

Total Synthesis of *cis*-Solamin

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Supporting Information

All melting points are uncorrected. Optical rotations were measured with a JASCO DIP-1000 digital polarimeter. ^1H and ^{13}C NMR spectra were recorded in CDCl_3 on Bruker DRX 500 (500, 125 MHz) spectrometer. IR spectra were taken with a JASCO IR-810 infrared spectrometer. Mass spectra were recorded with a JEOL JMS-700 instrument. Column chromatography was carried out using Merck silica gel 60 (70~230 mesh). All air and/or moisture-sensitive reactions were carried out in flame dried glassware under an atmosphere of Ar. All solvents were dried and distilled according to standard procedures.

(*Z*, 9*S*, 10*S*)-10-(Methoxymethoxy)docos-5-en-1-yn-9-ol (2). This compound was prepared as we had reported before^{4b} $[\alpha]_{\text{D}}^{27} + 7.0$ (*c* 0.49, CHCl_3). ^1H NMR (CDCl_3 , Me_4Si) δ : 0.88 (3H, t, $J = 6.6$ Hz), 1.26-1.58 (24H, m), 1.95 (1H, t, $J = 2.7$ Hz), 2.21-2.32 (6H, m), 2.29 (1H, d, $J = 4.4$ Hz, -OH), 3.35 (1H, m), 3.41 (3H, s), 3.52 (1H, m), 4.70 (2H, s), 5.47 (2H, m) ppm; ^{13}C NMR (CDCl_3 , Me_4Si) δ : 14.12, 18.83, 22.71, 23.56, 25.22, 26.34, 29.37, 29.60, 29.63, 29.67, 29.69, 29.84, 31.11, 31.94, 33.23, 55.85, 68.37, 72.25, 83.44, 84.20, 97.06, 97.12, 128.19, 130.91 ppm. HREIMS; Calcd for $\text{C}_{24}\text{H}_{44}\text{O}_3$: 380.3290. Found: 380.3286.

(2*R*, 5*S*, 1'*R*, 1''*S*)- and (2*S*, 5*S*, 1'*S*, 1''*S*)-2-(1'-Hydroxypent-4'-ynyl)-5-(1''-methoxymethoxytridecyl)tetrahydrofuran (3a and 3b). To a solution of compound 2 (2.90

g, 7.7 mmol) in CH_2Cl_2 was added TBHP (2.67 ml, 8.0 mmol, 3.0 M in toluene) and $\text{VO}(\text{acac})_2$ (220 mg, 0.77 mmol) at 23 °C in the presence of Molecular Sieves 4A (3.0 g). After the mixture had been stirred for 12 h, the reaction mixture was quenched with water (5 ml) and extracted with Et_2O . The organic layer was washed with saturated NaCl, dried over MgSO_4 and concentrated *in vacuo* to afford an inseparable mixture of **3a** and **3b** as a colorless oil.

Determination of the ratio of 3a and 3b. This reaction was carried out as reported previously^{4b}. The ^1H NMR spectrum showed that the ratio of **3a** and **3b** was 89:11.

(2R, 5S, 1'R, 1''S)-2-(1'-Benzolyloxy-4'-pentynyl)-5-(1''-methoxymethoxytridecyl) tetrahydrofuran (4a). To a solution of the mixture of **3a** and **3b** (909 mg, 2.3 mmol) in pyridine (10 mL) was added benzoyl chloride (0.18 mL, 3.5 mmol) at 0 °C. After being stirred in an ice bath for 1h and then at room temperature for 5 h, the mixture was poured into sat. NaHCO_3 and extracted with Et_2O . Drying with MgSO_4 and subsequent evaporation of the extract afforded a crude product, which was purified by preparative TLC (benzene-AcOEt, 20 : 1) gave **4a** as a colorless oil (828 mg, 72 %): $[\alpha]_D^{27} +4.1$ (c 0.95, CHCl_3). ^1H NMR (CDCl_3 , Me_4Si) δ : 0.88 (3H, t, $J = 6.7$ Hz), 1.20-1.65 (22H, m), 1.70-2.10 (6H, m), 1.94 (1H, t, $J = 2.7$ Hz), 2.25-2.35 (2H, m), 3.36 (3H, s), 3.5-3.6 (1H, m), 3.85-3.95 (1H, m), 4.10-4.2 (1H, m), 4.65 (1H, d, $J = 6.5$ Hz), 4.83 (1H, d, $J = 6.5$ Hz), 5.3-5.4 (1H, m), 7.4-7.5 (2H, m), 7.5-7.6 (1H, m), 8.05-8.1 (2H, m) ppm; ^{13}C NMR (CDCl_3 , Me_4Si) δ : 14.11, 14.21, 15.10, 22.70, 25.36, 27.68, 27.94, 29.37, 29.64(2xC), 29.65, 29.66, 29.68, 29.70, 29.83, 30.44, 31.30, 31.94, 55.68, 68.86, 74.51, 79.49, 79.96, 82.55, 83.36, 96.78, 128.39, 129.80, 130.22, 133.00, 166.21 ppm. HREIMS; Calcd for $\text{C}_{31}\text{H}_{48}\text{O}_5$: 500.3502. Found: 500.3505.

(2R, 5S, 1'R, 1''S)-2-(1'-Methoxymethoxy-4'-pentynyl)-5-(1''-hydroxytridecyl)

tetrahydrofuran (5). To a solution of **4a** (219 mg, 0.44 mmol) in MeOH (10 mL) was added NaOH (50 mg). After the mixture had been stirred for 5 h, the solvent was evaporated and the mixture was extracted with Et₂O. The organic layer was washed with saturated NaCl, dried over MgSO₄ and concentrated *in vacuo* to afford crude product, which was chromatographed over silica gel with hexane-AcOEt (4 : 1) to give **5** as colorless oil (169 mg, 92%):

$[\alpha]_D^{24} +12.0$ (c 1.70, CHCl₃). ¹H NMR (CDCl₃, Me₄Si) δ : 0.88 (3H, t, *J* = 6.6 Hz), 1.20-1.45 (21H, m), 1.45-2.00 (7H, m), 1.93 (1H, t, *J* = 2.7 Hz), 2.25-2.35 (2H, m), 3.08 (1H, br. OH), 3.37 (3H, s), 3.4-3.45 (1H, m), 3.5-3.55 (1H, m), 3.85-3.9 (1H, m), 3.95-4.0 (1H, m), 4.70 (1H, d, *J* = 6.5 Hz), 4.73 (1H, d, *J* = 6.5 Hz) ppm; ¹³C NMR (CDCl₃, Me₄Si) δ : 14.11, 15.04, 22.70, 25.44, 28.09, 28.15, 29.37, 29.62(2xC), 29.66(2xC), 29.69, 29.85, 31.94, 33.59, 55.89, 68.31, 72.49, 80.36, 81.28, 82.09, 84.40, 96.50 ppm. HREIMS; Calcd for C₂₄H₄₄O₄: 396.3240. Found: 396.3242.

(2R, 5S, 1'R, 1''S)-2-(1'-Methoxymethoxy-4'-pentynyl)-5-(1''-methoxymethoxytridecyl)

tetrahydrofuran (6). An ice-cooled mixture of alcohol **5** (169mg, 0.43 mmol) and chloromethyl methyl ether (0.07mL, 0.9 mmol) in CH₂Cl₂ (5 mL) was treated with *i*-Pr₂NEt (0.17 mL, 1.0 mmol) and the resulting mixture was allowed to warm to room temperature and stirred for 24 h. After completion of the reaction, the reaction mixture was cooled to 0 °C and saturated NH₄Cl was added to it. The mixture was extracted with ether and the extract was washed with brine, dried with MgSO₄ and concentrated. The residue was purified by silica gel column chromatography (hexane-AcOEt = 5:1) afforded **6** (176 mg, 94 %) as a colorless oil.

$[\alpha]_D^{17} +9.1$ (c 0.84, CHCl₃). ¹H NMR (CDCl₃, Me₄Si) δ : 0.88 (3H, t, *J* = 6.6 Hz), 1.20-1.55

(24H, m), 1.6-1.85 (4H, m), 1.94 (1H, t, $J = 2.7$ Hz), 2.25-2.35 (2H, m), 3.38 (3H, s), 3.40 (3H, s), 3.45-3.5 (1H, m), 3.5-3.6 (1H, m), 3.85-4.0 (2H, m), 4.67 (1H, d, $J = 6.5$ Hz), 4.69 (1H, d, $J = 6.5$ Hz), 4.81 (1H, d, $J = 6.5$ Hz), 4.82 (1H, d, $J = 6.5$ Hz) ppm; ^{13}C NMR (CDCl_3 , Me_4Si) δ : 14.12, 14.79, 22.70, 25.42, 27.48, 27.69, 29.37, 29.62, 29.65, 29.66, 29.68, 29.70, 29.84, 30.32, 31.36, 31.94, 55.72, 55.88, 68.55, 78.63, 79.80, 81.48, 82.02, 84.19, 96.71, 97.10 ppm. HREIMS; Calcd for $\text{C}_{26}\text{H}_{48}\text{O}_5$: 440.3502. Found: 440.3505.

(1''S, 2''R, 3RS, 5''S, 13'R)-3-{13'-Meythoxymethoxy-13'-[5''-(1'''-methoxymethoxytridecyl)tetrahydrofuran-2''-yl]tridec-7'-en-9'-ynyl}-5-methyl-3-(phenylsulfanyl)tetrahydrofuran-2-one (9). To a solution of the vinyl iodide **8** (60 mg, 0.14 mmol) in THF (1 mL) was added Et_3N (0.05 mL, 0.27 mmol) and $\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$ (2.8 mg, 0.007 mmol) and the resulting solution was stirred for 1 h. The acetylenic ether **6** (60 mg, 0.14 mmol) along with CuI (1.4 mg, 0.014 mmol) were then added to the mixture, which after being stirred for a further 8 h, the reaction was quenched with saturated NH_4Cl . The organic materials were extracted with ether and the extract was washed with brine. Drying over MgSO_4 and the evaporation of the solvent gave an oil, which was chromatographed over silica gel (hexane-AcOEt = 4:1) to give **9** (75 mg, 74 %) as a colorless oil. ^1H NMR (CDCl_3 , Me_4Si) δ : 0.88 (3H, t, $J = 6.6$ Hz), 1.22 (2.4 H, d, $J = 6.2$ Hz), 1.38 (0.6 H, d, $J = 6.2$ Hz), 1.2-2.0 (39H, m), 2.05-2.1 (2H, m), 2.35-2.55 (3H, m), 3.39 (3H, s), 3.40 (3H, s), 3.45-3.55 (1H, m), 3.6-3.65 (1H, m), 3.85-4.0 (2H, m), 4.45-4.65 (1H, m), 4.67 (1H, d, $J = 6.5$ Hz), 4.69 (1H, d, $J = 6.5$ Hz), 4.81 (1H, d, $J = 6.5$ Hz), 4.82 (1H, d, $J = 6.5$ Hz), 5.4-5.5 (1H, m), 5.95-6.1 (1H, m), 7.3-7.45 (3H, m), 7.5-7.6 (2H, m) ppm. HRFABMS($\text{M}+\text{Na}$); Calcd for $\text{C}_{45}\text{H}_{72}\text{O}_7\text{SNa}$: 779.4896. Found: 778.4894.

(1'''S, 2''R, 3RS, 5''S, 13'R)-3-{13'-Meythoxymethoxy-13'-[5''-(1'''-methoxymethoxy-tridecyl)tetrahydrofuran-2''-yl]tridecyl}-5-methyl-3-(phenylsulfanyl)tetrahydrofuran-2-one (10). A solution of **9** (15 mg, 0.20 mmol) in benzene-EtOH (4:1, 5 mL) was hydrogenated over chlorotris(triphenylphosphine)rhodium (37 mg, 0.04 mmol) for 24 h. Filtration and concentration afforded an oil, which was chromatographed over silica gel (hexane-AcOEt = 4:1) to give **10** (10 mg, 68%) as a colorless oil. ¹H NMR (CDCl₃, Me₄Si) δ: 0.88 (3H, t, *J* = 6.6 Hz), 1.19 (2.4 H, d, *J* = 6.2 Hz), 1.38 (0.6 H, d, *J* = 6.2 Hz), 1.2-2.1 (51H, m), 2.05-2.1 (2H, m), 2.32 (0.2H, dd, *J* = 13.9, 5.5 Hz), 2.52 (0.8H, dd, *J* = 13.9, 7.5 Hz), 3.39 (3H, s), 3.40 (3H, s), 3.45-3.55 (2H, m), 3.85-3.95 (2H, m), 4.45-4.65 (1H, m), 4.67 (1H, d, *J* = 6.5 Hz), 4.69 (1H, d, *J* = 6.5 Hz), 4.81 (1H, d, *J* = 6.5 Hz), 4.82 (1H, d, *J* = 6.5 Hz), 7.3-7.45 (3H, m), 7.5-7.6 (2H, m) ppm. HRFABMS(M+Na); Calcd for C₄₅H₇₈O₇SNa: 785.5366.

Found:785.5368

cis-Solamin (1a). To a solution of **10** (10 mg, 13.6 mmol) in CH₂Cl₂ (1 ml) was added *m*CPBA (80%, 5.4 mg, 25 mmol) at 0 °C. After the mixture had been stirred at this temperature for 10 min, Na₂S₂O₃/NaHCO₃ (1:1, 1 ml) was added. After stirring at room temperature for 1 h, the mixture was extracted with ether and the extract was washed with brine. Drying over MgSO₄ and subsequent concentration gave an oil, which was dissolved in toluene (2 mL) and the solution was refluxed for 1 h. After completion of the reaction, concentration of the mixture gave an oil, which was then dissolved in dimethyl sulfide, (0.5 mL) at 0 °C. After the mixture had been stirred for 10 min at this temperature, the reaction mixture was quenched with sat. NaHCO₃ and diluted with AcOEt. The mixture was washed with water and brine. Drying over MgSO₄ and evaporation of the solvent gave a colorless solid, which was purified by silica gel chromatography (AcOEt) gave **1a** (3.4 mg, 60 %) as a

colorless solid, mp 66~68 °C, $[\alpha]_D^{21} +26$ (c 0.45, MeOH). ^1H and ^{13}C NMR spectra were identical with those reported in ref. 3. HREIMS; Calcd for $\text{C}_{35}\text{H}_{64}\text{O}_5$: 564.4753.

Found: 564.4720.

Preparation of the Bis-(*R*)-MTPA Ester of 1a. To a stirred solution of **1a** (1.0 mg, 1.8 μmol) in CH_2Cl_2 (0.2 mL) at room temperature was sequentially added Et_3N (0.4 mg, 2.5 equiv.), 4-dimethylamino pyridine (0.1 mg, 0.8 μmol), and (*S*)-MTPACl (~5 μL , 0.027 mmol, 15 equiv.). After the mixture was allowed to sit for 8 h at room temperature, saturated NaHCO_3 and Et_2O were added. This mixture was stirred vigorously for 1 h. The organic phase was extracted with Et_2O and the extract was washed with brine. Drying over MgSO_4 and the evaporation of the solvent gave an oil, which was chromatographed over silica gel (hexane-AcOEt = 4:1) to bis-(*R*)-MTPA Ester of **1a** (1.2 mg, 90 %) as a light yellow oil: ^1H NMR (CDCl_3 , Me_4Si) δ : 0.88 (3H, t, $J = 6.6$ Hz), 1.39 (3 H, d, $J = 6.2$ Hz), 1.2-1.9 (50H, m), 2.26 (2H, t, $J = 7.6$ Hz), 3.60 (3H, s), 3.68 (3H, s), 3.87(1H, m), 4.08 (1H, m), 4.92 (1H, m), 4.98 (1H, qd, $J = 6.2, 1.4$ Hz), 5.06 (1H, ddd, $J = 6.5$ Hz), 6.97 (1H, d, $J = 1.4$ Hz), 7.35-7.65 (10H, m) ppm.

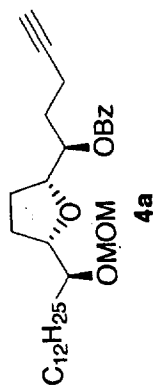
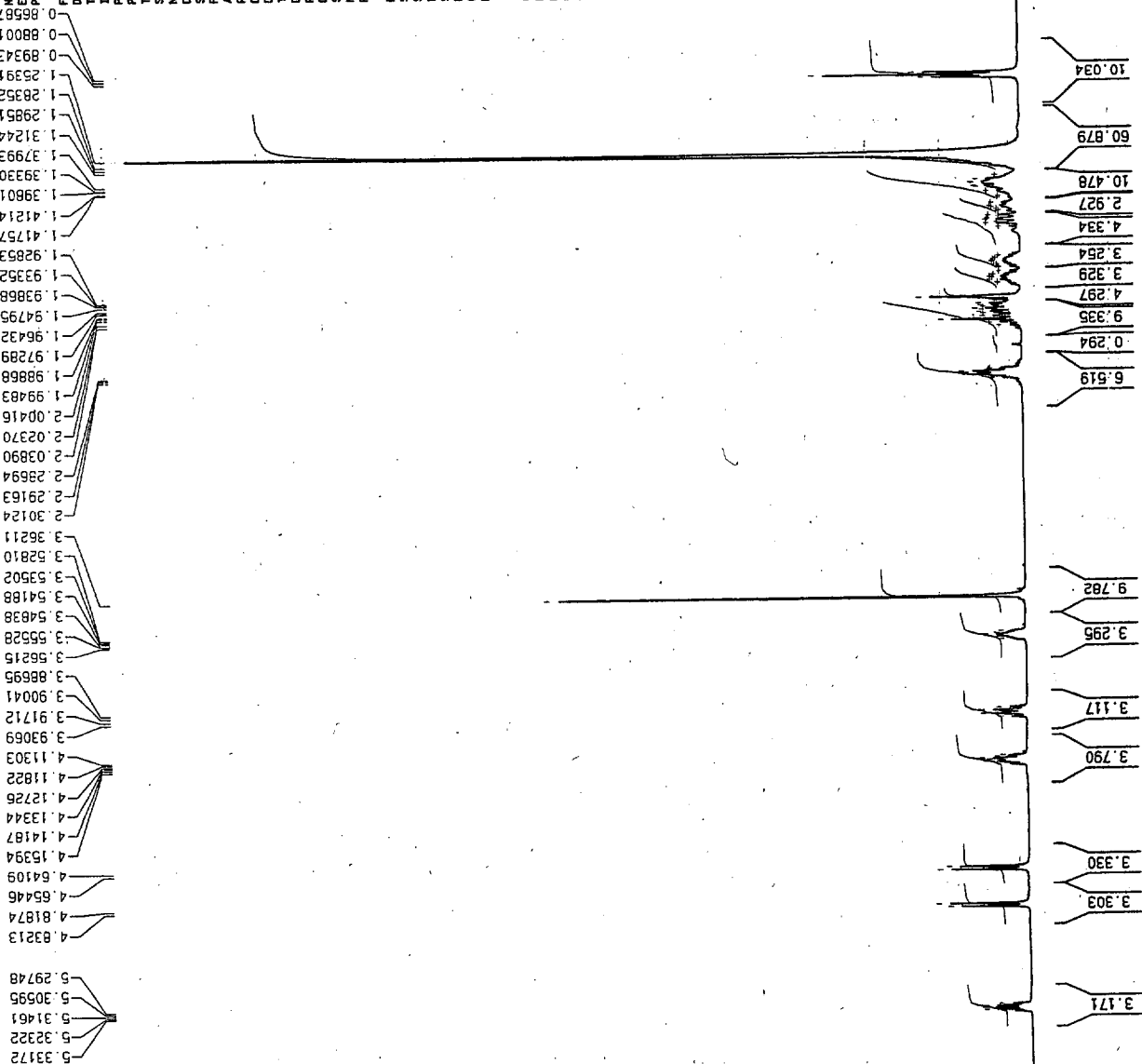
Bis-(*S*)-MTPA Ester of 1a. ^1H NMR (CDCl_3 , Me_4Si) δ : 0.88 (3H, t, $J = 6.6$ Hz), 1.39 (3 H, d, $J = 6.2$ Hz), 1.2-1.9 (50H, m), 2.26 (2H, t, $J = 7.6$ Hz), 3.60 (3H, s), 3.68 (3H, s), 3.86(1H, m), 4.09 (1H, m), 4.93 (1H, m), 4.98 (1H, qd, $J = 6.2, 1.4$ Hz), 5.06 (1H, ddd, $J = 6.5$ Hz), 6.97 (1H, d, $J = 1.4$ Hz), 7.35-7.65 (10H, m) ppm.

Bis-(*R*)-MTPA Ester of 1b. ^1H NMR (CDCl_3 , Me_4Si) δ : 0.88 (3H, t, $J = 6.6$ Hz), 1.39 (3 H, d, $J = 6.2$ Hz), 1.2-1.9 (50H, m), 2.26 (2H, t, $J = 7.6$ Hz), 3.60 (3H, s), 3.68 (3H, s), 3.86(1H, m), 4.10 (1H, m), 4.93 (1H, m), 4.98 (1H, qd, $J = 6.2, 1.4$ Hz), 5.06 (1H, ddd, $J = 6.5$ Hz),

6.97 (1H, d, $J = 1.4$ Hz), 7.35-7.65 (10H, m) ppm.

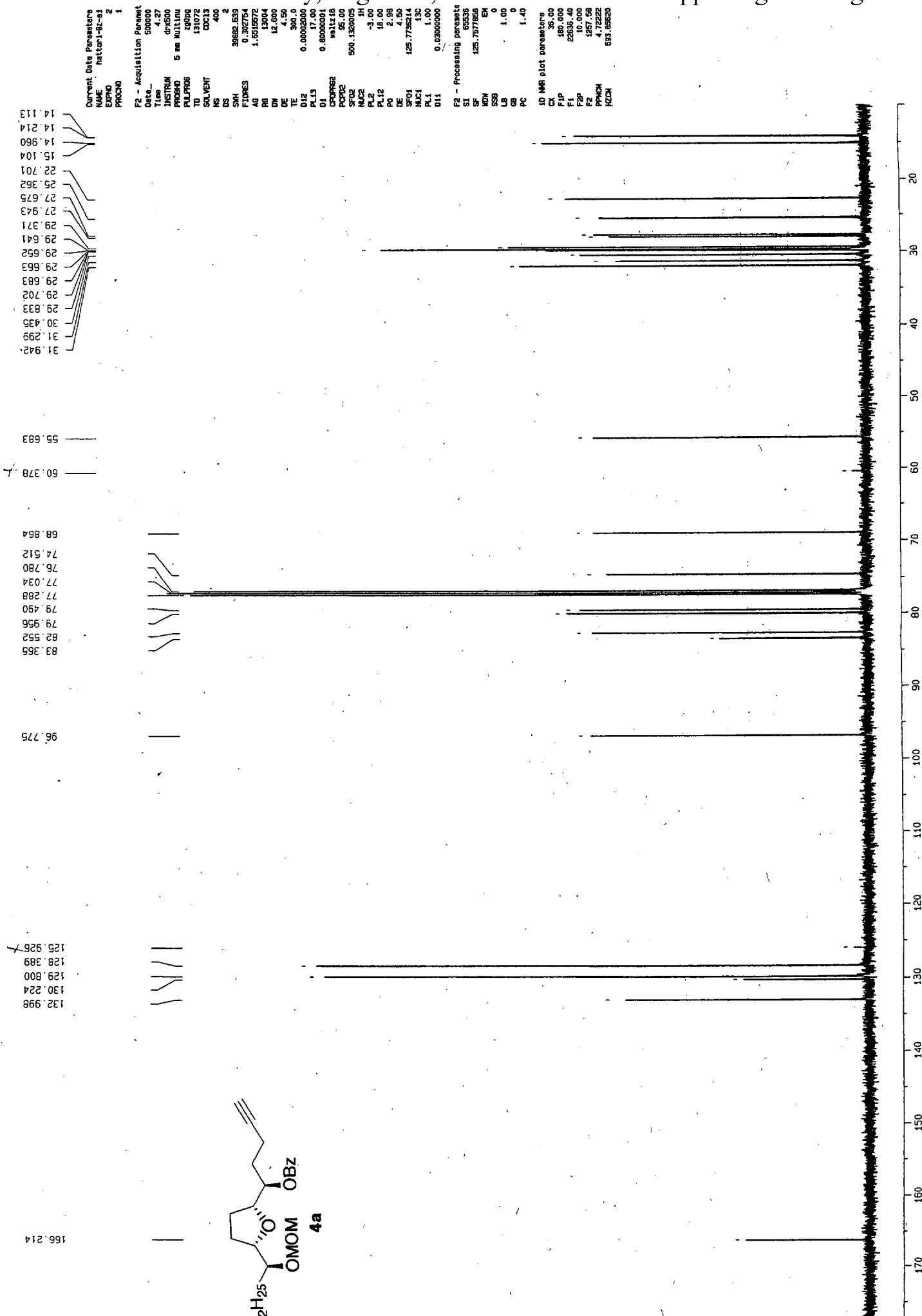
Bis-(*S*)-MTPA Ester of 1b. ^1H NMR (CDCl_3 , Me_4Si) δ : 0.88 (3H, t, $J = 6.6$ Hz), 1.39 (3 H, d, $J = 6.2$ Hz), 1.2-1.9 (50H, m), 2.26 (2H, t, $J = 7.6$ Hz), 3.60 (3H, s), 3.68 (3H, s), 3.87(1H, m), 4.08 (1H, m), 4.92 (1H, m), 4.98 (1H, qd, $J = 6.2, 1.4$ Hz), 5.06 (1H, ddd, $J = 6.5$ Hz), 6.97 (1H, d, $J = 1.4$ Hz), 7.35-7.65 (10H, m) ppm.

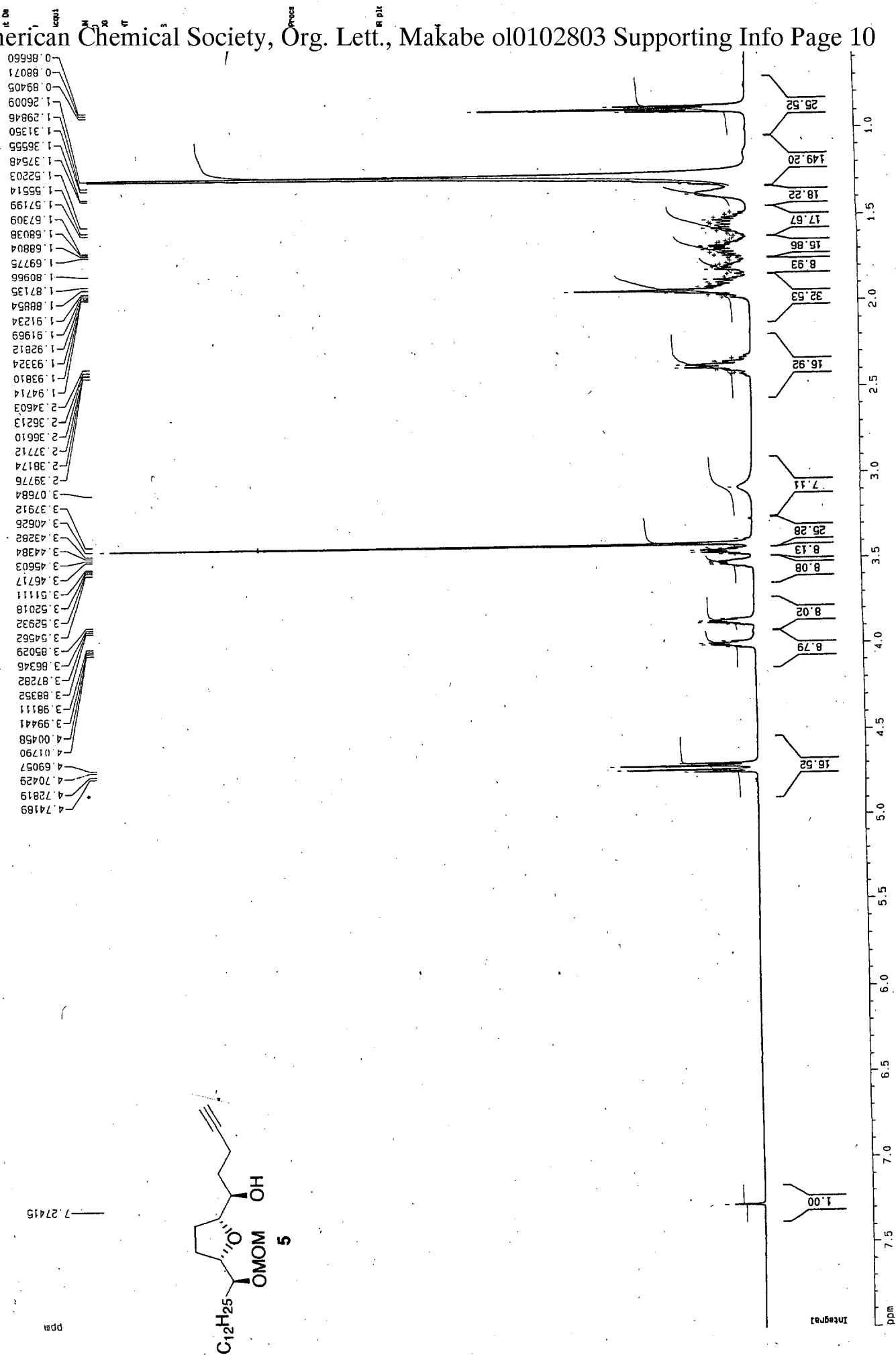
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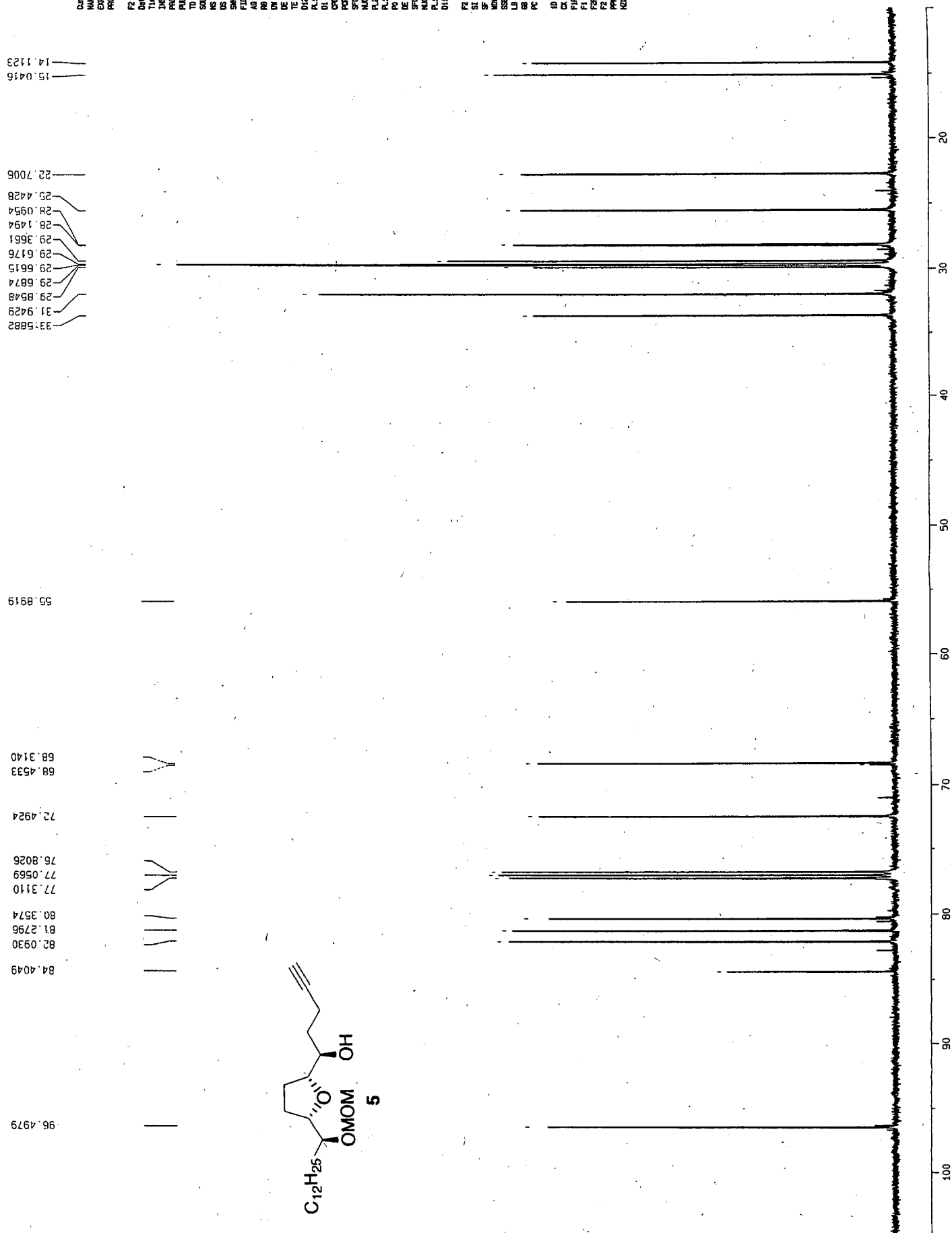


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Chemical shifts (ppm) labeled on the left side of the spectrum (from top to bottom):
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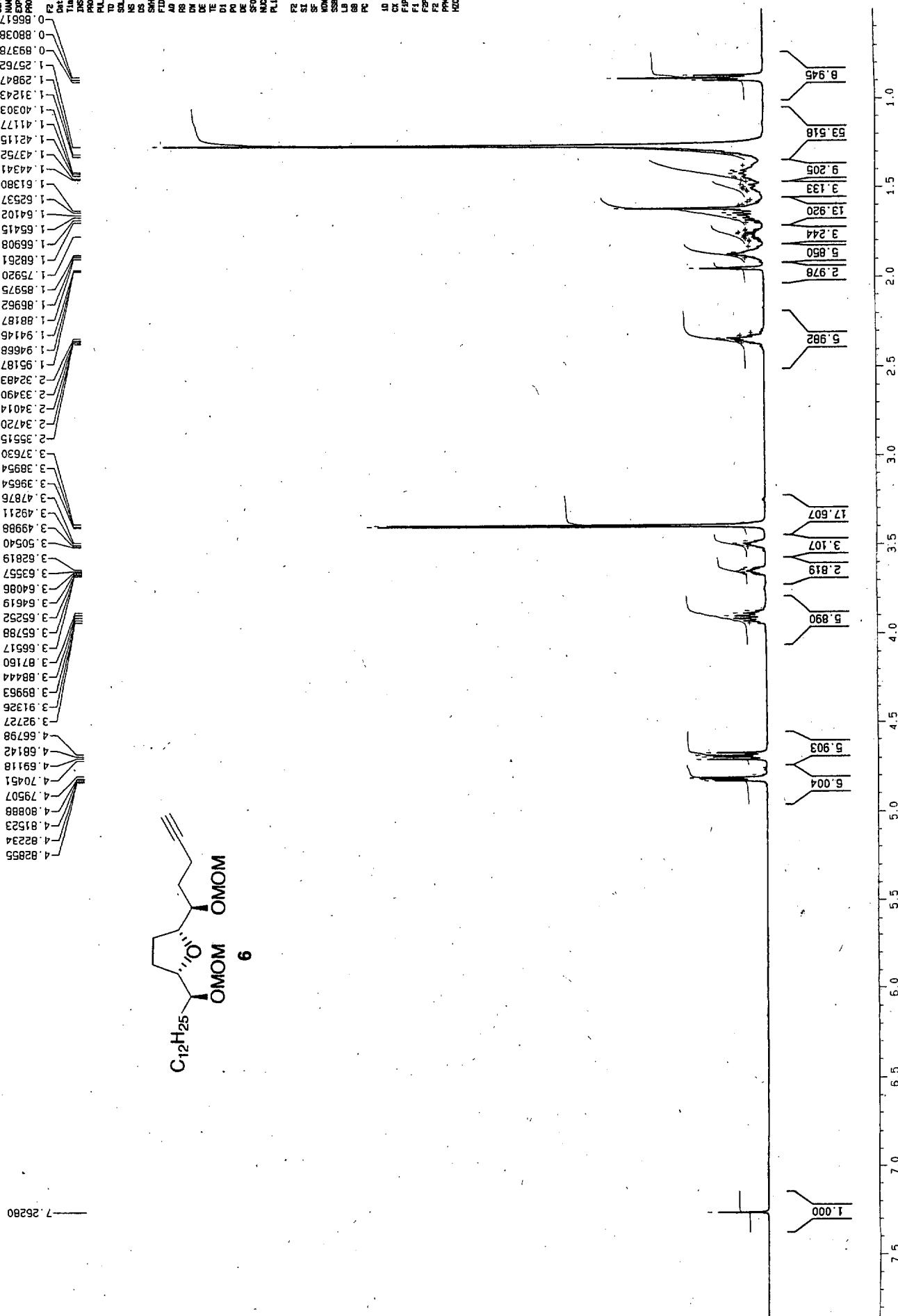


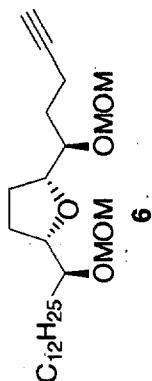
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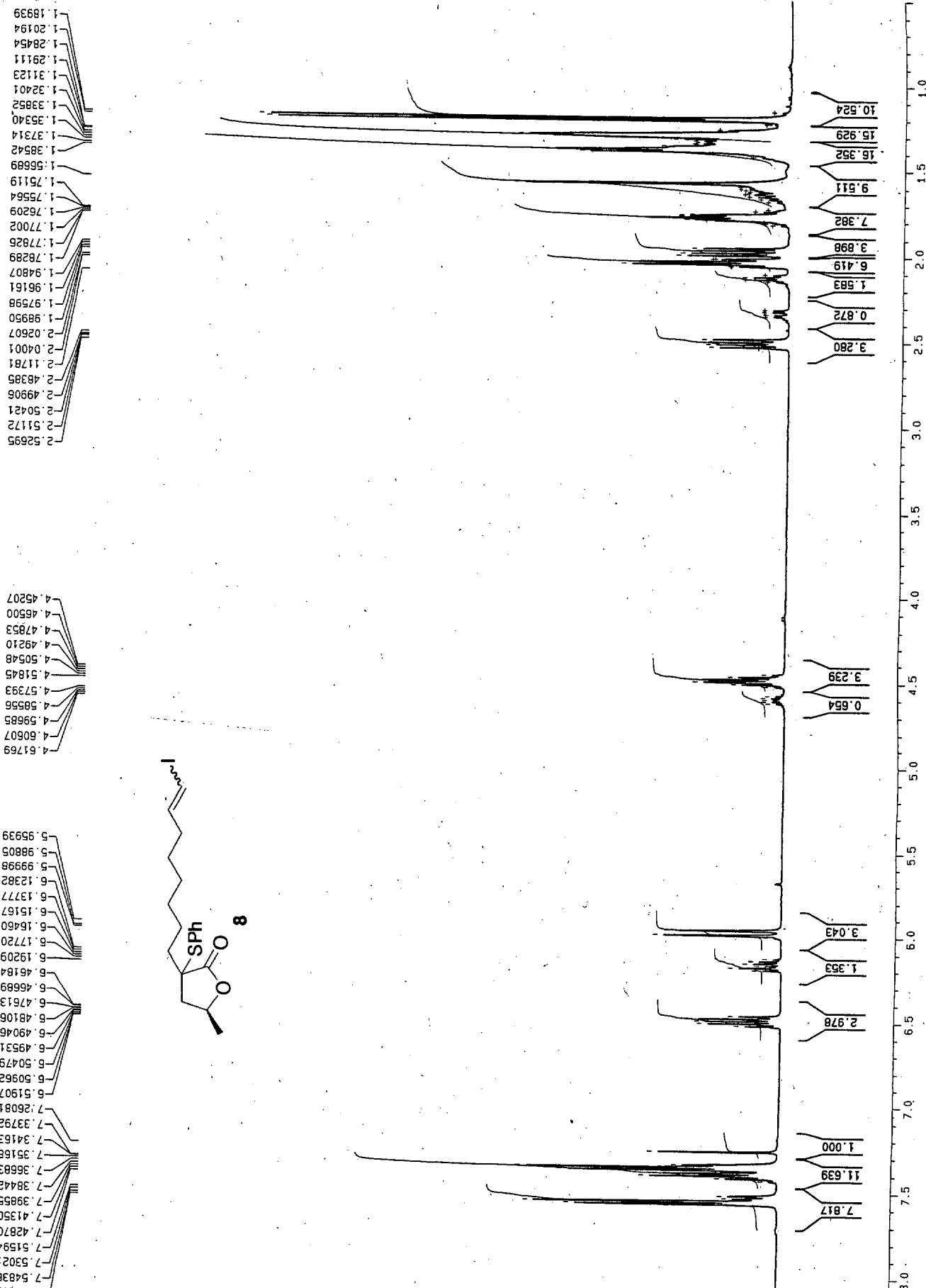
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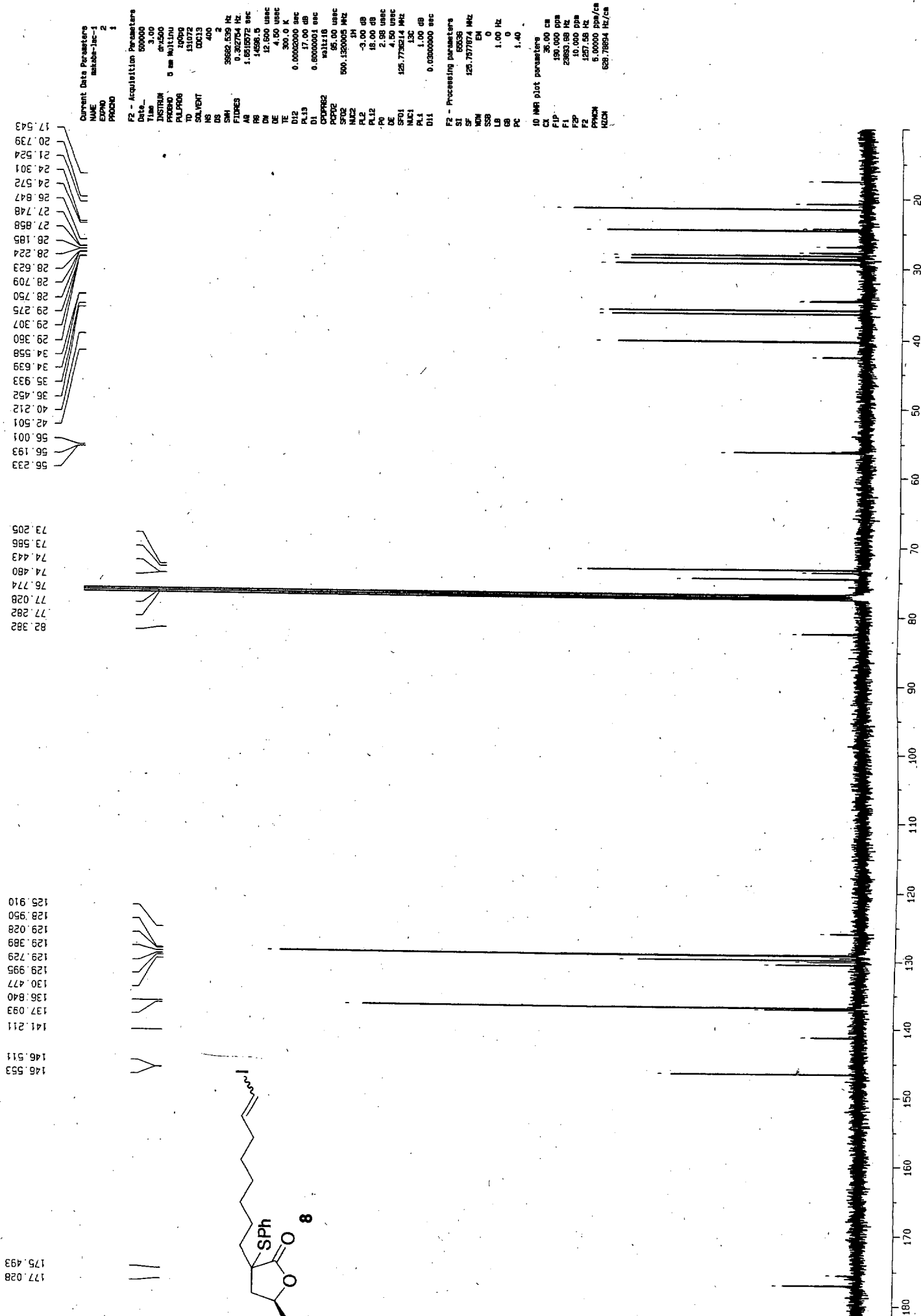
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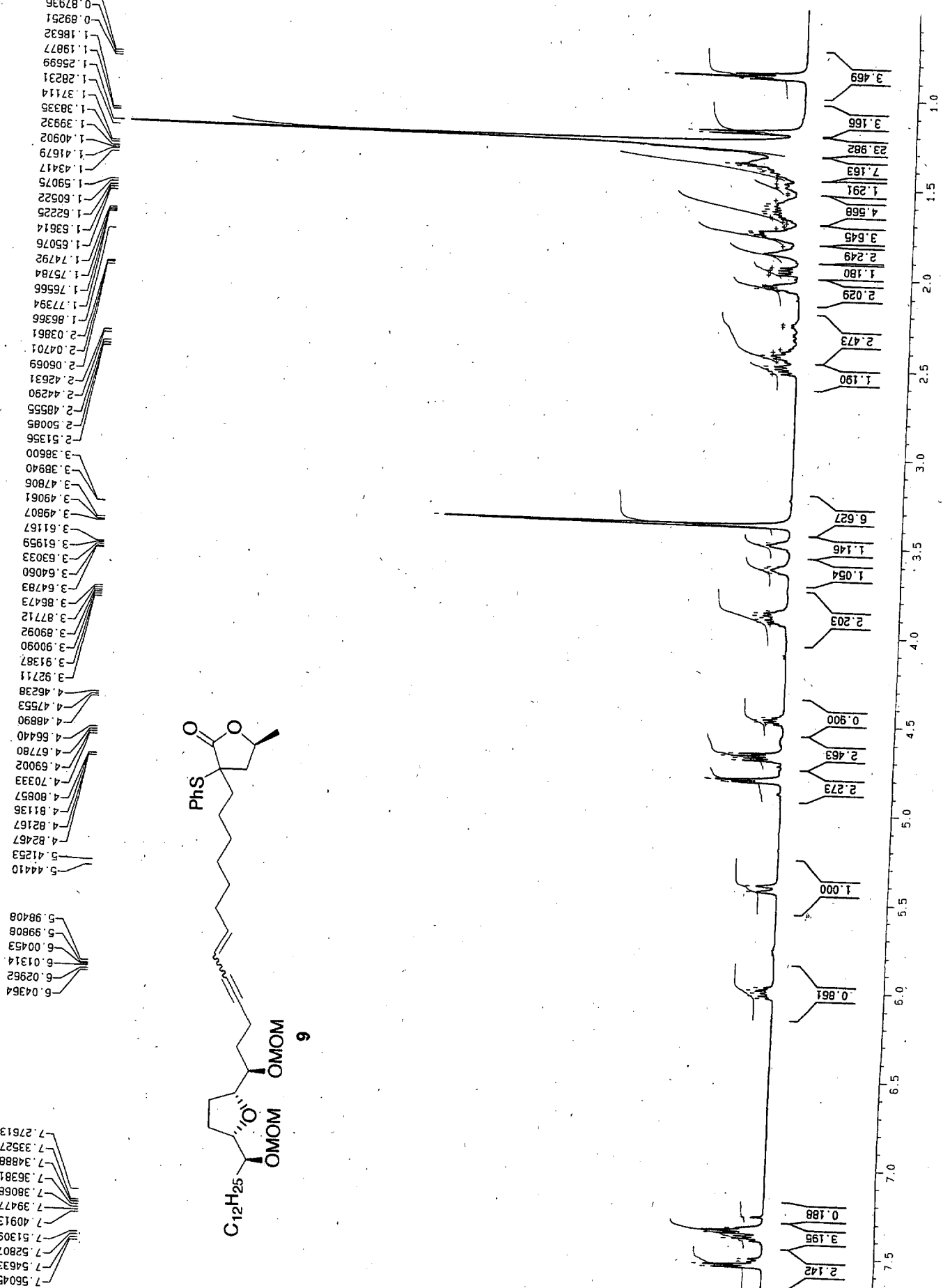


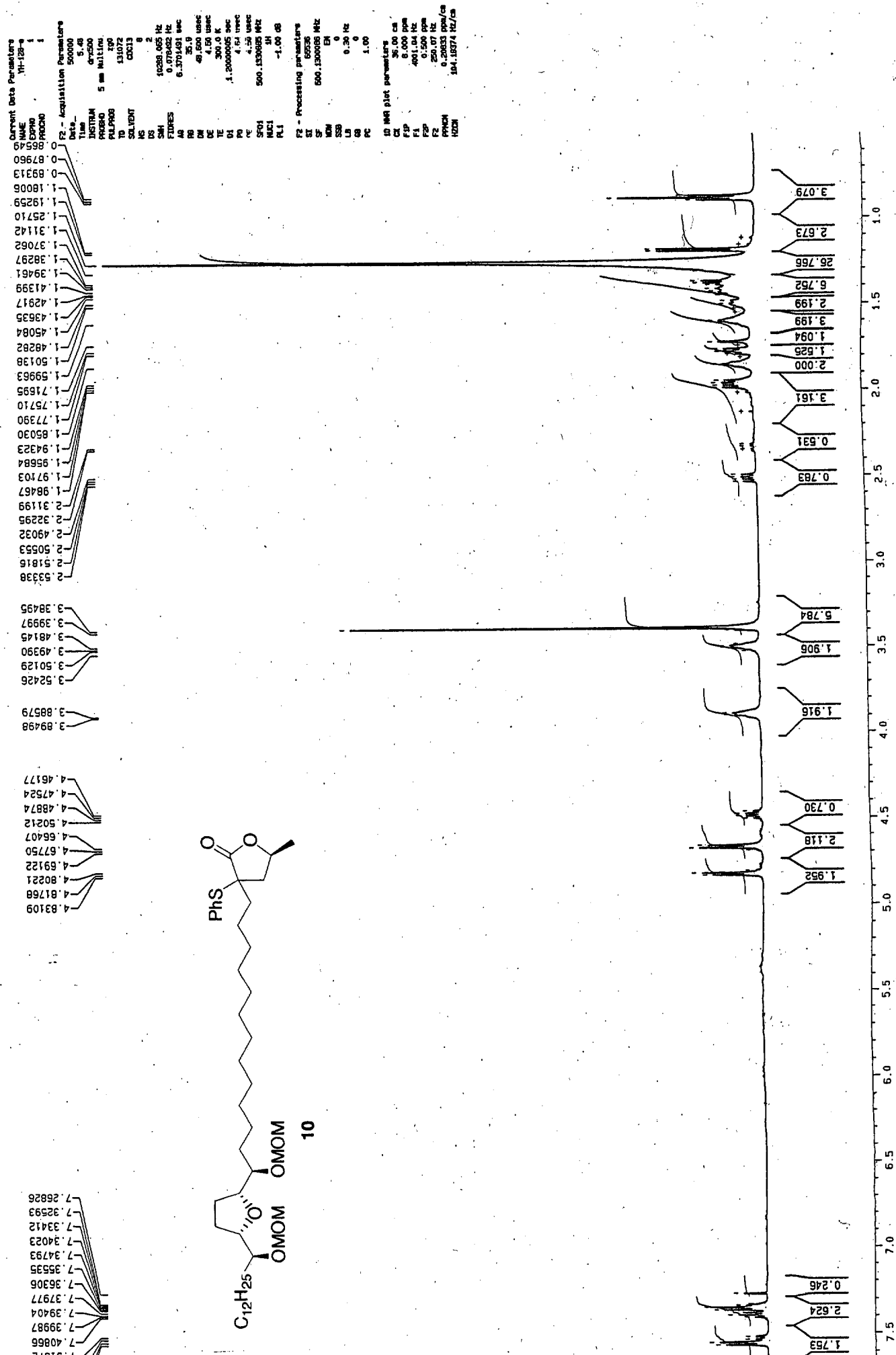
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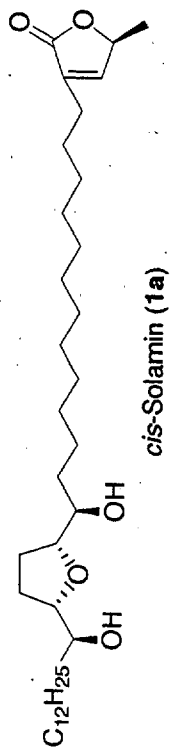
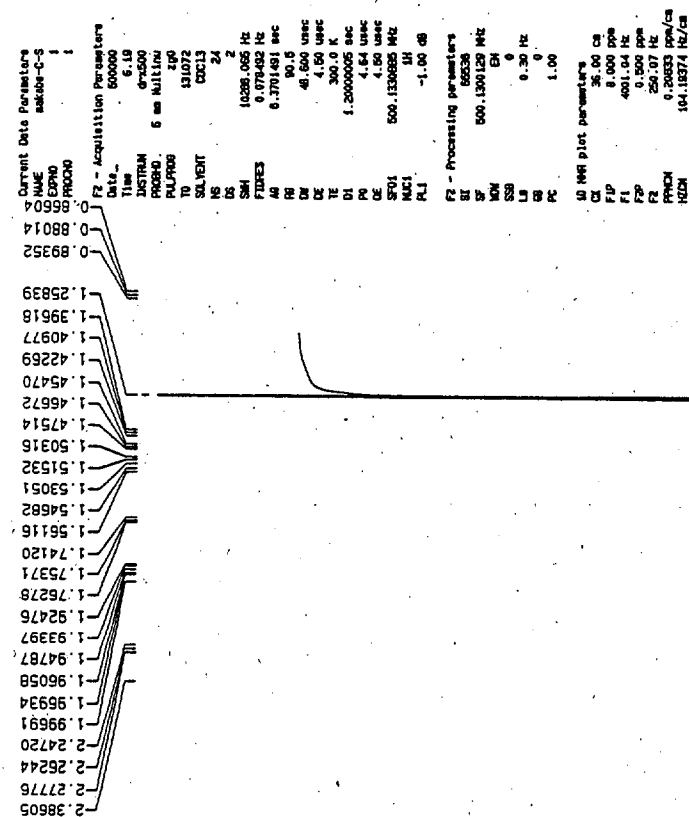




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WDW: EM
SSB: 0
LB: 1.00 Hz
GB: 0
PC: 1.40

1D NMR plot parameters
CX: 36.00 cm
FIP: 180,000 ppm
F1: 22636.40 Hz
F2: 10,000 ppm
F2: 1257.08 Hz
PPMCM: 4.72222 ppm/cm
HZCM: 693.06620 Hz/cm

