Electronic Supplementary Information

Asymmetric Alkynylation of Aldehydes with Propiolate without High Reagent Loading and Any Additives

Naoto Kojima,* Shogo Nishijima, Kaoru Tsuge, Tetsuaki Tanaka*

Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamadaoka, Suita, Osaka 565-0871, Japan

kojima@phs.osaka-u.ac.jp, t-tanaka@phs.osaka-u.ac.jp

Generals: S1
Preparation of chiral ligand **2d**: S2
General procedure for asymmetric alkynylation of aliphatic aldehydes: S3
γ-hydroxy-α,β-acetylenic esters **1a-d**: S4
General procedure for asymmetric alkynylation of aromatic aldehydes: S5
γ-hydroxy-α,β-acetylenic esters **1e-k**: S5
Conversion of ethyl ester **1e** into the known methyl ester **S3** to determine the stereochemistry: S8
Conversion of alkynes **1f-j** into allyl alcohols **S4-6** in order to determine the stereochemistry by the modified Mosher method: S8
Preparation of MTPA esters **S7-12**: S9
Determination of the stereochemistry of allyl alcohols S4-6 by the modified Mosher method: S11
References:
^{1}H NMR/^{13}C NMR Spectra: S12

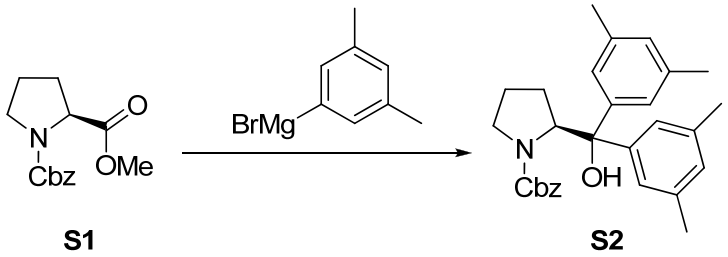
Generals:

Melting points are uncorrected. Optical rotations were measured by using a JASCO P-1020 digital polarimeter. ^{1}H NMR spectra were recorded in $CDCl_3$ solution with a JEOL JNM-GX-500 spectrometer (500 MHz) or a JEOL JNM-ECS400 (400 MHz). ^{13}C NMR spectra were recorded in $CDCl_3$ solution with a JEOL JNM-ECS400 (100 MHz) or a JNM-GX-500 (125 MHz). All signals are expressed as δ values in ppm downfield from the internal standard tetramethylsilane. The following abbreviations are used: broad = br, singlet = s, doublet = d, triplet = t, quartet = q, quintet = qn and multiplet = m. IR absorption spectra (FT = diffuse reflectance spectroscopy) were recorded for samples loaded as neat films on NaCl plates by using a Shimazu FTIR-8400S and only noteworthy absorptions (in cm^{-1}) are listed. Mass spectra were obtained with a JEOL JMS-600H or a JEOL JMS-700 mass spectrometer. Column chromatography was carried out by using Kanto Chemical silica gel 60N (spherical, neutral, 63–210 μm) and flash column chromatography was carried out by using Merck silica gel 60 (40–63 μm). All air- or moisture-sensitive reactions were

carried out in flame-dried glassware under an atmosphere of Ar. All reagents were used as received from commercial suppliers unless otherwise noted. All solvents were dried and distilled according to standard procedures. All organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure with rotary evaporator.

Preparation of chiral ligand 2d:

(*S*)-Benzyl 2-(bis(3,5-dimethylphenyl)hydroxymethyl)pyrrolidine-1-carboxylate (S2)

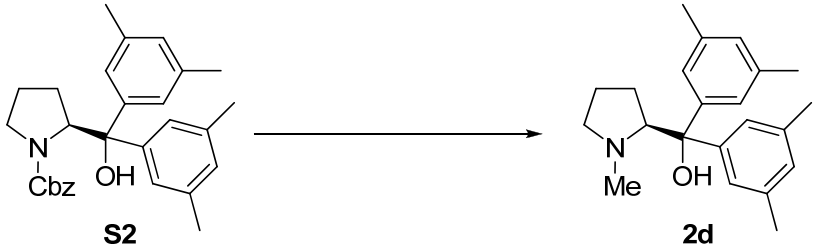


S1 **S2**

A three-necked, round-bottomed flask with a reflux condenser was charged with magnesium turnings (369 mg, 15.2 mmol). Vacuum (10 mmHg) was applied and the flask was heated with a heat gun. After the flask was cooled to rt, the vacuum was released. After THF (17 mL) and small amount of I_2 were added to the flask, 5-bromo-*m*-xylene (2.08 mL, 15.2 mmol) was added dropwise to the mixture with stirring at rt. The reaction mixture was stirred for 1 h at 80 °C to give a solution of 3,5-dimethylphenylmagnesium bromide in THF. The prepared Grignard reagent was added dropwise to a solution of ester **S1**[S1] (1.00 g, 3.80 mmol) in THF (4.0 mL) at 0 °C with stirring. After 1 h at rt, the reaction was quenched with sat. NH_4Cl, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine prior to drying and solvent evaporation. Purification by flash column chromatography over silica gel with Et_2O–*n*-hexane (1:5 to 1:2) as eluent yielded alcohol **S2** (1.32 g, 78%) as a white amorphous.

S2: $[\alpha]^{20}_D = -121.5$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.71–0.85 (m, 1H), 1.43–1.56 (m, 1H), 1.91–1.99 (m, 1H), 2.04–2.15 (m, 1H), 2.26 (s, 6H), 2.27 (s, 6H), 2.90–3.05 (m, 1H), 3.37–3.56 (m, 1H), 4.91 (dd, 1H, J = 9.1, 3.1 Hz), 5.04 (br s, 1H), 5.21 (d, 1H, J = 12.2 Hz), 6.90 (s, 2H), 6.99 (s, 2H), 7.00 (s, 2H), 7.28–7.37 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.4 (2C), 21.5 (2C), 22.9, 29.7, 47.8, 66.2, 67.3, 81.6, 125.4 (2C), 125.9 (2C), 127.6 (2C), 127.9, 128.5 (2C), 128.66, 128.73, 136.6, 136.7, 137.1, 143.5, 146.3; IR (neat) cm^{-1}: 3420, 1678; MS (FAB) *m/z*: 466 $[M + Na]^+$; HRMS (FAB) calcd for $C_{29}H_{33}NO_3Na$ $[M + Na]^+$ 466.2358; found: 466.2358.

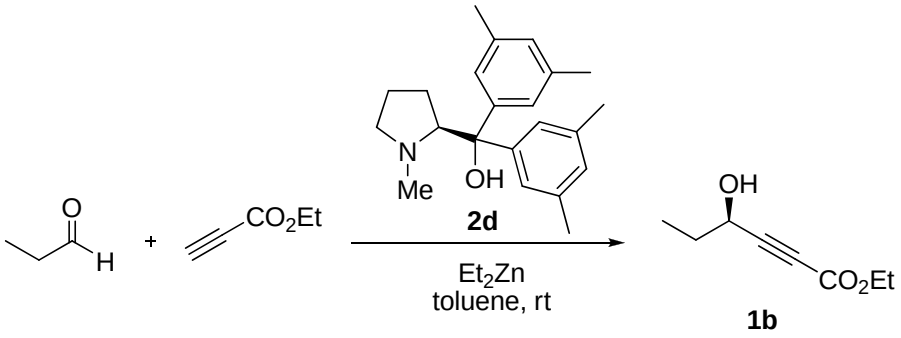
(*S*)-Bis(3,5-dimethylphenyl)(1-methylpyrrolidin-2-yl)methanol (2d)



$LiAlH_4$ (2.47 g, 65.2 mmol) was carefully added to a solution of alcohol **S2** (9.64 g, 21.7 mmol) in THF (210 mL) at 0 °C with stirring. After 0.5 h at 90 °C, the reaction was quenched with sat. NH_4Cl. After filtration through Celite, the solvent was evaporated under the reduced pressure. The residue was recrystallized from *n*-hexane to give ligand **2d** (5.86 g, 84%) as a colorless plate.

2d: M.p. 149.5–152.0 °C (*n*-hexane); $[\alpha]^{22}_D$ = +59.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.57–1.70 (m, 3H), 1.81–1.91 (m, 4H), 2.27 (s, 12H), 2.39–2.44 (m, 1H), 3.01–3.13 (m, 1H), 3.55–3.58 (m, 1H), 4.66 (br s, 1H), 6.74 (s, 1H), 6.75 (s, 1H), 7.12 (s, 2H), 7.23 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.55 (2C), 21.57 (2C), 24.0, 29.9, 43.1, 59.2, 72.0, 77.3, 123.2 (2C), 123.3 (2C), 127.70, 127.74, 137.17 (2C), 137.20 (2C), 146.7, 148.2; IR (neat) cm^{-1}: 3354; MS (FAB) *m/z*: 324 $[M + H]^+$; HRMS (FAB) calcd for $C_{22}H_{30}NO$ $[M + H]^+$ 324.2322; found: 324.2357.

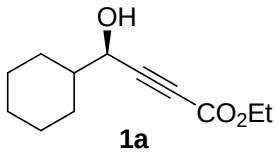
General procedure for asymmetric alkynylation of aliphatic aldehydes (Table 3, Entry 1):



A round-bottomed flask equipped with a three-way stopcock connected to an argon balloon through a disposable plastic tube filled with blue silica gel and calcium chloride was charged with a solution of ligand **2d** (97.0 mg, 0.300 mmol) in toluene (6.0 mL). To the solution, Et_2Zn (1.0 M in *n*-hexane, 1.20 mL, 1.20 mmol), ethyl propiolate (0.101 mL, 1.00 mmol), and propionaldehyde (72.1 μL, 1.00 mmol) were added at rt with stirring. After 2 h, the reaction was quenched with sat. NH_4Cl. 1N HCl aq. was added to the mixture and the mixture was extracted with EtOAc. The combined organic layers were washed with brine prior to drying and solvent evaporation. Purification by flash column chromatography over silica gel with Et_2O–*n*-hexane (1:15) as eluent yielded alcohol **1b** (99.0 mg, 63%, 89% ee) as a yellow oil.

(*R*)-Ethyl 4-hydroxyhex-2-ynoate (1b)

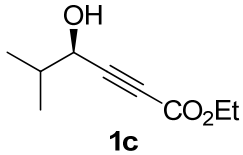
1b: yellow oil: $[\alpha]^{23}_{D}$ = +6.2 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.97 (t, 3H, *J* = 7.3 Hz), 1.25 (t, 3H, *J* = 7.3 Hz), 1.73 (qn, 2H, *J* = 7.3 Hz), 2.88 (br s, 1H), 4.17 (q, 2H, *J* = 7.3 Hz), 4.38–4.40 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 9.2, 13.9, 29.9, 62.1, 63.1, 76.4, 87.9, 153.5; IR (neat) cm^{-1}: 3395, 1713; MS (FAB) *m/z*: 157 $[M + H]^+$; HRMS (FAB) calcd for $C_8H_{13}O_3$ $[M + H]^+$ 157.0859; found: 157.0872; HPLC column: DAICEL CHIRALPAK® IC (250 × 4.6 mm), EtOAc–*n*-hexane (20:80), 0.1 mL/min, t_R = 60.7 min for ent-**1b** and t_R = 63.6 min for **1b**.



1a

(*R*)-Ethyl 4-cyclohexyl-4-hydroxybutynoate (1a)

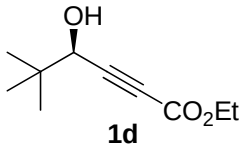
1a: yellow oil: $[\alpha]^{26}_{D}$ = –5.8 (*c* 1.13, $CHCl_3$); MS (FAB) *m/z*: 211 $[M + H]^+$; HRMS (FAB) calcd for $C_{12}H_{19}O_3$ $[M + H]^+$ 211.1329; found: 211.1354; HPLC column: DAICEL CHIRALPAK® IC (250 × 4.6 mm), *i*-PrOH–*n*-hexane (3:97), 0.1 mL/min, t_R = 38.8 min for ent-**1a** and t_R = 46.6 min for **1a**; Other spectroscopic data of this material were identical with those reported.[S2)]



1c

(*R*)-Ethyl 5-methyl-4-hydroxyhex-2-ynoate (1c)

1c: yellow oil: $[\alpha]^{20}_{D}$ = +1.3 (*c* 2.40, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.95 (d, 3H, *J* = 6.1 Hz), 0.96 (d, 3H, *J* = 6.1 Hz), 1.24 (t, 3H, *J* = 7.3 Hz), 1.85–1.92 (m, 1H), 3.22 (br s, 1H), 4.16 (q, 2H, *J* = 7.3 Hz), 4.22 (d, 1H, *J* = 4.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.8, 17.4, 17.9, 34.0, 62.1, 67.3, 77.0, 87.2, 153.5; IR (neat) cm^{-1}: 3418, 1715; MS (FAB) *m/z*: 171 $[M + H]^+$; HRMS (FAB) calcd for $C_9H_{15}O_3$ $[M + H]^+$ 171.1016; found: 171.1040; HPLC column: DAICEL CHIRALPAK® IC (250 × 4.6 mm), EtOAc–*n*-hexane (20:80), 0.1 mL/min, t_R = 50.3 min for ent-**1c** and t_R = 59.7 min for **1c**.



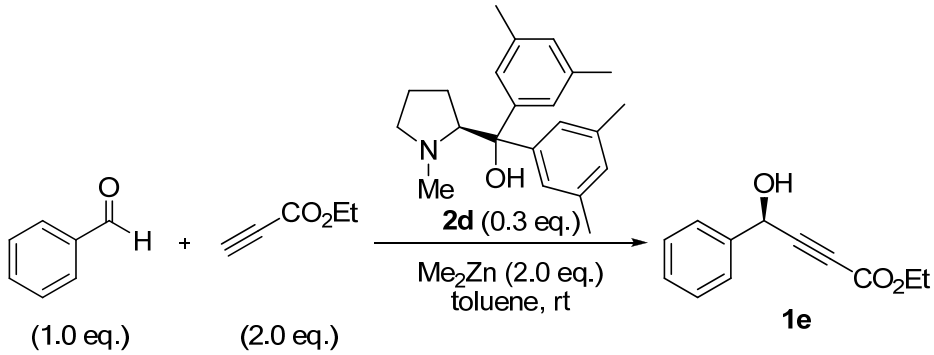
1d

(*R*)-Ethyl 5,5-dimethyl-4-hydroxyhex-2-ynoate (1d)

1d: yellow oil: $[\alpha]^{25}_{D}$ = +2.8 (*c* 1.53, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.03 (s, 9H), 1.32 (t,

3H, J = 7.3 Hz), 1.87 (d, 1H, J = 5.5 Hz), 4.14 (d, 1H, J = 5.5 Hz), 4.24 (q, 2H, J = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ : 13.9, 25.2 (3C), 35.9, 62.1, 70.7, 77.3, 87.2, 153.5; IR (neat) cm^{-1}: 3453, 1713; MS (FAB) *m/z*: 185 $[M + H]^+$; HRMS (FAB) calcd for $C_{10}H_{17}O_3$ $[M + H]^+$ 185.1172; found: 185.1188; HPLC column: DAICEL CHIRALPAK® IC (250 × 4.6 mm), EtOAc–*n*-hexane (20:80), 0.1 mL/min, t_R = 43.3 min for ent-**1d** and t_R = 56.5 min for **1d**.

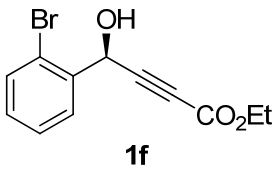
General procedure for asymmetric alkynylation of aromatic aldehydes (Table 4, Entry 3):



A round-bottomed flask equipped with a three-way stopcock connected to an argon balloon through a disposable plastic tube filled with blue silica gel and calcium chloride was charged with a solution of ligand **2d** (97.0 mg, 0.300 mmol) in toluene (6.0 mL). To the solution, Me_2Zn (1.0 M in *n*-hexane, 2.00 mL, 2.00 mmol), ethyl propiolate (0.203 mL, 2.00 mmol), and benzaldehyde (0.102 mL, 1.00 mmol) were added at rt with stirring. After 10 h, the reaction was quenched with sat. NH_4Cl. 1N HCl aq. was added to the mixture and the mixture was extracted with EtOAc. The combined organic layers were washed with brine prior to drying and solvent evaporation. Purification by flash column chromatography over silica gel with EtOAc–*n*-hexane (1:15) as eluent yielded (*R*)-ethyl 4-phenyl-4-hydroxybut-2-ynoate **1e** (159 mg, 78%, 95% ee) as a yellow oil.

(*R*)-ethyl 4-hydroxy-4-phenylbut-2-ynoate (1e)

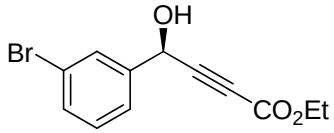
1e: yellow oil: $[\alpha]^{25}_D$ = +2.3 (*c* 1.27, CH_3Cl); IR (neat) cm^{-1}: 3408, 1713; MS (EI) *m/z* (%): 204 (73.8) $[M]^+$, 175 (100) $[M - Et]^+$, 159 (28.9) $[M - OEt]^+$, 131 (46.0) $[M - CO_2Et]^+$; HRMS (EI) calcd for $C_{12}H_{12}O_3$ $[M]^+$ 204.0786; found: 204.0789; HPLC column: DAICEL CHIRALPAK® IC (250 × 4.6 mm), EtOAc–*n*-hexane (20:80), 0.5 mL/min, t_R = 12.4 min for ent-**1e** and t_R = 13.6 min for **1e**; Other spectroscopic data of this material were identical with those reported.[S3)]



(*S*)-Ethyl 4-(2-bromophenyl)-4-hydroxybut-2-ynoate (1f)

1f: yellow oil: $[\alpha]^{25}_D$ = –48.7 (*c* 2.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ : 1.32 (t, 3H, J = 7.3

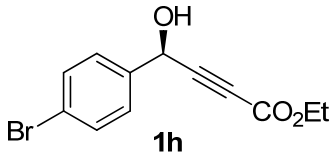
Hz), 3.07 (d, 1H, J = 4.3 Hz), 4.24 (q, 2H, J = 7.3 Hz), 5.90 (d, 1H, J = 4.3 Hz), 7.22 (dd, 1H, J = 9.8, 7.3 Hz), 7.38 (dd, 1H, J = 8.5, 7.3 Hz), 7.57 (d, 1H, J = 8.5 Hz), 7.72 (d, 1H, J = 9.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.9, 62.3, 63.8, 77.7, 85.1, 122.5, 128.0, 128.6, 130.4, 133.1, 137.6, 153.3; IR (neat) cm^{-1}: 3404, 1711; MS (EI) *m/z* (%): 282 (38.1) $[M]^+$, 253 (62.1) $[M - Et]^+$, 237 (25.9) $[M - OEt]^+$, 209 (49.9) $[M - CO_2Et]^+$, 102 (100); HRMS (EI) calcd for $C_{12}H_{11}BrO_3$ $[M]^+$ 281.9892; found: 281.9893; HPLC column: DAICEL CHIRALPAK® IC (250 × 4.6 mm), EtOAc–*n*-hexane (20:80), 0.5 mL/min, t_R = 10.5 min for ent-**1f** and t_R = 11.2 min for **1f**.



1g

(*R*)-Ethyl 4-(3-bromophenyl)-4-hydroxybut-2-ynoate (1g)

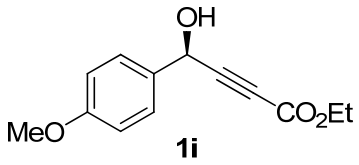
1g: yellow oil: $[\alpha]^{25}_D$ = +11.1 (*c* 2.67, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.33 (t, 3H, J = 7.3 Hz), 2.45 (d, 1H, J = 6.2 Hz), 4.26 (q, 2H, J = 7.3 Hz), 5.56 (d, 1H, J = 6.2 Hz), 7.28 (t, 1H, J = 7.8 Hz), 7.46 (d, 1H, J = 7.8 Hz), 7.50 (d, 1H, J = 7.8 Hz), 7.68 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 62.5, 63.4, 78.1, 85.3, 122.8, 125.2, 129.7, 130.3, 131.9, 140.5, 153.2; IR (neat) cm^{-1}: 3393, 1713; MS (EI) *m/z* (%): 282 (82.4) $[M]^+$, 253 (100) $[M - Et]^+$, 237 (34.2) $[M - OEt]^+$, 209 (49.6) $[M - CO_2Et]^+$; HRMS (EI) calcd for $C_{12}H_{11}BrO_3$ $[M]^+$ 281.9892; found: 281.9885; HPLC column: DAICEL CHIRALPAK® IC (250 × 4.6 mm), EtOAc–*n*-hexane (20:80), 0.1 mL/min, t_R = 49.8 min for ent-**1g** and t_R = 52.3 min for **1g**.



1h

(*R*)-Ethyl 4-(4-bromophenyl)-4-hydroxybut-2-ynoate (1h)

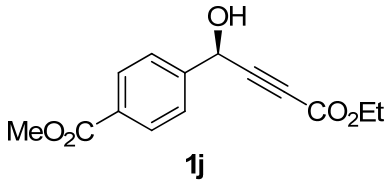
1h: yellow oil: $[\alpha]^{25}_D$ = +4.5 (*c* 0.95, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.32 (t, 3H, J = 7.3 Hz), 2.39 (d, 1H, J = 6.1 Hz), 4.26 (q, 2H, J = 7.3 Hz), 5.55 (d, 1H, J = 6.1 Hz), 7.40 (d, 2H, J = 8.5 Hz), 7.54 (d, 2H, J = 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.0, 62.4, 63.5, 78.0, 85.5, 122.9, 128.3 (2C), 131.9 (2C), 137.5, 153.3; IR (neat) cm^{-1}: 3395, 1713; MS (EI) *m/z* (%): 282 (98.2) $[M]^+$, 253 (95.3) $[M - Et]^+$, 237 (33.2) $[M - OEt]^+$, 203 (76.1) $[M - Br]^+$, 175 (100); HRMS (EI) calcd for $C_{12}H_{11}BrO_3$ $[M]^+$ 281.9892; found: 281.9895; HPLC column: DAICEL CHIRALPAK® IC (250 × 4.6 mm), EtOAc–*n*-hexane (20:80), 0.1 mL/min, t_R = 53.5 min for ent-**1h** and t_R = 57.8 min for **1h**.



1i

(*R*)-Ethyl 4-hydroxy-4-(4-methoxyphenyl)but-2-ynoate (1i)

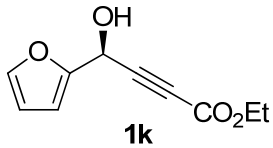
1i: yellow oil: $[\alpha]^{25}_{D}$ = +4.4 (*c* 0.70, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.23 (t, 3H, *J* = 7.3 Hz), 2.90 (br s, 1H) 3.72 (s, 3H), 4.16 (q, 2H, *J* = 7.3 Hz), 5.42 (s, 1H), 6.82 (d, 2H, *J* = 8.5 Hz), 7.34 (d, 2H, *J* = 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.9, 55.3, 62.2, 63.8, 77.7, 86.4, 114.1 (2C), 128.1 (2C), 130.9, 153.4, 159.9; IR (neat) cm^{-1}: 3403, 1703; MS (EI) *m/z* (%): 234 (71.1) $[M]^+$, 205 (100) $[M - Et]^+$, 161 (56.7) $[M - CO_2Et]^+$; HRMS (EI) calcd for $C_{13}H_{14}O_4$ $[M]^+$ 234.0892; found: 262.0893; HPLC column: DAICEL CHIRALPAK® IC (250 × 4.6 mm), CH_2Cl_2–*n*-hexane (70:30), 0.3 mL/min, t_R = 19.0 min for **1i** and t_R = 20.7 min for ent-**1i**.



1j

(*R*)-Ethyl 4-hydroxy- 4-[4-(methoxycarbonyl)phenyl]but-2-ynoate (1j)

1j: yellow oil: $[\alpha]^{20}_{D}$ = +3.8 (*c* 1.23, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.29 (t, 3H, *J* = 7.3 Hz), 3.91 (s, 3H), 4.23 (q, 2H, *J* = 7.3 Hz), 5.63 (s, 1H), 7.57 (d, 2H, *J* = 8.5 Hz), 8.02 (d, 2H, *J* = 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.8, 52.2, 62.3, 63.5, 77.9, 85.6, 126.5 (2C), 129.9 (2C), 130.2, 143.4, 153.2, 166.7; IR (neat) cm^{-1}: 3441, 1715; MS (EI) *m/z* (%): 262 (74.4) $[M]^+$, 233 (49.6) $[M - Et]^+$, 203 (100) $[M - CO_2Me]^+$, 175 (42.0) $[M - CO_2Me - Et]^+$; HRMS (EI) calcd for $C_{14}H_{14}O_5$ $[M]^+$ 262.0841; found: 262.0841; HPLC column: DAICEL CHIRALPAK® AD–3 (250 × 4.6 mm), *i*-PrOH–*n*-hexane (10:90), 0.5 mL/min, t_R = 18.9 min for ent-**1j** and t_R = 20.2 min for **1j**.



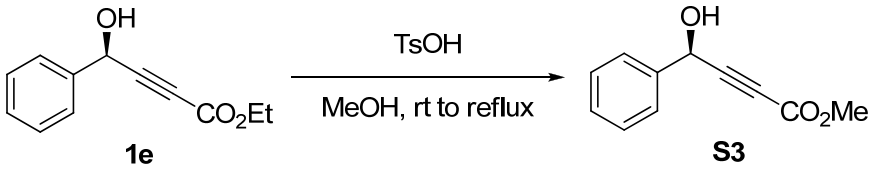
1k

(*S*)-Ethyl 4-(furan-2-yl)-4-hydroxybut-2-ynoate (1k)

1k: yellow oil: $[\alpha]^{24}_{D}$ = +5.9 (*c* 1.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.22 (t, 3H, *J* = 6.9 Hz), 3.66 (br s, 1H), 4.16 (q, 2H, *J* = 6.9 Hz), 5.49 (d, 1H, *J* = 5.5 Hz), 6.27 (dd, 1H, *J* = 3.2, 1.8 Hz), 6.40 (dd, 1H, *J* = 3.2, 0.9 Hz), 7.34 (dd, 1H, *J* = 1.8, 0.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.8, 57.6, 62.4, 76.6, 83.8, 108.5, 110.4, 143.3, 150.7, 153.3; IR (neat) cm^{-1}: 3408, 1714; MS (EI) *m/z* (%): 194 (95.5) $[M]^+$, 165 (38.0) $[M - Et]^+$, 149 (37.7) $[M - OEt]^+$, 121 (100) $[M - CO_2Et]^+$; HRMS (EI) calcd for $C_{10}H_{10}O_4$ $[M]^+$ 194.0579; found: 194.0581; HPLC column: DAICEL CHIRALPAK® IC (250 × 4.6 mm), CH_2Cl_2–*n*-hexane (70:30), 0.3 mL/min, t_R = 20.4 min for **1k**

and t_R = 23.2 min for ent-**1k**.

Conversion of ethyl ester 1e into the known methyl ester S3 to determine the stereochemistry:



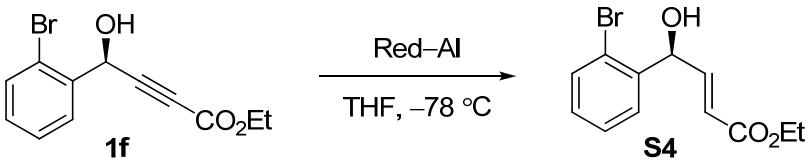
1e **S3**

To a solution of **1e** (157 mg, 0.766 mmol) in MeOH (7.7 mL), TsOH (58.2 mg, 0.306 mmol) was added at rt with stirring. After 5 h, the solvent was evaporated and the residue was distributed with EtOAc and H_2O. Organic layers were washed with sat. NH_4Cl and brine prior to drying and solvent evaporation. To a solution of the residue in MeOH (7.7 mL), TsOH (58.2 mg, 0.306 mmol) was added at rt and the mixture was stirred under reflux for 17 h. The solvent was evaporated and the residue was distributed with EtOAc and H_2O. Organic layers were washed with sat. NH_4Cl and brine prior to drying and solvent evaporation. Purification by flash column chromatography over silica gel with Et_2O–*n*-hexane (1:5) as eluent yielded methyl ester **S3** (136 mg, 93%) as a pale yellow oil.

(*R*)-Methyl 4-hydroxy-4-phenylbut-2-ynoate (S3)

S3: $[\alpha]^{25}_D$ = +3.9 (*c* 1.65, $CHCl_3$); *lit*. $[\alpha]^{28}_D$ = –3.56 (*c* 0.73, $CHCl_3$) for (*S*)-isomer [S4] ; Other spectroscopic data of this material were identical with those reported.

Conversion of alkynes 1f-j into allyl alcohols S4-6 in order to determine the stereochemistry by the modified Mosher method:



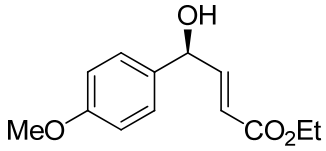
1f **S4**

To a solution of **1f** (84.9 mg, 0.300 mmol) in THF (3.0 mL), sodium bis(2-methoxyethoxy)aluminum hydride solution (65% in toluene, 0.183 mL, 0.600 mmol) was added at −78 °C with stirring. After 0.5 h, the reaction was quenched with 3N HCl aq. and the mixture was extracted with Et_2O. The combined organic layers were washed with brine prior to drying and solvent evaporation. Purification by flash column chromatography over silica gel with EtOAc−toluene (1:5) as eluent yielded allyl alcohol **S4** (79.2 mg, 93%) as a yellow oil.

(*S*,*E*)-Ethyl 4-(2-bromophenyl)-4-hydroxybut-2-enoate (S4)

S4: $[\alpha]^{20}_D$ = −106.9 (*c* 0.70, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.29 (t, 3H, *J* = 7.3 Hz), 2.27 (d, 1H, *J* = 4.3 Hz), 4.20 (q, 2H, *J* = 7.3 Hz), 5.81 (td, 1H, *J* = 4.3, 1.8 Hz), 6.22 (dd, 1H, *J* = 15.3, 1.8 Hz), 7.04 (dd, 1H, *J* = 15.3, 4.3 Hz), 7.18 (td, 1H, *J* = 7.9, 1.2 Hz), 7.35 (td, 1H, *J* = 7.9, 1.2 Hz), 7.49 (dd,

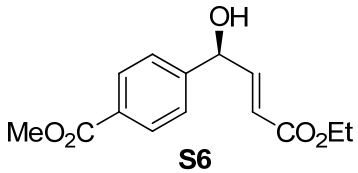
1H, J = 7.9, 1.2 Hz), 7.56 (dd, 1H, J = 7.9, 1.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.2, 60.6, 71.8, 120.7, 122.4, 128.0, 128.2, 129.6, 132.8, 140.0, 146.9, 166.5; IR (neat) cm^{-1}: 3431, 1717; MS (EI) *m/z* (%): 284 (5.2) $[M]^+$, 255 (100) $[M - Et]^+$, 239 (30.6) $[M - OEt]^+$, 211 (59.8) $[M - CO_2Et]^+$; HRMS (EI) calcd for $C_{12}H_{13}BrO_3$ $[M]^+$ 284.0048; found: 284.0044.



S5

(*S*,*E*)-Ethyl 4-hydroxy-4-(4-methoxyphenyl)but-2-enoate (S5)

S5: yellow oil: $[\alpha]^{20}_D$ = −70.4 (c = 0.58, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.29 (t, 3H, J = 7.3 Hz), 1.96 (d, 1H, J = 3.7 Hz), 3.81 (s, 3H), 4.20 (q, 2H, J = 7.3 Hz), 5.31–5.34 (m, 1H), 6.15 (dd, 1H, J = 15.9, 1.2 Hz), 6.90 (d, 2H, J = 8.5 Hz), 7.04 (dd, 1H, J = 15.9, 4.6 Hz), 7.28 (d, 2H, J = 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.2, 55.3, 60.5, 73.1, 114.2, 120.0, 128.0, 133.1, 148.7, 159.6, 166.5; IR (neat) cm^{-1}: 3447, 1716; MS (EI) *m/z* (%): 236 (69.0) $[M]^+$, 207 (86.5) $[M - Et]^+$, 163 (47.3) $[M - CO_2Et]^+$, 161 (100); HRMS (EI) calcd for $C_{13}H_{16}O_4$ $[M]^+$ 236.1049; found: 236.1065.



S6

(*S*,*E*)-Ethyl 4-hydroxy-4-[4-(methoxycarbonyl)phenyl]but-2-enoate (S6)

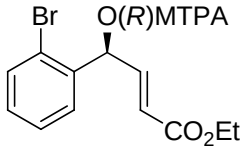
S6: yellow oil: $[\alpha]^{18}_D$ = −47.3 (c = 0.55, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.29 (t, 3H, J = 7.3 Hz), 2.15 (d, 1H, J = 3.7 Hz), 3.92 (s, 3H), 4.20 (q, 2H, J = 7.3 Hz), 5.43–5.46 (m, 1H), 6.17 (dd, 1H, J = 15.9, 1.5 Hz), 7.02 (dd, 1H, J = 15.9, 4.9 Hz), 7.44 (d, 2H, J = 8.2 Hz), 8.05 (d, 2H, J = 8.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.2, 52.2, 60.6, 73.0, 120.9, 126.4, 130.0, 130.1, 145.8, 147.6, 166.2, 166.7; IR (neat) cm^{-1}: 3458, 1721; MS (EI) *m/z* (%): 264 (2.8) $[M]^+$, 235 (100) $[M - Et]^+$, 219 (39.8) $[M - OEt]^+$, 191 (46.6) $[M - CO_2Et]^+$; HRMS (EI) calcd for $C_{14}H_{16}O_5$ $[M]^+$ 264.0998; found: 264.0997.

Preparation of the Mosher esters S7-12:

S4 **S7**

To a solution of **S4** (10.0 mg, 35.1 μmol) and (*R*)-(+)-α-methoxy- α-trifluoromethylphenylacetic acid (24.6 mg, 0.105 mmol) in CH_2Cl_2 (0.4 mL), DCC (21.7 mg, 0.105 mmol) and DMAP (2.1 mg, 17.5 μmol) was added at rt and the mixture was stirred for 30 min at the same temperature. After filtration through silica gel, the solvent was evaporated under the reduced pressure. A part of the

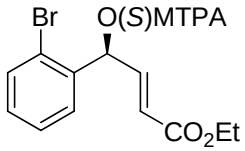
mixture was purified by thin-layer chromatography with EtOAc–*n*-hexane (1:5) as eluent to give Mosher ester **S7** as a yellow oil.



S7

(*S*,*E*)-Ethyl 4-(2-bromophenyl)-4-hydroxybut-2-enoate (*R*)-MTPA Ester (S7)

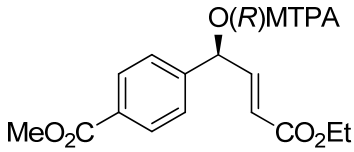
S7: yellow oil: ^{1}H NMR (500 MHz, C_6D_6) δ: 0.86 (t, 3H, J = 6.7 Hz), 3.30 (s, 3H), 3.898 (q, 1H, J = 6.7 Hz), 3.904 (q, 1H, J = 6.7 Hz), 6.23 (d, 1H, J = 15.3 Hz), 6.54 (t, 1H, J = 7.3 Hz), 6.64 (t, 1H, J = 7.3 Hz), 6.86 (d, 1H, J = 7.9 Hz), 6.97−7.13 (m, 6H), 7.50 (d, 2H, J = 7.3 Hz).



S8

(*S*,*E*)-Ethyl 4-(2-bromophenyl)-4-hydroxybut-2-enoate (*S*)-MTPA Ester (S8)

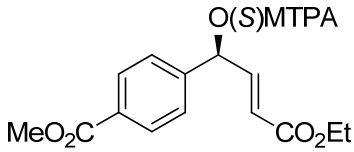
S8: yellow oil: ^{1}H NMR (500 MHz, C_6D_6) δ: 0.87 (t, 3H, J = 6.7 Hz), 3.28 (s, 3H), 3.90 (q, 2H, J = 6.7 Hz), 6.09 (d, 1H, J = 15.3 Hz), 6.55 (t, 1H, J = 7.6 Hz), 6.70 (t, 1H, J = 7.6 Hz), 7.00−7.16 (m, 7H), 7.58 (d, 2H, J = 7.3 Hz).



S9

(*S*,*E*)-Ethyl 4-hydroxy- 4-[4-(methoxycarbonyl)phenyl]but-2-enoate (*R*)-MTPA Ester (S9)

S9: yellow oil: ^{1}H NMR (500 MHz, C_6D_6) δ: 0.91 (t, 3H, J = 7.3 Hz), 3.31 (s, 3H), 3.48 (s, 3H), 3.95 (q, 1H, J = 7.3 Hz), 3.96 (q, 1H, J = 7.3 Hz), 6.10 (dd, 1H, J = 15.9, 1.8 Hz), 6.25−6.27 (m, 1H), 6.88−6.98 (m, 6H), 7.46−7.47 (m, 2H), 7.91 (d, 2H, J = 7.9 Hz).

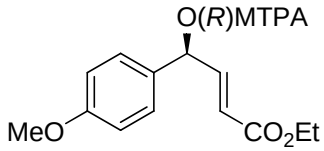


S10

(*S*,*E*)-Methyl 4-(4-ethoxy-1-hydroxy-4-oxobut-2-en-1-yl)benzoate (*S*)-MTPA Ester (S10)

S10: yellow oil: ^{1}H NMR (500 MHz, C_6D_6) δ: 0.89 (t, 3H, J = 7.3 Hz), 3.24 (s, 3H), 3.47 (s, 3H), 3.930 (q, 1H, J = 7.3 Hz), 3.934 (q, 1H, J = 7.3 Hz), 6.01 (dd, 1H, J = 15.6, 1.8 Hz), 6.34−6.36 (m, 1H), 6.89 (dd, 1H, J = 15.6, 4.9 Hz), 6.97−7.04 (m, 5H), 7.53 (d, 2H, J = 7.9 Hz), 7.94 (d, 2H, J =

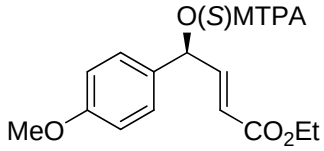
7.9 Hz).



S11

(*S*,*E*)-Ethyl 4-hydroxy-4-(4-methoxyphenyl)but-2-enoate (*R*)-MTPA Ester (S11)

S11: yellow oil: ^{1}H NMR (500 MHz, C_6D_6) δ: 0.91 (t, 3H, J = 7.3 Hz), 3.20 (s, 3H), 3.32 (s, 3H), 3.95 (q, 1H, J = 7.3 Hz), 3.96 (q, 1H, J = 7.3 Hz), 6.19 (dd, 1H, J = 15.6, 1.8 Hz), 6.36 (dd, 1H, J = 4.9, 1.8 Hz), 6.57 (d, 2H, J = 8.5 Hz), 6.96−7.11 (m, 6H), 7.48−7.50 (m, 2H).

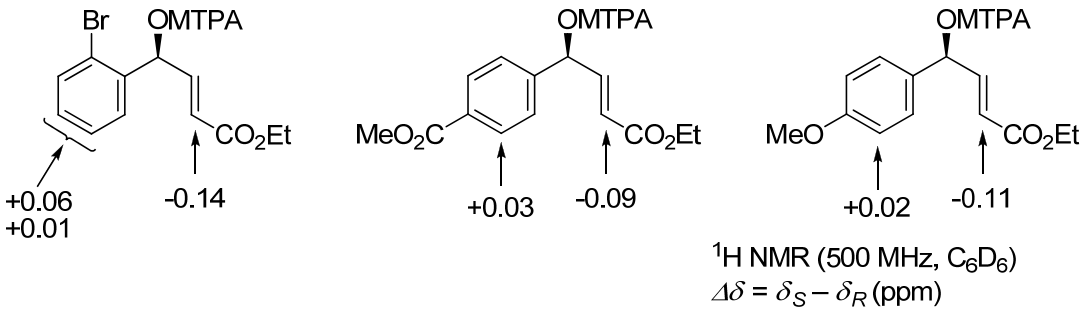


S12

(*S*,*E*)-Ethyl 4-hydroxy-4-(4-methoxyphenyl)but-2-enoate (*S*)-MTPA Ester (S12)

S12: yellow oil: ^{1}H NMR (500 MHz, C_6D_6) δ: 0.90 (t, 3H, J = 7.3 Hz), 3.19 (s, 3H), 3.28 (s, 3H) , 3.937 (q, 1H, J = 7.3 Hz), 3.944 (q, 1H, J = 7.3 Hz), 6.08 (dd, 1H, J = 15.3, 1.8 Hz), 6.46 (dd, 1H, J = 4.9, 1.8 Hz), 6.59 (d, 2H, J = 8.5 Hz), 6.95−7.04 (m, 6H), 7.55 (d, 2H, J = 6.7 Hz).

Determination of the stereochemistry of allyl alcohols S4-6 by the modified Mosher method[S5]:



References:

S1) M. E. Pfeifer, A. Linden and J. A. Robinson, *Helv. Chim. Acta*, 1997, **80**, 1513.

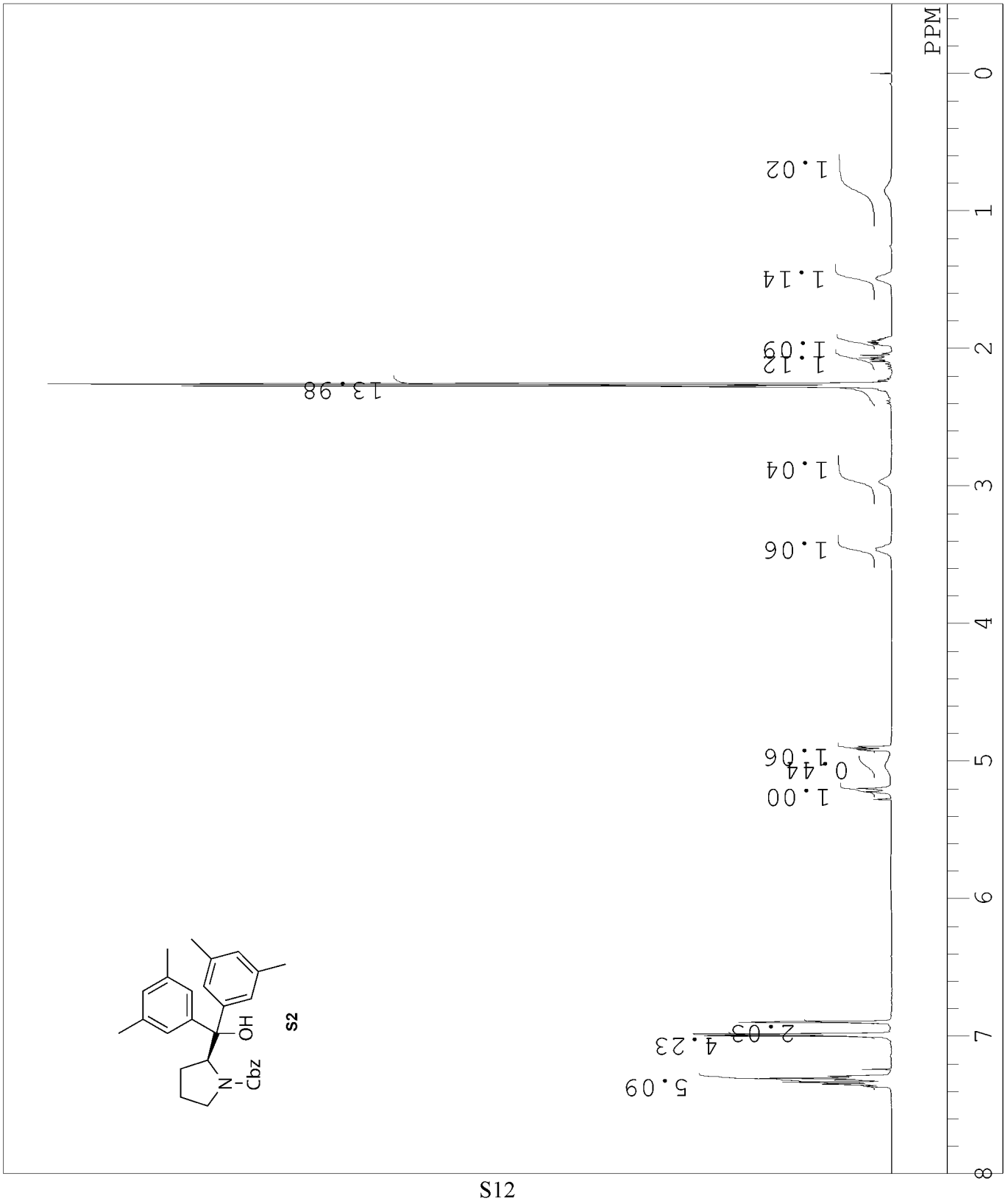
S2) T. Ishikawa, T. Mizuta, K. Hagiwara, T. Aikawa, T. Kudo and S. Saito, *J. Org. Chem.*, 2003, **68**, 3702.

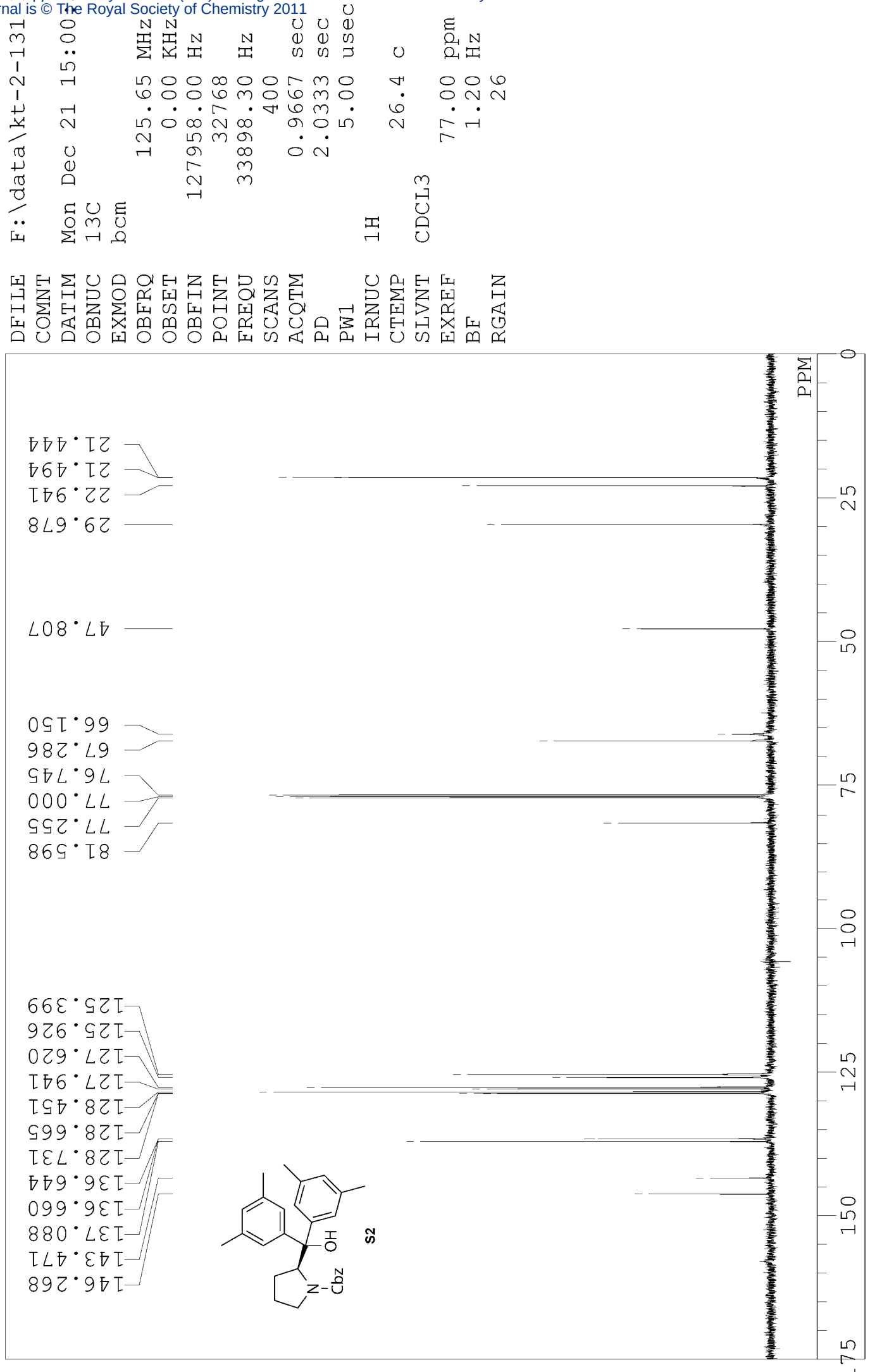
S3) J. Mao and J. Gou, *Synlett*, 2009, **14**, 2295.

S4) G. Gao, Q. Wang, X.-Q. Yu, R.-G. Xie and L. Pu, *Angew. Chem. Int. Ed.*, 2006, **45**, 122.

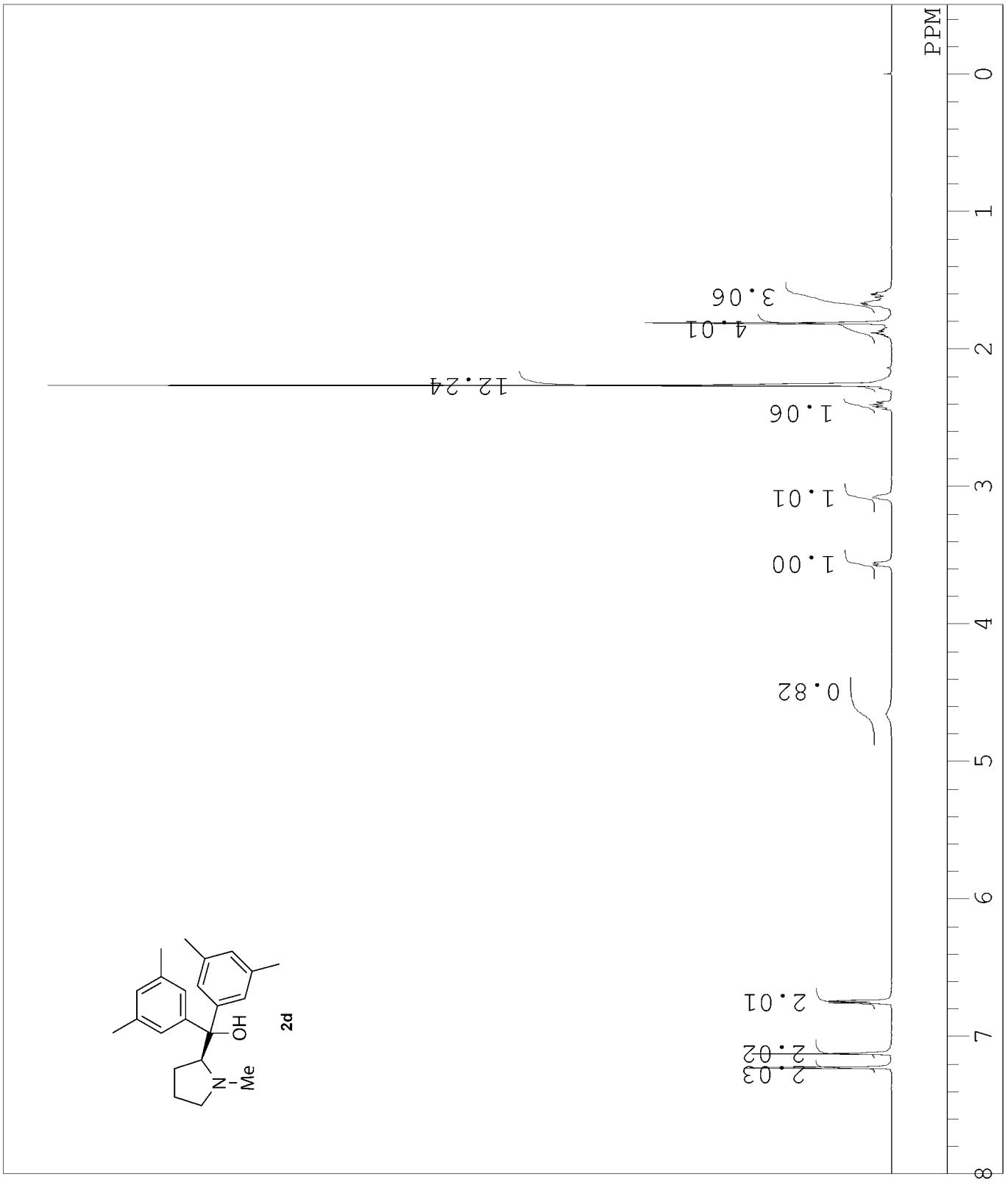
S5) (*a*) I. Ohtani, T. Kusumi, Y. Kashman and H. Kakisawa, *J. Am. Chem. Soc.*, 1991, **113**, 4092; (*b*) J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, 1973, **95**, 512; (*c*) J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543.

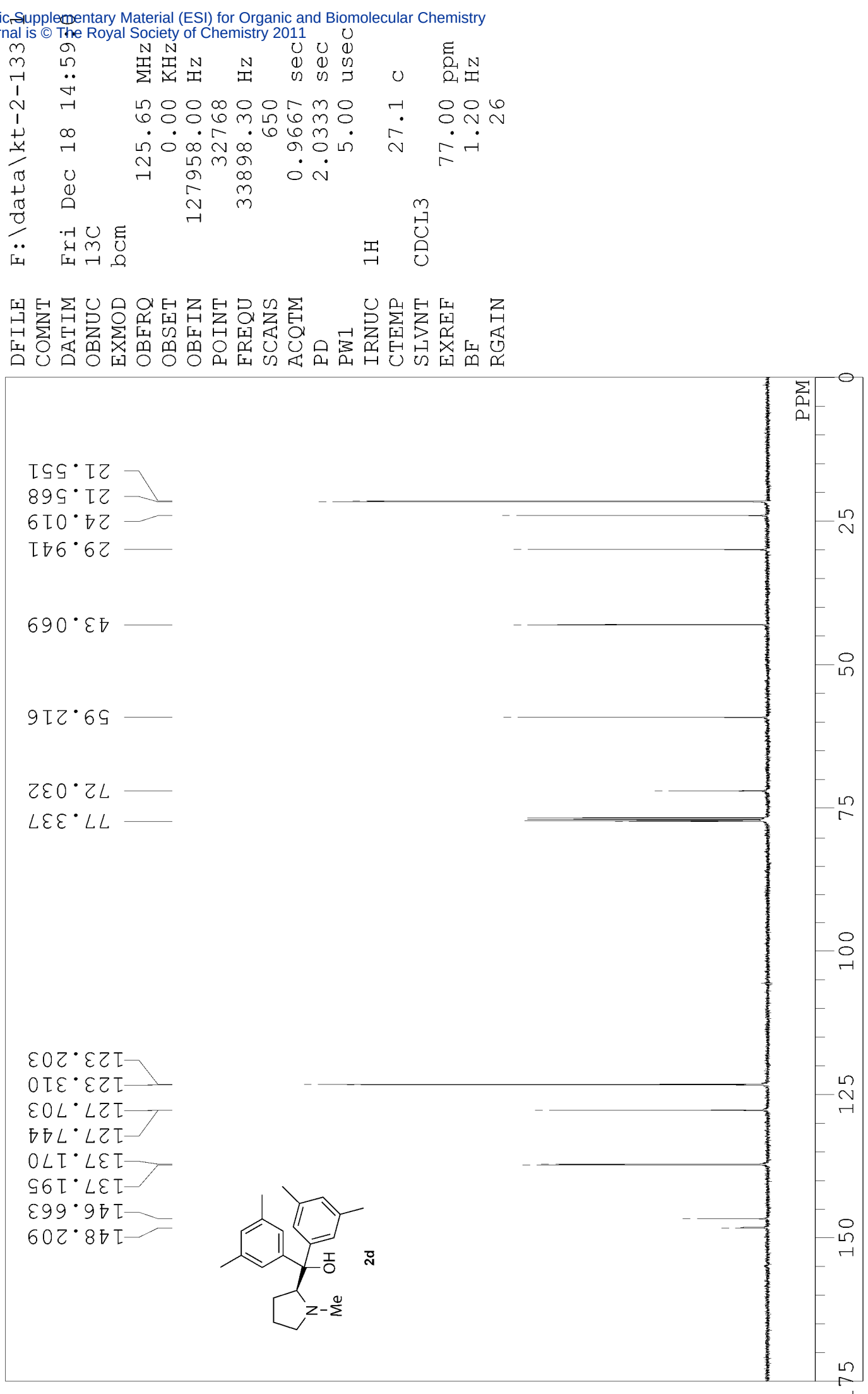
```
DFILE   F:\data\kt-2-131
COMNT
DATIM   Mon Dec 21 14:23:
OBNUC   1H
EXMOD   non
OBFRQ     500.00 MHz
OBSET       0.00 KHz
OBFIN  162160.00 Hz
POINT       8192
FREQU   10000.00 Hz
SCANS          8
ACQTM       0.8192 sec
PD          6.1808 sec
PW1            5.70 usec
IRNUC   1H
CTEMP     23.9 c
SLVNT   CDCL3
EXREF       0.00 ppm
BF          0.12 Hz
RGAIN         12
```

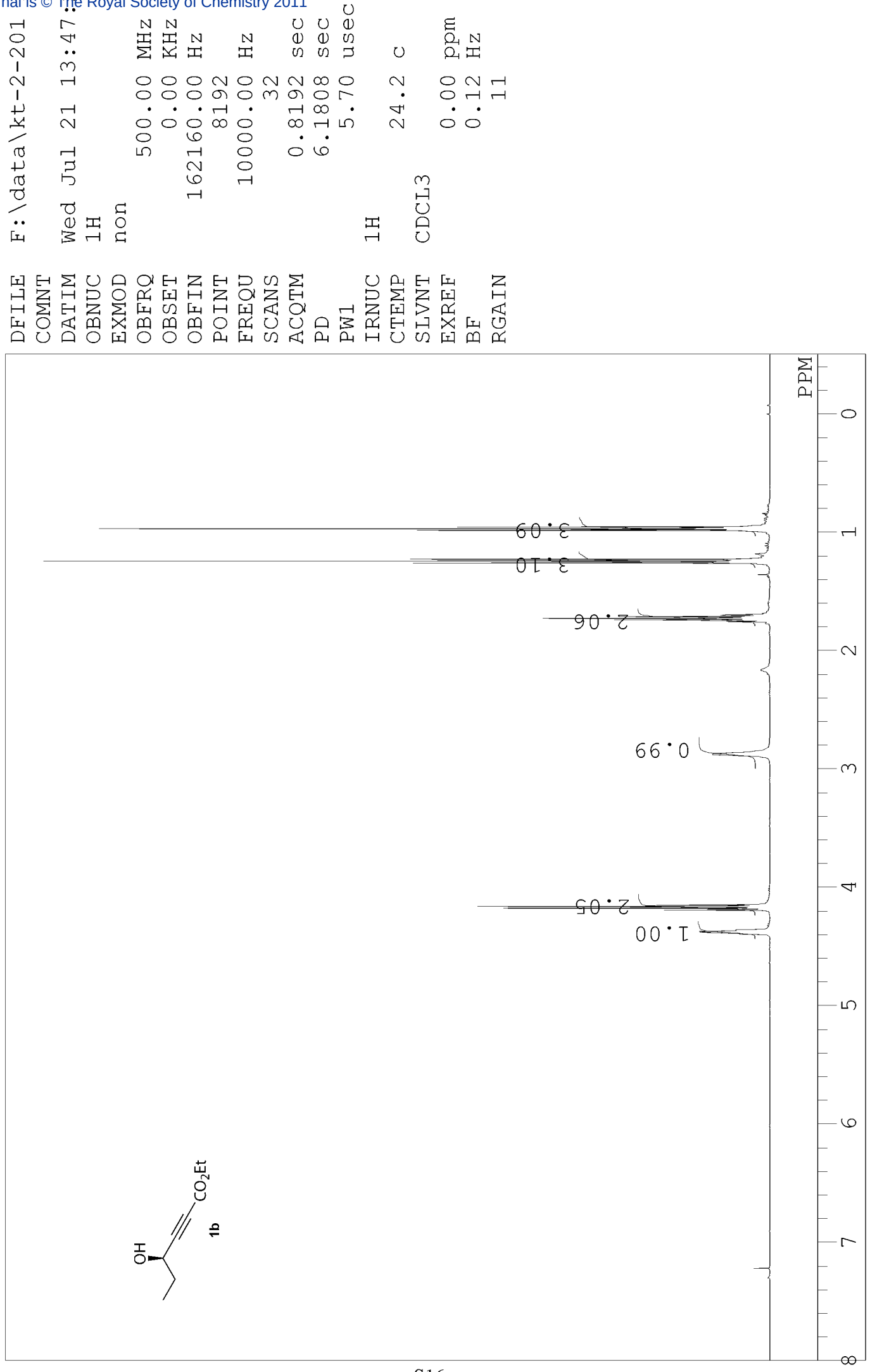


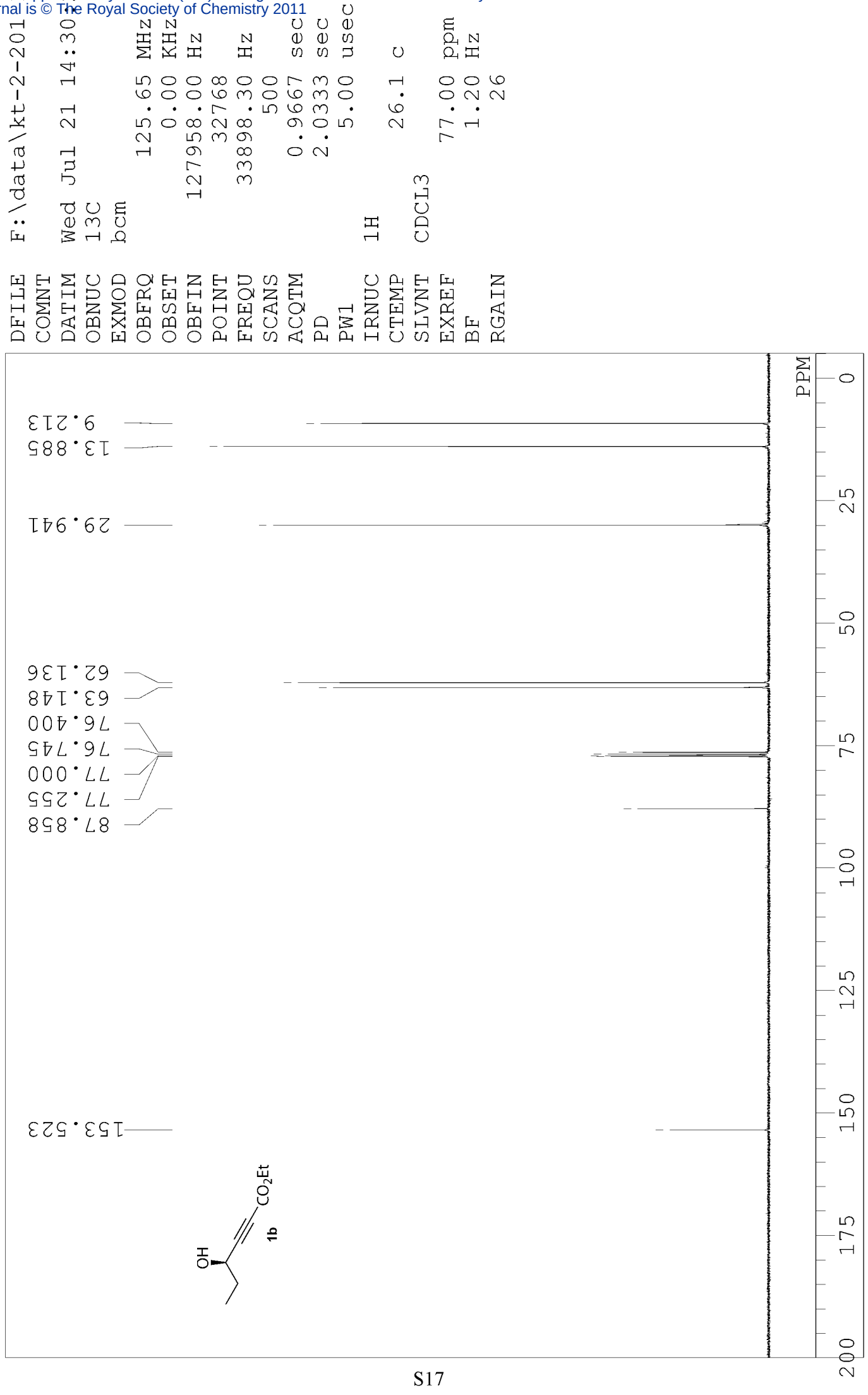


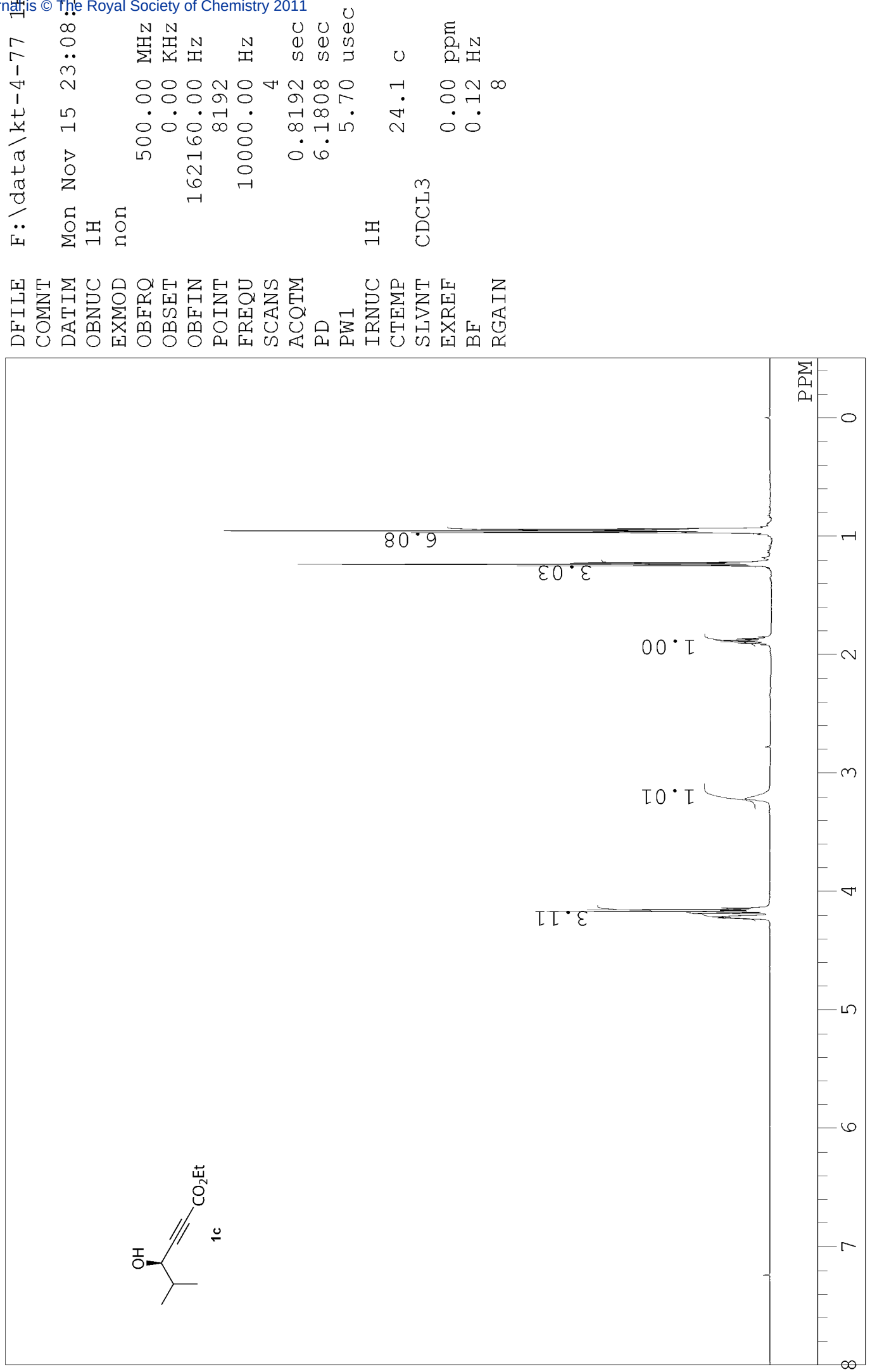
```
DFILE   F:\data\kt-2-133
COMNT
DATIM   Fri Dec 18 14:08:
OBNUC   1H
EXMOD   non
OBFRQ     500.00 MHz
OBSET       0.00 KHz
OBFIN  162160.00 Hz
POINT      8192
FREQU   10000.00 Hz
SCANS         8
ACQTM       0.8192 sec
PD          6.1808 sec
PW1            5.70 usec
IRNUC   1H
CTEMP     24.9 c
SLVNT   CDCL3
EXREF       0.00 ppm
BF          0.12 Hz
RGAIN         11
```

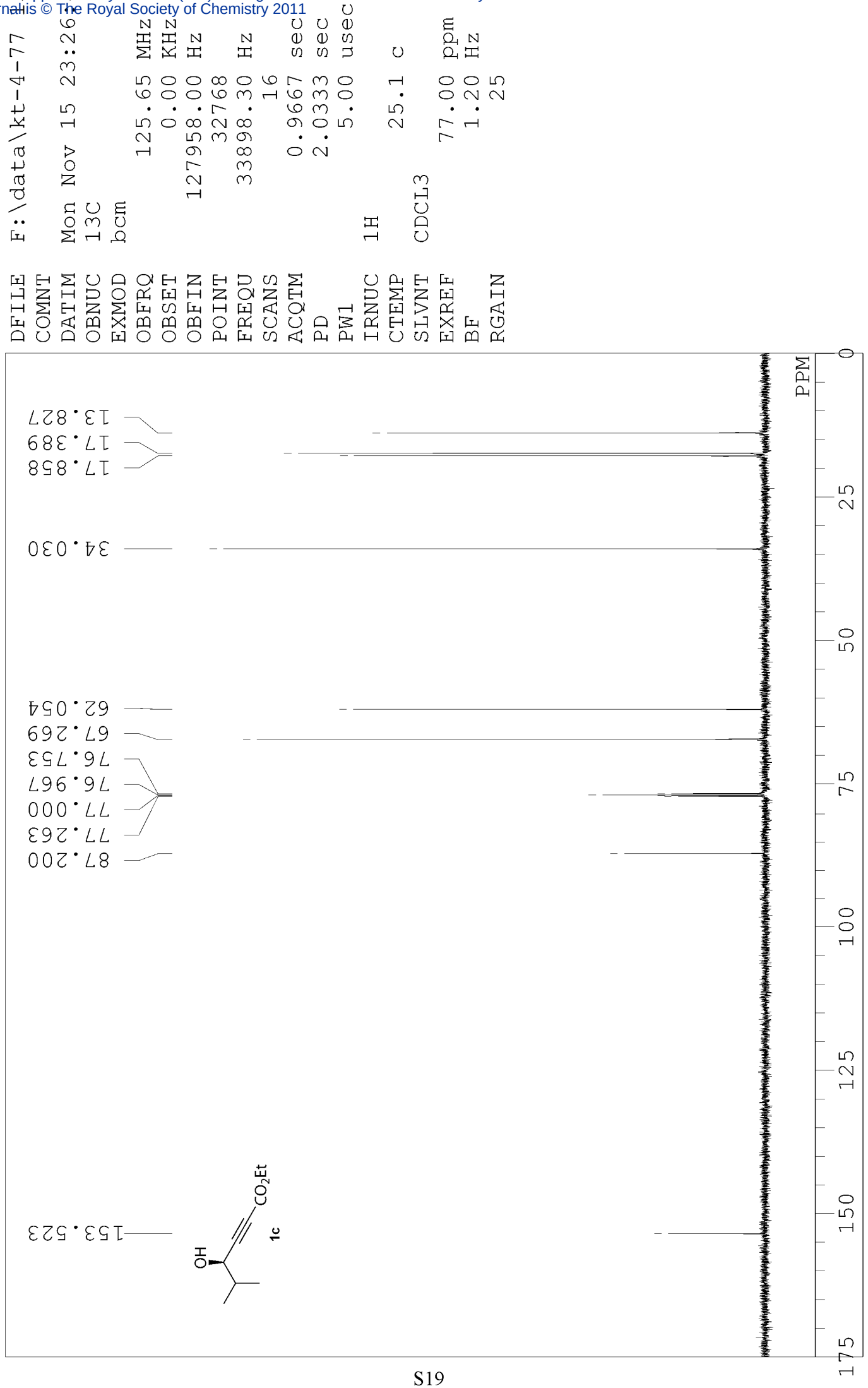


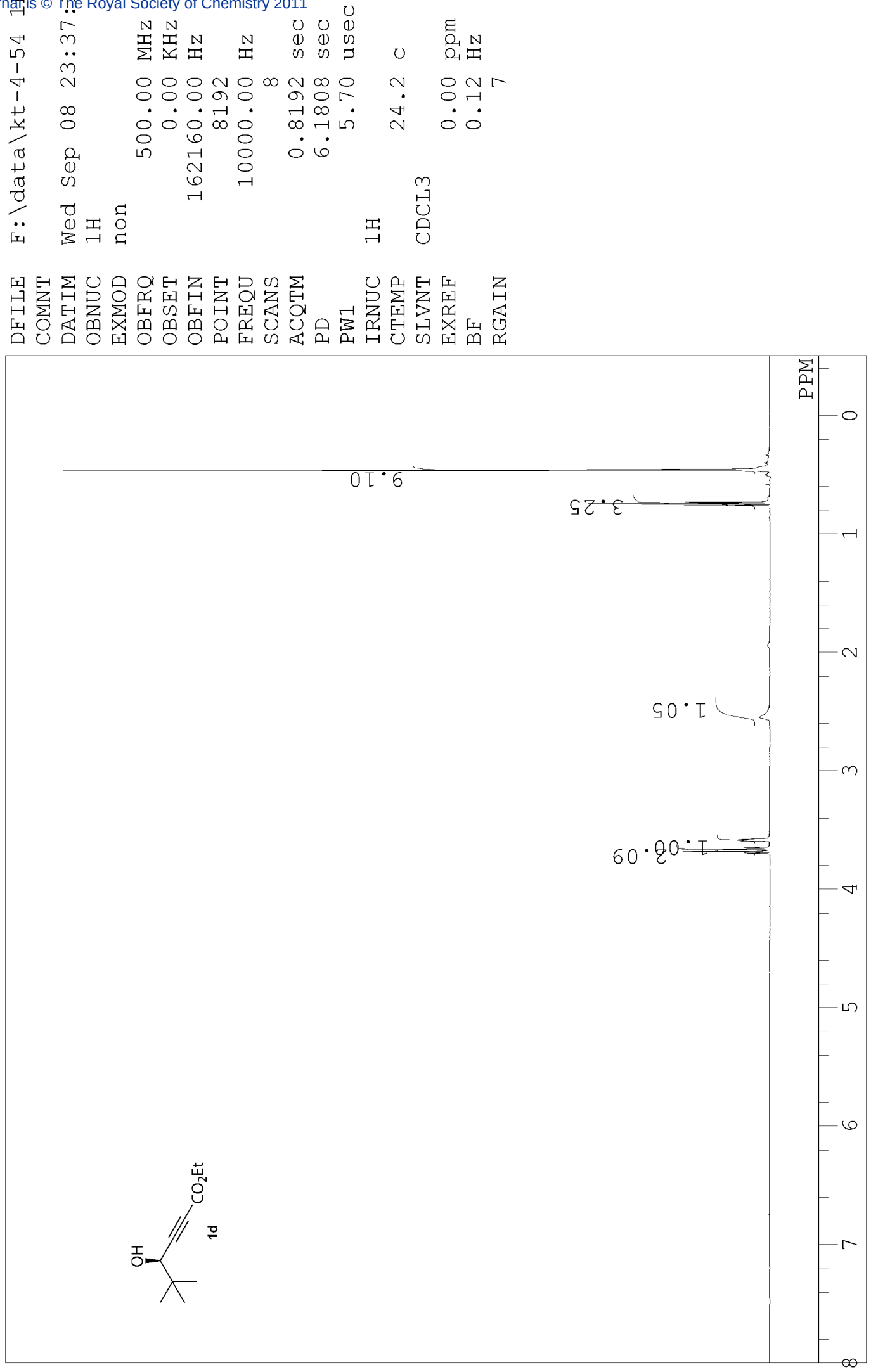


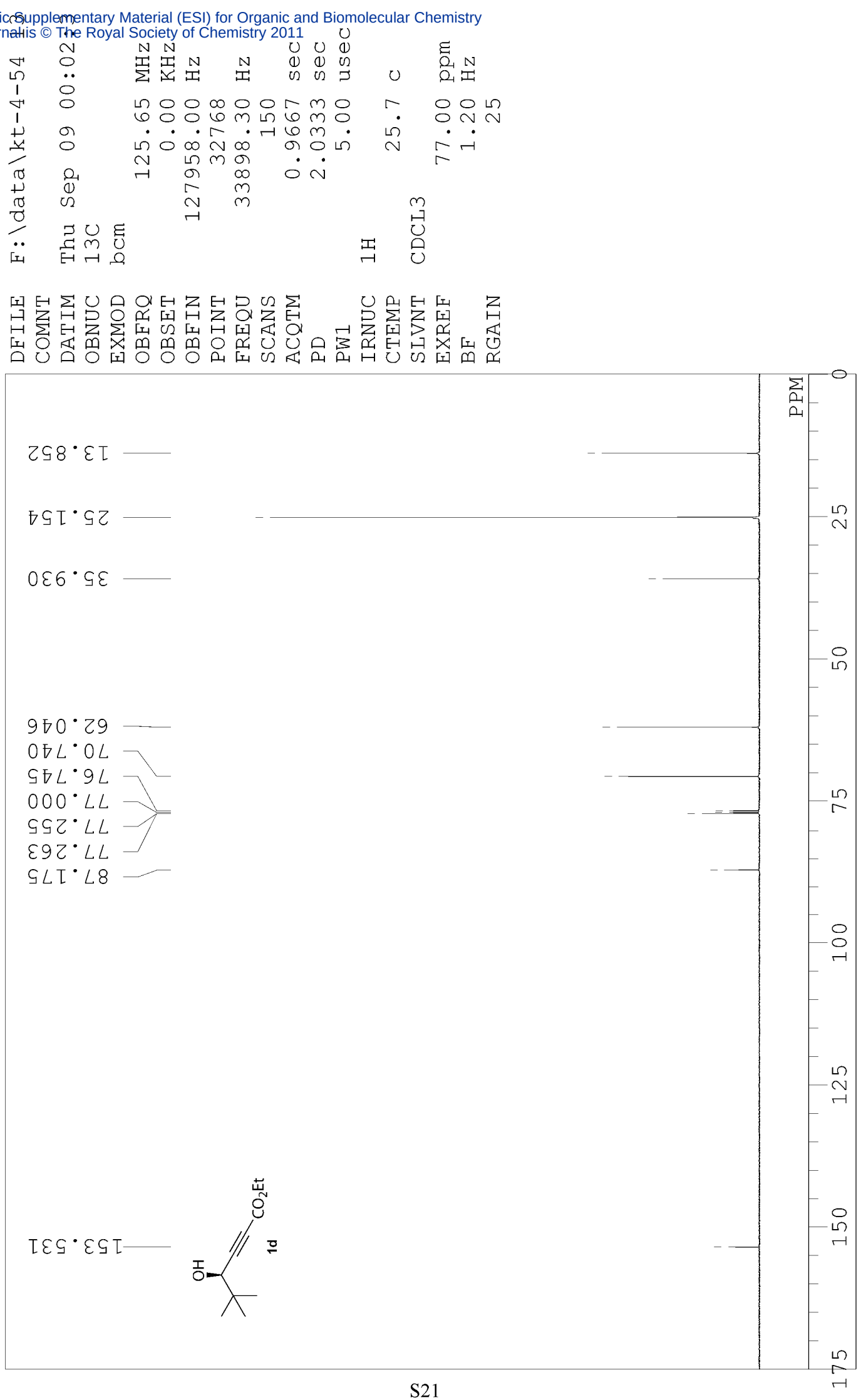


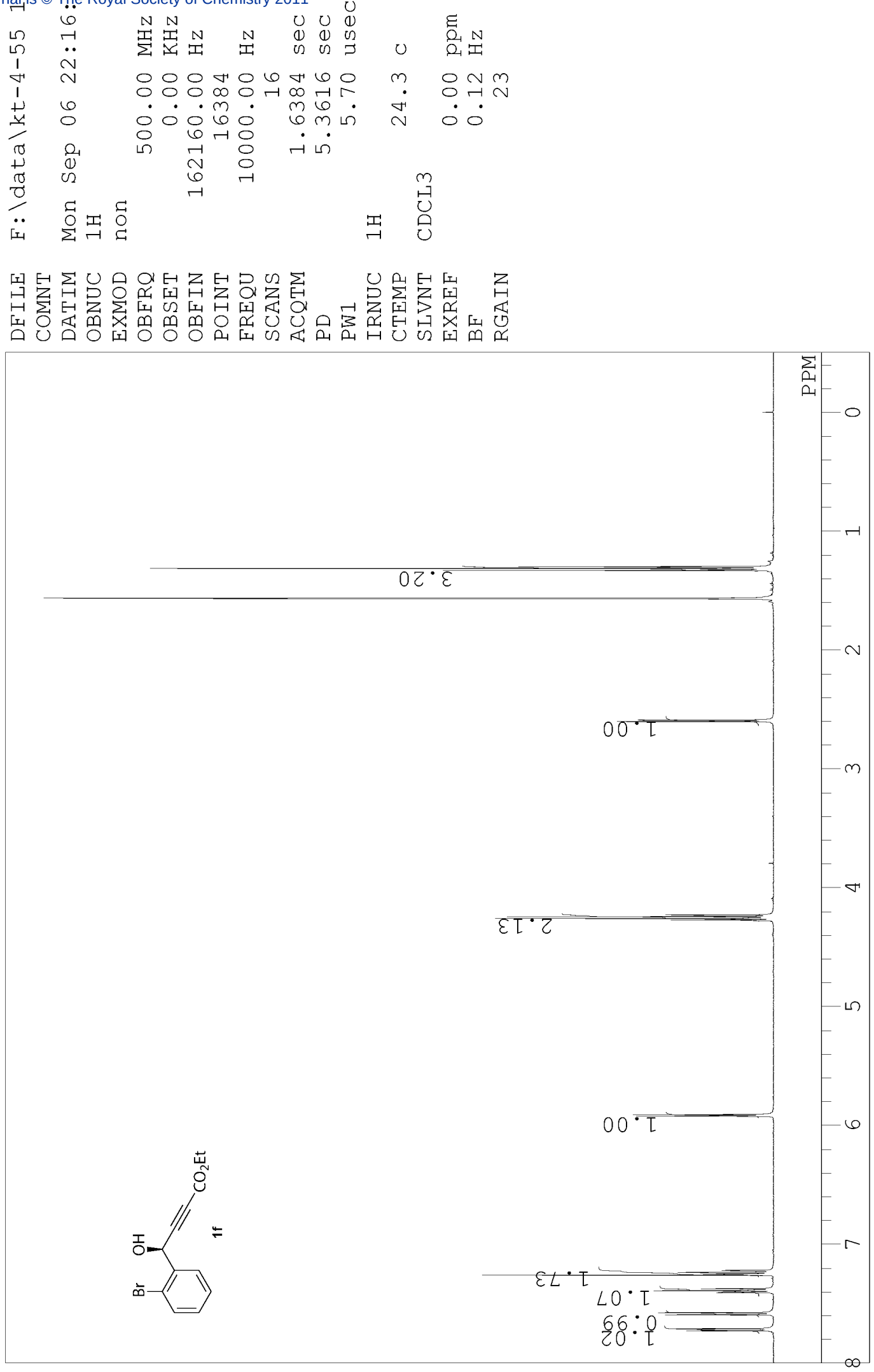


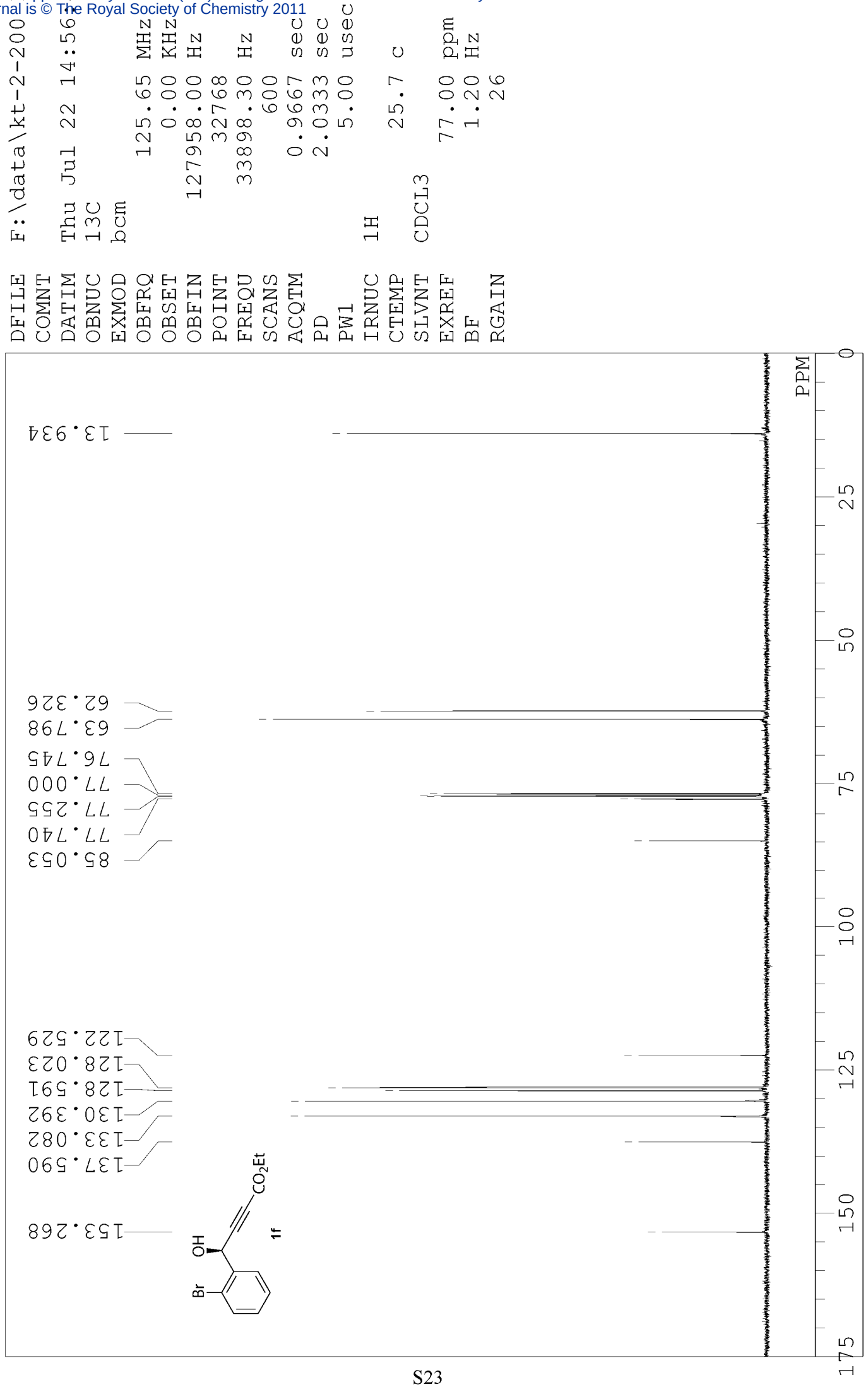


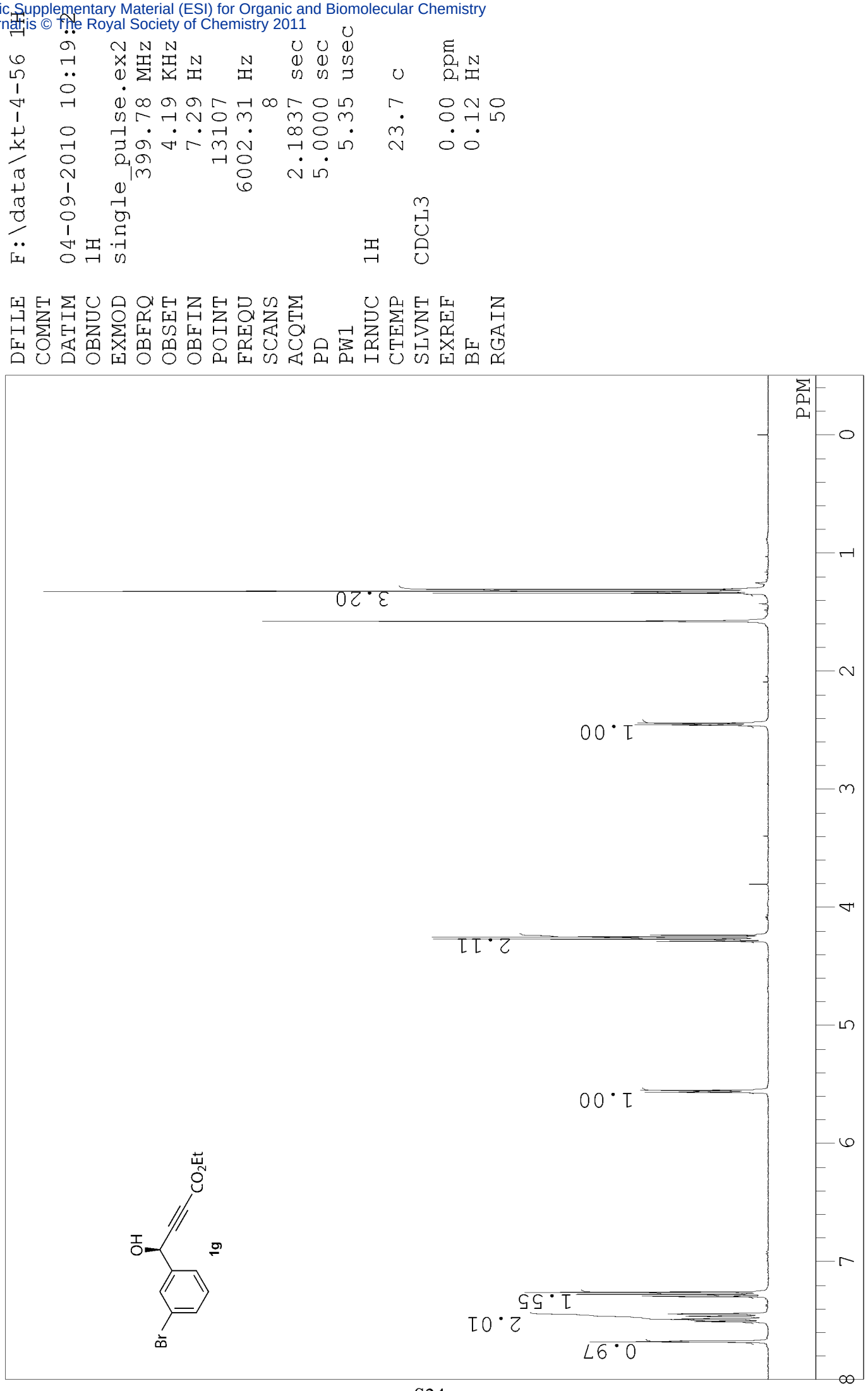


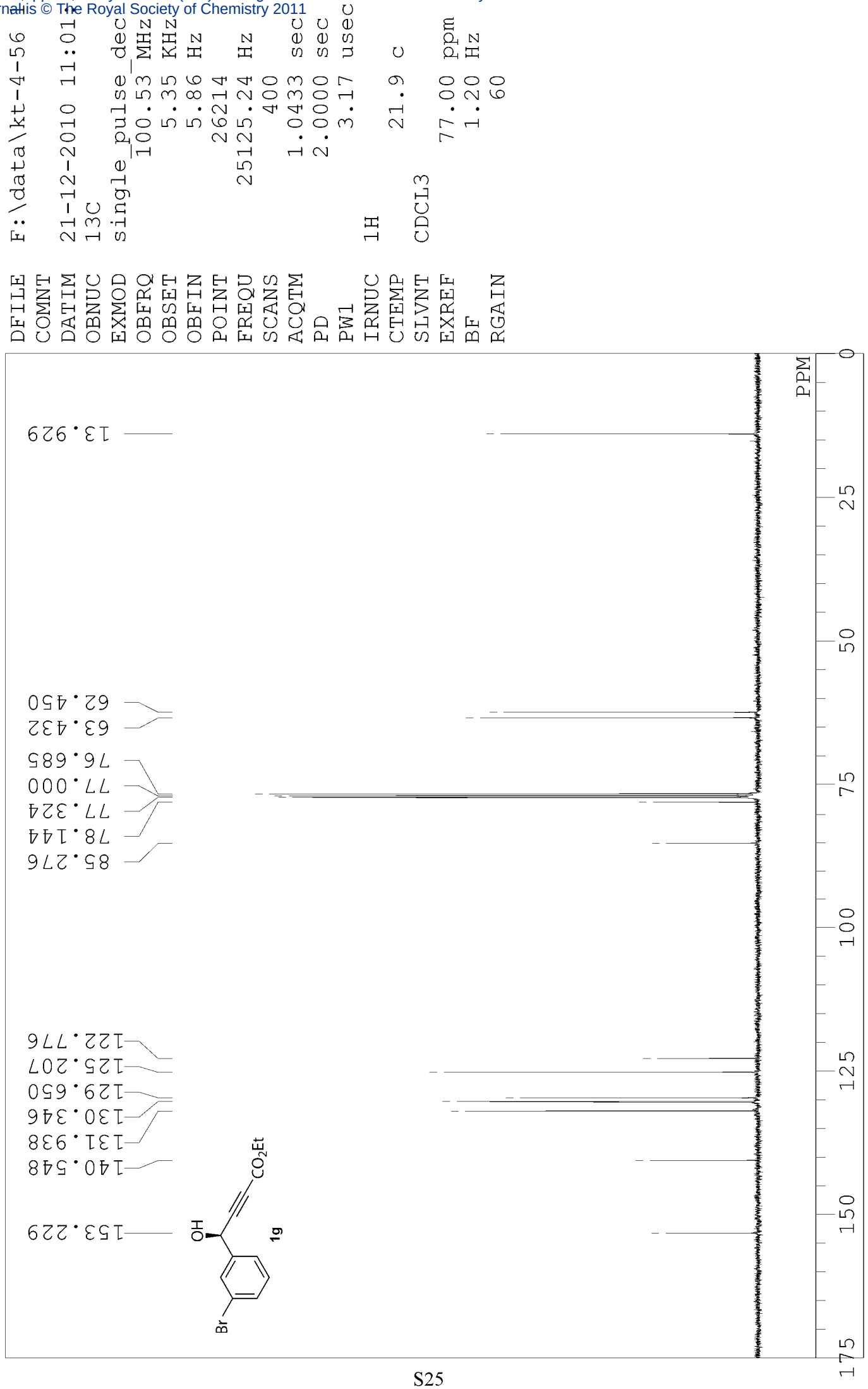


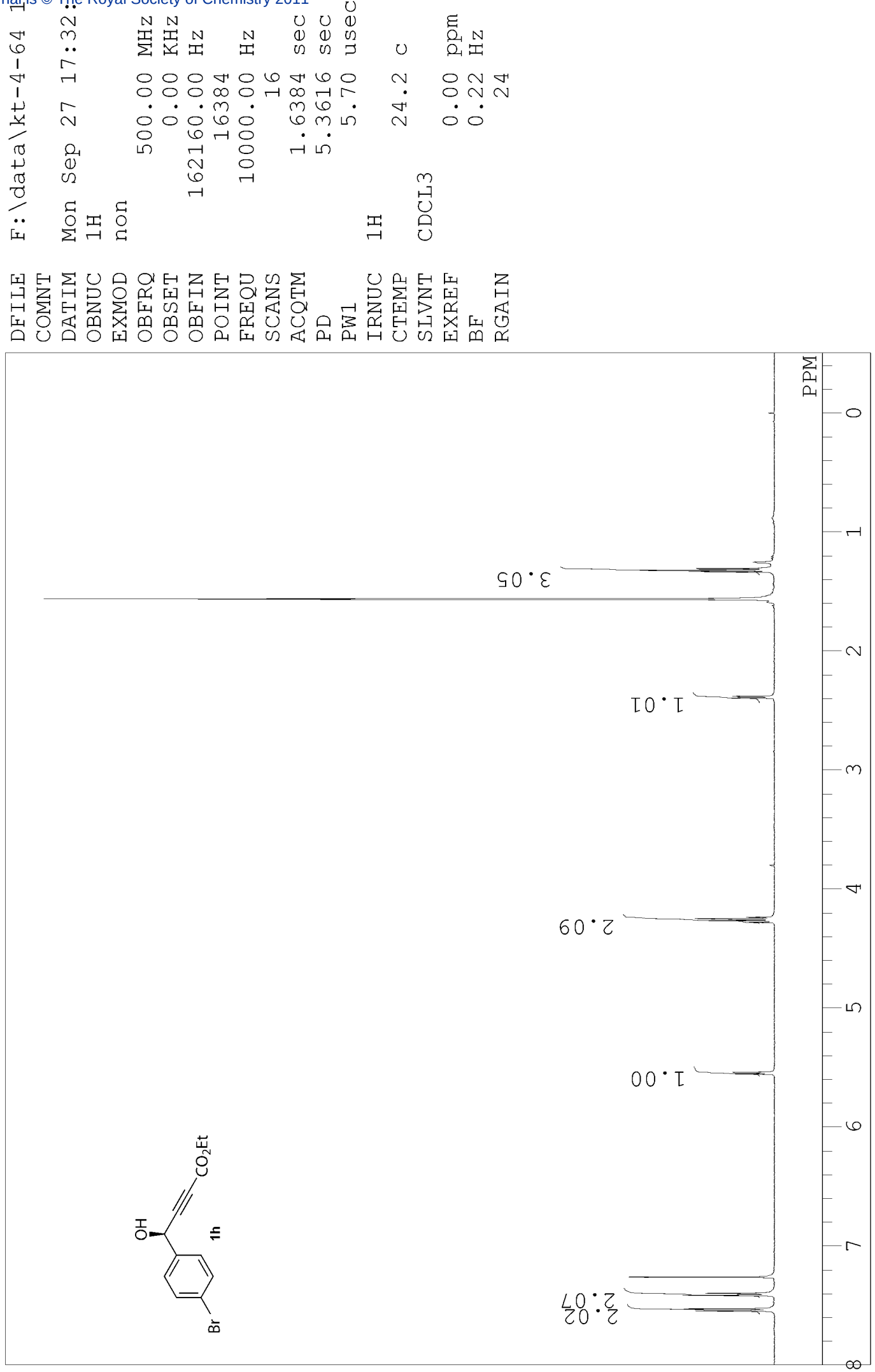


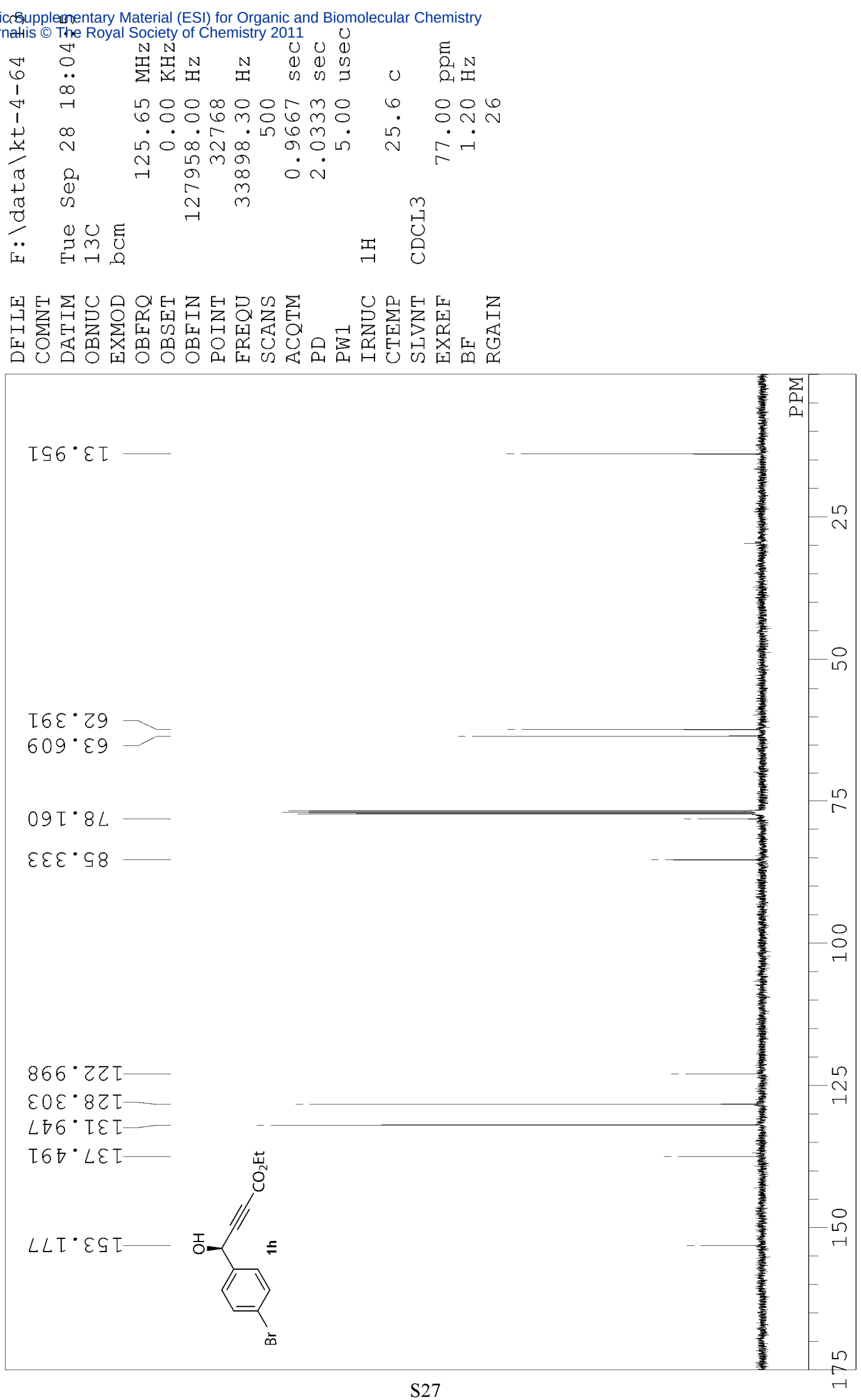


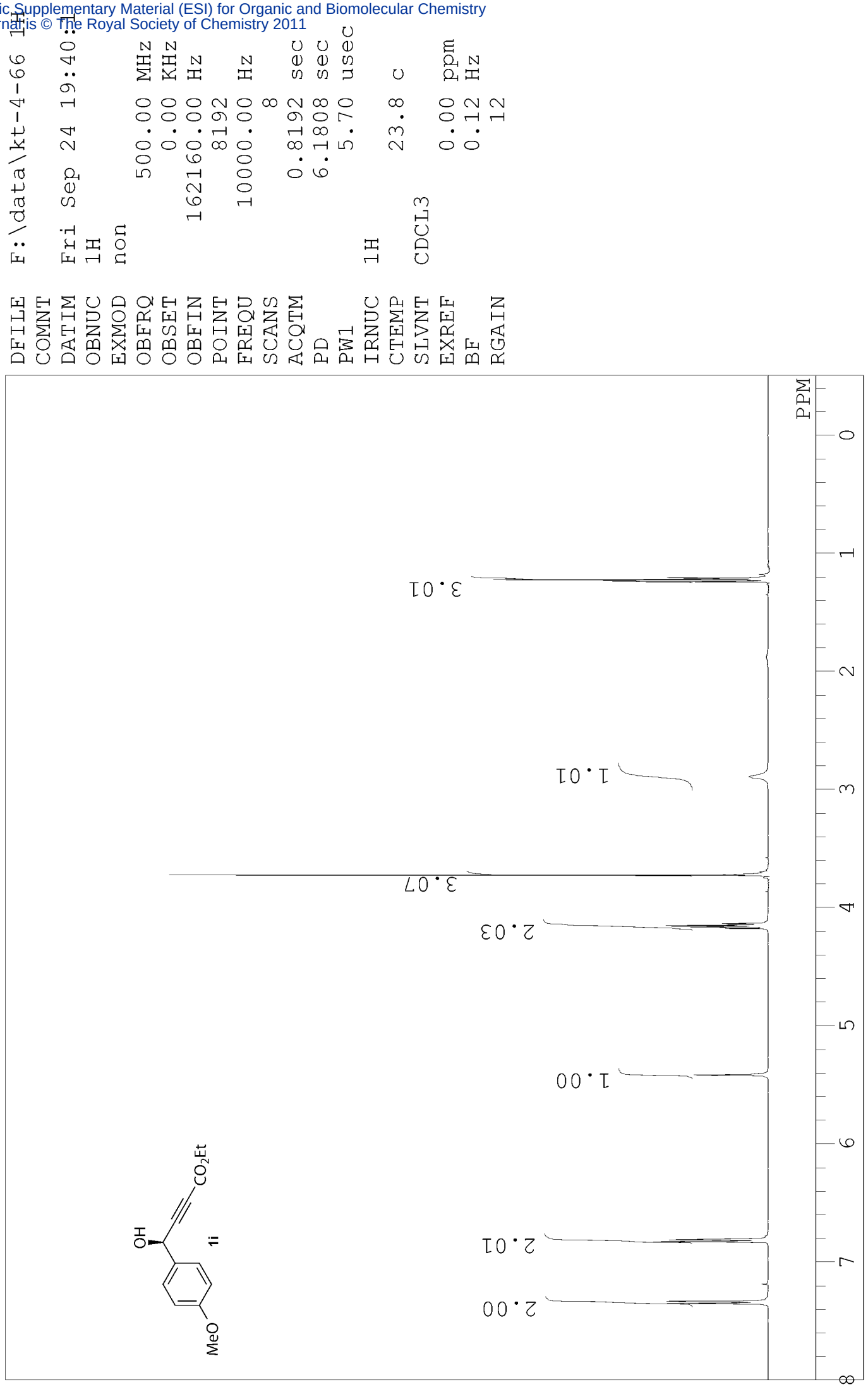


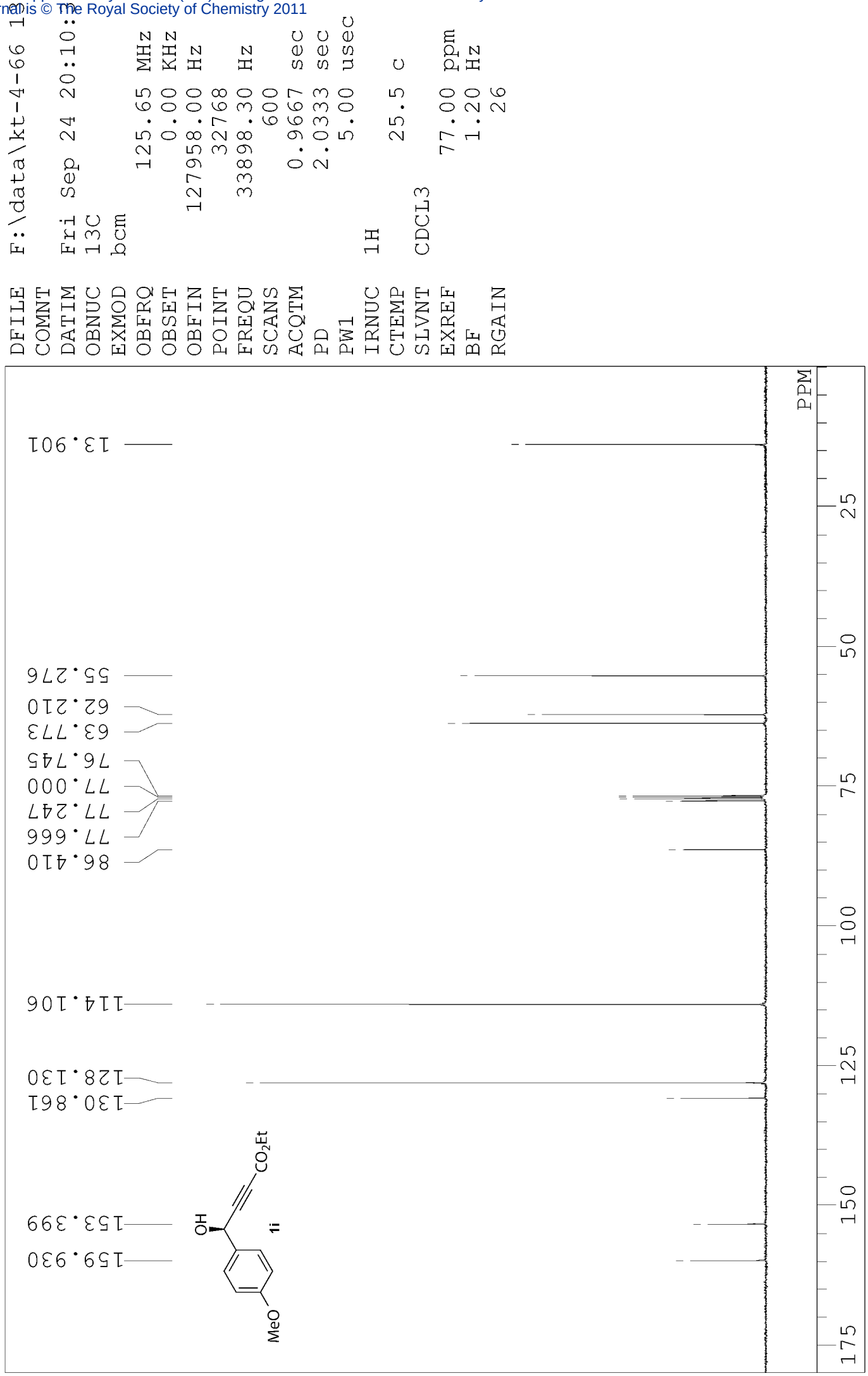


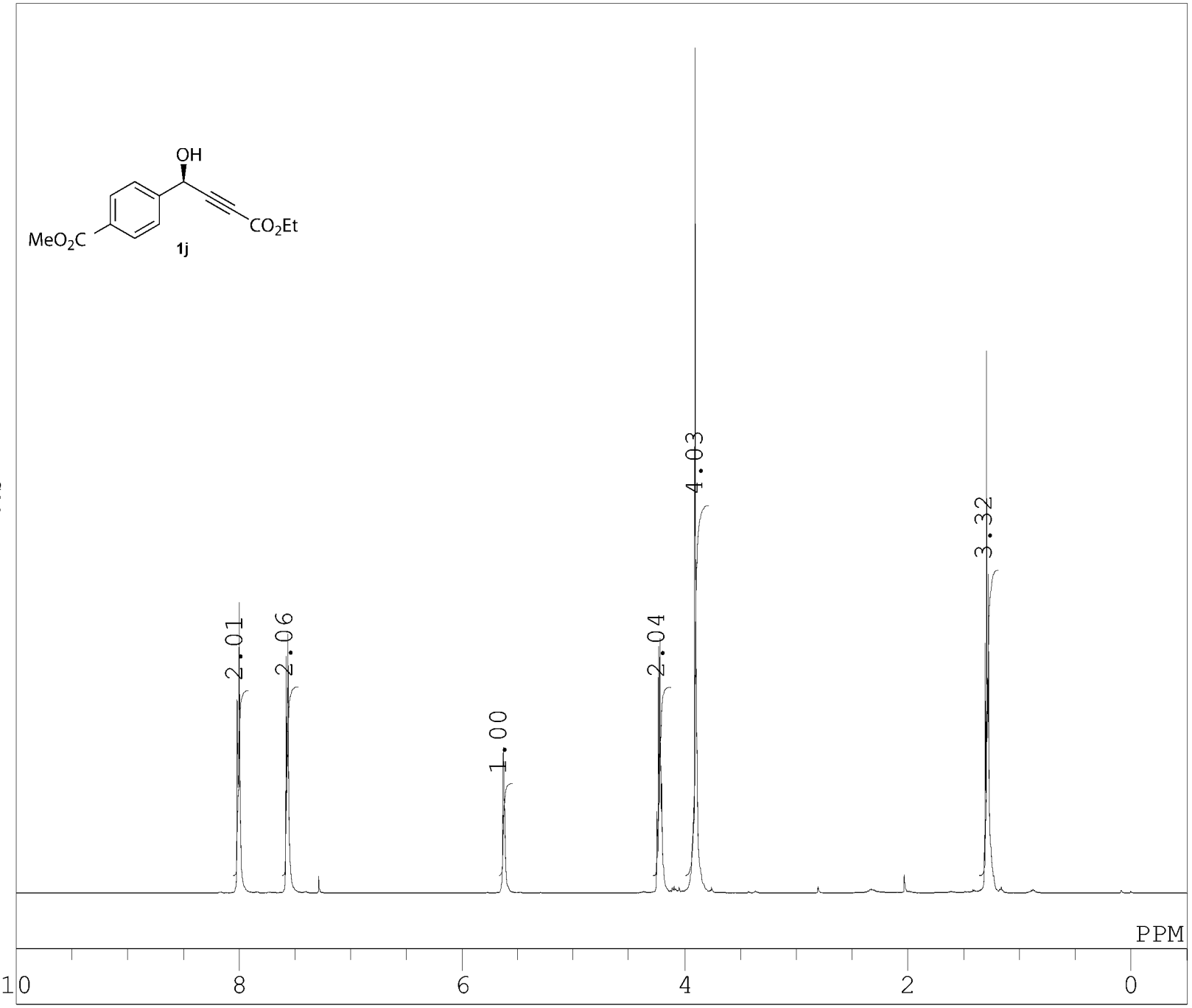




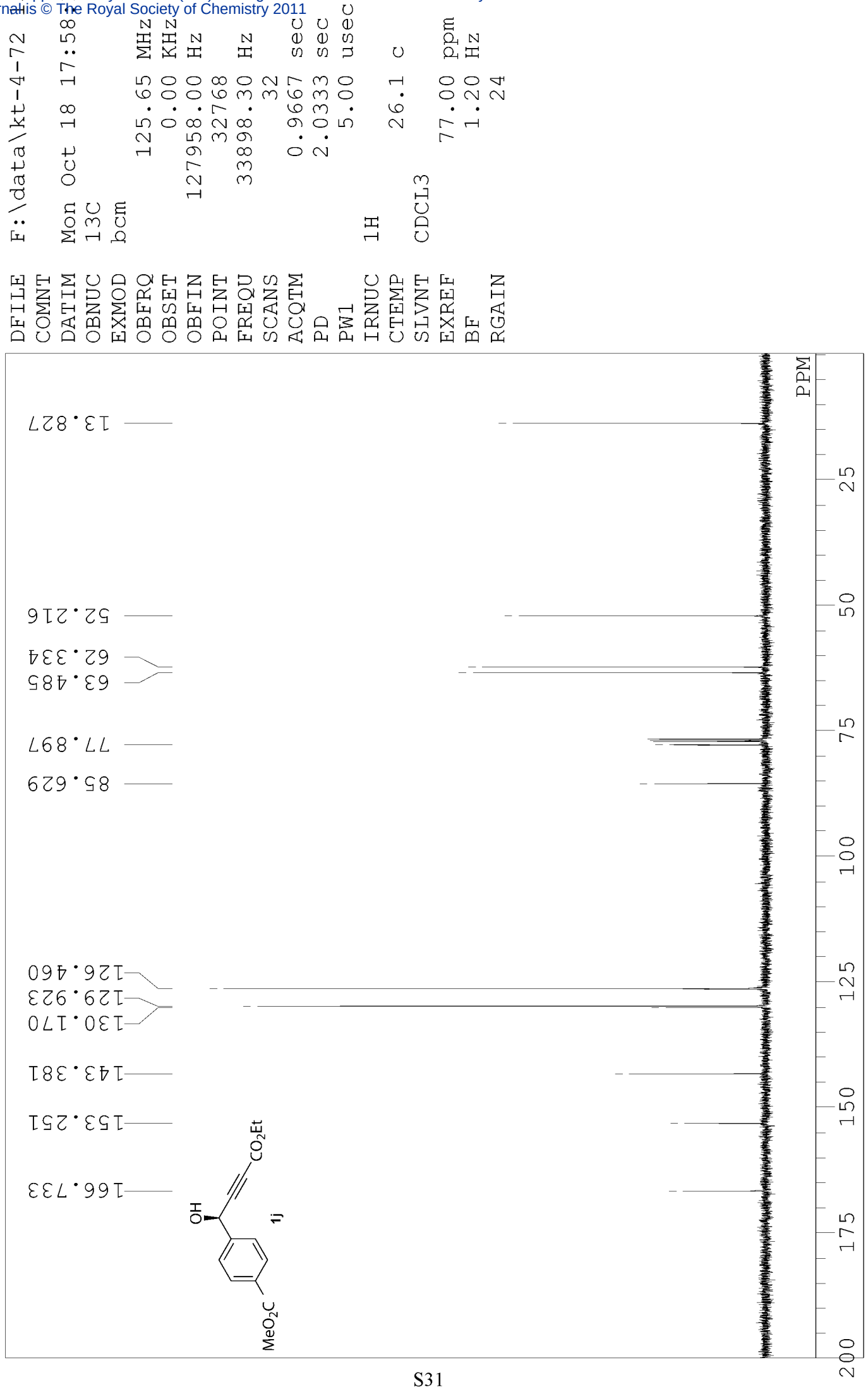


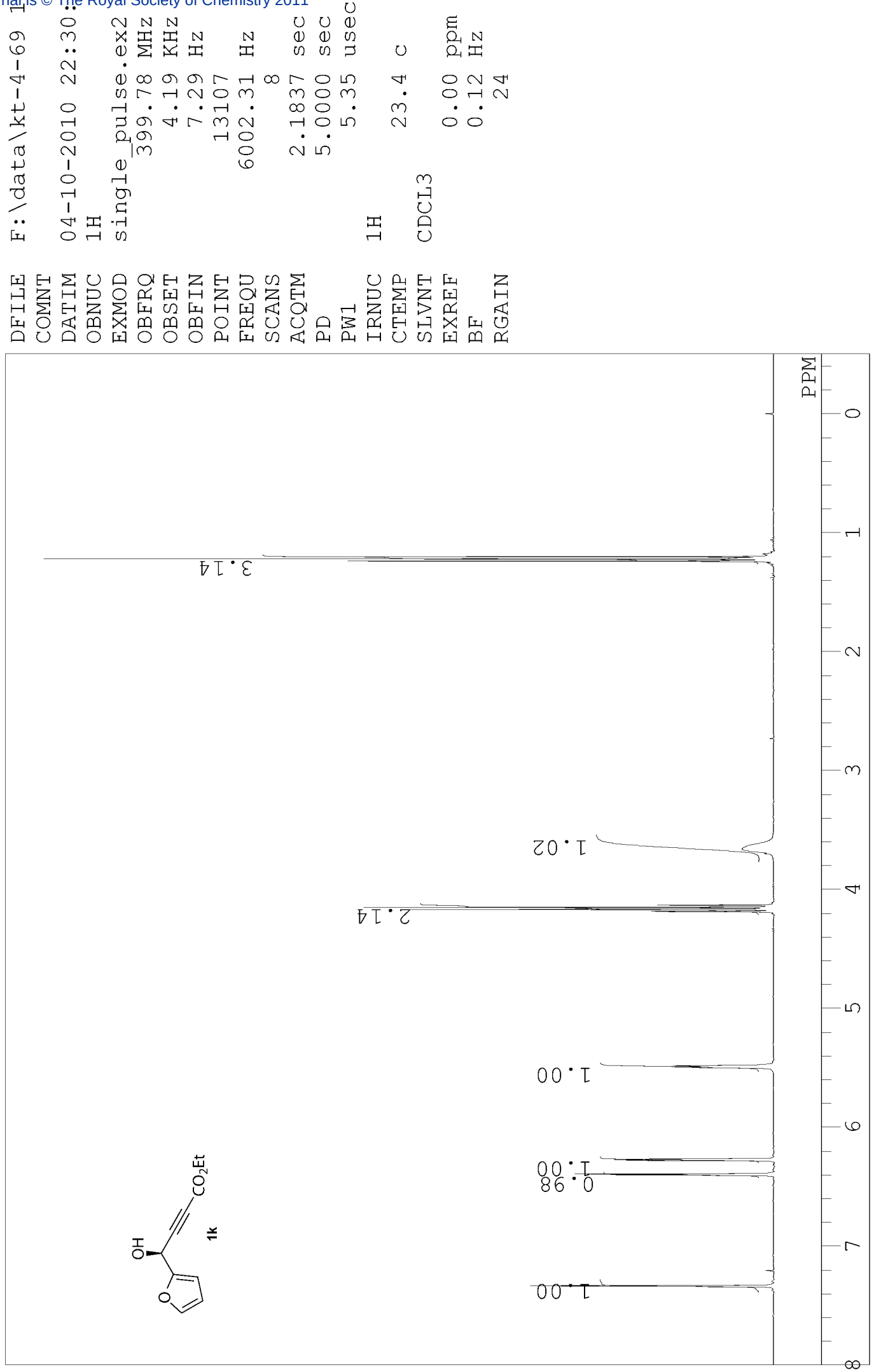


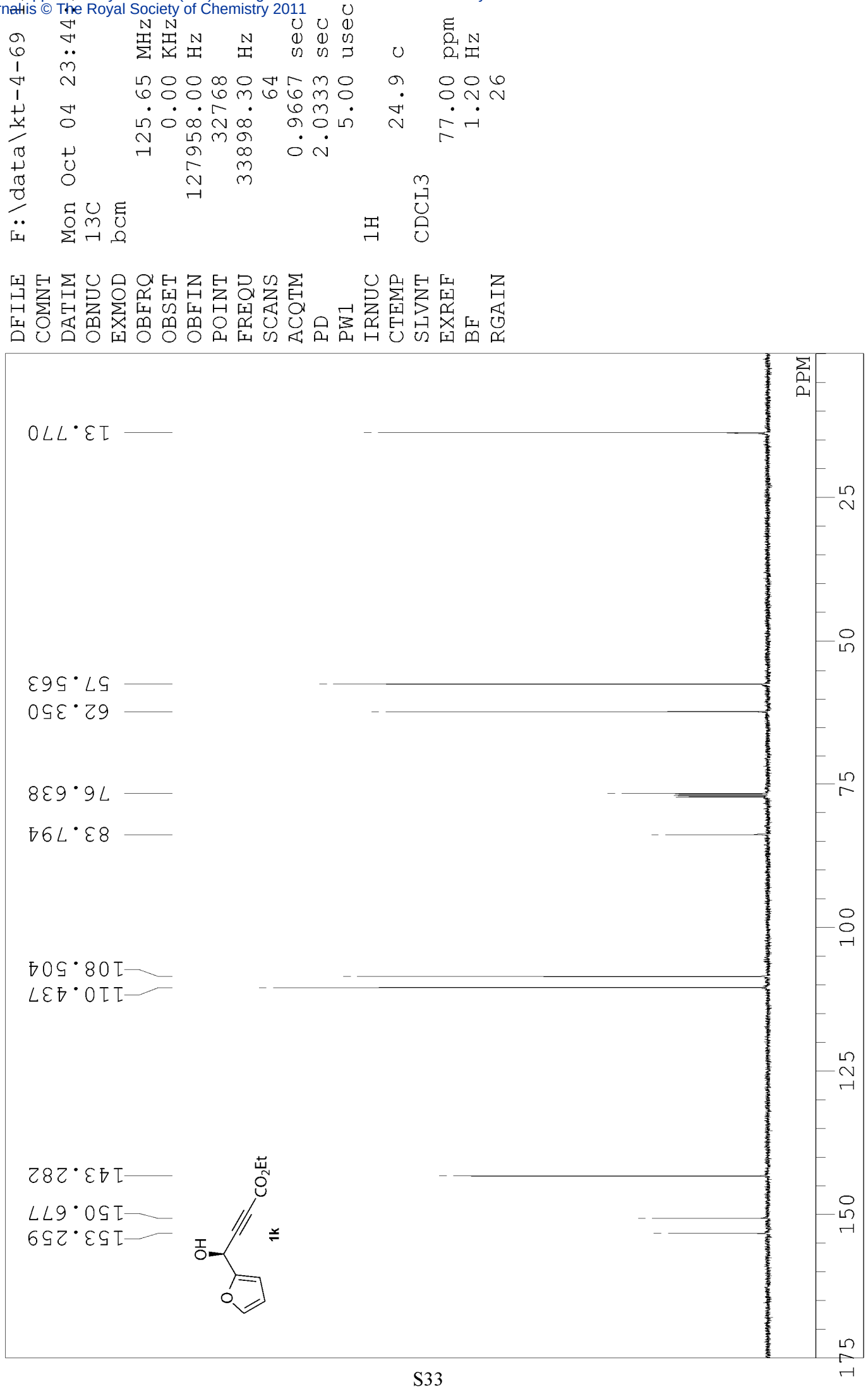





```
DFILE   F:\data\kt-4-72 1H
COMNT
DATIM   Mon Oct 18 17:56:
OBNUC   1H
EXMOD   non
OBFRQ          500.00 MHz
OBSET            0.00 KHz
OBFIN       162160.00 Hz
POINT            8192
FREQU        10000.00 Hz
SCANS               8
ACQTM          0.8192 sec
PD             6.1808 sec
PW1              5.70 usec
IRNUC   1H
CTEMP             25.1 c
SLVNT   CDCL3
EXREF             0.00 ppm
BF                0.12 Hz
RGAIN               10
```







```
DFILE   F:\data\kt-4-120
COMNT
DATIM   Wed Jan 12 22:05:
OBNUC   1H
EXMOD   non
OBFRQ     500.00 MHz
OBSET       0.00 KHz
OBFIN  162160.00 Hz
POINT      16384
FREQU   10000.00 Hz
SCANS         32
ACQTM      1.6384 sec
PD         2.0000 sec
PW1           5.15 usec
IRNUC   1H
CTEMP     23.0 c
SLVNT   CDCL3
EXREF        0.00 ppm
BF           0.12 Hz
RGAIN          22
```