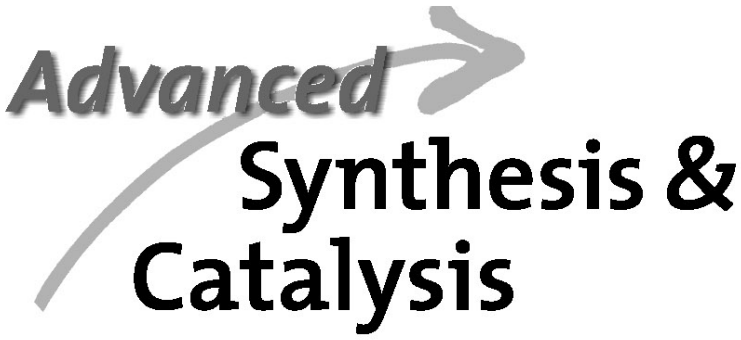

Supporting Information

Small Peptide-Catalyzed Enantioselective Michael Additions of Ketones to Nitroolefins

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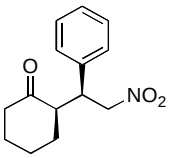
Supporting Information

General. ^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer for solution in $CDCl_3$ with tetramethylsilane (TMS) as internal standard; *J*-values are in Hz. Nitro olefins except *trans*-®-nitrostyrene were prepared according to the literature.[1] Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with silica gel coated plates. Flash Column Chromatography was performed with Merck silica gel 60 (230-400 mesh) at increased pressure. The optical purities of the Michael adducts were determined by HPLC analysis using a chiral stationary phase column. The HPLC was carried out using a Waters 2690 Millennium with photodiode array detector. Optical rotations were recorded on a Perkin Elemer 241 Polarimeter (λ = 589 nm, 1 dm cell). High-resolution mass spectra were recorded on an IonSpec FTMS mass spectrometer with a DHB-matrix.

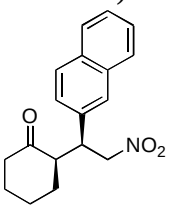
General procedure for the conjugate addition of a ketone to a nitroolefin

To a suspension of catalyst (30 mol%) in DMSO (0.5 mL), NMP (0.5 mL) and H_2O (45 μL, 10 equiv.) was added the relevant ketone (0.75 mmol) and nitroolefin (0.25 mmol). The resulting mixture was stirred for the time and temperature given in the tables. The reaction was quenched with brine and extracted with ethyl acetate (3x10 mL), the combined organic phase was dried over anhydride Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel/pentane: ethyl acetate = 10:1~4:1) to give the Michael products. The ee of the product was determined by chiral HPLC analysis. Relative (*syn*) and absolute configuration of the product was determined by comparison with the known ^{1}H-NMR data and optical rotation values. Compounds **3a**, **3b**, **3c**, **3d**, **3h, 3i** and **3k** are known.[1]

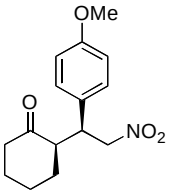
1 (a) McNulty, J.; Steere, J. A.; Wolf, S. *Tetrahedron Letters* **1998**, *39*, 8013-8016.; (b) Mahmood, S. Y.; Lallemand, Marie-Christine; Sader-Bakaouni, L.; Charton, O.; Verite, P.; Dufat, H.; Tillequin, F. Tetrahedron **2004**, *60*, 5105-5110. (c) Andrey, O.; Alexakis, A.; Tomassini, A.; Bernardinelli, G. *Adv. Synth. Catal.* **2004**, 346, 1147. $[\alpha]_D^{20}$ = -17.9 (c 0.5, $CHCl_3$) for *ent*-**3a**. (d) List, B.; Porjarliev, P.; Martin, H. J. *Org.Lett.* **2001**, *3*, 2423. (e) Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H.; *J. Am. Chem. Soc.* **2004**, *126*, 9558. (f) Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, III, C. F. *Org. Lett*. **2004**, *6*, 2527.



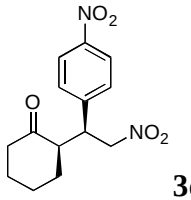
3a: a white solid (96.6% ee): $[\alpha]_D^{25}$ = +27.4 (c 0.5, $CHCl_3$).[1c] ^1H NMR ($CDCl_3$, TMS, 400 MHz) δ = 7.40-7.10 (5H, m), 4.93 (1H, dd, *J* = 12.4, 4.4 Hz), 4.64 (1H, dd, *J* = 12.4, 9.6 Hz), 3.76 (1H, dt, *J* = 9.6, 4.4 Hz), 2.78-2.72 (1H, m), 2.52-2.32 (2H, m), 2.15-2.05 (1H, m), 1.84-1.48 (4H, m), 1.30-1.18 (1H, m). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ = 211.90, 137.74, 128.93, 128.16, 127.77, 78.88, 52.53, 43.93, 42.73, 33.19, 28.51, 25.02. The ee of the product was determined by chiral HPLC analysis (Chiralpak AD column, isohexane/2-propanol = 90/10, 0.5 mL/min, t_R (major) = 19.45 min, t_R (minor) = 22.82 min). MALDI-TOF MS: 270.1108; $C_{14}H_{17}NO_3$ ($M+Na^+$: calcd 270.1106).



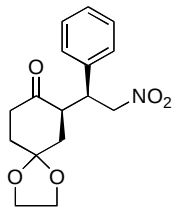
3b: a white solid (98.4% ee, 79.5% yield), $[\alpha]_D^{25}$ = +39.2 (c 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.83-7.75 (2H, m), 7.63 (1H, s), 7.51-7.45 (2H, m), 7.28 (1H, dd, *J* = 8.4, 1.8 Hz), 5.03 (1H, dd, *J* = 12.6, 4.5 Hz), 4.73 (1H, dd, J = 12.6, 9.9 Hz), 3.95 (1H, dt, *J* = 9.9, 4.5Hz), 2.84-2.73 (1H, m), 2.53-2.34 (2H, m), 2.10-2.03 (1H, m), 1.78-1.48 (4H, m), 1.33-1.19 (1H, m). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ = 211.81, 135.07, 133.28, 132.76, 128.79, 127.73, 127.72, 127.59, 126.38, 126.11, 125.18, 78.79, 52.39, 44.03, 42.69, 33.23, 28.42, 24.93. The ee of the product was determined by chiral HPLC analysis (Chiralpak AD column, isohexane/2-propanol = 90/10, 0.5 mL/min, t_R (major) = 27.15 min, t_R (minor) = 31.26 min).



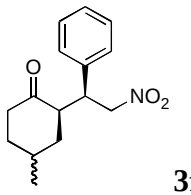
3c: a white solid (92% ee): $[\alpha]_D^{25}$ = +22.7 (c 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.08 (2H, d, *J* = 8.8 Hz), 6.83 (2H, d, *J* = 8.8 Hz), 4.91 (1H, dd, *J* = 12.4, 4.8 Hz), 4.57 (1H, dd, *J* = 12.4, 9.6 Hz), 3.77 (3H, s), 3.71 (1H, dt, *J* = 9.6, 4.8 Hz), 2.69-2-60 (1H, m), 2.48-2.32 (2H, m), 2.11-2.03 (1H, m), 1.88-1.50 (4H, m), 1.28-1.17 (1H, m). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ = 212.01, 158.98, 129.49, 129.12, 114.26, 79.05, 55.16, 52.63, 43.16, 42.66, 33.08, 28.46, 24.95. The ee of the product was determined by chiral HPLC analysis (Chiralpak AD column, isohexane/2-propanol = 90/10, 0.5 mL/min, t_R (major) = 23.81 min, t_R (minor) = 30.07 min).



3d: a yellow viscous liquid (93.5% ee): $[\alpha]_D^{25}$ = +34.3 (c 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$, TMS, 400 MHz) δ = 8.20 (2H, d, *J* = 8.8 Hz), 7.38 (2H, d, *J* = 8.8 Hz), 4.98 (1H, dd, *J* = 13.2, 4.4 Hz), 4.69 (1H, dd, *J* = 13.2, 10.0 Hz), 3.92 (1H, dt, *J* = 10.0, 4.4 Hz), 2.75-2.67 (1H, m), 2.52-2.34 (2H, m), 2.14-2.09 (1H, m), 1.84-1.55 (4H, m), 1.30-1.18 (1H, m). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ = 210.76, 147.46, 145.51, 129.29, 124.08, 77.95, 52.21, 43.73, 42.70, 33.16, 28.26, 25.08. The ee of the product was determined by chiral HPLC analysis (Chiralpak OJ column, isohexane/2-propanol = 80/20, 0.5 mL/min, t_R (major) = 101.45 min, t_R (minor) = 93.69 min).



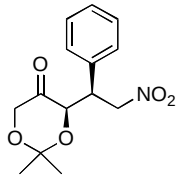
3e: a white solid (92.8% ee): $[\alpha]_D^{25}$ = +11.7 (c 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$, TMS, 400 MHz) δ = 7.33-7.25 (3H, m), 7.15 (2H, *J* = 6.8 Hz), 4.94 (1H, dd, *J* = 12.4, 4.8 Hz), 4.61 (1H, dd, *J* = 12.4, 9.6 Hz), 3.97-3.81 (5H, m), 3.09-3.01 (1H, m), 2.74-2.65 (1H, m), 2.44 (1H, ddd, *J* = 14.0, 5.2, 3.6 Hz), 2.06-2.01 (1H, m), 1.98 (1H, dt, *J* = 13.2, 5.2 Hz), 1.68 (1H, ddd, *J* = 13.2, 5.6, 3.6 Hz), 1.54 (1H, t, *J* = 13.2 Hz). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ = 210.32, 137.23, 128.99, 128.19, 127.86, 106.98, 78.87, 64.76, 64.50, 48.12, 43.38, 39.27, 38.57, 35.02. The ee of the product was determined by chiral HPLC analysis (Chiralpak AD column, isohexane/2-propanol = 80/20, 0.5 mL/min, t_R (major) = 17.68 min, t_R (minor) = 27.81 min).



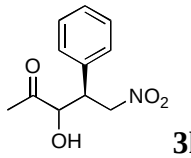
3f: (**3f**:**3f'** = 2:1)^1H NMR ($CDCl_3$, TMS, 400 MHz) δ = 7.36-7.25 (3H, m), 7.16 (2H, *J* = 6.8 Hz), 4.69 (1H, dd, *J* = 12.8, 4.4 Hz), 4.61 (1H, dd, *J* = 12.8, 10.0 Hz), 3.79 (1H, dt, *J* = 10.8, 4.4 Hz), 2.72 (1H, ddd, *J* = 12.8, 6.0, 4.4 Hz), 2.50 (2H, t, *J* = 6.0 Hz), 2.06-1.97 (2H, m), 1.65-1.57 (1H, m), 1.47-1.39 (2H, m), 0.97 (3H, t, *J* = 6.8 Hz). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ = 212.64, 136.91, 128.78, 127.68, 127.67, 78.77, 49.73, 43.76, 38.22, 37.53, 34.04, 26.15, 19.08. The ee of the product could not be determined by chiral HPLC analysis.

3f' (92% ee):^1H NMR ($CDCl_3$, TMS, 400 MHz) δ = 7.34-7.25 (3H, m), 7.15 (2H, *J* = 7.2 Hz), 4.97 (1H, dd, *J* = 12.4, 4.8 Hz), 4.63 (1H, dd, *J* = 12.4, 9.6 Hz), 3.71 (1H, dt, *J* = 9.6, 4.8 Hz), 2.80-2.72 (1H, m), 2.46-2.41 (2H, m), 2.07-2.02 (1H, m), 1.85-1.70 (1H, m), 1.68-1.61 (1H, m), 1.43-1.32 (1H, m), 1.09-0.86 (1H, m), 0.85 (1H, t, *J* = 6.4 Hz). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ = 212.45, 137.80, 128.91, 128.19, 127.73, 78.86, 51.27, 43.91, 42.17, 41.24, 36.43, 32.25, 20.95. The ee of the product was determined by

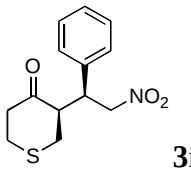
chiral HPLC analysis (Chiralpak AD column, isohexane/2-propanol = 90/10, 0.5 mL/min, t_R (major) = 15.45 min, t_R (minor) = 21.91 min).



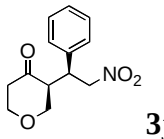
3g: a colorless liquid (92% ee): $[\alpha]_D^{25}$ = +112.5 (c 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$, TMS, 400 MHz) δ = 7.38-7.21 (5H, m), 4.92 (1H, dd, *J* = 12.8, 9.2 Hz), 4.67 (1H, dd, *J* = 12.8, 6.8 Hz), 4.58 (1H, dd, *J* = 3.6, 1.2 Hz), 4.12 (1H, ddd, *J* = 9.2. 6.8, 4.0 Hz), 3.90-3.86 (2H, m), 1.46 (3H, s), 1.45 (3H, s). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ = 206.72, 134.82, 129.39, 128.49, 128.07, 101.13, 76.34, 74.54, 66.99, 43.22, 24.01, 23.22. The ee of the product was determined by chiral HPLC analysis (Chiralpak AS column, isohexane/2-propanol = 90/10, 0.5 mL/min, t_R (major) = 18.48 min, t_R (minor) = 21.28 min). MALDI-TOF MS: 302.1007; $C_{14}H_{17}NO_5$ ($M+Na^+$: calcd 302.1004).



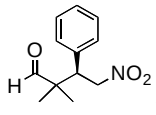
3h: a white solid (2:1 dr (*anti*-isomer:*syn*-isomer*)): ^1H NMR ($CDCl_3$, TMS, 400 MHz) δ = 8.42-7.16 (5H+2.5H*, m), 5.03 (0.5H*, dd, *J* = 7.7, 13.14 Hz), 4.83 (1H, dd, *J* = 6.2, 13.5 Hz), 4.74 (0.5H*, dd, *J* = 7.1, 13.4 Hz), 4.65 (1H, dd, *J* = 8.2, 13.2 Hz), 4.52 (0.5H*, m), 4.40 (1H, m), 4.03 (0.5H*, m), 3.86-3.80 (1H, m), 3.73 (1H+0.5H*, m), 2.17 (1.5H*, s), 2.08 (3H, s). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ = 208.2, 206.5, 137.4, 134.0, 129.6, 129.2, 128.9, 128.7 (2C), 128.2, 78.9, 76.3, 47.2, 46.0, 26.7, 25.7. The ee of the product was determined by chiral HPLC analysis (Chiralpak AD column, hexane/2-propanol = 90/10, 0.5 mL/min, $t_{R,\ anti}$ (major) = 27.43 min, $t_{R,\ anti}$ (minor) = 25.28 min, $t_{R,\ syn}$ (major) = 22.63 min, $t_{R,\ anti}$ (minor) = 21.22 min).



3i: a white solid (98% ee): $[\alpha]_D^{25}$ = +28.6° (c 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, TMS, 400 MHz) δ = 7.37-7.17 (5H, m), 4.75 (1H, dd, *J* = 12.4, 4.4 Hz), 4.62 (1H, dd, *J* = 12.4, 9.6 Hz), 3.76 (1H, dt, *J* = 10.4, 4.4 Hz), 3.07-2.92 (3H, m), 2.88-2.75 (2H, m), 2.63-2.56 (1H, m), 2.48-2.41 (4H, m). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ = 209.49, 136.47, 129.28, 128.27, 128.13, 78.58, 54.95, 44.48, 43.45, 35.08, 31.55. The ee of the product was determined by chiral HPLC analysis (Chiralpak AS column, isohexane/2-propanol = 50/50, 0.5 mL/min, t_R (major) = 16.40 min, t_R (minor) = 18.52 min).

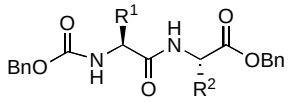


3j: a white solid (90% ee): $[\alpha]_D^{25}$ = +30.2° (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ = 7.34-7.17 (5H, m), 4.93 (1H, dd, *J* = 12.8, 4.8 Hz), 4.64 (1H, dd, *J* = 12.8, 10.4 Hz), 4.14 (1H, m), 3.86-3.75 (2H, m), 3.70 (1H, ddd, *J* = 11.6, 5.2, 1.2 Hz), 3.27 (1H, dd, *J* = 11.6, 8.8 Hz), 2.88 (1H, dddd, J = 10.4, 8.8, 5.6, 1.2 Hz), 2.67 (1H, dddd, *J* = 14.0, 10.0, 6.4, 1.2 Hz), 2.56 (1H, dt, *J* = 14.0, 4.0 Hz). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ = 207.32, 136.21, 129.18, 128.23, 127.87, 78.64, 71.52, 68.92, 53.20, 42.91, 41.26. The ee of the product was determined by chiral HPLC analysis (Chiralpak AD column, isohexane/2-propanol = 70/30, 0.5 mL/min, t_R (major) = 16.50 min, t_R (minor) = 27.55 min).



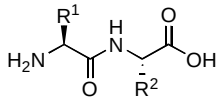
3k: a colorless liquid (57% ee): $[\alpha]_D^{25}$ = +5.0° (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ = 9.52 (1H, s), 7.32-7.17 (5H, m), 4.85 (1H, dd, *J* = 12.8, 11.2 Hz), 4.68 (1H, dd, *J* = 12.8, 4.4 Hz), 3.77 (1H, dd, J = 11.2, 4.4 Hz), 1.12 (3H, s), 0.99 (3H, s). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ = 204.19, 135.33, 129.02, 128.65, 128.08, 76.26, 48.41, 48.16, 21.59, 18.82. The ee of the product was determined by chiral HPLC analysis (Chiralpak AS column, isohexane/2-propanol = 90/10, 0.5 mL/min, t_R (major) = 24.99 min, t_R (minor) = 22.30 min).

General procedure for the preparation of di-peptides:

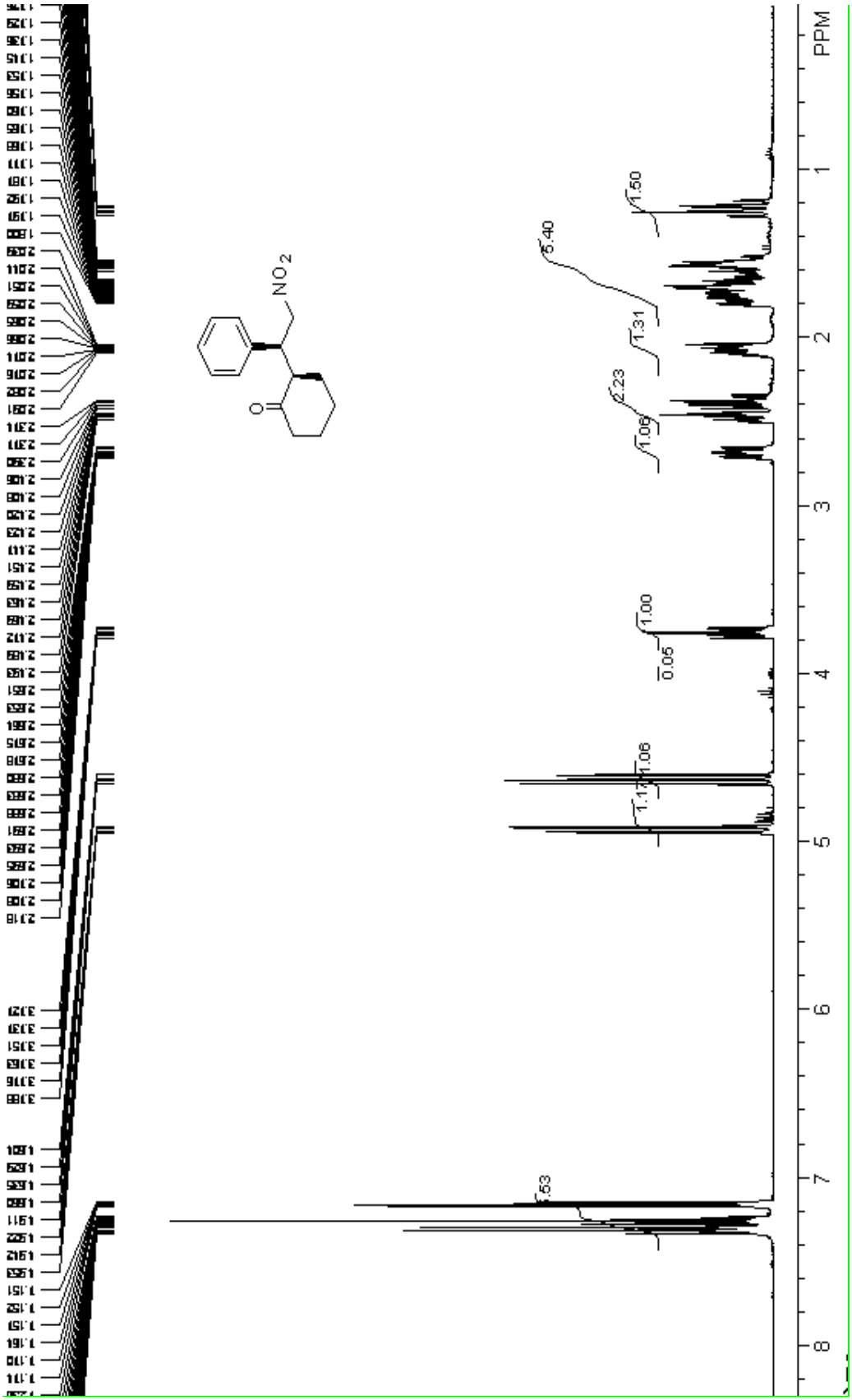


A stirred solution of Cbz-protected α-amino acid (10mmol) in 30 mL dichlomethane is cooled down to -15 °C and neutralized with NMM (N-methyl morpholine, 10 mmol). Next, isobutyl chlorocarbornate (10 mmol) was added. After 20 minutes of stirring a solution of the salt of amino acid ester (10 mmol) and NMM (10 mmol) in 30 mL dichlomethane was added. The mixture is stirred at -15 °C for 1 hour and is next allowed to warm up to room temperature. TLC using AMC stain monitored the reaction progress. At the completion, wash the reaction mixture was extracted with 1N HCl (3×20 mL), 1N Na_2CO_3 (3×20 mL), and brine (30 mL). The organic layer was dried with sodium sulphate. The dipeptide product was checked with TLC and NMR, in most case it was

pure enough for next step. If not, the product was purified by silica-gel column chromatography.



To a solution of protected dipeptide 1g in 20mL methanol, palladium on activated carbon (100 mg, 10wt.%) was added under Argon atmosphere. The reaction mixture was stirred under hydrogen (90 psi) for one day. The reaction was checked by TLC and NMR analyses. At the completion of hydrogenolysis, the Pd/C catalyst was removed by filtration on celite and washed with methanol and water. The combined filtrates were evaporated under reduced pressure. The di-peptide product was checked by NMR analyses and if necessary recrystallization was made in proper solvent.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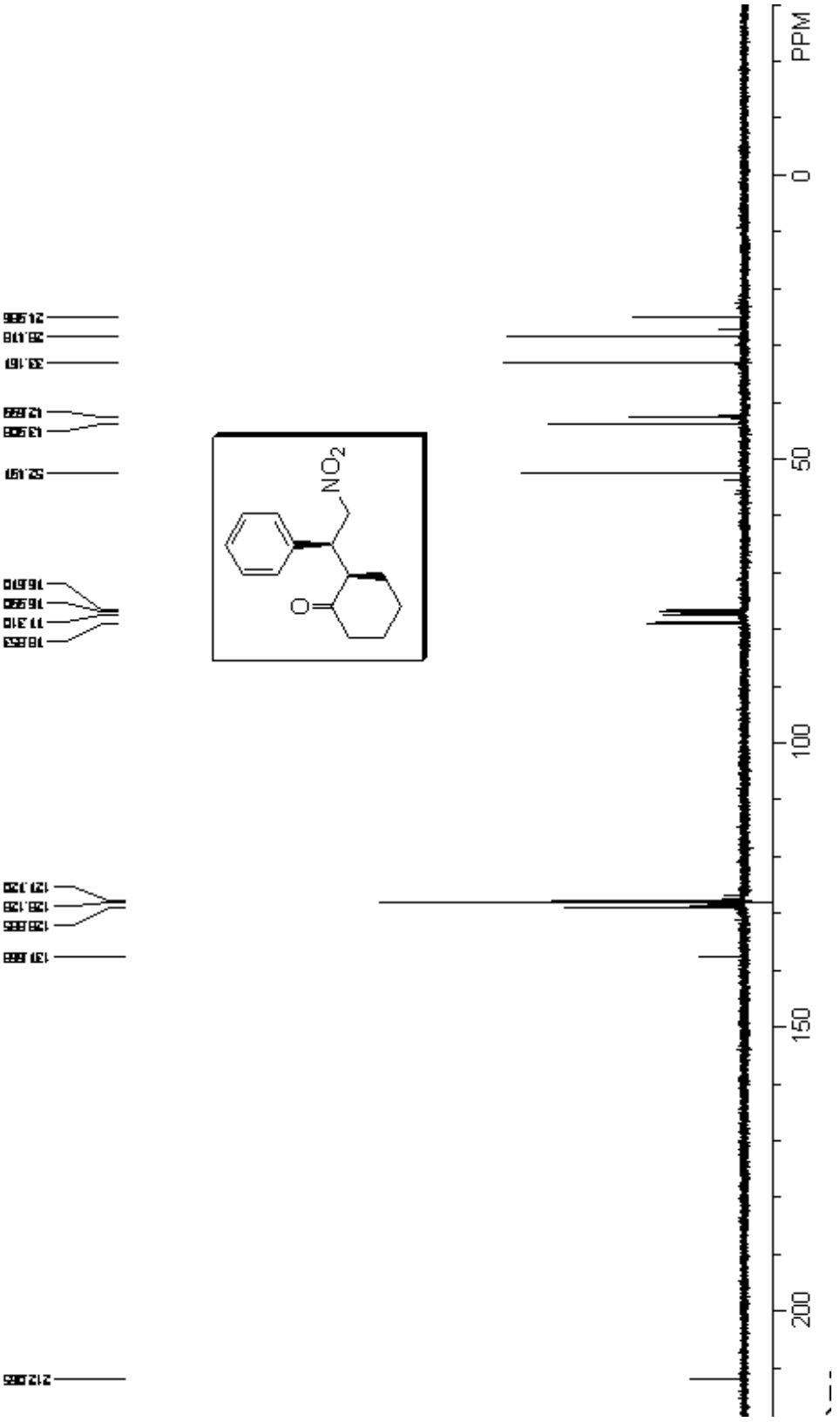
1.06
1.00
0.05
5.40
1.31
2.23
1.06
1.50
PPM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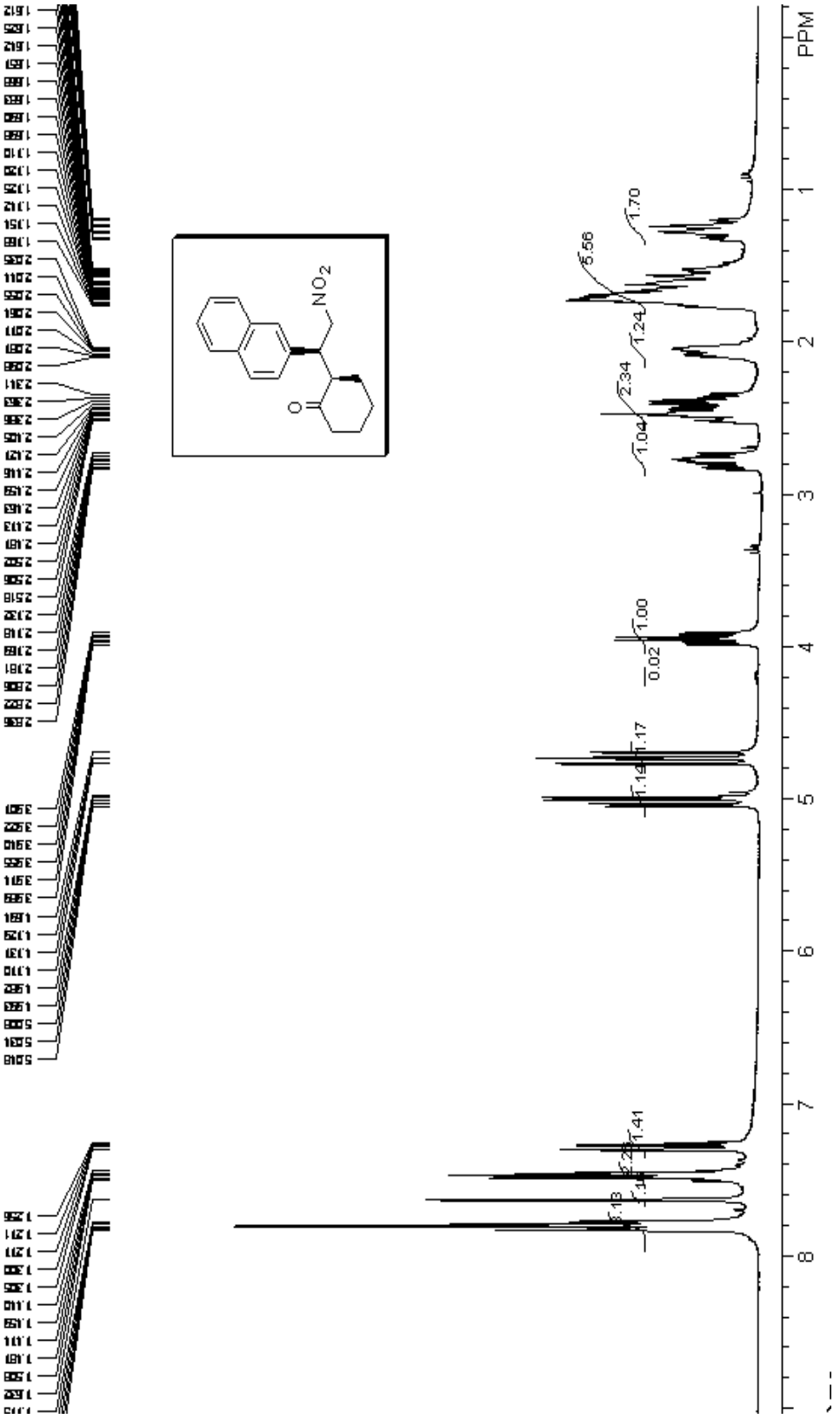
100
150
200
NO2
O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O
PPM
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2
3
4
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6
7
8
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0.02
1.17
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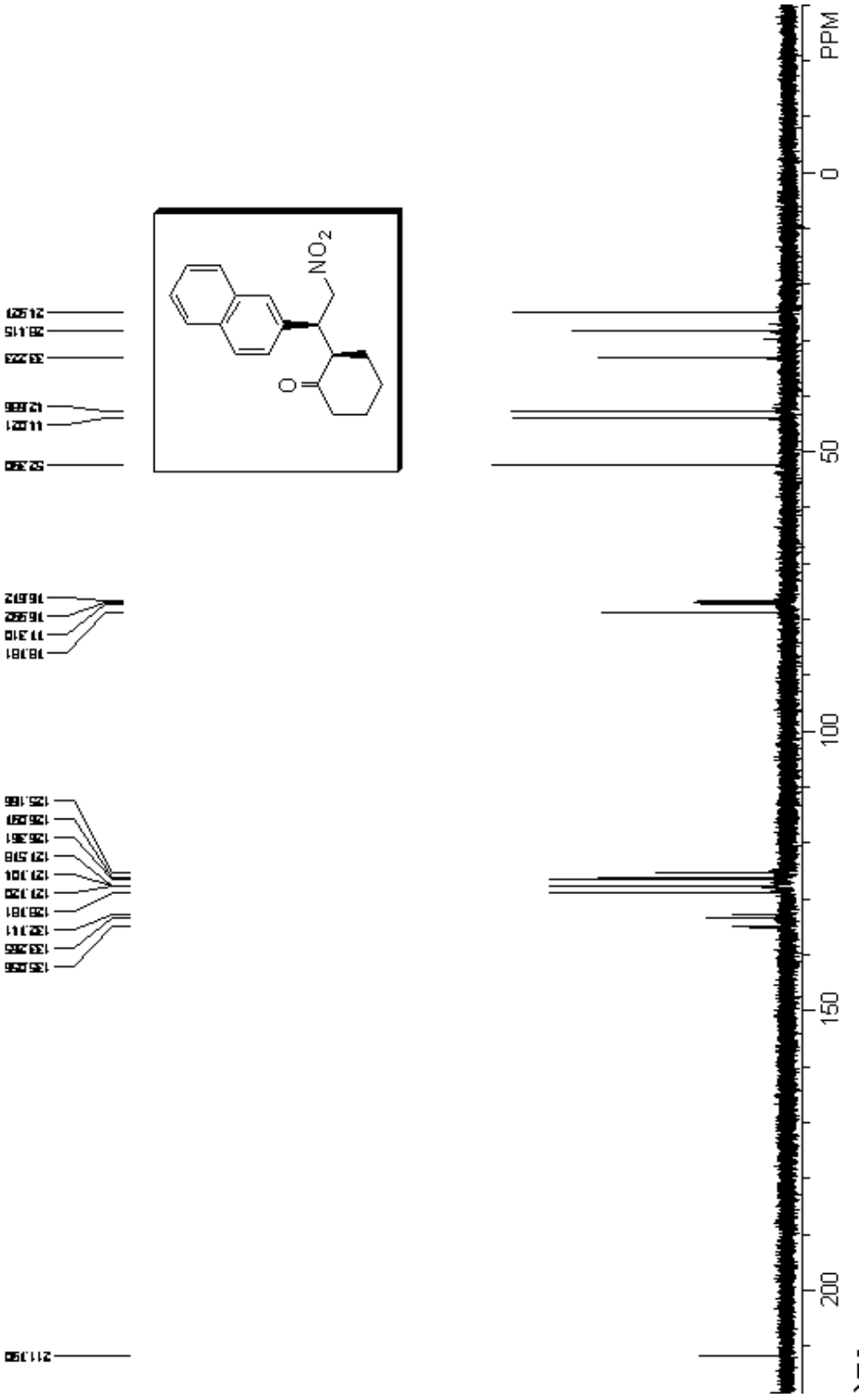
1.41
1.18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O
PPM
0
50
100
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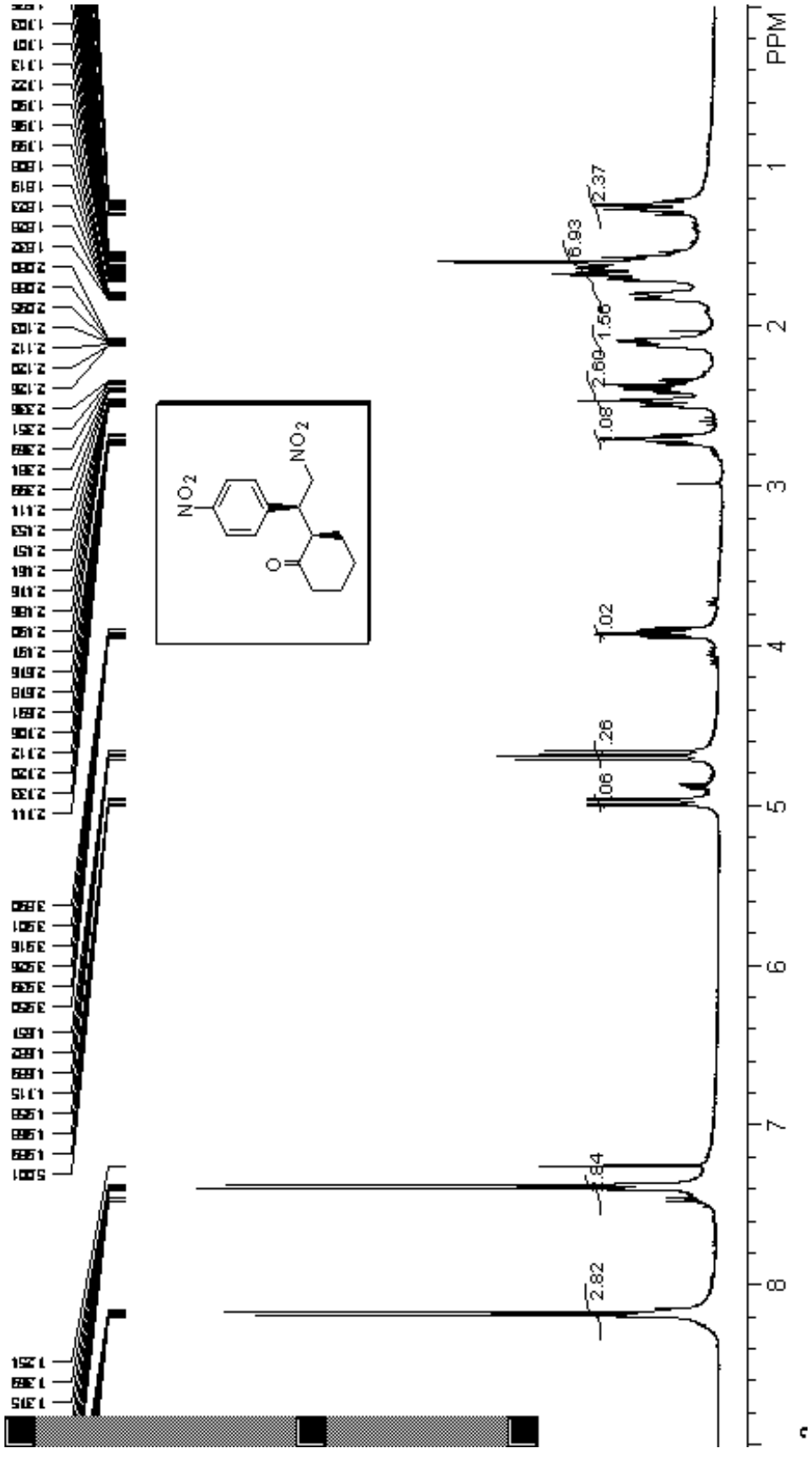
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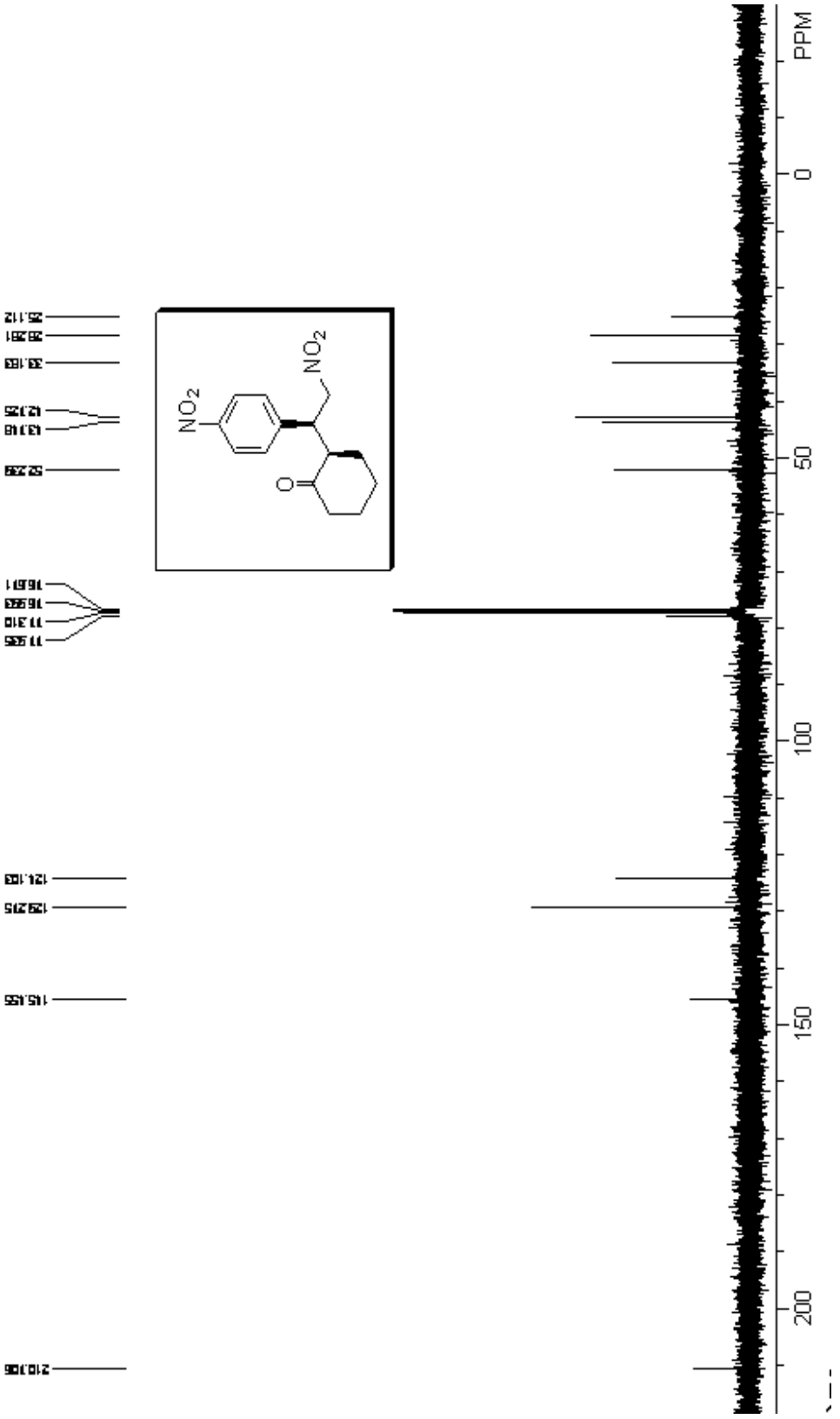
2.82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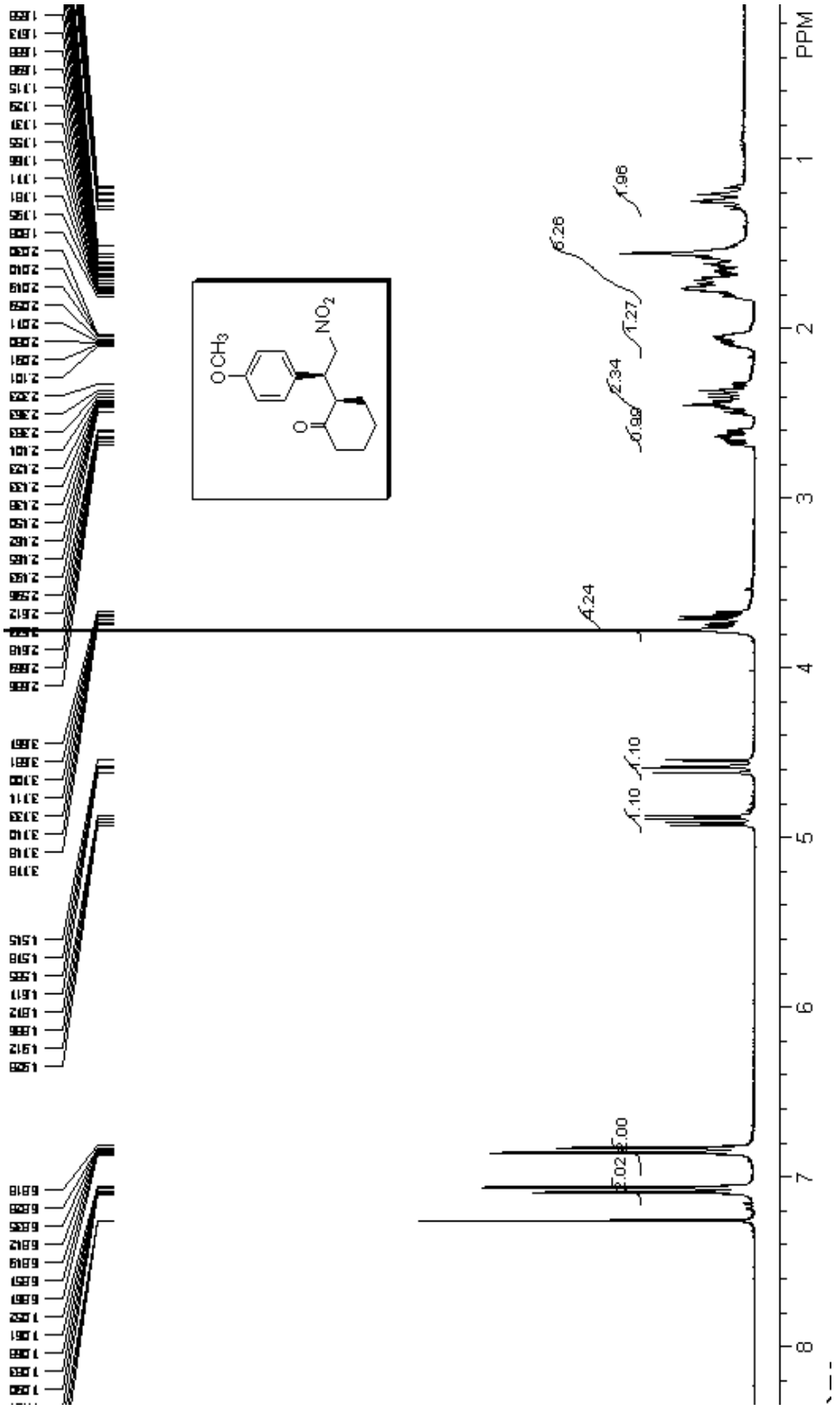
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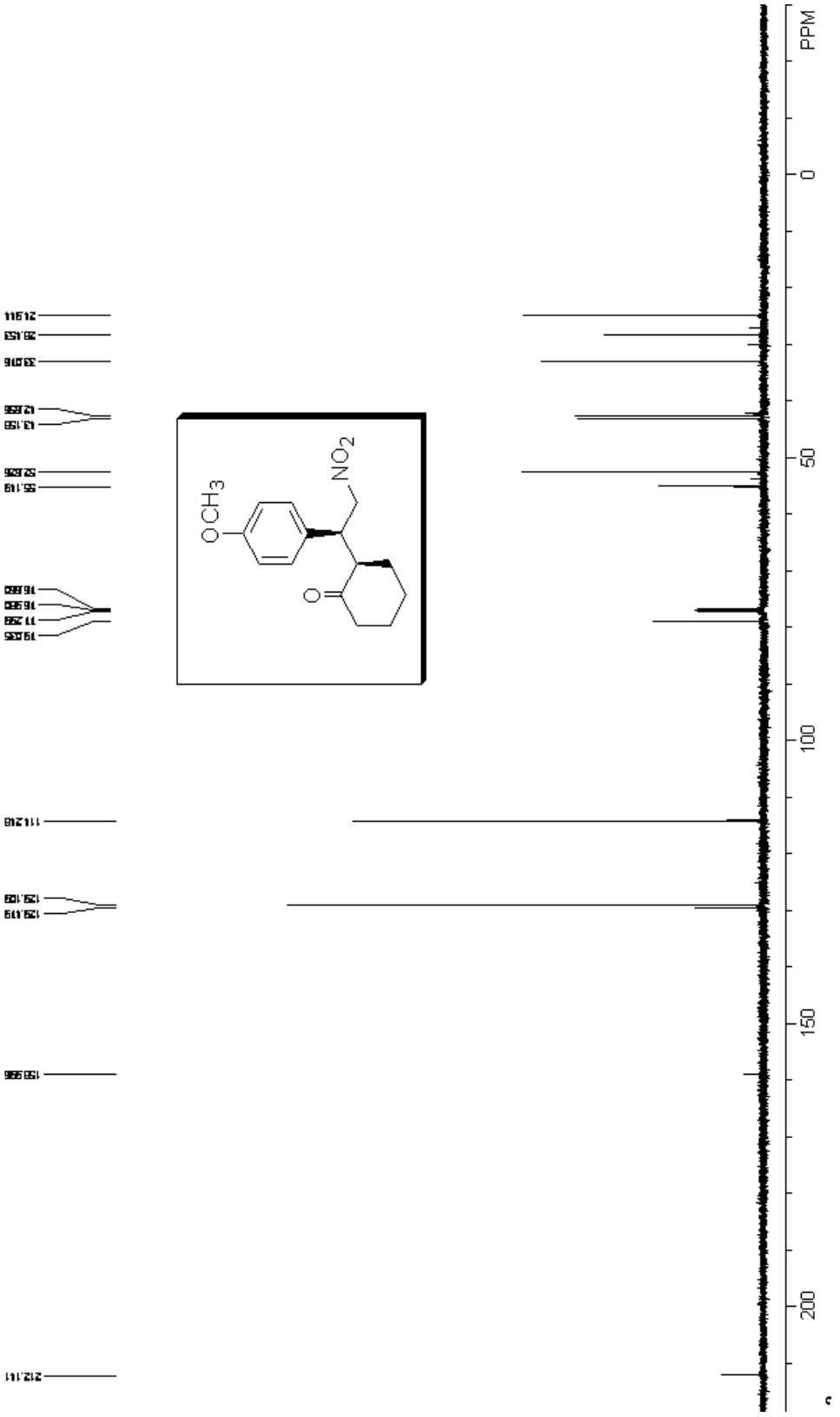
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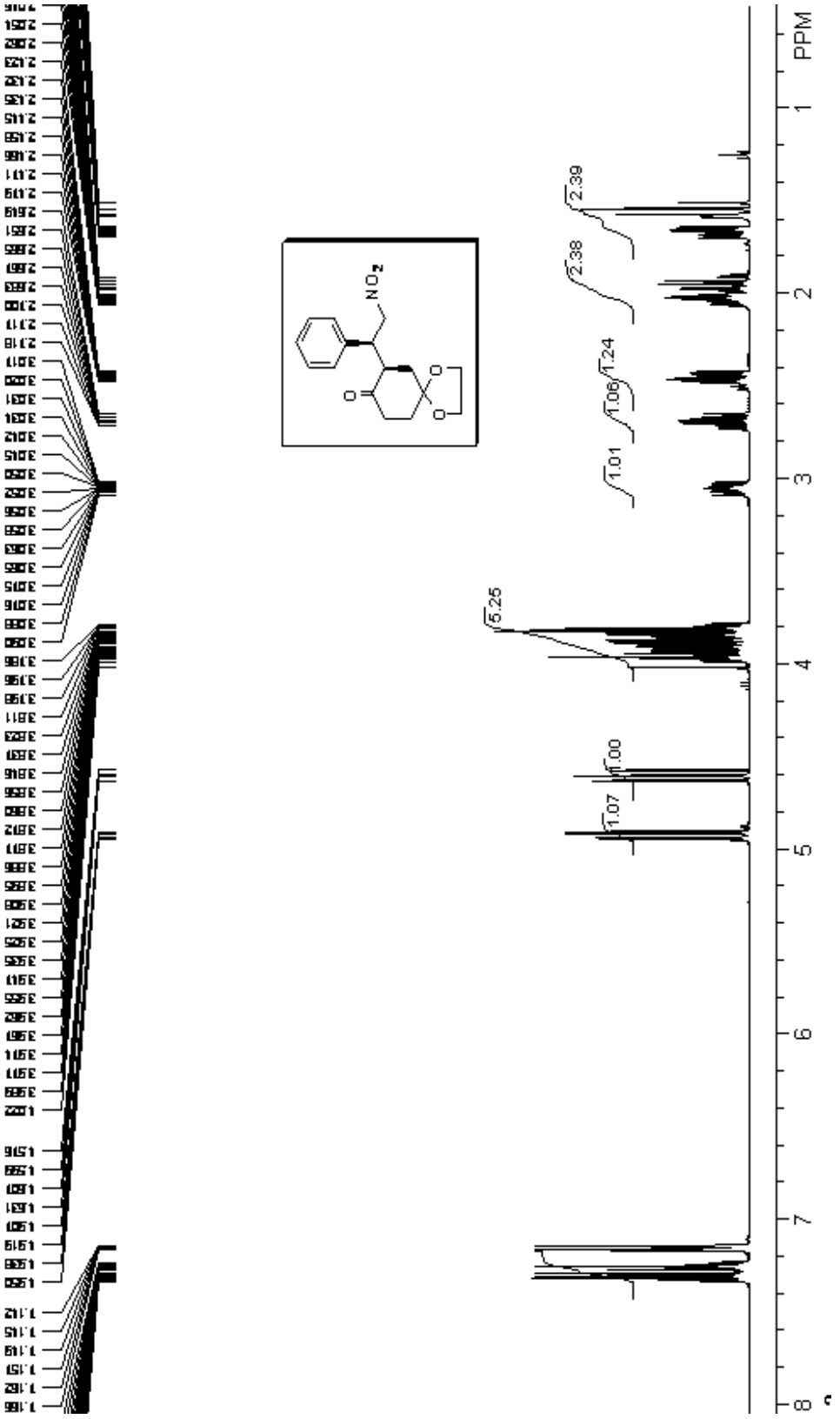
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PPM
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5
6
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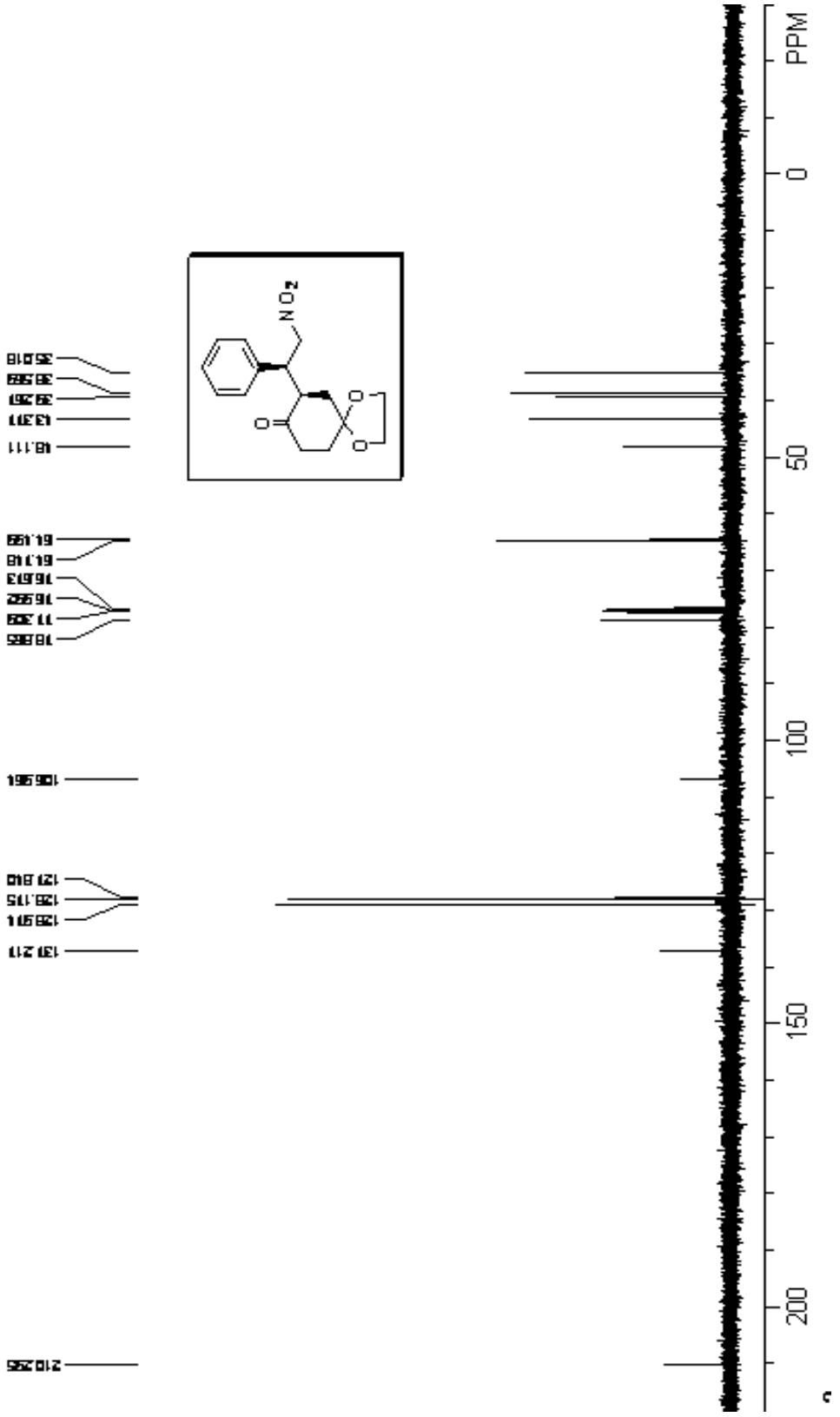
8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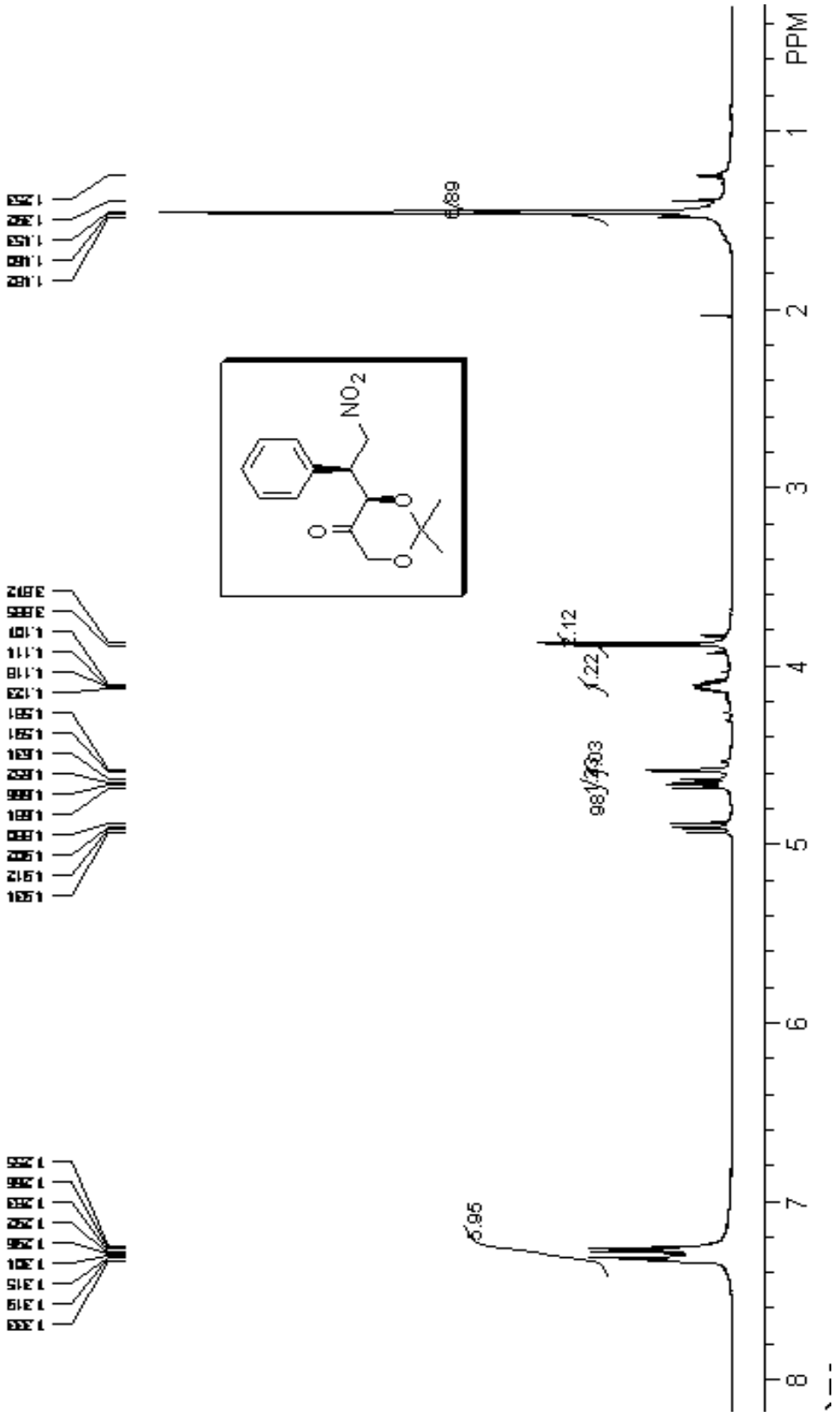
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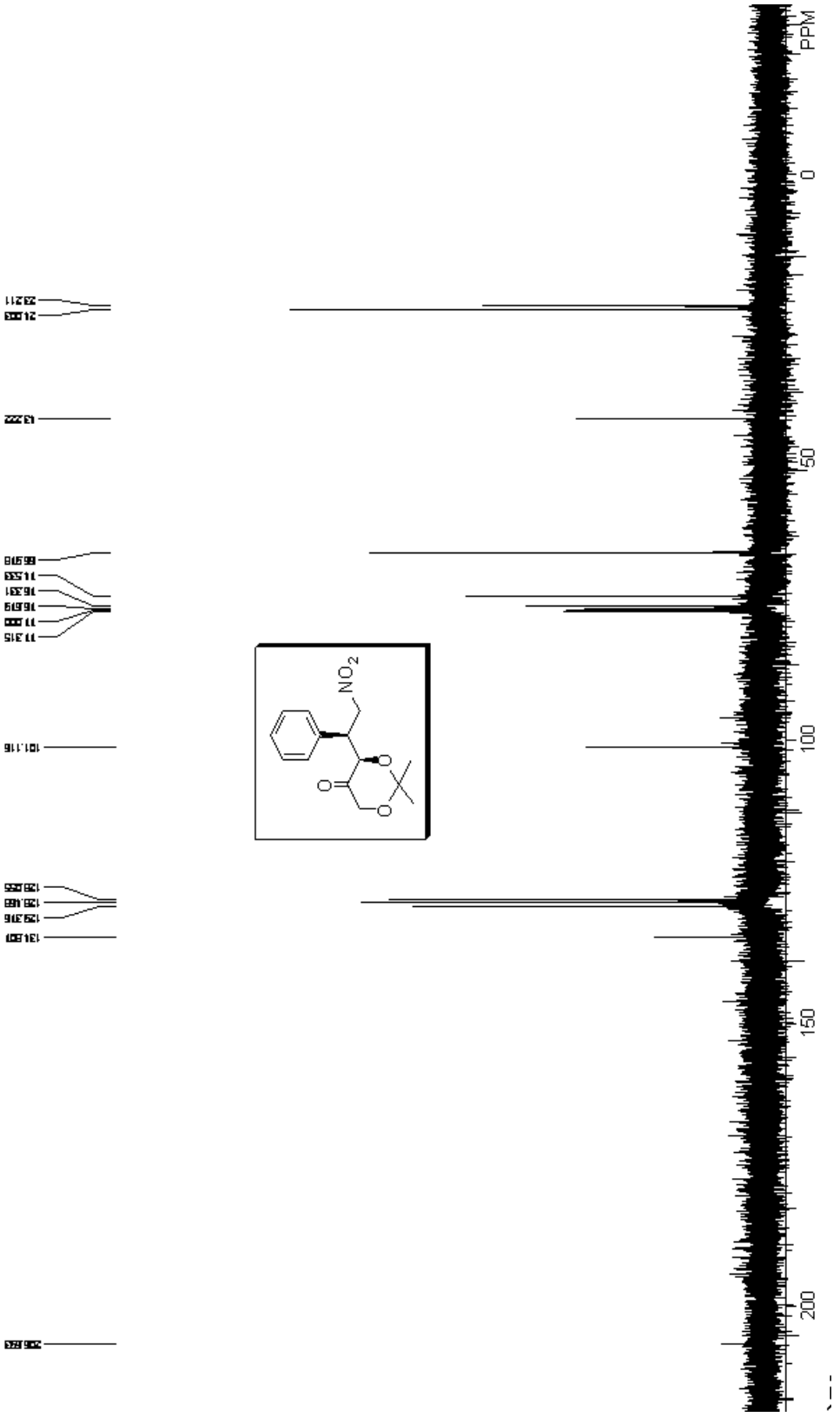
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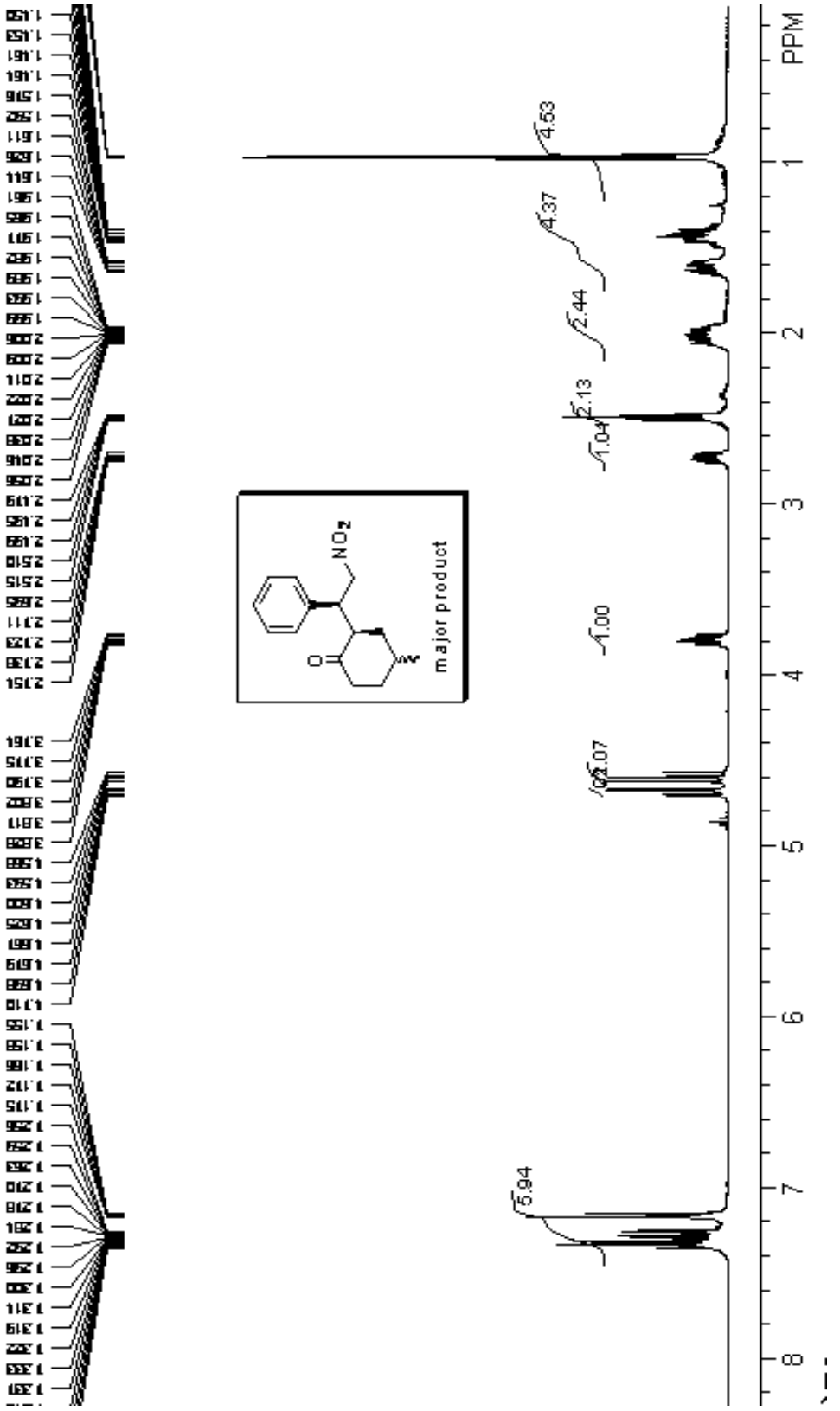
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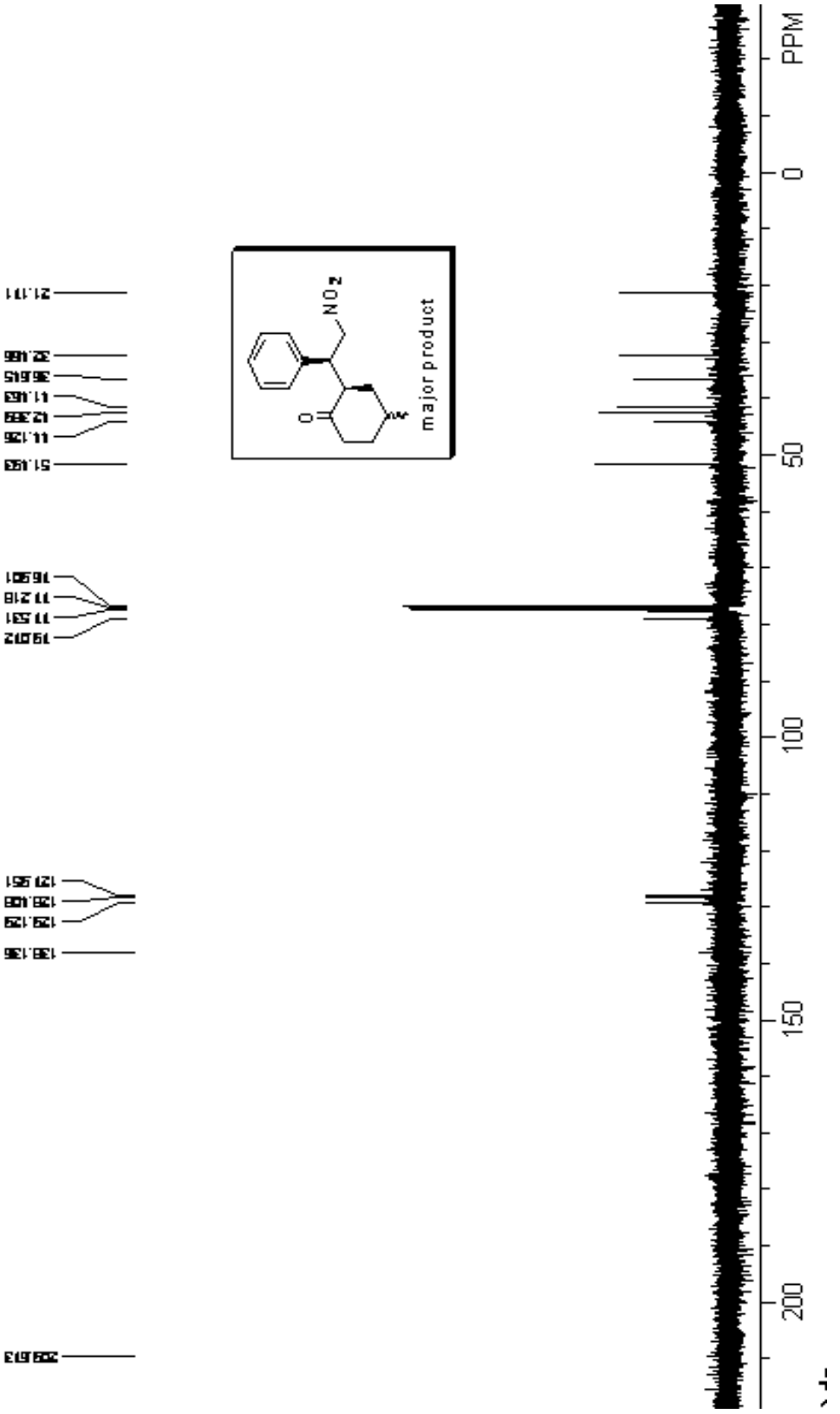
4.53
PPM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PPM
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150
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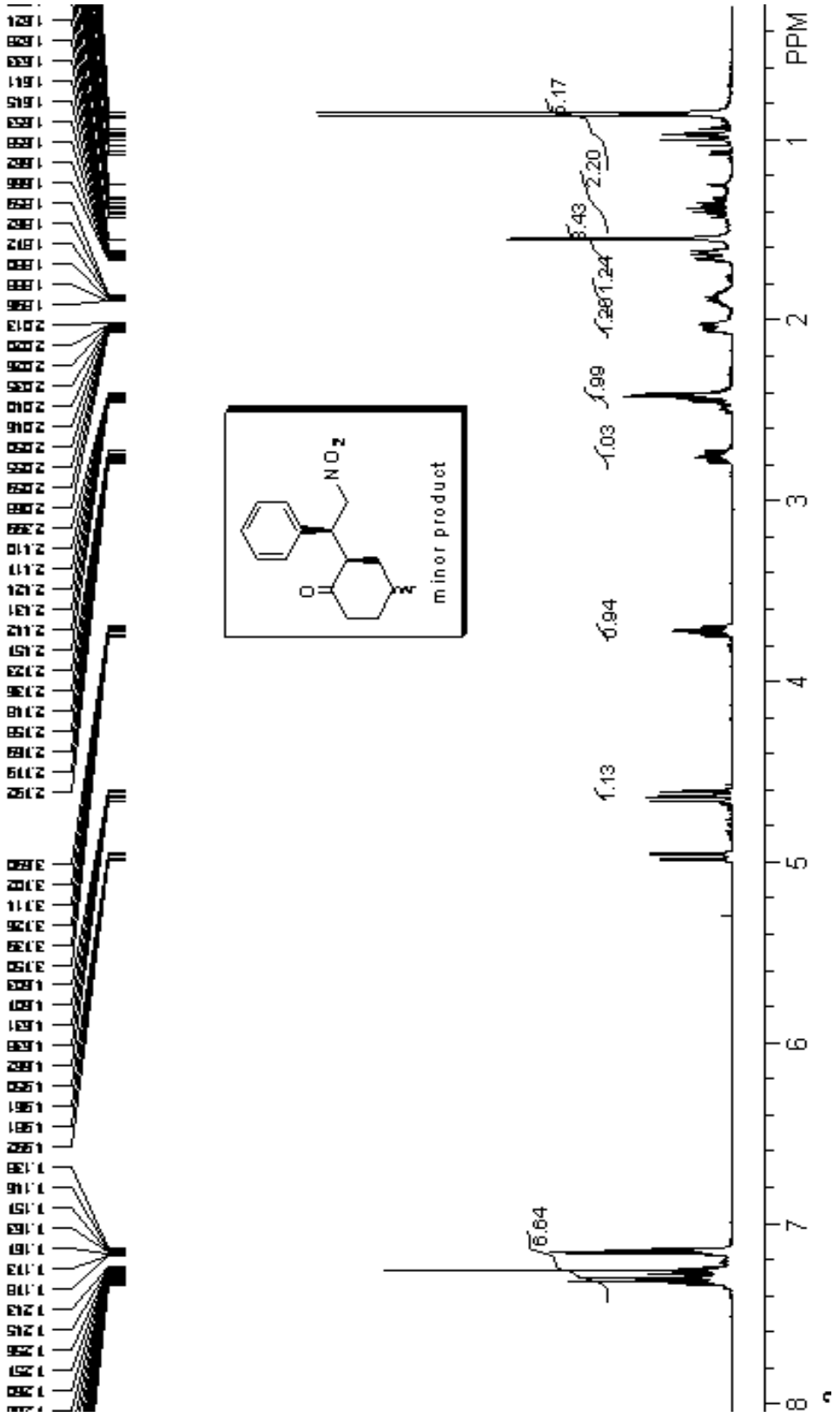
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1.28
1.24
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2.20
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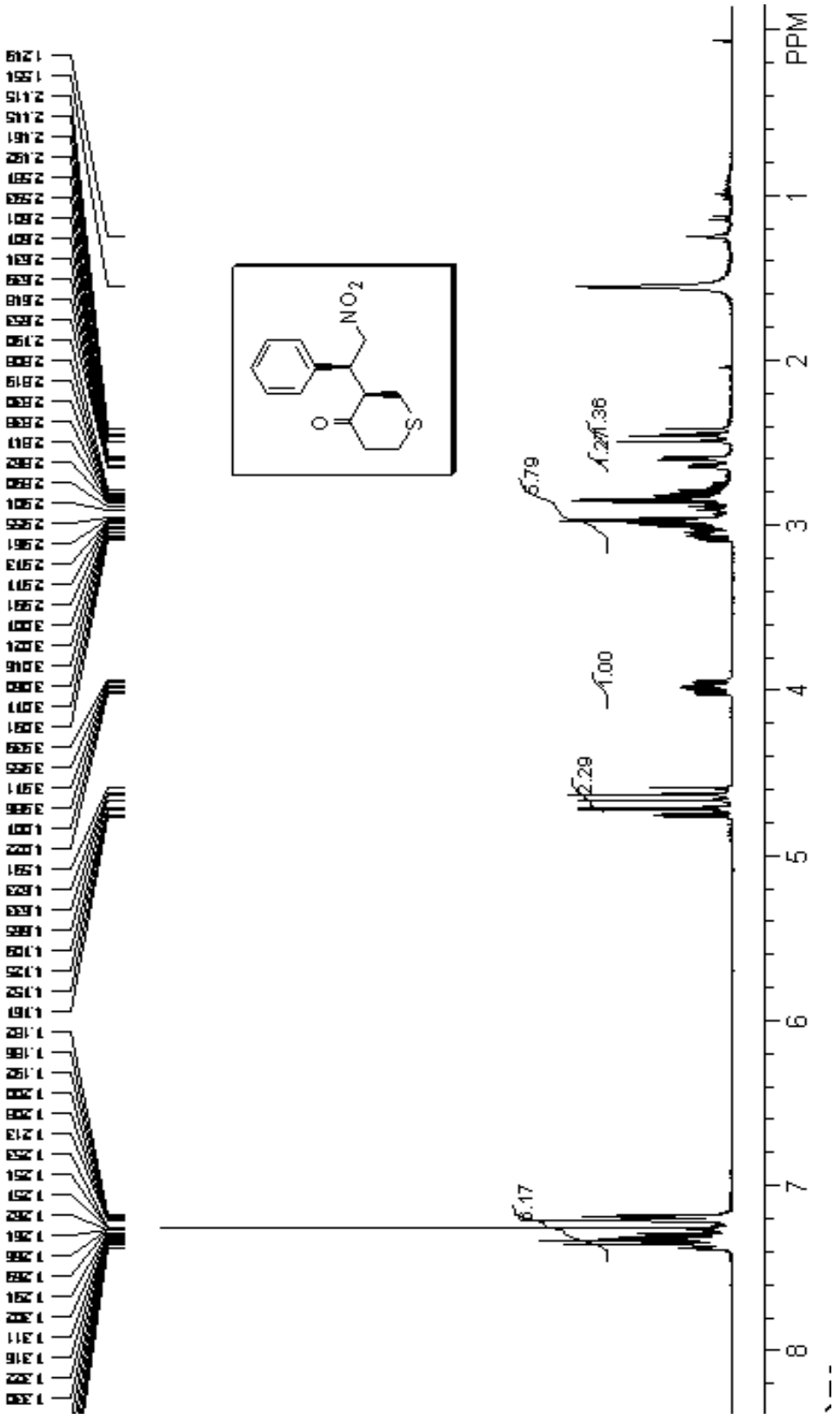
PPM


NO2
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1.36
PPM
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6
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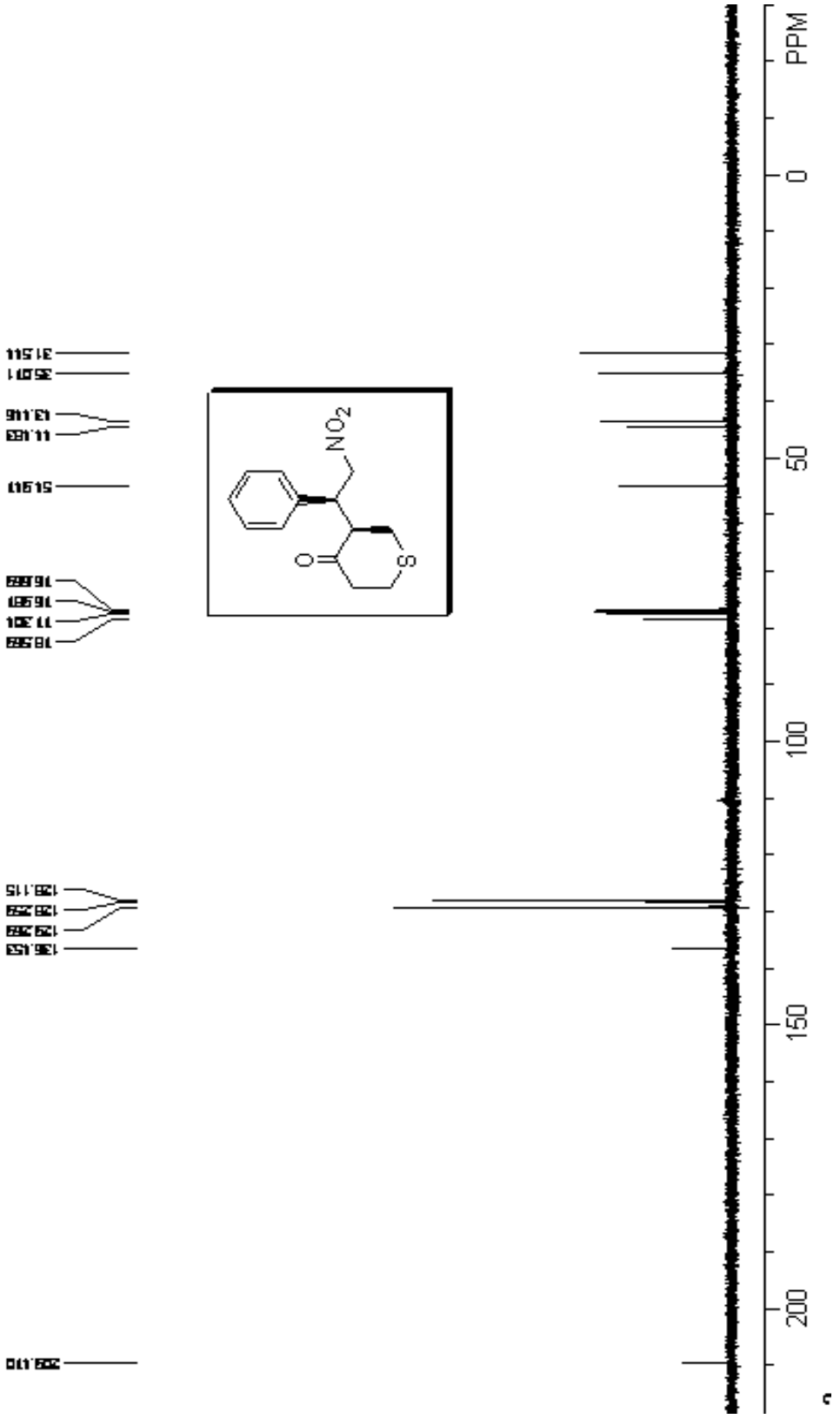
8


PPM
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100
150
200
NO2
O
S