Polyol Synthesis with β-Oxyanionic Alkyllithium Reagents: Syntheses of Aculeatins A, B and D

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SUPPORTING INFORMATION

General Experimental Details. All moisture sensitive reactions were carried out under a positive pressure of argon in flame- or oven-dried glassware. The solvents tetrahydrofuran (THF), diethyl ether (Et_2O), toluene (PhMe), acetonitrile, hexane, and dichloromethane (CH_2Cl_2) were degassed with Ar and then passed through two 4 × 36 inch columns of anhydrous neutral alumina A-2 (8 × 14 mesh; LaRoche Chemicals; activated under a flow of Ar 350 ºC for 12 h) to remove H_2O according to the procedure by Grubbs.[1] Thin layer chromatography (TLC) was performed on Whatman K6F (250 μm) silica gel plates and visualized using either UV light or *p*-anisaldehyde or vanillin TLC staining solutions. Flash chromatography was carried out using the indicated solvent with Sorbent Technologies 230–400 mesh silica gel. All melting points (mp) were obtained using a Mel-Temp melting point apparatus and are not corrected.

^{1}H NMR ^{13}C NMR spectra were obtained on a CRYO-500 (500 MHz ^{1}H, 125.7 MHz ^{13}C) spectrometer using $CDCl_3$ or benzene-d_6. Chemical shifts (δ) for ^{1}H NMR and ^{13}C NMR were referenced to the residual solvent peaks (i.e. for $CDCl_3$, 7.27 and 77.23 ppm, respectively). Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), integration, and coupling constants (in Hertz). Multiplets (m) were reported over the indicated range (ppm) in which they appear. Infrared spectra were obtained on a MIDAC Prospect FT-IR spectrometer and are reported in order of decreasing frequency (cm^{-1}). Optical rotations were obtained on a Jasco DIP-370 digital polarimter and are reported as follows: $[\alpha]_D^T$, temperature (T), concentration (*c* = g/100 mL) and solvent. High

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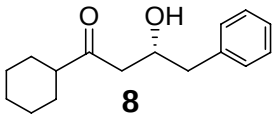
[1] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.

resolution mass spectrometry was performed by the University of California, Irvine Mass Spectrometry Center.

General procedure for the preparation of 0.40 M LiDBB stock solutions. An oven-dried 25 mL round bottom flask is equipped with a glass stir bar and flushed with argon. The flask is charged single crystal of 1,10-phenanthroline and 4,4'-di-*tert*-butylbiphenylide (1.00 g, 3.75 mmol) in anhydrous THF (9.4 mL). The solution is cooled to 0 ºC and *n*-butyllithium (ca. 2.78 M in hexane) is added dropwise until a brown color persisted (typically 1-2 drops). Lithium wire (ca. 0.262 g, 37.5 mmol) was then cut into thin strips directly into the flask under a purge of argon. The solution turns a dark green color within 2-3 min of stirring. The solution is left to stir at 0 ºC for 6 h, producing a stock solution of lithium di-*tert*-butylbiphenylide (LiDBB) that is assumed to have a concentration of 0.40 M.



8

Sample Procedures for Synthesis of β-Hydroxy Ketone (8).

From phenylthio alcohol (**9**):

A stirred solution of phenylthio alcohol **9** (0.10 g, 0.41 mmol) and a single crystal of 1,10-phenanthroline in anhydrous THF (1.5 mL) at 0 ºC was slowly titrated with *n*-BuLi (2.8 M in THF) until a brown color persisted. The solution was further cooled to −78 ºC, followed by the slow addition of freshly prepared LiDBB (1.7 mL, 0.86 mmol, 0.40 M THF). The green mixture was allowed to stir at this same temperature for 1 h before a pre-cooled (−78 ºC) THF solution of Weinreb amide **7** (0.71 g, 0.41 mmol, ~0.20–0.40 M with washings) was slowly transferred *via*

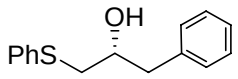
cannula. After stirring at −78 ºC for 12 h, the reaction was warmed to −40 ºC and quenched with 2 mL of saturated aqueous NH_4Cl solution. The mixture was poured in a separatory funnel and extracted with diethyl ether (2 × 15 mL). The organic fractions were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude residue was purified by flash chromatography (60:30:5:5 hexanes: dichloromethane: ethyl acetate: diethyl ether) to elute the desired β-hydroxy ketone **8** as a viscous oil (0.086 g, 85%).

From epoxide (**5**) and catalytic thiophenol:

To a stirred solution of epoxide **5** (100. mg, 0.745 mmol), thiophenol (15 μL, 0.15 mmol) and a single crystal of 1,10-phenanthroline in anhydrous THF (2.0 mL) at −78 ºC was slowly titrated with *n*-BuLi (2.8 M in THF) until a brown color persisted. Then a freshly prepared solution of LiDBB (4.3 mL, 1.72 mmol, 0.40 M THF) was added, the green mixture was allowed to stir at this temperature for 1 h before a pre-cooled (−78 ºC) THF solution of Weinreb amide **7** (95 mg, 0.56 mmol, ~0.20–0.40 M with washings) was slowly transferred *via* cannula. After stirring at −78 ºC for 12 h, the reaction was warmed to −40 ºC and quenched with 5 mL of saturated aqueous NH_4Cl solution. The mixture was poured in a separatory funnel and extracted with ether (2 × 25 mL). The organics were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude residue was purified by flash chromatography (60:30:5:5 hexanes: dichloromethane: ethyl acetate: diethyl ether) to yield the desired β-hydroxy ketone **8** as a viscous oil (0.020 g, 13%).

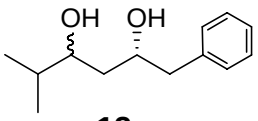
β-Hydroxy Ketone (8) showed the following spectral properties: R_f = 0.17 (5% EtOAc/5% ether/30% DCM/60% hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.32 (dd, *J* = 7.5, 7.3, 1H),

7.27–7.20 (m, 3H), 4.34–4.26 (m, 1H), 3.14 (d, J = 2.8, 1H), 2.87 (dd, J = 13.6, 7.2, 1H), 2.74 (dd, J = 13.6, 6.3, 1H), 2.63 (dd, J = 17.7, 3.3, 1H), 2.57 (dd, J = 17.7, 8.5, 1H), 2.36–2.27 (m, 1H), 1.88–1.75 (m, 4H), 1.70–1.64 (m, 1H), 1.38–1.15 (br m, 5H); ^{13}C NMR ($CHCl_3$, 125 MHz) δ 215.4, 138.2, 129.6, 128.7, 126.7, 68.9, 51.5, 46.2, 43.0, 28.5, 28.4, 26.0, 25.8, 25.7; IR (thin film) 3408, 3062, 3027, 2931, 1699 cm^{-1}; HRMS (ES/MeOH) *m/z* calcd for $C_{16}H_{22}O_2$ [M + Na]$^+$ 269.1518, found 269.1519.



9

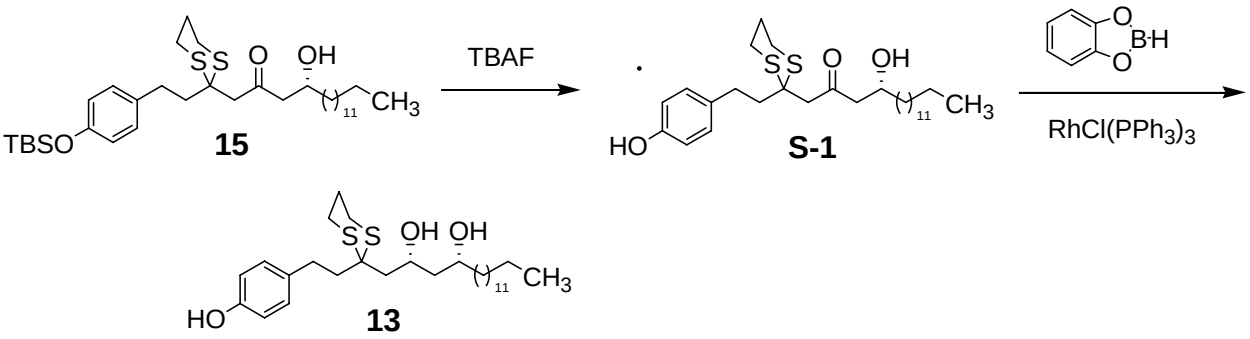
Phenylthio Alcohol (9). To neat *(R)*-2-benzyloxirane (0.62 g, 4.6 mmol) and $LiClO_4$ (59 mg, 0.55 mmol) was added thiophenol (0.48 mL, 4.6 mmol). The mixture was allowed to stir at room temperature for 24 h. The crude mixture was diluted with diethyl ether (50 mL) and washed with H_2O (2 × 30 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude residue by flash chromatography (20–30% diethyl ether/hexane) provided **9** as a slightly yellow oil (1.09 g, 96%): $[\alpha]^{24}_D$ –2.5 (*c* 1.08, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36–7.31 (m, 3H), 7.31–7.27 (m, 2H), 3.98–3.91 (m, 1H), 3.15 (dd, J = 13.7, 4.0, 1H), 2.92 (dd, J = 13.8, 8.2, 1H), 2.91–2.86 (m, 2H), 2.37 (d, J = 3.4, 1H); ^{13}C NMR ($CHCl_3$, 125 MHz) δ 137.9, 135.5, 130.1, 129.6, 129.3, 128.8, 126.8, 126.8, 70.7, 42.6, 41.2; IR (thin film) 3402, 3060, 3028, 2920, 1950 cm^{-1}; GCMS (CI/MeOH) *m/z* calcd for $C_{15}H_{16}OS$ [M + NH_4]$^+$ 262.1266, found 262.1274.



12

Diol (12). A stirred solution of phenylthio alcohol **9** (150 mg, 0.61 mmol) and a single crystal of 1,10-phenanthroline in anhydrous THF (1.5 mL) at 0 ºC was slowly titrated with *n*-BuLi (2.8 M in THF) until a brown color persisted. The solution was further cooled to −78 ºC, followed by the slow addition of freshly prepared LiDBB (3.3 mL, 1.3 mmol, 0.40 M THF). The green mixture was allowed to stir at this temperature for 1 h before a neat solution of distilled isobutyraldehyde **11** (84 μL, 0.92 mmol) was added slowly *via* syringe. After an additional hour, the reddish mixture was quenched with methanol (1 mL) and warmed to room temperature. The mixture was poured in a separatory funnel containing 10 mL of saturated aqueous NH_4Cl and extracted with diethyl ether (2 × 15 mL). The organic fractions were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude residue was purified by flash chromatography (20%–100% diethyl ether/hexane) to provide diol **12** as a crystalline white solid (118 mg, dr: 57:43 *anti:syn*, 0.57 mmol, 92%) whose spectral properties matched those reported in the literature.[2]

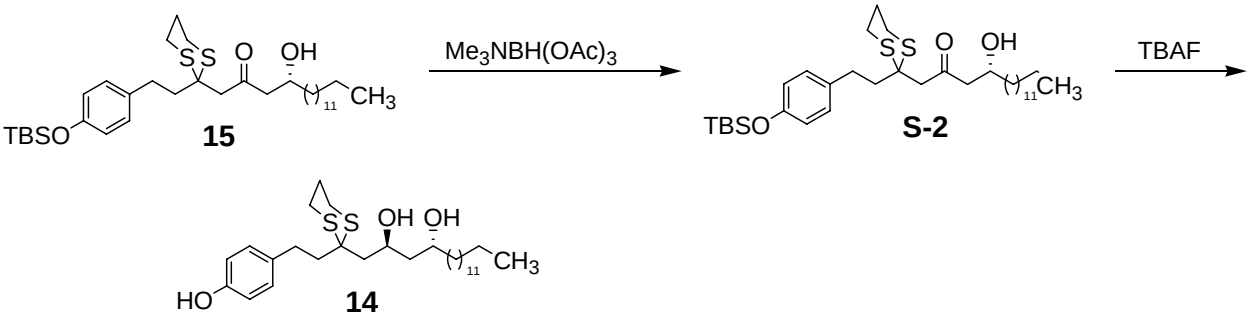
[2] Bartoli, G.; Bosco, M.; Bellucci, M. Cristina; Dalpozzo, R.; Marcantoni, E.; Sambri, L. *Org. Lett.,* **2000**, *2*, 45–47.



***syn*-Diol (13).** Tetrabutylammonium fluoride (38 μL, 0.038 mmol, 1.0 M in THF) was slowly added to a solution of silyl phenyl ether **15** (19 mg, 0.030 mmol) in anhydrous THF (1.0 mL) at 0 ºC. After stirring at that temperature for 1 h, the reaction mixture was quenched by the addition of 2 mL of saturated aqueous NH_4Cl. The aqueous layer was re-extracted with diethyl ether (3 × 7 mL). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The desired phenol adduct **S-1** (14 mg, 88%) was obtained as a colorless oil after purification by flash chromatography (50% diethyl ether/hexane) and had the following spectral properties: R_f = 0.16 (50% ether/hexane); $[\alpha]^{24}_D$ −16.1 (*c* 0.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.10 (d, *J* = 8.3, 2H), 6.77 (d, *J* = 8.3, 2H), 4.10–4.06 (m, 1H), 3.11 (t, *J* = 15.0, 1H), 3.10 (t, *J* = 15.0, 1H), 2.91–2.85 (m, 3H), 3.00–2.69 (m, 3H), 2.62 (dd, *J* = 17.7, 9.1, 1H), 2.39–2.32 (m, 2H), 2.06–1.96 (m, 2H), 1.55–1.48 (m, 1H), 1.44–1.38 (m, 2H), 1.34–1.15 (br m, 22H), 0.89 (t, *J* = 6.9, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 208.5, 154.1, 133.7, 129.9, 125.7, 115.5, 68.0, 51.7, 50.3, 50.2, 41.0, 36.6, 32.1, 30.5, 30.1, 30.0–29.9 (unresolved alkyl carbons), 29.9, 29.8, 29.6, 26.6 (2), 25.7, 25.1, 22.9, 14.4; IR (thin film) 3357, 3022, 2924, 2852, 1705 cm^{-1}; HRMS (ES/MeOH) *m/z* calcd for $C_{29}H_{48}O_3S_2$ $[M + Na]^+$ 531.2943, found 531.2953.

A solution of the above β-hydroxy ketone (**S-1)** (41 mg, 0.080 mmol) and Wilkinson's catalyst (2.0 mg, 0.0030 mmol) in anhydrous THF (2 mL) was cooled to −5 ºC. Catecholborane (0.40 mL, 0.40 mmol, 1.0 M in hexanes) was added dropwise and the solution was allowed to

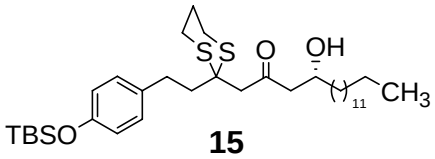
stir at −5–0 ºC for 3 h. The reaction mixture was quenched by the addition of methanol (0.3 mL) and saturated aqueous Rochelle's salt (10 mL). The mixture was then allowed to warm to room temperature. After stirring for 1 h, the layers were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried over Mg_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (60% ether/hexane) of the crude brown residue afforded **13** as a colorless oil (30 mg, dr 5:1 *syn: anti, cal.* 57%): R_f = 0.21 (60% ether/hexane); $[\alpha]^{24}_D$ +1.5 (*c* 0.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.07 (d, *J* = 8.4, 2H), 6.77 (d, *J* = 8.4, 2H), 5.54 (br s, 1H), 4.28 (t, *J* = 9.0, 1H), 4.10 (s, 1H), 4.00–3.85 (m, 1H), 3.81 (s, 1H), 3.50–3.47 (m, 1H), 3.04–2.97 (m, 1H), 2.97–2.91 (m, 1H), 2.89–2.75 (m, 4H), 2.68 (ddd, *J* = 12.6, 12.6, 5.4, 1H), 2.42 (dd, *J* = 15.3, 9.3, 1H), 2.28 (ddd, *J* = 14.3, 12.0, 4.8, 1H), 2.15 (ddd, *J* = 14.3, 12.0, 5.2, 1H), 2.09–2.01 (m, 1H), 1.92 (d, *J* = 14.8, 2H), 1.67–1.47 (br m, 3H), 1.64–1.38 (m, 2H), 1.33–1.21 (br m, 20H), 0.89 (t, *J* = 6.9, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.4, 133.5, 129.7, 72.5, 70.3, 52.0, 45.6, 43.8, 42.4, 37.9, 32.1, 30.0–29.9 (unresolved alkyl carbons), 29.8, 29.6, 26.6, 26.3, 25.6, 25.0, 22.9, 14.3; IR (thin film) 3375, 2924, 2854, 1614, 1515 cm^{-1}; HRMS (ES/MeOH) *m/z* calcd for $C_{29}H_{50}O_3S_2$ [M + Na]$^+$ 533.3099, found 533.3108.



***anti*-Diol (14).** $Me_3NBH(OAc)_3$ (139 mg, 0.53 mmol) was added to a solution of 1:1 dry acetonitrile:acetic acid (4 mL) and allowed to stir at room temperature for 15 min. The mixture was then cooled to 0 ºC before the addition of a solution of β-hydroxy ketone **15** (55 mg, 0.088 mmol) in dry dichloromethane (2.5 mL) *via* cannula. After stirring at 0 ºC for 3 h, the reaction was quenched by the addition of saturated aqueous Rochelle's salt (2 mL). The solution was left to stir for 1 h at room temperature, followed by removal of the precipitate by filtration. The filtrate was extracted with EtOAc (3 × 15 mL). The combined organic fractions were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography (40% ether/hexane) provided the desired *trans*-diol **S-2** as a colorless oil (50 mg, dr 10:1 *anti:syn*, 91%): R_f = 0.36 (50% ether/hexanes); $[\alpha]^{24}_D$ –0.5 (*c* 1.25, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.05 (d, *J* = 8.3, 2H), 6.76 (d, *J* = 8.3, 2H), 4.41–4.34 (m, 1H), 3.98–3.90 (m, 1H), 3.84 (s, 1H), 3.05–2.98 (br m, 2H), 2.90–2.82 (m, 2H), 1.82–2.75 (m, 2H) , 2.66 (ddd, *J* = 13.1, 12.4, 5.1, 1H), 2.51 (dd, *J* = 15.2, 9.6, 1H), 2.32–2.24 (m, 1H), 2.21–2.13 (m, 1H), 2.09–2.02 (m, 1H), 1.70–1.63 (m, 1H), 1.60–1.53 (m, 2H), 1.35–1.22 (br m, 22H), 0.99 (s, 9H), 0.89 (t, *J* = 6.9, 3H), 0.19 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.1, 134.2, 129.5, 120.2, 69.2, 66.6, 52.1, 44.8, 43.5, 42.2, 37.8, 32.1, 30.5, 30.0–29.9 (unresolved alkyl carbons), 29.8, 29.6, 26.6, 25.3, 26.0, 25.9, 25.1, 22.9, 14.4, 14.3, –4.2; IR (thin film) 3434, 2927, 2854, 1510, 1257 cm^{-1}; HRMS (ES/MeOH) *m/z* calcd for $C_{35}H_{64}O_3S_2Si$ $[M + Na]^+$ 647.3964, found 647.3978.

Tetrabutylammonium fluoride (96 μL, 0.096 mmol, 1.0 M in THF) was slowly added to a solution of above silyl phenyl ether **(S-2)** (61 mg, 0.096 mmol) in anhydrous THF (1.5 mL) at 0 ºC. After stirring at that temperature for 45 min, the reaction was quenched by the addition of saturated aqueous NH_4Cl (2 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL).

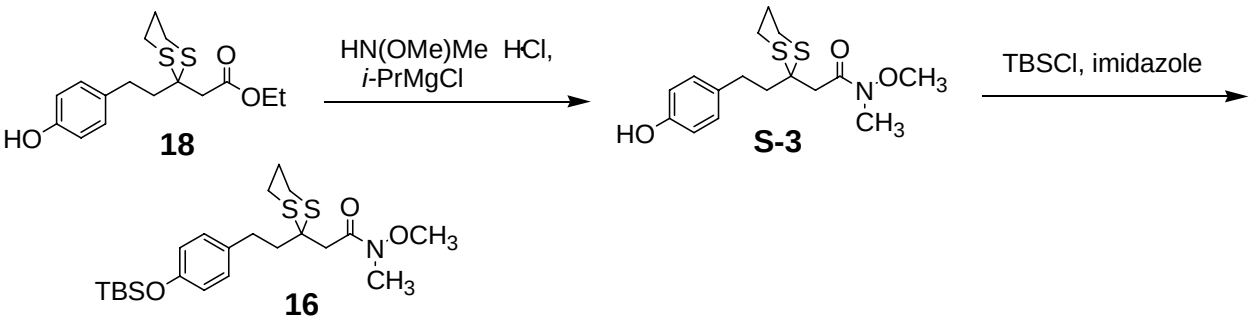
The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Phenol **14** (45 mg, 92%) was obtained as a colorless oil after purification by flash chromatography (2:1 petroleum ether:hexane): R_f = 0.42 (2:1 petroleum ether/EtOAc); $[\alpha]^{24}_D$ +7.2 (*c* 0.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.06 (d, *J* = 8.3, 2H), 6.76 (d, *J* = 8.4, 2H), 4.38 (appar dt, *J* = 8.4, 2.6, 1H), 3.98–3.95 (m, 1H), 3.04–2.94 (m, 3H), 2.87–2.76 (m, 3H), 2.66 (dd, *J* = 12.3, 5.5, 1H), 2.51 (dd, *J* = 15.2, 9.6, 1H), 2.28 (ddd, *J* = 14.5, 12.3, 5.2, 1H), 2.16 (ddd, *J* = 14.4, 12.3, 5.3, 1H), 2.09–2.01 (m, 1H), 1.95 (d, *J* = 15.1, 2H), 1.68 (ddd, *J* = 14.4, 8.1, 2.4, 1H), 1.62–1.50 (m, 2H), 1.49–1.39 (m, 2H), 1.35–1.17 (br m, 20H), 0.89 (t, *J* = 6.7, 3H) ; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.2, 133.6, 129.8, 115.6, 69.3, 66.7, 52.1, 44.7, 43.5, 42.3, 37.7, 32.1, 29.9 (several overlapping peaks), 29.6, 26.6, 26.3, 26.0, 25.1, 22.9, 14.4; IR (thin film) 3376, 2925, 2854, 2360, 1614, 1516 cm^{-1}; HRMS (ES/MeOH) *m/z* calcd for $C_{29}H_{50}O_3S_2$ $[M + Na]^+$ 533.3099, found 533.3081.



15

β-Hydroxy Ketone (15). To a cooled (0 ºC) solution of phenylthio alcohol **17** (279 mg, 0.83 mmol) and a single crystal of 1,10-phenanthroline in 1:1 dry THF: hexane (4 mL) was added slowly *n*-BuLi (2.98 M in hexanes) until a brown color persisted. The solution was cooled to –78 ºC before a freshly prepared solution of LiDBB (4.4 mL, 0.40 M in THF, 1.74 mmol) was transferred dropwise by syringe. The green solution was allowed to stir for 1 h, followed by the slow cannula addition of a pre-cooled (–78 ºC) solution of Weinreb amide **16** (250 mg, 0.55 mmol) in THF (2 mL). The resulting reddish-orange mixture was stirred at the same temperature

for 18 h before it was warmed to –40 ºC, and the reaction was quenched by the addition of MeOH (1 mL). After further warming the solution to 0 ºC, saturated aqueous NH_4Cl (30 mL) was pour over the mixture and the aqueous layer was extracted with diethyl ether (2 × 40 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification of the crude rersidue by column chromatography (40% ether/hexane) provided **15** as a colorless oil (271 mg, 79 %): R_f = 0.20 (40% ether/hexane); $[\alpha]^{24}_D$ –11.5 (*c* 0.79, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.08 (d, *J* = 8.4, 2H), 6.76 (d, *J* = 8.4, 2H), 4.09–4.03 (m, 1H), 3.10 (dd, *J* = 21.2, 14.9, 2H), 2.89 (dt, *J* = 6.0, 5.3, 4H), 2.75 (t, *J* = 8.5, 2H), 2.63 (dd, *J* = 9.0, 17.7, 1H), 2.60 (br s, 1H), 2.38–2.32 (m, 2H), 2.36–2.33 (m, 1H), 2.05–1.94 (m, 2H), 1.54–1.48 (m, 1H), 1.30–1.23 (m, 22H), 0.99 (s, 9H), 0.89 (t, *J* = 6.8, 3H), 0.19 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 208.3, 154.0, 129.6, 134.2, 129.6, 120.2, 120.1, 67.8, 51.8, 50.3, 50.2, 40.9, 36.6, 32.1, 30.2, 29.9 (3C), 29.8, 29.6, 26.6, 26.5, 25.9, 25.7, 25.1, 22.9, 18.4, 14.3, –4.2; IR (thin film) 3444, 3028, 2925, 2360, 1705 cm^{-1}; HRMS (ES/MeOH) *m/z* calcd for $C_{35}H_{62}O_3S_2Si$ $[M + Na]^+$ 645.3807, found 645.3823.



Weinreb amide (16). To a cooled solution (–20 ºC) of ester[3] **18** (3.36 g, 10.8 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (1.26 g, 13.0 mmol) in anhydrous THF (100 mL) was slowly added *iso*-propylmagnesium chloride (13.5 mL, 26.9 mmol, 2 M in ether). After stirring at –20 ºC for 2 h, the solution was warmed to 0 ºC, and the reaction was quenched by the addition of saturated aqueous NH_4Cl (50 mL). The mixture was extracted with ether (3 × 50 mL). The organics were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography (10–30% ether/dichloromethane) of the crude residue furnished the desired Weinreb amide intermediate **S-3** (2.15 g, 72%) as a white solid with the following spectral properties: mp 56–57 ºC; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.07 (d, *J* = 8.3, 2H), 6.77 (d, *J* = 8.3, 2H), 3.77 (s, 3H), 3.25 (s, 3H), 3.23 (s, 2H), 3.00–2.91 (m, 2H), 2.90–2.84 (m, 2H), 2.83–2.80 (m, 2H), 2.52–2.48 (m, 2H), 2.09–2.00 (m, 1H), 2.00–1.90 (m, 1H); ^{13}C NMR ($CHCl_3$, 125 MHz) δ 170.0, 154.5, 133.4, 129.8, 115.5, 61.8, 51.3, 41.3, 38.5, 32.4, 30.2, 26.6, 25.4; IR (thin film) 3263, 3006, 2932, 2898, 1630 cm^{-1}; HRMS (ES/MeOH) *m/z* calcd for $C_{16}H_{23}NO_3S_2$ $[M + Na]^+$ 364.1017, found 364.1011.

To a solution of the above phenol (**S-3)** (300 mg, 0.88 mmol) and imidazole (150 mg, 2.2 mmol) in DMF (6 mL) was added TBSCl (264 mg, 1.76 mmol) in one portion at room temperature. After stirring for 18 h, the reaction was quenched by the addition of brine (20 mL). The aqueous layer was extracted with diethyl ether (1 × 20 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (40% ether/hexane) afforded **16** as a colorless oil (396 mg, 99%): R_f = 0.14

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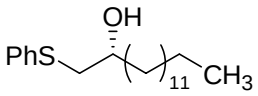
[3] Peuchmaur, M.; Saidani, N.; Botte, C.; Marechal, E.; Vial, H.; Wong, Y.-S. *J. Med. Chem.* **2008**, *51*, 4870–4873.

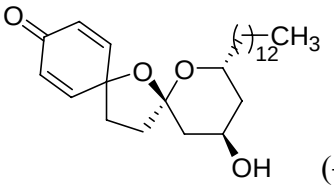
(40% ether/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.11 (d, *J* = 8.3, 2H), 6.75 (d, *J* = 8.3, 2H), 3.76 (s, 3H), 3.23 (s, 3H), 3.20 (s, 2H), 3.00–2.91 (m, 2H), 2.90–2.84 (m, 2H), 2.83–2.79 (m, 2H), 2.52–2.48 (m, 2H), 2.10–2.00 (m, 1H), 2.00–1.90 (m, 1H), 0.98 (s, 9H), 0.18 (s, 6H); ^{13}C NMR ($CHCl_3$, 125 MHz) δ (amide carbonyl peak not observed), 153.8, 134.6, 129.6, 120.1, 61.6, 51.3, 41.0, 38.5, 32.2, 30.3, 26.6, 25.9, 25.2, 18.4, –4.3; IR (thin film) 3028, 2931, 2858, 1653, 1506 cm^{-1}; HRMS (ES/MeOH) *m/z* calcd for $C_{22}H_{37}NO_3S_2Si$ $[M + Na]^+$ 478.1182, found 478.1871.



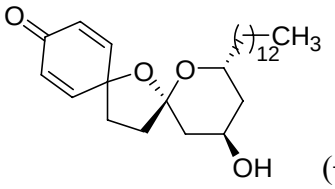
17

Phenylthio Alcohol (17). To stirred solution of neat *(R)*-(+)-1,2-epoxypentadecane (1.09 g, 4.81 mmol) and $LiClO_4$ (64 mg, 0.60 mmol) was slowly added thiophenol (0.50 mL, 4.8 mmol) at room temperature. After 24 h, the crude reaction mixture was diluted with diethyl ether (50 mL) and washed with water (40 mL) and brine (40 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by column chromatography (10% ether/hexanes) afforded **17** as a crystalline white solid (1.44 g, 89%): R_f = 0.37 (20% ether/hexanes); $[\alpha]^{24}_D$ –27.2 (*c* 0.99, $CHCl_3$); mp 142–144 ºC; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39 (d, *J* = 7.3, 2H), 7.31 (t, *J* = 7.4, 2H), 7.23 (t, *J* = 7.4, 1H), 3.70–3.64 (m, 1H), 3.17 (dd, *J* = 13.7, 3.3, 1H), 3.85 (dd, *J* = 13.7, 8.8, 1H), 2.0 (br s, 1H), 1.56–1.51 (m, 2H), 1.40–1.22 (br m, 22H) 0.89 (t, *J* = 6.9, 3H); ^{13}C NMR (C_6D_6, 125 MHz) δ 135.5, 130.3, 129.3, 126.8, 70.6, 42.5, 36.4, 32.1, 29.9–29.8 (unresolved alkyl carbons), 29.6, 25.9, 22.9, 14.4; IR (KBr) 3432,

3057, 2918, 2848, 1938 cm^{-1}; HRMS (ES/MeOH) *m/z* calcd for $C_{21}H_{36}OS$ $[M + Na]^+$ 359.2385, found 359.2380.



(–)-aculeatin A



(+)-aculeatin B

(–)-Aculeatin A and (+)-aculeatin B. Phenyliodine(III) bis(trifluoracetate) (38 mg, 0.088 mmol) was added to a cooled (0 ºC) solution of *syn* 1,3-diol **13** (dr 5:1 *syn:anti*, 15 mg, 0.029 mmol) in acetone (1 mL) and citrate-phosphate buffer (0.2 mL, pH 6; prepared by mixing 63 mL of 0.2 M Na_2HPO_4 and 37 mL of 0.1 M citric acid according to the literature[4]). The mixture was allowed to stir at 0 ºC in the dark for 1 h when TLC showed trace amount of the starting material. The reaction was quenched by the addition of saturated aqueous Na_2SO_3 (5 mL). The mixture was diluted with ethyl acetate (20 mL) and washed with saturated aqueous $CuSO_4$ (1 × 15 mL) and saturated aqueous Na_2SO_4 (1 × 15 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo.* Chromatography (40% EtOAc/hexane) on the crude residue gave (–)-aculeatin A (4 mg, 0.0096 mmol, 33%) and (+)-aculeatin B (2 mg, 0.0048 mmol, 17%) as colorless oils. **(–)-Aculeatin A** had the following spectral properties; R_f = 0.22 (40% EtOAc/hexane); $[\alpha]^{24}_D$ –5.4 (*c*. 0.17, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.85 (dd, *J* = 10, 2.9, 1H), 6.77 (dd, *J* = 10, 2.9, 1H), 6.14 (dd, *J* = 10, 1.8, 1H), 6.10 (dd, *J* = 10, 1.8, 1H), 4.16–4.09 (m, 2H), 3.37 (d, *J* = 10, 1H), 2.43–2.37 (m, 1H), 2.24 (dd, *J* = 10.1, 8.3, 1H),

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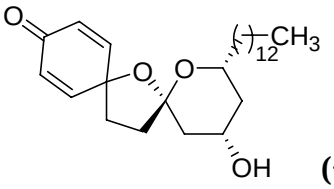
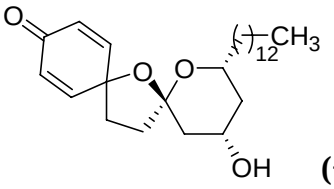
[4] Armarego, W. L. F.; Perrin, D. D.; *Purification of Laboratory Chemicals*, 4th ed.; Butterworth-Heinemann: Oxford, UK, **1996**, p. 43.

2.04–1.99 (m, 3H), 1.94 (br d, J = 14.1, 1H), 1.80 (br dd, J = 13.9, 2.0, 1H), 1.60–1.40 (br m, 4H),1.40–1.20 (m, 21H), 0.89 (t, J = 7.0, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 185.5, 151.1, 149.0, 127.6, 127.3, 109.3, 80.0, 65.6, 65.1, 39.3, 38.2, 36.1, 34.4, 32.1, 29.9 (several overlapping signals), 29.4, 29.6, 25.9, 22.9, 14.4; IR (thin film) 3415, 2925, 2854, 1674, 1631 cm^{-1}; HRMS (ES/MeOH) *m/z* calcd for $C_{26}H_{42}O_4$ [M + Na]$^+$ 441.2981, found 441.2970. **(+)-Aculeatin B** had the following spectral properties: R_f = 0.18 (40% EtOAc/hexane); $[\alpha]^{24}_D$ +47.5 (*c* 0.13, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.00 (dd, J = 10, 3.0, 1H), 6.77 (dd, J = 10, 3.0, 1H), 6.14 (dd, J = 10.1, 2.0, 1H), 6.10 (dd, J = 10.1, 2.0, 1H), 4.38 (appar quint., J = 3.1 , 1H), 3.90–3.85 (m, 1H), 2.69 (ddd, J = 12.0, 6.1, 1.3, 1H), 2.35–2.29 (m, 1H), 2.09 (dd, J = 13.9, 3.3, 1H), 2.06–2.03 (m, 1H), 1.96–1.87 (m, 2H), 1.65–1.48 (br m, 8H),1.48–1.25 (br m, 19H), 0.89 (t, J = 6.9, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 185.9, 152.4, 149.3, 127.4 (2), 108.7, 77.5, 69.7, 65.4, 40.8, 38.2, 36.0, 35.6, 35.6, 35.5, 32.1, 29.9 (several overlapping signals), 29.7, 29.6, 26.1, 22.9, 14.3; IR (thin film) 3448, 2925, 2854, 1670, 1628 cm^{-1}; HRMS (ES/MeOH) *m/z* calcd for $C_{26}H_{42}O_4$ [M + Na]$^+$ 441.2981, found 441.2987.



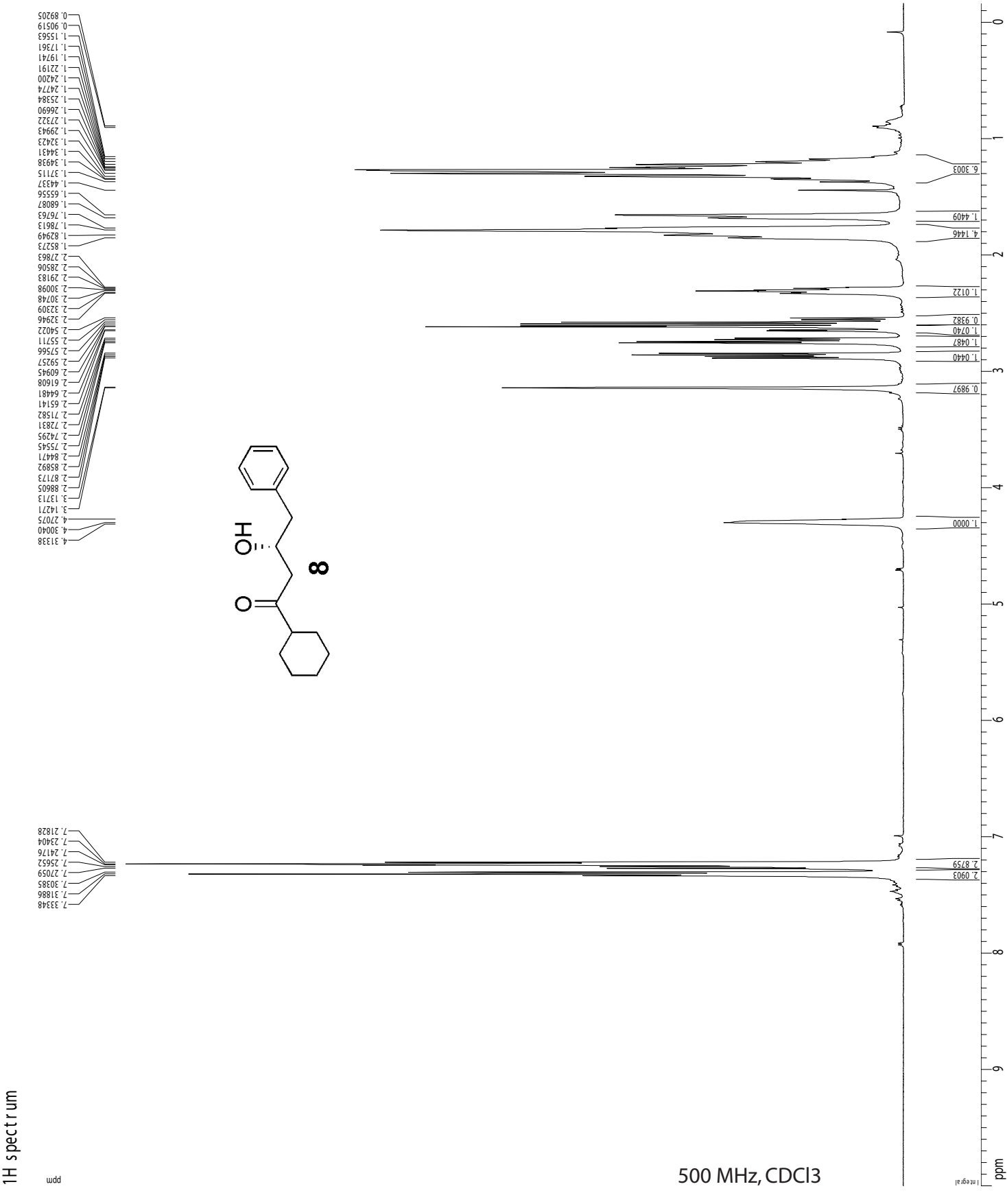
(+)-aculeatin D



(+)-6-*epi*-aculeatin D

(+)-Aculeatin D and (+)-6-*epi*-aculeatin D. Phenyliodine(III) bis(trifluoracetate) (50 mg, 0.12 mmol) was added to a cooled (0 ºC) solution of *trans* 1,3-diol **14** (25 mg, dr 10:1 *anti:syn,* 0.049 mmol) in acetone (1 mL) and citrate-phosphate buffer (pH 6, 0.2 mL). The mixture was allowed to stir at 0 ºC in the dark for 20 min, when TLC showed consumption of the starting material. The reaction was quenched by the addition of saturated aqueous Na_2SO_3 (5 mL). The mixture

was diluted with diethyl ether (20 mL) and washed with saturated aqueous $CuSO_4$ (1 × 15 mL) and saturated aqueous Na_2SO_4 (1 × 15 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo.* Chromatography (40% EtOAc/petroleum ether) of the crude residue gave (+)-6-*epi*-aculeatin D (7 mg, 0.017 mmol, 35%) and (+)-aculeatin D (6 mg, 0.014 mmol, 30%) as colorless oils. **(+)-Aculeatin D** had the following spectral properties: R_f = 0.12 (40% EtOAc/petroleum ether); $[\alpha]^{24}_D$ +42.8 (*c* 0.35, $CHCl_3$); ^{1}H NMR (C_6D_6, 500 MHz) δ 6.89 (dd, *J* = 10.0, 2.9, 1H), 6.19 (dd, *J* = 10.0, 2.9, 1H), 6.07 (dd, *J* = 10.0, 1.8, 1H), 6.04 (dd, *J* = 10.0, 1.8, 1H), 3.37–3.30 (m, 1H), 2.96–2.88 (m, 1H), 1.91–1.85 (m, 1H), 1.82–1.79 (m, 1H), 1.75–1.69 (m, 1H), 1.59–1.49 (m, 2H), 1.45–1.41 (m, 2H), 1.38–1.30 (br m, 24H), 0.98 (q, *J* = 11.6, 1H), 0.92 (t, *J* = 6.9, 3H); ^{13}C NMR (C_6D_6, 125 MHz) 185.0, 152.0, 149.0, 127.7, 127.6, 109.5, 78.5, 71.8, 67.0, 44.4, 41.6, 36.6, 35.5, 33.4, 32.7, 30.8, 30.6, 30.5 (several overlapping signals), 30.3, 30.2, 26.6, 23.5, 14.7; IR (thin film) 3427, 2923, 2852, 1670, 1464 cm^{-1}; HRMS (ES/MeOH) *m/z* calcd for $C_{26}H_{42}O_4$ $[M + Na]^+$ 441.2981, found 441.2971. **(+)-6-*epi*-Aculeatin D** had the following spectral properties: R_f = 0.17 (40% EtOAc/petroleum ether); $[\alpha]^{24}_D$ +7.6 (*c* 0.34, $CHCl_3$); ^{1}H NMR (C_6D_6, 500 MHz) δ 6.69 (dd, *J* = 10.1, 2.9, 1H), 6.13 (dd, *J* = 10, 3.0, 1H), 6.12 (dd, *J* = 10, 1.9, 1H), 6.03 (dd, *J* = 10.1, 1.8, 1H), 3.94–3.89 (m, 1H), 3.72–3.69 (m, 1H), 2.05–1.99 (m, 1H), 1.90–1.83 (m, 2H), 1.66–1.62 (m, 1H), 1.55–1.53 (m, 1H), 1.50–1.25 (br m, 27H), 1.07 (q, *J* = 11.7, 1H), 0.92 (t, *J* = 6.8, 3H); ^{13}C NMR (C_6D_6, 125 MHz) 184.9, 151.2, 149.1, 127.8, 127.4, 126.2, 109.3, 79.5, 69.5, 65.5, 43.7, 41.6, 39.2, 36.7, 35.2, 32.7, 30.8, 30.6 (several overlapping signals), 30.5, 30.2, 26.4, 23.5, 14.7; IR (thin film) 3437, 2925, 2854, 1674, 1516 cm^{-1}; HRMS (ES/MeOH) *m/z* calcd for $C_{26}H_{42}O_4$ $[M + Na]^+$ 441.2981, found 441.2975.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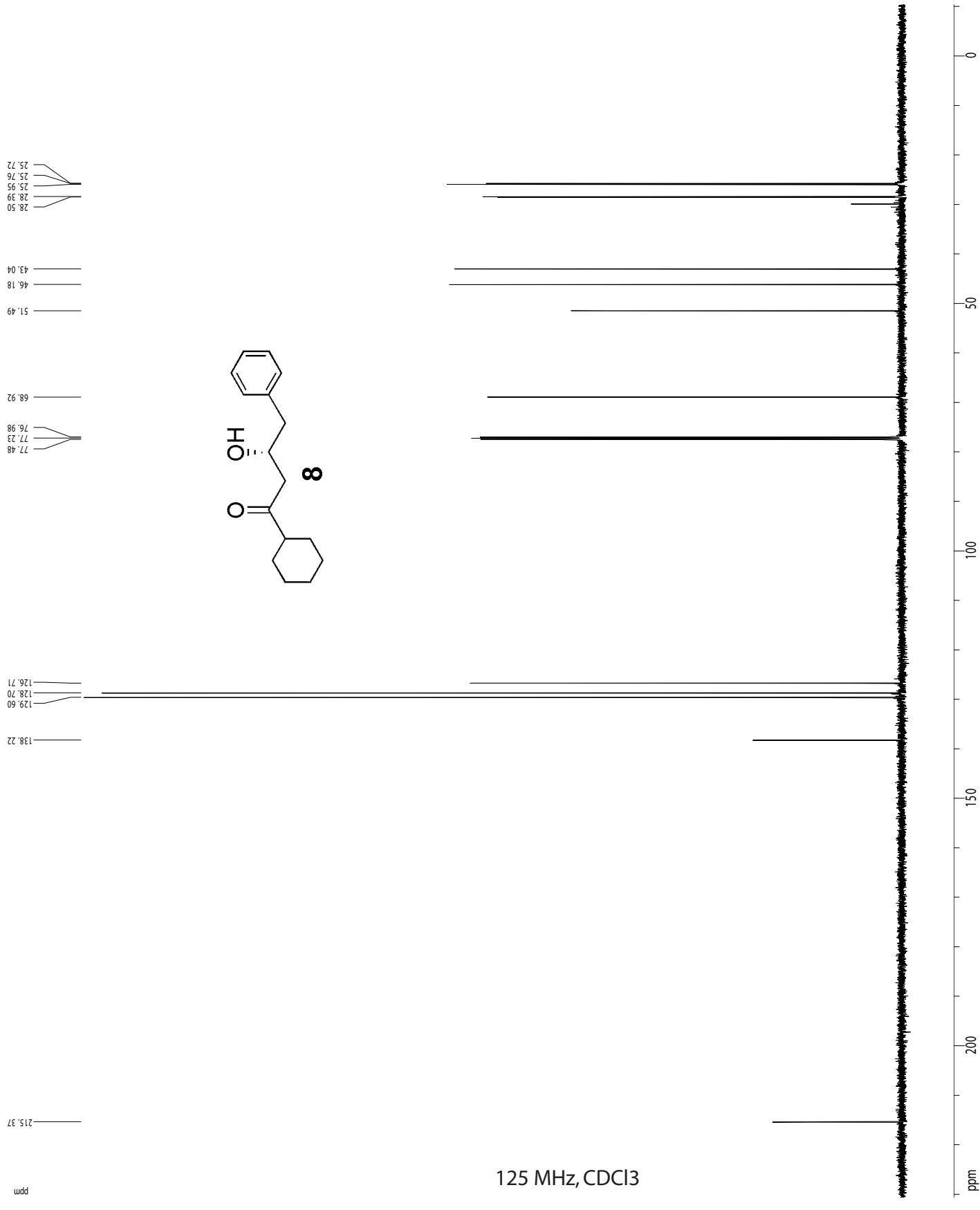
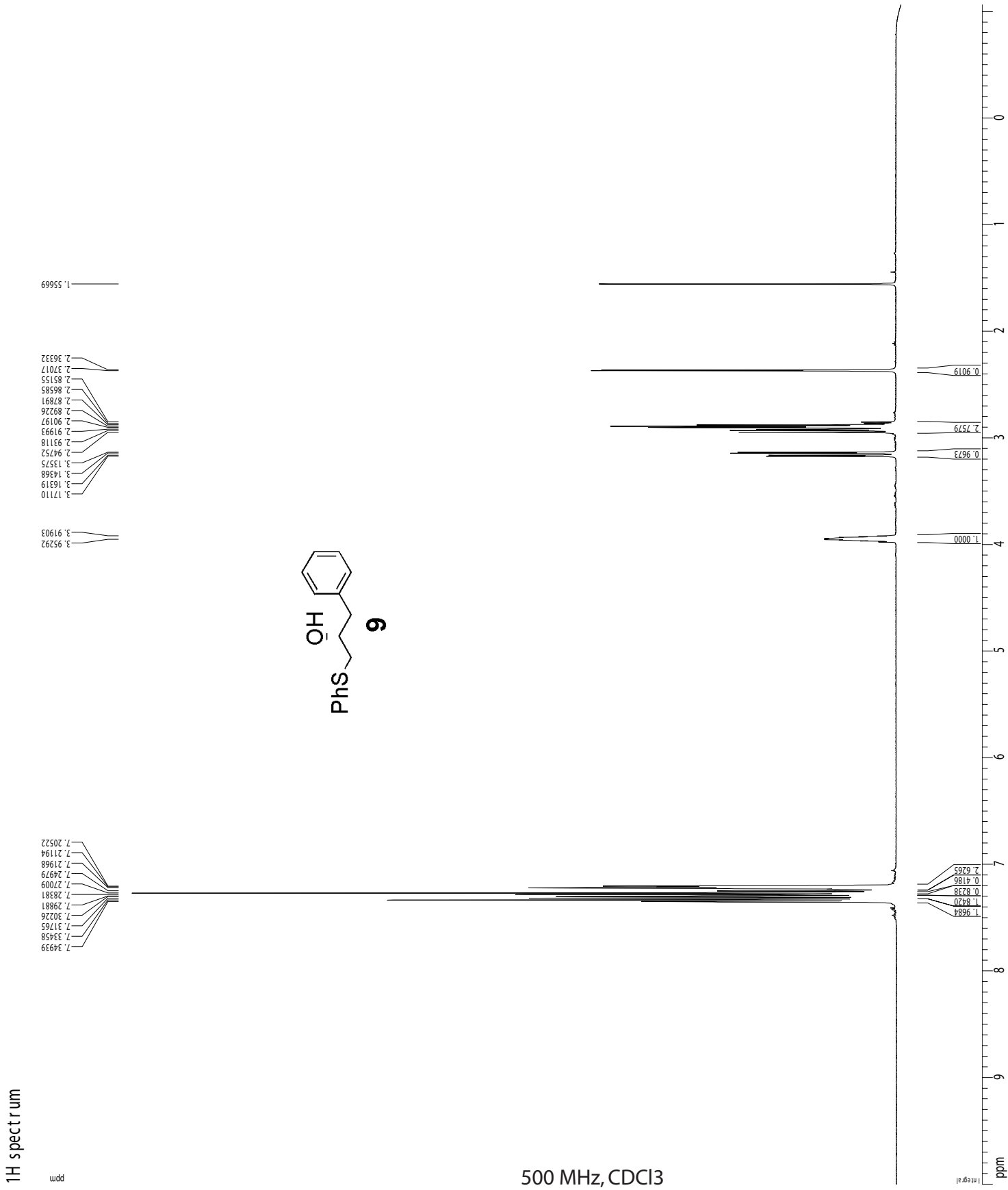
O



125 MHz, CDCl3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7.24979
7.27009
7.28381
7.29881
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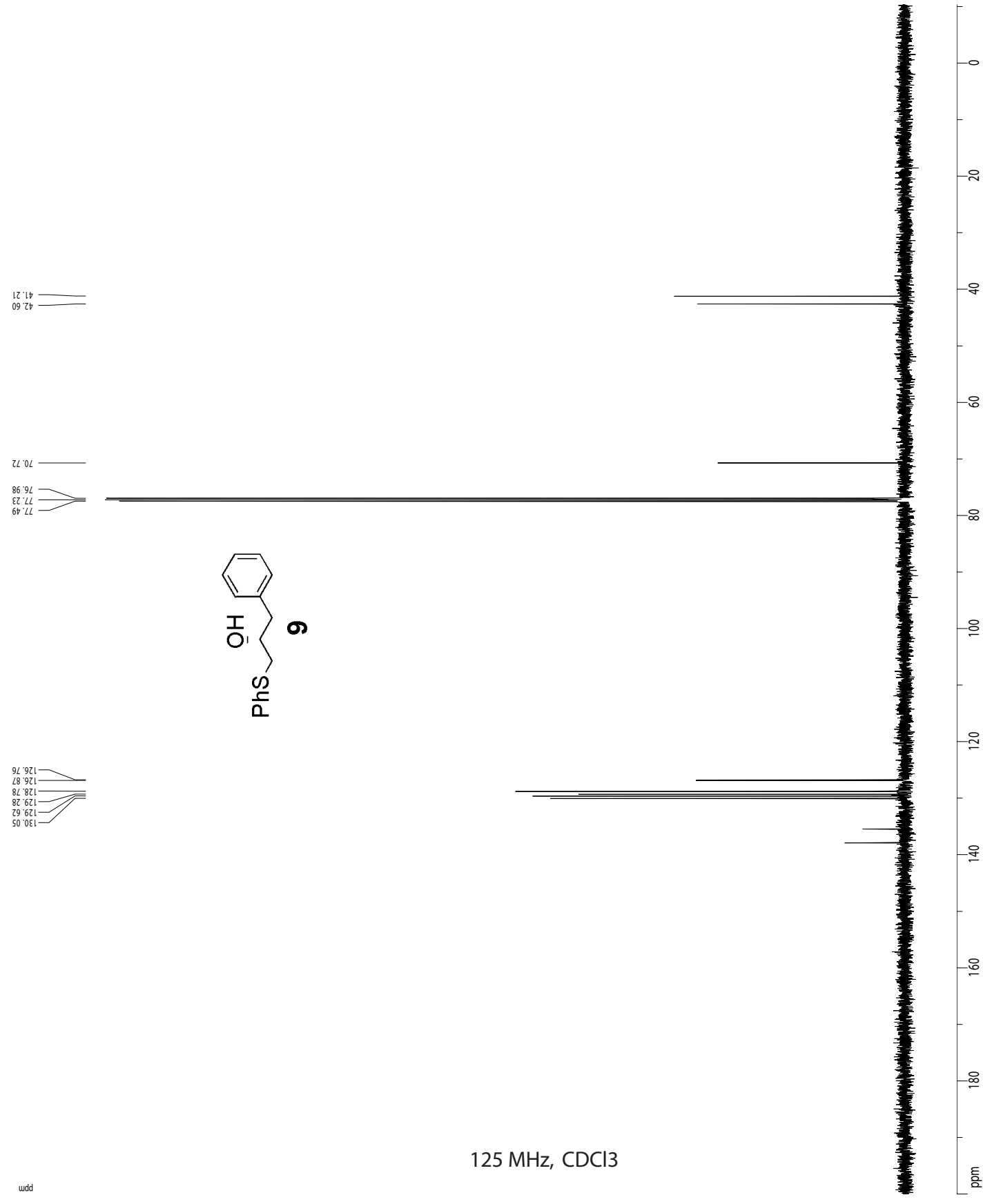
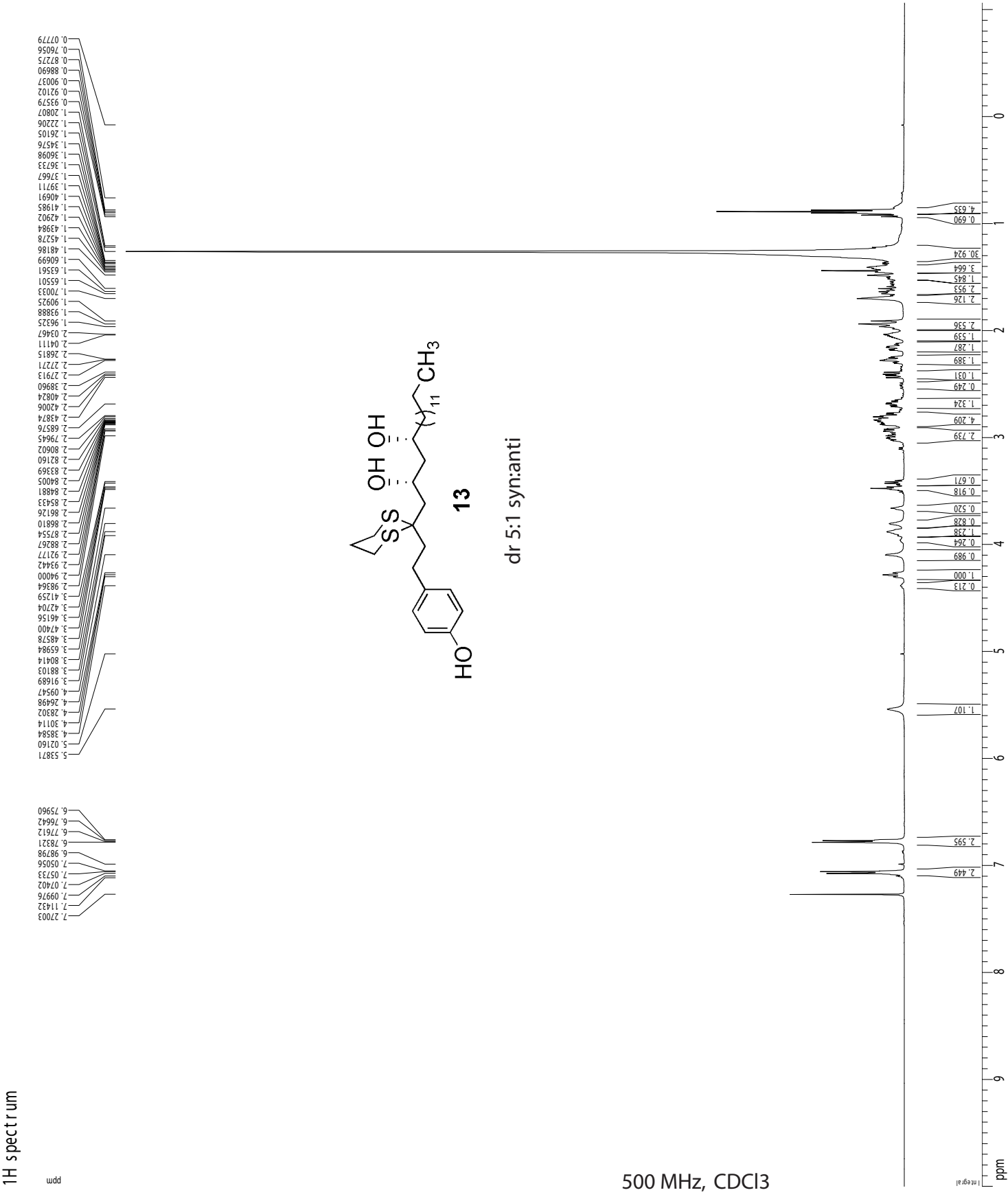


125 MHz, CDCl3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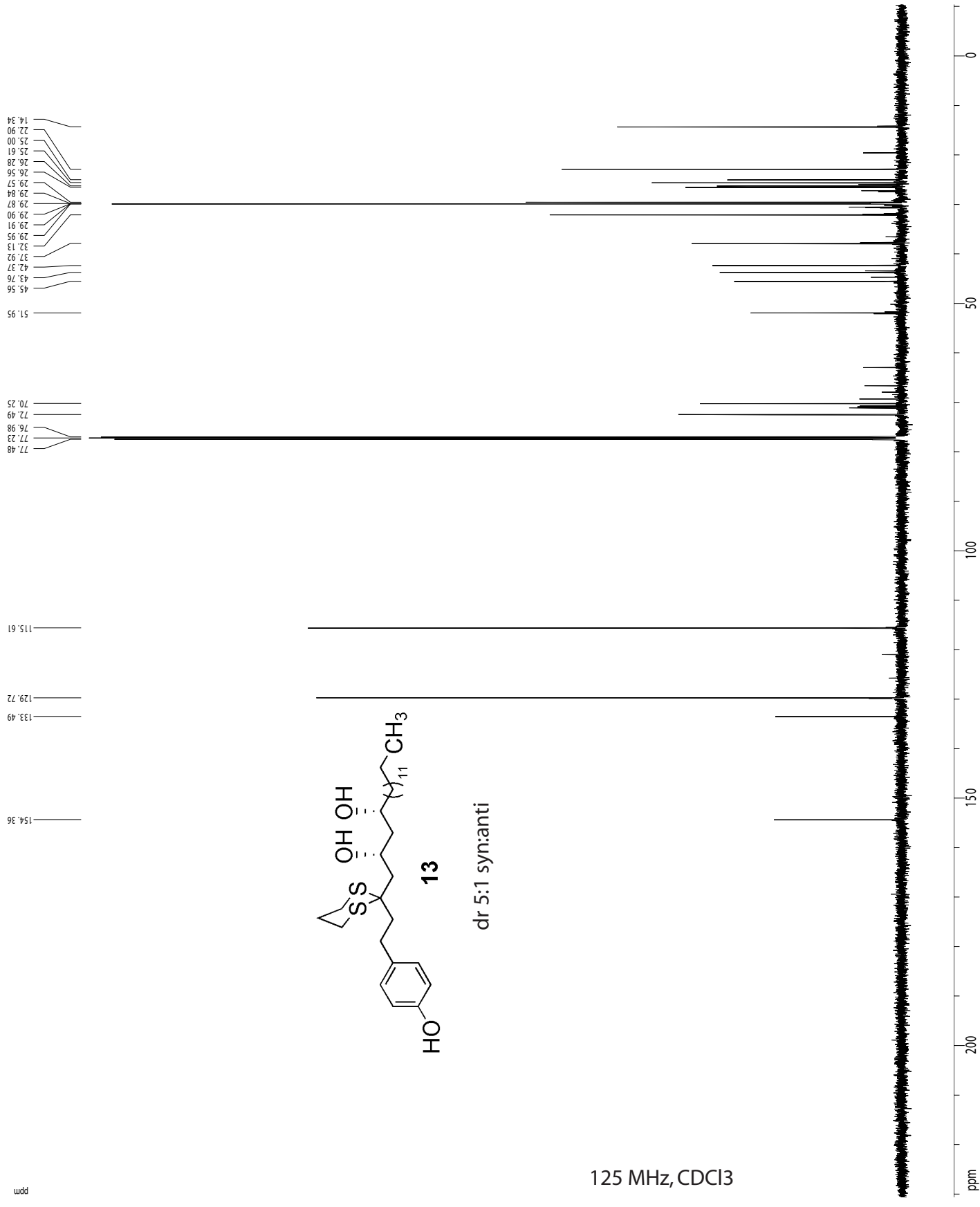
S
CH3
11
HO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37.92
42.37
43.76
45.56
51.95
70.25
72.49
76.98
77.23
77.48
115.61
129.72
133.49
154.36
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0
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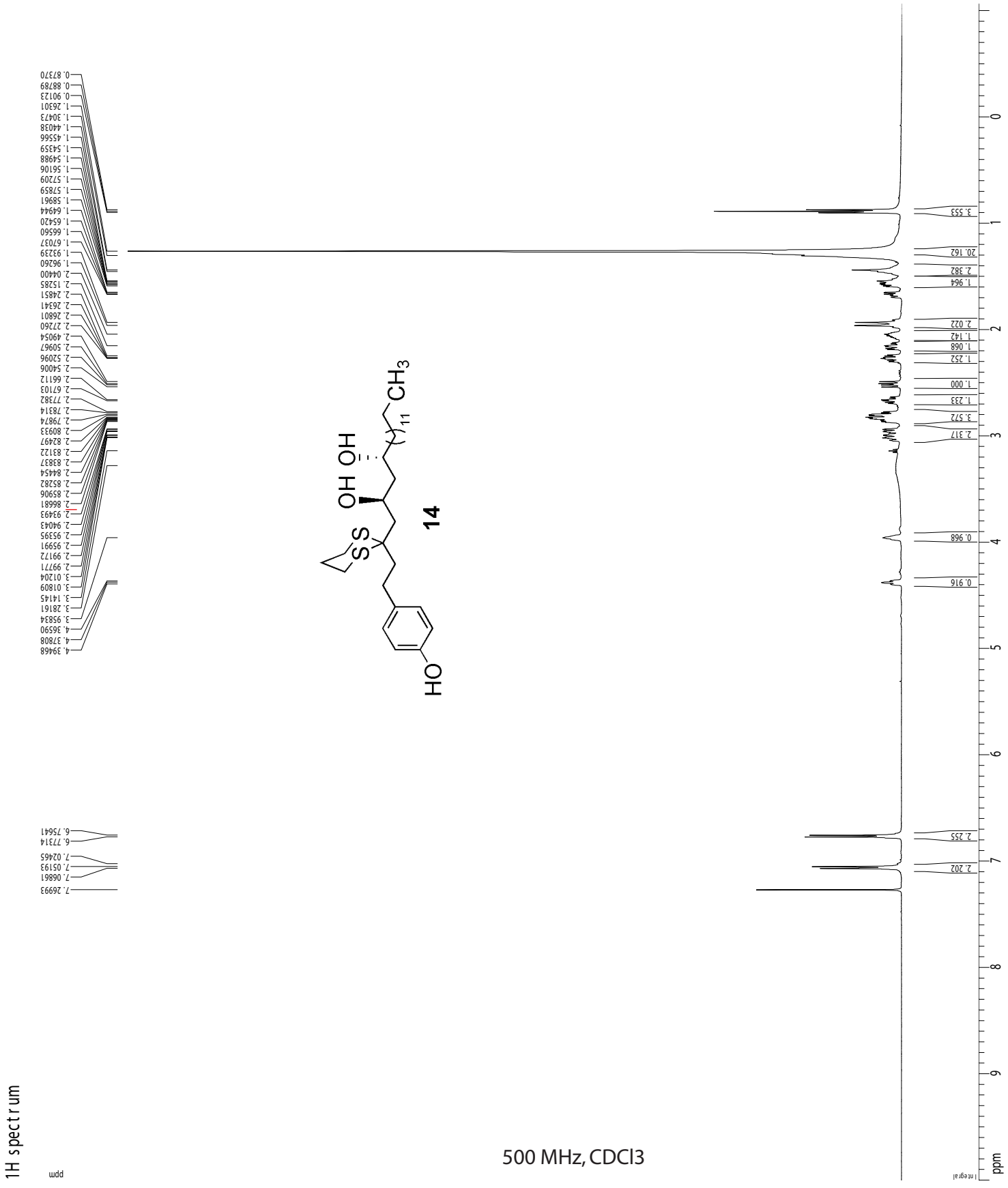
100
150
200
ppm
OH OH
S S
11
CH3
HO
13
dr 5:1 syn:anti
125 MHz, CDCl3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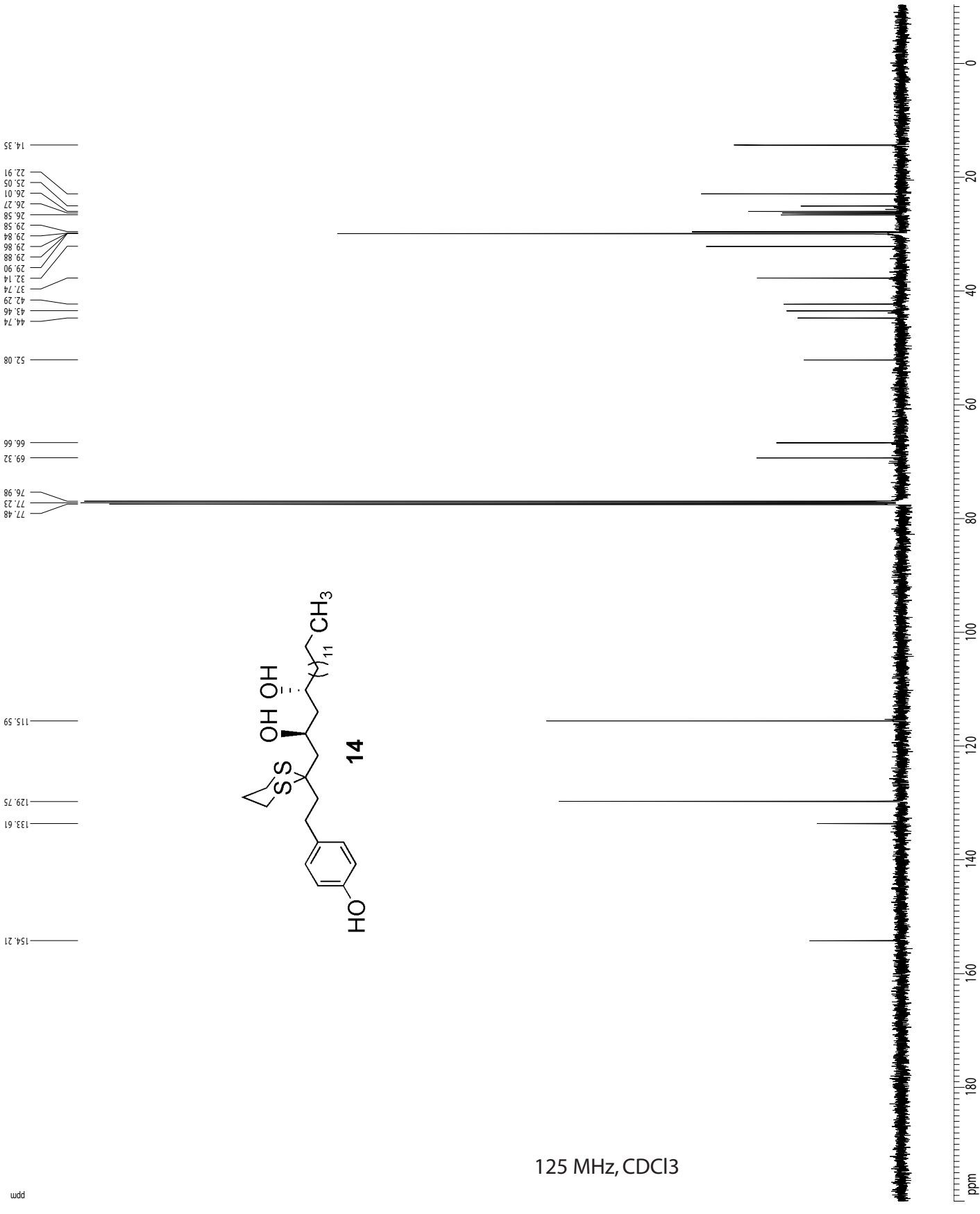
S S
HO
CH3
11
ppm
Integral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44.74
52.08
66.66
69.32
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77.23
77.48
115.59
129.75
133.61
154.21
OH OH
SS
11
CH3
HO
14
125 MHz, CDCl3
ppm
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40
60
80
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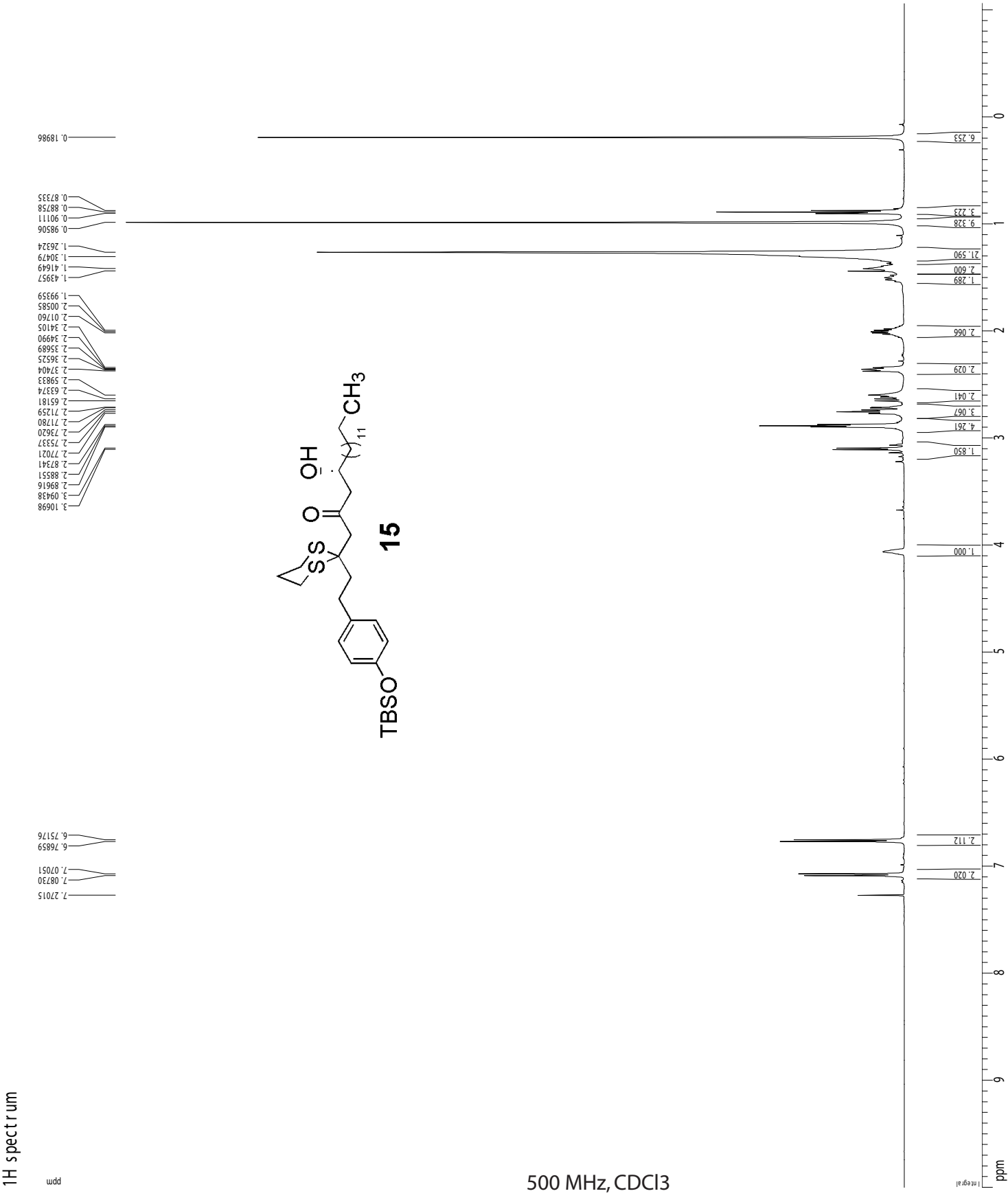
120
140
160
180
ppm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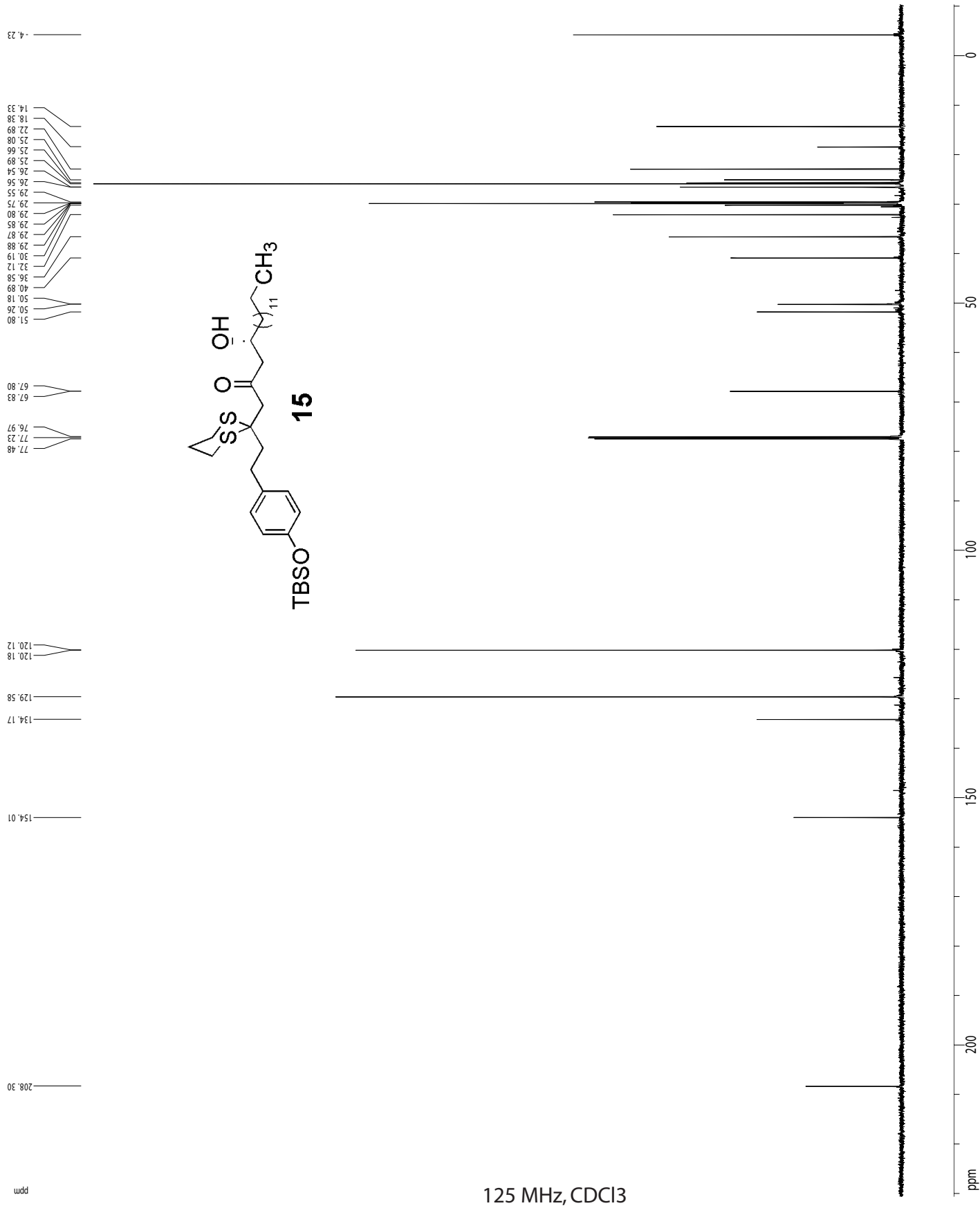
TBSO
OH
CH3
11
1H spectrum
500 MHz, CDCl3
ppm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29.88
30.19
32.12
36.58
40.89
50.18
50.26
51.80
67.80
67.83
76.97
77.23
77.48
120.12
120.18
129.58
134.17
154.01
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ppm
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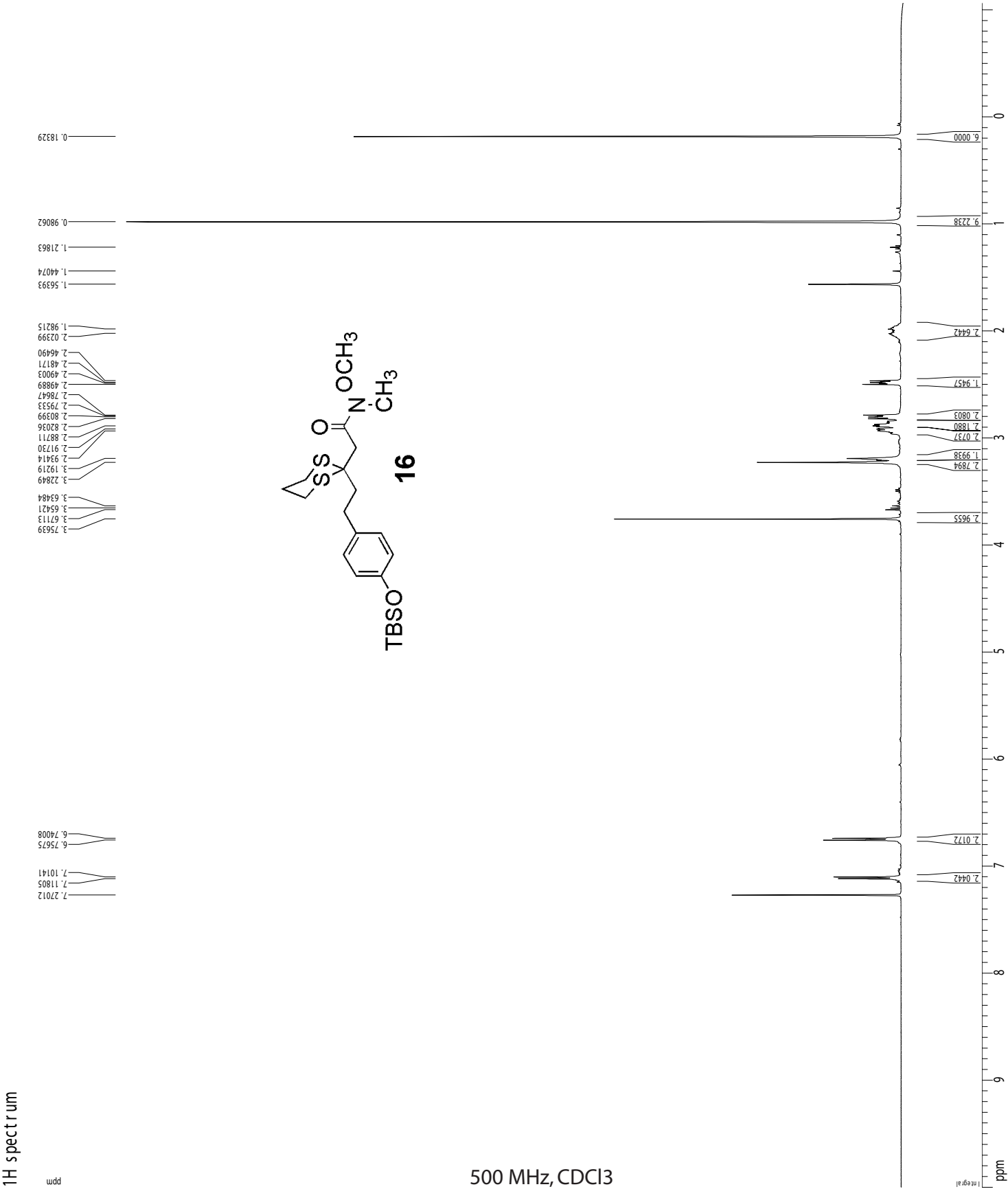
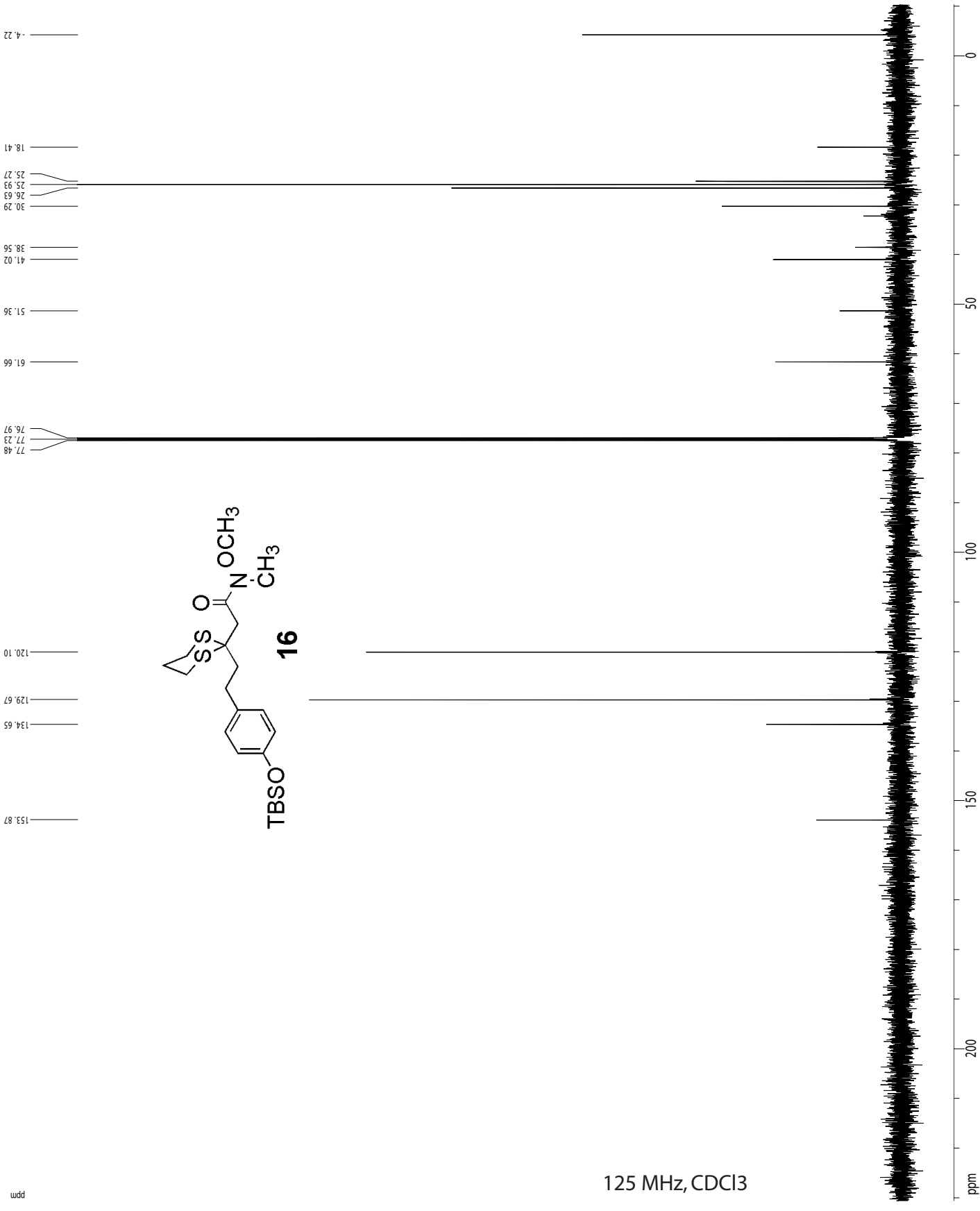
50
100
150
200
ppm
OH
O
S
S
CH3
11
TBSO
15
125 MHz, CDCl3


16
TBSO
1H spectrum
500 MHz, CDCl3
ppm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61.66
76.97
77.23
77.48
120.10
129.67
134.65
153.87
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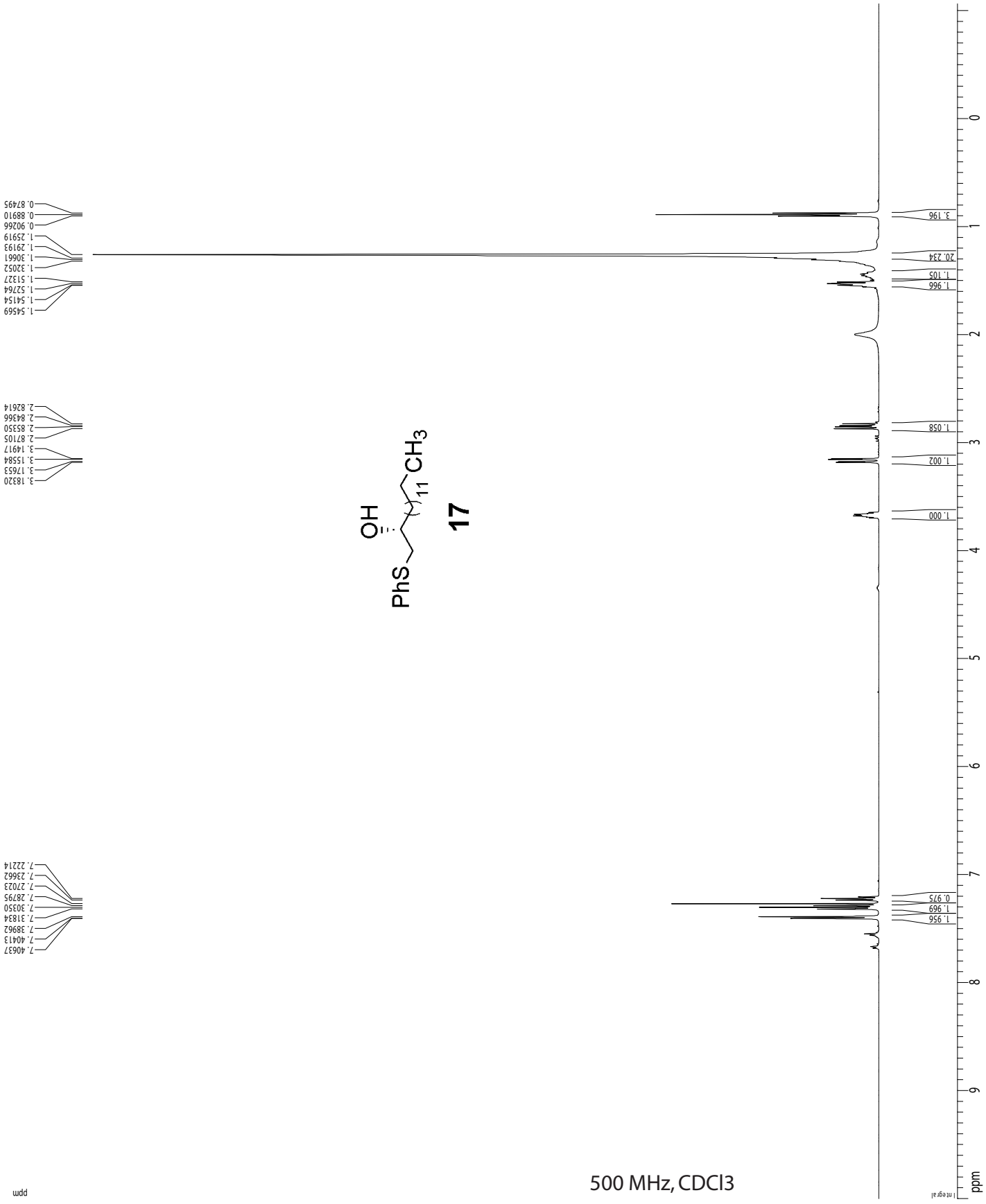
N
CH3
O
S
S
TBSO
16
0
50
100
150
200
ppm
125 MHz, CDCl3


1H spectrum
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500 MHz, CDCl3
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20.234
1.105
1.966
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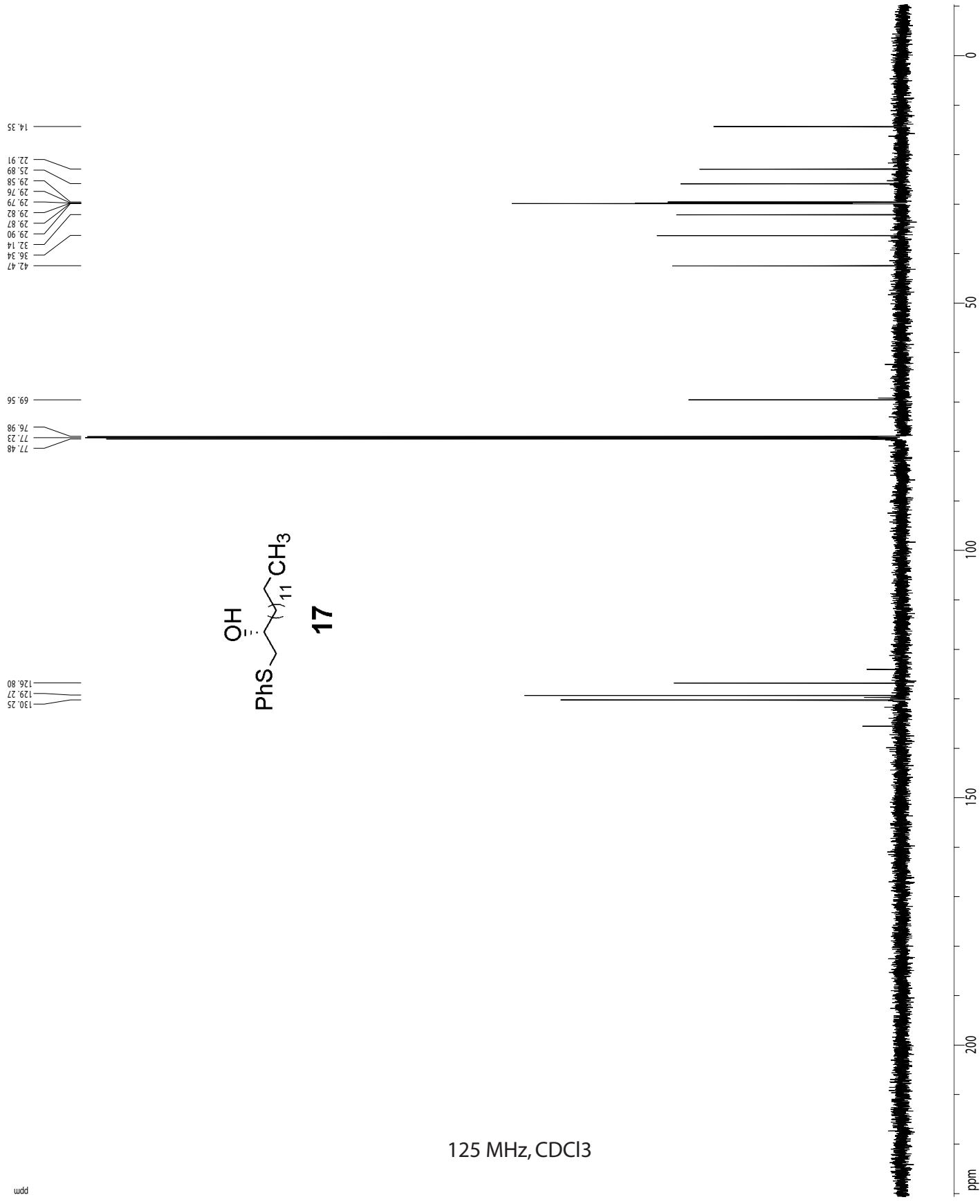
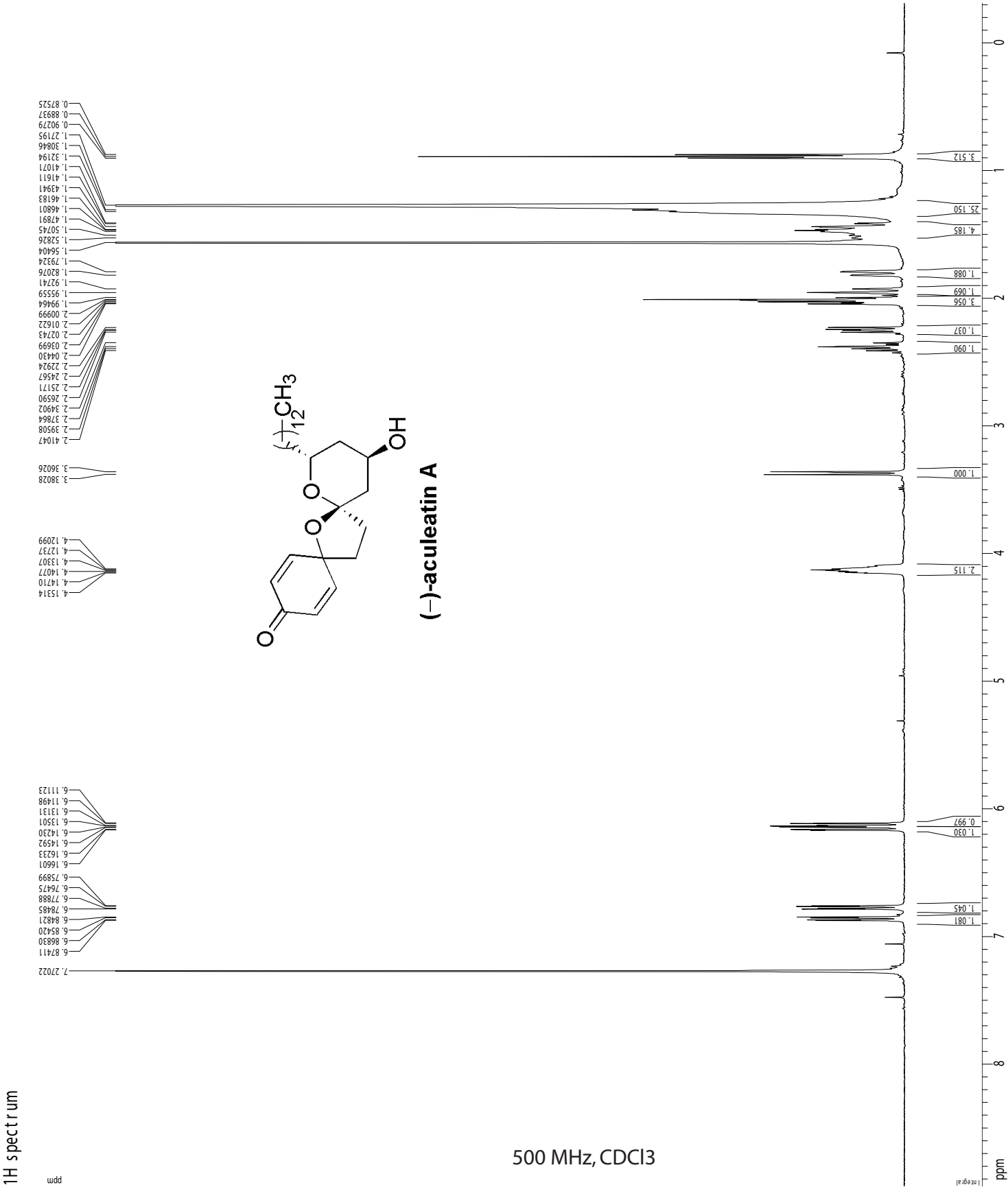
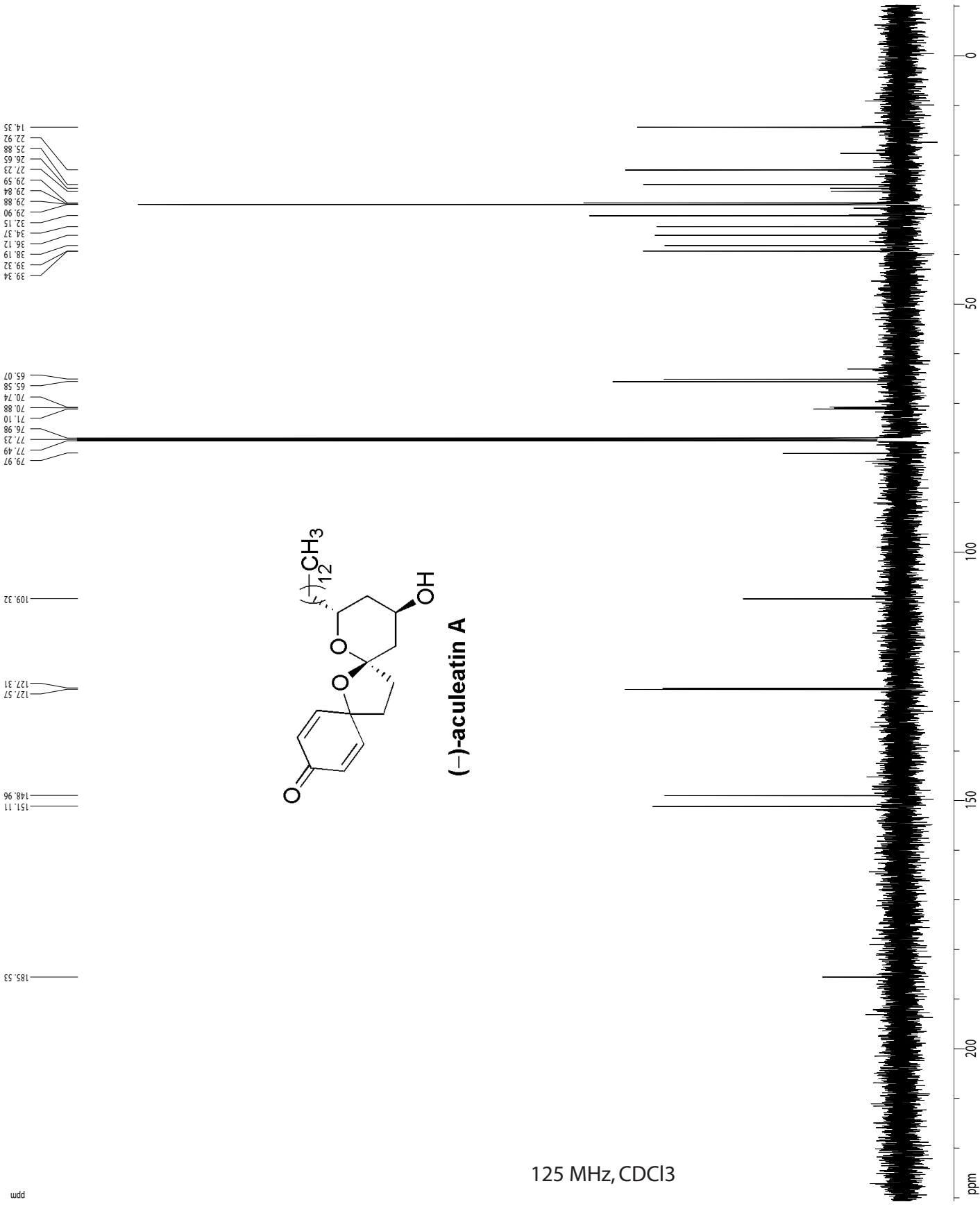
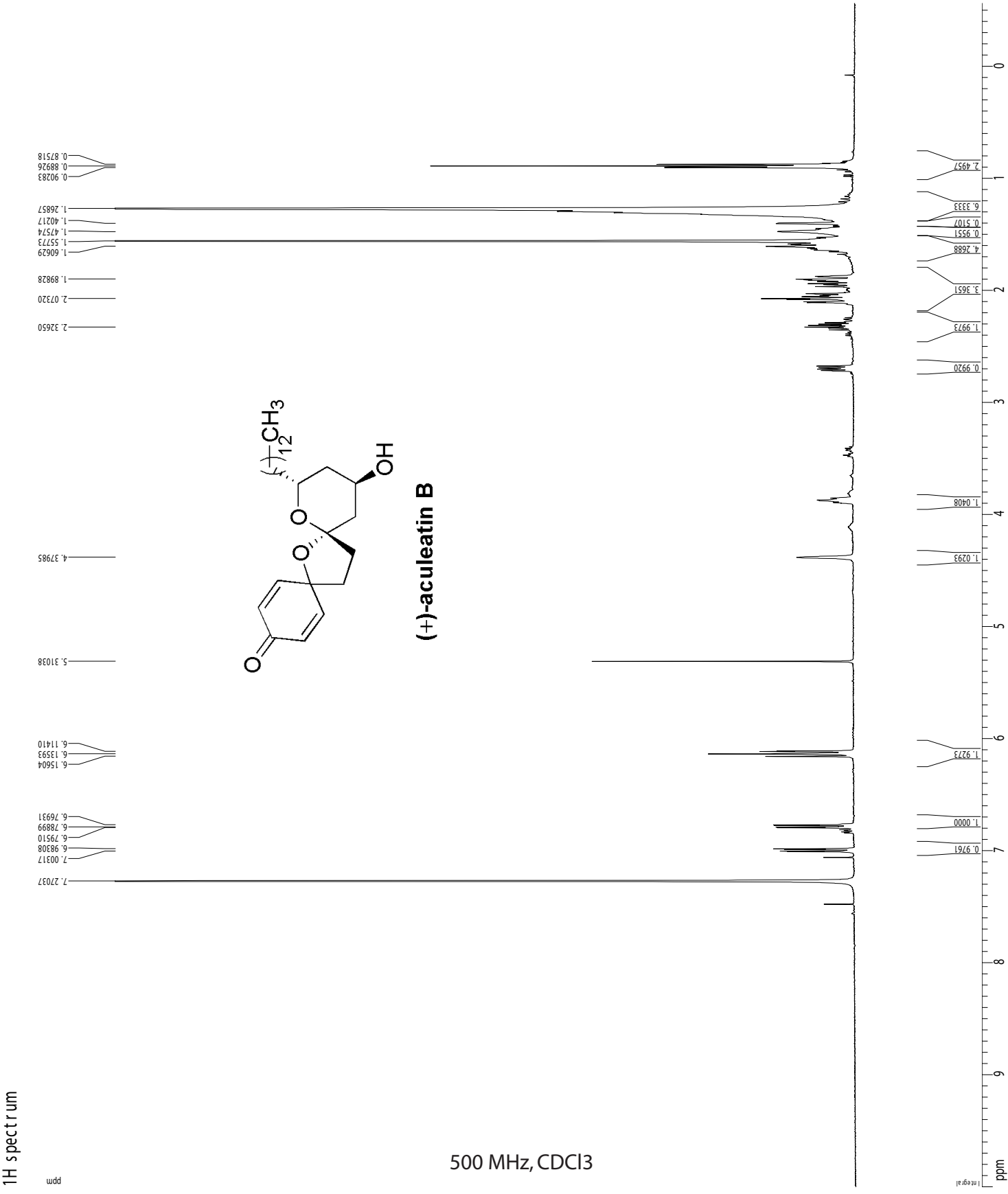
PhS
11
CH3
17



125 MHz, CDCl3

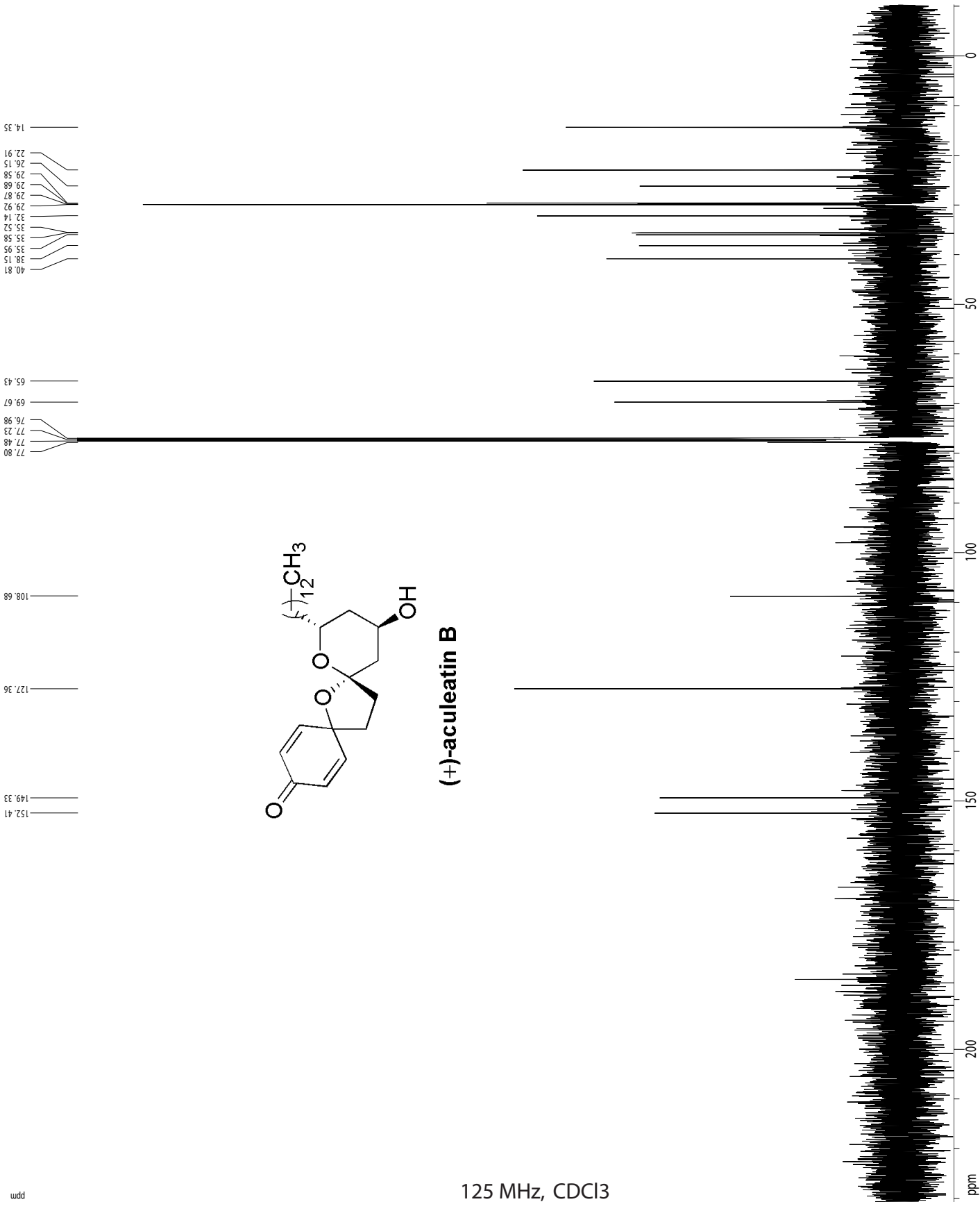

(−)-aculeatin A
500 MHz, CDCl3
1H spectrum
ppm
Integral


14.35
22.92
25.88
26.65
27.23
29.59
29.84
29.88
29.90
32.15
34.37
36.12
38.19
39.32
39.34
65.07
65.58
70.74
70.88
71.10
76.98
77.23
77.49
79.97
109.32
127.57
127.31
148.96
151.11
185.53
ppm
0
50
100
150
200
ppm
(–)-aculeatin A
125 MHz, CDCl3

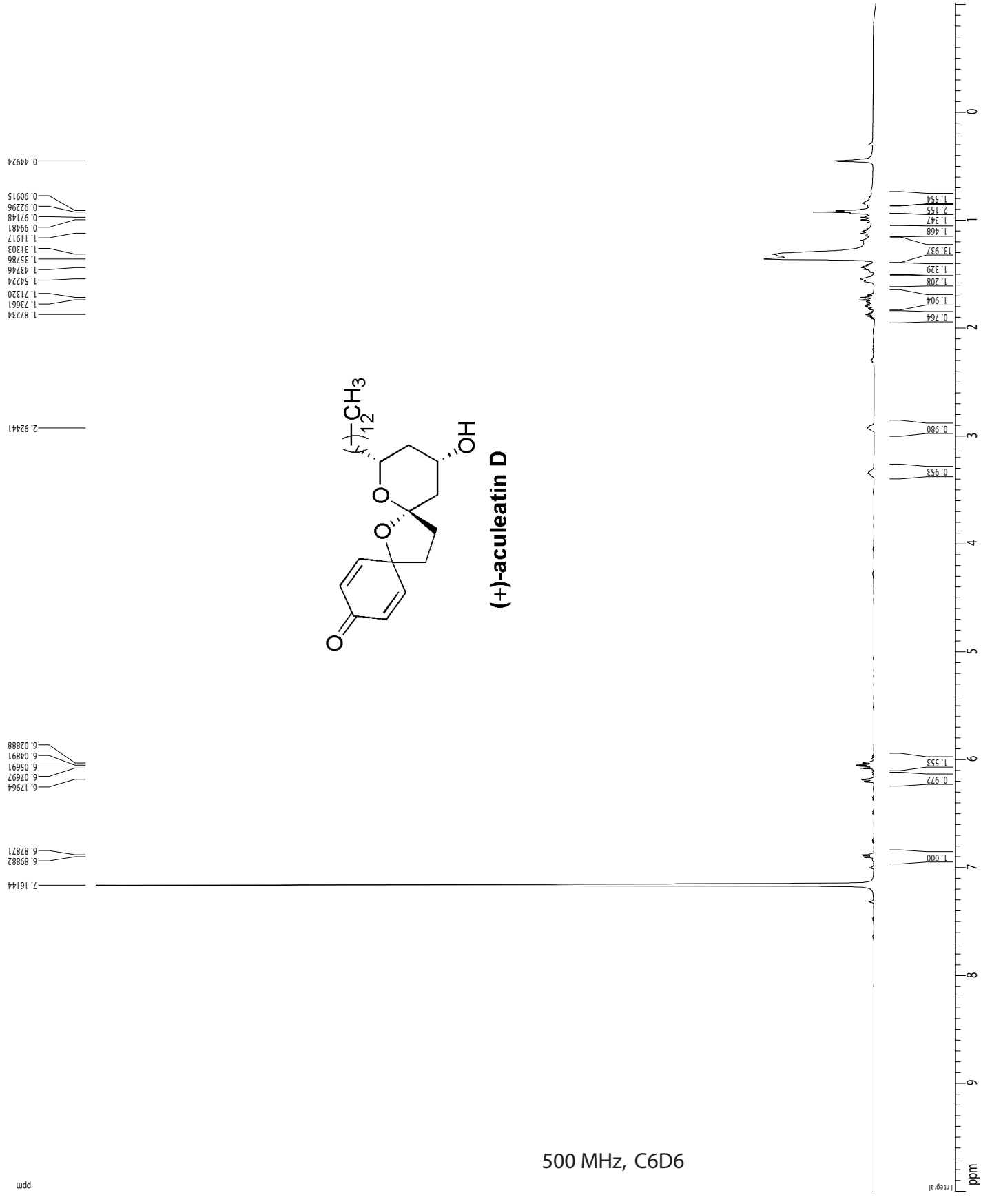


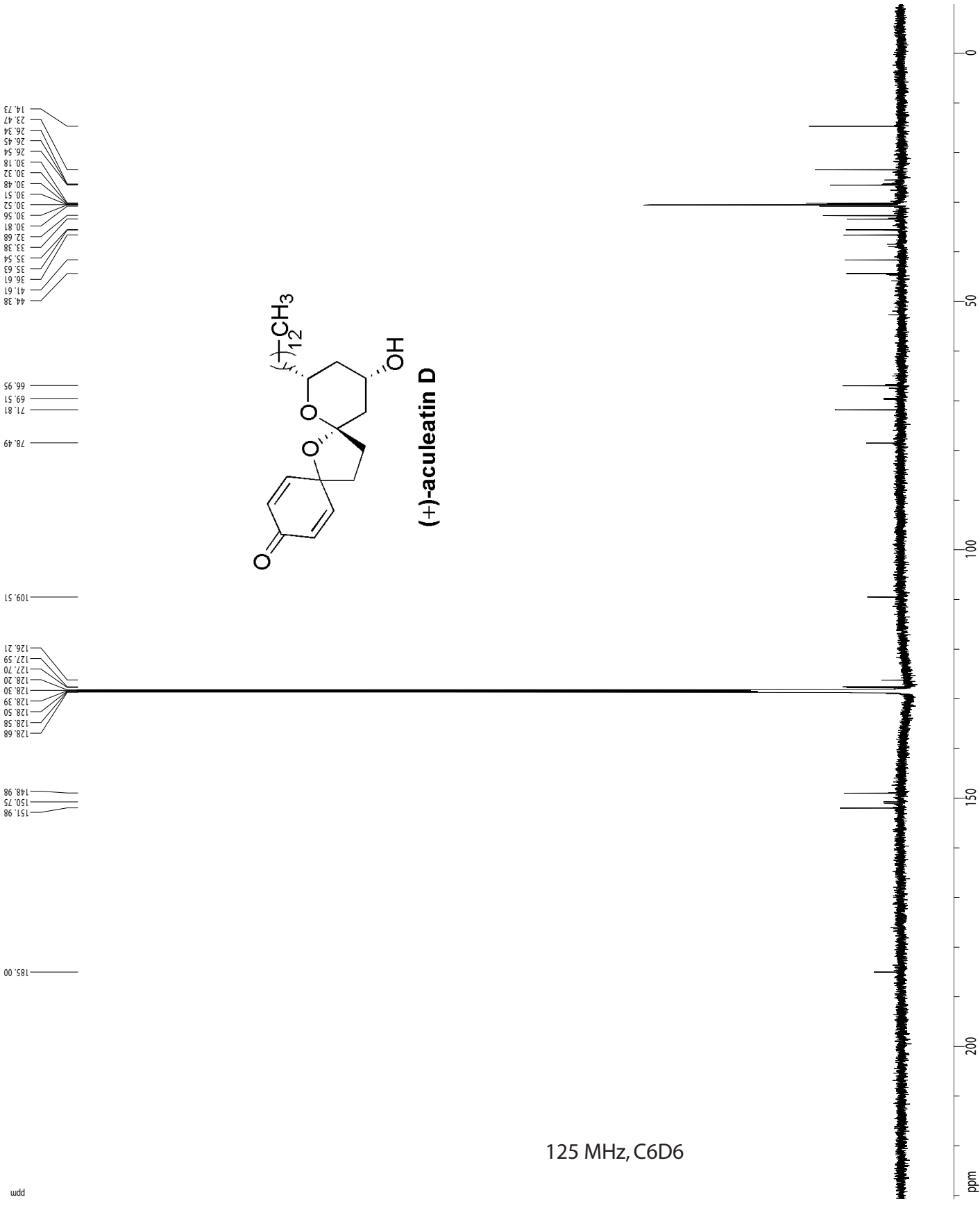
1H spectrum

500 MHz, CDCl3



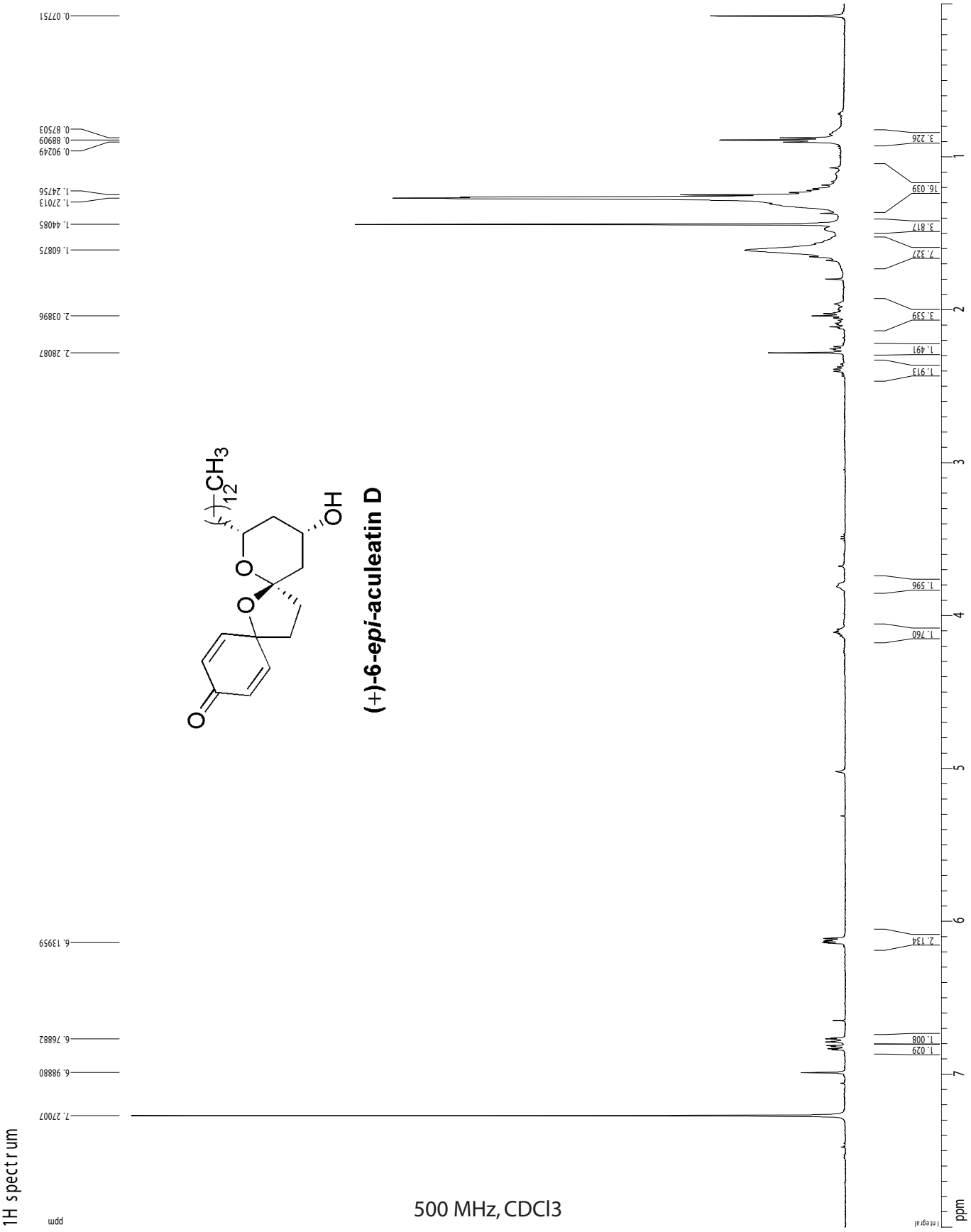
125 MHz, CDCl3

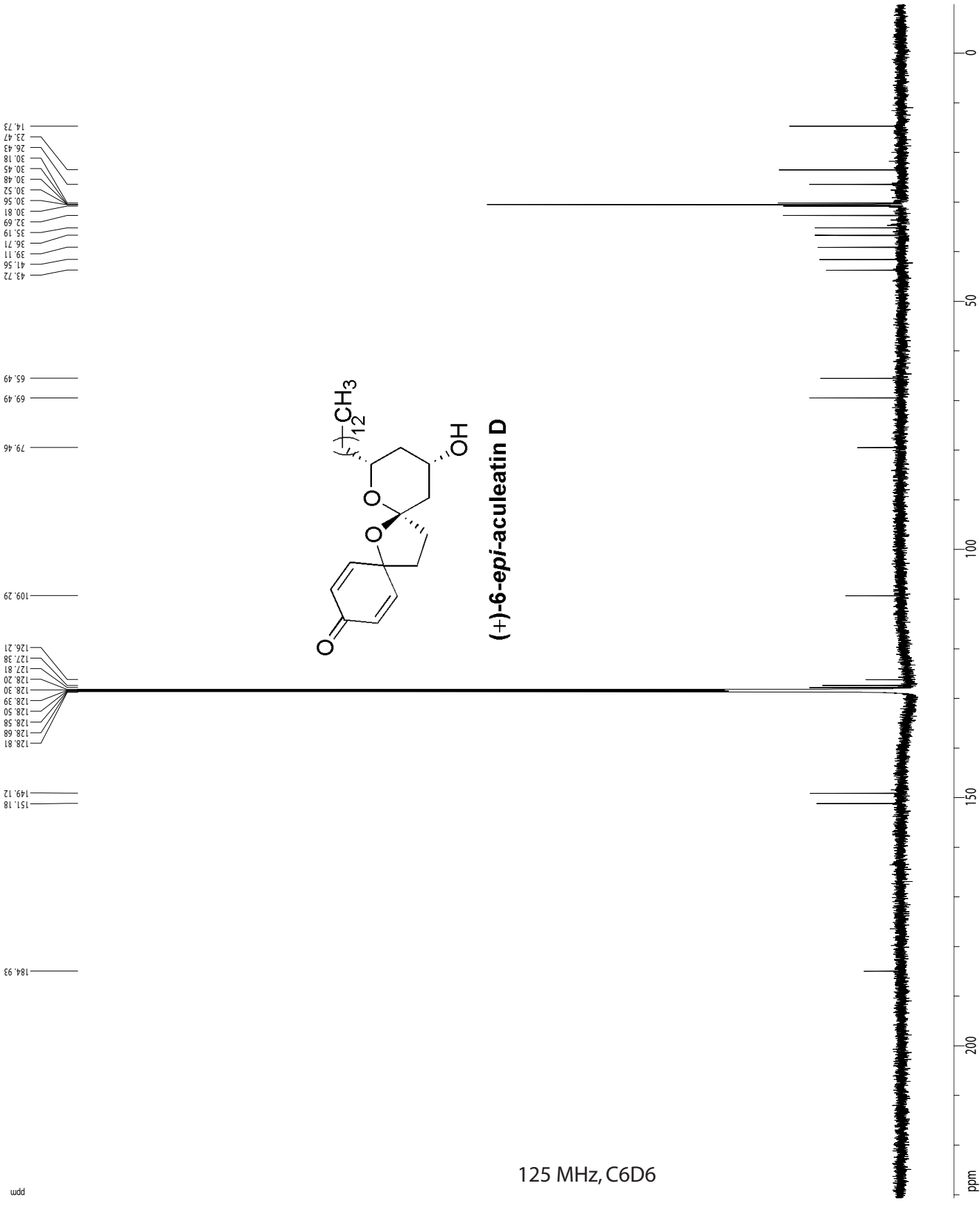

(+)-aculeatin D
500 MHz, C6D6
ppm



(+)-aculeatin D

125 MHz, C6D6


1H spectrum
500 MHz, CDCl3
(+)-6-epi-aculeatin D
OH
O
O
O
CH3
12
ppm
integral


14.73
23.47
26.43
30.18
30.45
30.48
30.52
30.56
30.81
32.69
35.19
36.71
39.11
41.56
43.72
65.49
69.49
79.46
109.29
126.21
127.38
127.81
128.20
128.30
128.39
128.50
128.58
128.68
128.81
149.12
151.18
184.93
ppm
0
50
100
150
200
ppm
(+)-6-epi-aculeatin D
125 MHz, C6D6