Supporting Information

Highly efficient and selective phosphorylation of amino acid derivatives and polyols catalysed by 2-aryl-4-(dimethylamino)pyridine-*N*-oxides– towards kinase-like reactivity

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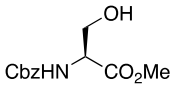
1. General Directions:

All reactions were performed under anhydrous conditions and an atmosphere of nitrogen in flame-dried glassware. Yields refer to chromatographically and spectroscopically (^{1}H-NMR) homogenous materials, unless otherwise indicated. *Solvents and reagents:* Solvents were dried as follows: MeCN, CH_2Cl_2 and MeOH were distilled over CaH_2, CH_3Cl over $MgSO_4$, THF and Et_2O over Na-benzophenone ketyl and toluene over Na. Otherwise MeCN, CH_2Cl_2, THF, Et_2O and toluene were dried and deoxygenated with a Grubbs Pure-Solv 400 solvent purification system. The moisture content of the solvents was monitored by Karl Fischer coulometric titration (Mettler-Toledo DL39). All other materials were obtained from commercial suppliers and used without further purification. *Chromatography:* Flash chromatography (FC) was always performed on silica gel (Merck Kieselgel 60 F_{254} 230-400 mesh) according to the method of W.C. Still,[1] unless otherwise stated. Thin Layer Chromatography (TLC) was performed on Merck aluminium-backed plates pre-coated with silica (0.2 mm, 60 F_{254}) which were visualized either by quenching of ultraviolet fluorescence (λ_{max} = 254 and 366 nm) or by charring with 10% $KMnO_4$ in 1 M H_2SO_4. *Melting points:* These were determined on a Khofler hot stage. *Infra red spectra:* These were recorded as KBr discs on Perkin-Elmer Paragon 1000 Fourier transform spectrometer. Only selected absorbances (υ_{max}) are reported. *^{1}H NMR spectra:* These were recorded at on a Bruker DRX-400 instrument. Chemical shifts (δ_H) are quoted in parts per million (ppm), referenced to the appropriate residual solvent peak. Coupling constants (*J*) are reported to the nearest 0.1 Hz. *^{13}C NMR spectra:* These were recorded at 400 MHz on Bruker AMX-400 instrument. Chemical shifts (δ_C) are quoted in ppm, referenced to the appropriate residual solvent peak. Degenerate peaks are suffixed by the number of carbons. *Optical rotations:* These were recorded at 589 nm (Na D-line) with a path length of 1 dm. Concentrations (c.) are quoted in g/100 mL and specific rotations, $[\alpha]_D^T$, are quoted in units of 10^{-1} deg cm^2 g^{-1} at the specified temperature, T. *Mass spectra:* Low and high resolution non-peptidic mass spectra (*m/z*) were recorded on Micromass Autospec Premier spectrometer with magnetic sector detector. High Resolution Mass Spectrometry (HRMS) measurements are valid to ± 5ppm. *Peptide LCMS and LCUV*: These were performed using a Waters LCT Premier Es-ToF mass spectrometer operating in ES+ mode [Capillary Voltage: 2000V, Cone Voltage 30V, Desolvation Temperature 350 degrees, Source Temperature 120 degrees, Cone Gas Flow 10 L/hr, Desolvation Gas Flow 400 L/hr], coupled to a Waters Aquity UPLC system [Column: BEH C18 50mm x 2.1 mm, 1.7um at 40 degrees, Flow: 0.5 ml/min, 10uL injection, Mobile Phase: Water A (0.1% Formic acid), Acetonitrile B (0.1% formic acid) with the following gradient: t = 0 (A = 95%, B=5%) → t = 3.2 min (A=5%, B=95%) → t = 3.5min (A=95%, B=5%), total run time 4min, PDA operating between 210nm and 280 nm]. *MS-MS (MS^2) studies*: These were performed on a Thermo Scientific Q-Exactive instrument [Sample was directly infused *via* syringe pump at 5uL/min, Spray Voltage: 4kV, Capillary temperature 325 degrees, Sheath Gas Flow: 20 (arbitrary unit)]. *Chiral Stationary phase (CSP) HPLC*: Analytical CSP-HPLC was performed using a CHIRALCEL OD-H column (size: 0.46 cm I.D. × 25 cm L) eluting with *n*-hexane/*i*-propanol (55:45) at 1 mL/min (25 ˚C) and detecting at UV 210 nm (injection volume 5 µL; sample conc. 10 mg/mL).

2. General Method 1: Synthesis of protected amino acid substrates by esterification

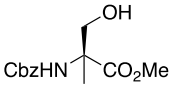
Acetyl chloride (5 mL) was added dropwise to dry MeOH (40 mL) at 0 °C. The resulting solution was allowed to stir at this temperature for 5 min before the addition of the *N*-Cbz protected amino acid (12-16 mmol). The resulting solution was heated to 70 °C and stirred at this temperature for 12 h. The reaction mixture was then allowed to cool before being concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 mL) and the organic phase washed with sat. $NaHCO_3$ (3 × 50 mL) before being dried over $MgSO_4$ and concentrated *in vacuo* to afford the product.

(*S*)-*N*-Cbz-Ser(OH)-OMe (1)[2]



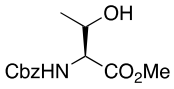
According to **General Method 1**, (*S*)-*N*-Cbz-Ser(OH)-OH (4.0 g, 16.7 mmol) afforded *methyl ester* **1** as a pale brown oil (3.64 g, 14.4 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.39-7.28 (m, 5H), 5.74 (br d, J = 6.3 Hz, 1H), 5.16 (s, 2H), 4.49 (s, 1H), 4.05-3.94 (m, 2H), 3.81 (s, 3H). ^{1}H NMR (400 MHz, methanol-d_4, ppm): δ 7.41-7.29 (m, 5H), 5.12 (s, 2H), 4.34 (t, J = 4.5 Hz, 1H), 3.91-3.75 (m, 2H), 3.75 (s, 3H). Spectroscopic data in agreement with the literature.[2]

***(*S)-*N*Cbz-(α-Me)Ser(OH)-OMe (5)**[3]



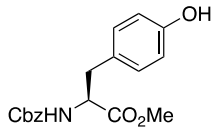
To a solution of (*S*)-α-MeSer(OH)-OH (0.75 g, 6.3 mmol) in 10% Na_2CO_3 (18 ml) was added *N*-(Benzyloxycarbonyloxy)succinimide (3.14 g, 12.6 mmol) followed by 1,4-dioxane (12 ml). The resulting mixture was stirred at RT for 24 h at which time it was extracted with Et_2O (3 × 10 mL). The aqueous phase was then acidified to pH 3 before being extracted with EtOAc (4 × 15 mL). The combined organic phases were then washed with brine and dried over $MgSO_4$ before being concentrated *in vacuo* to afford crude (*S*)-*N*-Cbz-α-MeSer(OH)-OH (1.1 g, 6.7 mmol) which was used directly in the following esterification reaction. Using a diazomethane distillation kit, Diazald® (2.7 g, 12.6 mmol) in ether (20 ml) was added dropwise to a mixture of KOH (2 g) in water (15 mL), carbitol© (25 mL) and ether (20 mL) at 85 °C. The resulting diazomethane was distilled through the diazomethane distillation apparatus into a solution of crude *N*-Cbz-*α*-MeSer(OH)-OH (1.1 g, 6.7 mmol) in CH_2Cl_2 (25 mL). The reaction mixture was allowed to stand for 12 h to allow evaporation of any excess diazomethane before being concentrated *in vacuo* to afford the *methyl ester* **5** as a brown oil (1.12 g, 4.2 mmol, 67%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.47–7.35 (m, 5H), 5.72 (br s, 1H), 5.12 (s, 2H), 4.01–3.83 (m, 1H), 3.83–3.75 (m, 1H), 3.75 (s, 3H), 3.10 (br s, 1H), 1.49 (s, 3H, Me). Spectroscopic data in agreement with the literature.[3]

(*S*)-*N*-Cbz-Thr(OH)-OMe (8)[4]



According to **General Method 1**, (*S*)-*N*-Cbz-Thr(OH)-OH (4.0 g, 15.8 mmol) afforded *methyl ester* **8** as an off white solid (3.42 g, 12.8 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.40-7.34 (m, 5H), 5.65 (br d, J = 8.5 Hz, 1H), 4.36 (br d, J = 6.9 Hz, 2H), 5.16 (s, 2H), 3.80 (s, 3H), 1.28 (d, J = 6.4 Hz, 3H). ^{1}H NMR (400 MHz, methanol-d_4, ppm): δ 7.42-7.32 (m, 5H), 5.14 (s, 2H), 4.29 (dd, J = 6.4, 3.1 Hz, 1H), 4.24 (br d, J = 2.9 Hz, 1H), 3.73 (s, 3H), 3.69 (s, 1H), 2.63 (br s, 1H), 1.22 (d, J = 6.4 Hz, 3H). Spectroscopic data in agreement with the literature.[4]

(*S*)-*N*-Cbz-Tyr(OH)-OMe (10)[5]



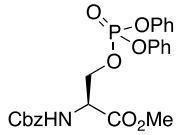
According to **General Method 1**, but omitting the basic wash, (*S*)-*N*-Cbz-Tyr(OH)-OH (4 g, 12.7 mmol) following dissolution of the crude residue in 1:1 EtOAc/hexanes, passing through a silica plug and concentrating *in vacuo* afforded *methyl ester* **10** as a brown solid (3.80 g, 11.6 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.42-7.33 (m, 5H), 6.97 (d, J = 8.4 Hz, 2H), 6.74 (d, J = 8.4 Hz, 2H), 5.24 (br d, J = 8.3 Hz, 1H), 5.18-5.04 (m, 2H), 4.65-4.62 (m, 1H), 3.75 (s, 3H), 3.12-3.00 (m, 2H). ^{1}H NMR (400 MHz, methanol-d_4, ppm): δ 7.36-7.29 (m, 5H), 7.02 (d, J = 8.5 Hz, 2H), 6.71 (d, J = 8.5 Hz, 2H), 5.09-5.01 (m, 2H), 4.41-4.37 (m, 1H), 3.69 (s, 3H), 3.07-2.82 (m, 2H). CAS: 13512-31-7. Spectroscopic data in agreement with the literature.[5]

3. General Method 2: Synthesis of phosphorylated amino acid derivatives using DMAP-*N*-oxide derived catalysis

To a solution of (*S*)-*N*-Cbz-Xxx(OH)-OMe (1 eq.) in dry CH_2Cl_2 (0.2 M) was added base (2 eq.), diphenylphosphoryl chloride (1.2 eq.) followed by catalyst (5 mol %) under nitrogen. The reaction was allowed to stir at RT and reaction progress monitored by ^{1}H NMR (sample aliquots quenched in methanol-d_4). At the appropriate time point, CH_2Cl_2 (2 mL) was added and the organic phase washed with 2 M HCl (2 × 5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography (eluent: EtOAc/hexanes) to afford product.

(2*S*)-Methyl 2-{[(benzyloxy)carbonyl]amino}-3-[(diphenoxyphosphoryl)oxy]propanoate (3)

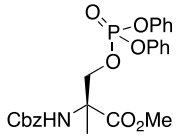
Representative procedure using cat. 2l and propylene oxide (Table 1, Entry 13):



According to **General Method 2**, (*S*)-*N*-Cbz-Ser(OH)-OMe (**1**, 150 mg, 0.59 mmol), propylene oxide (0.082 mL, 1.2 mmol), diphenylphosphoryl chloride (0.147 mL, 0.71 mmol) and **cat. 2l** (9.9 mg, 0.03 mmol) after 8 h and following flash chromatography (0-30% EtOAc/hexanes) afforded *phosphate* **3** as a white solid (271 mg, 0.56 mmol, 95%). M.p. 50-51 ^{o}C. IR (ν_{max}/cm^{-1}): 3313, 3067, 3039, 2957, 1721, 1590, 1514, 1488, 1456, 1288, 1185, 1163, 948, 754, 688. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.37-7.21 (m, 15H), 5.67 (d, J = 7.6 Hz, 1H), 5.12 (s, 2H), 4.70-4.64 (m, 2H), 4.59-4.55 (m, 1H), 3.72 (s, 3H). ^{1}H NMR (400 MHz, methanol-d_4, ppm): δ 7.39-7.21 (m, 15H), 5.11 (s, 2H), 4.64-4.60 (m, 3H), 3.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 169.0, 155.7, 150.3, 150.2, 135.9, 129.9, 128.6, 128.1, 125.6, 120.0, 120.0, 110.0, 68.6, 67.3, 54.3, 53.0. ^{31}P NMR (161 MHz, $CDCl_3$, ppm): δ -12.28. HRMS (*m*/*z* +ES): Found: 486.1327 (M^+ $C_{24}H_{25}NO_8P$ Requires: 486.1328). $[\alpha]_D^{23}$ + 79 (*c* 1.04, $CHCl_3$); > 99% *ee* by CSP-HPLC – see section 4, below.

(*S*)-Methyl 2-{[(benzyloxy)carbonyl]amino}-3-[(diphenoxyphosphoryl)oxy]-2-methylpropanoate (7)

Representative procedure using cat. 2l and Proton Sponge® (Table 2, Entry 4)

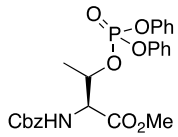


According to **General Method 2**, (*S*)-*N*-Cbz-α-MeSer(OH)-OMe (**5**, 15, 100 mg, 0.40 mmol), Proton Sponge® (172 mg, 0.80 mmol), diphenylphosphoryl chloride (0.1 mL, 0.48 mmol) and **cat. 2l** (7.0 mg, 0.02 mmol) after 2 h and following flash chromatography (0-40% EtOAc/hexanes) afforded *phosphate* **7** as a colourless oil (174 mg, 0.35 mmol,

87%). IR (ν_{max}/cm^{-1}): 3308, 3070, 3040, 2955, 1721, 1590, 1488, 1286, 1218, 1186, 1162, 1047, 947, 754, 689. ^{1}H NMR (400 MHz, methanol-d_4, ppm): δ 7.41-7.20 (m, 15H), 5.07-4.95 (m, 2H), 4.84-4.51 (m, 2H), 3.71 (s, 3H), 1.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 171.8, 154.5, 150.4, 150.4, 129.8, 128.5, 128.2, 128.0, 125.5, 120.1, 69.4, 66.7, 59.9, 53.1, 20.0. ^{31}P NMR (161 MHz, methanol-d_4, ppm): δ -12.47. HRMS (*m*/*z* +ES): Found: 522.1268 (M+ $C_{25}H_{26}NO_8P$ Na Requires: 522.1294). $[\alpha]_D^{23}$ + 115 (*c* 1.01, $CHCl_3$).

(2*S*, 3*S*)-Methyl 2-{[(benzyloxy)carbonyl]amino}-3-[(diphenoxyphosphoryl)oxy]butanoate (9)

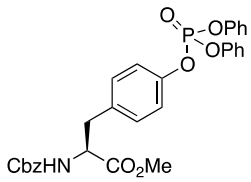
Representative procedure using cat. 2l and Proton Sponge® (Table 3, Entry 6)



According to **General Method 2**, (*S*)-*N*-Cbz-Thr(OH)-OMe (**8**, 100 mg, 0.4 mmol), Proton Sponge® (171 mg, 0.8 mmol), diphenylphosphoryl chloride (0.088 mL, 0.48 mmol) and **cat. 2l** (6.7 mg, 0.04 mmol) after 24 h and following flash chromatography (0-40% EtOAc/hexanes) afforded *phosphate* **9** as a colourless oil (179 mg, 0.36 mmol, 96%). IR (ν_{max}/cm^{-1}): 3315, 3077, 3038, 2955, 1718, 1498, 1294, 1215, 1162, 1009, 947, 754, 689. ^{1}H NMR (400 MHz, methanol-d_4, ppm): δ 7.64 (br d, *J* = 9.4 Hz, 1H), 7.40-7.21 (m, 15H), 5.31-5.28 (m, 1H), 5.14 (s, 2H), 4.60 (t, *J* = 2.9 Hz, 1H), 3.59 (s, 3H), 1.41 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, methanol-d_4, ppm): δ 160.7, 157.7, 150.3, 136.7, 129.7, 128.1, 127.5, 125.5, 119.9, 119.8, 77.6, 66.6, 58.5, 51.8, 17.3. ^{1}P NMR (161 MHz, methanol-d_4, ppm): δ -12.87. HRMS (*m*/*z* +ES): Found: 500.1043 (M+H$^+$ $C_{25}H_{27}NO_8P$ Requires: 500.1074). $[\alpha]_D^{23}$ + 85 (*c* 0.98, $CHCl_3$).

(2*S*)-Methyl 2-{[(benzyloxy)carbonyl]amino}-3-{4-[(diphenoxyphosphoryl)oxy]phenyl}propanoate (11)

Representative procedure using cat. 2l and NEt_3 (Table 3, Entry 10)



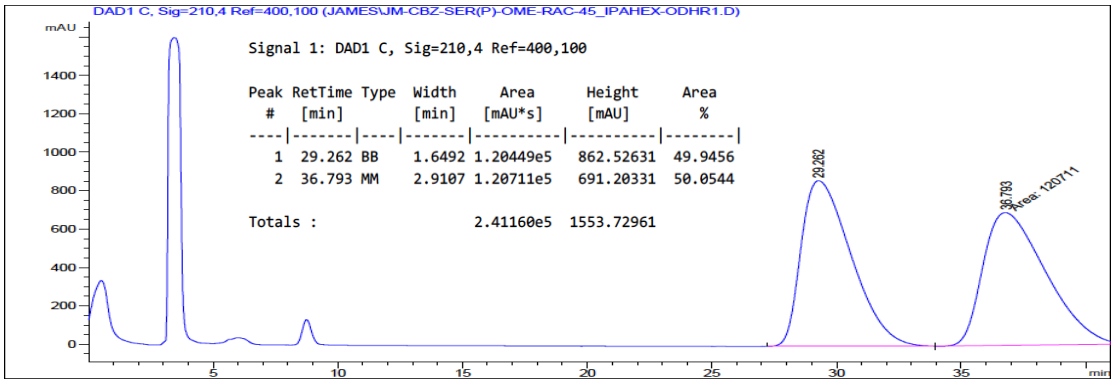
According to **General Method 2**, (*S*)-*N*Cbz-Tyr(OH)-OMe (**7**, 100 mg, 0.30 mmol), NEt_3 (0.083 mL, 0.60 mmol), diphenylphosphoryl chloride (0.074 mL, 0.36 mmol) and **cat. 2l** (5.2 mg, 0.02 mmol) after 2 h and following flash chromatography (0-20% EtOAc/hexanes) afforded *phosphate* **11** as a colourless oil (165 mg, 0.29 mmol, 95%). IR (ν_{max}/cm^{-1}): 3324, 3072, 3038, 2955, 1720, 1590, 1488, 1291, 1184, 1161, 954, 754, 688. ^{1}H NMR (400 MHz, methanol-d_4, ppm): δ 7.44-7.22 (m, 17H), 7.15 (d, *J* = 8.7 Hz, 2H), 5.03 (s, 1H), 4.48-4.44 (m, 1H), 3.71 (s, 3H), 3.20-2.92 (m, 2H). ^{13}C NMR (100 MHz, methanol-d_4, ppm): δ 172.2, 156.9, 150.3, 149.0, 136.8, 135.1, 130.6, 129.8, 128.0, 127.6, 127.3, 125.7, 119.7, 66.2, 60.1, 55.4, 51.4. ^{31}P NMR (161 MHz, methanol-d_4, ppm): δ –17.41. HRMS (*m*/*z* +ES): Found: 563.1632 (M+H$^+$ $C_{30}H_{29}NO_8P$ Requires: 562.1631). $[\alpha]_D^{23}$ + 176 (*c* 1.09, $CHCl_3$).

4. Checking the stereochemical integrity of phosphoryl serine 3.

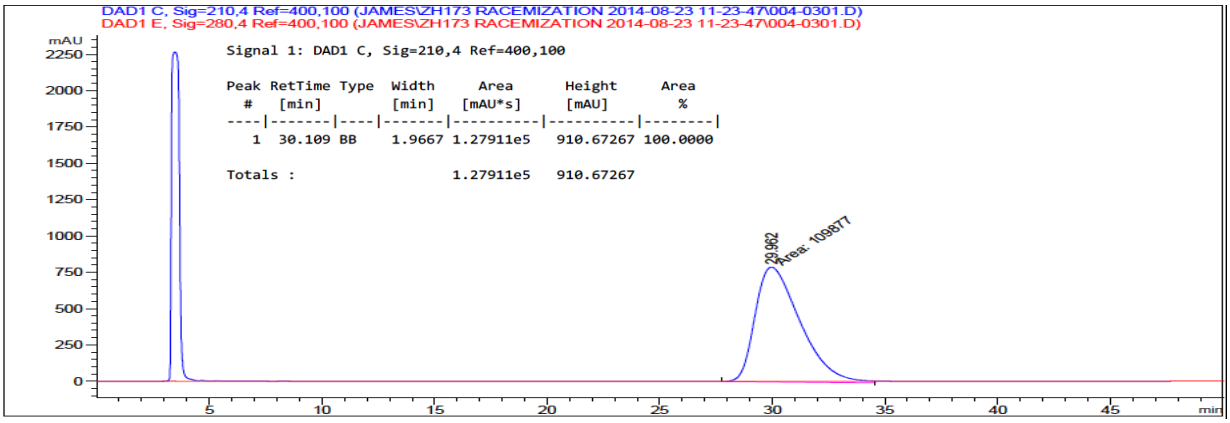
To ascertain whether there had been any racemisation during the phosphorylation of serine derivative **1**, the products of the using PPO, Proton Sponge©, and PMP (Table 2, entries 2, 4 and 5) were analysed by CSP-HPLC [For the chromatography conditions see'General Directions' (page 2, above)]. Moreover, the products of each of these reactions were also resubjected to the reaction conditions for

24 h in the *absence* of phosphorylating agent and re-analysed. In all cases, the products were enantiomerically pure within the limits of detection (~>98% ee), see below.

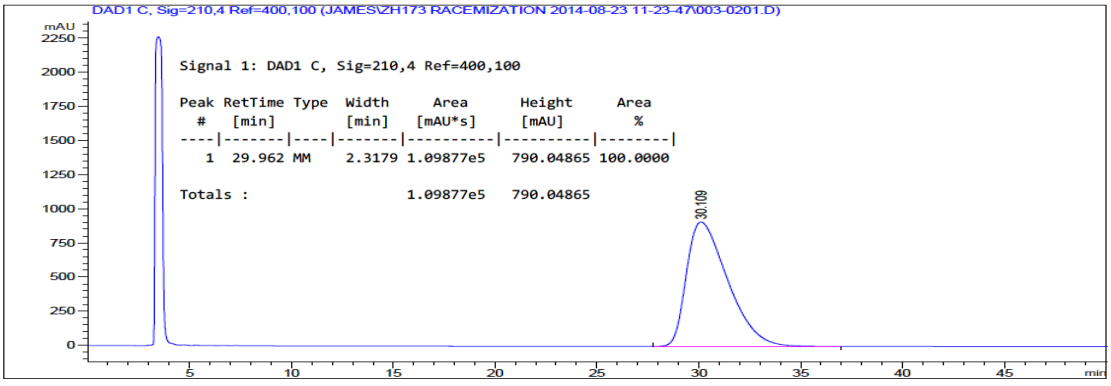
Racemic phosphoryl serine 3 (control).



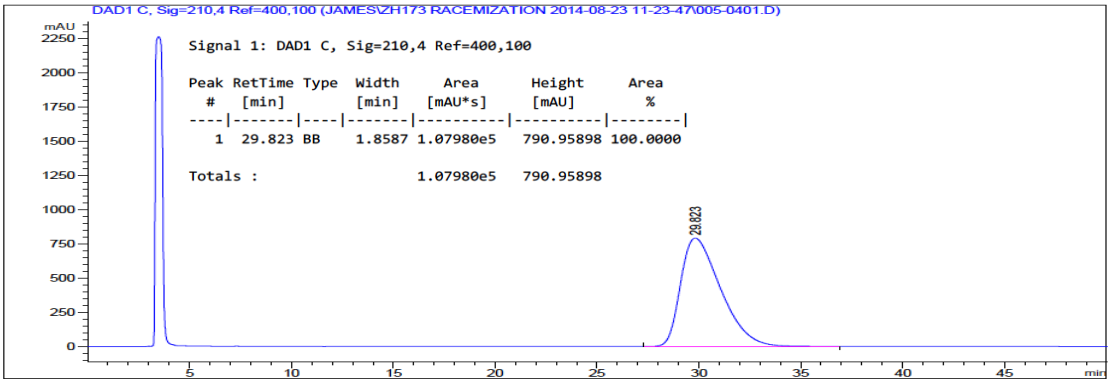
Phosphoryl serine 3 from reaction using PPO.



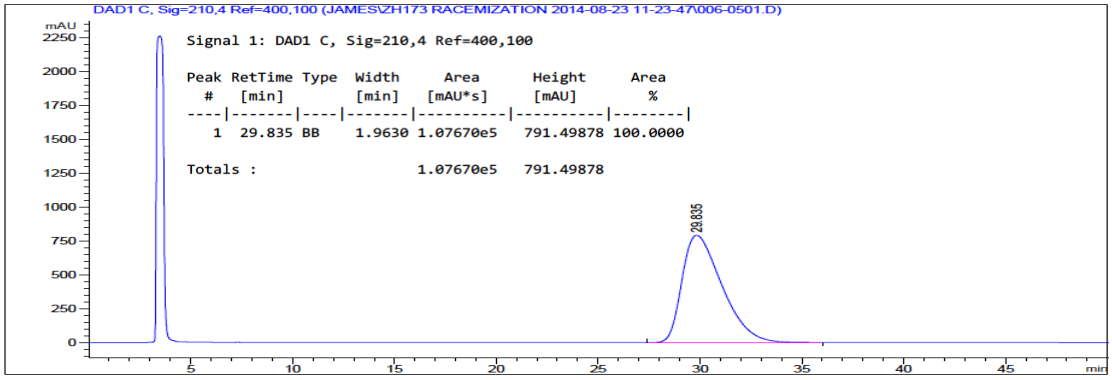
Phosphoryl serine 3 following resubjection to the PPO reaction conditions [5 mol% cat. **2l**, PPO (2 eq.), CH_2Cl_2 (0.2 M), 24 h].



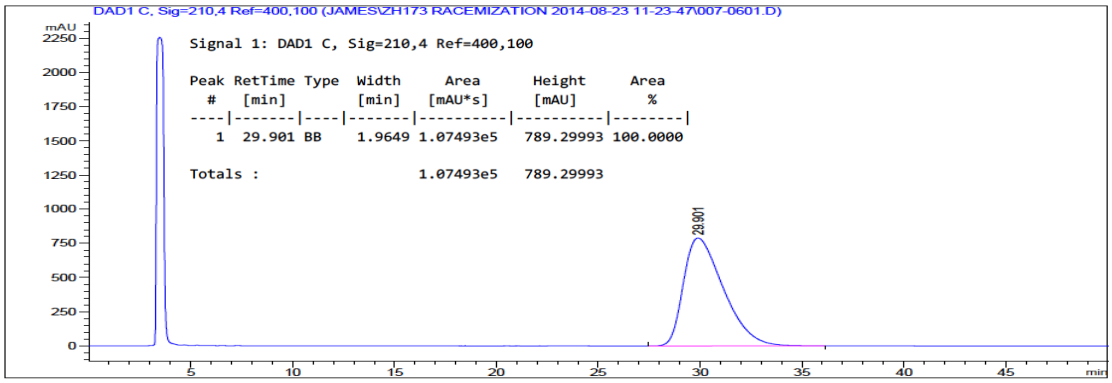
Phosphoryl serine 3 from reaction using Proton Sponge©.



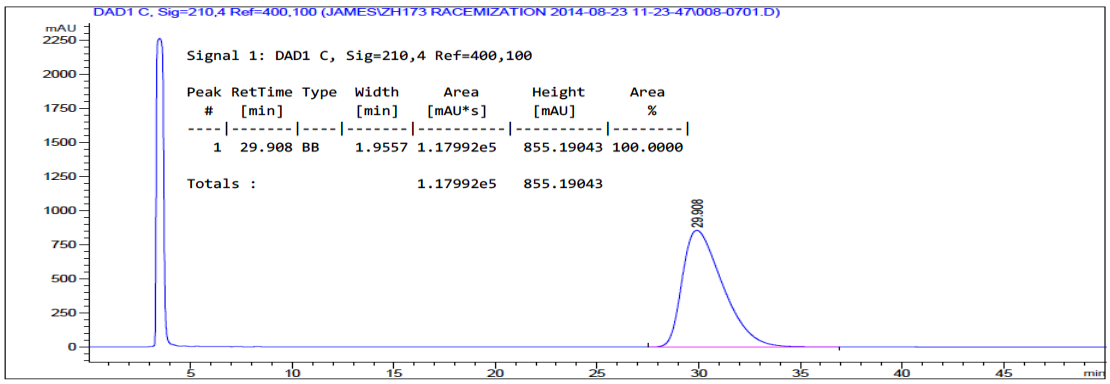
Phosphoryl serine 3 following resubjection to the Proton Sponge© reaction conditions [5 mol% cat. **2l**, Proton Sponge© (2 eq.), CH_2Cl_2 (0.2 M), 24 h].



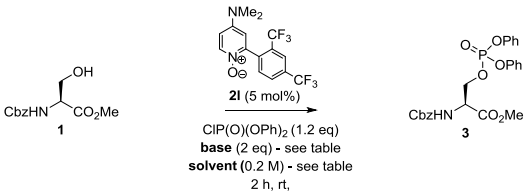
Phosphoryl serine 3 from reaction using PMP.



Phosphoryl serine 3 following resubjection to the PMP reaction conditions [5 mol% cat. **2l**, PMP (2 eq.), CH_2Cl_2 (0.2 M), 24 h].



5. Use of alternative solvents in place of CH_2Cl_2 for the phosphorylation of Serine derivative 1. See below.

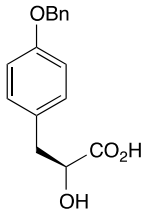


Entry	Solvent	Base/H^+ scavenger	Yield[a] (**3**/%)	Yield[a] (**4**/%)
1[b]	CH_2Cl_2	None	0	0
2[c]	CH_2Cl_2	PPO	53	0
3	DMF	None	0	0
4	DMF	PPO	17	0
5	MeCN	None	0	0
6	MeCN	PPO	43	0
7	DMSO	None	0	0
8	DMSO	PPO	31	0

[a]Isolated yield after chromatographic purification. [c]Corresponds to entry 1, Table 2 in main manuscript. [c]Corresponds to entry 2, Table 2 in main manuscript.

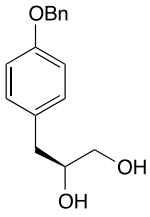
6. Synthesis of 3-(*p*-hydroxyphenyl)-1,2-propanediol (12)[6]

6-1: [(*S*)-3-(4-(Benzyloxy)phenyl]-2-hydroxypropanoic acid[7]



To an ice-cooled solution of (*S*)-2-amino-3-[4-(benzyloxy)phenyl]propanoic acid (0.5 g, 1.8 mmol) in H_2SO_4 (1M, 5 mL) and DMF (2.8 mL) was added dropwise $NaNO_2$ (635 mg, 9.2 mmol) in water (1.5 mL). After 1 h, H_2SO_4 (3 M, 2 mL) was added and the resulting solution stirred at RT for 12 h. The reaction mixture was then extracted with EtOAc (3 × 50 mL), brine (6 × 50 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to afford a yellow liquid, to which was added EtOAc (20 mL) and washed with LiCl solution (7.5%, 3 × 25 mL) followed by brine and dried over $MgSO_4$ before being concentrated *in vacuo* to afford (*S*)-*2-amino-3-[4-(benzyloxy)phenyl]propanoic acid* as a yellow solid (300 mg, 1.1 mmol, 62%). ^{1}H NMR (400 MHz, methanol-d_4, ppm): δ 7.43 (d, J = 7.1 Hz, 2H), 7.40 (t, J = 7.1 Hz, 2H), 7.31 (t, J = 7.1 Hz, 1H), 7.19 (d, J = 8.2 Hz, 2H), 6.94 (d, J = 8.2 Hz, 2H), 5.03 (s, 2H), 4.51 (dd, J = 7.1, 4.3 Hz, 1H), 3.18 (dd, J = 14.6, 4.3 Hz, 1H), 2.96 (dd, J = 14.6, 7.6 Hz, 1H), 2.60 (br s, 2H). Spectroscopic data in agreement with literature.[7]

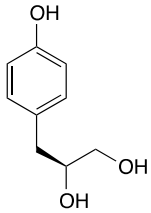
6-2: (*S*)-3-[4-(Benzyloxy)phenyl]propane-1,2-diol[8]



To a stirred solution of $NaBH_4$ (125 mg, 3.3 mmol) in dry THF (5 mL) at 0 ^{o}C was added iodine (420 mg, 1.6 mmol) in dry THF (2 mL) in a dropwise manner. To this solution was added (*S*)-3-[4-(benzyloxy)phenyl]-2-hydroxypropanoic acid (300 mg, 1.1 mmol) in dry THF (3 mL) in a dropwise manner. The resulting solution was heated to 60 ^{o}C for 12 h. To the reaction mixture was added MeOH (2 mL) before being concentrated *in vacuo*. The residue was then dissolved in EtOAc (5 mL) and the organic phase washed with sat. $NaHCO_3$ (3 × 5 mL) before being dried over $MgSO_4$ and concentrated

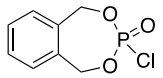
in vacuo to afford a yellow oil which was purified by flash chromatography (50-100% EtOAc/hexanes) to afford (*S*)-*3-[4-(benzyloxy)phenyl]propane-1,2-diol* as yellow solid (140 mg, 0.54 mmol, 49%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.47-7.39 (m, 5H), 7.17 (d, J = 8.6 Hz, 2H), 6.96 (d, J = 8.6 Hz, 2H), 5.08 (s, 2H), 3.96- 3.91 (m, 1H), 3.74-3.71 (m, 1H), 3.57-3.54 (m, 1H), 2.80-2.69 (m, 2H), 1.83 (br s, 2H). LRMS (*m*/*z* +ES): Found: 259 ($M+H^+$ $C_{16}H_{19}O_3$ Requires: 259). Spectroscopic data in agreement with literature.[8]

6-3: (*S*)-3-(4-Hydroxyphenyl)propane-1,2-diol (12)[6]



To a solution of (*S*)-3-[4-(benzyloxy)phenyl]propane-1,2-diol (150 mg, 0.59 mmol) in MeOH (4 mL) and AcOH (0.1 mL) was added Pd/C (3 mg, 0.03 mmol). The reaction vessel was evacuated and refilled with hydrogen (× 3) and the reaction mixture stirred under at RT for 12 h. The reaction mixture was then concentrated *in vacuo* and the residue purified by flash chromatography (50-100% EtOAc/hexanes) to afford (*S*)-*3-(4-hydroxyphenyl)propane-1,2-diol* (**12**) as a pale brown oil that solidified over a period of 12 h to form an off white solid (96 mg, 0.57 mmol, 99%). ^{1}H NMR (400 MHz, methanol-d_4, ppm): δ 7.07 (d, J = 8.5 Hz, 2H), 6.72 (d, J = 8.5 Hz, 2H), 3.78-3.71 (m, 1H), 3.53-3.41 (m, 2H), 2.76-2.58 (m, 2H). Spectroscopic data in agreement with literature.[6]

7. Synthesis of *ortho*-xylenyl phosphoryl chloride (14, *o*-XPCl)[9]

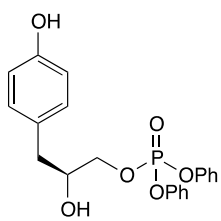


To a solution of $POCl_3$ (1.22 mL, 13.0 mmol) in CH_2Cl_2 (50 mL) at 0 ^{o}C was added NEt_3 (3.63 mL) dropwise. To the resulting yellow suspension was added a solution phthalyl alcohol (1.80 g, 13.0 mmol) in CH_2Cl_2 (25 mL) dropwise. The resulting reaction mixture was allowed to warm to RT and stirred at this temperature for a further 2 h. The reaction mixture was then washed with citric acid (1 M, 3 × 50 mL). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo* to afford *ortho-xylenyl phosphoryl chloride* (**14**) as an off white solid (1.72 g, 7.93 mmol, 61%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.50-7.37 (m, 4H), 5.49 (dd, J = 13.4, 10.1 Hz, 2H), 5.11 (dd, J = 13.4, 10.1 Hz, 2H). ^{31}P NMR (161 MHz, $CDCl_3$, ppm): δ 3.00. Spectroscopic data in agreement with literature.[9]

8. General Method 3: Chemoselective phosphorylation of (*S*)-3-(*p*-hydroxyphenyl)-1,2-propanediol (12) and Chloramphenicol© (16)

To a solution of hydroxyl-containing substrate (1 eq.) in dry CH_2Cl_2:MeCN (9:1, 0.2 M) was added base, phosphorylating agent followed by catalyst (5 mol %) under nitrogen. The reaction was allowed to stir at RT for the time indicated. At the appropriate time point, MeOH (2 mL) was added and the reaction mixture concentrated *in vacuo* concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography (EtOAc/hexanes) to afford product.

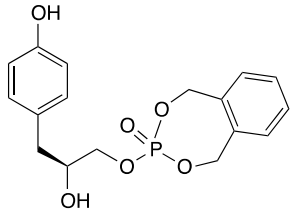
(*S*)-2-Hydroxy-3-(4-hydroxyphenyl)propyl diphenyl phosphate [13a, R^3 = P(O)(OPh)$_2$] (Table 4, Entry 1)



According to **General Method 4**, (*S*)-3-(4-hydroxyphenyl)propane-1,2-diol (**12**, 100 mg, 0.59 mmol), propylene oxide (0.083 mL, 1.19 mmol),

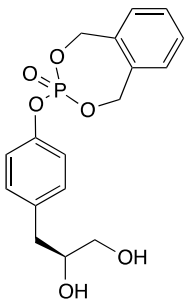
diphenylphosphoryl chloride (0.147 mL, 0.71 mmol) and catalyst **2l** (10 mg, 0.03 mmol) stirred at RT for 8 h. Flash chromatography (50-75% EtOAc/hexanes) afforded *mono-phosphate derivative* **13a [R^3 = P(O)(OPh)$_2$]** as a pale yellow oil (221 mg, 0.55 mmol, 94%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.37-7.15 (m, 10H), 7.03 (d, J = 8.4 Hz, 2H), 6.74 (d, J = 8.4 Hz, 2H), 4.54-4.46 (m, 2H), 3.82 (d, J = 5.5 Hz, 2H), 3.11-3.09 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 155.6, 150.3, 129.9, 129.3, 125.6, 120.1, 115.7, 69.6, 62.9, 47.3, 31.0. ^{31}P NMR (161 MHz, $CDCl_3$, ppm): δ -11.44. HRMS (*m*/*z* +ES): Found: 401.1155 (M^+ $C_{21}H_{22}O_6P$ Requires: 401.1154). $[\alpha]_D^{23}$ - 135 (*c* 1.01, $CHCl_3$).

(*S*)-3-(2-Hydroxy-3-(4-hydroxyphenyl)propoxy)-1,5-dihydrobenzo[*e*][1,3,2]dioxaphosphepine 3-oxide (13a, R^3 = *o*-XP) (Table 4, Entry 1)



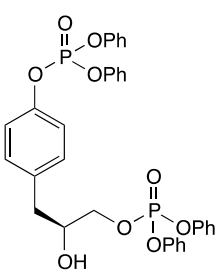
According to **General Method 4**, (*S*)-3-(4-hydroxyphenyl)propane-1,2-diol (**12**, 100 mg, 0.59 mmol), propylene oxide (0.083 mL, 1.19 mmol), *ortho*-xylenyl phosphoryl chloride (**14**, 155 mg, 0.71 mmol) and catalyst **2l** (10 mg, 0.03 mmol) in CH_2Cl_2:DMF (9:1, 0.2 M) at RT for 8 h. Flash chromatography (50-75% EtOAc/hexanes) afforded *mono-phosphate derivative* **13a [R^3 = *o*-XP]** as a pale purple oil (181 mg, 0.52 mmol, 87%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.44-7.41 (m, 2H), 7.38-7.34 (m, 2H), 7.27-7.23 (m, 4H), 5.44-5.37 (m, 2H), 5.29-5.20 (m, 2H), 4.29-4.27 (m, 1H), 4.15-4.12 (m, 2H), 2.85-2.78 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 135.1, 134.2, 130.9, 129.5, 129.2, 120.0, 70.3, 69.0, 67.0, 39.1. ^{31}P NMR (161 MHz, $CDCl_3$, ppm): δ - 7.09. HRMS (*m*/*z* +ES): Found: 351.1003 (M^+ $C_{17}H_{20}O_6P$ Requires: 351.0998). $[\alpha]_D^{23}$ -187 (*c* 0.98, $CHCl_3$).

(*S*)-3-(4-(2,3-Dihydroxypropyl)phenoxy)-1,5-dihydrobenzo[*e*][1,3,2]dioxaphosphepine 3-oxide (13b, R^3 = *o*-XP) (Table 4, Entry 2)



According to **General Method 4**, (*S*)-3-(4-hydroxyphenyl)propane-1,2-diol (**12**, 100 mg, 0.59 mmol), pentamethylpiperidine (0.108 mL, 0.59 mmol), *ortho*-xylenyl phosphoryl chloride (**14**, 129 mg, 0.59 mmol) and catalyst **2l** (10 mg, 0.03 mmol) in CH_2Cl_2:DMF (9:1, 0.2 M) at RT for 1 h. Flash chromatography (50-75% EtOAc/hexanes) afforded *mono-phosphate derivative* **13b** (**R^3 = *o*-XP**) as a colourless oil (169 mg, 0.48 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.44-7.41 (m, 2H), 7.38-7.34 (m, 2H), 5.45-5.38 (m, 2H), 5.28-5.19 (m, 2H), 3.92-4.87 (m, 1H), 3.70-3.65 (m, 1H), 3.53-3.47 (m, 1H), 2.80-2.71 (m, 2H, H^3). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 135.1, 130.8, 129.5, 129.2, 119.9, 110.0, 72.9, 69.1, 66.0, 39.00. ^{31}P NMR (161 MHz, $CDCl_3$, ppm): δ - 7.03. HRMS (*m*/*z* +ES): Found: 351.1003 (M^+ $C_{17}H_{20}O_6P$ Requires: 351.0998). $[\alpha]_D^{23}$ + 92 (*c* 1.03, $CHCl_3$).

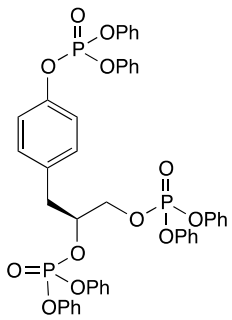
4-[(2*S*)-3-[(Diphenoxyphosphoryl)oxy]-2-hydroxypropyl]phenyl diphenyl phosphate [13c, R^2 & R^3 = P(O)(OPh)$_2$] (Table 4, Entry 3)



According to **General Method 4**, (*S*)-3-(4-hydroxyphenyl)propane-1,2-diol (**12**, 100 mg, 0.59 mmol), pentamethylpiperidine (0.258 mL, 1.43 mmol), diphenylphosphoryl chloride (0.283 mL, 1.37 mmol) and catalyst **2l** (10 mg,

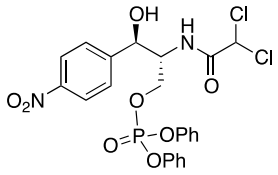
0.03 mmol) stirred at RT for 4 h. Flash chromatography (50-70% EtOAc/hexanes) afforded *di-phosphate derivative* **13c** [**R^2 & R^3 = P(O)(OPh)$_2$]** as a colourless oil (321 mg, 0.51 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.41-7.16 (m, 24H), 4.60-4.50 (m, 2H), 3.83 (d, J = 6.0 Hz, 1H), 3.16-3.13 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 150.4, 150.3, 129.9, 125.7, 120.4, 120.1, 115.3, 68.8, 62.3, 47.5. ^{31}P NMR (161 MHz, $CDCl_3$, ppm): δ - 10.86, -17.61. HRMS (*m*/*z* +ES): Found: 633.1453 (M^+ $C_{33}H_{31}O_9P_2$ Requires: 633.1443). $[\alpha]_D^{23}$ - 197 (*c* 1.00, $CHCl_3$).

4-[(2*S*)-2,3-*bis*[(Diphenoxyphosphoryl)oxy]propyl]phenyl diphenyl phosphate [13d, R^1, R^2 & R^3 = P(O)(OPh)$_2$] (Table 4, Entry 4)



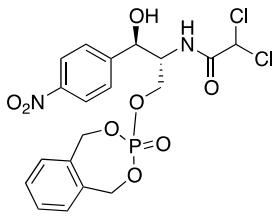
According to **General Method 4**: (*S*)-3-(4-hydroxyphenyl)propane-1,2-diol (**12**, 100 mg, 0.59 mmol), Proton Sponge© (383 mg, 1.78 mmol), diphenylphosphoryl chloride (0.394 mL, 1.90 mmol) and catalyst **2l** (10 mg, 0.03 mmol) stirred at RT for 24 h. Flash chromatography (25-50% EtOAc/hexanes) afforded *tri-phosphate derivative* **13d [R^1, R^2 & R^3 = P(O)(OPh)$_2$]** as a colourless oil (487 mg, 0.56 mmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.39-6.96 (m, 32H), 4.51-4.46 (m, 1H), 4.39-4.23 (m, 2H), 3.02 (d, J = 6.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 150.4, 149.5, 132.4, 131.0, 130.6, 129.9, 129.8, 125.7, 125.5, 120.3, 120.1, 120.0, 119.9, 68.0, 60.4, 36.9. ^{31}P NMR (161 MHz, $CDCl_3$, ppm): δ -12.2, -12.6, - 17.4. HRMS (*m*/*z* +ES): Found: 865.1738 (M^+ $C_{45}H_{40}O_{12}P_3$ Requires: 865.1735). $[\alpha]_D^{23}$ - 162 (*c* 0.96, $CHCl_3$).

Chloramphenicol© diphenyl phosphate (17)



According to **General Method 4**, chloramphenicol© (**16**, 200 mg, 0.62 mmol), pentamethylpiperidine (0.224 mL, 1.24 mmol), diphenyl phosphoryl chloride (0.154 mL, 0.75 mmol) and catalyst **2l** (10 mg, 0.03 mmol) in CH_2Cl_2:MeCN (9:1, 0.2 M) at RT for 4 h. Flash chromatography (50-75% CH_2Cl_2/EtOAc) afforded *mono-phosphate derivative* **17** as a colourless oil (317 mg, 0.57 mmol, 92%). ^{1}H NMR (400 MHz, methanol-d_4, ppm): δ 8.19 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 8.8 Hz, 2H), 7.45-7.25 (m, 10H), 6.21 (s, 1H), 5.10 (d, J = 2.7 Hz, 1H), 4.64-4.58 (m, 1H), 4.49 (td, J = 6.6 Hz, 5.6 Hz, 2.8 Hz, 1H), 4.41-4.37 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 164.4, 150.0, 147.5, 147.1, 130.1, 126.7, 126.1, 123.6, 120.2, 120.0, 69.1, 65.9, 54.6, 54.5. ^{31}P NMR (161 MHz, methanol-d_4, ppm): δ -12.12. HRMS (*m*/*z* +ES): Found: 555.0484 ($M+H^+$ $C_{23}H_{22}N_2O_8{}^{35}Cl_2P$ Requires: 555.0491). $[\alpha]_D^{23}$ + 42 (*c* 1.01, $CHCl_3$).

Chloramphenicol© *ortho*-xylenyl phosphate (18)

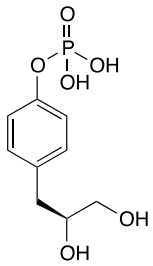


According to **General Method 4**, chloramphenicol© (**16**, 200 mg, 0.62 mmol), pentamethylpiperidine (0.224 mL, 1.24 mmol), *ortho*-xylenyl phosphoryl chloride (161 mg, 0.75 mmol) and catalyst **2l** (10 mg, 0.03 mmol) in CH_2Cl_2:MeCN (9:1, 0.2 M) at RT for 4 h. Flash chromatography (25-75% CH_2Cl_2/EtOAc) afforded *mono-phosphate derivative* **18** as pale yellow oil (302 mg, 0.60 mmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm):

δ 8.21 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 8.8 Hz, 2H), 7.62-7.60 (m, 2H), 7.46-7.44 (m, 2H), 5.78 (s, 1H), 5.39-5.13 (m, 4H), 4.52-4.45 (m, 2H), 4.34-4.30 (m, 1H), 3.98-3.96 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 164.5, 147.4, 134.8, 129.8, 129.4, 129.3, 126.8, 123.6, 69.2, 66.0, 60.4, 54.7. ^{31}P NMR (161 MHz, $CDCl_3$, ppm): δ 0.76. HRMS (m/z +ES): Found: 505.0332 (M^+ $C_{19}H_{20}N_2O_8{}^{35}Cl_2P$ Requires: 505.0334). $[\alpha]_D{}^{23}$ - 123 (c 0.98, $CHCl_3$).

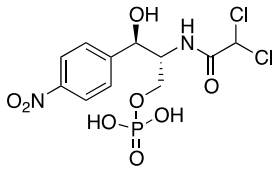
9. Deprotection of *ortho*-xylenyl phosphates

(*S*)-4-(2,3-Dihydroxypropyl)phenyl dihydrogen phosphate (15)



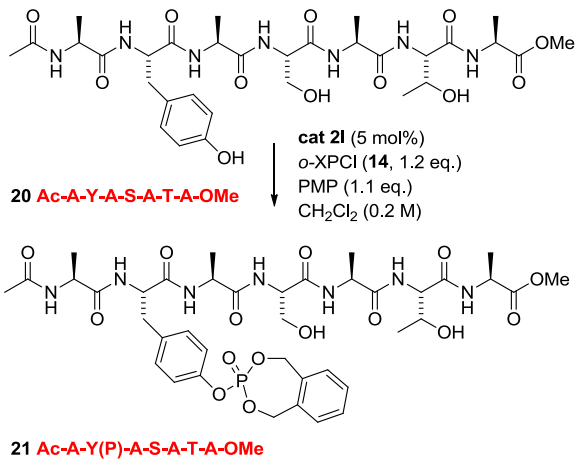
To a solution of *ortho*-xylenyl-phosphate **13b** (**R^3 = *o*-XP**, 10 mg, 0.029 mmol) in MeOH (2 mL) was added Pd/C (1 mg, 10 mol%). The resulting reaction mixture was stirred under an atmosphere of hydrogen for 2 h. The reaction mixture was then filtered through a pad of Celite® to remove Pd/C before being concentrated *in vacuo*. The resulting crude product was left under a flow of nitrogen for 12 h to remove the *ortho*-xylene by product and afforded *mono-phosphate* **15** as a colourless oil (7 mg, 0.028 mmol, 99%). ^{1}H NMR (400 MHz, methanol-d_4, ppm): δ 7.25 (d, J = 8.3 Hz, 2H), 7.15 (d, J = 8.3 Hz, 2H), 3.82-3.79 (m, 1H), 3.54-3.44 (m, 2H), 2.88-2.64 (m, 2H). ^{13}C NMR (100 MHz, methanol-d_4, ppm): 149.9, 135.0, 130.1, 119.7, 73.0, 65.1, 38.7. ^{31}P NMR (161 MHz, methanol-d_4, ppm): δ - 4.93. HRMS (m/z +ES): Found: 497.0973 [$(2M+H)^+$ $C_{18}H_{27}O_{12}P_2$ Requires: 497.0978]. $[\alpha]_D{}^{23}$ + 63 (c 0.95, $CHCl_3$).

Chloramphenicol© dihydrogen phosphate (19)



To a solution of chloramphenicol *ortho*-xylenyl phosphate (**18**, 10 mg, 0.02 mmol) in AcOH (0.2 mL) at RT, was added a solution of HBr (0.2 mL, 48% w/v in AcOH). The reaction mixture was stirred for 1 h at this temperature before being concentrated *in vacuo*. To the residue was added MeOH and this was removed under a flow of nitrogen repeatedly until no *ortho*-xylene byproduct remained, affording *mono*-phosphate **19** as a white solid (8 mg, 0.02 mmol, 99%). M.p. 102-103 ^{o}C. ^{1}H NMR (400 MHz, methanol-d_4, ppm): δ 8.19 (d, J = 7.7 Hz, 2H, H^1), 7.68 (d, J = 7.7 Hz, 2H, H^1), 6.25 (s, 1H, H^6), 5.26-5.24 (m, 1H, H^3), 4.38-4.17 (m, 1H, H^5), 4.15-4.11 (m, 1H, H^5), 3.94-3.89 (m, 1H, H^4). ^{13}C NMR (125 MHz, methanol-d_4, ppm): 166.5, 151.2, 148.6, 128.5, 124.8, 124.1, 116.0, 70.8, 67.3, 64.7, 57.0. ^{31}P NMR (201 MHz, methanol-d_4, ppm): δ -0.24. HRMS (m/z +ES): Found: 440.0140 [$(M+MeCN+H)^+$ $C_{13}H_{17}N_3O_8P^{35}Cl_2$ Requires: 440.0130]. $[\alpha]_D{}^{23}$ + 76 (c 1.03, $CHCl_3$).

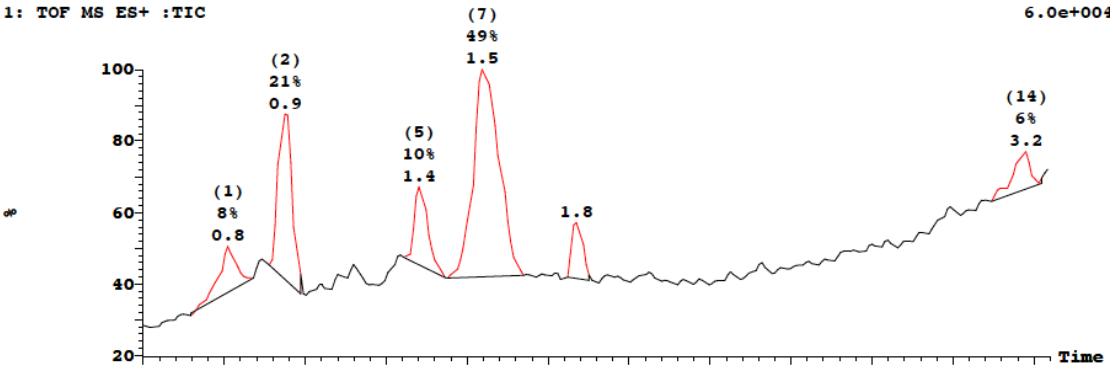
10. Chemoselective phosphorylation of Ac-Ala-Tyr-Ala-Ser-Ala-Thr-Ala-OMe (20)



Peptide **20** was purchased from ChinaPeptides Co., Ltd, 365 Chuanhong Road, Chuansha, Pudong new area, Shanghai, China, 201202 (www.chinapeptides.com).

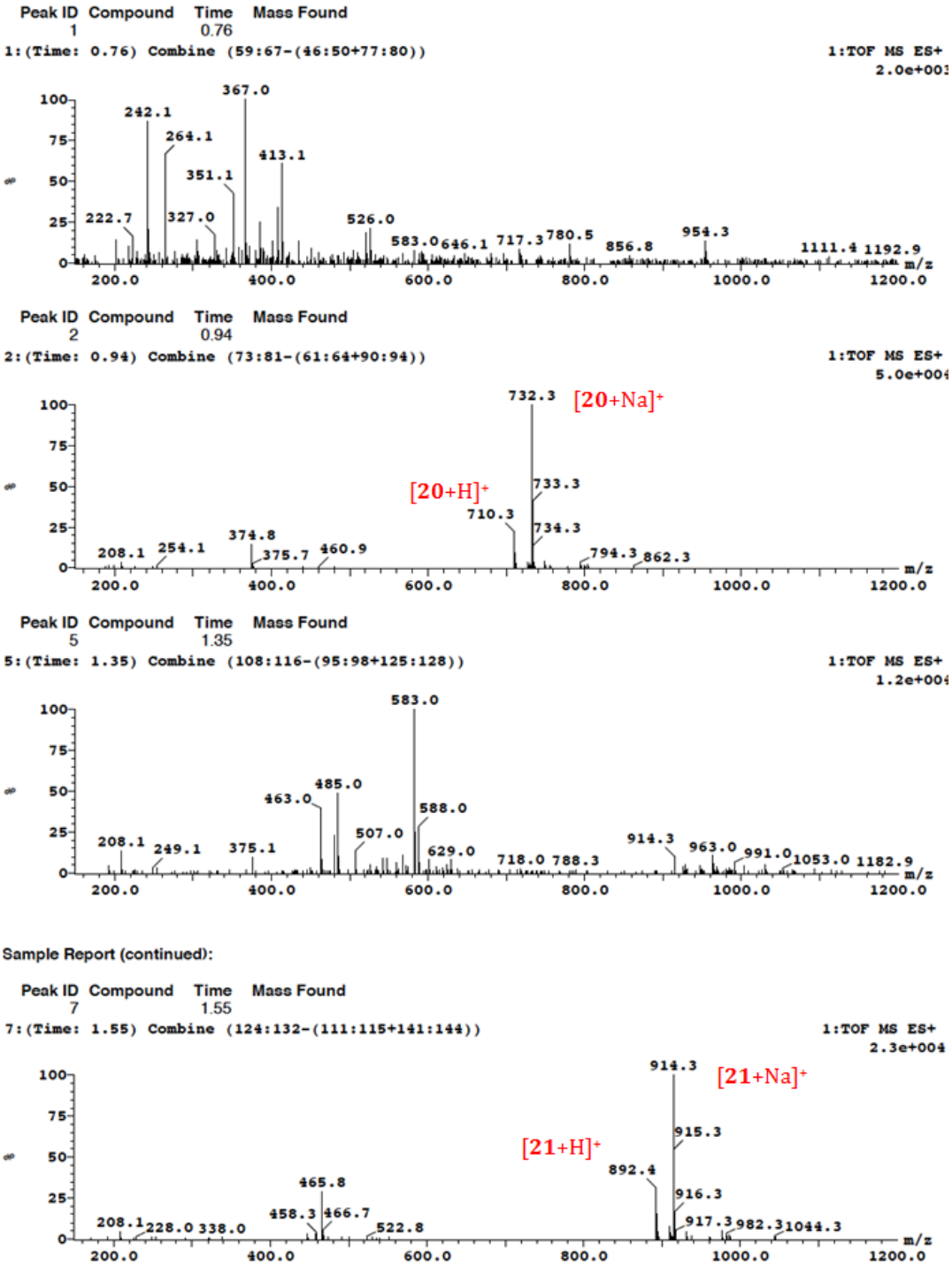
To a solution of peptide **20** (10 μL, 0.14 μmol, 0.14 M solution in CH_2Cl_2) in CH_2Cl_2 (40 μL) was added **cat. 2l** (10 μL, 7.1 nmol, 7.1 mM in CH_2Cl_2) and pentamethylpiperidine (10 μL, 0.16 μmol, 0.15 M solution in CH_2Cl_2) followed by *ortho*-xylenyl phosphoryl chloride (**14**, 10 μL, 0.17 μmol, 0.17 M solution in CH_2Cl_2). The reaction vessel was sealed and the reaction mixture agitated for 24 h. To the reaction mixture was added MeOH (0.1 mL) and the solvent evaporated under a flow of nitrogen to afford crude product which was analysed by LC-MS. Integration of the TIC chromatogram indicates ~21% recovered unreacted peptide (R_t = 0.92 min) and ~49% phosphorylated product (R_t = 1.55 min) (see below).

LC-MS chromatogram of crude reaction mixture.



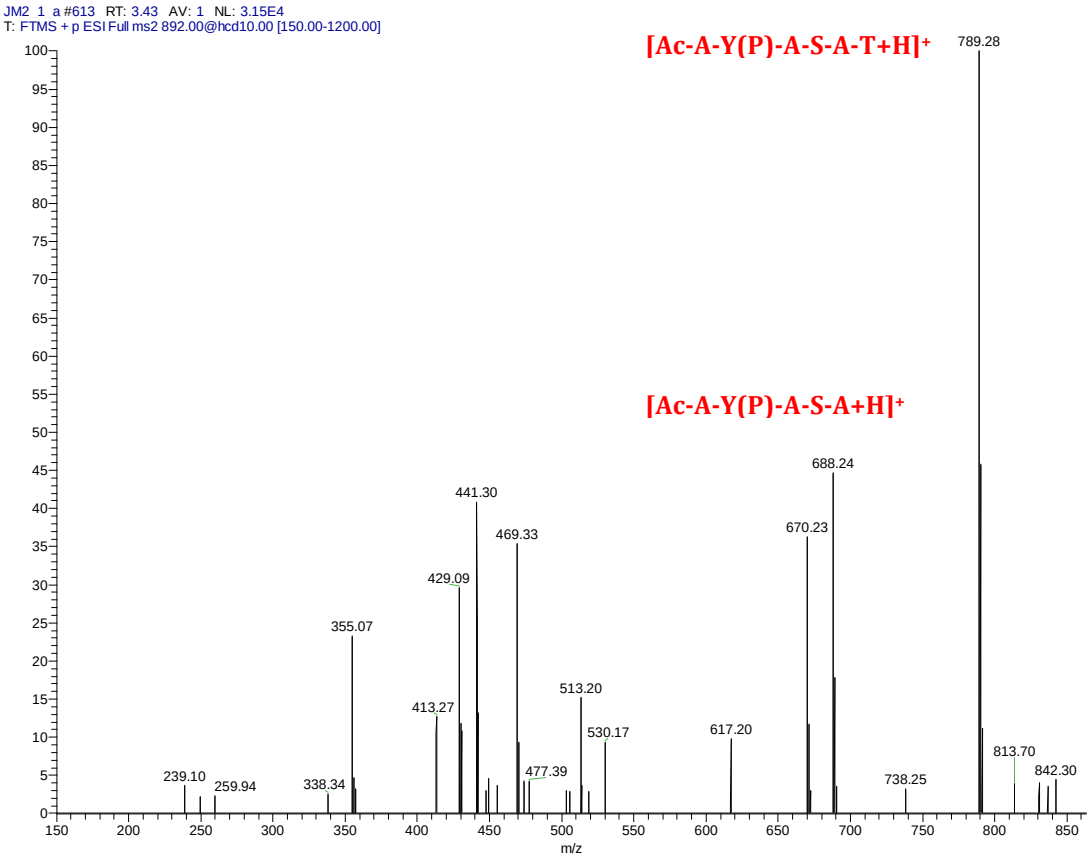
Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		0.76	5e+002	7.70	0	8e+003	
2		0.94	1e+003	21.33	0	3e+004	
5		1.35	7e+002	9.92	0	1e+004	
7		1.55	3e+003	49.22	0	4e+004	
8		1.84	4e+002	5.75	0	9e+003	
14		3.23	4e+002	6.07	0	6e+003	

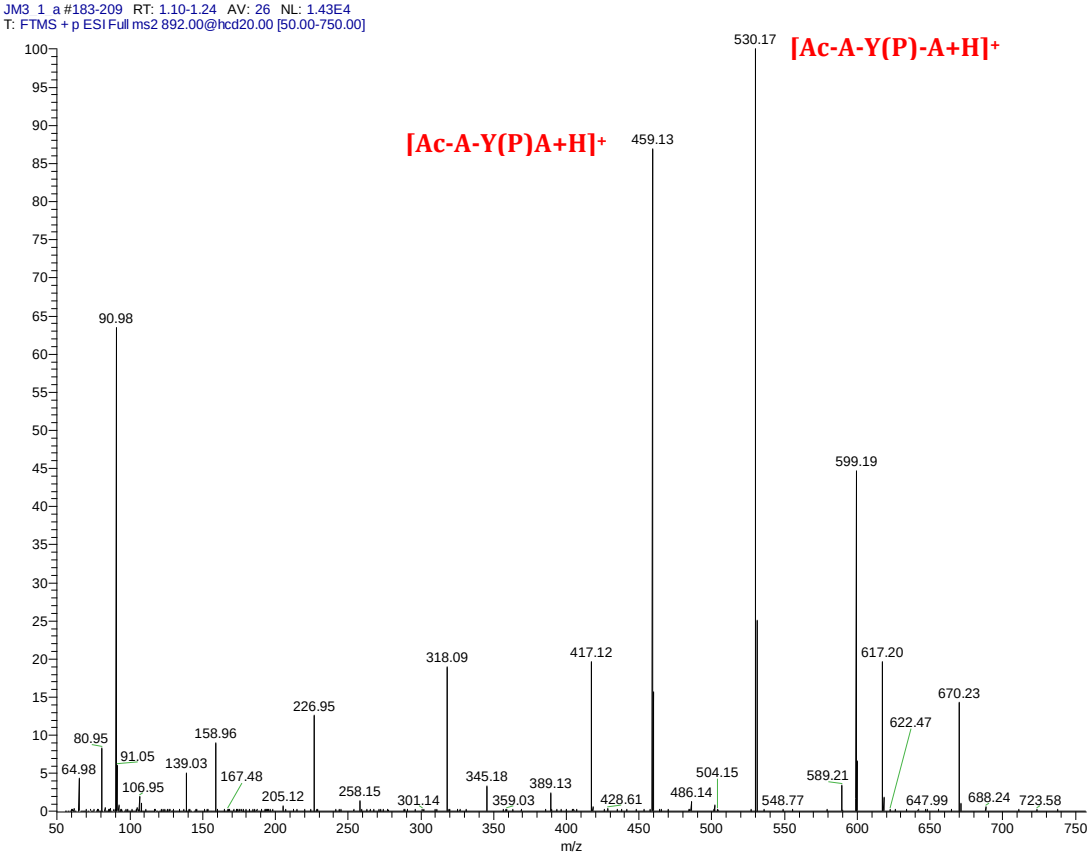
MS traces for the indicated peaks.



MS-MS analysis of the product peak at R_t = 1.55 min confirmed this as having the *ortho*-xylenyl phosphate moiety attached at the tyrosine residue (see below).

MS/MS of purified product: RT: 1.55, MS $[P + H]^+$ = 892, MS $[P + Na]^+$ = 914



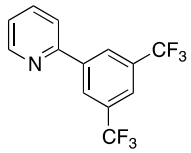


11. Synthesis of 2-aryl-pyridine/DMAP-*N*-oxide derived catalysts

11a. General Method 4-1: Synthesis of (2-aryl)pyridines *via* Suzuki coupling

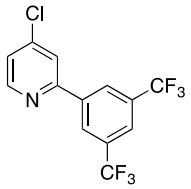
A procedure modified from that described by Bob-Egbe[10] was developed in which 2,4-dichloropyridine/2-chloropyridine (1 eq.), boronic acid (1.5 eq.) and tetrakis(triphenylphospine)palladium (5 mol%) in degassed THF (10 mL) were stirred at RT under a purged nitrogen atmosphere. After 5 min, K_2CO_3 (2 eq.) in degassed H_2O (5 mL) was added and the resulting biphasic orange solution heated to reflux for 16 h. The reaction mixture was allowed to cool to RT and diluted with EtOAc (20 mL) and the organic layer washed with brine, separated and dried over $MgSO_4$ before being concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography and the appropriate fractions concentrated *in vacuo* to afford the desired product.

2-[3,5-*bis*(Trifluoromethyl)phenyl]pyridine[11]



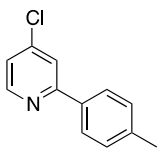
According to **General Method 4-1**, 2-chloropyridine (1 g, 8.8 mmol), 2,4-bis(trifluoromethyl)phenylboronic acid (3.4 g, 13.2 mmol, 1.5 eq.), K_2CO_3 (2.44 g, 17.7 mmol, 2 eq.) and tetrakis(triphenylphospine)palladium (493 mg, 0.4 mmol, 5 mol%) followed by flash chromatography (0-20% CH_2Cl_2/hexanes) afforded *2-[3,5-bis(trifluoromethyl)phenyl]pyridine* as an off white solid (1.90 g, 0.7 mmol, 83%). M.p. 42-44 ^oC. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 8.79 (d, J = 5.0 Hz, 1H), 8.52 (s, 2H), 7.95 (s, 1H), 7.90-7.84 (m, 2H), 7.40-7.33 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ154.1, 150.1, 141.2, 137.3, 133.8, 132.3, 127.8, 127.0, 123.6, 122.4, 120.7. HRMS (m/z +ES): Found: 292.0575 (M^+ $C_{13}H_8NF_6$ Requires: 292.0561). Spectroscopic data in agreement with the literature.[11]

2-[3,5-*bis*(Trifluoromethyl)phenyl]-4-chloropyridine



According to **General Method 4-1**, 2,4-dichloropyridine (0.8 g, 5.4 mmol), 2,4-bis(trifluoromethyl)phenylboronic acid (2.09 g, 8.1 mmol, 1.5 eq.), K_2CO_3 (1.86 g, 13.5 mmol, 2.5 eq.) and tetrakis(triphenylphenylphospine)palladium (624 mg, 0.5 mmol, 5 mol%) followed by flash chromatography (0-20% EtOAc/hexanes) afforded *2-[3,5-bis(trifluoromethyl)phenyl]-4-chloropyridine* as an off white solid (1.51 g, 0.69 mmol, 86%). M.p. 45-47 ^oC. IR (ν_{max}/cm^{-1}): 1637, 1376, 1281, 1177, 1133. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.39 (d, J = 8 Hz, 1H), 7.85 (s, 1H), 7.98 (s, 1H), 8.50 (s, 2H), 8.68 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 155.6, 150.9, 145.5, 140.0, 132.5, 132.2, 127.0, 123.8, 123.1, 121.1. HRMS (m/z +EI): Found: 325.0098 (M^+ $C_{13}H_6NF_6{}^{35}Cl$ Requires: 325.0093).

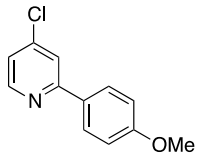
4-Chloro-2-(*p*-tolyl)pyridine



According to **General Method 4-1**, 2,4-dichloropyridine (1.5 g, 10.2 mmol), 4-methylbenzeneboronic acid (2.08 g, 15.2 mmol, 1.5 eq.), K_2CO_3 (3.45 g, 25.5 mmol, 2.5 eq.) and tetrakis(triphenylphospine)palladium (352 mg, 0.30 mmol, 5 mol%) followed by Flash chromatography (0-20% ether/hexanes) afforded *4-chloro-2-(p-tolyl)pyridine* as an off white solid (1.44 g, 7.2 mmol, 70%). M.p. 53-54 ^oC. IR (ν_{max}/cm^{-1}): 3034, 2922, 1574, 1552, 1513, 1460, 1381, 1106, 909, 818, 733. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 8.59 (d, J = 5.7 Hz), 7.90 (d, J = 7.9 Hz), 7.74 (d, J = 1.9 Hz), 7.31 (d, J = 7.9 Hz), 7.24 (dd, J = 5.7, 1.9 Hz), 2.44

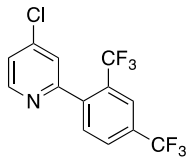
(s, 3H, Me). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 159.0, 150.4, 144.7, 139.8, 135.3, 129.6, 126.9, 122.0, 120.5, 21.3. HRMS (*m*/*z* +EI): Found: 203.0507 (M^+ $C_{12}H_{10}N^{35}Cl$ Requires: 203.0502).

4-Chloro-2-(4-methoxyphenyl)pyridine



According to **General Method 4-1**, 2,4-dichloropyridine (1.0 g, 6.76 mmol), 4-methoxybenzeneboronic acid (1.23 g, 10.14 mmol, 1.5 eq.), K_2CO_3 (2.33 g, 16.9 mmol, 2.5 eq.) and tetrakis(triphenylphospine)palladium (236 mg, 0.33 mmol, 5 mol%) followed by flash chromatography (0-20% ether/hexanes) afforded *4-chloro-2-(4-methoxyphenyl)pyridine* as an off white solid (1.05 g, 4.8 mmol, 71.1%). M.p. 118-120 ^{o}C. IR (ν_{max}/cm^{-1}): 3016, 1608, 1574, 1549, 1514, 1458, 1249, 1176, 820, 696. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.56 (d, *J* = 5.7 Hz, 1H), 7.98-7.94 (m, 2H), 7.69 (d, *J* = 2.3 Hz, 1H), 7.21 (dd, *J* = 5.7 Hz, 2.3 Hz, 1H), 7.04-7.00 (m, 2H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 161.0, 158.6, 150.3, 144.7, 130.7, 128.3, 121.6, 120.0, 114.2, 55.4. HRMS (*m*/*z* +EI): Found: 219.0460 (M+ $C_{12}H_{10}NO^{35}Cl$ Requires: 219.0451).

2-[2,4-*bis*(Trifluoromethyl)phenyl]-4-chloropyridine

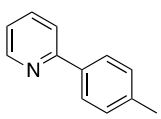


According to **General Method 4-1**, 2,4-dichloropyridine (1.0 g, 6.76 mmol), 2,4-(*bis*-trifluoromethyl)phenyboronic acid (2.61 g, 10.14 mmol, 1.5 eq.), K_2CO_3 (2.33 g, 16.9 mmol, 2.5 eq.) and tetrakis(triphenylphospine)palladium (780 mg, 0.68 mmol, 5 mol%) followed by flash chromatography (0-20% EtOAc/hexanes) afforded *2-[2,4-bis(trifluoromethyl)phenyl]-4-chloropyridine* as an off white solid (2.15 g, 6.62 mmol, 98%). M.p. 44-46 ^{o}C. IR (ν_{max}/cm^{-1}): 1673, 1401, 1254, 1204, 1137. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.64 (d, *J* = 5.4 Hz, 1H), 8.06 (s, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.48 (s, 1H), 7.42 (dd, *J* = 5.4, 1.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 157.7, 150.2, 144.3, 142.2, 132.3, 128.5, 127.2, 124.5, 124.2, 123.8, 123.5, 121.8, 119.0. HRMS (*m*/*z* +ES): Found: 326.0175 (M+$C_{13}H_6NF_6{}^{35}Cl$ Requires: 326.0171).

11b. General Method 4-2: Synthesis of (2-aryl)pyridines by hydrogenation of (2-aryl)-4-chloropyridines

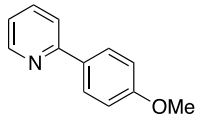
To a solution of (2-aryl)-4-chloropyridine (1 eq.) in MeOH (5 mL) was added Pd/C (10 mol%). The reaction vessel was evacuated and refilled with hydrogen (× 5). The reaction mixture was then allowed to stir under an atmosphere of hydrogen at RT for 12 h before being filtered through a pad of Celite® and concentrated *in vacuo*. The crude product was purified by flash chromatography (EtOAc/hexanes).

2-(*para*-Tolyl)pyridine[12]



According to **General Method 4-2**, 4-chloro-2-(*p*-tolyl)pyridine (500 mg, 2.46 mmol) and Pd/C (26 mg, 0.25 mmol) followed by flash chromatography (0-25% EtOAc/hexanes) afforded *2-(para-tolyl)pyridine* as white solid (353 mg, 2.09 mmol, 85%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.66 (d, *J* = 4.4 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 2H), 7.70 (m, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.17 (m, 1H), 2.39 (s, 3H). HRMS (*m*/*z* +EI): Found: 169.0887 (M^+ $C_{12}H_{11}N$ Requires: 169.0891). Spectroscopic data in agreement with literature.[12]

2-(*para*-Methoxyphenyl)pyridine[13]

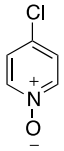


According to **General Method 4-2**, 4-chloro-2-(4-methoxyphenyl)pyridine (500 mg, 2.28 mmol) and Pd/C (24 mg, 0.22 mmol) followed by flash chromatography (0-25% EtOAc/hexanes) afforded *2-(para-methoxyphenyl)pyridine* as off white solid (333 mg, 1.80 mmol, 79 %). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.65 (d, J = 4.5 Hz, 1H), 7.96 (d, J = 8.5 Hz, 2H), 7.73-7.68 (m, 2H), 7.20-7.16 (m, 1H), 7.01 (d, J = 8.5 Hz, 2H), 3.87 (s, 3H, OMe). HRMS (*m*/*z* +EI): Found: 185.0834 (M^+ $C_{12}H_{11}N$ Requires: 185.0841). Spectroscopic data in agreement with literature.[13]

11c. General Method 4-3: Synthesis of (2-aryl)pyridine-*N*-oxides *via m*CPBA oxidation

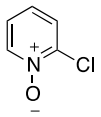
A procedure modified from that described by Bob-Egbe[10] was developed in which a solution (2-aryl)-(4-chloro)pyridine (1 eq.) in CH_2Cl_2 (10 mL) at 0 ^{o}C was added *m*CPBA (2.5 eq.) and $NaHCO_3$ (1 eq. in 4 mL H_2O). The resulting solution was heated to 40 ^{o}C for 12 h. The reaction mixture was allowed to cool to RT and quenched with sat. sodium sulfate solution. The reaction mixture was extracted into CH_2Cl_2 and the combined organic phases washed with sat. $NaHCO_3$ followed by brine before being dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by flash chromatography and the appropriate fractions concentrated *in vacuo* to afford product. *N.B.* Only starting material and product present in each reaction. Recovered starting material was re-isolated and further oxidised where required.

4-Chloropyrdine-*N*-oxide (2b)[14]



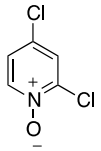
According to **General Method 4-3**, 4-chloropyridine (2 g, 17.7 mmol), *m*CPBA (4.16 g, 44.2 mmol) and $NaHCO_3$ (1.48 g, 17.7 mmol) followed by flash chromatography (0-10% MeOH/EtOAc) afforded *N-oxide* **2b** as a white solid (1.58 g, 12.2 mmol, 69%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.15 (d, J = 3.4 Hz, 2H), 7.28 (d, J = 3.4 Hz, 2H). Spectroscopic data in agreement with the literature.[14]

2-Chloropyrdine-*N*-oxide (2c)[15]



According to **General Method 4-3**, 2-chloropyridine (1 g, 8.8 mmol), *m*CPBA (3.8 g, 22.1 mmol) and $NaHCO_3$ (0.966 g, 11.5 mmol) followed by flash chromatography (0-10% MeOH/EtOAc) afforded *N-oxide* **2c** as a white solid (730 mg, 5.6 mmol, 64%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.39-8.37 (m, 1H), 7.53-7.51 (m, 1H), 7.25-7.23 (m, 2H). Spectroscopic data in agreement with the literature.[15]

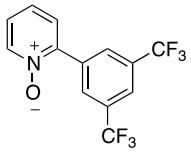
2,4-Dichloropyridine-*N*-oxide



According to **General Method 4-3**, 2,4-dichloropyridine (2 g, 13.5 mmol), *m*CPBA (5.8 g, 33.7 mmol) and $NaHCO_3$ (1.25 g, 14.8 mmol) were employed. flash chromatography (100% EtOAc) afforded *2,4-dichloropyridine-N-oxide* as a yellow oil (774 mg, 4.7 mmol, 34%). M.p. 56-57 ^{o}C. IR (ν_{max}/cm^{-1}): 3434, 3056, 3013, 1446, 1392, 1257, 1107, 1072, 865,

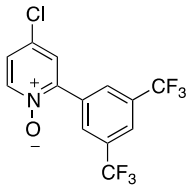
822, 753, 668. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.30 (d, J = 7.1 Hz, 1H), 7.53 (d, J = 2.8 Hz, 1H), 7.22 (dd, J = 7.1, 2.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 142.6, 140.7, 131.2, 126.9, 124.5. HRMS (*m*/*z* +EI): Found: 162.9584 (M^+ $C_5H_3NO^{35}Cl_2$ Requires: 162.9592).

2-[3,5-*bis*(Trifluoromethyl)phenyl]pyridine-*N*-oxide (2j)



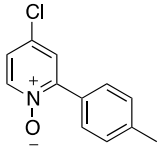
According to **General Method 4-3**, 2-[3,5-bis(trifluoromethyl)phenyl] chloropyridine (758 mg, 2.6 mmol), *m*CPBA (1.12 g, 6.5 mmol) and $NaHCO_3$ (284 mg, 3.4 mmol) followed by flash chromatography (0-10% MeOH/EtOAc) afforded *N-oxide* **2j** as a yellow oil solidified over time to form a yellow solid (627 mg, 2.04 mmol, 79%). M.p. 156-157 ^{o}C. IR (ν_{max}/cm^{-1}): 2976, 1552, 1453, 1280, 1161, 1127. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.39 (dd, J = 5.9, 1.5 Hz, 1H), 8.34 (s, 2H), 7.97 (s, 1H), 7.76-7.71 (m, 1H), 7.58-7.46 (m, 1H), 7.43-7.35 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 146.3, 140.7, 134.4, 132.0, 129.7, 128.6, 128.6, 127.3, 126.0, 124.5, 123.3. HRMS (*m*/*z* +ES): Found: 308.0522 ($M+H^+$ $C_{13}H_8NO$ Requires: 308.0510).

2-[3,5-*bis*(Trifluoromethyl)phenyl]-4-chloropyridine-*N*-oxide



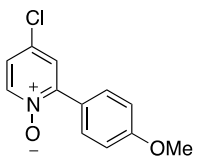
According to **General Method 4-3**, 2-[3,5-bis(trifluoromethyl)phenyl]-4-chloropyridine (1.6 g, 4.9 mmol), *m*CPBA (2.12 g, 12.3 mmol) and $NaHCO_3$ (454 mg, 5.4 mmol) followed by flash chromatography (0-10% MeOH/EtOAc) afforded *2-[3,5-bis(trifluoromethyl)phenyl]-4-chloropyridine-N-oxide* as a yellow oil which solidified over time to form a yellow solid (912 mg, 2.68 mmol, 55%). M.p. 141-143 ^{o}C. IR (ν_{max}/cm^{-1}): 2925, 1574, 1280, 1178, 1136. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.33-8.31 (m, 3H), 8.02 (s, 1H), 7.52 (d, J = 2.6 Hz, 1H), 7.37 (d, J = 6.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 147.1, 141.3, 133.3, 131.9, 129.7, 127.2, 126.2, 124.3, 123.9, 121.6. HRMS (*m*/*z* +ES): Found: 342.0121 (M $C_{13}H_7NO^{35}ClF_6$ Requires: 342.0120).

4-Chloro-2-(*para*-tolyl)pyridine-*N*-oxide



According to **General Method 4-3**, 4-chloro-2-(*p*-tolyl)pyridine (1.0 g, 4.9 mmol), *m*CPBA (2.12 g, 12.3 mmol) and $NaHCO_3$ (455 mg, 5.4 mmol) followed by flash chromatography (100% EtOAc) afforded *4-chloro-2-(para-tolyl)pyridine-N-oxide* as a white solid (880 mg, 4.0 mmol, 82%). M.p. 110-112 ^{o}C. IR (ν_{max}/cm^{-1}): 2942, 1607, 1515, 1458, 1392, 1302. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.24 (d, J = 7.0 Hz, 1H), 7.71 (d, J = 8.1 Hz, 2H), 7.41 (d, J = 3.0 Hz, 1H), 7.29 (d, J = 8.1 Hz, 2H), 7.17 (dd, J = 7.0, 3.0 Hz, 1H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 150.1, 141.1, 140.5, 131.5, 129.1, 128.6, 127.0, 124.4 (2C), 21.5. HRMS (*m*/*z* +EI): Found: 219.0465 (M^+ $C_{12}H_{10}NO^{35}Cl$ Requires: 219.0451).

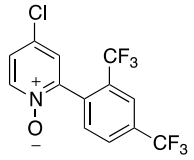
4-Chloro-2-(4-methoxyphenyl)pyridine-*N*-oxide



According to **General Method 4-3**, 4-chloro-2-(4-methoxyphenyl)pyridine (432 mg, 2.0 mmol), *m*CPBA (858 mg, 4.9 mmol) and $NaHCO_3$ (182 mg, 2.1 mmol) followed by flash chromatography (100% EtOAc) afforded *4-chloro-2-(4-methoxyphenyl)pyridine-N-oxide* as a white solid (272 mg, 1.2 mmol, 59%). M.p. 98-100 ^{o}C. IR (ν_{max}/cm^{-1}): 2952, 1608, 1574, 1547, 1514, 1458, 1249, 1176, 820, 672. ^{1}H NMR (400

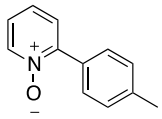
MHz, $CDCl_3$, ppm): δ 8.26 (d, J = 7.0 Hz, 1H), 7.84 (d, J = 9.0 Hz, 1H), 7.43 (d, J = 3.0 Hz, 1H), 7.16 (dd, J = 7.0, 3.0 Hz, 1H), 7.01 (d, J = 9.0 Hz, 1H), 3.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 161.0, 149.8, 141.2, 131.7, 130.8, 126.7, 124.0, 123.7, 113.8, 55.4. HRMS (*m*/*z* +ES): Found: 236.0460 ($M+H^+$ $C_{12}H_{11}N_2O^{35}Cl$ Requires: 236.0478).

2-[2,4-*bis*(Trifluoromethyl)phenyl]-4-chloropyridine-*N*-oxide



According to **General Method 4-3**, 2-(2,4-bis(trifluoromethyl)phenyl)-4-chloropyridine (125 mg, 0.4 mmol), *m*CPBA (165 mg, 1.0 mmol) and $NaHCO_3$ (35 mg, 0.4 mmol) followed by flash chromatography (0-10% MeOH/EtOAc) afforded *2-[2,4-bis(trifluoromethyl]phenyl)-4-chloropyridine-N-oxide* as an off white solid (47 mg, 0.15 mmol, 36%). M.p. 143-145 ^{o}C. IR (ν_{max}/cm^{-1}): 2957, 1614, 1287, 1195, 1236. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.29 (d, J = 7.0 Hz, 1H), 8.09 (s, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.39 (dd, J = 7.0, 2.9 Hz, 1H), 7.33 (d, J = 2.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 147.6, 140.9, 132.4, 131.2, 130.7, 130.4, 129.0, 127.3, 126.4, 124.2, 121.6, 121.4. HRMS (*m*/*z* +ES): Found: 342.0110 ($M+H^+$ $C_{13}H_7NO^{35}ClF_6$ Requires: 342.0120).

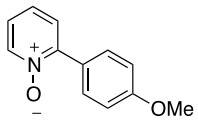
2-(*p*ara-Tolyl)pyridine-*N*-oxide (2h)[16]



According to **General Method 4-3**, 2-(*p*-tolyl)pyridine (411 mg, 2.4 mmol), *m*CPBA (1.05 g, 6.08 mmol) and $NaHCO_3$ (224 mg, 2.68 mmol) followed by flash chromatography (0-10% MeOH/EtOAc) afforded *N-oxide* **2h** as an off white solid (364 mg, 0.2 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.25 (1H, m), 7.81 (d, J = 8.5 Hz, 2H), 7.56 (m, 1H), 7.33 (m, 2H), 7.27 (d, J = 8.5 Hz), 2.38 (s, 3H). HRMS (*m*/*z* +EI): Found: 185.0485 (M+ $C_{12}H_{11}NO$ Requires: 185.0841). Spectroscopic data in agreement with literature.[16]

2-(*para*-Methoxy)pyridine-*N*-oxide (2f)[16]

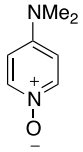
According to **General Method 4-3**, 2-(*p*-methoxyphenyl)pyridine (417 mg, 2.25 mmol), *m*CPBA (972 mg, 6.64 mmol) and $NaHCO_3$ (208 mg, 2.50 mmol) followed by flash chromatography (0-10% MeOH/EtOAc) afforded *N-oxide* **2f** as off white solid (303 mg, 1.5 mmol, 67%). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.26-8.24 (m, 1H), 7.91 (d, J = 8.5 Hz, 2H), 7.56 (dd, J = 7.5, 3.5 Hz, 1H), 7.28-7.35 (m, 2H), 7.04 (d, J = 9.0 Hz, 2H), 3.87 (s, 3H). Spectroscopic data in agreement with literature.[16]



11d. General Method 4-4: Synthesis of (2-aryl)-4-DMAP-*N*-oxides *via* S_NAr substitution

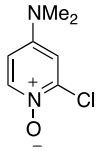
(2-Aryl)-4-chloropyridine-*N*-oxide (1 eq.) was dissolved in MeCN (2 mL). $HNMe_2$ (40% w/w in H_2O, 4 mL) was added and the resulting yellow solution heated to 110 ^{o}C in a Biotage Initator microwave for 90 min. The reaction mixture was then diluted with CH_2Cl_2 (5 mL) and washed with $NaHCO_3$ (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford product.

4-Dimethylaminopyridine-*N*-oxide (2d)[17]



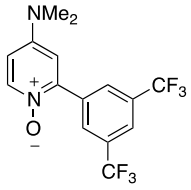
According to **General Method 4-4**, 4-chloropyridine-*N*-oxide (**2c**, 500 mg, 3.8 mmol) afforded *4-DMAP-N-oxide* (**2d**) as a pale brown solid (479 mg, 3.5 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.06 (d, J = 7.9 Hz, 2H), 6.61 (d, J = 7.9 Hz, 2H), 3.10 (s, 6H, NMe_2). Spectroscopic data in agreement with the literature.[17]

2-Chloro-4-dimethylaminopyridine-*N*-oxide (2e)



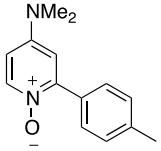
According to **General Method 4-4**, 2,4-dichloropyridine-*N*-oxide (200 mg, 1.2 mmol) followed by flash chromatography (0-10% MeOH/EtOAc) afforded *dimethylamine* **2e** as an off white solid (45 mg, 0.3 mmol, 22%). M.p. 76-78 ^{o}C. IR (ν_{max}/cm^{-1}): 3371, 2960, 2859, 1601, 1546, 1502, 1427, 1398, 1206, 1179, 1105, 986, 765, 672. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.06 (d, J = 7.6 Hz, 1H), 6.79-6.78 (m, 2H), 3.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 155.5, 140.8, 133.0, 117.1, 114.4, 40.5. HRMS (*m*/*z* +ES): Found: 172.0399 (M^+ $C_7H_9N_2O^{35}Cl$ Requires: 172.0403).

2-[3,5-*bis*(Trifluoromethyl)phenyl]-4-dimethylaminopyridine-*N*-oxide (2k)



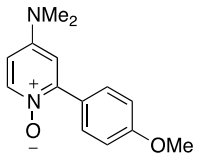
According to **General Method 4-4**, 2-(3,5-bis(trifluoromethyl)phenyl)-4-chloropyridine-*N*-oxide (100 mg, 0.3 mmol) afforded *dimethylamine* **2k** as a yellow solid (102 mg, 0.29 mmol, 99%). M.p. 118-119 ^{o}C. IR (ν_{max}/cm^{-1}): 1574, 1361, 1280, 1136. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.29 (s, 2H), 8.15 (d, J = 7.4 Hz, 1H), 7.93 (s, 1H), 6.49 (dd, J = 7.4, 3.5 Hz, 1H), 6.55 (d, J = 3.5 Hz, 1H), 3.10 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 148.4, 145.8, 140.4, 135.5, 129.9, 124.5, 123.1, 121.8, 108.5, 108.3, 39.9. HRMS (*m*/*z* +ES): Found: 351.0921 ($M+H^+$ $C_{15}H_{13}N_2OF_6$ Requires: 351.0932).

2-(*para*-Tolyl)-4-dimethylaminopyridine-*N*-oxide (2i)



According to **General Method 4-4**, 4-chloro-2-(*p*-tolyl)pyridine-*N*-oxide (500 mg, 2.3 mmol) afforded *dimethylamine* **2i** as a yellow solid (516 mg, 2.2 mmol, 99%). M.p. 78-79 ^{o}C. IR (ν_{max}/cm^{-1}): 2922, 1636, 1599, 1516, 1448, 987, 817. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.12 (d, J = 7.4 Hz, 1H), 7.71 (d, J = 7.9 Hz, 2H), 7.29 (d, J = 7.9 Hz, 2H), 6.54 (d, J = 3.5 Hz, 1H), 6.49 (dd, J = 7.4, 3.6 Hz, 1H), 3.06 (s, 6H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 148.9, 148.1, 140.2, 139.3, 130.9, 129.3, 128.8, 108.7, 107.0, 39.8, 21.4. HRMS (*m*/*z* +ES): Found: 229.1331 ($M+H^+$ $C_{14}H_{17}N_2O$ Requires: 229.1341).

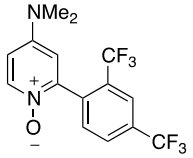
2-(4-Methoxyphenyl)-4-dimethylaminopyridine-*N*-oxide (2g)



According to **General Method 4-4**, 4-chloro-2-(4-methoxyphenyl)pyridine-*N*-oxide **(**500 mg, 2.3 mmol) afforded *dimethylamine* **2g** as a yellow solid (550 mg, 2.2 mmol, 99%). M.p. 75-76 ^{o}C. IR (ν_{max}/cm^{-1}): 3171, 3104, 2924, 1630, 1512, 1439, 1252, 1201, 1179, 1022, 818, 798, 762. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.09 (d, J = 7.5 Hz, 1H), 7.79 (d, J = 8.9 Hz, 2H), 6.98 (d, J = 8.9 Hz, 2H), 6.58

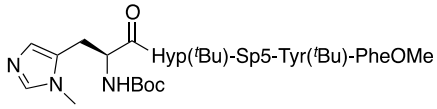
(d, *J* = 3.5 Hz, 1H), 6.47 (dd, *J* = 7.5, 3.5 Hz, 1H), 3.85 (s, 3H, OMe), 3.06 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 160.4, 148.6, 148.4, 140.2, 130.9, 125.9, 113.6, 108.4, 106.8, 55.4, 39.8. HRMS (*m*/*z* +ES): Found: 245.1228 ($M+H^+$ $C_{14}H_{17}N_2O_2$ Requires: 245.1290).

2-[2,4-*bis*(Trifluoromethyl)phenyl]-4-dimethylaminopyridine-*N*-oxide (2l)



According to **General Method 4-4** 2-[2,4-bis(trifluoromethyl)phenyl]-4-chloropyridine-*N*-oxide (340 mg, 1.0 mmol) afforded *dimethylamine* **2l** as a yellow solid (330 mg, 0.94 mmol, 94%). M.p. 115-116 ^{o}C. IR (ν_{max}/cm^{-1}): 1617, 1382, 1271, 1096. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.16 (d, *J* = 7.5 Hz, 1H), 8.07 (s, 1H), 7.96 (d, *J* = 8.1 Hz, 1H), 7.78 (d, *J* = 8.1 Hz, 1H), 6.65 (dd, *J* = 7.5, 3.5 Hz, 1H), 6.49 (d, *J* = 3.5 Hz, 1H), 3.11 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 147.6, 145.5, 139.9, 135.8, 132.6, 130.3, 128.7, 123.8, 123.8, 121.8, 121.6, 108.9, 108.3, 39.8. HRMS (*m*/*z* +ES): Found: 351.0919 ($M+H^+$ $C_{15}H_{13}N_2OF_6$ Requires: 351.0932).

12. Synthesis of histidine-based pentapeptide catalyst 6 (Miller catalyst)[18]

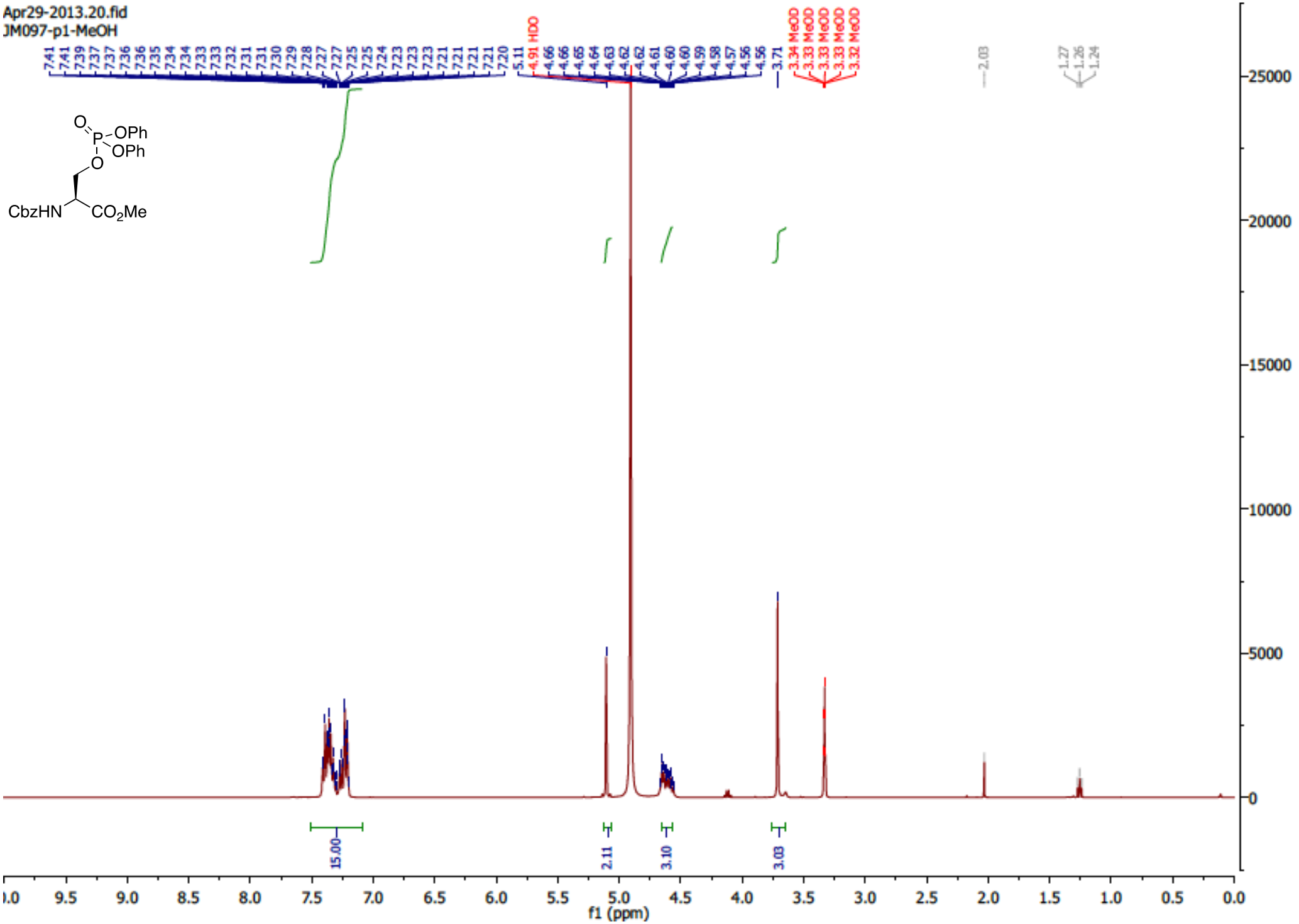


This peptide corresponds to the catalyst numbered '**24**' in ref 18 and was synthesized by SPPS using commercially available Wang polystyrene resin preloaded with (*S*)-Phe. Couplings were performed using 4 eq. of appropriate amino acid derivative, HBTU (4 eq.) and Hünig's base (8 eq.) in DMF. Deprotections were performed using 20% piperidine in DMF for 20 min. The peptide was then cleaved from the solid support using a 9:1:1 mixture of MeOH:DMF:NEt_3 for 4 days. The solvent was removed at RT under a flow of nitrogen to afford crude product (121 mg; still traces of DMF present). The peptide was purified using reverse phase LCMS, performed using a RP-18 X Terra (Waters) column. Preparative LCMS was performed over 18 min by eluting with 50-75% MeOH in water to afford the desired peptide **6** (57 mg, 0.06 mmol, 13%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.37 (s, 1H), 7.23-7.06 (m, 9H), 6.85-6.82 (m, 3H), 6.67 (s, 1H), 5.18 (d, *J* = 6.6 Hz, 1H), 4.76 (q, *J* = 7 Hz, 1H), 4.50-4.47 (m, 2H), 4.32 (t, *J* = 7.5 Hz, 1H), 4.24 (s, 1H), 3.62 (s, 3H), 3.52 (s, 3H), 3.25-3.09 (m, 2H), 3.08-2.97 (m, 2H), 2.95-2.81 (m, 2H), 2.36-2.24 (m, 1H), 2.08-1.91 (m, 2H), 1.87-1.83 (m, 1H), 1.77-1.67 (m, 5H), 1.58-1.52 (m, 3H), 1.41 (s, 9H), 1.26 (s, 9H), 1.16 (s, 9H). LRMS (*m*/*z* +ES): Found: 930.5 (M^+ $C_{50}H_{71}N_7O_{10}$ Requires: 930.1). Spectroscopic data in agreement with the literature.[18]

13. References

1. W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923–2925.
2. M. Kang, J. Park, A. W. Konradi, and S. F. Pedersen, *J. Org. Chem.*, 1996, **61**, 5528–5531.
3. F. W. Foss, T. P. Mathews, Y. Kharel, P. C. Kennedy, A. H. Snyder, M. D. Davis, K. R. Lynch, and T. L. Macdonald, *Bioorg. Med. Chem.*, 2009, **17**, 6123–36.
4. A. Bongini, M. Panunzio, E. Bandini, G. Martelli, and G. Spunta, *J. Org. Chem.*, 1997, **62**, 8911–8913.
5. S. Lin, Z.-Q. Yang, B. H. B. Kwok, M. Koldobskiy, C. M. Crews, and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2004, **126**, 6347–55.
6. I. Manet, S. Monti, P. Bortolus, M. Fagnoni, and A. Albini, *Chem. Eur. J.*, 2005, **11**, 4274–82.

7. Q. L. Zeng, H. Q. Wang, Z. R. Liu, B. G. Li, and Y. F. Zhao, *Amino Acids*, 2007, **33**, 537–41.
8. C. R. Reddy, N. N. Rao, and B. Srikanth, *Eur. J. Org. Chem.*, 2010, **2010**, 345–351.
9. T. Sato and K. Goto, *J. Chem. Soc., Chem. Commun.*, 1973, 494.
10. Bob-Edge, *PhD Thesis (Imperial College London)*, 2011.
11. J. Yang, S. Liu, J.-F. Zheng, and J. S. Zhou, *Eur. J. Org. Chem.*, 2012, **2012**, 6248–6259.
12. Z. Xi, B. Liu, and W. Chen, *J. Org. Chem.*, 2008, **73**, 3954–7.
13. X.-X. Zhou and L.-X. Shao, *Synthesis.*, 2011, **2011**, 3138–3142.
14. H. J. den Hertog and W. P. Combé, *Recl. des Trav. Chim. des Pays-Bas*, 2010, **70**, 581–590.
15. Y. Ding, W. Zhao, W. Song, Z. Zhang, and B. Ma, *Green Chem.*, 2011, **13**, 1486.
16. L.-C. Campeau, S. Rousseaux, and K. Fagnou, *J. Am. Chem. Soc.*, 2005, **127**, 18020–1.
17. S. Mukaiyama, J. Inanaga, and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 2221–2222.
18. B. R. Sculimbrene, A. J. Morgan, and S. J. Miller, *J. Am. Chem. Soc.*, 2002, **124**, 11653–11656.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OPh
OPh
O
CbzHN
CO2Me
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5.11
4.91 HDO
4.66 4.66 4.65 4.64 4.63 4.62 4.62 4.61 4.60 4.60 4.59 4.58 4.57 4.56 4.56
3.71
3.34 MeOD 3.33 MeOD 3.33 MeOD 3.33 MeOD 3.32 MeOD
2.03
1.27 1.26 1.24
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2.11
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f1 (ppm)

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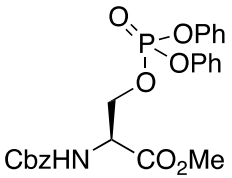

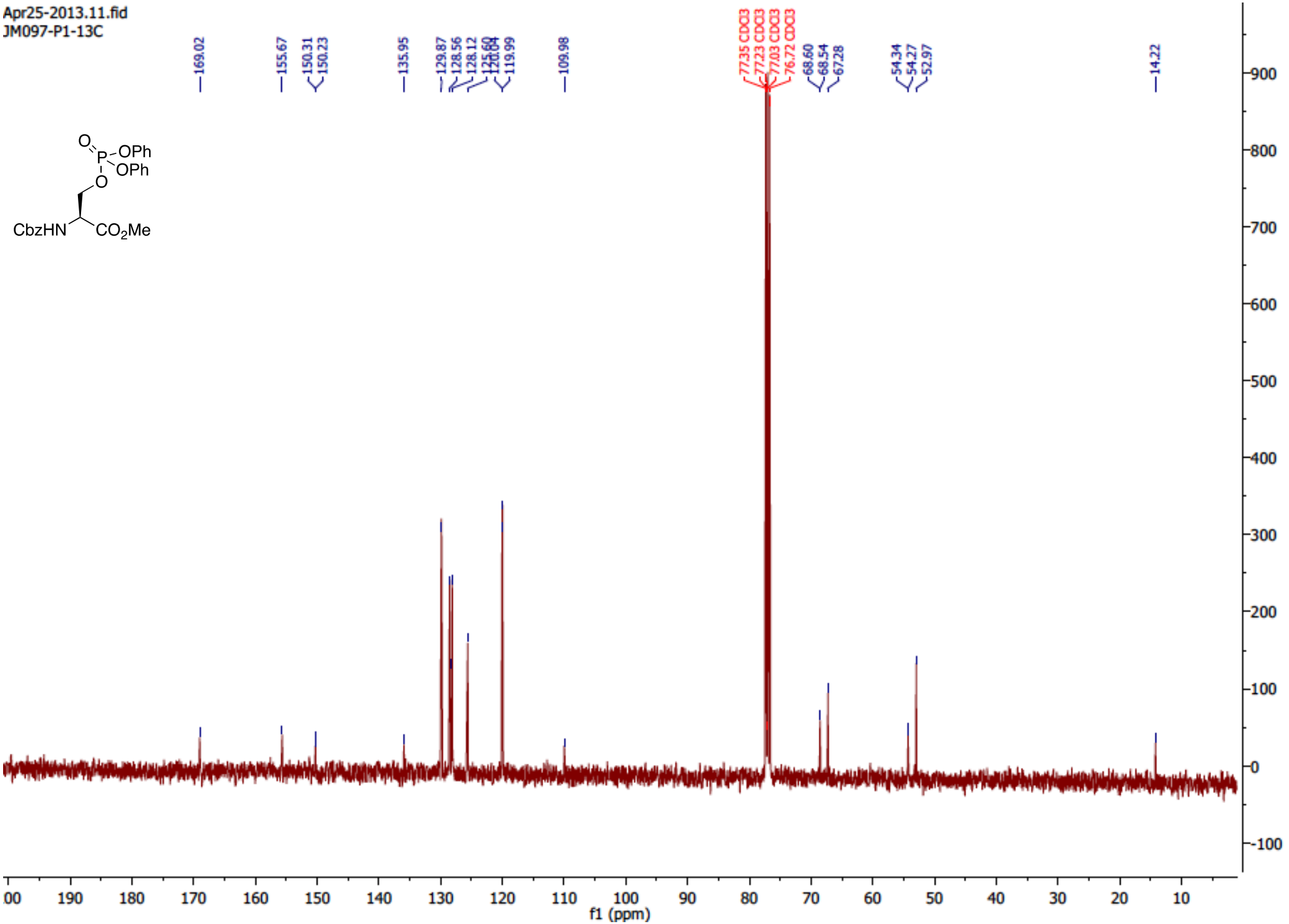
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CO2Me
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700
600
500
400
300
200
100
0
-100
00
190
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100
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50
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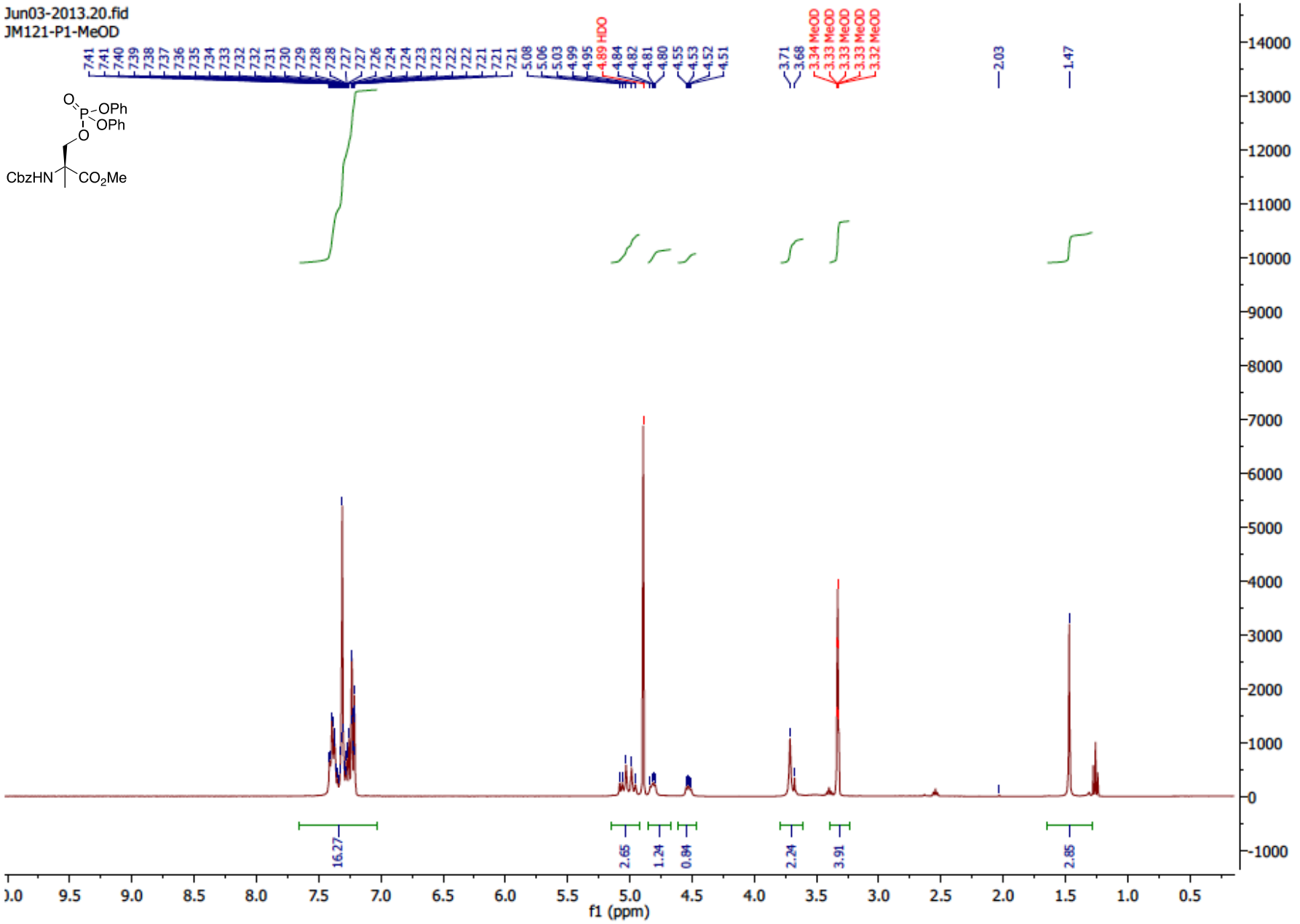
10
f1 (ppm)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OPh
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CO2Me
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f1 (ppm)

Jun03-2013.11.fid
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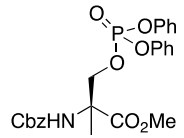

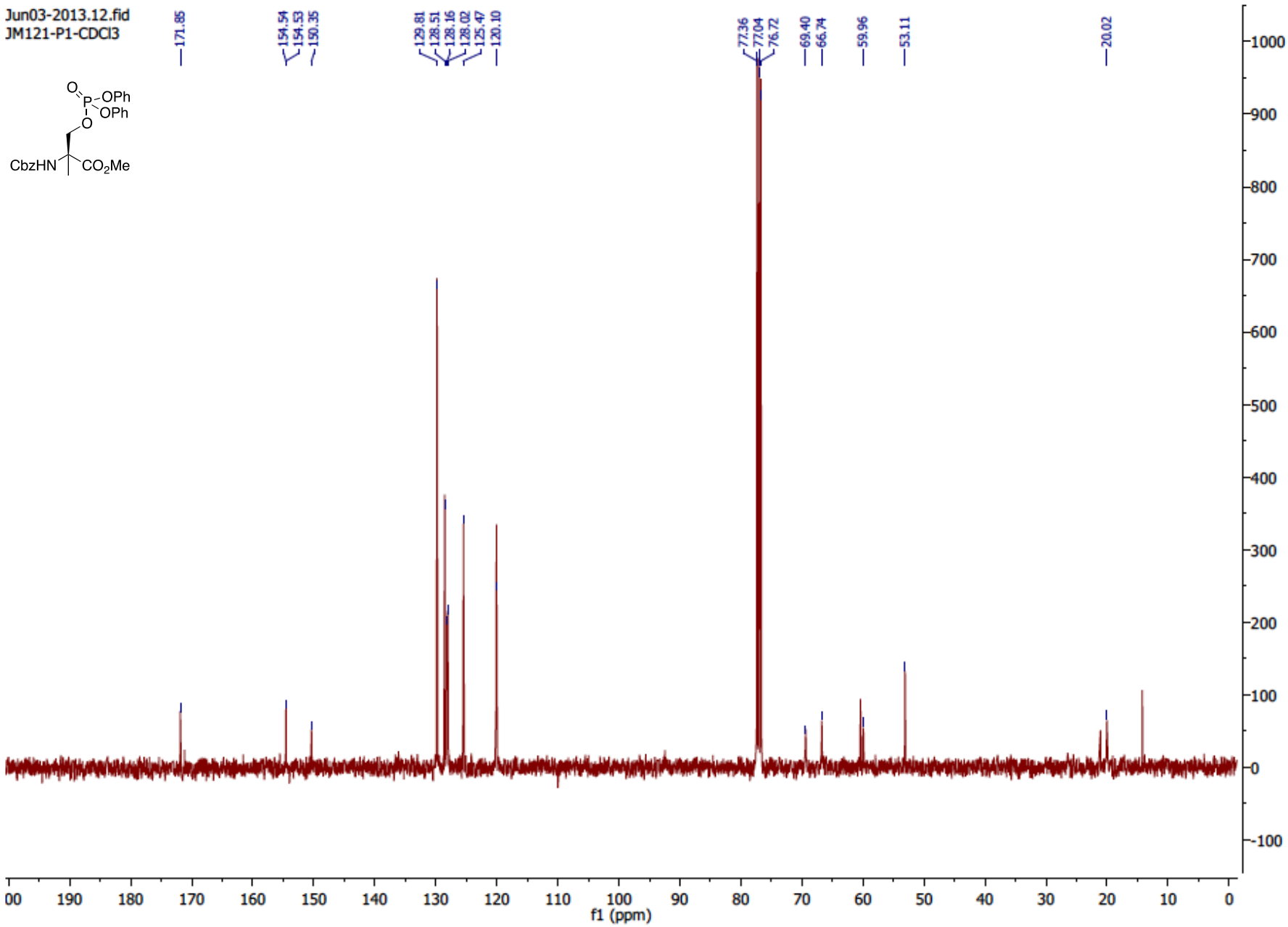
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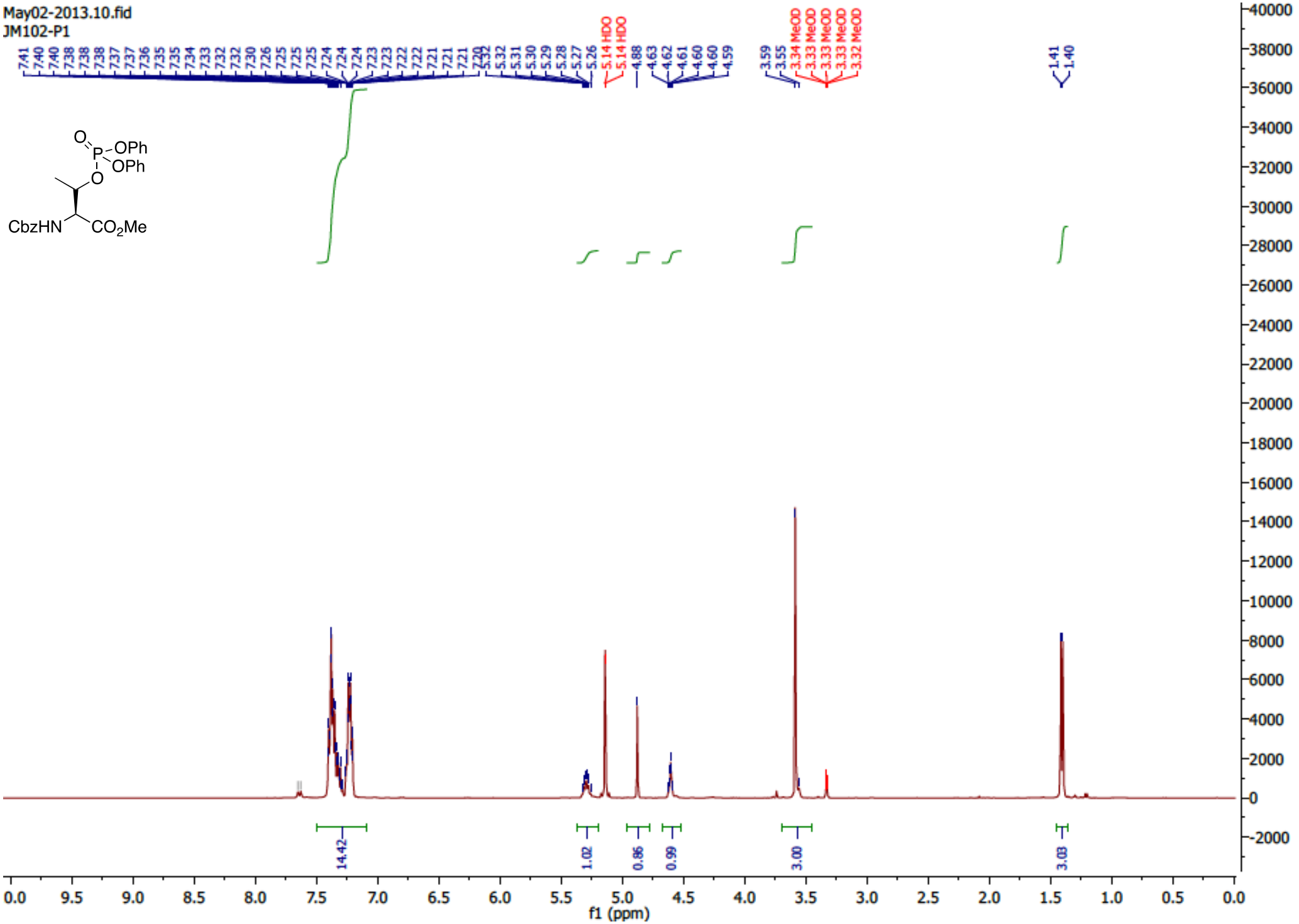
f1 (ppm)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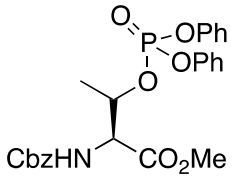
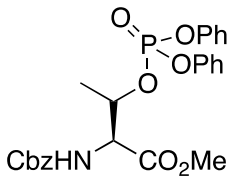
CbzHN
CO2Me
7.41 7.40 7.40 7.38 7.38 7.38 7.37 7.37 7.36 7.35 7.35 7.34 7.33 7.32 7.32 7.30 7.26 7.25 7.25 7.25 7.24 7.24 7.24 7.23 7.23 7.22 7.22 7.21 7.21 7.21 5.32 5.32 5.31 5.30 5.29 5.28 5.27 5.26
5.14 HDO
5.14 HDO
4.88
4.63 4.62 4.61 4.60 4.60 4.59
3.59 3.55
3.34 MeOD
3.33 MeOD
3.33 MeOD
3.33 MeOD
3.32 MeOD
1.41 1.40
14.42
1.02
0.86
0.99
3.00
3.03
f1 (ppm)

May02-2013.12.fid
JM102-P1

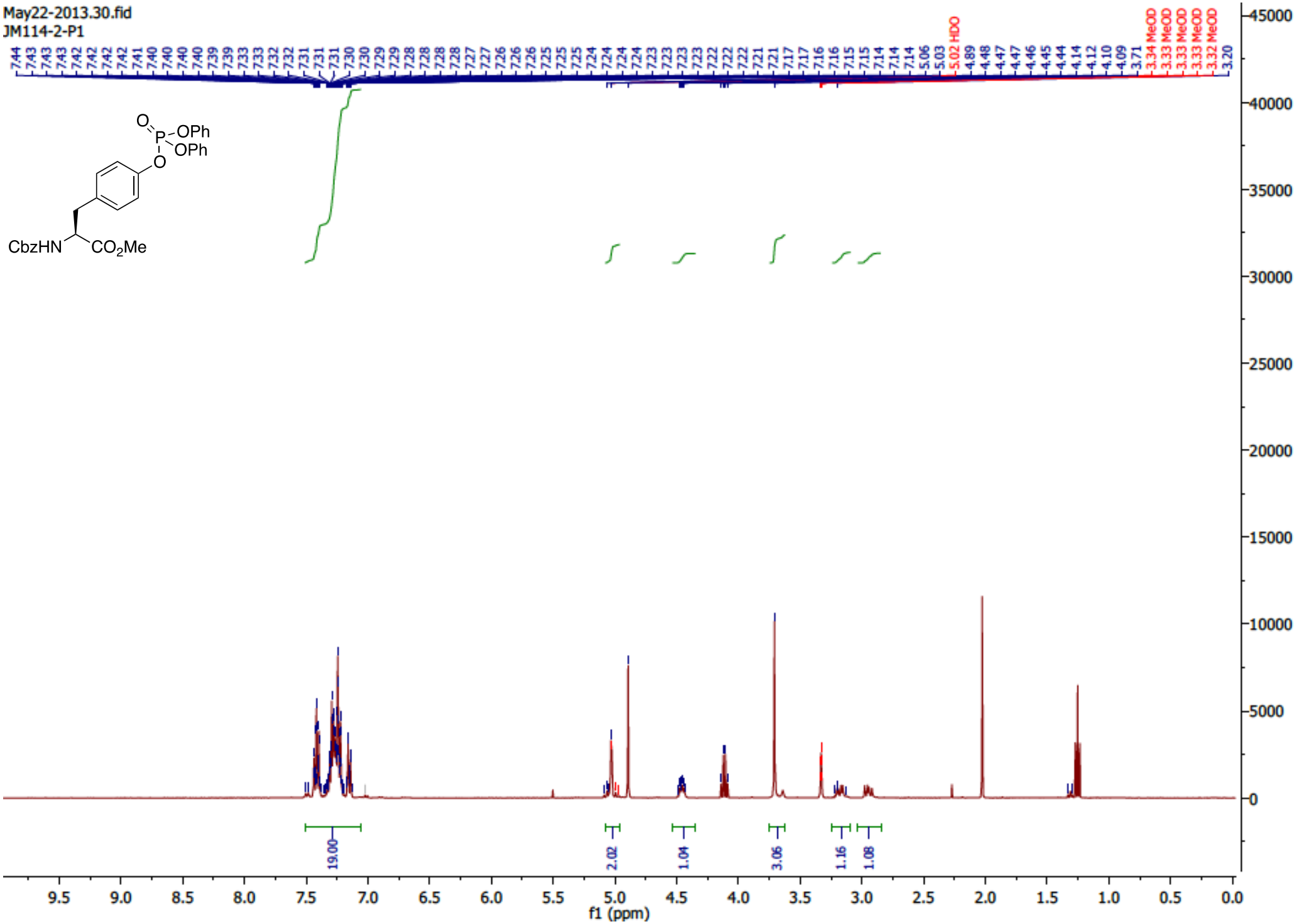


May02-2013.11.fid
JM102-P1

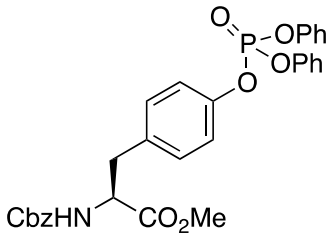


169.65
157.55
150.36
150.33
150.29
150.26
136.68
129.69
128.13
127.48
125.53
125.47
125.44
119.94
119.90
119.87
119.82
77.61
77.55
66.61
58.45
58.37
51.79
48.32 MeOD
48.11 MeOD
47.89 MeOD
47.68 MeOD
47.47
47.26
47.04
17.32

f1 (ppm)


May22-2013.30.fid
JM114-2-P1
O
P
OPh
OPh
O
CbzHN
CO2Me
19.00
2.02
1.04
3.06
1.16
1.08
f1 (ppm)

May22-2013.31.fid
JM114-2-P1

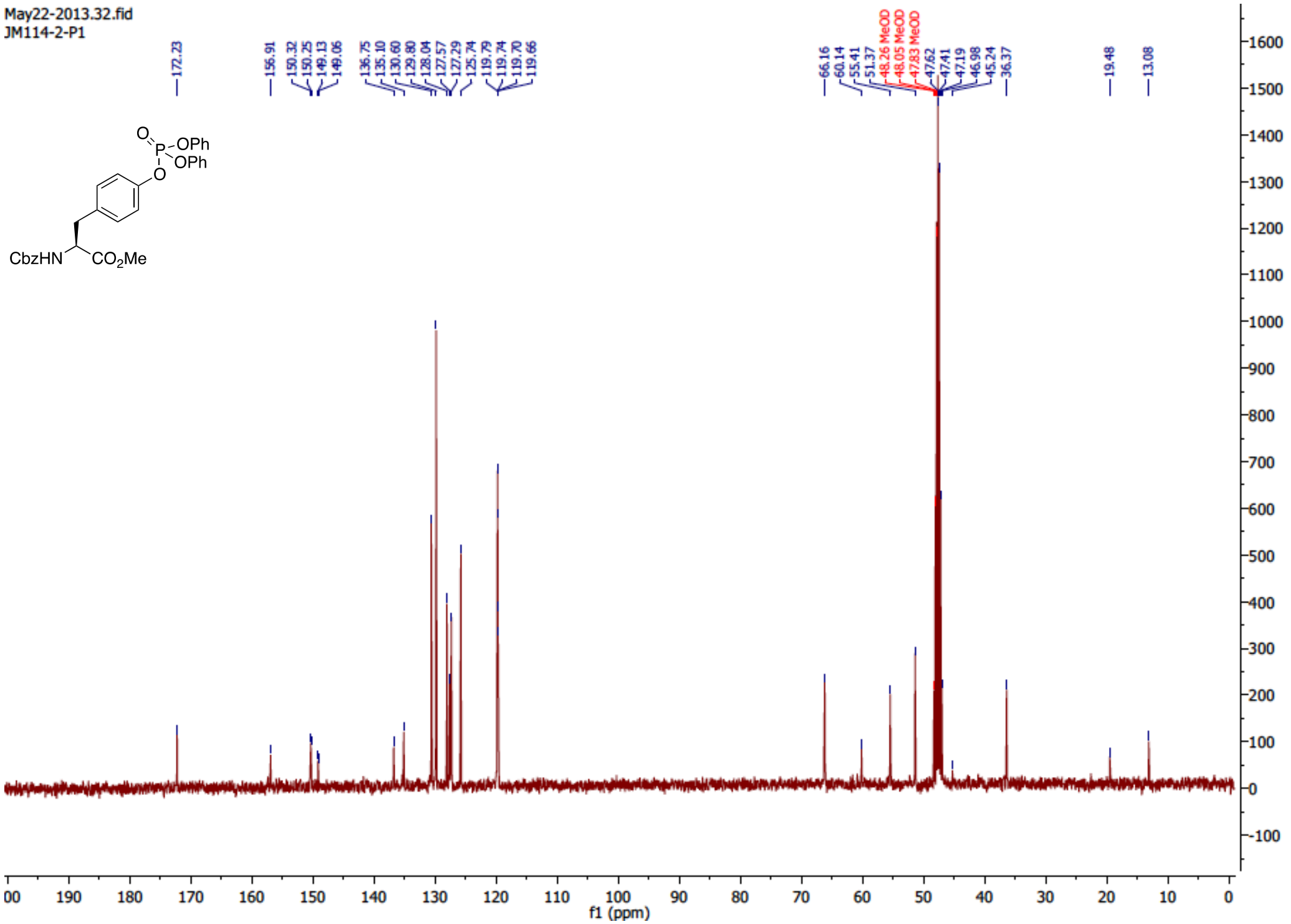


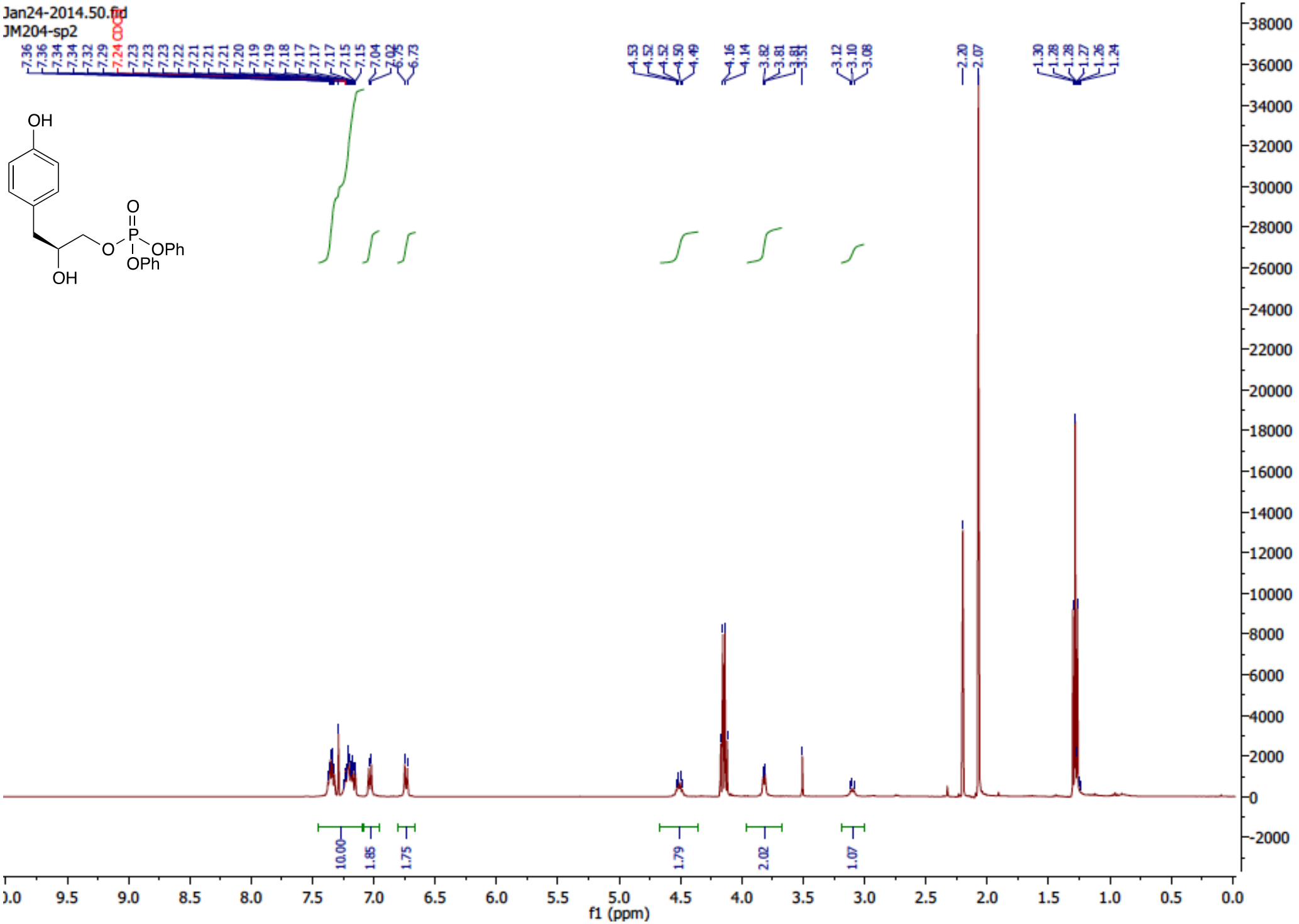
-17.41

13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000

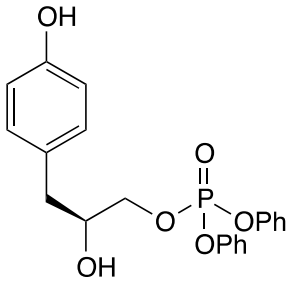
200 180 160 140 120 100 80 60 40 20 0 -20 -40 -60 -80 -100 -120 -140 -160 -180

f1 (ppm)


May22-2013.32.fid
JM114-2-P1
172.23
156.91
150.32
150.25
149.13
149.06
136.75
135.10
130.60
129.80
128.04
127.57
127.29
125.74
119.79
119.74
119.70
119.66
66.16
60.14
55.41
51.37
48.26 MeOD
48.05 MeOD
47.83 MeOD
47.62
47.41
47.19
46.98
45.24
36.37
19.48
13.08
O
P
OPh
OPh
O
CbzHN
CO2Me
f1 (ppm)


Jan24-2014.50.fid
JM204-sp2
OH
O
P
O
OPh
OPh
OH
f1 (ppm)

Jan24-2014.41.fid
JM204-ssp1



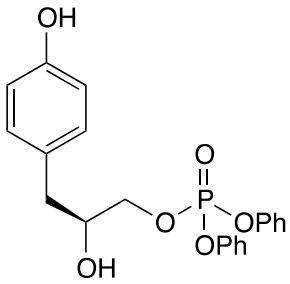
11.44

5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500

180 160 140 120 100 80 60 40 20 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200

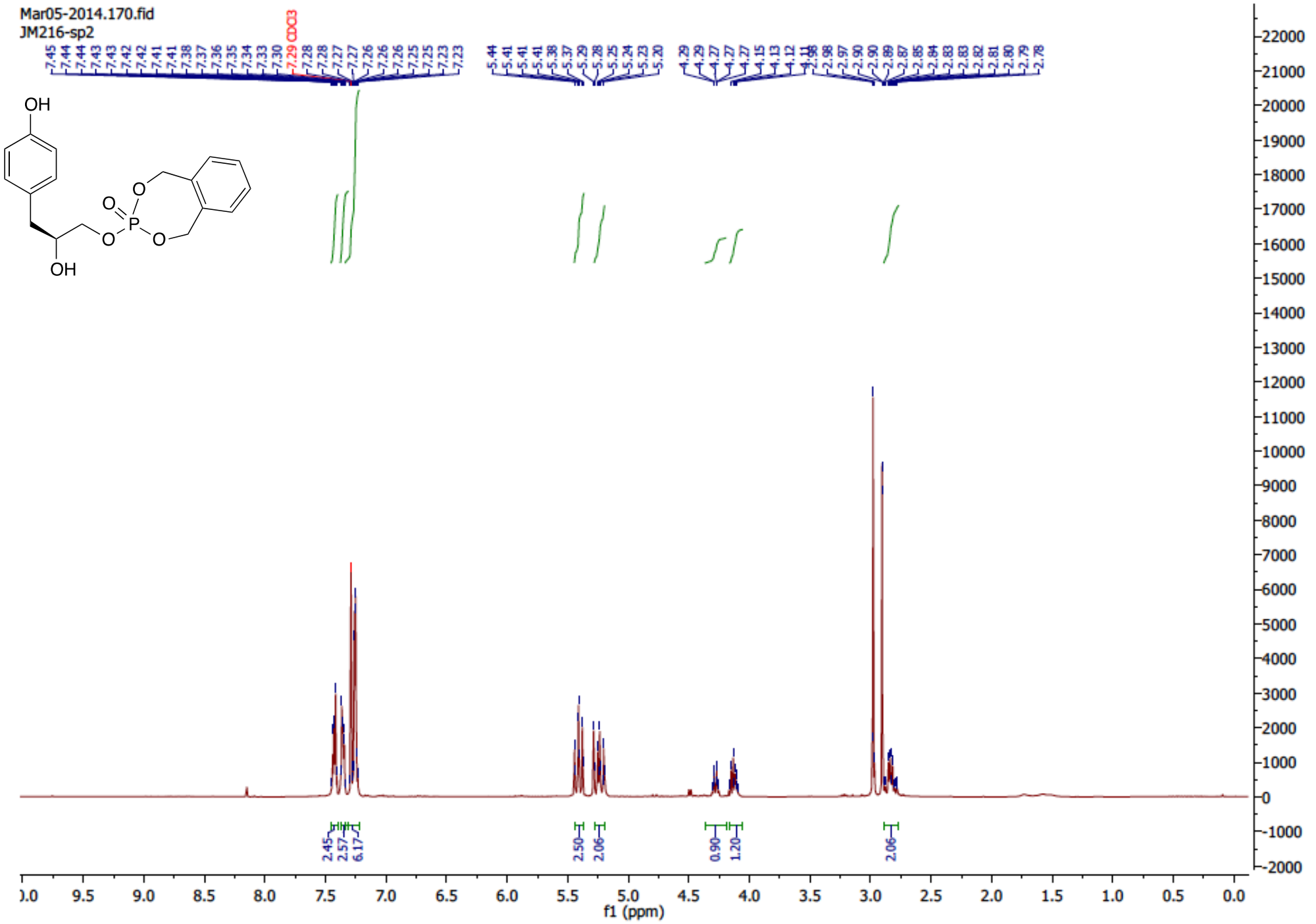
f1 (ppm)

Jan28-2014.70.fid
JM204-2

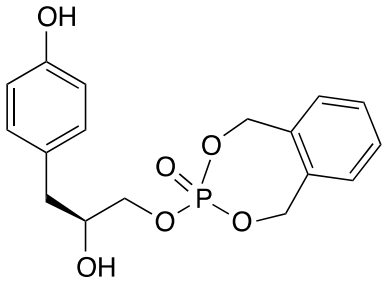


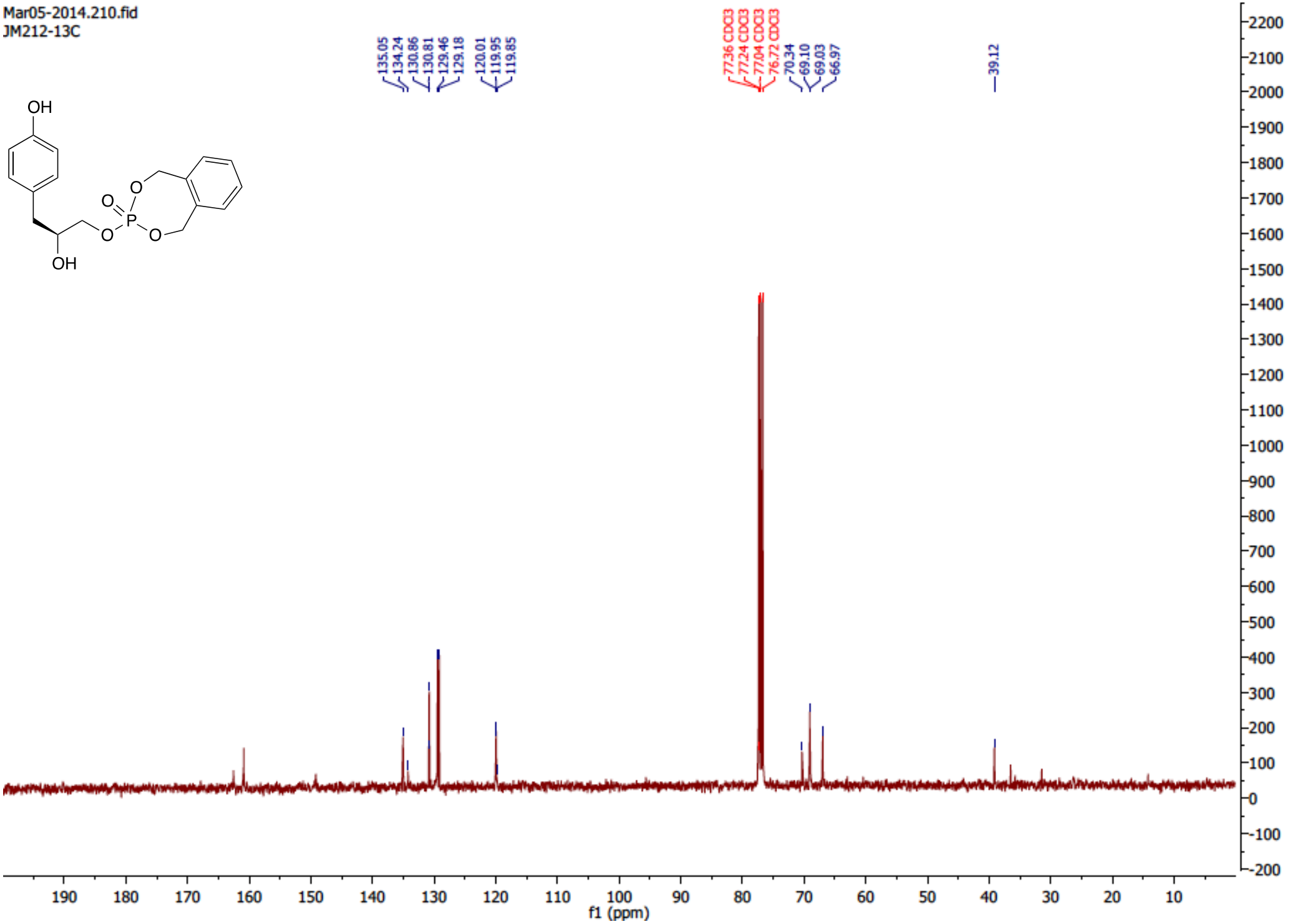
171.29
155.58
150.35
150.28
129.87
129.57
129.48
129.31
125.58
120.36
120.08
120.04
115.68
115.31
109.97
77.36
77.24 CDCl3
77.04 CDCl3
76.72 CDCl3
69.59
69.52
62.85
60.46
47.38
47.32
30.96
21.08
14.20

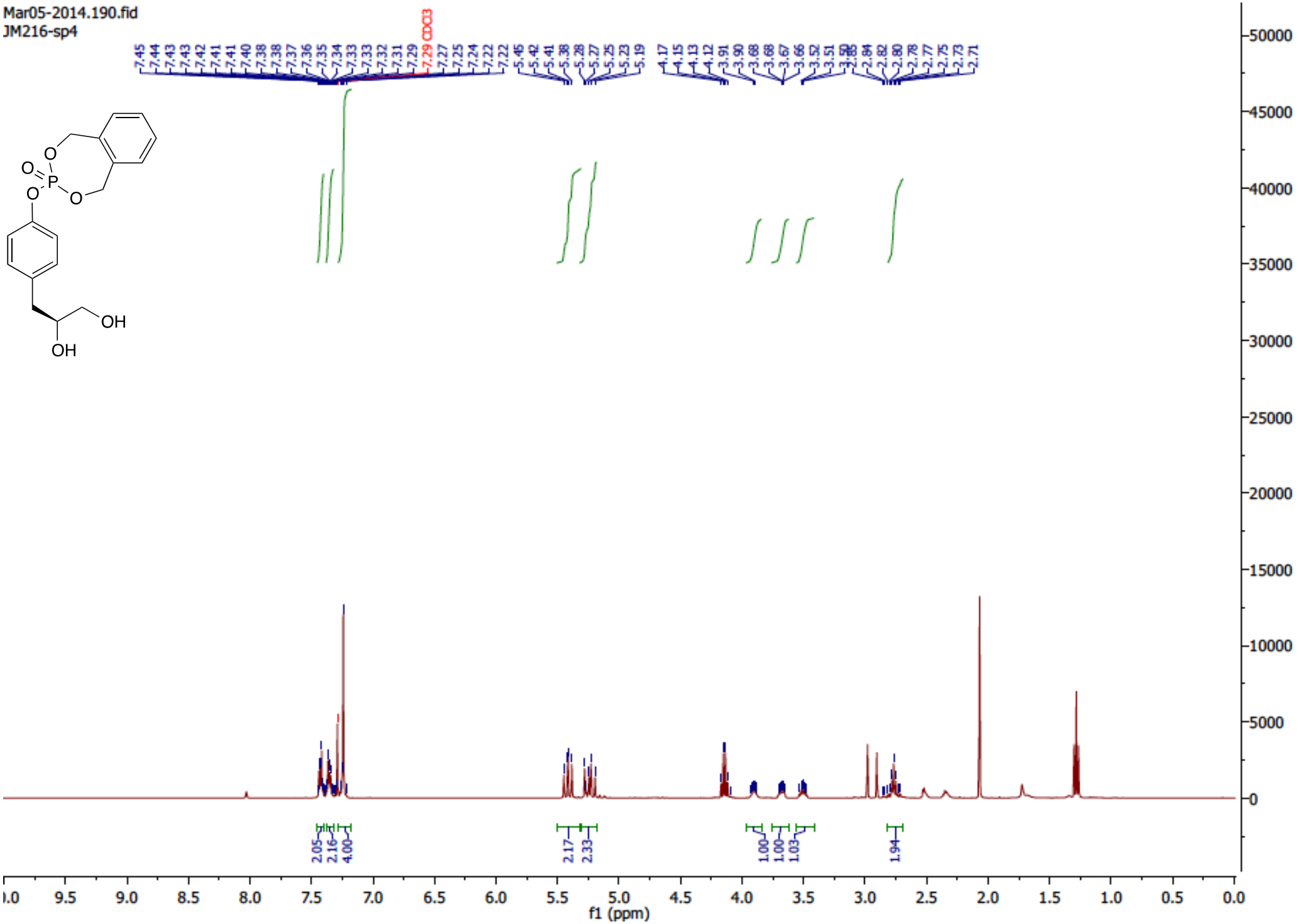
f1 (ppm)


Mar05-2014.170.fid
JM216-sp2
OH
OH
O
O
P
O
O
f1 (ppm)

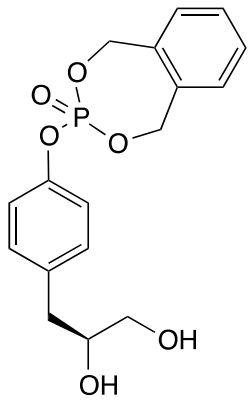
Mar05-2014.171.fid
JM216-sp2



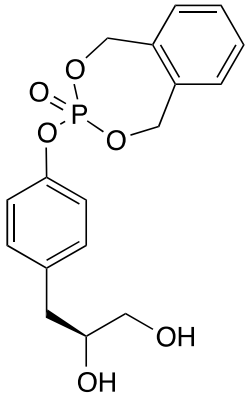

Mar05-2014.210.fid
JM212-13C
135.05
134.24
130.86
130.81
129.46
129.18
120.01
119.95
119.85
77.36 CDCl3
77.24 CDCl3
77.04 CDCl3
76.72 CDCl3
70.34
69.10
69.03
66.97
39.12
OH
OH
O
O
P
O
O
f1 (ppm)


Mar05-2014.190.fid
JM216-sp4
7.45 7.44 7.43 7.43 7.42 7.41 7.41 7.40 7.38 7.38 7.37 7.36 7.35 7.34 7.33 7.33 7.32 7.31 7.29 7.29 CDCl3 7.27 7.25 7.24 7.22 7.22 5.45 5.42 5.41 5.38 5.28 5.27 5.25 5.23 5.19 4.17 4.15 4.13 4.12 3.91 3.90 3.68 3.68 3.67 3.66 3.52 3.51 2.84 2.82 2.80 2.78 2.77 2.75 2.73 2.71
O
O
P
O
O
OH
OH
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
2.05
2.16
4.00
2.17
2.33
1.00
1.00
1.03
1.94
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

Mar05-2014.191.fid
JM216-sp4

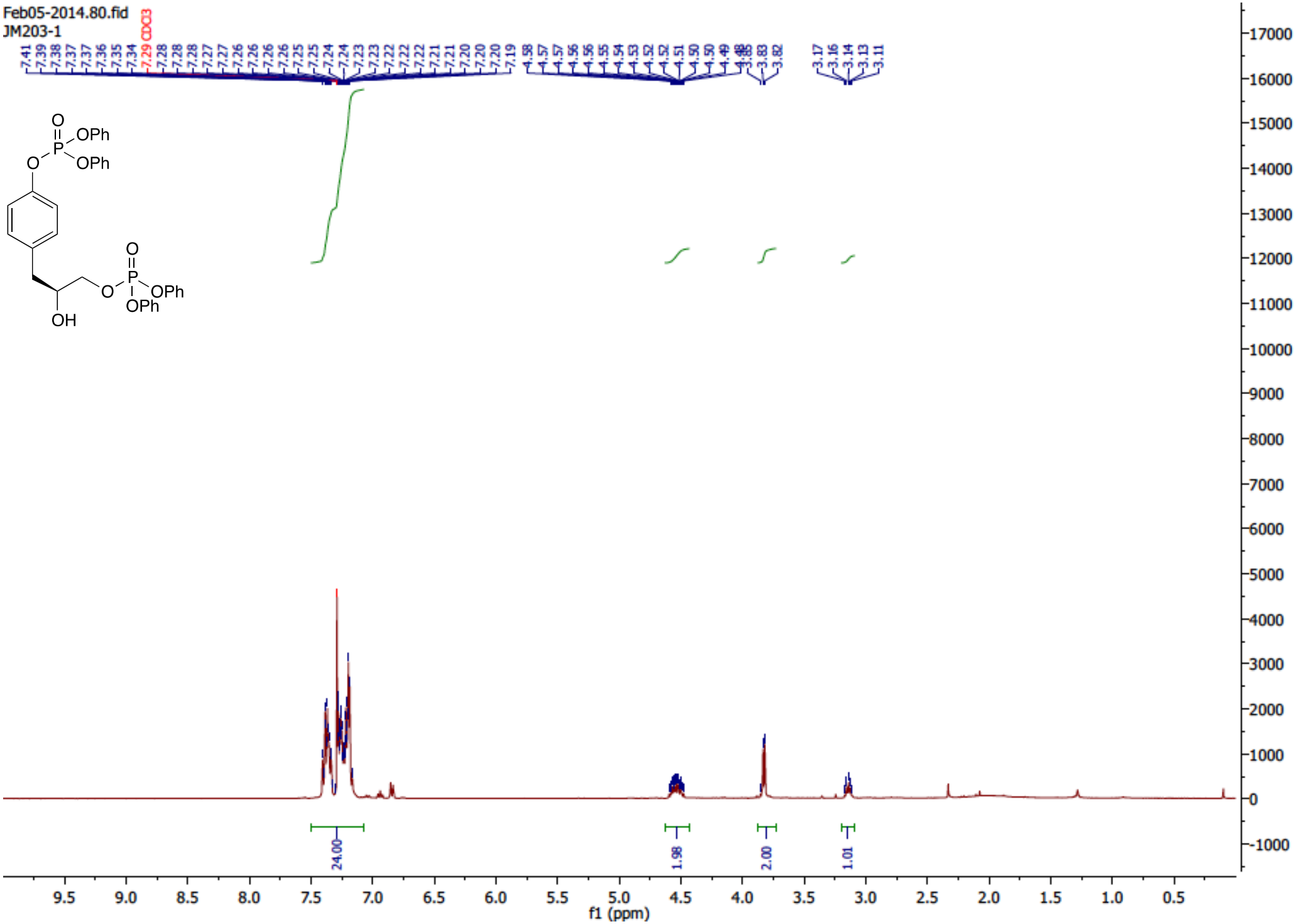


Mar05-2014.220.fid
JM217-13C

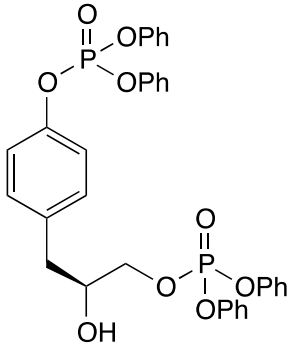


135.06
130.77
129.45
129.18
119.91
119.87
77.35 CDCl3
77.23 CDCl3
77.03 CDCl3
76.71
72.89
69.09
69.02
65.95
60.42
39.00

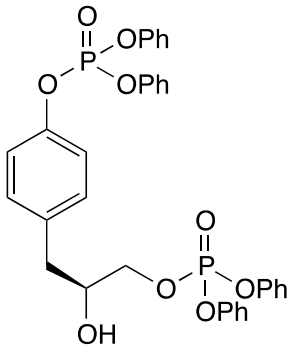
f1 (ppm)

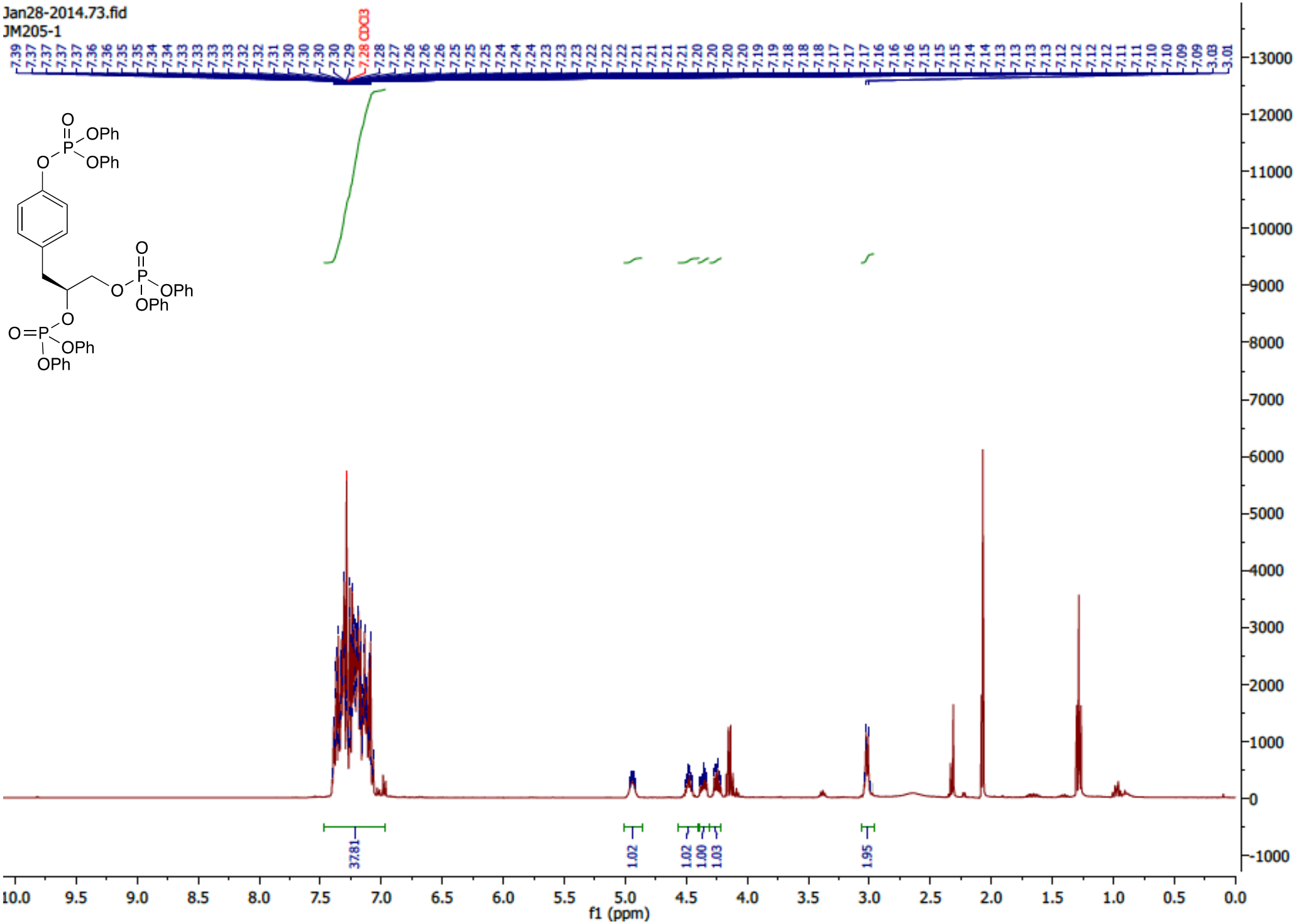

Feb05-2014.80.fid
JM203-1
CDCl3
OPh
OPh
OPh
OPh
OH
24.00
1.98
2.00
1.01
f1 (ppm)

Feb05-2014.81.fid
JM203-1

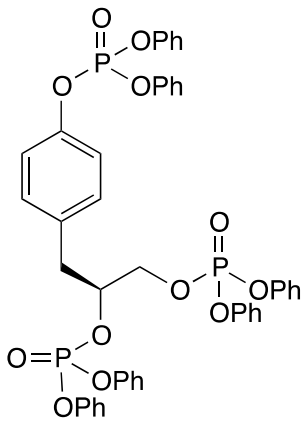


Feb06-2014.20.fid
JM208-P1-13C

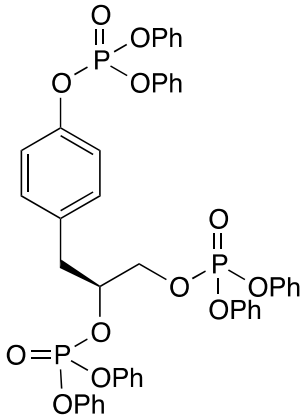



Jan28-2014.73.fid
JM205-1
CDCl3
OPh
OPh
OPh
OPh
OPh
OPh
37.81
1.02
1.02
1.00
1.03
1.95
f1 (ppm)

Jan28-2014.74.fid
JM205-1

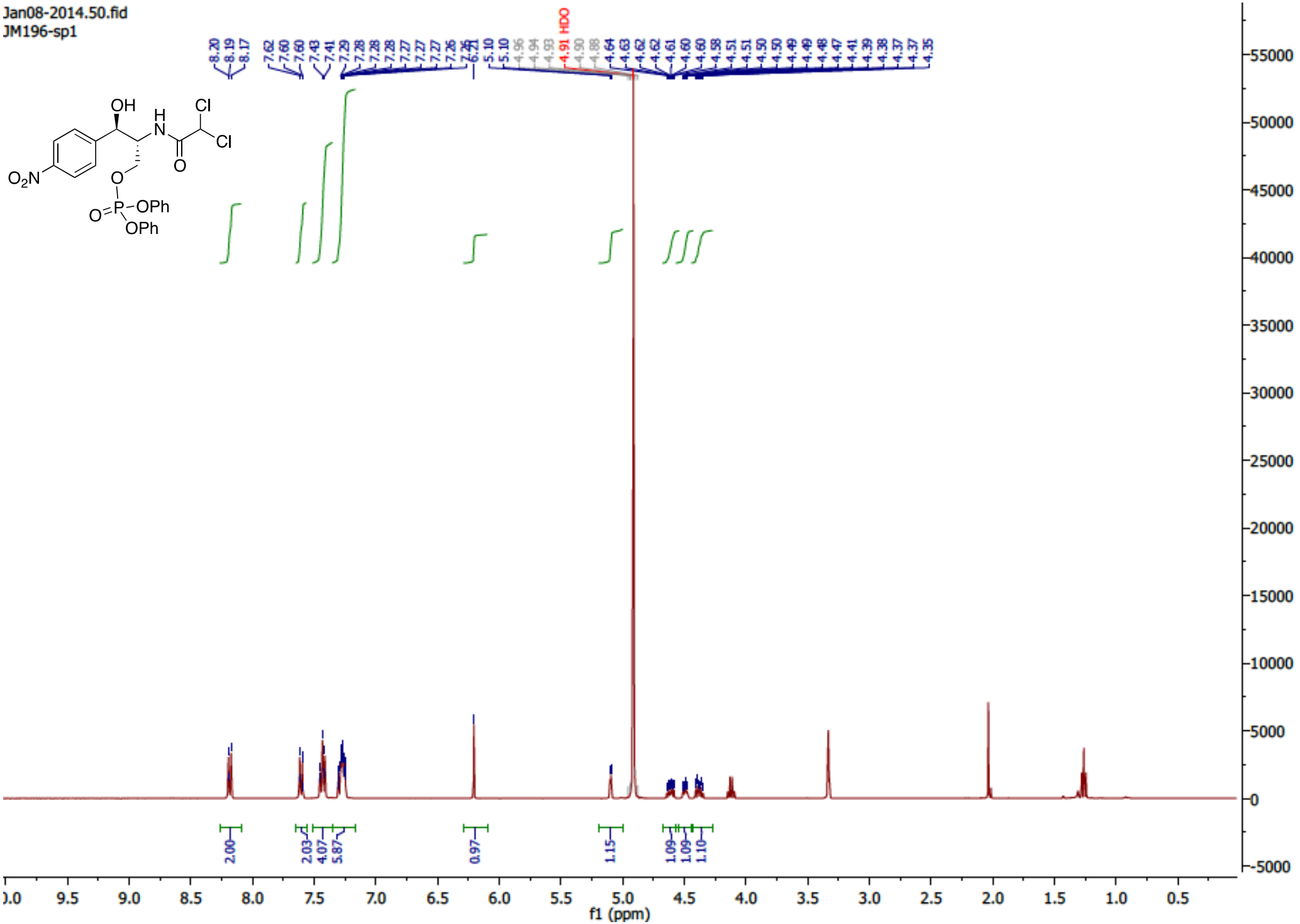


Jan28-2014.75.fid
JM205-1

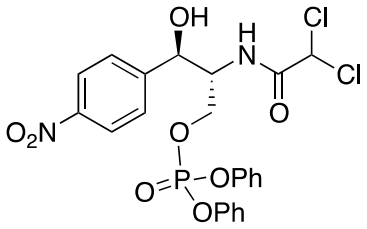


150.35
150.27
149.50
132.40
131.04
130.62
129.93
129.88
125.73
125.68
125.50
120.33
120.13
120.09
120.00
119.95
78.25
77.36 CDCl3
77.25 CDCl3
77.05 CDCl3
76.73 CDCl3
68.09
60.43
36.88

f1 (ppm)


Jan08-2014.50.fid
JM196-sp1
HDO
f1 (ppm)

Jan08-2014.51.fid
JM196-sp1

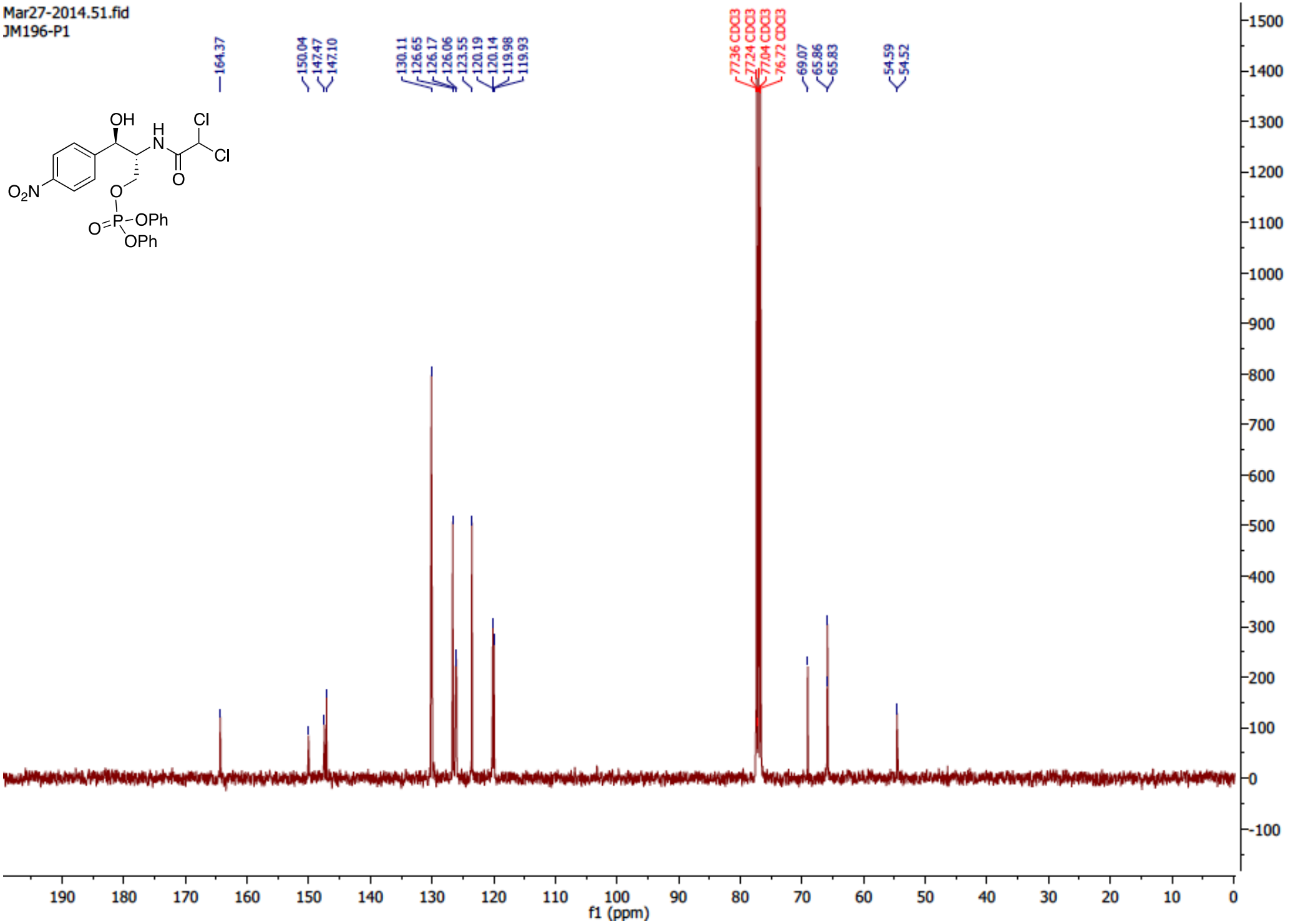


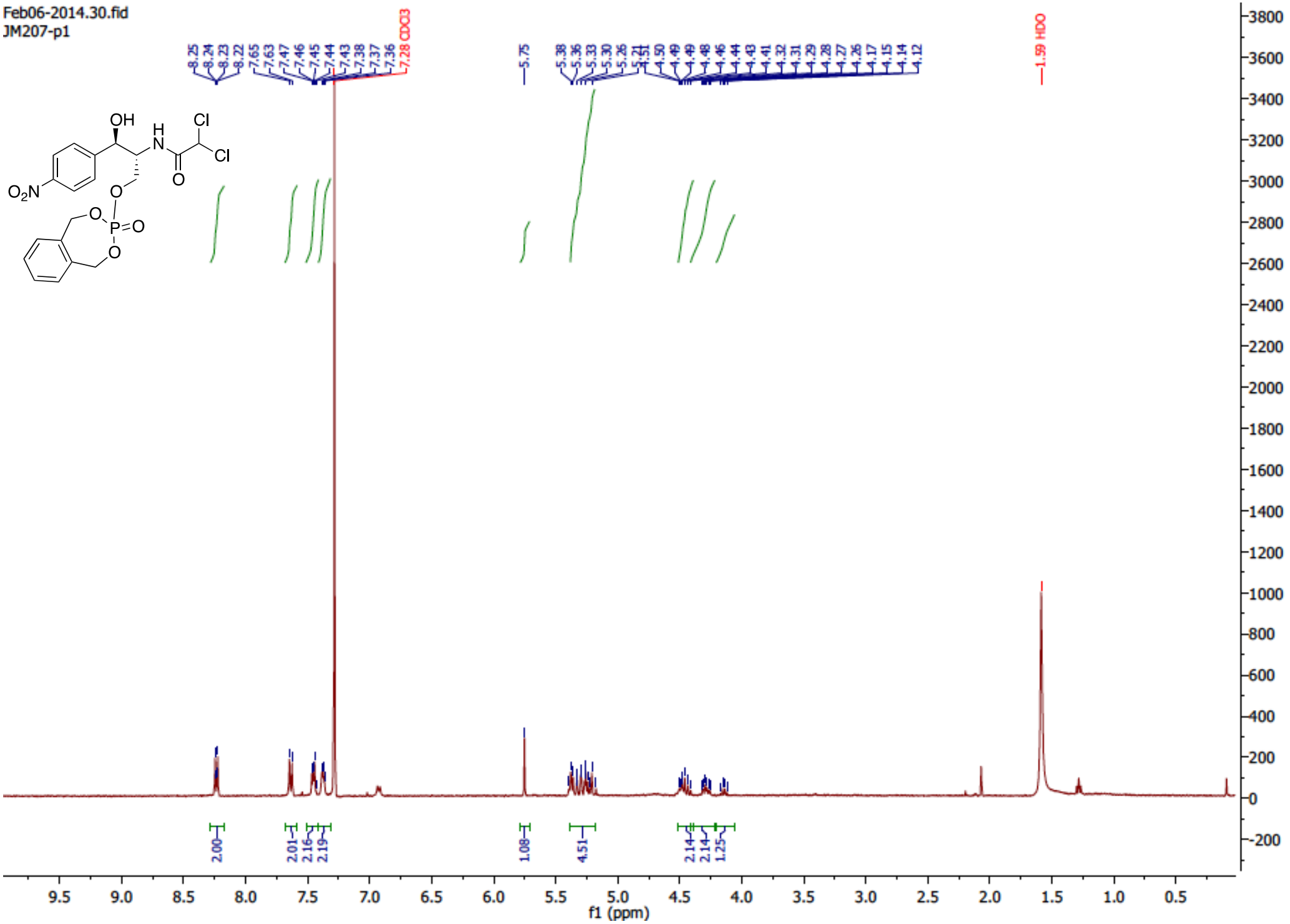
-12.12

1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700 600 500 400 300 200 100 0 -100 -200

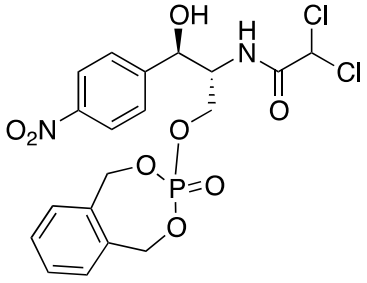
180 160 140 120 100 80 60 40 20 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200

f1 (ppm)


Mar27-2014.51.fid
JM196-P1
164.37
150.04
147.47
147.10
130.11
126.65
126.17
126.06
123.55
120.19
120.14
119.98
119.93
77.36 CDCl3
77.24 CDCl3
77.04 CDCl3
76.72 CDCl3
69.07
65.86
65.83
54.59
54.52
OH
H
N
Cl
Cl
O
O2N
O
O=P-OPh
OPh
f1 (ppm)


Feb06-2014.30.fid
JM207-p1
8.25
8.24
8.23
8.22
7.65
7.63
7.47
7.46
7.45
7.44
7.43
7.38
7.37
7.36
7.28 CDCl3
5.75
5.38
5.36
5.33
5.30
5.26
5.21
4.50
4.49
4.49
4.48
4.46
4.44
4.43
4.41
4.32
4.31
4.29
4.28
4.27
4.26
4.17
4.15
4.14
4.12
1.99 HDO
OH
H
N
Cl
Cl
O
O2N
O
O
P
O
O
2.00
2.01
2.16
2.19
1.08
4.51
2.14
2.14
1.25
f1 (ppm)

Feb06-2014.31.fid
JM207-p1



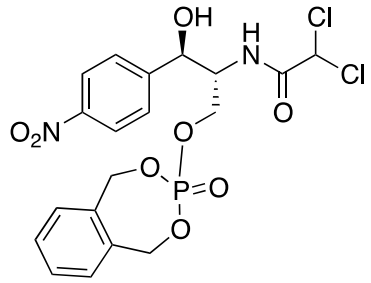
0.76

450
400
350
300
250
200
150
100
50
0
-50

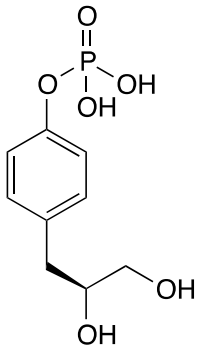
180 160 140 120 100 80 60 40 20 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200

f1 (ppm)

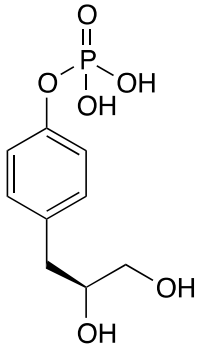
Feb04-2014.30.fid
JM206-P1-13c

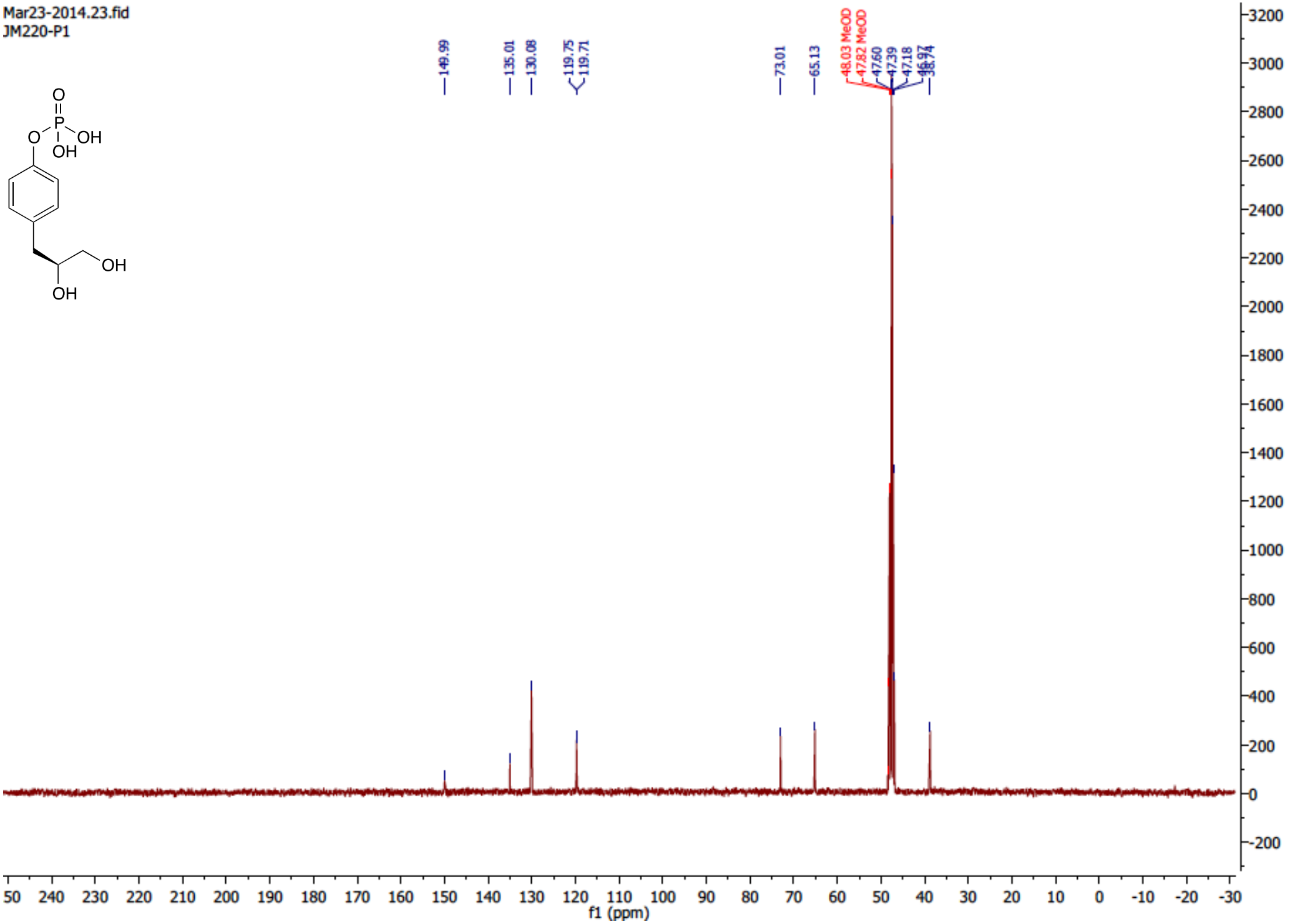


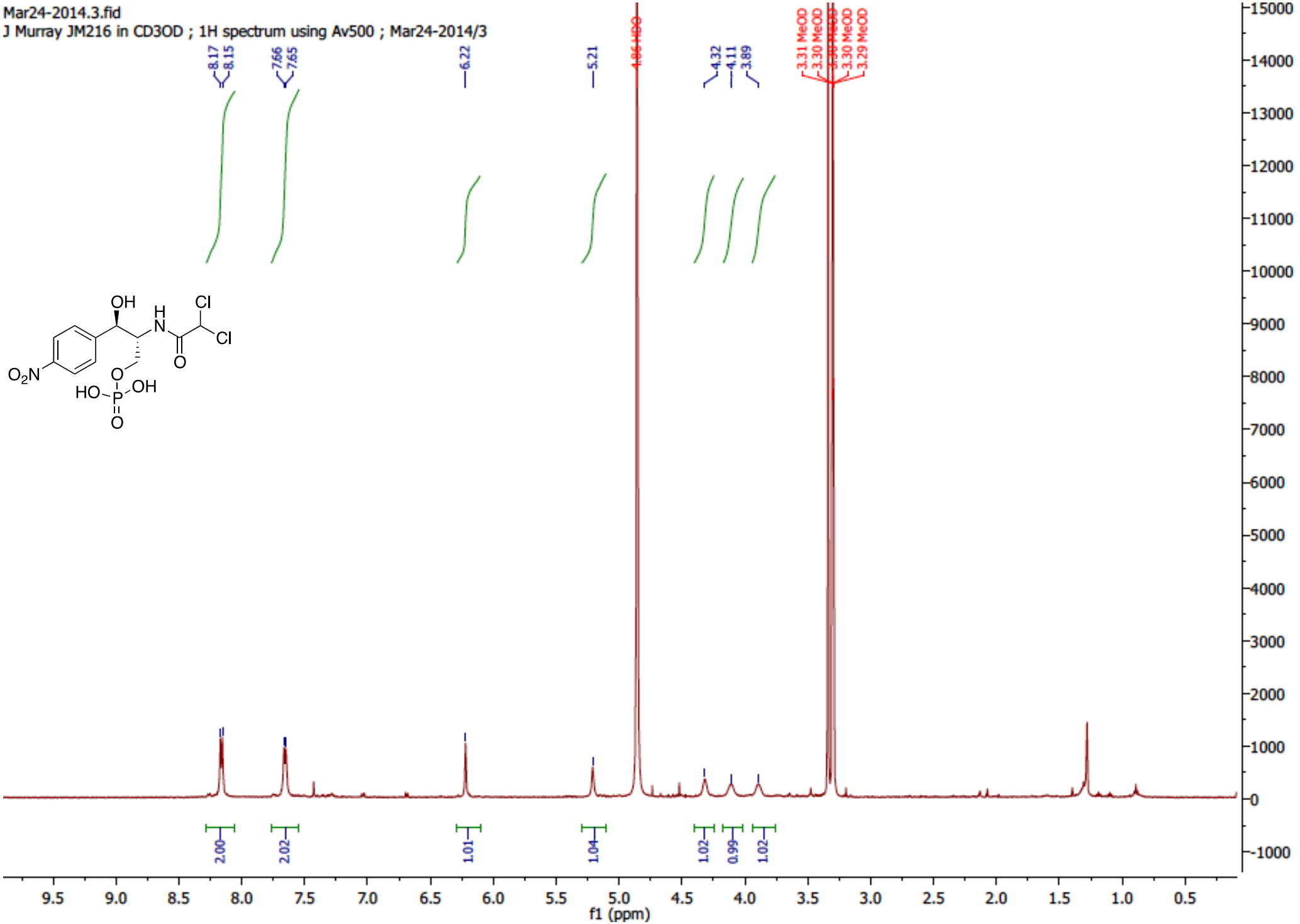
Mar23-2014.21.fid
JM220-P1



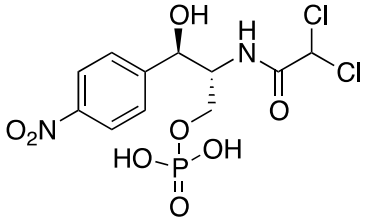
Mar23-2014.25.fid
JM220-P1

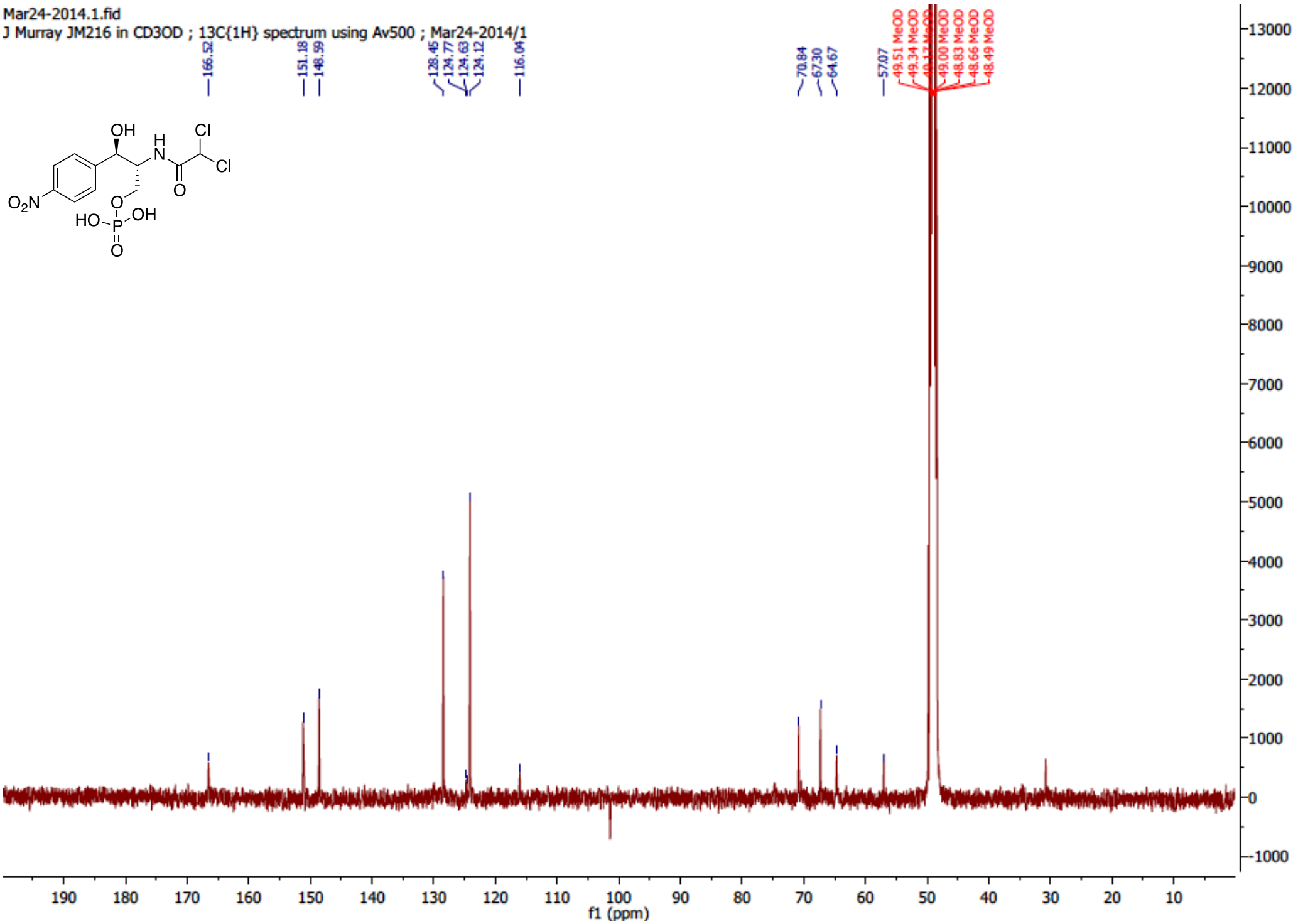



Mar23-2014.23.fid
JM220-P1
149.99
135.01
130.08
119.75
119.71
73.01
65.13
48.03 MeOD
47.82 MeOD
47.60
47.39
47.18
46.97
38.74
O
P
O
OH
OH
OH
OH
f1 (ppm)

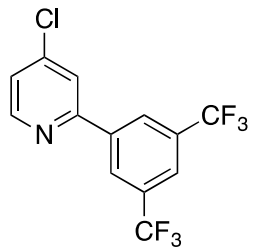

Mar24-2014.3.fid
J Murray JM216 in CD3OD ; 1H spectrum using Av500 ; Mar24-2014/3
8.17
8.15
7.66
7.65
6.22
5.21
4.86 HDO
4.32
4.11
3.89
3.31 MeOD
3.30 MeOD
3.30 MeOD
3.30 MeOD
3.29 MeOD
OH
H
N
Cl
Cl
O
O_2N
O
HO
P
OH
O
2.00
2.02
1.01
1.04
1.02
0.99
1.02
f1 (ppm)

Mar24-2014.2.fid
J Murray JM216 in CD3OD ; 31P{1H} spectrum using Av500 ; Mar24-2014/2




Mar24-2014.1.fid
J Murray JM216 in CD3OD ; 13C{1H} spectrum using Av500 ; Mar24-2014/1
166.52
151.18
148.59
128.45
124.77
124.63
124.12
116.04
70.84
67.30
64.67
57.07
49.51 MeOD
49.34 MeOD
49.17 MeOD
49.00 MeOD
48.83 MeOD
48.66 MeOD
48.49 MeOD
OH
H
N
Cl
Cl
O
O_2N
O
HO
P
OH
O
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

May07-2013.70.fid
JM105-P1



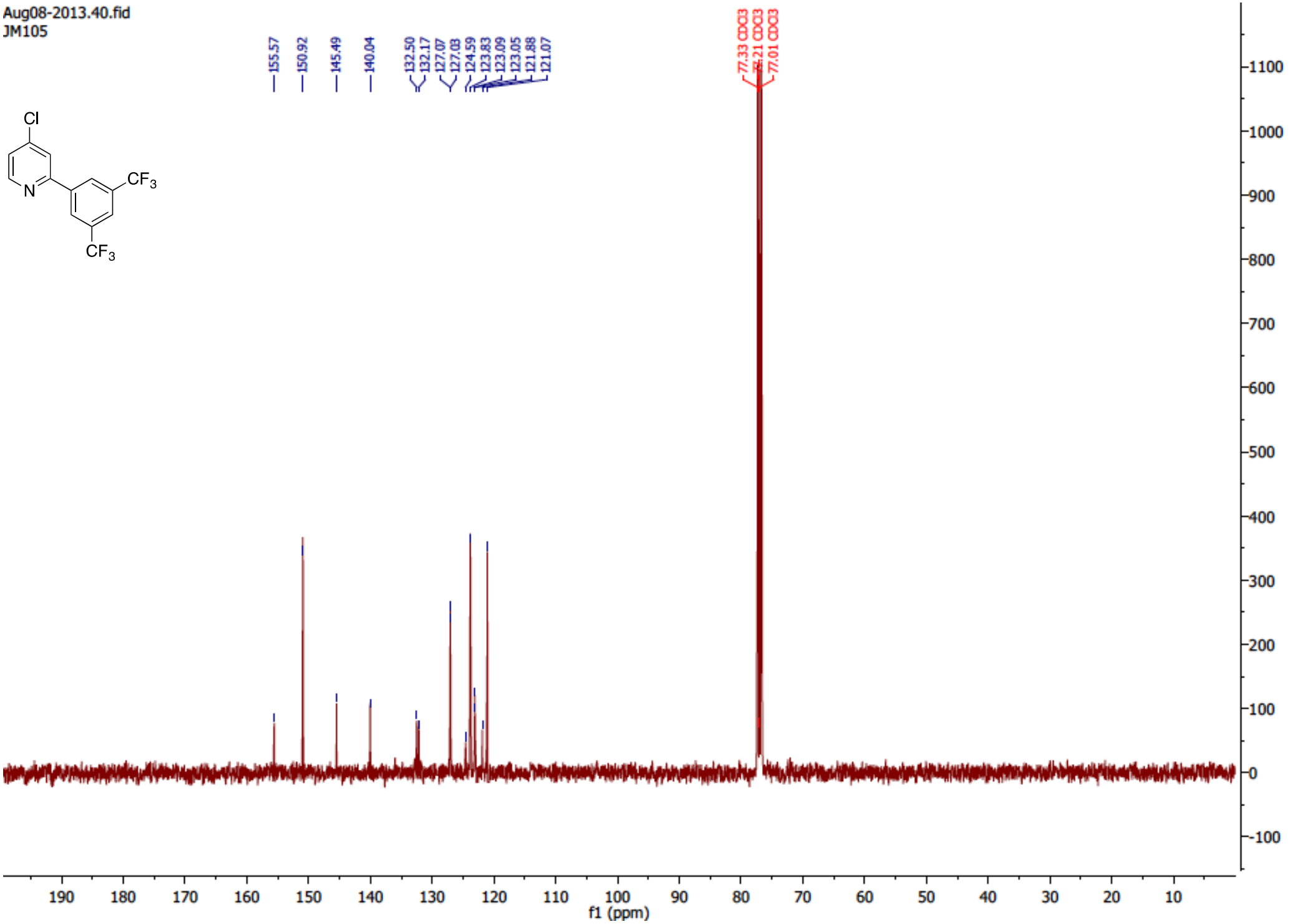
8.69 8.67 8.50 8.50 8.49 7.98 7.85 7.85 7.85 7.84 7.41 7.41 7.40 7.40 7.38 7.37 7.37 7.37 7.36 7.36 7.36 7.35 7.35 7.35 7.35 7.34 7.34 7.34 7.33 7.33 7.32 7.32 7.31 7.31 7.29 CDCl3 7.29 7.28 7.27 7.27

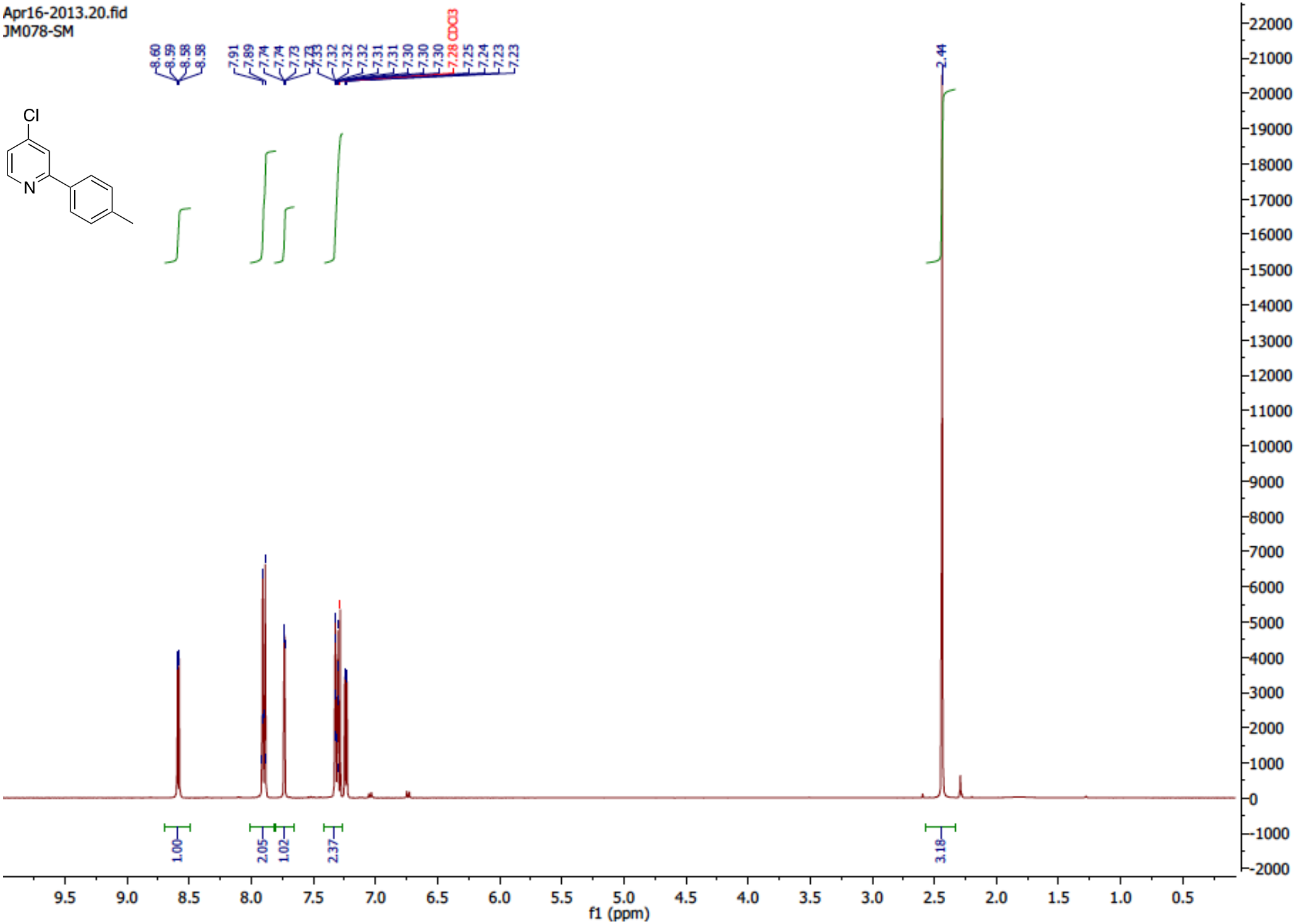
45000 40000 35000 30000 25000 20000 15000 10000 5000 0

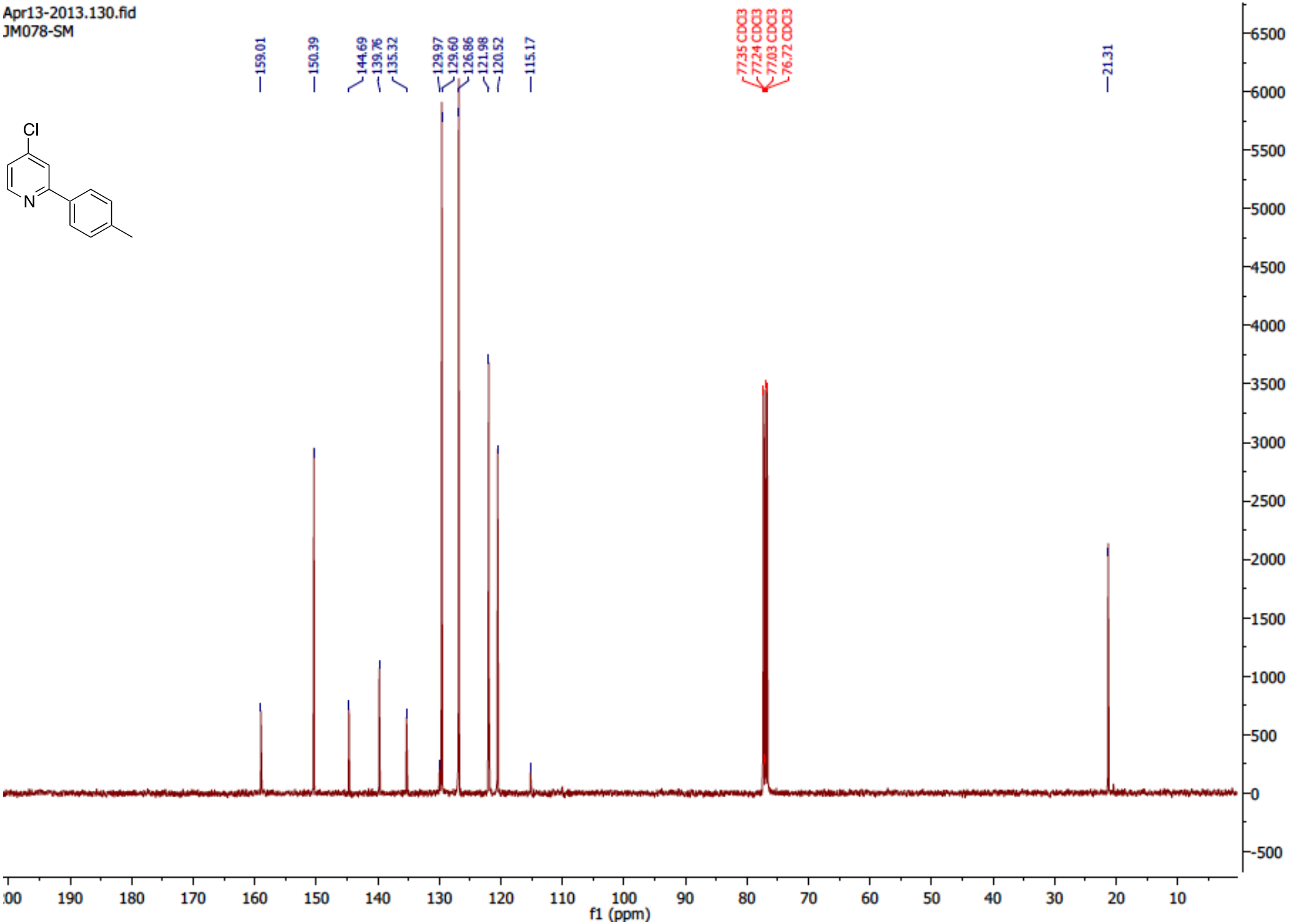
1.00 1.92 0.97 1.01 2.16

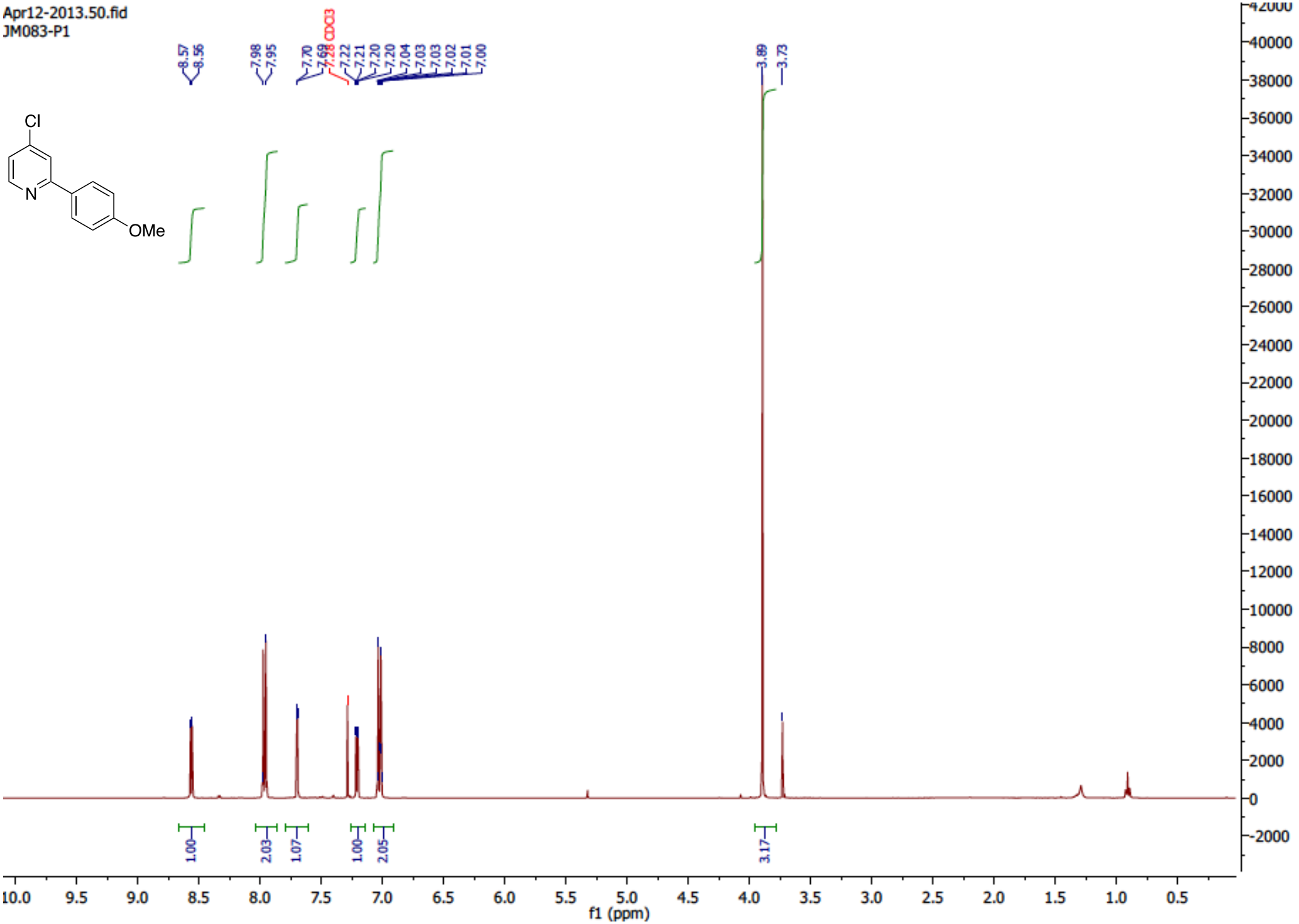
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

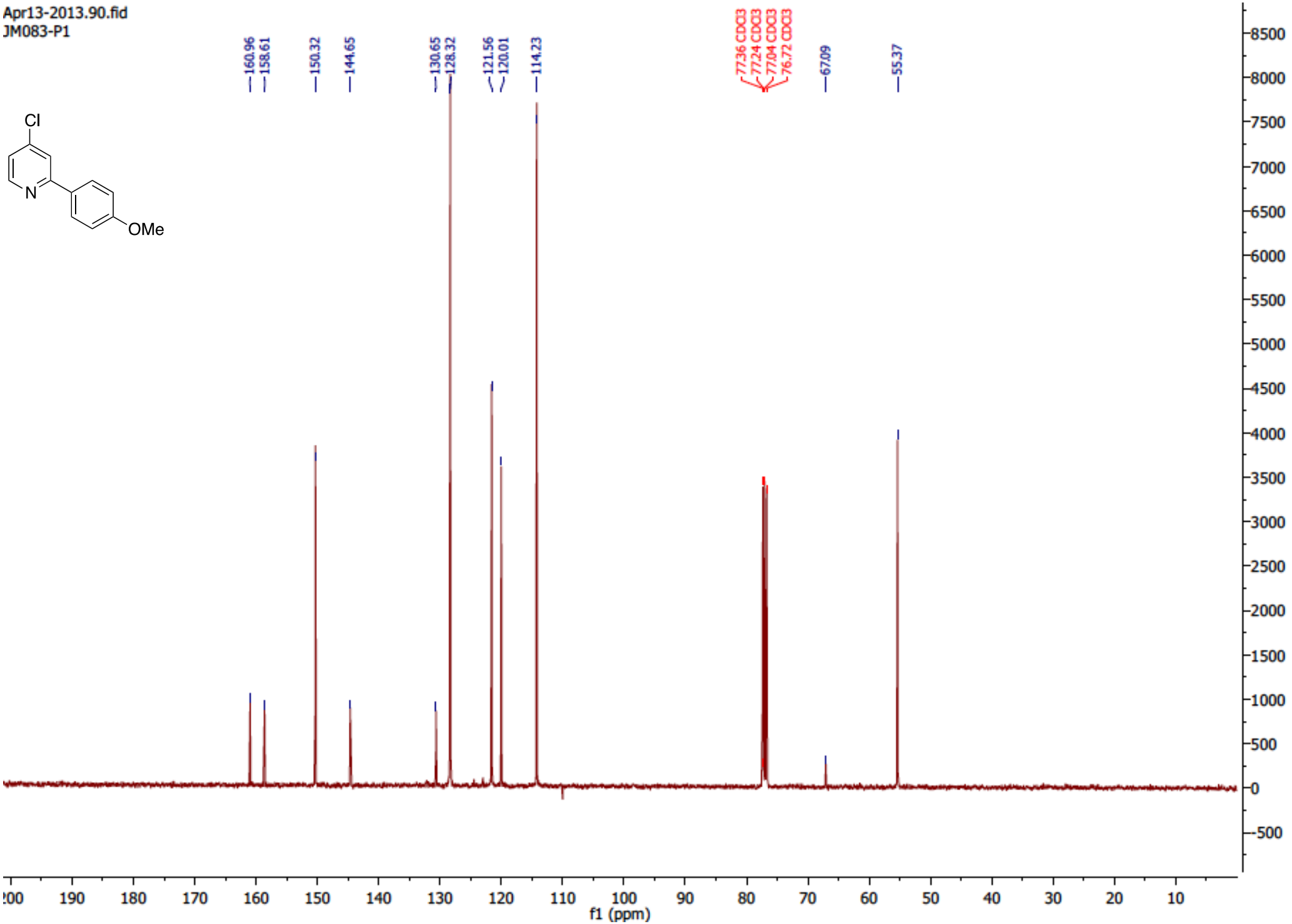
f1 (ppm)

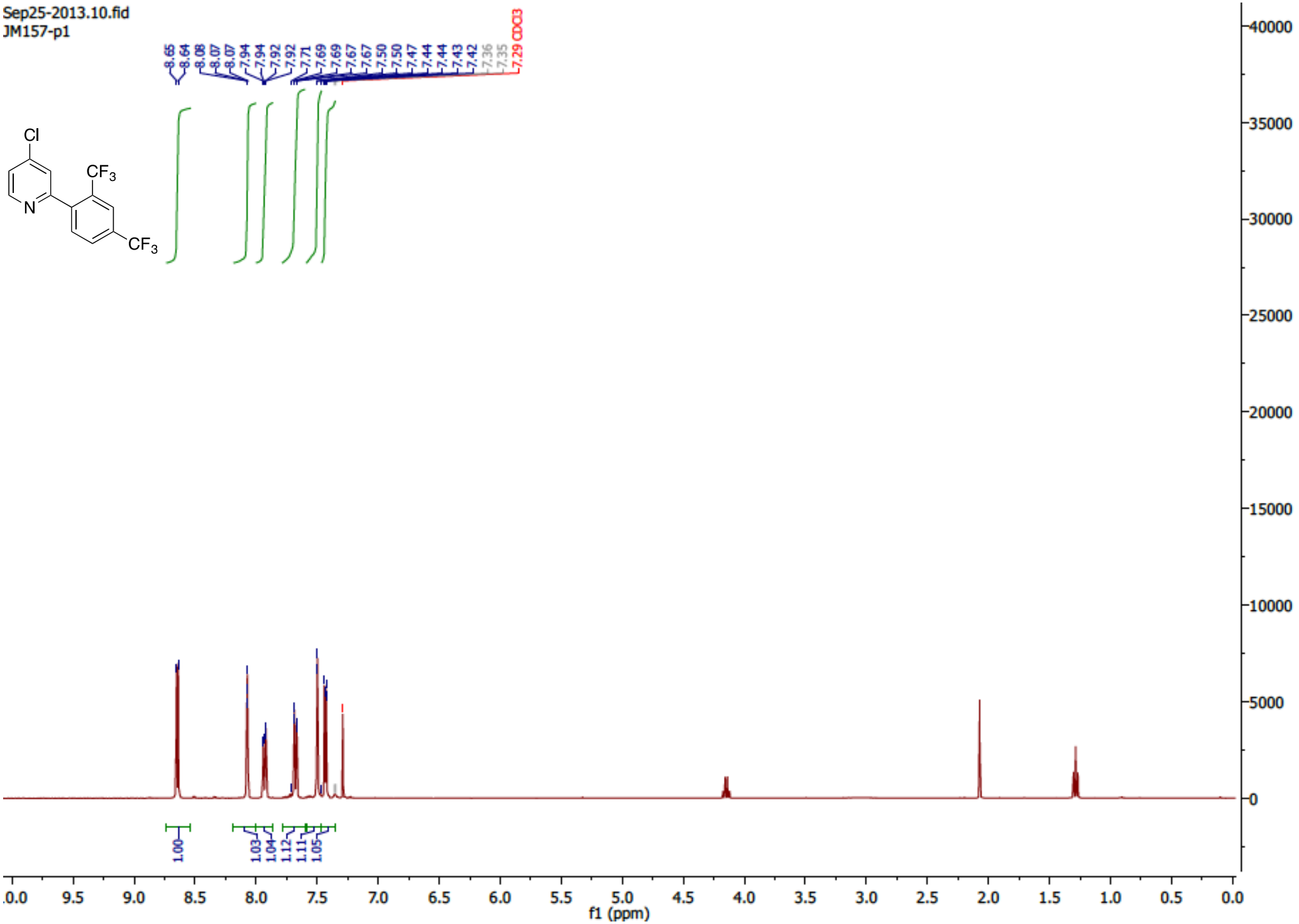

Aug08-2013.40.fid
JM105
155.57
150.92
145.49
140.04
132.50
132.17
127.07
127.03
124.59
123.83
123.09
123.05
121.88
121.07
77.33 CDCl3
77.21 CDCl3
77.01 CDCl3
Cl
N
CF3
CF3
f1 (ppm)


Apr16-2013.20.fid
JM078-SM
Cl
N
8.60
8.59
8.58
8.58
7.91
7.89
7.74
7.74
7.73
7.33
7.32
7.32
7.32
7.31
7.31
7.30
7.30
7.30
7.28 CDCl3
7.25
7.24
7.23
7.23
2.44
1.00
2.05
1.02
2.37
3.18
f1 (ppm)

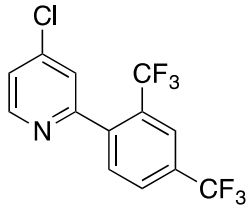

Apr13-2013.130.fid
JM078-SM
159.01
150.39
144.69
139.76
135.32
129.97
129.60
126.86
121.98
120.52
115.17
77.35 CDCl3
77.24 CDCl3
77.03 CDCl3
76.72 CDCl3
21.31
Cl
N
f1 (ppm)


Apr12-2013.50.fid
JM083-P1
8.57
8.56
7.98
7.95
7.70
7.69
7.28 CDCl3
7.22
7.21
7.20
7.20
7.04
7.03
7.03
7.02
7.01
7.00
3.89
3.73
Cl
N
OMe
1.00
2.03
1.07
1.00
2.05
3.17
f1 (ppm)


Apr13-2013.90.fid
JM083-P1
160.96
158.61
150.32
144.65
130.65
128.32
121.56
120.01
114.23
77.36 CDCl3
77.24 CDCl3
77.04 CDCl3
76.72 CDCl3
67.09
55.37
Cl
N
OMe
f1 (ppm)


Sep25-2013.10.fid
JM157-p1
8.65
8.64
8.08
8.07
8.07
7.94
7.94
7.92
7.92
7.71
7.69
7.69
7.67
7.67
7.50
7.50
7.47
7.44
7.44
7.43
7.42
7.36
7.35
7.29
CDCl3
Cl
CF3
N
CF3
40000
35000
30000
25000
20000
15000
10000
5000
0
1.00
1.03
1.04
1.12
1.11
1.05
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

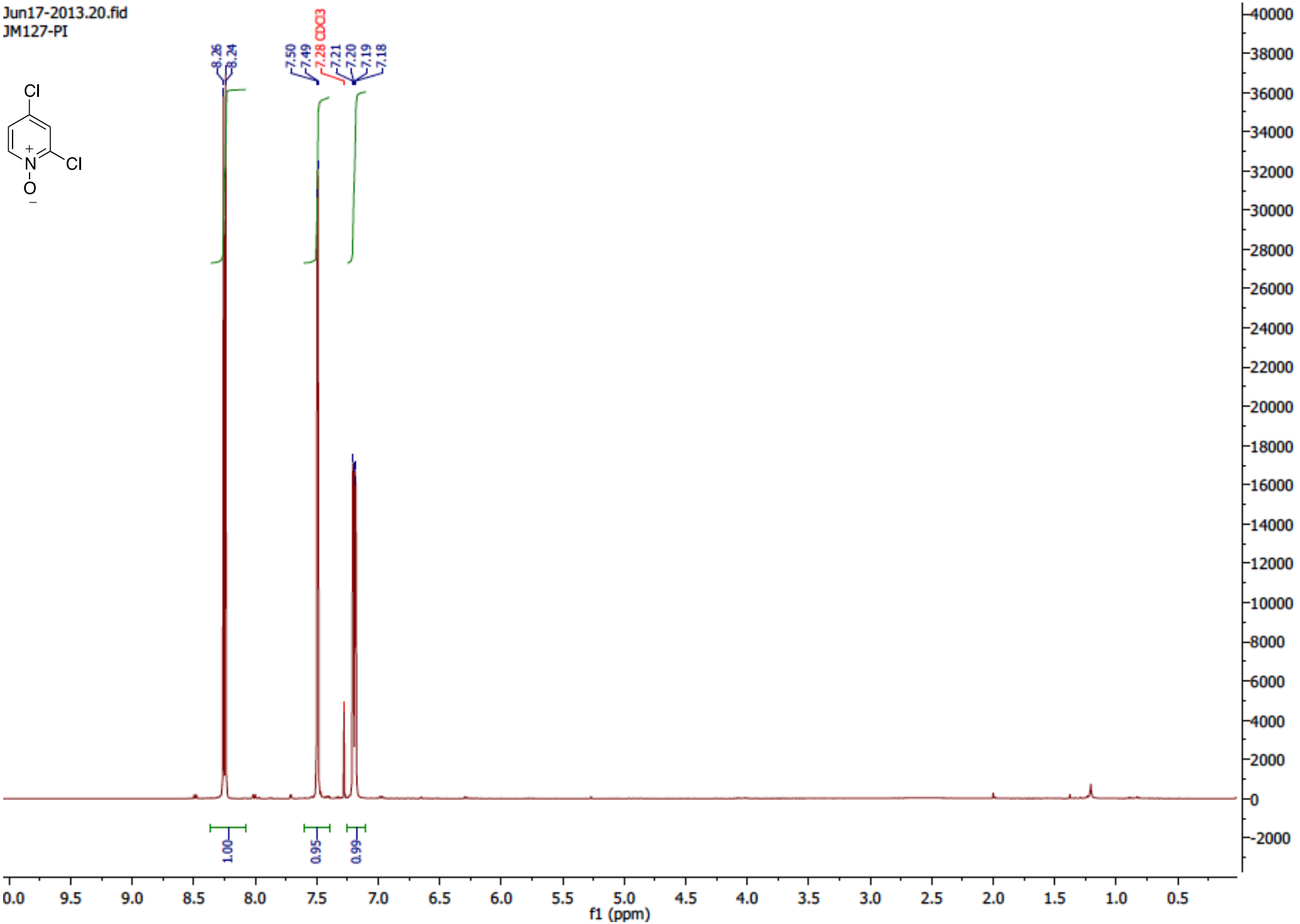
Apr13-2013.120.fid
JM039-P1

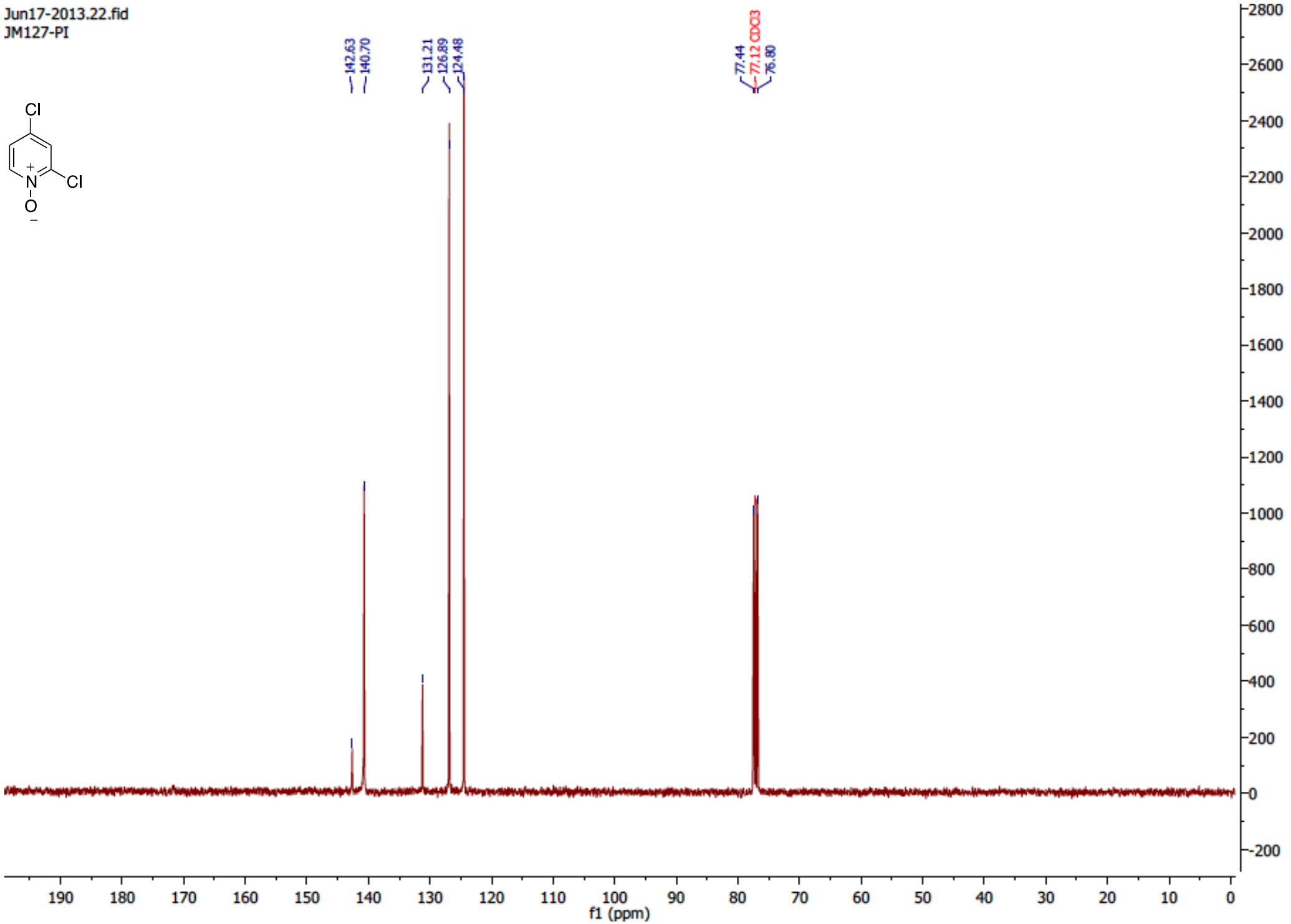


157.65
150.23
149.37
149.19
144.30
142.21
132.26
131.50
131.16
129.48
129.16
128.53
128.49
128.45
128.42
127.20
124.56
124.48
124.17
124.14
123.89
123.84
123.80
123.75
123.70
123.66
123.61
123.49
121.84
121.75
77.33 CDCl3
77.01 CDCl3
76.69 CDCl3

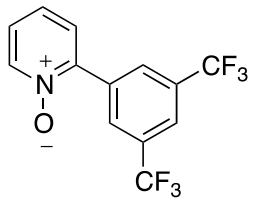
45000
40000
35000
30000
25000
20000
15000
10000
5000
0

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


Jun17-2013.20.fid
JM127-PI
Cl
Cl
N
O
8.26
8.24
7.50
7.49
7.28 CDCl3
7.21
7.20
7.19
7.18
1.00
0.95
0.99
f1 (ppm)


Jun17-2013.22.fid
JM127-PI
142.63
140.70
131.21
126.89
124.48
77.44
77.12 CDCl3
76.80
Cl
Cl
N
O
f1 (ppm)

May08-2013.20.fid
JM108-P1

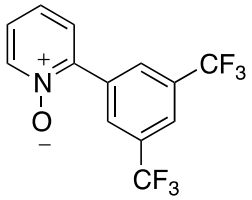


8.40 8.39 8.39 8.38 8.38 8.34 8.34 8.34 8.33 7.98 7.97 7.71 7.71 7.71 7.70 7.69 7.69 7.68 7.68 7.68 7.67 7.66 7.66 7.58 7.58 7.58 7.57 7.57 7.56 7.56 7.55 7.55 7.54 7.54 7.53 7.52 7.51 7.51 7.51 7.50 7.50 7.49 7.49 7.49 7.48 7.48 7.47 7.47 7.47 7.46 7.46 7.46 7.45 7.43 7.43 7.41 7.41 7.40 7.39 7.39 7.38 7.37 7.37 7.36 7.35 7.35 7.28 CDCl3

1.03 1.97 1.00 0.75 2.13 2.05

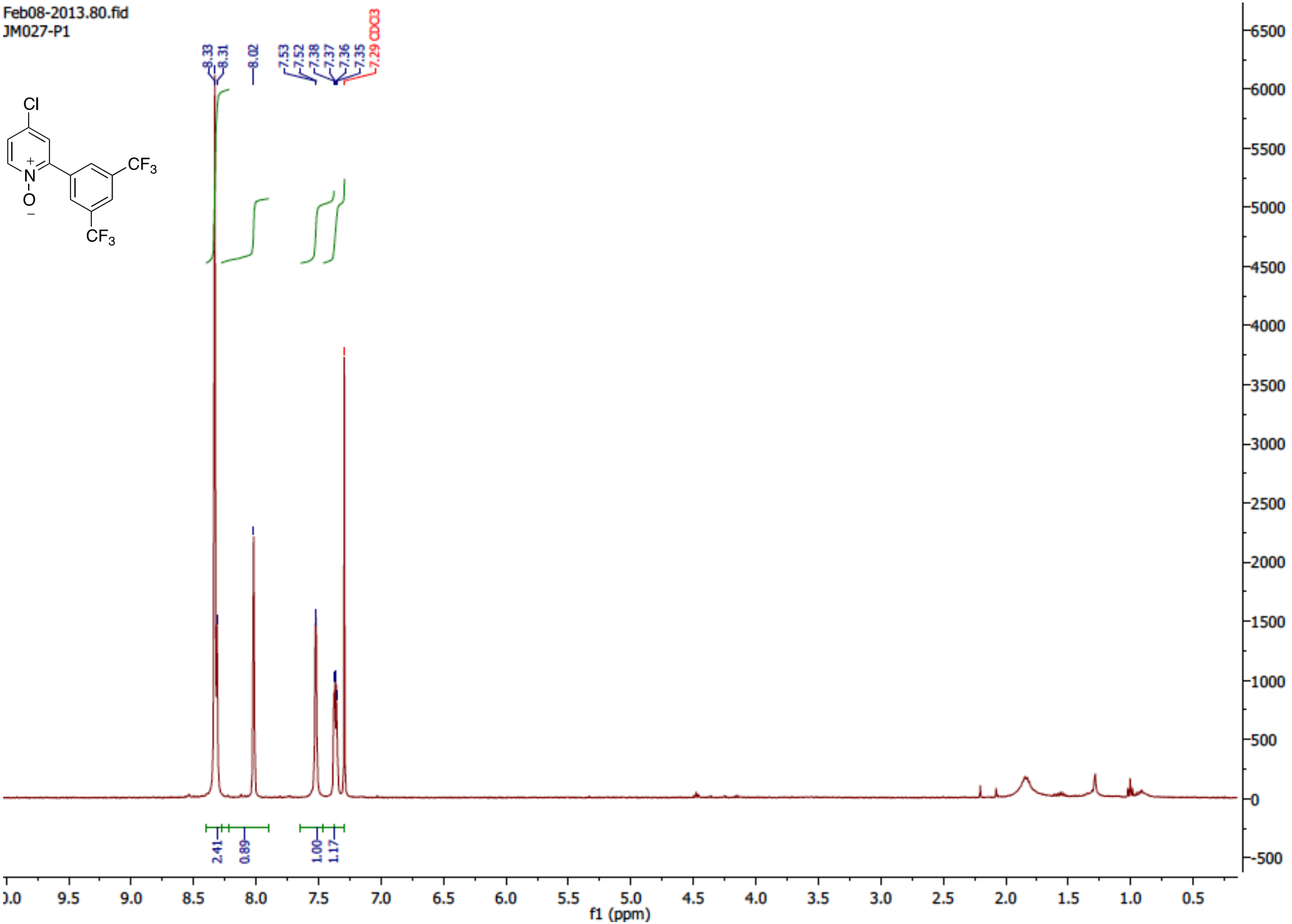
f1 (ppm)

May08-2013.21.fid
JM108-P1

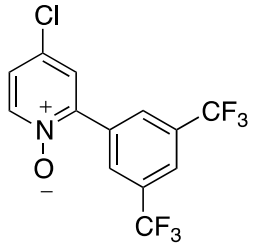


146.29
140.65
134.44
132.23
132.14
132.03
131.95
131.91
131.57
131.23
129.68
129.64
128.56
128.43
127.32
126.02
125.99
124.46
123.37
123.33
123.29
123.25
121.74
119.04
77.36
77.25 CDCl3
77.04 CDCl3
76.72 CDCl3

f1 (ppm)


Feb08-2013.80.fid
JM027-P1
Cl
CF3
CF3
N
O
8.33
8.31
8.02
7.53
7.52
7.38
7.37
7.36
7.35
7.29 CDCl3
2.41
0.89
1.00
1.17
f1 (ppm)

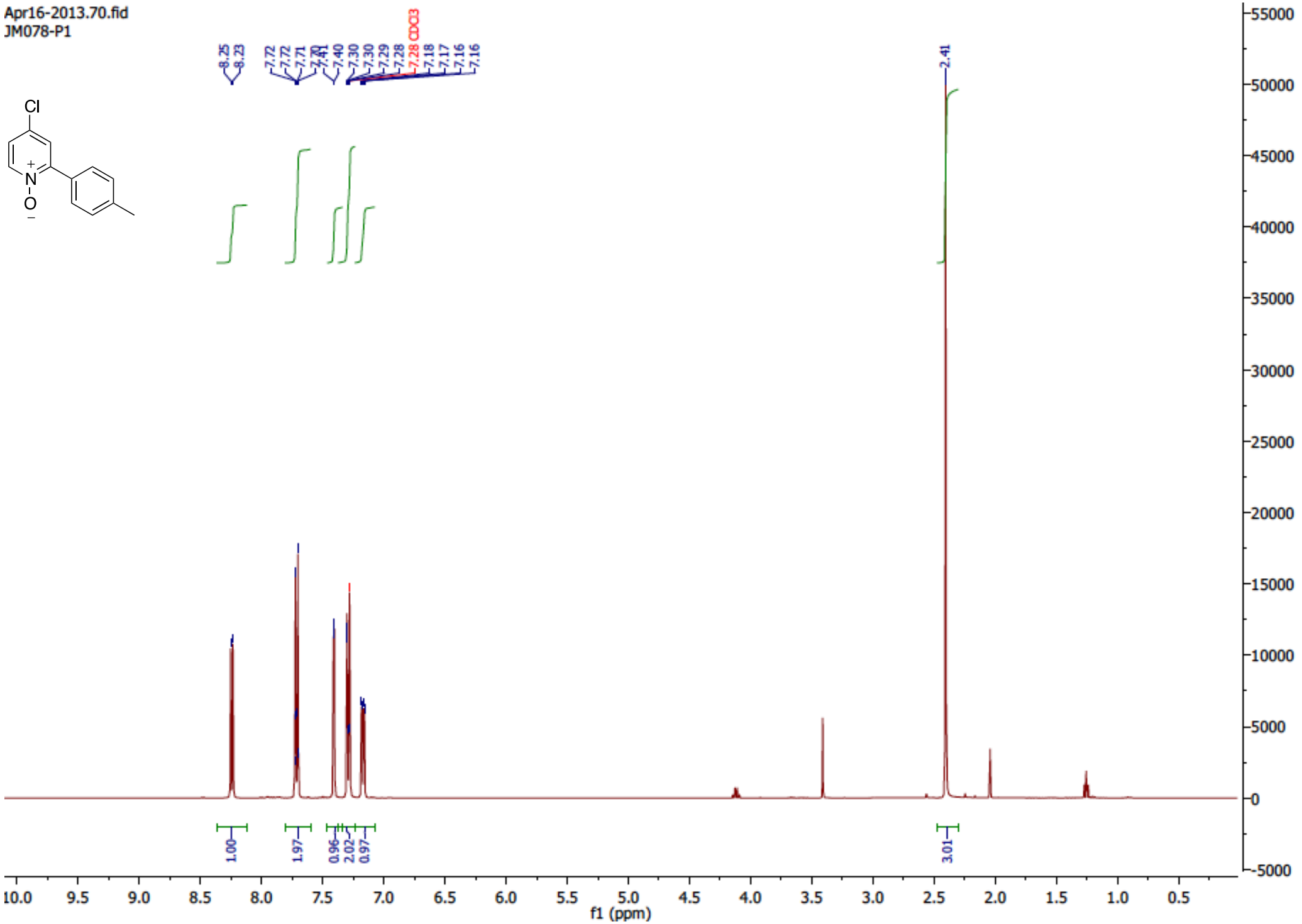
Apr13-2013.70.fid
JM040-P1

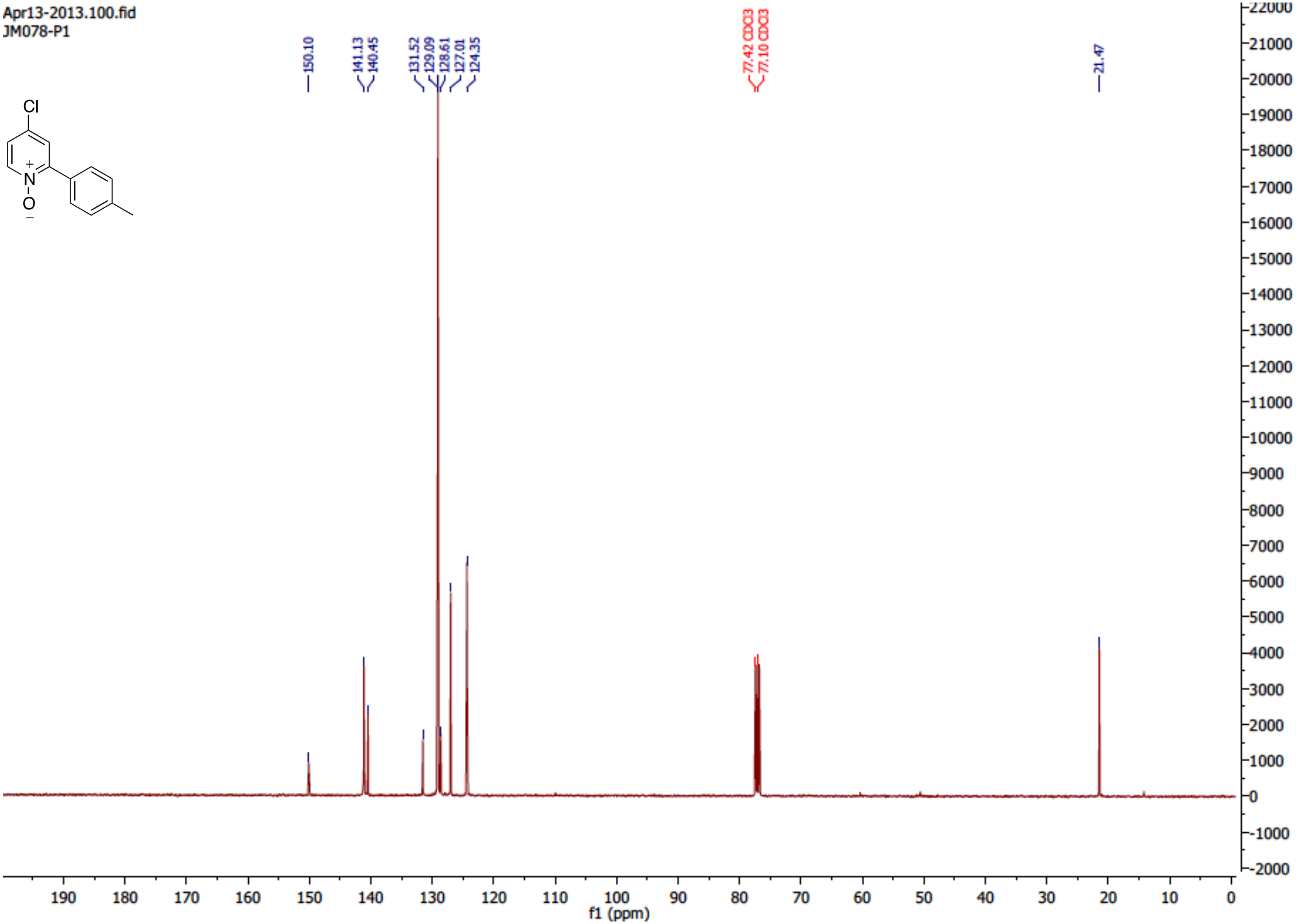


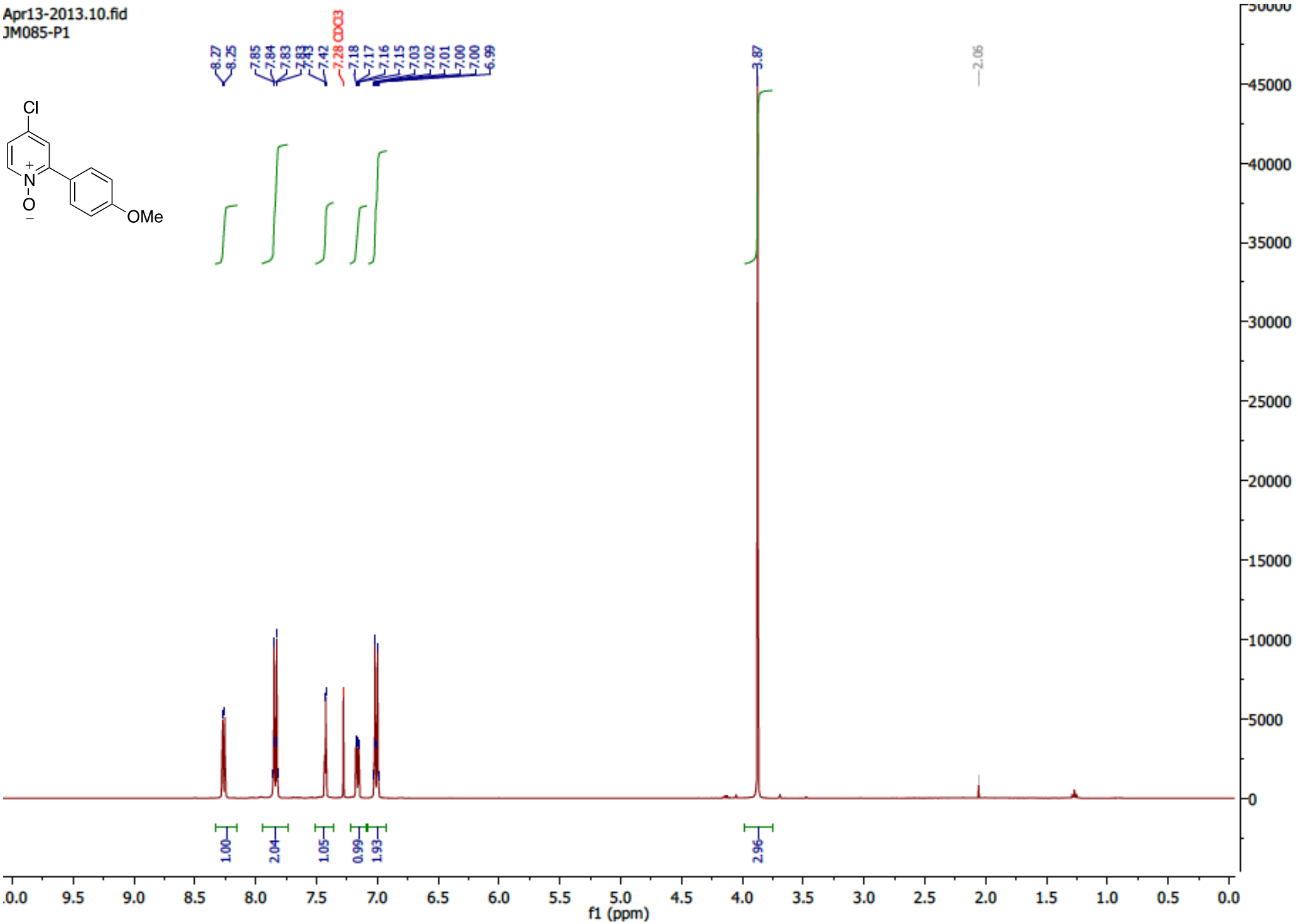
147.04
141.32
133.27
132.16
131.82
129.64
127.23
126.19
124.32
123.93
123.88
121.60

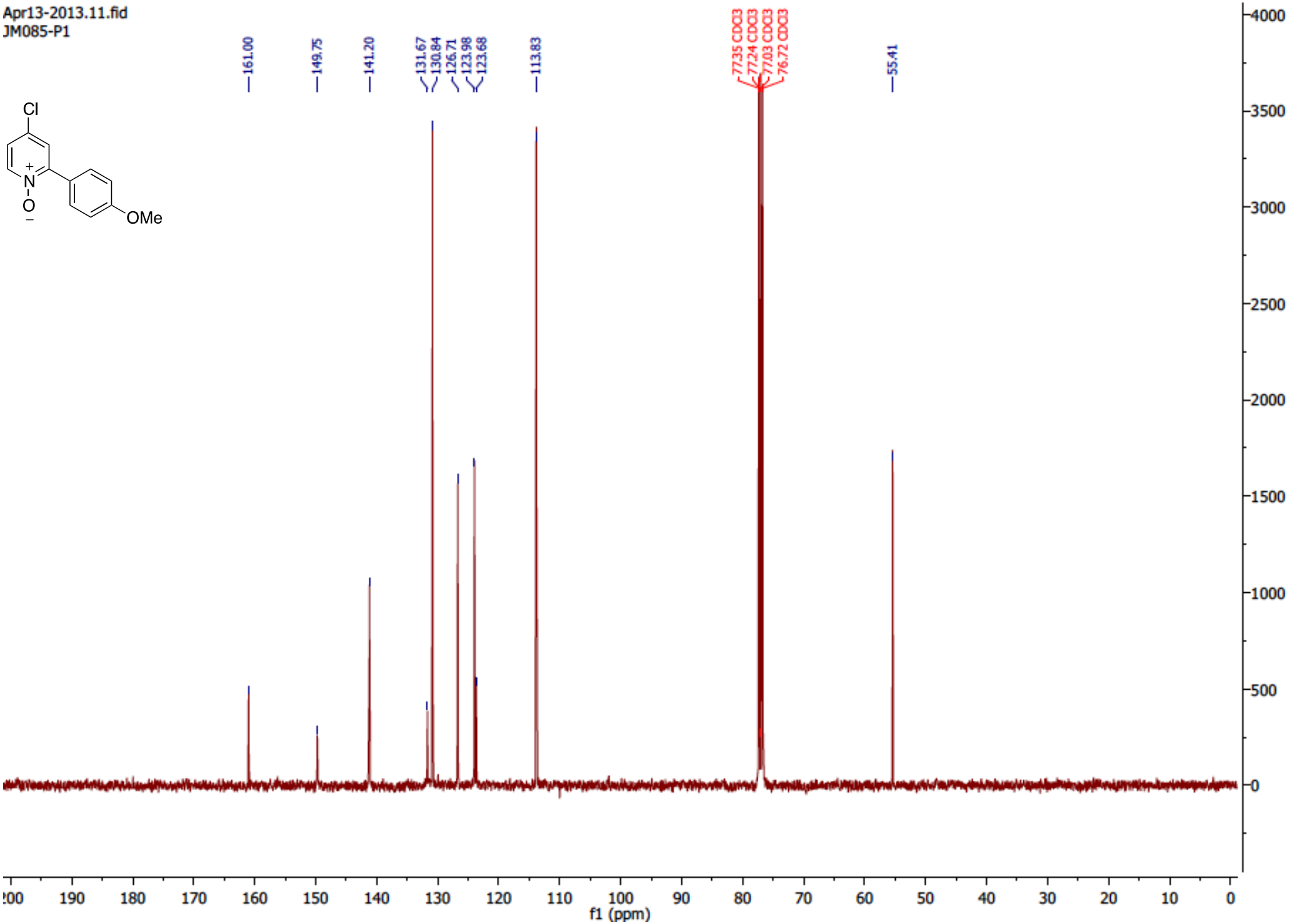
77.32 CDCl3
77.21 CDCl3
77.01 CDCl3
76.69 CDCl3

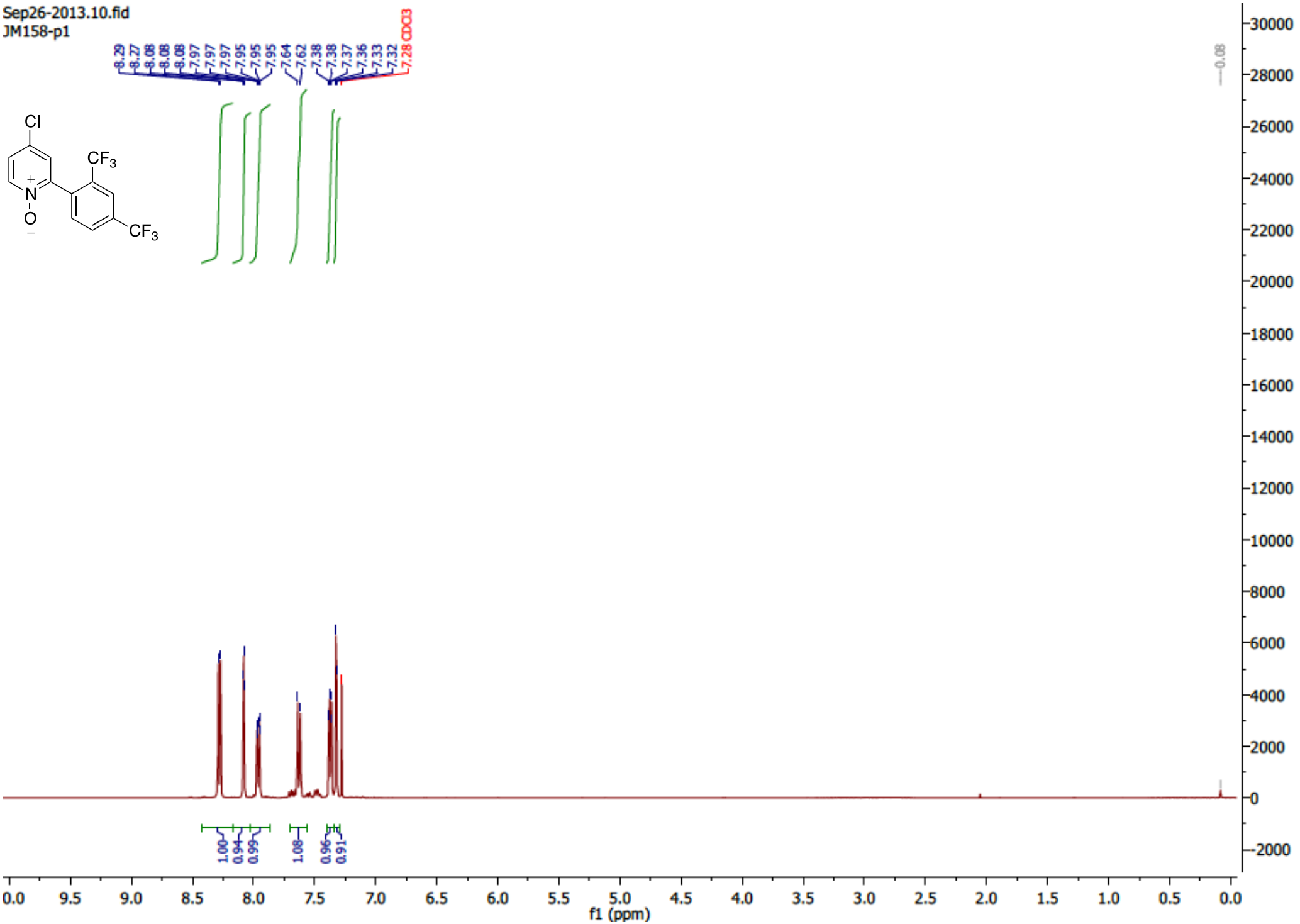
f1 (ppm)

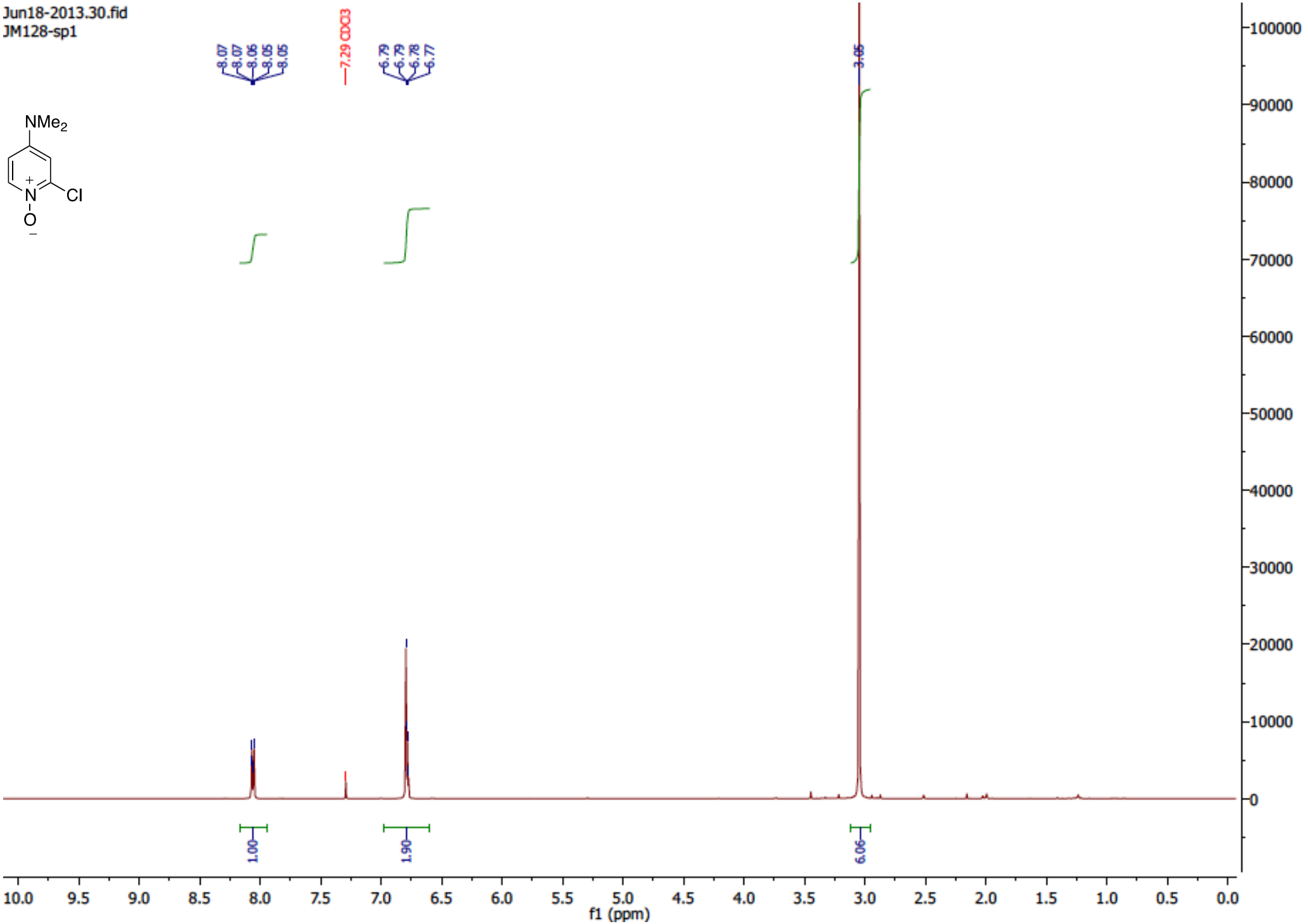

Apr16-2013.70.fid
JM078-P1
Cl
N
O
8.25
8.23
7.72
7.72
7.71
7.41
7.40
7.30
7.30
7.29
7.28
7.28 CDCl3
7.18
7.17
7.16
7.16
2.41
1.00
1.97
0.96
2.02
0.97
3.01
f1 (ppm)

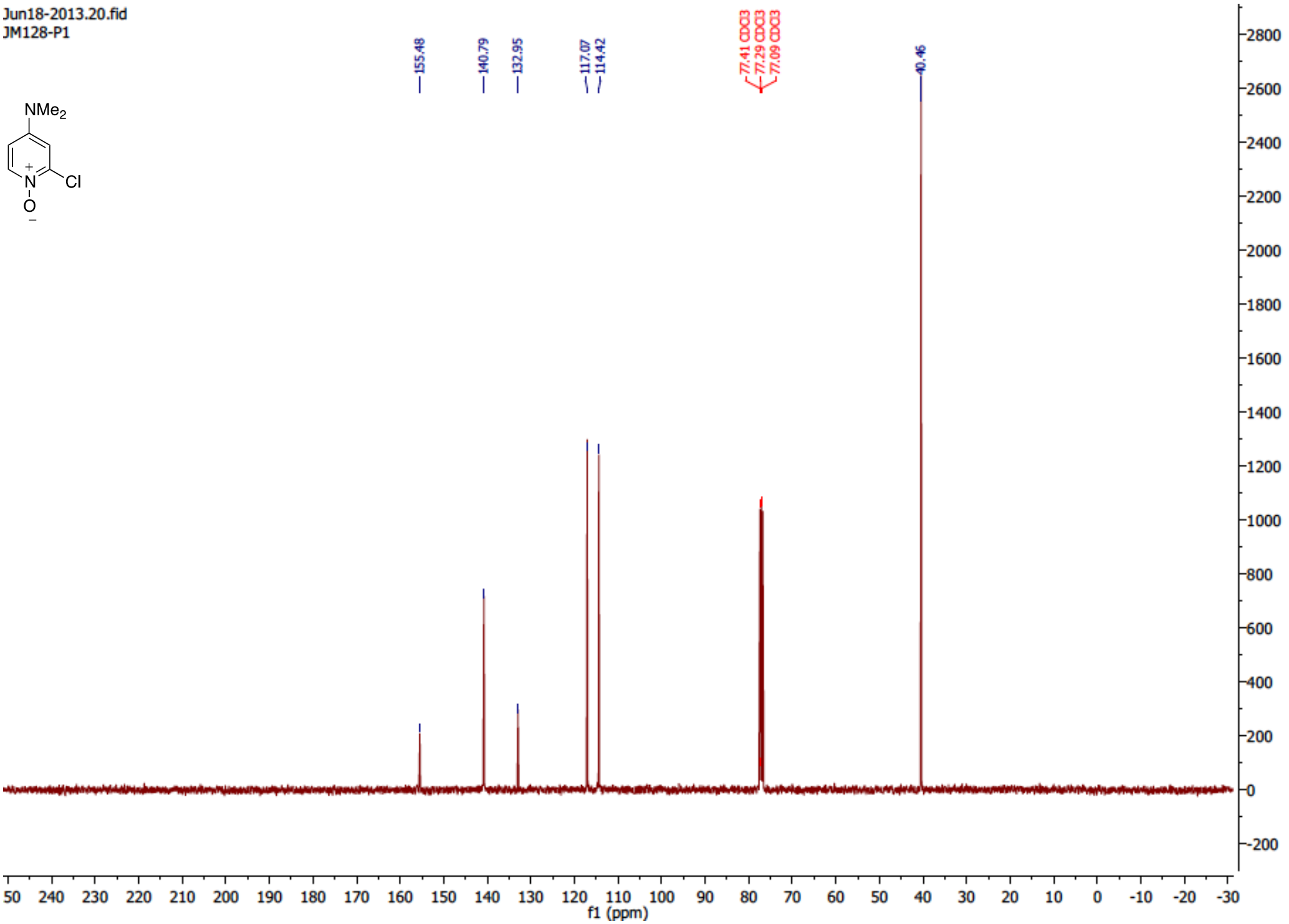

Apr13-2013.100.fid
JM078-P1
Cl
N
O
150.10
141.13
140.45
131.52
129.09
128.61
127.01
124.35
77.42 CDCl3
77.10 CDCl3
21.47
f1 (ppm)

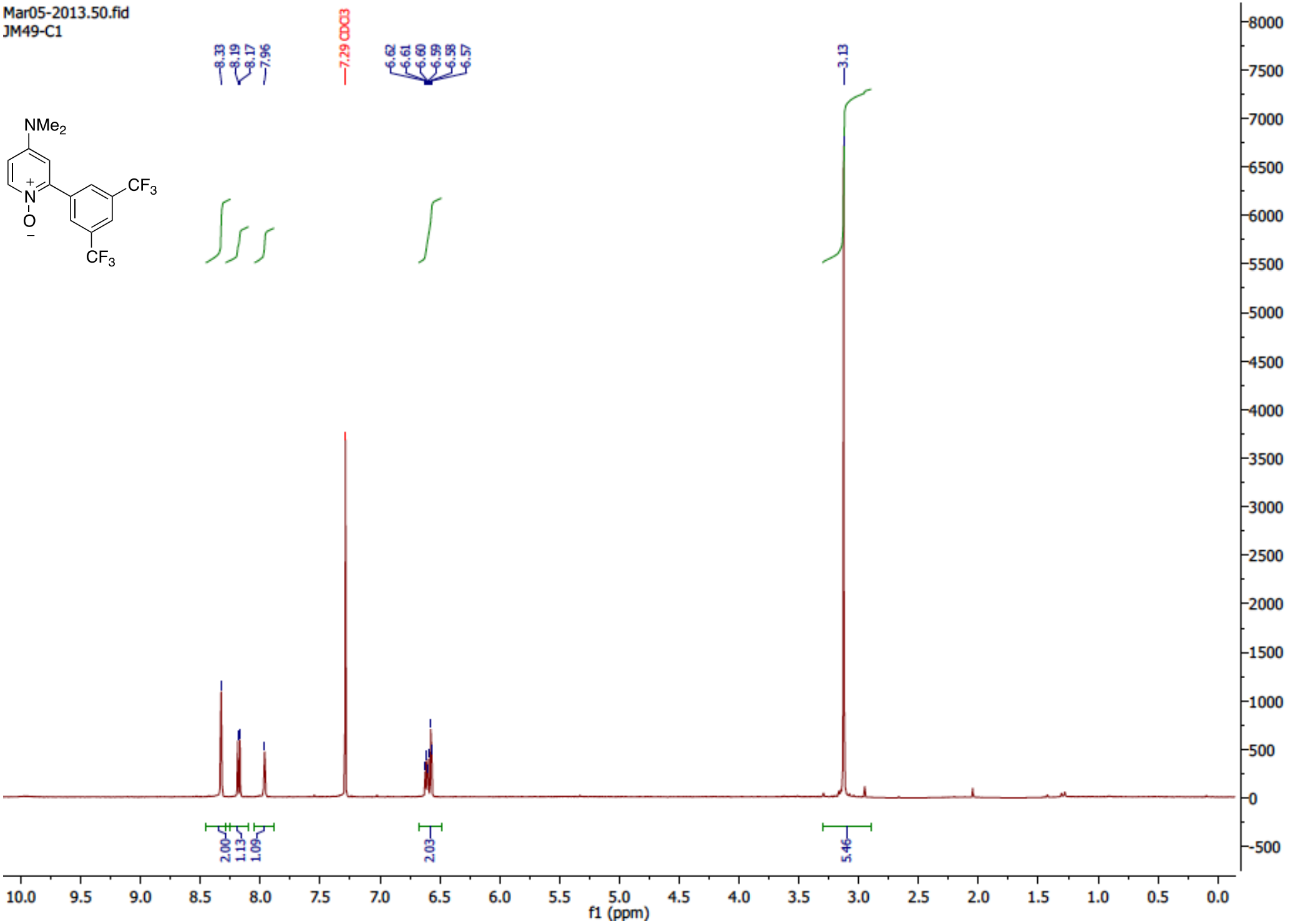

Apr13-2013.10.fid
JM085-P1
Cl
N
O
OMe
8.27
8.25
7.85
7.84
7.83
7.43
7.42
7.28 CDCl3
7.18
7.17
7.16
7.15
7.03
7.02
7.01
7.00
7.00
6.99
3.87
2.06
1.00
2.04
1.05
0.99
1.93
2.96
f1 (ppm)


Apr13-2013.11.fid
JM085-P1
161.00
149.75
141.20
131.67
130.84
126.71
123.98
123.68
113.83
77.35 CDCl3
77.24 CDCl3
77.03 CDCl3
76.72 CDCl3
55.41
Cl
N
O
OMe
4000
3500
3000
2500
2000
1500
1000
500
0
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

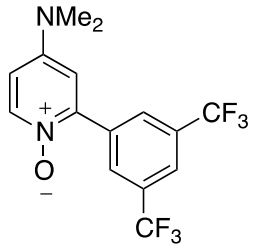

Sep26-2013.10.fid
JM158-p1
8.29
8.27
8.08
8.08
8.08
7.97
7.97
7.97
7.95
7.95
7.95
7.64
7.62
7.38
7.38
7.37
7.36
7.33
7.32
7.28 CDCl3
Cl
CF3
CF3
N
O
1.00
0.94
0.99
1.08
0.96
0.91
f1 (ppm)


Jun18-2013.30.fid
JM128-sp1
8.07
8.07
8.06
8.05
8.05
7.29 CDCl3
6.79
6.79
6.78
6.77
3.05
NMe2
Cl
N
O
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
1.00
1.90
6.06
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Jun18-2013.20.fid
JM128-P1
NMe2
N
Cl
O
155.48
140.79
132.95
117.07
114.42
77.41 CDCl3
77.29 CDCl3
77.09 CDCl3
40.46
f1 (ppm)


Mar05-2013.50.fid
JM49-C1
8.33
8.19
8.17
7.96
7.29 CDCl3
6.62
6.61
6.60
6.59
6.58
6.57
3.13
NMe2
CF3
CF3
2.00
1.13
1.09
2.03
5.46
f1 (ppm)

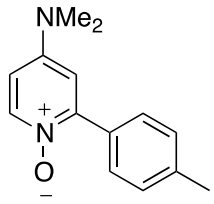
Apr13-2013.40.fid
JM046-P1



148.37
145.82
140.36
135.46
131.66
131.33
129.90
123.09
123.05
123.00
121.80
108.46
77.34 CDCl3
77.22 CDCl3
77.02 CDCl3
39.91

f1 (ppm)

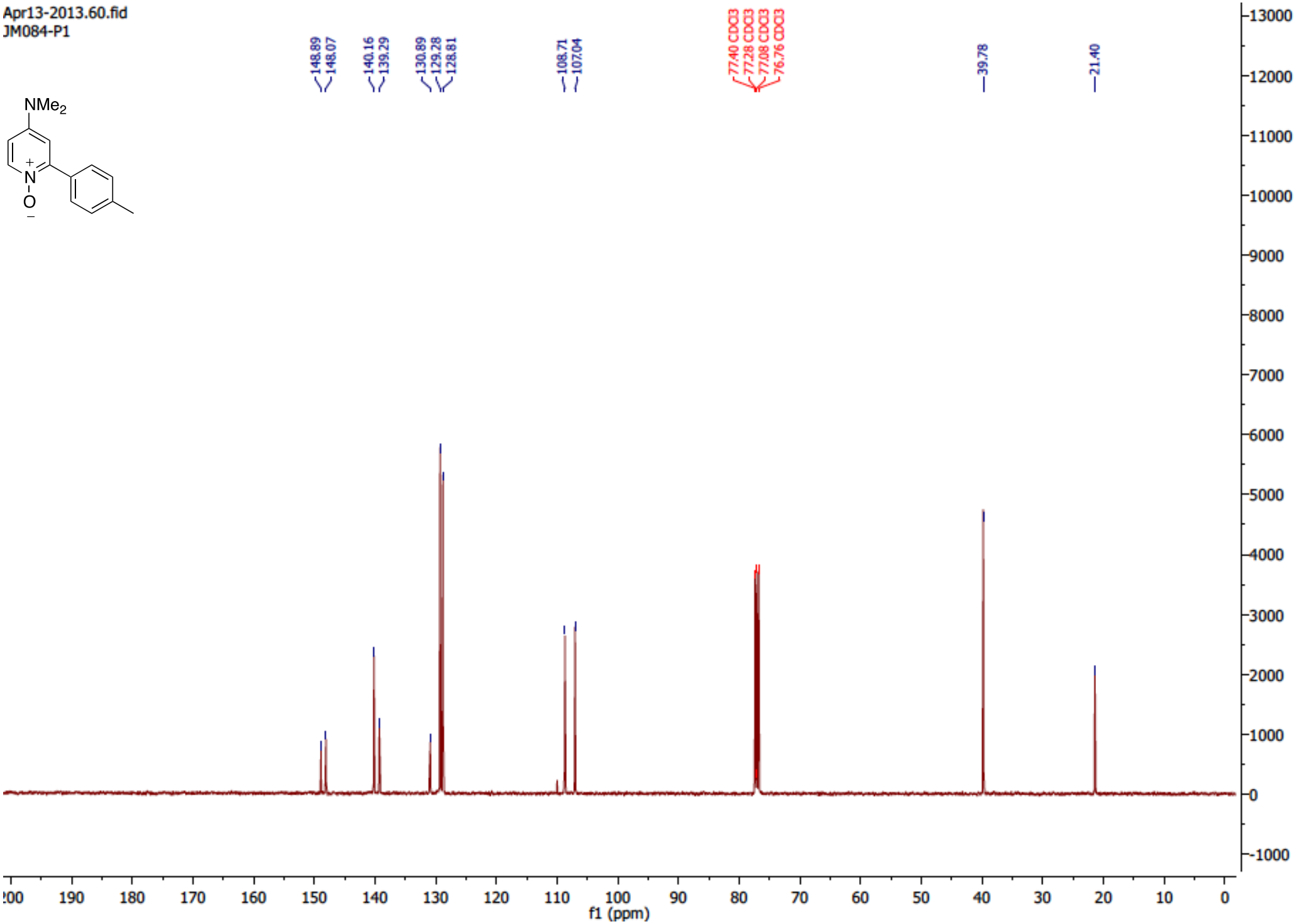
Apr11-2013.10.fid
JM084-p1

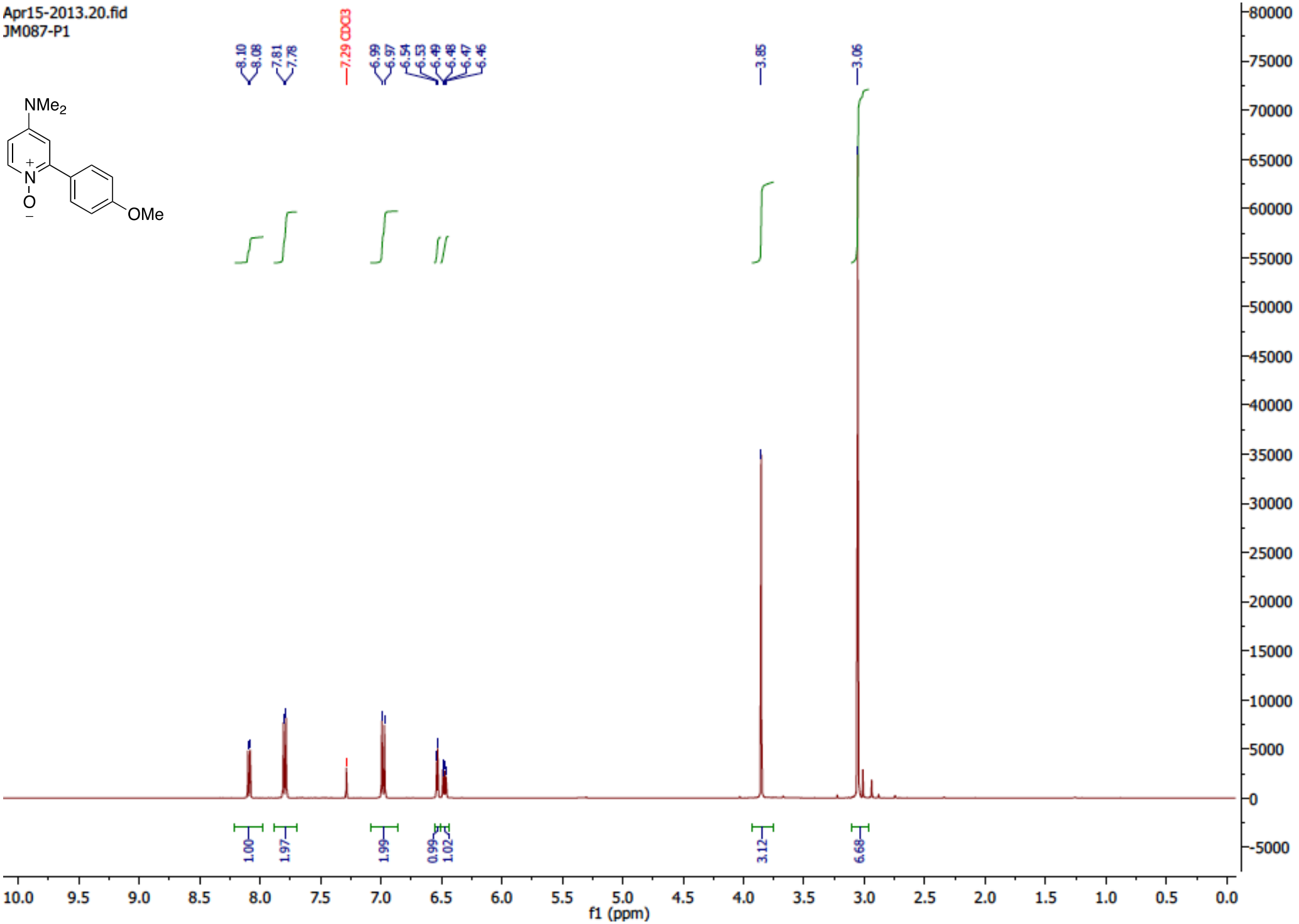


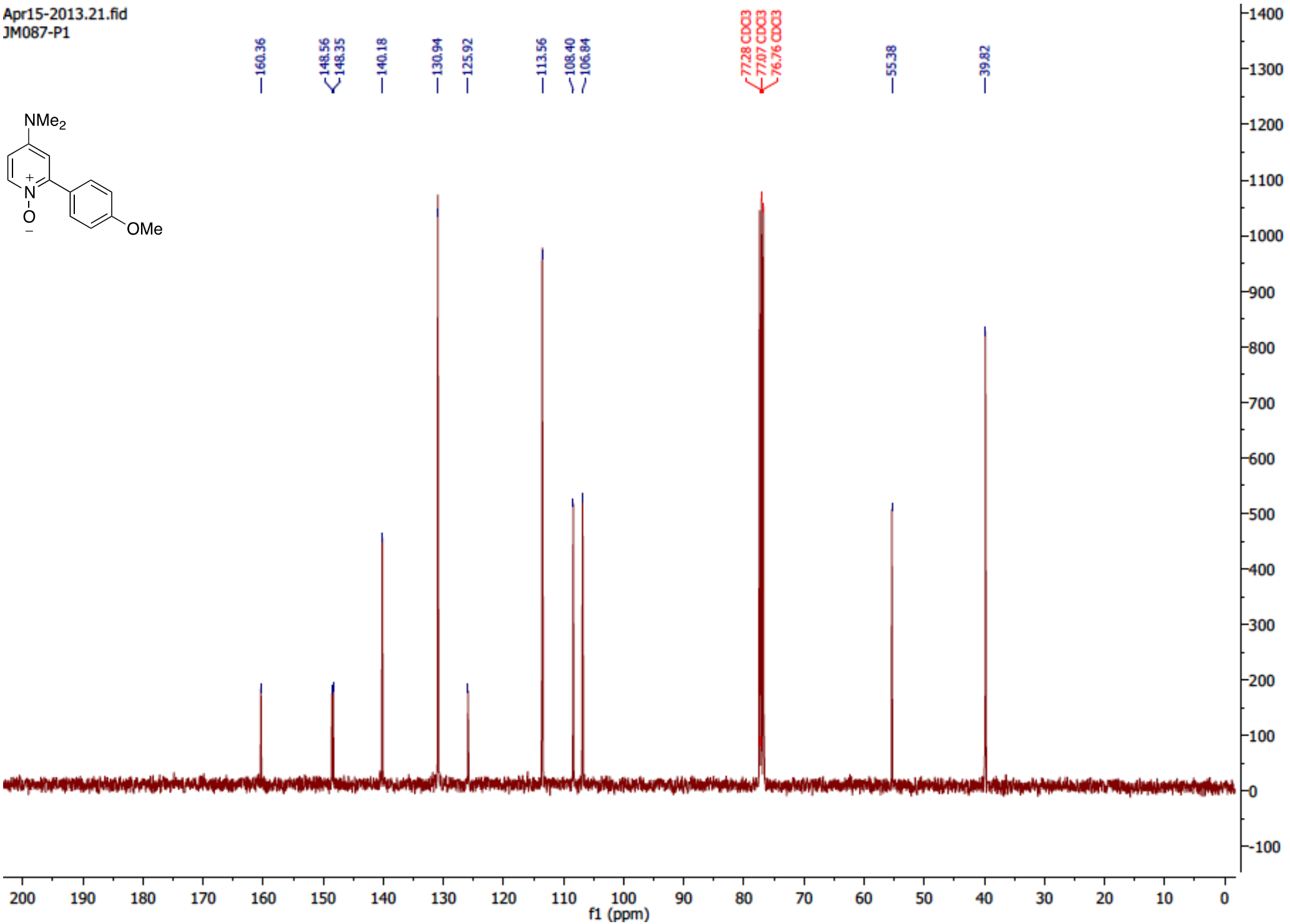
8.13
8.11
7.72
7.70
7.29
7.29
7.29 CDCl3
7.27
6.54
6.51
6.50
6.49
6.48
5.31
3.06
2.41

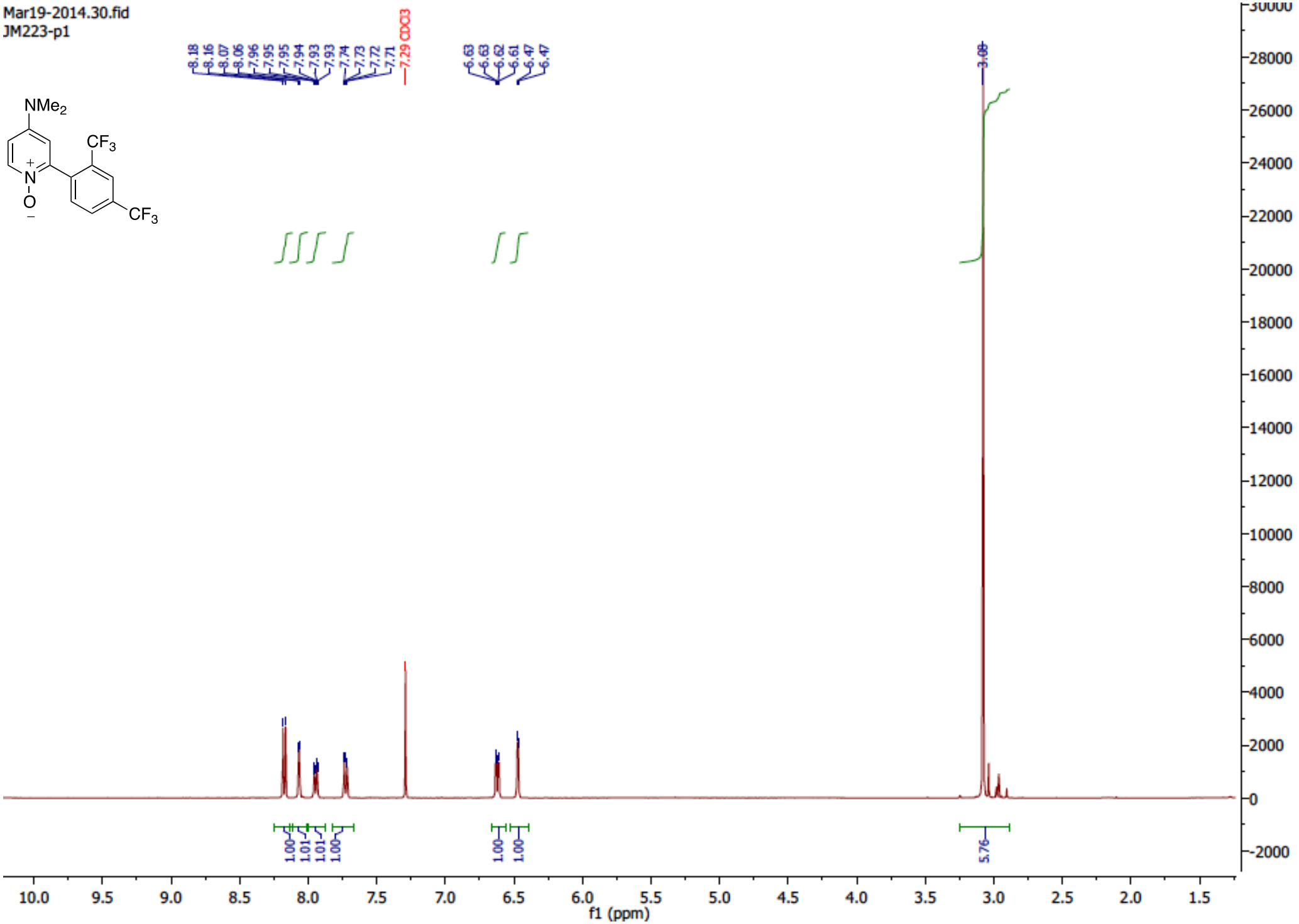
1.01
2.00
2.34
1.01
1.00
5.95
3.14

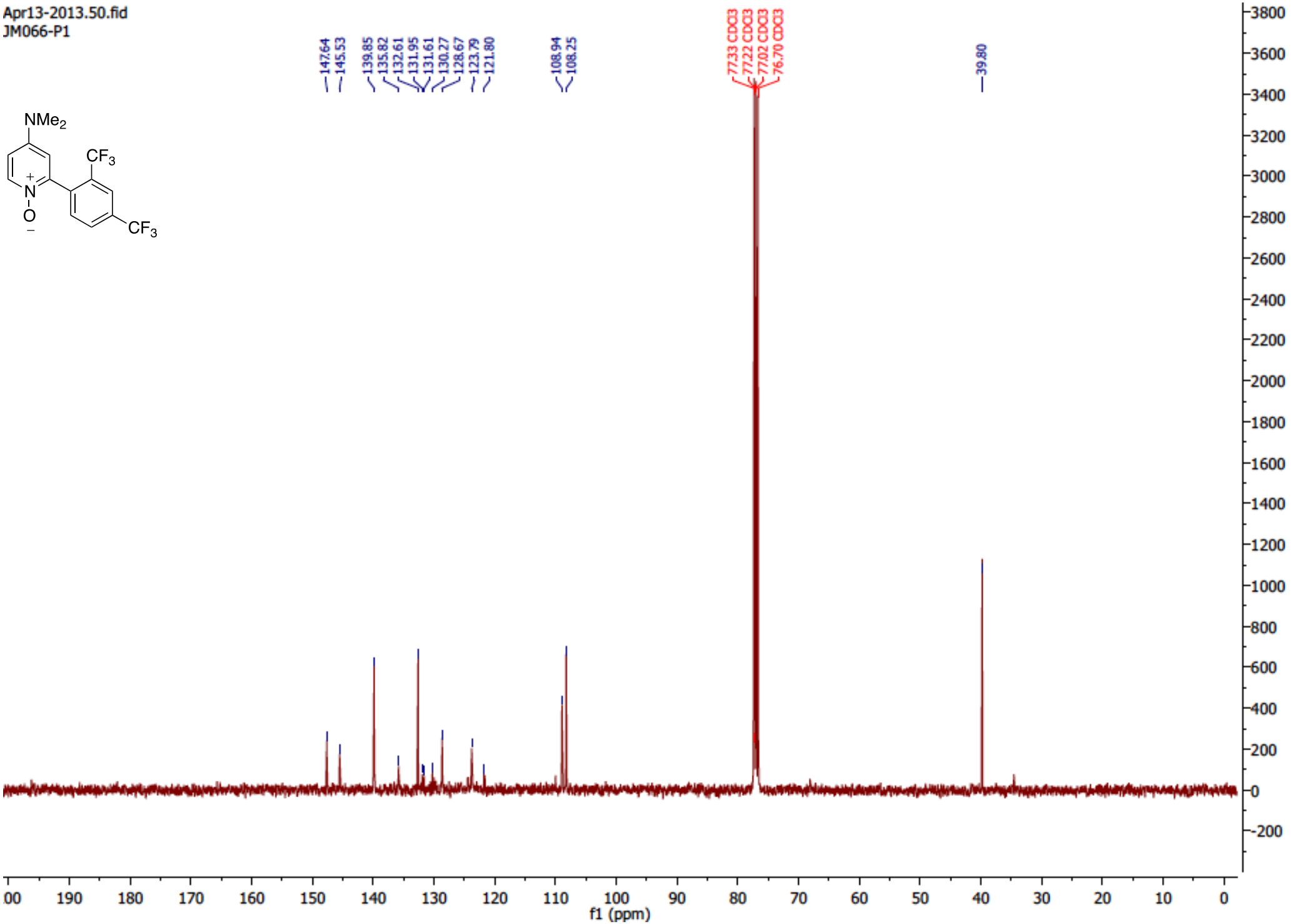
f1 (ppm)


Apr13-2013.60.fid
JM084-P1
NMe2
148.89
148.07
140.16
139.29
130.89
129.28
128.81
108.71
107.04
77.40 CDCl3
77.28 CDCl3
77.08 CDCl3
76.76 CDCl3
39.78
21.40
f1 (ppm)


Apr15-2013.20.fid
JM087-P1
NMe2
N
O
OMe
8.10
8.08
7.81
7.78
7.29 CDCl3
6.99
6.97
6.54
6.53
6.49
6.48
6.47
6.46
3.85
3.06
1.00
1.97
1.99
0.99
1.02
3.12
6.68
f1 (ppm)


Apr15-2013.21.fid
JM087-P1
160.36
148.56
148.35
140.18
130.94
125.92
113.56
108.40
106.84
77.28 CDCl3
77.07 CDCl3
76.76 CDCl3
55.38
39.82
NMe2
N
O
OMe
f1 (ppm)


Mar19-2014.30.fid
JM223-p1
NMe2
CF3
CF3
N
O
8.18
8.16
8.07
8.06
7.96
7.95
7.95
7.94
7.93
7.93
7.74
7.73
7.72
7.71
7.29 CDCl3
6.63
6.63
6.62
6.61
6.47
6.47
3.08
1.00
1.01
1.01
1.00
1.00
1.00
5.76
f1 (ppm)


Apr13-2013.50.fid
JM066-P1
147.64
145.53
139.85
135.82
132.61
131.95
131.61
130.27
128.67
123.79
121.80
108.94
108.25
77.33 CDCl3
77.22 CDCl3
77.02 CDCl3
76.70 CDCl3
39.80
NMe2
CF3
CF3
N
O
f1 (ppm)