Synthesis of (±)-Desethylrhazinal using a tandem radical addition-cyclization process.

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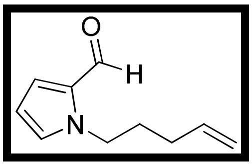
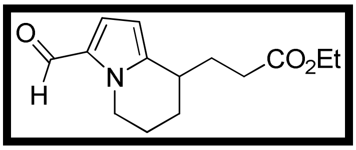
General Information

Unless otherwise stated, all reactions were carried out in dry glassware under an argon atmosphere using standard techniques for the manipulation of solvents and reagents. CH_2Cl_2, triethylamine and DMF were distilled from CaH_2, THF was distilled from Na/Benzophenone. All other starting materials and solvents are commercially available and were used without further purification. Chromatography was performed on Macherey – Nagel silica gel 230 – 400.

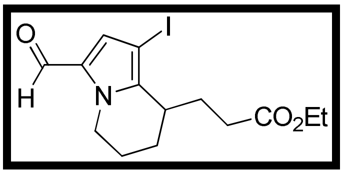
^{1}H-NMR and ^{13}C-NMR were recorded in $CDCl_3$ (7.27 ppm and 77.23 ppm respectively) in a 300MHz spectrometer employing $(CH_3)_4Si$ as internal standard.



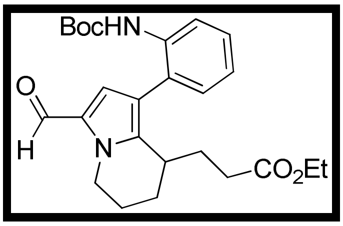
1-(pent-4-enyl)-1H-pyrrole-2-carbaldehyde (5b): To a suspension at 60% of NaH (0.684 g, 17.35 mmol) in N,N-dimethylformamide at 0 °C, a solution of pyrrole-2-carboxaldehyde (0.75 g, 7.89 mmol) in DMF was added. The reaction was then warmed to room temperature and stirred for 40 minutes. The reaction mixture was then cooled to 0 °C and 5-bromopentene **(8b)** (1.29 g, 8.68 mmol) was added slowly. The reaction was then warmed to room temperature and was further stirred for 30 minutes. The reaction was quenched with saturated NH_4Cl and the resulting mixture was extracted with ethyl acetate. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 6:1) to afford the product as a yellow oil in 85% yield (2.4 g, 14.74 mmol).^{1}H-NMR δ_H (300 MHz, $CDCl_3$) 2.13 – 1.78 (4 H, m), 4.38 – 4.25 (2 H, m), 5.12 – 4.94 (2 H, m), 5.79 (1 H, ddt, *J* 16.8, 10.2, 6.5), 6.21 (1 H, dd, *J* 3.8, 2.7), 6.98 – 6.86 (2 H, m), 9.53 (1 H, d, *J* 0.9). ^{13}C-NMR δ_C (75 MHz, $CDCl_3$) 179.19, 137.42, 131.27, 124.79, 115.38, 109.45, 77.42, 77.00, 76.58, 48.44, 30.45, 30.30. IR ($CHCl_3$, cm^{-1}) ν_{max}: 3077, 2928, 2854, 2805, 2767, 1664 (CO), 1405, 1322, 763, 747. *m/z* (EI) 163 (M$^+$, 22%), 146 (10), 134 (100), 108 (32), 97 (30), 81 (42), 41 (30), 28 (12). HRMS (FAB+) *m/z* Calculated for: $C_{13}H_{13}NO$ (M+) 163.0997, (found) 163.0990.



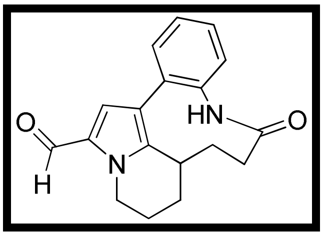
Ethyl 3-(3-formyl-5,6,7,8-tetrahydroindolizin-8-yl)propanoate (4b): In a round bottom flask, 1-(pent-4-enyl)-1H-pyrrole-2-carbaldehyde (0.65 g, 3.98 mmol) and the ethyl 2-(ethoxycarbonothioylthio) acetate (0.99 g, 4.77 mmol), prepared as previously reported[7], were dissolved in 1,2-dichloroethane. The mixture was was degassed with argon in an ultrasound bath. The reaction was heated to reflux temperature and the lauroyl peroxide (2.06 g, 5.18 mmol) was added portionwise every hour, for 7 hours. The reaction mixture was concentrated in vacuo and purified by flash column chromatography on basic alumina (hexanes:ethyl acetate 4:1) to afford the product as a brown oil in 69% yield (0.683 g, 2.74 mmol). ^{1}H-NMR δ_H (300 MHz, $CDCl_3$) 1.26 (3 H, t, *J* 7.1), 1.47 (1 H, m), 2.46 – 1.8 (6 H), 2.41 (2 H, m), 2.9 (1 H, m), 4.15 (2 H, m), 4.54 (1 H, m), 6.11 (1 H, m), 6.89 (1 H, m), 9.42 (1 H, s). ^{13}C-NMR δ_C (75 MHz, $CDCl_3$) 178.44, 173.08, 143.33, 130.89, 124.3, 107.35, 107.35, 60.35, 45.47, 33.7, 31.32, 29.55, 25.11, 21.47, 14.02. IR ($CHCl_3$ cm^{-1}) ν_{max}: 2977, 2933, 2862, 1732 (CO), 1658 (CO), 1489, 1321, 1177, 1037, 784. *m/z* (EI) 249 (M^+, 70%), 220 (15), 176 (25), 161 (100), 148 (95), 134 (20), 120 (22), 118 (15), 83 (10), 55 (11), 41 (18). HRMS (FAB+) *m/z* Calculated for: $C_{14}H_{20}NO_3$ (M+1) 250.1443, (found) 250.1448.



Ethyl 3-(3-formyl-1-iodo-5,6,7,8-tetrahydroindolizin-8-yl)propanoate (11): To a solution of **4b** (0.5 g, 2.008 mmol), in $CHCl_3$ at 0 °C, silver trifluoroacetate (0.488 g, 2.21 mmol) and iodine (0.561 g, 2.21 mmol) were added, after that, the reaction was warmed to room temperature and stirred for 16 h. The reaction was then quenched with 5 mL of 20% aqueous $Na_2S_2O_5$ and the resulting mixture was extracted with ethyl acetate. The combined organic extracts were washed with saturated $NaHCO_3$ and brine, dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 4:1) to afford the product as a yellow oil in 83% yield (0.62 g, 1.66 mmol). . ^{1}H-NMR δ_H (300 MHz, $CDCl_3$) 1.27 (3 H, t, *J* 7.16), 2.24 – 1.72 (6 H), 4.45 (2 H, m), 2.93 (1 H, m), 4.04 (1 H, m), 4.15 (2 H, q, *J* 7.2), 4.66 (1 H, m), 7.02 (1 H, s), 9.41 (1 H, s). ^{13}C-NMR δ_C (75 MHz, $CDCl_3$) 178.08, 172.88, 143.32, 132.64, 130.76, 62.53, 60.54, 46.18, 32.63, 32.29, 29.67, 28.15, 22.73, 18.31, 14.25. IR ($CHCl_3$ cm^{-1}) ν_{max}: 2947, 2866, 2789, 1731 (CO), 1660 (CO), 1468, 1396, 1312, 1171, 1036, 871, 660. *m/z* (EI) 375 (M^+, 15%), 302 (20), 287 (25), 274 (75), 248 (100), 220 (10), 174 (55), 146 (22), 118 (20), 97 (15), 85 (18), 57 (30), 43 (15). HRMS (FAB+) *m/z* Calculated for: $C_{14}H_{19}NO_3I$ (M+1) 376.0410, (found) 376.0413.

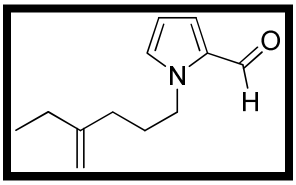


Ethyl 3-(1-(2-(tert-butoxycarbonylamino)phenyl)-3-formyl-5,6,7,8-tetrahydroindolizin-8-yl)propanoate (13): In a round bottom flask **11** (0.55 g, 1.466 mmol), *tert*-butyl-*N*-[2-(4,4,5,5-tetramethyl-1,3,2- dioxaborolan-2-yl)phenyl]-carbamate **(12)** (0.71 g, 2.2 mmol), K_3PO_4 (1.246 g, 5.87 mmol), $Pd_2(dba)_3$ (0.068 g, 0.074 mmol) and SPhos (0.054 g, 0.132 mmol) ligand, were dissolved in THF and degassed H_2O as solvent system. The resulting solution was stirred at room temperature for 1 h and then at 40 °C for 36 h. The reaction was quenched with saturated aqueous NH_4Cl and the resulting mixture was extracted with ethyl acetate. The combined organic extracts were washed consecutively with saturated aqueous $NaHCO_3$ and brine, dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 4:1) to afford the product as a pale yellow oil in 86% yield (0.554 g, 1.26 mmol). ^{1}-H-NMR δ_H (300 MHz, $CDCl_3$) 1.15 (3 H, t, *J* 7.2), 1.49 (9 H, s), 1.76 – 1.55 (3 H), 1.92 (1 H, m), 2.14 – 2.01 (3 H), 3.05 (1 H, m), 3.97 (2 H, m), 4.41 (2 H, m), 6.48 (1 H, bs), 6.87 (1 H, s), 7.04 (1 H, dt, *J* 7.6, 1.6), 7.14 (1 H, dd, *J* 7.8, 1.8), 7.31 (1 H, dt, *J* 8.4, 1.5), 8.09 (1 H, d, *J* 8.4), 9.51 (1 H, s). ^{13}C-NMR δ_C (75 MHz, $CDCl_3$) 178.81, 172.72, 152.72, 140.9, 136.3, 131.01, 130.42, 128.45, 124.95, 124.27, 122.81, 119.4, 118.58, 80.53, 60.32, 45.99, 32.05, 31.46, 28.57, 28.31, 24.24, 19.73, 14.07. IR ($CHCl_3$ cm^{-1}) ν_{max}: 3227 (NH), 3105, 2979, 2940, 1722 (CO), 1653 (CO), 1526, 1446, 1308, 1237, 1156, 756. *m/z* (EI) 440 (M^+, 30%), 384 (100), 339 (40), 297 (31), 253 (90), 237 (47), 211 (43), 209 (20), 181 (15), 57 (75), 41 (20), 28 (18). HRMS (FAB+) *m/z* Calculated for: $C_{25}H_{33}N_2O_5$ (M+1) 441.2389, (found) 441.2394.

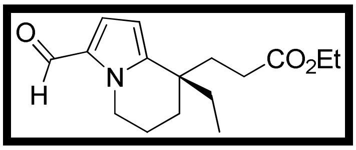


Des-ethylrhazinal (3): To a solution of **13** (0.15 g, 0.341 mmol) in methanol, $Ba(OH)_2\cdot 8H_2O$ (2.16 g, 6.82 mmol) was added. The resulting solution was stirred for 3 h at room temperature. Aqueous 1N HCl was added to the reaction mixture until pH 2, and the resulting solution was extracted with ethyl acetate. The combined organic extracts were washed consecutively with H_2O and brine, dried with Na_2SO_4, and concentrated. The residue was dried under high vacuum and then dissolved in CH_2Cl_2 (50 mL) containing trifluoroacetic acid (6 mL). The reaction was stirred at room temperature for 1 h, following that time, the volatiles were evaporated in vacuo to afford an oily residue that was used in the next step without further purification. A solution of latter crude residue in CH_2Cl_2 (50 mL) was added via syringe pump over 12 h to a stirred solution of *O*-(7-azabenzotriazole-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate (HATU) (0.389 g, 1.023

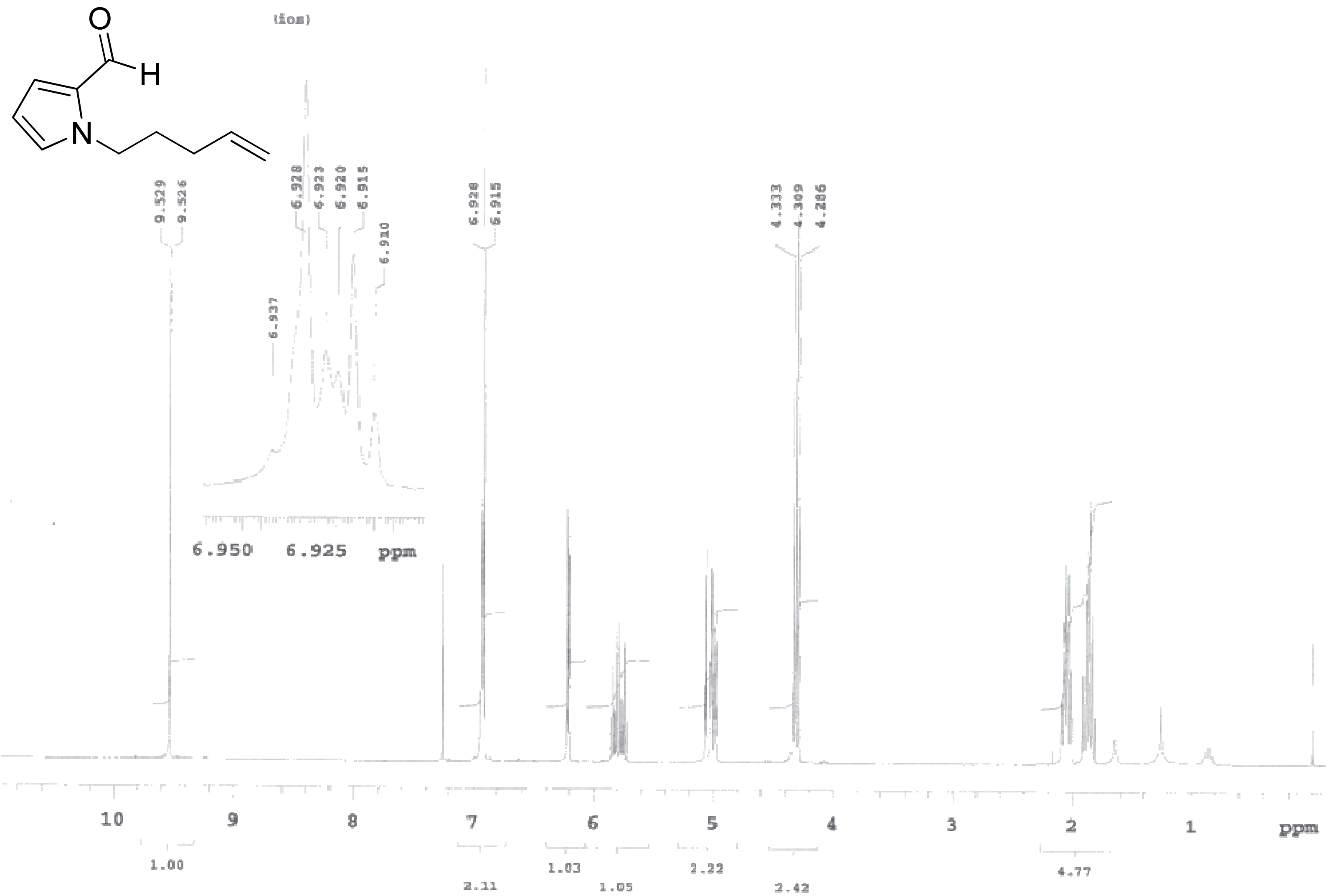
mmol); and *N*, *N*-diisopropylethylamine (0.191 mL, 1.364 mmol) in DMF (100 mL) and CH_2Cl_2 (50 mL). Once the addition was completed, the reaction was stirred for additional 4 h and then extracted with ethyl acetate. The combined organic extracts were washed consecitively with aqueous 5% HCl, aqueous 1 N NaOH, saturated aqueous $NaHCO_3$, brine and then dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 1:1) to afford the product as pale yellow solid in 29% yield (0.029 g, 0.099 mmol). ^1H-NMR δ_H (300 MHz, $CDCl_3$) 2.02 – 1.66 (4 H, m), 2.38 – 2.09 (4 H, m), 2.74 (1 H, m), 3.98 (1H, ddd, *J* 14.2, 12.0, 2.1), 4.78 (1H, dd, *J* 14.7, 5.7), 6.63 (1 H, s), 6.92 (1 H, bs), 7.48 – 7.2 (4 H), 9.43 (1 H, s). ^{13}C-NMR δ_C (75 MHz, $CDCl_3$) 178.89, 176.62, 139.99, 137.68, 136.69, 131.88, 130.97, 129.25, 128.18, 127.86, 124.05, 120.49, 45.96, 33.53, 32.44, 32.06, 29.69, 27.04. IR ($CHCl_3$ cm^{-1}) ν_{max}: 3207 (NH), 2976, 1718 (CO), 1661 (CO), 1442, 1248, 1031, 758. *m/z* (EI) 294 (M^+, 100%), 265 (25), 251 (40), 237 (85), 223 (45), 209 (31), 181 (30), 168 (15), 154 (18), 72 (22), 57 (25), 28 (45). HRMS (FAB+) *m/z* Calculated for: $C_{18}H_{19}N_2O_2$ (M+1) 295.1447, (found) 295.1436.



1-(4-methylenehexyl)-1H-pyrrole-2-carbaldehyde (5a): To a suspension of NaH (0.46 g, 11.46 mmol) in N,N-dimethylformamide at 0 °C, a solution of pyrrole-2-carboxaldehyde (0.545 g, 5.73 mmol) in DMF, was added. The reaction was then warmed to room temperature and stirred for 40 minutes. The reaction mixture was then cooled to 0 °C and a solution of the corresponding mesylate **(8a)** (1.21 g, 6.3 mmol) in DMF was slowly added. The reaction was then warmed to room temperature and was stirred for additional 30 minutes. The reaction was quenched with saturated NH_4Cl and the resulting mixture was extracted with ethyl acetate. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 6:1) to afford the product as a orange oil in 89% yield (0.97 g, 5.1 mmol). ^1H-NMR δ_H (300 MHz, $CDCl_3$) 1.01 (3 H, t, *J* 7.5), 1.01 (3 H, t, *J* 7.5), 1.85 – 1.65 (2 H, m), 2.1 – 1.9 (4 H, m), 4.3 (2 H, t, *J* 7.2), 4.73 (2 H, m), 6.22 (1 H, m), 6.94 – 6.91 (2 H, m), 9.53 (1 H, d, *J* 0.9). ^{13}C-NMR δ_C (75 MHz, $CDCl_3$) 179.22, 150.09, 131.31, 124.81, 109.45, 108.3, 48.75, 32.88, 29.69, 29.24, 28.67, 12.28. IR ($CHCl_3$ cm^{-1}) ν_{max}: 2965, 2931, 1662 (CO), 1481, 1405, 1369, 1241, 1074, 894. *m/z* (EI)191 (M^+, 18%), 162 (25), 149 (45), 111 (25), 71 (62), 57 (100), 55 (70), 43 (60), 29 (25).



Ethyl 3-(8-ethyl-3-formyl-5,6,7,8-tetrahydroindolizin-8-yl)propanoate (4a): In a round bottom flask, 1-(4-methylenehexyl)-1H-pyrrole-2-carbaldehyde **(5a)** (0.2 g, 1.045 mmol) and ethyl 2-(ethoxycarbonothioylthio) acetate (0.24 g, 1.15 mmol) were dissolved in 1,2-dichloroethane. This mixture was degassed with argon in an ultrasound bath. The reaction was heated to reflux temperature and the lauroyl peroxide (0.54 g, 1.36 mmol) was added portionwise every hour for 7 hours. The reaction mixture was concentrated and purified by flash column chromatography on basic alumina (hexanes:ethyl acetate 4:1) to afford the product as yellow oil in 71% yield (0.205 g, 0.74 mmol). ^{1}H-NMR δ_H (300 MHz, $CDCl_3$)), 0.83 (3 H, t, *J*, 7.5), 1.22 (3 H, t, *J* 6.9), 1.67 (4 H, m), 1.96, (4 H, m), 2.2 (2 H, m), 4.09 (4 H, q, *J*, 6.9), 4.34 (2 H, t, *J* 6), 6.04 (1 H, d, 4.2), 6.89 (1 H, d, *J*, 4.2), 9.4 (1 H, s). ^{13}C-NMR δ_C (75 MHz, $CDCl_3$) 178.45, 173.51, 130.79, 124.59, 107.59, 60.46, 45.4, 38.13, 34.81, 33.26, 29.8, 26.69, 28.89, 19.6, 14.16, 8.53. IR ($CHCl_3$ cm^{-1}) ν_{max}: 2935, 2872, 1733 (CO), 1658 (CO), 1487, 1440, 1322, 1176, 1040, 783. *m/z* (EI) 277 (M^+, 28%), 248 (40), 204 (15), 176 (100), 146 (28), 132 (18), 118 (12), 80 (10), 29 (18).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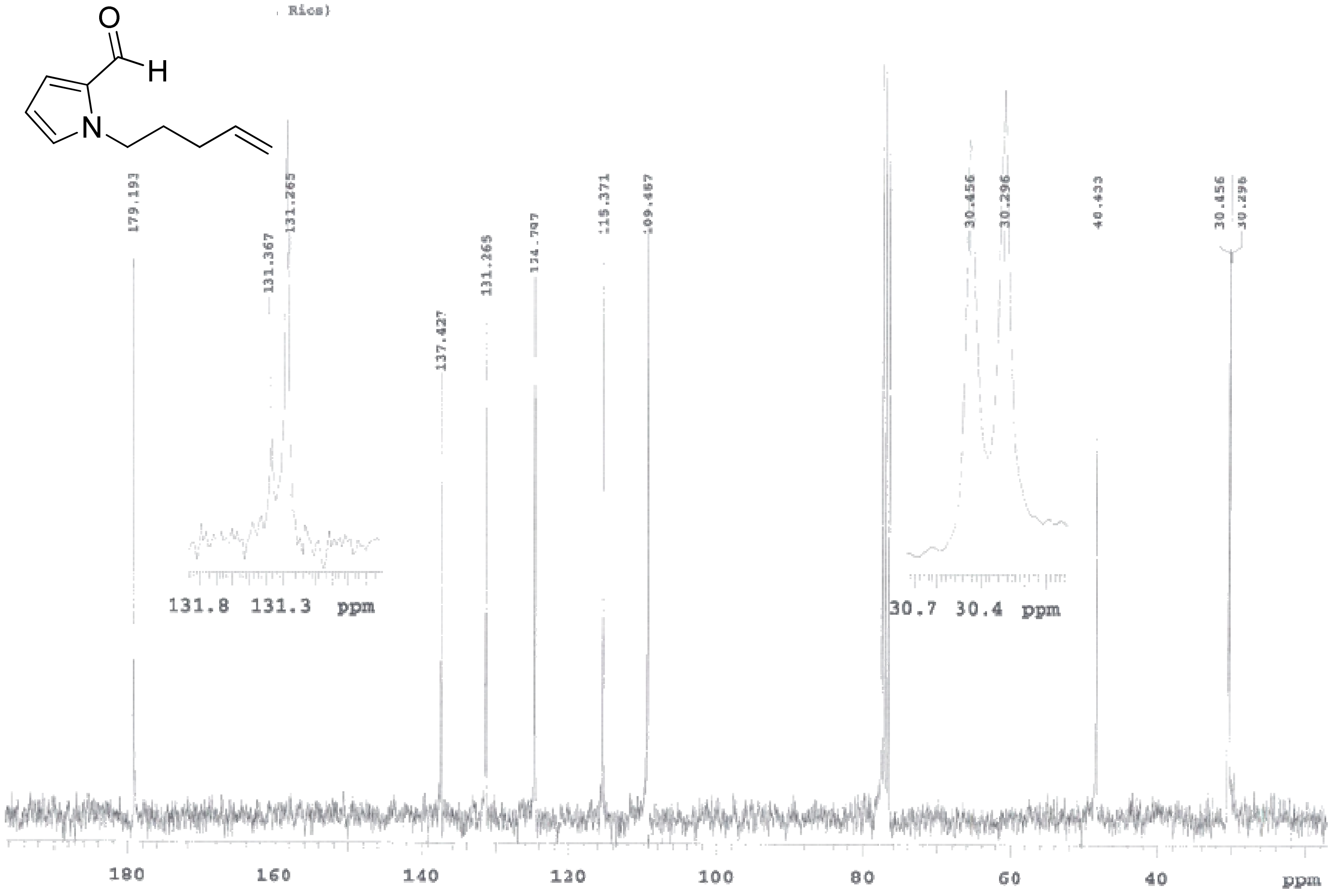
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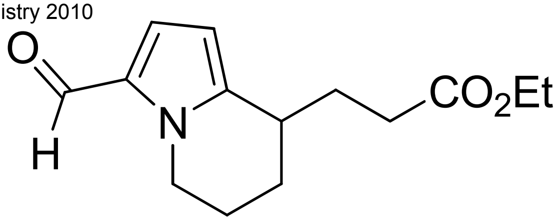
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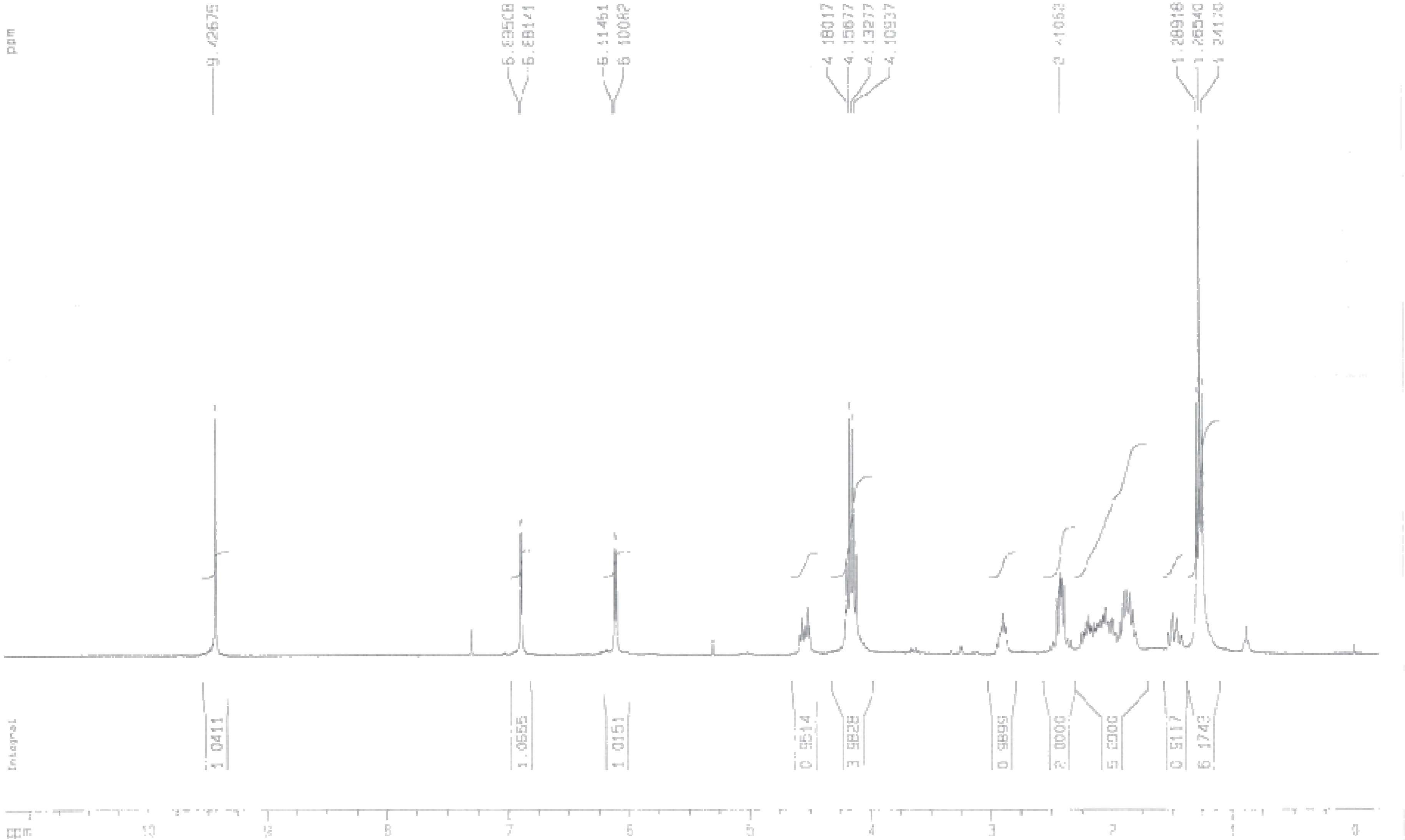
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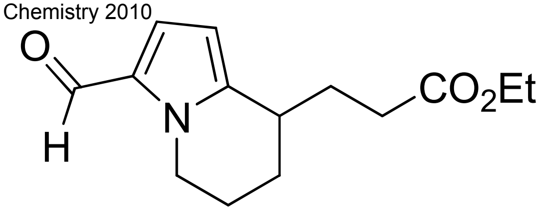
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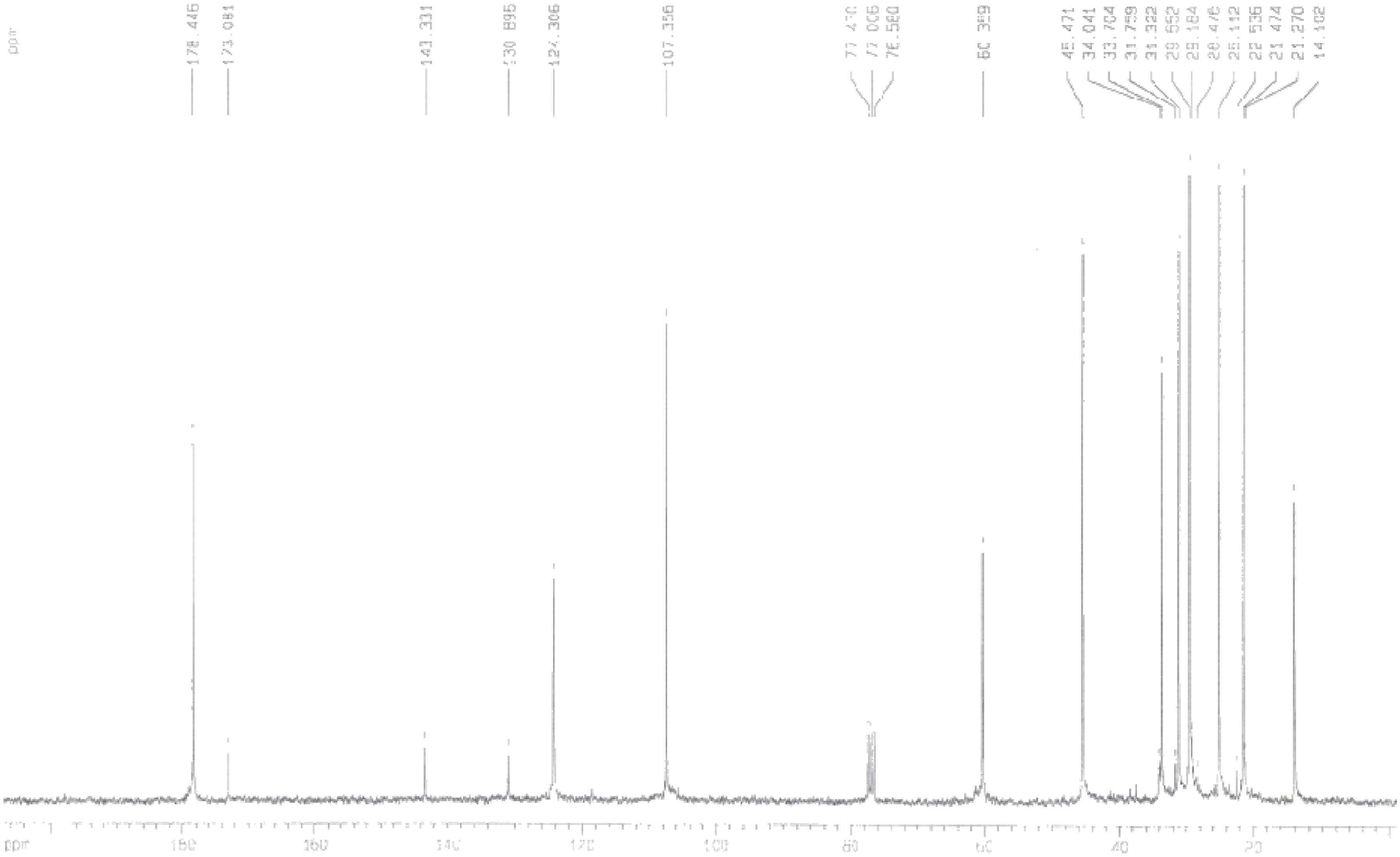
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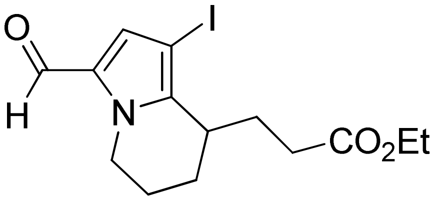
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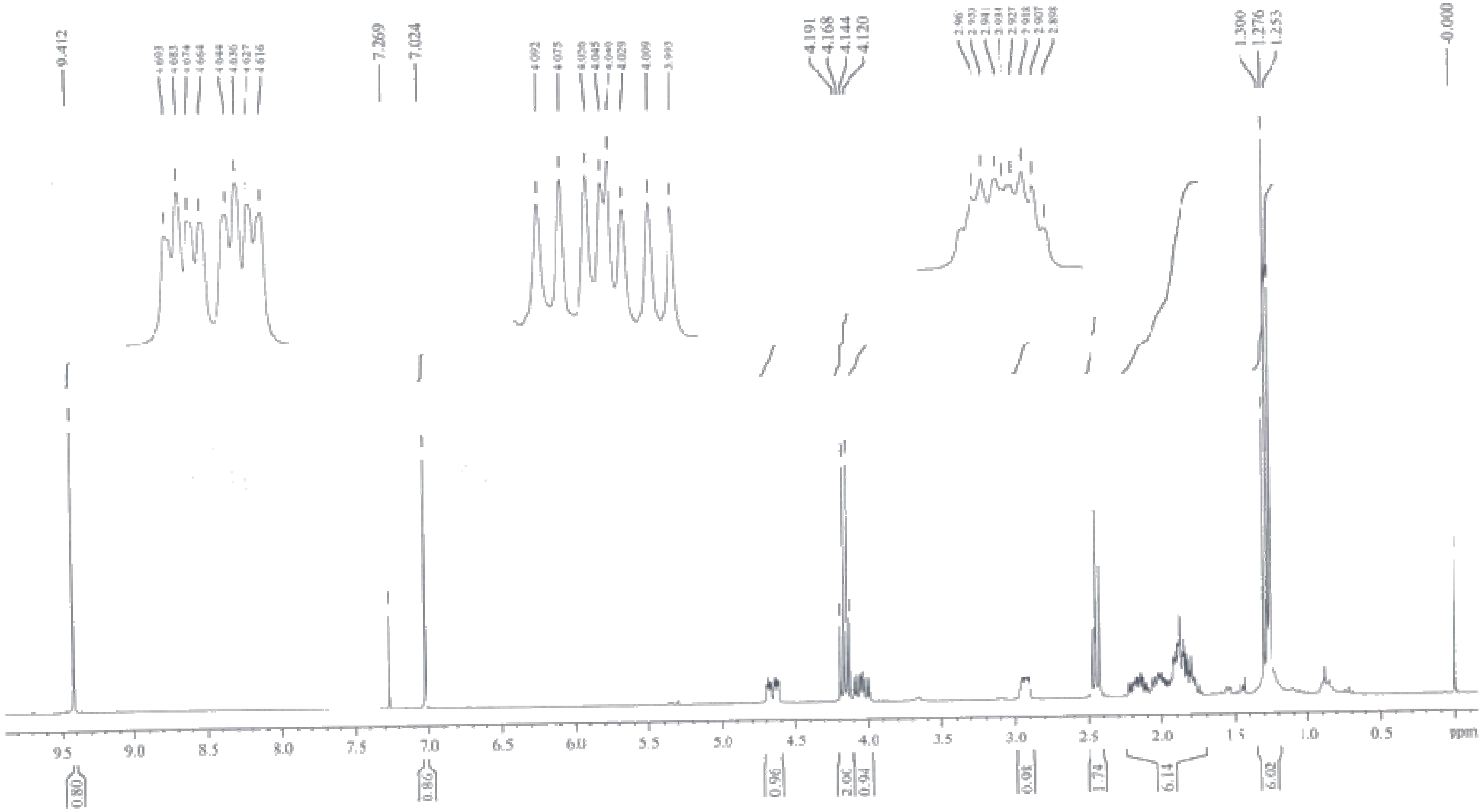
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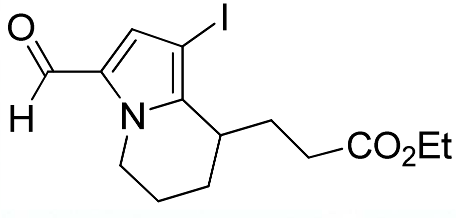
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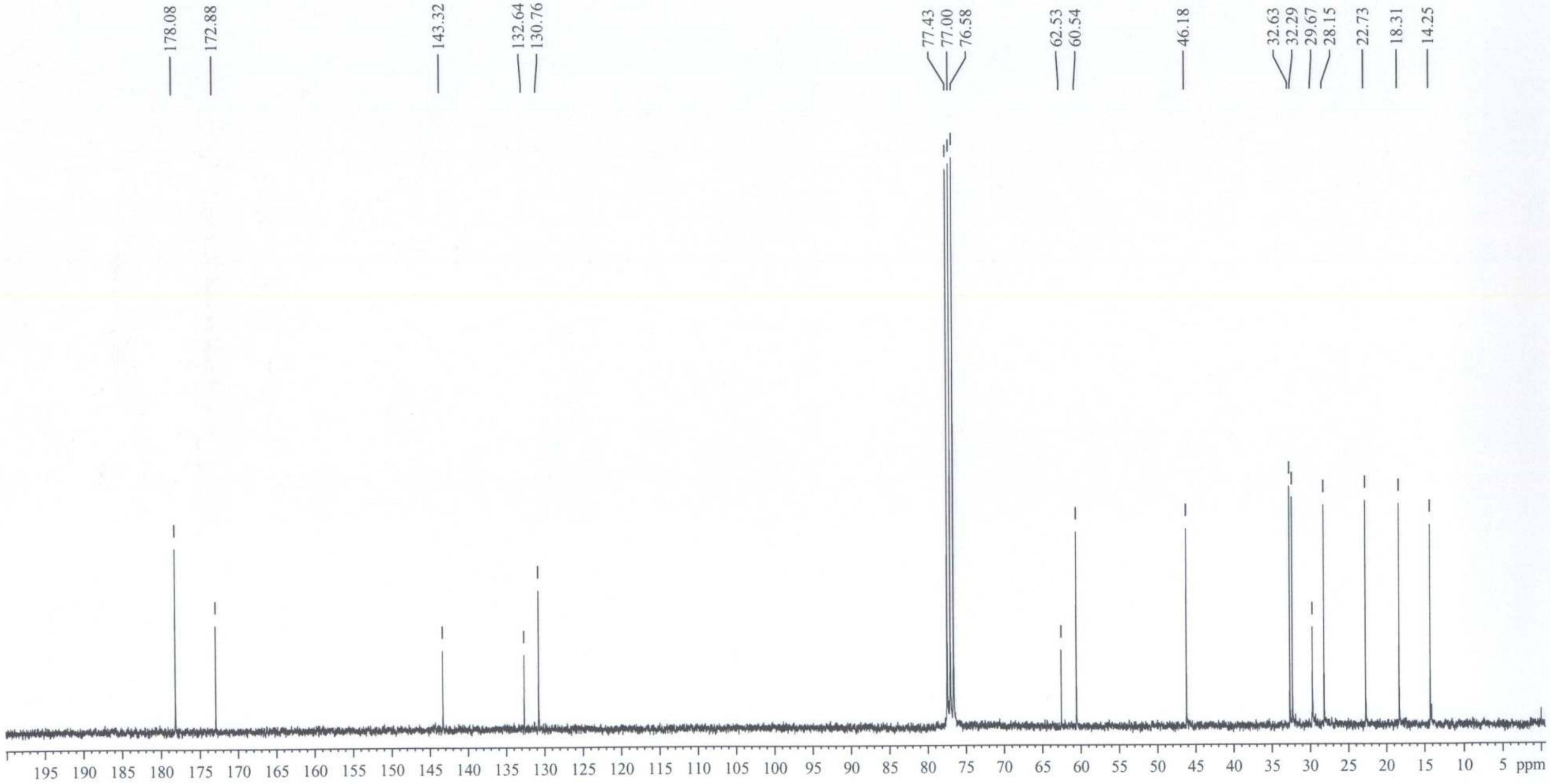
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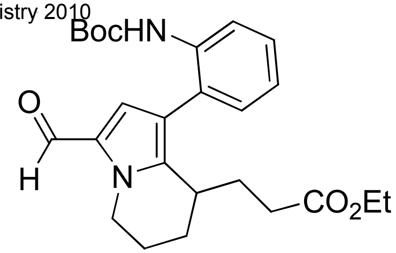
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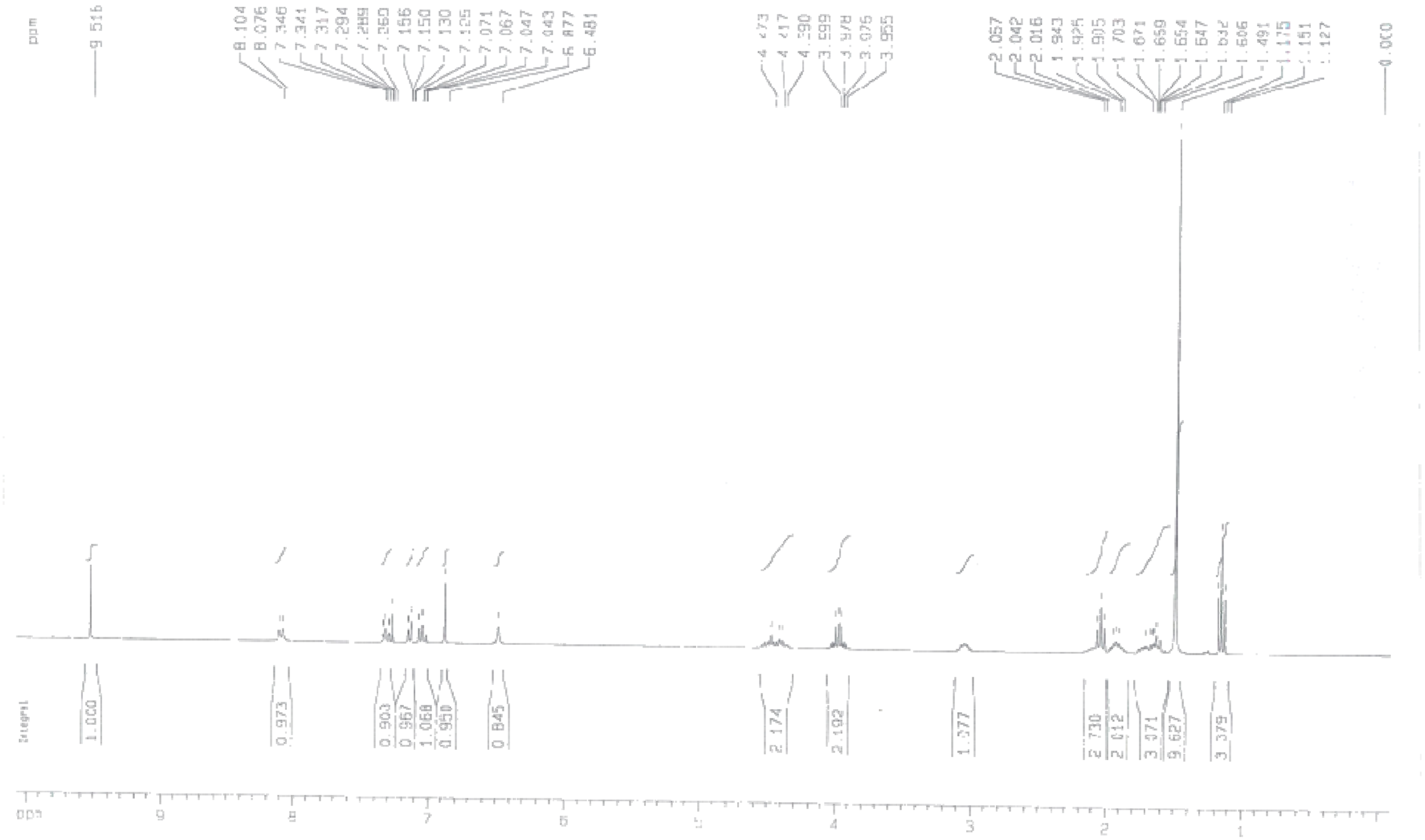
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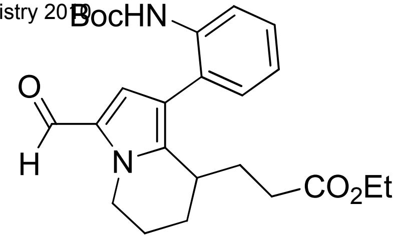
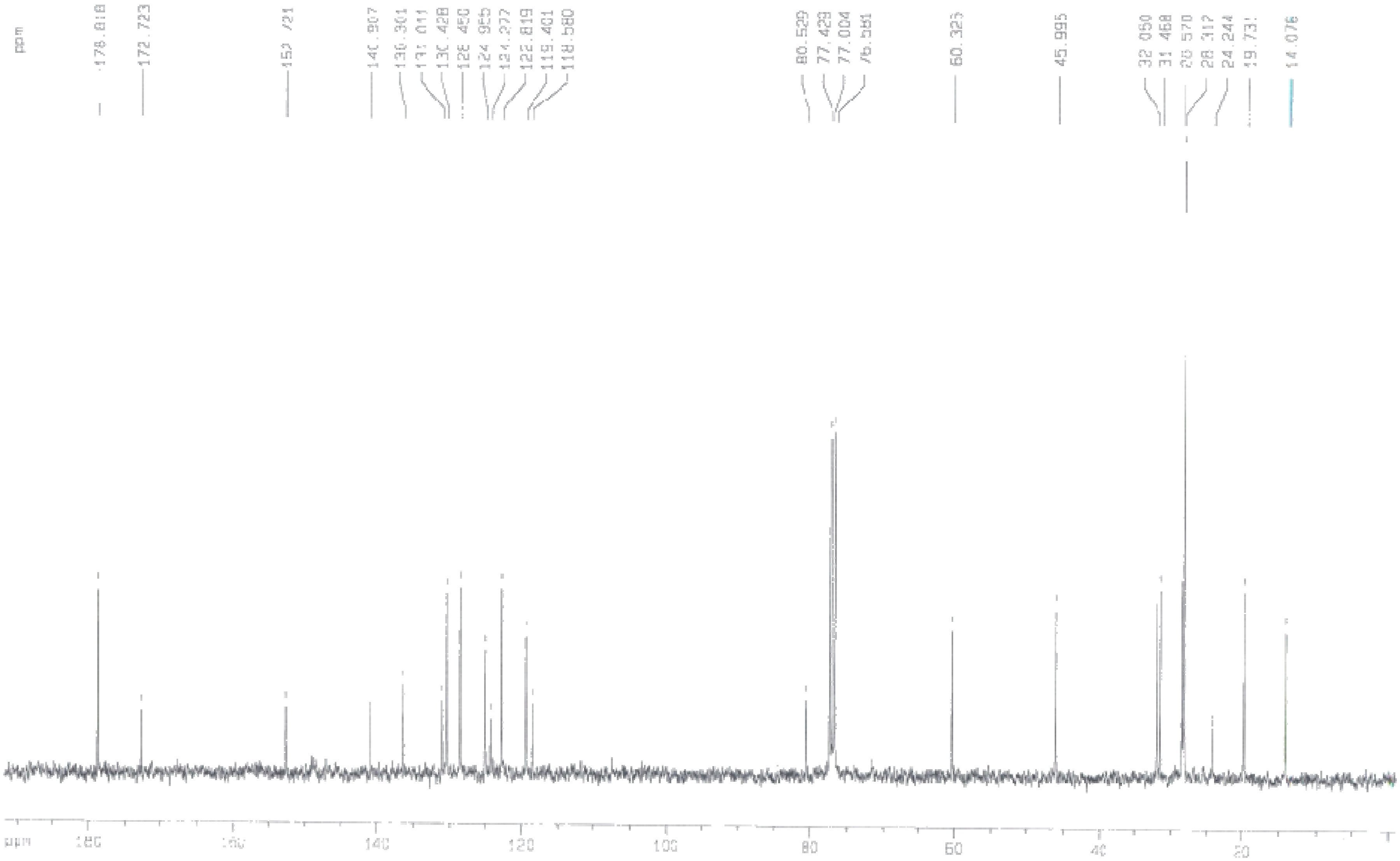
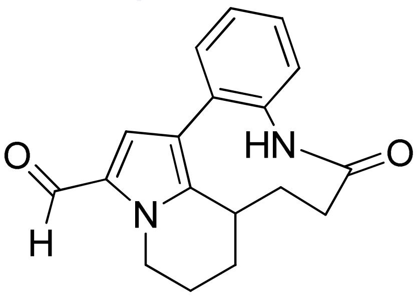
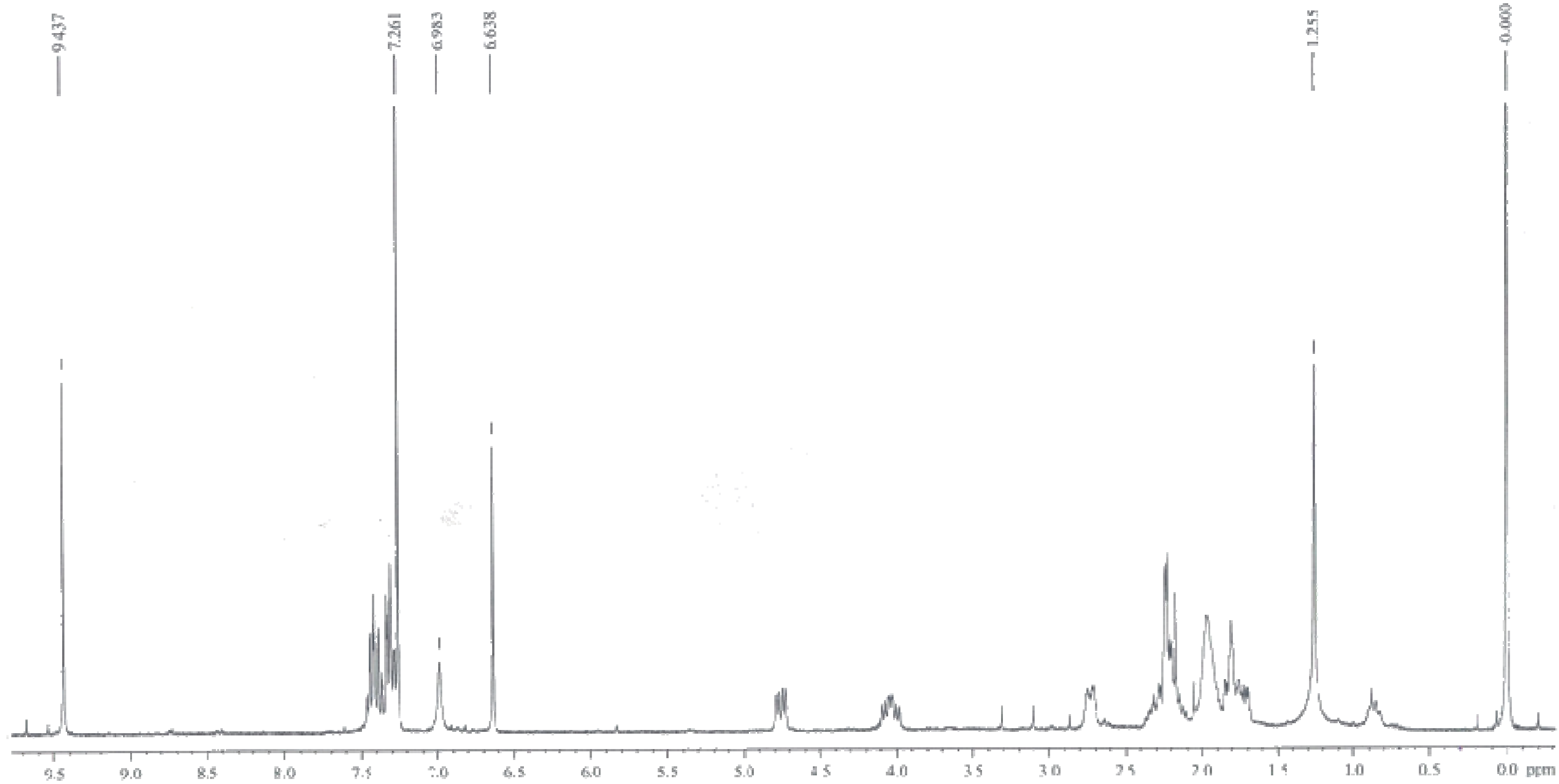
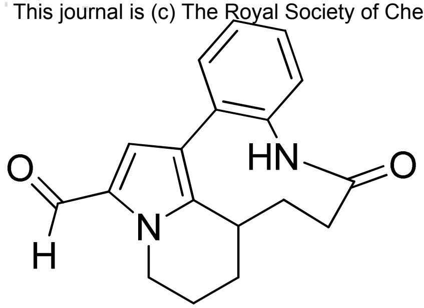
0.000
Integral
1.000
0.973
0.903
0.967
1.068
0.950
0.845
2.174
2.192
1.377
2.730
2.012
3.071
9.627
3.379
ppm
9
8
7
6
5
4
3
2
1

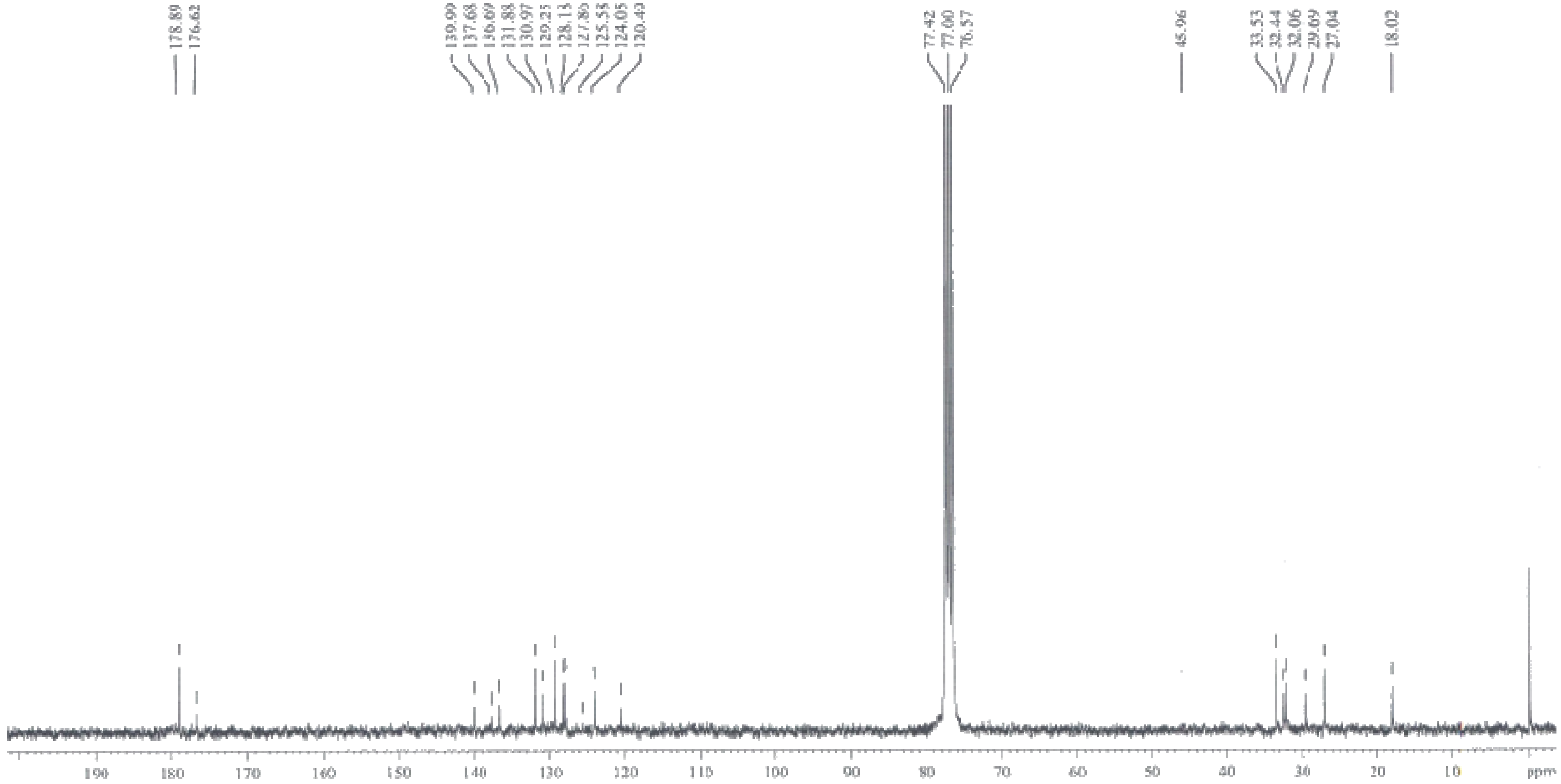

BocHN
O
H
N
CO2Et

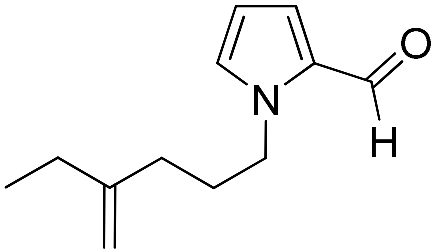

ppm
178.818
172.723
152.721
140.907
136.301
131.011
130.428
128.450
124.965
124.277
122.819
119.401
118.580
80.529
77.429
77.004
76.581
60.325
45.995
32.050
31.468
28.570
28.317
24.244
19.731
14.076
ppm
180
160
140
120
100
80
60
40
20

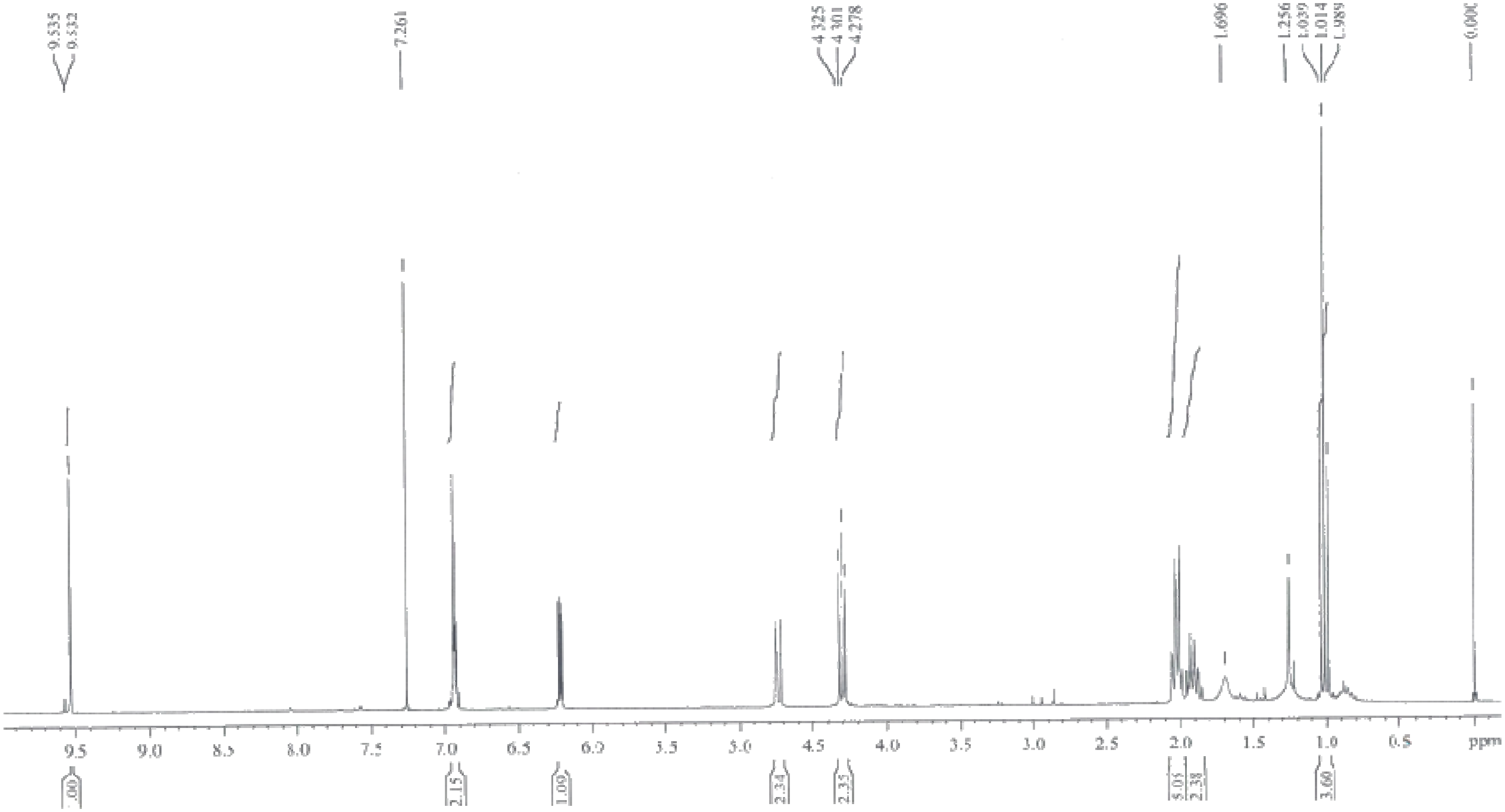

O
HN
O
N
H

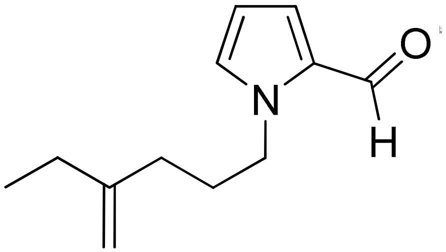

9.437
7.261
6.983
6.638
1.255
0.000
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0 ppm

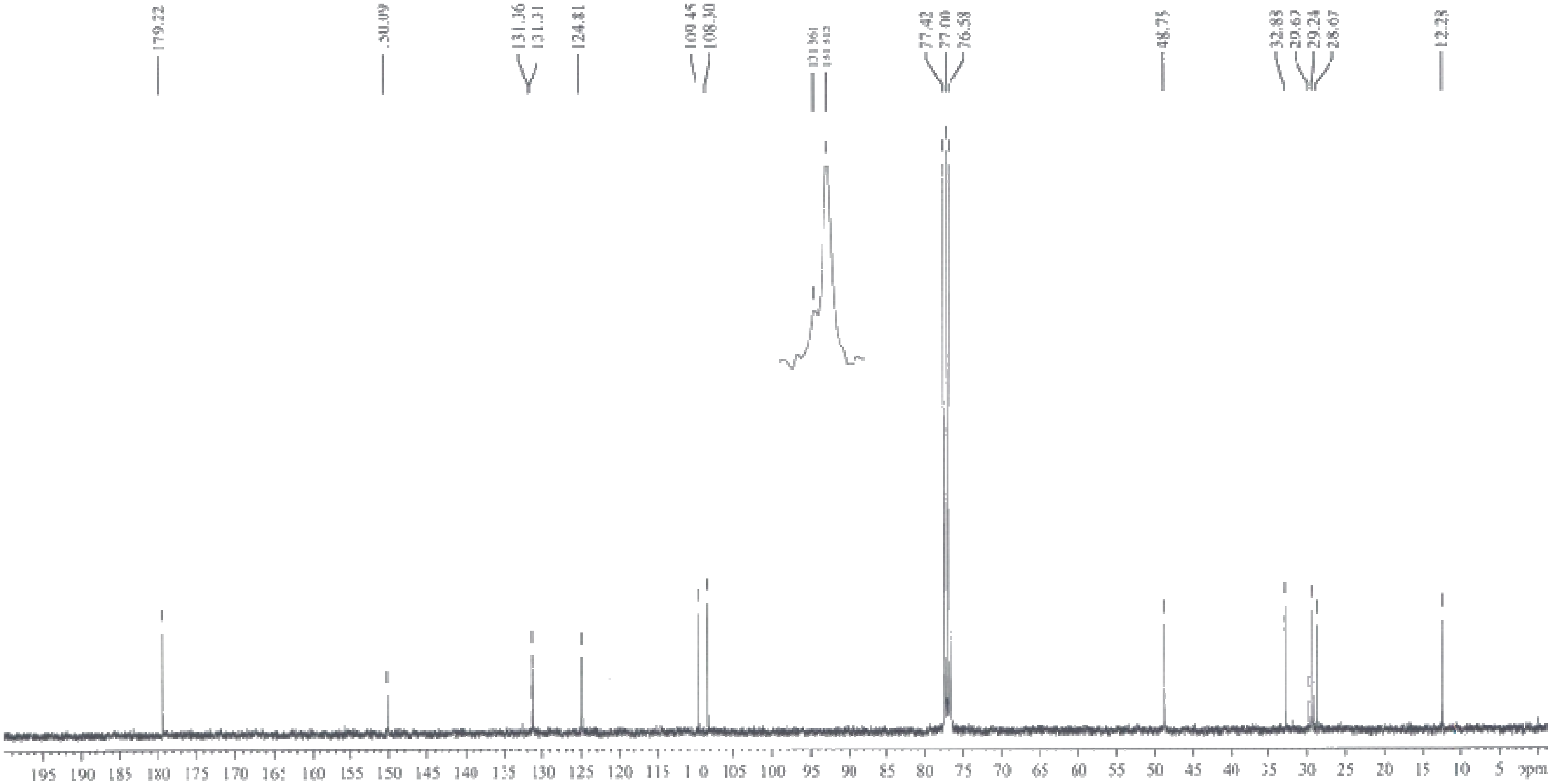

O
H
N
HN
O

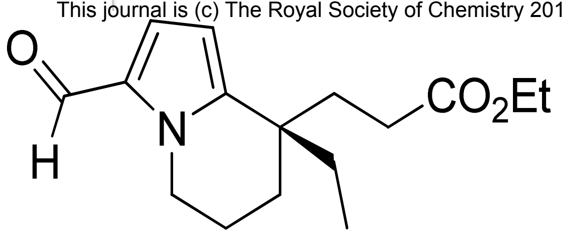

ta
178.89
176.62
139.99
137.68
136.69
131.88
130.97
129.25
128.13
127.86
125.53
124.05
120.49
77.42
77.00
76.57
45.96
33.53
32.44
32.06
29.69
27.04
18.02
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

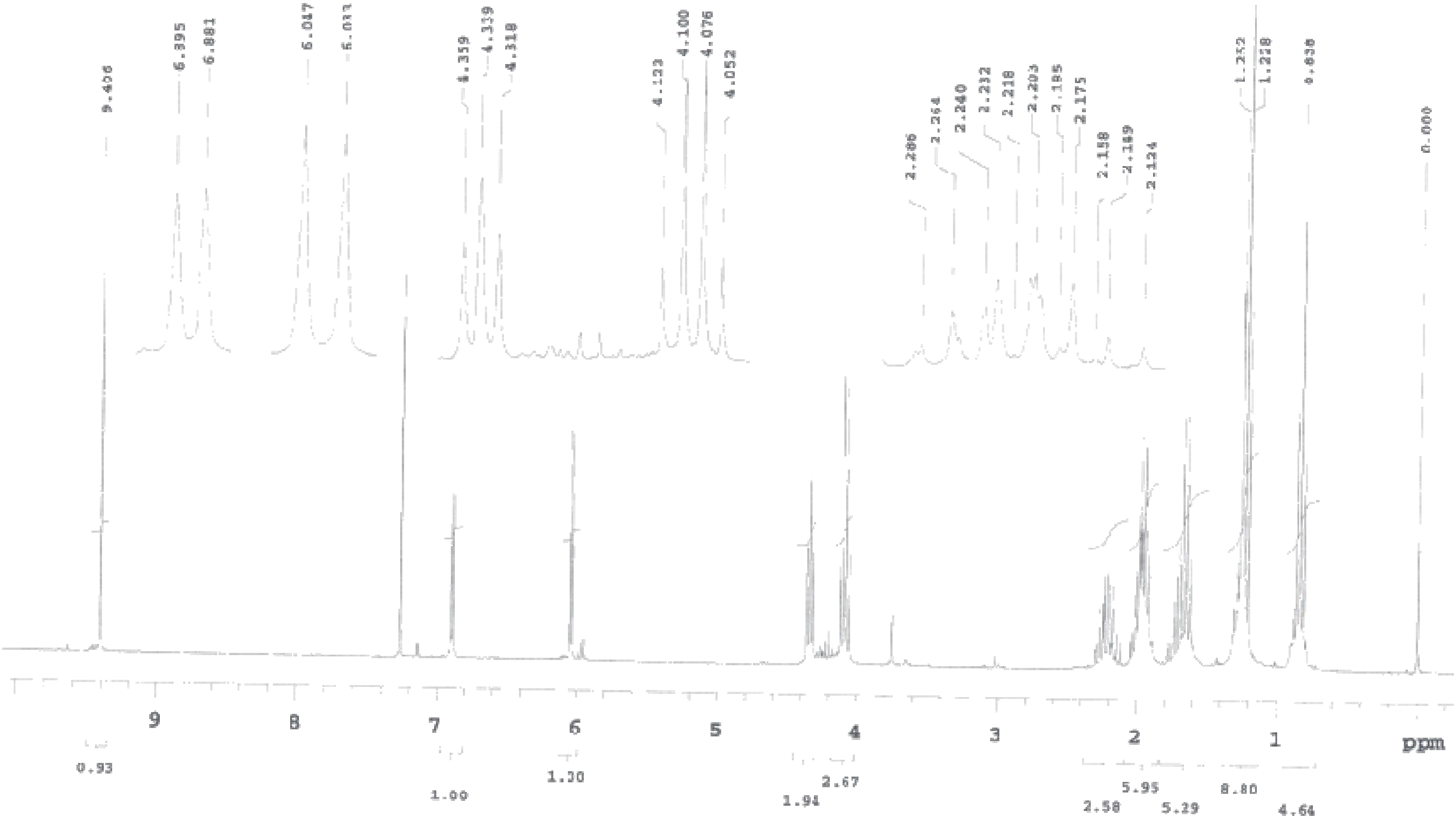

O
N
H

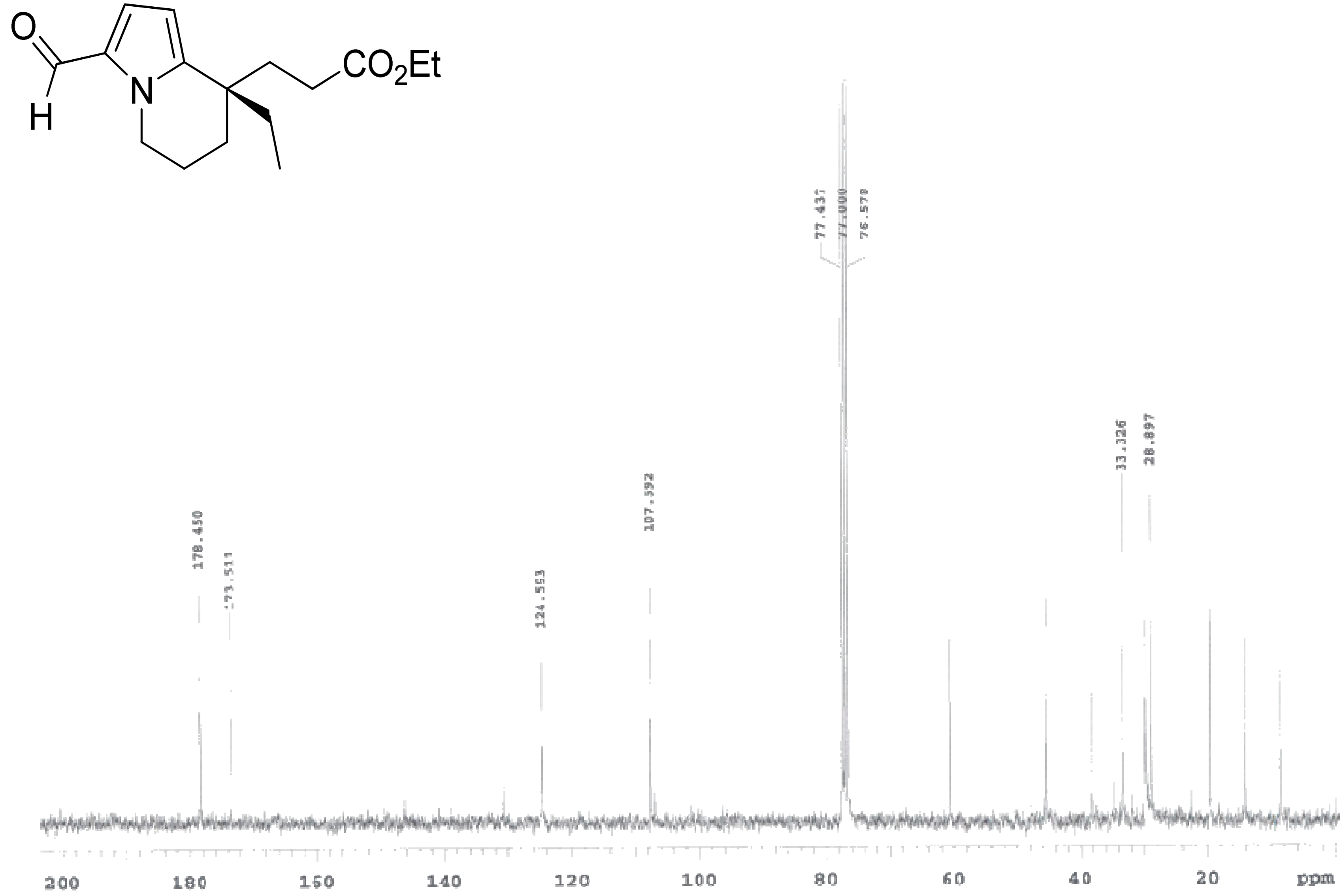

9.535
9.532
7.261
4.325
4.301
4.278
1.696
1.256
1.039
1.014
0.989
0.000
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
2.15
1.09
2.34
2.35
5.05
2.38
3.60


N
O
H


179.22
150.09
131.36
131.31
124.81
109.45
108.30
77.42
77.00
76.58
48.75
32.83
29.67
29.24
28.07
12.28
195 190 185 180 175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 ppm


O
H
N
CO2Et


9.406
6.895
6.881
6.047
6.033
4.359
4.339
4.318
4.123
4.100
4.076
4.052
2.286
2.264
2.240
2.232
2.218
2.203
2.185
2.175
2.158
2.149
2.134
1.252
1.228
0.838
0.000
9
8
7
6
5
4
3
2
1
ppm
0.93
1.00
1.30
1.94
2.67
2.58
5.95
5.29
8.80
4.64


O
H
N
CO2Et
178.450
173.511
124.553
107.592
77.431
77.000
76.578
33.326
28.897
200
180
160
140
120
100
80
60
40
20
ppm