Electronic Supplementary Material (ESI) for Chemical Communications

General Switch in Regioselectivity in the Mukaiyama Aldol Reaction of Silyloxyfuran with Aldehydes in Aqueous Solvents

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General procedures:

General procedures

Synthesis of racemic compounds (Table 2)

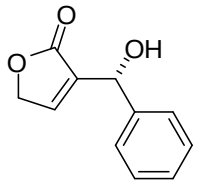
Aldehyde (0.71 mmol, 1.0 equiv.) and silyloxyfuran (0.85 mmol, 1.2 equiv.) **1** were added to a solution of $Zn(OTf)_2$ (0.077 mmol, 10 mol%) in THF/H_2O (2 ml, 9:1 v/v) at 0 °C. The resulting mixture was stirred for specified time at RT and purified directly using silica gel column (3:2 hexane/methyl *tert*-butyl ether). The volatiles were removed under reduced pressure to yield products **3a-l**.

Asymmetric version (Table 3)

The mixture of chiral ligand (0.082 mmol, 12 mol%) and $Zn(OTf)_2$ (0.077 mmol, 10 mol%) in EtOH/H_2O (2 ml, 9:1 v/v) was stirred for 10 min. at -30 °C. Aldehyde (0.71 mmol, 1.0 equiv.) and silyloxyfuran (0.85 mmol, 1.2 equiv.) **1** were added, and the resulting mixture was stirred for 4 h at -30 °C. The mixture was purified directly using silica gel column (3:2 hexane/methyl *tert*-butyl ether) and the volatiles were removed under reduced pressure to yield products.

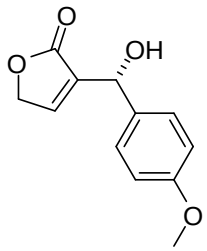
NMR data for compounds 3a-l (Table2)

3-(hydroxy(phenyl)methyl)furan-2(5*H*)-one (3a)[1]



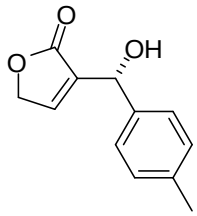
^{1}H NMR: 3.86 (s, br, 1H), 4.76 (t, 2H, *J*=1.78 Hz), 5.55 (s, br, 1H), 7.16 (q, 1H, *J*=1.65 Hz), 7.27-7.41 (m, 5H) ppm
^{13}C NMR: 69.0, 70.5, 126.4, 128.6, 136.3, 140.1, 146.1, 172.2 ppm

3-(hydroxy(4-methoxyphenyl)methyl)furan-2(5*H*)-one (3b)



^{1}H NMR: 3.81(s, 3H), 4.82 (td, 2H, *J*=0.58, 1.9 Hz), 5.55 (s, br, 1H), 6.89-6.92 (m, 2H), 7.18 (q,1H, *J* =1.64 Hz), 7.33-7.36 (m, 2H) ppm
^{13}C NMR: 56.0, 69.7, 71.1, 114.8, 128.4, 132.9, 137.3, 146.1, 160.3 ppm

3-(hydroxyl(4-tolyl)methyl)furan-2(5*H*)-one (3c)

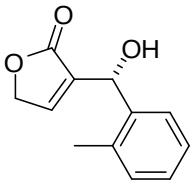


^{1}H NMR: 2.35 (s, 3H), 4.81 (t, 2H, *J*=1.78 Hz), 5.56 (s, br, 1H), 7.17-7.19 (m, 3H), 7.29-7.32 (m, 2H) ppm

^{13}C NMR: 20.6, 69.8, 71.3, 127.1, 129.3, 138.8, 139.6, 146.5, 146.8, 173.0 ppm

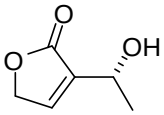
[1] Bugarin, A.; Connell, B. T. *J. Org. Chem.* **2009**, *74*, 4638

3-(hydroxy(2-tolyl)methyl)furan-2(5*H*)-one (3d)



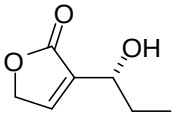
^{1}H NMR: 2.34 (s, 3H), 4.82 (t, 2H, *J*=1.85 Hz), 5.79 (s, br, 1H), 7.02 (q, 1H, *J*=1.65 Hz), 7.16-7.25 (m, 4H) ppm
^{13}C NMR: 19.1, 65.8, 70.5, 126.2, 126.4, 128.2, 130.6, 135.2, 136.0, 138.0, 146.3, 173.1 ppm

3-(1-hydroxyethyl)furan-2(5*H*)-one (3e)



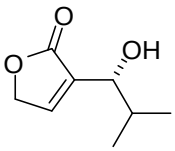
^{1}H NMR: 1.48 (d, 3H, *J*=6.52 Hz), 4.64-4.73 (m, 1H), 4.84 (t, 2H, *J*=1.82 Hz), 7.33 (q, 1H, *J*=1.60 Hz) ppm
^{13}C NMR: 21.5, 63.1, 70.4, 137.4, 144.2, 173.2 ppm

3-(1-hydroxypropyl)furan-2(5*H*)-one (3f)



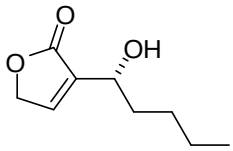
^{1}H NMR: 1.00 (t, 3H, *J*=7.42 Hz), 1.68-1.81 (m, 2H), 4.44-4.49 (m, 1H), 4.84 (t, 2H, *J*=1.73 Hz), 7.32 (q, 1H, *J*=1.63 Hz) ppm
^{13}C NMR: 10.2, 30.3, 69.1, 71.1, 136.9, 145.5, 173.8 ppm

3-(1-hydroxy-2-methylpropyl)furan-2(5*H*)-one (3g)



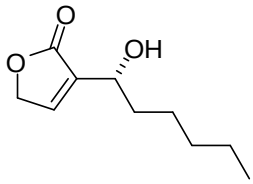
^{1}H NMR: 0.85-0.90 (dd, 6H, J_1=6.81, 9.20 Hz), 1.98-2.07 (m, 1H), 4.22-4.25 (m, 1H), 4.78 (t, 2H, *J*=1.66 Hz), 7.28 (q, 1H, *J*=1.69 Hz) ppm
^{13}C NMR: 16.6, 18.9, 32.3, 70.5, 72.3, 135.4, 146.0, 173.2 ppm

3-(1-hydroxypentyl)furan-2(5*H*)-one (3h)



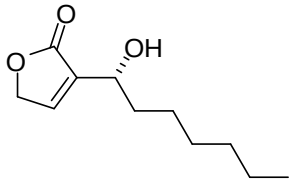
^{1}H NMR: 0.83-0.88 (m, 3H), 1.25-1.30 (m, 4H), 1.59-1.80 (m, 2H), 4.44-4.49 (m, 1H), 4.79 (t, 2H, *J*=1.72 Hz), 7.26 (q, 1H, *J*=1.68 Hz) ppm
^{13}C NMR: 14.5, 23.1, 27.6, 30.3, 67.9, 71.1, 123.5, 145.2 ppm

3-(1-hydroxyhexyl)furan-2(5*H*)-one (3i)



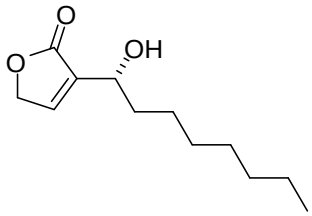
^{1}H NMR: 0.87-0.92 (m, 3H), 1.26-1.34 (m, 6H), 1.63-1.84 (m, 2H), 4.48-4.53 (m, 1H), 4.83 (t, 2H, *J*=1.65 Hz), 7.30 (q, 1H, J=1.46 Hz) ppm
^{13}C NMR: 13.9, 22.5, 24.9, 31.5, 35.4, 67.2, 70.4, 136.6, 144.6, 173.1 ppm

3-(1-hydroxyheptyl)furan-2(5*H*)-one (3j)



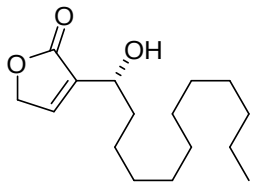
^{1}H NMR: 0.83-0.91 (m, 3H), 1.26-1.29 (m, 8H), 1.68-1.81 (m, 2H), 4.51 (m, 1H), 4.83 (t, 2H, *J*=1.73 Hz), 7.30 (q, 1H, J=1.71 Hz) ppm
^{13}C NMR: 14.0, 22.6, 25.2, 29.0, 29.7, 31.7, 67.2, 70.4, 136.6, 144.5 ppm

3-(1-hydroxyoctyl)furan-2(5*H*)-one (3k)



^{1}H NMR: 0.86-0.90 (m, 3H), 1.26-1.36 (m, 10H), 1.66-1.84 (m, 2H), 4.48-4.54 (m, 1H), 4.83 (t, 2H, *J*=1.70 Hz), 7.29 (q, 1H, *J*=1.50 Hz) ppm
^{13}C NMR: 14.0, 22.6, 25.3, 29.2, 29.3, 31.8, 35.5, 67.2, 70.4, 136.6, 144.5, 173.1 ppm

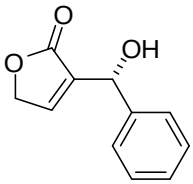
3-(1-hydroxydodecyl)furan-2(5*H*)-one (3l)



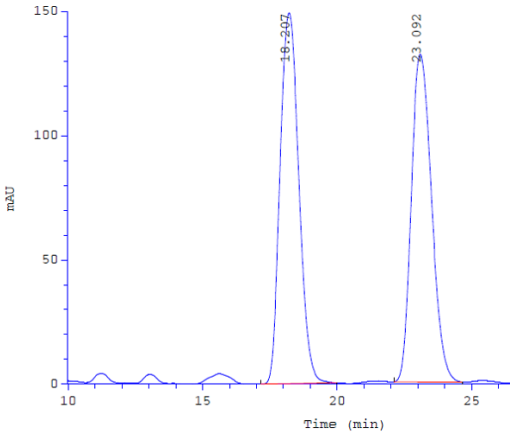
^{1}H NMR: 0.86-0.90 (m, 3H), 1.26 (m, 18H), 1.57-1.83 (m, 2H), 4.47-4.52 (m, 1H), 4.83 (t, 2H, *J*=1.71 Hz), 7.34 (q, 1H, *J*=1.63 Hz) ppm
^{13}C NMR: 14.7, 23.3, 25.9, 29.9, 30.0, 30.2, 32.5, 36.1, 67.7, 71.1, 137.3, 145.6, 173.9 ppm

HPLC data for compounds 3a-3e, 3h, 3l (Table 3)

(*R*)-3-(hydroxy(phenyl)methyl)furan-2(5*H*)-one (3a)



HPLC (CHIRALPAK AD-H, hexane/*i*-PrOH = 90:10, flow rate = 1 mL/min, λ = 225 nm) t_R = 18.4 min (*S*), t_R = 24.1 min (*R*)



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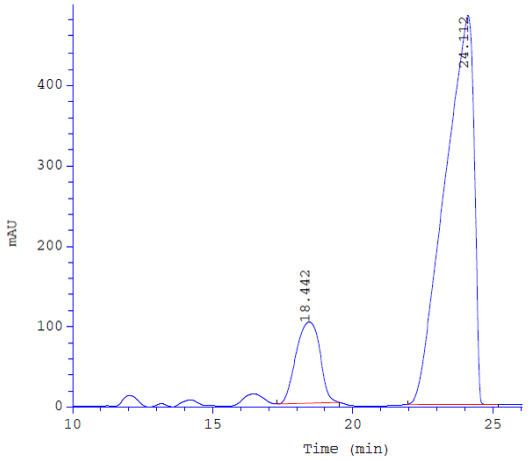
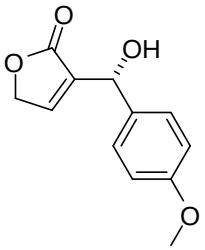
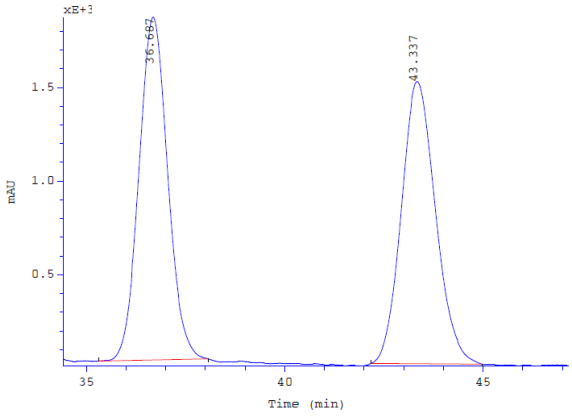


Table 3. Entry 3

(*R*)-3-(hydroxy(4-methoxyphenyl)methyl)furan-2(5*H*)-one (3b)



HPLC (CHIRALPAK AD-H, hexane/
i-PrOH = 90:10, flow rate = 1 mL/min, λ = 225 nm) t_R = 36.7 min (minor, *S*), t_R = 42.9 min (major, *R*)



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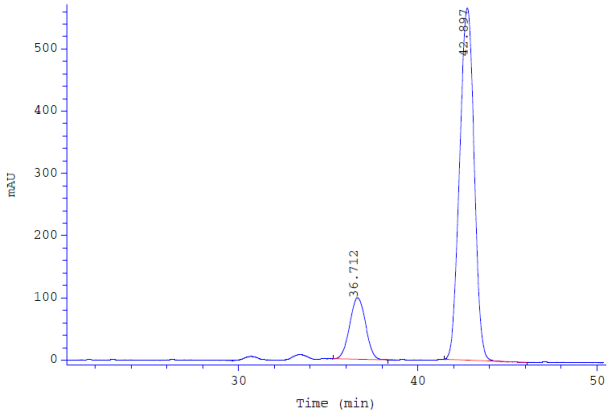
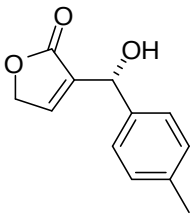
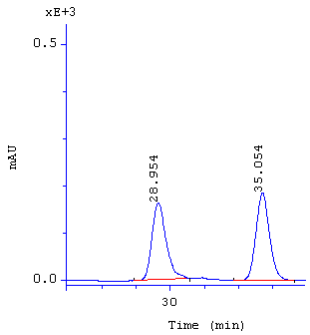


Table 3. Entry 7

(*R*)-3-(hydroxyl(4-tolyl)methyl)furan-2(5*H*)-one (3c)



HPLC (CHIRALPAK AD-H, hexane/*i*-PrOH = 90:10, flow rate = 1 mL/min, λ = 225 nm)
t_R = 29.8 min (minor, *S*), t_R = 35.6 min (major, *R*)



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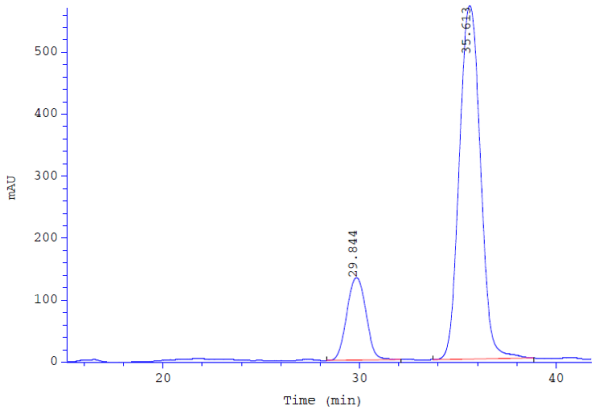
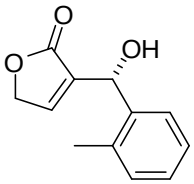
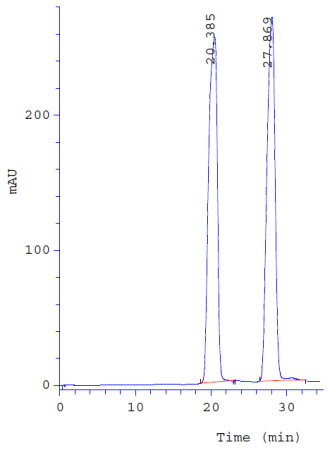


Table 3. Entry 5

(*R*)-3-(hydroxy(2-tolyl)methyl)furan-2(5*H*)-one (3d)



HPLC (CHIRALPAK AD-H, hexane/*i*-PrOH = 90:10, flow rate = 1 mL/min, λ = 225 nm)
t_R = 20.5 min (minor, *S*), t_R = 28.9 min (major, *R*)



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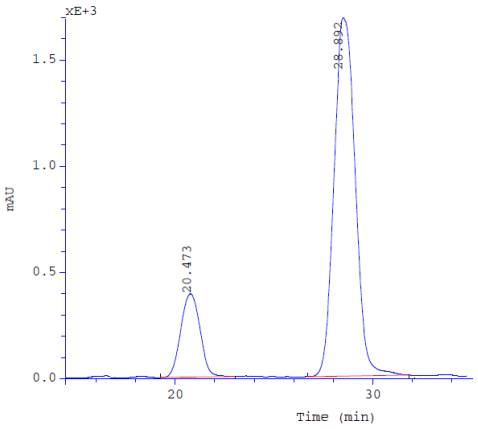
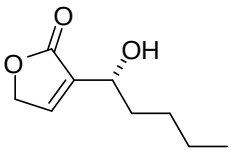
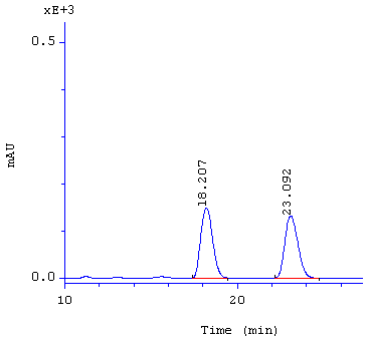


Table 3. Entry 6

(*R*)-3-(1-hydroxypentyl)furan-2(5*H*)-one (3h)



HPLC (CHIRALPAK AD-H, hexane/*i*-PrOH = 90:10, flow rate = 1 mL/min, λ = 225 nm)
t_R = 16.3 min (minor, *S*), t_R = 22.1 min (major, *R*)



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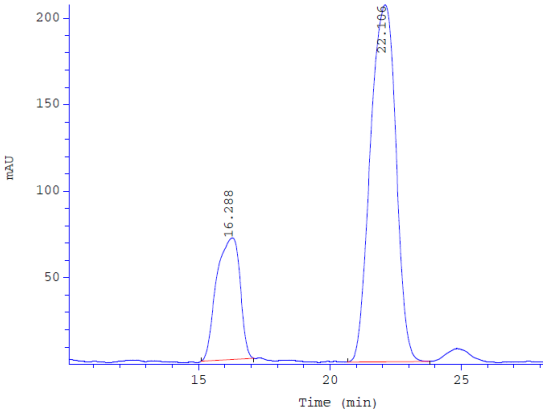
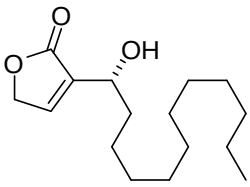
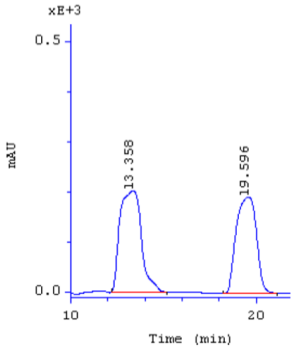


Table 3. Entry 8

(*R*)-3-(1-hydroxydodecyl)furan-2(5*H*)-one (3l)



HPLC (CHIRALPAK AD-H, hexane/*i*-PrOH = 90:10, flow rate = 1 mL/min, λ = 225 nm)
t_R = 12.3 min (minor, *S*), t_R = 19.9 min (major, *R*)



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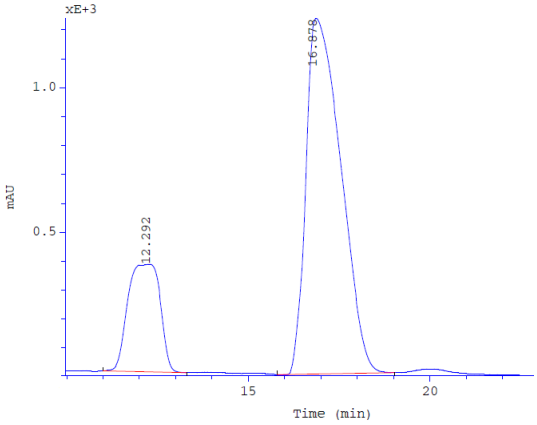
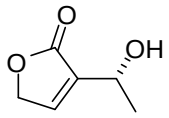


Table 3. Entry 9

Determination of absolute configuration of aldols

(*R*)-3-(1-hydroxyethyl)furan-2(5*H*)-one (3e)

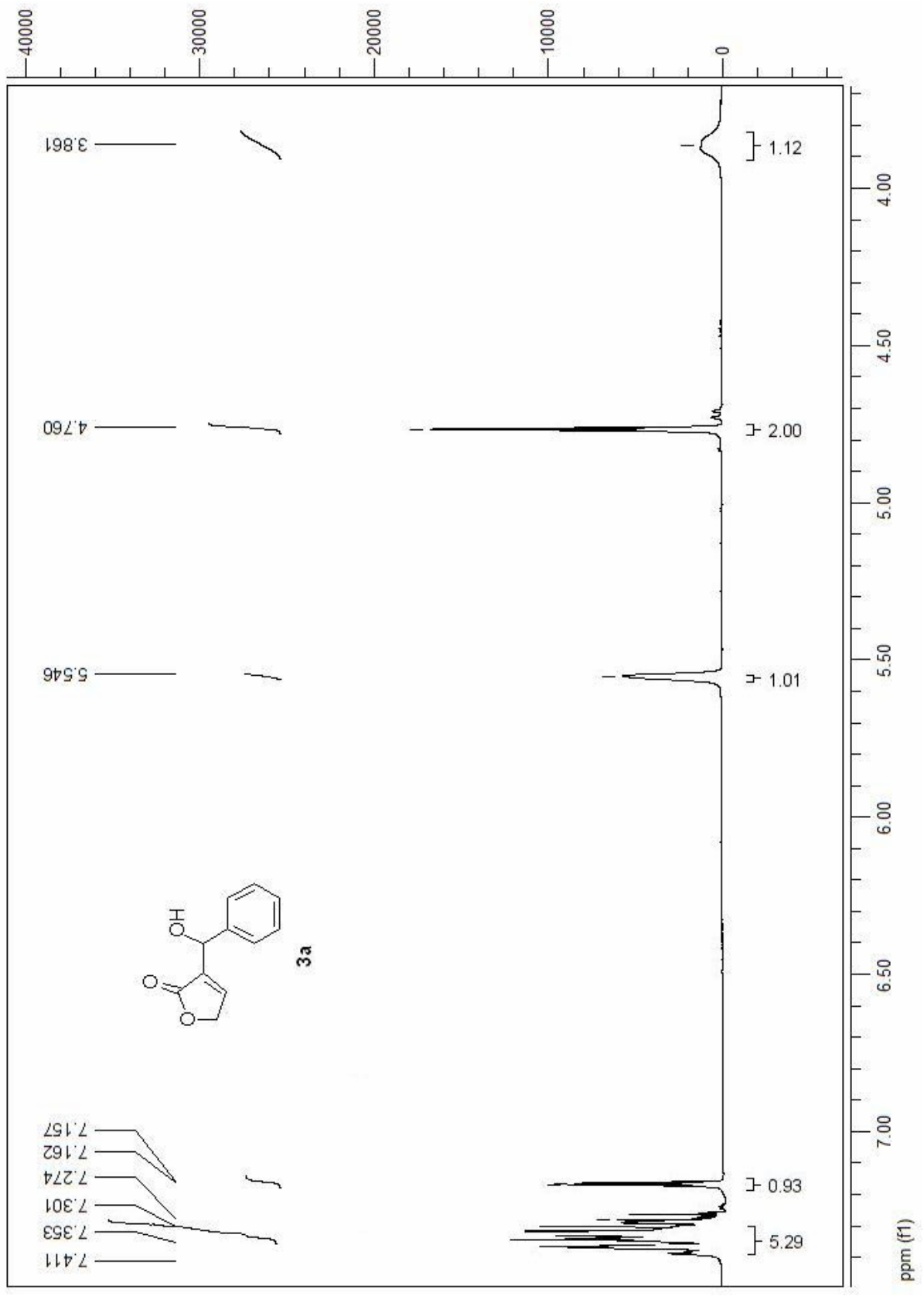


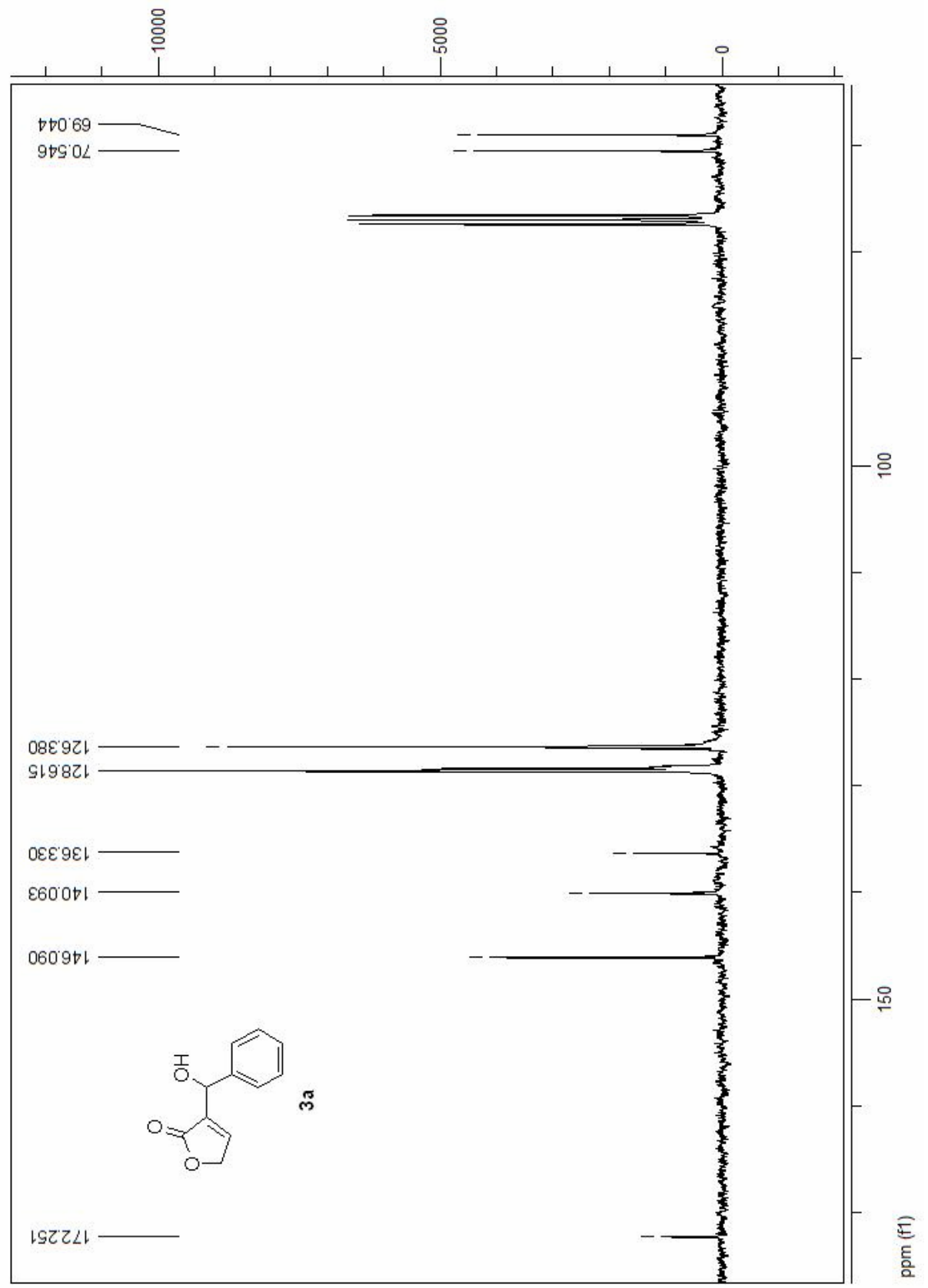
The asymmetric Mukaiyama aldol reaction of siloxy furan **1** with acetaldehyde was proceeded under conditions based on General procedure from **Table 3** and delivered aldol **3e** in 73% yield and 40% ee. The optical rotation of product was measured ($[\alpha]_D$ = +10.9, EtOH, *c* 0.011) and compared to published data[2] (+34.6) for *R* enantiomer.

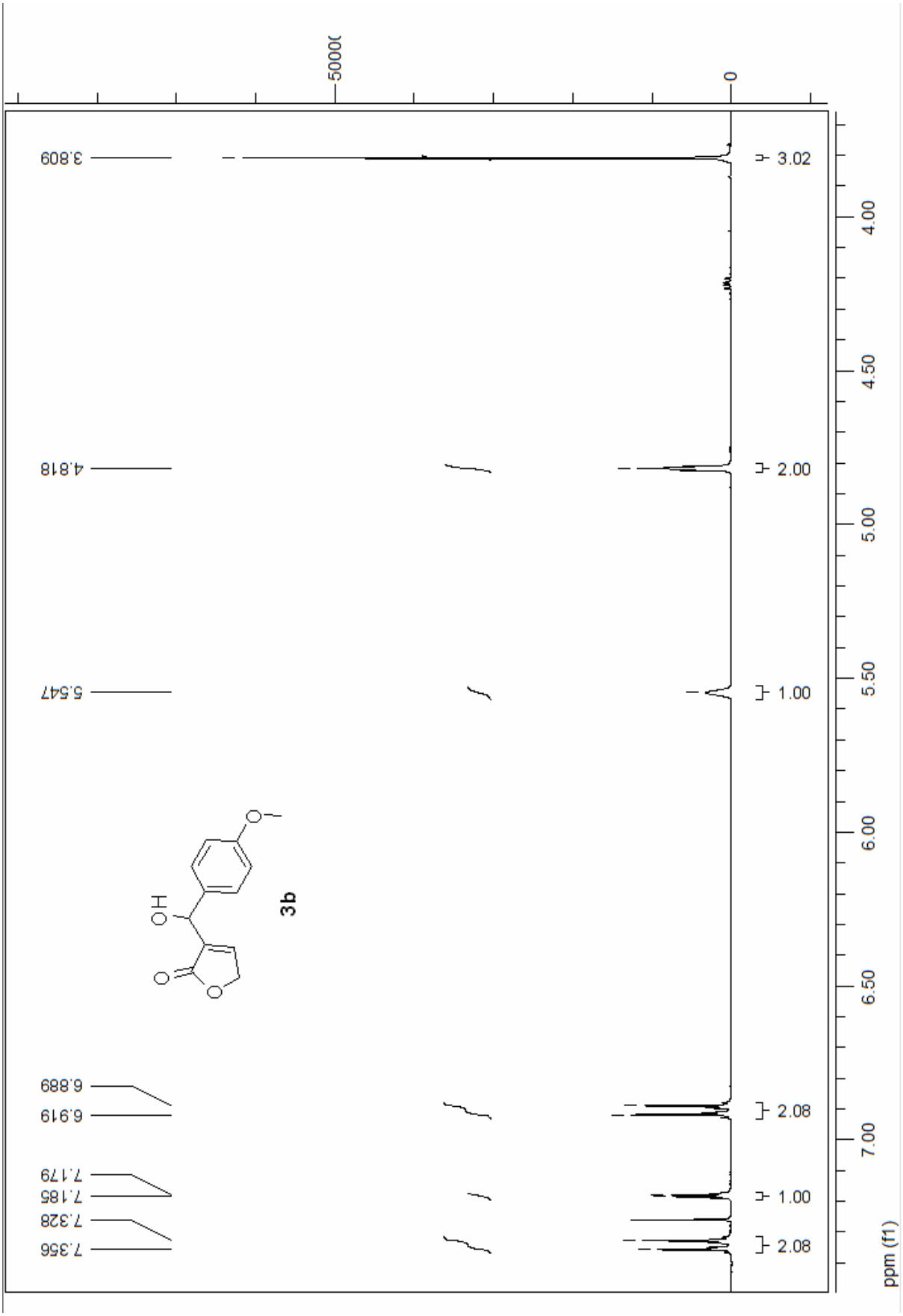
The results indicate that elaborated reaction conditions delivers compounds with the *R* enantiomer predominantly.

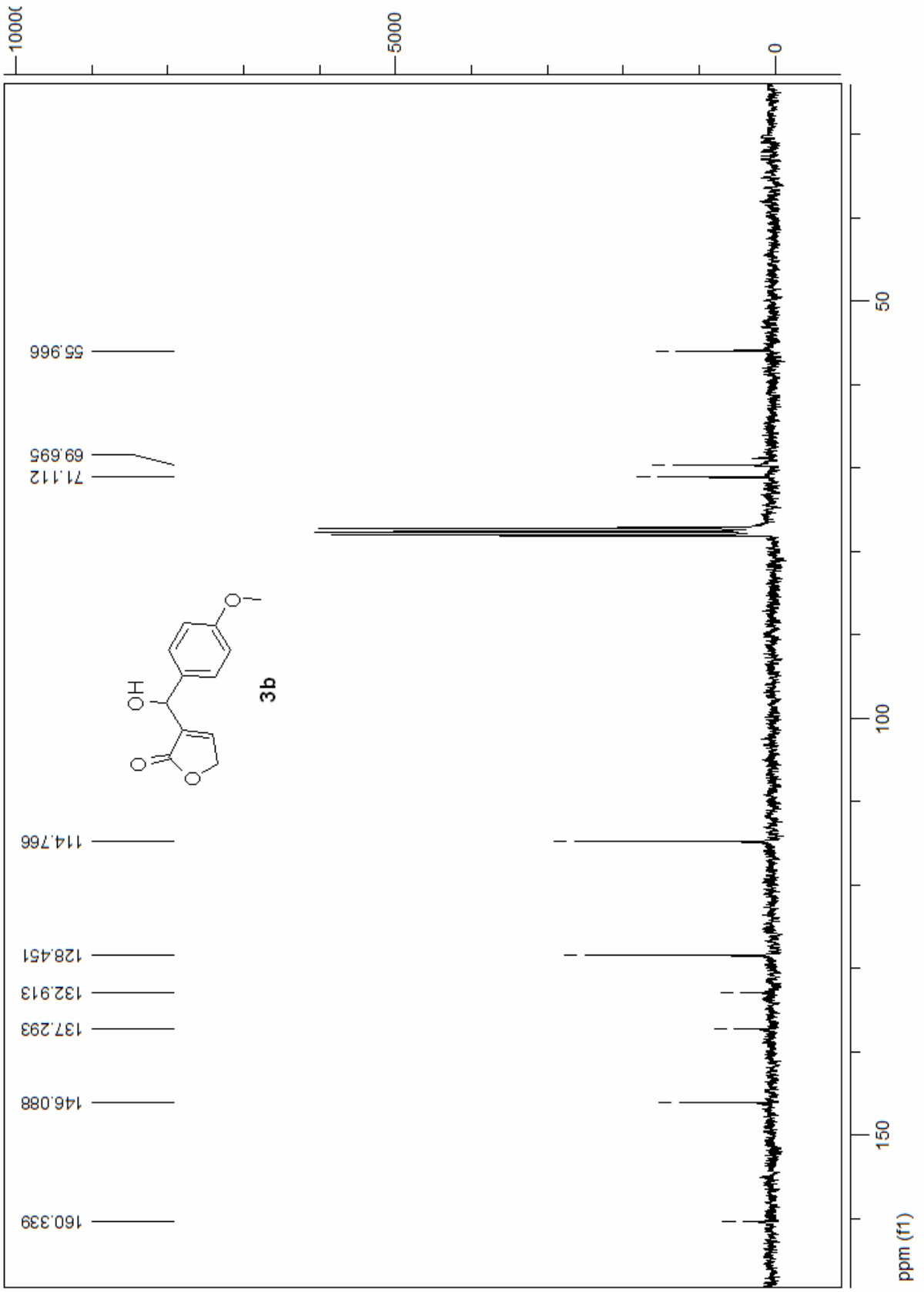
[2] Horne, D. A.; Fugmann, B.; Yakushijin, K.i; Buechi, G. *J. Org. Chem.* **1993** , *58*, 62

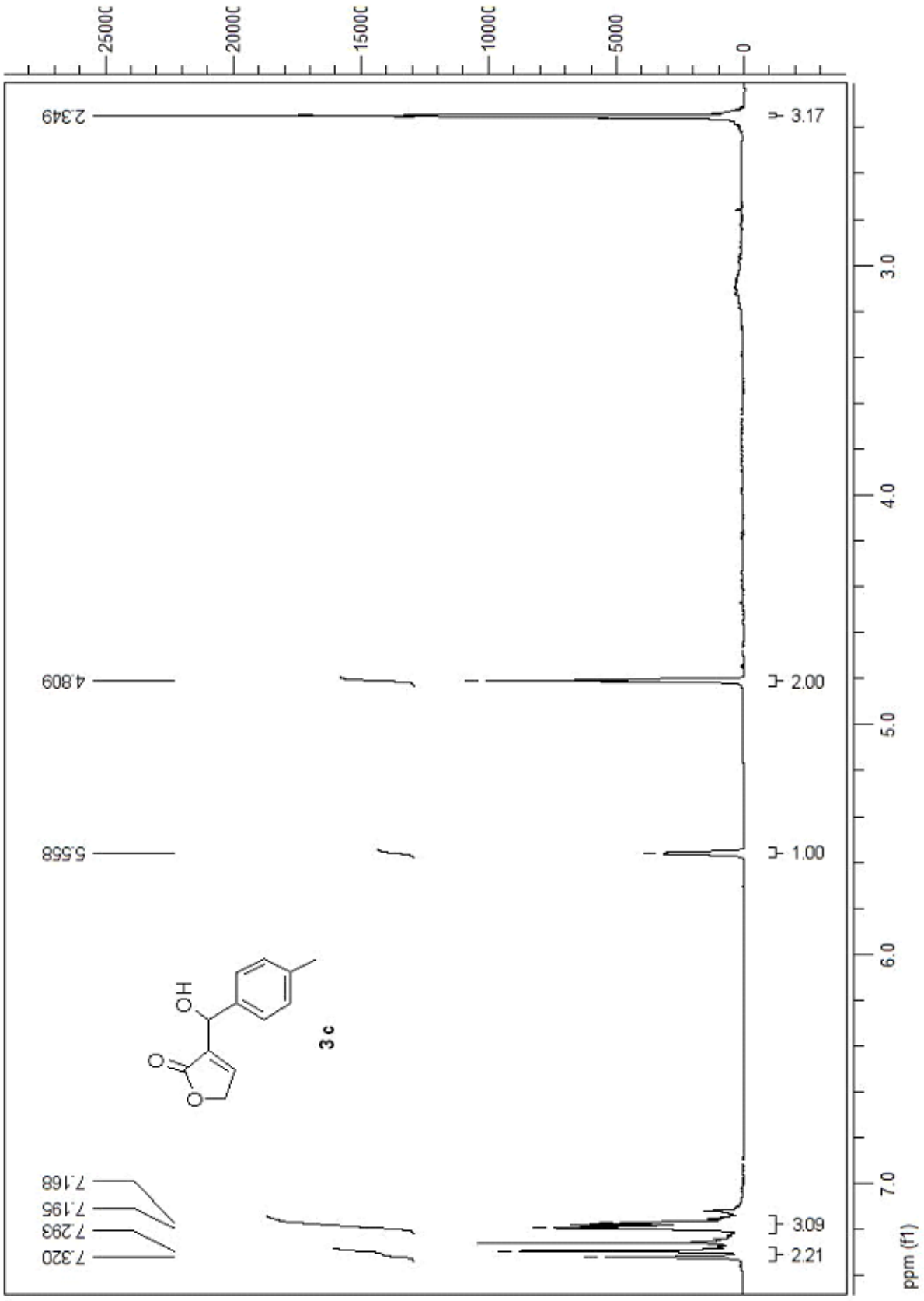
NMR spectra for compounds 3a-l (Table 2)

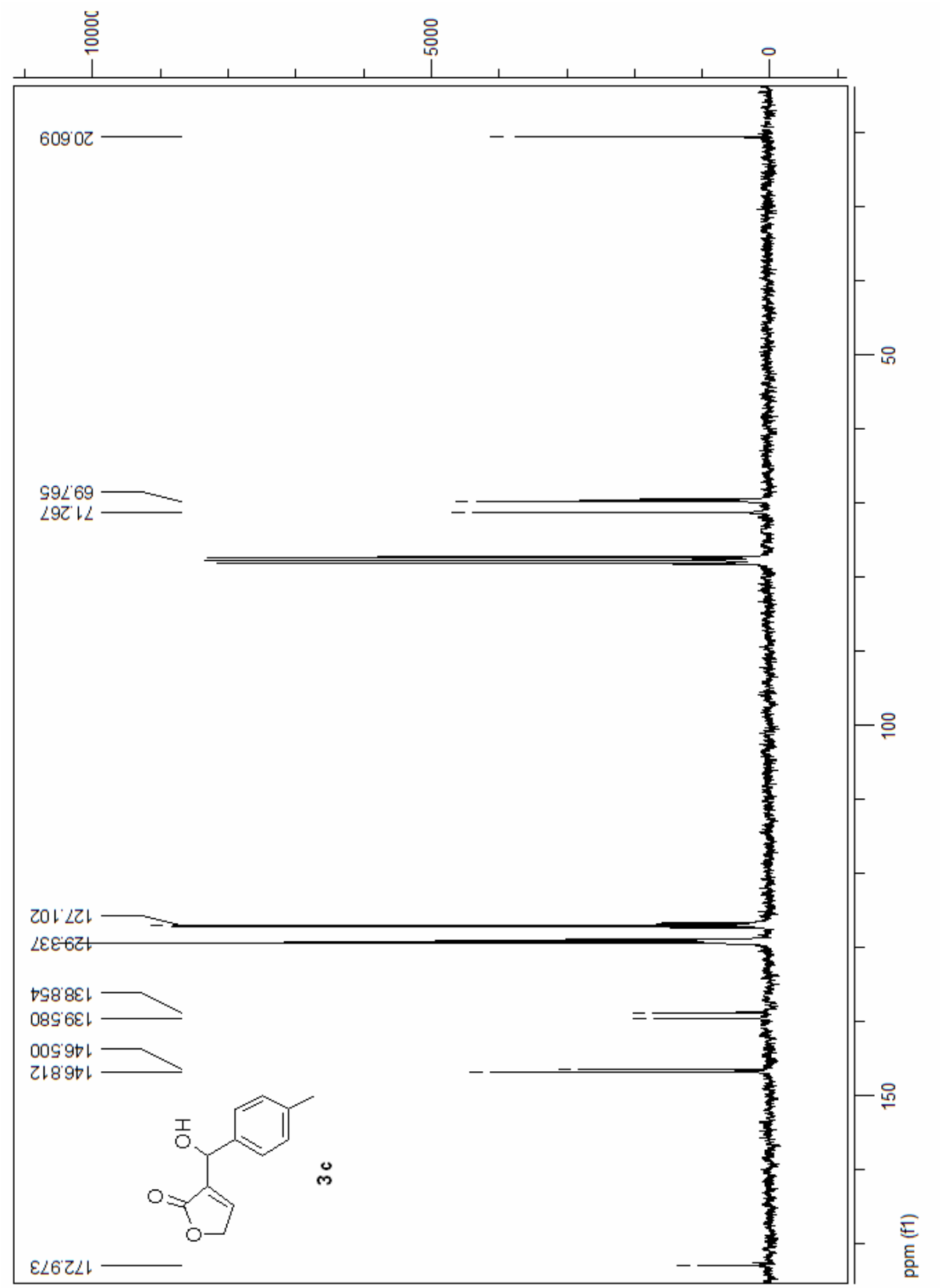


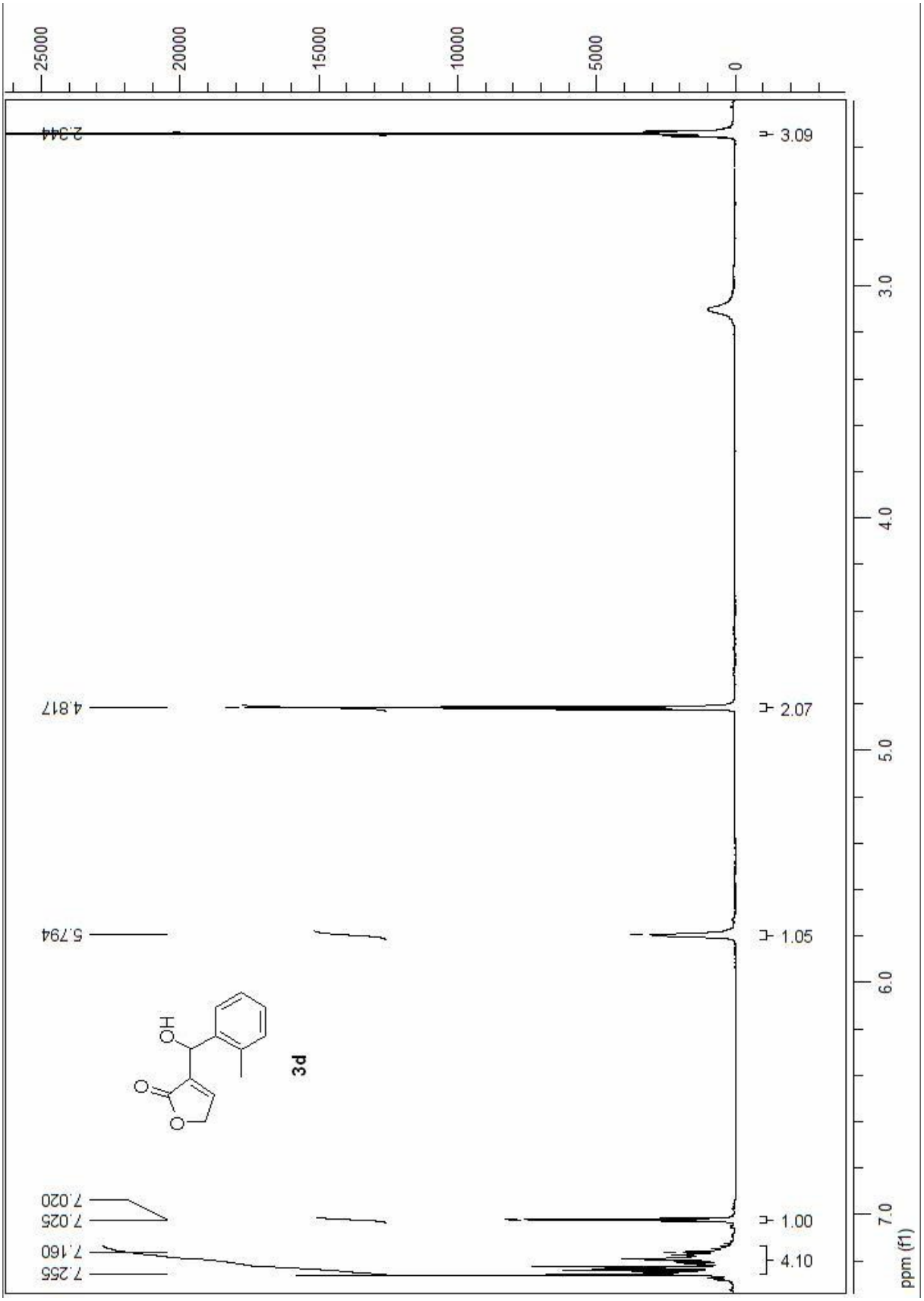

10000
5000
0
69.044
70.546
126.380
128.615
136.330
140.093
146.090
172.251
OH
O
O
3a
100
150
ppm (f1)

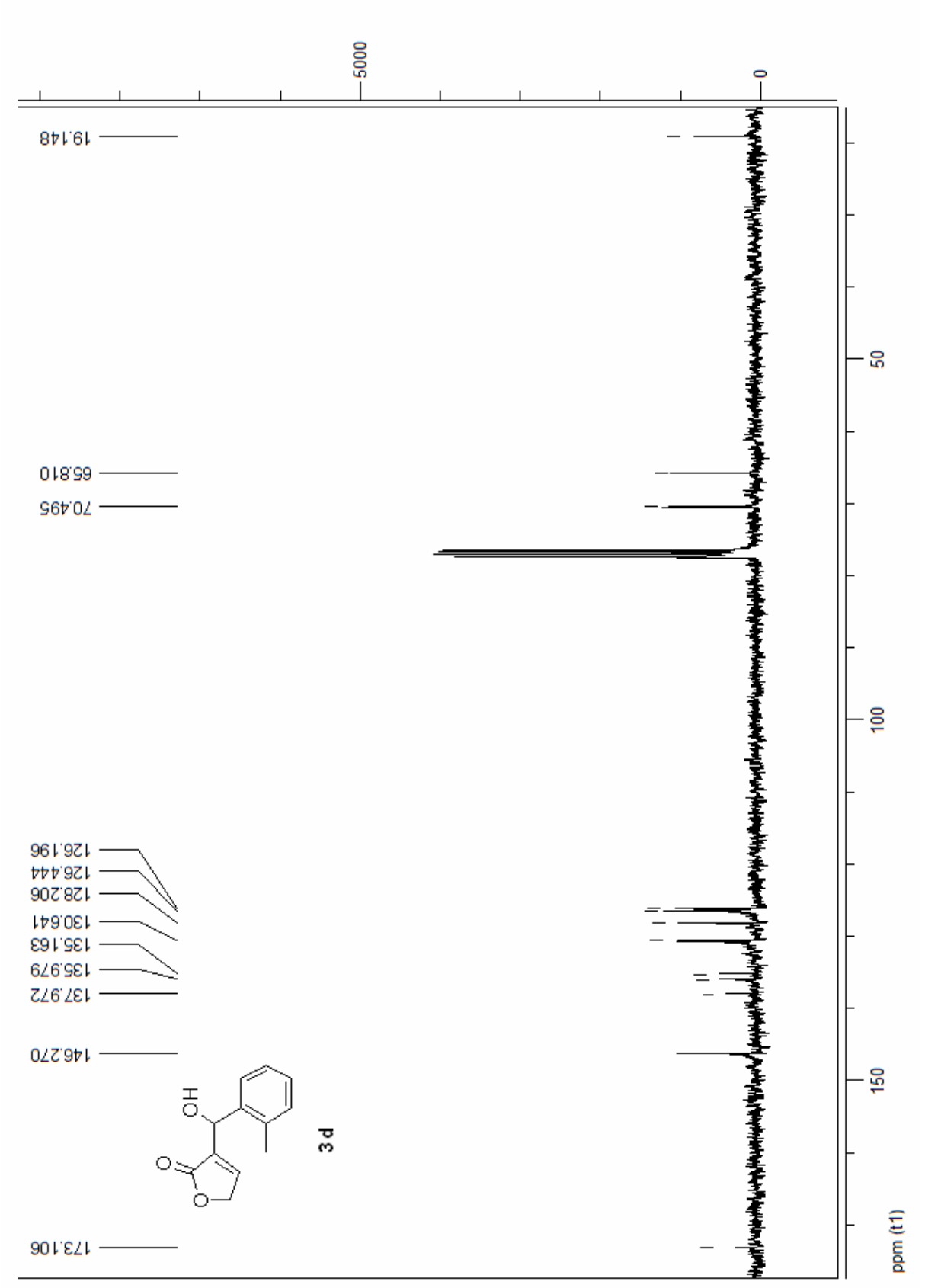

5000
0
3.809
4.818
5.547
6.889
6.919
7.179
7.185
7.328
7.356
3.02
2.00
1.00
2.08
1.00
2.08
4.00
4.50
5.00
5.50
6.00
6.50
7.00
ppm (f1)
HO
O
O
O
3b

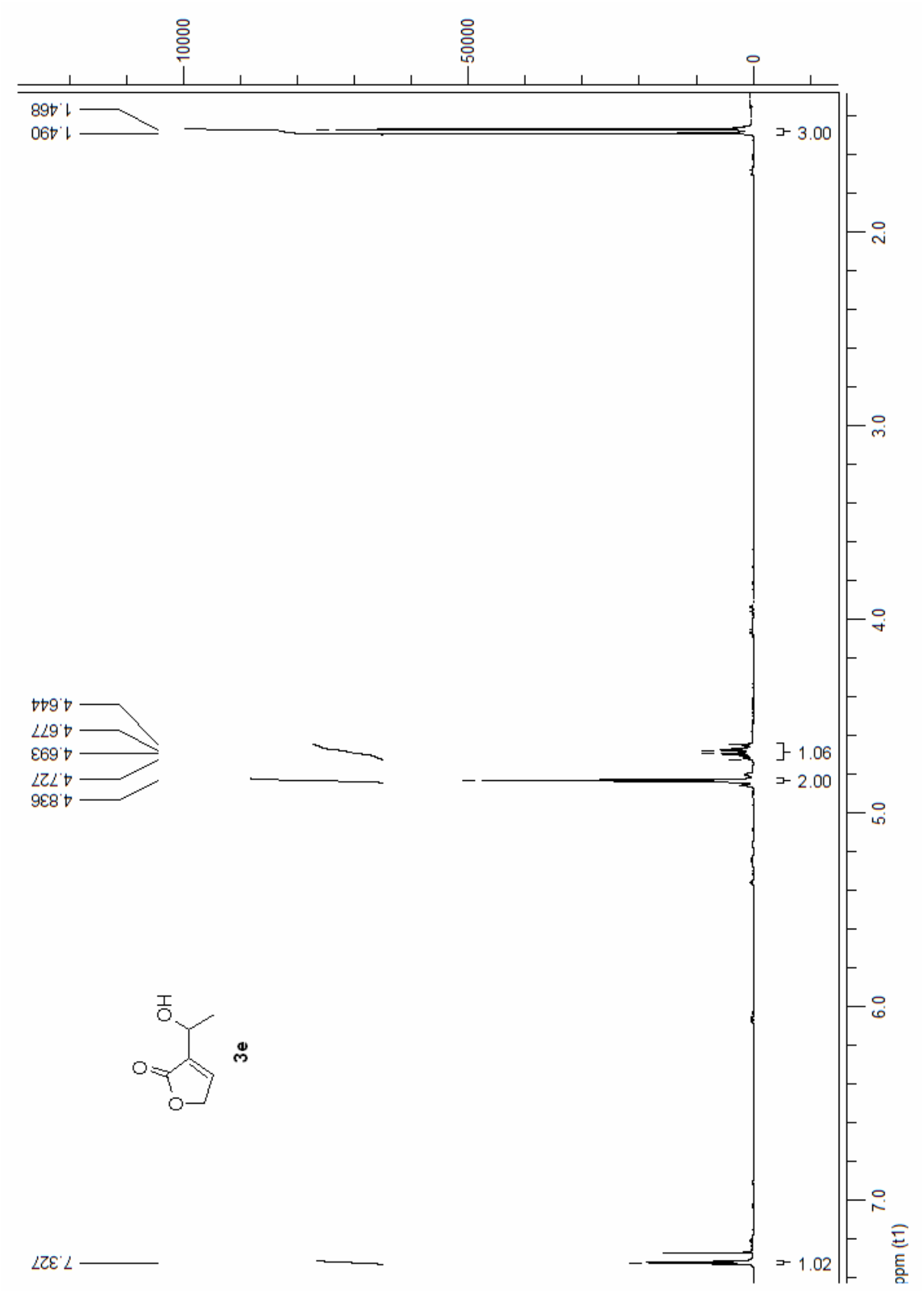





10000
5000
0
20.609
69.765
71.267
127.102
129.337
138.854
139.580
146.500
146.812
172.973
OH
O
O
3c
50
100
150
ppm (f1)


25000
20000
15000
10000
5000
0
2.344
4.817
5.794
7.020
7.025
7.160
7.255
3.09
2.07
1.05
1.00
4.10
3d
OH
O
O
3.0
4.0
5.0
6.0
7.0
ppm (f1)


5000
0
19.148
65.810
70.495
126.196
126.444
128.206
130.641
135.163
135.979
137.972
146.270
173.106
OH
O
O
3 d
50
100
150
ppm (t1)


10000
50000
0
1.468
1.490
4.644
4.677
4.693
4.727
4.836
7.327
3.00
1.06
2.00
1.02
2.0
3.0
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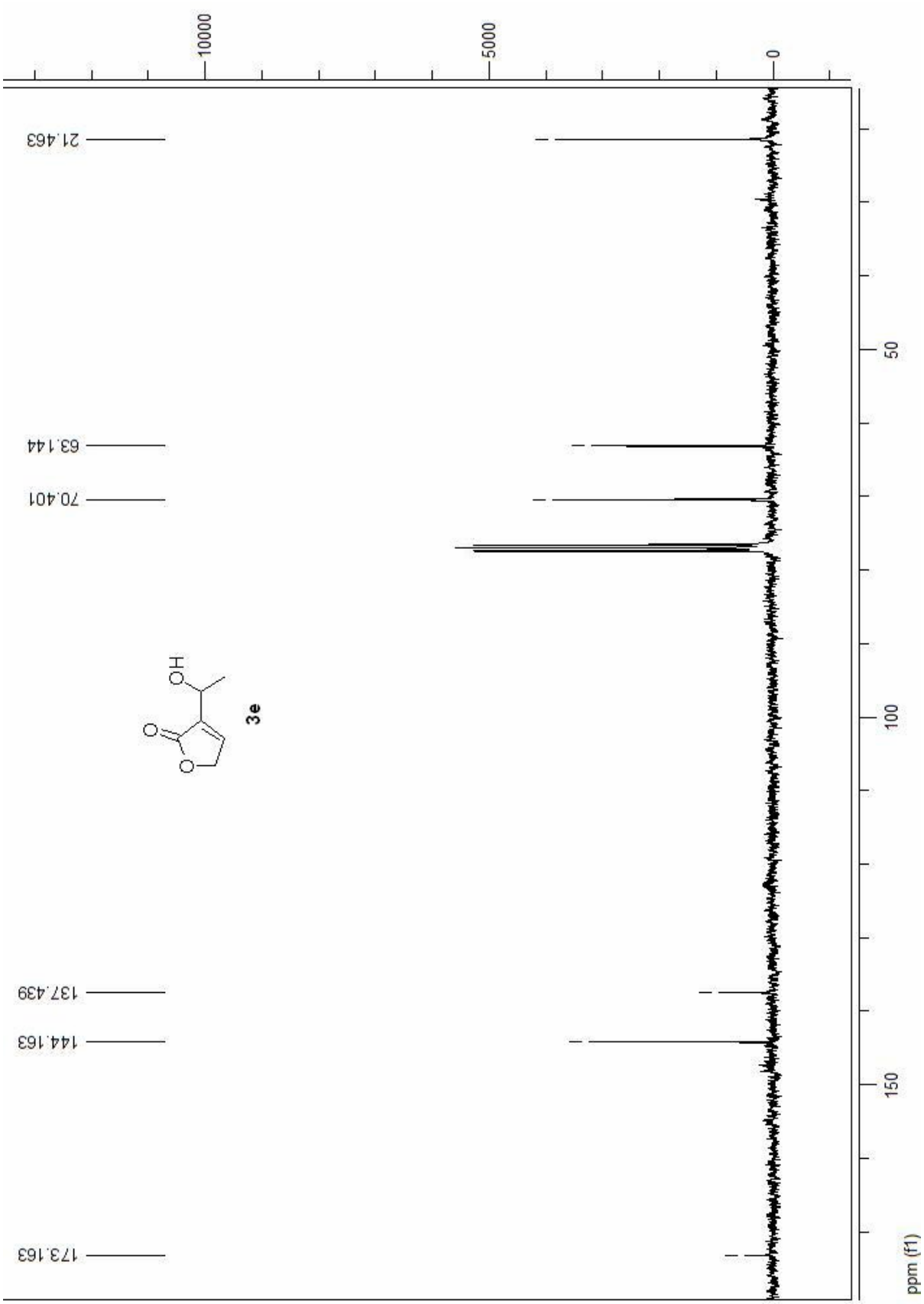
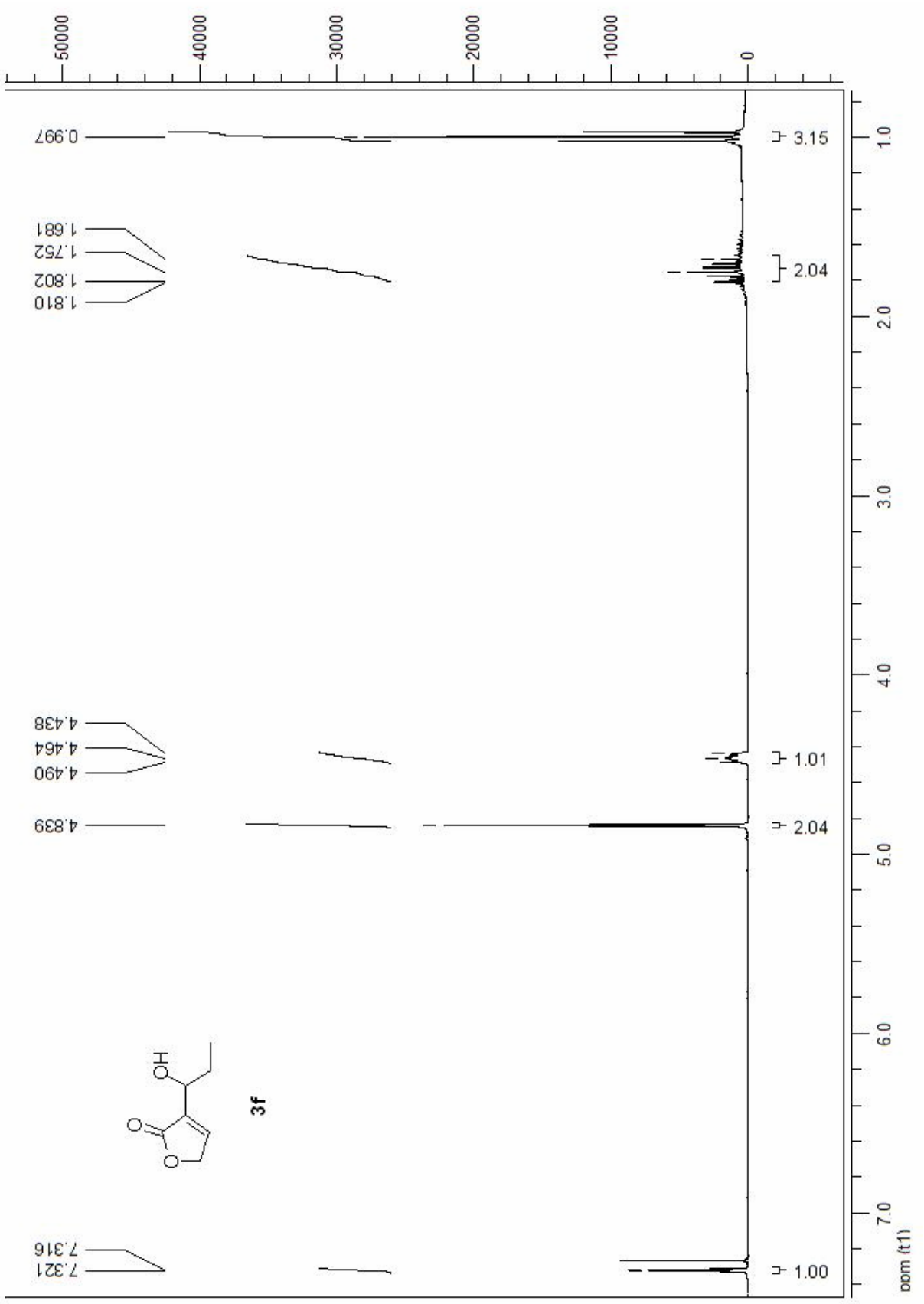
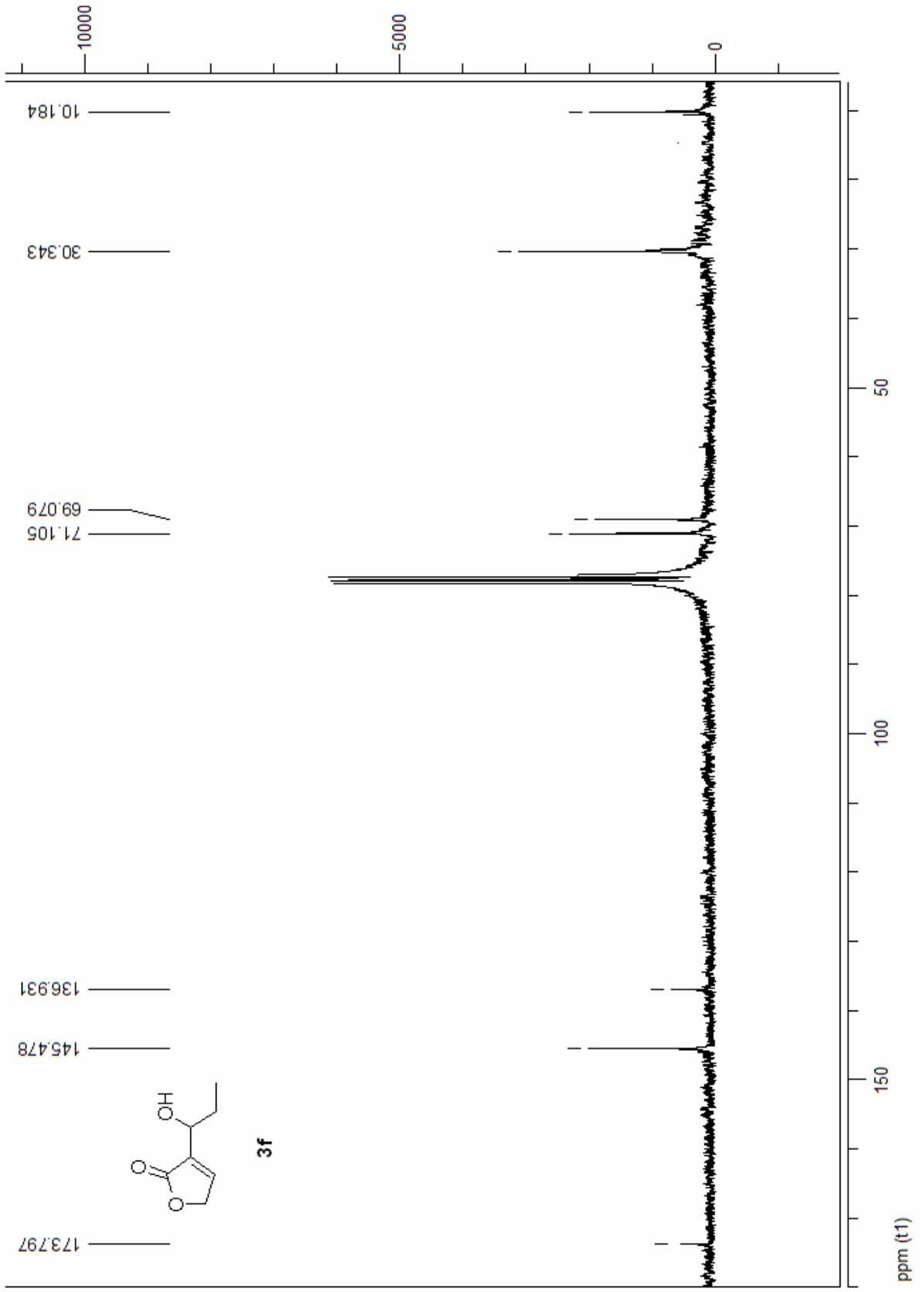
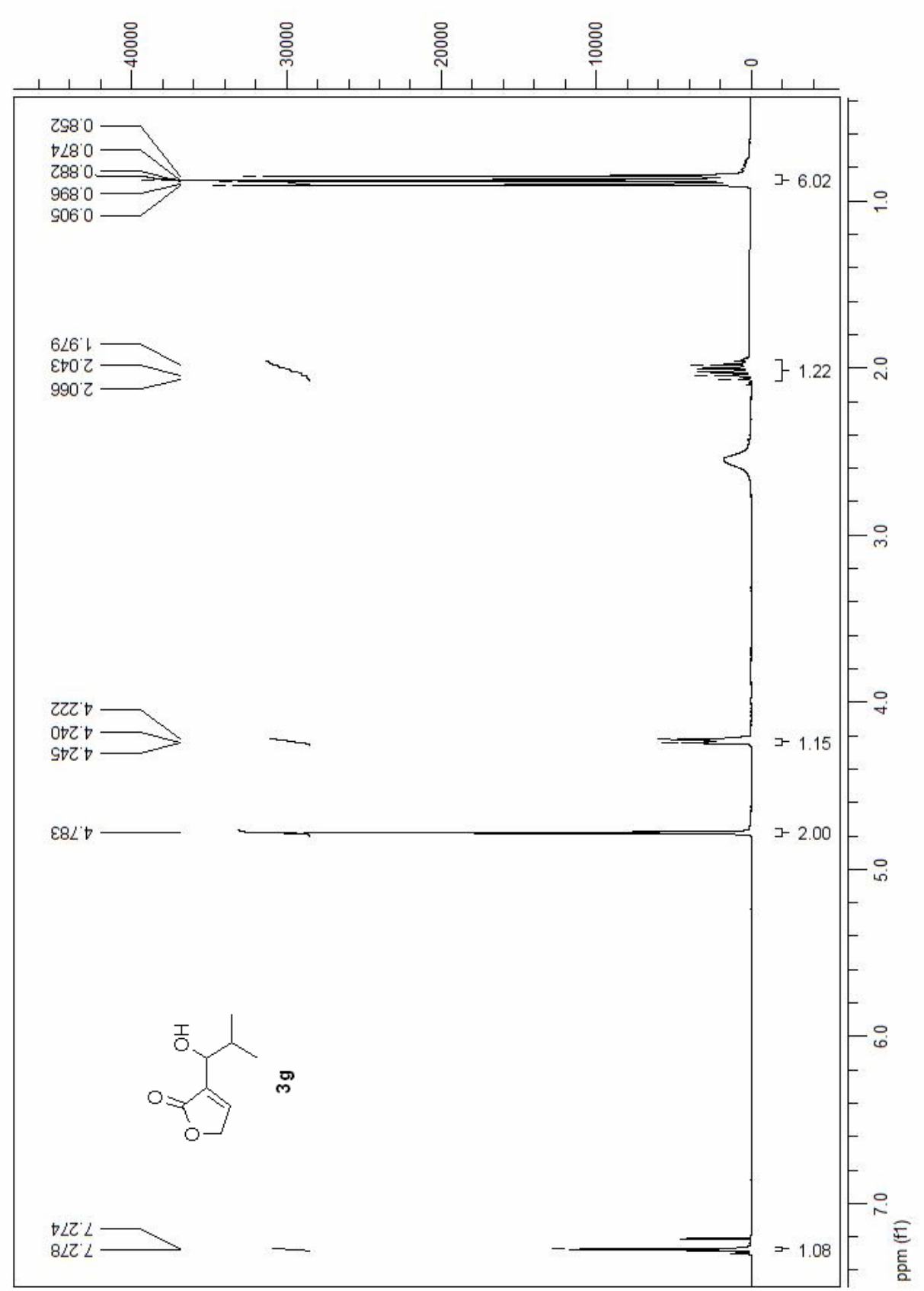
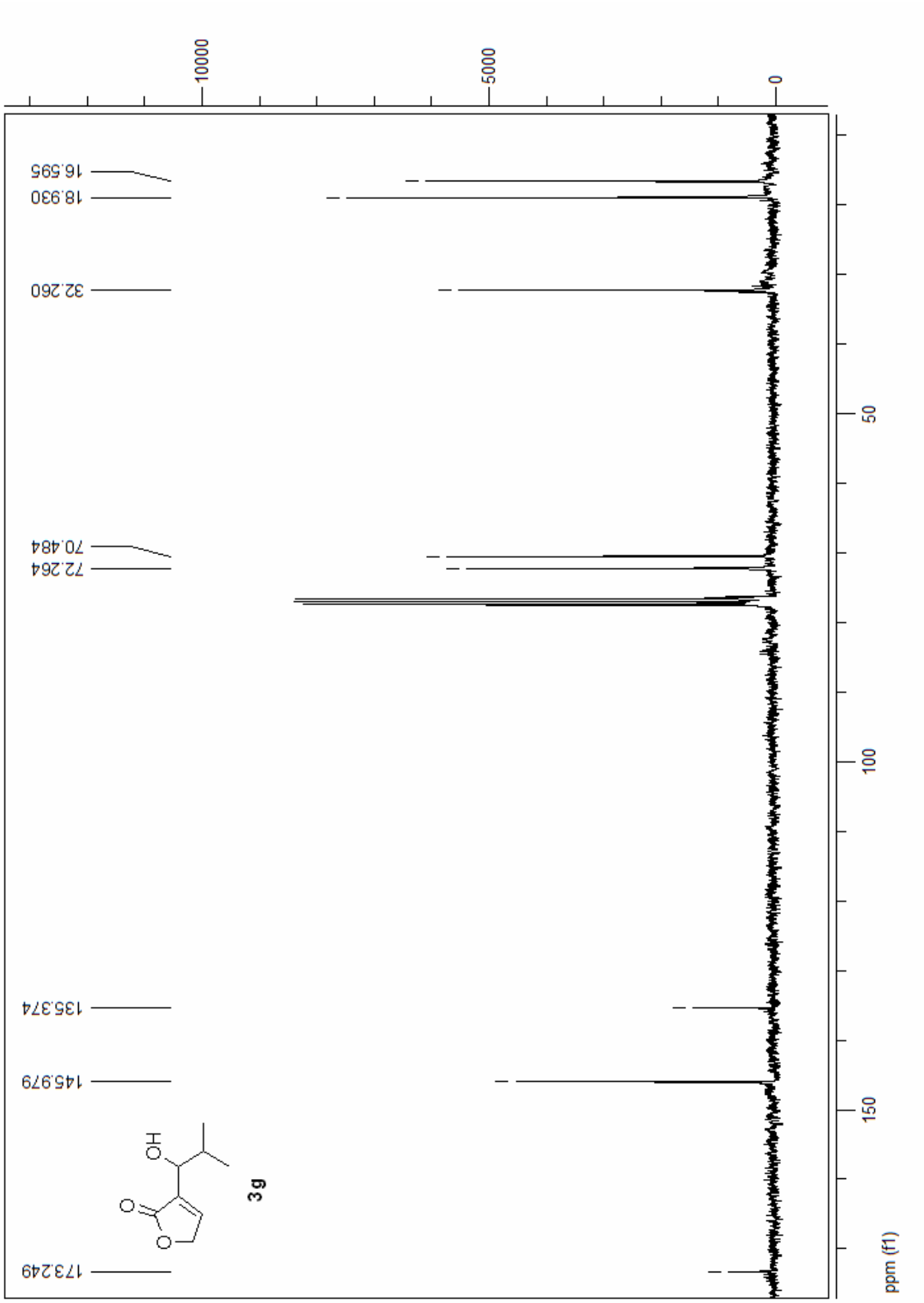
6.0
7.0
ppm (t1)
OH
O
O
3e

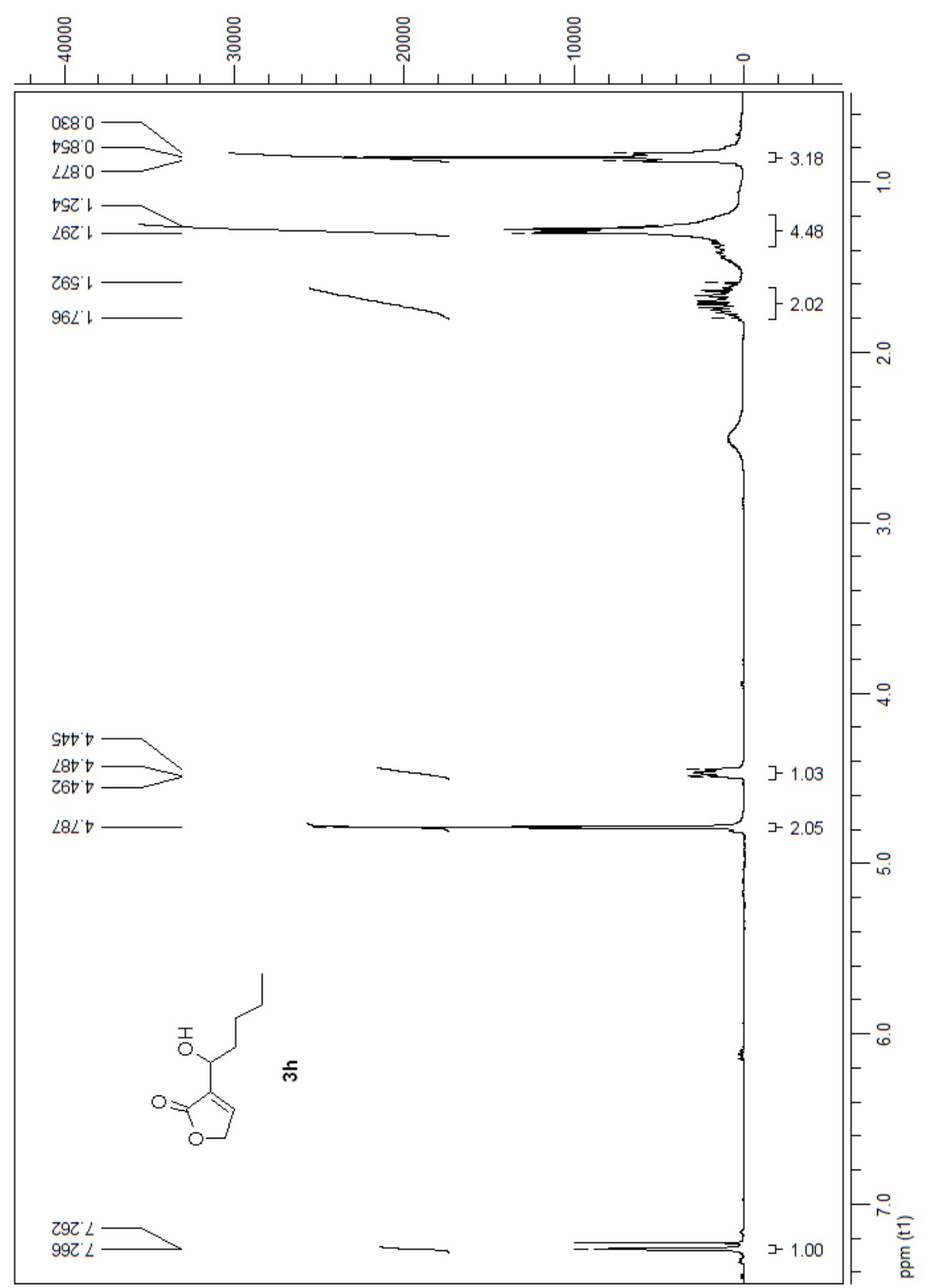

10000
5000
0
21.463
63.144
70.401
137.439
144.163
173.163
50
100
150
ppm (f1)
OH
O
O
3e

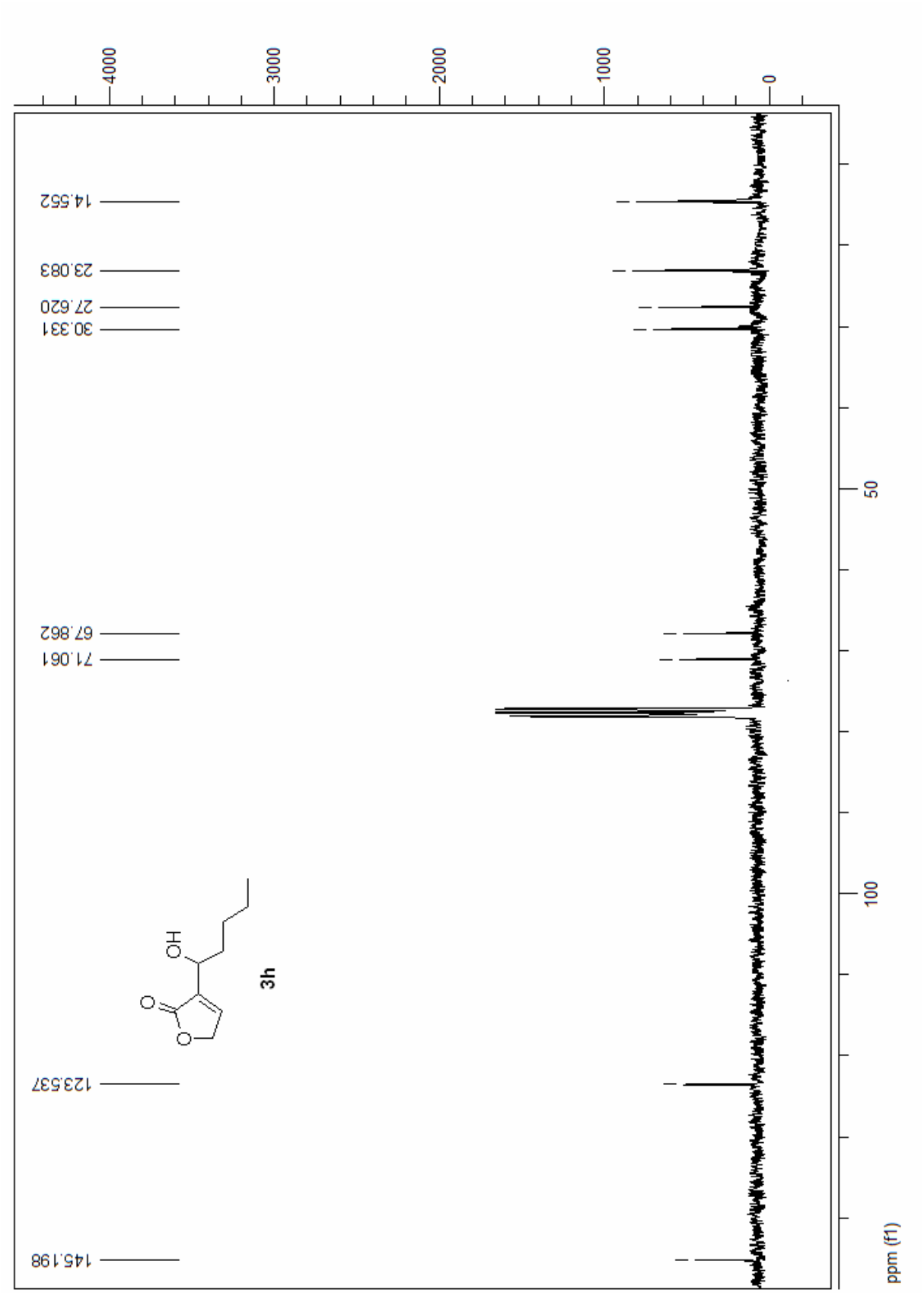


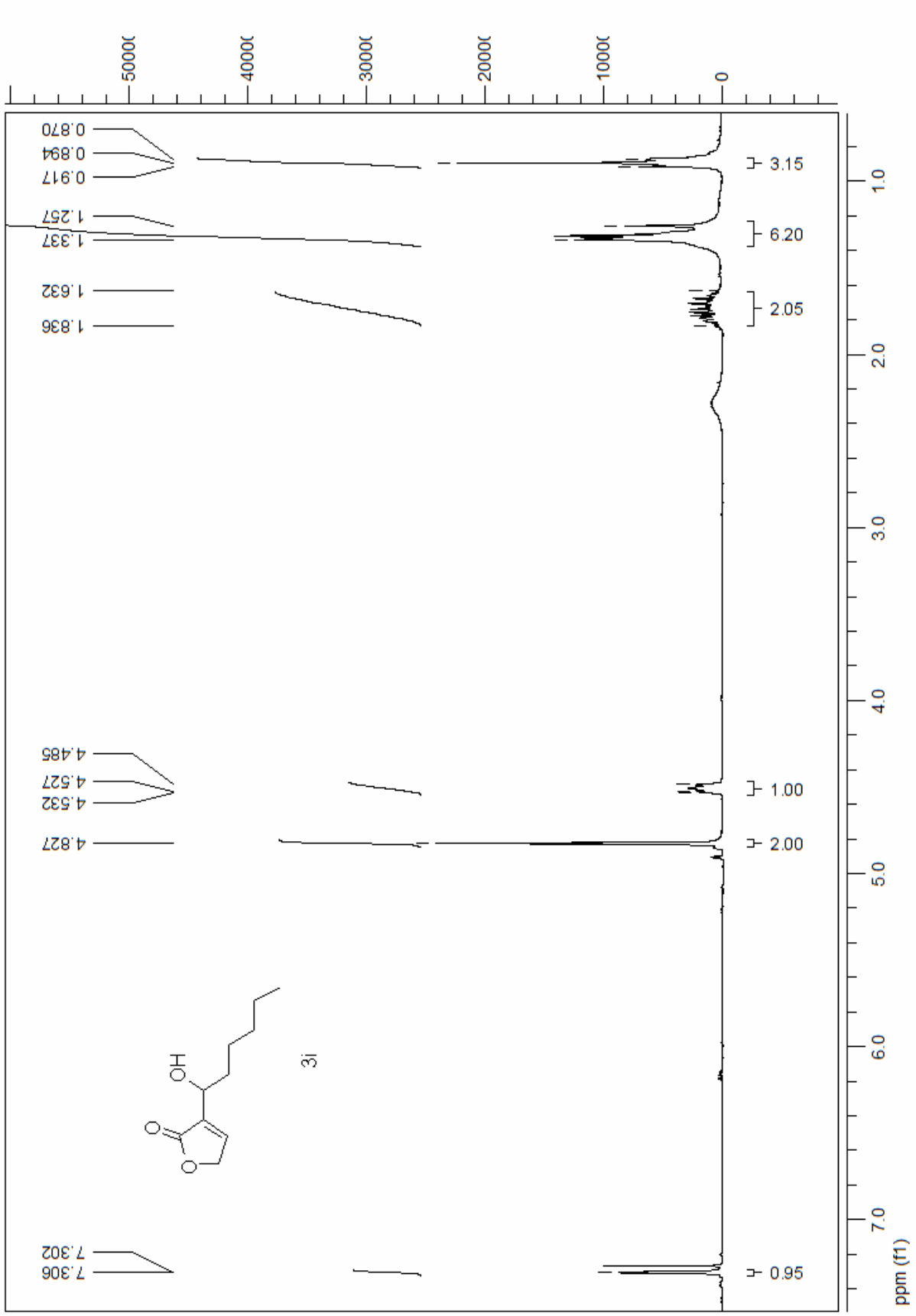


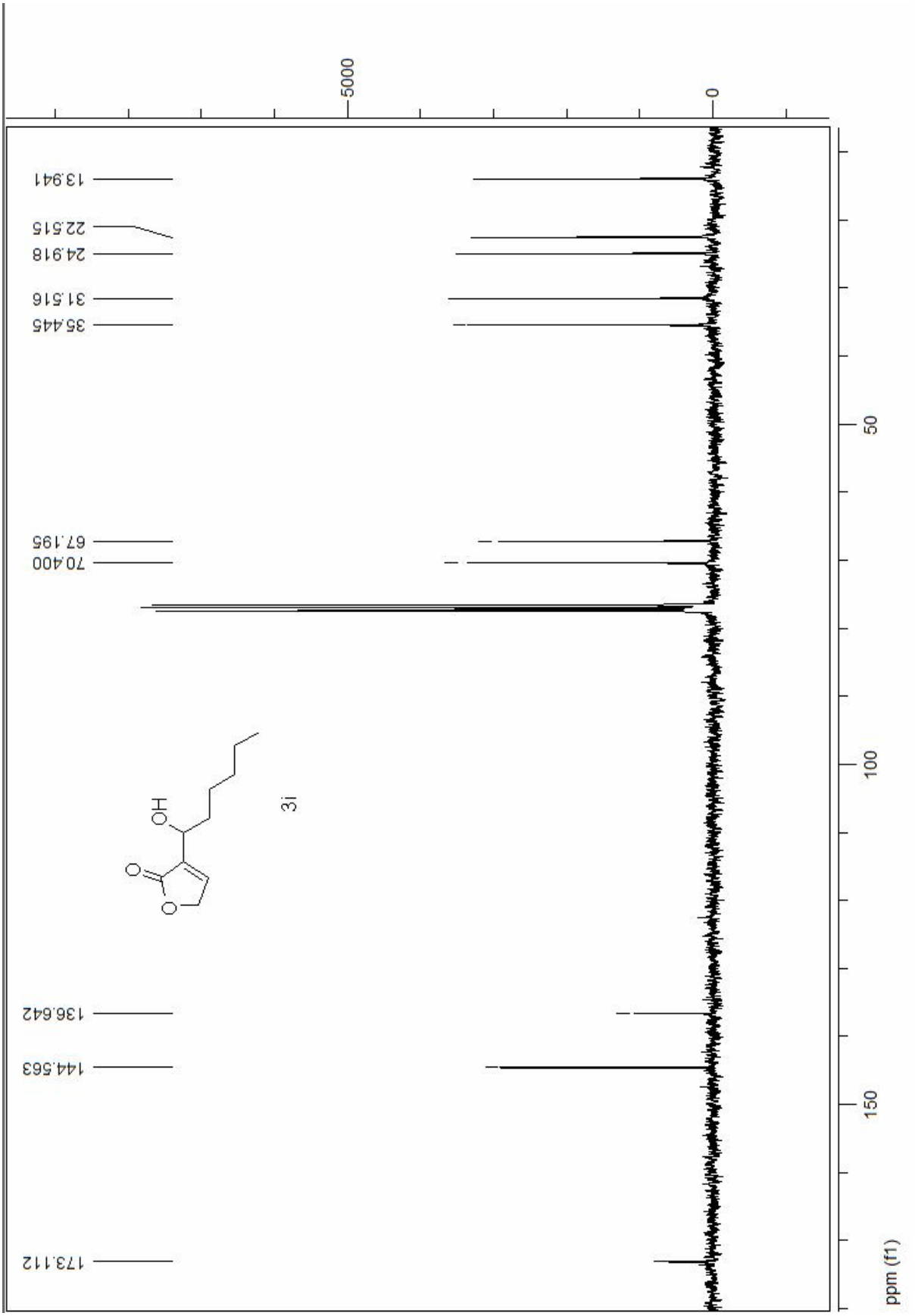

40000
30000
20000
10000
0
0.852
0.874
0.882
0.896
0.905
1.979
2.043
2.066
4.222
4.240
4.245
4.783
7.274
7.278
6.02
1.22
1.15
2.00
1.08
1.0
2.0
3.0
4.0
5.0
6.0
7.0
ppm (f1)
OH
O
O
3g

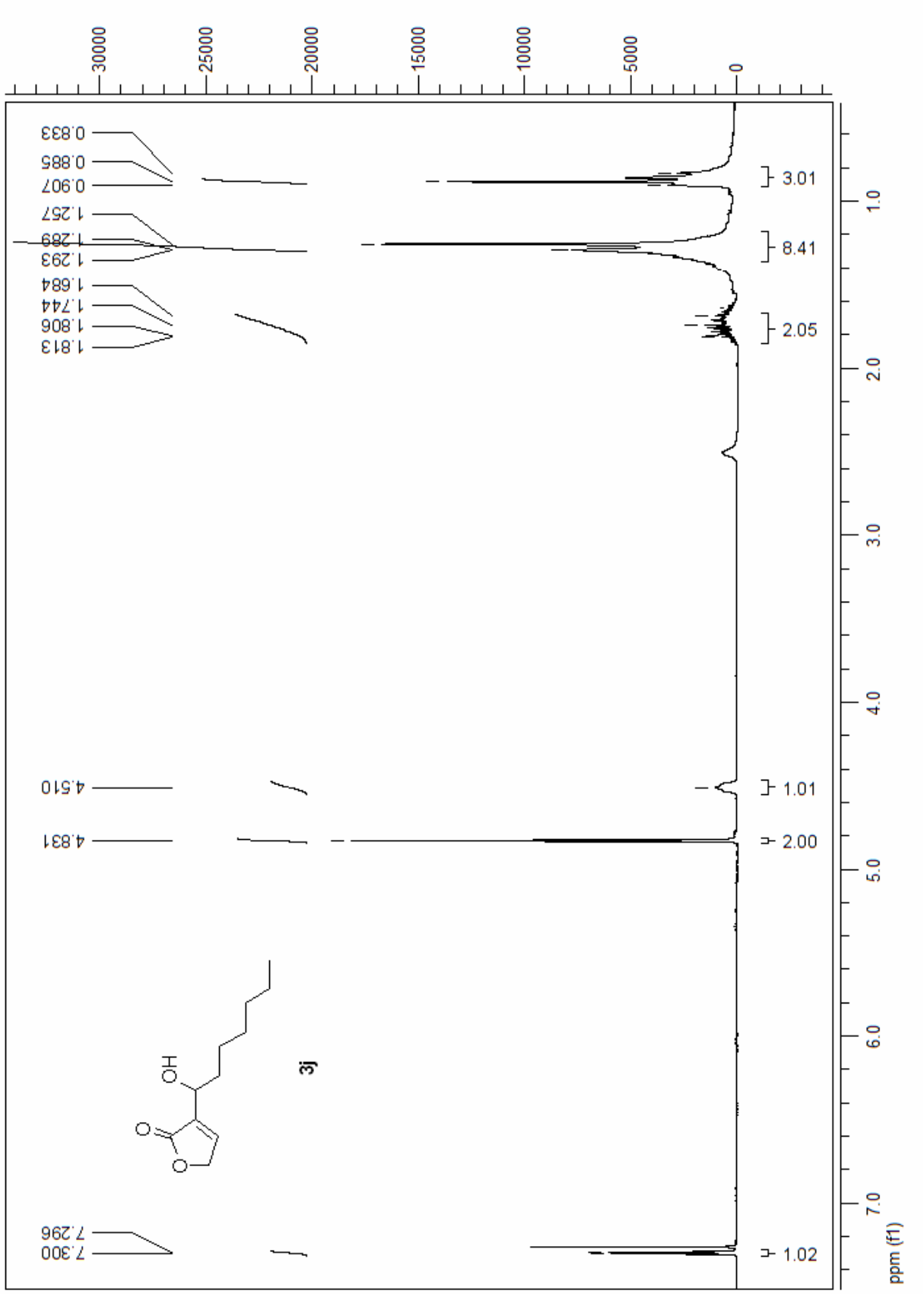

10000
5000
0
16.595
18.930
32.260
70.484
72.264
135.374
145.979
173.249
50
100
150
ppm (f1)
OH
O
O
3g

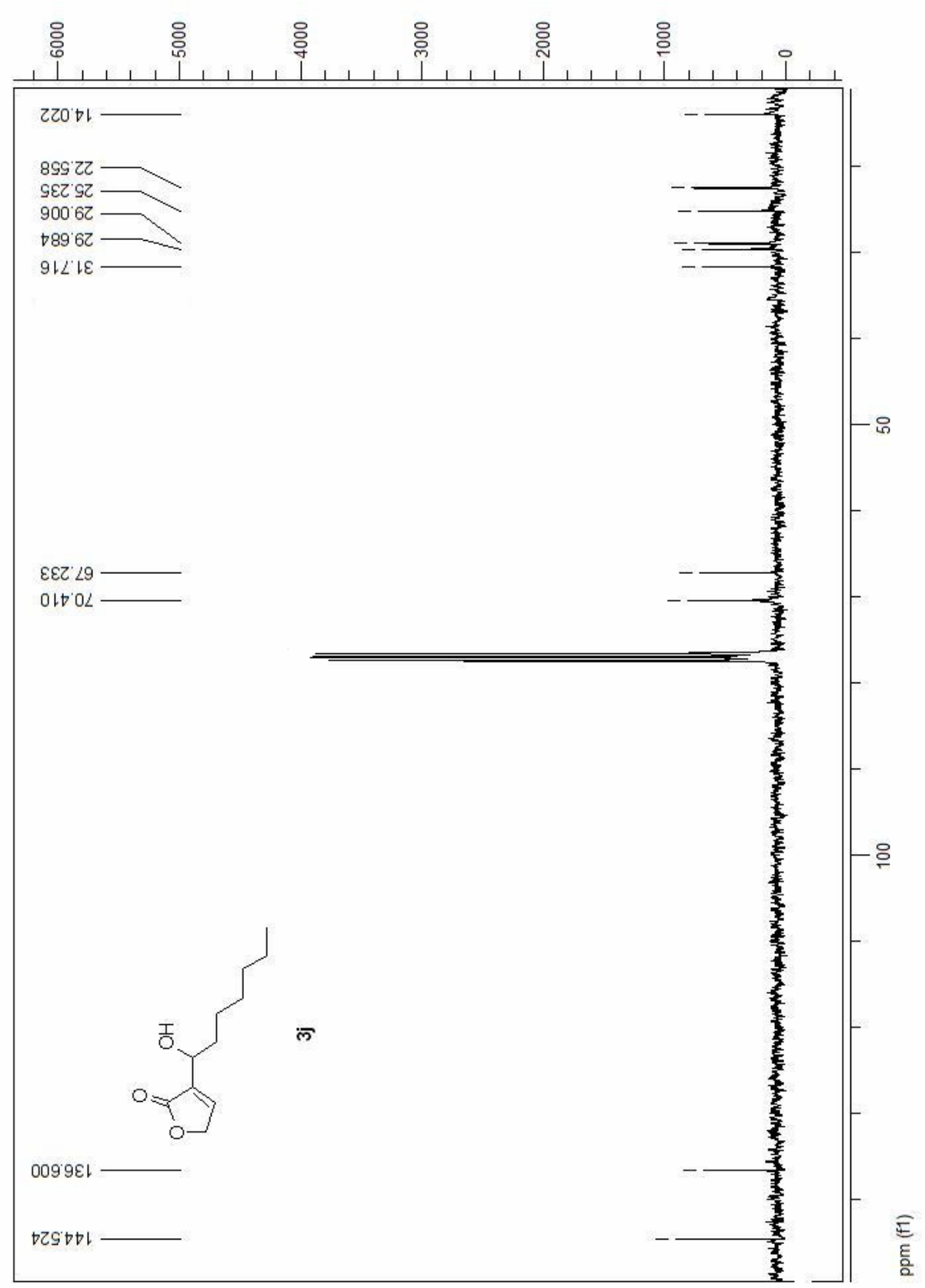


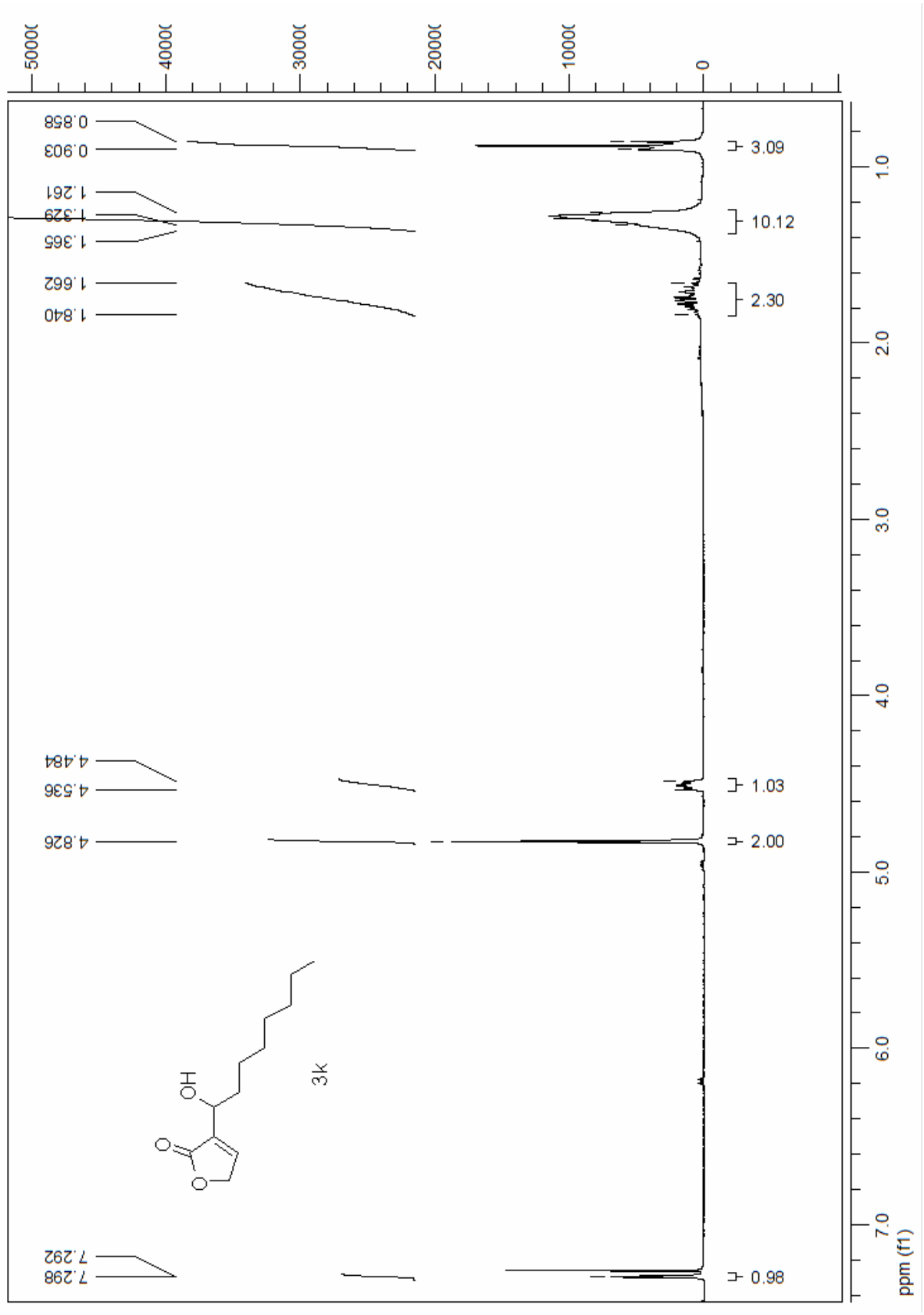

4000
3000
2000
1000
0
14.552
23.083
27.620
30.331
67.862
71.061
123.537
145.198
50
100
ppm (f1)
OH
O
O
3h

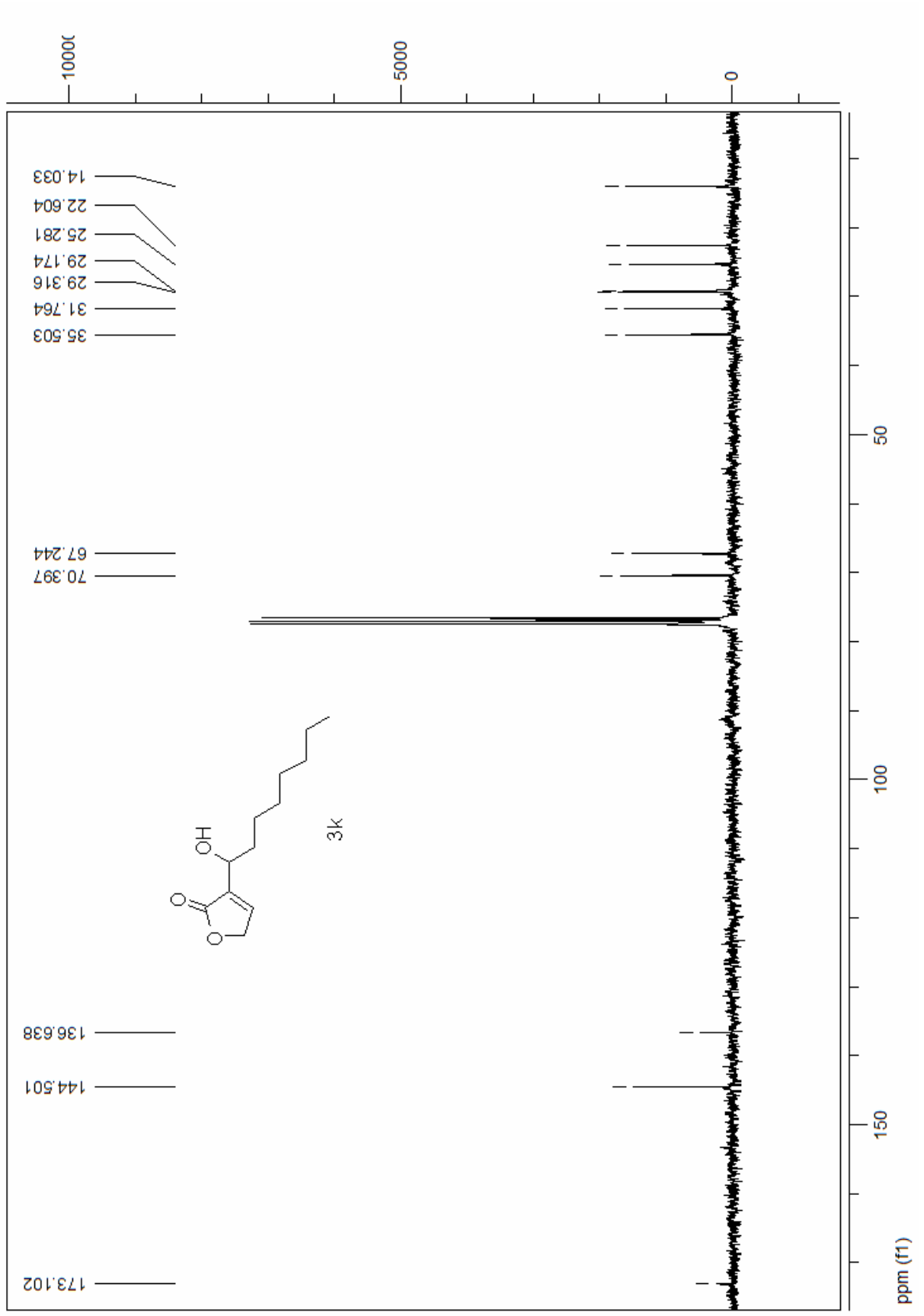


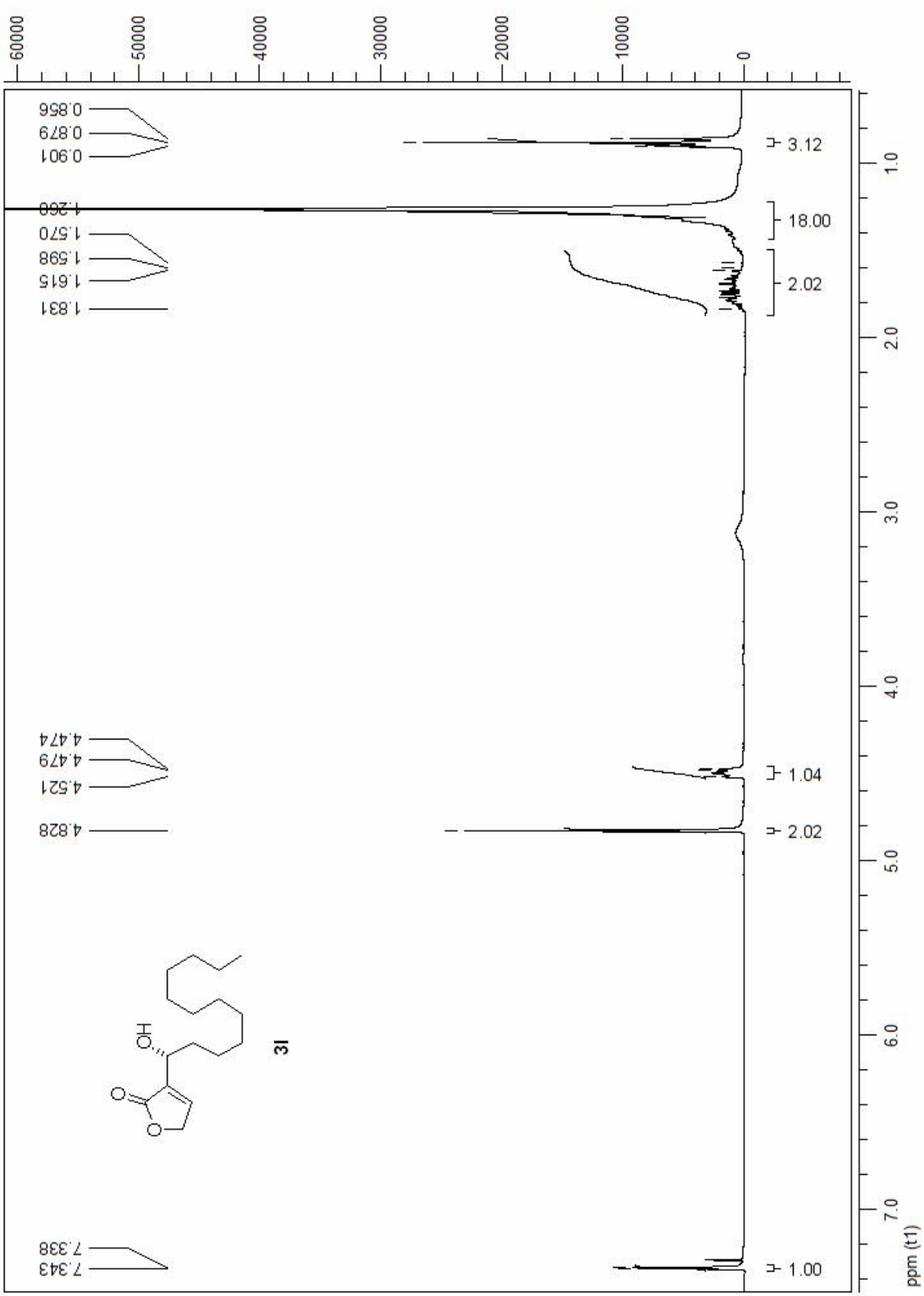


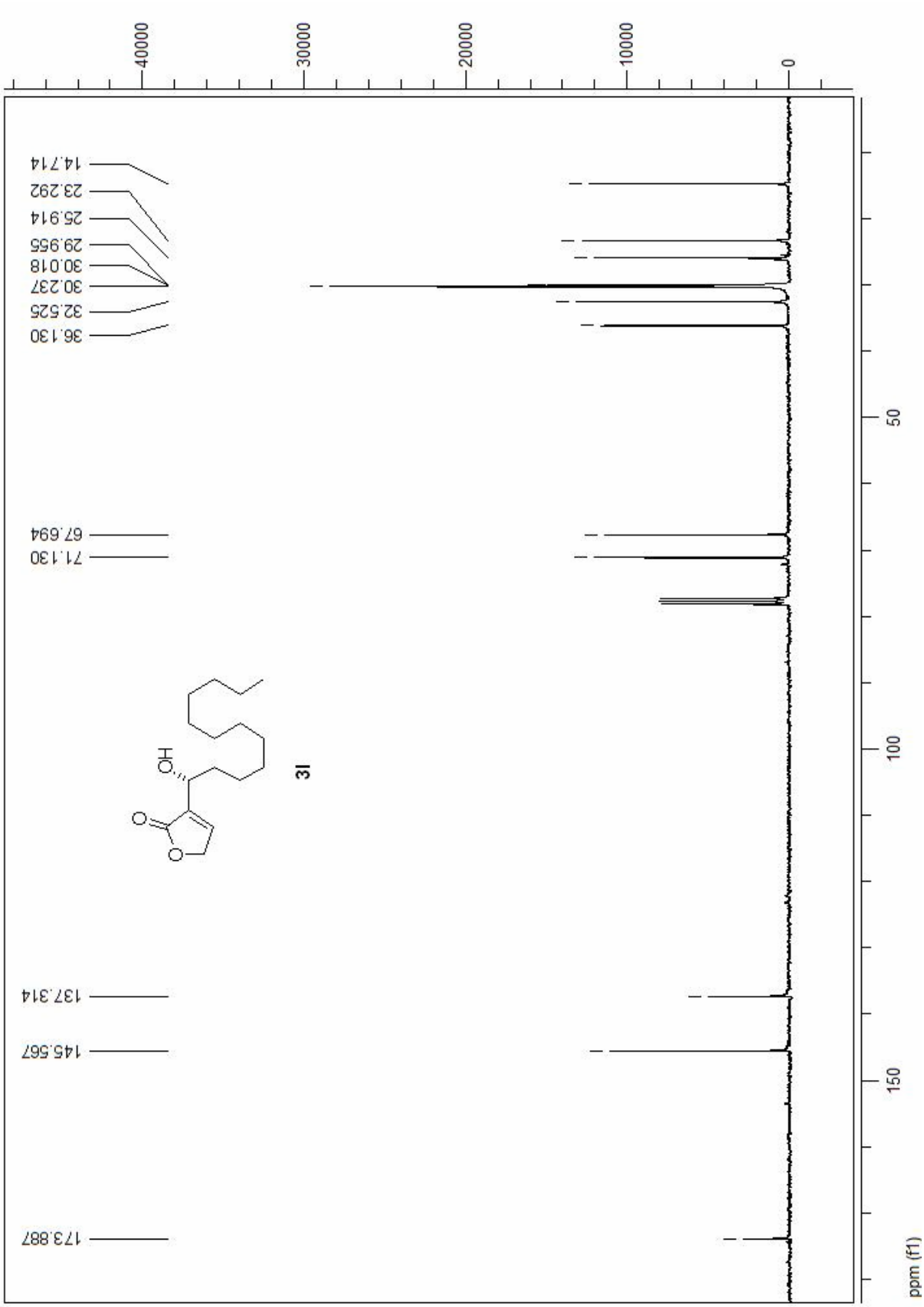











40000
30000
20000
10000
0
14.714
23.292
25.914
29.955
30.018
30.237
32.525
36.130
67.694
71.130
137.314
145.567
173.887
50
100
150
ppm (f1)
OH
O
O
3l