Ni(II) Salts and 2-Propanol Effect Catalytic Reductive Coupling of Epoxides and Alkynes

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Supporting Information

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I. General Experimental

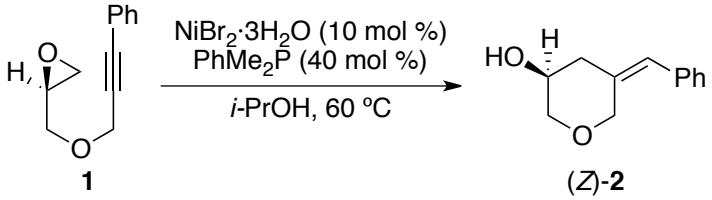
All reactions were performed under an atmosphere of argon under anhydrous conditions, unless otherwise noted. Dichloromethane, tetrahydrofuran (THF), Et_2O, and triethylamine were purified via an SG Water USA solvent column system. Solvents used for Ni-catalyzed reductive coupling reactions were sparged with argon prior to use. Unless otherwise noted, all reagents were commercially obtained and used without further purification. Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F_{254} plates, visualizing with a UV lamp (254 nm), $KMnO_4$, or *p*-anisaldehyde. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on Silicycle silica gel (230–400 mesh).

^{1}H NMR and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded at ambient temperature at 600 MHz and 150 MHz, respectively, using a Bruker AVANCE-600 spectrometer, 400 MHz and 125 MHz, respectively, using a Bruker AVANCE-400 spectrometer, or 500 MHz and 125 MHz, respectively, using a

Varian Inova-500 spectrometer. The ^{1}H NMR data are reported as follows: chemical shift in parts per million (ppm) from internal tetramethylsilane (0.00 ppm) on the δ scale, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in hertz (Hz), and integration (H). Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of CDCl3 (77.2 ppm).

Infrared (IR) spectra were recorded on a Perkin-Elmer Model 2000 FT-IR. High resolution mass spectra (HR-MS) were acquired on a Bruker Daltronics APEXIV 4.7 Tesla Fourier Transform Ion Cyclotron Resonance Mass Spectrometer by Li Li of the Massachusetts Institute of Technology Department of Chemistry Instrumentation Facility. Optical rotations were measured using a Jasco Model 1010 digital polarimeter at 589 nm and calculated using the formula: $[\alpha]_D = \alpha_{obs}/(l(c/1000))$, where c = (g of substrate/100 mL of solvent) and l = 1 dm. Enantiomeric excess was determined using analytical gas chromatography (GC) performed on a Varian CP-3800 equipped with a flame ionization detector. A fused silica capillary column (30 m x 0.25 mm x 0.12 μm) wall coated with B-DM (Astec CHIRALDEX™ B-DM) was used with hydrogen as the carrier gas (1 mL/min). Method of chromatography is as follows: start temperature = 100 ºC; ramp = 2 ºC/min; final temperature = 180 ºC. Melting points are reported uncorrected.

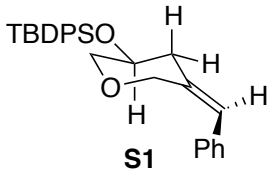
II. Representative procedure for the Ni-catalyzed reductive coupling of alkynes and epoxides



1 (*Z*)-**2**

(*S*,*Z*)-5-benzylidenetetrahydro-2*H*-pyran-3-ol (2). To a 20 mL vial equipped with a magnetic stir bar was added $NiBr_2 \cdot 3H_2O$ (14.5 mg, 0.0531 mmol), which was then closed with a screw cap containing a teflon-lined septum and purged with argon for 5 minutes. At room temperature, $PhMe_2P$ (30.2 μL, 0.212 mmol) was added followed by *i*-PrOH (8.6 mL). The reaction mixture was stirred vigorously for 10 minutes until a

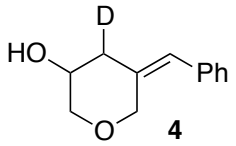
homogeneous dark green solution was obtained. To the reaction mixture was then added a solution of epoxide **1** (0.101 mg, 0.531 mmol) in *i*-PrOH (2 mL). The argon source was removed and the sealed vial placed into a pre-heated 60 ºC oil bath with stirring. After consumption of the starting material (3 h, as determined by TLC analysis) the deep orange solution was cooled to room temperature and concentrated *in vacuo*. The crude reaction mixture was diluted with Et_2O (5 mL) and filtered through a plug of silica gel (eluting with Et_2O). The crude reaction mixture was concentrated *in vacuo* (^{1}H NMR spectroscopy analysis of the crude reaction mixture indicated a 90:10 (*Z*/*E*) mixture of olefin isomers) and the resulting oil was purified by flash chromatography (30-45% EtOAc/hexanes) to afford the title compound as a colorless oil (0.83 mg, 82% yield): mp 53–56 ºC; $[\alpha]^{24}_D$ +37 (*c* 0.54, $CHCl_3$, 88% ee); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (m, 2H), 7.24 (m, 1H), 7.13 (m, 2H), 6.47 (s, 1H), 4.50 (d, *J* = 12.8 Hz, 1H), 4.17 (d, *J* = 12.7 Hz, 1H), 3.93 (m, 1H), 3.77 (m, 1H), 3.70 (m, 1H), 2.73 (d, *J* = 13.8 Hz, 1H), 2.48 (dd, *J* = 13.8, 4.4 Hz, 1H), 2.38 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.4, 133.3, 129.0, 128.7, 128.4, 127.1, 72.5, 67.4, 67.3, 41.6; IR (thin film) 3313, 3022, 2946, 2839 cm^{-1}; HRMS (ESI) *m* / *z* calcd for $C_{12}H_{15}O_2$ $(M + H)^+$ 189.0910, found 189.0914.



S1

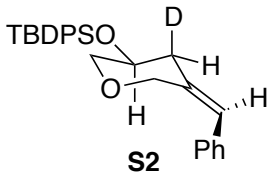
(*S*,*Z*)-((5-benzylidenetetrahydro-2*H*-pyran-3-yl)oxy)(*tert*-butyl)diphenylsilane (S1). To a solution of alcohol **2** (20 mg, 0.11 mmol) in DMF (0.1 mL) was added imidazole (18 mg, 0.26 mmol) and *tert*-butylchlorodiphenylsilane (32 μL, 0.12 mmol). After 42 h, saturated aqueous ammonium chloride (2 mL) was added and the aqueous layer was extracted with EtOAc (3 x 2 mL). The combined organic layers were washed with H_2O (3 x 2 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (2% Et_2O/hexanes) to afford the title compound as a colorless oil (42 mg, 93% yield).

The spectral data correlate with the previously reported data for the title compound:[1] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (m, 4H), 7.40 (m, 6H), 7.29 (m, 2H), 7.21 (m, 1H), 7.07 (m, 2H), 6.24 (s, 1H), 4.45 (d, *J* = 12.8 Hz, 1H), 3.97 (d, *J* = 12.8 Hz, 1H), 3.87 (tt, *J* = 8.7, 4.4 Hz, 1H), 3.78 (dd, *J* = 10.9, 3.9 Hz, 1H), 3.37 (dd, *J* = 10.7, 8.6 Hz, 1H), 2.59 (dd, *J* = 13.3, 4.4 Hz, 1H), 2.41 (dd, *J* = 13.0, 9.3 Hz, 1H), 1.08 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.8, 135.94, 135.87, 135.0, 134.2, 134.0, 129.97, 129.95, 129.0, 128.3, 127.87, 127.84, 126.9, 126.8, 72.8, 68.9, 66.8, 43.1, 27.1, 19.4.



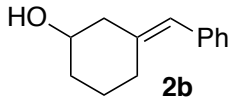
4

[*d*1]-(*Z*)-5-benzylidenetetrahydro-2*H*-pyran-3-ol (4). The representative procedure was followed using $NiBr_2 \cdot 3H_2O$ (2.9 mg, 0.011 mmol), $PhMe_2P$ (6.0 μL, 0.042 mmol), and epoxide **3** (20.4 mg, 0.108 mmol). ^{1}H NMR spectroscopy analysis of the crude reaction mixture indicated an 82:18 (*Z*/*E*) mixture of olefin isomers. The crude product was purified by flash chromatography (30-45% EtOAc/hexanes) to afford the title compound (86:14 mixture of olefin isomers) as a colorless oil (16.8 mg, 81% yield). The spectral data correlate to those obtained for protio alcohol **2**: ^{1}H NMR (600 MHz, $CDCl_3$, major olefin isomer) δ 7.33 (m, 2H), 7.25 (m, 1H), 7.13 (m, 2H), 6.47 (s, 1H), 4.53 (dd, *J* = 12.8, 5.2 Hz, 1H), 4.16 (m, 1H), 3.94 (m, 1H), 3.77 (m, 1H), 3.72 (m, 1H), 2.72 (m, 0.75H), 2.49 (m, 0.17H), 2.27 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$, major olefin isomer) δ 136.4, 133.3, 129.0, 128.8, 128.4, 127.2, 72.5, 67.4, 67.3, 41.2 (t, *J* = 20.1 Hz); IR (thin film) 3396, 3024, 2959, 2841, 1446, 1083 cm^{-1}; HRMS (ESI) *m* / *z* calcd for $C_{12}H_{14}DO_2$ $(M + H)^+$ 192.1129, found 192.1125.



S2

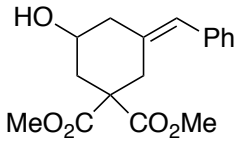
[*d*1]-(*Z*)-((5-benzylidenetetrahydro-2*H*-pyran-3-yl)oxy)(*tert*-butyl)diphenylsilane (S2). To a solution of [*d*1]-alcohol **4** (17 mg, 0.086 mmol) in DMF (0.1 mL) was added imidazole (15 mg, 0.22 mmol) and *tert*-butylchlorodiphenylsilane (25 μL, 0.095 mmol). After 42 h, saturated aqueous ammonium chloride (2 mL) was added and the aqueous layer was extracted with EtOAc (3 x 2 mL). The combined organic layers were washed with H_2O (3 x 2 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (2% Et_2O/hexanes) to afford the title compound as a colorless oil (33 mg, 88% yield). The spectral data correlate to those obtained for protio **S1**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 4H), 7.40 (m, 6H), 7.29 (m, 2H), 7.20 (m, 1H), 7.07 (m, 2H), 6.24 (s, 1H), 4.45 (d, *J* = 12.8 Hz, 1H), 3.98 (d, *J* = 13.0 Hz, 1H), 3.87 (m, 1H), 3.78 (dd, *J* = 10.9, 4.0 Hz, 1H), 3.38 (dd, *J* = 10.9, 8.3 Hz, 1H), 2.57 (m, 0.86H), 2.40 (m, 0.18H), 1.08 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.9, 136.0, 135.9, 135.1, 134.2, 134.1, 129.97, 129.95, 129.0, 128.3, 127.88, 127.86, 126.9, 126.8, 72.8, 68.9, 66.8, 42.7 (t, *J* = 19.2 Hz), 27.1, 19.4.; IR (thin film) 3070, 2959, 2930, 2856, 1105 cm^{-1}; HRMS (ESI) *m* / *z* calcd for $C_{28}H_{32}DO_2Si$ $(M + H)^+$ 447.2573, found 447.2578.



2b

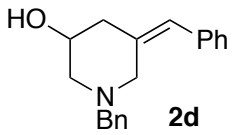
(*E*)-3-benzylidenecyclohexanol (2b). The representative procedure was followed using $NiBr_2 \cdot 3H_2O$ (4.9 mg, 0.018 mmol), $PhMe_2P$ (10.3 μL, 0.0724 mmol), and epoxide **1b** (33.8 mg, 0.181 mmol). ^{1}H NMR spectroscopy analysis of the crude reaction mixture indicated a 88:12 (*Z*/*E*) mixture of olefin isomers. The crude product was purified by flash chromatography (30-45% EtOAc/hexanes) to afford the title compound as a colorless oil (23.7

mg, 70% yield). The spectral data correlate with the previously reported data for the title compound:[1] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (m, 2H), 7.20 (m, 3H), 6.32 (s, 1H), 3.84 (tt, *J* = 8.1, 3.7 Hz, 1H), 2.62 (dd, *J* = 12.8, 3.6 Hz, 1H), 2.53 (dt, *J* = 13.5, 5.1 Hz, 1H), 2.24 (dd, *J* = 12.5, 8.6 Hz, 1H), 2.13 (ddd, *J* = 13.9, 10.1, 4.3 Hz, 1H), 1.94 (m, 1H), 1.77 (m, 1H), 1.72 (m, 1H), 1.55 (m, 1H), 1.40 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.4, 138.0, 129.0, 128.2, 126.3, 125.2, 70.6, 46.2, 34.9, 28.5, 23.7.



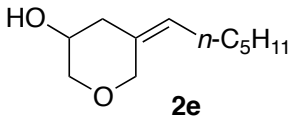
2c

(*E*)-dimethyl 3-benzylidene-5-hydroxycyclohexane-1,1-dicarboxylate (2c). The representative procedure was followed using $NiBr_2 \cdot 3H_2O$ (5.0 mg, 0.018 mmol), $PhMe_2P$ (10.4 μL, 0.0732 mmol), and epoxide **1c** (54.9 mg, 0.0.182 mmol). ^{1}H NMR spectroscopy analysis of the crude reaction mixture indicated a >95:5 (*Z*/*E*) mixture of olefin isomers. The crude product was purified by flash chromatography (30-45% EtOAc/hexanes) to afford the title compound as a colorless oil (42.0 mg, 76% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 2H), 7.23 (m, 3H), 6.46 (s, 1H), 4.07 (tq, *J* = 8.6, 4.5 Hz, 1H), 3.60 (s, 3H), 3.50 (s, 3H), 3.13 (d, *J* = 13.9 Hz, 1H), 2.74 (d, *J* = 14.0 Hz, 1H), 2.59 (dd, *J* = 13.0, 4.3 Hz, 1H), 2.48 (dd, *J* = 13.4, 4.0 Hz, 1H), 2.34 (d, *J* = 5.1 Hz, 1H), 2.28 (dd, *J* = 12.8, 8.5 Hz, 1H), 1.99 (dd, *J* = 13.4, 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 171.1, 137.4, 133.5, 128.8, 128.77, 128.3, 126.7, 67.4, 55.7, 53.0, 52.6, 44.9, 39.1, 33.3; IR (thin film) 3403, 3023, 2954, 2843, 1735, 1252 cm^{-1}; HRMS (ESI) *m* / *z* calcd for $C_{17}H_{21}O_5$ $(M + H)^+$ 305.1384, found 305.1400.



2d

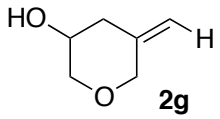
(*Z*)-1-benzyl-5-benzylidenepiperidin-3-ol (2d). The representative procedure was followed using $NiBr_2 \cdot 3H_2O$ (5.0 mg, 0.018 mmol), $PhMe_2P$ (10.4 μL, 0.0732 mmol), and *N*-benzyl-*N*-(oxiran-2-ylmethyl)-3-phenylprop-2-yn-1-amine **1d**[1] (49.8 mg, 0.180 mmol). ^{1}H NMR spectroscopy analysis of the crude reaction mixture indicated an 88:12 (*Z*/*E*) mixture of olefin isomers. The crude product was purified by flash chromatography (30-45% EtOAc/hexanes) to afford the title compound (88:12 mixture of olefin isomers) as a colorless oil (37.0 mg, 74% yield): ^{1}H NMR (600 MHz, $CDCl_3$, major olefin isomer) δ 7.27 (m, 6H), 7.18 (m, 2H), 7.04 (m, 2H), 6.38 (s, 1H), 3.97 (s, 1H), 3.66 (d, *J* = 12.1 Hz, 1H), 3.54 (s, 2H), 2.85 (d, *J* = 11.2 Hz, 1H), 2.72 (d, *J* = 12.1 Hz, 1H), 2.46 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, major olefin isomer) δ 137.8, 137.1, 134.2, 129.4, 128.9, 128.4, 128.2, 127.1, 127.4, 126.6, 66.5, 62.6, 59.7, 54.5, 42.9; IR (thin film) 3381, 3059, 3026, 2938, 2797, 1061 cm^{-1}; HRMS (ESI) *m* / *z* calcd for $C_{19}H_{22}NO$ $(M + H)^+$ 280.1696, found 280.1680.



2e

(*Z*)-5-hexylidenetetrahydro-2*H*-pyran-3-ol (2e). The representative procedure was followed using $NiBr_2 \cdot 3H_2O$ (5.0 mg, 0.018 mmol), $PhMe_2P$ (10.4 μL, 0.0732 mmol), and epoxide **1e** (33.5 mg, 0.184 mmol). ^{1}H NMR spectroscopy analysis of the crude reaction mixture indicated a >95:5 (*Z*/*E*) mixture of olefin isomers. The crude product was purified by flash chromatography (30-45% EtOAc/hexanes) to afford the title compound as a colorless oil (25.5 mg, 75% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.33 (t, *J* = 7.5 Hz, 1H), 4.32 (d, *J* = 12.5 Hz, 1H), 3.93 (d, *J* = 12.5 Hz, 1H), 3.83 (m, 1H), 3.70 (d, *J* = 2.9 Hz, 2H), 2.53 (d, *J* = 12.4 Hz, 1H), 2.28 (dd, *J* = 13.6, 4.9 Hz, 1H), 2.10 (d, *J* = 9.5 Hz, 1H), 2.03 (m, 2H), 1.30 (m, 6H), 0.88 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR

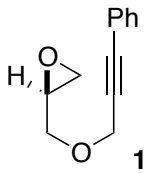
(150 MHz, $CDCl_3$) δ 129.6, 129.3, 72.7, 67.3, 66.9, 41.4, 31.6, 29.7, 27.4, 22.7, 14.2; IR (thin film) 3393, 3058, 2958, 2927, 1090, 1061 cm^{-1}; HRMS (ESI) *m* / *z* calcd for $C_{11}H_{21}O_2$ $(M + H)^+$ 185.1536, found 185.1541.



2g

5-methylenetetrahydro-2*H*-pyran-3-ol (2g). The representative procedure was followed using $NiBr_2 \cdot 3H_2O$ (24.3 mg, 0.0892 mmol), $PhMe_2P$ (50.8 μL, 0.357 mmol), and epoxide **1g** (96.9 mg, 0.864 mmol). The substrate was added as a solution in *i*-PrOH (15 mL) via syringe pump over 3 h. The crude product was purified by flash chromatography (50-70% Et_2O/pentane) to afford the title compound as a colorless oil (54.0 mg, 55% yield): ^1H NMR (600 MHz, $CDCl_3$) δ 4.98 (s, 1H), 4.92 (s, 1H), 4.08 (d, *J* = 12.2 Hz, 1H), 3.98 (dq, *J* = 12.2 Hz, 1H), 3.87 (m, 1H), 3.70 (d, *J* = 2.4 Hz, 3H), 2.57 (dd, *J* = 13.6, 1.7 Hz, 1H), 2.39 (dd, *J* = 13.7, 4.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.2, 113.6, 72.6, 72.2, 67.2, 40.1; IR (thin film) 3421, 3077, 2957, 2923, 2851, 1088 cm^{-1}; HRMS (ESI) *m* / *z* calcd for $C_6H_{11}O_2Na$ $(M + H)^+$ 115.0754, found 115.0748.

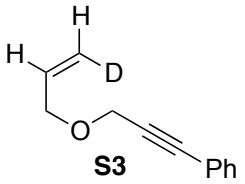
III. Synthesis of Substrates



1

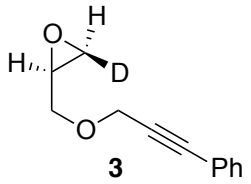
(*S*)-2-(((3-phenylprop-2-yn-1-yl)oxy)methyl)oxirane (1). To a cooled (0 °) solution of 50% w/w aqueous sodium hydroxide (10 mL), (*S*)-(+)-epichlorohydrin (1.9 mL, 24 mmol), and tetrabutylammonium hydrogen sulfate (0.407 g, 1.20 mmol), was added 3-phenyl-2-propyn-1-ol (1.5 mL, 12 mmol). After 30 min, the solution was allowed to warm to room temperature. After 3 h, the solution was diluted with H_2O (50 mL) and the aqueous layer was extracted with Et_2O (3 x 50mL). The combined organic layers were washed with brine (50

mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting clear oil was purified by flash chromatography (10-20% EtOAc/hexanes) to afford the title compound as a colorless oil (1.6 g, 71%): $[\alpha]^{24}_D$ +12 (*c* 0.62, $CHCl_3$, 88% ee); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 (m, 2H), 7.32 (m, 3H), 4.45 (m, 2H), 3.89 (dd, *J* = 11.3, 3.1 Hz, 1H), 3.57 (dd, *J* = 11.3, 5.8 Hz, 1H), 3.22 (m, 1H), 2.83 (t, *J* = 4.6 Hz, 1H), 2.67 (dd, *J* = 4.9, 2.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 132.0, 128.7, 128.5, 122.7, 86.8, 84.8, 70.6, 59.4, 50.7, 44.6; IR (thin film) 3060, 3026, 2924, 1493, 1452 cm^{-1}; HRMS (ESI) *m* / *z* calcd for $C_{12}H_{13}O_2$ $(M + H)^+$ 189.0910, found 189.0902.



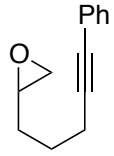
S3

[*d*1]-(3-(allyloxy)prop-1-yn-1-yl)benzene (S3). To a cooled (0 ºC) solution of NaH (0.22 g, 9.2 mmol) in THF (60 mL) was added a solution of (*Z*)-3-(D)-prop-2-en-1-ol[2] (0.50 g, 8.3 mmol) in THF (10 mL) and the solution was allowed to warm to room temperature. After 1 h, the solution was cooled (0 ºC) and (3-bromoprop-1-yn-1-yl)benzene[3] (1.6 g, 8.3 mmol) in THF (10 mL) was added and the solution was allowed to warm to room temperature. After 12 h, the solution was washed with saturated aqueous ammonium chloride (50 mL). The aqueous layer was extracted with Et_2O (3 x 50 mL) and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting yellow oil was purified by flash chromatography (10% Et_2O/hexanes) to afford the title compound as a yellow oil (0.94 g, 66%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 (m, 2H), 7.31 (m, 3H), 5.94 (m, 1H), 5.34 (m, 0.15H), 5.23 (dt, *J* = 10.4, 1.1 Hz, 0.76H), 4.38 (s, 2H), 4.14 (d, *J* = 5.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.1, 131.9, 128.6, 128.4, 122.8, 117.8 (t, *J* = 23.8 Hz), 86.4, 85.2, 70.8, 58.1; IR (thin film) 3057, 2936, 2850, 1358, 1086 cm^{-1}; HRMS (ESI) *m* / *z* calcd for $C_{12}H_{12}DO$ $(M + H)^+$ 174.1024, found 174.1030.



3

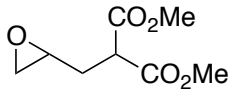
[*d*1]-2-(((3-phenylprop-2-yn-1-yl)oxy)methyl)oxirane (3). To a cooled (0 ºC) solution of [*d*1]-alkene **S3** (0.50 g, 2.9 mmol) in CH_2Cl_2 (1.5 mL) was added *m*CPBA (1.1 g, 4.6 mmol) and the solution was allowed to warm to room temperature. After 14 h, the crude reaction mixture was filtered through a plug of silica gel (50% EtOAc/hexanes as the eluent). The solution was diluted with EtOAc (50 mL) and washed with 1M NaOH (3 x 50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting yellow oil was purified by flash chromatography (10-20% EtOAc/hexanes) to provide the title compound as a colorless oil (0.18 g, 32%). The spectral data correlate to those obtained for protio epoxide **1**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 (m, 2H), 7.32 (m, 3H), 4.45 (m, 2H), 3.90 (dd, *J* = 11.3, 3.0 Hz, 1H), 3.56 (dd, *J* = 11.3, 5.8 Hz, 1H), 3.22 (m, 1H), 2.83 (d, *J* = 4.2 Hz, 0.74H), 2.67 (m, 0.17H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 132.0, 128.7, 128.5, 122.7, 86.8, 84.8, 70.5, 59.5, 50.7, 44.3 (t, *J* = 26.8 Hz); IR (thin film) 3057, 3020, 2851, 1362, 1091 cm^{-1}; HRMS (ESI) *m* / *z* calcd for $C_{12}H_{12}DO_2$ $(M + H)^+$ 190.0973, found 190.0975.



1b

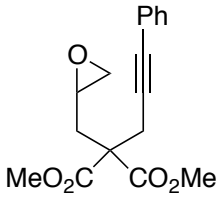
2-(5-phenylpent-4-yn-1-yl)oxirane (1b). To a cooled (0 ºC) solution of trimethylsulfonium iodide (0.73 g, 3.6 mmol) in THF (20 mL) was added a solution of *n*-butyllithium in hexanes (2.2 mL, 1.6 M, 3.6 mmol). After 5 min, a solution of 6-phenylhex-5-ynal[4] (0.49 mg, 2.9 mmol) in THF (5 mL) was added and after 30 min the solution was allowed to warm to room temperature. After 4 h, brine (30 mL) was added and the aqueous layer

was extracted with Et_2O (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (100% CH_2Cl_2) to afford the title compound as a colorless oil (0.11 g, 21%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 (m, 2H), 7.27 (m, 3H), 2.97 (m, 1H), 2.77 (t, *J* = 9.0 Hz, 1H), 2.49 (m, 3H), 1.77 (m, 3H), 1.68 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 131.7, 128.4, 127.8, 124.0, 89.6, 81.3, 52.0, 47.2, 31.8, 25.3, 19.4; IR (thin film) 3051, 2941, 2864, 1259, 1070 cm^{-1}; HRMS (ESI) *m* / *z* calcd for $C_{13}H_{15}O$ $(M + H)^+$ 187.1117, found 187.1121.



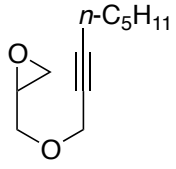
S4

Dimethyl 2-(oxiran-2-ylmethyl)malonate (S4). To a cooled (0 ºC) solution of dimethyl 2-allylmalonate (3.00 mL, 18.7 mmol) in CH_2Cl_2 (9 mL) was added *m*CPBA (5.2 g, 30 mmol) and the reaction mixture was allowed to warm to room temperature. After 16 h, the reaction mixture was filtered through a plug of silica gel (50% EtOAc/hexanes as the eluent). The solution was diluted with EtOAc (100 mL) and washed with 1M NaOH (3 x 50 mL) and then brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (20-30% EtOAc/hexanes) to afford the title compound as a colorless oil (1.46 g, 42%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.78 (s, 3H), 3.76 (s, 3H), 3.59 (dd, *J* = 8.6, 6.3 Hz, 1H), 3.03 (m, 1H), 2.79 (t, *J* = 4.3 Hz, 1H), 2.53 (dd, *J* = 4.8, 2.6 Hz, 1H), 2.31 (ddd *J* = 13.1, 8.6, 4.3 Hz, 1H), 1.99 (dt, *J* = 13.2, 6.3 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.5, 169.4, 53.0, 52.9, 49.9, 48.7, 47.4, 31.9; IR (thin film) 3003, 2957, 2849, 1734, 1437 cm^{-1}; HRMS (ESI) *m* / *z* calcd for $C_8H_{13}O_5$ $(M + H)^+$ 189.0757, found 189.0761.



1c

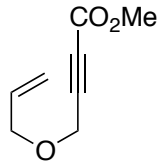
Dimethyl 2-(oxiran-2-ylmethyl)-2-(3-phenylprop-2-yn-1-yl)malonate (1c). To a cooled (0 ºC) solution of (3-bromoprop-1-yn-1-yl)benzene[3] (1.0 g, 5.1 mmol) in THF (17 mL) was added NaH (0.15 g, 3.8 mmol, 60% dispersion in mineral oil). The reaction mixture was then allowed to warm to room temperature. After 12 h, the reaction mixture was diluted with Et_2O (100 mL) and washed with H_2O (2 x 50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting orange oil was purified by flash chromatography (20-30% EtOAc/hexanes) to afford the title compound as a colorless oil (0.98 g, 95%). The spectral data correlate with the previously reported data for the title compound:[1] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 (m, 2H), 7.28 (m, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.17 (m, 2H), 3.05 (m, 1H), 2.78 (t, *J* = 4.5 Hz, 1H), 2.52 (dd, *J* = 5.1, 2.6 Hz, 1H), 2.49 (dd, *J* = 14.6, 4.6 Hz, 1H), 2.18 (dd, *J* = 14.6, 7.3 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.52, 170.47, 131.8, 128.4, 128.3, 123.1, 84.1, 84.0, 56.2, 53.22, 53.16, 48.5, 47.0, 36.3, 24.9.



1e

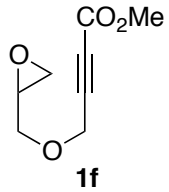
2-((oct-2-yn-1-yloxy)methyl)oxirane (1e). To a cooled (0 ºC) solution of 50% w/w aqueous sodium hydroxide (6 mL), epichlorohydrin (1.1 mL, 14 mmol), and tetrabutylammonium hydrogen sulfate (0.237 g, 0.697 mmol) was added oct-2-yn-1-ol (1.0 mL, 7.0 mmol). The solution was then allowed to warm to room temperature. After 3 h, the solution was diluted with H_2O (50 mL) and the aqueous layer was extracted with Et_2O (3 x 50mL). The combined organic layers were washed with brine (2 x 50 mL), dried over $MgSO_4$, filtered and

concentrated *in vacuo*. The resulting clear oil was purified by flash chromatography (10-20% EtOAc/hexanes) to afford the title compound as a colorless oil (1.1 g, 83%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.21(m, 2H), 3.81 (dd, *J* = 11.3, 3.1 Hz, 1H), 3.47 (dd, *J* = 11.3, 5.9 Hz, 1H), 3.20 (m, 1H), 2.83 (t, *J* = 4.6 Hz, 1H), 2.65 (dd, *J* = 4.9, 2.7 Hz, 1H), 2.22 (tt, *J* = 7.2, 2.0 Hz, 2H), 1.52 (m, 2H), 1.34 (m, 4H), 0.90 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 87.7, 75.4, 70.2, 59.2, 50.7, 44.6, 31.2, 28.4, 22.3, 18.8, 14.1; IR (thin film) 3054, 2933, 2860, 1137, 1092 cm^{-1}; HRMS (ESI) *m* / *z* calcd for $C_{11}H_{19}O_2$ $(M + H)^+$ 183.1380, found 183.1371.



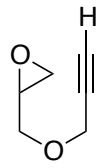
S5

Methyl 4-(allyloxy)but-2-ynoate (S5). To a cooled (−78 ºC) solution of 3-(prop-2-yn-1-yloxy)prop-1-ene[5] in THF (20 mL) was added *n*-butyllithium in hexanes (6.6 mL, 1.5 M, 9.9 mmol). After 1 h at −78 ºC, methyl chloroformate (0.84 mL, 11 mmol) was added and the solution was allowed to warm to room temperature. After 2 h, the solution was cooled to 0 ºC and washed with 1N HCl (20 mL). The aqueous layer was extracted with Et_2O (3 x 20mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting yellow oil was purified by flash chromatography (5-15% EtOAc/hexanes) to afford the title compound as a pale yellow oil (0.64 g, 42%). The spectral data correlate with the previously reported data for the title compound:[6] ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.89 (m, 1H), 5.34 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.26 (d, *J* = 10.4 Hz, 1H), 4.29 (s, 2H), 4.09 (d, *J* = 5.8 Hz, 2H) 3.79 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.7, 133.5, 118.7, 83.8, 77.9, 71.2, 56.9, 53.0.



1f

Methyl 4-(oxiran-2-ylmethoxy)but-2-ynoate (1f). To a cooled (0 ºC) solution of methyl 4-(allyloxy)but-2-ynoate **S5** (0.50 g, 3.2 mmol) in CH_2Cl_2 (1.6 mL) was added *m*CPBA (1.3 g, 5.2 mmol) and the reaction mixture was allowed to warm to room temperature. After 16 h, the reaction mixture was filtered through a plug of silica gel (50% EtOAc/hexanes). The solution was washed with 1M NaOH (3 x 20 mL) and then brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting clear oil was purified by flash chromatography (15-25% EtOAc/hexanes) to afford the title compound as a colorless oil (0.15 g, 28%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.35 (m, 2H), 3.86 (dd, *J* = 11.4, 2.8 Hz, 1H), 3.78 (s, 3H), 3.47 (dd, *J* = 11.4, 6.0 Hz, 1H), 3.17 (m, 1H), 2.81 (t, *J* = 4.6 Hz, 1H), 2.64 (dd, *J* = 4.9, 2.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6, 83.2, 78.2, 70.9, 58.4, 53.0, 50.5, 44.3; IR (thin film) 3005, 2957, 2925, 1719 cm^{-1}; HRMS (ESI) *m* / *z* calcd for $C_8H_{11}O_4$ $(M + H)^+$ 171.0652, found 171.0653.



1g

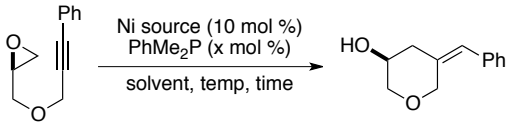
2-((prop-2-yn-1-yloxy)methyl)oxirane (1g). To a cooled (0 ºC) solution of 50% w/w aqueous sodium hydroxide (14 mL), epichlorohydrin (2.7 mL, 34 mmol), and tetrabutylammonium hydrogen sulfate (0.574 g, 1.69 mmol), was added prop-2-yn-1-ol (1.0 mL, 17 mmol). The solution was then allowed to warm to room temperature. After 3 h, the solution was diluted with H_2O (50 mL) and the aqueous layer was extracted with Et_2O (3 x 50mL). The combined organic layers were washed with brine (2 x 50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting clear oil was purified by flash chromatography (30-40%

Et_2O/pentane) to afford the title compound as a colorless oil (1.2 g, 63%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.23 (m, 2H), 3.84 (dd, *J* = 11.3, 3.0 Hz, 1H), 3.50 (dd, *J* = 11.3, 5.9 Hz, 1H), 3.18 (m, 1H), 2.82 (t, *J* = 4.6 Hz, 1H), 2.65 (dd, *J* = 4.9, 26 Hz, 1H), 2.46 (t, *J* = 2.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 79.4, 75.0, 70.5, 58.6, 50.6, 44.4; IR (thin film) 3059, 3002, 2923, 2116 cm^{-1}; HRMS (ESI) *m* / *z* calcd for $C_8H_9O_2$ $(M + H)^+$ 113.0597, found 113.0587.

IV. Additional Details of Reaction Optimization

Additional reaction conditions were investigated in order to optimize the Ni-catalyzed reductive coupling of epoxides and alkynes. Of the Ni sources examined (Table 1, entries 1–4 and Table *S*1, entries 1–3), $NiBr_2 \cdot 3H_2O$ provided the highest yields of homoallylic alcohol **2a**. *i*-PrOH was determined to be the most efficient reducing agent for the reductive coupling process (Table 1, entry 1). Employing methanol as the reducing agent resulted in a diminished yield and an increased amount of olefin isomerization (Table *S*1, entry 4). Ethanol provided yields comparable to that observed for *i*-PrOH, but a significant degree of olefin isomerization was observed (Table *S*1, entry 5). The use of other simple alcohol reducing agents did not result in product formation (Table *S*1, entry 6–9). Decreasing the reaction temperature was tolerated, but significantly longer reaction times were necessary to provide complete conversion to the desired product (Table *S*1, entry 10).

Table S1. Effect of Ni(II) precatalyst, alcohol reducing agent and temperature of the efficiency of reductive coupling



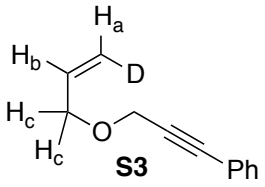
1a (*Z*)-**2a**

entry	Ni source	x mol %	solvent	temp (°C)	time (h)	yield (%)	*Z*:*E* [a]
1	$Ni(cod)_2$	20	MeOH/THF (8:1)	60	8	80[b]	90:10
2	$NiCl_2$ (anhydrous)	40	*i*-PrOH/THF (8:1)	60	8	<5[c]	---
3	$Ni(OAc)_2 \cdot 4H_2O$	40	MeOH/THF (8:1)	60	8	<5[c,d]	---
4	$NiBr_2 \cdot 3H_2O$	40	MeOH	60	8	55[b]	74:26
5	$NiBr_2 \cdot 3H_2O$	40	EtOH	60	5	79[b]	67:33
6	$NiBr_2 \cdot 3H_2O$	40	TFE	60	8	<5[c]	---
7	$NiBr_2 \cdot 3H_2O$	40	HFIP	60	8	<5[c]	---
8	$NiBr_2 \cdot 3H_2O$	40	benzhydrol/THF[e]	60	8	<5[c]	---
9	$NiBr_2 \cdot 3H_2O$	40	*t*-BuOH	60	8	<5[c]	---
10	$NiBr_2 \cdot 3H_2O$	40	*i*-PrOH	40	8	63[c,f]	87:13

[a] Determined by ^{1}H NMR spectroscopy analysis of the crude reaction mixture. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy analysis relative to mesitylene as an internal standard. [d] Product of epoxide ring opening with MeOH observed (44% yield). [e] Benzyhdrol (20 equiv) in THF. [f] Starting material recovered (15%).

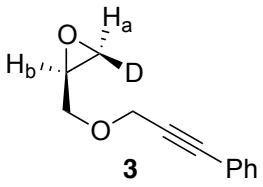
V. Stereochemical Analysis

The relative configuration of [*d*1]-(3-(allyloxy)prop-1-yn-1-yl)benzene (**S3**), prepared from the known allylic alcohol (*Z*)-3-(D)-prop-2-en-1-ol,[2] was determined by analysis of ^{1}H NMR coupling constant data. Stereospecific epoxidation of the alkene then resulted in the formation of monodeuterated epoxide **3**, with the deuterium located at the terminal epoxide site bearing a cis relationship to the alkyne tether. The relative configuration of deuterated epoxide **3** was determined by analysis of ^{1}H NMR coupling constant data.



S3

H_a: dt, J = 10.4 Hz (H_a to H_b [cis]), 1.1 Hz (H_a to H_c)

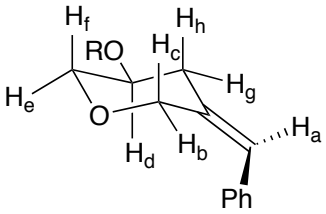


3

H_a: d, J = 4.2 Hz (H_a to H_b [cis])

The relative configuration of homoallylic alcohol **4** was determined by preparation of the TBDPS ether (**S2**) and comparison to the protio congener (**S1**). Stereochemistry was determined by analysis of ^{1}H NMR coupling constant data and relevant nOe correlations. Resonances in the ^{1}H NMR spectrum were assigned using ^{1}H/^{1}H COSY experiments, chemical shifts, and coupling constants.

Relevant ^{1}H NMR coupling constant data:

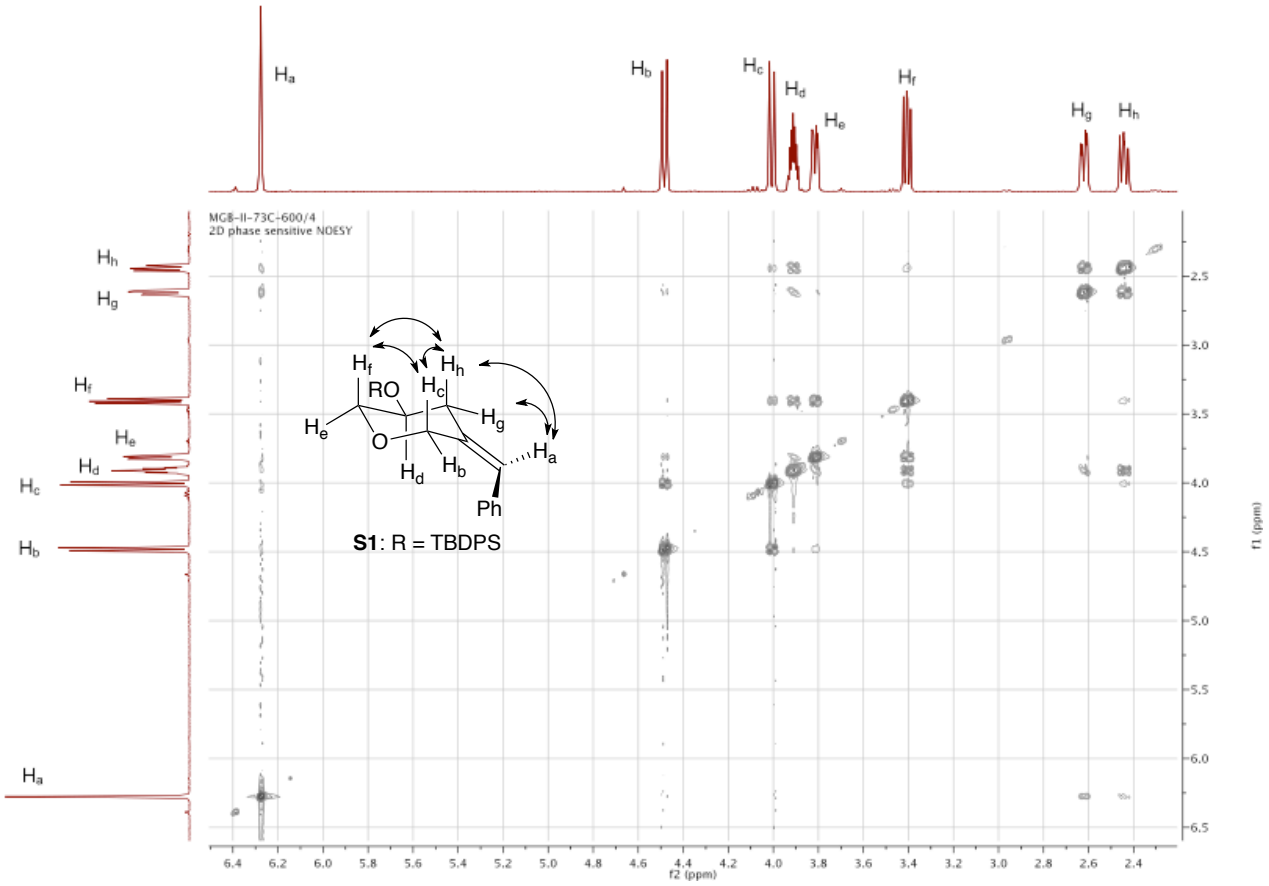


S1: R = TBDPS

H_d: tt, J = 8.7 Hz (ax H_d to ax H_h and H_f), 4.4 Hz (ax H_d to eq H_g and eq H_e)

H_h: dd, J = 13.0 Hz (gem), 9.3 Hz (ax H_h to ax H_d)

H_g: dd, J = 13.3 Hz (gem), 4.4 Hz (eq H_g to ax H_d)



[1] Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 8076–8077.
[2] Korth, H.-G.; Trill, H.; Sustmann, R. *J. Am. Chem. Soc.* **1981**, *103*, 4483–4489.
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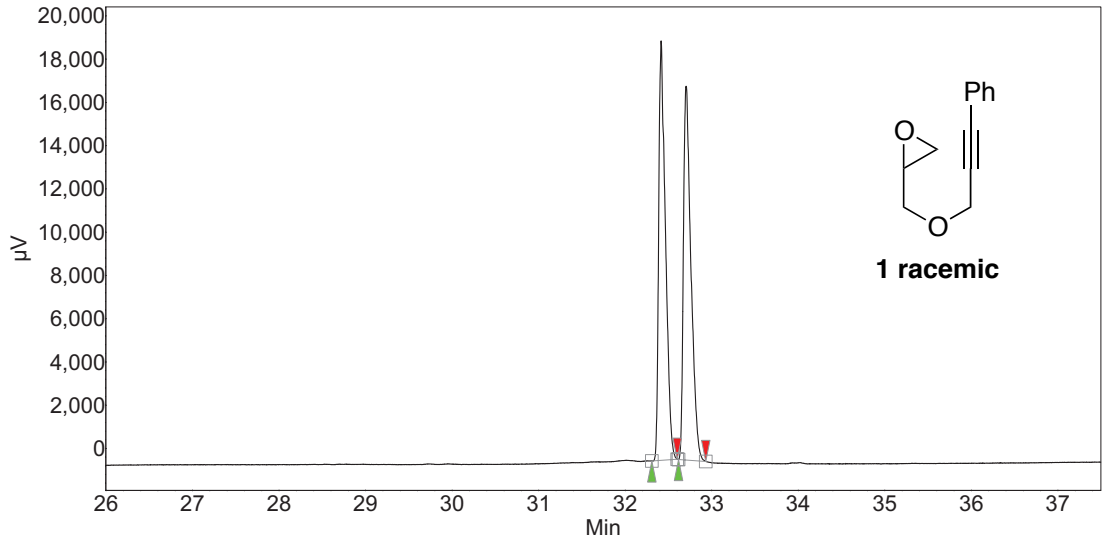
[5] Sylvester, K. T.; Chirik, P. J. *J. Am. Chem. Soc.* **2009**, *131*, 8772–8774.
[6] Yamamoto, Y.; Kuwabara, S.; Ando, Y.; Nagata, H.; Nishiyama, H.; Itoh, K. *J. Org. Chem.* **2004**, *69*, 6697–6705.

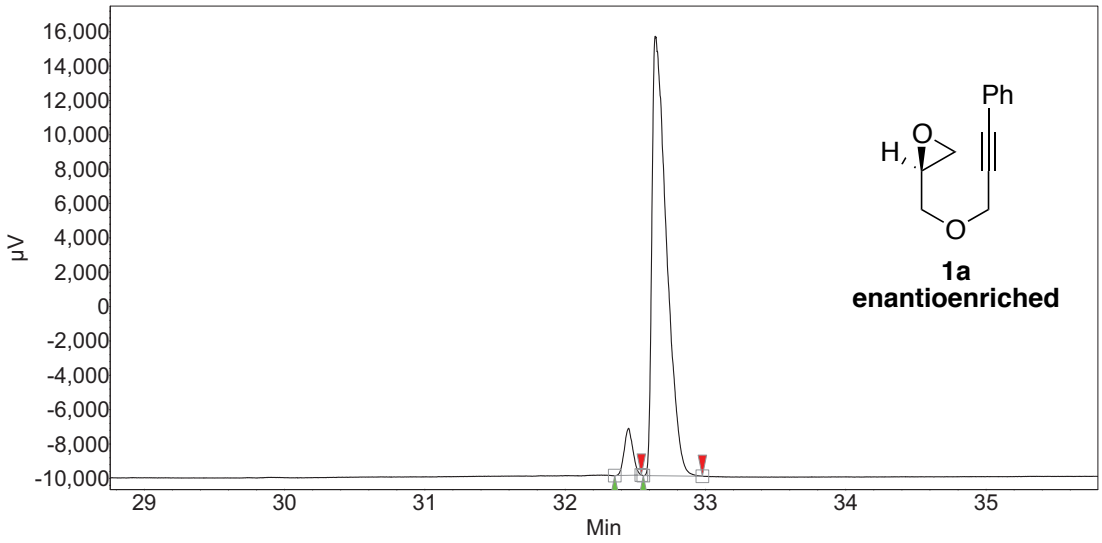
V. Analytical Data

A. GC data



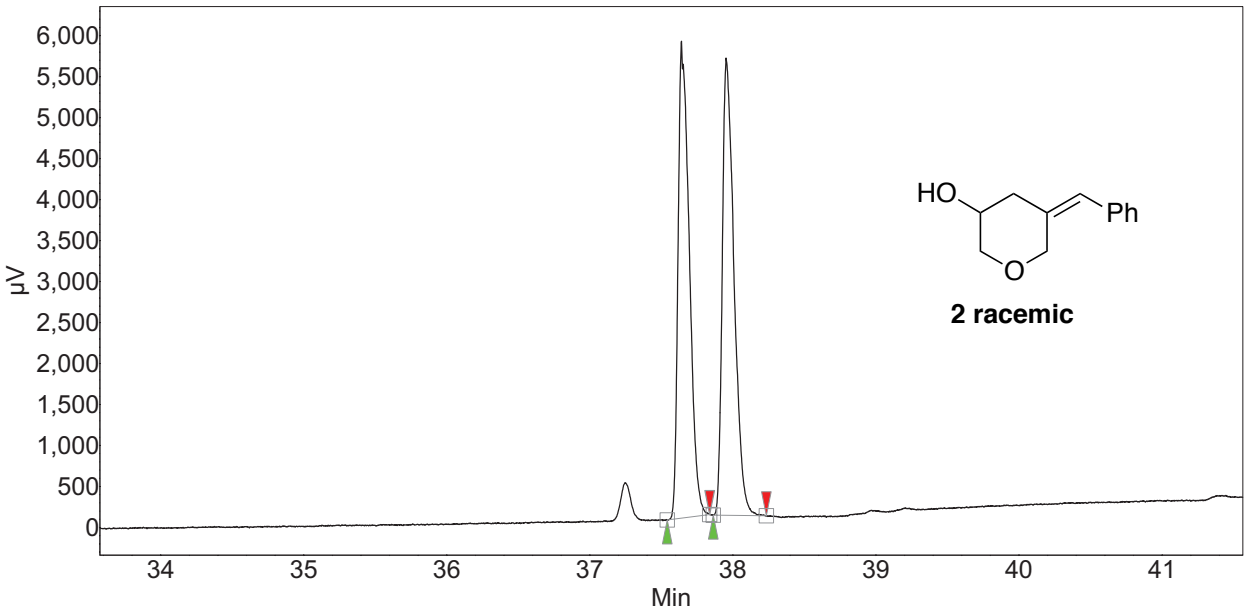
Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [µV]	Area [µV.Min]	Area % [%]
1	UNKNOWN	32.42	50.17	19397.1	1756.2	50.169
2	UNKNOWN	32.70	49.83	17285.1	1744.3	49.831
Total			100.00	36682.2	3500.5	100.000



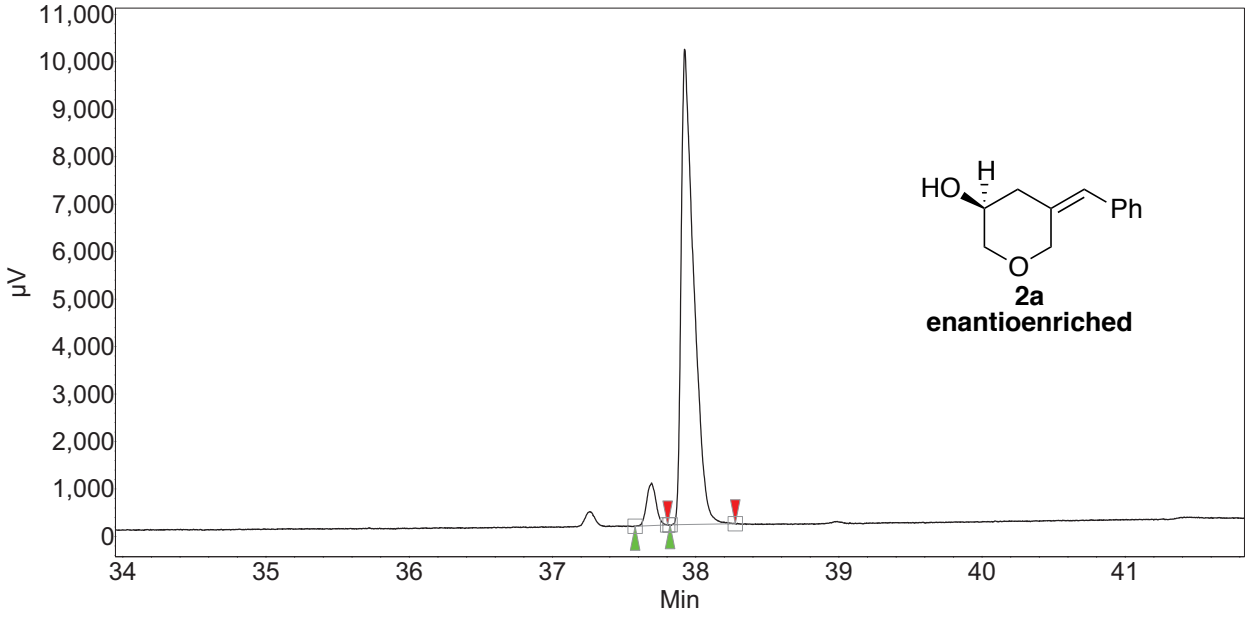
Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [µV]	Area [µV.Min]	Area % [%]
1	UNKNOWN	32.45	5.90	2738.1	192.6	5.897
2	UNKNOWN	32.64	94.10	25581.2	3072.9	94.103
Total			100.00	28319.2	3265.5	100.000



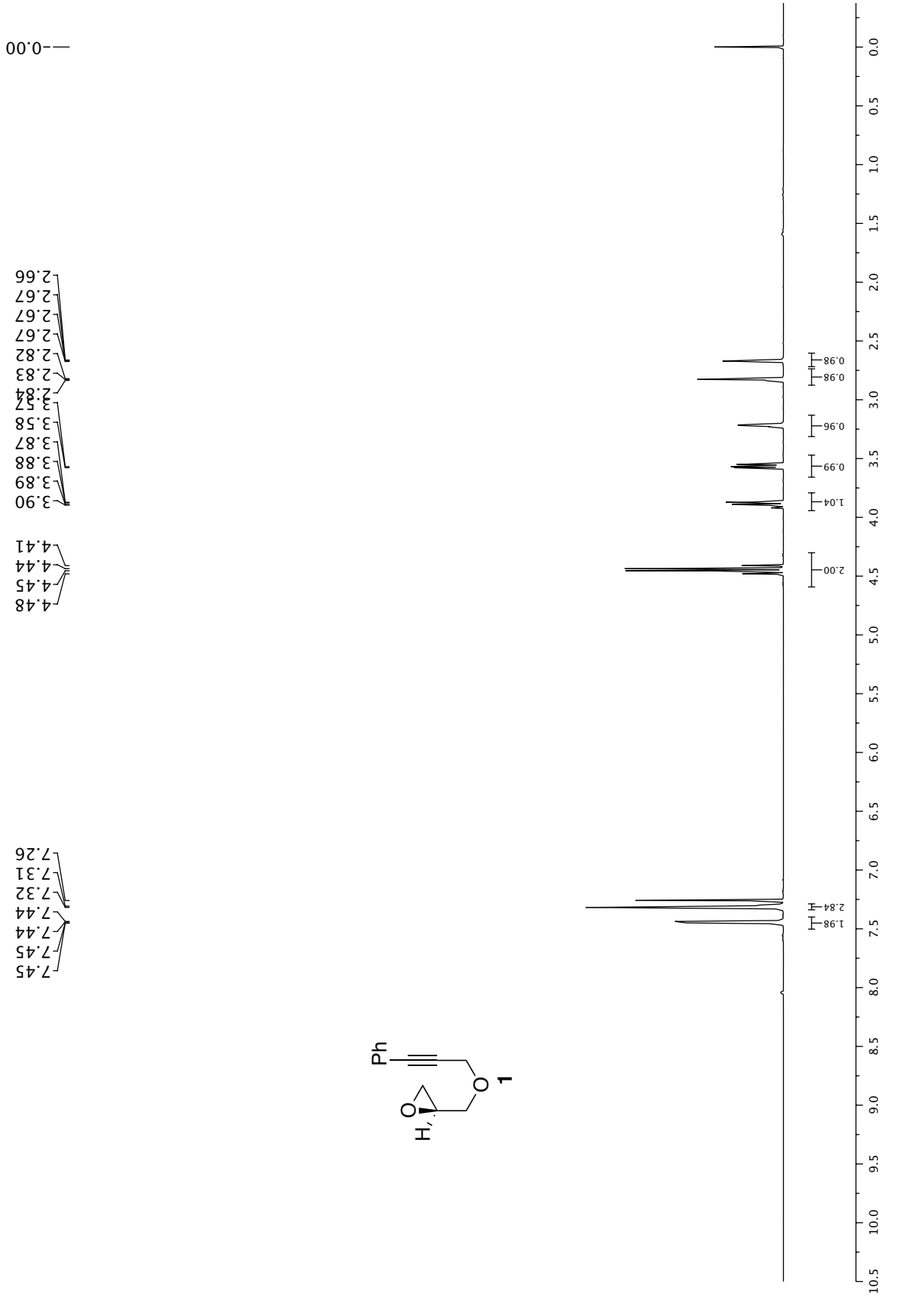
Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [µV]	Area [µV.Min]	Area % [%]
1	UNKNOWN	37.64	49.98	5820.1	527.8	49.978
2	UNKNOWN	37.95	50.02	5580.3	528.3	50.022
Total			100.00	11400.4	1056.0	100.000



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [µV]	Area [µV.Min]	Area % [%]
1	UNKNOWN	37.69	6.32	899.6	68.3	6.322
2	UNKNOWN	37.92	93.68	10015.5	1012.3	93.678
Total			100.00	10915.1	1080.6	100.000


0.00
2.66
2.67
2.67
2.67
2.82
2.83
2.84
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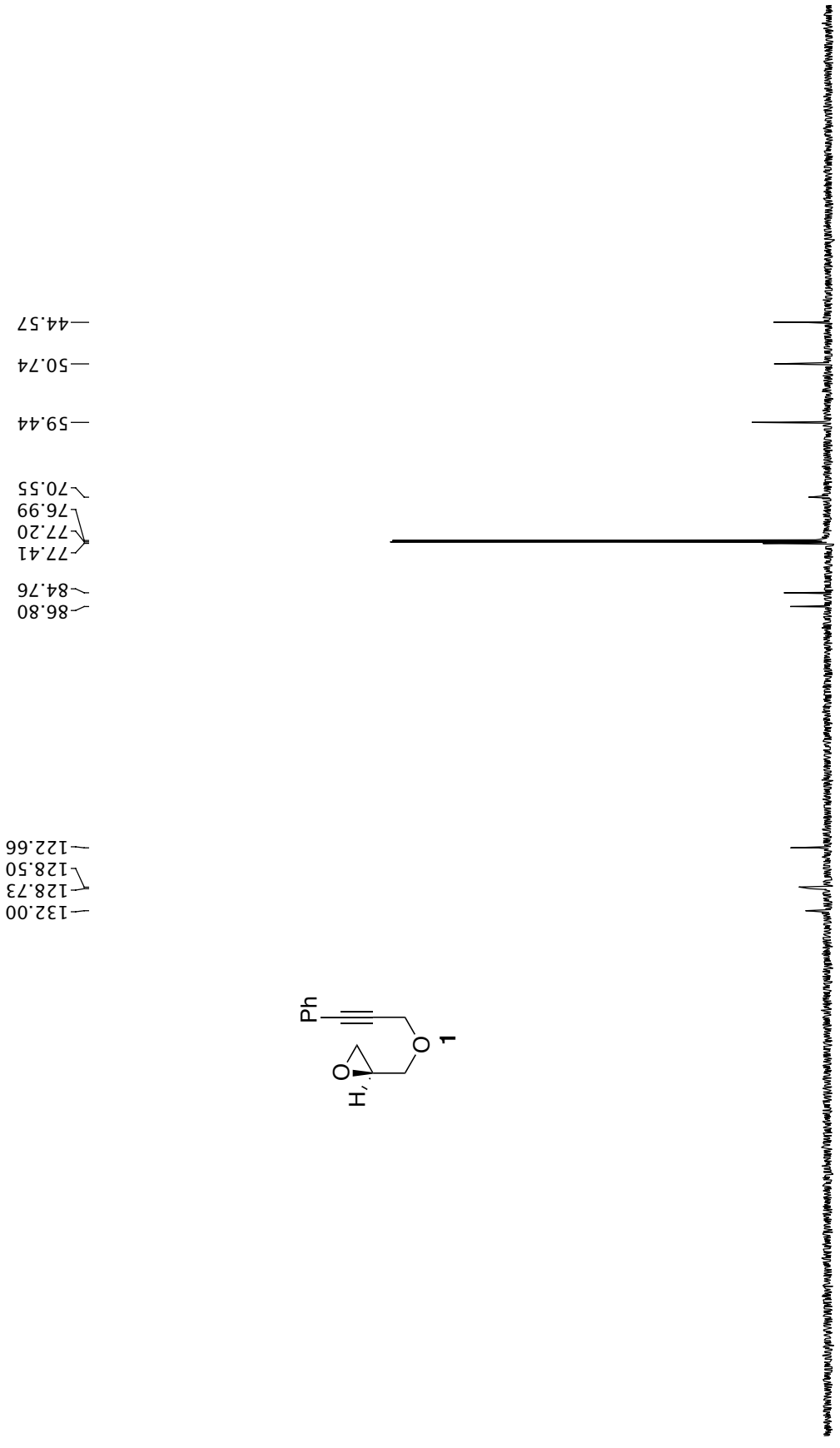
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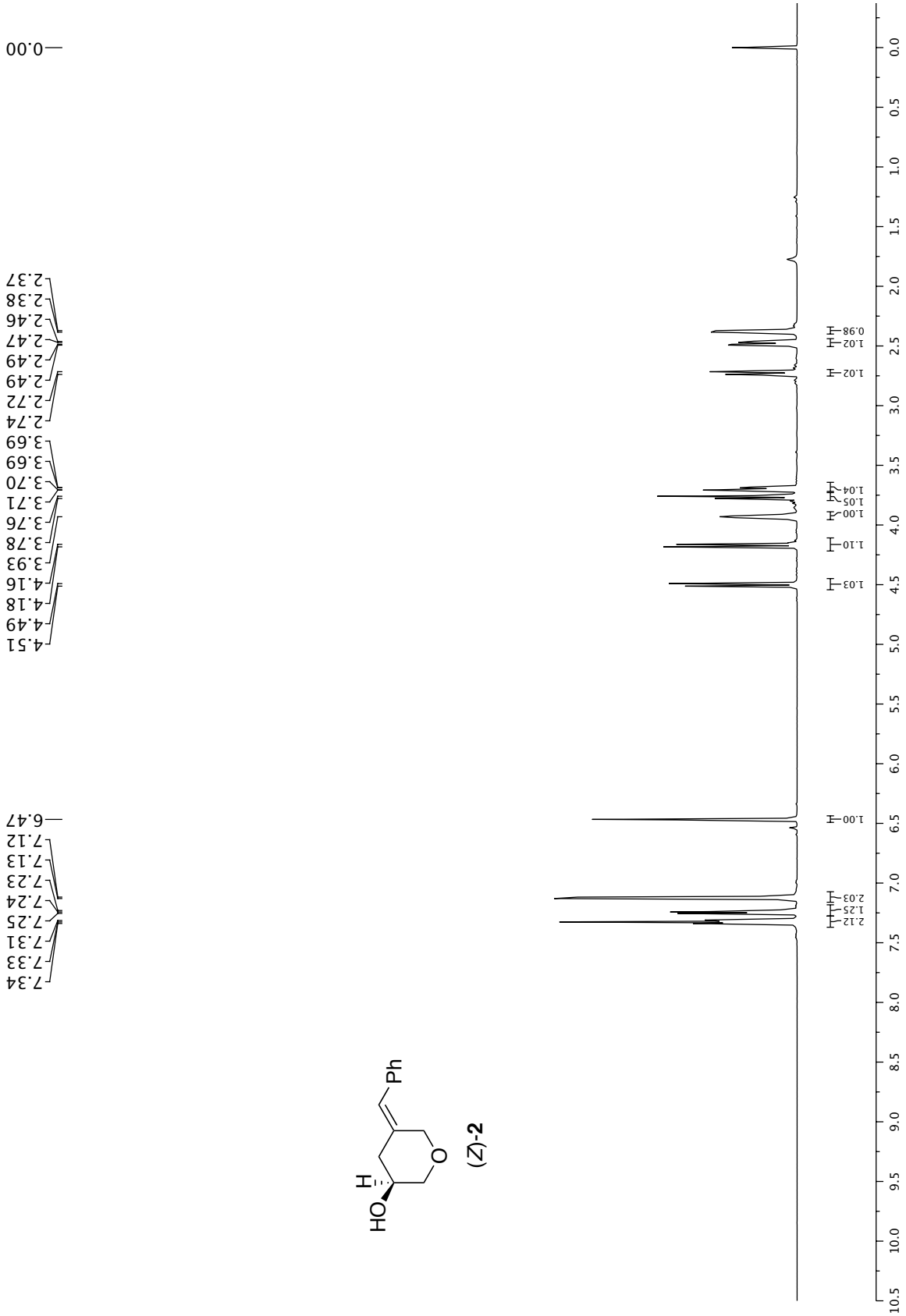
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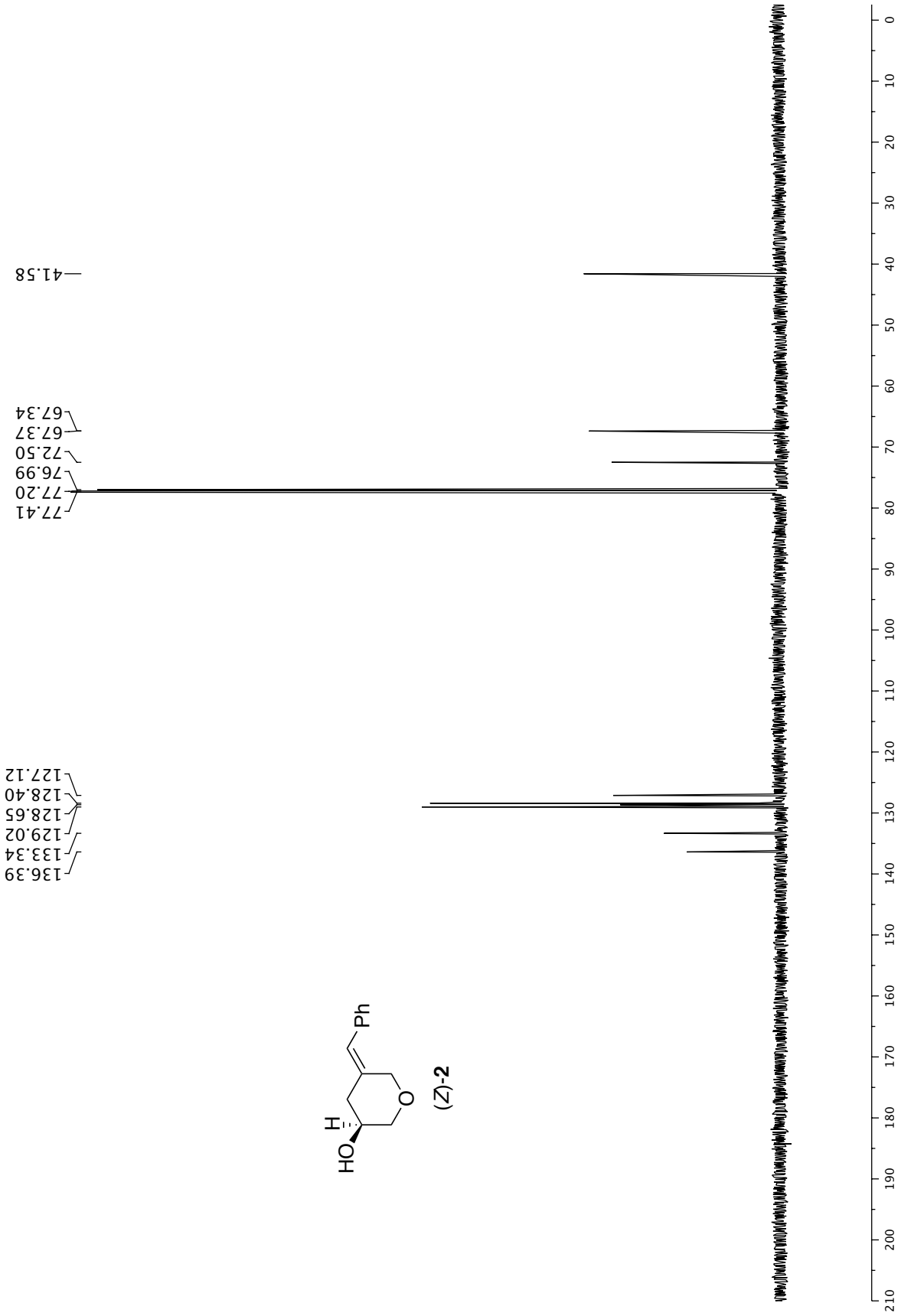
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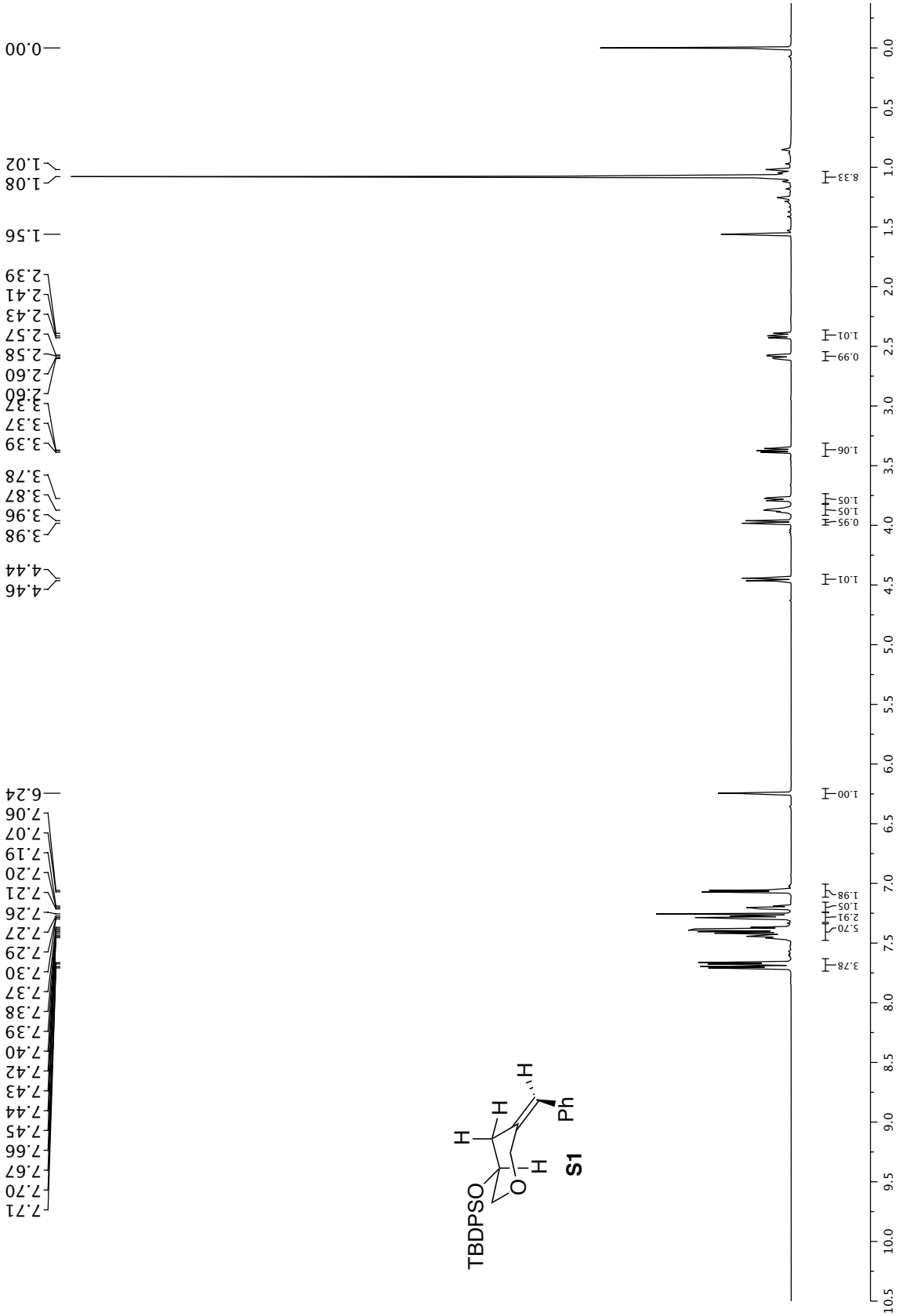
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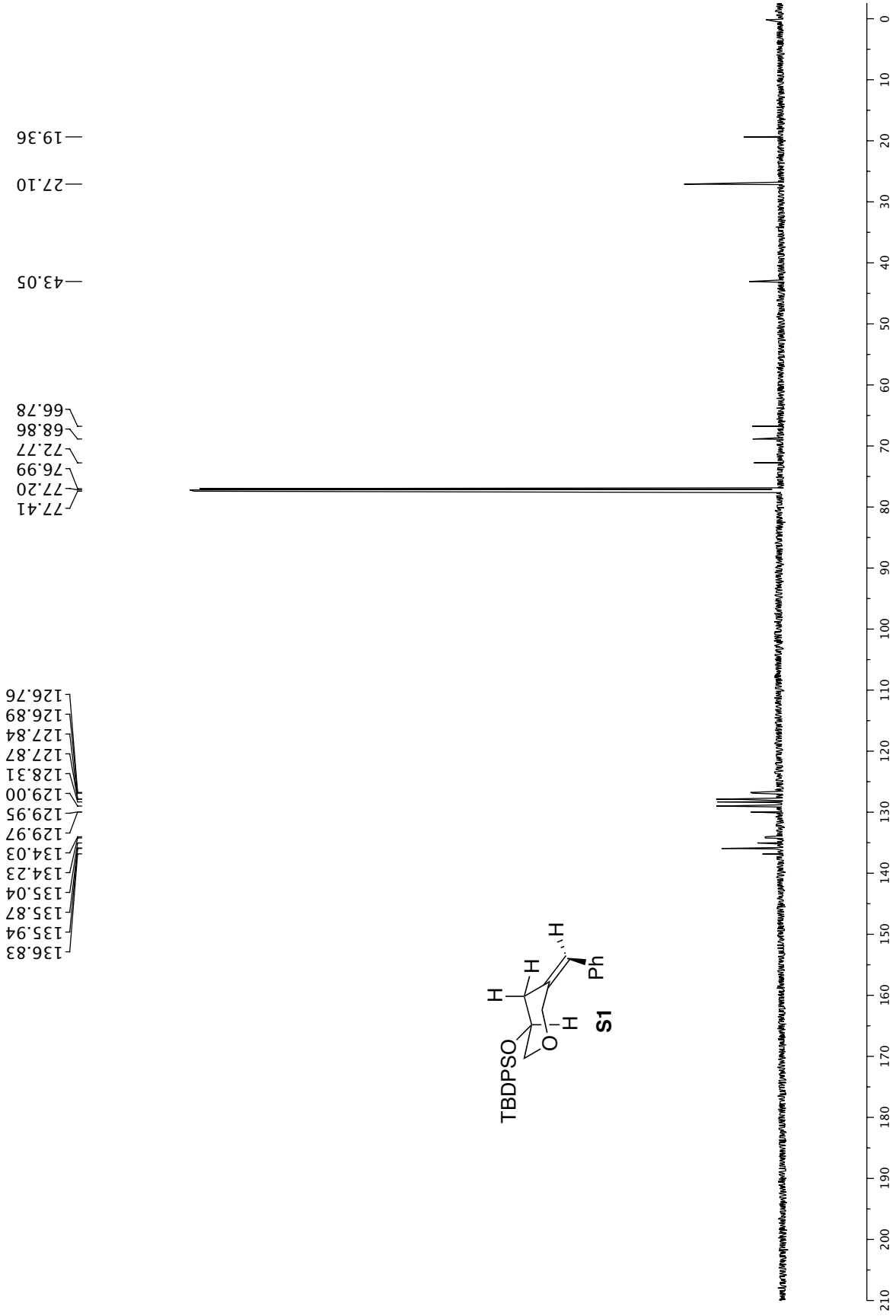
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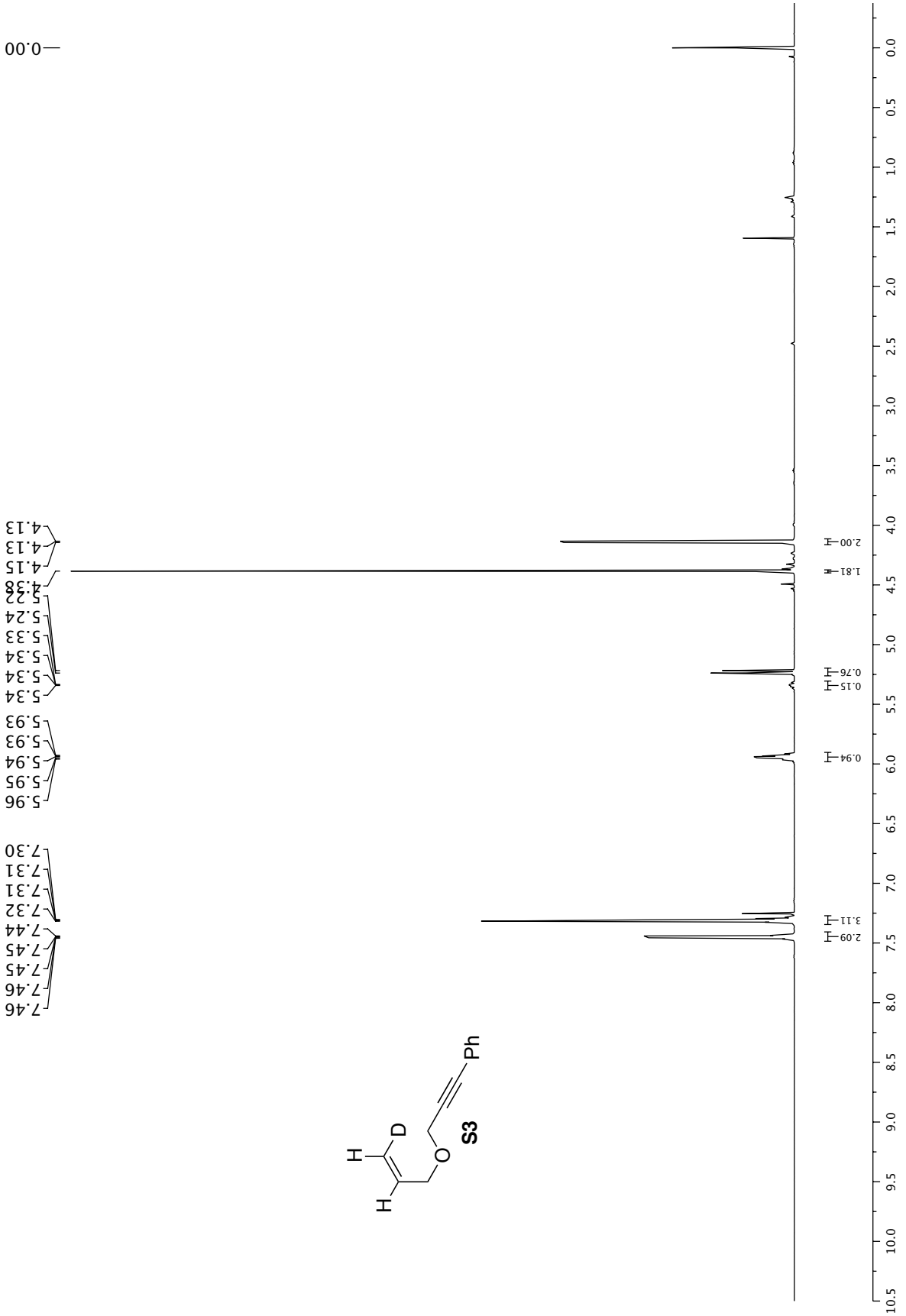
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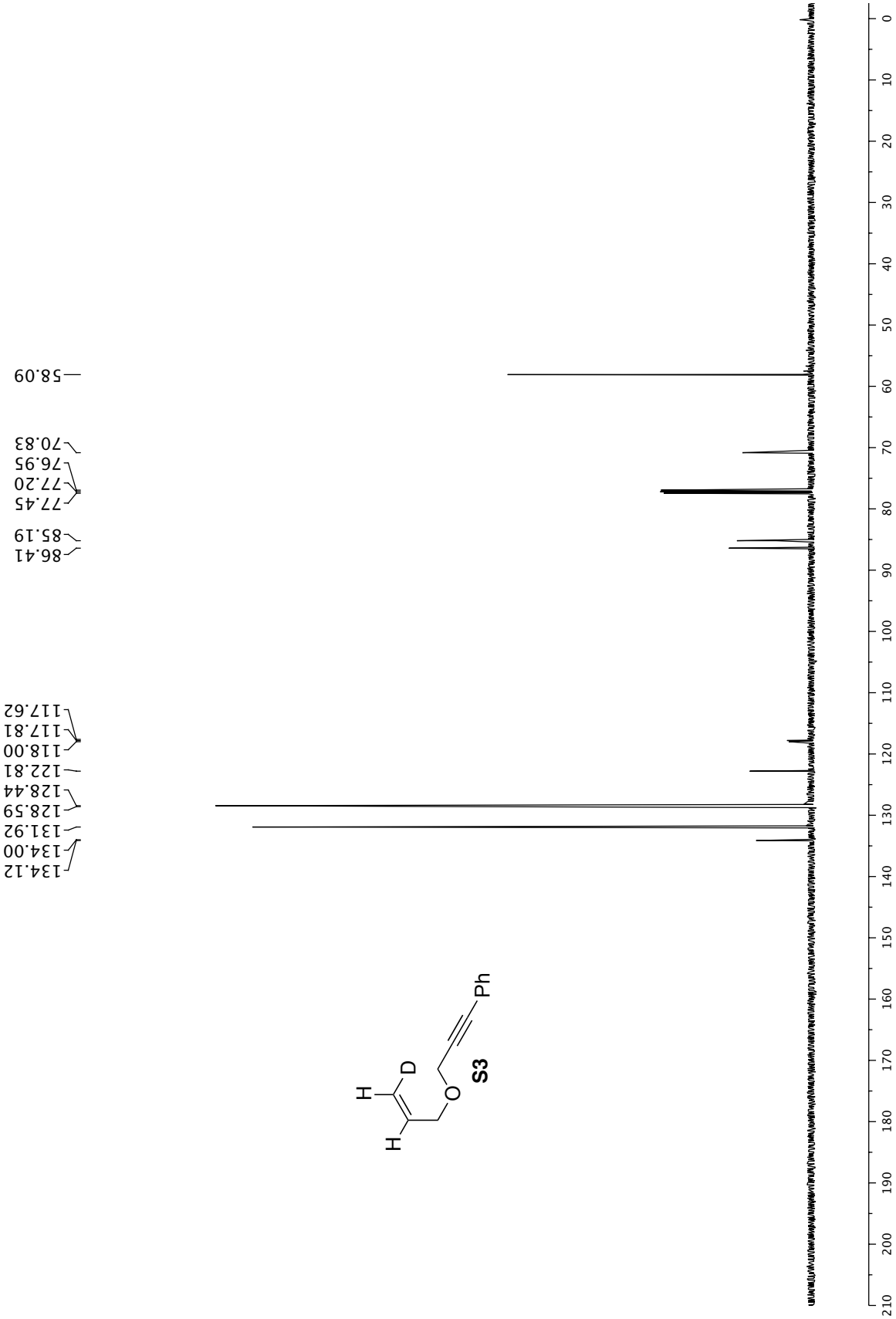
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D
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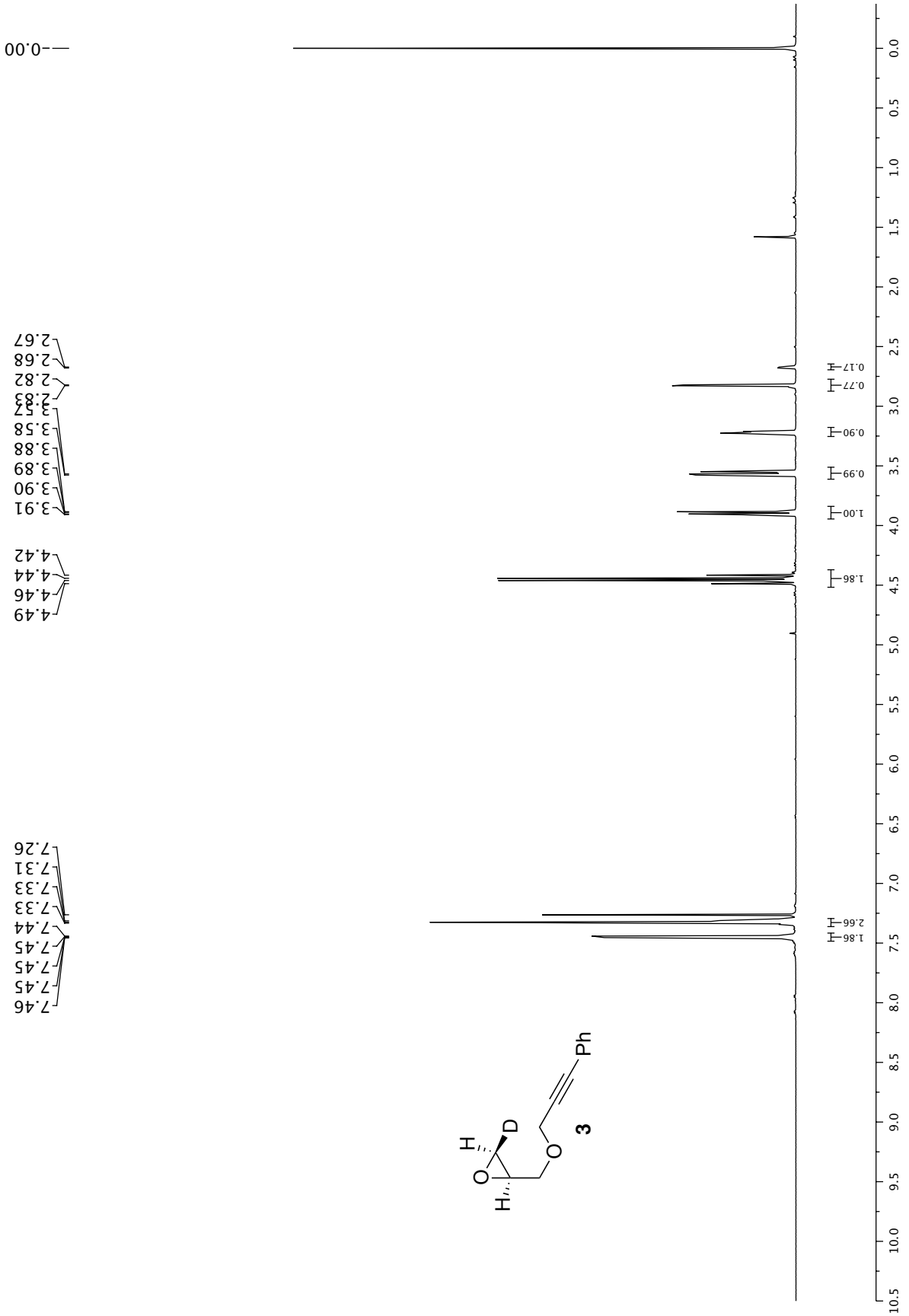
S3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7.45
7.45
7.45
7.46
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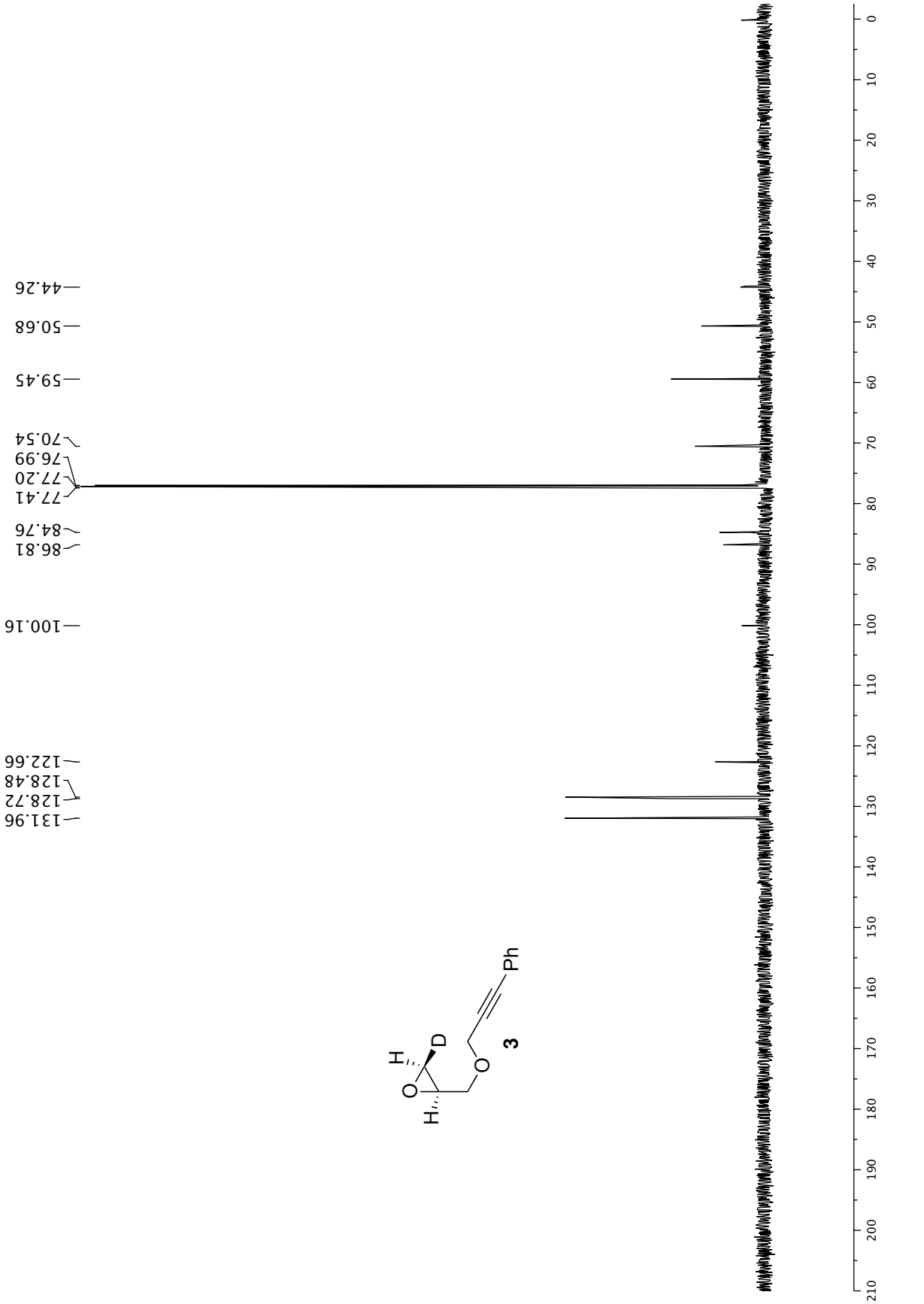
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H
D
O
H
O
Ph
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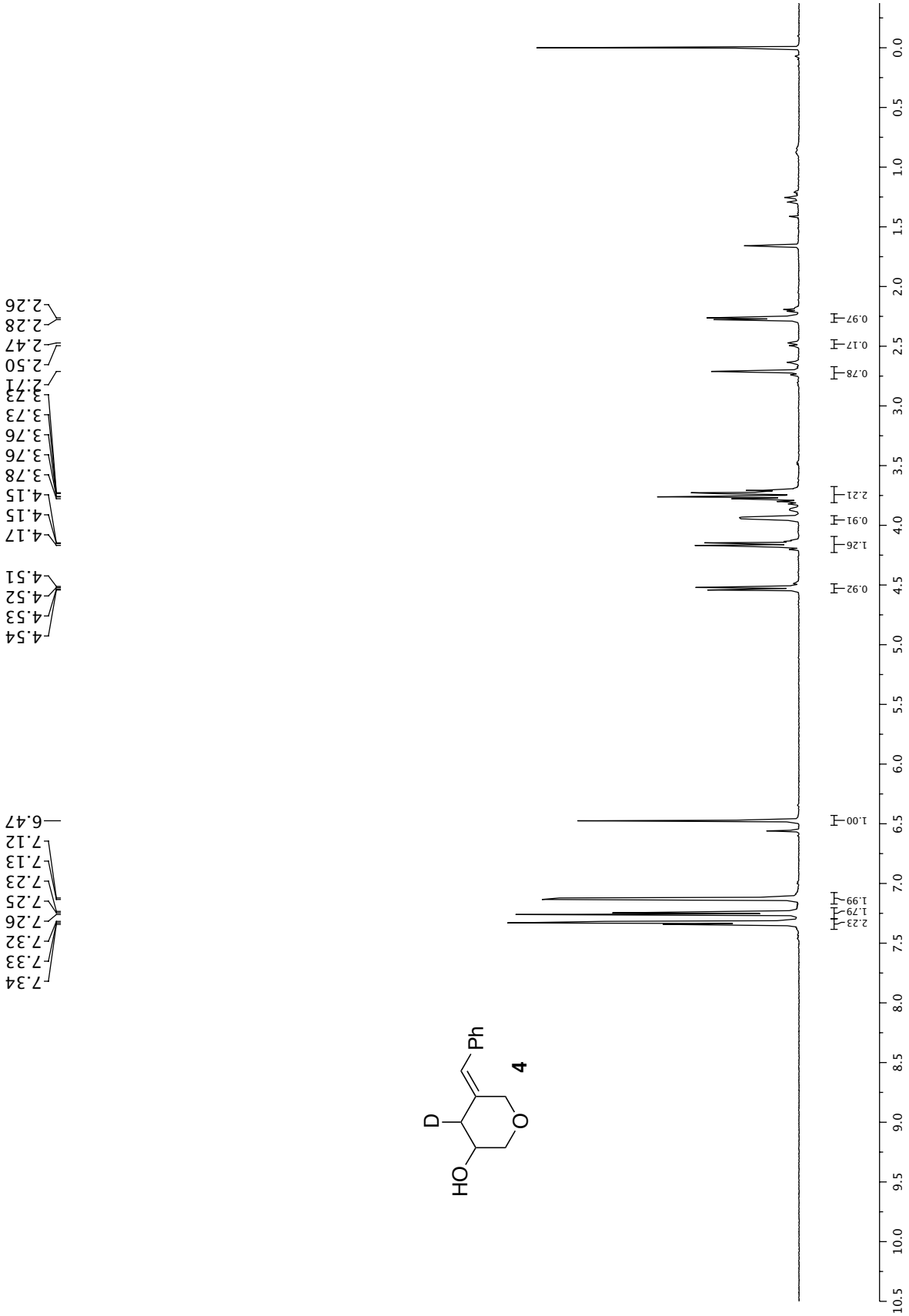
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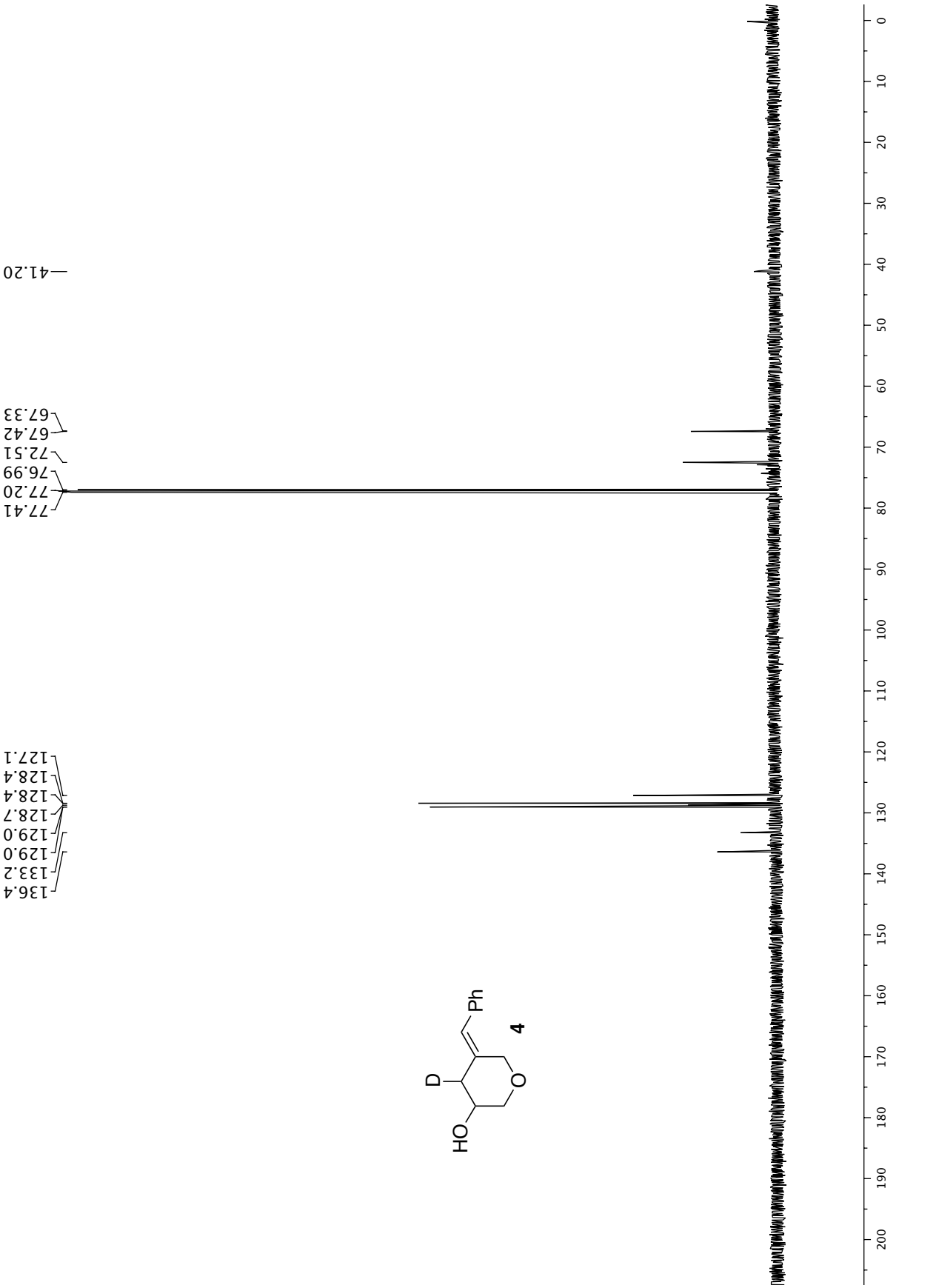
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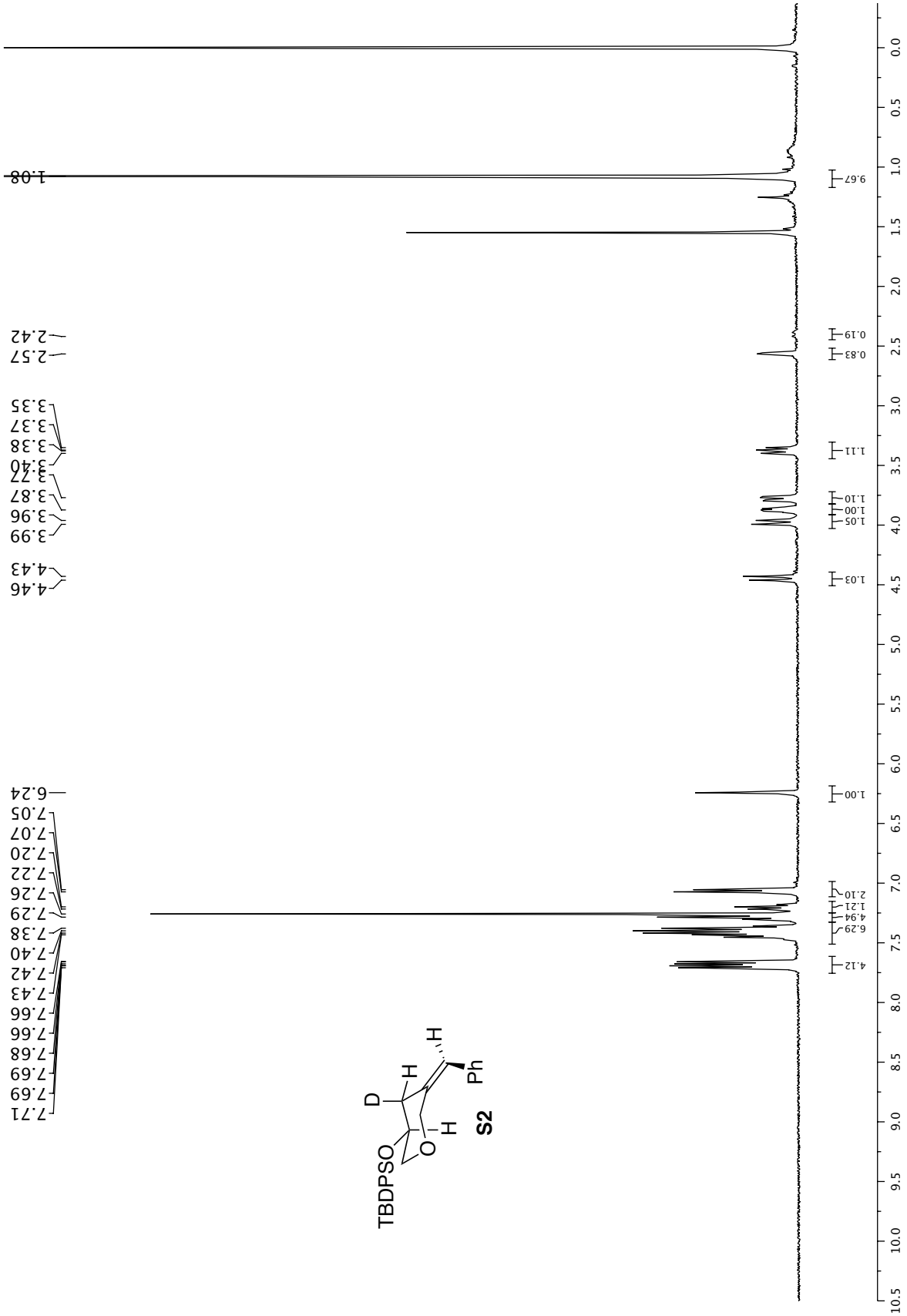
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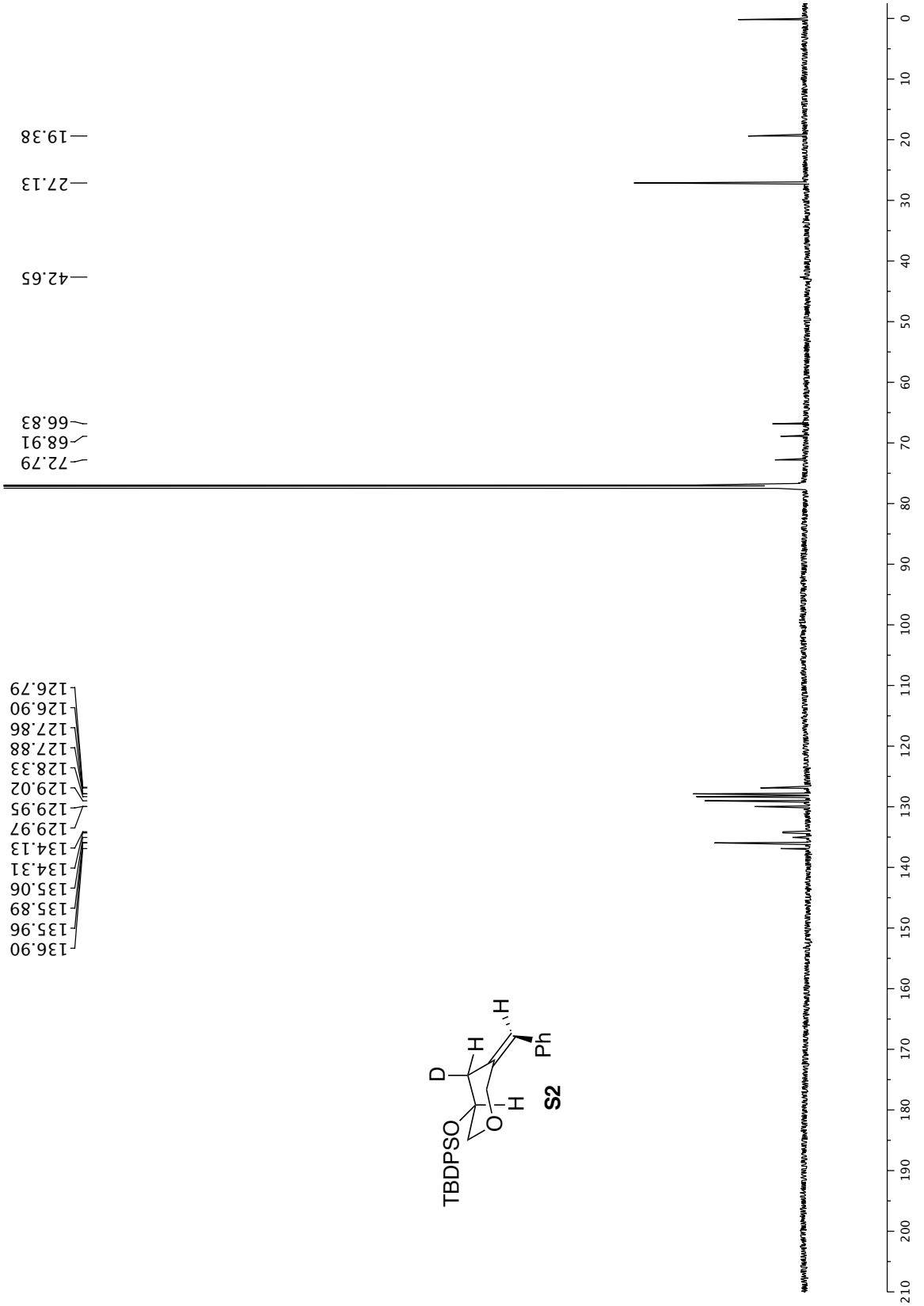
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D
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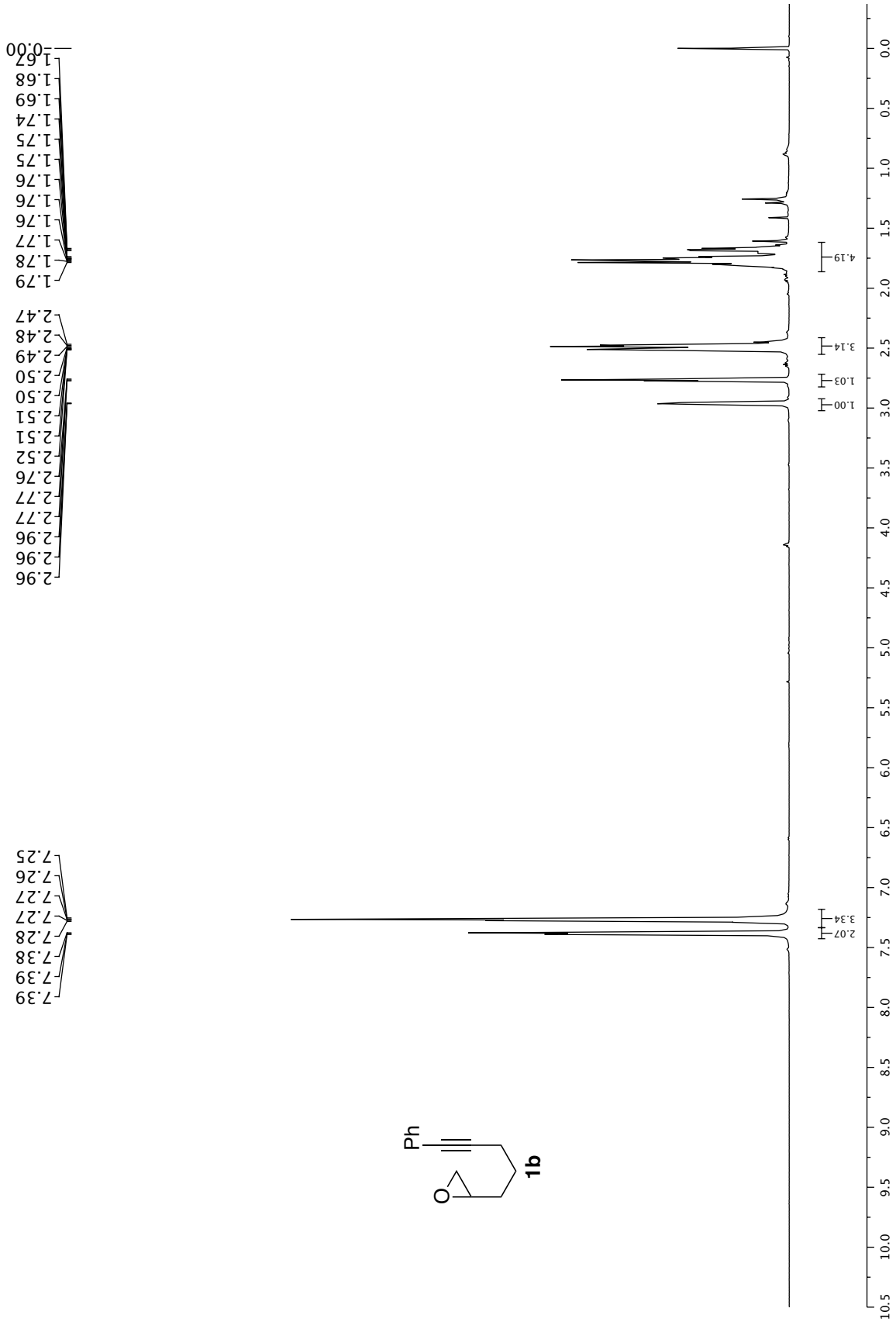
S2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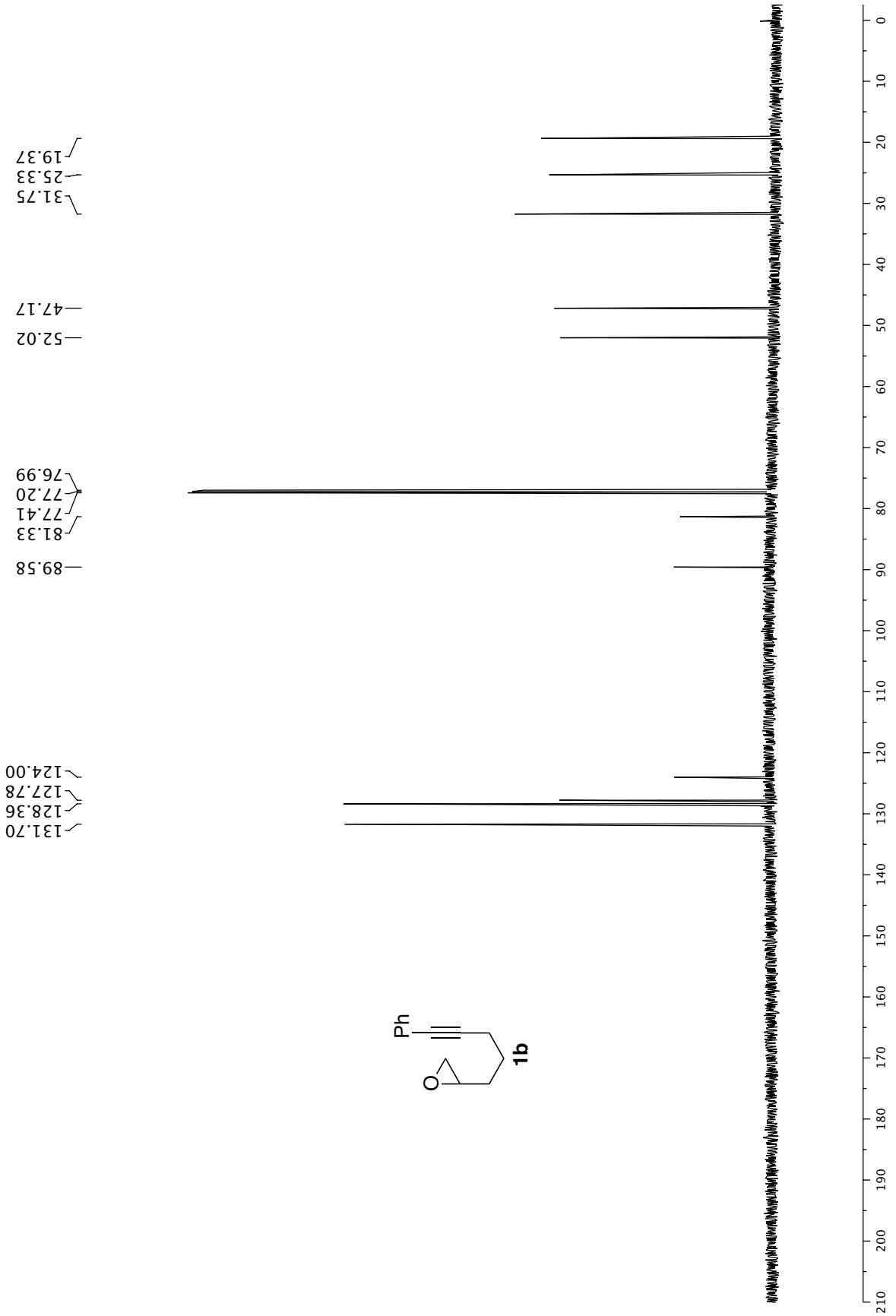
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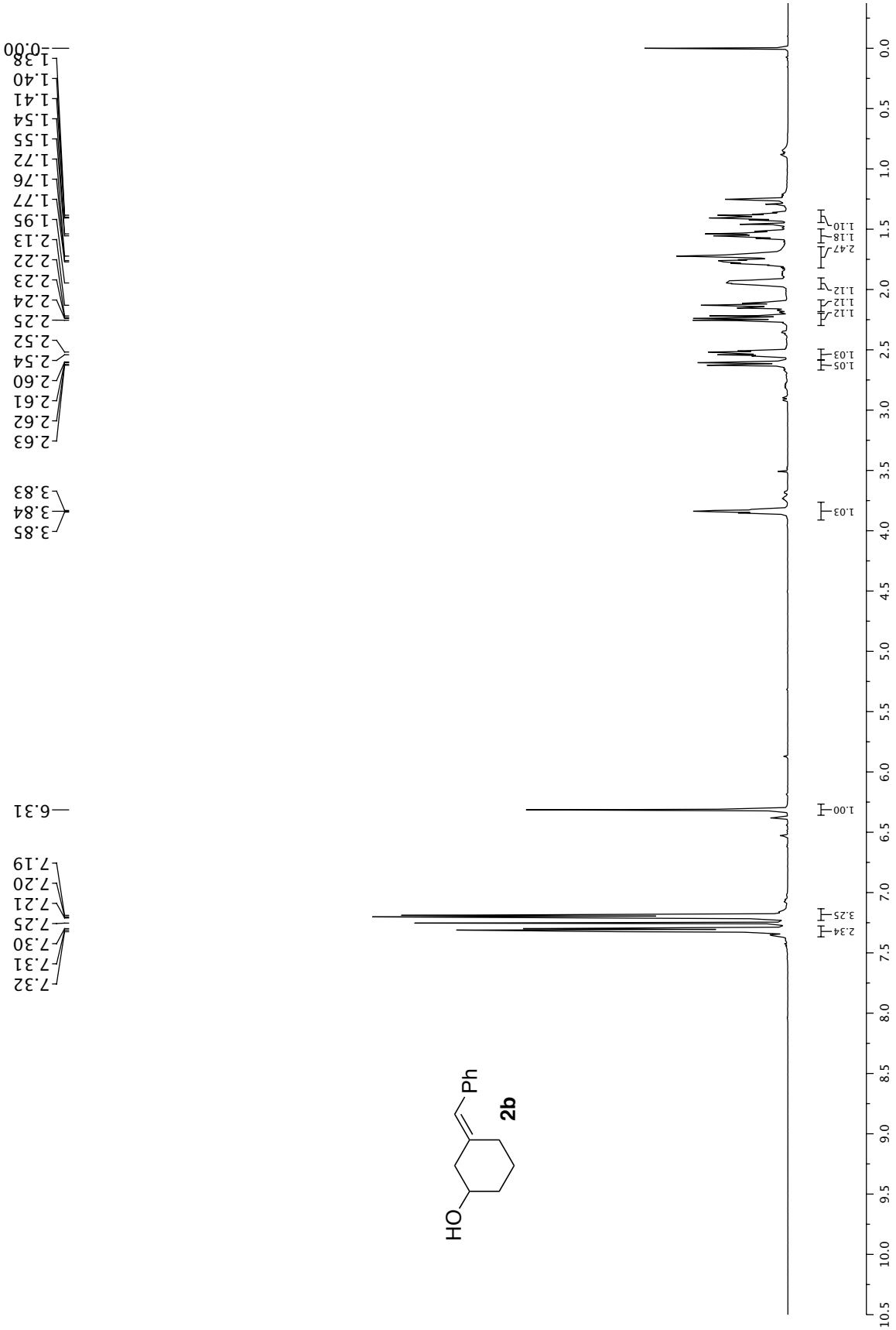
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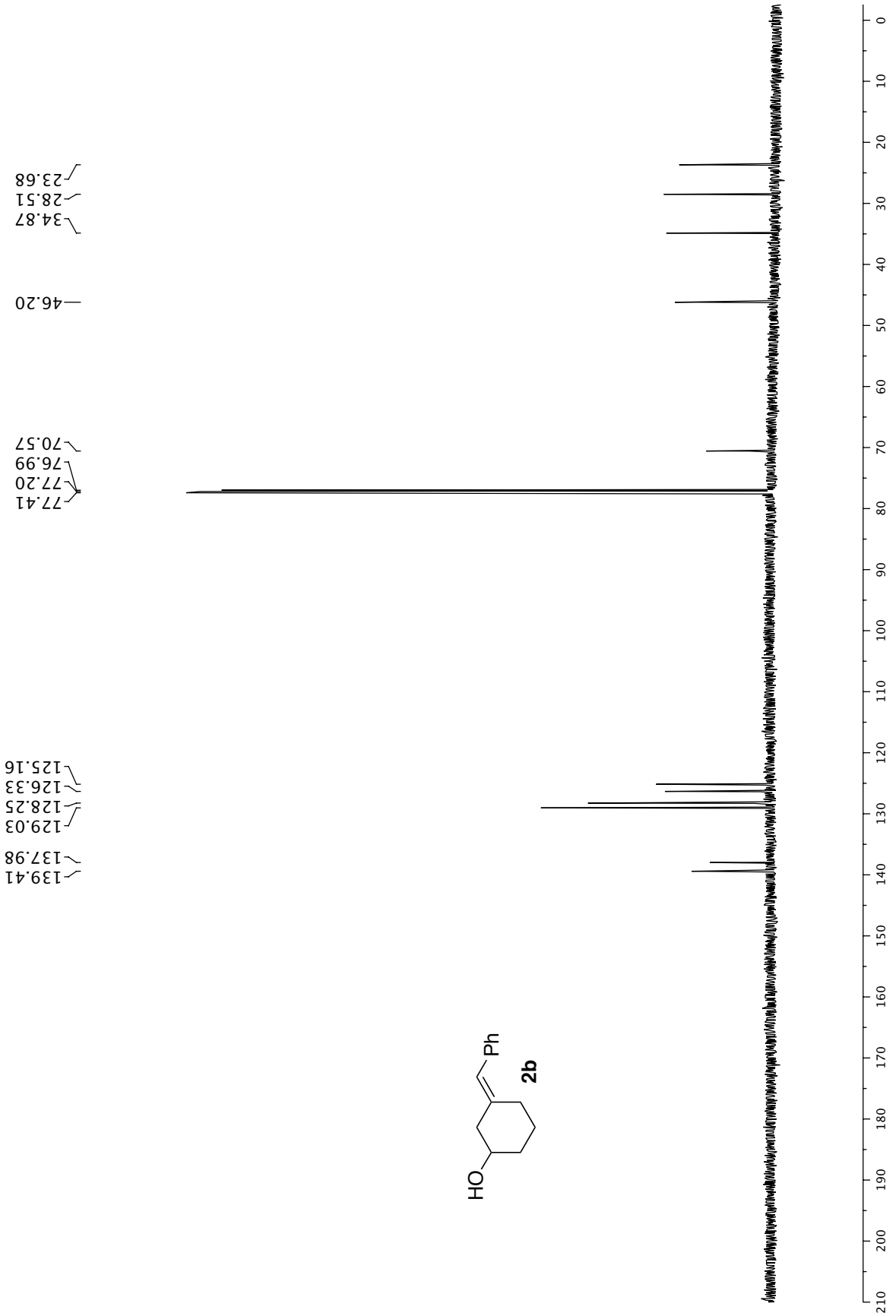
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Ph
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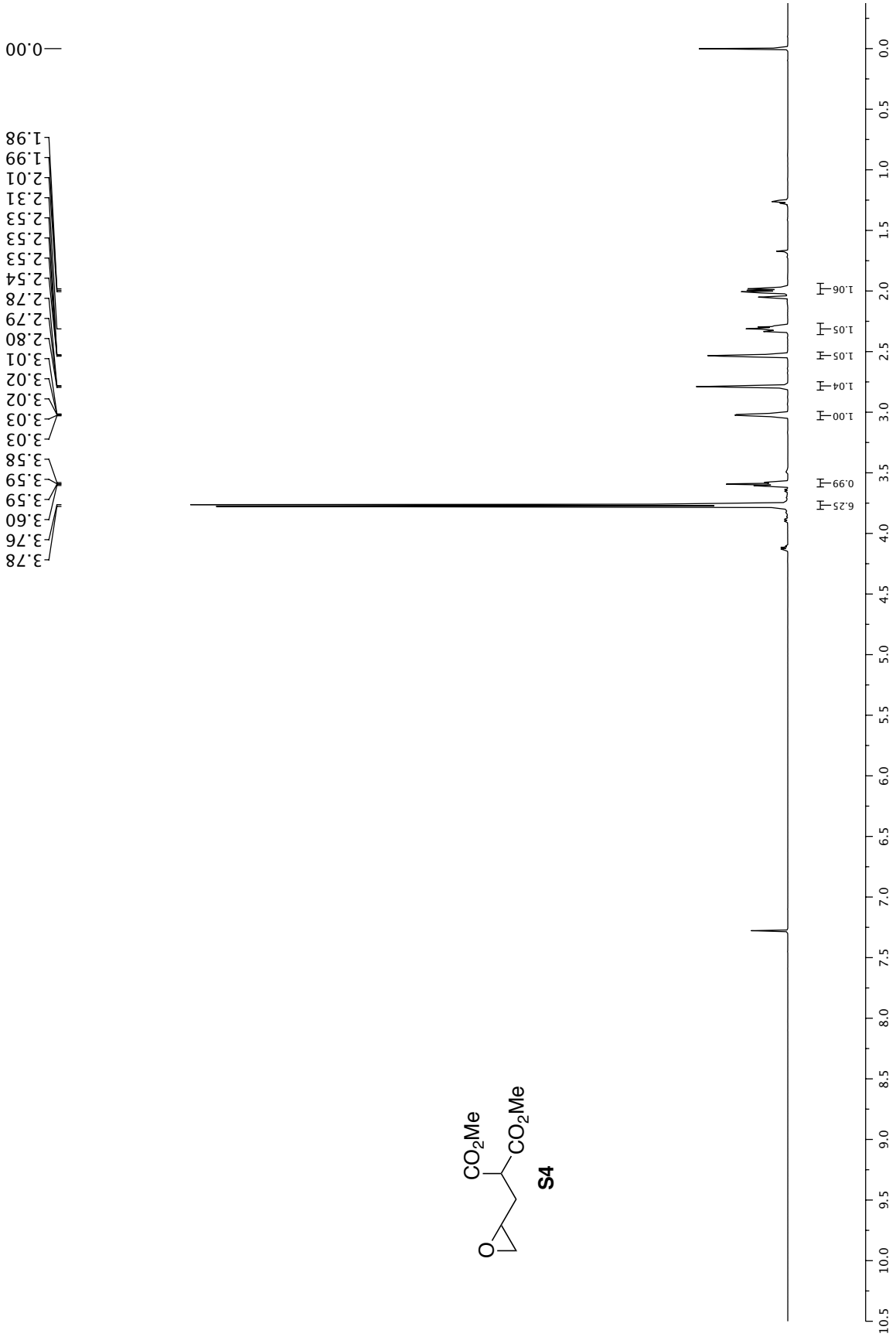
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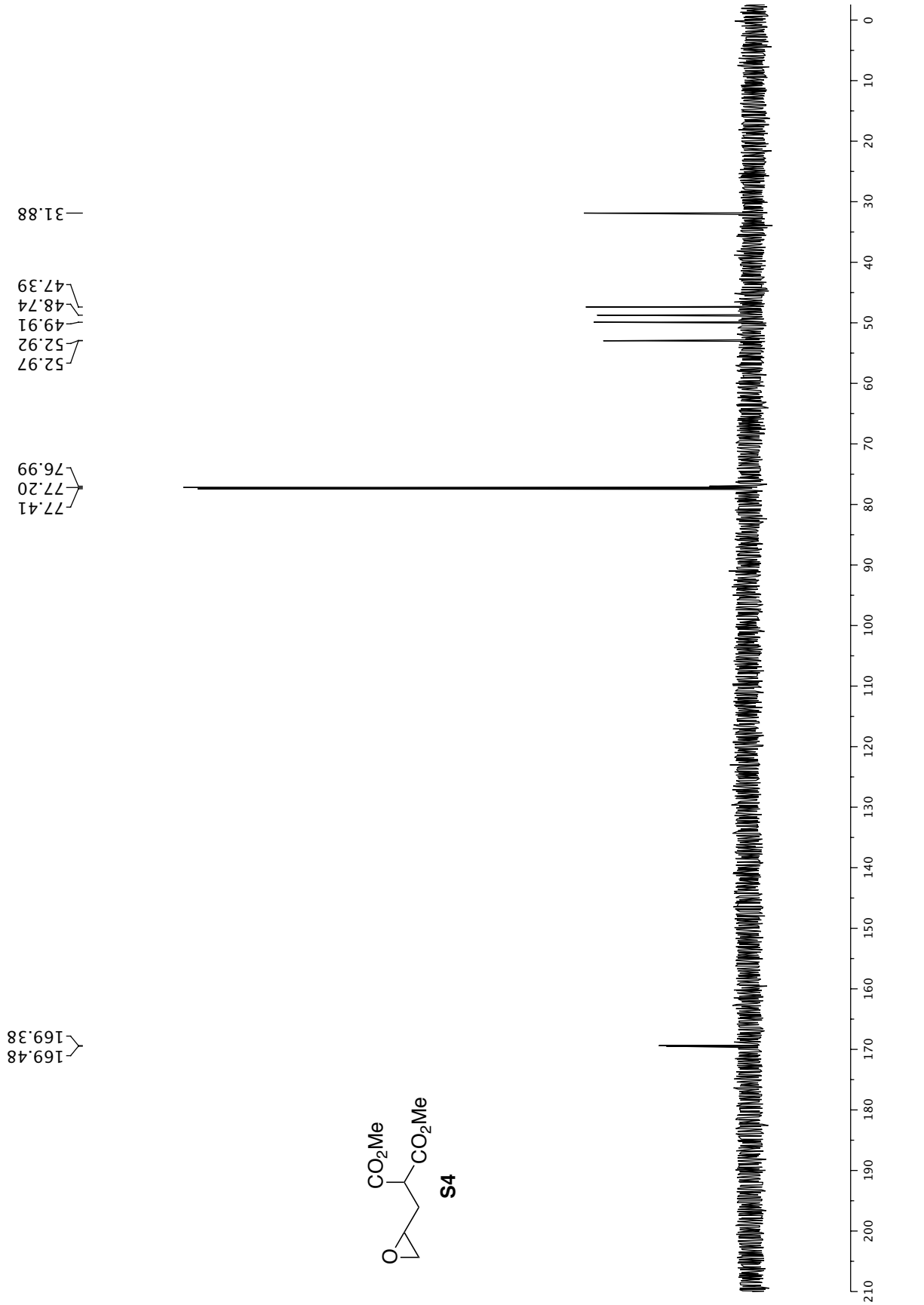
CO2Me
O
S4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CO2Me
O
S4
0
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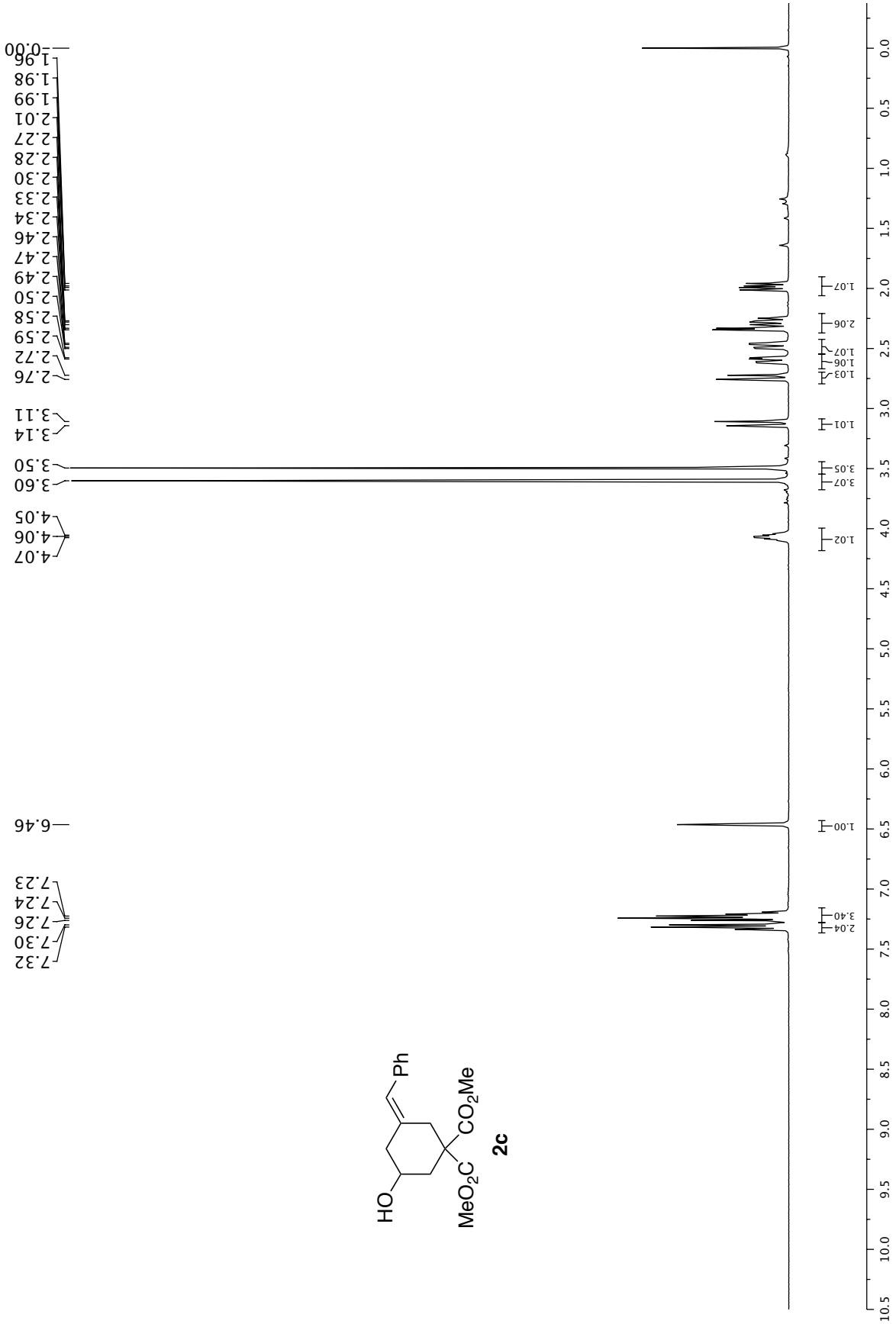
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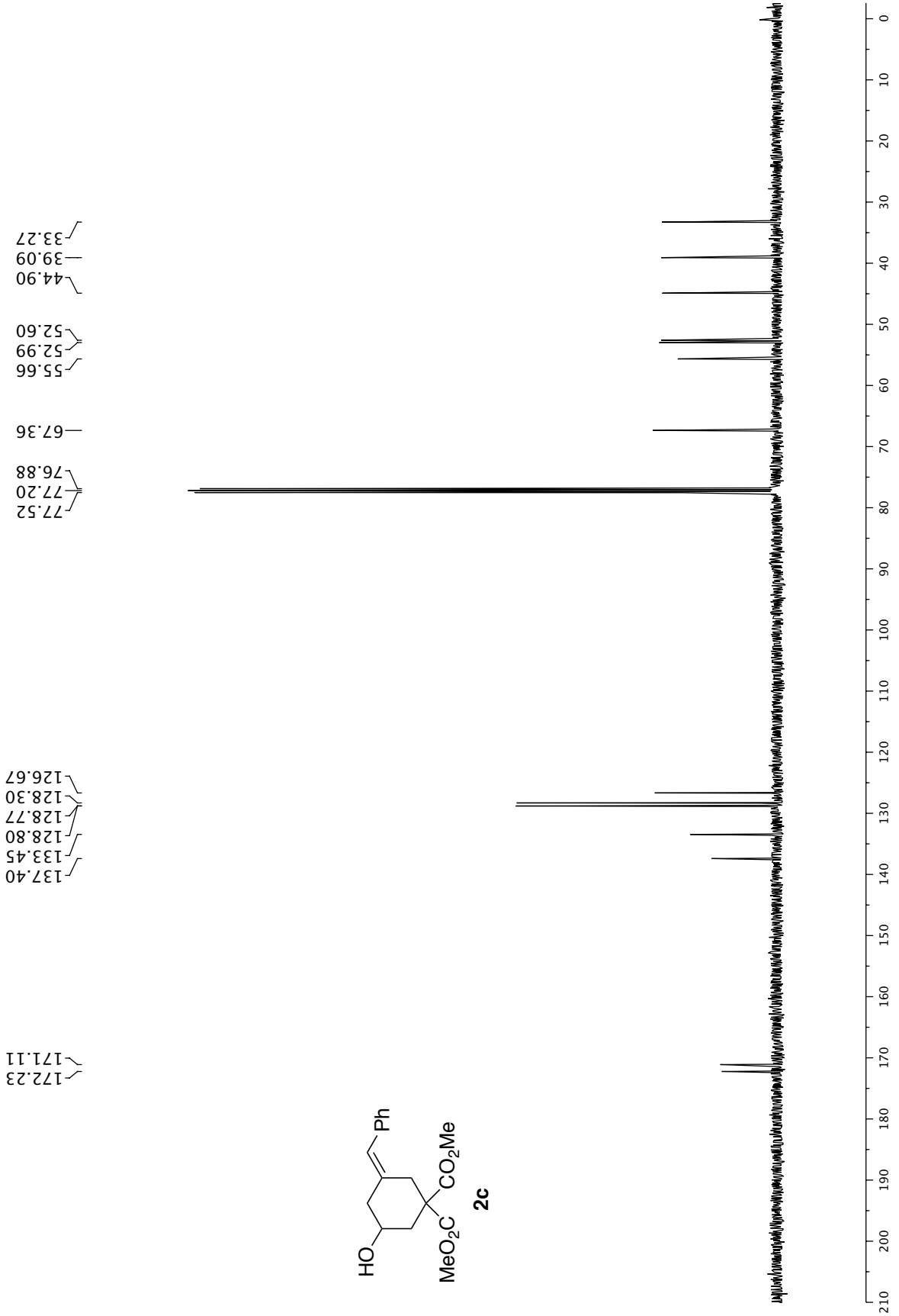
MeO2C
HO
2c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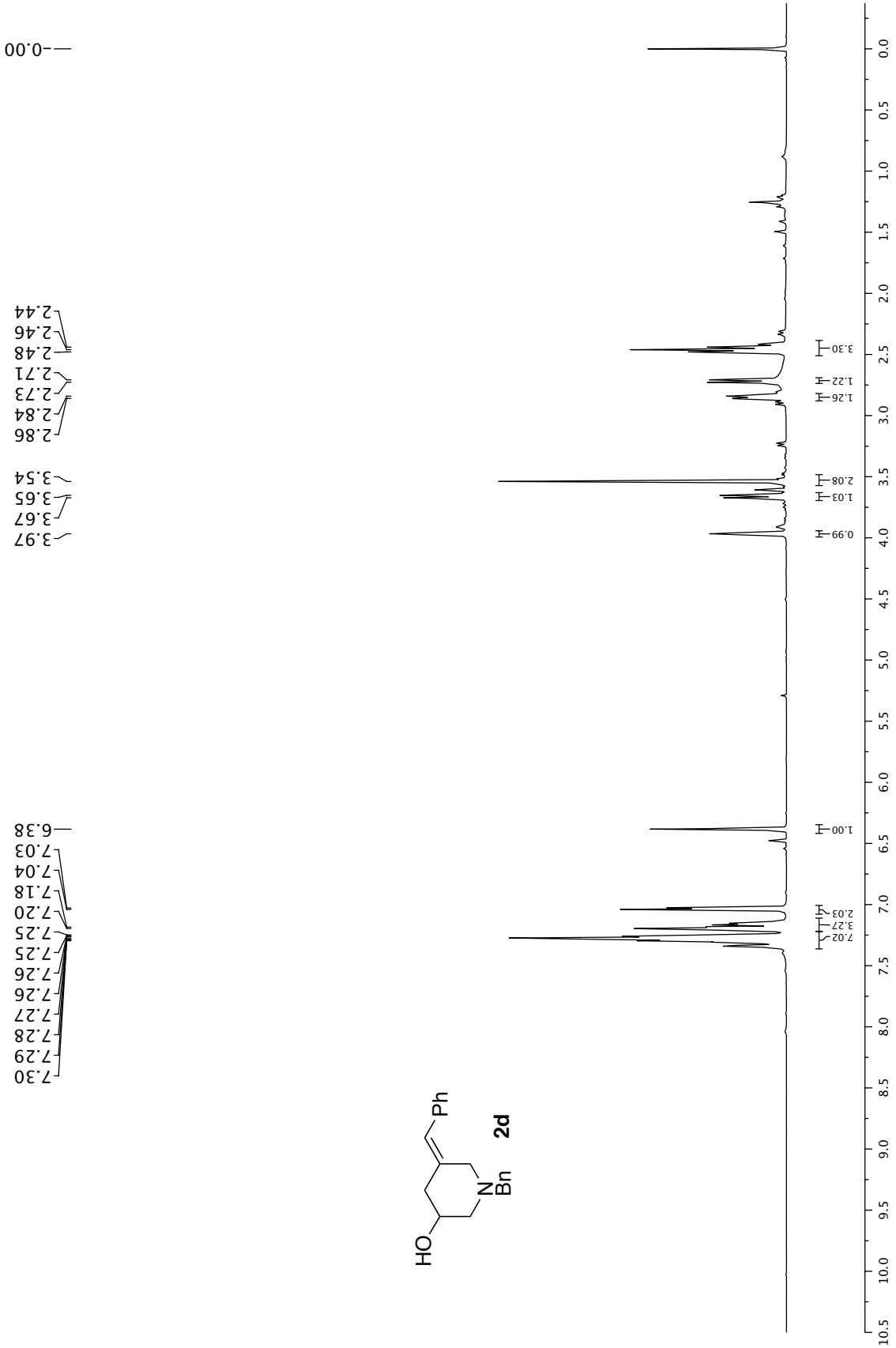
MeO2C
CO2Me
Ph
2c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Bn
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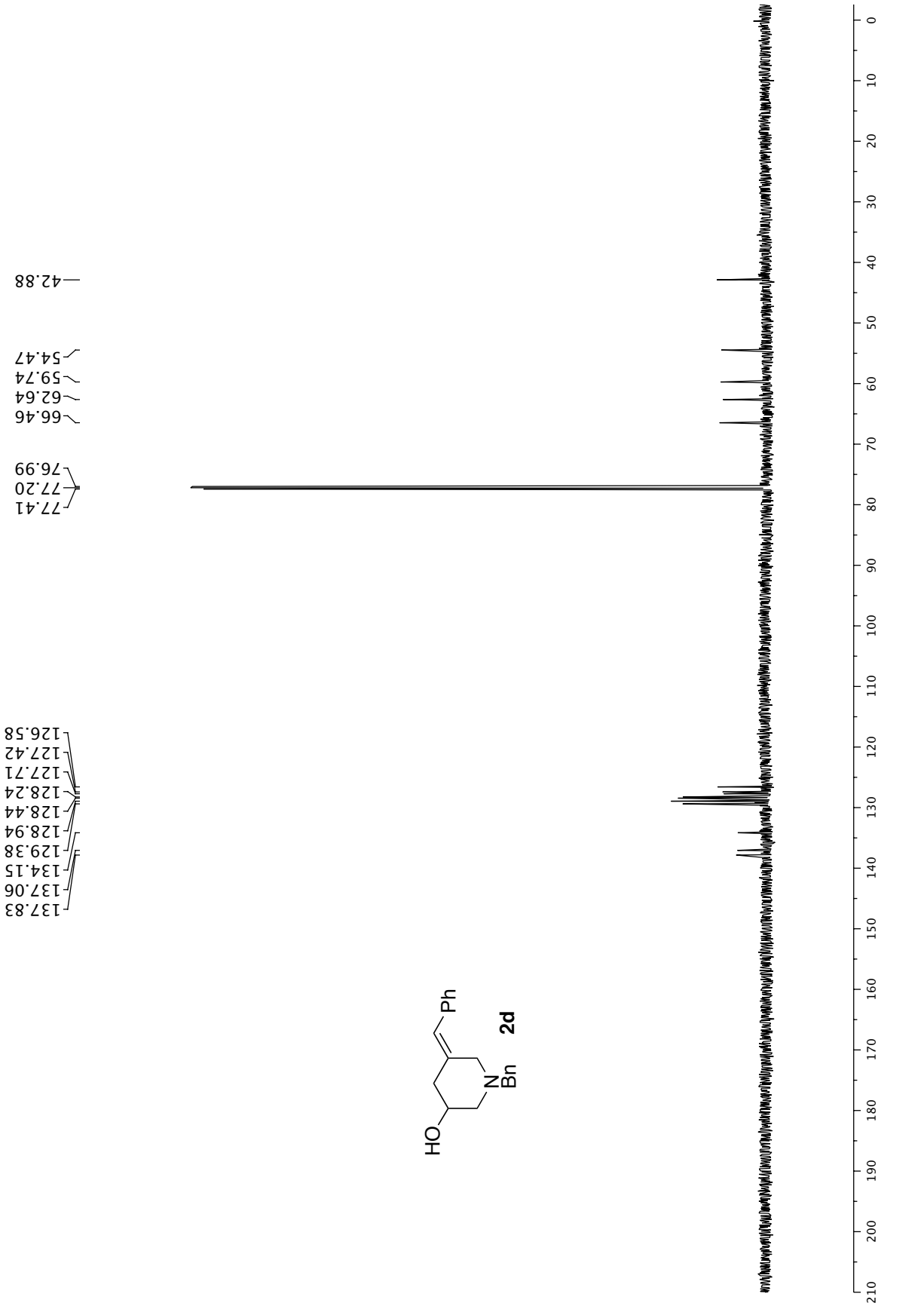
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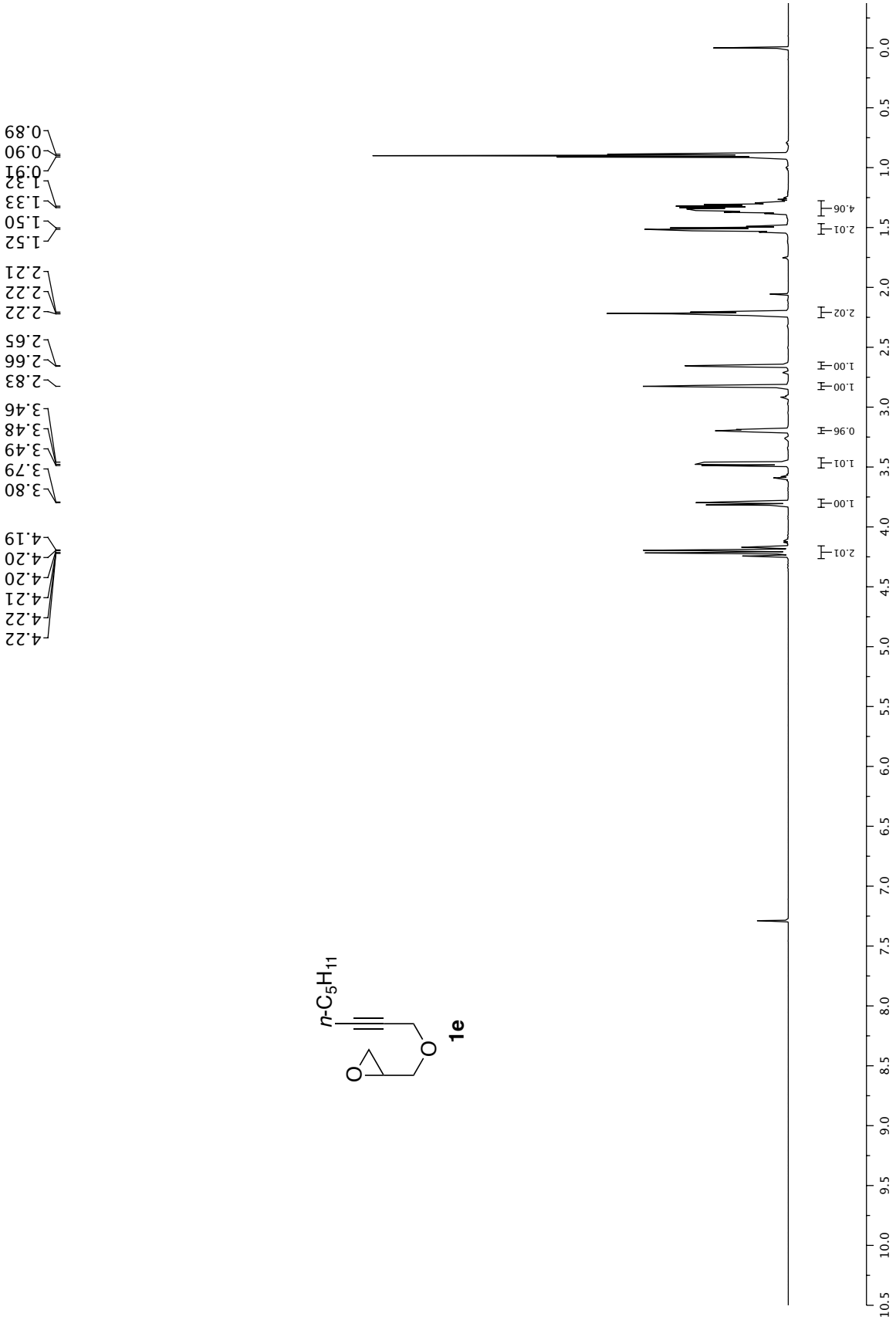
Bn
Ph
2d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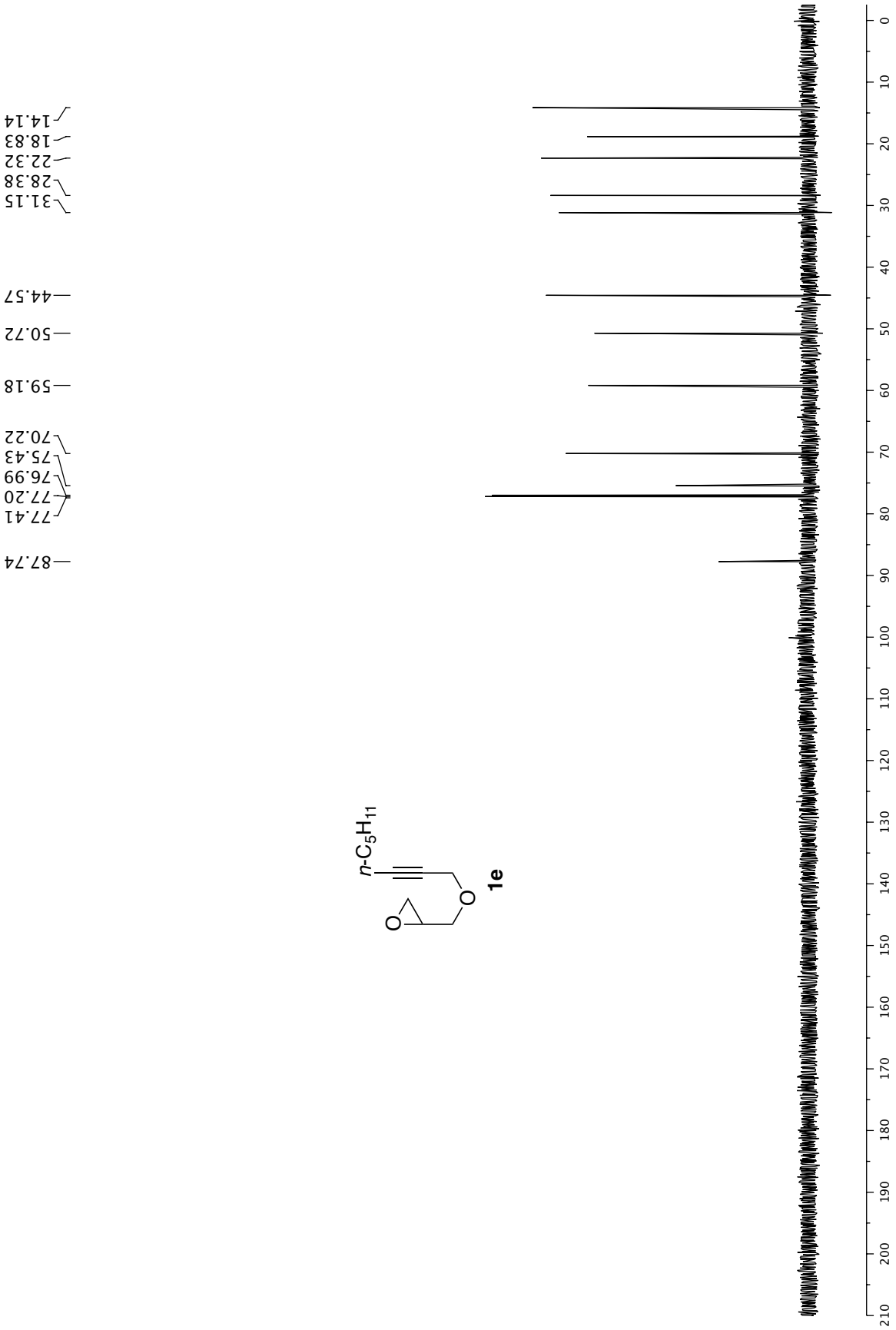
4.06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87.74
n-C5H11
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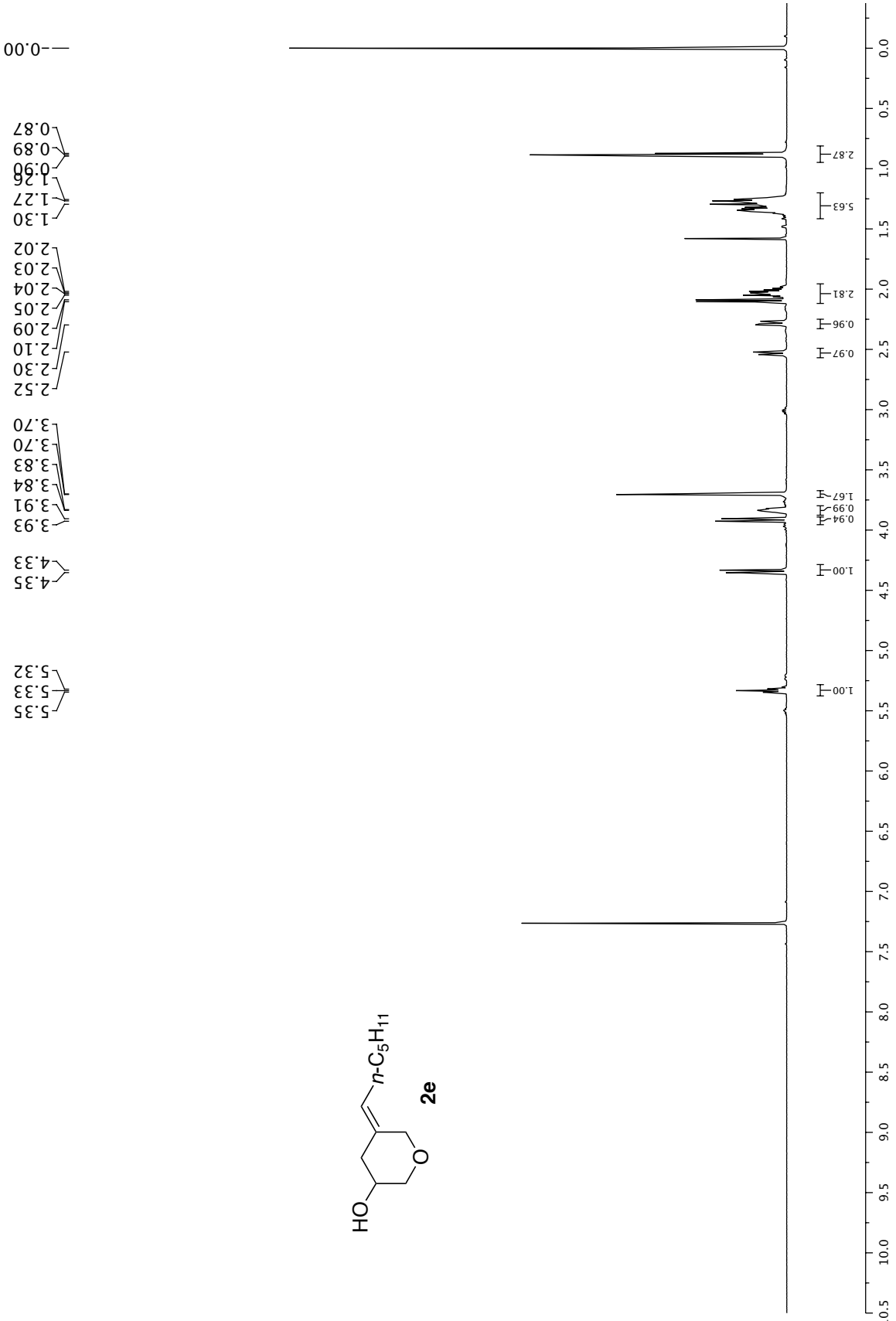
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1.00
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n-C5H11
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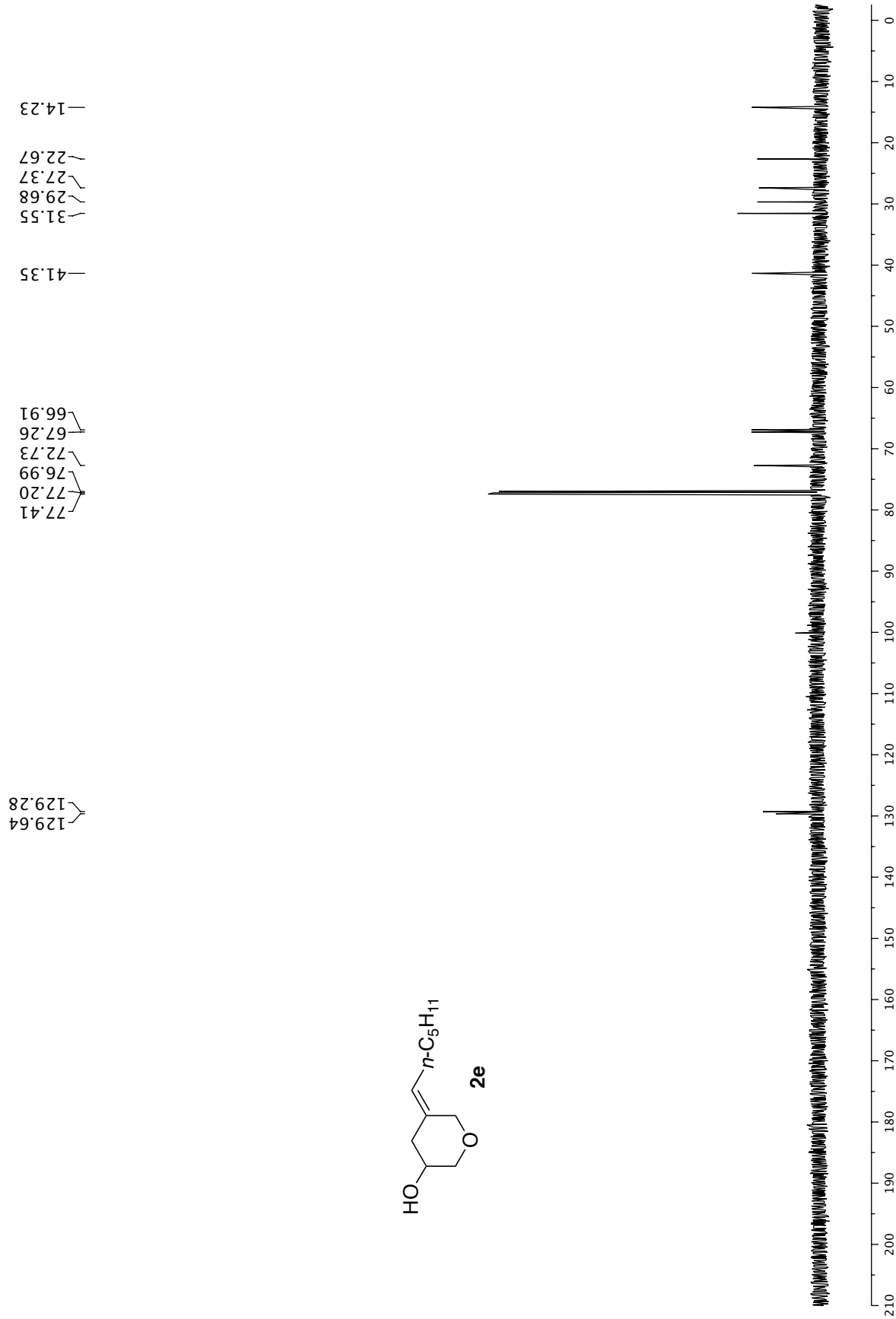
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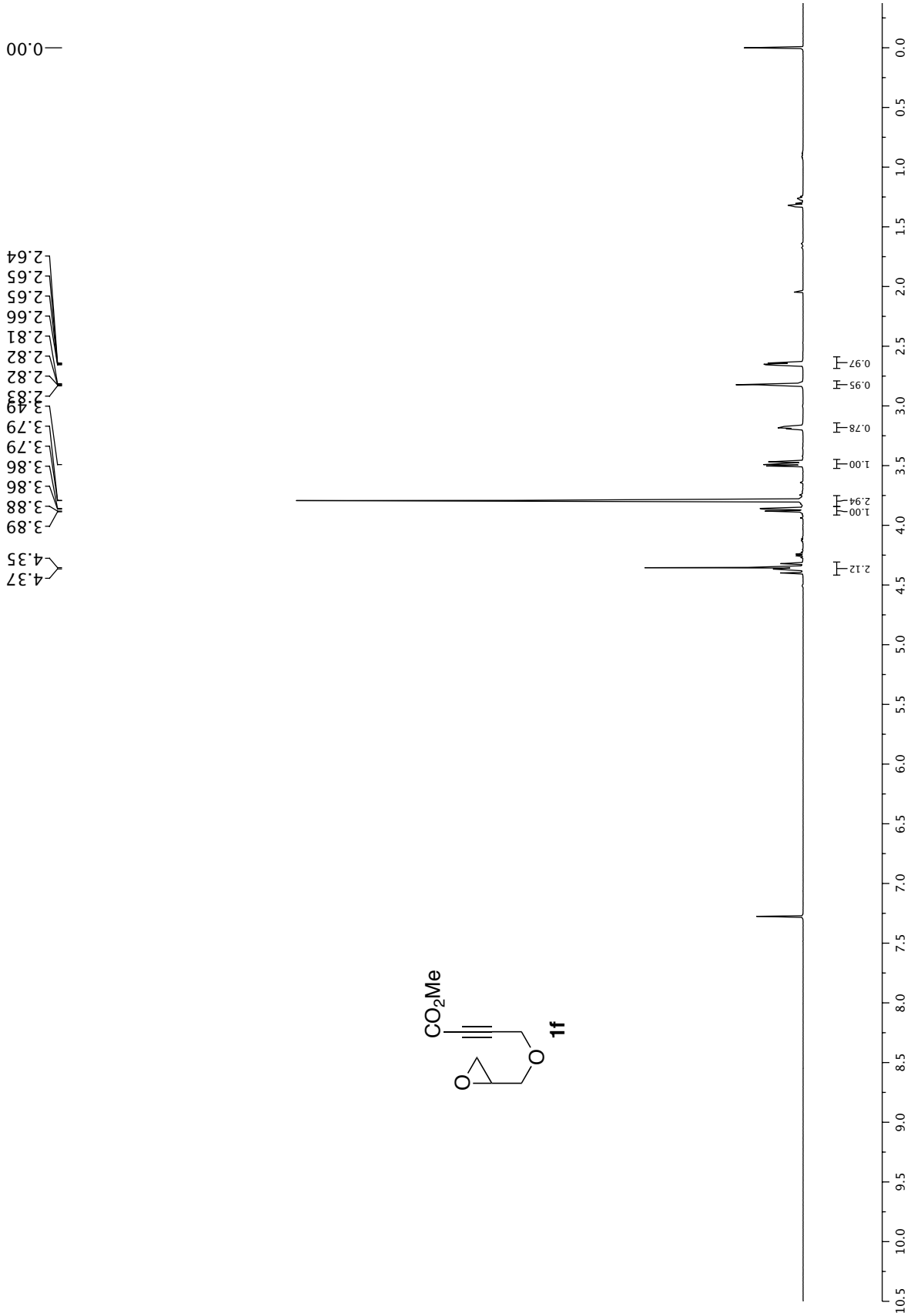
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3.86
3.86
3.88
3.89
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CO2Me
O
O
1f
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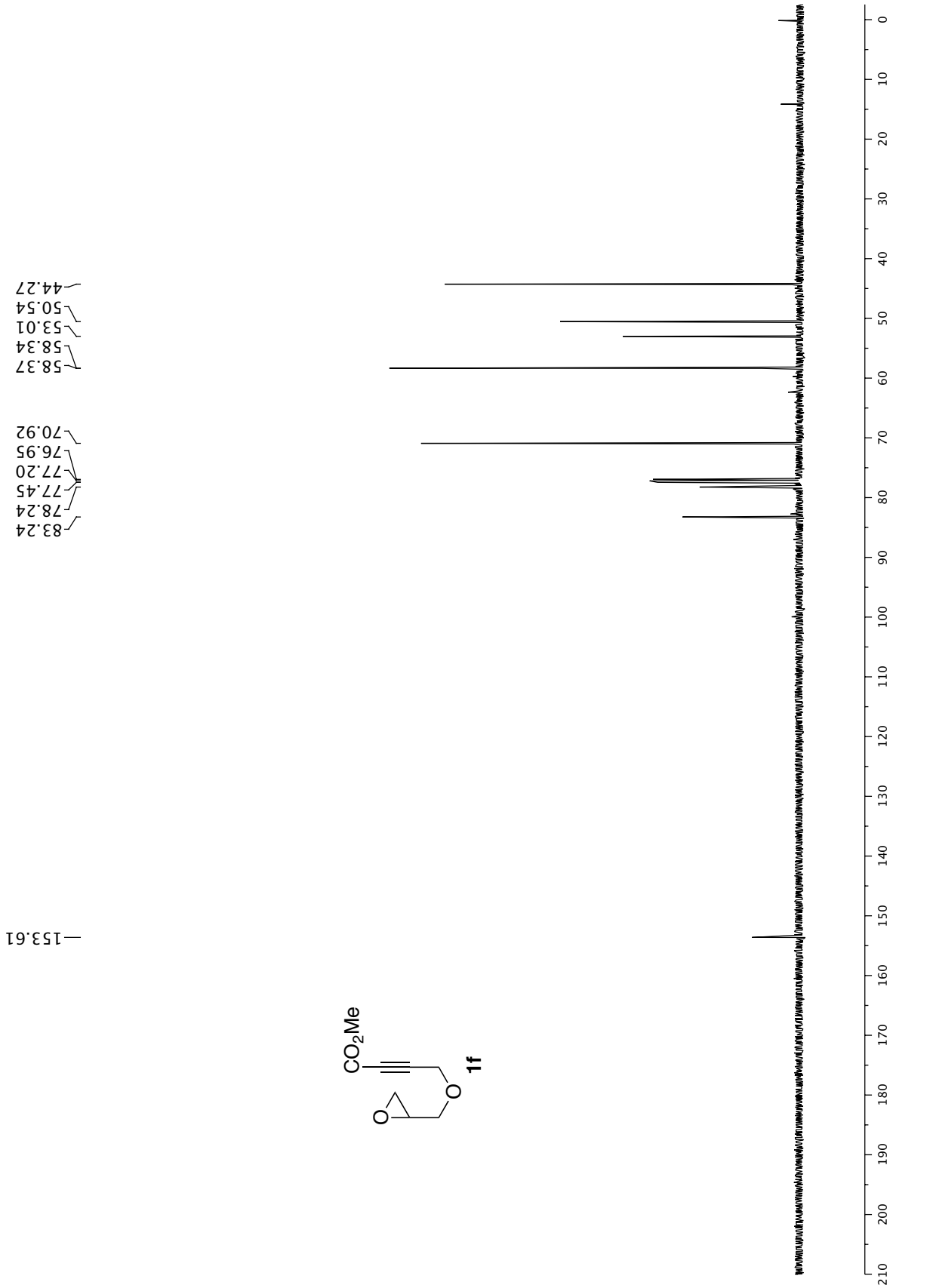
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O
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90
100
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140
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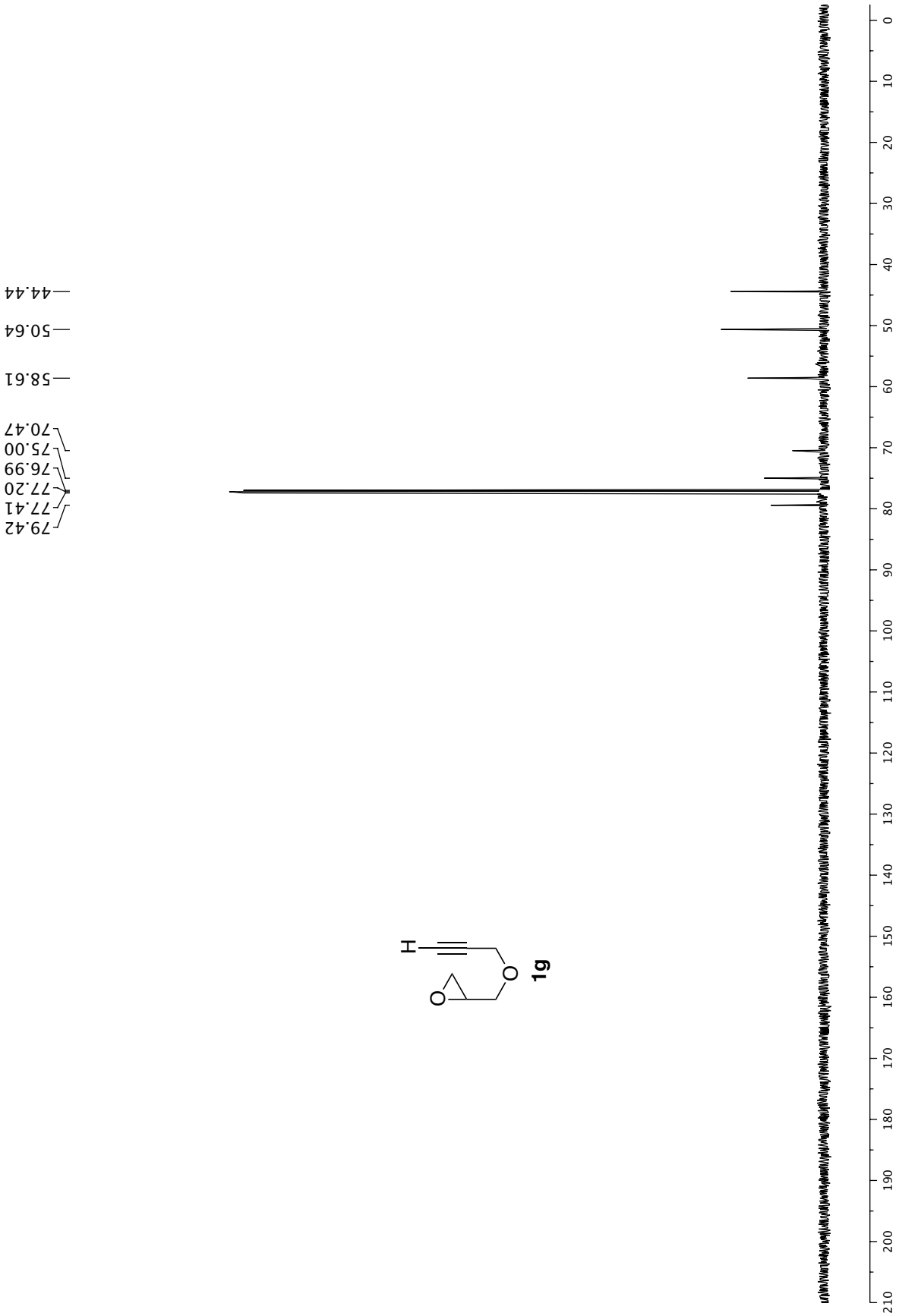
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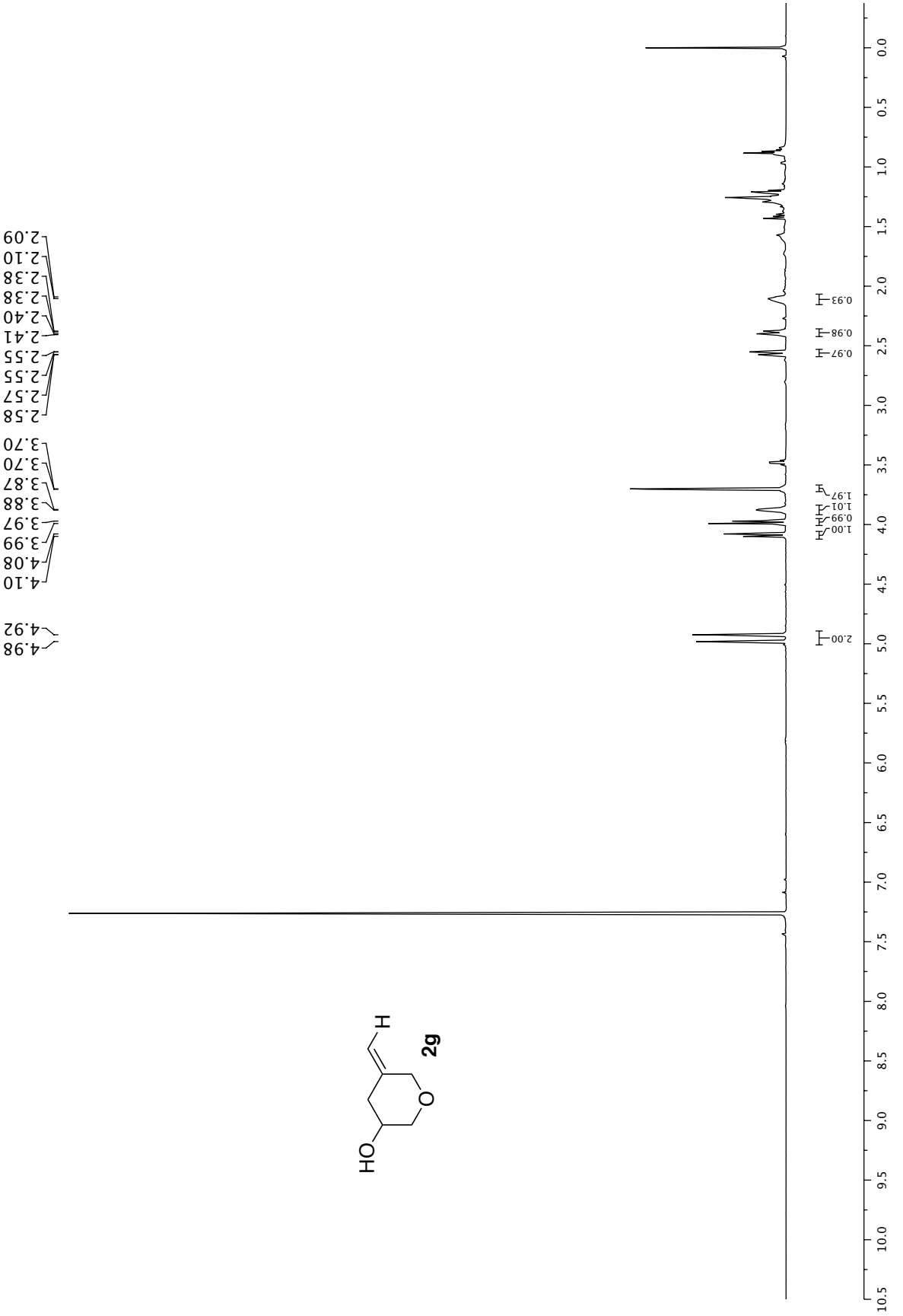
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H
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2.58
2.57
2.55
2.55
2.41
2.40
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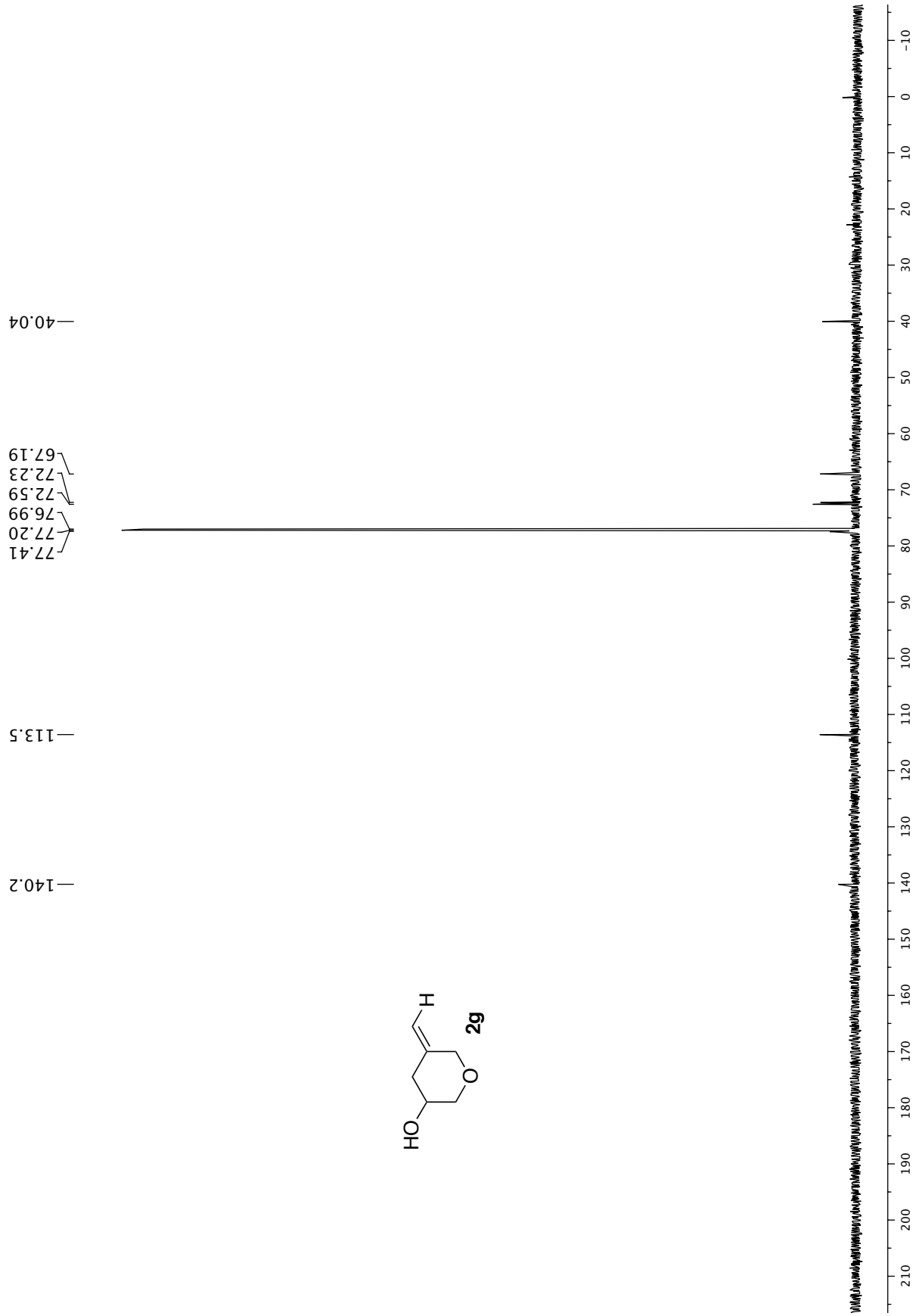
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2g
HO
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H