

Organopromoted Selectivity-Switchable Synthesis of Polyketones

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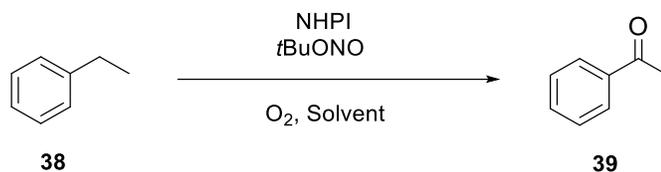
1. General information

Solvents were pre-dried over activated 4 Å molecular sieves and heated to reflux over calcium hydride (CH₃CN, DCM, Et₃N, THF) under argon atmosphere and collected by distillation. ¹H, ¹³C NMR spectra were recorded on a Bruker 400 spectrometer; Chemical shifts are reported in δ units relative to CDCl₃ [¹H δ = 7.26, ¹³C δ = 77.00]. HRMS were recorded by the mass spectrometry service at University of Science and Technology of China (Cl-35, Br-79). Methylarenes and other chemicals without notes in experimental section were purchased from commercial sources.

2. Experimental procedures

2.1. Screening reaction conditions

N-hydroxyphthalimide (NHPI) (0-1.0 equiv) was weighed into a Schlenk tube. After dried *in vacuo* for 15 min under an oxygen atmosphere, MeCN (1 mL) was added. Then *t*-BuONO (TBN) (0-3.0 equiv) was added. Ethylbenzene (0.5 mmol, 1.0 equiv) was last added and stirred at 70-80 °C for 24 h. After cooling to rt, the reaction mixture was diluted with CH₂Cl₂ (2 mL), concentrated and the residue was examined on ¹H NMR spectrometer to determine the conversion using nitromethane and *tert*-butyl methyl ether as internal standard.

Table S1. Screening Reaction Conditions^a

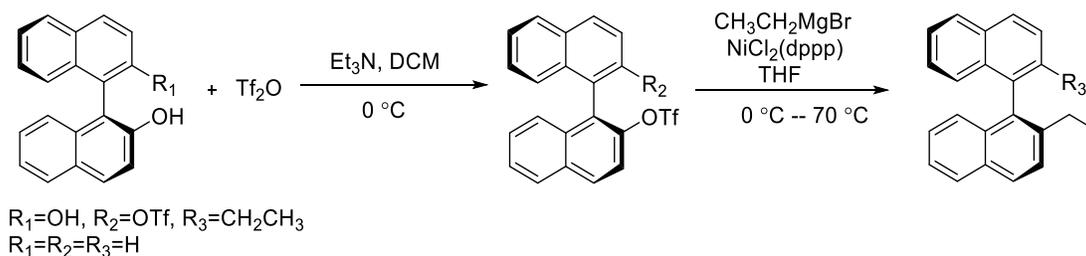
entry	NHPI (equiv)	TBN (equiv)	Solvent	T (°C)	39 (%) ^b
1	0.1	3.0	MeCN	80	37
2	0.3	3.0	MeCN	80	57
3	0.5	3.0	MeCN	80	62
4	1.0	3.0	MeCN	80	64
5	0.5	2.0	MeCN	80	71
6	0.5	1.0	MeCN	80	74
7	0.5	0.5	MeCN	80	62
8	0.5	1.0	MeCN	70	60
9	0.5	1.0	DMF	80	trace
10	0.5	1.0	1,4-dioxane	80	66
11	0.5	1.0	MeOH	80	57
12 ^c	0.5	1.0	MeCN	80	13
13	0	1.0	MeCN	80	7
14	0.5	0	MeCN	80	9
15 ^d	0.5	1.0	MeCN	80	42

^a Conditions (A): **60** (0.5 mmol), *t*BuONO (0.5 mmol), NHPI (0.25 mmol), dry MeCN (1 mL), 80 °C, oxygen, 24 h. ^b Determined by ¹H NMR. ^c Without oxygen. ^d Oxygen changed to air.

2.2. General Procedure for Preparation of *t*BuONO

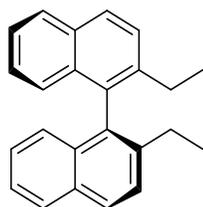
To an ice-cold solution of (c) H₂SO₄ (22 mL, 0.4 mol) in H₂O (25 mL) was added *t*-BuOH (38 mL, 0.4 mol) dropwise followed by the addition of a solution of sodium nitrite (42 g, in 100 mL of H₂O). The reaction was kept at 0 °C during the addition, which was complete of 1 h. The reaction mixture was warmed to r.t. and stirred overnight. The aqueous layer was separated and the organic portion was washed with saturated aq. NaHCO₃ solution and saturated aq. NaCl solution. The organic portion was then dried over Na₂SO₄ and purified by distillation. A light yellow fraction (ca. 20-30 mL) was collected at 80-90 °C and used for all ammoxidation reactions. It was stored at 4 °C.

2.3. Preparation of Starting Materials



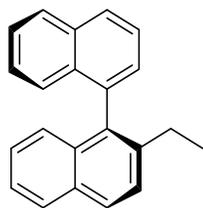
(S)-1,1'-bi-2-naphthol (2.0 g, 7 mmol, 1.0 equiv) was weighed into a 100 mL round-bottomed flask. After dried in *vacuo* for 15 min under argon atmosphere, and 20 mL dry DCM was added into the flask to form a suspension. Then Et₃N (3 mL, 21 mmol, 3.0 equiv) was added into the mixture and the reaction mixture turned into a solution. Then Tf₂O (3 mL, 17 mmol, 2.4 equiv) was added dropwise into the solution cooled by an ice-bath. During addition the solution turned into dark brown. After disappearing of the substrate on TLC, the reaction mixture was concentrated by rotary evaporation under reduced pressure and purified on silica gel column, eluted with petroleum ether and ethyl acetate to give the desired product.

The intermediate from the above step (1.0 equiv) was dried in *vacuo* for 15 min under argon atmosphere. Then NiCl₂(dppp) (0.05 equiv) was weighed into the flask in a glovebox, which was diluted by 30 mL of dry THF out of the glovebox. CH₃CH₂MgBr (6.0 equiv) in Et₂O was added dropwise into the solution cooled by an ice-bath. After addition, the mixture was warmed to room temperature, then was refluxed for 24 h. After disappearing of the substrate on TLC, the reaction mixture was quenched by 1 M HCl aqueous solution. The aqueous layer was extracted with Et₂O (30 mL × 4), then the organic layer were combined, dried over anhydrous sodium sulfate, concentrated by rotary evaporation under reduced pressure and purified on silica gel column eluted with petroleum ether and ethyl acetate to give the desired products.



(S)-2,2'-diethyl-1,1'-binaphthalene (23)¹

Prepared according to the general procedure, purified by flash column chromatography (PE/EA = 100:1), yellow oil (2.0 g, 73% yield). ¹H NMR (CDCl₃, 400 MHz) δ 7.85 (d, *J* = 8.4 Hz, 2 H), 7.53-7.59 (m, 2 H), 7.42-7.46 (m, 2 H), 7.35-7.39 (m, 2 H), 7.23-7.27 (m, 2 H), 7.15-7.22 (m, 2 H), 2.30-2.44 (m, 4 H), 1.03 (t, *J* = 8.4 Hz 6 H).



(S)-2-ethyl-1,1'-binaphthalene (26)²

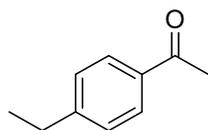
Prepared according to the general procedure, purified by flash column chromatography (PE/EA = 100:1), yellow oil (2.3 g, 67% yield). ¹H NMR (CDCl₃, 400 MHz) δ 7.81-7.86 (m, 3 H), 7.77 (d, *J* = 8.4 Hz, 1 H), 7.49 (t, *J* = 7.6 Hz, 1 H), 7.44 (d, *J* = 8.4 Hz, 1 H), 7.33-7.38 (m, 1 H), 7.26-7.31 (m, 2 H), 7.07-7.14 (m, 3 H), 7.00 (d, *J* = 8.4 Hz, 1 H), 2.22-2.39 (m, 2 H), 0.95 (t, *J* = 7.6 Hz, 3 H).

2.3.1. General procedure A

N-hydroxyphthalimide (NHPI) (41 mg, 0.25 mmol, 0.5 equiv) was weighed into a Schlenk tube. After dried *in vacuo* for 15 min under an oxygen atmosphere, dry MeCN (1 mL) was added. Then *t*-BuONO (TBN) (60 μL, 0.5 mmol, 1.0 equiv) was added. Ethylarene (0.5 mmol, 1.0 equiv) was last added and stirred at 80 °C for 24 h. After cooling to rt, the reaction mixture was diluted with CH₂Cl₂ (2 mL), concentrated and purified on column chromatography to give the pure product.

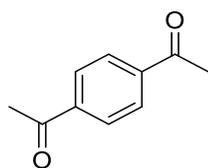
2.3.2. General procedure B

N-hydroxyphthalimide (NHPI) (82 mg, 0.5 mmol, 1.0 equiv) was weighed into a Schlenk tube. After dried *in vacuo* for 15 min under an oxygen atmosphere, dry MeCN (1 mL) was added. Then *t*-BuONO (TBN) (120 μL, 1.0 mmol, 2.0 equiv) was added. Ethylarene (0.5 mmol, 1.0 equiv) was last added and stirred at 80 °C for 24 h. After cooling to rt, the reaction mixture was diluted with CH₂Cl₂ (2 mL), concentrated and purified on column chromatography to give the pure product.



4-Ethylacetophenone (4)³

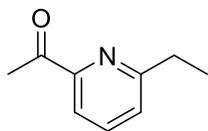
Prepared according to the general procedure A, purified by flash column chromatography (PE/EA = 40:1), light yellow oil (61.0 mg, 82% yield). ¹H NMR (CDCl₃, 400 MHz): δ 7.90 (d, *J* = 8.0 Hz, 2 H), 7.29 (d, *J* = 8.8 Hz, 2 H), 2.72 (q, *J* = 7.6 Hz, 2 H), 2.59 (s, 3 H), 1.27 (t, *J* = 7.8 Hz, 3 H). ¹³C NMR (CDCl₃, 100 MHz): δ 197.8, 149.9, 134.9, 128.5, 128.0, 28.8, 26.4, 15.1.



1,4-Diacetylbenzene (5)³

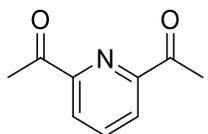
Prepared according to the general procedure B, purified by flash column chromatography

(PE/EA = 10:1), white solid (57.5 mg, 71% yield). $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 8.00 (s, 4 H), 2.62 (s, 6 H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 197.4, 140.1, 128.4, 26.8.



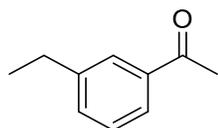
1-(6-ethylpyridin-2-yl)ethan-1-one (8)¹⁰

N-hydroxyphthalimide (NHPI) (41 mg, 0.25 mmol, 0.5 equiv) was weighed into a Schlenk tube. After dried *in vacuo* for 15 min under an oxygen atmosphere, dry MeCN (1 mL) was added. Then *t*-BuONO (TBN) (60 μL , 0.5 mmol, 1.0 equiv) was added. 2,6-diethylpyridine (67.6 mg, 0.5 mmol, 1.0 equiv) was last added and stirred at 80 $^\circ\text{C}$ for 36 h under oxygen atmosphere. After cooling to rt, the reaction mixture was diluted with CH_2Cl_2 (2 mL), concentrated and purified on column chromatography to give the pure product (PE/EA = 10:1), oil (48.7 mg, 63% yield). $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 7.97 (t, J = 7.6 Hz, 1 H), 7.63-7.71 (m, 2 H), 3.42 (q, J = 7.3 Hz, 2 H), 2.69 (s, 3 H), 1.66 (t, J = 7.6 Hz, 3 H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 198.5, 154.1, 141.2, 139.1, 131.7, 120.4, 28.0, 25.7, 19.3.



1,1'-(pyridine-2,6-diyl)bis(ethan-1-one) (7)¹⁰

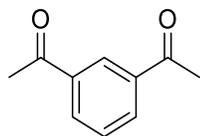
N-hydroxyphthalimide (NHPI) (82 mg, 0.5 mmol, 1.0 equiv) was weighed into a Schlenk tube. After dried *in vacuo* for 15 min under an oxygen atmosphere, dry MeCN (1 mL) was added. Then *t*-BuONO (TBN) (120 μL , 1.0 mmol, 2.0 equiv) was added. 2,6-diethylpyridine (67.6 mg, 0.5 mmol, 1.0 equiv) was last added and stirred at 90 $^\circ\text{C}$ for 36 h under oxygen atmosphere. After cooling to rt, the reaction mixture was diluted with CH_2Cl_2 (2 mL), concentrated and purified on column chromatography to give the pure product (PE/EA = 5:1), solid (44 mg, 54% yield). $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 7.98 (d, J = 6.8 Hz, 2 H), 7.69 (t, J = 7.6 Hz, 1 H), 2.70 (s, 6 H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 197.4, 150.9, 142.7, 121.2, 26.7.



3-Ethylacetophenone (9)⁵

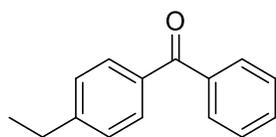
N-hydroxyphthalimide (NHPI) (0.91 g, 5.6 mmol, 0.5 equiv) was weighed into a 50 mL flask. After dried *in vacuo* for 15 min under an oxygen atmosphere, dry MeCN (10 mL) was added. Then *t*-BuONO (TBN) (1.3 mL, 11.2 mmol, 1.0 equiv) was added. 1,3-diethylbenzene (1.5 g, 11.2 mmol, 1.0 equiv) was last added and stirred at 80 $^\circ\text{C}$ for 24 h. After cooling to rt, the reaction mixture was diluted with CH_2Cl_2 (20 mL), concentrated and purified on column chromatography

to give the pure product (PE/EA = 30:1), light yellow oil (1.23 g, 74% yield) (for 0.5 mmol, 59.2 mg, 80% yield). **¹H NMR** (CDCl₃, 400 MHz): δ 7.77 (t, *J* = 8.0 Hz, 2 H), 7.35-7.41 (m, 2 H), 2.70 (q, *J* = 7.6 Hz, 2 H), 2.60 (s, 3 H), 1.26 (t, *J* = 7.6 Hz, 3 H). **¹³C NMR** (CDCl₃, 100 MHz): δ 198.4, 144.7, 137.2, 132.7, 128.5, 127.5, 125.8, 28.7, 26.6, 15.4.



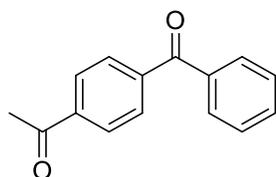
1,3-Diacetylbenzene (10)⁴

N-hydroxyphthalimide (NHPI) (1.88 g, 11.5 mmol, 1.0 equiv) was weighed into a 50 mL flask. After dried *in vacuo* for 15 min under an oxygen atmosphere, dry MeCN (10 mL) was added. Then *t*-BuONO (TBN) (2.7 mL, 23.0 mmol, 2.0 equiv) was added. 1,3-diethylbenzene (1.54 g, 11.5 mmol, 1.0 equiv) was last added and stirred at 80 °C for 24 h. After cooling to rt, the reaction mixture was diluted with CH₂Cl₂ (20 mL), concentrated and purified on column chromatography to give the pure product (PE/EA = 10:1), colorless oil (1.3 g, 70% yield) (for 0.5 mmol, 59.2 mg, 73% yield). **¹H NMR** (CDCl₃, 400 MHz): δ 8.47 (s, 1 H), 8.11 (d, *J* = 7.6 Hz, 2 H), 7.55 (t, *J* = 7.8 Hz, 1 H), 2.62 (s, 6 H). **¹³C NMR** (CDCl₃, 100 MHz): δ 197.3, 137.3, 132.4, 128.9, 127.9, 26.4.



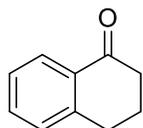
(4-Ethylphenyl)(phenyl)methanone (11)¹⁶

Prepared according to the general procedure A, purified by flash column chromatography (PE/EA = 40:1), light yellow oil (76.7 mg, 73% yield). **¹H NMR** (CDCl₃, 400 MHz): δ 7.74-7.81 (m, 4 H), 7.58 (t, *J* = 7.4 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 2 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 2.74 (q, *J* = 7.6 Hz, 2 H), 1.28 (t, *J* = 7.6 Hz, 3 H). **¹³C NMR** (CDCl₃, 100 MHz): δ 196.5, 149.4, 137.9, 135.0, 132.1, 130.4, 129.9, 128.1, 127.7, 28.9, 15.2.



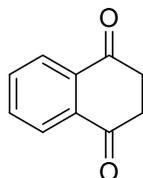
1-(4-Benzoylphenyl)ethan-1-one (12)¹⁷

Prepared according to the general procedure B, purified by flash column chromatography (PE/EA = 20:1), light yellow solid (90.8 mg, 81% yield). **¹H NMR** (CDCl₃, 400 MHz): δ 8.05 (d, *J* = 8.4 Hz, 2 H), 7.86 (d, *J* = 8.8 Hz, 2 H), 7.80 (d, *J* = 7.2 Hz, 2 H), 7.62 (t, *J* = 7.4 Hz, 1 H), 7.50 (t, *J* = 7.4 Hz, 2 H), 2.67 (s, 3 H). **¹³C NMR** (CDCl₃, 100 MHz): δ 197.5, 195.9, 141.3, 139.5, 136.9, 132.9, 130.1, 130.0, 128.4, 128.1, 26.9.



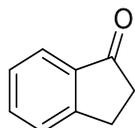
1-Tetralone (13)³

Prepared according to the general procedure A, purified by flash column chromatography (PE/EA = 20:1), yellow liquid (62.9 mg, 86% yield). **¹H NMR** (CDCl₃, 400 MHz): δ 8.03 (d, *J* = 7.6 Hz, 1 H), 7.44-7.48 (m, 1 H), 7.24-7.32 (m, 2 H), 2.96 (t, *J* = 6.0 Hz, 2 H), 2.65 (t, *J* = 6.6 Hz, 2 H), 2.10-2.16 (m, 2 H). **¹³C NMR** (CDCl₃, 100 MHz): δ 198.3, 144.4, 133.3, 132.5, 128.7, 127.1, 126.5, 39.1, 29.6, 23.2.



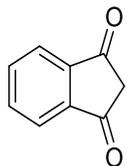
2,3-Dihydro-1,4-naphthoquinone (14)³

Prepared according to the general procedure B, purified by flash column chromatography (PE/EA = 10:1), gray solid (60.9 mg, 72% yield). **¹H NMR** (CDCl₃, 400 MHz): δ 7.99-8.04 (m, 2 H), 7.70-7.74 (m, 2 H), 3.07 (s, 4 H). **¹³C NMR** (CDCl₃, 100 MHz): δ 195.9, 135.2, 134.2, 126.7, 37.5.



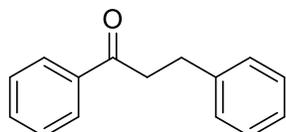
1-Indanone (15)⁶

Prepared according to the general procedure A, purified by flash column chromatography (PE/EA = 20:1), solid (51.5 mg, 78% yield). **¹H NMR** (CDCl₃, 400 MHz): δ 7.74-7.76 (m, 1 H), 7.55-7.59 (m, 1 H), 7.46-7.48 (m, 1 H), 7.34-7.37 (m, 1 H), 3.12-3.15 (m, 2 H), 2.66-2.70 (m, 2 H). **¹³C NMR** (CDCl₃, 100 MHz): δ 207.0, 155.1, 137.0, 134.5, 127.2, 126.7, 123.7, 36.2, 25.7.



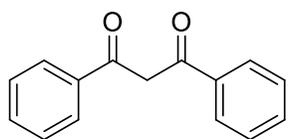
1,3-Indanedione(16)⁶

Prepared according to the general procedure B, purified by flash column chromatography (PE/EA = 10:1), light brown solid (44.7 mg, 61% yield). **¹H NMR** (CDCl₃, 400 MHz): δ 7.96-7.99 (m, 2 H), 7.83-7.86 (m, 2 H), 3.24 (s, 2 H). **¹³C NMR** (CDCl₃, 100 MHz): δ 197.4, 143.4, 135.6, 123.2, 45.0.



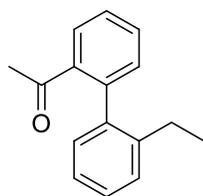
1,3-Diphenylpropan-1-one (17)⁷

Prepared according to the general procedure A, purified by flash column chromatography (PE/EA = 20:1), white solid (77.8 mg, 74% yield). **¹H NMR** (CDCl₃, 400 MHz): δ 7.98 (t, *J* = 7.2 Hz, 2 H), 7.58 (t, *J* = 7.4 Hz, 1 H), 7.48 (t, *J* = 7.6 Hz, 2 H), 7.22-7.35 (m, 5 H), 3.34 (t, *J* = 7.6 Hz, 2 H), 3.11 (t, *J* = 7.6 Hz, 2 H). **¹³C NMR** (CDCl₃, 100 MHz): δ 199.2, 141.3, 136.8, 133.0, 128.6, 128.5, 128.4, 128.0, 126.1, 40.4, 30.1.



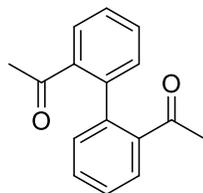
1,3-Diphenylpropane-1,3-dione (18)⁸

Prepared according to the general procedure B, purified by flash column chromatography (PE/EA = 10:1), white solid (68.4 mg, 62% yield). **¹H NMR** (CDCl₃, 400 MHz): δ 16.9 (s, 1 H), 8.00 (d, *J* = 7.6 Hz, 4 H), 7.57 (t, *J* = 7.2 Hz, 2 H), 7.50 (t, *J* = 7.2 Hz, 4 H), 6.87 (s, 1 H). **¹³C NMR** (CDCl₃, 100 MHz): δ 185.7, 135.5, 132.4, 128.7, 127.1, 93.1.



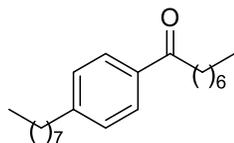
1-(2'-ethyl-[1,1'-biphenyl]-2-yl)ethan-1-one (19)⁹

Prepared according to the general procedure A, purified by flash column chromatography (PE/EA = 20:1), light yellow oil (87.4 mg, 78% yield). **¹H NMR** (CDCl₃, 400 MHz): δ 7.51-7.56 (m, 2 H), 7.41 (q, *J* = 8.0 Hz, 2 H), 7.32 (t, *J* = 7.2 Hz, 1 H), 7.24 (t, *J* = 7.6 Hz, 2 H), 7.02-7.07 (m, 1 H), 2.76 (q, *J* = 7.6 Hz, 2 H), 2.65 (s, 3 H), 1.23 (t, *J* = 7.4 Hz, 3 H). **¹³C NMR** (CDCl₃, 100 MHz): δ 200.5, 143.2, 139.0, 132.6, 131.9, 131.2, 130.6, 129.4, 129.3, 127.4, 127.3, 126.9, 124.2, 30.7, 29.3, 14.2. **HRMS (ESI)** calcd for C₁₆H₁₆O [M+Na]⁺ 247.1093, found 247.1096.



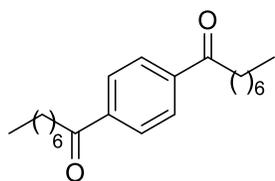
1,1'-([1,1'-biphenyl]-2,2'-diyl)bis(ethan-1-one) (20)⁹

Prepared according to the general procedure B, purified by flash column chromatography (PE/EA = 10:1), brown solid (86.9 mg, 73% yield). **¹H NMR** (CDCl₃, 400 MHz): δ 7.72 (d, *J* = 7.6 Hz, 2 H), 7.42-7.50 (m, 4 H), 7.16 (d, *J* = 7.2 Hz, 2 H), 2.25 (s, 6 H). **¹³C NMR** (CDCl₃, 100 MHz): δ 201.6, 140.5, 138.6, 130.9, 130.6, 128.5, 127.5, 29.2. **HRMS (ESI)** calcd for C₁₆H₁₄O₂ [M+Na]⁺ 261.0886, found 261.0888.



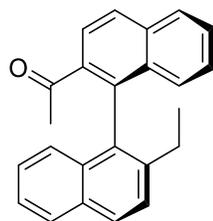
1-(4-octylphenyl)octan-1-one (21)¹⁵

Prepared according to the general procedure A, purified by flash column chromatography (PE/EA = 40:1), yellow solid (110.7 mg, 70% yield). **¹H NMR** (CDCl₃, 400 MHz): δ 7.88 (d, *J* = 8.0 Hz, 2 H), 7.25 (d, *J* = 8.0 Hz, 2 H), 2.93 (t, *J* = 7.4 Hz, 2 H), 2.65 (t, *J* = 7.8 Hz, 2 H), 1.69-1.76 (m, 2 H), 1.58-1.66 (m, 2 H), 1.27-1.34 (m, 18 H), 0.88 (t, *J* = 5.8 Hz, 6 H). **¹³C NMR** (CDCl₃, 100 MHz): δ 200.3, 148.5, 134.7, 128.5, 128.1, 38.5, 35.9, 31.8, 31.7, 31.1, 29.4, 29.3, 29.2, 29.19, 29.12, 24.4, 22.6, 22.5, 14.0. **HRMS (ESI)** calcd for C₂₂H₃₆O [M+Na]⁺ 339.2658, found 339.2662.



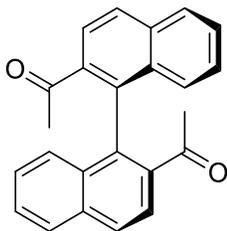
1,1'-(1,4-phenylene)bis(octan-1-one) (22)¹⁵

Prepared according to the general procedure B, purified by flash column chromatography (PE/EA = 10:1), white solid (104.1 mg, 61% yield). **¹H NMR** (CDCl₃, 400 MHz): δ 8.01 (s, 4 H), 2.98 (t, *J* = 7.2 Hz, 4 H), 1.69-1.76 (m, 4 H), 1.28-1.35 (m, 16 H), 0.87 (t, *J* = 6.0 Hz, 6 H). **¹³C NMR** (CDCl₃, 100 MHz): δ 200.1, 140.0, 128.2, 38.9, 31.7, 29.2, 29.1, 24.2, 22.6, 14.0. **HRMS (ESI)** calcd for C₂₂H₃₄O₂ [M+Na]⁺ 353.2451, found 353.2453.



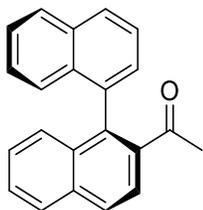
(S)-1-(2'-ethyl-[1,1'-binaphthalen]-2-yl)ethan-1-one (24)¹¹

Prepared according to the general procedure A (TBN 0.5 equiv, 90 °C, 48 h, repeat twice), purified by flash column chromatography (PE/EA = 20:1), light yellow oil (99.7 mg, 60% yield). **¹H NMR** (CDCl₃, 400 MHz): δ 7.94-8.01 (m, 4 H), 7.83 (d, *J* = 8.0 Hz, 1 H), 7.59 (t, *J* = 7.6 Hz, 1 H), 7.48-7.55 (m, 2 H), 7.42 (d, *J* = 6.8 Hz, 1 H), 7.29 (t, *J* = 6.4 Hz, 3 H), 3.43 (q, *J* = 7.2 Hz, 2 H), 1.77 (s, 3 H), 1.67 (t, *J* = 7.2 Hz, 3 H). **¹³C NMR** (CDCl₃, 100 MHz): δ 203.7, 138.4, 137.0, 136.1, 134.4, 133.4, 132.9, 132.7, 128.7, 128.6, 128.4, 127.9, 127.8, 127.4, 126.7, 126.7, 126.1, 125.5, 124.7, 30.2, 27.9, 19.3. [α]_D²⁰ + 441 ° (c 0.1, CHCl₃). The enantiomeric excess was determined to be >99.9 % by HPLC analysis on Daicel AD-H column (2-propanol:*n*-hexane = 10:90 (v:v), 0.5 mL/min), UV 254 nm, *t*_{minor} = 10.99 min, *t*_{major} = 10.00 min.



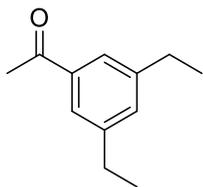
(S)-1,1'-([1,1'-binaphthalene]-2,2'-diyl)bis(ethan-1-one) (25)¹¹

Prepared according to the general procedure B, purified by flash column chromatography (PE/EA = 10:1), yellow solid (113.4 mg, 67% yield). ¹H NMR (CDCl₃, 400 MHz): δ 8.05 (d, *J* = 8.4 Hz, 2 H), 7.94 (t, *J* = 7.8 Hz, 4 H), 7.52 (t, *J* = 7.4 Hz, 2 H), 7.26-7.30 (m, 2 H), 7.16 (d, *J* = 8.4 Hz, 2 H), 2.10 (s, 6 H); ¹³C NMR (CDCl₃, 100 MHz): δ 201.4, 136.9, 136.1, 134.5, 132.8, 128.5, 128.1, 127.6, 127.2, 127.1, 124.8, 29.4. [α]_D²⁰ + 20.9 ° (*c* 0.1, CHCl₃). The enantiomeric excess was determined to be >99.9 % by HPLC analysis on Daicel AD-H column (2-propanol:*n*-hexane = 10:90 (v:v), 0.5 mL/min), UV 254 nm, *t*_{minor} = 25.53 min, *t*_{major} = 23.41 min.



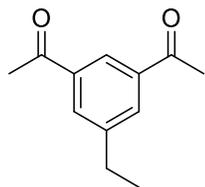
(S)-1-([1,1'-binaphthalen]-2-yl)ethan-1-one (27)¹²

Prepared according to the general procedure B, purified by flash column chromatography (PE/EA = 20:1), light yellow oil (105.2 mg, 71% yield). ¹H NMR (CDCl₃, 400 MHz): δ 7.93-8.01 (m, 5 H), 7.82 (d, *J* = 8.4 Hz, 1 H), 7.59 (t, *J* = 7.6 Hz, 1 H), 7.48-7.55 (m, 2 H), 7.42 (d, *J* = 7.2 Hz, 1 H), 7.31-7.35 (m, 3 H), 1.77 (s, 3 H). ¹³C NMR (CDCl₃, 100 MHz): δ 203.6, 138.4, 137.0, 136.0, 134.4, 133.3, 132.8, 132.6, 128.7, 128.6, 128.3, 127.9, 127.7, 127.3, 126.7, 126.6, 126.1, 125.4, 124.6, 30.1. HRMS (ESI) calcd for C₂₂H₁₆O [M+Na]⁺ 319.1093, found 319.1095. [α]_D²⁰ + 984.0 ° (*c* 0.1, CHCl₃) The enantiomeric excess was determined to be 98.4 % by HPLC analysis on Daicel AD-H column (2-propanol:*n*-hexane = 10:90 (v:v), 0.5 mL/min), UV 254 nm, *t*_{minor} = 13.64 min, *t*_{major} = 11.99 min.



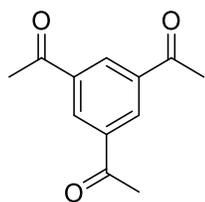
1-(3,5-diethylphenyl)ethan-1-one (29)¹³

Prepared according to the general procedure A (TBN 0.5 equiv, 36 h), purified by flash column chromatography (PE/EA = 40:1), light yellow oil (56.4 mg, 64% yield). ¹H NMR (CDCl₃, 400 MHz): δ 7.98 (s, 2 H), 7.84 (s, 1 H), 3.42 (q, *J* = 7.2 Hz, 4 H), 2.57 (s, 3 H), 1.66 (t, *J* = 7.4 Hz, 6 H). ¹³C NMR (CDCl₃, 100 MHz): δ 195.1, 139.7, 138.2, 130.1, 123.4, 27.9, 26.6, 19.3.



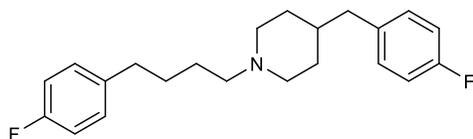
1,1'-(5-ethyl-1,3-phenylene)bis(ethan-1-one) (30)¹³

Prepared according to the general procedure B (36 h), purified by flash column chromatography (PE/EA = 10:1), light yellow oil (72.2 mg, 76% yield). ¹H NMR (CDCl₃, 400 MHz): δ 8.49 (s, 1 H), 8.14 (s, 2 H), 3.40 (q, *J* = 7.4 Hz, 2 H), 2.64 (s, 6 H), 1.64 (t, *J* = 8.0 Hz, 3 H). ¹³C NMR (CDCl₃, 100 MHz): δ 197.3, 137.3, 132.4, 128.9, 127.9, 27.9, 26.7, 19.2.



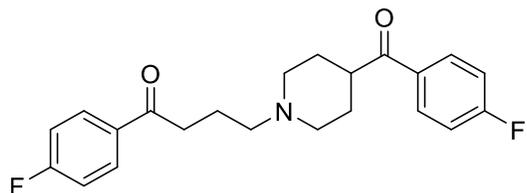
1,1',1''-(benzene-1,3,5-triyl)tris(ethan-1-one) (31)¹⁴

Prepared according to the general procedure B (90 °C, 36 h), purified by flash column chromatography (PE/EA = 5:1), light yellow solid (52.1 mg, 51% yield). ¹H NMR (CDCl₃, 400 MHz): δ 7.98 (s, 3 H), 2.57 (s, 9 H). ¹³C NMR (CDCl₃, 100 MHz): δ 195.2, 138.2, 130.1, 26.6.



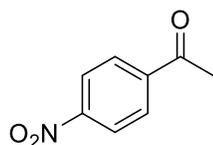
4-(4-fluorobenzyl)-1-(4-(4-fluorophenyl)butyl)piperidine (2)¹⁸

To a 100 mL round bottom flask charged with a stir bar were sequentially added amine **32** (1.93 g, 10.0 mmol, 1.0 equiv), acetonitrile (30 mL), K₂CO₃ (2.07 g, 15 mmol, 1.5 equiv), KI (166 mg, 1.0 mmol, 0.1 equiv), and alkyl bromide **33** (4.62 g, 20.0 mmol, 2.0 equiv). The resulting mixture was heated at reflux for approximately 24 h. The reaction mixture was allowed to cool to room temperature. K₂CO₃ was removed by filtration, and the filtrate was concentrated under vacuum. The crude material was purified by column chromatography (Et₃N/EA/PE = 1:10:10) to give the product as a light yellow oil (2.30 g, 67% yield). ¹H NMR (CDCl₃, 400 MHz) δ 7.06-7.12 (m, 4 H), 6.92-6.97 (m, 4 H), 2.87 (d, *J* = 11.2 Hz, 2 H), 2.58 (t, *J* = 7.4 Hz, 2 H), 2.49 (d, *J* = 7.2 Hz, 2 H), 2.29 (t, *J* = 7.6 Hz, 2 H), 1.81 (t, *J* = 11.2 Hz, 2 H), 1.54-1.61 (m, 4 H), 1.34-1.49 (m, 3 H), 1.23-1.30 (m, 2 H). ¹³C NMR (CDCl₃, 100 MHz): δ 162.3 (d, *J* = 10.4 Hz), 159.9 (d, *J* = 9.7 Hz), 138.0 (d, *J* = 3.3 Hz), 136.2 (d, *J* = 3.2 Hz), 130.4 (d, *J* = 7.3 Hz), 129.6 (d, *J* = 7.6 Hz), 115.0 (d, *J* = 7.2 Hz), 114.8 (d, *J* = 7.8 Hz), 58.9, 53.9, 42.3, 38.0, 34.9, 32.0, 29.6, 26.6.



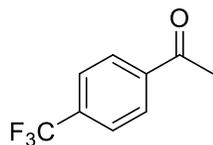
Lenperone (1)¹⁸

N-hydroxyphthalimide (NHPI) (0.78 g, 4.78 mmol, 1.0 equiv) was weighed into a 50 mL flask. After dried *in vacuo* for 15 min under an oxygen atmosphere, dry MeCN (10 mL) was added. Then *t*-BuONO (TBN) (1.1 mL, 9.56 mmol, 2.0 equiv) was added. **2** (1.64 g, 4.78 mmol, 1.0 equiv) was last added and stirred at 90 °C for 36 h under oxygen atmosphere. After cooling to rt, the reaction mixture was diluted with CH₂Cl₂ (15 mL), concentrated and purified on column chromatography to give the pure product (PE/EA/Et₃N = 10:10:1), light yellow solid (1.1 g, 62% yield). **¹H NMR** (CDCl₃, 400 MHz) δ 7.93-8.01 (m, 4 H), 7.12 (t, *J* = 8.4 Hz, 4 H), 3.16-3.23 (m, 1 H), 2.91-3.00 (m, 4 H), 2.44 (t, *J* = 7.6 Hz, 2 H), 2.06-2.15 (m, 2 H), 1.95 (t, *J* = 7.0 Hz, 2 H), 1.75-1.85 (m, 4 H). **¹³C NMR** (CDCl₃, 100 MHz): δ 201.0, 198.5, 166.8 (d, *J* = 1.3 Hz), 164.3 (d, *J* = 2.0 Hz), 132.3 (d, *J* = 2.9 Hz), 131.3 (d, *J* = 8.1 Hz), 130.8 (d, *J* = 8.7 Hz), 130.6 (d, *J* = 9.9 Hz), 115.9 (d, *J* = 15.7 Hz), 115.8 (d, *J* = 14.3 Hz), 57.8, 53.1, 43.3, 36.2, 28.6, 21.6.



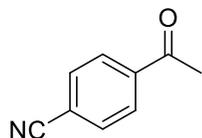
4-Nitroacetophenone (34)³

Prepared according to the general procedure B, purified by flash column chromatography (PE/EA = 20:1), light yellow solid (62.1 mg, 66% yield). **¹H NMR** (400 MHz, CDCl₃) δ 8.29 (d, *J* = 8.8 Hz, 2 H), 8.10 (d, *J* = 8.8 Hz, 2 H), 2.67 (s, 3 H). **¹³C NMR** (CDCl₃, 100 MHz): δ 196.3, 150.3, 141.4, 129.3, 123.8, 26.9.



4-Trifluoromethylacetophenone (35)³

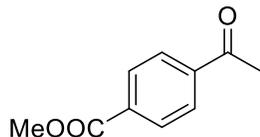
Prepared according to the general procedure B, purified by flash column chromatography (PE/EA = 20:1), light yellow solid (68.6 mg, 73% yield). **¹H NMR** (CDCl₃, 400 MHz): δ 8.05 (d, *J* = 8.4 Hz, 2 H), 7.72 (d, *J* = 8.4 Hz, 2 H), 2.64 (s, 3 H). **¹³C NMR** (CDCl₃, 100 MHz): δ 196.9, 139.7, 134.4 (q, *J* = 32.4 Hz), 128.6, 125.7 (q, *J* = 3.9 Hz), 124.9, 122.2, 26.7.



4-Acetylbenzonitrile (36)⁴

Prepared according to the general procedure B, purified by flash column chromatography

(PE/EA = 10:1), light yellow solid (50.8 mg, 70% yield). **¹H NMR** (CDCl₃, 400 MHz): δ 8.03 (d, *J* = 8.8 Hz, 2 H), 7.76 (d, *J* = 8.4 Hz, 2 H), 2.63 (s, 3 H). **¹³C NMR** (CDCl₃, 100 MHz): δ 196.6, 139.8, 132.5, 128.6, 117.9, 116.3, 26.7.



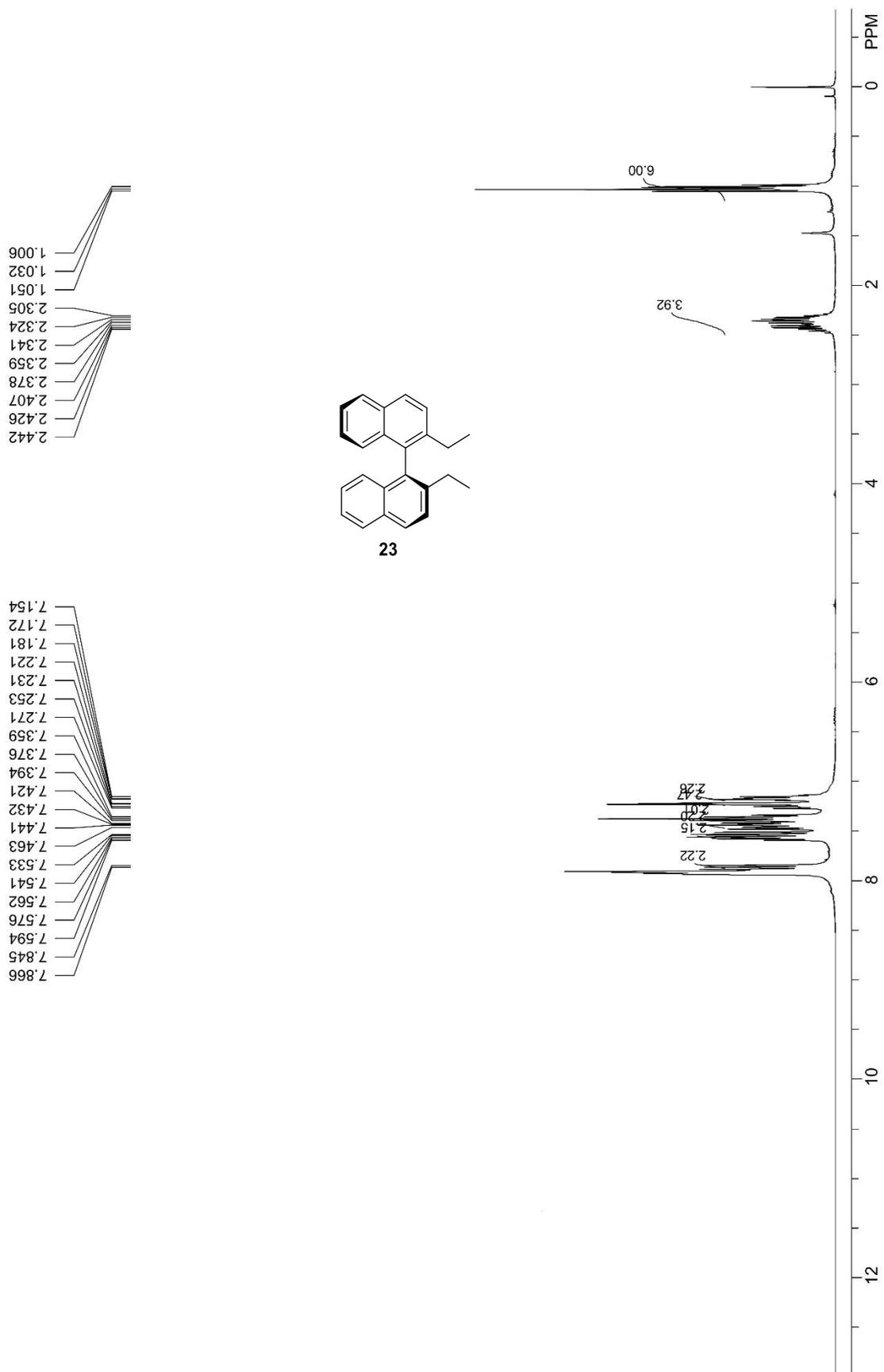
Methyl-4-acetylbenzoate (37)⁴

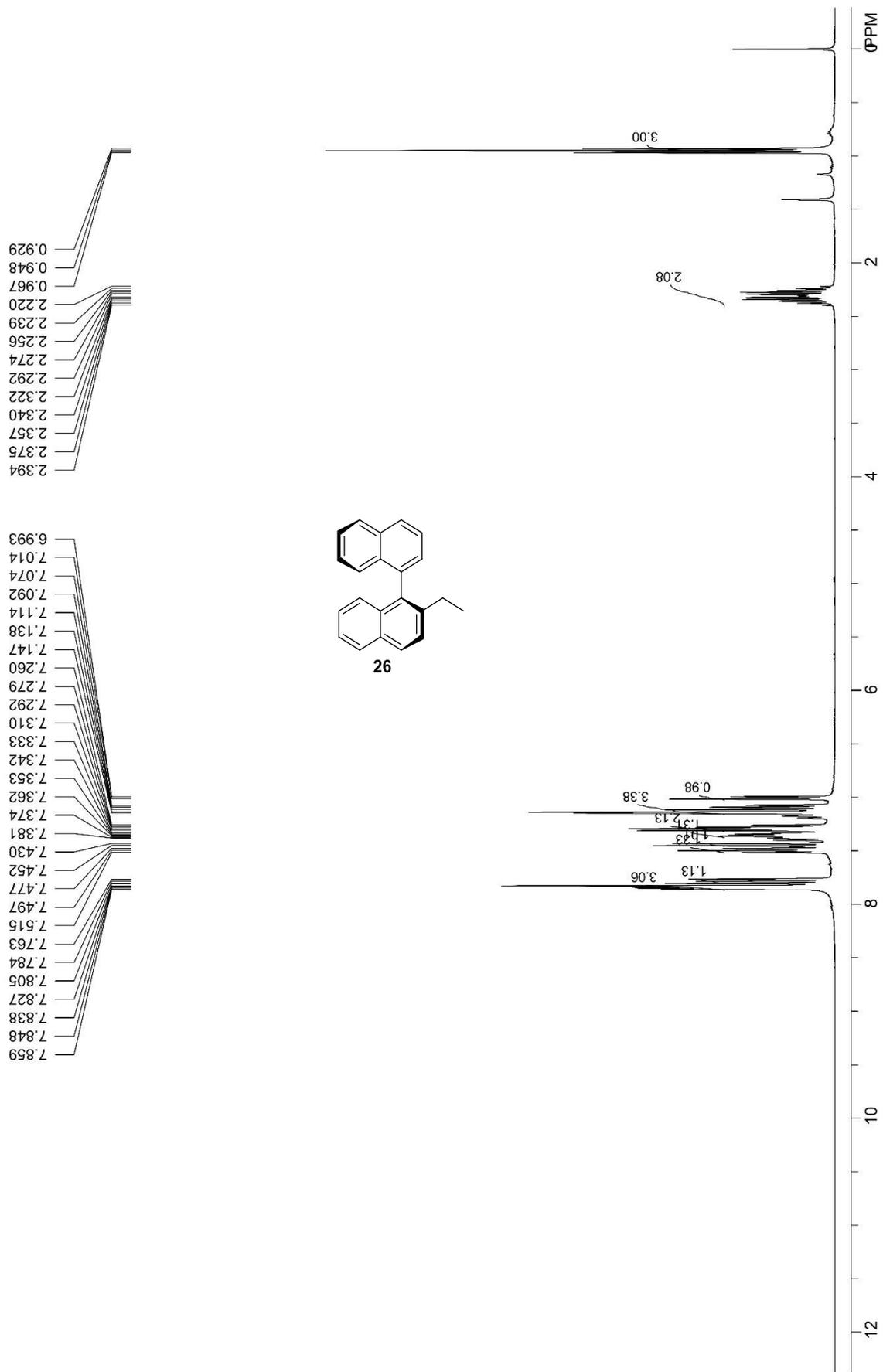
Prepared according to the general procedure B, purified by flash column chromatography (PE/EA = 10:1), white solid (62.3 mg, 70% yield). **¹H NMR** (CDCl₃, 400 MHz): δ 8.10 (d, *J* = 8.4 Hz, 2 H), 7.99 (d, *J* = 8.0 Hz, 2 H), 3.93 (s, 3 H), 2.63 (s, 3 H). **¹³C NMR** (CDCl₃, 100 MHz): δ 197.5, 166.2, 140.1, 133.8, 129.8, 128.2, 52.4, 26.8.

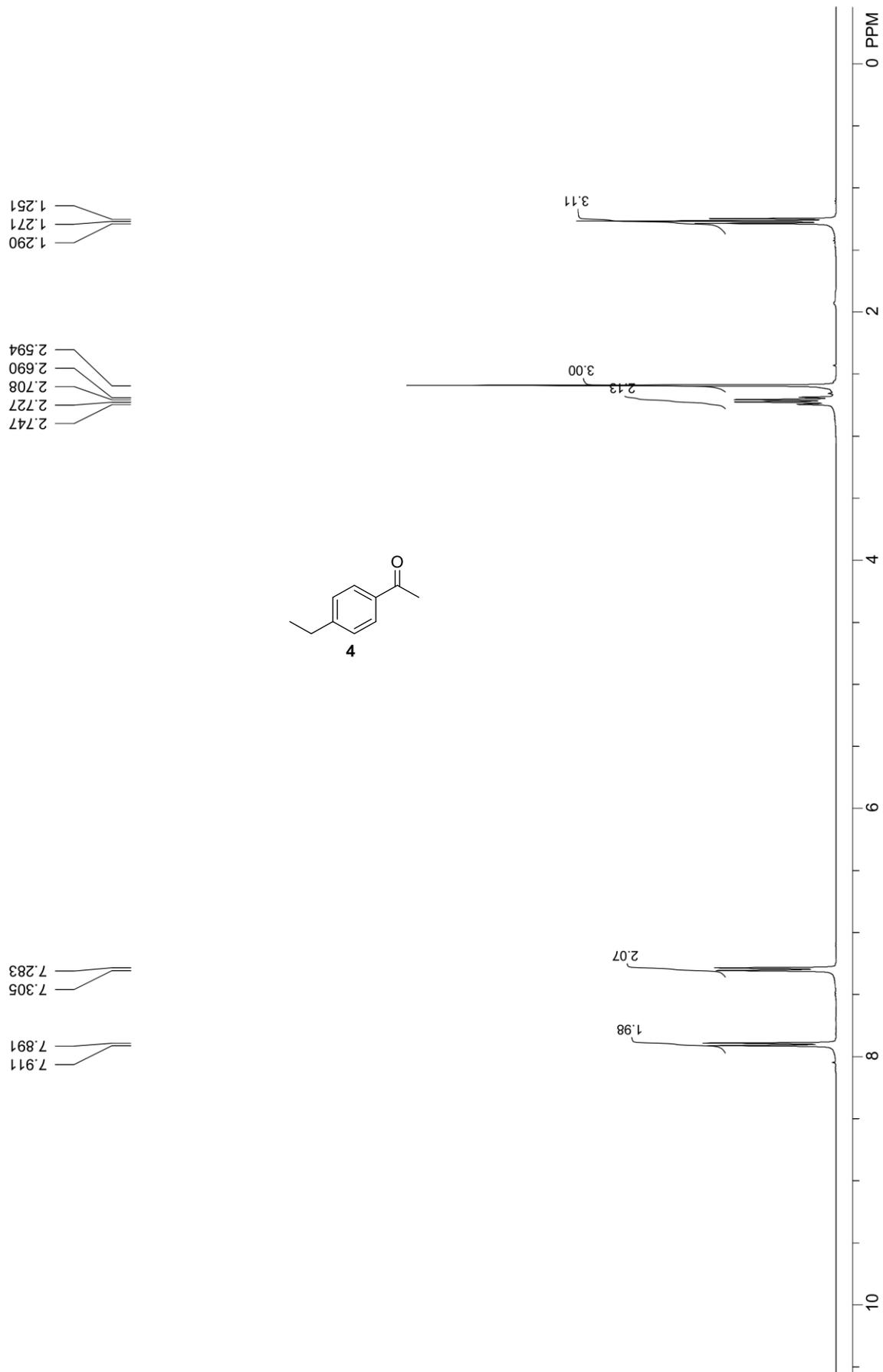
3. References

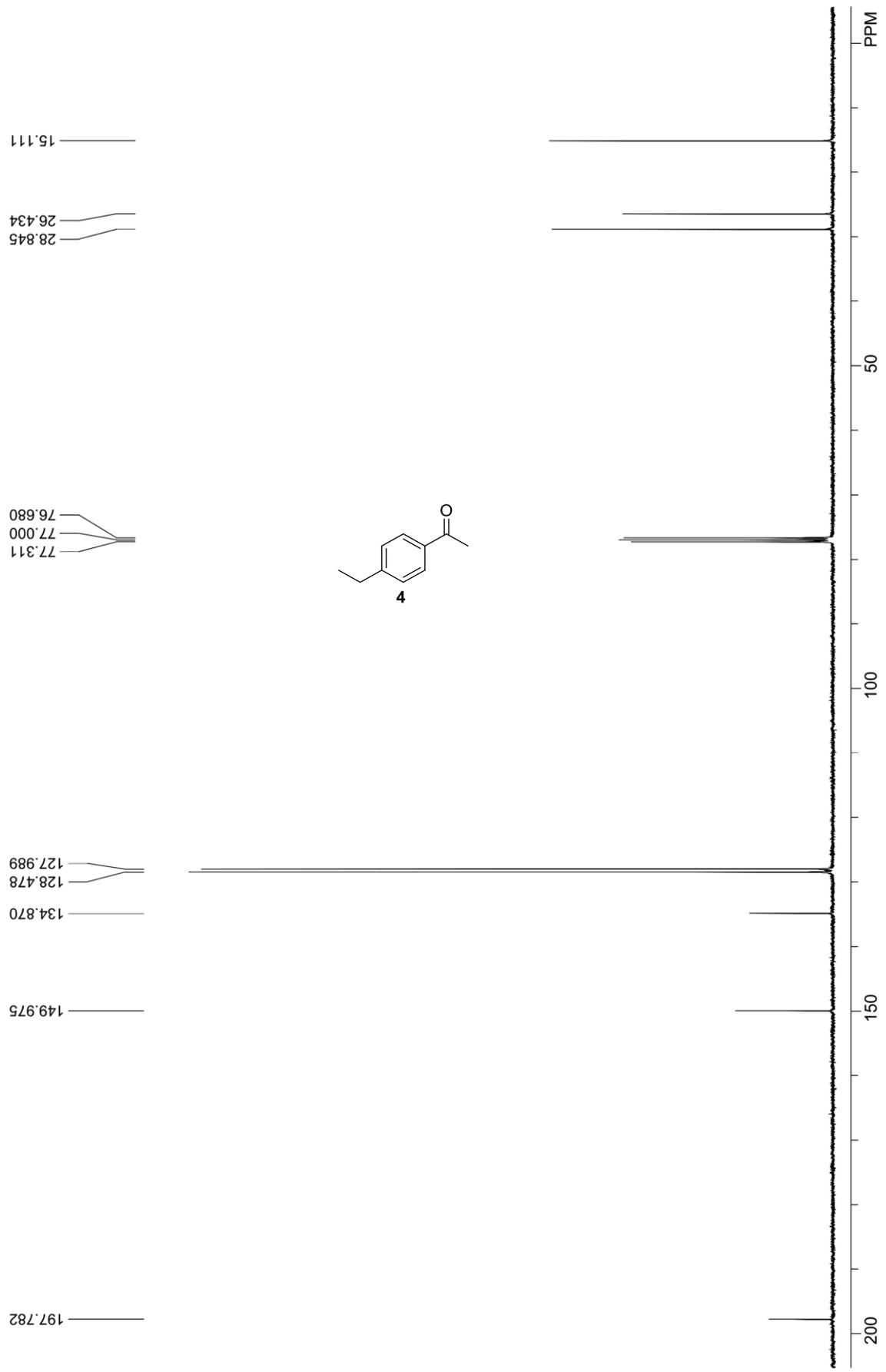
- 1 Peter, K.; Martin, P. *Tetrahedron Lett.* **2004**, *45*, 5279.
- 2 Tamio, H.; Keiichi, H.; Takao, K.; Yoshihiko, I. *J. Am. Chem. Soc.* **1988**, *110*, 8153.
- 3 Francois, N.; Raphaëlle, K.; Ludivine, J. G.; Catherine, G. H.; Micheline, D.; Bruno, A. *Tetrahedron Lett.* **2015**, *56*, 2517.
- 4 Li, F.; Wang, N.; Lu, L.; Zhu, G. *J. Org. Chem.* **2015**, *80*, 3538.
- 5 Wang, B.; Sun, H.; Sun, Z. *Eur. J. Org. Chem.* **2009**, 3688.
- 6 Shen, D.; Miao, C.; Xu, D.; Xia, C.; Sun, W. *Org. Lett.* **2015**, *17*, 54.
- 7 Elangovan, S.; Sortais, J. B.; Beller, M.; Darcel, C. *Angew. Chem., Int. Ed.* **2015**, *54*, 14483.
- 8 He, Z.; Qi, X.; Li, S.; Zhao, Y.; Gao, G.; Lan, Y.; Wu, Y.; Lan, J.; You, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 855.
- 9 Su, X.; Fox, D. J.; Blackwell, D. T.; Tanaka, K.; Spring, D. R. *Chem. Commun.* **2006**, 3883.
- 10 Ivchenko, P. V.; Nifantev, I. E.; Buslov, I. V. *Tetrahedron Lett.* **2013**, *54*, 217.
- 11 Jozak, T.; Fischer, M.; Thiel, J.; Sun, Y.; Kelm, H.; Thiel, W. R. *Eur. J. Org. Chem.* **2009**, 1445.
- 12 Steliou, K.; Salama, P.; Yu, X. *J. Am. Chem. Soc.* **1992**, *114*, 1456.
- 13 McNulty, P. J.; Pearson, D. E. *J. Am. Chem. Soc.* **1959**, *81*, 612.
- 14 Girling, P. R.; Batsanov, A. S.; Calow, A. D. J.; Shen, H.-C.; Whiting, A. *Tetrahedron* **2016**, *72*, 1105.
- 15 Issac, Y. A.; Zein, S. M.; Barakat, Y. *Rev. Roum. Chim.* **1995**, *40*, 463.
- 16 Doan, T. L. H.; Dao, T. Q.; Tran, H. N.; Tran, P. H.; Le, T. N. *Dalton Trans.* **2016**, *45*, 7875.
- 17 Wang, G.-Z.; Li, X.-L.; Dai, J.-J.; Xu, H.-J. *J. Org. Chem.* **2014**, *79*, 7220.
- 18 Mbofana, C. T.; Chong, E.; Lawiczak, J.; Sanford, M. S. *Org. Lett.* **2016**, *18*, 4258.

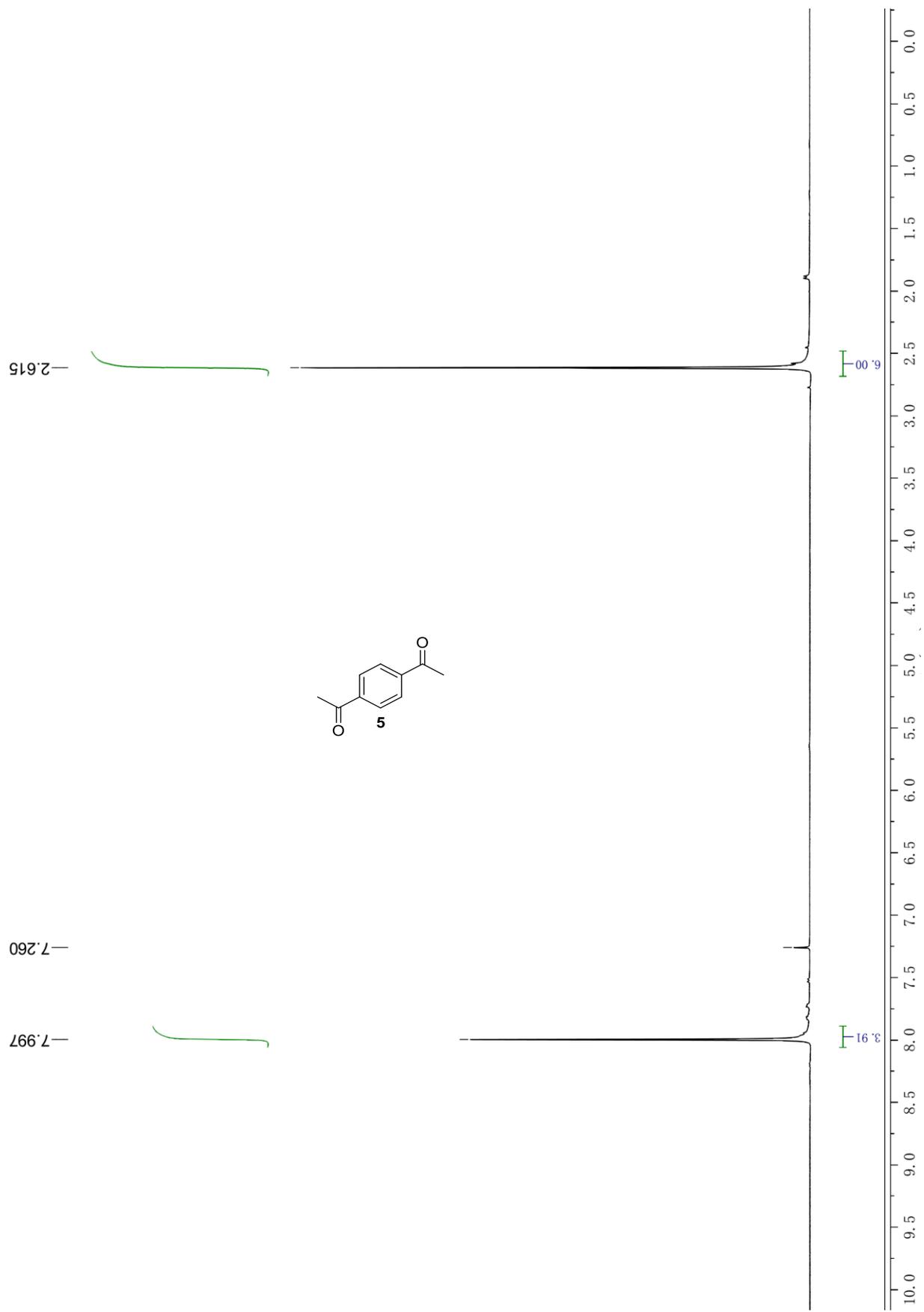
4. NMR Spectra and HPLC Spectra

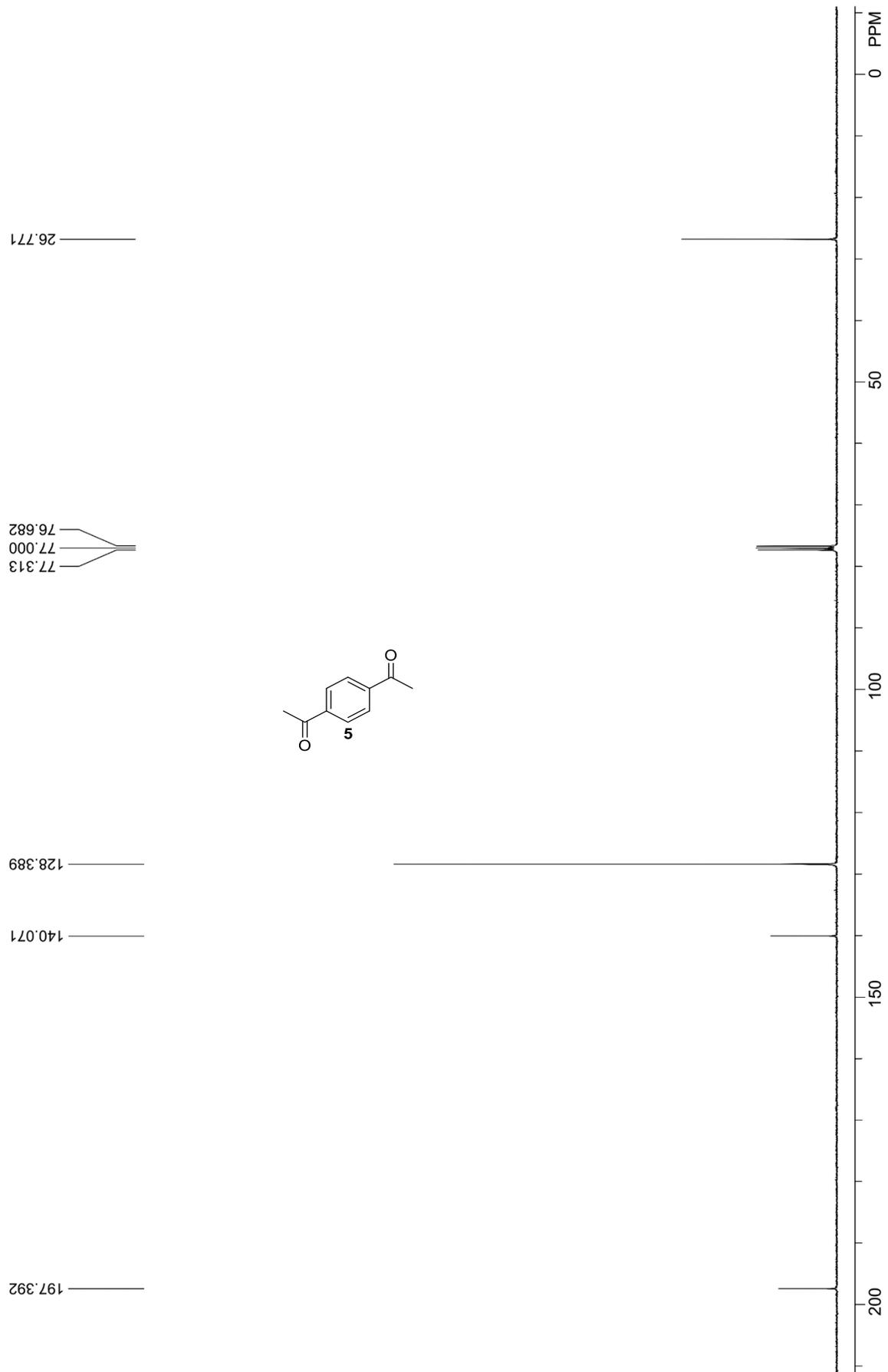


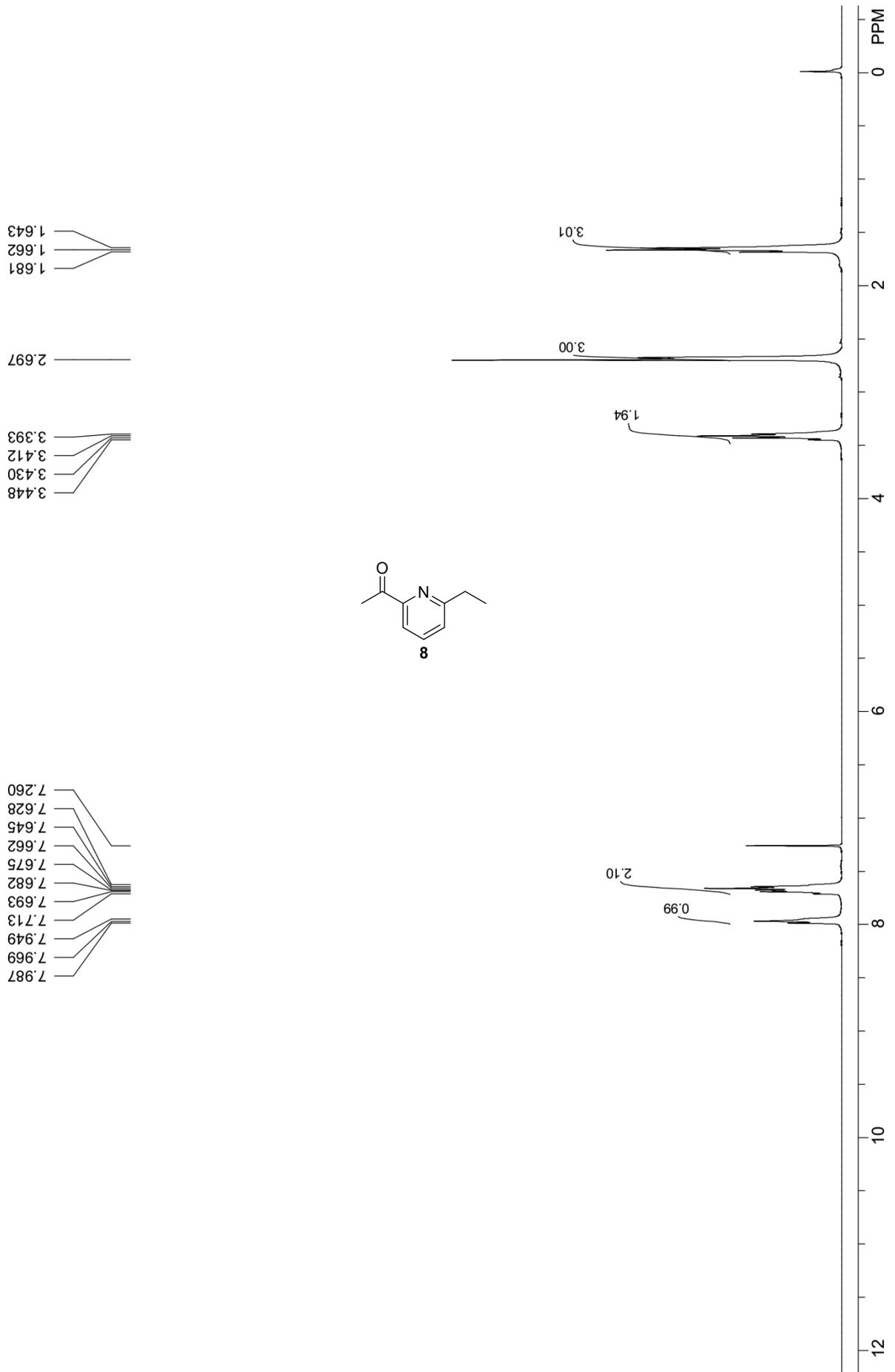


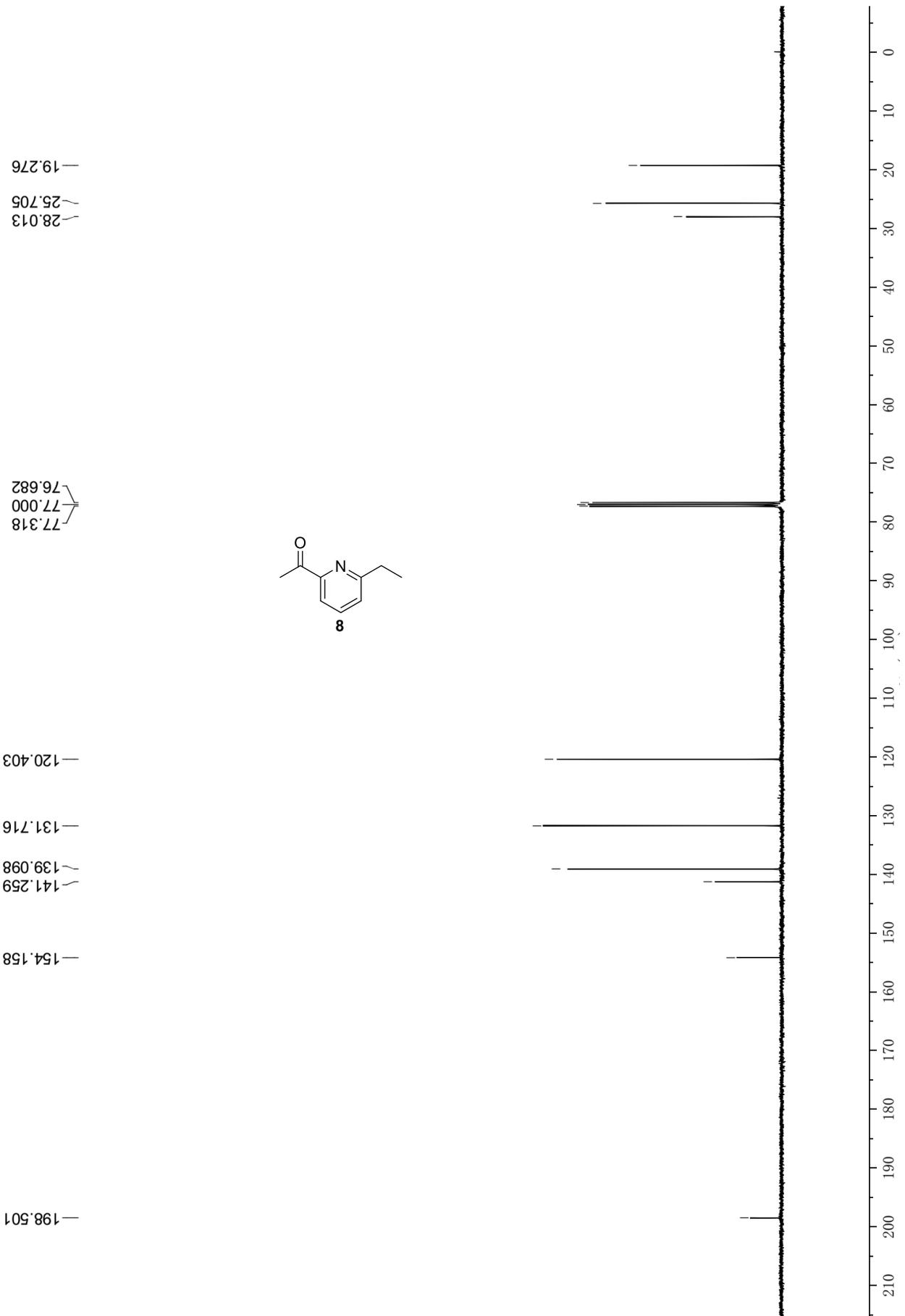


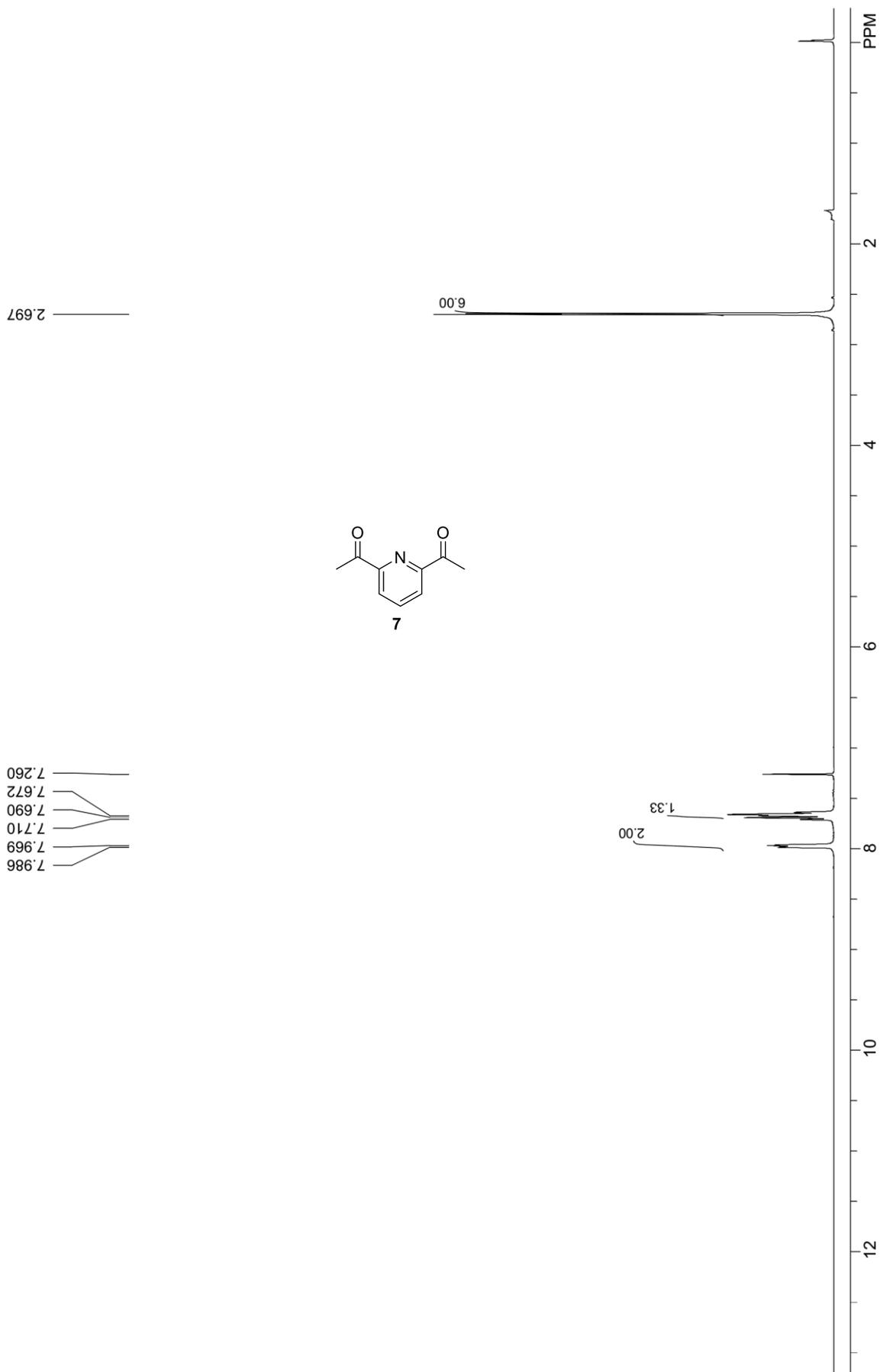


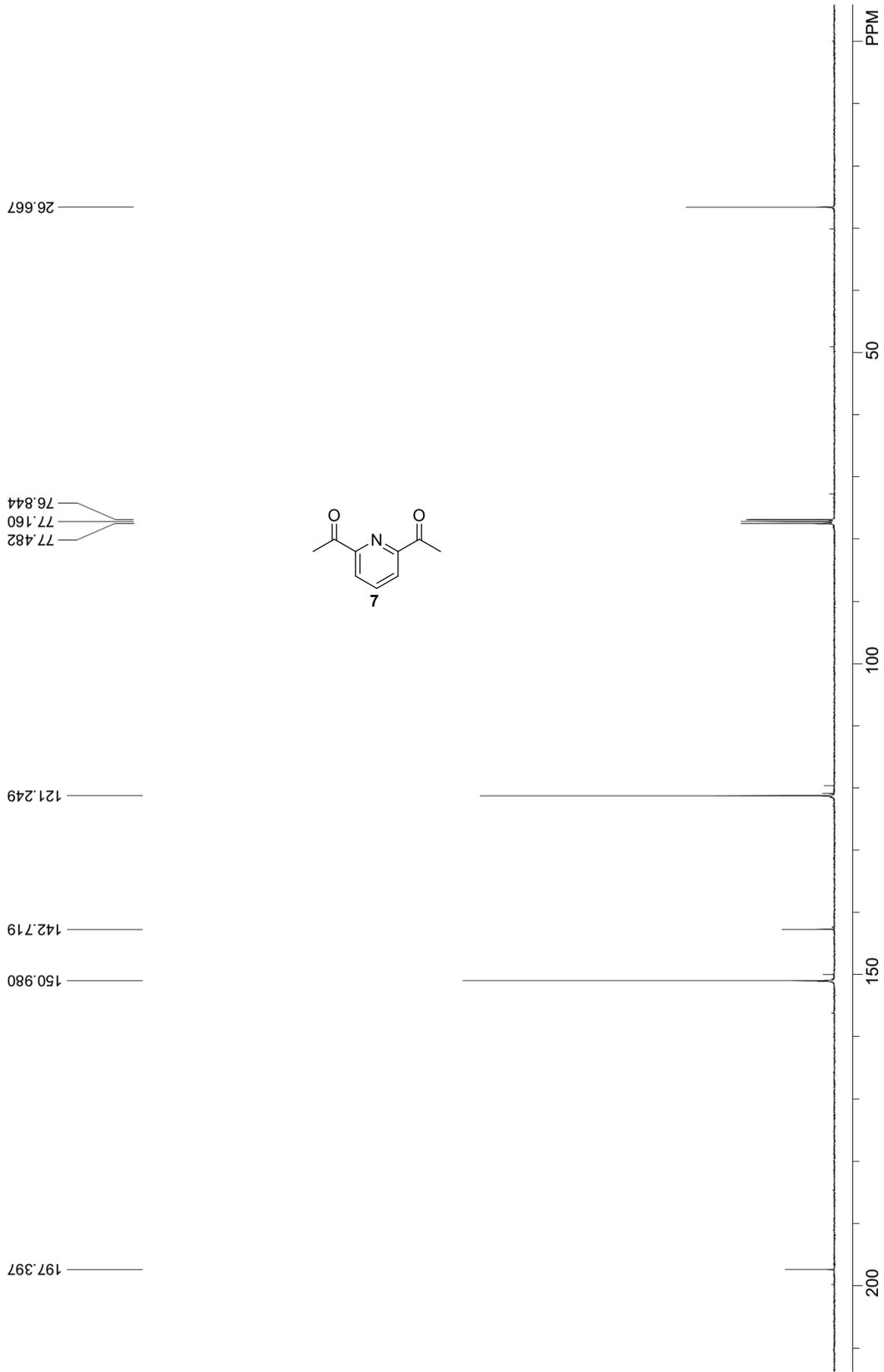








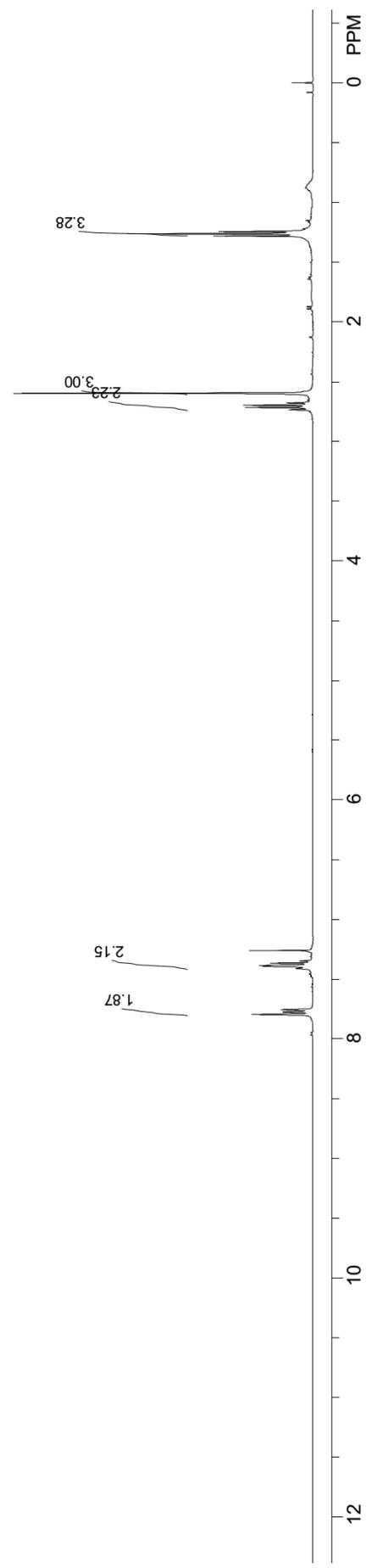
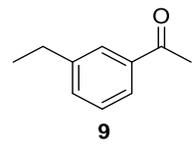


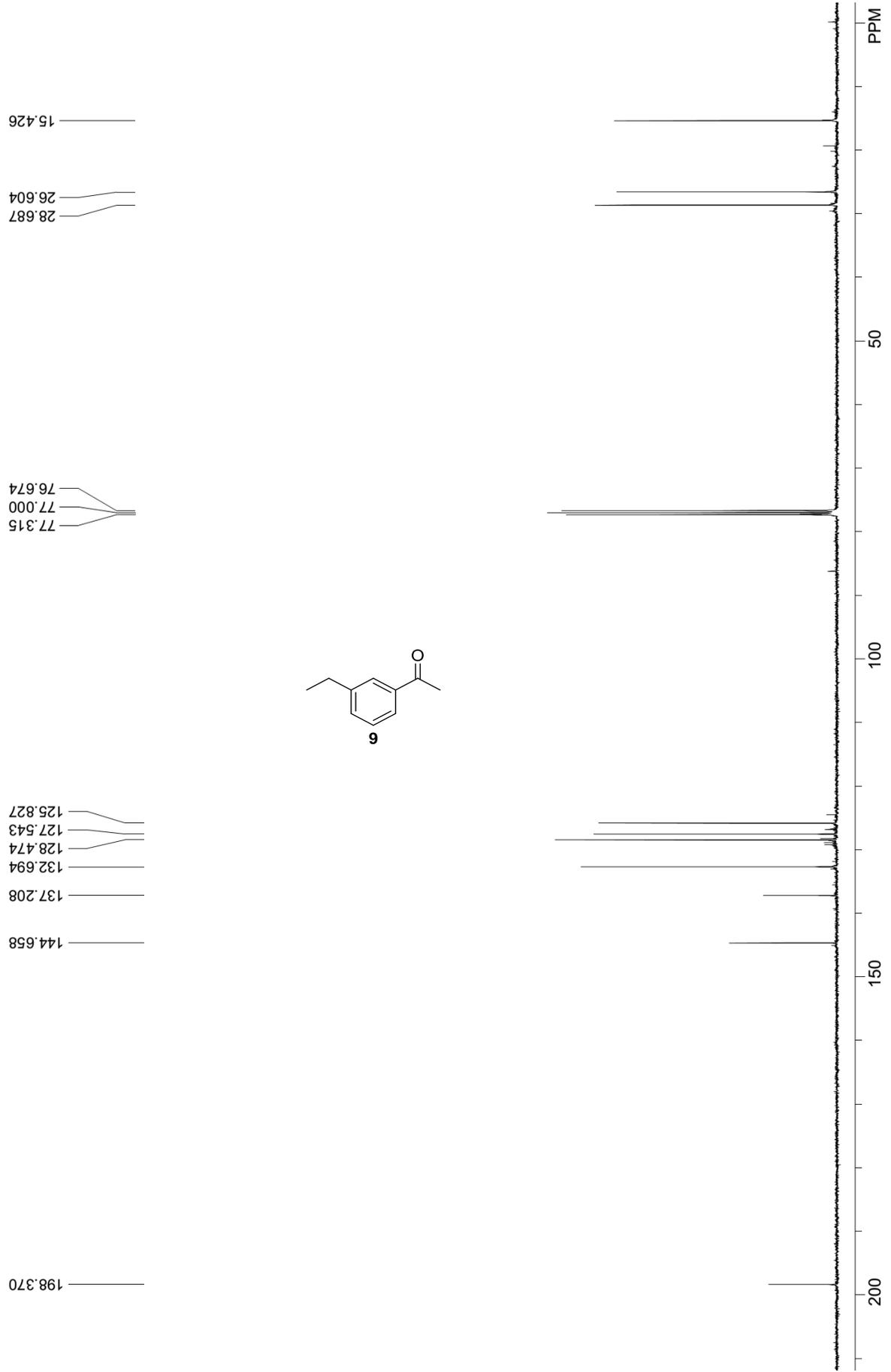


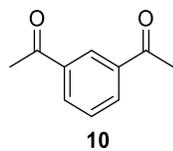
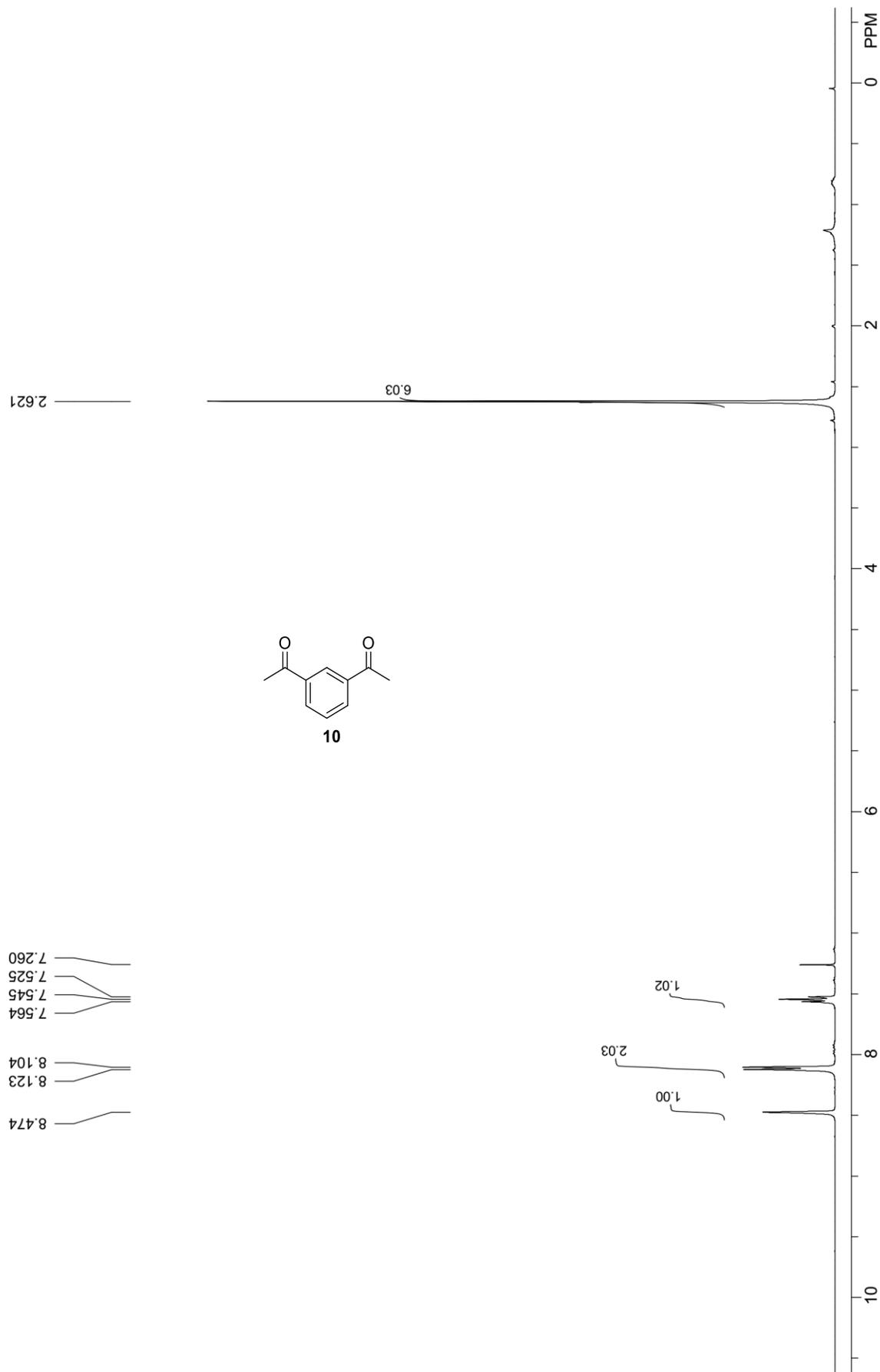
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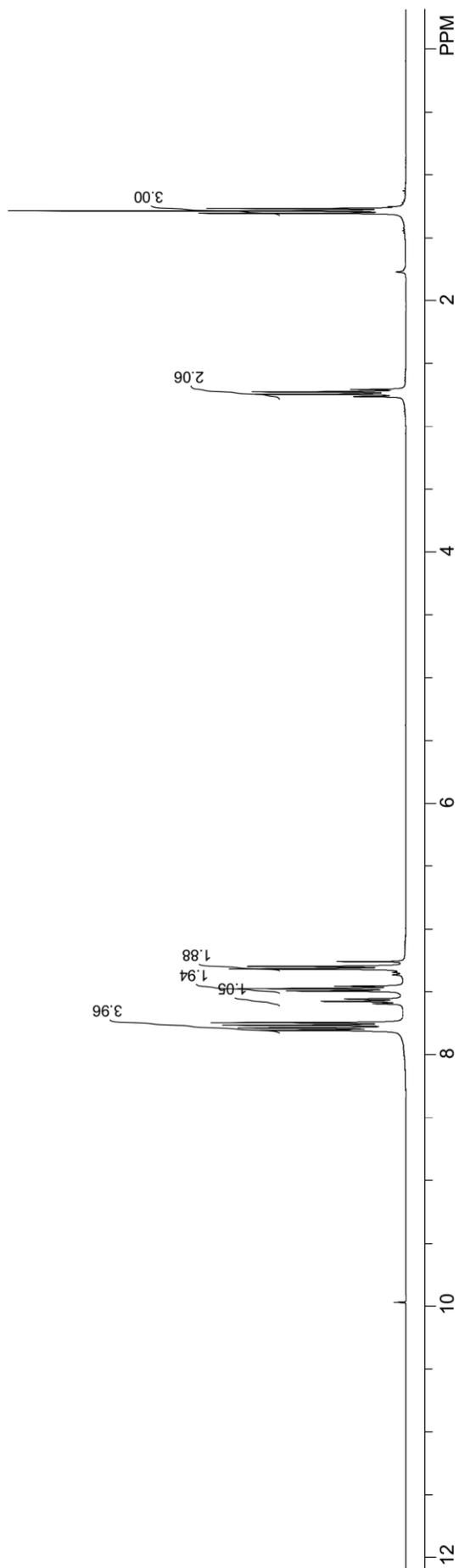
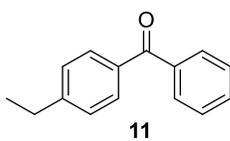




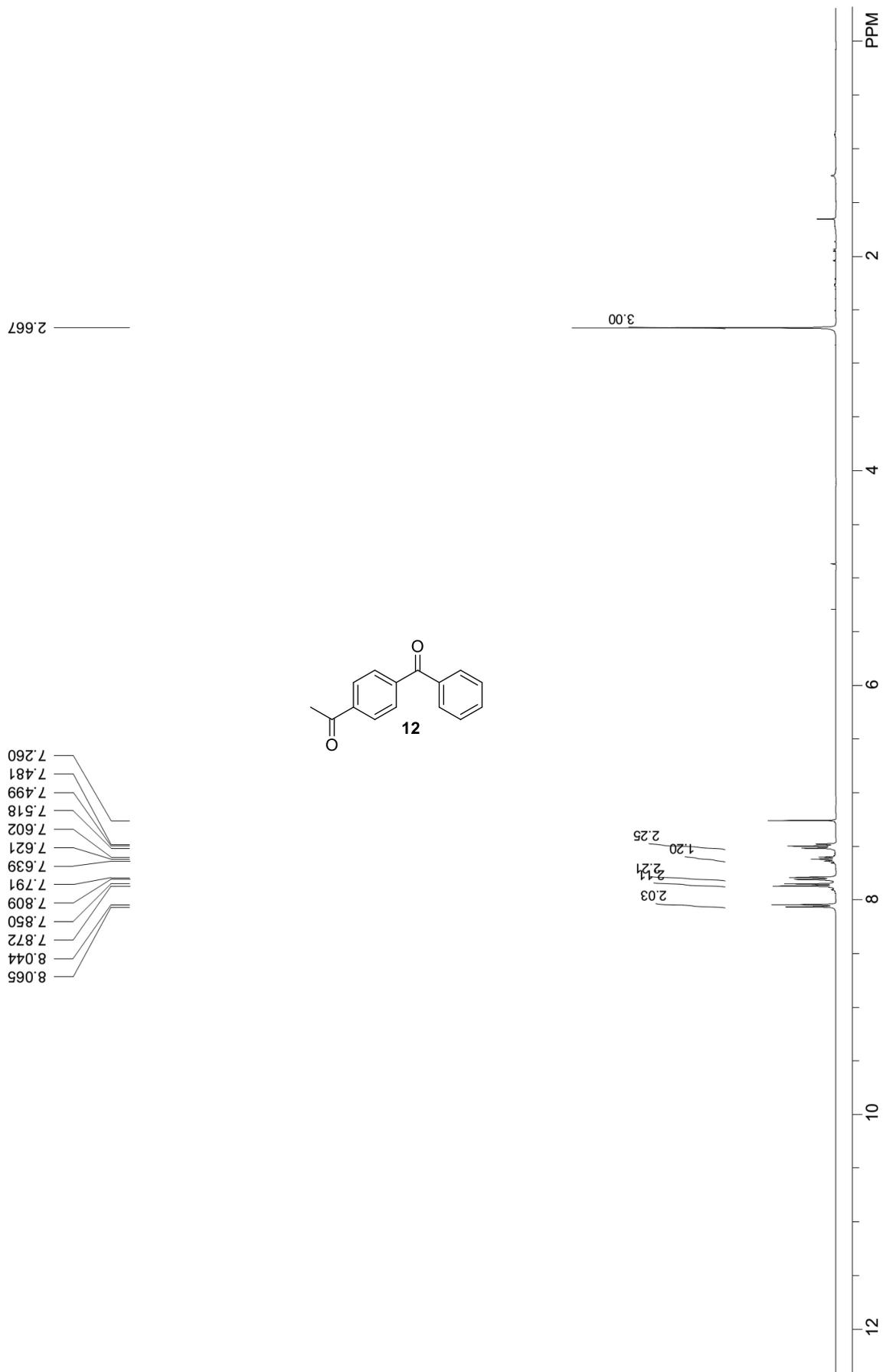
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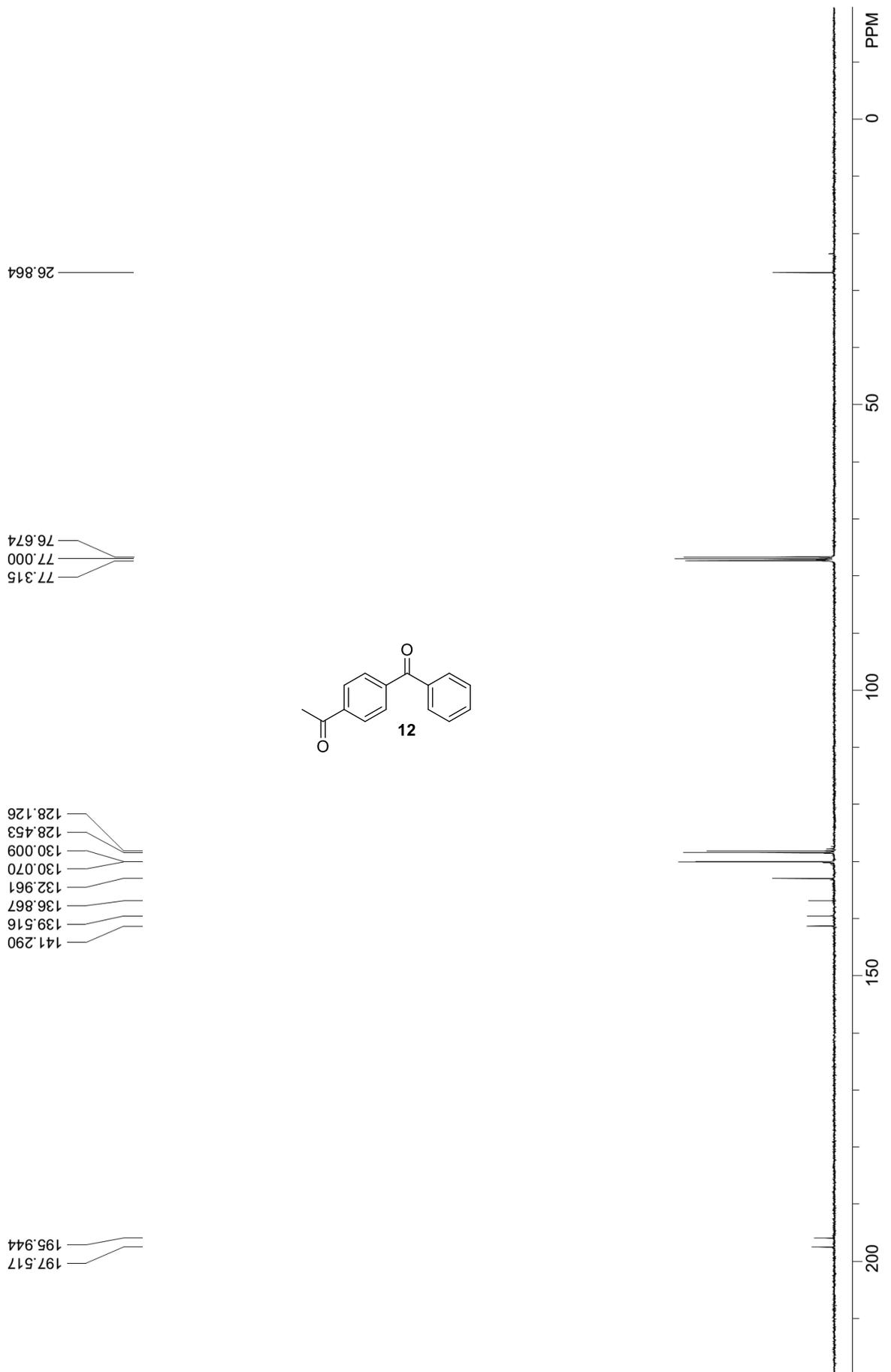
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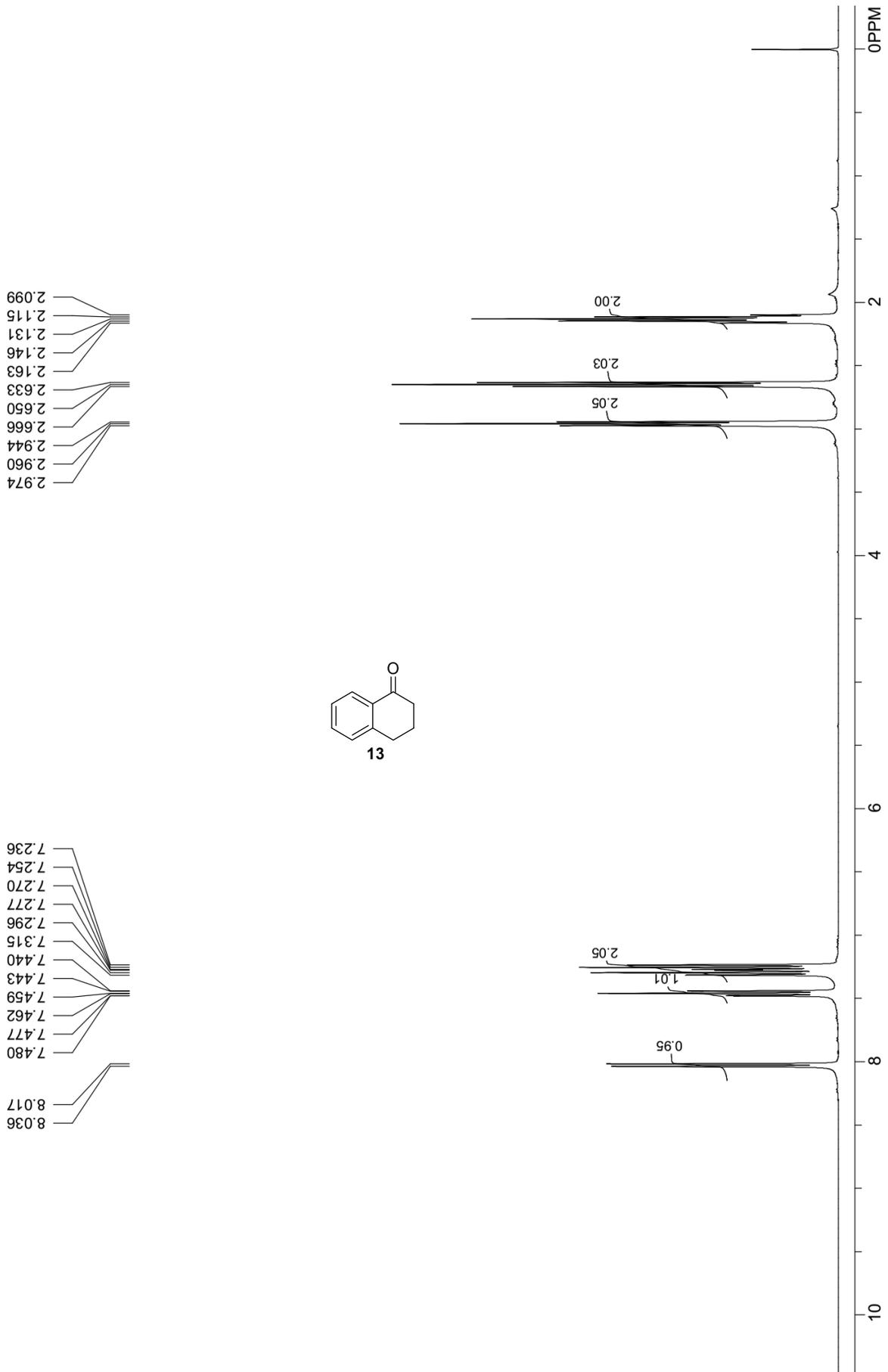
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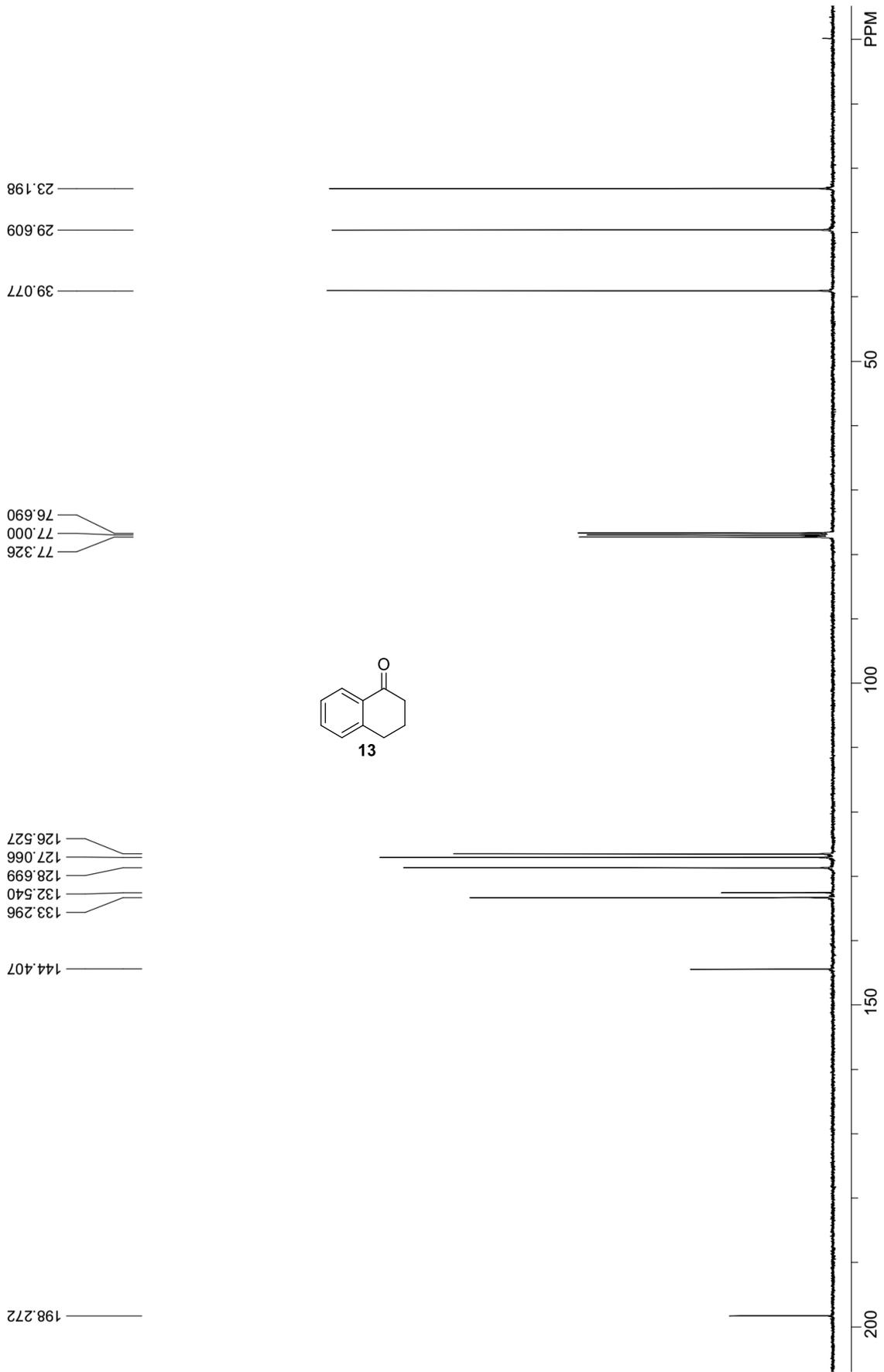


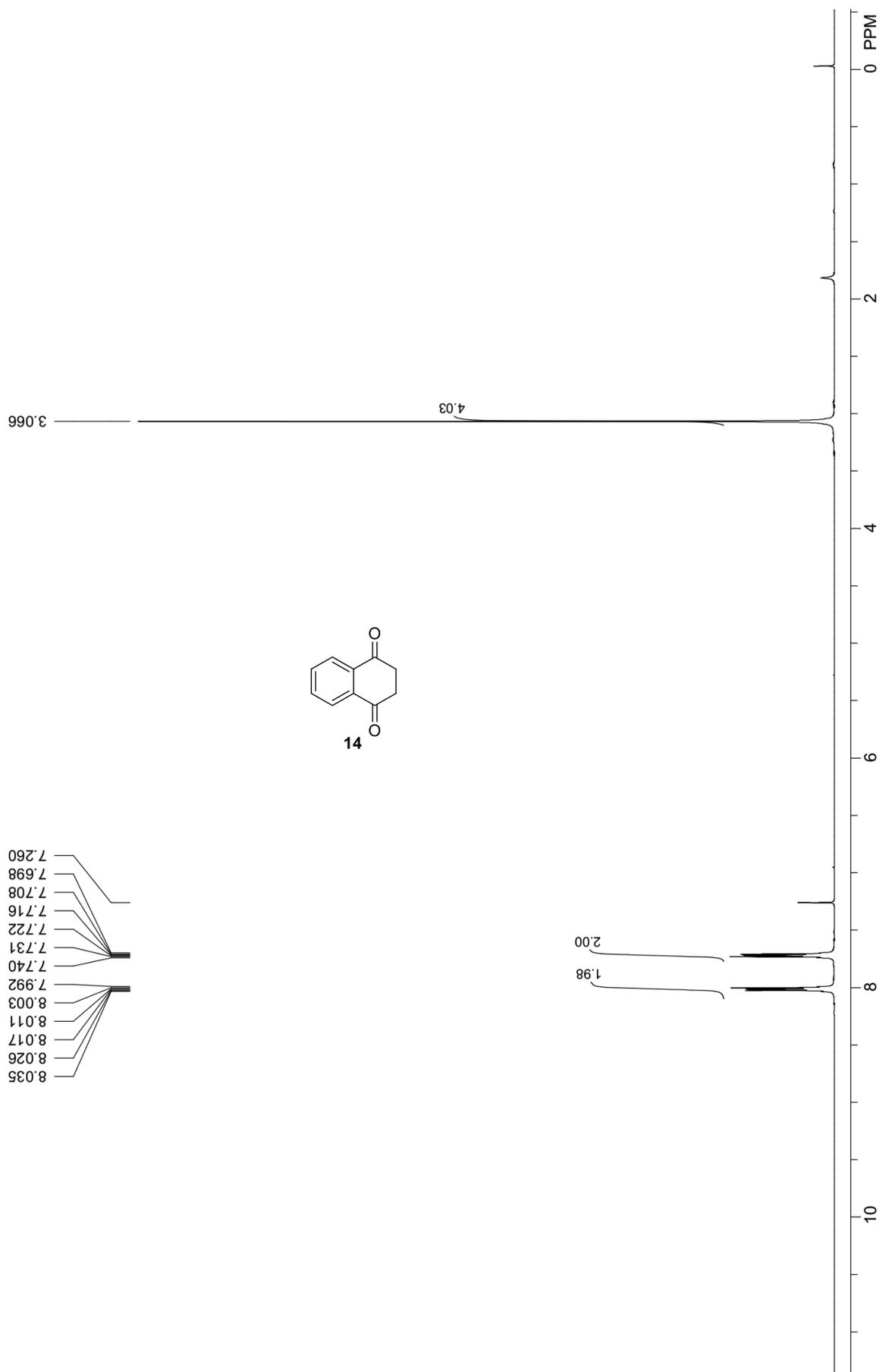


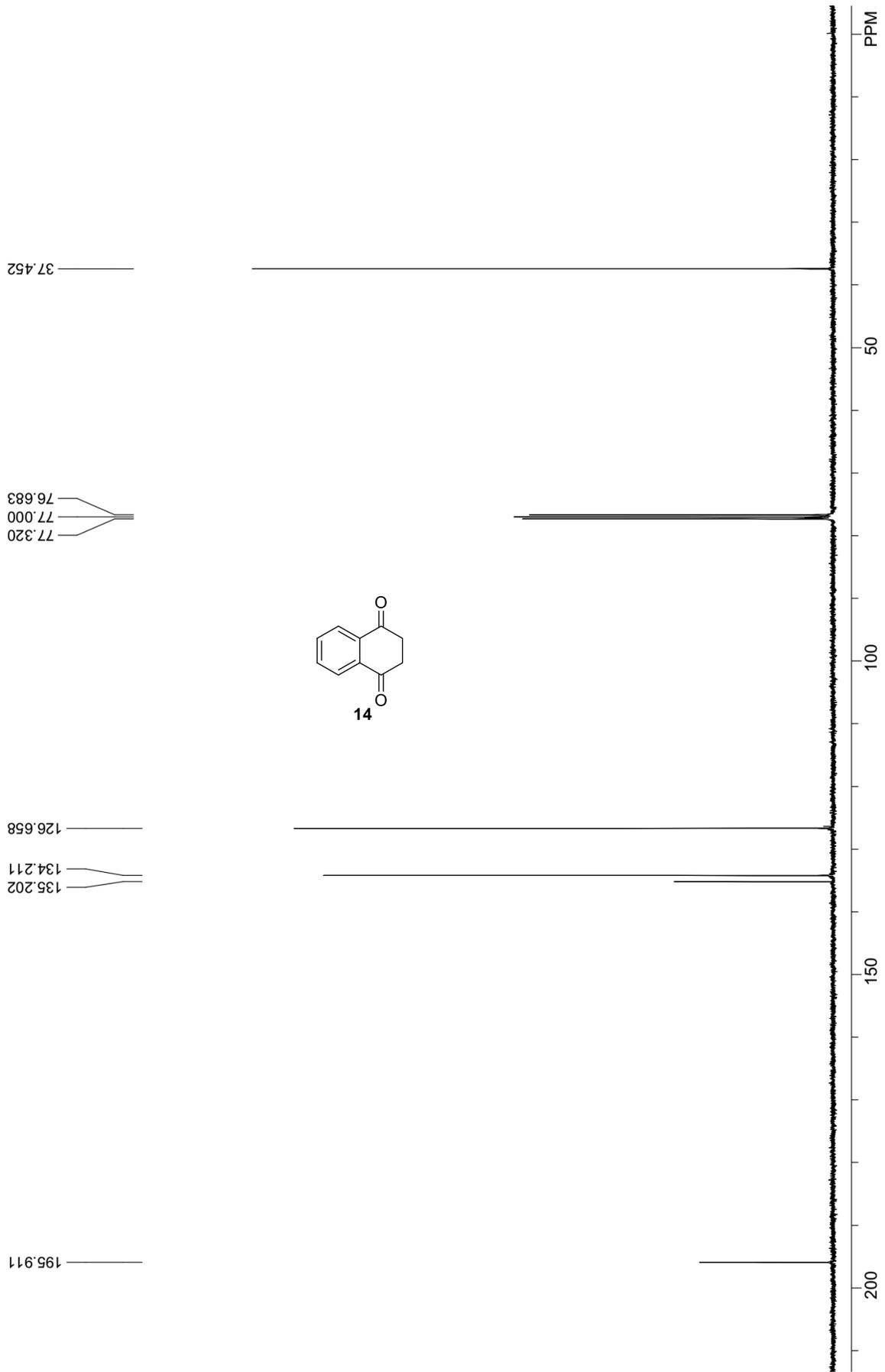


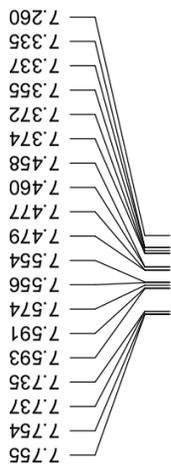
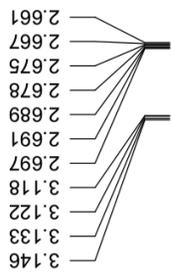
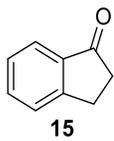
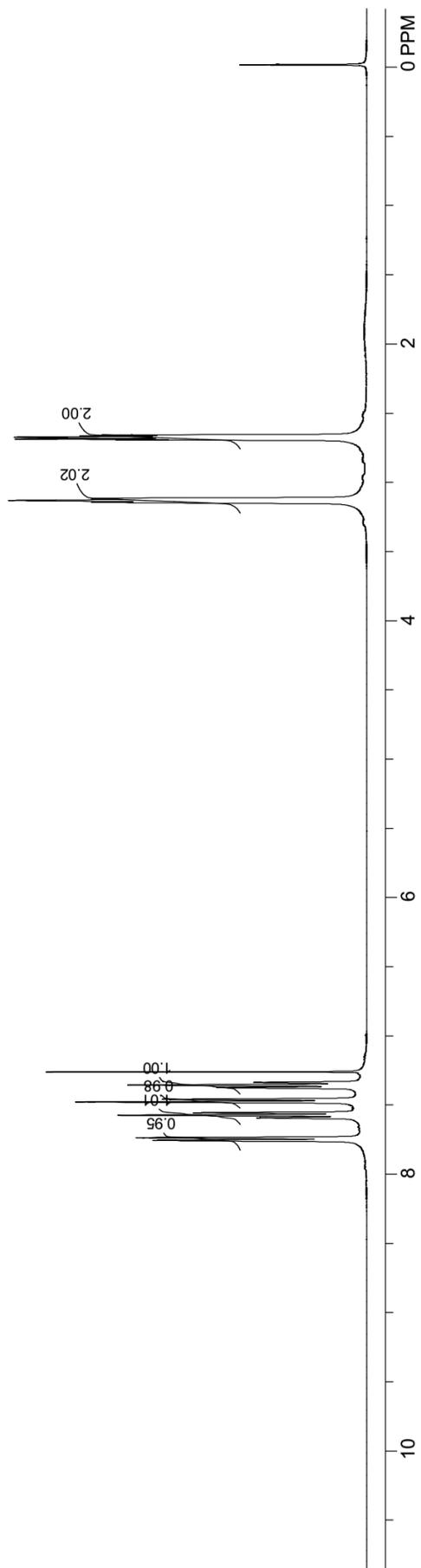


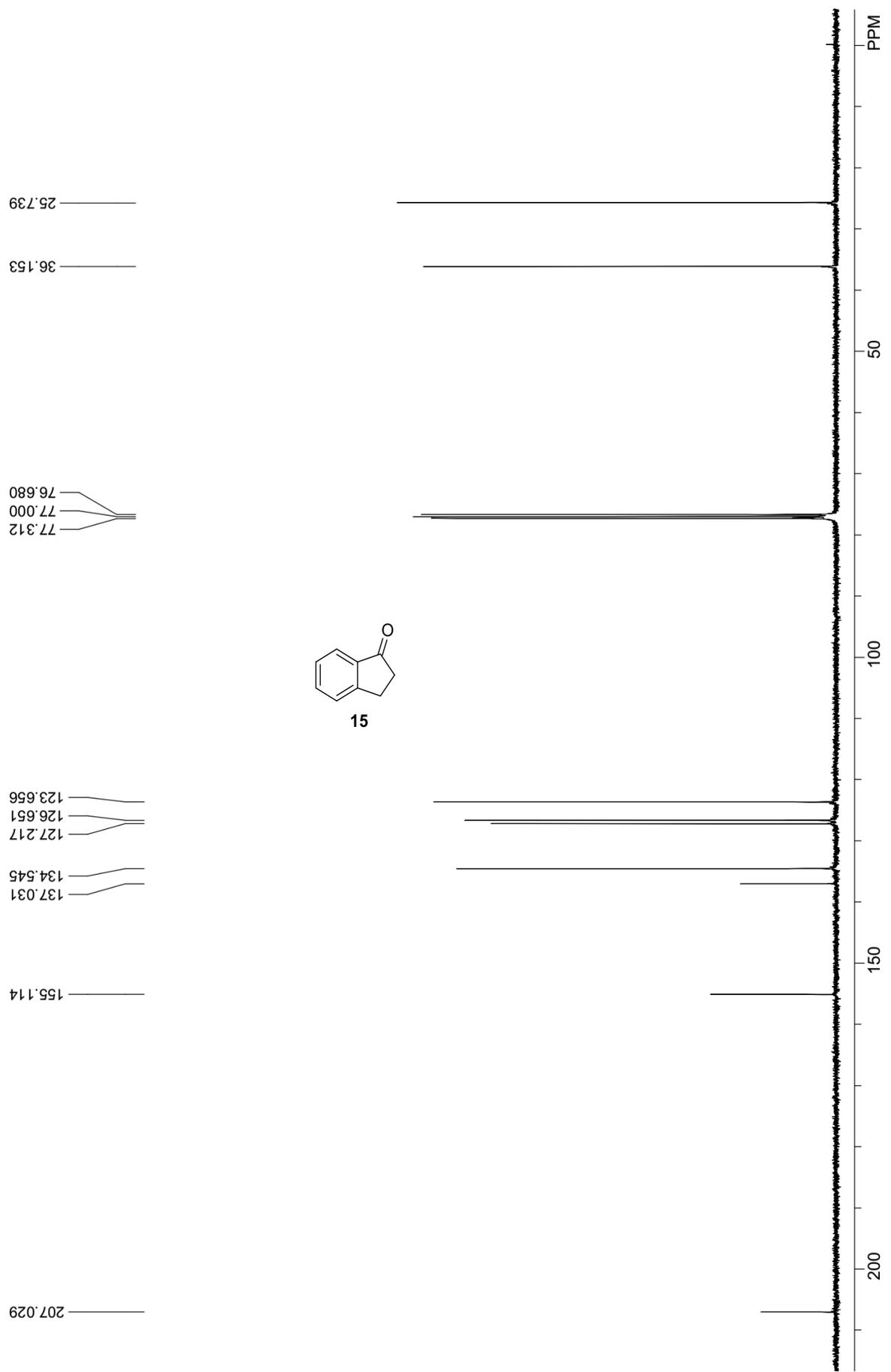


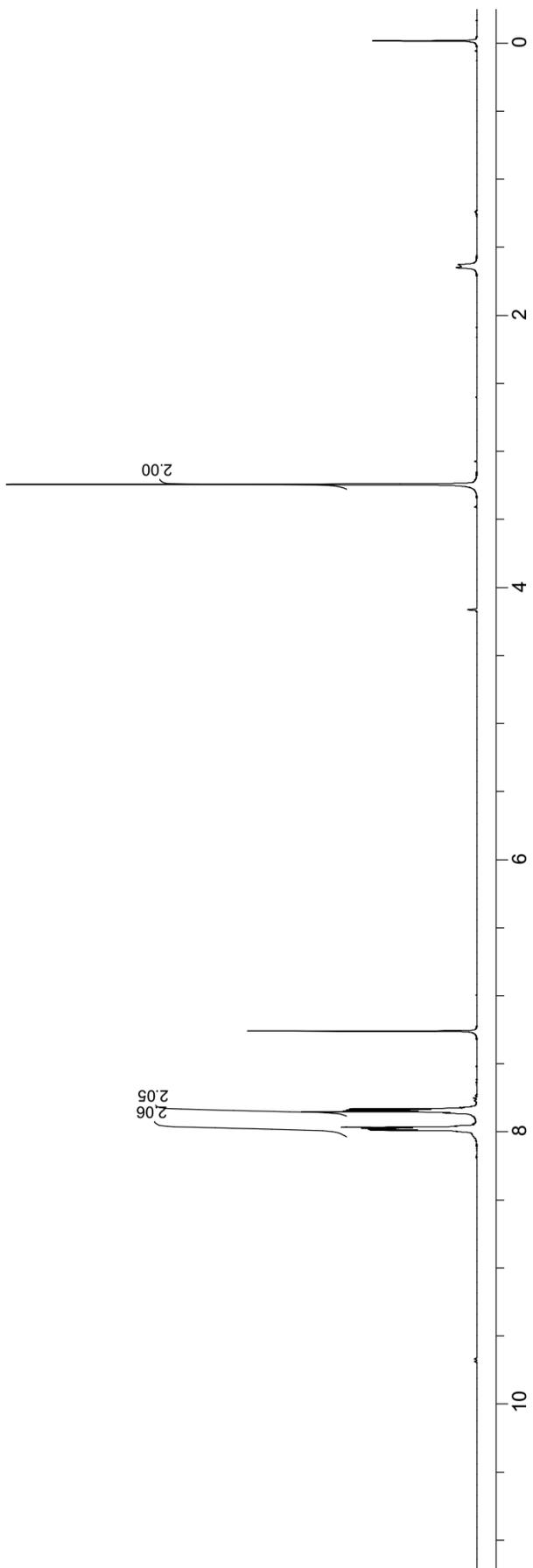
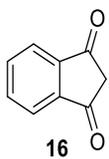






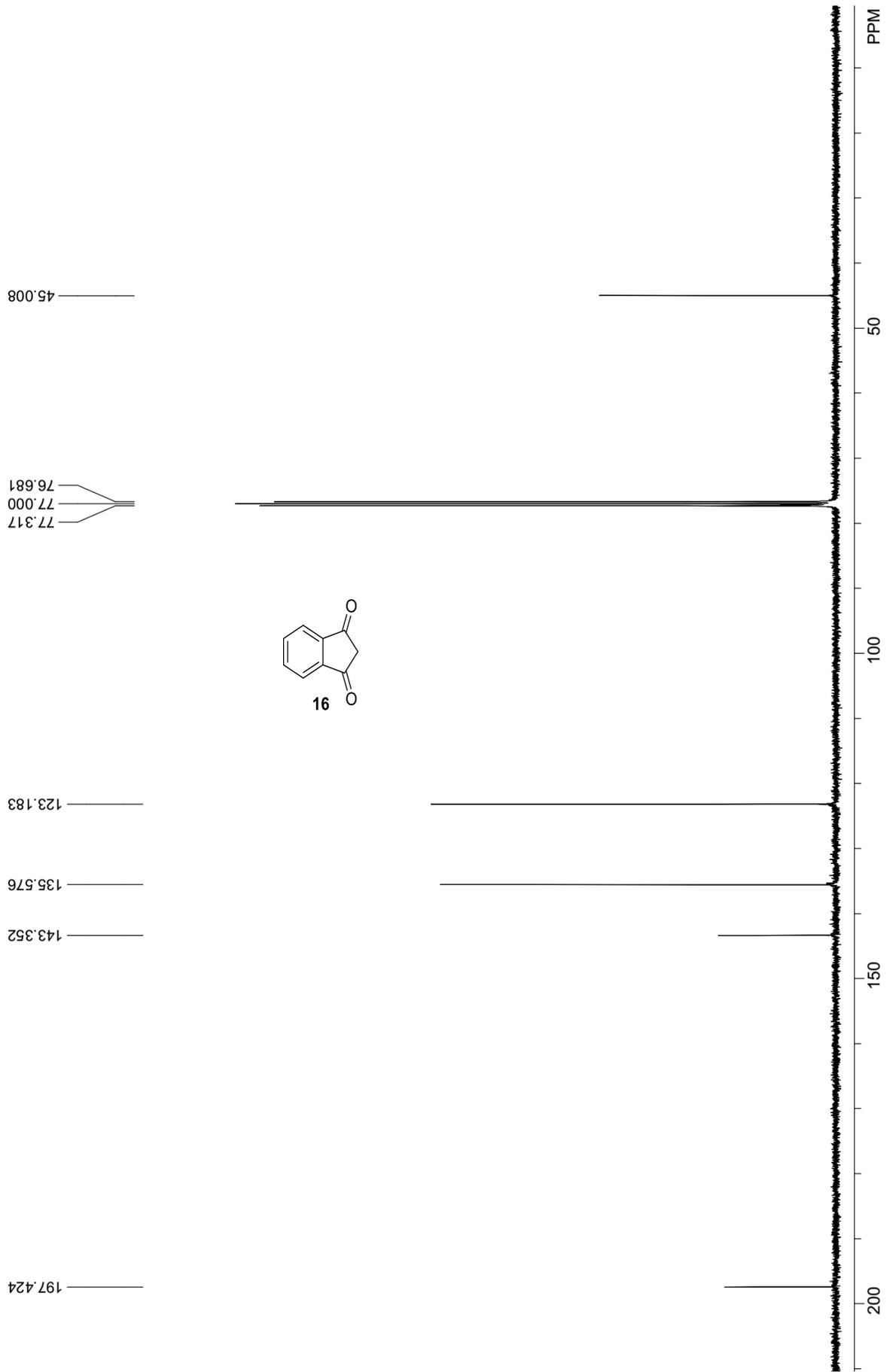


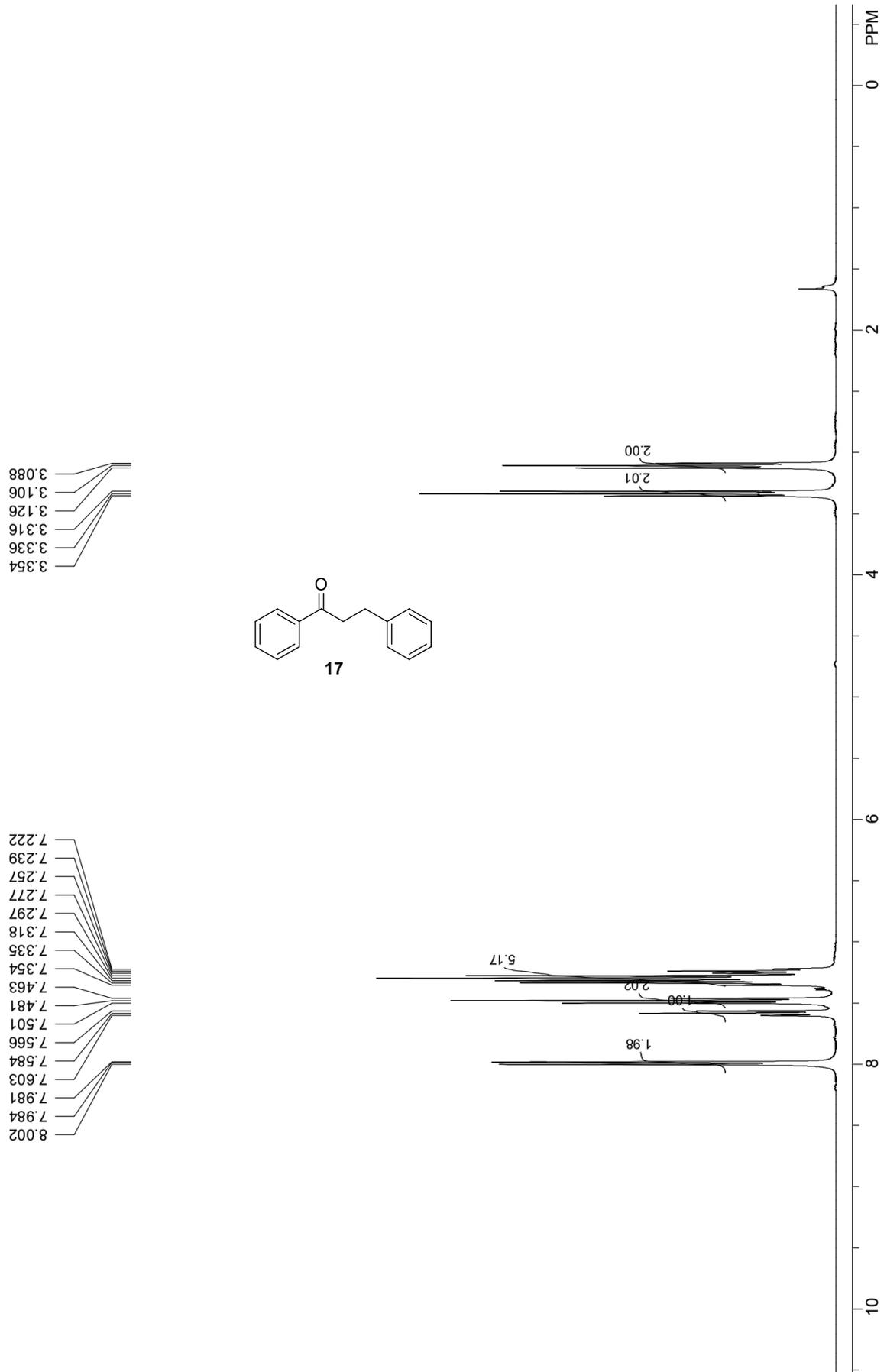




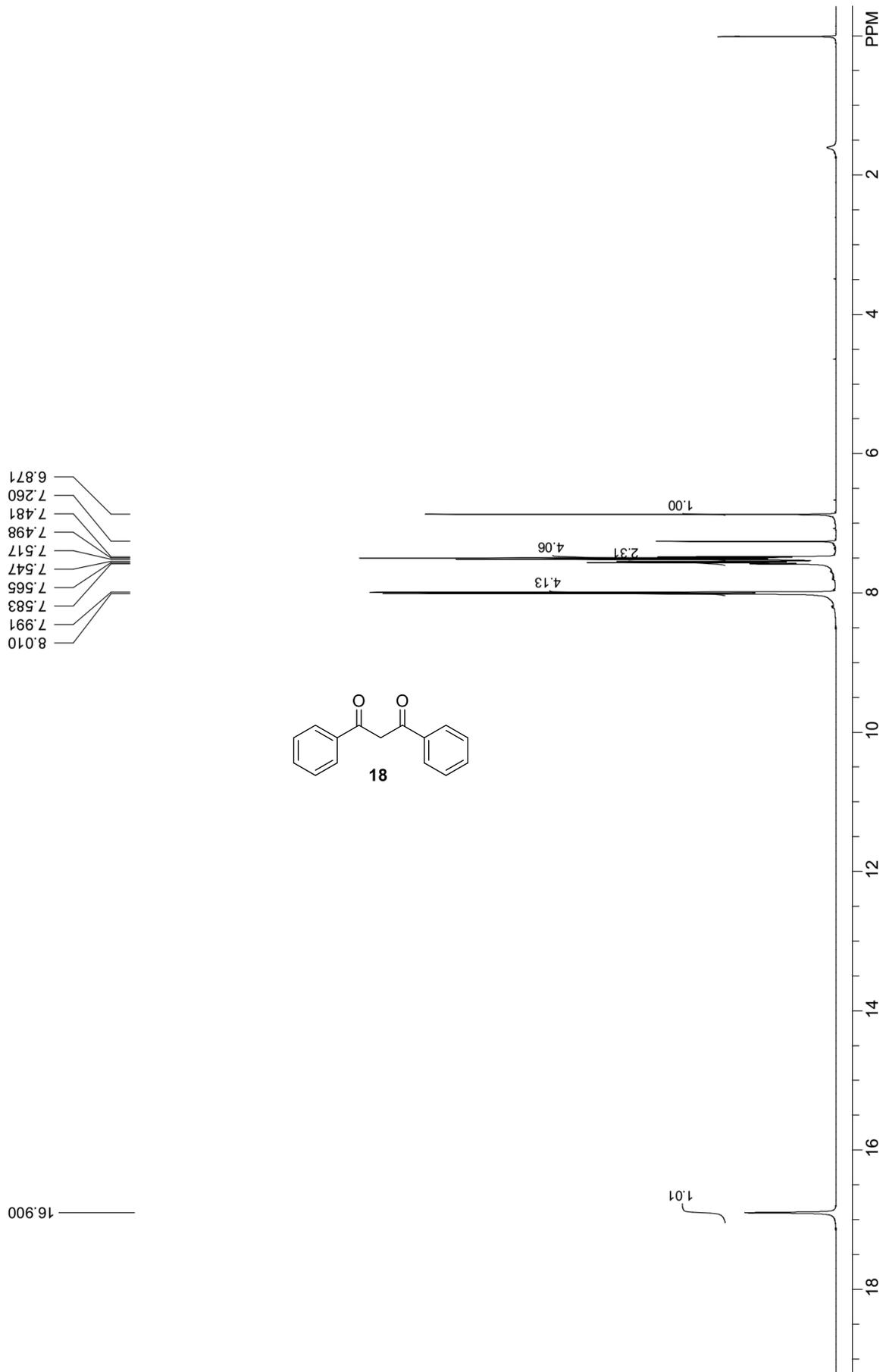
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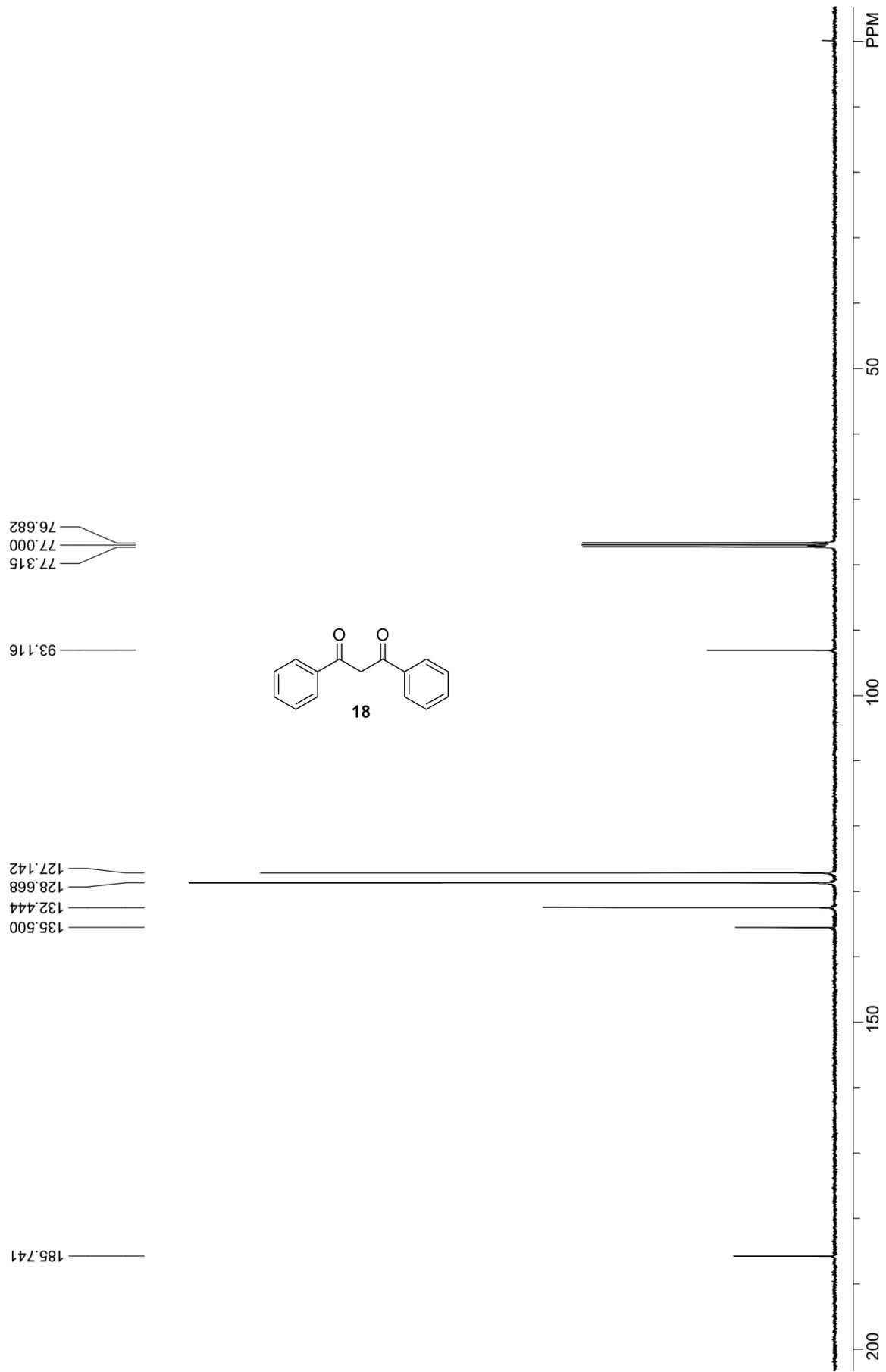
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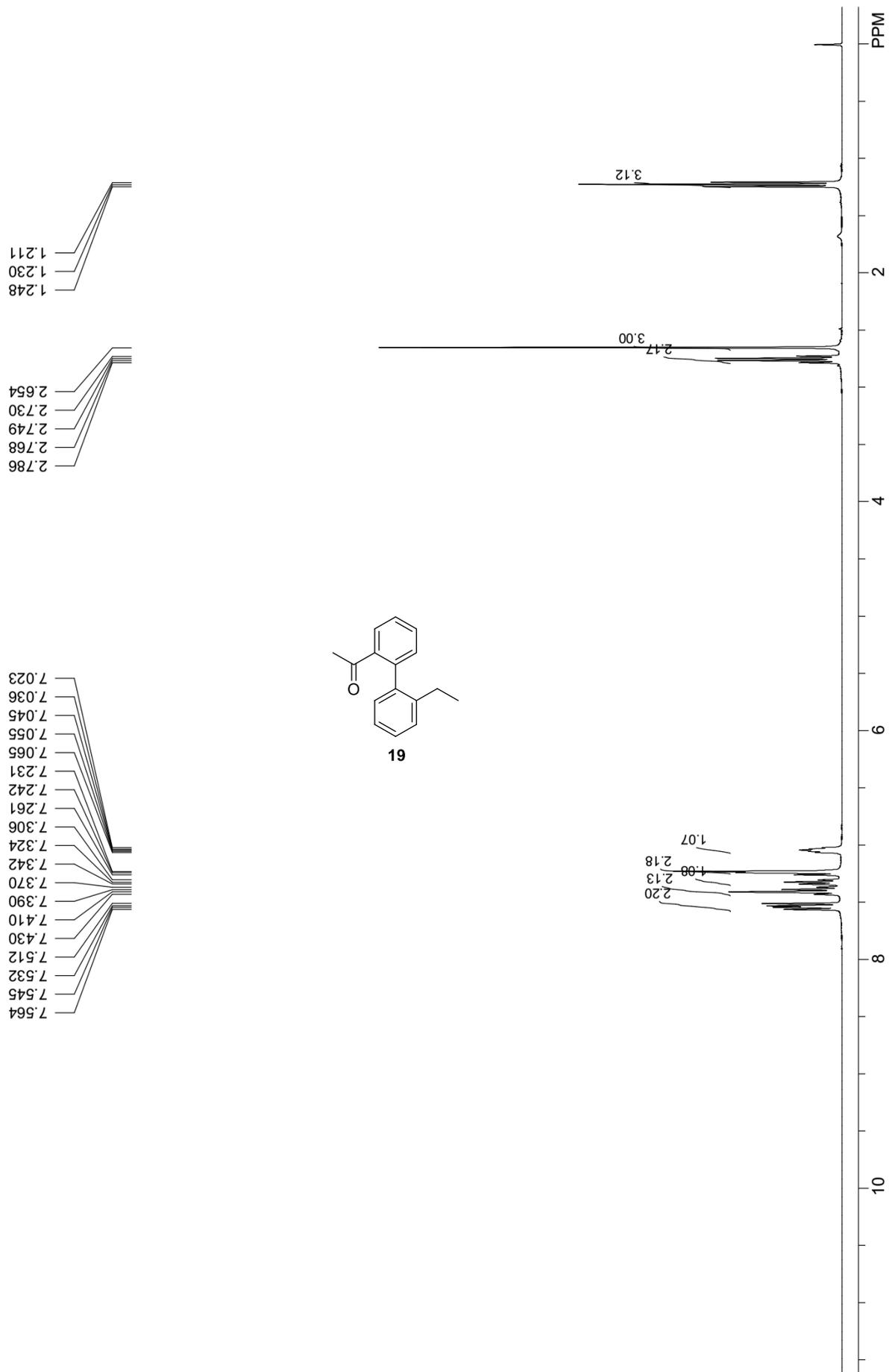


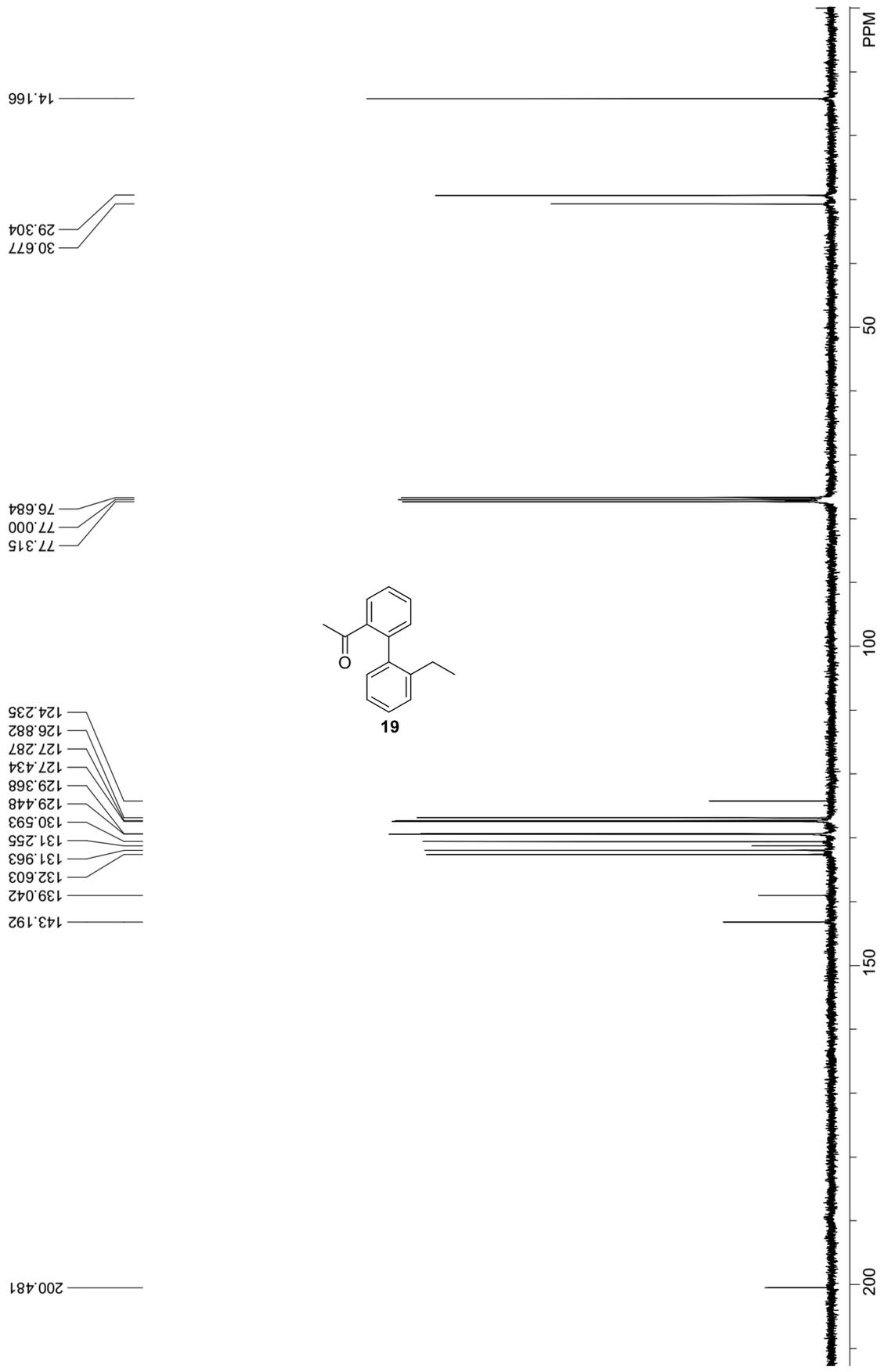






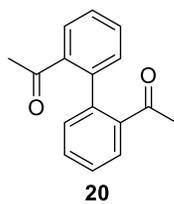






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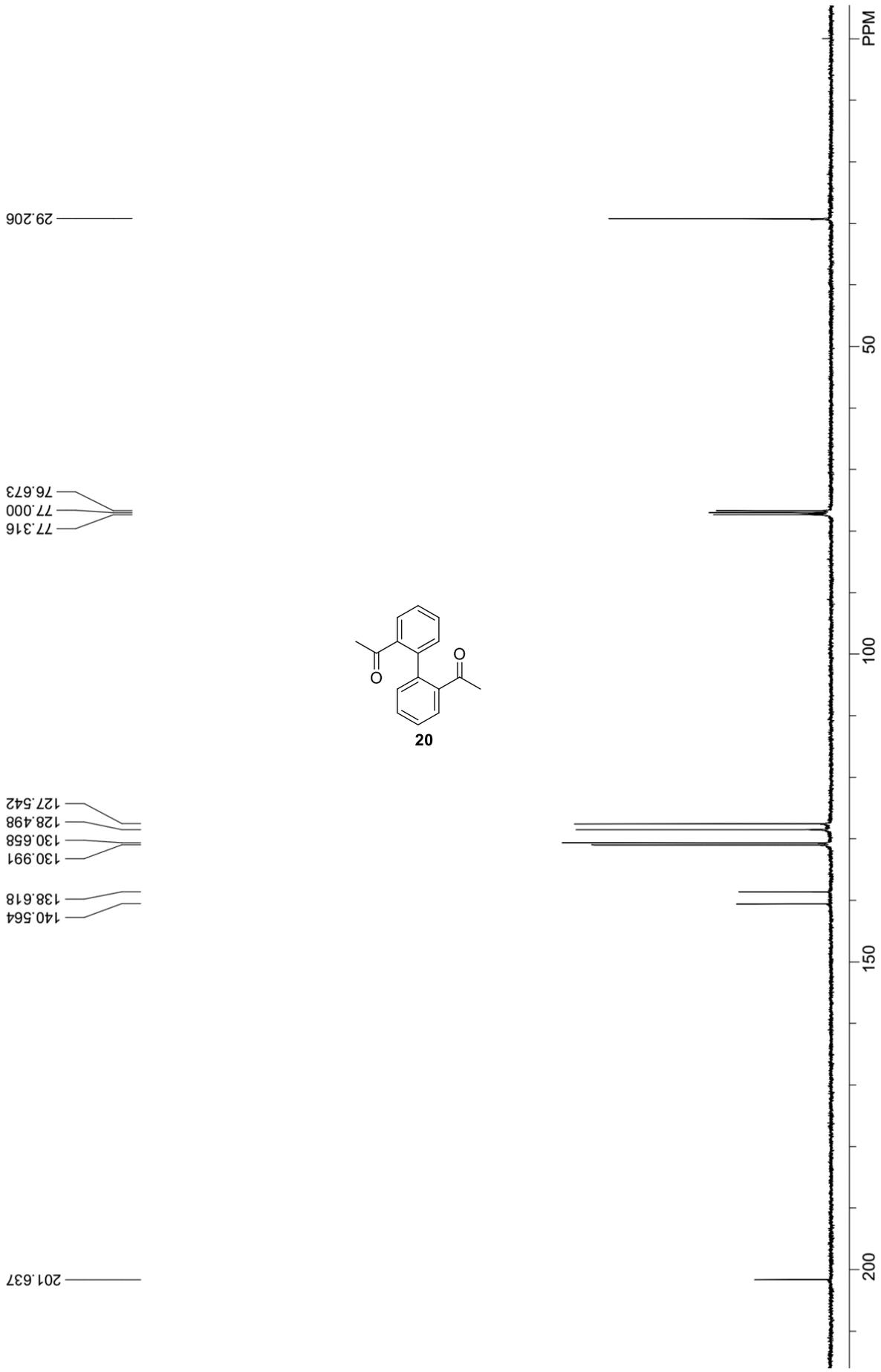
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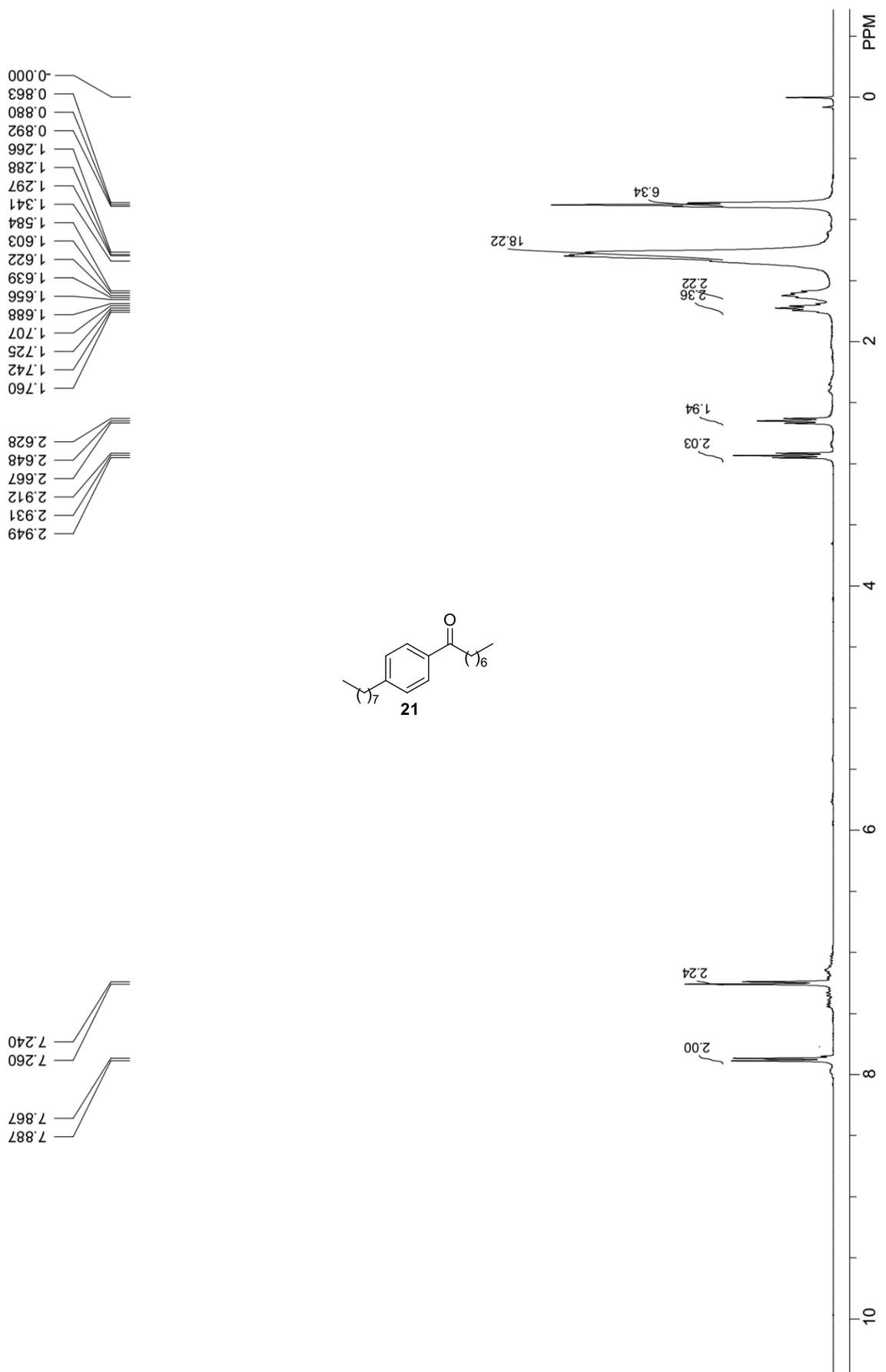


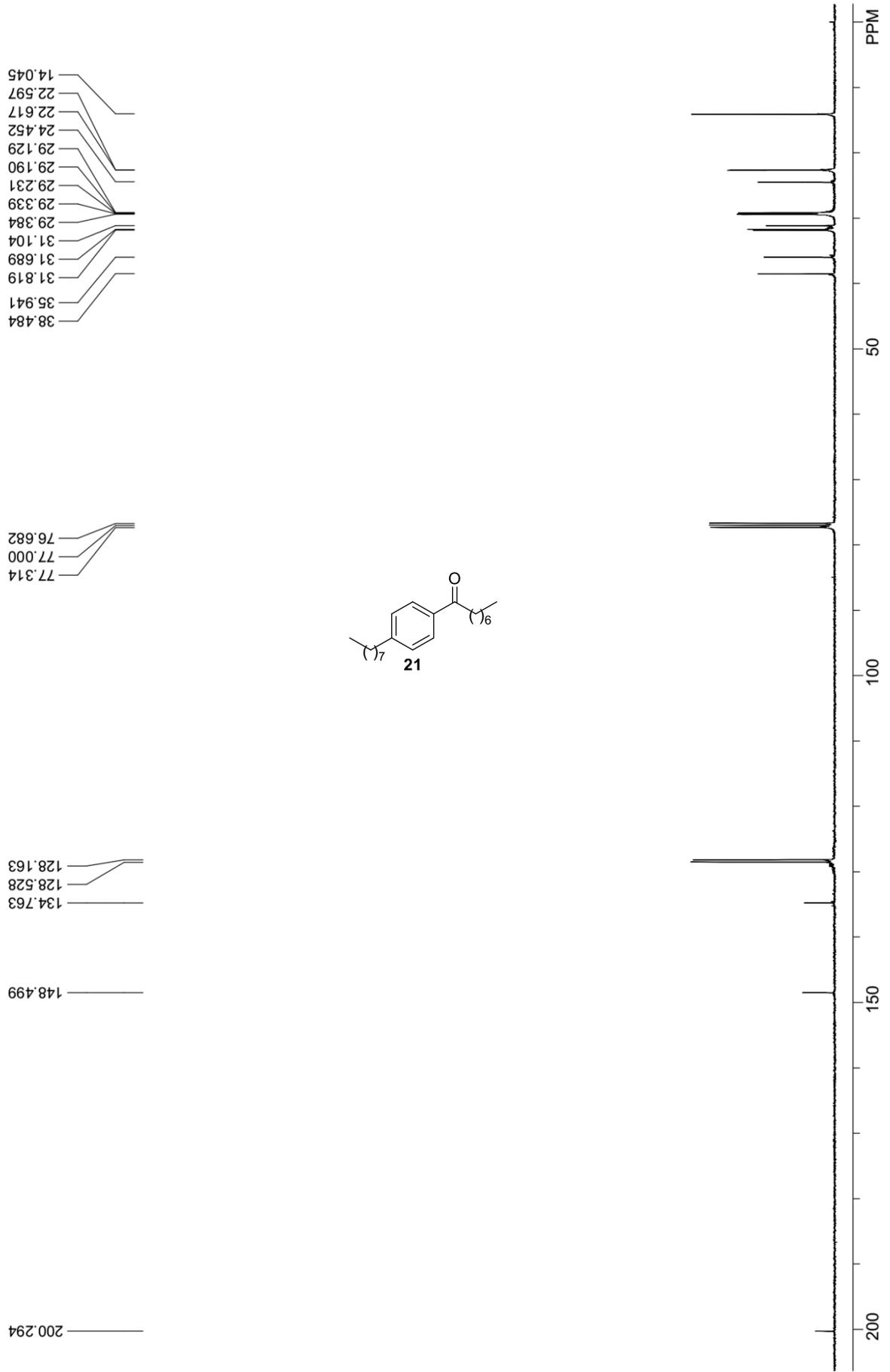
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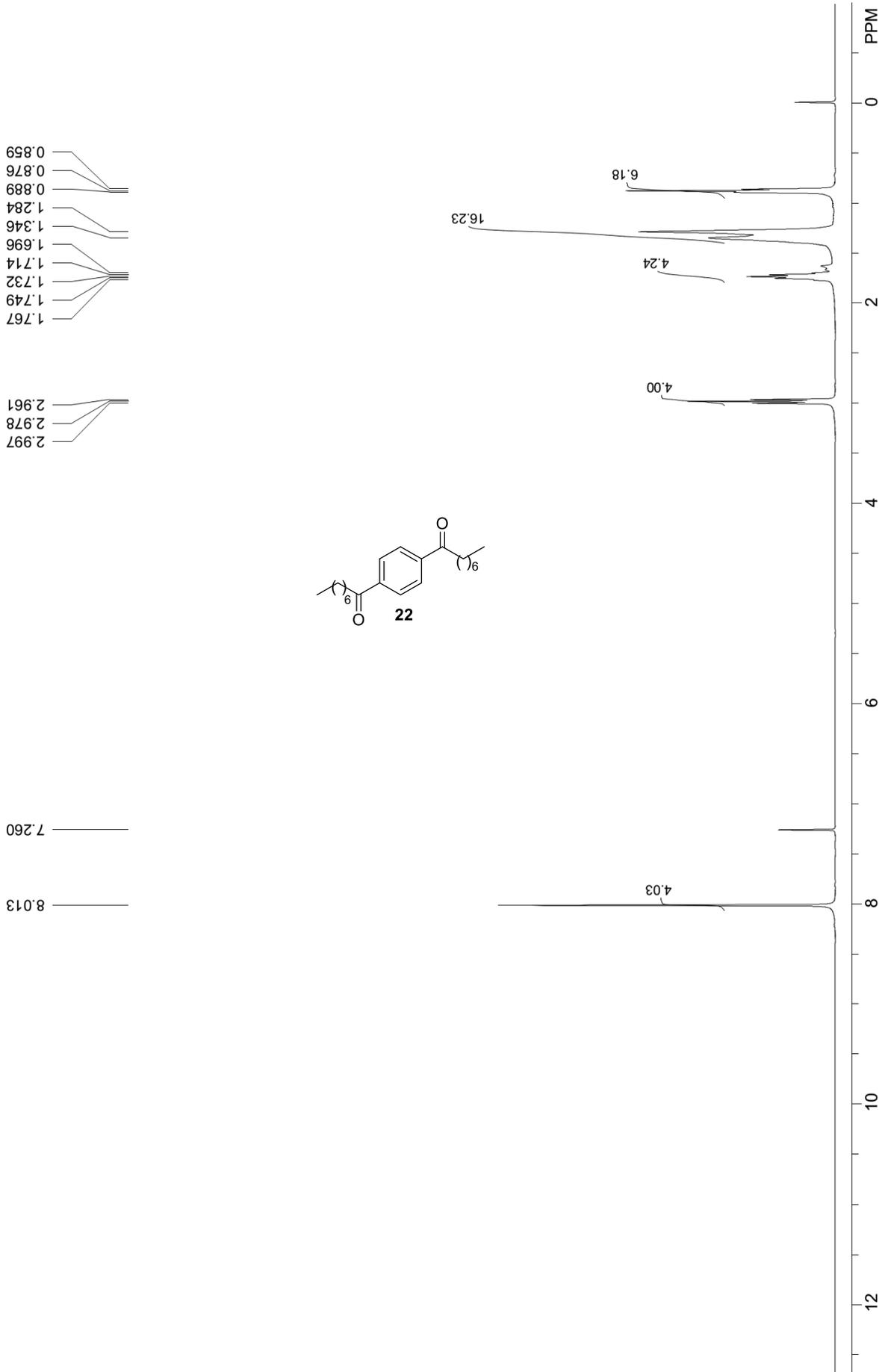
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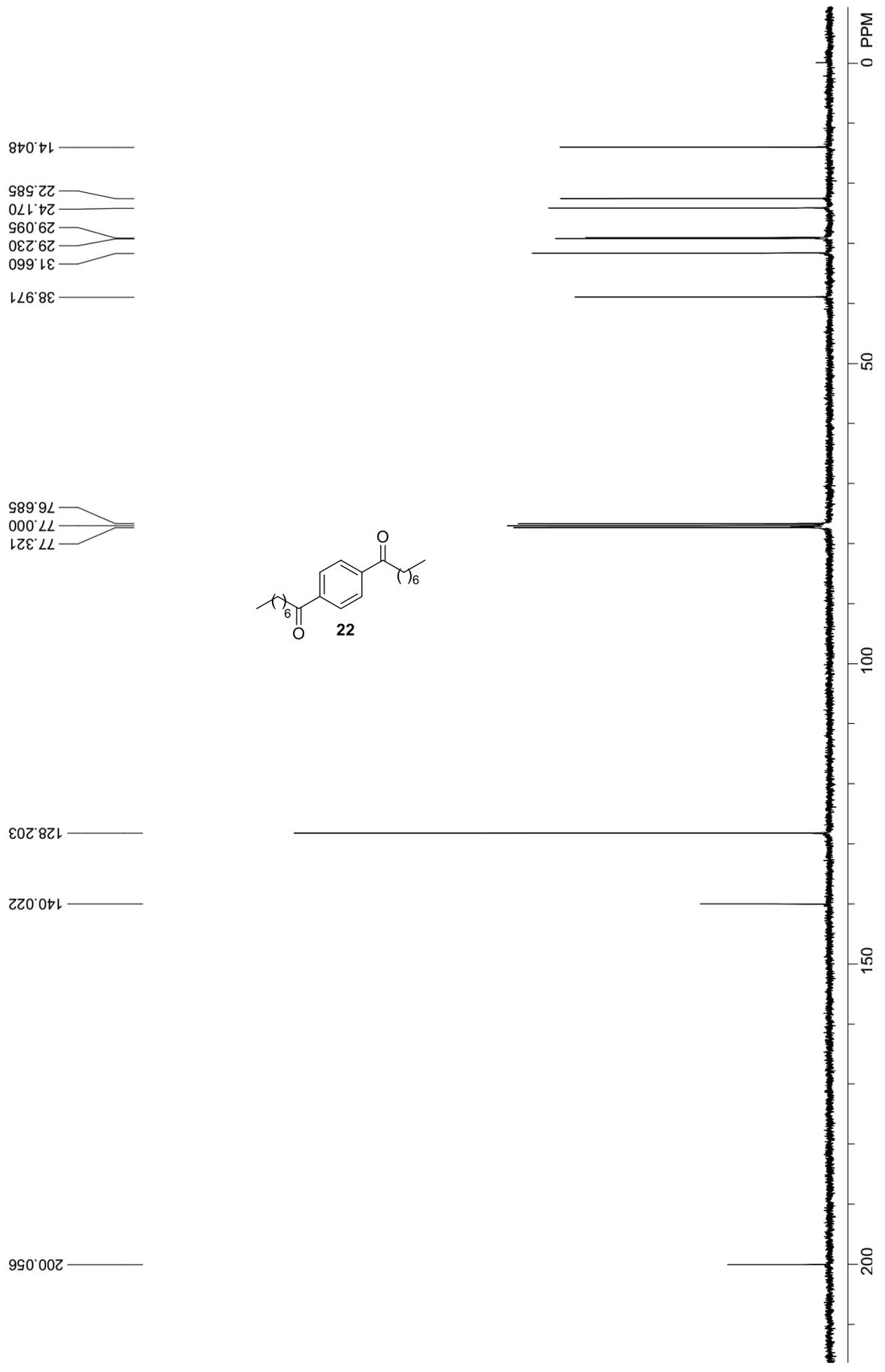


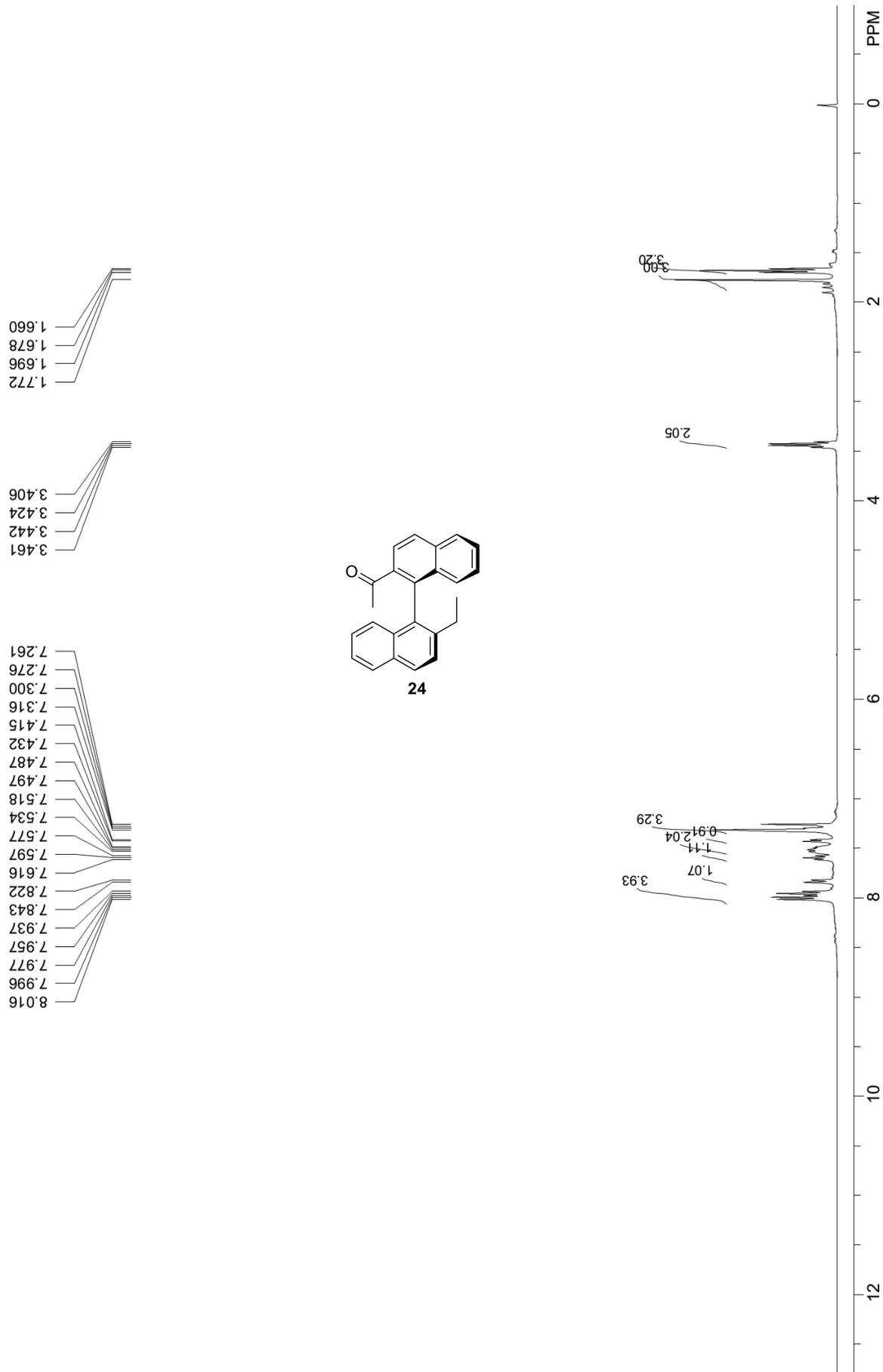


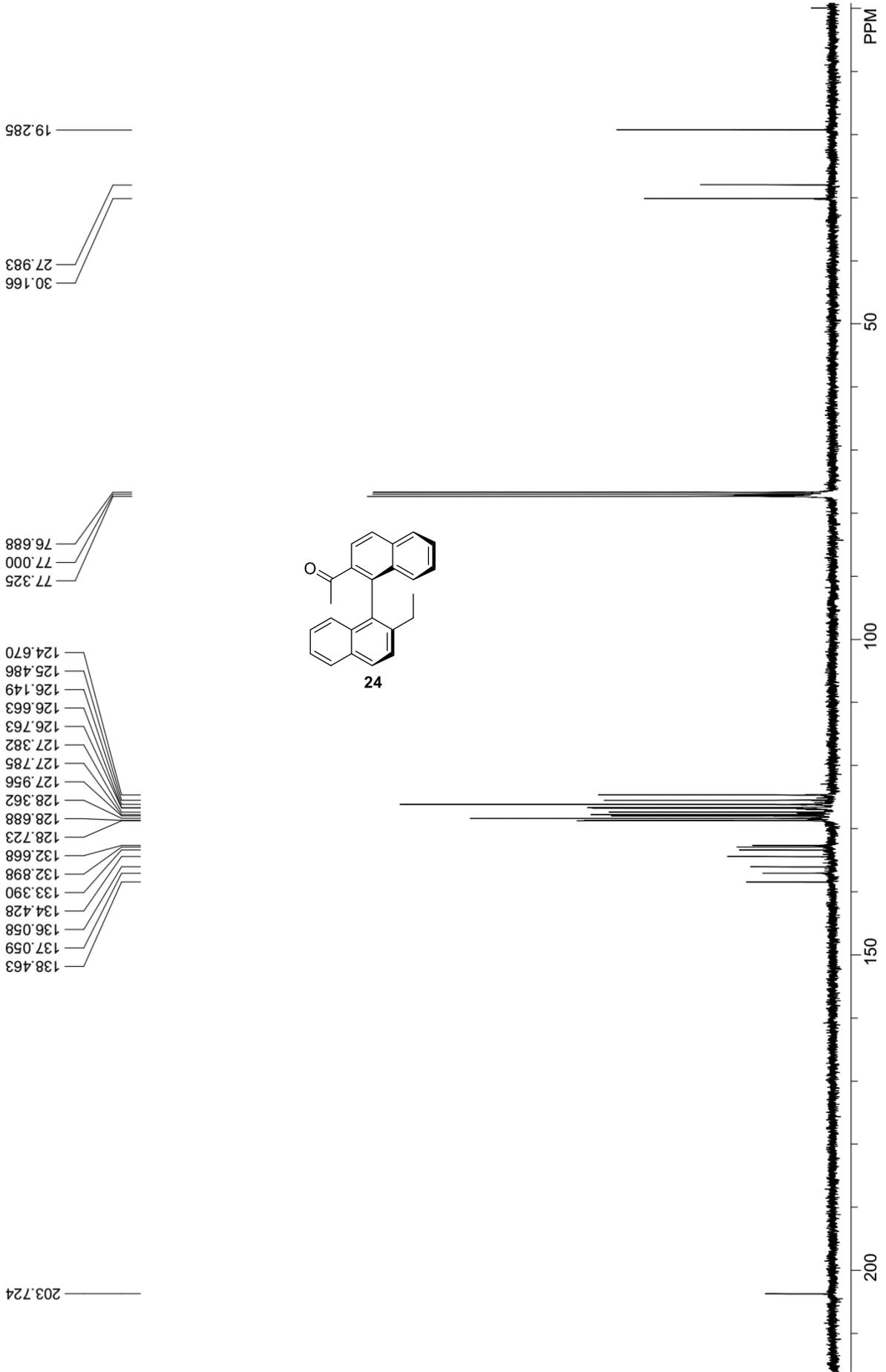


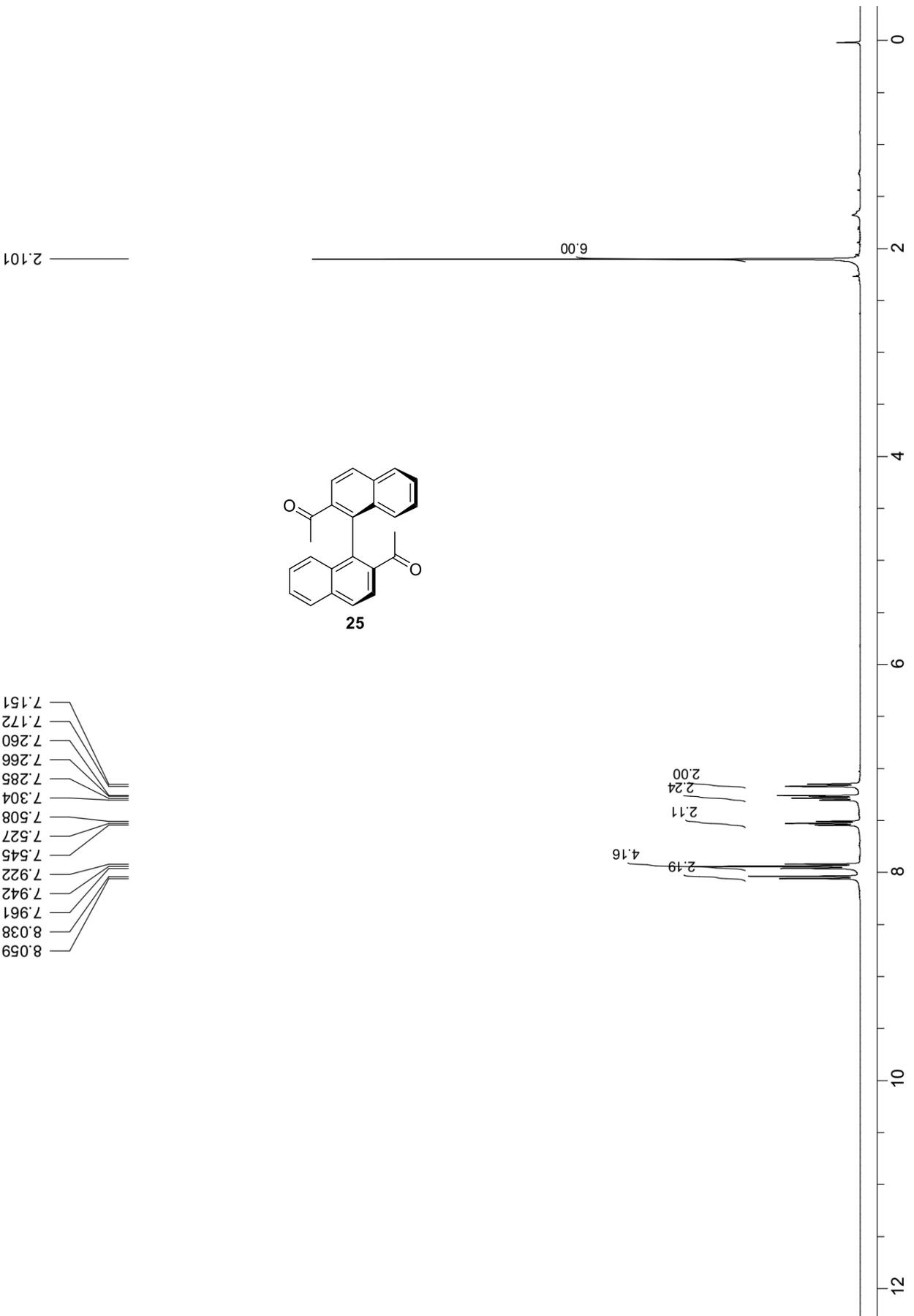


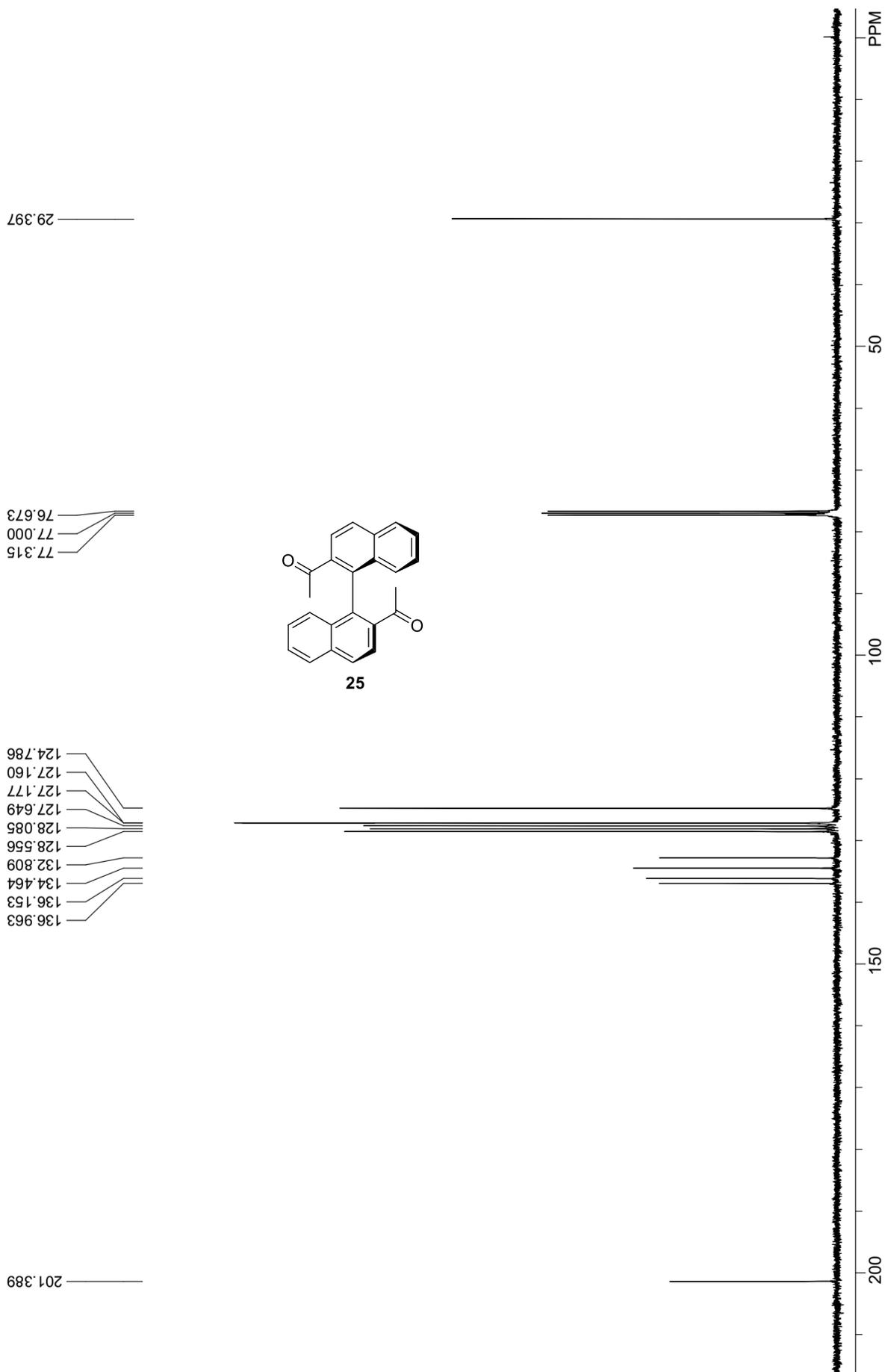


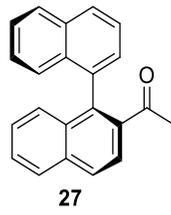
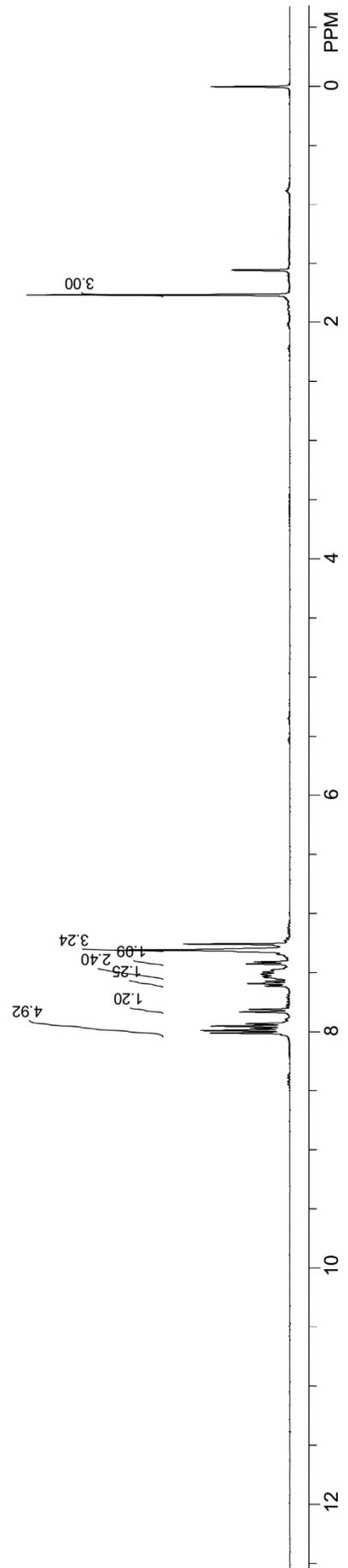






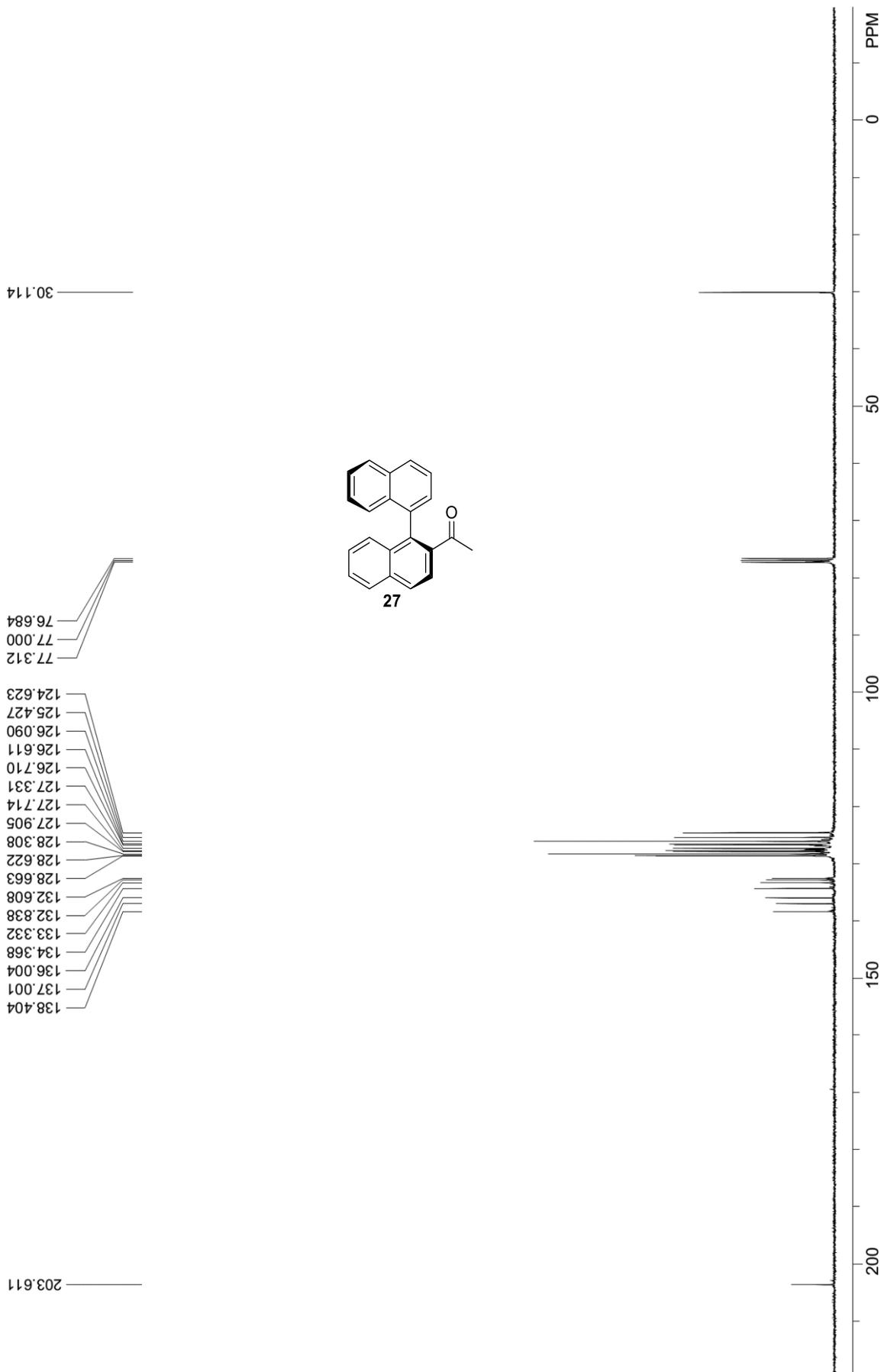


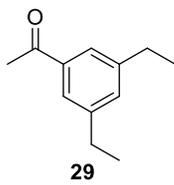
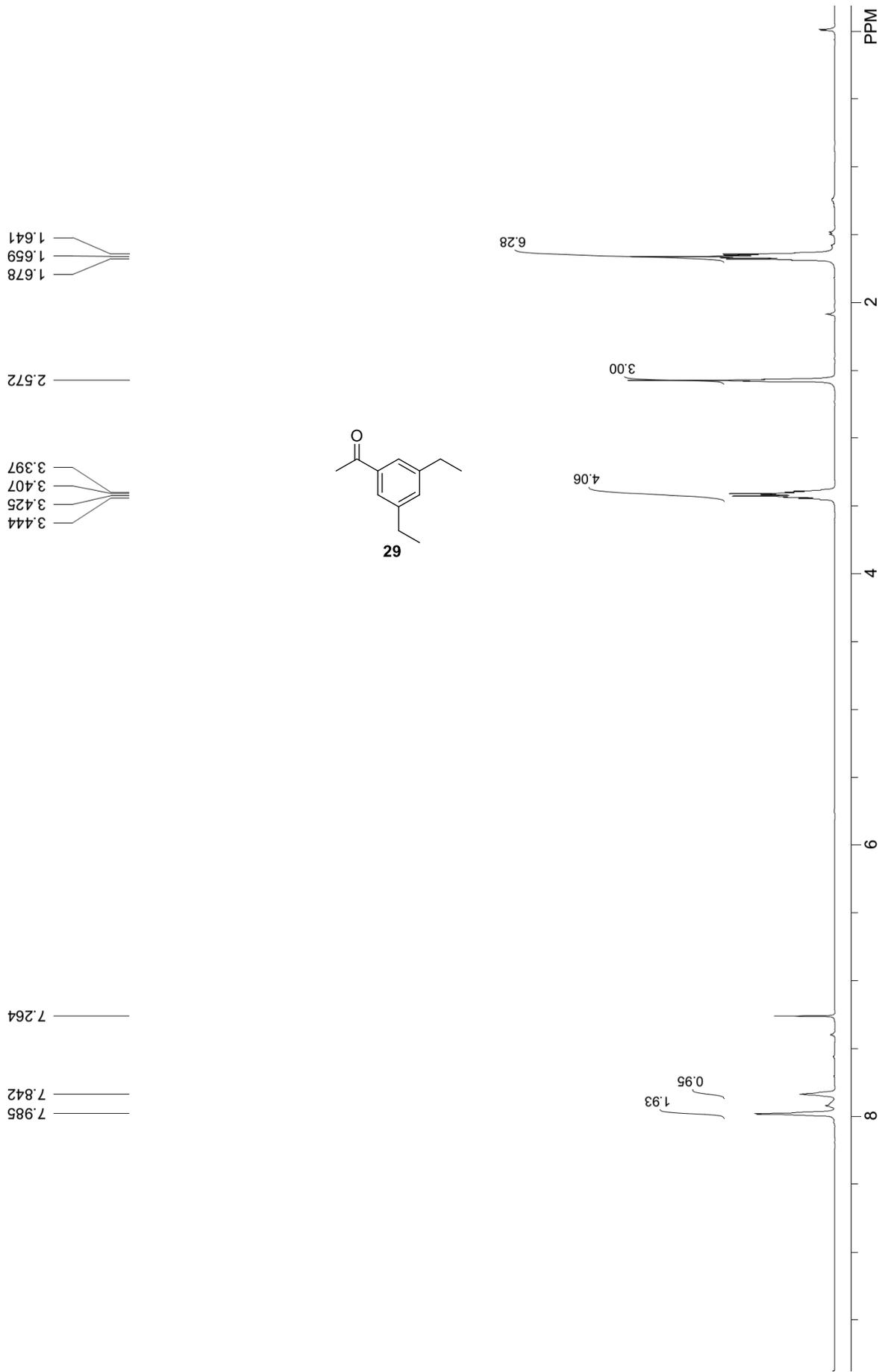




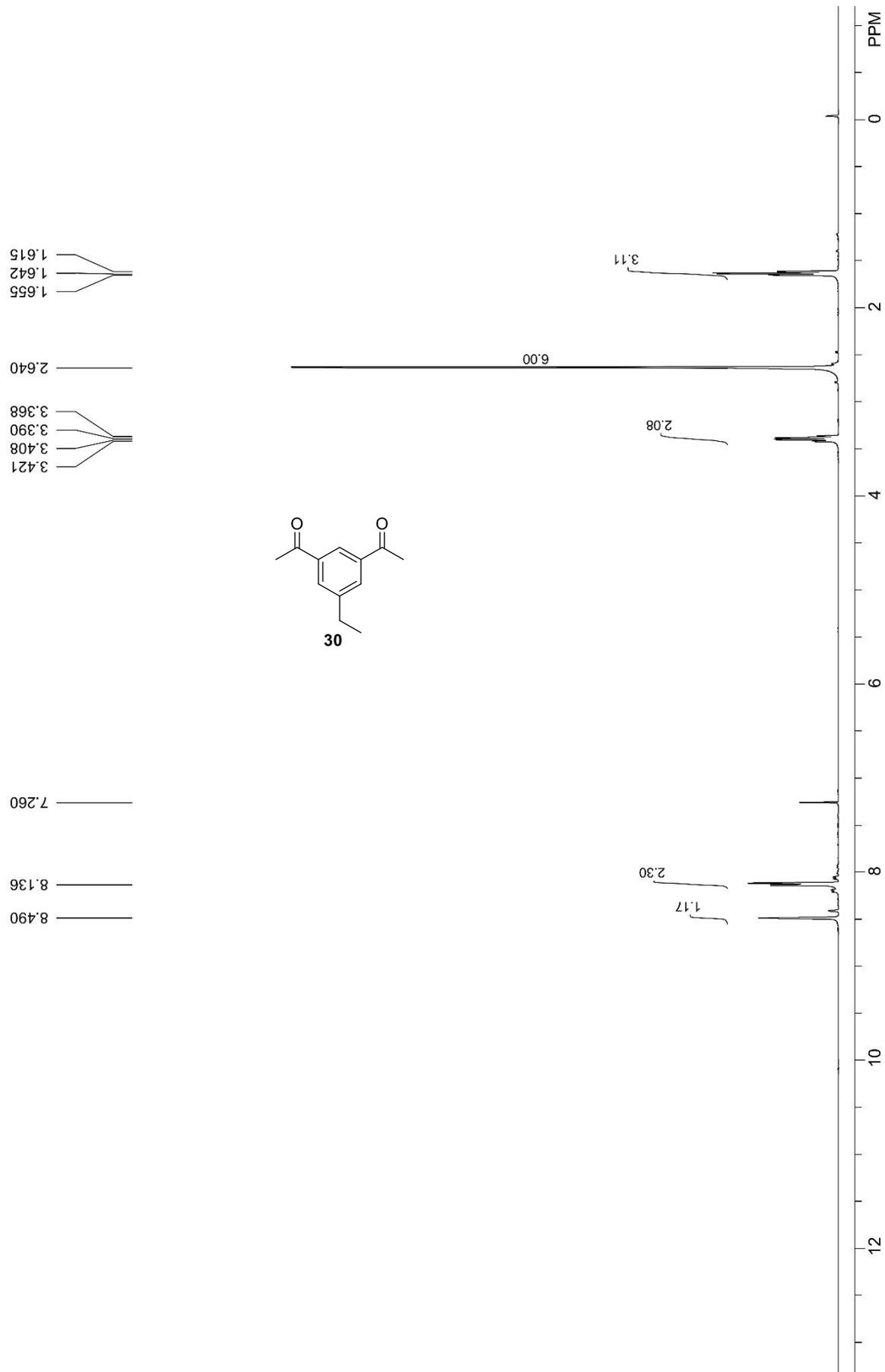
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7.261







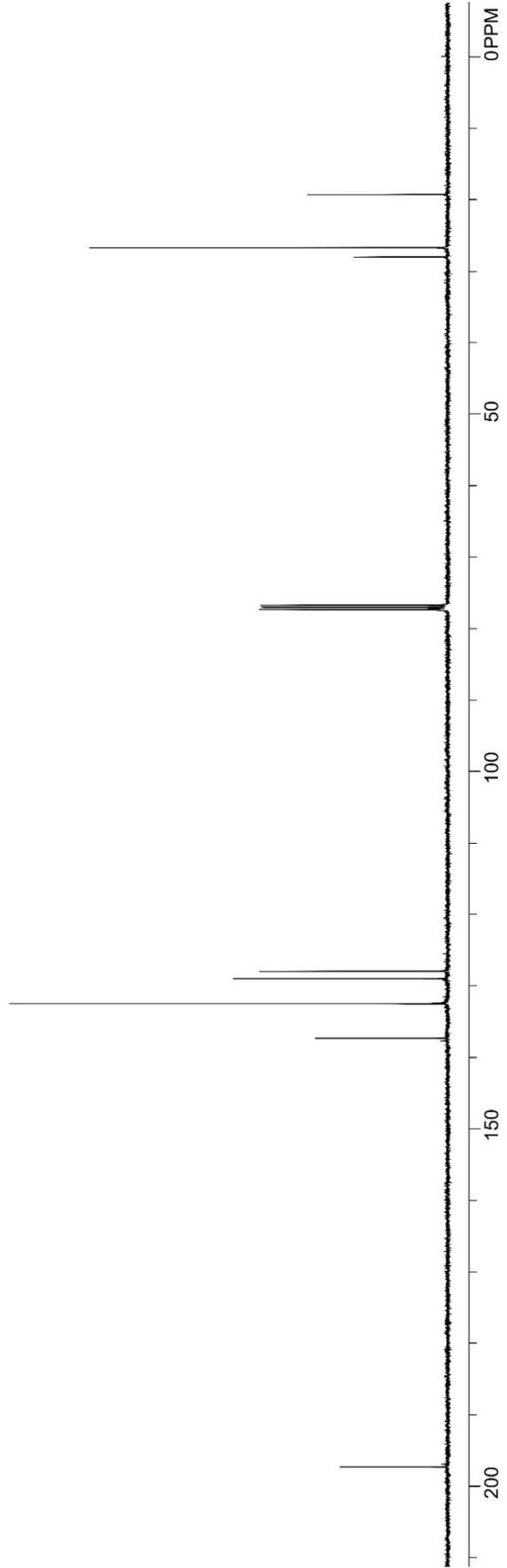
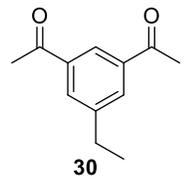


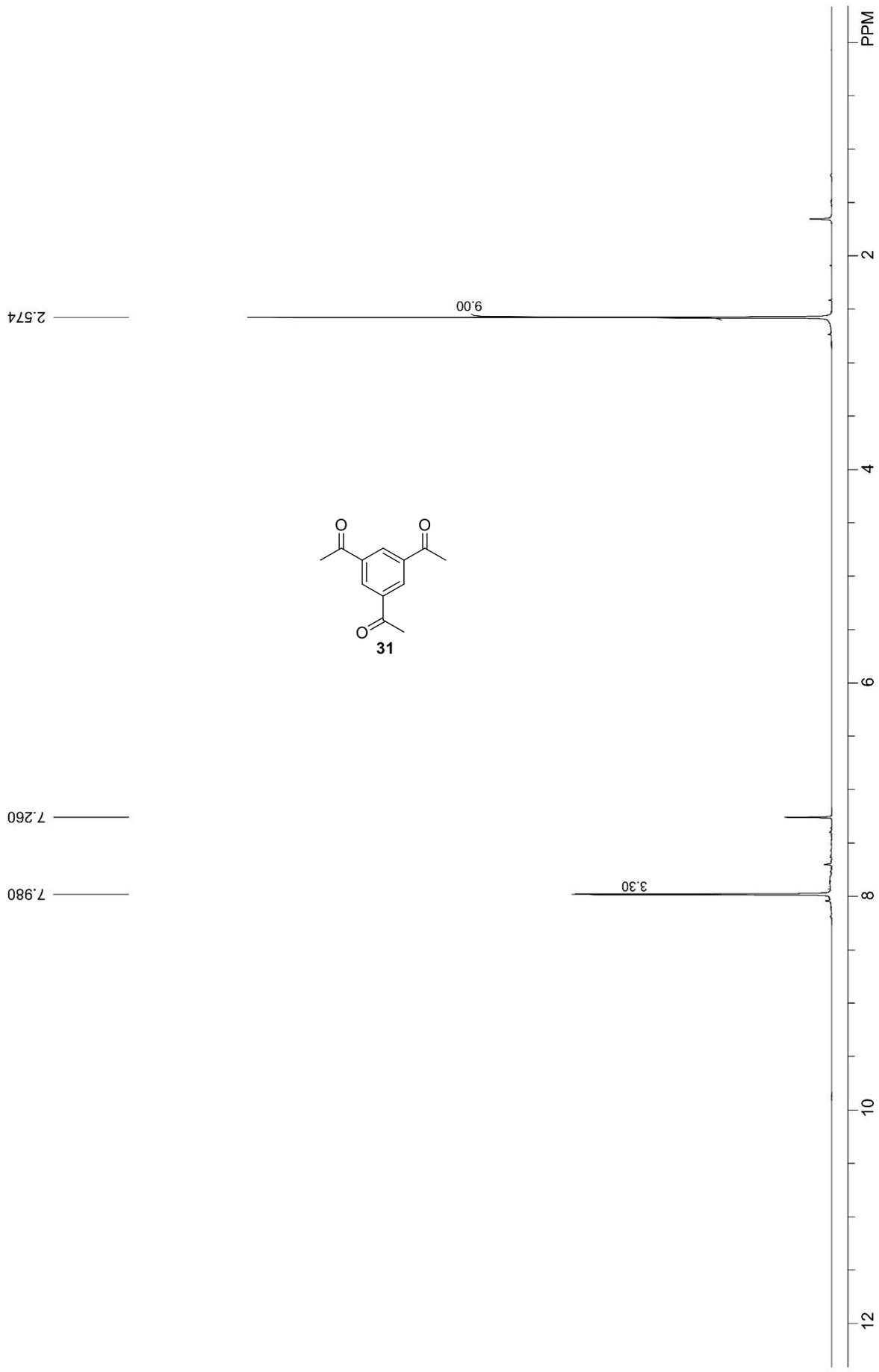
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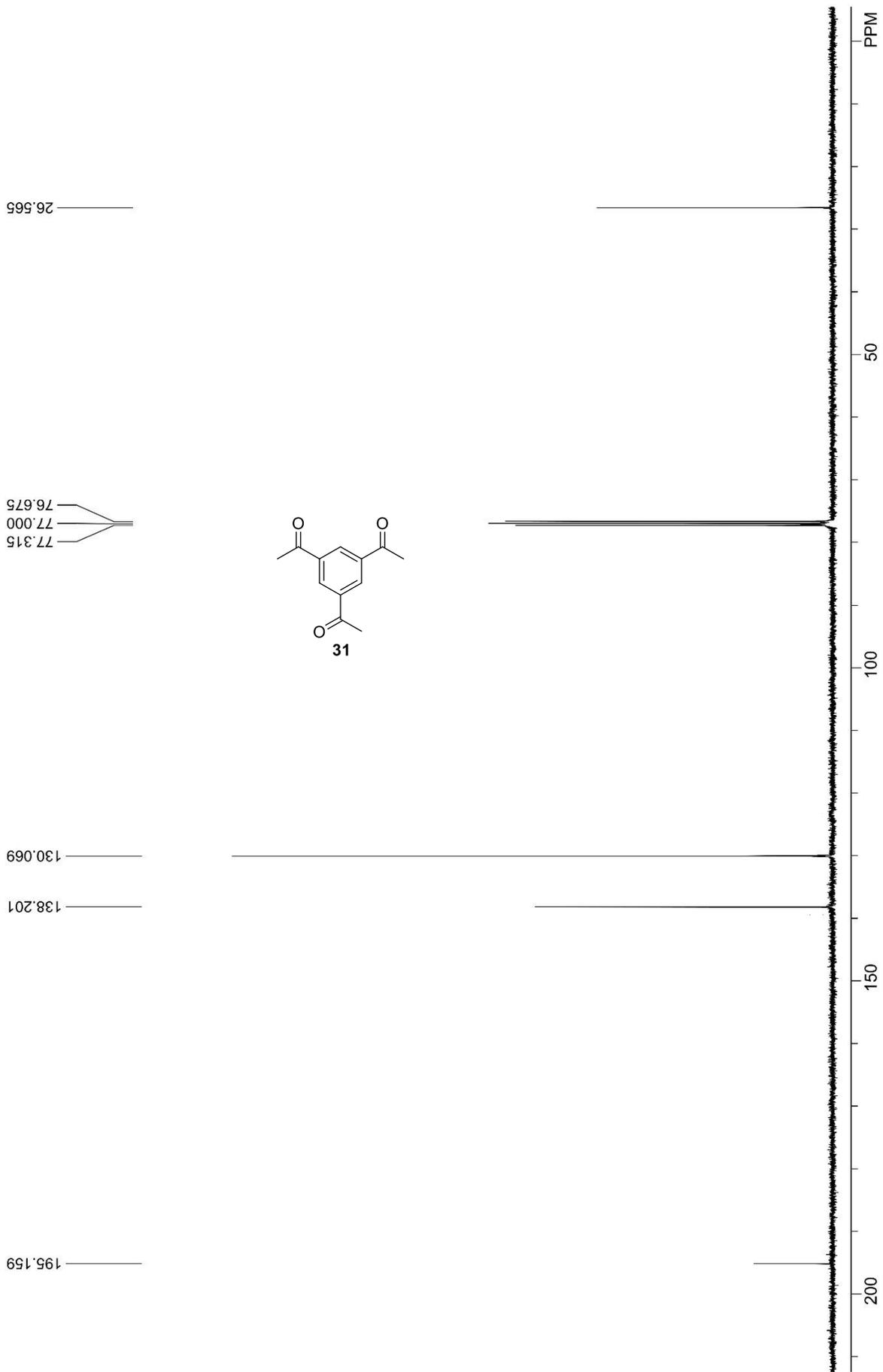
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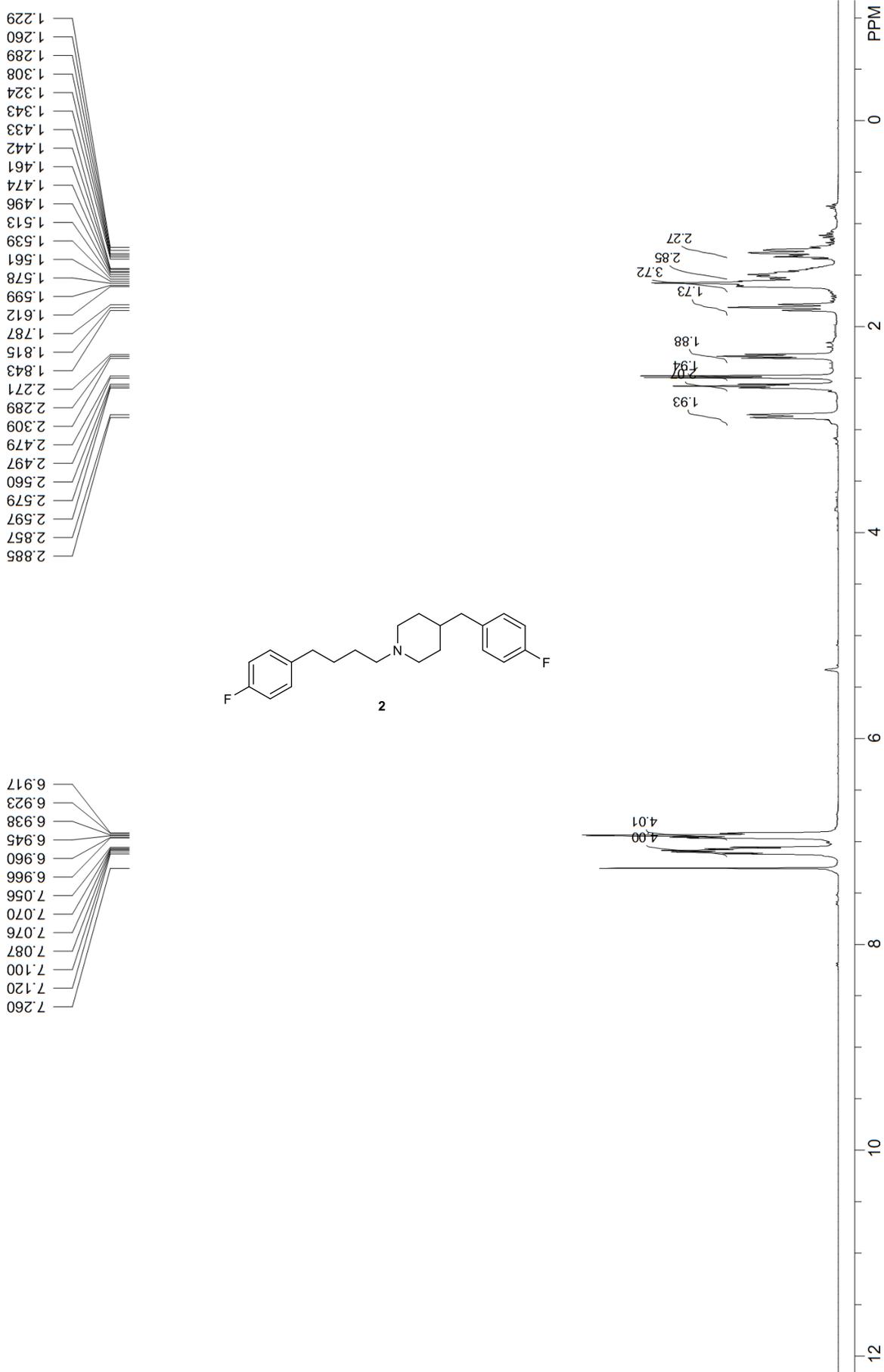
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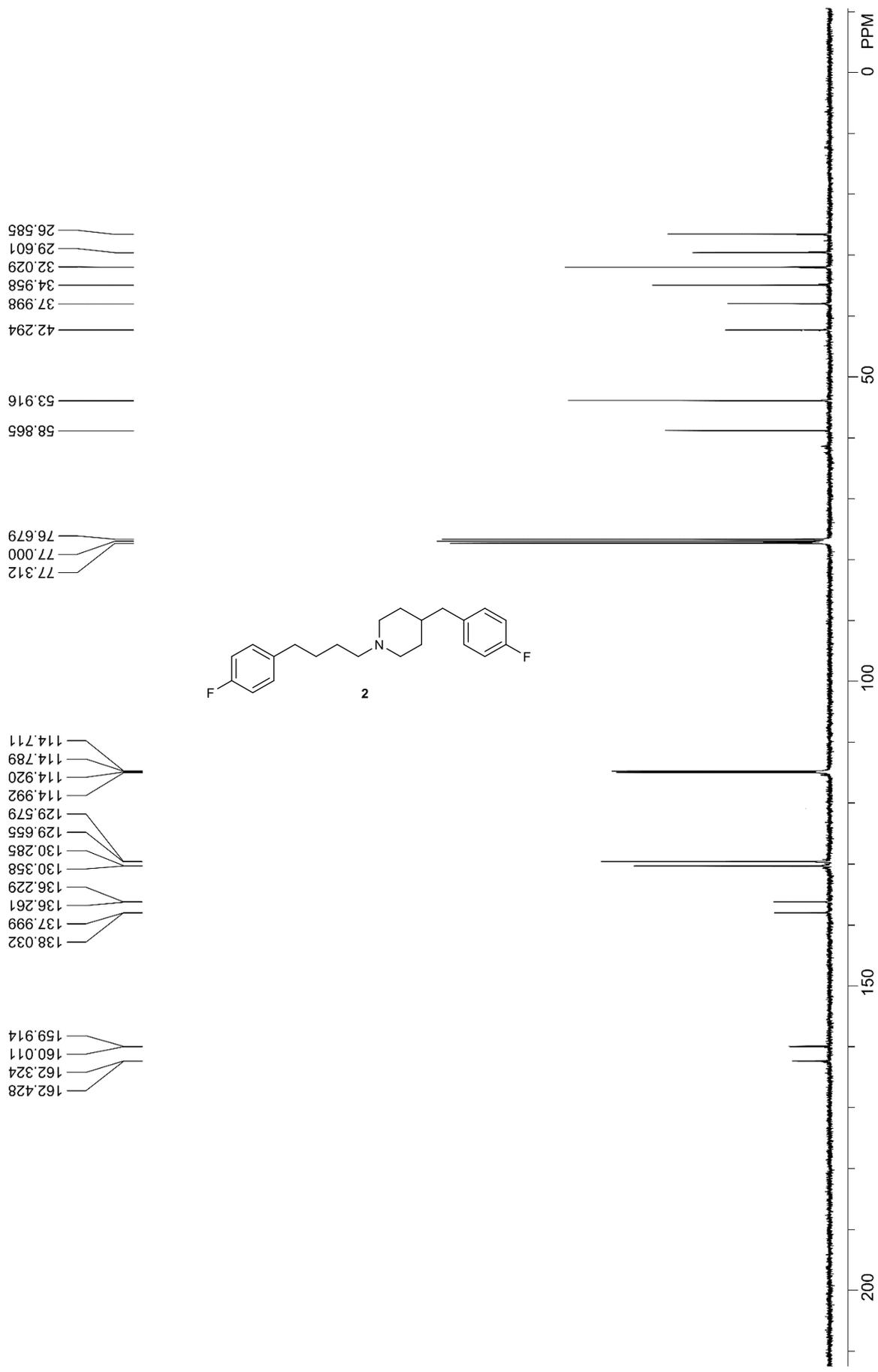
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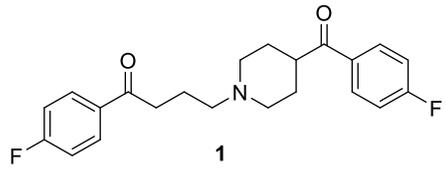




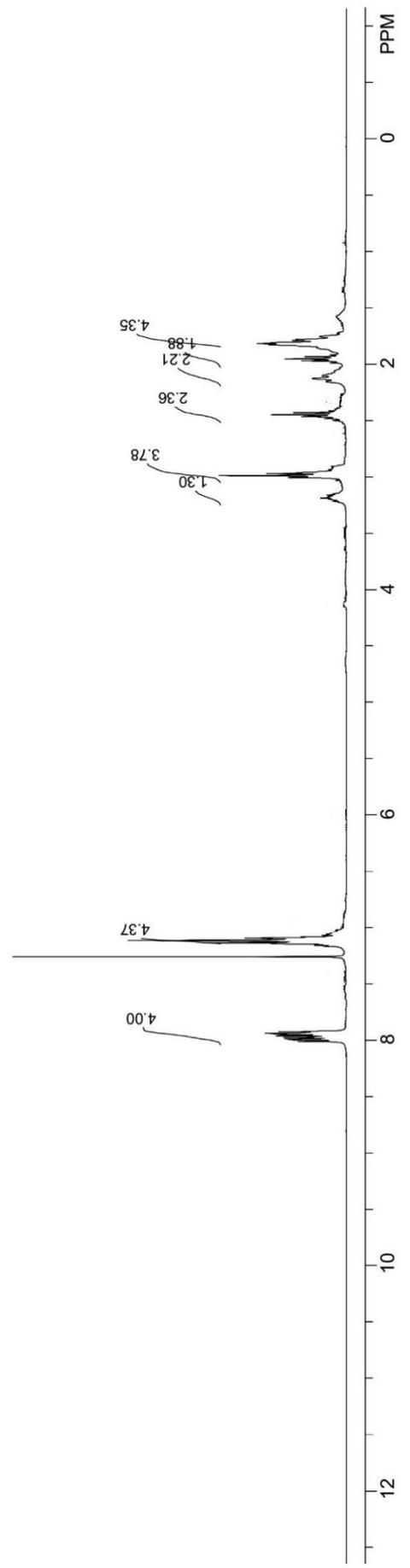


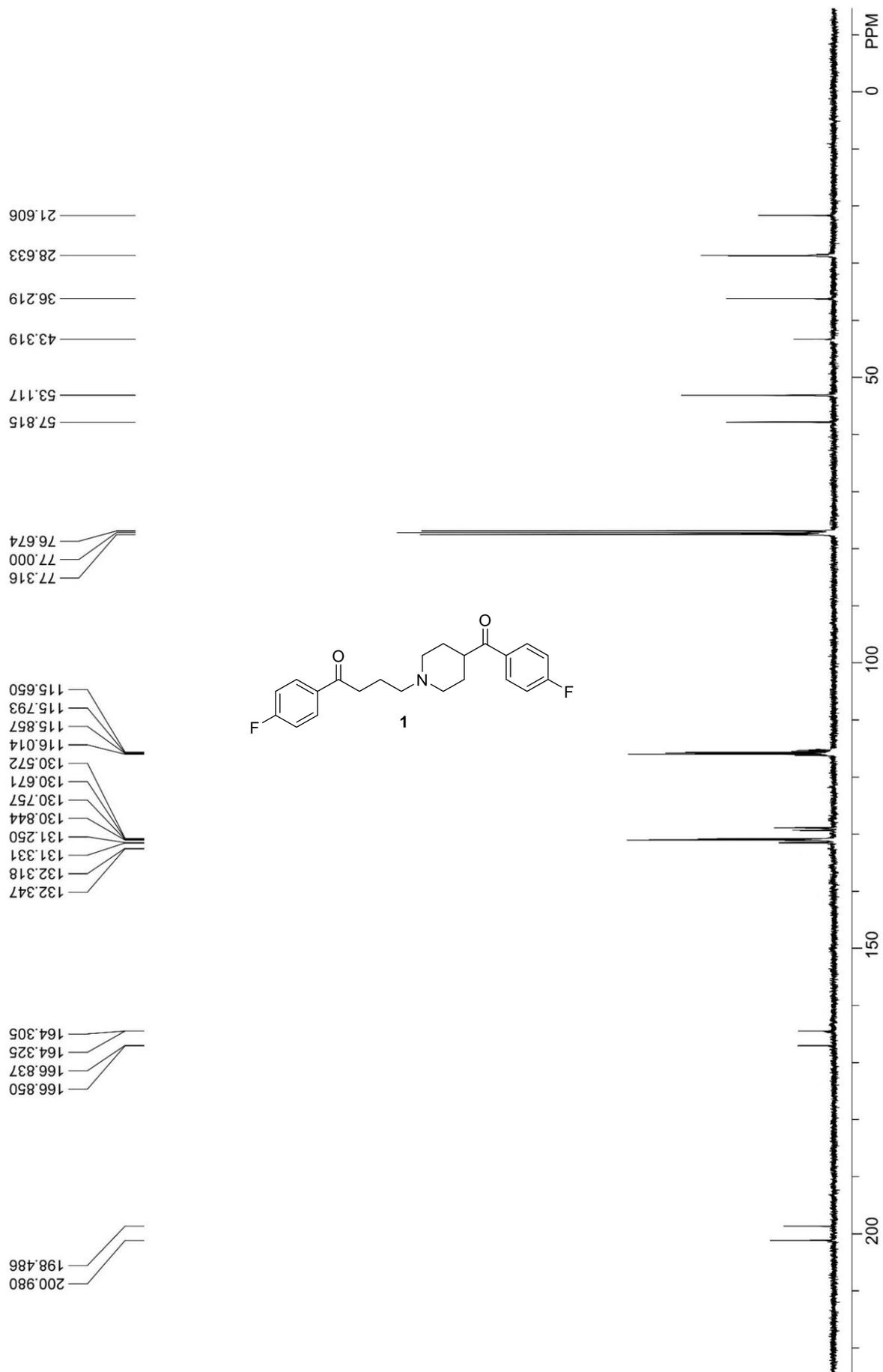


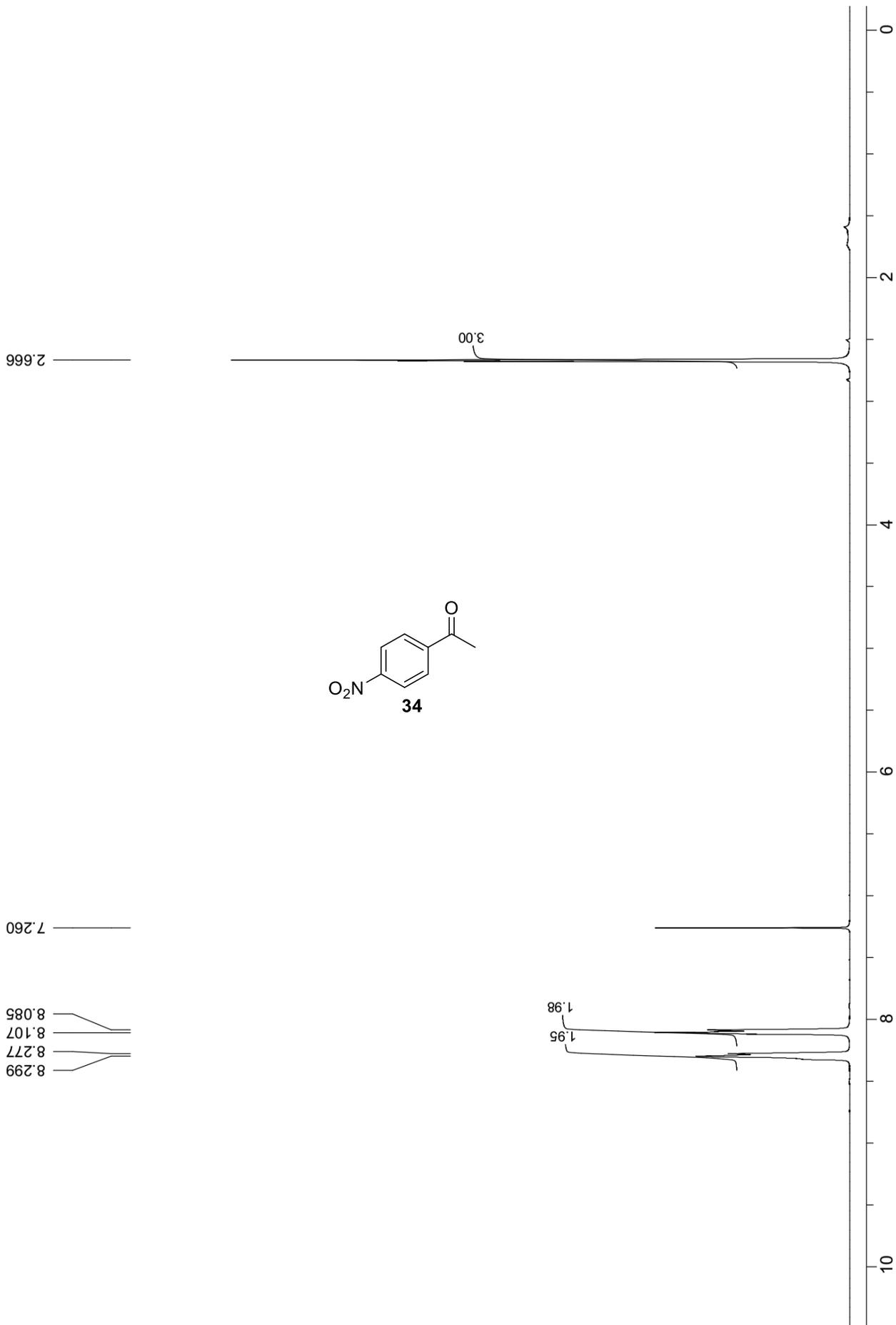
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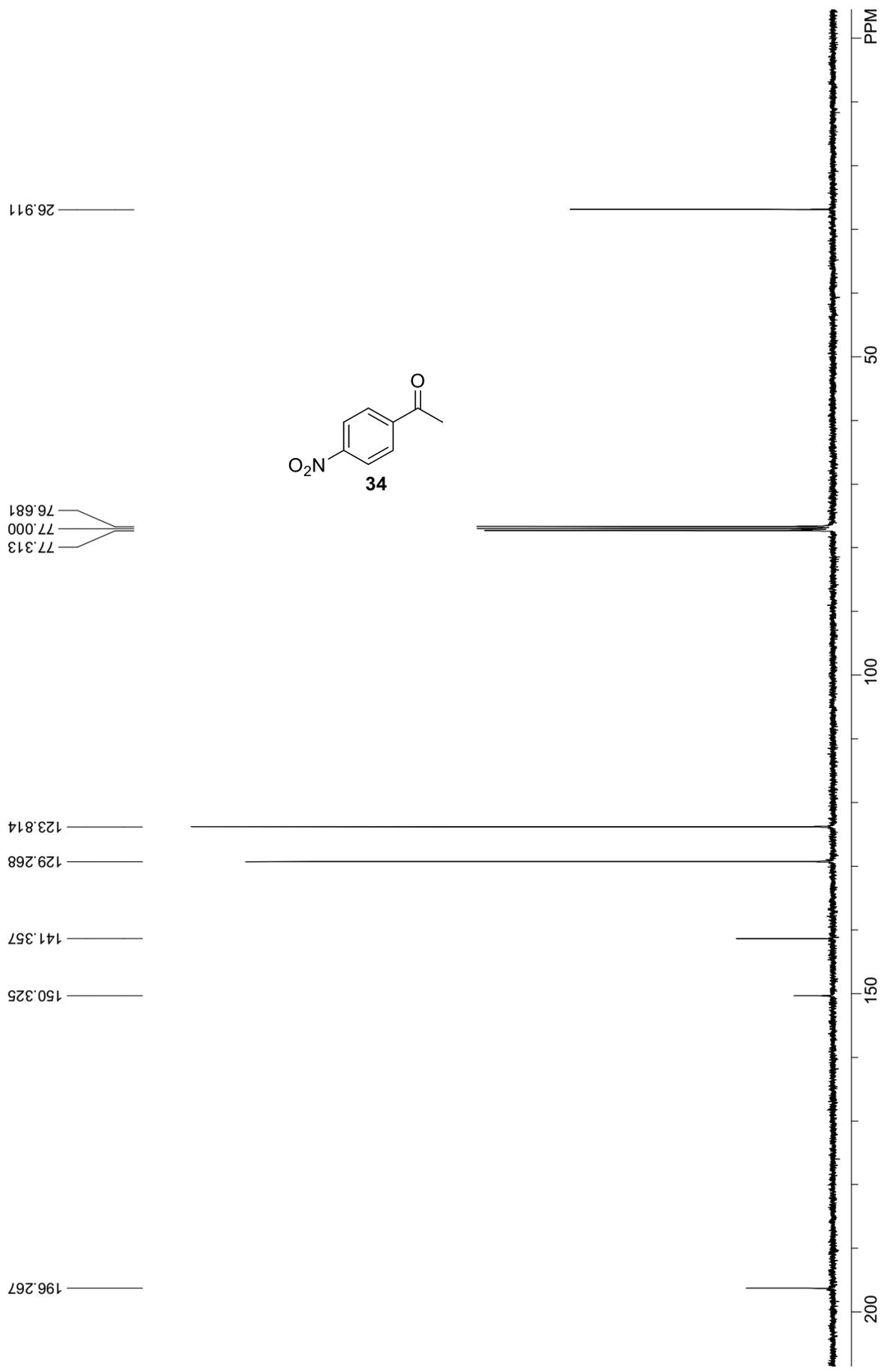


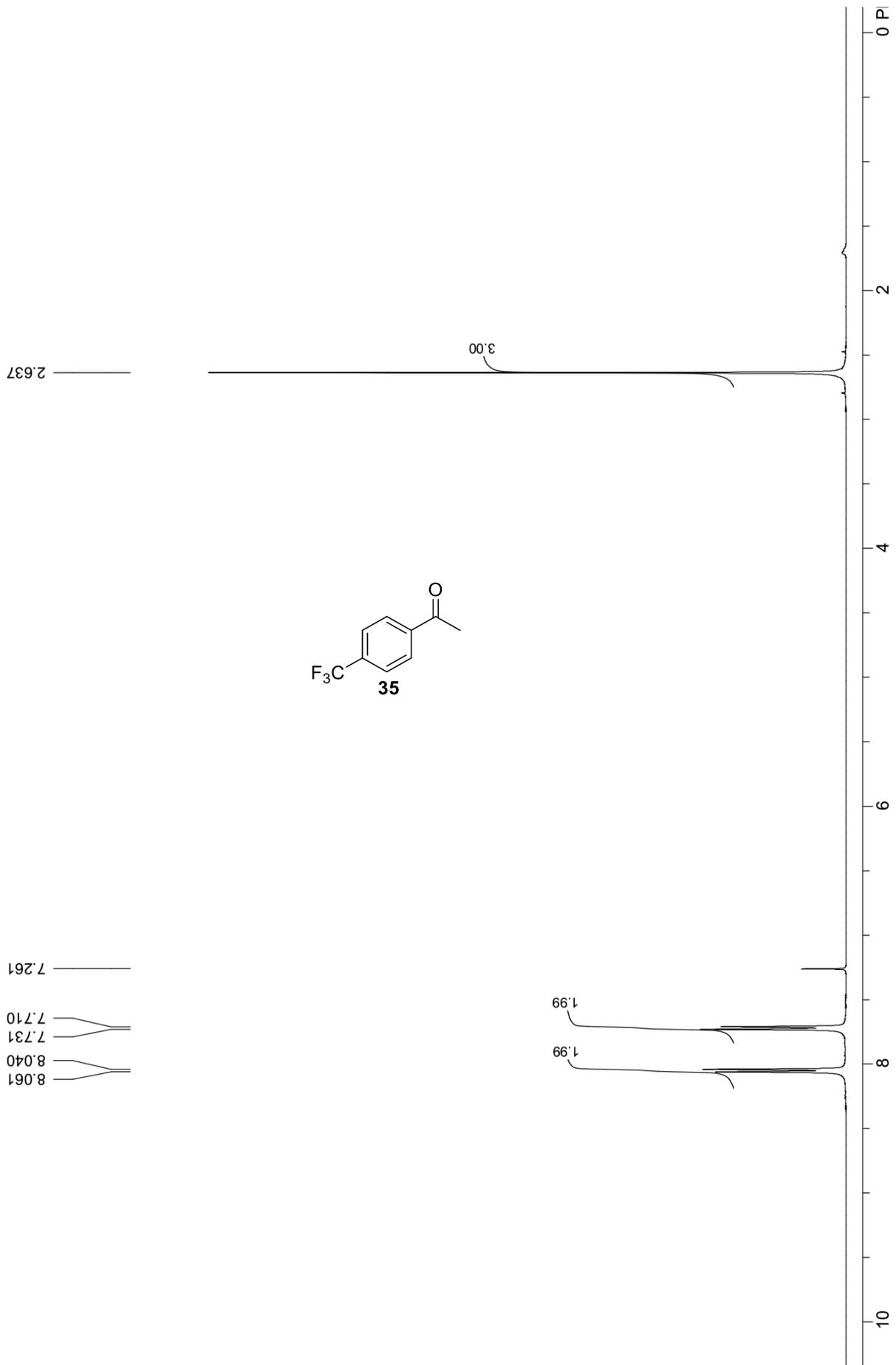
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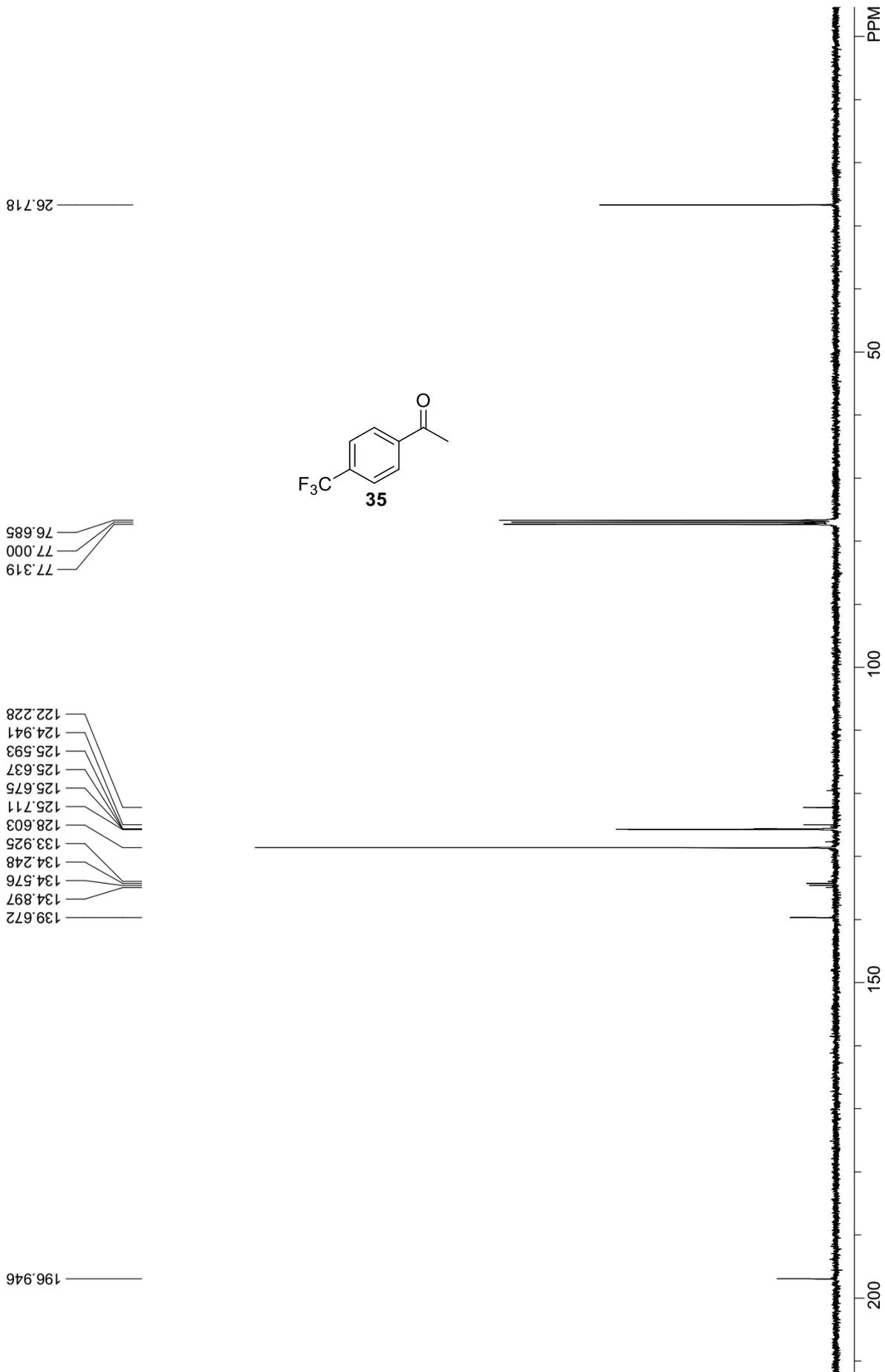




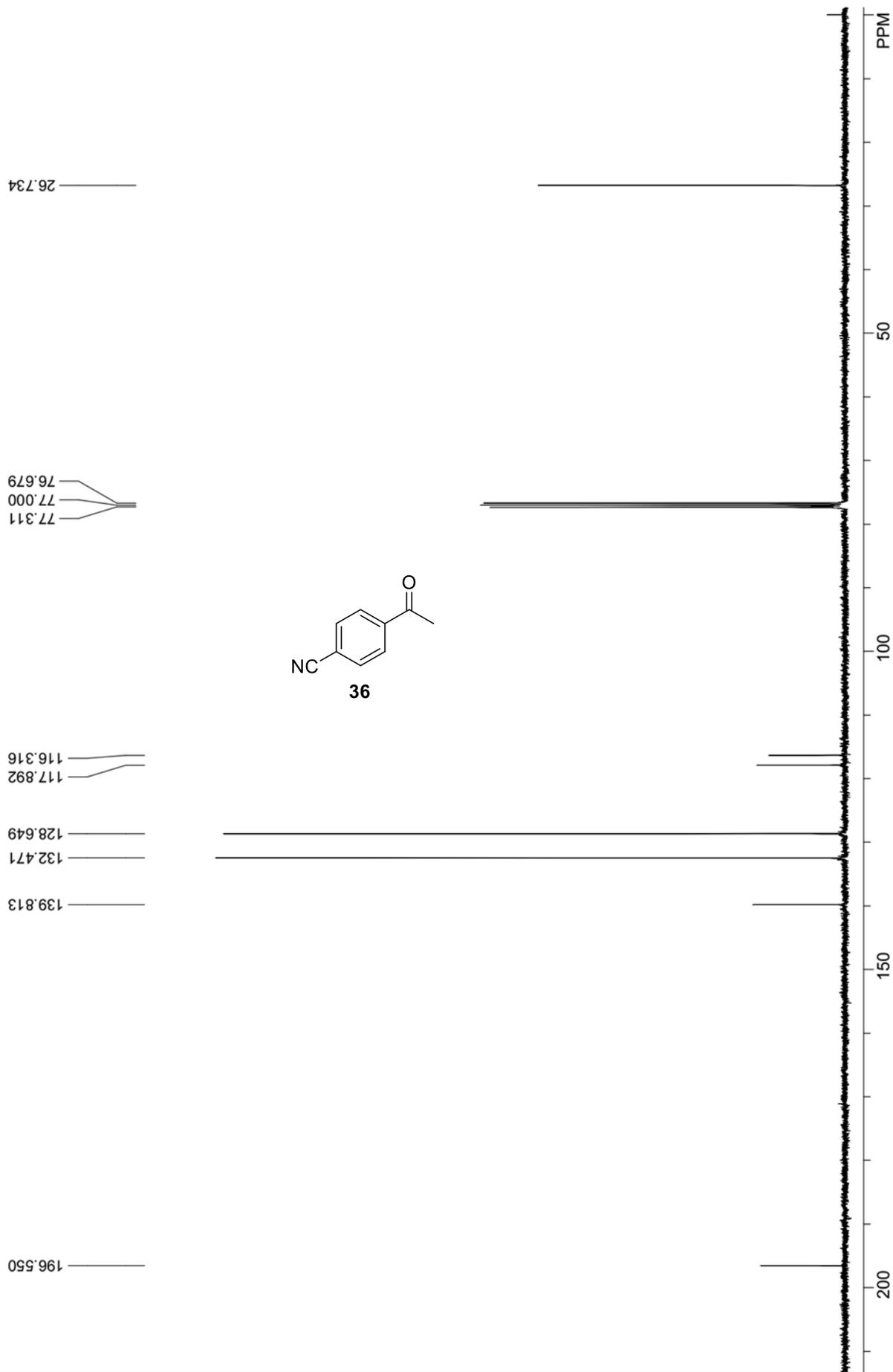


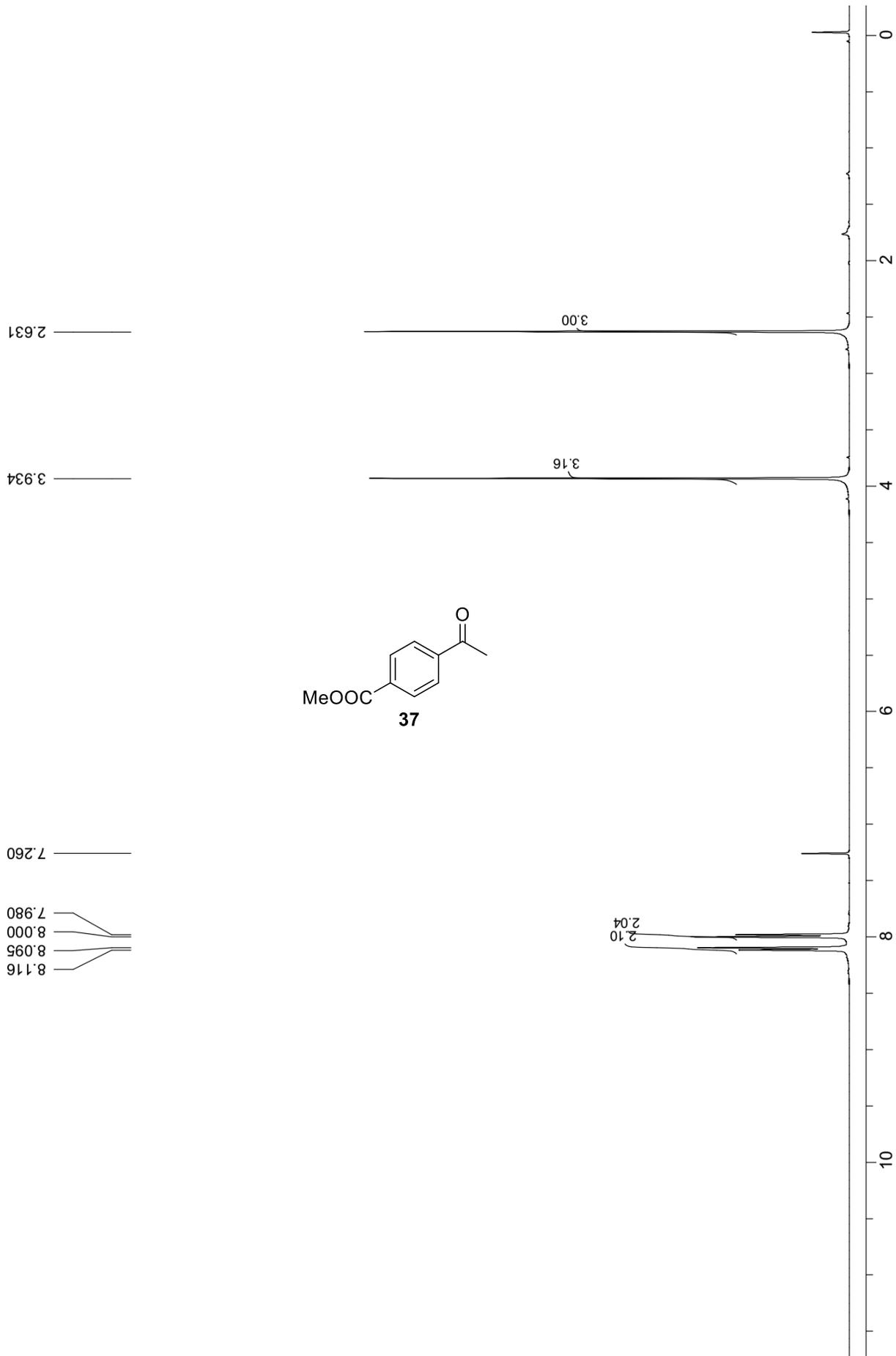


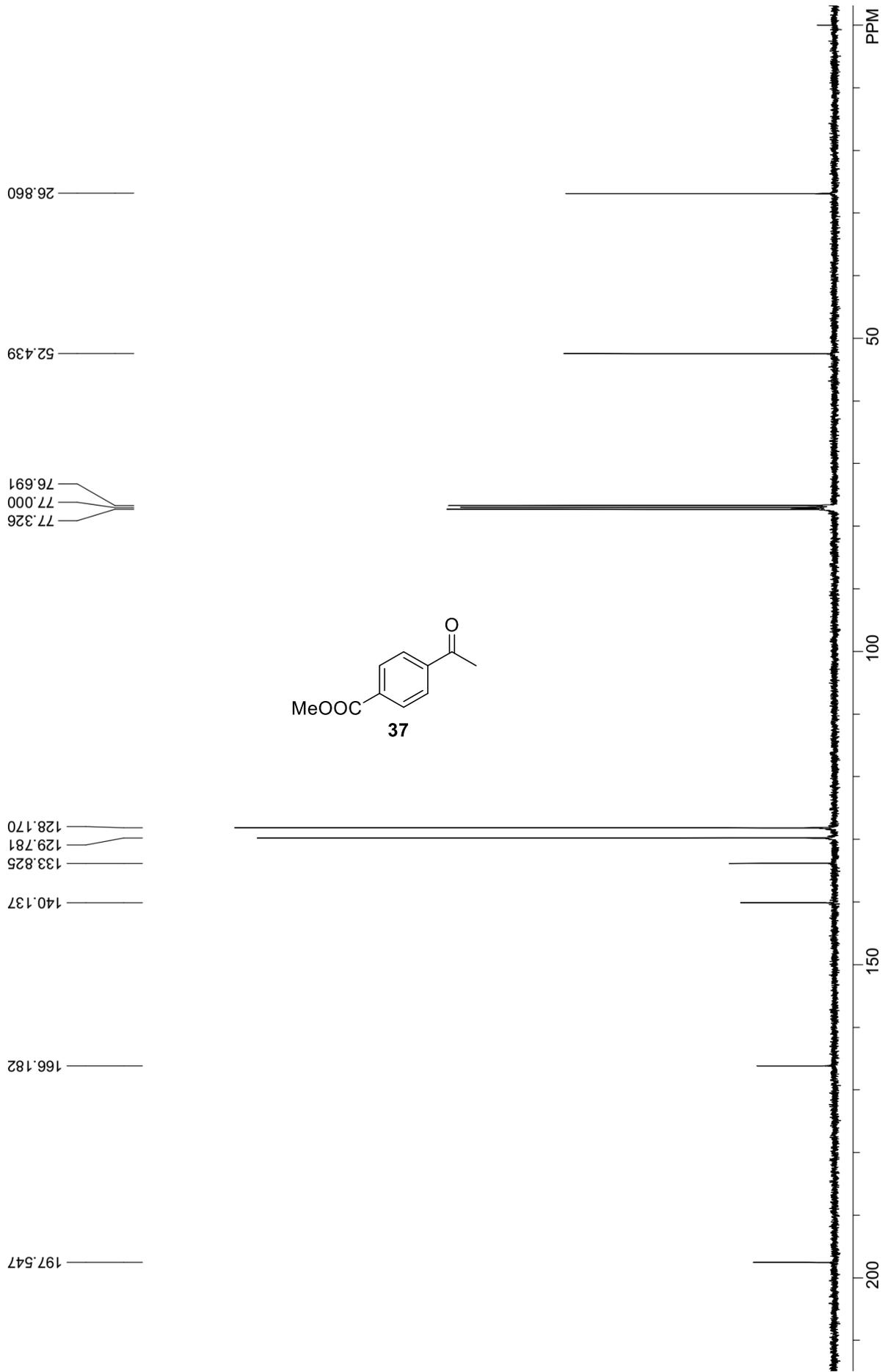




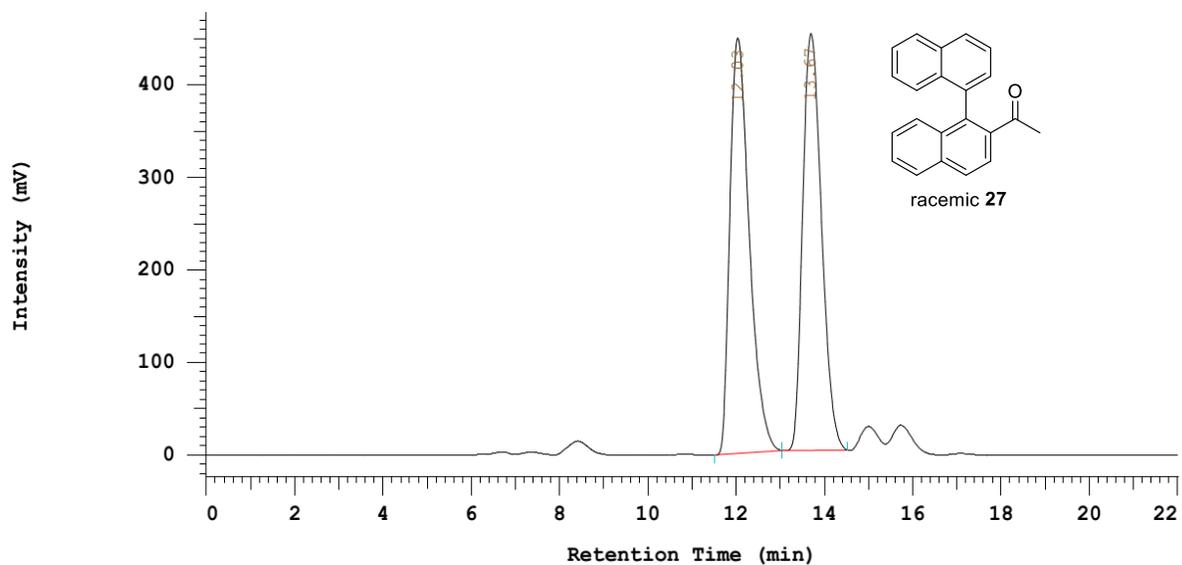






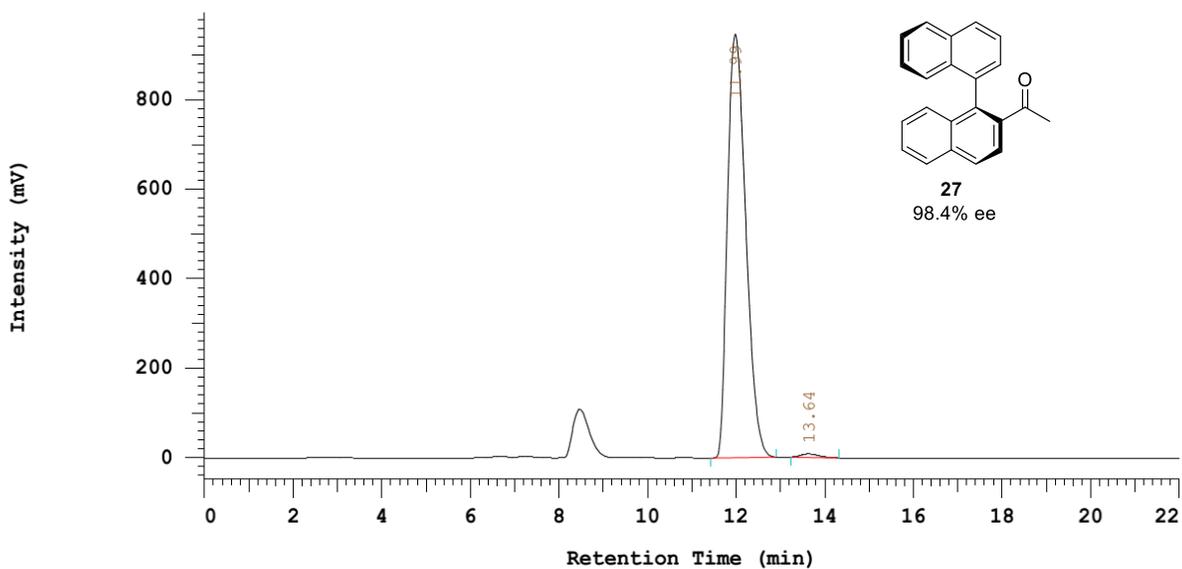


Chrom Type: HPLC Channel : 1



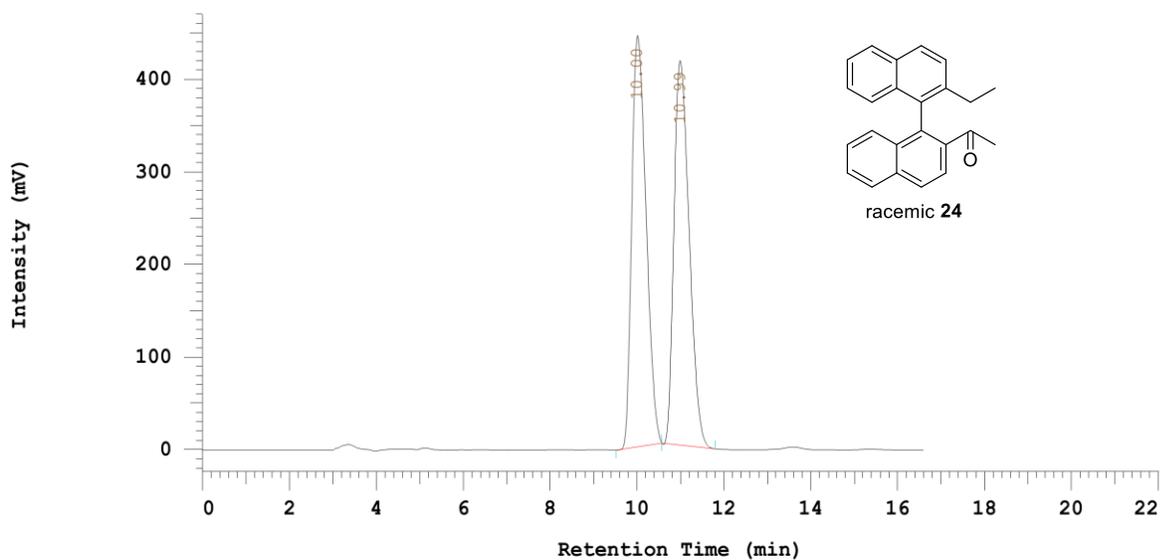
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2	13.67	13395036	49.527	MC
			100.000	

Chrom Type: HPLC Channel : 1



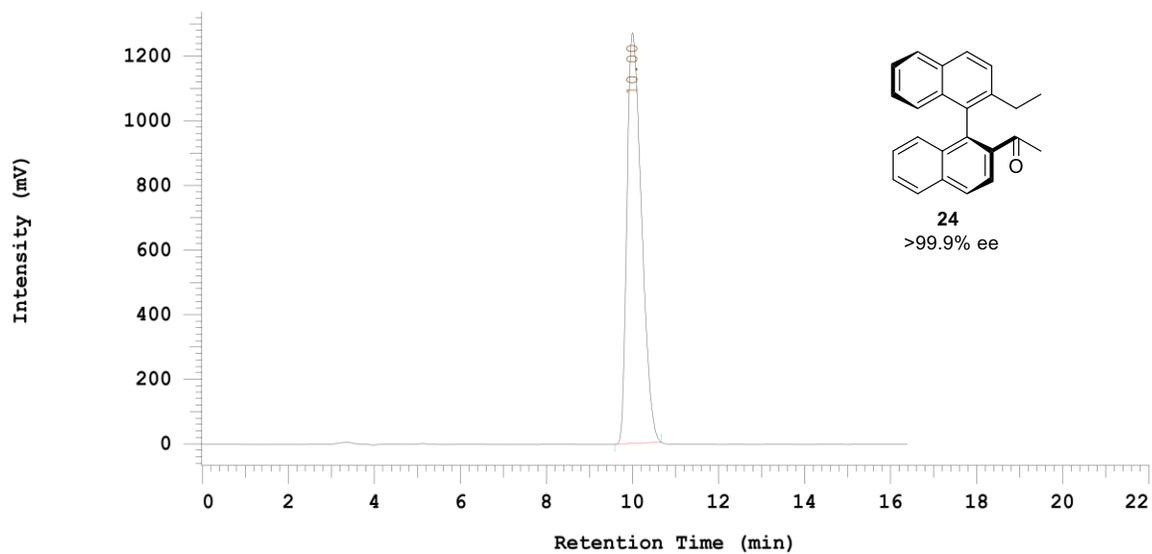
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2	13.64	219647	0.805	MC
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Chrom Type: HPLC Channel : 1



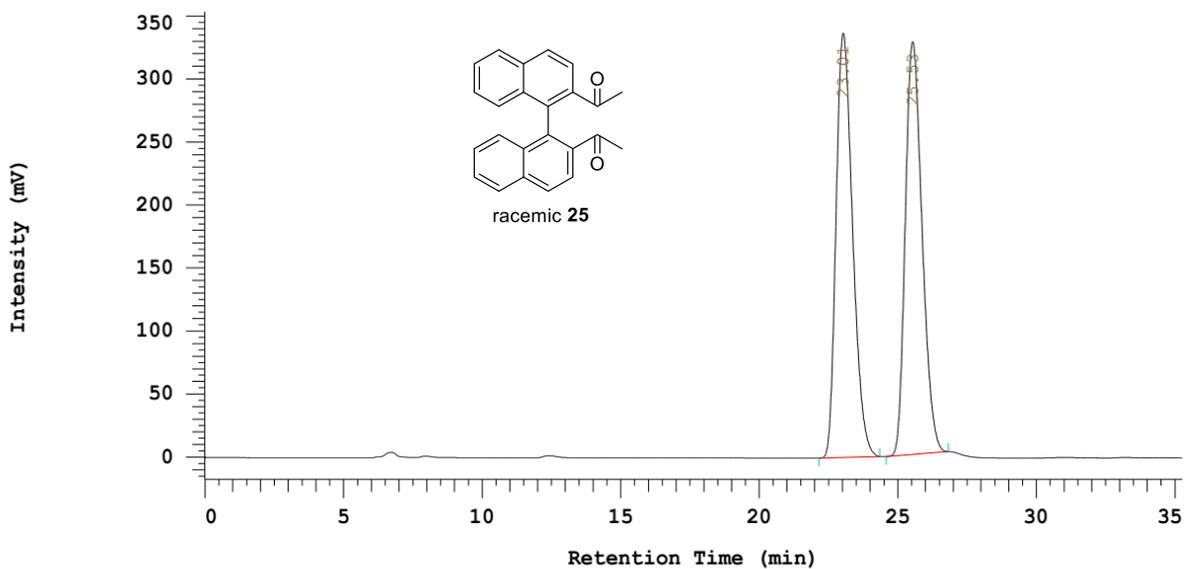
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		20379641	100.000	

Chrom Type: HPLC Channel : 1



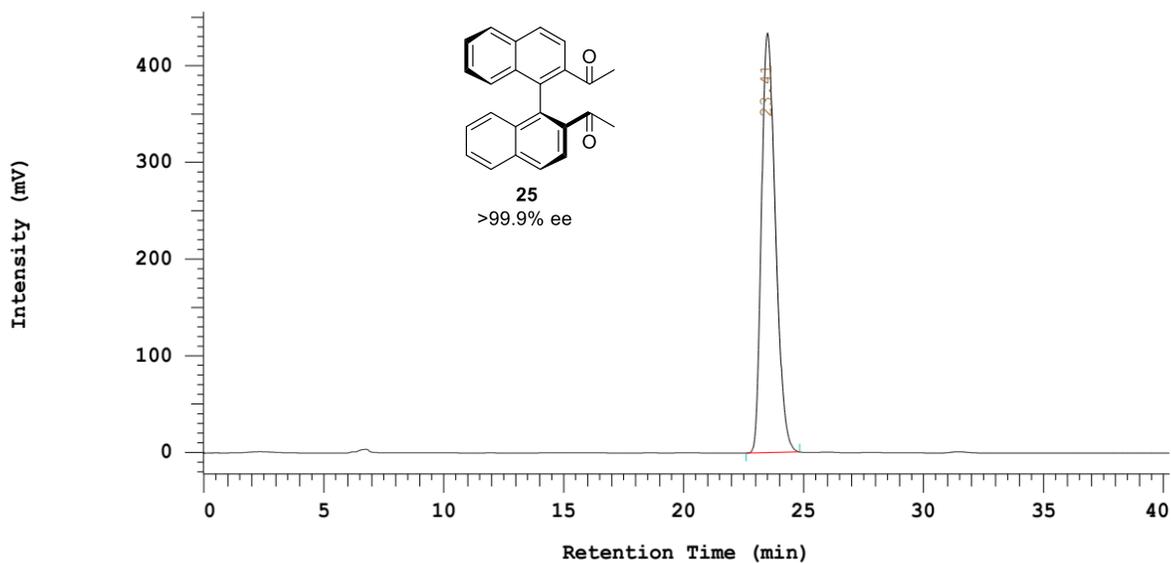
No.	RT	Area	Conc 1	BC
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		30031849	100.000	

Chrom Type: HPLC Channel : 1



No.	RT	Area	Conc 1	BC
1	23.01	13974478	50.344	MC
2	25.53	13783612	49.656	MC
			100.000	

Chrom Type: HPLC Channel : 1



No.	RT	Area	Conc 1	BC
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			100.000	