Chiral Organic Contact Ion Pairs in Metal-Free Catalytic Asymmetric Oxidative Coupling of Tertiary Amines

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Supporting information

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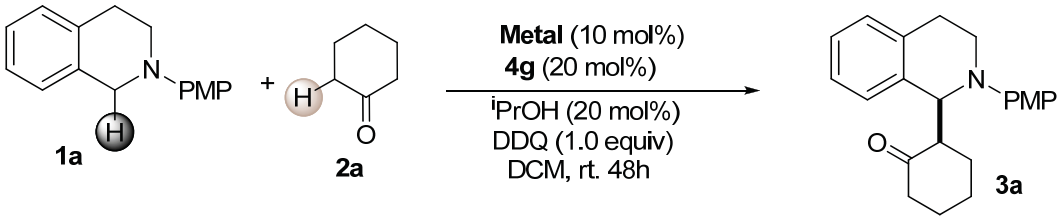
1.0 General Methods

All reactions were carried out under an argon atmosphere condition unless otherwise noted and solvents were dried according to established procedures. Reactions were monitored by thin layer chromatography (TLC), column chromatography purifications were carried out using silica gel GF254. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Brucker 300 MHz spectrometer in $CDCl_3$ unless otherwise noted and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Brucker 300 MHz spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as internal standard unless otherwise noted. Data are presented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, cm = complex multiplet) and coupling constant in Hertz (Hz). Infrared (IR) spectra were recorded on a FT-IR spectrometer. Optical rotations were recorded on a Perkin-Elmer 341 polarimeter. HR-MS was measured with an APEX II 47e mass spectrometer. Melting points were measured on an XT-4 melting point apparatus and were uncorrected. The ee values determination was carried out using chiral high-performance liquid chromatography (HPLC) with Daicel Chiracel AS-H or OD-H column on Waters with a 2996 UV-detector. N-aryl tetrahydroisoquinolins **1a-m** and organocatalysts **4a-c** were prepared according to the previous reported procedures. [1], [2], [3], [4], [5]

2.0. The Metal and Solvent Optimization Results

Table S1. The metal optimization results [a]

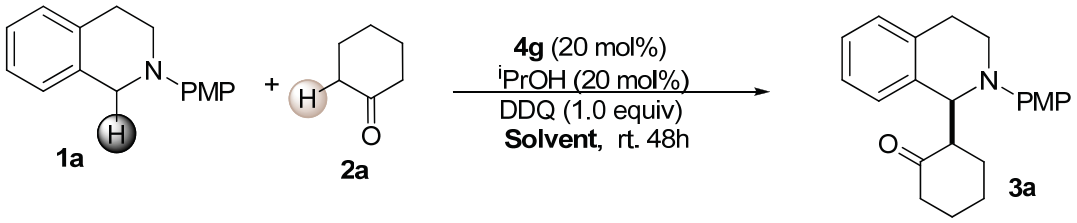


Entry	Metal	Yield [%] [b]	ee [%] [c]
1	AgOTf	55	29
2	$Yb(OTf)_3$	68	33
3	CuOTf	51	43
4	$Cu(OTf)_2$	70	55
5	$La(OTf)_3$	45	47
6	$Pd(OAc)_2$	53	45
7	$Mg(OTf)_2$	38	58

8	$Zn(OTf)_2$	41	31
9	$Sc(OTf)_3$	36	63
10	-	**66**	**89**

[a] Unless otherwise specified, the reaction was carried out with **1a** (0.1 mmol) and **2a** (0.4 mmol) in the presence of metal salts (0.01 mmol) and **4g** (0.02 mmol), anhydrous ^{i}PrOH (0.02 mmol), and DCM (1.0 mL) at rt for 48 h. [b] Isolated yield. [c] Determined by HPLC on a Chiralpak OD column.

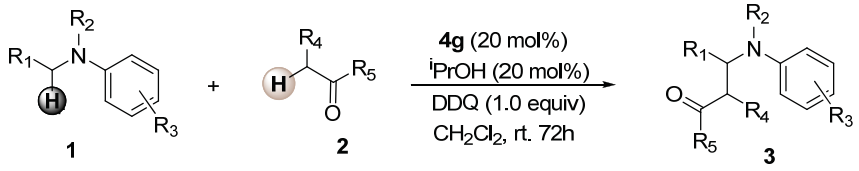
Table S2. The Solvent optimization results [a]

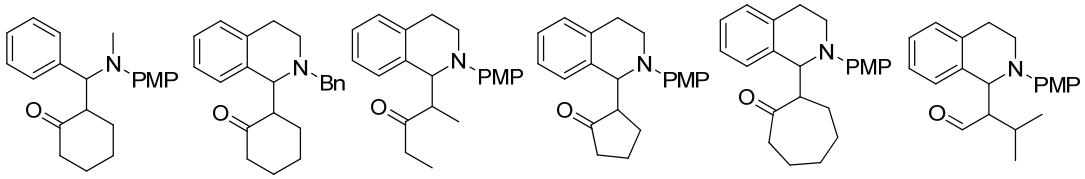


Entry	Solvent	Yield [%] [b]	ee [%] [c]
1	Tol	60	71
2	THF	53	63
3	MeCN	76	74
4	**DCM**	**64**	**90**
5	DCE	62	82
6	$CHCl_3$	63	85
7	Xylene	58	67
8	MeOH	65	56
9	DMF	57	73
10	DMSO	61	70

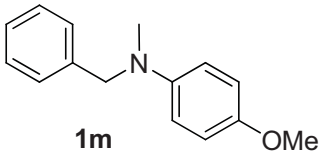
[a] Unless otherwise specified, the reaction was carried out with **1a** (0.1 mmol) and **2a** (0.4 mmol) in the presence of **4g** (0.02 mmol), anhydrous ^{i}PrOH (0.02 mmol), and solvent (1.0 mL) at rt for 48 h. [b] Isolated yield. [c] Determined by HPLC on a Chiralpak OD column.

3.0 Other Unsuccessful Examples for Asymmetric Oxidative sp^3 C-H Alkylation



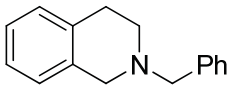


3p, <10% yield **3q**, <10% yield **3r**, <10% yield **3s**, complexes **3t**, <10% yield **3u**, <10% yield



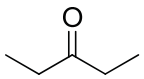
1m

N-benzyl-4-methoxy-N-methylaniline (known compounds): colorless oil, **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.25-7.31(m, 3 H), 7.22-7.24 (m, 2 H), 6.81-6.854 (d, *J* = 9.3 Hz, 2 H), 6.72-6.75 (d, *J* = 9.0 Hz, 2 H), 4.43 (s, 2 H), 3.75 (s, 3 H), 2.91 (s, 3 H) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$): δ 151.7, 144.8, 139.2, 128.4, 127.1, 126.9, 114.7, 114.5, 58.0, 55.7, 39.1 ppm.



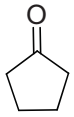
1n

2-benzyl-1,2,3,4-tetrahydroisoquinoline (known compounds): colorless oil, **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.29-7.41 (m, 5 H), 7.08-7.11 (m, 3 H), 6.17 (s, 1 H), 3.68 (s, 2 H), 3.63 (s, 2 H), 2.88-2.92 (t, *J* = 6.0 Hz, 2 H), 2.72-2.76 (t, *J* = 6.0 Hz, 2 H) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$): δ 138.4, 134.9, 134.4, 129.2, 128.7, 128.3, 127.1, 126.6, 126.1, 125.6, 62.8, 56.1, 50.4, 29.2 ppm.



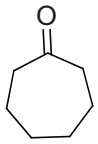
2d

pentan-3-one (known compounds): colorless oil, **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.40-2.47 (dd, *J* = 7.5. 15.0 Hz, 4 H), 1.04-1.09 (t, *J* = 7.5 Hz, 6 H) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$): δ 212.3, 35.4, 7.9 ppm.



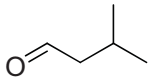
2e

cyclopentanone (known compounds): colorless oil, **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.15-2.20 (m, 4 H), 1.94-1.99 (m, 4 H) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$): δ 219.5, 38.4, 23.2 ppm.



2f

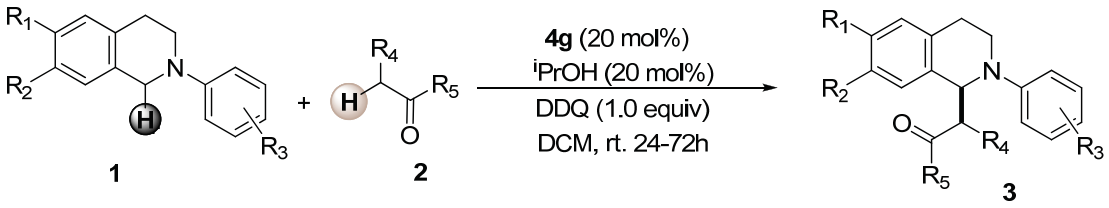
cycloheptanone (known compounds): colorless oil, **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.48-2.52 (m, 4 H), 1.69-1.74 (m, 8 H) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$): δ 215.6, 43.9, 30.4, 24.3 ppm.



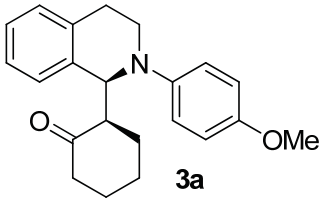
2g

3-methylbutanal (known compounds): colorless oil, **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.75-9.77 (t, *J* = 2.1 Hz, 1 H), 2.29-2.32 (m, 2 H), 2.16-2.25 (m, 1 H), 0.98-1.00 (d, *J* = 6.6 Hz, 6 H) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$): δ 203.0, 52.6, 23.4, 22.6 ppm.

4.0 General Procedure for the Preparation of Optically Active C_1-Alkylated Tetrahydroisoquinolins

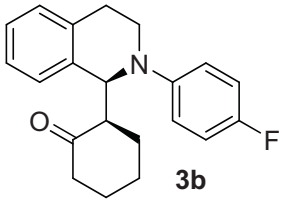


Typical experimental procedure: Typical experimental procedure: Under N_2, a solution of simple ketone (0.4 mmol), chiral amino acid **4g** (0.02 mmol) and anhydrous ^{i}PrOH (0.02 mmol) in DCM (0.3 mL) was stirred at room temperature for 1 h. And a solution of aryl-substituted 1,2,3,4-tetrahydroisoquinolin **1** (0.1 mmol) in DCM (0.2 mL) was added to the mixture above mentioned and the resultant mixture was stirred for 0.5 h. Finally, a solution of DDQ (0.1 mol) DCM (0.5 mL) was slowly added to the mixture above prepared and the resultant reaction mixture was stirred at RT for the appropriate time. After the reaction was completed (monitored by TLC), the resulting mixture was concentrated under reduced pressure and the residue was purified through column chromatography on silica gel (eluent, ethyl acetate / hexane 1:5). After filteration and the solvent was removed at reduced pressure to give the pure products.



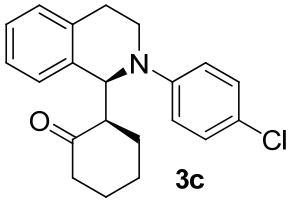
3a

(*R*)-2-((*S*)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)cyclohexanone: yellow oil, 65% yield; 90% *ee* determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254nm, t_{major} = 5.81 min, t_{minor} = 7.77 min); $[\alpha]^{20}_{D}$= -29 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.10-7.16 (m, 4 H), 6.87-6.90 (d, *J* = 9.0 Hz, 2 H), 6.77-6.80 (d, *J* = 9.0 Hz, 2 H), 5.34-5.36 (d, *J* = 5.7 Hz, 1 H), 3.73 (s, 3 H), 3.61-3.66 (m, 1 H), 3.45-3.50 (m, 1 H), 2.73-2.96 (m, 4 H), 2.41-2.48 (m, 1 H), 2.24-2.34 (m, 2 H), 2.00-2.06 (m, 1 H), 1.82-1.86 (m, 3 H) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$): δ 212.0, 153.1, 144.0, 136.1, 135.0, 128.9, 127.8, 126.6, 125.6, 118.3, 114.6, 56.4, 55.6, 43.9, 41.1, 30.3, 29.7, 27.5, 26.6, 23.4 ppm; **IR** (neat): 3316, 3062, 2926, 2854, 2359, 1706, 1511, 1462, 1246, 909, 734 cm^{-1}; **HRMS** (ESI): $C_{22}H_{25}NO_2$ $[M+H]^+$ calcd: 336.1958, found: 336.1965.



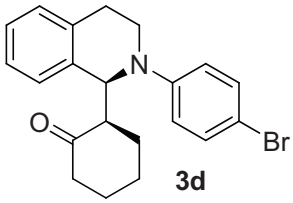
3b

(*R*)-2-((*S*)-2-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)cyclohexanone: yellow oil, 78% yield; 90% *ee* determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254nm, t_{major} = 4.80 min, t_{minor} = 5.49 min); $[\alpha]^{20}_{D}$= -24 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.07-7.17 (m, 4 H), 6.86-6.94 (m, 4 H), 5.42-5.43 (d, *J* = 5.1 Hz, 1 H), 3.63-3.70 (m, 1 H), 3.46-3.54 (m, 1 H), 2.90-2.99 (m, 1 H), 2.76-2.88 (m, 2 H), 2.41-2.48 (m, 1 H), 2.29-2.36 (m, 2 H), 1.82-1.90 (m, 3 H), 1.63-1.80 (m, 2 H) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$): δ 211.9, 146.1, 135.7, 134.9, 128.9, 127.9, 126.7, 125.8, 117.2, 115.8, 115.5, 56.4, 55.7, 43.4, 41.6 (J = 54 Hz), 30.4, 27.3 (J = 33.8 Hz), 26.7, 23.7 ppm; **IR** (neat): 3308, 3056, 2932, 2859, 2250, 1706, 1510, 1451, 1233, 939, 775 cm^{-1}; **HRMS** (ESI): $C_{21}H_{22}FNO$ $[M+Na]^+$ calcd: 346.1578, found: 346.1581.



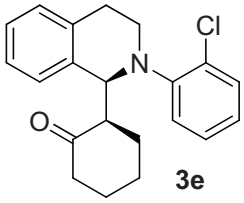
3c

(*R*)-2-((*S*)-2-(4-chlorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)cyclohexanone: yellow oil, 75% yield; 84% *ee* determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, 254nm, t_{major} = 4.58 min, t_{minor} = 5.41 min); $[\alpha]^{20}_{D}$= -19 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.12-7.17 (m, 6 H), 6.81-6.84 (d, *J* = 9.0 Hz, 2 H), 5.53-5.55 (d, *J* = 4.5 Hz, 1 H), 3.48-3.71 (m, 2 H), 2.81-3.02 (m, 3 H), 2.29-2.48 (m, 3 H), 1.81-1.90 (m, 3 H), 1.58-1.73 (m, 2 H) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$): δ 211.8, 147.8, 135.5, 134.8, 129.5, 128.9, 127.9, 126.8, 125.9, 116.1, 113.3, 56.4, 55.2, 42.7, 41.5, 30.3, 27.7, 27.3, 23.9 ppm; **IR** (neat): 3315, 3030, 2935, 2861, 2319, 1705, 1594, 1496, 1331, 938, 746 cm^{-1}; **HRMS** (ESI): $C_{21}H_{22}ClNO$ $[M+Na]^+$ calcd: 362.1282, found: 362.1288.



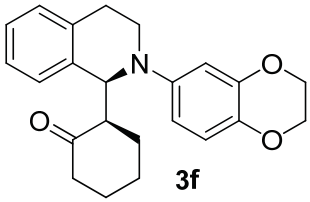
3d

(*R*)-2-((*S*)-2-(4-bromophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)cyclohexanone: yellow oil, 72% yield; 78% *ee* determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254nm, t_{major} = 5.06 min, t_{minor} = 6.33 min); $[\alpha]^{20}_{D}$= -16 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.07-7.17 (d, *J* = 9.0 Hz, 2 H), 7.15-7.16 (m, 4 H), 6.76-6.79 (d, *J* = 9.0 Hz, 2 H), 5.54-5.56 (d, *J* = 4.5 Hz, 1 H), 3.44-3.72 (m, 2 H), 2.90-3.01 (m, 1H), 2.81-2.88 (m, 2 H), 2.42-2.48 (m, 1 H), 2.29-2.35 (m, 1 H), 2.18-2.25 (m, 1 H), 1.80-2.06 (m, 2 H), 1.65-1.69 (m, 3 H) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$): δ 211.7, 148.2, 135.5, 134.8, 128.7, 127.9, 126.8, 125.9, 116.4, 113.8, 110.0, 56.3, 55.0, 42.6, 41.5, 30.3, 27.3, 27.1, 24.0 ppm; **IR** (neat): 3314, 3063, 2933, 2859, 1958, 1705, 1587, 1494, 1230, 938, 748 cm^{-1}; **HRMS** (ESI): $C_{21}H_{22}BrNO$ $[M+Na]^+$ calcd: 406.0782, found: 406.0784.



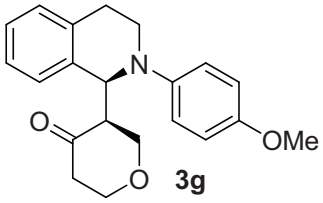
3e

(*R*)-2-((*S*)-2-(2-chlorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)cyclohexanone: yellow oil, 81% yield; 88% *ee* determined by HPLC on a Chiralpak AS-H column (hexane/2-propanol = 99/1, flow rate = 1.0 mL/min, 254nm, t_{major} = 14.93 min, t_{minor} = 12.78 min); $[\alpha]^{20}_{D}$= -22 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.30-7.34 (m, 1 H), 7.13-7.17 (m, 5 H), 6.81-6.84 (d, *J* = 9.0 Hz, 2 H), 5.53-5.54 (d, *J* = 4.8 Hz, 1 H), 3.64-3.73 (m, 1 H), 3.49-3.57 (m, 1H), 2.92-3.02 (m, 1 H), 2.81-2.88 (m, 2 H), 2.42-2.49 (m, 1 H), 2.29-2.34 (m, 1 H), 1.81-1.92 (m, 3 H), 1.59-1.71 (m, 3 H) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$): δ 211.8, 147.8, 135.5, 134.8, 129.5, 129.1, 128.7, 128.0, 126.8, 125.9, 118.9, 116.1, 113.3, 56.3, 55.1, 42.7, 41.5, 30.3, 27.3, 27.1, 23.9 ppm; **IR** (neat): 3298, 3065, 2938, 2863, 2251, 1704, 1595, 1496, 1230, 910, 773 cm^{-1}; **HRMS** (ESI): $C_{21}H_{22}ClNO$ $[M+Na]^+$ calcd: 362.1282, found: 362.1289.



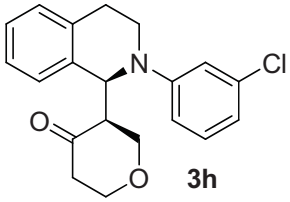
3f

(*R*)-2-((*S*)-2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)cyclohexanone: yellow oil, 69% yield; 61% *ee* determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254nm, t_{major} = 8.75 min, t_{minor} = 13.18 min); $[\alpha]^{20}_{D}$= -19 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.29-7.32 (m, 1 H), 7.10-7.11 (m, 3 H), 6.71-6.74 (m, 1 H), 6.34-6.36 (m, 2 H), 5.42-5.45 (d, *J* = 8.4 Hz, 1 H), 4.21-4.25 (m, 2 H), 4.17-4.18 (m, 2 H), 3.45-3.49 (t, *J* = 6.3 Hz, 2 H), 2.95-2.99 (m, 1 H), 2.68-2.86 (m, 2 H), 2.45-2.49 (m, 1 H), 2.21-2.31 (m, 3 H), 2.04-2.08 (m, 2 H), 1.69-2.08 (m, 2 H) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$): δ 212.1, 144.4, 143.8, 140.0, 135.1, 134.5, 128.0, 127.3, 126.6, 126.2, 117.4, 106.7, 102.0, 64.8, 64.2, 59.2, 54.7, 43.8, 32.6, 28.7, 27.2, 25.5 ppm; **IR** (neat): 3317, 3060, 2971, 2862, 2250, 1715, 1511, 1457, 1249, 1070, 733 cm^{-1}; **HRMS** (ESI): $C_{23}H_{23}NO_3$ $[M+Na]^+$ calcd: 386.1727, found: 386.1729.



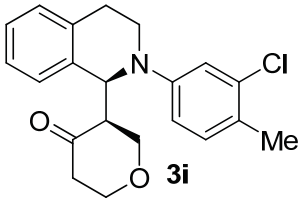
3g

(*S*)-3-((*S*)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)dihydro-2H-pyran-4(3H)-one: yellow oil, 73% yield; 94% *ee* determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254nm, t_{major} = 5.61 min, t_{minor} = 6.48 min); $[\alpha]^{20}_{D}$= -38 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.15-7.21 (m, 2 H), 7.07-7.13 (m, 2 H), 6.86-6.89 (d, *J* = 9.0 Hz, 2 H), 6.73-6.77 (d, *J* = 9.3 Hz, 2 H), 5.22-5.24 (d, *J* = 8.7 Hz, 1 H), 4.05-4.16 (m, 2 H), 3.89-3.91 (d, J = 7.5 Hz, 1 H), 3.72 (s, 3 H), 3.51-3.58 (m, 1 H), 2.88-3.02 (m, 1 H), 2.79-2.86 (m, 2 H), 2.70-2.77 (m, 1 H), 2.66-2.69 (m, 1 H), 2.52-2.64 (m, 1 H), 2.24-2.31 (m, 1 H) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$): δ 206.8, 153.6, 143.8, 135.7, 134.8, 129.6, 127.1, 125.8, 119.3, 116.3, 115.4, 69.9, 68.9, 58.8, 55.8, 55.5, 43.7, 41.1, 24.9 ppm; **IR** (neat): 3317, 2925, 2853, 2354, 1959, 1713, 1510, 1464, 1245, 1037, 761 cm^{-1}; **HRMS** (ESI): $C_{21}H_{23}NO_3$ $[M+Na]^+$ calcd: 360.1570, found: 360.1577.



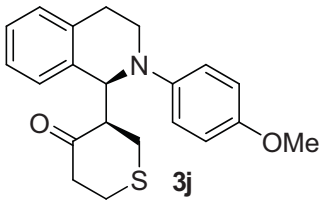
3h

(*S*)-3-((*S*)-2-(3-chlorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)dihydro-2H-pyran-4(3H)-one: yellow oil, 77% yield; 83% *ee* determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254nm, t_{major} = 6.77 min, t_{minor} = 9.22 min); $[\alpha]^{20}_{D}$= -51 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.32-7.41 (m, 1 H), 7.18-7.21 (m, 2 H), 7.08-7.13 (m, 2 H), 6.89 (s, 1 H), 6.80-6.83 (d, *J* = 8.4 Hz, 1 H), 6.73-6.80 (d, *J* = 21.0 Hz, 1 H), 5.41-5.44 (d, *J* = 8.1 Hz, 1 H), 4.11-4.16 (m, 1 H), 3.98-4.05 (m, 1 H), 3.65-3.84 (m, 4 H), 2.62-2.96 (m, 4 H), 2.29-2.34 (m, 1 H) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$): δ 206.6, 150.4, 135.1, 135.0, 134.4, 130.3, 129.5, 127.6, 127.5 , 126.0, 118.9, 115.7, 113.8, 69.8, 68.8, 58.3, 55.0, 42.4, 41.1, 25.5 ppm; **IR** (neat): 3404, 3067, 2967, 2856, 2249, 1714, 1592, 1485, 1207, 911, 733 cm^{-1}; **HRMS** (ESI): $C_{20}H_{20}ClNO_2$ $[M+Na]^+$ calcd: 364.1075, found: 364.1071.



3i

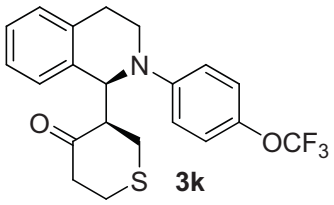
(*S*)-3-((*S*)-2-(3-chloro-4-methylphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)dihydro-2H-pyran-4(3H)-one: yellow solid, 71% yield; 90% *ee* determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254nm, t_{major} = 9.59 min, t_{minor} = 6.53 min); $[\alpha]^{20}_{D}$= -43 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.25-7.28 (m, 1 H), 7.17-7.22 (m, 2 H), 7.08-7.11 (m, 1 H), 7.00-7.03 (d, *J* = 9.0 Hz, 1 H), 6.91-6.92 (m, 1 H), 6.73-6.77 (m, 1 H), 5.33-5.35 (d, *J* = 8.4 Hz, 1 H), 4.13-4.18 (m, 1 H), 4.04-4.09 (m, 1 H), 3.77-3.82 (m, 1 H), 3.73-3.74 (m, 1 H), 3,.67-3.71 (m, 1 H), 3.58-3.66 (m, 1 H), 2.89-2.98 (m, 1 H), 2.82-2.86 (m, 1 H), 2.72-2.75 (m, 1 H), 2.64-2.71 (m, 1 H), 2.26-2.33 (m, 1 H), 2.23 (s, 3 H) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$): δ 206.7, 148.5, 135.1, 134.9, 134.4, 131.3, 129.6, 127.6, 127.4, 126.3, 126.0, 116.8, 114.7, 69.8, 68.9, 58.5, 55.1, 42.5, 41.1, 25.2, 18.9 ppm; **IR** (neat): 3408, 3021, 2924, 2854, 2358, 1715, 1610, 1502, 1208, 948, 732 cm^{-1}; **HRMS** (ESI): $C_{21}H_{22}ClNO_2$ $[M+Na]^+$ calcd: 378.1231, found: 378.1240.



3j

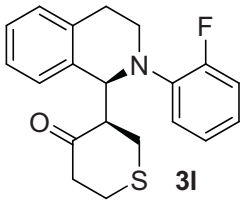
(*R*)-3-((*S*)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)dihydro-2H-thiopyran-4(3H)-one: yellow solid, 75% yield; 90% *ee* determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254nm, t_{major} = 5.89 min, t_{minor} = 6.64 min); $[\alpha]^{20}_{D}$= -18 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.18-7.19 (m, 3 H), 7.08-7.11 (m, 1 H), 6.88-6.91 (d, *J* = 9.0 Hz, 2 H), 6.74-6.77 (d, *J* = 9.3 Hz, 2 H), 5.55-5.58 (d, *J* = 9.6 Hz, 1 H), 5.55 (s, 3 H), 3.68-3.74 (m, 1 H), 3.53-3.66 (m, 1 H), 3.02-3.09 (m, 1 H), 2.94-3.00 (m, 2 H), 2.89-2.90 (m, 1 H), 2.77-2.87 (m, 2 H), 2.69-2.74 (m, 1 H), 2.59-2.67 (m, 1 H), 2.47-253 (m, 1 H) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$): δ 208.6, 153.7, 143.8, 135.8, 134.8, 129.7, 127.3, 127.2, 125.8, 119.5, 114.5, 57.9, 55.5, 44.0, 41.5, 33.6, 31.4, 30.1, 24.5 ppm; **IR** (neat): 3317, 2952, 2921, 2833, 1959, 1707, 1510, 1460, 1244, 1036, 772 cm^{-1}; **HRMS** (ESI): $C_{21}H_{23}NO_2S$ $[M+H]^+$ calcd:

354.1522, found: 354.1529.



3k

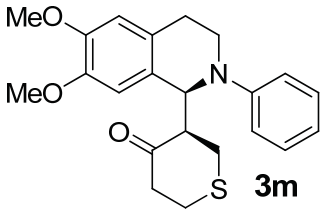
(*R*)-3-((*S*)-2-(4-(trifluoromethoxy)phenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)dihydro-2H-thiopyran-4(3H)-one: yellow solid, 70% yield; 80% *ee* determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254nm, t_{major} = 5.31 min, t_{minor} = 6.13 min); $[\alpha]^{20}_{D}$= -17 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.19-7.21 (m, 3 H), 7.10-7.12 (m, 1 H), 7.04-7.07 (d, *J* = 9.0 Hz, 2 H), 6.92-6.95 (d, *J* = 9.3 Hz, 2 H), 5.70-5.73 (d, *J* = 9.0 Hz, 1 H), 3.58-3.80 (m, 2 H), 3.09-3.13 (m, 1 H), 2.94-3.06 (m, 2 H), 2.91-2.95 (m, 3 H), 2.87-2.89 (m, 1 H), 2.75-2.79 (m, 1 H), 2.50-2.57 (m, 1 H) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$): δ 208.5, 148.2, 141.7, 135.2, 134.4, 129.7, 127.5, 126.0, 122.2, 117.1, 113.4, 57.7, 55.8, 44.1, 42.3 (J = 93.8 Hz), 33.5, 31.2, 30.1, 25.0 ppm; **IR** (neat): 3316, 3061, 2923, 2854, 1707, 1608, 1511, 1260, 1112, 939, 760 cm^{-1}; **HRMS** (ESI): $C_{21}H_{20}F_3NO_2S$ $[M+Na]^+$ calcd: 430.1059, found: 430.1069.



3l

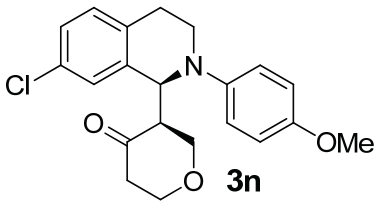
(*R*)-3-((*S*)-2-(2-fluorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)dihydro-2H-thiopyran-4(3H)-one: yellow solid, 67% yield; 70% *ee* determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254nm, t_{major} = 5.61 min, t_{minor} = 6.01 min); $[\alpha]^{20}_{D}$= -19 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.20-7.23 (m, 3 H), 6.96-7.04 (m, 1 H), 6.89-6.93 (m, 1 H), 6.82-6.87 (m, 3 H), 5.42-5.45 (d, *J* = 9.3 Hz, 1 H), 3.64-3.74 (m, 1 H), 3.50-3.56 (m, 1 H), 3.08-3.12 (m, 2 H), 2.93-3.03 (m, 3 H), 2.50-2.90 (m, 3 H), 2.29-2.34 (m, 1 H) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$): δ 208.4, 138.6, 138.5, 135.7, 134.7, 129.8, 127.3, 127.1, 126.0, 124.3, 123.0, 122.0, 116.4, 57.9, 56.9, 43.5, 41.4, 33.5, 31.5, 30.1, 25.1 ppm; **IR** (neat): 3391, 3020, 2951, 2854, 2253, 1704, 1511, 1451, 1227, 910, 759 cm^{-1}; **HRMS** (ESI): $C_{20}H_{20}FNOS$

$[M+Na]^+$ calcd: 364.1142, found: 364.1149.



3m

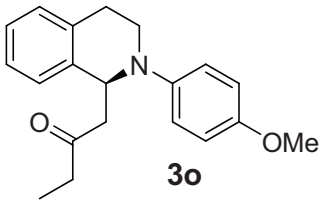
(*R*)-3-((*S*)-6,7-dimethoxy-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)dihydro-2H-thiopyran-4(3H)-one: yellow solid, 61% yield; 90% *ee* determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 90/10, flow rate = 1.0 mL/min, 254nm, t_{major} = 9.92 min, t_{minor} = 11.08 min); $[\alpha]^{20}_D$= -22 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.19-7.22 (m, 2 H), 6.96-6.98 (d, *J* = 8.1 Hz, 2 H), 6.78-6.83 (t, *J* = 7.2 Hz, 1 H), 6.71 (s, 1 H), 6.57 (s, 1 H), 5.66-5.69 (d, *J* = 8.4 Hz, 1 H), 3.88 (s, 3 H), 3.83 (s, 3 H), 3.67-3.71 (m, 2 H), 3.10-3.15 (m, 1 H), 3.04-3.05 (m, 1 H), 2.85-2.98 (m, 4 H), 2.75-2.82 (m, 2 H), 2.53-2.57 (m, 1 H) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$): δ 208.8, 149.5, 148.2, 147.0, 129.3, 127.3, 126.9, 119.4, 116.7, 112.1, 110.4, 58.0, 56.1, 55.8, 55.2, 42.8, 41.7, 33.7, 31.1, 24.7 ppm; **IR** (neat): 3530, 3001, 2929, 2835, 2253, 1706, 1514, 1245, 1111, 911, 732 cm^{-1}; **HRMS** (ESI): $C_{22}H_{25}NO_3S$ $[M+Na]^+$ calcd: 406.1447, found: 406.1447.



3n

(*S*)-3-((*S*)-7-chloro-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)dihydro-2H-pyran-4(3H)-one: yellow solid, 52% yield; 77% *ee* determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 90/10, flow rate = 1.0 mL/min, 254nm, t_{major} = 6.87 min, t_{minor} = 8.08 min); $[\alpha]^{20}_D$= -16 (*c* = 0.5, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.26-7.30 (m, 1 H), 7.15-7.18 (m, 1 H), 7.04-7.04 (d, *J* = 8.1 Hz, 1 H), 6.84-6.87 (d, *J* = 9.3 Hz, 2 H), 6.74-6.77 (d, J = 9.3 Hz, 2 H), 5.14-5.17 (d, *J* = 8.7 Hz, 1 H), 4.07-4.20 (m, 2 H), 3.69 (s, 3 H), 3.62-3.68 (m, 1 H), 3.51-3.58 (m, 1 H), 2.69-2.83 (m, 3 H), 2.51-2.63 (m, 2 H), 2.26-2.33 (m, 1 H), 2.04-2.06 (m, 1 H) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$): δ 206.4, 153.8, 143.4, 137.4, 133.2, 131.3, 131.0, 127.4, 127.2, 119.5, 114.5, 69.8, 69.0, 58.6, 55.5, 44.7, 43.5, 41.0, 24.1 ppm; **IR** (neat): 3297, 2924, 2854, 2251,

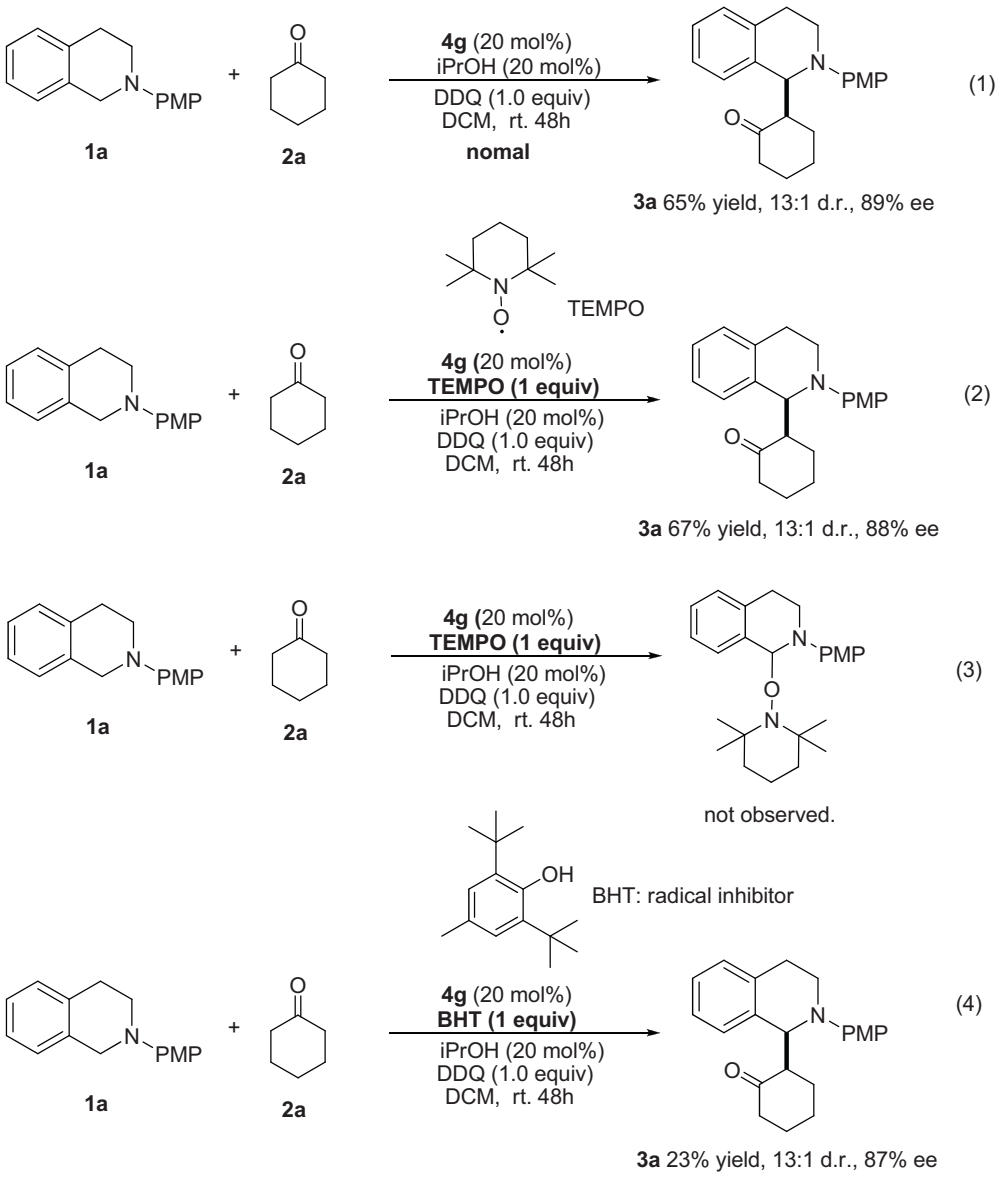
2053, 1717, 1510, 1246, 1146, 907, 733 cm^{-1}; **HRMS** (ESI): $C_{21}H_{22}ClNO_3$ $[M+H]^+$ calcd: 372.1361, found: 372.1359.



3o

(*S*)-1-(2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)butan-2-one: yellow oil, 63% yield; 30% *ee* determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254nm, t_{major} = 15.25 min, t_{minor} = 7.19 min); $[\alpha]^{20}_D$= -6 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.10-7.16 (m, 4 H), 6.89-6.92 (d, *J* = 9.3 Hz, 2 H), 6.79-6.82 (d, *J* = 9.0 Hz, 2 H), 5.25-5.29 (t, *J* = 6.6 Hz, 1 H), 3.74 (s, 3 H), 3.41-3.59 (m, 2 H), 2.95-3.07 (m, 2 H), 2.68-2.78 (m, 2 H), 2.25-2.32 (m, 2 H), 0.94-0.99 (t, *J* = 7.2 Hz, 3 H) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$): δ 210.0, 153.2, 143.7, 138.4, 134.3, 128.9, 126.8, 126.6, 118.1, 114.7, 56.2, 55.6, 48.7, 42.9, 37.0, 26.9, 7.5 ppm; **IR** (neat): 3313, 3061, 2933, 2833, 2061, 1710, 1511, 1460, 1245, 949, 756 cm^{-1}; **HRMS** (ESI): $C_{20}H_{23}NO_2$ $[M+Na]^+$ calcd: 332.1621, found: 332.1626.

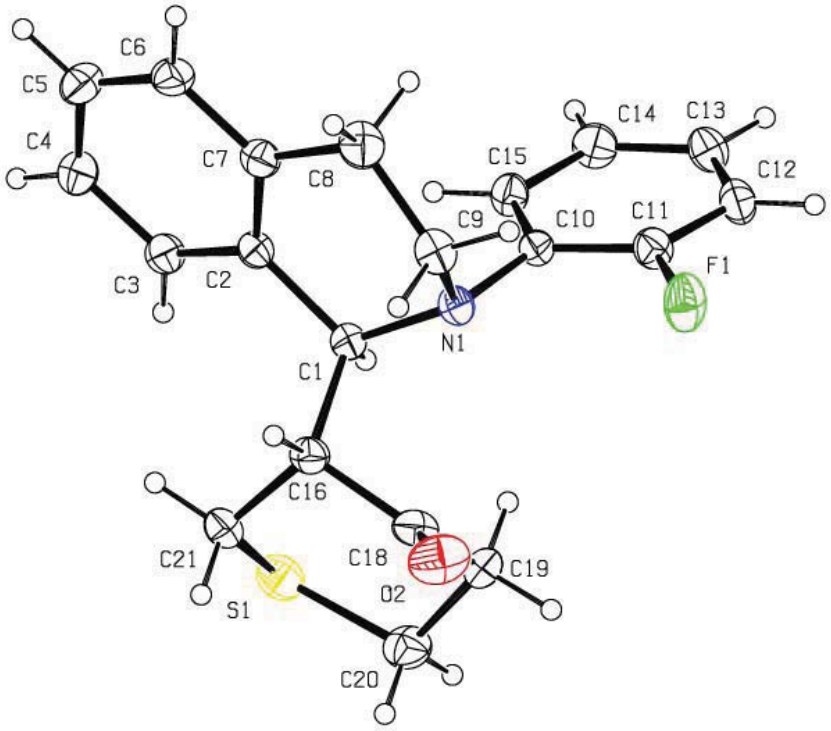
5.0 Mechanistic Experiments and Proposed Reaction Pathways

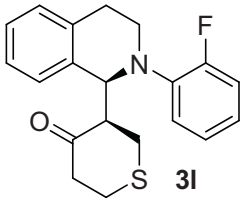


The possible reaction pathways of this novel oxidative coupling of N-aryl tetrahydroisoquinolines with simple ketones is assumed to involve a single-electron transfer (SET) radical mechanism. When DDQ reacts with the **1a**, a single-electron transfer from **1a** would occur to afford the radical cation, which was subsequently transferred to iminium cation as a key intermediate. To trap the radical intermediate, the same equivalent of TEMPO or 2,6-di-tert-butyl-4-methylphenol (BHT) was respectively added to this reaction system. With addition of TEMPO, no significant change in the yield and stereoselective of the coupling product could be detected, and the addition product of N-aryl tetrahydroisoquinolines with TEMPO was not formed either. However, the situation was changed when BHT was added, which the yield of the coupling product was decreased from 65 to

23%, although little influence on stereoselectivity.

6.0 X-ray Structure of 3l:





3l

CCDC 911181

Bond precision: C-C = 0.0037 A Wavelength=0.71070

Cell: a=6.7008(2) b=14.8959(6) c=16.9986(6)

alpha=90 beta=93.806(3) gamma=90

Temperature: 292 K

	Calculated	Reported

Volume	1692.96(10)	1692.96(11)
Space group	P 21/n	P 1 21/n 1
Hall group	-P 2yn	-P 2yn
Moiety formula	C20 H20 F N O S	C20 H20 F N O S
Sum formula	C20 H20 F N O S	C20 H20 F N O S
Mr	341.44	341.43
Dx,g cm-3	1.340	1.340
Z	4	4
Mu (mm-1)	0.207	0.207
F000	720.0	720.0
F000'	720.80	
h,k,lmax	9,20,22	8,19,22
Nref	4317	3798
Tmin,Tmax	0.936,0.950	0.879,1.000
Tmin'	0.936	

Correction method= MULTI-SCAN

Data completeness= 0.880 Theta(max)= 28.600

R(reflections)= 0.0540(2638) wR2(reflections)= 0.1823(3798)

S = 1.014 Npar= 217

7.0 References

[1] X.-Z. Shu, X.-F. Xia, Y.-F. Yang, K.-G. Ji, X.-Y. Liu, Y.-M. Liang, *J. Org. Chem.* **2009**, *74*, 7464-7469.

[2] Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2005**, *127*, 6968-6969.

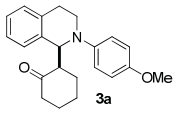
[3] N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 7894-7895

[4] Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* **2005**, *44*, 4212-4215.

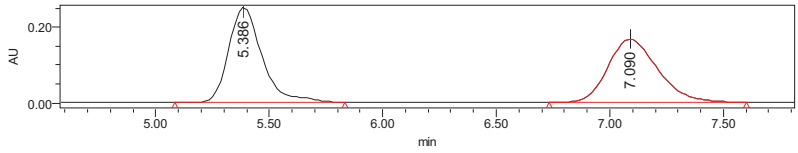
[5] Z. Qiao, Z. Shafiq, L. Liu, Z.-B. Yu, Q.-Y. Zheng, D. Wang, Y.-J. Chen, *Angew. Chem. Int. Ed.* **2010**, *49,* 7294-7298.

7.0 Copies of HPLC Spectra of Racemic /Chiral Products

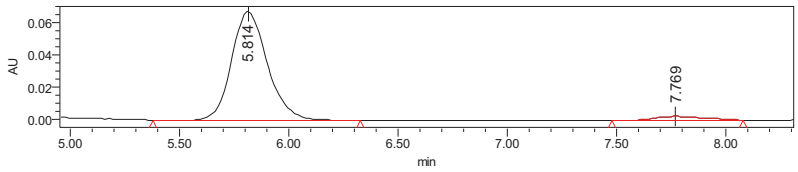
HPLC using an OD (*n*-Hexane/*i*PrOH= 80/20, flow rate 1.0 mL/min)



3a

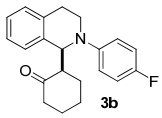


	Retention Time	Area	% Area	Height	Int Type	Peak Type
1	5.386	2561296	50.27	250322	bb	Unknown
2	7.090	2533856	49.73	166888	bb	Unknown



	Retention Time	Area	% Area	Height	Int Type	Peak Type
1	5.814	766180	94.90	67926	bb	Unknown
2	7.769	41136	5.10	2557	bb	Unknown

HPLC using an OD (*n*-Hexane/*i*PrOH= 80/20, flow rate 1.0 mL/min



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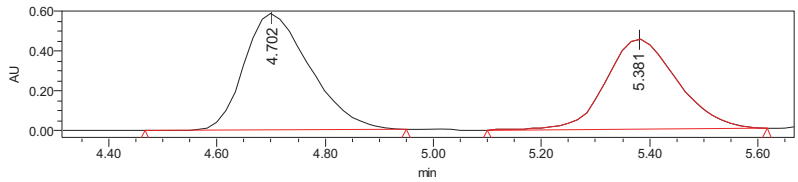
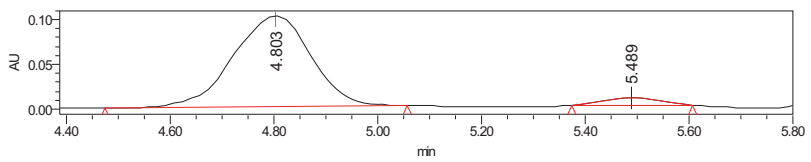
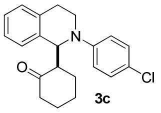


	Retention Time	Area	% Area	Height	Int Type	Peak Type
1	4.702	4653519	52.89	574457	bb	Unknown
2	5.381	4145473	47.11	451067	bb	Unknown



	Retention Time	Area	% Area	Height	Int Type	Peak Type
1	4.803	1050934	95.12	101644	bb	Unknown
2	5.489	53972	4.88	7483	bb	Unknown

HPLC using an OD (*n*-Hexane/*i*PrOH= 60/40, flow rate 1.0 mL/min



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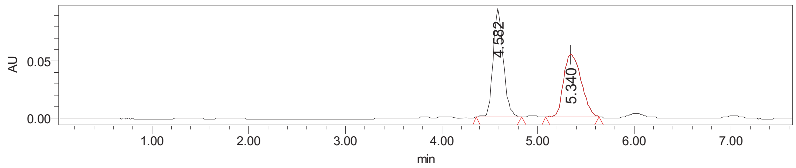
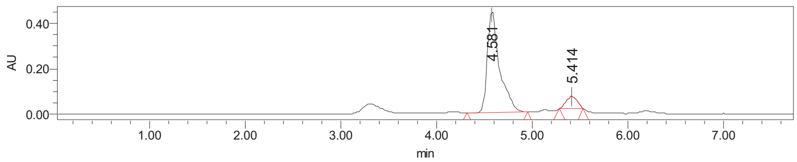
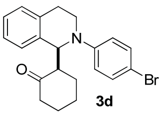


	Retention Time	Area	% Area	Height	Int Type	Peak Type
1	4.582	696241	50.59	94271	bb	Unknown
2	5.340	680135	49.41	54531	bb	Unknown



	Retention Time	Area	% Area	Height	Int Type	Peak Type
1	4.581	3984697	91.79	443349	bb	Unknown
2	5.414	360424	8.21	49434	bb	Unknown

HPLC using an OD (*n*-Hexane/*i*PrOH= 80/20, flow rate 1.0 mL/min



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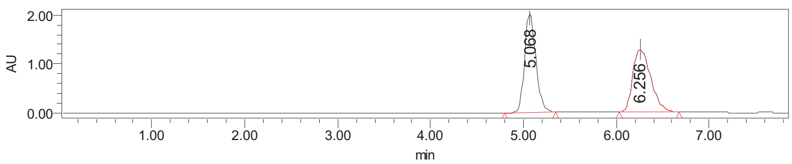
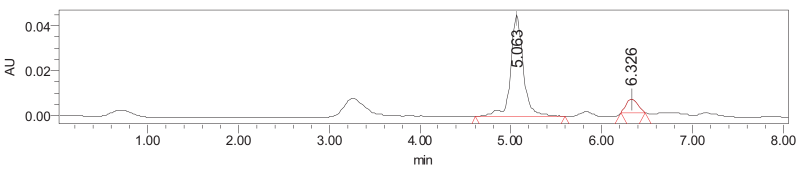
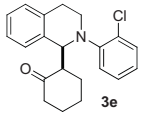


	Retention Time	Area	% Area	Height	Int Type	Peak Type
1	5.068	16929256	49.22	2019711	bb	Unknown
2	6.256	17462763	50.78	1283231	bb	Unknown



	Retention Time	Area	% Area	Height	Int Type	Peak Type
1	5.062	424732	88.76	43877	bb	Unknown
2	6.327	53795	11.24	5888	bb	Unknown

HPLC using an AS (*n*-Hexane/*i*PrOH= 99/1, flow rate 1.0 mL/min



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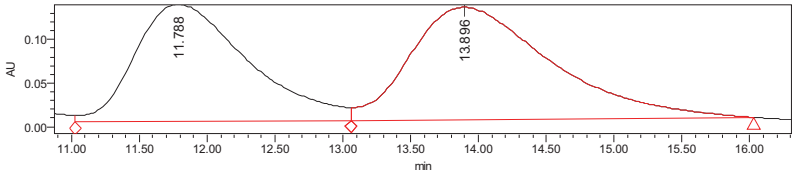
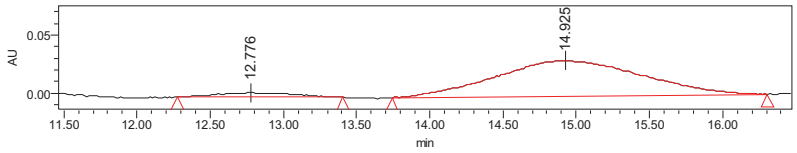
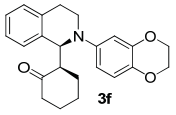


	Retention Time	Area	% Area	Height	Int Type	Peak Type
1	11.788	7791813	45.56	134488	VV	Unknown
2	13.896	9308697	54.44	128497	Vb	Unknown



	Retention Time	Area	% Area	Height	Int Type	Peak Type
1	12.776	142743	6.23	3821	bb	Unknown
2	14.925	2147374	93.77	30673	bb	Unknown

HPLC using an OD (*n*-Hexane/*i*PrOH= 80/20, flow rate 1.0 mL/min



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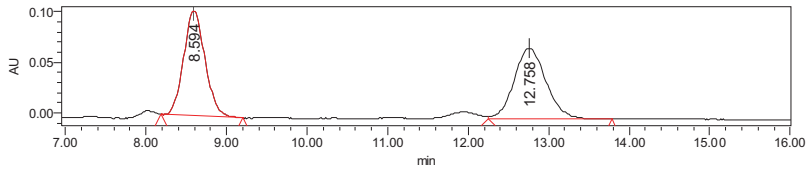
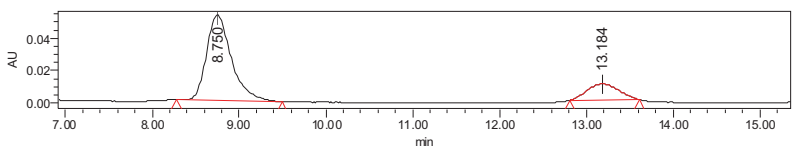
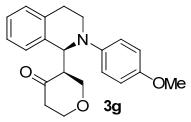


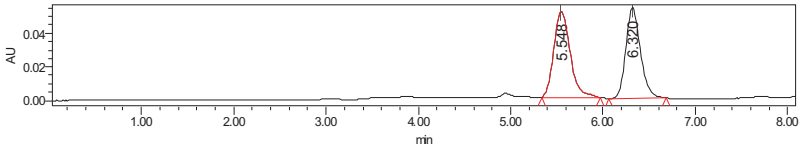
	Retention Time	Area	% Area	Height	Int Type	Peak Type
1	8.750	1044253	80.77	52752	bb	Unknown
2	13.184	248566	19.23	9859	bb	Unknown



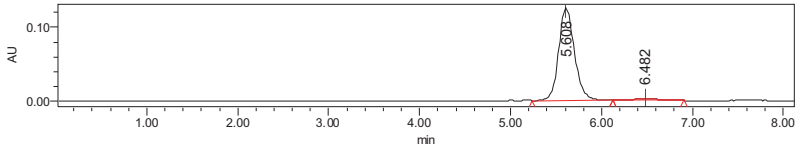
	Retention Time	Area	% Area	Height	Int Type	Peak Type
1	8.750	1044253	80.77	52752	bb	Unknown
2	13.184	248566	19.23	9859	bb	Unknown

HPLC using an OD (*n*-Hexane/*i*PrOH= 80/20, flow rate 1.0 mL/min



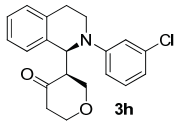


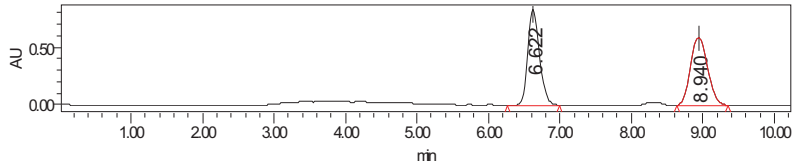
	Retention Time	Area	% Area	Height	Int Type	Peak Type
1	5.548	621370	50.92	51043	bb	Unknown
2	6.320	598907	49.08	54194	bb	Unknown



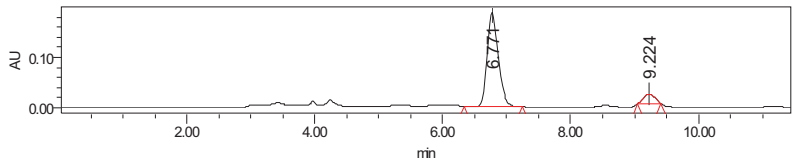
	Retention Time	Area	% Area	Height	Int Type	Peak Type
1	5.608	1518781	97.07	124585	bb	Unknown
2	6.482	45854	2.93	2812	bb	Unknown

HPLC using an OD (*n*-Hexane/*i*PrOH= 80/20, flow rate 1.0 mL/min



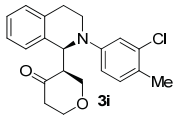


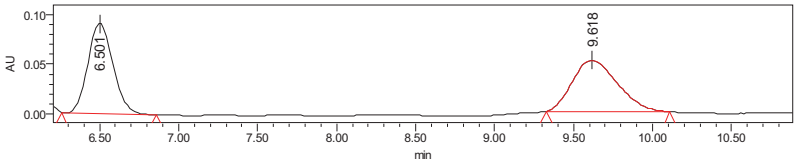
	Retention Time	Area	% Area	Height	Int Type	Peak Type
1	6.622	9665184	50.36	831741	bb	Unknown
2	8.940	9527637	49.64	589565	bb	Unknown



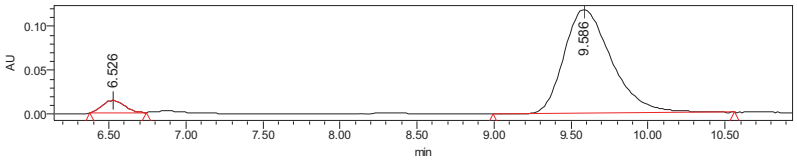
	Retention Time	Area	% Area	Height	Int Type	Peak Type
1	6.771	2258635	91.44	187924	bb	Unknown
2	9.224	211400	8.56	17961	bb	Unknown

HPLC using an OD (*n*-Hexane/*i*PrOH= 80/20, flow rate 1.0 mL/min



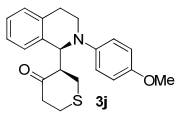


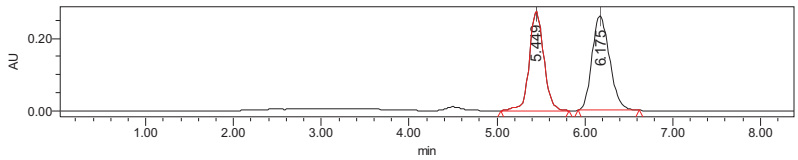
	Retention Time	Area	% Area	Height	Int Type	Peak Type
1	6.501	1001809	49.40	90829	bb	Unknown
2	9.618	1026326	50.60	51601	bb	Unknown



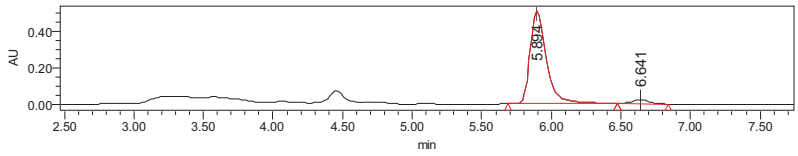
	Retention Time	Area	% Area	Height	Int Type	Peak Type
1	6.526	137638	5.13	14084	bb	Unknown
2	9.586	2543916	94.87	118049	bb	Unknown

HPLC using an OD (*n*-Hexane/*i*PrOH= 80/20, flow rate 1.0 mL/min



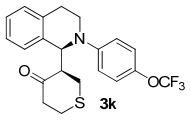


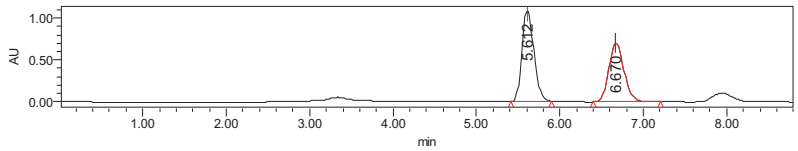
	Retention Time	Area	% Area	Height	Int Type	Peak Type
1	5.449	3130095	46.18	273432	bb	Unknown
2	6.175	3648083	53.82	260348	bb	Unknown



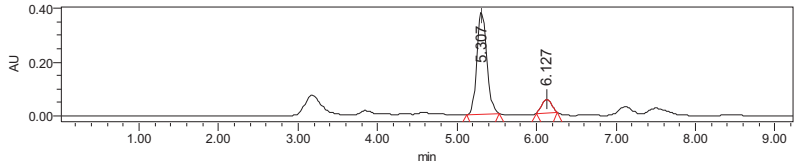
	Retention Time	Area	% Area	Height	Int Type	Peak Type
1	5.894	4035036	95.64	504891	bb	Unknown
2	6.641	184007	4.36	20452	bb	Unknown

HPLC using an OD (*n*-Hexane/*i*PrOH= 80/20, flow rate 1.0 mL/min



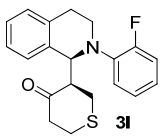


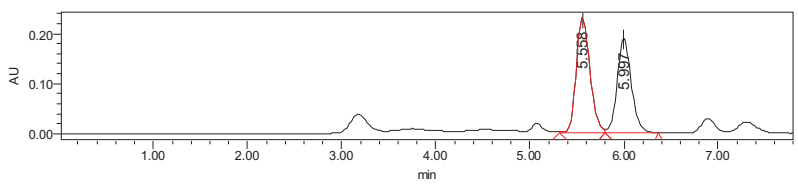
	Retention Time	Area	% Area	Height	Int Type	Peak Type
1	5.612	10921192	54.87	1091460	bb	Unknown
2	6.670	8980784	45.13	709469	bb	Unknown



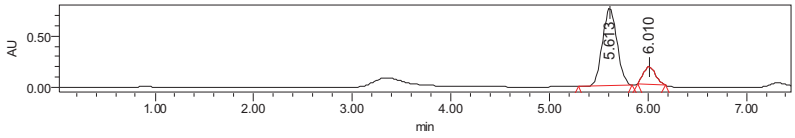
	Retention Time	Area	% Area	Height	Int Type	Peak Type
1	5.307	3277759	90.10	379588	bb	Unknown
2	6.127	360149	9.90	45671	bb	Unknown

HPLC using an OD (*n*-Hexane/*i*PrOH= 80/20, flow rate 1.0 mL/min



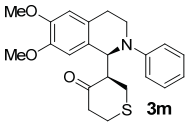


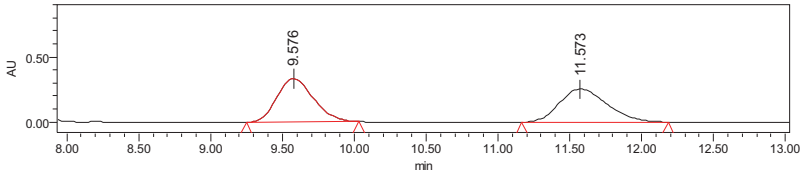
	Retention Time	Area	% Area	Height	Int Type	Peak Type
1	5.558	2320873	54.08	230969	VV	Unknown
2	5.997	1970322	45.92	187553	VB	Unknown



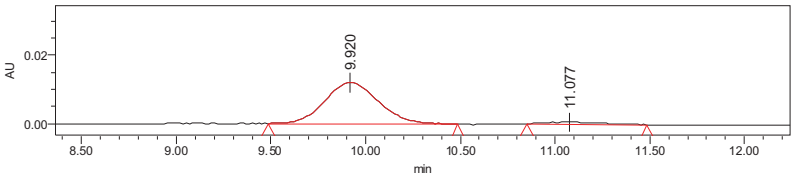
	Retention Time	Area	% Area	Height	Int Type	Peak Type
1	5.613	7626239	84.81	742107	bb	Unknown
2	6.010	1365829	15.19	161143	bb	Unknown

HPLC using an OD (*n*-Hexane/*i*PrOH= 90/10, flow rate 1.0 mL/min



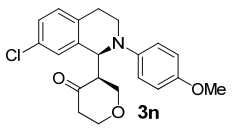


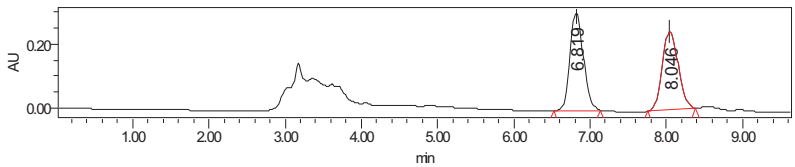
	Retention Time	Area	% Area	Height	Int Type	Peak Type
1	9.576	5907366	50.24	333241	bb	Unknown
2	11.573	5850933	49.76	252841	bb	Unknown



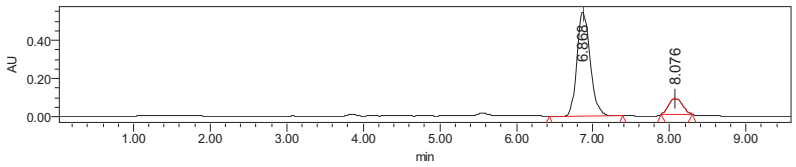
	Retention Time	Area	% Area	Height	Int Type	Peak Type
1	9.920	237231	95.34	11989	bb	Unknown
2	11.077	11599	4.66	588	bb	Unknown

HPLC using an OD (*n*-Hexane/*i*PrOH= 90/10, flow rate 1.0 mL/min



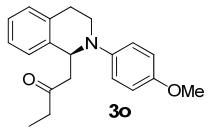


	Retention Time	Area	% Area	Height	Int Type	Peak Type
1	6.819	3697313	50.82	304768	bb	Unknown
2	8.046	3578170	49.18	244176	bb	Unknown



	Retention Time	Area	% Area	Height	Int Type	Peak Type
1	6.868	6569912	88.28	547515	bb	Unknown
2	8.076	871913	11.72	75521	bb	Unknown

HPLC using an OD (*n*-Hexane/*i*PrOH= 80/20, flow rate 1.0 mL/min



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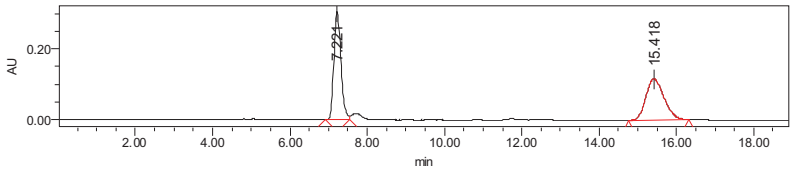
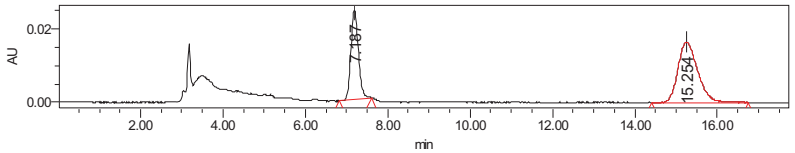
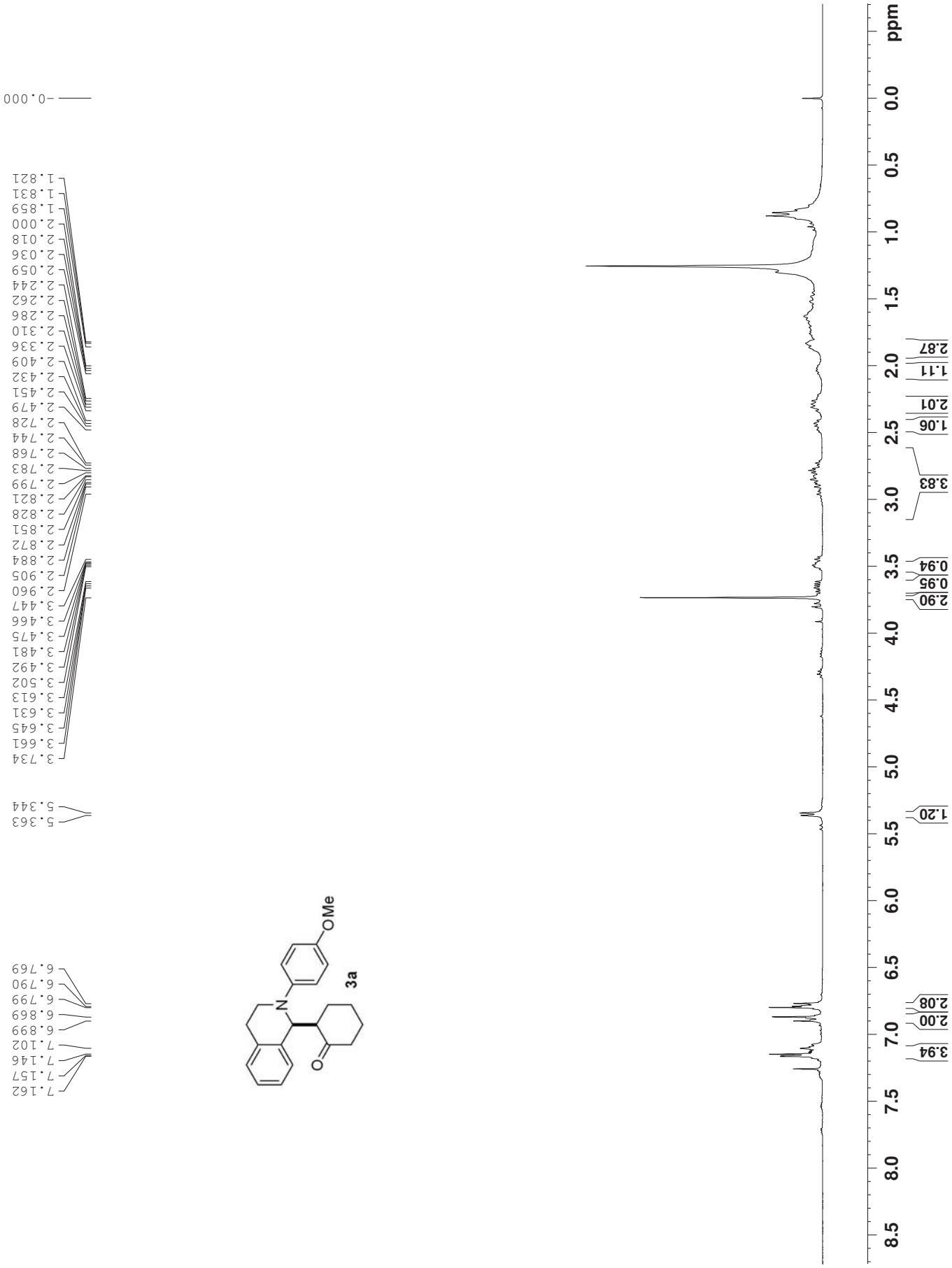
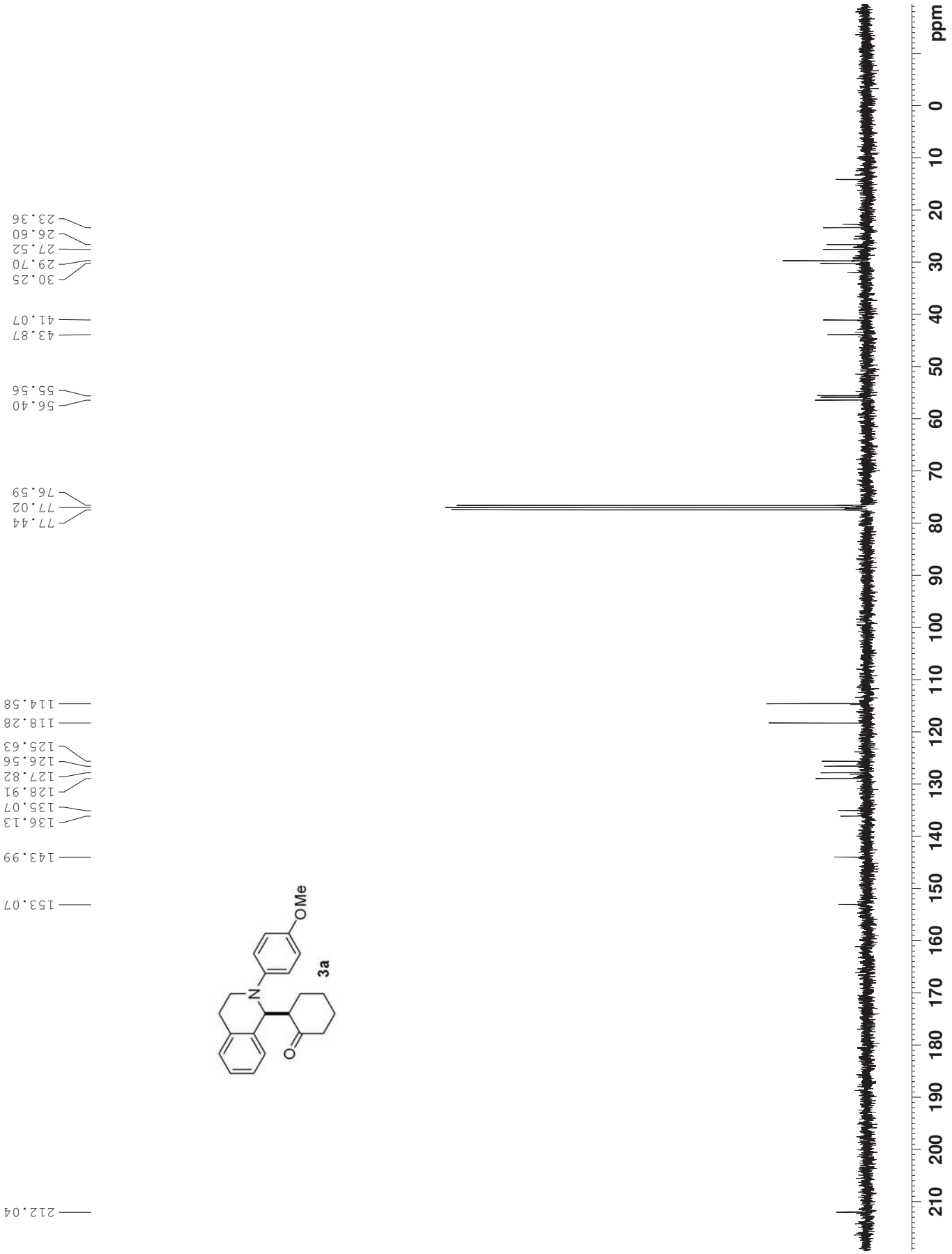


	Retention Time	Area	% Area	Height	Int Type	Peak Type
1	7.221	3914546	51.00	307065	VV	Unknown
2	15.418	3760414	49.00	115505	BB	Unknown



	Retention Time	Area	% Area	Height	Int Type	Peak Type
1	7.187	303218	35.63	24323	bb	Unknown
2	15.254	547914	64.37	16548	bb	Unknown

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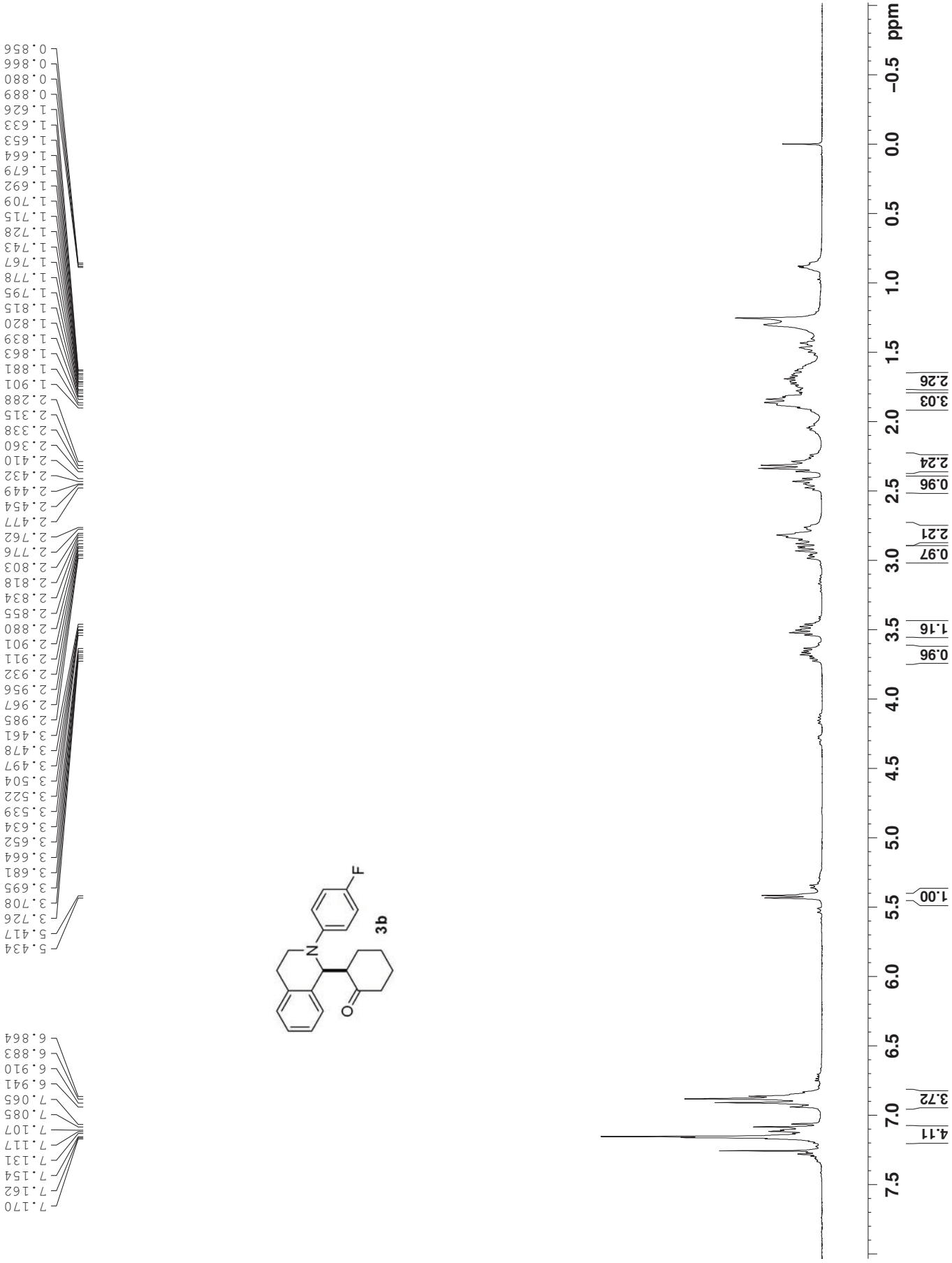
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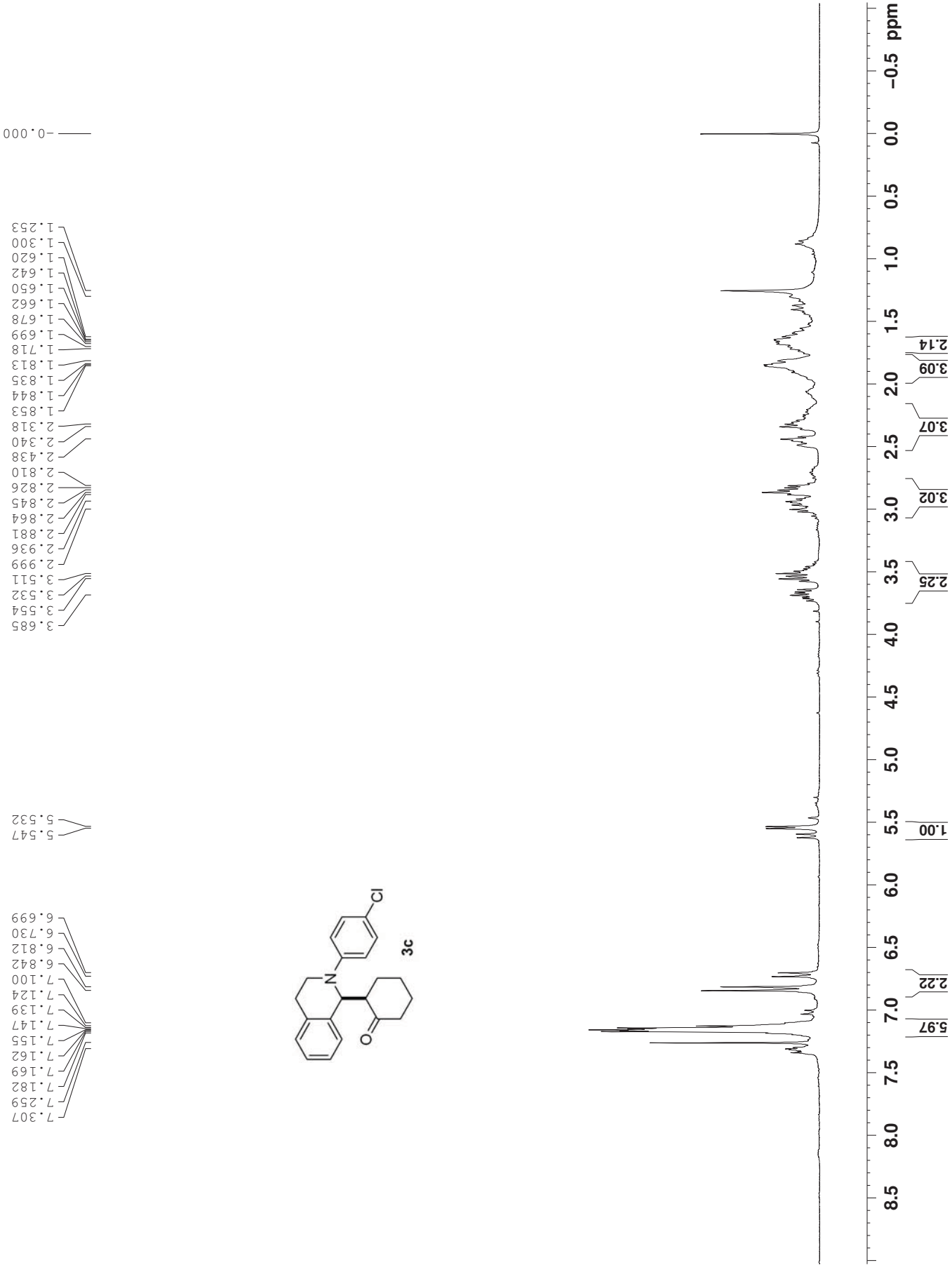
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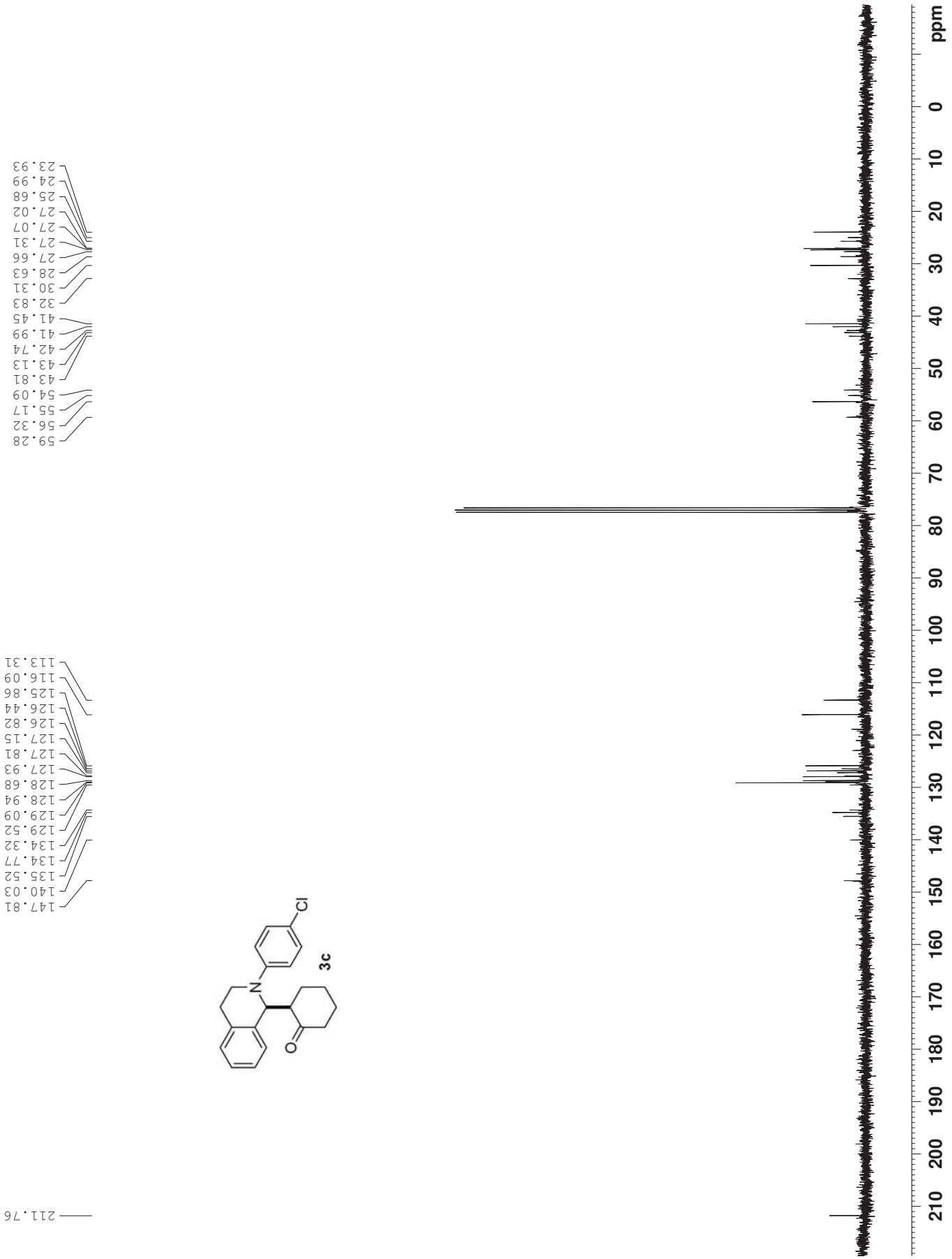
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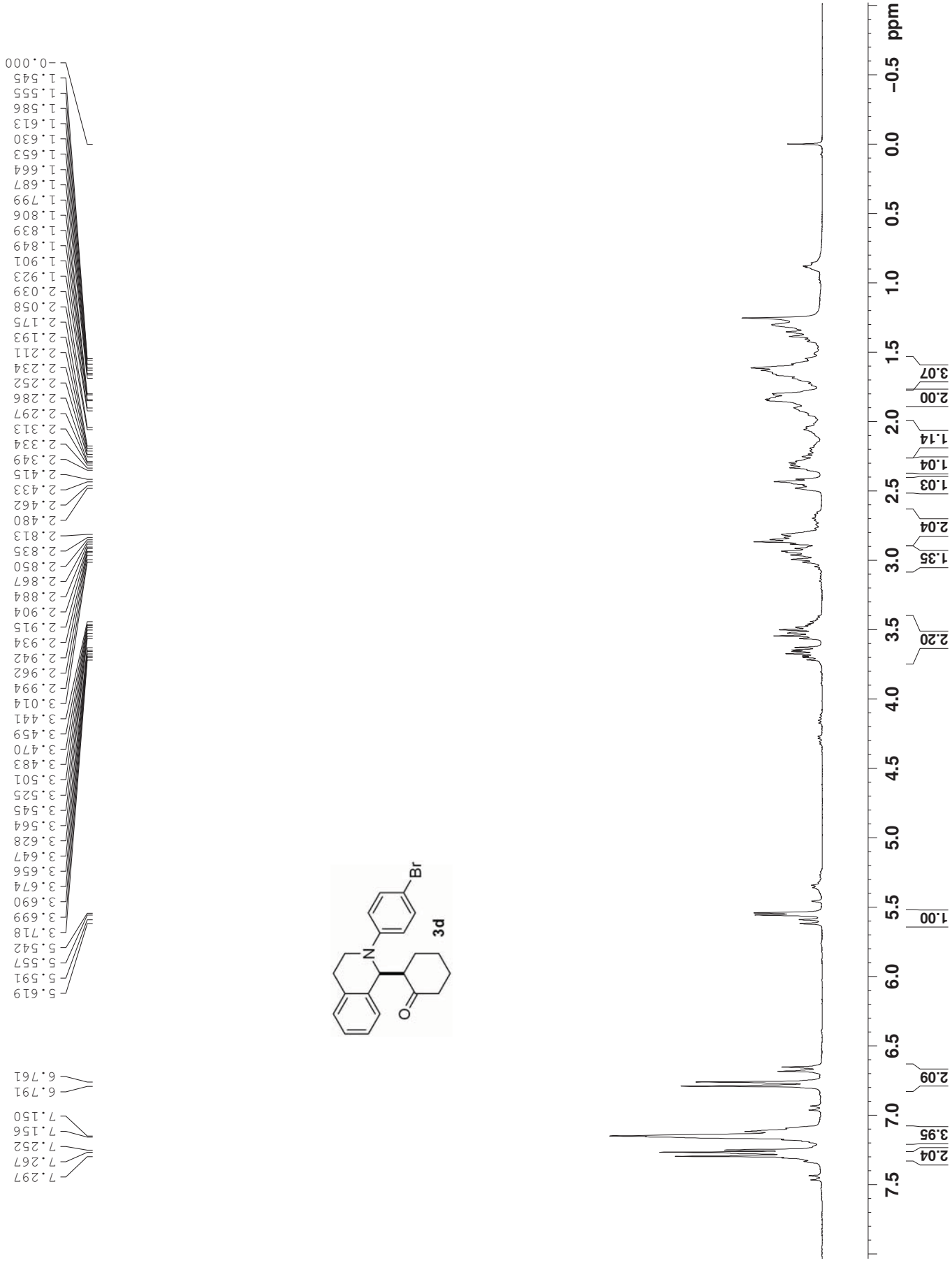
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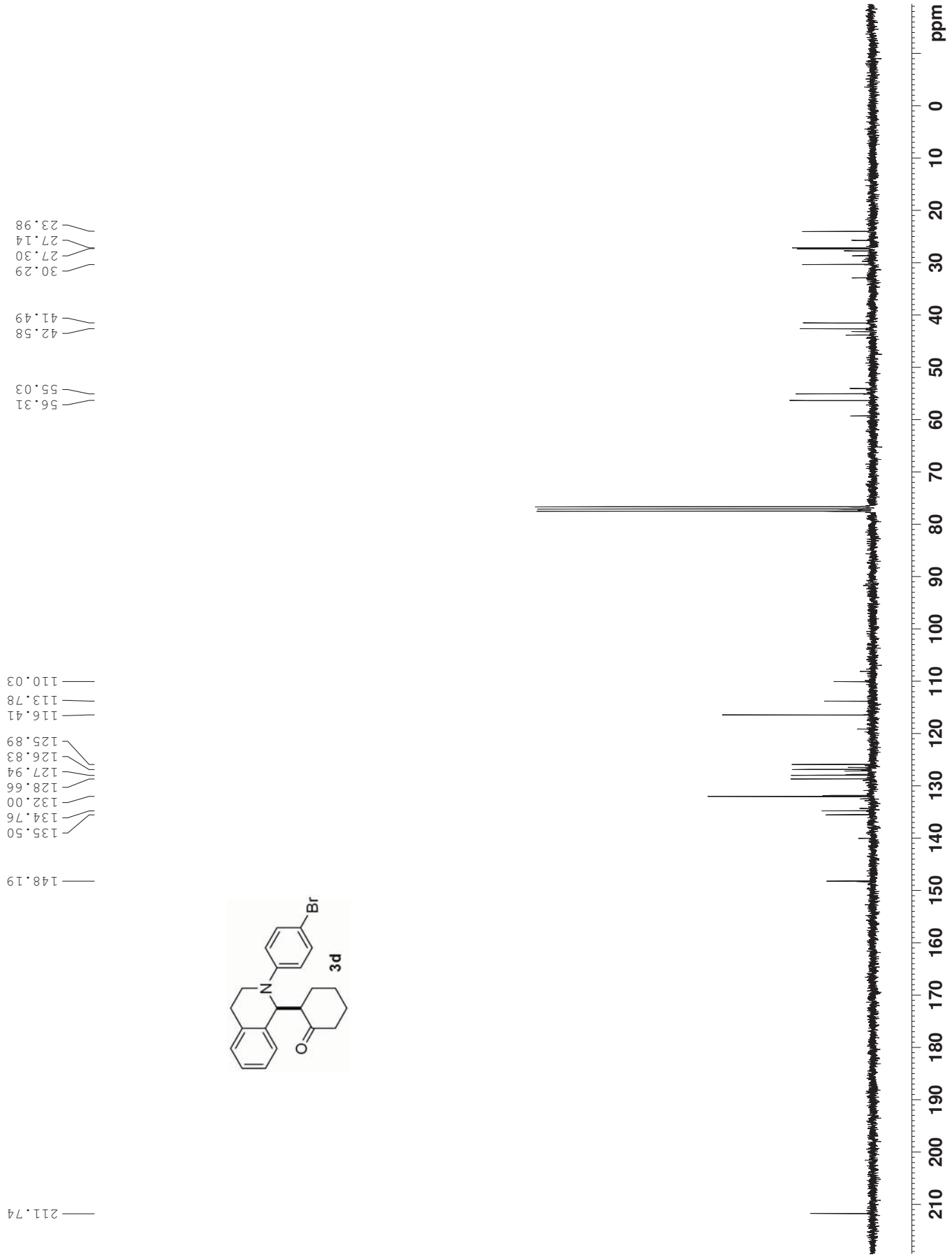
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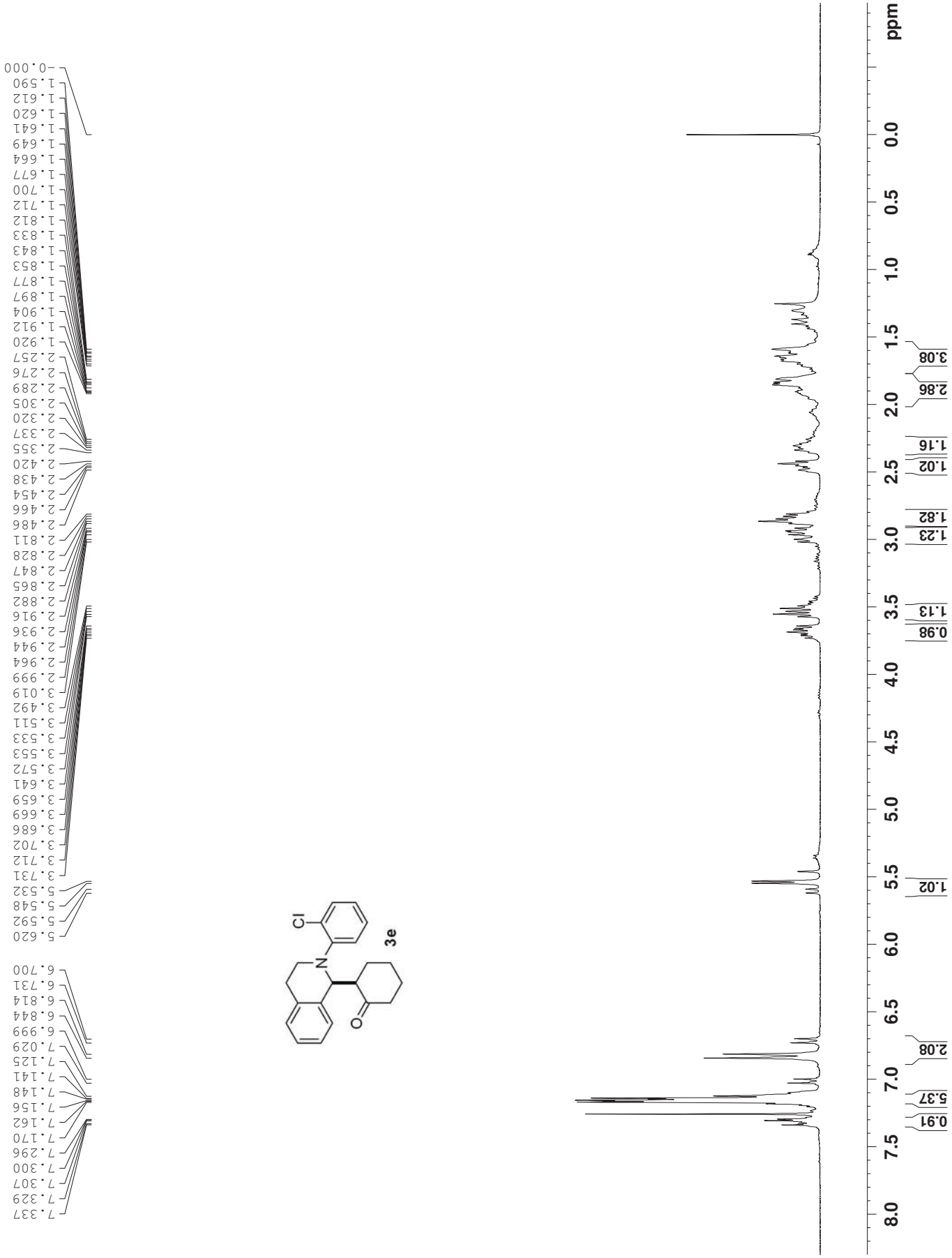

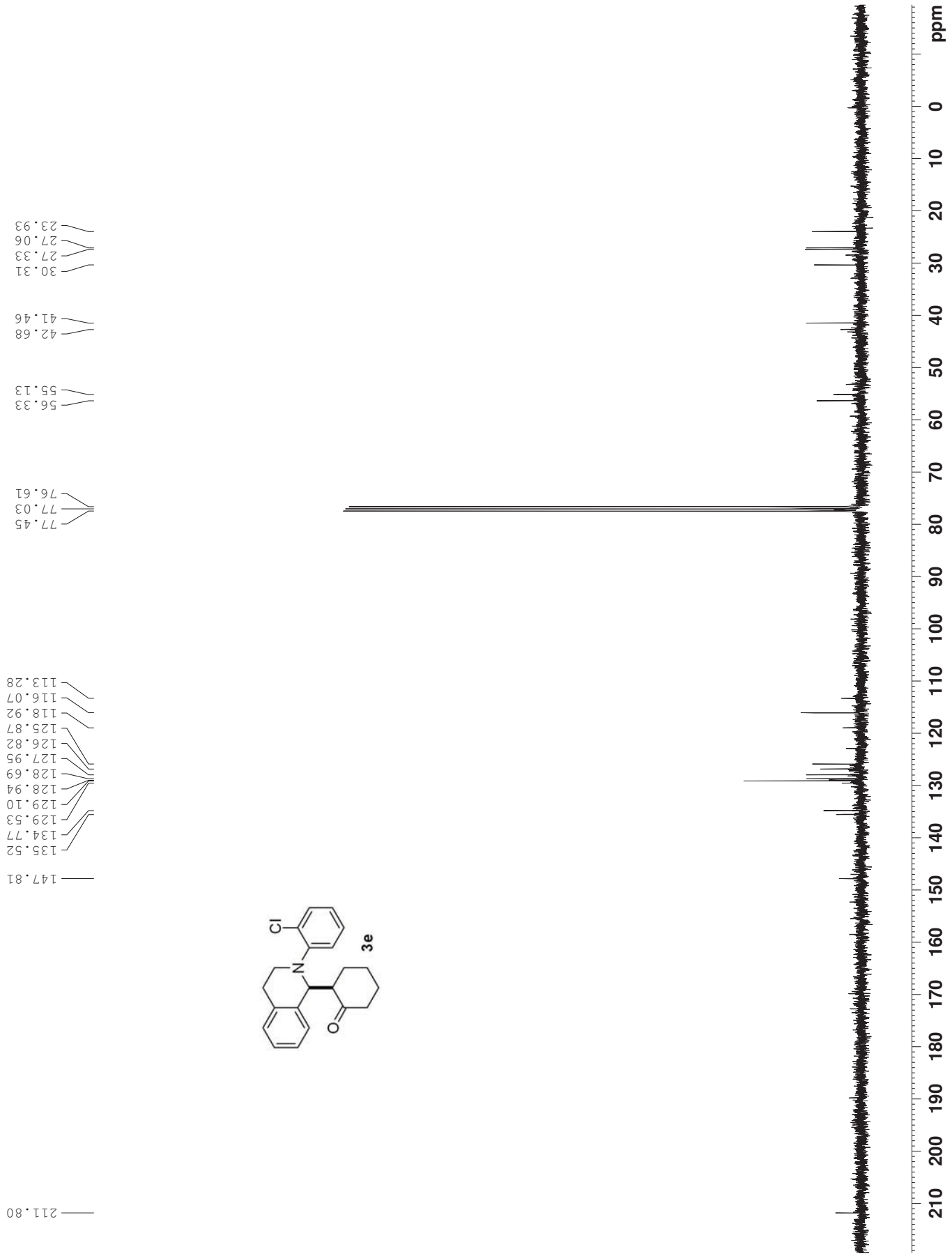
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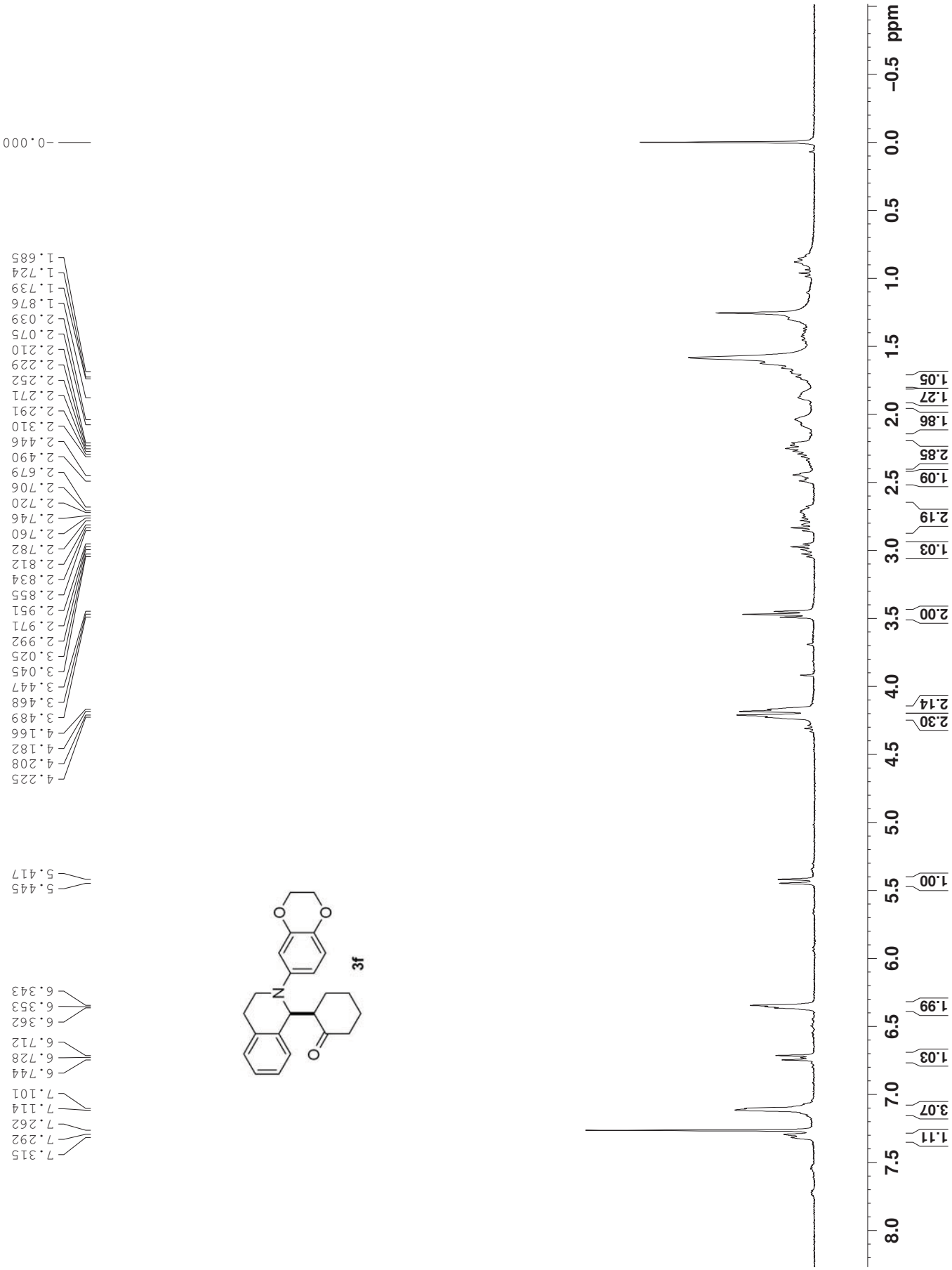
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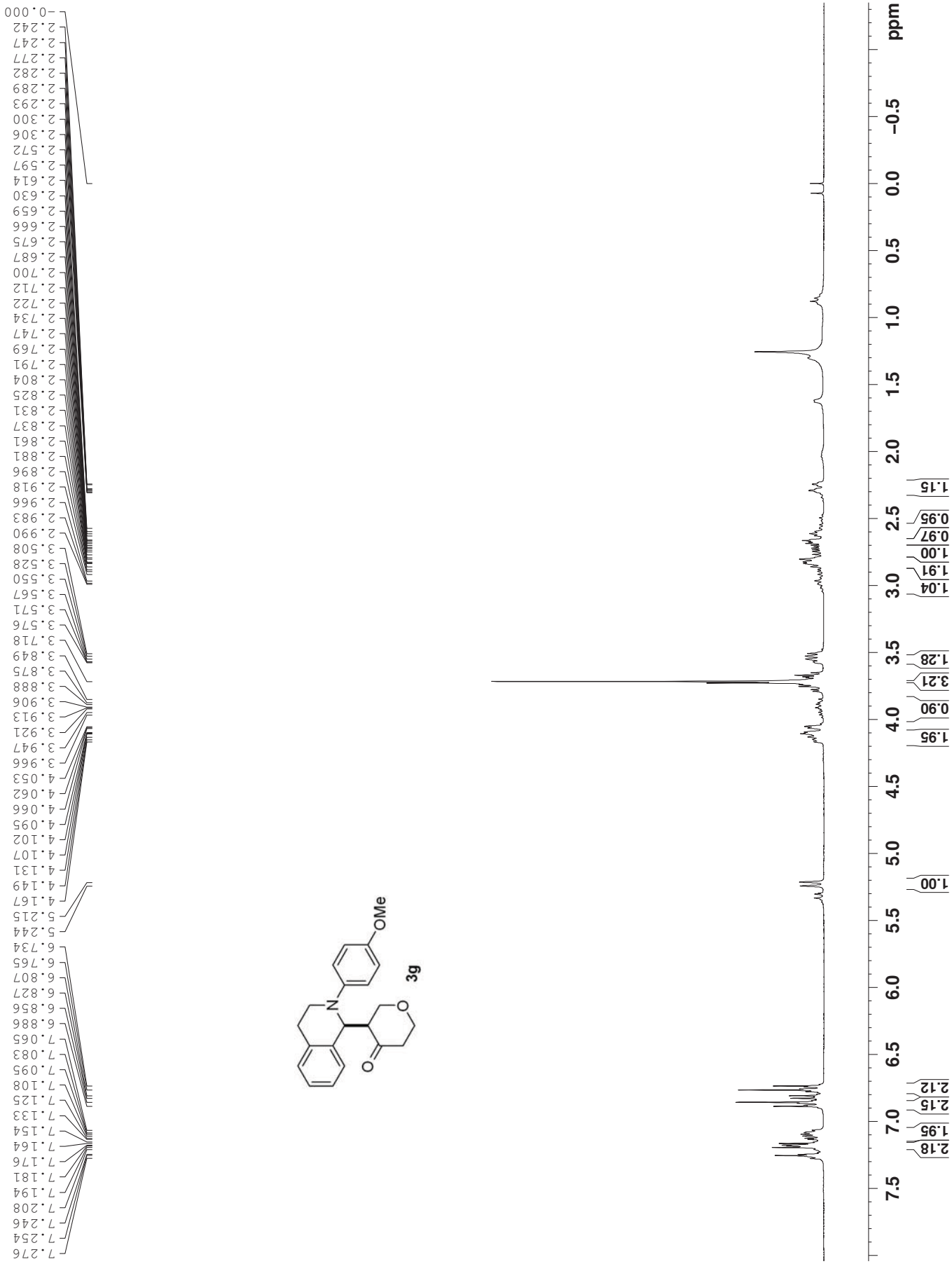

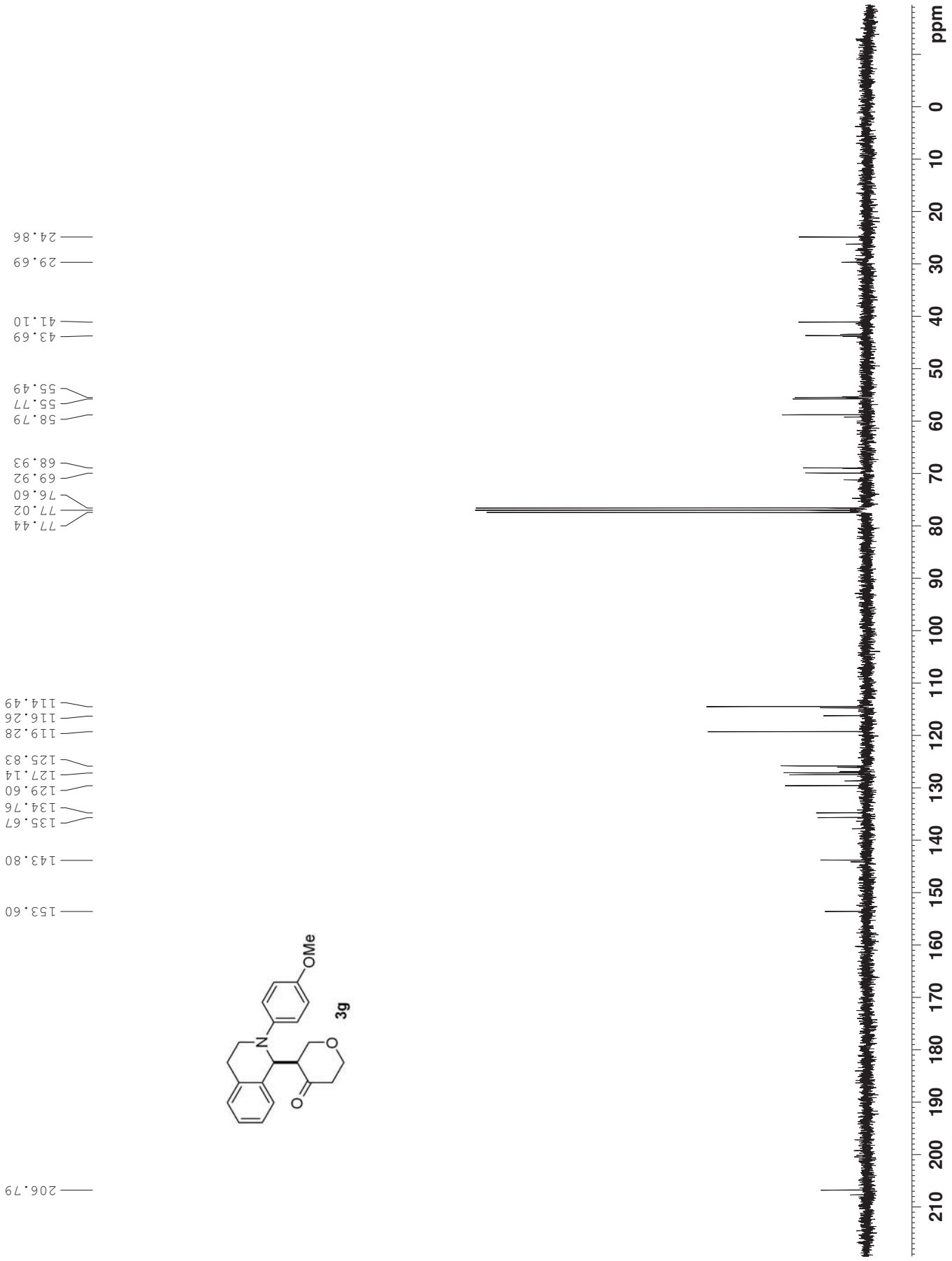
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O
O
ppm
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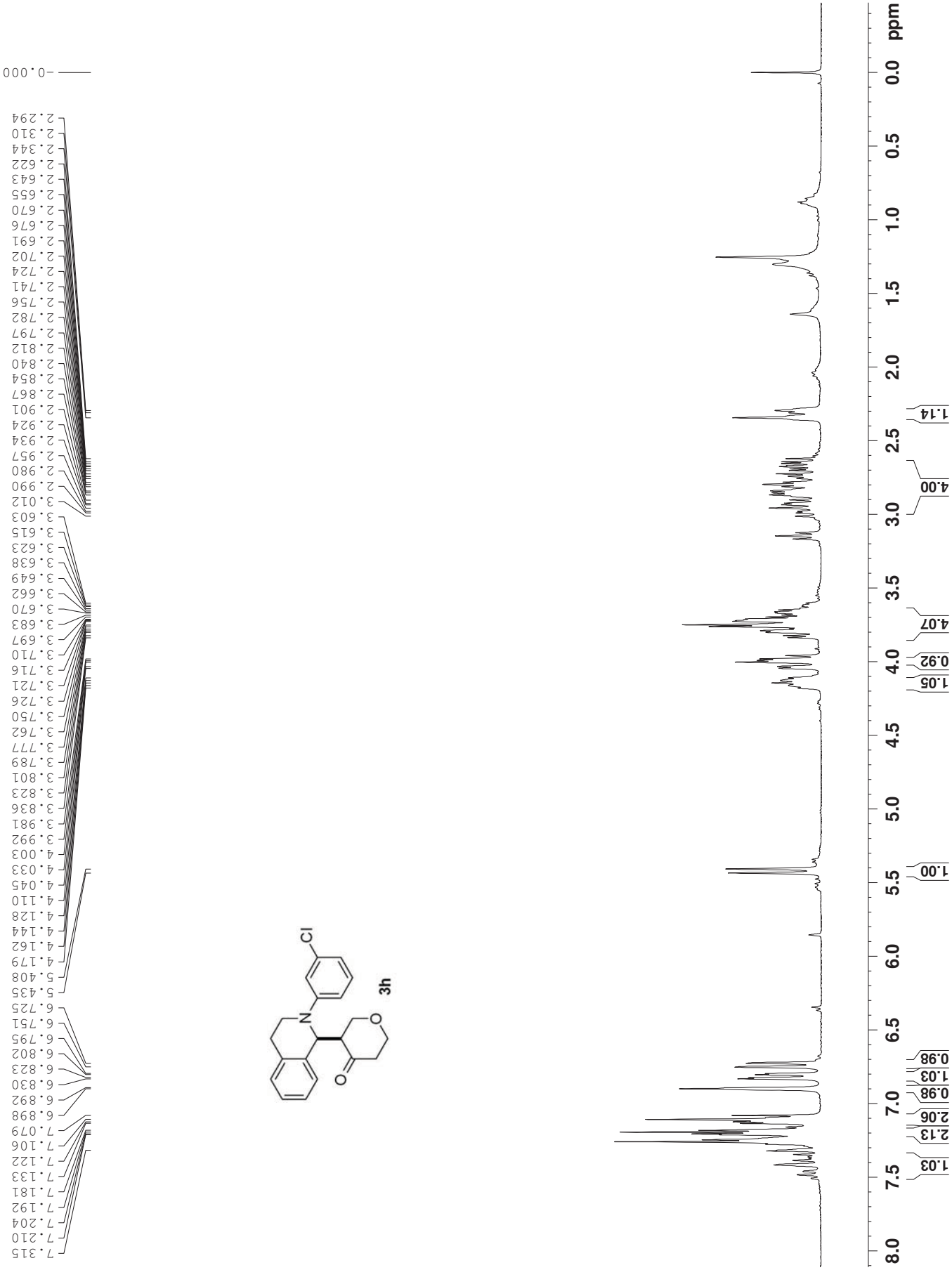

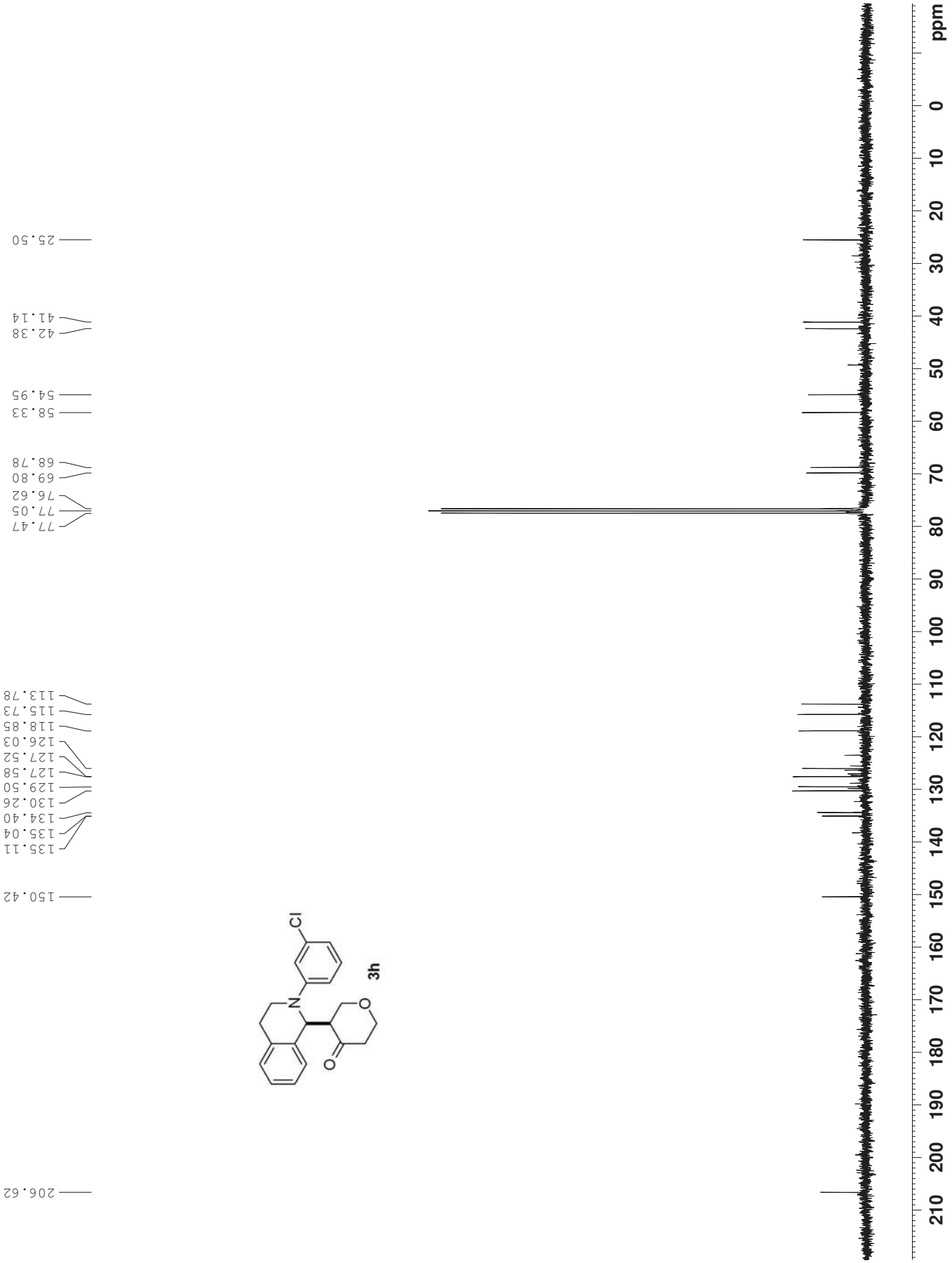
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O
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ppm
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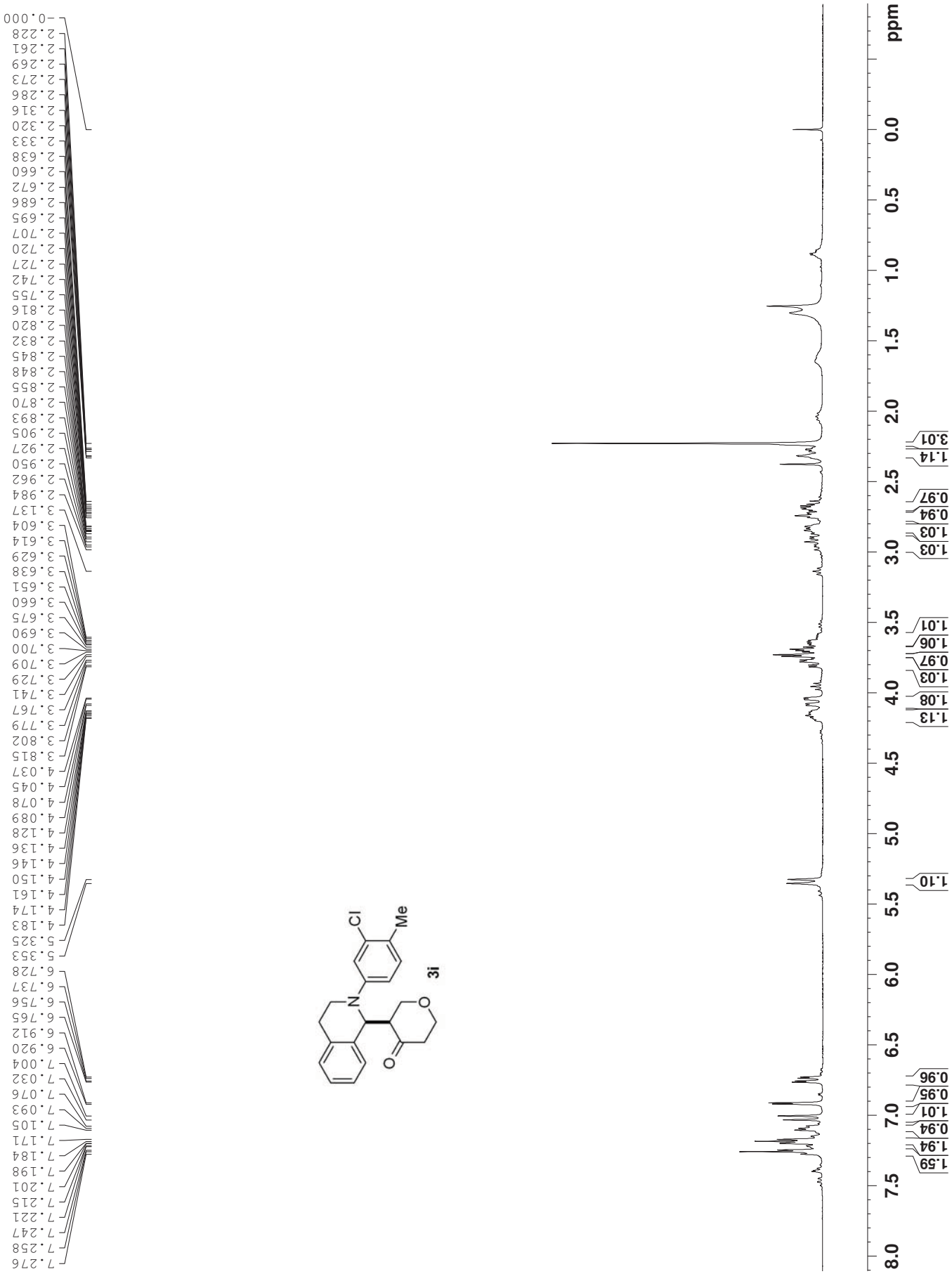

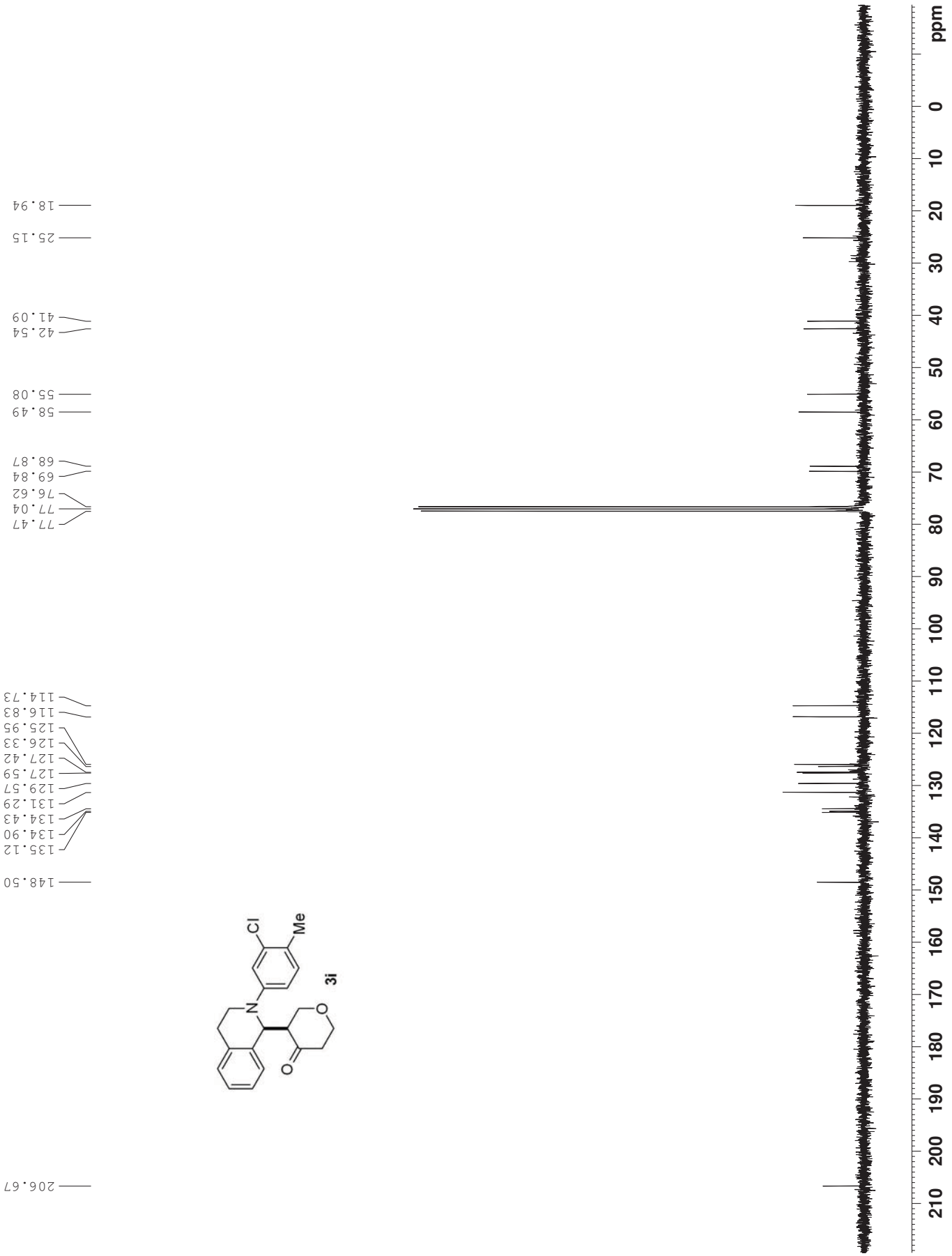

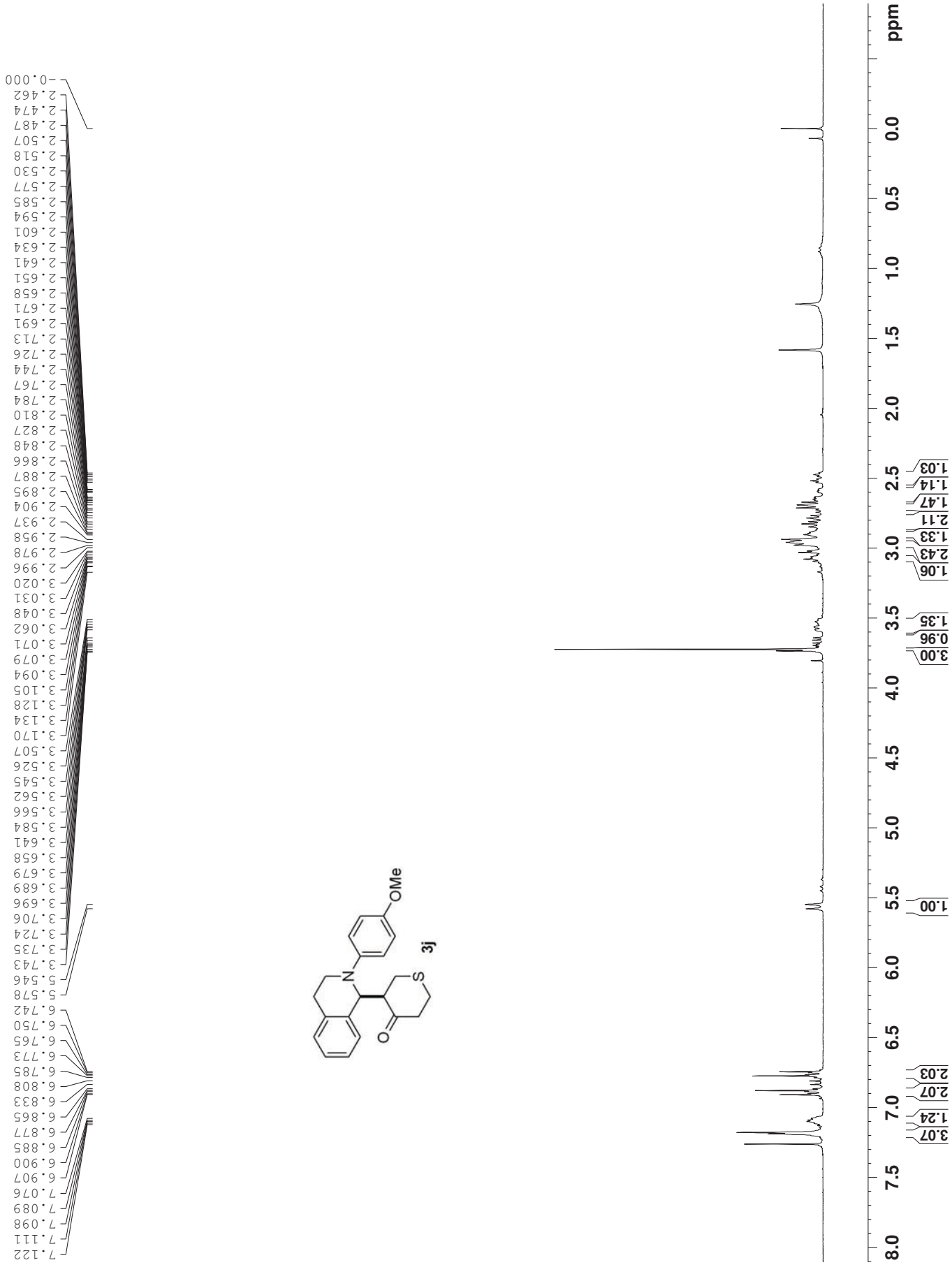

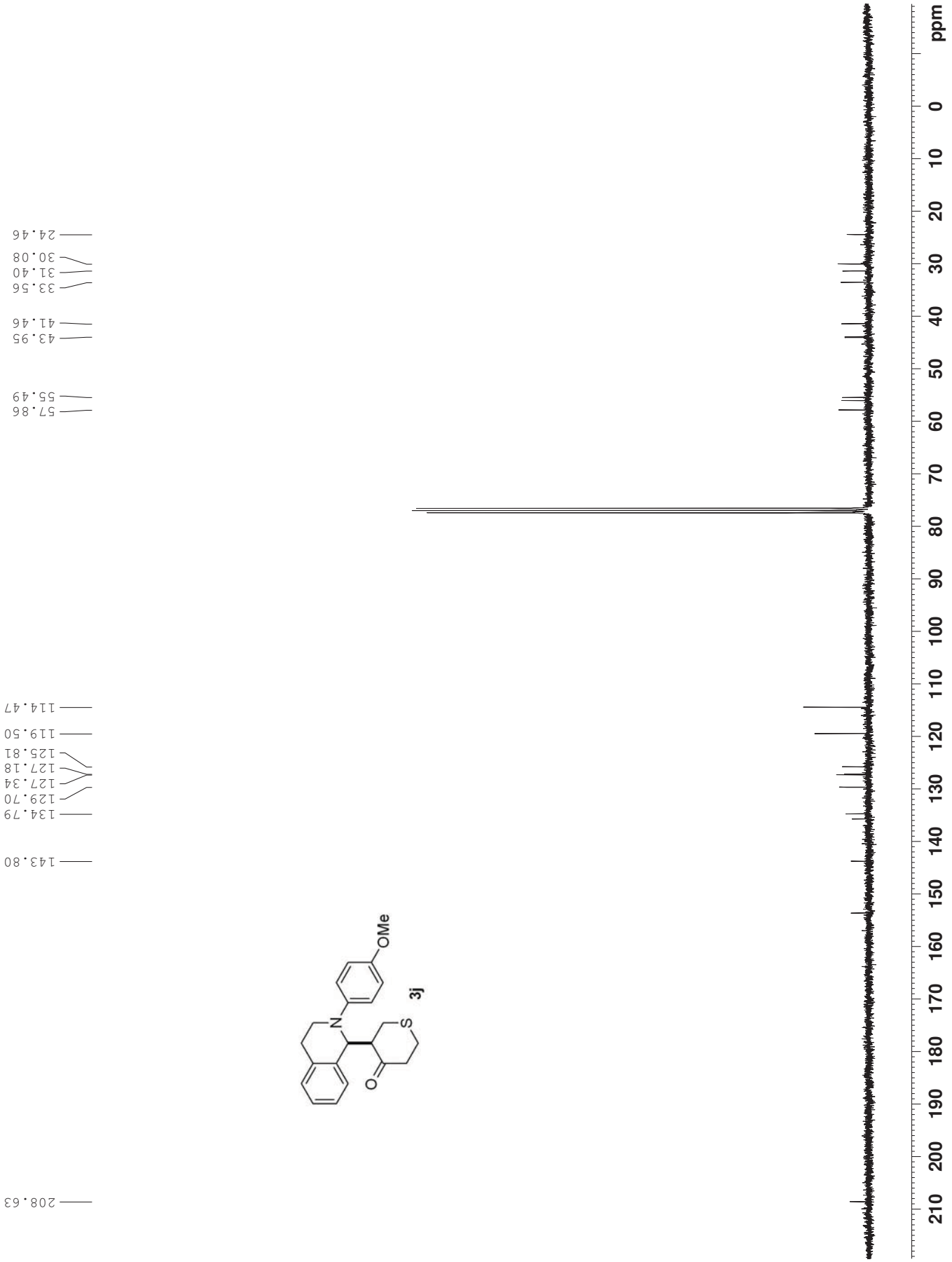
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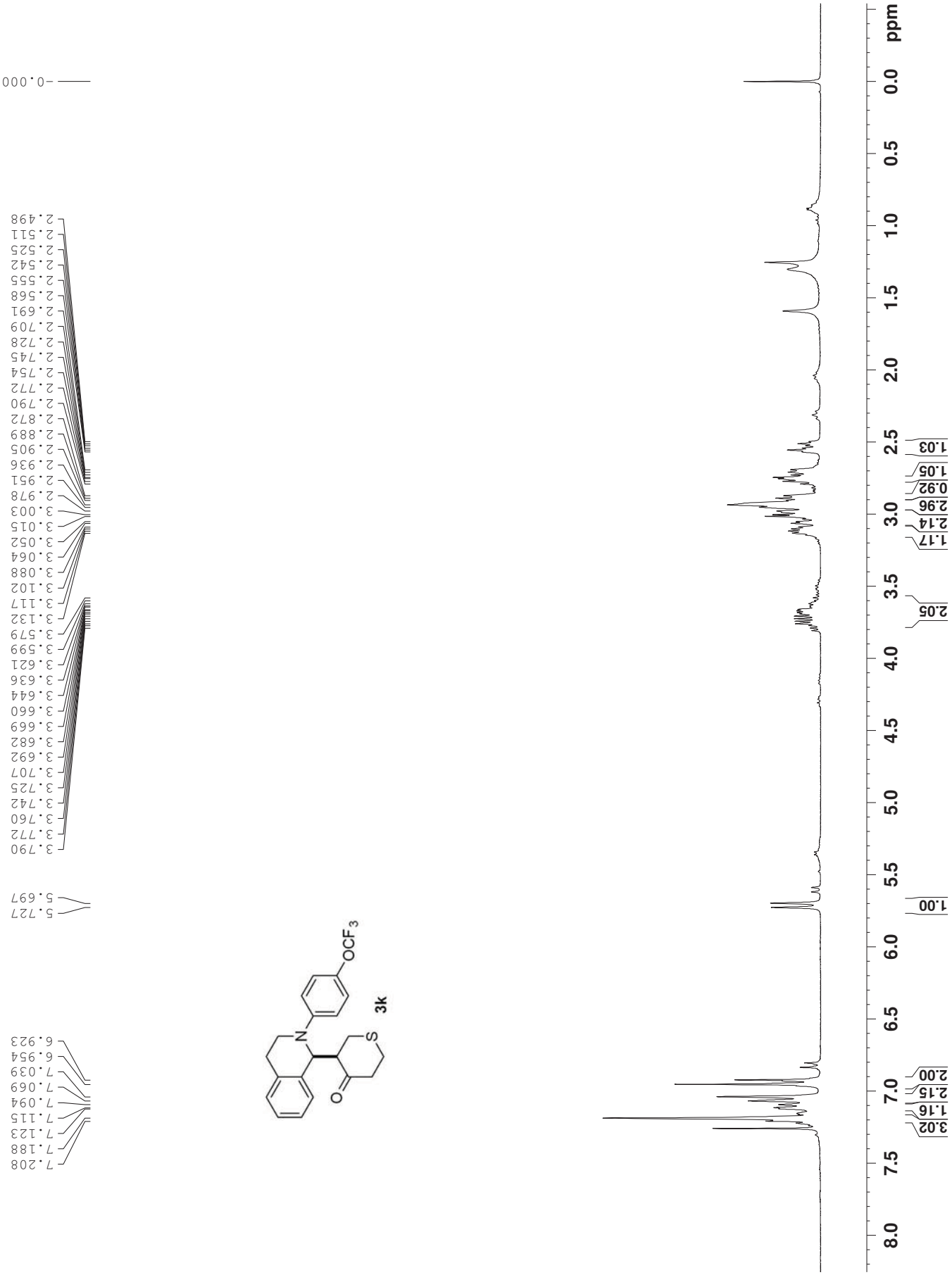
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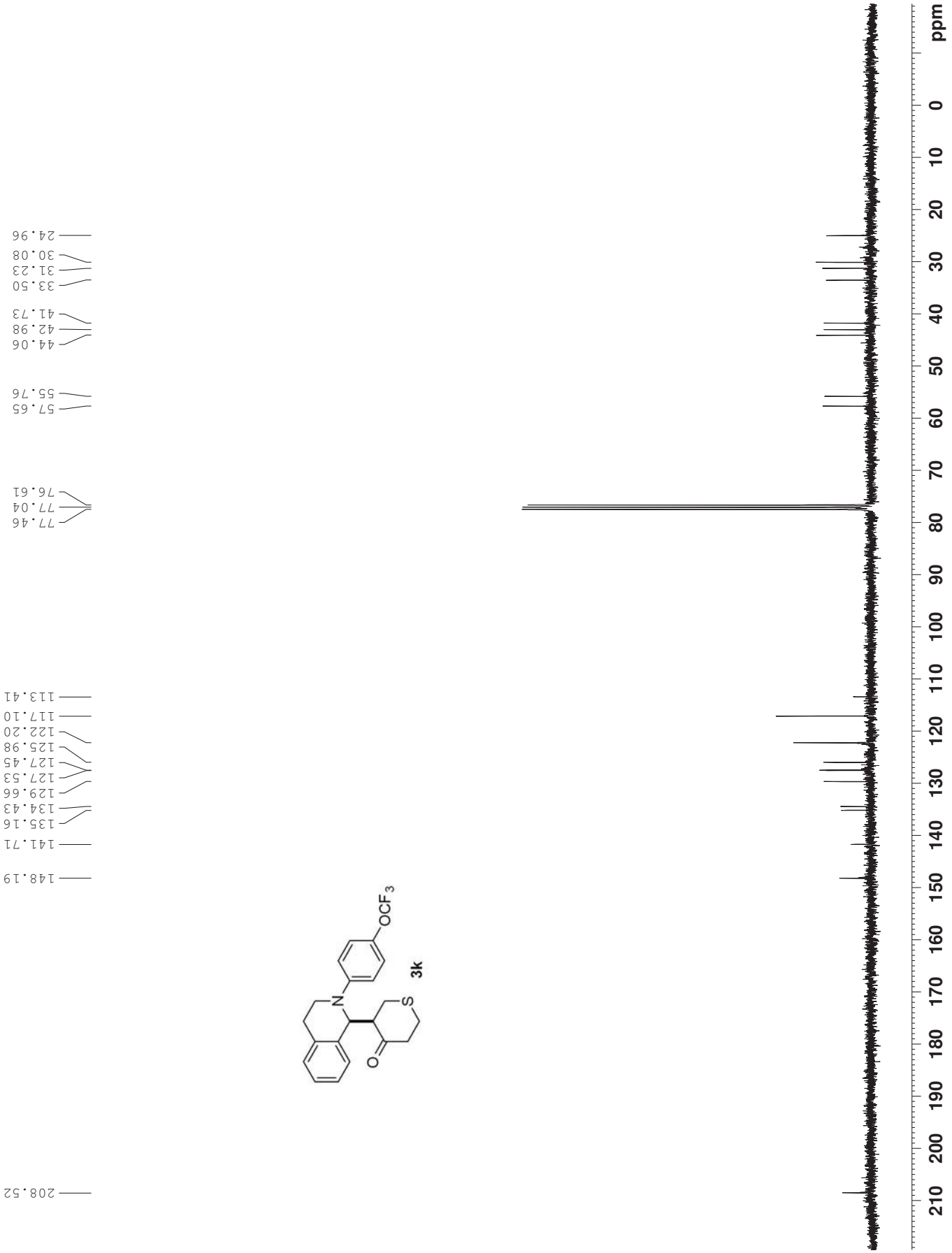
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S
O
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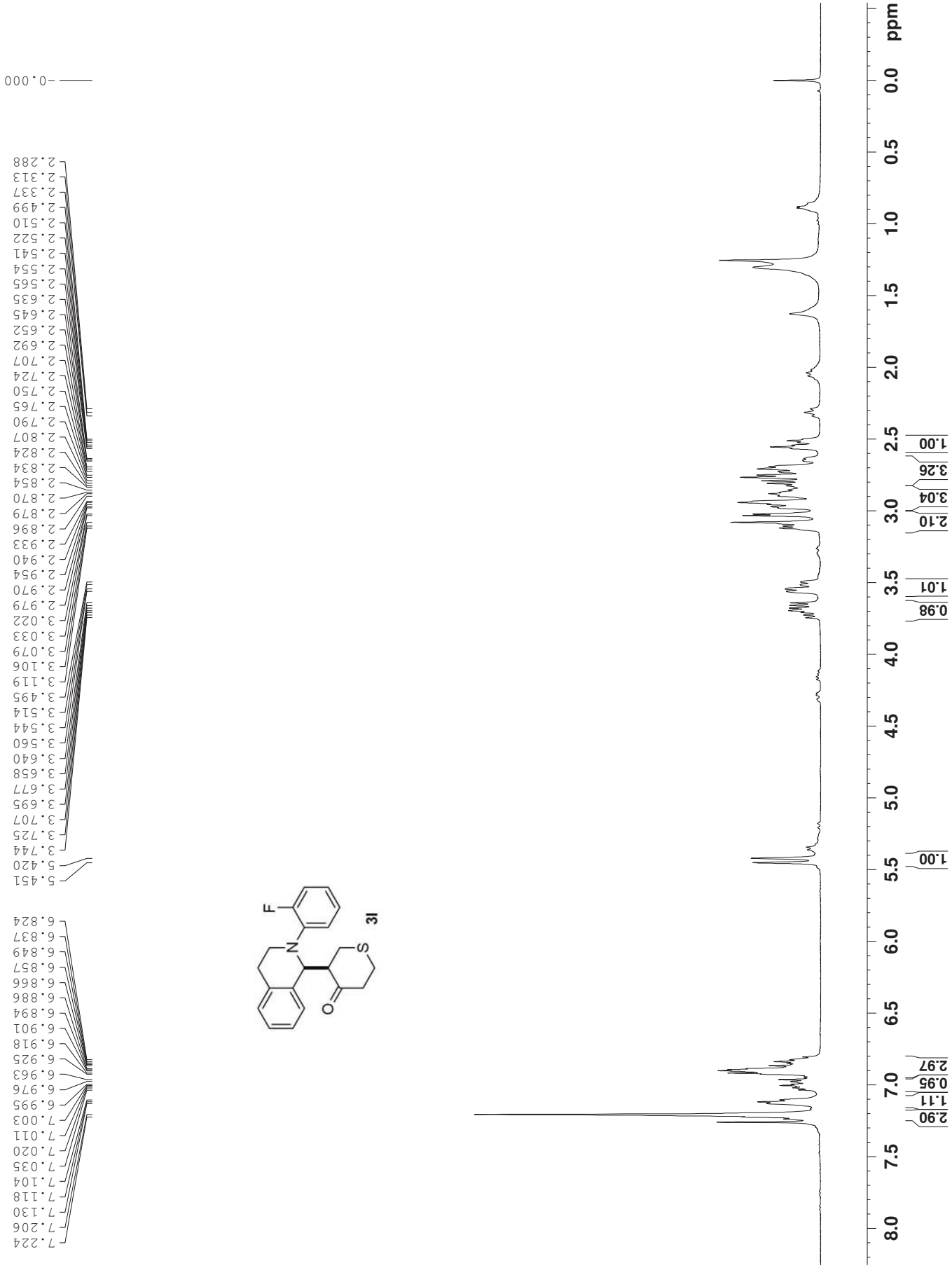

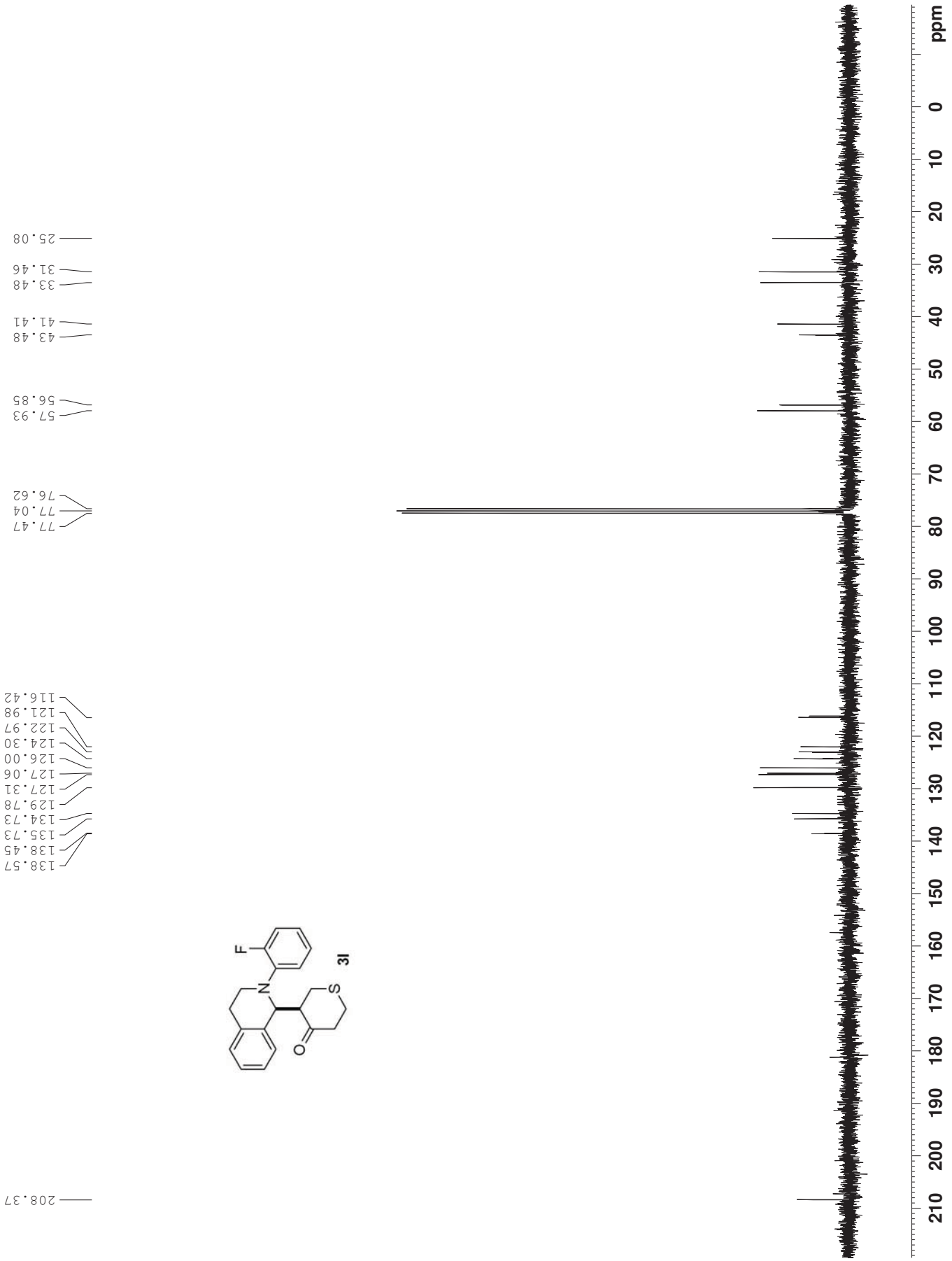
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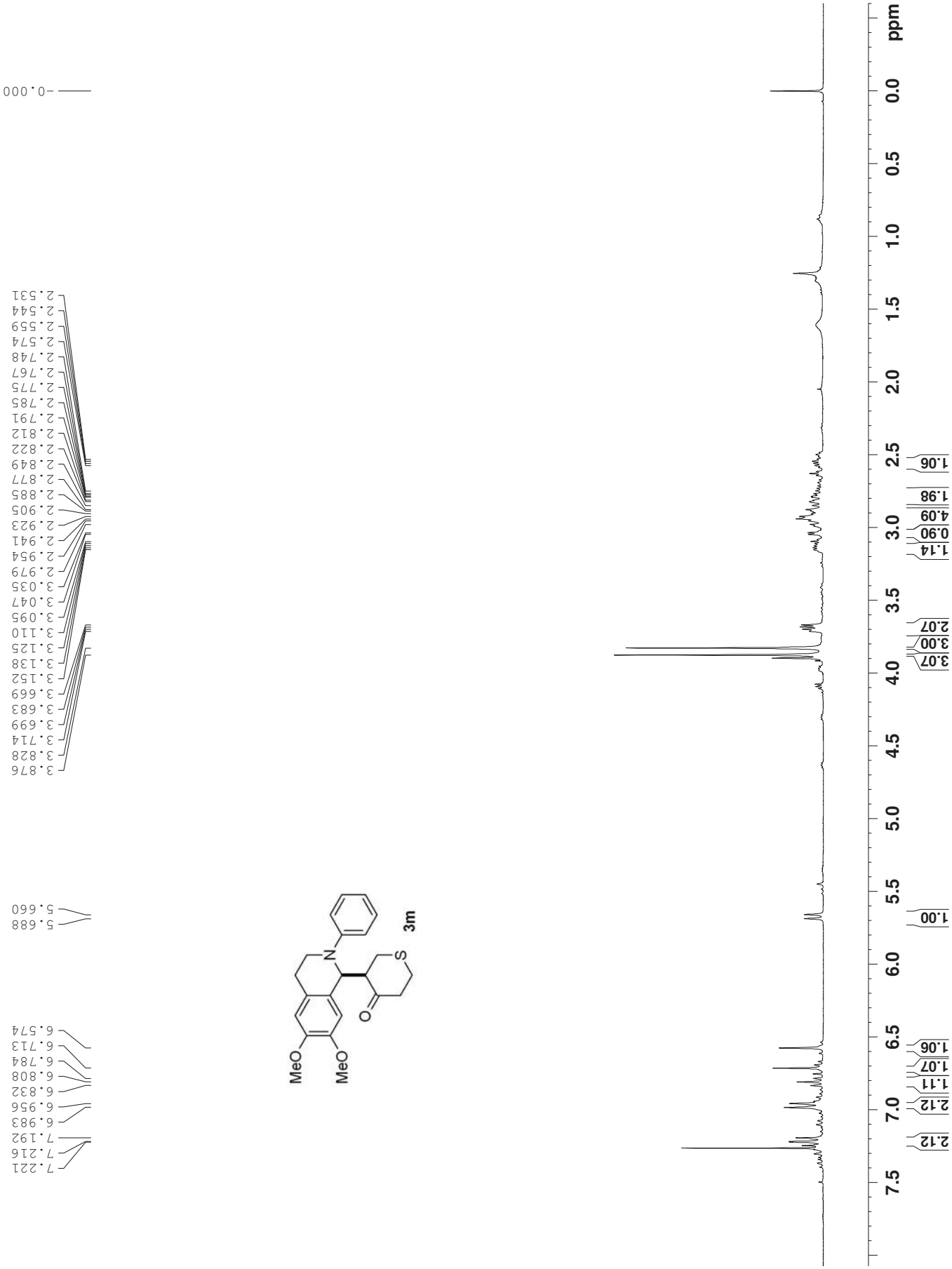
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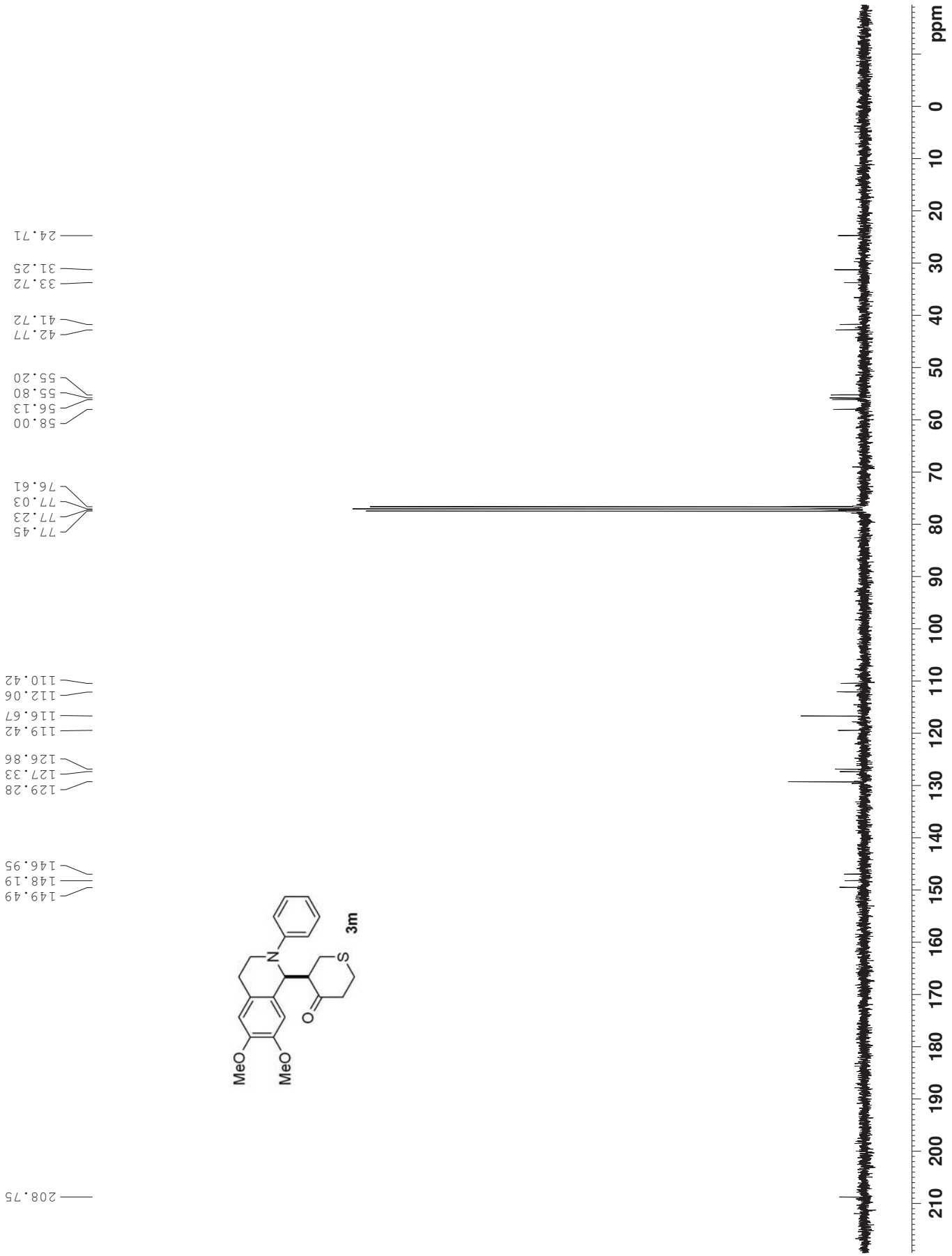
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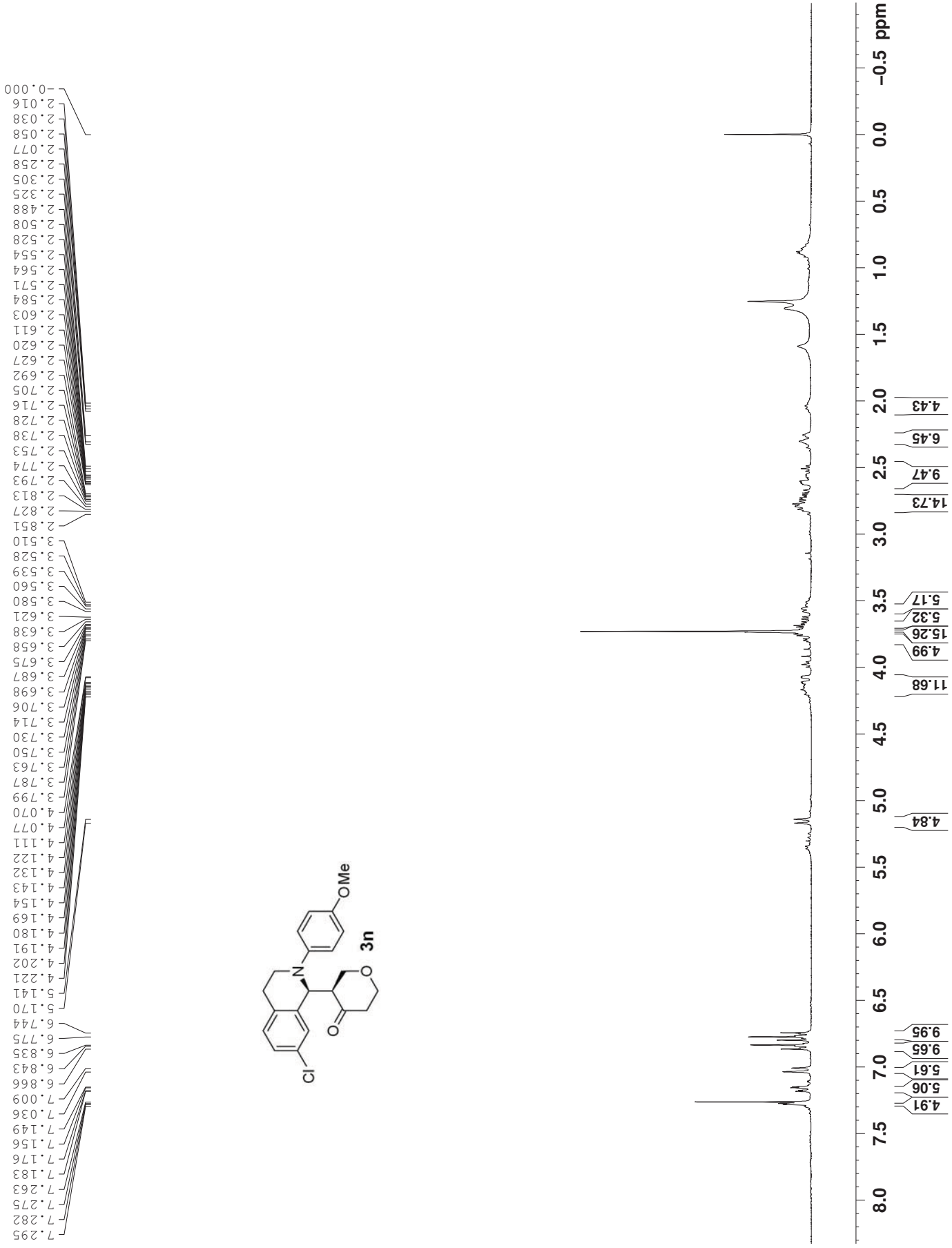

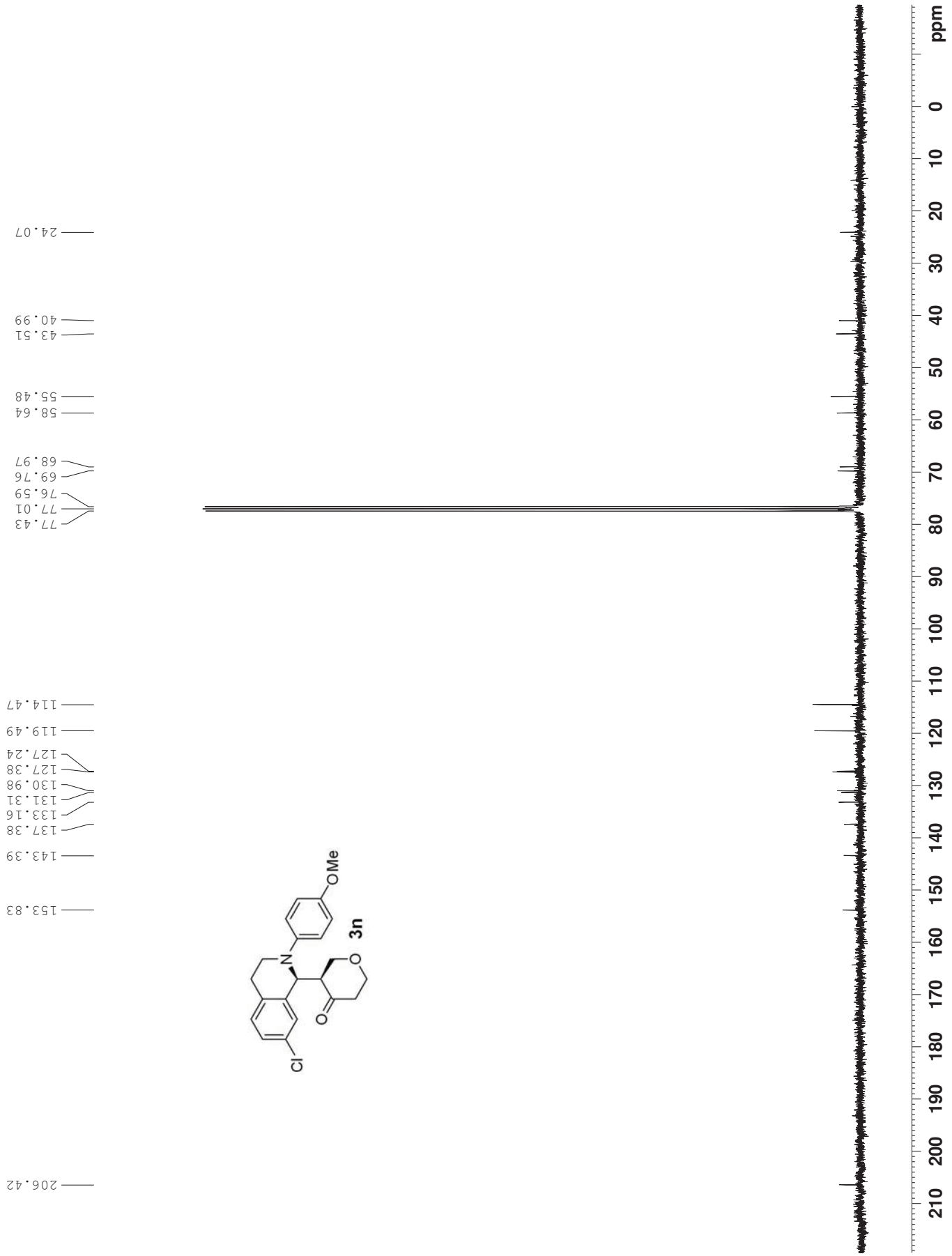
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Cl
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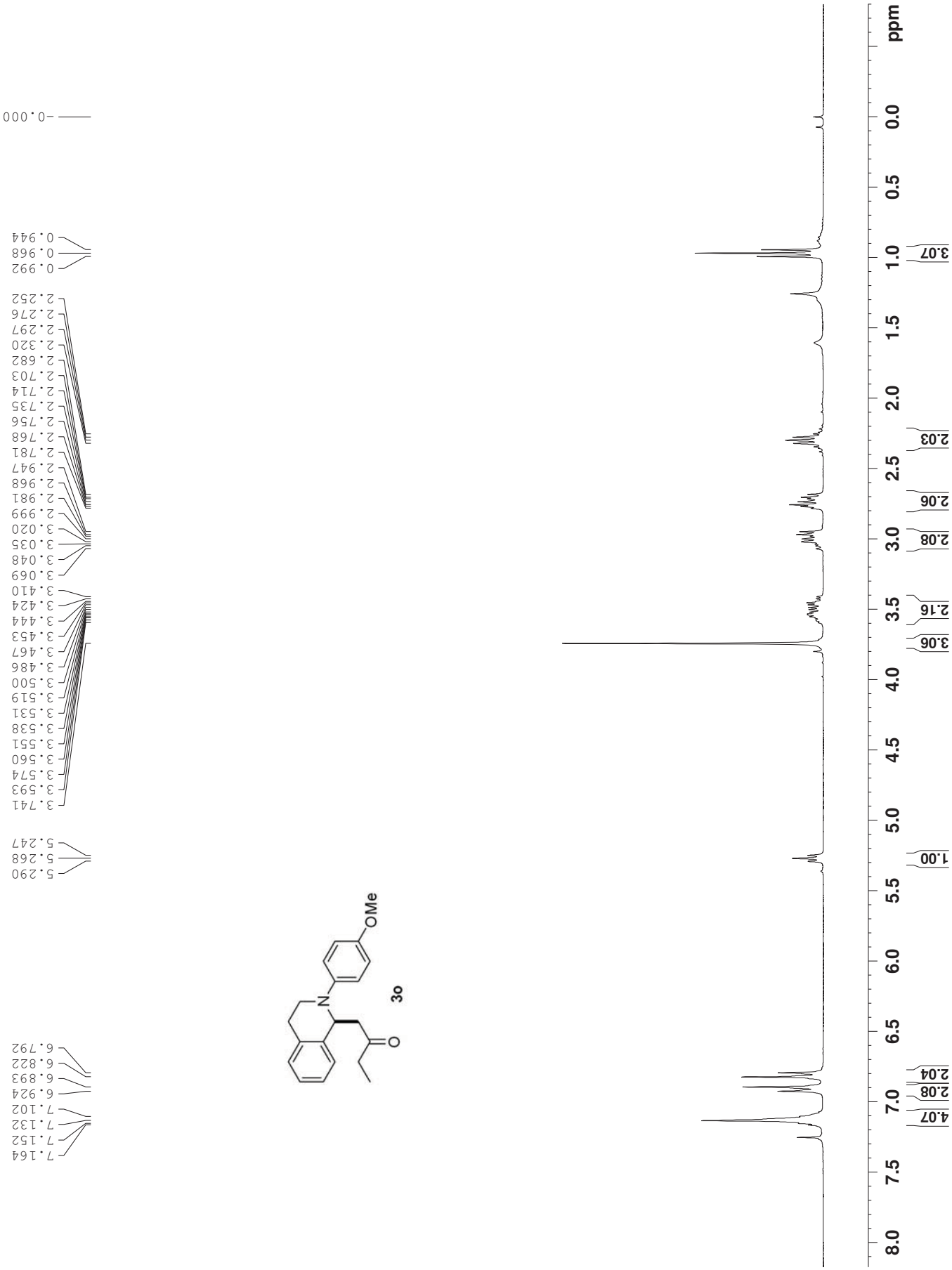
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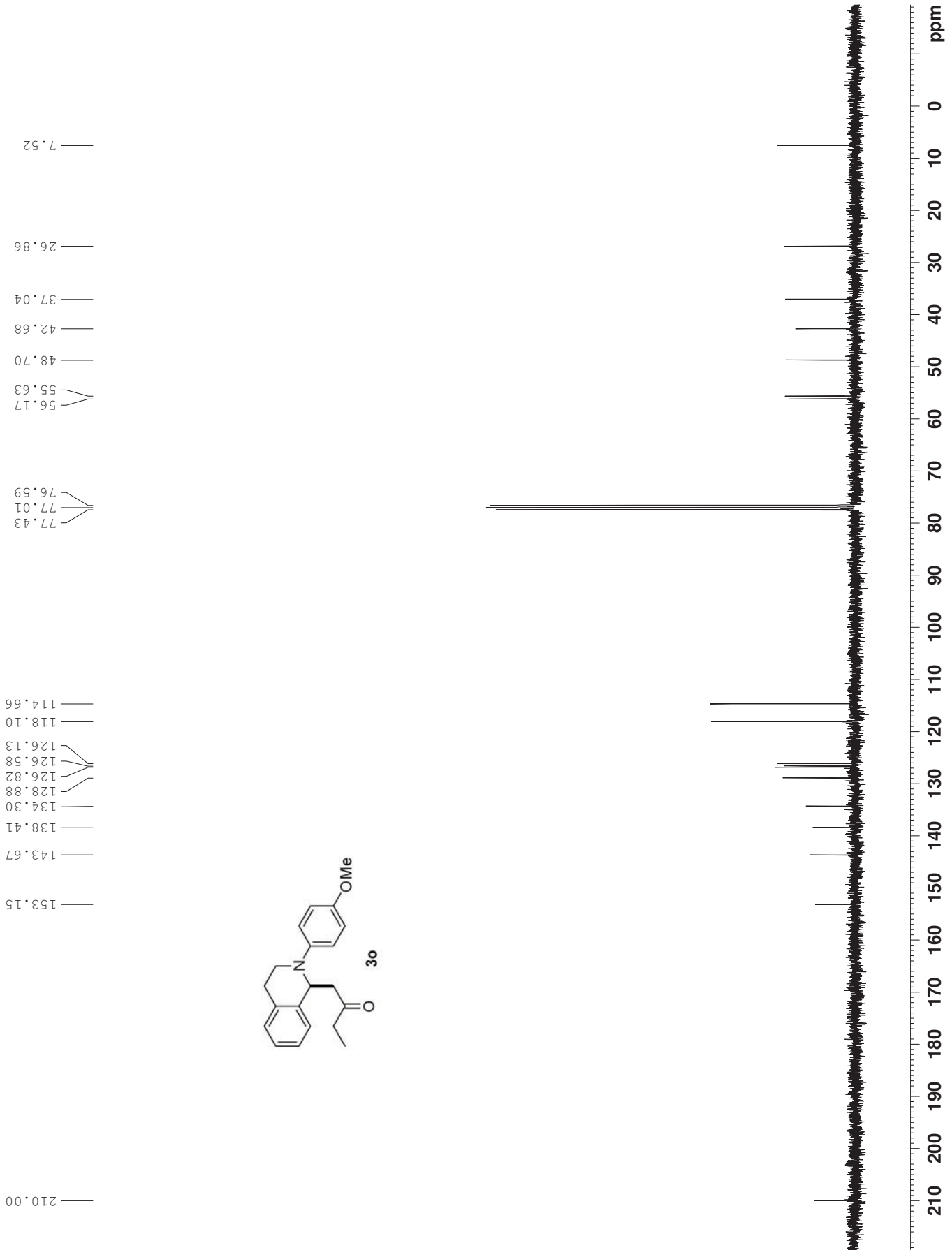
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