

Ortho-lithiation of free ferrocenyl-alcohols: A new method for the synthesis of planar-chiral ferrocene-derivatives

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Electronic Supplementary Information

Table of Contents	Page
General Experimental	1
General Procedure for Ortho-Metalation	1
Analytical data for ortho-substituted Ferrocenyl-alcohols	1
NMR-Spectra of new compounds	5

General experimental procedures:

All reagents and solvents were obtained from commercial sources and appropriately purified, if necessary. Analytical thin layer chromatography was carried out on Merck silica gel 60 F₂₅₄ plates. Flash chromatography was performed on Merck silica gel 60, 230–400 mesh.

Analytical HPLC was carried out with a Hewlett Packard Series 1100 HPLC using a G1315A diode array detector or MWD detector. ¹H and ¹³C NMR spectra were recorded on a Varian INOVA 500 (¹H 499.82 MHz, ¹³C 125.69 MHz) or on a Varian GEMINI 200 (¹H 199.98 MHz, ¹³C 50.29 MHz). Melting points were determined on a Electrothermal MEL-TEMP apparatus and are uncorrected. $[\alpha]_D^{20}$ -values were measured on a Perkin Elmer Polarimeter 341.

Ortho-lithiation of Ferrocenyl-alcohols. General Procedure.

Under an atmosphere of argon, the ferrocenyl-alcohol (0.87 mmol) was dissolved in anhydrous Et₂O (5 ml) and the solution cooled to -20°C. n-BuLi [1.2 ml (1.91 mmol) of an 1.6 M solution in hexane] was added dropwise and stirring continued for 10 h. The temperature was lowered to -50°C and the electrophile (1.74 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for additional 2h. Then the mixture was poured onto ice, washed with NaHCO₃ solution and brine, dried over Na₂SO₄ and concentrated *in vacuo* to give the 1,2-substituted ferrocene derivative **3a-f** and **6a,b**. The crude products were purified by silica gel chromatography

(*S_pR*)-2-(1-Hydroxyethyl)-1-phenylthio-ferrocene **3a**:

Following the general procedure described above, reaction of (*S*)-**7** (200 mg, 0.87 mmol), with diphenyldisulphide (379 mg, 1.74 mmol) gave (*S_pR*)-**3a** as a yellow solid (230 mg, 79 %, 95:5 *d.r.*). mp: 55-60°C; $[\alpha]_D^{20}$ +17.9° (c 0.5, CHCl₃); ¹H-NMR (500 MHz, CDCl₃): δ = 1.51 (3H, d, J=6.3 Hz, CH₃), 1.68 (1H, s, OH), 4.23 (5H, s, Cp-H), 4.38 (1H, s, Cp-H), 4.48 (2H, s, Cp-H), 4.98 (1H, q, J=6.3 Hz, Cp-CH), 7.05-7.10 (3H, m, Ph-H), 7.19 (2H, t, J=7.3 Hz, Ph-H); ¹³C-NMR (100 MHz, CDCl₃): δ = 21.60, 65.06, 68.02, 69.08, 70.39, 75.12, 76.06, 94.68, 125.45, 125.88, 129.16, 140.44.

HPLC: ADH column; 10°C; eluent: Heptane/Isopropanol = 80/20; Flow rate: 0.5 mL/min; *t*_{minor}(*S_pS*) = 13.29 min, *t*_{major}(*S_pR*) = 14.37 min, *d.r.* 95:5.

(S_pR)-2-(1-Hydroxyethyl)-1-methylthio-ferrocene 3b:

Following the general procedure described above, reaction of (S)-**7** (200 mg, 0.87 mmol), with dimethyldisulphide (163 mg, 1.74 mmol) gave (S_pR)-**3b** as an orange oil (153 mg, 64 %, 94:6 *d.r.*). ¹H-NMR (500 MHz, CDCl₃): δ = 1.57 (3H, d, J=6.3 Hz, CH₃), 2.29 (3H, s, S-CH₃), 4.15 (5H, s, Cp-H), 4.19 (1H, t, J=2.4 Hz, Cp-H), 4.27 (1H, s, Cp-H), 4.36 (1H, dd, J=1.5 and 2.4 Hz, Cp-H), 4.97 (1H, q, J=6.3 Hz, Cp-CH); ¹³C-NMR (125 MHz, CDCl₃): δ = 21.37, 22.89, 65.71, 66.87, 67.72, 70.14, 73.48, 81.29, 93.23.

2-(1-Hydroxyethyl)-1-tert-butyl-ferrocene 3c:

Following the general procedure described above, reaction of (S)-**1** (200 mg, 0.87 mmol), with di-*tert*-butyl-disulphide (309 mg, 1.74 mmol) gave **3c** as a yellow solid (58 mg, 21 %, inseparable mixture of isomers). ¹H-NMR (500 MHz, CDCl₃): δ = 1.21 (9H, s, t-butyl_{minor}), 1.27 (9H, s, t-butyl_{major}), 1.40 (3H, d, J=6.4 Hz, CH₃ minor), 1.61 (3H, d, J=6.5 Hz, CH₃), 2.22 (1H, d, J=4.8 Hz), 2.40 (1H, d, J=4.8 Hz), 4.15 (5H, m, Cp-H), 4.18 (1H, m, Cp-H), 4.20 (1H, m, Cp-H), 4.24 (1H, m, Cp-H_{minor}), 4.28 (2H, m, Cp-H), 4.33 (1H, m, Cp-H_{minor}), 4.37 (1H, m, Cp-H_{major}), 4.46 (1H, m, Cp-H_{major}), 4.62 (1H, m, Cp-CH_{minor}), 4.99 (1H, m, Cp-H_{major}); ¹³C-NMR (125 MHz, CDCl₃): δ = 23.55_{major}, 24.75_{minor}, 30.85_{minor}, 31.45_{major}, 45.81_{minor}, 46.06_{major}, 65.11_{major}, 65.74_{minor}, 67.27_{major}, 67.39_{minor}, 67.63_{minor}, 68.85_{major}, 69.16_{minor}, 69.30_{minor}, 70.22_{minor}, 70.28_{minor}, 70.55_{major}, 75.84_{minor}, 75.90_{minor}, 75.54_{major}, 77.04_{minor}, 77.13_{major}, 94.24_{major}, 96.39_{minor}.

(S_pR)-2-(1-Hydroxyethyl)-1-phenylselenenyl-ferrocene 3d:

Following the general procedure described above, reaction of (S)-**1** (200 mg, 0.87 mmol), with diphenyldiselenide (542 mg, 1.74 mmol) gave (S_pR)-**3d** as an orange oil (258 mg, 77 %, 95:5 *d.r.*). ¹H-NMR (500 MHz, CDCl₃): δ = 1.52 (3H, d, J=5.9 Hz, CH₃), 1.65, (1H, s, OH), 4.21 (5H, s, Cp-H), 4.37 (1H, s, Cp-H), 4.44 (1H, s, Cp-H), 4.49 (1H, s, Cp-H), 4.98 (1H, d, J=5.9 Hz, Cp-CH), 7.13 (1H, d, J=6.3 Hz, Ph-H), 7.17 (2H, t, J=7.1 Hz, Ph-H), 7.25 (2H, d, J=7.8 Hz, Ph-H); ¹³C-NMR (125 MHz, CDCl₃): δ = 21.38, 65.82, 67.82, 69.66, 70.15, 77.03, 94.93, 126.36, 129.05, 129.46, 134.62.

(S_pR)-2-(1-Hydroxyethyl)-1-diphenylphosphino-ferrocene 3e:

Following the general procedure described above, reaction of (S)-**1** (200 mg, 0.87 mmol), with chlordiphenylphosphine (366 mg, 1.74 mmol) gave (S_pR)-**3e** as an orange solid (226 mg, 63 %, 96:4 *d.r.*); mp: 57°C; [α]_D²⁰ +286° (c 0.5, CHCl₃); ¹H-NMR (500 MHz, CDCl₃): δ =

1.51 (3H, d, $J=6.5$ Hz, CH_3), 1.65 (1H, bs, OH), 3.79 (1H, t, $J=1.2$ Hz, Cp-H), 4.08 (5H, s, Cp-H), 4.32 (1H, t, $J=2.5$ Hz, Cp-H), 4.52 (1H, m, Cp-H), 5.01 (1H, dq, $J=2.0$ and 6.5 Hz, Cp-CH), 7.25-7.31 (6H, m Ph-H), 7.38-7.41 (3H, m, Ph-H), 7.50-7.56 (1H, m, Ph-H); ^{13}C -NMR (125 MHz, CDCl_3): δ = 22.46, 65.79 (d, $J_{\text{C-P}}=8\text{Hz}$), 69.25 (d, $J_{\text{C-P}}=4\text{Hz}$), (69.53), 69.82, 71.75 (d, $J_{\text{C-P}}=4\text{Hz}$), 75.37 (d, $J_{\text{C-P}}=8\text{Hz}$), 96.97 (d, $J_{\text{C-P}}=22$ Hz), 128.33 (d, $J_{\text{C-P}}=8\text{Hz}$), 128.59 (d, $J_{\text{C-P}}=2\text{Hz}$), 128.64, 128.34, 132.80 (d, $J_{\text{C-P}}=18$ Hz), 134.86 (d, $J_{\text{C-P}}=21$ Hz), 136.83 (d, $J_{\text{C-P}}=8$ Hz), 139.80 (d, $J_{\text{C-P}}=9$ Hz).

(*S*,*p*,*R*)-1-Hydroxydiphenylmethyl-2-(1-hydroxyethyl)-ferrocene 3f:

Following the general procedure described above, reaction of (*S*)-**1** (200 mg, 0.87 mmol), with benzophenone (317 mg, 1.74 mmol) gave (*S*,*p*,*R*)-**3f** as an orange solid (268 mg, 75 %, 95:5 *d.r.*). mp: 154-156°C; ^1H -NMR (500 MHz, CDCl_3): δ = 1.17 (3H, d, $J=6.3$ Hz, $-\text{CH}_3$), 1.82 (1H, s, OH), 3.60 (1H, s, Cp-H), 4.15 (1H, d, $J=1.5$ Hz, Cp-H), 4.24 (5H, s, Cp-H), 4.31 (1H, s, Cp-H), 4.80 (1H, d, $J=6.3$ Hz, Cp-CH), 5.12 (1H, s, OH), 7.21-7.29 (6H, m, Ph-H), 7.33 (2 H, t, $J=7.3$ Hz, Ph-H), 7.51 (2H, d, $J=7.3$ Hz, Ph-H); ^{13}C -NMR (125 MHz, CDCl_3): δ = 23.02, 66.49, 69.12, 69.60, 72.72, 77.57, 88.70, 97.86, 126.68, 126.91, 127.28, 127.41, 127.44, 127.98, 146.15, 148.39.

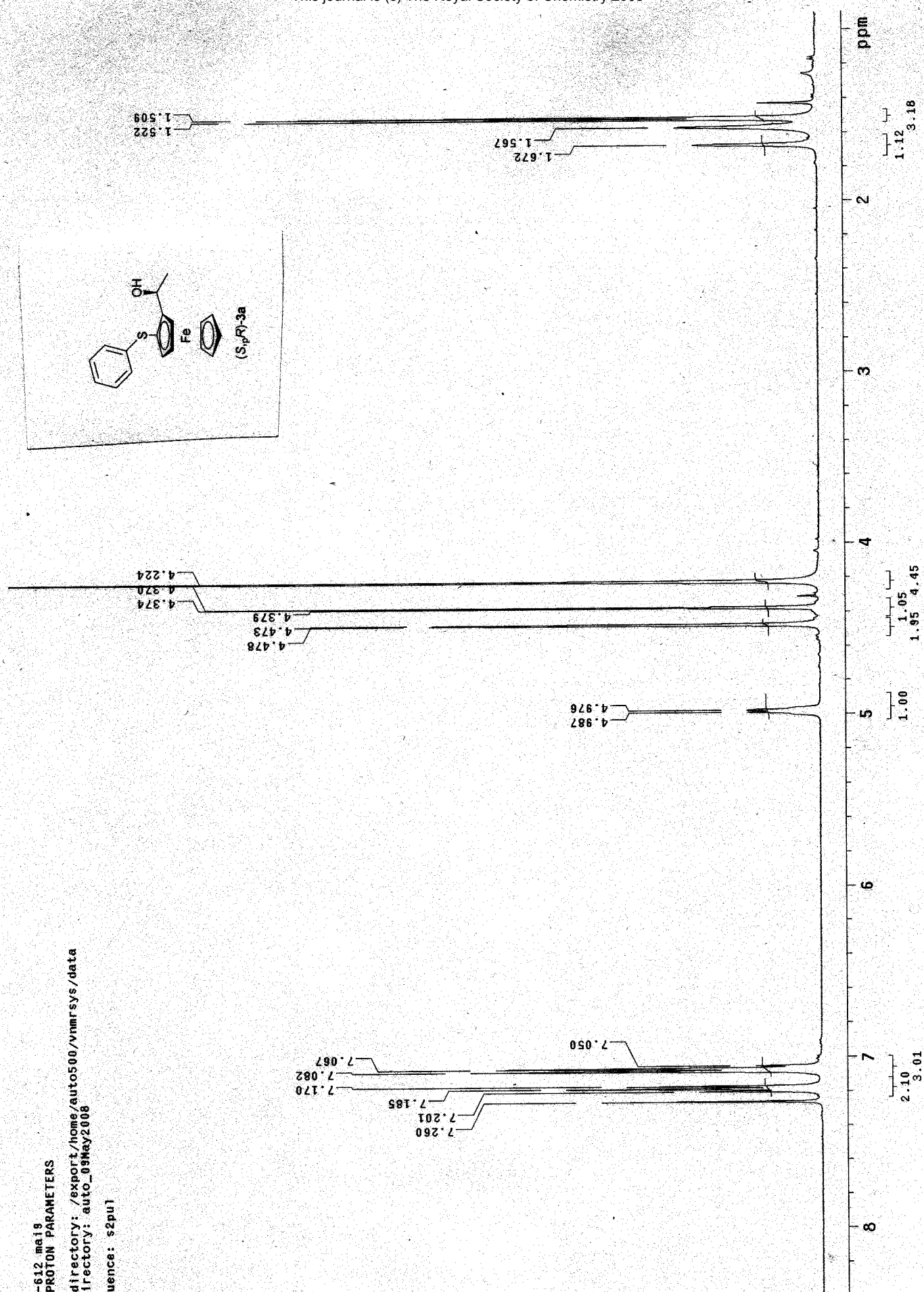
(*rac*)-1-(Hydroxydiphenylmethyl)-2-[hydroxy(phenyl)methyl]-ferrocene 6a:

Following the general procedure described above, reaction of **4a** (254 mg, 0.87 mmol), with benzophenone (317 mg, 1.74 mmol) gave **6a** as a yellow solid (273 mg, 66 %, > 95:5 *d.r.*) mp: 163-164°C; ^1H -NMR (500 MHz, CDCl_3): δ = 2.35 (1H, s, OH), 3.39 (1H, s, Cp-H), 4.02 (5H, s, Cp-H), 4.11 (1H, s, Cp-H), 4.21 (1H, s, Cp-H), 4.67 (1H, s, Cp-CH), 5.59 (1H, s, OH), 7.05-7.13 (7H, m, Ph-H), 7.17 (3H, d, $J=7.8$ Hz, Ph-H), 7.24 (2H, t, $J=7.8$ Hz, Ph-H), 7.40 (2H, d, $J=7.8$ Hz, Ph-H); ^{13}C -NMR (125 MHz, CDCl_3): δ = 67.17, 70.04, 70.66, 72.43, 72.68, 77.89, 126.28, 126.99, 127.24, 127.29, 127.33, 127.37, 127.51, 127.99, 128.09, 143.13, 146.38, 147.40.

(*rac*)-1-(hydroxydiphenylmethyl)-2-[cyclohexyl(hydroxy)methyl]-ferrocene 6b:

Following the general procedure described above, reaction of **4b** (258 mg, 0.87 mmol), with benzophenone (317 mg, 1.74 mmol) gave **6b** as a yellow solid (343 mg, 82 %, > 95:5 *d.r.*). mp: 186-188°C; ^1H -NMR (500 MHz, CDCl_3): δ = 0.01 (d, $J=9$ Hz), 0.19 (2H, m), 0.41 (2H, m), 0.62 (1H, d, $J=11.7$ Hz), 0.73 (1H, d, $J=6.8$ Hz), 1.10 (2H, dd, $J=2.7$ and 6.8 Hz), 1.57 (1H, s), 2.52 (1H, s, OH), 3.26 (1H, s, Cp-H), 3.45 (1H, d, $J=9.7$ Hz, Cp-CH), 3.80 (1H, s,

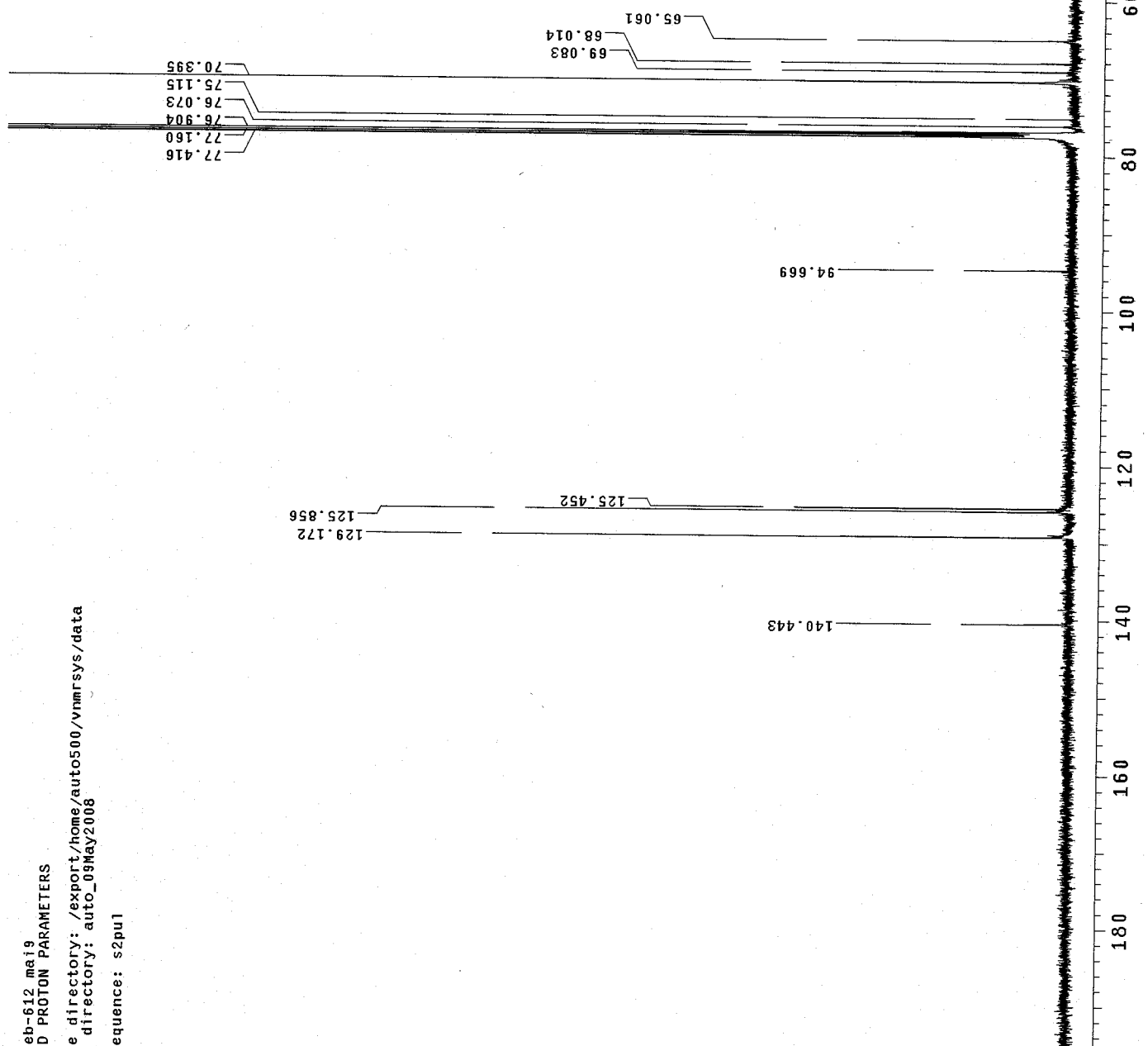
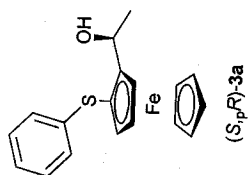
Cp-H), 3.88 (1H, s, Cp-H), 4.00 (5H, s, Cp-H), 6.25 (1H, s, OH), 6.9-7.0 (8H, m, Ph-H), 7.24 (2H, d, J=7.3 Hz, Ph-H); ^{13}C -NMR (100 MHz, CDCl_3): δ = 25.15, 25.73, 26.22, 29.81, 30.65, 41.15, 65.68, 69.63, 72.70, 73.57, 77.35, 87.16, 96.67, 126.82, 127.20, 127.27, 127.61, 127.99, 146.33, 149.25.



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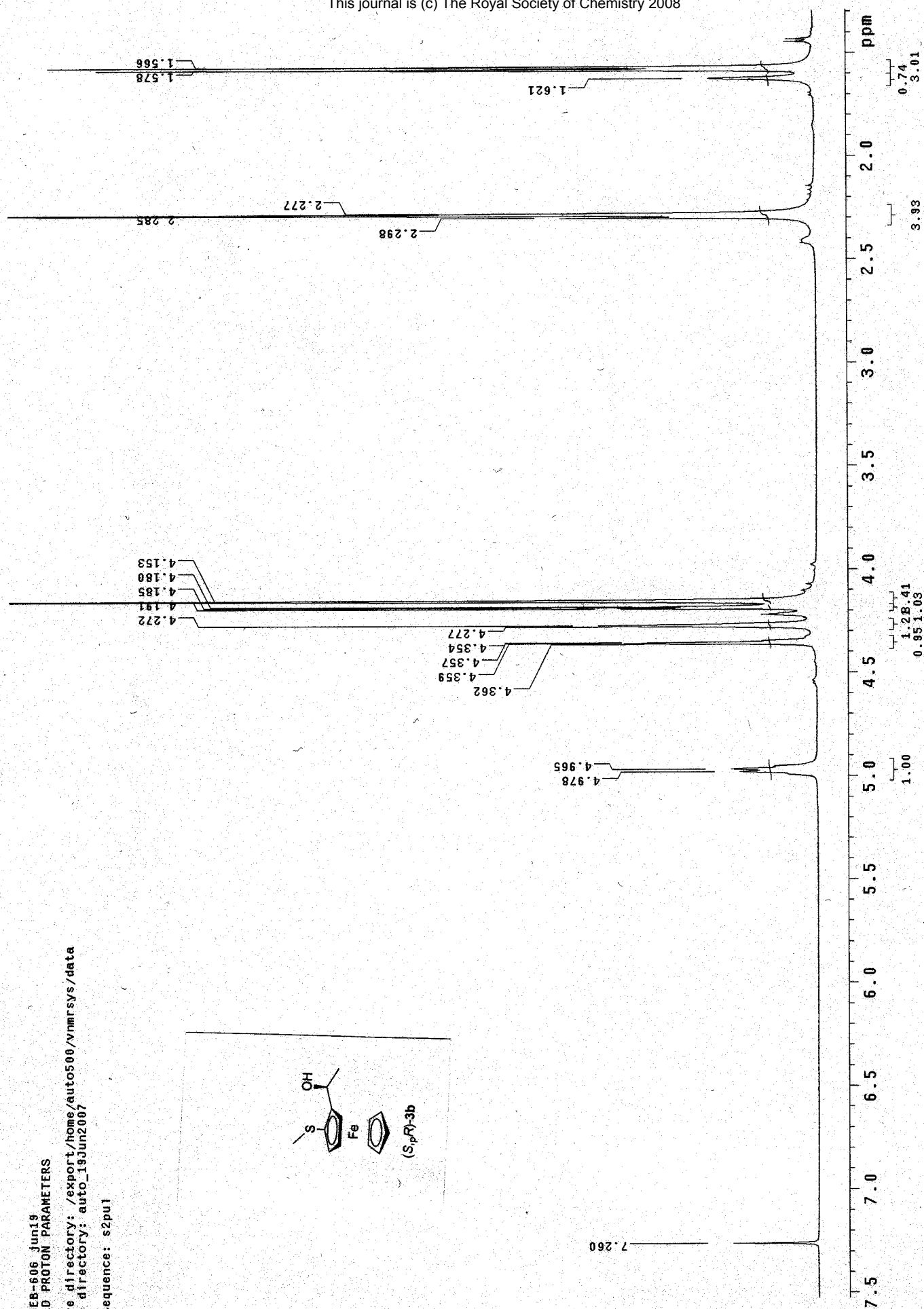
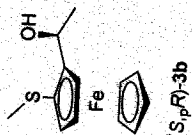


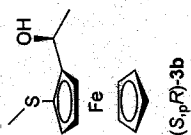
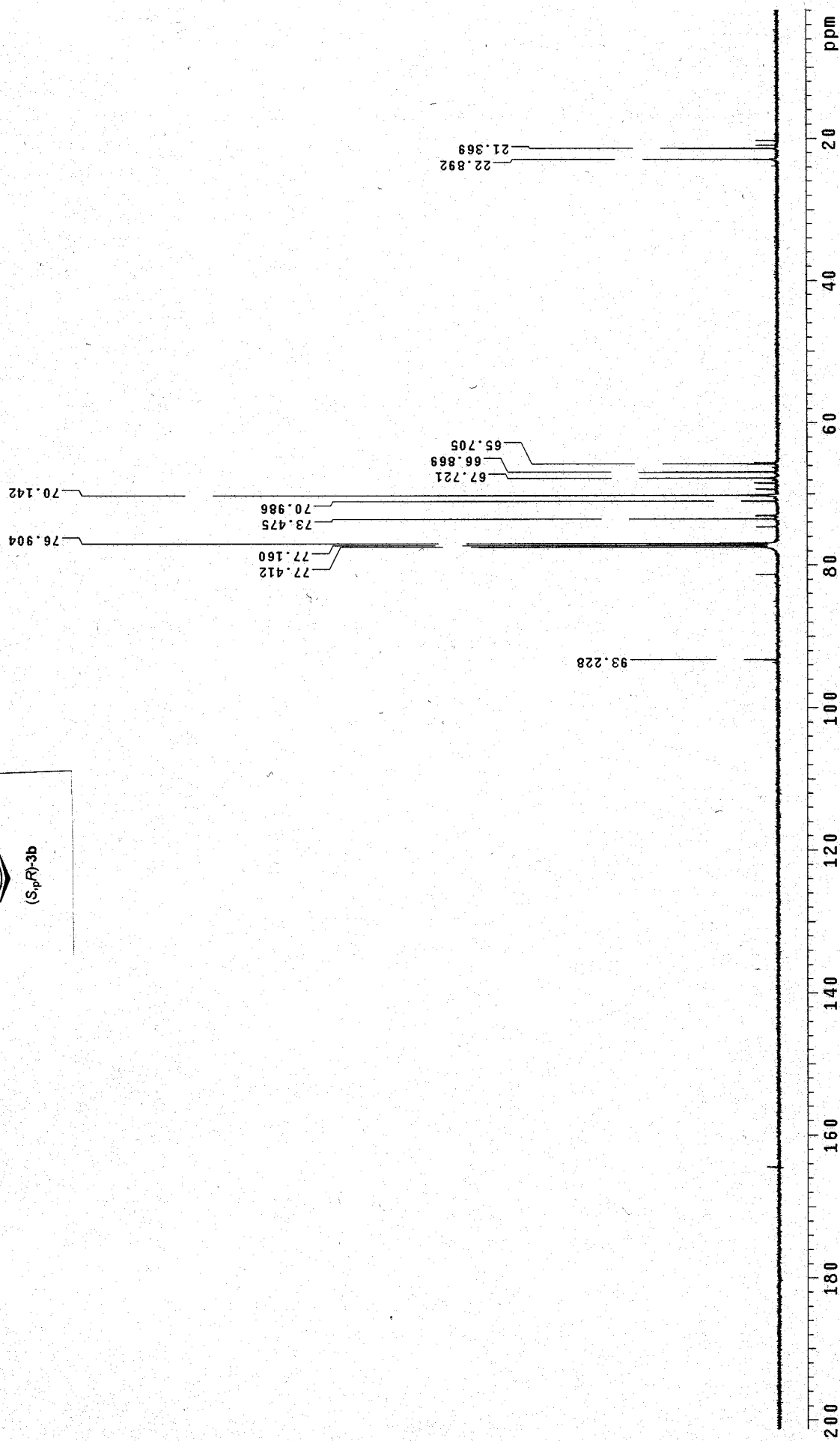
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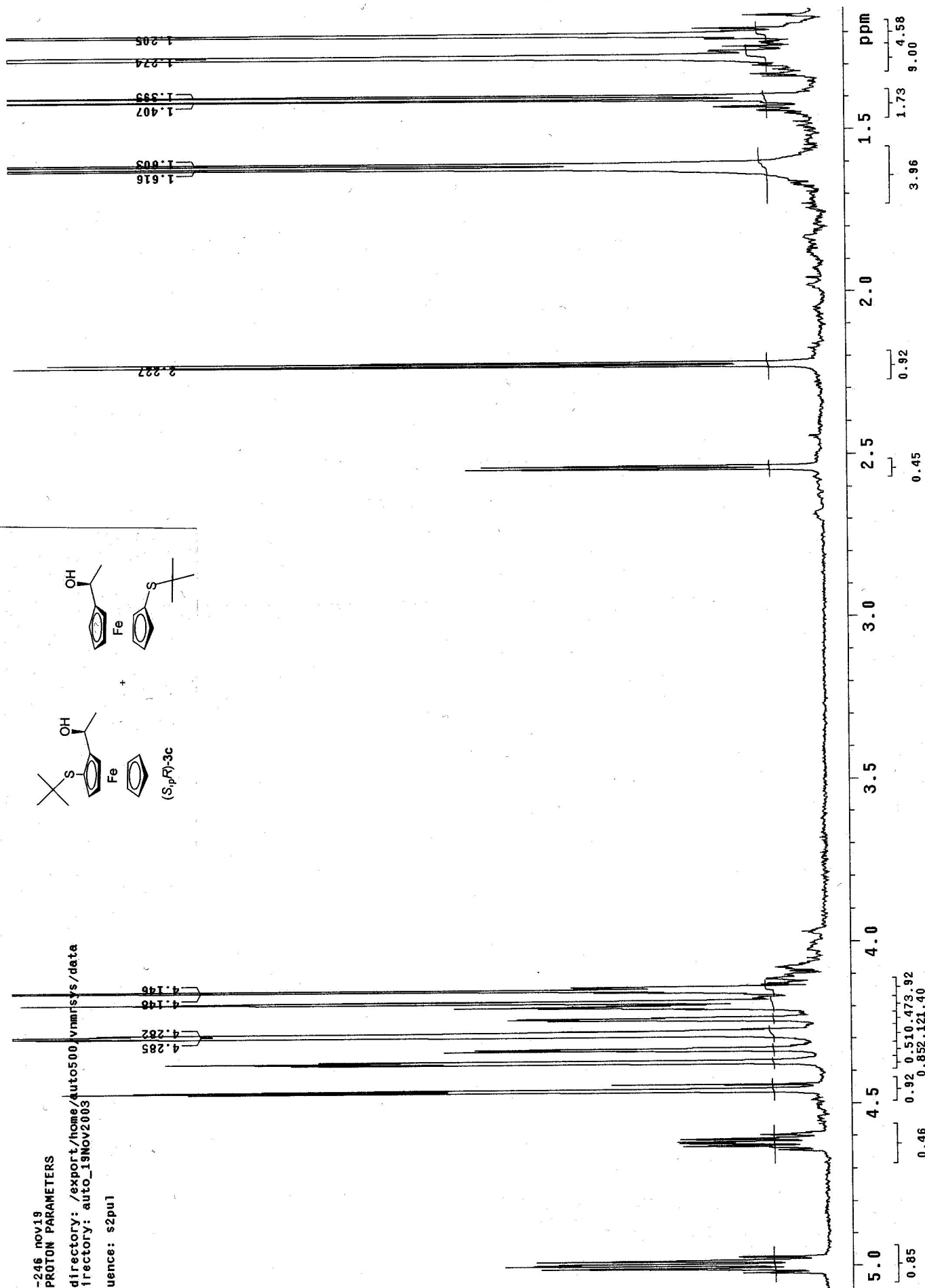
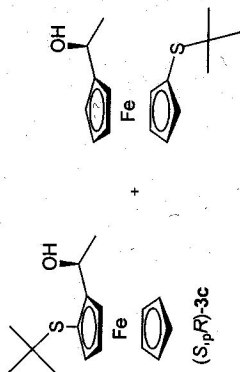
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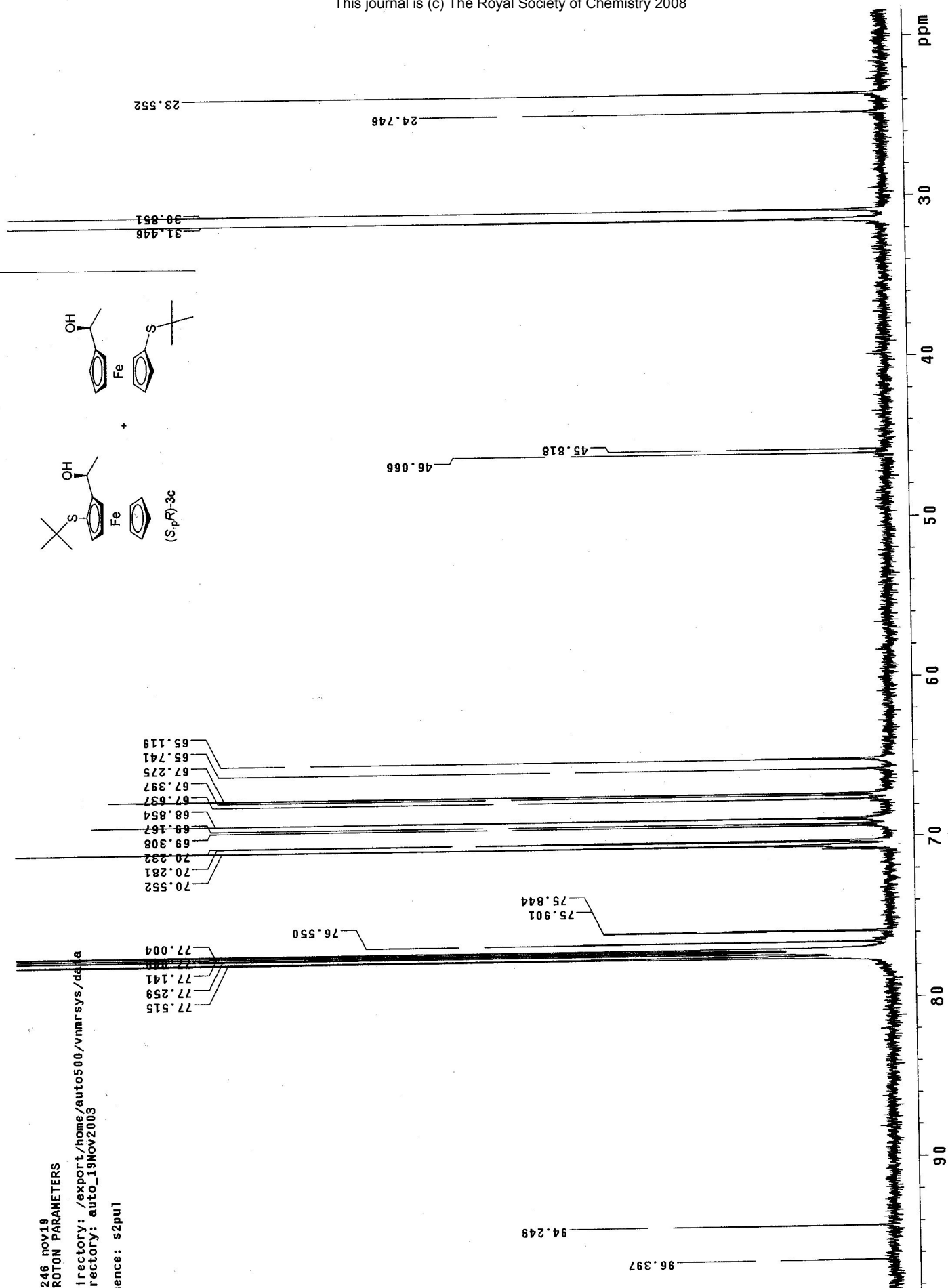
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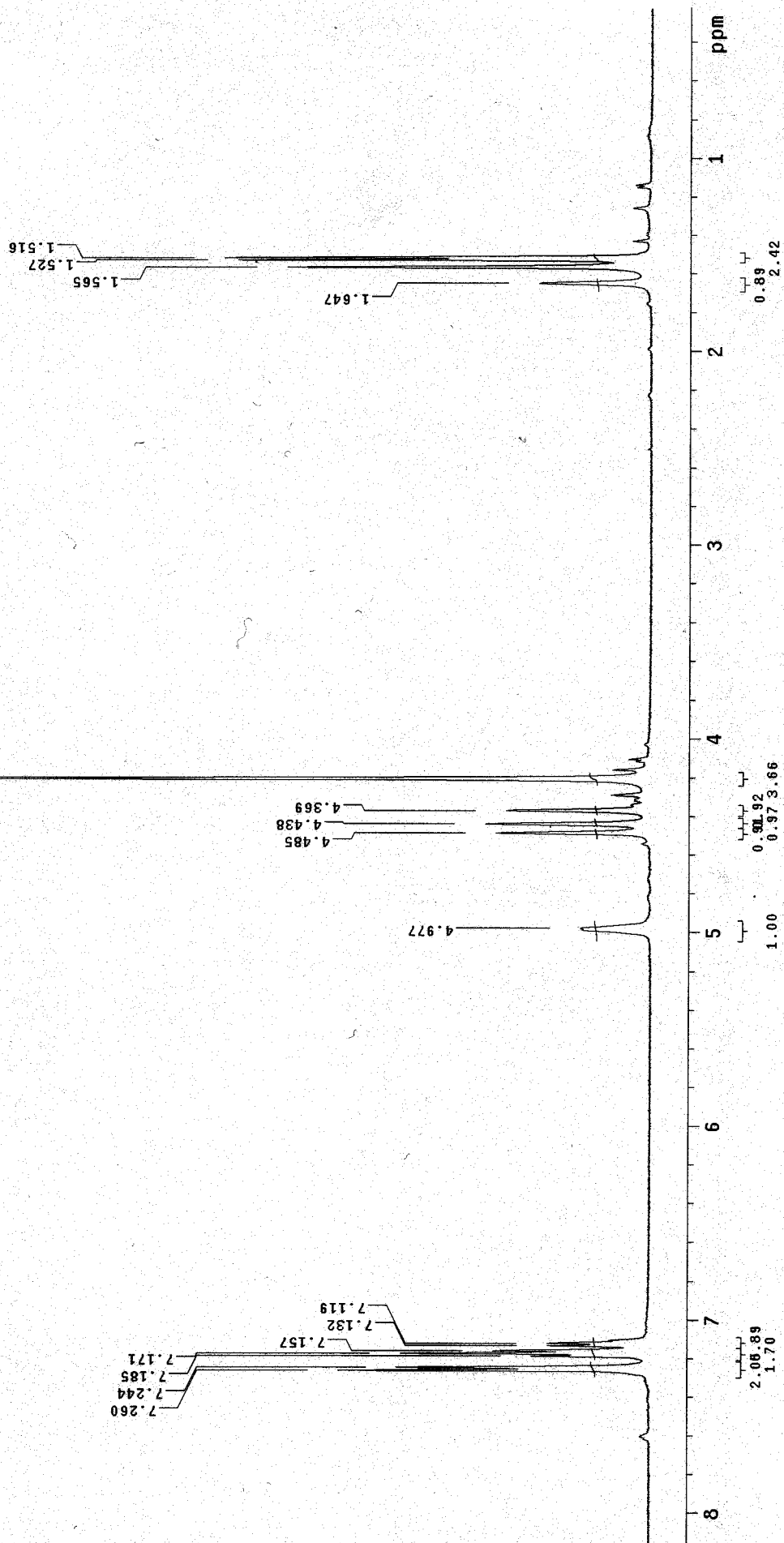
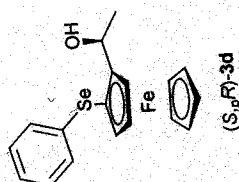


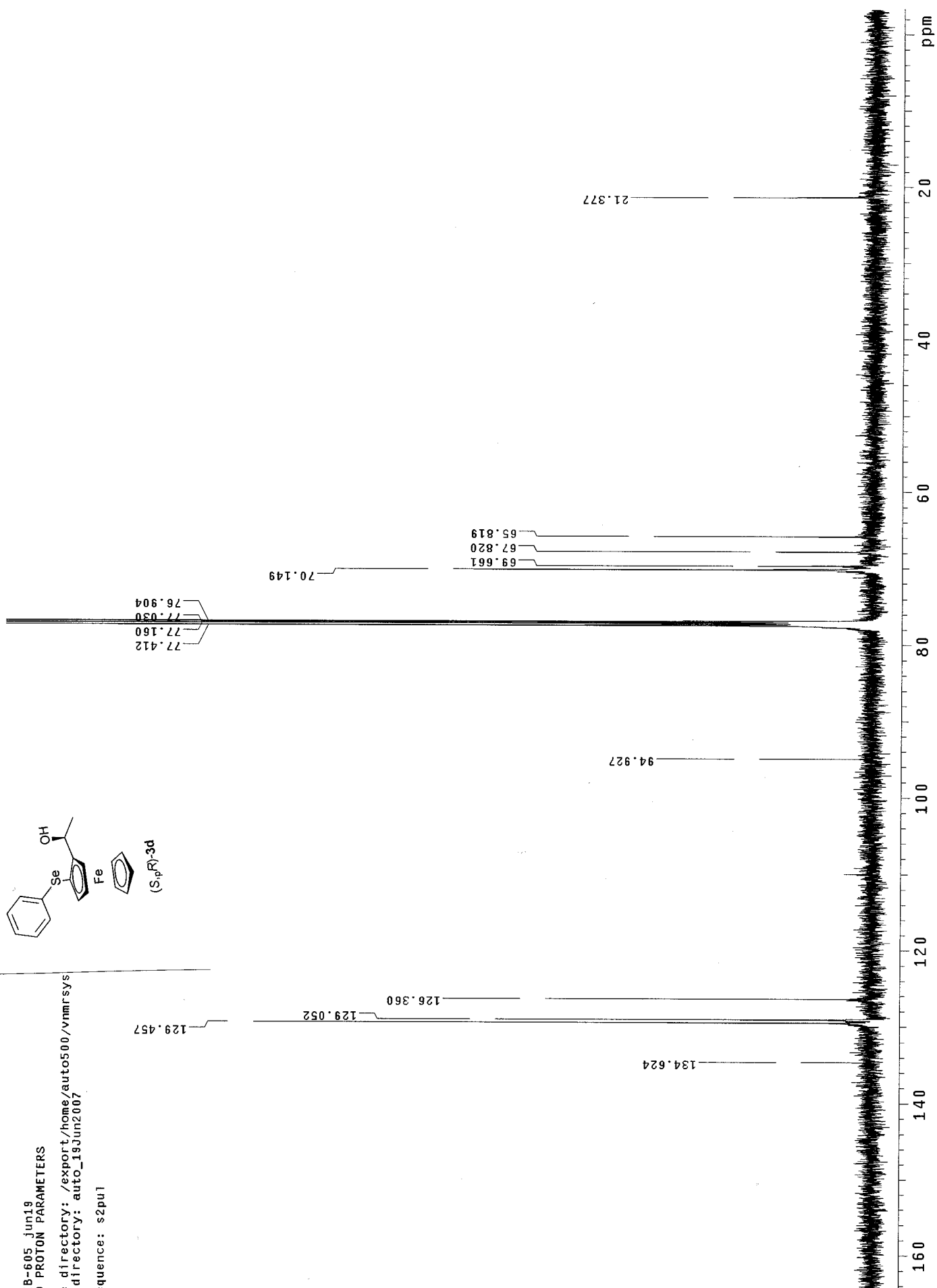
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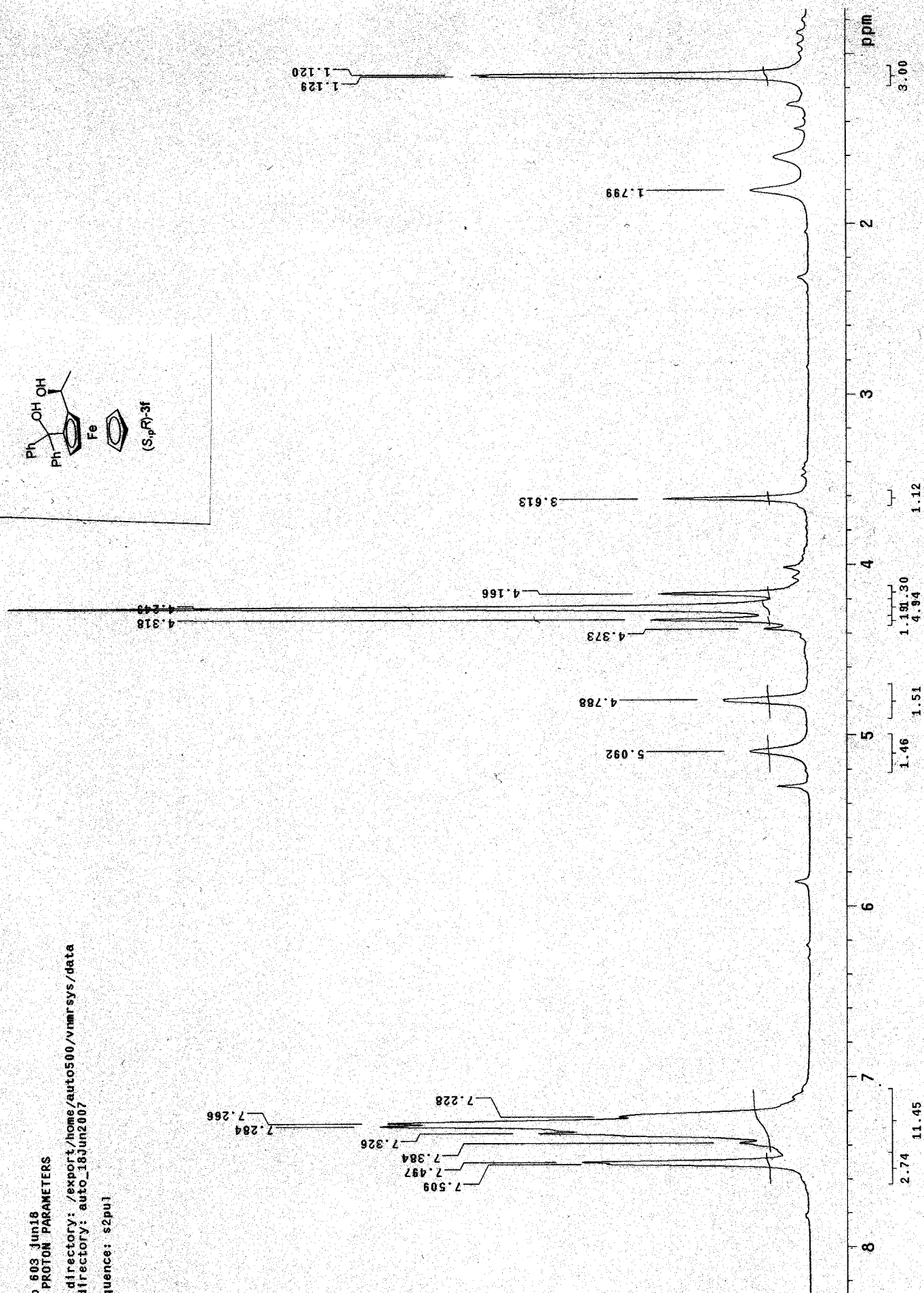
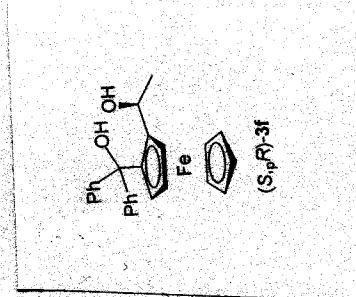
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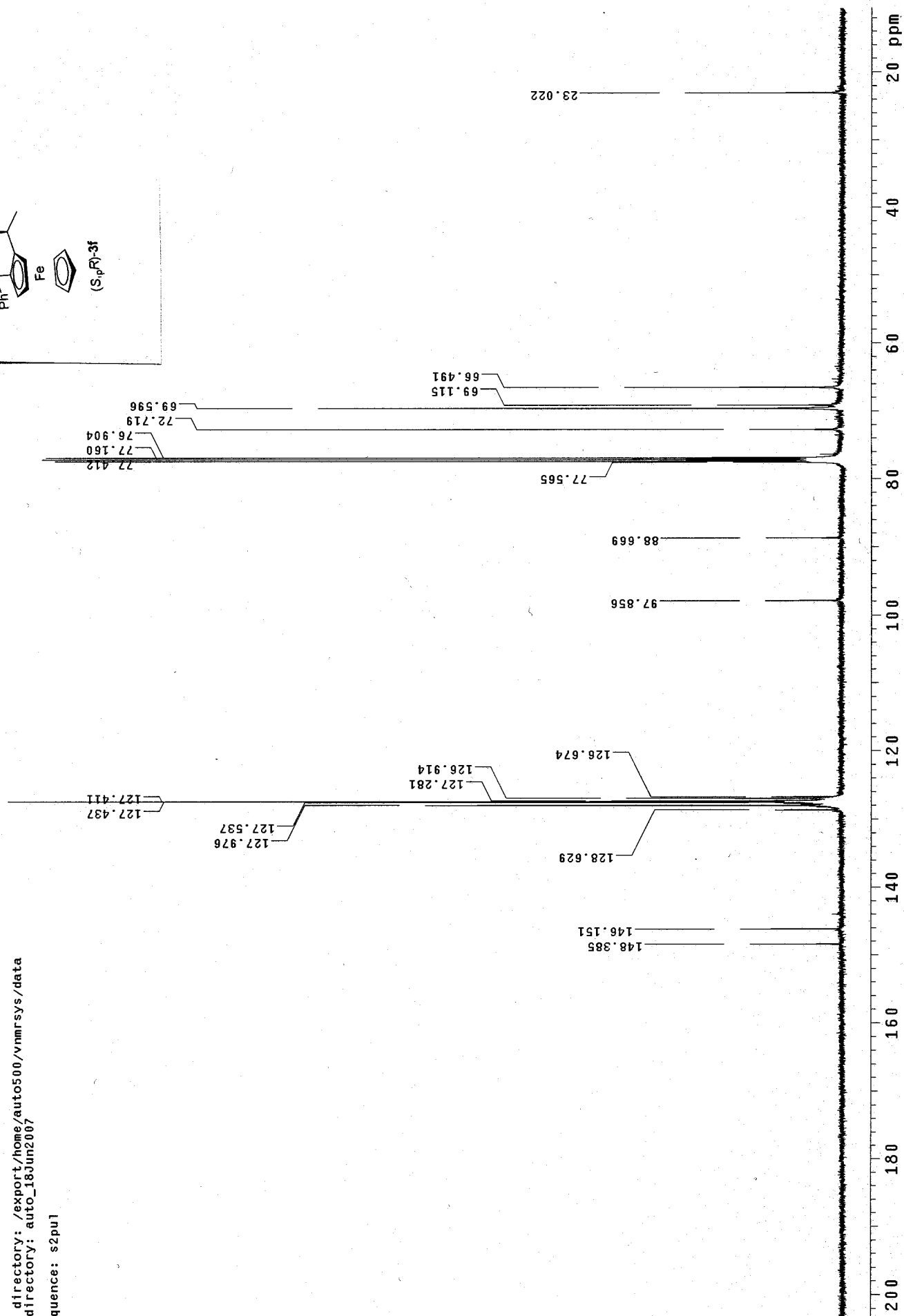
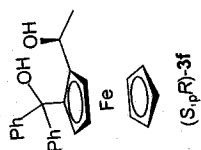
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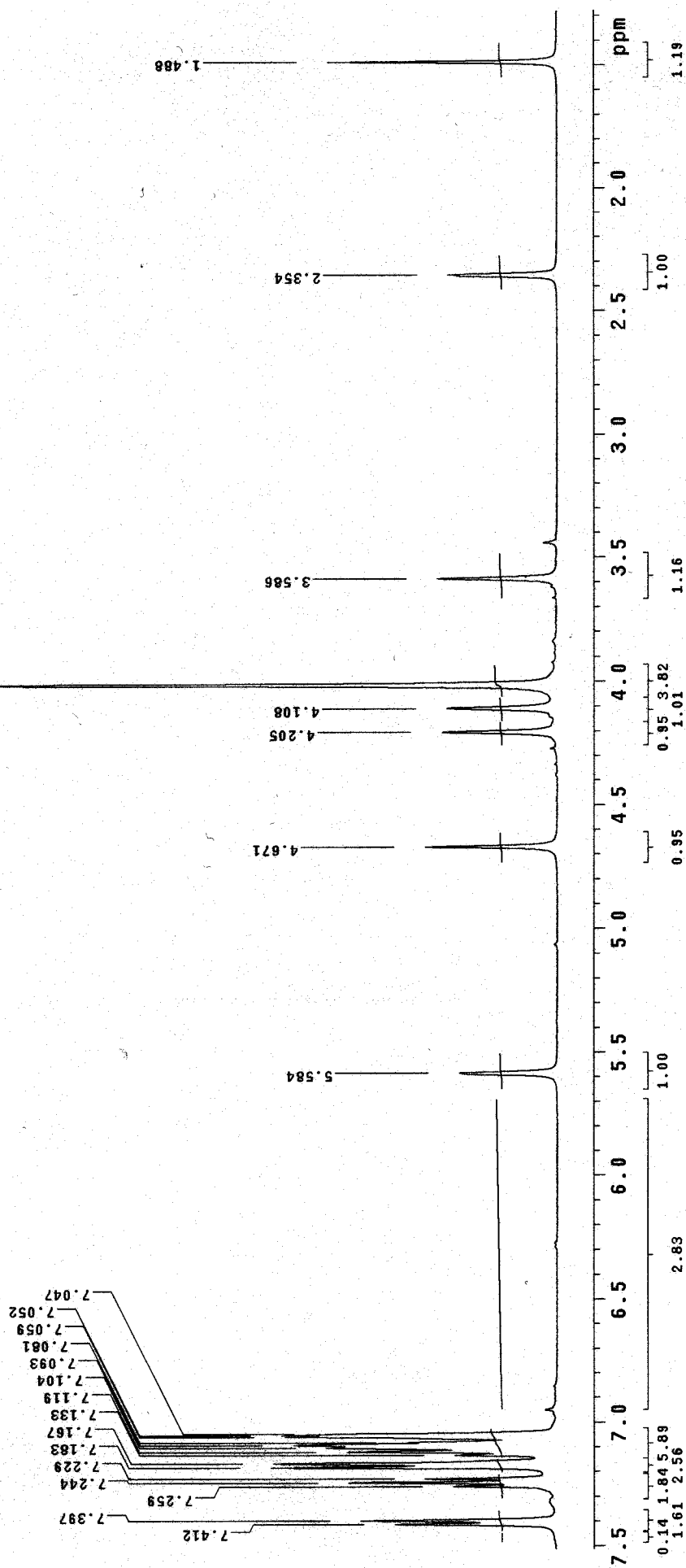
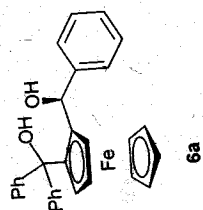


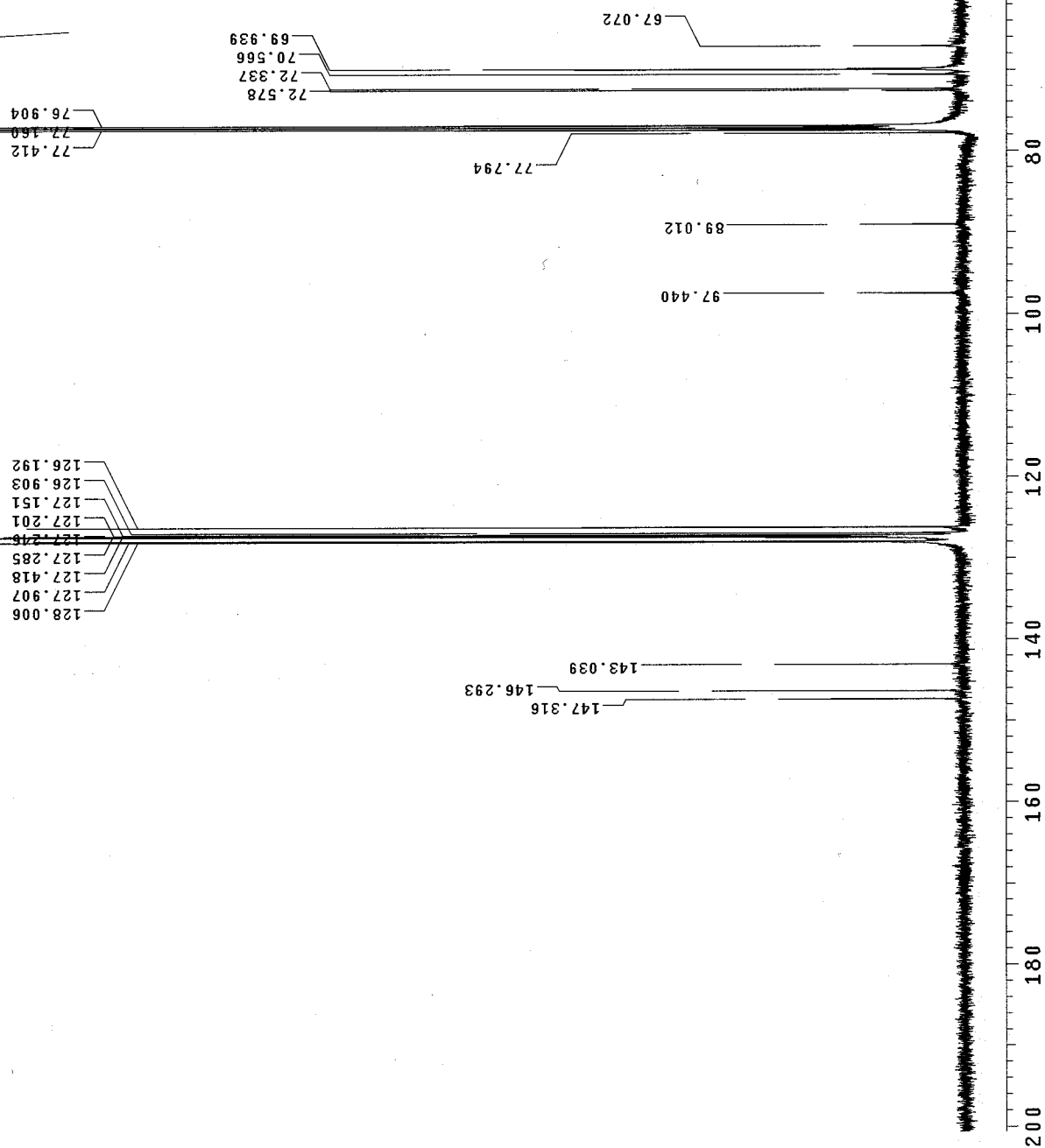
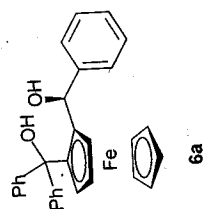
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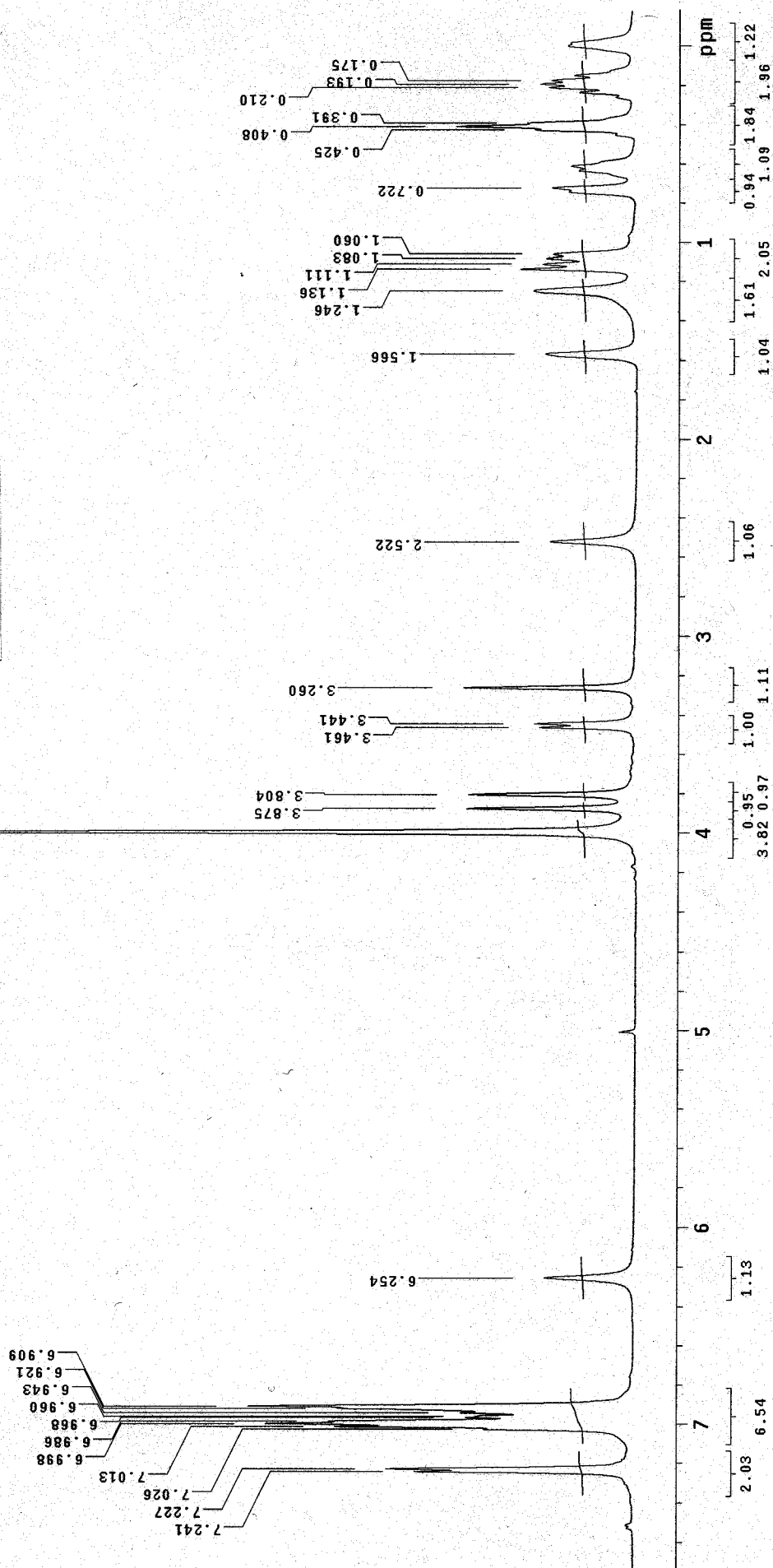
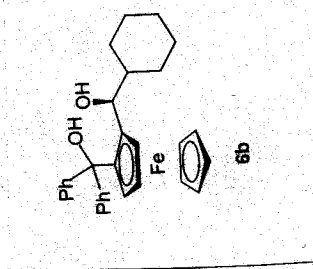


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