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A simply and novel synthesis of 3-(thio)phosphoryl-β-lactams by radical cyclization

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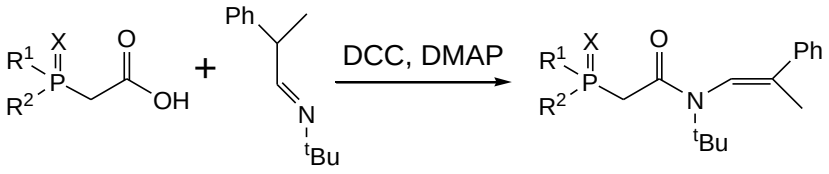
1. General Information

Reagents were purchased from Sigma-Aldrich. Toluene were distilled from potassium under argon. Analytical TLC was performed on aluminum sheets of silica gel UV-254 Merck. Flash chromatography was performed using 40-63 microns of Zeochem silica gel. The ^{1}H, ^{13}C were recorded on Varian Gemini 200 and Varian Unity Plus 500, chemical shifts (δ) in ppm rel. to internal Me_4Si; coupling constants J in Hz. High-resolution (HRMS) was recorded on *MicroMas Quattro LCT* mass spectrometer. Melting points were determined with *Warsztat Elektromechaniczny W-wa* apparatus and are not corrected.

2. General procedure for synthesis of phosphonoacetatenamides (3)



2 **3**

A solution of phosphonoacetic acid (**2**) (1 mmol) and tert-Butyl-(2-phenyl-propylidene)-amine (1 mmol, 0.189 g) in DMF 5 mL was stirred and cooled to 0°C. DCC (1 mmol, 0.206g) and DMAP (1mmol, 0.122g) was added. The reaction mixture was stirred for 3 days. DMF was removed under reduced pressure. Residue was dissolved in EtOAc 30 mL and DCU was filtered off. Organic layer was washed with 1 M HCl (10 mL), sat. aq $NaHCO_3$ (10 mL) and dried ($MgSO_4$). The residue was a subject to purification as specified below.

{[tert-Butyl-(2-phenyl-propenyl)-carbamoyl]-methyl}-phosphonic acid diethyl ester (3a)
Purification by flash column chromatography, (AcOEt/Hex, 1:2), ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.25-1.33 (m, 6 H), 1.45 (s, 9 H), 2.02 (s, 3 H), 2.87 (dd, 1 H, J = 22.7 Hz, J = 22.3 Hz), 3.25 (dd, 1 H, J = 22.3 Hz, J = 21.1 Hz), 4.07-4.18 (m, 4 H), 6.48 (s, 1 H), 7.32-7.45 (m, 5 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.1, 16.7 (d, J = 2.9 Hz), 16.8 (d, J = 2.9 Hz), 28.9, 36.4 (d, J = 133.8 Hz), 59.8, 62.6 (d, J = 6.3 Hz), 62.8 (d, J = 6.4 Hz), 126.5, 127.8, 128.6, 129.0, 139.1, 140.1, 165.7 (d, J = 5.2 Hz).

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N-tert-Butyl-2-(5,5-dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl)-N-(2-phenyl-propenyl)-acetamide (3b)

Purification by flash column chromatography, (AcOEt/Hex, 4:1), ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.02 (s, 3 H), 1.13 (s, 3 H), 1.46 (s, 9 H), 2.04 (d, 3 H, *J* = 1.4 Hz), 2.95 (dd, *J* = 21.7 Hz, *J* = 21.7 Hz), 3.34 (dd, *J* = 21.7 Hz, *J* = 21.7 Hz), 4.05-4.18 (m, 4 H), 6.48 (s, 1 H), 7.31-7.49 (m, 5 H).

{[tert-Butyl-(2-phenyl-propenyl)-carbamoyl]-methyl}-phenyl-phosphinic acid methyl ester (mixture of Z/E isomers) (3c)

Purification by flash column chromatography, (AcOEt/Hex, 1:1), ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.31 (s, 5 H), 1.41 (s, 4 H), 1.94 (d, 1.4 H, *J* = 1.4 Hz), 1.98 (d, 1.6 H, *J* = 1.4 Hz), 2.93-3.04 (m, 1 H), 3.37-3.50 (m, 1 H), 3.70 (d, 1.4 H, *J* = 11.2 Hz), 3.74 (d, 1.6 H, *J* = 11.2 Hz), 5.92 (s, 0.55 H), 6.41 (s, 0.45 H), 7.31-7.41 (m, 4 H), 7.41-7.46 (m, 3 H), 7.51-7.56 (m, 1 H), 7.77-7.81 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.0 (min), 16.1 (maj), 28.7 (maj), 28.8 (min), 39.6 (d, *J* = 89.4 Hz, maj), 40.4 (d, *J* = 91.1 Hz, min), 52.0 (d, *J* = 4.4 Hz, maj), 52.1 (d, *J* = 4.3 Hz, min), 59.8 (maj), 59.9 (min), 126.4 (maj), 126.5 (min), 127.5 (maj), 127.8 (min), 128.6 (min), 128.8 (maj), 129.0 (maj), 129.1 (min),132.2, 132.4 (maj), 132.6 (min), 132.8 (maj), 132.9 (min), 133.0 (maj), 133.1 (min), 139.0 (maj), 139.1 (min), 139.8 (maj), 140.0 (min), 165.6 (d, *J* = 5.4 Hz).

N-tert-Butyl-2-(dibutyl-phosphinoyl)-N-(2-phenyl-propenyl)-acetamide (3e)

Purification by flash column chromatography, (AcOEt/Hex, 2:3), ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.90 (t, 6 H, J = 6.96 Hz), 1.25-1.41 (m, 4 H), 1.51-1.63 (m, 4 H), 1.71-1.82 (m, 4 H), 2.08 (s, 3 H), 4.36-4.50 (m, 2 H), 6.25 (s, 1 H), 7.33-7.40 (m, 5 H).

3. **Synthesis of {[tert-Butyl-(2-phenyl-propenyl)-carbamoyl]-methyl}-phosphonothioic acid O,O-diethyl ester** (**3f)**

A solution of (diethoxy-thiophosphoryl)-acetic acid (**2f**) (1 mmol, 0.212g) and tert-Butyl-(2-phenyl-propylidene)-amine (1 mmol, 0.189 g) in DMF 5 mL was stirred and cooled to 0°C. DCC (1 mmol, 0.206g) and DMAP (1mmol, 0.122g) was added. The reaction mixture was stirred for 3 days. DMF was removed under reduced pressure. Residue was dissolved in EtOAc 30 mL and DCU was filtered off. Organic layer was washed with 1 M HCl (10 mL), sat. aq $NaHCO_3$ (10 mL) and dried ($MgSO_4$). The residue was a subject to purification by flash column chromatography, (AcOEt/Hex, 1:8) ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.27 (t, 3 H,

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J = 6.8 Hz), 1.31 (t, 3 H, *J* = 6.8 Hz), 1.47 (s, 9 H), 2.02 (d, 3 H, *J* = 1 Hz), 2.99 (dd, 1 H, *J* = 21.9 Hz, *J* = 21.9 Hz), 3.53 (dd, 1 H, *J* = 17.1 Hz, *J* = 17.6 Hz), 4.06-4.22 (m, 4 H), 6.55 (s, 1 H), 7.31-7.39 (m, 3 H), 7.45-7.47 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.2, 16.5 (d, *J* = 6.6 Hz), 16.7 (d, *J* = 6.5 Hz), 28.9, 44.1 (d, *J* = 103.3 Hz), 59.9, 62.9 (d, *J* = 6.4 Hz), 63.8 (d, *J* = 6.5 Hz), 126.6, 128.2, 128.6, 129.0, 138.7, 140.2, 165.6. ^{31}P NMR (200 MHz, $CDCl_3$): δ 88.5.

4. General procedure for synthesis of 3-phosphoryl β-lactams and 3-thiophosphoryl β-lactams (4)

To a stirred mixture of **3** (1 mmol) in acetic acid (10 mL) at reflux, was added $Mn(OAc)_3$*$2H_2O$ (2 mmol, 0.535 g). After 10 min., reaction mixture was cooled and poured into 50mL of ice water, and extracted with CH_2Cl_2 (5x20 mL). Organic layer was washed with aqueous 5 % $NaHCO_3$ (3x10mL), dried with $MgSO_4$ and concentrated. The residue was a subject to purification as specified below.

1-tert-butyl-2-oxo-4-(1-phenylvinyl)azetidin-3-ylphosphonate (**4a**)

Purification by flash column chromatography, (AcOEt/Hex, 1:1), yield 50%. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 1.24 (3 H, t, *J* = 6.9 Hz), 1.30 (3 H, t, *J* = 6.9 Hz), 1.38 (9 H, s), 3.23 (1 H, dd, J^{PH} = 13.9 Hz, J^{HH} = 2.4 Hz), 4.04-4.23 (4 H, m), 4.66 (1 H, dd, J^{PH} = 9.2 Hz, J^{HH} = 2.4 Hz), 5.51 (1 H, s), 5.59 (1 H, s), 7.33-7.49 (5 H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 16.7 (d, J^2 = 3.1 Hz), 16.8 (d, J^2 = 3.2 Hz), 28.3, 54.2 (d, J^1 = 29.3 Hz), 55.8 (d, J^2 = 2.2 Hz), 56.7, 62.8 (d, J^2 = 6.5 Hz), 63.2 (d, J^2 = 6.1 Hz), 115.8, 127.1, 128.7, 129.0, 139.2, 148.3 (d, J^3 = 2.8 Hz), 162.6 (d, J^2 = 6.3 Hz). HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{19}H_{28}NO_4PNa$: 388.1654; found: 388.1665

3-(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-2-yl)-1-tert-butyl-4-(1-phenylvinyl)azetidin-2-one (**4b**)

Purification by flash column chromatography, (CH_2Cl_2/MeOH, 30:1), yield 70%. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.97 (3 H, s), 1.20 (3 H, s), 1.36 (9 H, s), 3.40 (1 H, dd, J^{PH} = 13.6 Hz, J^{HH} = 2.4 Hz), 3.94-4.08 (2 H, m), 4.15 (1 H, dd, J^{PH} = 6.8 Hz, J^{HH} = 10.7 Hz), 4.36 (1 H, dd, J^{PH} = 6.8 Hz, J^{HH} = 10.7 Hz), 4.70 (1 H, dd, J^{PH} = 9.8 Hz, J^{HH} = 2.4 Hz), 5.56 (1 H, s), 5.61 (1 H, s), 7.30-7.38 (3 H, m), 7.53-7.55 (2 H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 21.1, 22.1, 28.0, 32.9, 53.9 (d, *J* = 39.5 Hz), 55.4 (d, *J* = 54.0 Hz), 76.1 (d, J^2 = 6.6 Hz),

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77.8 (d, J^2 = 7.0 Hz), 115.7, 126.8, 128.5, 128.8, 138.7, 147.7, 162.5. HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{20}H_{28}NO_4PNa$: 400.1654; found: 400.1666.

methyl 1-tert-butyl-2-oxo-4-(1-phenylvinyl)azetidin-3-yl(phenyl)phosphinate (1:1 mixture of diastereoisomers) (4c)

Purification by flash column chromatography, (AcOEt/Hex, 2:1), yield 34%. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 1.04 (4.5 H, s), 1.34 (4.5 H, s), 3.37 (0.5 H, dd, J^{PH} = 7.0 Hz, J^{HH} = 2.5 Hz), 3.53 (0.5 H, dd, J^{PH} = 14.9 Hz, J^{HH} = 2.4 Hz), 3.69 (1.5 H, d, J^{PH} = 11.2 Hz), 3.74 (1.5 H, d, J^{PH} = 11.3 Hz), 4.45 (0.5 H, dd, J^{PH} = 9.1 Hz, J^{HH} = 2.4 Hz), 4.72 (0.5 H, dd, J^{PH} = 8.8 Hz, J^{HH} = 2.5 Hz), 5.42 (0.5 H, s), 5.51 (1 H, s), 5.56 (0.5 H, s), 7.24-7.59 (8 H, m), 7.81-7.93 (3 H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 28.09, 28.31, 52.1 (d, *J* = 6.6 Hz), 52.4 (d, *J* = 6.2 Hz), 54.0 (d, *J* = 11.0 Hz), 55.6, 55.7 (d, *J* = 13.8 Hz), 57.2 (d, *J* = 4.7 Hz), 59.0 (d, *J* = 4.3 Hz) 77.3, 77.7, 116.1, 116.2, 127.0, 128.4 (d, *J* = 47.0 Hz), 128.6, 128.7, 129.0 (d, *J* = 5.7 Hz), 129.2 (d, *J* = 5.1 Hz), 132.4, 132.6, 133.3, 133.4, 133.5, 133.6, 139.0, 139.4, 148.0 (d, *J* = 2.6 Hz), 148.2 (d, *J* = 2.6 Hz), 162.6, 162.9. HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{22}H_{26}NO_3PNa$: 406.1548; found: 406.1552.

O,O-diethyl 1-tert-butyl-2-oxo-4-(1-phenylvinyl)azetidin-3-ylphosphonothioate (4f)

Purification by flash column chromatography, (EtOAc/hexanes, 1:8), yield 15%. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 1.16 (3 H, t, *J* = 6.8 Hz), 1.29 (3 H, t, *J* = 6.9 Hz), 1.38 (9 H, s), 3.39 (1 H, dd, J^{PH} = 13.8 Hz, J^{HH} = 2.5 Hz), 3.97-4.26 (4 H, m), 4.68 (1 H, dd, J^{PH} = 10.9 Hz, J^{HH} = 2.5 Hz), 5.50 (1 H, s), 5.58 (1 H, s), 7.26-7.44 (5 H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 16.4 (d, J^2 = 7.3 Hz), 16.6 (d, J^2 = 5.9 Hz), 28.5, 55.5, 55.8 (d, J^2 = 2.2 Hz), 61.2 (d, J^1 = 110.5 Hz), 62.9 (d, J^2 = 6.8 Hz), 64.1 (d, J^2 = 6.1 Hz), 116.1, 127.2, 128.6, 129.0, 139.3, 148.2 (d, J^3 = 2.8 Hz), 162.4. ^{31}P NMR (200 MHz, $CDCl_3$): δ 87.6. HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{19}H_{28}NO_3PSNa$: 404.1425; found: 404.1428.

1-[3-(diethoxyphosphorothioyl)-1-tert-butyl-4-oxoazetidin-2-yl]-1-phenylethyl acetate (1:2 mixture of diastereoisomers) (5f)

Purification by flash column chromatography, (EtOAc/hexanes, 1:8), yield 15%. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 0.94 (2 H, t, *J* = 7.0 Hz), 1.21 (2 H, t, *J* = 7.1 Hz), 1.26-1.34 (2 H, m), 1.35 (3 H, s), 1.51 (6 H, s), 1.93 (2 H, s), 1.99 (1 H, s), 2.05 (1 H, s), 2.07 (2 H, s), 3.00 (0.66 H, dd, J^{PH} = 16.2 Hz, J^{HH} = 2.2 Hz), 3.14 (0.33 H, dd, J^{PH} = 14.2 Hz, J^{HH} = 2.2 Hz),

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3.38-3.74 (1.33 H, m), 3.99-4.30 (3.66 H, m), 7.28-7.35 (5 H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 16.1 (d, J^2 = 6.5 Hz), 16.2 (d, J^2 = 7.0 Hz), 16.3 (d, J^2 = 7.8 Hz), 16.4 (d, J^2 = 7.3 Hz), 17.27, 20.8 (min), 22.4 (d, J = 6.6 Hz, maj), 28.9, 54.7 (d, J^1 = 112.7 Hz, maj), 55.2 (d, J^1 = 135.5 Hz, min), 55.8 (d, J^2 = 6.8 Hz, min), 61.8 (maj), 62.1 (d, J^2 = 7.5 Hz, maj), 62.7 (d, J^2 = 6.6 Hz, min), 64.2 (d, J^2 = 6.1 Hz, min), 64.4 (d, J^2 = 6.1 Hz, maj), 83.2 (d, J^3 = 4.3 Hz, min), 84.0 (d, J^3 = 4.8 Hz, maj), 125.4 (maj), 126.6 (min), 128.2 (maj), 128.4 (min), 128.5 (min), 128.9 (maj), 139.3 (min), 140.8 (maj), 161.7 (d, J^2 = 3.5 Hz, maj), 162.0 (d, J^2 = 3.3 Hz, min), 168.5 (maj), 168.8 (min). ^{31}P NMR (200 MHz, $CDCl_3$): δ 89.4, 89.3. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{21}H_{32}NO_5PSNa$: 464.1637; found: 464.1616.

5. (1-tert-Butyl-7-methylene-2-oxo-1,2,7,7a-tetrahydro-indeno[2,1-b]azet-2a-yl)-phosphonic acid diethyl ester (6a)

To a stirred mixture of 1-tert-butyl-2-oxo-4-(1-phenylvinyl)azetidin-3-ylphosphonate (**3a)** (0.5 mmol, 0.182 g) in acetic acid (10 mL) at reflux, was added $Mn(OAc)_3$*$2H_2O$ (1 mmol, 0.267 g). After 1 h aditional portion of $Mn(OAc)_3$*$2H_2O$ (1 mmol, 0.267 g) was added. Reaction mixture was cooled and poured into 50mL of ice water, and extracted with CH_2Cl_2 (5x20 mL). Organic layer was washed with aqueous 5 % $NaHCO_3$ (3x10mL), dried with $MgSO_4$ and concentrated. The residue was a subject to purification as specified below. Purification by flash column chromatography, (EtOAc/hexanes, 1:2), gave 0.023g of **5a**; yield 13%. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 1.27 (6 H, dt, J^{PH} = 2.5 Hz, J^{HH} = 7.3 Hz), 1.37 (9 H, s), 4.11-4.19 (4 H, m), 4.86 (1 H, d, J^{PH} = 6.3 Hz), 5.47 (1 H, s), 5.86 (1 H, s), 7.31-7.36 (2 H, m), 7.52-7.54 (1 H, m), 7.66-7.69 (1 H, m). HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{19}H_{26}NO_4P$: 386.1496; found: 386.1527.

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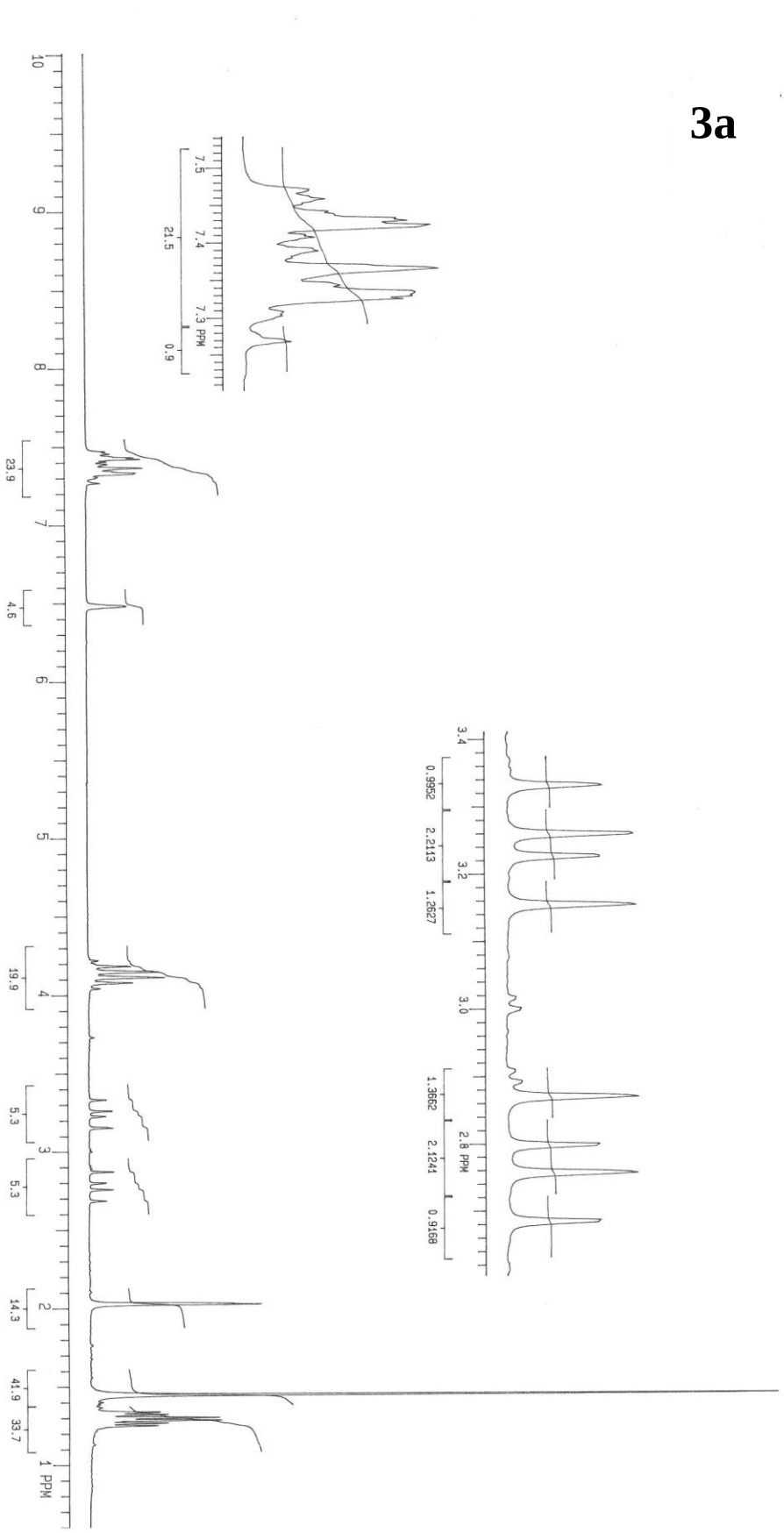

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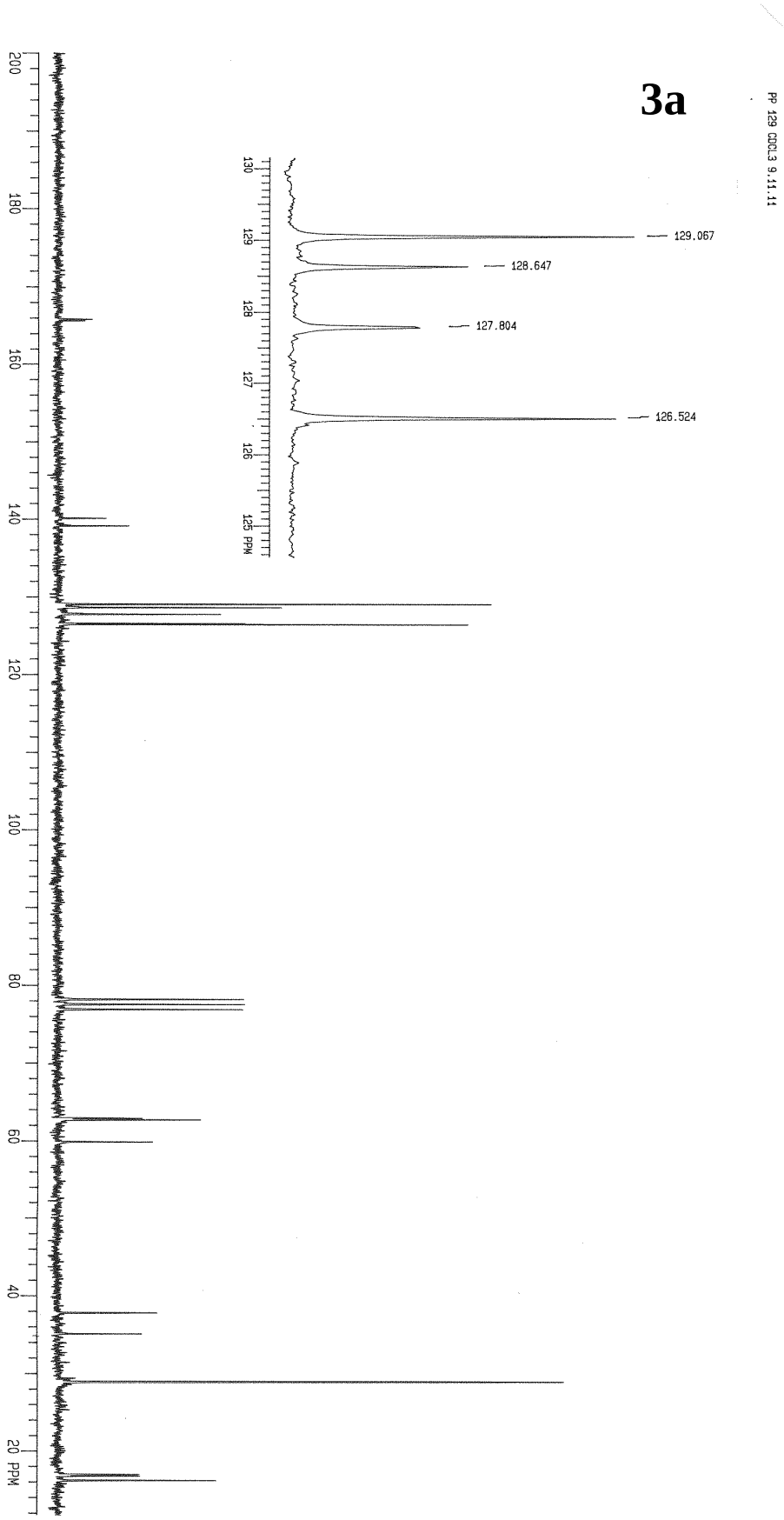

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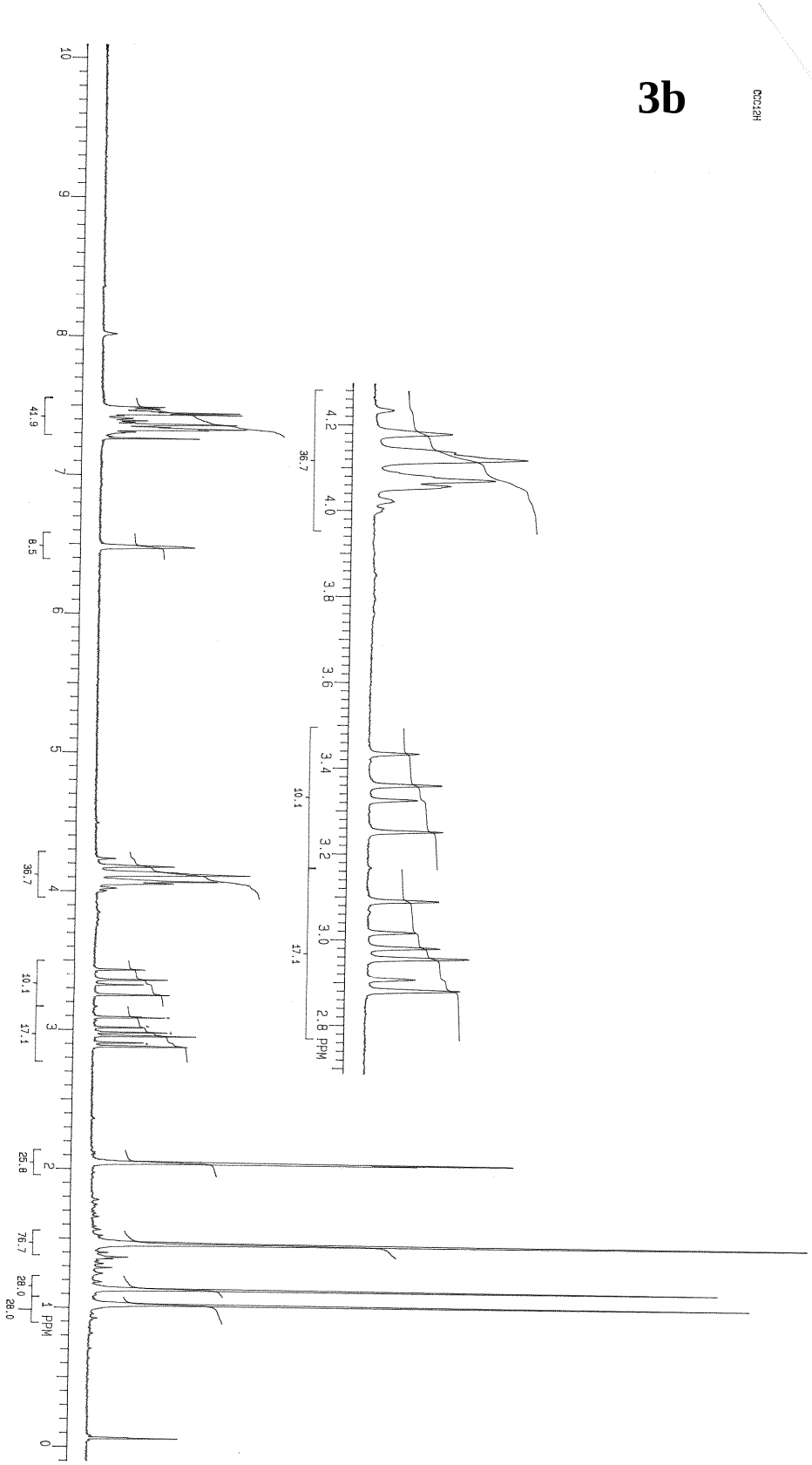

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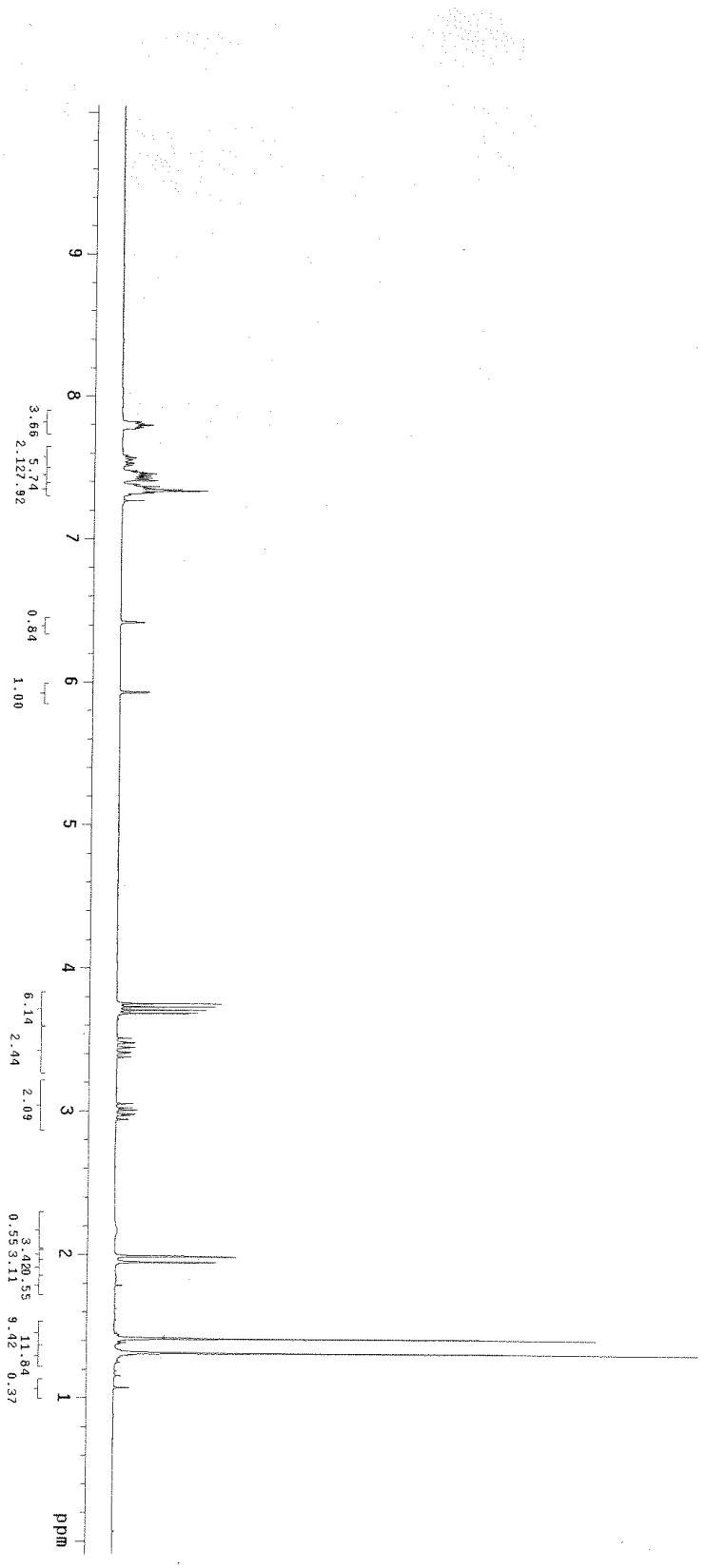

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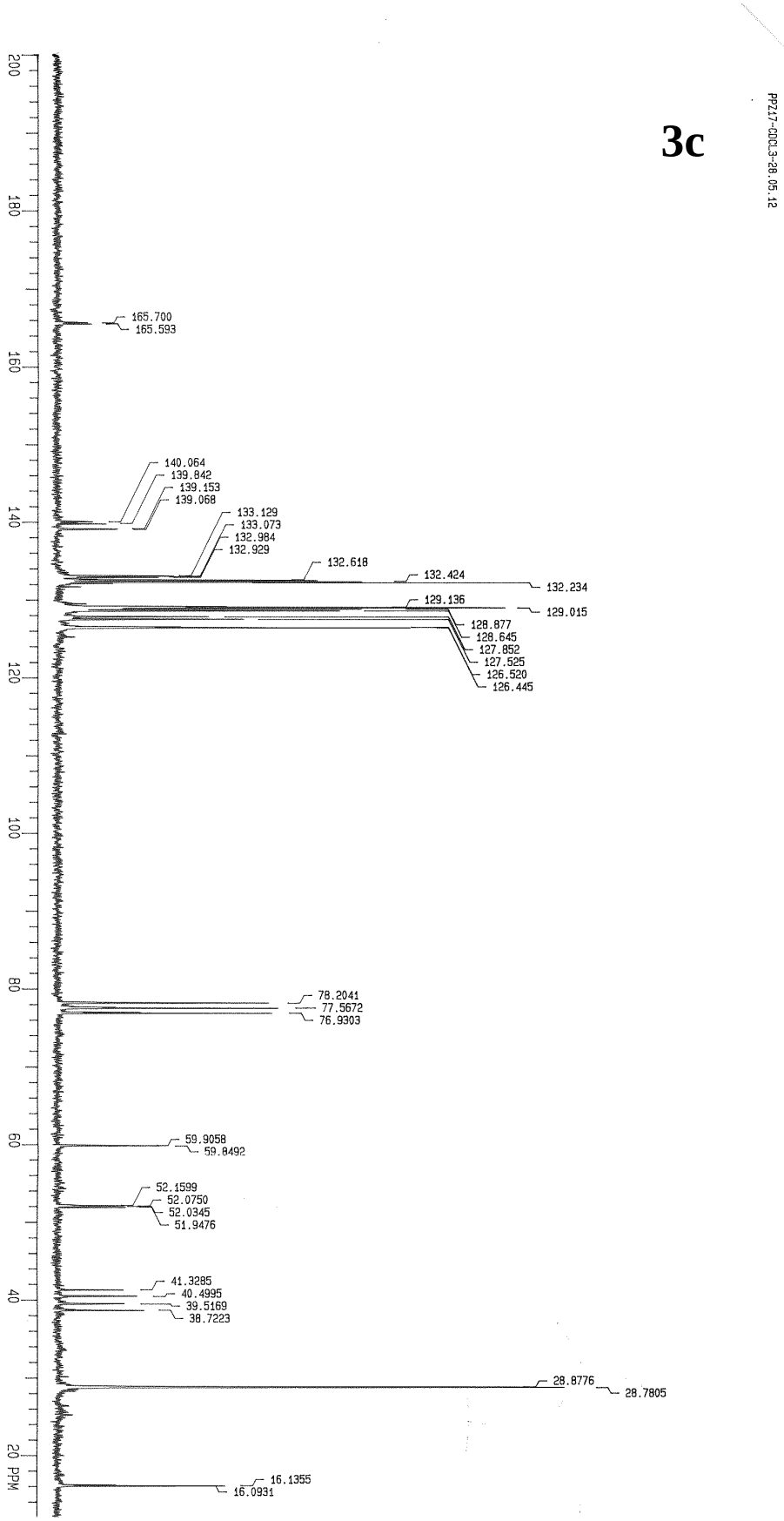

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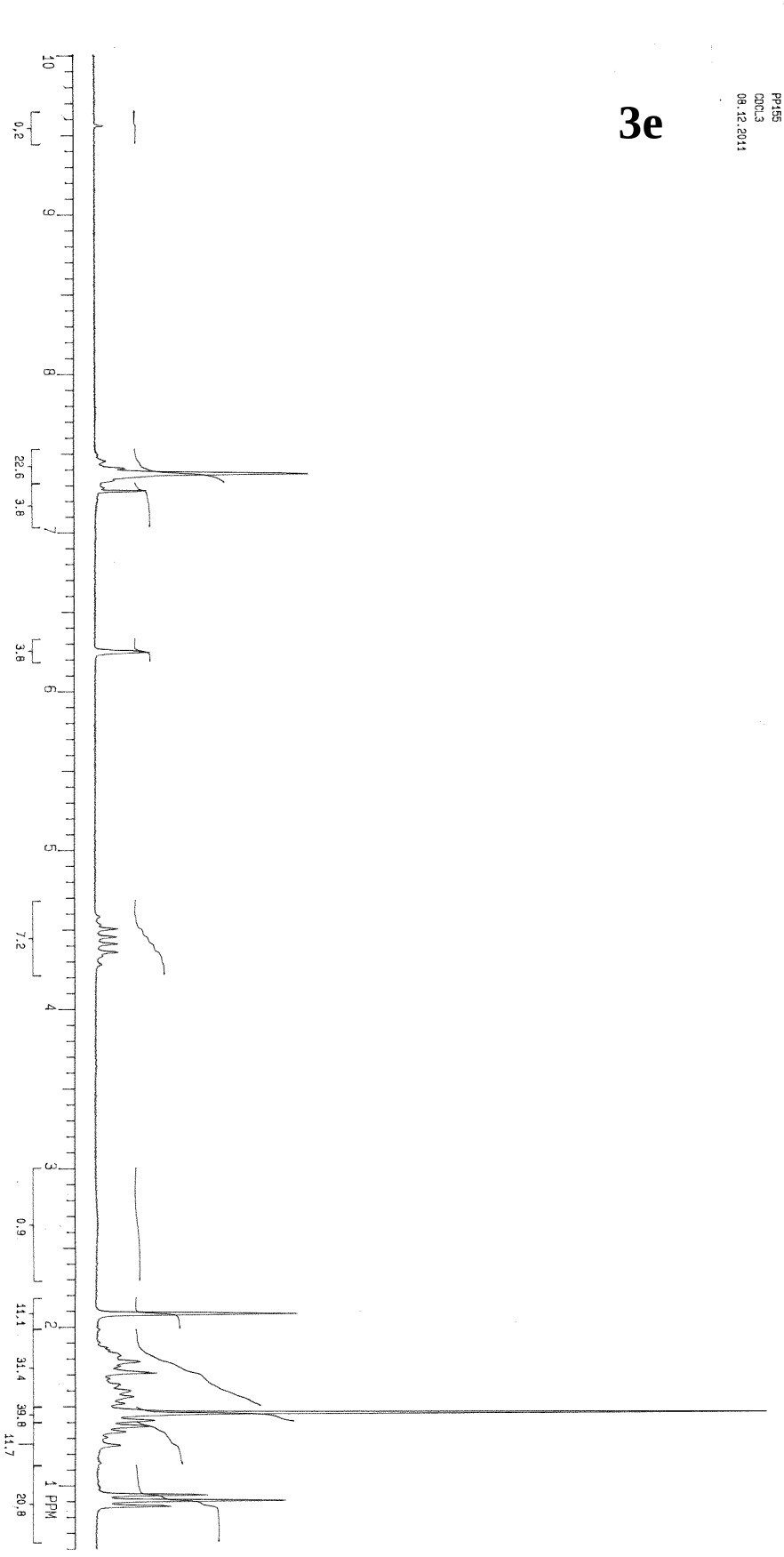

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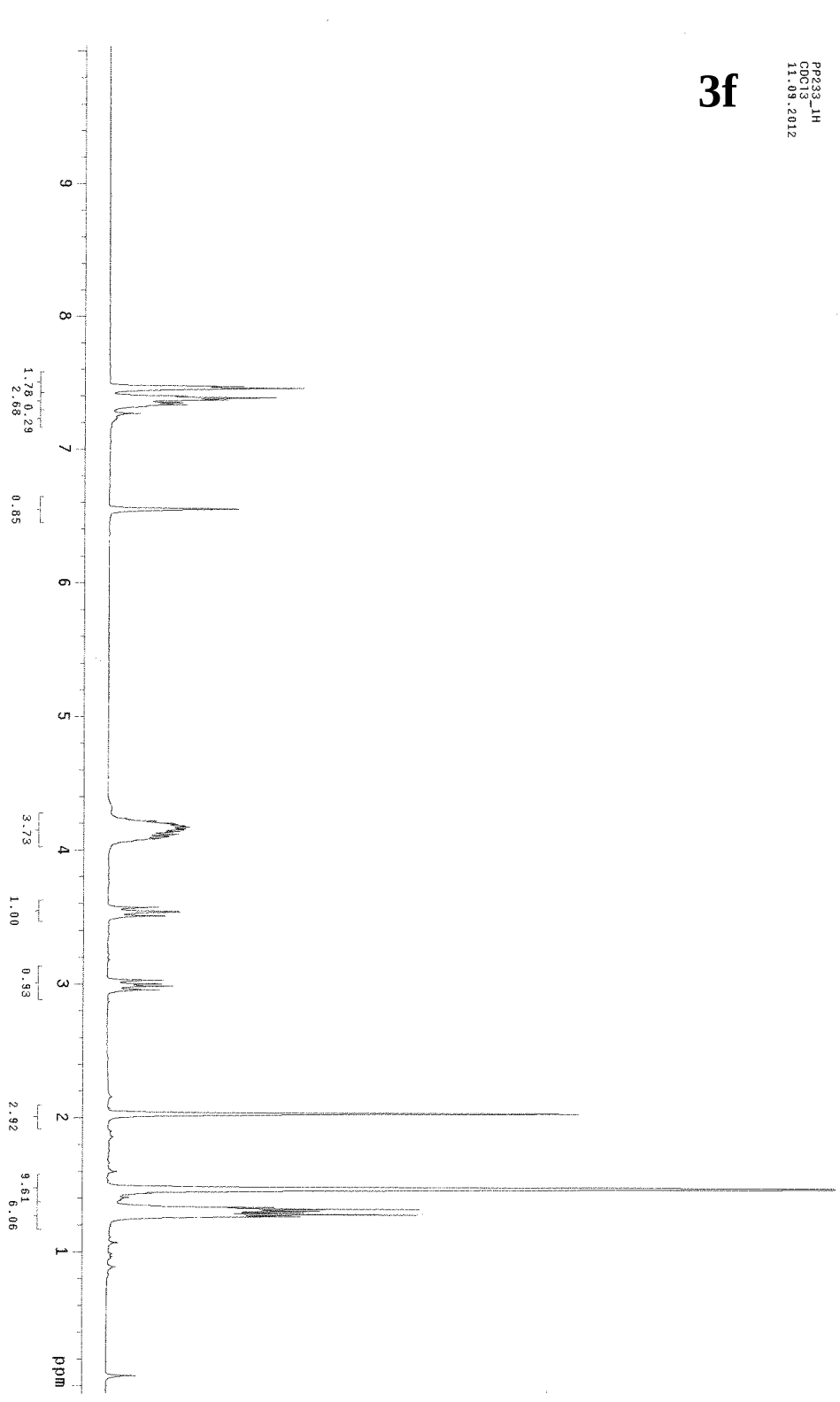

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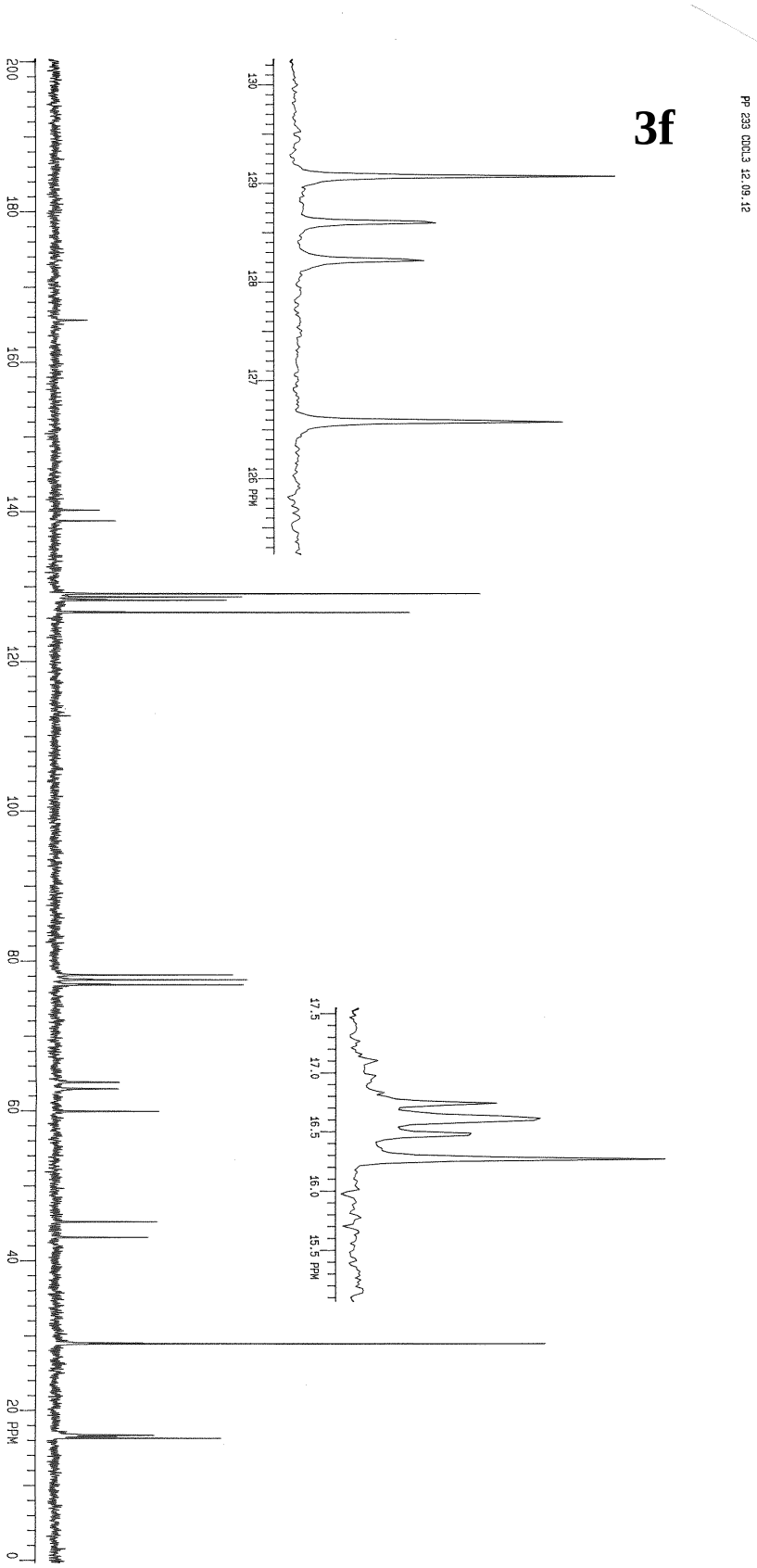

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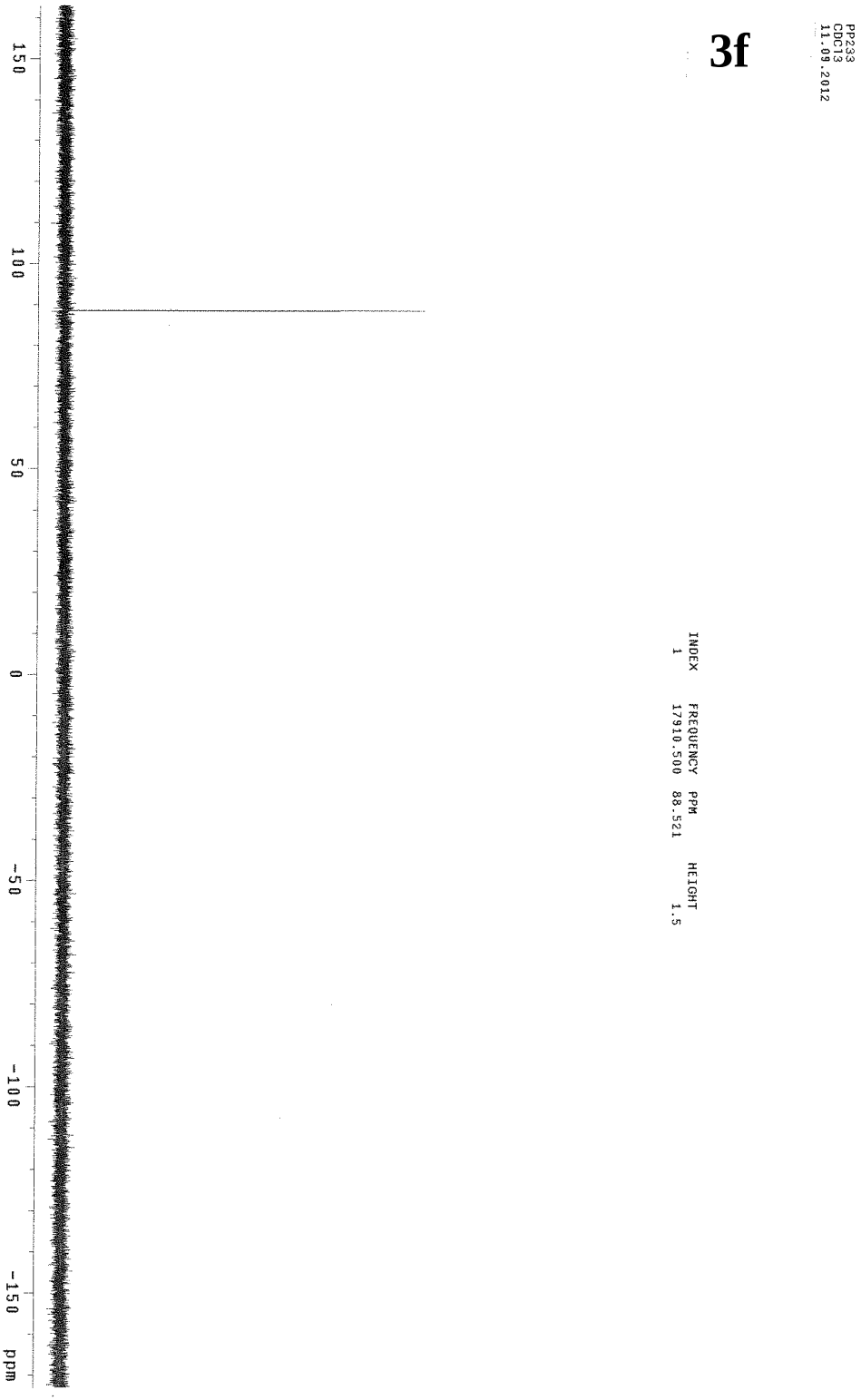

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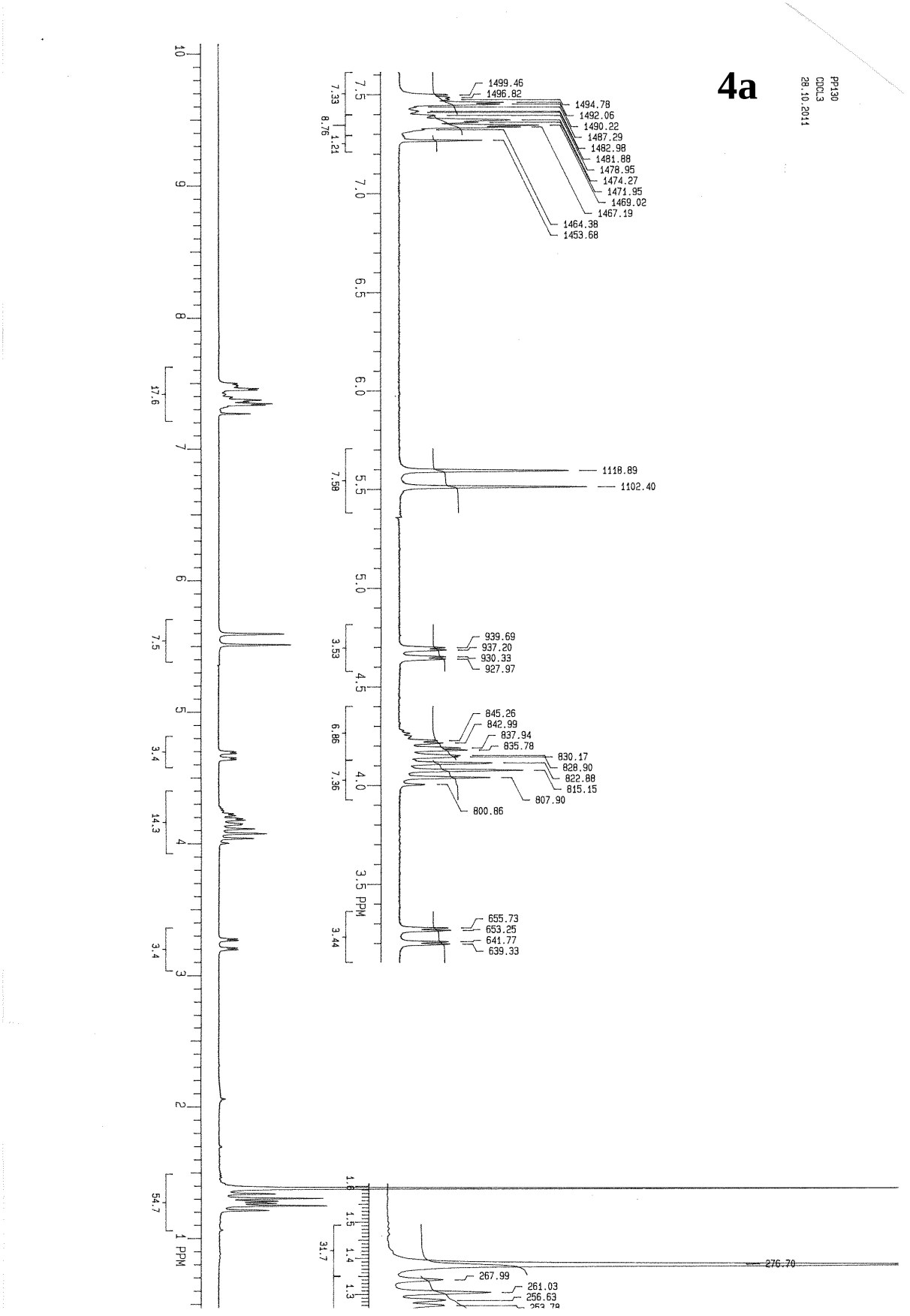

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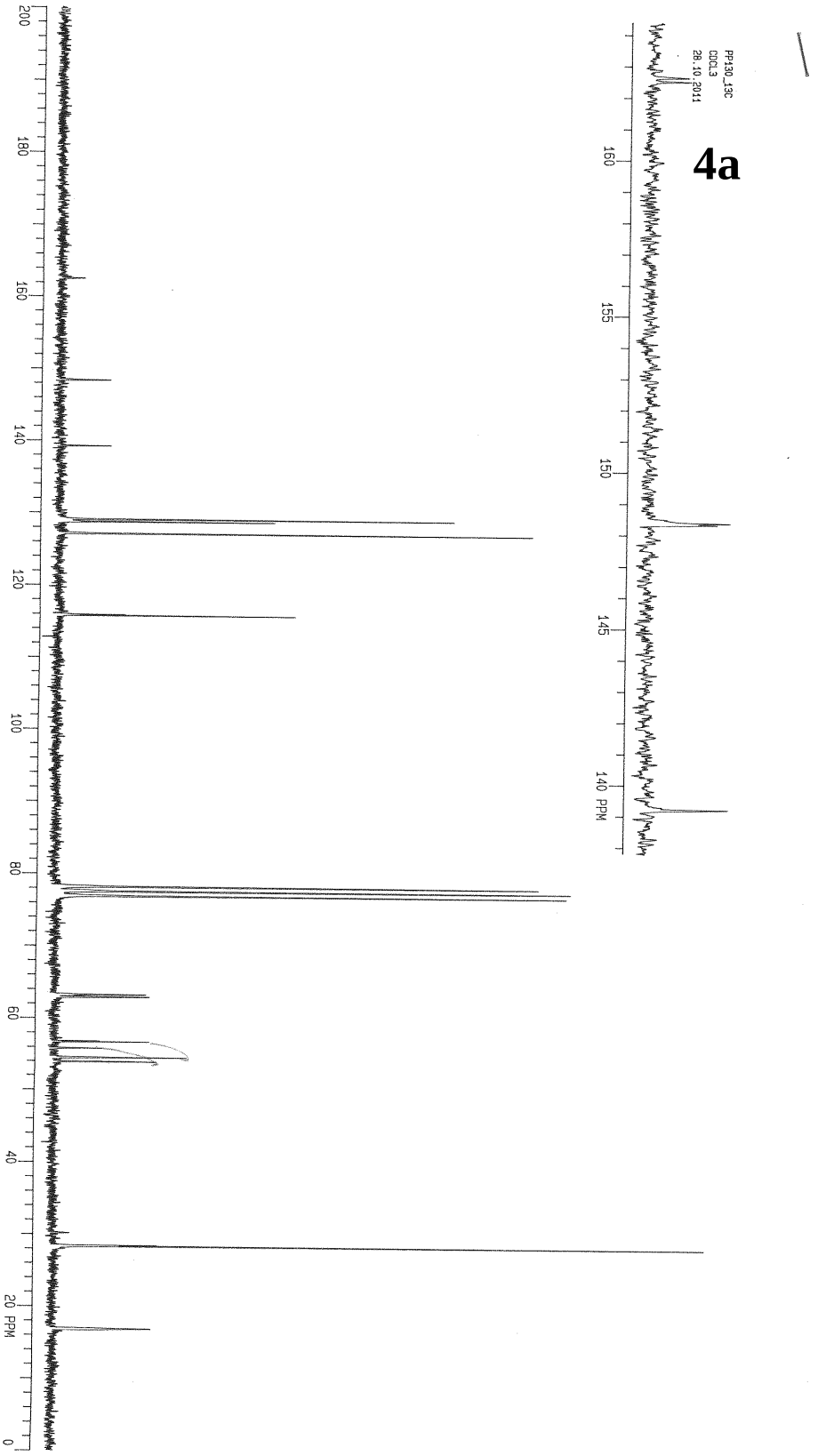

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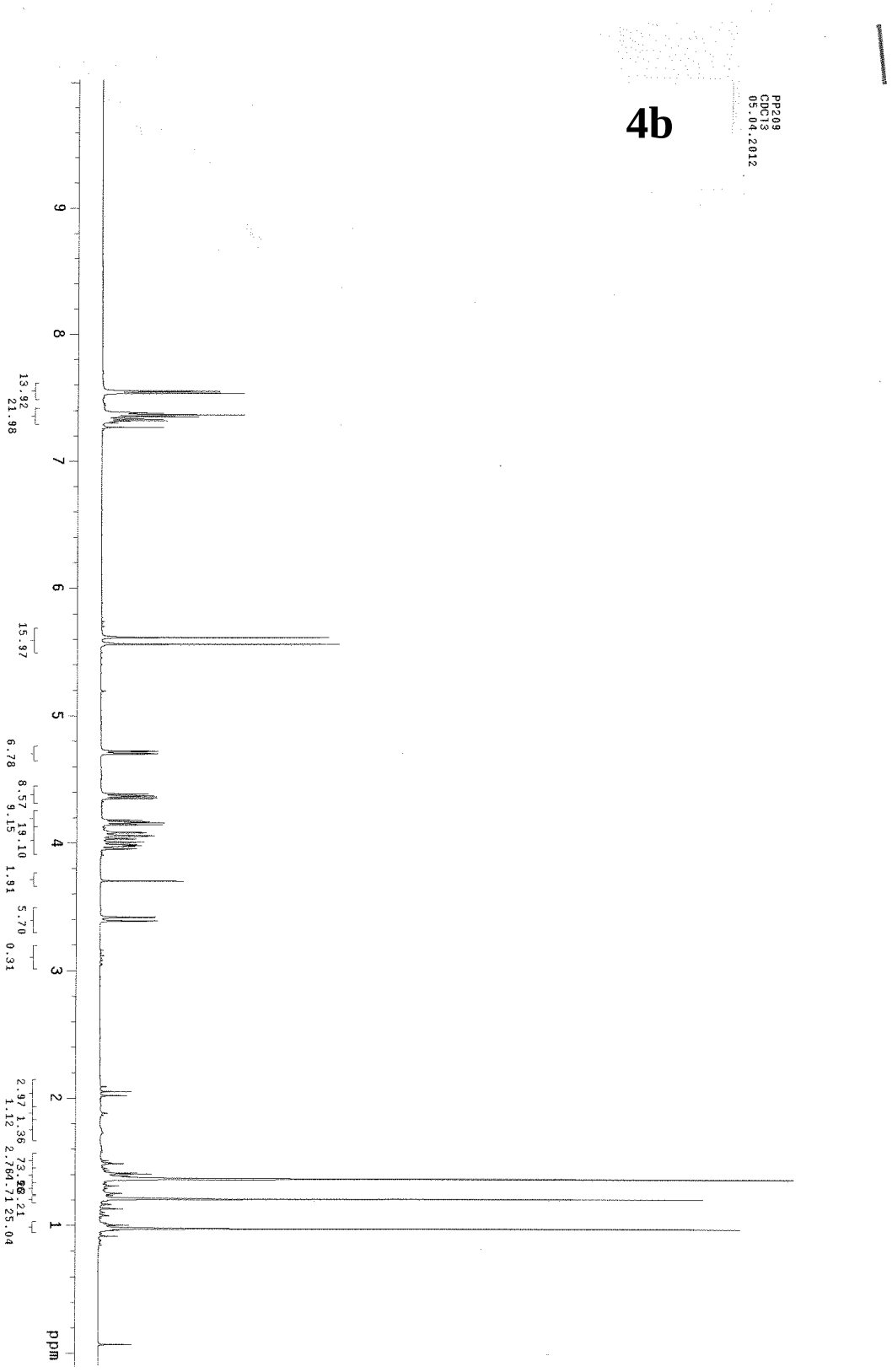

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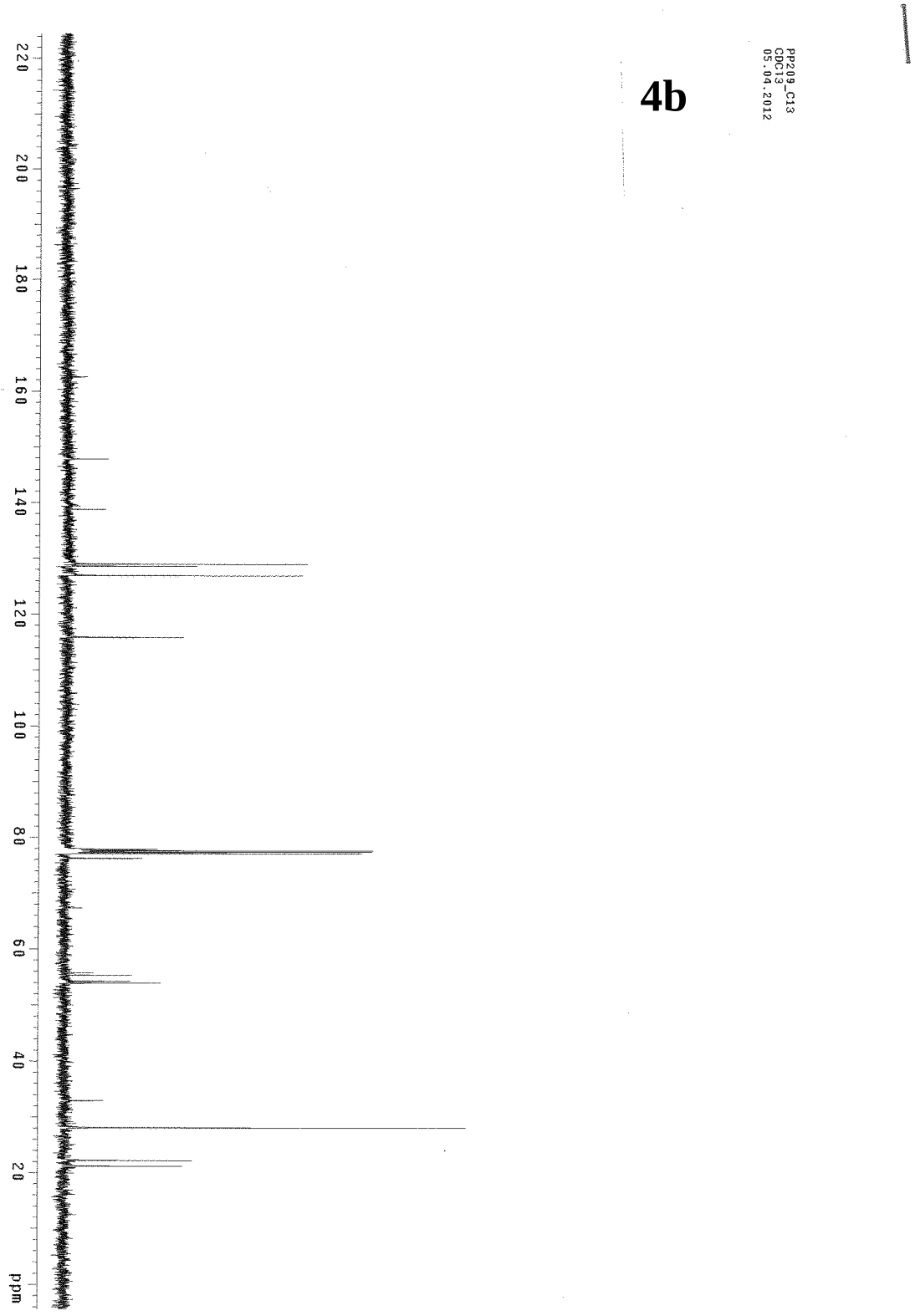

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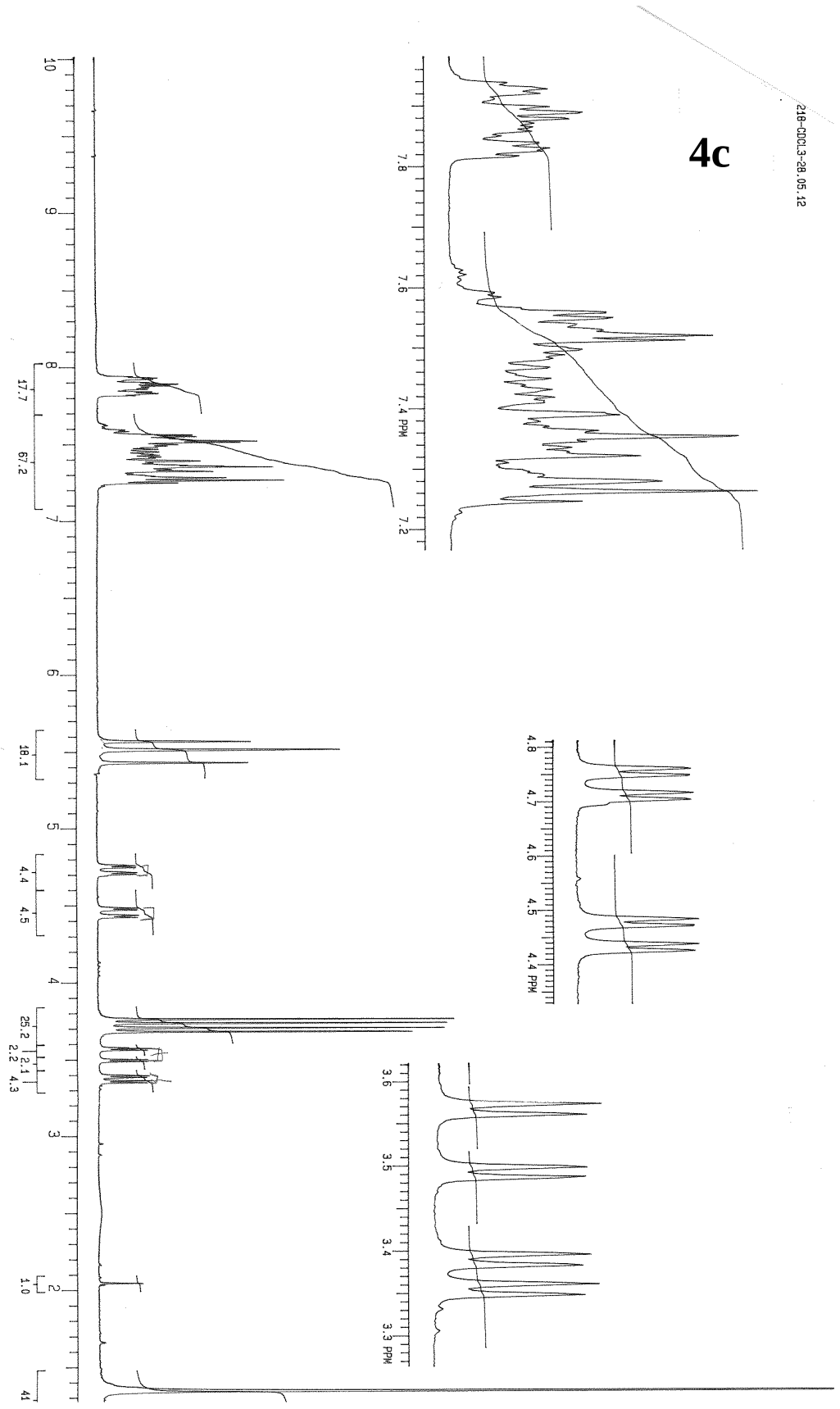

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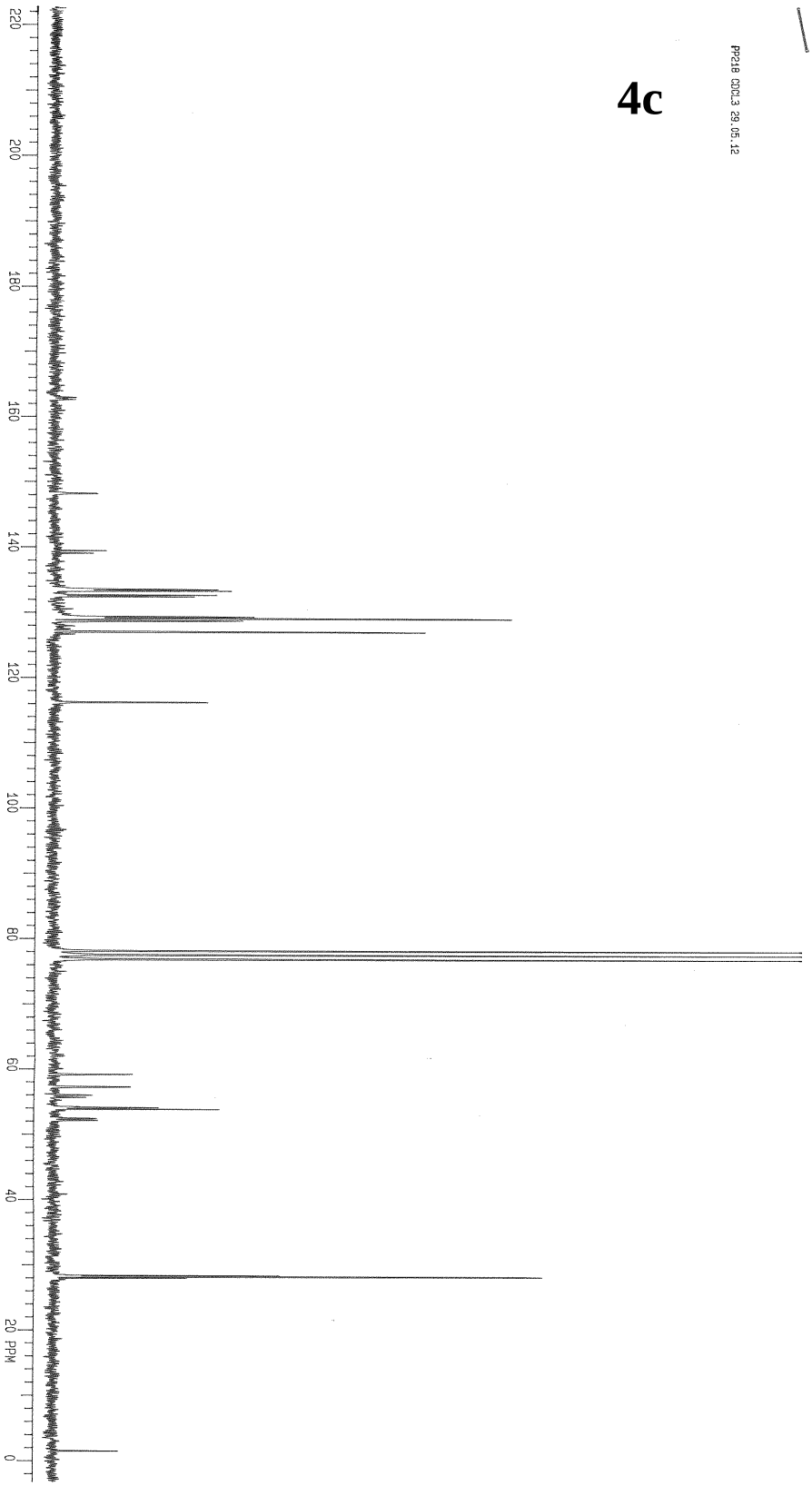

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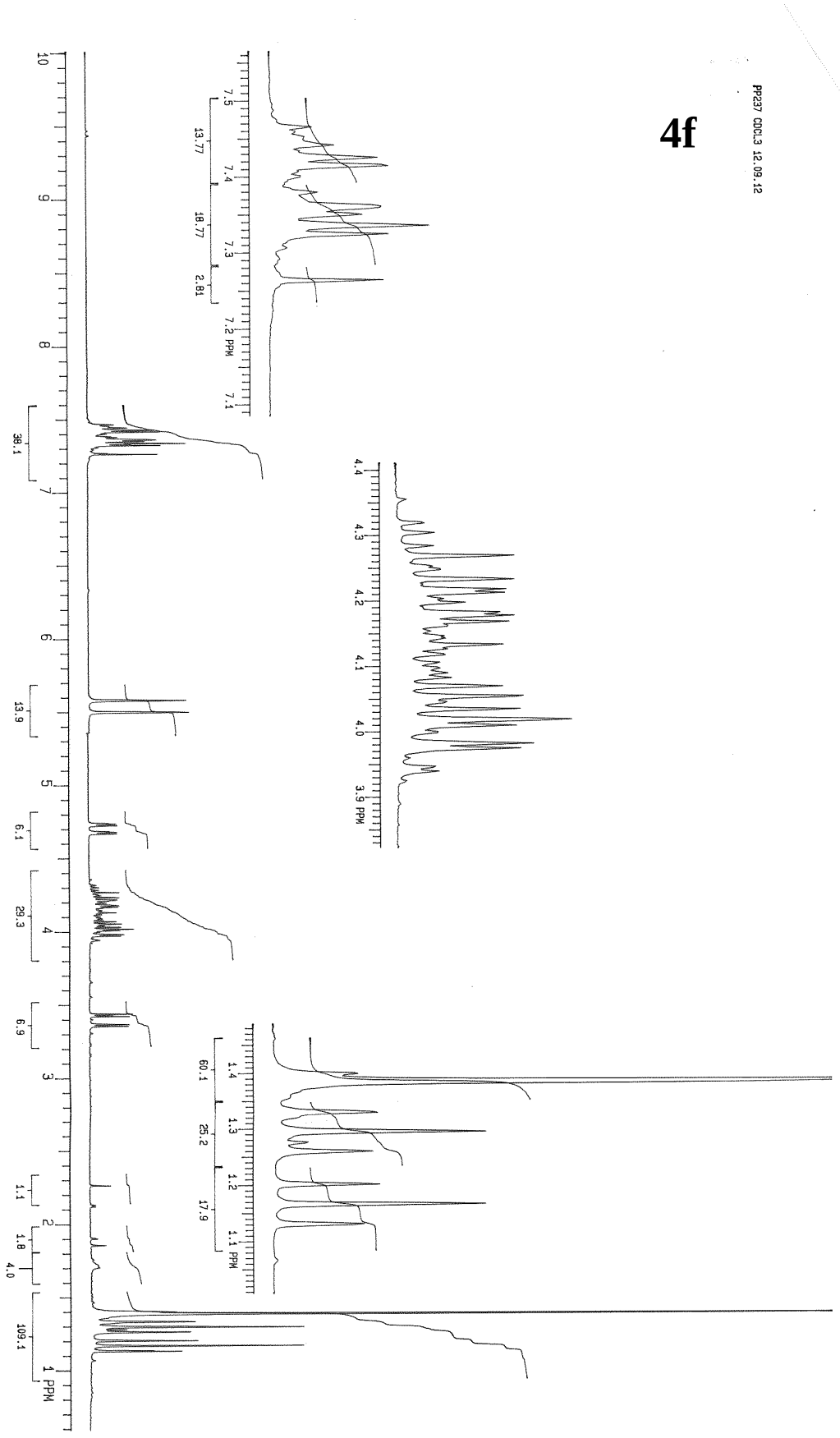

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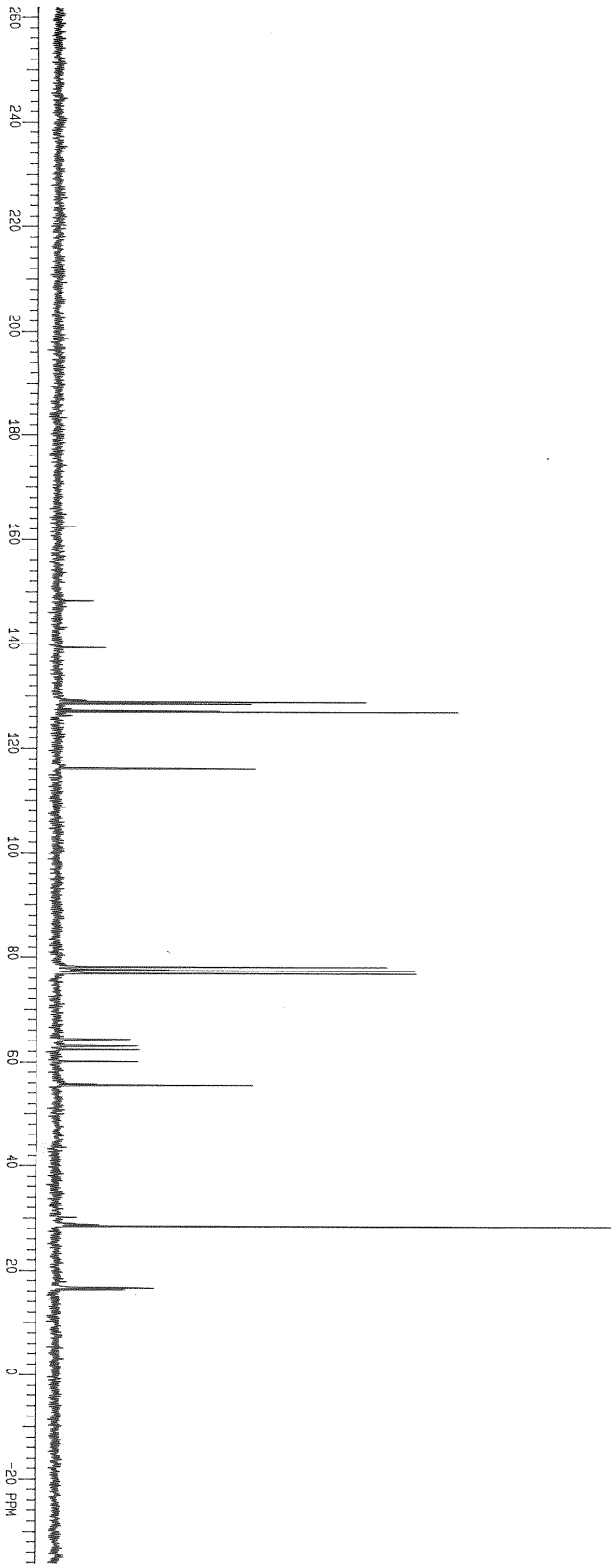

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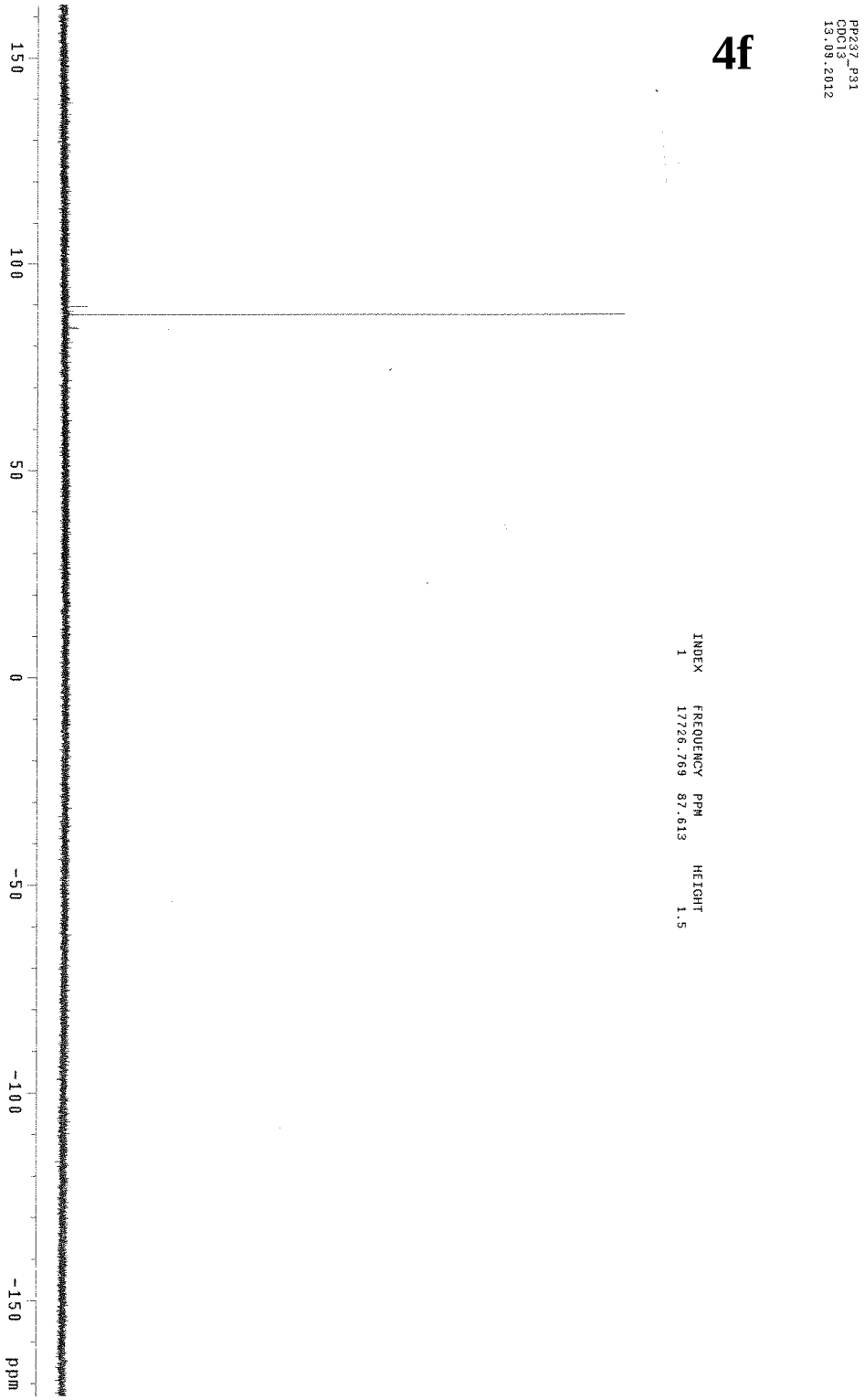

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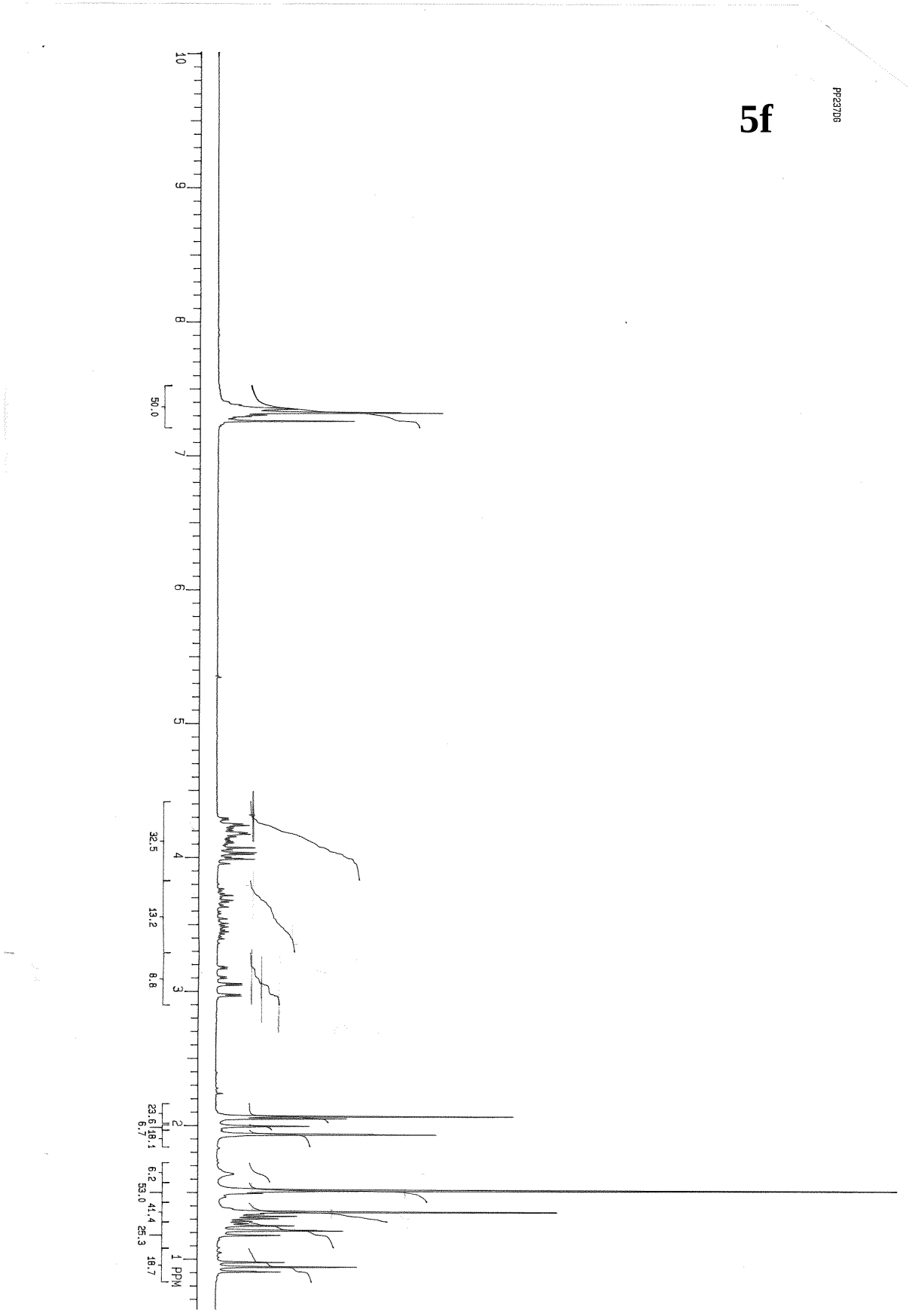

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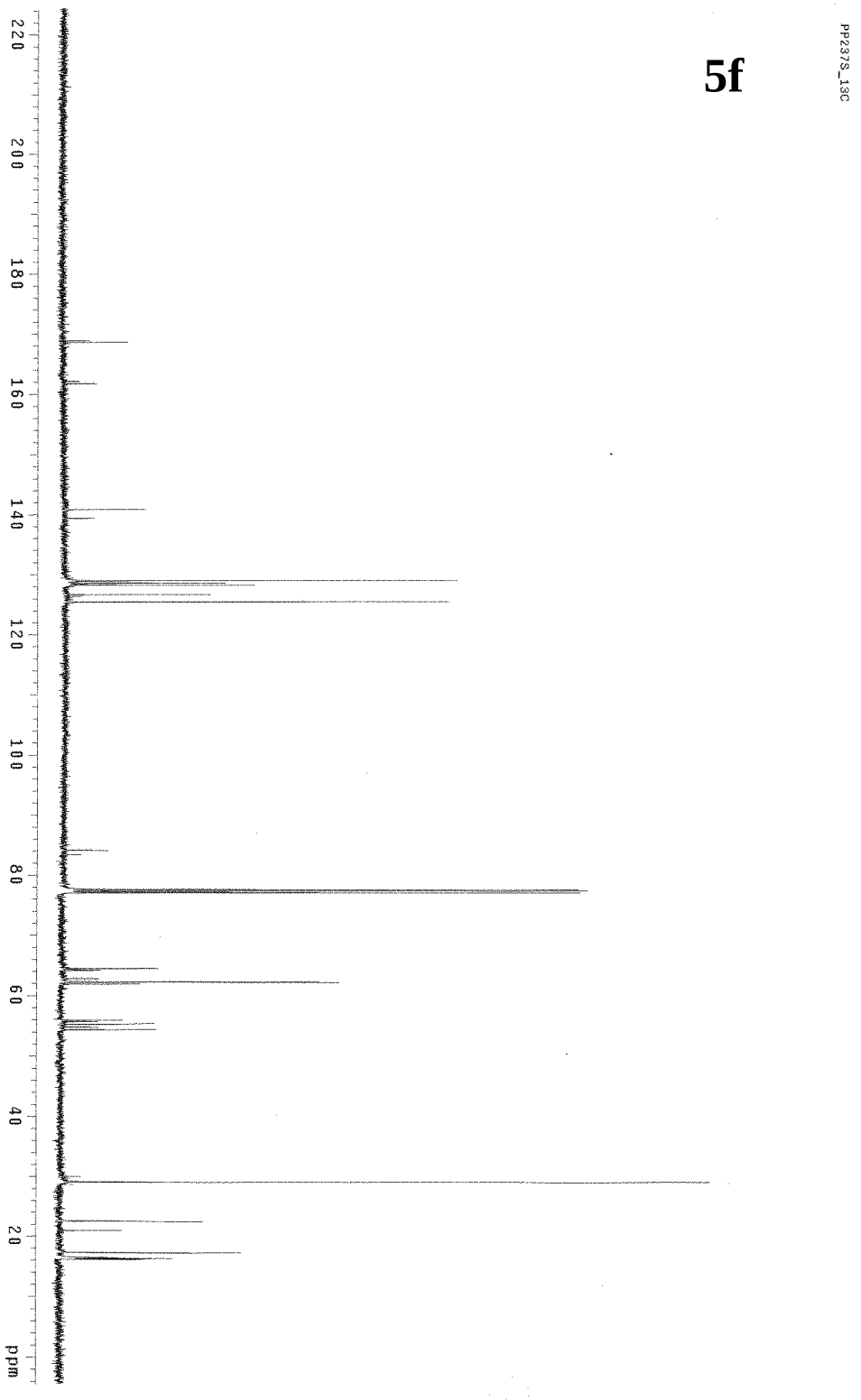

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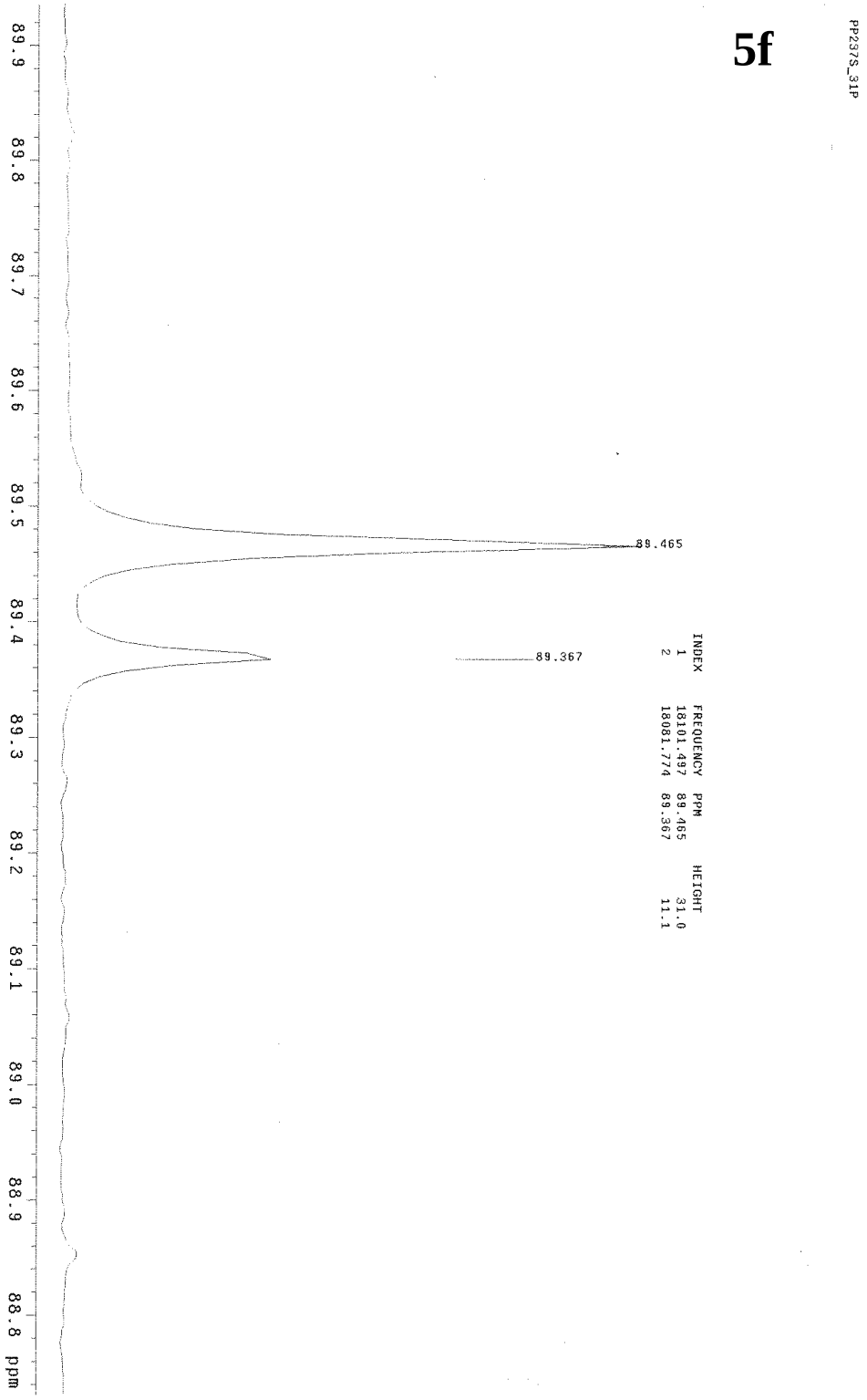

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