Electronic Supplementary Information for

Total Synthesis and Biological Evaluation of (−)-Exiguolide Analogues: Importance of the Macrocyclic Backbone

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Table S1 ^{1}H NMR chemical shift values of **1**–**5**.

^{1}H NMR (600 MHz, C_6D_6)[a]					
position	δ(**1**)/ppm	δ(**2**)/ppm	δ(**3**)/ppm	δ(**4**)/ppm	δ(**5**)/ppm
1					
2	2.09	1.95	2.08	2.04	2.12
	2.34	2.51	2.34	2.33	2.30
3	3.79	3.98	3.79	3.79	3.74
4	1.74	1.59	1.73	1.71	1.59
	4.07	4.00	4.06	4.04	4.05
5					
6	1.55	1.55	1.54	1.54	1.49
	1.84	1.65	1.84	1.82	1.72
7	2.99	3.14	2.99	2.99	2.95
8	1.36	1.05	1.35	1.34	1.31
	1.89	1.75	1.89	1.90	2.02
9	3.52	3.30	3.50	3.50	3.41
10	1.11	1.07	1.10	1.10	0.99
	1.48	1.15	1.46	1.47	1.30
11	1.48	1.26	1.46	1.47	1.44
	1.66	1.53	1.63	1.63	1.57
12	1.24	1.05	1.21	1.23	1.18
	1.29	1.17	1.27	1.31	1.20
13	3.39	3.30	3.41	3.41	3.22
14	1.04	1.30	1.23	1.23	1.10
	1.57	1.44	1.63	1.63	1.69
15			2.02	2.00	1.80
	2.84	2.84	2.69	2.71	2.83
16	5.10	5.48	5.30	5.32	5.37
17	5.80	5.02	5.81	5.87	5.39
18	2.34	3.38	2.34	2.18	2.59
				2.49	2.93
19	5.65	5.46	5.65	5.52	5.67
20	5.68	5.83	5.65	5.62	5.66
21	6.90	6.83	6.89	6.93	6.98

22	5.97	5.97	5.96	5.92	5.91
23	6.15	6.13	6.15	6.14	6.11
24	6.38	6.42	6.37	6.37	6.31
25					
26	2.81	2.84	2.81	2.81	2.78
	2.81	2.84	2.81	2.81	2.78
27					
28	5.63	5.64	5.65	5.61	5.59
29					
30	0.99	1.08			
31	1.16	1.32	1.14		
32	1.70	1.69	1.69	1.68	1.67
27-OCH_3	3.42	3.44	3.42	3.42	3.41
29-OCH_3	3.27	3.26	3.27	3.27	3.27

[a]Reference was set to the peak of undeuterated solvent (C_6HD_5 = 7.15 ppm).

Table S2 ^{13}C NMR chemical shift values of **1**–**5**.

^{13}C NMR (150 MHz, C_6D_6)[a]					
position	δ(**1**)/ppm	δ(**2**)/ppm	δ(**3**)/ppm	δ(**4**)/ppm	δ(**5**)/ppm
1	170.3	170.6	170.1	170.3	170.1
2	41.3	41.2	41.3	41.5	42.2
3	74.3	74.0	74.3	74.4	75.0
4	34.9	35.5	34.9	35.0	35.6
5	157.2	157.8	157.3	157.2	156.7
6	42.5	43.1	42.6	42.5	42.6
7	75.6	78.7	75.7	75.6	75.5
8	44.5	44.1	44.5	44.6	44.9
9	75.1	78.4	75.2	75.1	75.6
10	32.9	33.3	33.0	32.9	32.9
11	24.5	24.3	24.5	24.5	24.1
12	32.2	32.1	32.2	32.2	32.8
13	75.9	78.7	74.8	74.7	75.4
14	43.8	44.7	34.8	34.6	35.5
15	33.5	31.1	28.0	28.0	23.6
16	135.8	140.3	129.5	131.9	125.6
17	133.3	127.8	135.2	128.2	132.0
18	42.6	36.4	42.5	38.7	32.3
19	78.1	80.1	78.0	75.9	74.9
20	132.2	129.8	132.1	133.18	132.4
21	128.1	128.5	129.0	128.3	129.8

22	128.3	129.1	128.5	128.1	128.3
23	126.0	126.2	126.0	126.5	126.6
24	124.3	124.2	124.3	124.3	124.3
25	133.1	133.3	133.1	133.24	133.2
26	45.2	45.2	45.2	45.2	45.2
27	170.9	170.9	170.9	170.9	170.9
28	115.2	114.5	115.1	115.1	115.2
29	166.5	166.5	166.4	166.4	166.3
30	22.1	23.9			
31	14.7	18.7	14.5		
32	16.6	16.7	16.6	16.6	16.6
27-OCH_3	51.2	51.2	51.2	51.2	51.2
29-OCH_3	50.6	50.6	50.6	50.6	50.6

[a]Reference was set to the peak of C_6D_6 (128.0 ppm).

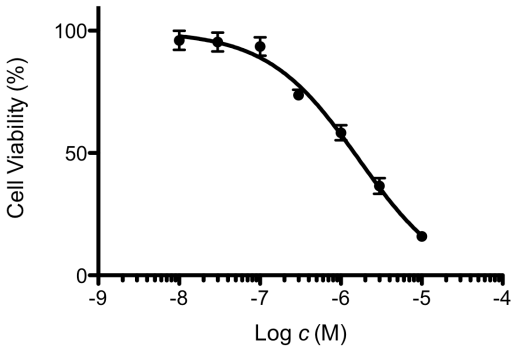
Table S3 Selected $^{3}J_{H,H}$ values of **1**, **3**, and **4** (600 MHz, C_6D_6).

Protons	**1** (Hz)	**3** (Hz)	**4** (Hz)	Protons	**1** (Hz)	**3** (Hz)	**4** (Hz)
H-2a/H-2b	14.4	14.2	14.4	H-14a/H-15a	12.1	13.2	13.4
H-2a/H-3	3.1	3.2	3.1	H-14b/H-15a	2.1	2.3	2.3
H-2b/H-3	10.6	10.6	10.3	H-14a/H-15b	N.A.[a]	N.D.[b]	N.D.[b]
H-3/H-4eq	2.4	2.3	2.3	H-14b/H-15b	N.A.[a]	N.D.[b]	N.D.[b]
H-3/H-4ax	11.6	11.0	11.0	H-15a/H-15b	N.A.[a]	13.3	13.4
H-4eq/H-4ax	13.7	13.3	13.7	H-15a/H-16	9.6	10.5	10.3
H-6eq/H-6ax	13.1	13.4	13.4	H-15b/H-16	N.A.[a]	4.6	3.4
H-6eq/H-7	<1.0	<1.0	<1.0	H-16/H-17	15.1	15.1	14.8
H-6ax/H-7	12.4	12.1	12.0	H-17/H-18a	9.7	9.6	10.6
H-7/H-8a	10.6	10.6	11.0	H-17/H-18b	N.A.[a]	N.A.[a]	3.1
H-7/H-8b	1.4	1.9	<1.0	H-18a/H-19	2.0	2.0	2.0
H-8a/H-8b	14.1	13.7	12.4	H-18b/H-19	N.A.[a]	N.A.[a]	10.0
H-8a/H-9	1.4	1.4	<1.0				
H-8b/H-9	8.2	8.3	10.0				
H-9/H-10eq	<1.0	<1.0	<1.0				
H-9/H-10ax	8.3	9.7	9.3				
H-10eq/H-10ax	14.3	13.7	12.7				

[a]N.A. = Not applicable. [b]N.D. = Not determined because of complex splitting pattern.

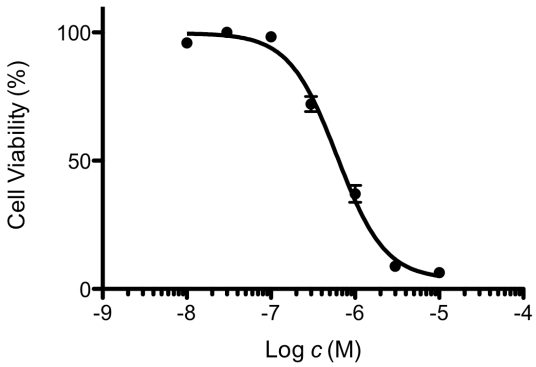
Table S4 Growth inhibition curves for compounds **1**, **3**, **35**, and **37**–**41**

Cpd. **1**/A549



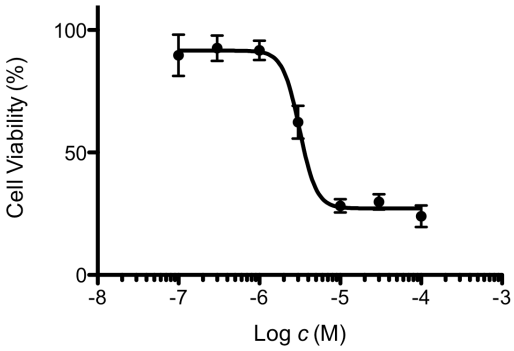
Tested at 0.01, 0.03, 0.1, 0.3, 1, 3, 10 μM

Cpd. **1**/NCI-H460



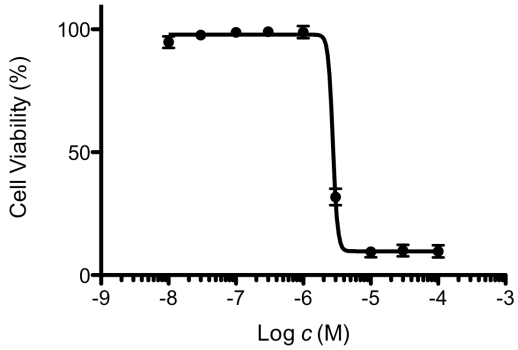
Tested at 0.01, 0.03, 0.1, 0.3, 1, 3, 10 μM

Cpd. **3**/A549



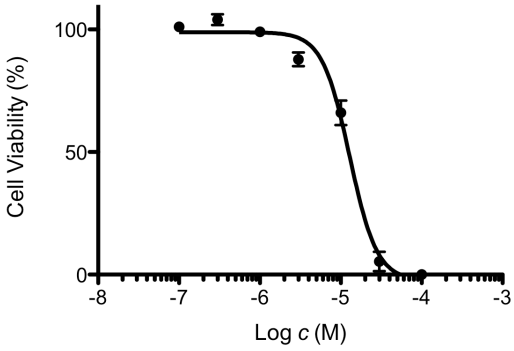
Tested at 0.1, 0.3, 1, 3, 10, 30, 100 μM

Cpd. **3**/NCI-H460



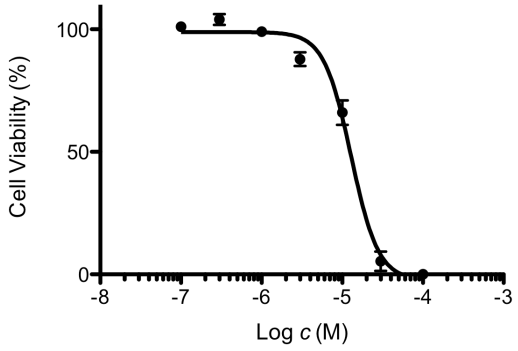
Tested at 0.01, 0.03, 0.1, 0.3, 1, 3, 10, 30, 100 μM

Cpd. **35**/A549



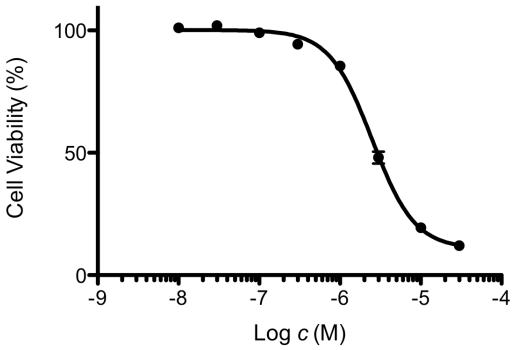
Tested at 0.1, 0.3, 1, 3, 10, 30, 100 μM

Cpd. **35**/NCI-H460



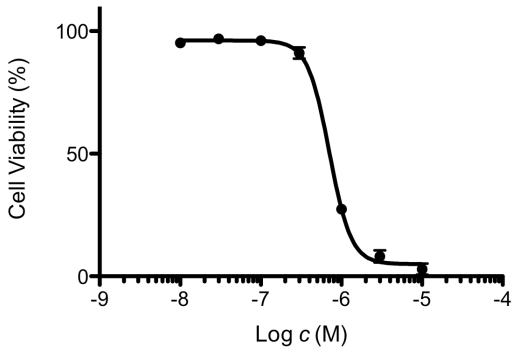
Tested at 0.1, 0.3, 1, 3, 10, 30, 100 μM

Cpd. **37**/A549



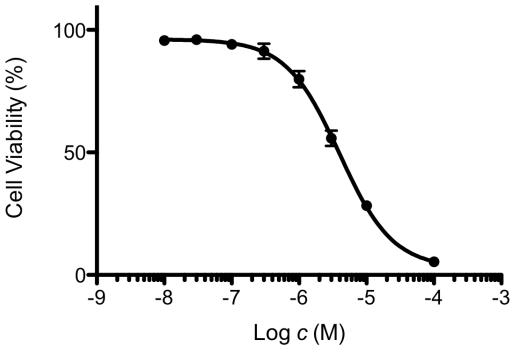
Tested at 0.01, 0.03, 0.1, 0.3, 1, 3, 10, 30 μM

Cpd. **37**/NCI-H460



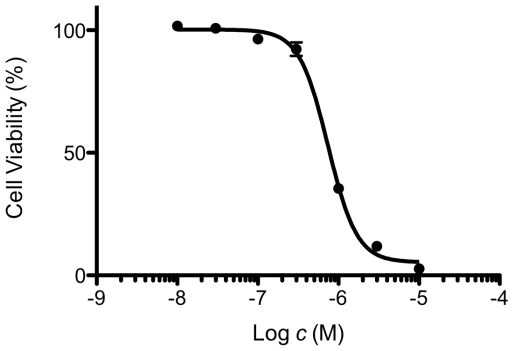
Tested at 0.01, 0.03, 0.1, 0.3, 1, 3, 10 μM

Cpd. **38**/A549



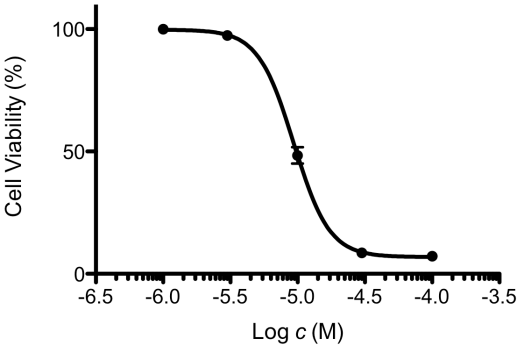
Tested at 0.01, 0.03, 0.1, 0.3, 1, 3, 10, 100 μM

Cpd. **38**/NCI-H460



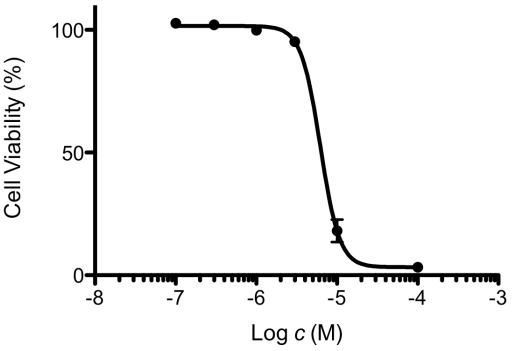
Tested at 0.01, 0.03, 0.1, 0.3, 1, 3, 10 μM

Cpd. **39**/A549



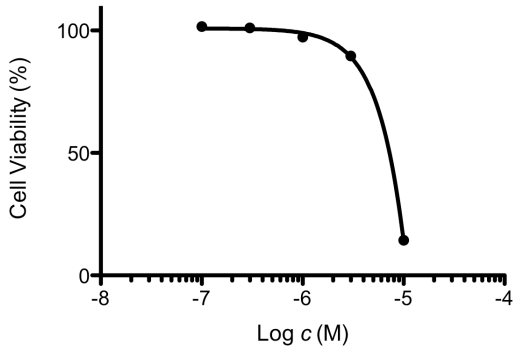
Tested at 1, 3, 10, 30, 100 μM

Cpd. **39**/NCI-H460



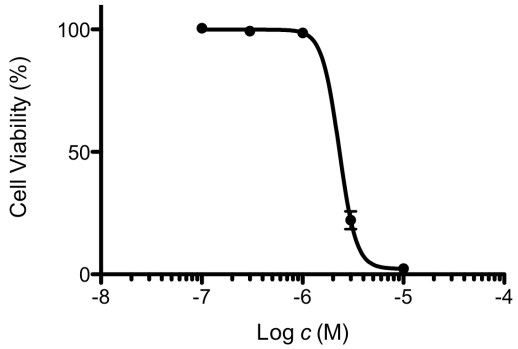
Tested at 0.1, 0.3, 1, 3, 10, 100 μM

Cpd. **40**/A549



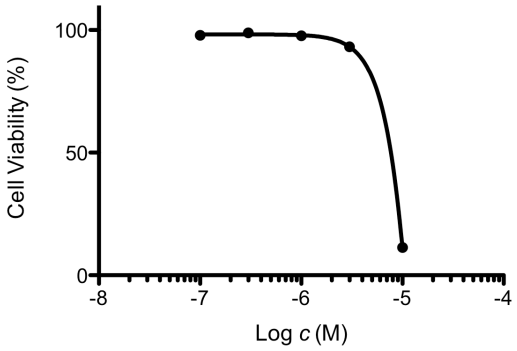
Tested at 0.1, 0.3, 1, 3, 10 μM

Cpd. **40**/NCI-H460



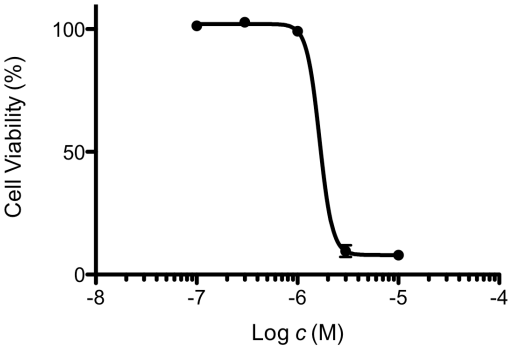
Tested at 0.1, 0.3, 1, 3, 10 μM

Cpd. **41**/A549



Tested at 0.1, 0.3, 1, 3, 10 μM

Cpd. **41**/NCI-H460



Tested at 0.1, 0.3, 1, 3, 10 μM

Experimental Section

General remarks. All reactions sensitive to moisture and/or air were carried out under an atmosphere of argon in dry, freshly distilled solvents under anhydrous conditions using oven-dried glassware unless otherwise noted. Anhydrous dichloromethane (CH_2Cl_2) was purchased from Kanto Chemical Co. Inc. and used directly without further drying. Anhydrous diethyl ether (Et_2O), tetrahydrofuran (THF), and toluene were purchased from Wako Pure Chemical Industries, Ltd. and further purified by a Glass Contour solvent purification system under an atmosphere of argon immediately prior to use. Diisopropylethylamine, triethylamine, 2,6-lutidine, and acetonitrile (CH_3CN) were distilled from calcium hydride under an atmosphere of argon. *N,N*-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were distilled from magnesium sulfate under reduced pressure. All other chemicals were purchased at highest commercial grade and used directly. Solvents were degassed by the freeze-thaw method where appropriate. Analytical thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F_{254} plates (0.25-mm thickness). Flash column chromatography was carried out using Kanto Chemical silica gel 60N (40–100 mesh, spherical, neutral) or Fuji Silysia silica gel BW-300 (200–400 mesh). Optical rotations were recorded on a JASCO P-1020 digital polarimeter. IR spectra were recorded on a JASCO FT/IR-4100 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM ECA-600 spectrometer, and chemical shift values are reported in ppm (δ) downfield from tetramethylsilane with reference to internal solvent [^{1}H NMR, C*H*Cl_3 (7.24), C_6HD_5 (7.15), C*H*D_2OD (3.31); ^{13}C NMR, *C*DCl_3 (77.0), C_6D_6 (128.0), CD_3OD (49.0)] unless otherwise noted. Coupling constants (*J*) are reported in Hertz (Hz). The following abbreviations were used to designate the multiplicities: s = singlet; d = doublet; t = triplet; m = multiplet; br = broad. ESI-TOF mass spectra were measured on a Bruker microTOFfocus spectrometer.

1. Synthesis of (16*Z*)-exiguolide (2)

Ketones 10 and 11. To a solution of alcohol **9** (a 15:1 mixture of stereoisomers at the C16–C17 double

bond, 136.8 mg, 0.2641 mmol) in CH_2Cl_2 (6 mL) at 0 °C was added Dess–Martin periodinane (560.0 mg, 1.320 mmol), and the resultant mixture was stirred at room temperature for 105 min. The reaction was quenched with a 1:1 mixture of saturated aqueous $NaHCO_3$ solution and saturated aqueous Na_2SO_3 solution. The resultant mixture was extracted with Et_2O, and the organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 20% EtOAc/hexanes), followed by a second flash column chromatography (silica gel, 5 to 8% Et_2O/benzene), gave ketone **10** (126.1 mg, 93%), along with ketone **11** (8.4 mg, 6%) as a colorless oil. Data for **11**: $[\alpha]_D^{23}$ +20.7 (*c* 0.42, C_6H_6); IR (film) 2927, 2851, 1733, 1459, 1258, 1181, 1131, 727, 668, 503 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.54 (dd, *J* = 14.5, 7.9 Hz, 1H), 6.36 (d, *J* = 14.5 Hz, 1H), 5.36 (dd, *J* = 10.7, 10.6 Hz, 1H), 5.02 (dd, *J* = 7.6, 4.8 Hz, 1H), 4.90 (dd, *J* = 10.6, 10.3 Hz, 1H), 4.14 (dddd, *J* = 10.3, 10.0, 5.2, 1.0 Hz, 1H), 3.67 (m, 1H), 3.40 (m, 1H), 3.17 (m, 1H), 2.96 (m, 1H), 2.66 (dd, *J* = 16.1, 10.0 Hz, 1H), 2.51 (m, 1H), 2.38–2.21 (m, 5H), 1.86 (m, 1H), 1.75 (m, 1H), 1.52–1.44 (m, 3H), 1.38 (m, 1H), 1.32 (m, 1H), 1.26–1.07 (m, 6H), 1.03 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.2, 170.0, 140.9, 140.3, 126.0, 81.2, 80.2, 78.6, 72.8, 48.2, 47.1, 44.1, 44.0, 41.0, 35.6, 32.9, 31.5, 30.6, 23.9, 23.3, 18.4, two carbons missing due to solvent overlap; HRMS (ESI) calcd for $C_{23}H_{33}O_5INa$ $[(M + Na)^+]$ 539.1265, found 539.1252.

(16*Z*)-Exiguolide (2). To a solution of phosphonate **12** (101.3 mg, 0.2507 mmol) in THF (1 mL) at −78 °C was added NaHMDS (1.0 M solution in THF, 0.210 mL, 0.210 mmol), and the resultant solution was stirred at −78 °C for 0.5 h. To this solution was added dropwise a solution of ketone **11** (12.4 mg, 0.0240 mmol) in THF (0.5 mL + 0.3 mL rinse). The resultant solution was allowed to warm to −40 °C and stirred at −40 °C for 17 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The resultant mixture was allowed to warm to room temperature and then extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the

residue by flash column chromatography (silica gel, 8 to 10% EtOAc/hexanes) gave an α,β-unsaturated ester (9.2 mg, 67%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.54 (dd, *J* = 14.4, 7.2 Hz, 1H), 6.35 (d, *J* = 14.4 Hz, 1H), 5.65 (s, 1H), 5.27 (dd, *J* = 10.8, 10.2 Hz, 1H), 5.02 (dd, *J* = 7.2, 6.6 Hz, 1H), 4.93 (dd, *J* = 10.8, 10.2 Hz, 1H), 3.83 (m, 1H), 3.77 (dd, *J* = 13.8, 1.8 Hz, 1H), 3.67 (s, 3H), 3.40–3.31 (m, 2H), 3.12 (apparent dd, *J* = 10.8, 10.8 Hz, 1H), 2.90 (m, 1H), 2.62–2.55 (m, 2H), 2.41 (dd, *J* = 15.0, 1.2 Hz, 1H), 2.14–2.08 (m, 2H), 1.90–1.80 (m, 2H), 1.75 (m, 1H), 1.54–1.40 (m, 3H), 1.38–1.31 (m, 2H), 1.28–1.09 (m, 3H), 1.05 (d, *J* = 6.6 Hz, 3H), 1.03 (d, *J* = 6.6 Hz, 3H); HRMS (ESI) calcd for $C_{26}H_{37}IO_6Na$ [$(M + Na)^+$] 595.1527, found 595.1546.

To a mixture of the above α,β-unsaturated ester (8.9 mg, 0.016 mmol) and (*Z*)-vinyl boronate **13** (18.7 mg, 0.0703 mmol) in THF/H_2O (10:1, v/v, 1.1 mL) were added Ag_2O (18.1 mg, 0.0781 mmol), $Pd_2(dba)_3$ (2.1 mg, 0.0023 mmol), and Ph_3As (5.7 mg, 0.019 mmol). The resultant mixture was stirred at room temperature for 30 min. Insoluble materials were filtered off, and the filtrate was concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 25 to 35% EtOAc/hexanes, gradient elution) gave (16*Z*)-exiguolide (**2**) (8.9 mg, 97%) as a colorless oil: $[\alpha]_D^{21}$ −34.0 (*c* 0.42, C_6H_6); IR (film) 2927, 2853, 1734, 1716, 1653, 1435, 1236, 1158, 1089 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 6.82 (dd, *J* = 15.2, 11.5 Hz, 1H), 6.42 (d, *J* = 11.5 Hz, 1H), 6.13 (dd, *J* = 11.5, 11.0 Hz, 1H), 5.97 (dd, *J* = 11.5, 11.0 Hz, 1H), 5.83 (dd, *J* = 15.2, 8.3 Hz, 1H), 5.64 (s, 1H), 5.48 (dd, *J* = 11.0, 10.6 Hz, 1H), 5.46 (dd, *J* = 8.3, 4.6 Hz, 1H), 5.03 (dd, *J* = 10.6, 10.1 Hz, 1H), 4.02–3.97 (m, 2H), 3.44 (s, 3H), 3.38 (m, 1H), 3.31–3.28 (m, 2H), 3.26 (s, 3H), 3.14 (m, 1H), 2.86–2.82 (m, 3H), 2.51 (dd, *J* = 16.5, 10.5 Hz, 1H), 1.95 (d, *J* = 16.5 Hz, 1H), 1.75 (ddd, *J* = 14.6, 10.6, 5.9 Hz, 1H), 1.69 (d, *J* = 1.0 Hz, 3H), 1.67–1.54 (m, 3H), 1.44 (ddd, *J* = 13.7, 11.0, 5.5 Hz, 1H), 1.35–1.20 (m, 8H), 1.16–1.03 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 170.6, 166.5, 157.8, 140.3, 133.3, 129.8, 129.1, 128.5, 127.1, 126.2, 124.2, 114.5, 80.1, 78.7, 77.0, 74.0, 51.2, 50.6, 45.2, 44.7, 44.1, 43.1, 41.2, 36.4, 35.5, 33.3, 32.1, 31.1, 24.3, 23.9, 18.7, 16.7;

HRMS (ESI) calcd for $C_{34}H_{48}O_8Na$ $[(M + Na)^+]$ 607.3241, found 607.3265.

2. Synthesis of 15-demethylexiguolide (3)

α,β-Unsaturated ester 15. To a solution of homoallylic alcohol **14** (1.65 g, 7.49 mmol) in CH_2Cl_2 (76 mL) were added methyl acrylate (7.20 mL, 80.0 mmol) and a solution of the Grubbs second-generation catalyst (0.141 g, 0.166 mmol) in CH_2Cl_2 (2 mL), and the resultant solution was stirred at 35 °C for 3 h. The reaction mixture was cooled to room temperature under air and then concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 20 to 30% EtOAc/hexanes) gave α,β-unsaturated ester **15** (1.90 g, 91%) as a brown oil: $[\alpha]_D^{26}$ −1.6 (*c* 0.76, $CHCl_3$); IR (film) 3416, 2947, 2854, 1717, 1654, 1436, 1271, 1093, 972, 738 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.35–7.25 (m, 5H), 6.97 (ddd, *J* = 15.5, 7.6, 7.2 Hz, 1H), 5.88 (d, *J* = 15.0 Hz, 1H), 4.51 (d, *J* = 12.7 Hz, 1H), 4.49 (d, *J* = 12.7 Hz, 1H), 3.74 (m, 1H), 3.71 (s, 3H), 3.52–3.47 (m, 2H), 2.76 (br s, 1H), 2.36–2.34 (m, 2H), 1.75–1.71 (m, 2H), 1.66 (m, 1H), 1.49 (dddd, *J* = 13.7, 8.6, 6.9, 6.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.8, 145.8, 137.9, 128.4 (2C), 127.7 (3C), 123.2, 73.1, 70.34, 70.26, 51.4, 40.2, 34.7, 26.3; HRMS (ESI) calcd for $C_{16}H_{22}O_4Na$ $[(M + Na)^+]$ 301.1410, found 301.1407.

Triethylsilyl ether 16. To a solution of α,β-unsaturated ester **15** (1.69 g, 6.07 mmol) in EtOAc (60 mL) was added 10% Pd/C (0.175 g), and the resultant suspension was stirred at room temperature under an atmosphere of hydrogen (balloon) for 1.8 h. The resultant mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure to give a crude ester. This material was used in the next step without further purification.

To a suspension of MeONHMe·HCl (1.78 g, 18.2 mmol) in CH_2Cl_2 (36 mL) at 0 °C was added $AlMe_3$ (1.08 M solution in *n*-hexane, 17.0 mL, 18.4 mmol). The resultant mixture was stirred at 0 °C for 35 min, at which point it was treated with a solution of the above ester in CH_2Cl_2 (2 mL + 2 mL rinse). The resultant mixture was stirred at 0 °C for 55 min. The reaction was quenched with saturated aqueous potassium sodium tartrate solution. The resultant mixture was diluted with EtOAc and then stirred at room

temperature for a while. The insoluble materials were filtered off, and the filtrate was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a crude Weinreb amide. This material was used in the next step without further purification.

To a solution of the above Weinreb amide in CH_2Cl_2 (40 mL) at 0 °C were added Et_3N (2.55 mL, 18.3 mmol), DMAP (77.2 mg, 0.632 mmol), and TESCl (2.00 mL, 11.9 mmol), and the resultant solution was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. The resultant mixture was extracted with EtOAc, and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10 to 30% EtOAc/hexanes) gave triethylsilyl ether **16** (2.42 g, 94% for the three steps) as a colorless oil: $[\alpha]_D^{27}$ −0.028 (*c* 1.00, C_6H_6); IR (film) 2952, 2911, 2874, 1669, 1455, 1415, 1382, 1005, 740, 698 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.31 (d, *J* = 7.9 Hz, 2H), 7.18 (dd, *J* = 7.9, 7.6 Hz, 2H), 7.09 (dd, *J* = 7.6, 7.6 Hz, 1H), 4.35 (d, *J* = 12.8 Hz, 1H), 4.33 (d, *J* = 12.8 Hz, 1H), 3.73 (m, 1H), 3.35–3.33 (m, 2H), 3.02 (br s, 3H), 2.87 (br s, 3H), 2.34 (br s, 2H), 1.29–1.66 (m, 4H), 1.63–1.55 (m, 4H), 1.04–0.98 (m, 9H), 0.63 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR (150 MHz, C_6D_6) δ 174.3, 139.5, 128.5 (2C), 127.7 (2C), 127.5, 72.9, 72.3, 70.7, 60.5, 37.3, 34.1, 32.2, 32.1, 26.0, 20.8, 7.3 (3C), 5.5 (3C); HRMS (ESI) calcd for $C_{23}H_{41}O_4NSiNa$ [$(M + Na)^+$] 446.2697, found 446.2682.

α,β-Unsaturated ketone 17. To a solution of tetravinyltin (0.60 mL, 3.66 mmol) in THF (45 mL) at −78 °C was added MeLi (1.07 M solution in Et_2O, 10.0 mL, 10.7 mmol), and the solution was stirred at −78 °C for 1 h. To the solution was added dropwise a solution of triethylsilyl ether **16** (2.25 g, 5.31 mmol) in THF (2 mL + 3 mL rinse). The reaction mixture was stirred at −78 °C for 50 min, and the reaction was quenched with saturated aqueous NH_4Cl solution. The resultant mixture was extracted with EtOAc, and the organic layer was washed successively with H_2O, saturated aqueous $NaHCO_3$ solution, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the

residue by flash column chromatography (silica gel, 0 to 5 to 7% EtOAc/hexanes) gave α,β-unsaturated ketone **17** (1.96 g, 94%) as a colorless clear oil: $[\alpha]_D^{24}$ +1.2 (*c* 1.00, C_6H_6); IR (film) 2952, 2874, 1683, 1455, 1402, 1238, 1098, 1008, 736, 697 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.32 (d, *J* = 7.2 Hz, 2H), 7.19 (dd, *J* = 7.6, 7.2 Hz, 2H), 7.09 (dd, *J* = 7.6, 7.2 Hz, 1H), 6.07 (dd, *J* = 17.5, 10.6 Hz, 1H), 5.85 (d, *J* = 17.5 Hz, 1H), 5.18 (d, *J* = 10.6 Hz, 1H), 4.36 (d, *J* = 12.4 Hz, 1H), 4.34 (d, *J* = 12.4 Hz, 1H), 3.66 (m, 1H), 3.35–3.33 (m, 2H), 2.18–2.16 (m, 2H), 1.76–1.56 (m, 6H), 1.45–1.36 (m, 2H), 1.02 (t, *J* = 7.9 Hz, 9H), 0.62 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR (150 MHz, C_6D_6) δ 198.9, 139.5, 136.7, 128.5 (2C), 127.7 (2C), 127.5, 126.7, 73.0, 72.2, 70.6, 39.8, 36.9, 34.1, 26.0, 20.0, 7.3 (3C), 5.5 (3C); HRMS (ESI) calcd for $C_{23}H_{38}O_3SiNa$ $[(M + Na)^+]$ 413.2482, found 413.2472.

Methylene bis(tetrahydropyran) 20. To a solution of alcohol **18** (18.7 mg, 33.7 μmol) and α,β-unsaturated ketone **17** (28.2 mg, 72.2 μmol) in CH_2Cl_2 (1 mL) placed in a Biotage microwave vial was added the Hoveyda–Grubbs' second-generation catalyst (2.1 mg, 3.4 μmol). The vial was flushed with nitrogen and then sealed. The reaction mixture was heated at 100 °C under microwave irradiation for 30 min. The reaction mixture was cooled to room temperature and diluted with Et_3SiH (0.2 mL). The resultant mixture was cooled to −60 °C and treated with $BF_3{\cdot}OEt_2$ (0.021 mL, 0.17 mmol). The resultant solution was allowed to warm to −32 °C over a period of 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. The resultant mixture was allowed to warm to room temperature and then extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 0 to 5% EtOAc/hexanes, gradient elution) gave methylene bis(tetrahydropyran) **20** (25.4 mg, 96%, dr 10:1 as judged by 600 MHz ^1H NMR) as a colorless oil: $[\alpha]_D^{22}$ +4.3 (*c* 1.00, $CHCl_3$); IR (film) 2940, 2863, 1463, 1362, 1111, 1089, 882, 736, 701, 504 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.67–7.64 (m, 4H), 7.41–7.34 (m, 6H), 7.33–7.30 (m, 4H), 7.25 (m, 1H), 4.48 (d, *J* = 12.5 Hz, 1H), 4.46 (d, *J* = 12.5 Hz, 1H), 3.85–3.69 (m, 3H), 3.52–3.35 (m, 6H),

3.18 (m, 1H), 1.90 (m, 1H), 1.88–1.38 (m, 12H), 1.26–1.11 (m, 4H), 1.05–1.02 (m, 30H); ^{13}C NMR (150 MHz, C_6D_6) δ 138.7, 135.5 (4C), 134.02, 133.99, 129.5 (2C), 128.3 (2C), 127.58 (3C), 127.56 (3C), 127.4, 77.6, 74.3, 72.8, 72.2, 72.1, 70.4, 68.9, 60.5, 42.4, 42.1, 41.5, 39.0, 33.1, 31.7, 31.5, 26.8 (3C), 26.1, 23.6, 19.2, 18.1 (6C), 12.3 (3C); HRMS (ESI) calcd for $C_{48}H_{74}O_5Si_2Na$ [$(M + Na)^+$] 809.4967, found 809.4981.

Alcohol 21. To a solution of methylene bis(tetrahydropyran) **20** (654.8 mg, 0.832 mmol) in EtOAc/MeOH (1:1, v/v, 8 mL) was added 20% $Pd(OH)_2/C$ (196.9 mg), and the resultant suspension was stirred at room temperature under an atmosphere of hydrogen (balloon) for two days. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10 to 12% EtOAc/hexanes, gradient elution) gave alcohol **21** (450.9 mg, 78%) as a colorless oil: $[\alpha]_D^{23}$ +2.2 (*c* 0.53, $CHCl_3$); IR (film) 3426, 2940, 2864, 1463, 1111, 1087, 882, 702, 687, 504 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65–7.63 (m, 4H), 7.41–7.34 (m, 6H), 3.84–3.71 (m, 3H), 3.62–3.55 (m, 2H), 3.46–3.42 (m, 2H), 3.38 (m, 1H), 3.38 (m, 1H), 3.24 (dddd, *J* = 8.3, 8.2, 3.4, 2.0 Hz, 1H), 1.89–1.81 (m, 3H), 1.78–1.73 (m, 2H), 1.69–1.61 (m, 3H), 1.58–1.43 (m, 5H), 1.39 (dddd, *J* = 13.1, 13.0, 4.1, 3.8 Hz, 1H), 1.25–1.12 (m, 4H), 1.05–1.02 (m, 30H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.5 (4C), 134.0 (2C), 129.5 (2C), 127.6 (4C), 77.8, 74.7, 72.2, 72.0, 68.9, 62.8, 60.6, 42.2, 42.0, 41.7, 39.0, 33.3, 31.6, 31.0, 29.3, 26.8 (3C), 23.5, 19.2, 18.1 (6C), 12.3 (3C); HRMS (ESI) calcd for $C_{41}H_{68}O_5Si_2Na$ [$(M + Na)^+$] 719.4497, found 719.4503.

Olefin 22. To a solution of alcohol **21** (360.8 mg, 0.5180 mmol) and Et_3N (0.360 mL, 2.59 mmol) in CH_2Cl_2/DMSO (1:1, v/v, 5 mL) at 0 °C were added SO_3·pyridine complex (330 mg, 2.07 mmol), and the resultant mixture was stirred at 0 °C for 1 h. The resultant mixture was diluted with Et_2O. The organic layer was washed with successively 1 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5 to 20% EtOAc/hexanes) gave an aldehyde (354.9 mg, 99%), which

was immediately used in the next reaction. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.71 (s, 1H), 7.64–7.63 (m, 4H), 7.40–7.34 (m, 6H), 3.84 (m, 1H), 3.78 (m, 1H), 3.72 (m, 1H), 3.47 (m, 1H), 3.40–3.35 (m, 2H), 3.20 (m, 1H), 2.51 (ddd, *J* = 15.5, 8.3, 6.4 Hz, 1H), 2.44 (ddd, *J* = 15.5, 8.3, 6.4 Hz, 1H), 1.88–1.62 (m, 8H), 1.54–1.50 (m, 2H), 1.43–1.39 (m, 2H), 1.23–1.11 (m, 4H), 1.06–1.02 (m, 30H).

To a solution of sulfone **7** (598.6 mg, 1.080 mmol) in THF/HMPA (3:1, v/v, 4 mL) at −78 °C was added LHMDS (1.0 M solution in THF, 1.05 mL, 1.05 mmol), and the resultant solution was stirred at −78 °C for 20 min. To this solution was added a solution of the above aldehyde (354.9 mg, 0.0.511 mmol) in THF (1 mL). After being stirred at −78 °C for 20 min, the resultant solution was allowed to warm to room temperature over a period of 3 h. The reaction was quenched with saturated aqueous NH_4Cl solution at 0 °C, and the mixture extracted with EtOAc. The combined organic layer was washed brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5 to 20% EtOAc/hexanes, gradient elution) gave olefin **22** (462.0 mg, 88%, *E*/*Z* ca. 14:1 as judged by 600 MHz ^{1}H NMR), along with sulfone **17** (322.7 mg, 93% recovery): $[\alpha]_D^{24}$ +29.8 (*c* 2.00, $CHCl_3$); IR (film) 2938, 2863, 1612, 1514, 1463, 1248, 1085, 882, 822, 702 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65–7.64 (m, 4H), 7.41–7.36 (m, 6H), 7.22 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.40 (dd, *J* = 14.7, 8.3 Hz, 1H), 6.17 (d, *J* = 14.7 Hz, 1H), 5.40 (ddd, *J* = 15.1, 6.8, 6.4 Hz, 1H), 5.28 (dd, *J* = 15.1, 7.3 Hz, 1H), 4.50 (d, *J* = 11.5 Hz, 1H), 4.25 (d, *J* = 11.5 Hz, 1H), 3.85–3.73 (m, 6H), 3.47–3.38 (m, 4H), 3.18 (m, 1H), 2.29 (m, 1H), 2.18 (m, 1H), 1.99–1.83 (m, 4H), 1.80–1.75 (m, 2H), 1.67 (m, 1H), 1.56–1.50 (m, 3H), 1.48–1.35 (m, 3H), 1.30–1.12 (m, 4H), 1.05–1.03 (m, 30H), 0.99 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.1, 145.8, 135.5 (4C), 134.01, 133.99, 131.19, 131.16, 130.3, 129.5 (2C), 129.2 (2C), 127.6 (4C), 113.7 (2C), 85.1, 78.1, 77.4, 74.3, 72.22, 72.19, 70.3, 69.0, 60.6, 55.2, 42.4, 42.1, 41.5, 41.2, 39.0, 36.5, 31.6, 31.5, 28.9, 26.9 (3C), 23.6, 19.2, 18.1 (6C), 16.4, 12.3 (3C); HRMS (ESI) calcd for $C_{55}H_{83}O_6ISi_2Na$ [$(M + Na)^+$] 1045.4671, found 1045.4665.

Ester 23. To a solution of olefin **22** (140 mg, 0.137 mmol) in THF (1.5 mL) was added 10% KOH/MeOH (w/w, 3 mL), and the resultant solution was stirred at 60 °C for 24 h. The reaction mixture was cooled to 0 °C and neutralized with saturated aqueous NH_4Cl solution. The resultant mixture was extracted with EtOAc, and the organic layer was washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 8 to 12 to 15% EtOAc/hexanes) gave an alcohol (93 mg, 86%) as a colorless oil: $[\alpha]_D^{25}$ +43.0 (*c* 1.00, $CHCl_3$); IR (film) 3478, 2939, 2864, 1612, 1514, 1463, 1248, 1083, 823, 681 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.39 (dd, *J* = 14.7, 7.8 Hz, 1H), 6.17 (d, *J* = 14.7 Hz, 1H), 5.39 (ddd, *J* = 15.6, 6.9, 6.8 Hz, 1H), 5.27 (dd, *J* = 15.6, 7.8 Hz, 1H), 4.49 (d, *J* = 11.5 Hz, 1H), 4.24 (d, *J* = 11.5 Hz, 1H), 3.82 (m, 1H), 3.78 (s, 3H), 3.76–3.71 (m, 2H), 3.53–3.48 (m, 2H), 3.46 (dd, *J* = 7.3, 7.3 Hz, 1H), 3.37 (m, 1H), 3.18 (m, 1H), 2.29 (m, 1H), 2.10 (m, 1H), 1.96–1.91 (m, 2H), 1.87–1.72 (m, 4H), 1.66 (m, 1H), 1.54–1.45 (m, 3H), 1.39–1.12 (m, 5H), 1.03–1.01 (m, 24H), 0.98 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.1, 145.8, 131.2, 131.1, 130.3, 129.2 (2C), 113.7 (2C), 85.1, 78.1, 77.5, 76.3, 74.4, 72.9, 70.3, 68.5, 61.6, 55.2, 42.3, 41.9, 41.12, 41.10, 37.7, 36.4, 31.7, 31.5, 29.0, 23.6, 18.1 (6C), 16.4, 12.3 (3C); HRMS (ESI) calcd for $C_{39}H_{65}O_6ISiNa$ $[(M + Na)^+]$ 807.3487, found 807.3479.

To a solution of the above alcohol (89.5 mg, 0.114 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C was added Dess–Martin periodinane (97.6 mg, 0.23 mmol), and the resultant mixture was stirred at room temperature for 1 h. The reaction was quenched with a 1:1 mixture of saturated aqueous $NaHCO_3$ solution and saturated aqueous Na_2SO_3 solution at 0 °C, and the resultant mixture was extracted with Et_2O. The combined organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude aldehyde thus obtained was used in the next reaction without further purification.

To a solution of the above material in *t*-BuOH/H_2O (4:1, v/v, 1.5 mL) cooled to 0 °C were added 2-methyl-2-butene (60 μL), NaH_2PO_4 (15.0 mg, 0.125 mmol), and $NaClO_2$ (36.1 mg, 0.399 mmol), and the

resultant mixture was stirred at room temperature for 1 h. The reaction mixture was acidified with 1 M aqueous HCl solution and extracted with EtOAc. The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude carboxylic acid thus obtained was used in the next reaction without further purification.

To a solution of the above material in MeOH/benzene (1:1, v/v, 2 mL) was added $TMSCHN_2$ (2.0 M solution in *n*-hexane, 0.17 mL, 0.34 mmol). The resultant solution was stirred at room temperature for 45 min, after which time it was concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5 to 10% EtOAc/hexanes) gave ester **23** (89.9 mg, 97% for the three steps) as a colorless oil: $[\alpha]_D^{24}$ +36.8 (*c* 1.00, $CHCl_3$); IR (film) 2940, 2864, 1742, 1514, 1457, 1249, 1065, 1028, 882, 682 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.40 (dd, *J* = 14.2, 7.8 Hz, 1H), 6.17 (d, *J* = 14.2 Hz, 1H), 5.39 (ddd, *J* = 15.5, 6.9, 6.8 Hz, 1H), 5.27 (dd, *J* = 15.5, 7.7 Hz, 1H), 4.50 (d, *J* = 11.5 Hz, 1H), 4.25 (d, *J* = 11.5 Hz, 1H), 3.85 (m, 1H), 3.78 (s, 3H), 3.70 (m, 1H), 3.65 (s, 3H), 3.47–3.45 (m, 2H), 3.38 (m, 1H), 3.17 (m, 1H), 2.54 (dd, *J* = 15.1, 8.2 Hz, 1H), 2.38 (dd, *J* = 15.1, 5.0 Hz, 1H), 2.10 (m, 1H), 1.97–1.82 (m, 4H), 1.78 (m, 1H), 1.55–1.43 (m, 4H), 1.37 (m, 1H), 1.29–1.11 (m, 3H), 1.04–1.01 (m, 24H), 0.98 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.7, 159.1, 145.8, 131.2, 131.1, 130.3, 129.2 (2C), 113.7 (2C), 85.1, 78.1, 77.4, 74.3, 72.5, 72.2, 70.3, 68.6, 55.2, 51.6, 42.1, 41.5, 41.2 (2C), 41.1, 36.5, 31.6, 31.3, 28.9, 23.7, 18.1 (6C), 16.4, 12.3 (3C); HRMS (ESI) calcd for $C_{40}H_{65}O_7ISiNa$ [$(M + Na)^+$] 835.3436, found 835.3442.

Macrolactone 24. To a solution of ester **23** (77.0 mg, 94.7 μmol) in Et_3SiH/CH_2Cl_2 (1:2, v/v, 2 mL) at −35 °C was added $BF_3{\cdot}OEt_2$ (60 μL, 0.47 mmol). The resultant solution was allowed to warm to 0 °C and stirred at 0 °C for 20 min. The reaction was quenched with Et_3N and saturated aqueous $NaHCO_3$ solution. The resultant mixture was extracted with EtOAc, and the combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash

column chromatography (silica gel, 8% EtOAc/hexanes) gave an alcohol (61.7 mg, 94%) as a colorless oil: $[\alpha]_D^{25}$ +8.4 (*c* 1.00, $CHCl_3$); IR (film) 3438, 2941, 2865, 1741, 1437, 1376, 1251, 1065, 882, 680 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.53 (dd, *J* = 14.2, 5.9 Hz, 1H), 6.29 (d, *J* = 14.2 Hz, 1H), 5.51 (ddd, *J* = 15.1, 6.9, 6.4 Hz, 1H), 5.28 (dd, *J* = 15.1, 8.3 Hz, 1H), 3.94 (m, 1H), 3.85 (m, 1H), 3.70 (m, 1H), 3.66 (s, 3H), 3.46 (m, 1H), 3.37 (m, 1H), 3.19 (m, 1H), 2.54 (dd, *J* = 15.1, 8.2 Hz, 1H), 2.38 (dd, *J* = 15.1, 5.0 Hz, 1H), 2.29 (m, 1H), 2.14 (m, 1H), 2.01 (m, 1H), 1.92–1.78 (m, 4H), 1.56–1.38 (m, 3H), 1.27–1.10 (m, 5H), 1.04–1.02 (m, 24H), 0.98 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.7, 146.4, 132.9, 130.5, 77.52, 77.48, 77.3, 74.4, 72.5, 72.2, 68.5, 51.6, 42.4, 42.1, 41.4, 41.2, 41.1, 36.2, 31.6, 31.2, 28.9, 23.7, 18.1 (6C), 15.4, 12.3 (3C); HRMS (ESI) calcd for $C_{32}H_{57}O_6ISiNa$ $[(M + Na)^+]$ 715.2861, found 715.2885.

To a solution of the above alcohol (61.4 mg, 88.6 μmol) in THF (1 mL) was added TMSOK (75.8 mg, 0.532 mmol). The resultant mixture was stirred at room temperature for 2 h, after which time it was cooled to 0 °C and acidified with 0.5 M aqueous HCl solution (pH was adjusted to ca. 5). The resultant mixture was extracted with EtOAc, and the combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. urification of the residue by flash column chromatography (silica gel, 20 to 40% EtOAc/hexanes) gave a hydroxy acid (58.8 mg, 98%) as a colorless oil: $[\alpha]_D^{25}$ +20.2 (*c* 1.00, $CHCl_3$); IR (film) 3414, 2940, 2865, 1714, 1456, 1375, 1263, 1013, 882, 681 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.53 (dd, *J* = 14.2, 5.9 Hz, 1H), 6.29 (d, *J* = 14.2 Hz, 1H), 5.51 (ddd, *J* = 15.1, 6.9, 6.4 Hz, 1H), 5.29 (dd, *J* = 15.1, 7.8 Hz, 1H), 3.95 (m, 1H), 3.86 (m, 1H), 3.72 (m, 1H), 3.54 (m, 1H), 3.39 (m, 1H), 3.20 (m, 1H), 2.56 (dd, *J* = 15.5, 8.7 Hz, 1H), 2.48 (dd, *J* = 15.5, 3.7 Hz, 1H), 2.29 (m, 1H), 2.13 (m, 1H), 2.02 (m, 1H), 1.94–1.84 (m, 3H), 1.79 (m, 1H), 1.58–1.39 (m, 5H), 1.32–1.24 (m, 2H), 1.20–1.13 (m, 2H), 1.04–1.02 (m, 24H), 0.97 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.2, 146.4, 132.8, 130.5, 77.6, 77.5, 77.4, 74.6, 71.9, 68.2, 60.4, 42.3, 42.1, 41.2, 41.1, 40.8, 36.1, 31.48, 31.45, 28.8, 23.6, 18.0 (6C), 15.4, 12.3 (3C); HRMS (ESI) calcd for $C_{31}H_{55}O_6ISiNa$ $[(M + Na)^+]$ 701.2705, found 701.2693.

To a solution of the above hydroxy acid (58.8 mg, 86.6 μmol) in THF (2 mL) at 0 °C were added Et_3N (36 μL, 0.26 mmol) and 2,4,6-$Cl_3C_6H_2COCl$ (20 μL, 0.13 mmol), and the resultant mixture was stirred at room temperature for 30 min. The resultant cloudy solution was diluted with toluene (20 mL) and added dropwise to a solution of DMAP (634.8 mg, 5.196 mmol) in toluene (140 mL) at 80 °C over a period of 6 h. The resultant mixture was stirred at 80 °C for additional 1 h and then cooled to room temperature. The reaction mixture was diluted with EtOAc, washed successively with H_2O, 1 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5% Et_2O/hexanes) gave macrolactone **24** (45.2 mg, 79%) as a colorless amorphous solid: $[\alpha]_D^{26}$ +0.9 (*c* 1.00, $CHCl_3$); IR (film) 2940, 2865, 1741, 1463, 1327, 1181, 1037, 977, 883 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.48 (dd, *J* = 14.2, 5.9 Hz, 1H), 6.31 (d, *J* = 14.2 Hz, 1H), 5.49 (dd, *J* = 15.1, 9.1 Hz, 1H), 5.30 (ddd, *J* = 15.1, 10.6, 4.6 Hz, 1H), 5.11 (m, 1H), 3.86 (m, 1H), 3.72 (m, 1H), 3.21 (m, 1H), 3.15 (m, 1H), 3.08 (m, 1H), 2.48 (dd, *J* = 14.2, 10.6 Hz, 1H), 2.41 (dd, *J* = 14.2, 2.8 Hz, 1H), 2.37–2.29 (m, 2H), 1.96 (m, 1H), 1.86 (m, 1H), 1.76–1.70 (m, 3H), 1.61 (m, 1H), 1.53–1.43 (m, 2H), 1.38–1.09 (m, 4H), 1.04–1.01 (m, 27H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 142.9, 133.8, 129.7, 79.4, 79.1, 75.4, 74.8, 73.0, 72.0, 68.6, 44.0, 41.7, 41.2, 41.1, 40.9, 34.0, 32.5, 31.6, 27.2, 24.0, 18.1 (6C), 14.1, 12.3 (3C); HRMS (ESI) calcd for $C_{31}H_{53}O_5ISiNa$ [$(M + Na)^+$] 683.2599, found 683.2589.

Ketone 25. To a solution of macrolactone **24** (40 mg, 0.061 mmol) in THF (2.5 mL) at 0 °C was added HF·pyridine (0.5 mL), and the resultant solution was stirred at room temperature for 5.5 h. The reaction mixture was poured into ice-cooled saturated aqueous $NaHCO_3$ solution. The resultant mixture was extracted with EtOAc, and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 40 to 50% EtOAc/hexanes) gave an alcohol (27.5 mg, 90%) as a colorless oil: $[\alpha]_D^{25}$ −0.4 (*c* 1.00,

$CHCl_3$); IR (film) 3308, 2928, 2852, 1733, 1716, 1507, 1006, 919, 589 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.47 (dd, *J* = 14.6, 6.4 Hz, 1H), 6.31 (d, *J* = 14.6 Hz, 1H), 5.46 (dd, *J* = 15.1, 8.7 Hz, 1H), 5.30 (ddd, *J* = 15.1, 11.0, 4.1 Hz, 1H), 5.11 (m, 1H), 3.83–3.74 (m, 2H), 3.20 (m, 1H), 3.16–3.09 (m, 2H), 2.50 (dd, *J* = 14.2, 10.6 Hz, 1H), 2.43 (dd, *J* = 14.2, 2.8 Hz, 1H), 2.35–2.29 (m, 2H), 1.95 (m, 1H), 1.83 (m, 1H), 1.75–1.71 (m, 2H), 1.61–1.59 (m, 2H), 1.52–1.43 (m, 3H), 1.37 (m, 1H), 1.27–1.06 (m, 6H), 1.01 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.7, 142.8, 133.7, 129.7, 79.4, 79.3, 75.3, 74.8, 73.0, 72.0, 68.1, 44.0, 41.2, 41.10, 41.07, 40.1, 34.0, 32.4, 31.6, 27.3, 24.0, 14.2; HRMS (ESI) calcd for $C_{22}H_{33}O_5INa$ $[(M + Na)^+]$ 527.1270, found 527.1278.

To a solution of the above alcohol (27.5 mg, 0.055 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added Dess–Martin periodinane (69.4 mg, 0.164 mmol), and the resultant mixture was stirred at room temperature for 1 h. The reaction was quenched with a 1:1 mixture of saturated aqueous $NaHCO_3$ solution and saturated aqueous Na_2SO_3 solution at 0 °C. The resultant mixture was extracted with EtOAc, and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10% Et_2O/benzene) gave ketone **25** (27.3 mg, quant) as a colorless oil: $[\alpha]_D^{25}$ +5.2 (*c* 0.39, $CHCl_3$); IR (film) 2929, 2846, 1739, 1717, 1373, 1265, 1175, 1032, 916, 753 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.48 (dd, *J* = 14.7, 6.4 Hz, 1H), 6.35 (d, *J* = 14.7 Hz, 1H), 5.44 (dd, *J* = 15.1, 9.1 Hz, 1H), 5.30 (ddd, *J* = 15.1, 10.1, 5.0 Hz, 1H), 5.19 (dd, *J* = 6.4, 0.9 Hz, 1H), 4.05 (m, 1H), 3.44 (m, 1H), 3.28 (m, 1H), 3.18 (m, 1H), 2.58 (dd, *J* = 14.2, 9.7 Hz, 1H), 2.54 (dd, *J* = 14.2, 3.7 Hz, 1H), 2.41–2.26 (m, 6H), 1.98 (m, 1H), 1.81 (ddd, *J* = 14.2, 10.1, 2.3 Hz, 1H), 1.76 (m, 1H), 1.59–1.44 (m, 4H), 1.39 (m, 1H), 1.31–1.09 (m, 3H), 1.02 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.1, 169.8, 142.5, 133.4, 130.0, 79.63, 79.59, 75.0, 74.9, 74.4, 73.0, 47.7, 46.5, 41.2, 41.0, 40.1, 34.0, 32.4, 31.6, 27.4, 23.8, 14.1; HRMS (ESI) calcd for $C_{22}H_{31}O_5INa$ $[(M + Na)^+]$ 525.1114, found 525.1111.

15-Demethylexiguolide (3). To a solution of phosphonate **12** (280 mg, 0.693 mmol) in THF (1.5 mL) at −78 °C was added NaHMDS (1.0 M solution in THF, 0.60 mL, 0.60 mmol), and the resultant solution was stirred at −78 °C for 30 min. To this solution was added a solution of ketone **25** (27.3 mg, 0.0543 mmol) in THF (1 mL + 0.5 mL rinse), and the resultant solution was stirred at −40 °C for 6.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The resultant mixture was extracted with EtOAc, and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 0 to 3% Et_2O/benzene) followed by a second flash column chromatography (silica gel, 0 to 8% EtOAc/hexanes) gave an α,β-unsaturated ester (28.1 mg, 93%) as an inseparable mixture of stereoisomers at the C5–C28 and C16–C17 double bonds and as a colorless oil: $[\alpha]_D^{25}$ −10.5 (*c* 1.00, $CHCl_3$); IR (film) 2930, 2844, 1739, 1716, 1435, 1375, 1235, 1156, 1086, 757 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.47 (dd, *J* = 14.6, 6.4 Hz, 1H), 6.32 (d, *J* = 14.6 Hz, 1H), 5.67 (s, 1H), 5.46 (dd, *J* = 15.1, 9.2 Hz, 1H), 5.30 (ddd, *J* = 15.1, 10.6, 4.6 Hz, 1H), 5.12 (dd, *J* = 6.4, 1.0 Hz, 1H), 3.85 (m, 1H), 3.76 (m, 1H), 3.67 (s, 2.5H), 3.65 (s, 0.5H), 3.24–3.10 (m, 2H), 2.54–2.53 (m, 2H), 2.37–2.27 (m, 2H), 2.10 (m, 1H), 1.97–1.88 (m, 2H), 1.79–1.73 (m, 2H), 1.58 (m, 1H), 1.53–1.43 (m, 3H), 1.37 (m, 1H), 1.28–1.06 (m, 5H), 1.02 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.4 (0.83C), 170.3 (0.17C), 166.7, 156.54 (0.83C), 156.50 (0.17C), 142.7 (0.83C), 140.5 (0.17C), 133.7 (0.83C), 133.6 (0.17C), 129.8 (0.17C), 129.7 (0.83C), 115.0, 79.5 (0.17C), 79.4 (1.66C), 77.3 (0.17C), 75.4 (0.83C), 75.2 (0.17C), 75.0 (0.17C), 74.9 (0.83C), 74.8, 74.3 (0.17C), 74.0 (0.83C), 51.0, 44.1 (0.17C), 43.9 (0.83C), 42.4 (0.83C), 41.5 (0.17C), 41.3 (0.83C), 41.2 (0.17C), 41.1 (0.83C), 35.6 (0.17C), 34.7 (0.83C), 34.0 (0.17C), 32.42 (0.83C), 32.38 (0.17C), 31.59 (0.83C), 31.56 (0.34C), 31.5 (0.17C), 27.3 (0.83C), 23.9 (0.83C), 22.6 (0.17C), 14.2 (0.17C), 14.1 (1.66C); HRMS (ESI) calcd for $C_{25}H_{35}O_6INa$ $[(M + Na)^+]$ 581.1371 found 581.1383.

To a solution of the above α,β-unsaturated ester (14.9 mg, 0.0267 mmol) and (*Z*)-vinyl boronate **13** (18.3

mg, 0.0725 mmol) in THF/H_2O (10:1, v/v, 1.1 mL) were added Ag_2O (30.9 mg, 0.134 mmol), $Pd_2(dba)_3$ (3.7 mg, 0.0040 mmol), and Ph_3As (9.8 mg, 0.032 mmol), and the resultant mixture was stirred at room temperature for 15 min. Insoluble materials were filtered off, and the filtrate was concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5 to 12% EtOAc/hexanes, gradient elution) gave 15-demethylexiguolide (**3**) (10.3 mg, 68%) as a mixture of *E*/*Z* isomers at the C5–C28 and C16–C17 double bonds and as a colorless oil. These *E*/*Z* isomers were separated by reverse-phase HPLC [Develosil C30-UG-5 packed column (20 mm I.D. × 250 mm); solvent: 90% CH_3CN/H_2O; flow rate: 8.0 mL/min; UV detection: 254 nm] to give **3** (6.6 mg, 43%): $[\alpha]_D^{25}$ −118.4 (*c* 0.52, C_6H_6); IR (film) 2930, 2844, 1736, 1716, 1651, 1435, 1375, 1156, 1086, 975 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 6.89 (dd, *J* = 13.7, 11.5 Hz, 1H), 6.37 (d, *J* = 11.5 Hz, 1H), 6.15 (dd, *J* = 11.5, 11.0 Hz, 1H), 5.96 (dd, *J* = 11.5, 11.0 Hz, 1H), 5.81 (dd, *J* = 15.1, 9.6 Hz, 1H), 5.69–5.62 (m, 3H), 5.30 (ddd, *J* = 15.1, 10.5, 4.6 Hz, 1H), 4.06 (m, 1H), 3.79 (dddd, *J* = 11.0, 10.6, 2.8, 2.3 Hz, 1H), 3.50 (m, 1H), 3.42–3.39 (m, 4H), 3.27 (s, 3H), 2.99 (dddd, *J* = 11.0, 11.0, 1.9, 1.8 Hz, 1H), 2.81 (s, 2H), 2.69 (m, 1H), 2.36–2.32 (m, 2H), 2.08 (dd, *J* = 14.2, 3.2 Hz, 1H), 2.02 (m, 1H), 1.89 (ddd, *J* = 13.7, 12.4, 1.4 Hz, 1H), 1.84 (m, 1H), 1.75–1.69 (m, 4H), 1.65–1.60 (m, 2H), 1.55 (m, 1H), 1.49–1.43 (m, 2H), 1.35 (ddd, *J* = 13.7, 8.3, 1.9 Hz, 1H), 1.29–1.20 (m, 3H), 1.14 (d, *J* = 6.9 Hz, 3H), 1.10 (m, 1H); ^{13}C NMR (150 MHz, C_6D_6) δ 170.9, 170.1, 166.4, 157.3, 135.2, 133.1, 132.1, 129.5, 129.0, 128.5, 126.0, 124.3, 115.1, 78.0, 75.7, 75.2, 74.8, 74.3, 51.2, 50.6, 45.2, 44.5, 42.6, 42.5, 41.3, 34.9, 34.8, 33.0, 32.2, 28.0, 24.5, 16.6, 14.5; HRMS (ESI) calcd for $C_{33}H_{46}O_8Na$ $[(M + Na)^+]$ 593.3085, found 593.3077.

3. Synthesis of 15,18-bis-demethylexiguolide (4) and (16*Z*)-15,18-bis-demethylexiguolide (5)

Olefin 26. To a solution of alcohol **21** (408.5 mg, 0.586 mmol) and Et_3N (0.41 mL, 2.93 mmol) in CH_2Cl_2/DMSO (1:1, v/v, 6 mL) at 0 °C were added SO_3·pyridine complex (376.3 mg, 2.36 mmol), and the resultant mixture was stirred at 0 °C for 1 h. The resultant mixture was diluted with Et_2O. The organic layer was washed with successively 1 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude aldehyde thus obtained was immediately used in the next reaction without further purification.

To a suspension of $Ph_3P^+CH_3Br^-$ (1.05 g, 2.93 mmol) in THF (4 mL) at 0 °C was added *n*-BuLi (1.65 M solution in *n*-hexane, 1.7 mL, 2.8 mmol), and the resultant mixture was stirred at 0 °C for 20 min. To this mixture was added a solution of the above aldehyde in THF (2 mL rinse), and the resultant mixture was stirred at 0 °C for 30 min. The reaction was quenched with saturated aqueous NH_4Cl solution. The resultant mixture was extracted with EtOAc. The organic layer was washed successively with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 2% EtOAc/hexanes) gave olefin **26** (326.1 mg, 80% for the two steps) as a colorless oil: $[\alpha]_D^{23}$ +6.6 (*c* 0.77, $CHCl_3$); IR (film) 2940, 2864, 1463, 1428, 1112, 883, 822, 702, 612, 505 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.64–7.63 (m, 4H), 7.41–7.34 (m, 6H), 5.79 (dddd, *J* = 16.9, 9.6, 6.4, 6.4 Hz, 1H), 4.97 (dd, *J* = 16.9, 1.7 Hz, 1H), 4.91 (dd, *J* = 9.7, 1.7 Hz, 1H), 3.85–3.71 (m, 3H), 3.48–3.35 (m, 3H), 3.19 (m, 1H), 2.16 (m, 1H), 2.04 (m, 1H), 1.92 (m, 1H), 1.88–1.82 (m, 2H), 1.78–1.74 (m, 2H), 1.66 (m, 1H), 1.59–1.51 (m, 4H), 1.46–1.38 (m, 3H), 1.24–1.12 (m, 3H), 1.05–1.02 (m, 30H); ^{13}C NMR (150 MHz, C_6D_6) δ 138.8, 135.5 (4C), 134.04, 134.01, 129.49, 129.47, 127.6 (4C), 114.3, 77.1, 74.3, 72.23, 72.20, 69.0, 60.5, 42.4, 42.1, 41.5, 39.0, 35.7, 31.7, 31.6, 30.0, 26.8 (3C), 23.6, 19.2, 18.1 (6C), 12.4 (3C); HRMS (ESI) calcd for $C_{42}H_{68}O_4Si_2Na$ $[(M + Na)^+]$ 715.4548 found 715.4520.

Carboxylic acid 27. To a solution of olefin **26** (283.5 mg, 0.409 mmol) in THF (6 mL) was added 10%

KOH/MeOH (9.5 mL). The resultant mixture was stirred at 60 °C for 26.5 h. The reaction mixture was cooled to 0 °C and then neutralized with saturated aqueous NH_4Cl solution. The resultant mixture was extracted with EtOAc. The organic layer was washed successively with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 8 to 20% EtOAc/hexanes) gave an alcohol (166.5 mg, 89%) as a colorless oil: $[\alpha]_D^{24}$ +11.2 (*c* 1.00, $CHCl_3$); IR (film) 3342, 2940, 2865, 1541, 1457, 1372, 1013, 917, 882, 583 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 5.79 (dddd, *J* = 17.0, 10.6, 6.4, 6.4 Hz, 1H), 4.99 (dd, *J* = 17.0, 1.9 Hz, 1H), 4.91 (dd, *J* = 10.6, 1.9 Hz, 1H), 3.83 (m, 1H), 3.77–3.71 (m, 2H), 3.55–3.50 (m, 2H), 3.36 (m, 1H), 3.20 (m, 1H), 2.81 (br s, 1H), 2.16 (m, 1H), 2.04 (m, 1H), 1.93 (dddd, *J* = 12.4, 4.6, 2.3, 2.3 Hz, 1H), 1.86 (ddd, *J* = 14.2, 8.7, 6.0 Hz, 1H), 1.83–1.73 (m, 3H), 1.66 (m, 1H), 1.60–1.40 (m, 6H), 1.33 (ddd, *J* = 11.9, 11.5, 11.5 Hz, 1H), 1.24–1.12 (m, 3H), 1.03 (s, 21H); ^{13}C NMR (150 MHz, C_6D_6) δ 138.7, 114.3, 77.3, 76.4, 74.4, 72.9, 68.5, 61.7, 42.4, 42.0, 41.1, 37.7, 35.6, 31.8, 31.6, 30.0, 23.6, 18.1 (6C), 12.3 (3C); HRMS (ESI) calcd for $C_{26}H_{50}O_4SiNa$ $[(M + Na)^+]$ 477.3371 found 477.3387.

To a solution of the above alcohol (158.6 mg, 0.349 mmol) and Et_3N (0.25 mL, 1.8 mmol) in CH_2Cl_2/DMSO (1:1, v/v, 3.6 mL) at 0 °C was added SO_3·pyridine complex (225.0 mg, 1.41 mmol), and the resultant mixture was stirred at 0 °C for 1 h. The resultant mixture was diluted with Et_2O. The organic layer was washed with successively 1 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude aldehyde thus obtained was immediately used in the next reaction without further purification.

To a solution of the above material in *t*-BuOH/H_2O (4:1, v/v, 3.5 mL) at 0 °C were added 2-methyl-2-butene (0.19 mL, 1.8 mmol), NaH_2PO_4 (46.9 mg, 0.391 mmol), and $NaClO_2$ (111.4 mg, 1.232 mmol). The resultant mixture was stirred at room temperature for 30 min before it was carefully acidified with 1 M aqueous HCl solution at 0 °C. The resultant mixture was extracted with EtOAc. The organic layer

was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 8 to 20% EtOAc/hexanes) gave carboxylic acid **27** (163.5 mg, quant for the two steps) as colorless oil: $[\alpha]_D^{25}$ +10.8 (*c* 1.00, $CHCl_3$); IR (film) 3144, 2940, 2865, 1713, 1145, 1083, 1056, 911, 882, 683 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.79 (dddd, *J* = 17.0, 10.6, 6.4, 6.4 Hz, 1H), 4.97 (dd, *J* = 17.0, 1.9 Hz, 1H), 4.91 (dd, *J* = 10.6, 1.9 Hz, 1H), 3.86 (m, 1H), 3.72 (m, 1H), 3.59 (m, 1H), 3.37 (m, 1H), 3.21 (m, 1H), 2.56 (dd, *J* = 16.0, 8.7 Hz, 1H), 2.50 (dd, *J* = 16.0, 4.1 Hz, 1H), 2.15 (m, 1H), 2.03 (m, 1H), 1.97–1.85 (m, 3H), 1.79 (m, 1H), 1.61–1.40 (m, 6H), 1.32–1.12 (m, 4H), 1.06–0.99 (m, 21H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.2, 138.7, 114.3, 77.3, 74.4, 73.1, 71.8, 68.3, 42.0, 41.3, 41.0, 40.8, 35.6, 31.5 (2C), 30.0, 23.6, 18.0 (6C), 12.3 (3C); HRMS (ESI) calcd for $C_{26}H_{47}O_5Si^-$ $[(M - H)^-]$ 467.3187 found 467.3170.

Alcohol (+)-28. To a solution of (*Z*)-β-iodoacrolein (**32**) (242 mg, 1.07 mmol) in CH_2Cl_2 (5 mL) at −78 °C was added DIBALH (1.03 M solution in *n*-hexane, 1.10 mL, 1.17 mmol), and the resultant solution was stirred at −78 °C for 20 min and then warmed to 0 °C over a period of 100 min. To the solution was added allylmagnesium chloride (2.0 M solution in THF, 2.15 mL, 4.30 mmol), and the reaction mixture was stirred at 0 °C for 90 min. The reaction was quenched with MeOH, and the reaction mixture diluted with EtOAc and saturated aqueous potassium sodium tartrate solution. The resultant biphasic mixture was stirred at room temperature for 2.5 h before it was extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5% EtOAc/hexanes) gave racemic alcohol (±)-**28** (162.1 mg, 68%) as a pale yellow oil.

To a solution of racemic alcohol (±)-**28** (818.9 mg, 3.655 mmol) in vinyl acetate (9 mL) was added Lipase AK (82.6 mg), and the resultant mixture was stirred at 40 °C for 7 h 20 min. The reaction mixture was cooled to room temperature and filtered through a pad of Celite. The filtrate was concentrated under

reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5% EtOAc/hexanes) gave acetate **34** (420.9 mg, 43%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.48 (dd, J = 14.4, 6.5 Hz, 1H), 6.41 (d, J = 14.4 Hz, 1H), 5.68 (dddd, J = 14.4, 9.6, 6.9, 6.5 Hz, 1H), 5.22 (ddd, J = 6.5, 6.5, 6.2 Hz, 1H), 5.11–5.07 (m, 2H), 2.35 (dd, J = 6.9, 6.8 Hz, 1H), 2.03 (s, 3H). The spectroscopic properties of this material matched those reported.[1]

To a solution of acetate **34** (409.8 mg, 1.540 mmol) in MeOH (15 mL) at 0 °C was added K_2CO_3 (21.6 mg, 0.156 mmol), and the resultant mixture was stirred at room temperature for 100 min. The reaction mixture was concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5 to 20% EtOAc/hexanes) gave alcohol (+)-**28** (337.8 mg, 97%) as a colorless oil: $[\alpha]_D^{23}$ +23.7 (*c* 1.00, $CHCl_3$), lit[1]: $[\alpha]_D^{22}$ −23.7 (*c* 1.27, $CHCl_3$) for the enantiomer; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.57 (dd, J = 14.5, 5.5 Hz, 1H), 6.37 (d, J = 14.5 Hz, 1H), 5.76 (dddd, J = 17.2, 10.7, 7.2, 7.2 Hz, 1H), 5.17–5.13 (m, 2H), 4.15 (m, 1H), 2.34 (ddd, J = 14.1, 7.2, 6.9 Hz, 1H), 2.26 (ddd, J = 14.1, 7.2, 6.9 Hz, 1H). The spectroscopic properties of this material matched those reported.[1] The optical purity of this material was determined to be 94%ee by chiral HPLC analysis (CHIRALPAK AD-H, solvent: 1% *i*-PrOH/*n*-hexane, flow rate: 1 mL/min, UV detection: 254 nm, major peak: t = 28.1 min; minor peak: t = 31.0 min).

Triene 29. To a solution of carboxylic acid **27** (97.0 mg, 0.207 mmol) in THF (4 mL) at 0 °C were added Et_3N (60 μL, 0.43 mmol) and 2,4,6-$Cl_3C_6H_2COCl$ (40 μL, 0.26 mmol). The resultant mixture was stirred at room temperature for 50 min before it was concentrated under reduced pressure. The residual mixed anhydride was immediately taken up in toluene (2.5 mL). To this mixture was added dropwise a solution of alcohol **26** (49.3 mg, 0.220 mmol) and DMAP (79.4 mg, 0.650 mmol) in toluene (2 mL). The resultant mixture was stirred at room temperature for 105 min. The reaction mixture was diluted with EtOAc,

[1] T. Oishi, M. Kanemoto, R. Swasono, N. Matsumori and M. Murata, *Org. Lett.*, 2008, **10**, 5203–5206.

washed successively with saturated aqueous NH_4Cl solution and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 2 to 5% EtOAc/hexanes) gave triene **29** (132.5 mg, 95%) as a colorless oil: $[\alpha]_D^{23}$ +28.1 (*c* 0.52, $CHCl_3$); IR (film) 3650, 2939, 2865, 1740, 1461, 1382, 1139, 1083, 669, 507 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.48 (dd, *J* = 14.5, 6.2 Hz, 1H), 6.40 (d, *J* = 14.5 Hz, 1H), 5.79 (dddd, *J* = 16.9, 10.0, 6.5, 6.5 Hz, 1H), 5.69 (m, 1H), 5.24 (ddd, *J* = 6.5, 6.5, 6.5 Hz, 1H), 5.11–5.08 (m, 2H), 4.98 (dd, *J* = 17.2, 1.7 Hz, 1H), 4.91 (dd, *J* = 10.3, 1.4 Hz, 1H), 3.84 (ddd, *J* = 15.5, 5.8, 5.3, 4.8 Hz, 1H), 3.70 (m, 1H), 3.48 (m, 1H), 3.36 (m, 1H), 3.19 (m, 1H), 2.52 (dd, *J* = 15.1, 8.3 Hz, 1H), 2.41–2.35 (m, 3H), 2.16 (m, 1H), 2.03 (m, 1H), 1.94–1.78 (m, 4H), 1.58–1.50 (m, 3H), 1.48–1.39 (m, 3H), 1.27–1.11 (m, 4H), 1.04 (s, 21H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 143.1, 138.8, 132.2, 118.7, 114.3, 80.0, 77.2, 74.7, 74.1, 72.6, 72.1, 68.5, 42.2, 41.42, 41.40, 41.0, 38.2, 35.7, 31.6, 31.5, 30.0, 23.6, 18.1 (6C), 12.3 (3C); HRMS (ESI) calcd for $C_{32}H_{55}O_5ISiNa$ [$(M + Na)^+$] 697.2756, found 697.2753.

Macrolactone 30. To a solution of triene **29** (20.6 mg, 30.5 μmol) and 1,4-benzoquinone (1.3 mg, 12 μmol) in degassed CH_2Cl_2 (13 mL) was added a solution of the Hoveyda–Grubbs second-generation catalyst (3.8 mg, 6.1 μmol) in degassed CH_2Cl_2 (1.5 mL), and the resultant solution was stirred at 40 °C for 20 h. At this point, additional portion of a solution of the Hoveyda–Grubbs second-generation catalyst (4.1 mg, 6.5 μmol) in degassed CH_2Cl_2 (1.5 mL) was added to the reaction mixture at room temperature. The resultant solution was stirred at 40 °C for additional 23 h. The reaction mixture was cooled to room temperature and stirred under air for 2 h. The resultant mixture was concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 5% EtOAc/hexanes) followed by second flash column chromatography (silica gel, benzene) gave macrolactone **30** (13.6 mg, 69%, *E*/*Z* 3:1, as judged by 600 MHz ^1H NMR): $[\alpha]_D^{23}$ +21.8 (*c* 0.82, $CHCl_3$); IR (film) 2940, 2864, 1739, 1248, 1181, 1085, 981, 882, 682, 506 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.52–6.43 (m, 2H), 5.52 (ddd, *J* = 15.4, 11.3,

2.4 Hz, 0.75H), 5.37 (m, 1H), 5.22 (ddd, *J* = 10.6, 6.5, 5.2 Hz, 0.25H), 5.14 (m, 0.25H), 5.01 (ddd, *J* = 10.2, 5.2, 1.4 Hz, 0.75H), 3.83 (m, 1H), 3.70 (m, 1H), 3.22–3.13 (m, 2H), 3.03 (m, 1H), 2.53–2.33 (m, 5.25H), 2.20 (ddd, *J* = 14.5, 10.3, 2.0 Hz, 0.75H), 1.95–1.71 (m, 6H), 1.63 (m, 1H), 1.53–1.41 (m, 3H), 1.39–1.14 (m, 4H), 1.10 (m, 1H), 1.02 (s, 21H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.1 (0.75C), 170.8 (0.25C), 144.0 (0.75C), 143.4 (0.25C), 132.4 (0.25C), 132.2 (0.75C), 128.3 (0.75C), 126.9 (0.75C), 124.0 (0.25C), 81.4 (0.25C), 80.5 (0.75C), 75.8 (0.25C), 75.7 (0.25C), 75.3 (0.75C), 75.2 (0.25C), 74.7 (0.75C), 73.2 (0.25C), 72.9 (0.75C), 72.7 (0.25C), 72.2 (0.75C), 68.5 (0.75C), 68.4 (0.25C), 44.4 (0.25C), 44.1 (0.75C), 42.0 (0.25C), 41.9 (0.25C), 41.8 (0.75C), 41.5 (0.25C), 41.4 (0.75C), 41.0 (0.75C), 37.3 (0.75C), 34.8 (0.25C), 33.8 (0.75C), 32.5 (0.25C), 32.4 (0.75C), 31.8 (0.25C), 31.6 (0.75C), 31.4 (0.25C), 27.2 (0.75C), 24.0 (0.75C), 23.7 (0.25C), 23.0 (0.25C), 18.0 (6C), 12.3 (3C); HRMS (ESI) calcd for $C_{30}H_{51}O_5ISiNa$ [(M + Na)$^+$] 669.2443, found 669.2463.

Ketone 31. To a solution of macrolactone **30** (34.4 mg, 53.2 μmol) in THF (2.5 mL) at 0 °C was added HF·pyridine (0.5 mL). The resultant solution was stirred at room temperature for 4.3 h before it was poured into saturated aqueous $NaHCO_3$ solution at 0 °C. The resultant mixture was extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 30 to 50% EtOAc/hexanes) gave an alcohol (26.0 mg, quant) as a colorless amorphous solid: $[\alpha]_D^{22}$ +19.5 (*c* 1.00, $CHCl_3$); IR (film) 3361, 2926, 2861, 1735, 1315, 1029, 937, 678, 506 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.53–6.43 (m, 2H), 5.50 (ddd, *J* = 14.8, 11.3, 4.8 Hz, 0.75H), 5.37 (m, 1H), 5.22 (ddd, *J* = 10.3, 6.2, 5.8 Hz, 0.25H), 5.14 (ddd, *J* = 11.3, 6.2, 4.1 Hz, 0.25H), 5.01 (m, 0.75H), 3.83–3.71 (m, 3H), 3.23–3.07 (m, 2.75H), 3.01 (m, 0.25H), 2.52–2.32 (m, 4H), 2.20 (ddd, *J* = 14.8, 9.7, 2.3 Hz, 0.75H), 1.98–1.93 (m, 2.25H), 1.86–1.72 (m, 3H), 1.65–1.58 (m, 2H), 1.52–1.42 (m, 2H), 1.36 (m, 1H), 1.29–1.17 (m, 4H), 1.08 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.0 (0.75C), 170.6 (0.25C), 143.9 (0.75C), 143.3 (0.25C), 132.4 (0.25C), 132.2 (0.75C),

126.8 (0.75C), 123.9 (0.25C), 81.4 (0.25C), 80.6 (0.75C), 77.1 (0.75C), 75.7 (0.25C), 75.6 (0.25C), 75.3 (0.25C), 75.2 (0.75C), 74.7 (0.75C), 73.1 (0.25C), 72.8 (0.75C), 72.6 (0.25C), 72.1 (0.75C), 67.9 (0.75C), 67.8 (0.25C), 44.4 (0.25C), 44.1 (0.75C), 41.9 (0.25C), 41.4 (0.75C), 41.12 (0.25C), 41.07 (0.75C), 40.7 (0.25C), 40.2 (0.75C), 37.3 (0.75C), 34.7 (0.25C), 33.8 (0.75C), 32.43 (0.25C), 32.37 (0.75C), 31.8 (0.25C), 31.5 (0.75C), 31.3 (0.25C), 27.2 (0.75C), 23.9 (0.75C), 23.6 (0.25C), 23.0 (0.25C); HRMS (ESI) calcd for $C_{21}H_{31}O_5INa$ [$(M + Na)^+$] 513.1108, found 513.1098.

To a solution of the above alcohol (26.0 mg, 53.0 μmol) in CH_2Cl_2 (1 mL) at 0 °C was added Dess–Martin periodinane (68.2 mg, 0.161 mmol). The resultant mixture was stirred at room temperature for 1 h. The reaction was quenched with a 1:1 mixture of saturated aqueous $NaHCO_3$ solution and saturated aqueous Na_2SO_3 solution. The resultant mixture was extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 10% Et_2O/benzene) gave ketone **31** (25.2 mg, 99%) as a colorless amorphous solid: $[\alpha]_D^{22}$ +23.1 (*c* 1.00, $CHCl_3$); IR (film) 2927, 2854, 1736, 1371, 1213, 1173, 1086, 1030, 977, 681 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.56–6.45 (m, 2H), 5.50 (ddd, *J* = 15.1, 10.3, 3.8 Hz, 0.75H), 5.41 (m, 1H), 5.25 (m, 0.25H), 5.18 (ddd, *J* = 10.7, 6.9, 4.5 Hz, 0.25H), 5.11 (m, 0.75H), 4.04 (m, 1H), 3.42 (m, 1H), 3.28 (m, 0.75H), 3.21 (m, 1H), 3.04 (m, 0.25H), 2.58–2.48 (m, 2H), 2.45–2.20 (m, 5H), 1.96 (m, 1H), 1.84 (ddd, *J* = 14.2, 10.1, 2.1 Hz, 1H), 1.77 (m, 1H), 1.67–1.44 (m, 6H), 1.39 (m, 1H), 1.29 (dddd, *J* = 13.3, 13.3, 1.6, 1.6 Hz, 1H) , 1.24–1.04 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.0 (0.75C), 205.3 (0.25C), 170.0 (0.75C), 169.7 (0.25C), 143.7 (0.75C), 143.1 (0.25C), 132.6 (0.25C), 132.5 (0.75C), 126.5 (0.75C), 123.7 (0.25C), 81.7 (0.25C), 80.9 (0.75C), 77.3 (0.75C), 76.0 (0.25C), 75.5 (0.25C), 75.3 (0.25C), 74.9 (0.75C), 74.8 (0.75C), 74.5 (0.25C), 74.4 (0.75C), 73.8 (0.25C), 73.2 (0.75C), 50.1 (0.25C), 47.9 (0.25C), 47.7 (0.75C), 47.1 (0.25C), 46.6 (0.75C), 44.4 (0.25C), 44.0 (0.75C), 42.2 (0.25C), 41.4 (0.75C), 37.1 (0.75C), 34.8 (0.25C), 33.9 (0.75C), 32.4 (0.75C), 31.7 (0.25C), 31.5 (0.75C), 31.3 (0.25C), 27.3

(0.75C), 23.8 (0.75C), 23.6 (0.25C), 23.1 (0.25C); HRMS (ESI) calcd for $C_{21}H_{29}O_5INa$ [$(M + Na)^+$] 511.0952, found 511.0945.

15,18-Bis-demethylexiguolide (4) and (16*Z*)-15,18-bis-demethylexiguolide (5). To a solution of phosphonate **12** (177.4 mg, 0.4387 mmol) in THF (1.5 mL) at −78 °C was added NaHMDS (1.0 M solution in THF, 0.30 mL, 0.30 mmol), and the resultant solution was stirred at −78 °C for 0.5 h. To this solution was added dropwise a solution of ketone **31** (25.5 mg, 52.2 μmol) in THF (1 + 0.5 mL). The resultant solution was allowed to warm to −40 °C and stirred at −40 °C for 7 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The resultant mixture was allowed to warm to room temperature and then extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 0 to 2 to 3% EtOAc/benzene) gave an α,β-unsaturated ester (25.0 mg, 88%) as a mixture of stereoisomers at the C5–C28 and C16–C17 double bonds. This material was used in the next reaction without separation of stereoisomers: $[\alpha]_D^{23}$ +2.1 (*c* 1.00, $CHCl_3$); IR (film) 2927, 2855, 1716, 1651, 1434, 1374, 1237, 1155, 1084, 754 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.54–6.44 (m, 2H), 5.68 (s, 1H), 5.51 (ddd, *J* = 14.1, 10.3, 2.0 Hz, 0.75H), 5.38 (m, 1H), 5.23 (m, 0.25H), 5.15 (ddd, *J* = 11.7, 6.5, 5.2 Hz, 0.25H), 5.04 (m, 0.75H), 3.90–3.71 (m, 2H), 3.67 (s, 3H), 3.25–3.11 (m, 2.75H), 3.01 (m, 0.25H), 2.53–2.44 (m, 2H), 2.42–2.31 (m, 2H), 2.25–2.18 (m, 2H), 2.09 (m, 1H), 1.96–1.74 (m, 4H), 1.65–1.43 (m, 3H), 1.37 (m, 1H), 1.31–1.02 (m, 4H); HRMS (ESI) calcd for $C_{24}H_{33}O_6INa$ [$(M + Na)^+$] 567.1214, found 567.1234.

To a mixture of the above α,β-unsaturated ester (13.2 mg, 24.2 μmol) and (*Z*)-vinyl boronate **13** (14.7 mg, 55.2 μmol) in THF/H_2O (10:1, v/v, 1.1 mL) were added Ag_2O (28.7 mg, 0.124 mmol), $Pd_2(dba)_3$ (4.0 mg, 4.4 μmol), and Ph_3As (10.1 mg, 33.0 μmol). The resultant mixture was stirred at room temperature for 50 min. Insoluble materials were filtered off, and the filtrate was concentrated under reduced pressure.

Purification of the residue by flash column chromatography (silica gel, 0 to 15% EtOAc/hexanes, gradient elution) followed by a second flash column chromatography (silica gel, 0 to 5% EtOAc/benzene, gradient elution) gave a mixture of **4**, **5**, and their C5–C28 stereoisomers (10.6 mg, 78%) as a colorless oil. These isomers were separated by reverse-phase HPLC [Develosil C30-UG-5 packed column (20 mm I.D. × 250 mm); solvent: 75% CH_3CN/H_2O; flow rate: 8.0 mL/min; UV detection: 254 nm] to give **4** (5.7 mg, 42%) and **5** (1.6 mg, 12%). Data for **4**: $[\alpha]_D^{24}$ −91.6 (*c* 0.57, C_6H_6); IR (film) 2923, 2853, 1734, 1716, 1457, 1157, 812, 743, 637, 590 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 6.93 (dd, *J* = 15.1, 11.6 Hz, 1H), 6.37 (d, *J* = 11.7 Hz, 1H), 6.14 (dd, *J* = 11.7, 11.0 Hz, 1H), 5.92 (dd, *J* = 11.3, 11.3 Hz, 1H), 5.87 (ddd, *J* = 14.8, 11.4, 3.1 Hz, 1H), 5.62 (dd, *J* = 14.8, 7.6 Hz, 1H), 5.61 (s, 1H), 5.52 (m, 1H), 5.32 (ddd, *J* = 14.8, 10.3, 2.8 Hz, 1H), 4.04 (d, *J* = 13.7 Hz, 1H), 3.79 (dddd, *J* = 11.0, 10.3, 3.1, 2.3 Hz, 1H), 3.50 (m, 1H), 3.42–3.39 (m, 4H), 3.27 (s, 3H), 2.99 (m, 1H), 2.81 (s, 2H), 2.71 (dddd, *J* = 12.8, 10.6, 10.3, 3.9 Hz, 1H), 2.49 (m, 1H), 2.33 (dd, *J* = 14.4, 10.3 Hz, 1H), 2.18 (ddd, *J* = 14.4, 10.6, 2.0 Hz, 1H), 2.04 (dd, *J* = 14.4, 3.1 Hz, 1H), 2.00 (d, *J* = 13.4 Hz, 1H), 1.90 (m, 1H), 1.82 (m, 1H), 1.73–1.60 (m, 4H), 1.54 (m, 1H), 1.49–1.43 (m, 2H), 1.35–1.19 (m, 6H), 1.10 (m, 1H); ^{13}C NMR (150 MHz, C_6D_6) δ 170.9, 170.3, 166.4, 157.2, 133.23, 133.18, 131.9, 128.2, 128.1, 127.9, 126.5, 124.3, 115.1, 75.9, 75.6, 75.1, 74.7, 74.4, 51.2, 50.6, 45.2, 44.6, 42.5, 41.5, 38.7, 35.0, 34.6, 32.9, 32.2, 28.0, 24.5, 16.6; HRMS (ESI) calcd for $C_{32}H_{44}O_8Na$ $[(M + Na)^+]$ 579.2934, found 579.2951. Data for **5**: $[\alpha]_D^{24}$ −76.0 (*c* 0.16, C_6H_6); IR (film) 2923, 2852, 1733, 1716, 1558, 1507, 1457, 1011, 608, 505 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 6.99 (m, 1H), 6.31 (d, *J* = 11.7 Hz, 1H), 6.11 (dd, *J* = 11.7, 11.3 Hz, 1H), 5.91 (dd, *J* = 11.3, 11.0 Hz, 1H), 5.69–5.64 (m, 2H), 5.59 (s, 1H), 5.42–5.37 (m, 2H), 4.04 (d, *J* = 13.4 Hz, 1H), 3.74 (ddd, *J* = 11.0, 3.4, 2.4 Hz, 1H), 3.41–3.39 (m, 4H), 3.27 (s, 3H), 3.22 (m, 1H), 2.97–2.91 (m, 2H), 2.71 (dddd, *J* = 12.4, 10.6, 10.3, 2.4 Hz, 1H), 2.78 (s, 2H), 2.59 (m, 1H), 2.30 (dd, *J* = 12.7, 10.7 Hz, 1H), 2.12 (dd, *J* = 12.7, 3.8 Hz, 1H), 2.04 (dd, *J* = 13.7, 10.3, 1.4 Hz, 1H), 1.80 (m, 1H), 1.75–1.67 (m, 5H), 1.61–1.55 (m, 2H), 1.49 (m, 1H), 1.44 (m, 1H), 1.35–1.27 (m,

2H), 1.21–1.17 (m, 2H), 1.10 (m, 1H), 1.00 (m, 1H); ^{13}C NMR (150 MHz, C_6D_6) δ 170.9, 170.1, 166.3, 156.7, 133.2, 132.4, 132.0, 129.8, 127.9, 126.6, 125.6, 124.3, 115.2, 75.6, 75.5, 75.4, 75.0, 74.9, 51.2, 50.6, 45.2, 44.9, 42.6, 42.2, 35.6, 35.5, 32.9, 32.8, 32.3, 24.1, 23.6, 16.6; HRMS (ESI) calcd for $C_{32}H_{44}O_8Na$ [(M + Na)$^+$] 579.2934, found 579.2924.

4. Synthesis of side chain analogues

(*Z*)-Vinyl boronate 44. To a mixture of $[Rh(COD)Cl]_2$ (2.8 mg, 5.8 μmol) and PCy_3 (6.5 mg, 23 μmol) in cyclohexane (1.5 mL) were added Et_3N (0.27 mL, 1.9 mmol) and pinacolborane (56 μL, 0.38 mmol), and the resultant mixture was stirred at room temperature for 30 min. To this mixture was added a solution of 6-(*t*-butyldiphenylsilyloxy)hexyne (127.4 mg, 0.3786 mmol) in cyclohexane (1.0 + 0.5 mL rinse). The resultant mixture was stirred at room temperature for 4 h before being concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 2% EtOAc/hexanes) gave a 1:3 mixture of *E*/*Z* isomers (110.0 mg, 62%), from which the desired (*Z*)-vinyl boronate **44** (66.6 mg, 38%) was separated in a stereochemically pure form as a colorless oil: IR (film) 2977, 2931, 2858, 1628, 1426, 1259, 1145, 1111, 702, 505 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.66–7.64 (m, 4H), 7.40–7.34 (m, 6H), 6.39 (ddd, *J* = 13.3, 7.3, 6.4 Hz, 1H), 5.93 (d, *J* = 13.3 Hz, 1H), 3.66–3.64 (m, 2H), 2.37 (dq, *J* = 7.3, 1.4 Hz, 2H), 1.59–1.55 (m, 2H), 1.47–1.42 (m, 2H), 1.21 (s, 12H), 1.03 (m, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.0, 135.5 (4C), 134.1 (2C), 129.5 (3C), 127.5 (4C), 82.7 (2C), 63.8, 32.0, 31.8, 26.8 (3C), 25.6, 24.8 (3C), 24.7, 19.2; HRMS (ESI) calcd for $C_{28}H_{41}O_3BNa$ $[(M + Na)^+]$ 487.2816, found 487.2823.

TBDPS ether 45. To a mixture of (*E*)-vinyl iodide **43** (15.9 mg, 27.8 μmol) and (*Z*)-vinyl boronate **44** (19.4 mg, 41.7 μmol) in THF/H_2O (10:1, v/v, 1.1 mL) were added Ag_2O (32.2 mg, 0.139 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (3.4 mg, 4.7 μmol), and Ph_3As (5.1 mg, 17 μmol). The resultant mixture was stirred at room temperature for 30 min. Insoluble materials were filtered off, and the filtrate was concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, hexanes to 5 to 10% EtOAc/hexanes) gave TBDPS ether **45** (20.5 mg, 94%) as a colorless oil: $[\alpha]_D^{25}$ −71.9 (*c* 0.51, $CHCl_3$); IR (film) 2930, 2863, 1738, 1716, 1428, 1364, 1236, 1154, 704, 508 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.65–7.64 (m, 4H), 7.41–7.34 (m, 6H), 6.45 (dd, *J* = 15.6, 11.5 Hz, 1H), 5.93 (dd, *J* = 11.0, 11.0 Hz, 1H), 5.68 (s, 1H), 5.58 (dd, *J* = 15.6, 7.4 Hz, 1H), 5.50 (dd, *J* = 15.6, 9.2 Hz, 1H), 5.41 (ddd, *J* = 11.5,

7.8, 7.3 Hz, 1H), 5.22 (m, 1H), 5.04 (dd, *J* = 15.6, 9.7 Hz, 1H), 3.84 (m, 1H), 3.77 (m, 1H), 3.67 (s, 3H), 3.64–3.62 (m, 2H), 3.28 (m, 1H), 3.21–3.16 (m, 2H), 2.56–2.48 (m, 3H), 2.31 (m, 1H), 2.22–2.09 (m, 4H), 1.95 (m, 1H), 1.78–1.74 (m, 2H), 1.60–1.36 (m, 10H), 1.26–1.03 (m, 14H), 0.92 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.7, 166.8, 156.8, 135.6 (4C), 135.3, 134.1, 133.2, 132.6, 129.9, 129.5 (3C), 127.9, 127.8, 127.6 (4C), 114.9, 78.7, 76.0, 75.4, 74.9, 74.2, 63.7, 51.0, 44.1, 43.1, 42.5, 42.1, 41.6, 34.8, 33.0, 32.5, 32.2, 31.6, 27.6, 26.9 (3C), 25.8, 23.9, 21.8, 19.2, 14.4; HRMS (ESI) calcd for $C_{48}H_{66}O_7Na$ [(M + Na)$^+$] 805.4470, found 805.4491.

Alcohol 35. To a solution of TBDPS ether **45** (18.1 mg, 23.1 μmol) in THF (0.5 mL) cooled to 0 °C were added AcOH (27.7 μL, 0.484 mmol) and TBAF (1.0 M solution in THF, 0.462 mL, 0.462 mmol), and the resultant solution was stirred at room temperature for 1 day. The reaction mixture was diluted with EtOAc and washed successively with saturated aqueous $NaHCO_3$ solution, and then brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (30 to 40% EtOAc/hexanes) gave alcohol **35** (12.4 mg, 98%) as a colorless oil: $[\alpha]_D^{23}$ −92.7 (*c* 1.00, $CHCl_3$); IR (film) 3323, 2929, 2870, 1716, 1646, 1376, 1237, 1156, 901, 587 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.47 (dd, *J* = 15.1, 11.0 Hz, 1H), 5.96 (dd, *J* = 11.0, 11.0 Hz, 1H), 5.67 (s, 1H), 5.58 (dd, *J* = 15.1, 6.9 Hz, 1H), 5.50 (dd, *J* = 15.1, 9.2 Hz, 1H), 5.43 (ddd, *J* = 11.0, 7.8, 7.8 Hz, 1H), 5.21 (m, 1H), 5.05 (dd, *J* = 15.1, 9.6 Hz, 1H), 3.84 (m, 1H), 3.76 (m, 1H), 3.67 (s, 3H), 3.64–3.61 (m, 2H), 3.27 (m, 1H), 3.20–3.15 (m, 2H), 2.56–2.47 (m, 3H), 2.31 (m, 1H), 2.22–2.18 (m, 3H), 2.09 (m, 1H), 1.94 (m, 1H), 1.77–1.73 (m, 2H), 1.63 (br s, 1H), 1.60–1.37 (m, 10H), 1.26–1.02 (m, 5H), 0.94 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.8, 166.8, 156.7, 135.3, 132.8, 132.6, 129.9, 128.0, 127.9, 114.9, 78.7, 76.0, 75.3, 74.9, 74.1, 62.7, 51.0, 44.1, 43.1, 42.5, 42.0, 41.6, 34.8, 33.0, 32.4, 32.1, 31.6, 27.4, 25.6, 23.9, 21.8, 14.3; HRMS (ESI) calcd for $C_{32}H_{48}O_7Na$ [(M + Na)$^+$] 567.3292, found 567.3296.

Methyl ether 36. To a solution of alcohol **35** (5.5 mg, 10.1 μmol) in CH_2Cl_2 (0.5 mL) were added 2,6-di-*tert*-butylpyridine (0.11 mL, 0.50 mmol) and MeOTf (44 μL, 0.40 mmol), and the resultant solution was stirred at room temperature overnight before the reaction was quenched with saturated aqueous $NaHCO_3$ solution at 0 °C. The reaction mixture was extracted with EtOAc, and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (10 to 15% EtOAc/hexanes) gave methyl ether **36** (4.2 mg, 74%) as a colorless amorphous solid: $[\alpha]_D^{22}$ −67.9 (*c* 0.42, $CHCl_3$); IR (film) 2929, 2856, 1739, 1717, 1652 1456, 1374, 1236, 1155, 732 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.46 (dd, *J* = 15.1, 11.0 Hz, 1H), 5.94 (dd, *J* = 11.0, 11.0 Hz, 1H), 5.68 (s, 1H), 5.58 (dd, *J* = 15.1, 6.8 Hz, 1H), 5.50 (dd, *J* = 15.1, 9.7 Hz, 1H), 5.43 (ddd, *J* = 10.6, 7.8, 7.8 Hz, 1H), 5.21 (m, 1H), 5.05 (dd, *J* = 15.1, 9.7 Hz, 1H), 3.85 (m, 1H), 3.77 (dddd, *J* = 11.5, 9.2, 4.1, 2.3 Hz, 1H), 3.67 (s, 3H), 3.37–3.35 (m, 2H), 3.31 (s, 3H), 3.21–3.16 (m, 2H), 2.54–2.48 (m, 3H), 2.31 (m, 1H), 2.22–2.17 (m, 3H), 2.10 (m, 1H), 1.95 (m, 1H), 1.77–1.74 (m, 2H), 1.60–1.37 (m, 10H), 1.23–1.02 (m, 3H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.7, 166.8, 156.8, 135.3, 132.9, 132.6, 129.9, 127.9, 127.8, 114.9, 78.6, 76.0, 75.4, 74.9, 74.2, 72.6, 58.6, 51.0, 44.1, 43.1, 42.5, 42.0, 41.6, 34.8, 33.0, 32.5, 31.6, 29.2, 27.6, 26.1, 23.9, 21.8, 14.3; HRMS (ESI) calcd for $C_{33}H_{50}O_7Na$ $[(M + Na)^+]$ 581.3449, found 581.3440.

Carboxylic acid 37. To a solution of alcohol **35** (7.2 mg, 13 μmol) in CH_2Cl_2 (0.5 mL) at 0 °C were added 0.05 M aqueous KBr solution (26 μL, 1.3 μmol), TEMPO (1.0 mg, 6.4 μmol), and a portion (0.18 mL) of a freshly prepared mixture of saturated aqueous $NaHCO_3$ solution (50 μL), aqueous NaClO solution (1.77 M, 50 μL), and H_2O (0.9 mL). The reaction mixture was stirred at 0 °C for 1 h before the reaction was quenched with saturated aqueous Na_2SO_3 solution. The reaction mixture was extracted with EtOAc, and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residual aldehyde was used in the next reaction without further purification.

To a solution of the above aldehyde in *t*-BuOH/H_2O (4:1, v/v, 0.5 mL) at 0 °C were added 2-methyl-2-butene (0.5 mL), NaH_2PO_4 (7.0 mg, 58 μmol), and $NaClO_2$ (16.6 mg, 0.18 mmol). The resultant mixture was stirred at room temperature for 45 min before it was carefully acidified with aqueous NH_4Cl solution at 0 °C. The resultant mixture was extracted with EtOAc. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 20 to 30 to 50% EtOAc/hexanes) gave carboxylic acid **37** (7.3 mg, 99% yield for the two steps) as colorless oil: $[\alpha]_D^{23}$ −69.0 (*c* 0.41, $CHCl_3$); IR (film) 3362, 2969, 2833, 1734, 1717, 1563, 1398, 1155, 740, 505 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.42 (dd, *J* = 15.1, 11.0 Hz, 1H), 6.00 (dd, *J* = 11.0, 11.0 Hz, 1H), 5.68 (s, 1H), 5.59 (dd, *J* = 15.1, 6.9 Hz, 1H), 5.49 (dd, *J* = 15.1, 9.7 Hz, 1H), 5.40 (ddd, *J* = 10.6, 7.8, 7.8 Hz, 1H), 5.22 (m, 1H), 5.05 (dd, *J* = 15.1, 9.6 Hz, 1H), 3.85 (m, 1H), 3.77 (m, 1H), 3.67 (s, 3H), 3.27 (m, 1H), 3.20–3.16 (m, 2H), 2.59–2.47 (m, 3H), 2.35–2.18 (m, 6H), 2.10 (m, 1H), 1.95 (m, 1H), 1.77–1.70 (m, 4H), 1.59 (m, 1H), 1.54–1.37 (m, 4H), 1.25–1.02 (m, 3H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.2, 171.3, 166.8, 156.8, 135.4, 132.5, 131.4, 130.3, 129.0, 127.4, 115.0, 78.8, 76.0, 75.4, 74.9, 74.2, 51.1, 44.0, 43.1, 42.5, 41.9, 41.6, 34.8, 33.0, 32.4, 32.3, 31.6, 26.5, 24.1, 23.9, 21.8, 14.3; HRMS (ESI) calcd for $C_{32}H_{45}O_8$ $[(M - H)^-]$ 557.3109, found 557.3125.

Ester 38. To a solution of carboxylic acid **37** (3.5 mg, 6.3 μmol) in MeOH/benzene (1:1, v/v, 0.5 mL) was added $TMSCHN_2$ (2.0 M solution in *n*-hexane, 31 μL, 62 μmol). The resultant solution was stirred at room temperature for 30 min, after which time it was concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 15% EtOAc/hexanes) gave esster **38** (2.7 mg, 75% for the two steps) as a colorless oil: $[\alpha]_D^{23}$ −82.6 (*c* 0.35, $CHCl_3$); IR (film) 2937, 2856, 1738, 1442, 1370, 1233, 1154, 1093, 728, 501 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.43 (dd, *J* = 15.1, 11.0 Hz, 1H), 5.98 (dd, *J* = 11.0, 11.0 Hz, 1H), 5.68 (s, 1H), 5.59 (dd, *J* = 15.1, 6.8 Hz, 1H), 5.50 (dd, *J* = 15.1, 9.7 Hz, 1H), 5.40

(ddd, *J* = 11.0, 7.8, 7.8 Hz, 1H), 5.21 (m, 1H), 5.05 (dd, *J* = 15.1, 9.7 Hz, 1H), 3.85 (m, 1H), 3.77 (m, 1H), 3.67 (s, 3H), 3.65 (s, 3H), 3.28 (m, 1H), 3.20–3.16 (m, 2H), 2.54–2.48 (m, 3H), 2.34–2.30 (m, 3H), 2.24–2.16 (m, 3H), 2.09 (m, 1H), 1.95 (m, 1H), 1.77–1.68 (m, 4H), 1.60–1.37 (m, 5H), 1.23–1.02 (m, 3H), 1.03 (d, *J* = 7.4 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.0, 170.7, 166.8, 156.8, 135.4, 132.6, 131.6, 130.5, 128.7, 127.5, 114.9, 78.6, 76.0, 75.4, 74.9, 74.2, 51.5, 51.0, 44.1, 43.1, 42.5, 42.0, 41.6, 34.8, 33.3, 33.0, 32.5, 31.6, 27.1, 24.7, 23.9, 21.8, 14.3; HRMS (ESI) calcd for $C_{33}H_{48}O_8Na$ [$(M + Na)^+$] 595.3241, found 595.3237.

Amide 39. To a solution of carboxylic acid **37** (2.9 mg, 5.2 μmol) in MeOH (0.5 mL) were added Me_2NH (2.0 M in MeOH, 78.0 μL, 0.156 mmol) and DMTMM (41.8 mg, 0.156 mmol), and the resultant mixture was stirred at room temperature for 3 days. The reaction was quenched with H_2O at 0 °C and the resultant mixture extracted with Et_2O. The combined organic layer was washed successively with saturated aqueous $NaHCO_3$ solution, saturated aqueous NH_4Cl solution and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 30 to 60% EtOAc/hexanes) gave amide **39** (1.6 mg, 53%) as a colorless oil: $[\alpha]_D^{23}$ −77.0 (*c* 0.16, C_6H_6); IR (film) 2930, 2866, 1732, 1715, 1651, 1373, 1155, 994, 921, 563 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 6.76 (m, 1H), 6.07 (dd, *J* = 11.0, 11.0 Hz, 1H), 5.80 (dd, *J* = 15.1, 9.6 Hz, 1H), 5.64–5.60 (m, 3H), 5.42 (ddd, *J* = 11.0, 7.8, 7.8 Hz, 1H), 5.08 (dd, *J* = 15.1, 9.6 Hz, 1H), 4.10 (m, 1H), 3.83 (m, 1H), 3.52 (m, 1H), 3.42 (s, 3H), 3.37 (m, 1H), 3.00 (m, 1H), 2.84 (m, 1H), 2.72 (s, 3H), 2.43 (dd, *J* = 14.2, 10.1 Hz, 1H), 2.37 (dd, *J* = 14.2, 3.2 Hz, 1H), 2.34 (m, 1H), 2.25–2.15 (m, 5H), 1.91–1.64 (m, 8H), 1.57–1.53 (m, 2H), 1.48–1.43 (m, 2H), 1.38–1.20 (m, 3H), 1.15 (d, *J* = 6.9 Hz, 3H), 1.12 (m, 1H), 1.03 (m, 1H), 0.98 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 171.5, 170.2, 166.4, 157.3, 135.7, 133.4, 132.7, 130.9, 129.0, 128.6, 115.2, 78.1, 75.9, 75.6, 75.1, 74.4, 50.6, 44.5, 43.8, 42.53, 42.48, 41.5, 36.1, 35.0, 34.9, 33.5, 32.9, 32.2, 32.0, 27.6, 25.0, 24.5, 22.2, 14.7; HRMS (ESI) calcd for $C_{34}H_{51}O_8NNa$ [$(M + Na)^+$]

608.3558, found 608.3572.

Tertiary amine 40. To a solution of alcohol **35** (3.0 mg, 5.5 μmol) in CH_2Cl_2 (0.5 mL) at 0 °C were added Et_3N (ca. 10 μL) and MsCl (ca. 5 μL), and the resultant mixture was stirred at 0 °C for 2 h. before being quenched with H_2O at 0 °C. The resultant mixture was extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residual crude mesylate was immediately used in the next reaction without further purification.

To a solution of the above crude material in MeOH (1 mL) at 0 °C were added Me_2NH (2.0 M in MeOH, 0.3 mL, 0.6 mmol). The resultant mixture was stirred at 30 °C for 4 days before the reaction was quenched with H_2O at 0 °C. The resultant mixture was extracted with CH_2Cl_2. The organic layer was concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, CH_2Cl_2 to 10% MeOH/CH_2Cl_2 + 1% *i*-Pr_2NH) gave tertiary amine **40** (3.1 mg, 98% yield for the two steps) as colorless oil: $[\alpha]_D^{24}$ −66.5 (*c* 0.31, CH_3OH); IR (film) 2929, 2860, 1716, 1653, 1558, 1507, 1457, 1155, 734, 669 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 6.50 (dd, *J* = 15.1, 11.0 Hz, 1H), 6.01 (dd, *J* = 11.0, 11.0 Hz, 1H), 5.76 (s, 1H), 5.64 (dd, *J* = 15.1, 6.4 Hz, 1H), 5.50–5.46 (m, 2H), 5.24 (m, 1H), 5.14 (dd, *J* = 15.1, 9.7 Hz, 1H), 3.89 (dd, *J* = 14.2, 2.3 Hz, 1H), 3.73 (m, 1H), 3.67 (s, 3H), 3.37–3.24 (m, 2H), 3.19 (m, 1H), 2.63 (dd, *J* = 14.6, 3.7 Hz, 1H), 2.57 (dd, *J* = 14.6, 10.5 Hz, 1H), 2.45 (m, 1H), 2.39–2.33 (m, 3H), 2.28 (s, 6H), 2.26–2.20 (m, 4H), 1.98 (m, 1H), 1.80 (m, 1H), 1.72–1.67 (m, 2H), 1.58–1.50 (m, 4H), 1.44–1.38 (m, 4H), 1.22–1.08 (m, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 172.8, 168.3, 158.3, 136.8, 134.2, 133.6, 131.2, 129.3, 128.8, 115.9, 80.2, 77.7, 76.8, 76.6, 75.5, 60.4, 51.5, 45.2 (2C), 44.9, 44.2, 43.4, 43.3, 42.5, 35.8, 34.5, 33.3, 32.8, 28.4 (2C), 27.5, 25.1, 22.2, 14.6; HRMS (ESI) calcd for $C_{34}H_{54}O_6N$ $[(M + H)^+]$ 572.3946, found 572.3946.

Primary amine 41. To a solution of alcohol **35** (3.5 mg, 6.4 μmol) in CH_2Cl_2 (0.5 mL) at 0 °C were added Et_3N (ca. 10 μL) and MsCl (ca. 5 μL), and the resultant mixture was stirred at 0 °C for 2 h. before being

quenched with H_2O at 0 °C. The resultant mixture was extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residual crude mesylate was immediately used in the next reaction without further purification.

To a solution of the above crude mesylate in DMF (0.5 mL) were added NaN_3 (2.1 mg, 32 μmol). The resultant mixture was stirred at 60 °C for 1.5 h. The reaction mixture was cooled to 0 °C, and the reaction quenched with H_2O. The resultant mixture was extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 0 to 10 to 20% EtOAc/hexanes) gave an azide (3.6 mg, 98% for the two steps) as a colorless oil: $[\alpha]_D^{23}$ −73.4 (*c* 0.39, CH_3OH); IR (film) 2924, 2852, 2090, 1716, 1654, 1541, 1504, 1152, 1092, 770 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 6.50 (dd, *J* = 15.1, 11.0 Hz, 1H), 6.02 (dd, *J* = 11.0, 11.0 Hz, 1H), 5.76 (s, 1H), 5.65 (dd, *J* = 15.1, 6.9 Hz, 1H), 5.50–5.46 (m, 2H), 5.24 (m, 1H), 5.15 (dd, *J* = 15.1, 9.7 Hz, 1H), 3.89 (dd, *J* = 13.7, 2.3 Hz, 1H), 3.73 (m, 1H), 3.67 (s, 3H), 3.36 (m, 1H), 3.31–3.25 (m, 3H), 3.19 (m, 1H), 2.64 (dd, *J* = 14.2, 3.2 Hz, 1H), 2.57 (dd, *J* = 14.2, 10.1 Hz, 1H), 2.45 (m, 1H), 2.37 (m, 1H), 2.28–2.20 (m, 4H), 1.98 (m, 1H), 1.80 (m, 1H), 1.71–1.29 (m, 10H), 1.23–1.08 (m, 3H), 1.05 (d, *J* = 7.3 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 172.9, 168.3, 158.3, 136.8, 134.2, 133.4, 131.2, 129.3, 128.7, 115.9, 80.2, 77.7, 76.8, 76.6, 75.5, 52.3, 51.5, 44.9, 44.1, 43.4, 43.3, 42.5, 35.8, 34.5, 33.3, 32.8, 29.3, 28.1, 27.7, 25.1, 22.2, 14.6; HRMS (ESI) calcd for $C_{32}H_{47}O_6N_3Na$ $[(M + Na)^+]$ 592.3357, found 592.3379.

To a solution of the above azide (3.0 mg, 5.3 μmol) in THF/H_2O (10:1, v/v, 1.1 mL) was added PPh_3 (2.1 mg, 7.9 μmol), and the resultant solution was stirred at 30 °C for 16 h. and then at 60 °C for 36 h. At this point, additional portion of PPh_3 (2.1 mg, 7.9 μmol) was added to the reaction mixture at room temperature. The resultant solution was stirred at 60 °C for additional 13.5 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Purification of the residue by flash

column chromatography (silica gel, 2% MeOH/CH_2Cl_2 + 1% *i*-Pr_2NH) gave primary amine **41** (2.1 mg, 73%): $[\alpha]_D^{24}$ −129.8 (*c* 0.12, CH_3OH); IR (film) 2966, 2838, 1714, 1649, 1566, 1556, 1415, 1377, 1006, 565 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 6.50 (dd, *J* = 15.1, 11.0 Hz, 1H), 6.03 (dd, *J* = 11.0, 11.0 Hz, 1H), 5.77 (s, 1H), 5.65 (dd, *J* = 15.1, 6.9 Hz, 1H), 5.50–5.46 (m, 2H), 5.23 (m, 1H), 5.14 (dd, *J* = 15.1, 9.6 Hz, 1H), 3.89 (dd, *J* = 13.7, 2.3 Hz, 1H), 3.73 (m, 1H), 3.67 (s, 3H), 3.37–3.18 (m, 3H), 2.73–2.71 (m, 2H), 2.63 (dd, *J* = 14.2, 3.7 Hz, 1H), 2.57 (dd, *J* = 14.2, 10.6 Hz, 1H), 2.45 (m, 1H), 2.36 (dddd, *J* = 16.0, 6.9, 6.9, 1.8 Hz, 1H), 2.27–2.20 (m, 4H), 1.98 (m, 1H), 1.80 (m, 1H), 1.73–1.66 (m, 2H), 1.58–1.38 (m, 7H), 1.23–1.09 (m, 4H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), two proton missing due to H/D exchange; ^{13}C NMR (150 MHz, CD_3OD) δ 172.7, 168.3, 158.3, 136.8, 134.2, 133.6, 131.2, 129.3, 128.8, 115.9, 80.3, 77.7, 76.8, 76.6, 75.5, 51.5, 44.9, 44.1, 43.5, 43.3, 42.5, 41.8, 35.8, 34.5, 33.3, 32.8, 28.3, 27.8, 25.1, 22.2, 21.3, 14.6; HRMS (ESI) calcd for $C_{32}H_{50}O_6N$ $[(M + H)^+]$ 544.3633, found 544.3633.

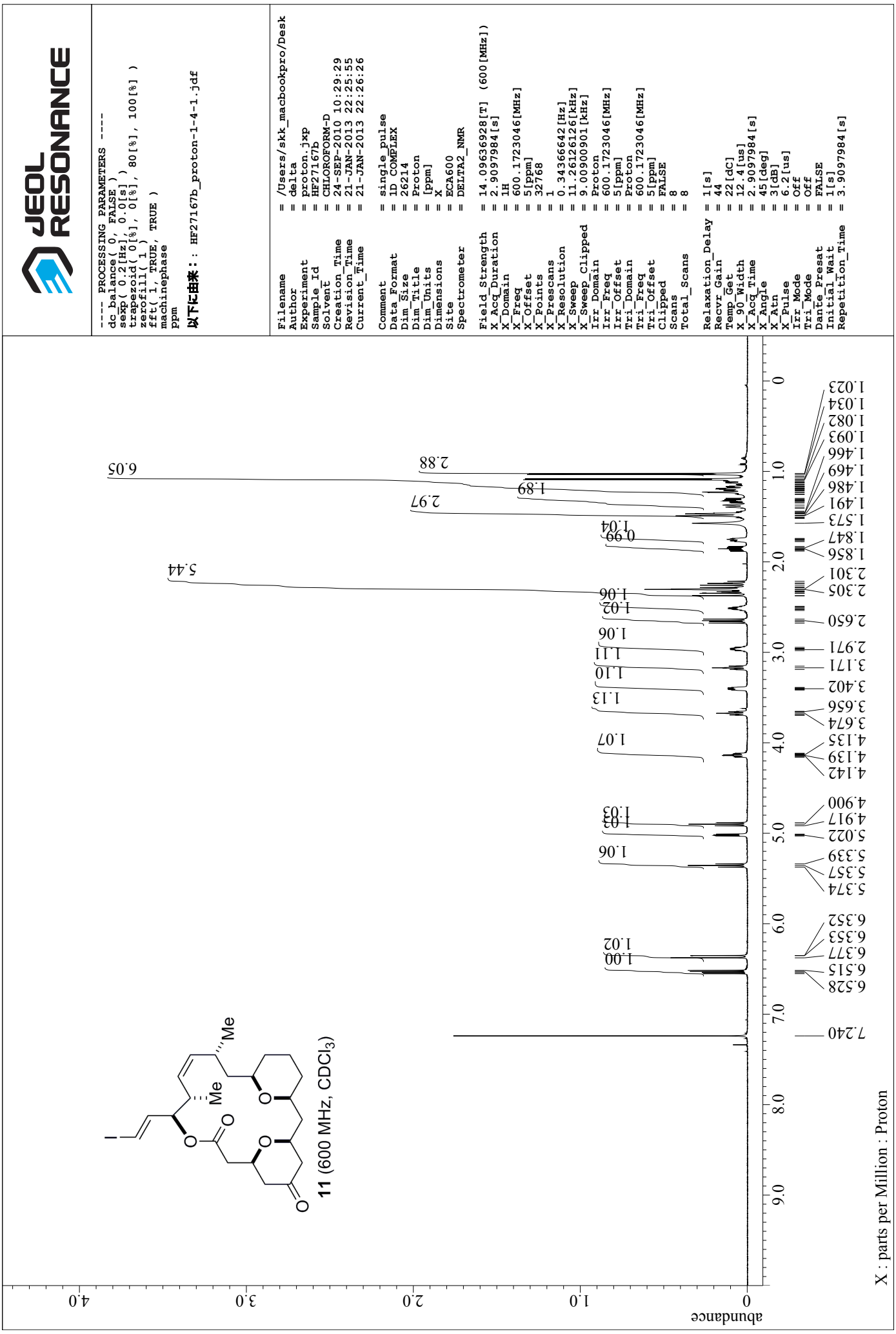
Alkyl chain analogue 42. To a solution of (*E*)-vinyl iodide **43** (5.5 mg, 9.6 μmol) and (*Z*)-vinylstannane **46** (17.2 mg, 46.1 μmol) in degassed DMF (1 mL) were added $Pd_2(dba)_3$ (1.3 mg, 1.4 μmol) and Ph_3As (3.5 mg, 11.5 μmol). The resultant mixture was stirred at room temperature for 5.8 h before being quenched with saturated aqueous $NaHCO_3$ solution at 0 °C. The reaction mixture was extracted with EtOAc, and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (0 to 2 to 6% EtOAc/hexanes) gave alkyl chain analogue **42** (4.4 mg, 87%) as a colorless amorphous solid: $[\alpha]_D^{21}$ −85.7 (*c* 0.44, $CHCl_3$); IR (film) 2926, 2862, 1741, 1717, 1374, 1235, 1154, 973, 859, 548 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.46 (dd, *J* = 15.1, 11.0 Hz, 1H), 5.93 (dd, *J* = 11.0, 11.0 Hz, 1H), 5.68 (s, 1H), 5.57 (dd, *J* = 15.1, 6.9 Hz, 1H), 5.50 (dd, *J* = 15.1, 9.2 Hz, 1H), 5.43 (dd, *J* = 11.0, 7.8, 7.3 Hz, 1H), 5.22 (m, 1H), 5.05 (dd, *J* = 15.1, 9.7 Hz, 1H), 3.85 (m, 1H), 3.77 (m, 1H), 3.67 (s, 3H), 3.28 (m, 1H), 3.20–3.16 (m, 3H), 2.56–2.48 (m, 3H), 2.32 (m, 1H), 2.22–2.09 (m, 4H), 1.95 (m, 1H), 1.77–1.73 (m, 2H), 1.66–1.05 (m, 12H), 1.03 (d, *J* = 7.3 Hz,

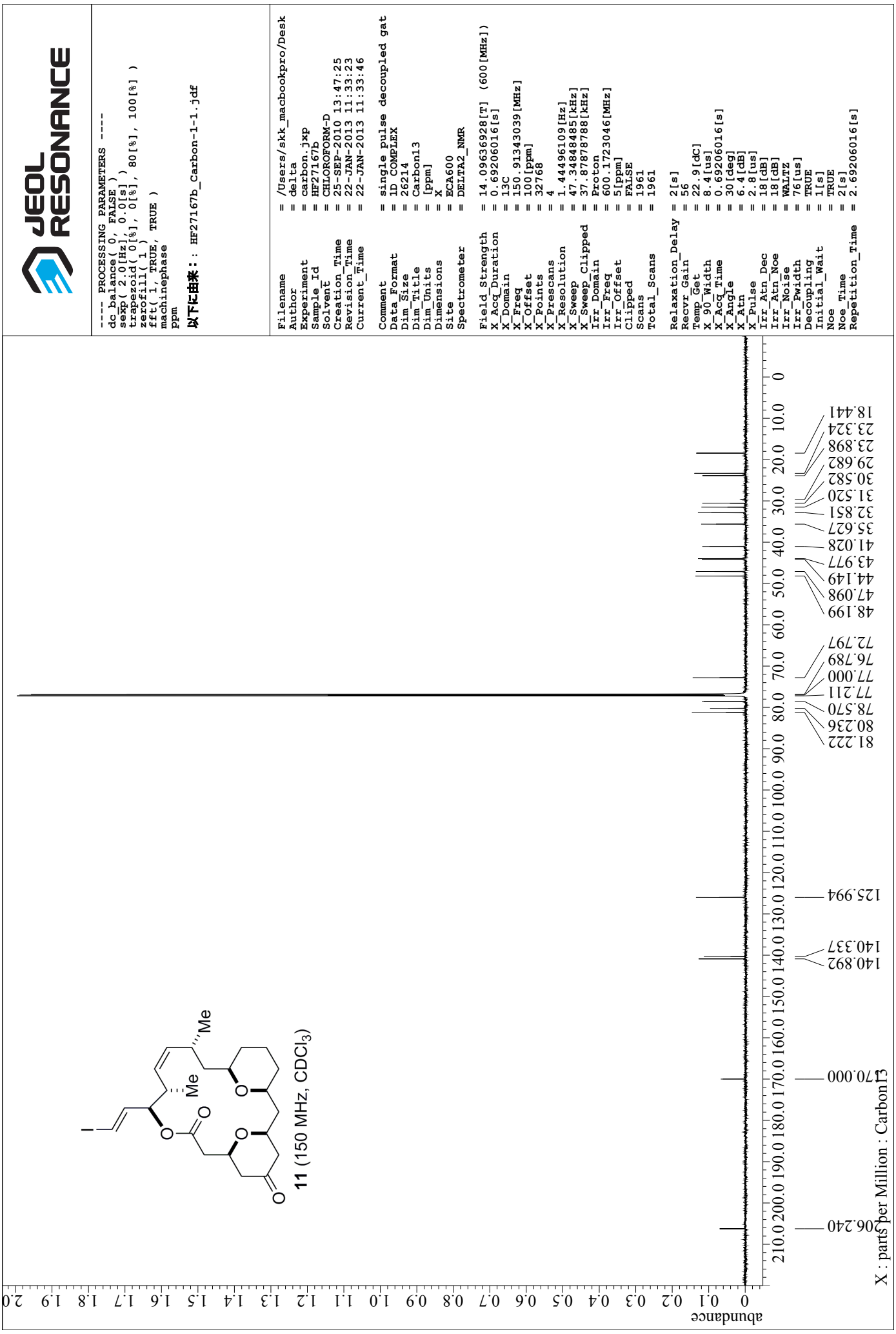
1H), 0.92–0.83 (m, 7H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.7, 166.8, 156.8, 135.3, 133.4, 132.6, 129.7, 127.8, 127.6, 114.9, 78.6, 76.0, 75.4, 74.9, 74.2, 51.0, 44.1, 43.1, 42.5, 42.0, 41.6, 34.8, 33.0, 32.5, 31.7, 31.6, 27.5, 23.9, 22.3, 21.8, 14.3, 14.0; HRMS (ESI) calcd for $C_{32}H_{48}O_6Na$ [$(M + Na)^+$] 551.3343, found 551.3356.

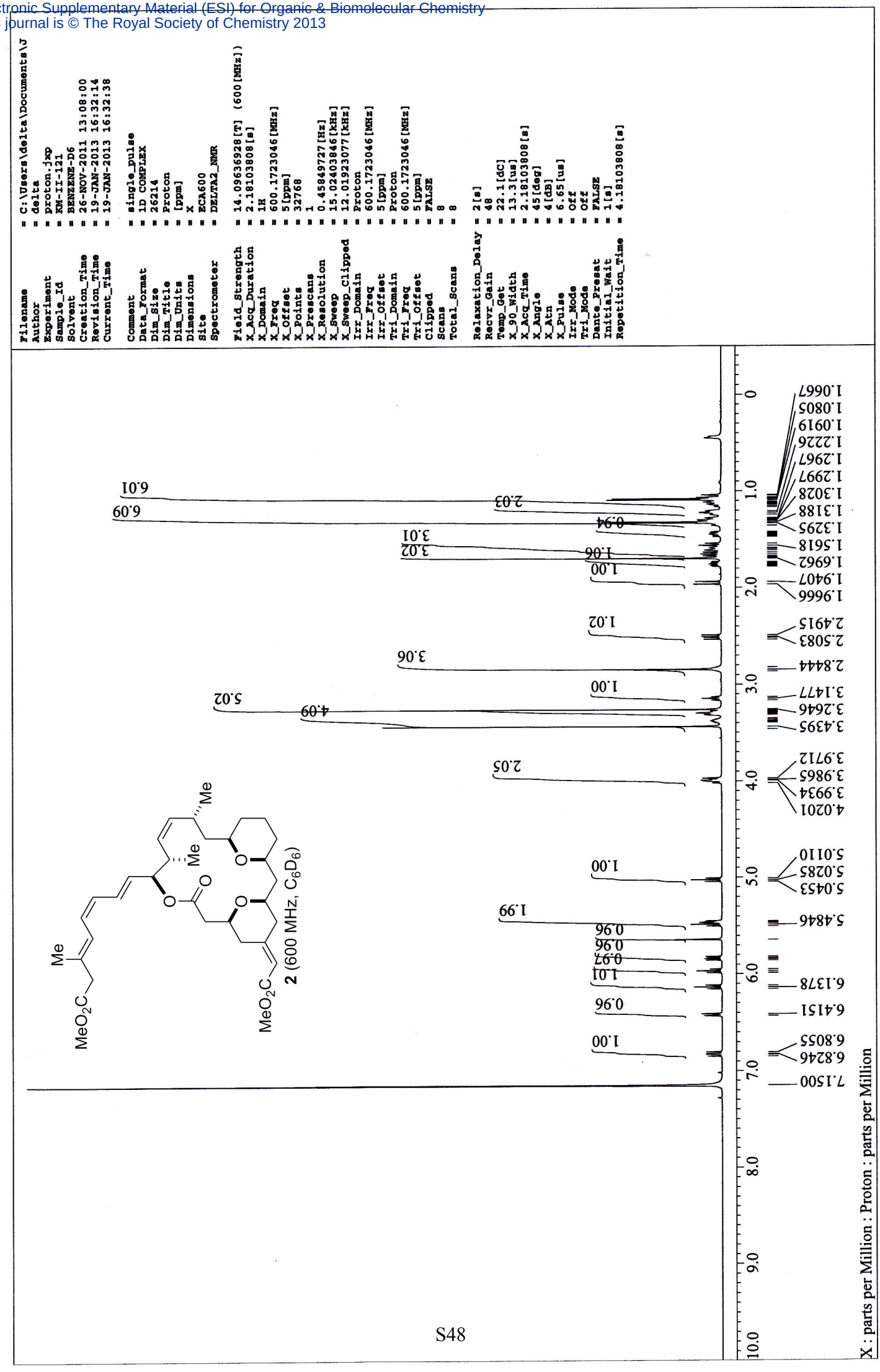
5. Evaluation of the antiproliferative activity of exiguolide and its synthetic analogues

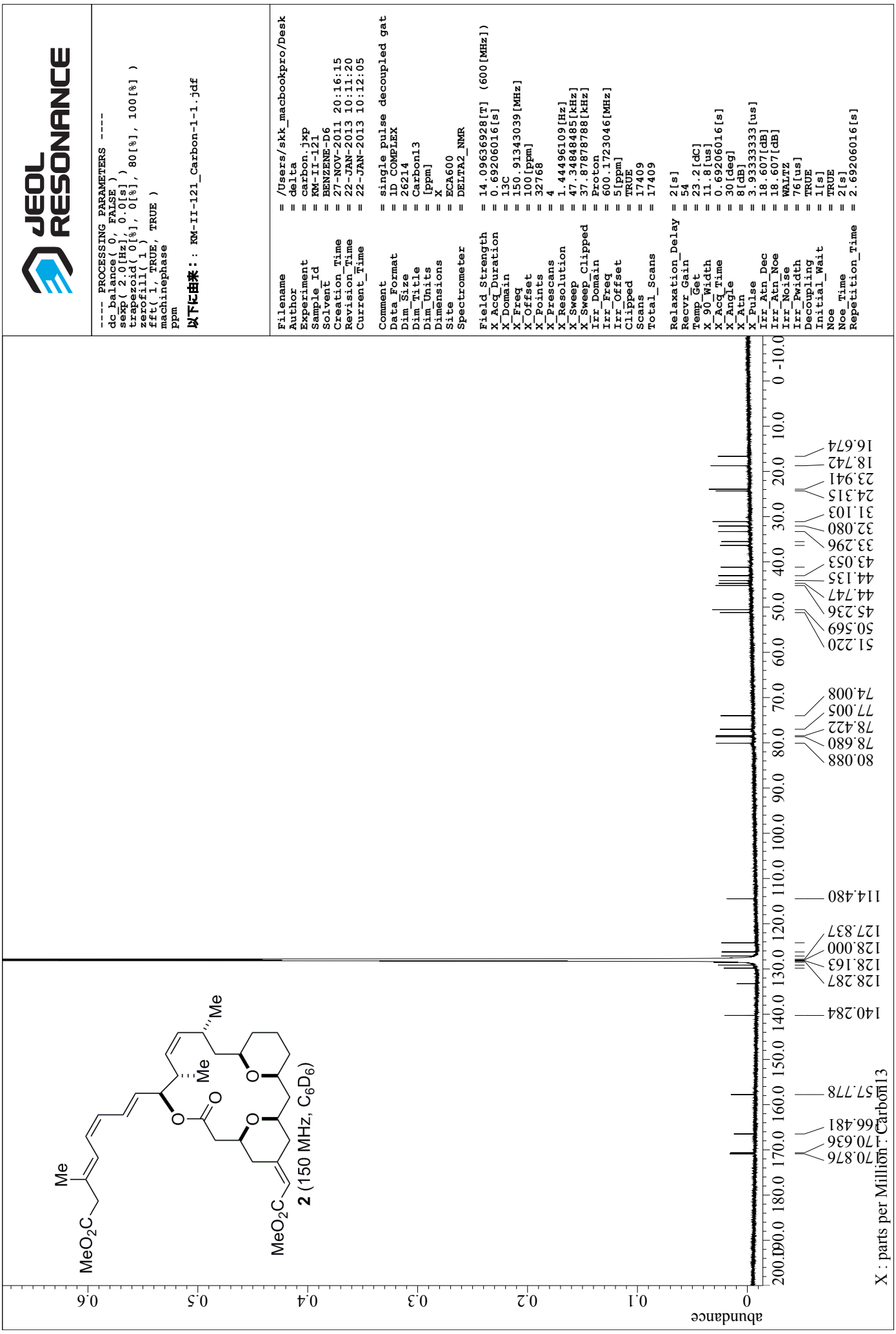
The antiproliferative activity of each compound against A549 human lung adenocarcinoma cells and NCI-H460 human lung large cell carcinoma cells was evaluated as the IC_{50} value by using the Alamar Blue assay, as detailed below.

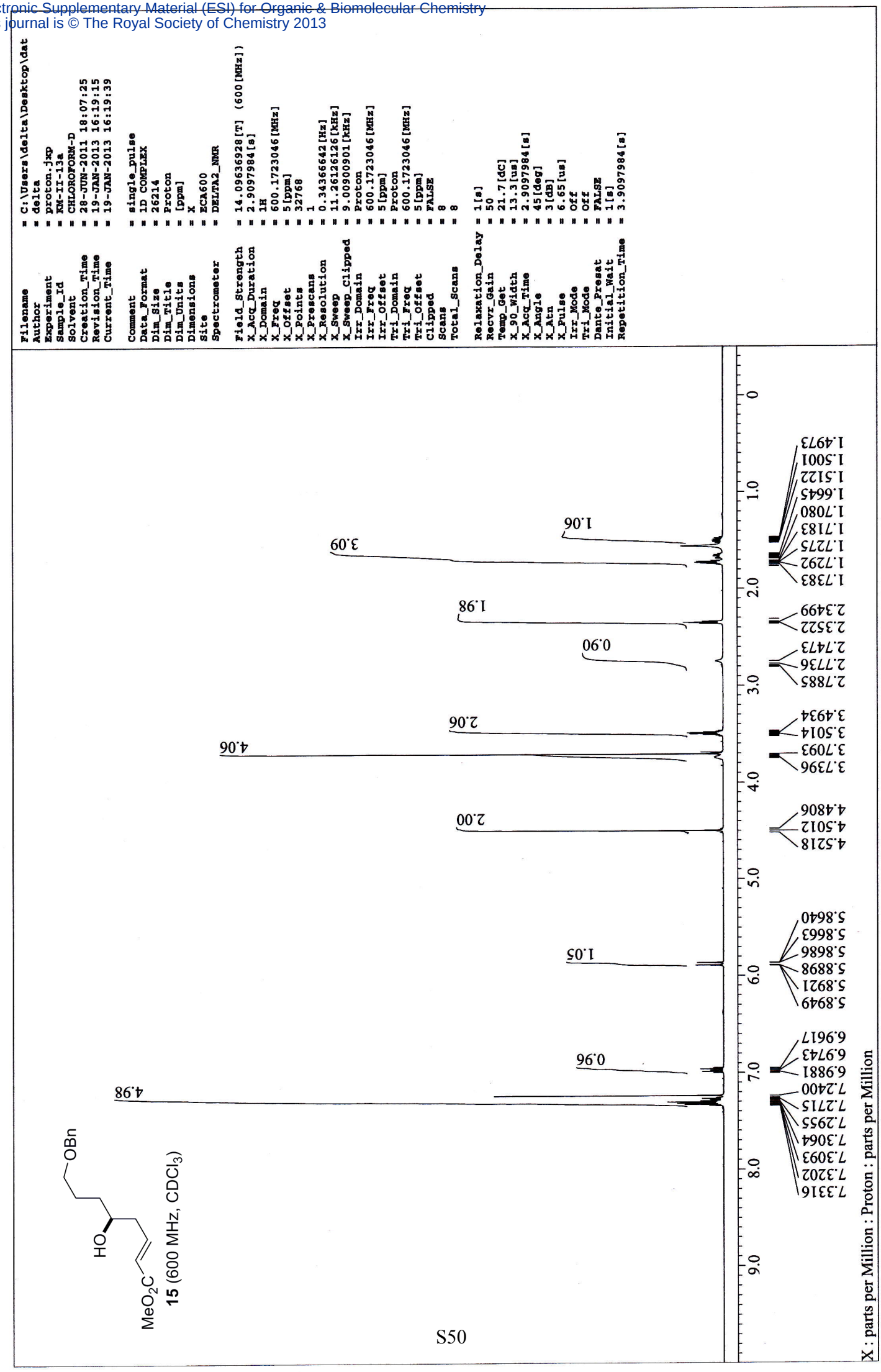
Exponentially growing A549 or NCI-H460 cells were cultured for 4–5 days in 10% FBS/RPMI1640 medium supplemented with 100 units/mL of penicillin and 100 μg/mL of streptomycin (Penicillin-Streptomycin, Liquid, GIBCO, Carlsbad, California), and maintained at 5% CO_2/air atomosphere in a CO_2 incubator. The cells were harvested and the concentration was adjusted to be 3–5 × 10^4 cells/mL. The cell suspension (100 μL) was distributed to the wells of a 96-well microplate and incubated overnight. Serially diluted sample solution (1 μL) was added to each well and cultured for 72–96 h (96 h for A549 and 72 h for NCI-H460). The medium was replaced with a 1:10 mixture of Alamar Blue solution (Invitrogen, Carlsbad, USA)/RPMI1640 medium (100 μL), and the cells were incubated for additional 5 hours. Fluorescence intensity, representing viable cell number, was measured using a microplate reader (iMark Microplate Reader, BioRad, Hercules, California). Relative fluorescence intensity was plotted and IC_{50} was calculated with a non-linear regression model of standard slope using the GraphPad Prism software.

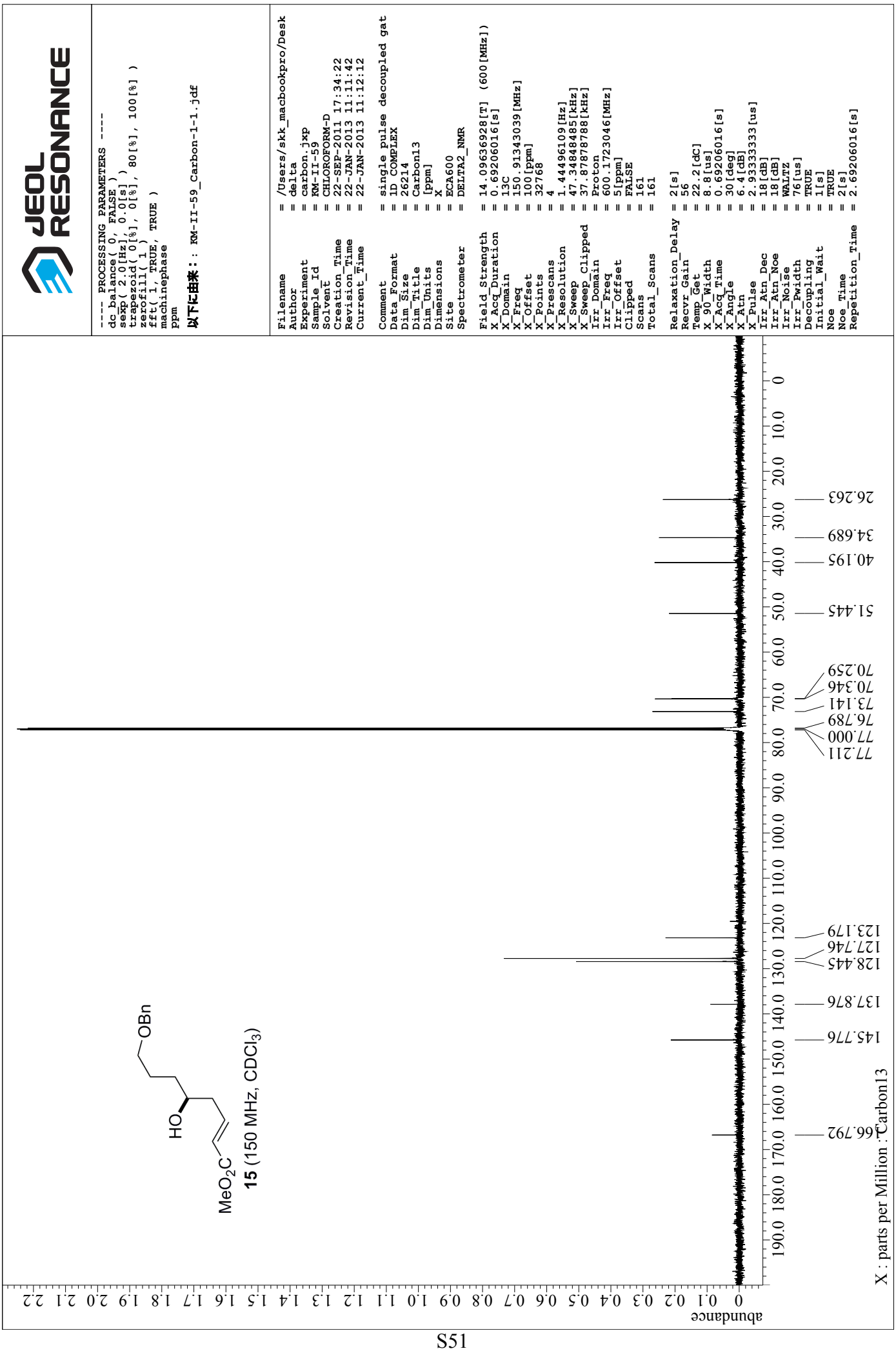


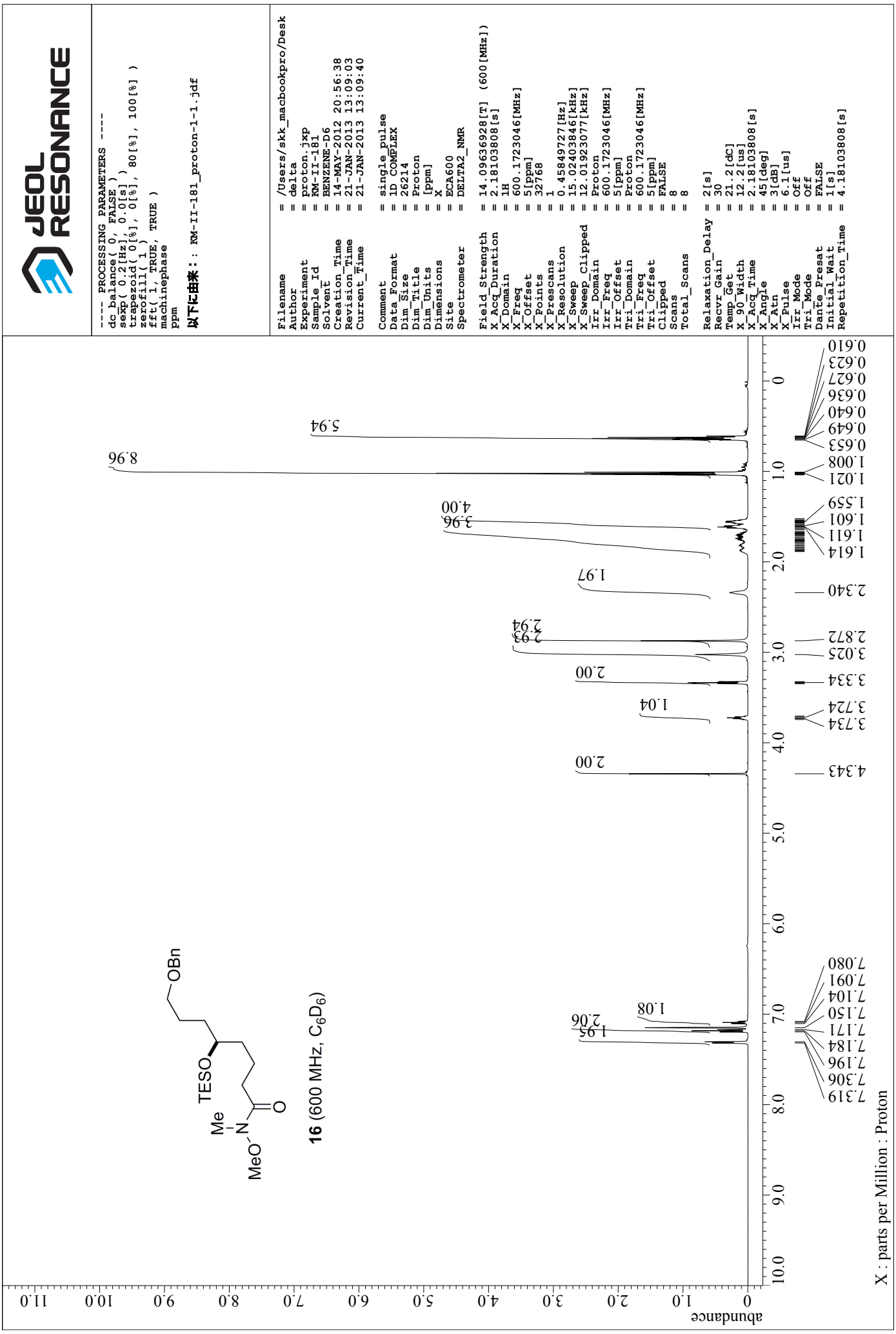


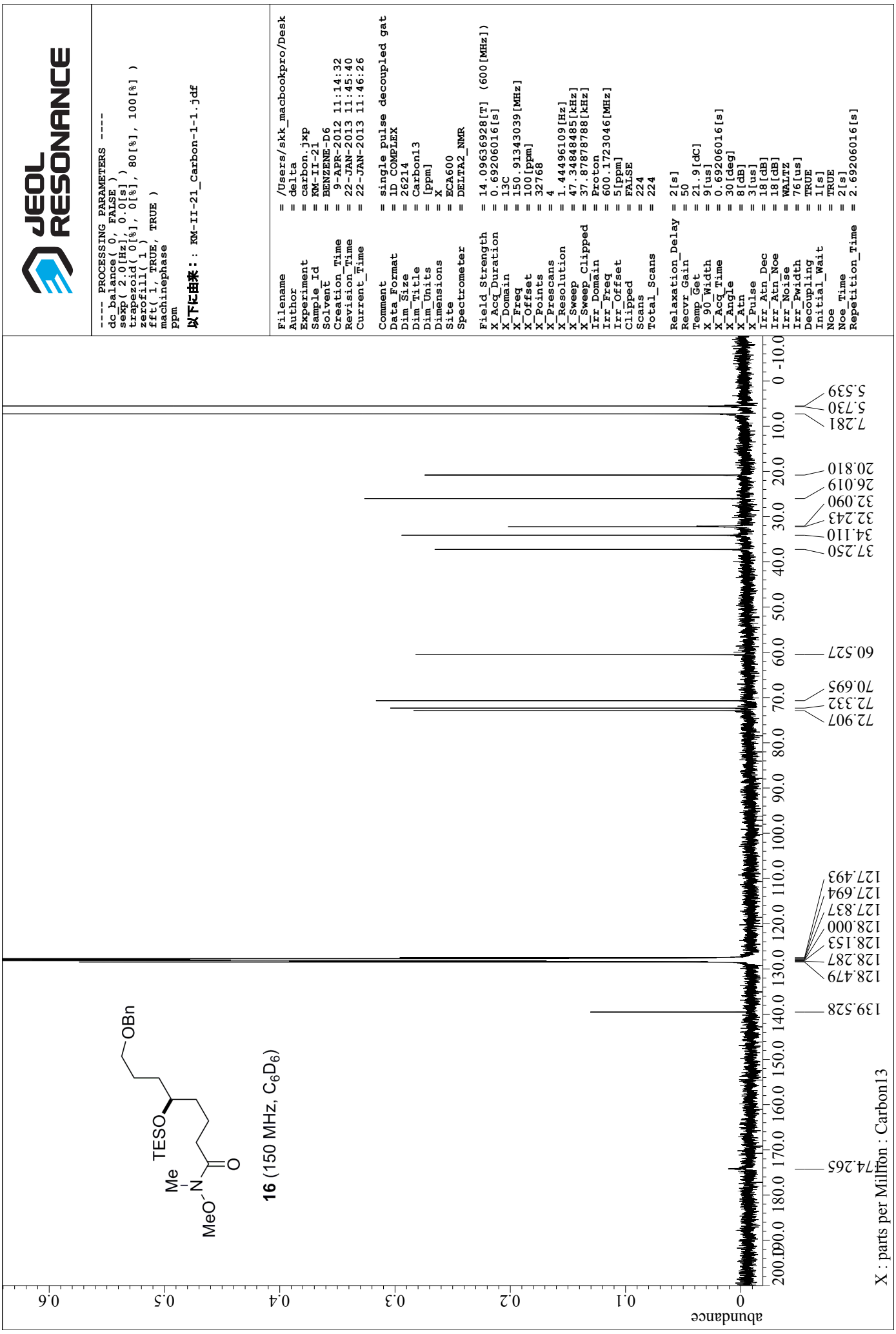


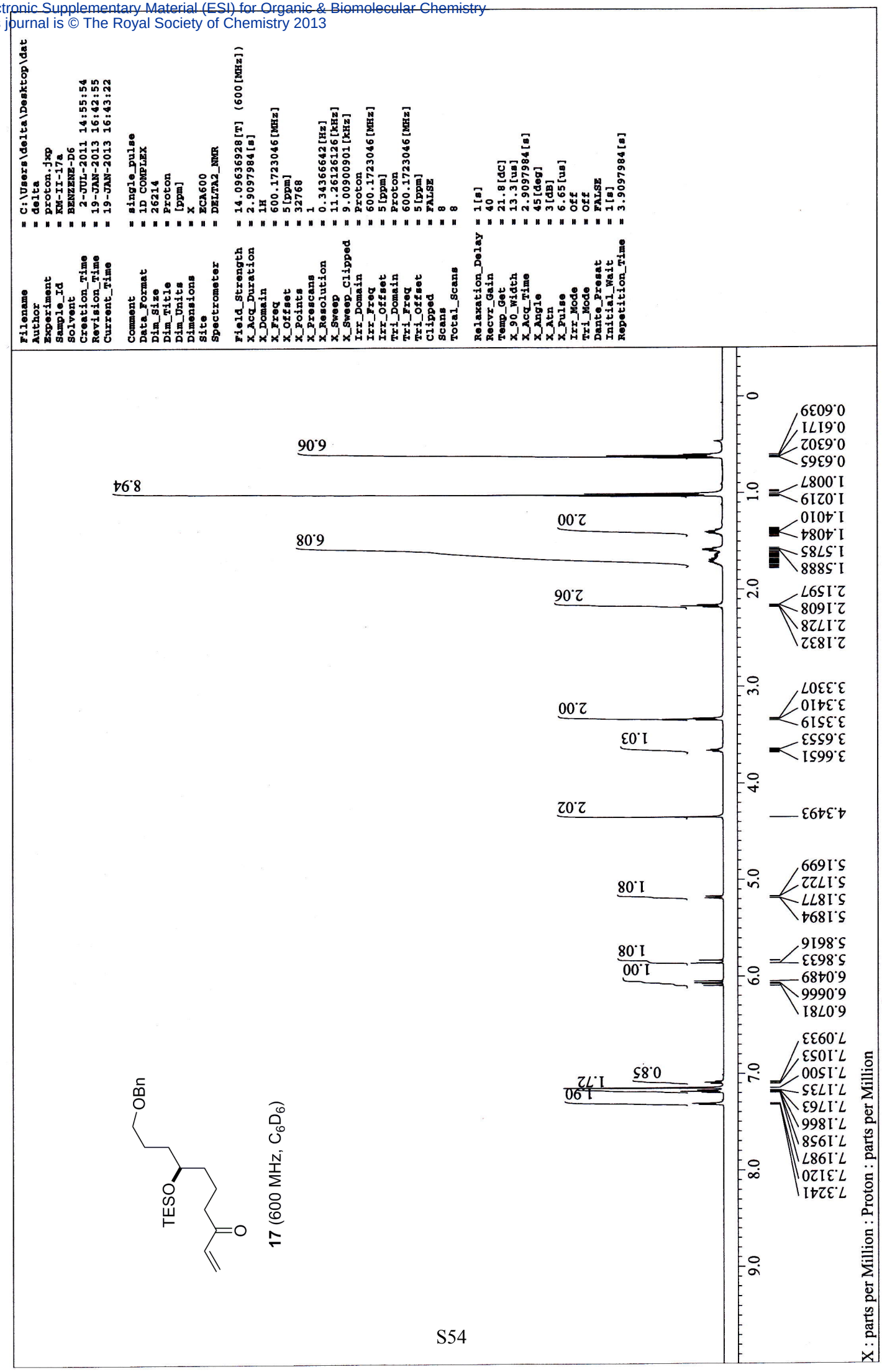


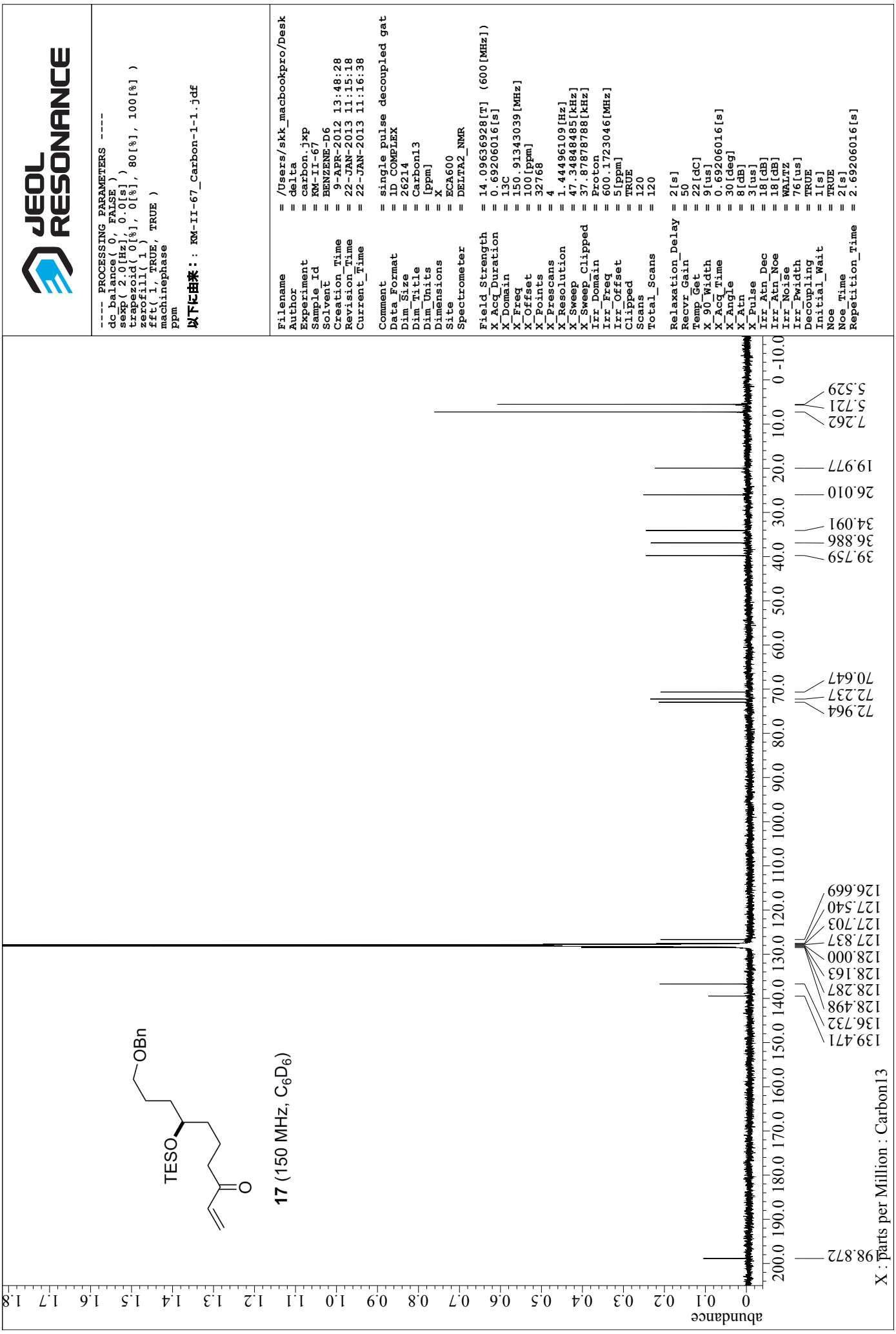


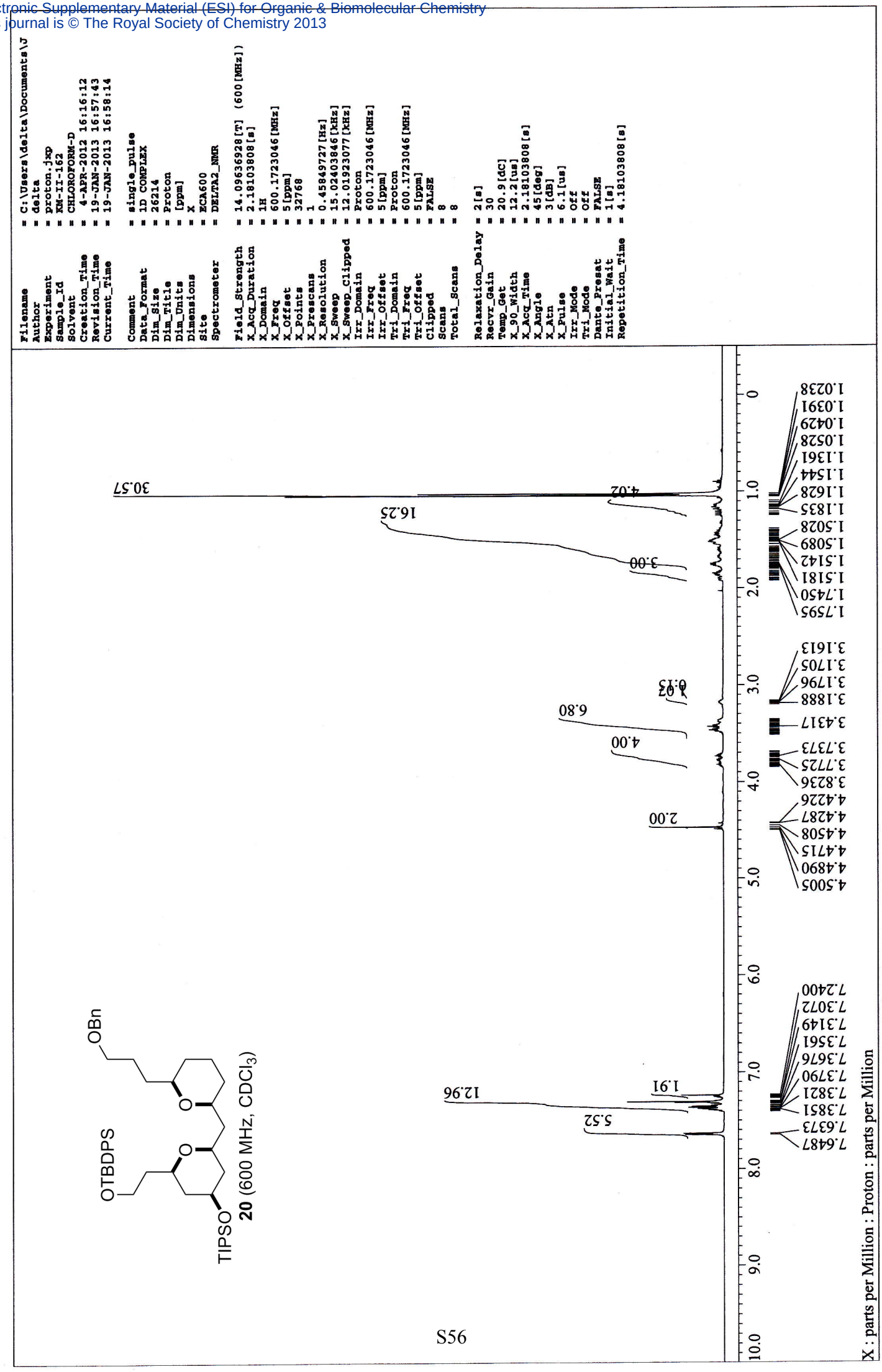


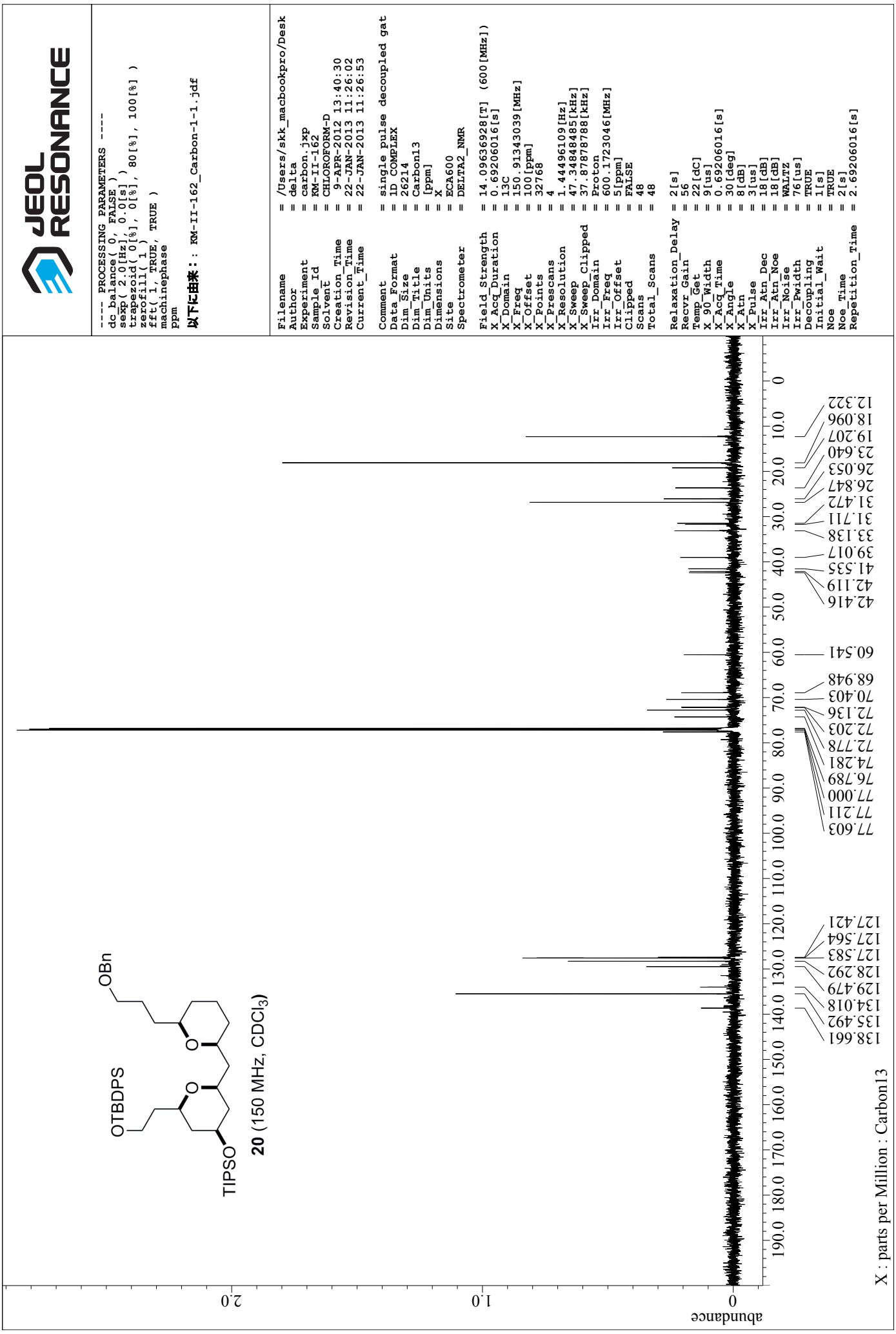








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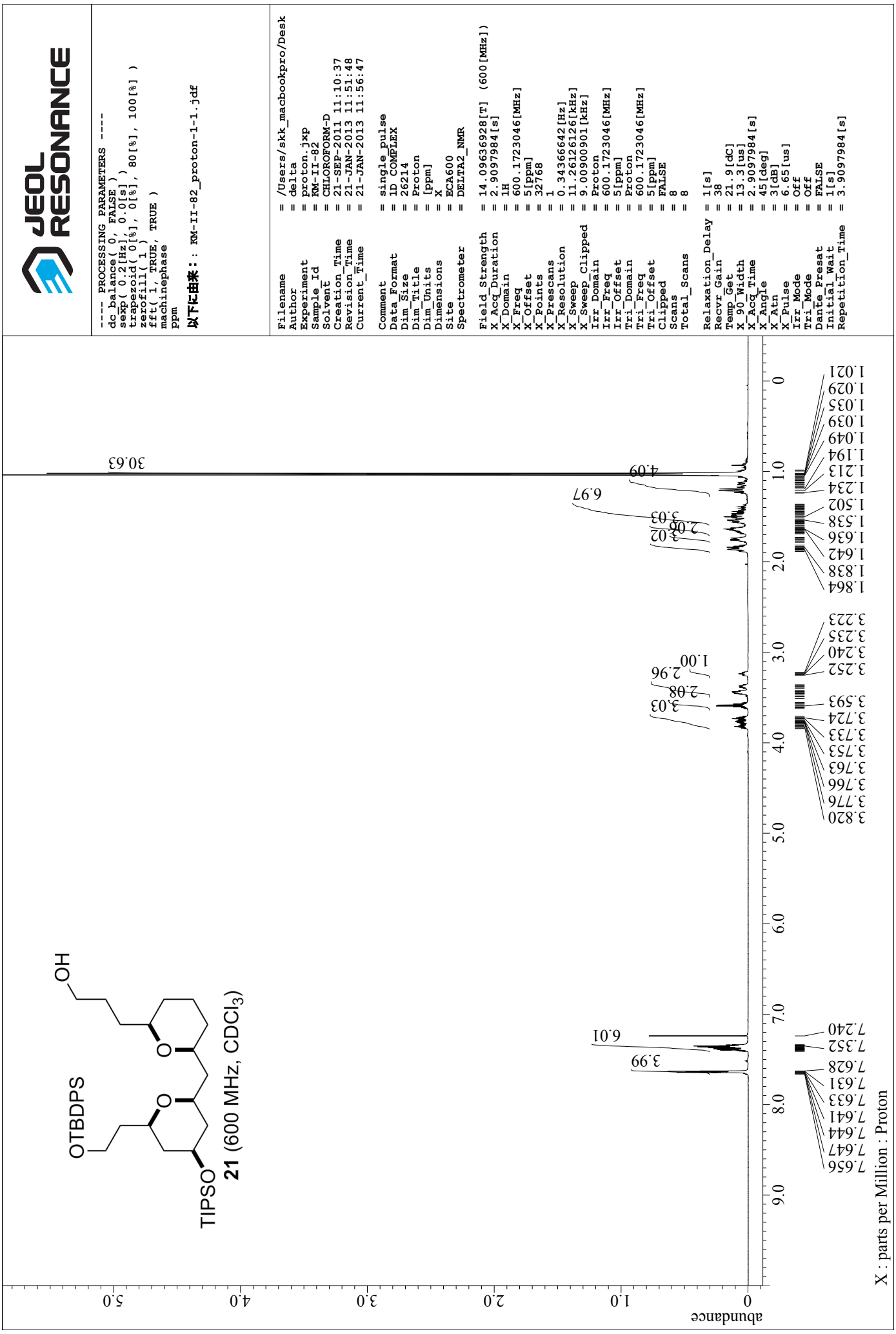

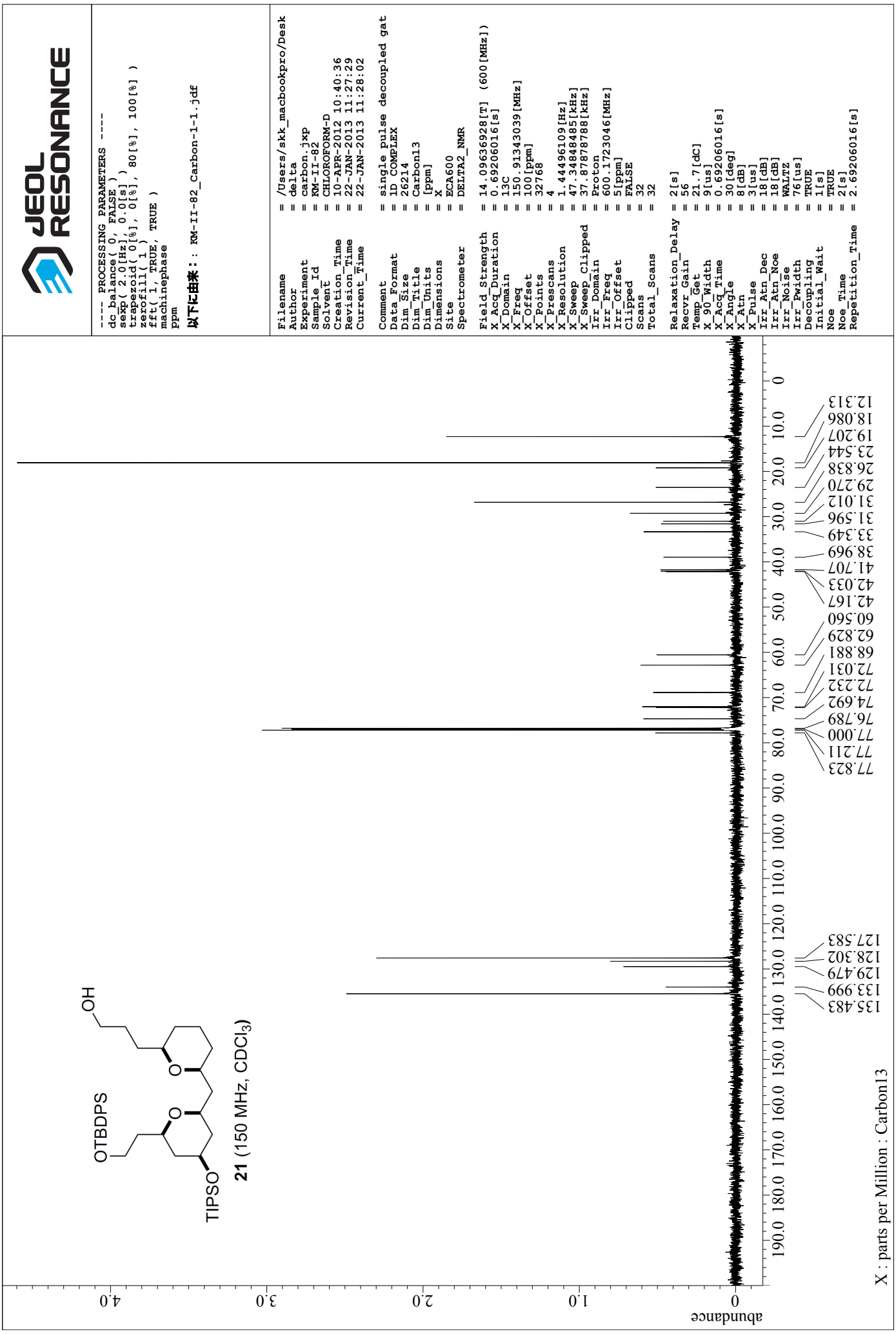

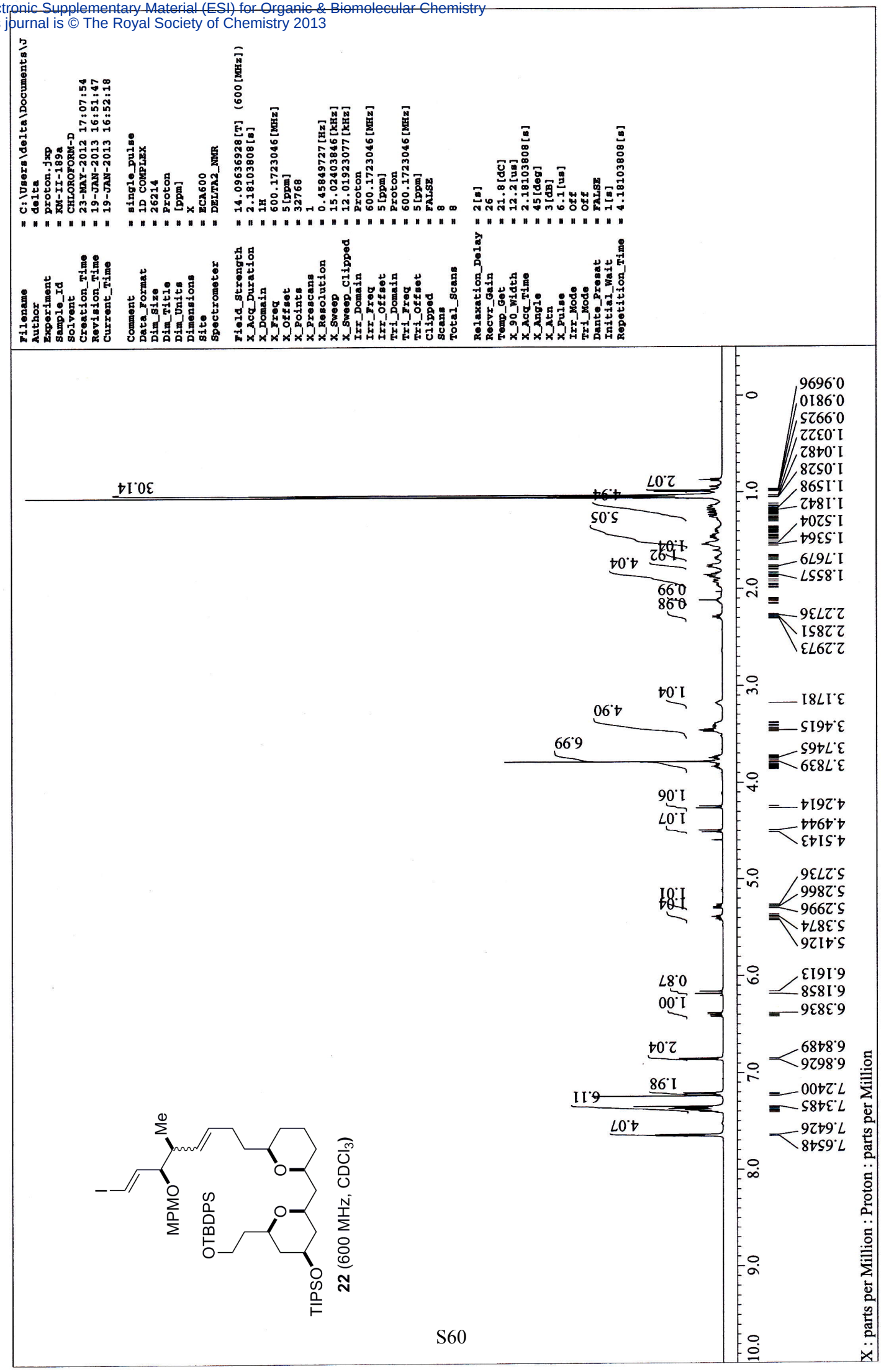

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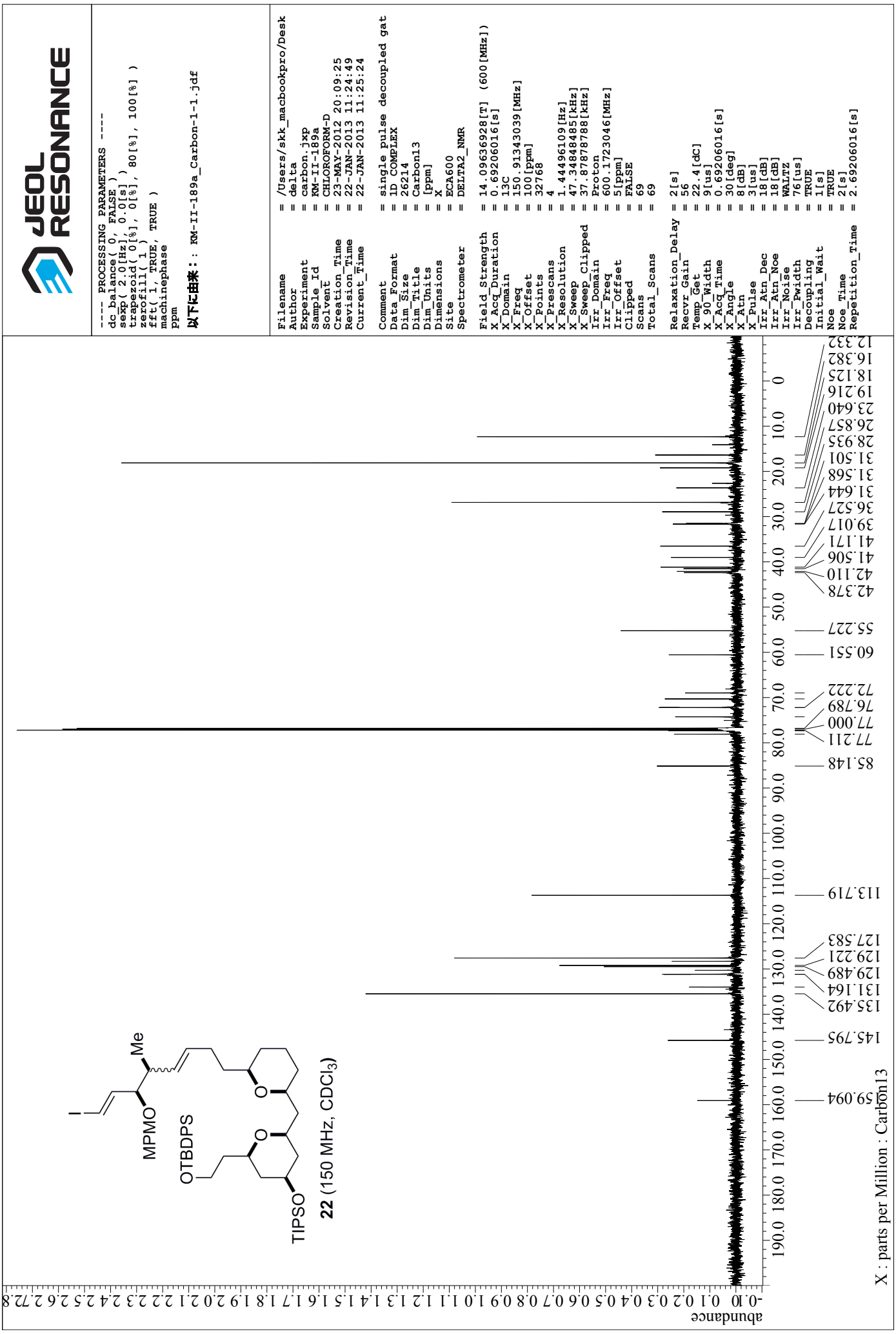
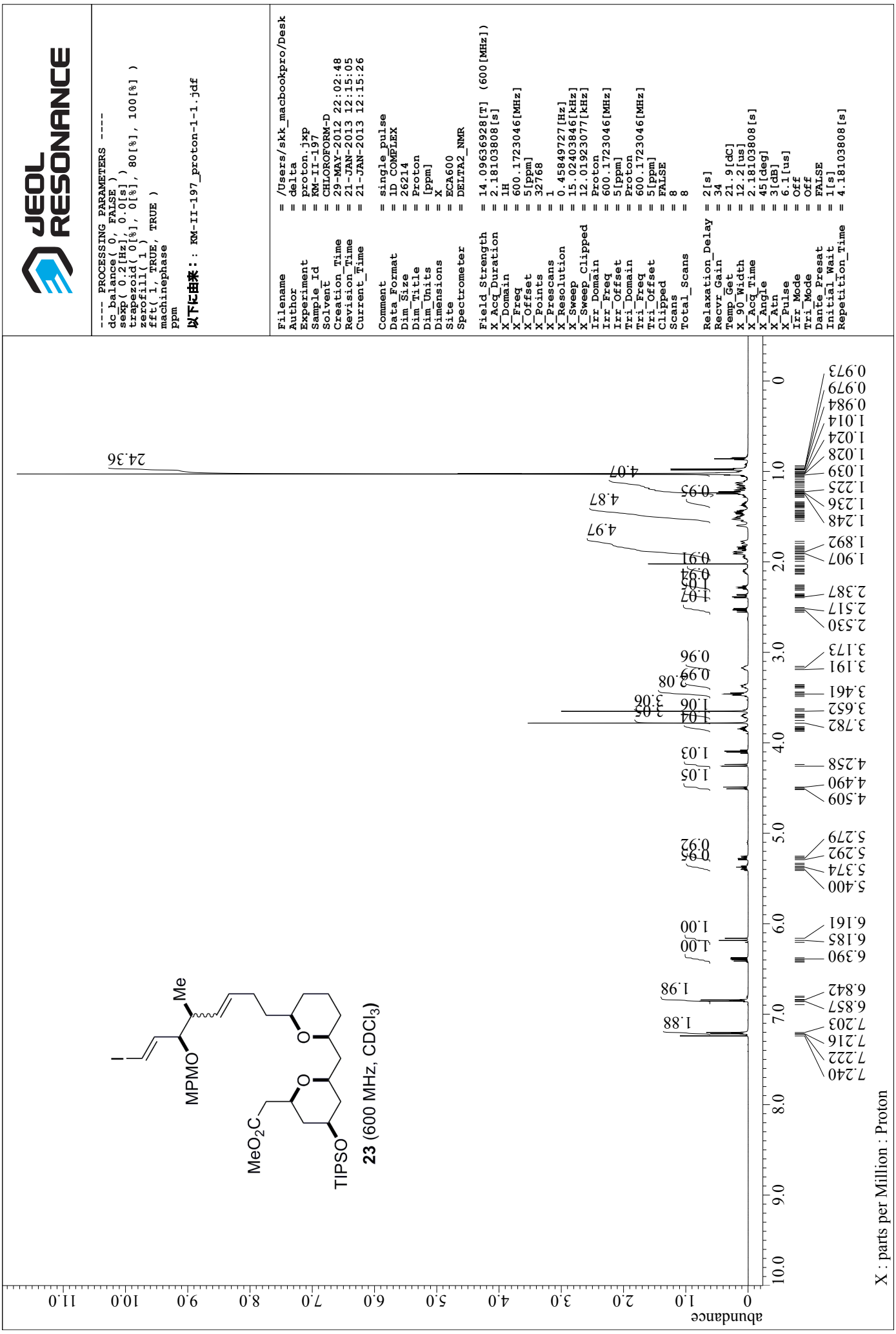
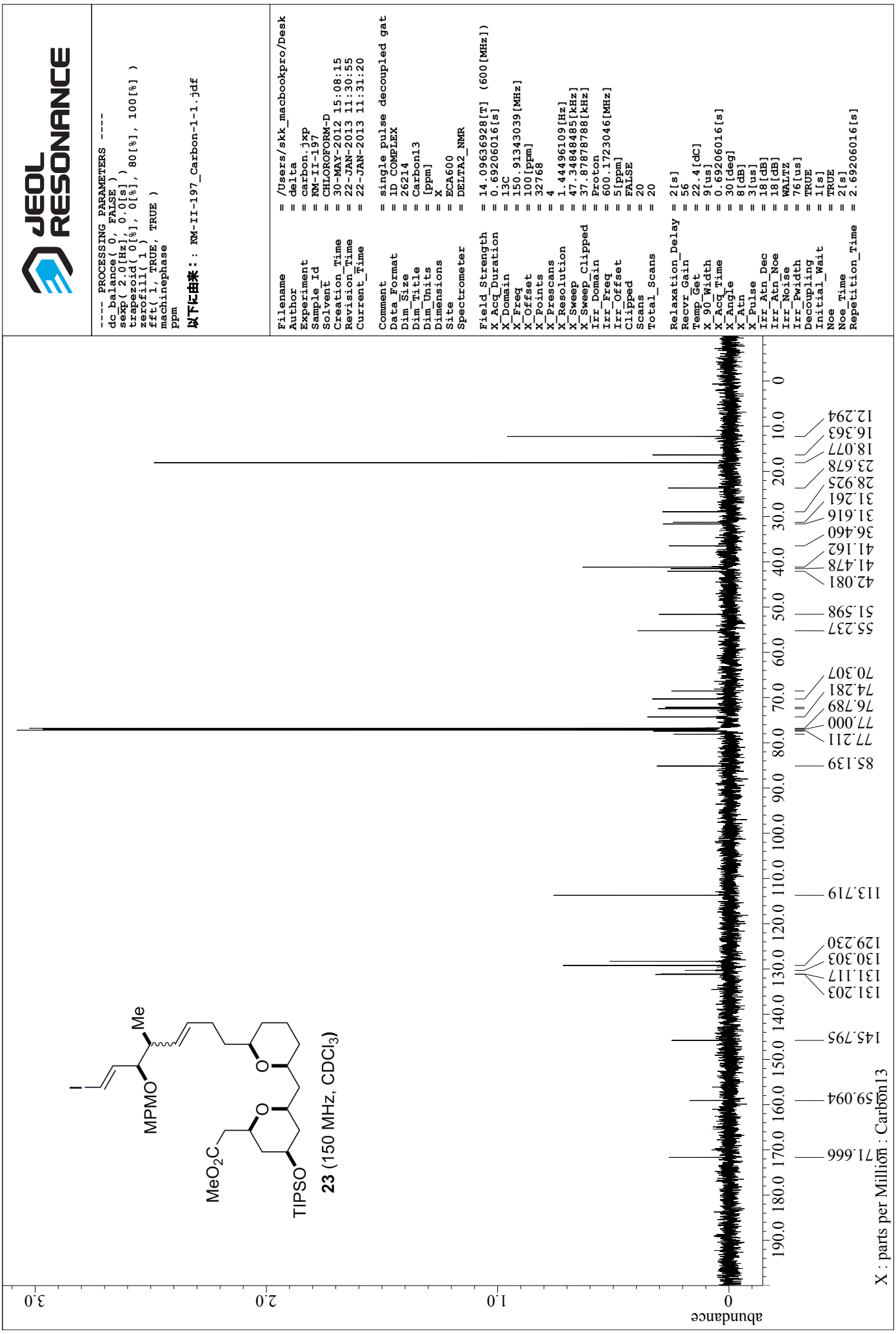
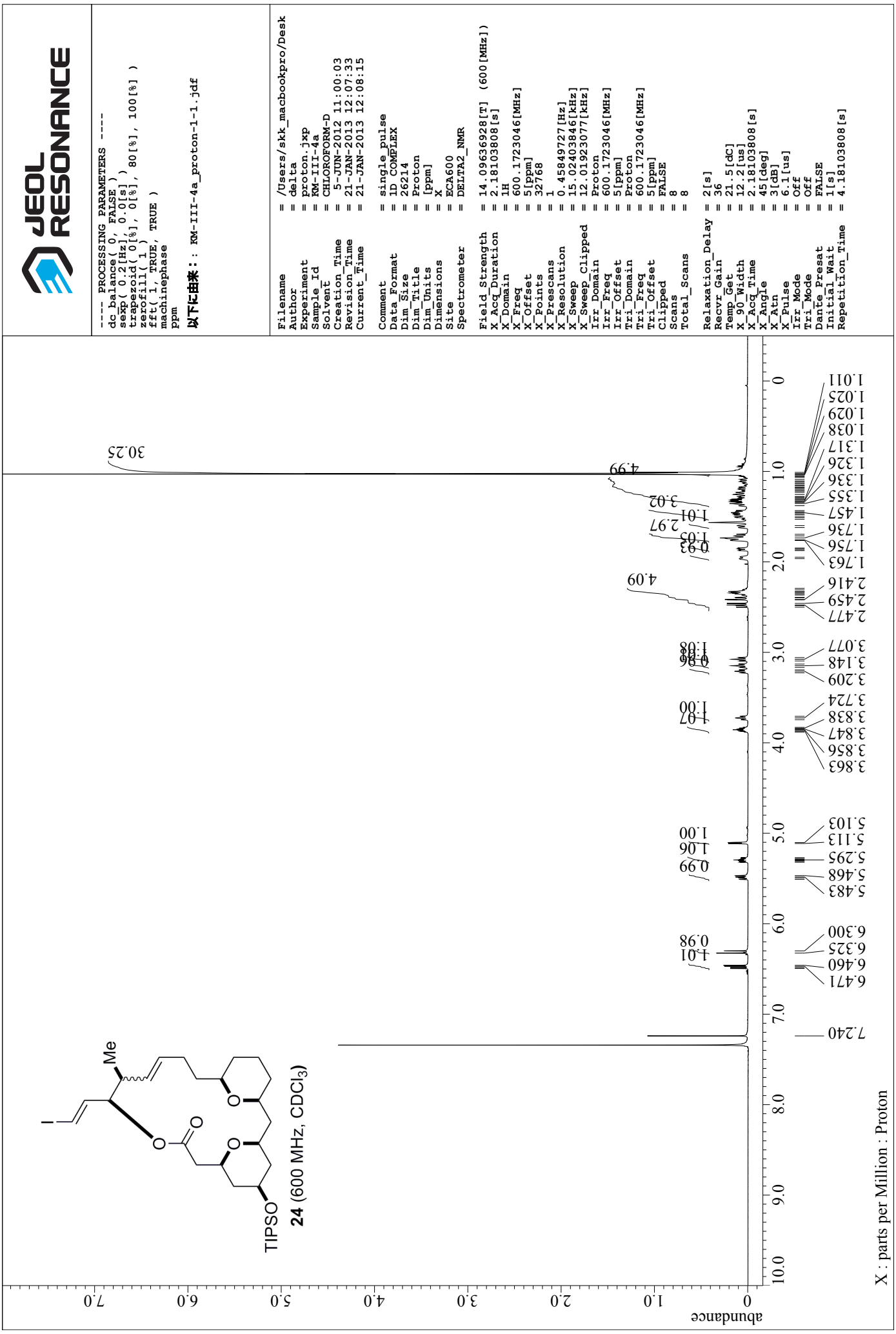
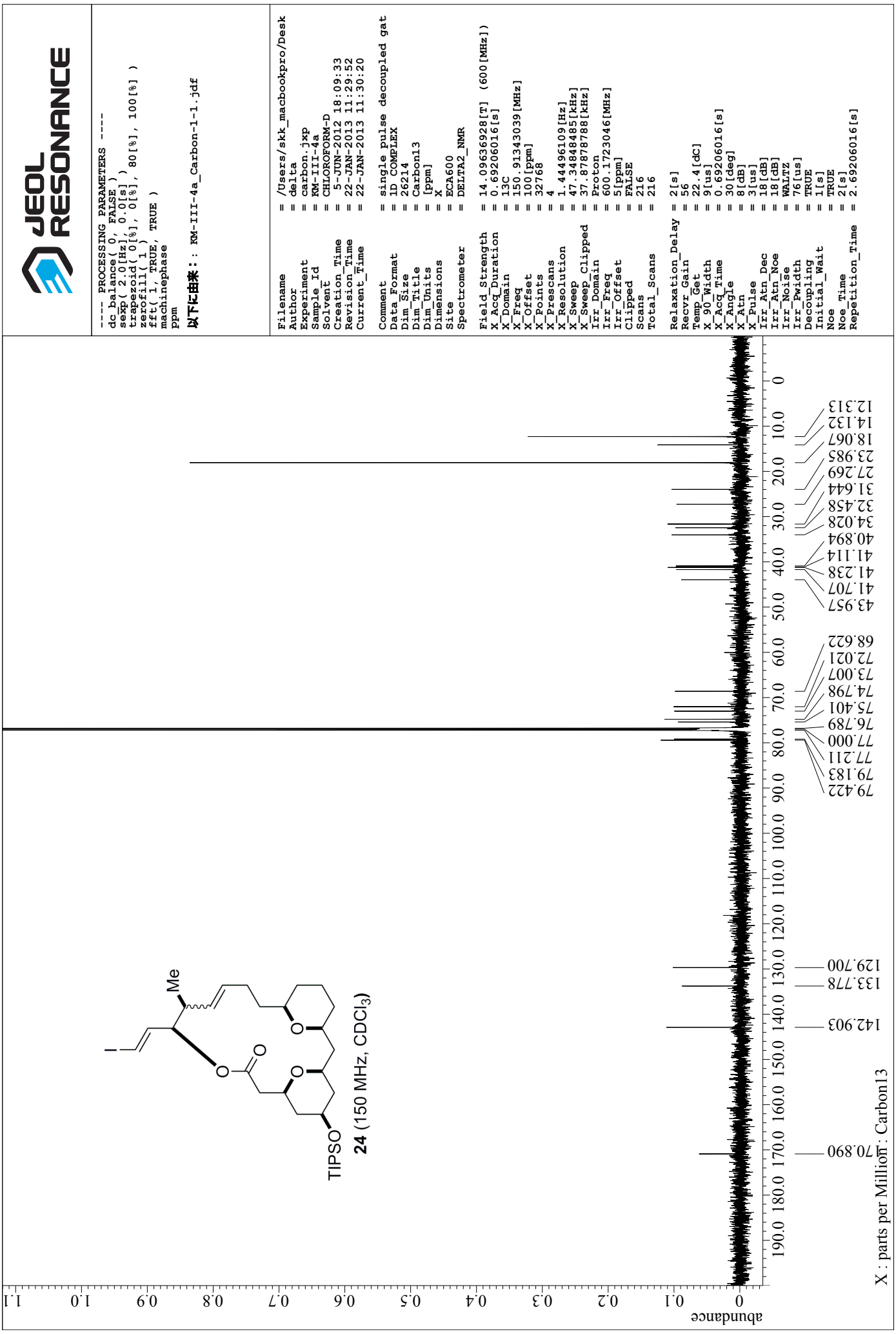
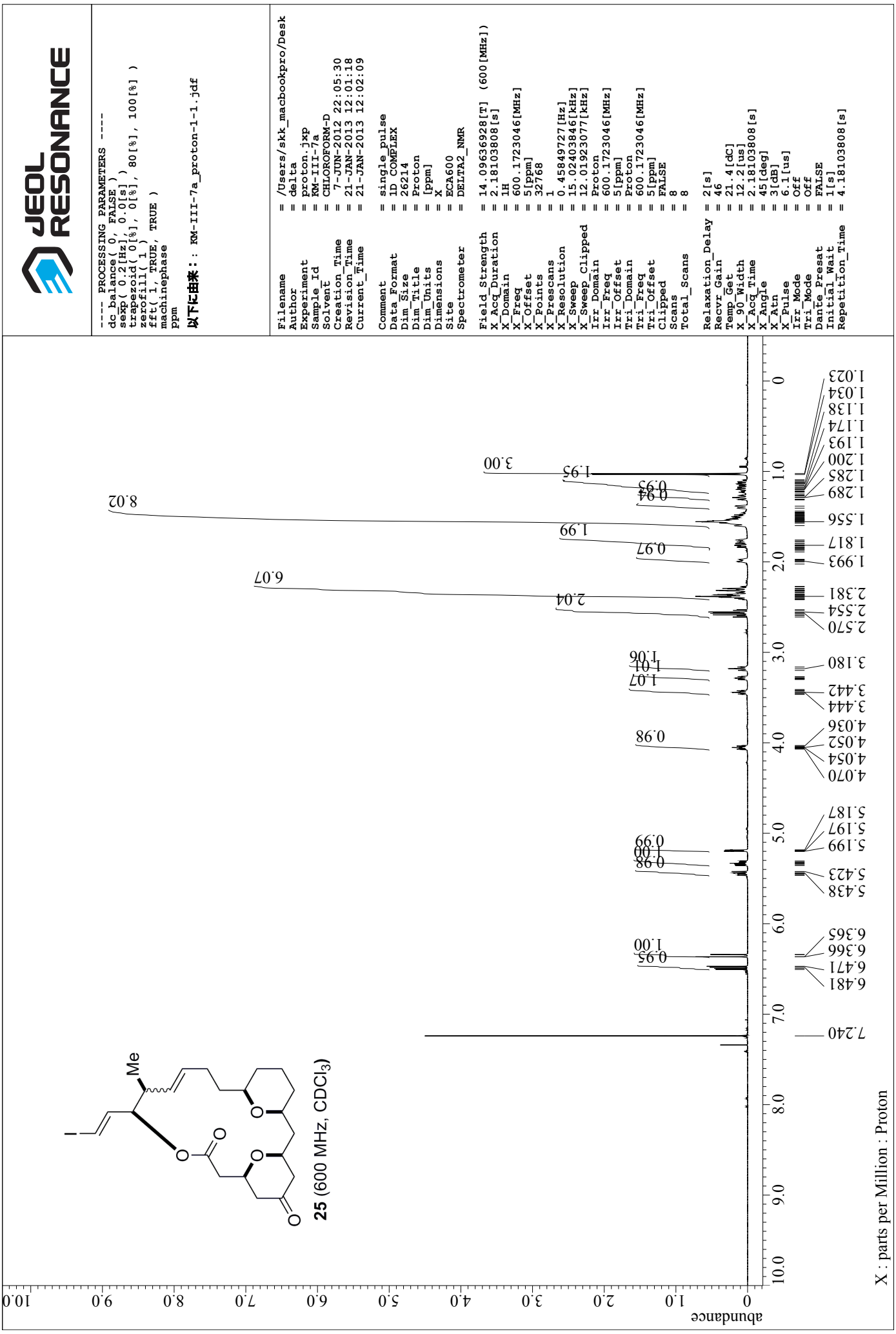


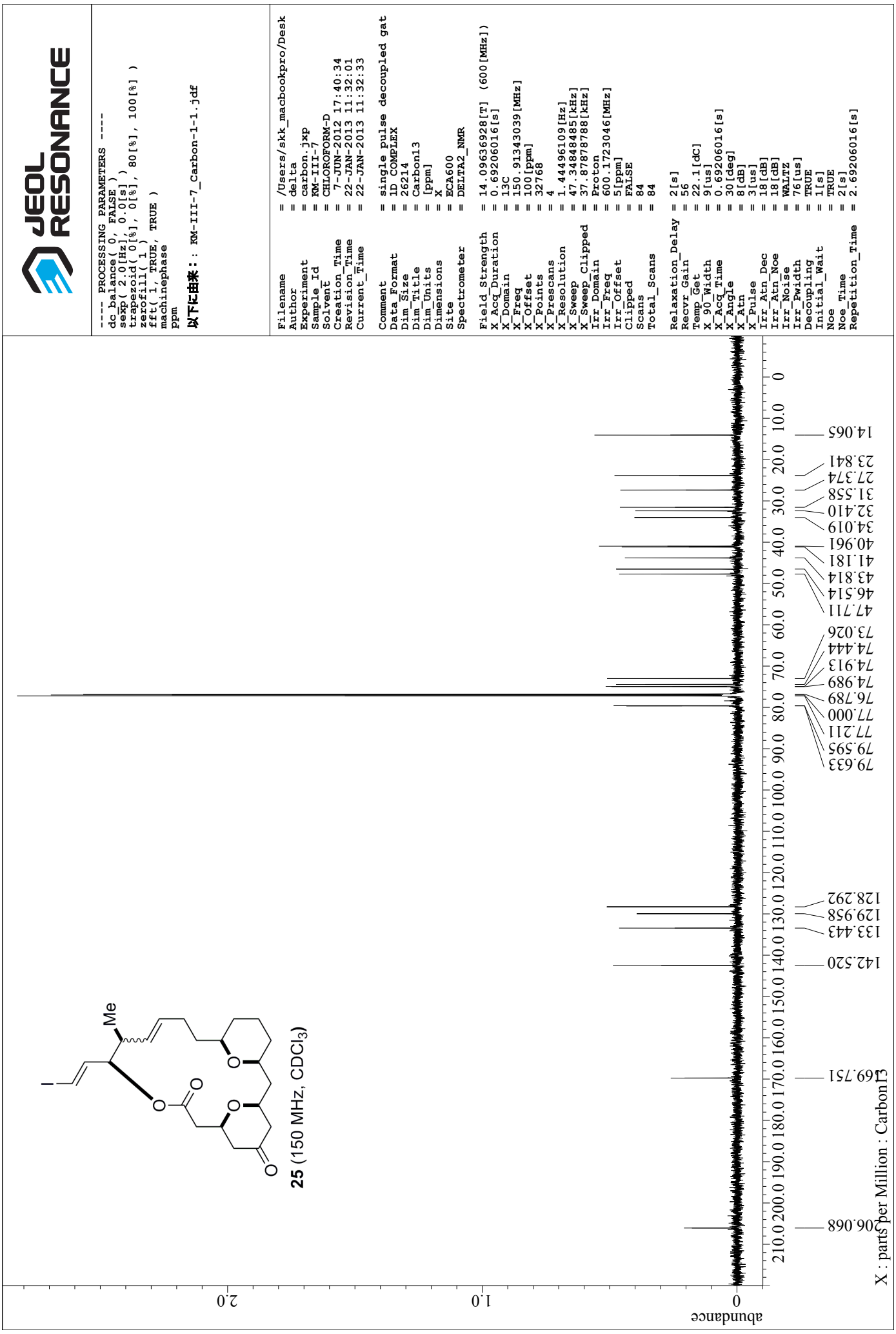


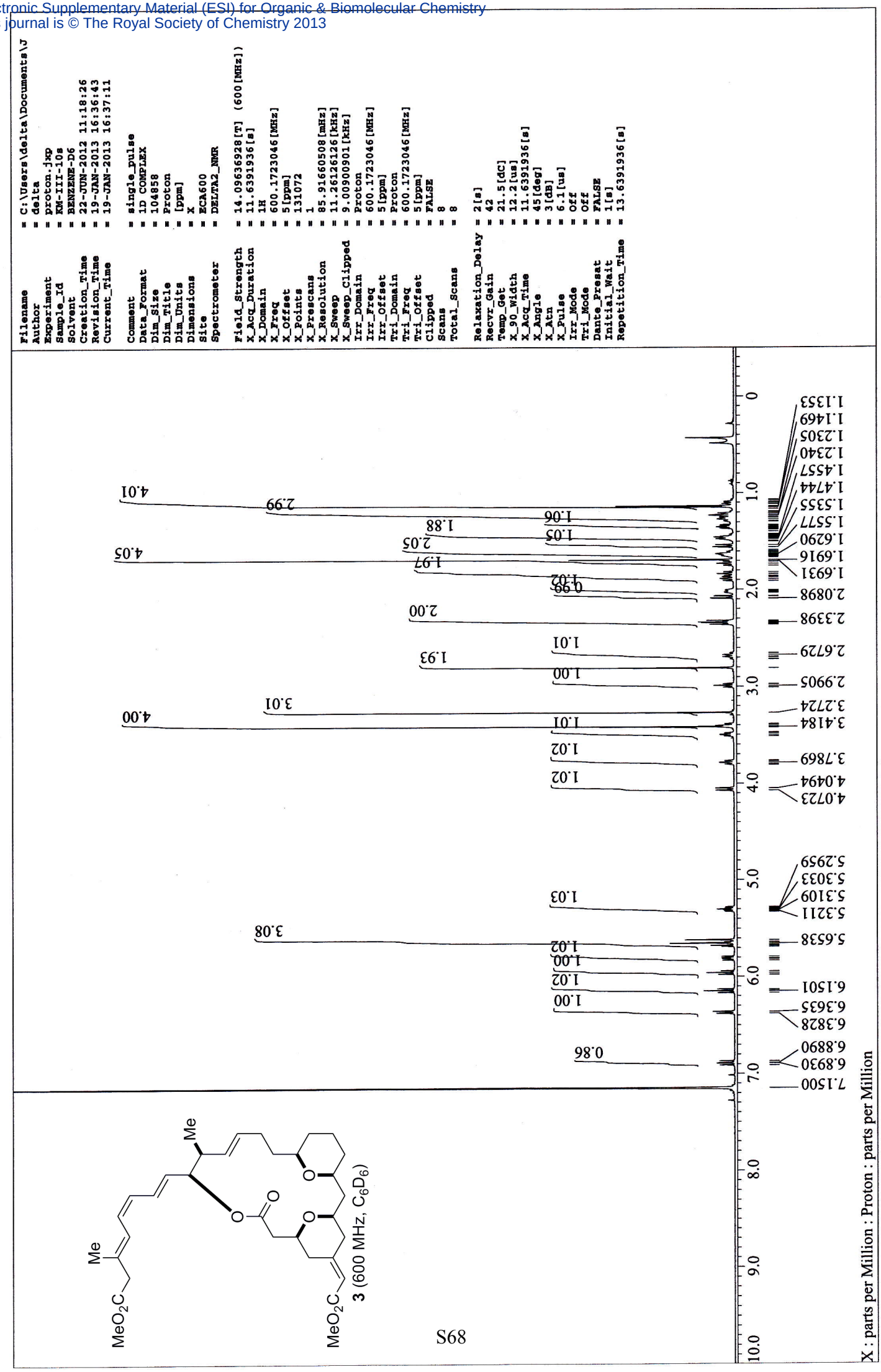


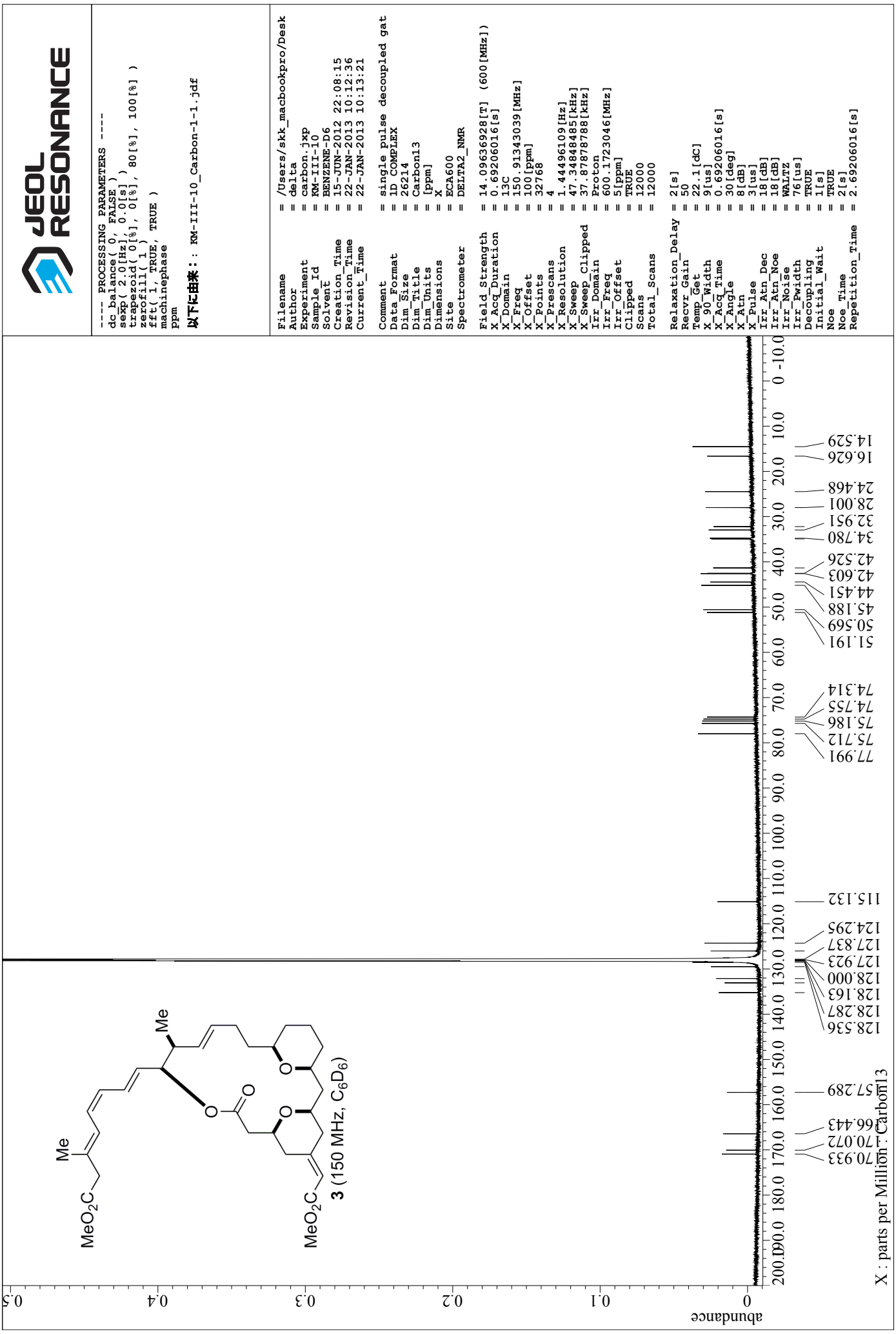


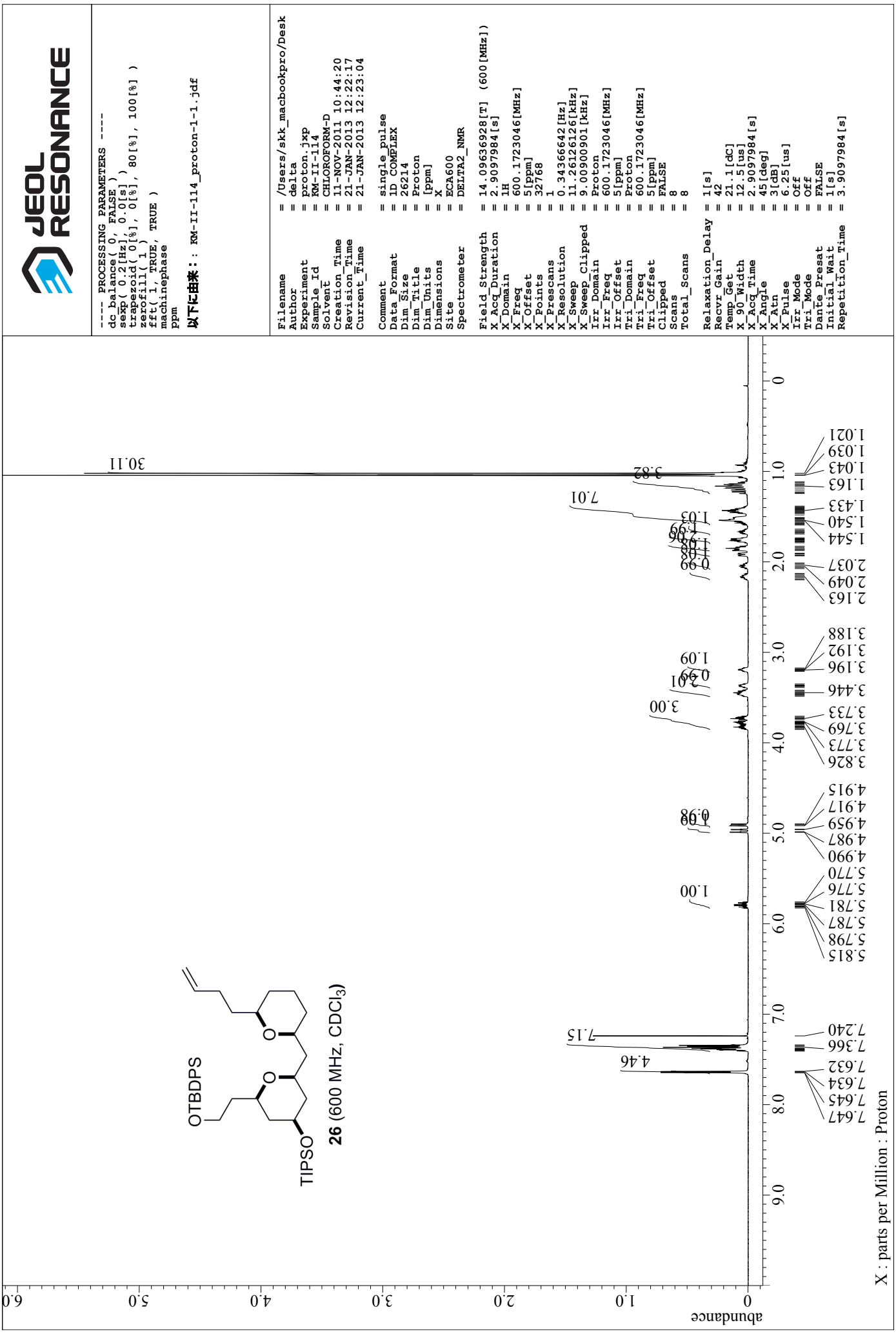


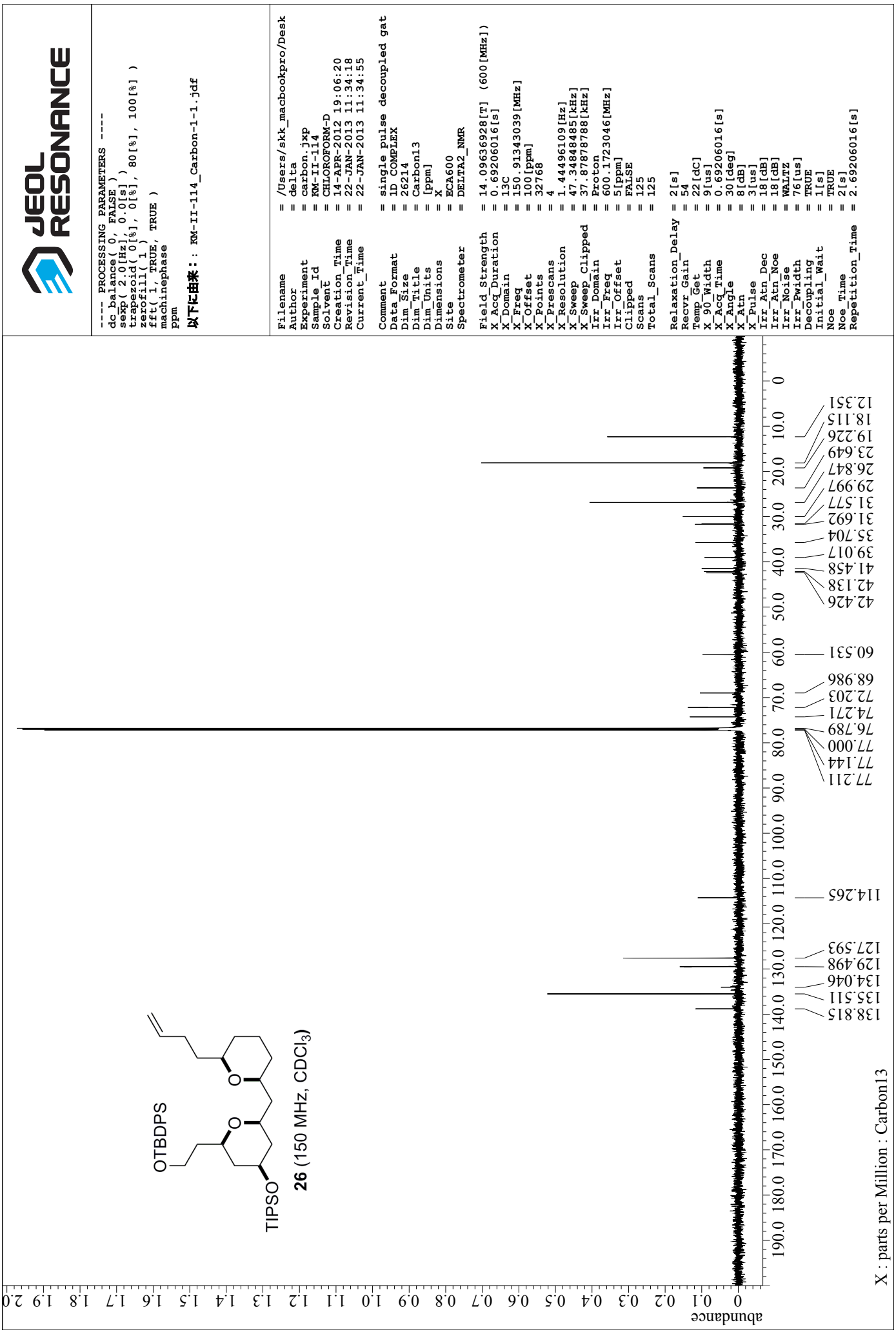


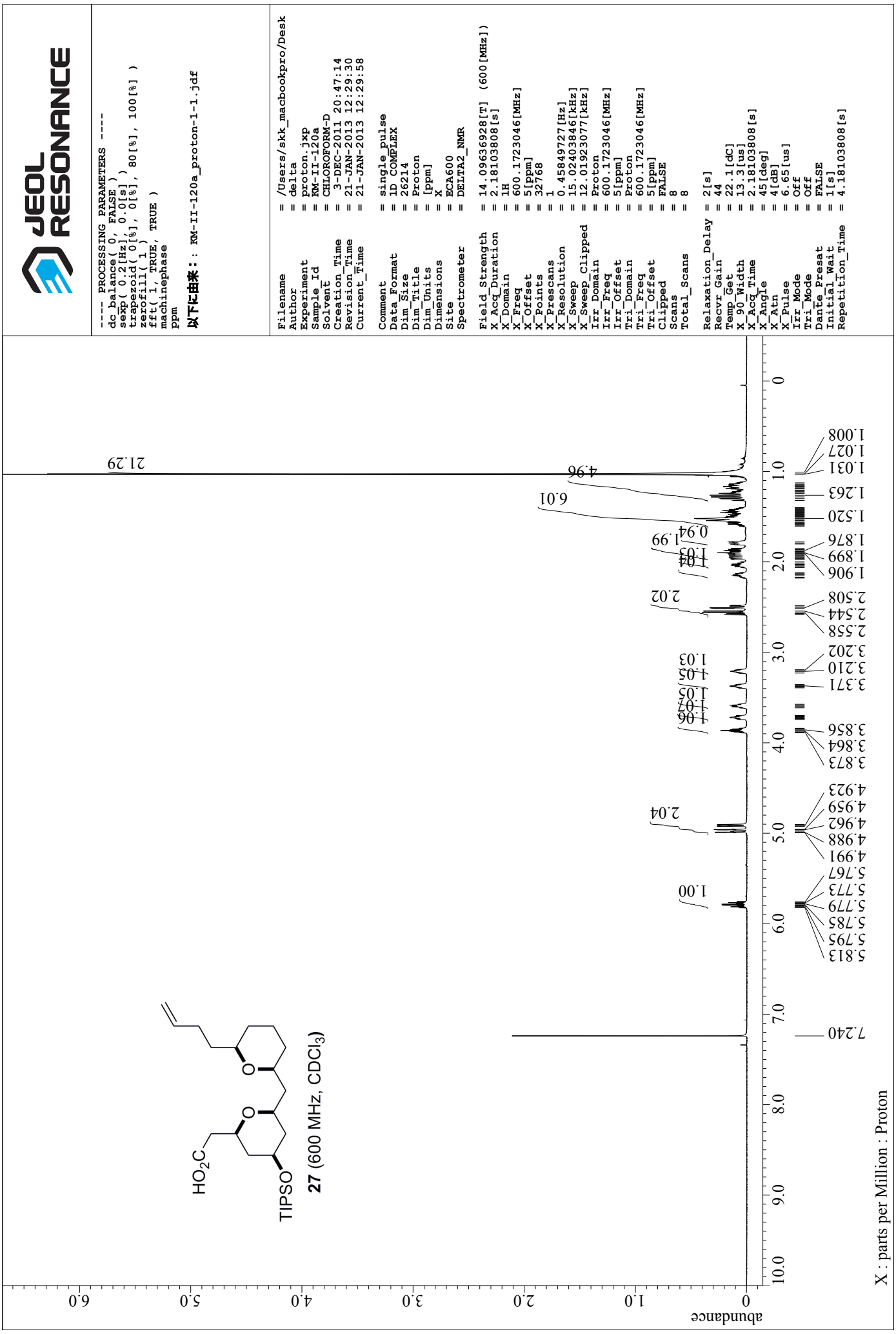


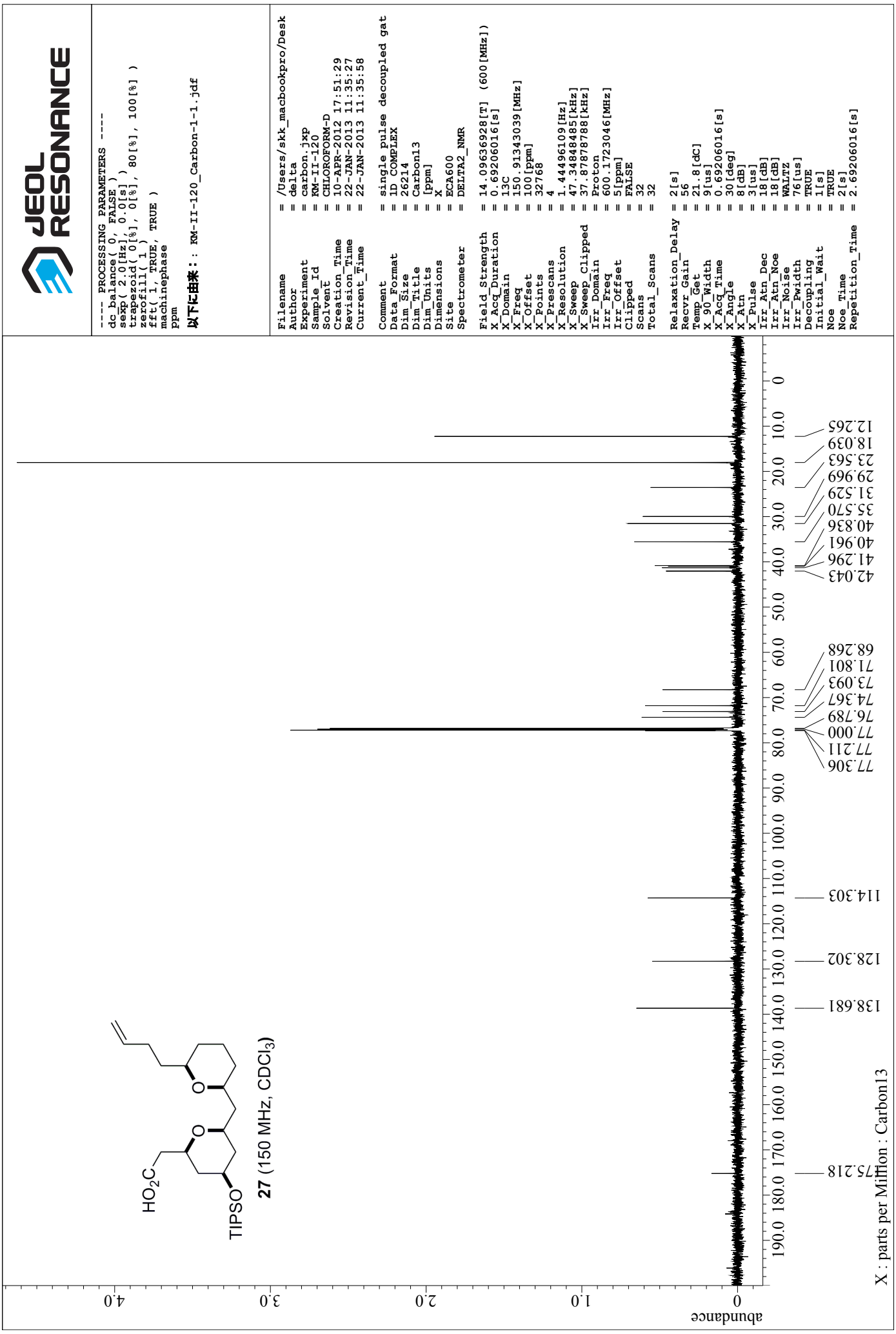




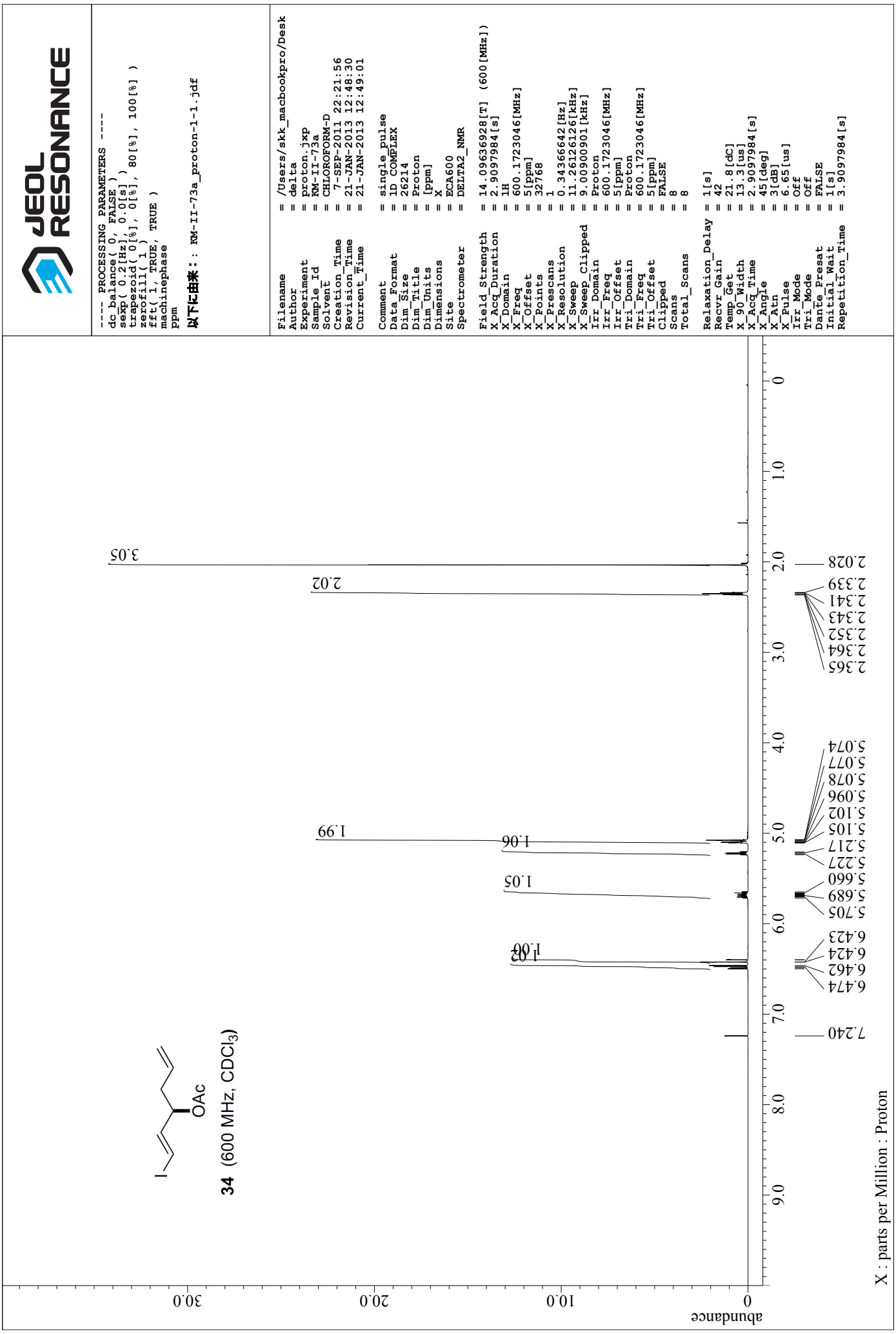


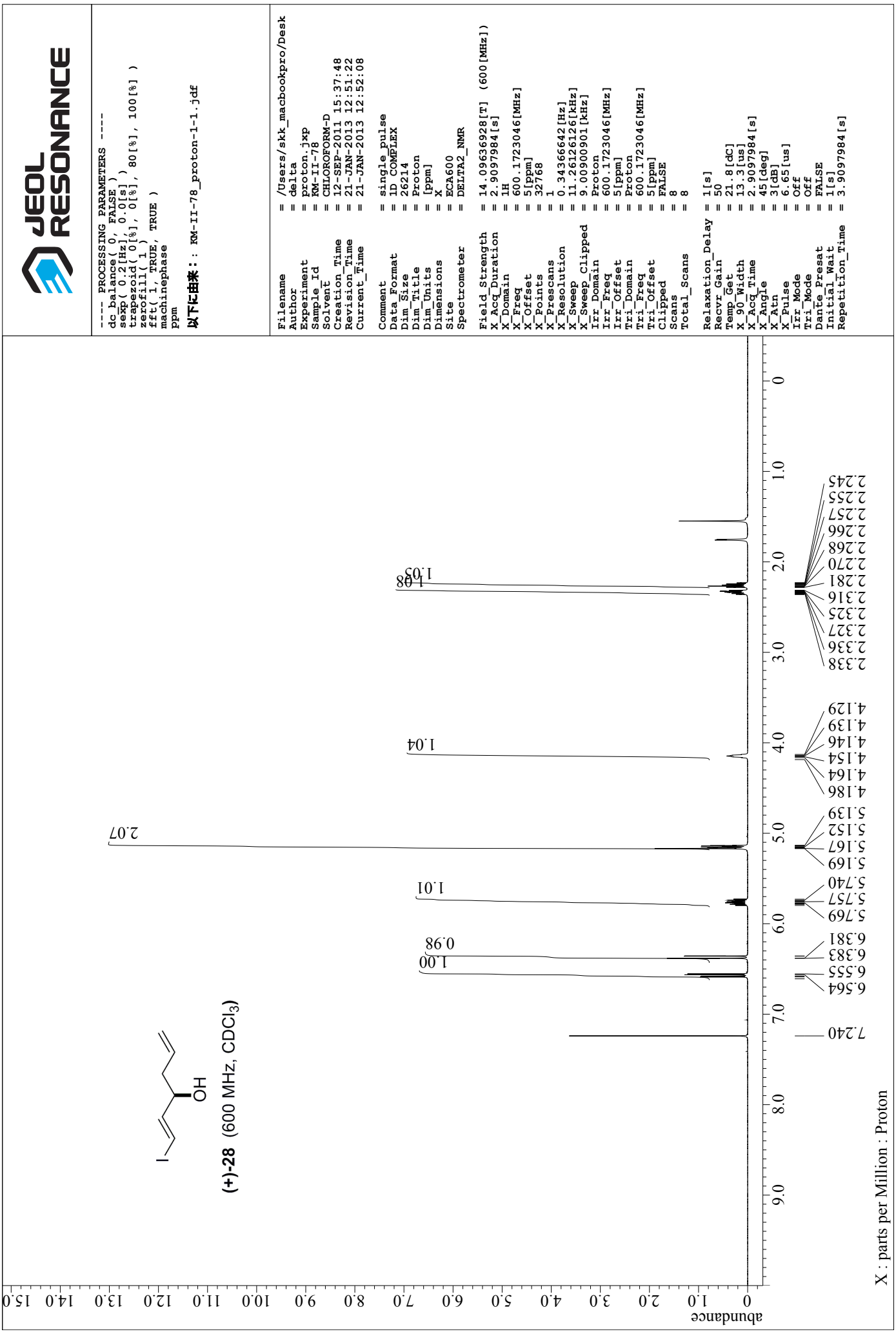


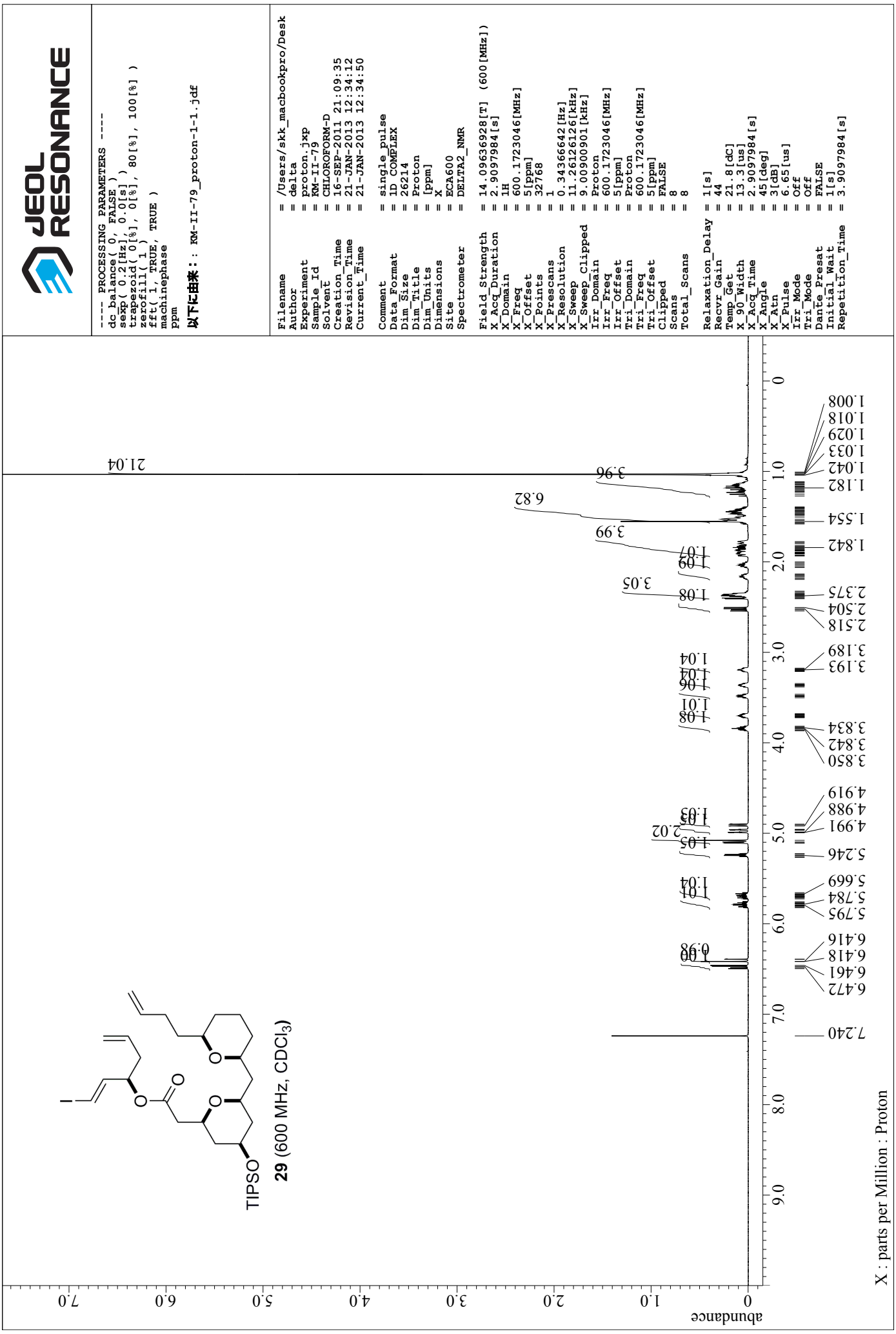


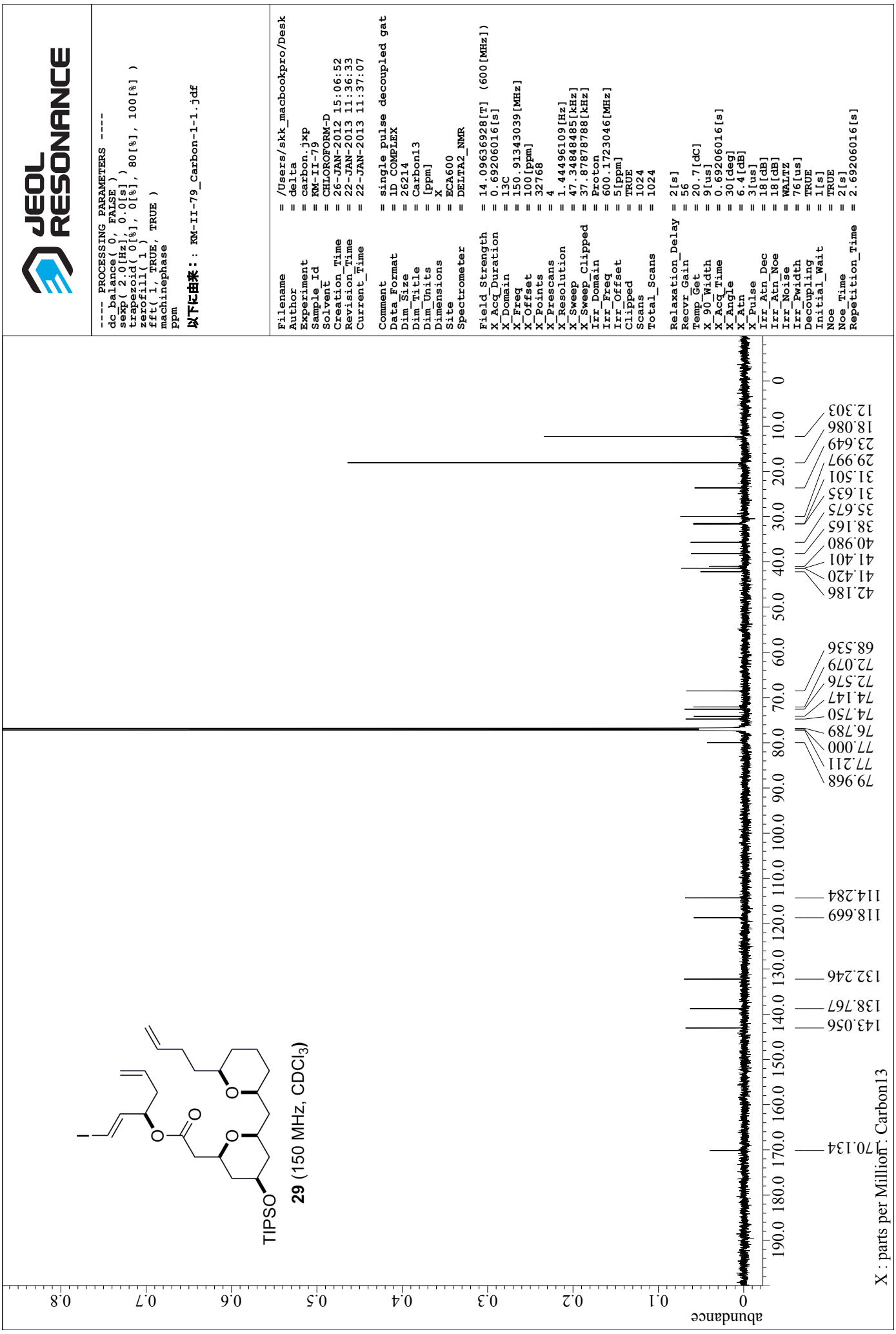


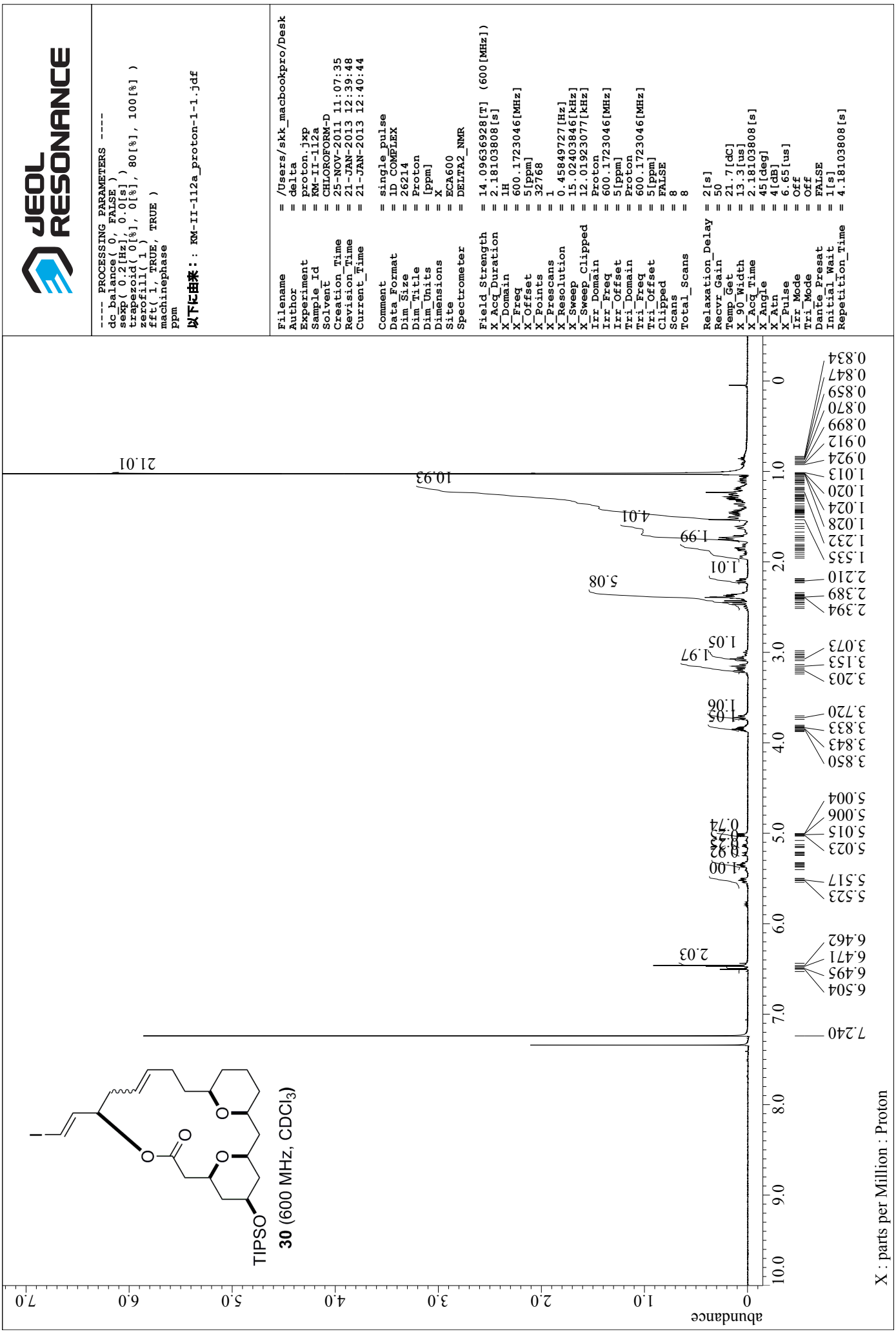
27 (150 MHz, $CDCl_3$)

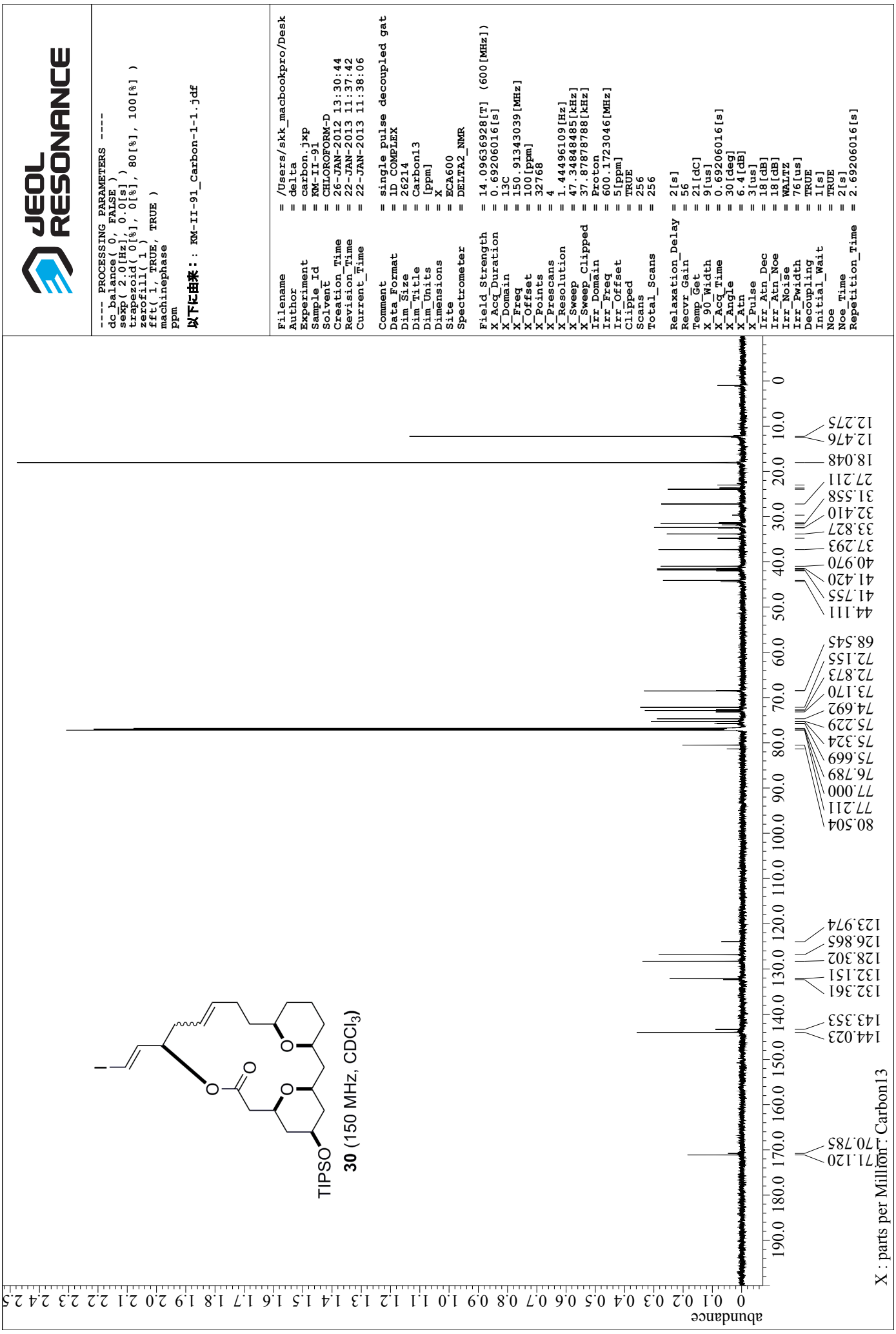


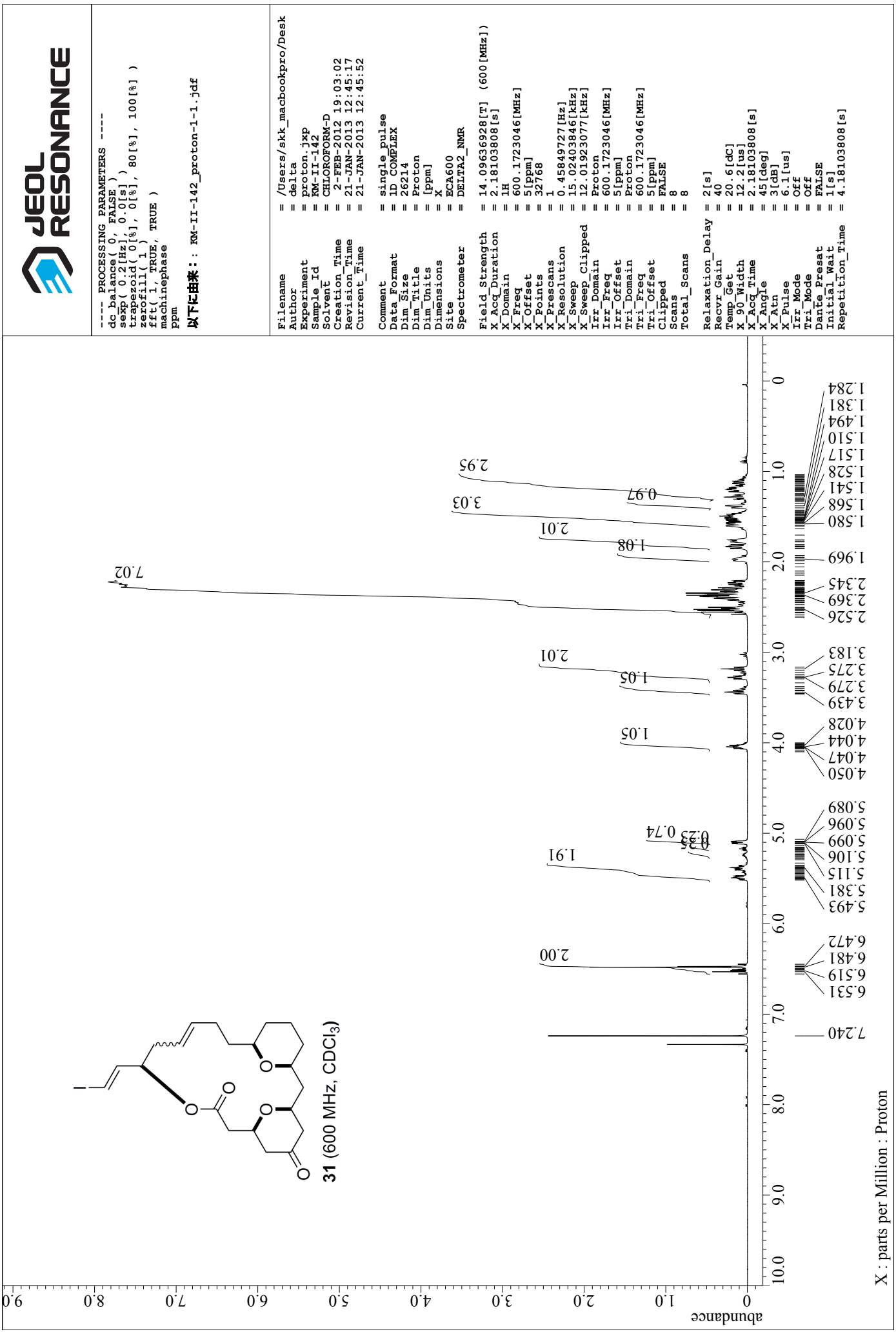


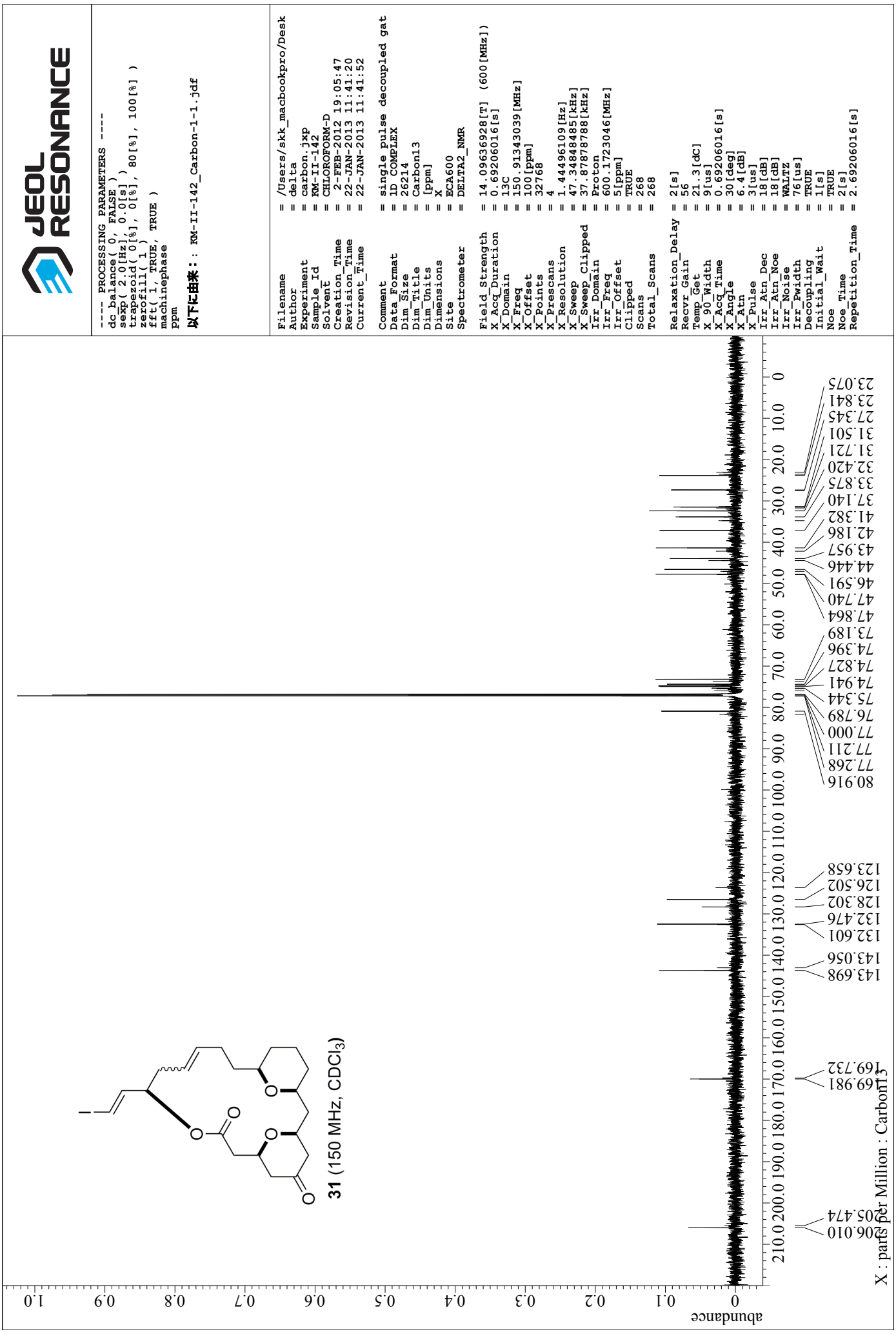


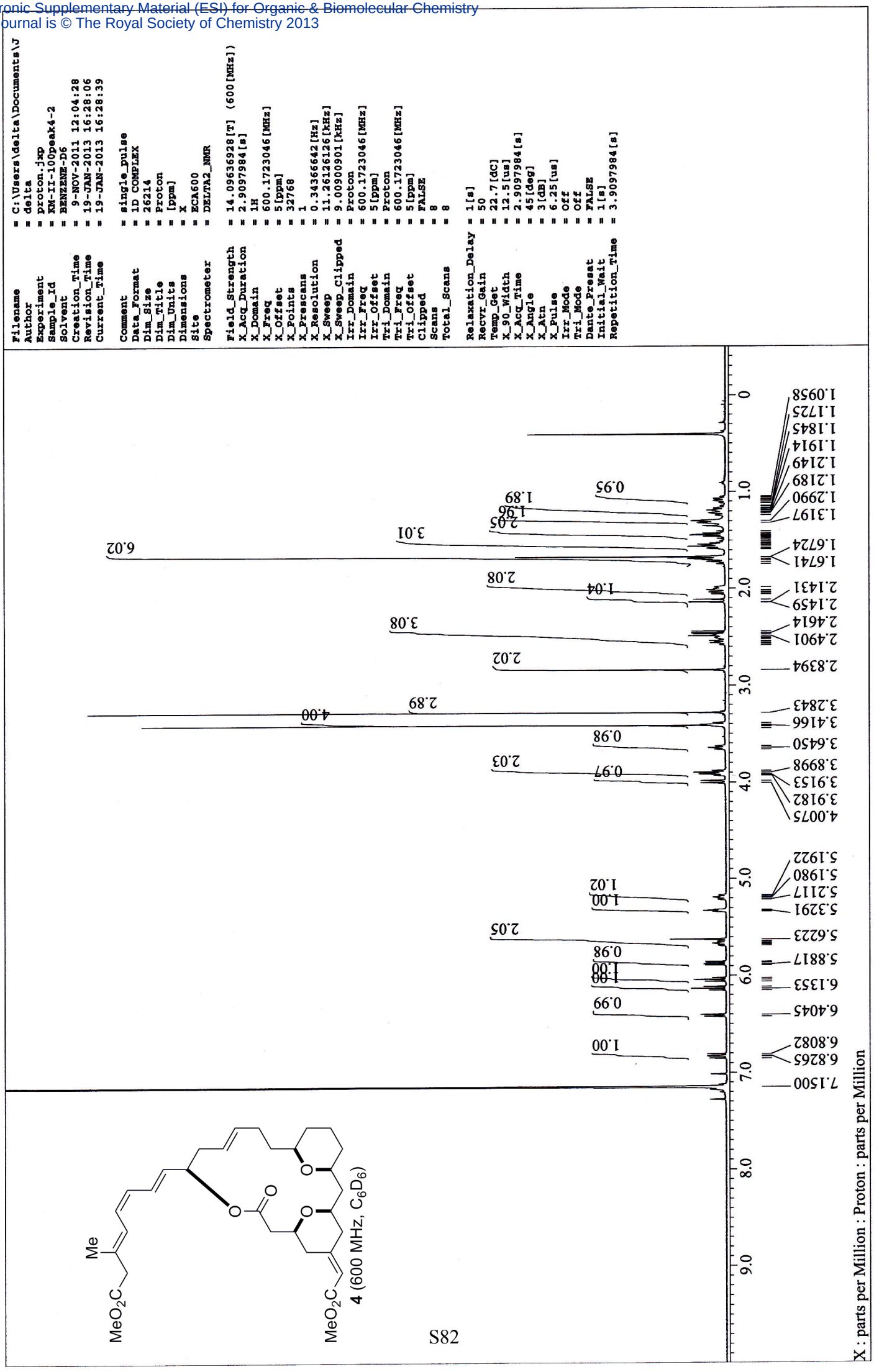


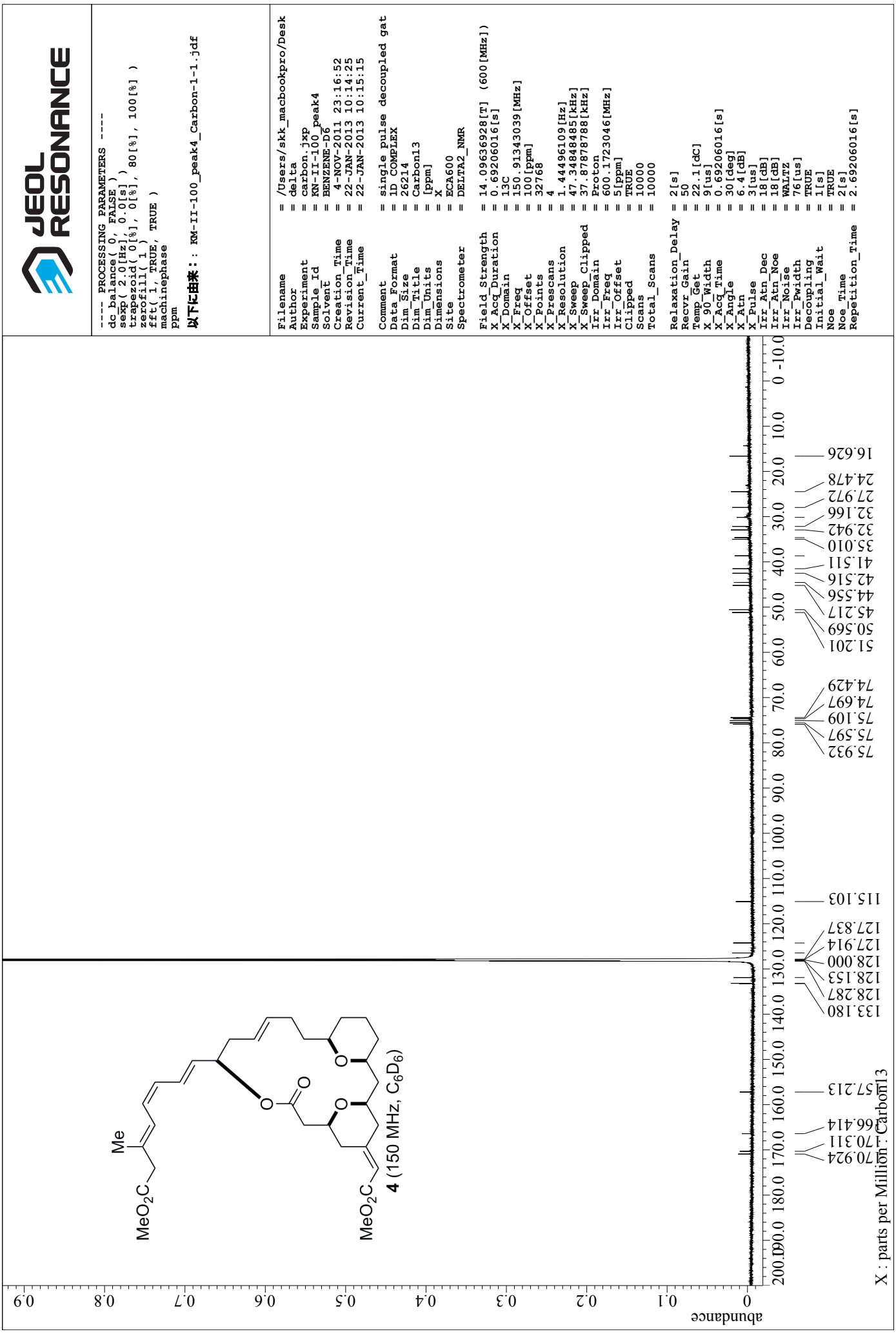


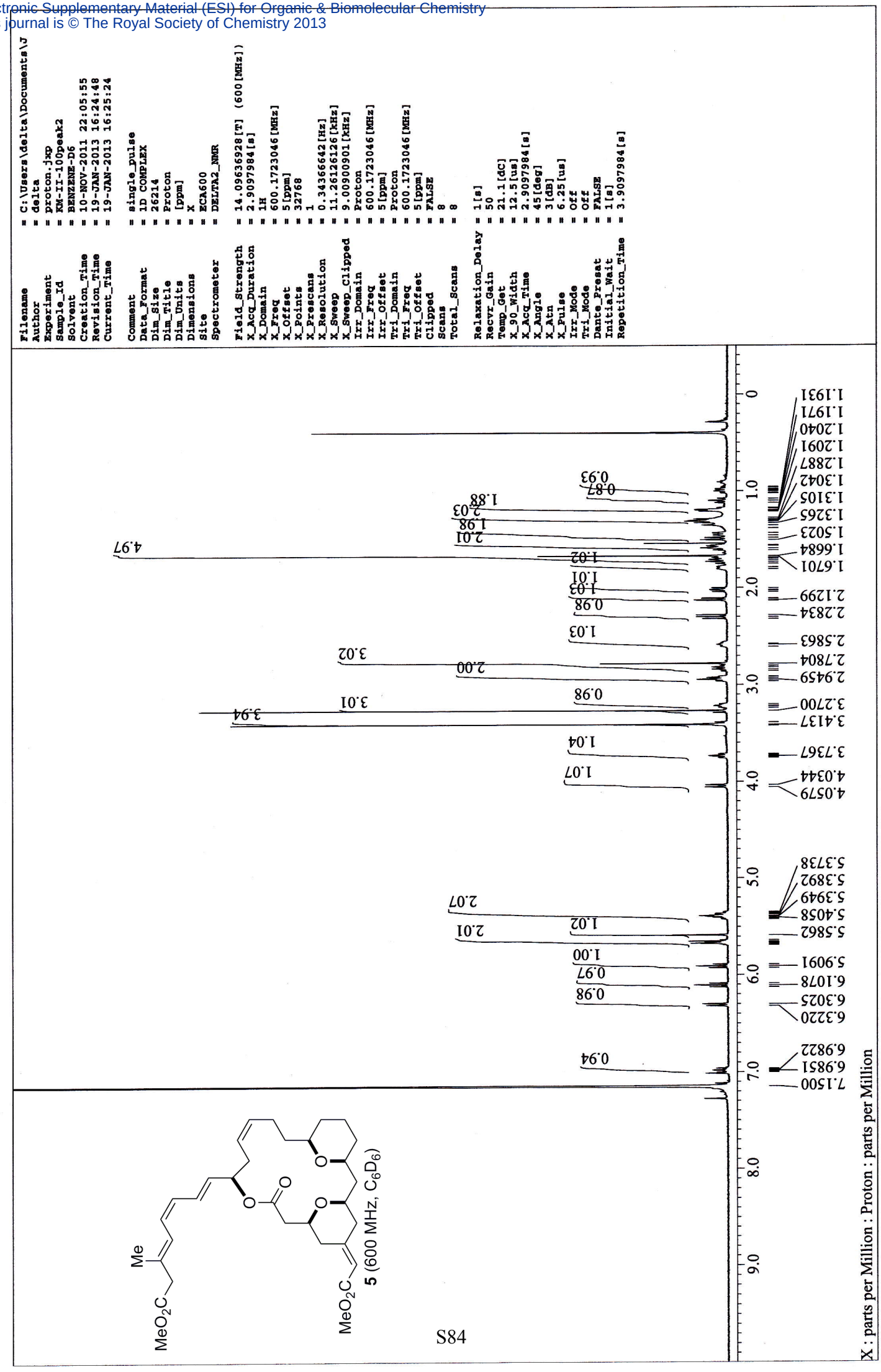


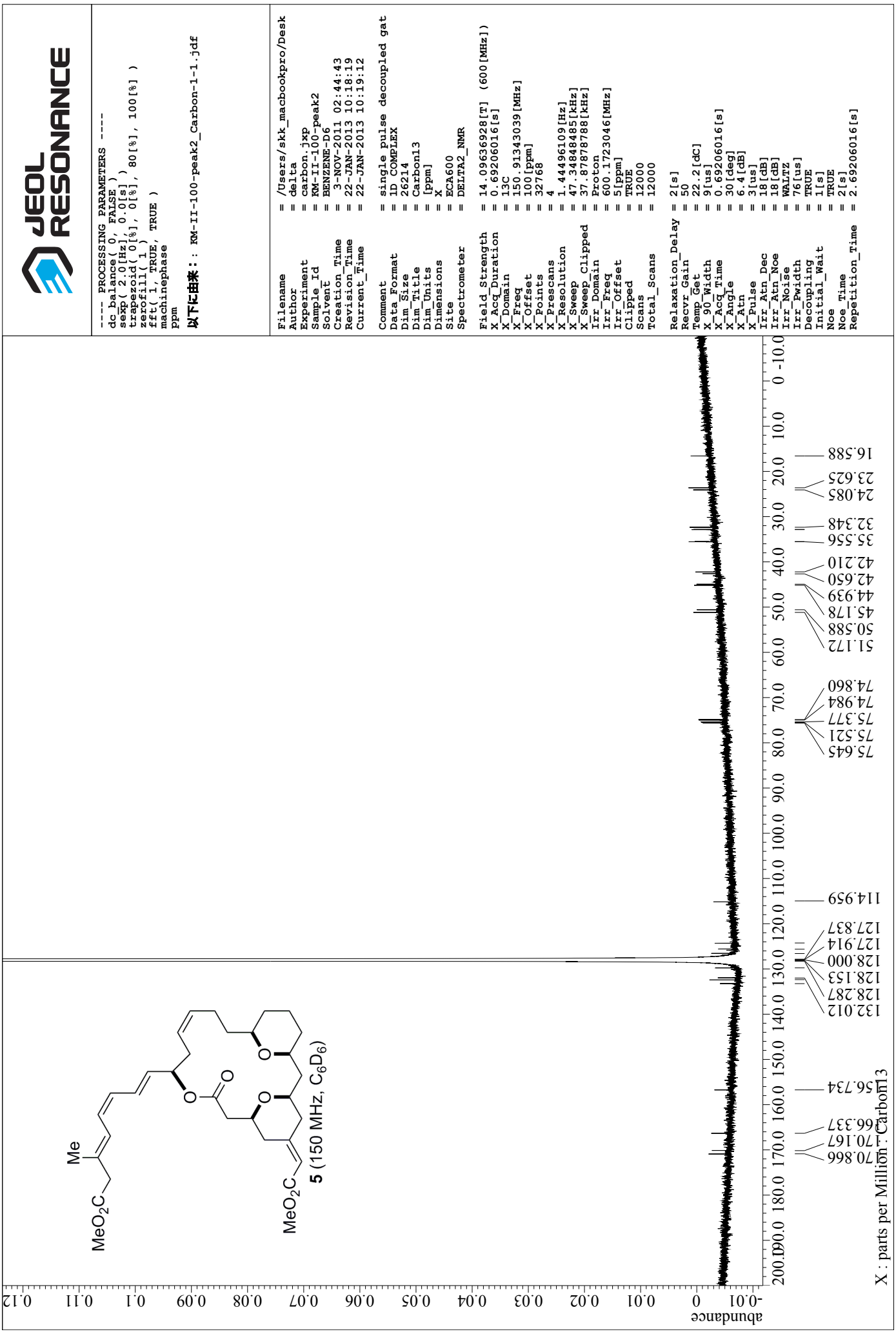


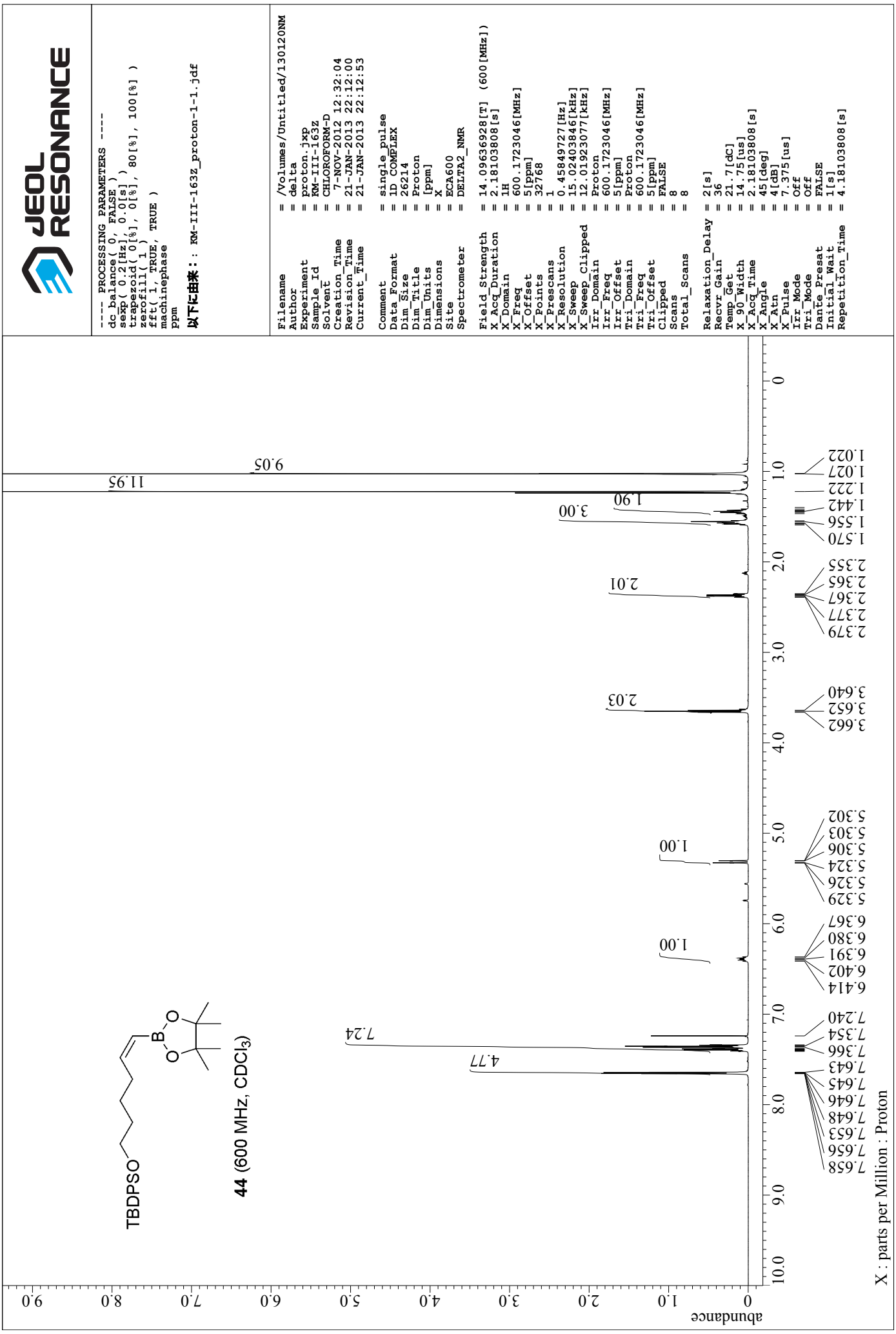


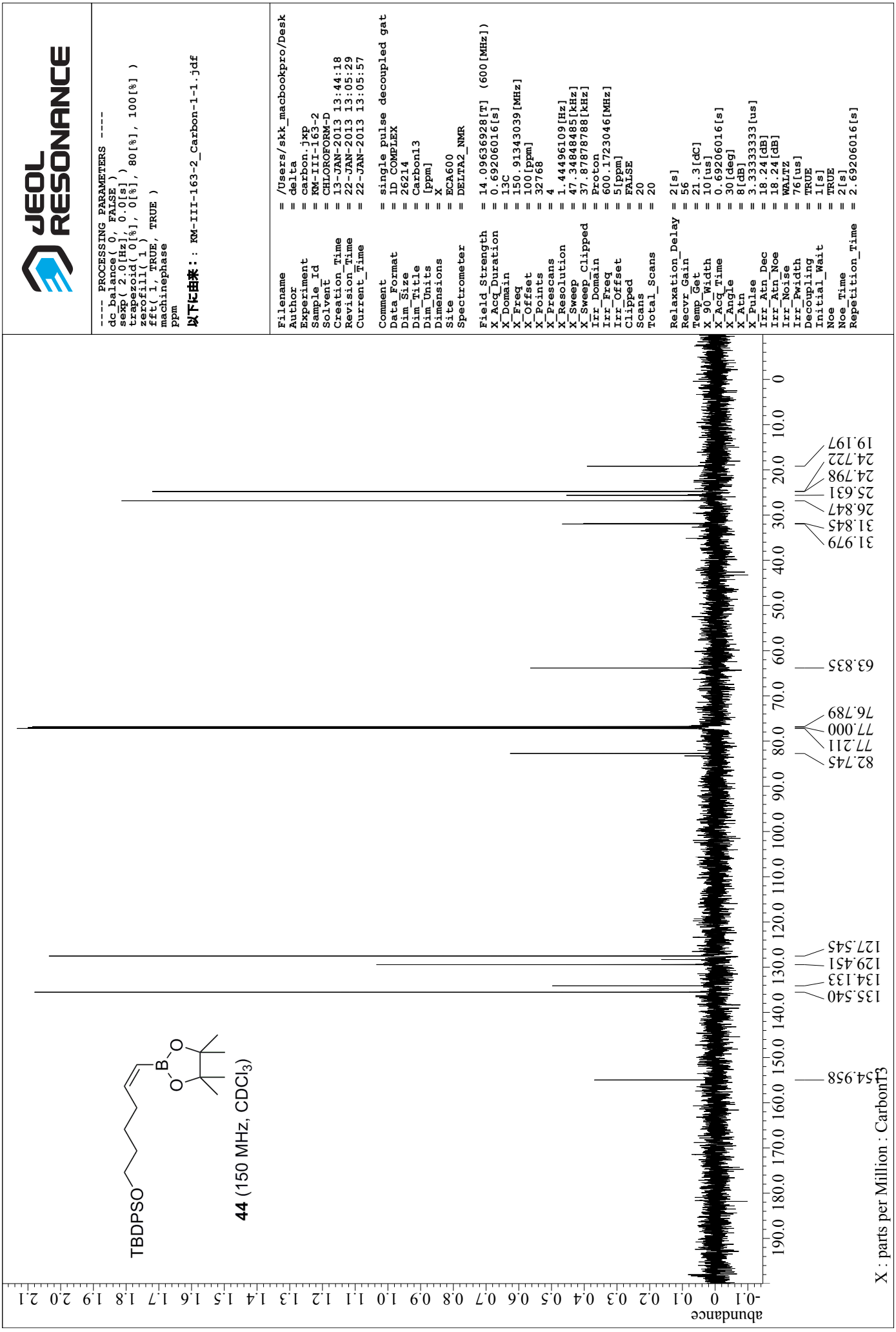


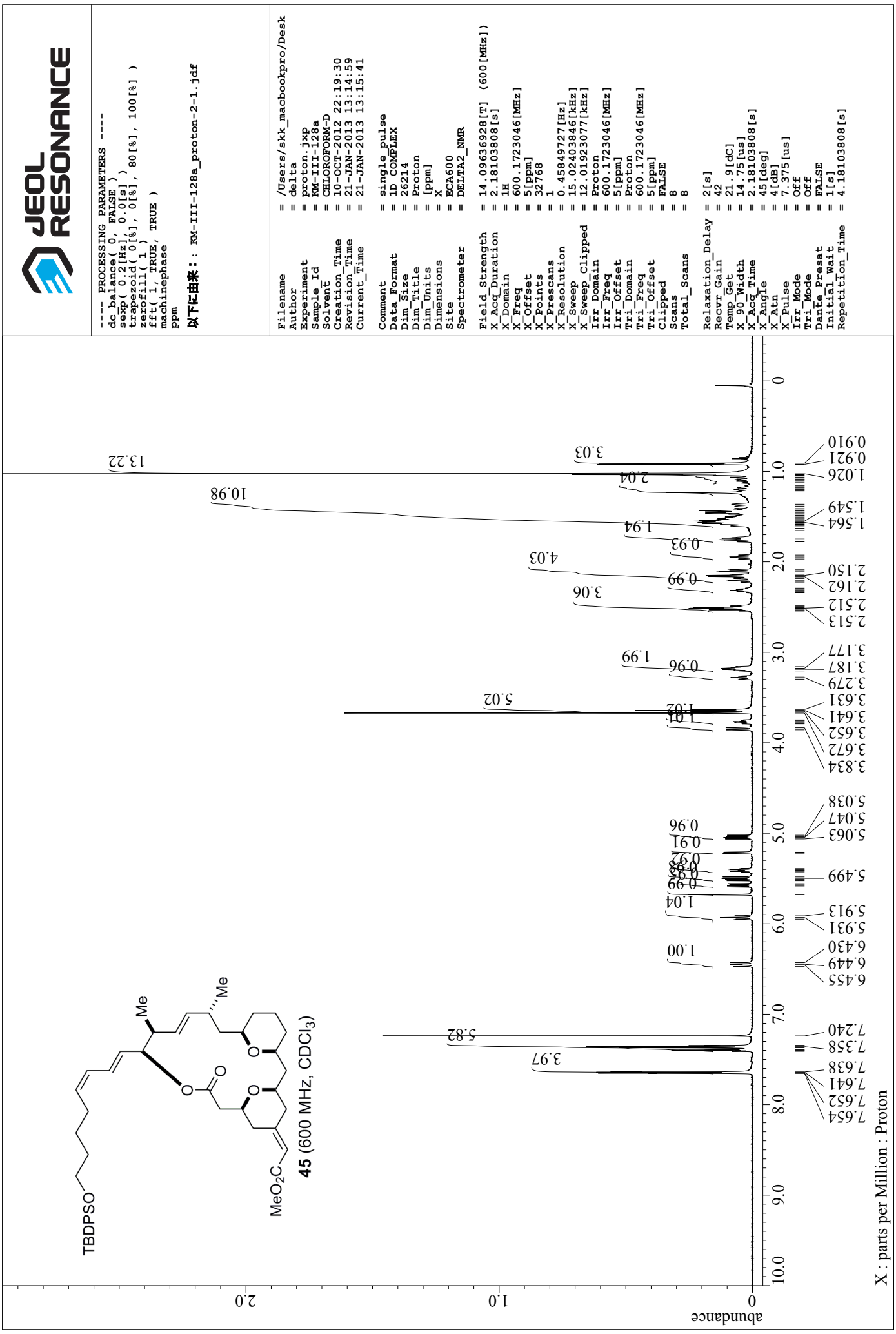


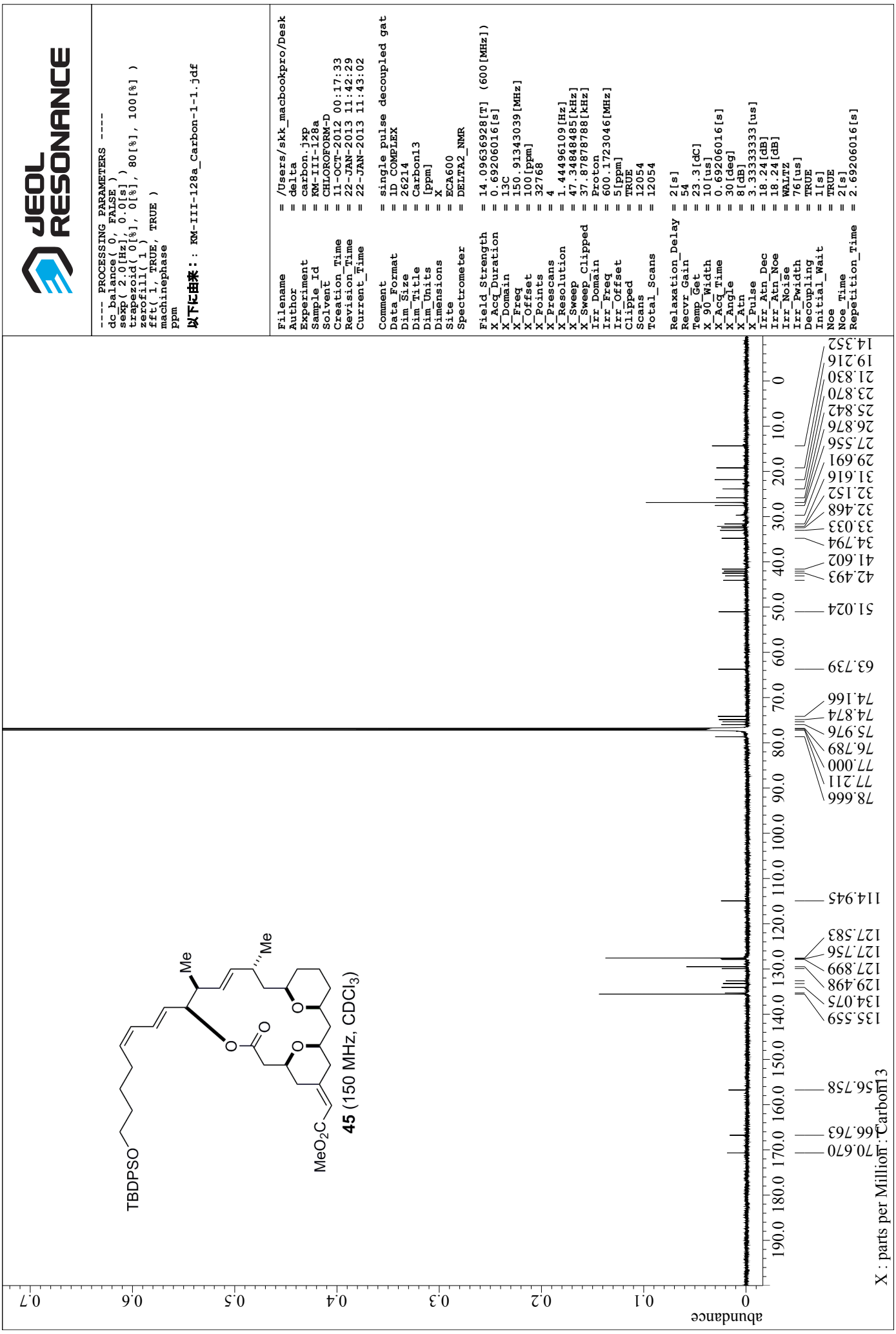


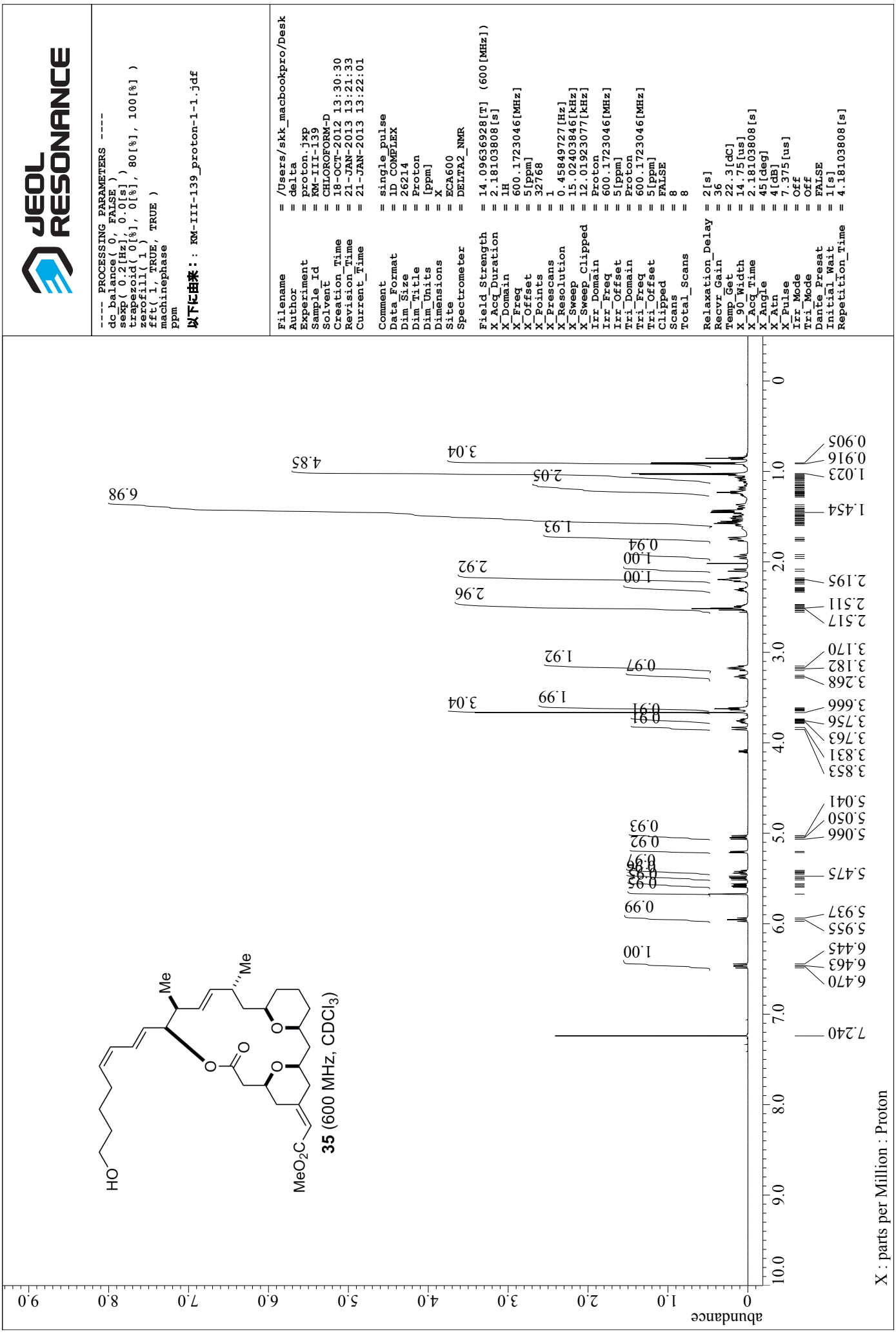


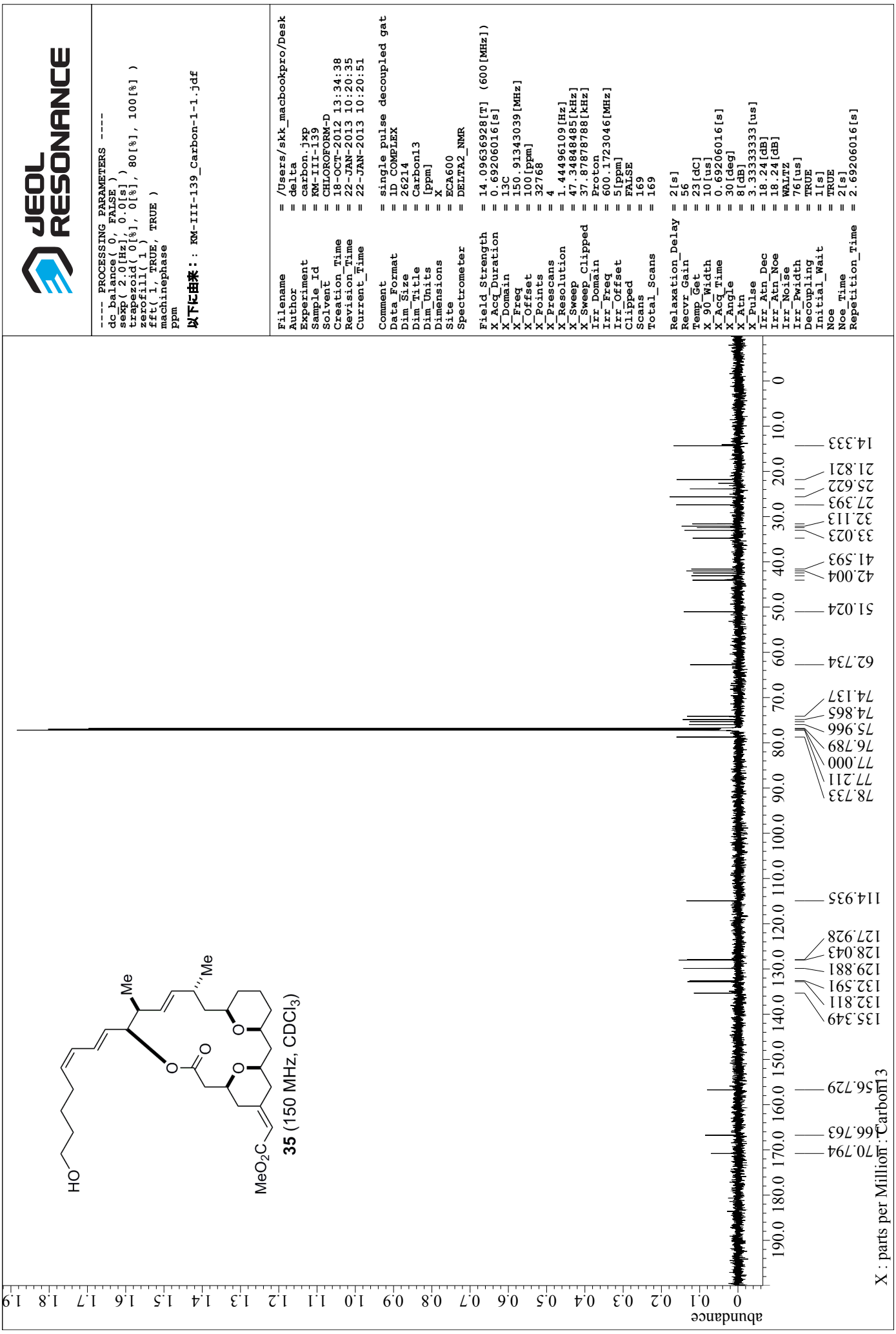


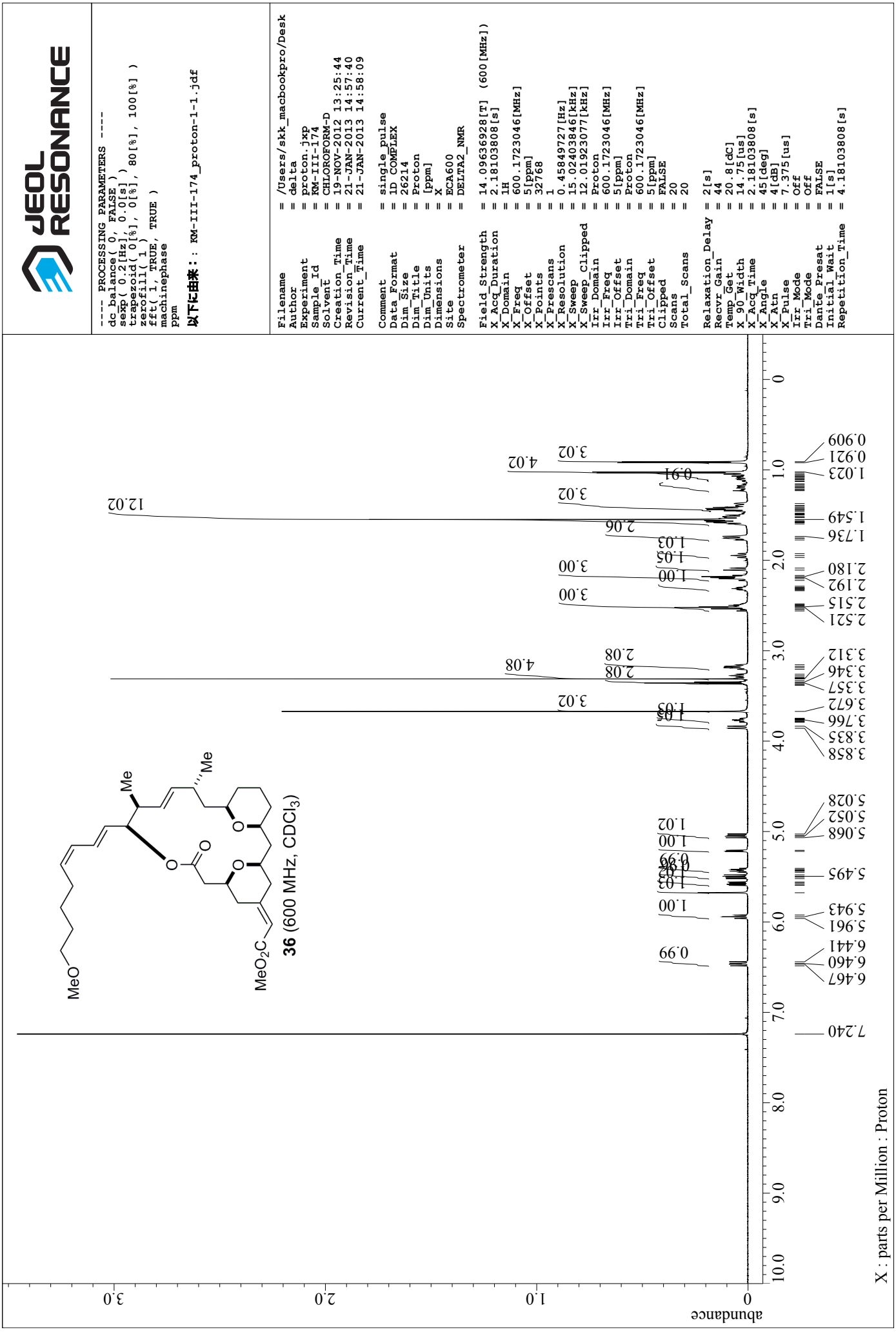


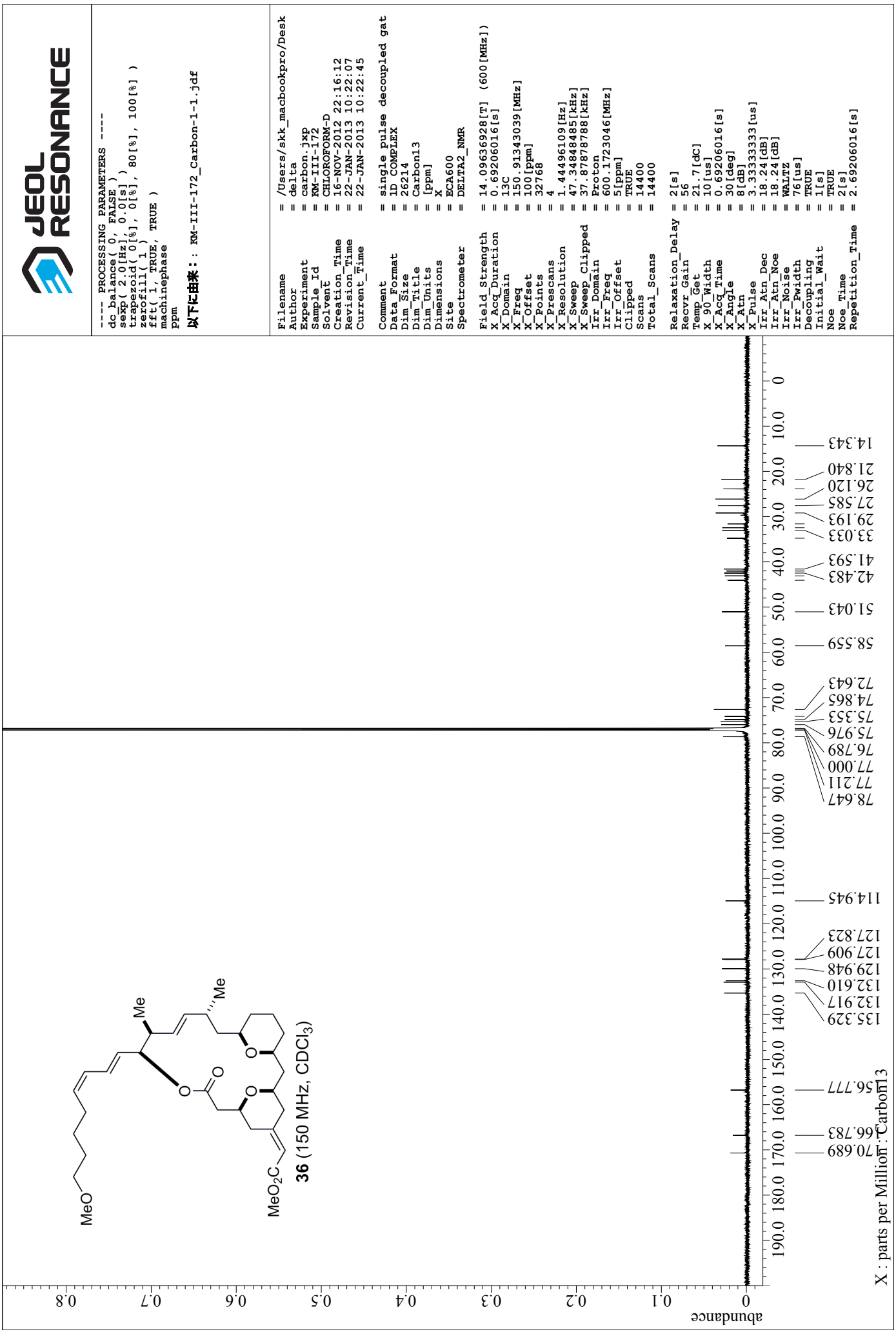


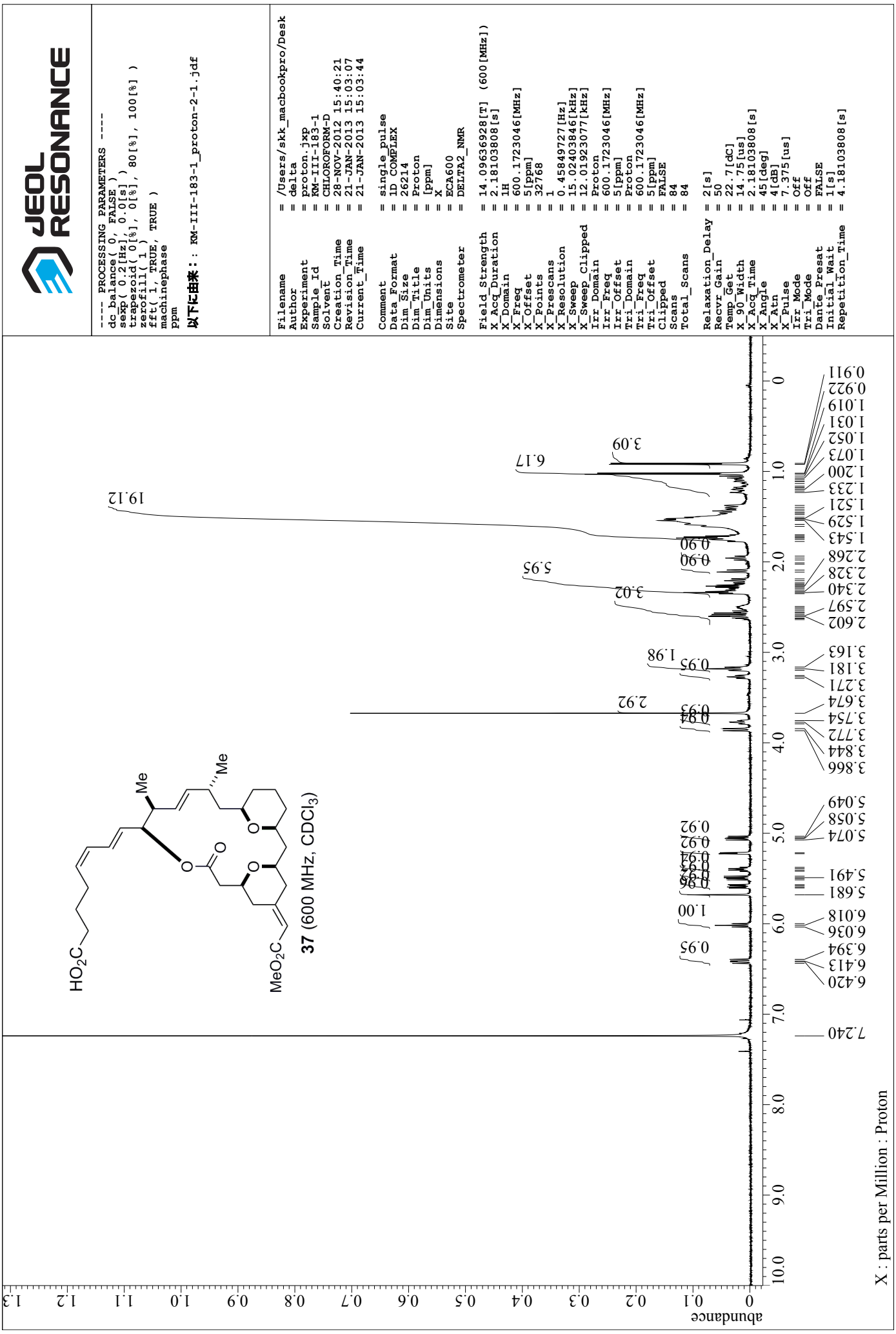


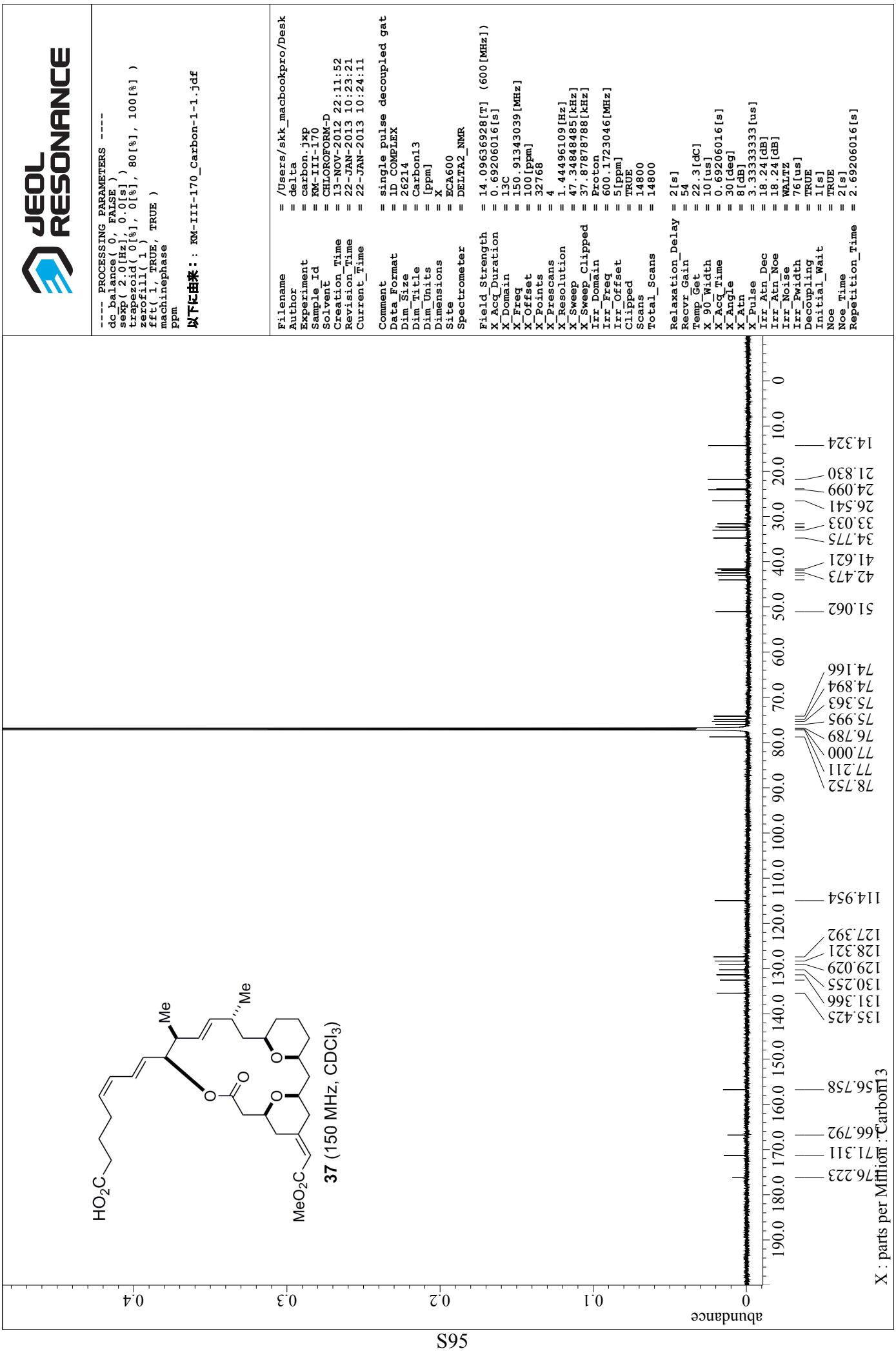


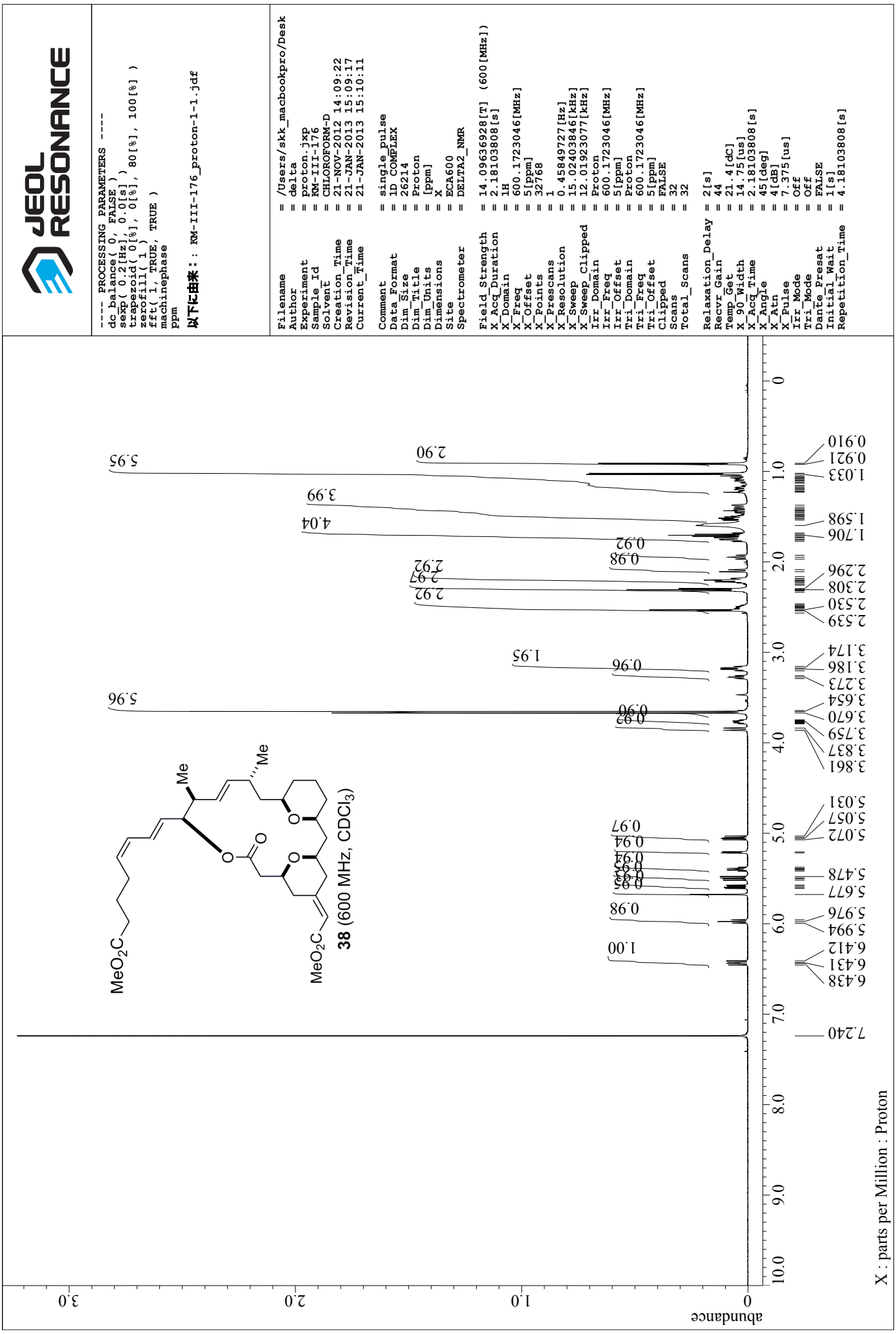


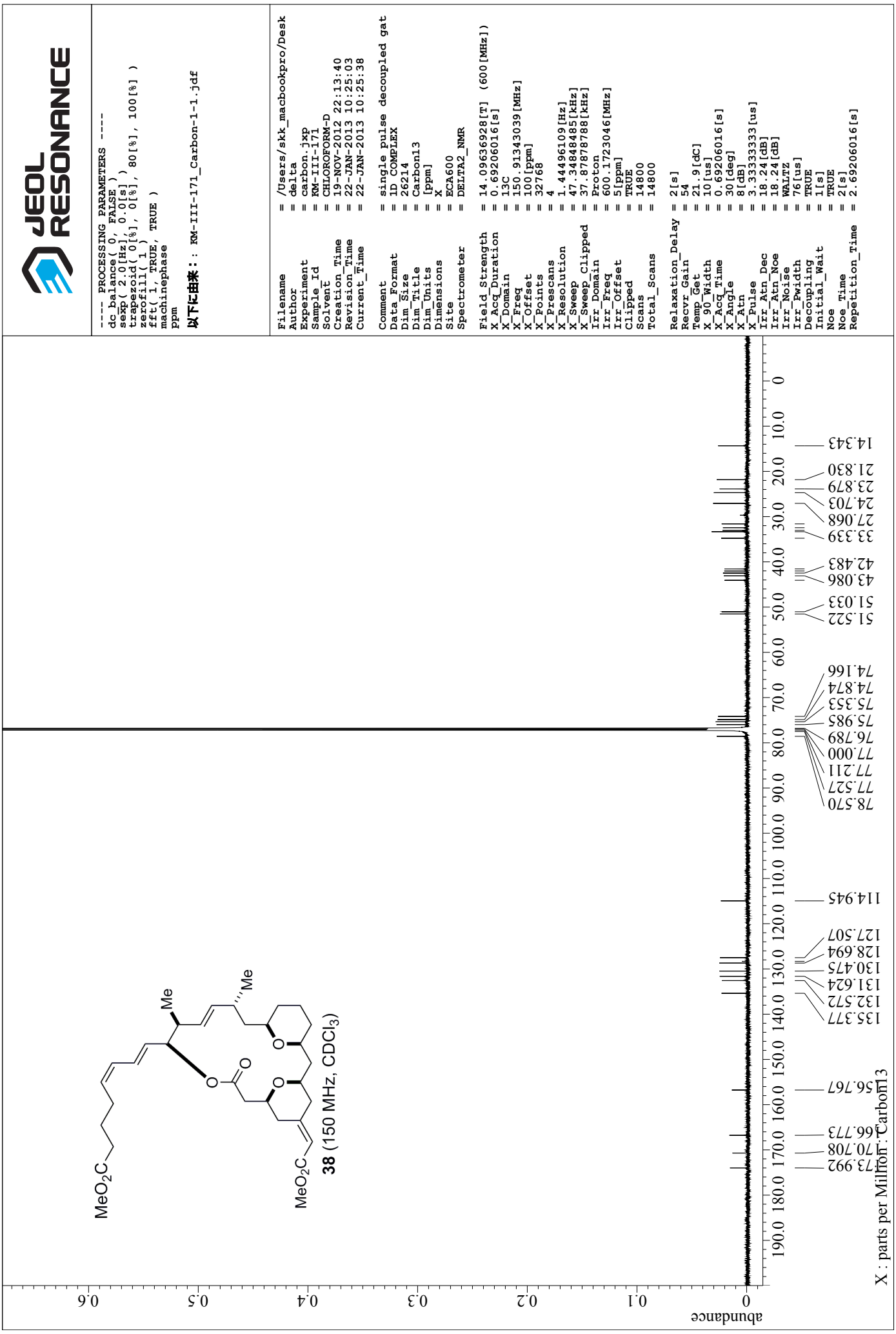


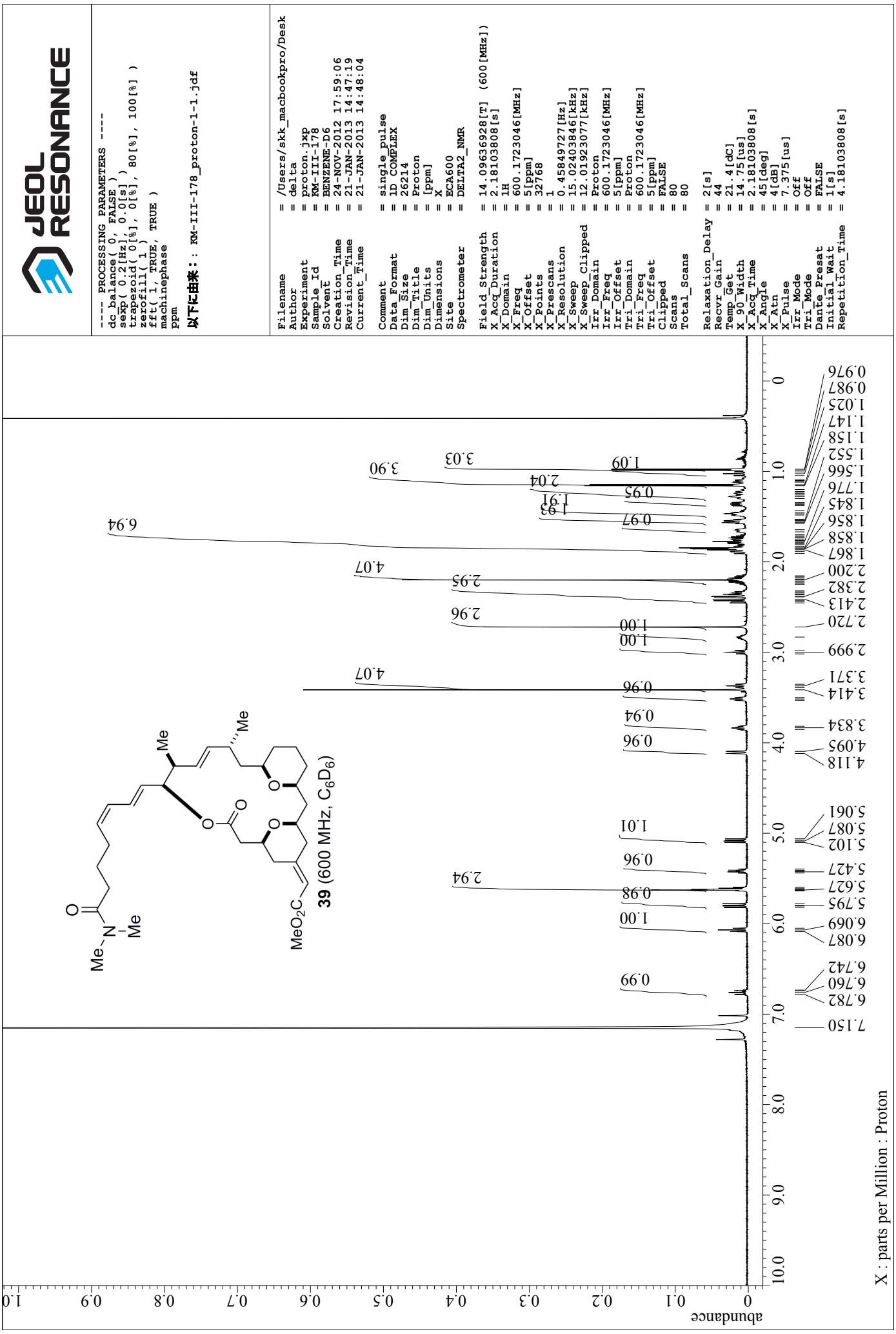


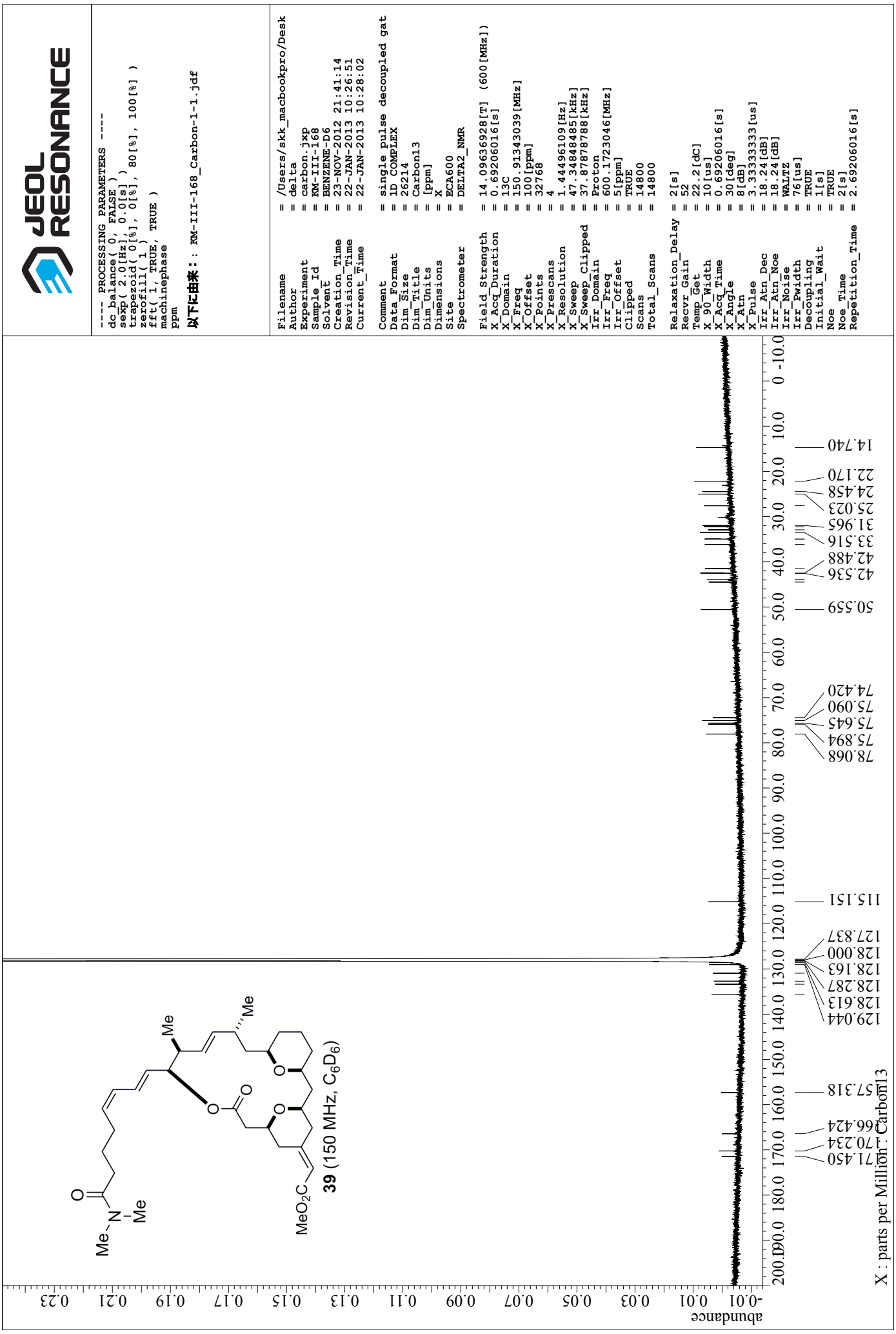


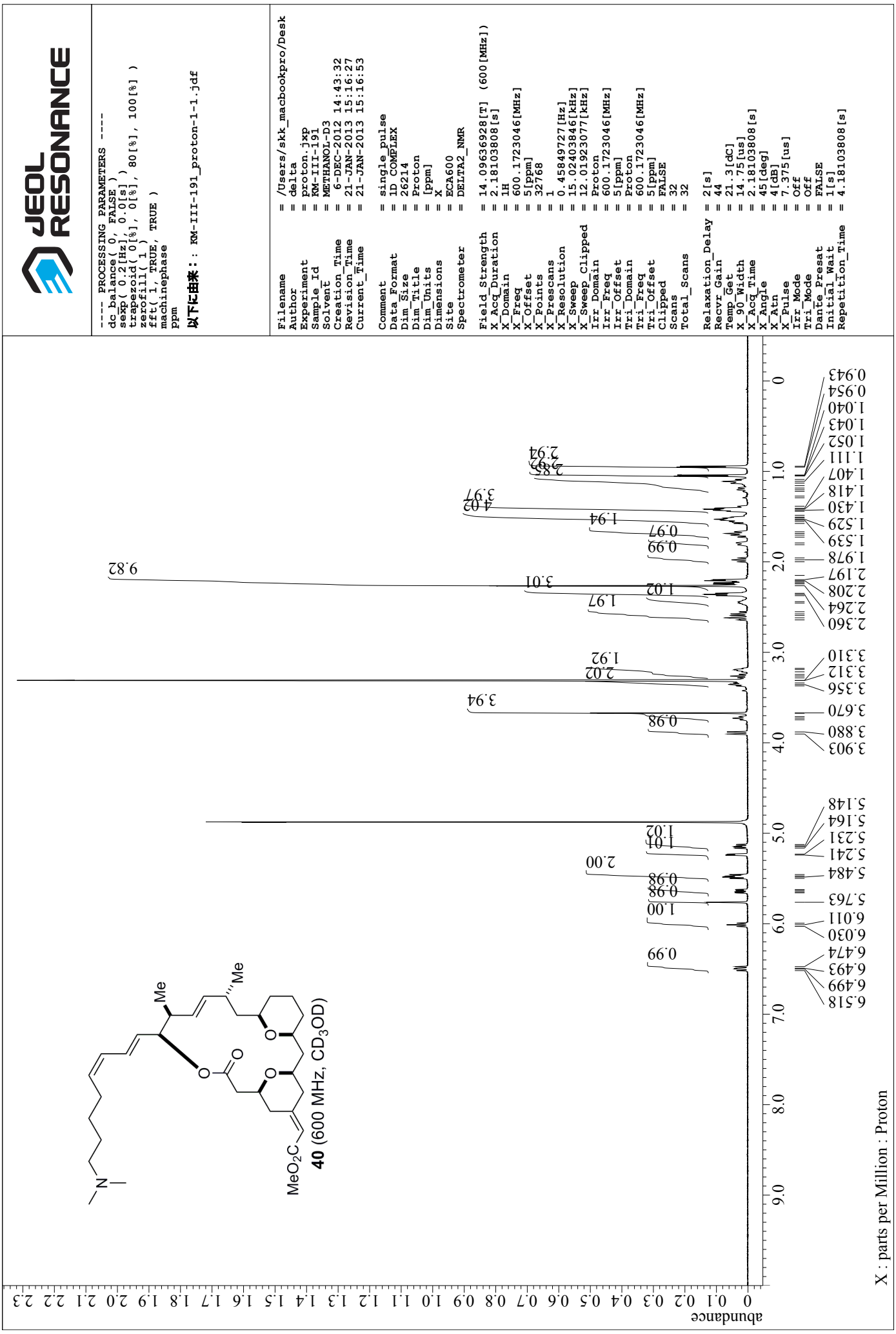


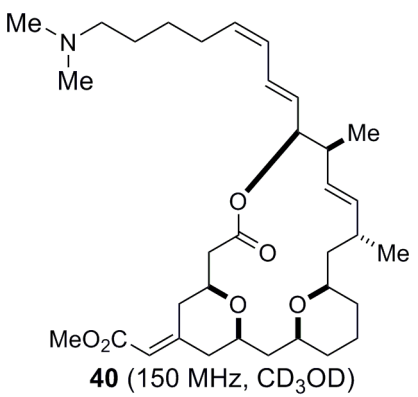












40 (150 MHz, CD_3OD)

JEOL RESONANCE

```
---- PROCESSING PARAMETERS ----
dc_balance( 0, FALSE )
sexp( 2.0[Hz], 0.0[s] )
trapezoid( 0[%], 0[%], 80[%], 100[%] )
zerofill( 1 )
fft( 1, TRUE, TRUE )
machinephase
ppm

以下に由来：: KM-III-159_Carbon-1-1.jdf
```

```
Filename          = /Users/skk_macbookpro/Desk
Author            = delta
Experiment        = carbon.jxp
Sample_Id         = KM-III-159
Solvent           = METHANOL-D3
Creation_Time     =  6-NOV-2012 22:22:51
Revision_Time     = 22-JAN-2013 11:06:11
Current_Time      = 22-JAN-2013 11:06:57

Comment           = single pulse decoupled gat
Data_Format       = 1D COMPLEX
Dim_Size          = 26214
Dim_Title         = Carbon13
Dim_Units         = [ppm]
Dimensions        = X
Site              = ECA600
Spectrometer      = DELTA2_NMR

Field_Strength    = 14.09636928[T] (600[MHz])
X_Acq_Duration    = 0.69206016[s]
X_Domain          = 13C
X_Freq            = 150.91343039[MHz]
X_Offset          = 100[ppm]
X_Points          = 32768
X_Prescans        = 4
X_Resolution      = 1.44496109[Hz]
X_Sweep           = 47.34848485[kHz]
X_Sweep_Clipped   = 37.87878788[kHz]
Irr_Domain        = Proton
Irr_Freq          = 600.1723046[MHz]
Irr_Offset        = 5[ppm]
Clipped           = TRUE
Scans             = 14768.0
Total_Scans       = 14768.0

Relaxation_Delay  = 2[s]
Recvr_Gain        = 54
Temp_Get          = 22.7[dC]
X_90_Width        = 10[us]
X_Acq_Time        = 0.69206016[s]
X_Angle           = 30[deg]
X_Atn             = 8[dB]
X_Pulse           = 3.33333333[us]
Irr_Atn_Dec       = 18.24[dB]
Irr_Atn_Noe       = 18.24[dB]
Irr_Noise         = WALTZ
Irr_Pwidth        = 76[us]
Decoupling        = TRUE
Initial_Wait      = 1[s]
Noe               = TRUE
Noe_Time          = 2[s]
Repetition_Time   = 2.69206016[s]
```