Enantioselective Synthesis of a Hydroxymethyl-*cis*-1,3-cyclopentendiol Building Block

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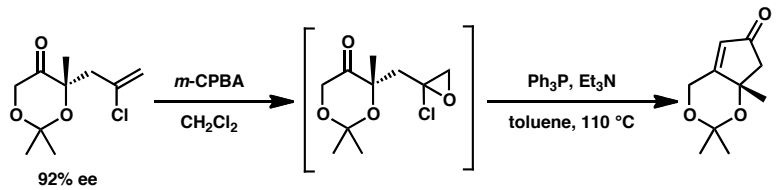
Materials and Methods

Unless stated otherwise, reactions were performed at ambient temperature (23 °C) in flame-dried glassware under an argon atmosphere using dry, deoxygentated solvents (distilled or passed over a column of activated alumina). Commercially available reagents were used as received. Reactions requiring external heat were modulated to the specified temperatures using an IKAmag temperature controller. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (250 nm) and visualized by UV fluorescence quenching, potassium permanganate, or *p*-anisaldehyde staining. Silicycle Silia*Flash* P60 Academic Silica gel (particle size 40-63 nm) was used for flash chromatography. (*S*)-*t*-BuPhox[1] and tris(4,4'-methoxydibenzylideneacetone)dipalladium(0) ($Pd_2(pmdba)_3$)[2] were prepared by known methods. Et_3N was distilled from calcium hydride immediately prior to use. MeOH was distilled from magnesium methoxide immediately prior to use. Reagent grade acetone was obtained from Sigma-Aldrich and used as received. Purified water was obtained using a Barnstead NANOpure Infinity UV/UF system. 4 Å molecular sieves were oven-dried at 120 °C for a minimum of 24 h and cooled in a desiccator to ambient temperature immediately prior to use. ^1H and ^{13}C NMR spectra were recorded on a Varian Inova 500 (500 MHz and 126 MHz, respectively) and a Varian Mercury 300 spectrometer (300 MHz and 76 MHz, respectively) and are reported in terms of chemical shift relative to $CHCl_3$ (δ 7.26 and δ 77.16, respectively). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Infrared (IR) spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). Analytical chiral gas chromatography was

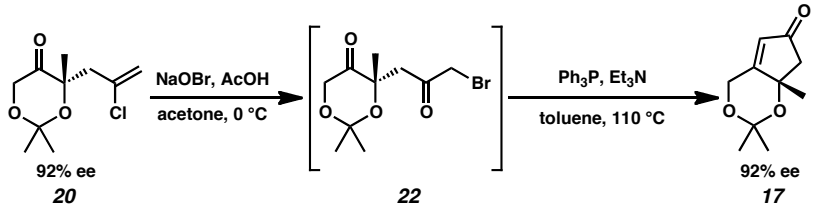
performed with an Agilent 6850 GC using a G-TA (30 m x 0.25 cm) column (1.0 mL/minute carrier gas flow). Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralcel OB-H column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd with visualization at 254 nm. High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer in fast atom bombardment (FAB+) or electron ionization (EI+) mode or acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in atmospheric pressure chemical ionization (APCI) or mixed (MultiMode ESI/APCI) ionization mode. Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path length cell at 589 nm.

Experimental Procedures



Cyclopentenone dimethyl ketal 17: A solution of chloroallylketone **20** (0.157 g, 0.72 mmol, 1.00 equiv) in CH_2Cl_2 (4.5 mL) was distributed evenly among three oven-dried one-dram vials. Solid *m*-CPBA (0.252 g, 1.46 mmol, 2.00 equiv) was divided into three equal portions and added to each vial. After 9 days, the reaction vessels were simultaneously cooled to 0 °C, filtered individually through celite plugs, rinsing with pentane. The organics were then combined, concentrated in vacuo (>300 torr) and purified immediately by column chromatography (5% Et_2O in pentane eluent) to afford volatile intermediate epoxide **21** (0.051 g, 30 % yield) as a pale yellow oil which was immediately carried onto the sequential reaction.[3]

Epoxide **21** (0.051 g, 0.22 mmol, 1.00 equiv) was added as a solution in toluene (2.5 mL) to a Schlenk flask. Upon the subsequent addition of Ph_3P (0.123 g, 0.47 mmol, 2.15 equiv) as a solid at ambient temperature, the reaction immediately turned bright yellow. The mixture was allowed to stir for 1 h, at which time the addition of Et_3N (0.13 mL, 0.91 mmol, 4.15 equiv) was accomplished dropwise. The reaction vessel was immediately sealed with a Teflon stopcock and introduced to a preheated 110 °C oil bath. After 4.5 h, the reaction was removed from the bath, cooled to ambient temperature, and purified directly by column chromatography (5%→10% Et_2O in pentane eluent) to furnish volatile cyclopentenone dimethyl ketal **17** (0.008 g, 20% yield) as a yellow oil: R_f = 0.29 (1:1 hexanes:Et_2O eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 (t, *J* = 1.7, 1H), 4.95–4.81 (m, 2H), 2.60 (d, *J* = 17.7, 1H), 2.47 (d, *J* = 17.7, 1H), 1.62 (s, 3H), 1.42 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.4, 175.9, 125.4, 100.8, 77.8, 60.9, 53.5, 30.2, 28.6, 25.4; IR (Neat Film, NaCl) 3072, 2991, 2937, 2861, 1723, 1639, 1445, 1408, 1382, 1372, 1349, 1316, 1267, 1226, 1200, 1169, 1139, 1094, 1060, 1010, 983, 952, 920, 903, 848, 831, 772, 752 cm^{-1}; HRMS (EI+) *m*/*z* calc'd for $C_{10}H_{14}O_3$ $[M\bullet]^+$:182.0943, found 182.0941; $[\alpha]_D^{23.6}$ –19.8° (*c* 1.53, $CHCl_3$).



Cyclopentenone dimethyl ketal 17: To a stirred solution of NaOH (0.942 g, 23.6 mmol, 17.2 equiv) in water (12 mL) at 0 °C (ice/water bath) was added Br_2 (0.40 mL, 7.81 mmol, 5.70 equiv) dropwise through a needleless plastic syringe. The resulting yellow solution of NaOBr was stirred for 30 minutes at 0 °C.

A flask was charged with a solution of chloroallylketone **20** (0.300 g, 1.37 mmol, 1.00 equiv), acetone (12 mL), and acetic acid (7.10 mL, 124 mmol, 90.5 equiv). The colorless solution was cooled to 0 °C (ice/water bath). The reaction was treated with NaOBr (8.20 mL, 5.44 mmol, 4.00 equiv) dropwise using a needleless plastic syringe over 1 h. At the completion of the addition, the reaction progress was monitored by TLC (1:1 hexanes:Et_2O eluent). If the reaction was not immediately complete, further addition of NaOBr (up to 1 mL) would have been carried out at the same rate. Upon completion of the reaction as determined by TLC, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and water (5 mL), followed by dropwise addition of a solution of K_2CO_3 (5.000 g) and $Na_2S_2O_3 \cdot 5H_2O$ (2.084 g) in water (10 mL). Quenching resulted in the vigorous evolution of gas and the dissipation of the orange color, affording two colorless phases. The aqueous layer was further diluted with water (15 mL) and extracted with CH_2Cl_2 (3 x 25 mL). Combined organic layers were dried over $MgSO_4$ for 1 minute, filtered, and concentrated under reduced pressure until around 2 mL of solution remained. The solution was diluted with heptane (10 mL), and the reaction was concentrated under reduced pressure until around 0.6 mL of solution remained. The reaction was quickly purified through an SiO_2 plug (10% Et_2O in hexanes eluent) and partially concentrated under reduced pressure to give the desired α-bromoketone **22** as a yellow solution, which was promptly diluted with anhydrous toluene (1 mL) and immediately employed.[4]

A 250 mL Schlenk flask and stir bar was charged with powdered Ph_3P (0.893 g, 3.40 mmol, 2.48 equiv) and toluene (10 mL). The colorless solution was treated dropwise with the solution of α-bromoketone **22** and rinsed with additional toluene (4 mL). The colorless solution was then treated dropwise with Et_3N (0.29 mL, 2.08 mmol, 1.50

equiv). The reaction vessel was immediately sealed with a Teflon stopcock and introduced to a preheated 110 °C bath. After 5 h, the reaction was removed from the bath, cooled to ambient temperature, and purified directly by column chromatography (25%→50% Et_2O in pentane eluent) to furnish the volatile cyclopentenone dimethyl ketal **17** (0.205 g, 82% yield) as a yellow oil.[5] See above for characterization data. Additionally, the enatiomeric excess of enone **17** generated by this procedure was determined by analytical chiral HPLC (Chiralcel OB-H column, 3:7 isopropyl alcohol:hexanes, 1 mL/minute, major retention time: 12.7 minutes, minor retention time: 16.5 minutes**,** 92% ee).

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POS 6

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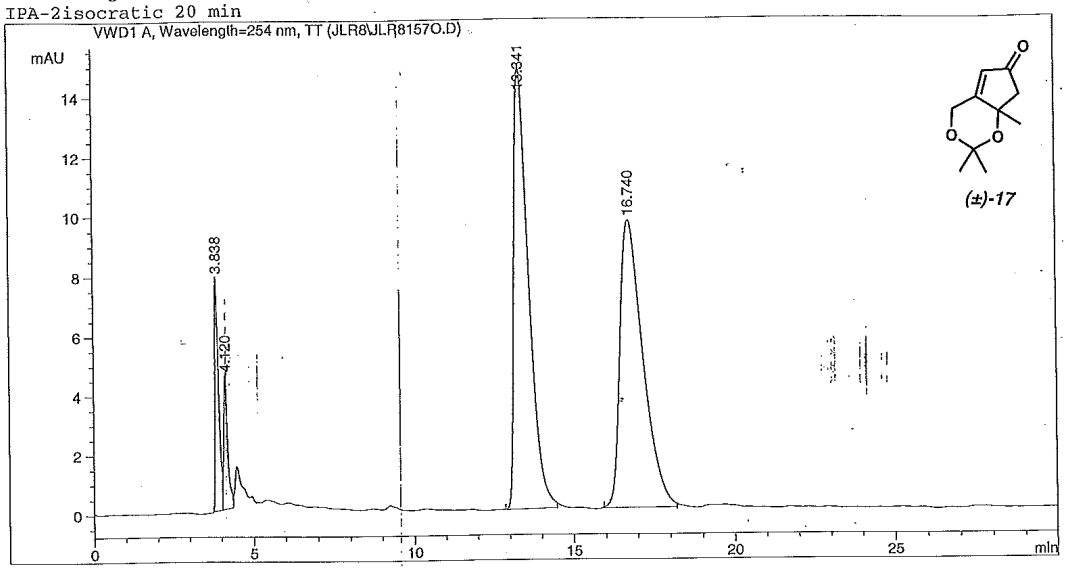

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Results obtained with enhanced integrator!

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P056

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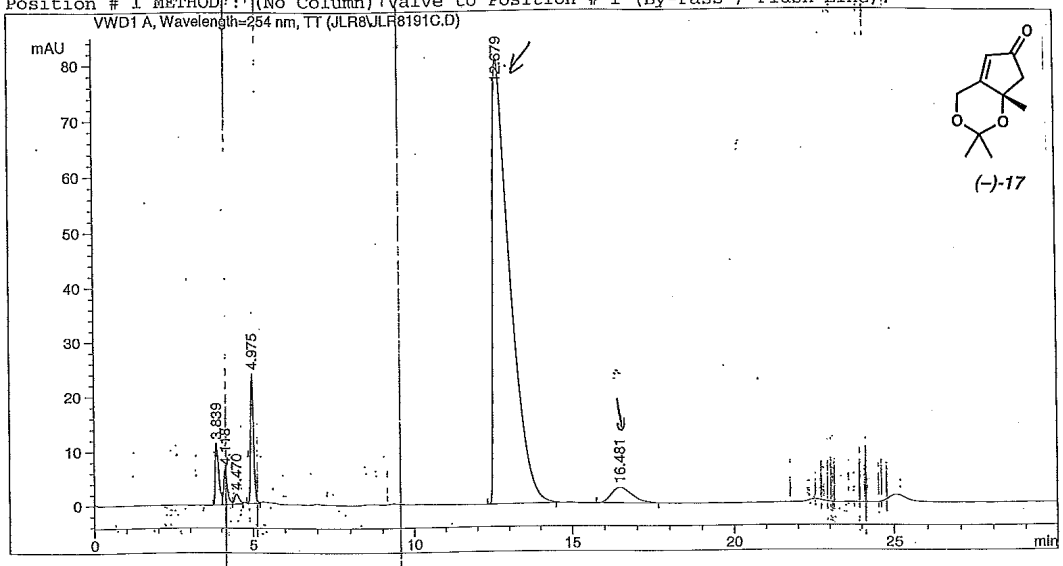

(–)-17

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3	4.470	VV	0.1666	19.66049	1.82274	0.5601
4	4.975	VB	0.1035	157.07748	23.70523	4.4747
5	12.679	PB	0.5472	3065.60059	80.84175	87.3311
6	16.481	PB	0.6167	128.56702	2.86517	3.6625
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Results obtained with enhanced integrator!

*** End of Report ***

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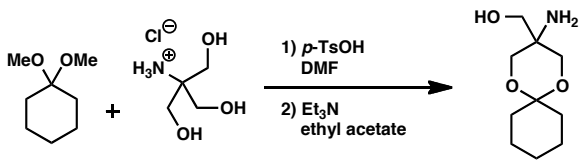
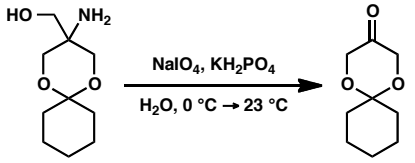


S1 *S2* *S3*

Aminoalcohol S3: To a suspension of Trizma•HCl (**S2**, 45.0 g, 286 mmol, 1.00 equiv) in DMF (365 mL) were added cyclohexanone dimethyl ketal (**S1**, 50.0 mL, 329 mmol, 1.15 equiv) and *p*-toluenesulfonic acid (1.63 g, 8.57 mmol, 0.03 equiv) in one portion with stirring. After 17 h, a distillation apparatus was attached directly to the reaction flask and the volatiles were distilled off (75 °C/6 torr). The semisolid residue was triturated with Et_2O (700 mL) until white solid precipitated. The resulting heterogeneous solution was filtered, washed with EtOAc (4 x 100 mL), and dried under high vacuum (0.50 torr) to afford a white solid.

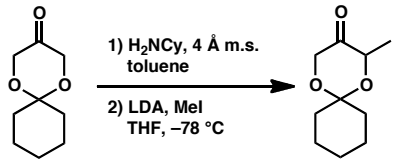
To a portion of the resulting crude white solid (19.7 g, 82.9 mmol, 1.00 equiv) as a suspension in EtOAc (276 mL) was added Et_3N (13.9 mL, 99.4 mmol, 1.20 equiv) dropwise with stirring. After 11 h, the reaction mixture was filtered, the solids washed with EtOAc (4 x 20 mL) and resuspended in EtOAc (150 mL) to which Et_3N (5.0 mL, 35.9 mmol) was added dropwise. The suspension was stirred for 48 h and then filtered and the solids were washed with EtOAc (4 x 120 mL). Combined organic filtrate was concentrated in vacuo to give aminoalcohol **S3** (16.68 g, 94% yield from **S2**) as a white solid: R_f = 0.17 (4:1 CH_2Cl_2:MeOH eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.80 (d, *J* = 11.9 Hz, 2H), 3.54 (d, *J* = 11.9 Hz, 2H), 3.49 (s, 2H), 1.87–1.64 (m, 7H), 1.59–1.52 (m, 2H), 1.52–1.46 (m, 2H), 1.42 (q, *J* = 6.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 98.7, 66.5, 65.2, 50.7, 34.0, 31.0, 25.8, 22.7; IR (Neat Film, NaCl) 3350, 3294, 2937, 2857,

1618, 1448, 1331, 1284, 1255, 1160, 1087, 918 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{10}H_{20}NO_3$ $[M+H]^+$: 202.1438, found 202.1434.



S3 *S4*

Dioxanone S4: Aminoalcohol **S3** (14.7 g, 73.0 mmol, 1.00 equiv) was dissolved in a solution of KH_2PO_4 (11.9 g, 87.6 mmol, 1.20 equiv) in H_2O (243 mL) and cooled to 0 °C (ice/water bath). To the resultant stirred homogenous solution was added a solution of $NaIO_4$ (15.6 g, 73.0 mmol, 1.00 equiv) in water (243 mL) dropwise over 2.5 h through a 250 mL additional funnel. The reaction was then allowed to stir at temperature for 40 minutes before being allowed to warm to ambient temperature. The starting material was consumed after an additional 4 h as determined by TLC. $Na_2S_2O_3$•$5H_2O$ (18.1 g, 73.0 mmol, 1.00 equiv) was then immediately added in one portion. The solution was allowed to stir for 40 minutes at which time the reaction mixture was extracted with CH_2Cl_2 (11 x 150 mL). Combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo (26 °C/100 torr) to afford dioxanone **S4** (12.4 g, >99% yield) as a pale yellow oil. This compound was carried to the next step without further purification: R_f = 0.80 (4:1 CH_2Cl_2:MeOH eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.12 (s, 4H), 1.72–1.65 (m, 4H), 1.59–1.51 (m, 4H), 1.44–1.35 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.3, 100.0, 66.7, 32.6, 25.3, 22.9; IR (Neat Film, NaCl) 2937, 2862, 1751, 1448, 1435, 1425, 1369, 1338, 1281, 1263, 1239, 1200, 1162, 1146, 1118, 1079, 1058, 1028, 922, 847, 825 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_9H_{14}O_3$ $[M•]^+$: 170.0943, found 170.0961.

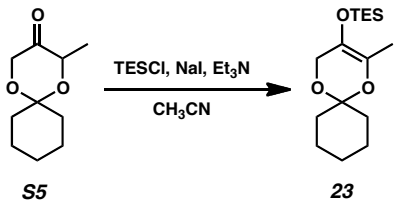


S4 *S5*

Methyldioxanone S5: A solution of dioxanone **S4** (12.4 g, 73.0 mmol, 1.00 equiv) in toluene (243 mL) was charged 4 Å molecular sieves (14.9 g, 1.20 equiv by mass) and cyclohexylamine (16.2 mL, 142 mmol, 1.94 equiv). After 13 h, the reaction mixture was filtered over celite, rinsing with toluene, and concentrated in vacuo to give the crude cyclohexylimine.

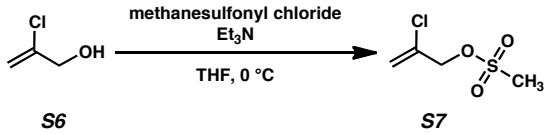
In a separate three-neck flask with an internal temperature probe, a solution of freshly prepared lithium diisopropylamine (LDA, 0.60 M in THF, 1.00 equiv) was cooled to –78 °C (dry ice/isopropanol bath). To the solution of LDA was added crude cyclohexylimine as a solution in THF (73 mL) dropwise through a cannula with an overpressure of argon. After 5 minutes, the reaction flask was introduced to a –15 °C bath (ice/methanol) and after 1.75 h was cooled back to –78 °C. To the reaction mixture was then added methyl iodide (4.77 mL, 76.7 mmol, 1.05 equiv) at a rate of 2.00 mL/h with a syringe pump, ensuring the internal temperature did not exceed –70 °C. Upon completion of addition, the reaction was allowed to stir for 30 minutes before being allowed to slowly warm to ambient temperature. Upon reaching ambient temperature, the reaction was quenched with saturated NH_4Cl (150 mL) and stirred for 14 h. The reaction mixture was then extracted with Et_2O (4 x 150 mL). Combined organic layers were then washed with water (50 mL), brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to afford an orange-tan oil. Purification of this residue by flash chromatography (10% Et_2O in hexanes eluent) furnished methyldioxanone **S5** (9.77 g, 73% yield) as a

clear, colorless oil: R_f = 0.30 (9:1 hexanes:Et_2O eluent); ^1H NMR (500 MHz, $CDCl_3$) δ 4.38 (qd, *J* = 6.8, 1.5 Hz, 1H), 4.28 (dd, *J* = 17.2, 1.5 Hz, 1H), 4.02 (d, *J* = 17.2 Hz, 1H), 1.84–1.76 (m, 1H), 1.76–1.66 (m, 3H), 1.62–1.54 (m, 4H), 1.47–1.39 (m, 2H), 1.31 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.4, 100.8, 70.8, 66.3, 33.3, 33.0, 25.4, 23.1, 23.0, 14.4; IR (Neat Film, NaCl) 2935, 2859, 1748, 1447, 1365, 1339, 1278, 1255, 1164, 1151, 1133, 1118, 1072, 1045, 991, 928, 846, 825 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{10}H_{16}O_3$ $[M\bullet]^+$: 184.1100, found 184.1129.



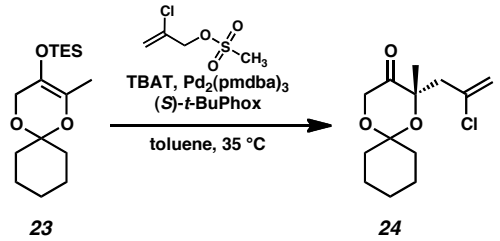
Silyl enol ether 23: A 250 mL round bottom was soaked in a 20:1 isopropanol:toluene bath saturated with KOH for 12 h, rinsed with deionized water, acetone, and allowed to dry. To a solution of methyldioxanone **S5** (9.77 g, 53.0 mmol, 1.00 equiv) in CH_3CN (88 mL) in a flame-dried 250 mL base-bathed round bottom flask with stir bar were added sodium iodide (10.3 g, 68.9 mmol, 1.30 equiv) in a single portion and Et_3N (11.8 mL, 84.8 mmol, 1.60 equiv) dropwise with stirring. After 5 minutes, triethylsilyl chloride (TESCl, 11.6 mL, 68.9 mmol, 1.30 equiv) was added dropwise. After 18 h, consumption of starting material was complete as determined by TLC and the reaction mixture was extracted with pentane (4 x 250 mL). Combined organic layers were washed with water (100 mL), brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to produce a yellow oil. Purification of this residue by flash chromatography (1.0% Et_2O / 0.5% Et_3N in hexanes eluent) on base–treated silica furnished silyl enol ether **23** (8.68 g, 55% yield) as a faintly pink, clear oil: R_f = 0.31 (19:1 hexanes:Et_2O eluent); ^1H NMR

(500 MHz, $CDCl_3$) δ 4.03 (q, *J* = 2.0 Hz, 2H), 1.78 (t, *J* = 2.0 Hz, 3H), 1.74–1.69 (m, 4H), 1.58–1.50 (m, 4H), 1.45–1.38 (m, 2H), 0.98 (t, *J* = 8.0 Hz, 9H), 0.64 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.1, 125.7, 98.5, 60.4, 33.0, 25.7, 22.8, 14.0, 6.8, 5.5; IR (Neat Film, NaCl) 2953, 2937, 2877, 1718, 1448, 1412, 1395, 1362, 1289, 1253, 1219, 1203, 1154, 1133, 1096, 1055, 1012, 946, 923, 866, 848, 830, 745 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{31}O_3Si$ $[M+H]^+$: 299.2037, found 299.2031.



S6 *S7*

Chloroallylmesylate S7: A flask was charged with 2-chloroallyl alcohol (**S6**, 4.78 mL, 60.0 mmol, 1.00 equiv), THF (120 mL), and Et_3N (17.2 mL, 120 mmol, 2.00 equiv) and cooled to 0 °C (ice/water bath) with stirring. To the solution was added methanesulfonyl chloride (6.96 mL, 90.0 mmol, 1.50 equiv) dropwise. After 2 h, the reaction was quenched saturated $NaHCO_3$ (120 mL). The reaction mixture was warmed to ambient temperature and extracted with Et_2O (3 x 180 mL). Combined organic layers were washed with 1 N HCl (120 mL), saturated $NaHCO_3$ (120 mL), brine (120 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to a crude tan oil. The residue was purified by bulb-to-bulb distillation using a Kügelrohr apparatus (150°C/3.5 torr) to furnish chloroallylmesylate **S7** (9.69 g, 95% yield) as a clear, colorless oil: R_f = 0.34 (2:1 hexanes:EtOAc eluent); ^1H NMR (300 MHz, $CDCl_3$) δ 5.65 (d, *J* = 0.5 Hz, 1H), 5.55 (d, *J* = 0.5 Hz, 1H), 4.77 (s, 2H), 3.10 (s, 3H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 134.3, 117.9, 71.1, 38.6; IR (Neat Film, NaCl) 3652, 3570, 3267, 3119, 3033, 2943, 2523, 2310, 2089, 1832, 1639, 1454, 1415, 1360, 1175, 1010, 923, 830, 757 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_4H_7{}^{35}ClO_3S$ $[M\bullet]^+$: 169.9804, found 169.9811.



23 ***24***

Chloroallyl ketal 24: A 500 mL Schlenk flask was soaked in a 20:1 isopropanol:toluene bath saturated with KOH for 12 h, rinsed with deionized water, acetone, and allowed to dry. To a flame-dried 500 mL base-bathed Schlenk flask in a nitrogen-filled glovebox were charged $Bu_4NPh_3SiF_2$ (TBAT, 7.53 g, 13.9 mmol, 1.00 equiv), $Pd_2(pmdba)_3$ (230 mg, 0.21 mmol, 0.015 equiv), (*S*)-*t*-BuPhox (190 mg, 0.49 mmol, 0.035 equiv), and toluene (280 mL, 0.0015 M in Pd). The reaction vessel was immediately removed from the glovebox, introduced to an argon atmosphere and placed a preheated 35 °C bath with stirring. After 20 minutes, a yellow-brown solution was observed. Chloroallylmesylate **S7** (2.85 g, 16.7 mmol, 1.20 equiv) was added quickly dropwise affording a blue-green solution. After 3 minutes, silyl enol ether **23** (4.16 g, 13.9 mmol, 1.00 equiv) was added quickly dropwise over 3 minutes. The resultant blue-green reaction mixture was allowed to stir for 20 h. The resultant yellow-brown reaction was then allowed to cool to ambient temperature, filtered through a pad of SiO_2 using hexanes as the eluent to remove toluene, at which time separate fractions were collected, eluting with Et_2O, to isolate the volatile reaction products. The filtrate was concentrated in vacuo to a bright yellow oil which was subsequently purified by flash chromatography (1%→3%→5% Et_2O in hexanes eluent) to afford volatile chloroallyl ketal **24** (2.95 g, 82% yield) as a clear, colorless oil: R_f = 0.41 (19:1 pentane:Et_2O eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.30 (d, J = 1.1 Hz, 1H), 5.23 (q, J = 0.8 Hz, 1H), 4.36 (d, J = 17.9 Hz, 1H), 4.20 (d, J = 17.9 Hz, 1H), 2.87 (dd, J =14.6, 0.9 Hz, 1H), 2.74 (d, J = 14.6 Hz, 1H), 1.84–1.76 (m, 2H), 1.76–1.69 (m, 2H),

1.66–1.58 (m, 2H), 1.57–1.50 (m, 2H), 1.47 (s, 3H), 1.45–1.41 (m, 1H), 1.41–1.36 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.2, 137.1, 116.9, 100.5, 81.1, 66.5, 48.2, 36.2, 35.0, 25.3, 25.2, 23.1, 23.0; IR (Neat Film, NaCl) 2937, 2862, 1743, 1635, 1447, 1364, 1332, 1280, 1258, 1245, 1172, 1159, 1113, 1052, 1005, 943, 889, 826 cm^{-1}; HRMS (APCI) *m/z* calc'd for $C_{13}H_{20}{}^{35}ClO_3$ $[M+H]^+$: 259.1095, found 259.1092; $[\alpha]_D^{25.0}$ –75.8° (*c* 1.41, $CHCl_3$, 92% ee).

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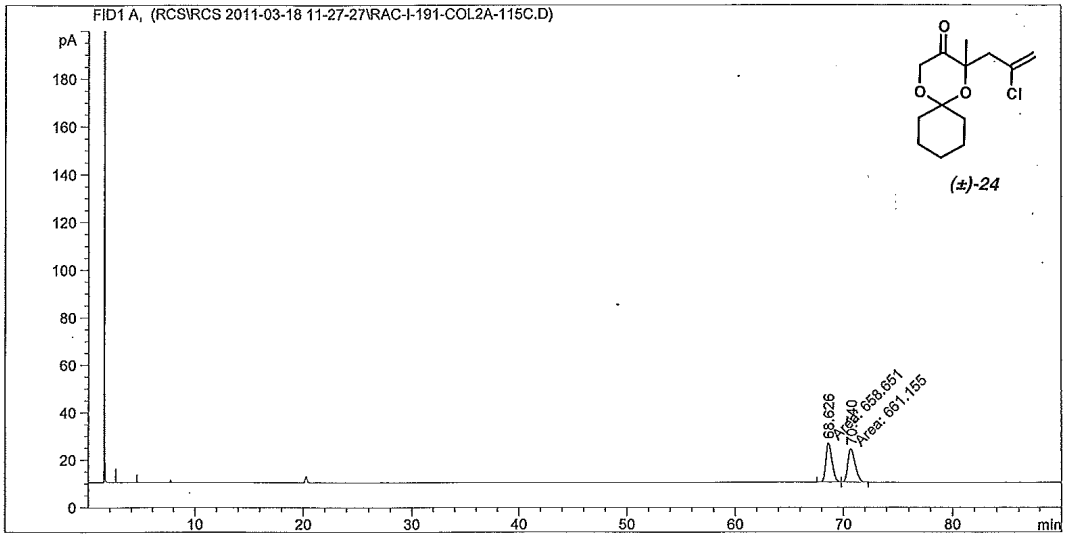

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*** End of Report ***

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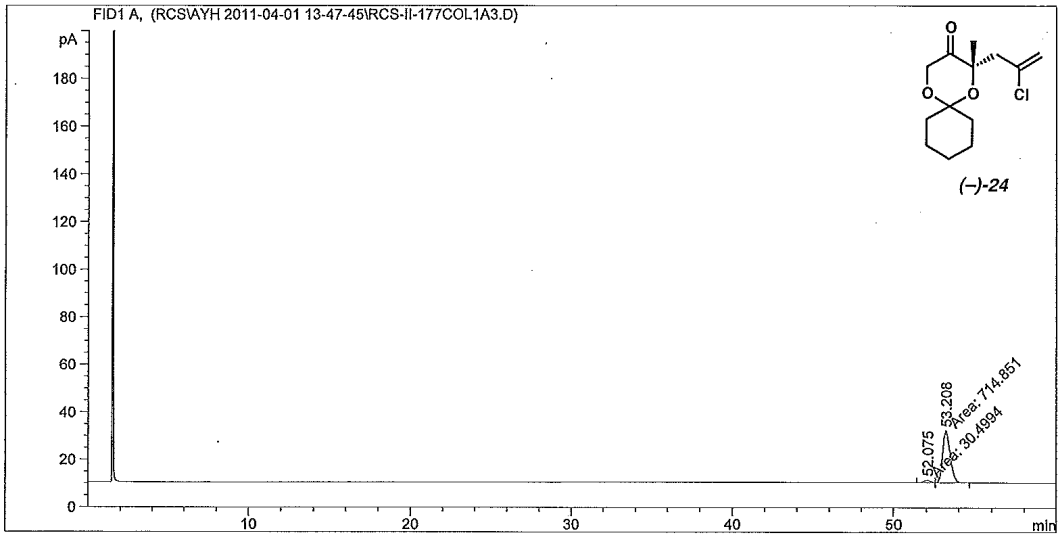

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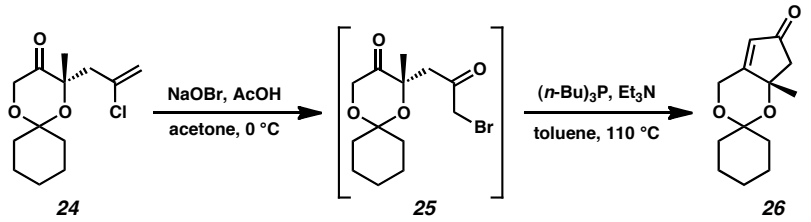


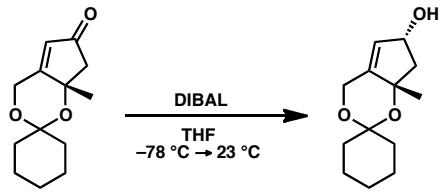
Cyclopentenone cyclohexyl ketal 26: To a stirred solution of NaOH (3.25 g, 81.2 mmol, 18.0 equiv) in water (54 mL) at 0 °C (ice/water bath) was added Br_2 (1.39 mL, 27.1 mmol, 6.00 equiv) dropwise through a needleless plastic syringe. The resulting yellow solution of NaOBr was stirred for 3 hours at 0 °C.

A solution of chloroallyl ketal **24** (1.17 g, 4.51 mmol, 1.00 equiv) in acetone (45 mL) was distributed equally to eight 20 mL scintillation vials with stir bars. Each vial was capped loosely with a septum and cooled to 0 °C under atmosphere. AcOH (23.2 mL, 406 mmol, 90.0 equiv) was distributed between the eight reaction vessels in a dropwise fashion. After 5 minutes, addition of NaOBr (28.0 mL, ca. 3.0 equiv) was accomplished by adding one drop every 30 seconds to each reaction vessel through a needleless plastic syringe.[6] Upon completion of addition (approximately 80 minutes), the bright orange reactions were allowed to stir for 10 minutes, at which time the consumption of starting material was complete as determined by TLC (4:1 hexanes:EtOAc eluent). If the consumption of starting material was determined incomplete, additional NaOBr (2.00 mL, ca. 0.21 equiv) would be added by the previously specified procedure and allowed to react for a maximum of 5 additional minutes. The reactions were then diluted with CH_2Cl_2 at 0 °C, quickly combined in a separatory funnel with additional CH_2Cl_2 (100 mL total), and carefully quenched with a solution of $Na_2S_2O_3 \cdot 5H_2O$ (11.2 g, 45.1 mmol, 10.0 equiv) and K_2CO_3 (12.5 g, 90.2 mmol, 20.0 equiv) in water (54 mL). Quenching resulted in the vigorous evolution of gas

and the dissipation of the orange color, affording a cloudy, white organic layer. The aqueous layer was washed with CH_2Cl_2 (3 x 100 mL). Combined organic layers were dried over $MgSO_4$ for 1 minute, filtered, concentrated in vacuo, and azeotroped with heptane (4 x 30 mL) to ensure thorough removal of AcOH and afford crude bromide **25** (1.440 g, >99% yield) as a white, viscous, opaque oil which was immediately subjected to the subsequent reaction conditions without further purification.[7]

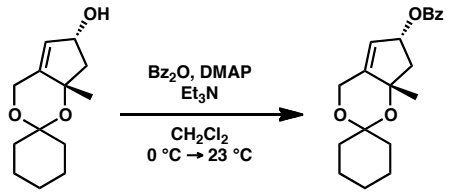
To a clear, colorless solution of neat $(n\text{-Bu})_3P$ (2.25 mL, 9.02 mmol, 2.00 equiv) in toluene (30 mL) in a Schlenk flask was added crude bromide **25** (1.440g, 4.51 mmol, 1.00 equiv) as a solution in toluene (15 mL) dropwise affording a clear, gold solution. After 90 minutes Et_3N (0.94 mL, 6.77 mmol, 1.50 equiv) was added dropwise, generating white precipitate on the first drops. The reaction was allowed to stir for 5 minutes, after which the vessel was sealed with a Teflon stopcock and introduced to a preheated 110 °C bath. The reaction solution was allowed to stir vigorously for 16 hours, after which the dark brown reaction mixture was removed from the bath and allowed to cool to ambient temperature with stirring. The vessel was then opened to the atmosphere in a well-ventilated fume hood and allowed to stir for an additional hour. The reaction mixture was filtered through a pad of SiO_2 using hexanes to remove toluene at which time separate fractions were collected, eluting with Et_2O, to isolate the volatile reaction products. The filtrate was concentrated in vacuo (>100 torr) and the resultant dark brown oil was purified by column chromatography (40% Et_2O in hexanes eluent) to furnish the volatile cyclopentenone cyclohexyl ketal **26** (0.939 mg, 94% yield) as a light yellow oil: $R_f = 0.28$ (3:2 Hexanes:Et_2O eluent); ^1H NMR (300 MHz, $CDCl_3$) δ 5.92–5.82 (m, 1H), 4.95–4.76 (m, 2H), 2.60 (app d, $J = 17.6$ Hz, 1H), 2.46 (app d, $J = 17.7$ Hz, 1H), 1.92–1.62 (m, 2H),

1.60 (s, 3H), 1.57–1.15 (m, 8H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.4, 176.4, 125.0, 101.0, 77.3, 60.2, 53.4, 39.0, 34.3, 28.7, 25.1, 23.4, 22.9; IR (Neat Film, NaCl) 3509, 3419, 2936, 2857, 1717, 1639, 1446, 1408, 1366, 1286, 1235, 1198, 1147, 1096, 1081, 1035, 984, 933, 855, 755 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{18}O_3$ $[M\bullet]^+$: 222.1256, found 222.1262; $[\alpha]_D^{25.0}$ –55.9° (*c* 13.02, $CHCl_3$).



26 ***27***

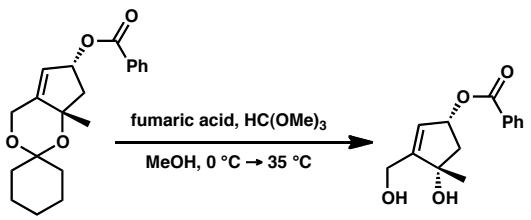
Allylic alcohol 27: To a pale yellow solution of cyclopentenone cyclohexyl ketal **26** (0.840 mg, 3.78 mmol, 1.00 equiv) in THF (38 mL) at –78 °C was added a solution of DIBAL (1.35 mL, 7.56 mmol, 2.00 equiv) in THF (7.6 mL) dropwise. After 30 minutes, the gold reaction mixture was removed from the bath and allowed to warm slowly. After an additional 30 minutes, the consumption of starting material was complete as determined by TLC (4:1 hexanes:EtOAc eluent) and the reaction mixture was cooled to 0 °C. The reaction was subsequently quenched with a 1:1 solution of saturated NH_4Cl and saturated Rochelle's salt (35 mL) dropwise, vigorously evolving gas on the first drops. The mixture was then diluted with CH_2Cl_2 (250 mL) and water (30 mL). The aqueous layer was the extracted with CH_2Cl_2 (3 x 60 mL). Combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to provide crude allylic alcohol **27** (0.848 g, >99% yield) which was used without further purification.



27 ***S8***

Benzoylated alcohol S8: To a stirred solution of crude allylic alcohol **27** (2.05 g, 9.14 mmol, 1.00 equiv) in CH_2Cl_2 (183 mL) were added 4-(dimethylamino)pyridine (DMAP, 2.233 g, 18.3 mmol, 2.00 equiv) and Et_3N (10.2 mL, 73.1 mmol, 8.00 equiv). The light yellow reaction mixture was cooled to 0 °C (ice/water bath) at which time benzoic anhydride (Bz_2O, 4.135 g, 18.28 mmol, 2.00 equiv) was added in one portion. After 30 minutes, the reaction was removed from the bath and allowed to warm to ambient temperature. After an additional 13 hours, at which time the consumption of starting material was complete as determined by TLC, the reaction was again cooled to 0 °C and quenched with saturated NH_4Cl (150 mL). The biphasic solution was further diluted with CH_2Cl_2 (240 mL) and water (200 mL). The aqueous was extracted with CH_2Cl_2 (2 x 240 mL). Combined organic layers were washed with saturated NH_4Cl (5 x 500 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to afford benzoylated alcohol **S8** (3.002 g, >99% yield) as a light gold oil at was typically utilized without further purification. A characterization sample of benzoylated alcohol **S8** was obtained through purification by column chromatography (1% Et_3N in CH_2Cl_2 eluent) to afford a clear colorless oil: R_f = 0.63 (4:1 hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (dt, J = 8.2, 1.0 Hz, 2H), 7.55 (td, J = 7.4, 1.3 Hz, 1H), 7.43 (td, J = 7.6, 1.1 Hz, 2H), 5.79 (ddq, J = 6.9, 3.8, 1.8 Hz, 1H), 5.64 (q, J = 1.6 Hz, 1H), 4.74–4.58 (m, 2H), 2.67 (dd, J = 12.7, 6.8 Hz, 1H), 2.12 (dd, J = 12.7, 6.7 Hz, 1H), 2.06–1.93 (m, 1H), 1.74–1.51 (m, 6H), 1.48 (s, 3H), 1.46–1.34 (m, 2H), 1.33–1.21 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5, 147.1,

133.1, 130.3, 129.7, 128.4, 121.5, 100.6, 80.6, 76.6, 59.7, 49.4, 38.9, 34.8, 28.8, 25.4, 23.6, 23.1; IR (Neat Film, NaCl) 2934, 2858, 1719, 1450, 1367, 1266, 1110, 1095, 1026, 984, 712 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{20}H_{25}O_4$ $[M+H]^+$: 329.1747, found 329.1745; $[\alpha]_D^{25.0}$ 48.7° (*c* 6.09, $CHCl_3$).



S8 ***28***

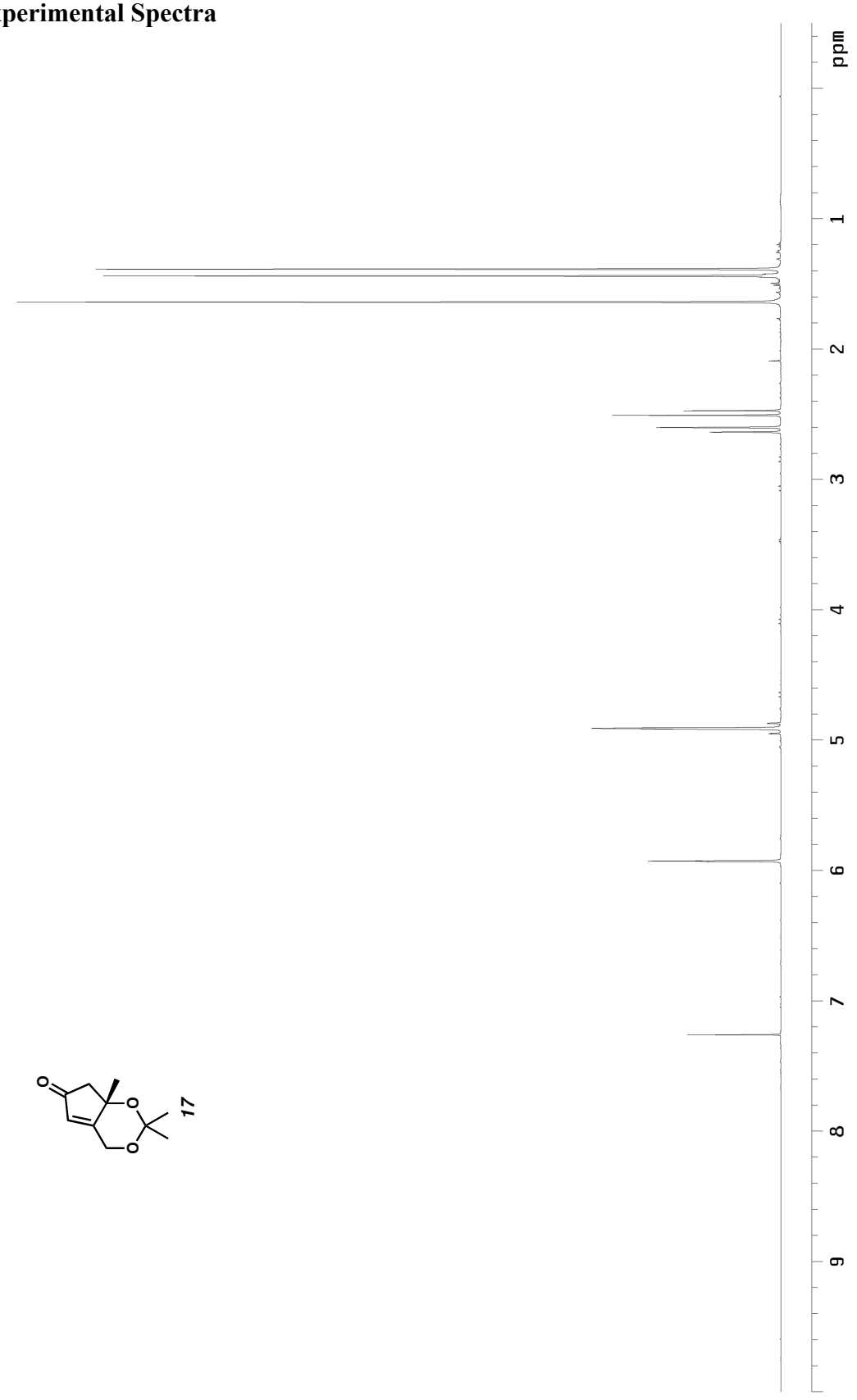
Diol 28: To a flask containing benzoylated alcohol **S8** (1.12 g, 3.40 mmol, 1.00 equiv) were added MeOH (68 mL) and $HC(OMe)_3$ (3.35 mL, 30.6 mmol, 9.00 equiv). The reaction mixture was cooled to 0 °C (ice/water bath) with stirring, at which time the addition of fumaric acid (0.988 g, 8.51 mmol, 2.50 equiv) was accomplished in one portion. After 10 minutes, the reaction was removed from the cold bath and immediately introduced to a preheated 35 °C oil bath. After 18 hours, the consumption of starting material was complete as determined by TLC and the reaction was allowed to cool to ambient temperature. The reaction mixture was diluted with EtOAc (150 mL) and poured over saturated $NaHCO_3$ (150 mL). The aqueous layer was extracted with EtOAc (3 x 150 mL). Combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ for 2 minutes, filtered, and concentrated in vacuo to generate a yellow oil. The crude residue was the purified by column chromatography (50% EtOAc in hexanes eluent) to afford diol **28** (0.816 g, 97% yield) as a pale yellow oil: R_f = 0.18 (1:1 hexanes:EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03–7.94 (m, 2H), 7.54–7.47 (m, 1H), 7.41–7.35 (m, 2H), 5.85 (q, *J* = 1.7 Hz, 1H), 5.66 (ddq, *J* = 7.8, 3.8, 1.8 Hz, 1H), 4.39 (td, *J* = 14.5, 1.7 Hz,

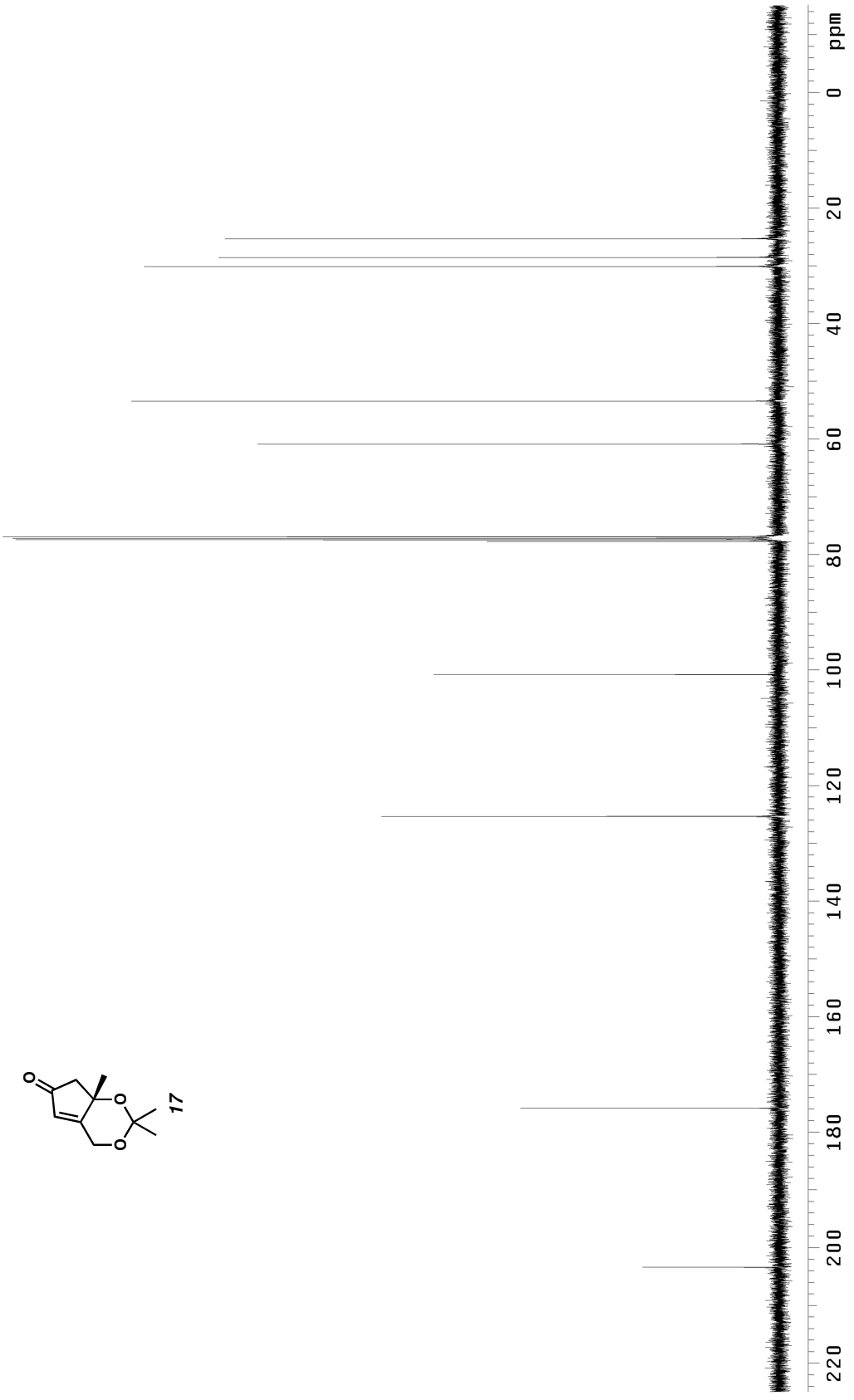
1H), 4.31 (td, *J* = 14.6, 1.3 Hz, 1H), 3.29 (bs, 2H), 2.64 (dd, *J* = 14.2, 7.3 Hz, 1H), 2.17 (dd, J = 14.2, 4.2 Hz, 1H), 1.39 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.6, 153.2, 133.2, 130.1, 129.7, 128.4, 125.6, 81.2, 76.3, 58.8, 48.3, 26.6; IR (Neat Film, NaCl) 3400, 2971, 1713, 1694, 1451, 1315, 1273, 1111, 1070, 1026, 952, 712 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{14}H_{17}O_4$ $[M+H]^+$: 249.1127, found 249.1132; $[\alpha]_D^{25.0}$ 115.1° (*c* 6.90, $CHCl_3$).

Notes and References

(1) (a) Peer, M.; de Jong, J. C.; Kiefer, M.; Langer, T.; Rieck, H.; Schell, H.; Sennhenn, P.; Sprinz, J.; Steinhagen, H.; Wiese, B.; Helmchen, G. *Tetrahedron* **1996**, *52*, 7547–7583; (b) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045; (c) Krout, M. R.; Mohr, J. T.; Stoltz, B. M. *Org. Synth.* **2009**, *86*, 181–193.
(2) Ukai, T.; Kawazura, H.; Ishii, Y.; Bonnet, J. J.; Ibers, J. A. *J. Organomet. Chem.* **1974**, *65*, 253–266; (b) Fairlamb, I. J. S.; Kapdi, A. R.; Lee, A. F. *Org. Lett.* **2004**, *6*, 4435–4438.
(3) The epoxidizing conditions tested include: Oxone, magnesium monoperoxyphthalate hydrate (MMPP•$6H_2O$), *t*-BuOOH/SiO_2, *t*-BuOOH/$VO(acac)_2$, *m*-CPBA, *m*-CPBA/Jacobsen's catayst.
(4) A variety of conditions were found to be ineffective in the formation of the desired brominated product including: NaOH/Br_2/$CeCl_3$, $Ca(OH)_2$/Br_2, Selectfluor/KBr, LiBr/$NaIO_4$/AcOH.
(5) Repetition of this procedure provided cyclopentenone **17** in yields ranging from 0 to 82%.
(6) It was observed that slow addition via addition funnel of the bright yellow, transparent NaOBr solution into the reaction mixture resulted in clouding and miscoloration of solution remaining in the funnel. We believed that the vapors in the headspace of the reaction vessel were facilitating this apparent decomposition and lower in the yield in the process.
(7) Although storage of this intermediate in a benzene matrix is possible for extended periods, purification by silica gel chromatography results in moderate decomposition.

Experimental Spectra

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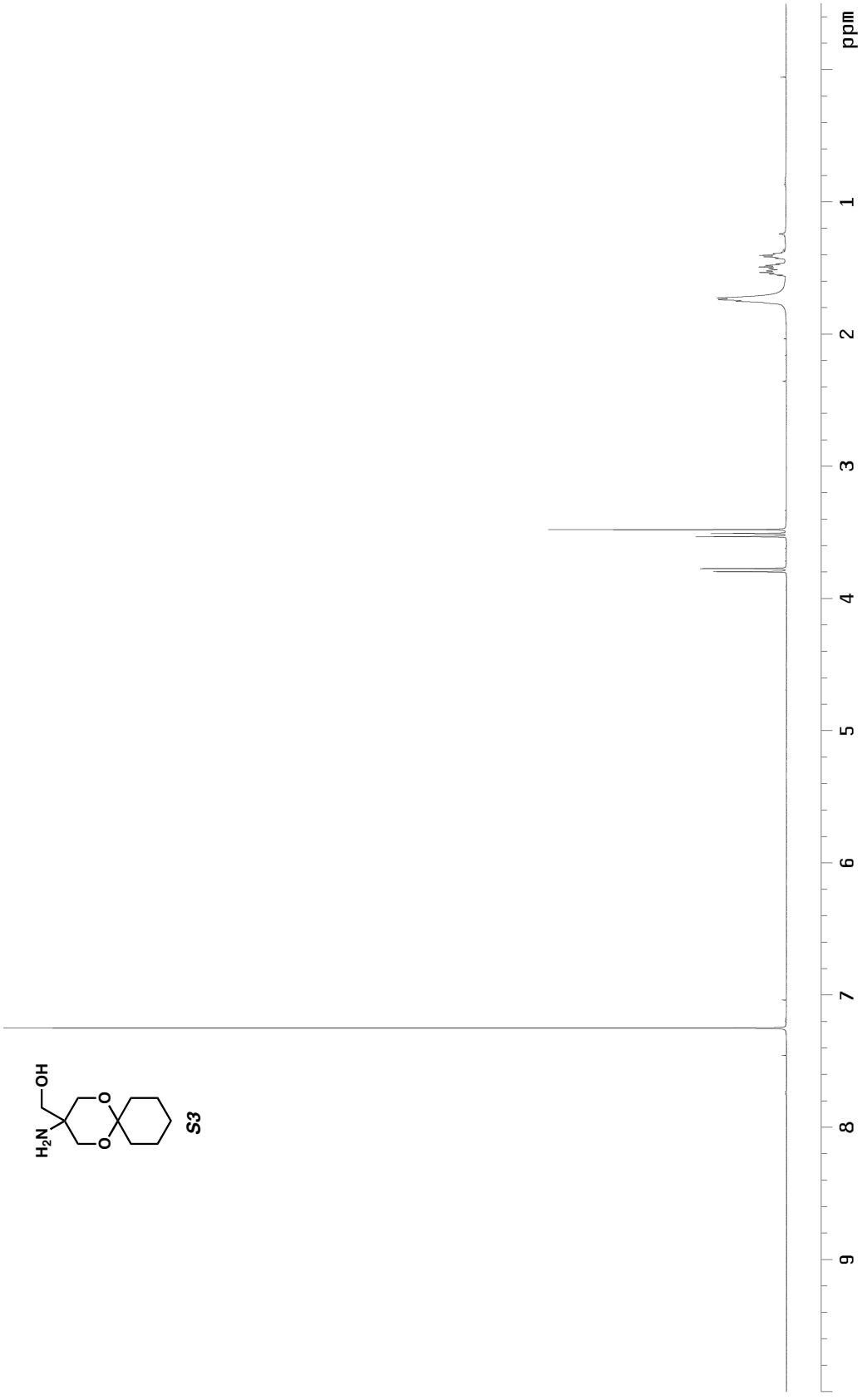
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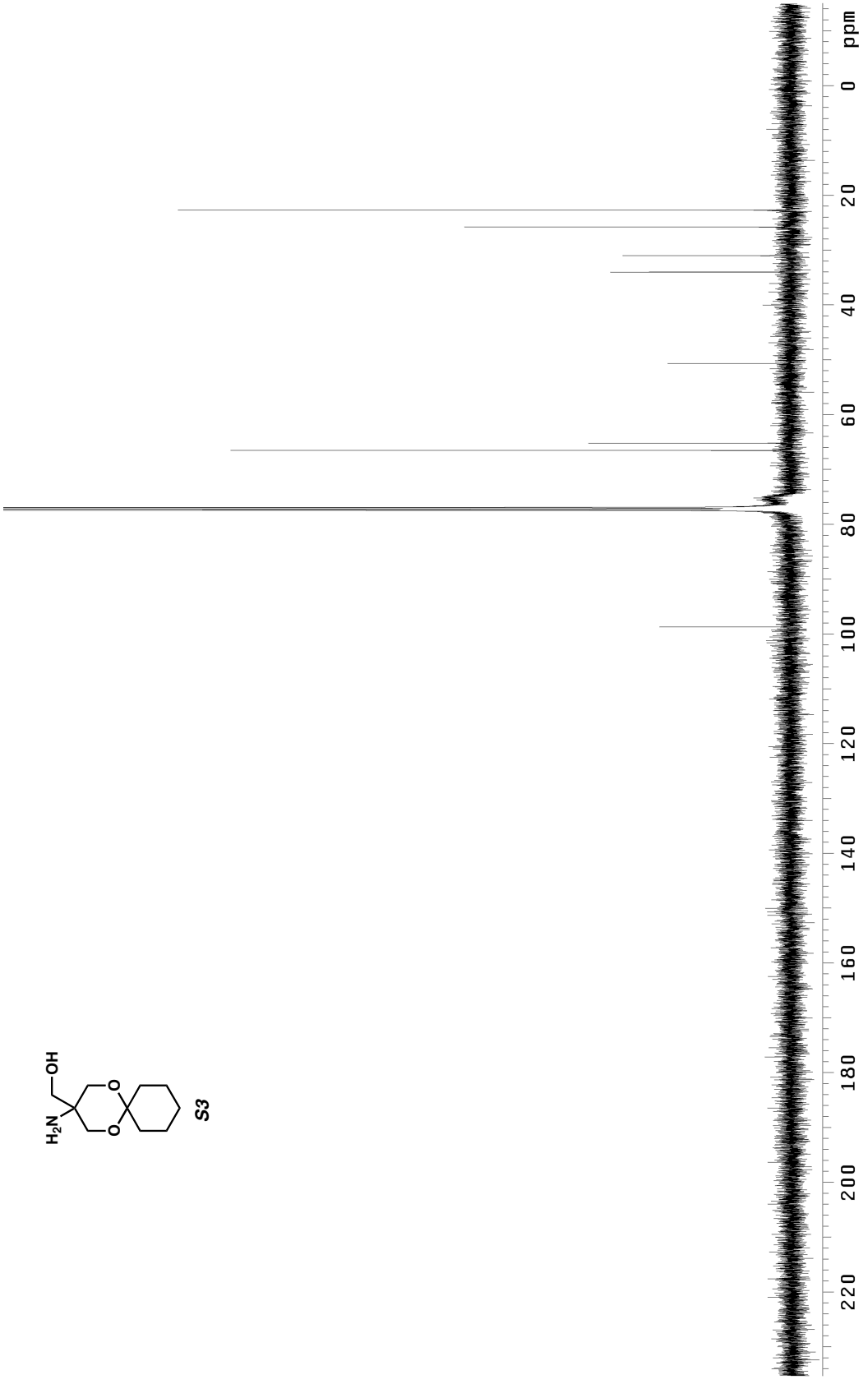
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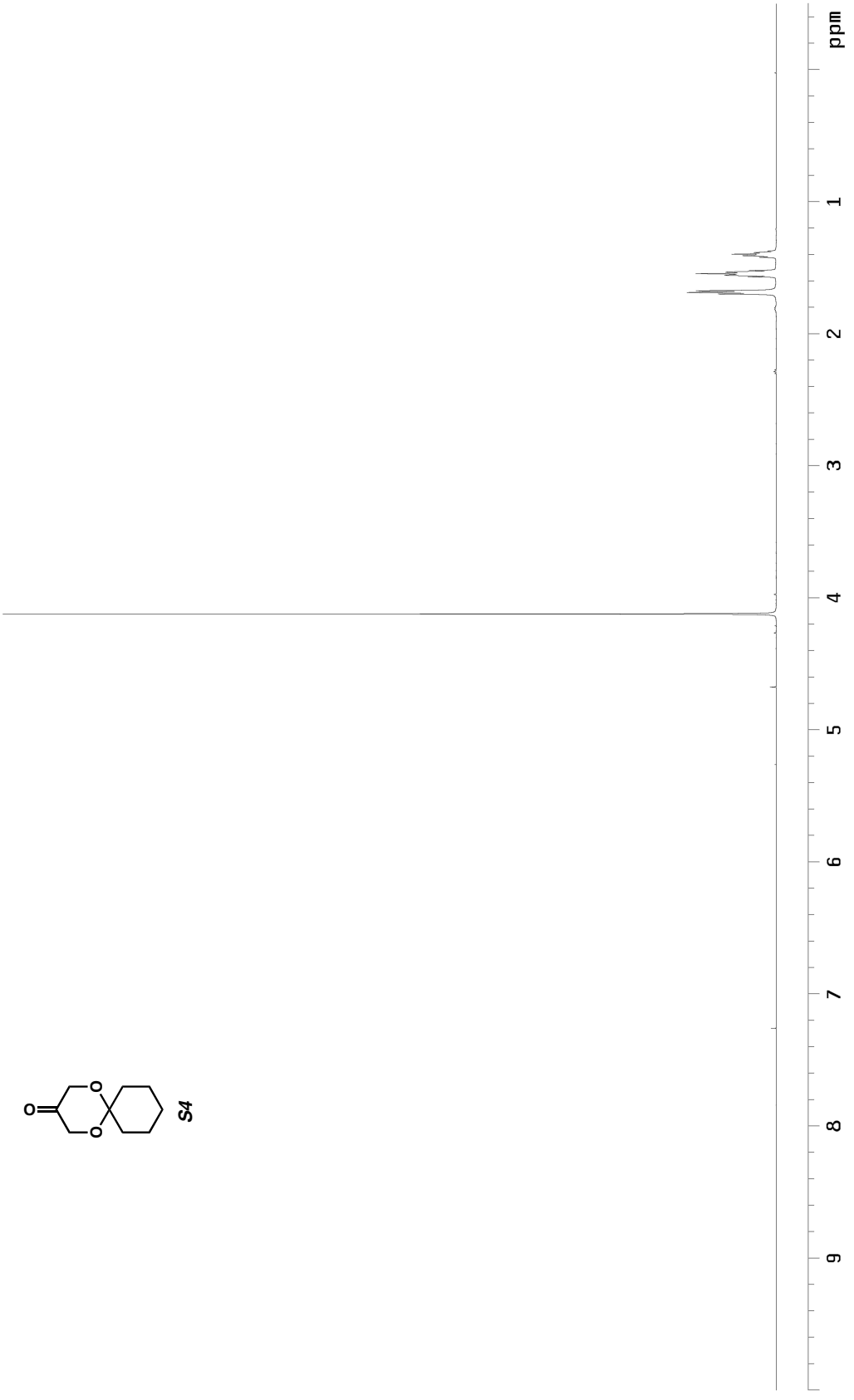

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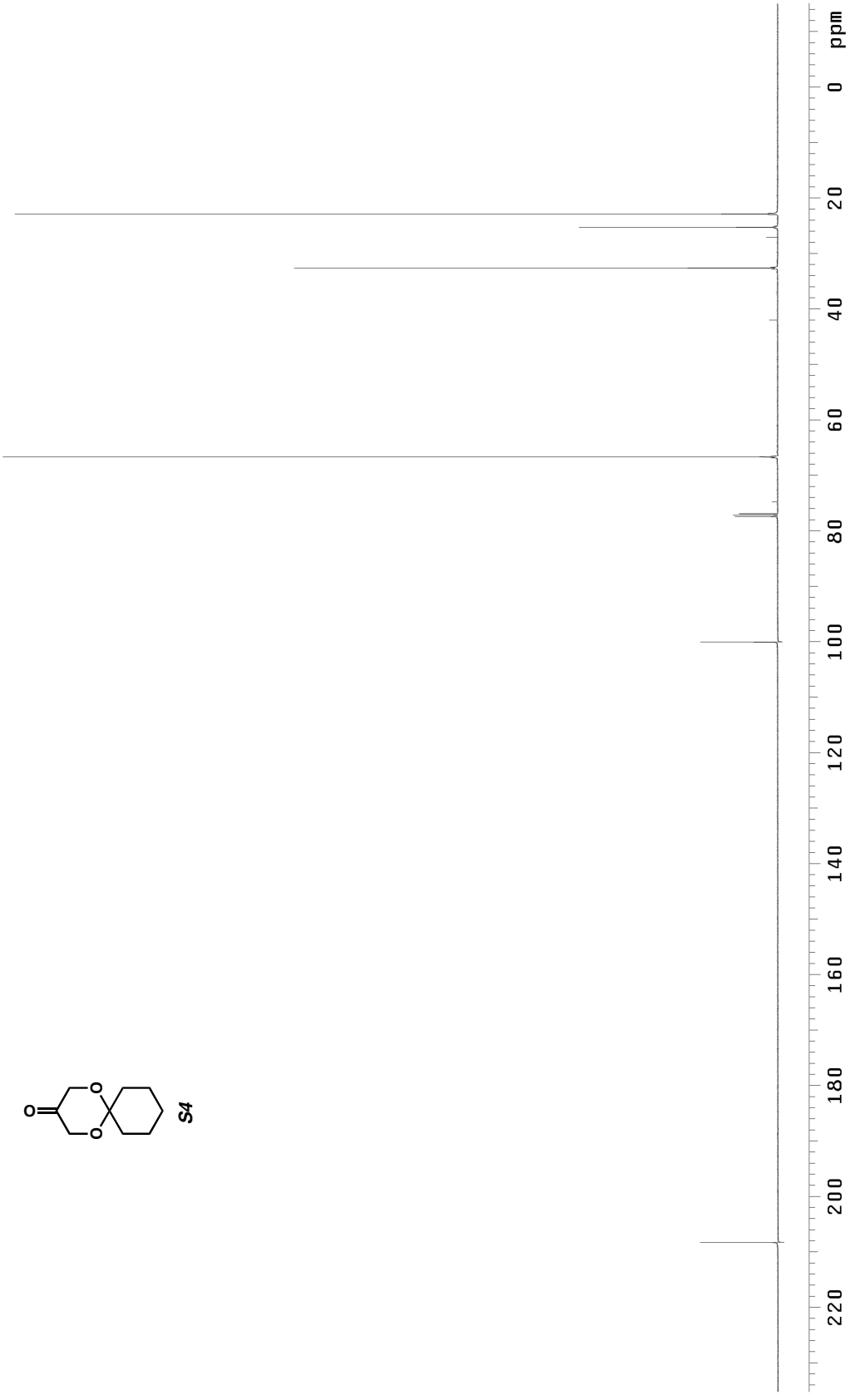

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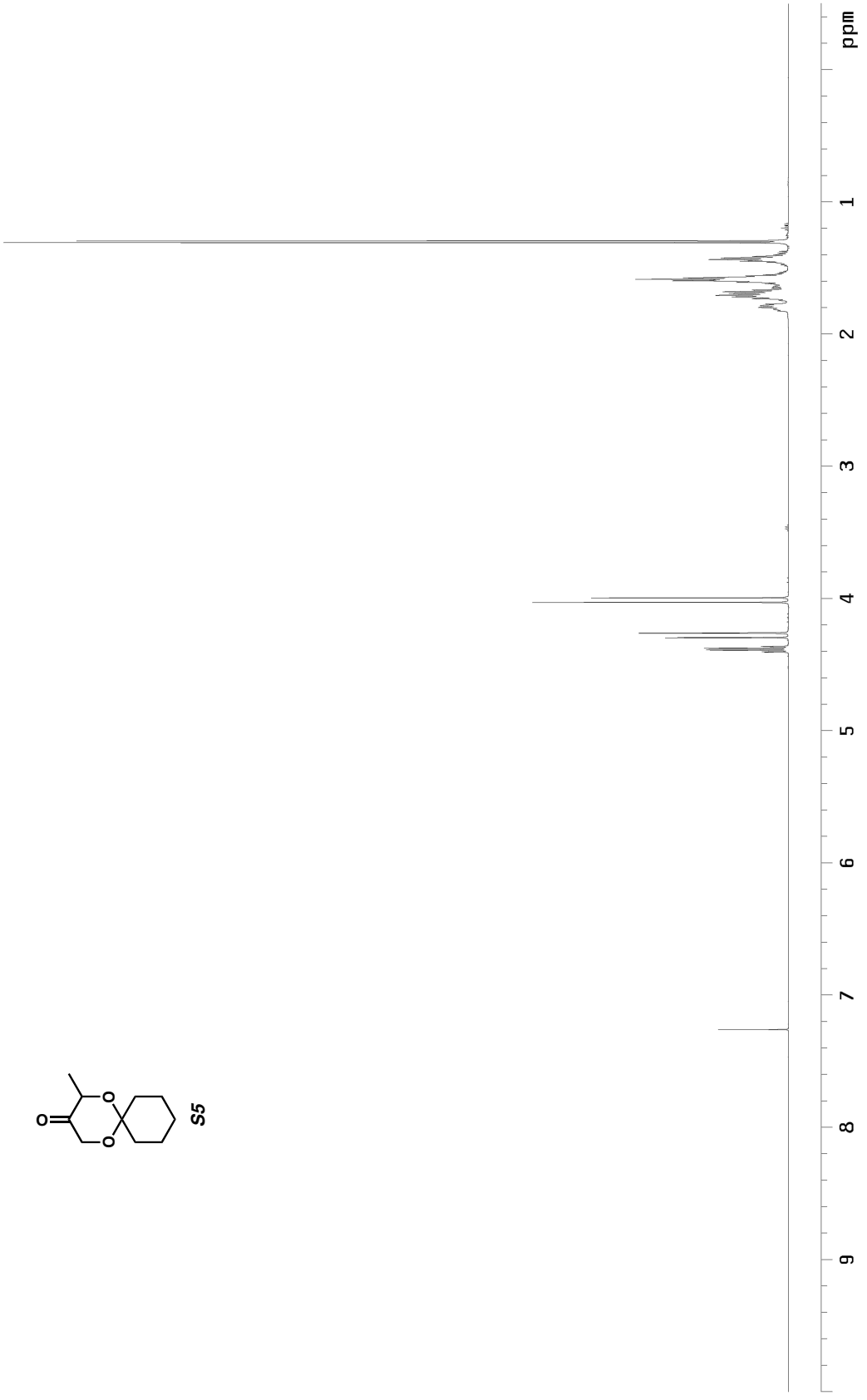
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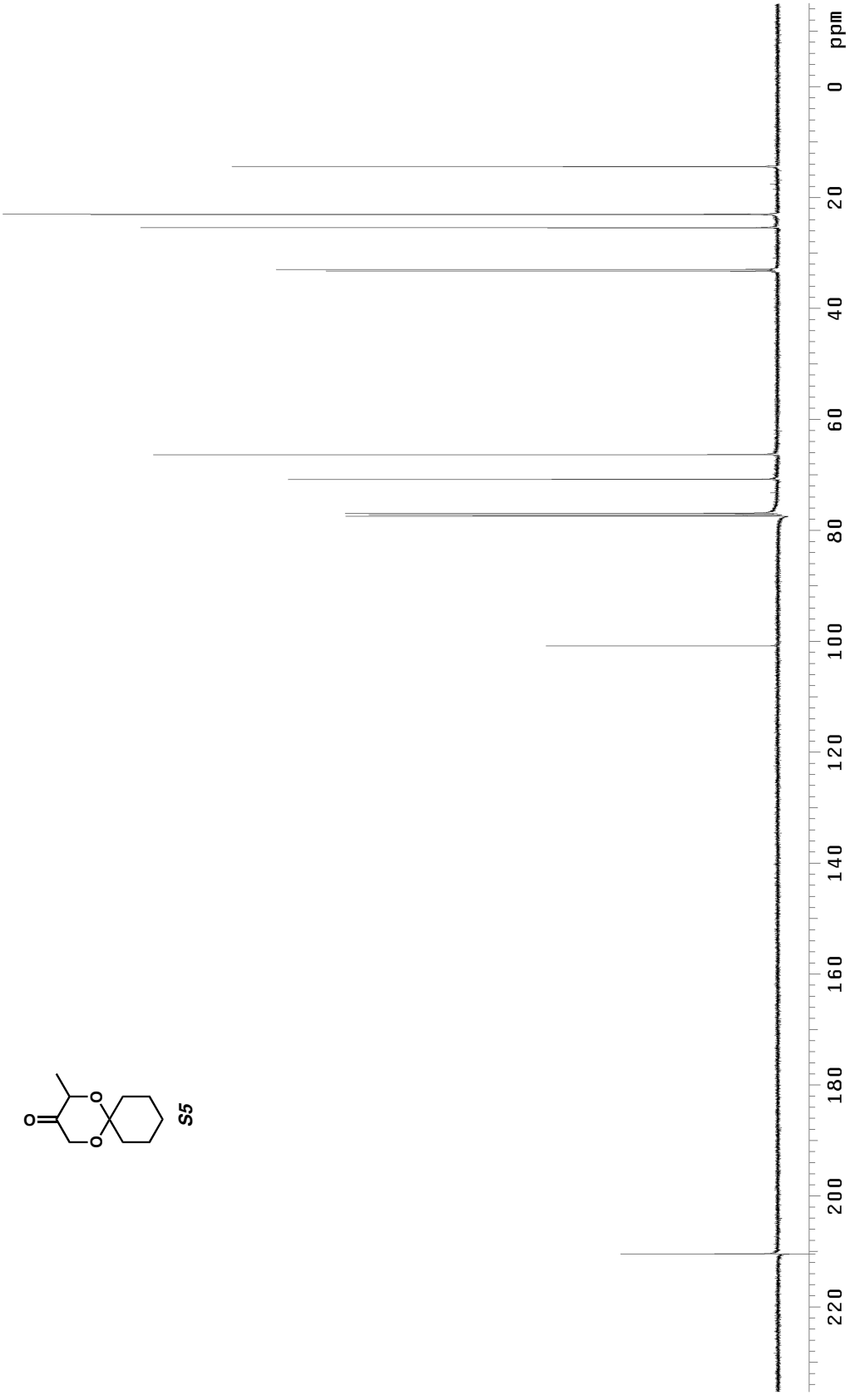
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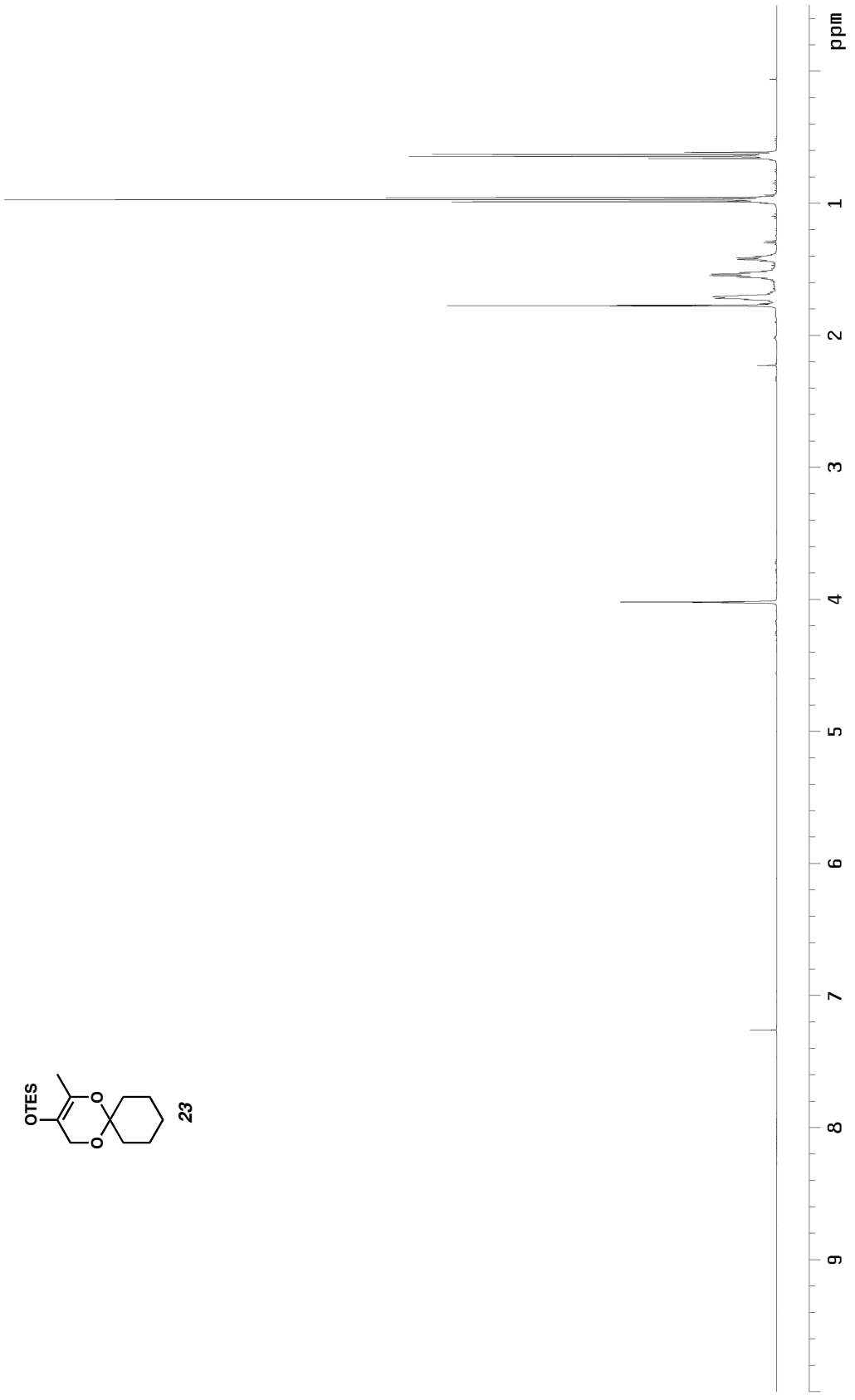
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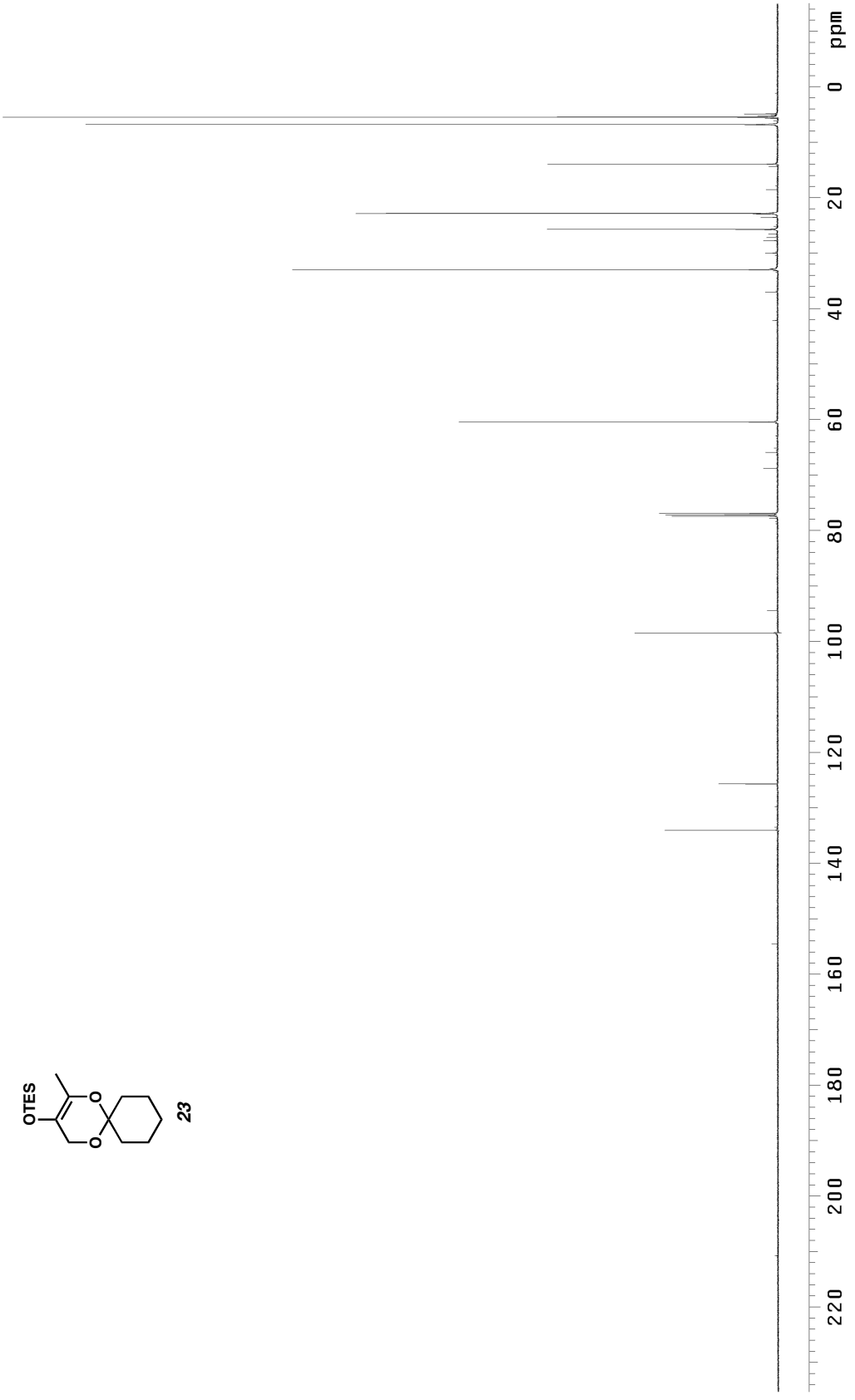
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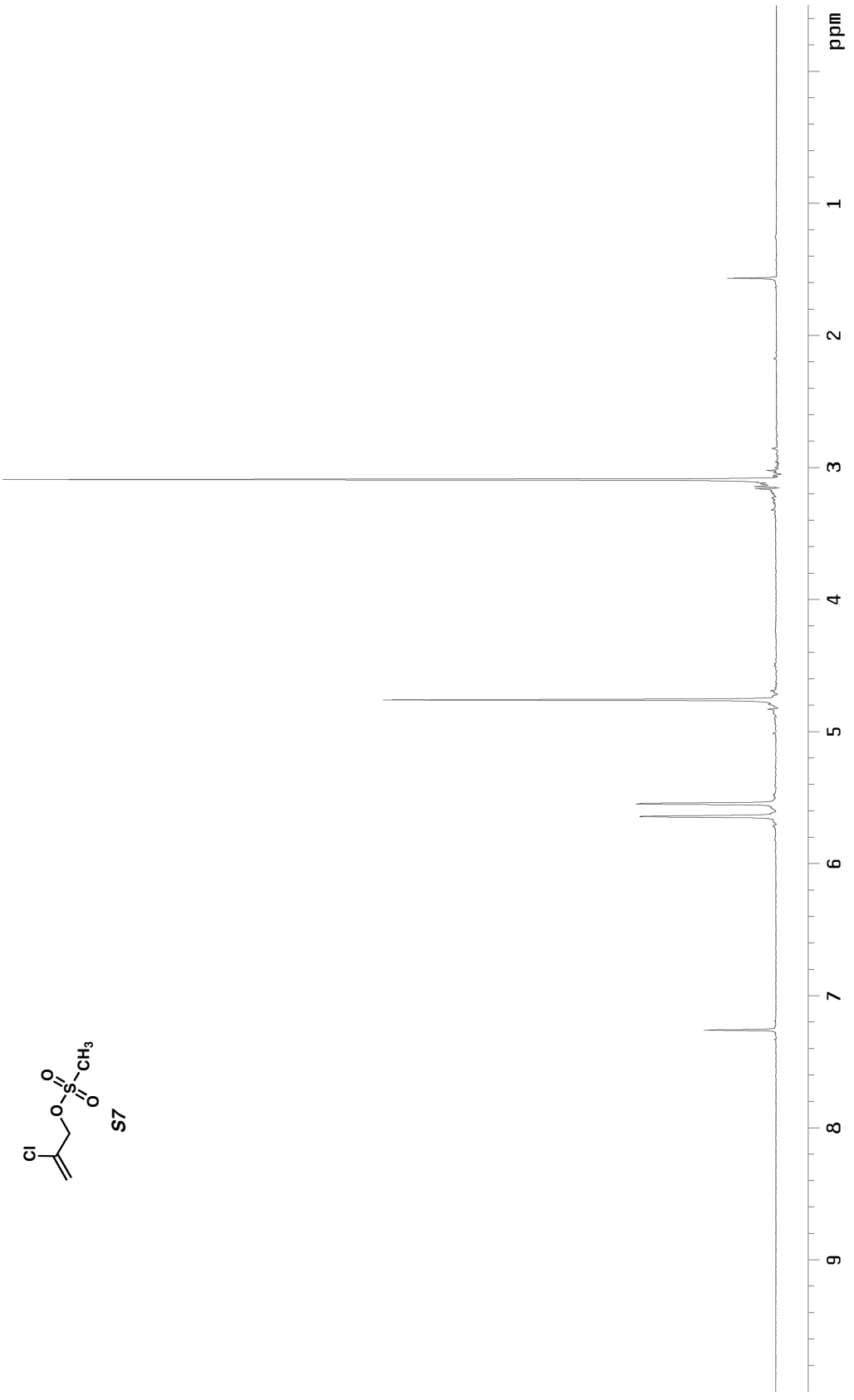
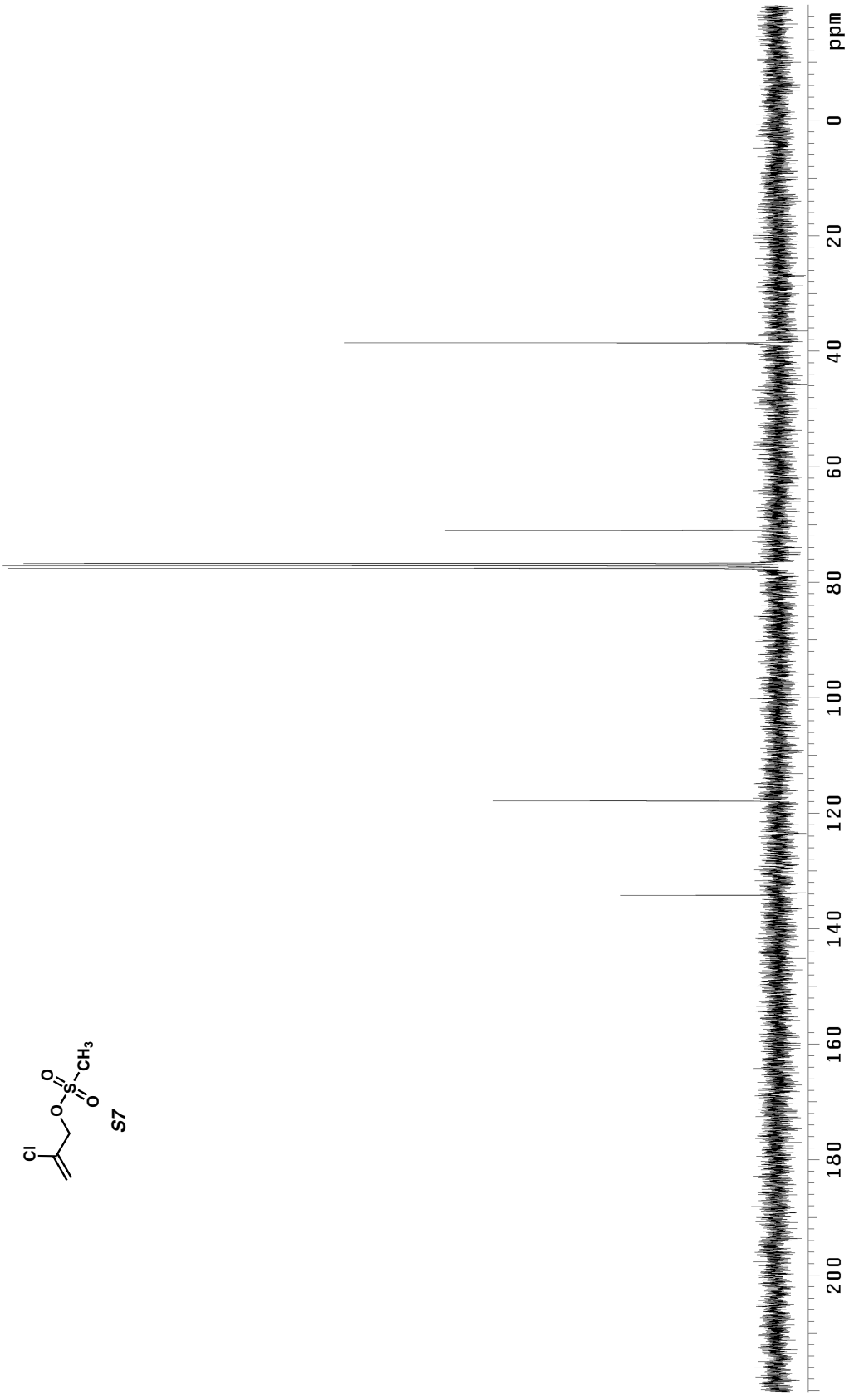


S7



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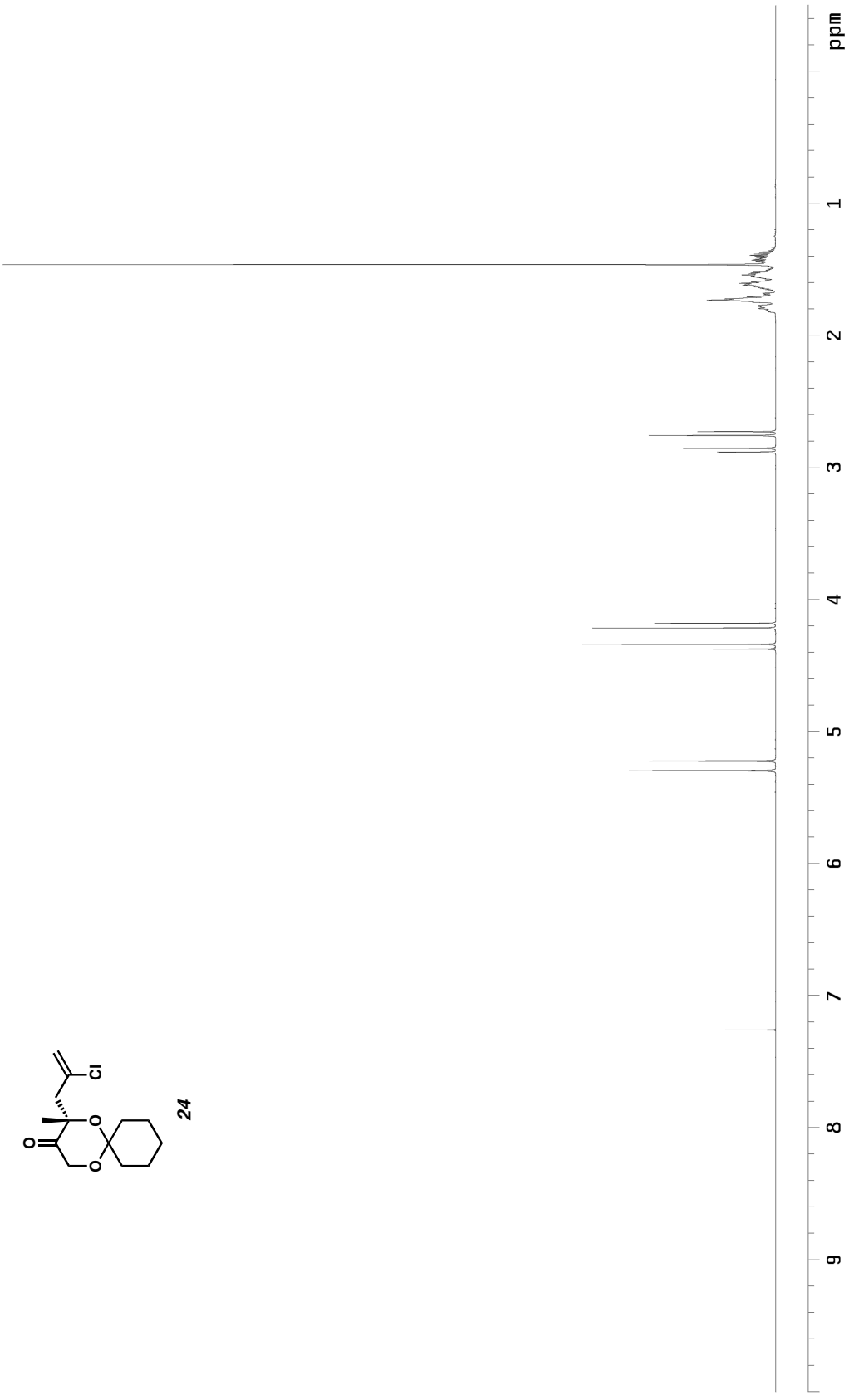
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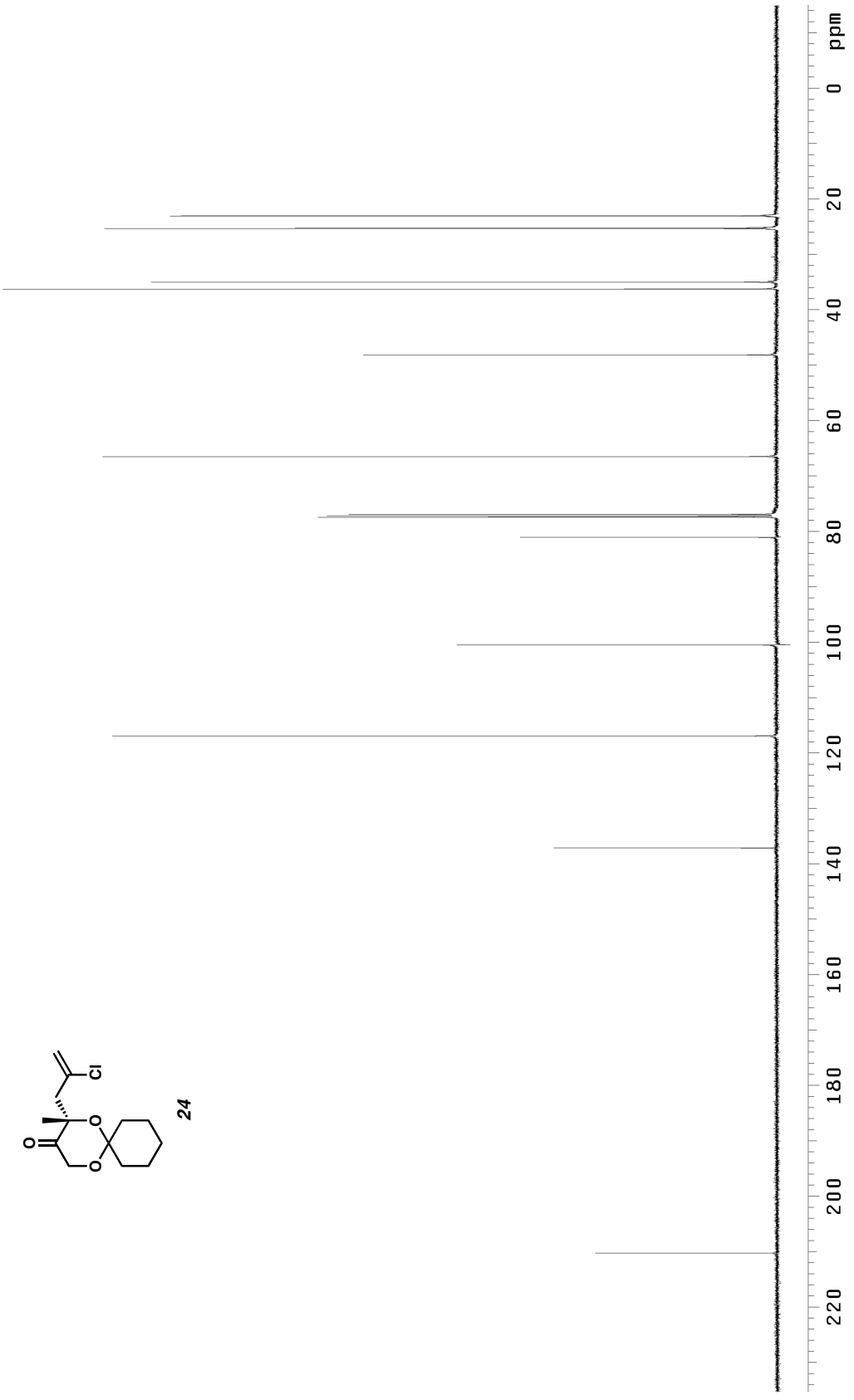
3
4
5
6
7
8
9
Cl
O
O
O
24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140
160
180
200
220
Cl
O
O
O
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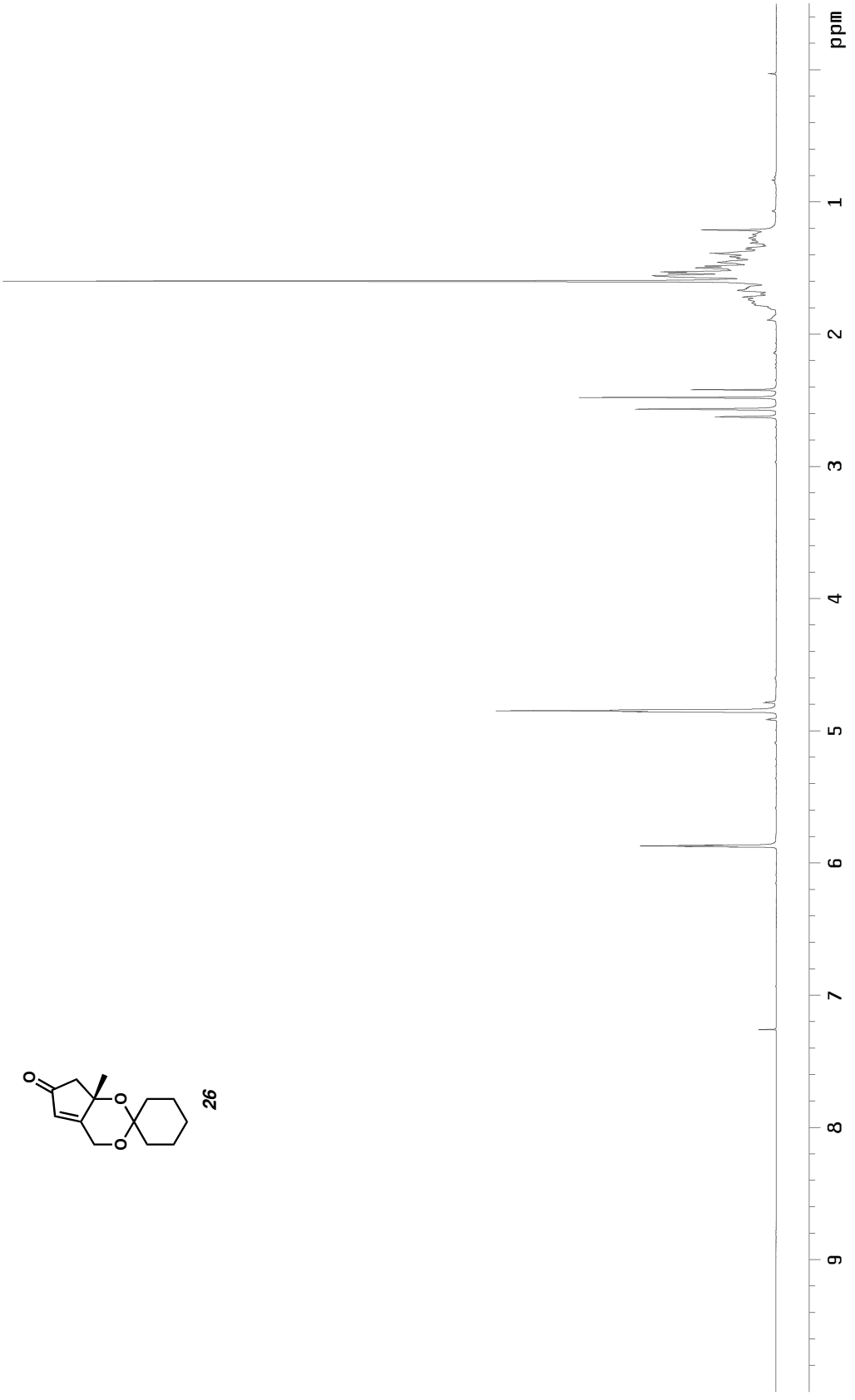

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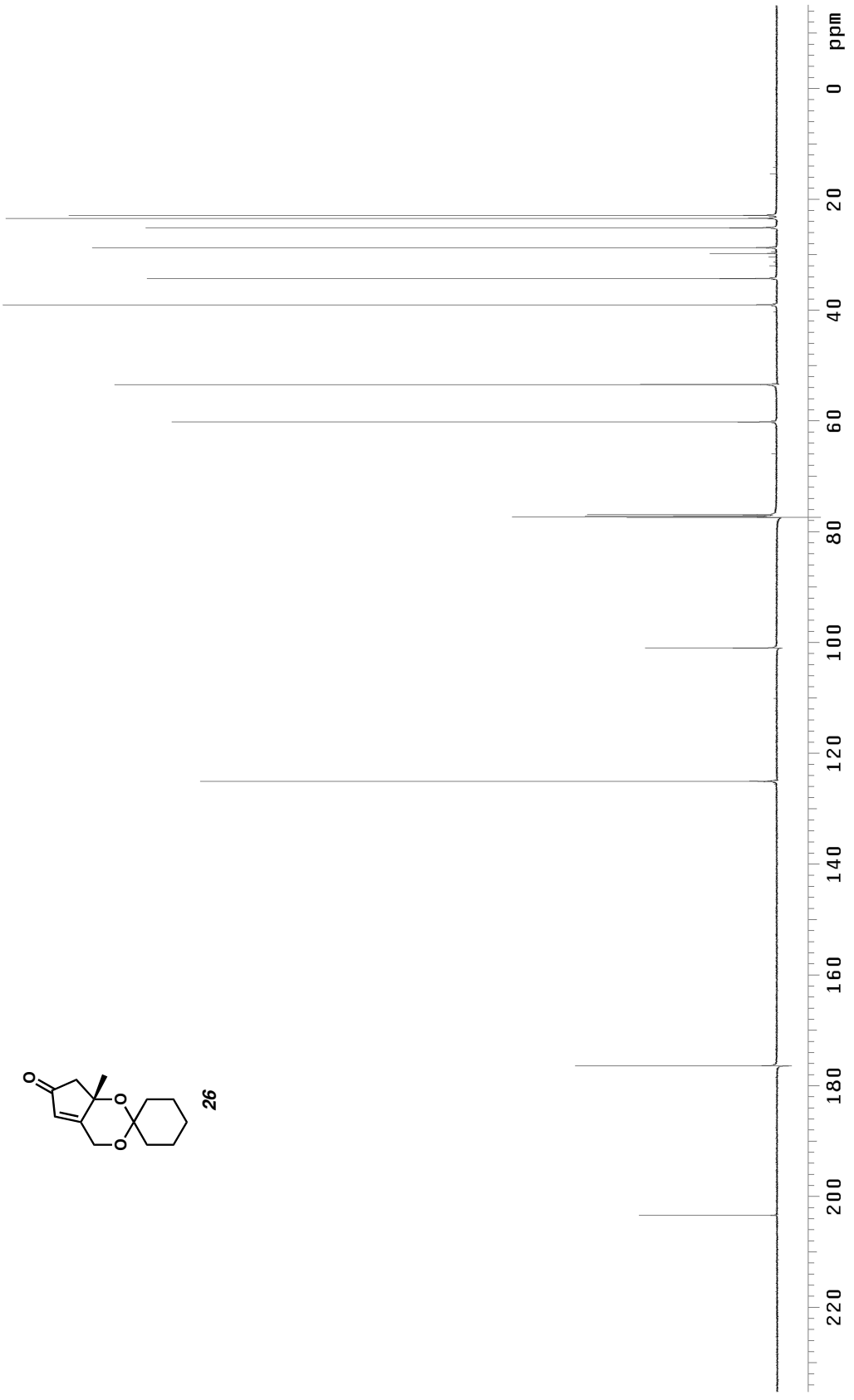

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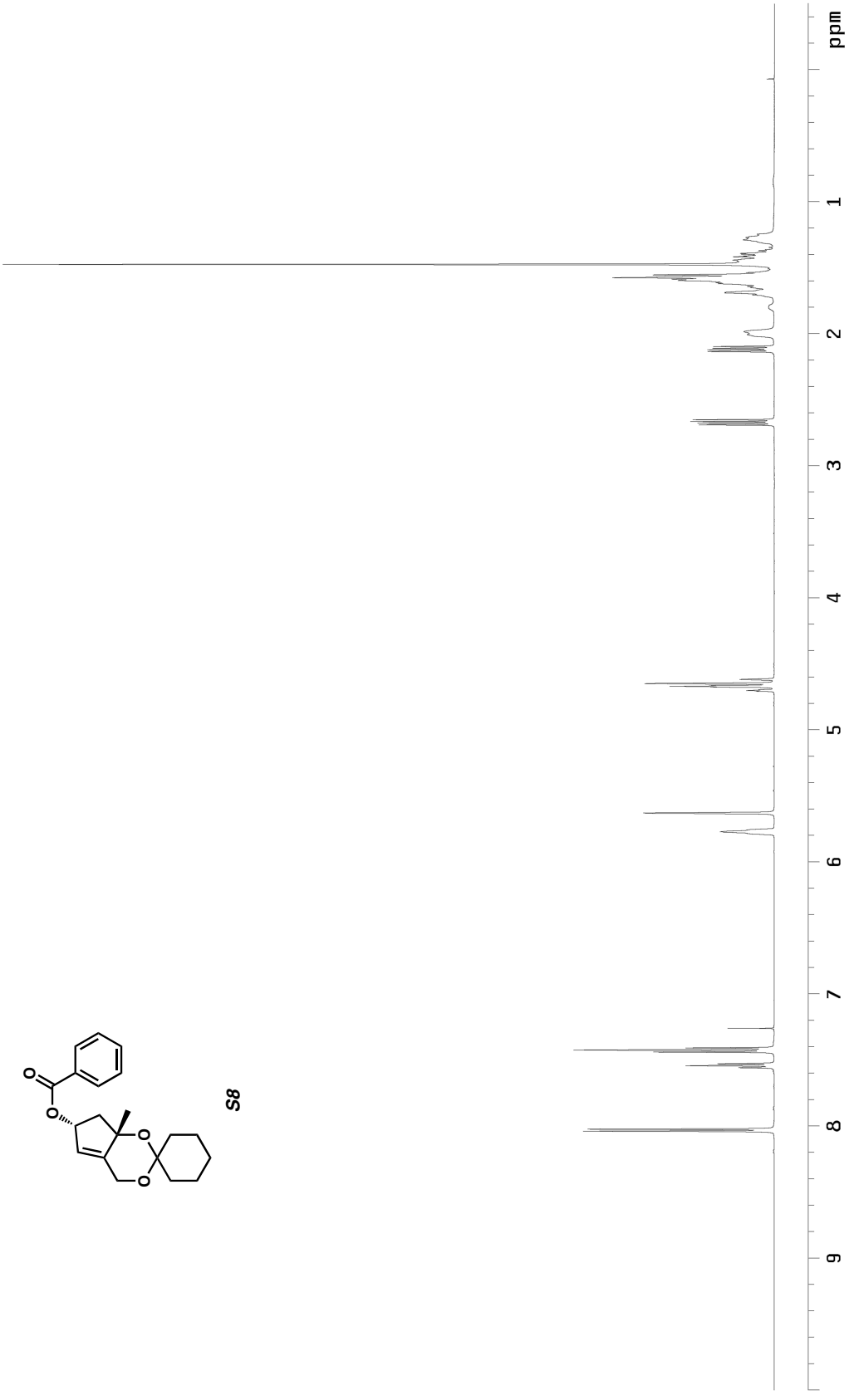

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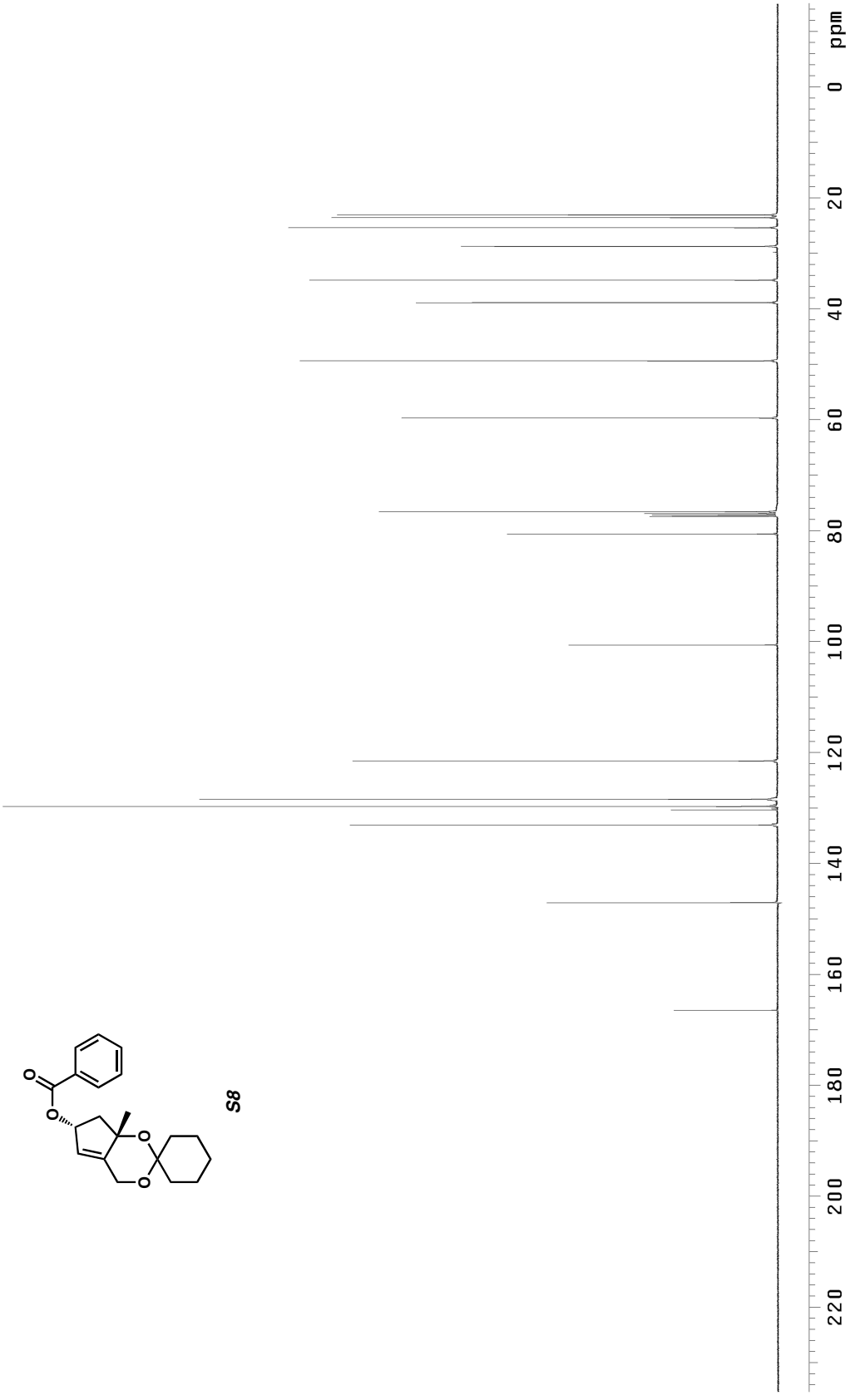

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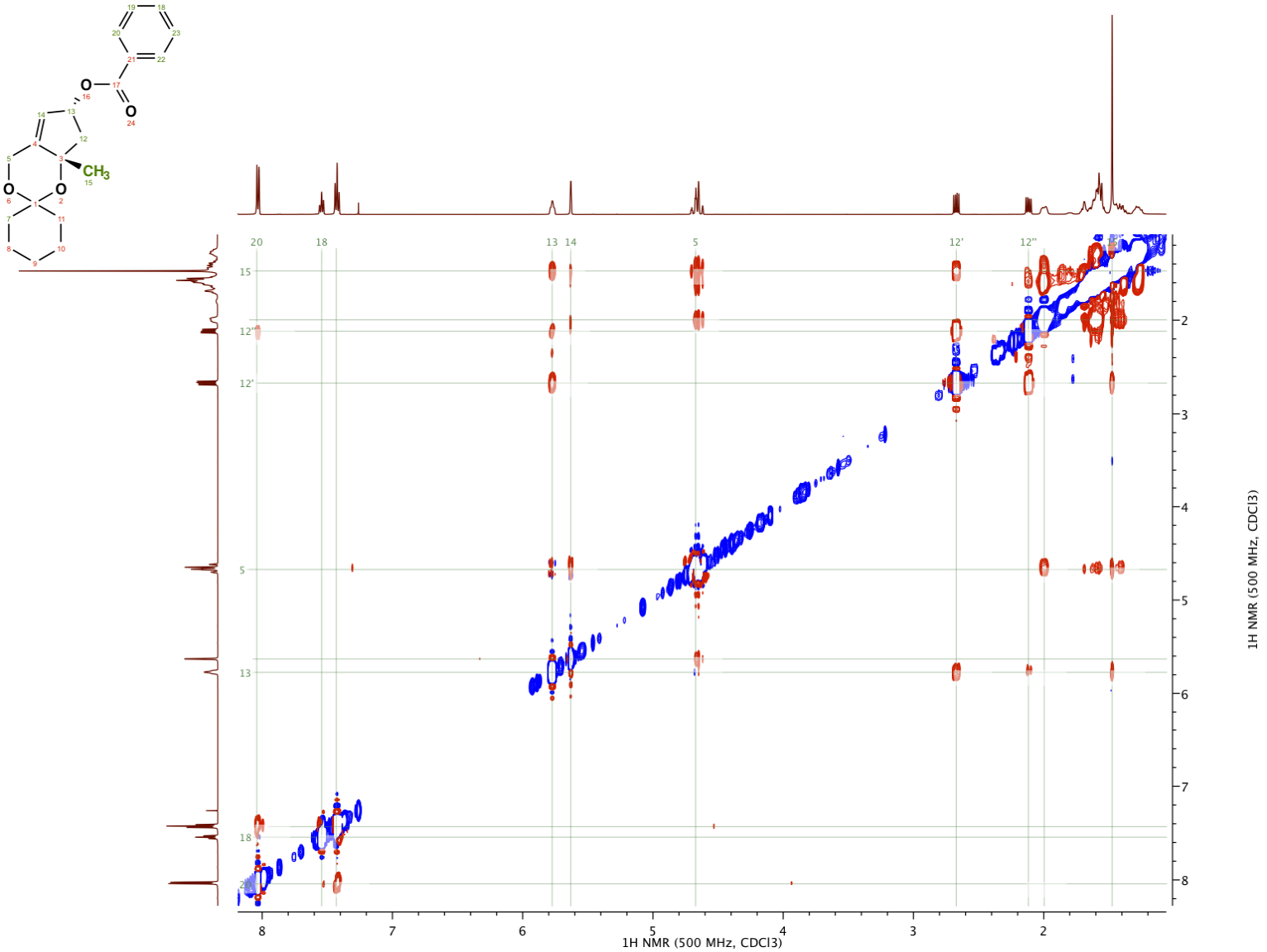
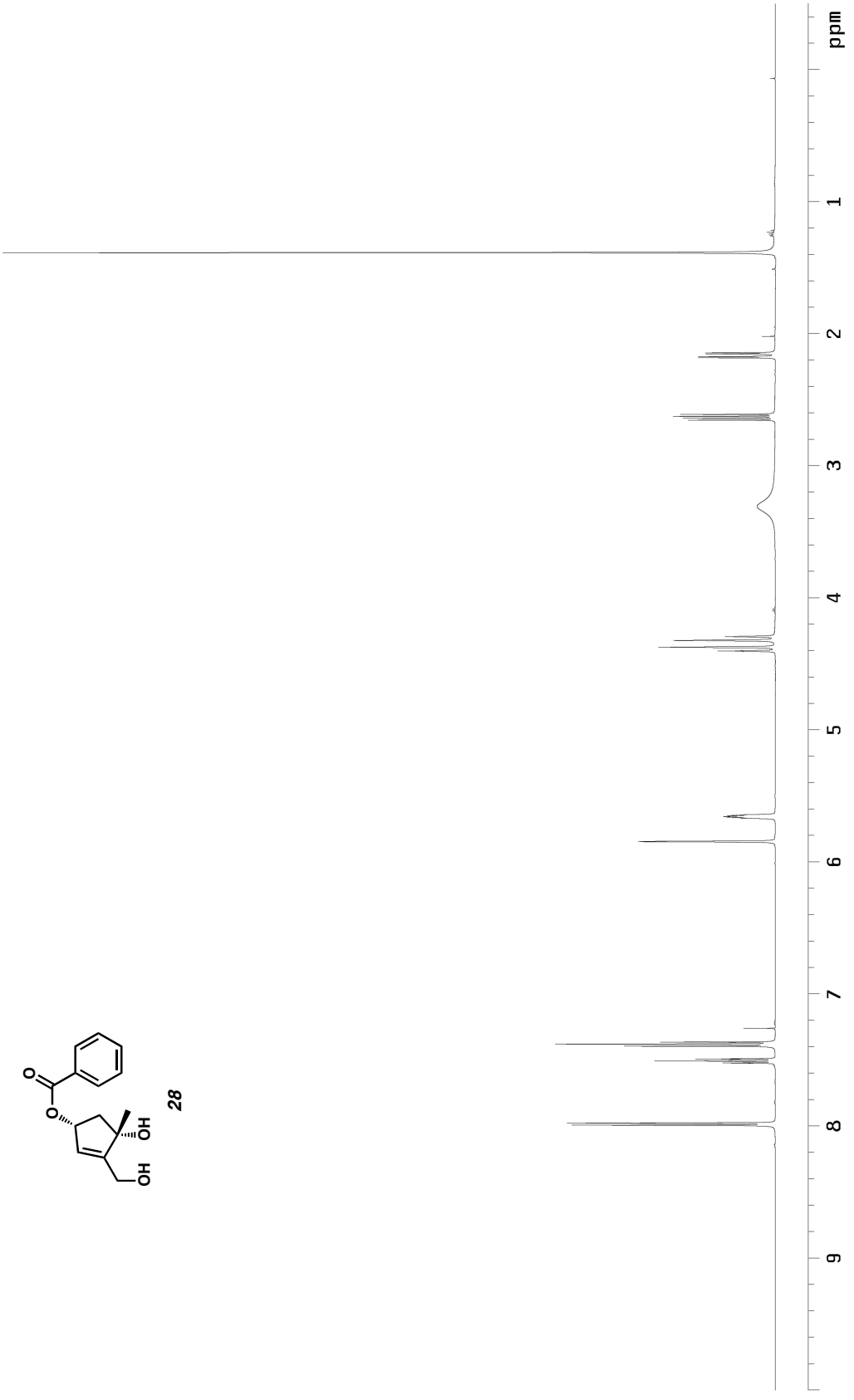
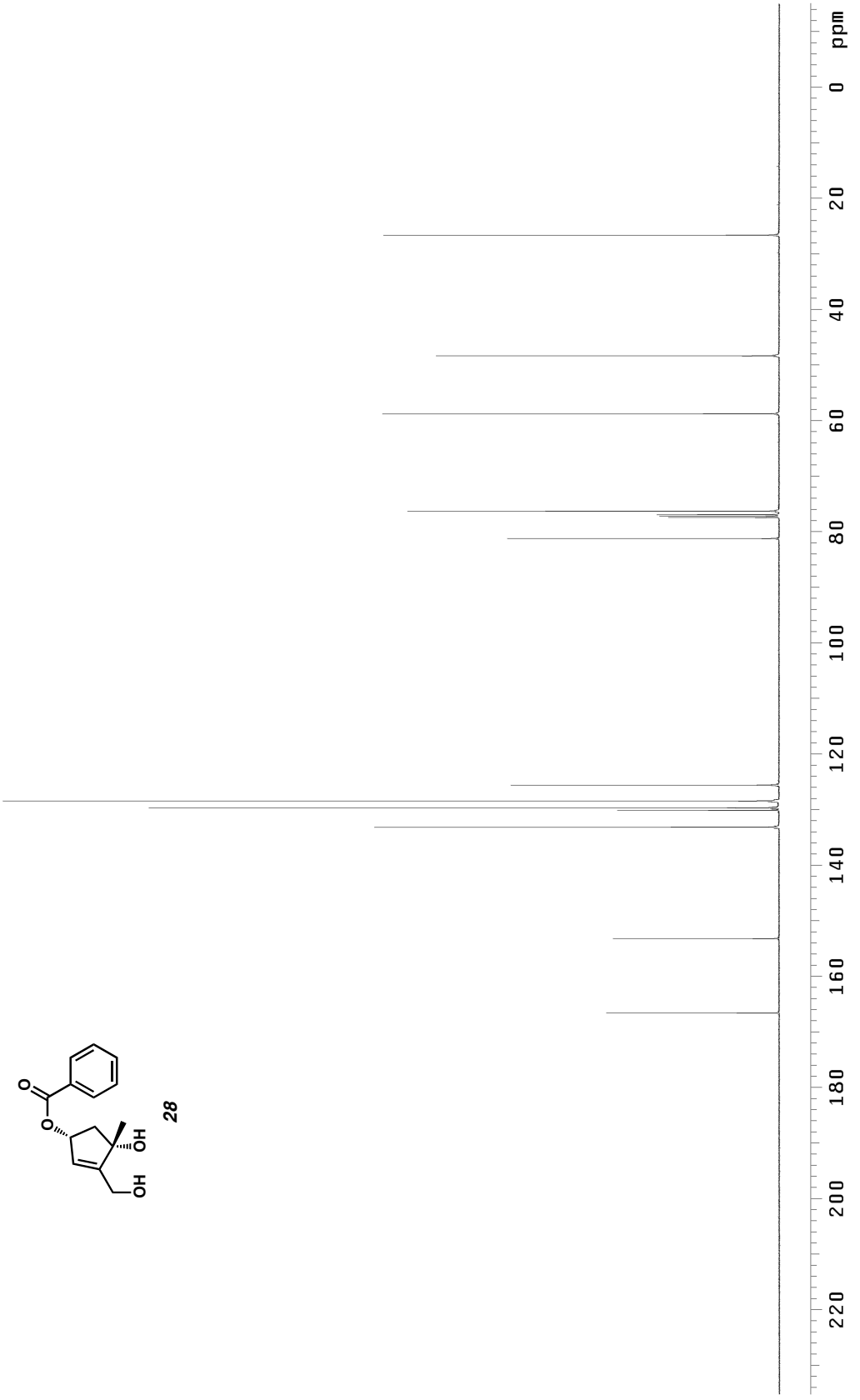

20
18
13 14
5
12'
12''
15
12''
12'
5
13
18
20
8
7
6
5
4
3
2
1H NMR (500 MHz, CDCl3)
2
3
4
5
6
7
8
1H NMR (500 MHz, CDCl3)



28



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