_{12}\text{H}_{18}\text{O}_2\text{Na}^+$: 217.1199; found: 217.1207.







Iodo alcohol SI-8:

In a 100-mL flask, diol **11** (1.3 g, 6.7 mmol, 1.0 equiv) was dissolved in $\text{C}_6\text{H}_6/\text{MeCN}/\text{CH}_2\text{Cl}_2$ (27 mL/6.7 mL/6.7 mL, 0.16 M). PPh_3 (3.51 g, 13.4 mmol, 2.0 equiv) was added, followed by imidazole (1.85 g, 27.2 mmol, 4.0 equiv). The resulting mixture was stirred for 15 minutes until a homogeneous solution formed. The reaction flask was then moved to a 0 °C bath and I_2 (2.54 g, 10.0 mmol, 1.5 equiv) was added in seven portions over 15 minutes. The reaction underwent 70% conversion after 21 hours. After a total of 90 hours, the reaction underwent full conversion as determined by TLC, and was quenched with sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$. The organic layer was separated, and the aqueous layer was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure by rotary evaporation. Purification by flash column chromatography on silica gel (hexanes \rightarrow 20% EtOAc/hexanes) afforded iodo alcohol **SI-8** (1.80 g, 88% yield) as a colorless oil.

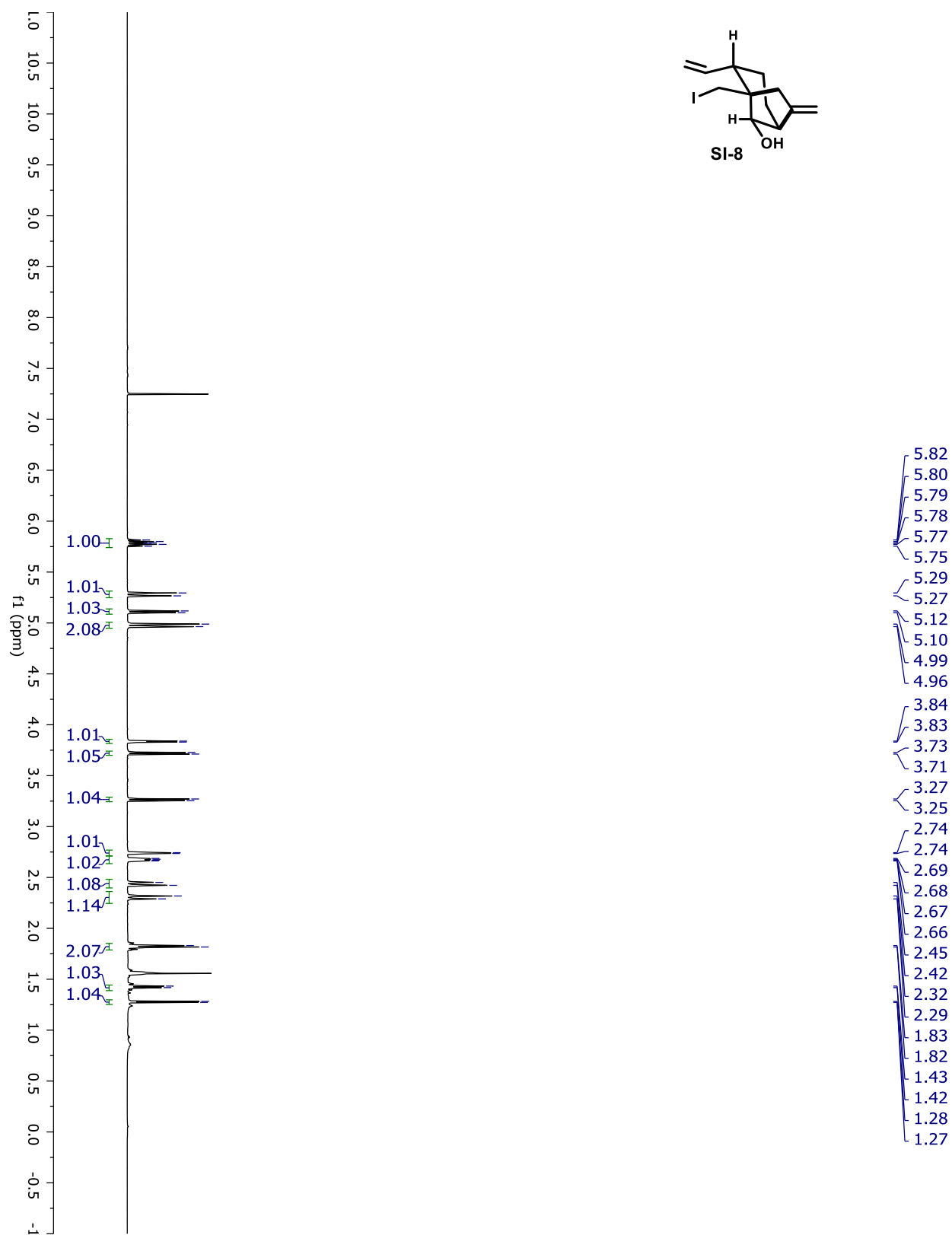
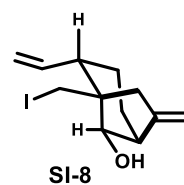
R_f = 0.46 (20% EtOAc in hexanes; UV-active, stains blue in *p*-anisaldehyde);

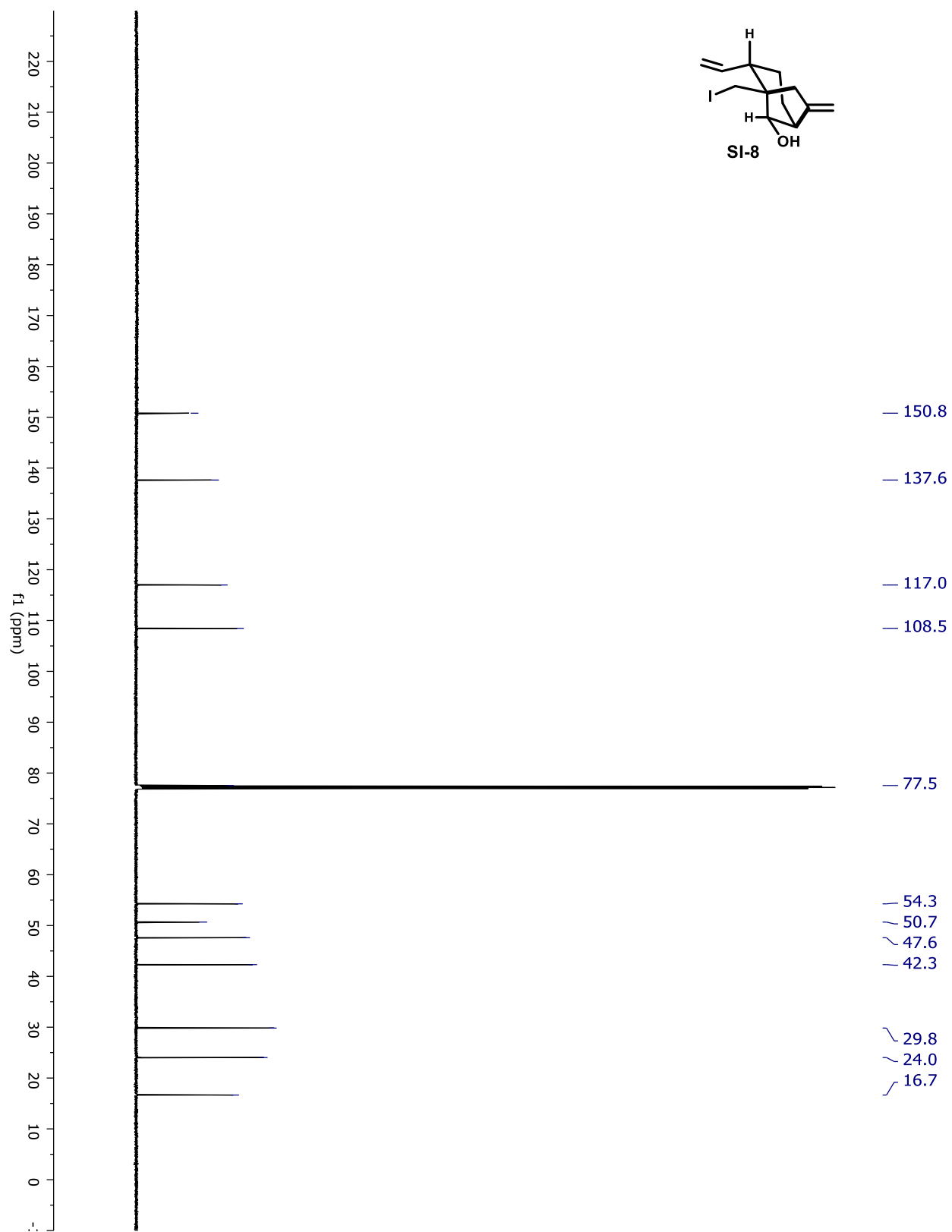
$^1\text{H NMR}$ (600 MHz, CDCl_3) δ 5.79 (dt, J = 17.0, 9.8 Hz, 1H), 5.28 (d, J = 17.0 Hz, 1H), 5.11 (d, J = 10.3 Hz, 1H), 4.98 (d, J = 14.8 Hz, 2H), 3.83 (d, J = 5.6 Hz, 1H), 3.72 (d, J = 9.6 Hz, 1H), 3.26 (d, J = 9.5 Hz, 1H), 2.74 (d, J = 4.8 Hz, 1H), 2.67 (dd, J = 9.5, 4.7 Hz, 1H), 2.44 (d, J = 17.2 Hz, 1H), 2.30 (d, J = 17.2 Hz, 1H), 1.82 (d, J = 8.5 Hz, 2H), 1.59 – 1.54 (m, 1H), 1.43 (d, J = 8.9 Hz, 1H), 1.28 (d, J = 5.6 Hz, 1H);

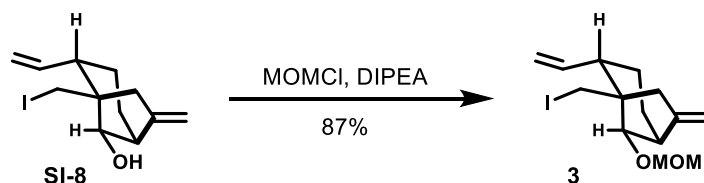
$^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 150.8, 137.6, 117.0, 108.5, 77.5, 54.3, 50.7, 47.6, 42.3, 29.8, 24.0, 16.7;

IR (cm^{-1}): 3373, 3071, 2938, 2856, 1660, 1635, 1424, 1208, 1191, 1046, 997, 923, 892;

GCMS (m/z): $[\text{M}]$ calc'd for $\text{C}_{12}\text{H}_{17}\text{IO}$: 304.0; found: 304.0.







MOM-protected iodo alcohol **3**:

In a 100-mL flask, iodo alcohol **SI-8** (1.8 g, 5.9 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (30 mL, 0.2 M). *N,N*-Diisopropylethylamine (5.4 mL, 30 mmol, 5.0 equiv) was added. The reaction flask was moved to a 0 °C bath, and chloromethyl methyl ether (1.7 mL, 30 mmol, 5.0 equiv) was added. The reaction mixture was allowed to slowly warm to 23 °C. After stirring for 72 hours, the reaction was quenched by addition of sat. aq. NaHCO_3 . The organic layer was separated, and the aqueous layer was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure by rotary evaporation. Purification by flash column chromatography on silica gel (hexanes \rightarrow 5% EtOAc/hexanes) afforded MOM-protected iodo alcohol **3** (1.78 g, 87% yield) as a white solid.

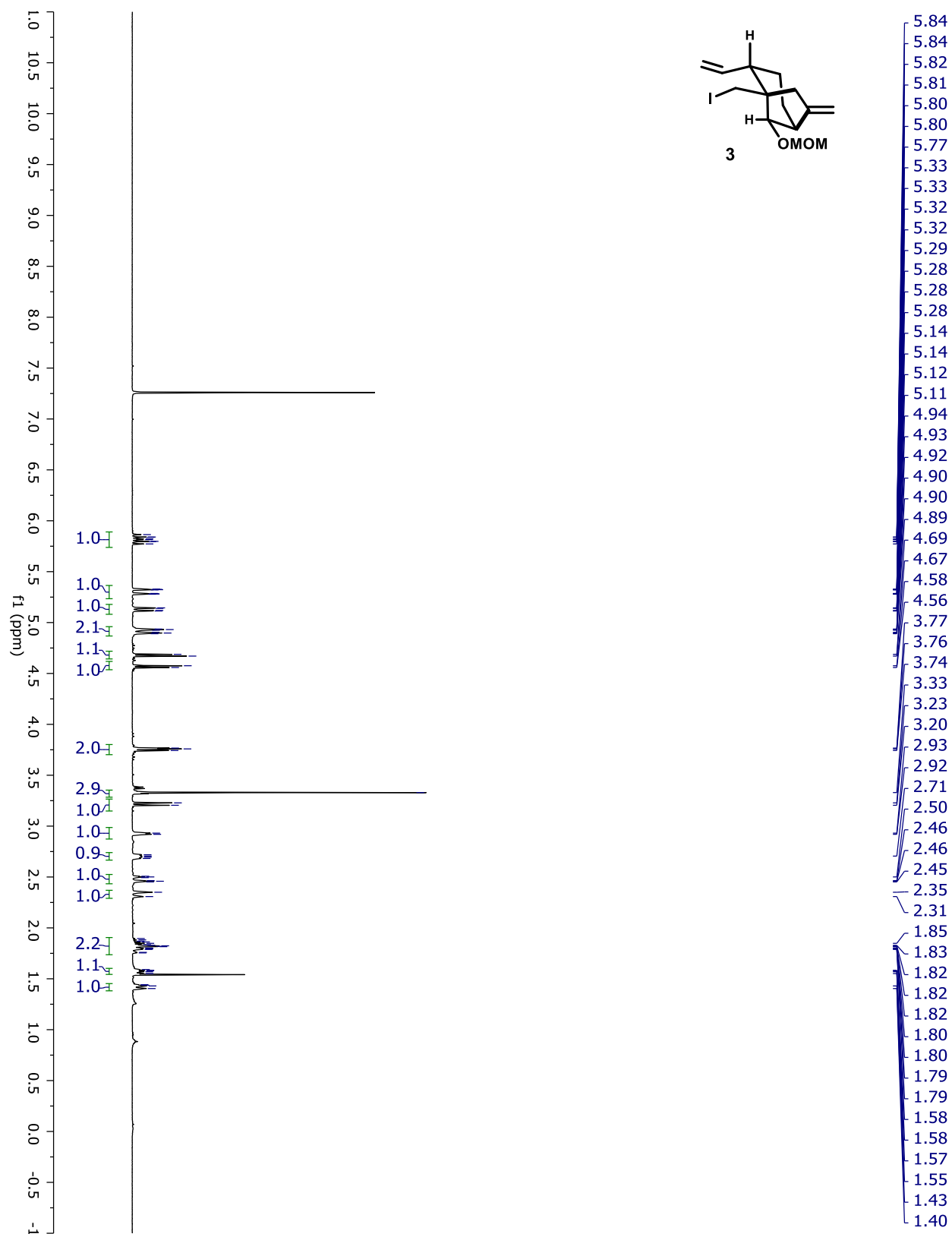
R_f = 0.52 (10% EtOAc in hexanes; not UV-active, stains blue in *p*-anisaldehyde);

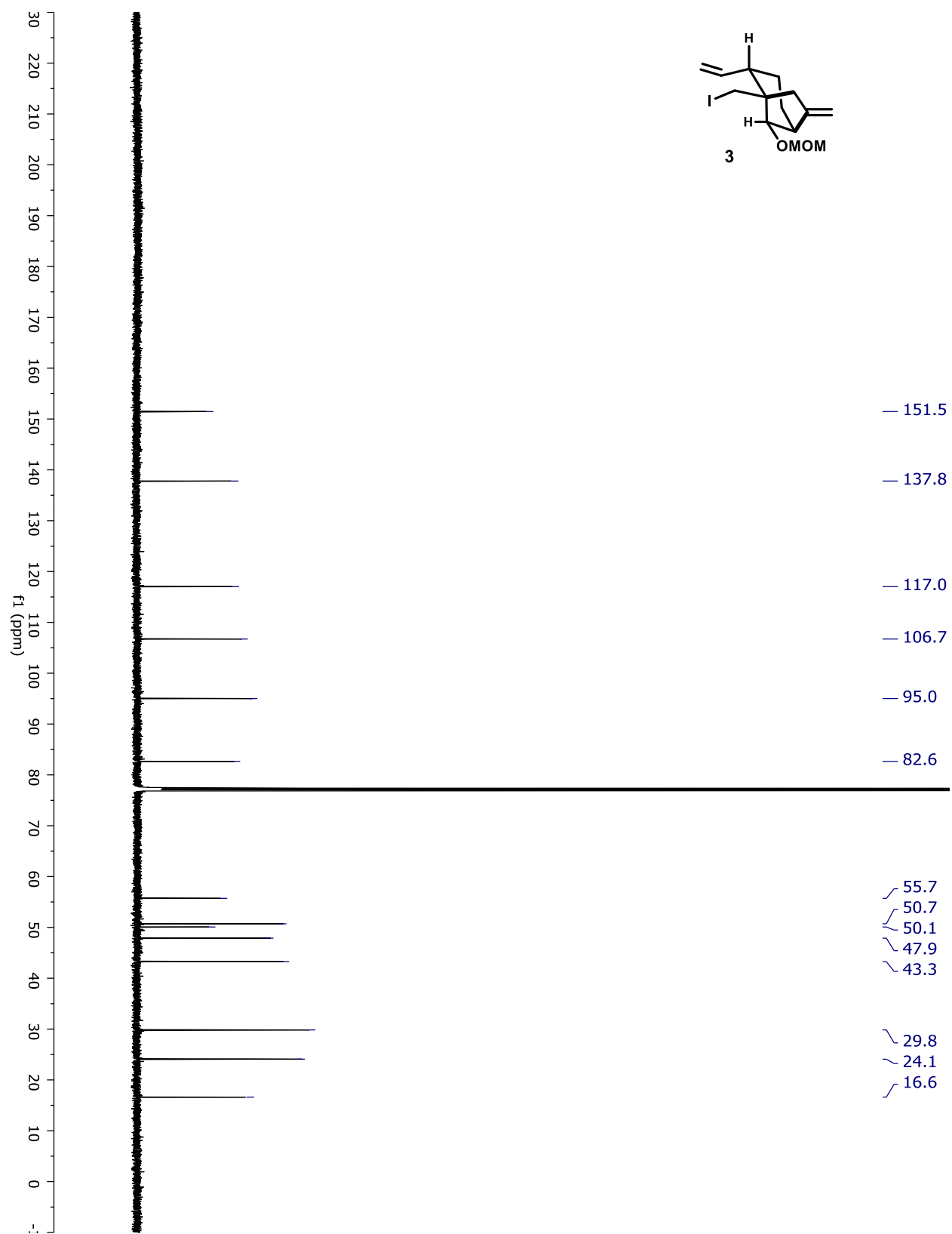
^1H NMR (400 MHz, CDCl_3) δ 5.82 (ddd, J = 17.0, 10.3, 9.4 Hz, 1H), 5.30 (ddd, J = 17.0, 2.1, 0.9 Hz, 1H), 5.13 (dd, J = 10.3, 2.0 Hz, 1H), 4.91 (d, J = 13.6 Hz, 2H), 4.68 (d, J = 6.9 Hz, 1H), 4.57 (d, J = 6.9 Hz, 1H), 3.79 – 3.72 (m, 2H), 3.33 (s, 3H), 3.22 (d, J = 9.4 Hz, 1H), 2.93 (d, J = 4.7 Hz, 1H), 2.70 (dd, J = 9.4, 5.1 Hz, 1H), 2.48 (dt, J = 16.9, 2.6 Hz, 1H), 2.33 (d, J = 17.0 Hz, 1H), 1.91 – 1.75 (m, 2H), 1.60 – 1.55 (m, 1H), 1.45 – 1.38 (m, 1H);

^{13}C NMR (151 MHz, CDCl_3) δ 151.5, 137.8, 117.0, 106.7, 95.0, 82.6, 55.7, 50.7, 50.1, 47.9, 43.2, 29.8, 24.1, 16.6;

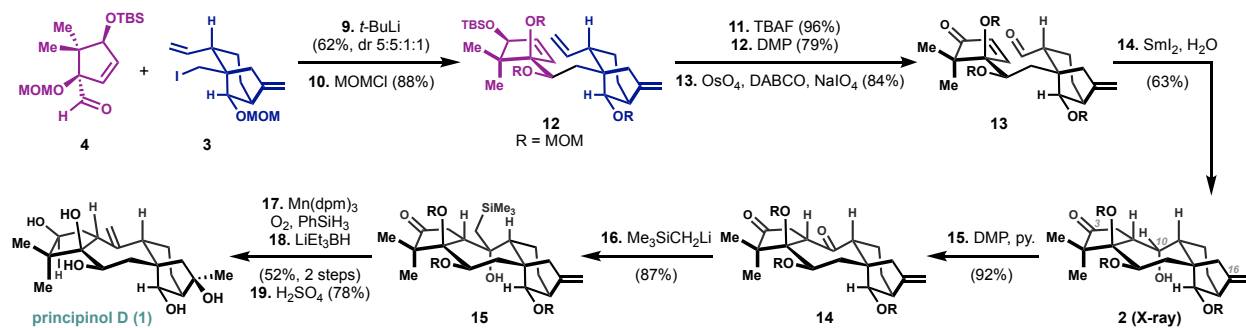
IR (cm^{-1}): 3070, 2941, 2887, 1661, 1425, 1211, 1107, 1047, 1027, 918, 881;

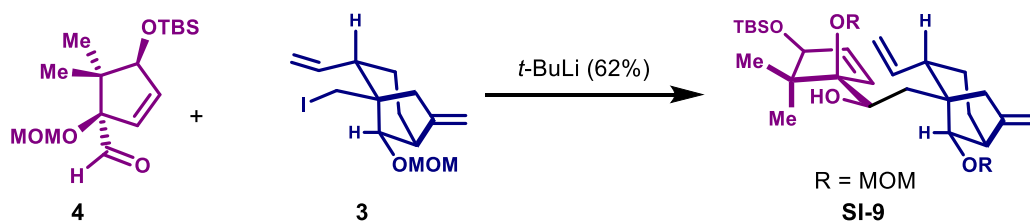
GCMS (m/z): $[M]$ calc'd for $\text{C}_{14}\text{H}_{21}\text{IO}_2$: 348.1; found: 348.1.





Fragment coupling and completion of synthesis





Fragment-coupling product SI-9:

Alkyl iodide fragment **3** (1.5 g, 4.4 mmol, 1.0 equiv) was dissolved in a solution of Et₂O (16 mL) in pentane (23 mL, 0.1 M). The reaction flask was cooled to $-78\text{ }^{\circ}\text{C}$ and *t*-butyllithium (1.7 M in pentane, 5.2 mL, 8.8 mmol, 2.0 equiv) was added. After stirring at the same temperature for 1 hour, a solution of aldehyde **4** (1.8 g, 5.7 mmol, 1.3 equiv) in Et₂O/pentane (2 mL/3 mL) was added. The reaction flask was slowly warmed to $0\text{ }^{\circ}\text{C}$ over the course of 1.5 hours. Sat. aq. NH₄Cl (50 mL) was added, and the organic layer was separated. The aqueous layer was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure by rotary evaporation. Purification by flash column chromatography on silica gel (hexanes \rightarrow 1.5% \rightarrow 2.5% EtOAc/hexanes) afforded fragment-coupling product **SI-9** (0.62 g, 26% yield; 62% yield of all diastereomers) as a colorless oil.

$R_f = 0.38$ (20% Et₂O in hexanes; not UV-active, stains blue-purple in *p*-anisaldehyde);

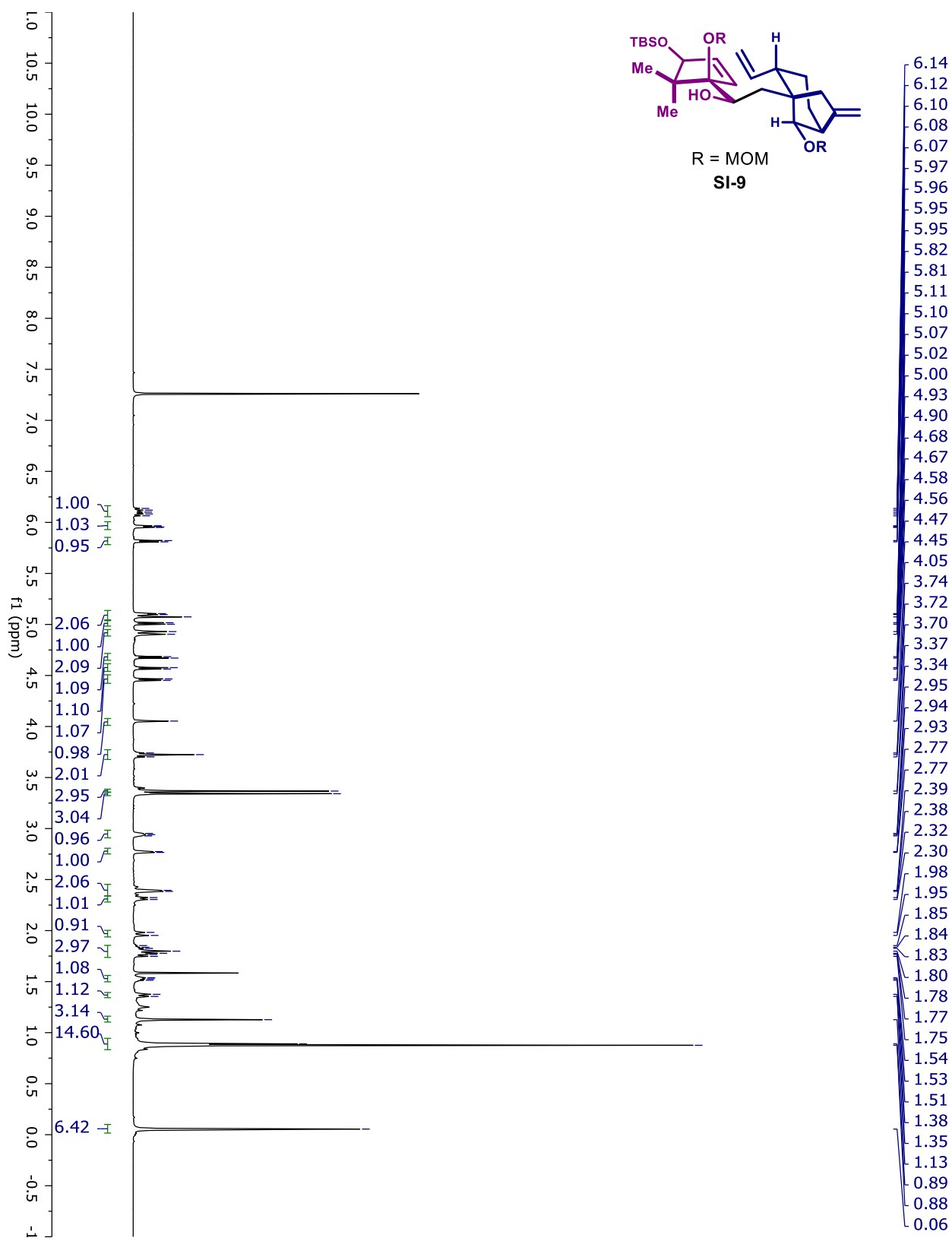
$[\alpha]_D^{20.0} : -16.0^{\circ}$ (*c* 1.0, CHCl₃);

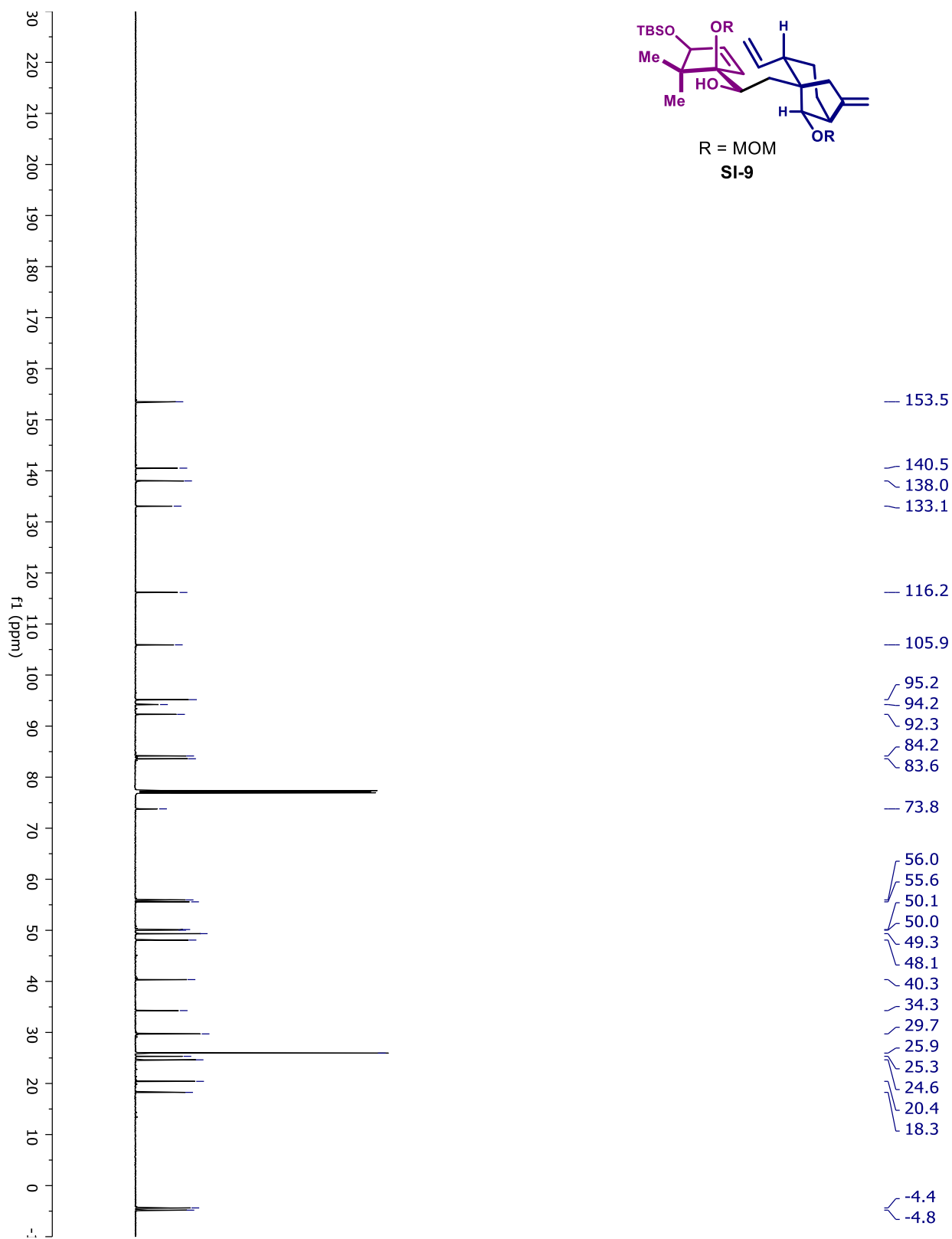
¹H NMR (600 MHz, CDCl₃) δ 6.15 – 6.06 (m, 1H), 5.96 (dd, *J* = 6.0, 2.2 Hz, 1H), 5.82 (d, *J* = 6.1 Hz, 1H), 5.10 (dd, *J* = 4.8, 1.0 Hz, 1H), 5.08 (d, *J* = 1.0 Hz, 1H), 5.00 (d, *J* = 7.3 Hz, 1H), 4.93 (s, 1H), 4.90 (s, 1H), 4.67 (d, *J* = 6.8 Hz, 1H), 4.57 (d, *J* = 6.8 Hz, 1H), 4.46 (d, *J* = 7.3 Hz, 1H), 4.06 (d, *J* = 2.3 Hz, 1H), 3.76 – 3.69 (m, 2H), 3.37 (s, 3H), 3.34 (s, 3H), 2.94 (t, *J* = 6.9 Hz, 1H), 2.77 (d, *J* = 4.8 Hz, 1H), 2.45 – 2.34 (m, 2H), 2.31 (d, *J* = 9.2 Hz, 1H), 1.97 (d, *J* = 14.8 Hz, 1H), 1.88 – 1.74 (m, 3H), 1.56 – 1.49 (m, 1H), 1.40 – 1.34 (m, 1H), 1.24 (ad, *J* = 20.2 Hz, 1H), 1.13 (s, 3H), 0.89 (s, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H);

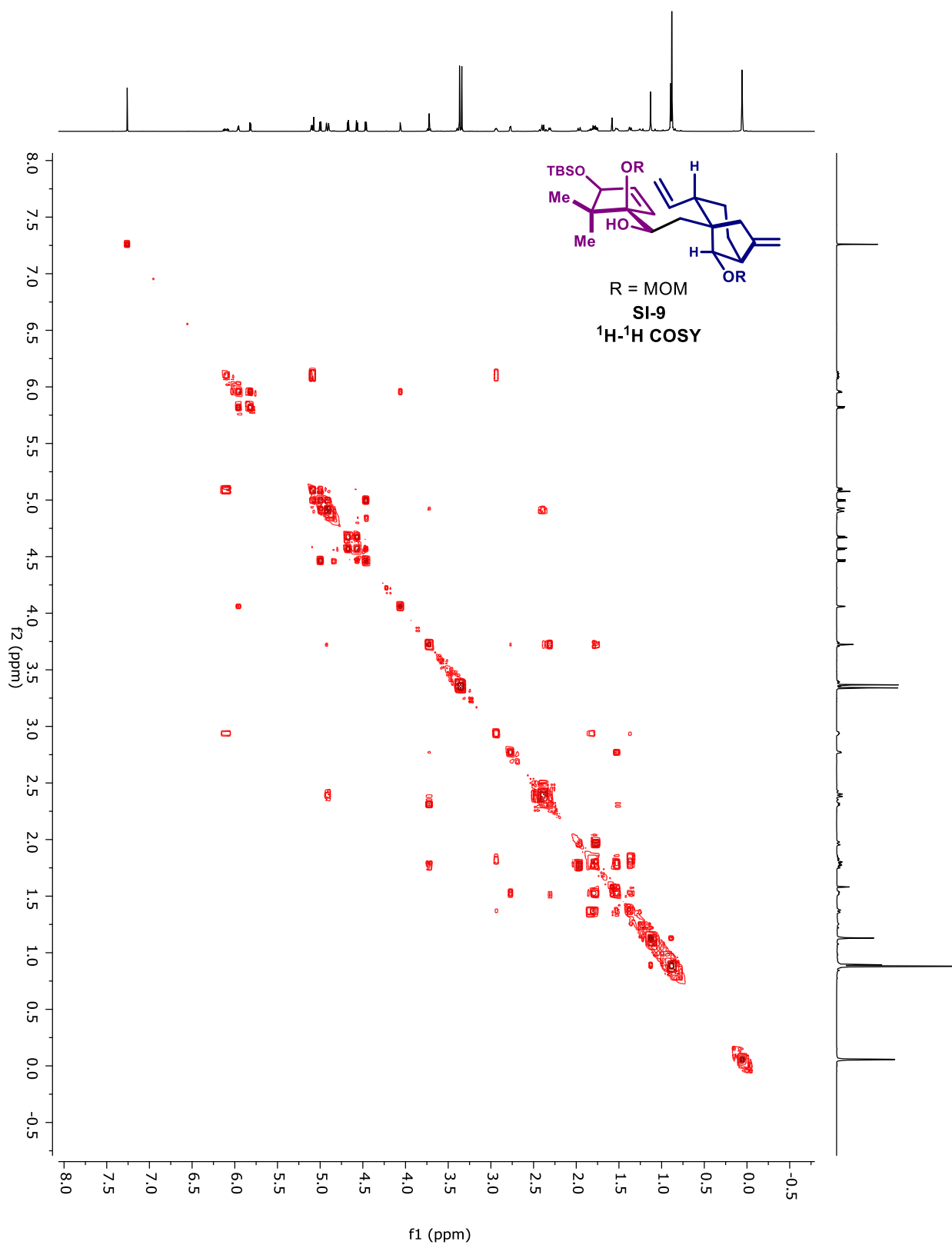
¹³C NMR (151 MHz, CDCl₃) δ 153.5, 140.5, 138.0, 133.1, 116.2, 105.9, 95.2, 94.2, 92.3, 84.1, 83.6, 73.8, 55.9, 55.6, 50.1, 50.1, 49.3, 48.1, 40.3, 34.3, 29.7, 25.9, 25.3, 24.6, 20.4, 18.3, -4.4, -4.8;

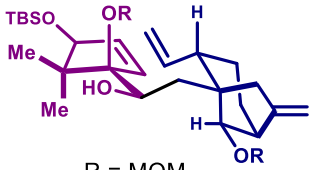
IR (cm⁻¹): 3520, 2929, 2887, 2821, 1660, 1471, 1386, 1361, 1254, 1150, 1127, 1065, 1038, 1027, 918, 875, 835, 775;

ESI-HRMS (*m/z*): [M+Na]⁺ calc'd for C₃₀H₅₂NaO₆Si⁺: 559.3425; found: 559.3474.

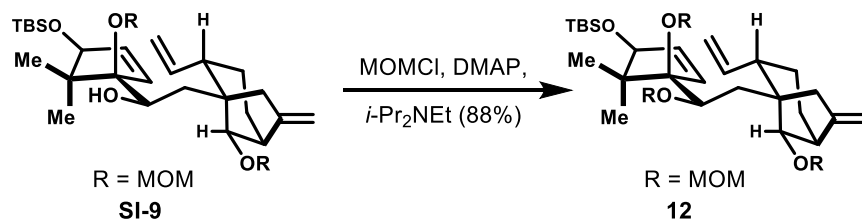








SI-45



MOM-protected secondary alcohol **12**:

Fragment-coupling product **SI-9** (0.580 g, 1.06 mmol, 1.0 equiv) was dissolved in dichloroethane (5.6 mL, 0.2 M). *N,N*-Diisopropylethylamine (2.8 mL, 2.1 g, 16 mmol, 15 equiv) was added, followed by *N,N*-dimethylpyridin-4-amine (0.28 g, 2.3 mmol, 2.2 equiv) and chloromethyl methyl ether (0.61 mL, 11 mmol, 10 equiv). The reaction vial was capped and heated to 80 °C. After 17 hours, the reaction mixture was cooled to 23 °C and quenched with sat. aq. NaHCO_3 (10 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure by rotary evaporation. Purification by flash column chromatography on silica gel (hexanes \rightarrow 7% EtOAc/hexanes) afforded MOM-protected secondary alcohol **12** (0.548 g, 88% yield) as a colorless oil.

R_f = 0.65 (25% EtOAc in hexanes; not UV-active, stains blue-purple in *p*-anisaldehyde);

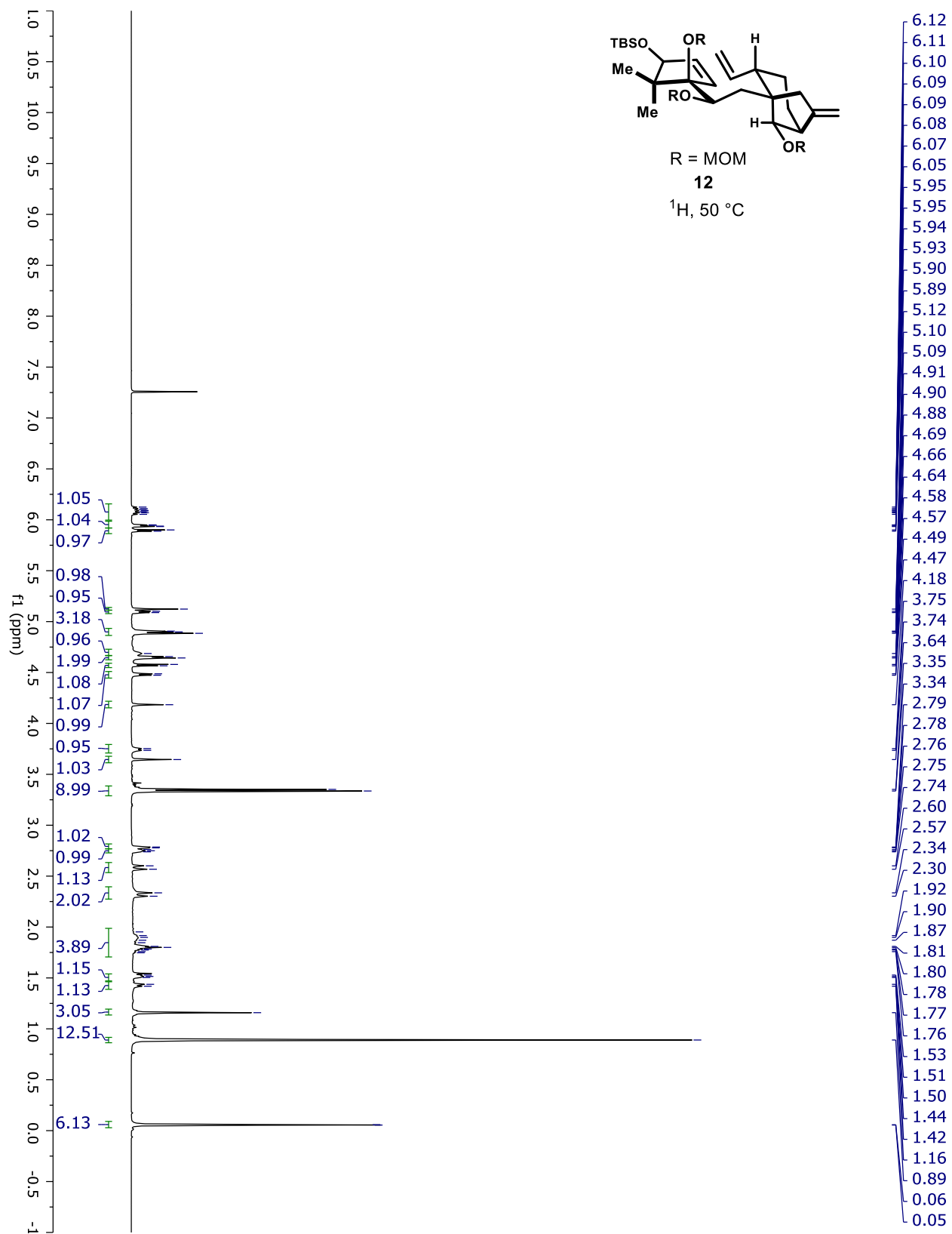
$[\alpha]_D^{20.0}$: +2.8° (*c* 1.0, CHCl_3);

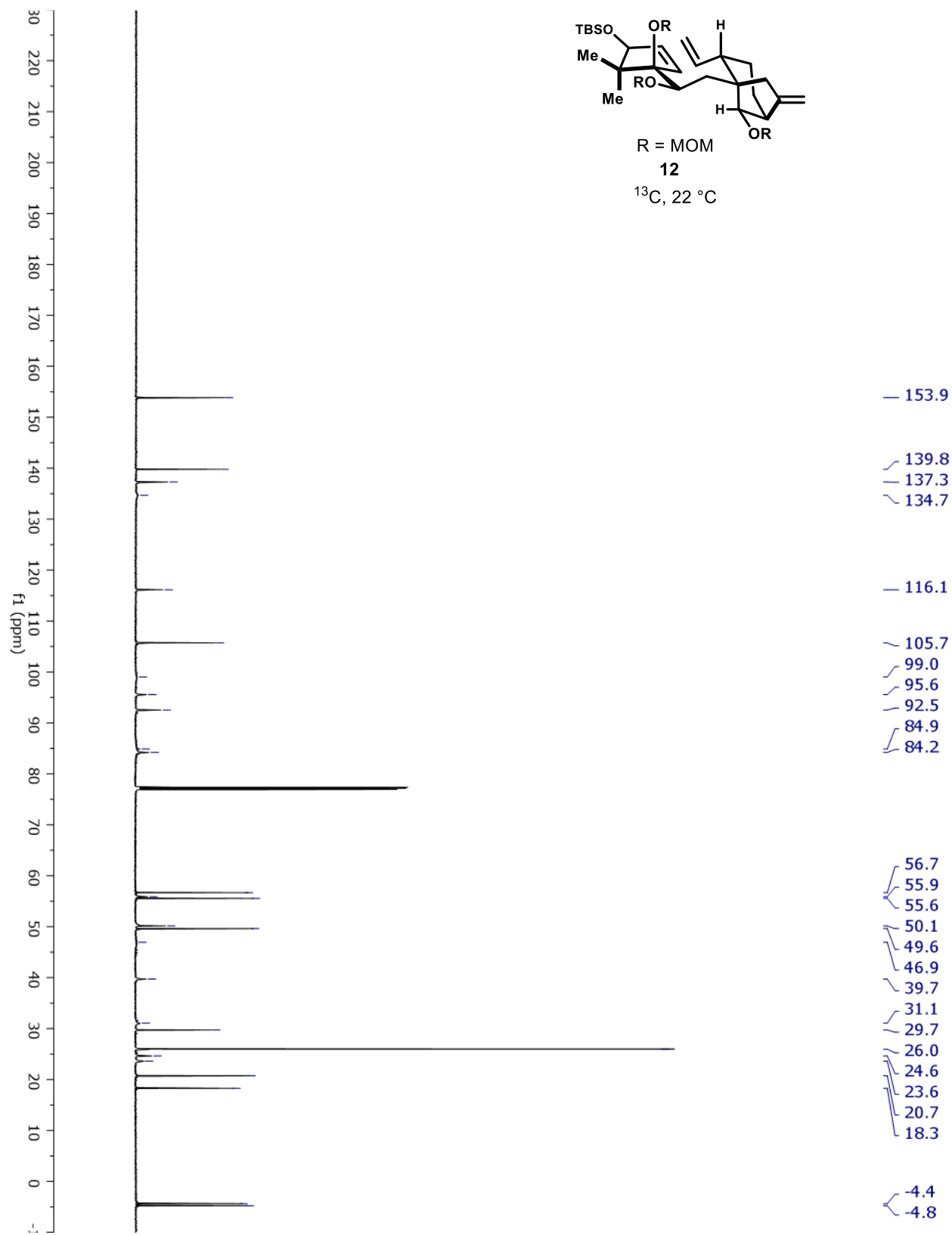
$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 6.09 (ddd, J = 16.5, 11.3, 7.8 Hz, 1H), 5.94 (dd, J = 6.0, 2.0 Hz, 1H), 5.89 (d, J = 6.1 Hz, 1H), 5.12 (s, 1H), 5.10 (d, J = 6.3 Hz, 1H), 4.93 – 4.88 (m, 3H), 4.69 (bs, 1H), 4.65 (d, J = 6.6 Hz, 2H), 4.57 (d, J = 6.7 Hz, 1H), 4.48 (d, J = 7.0 Hz, 1H), 4.18 (s, 1H), 3.74 (d, J = 8.6 Hz, 1H), 3.64 (s, 1H), 3.35 (s, 3H), 3.34 (s, 6H), 2.78 (d, J = 4.0 Hz, 1H), 2.77 – 2.73 (m, 1H), 2.58 (d, J = 16.6 Hz, 1H), 2.32 (d, J = 16.6 Hz, 2H), 1.97 – 1.74 (m, 4H), 1.52 (at, J = 6.0 Hz, 1H), 1.43 (ad, J = 9.2 Hz, 1H), 1.16 (s, 3H), 0.89 (s, 12H), 0.06 (d, J = 1.6 Hz, 6H);

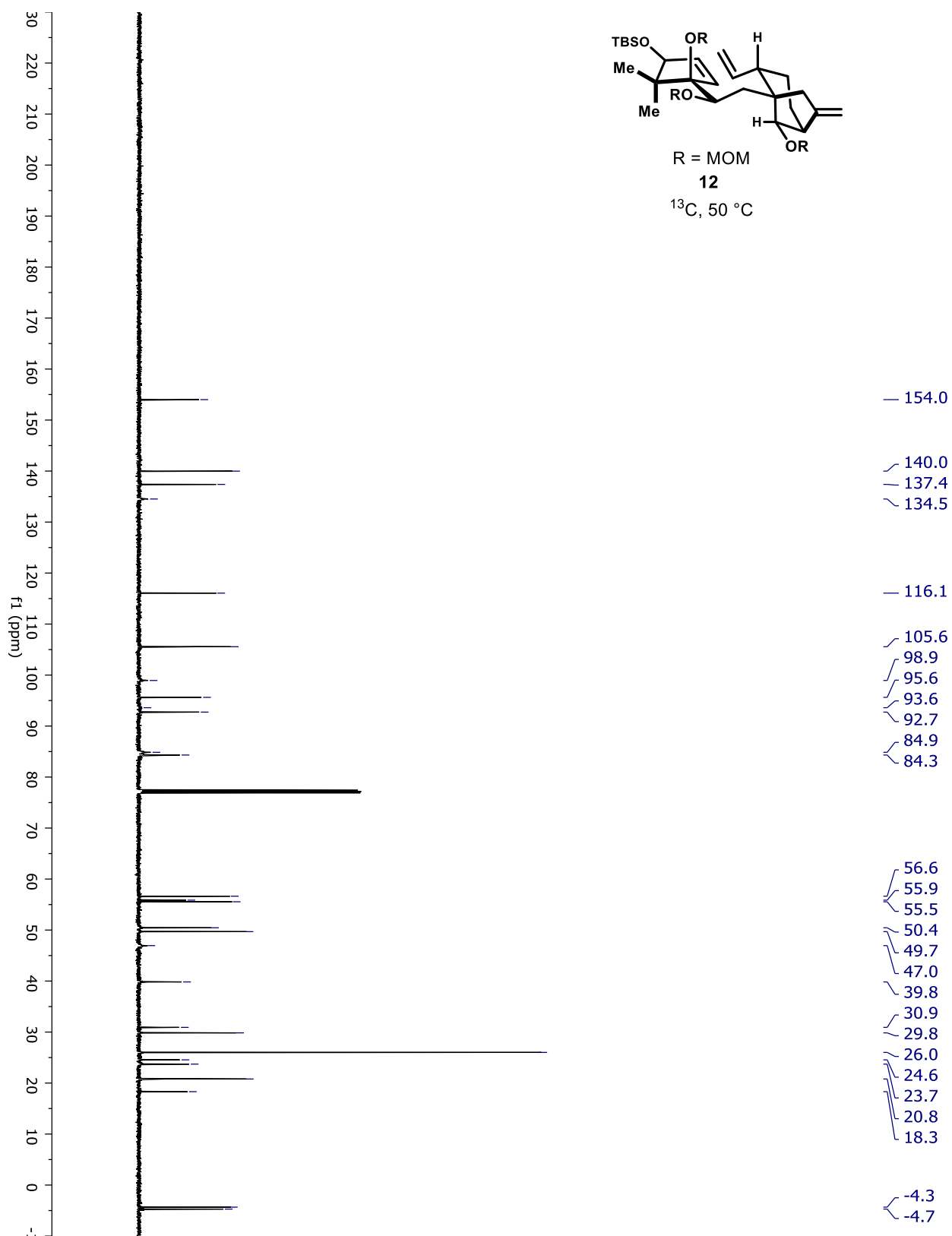
$^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 154.0, 140.0, 137.4, 134.5, 116.1, 105.6, 98.9, 95.6, 93.6, 92.7, 84.9, 84.3, 56.6, 55.9, 55.5, 50.4, 50.4, 49.7, 47.0, 39.8, 30.9, 29.8, 26.0, 24.6, 23.7, 20.8, 18.3, -4.3, -4.7;

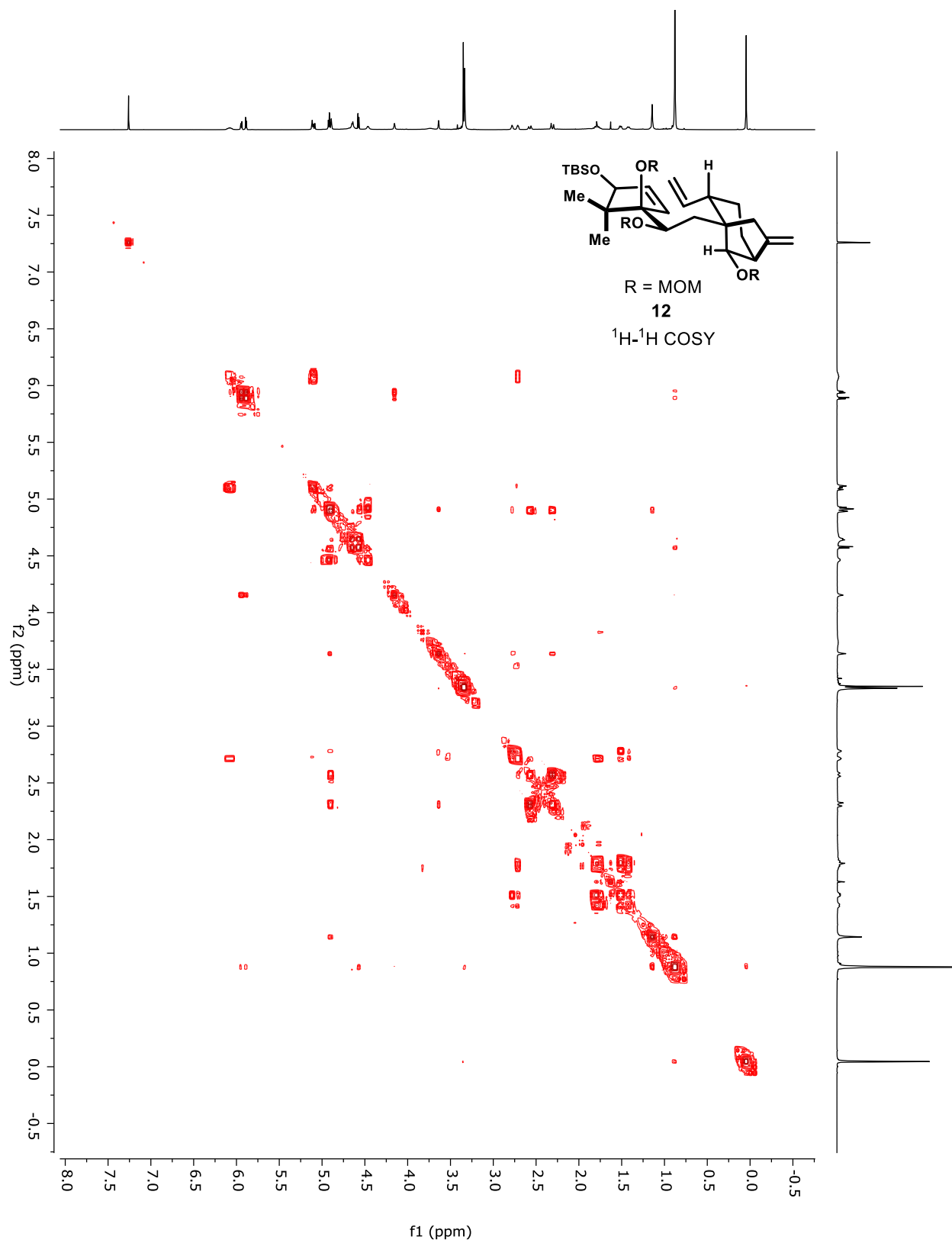
IR (cm^{-1}): 2930, 2885, 2857, 2822, 1471, 1362, 1252, 1210, 1150, 1092, 1039, 1026, 918, 877, 836, 791, 775;

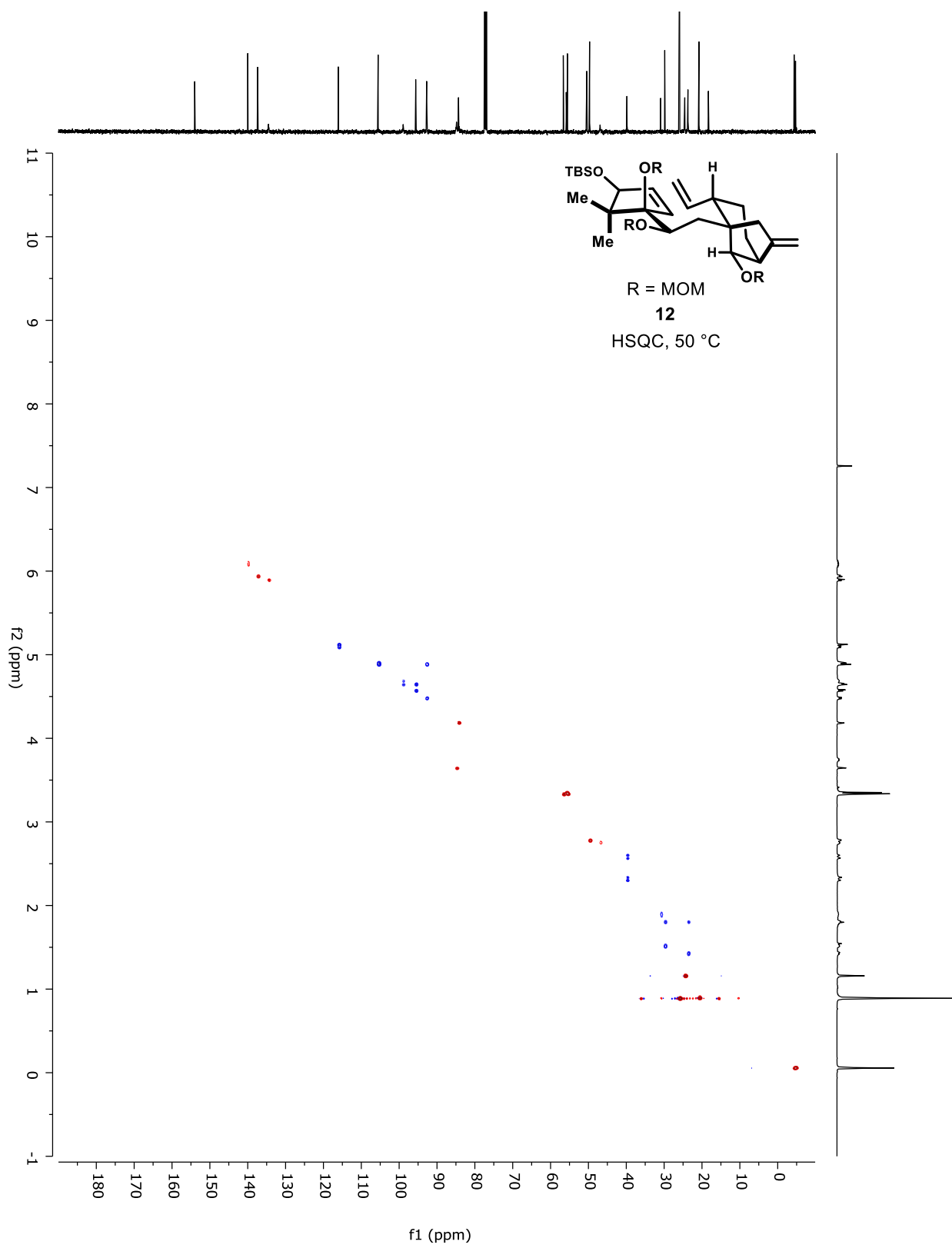
ESI-HRMS (m/z): $[\text{M}+\text{Na}]^+$ calc'd for $\text{C}_{32}\text{H}_{56}\text{NaO}_7\text{Si}^+$: 603.3688; found: 603.3703.

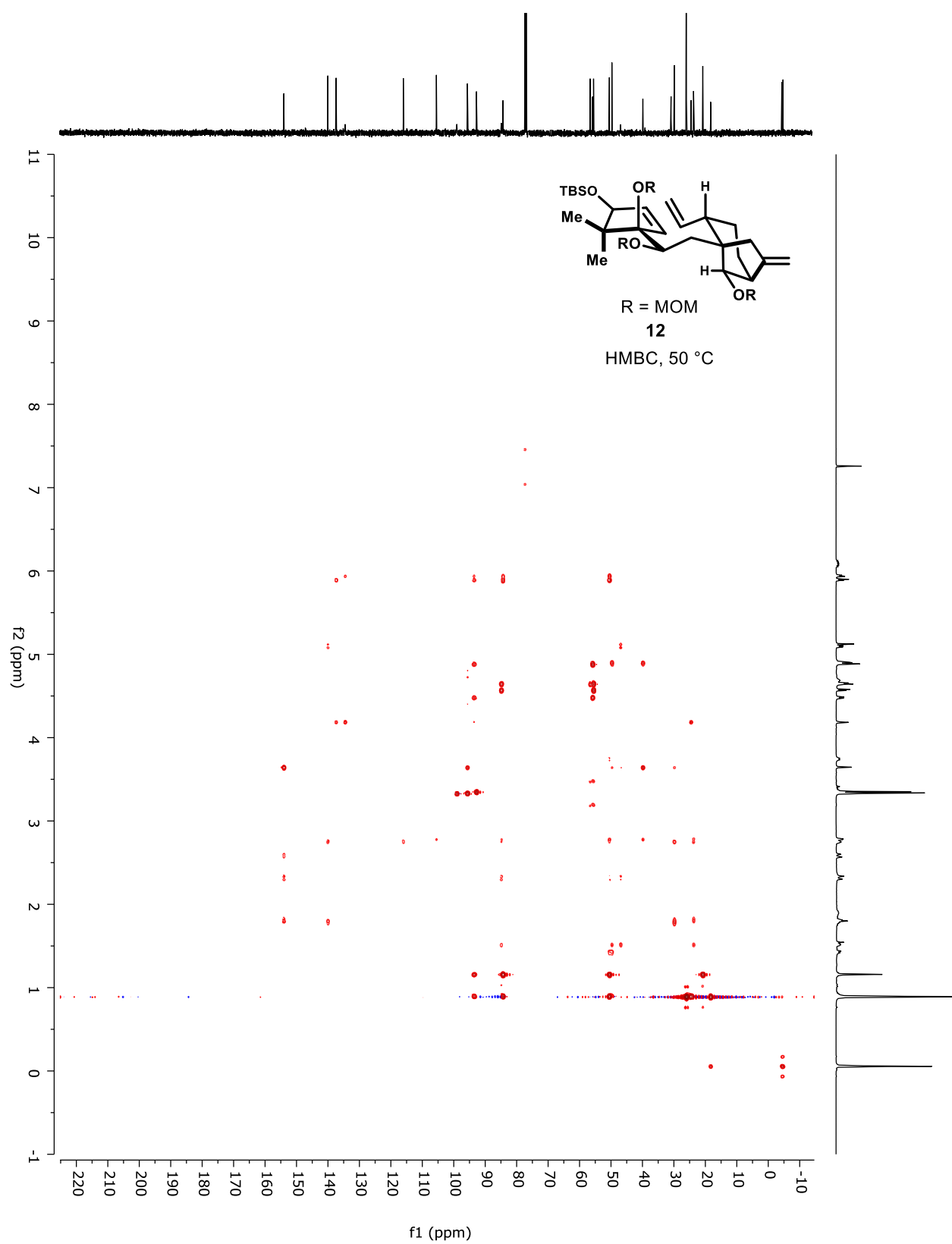


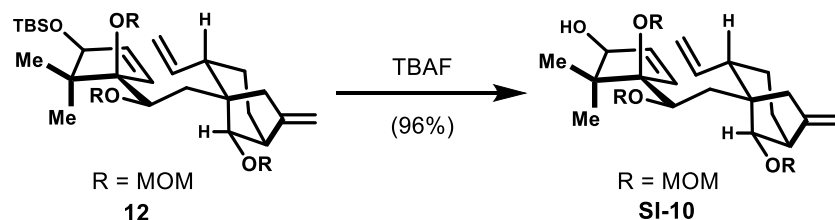












Allylic alcohol SI-11:

MOM-protected secondary alcohol **12** (0.515 g, 0.89 mmol, 1.0 equiv) was dissolved in THF (8.9 mL, 0.1 M). Tetrabutylammonium fluoride (1.0 M solution in THF, 4.4 mL, 4.4 mmol, 5.0 equiv) was added. After 3 hours, H₂O (30 mL) was added. The aqueous layer was extracted with EtOAc (30 mL x 3), and the combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure by rotary evaporation. Purification by flash column chromatography on silica gel (hexanes → 30% EtOAc/hexanes) afforded allylic alcohol **SI-10** (0.397 g, 96% yield) as a colorless oil.

$R_f = 0.19$ (25% EtOAc in hexanes; not UV-active, stains blue-purple in *p*-anisaldehyde);

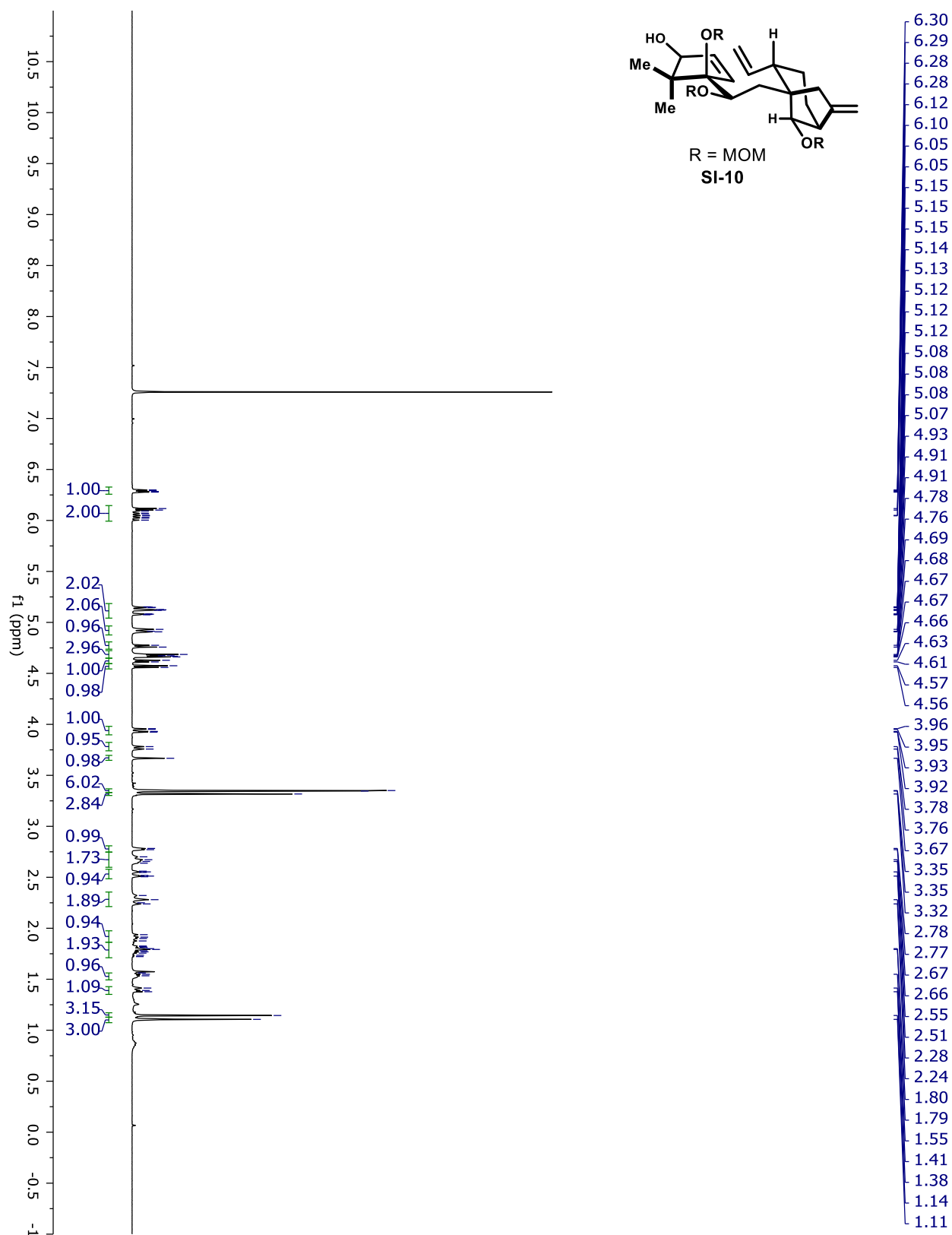
$[\alpha]_D^{20.0} : -14.4^\circ$ (*c* 1.0, CHCl₃);

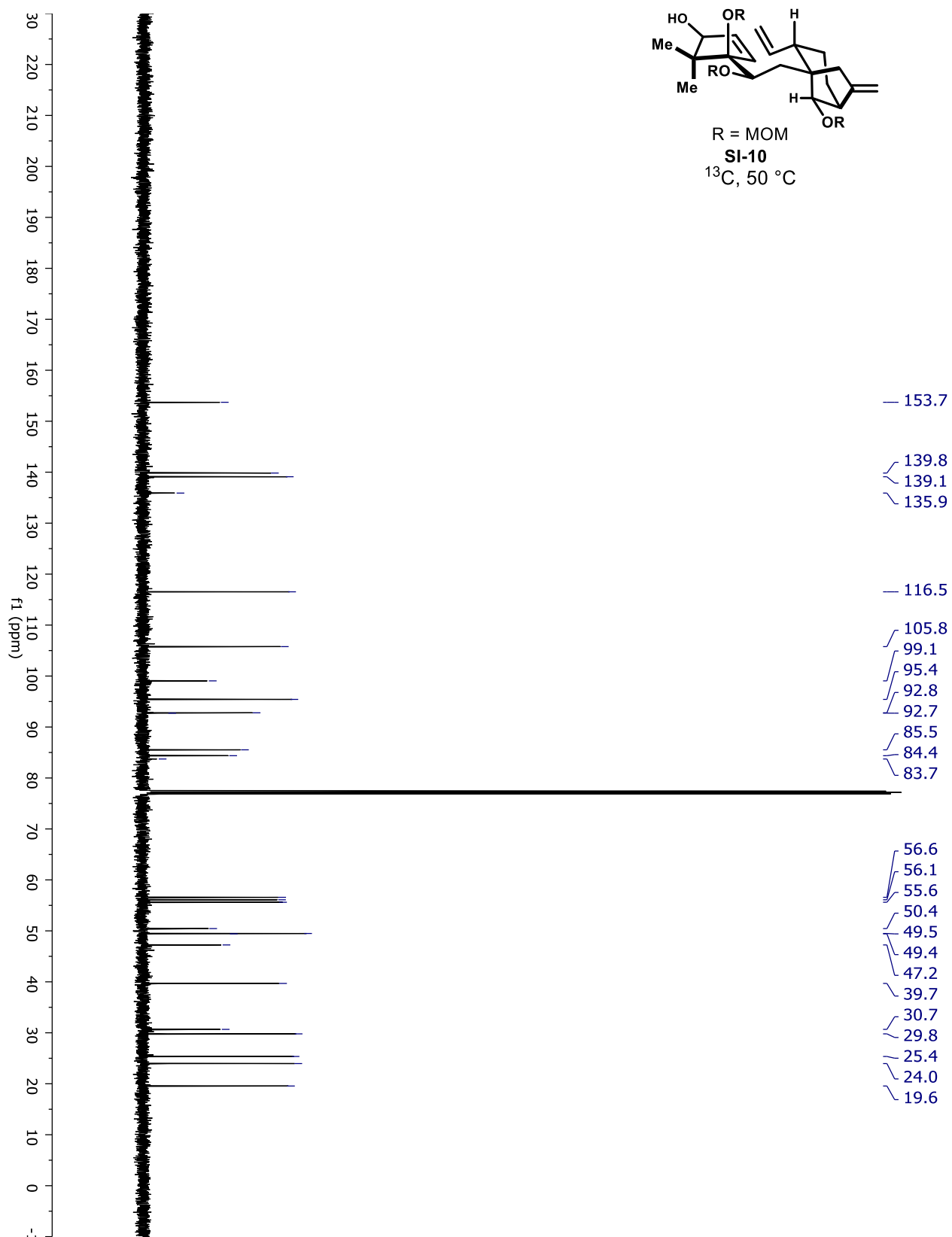
¹H NMR (400 MHz, CDCl₃) δ 6.29 (dd, *J* = 6.0, 2.6 Hz, 1H), 6.11 (d, *J* = 6.0 Hz, 1H), 6.05 (ddd, *J* = 17.1, 10.6, 8.2 Hz, 1H), 5.17 – 5.06 (m, 2H), 4.92 (d, *J* = 9.7 Hz, 2H), 4.77 (d, *J* = 7.1 Hz, 1H), 4.71 – 4.66 (m, 3H), 4.62 (d, *J* = 6.4 Hz, 1H), 4.57 (d, *J* = 6.8 Hz, 1H), 3.94 (dd, *J* = 10.9, 2.7 Hz, 1H), 3.77 (d, *J* = 9.5 Hz, 1H), 3.67 (s, 1H), 3.35 (s, 3H), 3.35 (s, 3H), 3.32 (s, 3H), 2.78 (d, *J* = 4.7 Hz, 1H), 2.73 – 2.62 (m, 2H), 2.53 (dt, *J* = 16.9, 2.7 Hz, 1H), 2.34 – 2.23 (m, 2H), 1.96 – 1.87 (m, 1H), 1.86 – 1.71 (m, 2H), 1.56 – 1.49 (m, 1H), 1.44 – 1.36 (m, 1H), 1.14 (s, 3H), 1.11 (s, 3H);

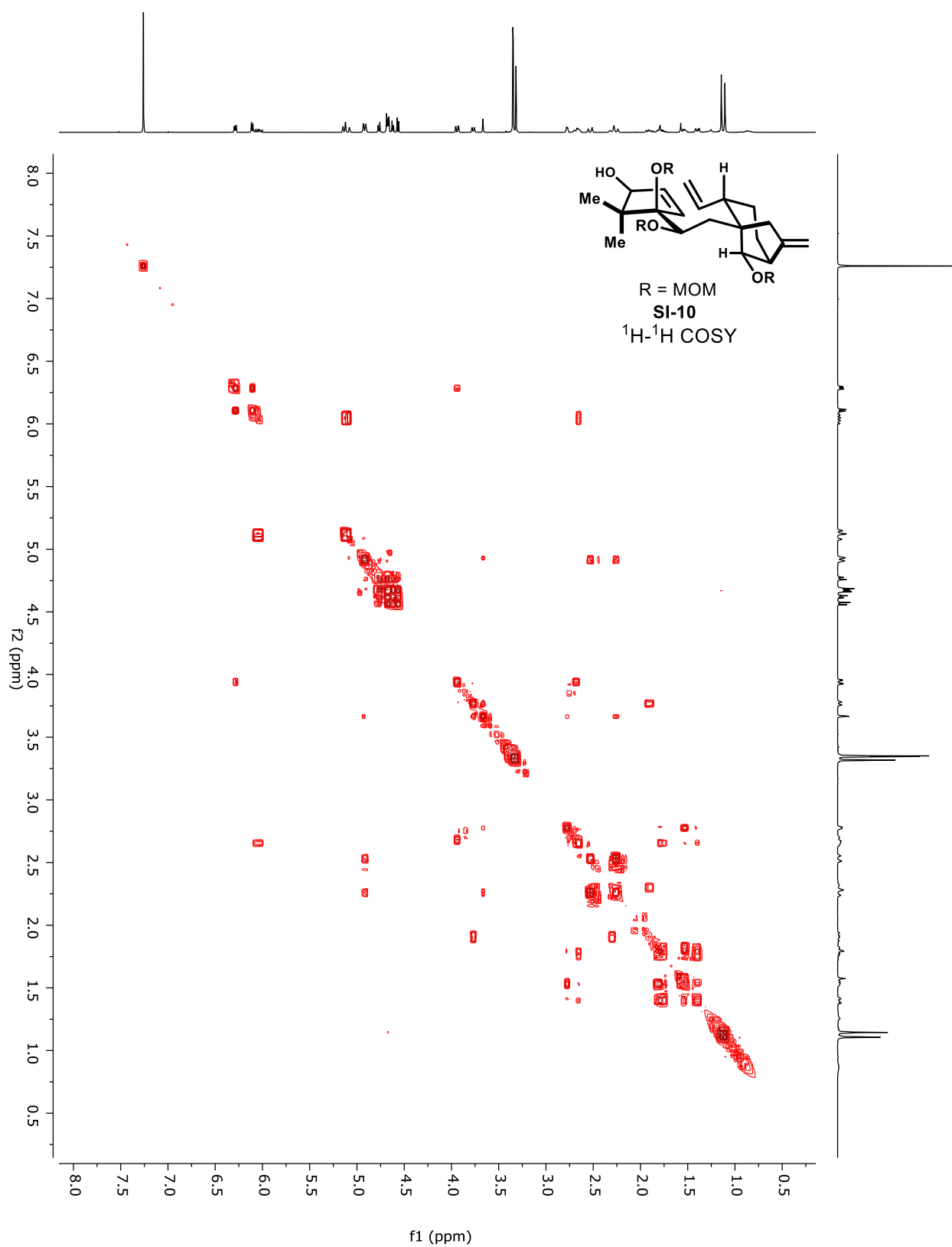
¹³C NMR (126 MHz, CDCl₃) δ 153.7, 139.8, 139.1, 135.9, 116.5, 105.8, 99.1, 95.4, 92.8, 92.7, 85.5, 84.4, 83.7, 56.6, 56.1, 55.6, 50.5, 49.5, 49.4, 47.2, 39.7, 30.7, 29.8, 25.4, 24.0, 19.6;

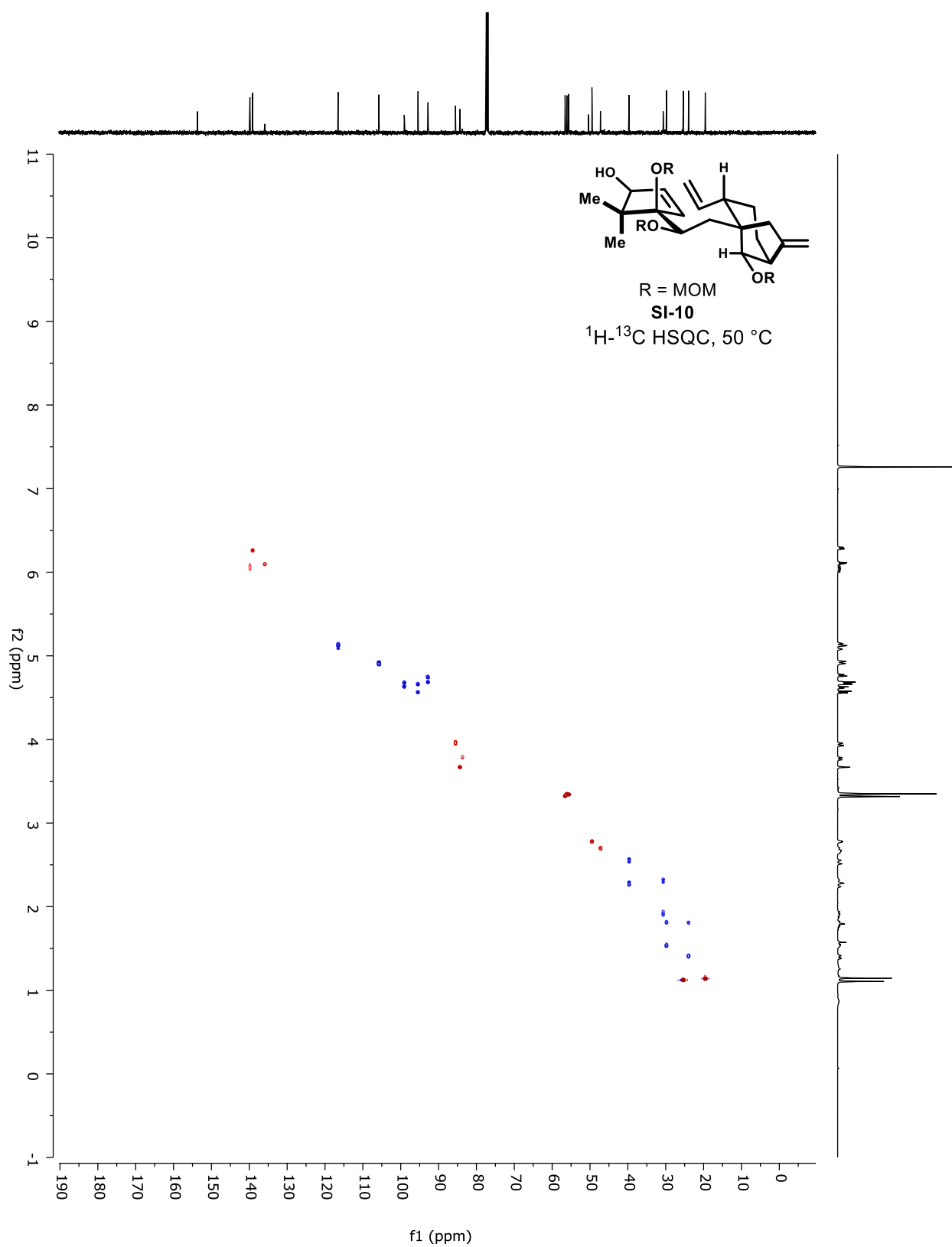
IR (cm⁻¹): 3457, 3068, 2934, 2823, 1660, 1466, 1446, 1211, 1150, 1130, 1099, 1043, 1022, 917, 877, 835;

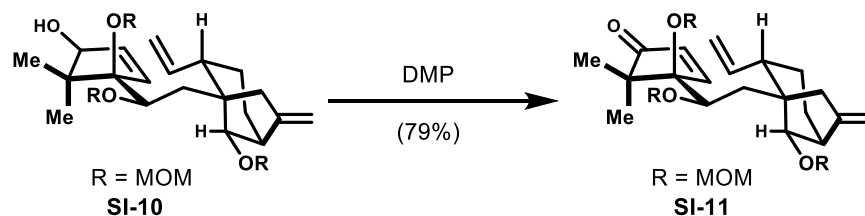
ESI-HRMS (*m/z*): [M+Na]⁺ calc'd for C₂₆H₄₂NaO₇⁺: 489.2823; found: 489.2857.











Enone SI-11:

Allylic alcohol **SI-10** (0.376 g, 0.81 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (8.9 mL, 0.1 M). Dess–Martin periodinane (1.7 g, 4.0 mmol, 5.0 equiv) was added at 0 °C. The reaction flask was slowly warmed to 23 °C over 10 hours. After a total of 30 hours, sat. aq. NaHCO_3 (30 mL) was added. The aqueous layer was extracted with EtOAc (20 mL x 3). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL), then dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure by rotary evaporation. Purification by flash column chromatography on silica gel (hexanes \rightarrow 25% EtOAc/hexanes) afforded enone **SI-11** (0.295 g, 79% yield) as a colorless oil.

$R_f = 0.32$ (25% EtOAc in hexanes; UV-active, stains purple in *p*-anisaldehyde);

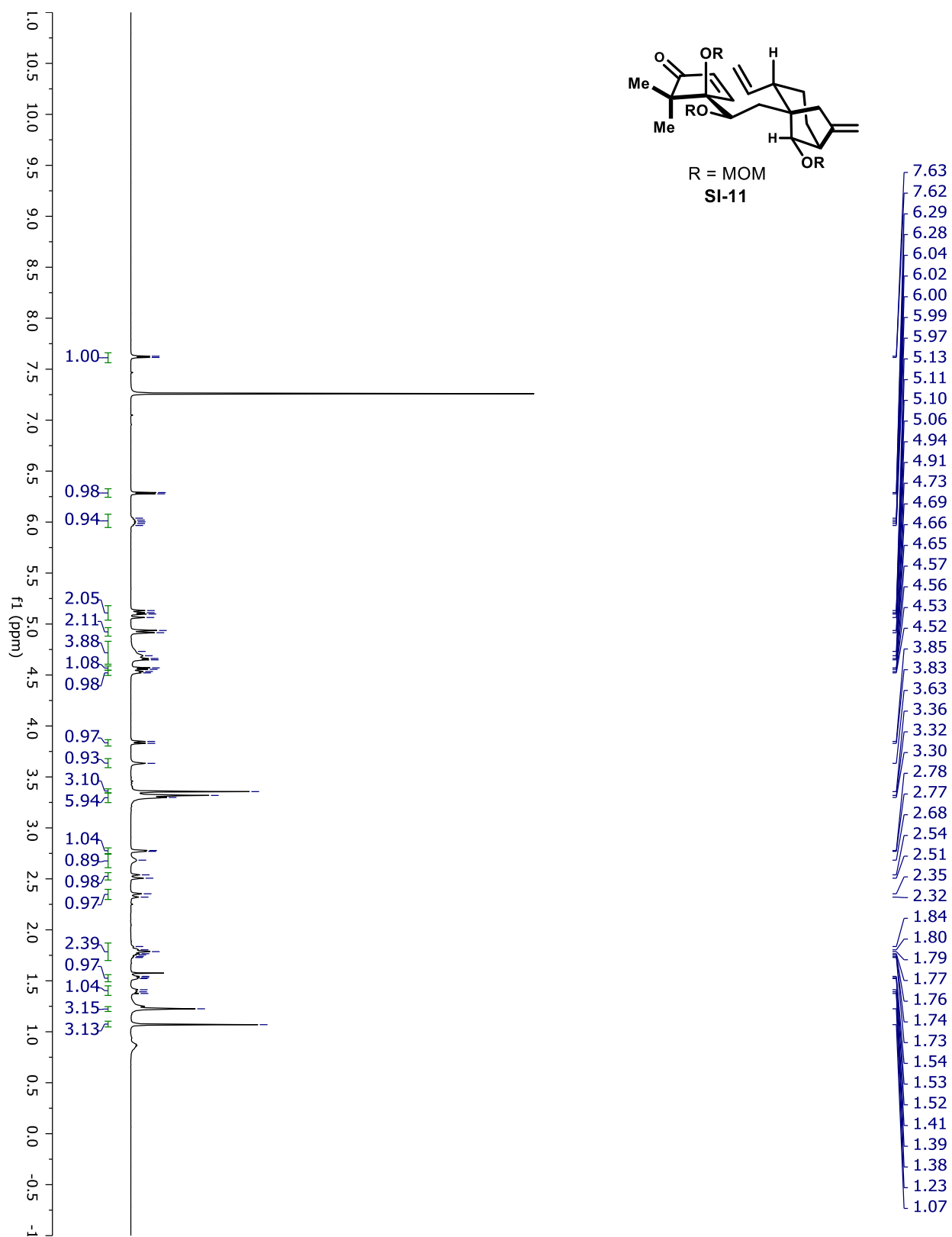
$[\alpha]_D^{20.0} : -7.5^\circ$ (*c* 1.0, CHCl_3);

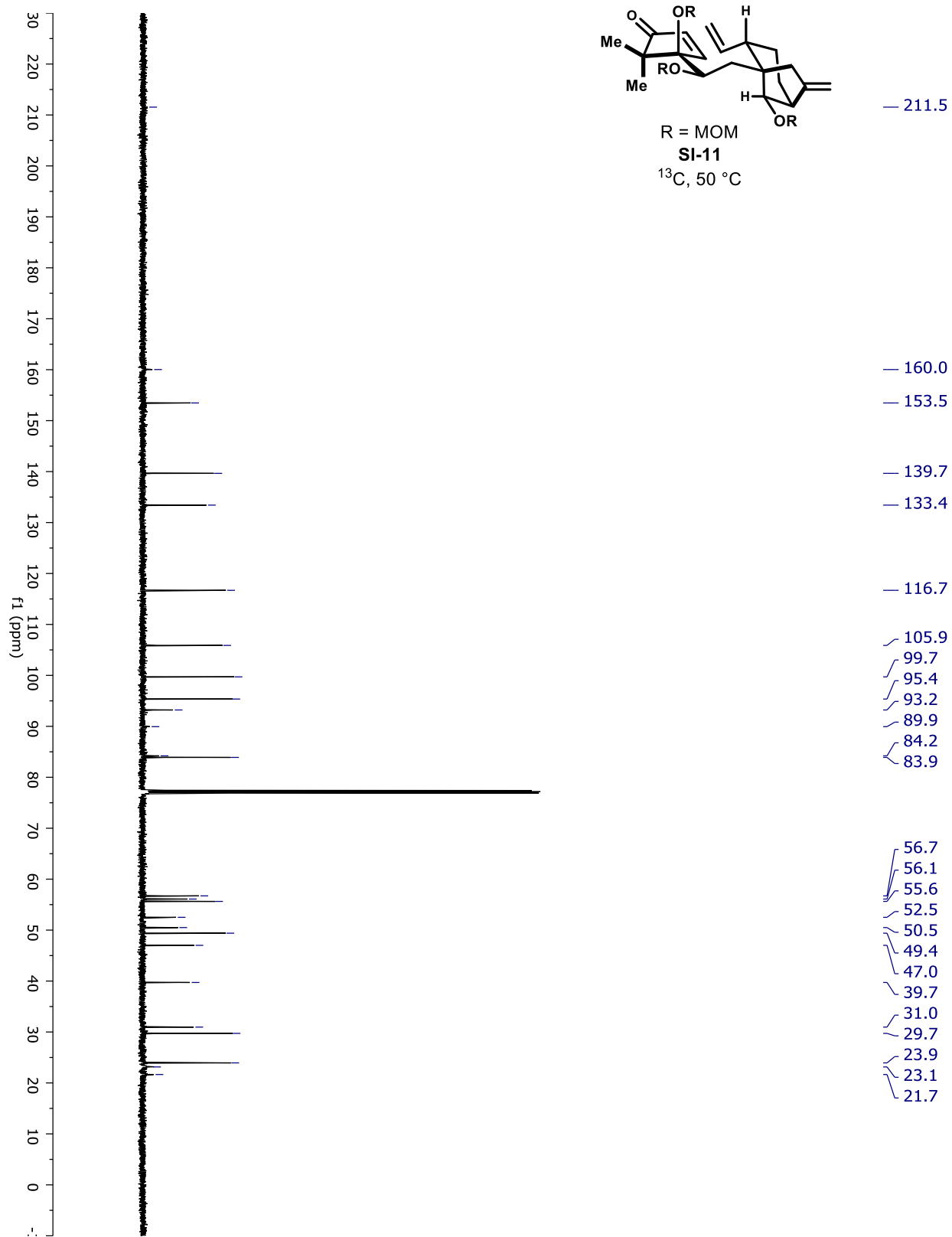
$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.62 (d, *J* = 6.1 Hz, 1H), 6.28 (d, *J* = 6.1 Hz, 1H), 6.00 (dt, *J* = 18.1, 9.4 Hz, 1H), 5.12 (d, *J* = 10.5 Hz, 1H), 5.08 (d, *J* = 17.3 Hz, 1H), 4.93 (d, *J* = 10.8 Hz, 2H), 4.81 – 4.67 (m, 3H), 4.66 (d, *J* = 6.8 Hz, 1H), 3.84 (d, *J* = 9.6 Hz, 1H), 3.63 (s, 1H), 3.36 (s, 3H), 3.32 (s, 3H), 3.30 (s, 3H), 2.77 (d, *J* = 4.2 Hz, 1H), 2.68 (s, 1H), 2.52 (d, *J* = 16.4 Hz, 1H), 2.34 (d, *J* = 16.3 Hz, 1H), 1.86 – 1.71 (m, 2H), 1.56 – 1.49 (m, 1H), 1.43 – 1.36 (m, 1H), 1.23 (s, 3H), 1.07 (s, 3H);

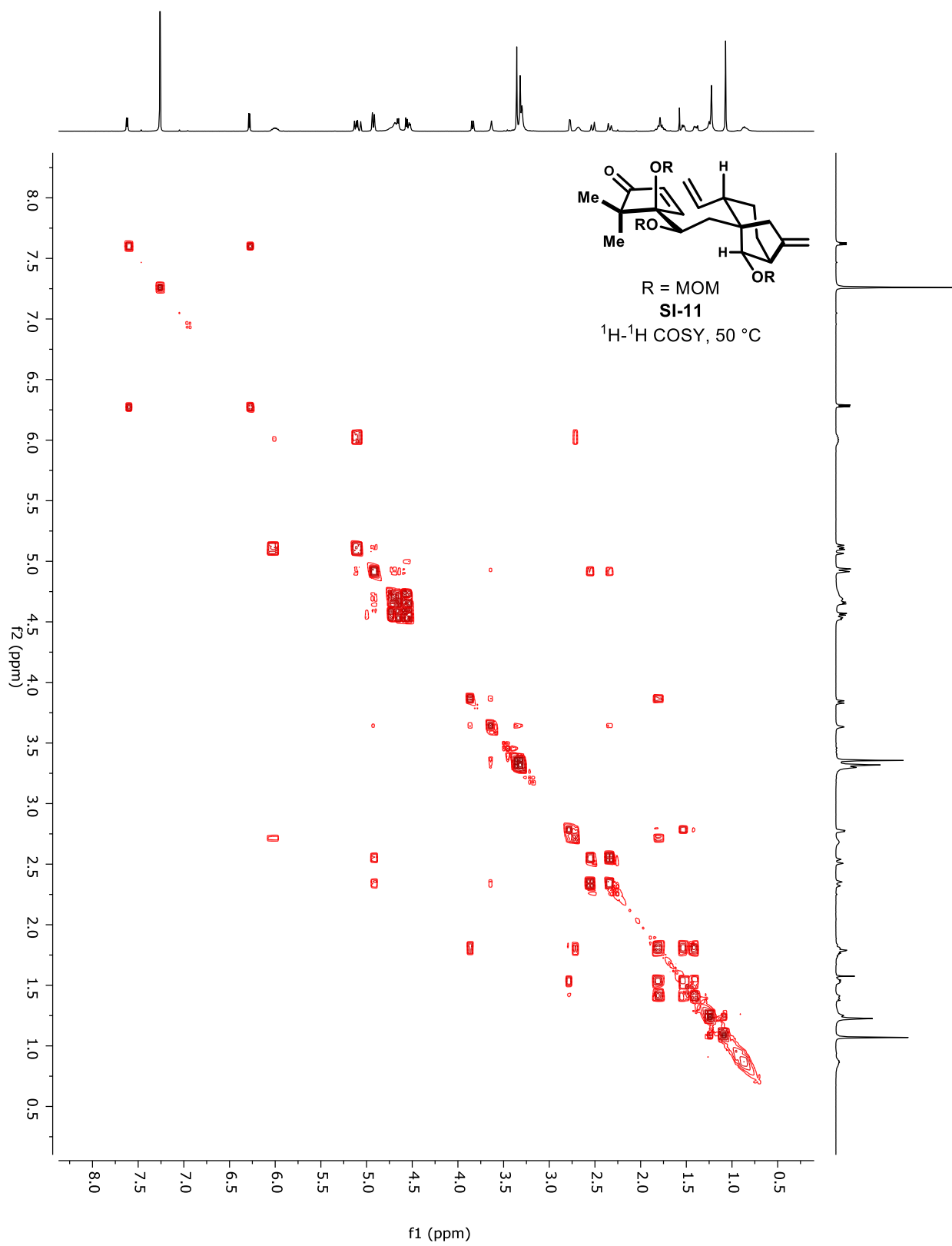
$^{13}\text{C NMR}$ (MHz, CDCl_3) δ 211.5, 160.0, 153.5, 139.6, 133.4, 116.7, 105.9, 99.7, 95.4, 93.2, 89.9, 84.2, 83.9, 56.7, 56.1, 55.6, 52.5, 50.5, 49.4, 47.0, 39.7, 31.0, 29.7, 23.9, 23.1, 21.7;

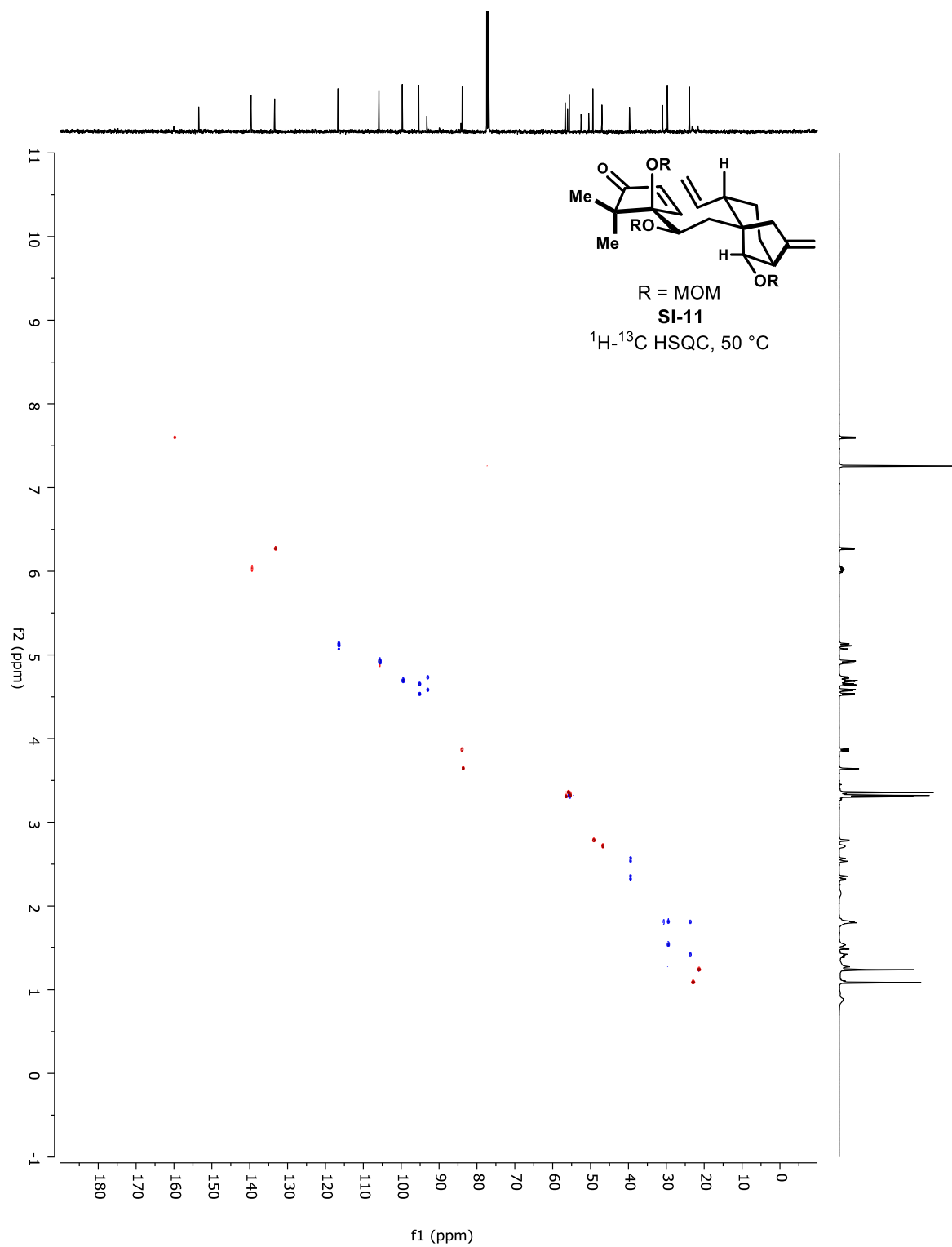
IR (cm^{-1}): 3069, 2929, 2823, 1719, 1661, 1465, 1448, 1385, 1210, 1151, 1100, 1030, 918, 878, 838;

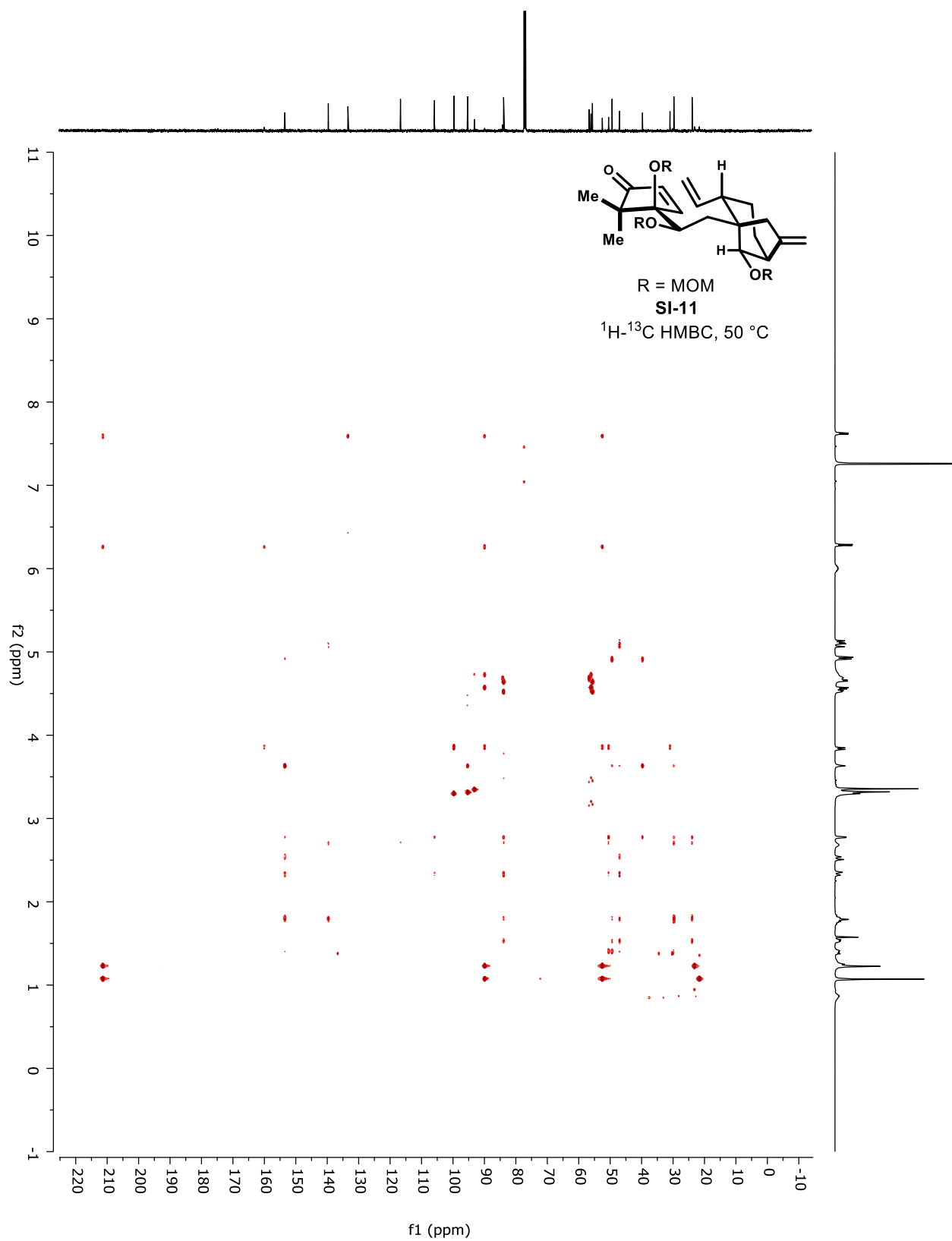
ESI-HRMS (*m/z*): $[\text{M}+\text{Na}]^+$ calc'd for $\text{C}_{26}\text{H}_{40}\text{NaO}_7^+$: 487.2666; found: 487.2675.

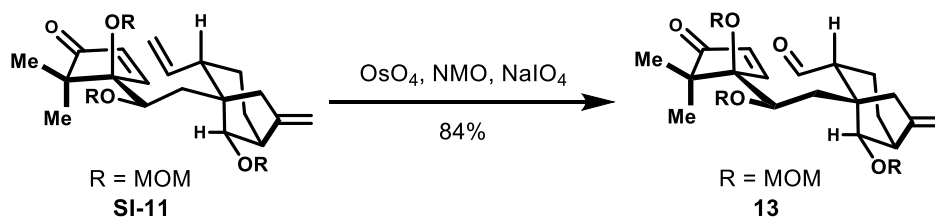












Aldehyde 13:

Alkene **SI-11** (20 mg, 0.042 mmol) was dissolved in a 2:1 solution of THF:H₂O (4.2 mL, 0.01 M). The reaction mixture was cooled to 0 °C. DABCO (0.0152 g, 0.126 mmol, 3.0 equiv) was added, followed by NaIO₄ (0.0281 g, 0.126 mmol, 3.0 equiv) and OsO₄ (4% sltn in water; 26 μL, 0.0042 mmol, 0.1 equiv). The reaction was stirred at 0 °C for 15 hours, followed by addition of H₂O. The aqueous layer was extracted with EtOAc (4 mL x 3). The combined organic layers were washed sat. aq. Na₂S₂O₃ (3 mL) and brine (3 mL), then dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure by rotary evaporation. Purification by flash column chromatography on silica gel (hexanes → 50% EtOAc/hexanes) afforded aldehyde **13** (16.9 mg, 84% yield) as a colorless oil.

R_f = 0.46 (50% EtOAc in hexanes; UV-active, stains purple in *p*-anisaldehyde);

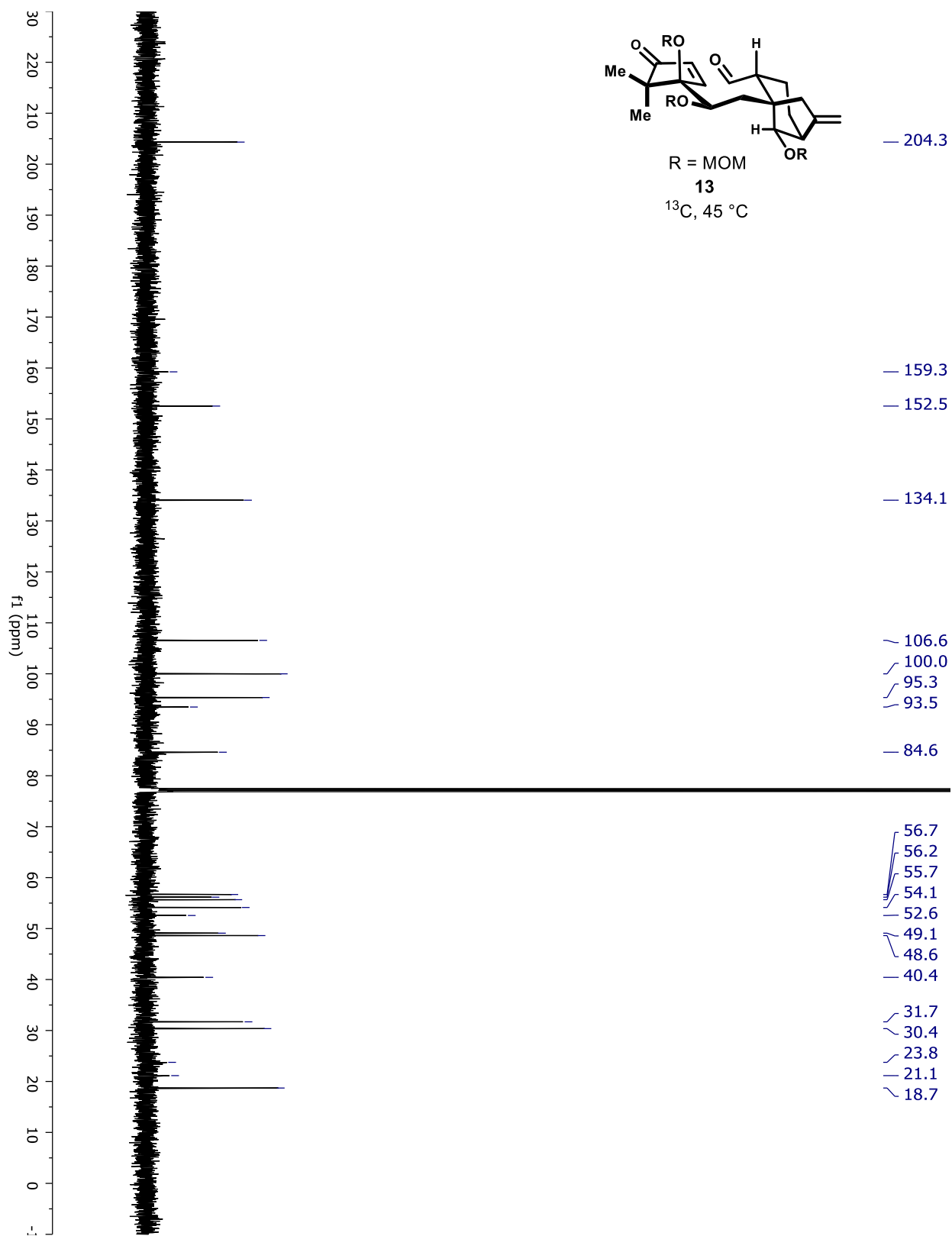
$[\alpha]_D^{20.0}$: +10.4 ° (*c* 1.0, CHCl₃);

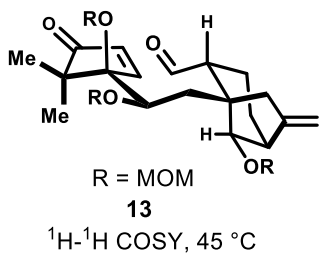
¹H NMR (500 MHz, CDCl₃) δ 9.90 (s, 1H), 7.57 (d, *J* = 6.1 Hz, 1H), 6.31 (d, *J* = 6.1 Hz, 1H), 4.94 (d, *J* = 8.5 Hz, 2H), 4.74 (d, *J* = 7.1 Hz, 1H), 4.67 (s, 1H), 4.66 (d, *J* = 6.7 Hz, 2H), 4.60 (d, *J* = 7.2 Hz, 1H), 4.58 (d, *J* = 6.7 Hz, 1H), 3.88 (dd, *J* = 9.4, 1.3 Hz, 1H), 3.75 (s, 1H), 3.38 (s, 3H), 3.34 (s, 3H), 3.28 (s, 3H), 3.13 (d, *J* = 5.4 Hz, 1H), 2.79 (d, *J* = 4.0 Hz, 1H), 2.52 (dt, *J* = 16.5, 2.4 Hz, 1H), 2.40 (d, *J* = 16.7 Hz, 1H), 2.36 – 2.28 (m, 1H), 2.16 – 2.07 (m, 1H), 1.82 (d, *J* = 9.0 Hz, 1H), 1.70 – 1.55 (m, 3H), 1.24 (s, 3H), 1.09 (s, 3H);

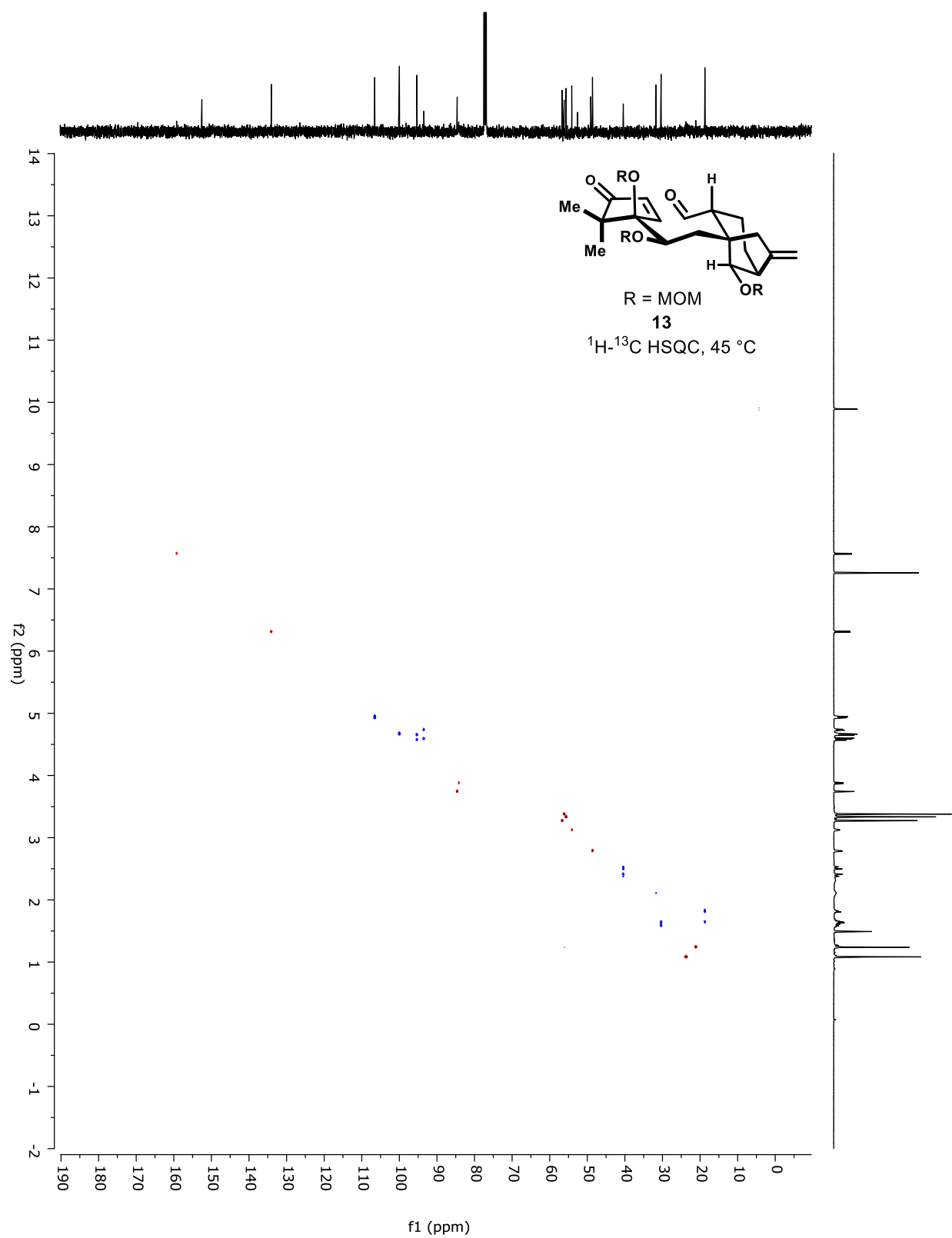
¹³C NMR (126 MHz, CDCl₃) δ 204.3, 159.3, 152.5, 134.1, 106.6, 100.0, 95.3, 93.5, 84.6, 56.7, 56.2, 55.7, 54.1, 52.6, 49.1, 48.6, 40.4, 31.7, 30.4, 23.78, 21.1, 18.7;

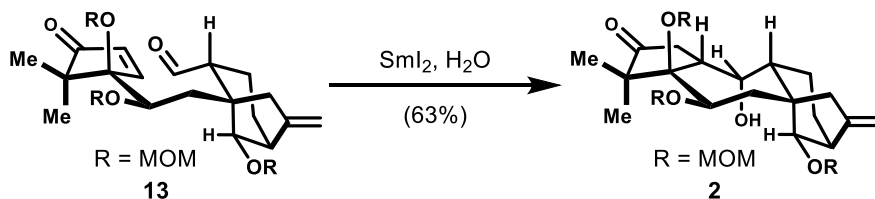
IR (cm⁻¹): 2937, 2826, 2824, 1717, 1465, 1445, 1384, 1151, 1106, 1029, 919, 881;

ESI-HRMS (*m/z*): [M+Na]⁺ calc'd for C₂₅H₃₈NaO₈⁺: 489.2459; found: 489.2515.









Tetracycle **2**:

Aldehyde **13** (29 mg, 0.062 mmol) was dissolved in THF (0.01 M, 6.2 mL). Water (2.9 μL , 0.16 mmol, 2.6 equiv) was added. The reaction mixture was cooled to -40°C . SmI_2 (0.1 M in THF; 15.5 mL, 1.55 mmol, 25 equiv) was added over 15 minutes. After 2 h, the flask was cooled to -72°C , then allowed to warm to 0°C over 2.5 hours. H_2O (10 mL) was added. The aqueous layer was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL) and brine (10 mL), then dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure by rotary evaporation. Purification by flash column chromatography on silica gel (hexanes \rightarrow 50% EtOAc/hexanes) afforded enone **2** (18.2 mg, 63% yield) as a white solid.

$R_f = 0.40$ (50% EtOAc in hexanes; not UV-active, stains blue-gray in *p*-anisaldehyde);

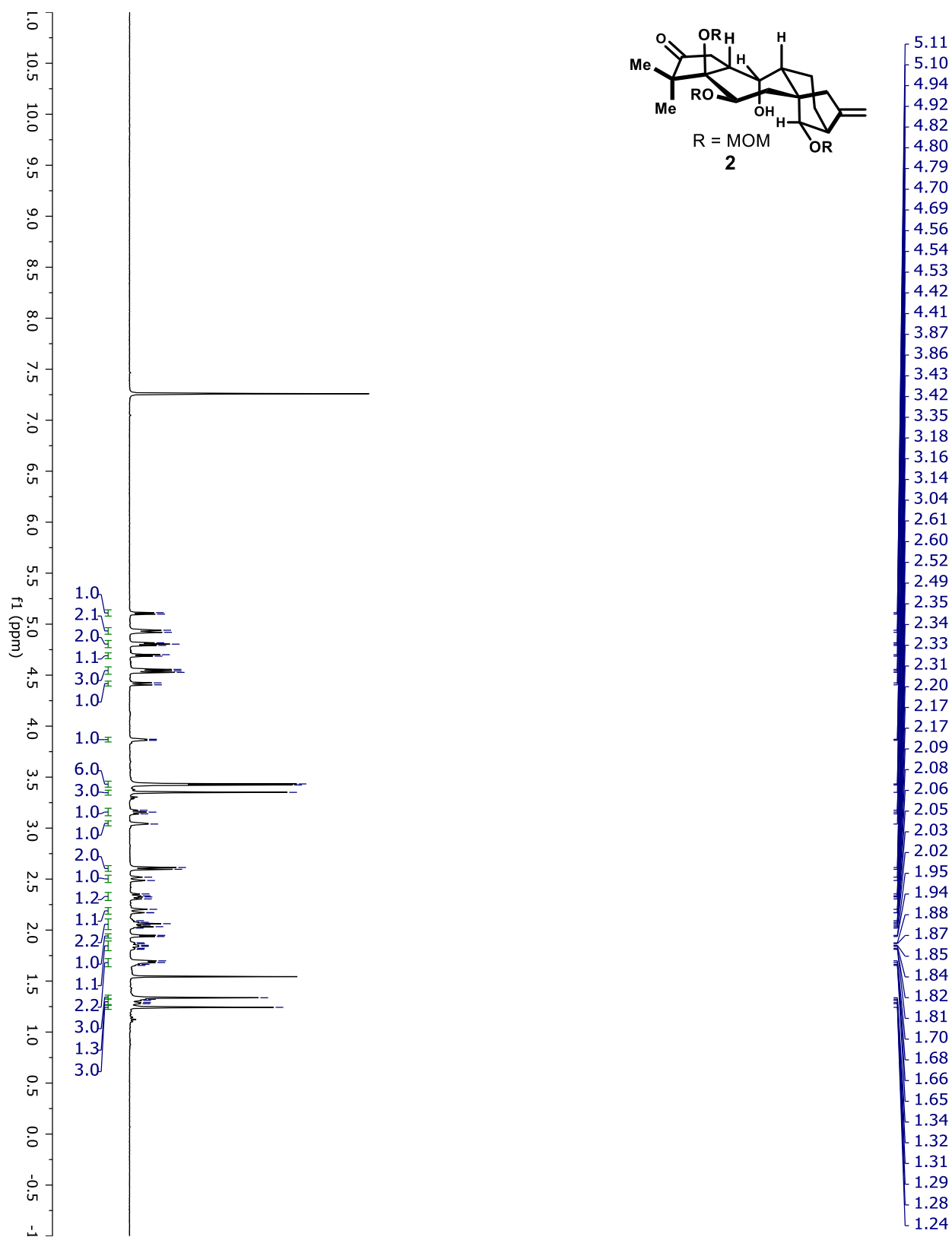
$[\alpha]_D^{20.0}$: -99.8° (*c* 1.0, CHCl_3);

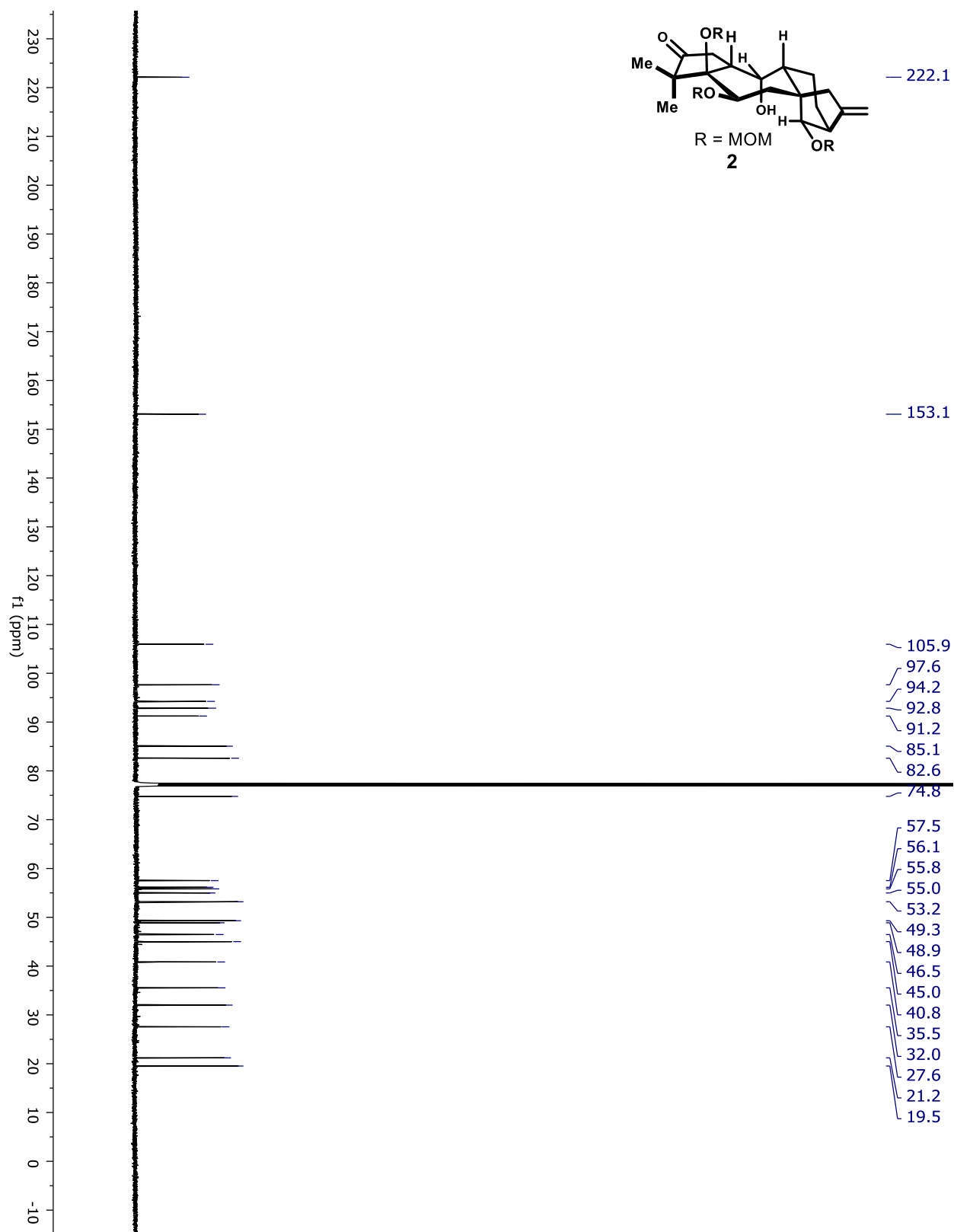
$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 5.11 (d, $J = 7.2$ Hz, 1H), 4.93 (d, $J = 10.2$ Hz, 2H), 4.81 (d, $J = 4.8$ Hz, 1H), 4.80 (d, $J = 6.3$ Hz, 1H), 4.69 (d, $J = 7.1$ Hz, 1H), 4.56 (s, 1H), 4.53 (d, $J = 7.4$ Hz, 2H), 4.41 (d, $J = 9.5$ Hz, 1H), 3.87 (d, $J = 5.2$ Hz, 1H), 3.43 (s, 3H), 3.42 (s, 3H), 3.35 (s, 3H), 3.16 (t, $J = 9.2$ Hz, 1H), 3.04 (d, $J = 2.7$ Hz, 1H), 2.60 (d, $J = 9.2$ Hz, 2H), 2.50 (d, $J = 16.6$ Hz, 1H), 2.33 (dd, $J = 14.8, 9.6$ Hz, 1H), 2.19 (d, $J = 17.0$ Hz, 1H), 2.11 – 2.00 (m, 2H), 1.94 (d, $J = 5.6$ Hz, 1H), 1.85 (td, $J = 14.0, 5.4$ Hz, 1H), 1.72 – 1.64 (m, 2H), 1.34 (s, 3H), 1.30 (dd, $J = 16.2, 6.2$ Hz, 1H), 1.24 (s, 3H);

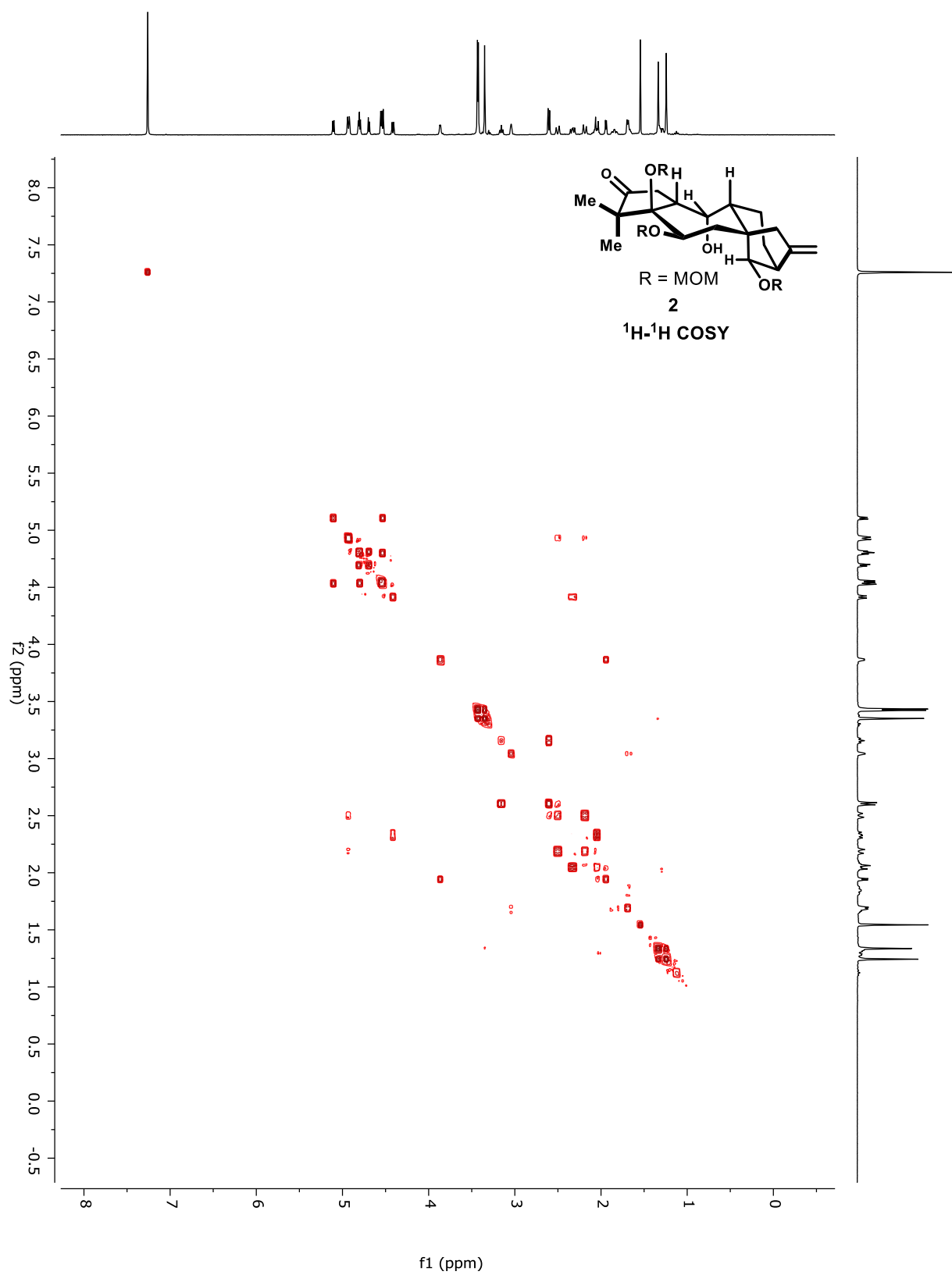
$^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 222.1, 153.1, 105.9, 97.6, 94.2, 92.8, 91.2, 85.1, 82.6, 74.8, 57.5, 56.1, 55.8, 55.0, 53.2, 49.3, 48.9, 46.5, 45.0, 40.8, 35.5, 32.0, 27.6, 21.2, 19.5;

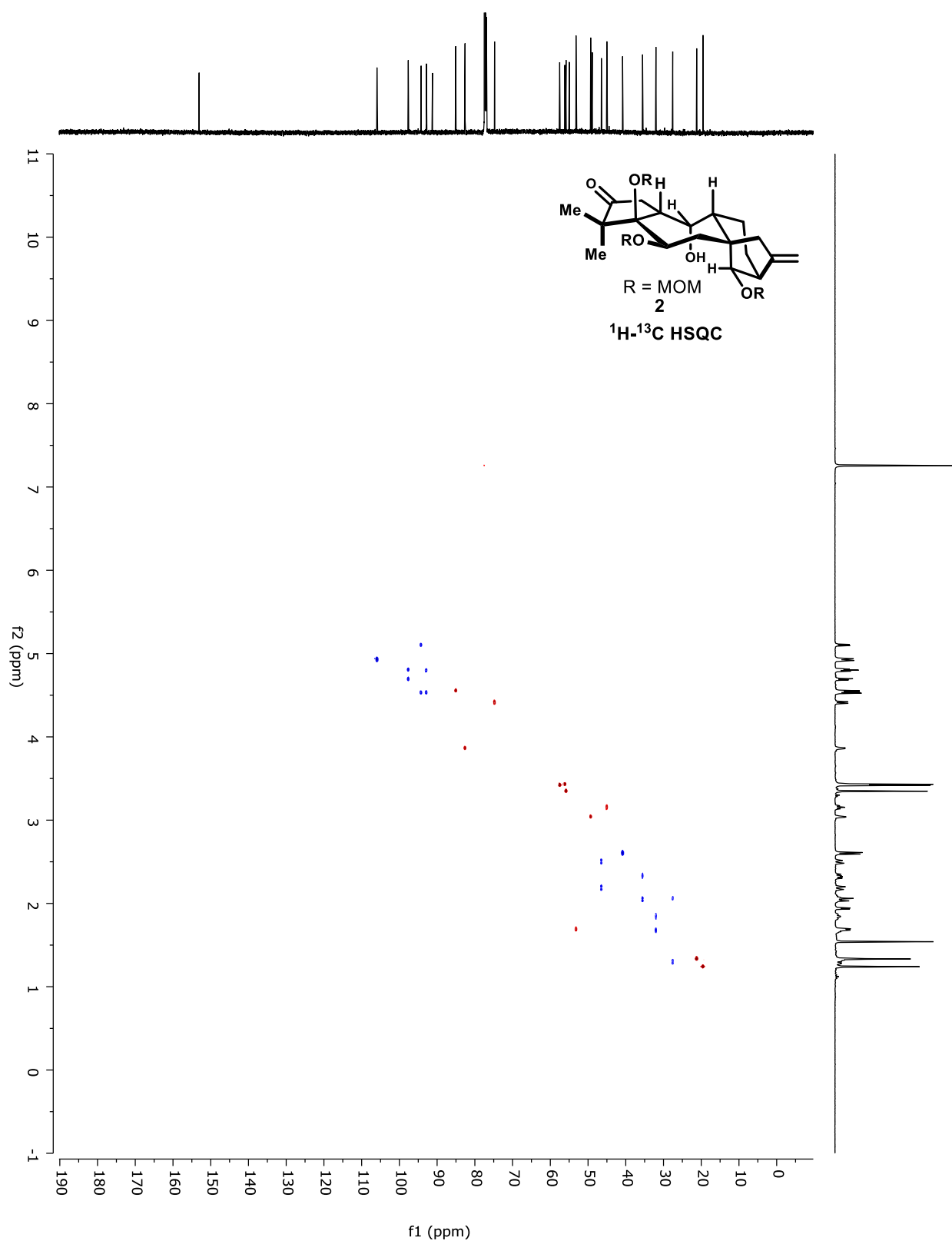
IR (cm^{-1}): 3479, 2953, 2824, 1735, 1660, 1448, 1380, 1278, 1212, 1148, 1104, 1087, 1063, 1030, 916;

ESI-HRMS (m/z): $[\text{M}+\text{Na}]^+$ calc'd for $\text{C}_{25}\text{H}_{40}\text{NaO}_8^+$: 491.2615; found: 491.2604.









Crystallographic Data for Compound 2

Experimental

Low-temperature diffraction data (ω -scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994+ CCD detector with Cu K α ($\lambda = 1.54178$ Å) for the structure of 007-16232. The diffraction images were processed and scaled using the Rigaku CrystalClear software (CrystalClear and CrystalStructure; Rigaku/MSK: The Woodlands, TX, 2005). The structure was solved with SHELXT and was refined against F^2 on all data by full-matrix least squares with SHELXL (Sheldrick, G. M. Acta Cryst. 2008, A64, 112–122). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl groups). Atom H3 was found in the difference map and freely refined. Many potential hydrogen bonds were identified that involved C–H...O interactions, but all hydrogen atoms associated with carbon were geometrically restrained (See table 7). The full numbering scheme of compound 007-16232 can be found in the full details of the X-ray structure determination (CIF), which is included as Supporting Information.

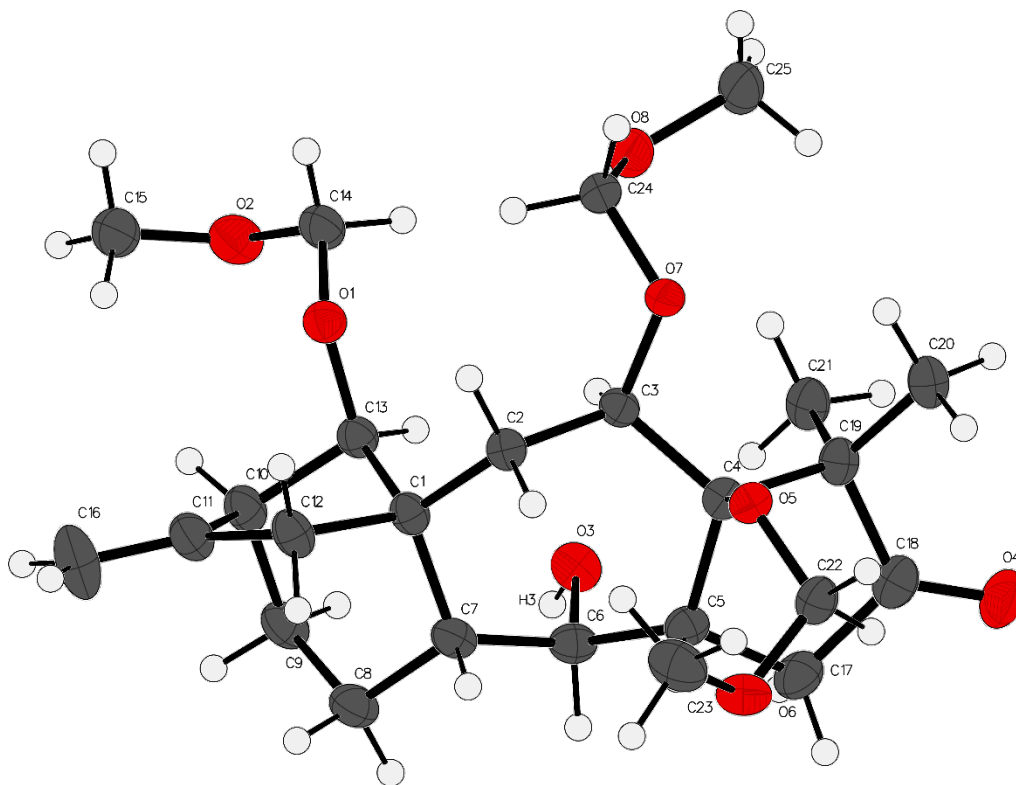


Figure SI-1. The complete numbering scheme of 007-16232 with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity.

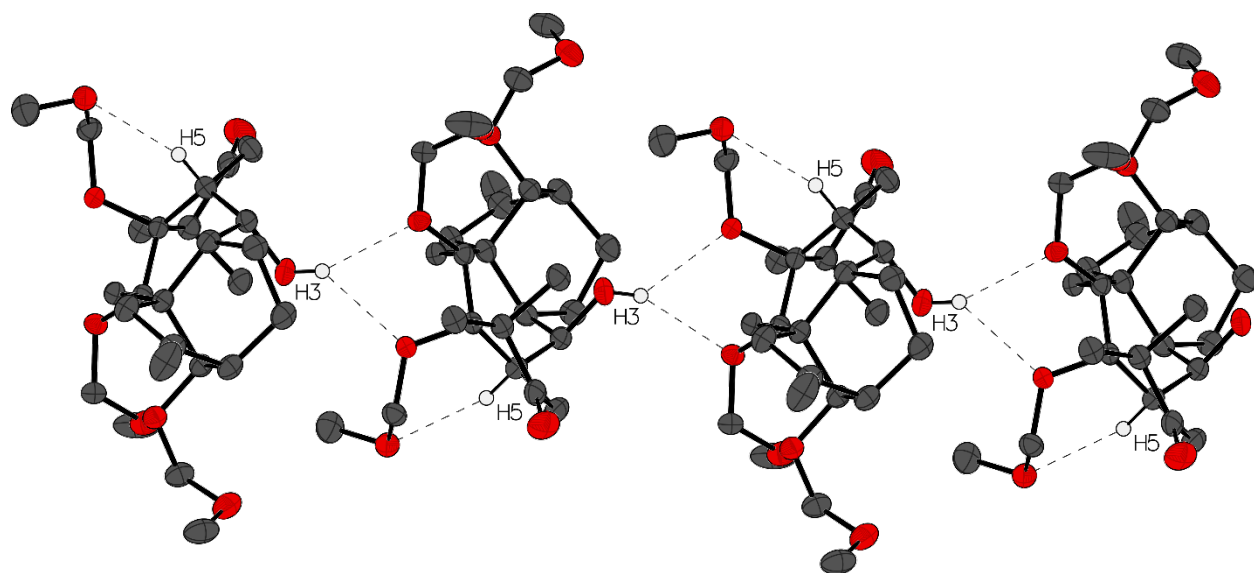
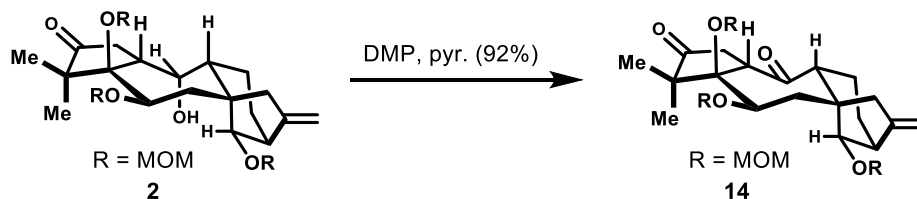


Figure SI-2. Hydrogen bonding network in 007-16232 with 50% thermal ellipsoid probability levels. Dashed lines highlight donor acceptor interactions.

Table SI-1. Crystal data and structure refinement for 007-16232.

Identification code	007-16232	
Empirical formula	C ₂₅ H ₄₀ O ₈	
Formula weight	468.57	
Temperature	93(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2 ₁ 2 ₁ 2 ₁	
Unit cell dimensions	a = 9.1723(6) Å	α = 90°.
	b = 13.1708(9) Å	β = 90°.
	c = 20.2598(14) Å	γ = 90°.
Volume	2447.5(3) Å ³	
Z	4	
Density (calculated)	1.272 Mg/m ³	
Absorption coefficient	0.769 mm ⁻¹	
F(000)	1016	
Crystal size	0.200 x 0.020 x 0.020 mm ³	
Theta range for data collection	4.003 to 67.841°.	
Index ranges	-11 ≤ h ≤ 10, -15 ≤ k ≤ 15, -24 ≤ l ≤ 24	
Reflections collected	87547	
Independent reflections	4431 [R(int) = 0.0409]	
Completeness to theta = 67.679°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.000 and 0.894	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	4431 / 0 / 307	
Goodness-of-fit on F ²	1.054	
Final R indices [I > 2σ(I)]	R1 = 0.0253, wR2 = 0.0654	
R indices (all data)	R1 = 0.0280, wR2 = 0.0665	
Absolute structure parameter	0.00(3)	
Largest diff. peak and hole	0.234 and -0.137 e.Å ⁻³	



Diketone **14**:

Alcohol **2** (24.0 mg, 0.051 mmol) was dissolved in a 2:1 solution of CH_2Cl_2 :pyridine (0.51 mL, 0.26 mL; 0.07 M). Dess-Martin periodinane (0.11 g, 0.26 mmol, 5.0 equiv) was added. After stirring for 20 hours, sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ was added. The resulting mixture was stirred for 30 minutes, followed by separation of the aqueous layer and extraction with EtOAc (4 mL x 3). The combined organic layers were washed with sat. aq. NaHCO_3 (3 mL), water (3 mL), and brine (3 mL), then dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure by rotary evaporation. Purification by flash column chromatography on silica gel (hexanes \rightarrow 25% EtOAc/hexanes) afforded diketone **14** (22.0 mg, 92% yield) as a white solid.

$R_f = 0.64$ (50% EtOAc in hexanes; not UV-active, stains blue-gray in *p*-anisaldehyde);

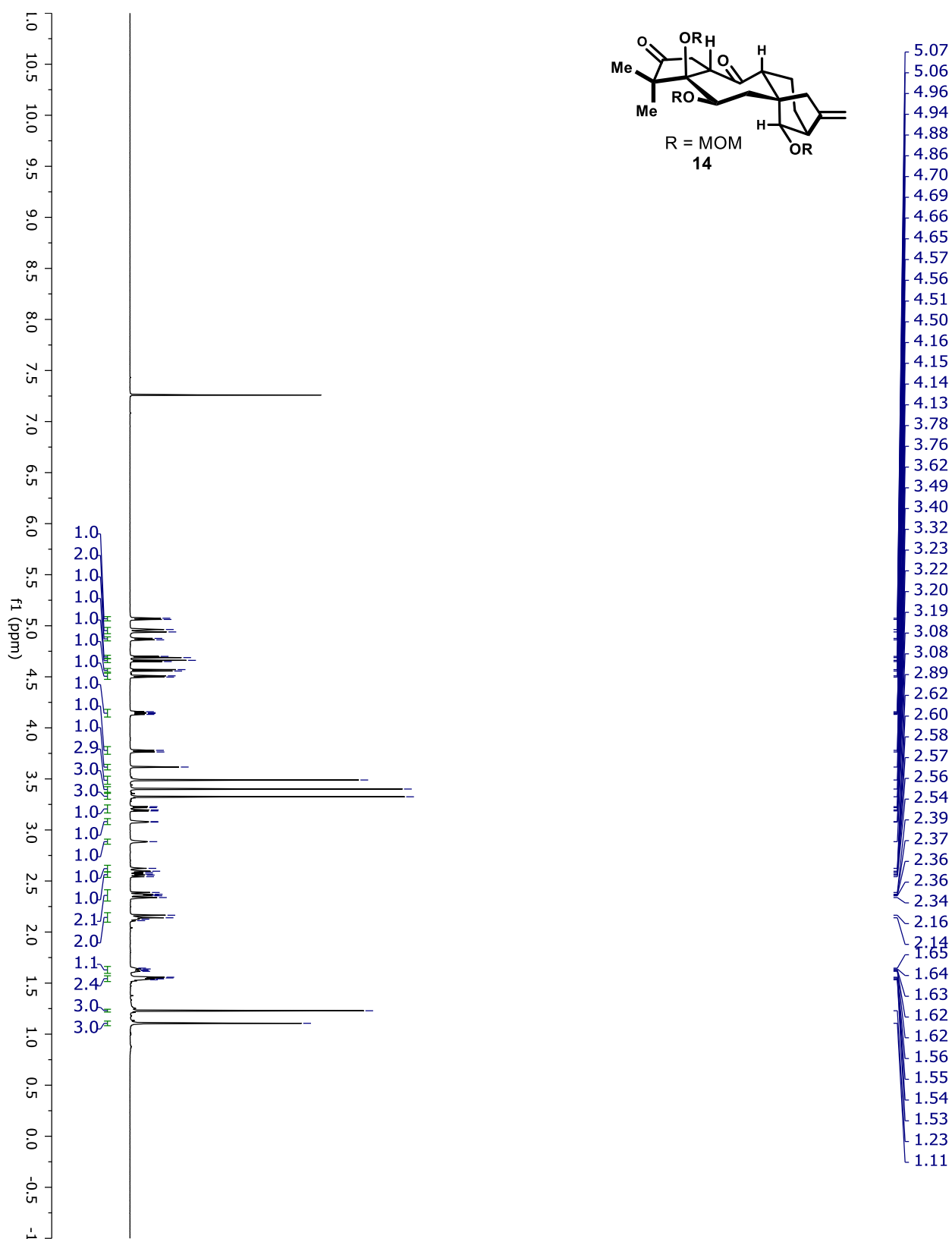
$[\alpha]_D^{20.0}$: -53.3° (c 1.0, CHCl_3);

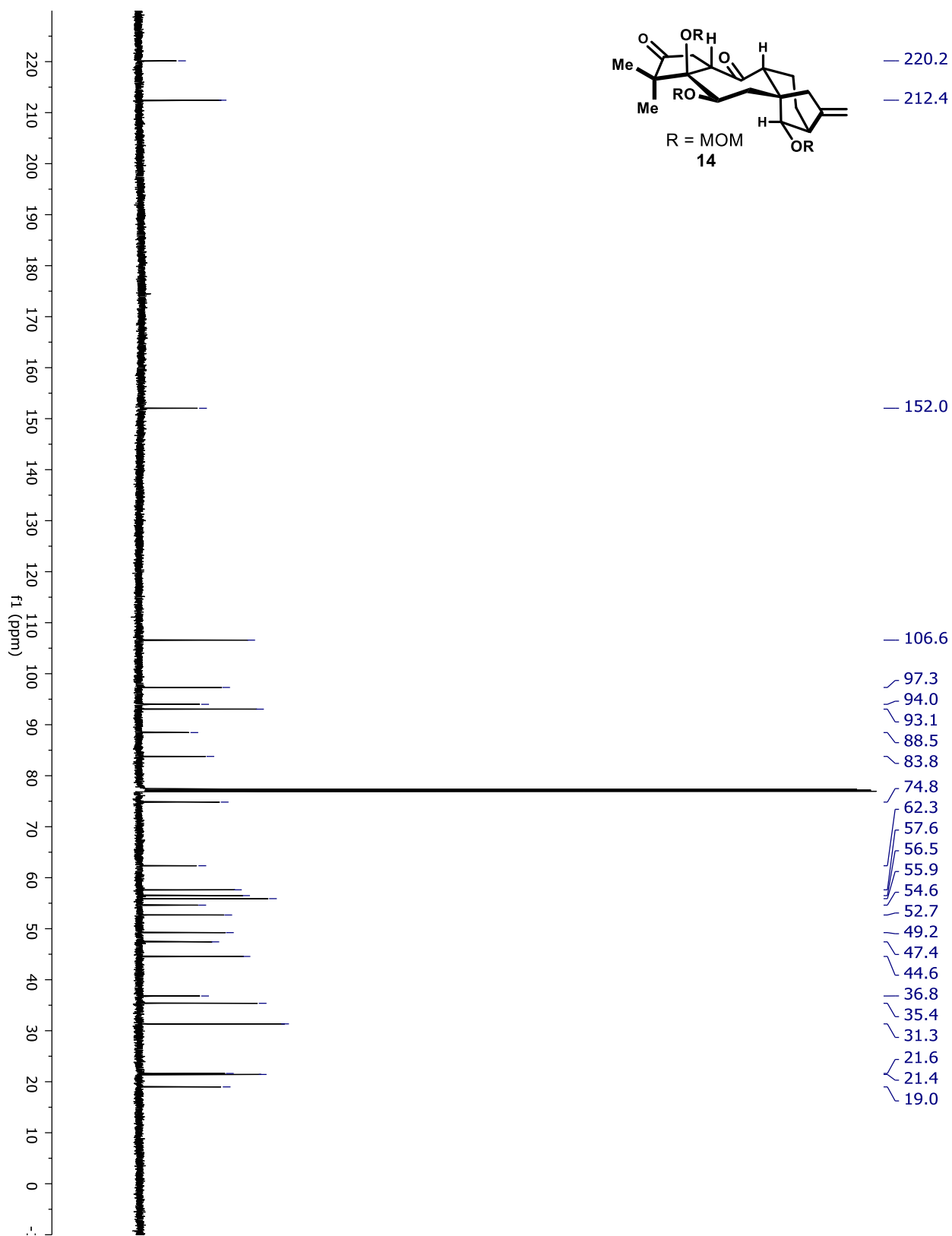
$^1\text{H NMR}$ (600 MHz, CDCl_3) δ 5.07 (d, $J = 7.2$ Hz, 1H), 4.95 (d, $J = 14.3$ Hz, 2H), 4.87 (d, $J = 8.3$ Hz, 1H), 4.69 (d, $J = 7.0$ Hz, 1H), 4.66 (d, $J = 7.0$ Hz, 1H), 4.56 (d, $J = 8.3$ Hz, 1H), 4.50 (d, $J = 7.2$ Hz, 1H), 4.14 (dd, $J = 10.1, 5.6$ Hz, 1H), 3.77 (d, $J = 9.6$ Hz, 1H), 3.62 (s, 1H), 3.49 (s, 3H), 3.40 (s, 3H), 3.32 (s, 3H), 3.21 (dd, $J = 19.3, 5.6$ Hz, 1H), 3.08 (ad, 1H), 2.89 (s, 1H), 2.64 – 2.59 (m, 1H), 2.56 (dd, $J = 15.1, 9.7$ Hz, 1H), 2.40 – 2.33 (m, 2H), 2.18 – 2.11 (m, 2H), 1.66 – 1.60 (m, 1H), 1.57 – 1.52 (m, 2H), 1.23 (s, 3H), 1.11 (s, 3H);

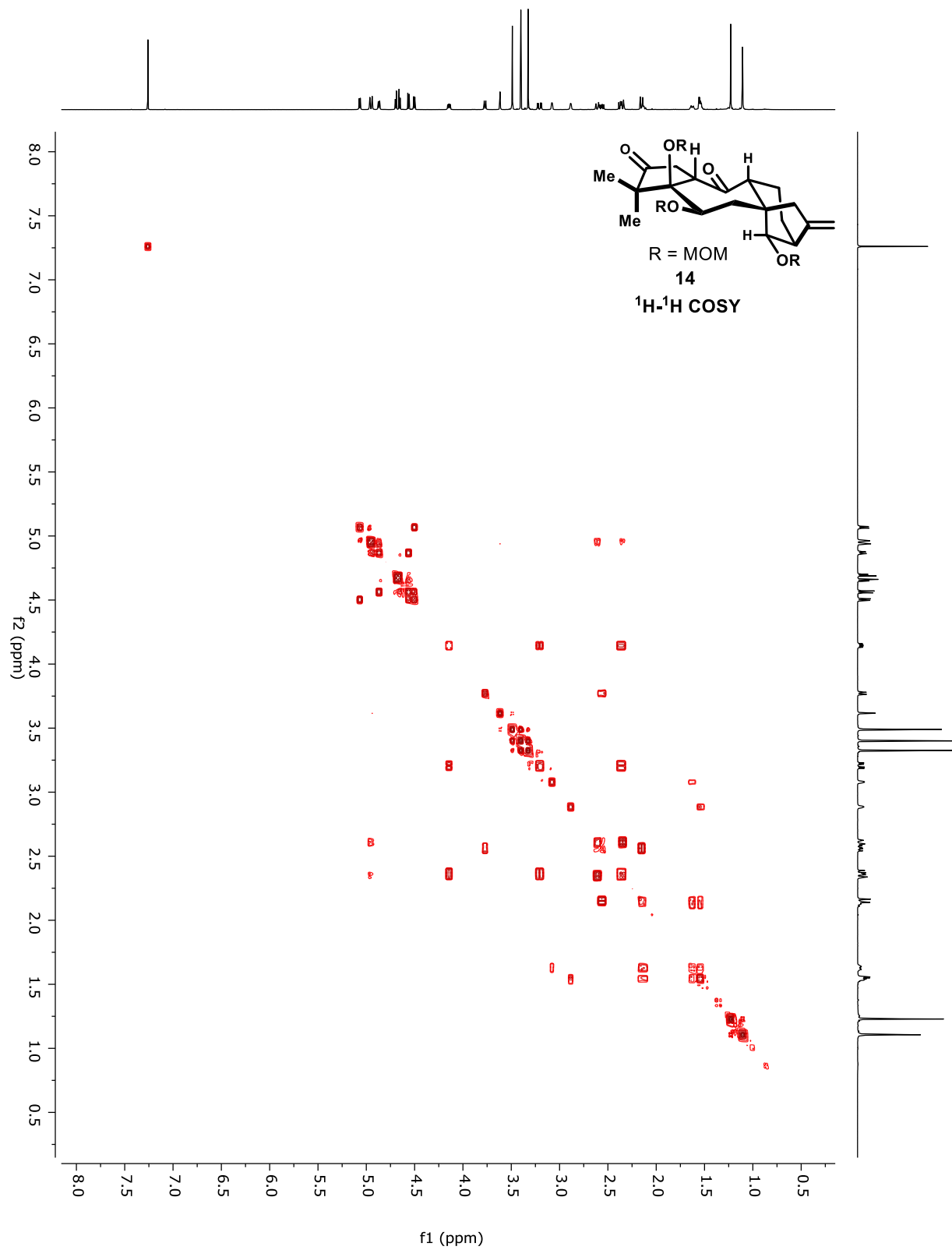
$^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 220.2, 212.4, 152.0, 106.6, 97.3, 94.0, 93.1, 88.5, 83.8, 74.8, 62.3, 57.6, 56.5, 55.9, 54.6, 52.7, 49.2, 47.4, 44.6, 36.8, 35.4, 31.3, 21.6, 21.4, 19.0;

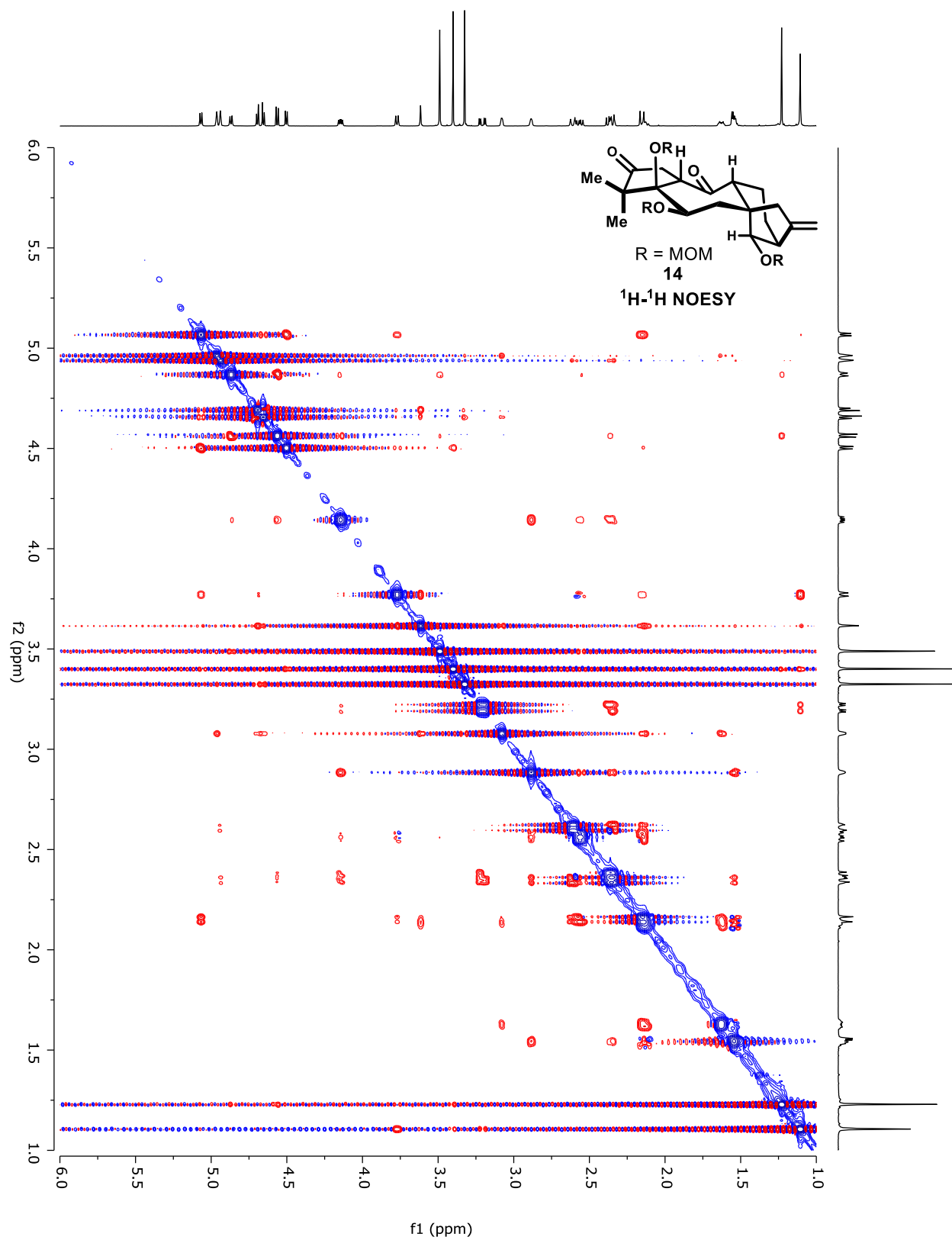
IR (cm^{-1}): 2934, 2825, 1742, 1706, 1449, 1403, 1380, 1213, 1149, 1107, 1079, 1037, 916;

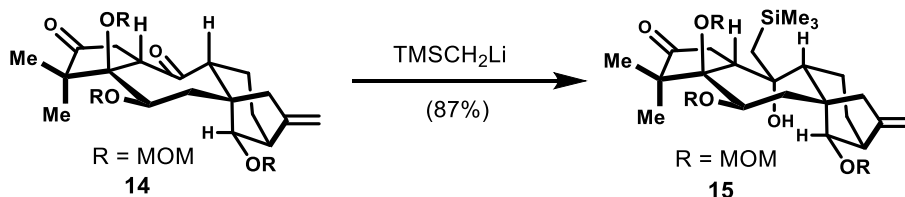
ESI-HRMS (m/z): $[\text{M}+\text{Na}]^+$ calc'd for $\text{C}_{25}\text{H}_{38}\text{NaO}_8^+$: 489.2459; found: 489.2433.











Tertiary alcohol **15**:

Diketone **14** (8.2 mg, 0.018 mmol) was dissolved in THF (1.8 mL, 0.01 M). The reaction mixture was cooled to 0 °C and (trimethylsilyl)methylolithium solution (1.0 M in pentane, 0.18 mL, 0.18 mmol, 10 equiv) was added. After stirring at the same temperature for 15 minutes, the reaction vial was removed from the ice bath. After two minutes, sat. aq. NH_4Cl was added, followed by extraction with EtOAc (4 mL x 3). The combined organic layers were washed with brine (3 mL), then dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure by rotary evaporation. Purification by flash column chromatography on silica gel (hexanes \rightarrow 25% EtOAc/hexanes) afforded tertiary alcohol **15** (8.4 mg, 87% yield) as a white solid.

$R_f = 0.75$ (25% in hexanes; not UV-active, stains blue-grey in *p*-anisaldehyde);

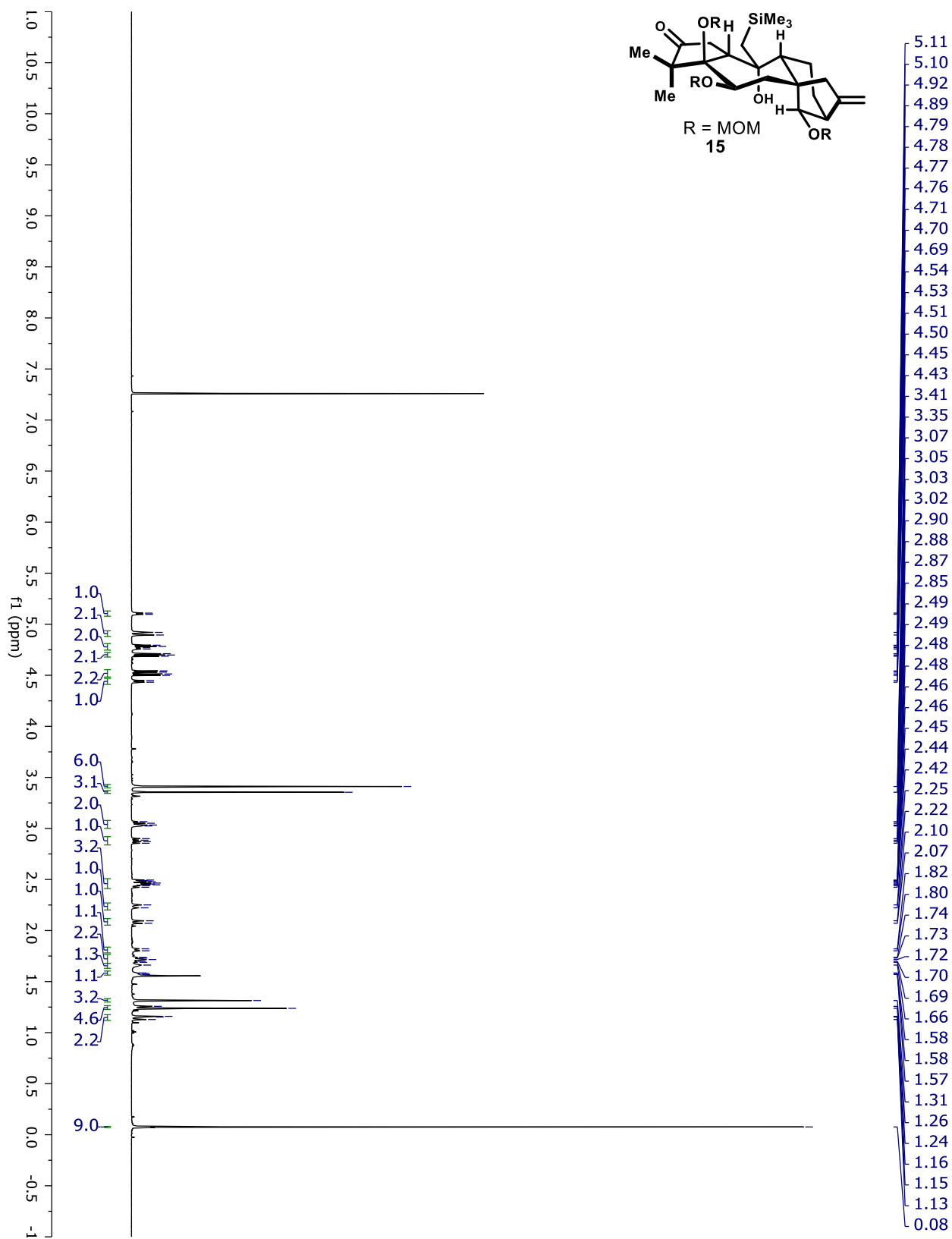
$[\alpha]_D^{20.0} : -40.2^\circ$ (*c* 1.0, CHCl_3);

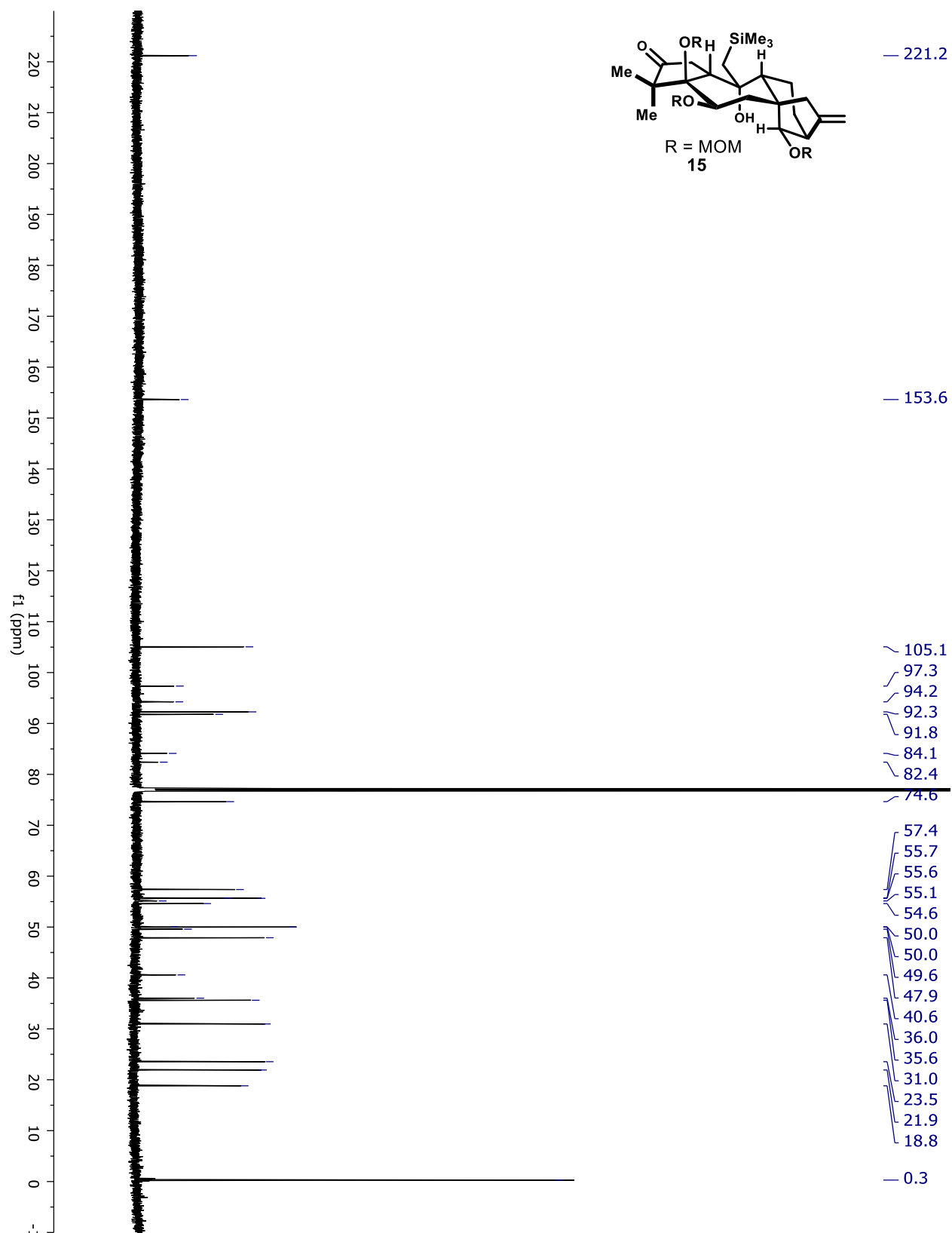
^1H NMR (600 MHz, CDCl_3) δ 5.10 (d, *J* = 7.1 Hz, 1H), 4.91 (d, *J* = 15.4 Hz, 2H), 4.79 (d, *J* = 7.0 Hz, 1H), 4.76 (d, *J* = 8.1 Hz, 1H), 4.71 (s, 1H), 4.69 (d, *J* = 7.0 Hz, 1H), 4.54 (d, *J* = 7.1 Hz, 1H), 4.51 (d, *J* = 8.2 Hz, 1H), 4.44 (d, *J* = 9.9 Hz, 1H), 3.41 (s, 6H), 3.35 (s, 3H), 3.08 – 3.00 (m, 2H), 2.88 (dd, *J* = 18.0, 9.4 Hz, 1H), 2.52 – 2.41 (m, 3H), 2.24 (d, *J* = 17.1 Hz, 1H), 2.08 (d, *J* = 14.9 Hz, 1H), 1.81 (d, *J* = 11.7 Hz, 1H), 1.75 – 1.69 (m, 2H), 1.66 (bs, 1H), 1.60 – 1.56 (m, 1H), 1.31 (s, 3H), 1.26 – 1.23 (m, 4H), 1.17 – 1.12 (m, 2H), 0.08 (s, 9H);

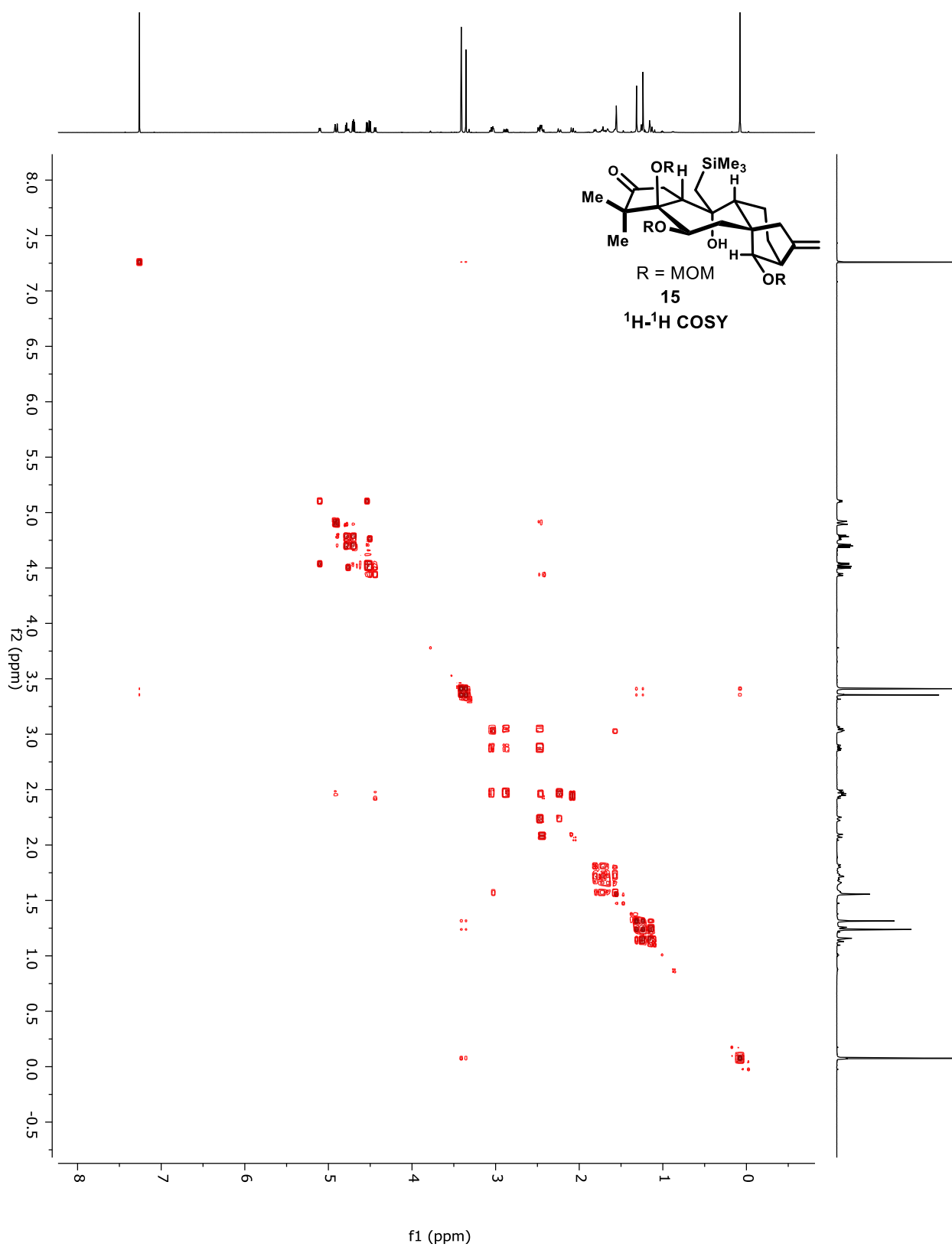
^{13}C NMR (151 MHz, CDCl_3) δ 221.2, 153.6, 105.1, 97.3, 94.2, 92.3, 91.8, 84.1, 82.4, 74.6, 57.4, 55.7, 55.6, 55.1, 54.6, 50.1, 50.0, 49.6, 47.9, 40.6, 36.0, 35.6, 31.0, 23.5, 21.9, 18.8, 0.3;

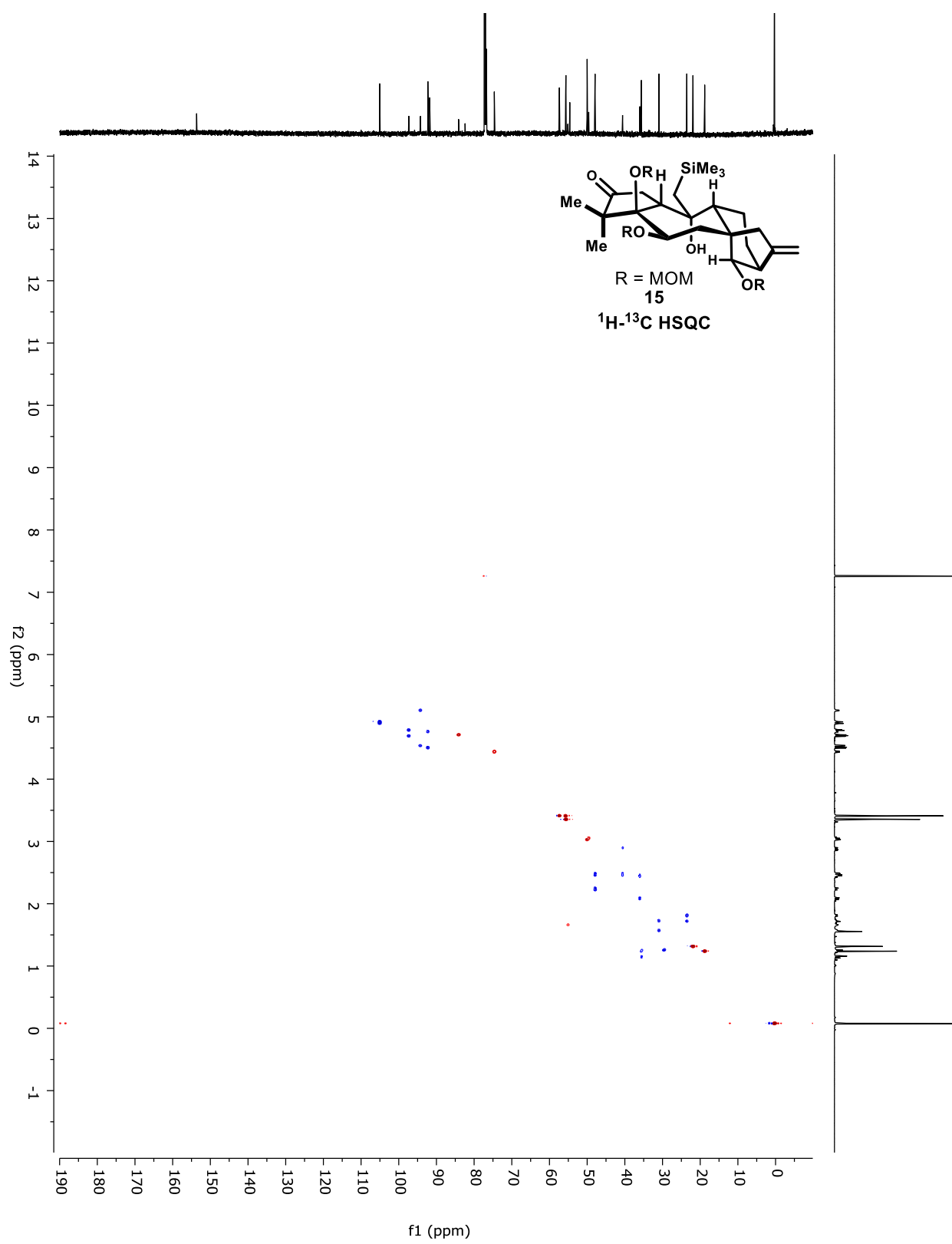
IR (cm^{-1}): 3500, 2935, 1738, 1443, 1380, 1250, 1210, 1148, 1105, 1038, 1015, 917, 854;

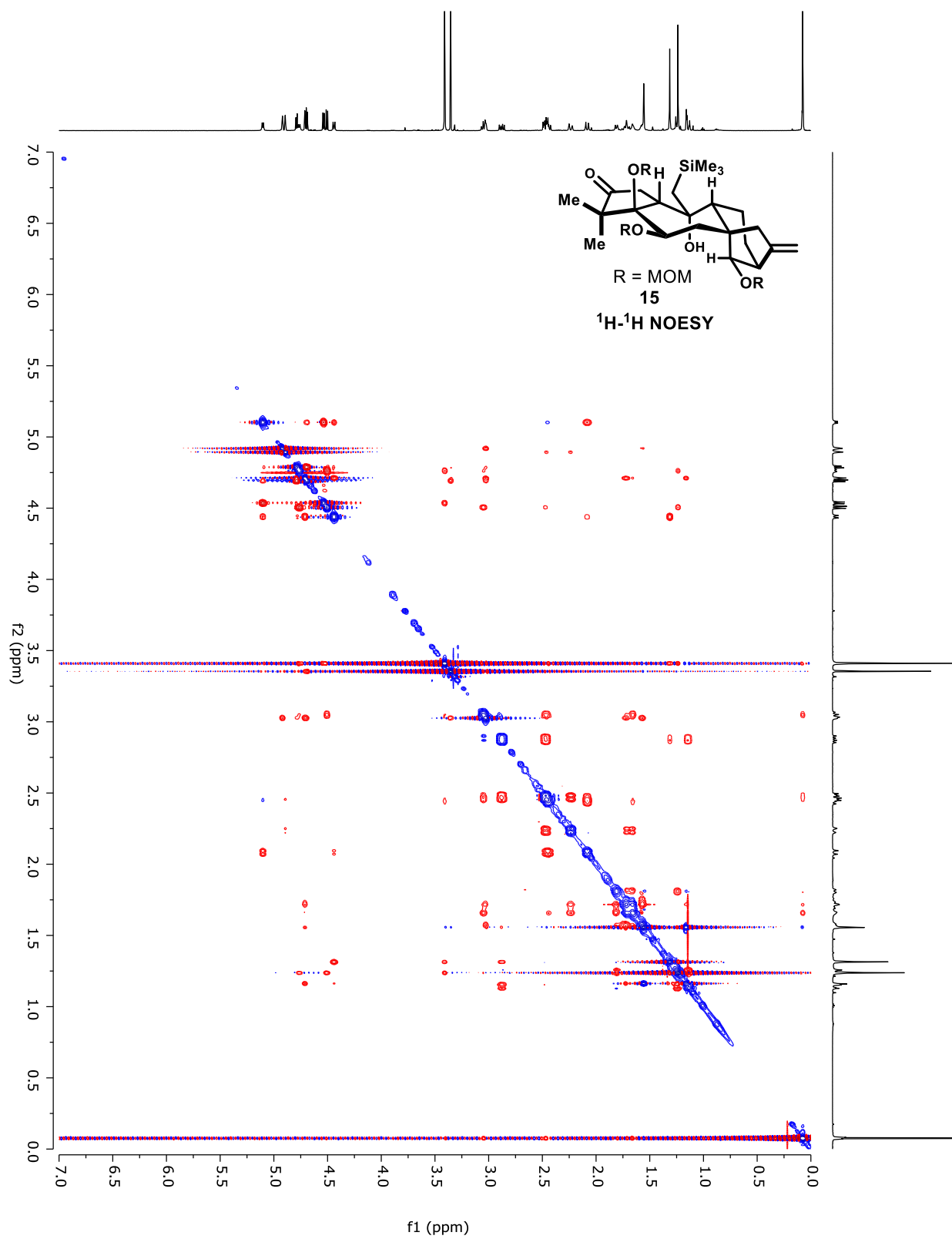
ESI-HRMS (*m/z*): $[\text{M}+\text{Na}]^+$ calc'd for $\text{C}_{29}\text{H}_{50}\text{NaO}_8\text{Si}^+$: 577.3167; found: 577.3189.

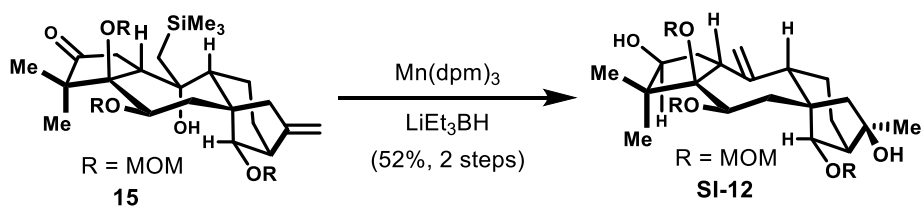












Diol (SI-12):

Olefin **15** (4.0 mg, 0.007 mmol) was dissolved in EtOH (0.4 mL, 0.02 M). Mn(dpm)_3 (0.6 mg, 0.15 equiv) was added. O_2 was bubbled through the solution for 3 minutes, followed by addition of PhSiH_3 (1.9 μL , 0.015 mmol, 2.2 equiv). After 1.5 h, water (2 mL) was added, followed by extraction with EtOAc (2 mL x 3). The combined organic layers were washed with brine (2 mL), then dried over anhydrous Na_2SO_4 , filtered through a SiO_2 plug, flushed with EtOAc, and concentrated under reduced pressure by rotary evaporation. The resulting material was used in the next step without further purification.

The hydration product was dissolved in THF (0.6 mL, 0.01 M) and cooled to 0 °C. LiEt_3BH (1.0 M in THF, 0.10 mL, 0.10 mmol, 14 equiv) was added. After 2 hours, the reaction vial was moved to a 65 °C bath. After 16 hours, water (2 mL) was added, followed by extraction with EtOAc (2 mL x 3). The combined organic layers were washed with brine (2 mL), then dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure by rotary evaporation. Purification by SiO_2 preparatory thin-layer chromatography eluting with 75% EtOAc/hexanes afforded diol **SI-12** (1.8 mg, 52% yield) as a white solid.

$R_f = 0.27$ (75% EtOAc in hexanes; not UV-active, stains blue-purple in *p*-anisaldehyde);

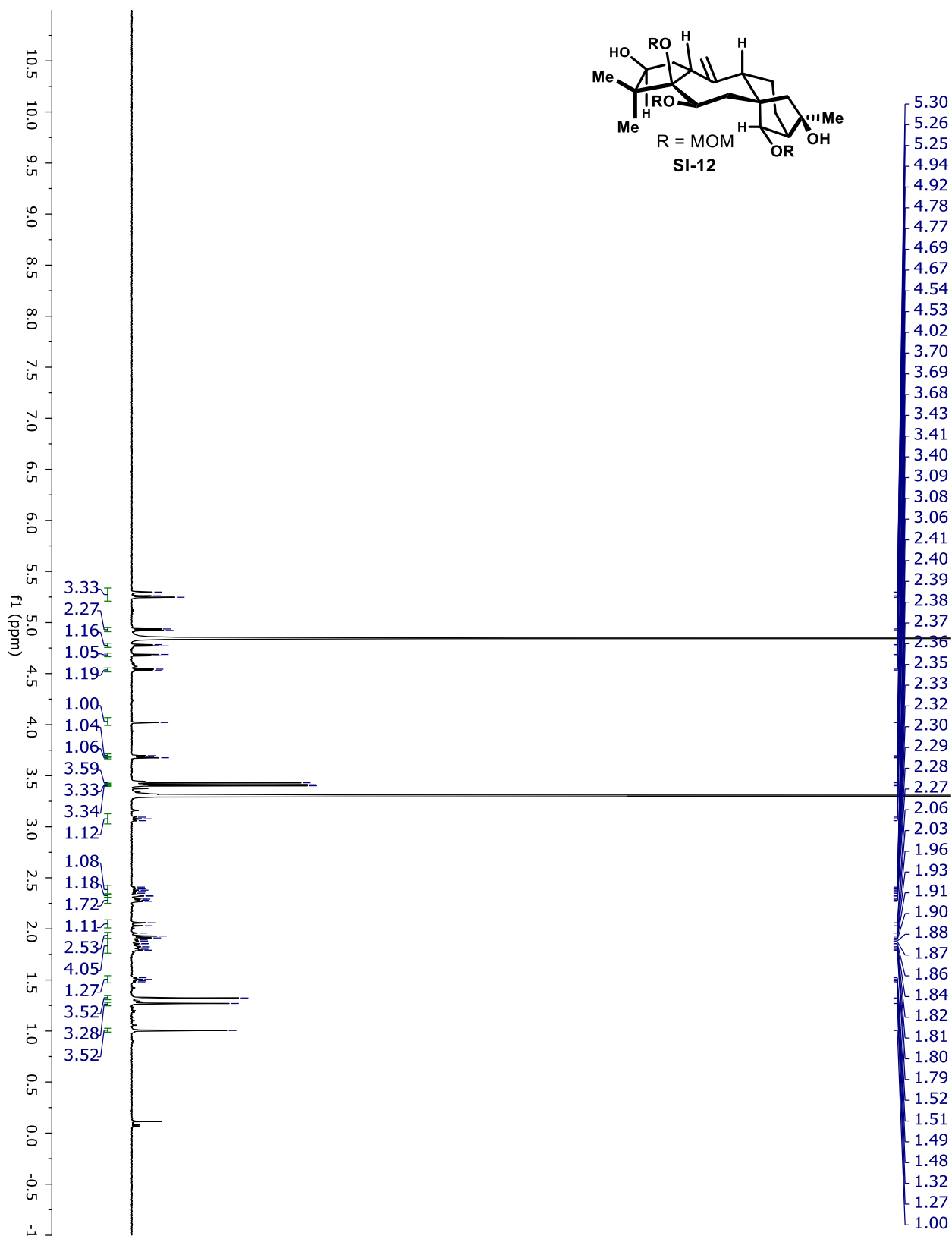
$[\alpha]_D^{20.0} : -14.6^\circ$ (*c* 0.3, MeOH);

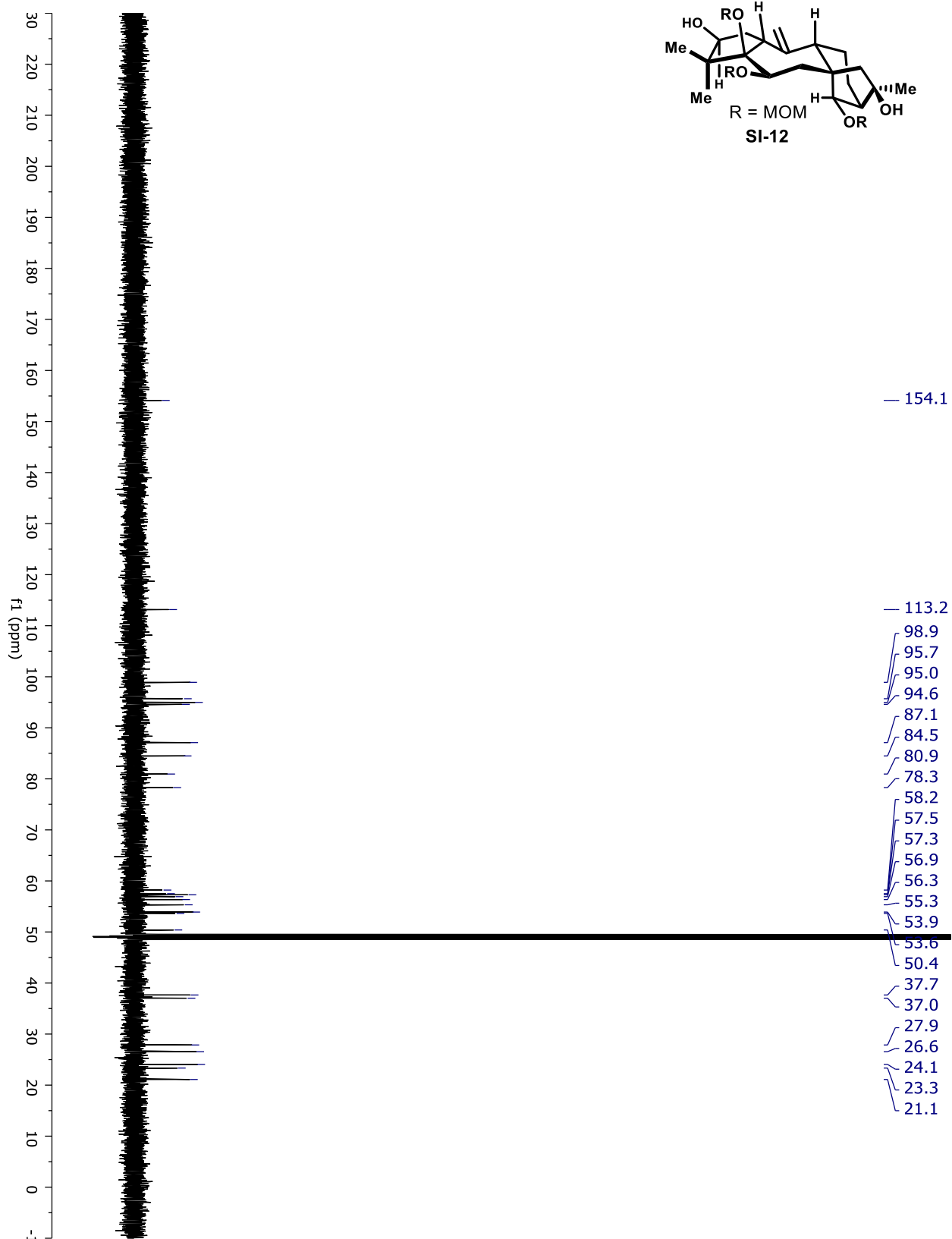
^1H NMR (500 MHz, CD_3OD) δ 5.30 (s, 1H), 5.26 (s, 1H), 5.25 (s, 1H), 4.93 (d, $J = 7.4$ Hz, 2H), 4.78 (d, $J = 6.6$ Hz, 1H), 4.68 (d, $J = 6.6$ Hz, 1H), 4.54 (d, $J = 6.8$ Hz, 1H), 4.02 (s, 1H), 3.69 (d, $J = 4.5$ Hz, 1H), 3.68 (s, 1H), 3.43 (s, 3H), 3.41 (s, 3H), 3.40 (s, 3H), 3.08 (t, $J = 8.6$ Hz, 1H), 2.38 (ddd, $J = 15.2, 9.0, 6.1$ Hz, 1H), 2.32 (ad, $J = 2.3$ Hz, 1H), 2.31 – 2.26 (m, 2H), 2.04 (d, $J = 14.9$ Hz, 1H), 1.96 – 1.90 (m, 2H), 1.90 – 1.77 (m, 4H), 1.54 – 1.46 (m, 1H), 1.32 (s, 3H), 1.27 (s, 3H), 1.00 (s, 3H);

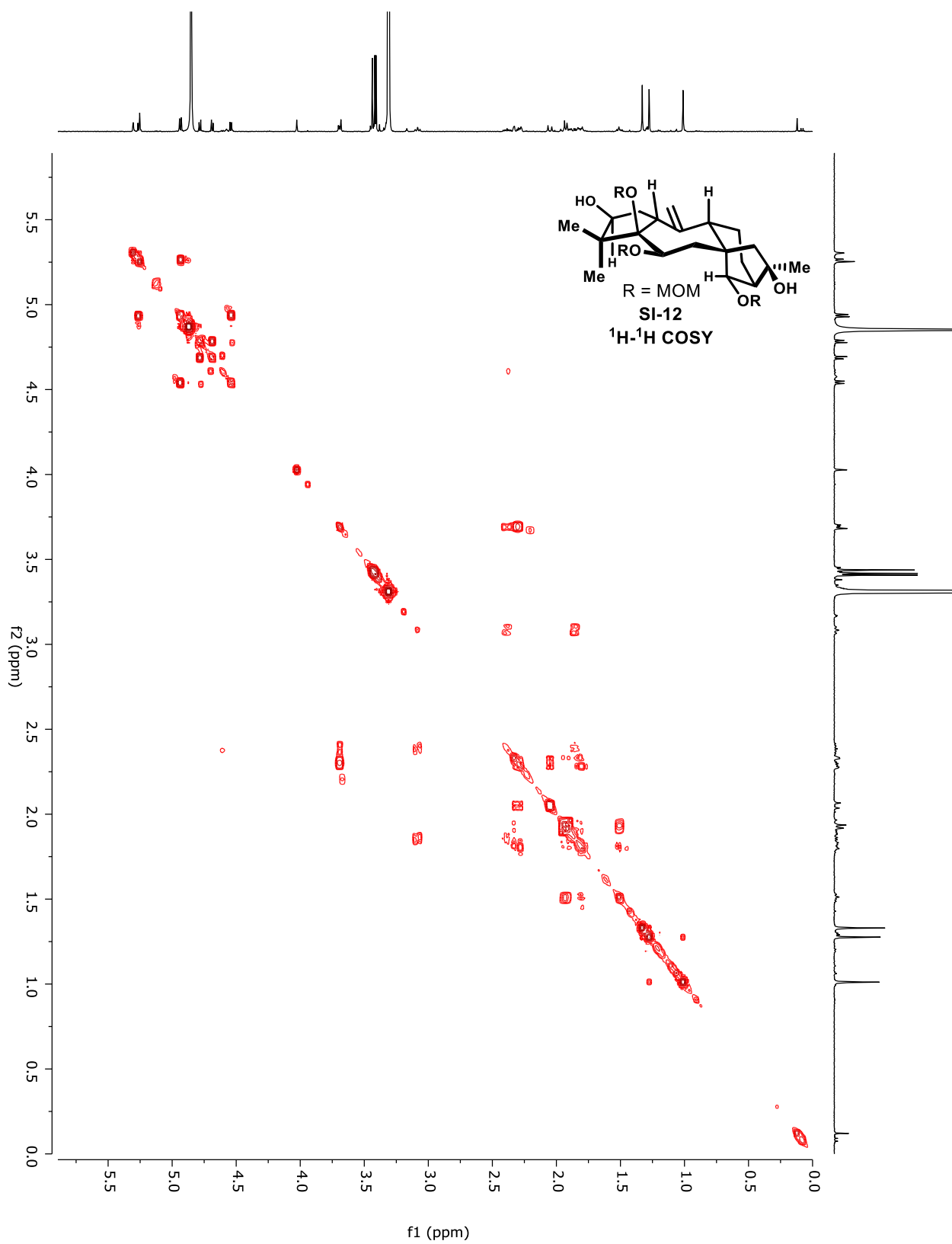
^{13}C NMR (151 MHz, CD_3OD) δ 154.1, 113.2, 98.9, 95.7, 95.0, 94.6, 87.11, 84.5, 80.9, 78.3, 58.2, 57.5, 57.3, 56.9, 56.3, 55.3, 53.9, 53.6, 50.4, 37.7, 37.0, 27.9, 26.6, 24.1, 23.3, 21.1;

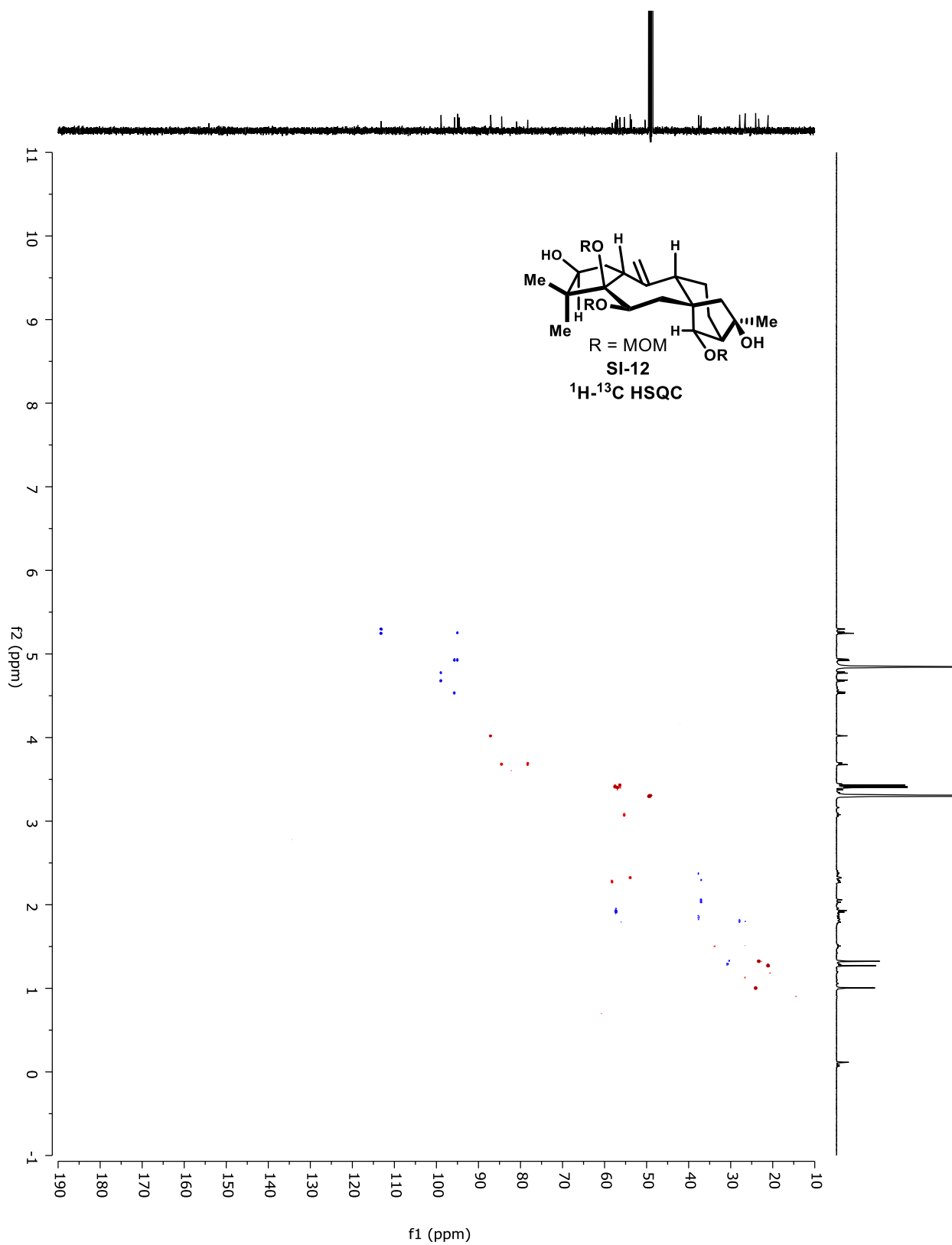
IR (cm^{-1}): 3474, 2935, 1447, 1414, 1248, 1212, 1147, 1093, 1057, 1029, 917, 860;

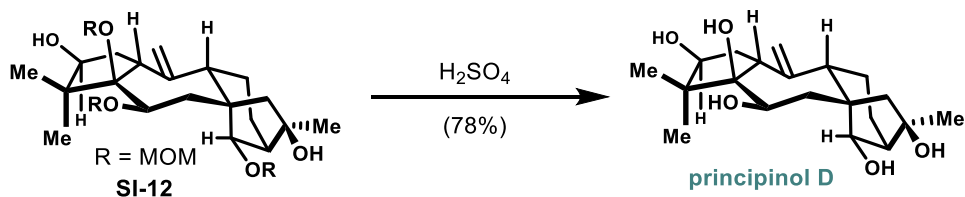
ESI-HRMS (m/z): $[\text{M}+\text{Na}]^+$ calc'd for $\text{C}_{26}\text{H}_{44}\text{NaO}_8^+$: 507.2928; found: 507.2978.











Principinol D:

Diol **SI-12** (2.0 mg, 0.0041 mmol, 1.0 equiv) was dissolved in 1,4-dioxane (0.30 mL, 0.01 M). 2 M H_2SO_4 (0.15 mL) was added. After 5 days, the reaction mixture was diluted with water (2 mL) and extracted with EtOAc (3 mL x 3). The combined organic layers were washed with brine (2 mL), then dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure by rotary evaporation. Purification by SiO_2 preparatory thin-layer chromatography eluting with 50% THF/pentane afforded **principinol D** (1.2 mg, 78%) as a white solid.

$R_f = 0.14$ (EtOAc; not UV-active, stains blue-purple in *p*-anisaldehyde);

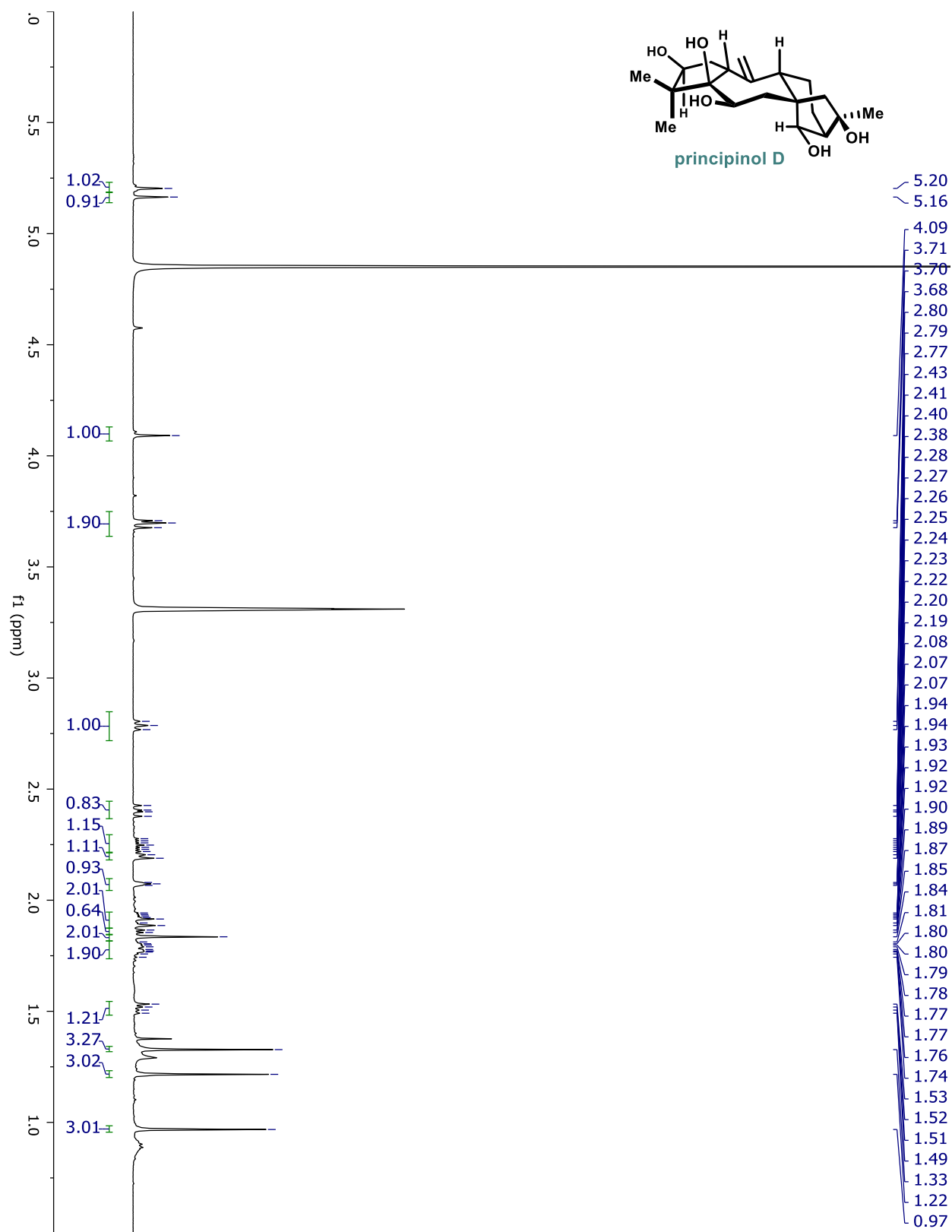
$[\alpha]_D^{20.0} : +6.0^\circ$ (*c* 0.2, MeOH);

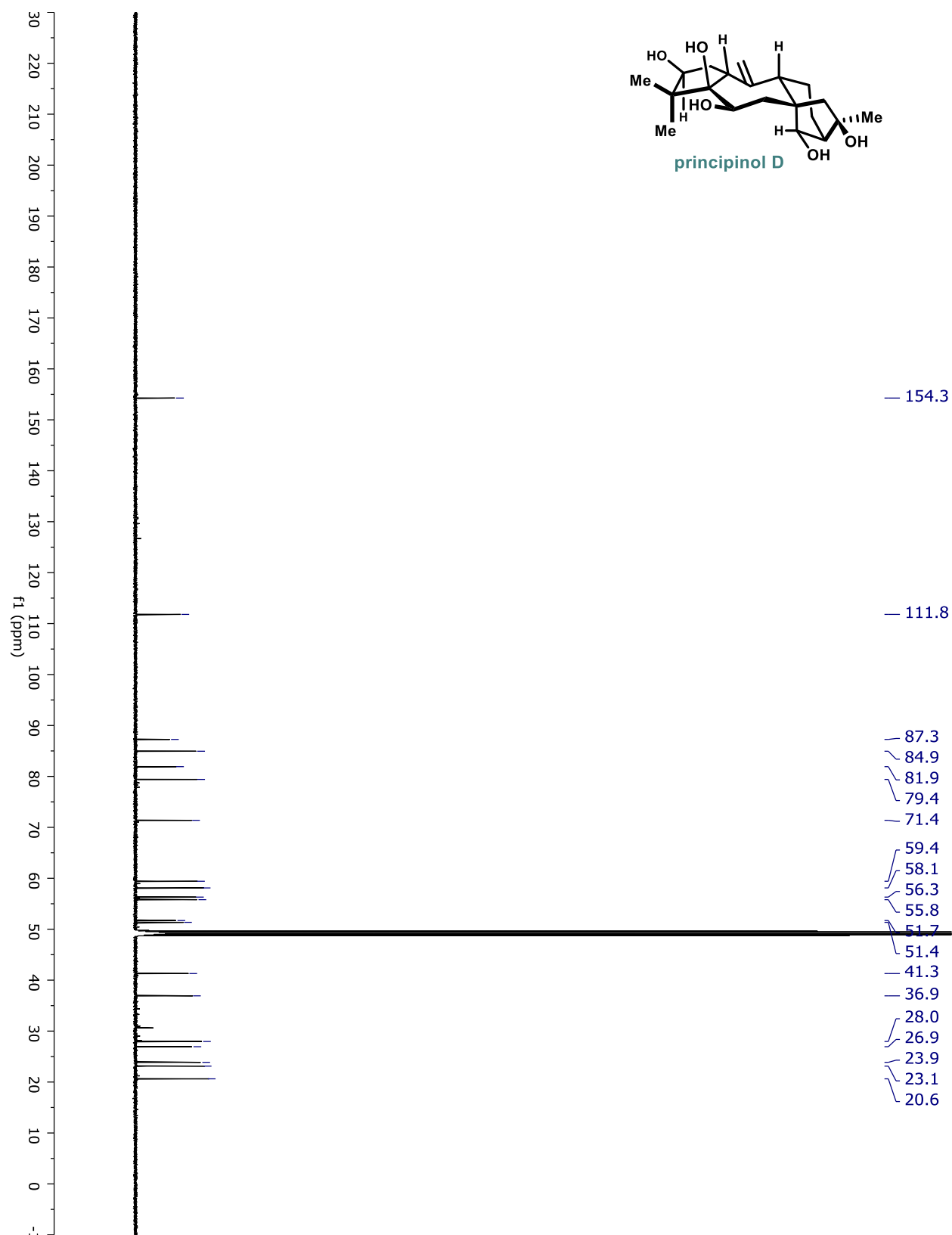
$^1\text{H NMR}$ (500 MHz, CD_3OD) δ 5.20 (s, 1H), 5.16 (s, 1H), 4.09 (s, 1H), 3.70 (d, $J = 5.0$ Hz, 1H), 3.68 (d, $J = 10.6$ Hz, 1H), 2.79 (t, $J = 9.3$ Hz, 1H), 2.40 (dd, $J = 14.2, 10.3$ Hz, 1H), 2.25 (ddd, $J = 14.5, 9.5, 4.9$ Hz, 1H), 2.20 (d, $J = 8.0$ Hz, 1H), 2.07 (t, $J = 3.0$ Hz, 1H), 1.95 – 1.92 (m, 1H), 1.90 (d, $J = 14.4$ Hz, 1H), 1.86 (m, 1H), 1.84 (s, 1H), 1.84 (s, 1H), 1.82 – 1.74 (m, 2H), 1.51 (dd, $J = 13.5, 6.7$ Hz, 1H), 1.33 (s, 3H), 1.22 (s, 3H), 0.97 (s, 3H);

$^{13}\text{C NMR}$ (151 MHz, CD_3OD) δ 154.3, 111.8, 87.3, 84.9, 81.9, 79.4, 71.4, 59.4, 58.1, 56.3, 55.8, 51.7, 51.3, 41.3, 36.9, 28.0, 26.9, 23.9, 23.1, 20.6;

ESI-HRMS (*m/z*): $[\text{M}+\text{Na}]^+$ calc'd for $\text{C}_{20}\text{H}_{32}\text{NaO}_5^+$: 375.2142; found: 375.2148.

There have been two reported isolations of principinol D. The assignment of absolute configuration in both cases is the same as this report. Hou et al.^{8a} determined the absolute configuration by X-ray crystallography of principinol D, and Zhang et al.^{8b} determined the absolute configuration based on analogy to a co-isolated acetate derivative of principinol D for which absolute configuration was determined by X-ray crystallography. Our report determines absolute configuration based on X-ray crystallography of compound **2**. However, the two isolation groups reported opposite signs for the optical rotations: $[\alpha]_D^{20.0} : -7.4^\circ$ (*c* 0.71, MeOH) disclosed by Hou et al.^{8a} and $[\alpha]_D^{20.0} : +9^\circ$ (*c* 0.2, MeOH) disclosed by Zhang et al.^{8b} The negative value may have been a tabulation error or due to a minor impurity with a large negative optical rotation.





Comparison of synthetic and natural principinol D (1)

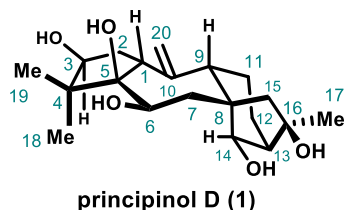


Table SI-2: Comparison of synthetic and natural principinol D (1) by ^1H NMR in CD_3OD

No.	This Report: Principinol D (CD_3OD , 600 MHz)	Zhang et al.: ⁸ Principinol D (CD_3OD , 400 MHz)	Difference (ppm)
1 β	2.79 (t, J = 9.3 Hz)	2.79 (t, J = 9.3 Hz)	0.00
2 α	2.25 (ddd, J = 14.5, 9.5, 4.9 Hz)	2.25 (ddd, J = 14.4, 9.3, 4.8 Hz)	0.00
2 β	1.86 (m)	1.86 (dd, J = 14.4, 9.3 Hz)	0.00
3	3.70 (d, J = 5.1 Hz)	3.70 (d, J = 4.8 Hz)	0.00
6 α	3.68 (d, J = 10.6 Hz)	3.69 (d, J = 10.3 Hz)	0.01
7 α	1.90 (d, J = 14.4 Hz)	1.90 (d, J = 14.1 Hz)	0.00
7 β	2.40 (dd, J = 14.2, 10.3 Hz)	2.40 (dd, J = 14.1, 10.3 Hz)	0.00
9	2.20 (d, J = 8.0 Hz)	2.20 (d, J = 7.6 Hz)	0.00
11 α	1.51 (dd, J = 13.7, 6.7 Hz)	1.51 (dd, J = 13.6, 6.7 Hz)	0.00
11 β	1.78 (m)	1.78, overlap	0.00
12 α	1.93 (m)	1.92, overlap	0.01
12 β	1.79 (m)	1.79, overlap	0.00
13	2.07 (t, J = 3.0 Hz)	2.07 (t, J = 2.9 Hz)	0.00
14 α	4.09 (s)	4.09 (s)	0.00
15 α	1.84 (s)	1.84 (s)	0.00
15 β	1.84 (s)	1.84 (s)	0.00
17	1.33 (s)	1.33 (s)	0.00
18	0.97 (s)	0.97 (s)	0.00
19	1.22 (s)	1.22 (s)	0.00
20a	5.20 (s)	5.20 (s)	0.00
20b	5.16 (s)	5.16 (s)	0.00

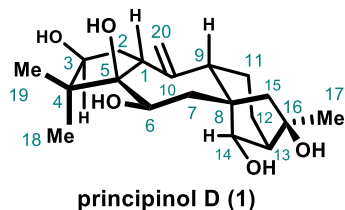


Table SI-3: Comparison of synthetic and natural principinol D (1) by ^{13}C NMR in CD_3OD

No.	This Report: Principinol D (CD_3OD)	Zhang et al.: ⁸ Principinol D (CD_3OD)	Difference
1	59.4	59.3	0.1
2	36.9	36.9	0.0
3	84.9	84.9	0.0
4	51.7	51.7	0.0
5	87.3	87.2	0.1
6	71.4	71.3	0.1
7	41.3	41.3	0.0
8	51.3	51.3	0.0
9	58.1	58.1	0.0
10	154.3	154.2	0.1
11	26.9	26.9	0.0
12	28.0	27.9	0.1
13	55.8	55.8	0.0
14	79.4	79.4	0.0
15	56.3	56.3	0.0
16	81.9	81.9	0.0
17	23.9	23.8	0.1
18	23.1	23.1	0.0
19	20.6	20.6	0.0
20	111.8	111.8	0.0

References

- ¹ Frigerio, M.; Santagostino, M.; Sputore, S. A User-Friendly Entry to 2-Iodoxybenzoic Acid (IBX). *J. Org. Chem.* **1999**, *64*, 4537–4538.
- ² Yeung, Y. Y.; Chein, R. J.; Corey, E. J. Conversion of Torgov's Synthesis of Estrone into a Highly Enantioselective and Efficient Process. *J. Am. Chem. Soc.* **2007**, *129*, 10346–10347.
- ³ Wang, J.; Sun, B.-F.; Cui, K.; Lin, G.-Q. An Efficient Total Synthesis of (–)-Epothilone B. *Org. Lett.* **2012**, *14*, 6354–6357.
- ⁴ Miyaoka, H.; Sagawa, S.; Nagaoka, H.; Yamada, Y. Efficient Synthesis of Enantiomerically Pure 5,5-Dimethyl-4-hydroxy-2-cyclopentenone. *Tetrahedron: Asymmetry* **1995**, *6*, 587–594.
- ⁵ Huang, D.; Zhao, Y.; Newhouse, T. R. Synthesis of Cyclic Enones by Allyl-Palladium-Catalyzed α,β -Dehydrogenation. *Org. Lett.* **2018**, *20*, 684–687.
- ⁶ Erickson, B. W.; Corey, E. J. Oxidative Hydrolysis of 1,3-Dithiane Derivatives to Carbonyl Compounds Using α -Halosuccinimide Reagents. *J. Org. Chem.* **1971**, *36*, 3553–3560.
- ⁷ Bruhn, J.; Heimgartner, H.; Schmid, H. 267. Die Cope-Umlagerung als Prinzip einer repetierbaren Ringerweiterung. *Helv. Chim. Acta* **1979**, *62*, 2630–2654.
- ⁸ (a) Liu, C.-C.; Lei, C.; Zhong, Y.; Gao, L.-X.; Li, J.-Y.; Yu, M.-H. Novel grayanane diterpenoids from *Rhododendron principis*. *Tetrahedron* **2014**, *70*, 4317–4322. (b) Zhang, M.; Xie, Y.; Zhan, G.; Lei, L.; Shu, P.; Chen, Y.; Xue, Y.; Luo, Z.; Wan, Q.; Yao, G.; Zhang, Y. Grayanane and leucothane diterpenoids from the leaves of *Rhododendron micranthum*. *Phytochemistry* **2015**, *117*, 107–115.

Principinol D - SI.pdf (13.41 MiB)

[view on ChemRxiv](#) • [download file](#)

Convergent Total Synthesis of (+)-Principinol D, a Rearranged Kaurane Diterpenoid

Aneta Turlik, Yifeng Chen, Anthony C. Scruse, and Timothy R. Newhouse*

Department of Chemistry, Yale University, 225 Prospect St., New Haven, Connecticut 06520-8107

Supporting Information Placeholder

ABSTRACT: The total synthesis of principinol D, a rearranged kaurane diterpenoid, is reported. This grayanane natural product is constructed via a convergent fragment coupling approach, wherein the central 7-membered ring is synthesized at a late stage. The bicyclo[3.2.1]octane fragment is accessed by a Ni-catalyzed α -vinylation reaction. Strategic reductions include a diastereoselective SmI₂-mediated ketone reduction with PhSH and a new protocol for selective ester reduction in the presence of ketones. The convergent strategy reported herein may be an entry point to the larger class of kaurane diterpenoids.

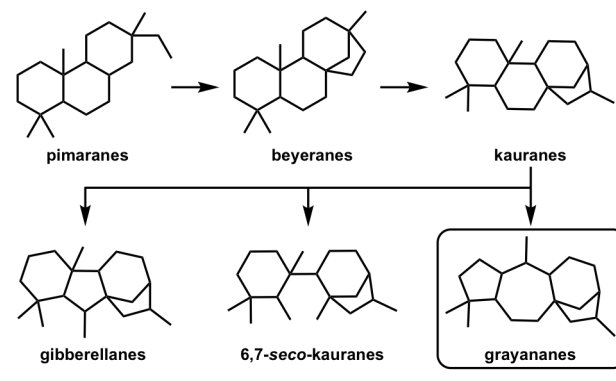
The grayanane diterpenoids – well known as the active components in “mad honey” due to inhibition of voltage-gated sodium ion channels¹ – have recently been identified as structurally novel allosteric inhibitors of carbonic anhydrases² and phosphatases.³ Due to the ubiquity of various subtypes of these molecular targets, potential therapeutic development could span numerous different disease areas from neurological dysfunction to cancer.^{4,5}

Grayananes are among a broader class of rearranged kauranes that also includes gibberellanes and 6,7-*seco*-kauranes (Figure 1A). The tetracyclic diterpenoid grayananes are formed by rearrangement of the kaurane 6,6-A/B ring system to a 5,7-ring system.⁶ The kauranes are derived from rearrangement and cyclization of pimaranes via the beyeranes.^{7,8} The first total synthesis of (±)-kaurene was completed in 1962 by Ireland and coworkers,⁹ and in recent years several groups have completed elegant syntheses of members of this broader class employing a diverse array of synthetic strategies.¹⁰ Nevertheless, much of the >1000 kaurane diterpenoids that have been isolated remain inaccessible by previously reported synthetic approaches.

Synthetic efforts towards the grayananes have been especially limited¹¹ despite their compelling biological activities.¹² To address the stereochemical complexities of these compounds, linear cyclization strategies have been employed. We speculated that a convergent retrosynthetic strategy, which isolates the two main constellations of stereocenters, would yield a laboratory route that could enable synthesis of grayanane analogs. Herein, we report the first total synthesis of the grayanane principinol D (**1**).

Similar to other grayanane diterpenoids, the principinols possess a highly oxidized tetracyclic framework, including a bicyclo[3.2.1]octane ring system.¹³ As can be seen in Figure 1B, principinol D (**1**) has four stereocenters proximal to the left-most 5-membered ring that are separated spatially from an additional five stereocenters that decorate the bicyclo[3.2.1]octane ring system. In order to provide access to structurally diverse analogs, we designed a convergent strategy wherein two fragments would be joined to assemble the core skeleton and simultaneously merge

A. Biosynthesis of the kauranes, their precursors, and derivatives



B. Retrosynthetic analysis: convergent approach

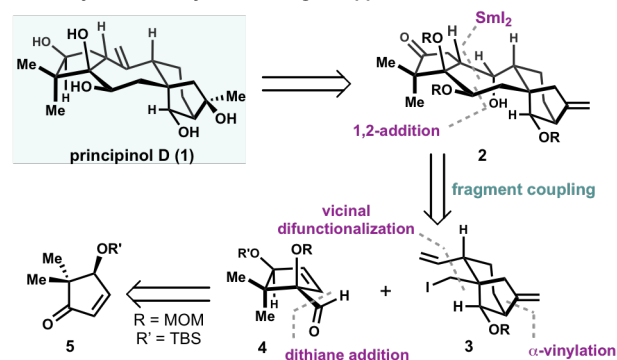
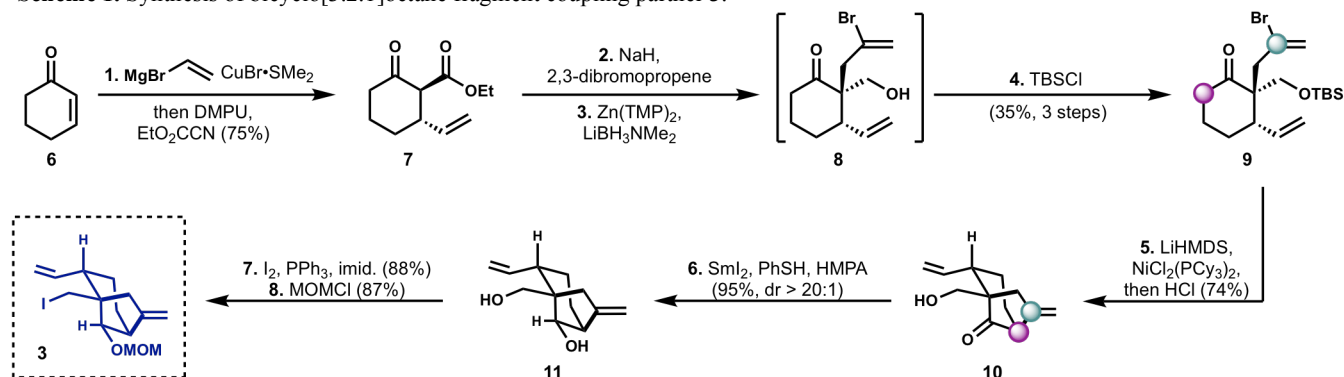


Figure 1. A. Precursors and derivatives of the kaurane diterpenes. B. Retrosynthetic analysis of principinol D (**1**).

the two constellations of stereocenters. This topological simplification to mark external rings for preservation differs significantly from prior work in the grayanane class, but is a powerful strategy in diterpenoid synthesis.¹⁴

We planned to utilize two robust C–C bond-forming reactions to merge the fragments, as this would maximize success for creating derivatives for SAR investigations: fragment union via a 1,2-addition reaction between a cyclopentyl fragment (**4**) and a bicyclo[3.2.1]octane fragment (**3**), and subsequent reductive cyclization using SmI₂. Dissection of the bicyclic fragment by an exendo bond using a Ni-catalyzed α -vinylation reaction would reveal a 6-membered ring that could be obtained by vicinal difunctionalization of cyclohexenone. Compound **4** was readily obtained from the known compound **5**¹⁵ by dithiane addition, MOM protection, and dithiane deprotection (not depicted, see Supporting Information for details).

Scheme 1. Synthesis of bicyclo[3.2.1]octane fragment coupling partner **3**.^a



^a(1) CH_2CHMgBr (1.1 equiv), $\text{CuBr}\cdot\text{SMe}_2$ (0.1 equiv), DMPU (3.5 equiv), EtO_2CCN (1.1 equiv), THF (0.6 M), $-50 \rightarrow -72 \rightarrow 23^\circ\text{C}$, 6 h, 75%; (2) NaH (1.3 equiv), 2,3-dibromopropene (1.2 equiv), DMF (0.4 M), $0 \rightarrow 23^\circ\text{C}$, 13 h; (3) $\text{Zn}(\text{TMP})_2$ (1.1 equiv), $\text{LiBH}_3\text{NMe}_2$ (1.0 equiv) THF (0.1 M), $0 \rightarrow 23^\circ\text{C}$, 1 h; (4) TBSCl (5.1 equiv), imid. (10.0 equiv), DMAP (0.3 equiv), DMF (0.1 M), 40°C , 16 h, 35% (3 steps); (5) LiHMDS (2.0 equiv), $\text{NiCl}_2(\text{PCy}_3)_2$ (0.3 equiv), THF (0.2 M), $-40 \rightarrow 50^\circ\text{C}$, 4 h, then 6 N HCl, 74%; (6) SmI_2 (3.0 equiv), PhSH (6.0 equiv), HMPA (10.0 equiv), THF (0.1 M), 0°C , 1 h, 95%, >20:1 dr; (7) I_2 (1.5 equiv), PPh_3 (2.0 equiv), imid. (4.0 equiv), $\text{C}_6\text{H}_6/\text{MeCN}/\text{CH}_2\text{Cl}_2$, (4:1:1, 0.2 M), $0 \rightarrow 23^\circ\text{C}$, 90 h, 88%; (8) MOMCl (5.0 equiv), $i\text{-Pr}_2\text{NEt}$ (5.0 equiv), CH_2Cl_2 (0.2 M), $0 \rightarrow 23^\circ\text{C}$, 72 h, 87%.

The synthesis of bicyclo[3.2.1]octane fragment **3** began with a vicinal difunctionalization of cyclohexenone with vinylmagnesium bromide in the presence of DMPU and catalytic $\text{CuBr}\cdot\text{SMe}_2$, followed by trapping with Mander's reagent.^{16,17} β -Ketoester **7** underwent allylation with 2,3-dibromopropene. It was hoped that reduction of the ester could occur in the presence of the ketone in order to eliminate unnecessary redox fluctuations.¹⁸ Common protocols that protect the ketone in situ via nucleophilic addition with metal amides¹⁹ or phosphines²⁰ failed. Likewise, initial efforts masking the ketone as an enolate (LiHMDS, KHMDS, NaHMDS, or LDA) and treatment with a reductant (LiAlH_4 , DIBAL-H, AlH_3 , LiBH_4 , or LiEt_3BH) led to base-mediated decomposition.²¹ More mild and selective conditions were identified, wherein an enolate formed by deprotonation with the weaker base $\text{Zn}(\text{TMP})_2$ underwent reduction with commercially available $\text{LiBH}_3\text{NMe}_2$ to form the base-sensitive keto-alcohol **8**. It is our expectation that this procedure will find additional application in the selective reduction of esters in the presence of enolizable carbonyl compounds, especially in the case of base-sensitive substrates. Protection of the resultant primary alcohol as the TBS ether provided the vinylation precursor **9** in 35% yield as a single diastereomer over 3 steps.

In order to form the bicycle **10** from the halide **9**, a variety of α -vinylation substrates and conditions were investigated. We found that the analogous β -ketoester (not depicted, the product of step 2) was not a viable substrate for the vinylation reaction. This may be due to the preference for the ester-containing compound to adopt the chair conformation wherein the ester is axial and the allyl group is equatorial, thus disfavoring the formation of the C-vinylation product, which is only accessible for the conformation wherein the allyl group is axial. We hypothesized that replacing the ester with a larger substituent would predispose the intermediate to adopt the necessary chair conformer in which the allyl substituent is axial, and thus lead to higher degrees of C-vinylation—this is indeed what we observed. Vinylation was ultimately performed using $\text{NiCl}_2(\text{PCy}_3)_2$ as a pre-catalyst and LiHMDS as base. These conditions proved to be more successful than either Pd-catalyzed conditions,²³ wherein cross-coupling can be problematic on such 1,1-disubstituted alkenes, or Ni-catalyzed conditions employing NHC ligands as recently reported by Helquist.²⁴

Following deprotection of the TBS-protected keto-alcohol, we required a diastereoselective reduction of ketone **10**. Unfortunately, reduction with boron or aluminum hydrides (NaBH_4 ,

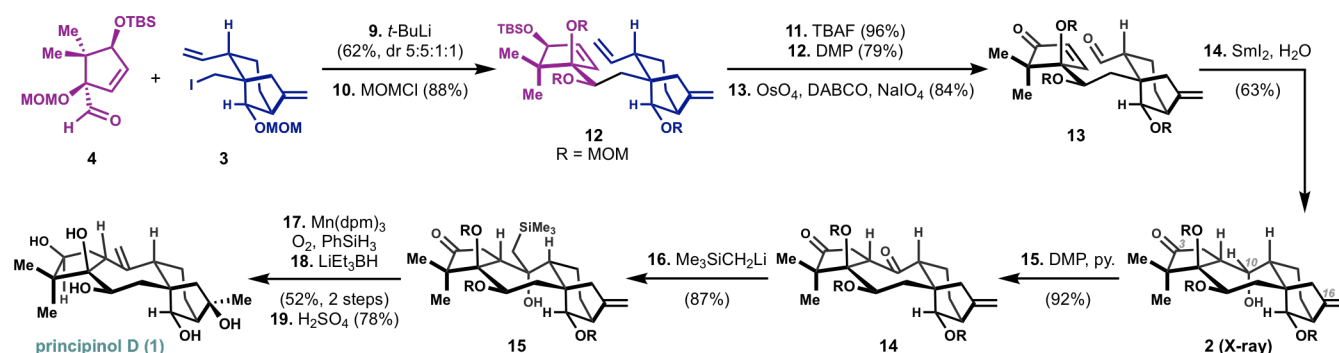
$\text{Et}_2\text{BOMe}/\text{NaBH}_4$, $\text{NaBH}_4/\text{CeCl}_3$, DIBAL, $\text{Al}(\text{O}-i\text{-Pr})_3$) produced predominantly the undesired diastereomer. With use of SmI_2 in the presence of H_2O the product was still disfavored (dr = 1:2). Addition of HMPA and PhSH,²⁵ which may act as an H-atom donor,²⁶ provided the desired product in an excellent yield (95%, >20:1 dr). The use of HMPA was required for the reaction to proceed to full conversion, presumably because it increases the reduction potential of the samarium complex.^{27,28} After the development of this protocol, it was successfully employed in the context of a different natural product synthesis and found to be similarly effective for the reduction of 1,3-diketones.⁶ These modified conditions of classic SmI_2 -mediated thermodynamic reduction may find additional utility in multistep synthesis.

Conversion of the primary alcohol in the presence of a secondary alcohol to the primary alkyl iodide occurred smoothly by the Appel reaction using a trisolvant system of $\text{C}_6\text{H}_6/\text{MeCN}/\text{CH}_2\text{Cl}_2$ in a ratio of 4:1:1. It is noteworthy that this trisolvant system proved to be uniquely effective for this transformation: experiments with a single solvent or combinations thereof resulted in prohibitively low yields. After MOM protection of the remaining secondary alcohol, the bicycle **3** necessary for fragment coupling was obtained.

To link the two fragments, the racemic bicyclo[3.2.1]octane **3** was treated with *tert*-butyllithium, followed by addition of enantiomer-enriched cyclopentyl aldehyde **4** (er = 93:7), which provided the adduct as a separable mixture of diastereomers in 5:5:1:1 dr with a combined yield of 62%. Proceeding forward with the single desired diastereomer that was formed in 26% yield, protection of the secondary alcohol with MOMCl formed **12**; due to the steric hindrance at this center, introduction of other protecting groups such as TBS and TES was not feasible. The allylic silyl ether could be converted to an enone, and selective oxidative cleavage of the monosubstituted alkene in the presence of the 1,1-disubstituted alkene afforded enone-aldehyde **13**. To obtain the observed selectivity, DABCO was a key additive, whereas NMO, 2,6-lutidine, methanesulfonamide, and various two-step procedures were less effective.²⁹

At this stage, closure of the seven-membered ring using SmI_2 was attempted.^{30,31} After extensive optimization, it was found that treatment of enone-aldehyde **13** with SmI_2 in the presence of water provided the desired tetracycle **2** in 63% yield as a single diastereomer. The structure and stereochemistry of this compound were determined by NOESY NMR and eventually confirmed by X-ray crystallography.

Scheme 2. Total synthesis of principinol D (**1**) via fragment coupling and reductive cyclization^a



^aReagents and conditions: (9) *t*-BuLi (2.0 equiv), pentane:Et₂O (3:2, 0.1 M), -70 → 0 °C, 2.5 h, 62%; (10) MOMCl (10 equiv), DMAP (2.2 equiv), *i*-Pr₂NEt (15 equiv), (CH₂Cl)₂ (0.2 M), 80 °C, 17 h, 88%; (11) TBAF (5.0 equiv), THF (0.1 M), 23 °C, 3 h, 96%; (12) DMP (5.0 equiv), CH₂Cl₂ (0.1 M), 23 °C, 30 h, 79%; (13) OsO₄ (0.1 equiv), DABCO (3.0 equiv), NaIO₄ (3.0 equiv), THF/H₂O (2:1, 0.01 M), 0 °C, 15 h, 84%; (14) SmI₂ (25 equiv), H₂O (2.6 equiv), THF (0.01 M), -72 → 0 °C, 2.5 h, 63%; (15) DMP (5.0 equiv), pyridine:CH₂Cl₂ (1:2, 0.07 M), 23 °C, 20 h, 92%; (16) Me₃SiCH₂Li (10 equiv), THF (0.01 M), 0 °C, 0.3 h, 87%; (17) Mn(dpm)₃ (0.15 equiv), PhSiH₃ (2.2 equiv), O₂, EtOH (0.02 M), 23 °C, 1.5 h; (18) LiEt₃BH (14 equiv), THF (0.01 M), 0 → 65 °C, 16 h, 52% over 2 steps; (19) 2 M H₂SO₄:1,4-dioxane (1:2, 0.02 M), 23 °C, 5 d.

After completion of the synthesis of the carbocyclic core structure **2**, significant challenges stood ahead: installation of the secondary alcohol at C3, alkene at C10, and tertiary alcohol at C16. Several sequences of events were investigated and it was found that intermediate **14**, prepared by oxidation of **2** using Dess-Martin periodinane buffered with pyridine, was a viable substrate to navigate chemoselectivity challenges. A selective olefination of the ketone on the seven-membered ring was attempted in the presence of the five-membered ring ketone. Standard olefination conditions (e.g. Wittig, Tebbe, Petasis, Nysted, etc.) were unable to form the desired exocyclic olefin. However, it was found that treatment with Me₃SiCH₂Li was efficient in producing Peterson adduct **15**.³² Thus, the three sites (C3, C10, C16) were differentiated in a synthetically productive way.

Mukaiyama hydration of the exocyclic olefin with Mn(dpm)₃, PhSiH₃, and O₂ installed the tertiary alcohol at C16. Reduction of cyclopentyl ketone **15** at C3 produced predominantly the undesired α-alcohol under most conditions that were attempted (e.g. DIBAL, LAH, NaBH₄, NaBH₃·CeCl₃·7H₂O, Na⁰, LiBH₄, Zn(BH₄)₂, SmI₂, etc.). Reaction with LiEt₃BH resulted in the exclusive formation of the desired alcohol at C3. Upon heating, concomitant elimination of the Peterson adduct released the methyldiene at C10, providing the product as one diastereomer in 52% yield over 2 steps. Global MOM deprotection occurred smoothly using H₂SO₄ in 1,4-dioxane, furnishing principinol D (**1**). The NMR spectral data was identical to those reported.¹³

The work described herein represents the first total synthesis of principinol D (**1**) by a 19-step approach. This synthesis features a convergent fragment coupling strategy, and a SmI₂-mediated reductive cyclization to form the central seven-membered ring of the grayanane skeleton. In addition, α-vinylation conditions are reported to form the bicyclo[3.2.1]octane, as well as a diastereoselective SmI₂-mediated reduction of a bicyclic ketone. This synthetic route is expected to lead to laboratory access to a variety of derivatives, including ones which selectively act on phosphatases, carbonic anhydrases, or voltage-gated sodium ion channels, all known targets of the grayananes.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

AUTHOR INFORMATION

Corresponding Author

*timothy.newhouse@yale.edu

ORCID

Aneta Turlik: 0000-0002-0907-8969

Yifeng Chen: 0000-0003-3239-6209

Anthony C. Scruse: 0000-0002-2387-9818

Timothy R. Newhouse: 0000-0001-8741-7236

Notes

The authors declare no competing financial interests.

Funding Sources

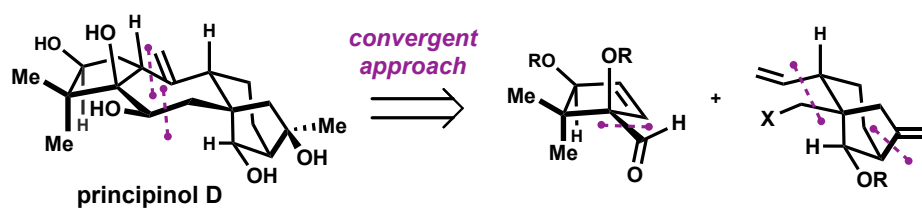
Financial support was provided by Yale University, Sloan Foundation, Amgen, the NIH (5R01-GM118614), and the American Cancer Society. We are grateful for support through National Science Foundation Graduate Research Fellowships (A.T. and A.C.S.), a Ford Foundation Predoctoral Fellowship (A.C.S) and a Rudolph J. Anderson postdoctoral fellowship (Y.C.).

REFERENCES

- (1) (a) Koca, A. F.; Koca, I. Poisoning by mad honey: A brief review. *Food Chem. Toxicol.* **2007**, *45*, 1315–1318. (b) Gunduz, A.; Turedi, S.; Russel, R. M.; Ayaz, F. A. Clinical review of grayanotoxin/mad honey poisoning past and present. *Clinical Toxicology* **2008**, *45*, 437–442. (c) Jansen, S. A.; Kleerekoper, I. Hofman, Z L.; Kappen, I. F. P.; Stary-Weinzinger, A.; van der Heyen, M. A. G. Grayanotoxin Poisoning: ‘Mad Honey Disease’ and Beyond. *Cardiovasc. Toxicol.* **2012**, *12*, 208–215.
- (2) Durdagi, S.; Scozzafava, G.; Vullo, D.; Sahin, H.; Kolayli, S.; Supuran, C. T. Inhibition of mammalian carbonic anhydrases I–XIV with grayanotoxin III: solution and in silico studies. *J. Enzyme Inhib. Med. Chem.* **2014**, *29*, 469–475.
- (3) Li, C.-H.; Zhang, J.-Y.; Zhang, X.-Y.; Li, S.-H.; Gao, J.-M. An overview of grayanane diterpenoids and their biological activities from the Ericaceae family in the last seven years. *Eur. J. Med. Chem.* **2019**, *166*, 400–416.
- (4) Regarding voltage-gated sodium ion channel applications, see: (a) Stevens, M.; Peigneur, S.; Tytgat, J. Neurotoxins and their binding areas on voltage-gated sodium channels. *Front. Pharmacol.* **2011**, *2*, 1–13. (b) Bagal, S. K.; Brown, A. D.; Cox, P. J.; Omoto, K.; Owen, R. M.; Pryde, D. C.; Sidders, B.; Skerratt, S. E.; Stevens, E. B.;

- Storer, R. I.; Swain, N. A. Ion Channels as Therapeutic Targets: A Drug Discovery Perspective. *J. Med. Chem.* **2013**, *56*, 593–624. (c) Nardi, A.; Damann, N.; Hertrampf, T.; Kless, A. Advances in Targeting Voltage-Gated Sodium Channels with Small Molecules. *ChemMedChem*, **2012**, *7*, 1712–1740. (d) de Lera Ruiz, M.; Kraus, R. L.; Voltage-Gated Sodium Channels: Structure, Function, Pharmacology, and Clinical Indications. *J. Med. Chem.* **2015**, *58*, 7093–7118.
- (5) For phosphatases as targets, see: (a) Zhang, S.; Zhang, Z. Y. PTP1B as a Drug Target: Recent Developments in PTP1B Inhibitor Discovery. *Drug Discov. Today* **2007**, *12*, 373–381. (b) Stuiblé, M.; Doody, K. M.; Tremblay, M. L. PTP1B and TC-PTP: regulators of transformation and tumorigenesis. *Cancer and Metastasis Rev.* **2008**, *27*, 215–230. (c) Lessard, L.; Stuiblé, M.; Tremblay, M. L. The two faces of PTP1B in cancer. *Biochim. Biophys. Acta* **2010**, *1804*, 613–619. For carbonic anhydrases as targets, see: (d) Supuran, C. T. Carbonic anhydrases: novel therapeutic applications for inhibitors and activators. *Nat. Rev. Drug Discov.* **2008**, *7*, 168.
- (6) For an example of a similar rearrangement in the justicanes, see: Elkin, M.; Scruse, A. C.; Turlík, A.; Newhouse, T. R. Computational and Synthetic Investigation of Cationic Rearrangement in the Putative Biosynthesis of Justicane Triterpenoids. *Angew. Chem. Int. Ed.* **2019**, *58*, 1025–1029.
- (7) Breitmaier, E. *Terpenes: Flavors, Fragrances, Pharmaca, Pheromones*. Wiley-VCH, 2006.
- (8) Toyomasu, T.; Sassa, T. In *Diterpenes in Comprehensive Natural Products II. Chemistry and Biology*; Mander, L., Liu, H.-W., Eds.; Newnes: 2010; Vol. 1.
- (9) Bell, R. A.; Ireland, R. E.; Partyka, R. A. The Total Synthesis of (±)-Kaurene. *J. Org. Chem.* **1962**, *27*, 3741–3744.
- (10) For examples, see: (a) Gong, J.; Lin, G.; Sun, W.; Li, C.-C.; Yang, Z. Total Synthesis of (±) Maoecrystal V. *J. Am. Chem. Soc.* **2010**, *132*, 16745–16746. (b) Cha, J. Y.; Yeoman, J. S. T.; Reisman, S. E. A Concise Total Synthesis of (–)-Maoecrystal Z. *J. Am. Chem. Soc.* **2011**, *133*, 14964–14967. (c) Peng, F.; Danishefsky, S. J. Total Synthesis of (±)-Maoecrystal V. *J. Am. Chem. Soc.* **2012**, *134*, 18860–18867. (d) Cherney, E. C.; Green, J. C.; Baran, P. S. Synthesis of *ent*-Kaurane and Beyerane Diterpenoids by Controlled Fragmentations of Overbred Intermediates. *Angew. Chem. Int. Ed.* **2013**, *52*, 9019–9022. (e) Yeoman, J. T. S.; Mak, V. W.; Reisman, S. E. A Unified Strategy to *ent*-Kauranoid Natural Products: Total Syntheses of (–)-Trichorabdal A and (–)-Longikaurin E. *J. Am. Chem. Soc.* **2013**, *135*, 11764–11767. (f) Liu, P.; Gu, Z.; Zakarian, A. Total Synthesis of Maoecrystal V: Early-Stage C–H Functionalization and Lactone Assembly by Radical Cyclization. *J. Am. Chem. Soc.* **2013**, *135*, 14552–14555. (g) Pan, Z.; Zheng, C.; Wang, H.; Chem, Y.; Li, Y.; Cheng, B.; Zhai, H. Total Synthesis of (±)-Sculponeatin N. *Org. Lett.* **2014**, *16*, 216–219. (h) Moritz, B. J.; Mack, D. J.; Tong, L.; Thomson, R. J. Total Synthesis of the Isodon Diterpene Sculponeatin N. *Angew. Chem. Int. Ed.* **2014**, *53*, 2988–2991. (i) Zheng, C.; Dubovik, I.; Lazarski, K. E.; Thomson, R. J. Enantioselective Total Synthesis of (–)-Maoecrystal V. *J. Am. Chem. Soc.* **2014**, *136*, 17750–17756. (j) Cernijenko, A.; Risgaard, Baran, P. S.; 11-Step Total Synthesis of (–)-Maoecrystal V. *J. Am. Chem. Soc.* **2016**, *138*, 9425–9428. (k) Zhao, X.; Li, W.; Wang, J.; Ma, D. Convergent Route to *ent*-Kaurane Diterpenoids: Total Synthesis of Lungshengenin D and 1a,6a-Diacetoxy-*ent*-kaura-9(11),16-dien-12-15-dione. *J. Am. Chem. Soc.* **2017**, *139*, 2932–2935. (l) He, C.; Hu, J.; Wu, Y.; Ding, H. Total Syntheses of Highly Oxidized *ent*-Kauranoids Pharicin A, Pharicin B, 7-O-Acetylpsourate C, and Psourate C: A [5+2] Cascade Approach. *J. Am. Chem. Soc.* **2017**, *139*, 6098–6101.
- (11) (a) Hamanaka, N.; Matsumoto, T. Partial Synthesis of Grayanotoxin. *Tetrahedron Lett.* **1972**, *30*, 3087–3090. (b) Gasa, S.; Hamanaka, N.; Matsunaga, S.; Okuno, T.; Takeda, N.; Matsumoto, T. Relay Total Synthesis of Grayanotoxin II. *Tetrahedron Lett.* **1976**, *7*, 553–556. (c) Kan, T.; Hosokawa, S.; Nara, S.; Oikawa, M.; Ito, S.; Matsuda, F.; et al. *J. Org. Chem.* **1994**, *59*, 5532–5534. (d) Borrelly, S.; Paquette, L. A.; Studies Directed to the Synthesis of the Unusual Cardiotoxic Agent Kalmanol. Enantioselective Construction of the Advanced Tetracyclic 7-Oxy-5,6-dideoxy Congener. *J. Am. Chem. Soc.* **1996**, *118*, 727–740. (e) Chow, S.; Kreß, C.; Albaek, N.; Jessen, C.; Williams, C. M. Determining a Synthetic Approach to Pierisformaside C. *Org. Lett.* **2011**, *13*, 5286–5289.
- (12) Li, Y.; Liu, Y.-B.; Yu, S.-S. Grayanoids from the Ericaceae family: structures, biological activities and mechanism of action. *Phytochem. Rev.* **2013**, *12*, 305–325.
- (13) (a) Liu, C.-C.; Lei, C.; Zhong, Y.; Gao, L.-X.; Li, J.-Y.; Yu, M.-H. Novel grayanane diterpenoids from *Rhododendron principis*. *Tetrahedron* **2014**, *70*, 4317–4322. (b) Zhang, M.; Xie, Y.; Zhan, G.; Lei, L.; Shu, P.; Chen, Y.; Xue, Y.; Luo, Z.; Wan, Q.; Yao, G.; Zhang, Y. Grayanane and leucothane diterpenoids from the leaves of *Rhododendron micranthum*. *Phytochemistry* **2015**, *117*, 107–115.
- (14) Urabe, D.; Asaba, T.; Inoue, M. Convergent Strategies in Total Syntheses of Complex Terpenoids. *Chem. Rev.* **2015**, *115*, 9207–9231.
- (15) Huang, D.; Zhao, Y.; Newhouse, T. R. Synthesis of Cyclic Enones by Allyl-Palladium-Catalyzed α,β -Dehydrogenation. *Org. Lett.* **2018**, *20*, 684–687.
- (16) Mander, L. N.; Sethi, S. P. Regioselective synthesis of β -ketoesters from lithium enolates and methyl cyanoformate. *Tetrahedron Lett.* **1983**, *24*, 5425–5428.
- (17) Bruhn, J.; Heimgartner, H.; Schmid, H. 267. Die Cope-Umlagerung als Prinzip einer repetierbaren Ringerweiterung. *Helv. Chim. Acta* **1979**, *62*, 2630–2654.
- (18) Burns, N. Z.; Baran, P. S.; Hoffman, R. W. Redox Economy in Organic Synthesis. *Angew. Chem. Int. Ed.* **2009**, *48*, 2854–2867.
- (19) Barrios, F. J.; Springer, B. C.; Colby, D. A. Control of Transient Aluminum–Aminals for Masking and Unmasking Reactive Carbonyl Groups. *Org. Lett.* **2013**, *15*, 3082–3085, and references therein.
- (20) Fujioka, H.; Yahata, K.; Kubo, O.; Sawama, Y.; Tomohito, H.; Tomohiro, M. Reversing the Reactivity of Carbonyl Functions with Phosphonium Salts: Enantioselective Total Synthesis of (+)-Centrolobine. *Angew. Chem. Int. Ed.* **2011**, *50*, 12232–12235.
- (21) (a) Isobe, K.; Mohri, K.; Sano, H.; Taga, J.; Tsuda, Y. Chemoselective Reduction of β -Keto-esters to β -Keto-alcohols. *Chem. Pharm. Bull.* **1986**, *34*, 3029–3032. (b) Heinz, U.; Adams, E.; Klintz, R.; Welzel, P. 2-Tosyloxymethylcyclohexanones: Ring Size Dependence of Fragmentation Versus Intramolecular Alkylation. *Tetrahedron* **1990**, *46*, 4217–4230. (c) Ye, Q.; Qu, P.; Snyder, S. A. Total Syntheses of Scaparin B, C, and D Enabled by a Key C–H Functionalization. *J. Am. Chem. Soc.* **2017**, *139*, 18428–18431.
- (22) (a) Fisher, G. B.; Fuller, J. C.; Harrison, J.; Alvarez, S. G.; Burkhardt, E. R.; Goralski, C. T.; Singram, B. Aminoborohydrides. 4. The Synthesis and Characterization of Lithium Aminoborohydrides: A New Class of Powerful, Selective, Air-Stable Reducing Agents. *J. Org. Chem.* **1994**, *59*, 6378–6385. (b) For a review on aminoborohydrides, see: Pasumansky, L.; Goralski, C. T.; Singaram, B. Lithium Aminoborohydrides: Powerful, Selective, Air-Stable Reducing Agents. *Org. Process Res. Dev.* **2006**, *10*, 959–970.
- (23) For a review of transition metal-catalyzed alkenylation reactions, see: Ankner, T.; Cosner, C. C. Helquist, P. Palladium- and Nickel-Catalyzed Alkenylation of Enolates. *Chem. Eur. J.* **2013**, *19*, 1858–1871.
- (24) Grigalunas, M.; Ankner, T.; Norrby, P.-O.; Wiest, O.; Helquist, P. Ni-Catalyzed Alkenylation of Ketone Enolates under Mild Conditions: Catalyst Identification and Optimization. *J. Am. Chem. Soc.* **2015**, *137*, 7019–7022.
- (25) Banwell, M. G.; Hockless, D. C. R.; McLeod, M. D. Chemoenzymatic total syntheses of the sesquiterpene (–)-patchoulene. *New J. Chem.* **2003**, *27*, 50–59.
- (26) (a) Mayer, J. M. Proton-Coupled Electron Transfer: A Reaction Chemist's View. *Annu. Rev. Phys. Chem.* **2004**, *55*, 363–390. (b) Chciuk, T. V.; Anderson Jr., W. R.; Flowers, R. A. Proton-Coupled Electron Transfer in the Reduction of Carbonyls by Samarium Diiiodide–Water Complexes. *J. Am. Chem. Soc.* **2016**, *138*, 8738–8741. (c) Kolmar, S. S.; Mayer, J. M. $\text{SmI}_2(\text{H}_2\text{O})_n$ Reduction of Electron Rich Enamines by Proton-Coupled Electron Transfer. *J. Am. Chem. Soc.* **2017**, *139*, 10687–10692. (d) Chciuk, T. V.; Anderson, W. R.; Flowers, R. A. Interplay between Substrate and Proton Donor Coordination in Reductions of Carbonyls by SmI_2 –Water Through Proton-Coupled Electron-Transfer. *J. Am. Chem. Soc.* **2018**, *140*, 15342–15352.
- (27) Flowers, R. A. Mechanistic Studies on the Roles of Cosolvents and Additives in Samarium(II)-Based Reductions. *Synlett* **2008**, *10*, 1427–1439.
- (28) Szostak, M.; Spain, M.; Procter, D. J. Recent advances in the chemoselective reduction of functional groups mediated by samarium(II) iodide: a single electron transfer approach. *Chem. Soc. Rev.* **2013**, *42*, 9155–9183.

- (29) Minato, M.; Yamamoto, K.; Tsuji, J. Osmium Tetraoxide Catalyzed Vicinal Hydroxylation of Higher Olefins by Using Hexacyanoferrate (III) Ion as a Cooxidant. *J. Org. Chem.* **1990**, *55*, 766–768.
- (30) Edmonds, D. J.; Johnston, D.; Procter, D. J. Samarium(II)-Iodide-Mediated Cyclizations in Natural Product Synthesis. *Chem. Rev.* **2004**, *104*, 3371–3403.
- (31) Szostak, M.; Fazakerley, N. J.; Parmar, D.; Procter, D. J. Cross-Coupling Reactions Using Samarium (II) Iodide. *Chem. Rev.* **2014**, *114*, 5959–6039.
- (32) Peterson, D. J. A Carbonyl Olefination Reaction Using Silyl-Substituted Organometallic Compounds. *J. Org. Chem.* **1968**, *33*, 780–784.



principinol D - ms.pdf (708.99 KiB)

[view on ChemRxiv](#) • [download file](#)

Other files

Compound 2.cif (2.63 MiB)

[view on ChemRxiv](#) • [download file](#)
