Supporting Information

Functionalized Templates for the Convergent Assembly of Polyethers: Synthesis of *HIJK* Rings of Gymnocin A

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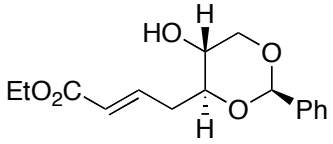
Experimental Procedures and Data for Compounds 1-18 and Intermediates S1-S12.

General Information. Unless otherwise noted, all non-aqueous reactions were performed under an oxygen-free atmosphere of nitrogen with rigid exclusion of moisture from reagents and glassware. All saturated (sat.) solutions are aqueous unless specified. Dichloromethane (DCM) was distilled from calcium hydride. Tetrahydrofuran (THF) and Et_2O were distilled from a blue solution of benzophenone ketyl. CuBr•DMS was recyrystallized from dimethyl sulfide and hexane. Hexamethylphosphoramide (HMPA) was distilled from CaH_2 and stored over molecular sieves. Silicic acid (100 mesh for chromatographic applications) was purchased from Sigma Aldrich. Methyl iodide was purified by passing through basic alumina, which itself was activated by heating to 140 °C prior to use. Dess-Martin periodinane was prepared via a two-step literature procedure.[1] Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F254 plates. The developed chromatogram was analyzed by UV lamp (254 nm) and ceric ammonium molybdate (CAM). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle Silica Gel (230-400 mesh). 1H and 13C NMR spectra were recorded in $CDCl_3$, unless otherwise noted, on a Bruker Avance 600 MHz, Bruker Avance 400 MHz or Varian Inova 500 MHz spectrometer. Chemical shifts in 1H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant in hertz (Hz), and integration. Chemical shifts of 13C NMR spectra are reported in ppm from the central peak of CDCl3 (77.23 ppm), acetone-d_6 (206.68 ppm), or CD_3CN (118.69 ppm) on the δ scale. Infrared (IR) spectra were recorded on a Perkin-Elmer 2000 FT-IR. High resolution mass spectra (HR-MS) were obtained on a Bruker Daltonics APEXII 3 Tesla Fourier Transform Mass Spectrometer by Dr. Li Li of the Massachusetts Institute of Technology Department of Chemistry Instrumentation Facility. Optical rotations were measured on a Jasco 1010 polarimeter at 589 nm.



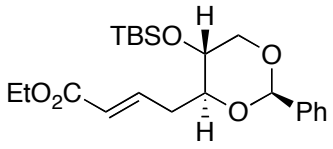
6

(*E*)-ethyl 4-((2*R*,4*S*,5*R*)-5-hydroxy-2-phenyl-1,3-dioxan-4-yl)but-2-enoate (6): To a slurry of 2-deoxyribose (92 g, 684 mmol) in THF (1.3 L) is added (carbethoxymethylene) triphenyphosphorane (262 g, 752 mmol). The mixture is refluxed for 3 h, cooled to room temperature, and concentrated *in vacuo*. The crude oil can be used without purification.[2] The oil

[1] Preparation of IBX: Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem*. **1999**, *64*, 4537–4538. Conversion of IBX to DMP: Ireland, R.; Liu, L. *J. Org. Chem*. **1993**, *58*, 2899.

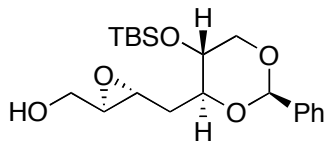
[2] If desired, the product can be purified by column chromatography (gradient: 3% to 10% MeOH in DCM) to afford the corresponding triol (27.3 g, 98%, 83:17 E:Z) as a colorless oil.

is dissolved in DCM (700 mL) followed by addition of camphorsulfonic acid (CSA) (48 g, 205 mmol), and benzaldehyde dimethyl acetal (185 mL, 1230 mmol). The reaction is stirred at ambient temperature for 12 h, then quenched by addition of Et_3N (29 mL). The reaction is concentrated *in vacuo* and crude material purified by column chromatography (gradient: 20 to 30% EtOAc in hexane) to afford alcohol **6** as a cream colored solid (146 g, 73%); Product was visualized with CAM stain, R_f = 0.29 (50% EtOAc in hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.29–1.32 (t, *J* = 7.1 Hz, 3H), 2.53–2.58 (ddd, *J* = 15.2, 7.6, 7.6 1.3 Hz, 1H), 2.76–2.77 (d, *J* = 5.4 Hz, 1H), 2.78–2.83 (dddd, *J* = 15.2, 6.9, 3.3, 1.5 Hz, 1H), 3.55–3.63 (m, 2H), 3.67–3.70 (td, *J* = 8.6, 3.3 Hz, 1H), 4.18–4.24 (m, 3H), 5.48 (s, 1H), 5.95–5.98 (d, *J* = 15.7 Hz, 1H), 7.07–7.12 (dt, *J* = 15.7, 7.2 Hz, 1H), 7.35–7.40 (m, 3H), 7.48–7.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.4, 34.7, 60.7, 65.3, 71.4, 80.6, 101.1, 123.9, 126.3, 128.4, 129.2, 137.6, 144.9, 166.9; IR (thin film NaCl): 3473, 3067, 3036, 2981, 2932, 2906, 2864, 1710, 1655, 1453, 1370, 1316, 1215, 1078, 979, 750, 698; $[\alpha]^{23}_D$ = -47.5 (*c* = 0.024, $CHCl_3$); HR-MS (ESI) Calcd for $C_{16}H_{20}O_5$ $(M+Na)^+$ 315.1203, found 315.1203.



7

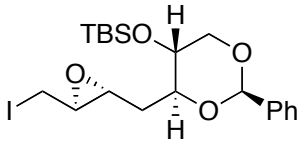
(*E*)-ethyl-4-((2*R*,4*S*,5*R*)-5-(*tert*-butyldimethylsilyloxy)-2-phenyl-1,3-dioxan-4-yl)but-2-enoate (7): To a solution of alcohol **6** (102 g, 349 mmol) in DMF (250 mL) at 0 °C is added imidazole (42 g, 698 mmol), and *tert*-butyldimethylsilyl chloride (TBSCl) (66 g, 437 mmol). The reaction is warmed to ambient temperature, stirred for 5 h, then quenched by addition of sat. NH_4Cl (500 mL). The mixture is extracted with EtOAc (3 x 500 mL), the combined organic extracts dried with $MgSO_4$, and concentrated *in vacuo*. The oil is purified by column chromatography (gradient: 5% to 20% EtOAc in hexane) to afford silyl ether **7** as a colorless oil (100 g, 71%); Product was visualized with CAM stain, R_f = 0.15 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.10 (s, 3H), 0.12 (s, 3H), 0.91 (s, 9H), 1.27–1.31 (t, *J* = 7.1 Hz, 3H), 2.43–2.51, (app dtd, *J* = 15.4, 8.5, 1.4 Hz, 1H), 2.73–2.80 (dddd, *J* = 15.2, 6.8, 2.8, 1.7 Hz, 1H), 3.56–3.64 (m, 2H), 3.67–3.72 (td, *J* = 8.3, 3.0 Hz, 1H), 4.17–4.22 (m, 3H), 5.49 (s, 1H), 5.93–5.98 (d, *J* = 15.7 Hz, 1H), 7.05–7.13 (dt, *J* = 15.7, 7.1 Hz, 1H), 7.33–7.39 (m, 3H), 7.47–7.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: -4.6, -4.0, 14.4, 18.0, 25.8, 34.6, 60.3, 66.4, 71.8, 81.1, 101.0, 123.8, 126.2, 128.3, 129.0, 137.8, 144.8, 166.5; IR (thin film NaCl): 3037, 2956, 2930, 2887, 2858, 1721, 1657, 1463, 1389, 1312, 1261, 1177, 1108, 1029, 838, 778, 698; $[\alpha]^{23}_D$ = -50.3 (*c* = 0.058, $CHCl_3$); HR-MS (ESI) Calcd for $C_{22}H_{34}O_5Si$ $(M+Na)^+$ 429.2068, found 429.2067.



S1

((2*R*,3*R*)-3-(((2*R*,4*S*,5*R*)-5-(*tert*-butyldimethylsilyloxy)-2-phenyl-1,3-dioxan-4-yl)methyl) oxiran-2-yl)methanol (S1): Ester **7** (50 g, 123 mmol) is dissolved in DCM (410 mL) and cooled to –78 °C. DIBAL-H solution (310 mL of 1M in DCM, 307 mmol) is added via addition funnel over 20 min and stirred at –78 °C an additional 30 min. The reaction is quenched at –78 °C by dropwise addition of MeOH (50 mL) and then poured into sat. Rochelle's salt (600 mL) at ambient temperature followed by vigorous stirring for 12 h. The mixture was extracted with DCM (3 x 1L), the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford the allylic alcohol which was used in the subsequent epoxidation without purification.

In a 1L round bottom flask, 4Å molecular sieves (25 g) are flame dried *in vacuo* for 8 min then cooled to ambient temperature. A magnetic stir bar, DCM (300 mL), and (–)-diethyl (D)-tartrate (3 g, 15 mmol) are then added and the slurry is cooled to –25 °C. Next, titanium(IV) tetraisopropoxide (3.7 mL, 12.3 mmol) is added followed by slow addition of a *tert*-butyl hydroperoxide solution (45 mL of 5.5M in decane, 246 mmol). The mixture is allowed to stir at –25 °C for 30 minutes followed by addition of a solution of the allylic alcohol (above) in DCM (50 mL). The reaction is stirred at –25 °C for an additional 15 h and warmed to 0 °C. In a separate flask, iron(II) sulfate heptahydrate (41g), tartaric acid (12.3 g), and H_2O (430 mL) are cooled to 0 °C. The crude epoxidation reaction is slowly poured into the aqueous solution, stirred at ambient temperature for 15 min, extracted with Et_2O (4 x 600 mL). To the combined organic extracts is added 300 mL 30% NaOH in brine[3] and the mixture is stirred at ambient temperature for 1 h. The organic layer is separated, dried over $MgSO_4$, and purified by column chromatography (30% EtOAc in hexane) affording epoxy alcohol **S1** as a colorless oil (44 g, 95%); Product was visualized with CAM stain, R_f = 0.42 (30% EtOAc in hexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.11 (s, 3H), 0.12 (s, 3H), 0.90 (s, 9H), 1.84–1.88 (dd, *J* = 7.2, 5.7 Hz, 1H), 1.97–2.08 (m, 2H), 2.97–3.00 (dt, *J* = 4.4, 2.3, 1H), 3.22–3.26 (td, *J* = 5.5, 2.3, 1H), 3.56–3.73 (m, 4H), 3.90–3.94 (ddd, *J* = 12.6, 5.7, 2.6 Hz, 1H), 4.20–4.23 (m, 1H), 5.52 (s, 1H), 7.34–7.40 (m, 3H), 7.48–7.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: -4.6, -4.0, 18.0, 25.9, 33.5, 53.1, 58.0, 61.9, 66.0, 72.0, 80.2, 101.0, 126.2, 128.5, 129.1, 137.9; IR (thin film NaCl): 3443, 2955, 2929, 2885, 2857, 1462, 1388, 1253, 1107, 1029, 857, 838, 778, 698; $[\alpha]^{23}_D$ = -38.6 (*c* = 0.03, $CHCl_3$); HR-MS (ESI) Calcd for $C_{20}H_{32}O_5Si$ $(M+Na)^+$ 403.1911, found 403.1908.

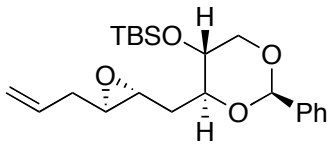


S2

***tert*-butyl((2*R*,4*S*,5*R*)-4-(((2*R*,3*S*)-3-(iodomethyl)oxiran-2-yl)methyl)-2-phenyl-1,3-dioxan-5-yloxy)dimethylsilane (S2)**: Combine triphenylphosphine (PPh_3) (18.2 g, 70 mmol), imidazole (4.7 g, 70 mmol), in Et_2O (180 mL) and CH_3CN (120 mL) and cool to 0 °C. With vigorous stirring, add iodine (17.6 g, 70 mmol) in portions over 10 min then warm to ambient temperature and stir for 15 min. Then cool the slurry to 0 °C and dropwise add a solution of epoxy alcohol **S1** (23 g, 60 mmol) in Et_2O (36 mL) over 10 min, warm to ambient temperature and stir for 15 min. Quench by addition of sat. $Na_2S_2O_3$ (400 mL), extract Et_2O (3 x 400 mL), dry combined organic

[3] 300 mL of 30% NaOH in brine is prepared by combining 15 g NaCl, 90 g NaOH, and 270 mL H_2O.

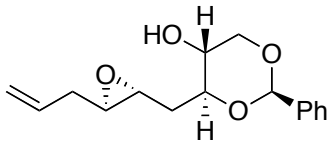
extracts over $MgSO_4$, and remove solvent *in vacuo*. The crude material is dissolved in a minimal amount of DCM and loaded onto silical gel for purification by column chromatography (5% EtOAc in hexane) to afford iodide **S2** as a yellow oil (24.6 g, 83%); Product was visualized with CAM stain, R_f = 0.61 (20% EtOAc in hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 0.11 (s, 6H), 0.90 (s, 9H), 1.93–1.96 (ddd, *J* = 14.3, 6.1, 3.0 Hz, 1H), 2.01–2.06 (ddd, *J* = 14.3, 8.2, 5.1 Hz, 1H), 3.01–3.04 (dd, *J* = 9.8, 7.3 Hz, 1H), 3.08–3.13 (m, 2H), 3.29–3.32 (dd, *J* = 9.9, 5.5 Hz, 1H), 3.58–3.62 (app t, *J* = 10.6 Hz, 1H), 3.66–3.70 (td, *J* = 9.8, 4.9 Hz, 1H), 3.74–3.77 (td, *J* = 8.7, 3.1 Hz, 1H), 4.20–4.23 (dd, *J* = 10.6, 4.9 Hz, 1H), 5.54 (s, 1H), 7.35–7.41 (m, 3H), 7.52–7.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: -4.6, -4.1, 5.1, 18.0, 25.9, 33.8, 57.9, 59.6, 66.2, 71.9, 80.3, 101.0, 126.2, 128.4, 129.1, 137.8; IR (thin film NaCl): 2955, 2928, 2885, 2856, 1462, 1387, 1253, 1111, 1029, 838, 78, 698; $[\alpha]^{23}_D$ = -36.8 (*c* = 0.25, $CHCl_3$); HR-MS (ESI) Calcd for $C_{20}H_{31}O_4ISi$ $(M+Na)^+$ 513.0929, found 513.0916.



S3

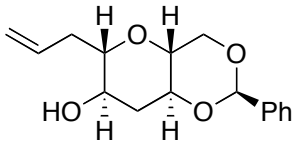
((2*R*,4*S*,5*R*)-4-(((2*R*,3*R*)-3-allyloxiran-2-yl)methyl)-2-phenyl-1,3-dioxan-5-yloxy)(*tert*-butyl) dimethylsilane (S3): To a solution of iodide **S2** (3 g, 6.1 mmol) in THF (30 mL) is added copper(I) bromide-dimethyl sulfide (430 mg, 2.1 mmol), and HMPA (4 mL, 25 mmol). The solution is immediately cooled to -25 °C and stirred for 5 min. Then a solution of vinyl magnesium bromide (15.3 mL of 1M in THF, 15.3 mmol) is added dropwise over 5 min with vigorous stirring. The reaction is stirred at -25 °C for 15 min, then quenched at -25 °C by addition of sat. NH_4Cl, extracted with EtOAc (3 x 100 mL). The combined organic extracts are dried over $MgSO_4$ and concentrated *in vacuo*. The crude material is purified by column chromatography (5% EtOAc in hexane) to afford olefin **S3** (1.79 g, 75%) as a colorless oil;[4] Product was visualized with CAM stain, R_f = 0.20 (5% EtOAc in hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 0.10 (s, 3H), 0.11 (s, 3H), 0.89 (s, 9H), 1.94–2.03 (m, 2H), 2.26–2.31 (m, 1H), 2.36–2.41 (m, 1H), 2.82–2.84 (td, *J* = 5.6, 2.2 Hz, 1H), 3.02–3.04 (td, *J* = 5.6, 2.2 Hz, 1H), 3.57–3.61 (m, 1H), 3.67–3.73 (m, 2H), 4.19–4.22 (dd, *J* = 10.7, 4.5 Hz, 1H), 5.09–5.11 (dd, *J* = 10.3, 1.4 Hz, 1H), 5.15–5.18 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.51 (s, 1H), 5.81–5.88 (ddt, *J* = 17.2, 10.3, 7.0 Hz, 1H), 7.35–7.40 (m, 3H), 7.49–7.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: -4.6, -4.1, 18.0, 25.9, 34.0, 36.4, 55.4, 57.2, 66.2, 72.0, 80.4, 101.0, 117.6, 126.2, 128.4, 129.1, 133.5, 138.0; IR (thin film NaCl): 3070, 2956, 2929, 2886, 2857, 1462, 1387, 1253, 1110, 1029, 857, 838, 778, 698; $[\alpha]^{23}_D$ = -43.0 (*c* = 0.1, $CHCl_3$); HR-MS (ESI) Calcd for $C_{22}H_{34}O_4Si$ $(M+Na)^+$ 413.2119, found 413.2116.

[4] Attempts to scale this reaction beyond 6.1 mmol iodide **S2** led to a precipitous drop in yield.



5

(2*R*,4*S*,5*R*)-4-(((2*R*,3*R*)-3-allyloxiran-2-yl)methyl)-2-phenyl-1,3-dioxan-5-ol (5): Silyl ether **S3** (14 g, 36 mmol) was dissolved in THF (180 mL) and cooled to 0 °C. A solution of tetrabutylammonium fluoride (TBAF) (54 mL of 1M in THF, 54 mmol) is added dropwise and the reaction stirred at 0 °C for 30 min. The reaction is quenched by addition of brine (300 mL), extracted with EtOAc (3 x 300 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The product is purified by column chromatography (40% EtOAc in hexane) to afford epoxy alcohol **5** (9.2 g, 93%) as a white solid; Product was visualized with CAM stain, R_f = 0.43 (50% EtOAc in hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.88–1.93 (ddd, *J* = 15.2, 7.6, 5.2 Hz, 1H), 2.26–2.29 (dt, *J* = 15.2, 3.5 Hz, 1H), 2.34–2.36 (app dd, *J* = 6.5, 5.7 Hz, 2H), 2.56–2.57 (d, *J* = 5.0 Hz, 1H), 2.89–2.91 (td, *J* = 5.5, 2.3 Hz, 1H), 3.10–3.12 (m, 1H), 3.61–3.64 (t, *J* = 10.7, 1H), 3.73–3.76 (m, *J* = 1H), 3.89–3.94 (app sp, *J* = 4.8 Hz, 1H), 4.31–4.34 (dd, *J* = 10.7, 4.8 Hz, 1H), 5.11–5.13 (dd, *J* = 10.3, 1.3 Hz, 1H), 5.15–5.18 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.51 (s, 1H), 5.80–5.87 (ddt, *J* = 17.2, 10.3, 6.8 Hz, 1H), 7.36–7.40 (m, 3H), 7.50–7.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.3, 36.2, 55.2, 57.4, 65.1, 71.2, 78.0, 101.4, 117.9, 126.3, 128.5, 129.2, 133.1, 137.8; IR (KBr pellet): 3309, 2983, 2917, 1460, 1409, 1385, 1220, 1126, 1067, 1013, 975, 917, 766; $[\alpha]^{23}_D$ = -0.5 (*c* = 0.02, $CHCl_3$); HR-MS (ESI) Calcd for $C_{16}H_{20}O_4$ $(M+Na)^+$ 299.1254, found 299.1253.



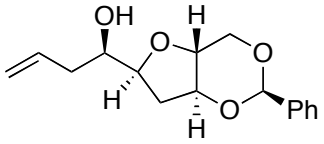
8

(2*R*,4a*R*,6*S*,7*R*,8a*S*)-6-allyl-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxin-7-ol (8):

Representative non-microwave procedure: To epoxy alcohol **5** (300 mg, 1.1 mmol) is added H_2O (50 mL) and NaOH (216 mg, 5.4 mmol), the reaction is stirred at ambient temperature for 12 h. The aqueous phase is extracted with EtOAc (5 x 50 mL), the combined extracts dried over $MgSO_4$, and concentrated *in vacuo*.[5] The crude reaction mixture is purified by column chromatography (30% EtOAc in hexane) to afford alcohols **8** (184 mg, 58%) and **9** (102 mg, 34%) as white solids.

[5] For reactions in organic solvents, after the prescribed reaction time the solvent is removed *in vacuo* and the crude reaction mixture purified directly by column chromatography (30% EtOAc in hexane).

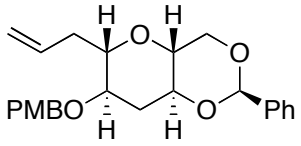
Microwave procedure:[6] Silicic acid (5.25 g, 35 mg/mg **5**) is loaded into a 20 mL microwave vial with magnetic stir bar. The vial is heated in an oven to 140 °C for 12 h then cooled to ambient temperature *in vacuo* (5 torr). Epoxy alcohol **5** (150 mg, 0.54 mmol) is added and the vial is capped quickly with a septum. With the vial attached to an argon inlet, solvent is added (18 mL), the argon inlet is removed, and vial is shaken manually to achieve mixing. The vial is heated in a microwave reactor to 135 °C for 10 min. Once the vial has cooled to ambient temperature the septum is pierced with a needle to release any pressure. The solvent is removed by filtration through a glass frit. The silicic acid is then washed with 95:5 Et_2O:MeOH (100 mL). The combined organic solvent is concentrated *in vacuo* and purified by column chromatography (30% EtOAc in Hexane) to afford alcohol **8** (108 mg, 72%) as a white solid. Product was visualized with CAM stain, R_f = 0.53 (50% EtOAc in hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.66–1.72 (ddd, *J* = 11.4, 11.4, 11.4 Hz, 1H), 1.76 (s, 1H), 2.31–2.36 (dt, *J* = 14.4, 7.2 Hz, 1H), 2.46–2.49 (dt, *J* = 11.4, 4.5 Hz, 1H), 2.57–2.61 (m, 1H), 3.28–3.32 (ddd, *J* = 9.2, 7.1, 4.0, 1H), 3.34–3.38 (td, *J* = 9.9, 4.9, 1H), 3.53–3.59 (m, 2H), 3.68–3.71 (dd, *J* = 10.2, 10.2, 1H), 4.31–4.34 (dd, *J* = 10.5, 4.9 Hz, 1H), 5.11–5.13 (d, *J* = 10.2 Hz, 1H), 5.16–5.19 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.53 (s, 1H), 5.90–5.97 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 7.37–7.39 (m, 3H), 7.50–7.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 36.4, 38.2, 69.3, 69.4, 73.1, 76.7, 81.6, 101.7, 117.4, 126.3, 128.5, 129.3, 134.6, 137.4; IR (thin film NaCl): 3419, 2983, 2952, 2872, 1644, 1452, 1366, 1120, 1097, 1008, 924; $[\alpha]^{23}_D$ = -19.5 (*c* = 0.02, $CHCl_3$); HR-MS (ESI) Calcd for $C_{16}H_{20}O_4$ $(M+Na)^+$ 299.1254, found 299.1261.



9

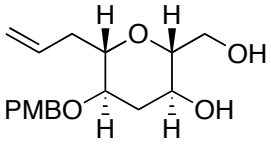
(*R*)-1-((2*R*,4a*R*,6*S*,7a*S*)-2-phenyltetrahydro-4*H*-furo[3,2-*d*][1,3]dioxin-6-yl)but-3-en-1-ol (9): Product was visualized with CAM stain, R_f = 0.51 (50% EtOAc in hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.99–2.00 (d, *J* = 3.6 Hz, 1H), 2.18–2.24 (m, 2H), 2.28–2.32 (dt, *J* = 12.6, 6.3 Hz, 1H), 2.33–2.38 (m, 1H), 3.73–3.78 (ddd, *J* = 11.3, 9.0, 6.4 Hz, 1H), 3.83–3.86 (dd, *J* = 9.9, 9.9 Hz, 1H), 3.88–3.91 (m, 1H), 4.12–4.15 (ddd, *J* = 9.3, 4.6, 6.2 Hz, 1H), 4.52–4.54 (dd, *J* = 9.7, 4.4 Hz, 1H), 5.17–5.21 (m, 2H), 5.56 (s, 1H), 5.82–5.89 (ddt, *J* = 17.2, 10.2, 7.2 Hz, 1H), 7.35–7.41 (m, 3H), 7.51–7.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.9, 37.6, 71.9, 72.4, 73.5, 80.2, 81.2, 102.5, 118.6, 126.5, 128.6, 129.4, 134.2, 137.3; IR (KBr pellet): 3423, 2979, 2930, 2891, 1451, 1411, 1369, 1340, 1220, 1137, 1105, 1095, 1045, 983, 751; $[\alpha]^{23}_D$ = -11.7 (*c* = 0.02, $CHCl_3$); HR-MS (ESI) Calcd for $C_{16}H_{20}O_4$ $(M+Na)^+$ 299.1254, found 299.1255.

[6] For cyclizations conducted in a microwave reactor, advantageous moisture will result in hydrolysis of the benzylidene acetal. Therefore, the silica promoter should be dried prior to use. Due to the size of vials accommodated by the microwave, the maximum scale per cyclization is 150 mg (0.54 mmol) of epoxy alcohol **5**. Furthermore, 1,2-dichloroethane (DCE) can replace DCM as solvent should high reaction pressures trigger an automatic shutdown of the microwave. Changing solvent to 1,2-DCE had no significant effect on selectivity or yield.



S4

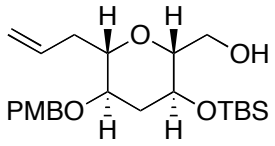
(2*R*,4a*R*,6*S*,7*R*,8a*S*)-6-allyl-7-(4-methoxybenzyloxy)-2-phenylhexahydropyrano[3,2-*d*][1,3] dioxine (S4): Potassium hydride (3 g of 30% in oil by weight, 22.5 mmol) is loaded into a round bottom flask. A solution of alcohol **8** (4.1 g, 15.0 mmol) in THF (150 mL) is added and the reaction heated to 50 °C for 40 min affording an orange/red solution. *Para*-methoxybenzyl chloride (PMB) (2.6 mL, 19.4 mmol) is added dropwise and the reaction stirred at 50 °C an additional 40 min. The reacion is cooled to 0 °C and quenched by dropwise addition of MeOH (6 mL) then brine (80 mL) and extracted with EtOAc (3 x 130 mL). The combined organic extracts are dried over $MgSO_4$ and remove solvent *in vacuo*. Crude material is purified by column chromatography (gradient: 5% to 10% to 30% EtOAc in hexane) to afford PMB ether **S4** (5.2 g, 94%) as a colorless oil; Product was visualized with CAM stain, R_f = 0.34 (in 30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.63–1.72 (ddd, *J* = 11.6, 11.6, 11.6 Hz, 1H), 2.23–2.31 (dt, *J* = 14.9, 7.4 Hz, 1H), 2.61–2.69 (m, 2H), 3.31–3.53 (m, 4H), 3.66–3.71 (dd, *J* = 10.4, 10.4 Hz, 1H), 3.83 (s, 3H), 4.31–4.34 (dd, *J* = 10.4, 4.9 Hz, 1H), 4.42–4.45 (d, *J* = 11.1 Hz, 1H), 4.58–4.61 (d, *J* = 11.1 Hz, 1H), 5.08–5.15 (m, 2H), 5.53 (s, 1H), 5.84–5.95 (dddd, *J* = 17.4, 10.2, 7.5, 6.4 Hz, 1H), 6.89–6.93 (d, *J* = 8.7 Hz, 2H), 7.26–7.29 (d, *J* = 8.7 Hz, 2H), 7.36–7.42 (m, 3H), 7.50–7.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.9, 36.2, 55.5, 69.6, 70.8, 73.2, 75.3, 76.9, 80.5, 101.8, 114.1, 117.2, 126.4, 128.5, 129.3, 129.7, 130.1, 134.9, 137.6, 159.5; IR (thin film NaCl): 3071, 3035, 2999, 2935, 2871, 1641, 1612, 1586, 1513, 1455, 1386, 1365, 1302, 1249, 1173, 1090, 1031, 1013, 966, 916, 820, 751, 698; $[\alpha]^{23}_D$ = -53.3 (*c* = 0.046, $CHCl_3$); HR-MS (ESI) Calcd for $C_{24}H_{28}O_5$ $(M+Na)^+$ 419.1829, found 419.1835.



S5

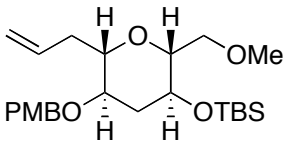
(2*R*,3*S*,5*R*,6*S*)-6-allyl-2-(hydroxymethyl)-5-(4-methoxybenzyloxy)tetrahydro-2*H*-pyran-3-ol (S5): PMB ether **S4** (4.5 g, 12.2 mmol) is dissolved in MeOH (225 mL) and THF (75 mL) followed by addition of CSA (860 mg, 3.7 mmol). The reaction is stirred at ambient temperature for 90 min, quenched by addition of Et_3N (0.5 mL) and the solvent removed *in vacuo*. The crude material is purified by column chromatography (gradient: 40% EtOAc in hexane to 100% EtOAc) to afford diol **S5** (3.3 g, 90%) as a colorless oil; Product was visualized with CAM stain, R_f = 0.30 (in 80% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.42–1.50 (ddd, *J* = 11.2, 11.2, 11.2 Hz, 1H), 2.17–2.24 (m, 2H), 2.30–2.31 (d, *J* = 5.3 Hz, 1H), 2.54–2.65 (m, 2H), 3.17–3.23 (m, 2H), 3.28–3.33 (ddd, *J* = 9.1, 7.8, 3.1 Hz, 1H), 3.55–3.64 (m, 1H), 3.72–3.78 (ddd, *J* = 11.5, 5.4, 5.3, 1H), 3.82–3.87 (m, 4H), 4.39–4.42 (d, *J* = 11.1 Hz, 1H), 4.55–4.58 (d, *J* = 11.1 Hz, 1H), 5.05–5.11 (m, 2H), 5.81–5.88 (dddd, *J* = 17.3, 10.2, 7.4, 6.5 Hz, 1H), 6.88–6.90 (d, *J* =

8.7 Hz, 2H), 7.25–7.27 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 36.2, 38.4, 55.5, 63.4, 66.9, 70.9, 75.2, 79.8, 81.0, 114.1, 117.1, 129.7, 130.2, 135.0, 159.5; IR (thin film NaCl): 3430, 3037, 3005, 2936, 2880, 2855, 1646, 1614, 1515, 1465, 1401, 1339, 1305, 1253, 1183, 1127, 1101, 1043, 999, 918, 824, 771, 669; $[\alpha]^{23}_D$ = -31.3 (c = 0.006, $CHCl_3$); HR-MS (ESI) Calcd for $C_{17}H_{24}O_5$ $(M+Na)^+$ 331.1516, found 331.1528.



10

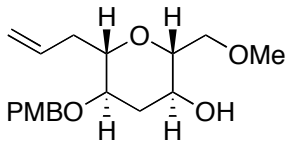
((2*R*,3*S*,5*R*,6*S*)-6-allyl-3-(*tert*-butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)tetrahydro-2*H*-pyran-2-yl)methanol (10): Diol **S5** (3.3 g, 10.8 mmol) is dissolved in DCM (108 mL), 2,6-lutidine (5 mL, 43.2 mmol) and cooled to 0 °C. *Tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) (6.2 mL, 27 mmol) is added dropwise and the reaction stirred at 0 °C for 30 min, quenched by addition of MeOH (3 mL) then diluted with EtOAc (200 mL). The organic layer is washed with 1M HCl (100 mL), then sat. $NaHCO_3$ (100 mL), then brine (100 mL). The organic layer is dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude residue is dissolved in MeOH (100 mL) and cooled to 0 °C followed by addition of CSA (1.5 g, 6.5 mmol) and stirred at 0 °C for 20 min. The reaction is quenched with Et_3N (0.9 mL), the solvent removed *in vacuo* and the crude material purified by column chromatography (gradient: 10% to 20% EtOAc in hexane) to afford silyl ether **10** (4.1 g, 91% over 2 steps) as a colorless oil; Product was visualized with CAM stain, R_f = 0.66 (in 50% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.06 (s, 6H), 0.88 (s, 9H), 1.40–1.49 (ddd, J = 11.2, 11.2, 11.2 Hz, 1H), 2.00–2.03 (dd, J = 7.2, 5.7 Hz, 1H), 2.17–2.24 (dt, J = 15.2, 7.6 Hz, 1H), 2.34–2.39 (dt, J = 11.8, 4.5 Hz, 1H), 2.59–2.65 (dddd, J = 14.7, 4.6, 3.1, 1.5 Hz, 1H), 3.13–3.21 (m, 2H), 3.28–3.33 (ddd, J = 9.2, 7.7, 3.0 Hz, 1H), 3.45–3.51 (ddd, J = 11.0, 9.1, 4.6 Hz, 1H), 3.54–3.59 (dt, J = 11.6, 5.6 Hz, 1H), 3.79–3.84 (m, 4H), 4.41–4.43 (d, J = 11.1 Hz, 1H), 4.53–4.56 (d, J = 11.1 Hz, 1H), 5.04–5.12 (m, 2H), 5.81–5.92 (dddd, J = 17.6, 10.2, 7.5, 6.2 Hz, 1H), 6.88–6.91 (d, J = 8.7 Hz, 2H), 7.26–7.28 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: -4.7, -4.0, 18.1, 25.9, 36.3, 39.2, 55.5, 63.0, 67.0, 71.0, 75.3, 79.7, 81.8, 114.1, 117.1, 129.7, 130.4, 135.0, 159.5; IR (thin film NaCl): 3480, 3075, 2953, 2929, 2857, 1641, 1612, 1514, 1463, 1360, 1302, 1250, 1173, 1095, 1004, 913, 861, 837, 777, 670; $[\alpha]^{23}_D$ = -0.004 (c = 0.011, $CHCl_3$); HR-MS (ESI) Calcd for $C_{23}H_{38}O_5Si$ $(M+Na)^+$ 445.2381, found 445.2384.



S6

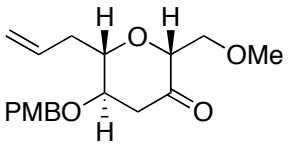
((2*R*,3*S*,5*R*,6*S*)-6-allyl-5-(4-methoxybenzyloxy)-2-(methoxymethyl)tetrahydro-2*H*-pyran-3-yloxy)(*tert*-butyl)dimethylsilane (S6): Alcohol **10** (3.2 g, 7.6 mmol) is dissolved in CH_3CN (75

mL) followed by addition of MeI (9.4 mL, 152 mmol) and silver(I) oxide (1.9 g, 8.4 mmol). The reaction is heated, in the dark, to 60 °C for 18 h then cooled to ambient temperature affording a milky colored solution. The solution was filtered through celite, the celite washed with Et_2O, and the organic solvent removed *in vacuo*. The crude material is purified by column chromatography (10% EtOAc in hexane) to afford methyl ether **S6** (2.5 g, 76%) as a colorless oil; Product was visualized with CAM stain, R_f = 0.52 (in 20% EtOAc in hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 0.05 (s, 3H), 0.06 (s, 3H), 0.88 (s, 9H), 1.38–1.44 (ddd, *J* = 11.3, 11.3, 11.3 Hz, 1H), 2.24–2.29 (dt, *J* = 14.7, 7.3 Hz, 1H), 2.34–2.38 (dt, *J* = 11.8, 4.5 Hz, 1H), 2.58–2.62 (m, 1H), 3.16–3.21 (m, 2H), 3.24–3.27 (td, *J* = 9.2, 3.2 Hz, 1H), 2.26 (s, 3H), 3.49–3.51 (dd, *J* = 10.4, 4.6 Hz, 1H), 3.56–3.61 (m, 2H), 3.81 (s, 3H), 4.41–4.42 (d, *J* = 11.1 Hz, 1H), 4.52–4.54 (d, *J* = 11.1 Hz, 1H), 5.04–5.05 (d, *J* = 10.2 Hz, 1H), 5.08–5.11 (d, *J* = 17.2 Hz, 1H), 5.90–5.97 (dddd, *J* = 17.2, 10.2, 6.9, 6.9 Hz, 1H), 6.88–6.89 (d, *J* = 8.5 Hz, 2H), 7.26–7.27 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: -4.9, -4.2, 17.9, 25.8, 36.1, 39.4, 55.3, 59.4, 66.0, 70.8, 71.7, 75.2, 80.4, 81.7, 113.9, 116.5, 129.6, 130.4, 135.3, 159.4; IR (thin film NaCl): 3074, 2953, 2929, 2885, 2857, 1641, 1612, 1586, 1514, 1471, 1463, 1302, 1250, 1203, 1173, 1102, 1037, 1004, 912, 862, 837, 776, 669; $[\alpha]^{23}_D$ = 0.4 (*c* = 0.0026, $CHCl_3$); HR-MS (ESI) Calcd for $C_{24}H_{40}O_5Si$ $(M+Na)^+$ 459.2537, found 459.2543.



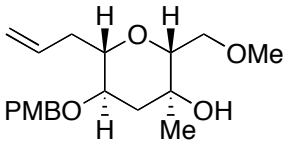
S7

(2*R*,3*S*,5*R*,6*S*)-6-allyl-5-(4-methoxybenzyloxy)-2-(methoxymethyl)tetrahydro-2*H*-pyran-3-ol (S7): Silyl ether **S6** (3.0 g, 6.9 mmol) is dissolved in THF (70 mL) and cooled to 0 °C. A solution of TBAF (10.3 mL of 1M in THF, 10.3 mmol) is added, the reaction is allowed to warm to ambient temperature and stirred for 1.75 h, then diluted with brine (100 mL). The aqueous layer is extracted with EtOAc (3 x 100 mL), the combined organic extracts dried over $MgSO_4$, and the solvent removed *in vacuo*. The crude material is purified by column chromatography (gradient: 40% to 60% EtOAc in hexanes then 100% EtOAc) to afford alcohol **S7** (2.1 g, 98%) as a colorless oil; Product was visualized with CAM stain, R_f = 0.2 (in 60% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.39–1.47 (ddd, *J* = 11.3, 11.3, 11.3 Hz, 1H), 2.18–2.25 (dt, *J* = 14.7, 7.4 Hz, 1H), 2.52–2.62 (m, 2H), 3.19–3.29 (m, 4H), 3.39 (s, 3H), 3.53–3.57 (m, 2H), 3.64–3.67 (dd, *J* = 9.9, 4.7 Hz, 1H), 3.79 (s, 3H), 4.37–4.40 (d, *J* = 11.1 Hz, 1H), 4.54–4.57 (d, *J* = 11.1 Hz, 1H), 5.03–5.10 (m, 2H), 5.85–5.93 (dddd, *J* = 17.1, 10.2, 6.9, 6.9 Hz, 1H), 6.87–6.89 (d, *J* = 8.7 Hz, 2H), 7.24–7.26 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 36.0, 37.8, 55.3, 59.7, 68.3, 70.6, 74.1, 75.0, 79.1, 80.0, 113.9, 116.7, 129.6, 130.2, 135.1, 159.3; IR (thin film NaCl): 3431, 3074, 2869, 1641, 1612, 1586, 1514, 1456, 1347, 1302, 1249, 1201, 1173, 1100, 916, 820; $[\alpha]^{23}_D$ = -56.2 (*c* = 0.042, $CHCl_3$); HR-MS (ESI) Calcd for $C_{18}H_{26}O_5$ $(M+Na)^+$ 345.1672, found 345.1673.



11

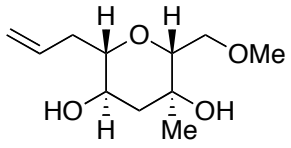
(2*R*,5*R*,6*S*)-6-allyl-5-(4-methoxybenzyloxy)-2-(methoxymethyl)dihydro-2*H*-pyran-3(4*H*)-one (11): Alcohol **S7** (2.1 g, 6.7 mmol) is dissolved in DCM (70 mL) to which is added Dess-Martin periodinane (6.0 g, 14.1 mmol). The reaction is stirred at ambient temperature for 90 min, quenched by addition of sat. $NaHCO_3$ (100 mL) then sat. $Na_2S_2O_3$ (100 mL), extracted with EtOAc (3 x 200 mL). The combined organic extracts are dried over $MgSO_4$ and the solvent is removed *in vacuo*. The crude material is purified by column chromatography (30% EtOAc in hexane) to afford ketone **11** (2.0 g, 96%) as a colorless oil; Product was visualized with CAM stain, R_f = 0.38 (in 40% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.43–2.47 (t, *J* = 6.4 Hz, 2H), 2.58–2.63 (dd, *J* = 15.3, 4.5 Hz, 1H), 2.80–2.85 (dd, *J* = 15.3, 4.5 Hz, 1H), 3.36 (s, 3H), 3.63–3.67 (dd, *J* = 10.7, 5.4 Hz, 1H), 3.71–3.76 (m, 2H), 3.79 (s, 3H), 3.83–3.86 (dd, *J* = 4.5, 4.5 Hz, 1H), 4.00–4.02 (dd, *J* = 5.3, 2.5 Hz, 1H), 4.31–4.34 (d, *J* = 11.3 Hz, 1H), 4.46–4.49 (d, *J* = 11.3 Hz, 1H), 5.09–5.13 (m, 2H), 5.81–5.92 (dddd, *J* = 17.2, 10.2, 7.0, 7.0 Hz, 1H), 6.85–6.88 (d, *J* = 8.6 Hz, 2H), 7.19–7.21 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 37.9, 41.5, 55.4, 59.7, 70.4, 71.5, 76.0, 79.7, 82.0, 114.0, 118.0, 129.5, 129.6, 133.8, 159.5, 208.5; IR (thin film NaCl): 2908, 1737, 1612, 1586, 1513, 1467, 1303, 1249, 1174, 1099, 920, 821; $[\alpha]^{23}_D$ = 52.7 (*c* = 0.045, $CHCl_3$); HR-MS (ESI) Calcd for $C_{18}H_{24}O_5$ $(M+Na)^+$ 343.1516, found 343.1518.



12

(2*R*,3*S*,5*R*,6*S*)-6-allyl-5-(4-methoxybenzyloxy)-2-(methoxymethyl)-3-methyltetrahydro-2*H*-pyran-3-ol (12): Ketone **11** (1.8 g, 5.7 mmol) is dissolved in toluene (60 mL) and cooled to –78 °C followed by addition of a solution of methyl magnesium bromide (4.7 mL of 3M in THF, 14.2 mmol). The reaction is stirred at –78 °C for 1 h then quenched at –78 °C by addition of sat. NH_4Cl (60 mL) and extracted with EtOAc (3 x 80 mL). The combined organic extracts are dried over $MgSO_4$ and solvent removed *in vacuo*. The crude material is purified by column chromatography (40% EtOAc in hexane) to afford alcohol **12** (1.4 g, 75%) as a colorless oil; Product was visualized with CAM stain, R_f = 0.18 (in 40% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.19 (s, 3H), 1.53–1.59 (m, 1H), 2.19–2.30 (m, 2H), 2.56–2.62 (dddd, *J* = 14.7, 4.8, 3.3, 1.6 Hz, 1H), 3.15–3.21 (ddd, *J* = 11.2, 9.2, 4.5 Hz, 1H), 3.28–3.32 (ddd, *J* = 9.2, 7.2, 3.3 Hz, 1H), 3.39 (s, 3H), 3.43–3.47 (dd, *J* = 7.6, 6.2 Hz, 1H), 3.50–3.58 (m, 2H), 3.81 (s, 3H), 4.36–4.38 (d, *J* = 11.0 Hz, 1H), 4.52–4.55 (d, *J* = 11.0 Hz, 1H), 5.03–5.10 (m, 2H), 5.81–5.92 (dddd, *J* = 17.5, 10.2, 7.5, 6.3 Hz, 1H), 6.87–6.90 (d, *J* = 8.7 Hz, 2H), 7.24–7.27 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.9, 36.1, 44.2, 55.5, 59.7, 70.7, 71.0, 72.6, 74.6, 79.4, 80.4, 114.0, 117.0, 129.7, 130.3, 135.0, 159.4; IR (thin film NaCl): 3460, 3074, 2934, 1641,

1612, 1586, 1514, 1464, 1376, 1301, 1249, 1202, 1173, 1095, 1035, 915, 821, 759; $[\alpha]^{23}_{D}$ = -19.8 (*c* = 0.016, $CHCl_3$); HR-MS (ESI) Calcd for $C_{19}H_{28}O_5$ $(M+Na)^+$ 359.1829, found 359.1813.



4

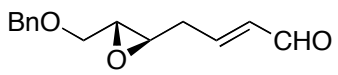
(2*R*,3*S*,5*R*,6*S*)-6-allyl-2-(methoxymethyl)-3-methyltetrahydro-2*H*-pyran-3,5-diol (4): PMB ether **12** (1.3 g, 3.7 mmol) is dissolved in DCM (36 mL), H_2O (1.8 mL) and cooled to 0 °C. 2,3-Dichloro-5,6-dicyano-1,4-benzo-quinone (DDQ) (1.7 g, 7.4 mmol) is added and the reaction is stirred at 0 °C for 1.5 h, quenched with $NaHCO_3$ (80 mL), then extracted with EtOAc (5 x 100 mL). The combined organic extracts are dried over $MgSO_4$, the solvent removed *in vacuo*, and the crude residue purified by column chromatography to afford diol **4** (750 mg, 93%) as a colorless oil; Product was visualized with CAM stain, R_f = 0.05 (in 40% EtOAc in hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.23 (s, 3H), 1.57–1.61 (t, *J* = 11.7 Hz, 1H), 1.63–1.64 (d, *J* = 5.4 Hz, 1H), 2.13–2.16 (dd, *J* = 11.7, 4.7 Hz, 1H), 2.28–2.33 (dt, *J* = 14.2, 7.2 Hz, 1H), 2.53–2.57 (m, 1H), 3.13 (s, 1H), 3.16–3.19 (ddd, *J* = 9.3, 6.9, 4.2 Hz, 1H), 3.40 (s, 3H), 3.41–3.47 (m, 2H), 3.51–3.58 (m, 2H), 5.07–5.09 (d, *J* = 10.2 Hz, 1H), 5.13–5.16 (d, *J* = 17.2 Hz, 1H), 5.88–5.95 (dddd, *J* = 17.2, 10.2, 7.0, 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.6, 36.3, 47.9, 59.6, 68.3, 70.9, 72.3, 80.1, 81.8, 117.1, 134.9; IR (thin film NaCl): 3383, 3076, 2978, 2933, 1642, 1463, 1377, 1285, 1202, 1099, 952, 916; $[\alpha]^{23}_{D}$ = -17.9 (*c* = 0.06, $CHCl_3$); HR-MS (ESI) Calcd for $C_{11}H_{20}O_4$ $(M+Na)^+$ 239.1254, found 239.1257.

S8

(2*R*,3*R*)-2-allyl-3-(benzyloxymethyl)oxirane (S8): NaH (1.14 g, 47.6 mmol) is added to THF (55 mL) at 0 °C followed by a solution of alcohol **13**[7] (3.62 g, 31.7 mmol) in THF (10 mL). The reaction is warmed to ambient temperature and stirred for 30 min. Benzyl bromide (5.66 mL, 47.6 mmol) is then added and the reaction is stirred an additional 3 h. The mixture is then cooled to 0 °C, quenched with sat. NH_4Cl, extracted with EtOAc (3 x 50mL). The combined organic extracts are dried over $MgSO_4$ and concentrated *in vacuo*. The crude product is purified by column chromatography (10% EtOAc in hexane) to afford benzyl ether **S8** (5.64 g, 87%). Product was visualized with CAM stain, R_f = 0.47 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.34–2.38 (2 dt, *J* = 5.4, 1.4 Hz, 2H), 2.93–2.96 (td, *J* = 5.4, 2.2 Hz, 1H), 2.99–3.02 (ddd, *J* = 5.6, 3.3, 2.2 Hz, 1H), 3.48–3.52 (dd, *J* = 11.5, 6.0 Hz, 1H), 3.72–3.76 (dd, *J* = 11.5, 3.3 Hz, 1H), 4.54–5.63 (2 d, *J* = 11.9 Hz, 2H), 5.10–5.14 (ddd, *J* = 10.3, 3.0, 1.2 Hz, 1H), 5.14–5.20 (ddd, *J* = 17.2, 3.0, 1.2 Hz, 1H), 5.78–5.88 (ddt, *J* = 17.2, 10.3, 6.7 Hz, 1H), 7.27–7.32 (m, 1H), 7.34–7.37 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 35.9, 55.1, 56.6, 70.4, 73.4, 77.6, 117.9, 127.9, 128.0, 128.6, 133.0, 138.1; IR (thin film NaCl): 3066, 3031, 2982, 2859, 1642, 1454,

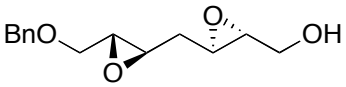
[7] Sabitha, G.; Sudhakar, K.; Reddy, N. M.; Rajkumar, M.; Yadav, J. S. *Tetrahedron Lett*. **2005**, *46*, 6567–6570.

1365, 1207, 1103, 1028, 997, 917, 738, 699; $[\alpha]^{23}_D = 9.0$ (c = 0.13, $CHCl_3$); HR-MS (ESI) Calcd for $C_{13}H_{16}O_2$ $(M+Na)^+$ 227.1043, found 227.1044.



S9

(*E*)-4-((2*R*,3*R*)-3-(benzyloxymethyl)oxiran-2-yl)but-2-enal (S9): To a solution of olefin **S8** (4.33 g, 21.2 mmol) in DCM (35 mL) is added acrolein (4.3 mL, 63.3 mmol) and the Hoveyda-Grubbs 2nd generation catalyst (331 mg, 0.5 mmol). A reflux condenser is attached and the reaction heated to reflux for 15 h. The reaction is cooled to ambient temperature and concentrated *in vacuo*. The crude reaction mixture is purified by column chromatography (gradient: 10% to 30% EtOAc in hexane) to afford aldehyde **S9** (4.08g, 83%). Product was visualized with CAM stain, R_f = 0.47 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.52–2.60 (dddd, J = 16.0, 7.4, 6.2, 1.5 Hz, 1H), 2.67–2.74 (dddd, J = 16.0, 6.2, 4.4, 1.5 Hz, 1H), 3.01–3.07 (m, 2H), 3.53–3.57 (dd, J = 11.5, 5.2 Hz, 1H), 3.71–3.75 (dd, J = 11.5, 3.3 Hz, 1H), 4.54–4.62 (2d, J = 12 Hz, 2H), 6.20–6.27 (ddt, J = 15.8, 7.8, 1.5 Hz, 1H), 6.79–6.87 (dt, J = 15.8, 6.7 Hz, 1H), 7.27–7.39 (m, 5H), 9.54 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.6, 53.6, 56.7, 73.6, 127.9, 128.0, 128.7, 135.0, 137.9, 152.0, 193.7; IR (thin film NaCl): 3063, 3031, 2993, 2859, 2744, 1689, 1454, 1366, 1102, 979, 911, 872, 740, 699; $[\alpha]^{23}_D = 9.2$ (c = 0.31, $CHCl_3$); HR-MS (ESI) Calcd for $C_{14}H_{16}O_3$ $(M + Na)^+$ 255.0992, found, 255.0998.



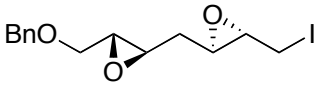
S10

((2*R*,3*R*)-3-(((2*R*,3*R*)-3-(benzyloxymethyl)oxiran-2-yl)methyl)oxiran-2-yl)methanol (S10): A solution of aldehyde **S9** (5.1 g, 22.0 mmol) in MeOH (45 mL) is cooled to 0 °C and $NaBH_4$ (625 mg, 16.5 mmol) is added in portions, after which the reaction is stirred at 0 °C for 20 min, quenched with sat. NH_4Cl (80 mL) and extracted with EtOAc (5 x 80 mL). The combined organic extracts are washed with brine (200 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude allylic alcohol is used without further purification.

Powdered 4Å molecular sieves (2.5 g) were flame dried under vacuum for 8 minutes and then cooled to ambient temperature. To the sieves is added DCM (44 mL), D-(–)-diethyl tartrate (542 mg, 2.63 mmol) and the mixture is cooled to –25 °C. $Ti(OiPr)_4$ (650 μL, 2.19 mmol) is added in one portion followed by the dropwise addition of *tert*-butyl hydrogen peroxide (8 mL of 5.5M in decane, 43.8 mmol) and the reaction is stirred at –25 °C for 30 min. The allylic alcohol is added as a solution in DCM (10 mL) and the reaction is stirred at –25 °C for 15 h. The reaction is quenched at –25 °C by addition of a solution of anhydrous citric acid (410 mg) in Et_2O (77 mL).[8] The reaction is stirred for 30 min at ambient temperature, filtered through celite and the solvent removed *in vacuo*. The crude material is purified by column chromatography (60% EtOAc in hexane) to afford epoxide **S10** (3.5 g, 64%). Product was visualized with CAM stain, R_f = 0.05 (60% EtOAc in hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.76–1.81 (ddd, J =

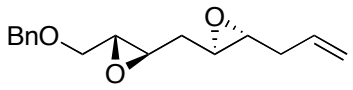
[8] Anhydrous citric acid is slow to dissolve in Et_2O, the solution is typically prepared overnight.

14.5, 6.8, 4.7 Hz, 1H), 1.84–1.88 (ddd, *J* = 14.5, 6.8, 4.2 Hz, 1H), 2.06 (bs, 1H), 2.98–3.00 (dt, *J* = 4.4, 2.4 Hz, 1H), 3.01–3.05 (m, 2H), 3.13–3.16 (ddd, 6.8, 4.7, 2.2 Hz, 1H), 3.50–3.52 (dd, *J* = 11.4, 5.4 Hz, 1H), 3.65 (d, *J* = 9.9 Hz, 1H), 3.72–3.75 (dd, *J* = 11.4, 3.2 Hz, 1H), 3.92 (d, *J* = 12.6 Hz, 1H), 4.54–4.61 (2 d, *J* = 11.9 Hz, 2H), 7.29–7.31 (m, 1H), 7.34–7.37 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.5, 52.9, 53.0, 57.0, 58.4, 61.5, 70.0, 73.5, 127.9, 128.0, 128.6, 137.9; IR (thin film NaCl): 3438, 3030, 2923, 2854, 1496, 1454, 1366, 1273, 1091, 844, 738, 699; $[\alpha]^{23}_D$ = 45.1 (*c* = 0.055 , $CHCl_3$); HR-MS (ESI) Calcd for $C_{14}H_{18}O_4$ $(M + Na)^+$ 273.1097, found 273.1086.



S11

(2*R*,3*R*)-2-(benzyloxymethyl)-3-(((2*R*,3*S*)-3-(iodomethyl)oxiran-2-yl)methyl)oxirane (S11): To a mixture of PPh_3 (3.70 g, 14 mmol) and imidazole (0.95 g, 14 mmol) is added Et_2O (30 mL) and CH_3CN (10 mL). The solution is cooled to 0 °C and I_2 (3.55g, 14 mmol) is added in portions over 15 min with vigorous stirring followed by stirring at ambient temperature for 15 min. The solution is then cooled to 0 °C and a solution of alcohol **S10** (3.05 g, 12.2 mmol) in 6 mL Et_2O and 2 mL CH_3CN is added. The reaction is stirred at ambient temperature for 30 min, quenched with sat. $Na_2S_2O_3$, then extracted with EtOAc (3 x 30 mL). The combined organic extracts are dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (30% EtOAc in hexane) to afford iodide **S11** (3.80 g, 87%): Product was visualized with CAM stain, R_f = 0.27 (30% EtOAc in hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.78–1.87 (m, 2 H), 2.99–3.10 (m, 5H), 3.23–3.27 (dd, *J* = 13.1, 8.8 Hz, 1H), 3.51–3.54 (dd, *J* = 11.4, 5.2 Hz, 1H), 3.72–3.75 (dd, *J* = 11.4, 3.1 Hz, 1H), 4.55–4.62 (2 d, *J* = 12 Hz, 2H), 7.30–7.32 (m, 1H), 7.34–7.38 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 4.5, 34.6, 52.7, 56.9, 58.2, 59.4, 70.0, 73.5, 127.9, 128.0, 128.6, 137.9; IR (thin film NaCl): 3495, 3062, 3029, 2989, 2858, 1454, 1366, 1246, 1207, 1175, 1096, 890, 739, 699, 608, 379; $[\alpha]^{23}_D$ = 14.8 (*c* = 0.025, $CHCl_3$); HR-MS (ESI) Calcd for $C_{14}H_{17}IO_3$ $(M+Na)^+$ 383.0115, found 383.0111.

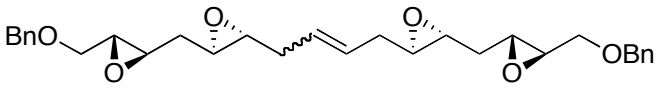


14

(2*R*,3*R*)-2-allyl-3-(((2*R*,3*R*)-3-(benzyloxymethyl)oxiran-2-yl)methyl)oxirane (14): Iodide **S11** (250 mg, 0.69 mmol) is dissolved in THF (3.5 mL) followed by addition of CuBr•DMS (57 mg, 0.28) and HMPA (0.29 mL, 2.8 mmol). The solution is immediately cooled to –25 °C and stirred for 5 min followed by dropwise addition of a solution of vinyl magnesium bromide (1 mL of 1M in THF, 1.0 mmol). The reaction is stirred at –25 °C for 20 min then quenched with sat NH_4Cl (5 mL), extracted with EtOAc (3 x 5 mL), and the combined organic extracts are dried over $MgSO_4$. The solvent is removed *in vacuo* and the crude material purified by column chromatography (20% EtOAc in hexane) to afford olefin **14** (150 mg, 84%) as a colorless oil.[9] Product was visualized with CAM stain, R_f = 0.31 (30% EtOAc in hexane); ^{1}H NMR (400 MHz,

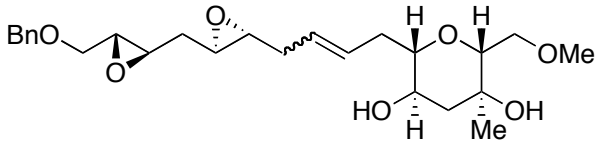
[9] Yields varied between 55-84% depending on reaction scale.

$CDCl_3$) δ: 1.78–1.81 (m, 2H), 2.33–2.35 (m, 2H), 2.82–2.85 (td, *J* = 5.4, 2.1 Hz, 1H), 2.88–2.92 (m, 1H), 3.00–3.04 (m, 2H), 3.49–3.53 (dd, *J* = 11.5, 3.4 Hz, 1H), 3.72–3.75 (dd, *J* = 11.5, 3.0 Hz, 1H), 4.54–4.57 (d, *J* = 11.9 Hz, 1H), 4.59–4.62 (d, *J* = 11.0 Hz, 1H), 5.10–5.19 (m, 2H), 5.77–5.87 (dddd, *J* = 17.0, 10.2, 6.6, 6.6 Hz, 1H), 7.28–7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.9, 36.1, 53.1, 55.1, 57.0, 57.5, 70.1, 73.5, 117.8, 127.9, 128.0, 128.6, 133.0, 138.0; IR (thin film NaCl): 3065, 3030, 2982, 2912, 2859, 1641, 1496, 1454, 1363, 1328, 1246, 1208, 1098, 1028, 996, 918, 738, 699; $[\alpha]^{23}_D$ = 42.4 (*c* = 0.029, $CHCl_3$); HR-MS (ESI) Calcd for $C_{16}H_{20}O_3$ $(M+Na)^+$ 283.1305, found 283.1305.



15

1,4-bis((2*R*,3*R*)-3-(((2*R*,3*R*)-3-(benzyloxymethyl)oxiran-2-yl)methyl)oxiran-2-yl)but-2-ene (15): To a solution of olefin **14** (56 mg, 0.215 mmol) in DCM (3 mL) is added 2nd generation Hoveyda-Grubbs catalyst (13 mg, 0.0215 mmol). A condenser is attached and the reaction heated to 40 °C for 12 h, followed by removal of the solvent *in vacuo*. The residue is purified by column chromatography (gradient: 20% to 50% EtOAc) to afford olefin **15** as a tan oil (45 mg, 85%). Product was visualized with CAM stain, R_f = 0.30 (50% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.77–1.79 (t, *J* = 5.6 Hz, 4H), 2.26–2.36 (m, 4H), 2.79–2.82 (td, *J* = 5.6, 2.1 Hz, 2H), 2.87–2.90 (td, *J* = 5.6, 2.1 Hz, 2H), 2.99–3.04 (m, 4H), 3.48–3.52 (dd, *J* = 11.4, 5.4 Hz, 2H), 3.72–3.75 (dd, *J* = 11.4, 3.1 Hz, 2H), 4.53–4.56 (d, *J* = 11.9 Hz, 2H), 4.59–4.62 (d, *J* = 11.9 Hz, 2H), 5.56–5.57 (m, 2H), 7.28–7.38 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.9, 35.0, 53.1, 55.1, 57.0, 57.7, 70.2, 73.5, 127.7, 127.9, 128.0, 128.6, 138.0; IR (thin film NaCl): 3089, 3062, 3030, 2992, 2895, 1721, 1689, 1497, 1471, 1453, 1422, 1367, 1329, 1272, 1244, 1210, 1112, 1028, 981, 939, 914, 892, 880, 858, 824, 734, 697, 620; $[\alpha]^{23}_D$ = 41.4 (*c* = 0.015, $CHCl_3$); HR-MS (ESI) Calcd for $C_{30}H_{36}O_6$ $(M+Na)^+$ 515.2404, found 515.2396.

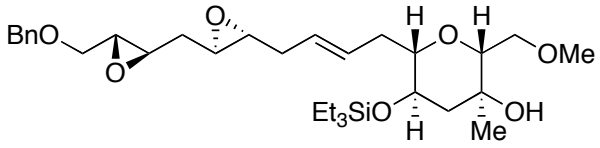


16

(2*R*,3*S*,5*R*,6*S*)-6-(4-((2*R*,3*R*)-3-(((2*R*,3*R*)-3-(benzyloxymethyl)oxiran-2-yl)methyl)oxiran-2-yl)but-2-enyl)-2-(methoxymethyl)-3-methyltetrahydro-2*H*-pyran-3,5-diol (16): To a solution of olefin **4** (156 mg, 0.72 mmol) and olefin **15** (1.7 g, 3.60 mmol) in DCM (4 mL) is added 2nd generation Hoveyda-Grubbs catalyst (68 mg, 0.11 mmol). A condenser is attached and the reaction heated to 40 °C for 12 h, followed by removal of the solvent *in vacuo*. The residue is purified by column chromatography (gradient: 20% EtOAc to 50% EtOAc to 100% EtOAc to 5% MeOH in EtOAc to 10% MeOH in EtOAc) to afford olefin **16** as a tan oil (244 mg, 74%). [10] Product was visualized with CAM stain, R_f = 0.07 (70% EtOAc in hexane); ^{1}H NMR (400 MHz,

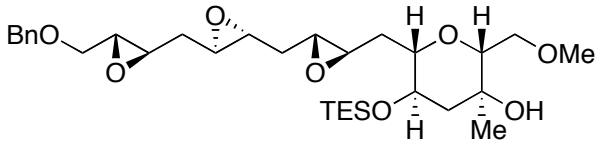
[10] Alternatively, the cross metathesis of olefin **4** with 300 mol% **14** afforded **16** in 44% yield as a 2.5:1 mixture of E:Z isomers.

$CDCl_3$) δ: 1.12 (s, 3H), 1.46–1.52 (m, 1H), 1.59–1.66 (m, 1H), 1.75–1.81 (m, 1H), 2.02–2.05 (m, 2H), 2.17–2.24 (m, 3H), 2.35–2.47 (m, 1H), 2.71–2.74 (ddd, *J* = 5.4, 5.4, 2.2 Hz, 1H), 2.79–2.82 (m, 1H), 2.93–2.94 (m, 2H), 3.02–3.13 (m, 2H), 3.30–3.36 (m, 5H), 3.40–3.47 (m, 3H), 3.62–3.68 (dd, *J* = 11.4, 3.0 Hz, 1H), 4.46–4.49 (d, *J* = 11.9 Hz, 1H), 4.51–4.54 (d, *J* = 11.9 Hz, 1H), 5.42–5.49 (m, 1H), 5.54–5.63 (m, 1H), 7.22–7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.8, 34.8, 35.1, 35.5, 47.9, 53.2, 55.2, 57.0, 58.0, 59.6, 68.4, 70.1, 70.9, 72.5, 73.5, 79.7, 81.8, 126.8, 127.9, 128.0, 128.6, 129.6, 137.9; IR (thin film NaCl): 3431, 2978, 2928, 1455, 1364, 1272, 1202, 1098, 978; $[\alpha]^{23}_D$ = -80.0 (*c* = 0.01, $CHCl_3$); HR-MS (ESI) Calcd for $C_{25}H_{36}O_7$ $(M+Na)^+$ 471.2353, found 471.2369.



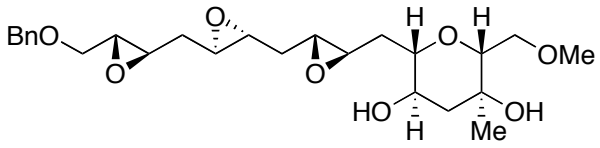
17

(2*R*,3*S*,5*R*,6*S*)-6-((*E*)-4-((2*R*,3*R*)-3-(((2*R*,3*R*)-3-(benzyloxymethyl)oxiran-2-yl)methyl)oxiran-2-yl)but-2-enyl)-2-(methoxymethyl)-3-methyl-5-(triethylsilyloxy) tetrahydro-2*H*-pyran-3-ol (17): To a solution of alcohol **16** (576 mg, 1.28 mmol) in DMF (6.5 mL) is added imidazole (192 mg, 3.2 mmol) and chlorotriethylsilane (0.32 mL, 1.86 mmol). The reaction is stirred at ambient temperature for 1.5 h then quenched by addition of brine (5 mL), extracted with EtOAc (5 x 5 mL), dried over $MgSO_4$ and the solvent is removed *in vacuo*. The crude oil is purified by column chromatography (gradient: 40% to 60% EtOAc) to afford silyl ether **17** as a colorless oil (591 mg, 82%). At this stage, the E:Z olefin isomers are separated by preparative HPLC (5μm silica column, hexanes:2-propanol, 97:3, 15 mL/min): t_R[**17**-Z] = 21.8 min, t_R[**17**-E] = 26.5 min. Product was visualized with CAM stain, R_f = 0.55 (80% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.56–0.62 (q, *J* = 7.9 Hz, 6H), 0.93–0.97 (t, *J* = 7.9 Hz, 9H), 1.21 (s, 3H), 1.59–1.65 (dd, *J* = 11.7, 11.7 Hz, 1H), 1.71–1.84 (m, 2H), 2.02–2.11 (m, 2H), 2.27–2.30 (t, *J* = 5.8 Hz, 2H), 2.49–2.55 (dd, *J* = 14.6, 6.0 Hz, 1H), 2.76–2.79 (ddd, *J* = 5.3, 5.3, 2.1 Hz, 1H), 2.87–2.89 (m, 1H), 2.99–3.03 (m, 2H), 3.08–3.13 (ddd, *J* = 8.7, 8.7, 2.8 Hz, 1H), 3.15 (s, 1H), 3.31–3.38 (m, 4H), 3.40–3.44 (dd, *J* = 7.6, 6.3 Hz, 1H), 3.47–3.56 (m, 3H), 3.72–3.75 (dd, *J* = 11.4, 3.1 Hz, 1H), 4.53–4.56 (d, *J* = 11.9 Hz, 1H), 4.59–4.61 (d, *J* = 11.9 Hz, 1H), 5.43–5.51 (ddd, *J* = 14.1, 6.6, 6.6 Hz, 1H), 5.58–5.65 (ddd, *J* = 14.1, 6.9, 6.9 Hz, 1H), 7.29–7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 5.2, 7.0, 21.9, 34.9, 35.0, 35.2, 48.4, 53.2, 55.1, 57.0, 58.0, 59.6, 69.3, 70.2, 70.9, 72.7, 73.5, 79.4, 82.5, 126.4, 127.9, 128.0, 128.6, 123.0, 138.0; IR (thin film NaCl): 3462, 2876, 1496, 1456, 1414, 1378, 1274, 1240, 1202, 1097, 1006, 964, 844, 788, 743, 698; $[\alpha]^{23}_D$ = -11.8 (*c* = 0.04, $CHCl_3$); HR-MS (ESI) Calcd for $C_{31}H_{50}O_7Si$ $(M+Na)^+$ 585.3218, found 585.3239.



S12

(2*R*,3*S*,5*R*,6*S*)-6-(((2*R*,3*R*)-3-(((2*R*,3*R*)-3-(((2*R*,3*R*)-3-(benzyloxymethyl)oxiran-2-yl)methyl)oxiran-2-yl)methyl)oxiran-2-yl)methyl)-2-(methoxymethyl)-3-methyl-5-(triethylsilyloxy)tetrahydro-2*H*-pyran-3-ol (S12): To a solution of olefin **17** (87 mg, 0.154 mmol) in 1:2 CH_3CN:DMM (5.0 mL) is added a solution of 0.05M $Na_2B_4O_7$•10 H_2O in 4.0 x 10^{-4} M Na_2(EDTA) (3.2 mL), and *n*$BuNHSO_4$ (26 mg, 0.077 mmol). The solution is cooled to 0 °C with rapid stirring. Then chiral ketone **20** (80 mg, 0.308 mmol) is added and immediately, a 0.89 M solution of K_2CO_3 (2.6 mL) and a solution of Oxone® (756 mg, 1.23 mmol) in 4.0 x 10^{-4} M Na_2(EDTA) (2.7 mL) are added simultaneously over 15 min via syringe pump. The reaction is stirred at 0 °C an additional 30 min then 1 g of NaCl is added. The solution is extracted with EtOAc (8 x 25 mL), the combined organic extracts dried over $MgSO_4$, and concentrated *in vacuo*. The crude material is purified by column chromatography (gradient: 50% to 60% EtOAc in hexane) to afford triepoxide **S12** (73 mg, 82%) as a colorless oil. Diastereomeric ratio (93:7) was established by chiral HPLC (Chiralcel OD-H, hexanes:2-propanol, 96:4, 2 mL/min): t_R [(minor)-**S12**] = 27.7 min, t_R [(major)-**S12**] = 38.0 min. Product was visualized with CAM stain, R_f = 0.22 (60% EtOAc in hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 0.57–0.61 (q, *J* = 8.1 Hz, 6H), 0.93–0.95 (t, *J* = 8.1 Hz, 9H), 1.23 (s, 3H), 1.60–1.64 (dd, *J* = 11.7, 11.7 Hz, 1H), 1.69–1.81 (m, 5H), 1.95–1.97 (m, 1H), 2.05–2.08 (dd, *J* = 12.2, 4.5 Hz, 1H), 2.85–2.86 (m, 1H), 2.90–2.92 (m, 3H), 3.01–3.04 (m, 2H), 3.12 (s, 1H), 3.22–3.24 (m, 1H), 3.38–3.43 (m, 4H), 3.45–3.53 (m, 3H), 3.56–3.58 (dd, *J* = 9.1, 6.0 Hz, 1H), 3.73–3.75 (dd, *J* = 11.5, 3.0 Hz, 1H), 4.54–4.56 (d, *J* = 11.9 Hz, 1H), 4.59–4.61 (d, *J* = 11.9 Hz, 1H), 7.30–7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 5.2, 7.0, 21.9, 34.1, 34.9, 35.3, 48.5, 53.1, 54.9, 55.4, 55.7, 56.2, 57.0, 59.7, 69.4, 70.2, 70.8, 72.6, 73.5, 79.5, 80.8, 128.0, 128.1, 128.6, 138.0; IR (thin film NaCl): 3465, 2954, 2876, 1456, 1414, 1376, 1275, 1240, 1202, 1097, 1006, 961, 844, 788, 743, 699; $[\alpha]^{23}_D$ = 3.0 (*c* = 0.01, $CHCl_3$); HR-MS (ESI) Calcd for $C_{31}H_{50}O_8Si$ $(M+Na)^+$ 601.3167, found 601.3181.



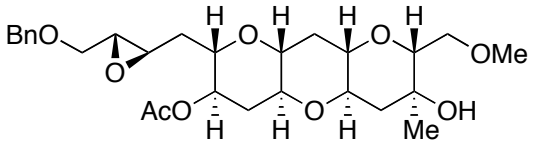
2

(2*R*,3*S*,5*R*,6*S*)-6-(((2*R*,3*R*)-3-(((2*R*,3*R*)-3-(((2*R*,3*R*)-3-(benzyloxymethyl)oxiran-2-yl)methyl)oxiran-2-yl)methyl)oxiran-2-yl)methyl)-2-(methoxymethyl)-3-methyltetrahydro-2*H*-pyran-3,5-diol (2): To a solution of silyl ether **S12** (116 mg, 0.20 mmol) in THF (0.5 mL) at 0 °C is added a solution of TBAF (0.3 mL, 1M in THF). The reaction is stirred at 0 °C for 20 min and then loaded directly onto a silica column for purification. The solution is purified by column chromatography (gradient: 50% EtOAc in hexanes to 100% EtOAc) to afford triepoxide **2** (71 mg, 77%) as a colorless oil. Product was visualized with CAM stain, R_f = 0.08 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.21 (s, 3H), 1.54–1.60 (dd, *J* = 11.8, 11.8 Hz, 1H), 1.68–1.78

(m, 4H), 1.80–1.88 (ddd, J = 14.2, 6.1, 3.8 Hz, 1H), 2.10–2.14 (dd, J = 11.6, 4.2 Hz, 2H), 2.63–2.64 (d, J = 5.1 Hz, 1H), 2.87–2.92 (m, 3H), 2.96–3.04 (m, 3H), 3.09 (s, 1H), 3.22–3.26 (ddd, J = 9.3, 5.6, 3.6 Hz, 1H), 3.37 (s, 3H), 3.42–3.57 (m, 5H), 3.70–3.74 (dd, J = 11.5, 3.0 Hz, 1H), 4.52–4.55 (d, J = 11.9 Hz, 1H), 4.57–4.60 (d, J = 11.9 Hz, 1H), 7.28–7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.8, 34.2, 34.8, 34.9, 47.8, 53.1, 55.2, 55.4, 55.5, 55.7, 57.0, 59.6, 68.0, 70.0, 70.8, 72.3, 73.5, 80.3, 80.5, 127.9, 128.0, 128.6, 137.9; IR (thin film NaCl): 3437, 2982, 2925, 2862, 1721, 1496, 1454, 1366, 1275, 1202, 1098, 981, 958, 933, 740, 700; $[\alpha]^{23}_D$ = 38.5 (c = 0.015, $CHCl_3$); HR-MS (ESI) Calcd for $C_{25}H_{36}O_8$ $(M+Na)^+$ 487.2302, found 487.2316.

Products of Water-Promoted Cascade (18 and 1):

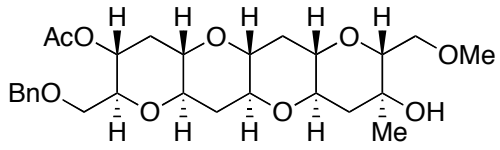
Representative Procedure: Triepoxide **2** (28mg, 0.06 mmol) is incubated in deionized H_2O (10 mL) at 60 °C for 5 days. [11] The water is removed *in vacuo* and the residue dissolved in DCM (6 mL) to which is added DMAP (3.5 mg, 0.03 mmol), Et_3N (0.17 mL, 1.21 mmol), Ac_2O (0.11 mL, 1.21 mmol) and the reaction is stirred at ambient temperature for 30 min. At which time SiO_2 is added and the solvent is removed *in vacuo*. The SiO_2 is then loaded onto a column and purified by column chromatography (70% EtOAc in hexane) to give a mixture of **18** and **1** which were purified further by preparative HPLC (5 micron SiO_2, hexanes:2-propanol, 92:8, 25 mL/min): t_R [**1**] = 13.7 min, t_R [**18**] = 15.2 min, to afford **1** (6.8 mg, 23%) and **18** (4.3 mg, 14%) as white solids.



18

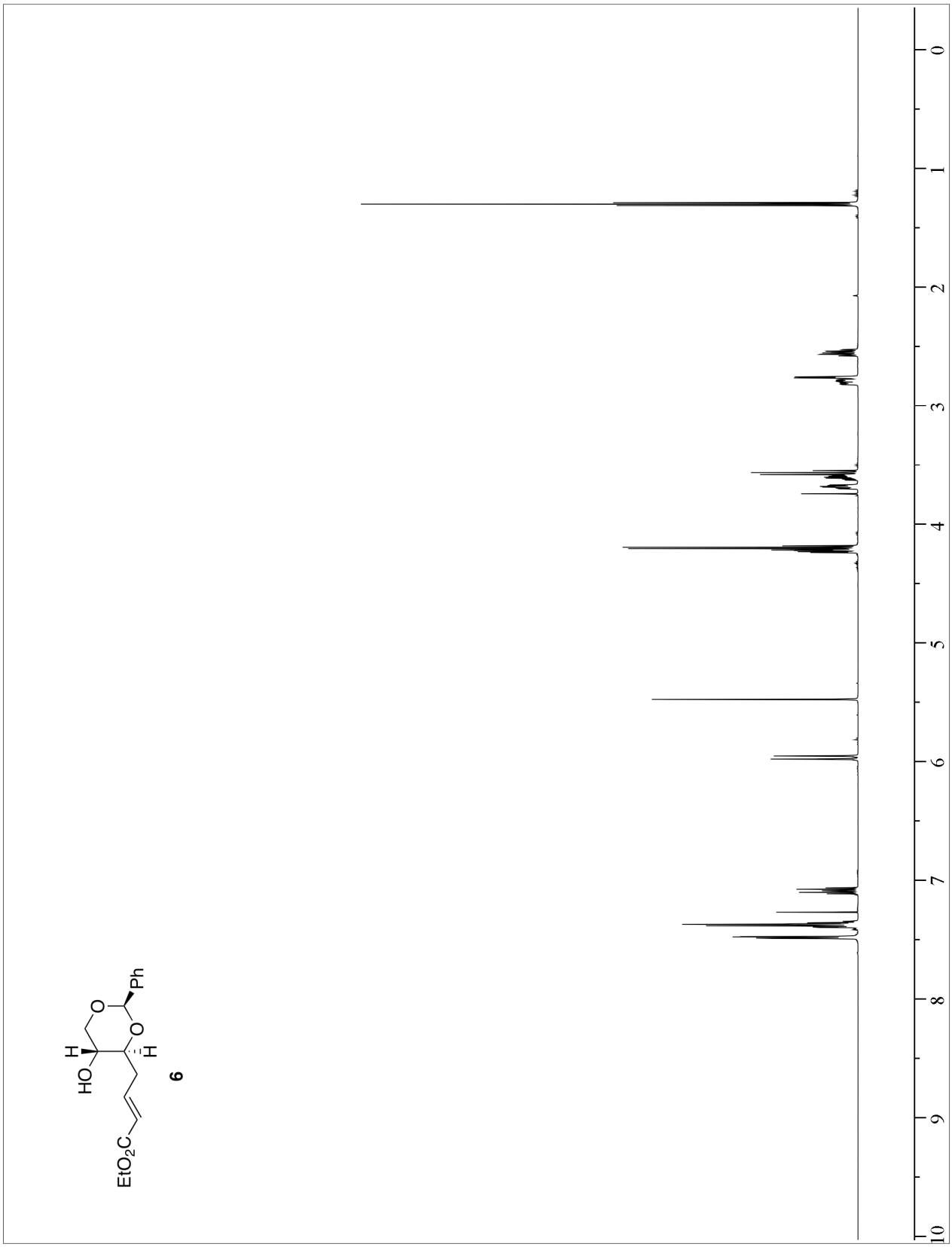
Triad 18: Product was visualized with CAM stain, R_f = 0.18 (70% EtOAc in hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.26 (s, 3H), 1.43–1.50 (dddd, J = 11.0, 11.0, 11.0, 11.0 Hz, 2H), 1.59–1.63 (dd, J = 11.8, 11.8 Hz, 1H), 1.74–1.79 (ddd, J = 13.4, 7.3, 6.0 Hz, 1H), 1.84–1.88 (ddd, J = 14.8, 4.6, 3.3 Hz, 1H), 2.05 (s, 3H), 2.10–2.13 (dd, J = 11.8, 4.1 Hz, 1H), 2.33–2.35 (ddd, J = 11.4, 3.6, 3.6 Hz, 1H), 2.47–2.50 (ddd, J = 11.8, 4.2, 4.2 Hz, 1H), 2.94 (s, 1H), 2.97–2.99 (m, 1H), 3.00–3.03 (m, 1H), 3.04–3.12 (m, 4H), 3.41 (s, 3H), 3.44–3.50 (m, 3H), 3.53–3.59 (m, 2H), 3.70–3.72 (dd, J = 11.4, 3.4 Hz, 1H), 4.54–4.56 (d, J = 11.9 Hz, 1H), 4.59–4.61 (d, J = 11.9 Hz, 1H), 4.65–4.69 (ddd, J = 10.7, 10.7, 4.7 Hz, 1H), 7.29–7.38 (m, 5H); ^{13}C NMR (100 MHz, acetone-d_6) δ: 21.6, 22.9, 35.2, 36.7, 36.8, 46.9, 53.8, 57.7, 59.7, 71.0, 71.7, 72.1, 73.1, 74.1, 77.4, 77.8, 78.3, 78.4, 78.9, 85.4, 128.9, 129.1, 129.8, 140.3, 170.7; IR (thin film NaCl): 3462, 3062, 2922, 2853, 1739, 1456, 1374, 1236, 1099, 1030, 974, 957, 801, 738, 700; $[\alpha]^{23}_D$ = -10.2 (c = 0.0026, $CHCl_3$); HR-MS (ESI) Calcd for $C_{27}H_{38}O_9$ $(M+Na)^+$ 529.2408, found 529.2405.

[11] Treatment of **2** in H_2O at 80 °C for 9 days followed by analogous acetylation and purification affords tetrad **1** (10.2 mg, 35%).



1

Tetrad 1: Product was visualized with CAM stain, R_f = 0.18 (70% EtOAc in hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.27 (s, 3H), 1.44–1.50 (ddd, *J* = 11.0, 11.0, 11.0 Hz, 2H), 1.54–1.58 (ddd, *J* = 11.0, 11.0, 11.0 Hz, 1H), 1.61–1.65 (dd, *J* = 11.8, 11.8 Hz, 1H), 1.91 (s, 3H), 2.12–2.15 (dd, *J* = 11.9, 4.1 Hz, 1H), 2.35–2.38 (ddd, *J* = 11.4, 3.9, 3.9 Hz, 1H), 2.39–2.42 (ddd, *J* = 11.6, 3.8, 3.8 Hz, 1H), 2.49–2.53 (ddd, *J* = 11.1, 4.4, 4.4 Hz, 1H), 2.91 (s, 1H), 3.04–3.18 (m, 6H), 3.40 (s, 3H), 3.48–3.59 (m, 6H), 4.48–4.50 (d, *J* = 12.3 Hz, 1H), 4.61–4.63 (d, *J* = 12.3 Hz, 1H), 4.82–4.86 (ddd, *J* = 11.2, 9.8, 4.9 Hz, 1H), 7.29–7.34 (m, 5H); ^{13}C NMR (125 MHz, CD_3CN) δ: 21.6, 22.4, 36.0, 36.2, 36.3, 46.2, 59.5, 68.1, 70.4, 71.0, 72.7, 74.2, 77.0, 77.4, 77.8, 77.9, 78.2, 78.4, 80.0, 84.5, 129.0, 129.3, 129.7, 139.8, 170.9; IR (thin film NaCl): 3495, 3030, 2935, 2875, 1740, 1496, 1455, 1370, 1338, 1237, 1205, 1153, 1100, 1067, 1042, 975, 954, 901, 735, 699; $[\alpha]^{23}_D$ = -16.5 (*c* = 0.0015, $CHCl_3$); HR-MS (ESI) Calcd for $C_{27}H_{38}O_9$ $(M+Na)^+$ 529.2408, found 529.2416.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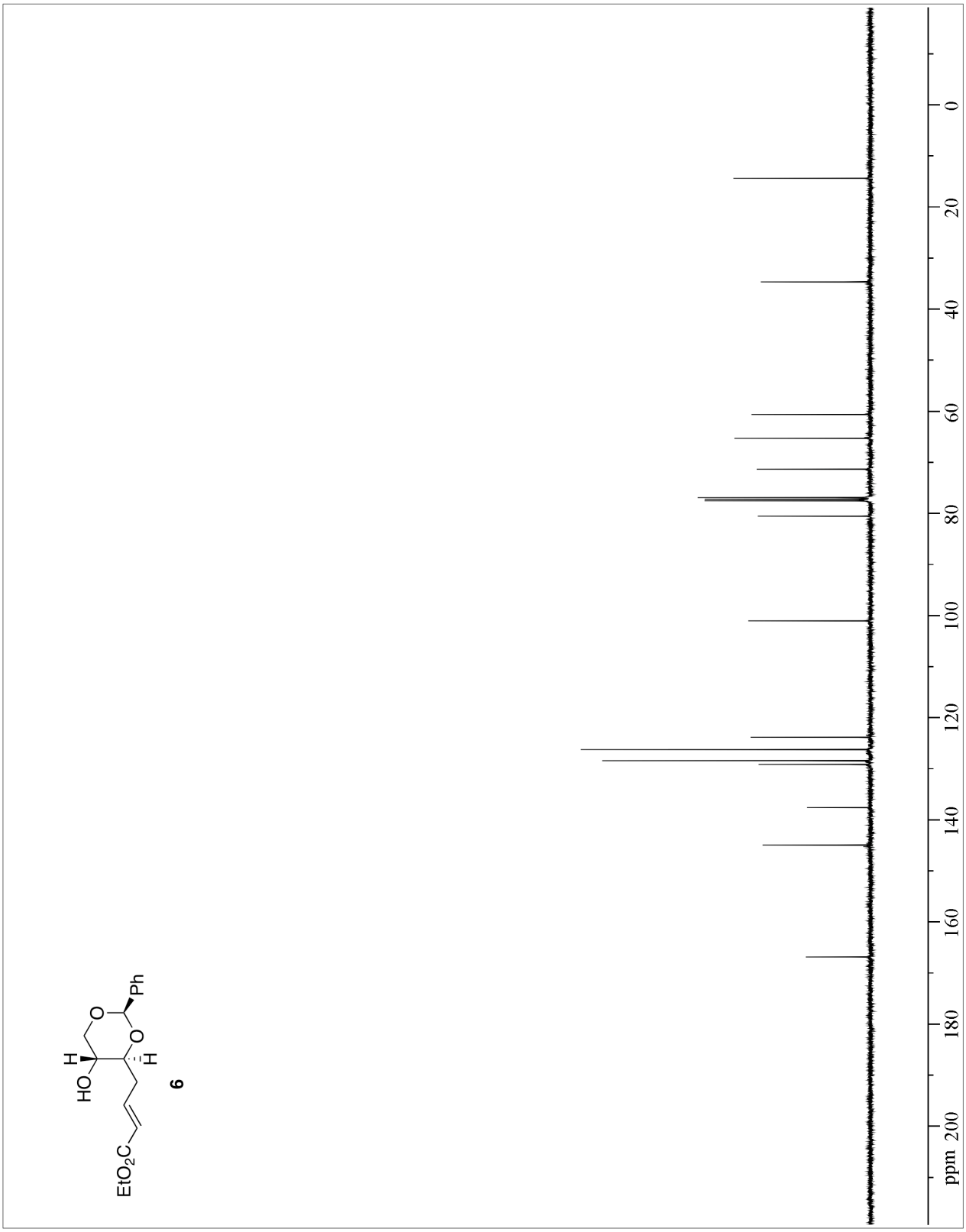
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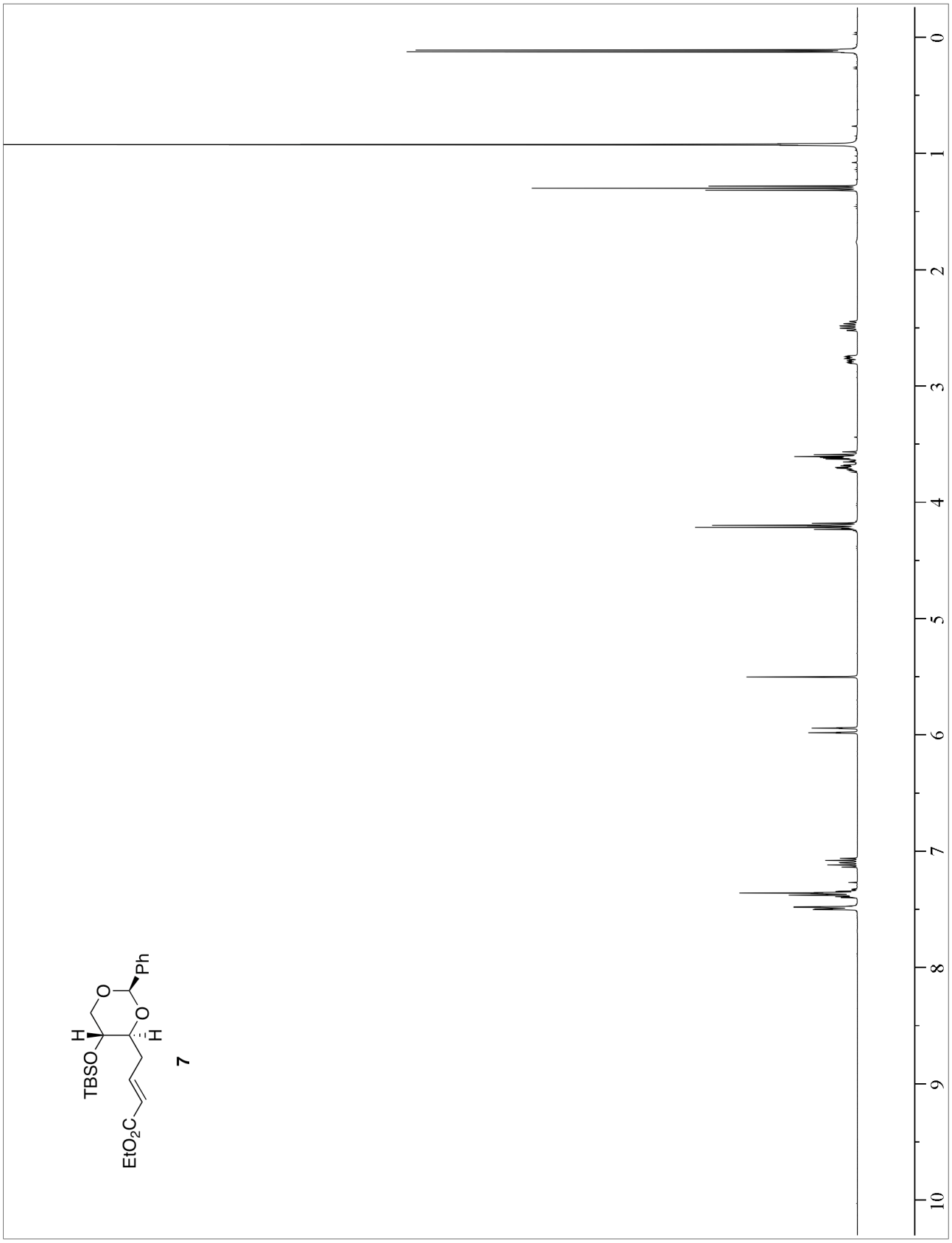
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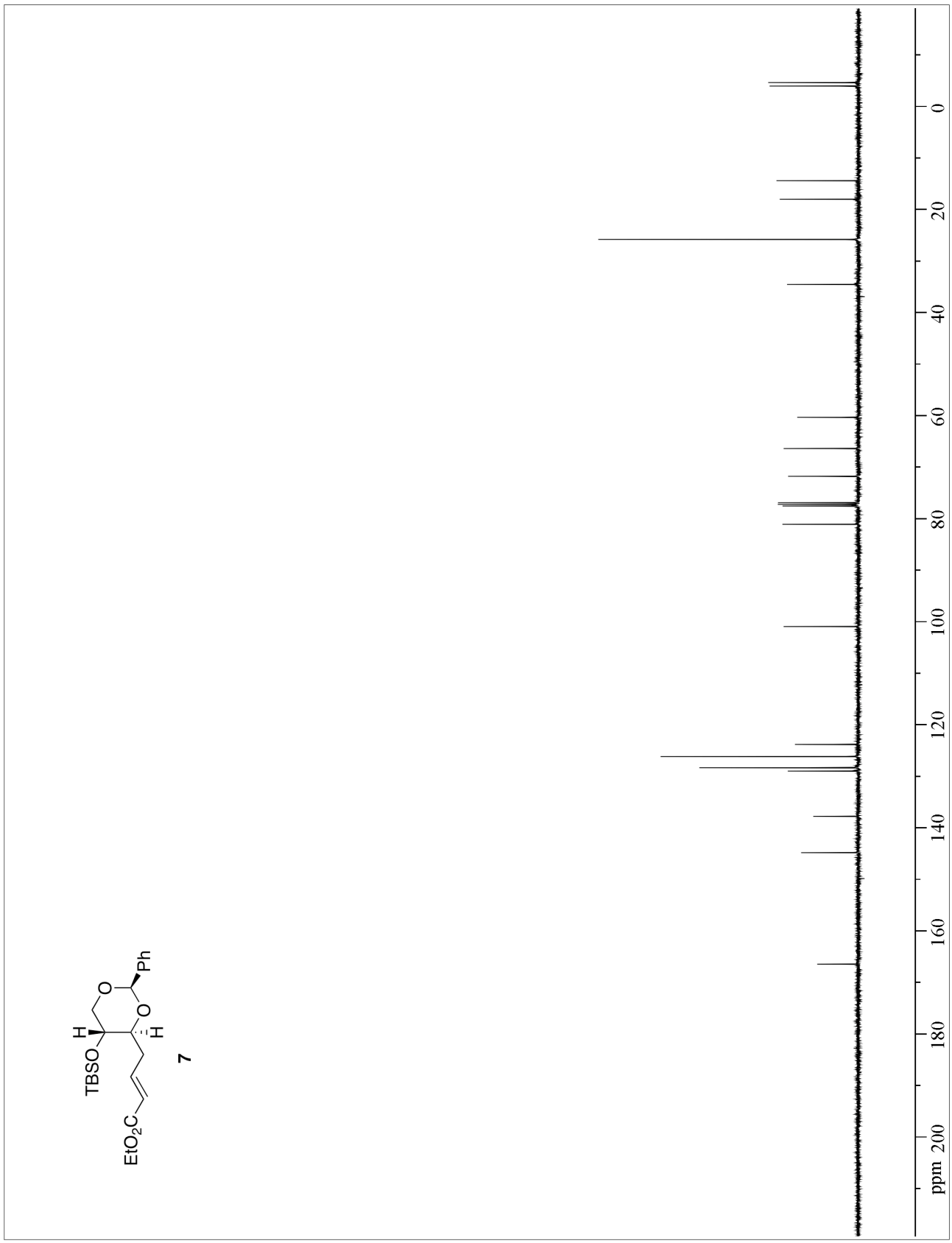
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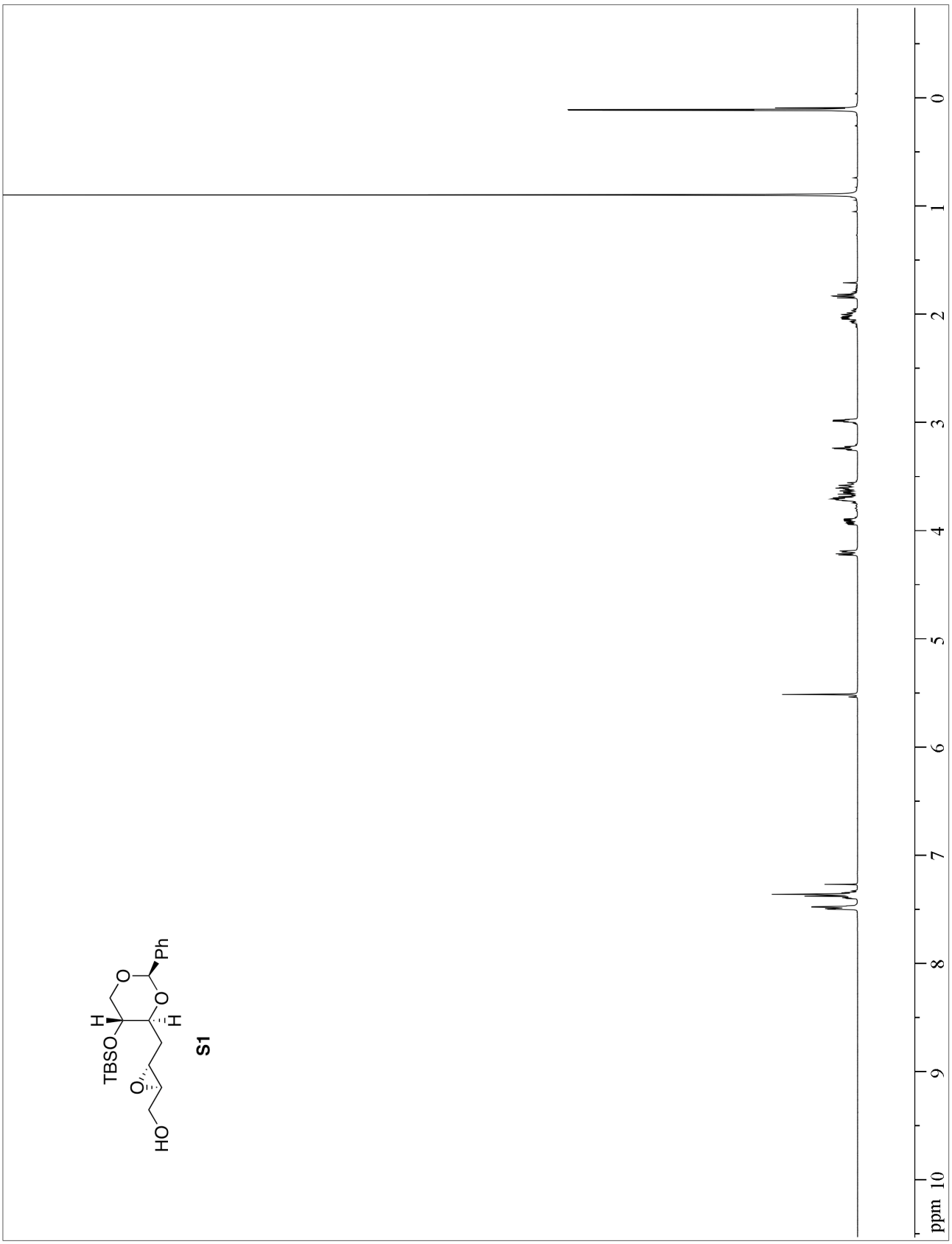
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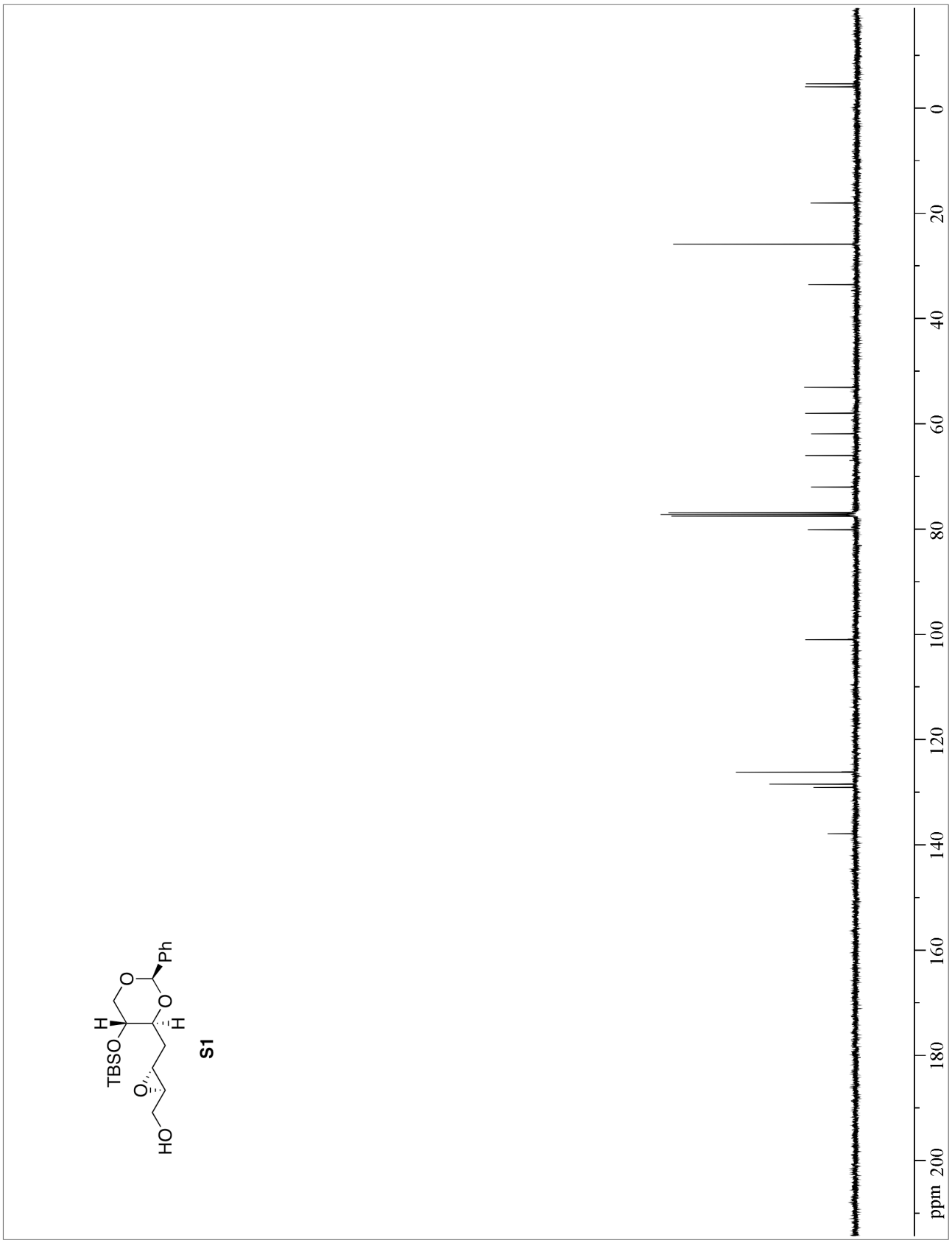
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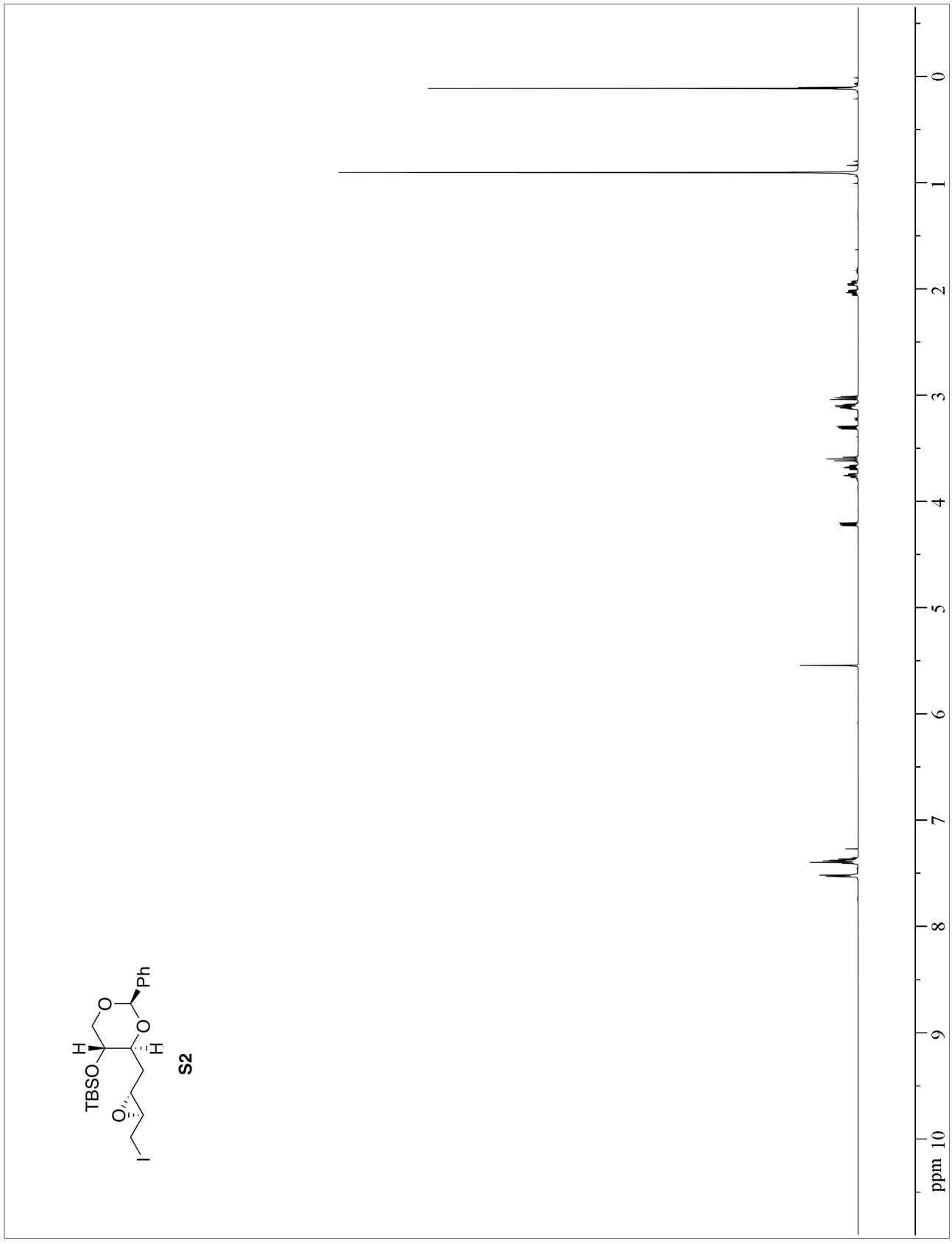
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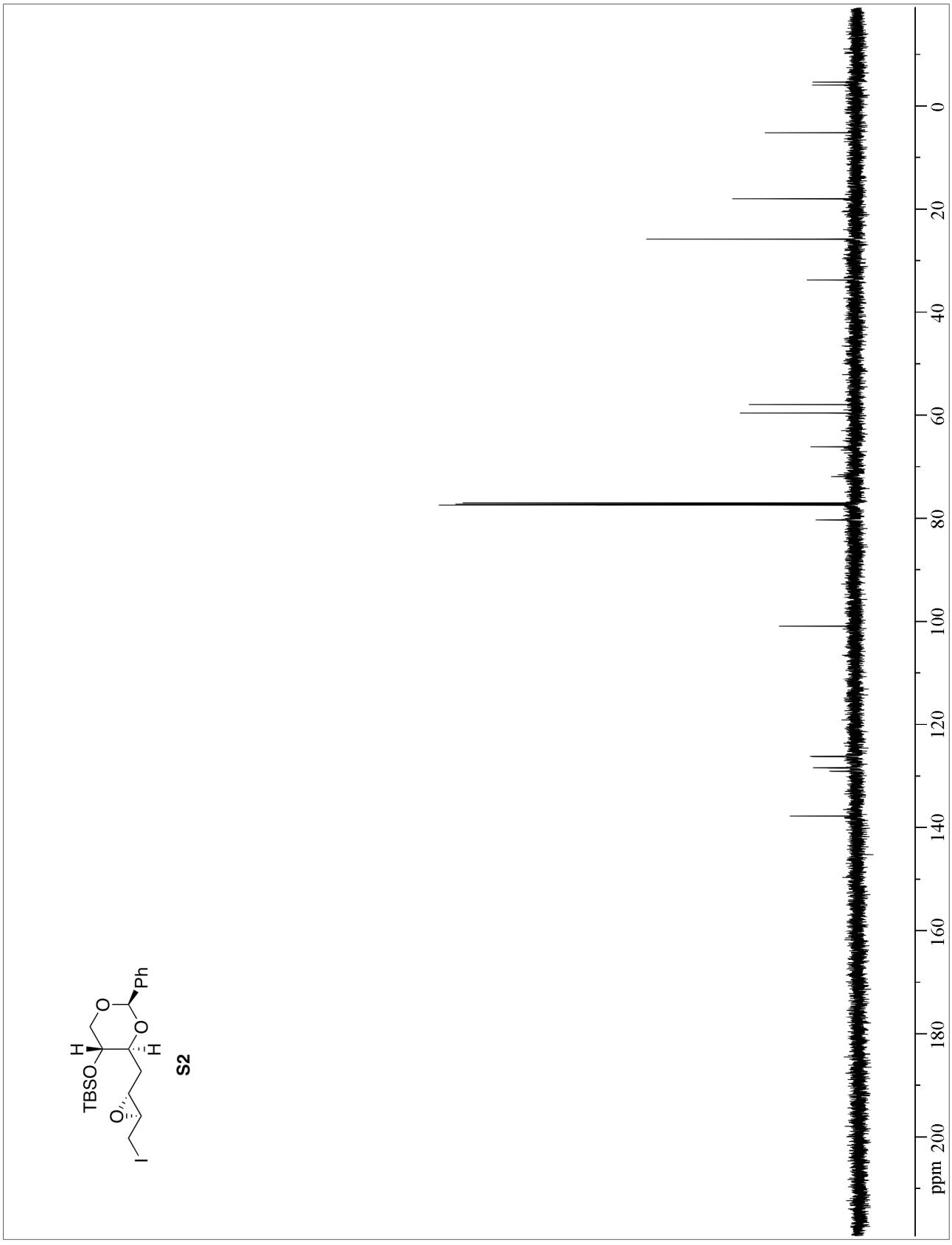
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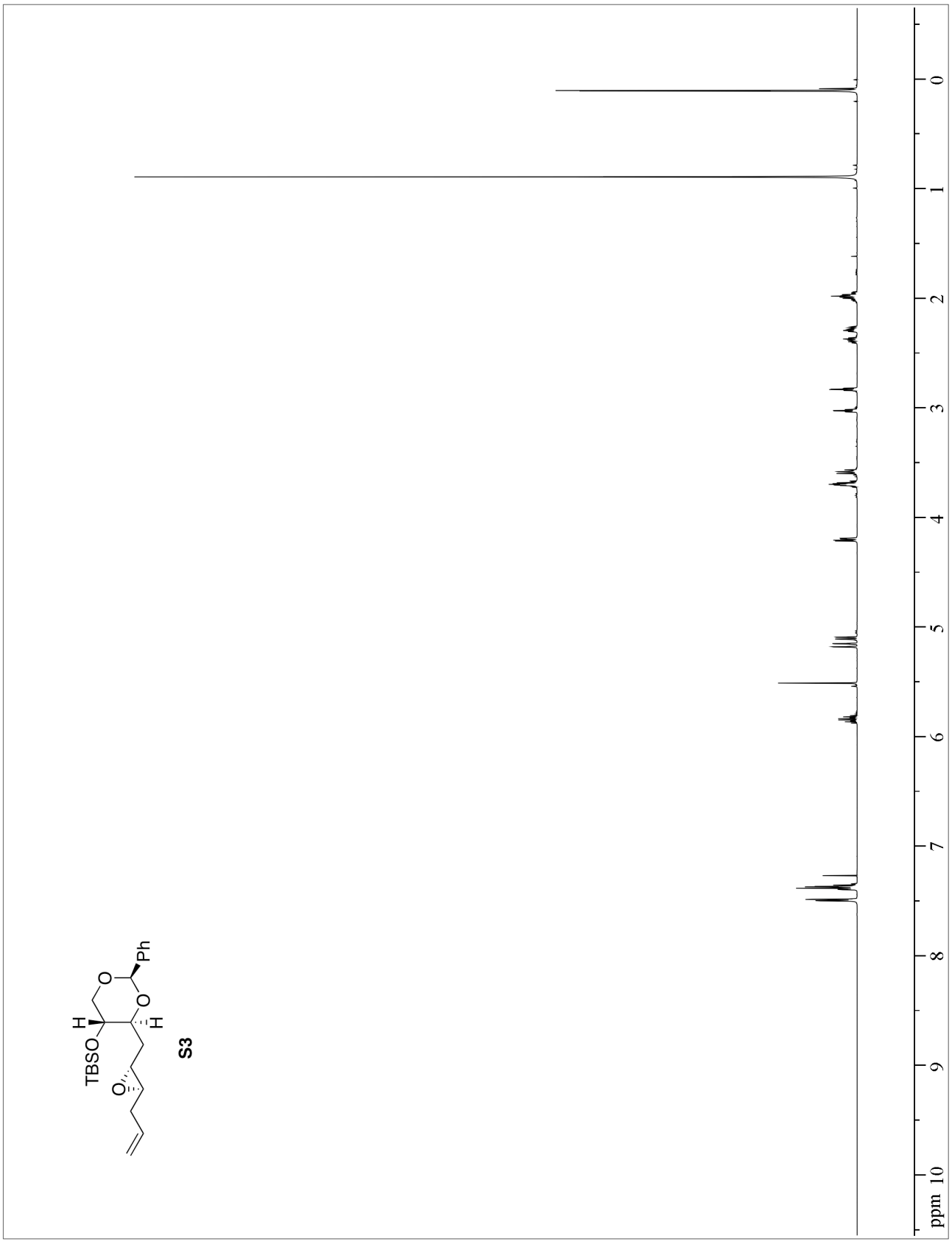
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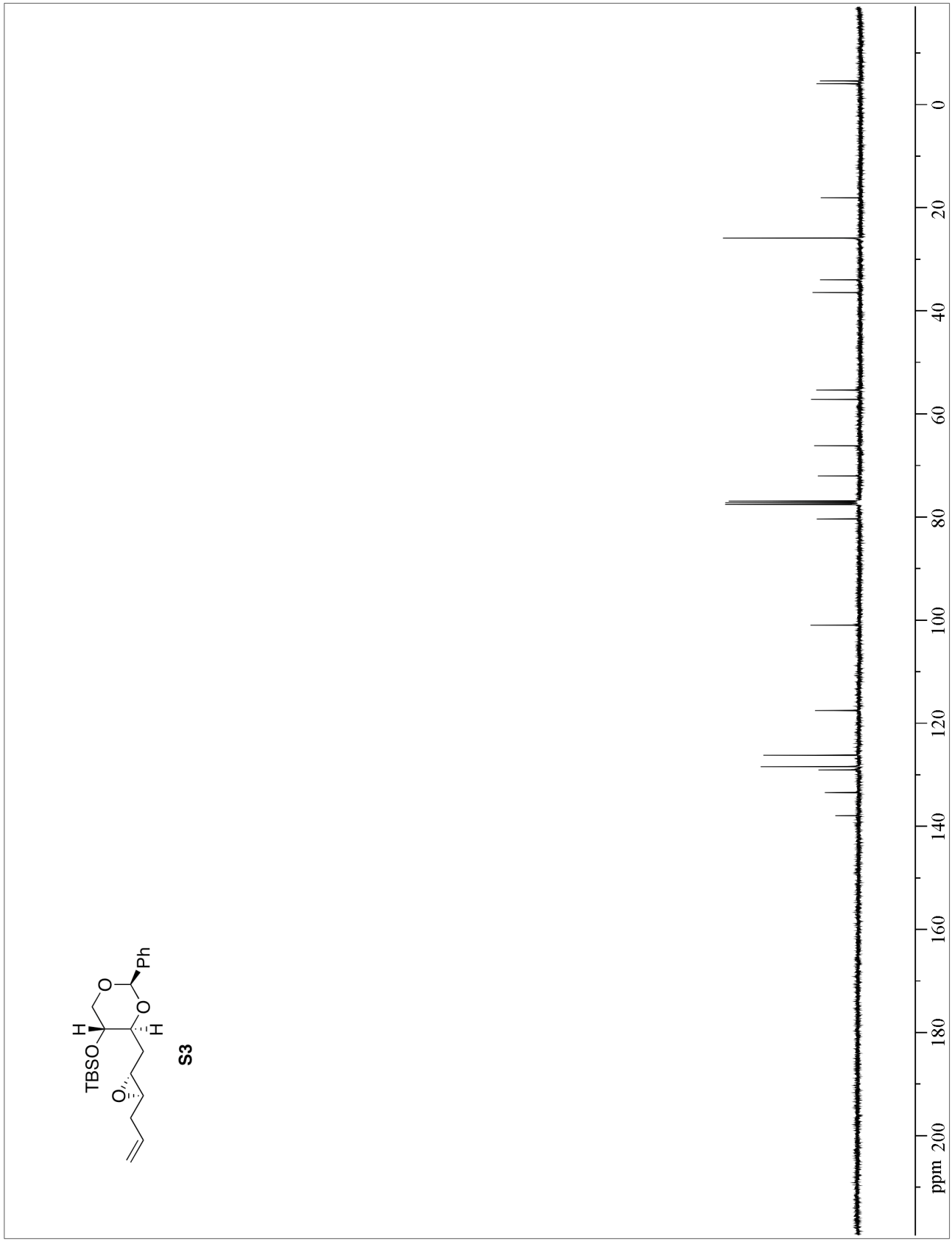
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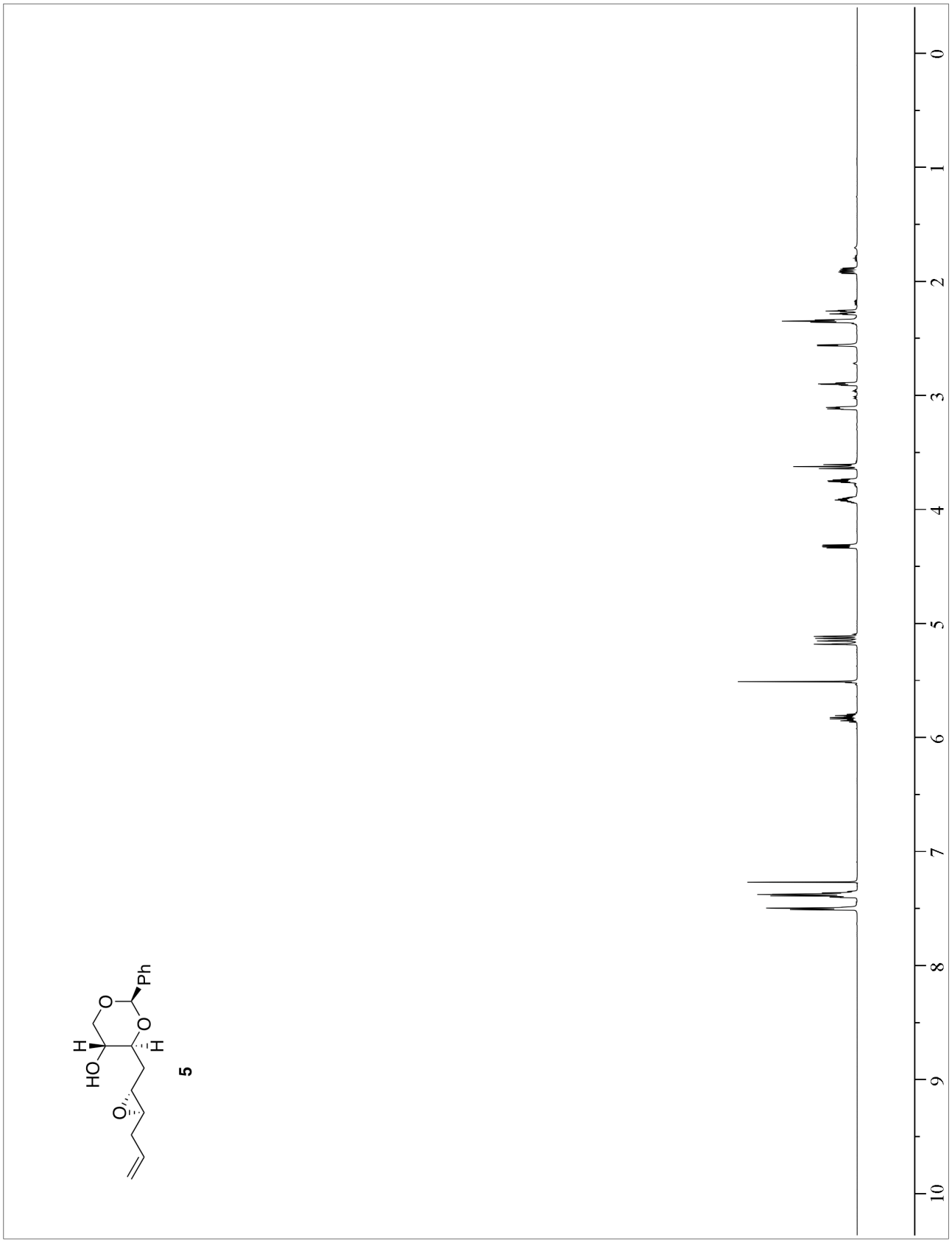
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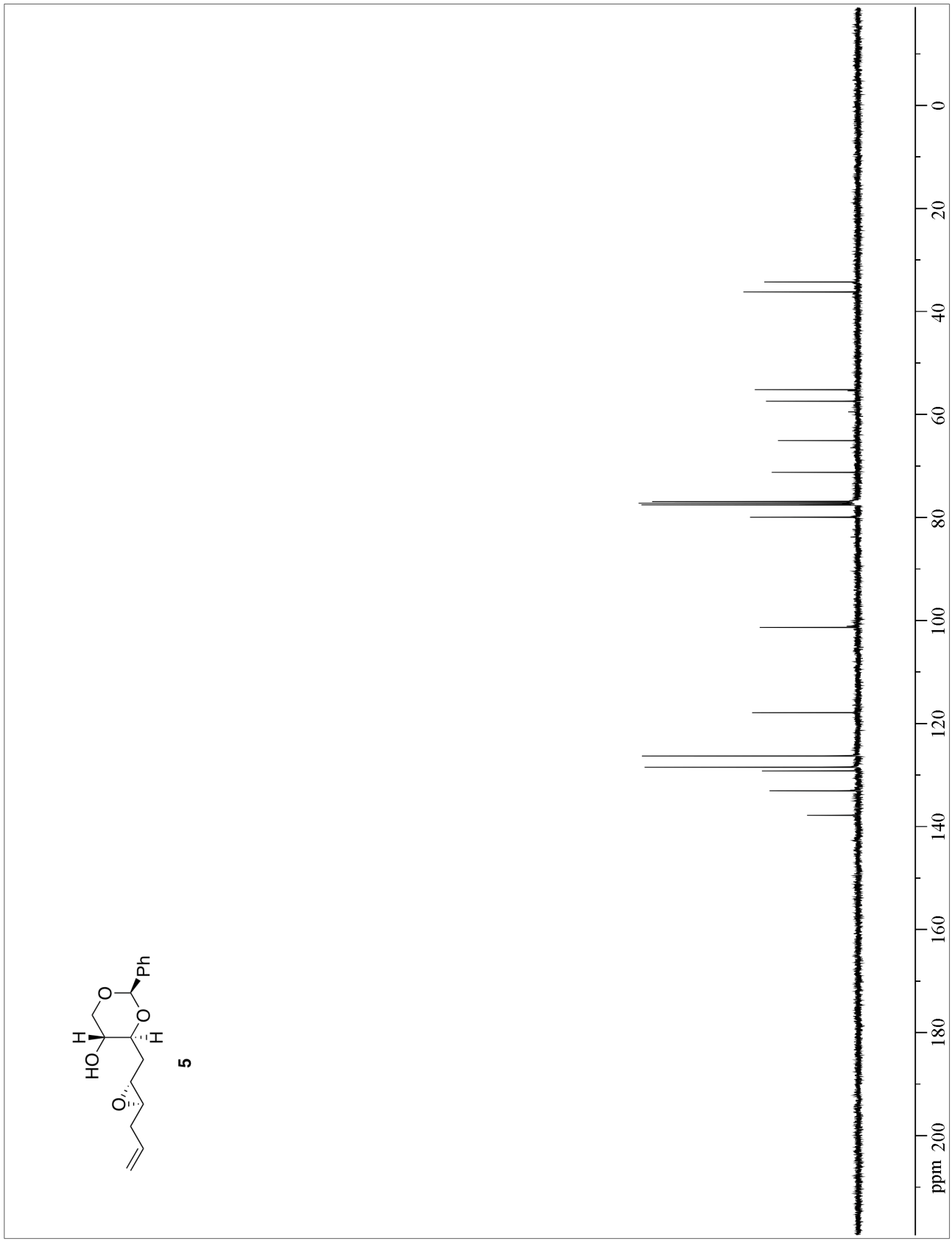
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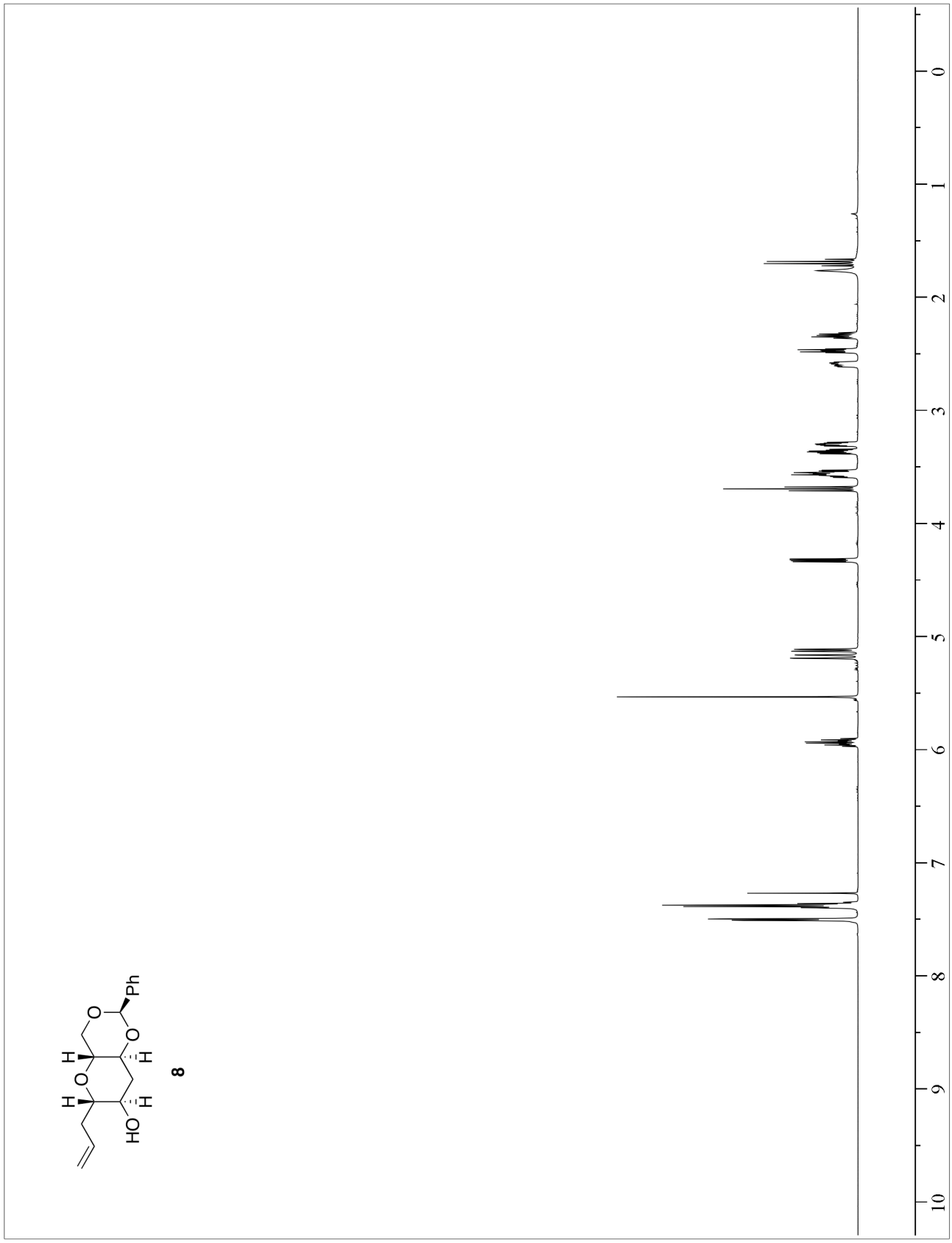
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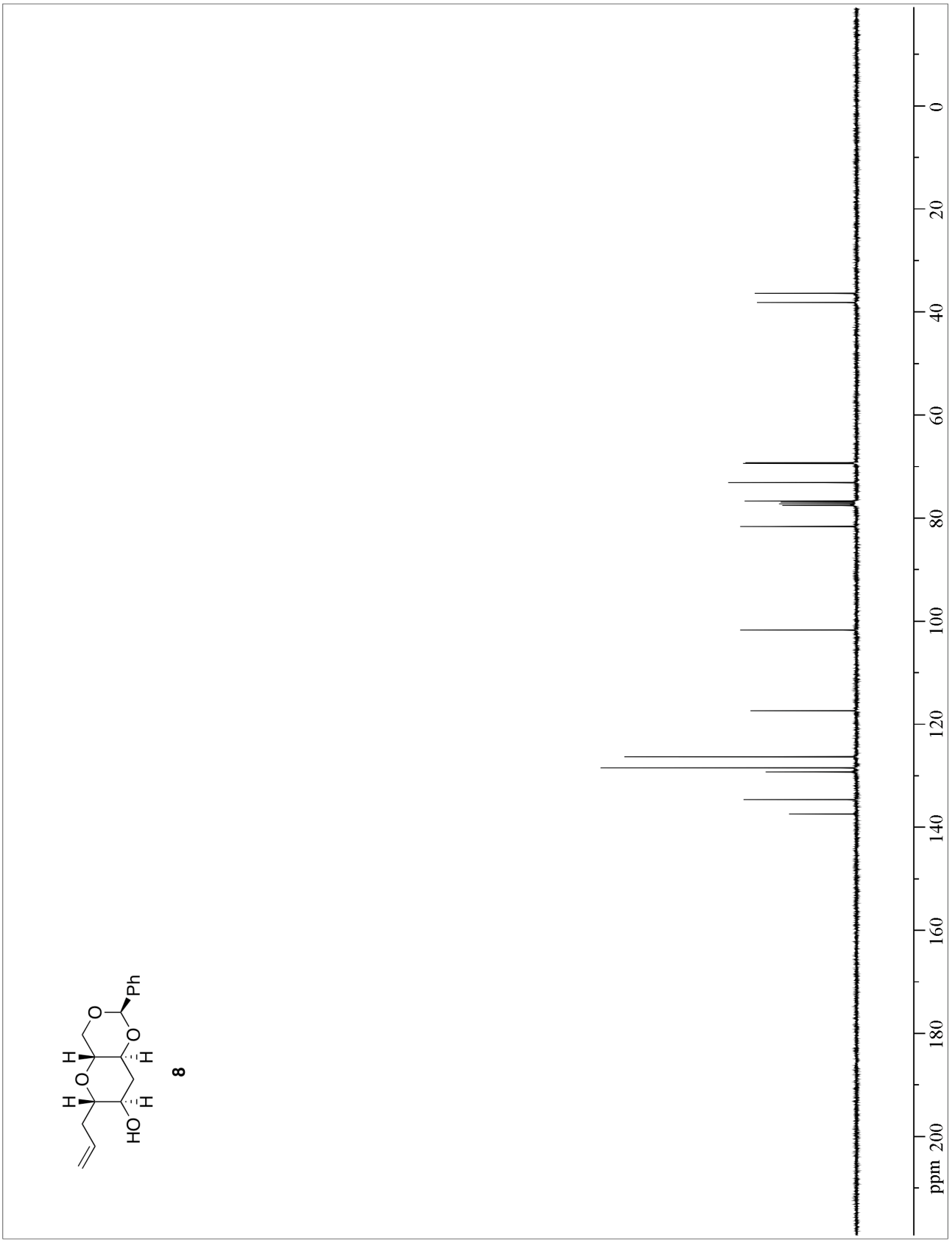
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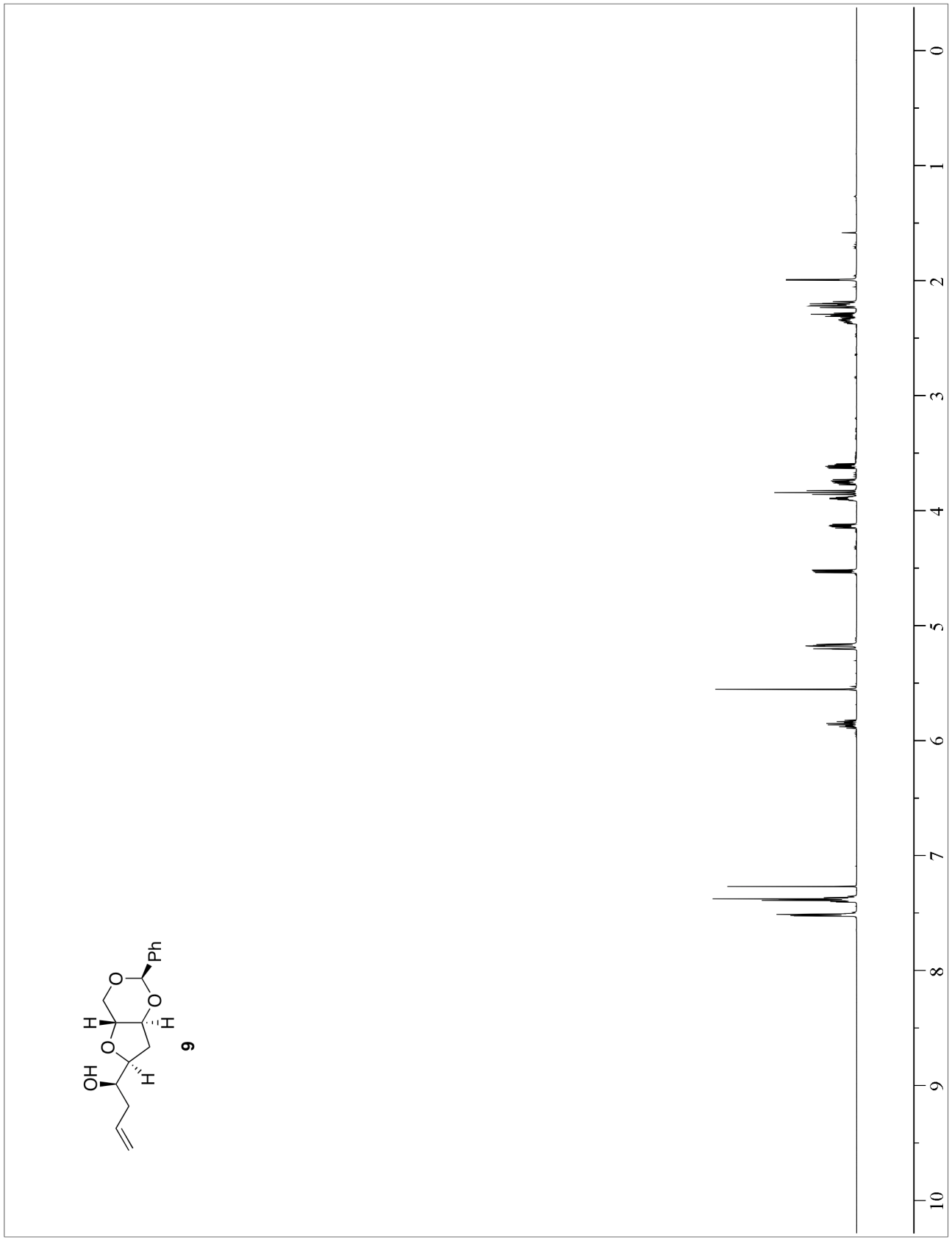
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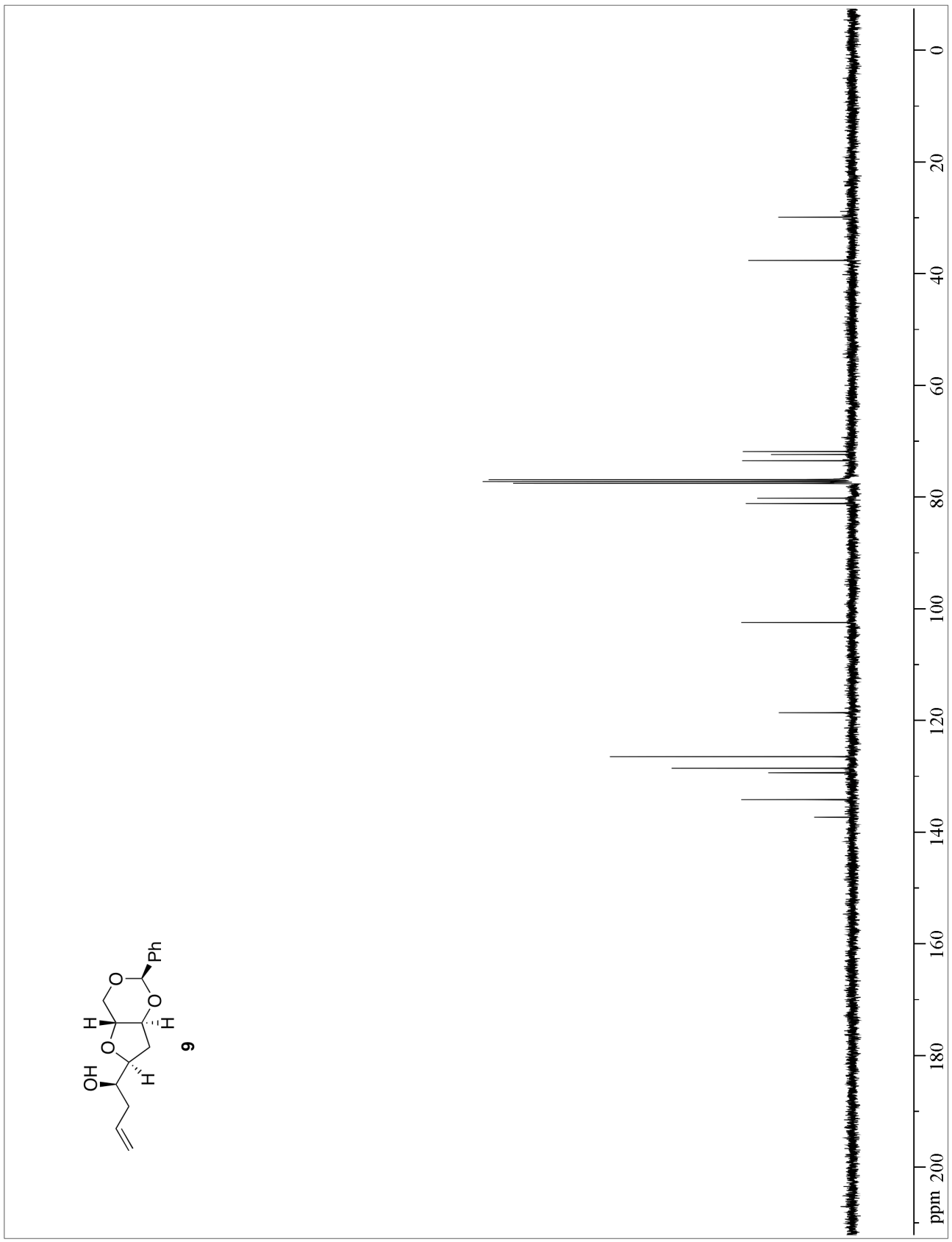
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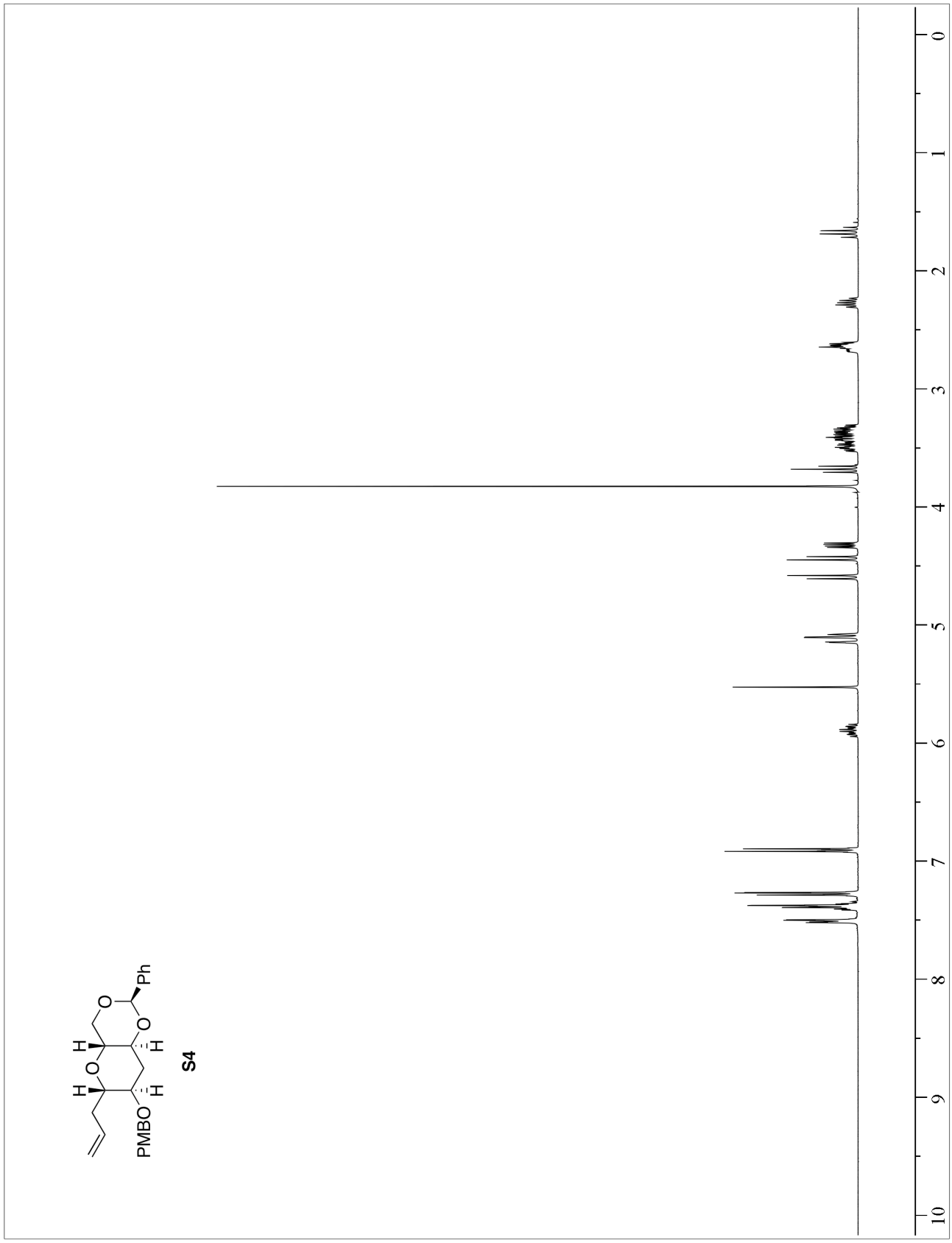
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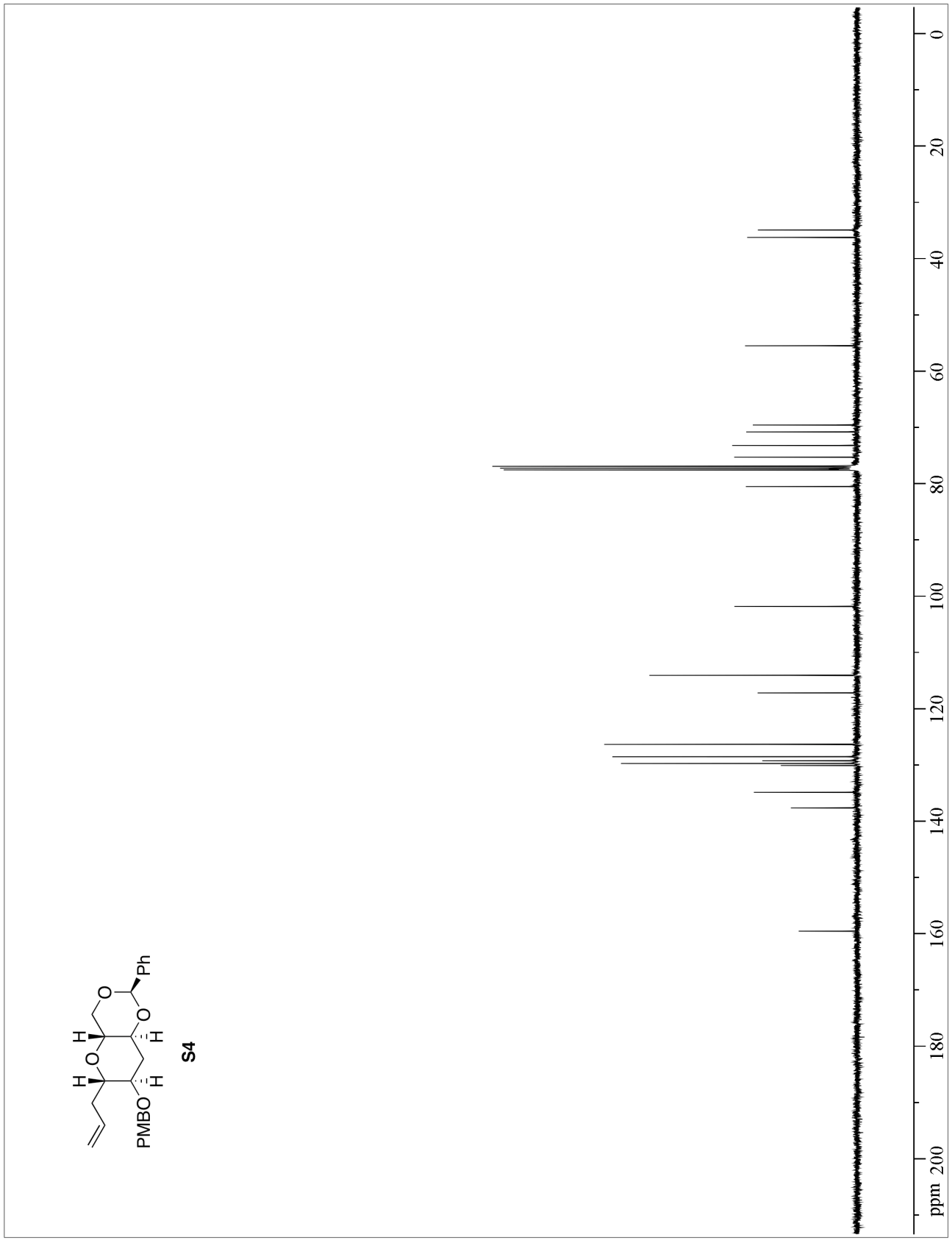
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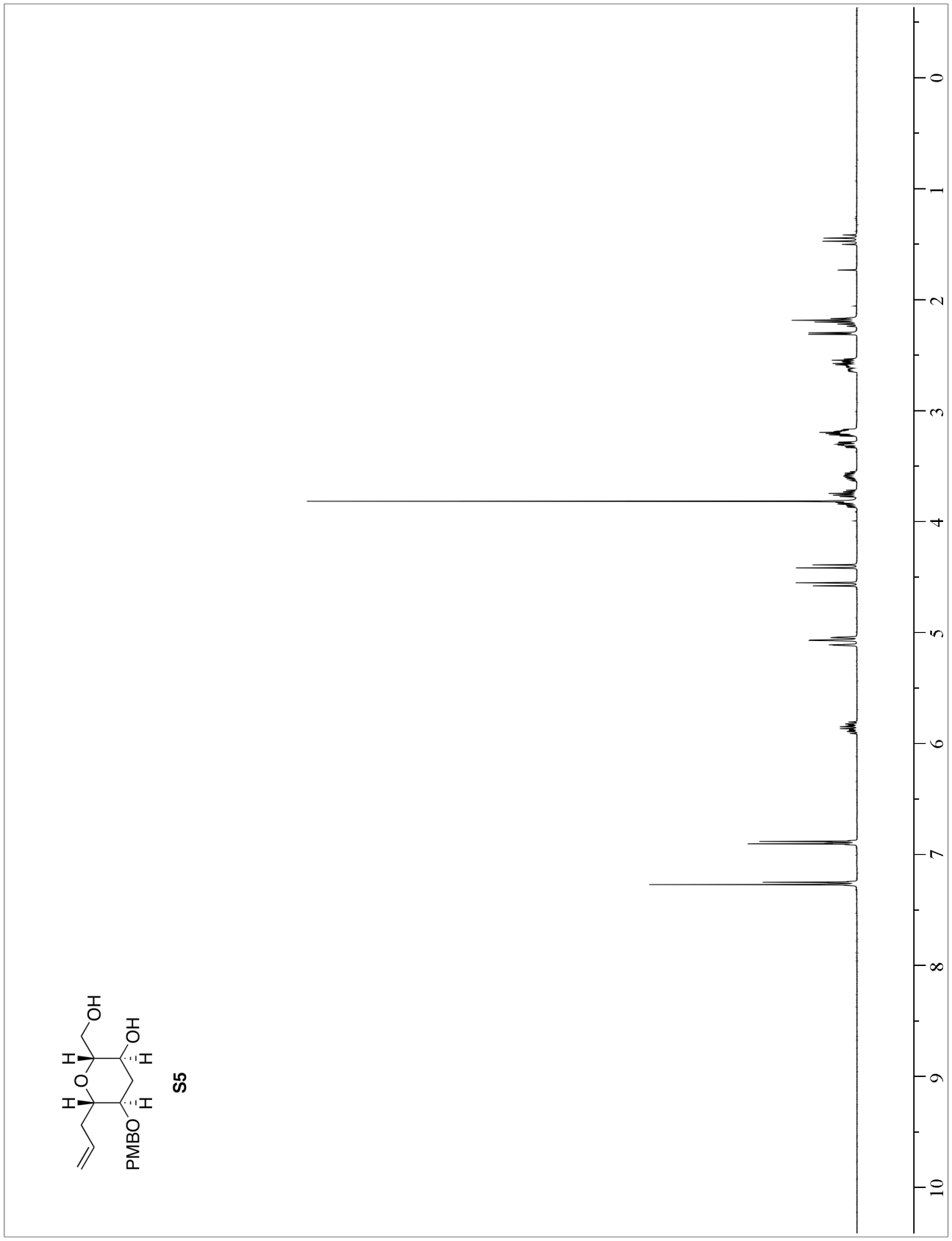
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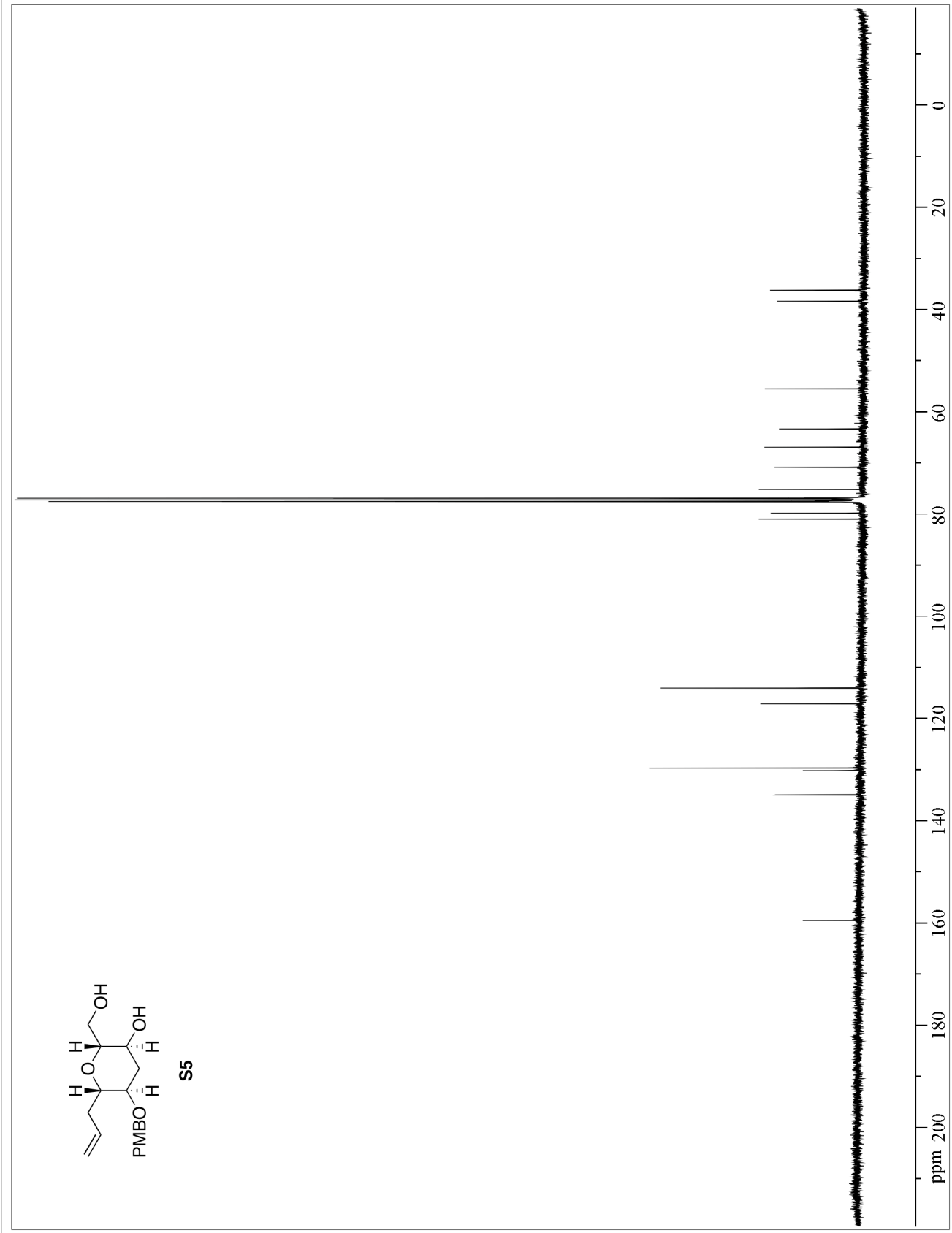
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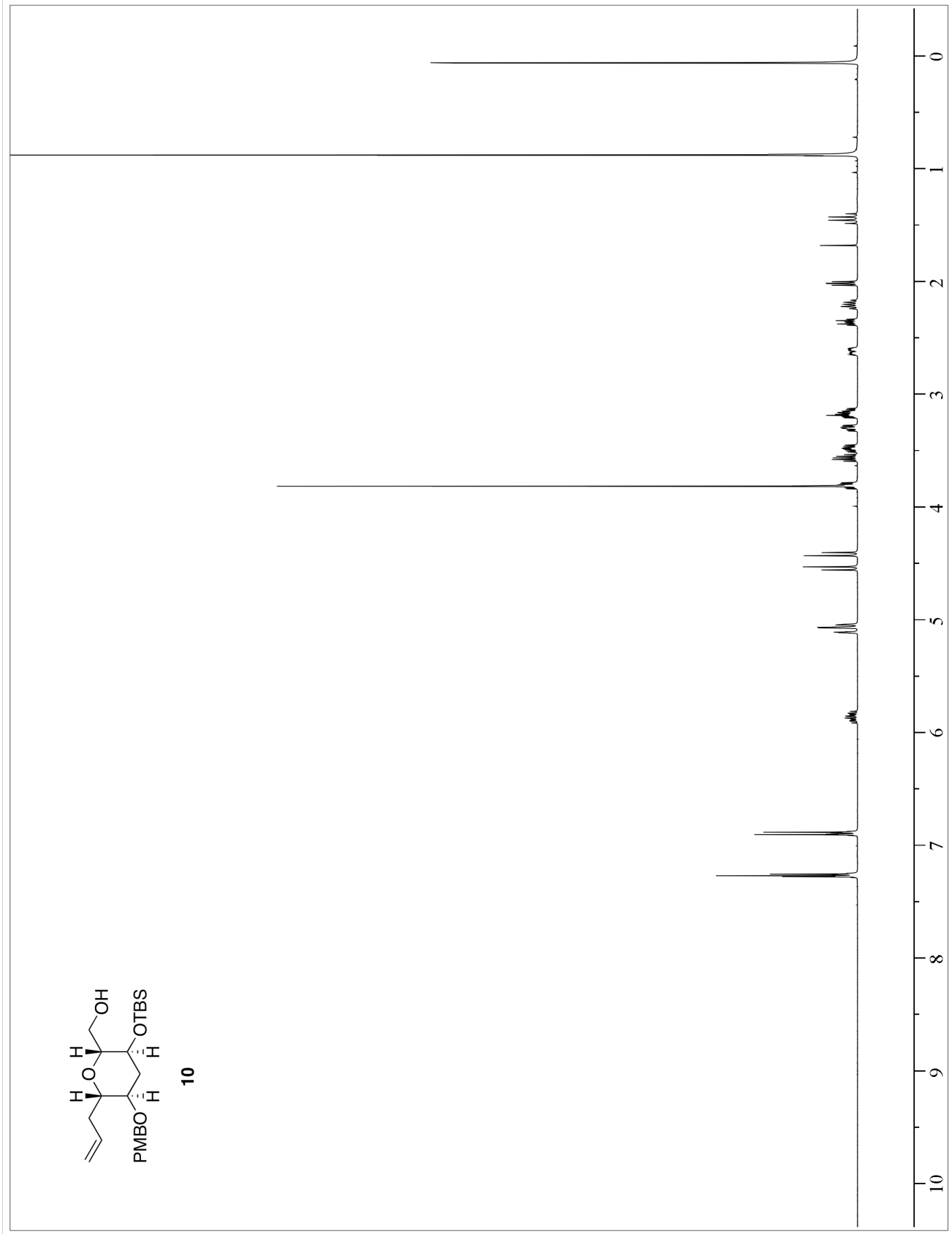
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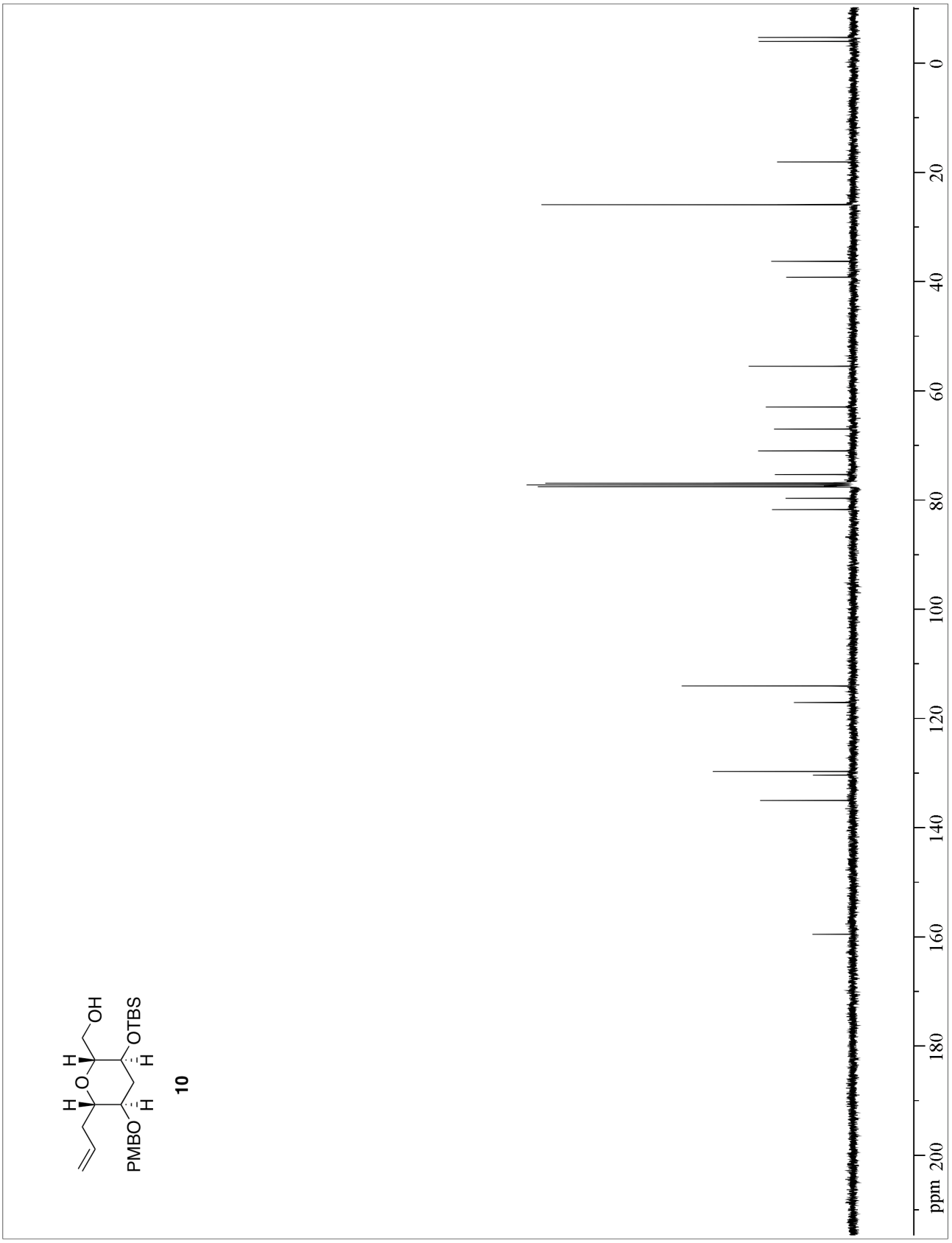
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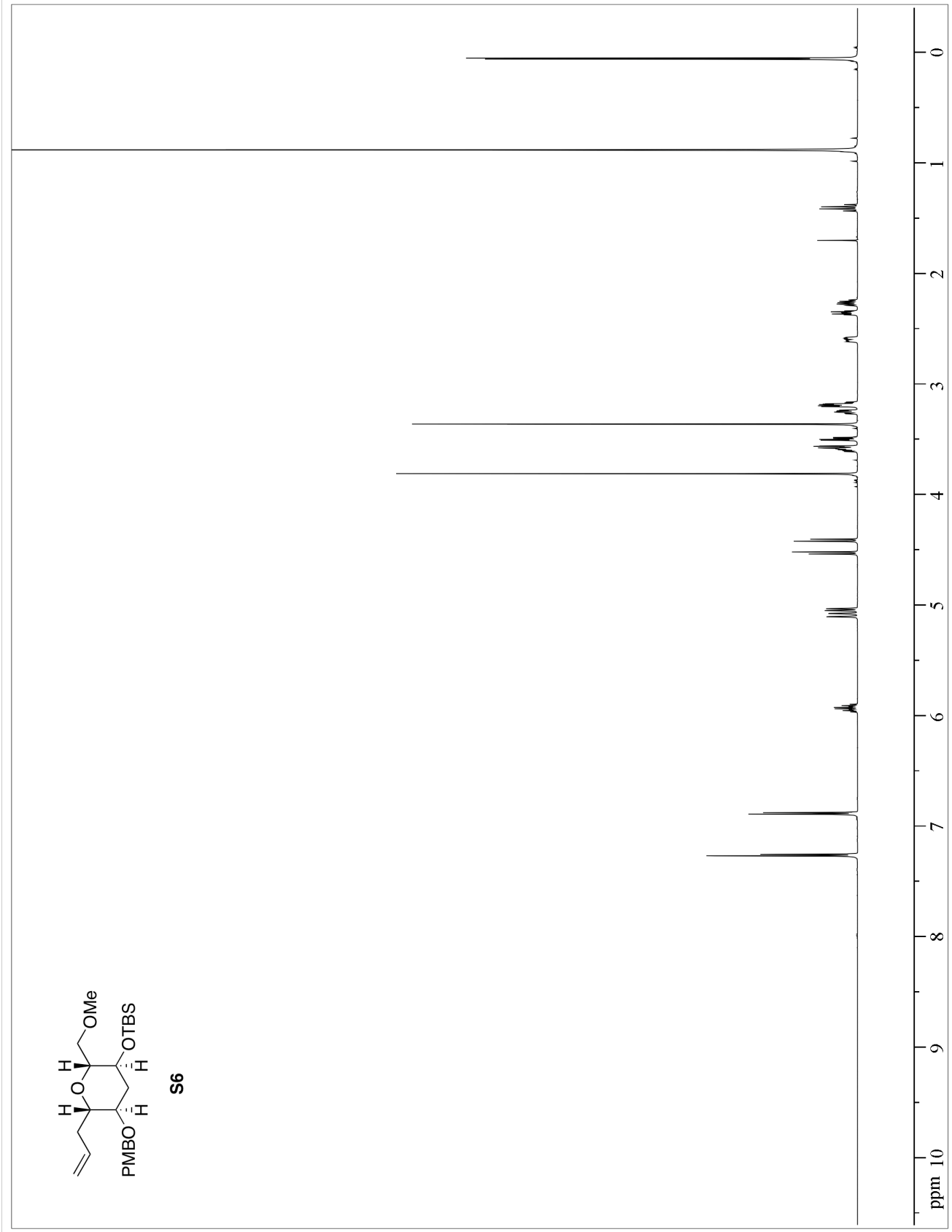
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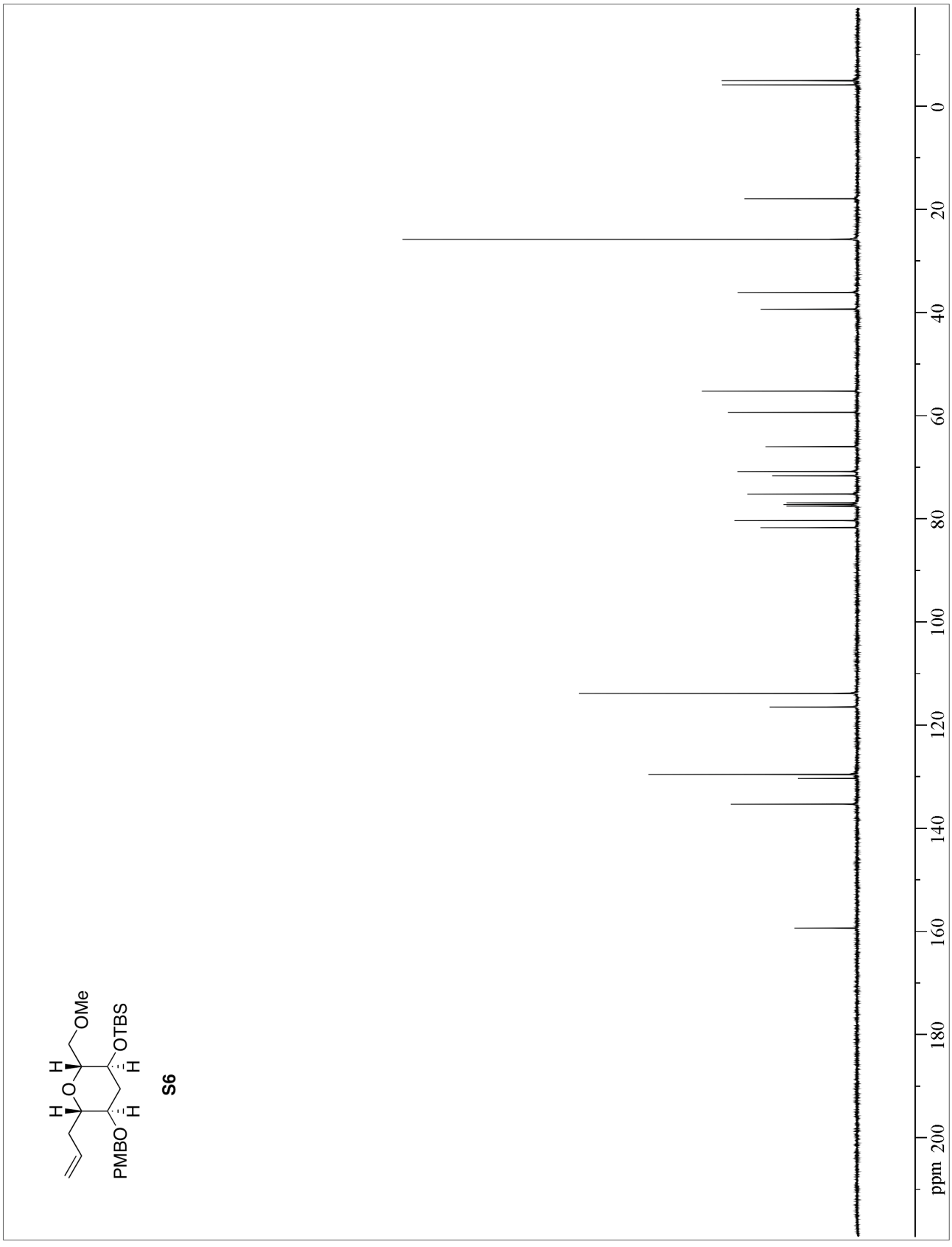
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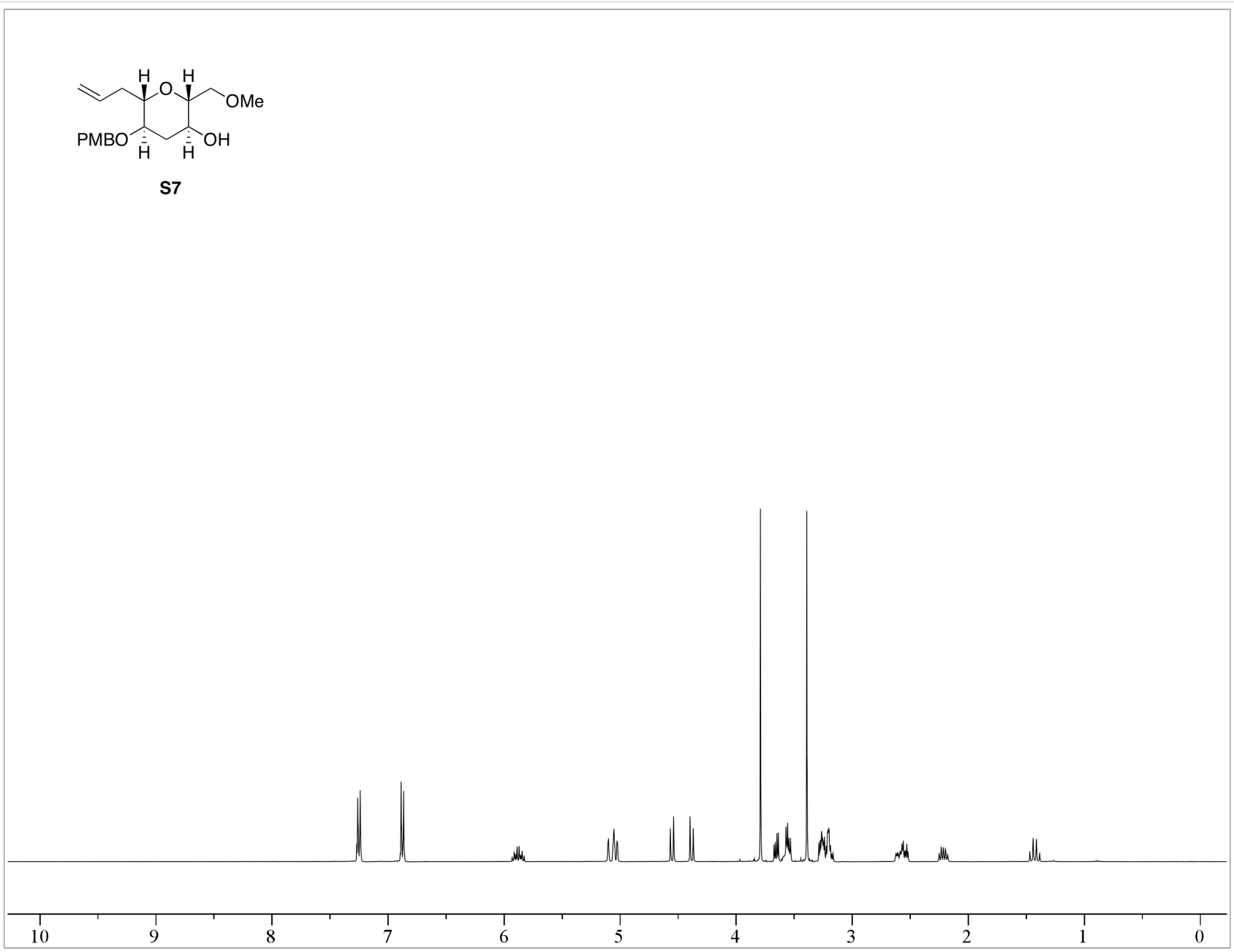

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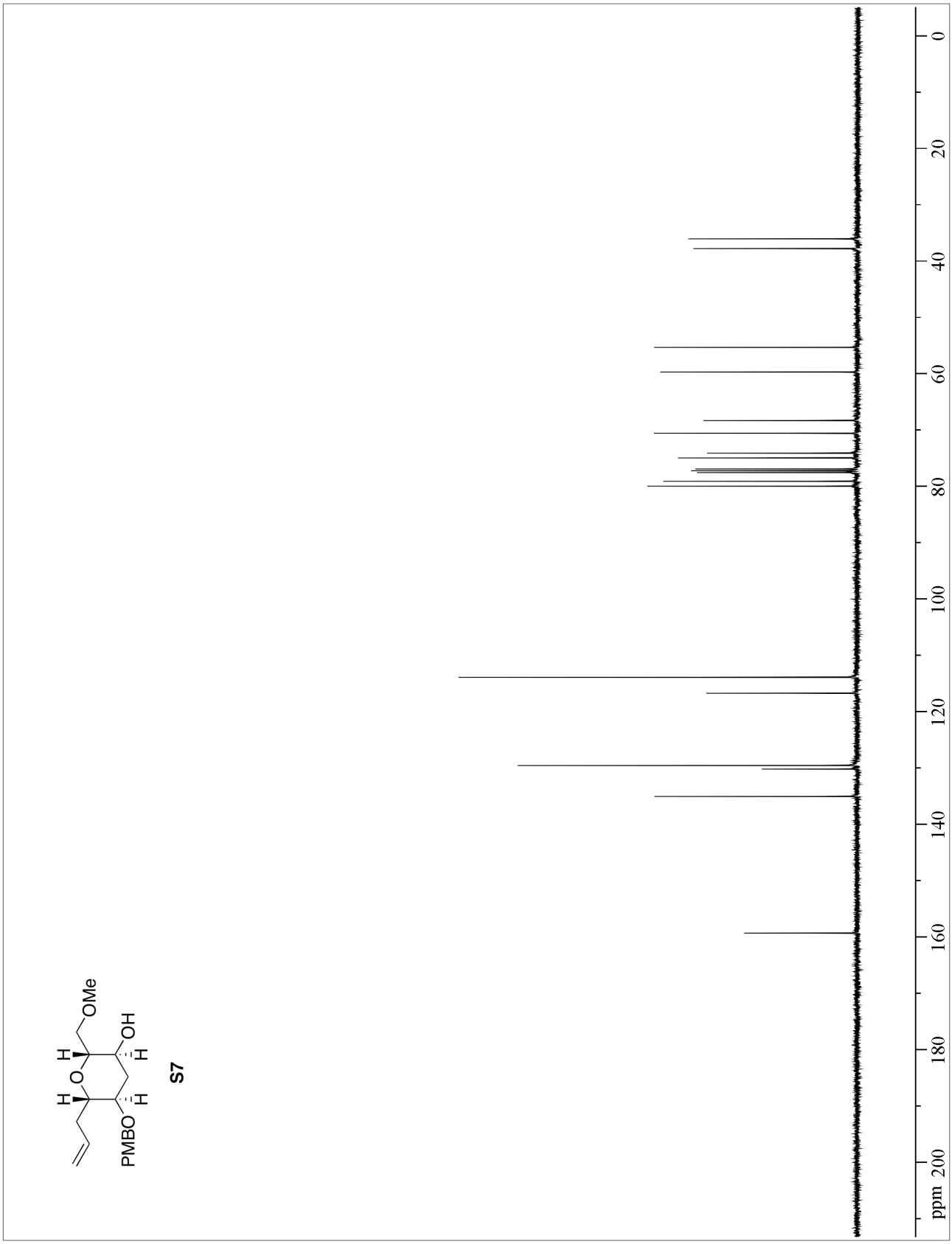
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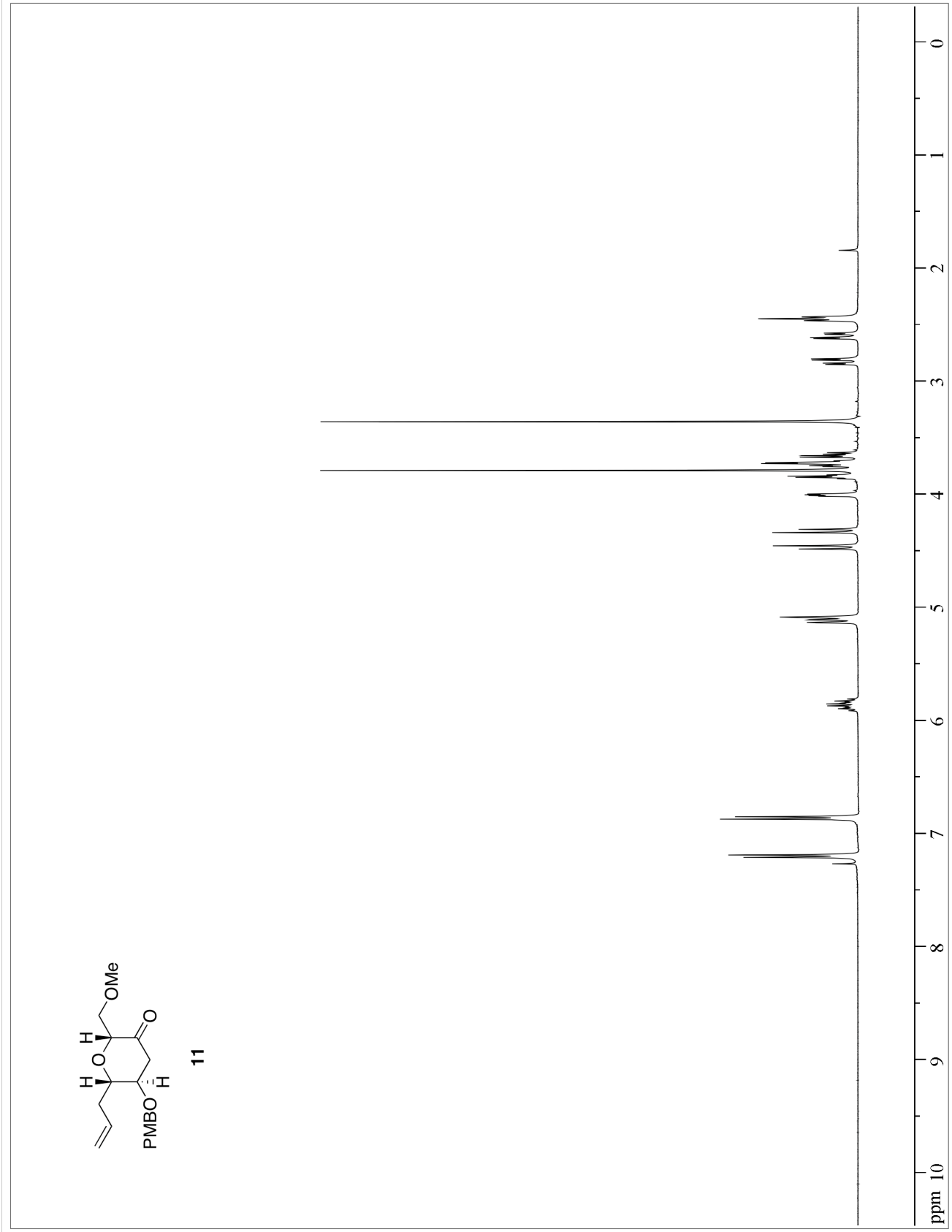
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PMBO
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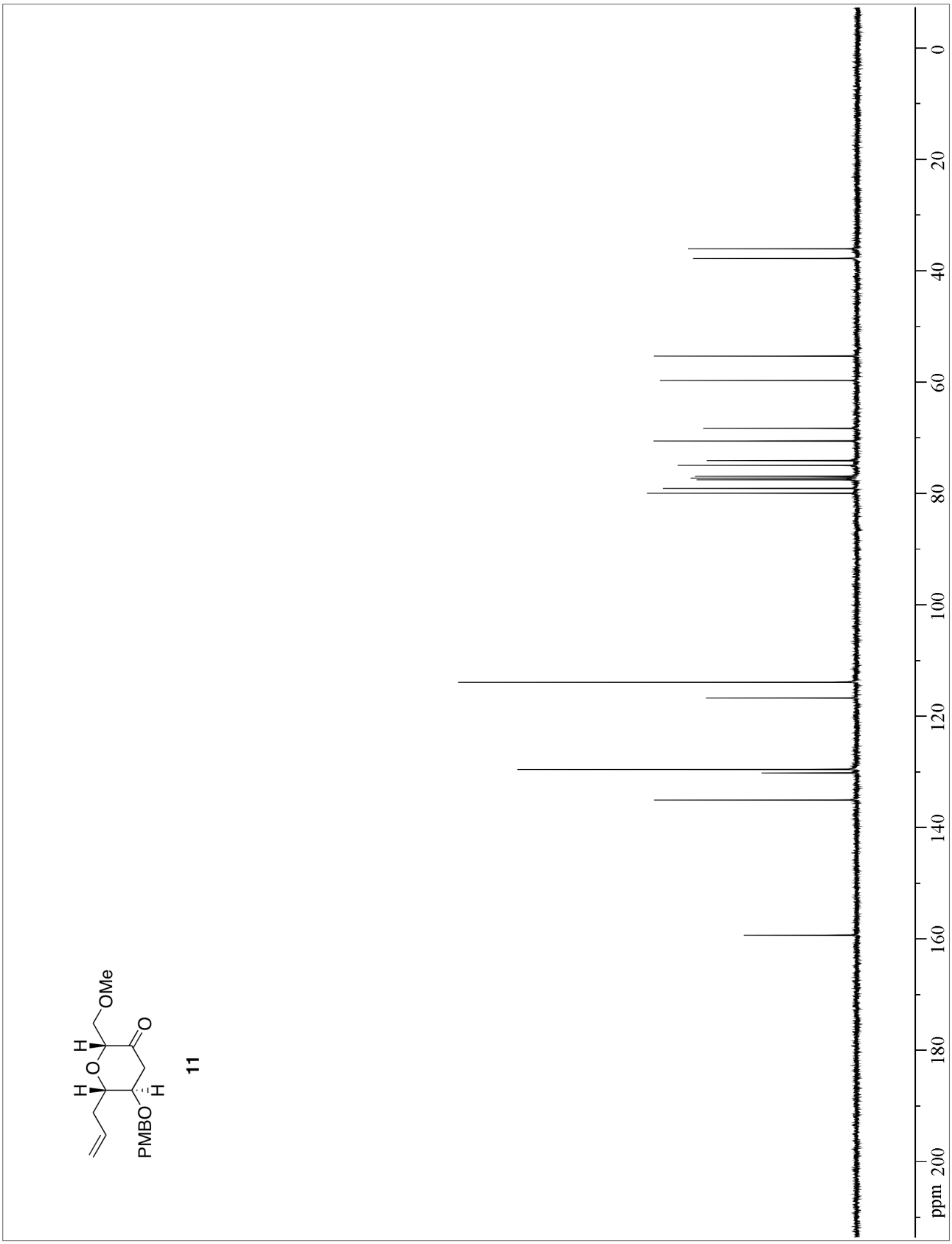
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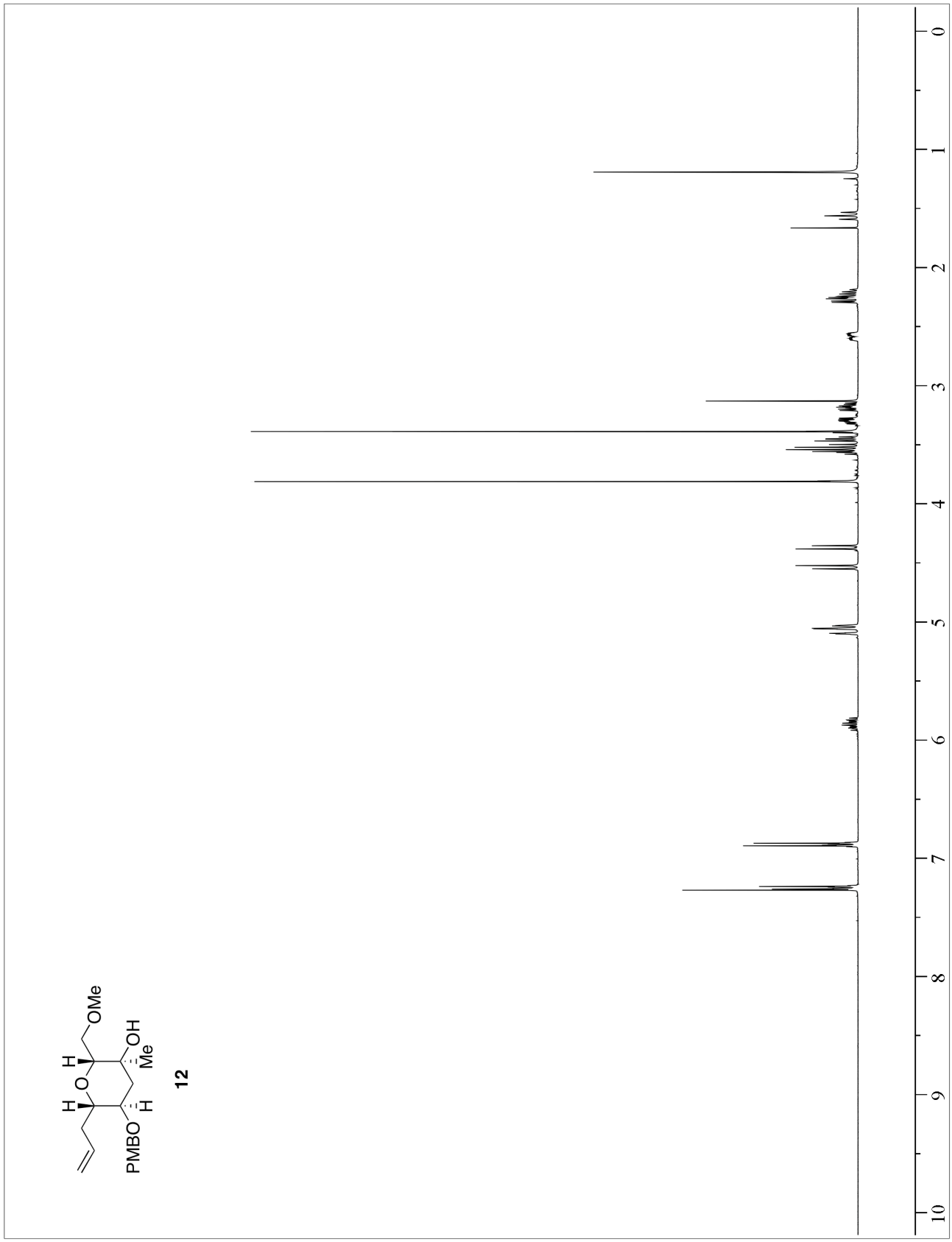
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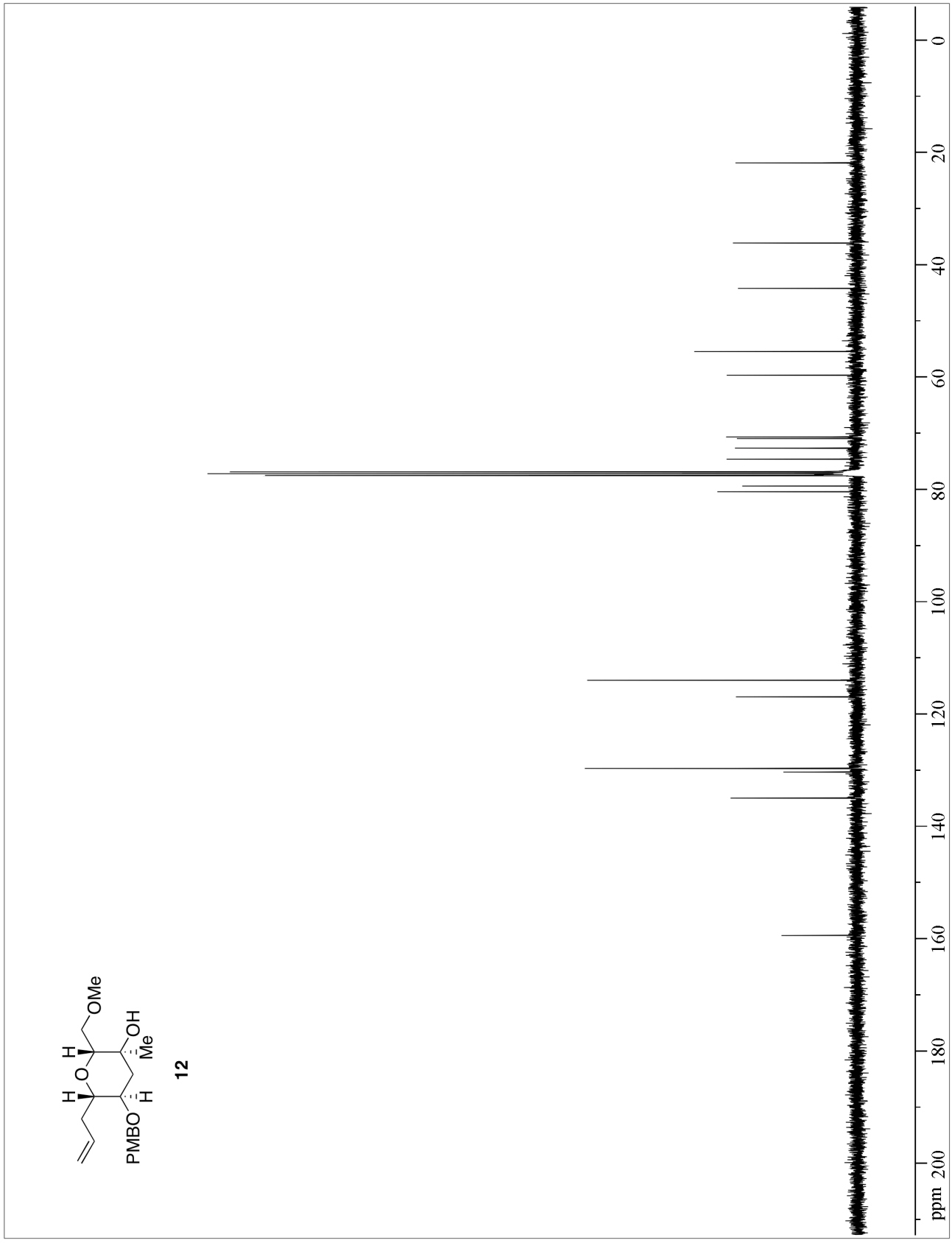
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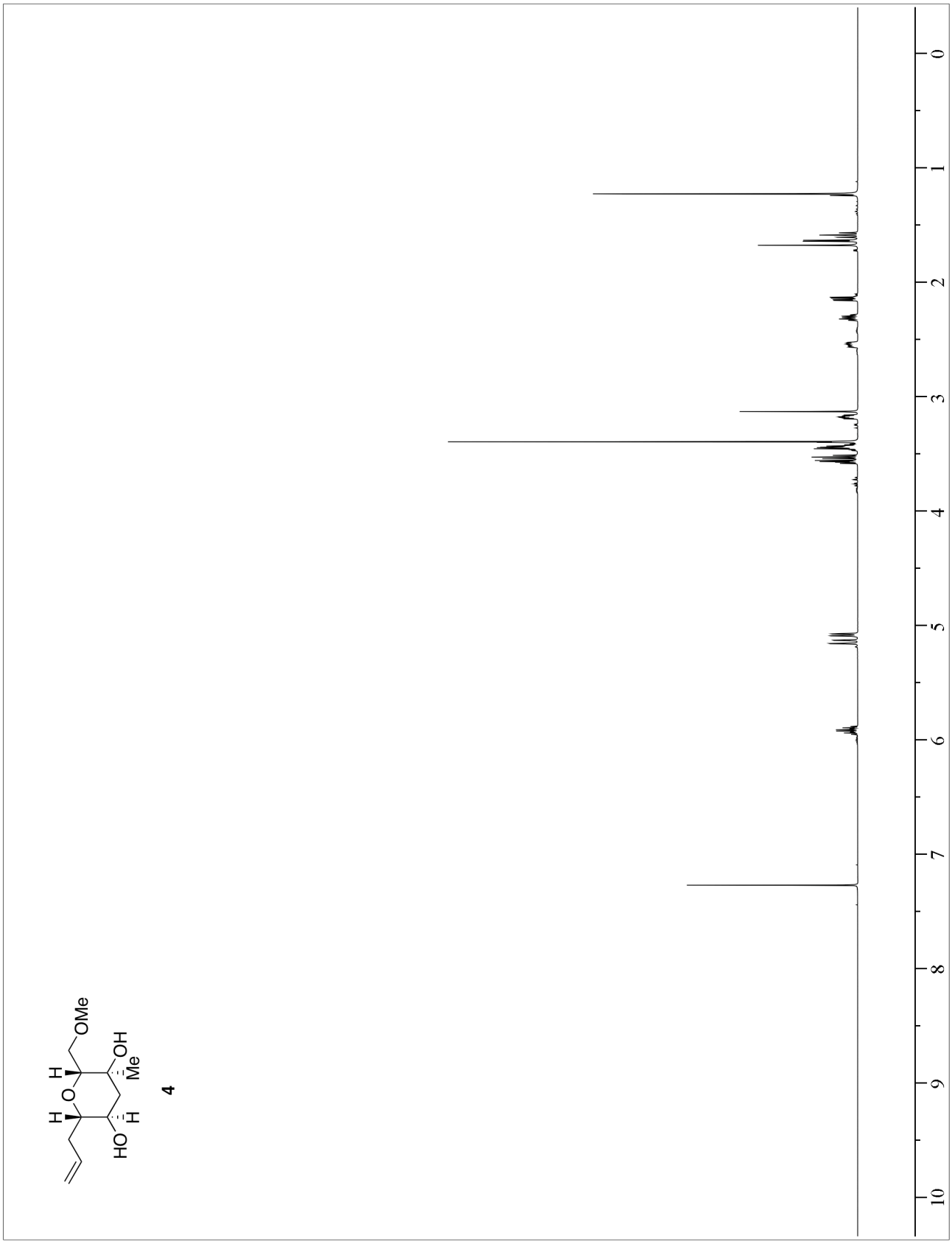
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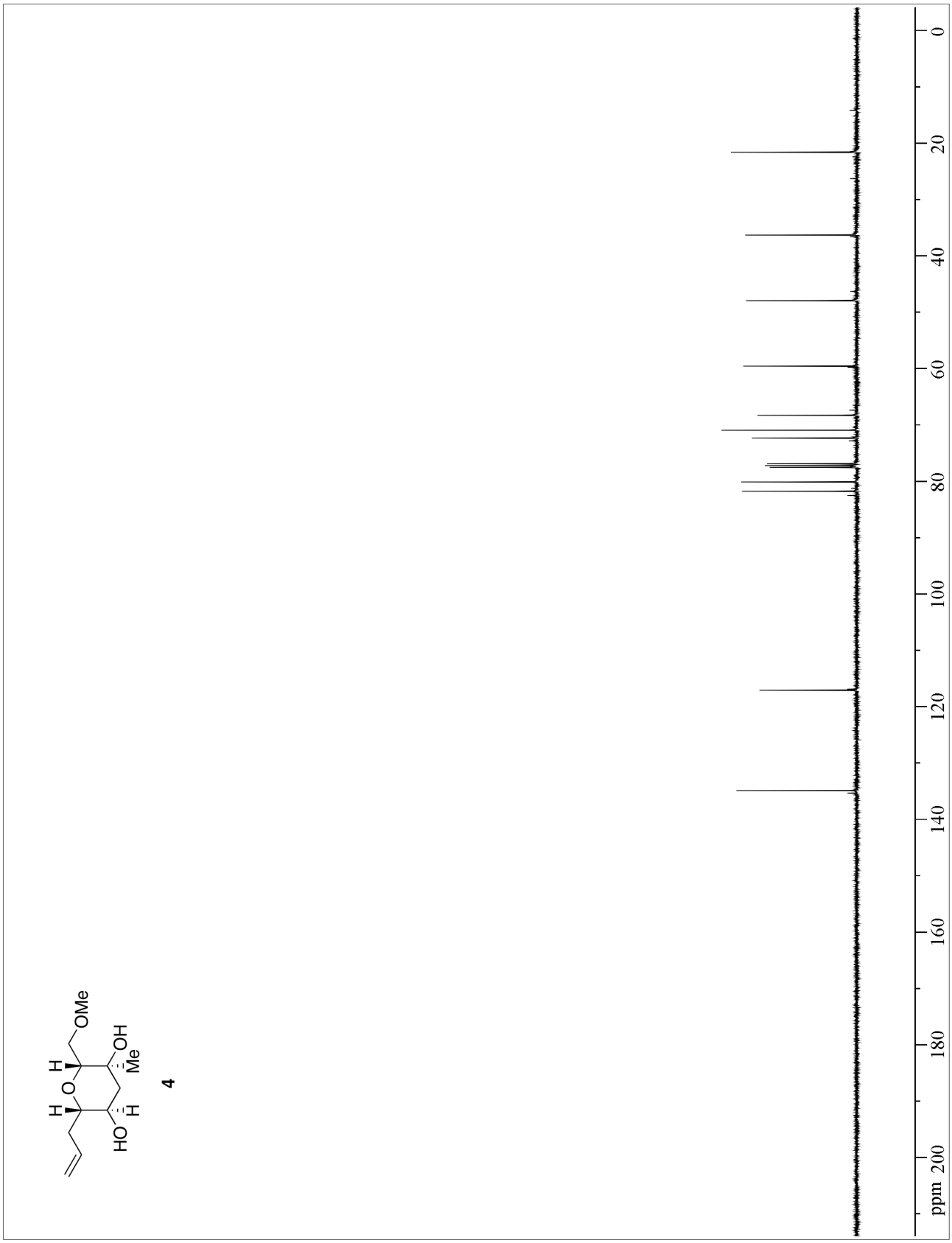
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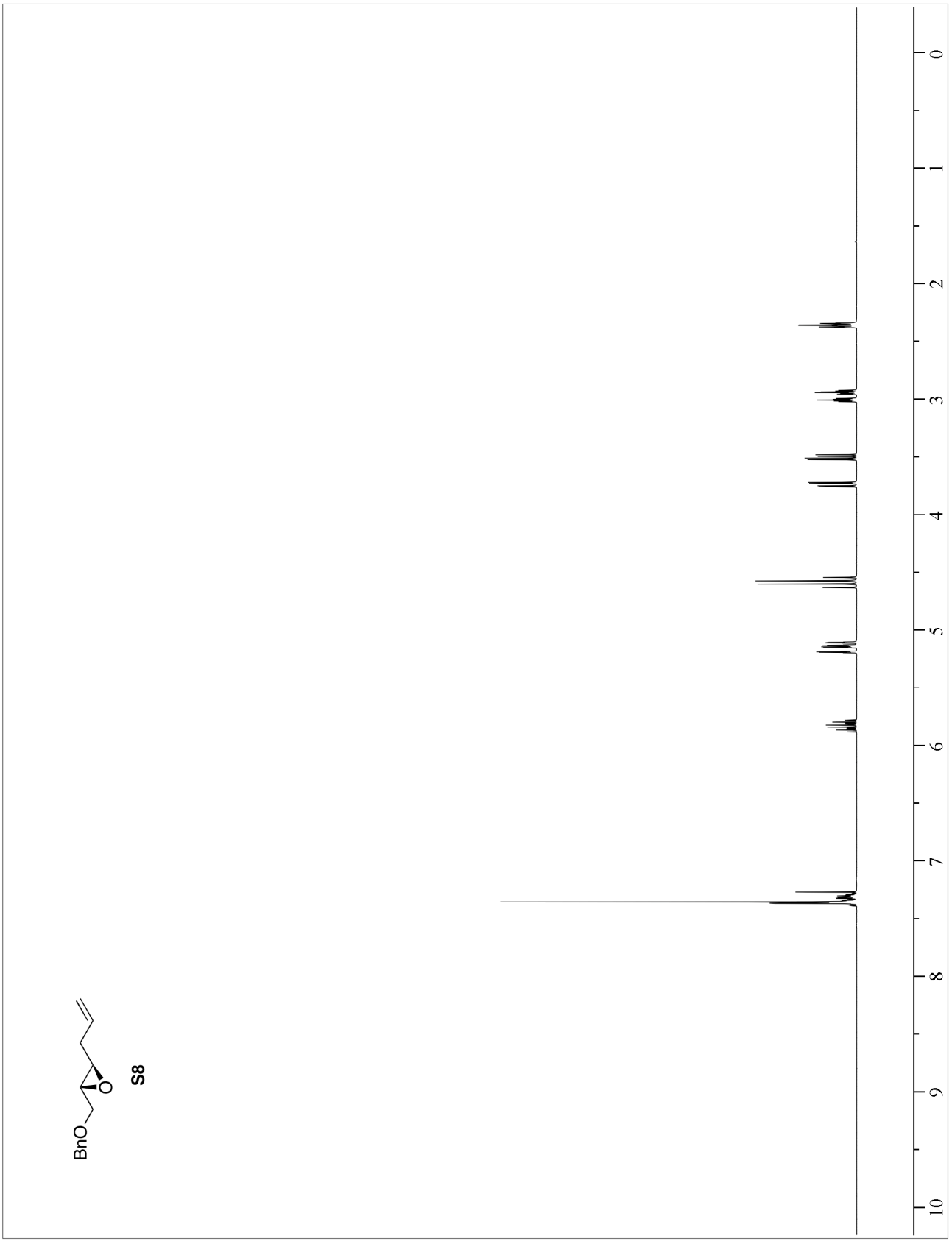
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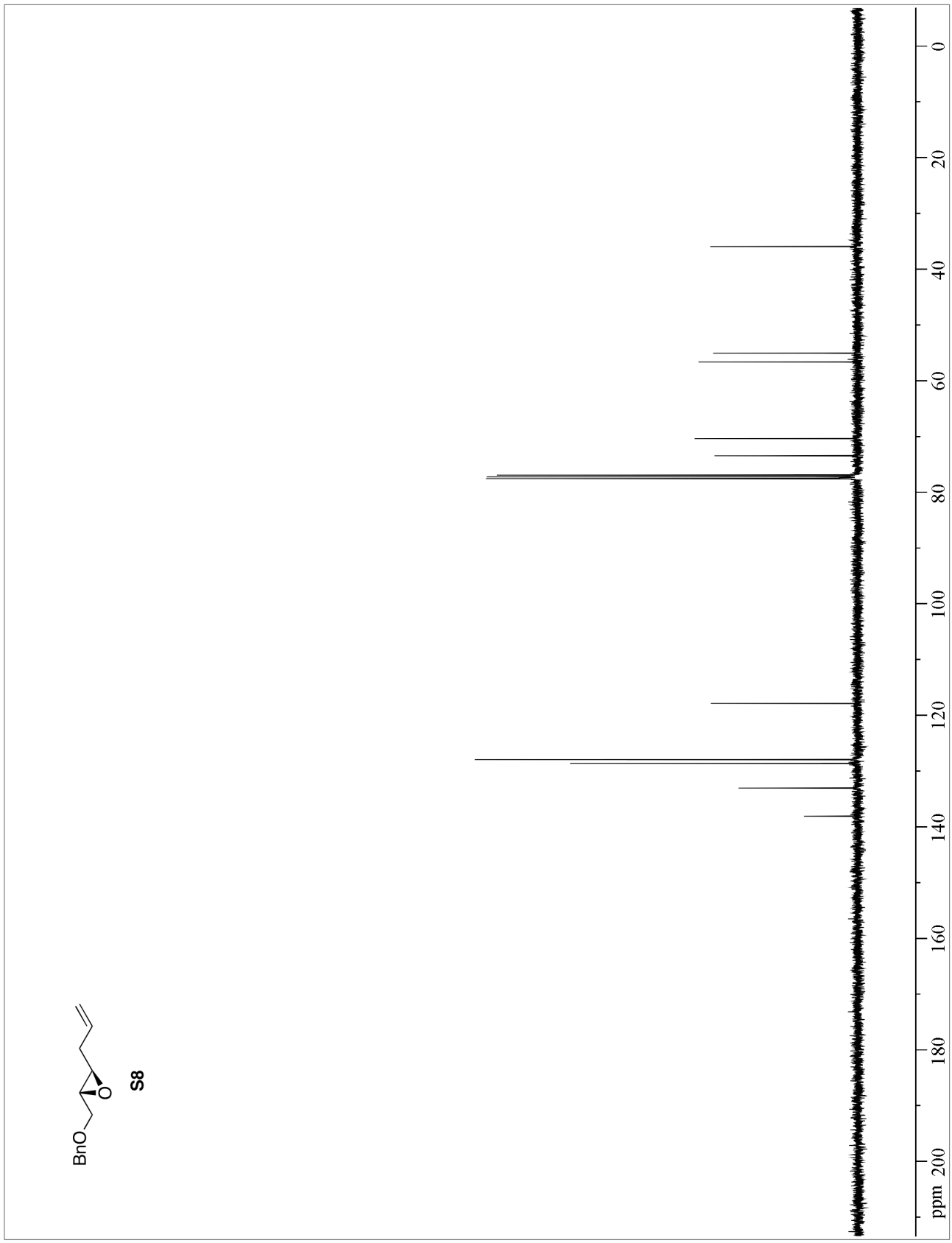
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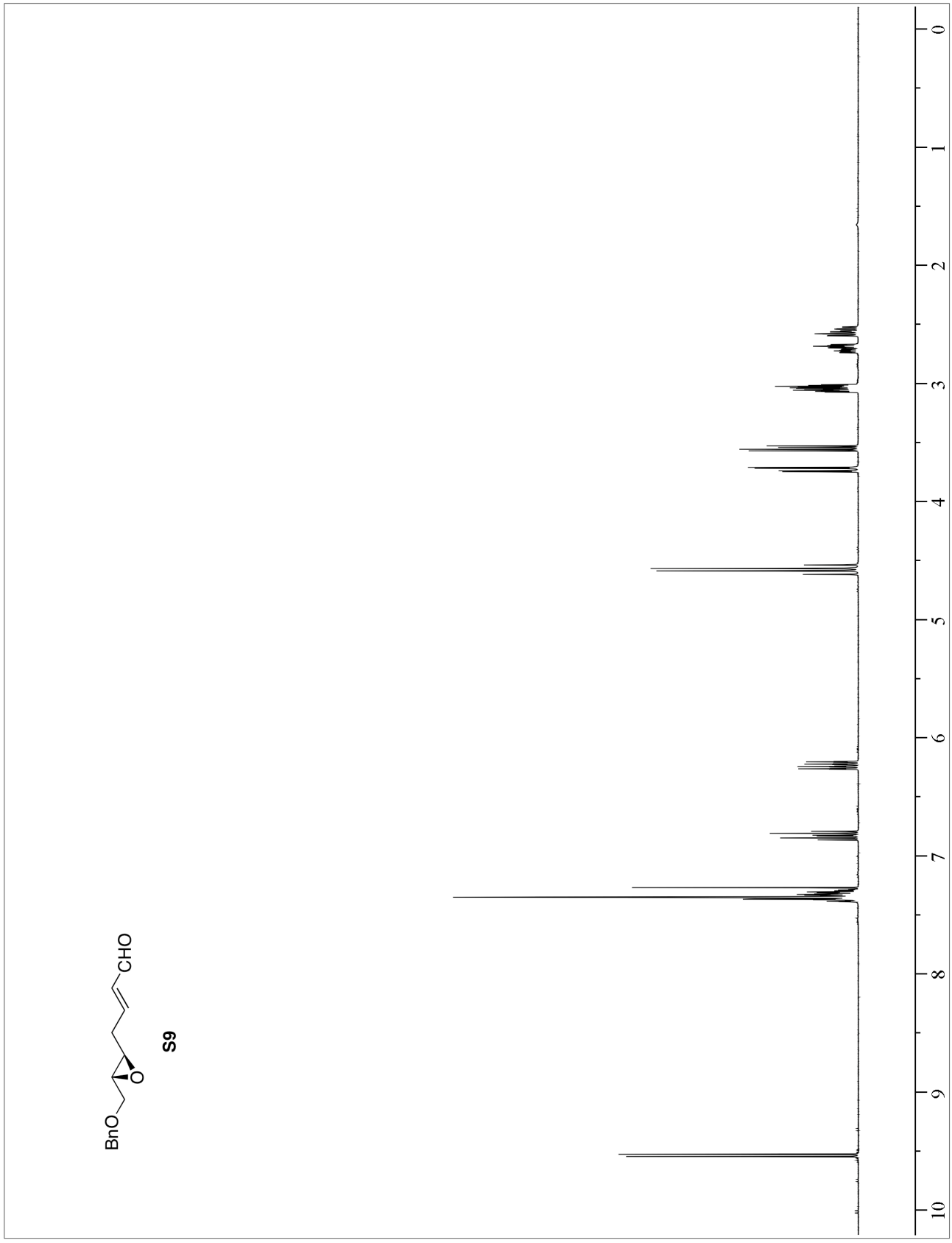
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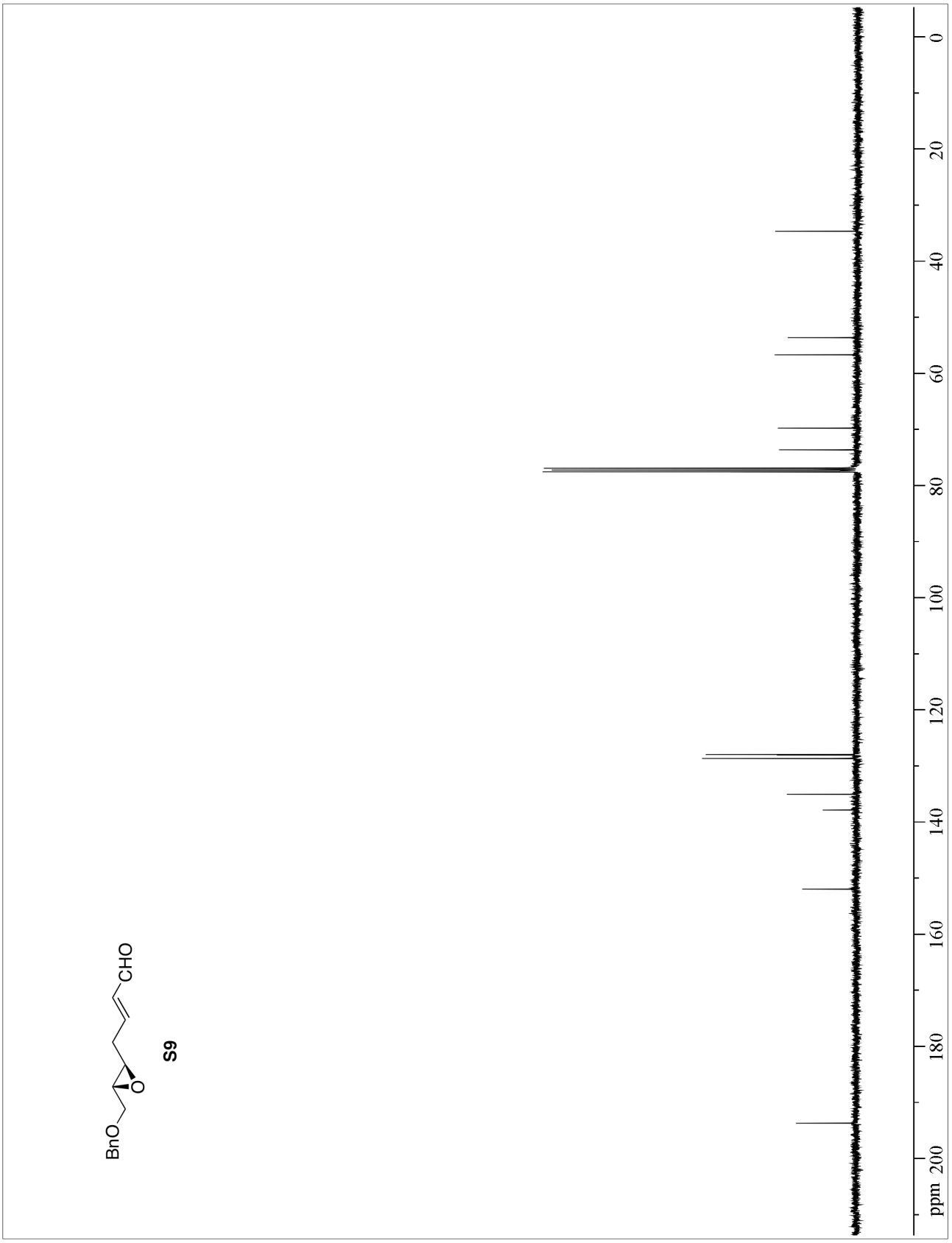
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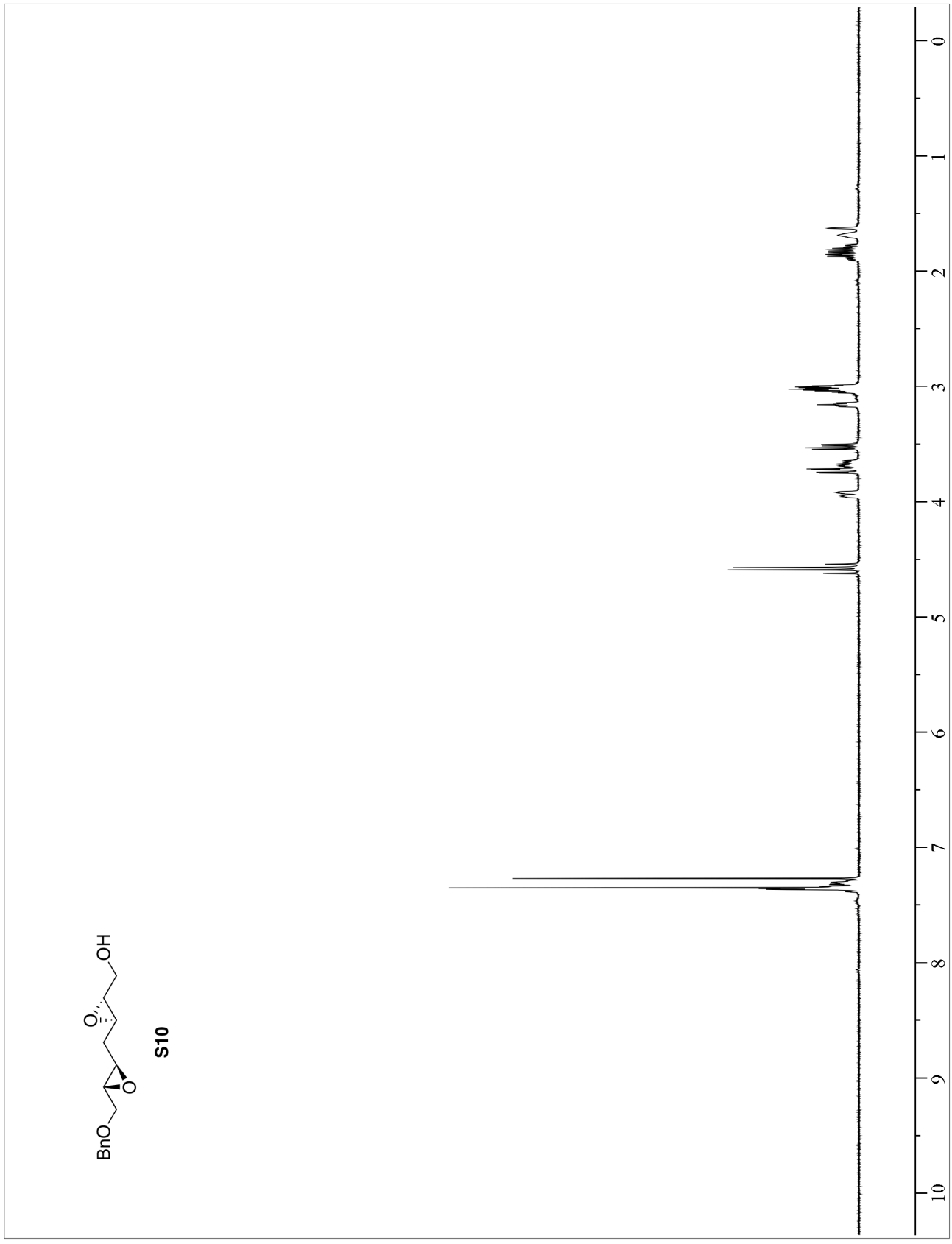
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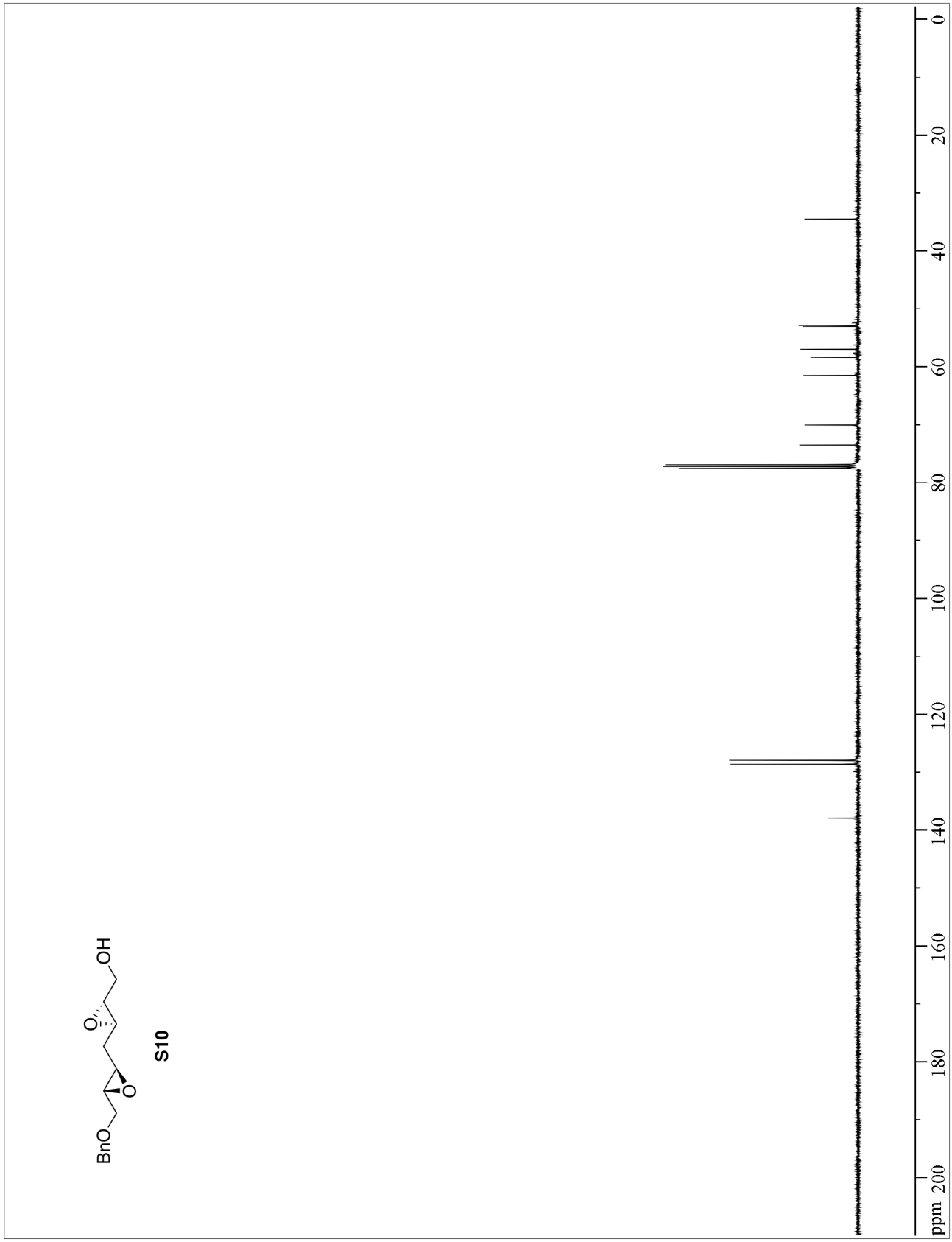
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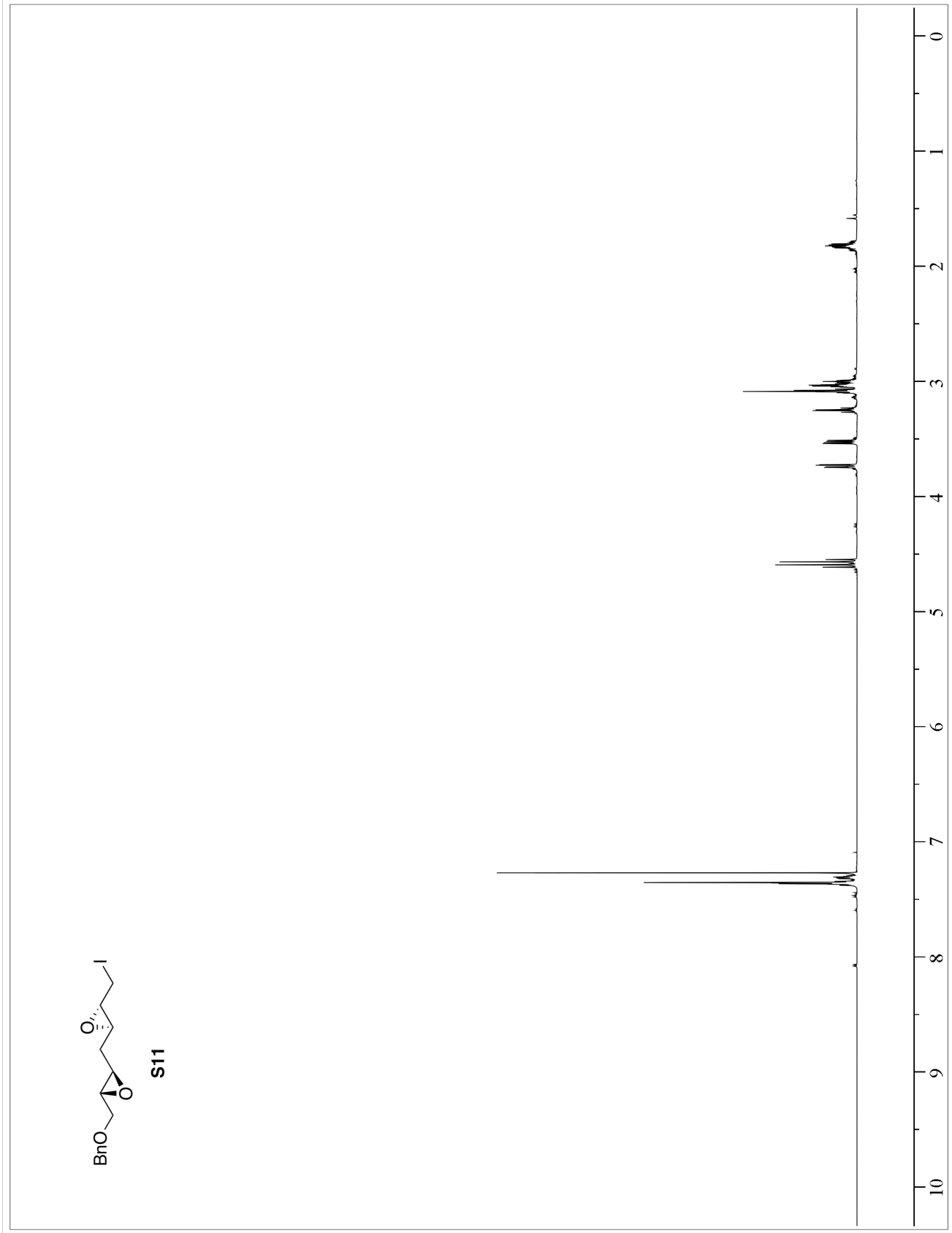
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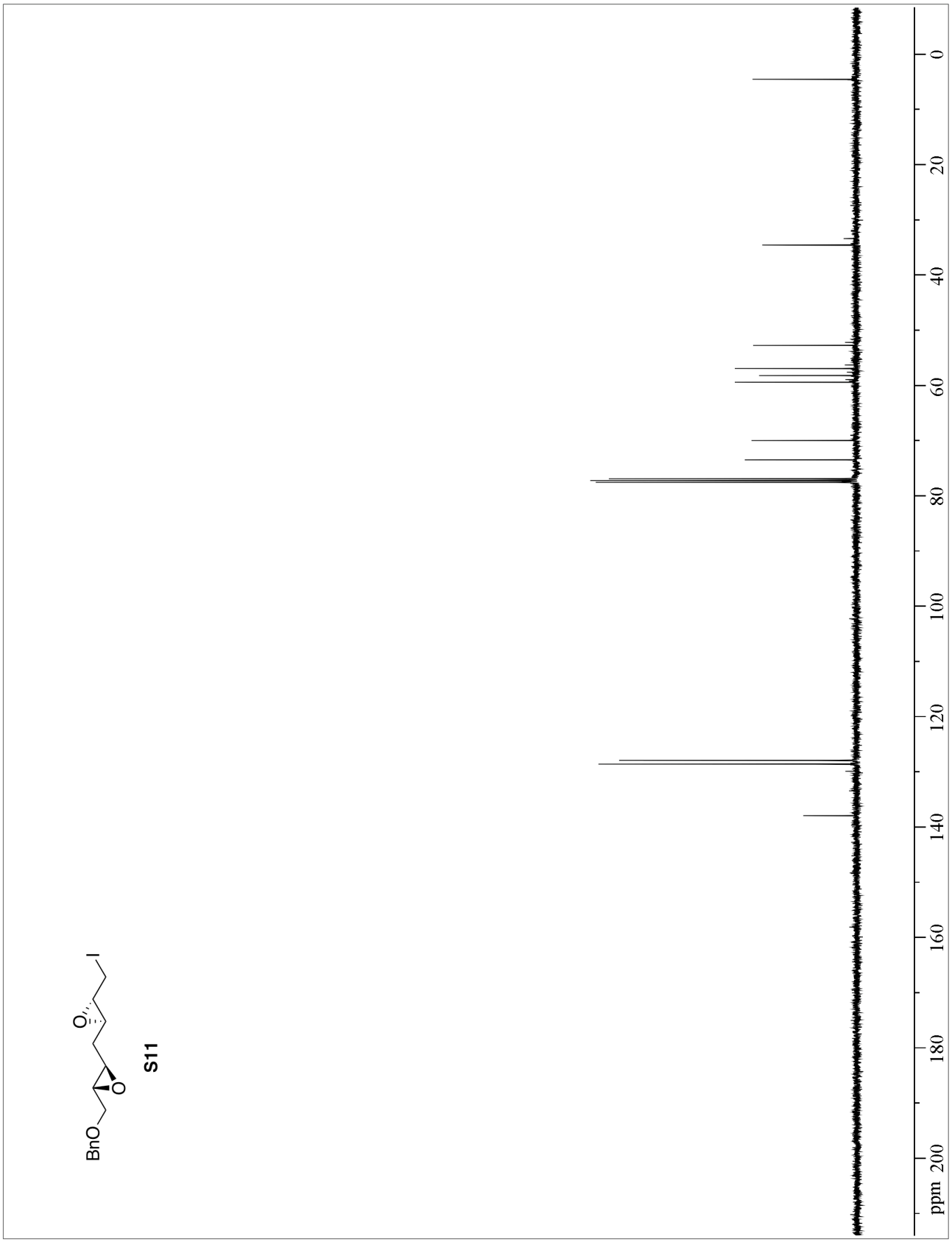
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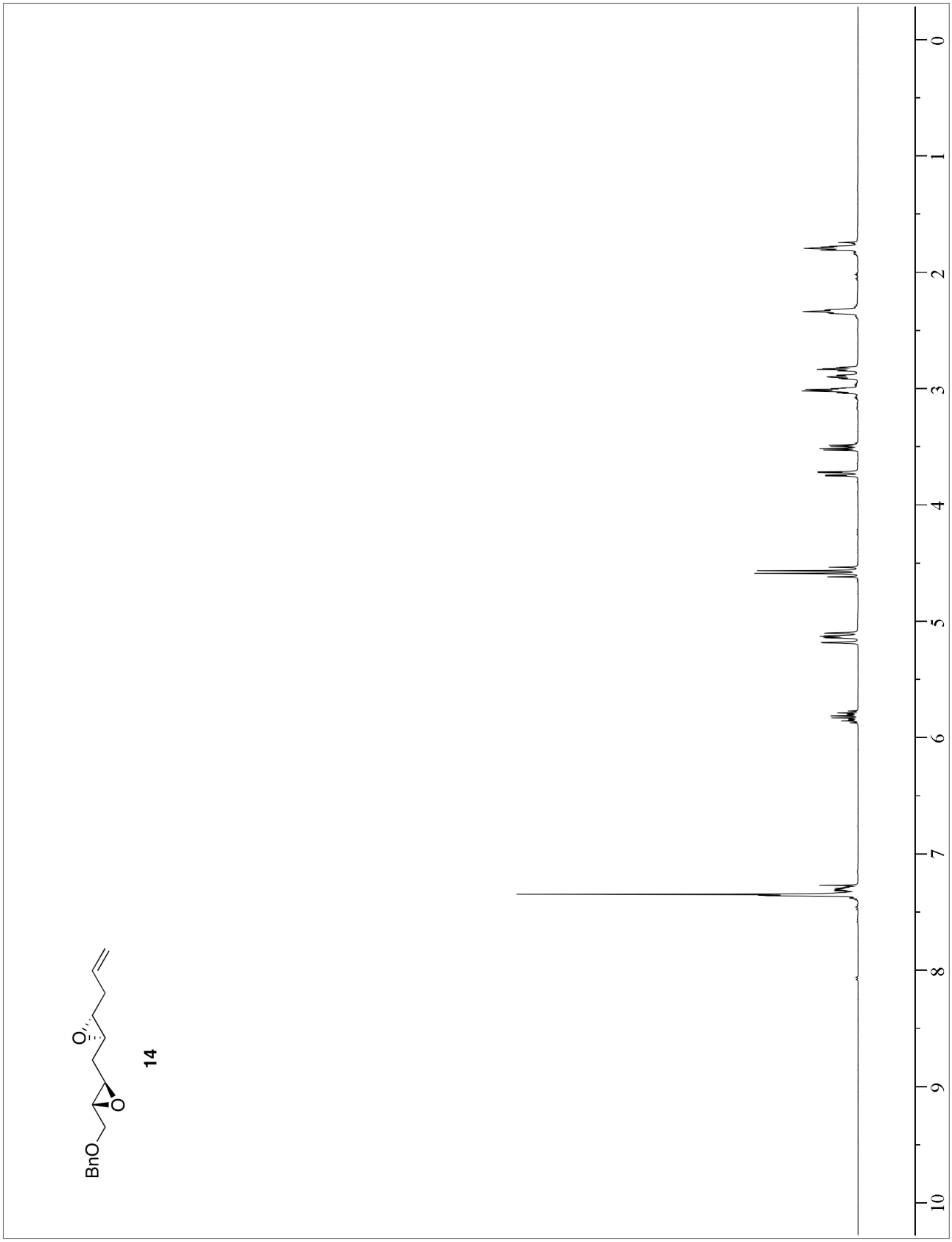
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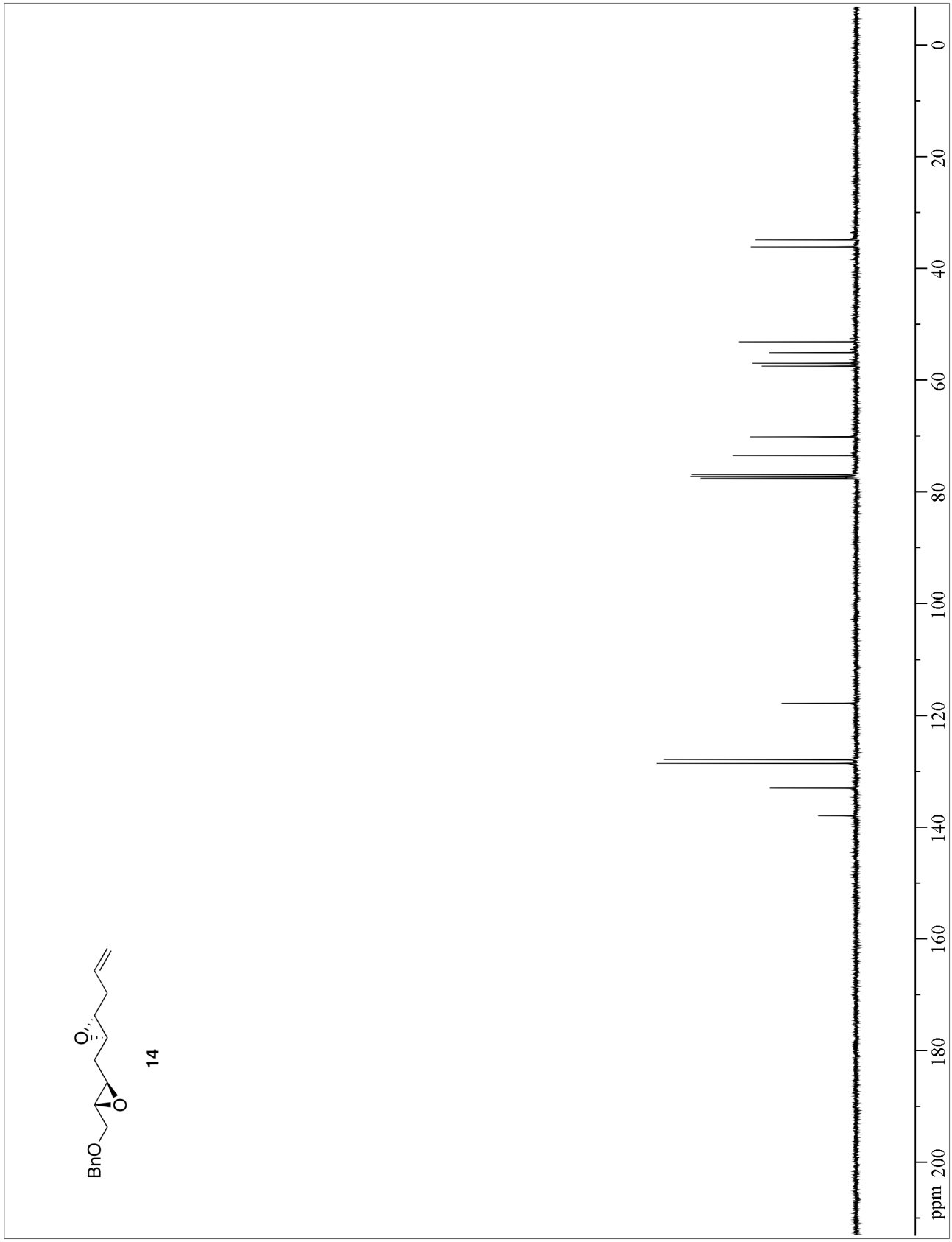
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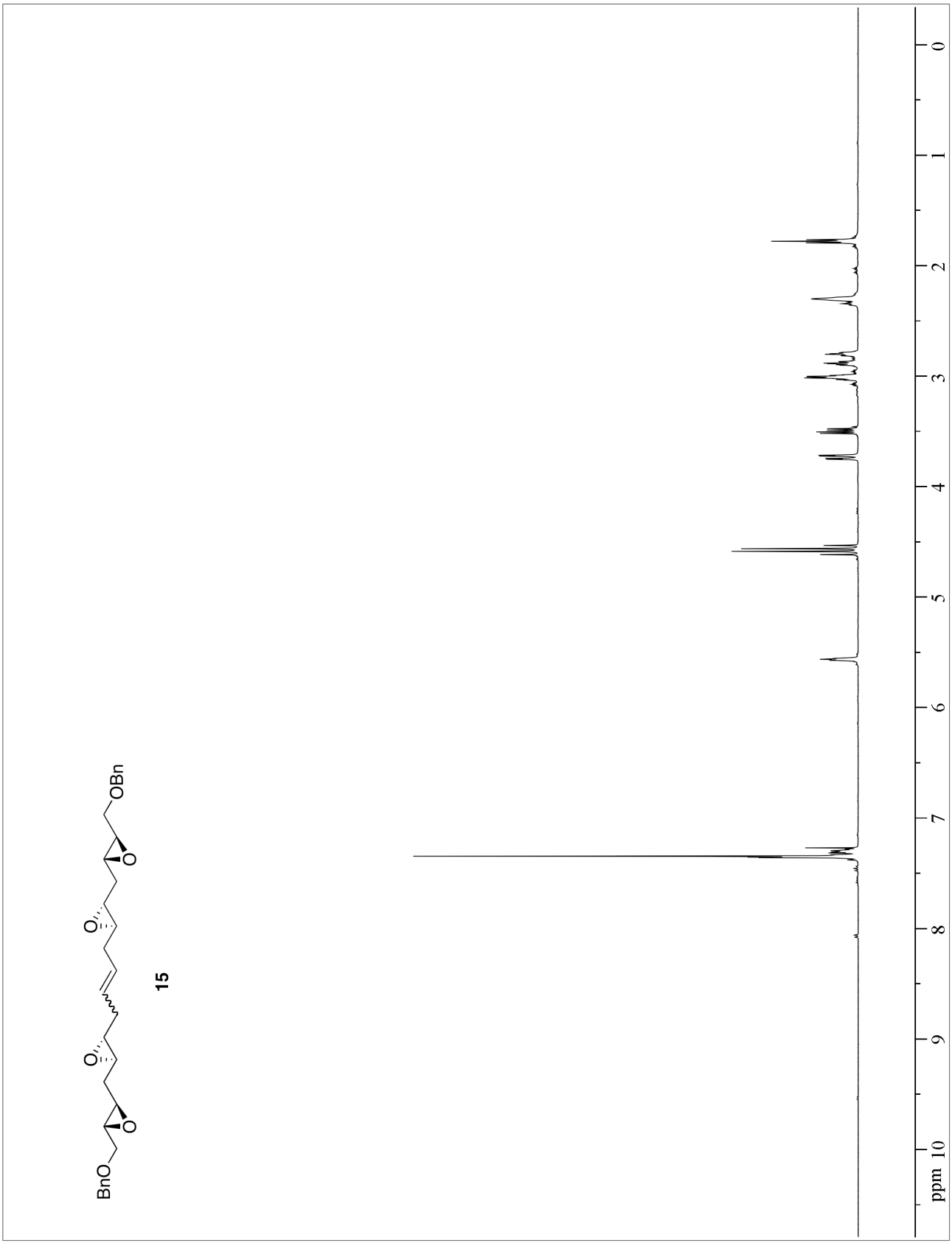
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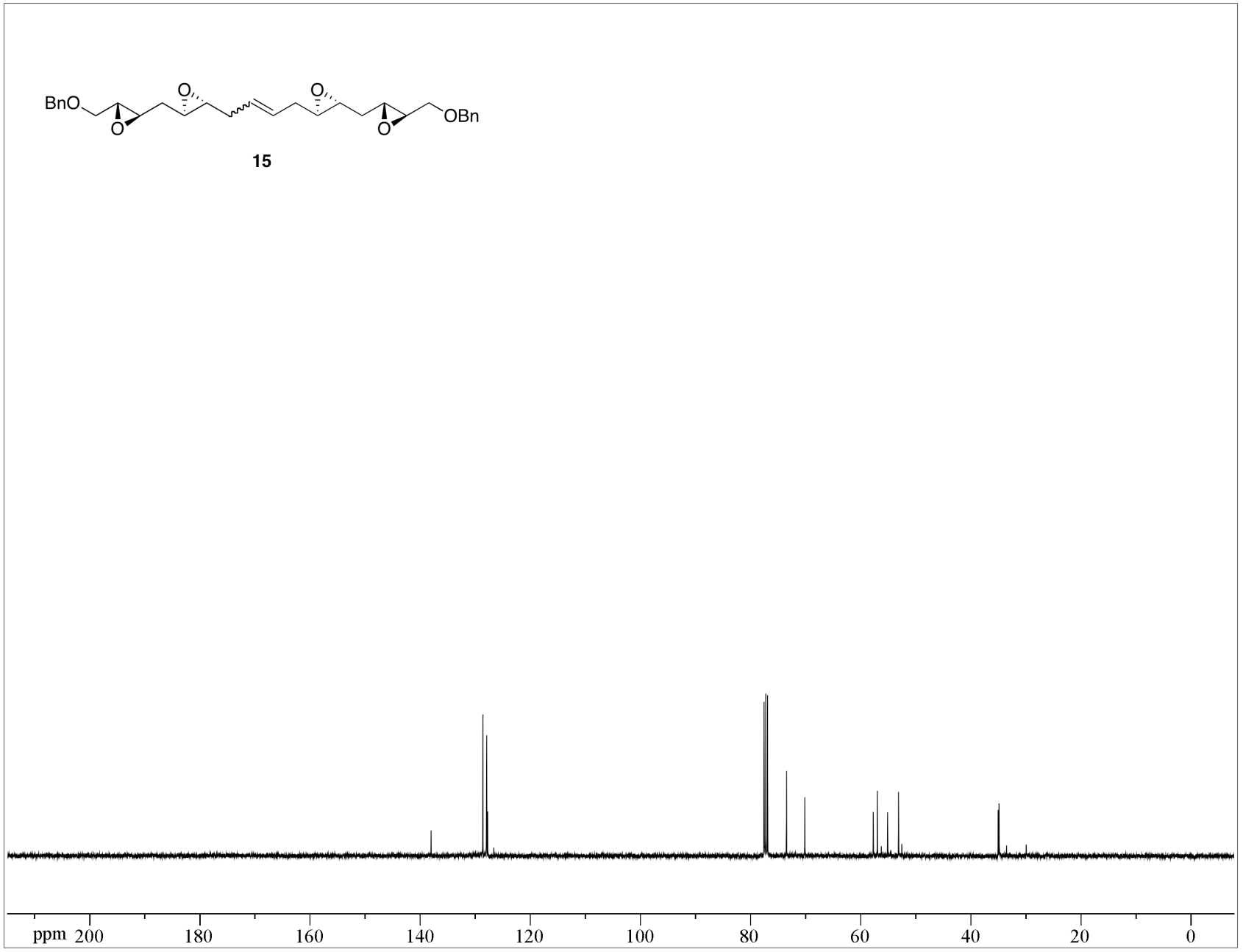
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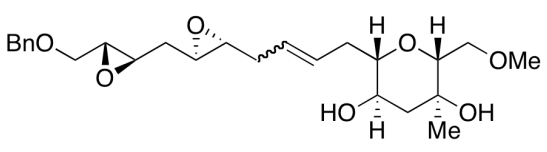

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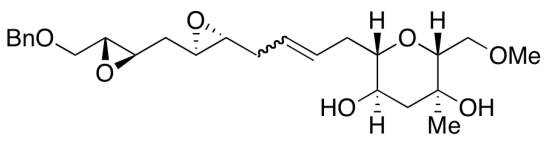

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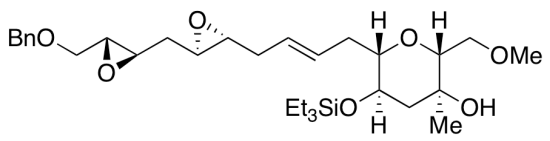

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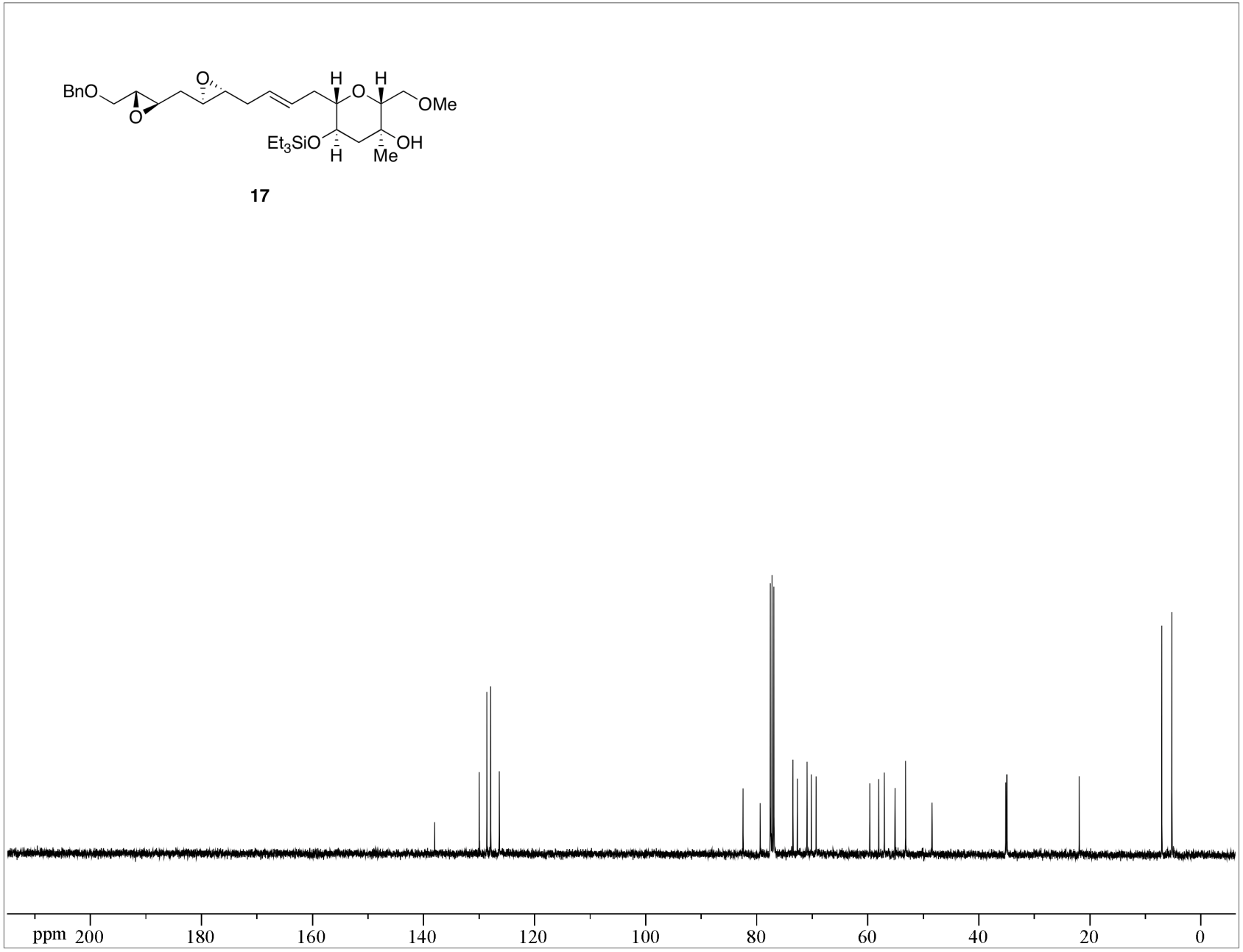
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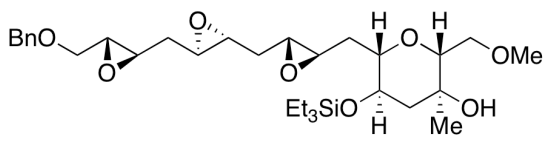

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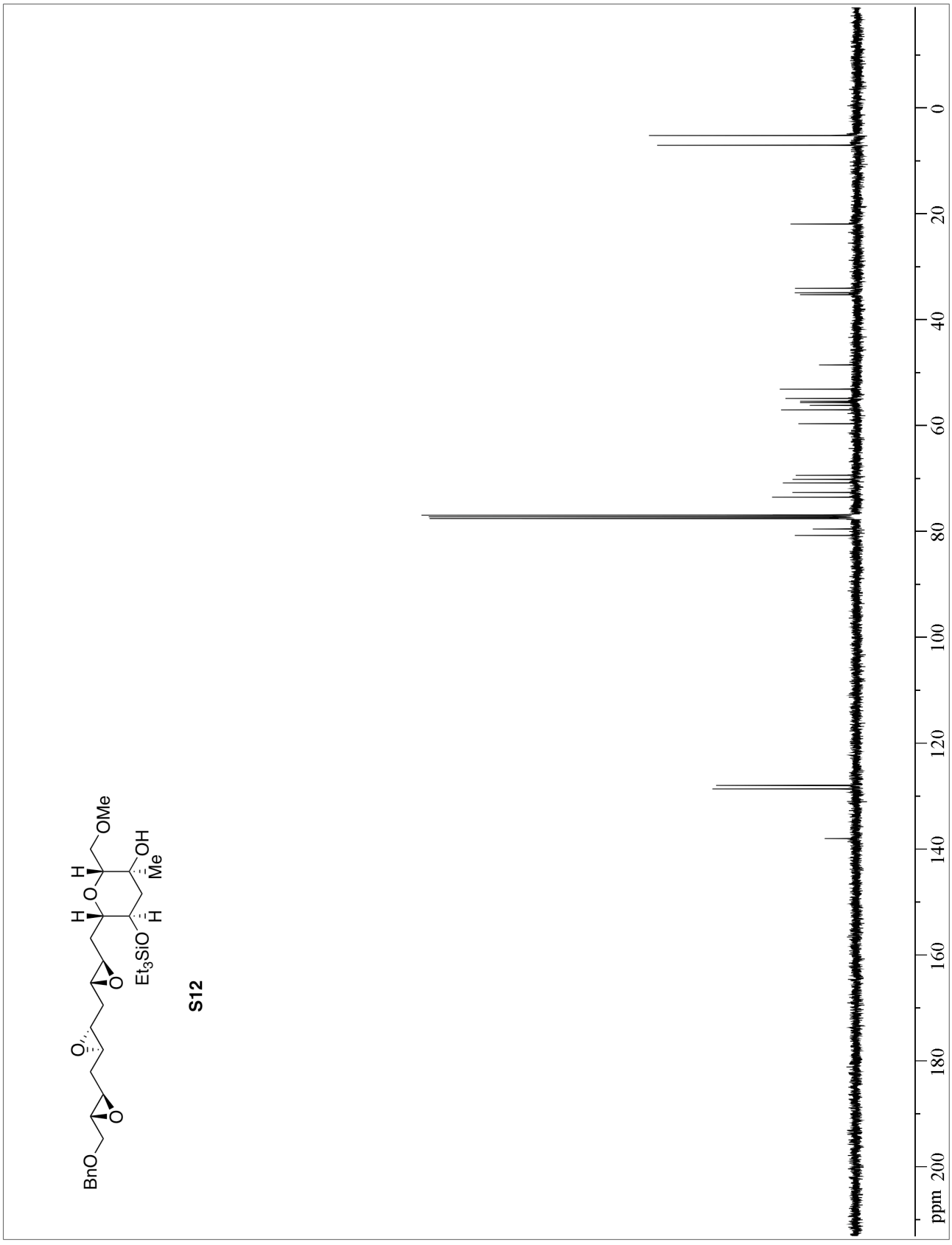
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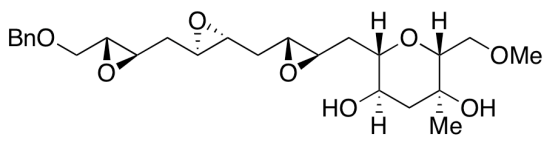
S12



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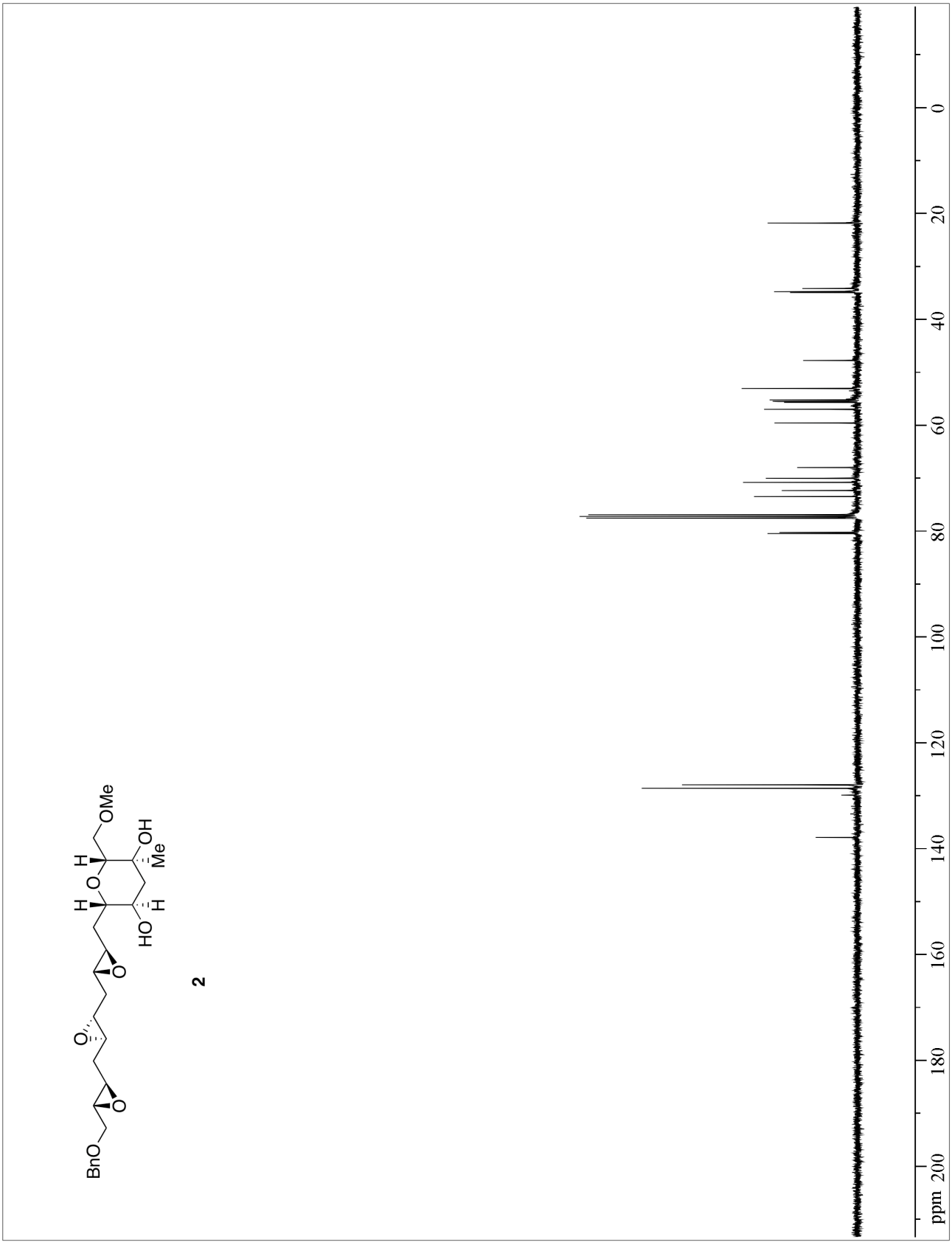
BnO
OMe
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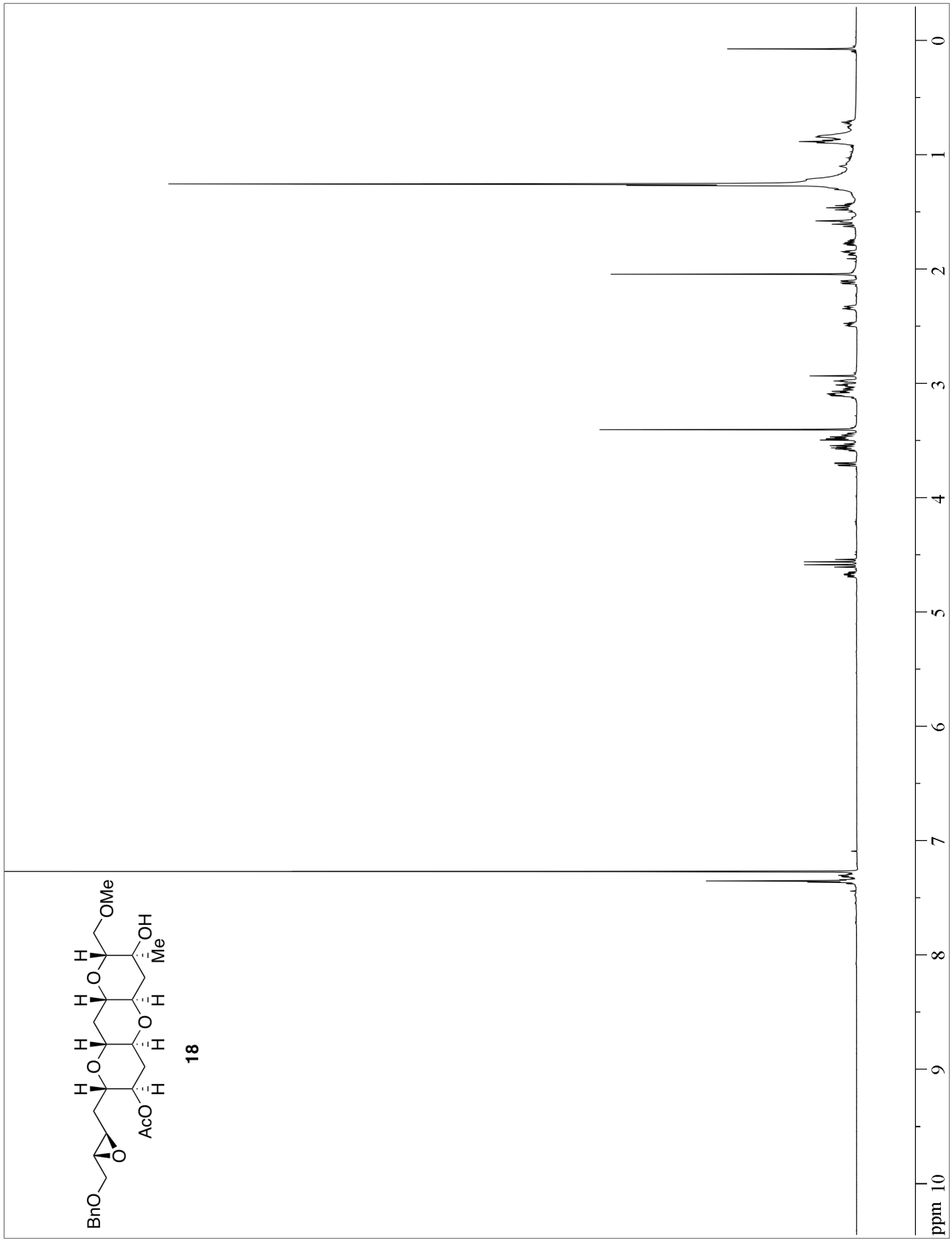
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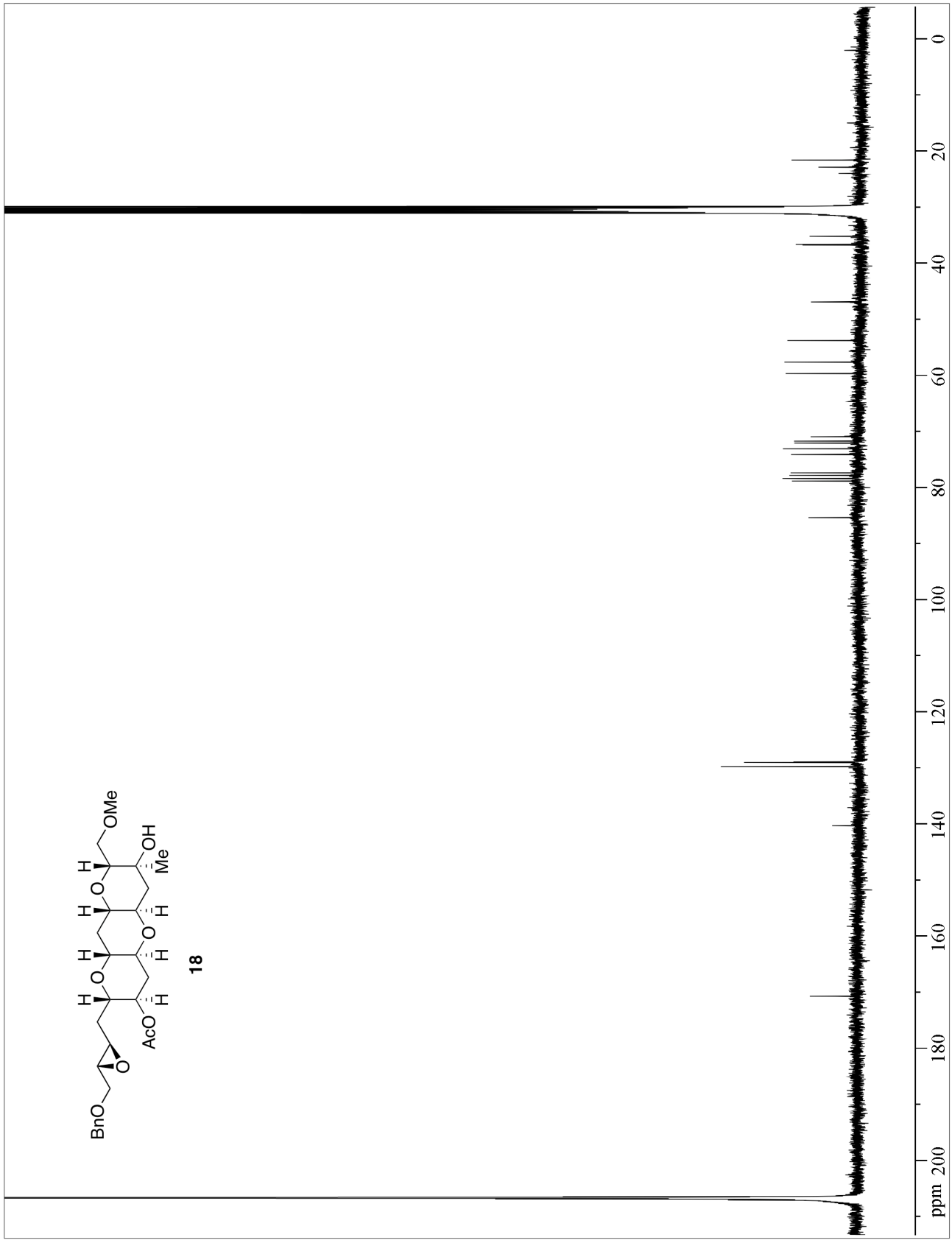
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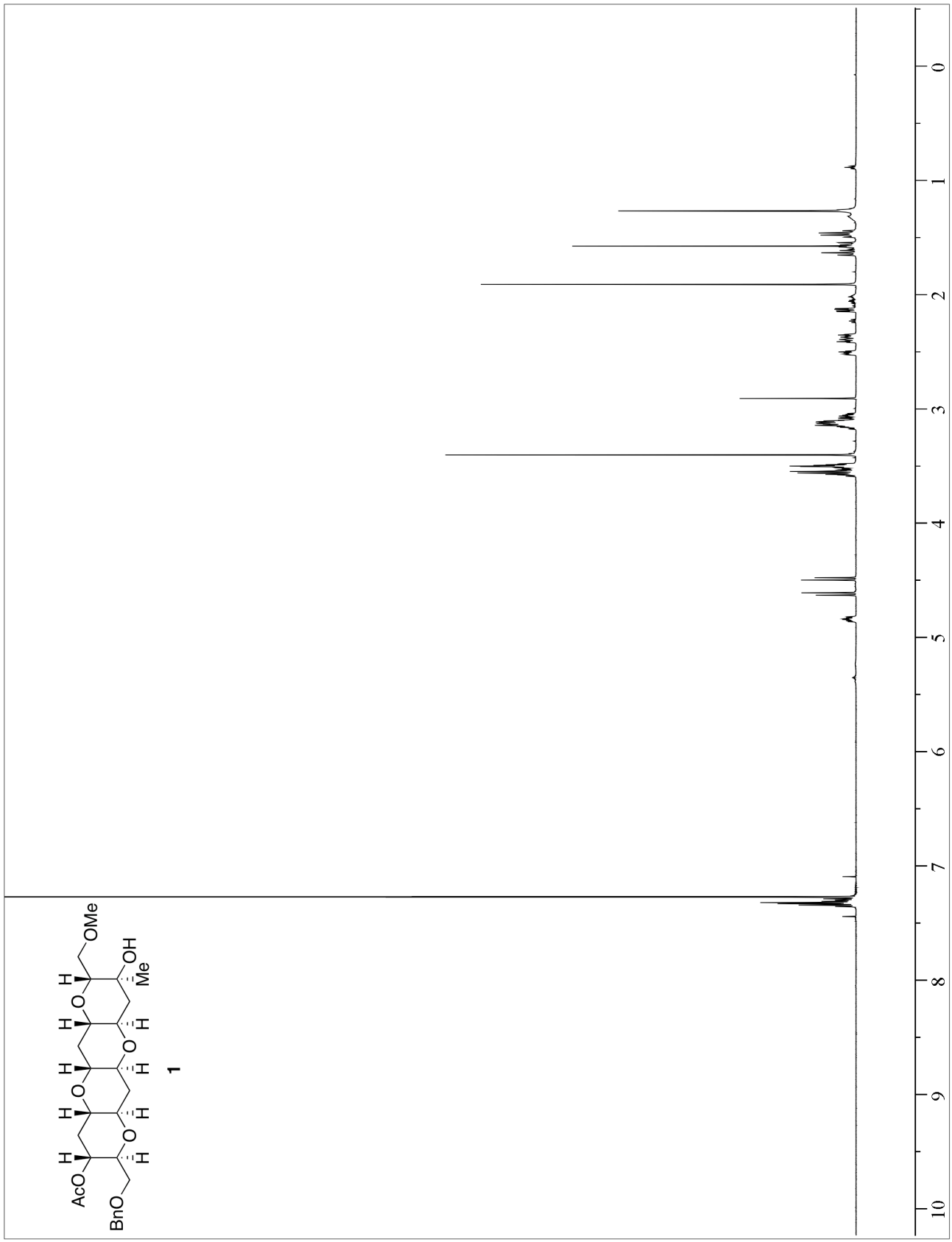
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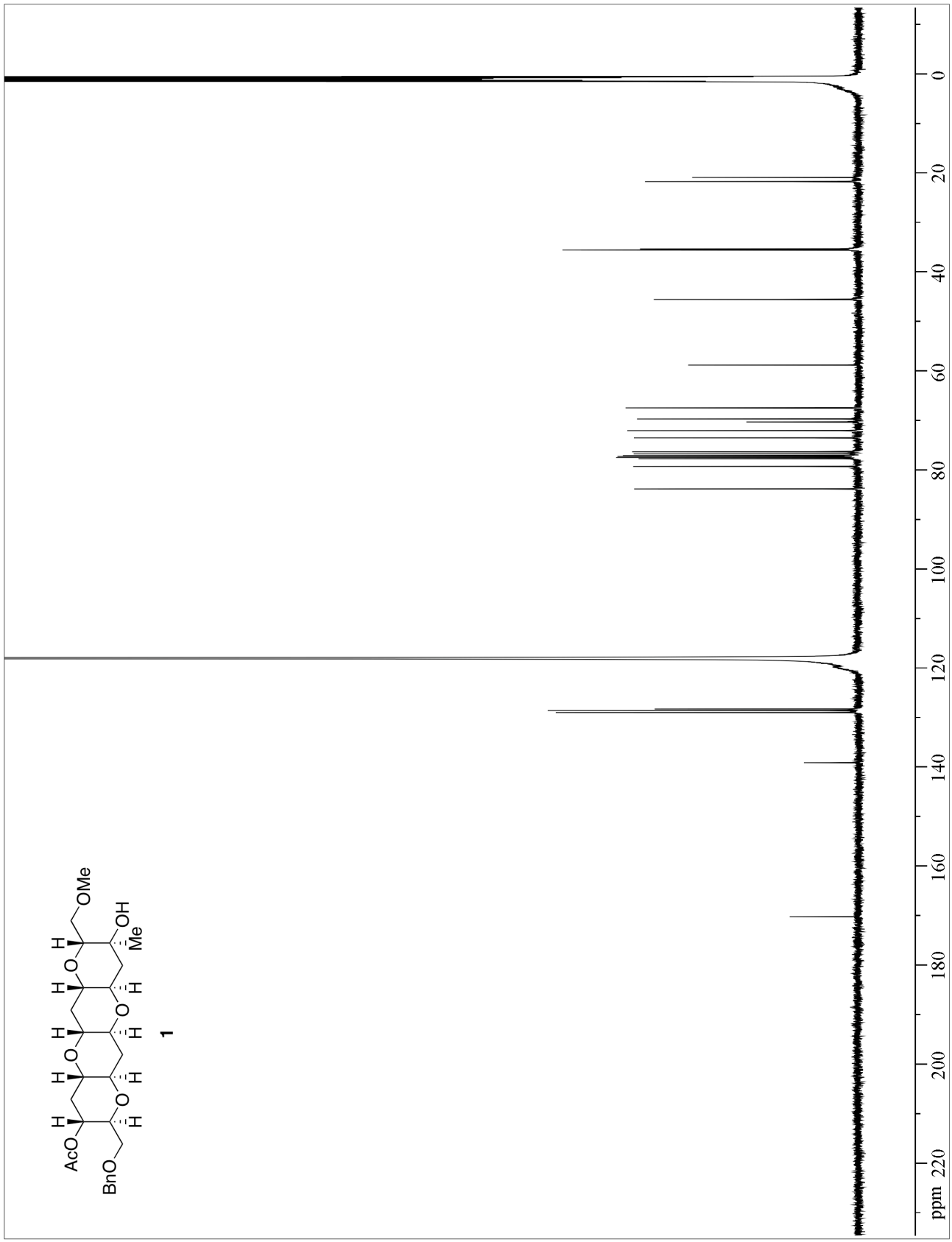
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