

## Enantioselective Total Synthesis of Phomallenic Acid C

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### General Remarks.

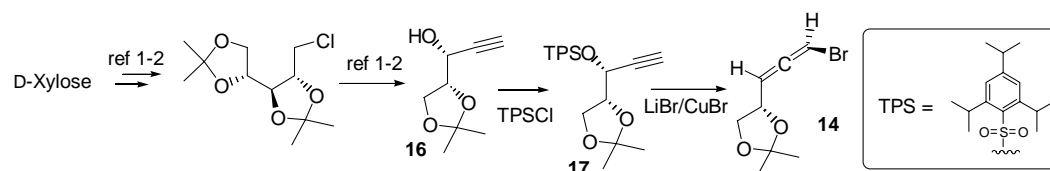
Dry THF was distilled over Na/Ph<sub>2</sub>CO under argon prior to use. Dry CH<sub>2</sub>Cl<sub>2</sub> was distilled over CaH<sub>2</sub> under argon prior to use. Column chromatography was performed on silica gel (300-400 mesh) under slightly positive pressure. PE stands for petroleum ether (bp 60-90°C). The LiBr and ZnBr<sub>2</sub> were dried in a flask by flame-dried under oil pump vacuum, respectively. <sup>1</sup>H NMR spectra were recorded at 300 or 400 MHz in CDCl<sub>3</sub> with reference to Me<sub>4</sub>Si unless otherwise indicated. <sup>13</sup>C NMR spectra were recorded at 75 or 100 MHz in CDCl<sub>3</sub> with reference to Me<sub>4</sub>Si unless otherwise indicated. IR spectra were recorded on an FT instrument with the oily sample smeared onto a KBr disc. EI-MS EI-HRMS, ESI-MS, ESI-HRMS data were all taken on commercially available instruments using direct injection technique. Optical rotations were measured at the sodium D line (589 nm) and are in units of deg·mL(dm·g)<sup>-1</sup> with the concentration and solvent individually specified.

**Chiral HPLC analysis.** Separation of the enantiomers of tosylate **10** was carried out on a CHIRAL OD column of 0.46 cm (i.d.) × 25 cm (length), eluting with 100:1 *n*-hexane/2-propanol at a flow rate of 0.6 mL/min with UV detection at 214 nm. The retention times for the major (*R*) and minor (*S*)-isomers were 88.6 and 83.9 min, respectively, with the ee value > 96% (ratio (*R*)-/(*S*)- > 49:1).

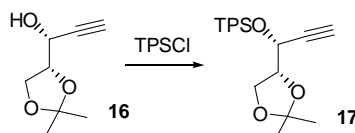
Separation of the enantiomers of bromoallene **11** was performed on a CHIRAPAK IC column of 0.46 cm (i.d.) × 25 cm (length), eluting with 99:1 *n*-hexane/2-propanol at a rate of 1.0 mL/min with UV detection at 220 nm. The retention times for the major (*S*)- and minor (*R*)-isomers were 41.9 and 38.7 min, respectively, with the ee value = 90% (ratio (*S*)-/(*R*)- = 20:1).

Separation of the enantiomers of MOM ester **13** was performed on a CHIRAPAK IC column of 0.46 cm (i.d.) × 25 cm (length), eluting with 99:1 *n*-hexane/2-propanol at a rate of 1.0 mL/min with UV detection at 220 nm. The retention times for the major (*R*)- and minor (*S*)- isomers were 54.0 and 73.7 min, respectively, with the ee value = 88% (ratio(*R*)-/(*S*)- = 16:1).

**Scheme S**

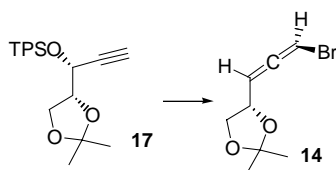


The bromoallene **14** in the main text was prepared (Scheme S) from the known alcohol **16** (ref.: (a) Kagawa, N.; Ihara, M.; Toyota, M. *Org. Lett.* **2006**, *8*, 875-878. (b) Mulzer, J.; Greifenberg, S.; Beckstett, A.; Gottwald, M. *Liebigs. Ann. Chem.* **1992**, 1131-1135. (c) Yadav, J. S.; Chander, M. V.; Rao, C. S. *Tetrahedron Lett.* **1989**, *30*, 5455-5458.), which could be readily synthesized from D-xylose following the literature procedure (ref.: Yadav, J. S.; Chander, M. V.; Rao, C. S. *Tetrahedron Lett.* **1989**, *30*, 5455-5458.). Later, it was found that using *p*-TsCl to replace the TPSCl could also eventually **14** of the same quality.

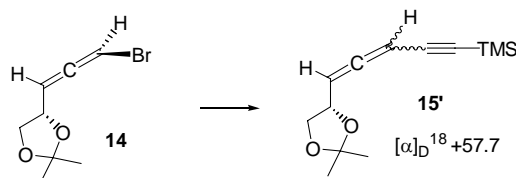


**Trisylation of alcohol 16 (17).** 2,4,6-Triisopropylbenzenesulfonyl chloride (2.160 g, 7.15 mmol) was added in portions to a solution of the alcohol **16** (1.105 g, 7.08 mmol) and DMAP (1.045 g, 8.56 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (22 mL)

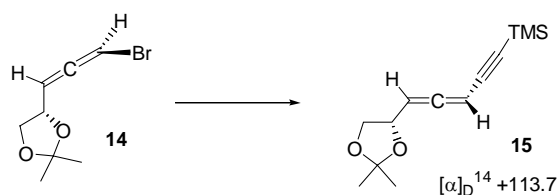
stirred at ambient temperature. After completion of the addition, the mixture was heated to 40°C (bath) with stirring until TLC showed completion of the reaction. Sat. aq.  $\text{NH}_4\text{Cl}$  and EtOAc were added to the reaction mixture. The phases were separated. The organic layer was washed with brine and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . Removal of the solvent by rotary evaporation and chromatography on silica gel (1:10 EtOAc/PE) gave the trisylate **17** as a colorless oil (2.670 g, 6.33 mmol, 89% yield):  $[\alpha]_{\text{D}}^{25} -8.9$  (*c* 1.80,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.17 (s, 2H), 5.16 (dd, *J* = 6.9, 2.5 Hz, 1H), 4.34 (qd, *J* = 6.4, 1.7 Hz, 1H), 4.19-4.10 (m, 3H), 4.05 (dd, *J* = 9.1, 5.4 Hz, 1H), 2.92 (heptet, *J* = 7.0 Hz, 1H), 2.37 (d, *J* = 2.2 Hz, 1H), 1.37 (s, 3H), 1.34 (s, 3H), 1.30-1.25 (m, 18H); FT-IR (film) 3278, 2131, 1598, 1178  $\text{cm}^{-1}$ ; EI-MS *m/z* (%) 407 (M- $\text{CH}_3$ , 35.4), 283 (61.7), 218 (53.3); 101 (100); 43 (47.7); HRMS calcd for  $\text{C}_{22}\text{H}_{31}\text{O}_5\text{S}$  ( $[\text{M}-\text{CH}_3]^+$ ) 407.1892; found 407.1880.



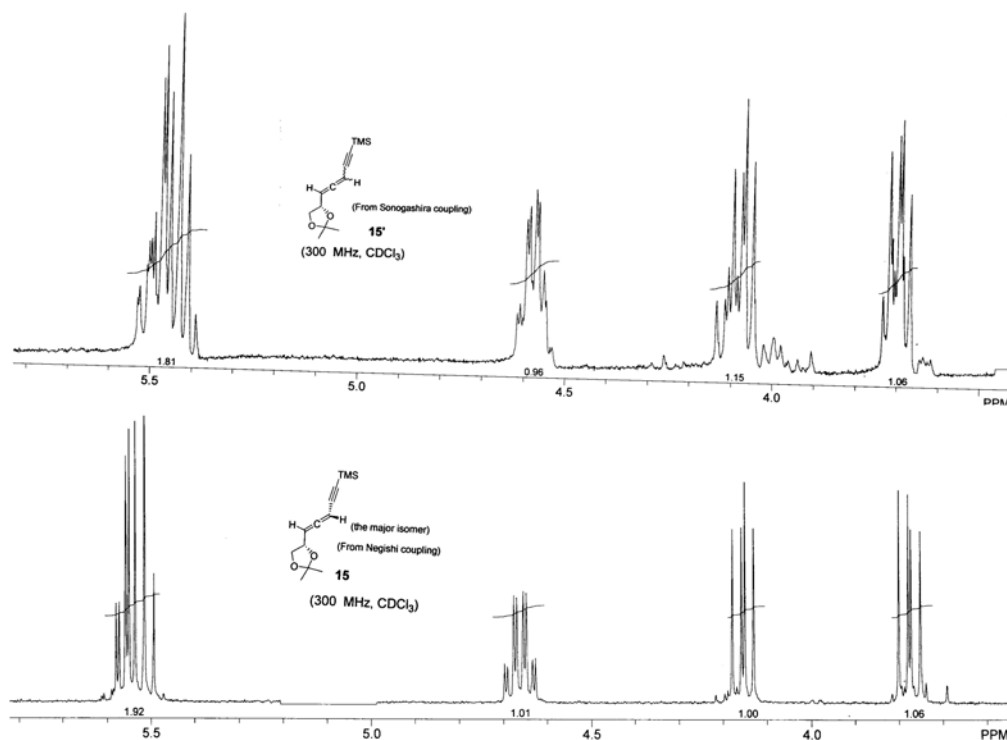
**Conversion of **17** into bromoallene **14**.** A solution of the sulfonate (780 mg, 1.85 mmol) in dry THF (4.5 mL, another 3 mL to assist the transfer) was added via a syringe to a dry flask containing  $\text{CuBr}\cdot\text{SMe}_2$  (1.410 g, 5.55 mmol, recrystallized) and LiBr (481 mg, 5.55 mmol, dried) stirred at ambient temperature under argon. The mixture was heated to reflux under argon for 3 h. After being cooled to ambient temperature, the reaction mixture was diluted with EtOAc, washed with sat. aq.  $\text{NH}_4\text{Cl}$ , and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . Removal of the solvent and chromatography (1:3 EtOAc/PE) gave bromoallene **14** as a colorless oil (357 mg, 1.63 mmol, 88% yield):  $[\alpha]_{\text{D}}^{18} -84.4$  (*c* 1.58,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.12 (dd, *J* = 5.9, 1.1 Hz, 1H), 5.43 (dd, *J* = 7.1, 6.3 Hz, 1H), 4.69 (qd, *J* = 6.4, 1.2 Hz, 1H), 4.20 (dd, *J* = 8.1, 5.9 Hz, 1H), 3.81 (dd, *J* = 8.2, 6.1 Hz, 1H), 1.44 (s, 3H), 1.39 (s, 3H); FT-IR (film) 2987, 1961, 1220  $\text{cm}^{-1}$ ; EI-MS *m/z* (%) 220 ( $\text{M}+\text{H}^+$ , 3), 101 (100), 43 (88). Anal. Calcd. for  $\text{C}_8\text{H}_{11}\text{BrO}_2$ : C 43.86, H 5.06. Found: C 43.84, H 5.40.



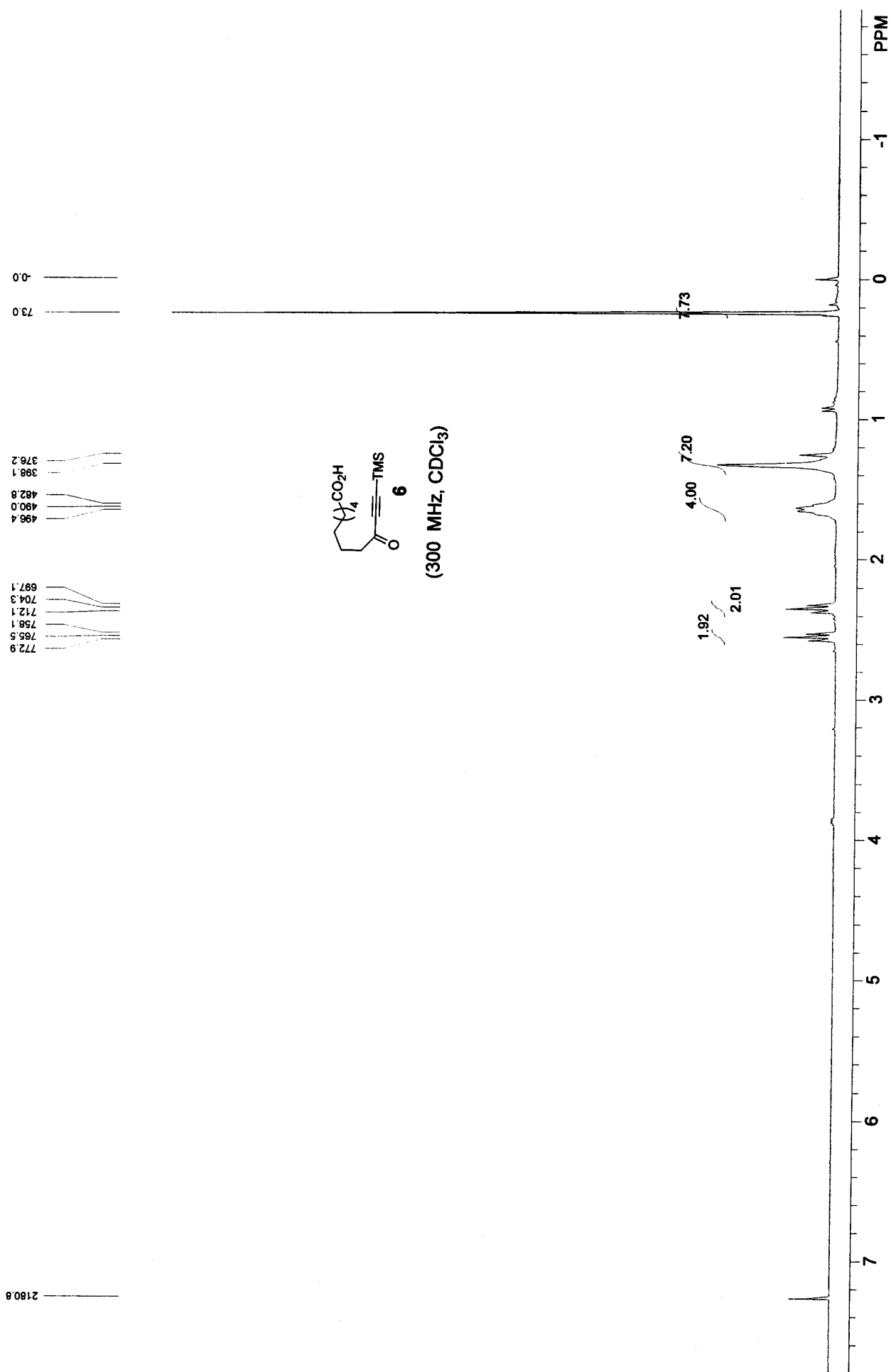
**Coupling of **14** with  $\text{TMSC}\equiv\text{CH}$  under the Sonogashira conditions (**15'**).**  $\text{PdCl}_2(\text{PPh}_3)_2$  (19.3 mg, 27.5  $\mu\text{mol}$ ), CuI (17.2 mg, 90  $\mu\text{mol}$ ), and *i*- $\text{Pr}_2\text{NH}$  (1.7 mL) were quickly added in turn to a solution of the bromoallene (80 mg, 0.36 mmol) and  $\text{TMSC}\equiv\text{CH}$  (70 mg, 0.57 mmol) in dry de-aired EtOAc (13 mL) at  $-20^\circ\text{C}$  under argon. The mixture was stirred while the temperature was allowed to rise to  $0^\circ\text{C}$  over 30 min. The stirring was then continued at ambient temperature until TLC showed completion of the reaction. Sat. aq.  $\text{NH}_4\text{Cl}$  and  $\text{Et}_2\text{O}$  were added. The phases were separated. The organic layer was washed with brine and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . Rotary evaporation and column chromatography on silica gel (1:30  $\text{Et}_2\text{O}$ /PE) gave the allen-yne **15'** as a yellowish oil (65 mg, 0.28 mmol, 77%):  $[\alpha]_{\text{D}}^{18} +57.7$  (*c* 0.65,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.58-5.49 (m, 2H), 4.67-4.62 (m, 1H), 4.21-4.12 (m, 1H), 3.81-3.74 (m, 1H), 1.45 (s, 3H), 1.40 (s, 3H), 0.18 (s, 9H). Cf. the attached spectrum (Figure 1).

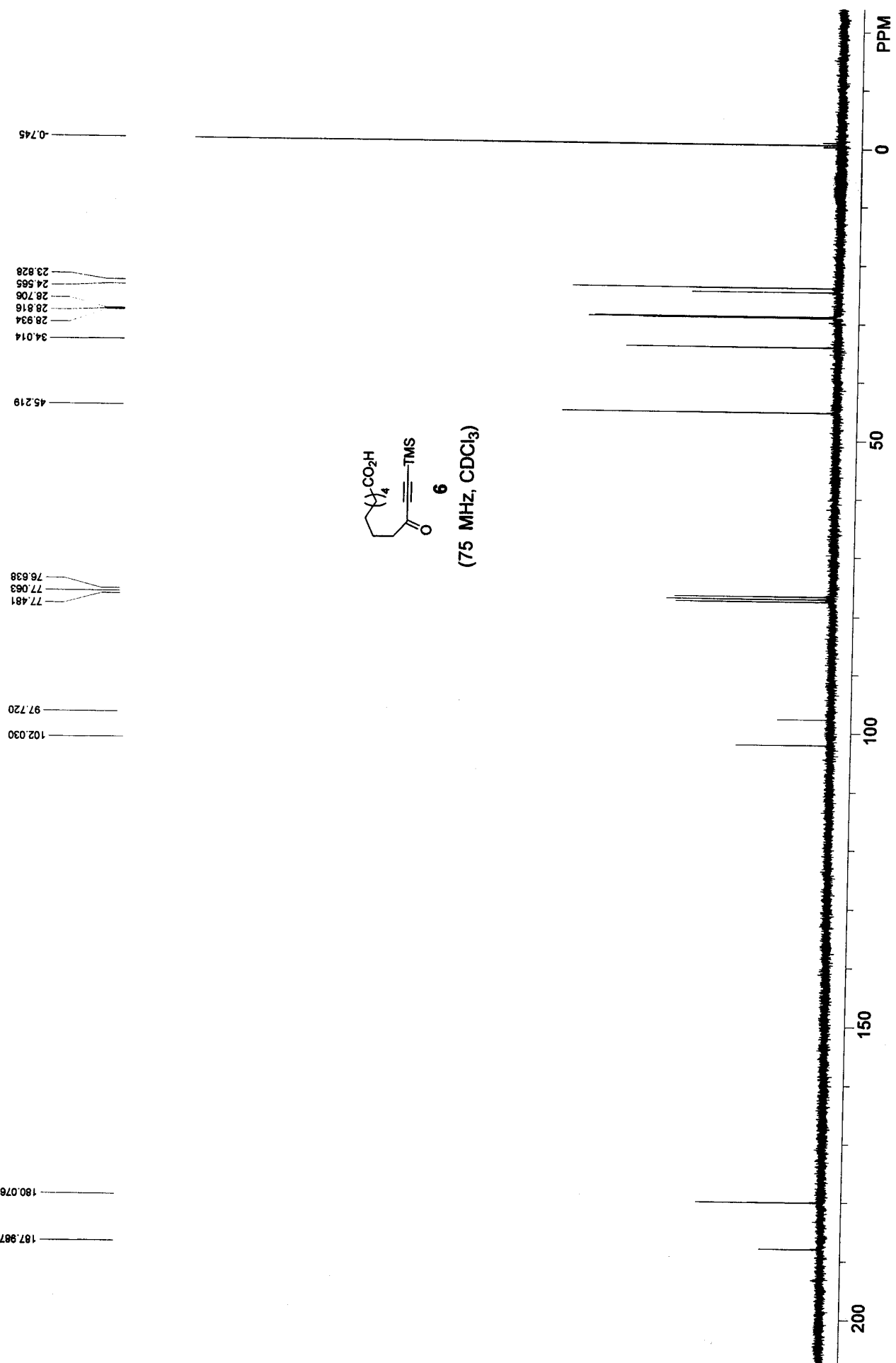


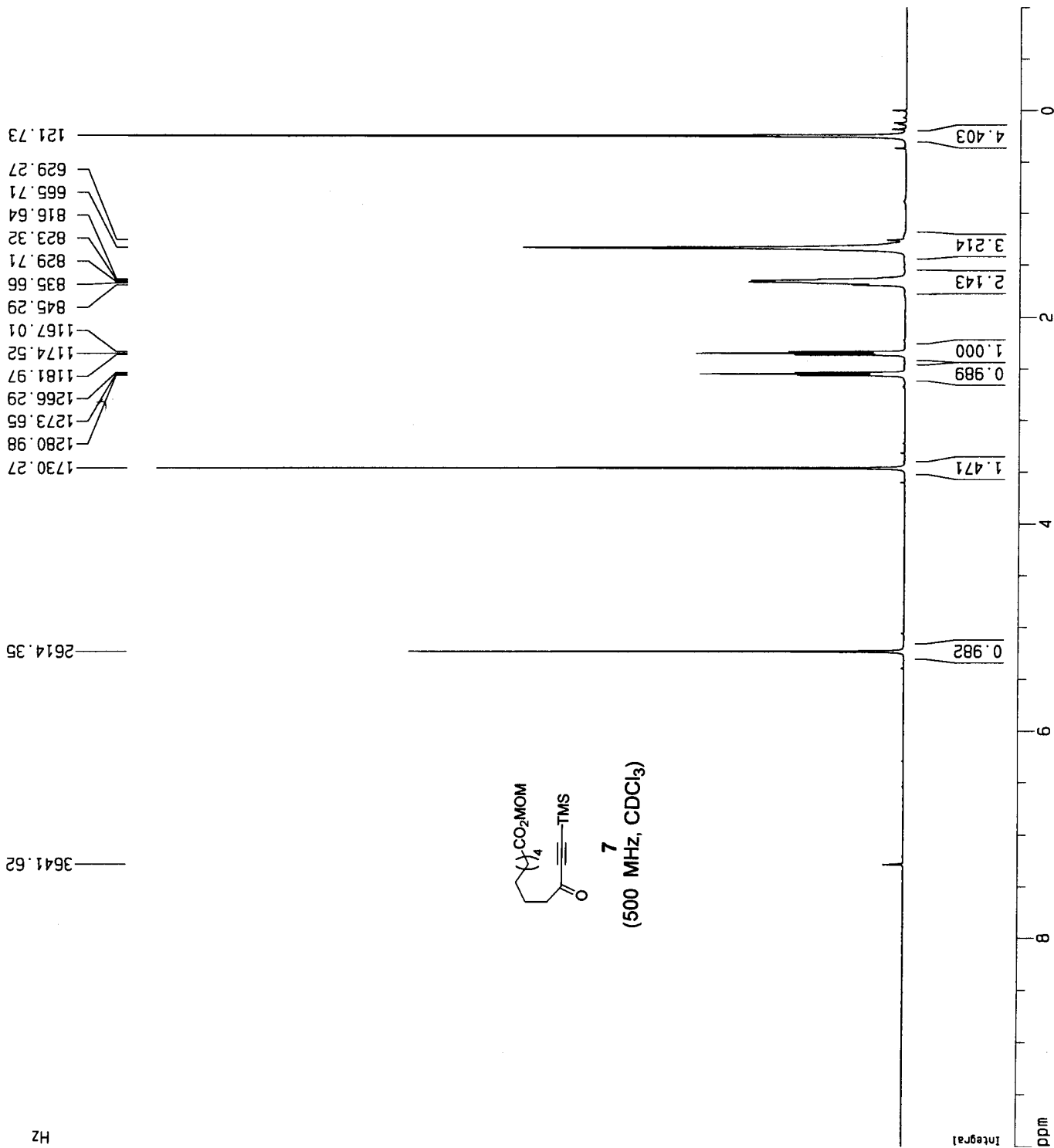
**Coupling of 14 with TMSCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub> under the Negishi conditions (15).** *n*-BuLi (0.80 mL, ca 1.6 M in hexanes, 1.28 mmol) was added via a syringe to a solution of the TMSCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub> (120 mg, 1.22 mmol) in dry THF (4 mL) stirred at  $-78^{\circ}\text{C}$  under argon. The mixture was stirred at this temperature for 5 min and then at ambient temperature for another 10 min. A THF solution of dried ZnBr<sub>2</sub> (1.3 mL, 1.0 M, 1.30 mmol) was introduced via a syringe. The mixture was stirred at ambient temperature for 5 min (to afford a 0.2 M solution of the zincated acetylene), before transferred to a flask containing Pd(PPh<sub>3</sub>)<sub>4</sub> (20 mg, 0.017 mmol) stirred at  $-78^{\circ}\text{C}$  under argon. A solution of the bromoallene (74 mg, 0.34 mmol) in dry THF (2 mL) was then introduced. After completion of the addition, the mixture was stirred at  $0^{\circ}\text{C}$  until TLC showed disappearance of the starting bromoallene (ca. 5 min). The mixture was diluted with Et<sub>2</sub>O, washed in turn with water and brine, and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvent and column chromatography (30:1 PE/Et<sub>2</sub>O) gave the coupling product **15** as a colorless oil (70 mg, 0.27 mmol, 80% yield):  $[\alpha]_D^{14} +113.7$  (*c* 0.85, CHCl<sub>3</sub>). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  5.58-5.50 (m, 2H), 4.66 (dq, *J* = 2.1, 6.5 Hz, 1H), 4.17 (dd, *J* = 8.3, 6.1 Hz, 1H), 3.79 (dd, *J* = 8.4, 6.4 Hz, 1H), 1.46 (s, 3H), 1.41 (s, 3H), 0.20 (s, 9H); FT-IR (film) 2987, 2157, 1953, 1251 cm<sup>-1</sup>; ESI-MS *m/z* 259.1 ([M+Na]<sup>+</sup>); ESI-HRMS calcd. for C<sub>13</sub>H<sub>20</sub>O<sub>2</sub>SiNa ([M+Na]<sup>+</sup>) 259.1131; found 259.1125.

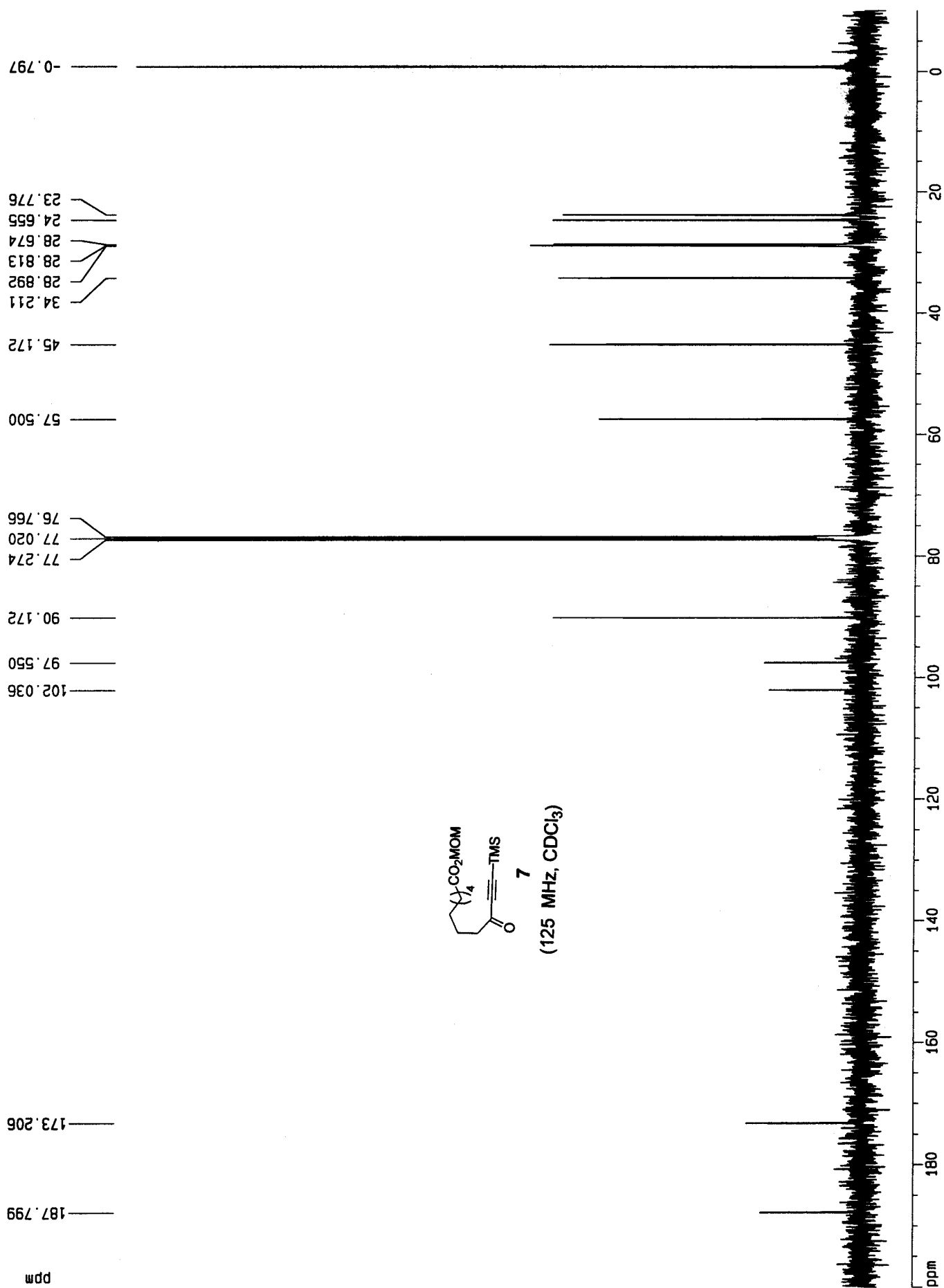


**Figure S.** Comparison of the partial <sup>1</sup>H NMR spectrum of **15'** and **15**. The coupling product under the Negishi conditions was of much better diastereomeric purity than that under the Sonogashira conditions.

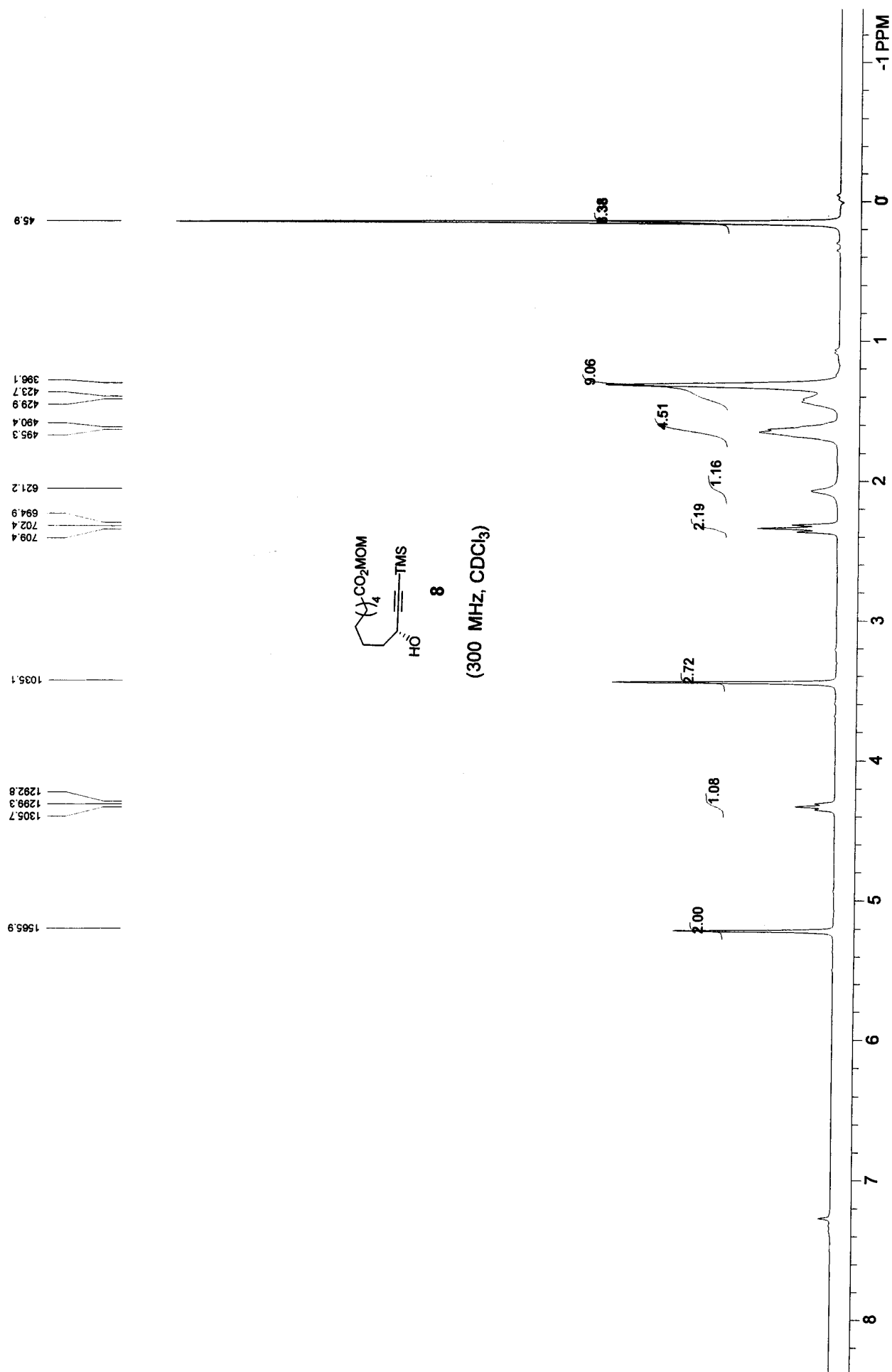


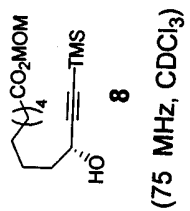
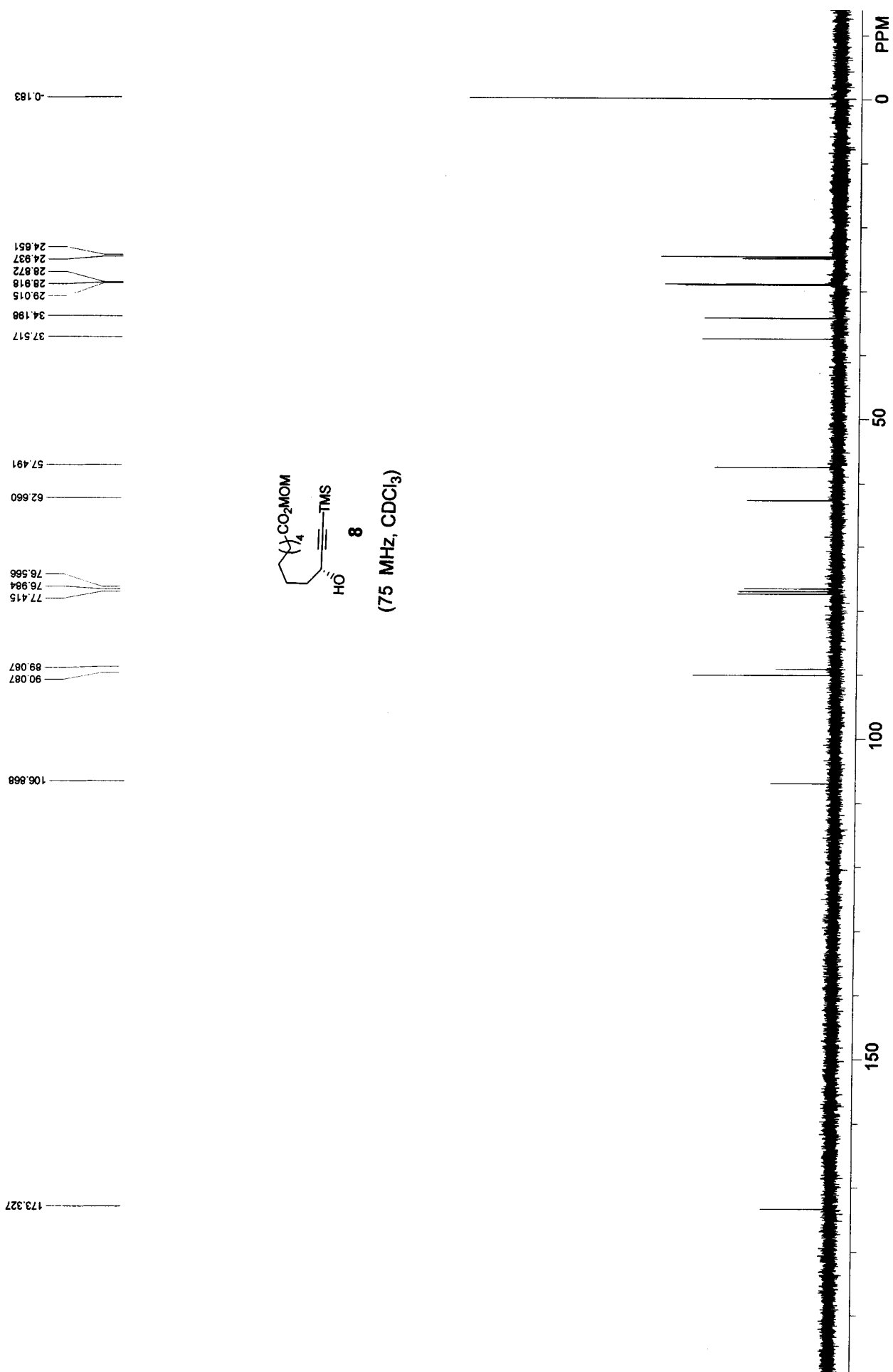


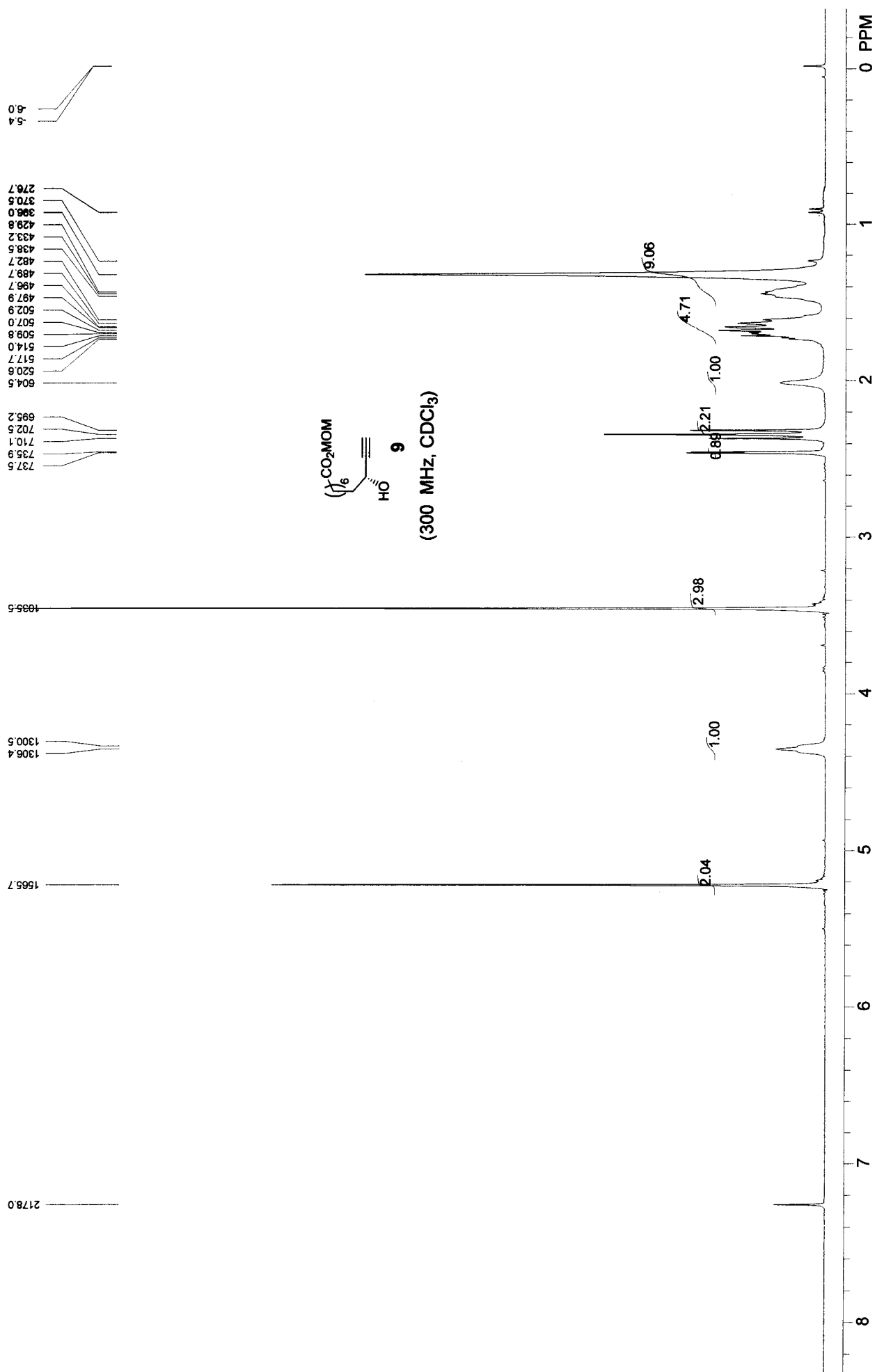


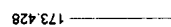


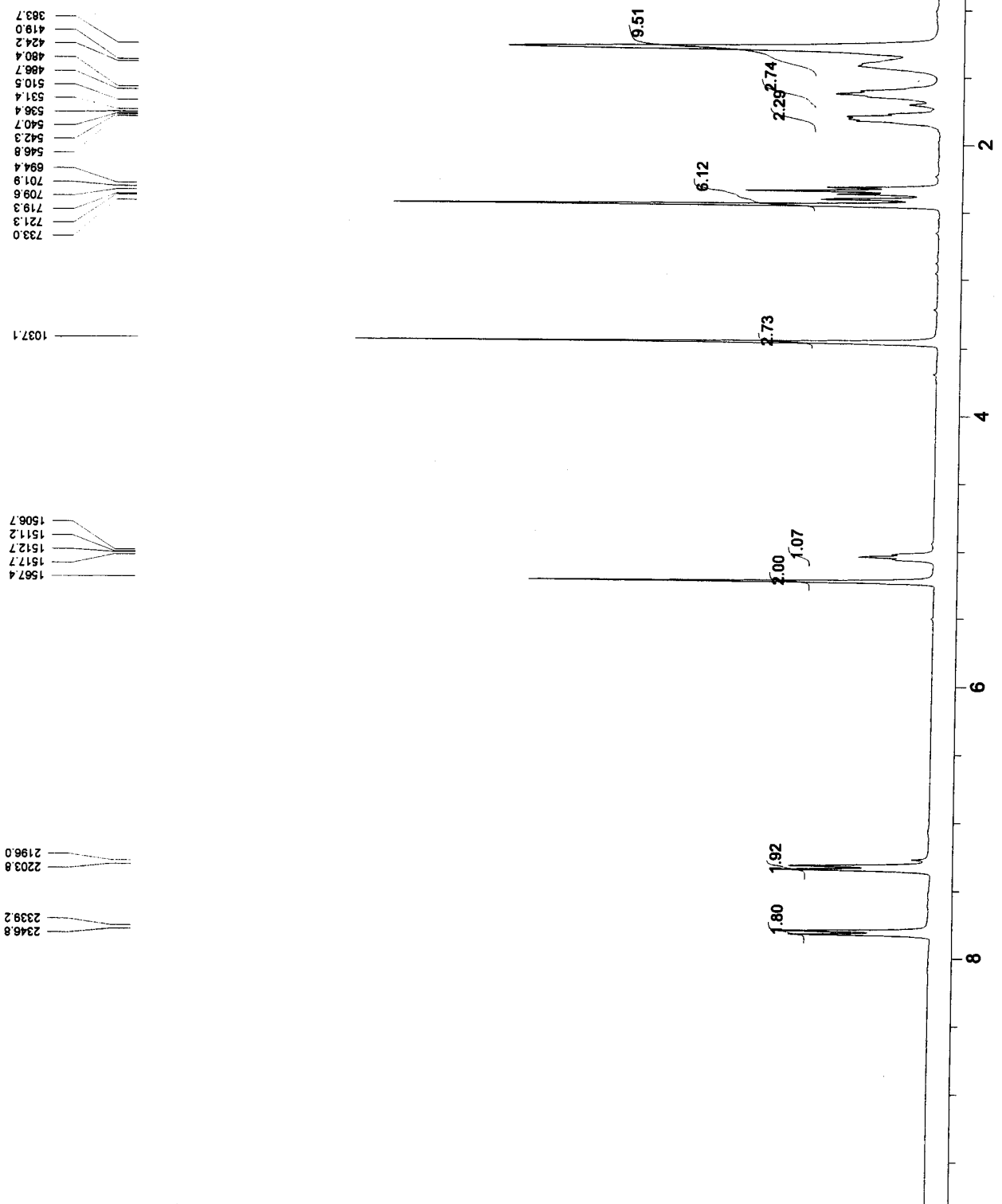
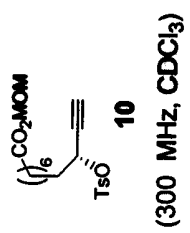












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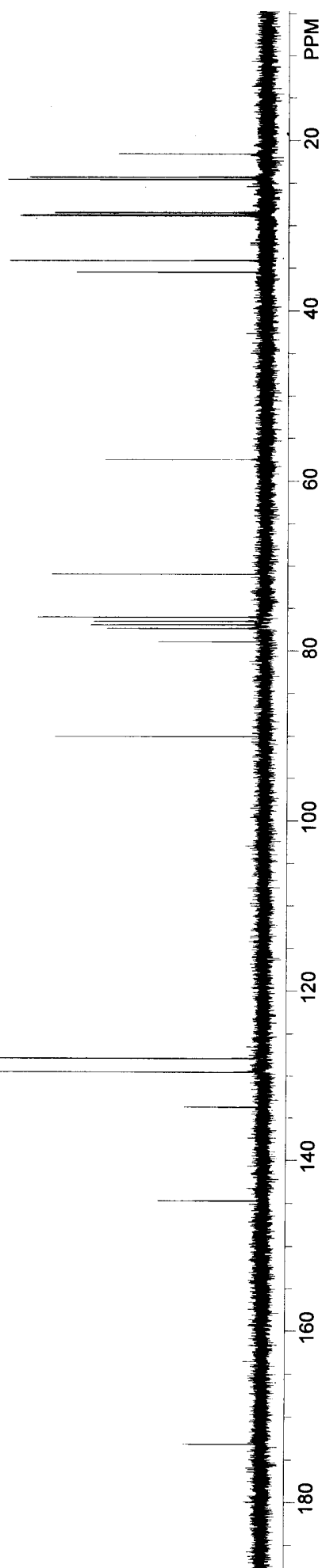
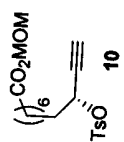
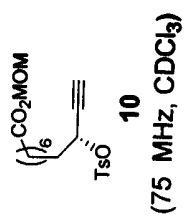
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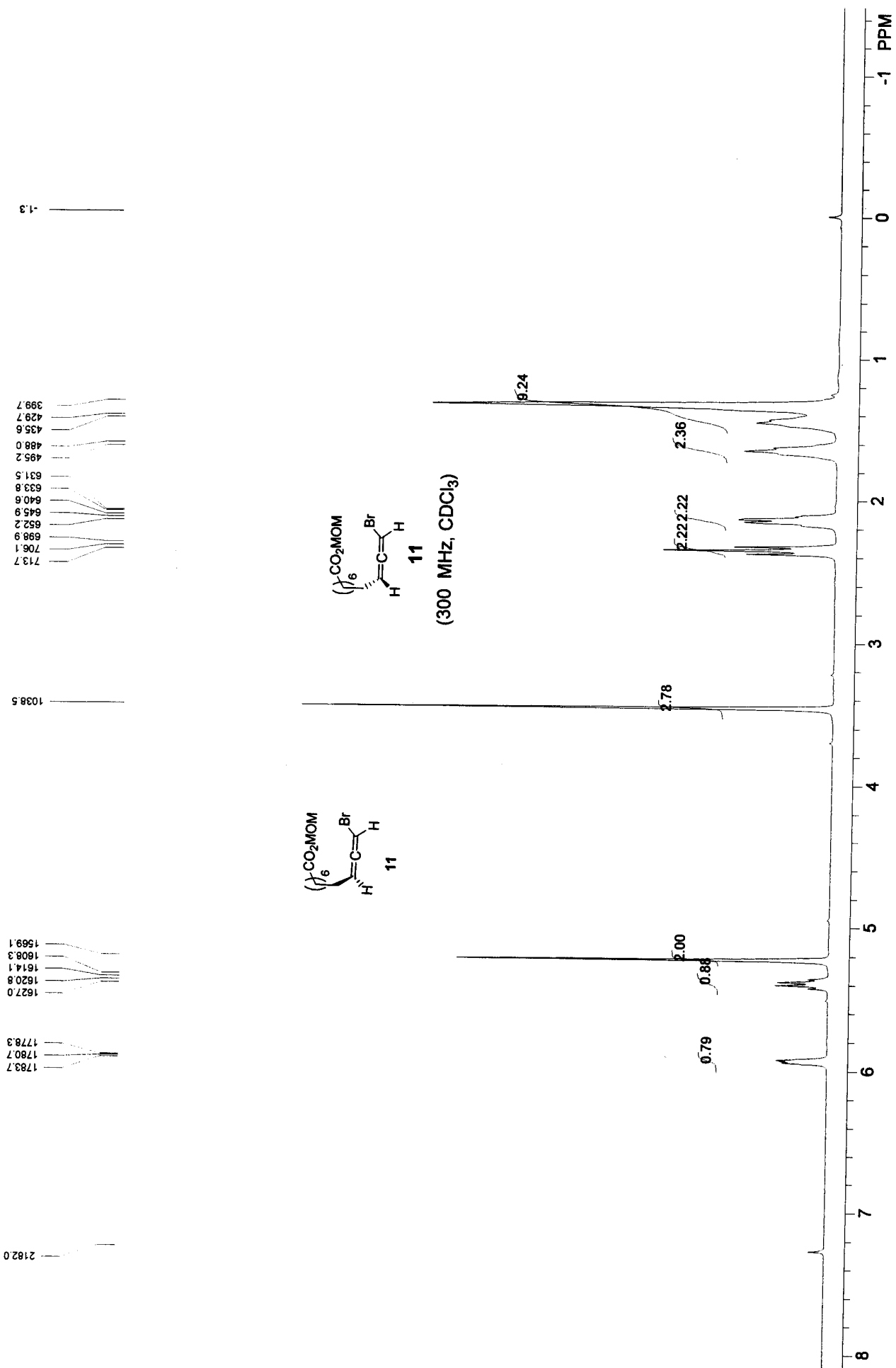
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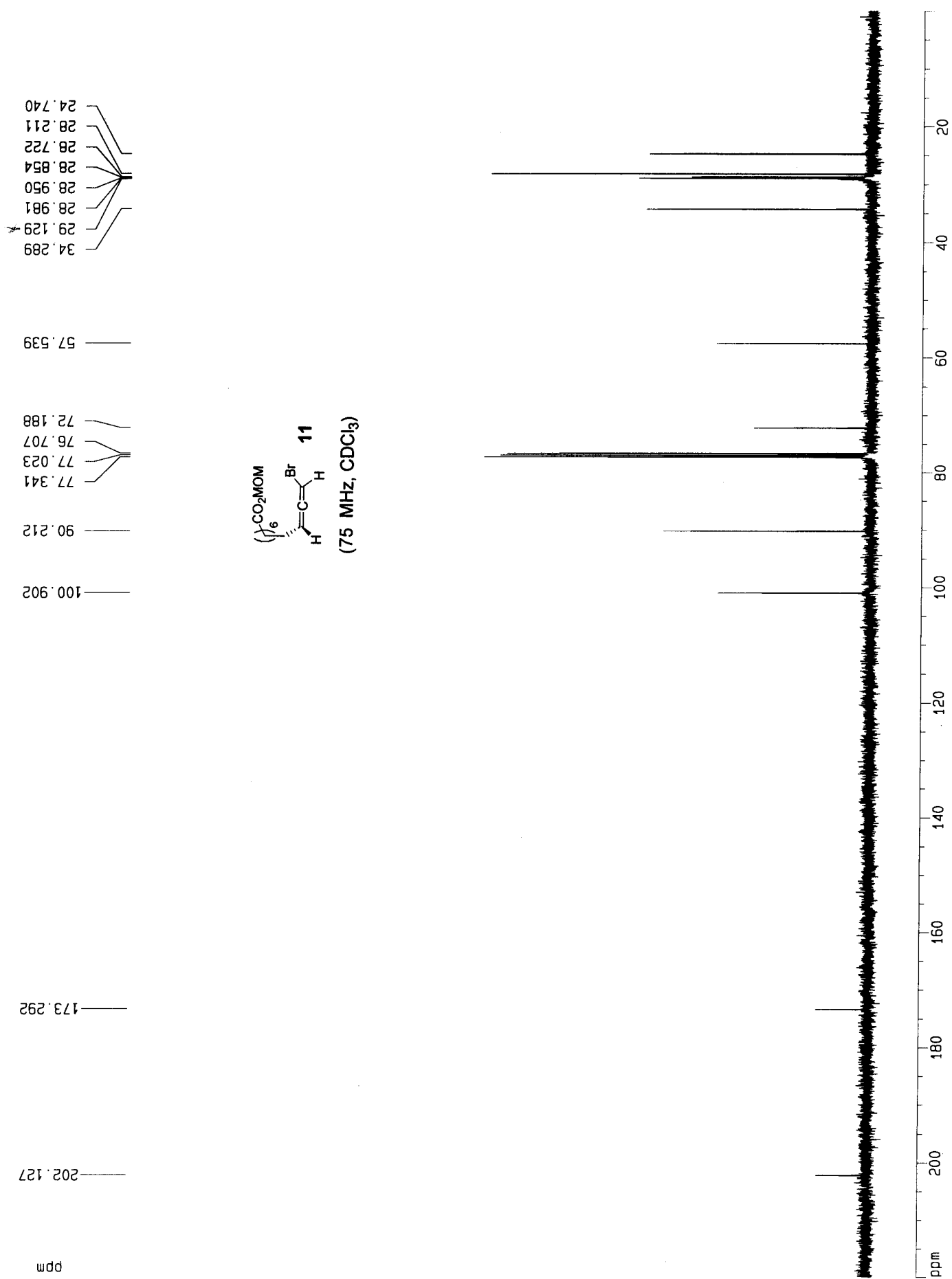
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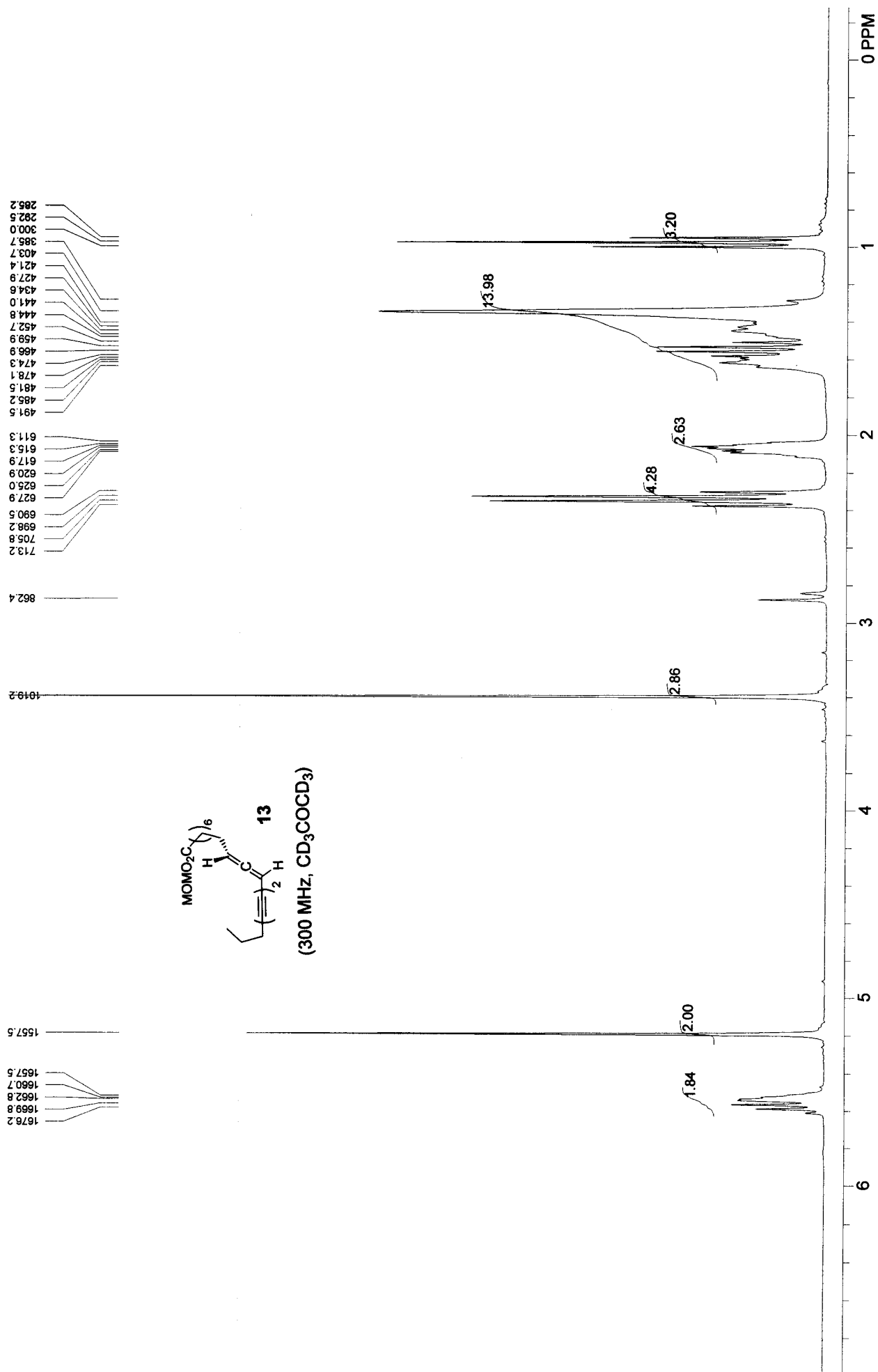
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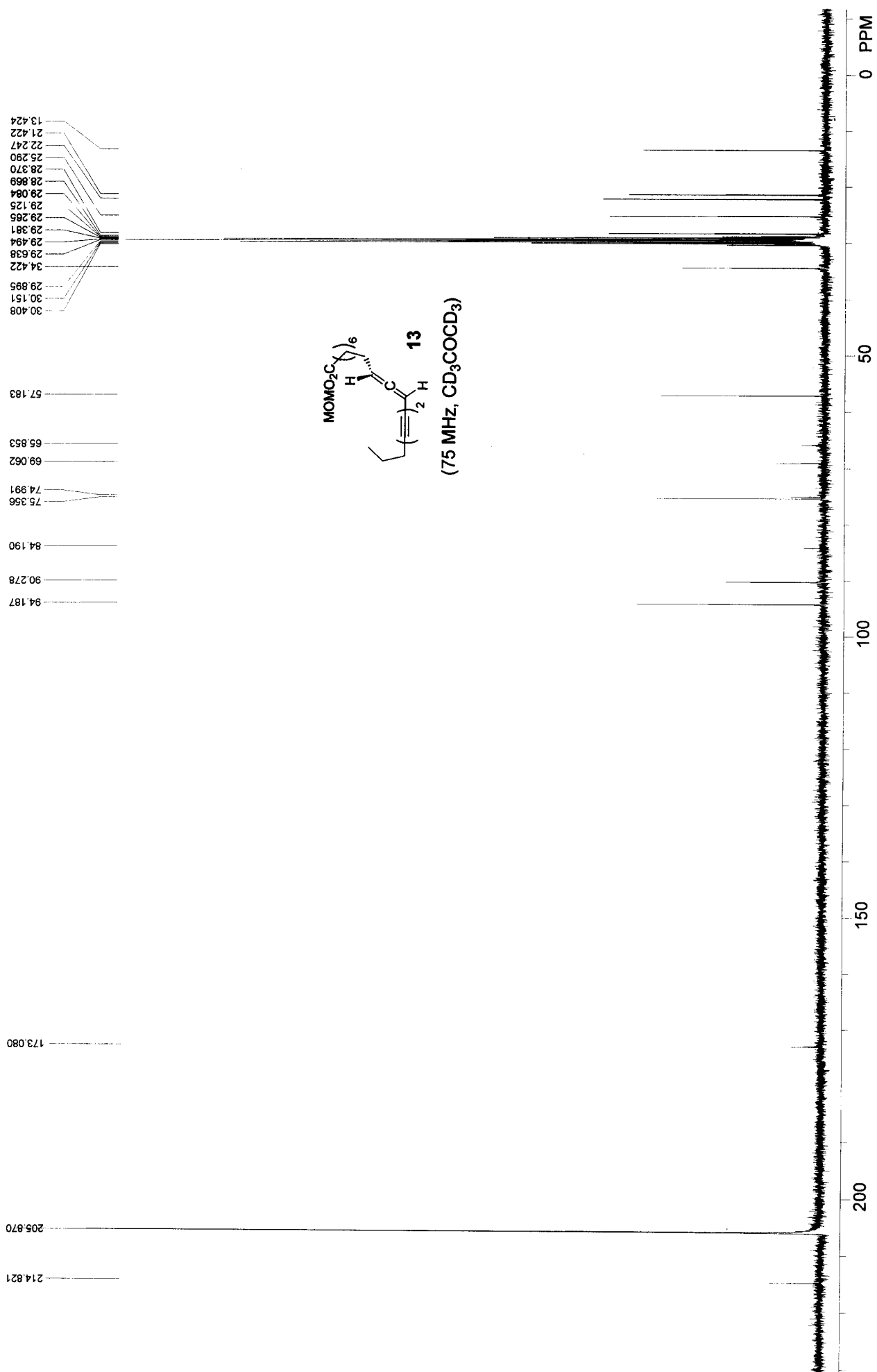














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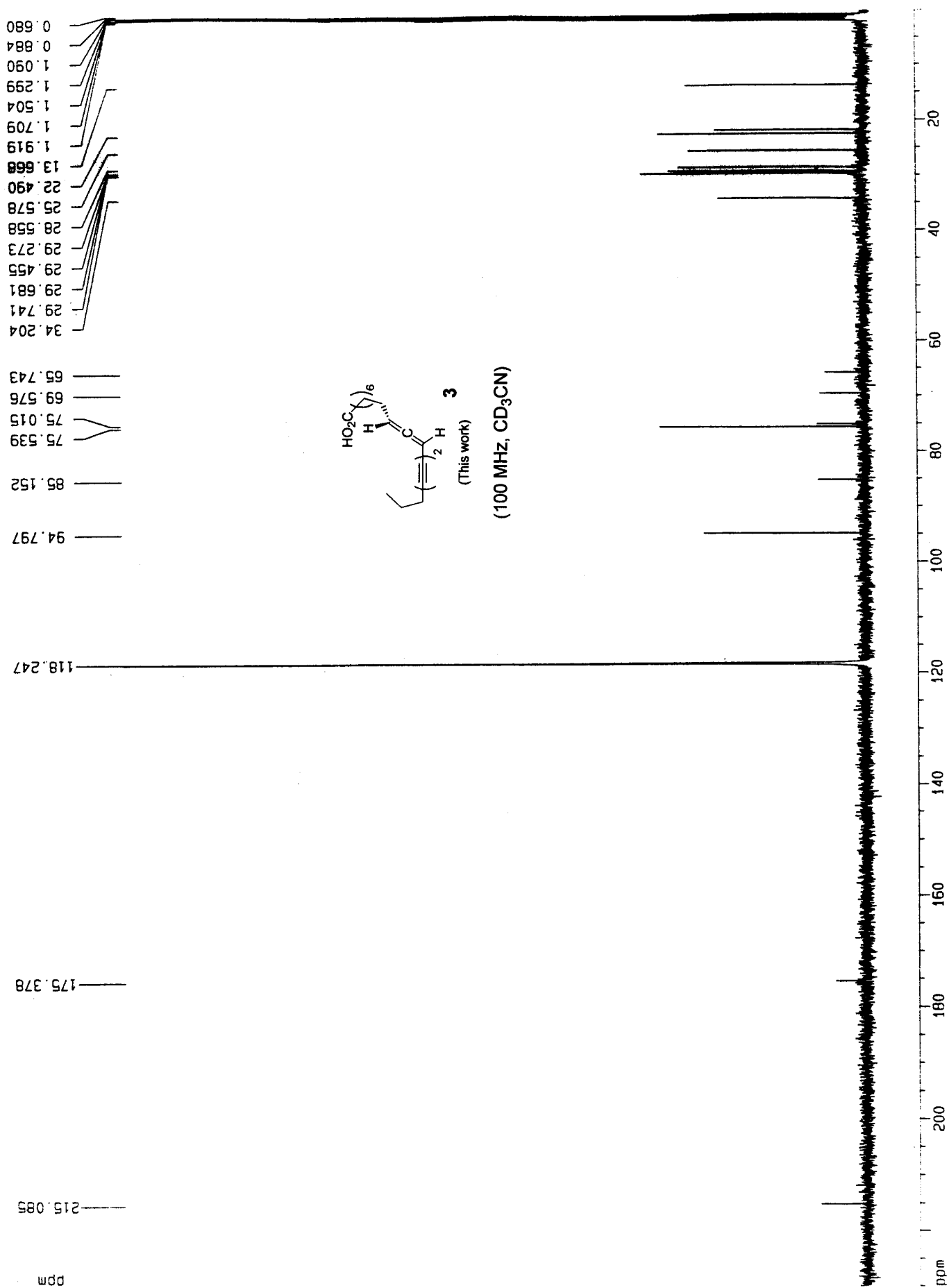
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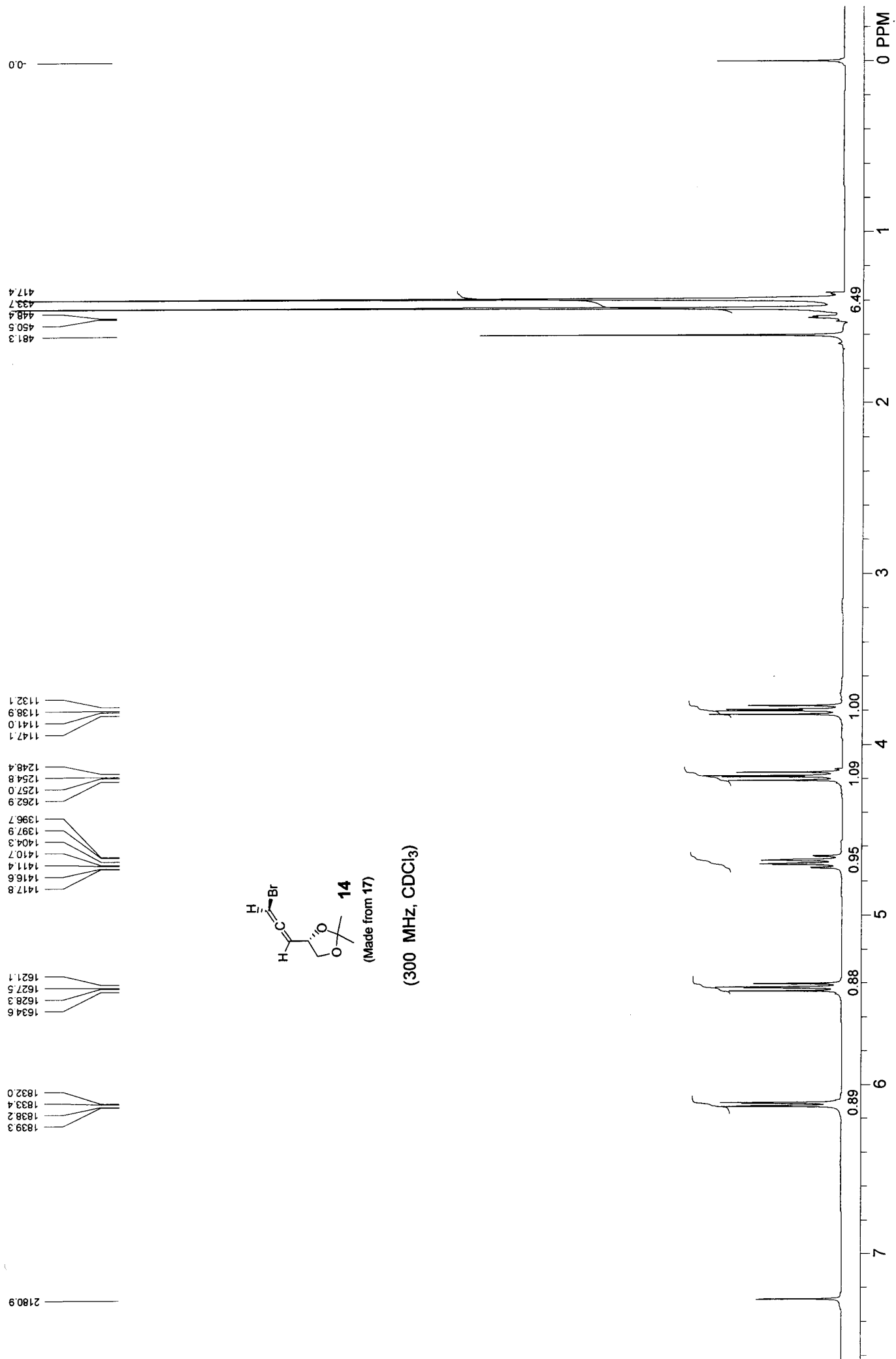
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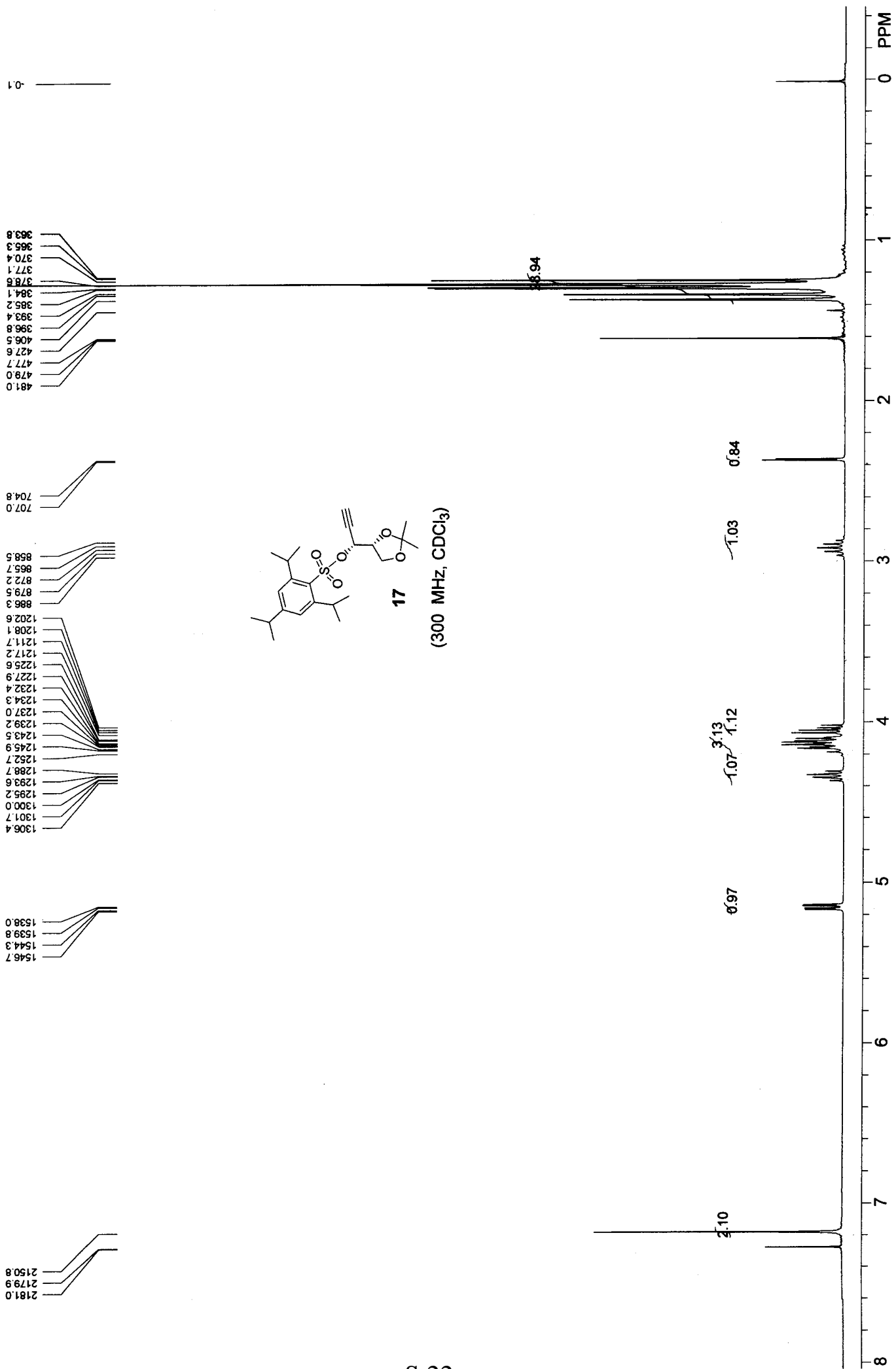
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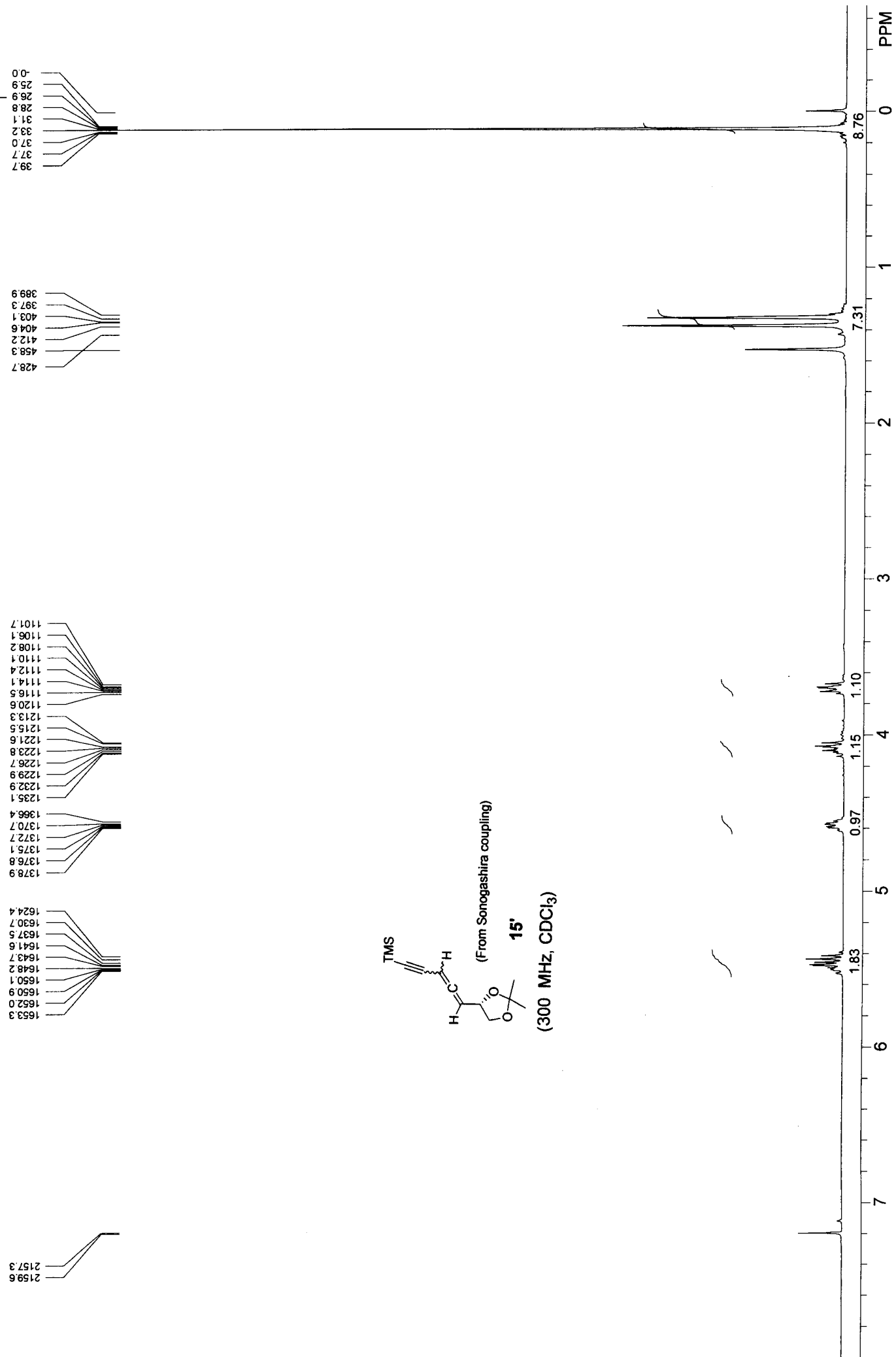
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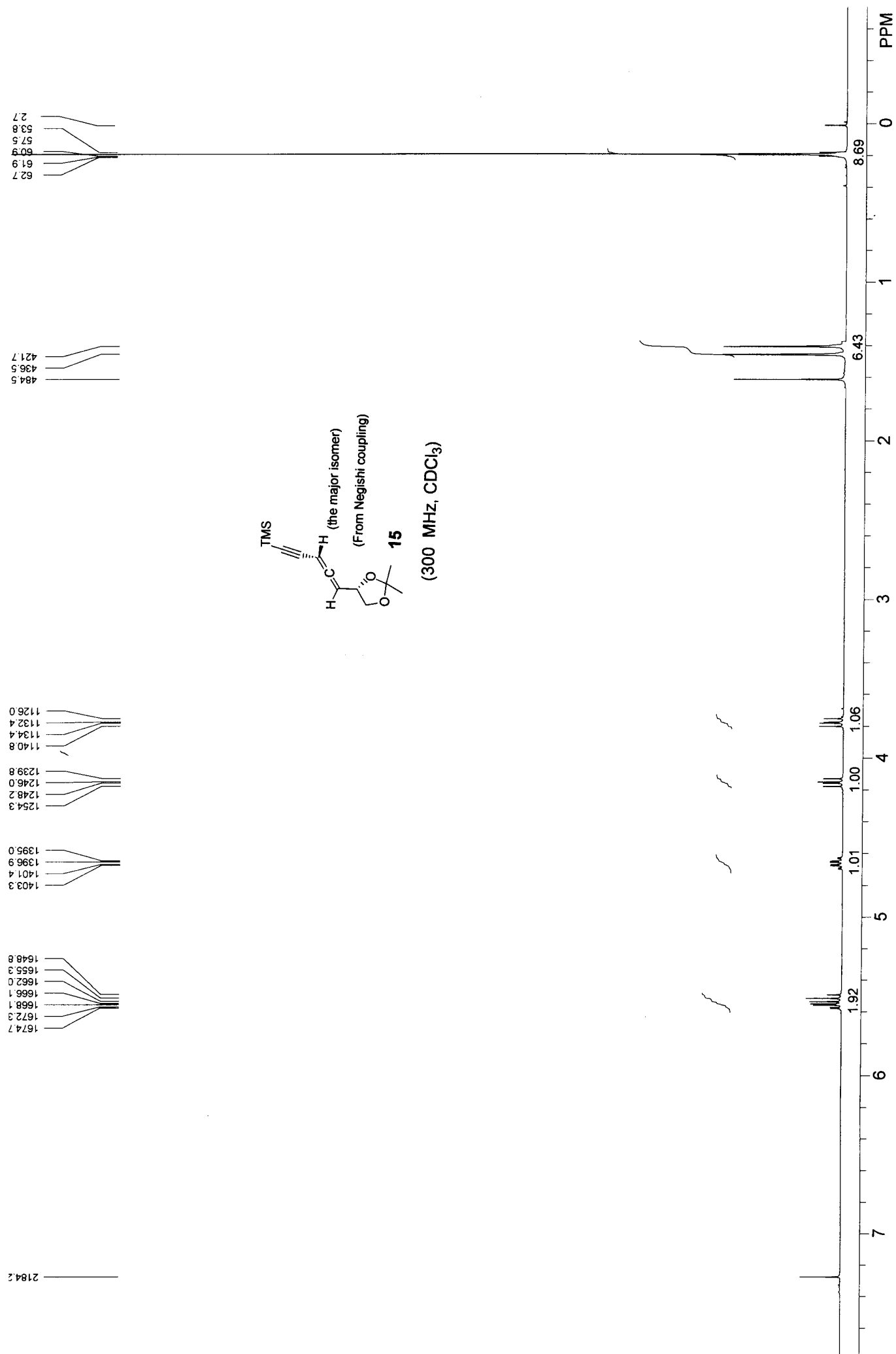
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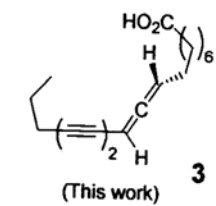




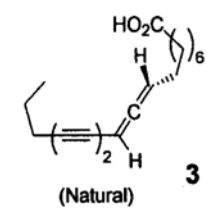
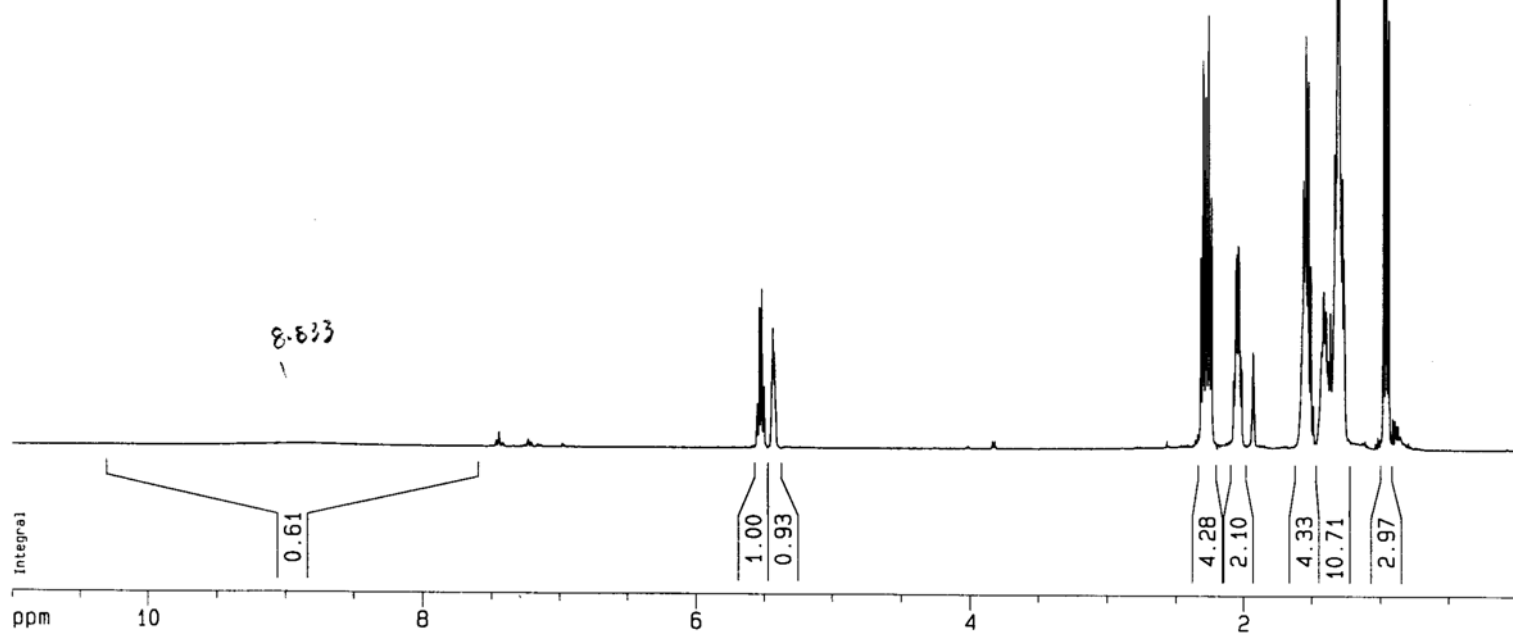








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Copied from ref 1a

(500 MHz, CD<sub>3</sub>CN)

