AN INTRAMOLECULAR NUCLEOPHILE-CATALYZED ALDOL-LACTONIZATION (NCAL) REACTION OF *S*-ARYL-(*E*)-6-OXOHEX-2-ENETHIOATE WITH *N*,*N*-4-DIMETHYLAMINOPYRIDINE *N*-OXIDE

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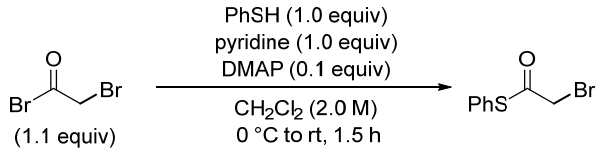
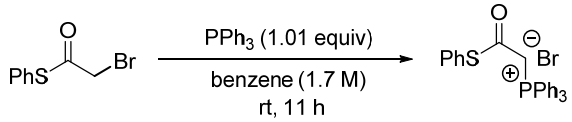
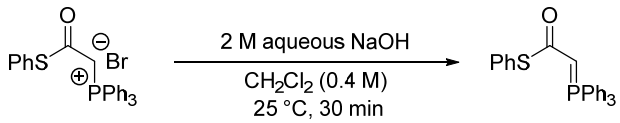
Synthesis of substrates 1c, 1f–j



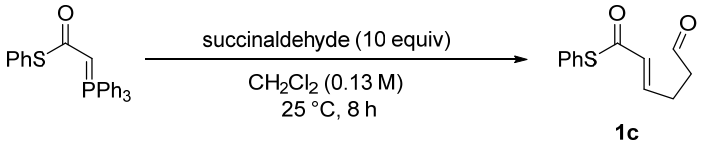
***S*-Phenyl α-bromothioacetate.**[1] To a solution of benzenethiol (22.5 g, 0.204 mol) in CH_2Cl_2 (100 mL) was added sequentially 2-bromoacetylbromide (46.4 g, 0.230 mol) and DMAP (2.45 g, 20.1 mmol), then pyridine (17.0 mL, 0.205 mol) was added dropwise to the stirred resulting mixture at 0 °C. After allowing to stir for 1.5 h at room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl (200 mL) and extracted with EtOAc (3 × 200 mL). The organic layer was washed with brine (200 mL) and dried over $MgSO_4$, and concentrated *in vacuo* to give crude *S*-phenyl α-bromothioacetate (5.04 g) as a yellow oil. This crude product was directly used for the following reaction without further purification.



(2-Oxo-2-(phenylthio)ethyl)triphenylphosphonium bromide. To a solution of crude product **8c** (5.04 g) in benzene (40 mL) was added a solution of triphenylphosphine (54.0 g, 0.206 mol) in benzene (80 mL). After the reaction mixture was stirred at room temperature for 11 h, the precipitate was collected by filteration and washed with Et_2O to give phosphonium salt (92.5 g, 0.188 mol) as a colorless solid. This crude product was directly used for the following reaction without further purification.

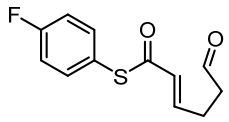


2-Phenylthio(triphenylphosphonylidene)ethan-2-one. To a solution of phosphonium bromide (9.84 g, 20.0 mmol) in CH_2Cl_2 (50 mL) was added 2 M aqueous NaOH (50 mL). After the reaction mixture was stirred at room temperature for 30 min, organic layer was separated, washed with brine (100 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give the ylide (7.87 g, 19.1 mmol) as a pale yellow solid. This crude product was directly used for the following reaction without further purification.



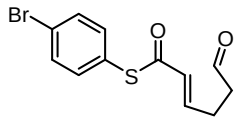
(*E*)-6-Phenylthio-6-oxo-4-hexenal (1c). To a solution (suspension) of ylide (4.68 g, 11.4 mmol) in CH_2Cl_2 (87 mL) was added succinaldehyde (9.77 g, 113.5 mmol). After stirring at room temperature for 8 h, the reaction mixture was elaborately dried under reduced pressure to remove the solvent and excess succinalde-

hyde. The purification of crude product by flash column chromatography on silica gel (eluent: hexane/Et_2O = 1/1, v/v and eluent: toluene/EtOAc = 10/1, v/v) gave unsaturated aldehyde **1c** (0.879 g, 3.99 mmol, 35% yield) as a pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 7.46–7.39 (m, 5H), 6.95 (dt, *J* = 15.6, 6.6 Hz, 1H), 6.21 (dt, *J* = 15.6, 1.4 Hz, 1H), 2.71–2.65 (m, 2H), 2.61–2.52 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.2, 187.7, 143.9, 134.6, 129.4, 129.2, 128.6, 127.4, 41.6, 24.5; **IR** (KBr) 3061, 2725, 2359, 1138, 746 cm^{-1}; **TLC R_f** 0.25 (hexane/Et_2O = 1/1), 0.5 (toluene/EtOAc = 10/1); **HRMS** (FAB) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{13}O_2S$: 221.0630, found: 221.0600



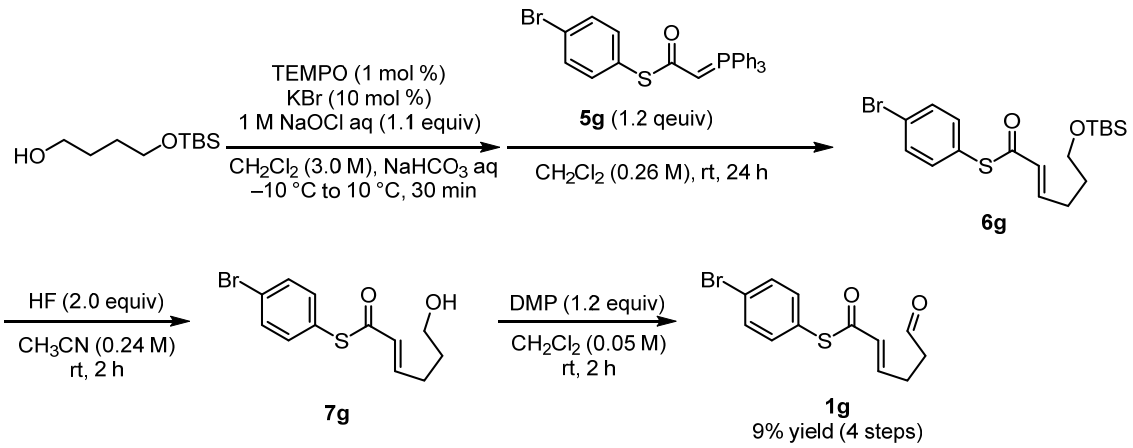
1f

(*E*)-6-(4-Fluorophenylthio)-6-oxo-4-hexenal (1f). According to similar procedure for synthesis of **1c**, the product **1f** was obtained as a yellow oil (0.235 g, 0.985 mmol, 7% overall yield from 4-fluorobenzenethiol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.43–7.35 (m, 2H), 7.15–7.07 (m, 2H), 6.94 (dt, *J* = 15.2, 6.9 Hz, 1H), 6.20 (dt, *J* = 15.2, 1.4 Hz, 1H), 2.67 (t, *J* = 6.9 Hz, 2H), 2.60–2.51 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 200.1, 187.8, 163.6 (d, *J* = 249.2 Hz), 144.2, 136.8 (d, *J* = 8.6 Hz), 128.6, 122.8 (d, *J* = 8.6 Hz), 116.6 (d, *J* = 22.0 Hz), 41.8, 24.6; **IR** (neat) 3069, 2826, 2725, 1225, 793 cm^{-1}; **HRMS** (FAB) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{12}FO_2S$: 239.0536, found: 239.0539



1g

(*E*)-6-(4-Methoxyphenylthio)-6-oxo-4-hexenal (1g). Because substrate **1g** cannot be synthesized efficiently by a similar procedure for the synthesis of **1c**, an alternative route was selected (Scheme S1).



Scheme S1. An overview of synthesis of **1g**.

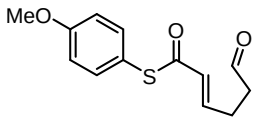
To a solution of the 4-(*tert*-Butyldimethylsilyl)oxy-1-butanol[2] (0.57 g, 2.79 mmol) in CH_2Cl_2 (1.0 mL) was

added 2,2,6,6-tetramethylpiperidin-1-oxyl (5.10 mg, 32.6 μmol) and potassium bromide (33.8 mg, 0.28 mmol). The reaction mixture was stirred and cooled to –10 °C with a salt-ice bath, then 1 M aqueous sodium hypochlorite (3.1 mL, 3.10 mmol) was added dropwise over 20 min with maintaining pH 8. The reaction mixture was kept between 10 and 15 °C and stirred for a further 10 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), washed with 3 M HCl aq (30 mL) containing potassium iodide (30.0 mg), 10% aqueous sodium thiosulfate (30 mL), and brine (30 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*.

The crude aldehyde was dissolved in CH_2Cl_2 (4.0 ml) and a solution of **5g** in CH_2Cl_2 (6.0 mL) was added at room temperature. After stirring for 24 h, the reaction mixture was dried under reduced pressure to remove the solvent. The filtration of the residue through a short pad of silica gel (eluent: hexane/Et_2O = 1/1, v/v) gave crude product **6g** (0.730 g) as an colorless oil.

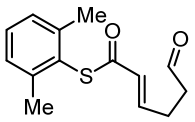
To a solution of crude product **6g** in CH_3CN (6.0 mL) was added HF aq (0.14 mL) at room temperature. After allowing to stir for 2 h, the reaction was quenched by $NaHCO_3$ aq, and the organic layer was extracted with EtOAc (3 × 20 mL). The organic layer was washed with brine (20 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give crude product **7g** (0.536 g) as a colorless oil.

To a solution of crude product **7g** in CH_2Cl_2 (26.0 mL) was added Dess-Martin Periodinane (0.662 g, 1.56 mmol) at room temperature. After allowing to stir for 2 h, the reaction mixture was diluted by Et_2O and $NaHCO_3/Na_2SO_3$ aq. The organic layer was extracted with CH_2Cl_2 (3 × 50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The purification of crude product by flash column chromatography on silica gel (eluent: toluene/Et_2O = 50/1, v/v) gave **1g** (72.2 mg, 0.24 mmol, 9% overall yield from 4-(*tert*-Butyldimethylsilyl)oxy-1-butanol) as an colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (d, *J* = 0.9 Hz, 1H), 7.55 (dt, *J* = 8.9, 2.0 Hz, 2H), 7.30 (dt, *J* = 8.9, 2.0 Hz, 2H), 6.96 (dt, *J* = 15.6, 6.7 Hz, 1H), 6.20 (dt, *J* = 15.6, 1.2 Hz, 1H), 2.69 (t, *J* = 6.7 Hz, 2H), 2.61–2.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.1, 187.2, 144.4, 136.2, 132.5, 128.6, 126.6, 124.3, 41.8, 24.6; IR (KBr) 2363, 1711, 1678, 1470, 1011, 818 cm^{-1}; **HRMS** (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{12}H_{11}BrO_2S$: 320.9555, found: 320.9555; m.p. = 76.5–77.0 °C.



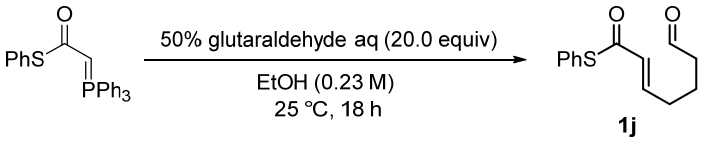
1h

(*E*)-6-(4-Methoxyphenylthio)-6-oxo-4-hexenal (1h). According to similar procedure for synthesis of **1c**, the product **1h** was obtained as a pale yellow solid (1.83 g, 7.89 mmol, 38% overall yield from 4-methoxybenzenethiol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.74 (s, 1H), 7.31 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.90 (dt, *J* = 15.6, 7.0 Hz, 1H), 6.18 (dt, *J* = 15.6, 1.5 Hz, 1H), 3.78 (s, 3H), 2.65–2.57 (m, 2H), 2.55–2.45 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 200.2, 188.6, 160.6, 143.6, 136.2, 128.5, 117.9, 114.8, 55.3, 41.6, 24.4; **IR** (KBr) 2965, 2839, 2743, 1717, 1246, 1051 cm^{-1}; **HRMS** (FAB) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{15}O_3S$: 251.0736, found: 251.0727; mp 52.5–53.0 °C



1i

(*E*)-6-(2,6-Dimethylphenylthio)-6-oxo-4-hexenal (1i). According to similar procedure for synthesis of **1c**, the product **1i** was obtained as a pale yellow oil (0.56 g, 2.26 mmol, 15% overall yield from 2.6-dimethylbenzenethiol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.82 (t, *J* = 1.1 Hz, 1H), 7.23 (dd, *J* = 8.0, 7.0 Hz, 1H), 7.16 (d, *J* = 7.0 Hz, 2H), 6.94 (dt, *J* = 15.6, 6.6 Hz, 1H), 6.25 (dt, *J* = 15.6, 1.6 Hz, 1H), 2.73–2.65 (m, 2H), 2.62–2.52 (m, 2H), 2.35 (s, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 200.3, 187.0, 143.5, 143.0, 130.0, 128.9, 128.4, 126.8, 41.8, 24.5, 21.8; **IR** (neat) 2723, 2386, 1726, 1632, 773 cm^{-1}; **HRMS** (FAB) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{17}O_2S$: 249.0943, found: 249.0941.

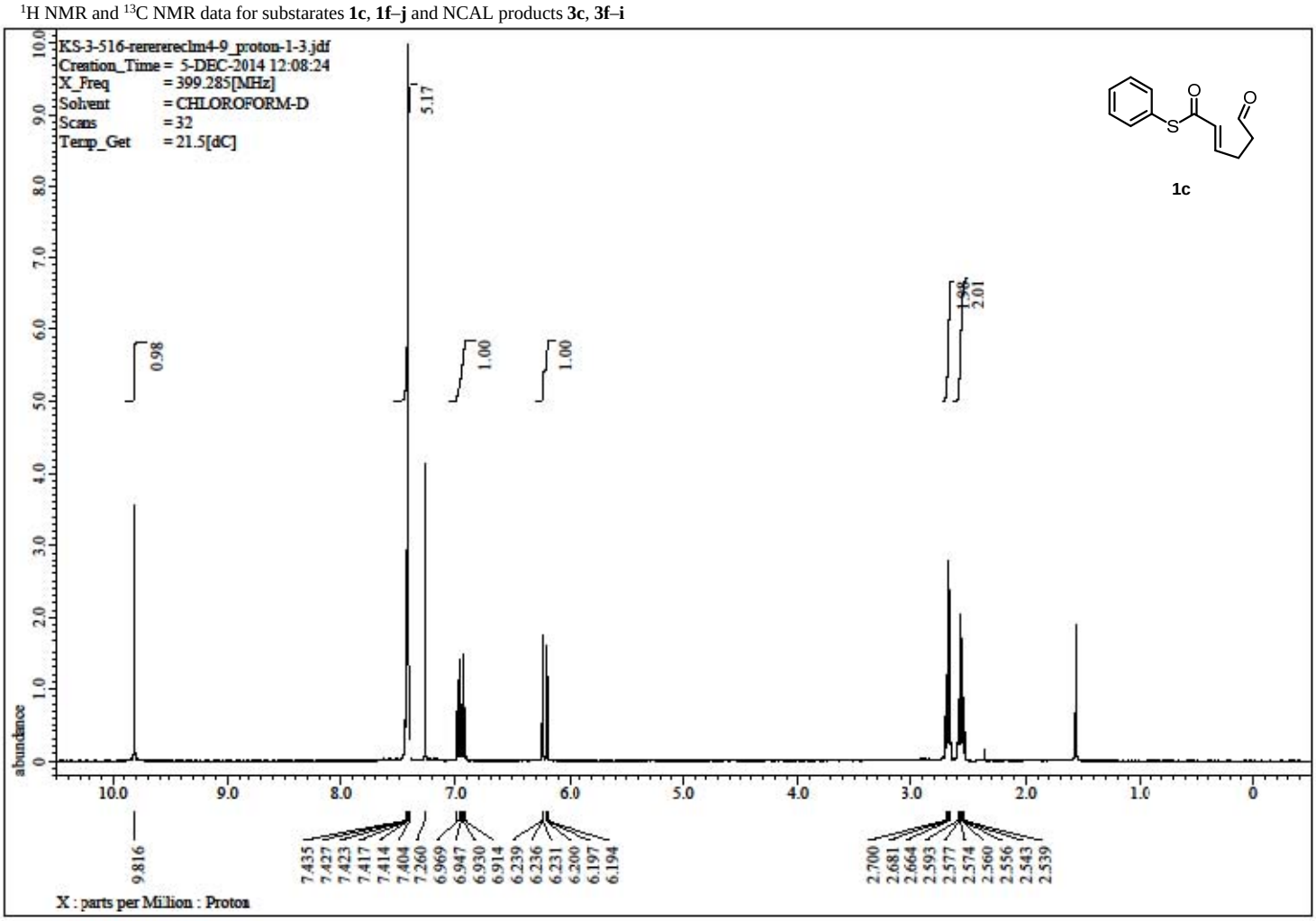


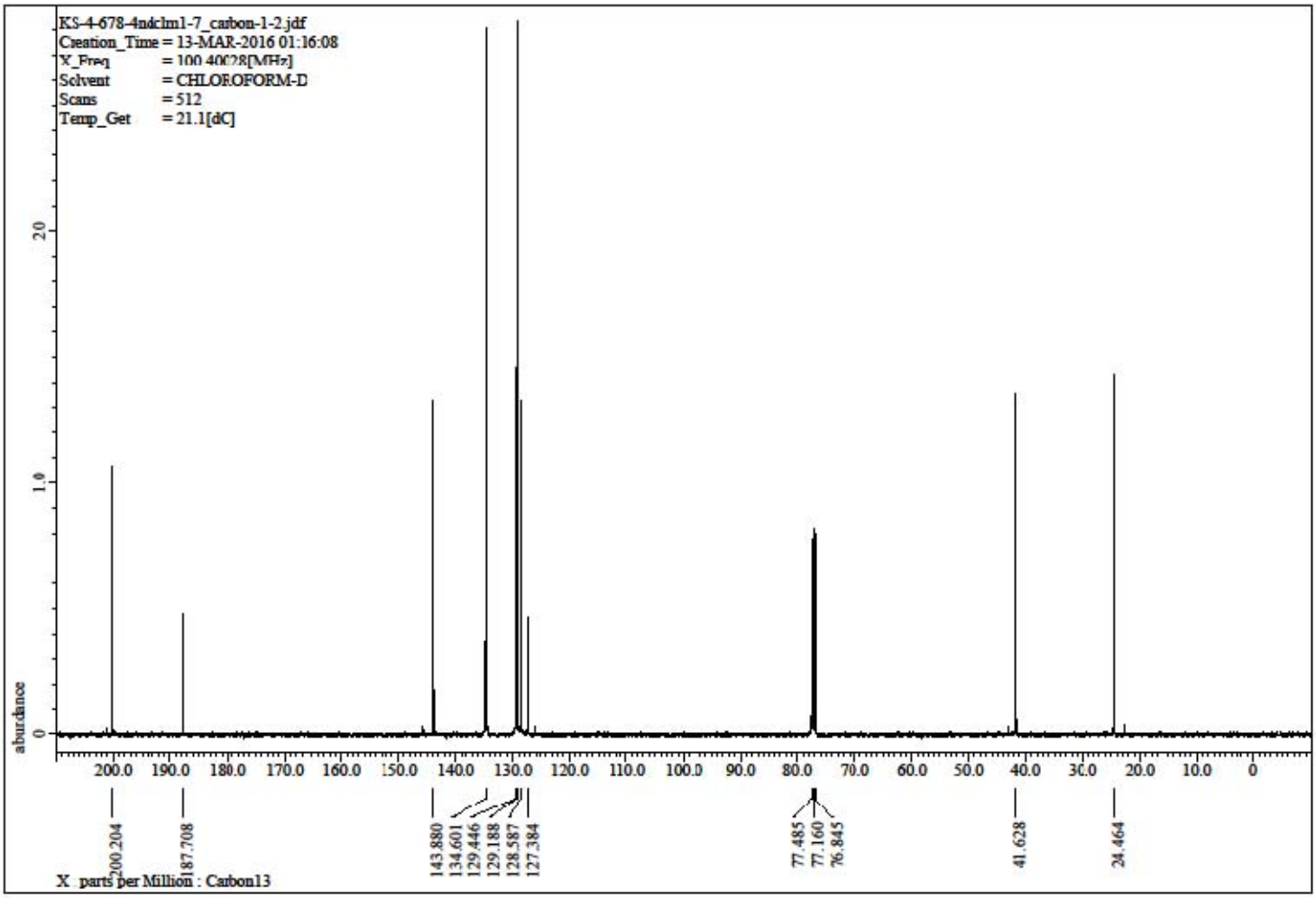
1j

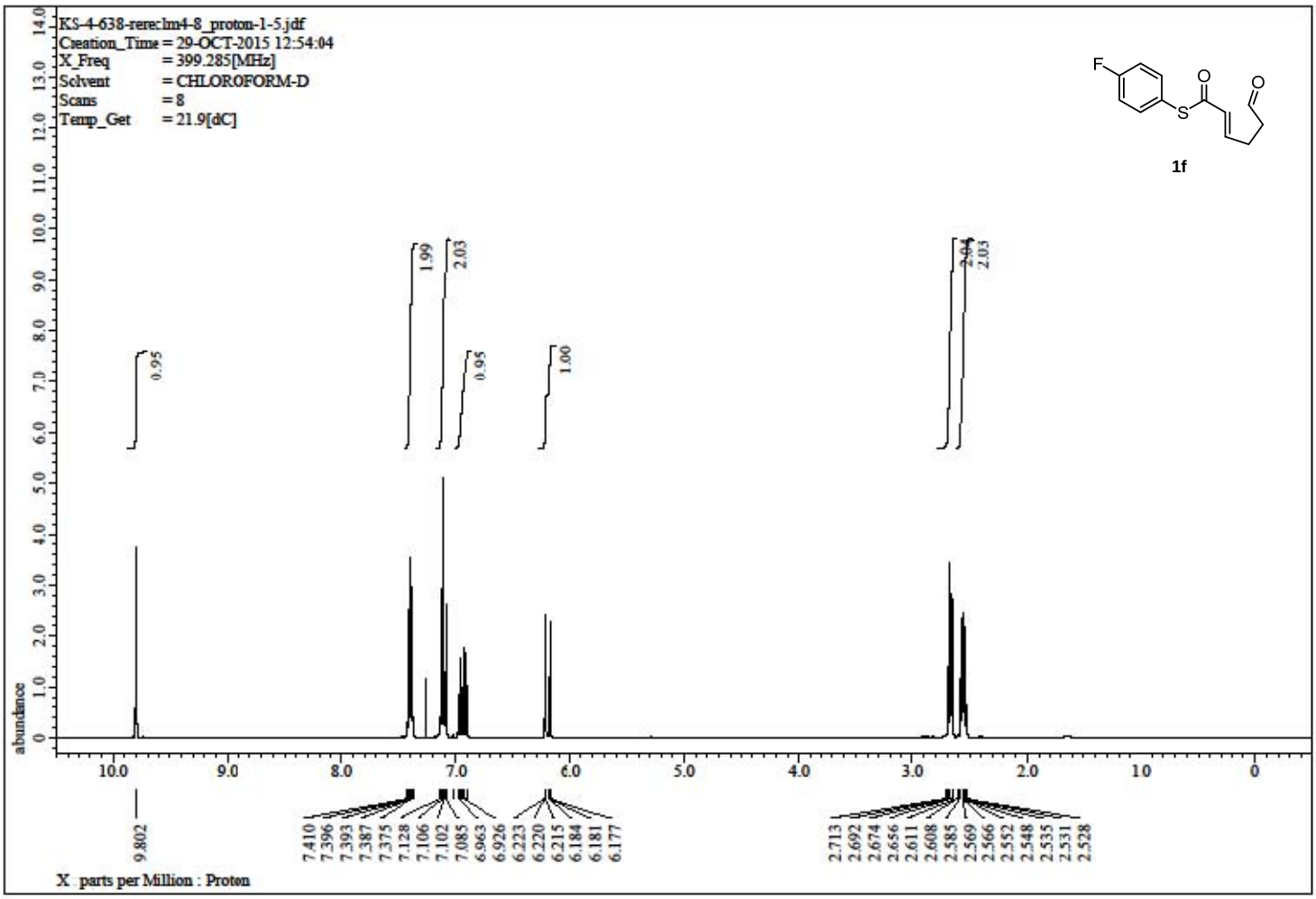
(*E*)-7-Phenylthio-7-oxo-5-heptenal (1j)

To a solution (suspension) of ylide (8.35 g, 20.2 mmol) in EtOH (78 mL) was added 50% aqueous glutaraldehyde solution (86 mL, 404 mmol). After stirring at room temperature for 18 h, water (100mL) was added to the solution and the combined layer was extracted with CH_2Cl_2 (3 × 80 mL). The organic layer was washed with HCl aq (0.2 M, 3 × 100 mL), brine (80 mL), and dried over $MgSO_4$. After evaporation, the crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/Et_2O = 1/1, v/v and eluent: toluene/EtOAc = 10/1, v/v) gave **1j** (1.48 g, 6.32 mmol, 11% overall yield from benzenethiol) as a pale yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.79 (t, *J* = 1.2 Hz, 1H), 7.45–7.41 (m, 5H), 6.94 (dt, *J* = 15.6, 6.9 Hz, 1H), 6.21 (dt, *J* = 15.6, 1.4 Hz, 1H), 2.51 (dt, *J* = 7.2, 1.2 Hz, 2H), 2.29 (dq, *J* = 7.2, 1.4 Hz, 2H), 1.84 (quin, *J* = 7.2 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 201.6, 187.9, 145.1, 134.7, 129.5, 129.2, 128.6, 127.5, 43.0, 31.4, 20.3; **IR** (neat) 2938, 2723, 1722, 1686, 1477, 1441, 976 cm^{-1}, **HRMS** (FAB) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{15}O_2S$: 235.0781, found: 235.0790.

^{1}H NMR and ^{13}C NMR data for substarates **1c**, **1f–j** and NCAL products **3c**, **3f–i**



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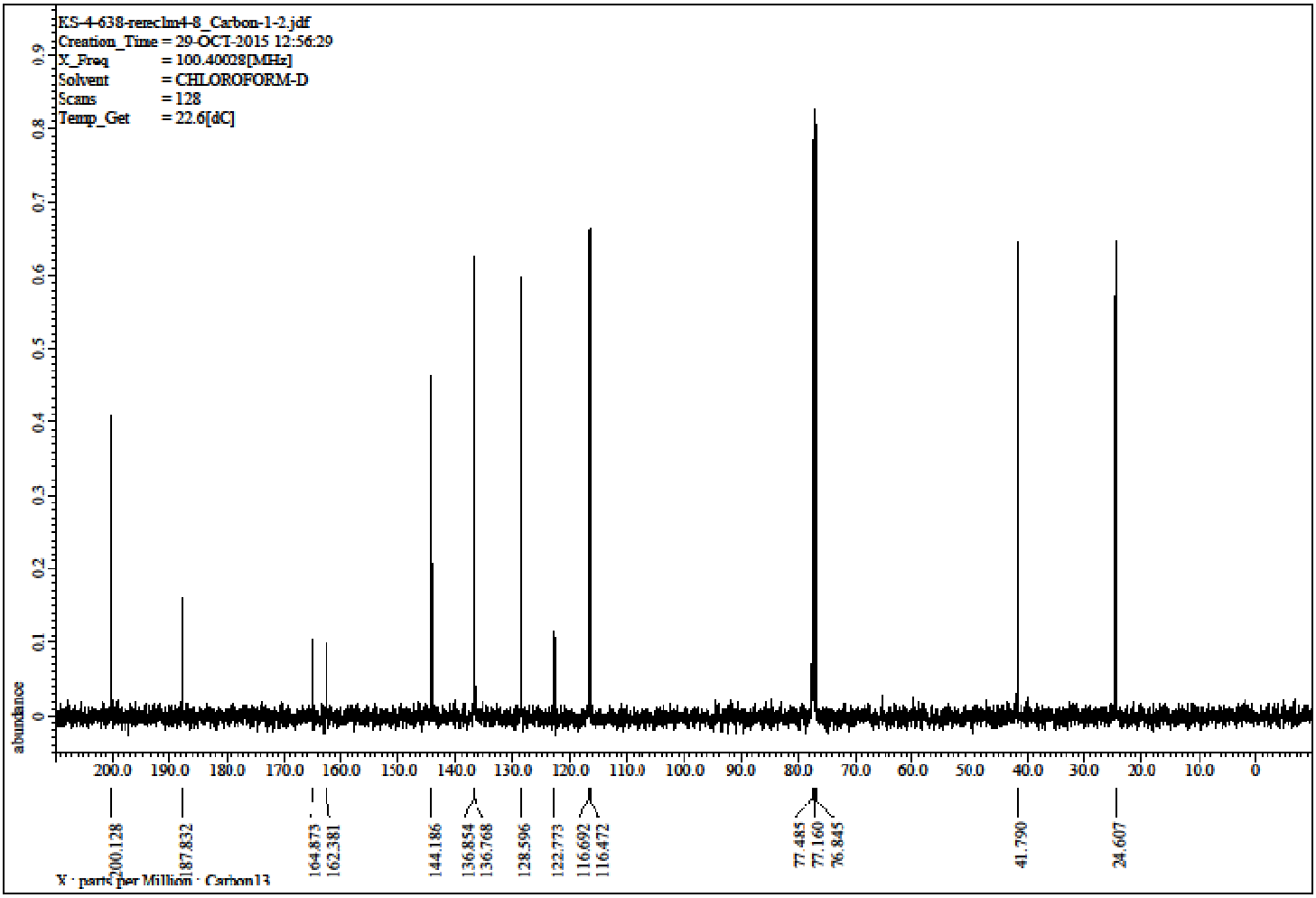
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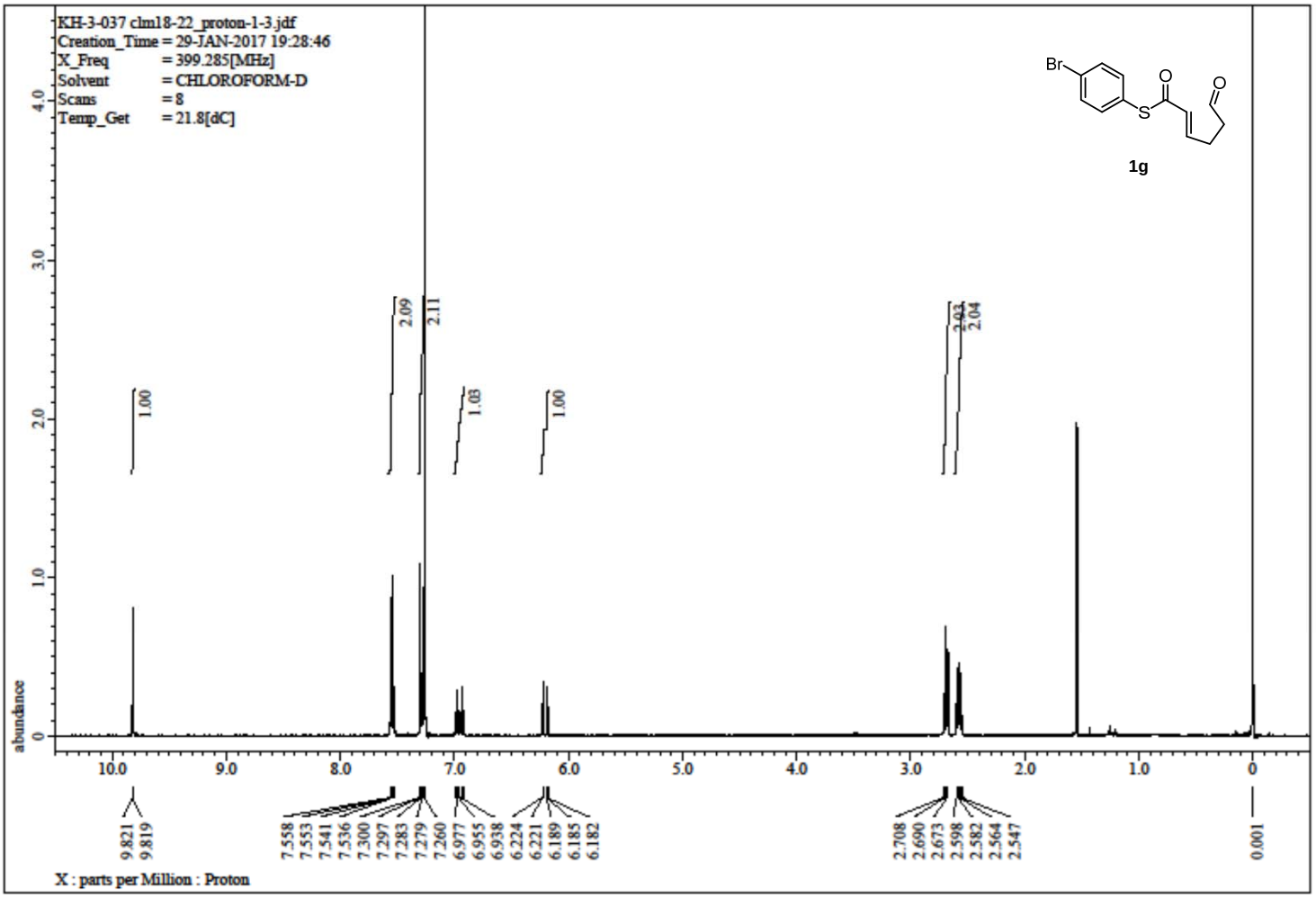
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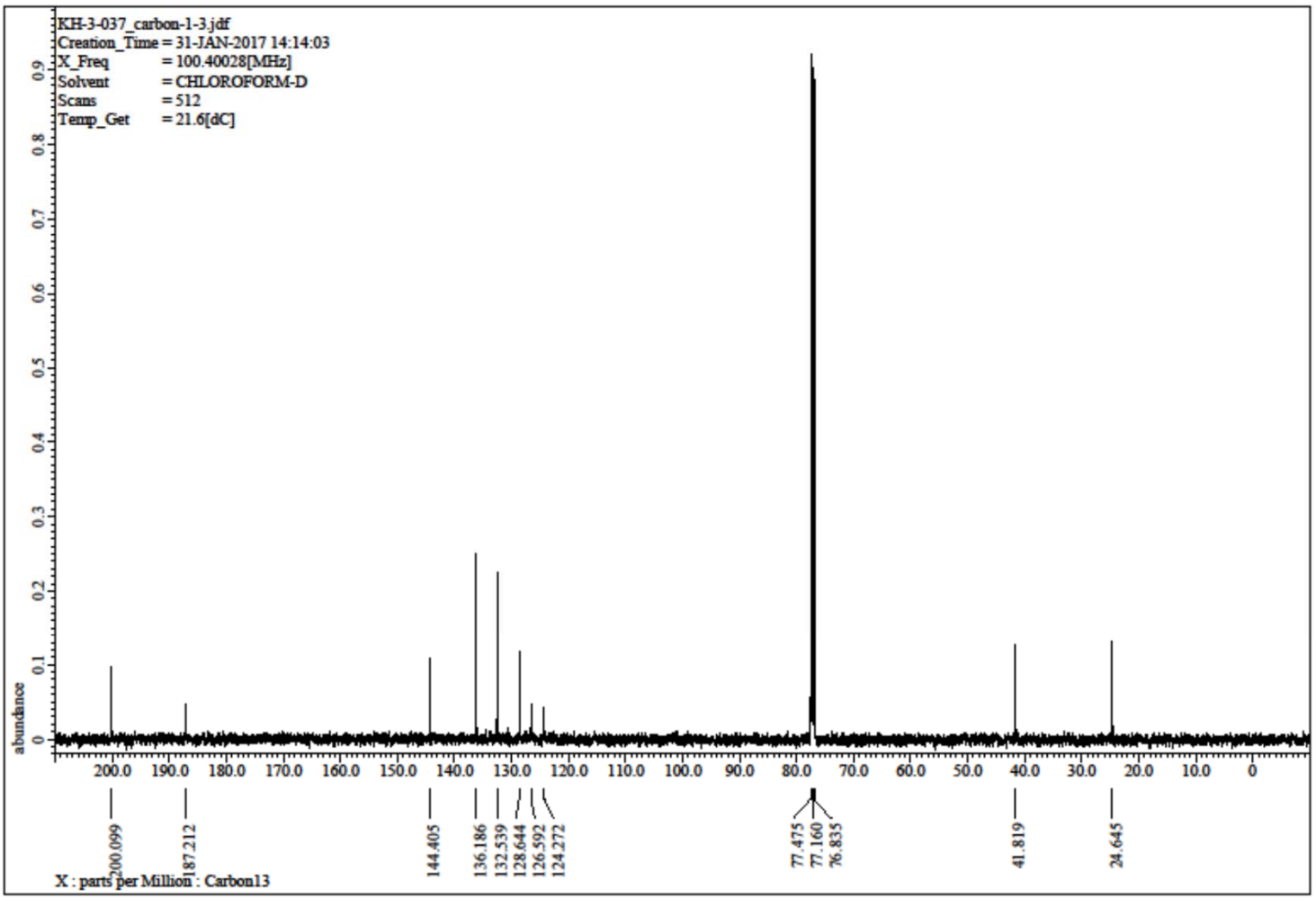
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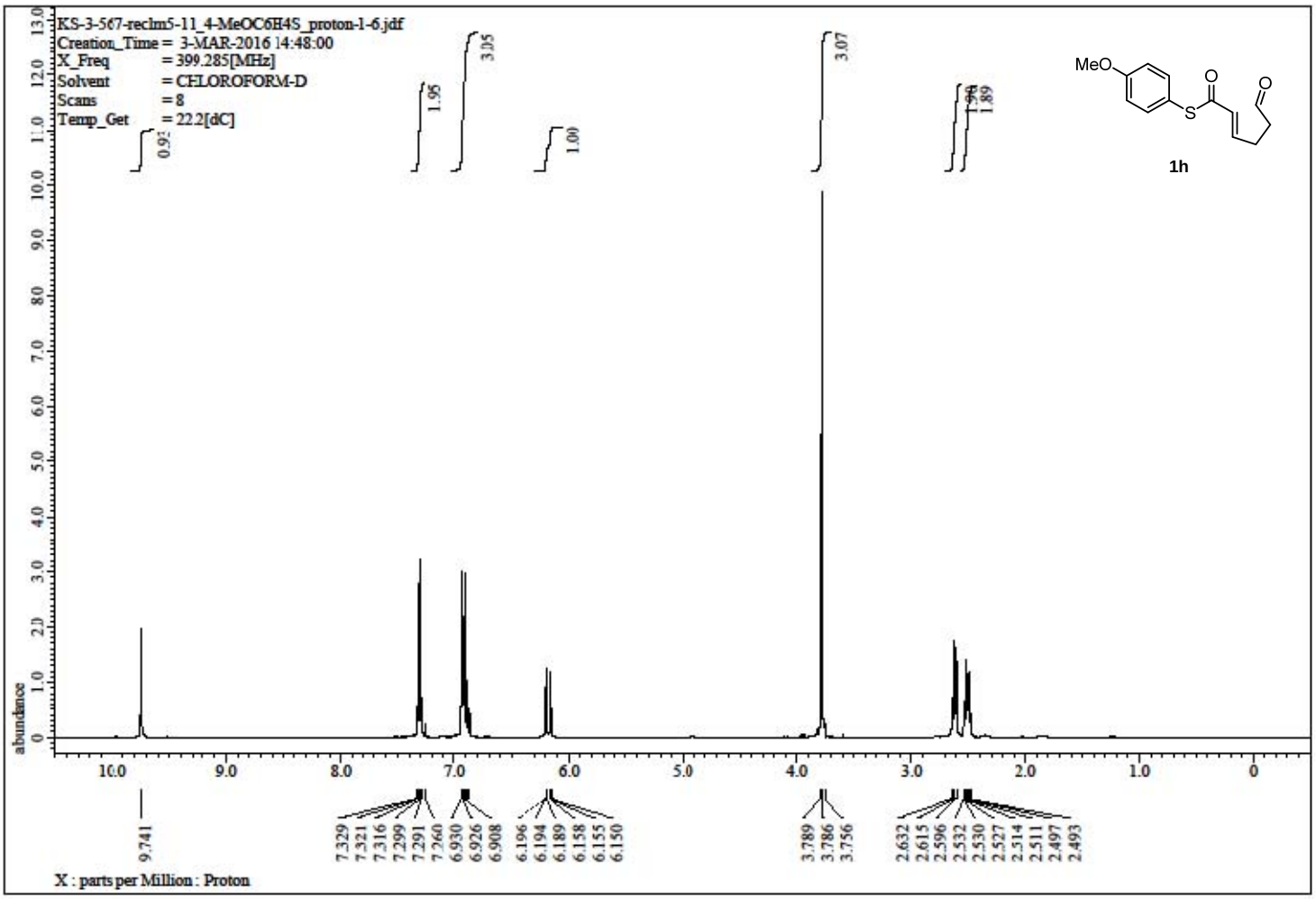
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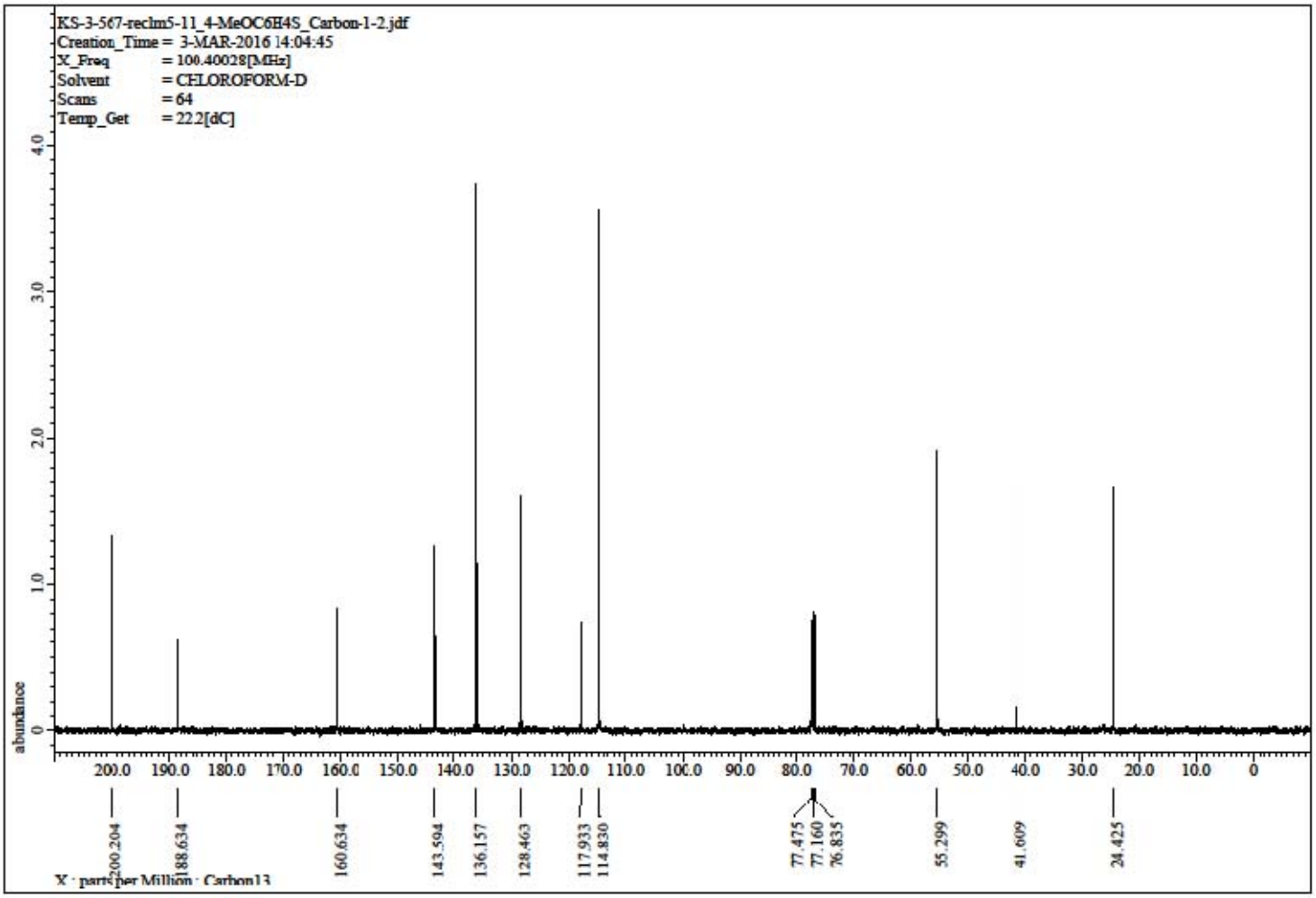
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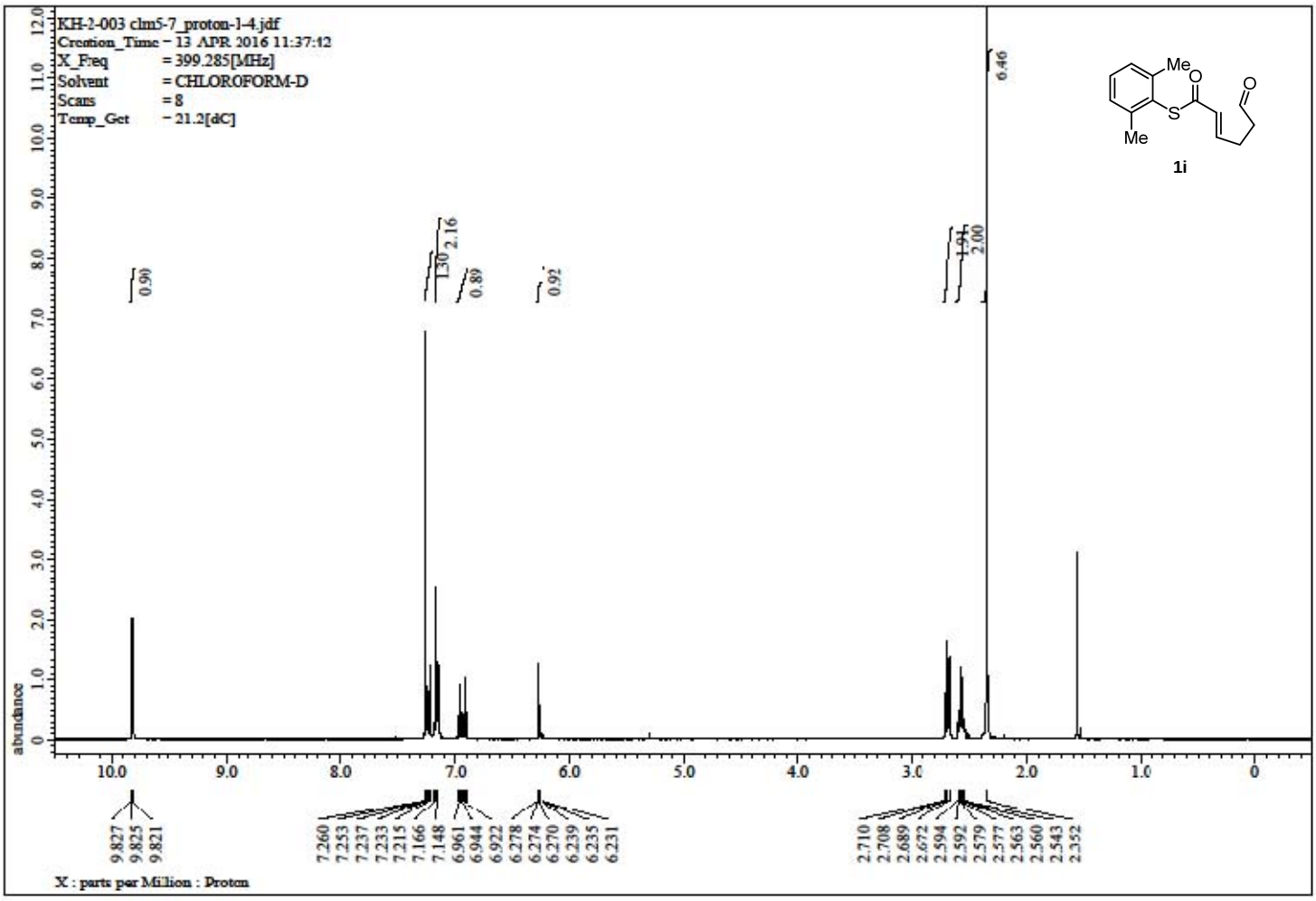
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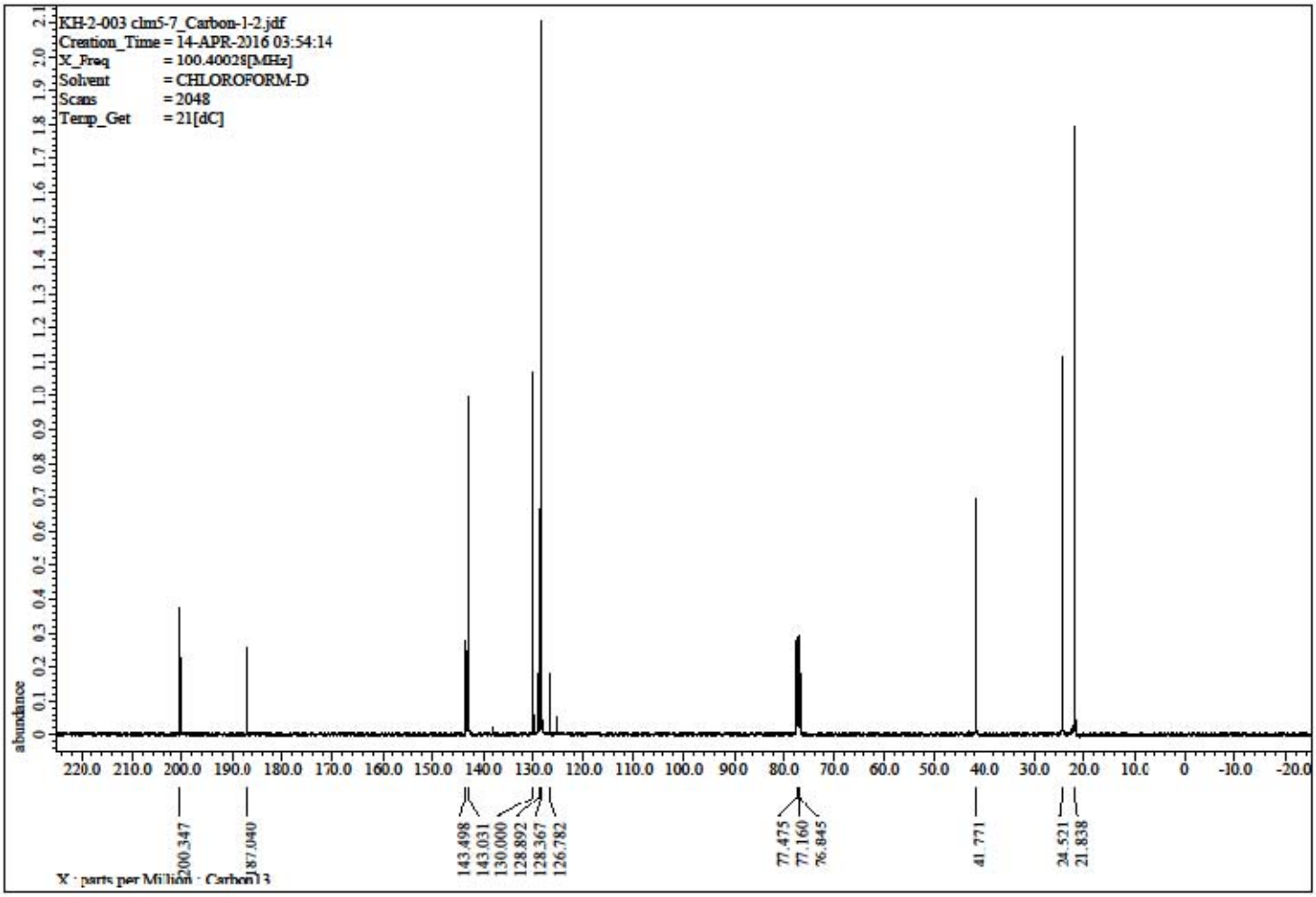
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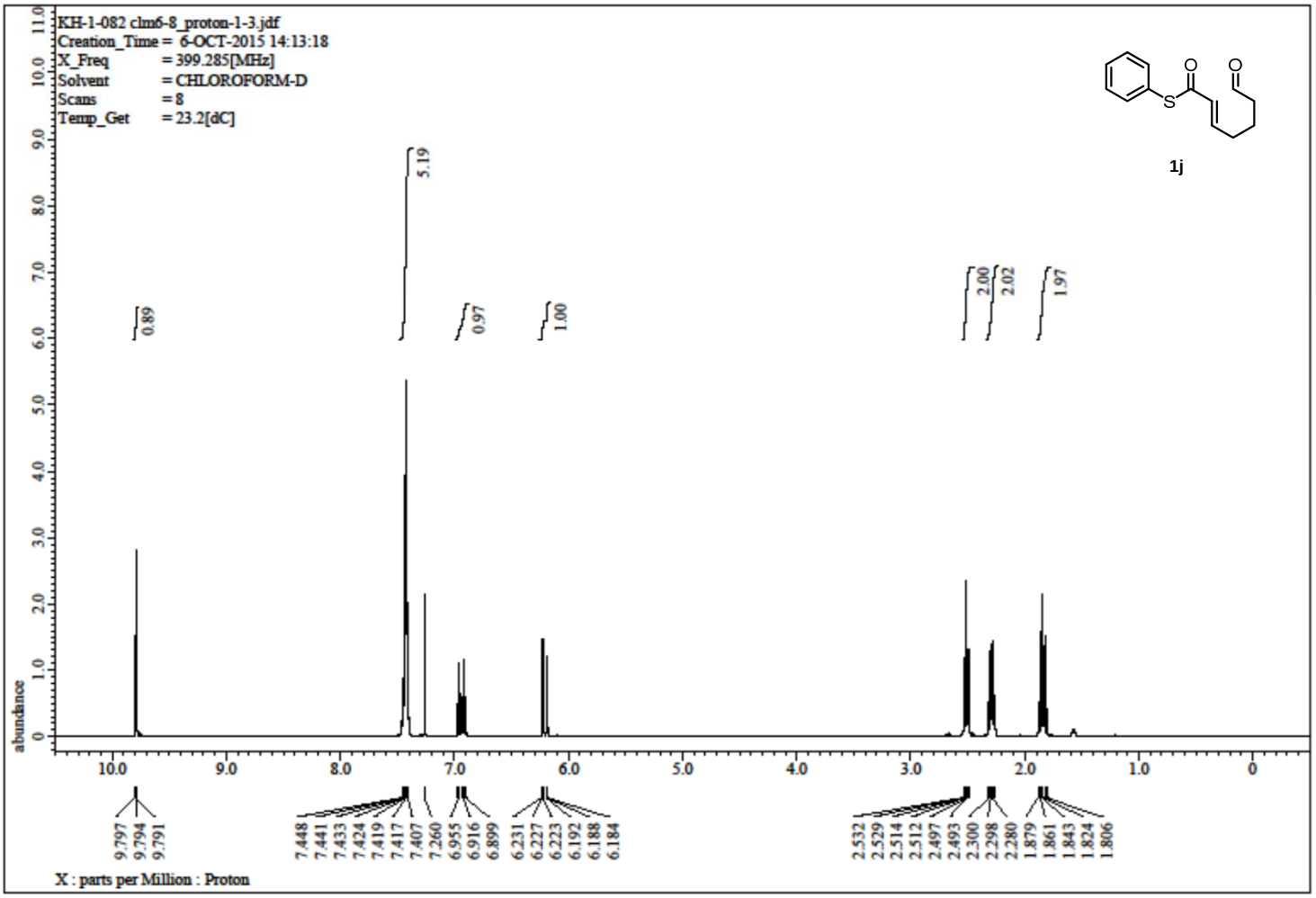
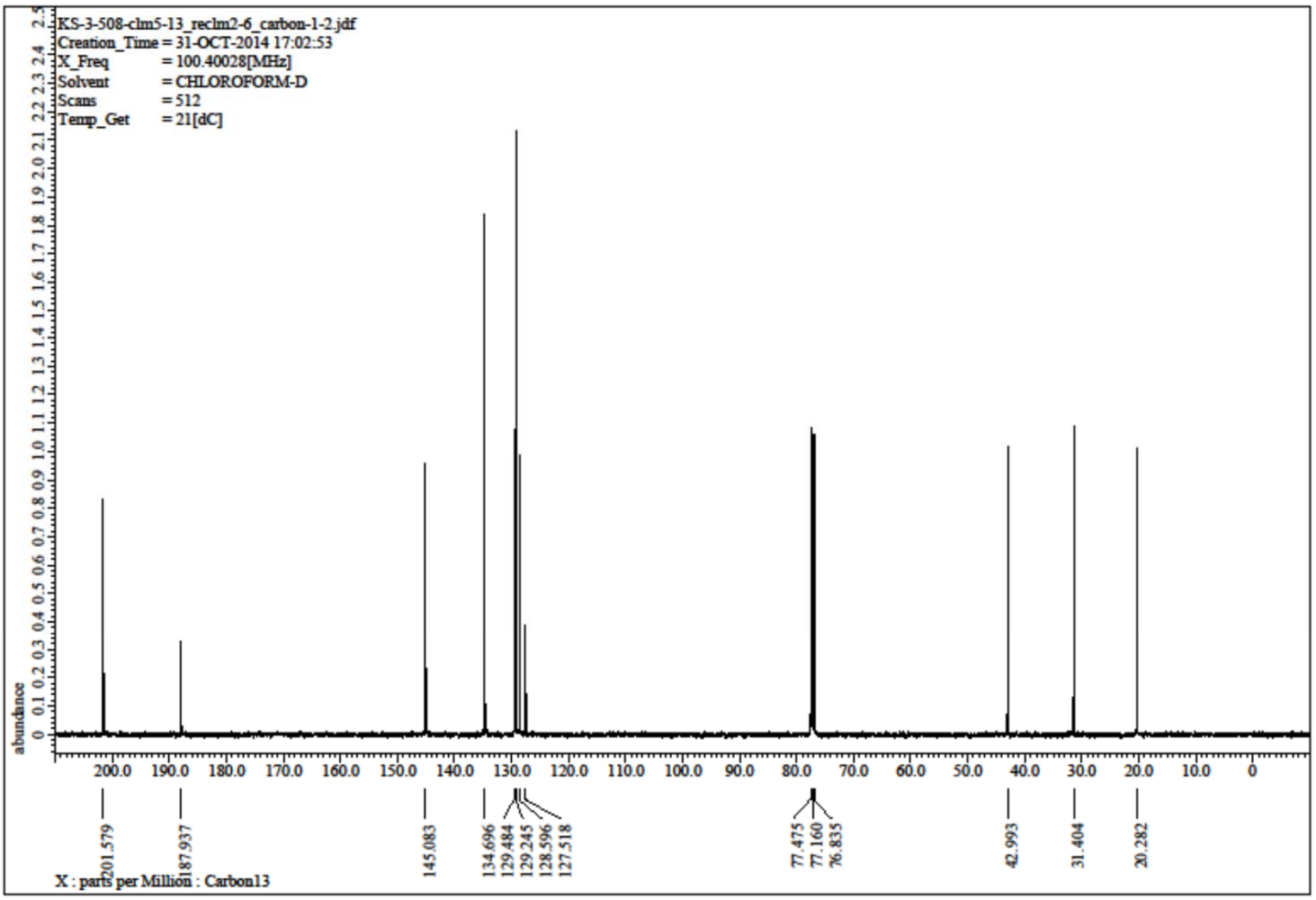
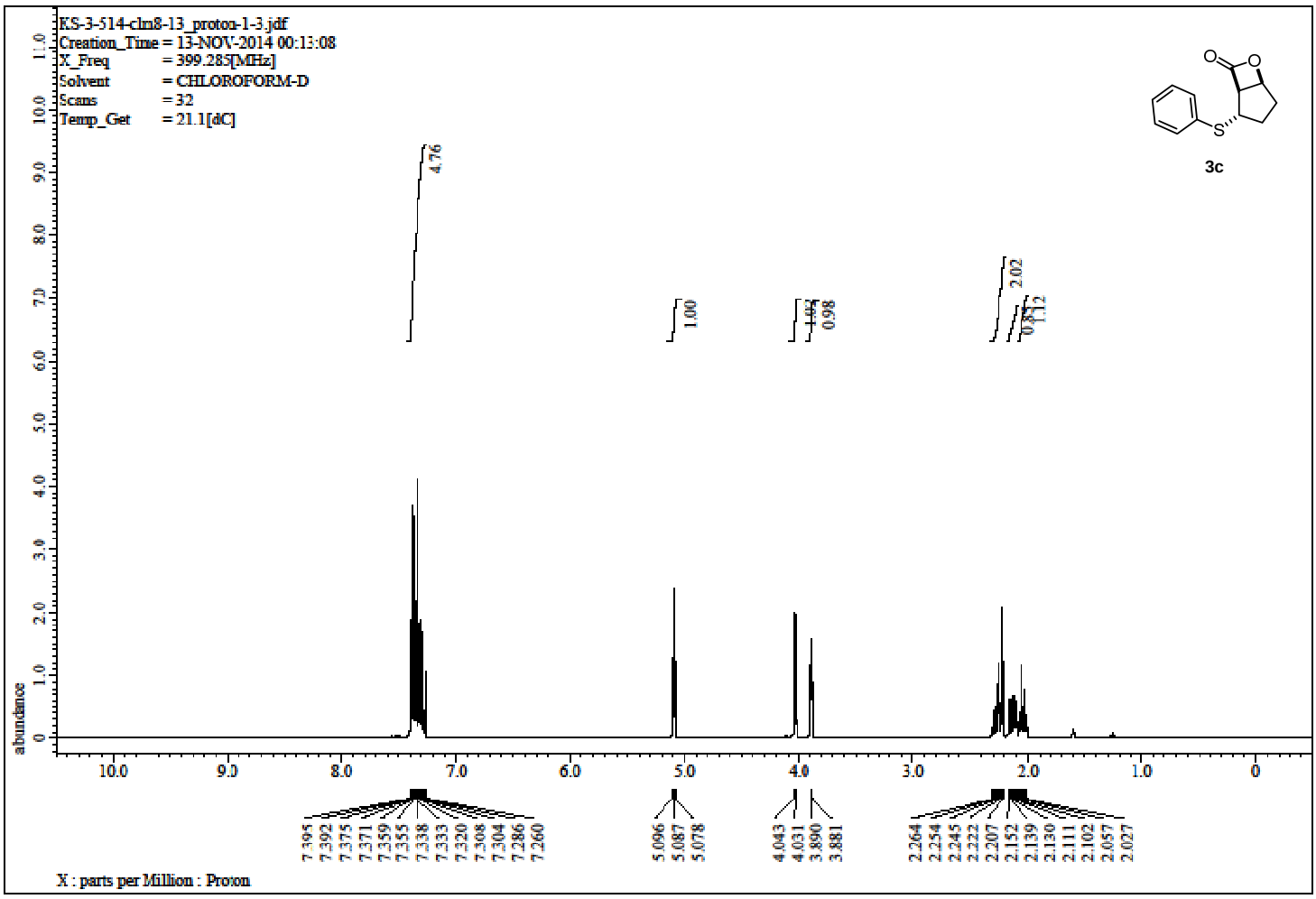
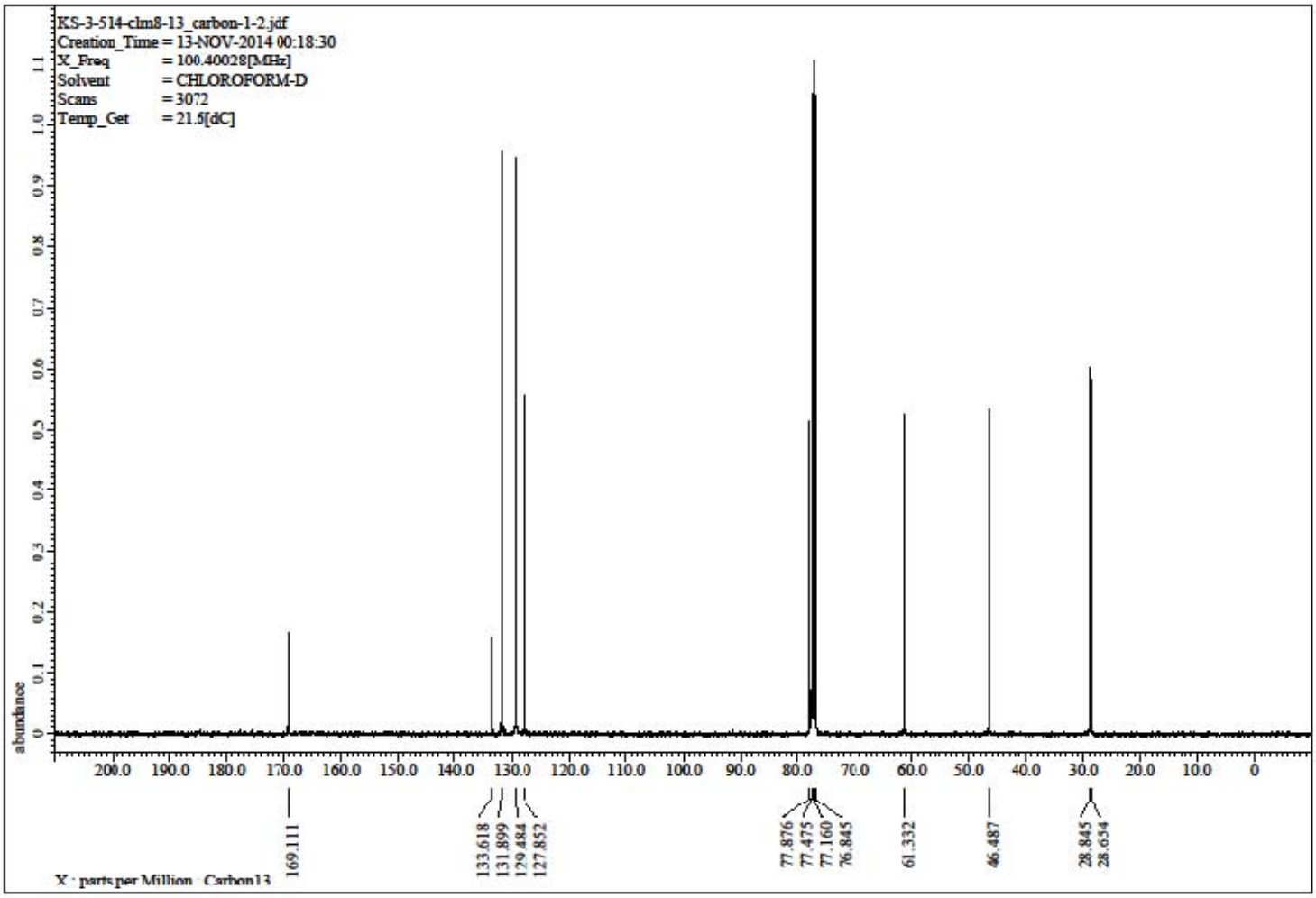
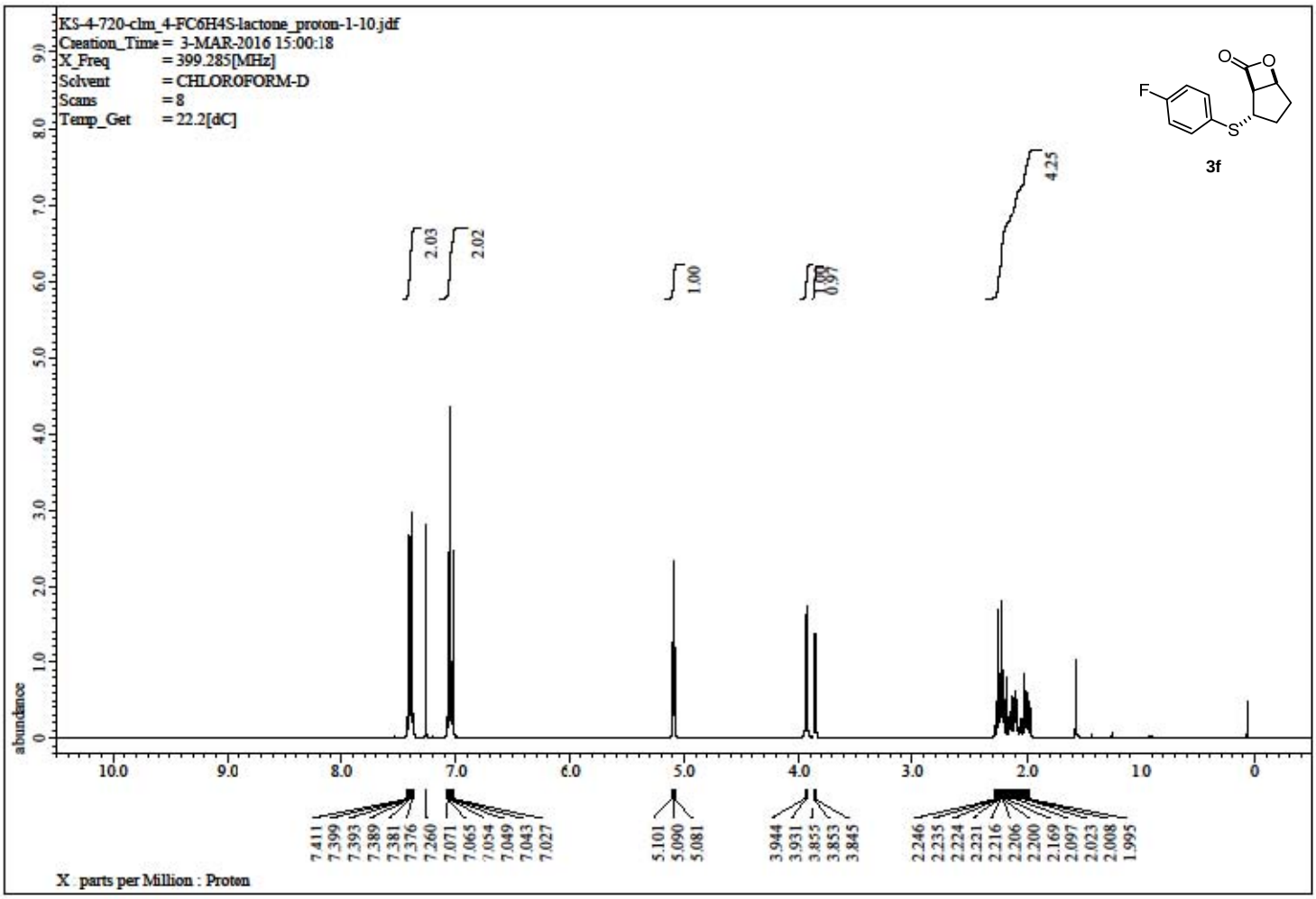
X : parts per Million : Carbon13

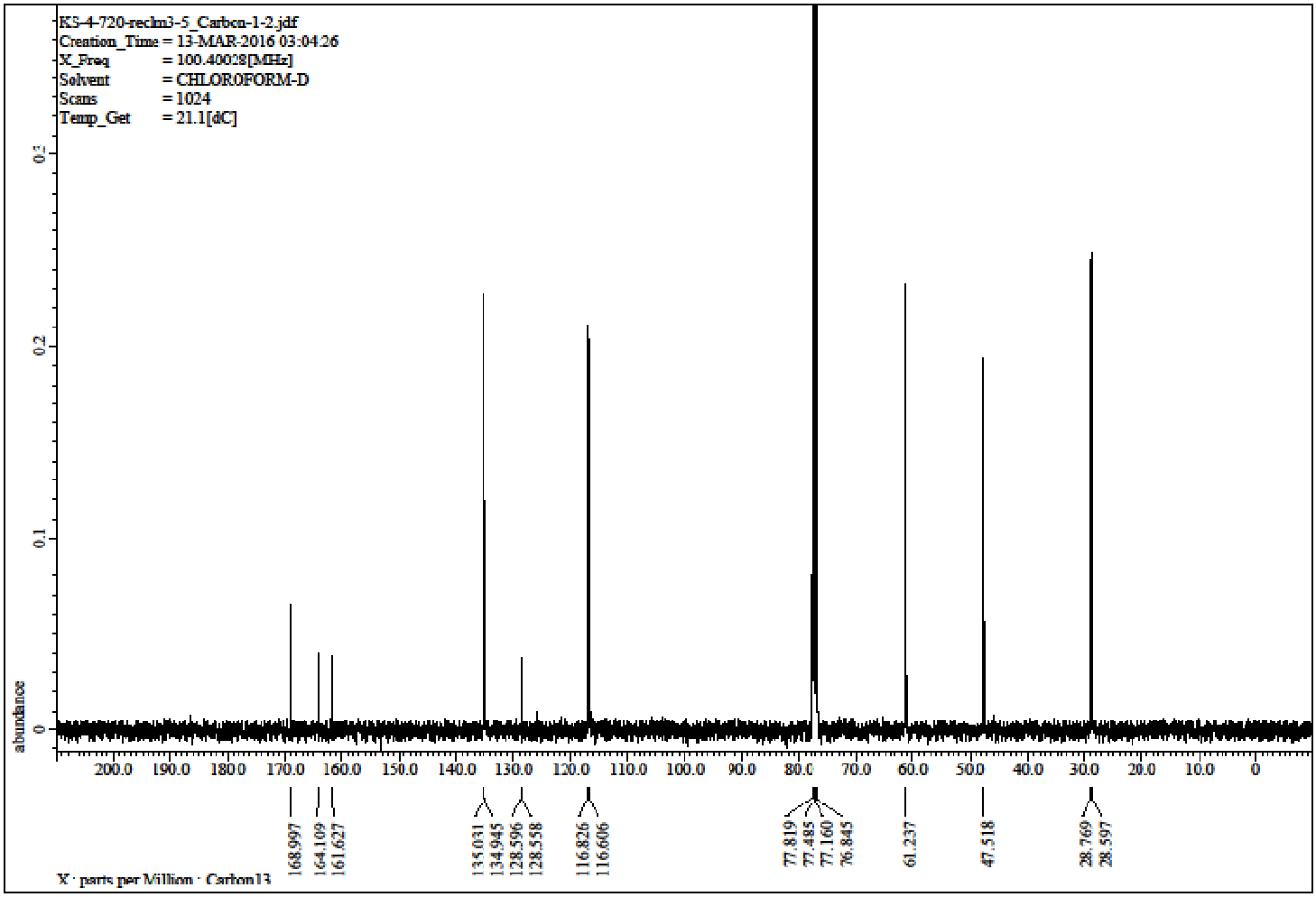

KH-1-082 clm6-8_proton-1-3.jdf
Creation_Time = 6-OCT-2015 14:13:18
X_Freq = 399.285[MHz]
Solvent = CHLOROFORM-D
Scans = 8
Temp_Get = 23.2[dC]
1j
abundance
X : parts per Million : Proton

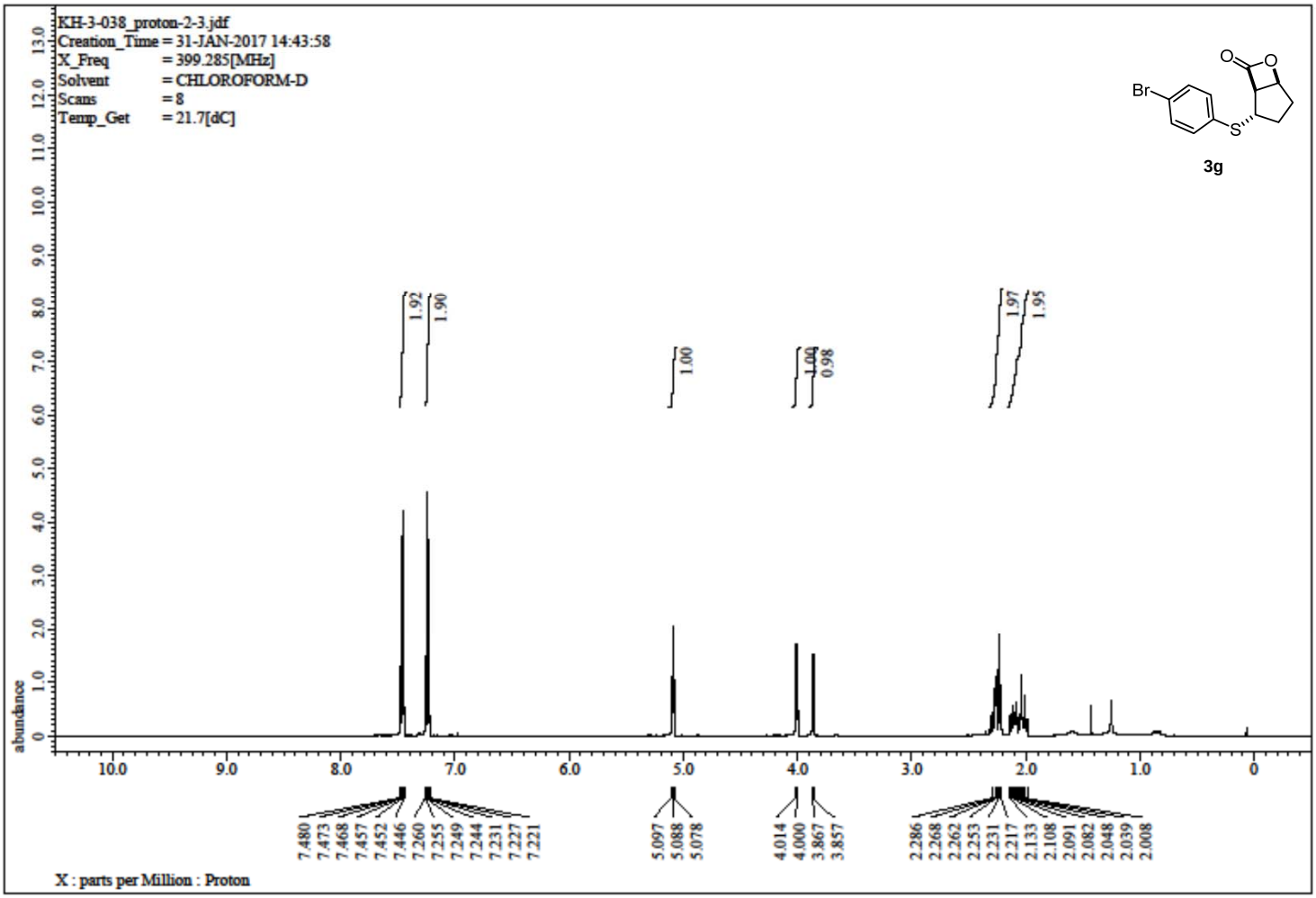

KS-3-508-clm5-13_reclm2-6_carbon-1-2.jdf
Creation_Time = 31-OCT-2014 17:02:53
X_Freq = 100.40028[MHz]
Solvent = CHLOROFORM-D
Scans = 512
Temp_Get = 21[dC]
abundance
X : parts per Million : Carbon13

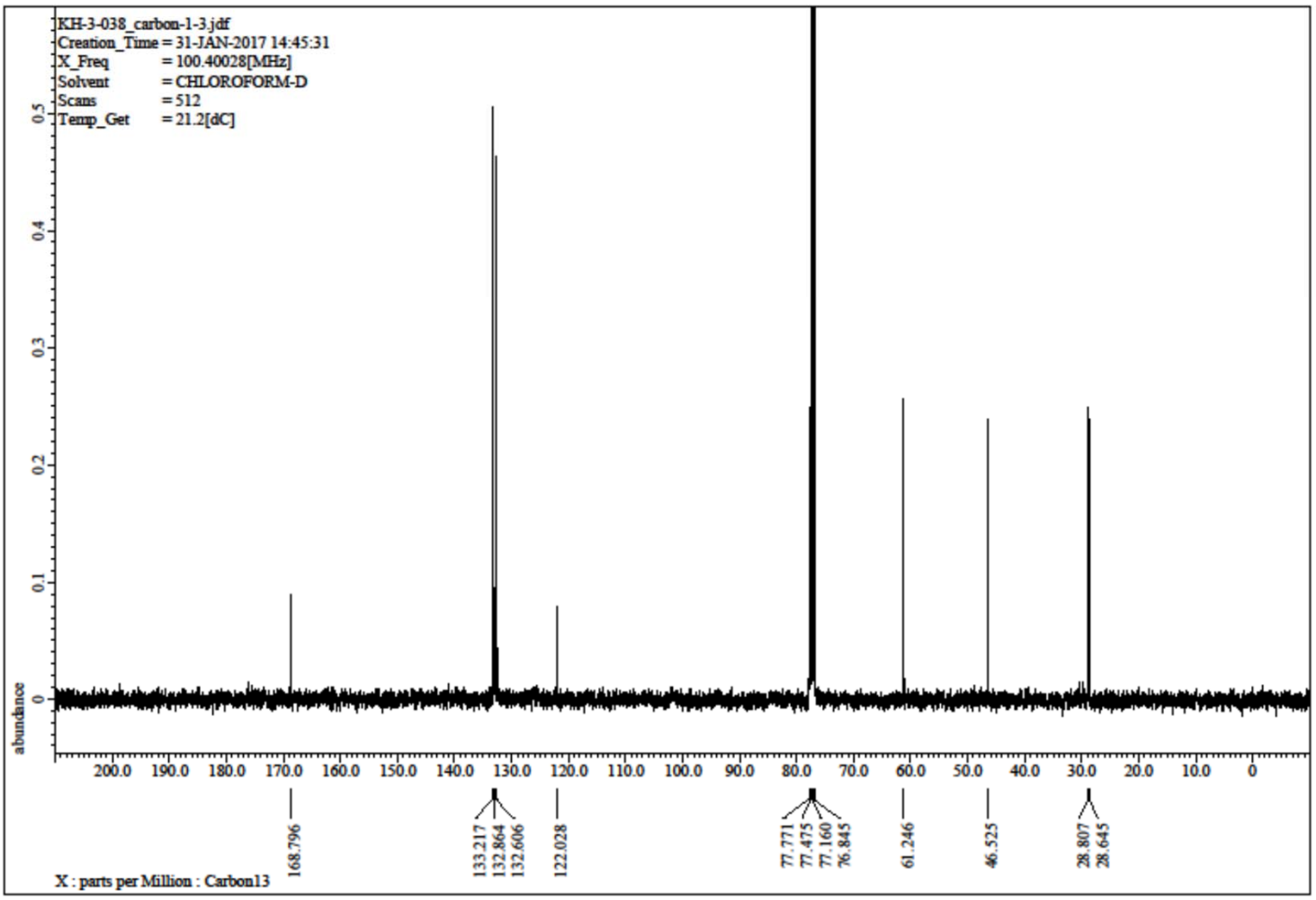

KS-3-514-clm8-13_proton-1-3.jdf
Creation_Time = 13-NOV-2014 00:13:08
X_Freq = 399.285[MHz]
Solvent = CHLOROFORM-D
Scans = 32
Temp_Get = 21.1[dC]
3c
4.76
1.00
0.98
2.02
1.12
abundance
7.395 7.392 7.375 7.371 7.359 7.355 7.338 7.333 7.320 7.308 7.304 7.286 7.260
5.096 5.087 5.078
4.043 4.031 3.890 3.881
2.264 2.254 2.245 2.222 2.207 2.152 2.139 2.130 2.111 2.102 2.057 2.027
X : parts per Million : Proton

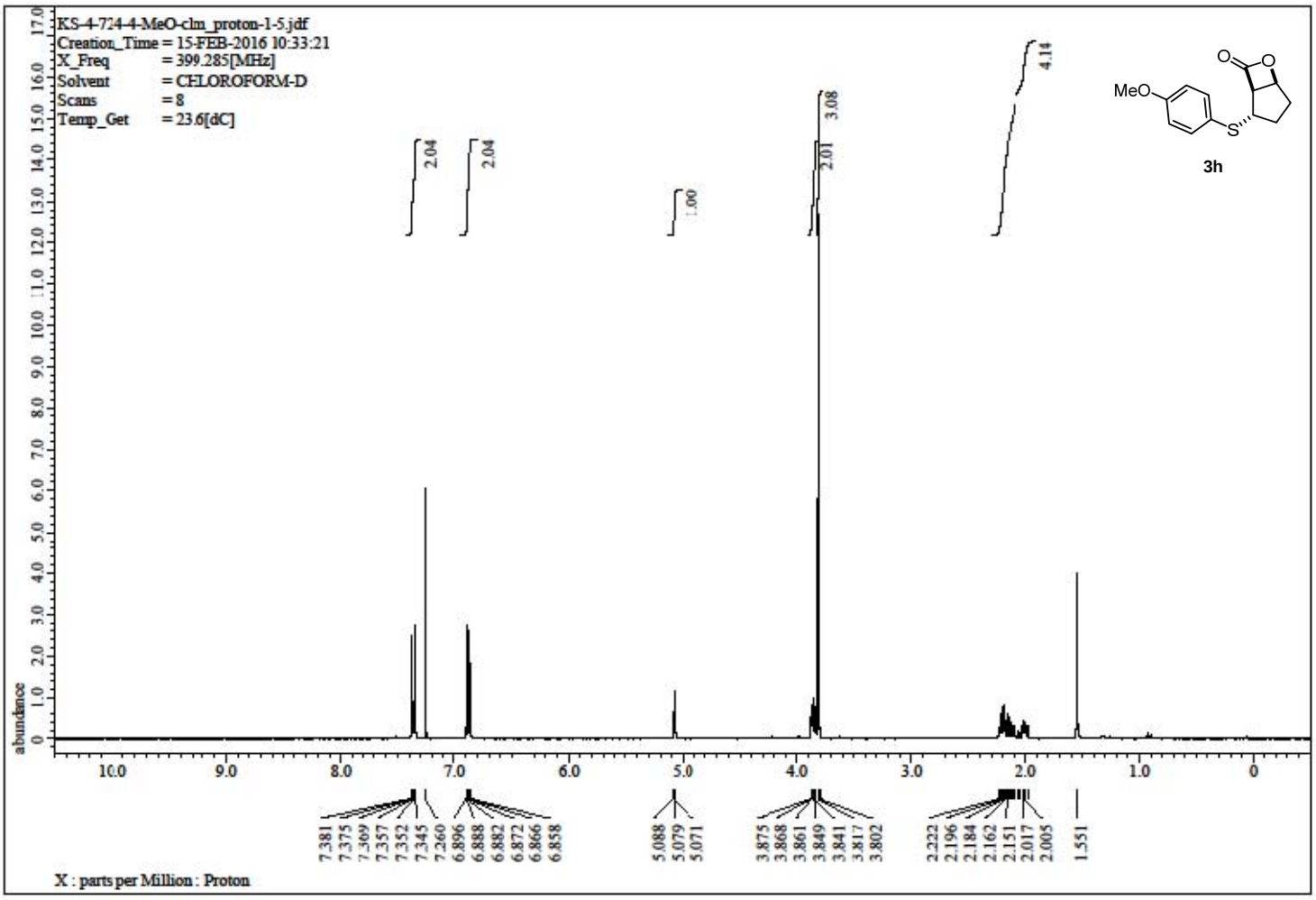

KS-3-514-clm8-13_carbon-1-2.jdf
Creation_Time = 13-NOV-2014 00:18:30
X_Freq = 100.40028[MHz]
Solvent = CHLOROFORM-D
Scans = 3072
Temp_Get = 21.5[dC]
abundance
169.111
133.618 131.899 129.484 127.852
77.876 77.475 77.160 76.845
61.332
46.487
28.845 28.654
X : parts per Million : Carbon13

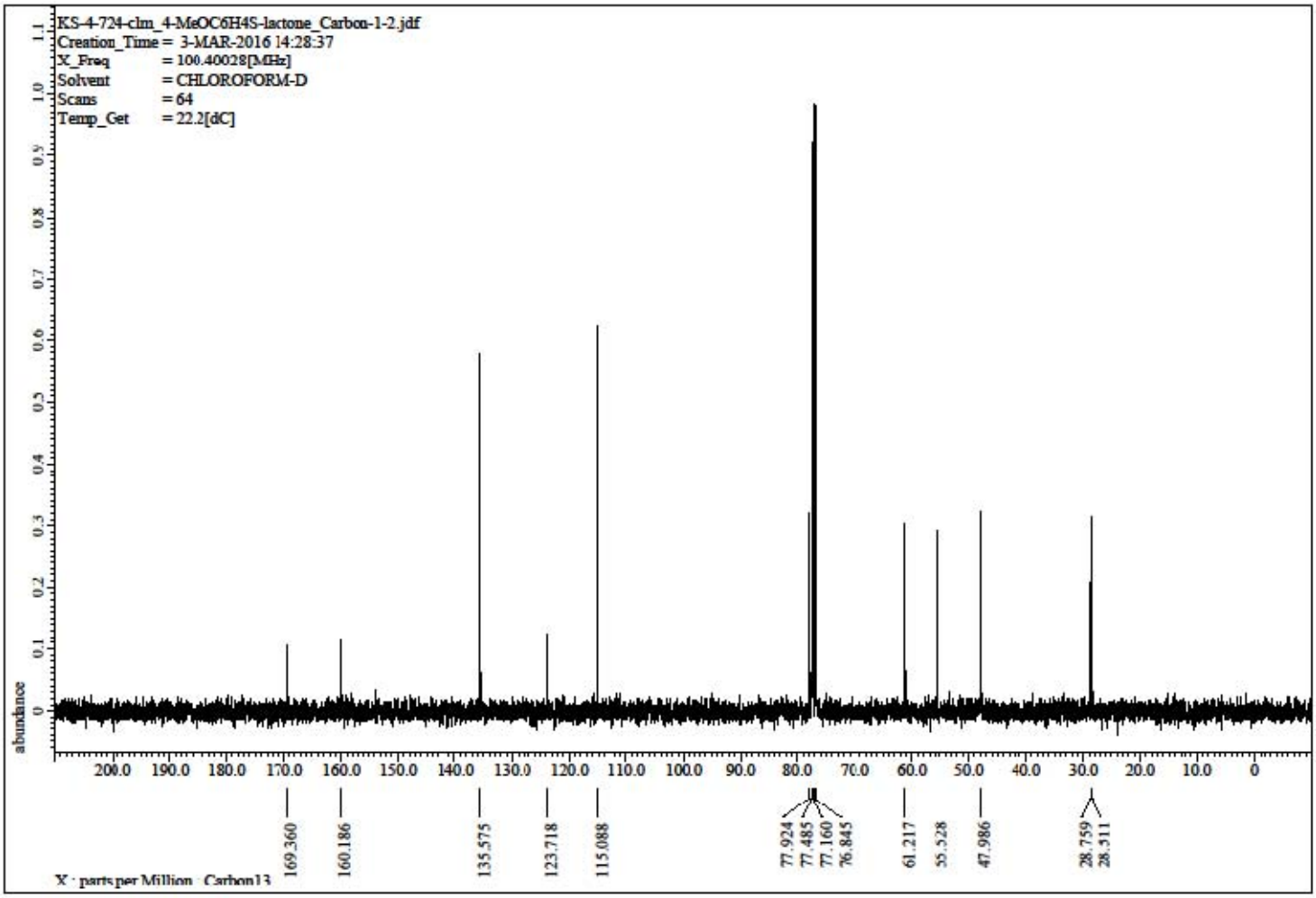

KS-4-720-clm_4-FC6H4S-lactone_proton-1-10.jdf
Creation_Time = 3-MAR-2016 15:00:18
X_Freq = 399.285[MHz]
Solvent = CHLOROFORM-D
Scans = 8
Temp_Get = 22.2[dC]
3f
2.03
2.02
1.00
0.97
4.25
abundance
X : parts per Million : Proton

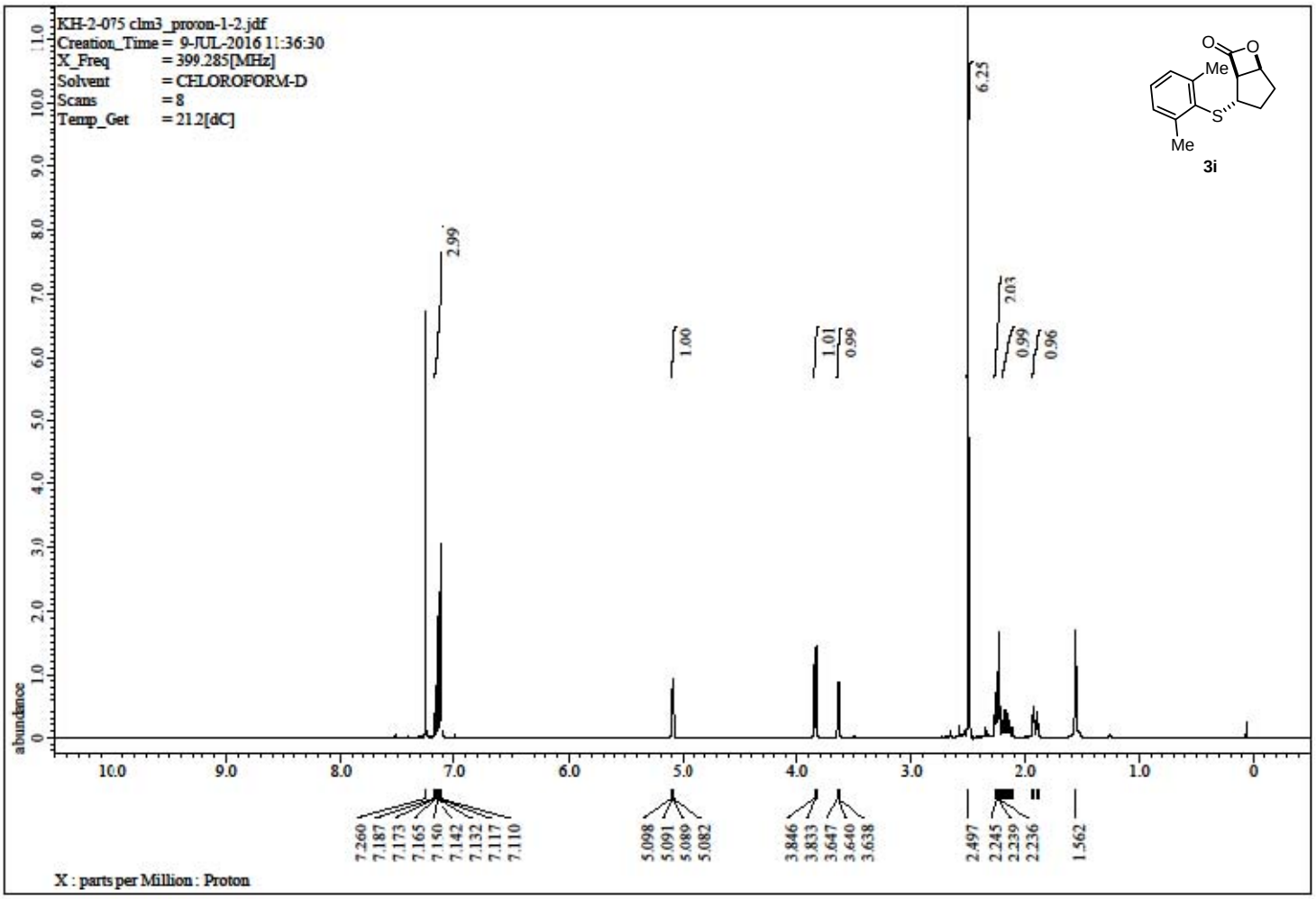

KS-4-720-reclm3-5_Carbon-1-2.jdf
Creation_Time = 13-MAR-2016 03:04:26
X_Freq = 100.40028[MHz]
Solvent = CHLOROFORM-D
Scans = 1024
Temp_Get = 21.1[dC]
abundance
X : parts per Million : Carbon13

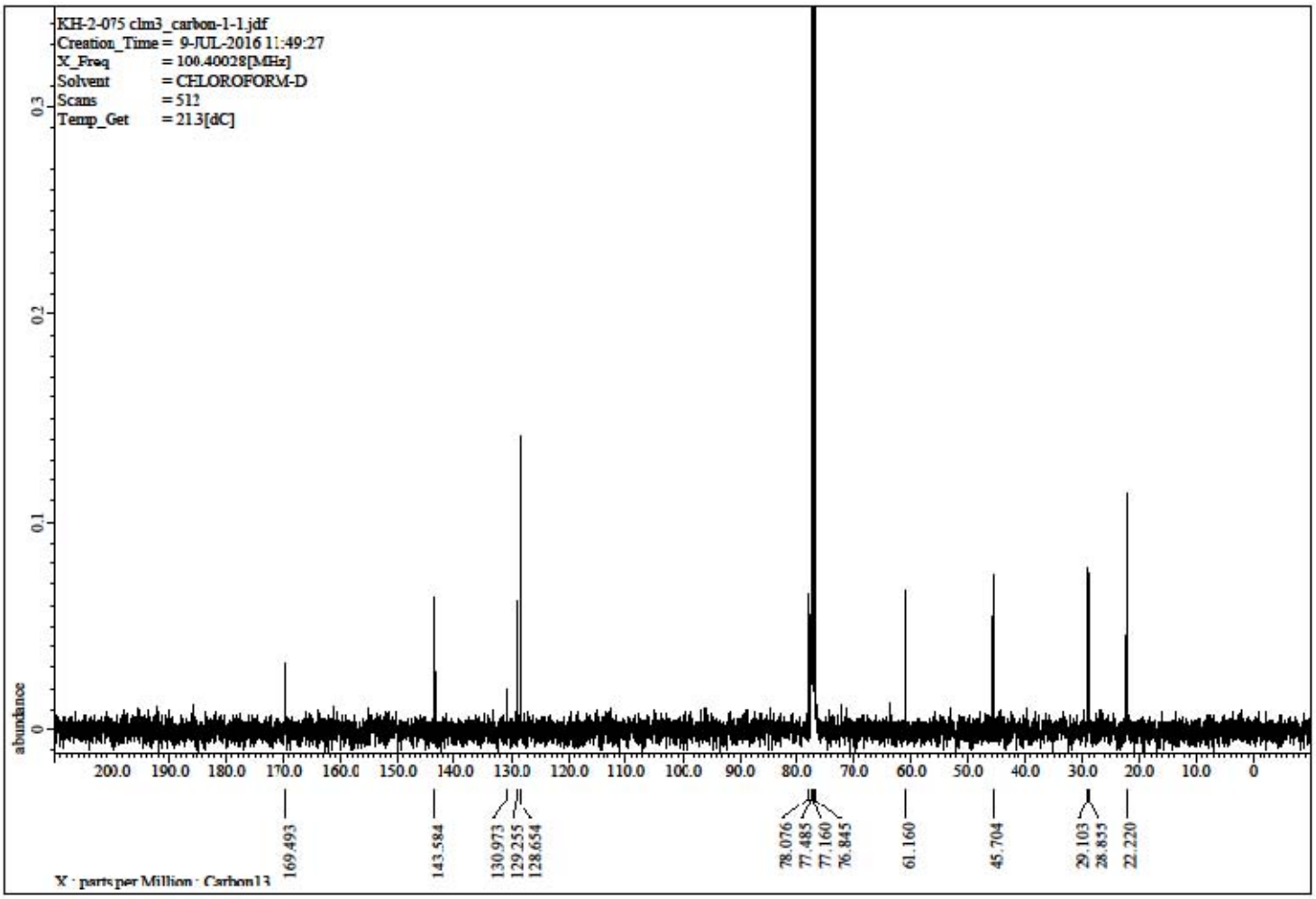

KH-3-038_proton-2-3.jdf
Creation_Time = 31-JAN-2017 14:43:58
X_Freq = 399.285[MHz]
Solvent = CHLOROFORM-D
Scans = 8
Temp_Get = 21.7[dC]
Br
3g
1.92
1.90
1.00
1.00
0.98
1.97
1.95
7.480 7.473 7.468 7.457 7.452 7.446 7.260 7.255 7.249 7.244 7.231 7.227 7.221
5.097 5.088 5.078
4.014 4.000 3.867 3.857
2.286 2.268 2.262 2.253 2.231 2.217 2.133 2.108 2.091 2.082 2.048 2.039 2.008
abundance
X : parts per Million : Proton


KH-3-038_carbon-1-3.jdf
Creation_Time = 31-JAN-2017 14:45:31
X_Freq = 100.40028[MHz]
Solvent = CHLOROFORM-D
Scans = 512
Temp_Get = 21.2[dC]
168.796
133.217 132.864 132.606
122.028
77.771 77.475 77.160 76.845
61.246
46.525
28.807 28.645
abundance
X : parts per Million : Carbon13


KS-4-724-4-MeO-clm_proton-1-5.jdf
Creation_Time = 15-FEB-2016 10:33:21
X_Freq = 399.285[MHz]
Solvent = CHLOROFORM-D
Scans = 8
Temp_Get = 23.6[dC]
MeO
3h
2.04
2.04
1.00
2.01
3.08
4.14
7.381
7.375
7.369
7.357
7.352
7.345
7.260
6.896
6.888
6.882
6.872
6.866
6.858
5.088
5.079
5.071
3.875
3.868
3.861
3.849
3.841
3.817
3.802
2.232
2.196
2.184
2.162
2.151
2.017
2.005
1.551
X : parts per Million : Proton


KS-4-724-clm_4-MeOC6H4S-lactone_Carbon-1-2.jdf
Creation_Time = 3-MAR-2016 14:28:37
X_Freq = 100.40028[MHz]
Solvent = CHLOROFORM-D
Scans = 64
Temp_Get = 22.2[dC]
169.360
160.186
135.575
123.718
115.088
77.924
77.485
77.160
76.845
61.217
55.528
47.986
28.759
28.311
X : parts per Million : Carbon13


KH-2-075 clm3_proton-1-2.jdf
Creation_Time = 9-JUL-2016 11:36:30
X_Freq = 399.285[MHz]
Solvent = CHLOROFORM-D
Scans = 8
Temp_Get = 21.2[dC]
Me
Me
3i
6.25
2.99
1.00
1.01
0.99
2.03
0.99
0.96
7.260
7.187
7.173
7.165
7.150
7.142
7.132
7.117
7.110
5.098
5.091
5.089
5.082
3.846
3.833
3.647
3.640
3.638
2.497
2.245
2.239
2.236
1.562
X : parts per Million : Proton


KH-2-075 clm3_carbon-1-1.jdf
Creation_Time = 9-JUL-2016 11:49:27
X_Freq = 100.40028[MHz]
Solvent = CHLOROFORM-D
Scans = 512
Temp_Get = 21.3[dC]
169.493
143.584
130.973
129.255
128.654
78.076
77.485
77.160
76.845
61.160
45.704
29.103
28.835
22.220
X : parts per Million : Carbon13

References

1) Yost, J. M.; Alfie, R. J.; Tarsis, E. M.; Chong, I.; Coltart, D. M. *Chem. Commun.* **2011**, *47*, 571.

2) Tan, H.; Chen, X.; Chen, H.; Liu, H.; Qiu, S. *Eur. J. Org. Chem.* **2015**, *2015*, 4956.