Formal [4+2] Cycloaddition of Imines with Alkoxyisocoumarins

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Supporting Information

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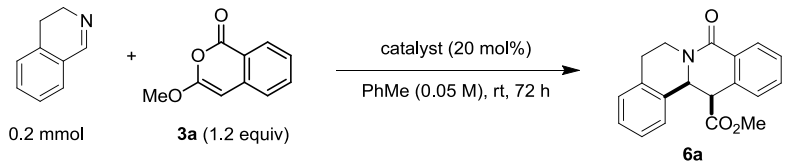
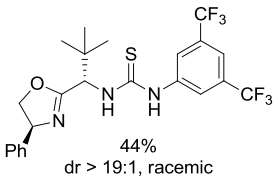
I. General information

Reagents and solvents were purchased from commercial sources and were purified by distillation or recrystallization prior to use. Purification of reaction products was carried out by flash column chromatography using EM Reagent silica gel 60 (230–400 mesh). All reactions were run under a nitrogen atmosphere unless stated otherwise. Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60 F_{254} plates. Visualization was accomplished with UV light, and potassium permanganate, Dragendorff-Munier and anisaldehyde stains, followed by heating. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on an ATI Mattson Genesis Series FT-Infrared spectrophotometer. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were recorded on a Varian VNMRS-500 MHz instrument and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br = broad, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, ddddd = doublet of doublet of doublet of doublet of doublets, m = multiplet, comp = complex; and coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C-NMR) were recorded on a Varian VNMRS-500 MHz instrument and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.16 ppm). Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer or on a Finnigan 2001 Fourier Transform Ion Cyclotron Resonance Mass Spectrometer. HPLC analysis was carried out on an Agilent 1100 series instrument with auto sampler and multiple wavelength detectors. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Jasco P–2000 polarimeter at 589 nm and at 20 °C. Racemic products **5a**–**5d** were prepared using racemic **2a**. Racemic products **6a**–**6d** were prepared using catalytic 1,3-bis(3,5-bis(trifluoromethyl)phenyl)thiourea.[1] Compound **3a**,[2] homophthalic anhydride **1**,[3] 3,4-dihydroisoquinoline,[4] 6,7-dimethoxy-3,4-dihydroisoquinoline,[5] 6-chloro-3,4-dihydroisoquinoline,[6] 1-methyl-3,4-dihydroisoquinoline,[7] 6-methoxy-3,4-dihydroisoquinoline,[8] and imine precursors[9] were prepared according to previously published procedures. Catalysts **2a**[10] and **2b**[11] were prepared according to previously reported procedures.

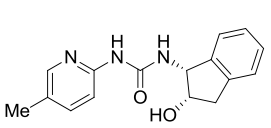
II. Reaction optimization

Evaluation of catalysts.[a]

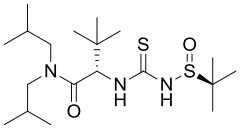




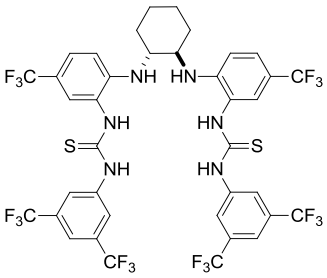
44%
dr > 19:1, racemic



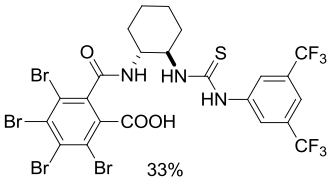
49%
dr > 19:1, racemic



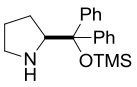
46%
dr > 19:1, 4% ee



trace product



33%
dr > 19:1, racemic



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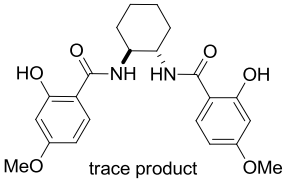

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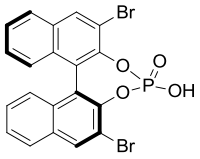

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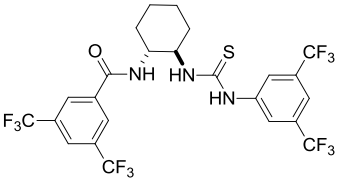

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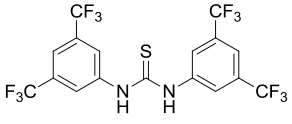
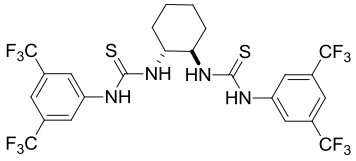
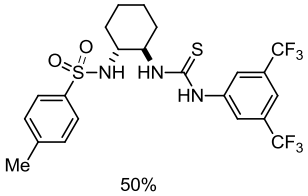


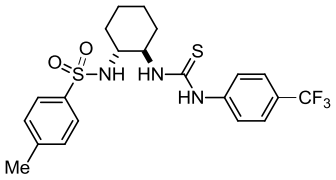
74%
dr > 19:1, racemic



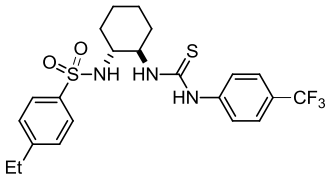
66%
dr > 19:1, 8% ee



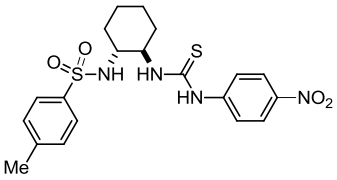
50%
dr > 19:1, 52% ee



24 h
29%, 11% *ee*
>19:1 dr



24 h
trace product



24 h
33%, 14% *ee*
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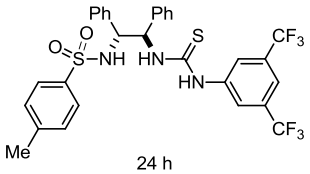
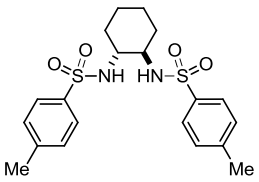
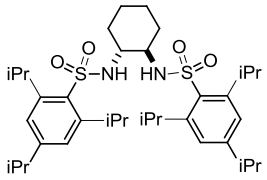


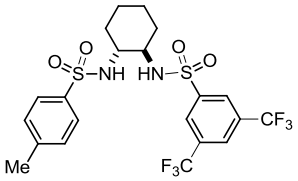
24 h
10%, 21% *ee*
>19:1 dr



32%, racemic
>19:1 dr



28%, racemic
>19:1 dr



24 h
5%, 18% *ee*
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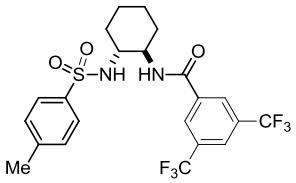
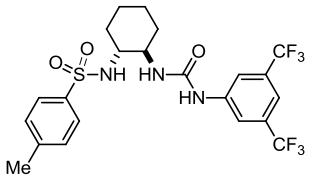
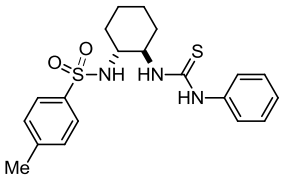


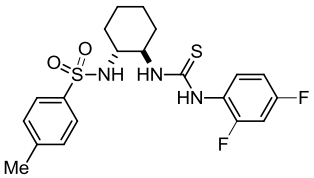
24 h
5%, 9% *ee*
>19:1 dr



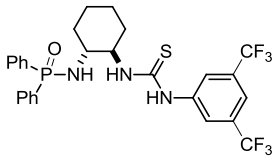
24 h
40%, 30% *ee*
>19:1 dr



24 h
21%, 12% *ee*
>19:1 dr



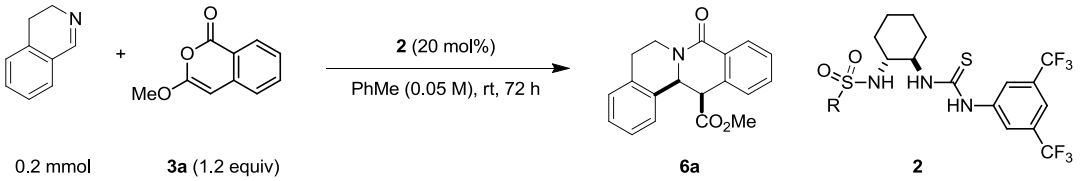
24 h
17%, 10% *ee*
>19:1 dr

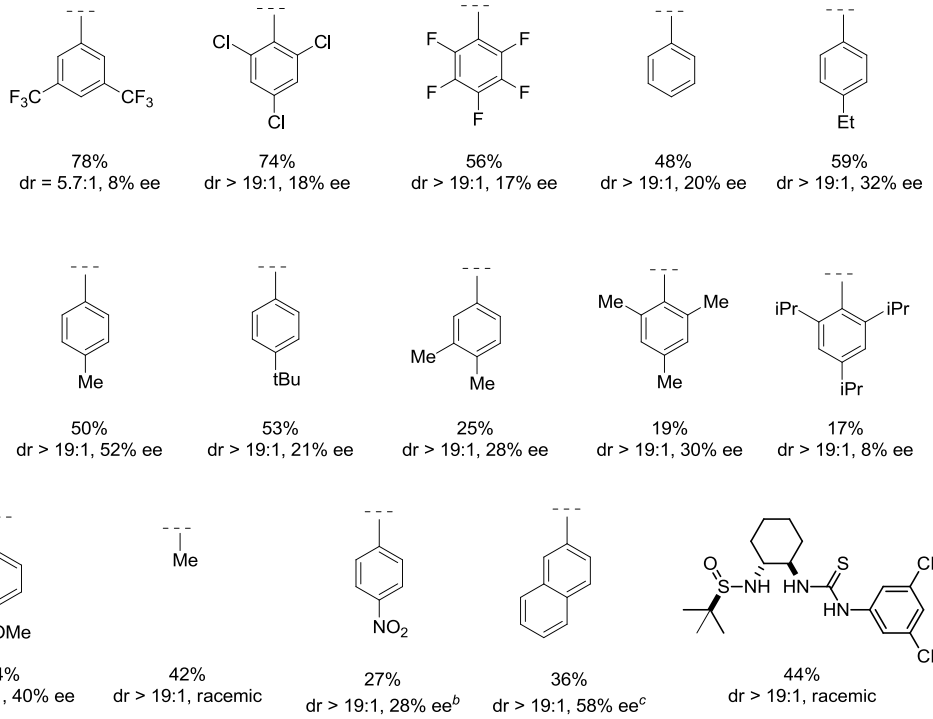


24 h,
trace product

[a] Yields are those of chromatographically purified compounds. The ee values were determined by HPLC analysis.

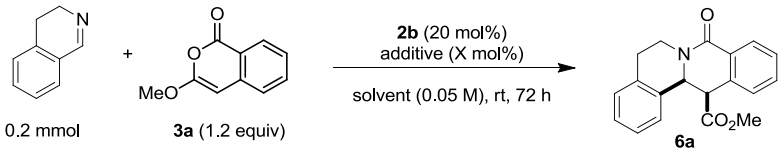
Evaluation of sulfonamide catalysts.[a]





[a] Yields are those of chromatographically purified compounds. The ee values were determined by HPLC analysis. [b] 30 h with $PhCF_3$ as the solvent. [c] 26 h with $PhCF_3$ as the solvent

Evaluation of additives and solvents.[a]

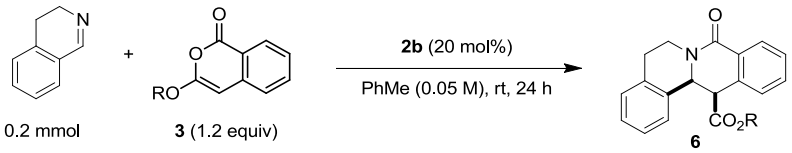


0.2 mmol **3a** (1.2 equiv) **6a**

entry	additive (mol%)	solvent	yield (%)	dr	ee (%)
1	0	PhMe	50	>19:1 dr	52
2[a]	0	$PhCF_3$	47	>19:1 dr	56
3	0	DCM	70	>19:1 dr	49
4	0	$CHCl_3$	61	>19:1 dr	46
5	0	PhMe:DCM (3:1)	68	>19:1 dr	52
6	0	PhMe:DCM (9:1)	51	>19:1 dr	31
7	Acetic Acid (20)	PhMe:DCM (3:1)	50	>19:1 dr	30
8	Acetic Acid (50)	PhMe:DCM (3:1)	15	>19:1 dr	52
9	Benzoic Acid (20)	PhMe:DCM (3:1)	15	>19:1 dr	35
10	Benzoic Acid (50)	PhMe:DCM (3:1)	28	>19:1 dr	32
11	Pyridine (20)	PhMe:DCM (3:1)	80	>19:1 dr	32
12[b]	Pyridine (10)	PhMe	39	>19:1 dr	50
13	Pyridine (20)	PhMe	65	>19:1 dr	50
14	Pyridine (25)	PhMe	76	>19:1 dr	50
15[b]	Pyridine (50)	PhMe	34	>19:1 dr	50
16	Imidazole (20)	PhMe	65	>19:1 dr	44
17	DABCO (20)	PhMe	49	>19:1 dr	30
18	2,6-Lutidine (20)	PhMe	71	>19:1 dr	50
19[b]	*N*,*N*-dimethylaniline (20)	PhMe	64	>19:1 dr	49
20[b]	CuCl (20)	PhMe	13	>19:1 dr	7
21[b]	H_2O (100)	PhMe	0	-	-

[a] Yields are those of chromatographically purified compounds. The ee values were determined by HPLC analysis. [b] Reaction run for 24 h.

Evaluation of other alkoxyisocoumarins. [a]

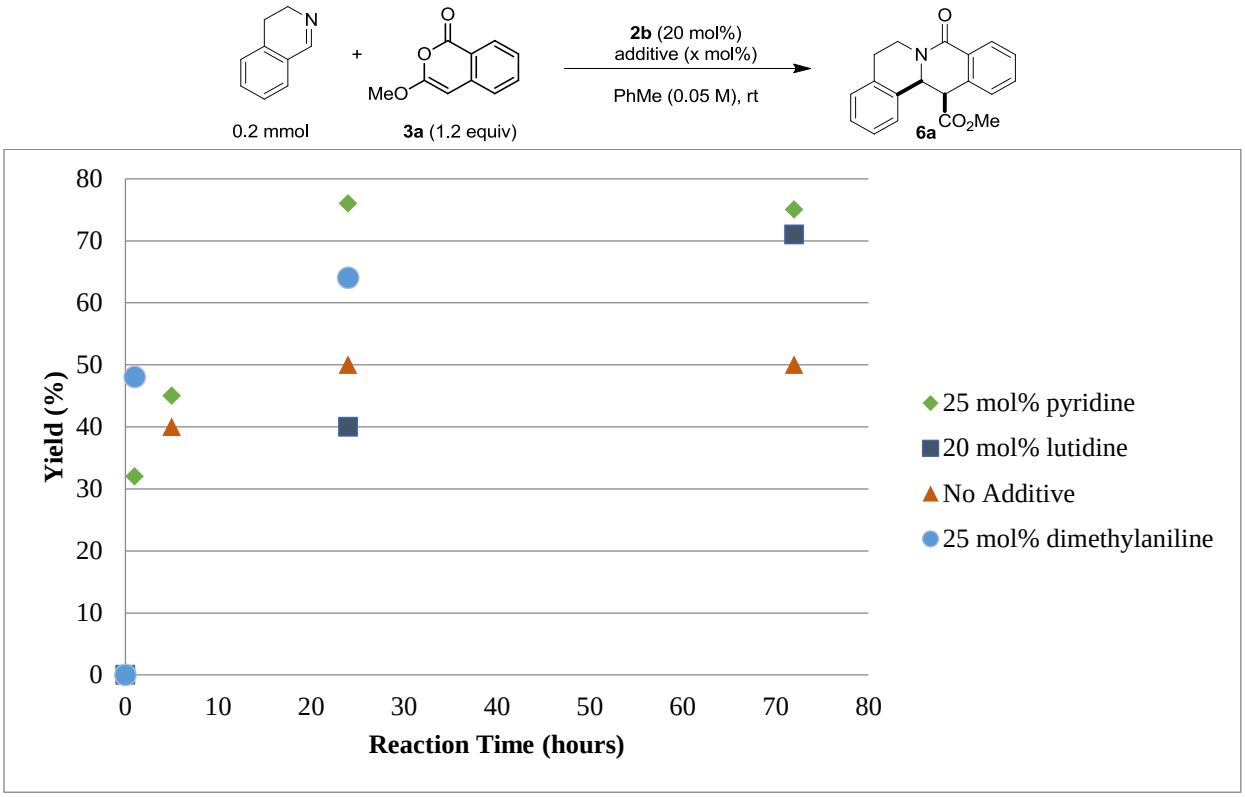


0.2 mmol **3** (1.2 equiv) **6**

entry	R	yield (%)	dr	ee (%)
1	Me	50	>19:1	52
2	Et	47	>19:1	65
3	*n*-Pr	24	>19:1	53
4	*i*-Pr	7	>19:1	51
5	*n*-Bu	39	>19:1	57
6	Bn	0	-	-
7	CH_2CH_2Cl	67	>19:1	52
8	CH_2CF_3	94	>19:1	18
9	$CH_2CH_2OCH_3$	0	-	-

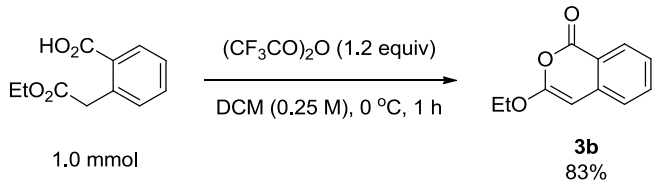
[a] Yields are those of chromatographically purified compounds. The ee values were determined by HPLC analysis.

Evaluation of basic additives on reaction conversion.



III. Synthesis of starting materials.

3-ethoxy-1H-isochromen-1-one (EIC) (3b)



To a solution of 2-(2-ethoxy-2-oxoethyl)benzoic acid[12] (200 mg, 1.0 mmol, 1 equiv) in DCM (3.3 mL, 0.25 M) at 0 °C was added trifluoroacetic anhydride (0.16 mL, 1.15 mmol, 1.2 equiv) in 0.5 mL DCM dropwise. The reaction mixture was stirred at 0 °C for 1 h then concentrated. The crude residue was dissolved in ethyl acetate and washed with water, sat. sodium bicarbonate, brine then dried over sodium sulfate, concentrated to afford **3b** in 83% yield; R_f = 0.71 (EtOAc/hexanes 3:7 v/v); mp = 63–65 °C; IR (KBr) 3053, 2987, 2685, 2306, 1741, 1641, 1564, 1484, 1421, 1363, 1312, 1261, 1218, 1186, 1037, 1008, 896, 873, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.33–8.08 (m, 1H), 7.68–7.52 (m, 1H), 7.35–7.16 (comp, 2H), 5.56 (s, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 1.46 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.41, 158.90, 140.21, 135.15, 129.95, 125.49, 124.67, 117.59, 80.03, 65.31, 14.46; *m/z* (ESI–MS) 191.3 $[M+H]^+$.

IV. Synthesis and characterization of products

General Procedure A for Lewis Acid Promoted Synthesis of Alkyl Ester:
An oven-dried vial was charged with alkoxyisocoumarin (0.3 mmol, 1 equiv) and imine (0.3 mmol, 1 equiv), powdered 4 A molecular sieves (50 mg) and acetonitrile (0.75 mL, 0.4 M). The reaction was charged with boron trifluoride diethyl etherate (46 μL, 0.33 mmol, 1.1 equiv). The reaction mixture was stirred at rt or 45 °C until the imine could no longer be detected by TLC analysis. The reaction mixture was quenched with sat. sodium bicarbonate (1 mL) and the aqueous layer extracted with diethyl ether. The combined organic layers were dried over sodium sulfate and concentrated.

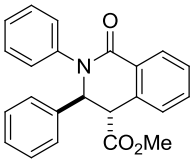
The crude residue was dissolved in methanol (0.5 mL). Sodium methoxide was added (360 μL, 25% wt. in MeOH, 1.59 mmol, 5.3 equiv) and the reaction mixture stirred for 30 minutes at room temperature. Water (2 mL) was added and the reaction mixture extracted with diethyl ether. The combined organic layers were washed with saturated sodium chloride, dried over sodium sulfate, concentrated and purified by flash column chromatography on silica gel. The resulting product was dried under high vacuum.

General Procedure B for Asymmetric Cycloaddition to Form Methyl Ester:
An oven-dried vial was charged with homophthalic anhydride **1** (36 mg, 0.22 mmol, 1.1 equiv), catalyst **2a** (25 mg, 0.04 mmol, 0.2 equiv), powdered 4 Å molecular sieves (200 mg) and MTBE (8 mL, 0.025 M). The reaction mixture was cooled to –55 °C and then charged with the imine (0.2 mmol, 1 equiv). The reaction mixture was stirred at –55 °C until the imine could no longer

be detected by TLC analysis, then MeOH (1 mL) and trimethylsilyldiazomethane (0.2 mL, 2.0 M in diethyl ether, 0.4 mmol, 2 equiv) was added and the reaction allowed to warm to room temperature. After one hour the reaction was quenched with 5 drops of glacial acetic acid. The reaction mixture was filtered through celite, concentrated and purified by flash column chromatography on silica gel. The resulting product was dried under high vacuum.

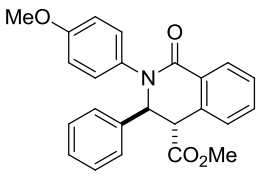
General Procedure C for Asymmetric Cycloaddition to Form Alkyl Ester:
An oven-dried vial was charged with alkoxyisocoumarin **3a** or **3b** (0.24 mmol, 1.2 equiv), catalyst **2b** (22 mg, 0.04 mmol, 0.2 equiv) and trifluorotoluene (4 mL, 0.05 M). The reaction mixture was cooled to 0 °C-and then charged with imine (0.2 mmol, 1 equiv) and pyridine (4 μL, 0.05 mmol, 0.25 equiv). The reaction mixture was stirred at 0 °C until the imine could no longer be detected by TLC analysis. The reaction was concentrated and purified by flash column chromatography in silica gel. The resulting product was dried under high vacuum.

(±)-**(3S,4S)-methyl 1-oxo-2,3-diphenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (4a):**



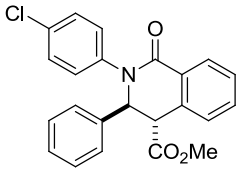
Following the general procedure A, **4a** was obtained as a white solid in 63% yield (68 mg, >19:1 dr); R_f = 0.30 (EtOAc/hexanes 3:7 v/v); mp = 150–153 °C; IR (KBr) 3026, 2947, 2871, 1749, 1655, 1619, 1478, 1464, 1402, 1349, 1241, 1133, 992 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.27–8.24 (m, 1H), 7.47–7.42 (comp, 2H), 7.35–7.34 (comp, 2H), 7.34–7.32 (comp, 2H), 7.26–7.14 (comp, 7H), 5.65 (d, *J* = 1.5 Hz, 1H), 4.04 (d, *J* = 1.5 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.20, 163.45, 142.45, 139.21, 132.49, 132.30, 129.62, 129.50, 129.12, 128.50, 128.00, 127.10, 126.73, 126.49, 65.00, 53.02, 51.86; *m/z* (ESI–MS) 358.3 $[M+H]^+$.

(±)-**(3S,4S)-methyl 2-(4-methoxyphenyl)-1-oxo-3-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (4b):**



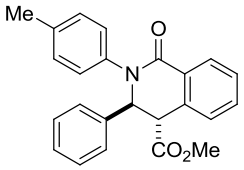
Following the general procedure A, compound **4b** was obtained as a white solid in 61% yield (71 mg, >19:1 dr); R_f = 0.20 (EtOAc/hexanes 3:7 v/v); mp: 192–194 ºC; IR (KBr) 3467, 3005, 2970, 2949, 1736, 1654, 1426, 1365, 1217, 1092, 898, 528 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.27–8.20 (m, 1H), 7.48–7.39 (comp, 2H), 7.29–7.15 (comp, 6H), 7.16–7.12 (comp, 2H), 6.85 (dd, *J* = 8.5, 5.5 Hz, 2H), 5.58 (d, *J* = 4.2 Hz, 1H), 3.99 (d, *J* = 4.3 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.31, 163.63, 158.44, 139.30, 135.33, 132.42, 132.33, 129.69, 129.56, 128.86, 128.69, 128.54, 128.06, 126.60, 114.44, 65.27, 55.52, 53.06, 51.84; *m/z* (ESI–MS) 387.4 $[M+H]^+$;

(±)-**(3S,4S)-methyl 2-(4-chlorophenyl)-1-oxo-3-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (4c):**

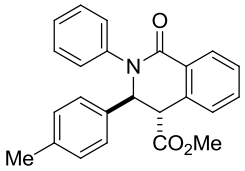


Following the general procedure A, **4c** was obtained as a white solid in 81% yield (95 mg, >19:1); R_f = 0.44 (EtOAc/hexanes 3:7 v/v); mp = 107–108 °C; IR (KBr) 3432, 2860. 2478, 2366, 2345, 1591, 1472, 1332, 1043, 529 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.23 (dd, *J* = 5.7, 3.5 Hz, 1H), 7.45 (dd, *J* = 5.7, 3.4 Hz, 2H), 7.32–7.28 (comp, 4H), 7.25–7.19 (comp, 4H), 7.13 (dd, *J* = 7.5, 2.0 Hz, 2H), 5.67–5.51 (m, 1H), 4.04 (d, *J* = 1.4 Hz, 1H), 3.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.11, 163.40, 140.93, 138.82, 132.69,

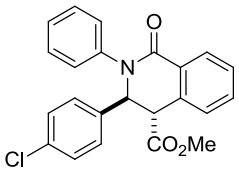
132.63, 132.25, 129.63, 129.25, 128.95, 128.74, 128.49, 128.17, 128.13, 126.39, 64.90, 53.05, 51.63; *m/z* (ESI–MS) 392.2 $[M+H]^+$.

(±)-**(3S,4S)-methyl 1-oxo-3-phenyl-2-(p-tolyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (4d):** 

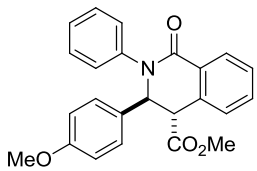
Following the general procedure A, **4d** was obtained as a white solid in 72% yield (81 mg, >19:1 dr); R_f = 0.49 (EtOAc/hexanes 3:7 v/v); mp = 169–172 °C; IR (KBr) 3042, 2947, 1736, 1701, 1432, 1325, 1239, 1183, 1002, 855, 723 617, 457 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.27–8.23 (m, 1H), 7.46–7.42 (comp, 2H), 7.21 (t, *J* = 8.2 Hz, 6H), 7.18–7.12 (comp, 4H), 5.62 (d, *J* = 1.2 Hz, 1H), 4.02 (d, *J* = 1.4 Hz, 1H), 3.74 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.23, 163.50, 139.85, 139.27, 136.90, 132.39, 132.29, 129.77, 129.69, 129.48, 128.81, 128.64, 128.49, 127.96, 126.55, 126.53, 65.08, 53.01, 51.86, 21.17; *m/z* (ESI–MS) 372.1 $[M+H]^+$.

(±)-**(3S,4S)-methyl 1-oxo-2-phenyl-3-(p-tolyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (4e):** 

Following the general procedure A, **4e** was obtained as a white solid in 73% yield (82 mg, >19:1 dr); R_f = 0.50 (EtOAc/hexanes 3:7 v/v); mp = 144–146 °C; IR (KBr) 3247, 3235, 3029, 2953, 2613, 2534, 1925, 1641, 1495, 1343, 1121, 936, 529 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.36 – 8.18 (m, 1H), 7.53–7.41 (comp, 2H), 7.37–7.30 (comp, 4H), 7.26–7.22 (m, 1H), 7.20–7.17 (m, 1H), 7.08-7.01 (comp, 4H), 5.60 (d, *J* = 1.4 Hz, 1H), 4.00 (d, *J* = 1.5 Hz, 1H), 3.74 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.31, 163.51, 142.54, 137.78, 136.23, 132.47, 132.43, 129.72, 129.56, 129.52, 129.13, 128.67, 128.53, 127.10, 126.74, 126.43, 64.86, 53.04, 52.01, 21.10; *m/z* (ESI–MS) 372.2 $[M+H]^+$.

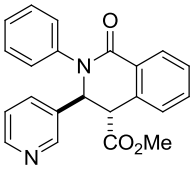
(±)-**(3S,4S)-methyl 3-(4-chlorophenyl)-1-oxo-2-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (4f):** 

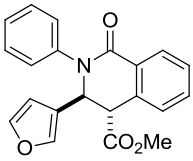
Following the general procedure A, **4f** was obtained as a white solid in 68% yield (80 mg, >19:1 dr); R_f = 0.45 (EtOAc/hexanes 3:7 v/v); mp = 97–99 °C; IR (KBr) 3457, 3006, 2969, 1736, 1427, 1366, 1216, 899, 528 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.24 (dd, *J* = 5.6, 3.6 Hz, 1H), 7.46 (dd, *J* = 5.7, 3.3 Hz, 2H), 7.37–7.29 (comp, 4H), 7.27–7.22 (m, 1H), 7.19 (d, *J* = 8.6 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 5.63 (d, *J* = 1.2 Hz, 1H), 3.98 (d, *J* = 1.5 Hz, 1H), 3.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.93, 163.30, 142.21, 137.78, 133.93, 132.66, 132.03, 129.53, 129.42, 129.21, 129.08, 128.84, 128.57, 127.90, 127.28, 126.70, 64.45, 53.09, 51.69; *m/z* (ESI–MS) 392.0 $[M+H]^+$.

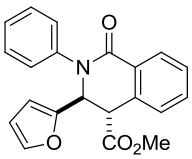
(±)-**(3S,4S)-methyl 3-(4-methoxyphenyl)-1-oxo-2-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (4g):** 

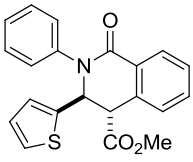
Following the general procedure A, **4g** was obtained as a colorless oil in 45% yield (49 mg, >19:1); R_f = 0.43 (EtOAc/hexanes 3:7 v/v); mp = 112–115 °C; IR (KBr) 3458, 3004, 2973, 1716, 1651, 1366, 1218, 1092, 901, 529 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.27–8.21 (m, 1H), 7.49–7.43 (comp, 2H), 7.37–7.29 (comp, 4H), 7.26–7.21 (m, 1H), 7.21–7.18 (m, 1H), 7.05 (d, *J* = 8.8 Hz, 2H), 6.74 (d, *J* = 8.8 Hz, 2H), 5.57 (d, *J* = 1.5 Hz, 1H), 3.99 (d, *J* = 1.6 Hz, 1H), 3.74 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.30, 163.42, 159.28, 142.50, 132.50, 131.18, 129.69, 129.55, 129.14, 128.68,

128.54, 127.72, 127.13, 126.80, 114.22, 64.59, 55.30, 53.02, 52.00; *m/z* (ESI–MS) 387.9 $[M+H]^+$.

(±)-**(3S,4S)-methyl 1-oxo-2-phenyl-3-(pyridin-3-yl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (4h):** 
Following the general procedure A, **4h** was obtained as a colorless oil in 95% yield (101 mg, >19:1 dr); R_f = 0.33 (EtOAc/hexanes 3:7 v/v); IR (KBr) 3458, 3004, 2946, 1739, 1435, 1365, 1227, 1217, 528 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.50 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.21–8.17 (m, 1H), 7.53 (td, *J* = 7.8, 1.8 Hz, 1H), 7.47 (dd, *J* = 8.6, 1.2 Hz, 1H), 7.39 (td, *J* = 5.8, 2.9 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.31–7.27 (comp, 2H), 7.25–7.22 (m, 1H), 7.22–7.19 (m, 1H), 7.08 (ddd, *J* = 7.6, 4.8, 1.0 Hz, 1H), 5.79 (d, *J* = 1.5 Hz, 1H), 4.53 (d, *J* = 1.6 Hz, 1H), 3.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.17, 163.58, 158.43, 149.76, 142.36, 136.95, 132.64, 132.45, 129.49, 129.44, 129.09, 128.53, 126.90, 126.25, 122.59, 120.79, 66.14, 52.94, 49.84; *m/z* (ESI–MS) 359.5 $[M+H]^+$.

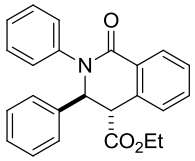
(±)-**(3S,4S)-methyl 3-(furan-3-yl)-1-oxo-2-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (4i):** 
Following the general procedure A, **4i** was obtained as a yellow solid in 71% yield (74 mg, >19:1 dr); R_f = 0.47 (EtOAc/hexanes 3:7 v/v); mp = 65–67 °C; IR (KBr) 3072, 3039, 1725, 1631, 1602, 1495, 1388, 1284, 1228, 1174, 1091, 1012 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.20 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.52 (td, *J* = 7.4, 1.6 Hz, 1H), 7.47 (td, *J* = 7.5, 1.4 Hz, 1H), 7.41–7.34 (comp, 4H), 7.32 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.32 – 7.25 (m, 1H), 7.22 (t, *J* = 1.7 Hz, 1H), 7.17–7.12 (m, 1H), 5.94 (d, *J* = 2.8 Hz, 1H), 5.55 (d, *J* = 1.5 Hz, 1H), 4.00 (d, *J* = 1.6 Hz, 1H), 3.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.88, 162.86, 143.59, 142.05, 140.24, 133.15, 132.53, 129.55, 129.39, 129.17, 128.72, 128.67, 127.26, 127.02, 124.50, 108.97, 57.84, 53.03, 50.52; *m/z* (ESI–MS) 348.1 $[M+H]^+$.

(±)-**(3S,4S)-methyl 3-(furan-2-yl)-1-oxo-2-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (4j):** 
Following the general procedure A, **4j** was obtained as a brown oil in 77% yield (80 mg, >19:1 dr); R_f = 0.51 (EtOAc/hexanes 3:7 v/v); IR (KBr) 3493, 3214, 2935, 1749, 16862 1611, 1430, 1371, 1397, 1022, 748, 530 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.19 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.49 (td, *J* = 7.5, 1.5 Hz, 1H), 7.47–7.36 (comp, 5H), 7.32 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.29 (dt, *J* = 6.5, 1.3 Hz, 2H), 7.23 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.18 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.07 (d, *J* = 3.3 Hz, 1H), 5.68 (d, *J* = 1.4 Hz, 1H), 4.24 (d, *J* = 1.7 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.61, 163.10, 151.96, 142.44, 142.07, 132.97, 132.42, 129.35, 129.18, 129.14, 128.65, 128.58, 127.24, 126.81, 59.57, 53.05, 48.68; *m/z* (ESI–MS) 348.3 $[M+H]^+$.

(±)-**(3S,4S)-methyl 1-oxo-2-phenyl-3-(thiophen-2-yl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (4k):** 
Following the general procedure A, **4k** was obtained as a yellow solid in 66% yield (72 mg, >19:1 dr); R_f = 0.53 (EtOAc/hexanes 3:7 v/v); mp = 61–62 °C; IR (KBr) 3426, 3107, 3020, 2733, 2458, 2337, 1721, 1658, 1510, 1436, 1363, 1194, 702, 529 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.22 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.54 (td, *J* = 7.4, 1.7 Hz, 1H), 7.50 (td, *J* = 7.5, 1.5 Hz, 1H), 7.40–7.31 (comp, 5H), 7.30–7.26 (m, 1H), 5.86 (d, *J* = 1.6 Hz, 1H), 4.13 (d, *J* = 1.6

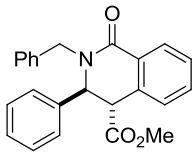
Hz, 1H), 3.75 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.69, 162.77, 142.43, 141.92, 132.82, 132.64, 129.93, 129.44, 129.21, 128.91, 128.83, 127.42, 127.20, 126.54, 126.35, 125.44, 61.40, 53.15, 51.62; *m/z* (ESI–MS) 364.0 $[M+H]^+$.

(±)-**(3S,4S)-ethyl 1-oxo-2,3-diphenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (4l):**



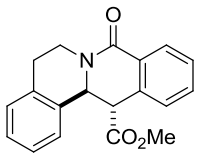
Following the general procedure A, **4l** was obtained as a white solid in 69% yield (77 mg, >19:1 dr), R_f = 0.32 (EtOAc/hexanes 3:7 v/v); mp = 149–151 °C; IR (KBr) 3033, 2955, 1734, 1687, 1503, 1457, 1308, 1233, 1171, 889, 707, 519 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.25 (dd, *J* = 5.8, 3.3 Hz, 1H), 7.46–7.42 (comp, 2H), 7.38–7.30 (comp, 4H), 7.25–7.15 (comp, 6H), 5.76–5.56 (m, 1H), 4.36–4.09 (comp, 2H), 4.02 (d, *J* = 1.3 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.69, 163.48, 142.50, 139.33, 132.48, 132.42, 129.58, 129.43, 129.06, 128.81, 128.57, 128.45, 127.96, 127.01, 126.64, 126.48, 64.96, 62.02, 52.00, 14.16; *m/z* (ESI–MS) 372.2 $[M+H]^+$.

(±)-**(3S,4S)-methyl 2-benzyl-1-oxo-3-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (4n):**

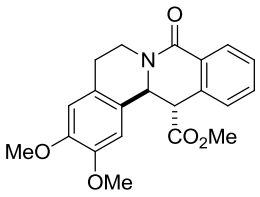


Following the general procedure A, **4n** was obtained as a white solid in 34% yield (38 mg, >19:1 dr); R_f = 0.66 (EtOAc/hexanes 3:7 v/v); mp = 77–79 °C; IR (KBr) 3066, 2954, 1737, 1657, 1606, 1453, 1411, 1269, 1237, 1164, 985 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.26 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.44 (td, *J* = 7.6, 1.4 Hz, 1H), 7.40 (td, *J* = 7.5, 1.6 Hz, 1H), 7.34–7.27 (comp, 5H), 7.25–7.20 (comp, 3H), 7.11–7.06 (comp, 2H), 7.03 (dd, *J* = 7.4, 1.3 Hz, 1H), 5.72 (d, *J* = 14.6 Hz, 1H), 5.12 (d, *J* = 1.5 Hz, 1H), 3.87 (d, *J* = 1.4 Hz, 1H), 3.62 (d, *J* = 14.6 Hz, 1H), 3.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.01, 164.12, 138.57, 137.14, 132.30, 132.01, 129.43, 129.08, 129.05, 129.01, 128.68, 128.60, 128.35, 128.17, 127.72, 126.44, 60.56, 52.70, 51.65, 48.98; *m/z* (ESI–MS) 372.4 $[M+H]^+$.

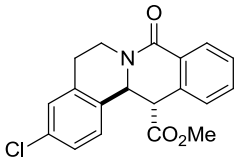
(*13S,13aS*)-methyl 8-oxo-6,8,13,13a-tetrahydro-5H-isoquinolino[3,2-a]isoquinoline-13-carboxylate (5a):



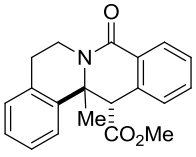
Following the general procedure B, compound **5a** was obtained as a white solid in 93% yield (57 mg, >19:1 dr); R_f = 0.24 (EtOAc/hexanes 3:7 v/v); mp: 159–160 ºC; $[\alpha]_D^{20}$ –142.2 (c 0.5, $CHCl_3$, 65% *ee*); IR (KBr) 3493, 3302, 3248, 2914, 2364, 1734, 1648, 1463, 1366, 1518, 1004, 913, 783, 744, 530 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (app dd, *J* = 7.7, 1.4 Hz, 1H), 7.49 (app dd, *J* = 7.5, 1.4 Hz, 1H), 7.42 (t, *J* = 7.3 Hz, 1H), 7.25–7.19 (comp, 2H), 7.19–7.14 (comp, 3H), 5.34 (d, *J* = 9.0 Hz, 1H), 4.89 (dd, *J* = 12.2, 4.7 Hz, 1H), 4.18 (d, *J* = 9.0 Hz, 1H), 3.76 (s, 3H), 3.15–3.03 (comp, 2H), 2.92–2.84 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.33, 163.81, 136.87, 135.04, 134.17, 132.35, 129.44, 128.89, 128.62, 128.39, 127.84, 126.78, 126.52, 125.61, 58.07, 52.52, 51.93, 40.99, 29.88; *m/z* (ESI–MS) 309.0 $[M+2H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 18.1 min (major) and t_R = 20.2 min (minor).

(*13R,13aS*)-methyl 2,3-dimethoxy-8-oxo-6,8,13,13a-tetrahydro-5H-isoquinolino[3,2-a]isoquinoline-13-carboxylate (5b): 

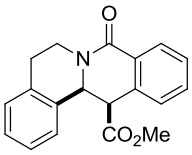
Following the general procedure B, compound **5b** was obtained as a white solid in 85% yield (65 mg, >19:1 dr); R_f = 0.11 (EtOAc/hexanes 3:7 v/v); mp: 167–169 ºC; $[\alpha]_D^{20}$ –210.2 (c 0.5, $CHCl_3$, 64% *ee*); IR (KBr) 3490, 3476, 3117, 3012, 2732, 2345, 2321, 1726, 1520, 1418, 1250, 1111, 744 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.48 (td, *J* = 7.5, 1.5 Hz, 1H), 7.43 (t, *J* = 7.0 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 6.72 (s, 1H), 6.70 (s, 1H), 5.26 (d, *J* = 10.1 Hz, 1H), 4.97–4.89 (m, 1H), 4.08 (d, *J* = 10.1 Hz, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 3.06–2.93 (comp, 2H), 2.81–2.74 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.65, 163.97, 148.47, 147.56, 135.51, 132.40, 129.34, 128.96, 128.62, 128.38, 126.13, 125.53, 112.02, 109.68, 57.88, 56.16, 55.99, 53.43, 52.43, 40.73, 29.77; *m/z* (ESI–MS) 368.1 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, t_R = 35.8 min (minor) and t_R = 42.1 min (major).

(*13S,13aS*)-methyl 3-chloro-8-oxo-6,8,13,13a-tetrahydro-5H-isoquinolino[3,2-a]isoquinoline-13-carboxylate (5c): 

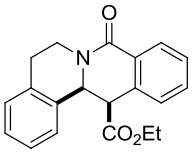
Following the general procedure B, compound **5c** was obtained as a white solid in 78% yield (53 mg, >19:1 dr); R_f = 0.26 (EtOAc/hexanes 3:7 v/v); mp: 80–81 ºC; $[\alpha]_D^{20}$ –64.1 (c 1.0, $CHCl_3$, 61% *ee*); IR (KBr) 3078, 3013, 2925, 2321, 1716, 1659, 1519, 1494, 1455, 1360, 1276, 1183, 914, 873, 826, 767, 659, 627, 616, 530 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.49 (td, *J* = 7.5, 1.5 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.21 (d, *J* = 2.0 Hz, 1H), 7.17–7.13 (comp, 2H), 7.09 (d, *J* = 8.4 Hz, 1H), 5.31 (d, *J* = 8.9 Hz, 1H), 4.91 (d, *J* = 4.5 Hz, 1H), 4.15 (d, *J* = 8.9 Hz, 1H), 3.77 (s, 3H), 3.14–3.00 (comp, 2H), 2.89–2.80 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.16, 163.77, 138.86, 134.77, 133.76, 132.75, 132.50, 129.41, 128.95, 128.52, 128.43, 127.03, 126.90, 126.68, 57.74, 52.64, 51.76, 40.73, 29.70; *m/z* (ESI–MS) 343.5 $[M+2H]^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 95/05, Flow rate = 1 mL/min, UV = 230 nm, t_R = 48.5 min (major).and t_R = 53.9 min (minor).

(*13S,13aS*)-methyl 13a-methyl-8-oxo-6,8,13,13a-tetrahydro-5H-isoquinolino[3,2-a]isoquinoline-13-carboxylate (5d): 

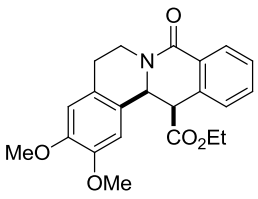
Following the general procedure B, compound **5d** was obtained as a white solid in 89% yield (57 mg, >19:1 dr); R_f = 0.37 (EtOAc/hexanes 3:7 v/v); mp: 113–116 ºC; $[\alpha]_D^{20}$ –205.8 (c 0.5, $CHCl_3$, 32% *ee*); IR (KBr) 3510, 3488, 3348, 3296, 2927, 2712, 1718, 1653, 1436, 1363, 1091, 895, 773, 721, 530 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.52–7.47 (m, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.33–7.16 (comp, 4H), 7.04 (d, *J* = 7.5 Hz, 1H), 5.14 (ddd, *J* = 12.6, 4.4, 1.8 Hz, 1H), 4.19 (s, 1H), 3.74 (s, 3H), 3.08–2.99 (m, 1H), 2.88–2.81 (comp, 2H), 1.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.42, 163.09, 139.16, 136.05, 134.67, 132.43, 129.84, 128.77, 128.55, 128.16, 127.43, 126.41, 126.34, 126.00, 62.01, 57.88, 52.03, 36.77, 31.28, 21.09; *m/z* (ESI–MS) 322.3 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, t_R = 8.6 min (minor) and t_R = 9.9 min (major).

(*13R,13aS*)-methyl 8-oxo-6,8,13,13a-tetrahydro-5H-isoquinolino[3,2-a]isoquinoline-13-carboxylate (6a): 

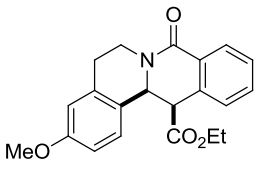
Following the general procedure C, **6a** was obtained as a white solid in 72% yield (66 mg, >19:1 dr); R_f = 0.22 (EtOAc/hexanes 3:7 v/v); mp = 163–166 °C; $[\alpha]_D^{20}$ –166.1 (c 0.5, $CHCl_3$, 74% *ee*); IR (KBr) 3501, 3319, 3254, 2919, 2364, 1727, 1644, 1458, 1371, 1525, 998, 912, 746, 531 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.15–8.10 (m, 1H), 7.47–7.36 (comp, 2H), 7.29 (d, *J* = 7.7 Hz, 1H), 7.24 – 7.10 (m, 4H), 5.20 (d, *J* = 4.3 Hz, 1H), 4.96 (dd, *J* = 11.0, 4.8 Hz, 1H), 4.17 (d, *J* = 4.3 Hz, 1H), 3.25 (s, 3H), 3.04–2.86 (comp, 2H), 2.79–2.68 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.45, 163.75, 136.51, 134.63, 133.29, 132.11, 129.28, 128.98, 128.82, 127.61, 127.31, 126.89, 126.23, 124.07, 56.62, 52.04, 51.30, 38.81, 28.98; *m/z* (ESI–MS) 307.8 $[M+H]^+$.

(*13R,13aS*)-ethyl 8-oxo-6,8,13,13a-tetrahydro-5H-isoquinolino[3,2-a]isoquinoline-13-carboxylate (6b): 

Following the general procedure C, **6b** was obtained as a white solid in 61% yield (39 mg, >19:1 dr); R_f = 0.23 (EtOAc/hexanes 3:7 v/v); mp = 150–153 °C; $[\alpha]_D^{20}$ –176.8 (c 0.5, $CHCl_3$, 84% *ee*); IR (KBr) 2982, 2941, 2903, 2841, 2750, 1752, 1691, 1566, 1494, 1401, 1235, 1150, 1034, 981, 854, 782, 529 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.17 (dd, *J* = 7.1, 1.8 Hz, 1H), 7.51–7.40 (comp, 2H), 7.36–7.31 (m, 1H), 7.27–7.24 (m, 1H), 7.24–7.12 (comp, 3H), 5.25 (d, *J* = 4.4 Hz, 1H), 5.11–4.92 (m, 1H), 4.21 (d, *J* = 4.4 Hz, 1H), 3.74 (q, *J* = 7.1 Hz, 2H), 3.11–2.90 (comp, 2H), 2.77 (d, *J* = 13.3 Hz, 1H), 0.80 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.10, 163.79, 136.56, 134.76, 133.40, 132.08, 129.29, 129.25, 128.95, 128.75, 127.53, 127.27, 126.83, 126.35, 60.98, 56.67, 51.26, 38.78, 28.99, 13.79; *m/z* (ESI–MS) 322.3 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, t_R = 15.9 min (major) and t_R = 27.3 min (minor).

(*13R,13aS*)-ethyl 2,3-dimethoxy-8-oxo-6,8,13,13a-tetrahydro-5H-isoquinolino[3,2-a]isoquinoline-13-carboxylate (6c): 

Following the general procedure C, **6c** was obtained as a white solid in 80% yield (61 mg, >19:1 dr); R_f = 0.14 (EtOAc/hexanes 3:7 v/v); mp = 164–165 °C; $[\alpha]_D^{20}$ –316.4 (c 0.5, $CHCl_3$, 83% *ee*); IR (KBr) 3488, 3125, 3027, 2679, 2368, 2315, 1734, 1531, 1413, 1261, 1109, 739, 528 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.19 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.51–7.42 (comp, 2H), 7.35 (d, *J* = 7.3 Hz, 1H), 6.75 (s, 1H), 6.66 (s, 1H), 5.19 (d, *J* = 4.4 Hz, 1H), 5.08–4.94 (m, 1H), 4.20 (d, *J* = 4.4 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.79 (q, *J* = 7.1 Hz, 2H), 3.08–2.89 (comp, 2H), 2.79–2.51 (m, 1H), 0.87 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.05, 163.77, 148.09, 134.66, 132.00, 129.31, 129.22, 128.98, 128.69, 127.42, 124.86, 111.40, 109.27, 60.91, 56.38, 56.33, 56.02, 51.16, 38.85, 28.48, 13.86; *m/z* (ESI–MS) 382.2 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, t_R = 13.3 min (major) and t_R = 50.9 min (minor).

(*13R,13aS*)-ethyl 3-methoxy-8-oxo-6,8,13,13a-tetrahydro-5H-isoquinolino[3,2-a]isoquinoline-13-carboxylate (6d): 

Following the general procedure C, **6d** was obtained as a white solid in 64% yield (45 mg, >19:1 dr); R_f = 0.17 (EtOAc/hexanes 3:7 v/v); mp = 157–159 °C; $[\alpha]_D^{20}$ –253.7 (c 0.5, $CHCl_3$, 79% *ee*); IR (KBr) 3522, 3479, 3361, 3293, 2950, 2743, 1709, 1652, 1414, 1376, 1088, 901, 717, 529 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.19 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.52–7.42 (comp, 2H), 7.38–7.33 (m, 1H), 7.21 (d, *J* = 8.6 Hz,

1H), 6.85 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.71 (d, *J* = 2.6 Hz, 1H), 5.23 (d, *J* = 4.4 Hz, 1H), 5.01 (dd, *J* = 12.5, 4.2 Hz, 1H), 4.20 (d, *J* = 4.4 Hz, 1H), 3.85–3.74 (comp, 5H), 3.11–2.94 (comp, 2H), 2.75 (d, *J* = 14.8 Hz, 1H), 0.87 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.17, 163.78, 158.53, 137.91, 134.73, 132.02, 129.28, 129.21, 128.69, 127.50, 127.47, 125.38, 113.37, 113.18, 60.94, 56.24, 55.42, 51.31, 38.69, 29.25, 13.86; *m/z* (ESI–MS) 552.4 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, t_R = 14.5 min (major) and t_R = 25.0 min (minor).

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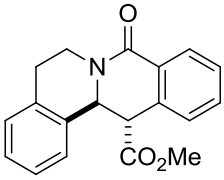
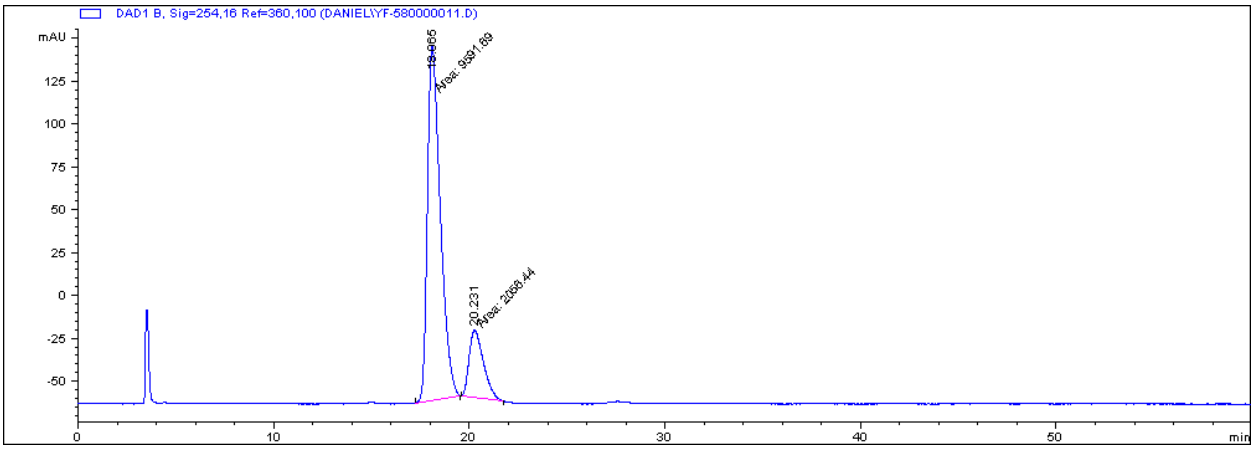
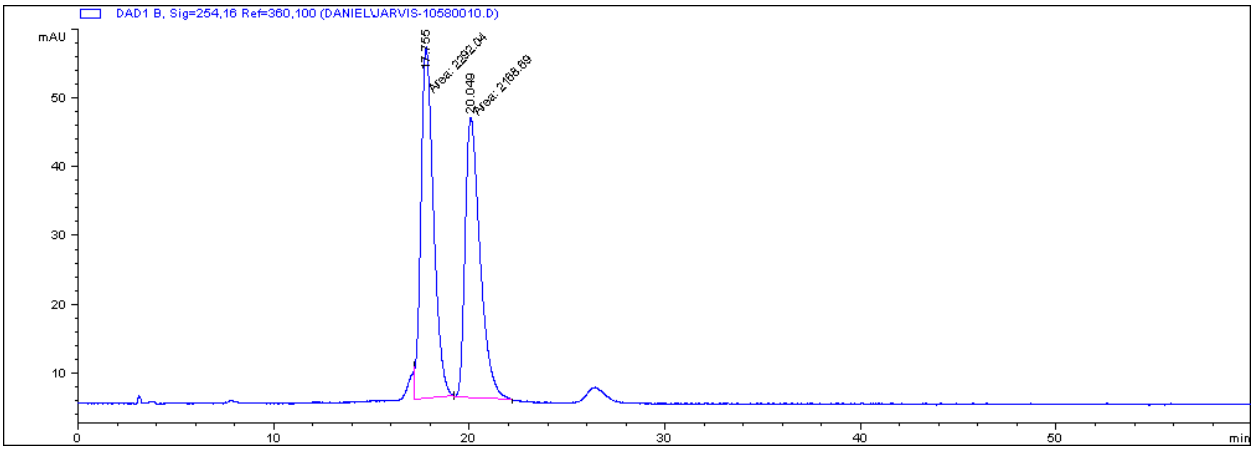
V. HPLC profiles of products.

HPLC Profile of **5a**





Racemic



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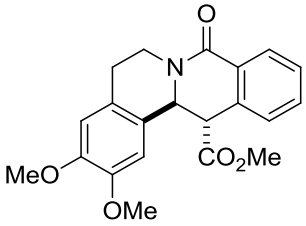

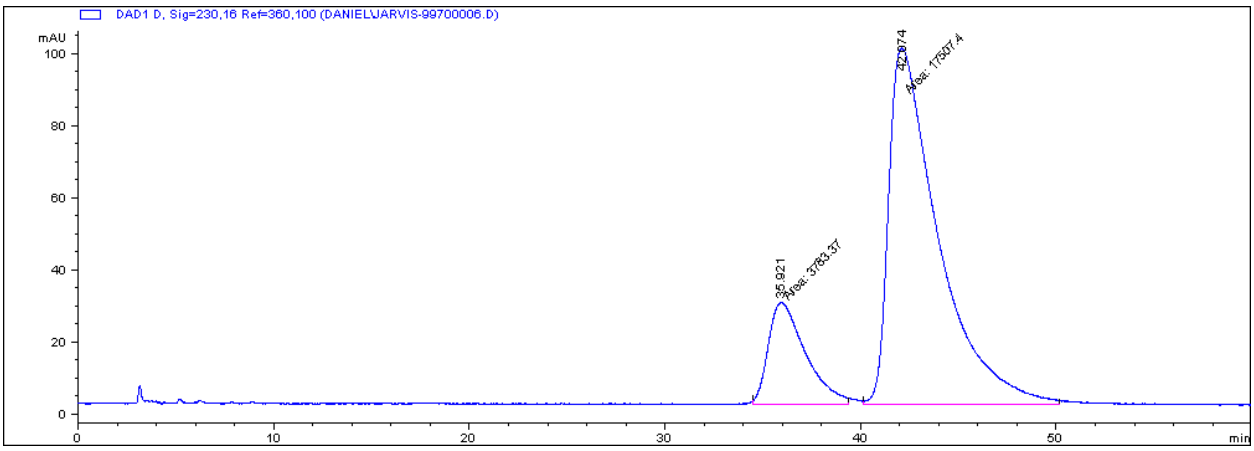

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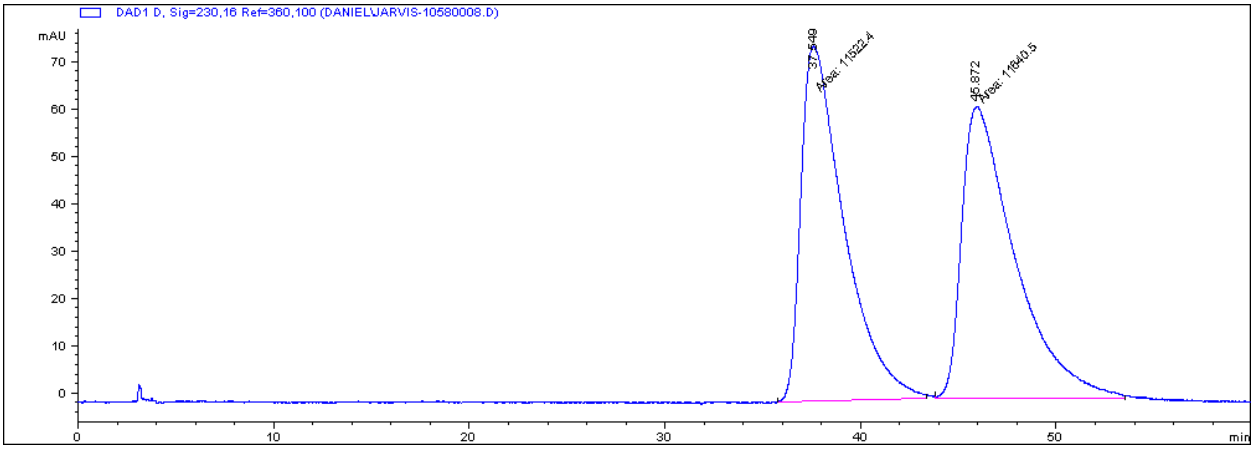

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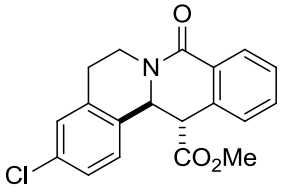

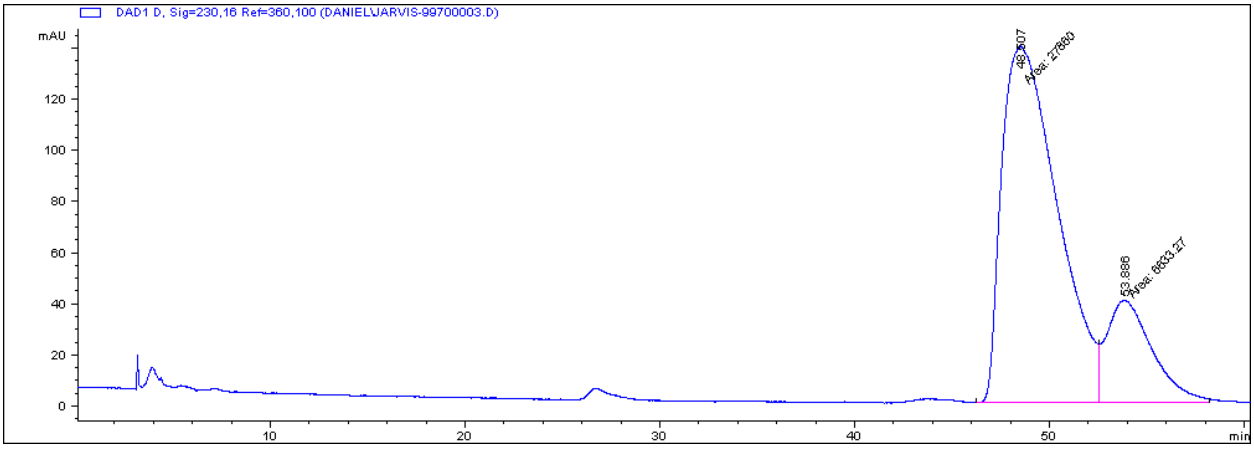

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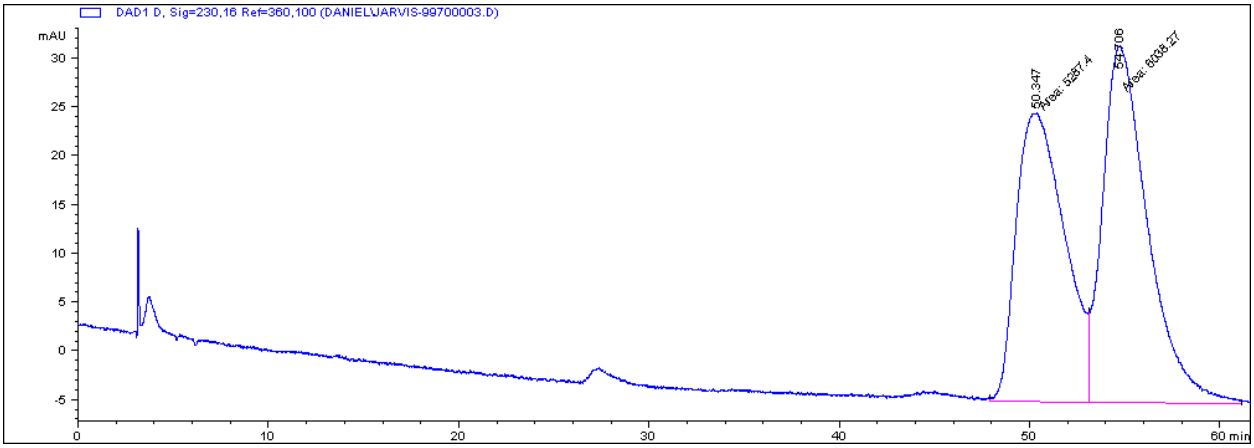
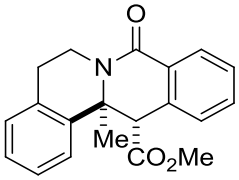
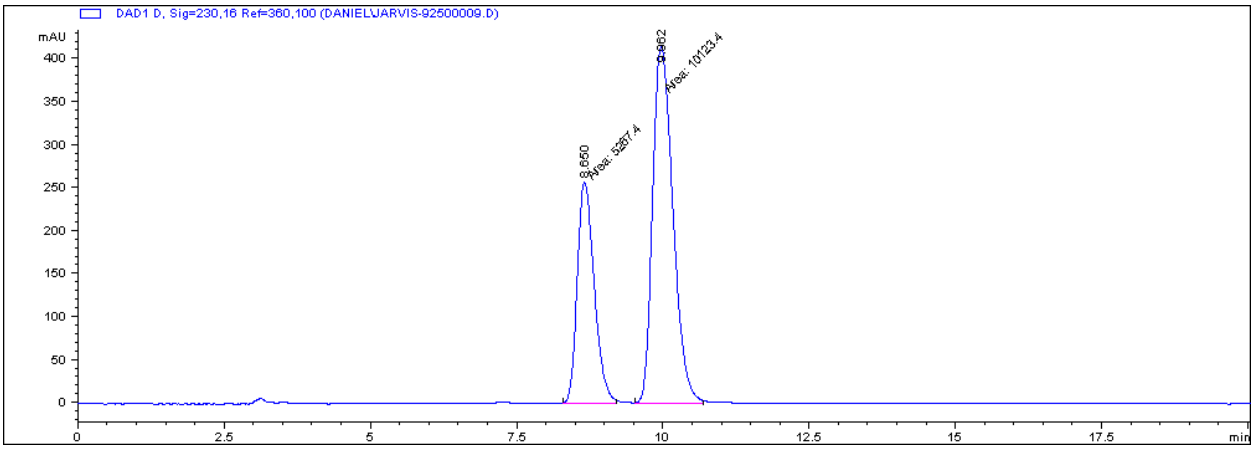


HPLC Profile of **5d**





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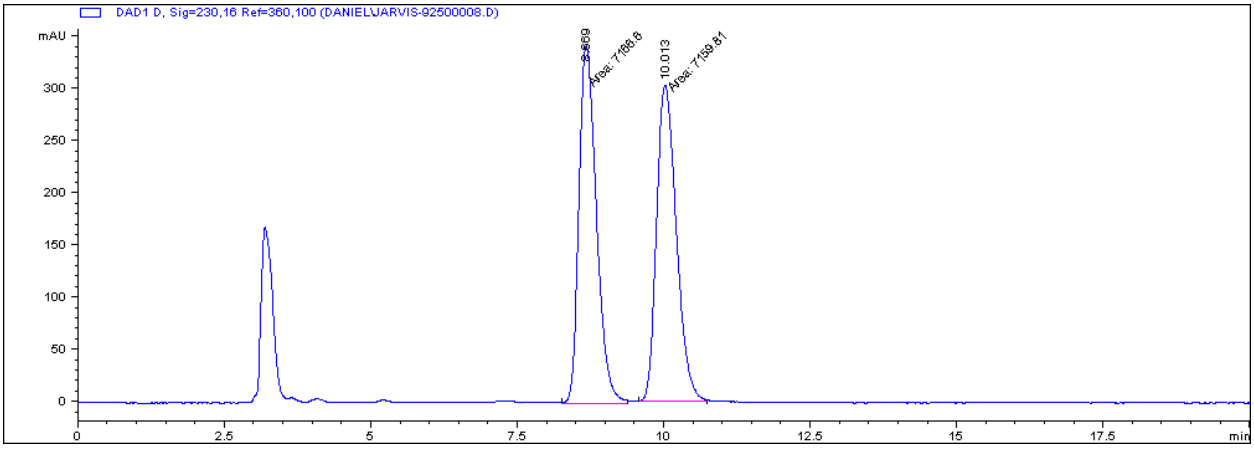
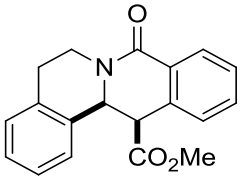
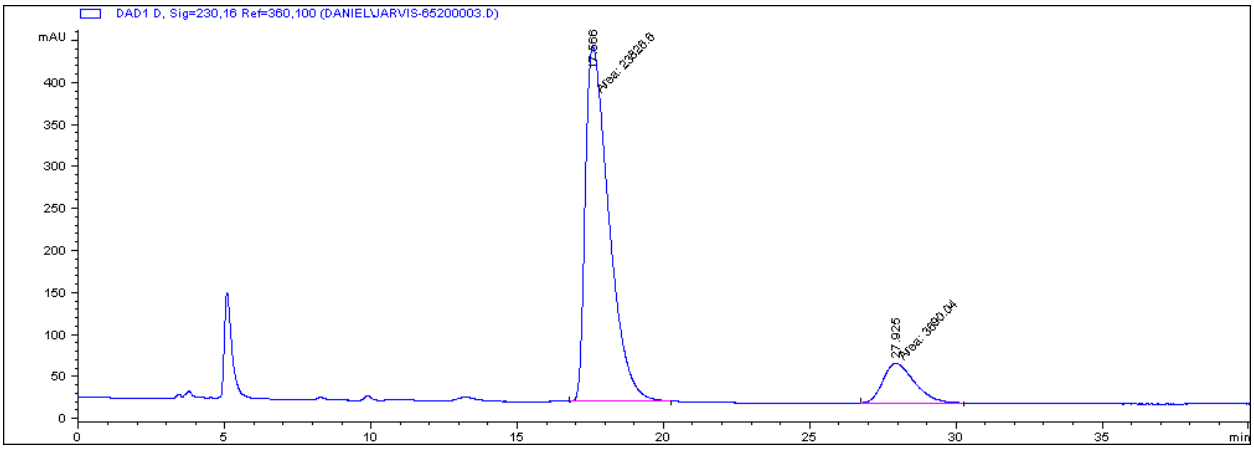
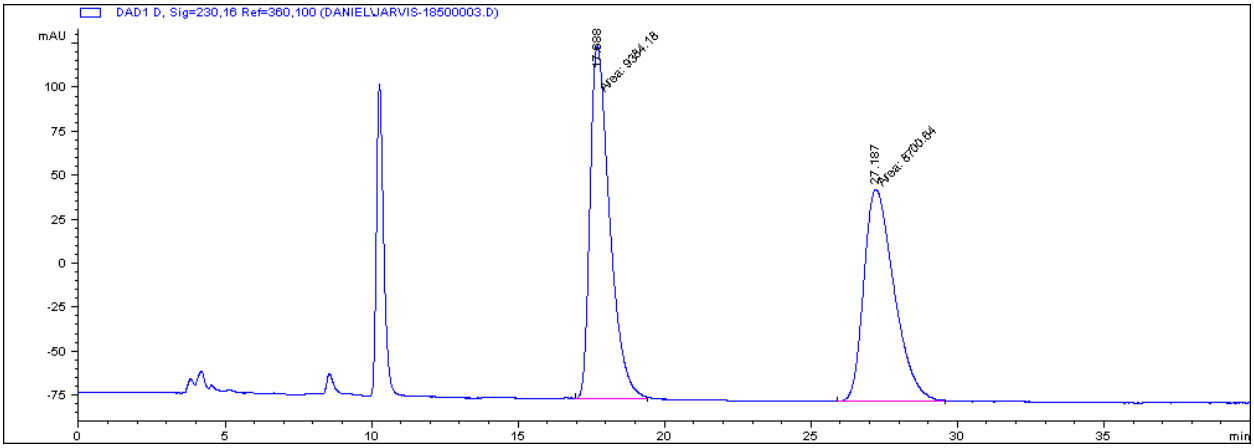


HPLC Profile of **6a**

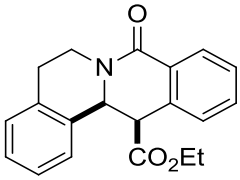


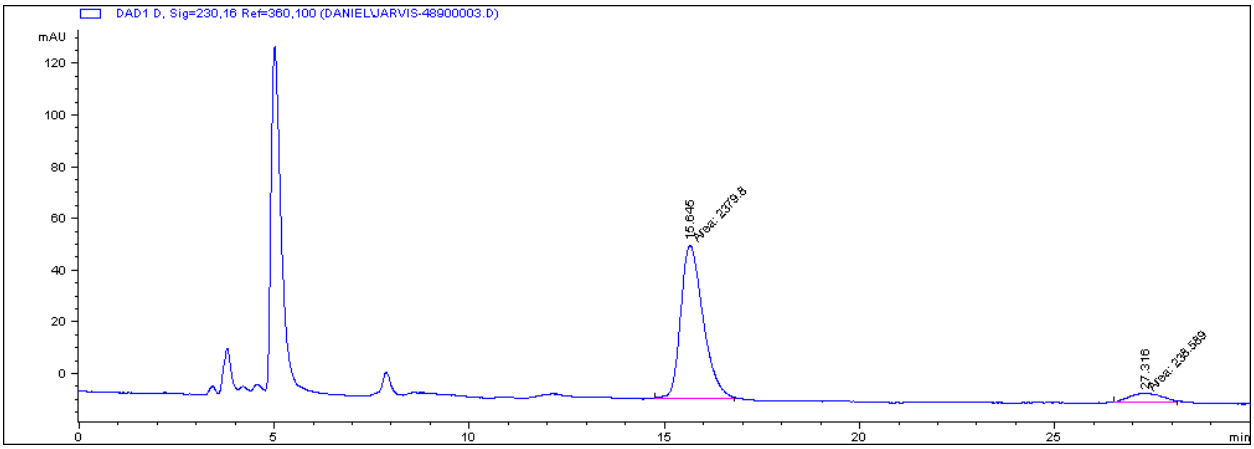


Racemic

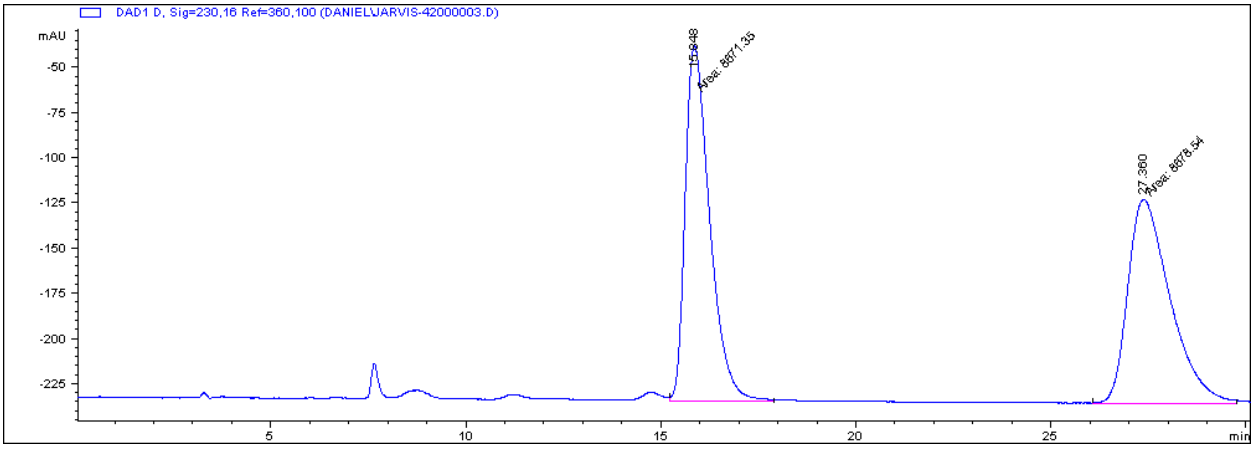


HPLC Profile of **6b**

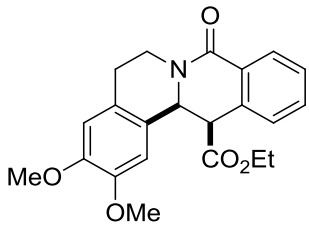


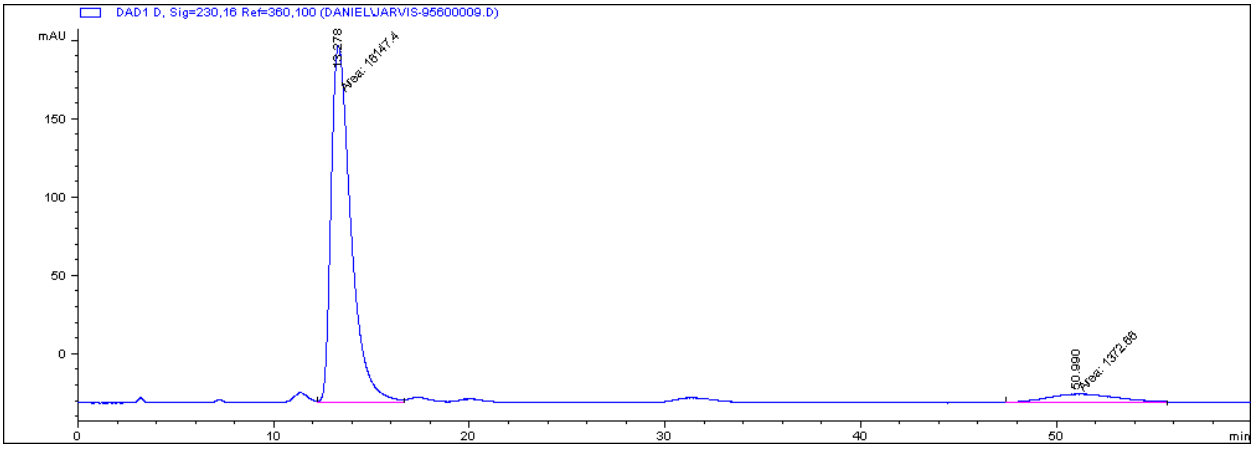


Racemic

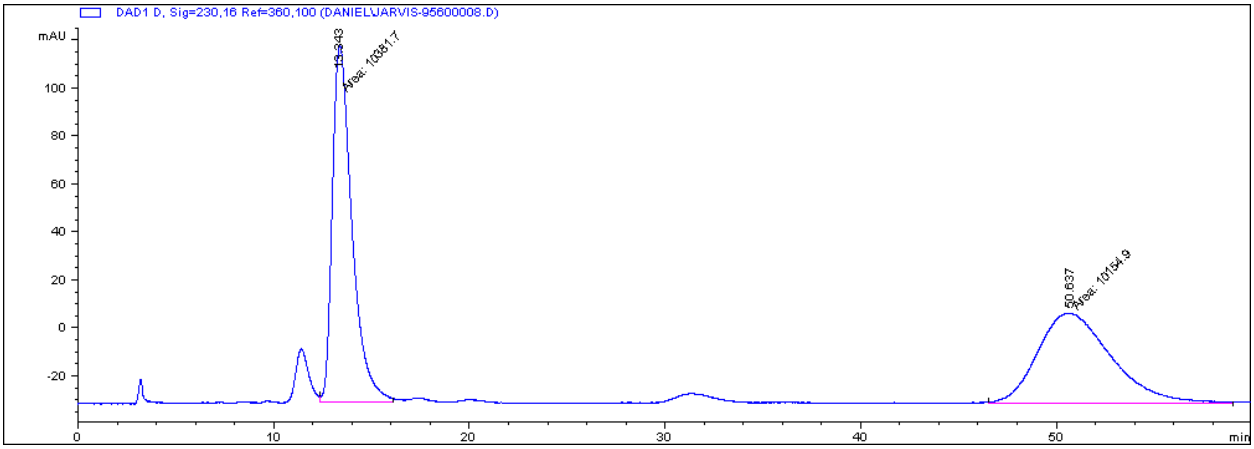


HPLC Profile of **6c**

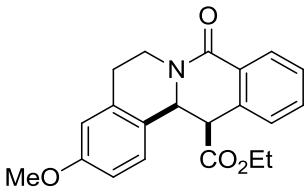


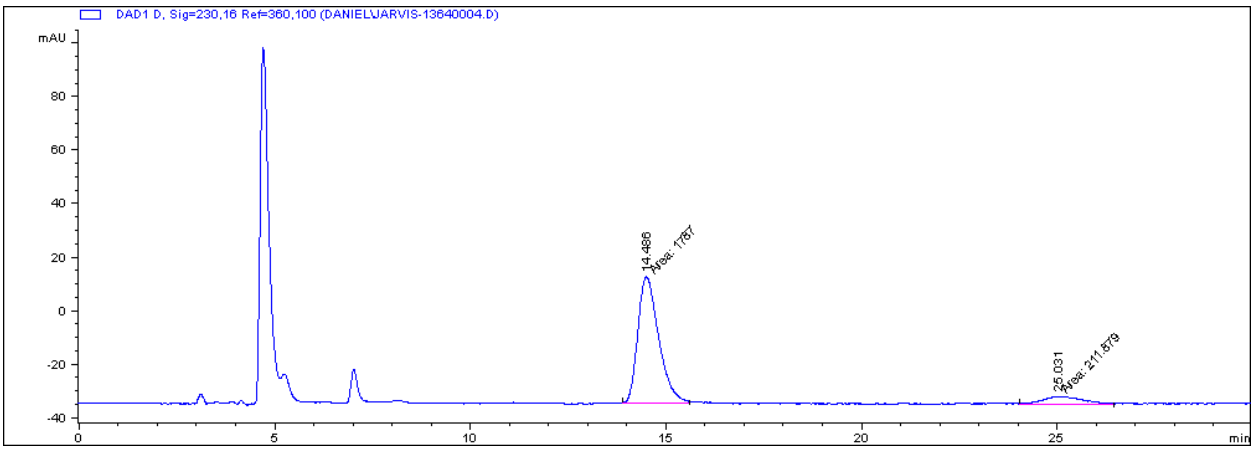


Racemic

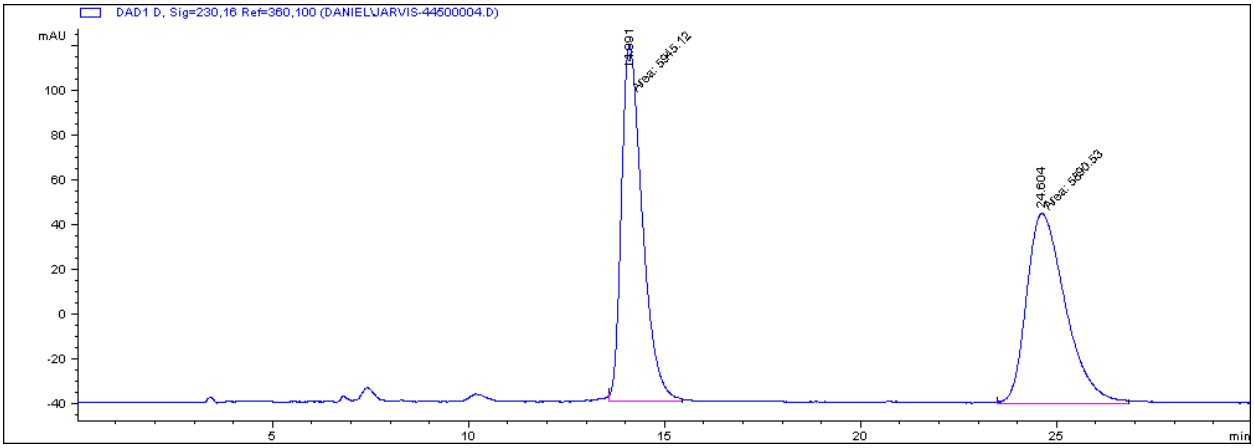


HPLC Profile of **6d**

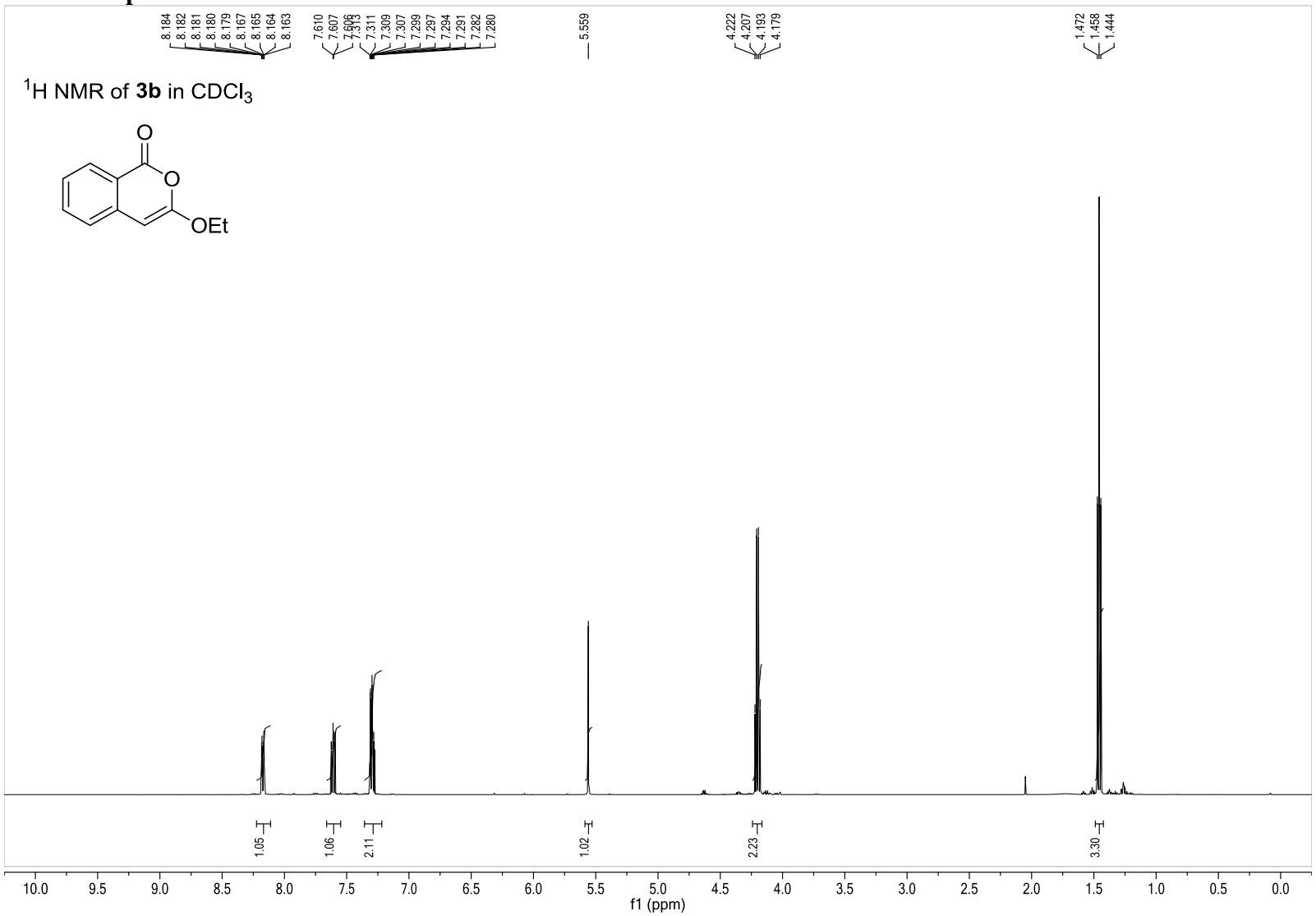


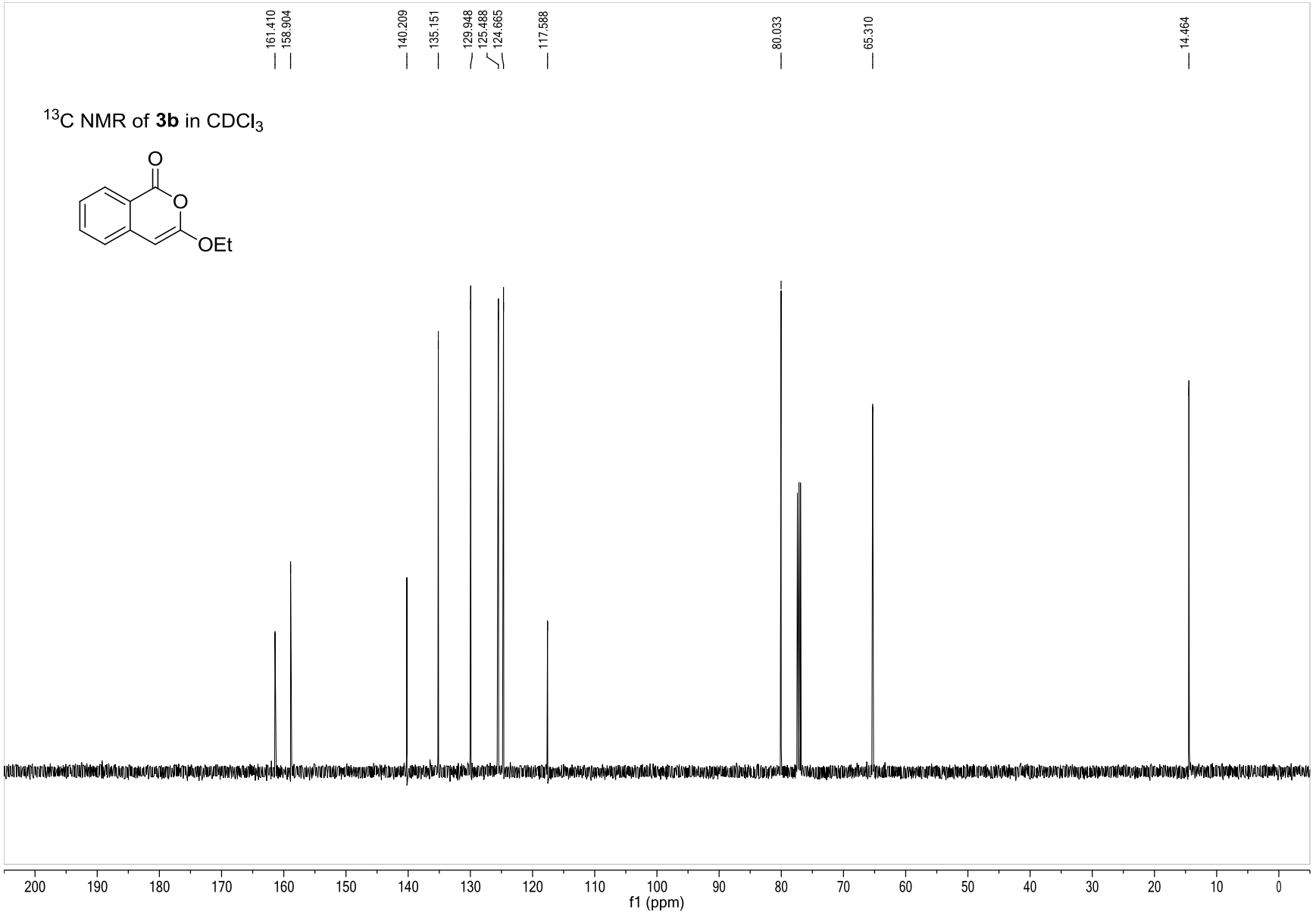


Racemic

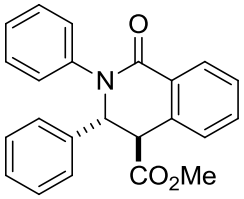


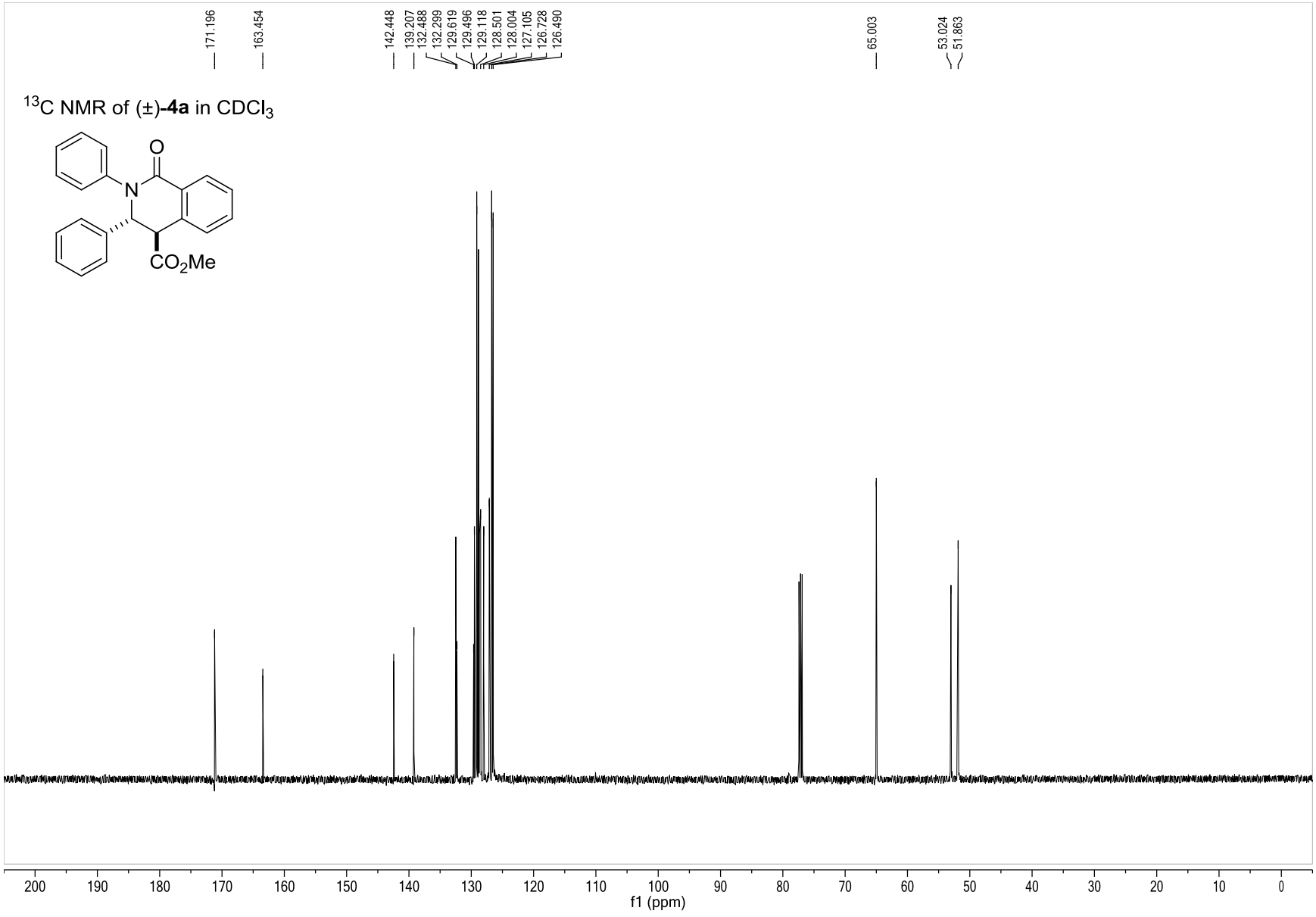
VI. NMR spectra



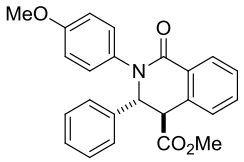

161.410
158.904
140.209
135.151
129.948
125.488
124.665
117.588
80.033
65.310
14.464
^{13}C NMR of **3b** in $CDCl_3$
O
O
OEt
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

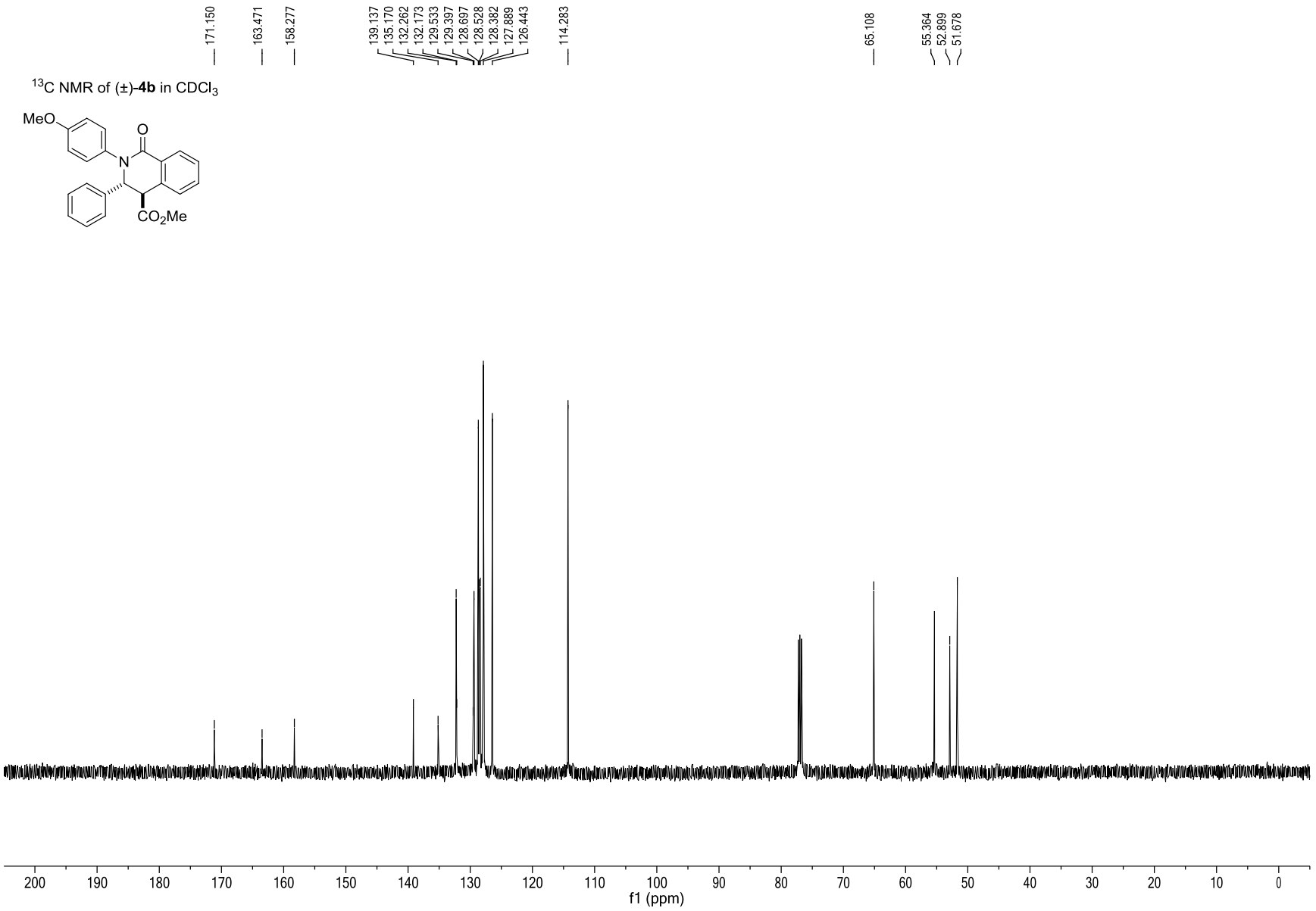
^{1}H NMR of (±)-**4a** in $CDCl_3$

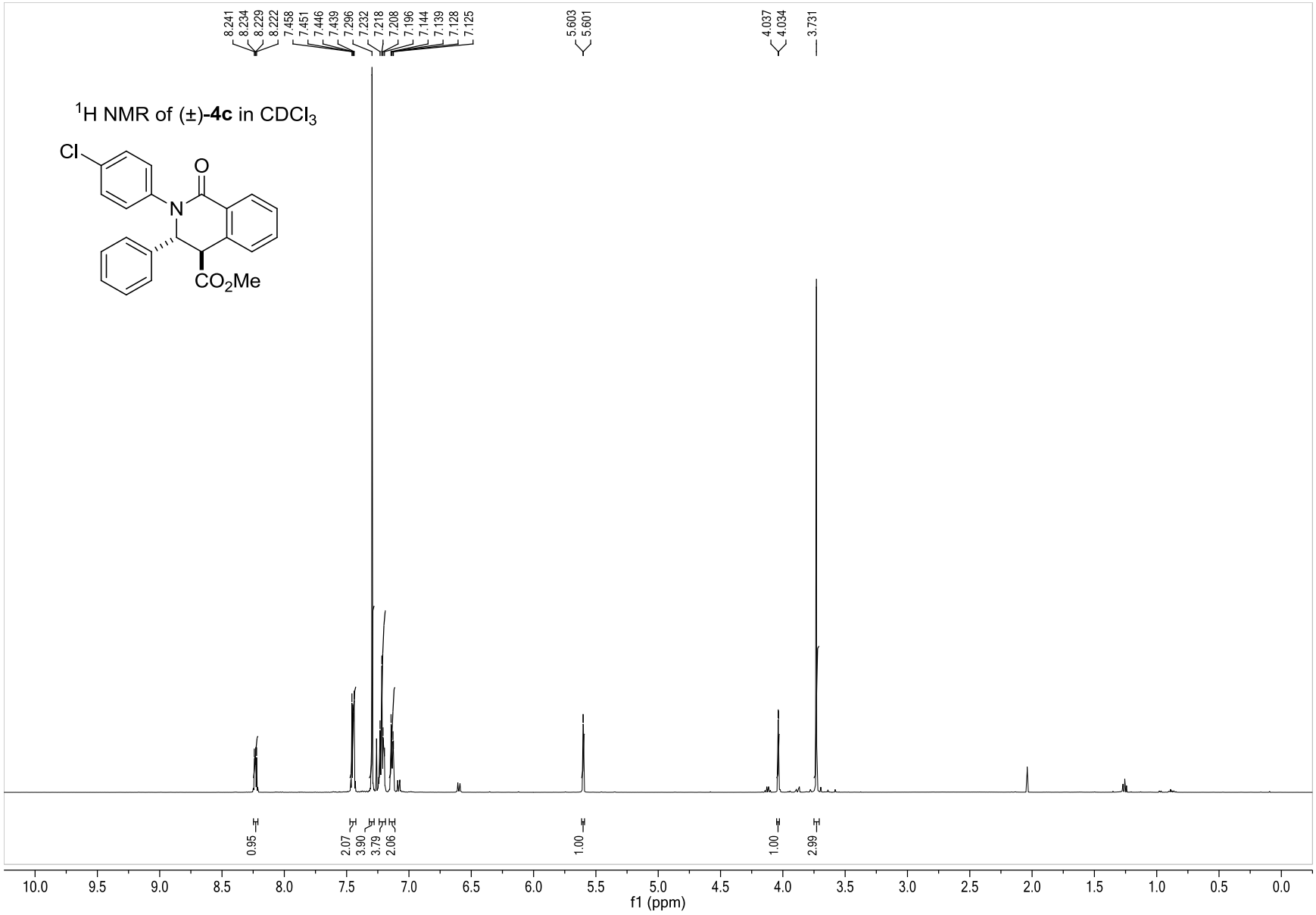


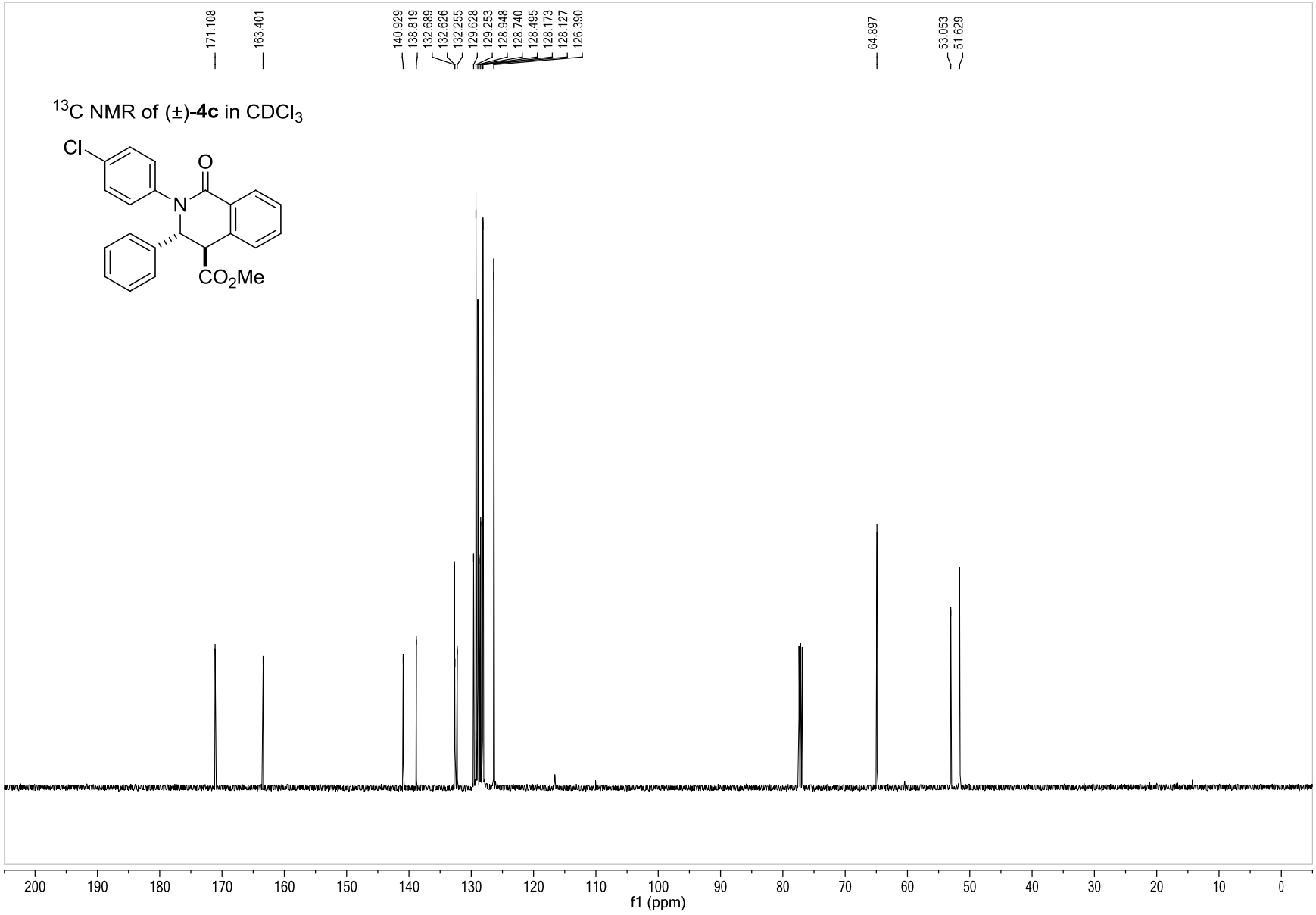

171.196
163.454
142.448
139.207
132.488
132.299
129.619
129.496
129.118
128.501
128.004
127.105
126.728
126.490
65.003
53.024
51.863
^{13}C NMR of (±)-**4a** in $CDCl_3$
O
N
CO_2Me
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

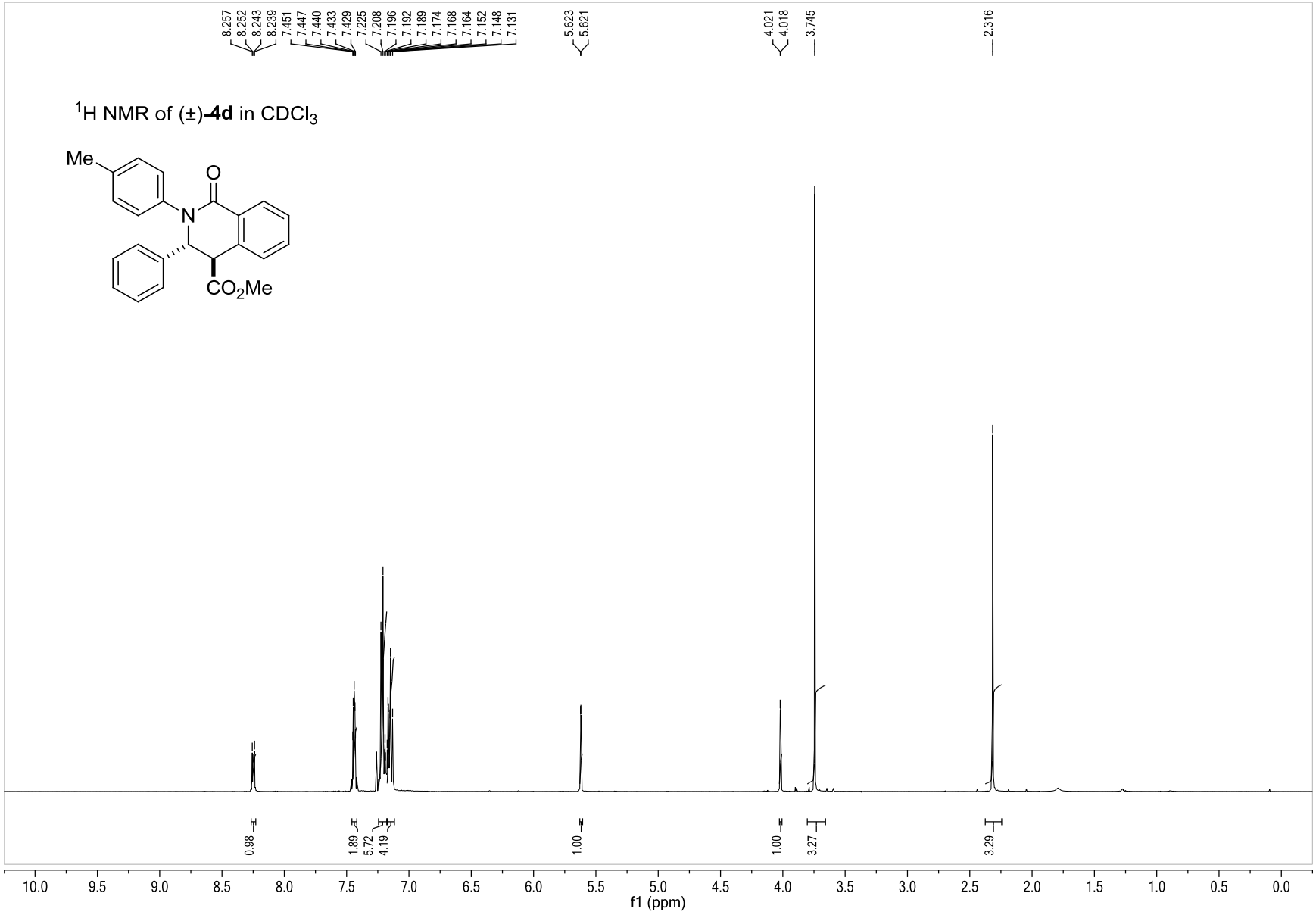
^{1}H NMR of (±)-**4b** in $CDCl_3$



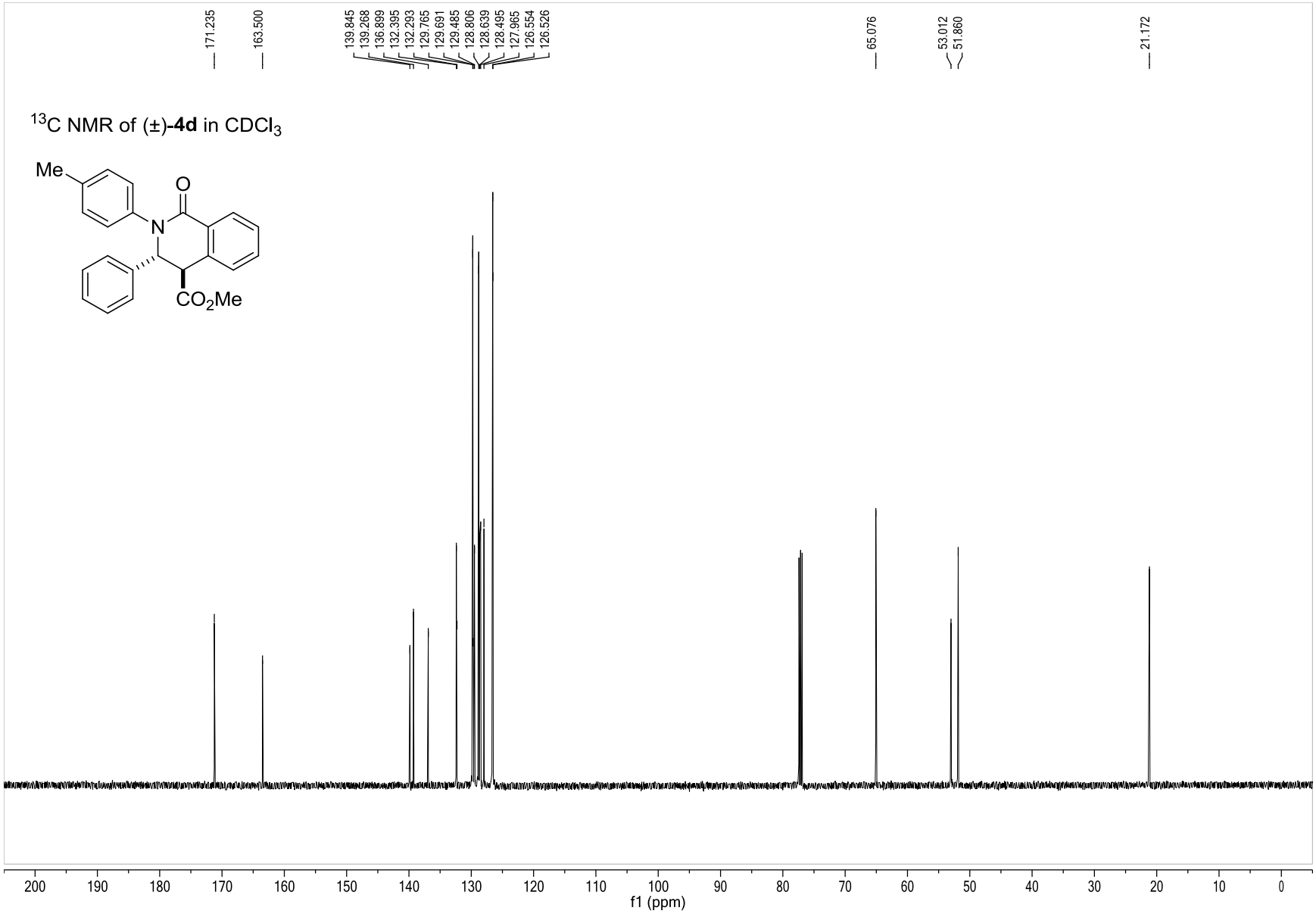

171.150
163.471
158.277
139.137
135.170
132.262
132.173
129.533
129.397
128.697
128.528
128.382
127.889
126.443
114.283
65.108
55.364
52.899
51.678
^{13}C NMR of (±)-**4b** in $CDCl_3$
MeO
O
N
CO_2Me
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


^{1}H NMR of (±)-**4c** in $CDCl_3$
Cl
O
N
CO_2Me
8.241
8.234
8.229
8.222
7.458
7.451
7.446
7.439
7.296
7.232
7.218
7.208
7.196
7.144
7.139
7.128
7.125
5.603
5.601
4.037
4.034
3.731
0.95
2.07
3.90
3.79
2.06
1.00
1.00
2.99
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

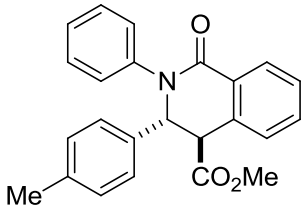

171.108
163.401
140.929
138.819
132.689
132.626
132.255
129.628
129.253
128.948
128.740
128.495
128.173
128.127
126.390
64.897
53.053
51.629
^{13}C NMR of (±)-**4c** in $CDCl_3$
Cl
O
N
CO_2Me
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

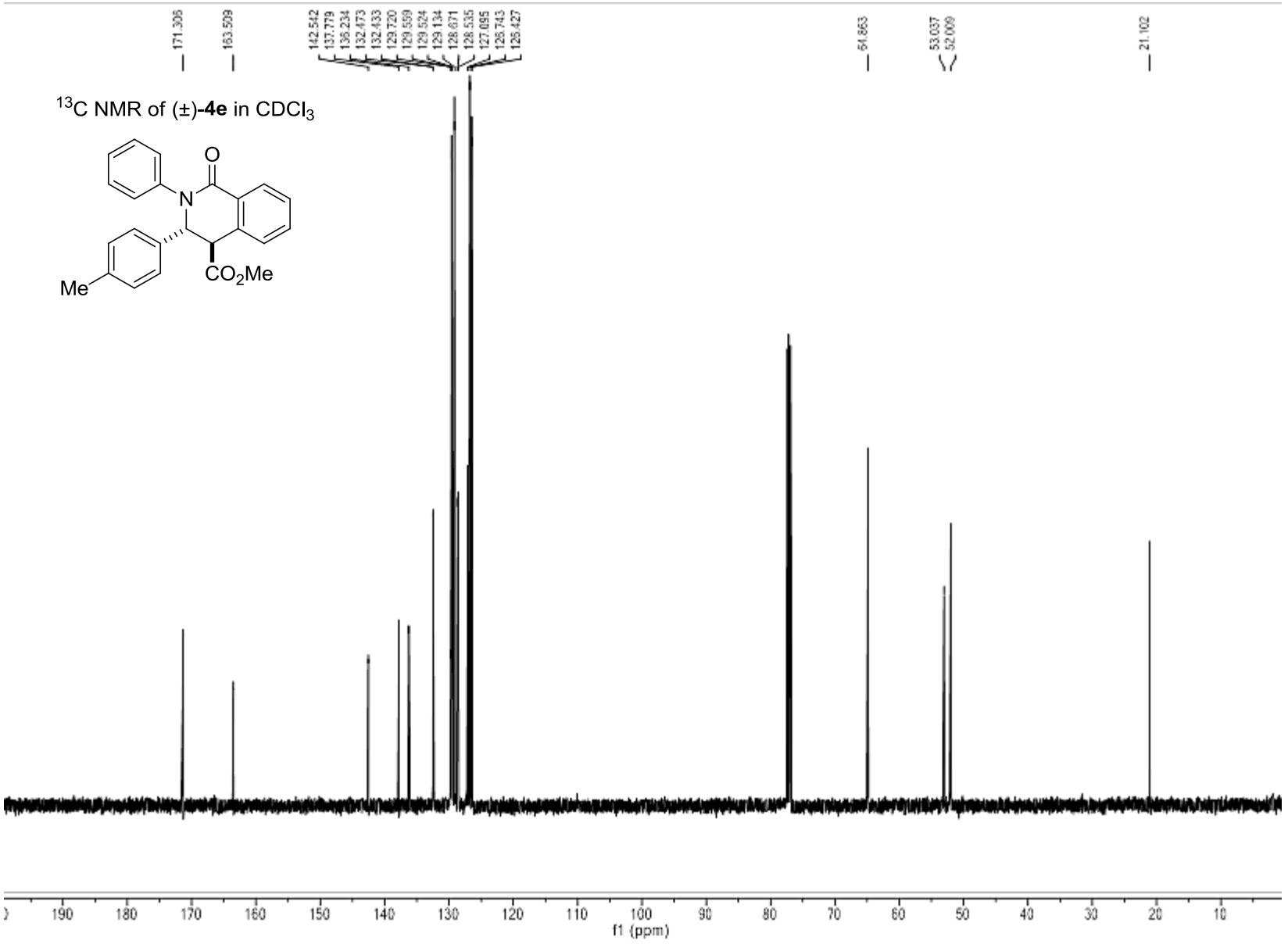


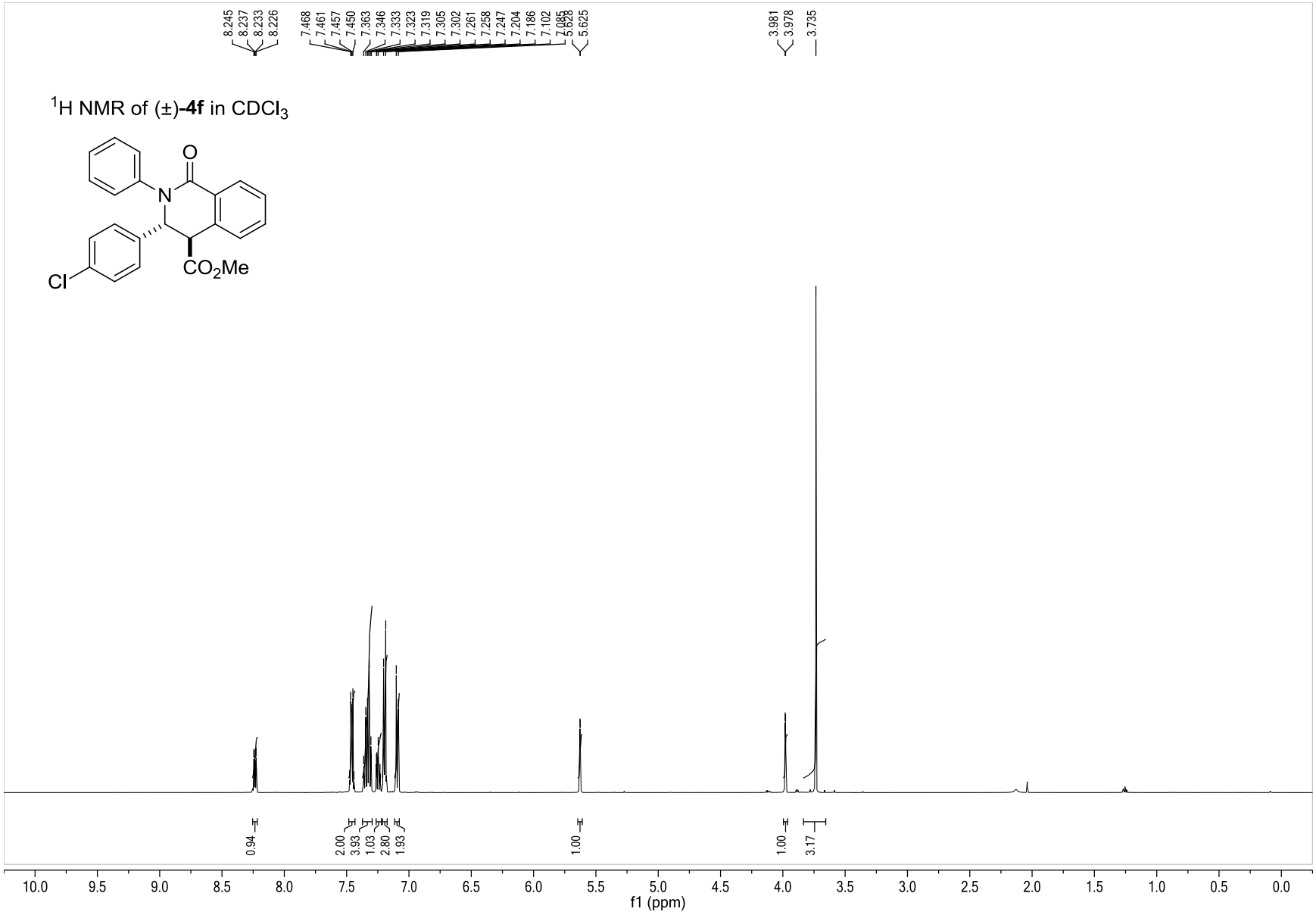
^{1}H NMR of (±)-**4d** in $CDCl_3$

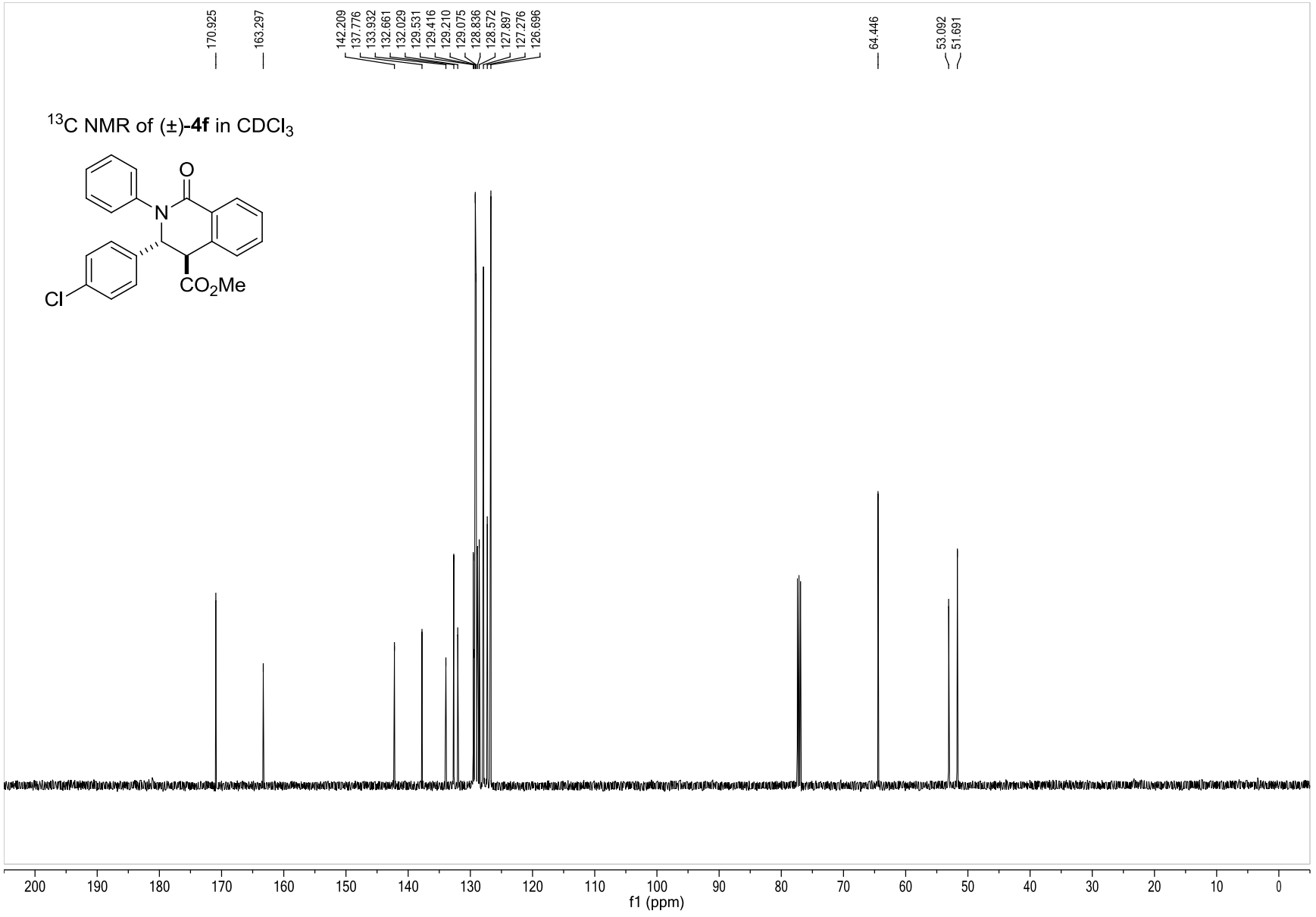

171.235
163.500
139.845
139.268
136.899
132.395
132.293
129.765
129.691
129.485
128.806
128.639
128.495
127.965
126.554
126.526
65.076
53.012
51.860
21.172
^{13}C NMR of (±)-**4d** in $CDCl_3$
Me
O
N
CO_2Me
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

^{1}H NMR of (±)-**4e** in $CDCl_3$

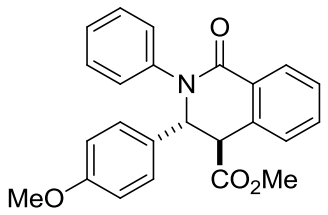


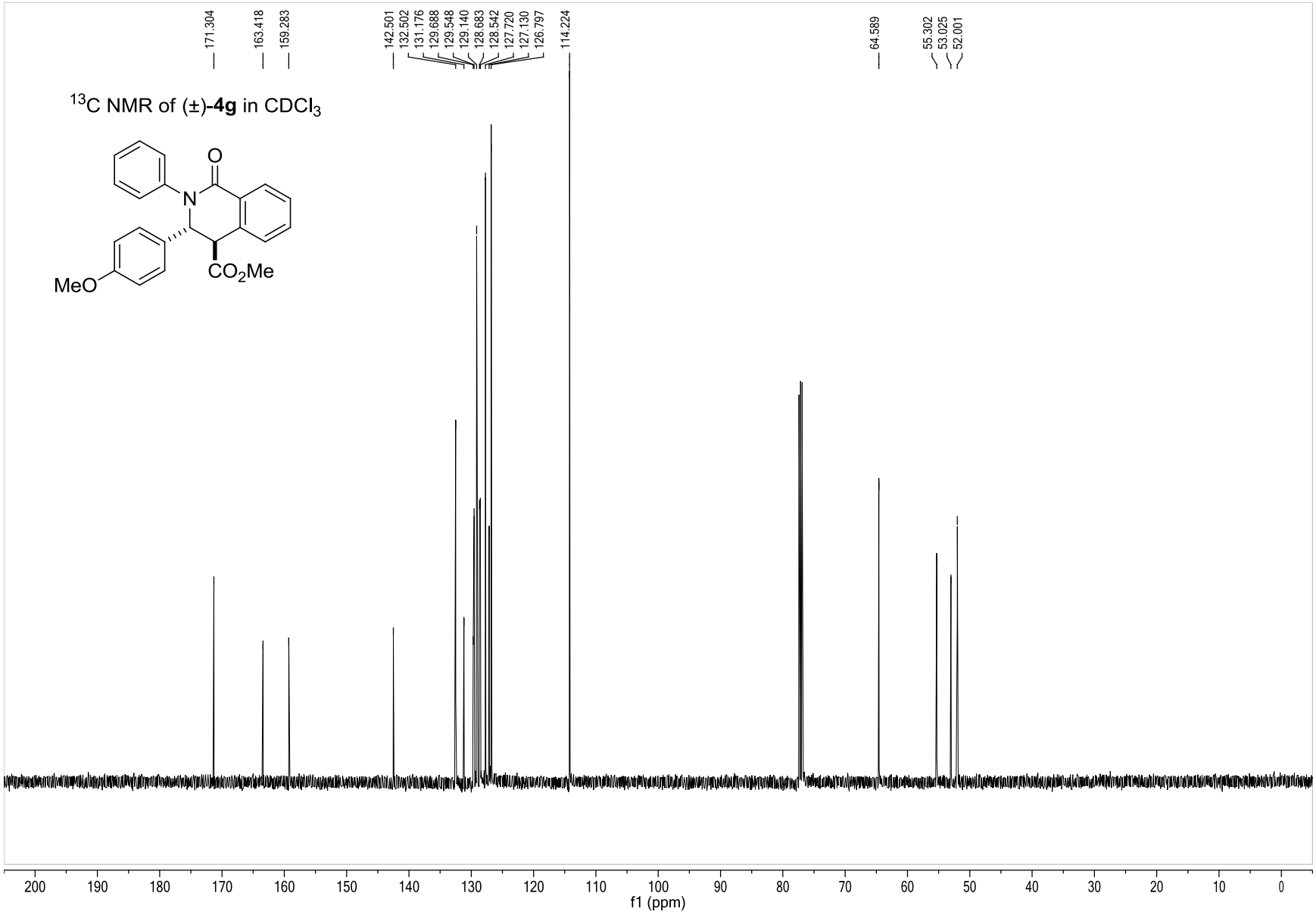

171.306
163.509
142.542
137.779
136.234
132.473
132.433
129.720
129.559
129.524
129.134
128.671
128.535
127.095
126.743
126.427
54.863
53.037
52.009
21.102
^{13}C NMR of (±)-**4e** in $CDCl_3$
O
N
Me
CO_2Me
f1 (ppm)

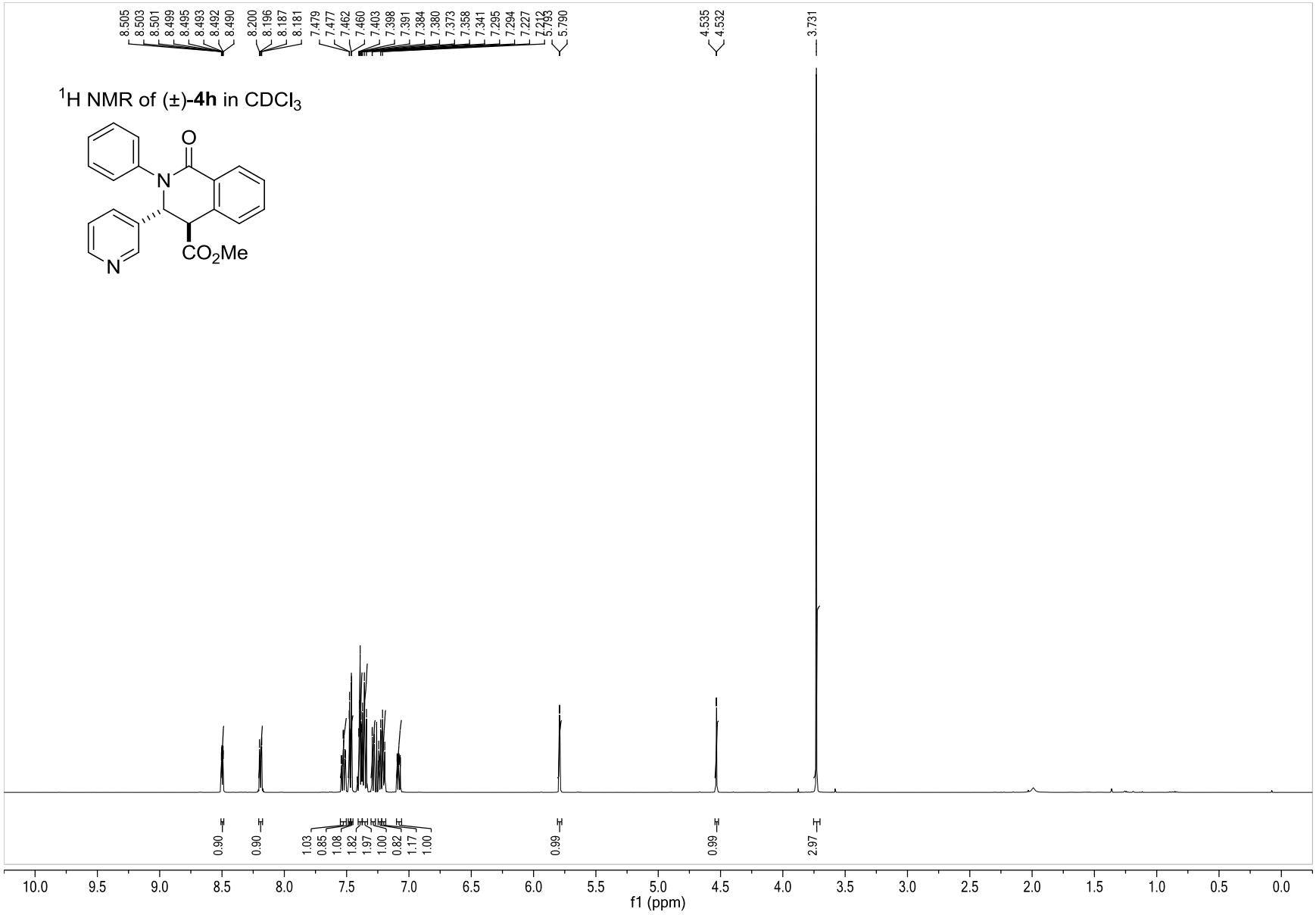

8.245
8.237
8.233
8.226
7.468
7.461
7.457
7.450
7.363
7.346
7.333
7.323
7.319
7.305
7.302
7.261
7.258
7.247
7.204
7.186
7.102
5.628
5.625
3.981
3.978
3.735
1H NMR of (±)-4f in CDCl3
O
N
Cl
CO2Me
0.94
2.00
3.93
1.03
2.80
1.93
1.00
1.00
3.17
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

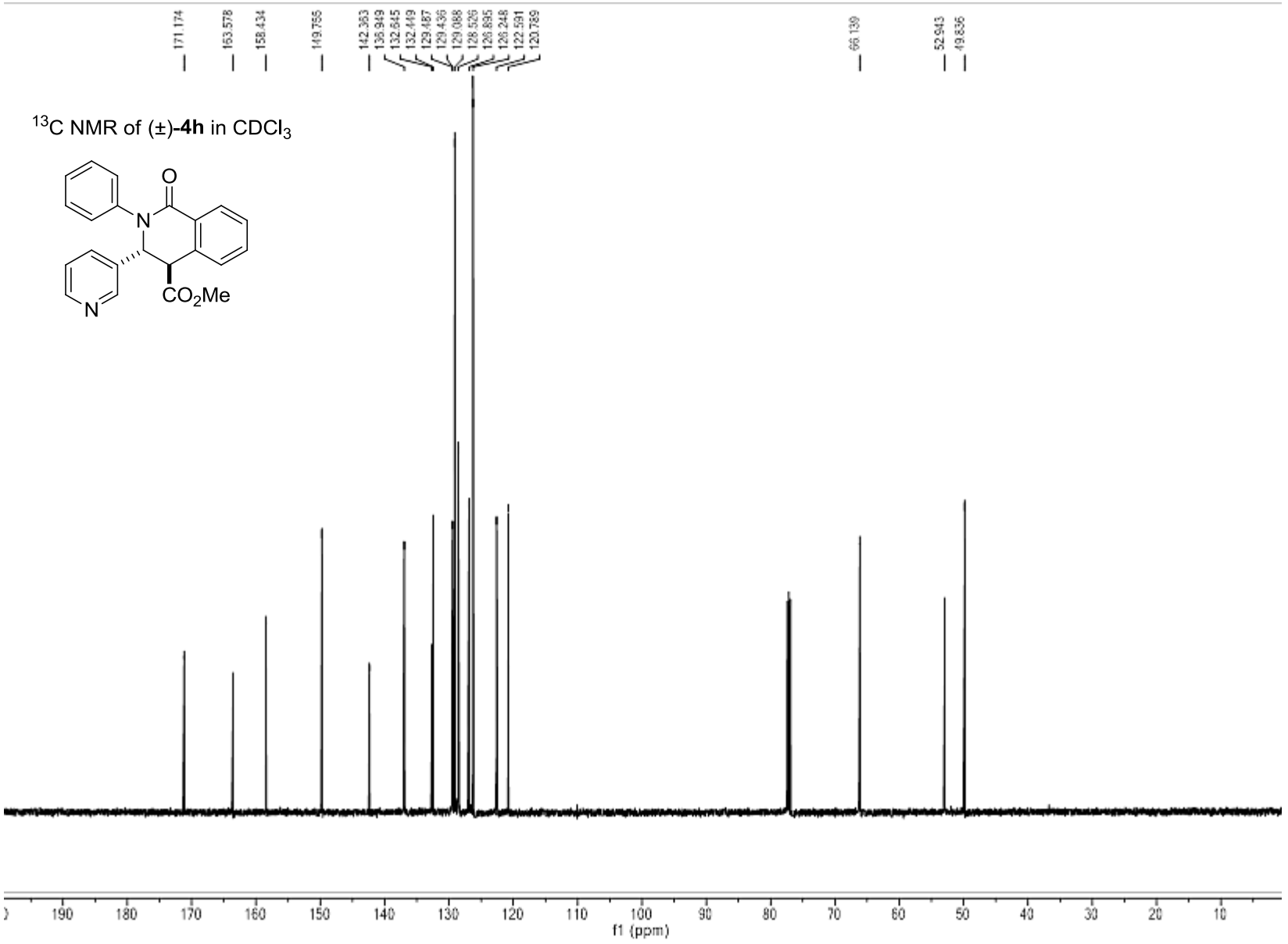

170.925
163.297
142.209
137.776
133.932
132.661
132.029
129.531
129.416
129.210
129.075
128.836
128.572
127.897
127.276
126.696
64.446
53.092
51.691
^{13}C NMR of (±)-**4f** in $CDCl_3$
O
N
Cl
CO_2Me
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

^{1}H NMR of (±)-**4g** in $CDCl_3$

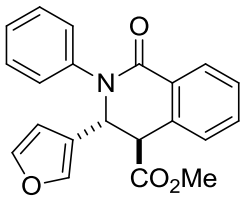



171.304
163.418
159.283
142.501
132.502
131.176
129.688
129.548
129.140
128.683
128.542
127.720
127.130
126.797
114.224
64.589
55.302
53.025
52.001
13C NMR of (±)-4g in CDCl3
O
N
MeO
CO2Me
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

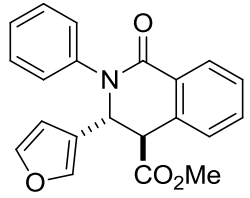

8.505
8.503
8.501
8.499
8.495
8.493
8.492
8.490
8.200
8.196
8.187
8.181
7.479
7.477
7.462
7.460
7.403
7.398
7.391
7.384
7.380
7.373
7.358
7.341
7.295
7.294
7.227
5.793
5.790
4.535
4.532
3.731
^{1}H NMR of (±)-**4h** in $CDCl_3$
O
N
CO_2Me
N
0.90
0.90
1.03
0.85
1.08
1.82
1.97
1.00
0.82
1.17
1.00
0.99
0.99
2.97
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


171.174
163.578
158.434
149.755
142.353
136.949
132.645
132.449
129.487
129.436
129.088
128.526
128.895
126.248
122.591
120.789
66.139
52.943
49.836
13C NMR of (±)-4h in CDCl3
O
N
N
CO2Me
f1 (ppm)

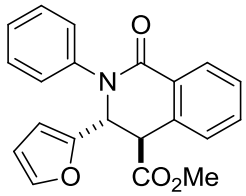
^{1}H NMR of (±)-**4i** in $CDCl_3$

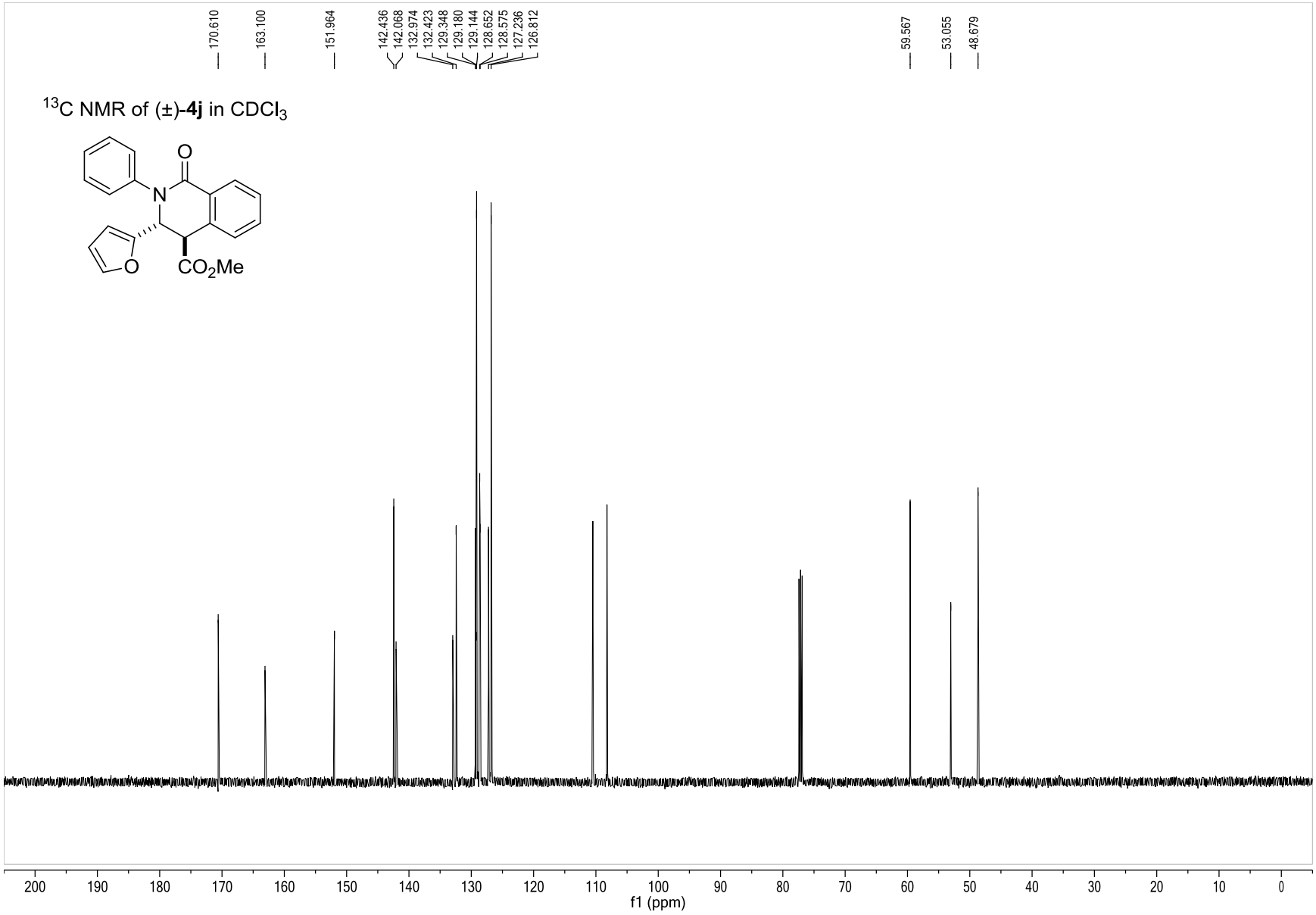


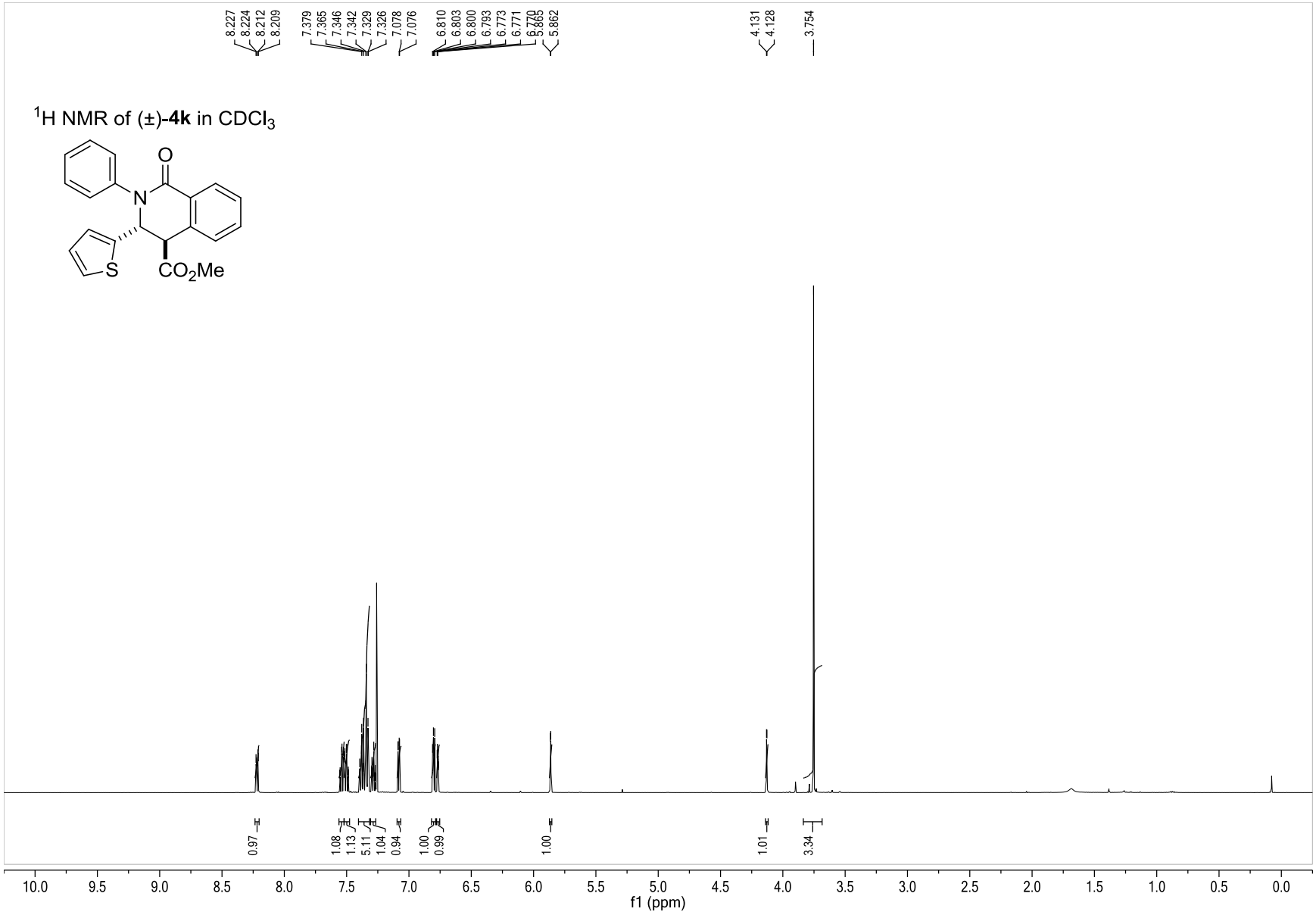
^{13}C NMR of (±)-**4i** in $CDCl_3$

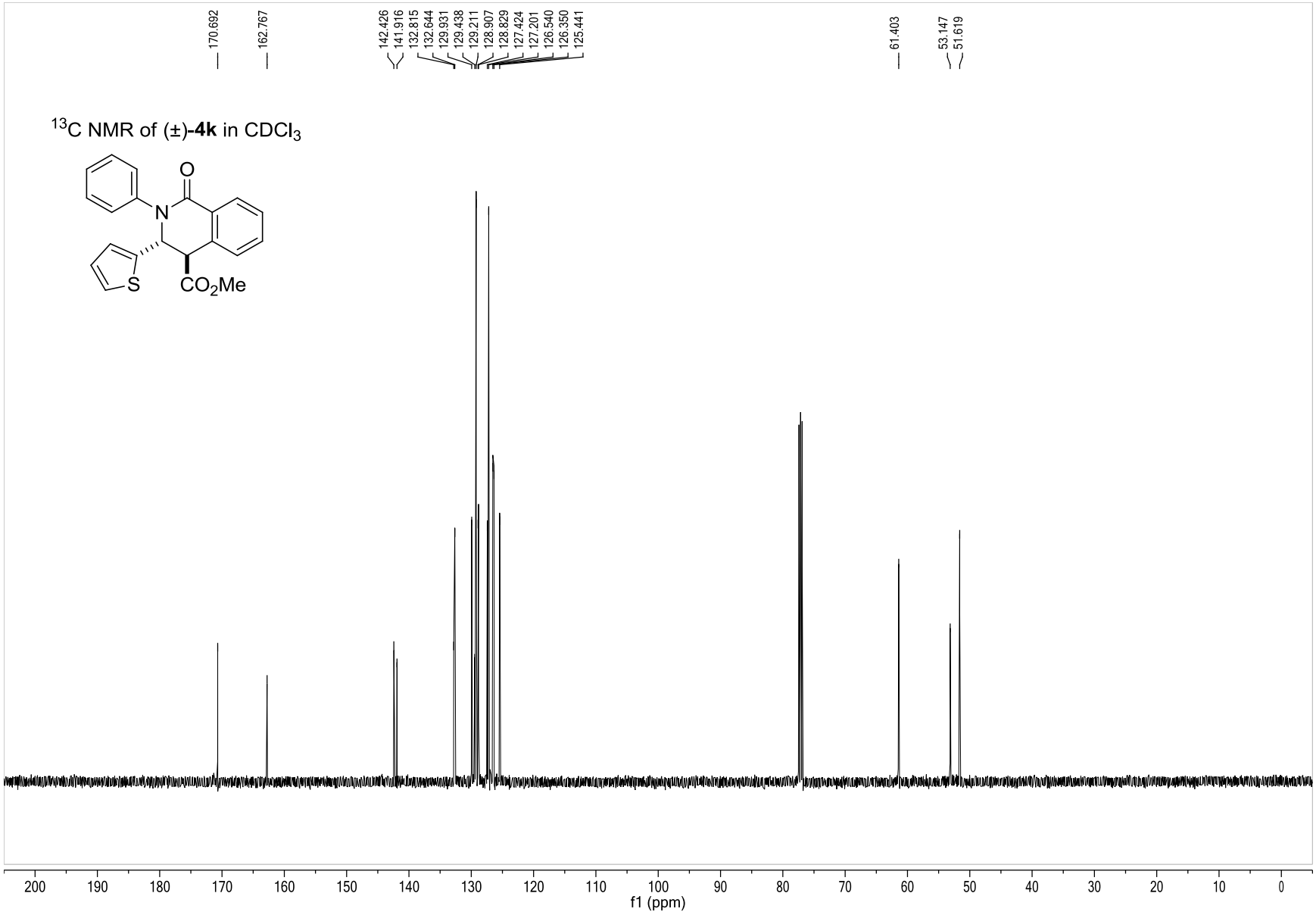


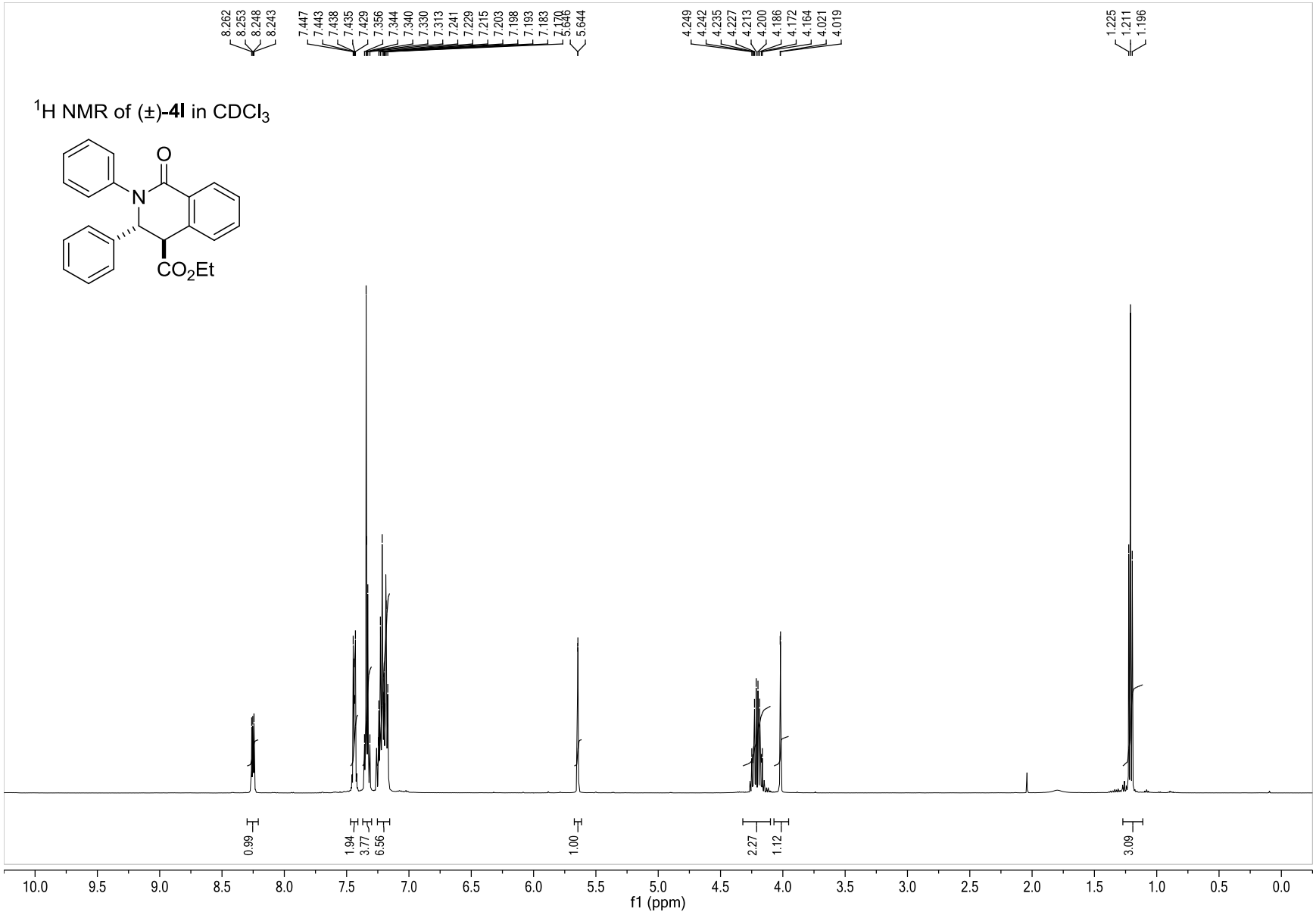
^{1}H NMR of (±)-**4j** in $CDCl_3$

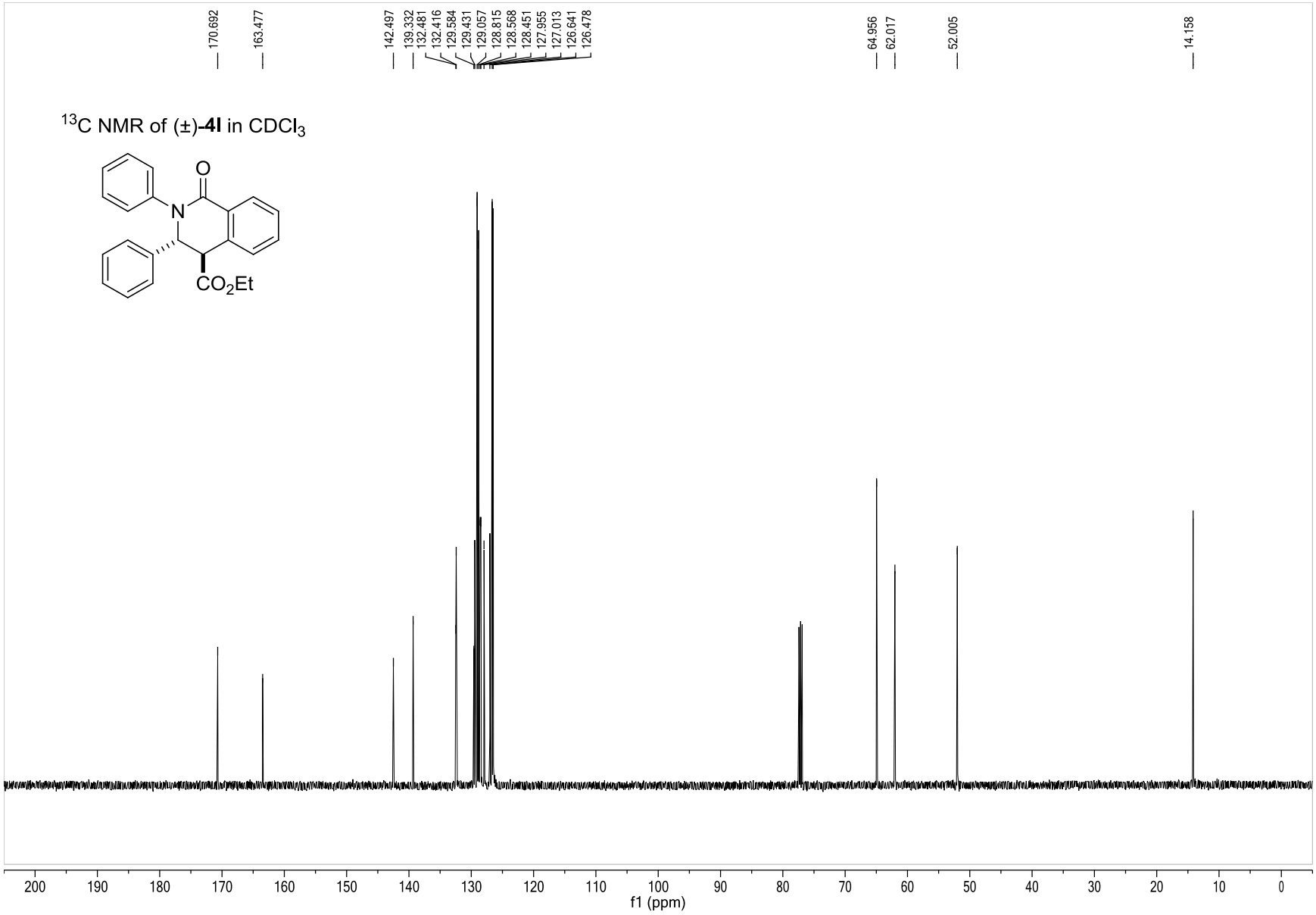


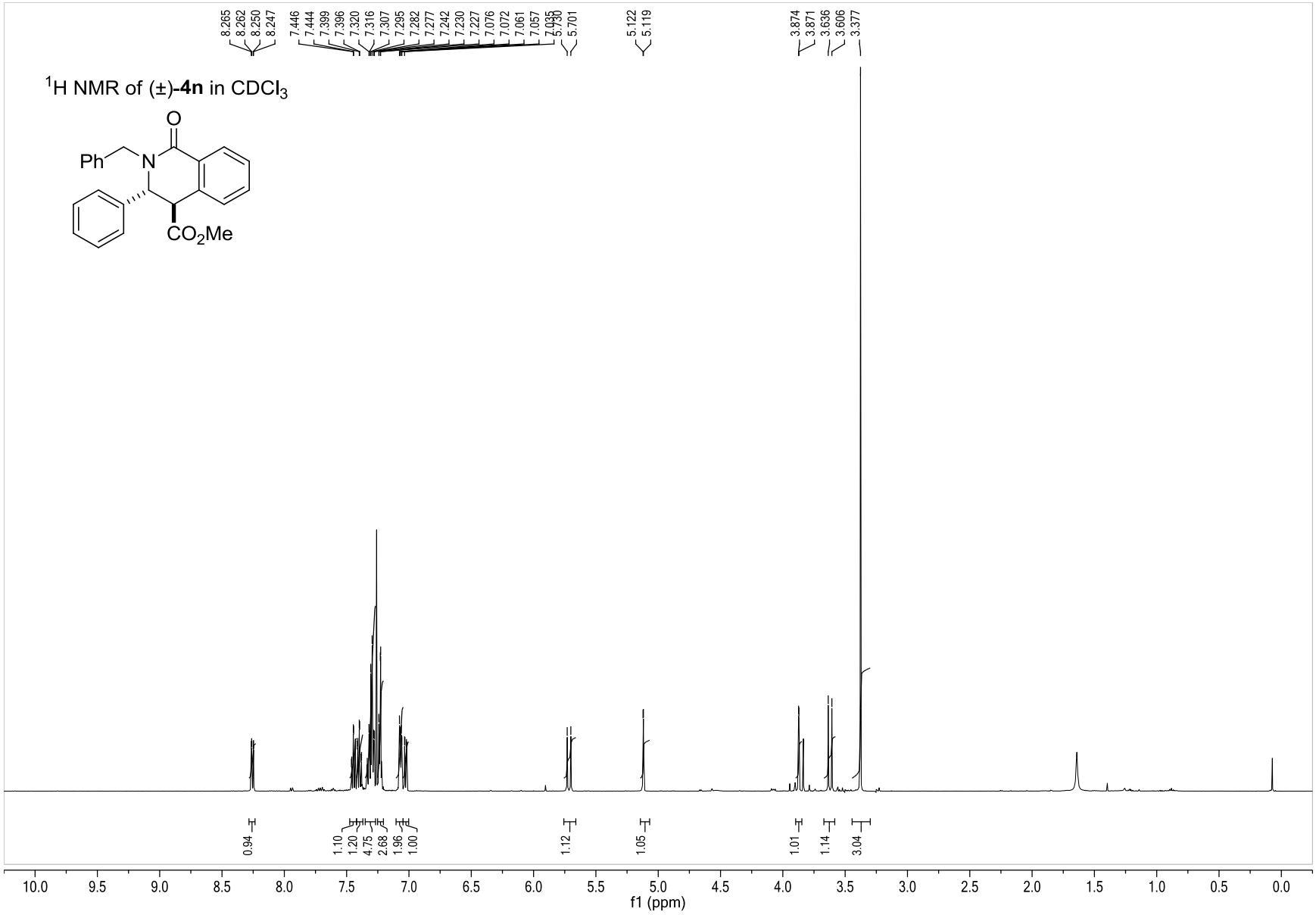

170.610
163.100
151.964
142.436
142.068
132.974
132.423
129.348
129.180
129.144
128.652
128.575
127.236
126.812
59.567
53.055
48.679
^{13}C NMR of (±)-**4j** in $CDCl_3$
O
N
O
CO_2Me
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.227
8.224
8.212
8.209
7.379
7.365
7.346
7.342
7.329
7.326
7.078
7.076
6.810
6.803
6.800
6.793
6.773
6.771
6.770
5.865
5.862
4.131
4.128
3.754
1H NMR of (±)-4k in CDCl3
O
N
S
CO2Me
0.97
1.08
1.13
5.11
1.04
0.94
1.00
0.99
1.00
1.01
3.34
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

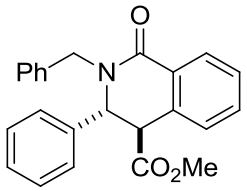

170.692
162.767
142.426
141.916
132.815
132.644
129.931
129.438
129.211
128.907
128.829
127.424
127.201
126.540
126.350
125.441
61.403
53.147
51.619
^{13}C NMR of (±)-**4k** in $CDCl_3$
O
N
S
CO_2Me
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.262
8.253
8.248
8.243
7.447
7.443
7.438
7.435
7.429
7.356
7.344
7.340
7.330
7.313
7.241
7.229
7.215
7.203
7.198
7.193
7.183
7.170
5.646
5.644
4.249
4.242
4.235
4.227
4.213
4.200
4.186
4.172
4.164
4.021
4.019
1.225
1.211
1.196
1H NMR of (±)-4l in CDCl3
O
N
CO2Et
0.99
1.94
3.77
6.56
1.00
2.27
1.12
3.09
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

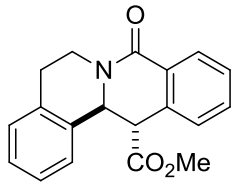

170.692
163.477
142.497
139.332
132.481
132.416
129.584
129.431
129.057
128.815
128.568
128.451
127.955
127.013
126.641
126.478
64.956
62.017
52.005
14.158
^{13}C NMR of (±)-**4l** in $CDCl_3$
O
N
CO_2Et
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

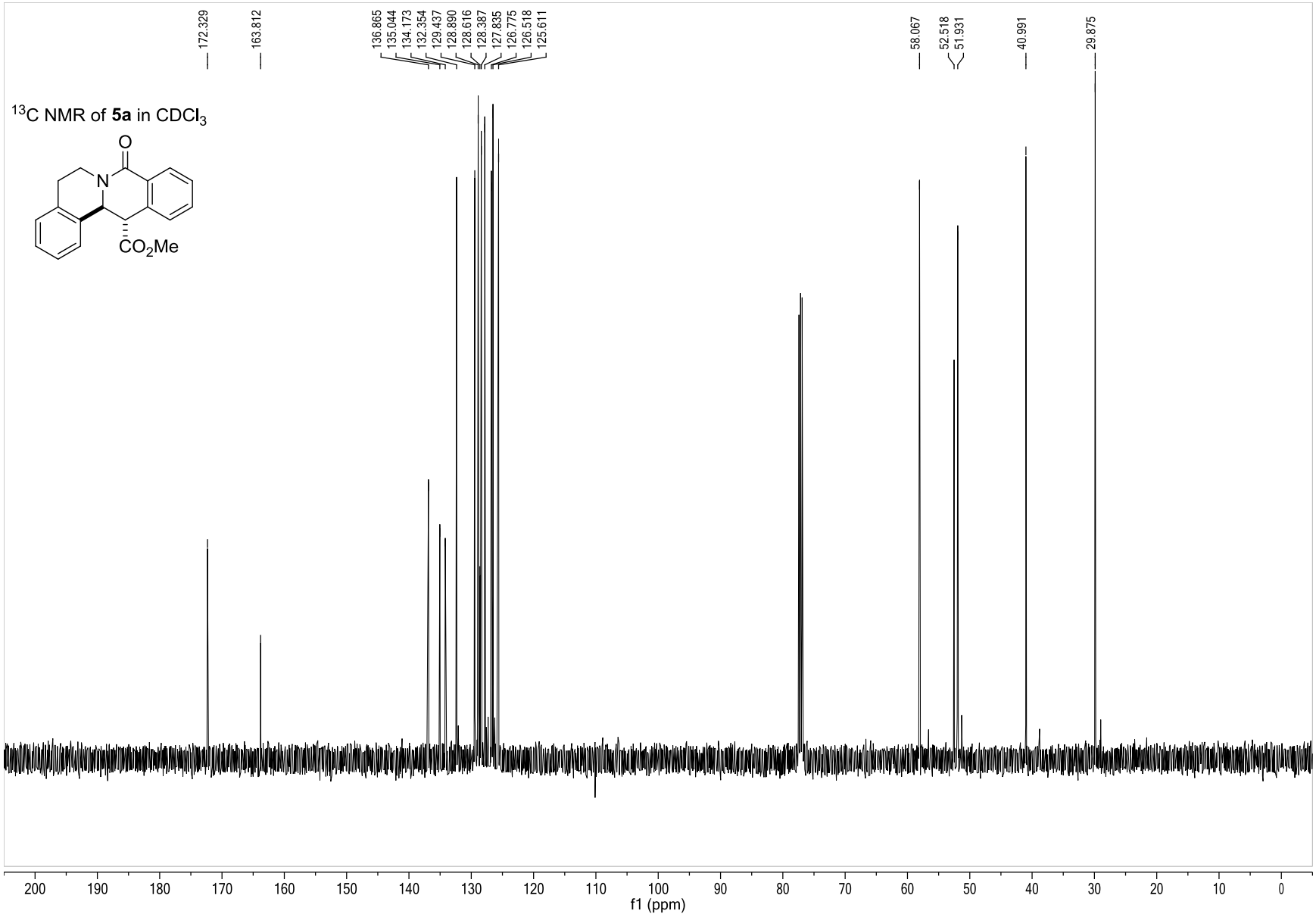

^{1}H NMR of (±)-**4n** in $CDCl_3$
O
Ph
N
CO_2Me
8.265
8.262
8.250
8.247
7.446
7.444
7.399
7.396
7.320
7.316
7.307
7.295
7.282
7.277
7.242
7.230
7.227
7.076
7.072
7.061
7.057
5.730
5.701
5.122
5.119
3.874
3.871
3.636
3.606
3.377
0.94
1.10
1.20
4.75
2.68
1.96
1.00
1.12
1.05
1.01
1.14
3.04
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

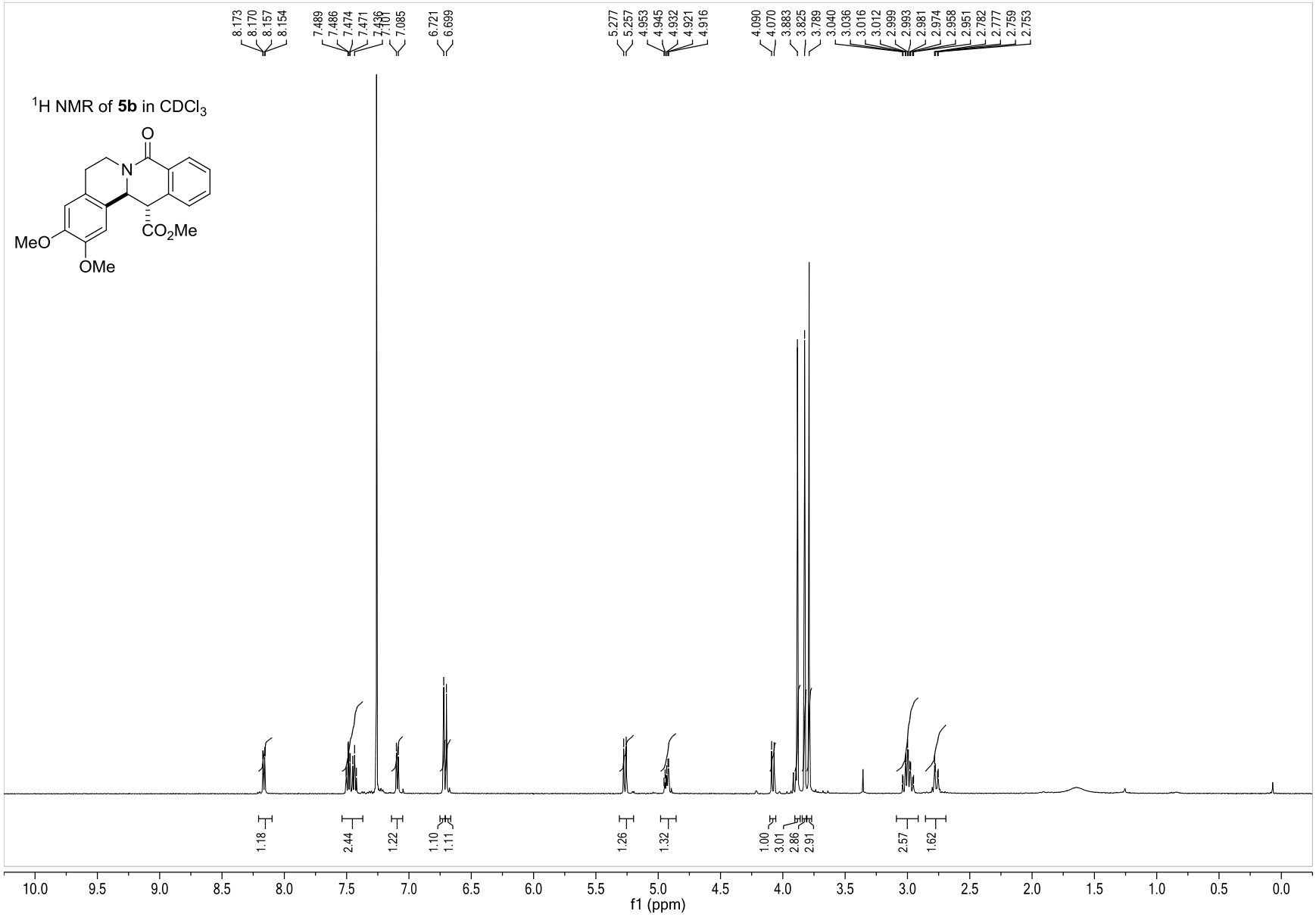
^{13}C NMR of (±)-**4n** in $CDCl_3$

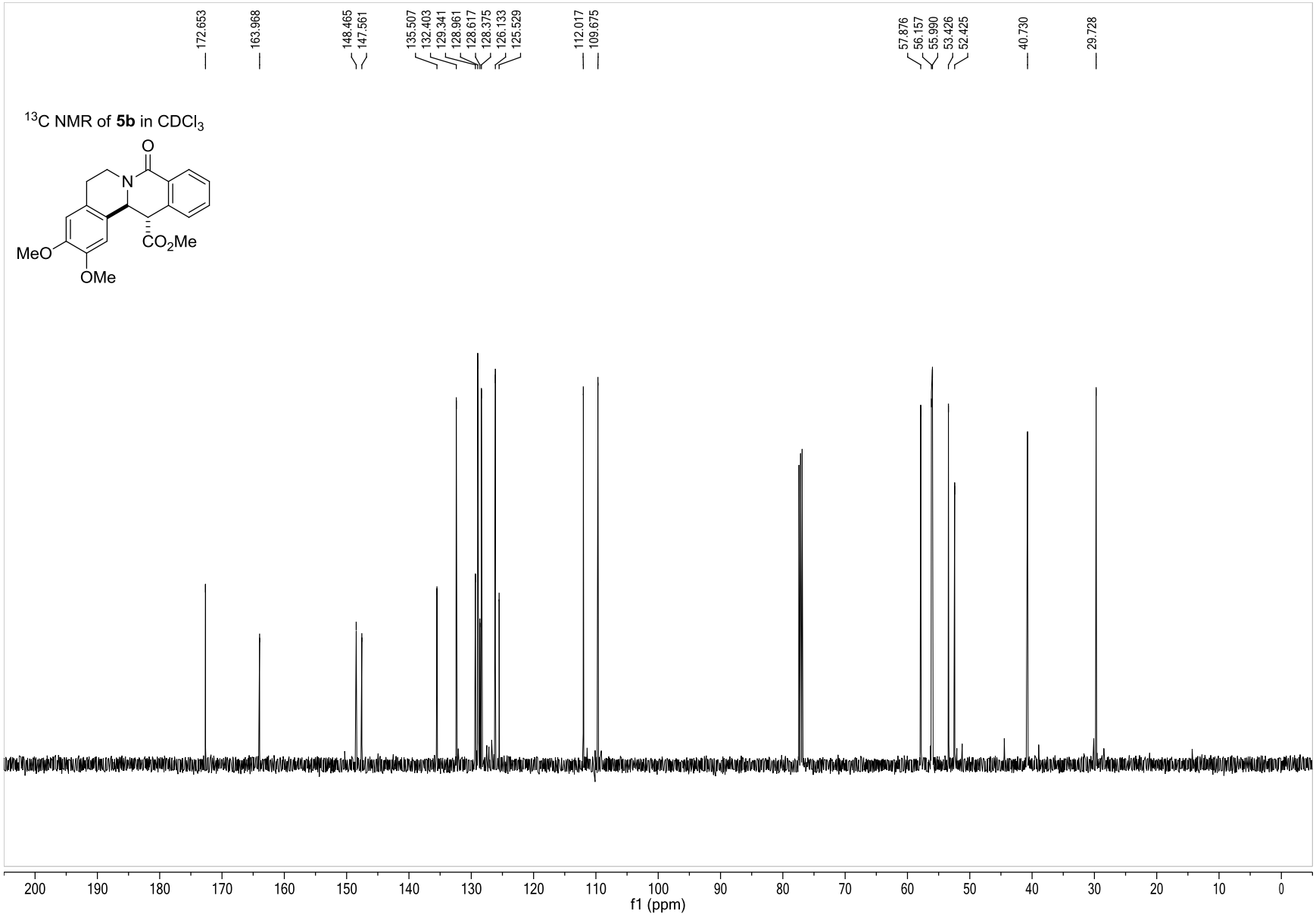


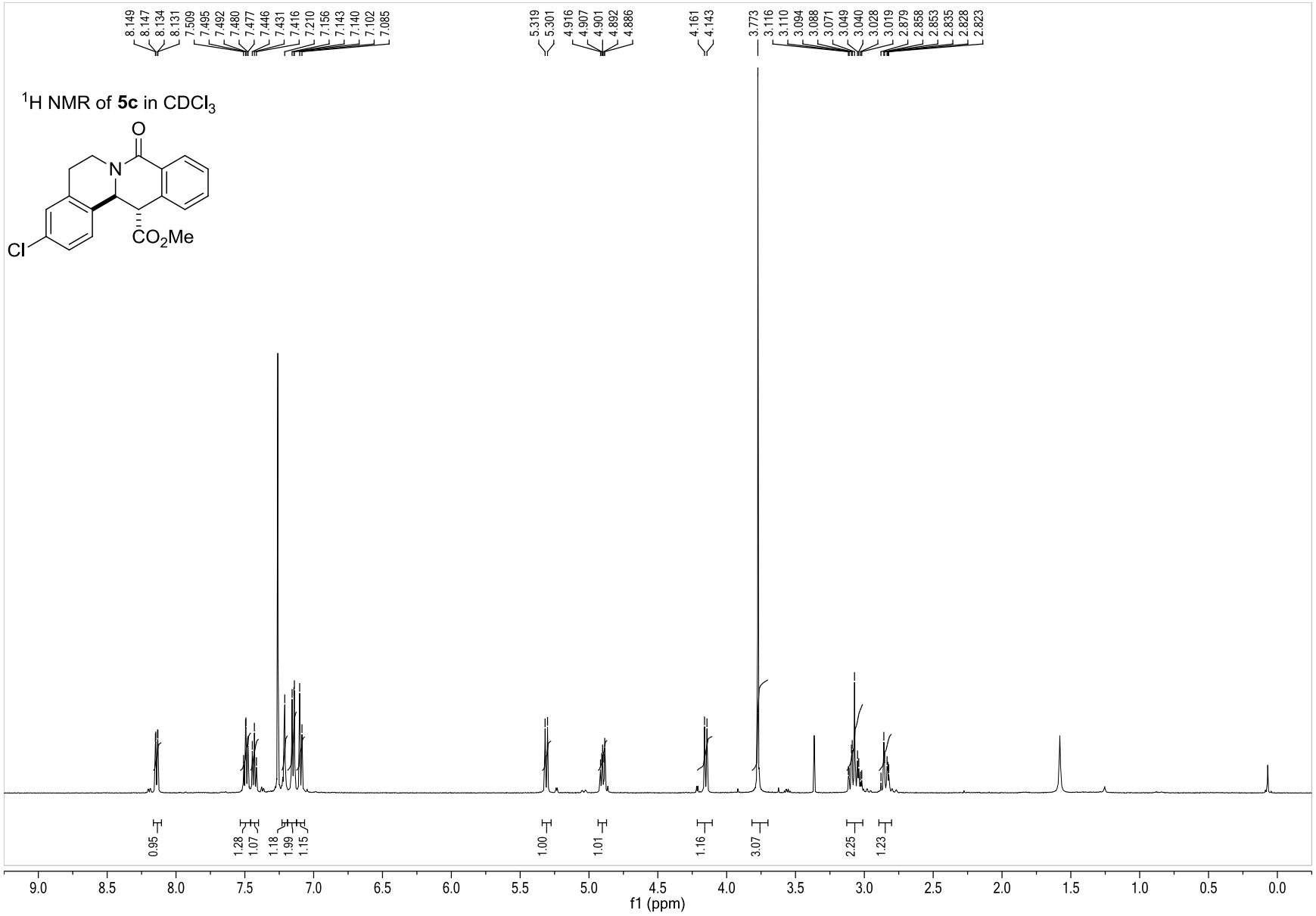
^{1}H NMR of **5a** in $CDCl_3$

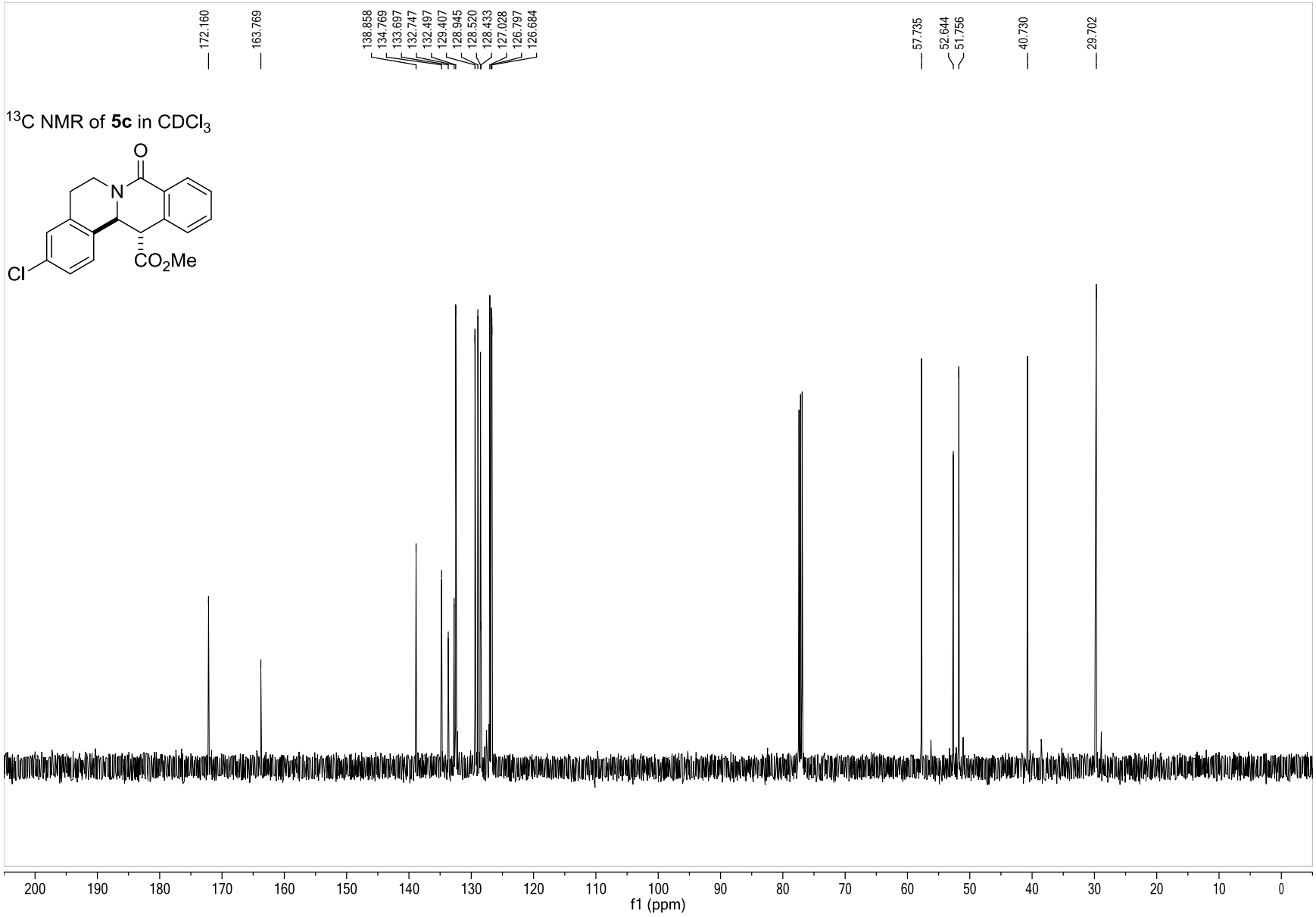


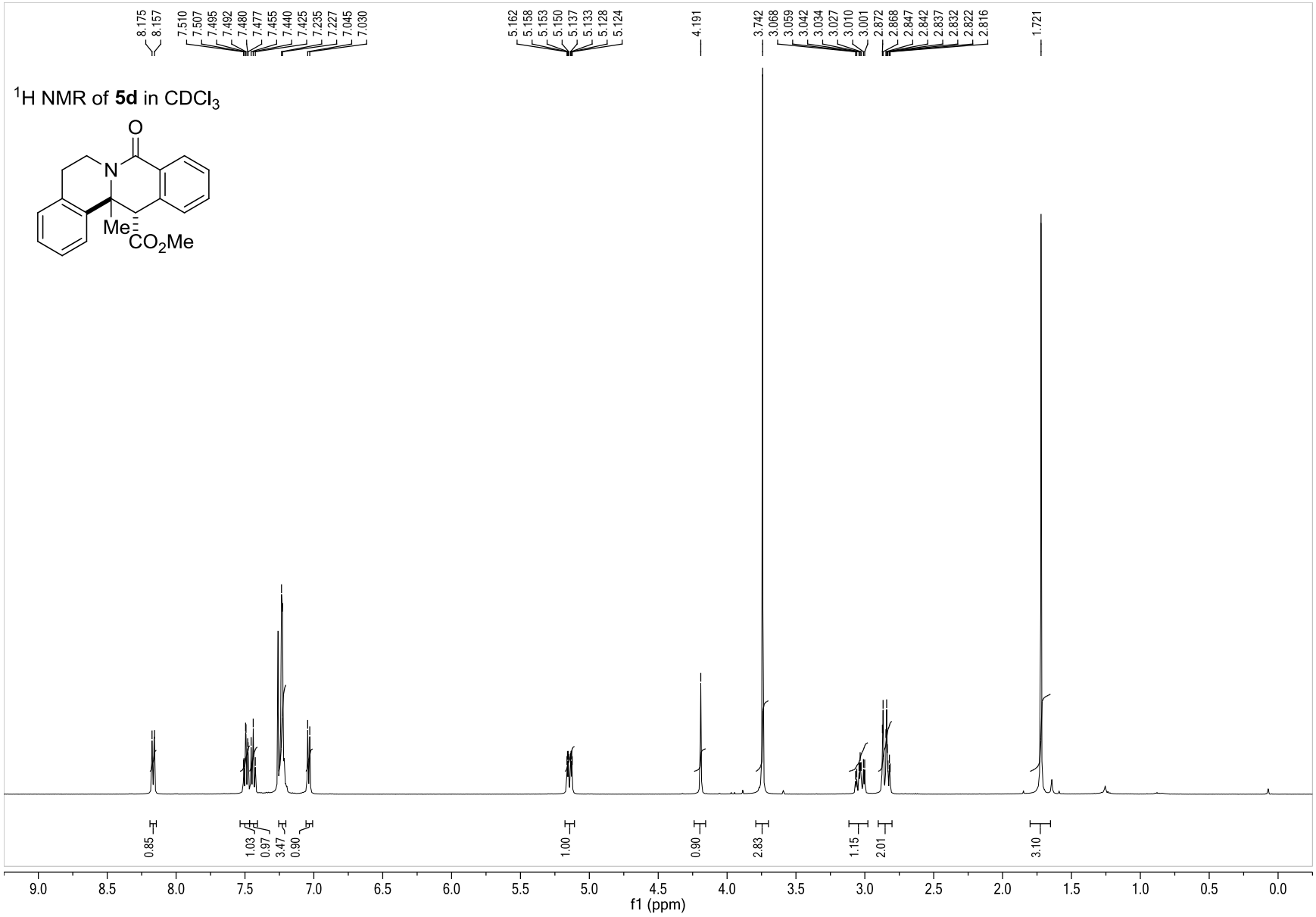

172.329
163.812
136.865
135.044
134.173
132.354
129.437
128.890
128.616
128.387
127.835
126.775
126.518
125.611
58.067
52.518
51.931
40.991
29.875
13C NMR of 5a in CDCl3
O
N
CO2Me
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

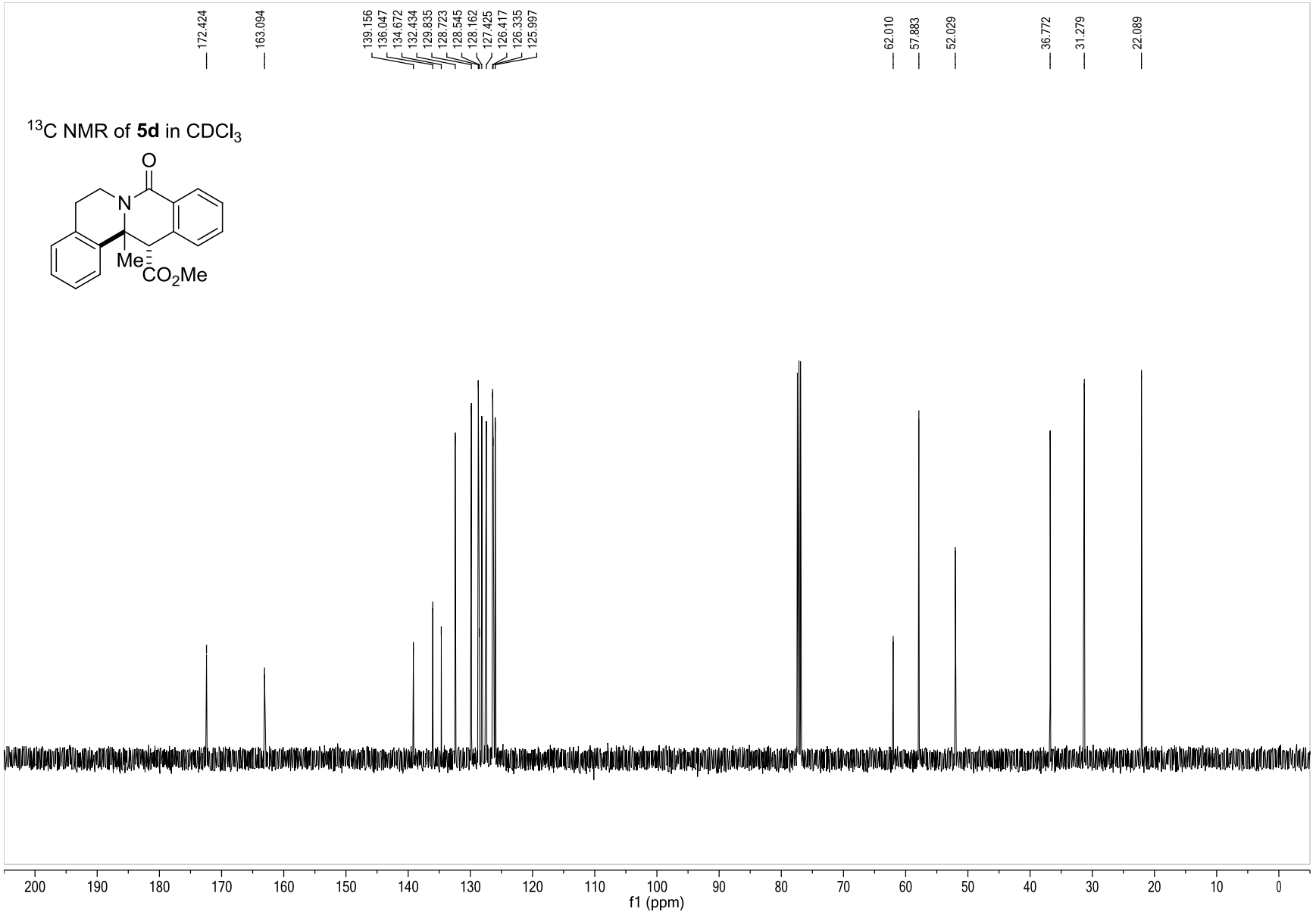

^{1}H NMR of **5b** in $CDCl_3$
O
N
CO_2Me
MeO
OMe
8.173
8.170
8.157
8.154
7.489
7.486
7.474
7.471
7.436
7.431
7.085
6.721
6.699
5.277
5.257
4.953
4.945
4.932
4.921
4.916
4.090
4.070
3.883
3.825
3.789
3.040
3.036
3.016
3.012
2.999
2.993
2.981
2.974
2.958
2.951
2.782
2.777
2.759
2.753
1.18
2.44
1.22
1.10
1.11
1.26
1.32
1.00
3.01
2.86
2.91
2.57
1.62
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


172.653
163.968
148.465
147.561
135.507
132.403
129.341
128.961
128.617
128.375
126.133
125.529
112.017
109.675
57.876
56.157
55.990
53.426
52.425
40.730
29.728
^{13}C NMR of **5b** in $CDCl_3$
O
N
MeO
OMe
CO_2Me
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

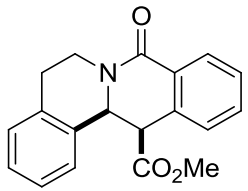

8.149
8.147
8.134
8.131
7.509
7.495
7.492
7.480
7.477
7.446
7.431
7.416
7.210
7.156
7.143
7.140
7.102
7.085
5.319
5.301
4.916
4.907
4.901
4.892
4.886
4.161
4.143
3.773
3.116
3.110
3.094
3.088
3.071
3.049
3.040
3.028
3.019
2.879
2.858
2.853
2.835
2.828
2.823
^{1}H NMR of **5c** in $CDCl_3$
O
N
Cl
CO_2Me
0.95
1.28
1.07
1.18
1.99
1.15
1.00
1.01
1.16
3.07
2.25
1.23
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

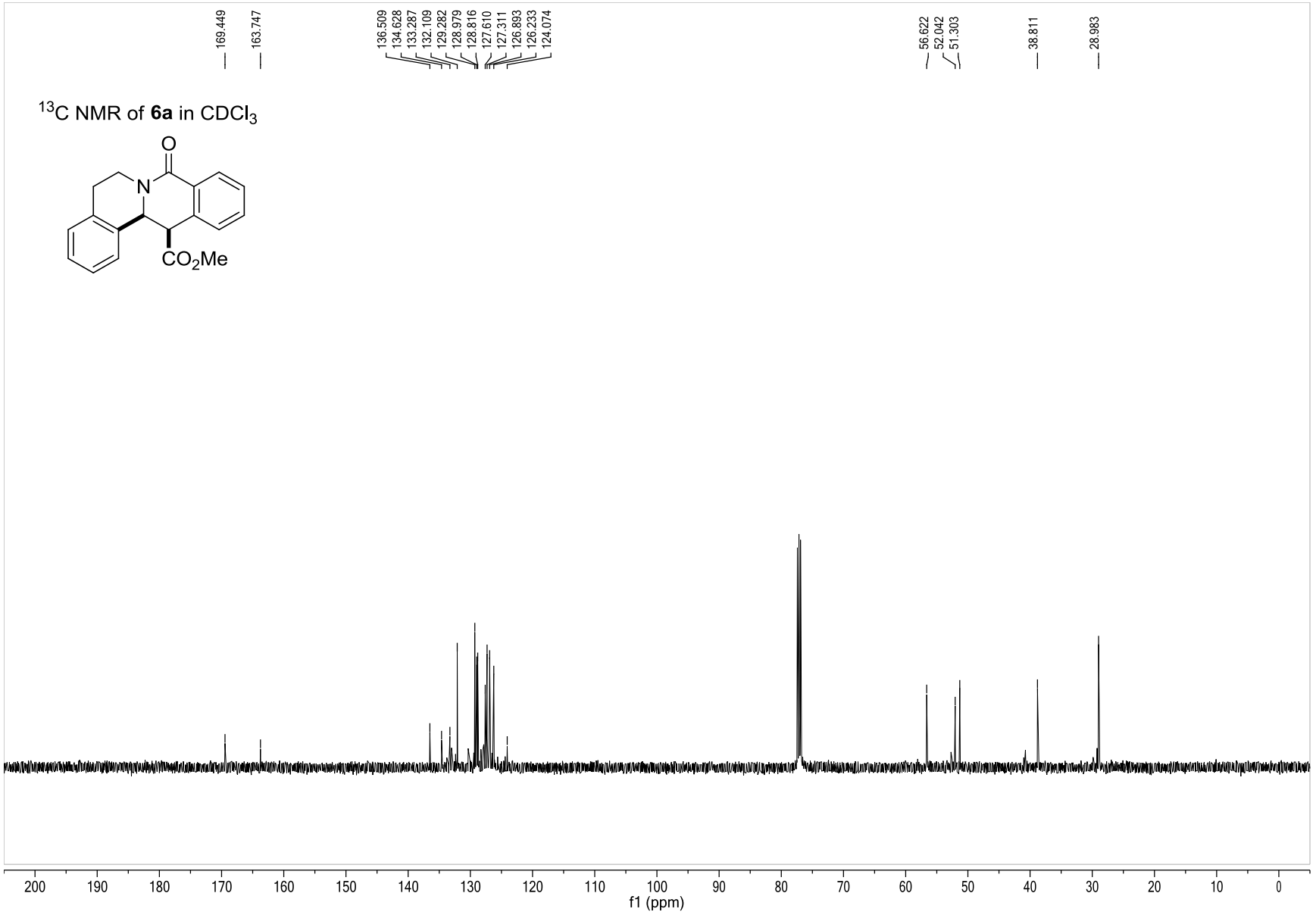

172.160
163.769
138.858
134.769
133.697
132.747
132.497
129.407
128.945
128.520
128.433
127.028
126.797
126.684
57.735
52.644
51.756
40.730
29.702
^{13}C NMR of **5c** in $CDCl_3$
O
N
Cl
CO_2Me
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.175
8.157
7.510
7.507
7.495
7.492
7.480
7.477
7.455
7.440
7.425
7.235
7.227
7.045
7.030
5.162
5.158
5.153
5.150
5.137
5.133
5.128
5.124
4.191
3.742
3.068
3.059
3.042
3.034
3.027
3.010
3.001
2.872
2.868
2.847
2.842
2.837
2.832
2.822
2.816
1.721
^{1}H NMR of **5d** in $CDCl_3$
O
N
Me
CO_2Me
0.85
1.03
0.97
3.47
0.90
1.00
0.90
2.83
1.15
2.01
3.10
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

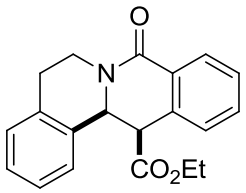

172.424
163.094
139.156
136.047
134.672
132.434
129.835
128.723
128.545
128.162
127.425
126.417
126.335
125.997
62.010
57.883
52.029
36.772
31.279
22.089
^{13}C NMR of **5d** in $CDCl_3$
O
N
Me
CO_2Me
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

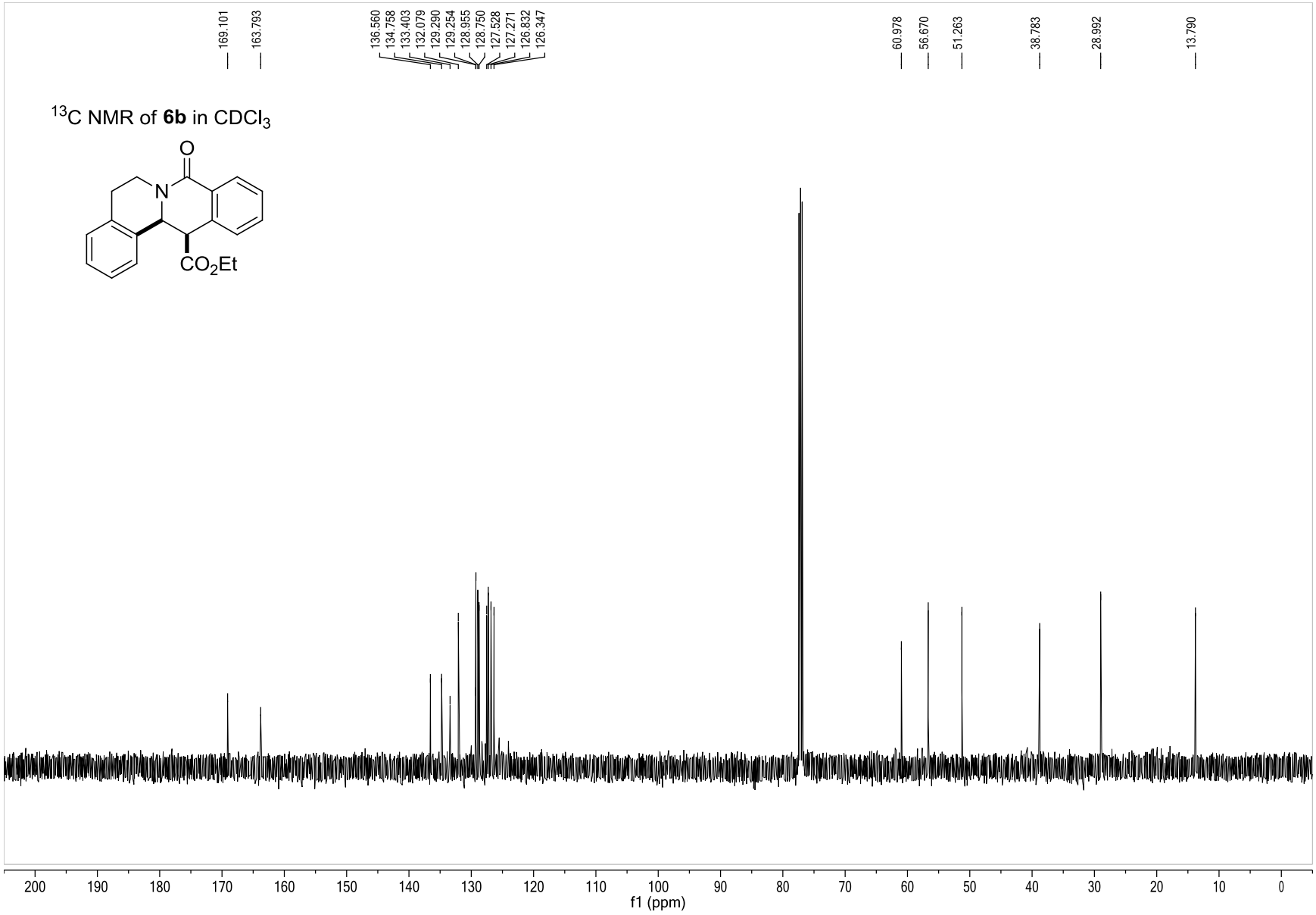
^{1}H NMR of **6a** in $CDCl_3$

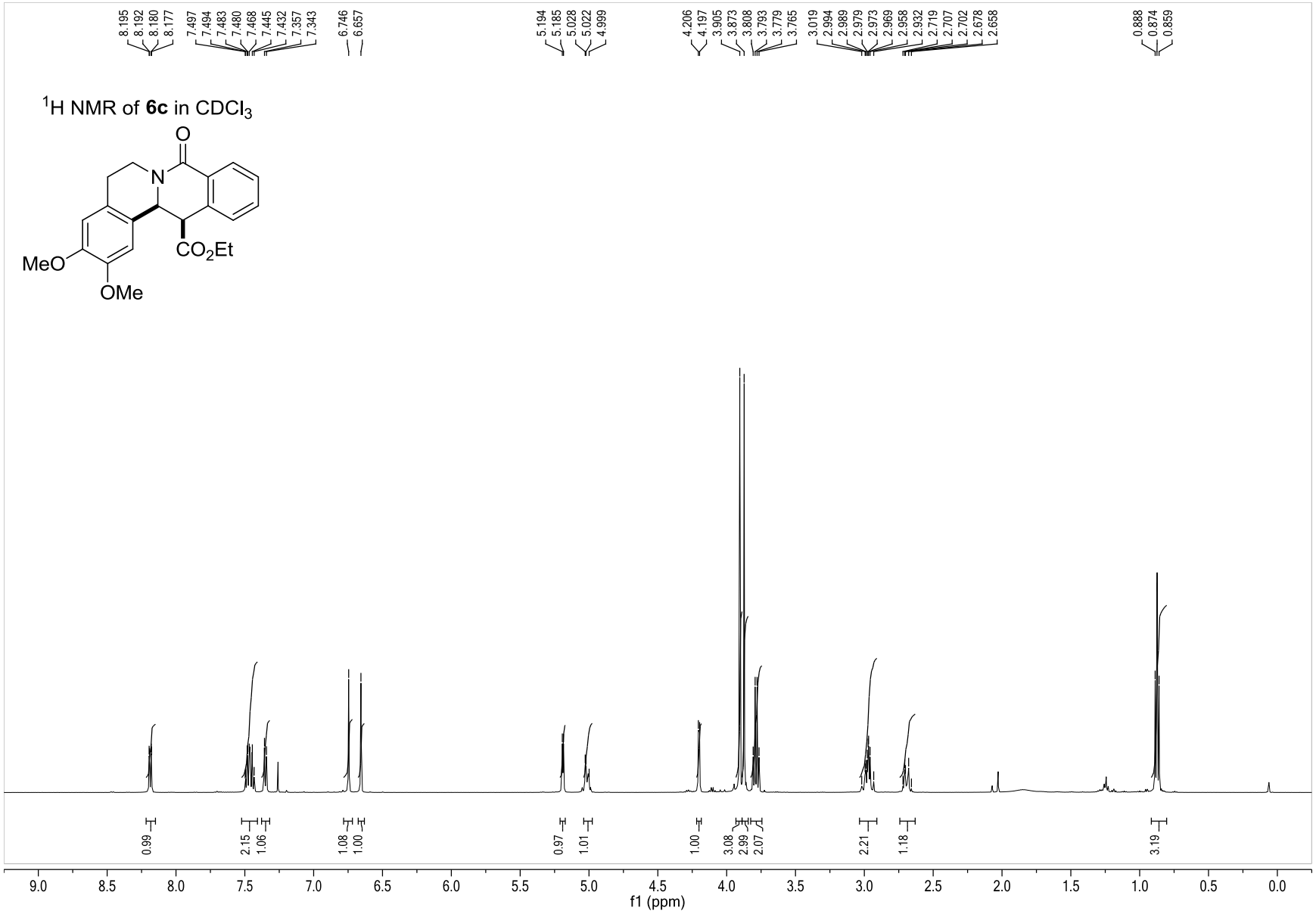



169.449
163.747
136.509
134.628
133.287
132.109
129.282
128.979
128.816
127.610
127.311
126.893
126.233
124.074
56.622
52.042
51.303
38.811
28.983
^{13}C NMR of **6a** in $CDCl_3$
O
N
CO_2Me
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

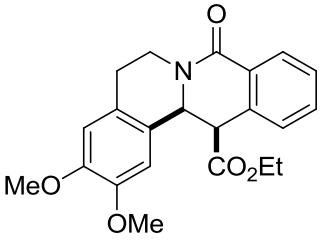
^{1}H NMR of **6b** in $CDCl_3$

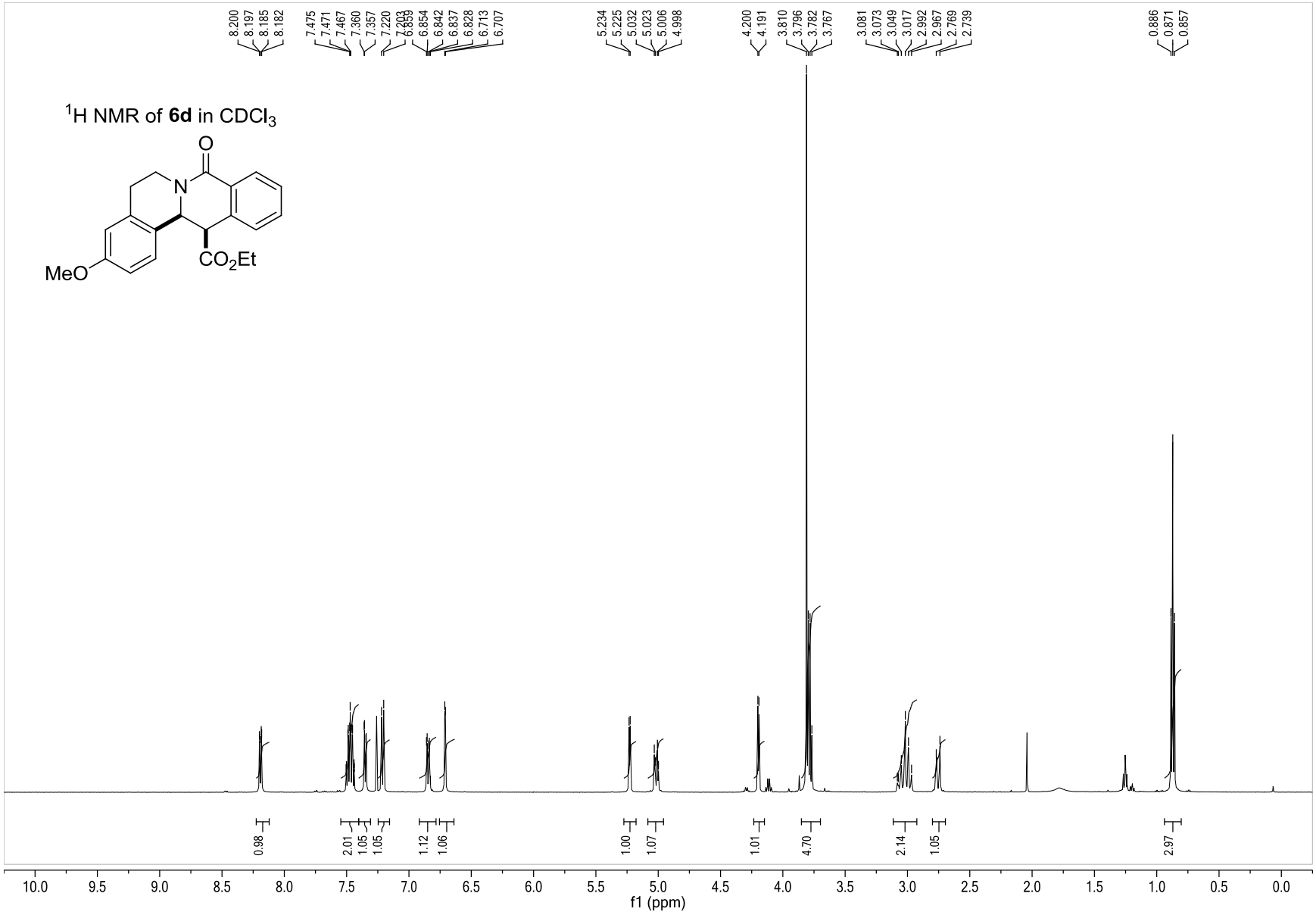



169.101
163.793
136.560
134.758
133.403
132.079
129.290
129.254
128.955
128.750
127.528
127.271
126.832
126.347
60.978
56.670
51.263
38.783
28.992
13.790
^{13}C NMR of **6b** in $CDCl_3$
O
N
CO_2Et
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

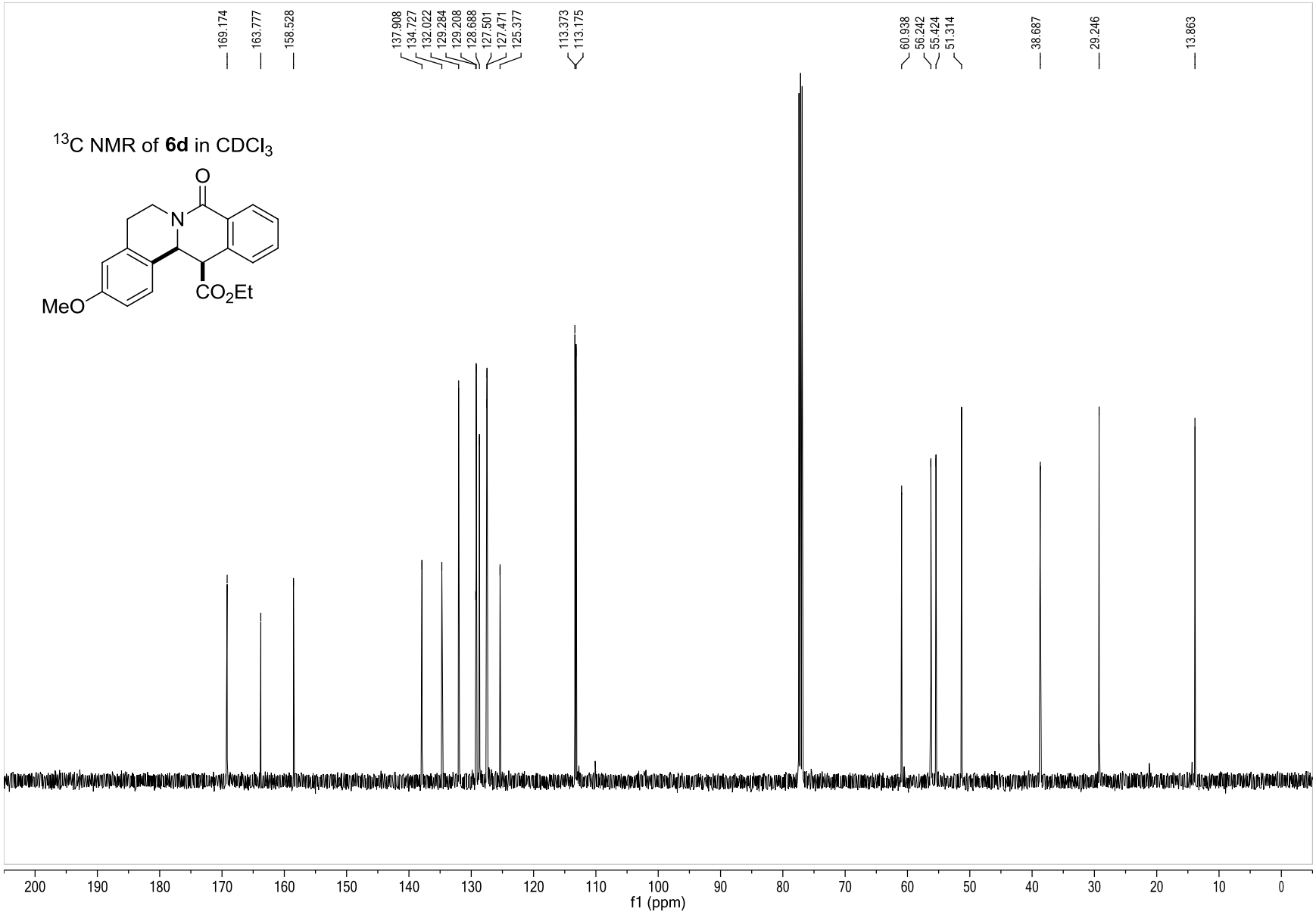

8.195
8.192
8.180
8.177
7.497
7.494
7.483
7.480
7.468
7.445
7.432
7.357
7.343
6.746
6.657
5.194
5.185
5.028
5.022
4.999
4.206
4.197
3.905
3.873
3.808
3.793
3.779
3.765
3.019
2.994
2.989
2.979
2.973
2.969
2.958
2.932
2.719
2.707
2.702
2.678
2.658
0.888
0.874
0.859
1H NMR of 6c in CDCl3
O
N
CO2Et
MeO
OMe
0.99
2.15
1.06
1.08
1.00
0.97
1.01
1.00
3.08
2.99
2.07
2.21
1.18
3.19
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

^{13}C NMR of **6c** in $CDCl_3$





^{1}H NMR of **6d** in $CDCl_3$


169.174
163.777
158.528
137.908
134.727
132.022
129.284
129.208
128.688
127.501
127.471
125.377
113.373
113.175
60.938
56.242
55.424
51.314
38.687
29.246
13.863
13C NMR of 6d in CDCl3
O
N
MeO
CO2Et
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)