Highly Efficient Indium(III) Mediated Cyclisation of 5-Hydroxy-1,3-diketones to 2,3-Dihydro-4*H*-pyran-4-ones; Mechanistic Insights from *in situ* Fourier Transform Infrared Spectroscopy

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Supplementary Information

Experimental

General synthetic procedures

All chemicals were obtained from Sigma-Aldrich and were used as received. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 300 spectrometer and Varian Unity Nova 500 spectrometer. Chemical shifts were recorded on the δ scale and referenced to the solvent. Solid-state IR spectra were recorded on a Bruker Equinox 55 Infrared Spectrometer fitted with a Specac Diamond ATR source. Solution RTIR scanning measurements were recorded using a Mettler Toledo ReactIR 10 spectrometer fitted with a DiComp probe connected to an MCT detector by a K6 Conduit and scanning in the region of 4000 to 650 wavenumbers at 8 wavenumber resolution. Elucidation of reaction components was performed using ConcIRT^{TM} software. All positive and negative electrospray ionization mass spectroscopy (ESI(+/-)-MS) was performed on a Micromass Platform II QMS spectrometer with cone voltages varying from 35 to 50 volts. Melting points were measured on a Stuart Scientific Melting Point Apparatus in an open capillary.

Synthesis of 5-hydroxy-1,3-diketones

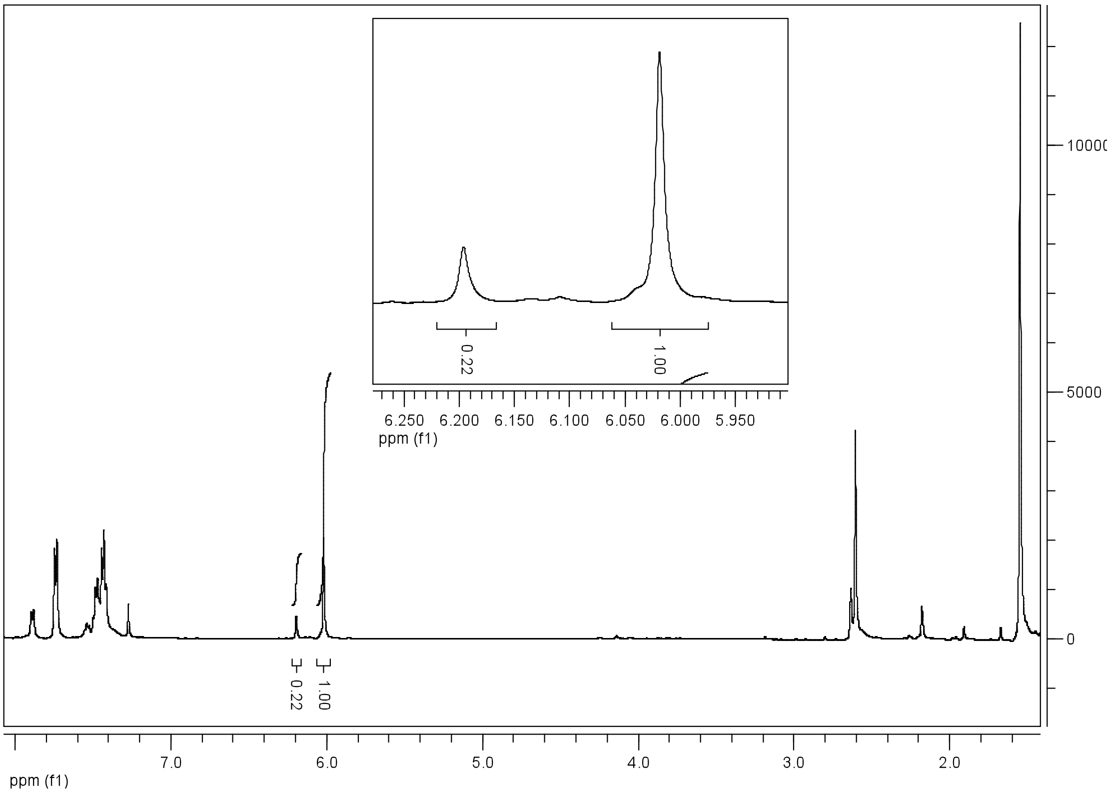
To a solution of freshly prepared LiHMDS (16.7mL, 1.6M in hexanes, 26.7mmol) in dry THF (15mL) at -78 ºC was added acetone (1.23mL, 17.27mmol) in one portion with rapid stirring. One equivalent of acid chloride was added with rapid stirring. After approximately five minutes two further equivalents of LiHMDS were added and the solution was stirred for an additional five minutes. A second equivalent of acetone was added and the solution allowed to warm to room temperature. The reaction was quenched with water (~30mL) and acidified to pH 5 with 1M HCl. The solution was then extracted with EtOAc (3x 100mL) and the organic washes dried ($MgSO_4$) and concentrated to dryness under reduced pressure. The crude product was then purified by column chromatography yielding the 5-hydroxy-1,3-diketone.

Synthesis of pyran-4-ones

Diketone **3** (55mg, 0.21mmol) and indium chloride (15.5mg, 0.070mmol) were combined in a nitrogen flushed, oven dried flask and suspended in dry toluene. The mixture was stirred at 80°C for 40 minutes. After this time the solution was filtered and evaporated under reduced presure yielding pyran-4-one **9** as a red crystaline solid (50mg, 97%).

Assignment of conversion ratios

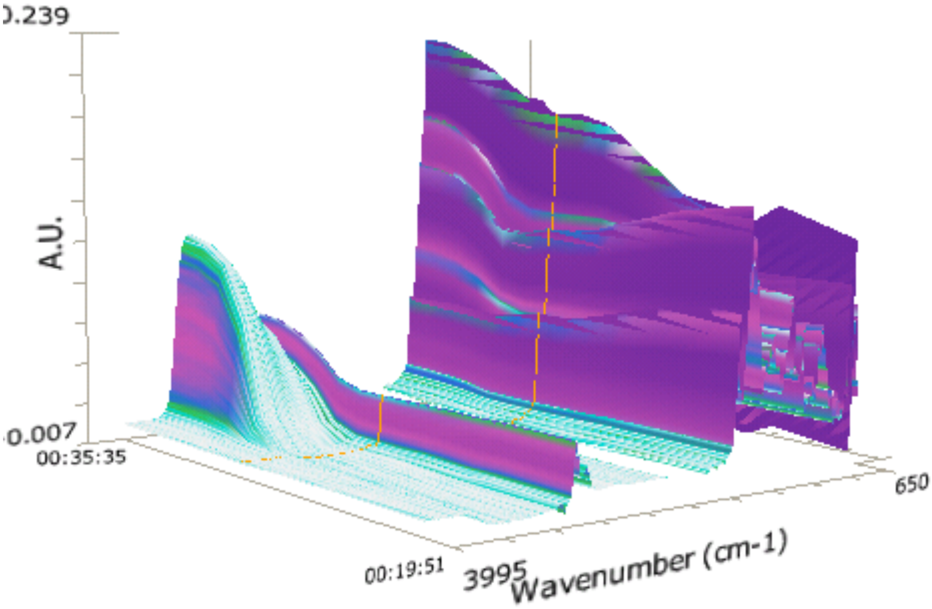
Cyclizations were carried out as per the general procedure listed above with the addition of molecular 4Å sieves or 1g of anhydrous $MgSO_4$ where indicated. The crude mixtures were then filtered and concentrated to dryness under reduced pressure. Comparison of the peak height for the vinylic carbon was undertaken to assign the ratio of starting material to product. The ^1H spectrum displaying the degree of conversion for diketone **1** mediated by $InCl_3$ (10% loading) after addition of 4Å molecular sieves is given below as an example:



Solution IR spectra

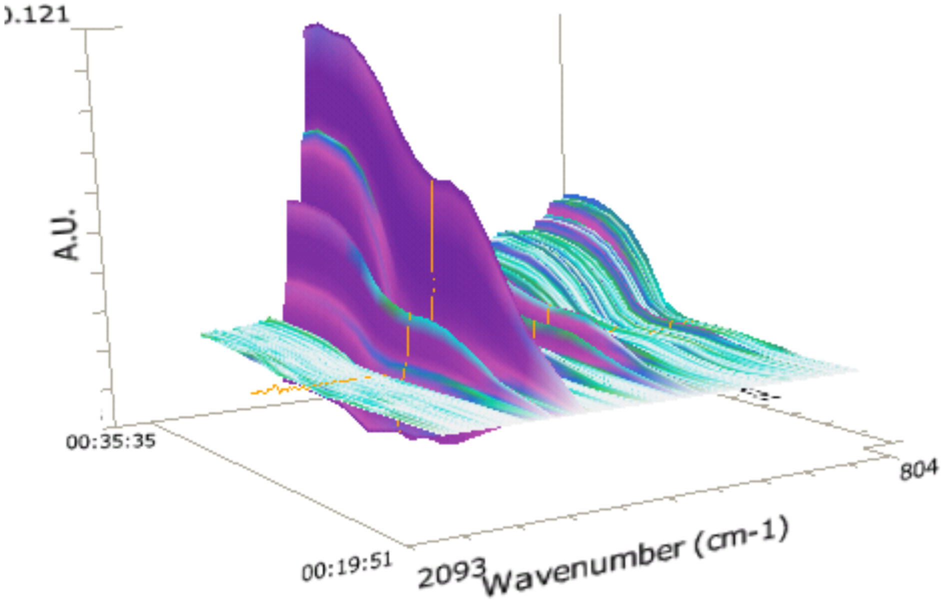
Optimisation of reaction

Figures 1 and 2 were obtained by monitoring both the disappearance of starting material, and appearance of product simultaneously. Identical conditions were used for each optimisation the with exception of the condition under investigation. In both Figure 1 and Figure 2 T=00:00 corresponds to the time when InCl3 was added to the reaction mixture and reaction commenced. A waterfall representation of the conversion given by 3:1 (diketone:$InCl_3$) is given below as an example.



Waterfall representation showing conversion of species from the addition of $InCl_3$ at T=19mins 51sec.

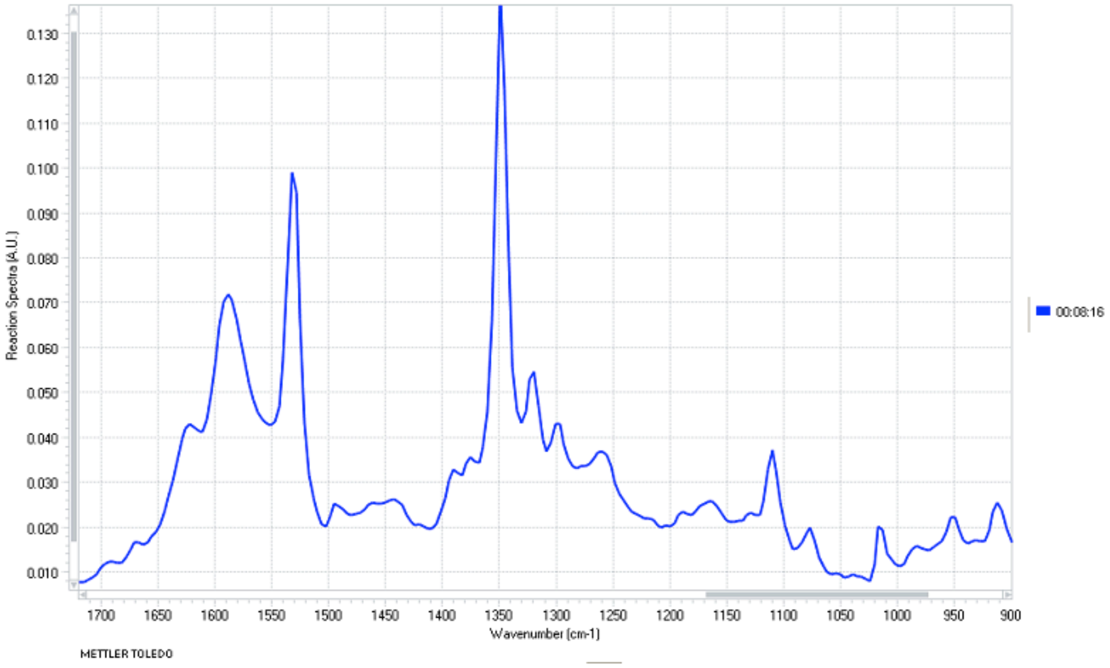
With the aid of the software ConcIRT, identification of bands corresponding to starting material allowed subtraction of this species. The resultant representation shown below gives only the appearance of the product and the water bands, giving a visual comparison to the trends reported.



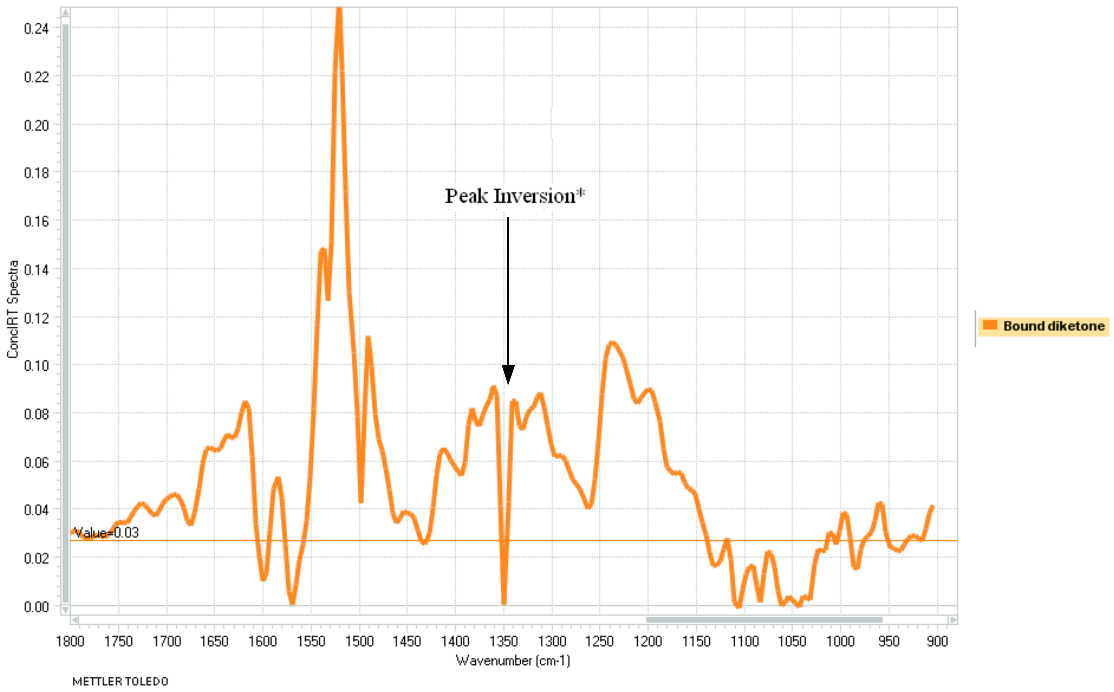
Waterfall representation showing the appearance of both product and water bands. Reaction was observed to be complete at T= 33min 01sec

Mechanistic study

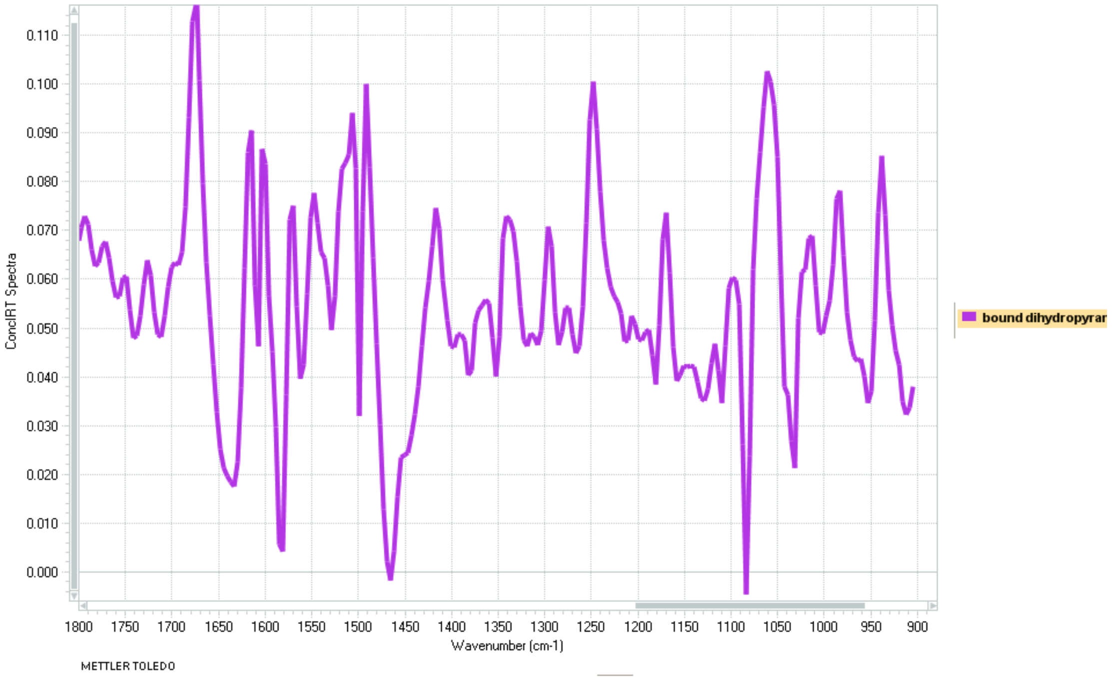
Isolated component specta 1700-900 wavenumbers.



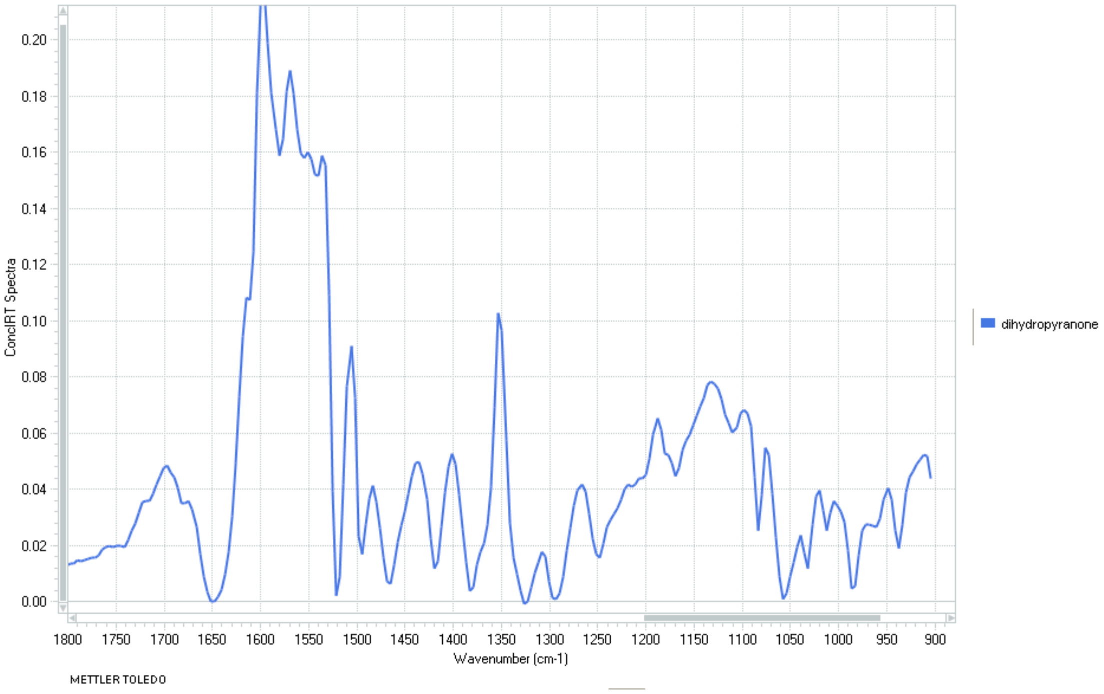
Diketone (**3**) – 1700 to 900 wavenumbers expansion.



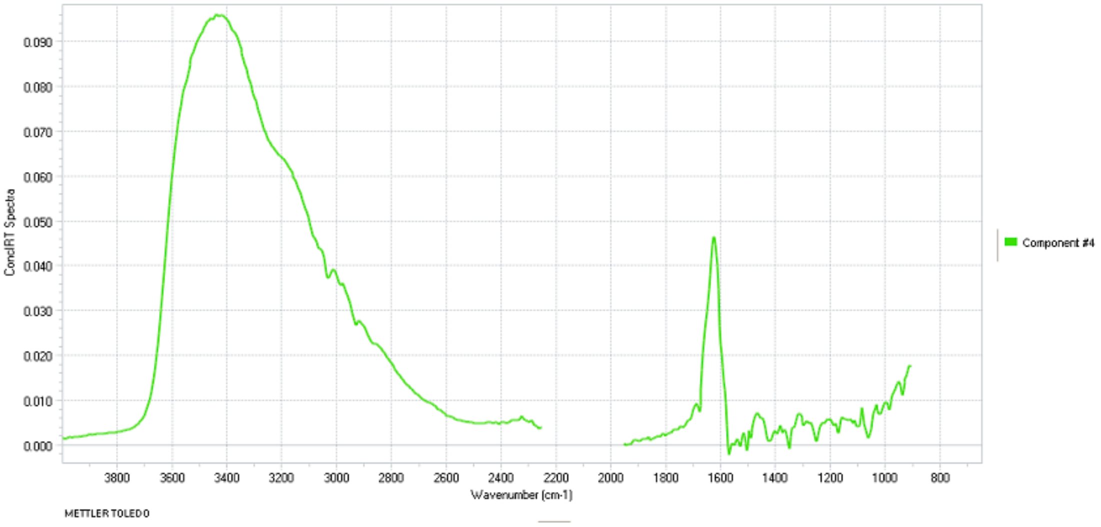
Bound diketone (**13**) – 1800 to 900 wavenumbers



Chelated pyranone (**14**) – 1800 to 900 wavenumbers

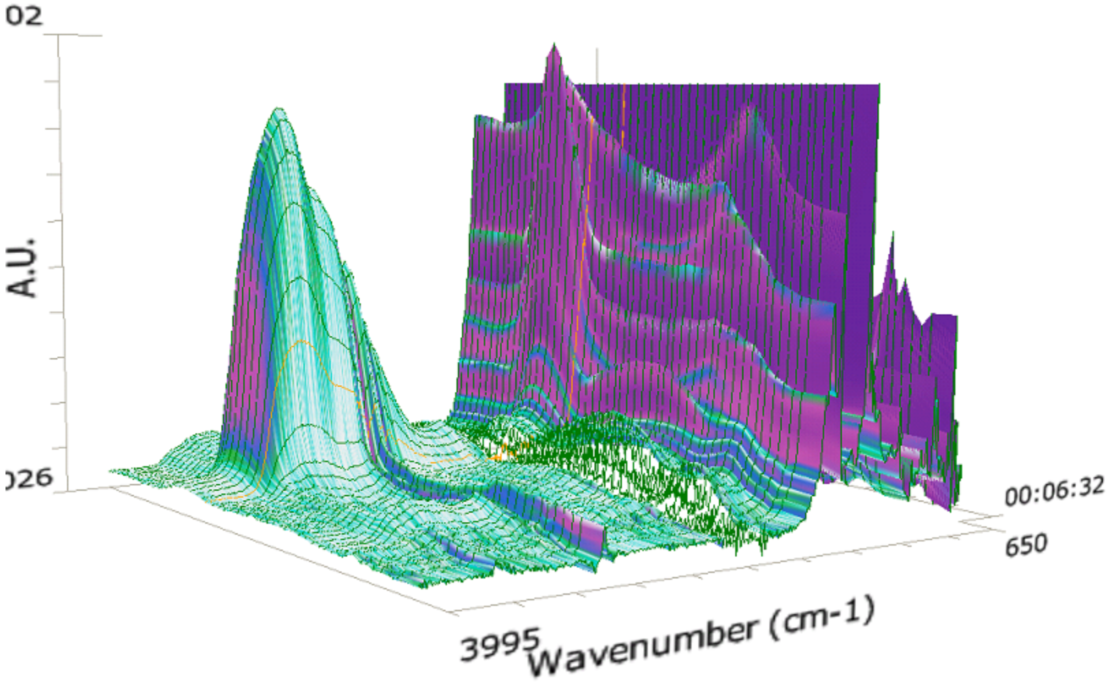


Dihydropyranone (**9**) – 1800 to 900 wavenumbers

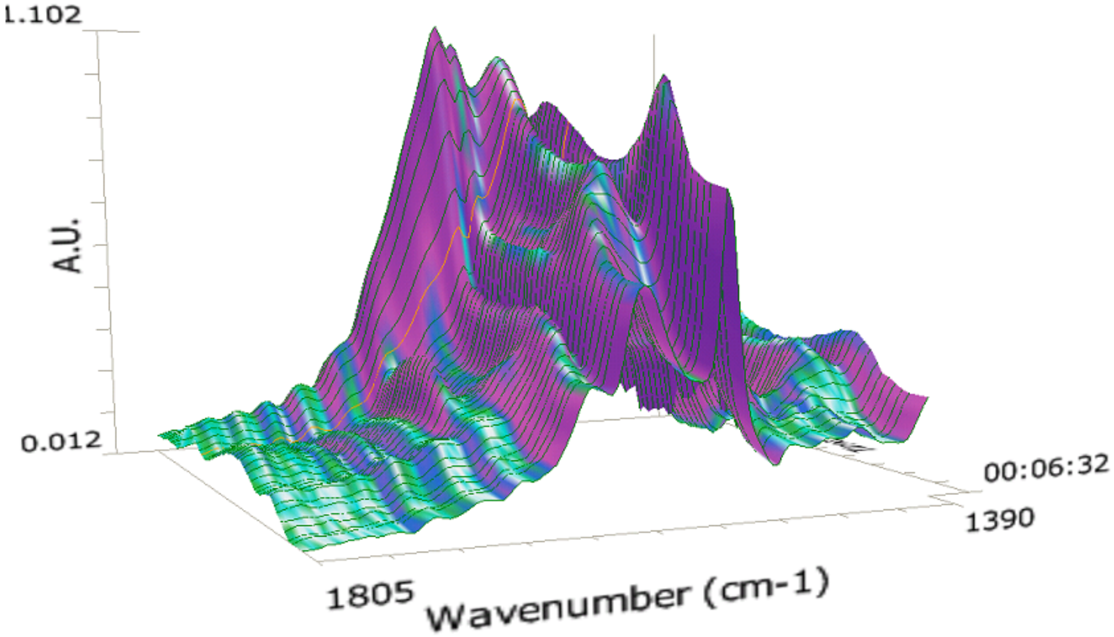


Water – 4000 to 900 wavenumbers

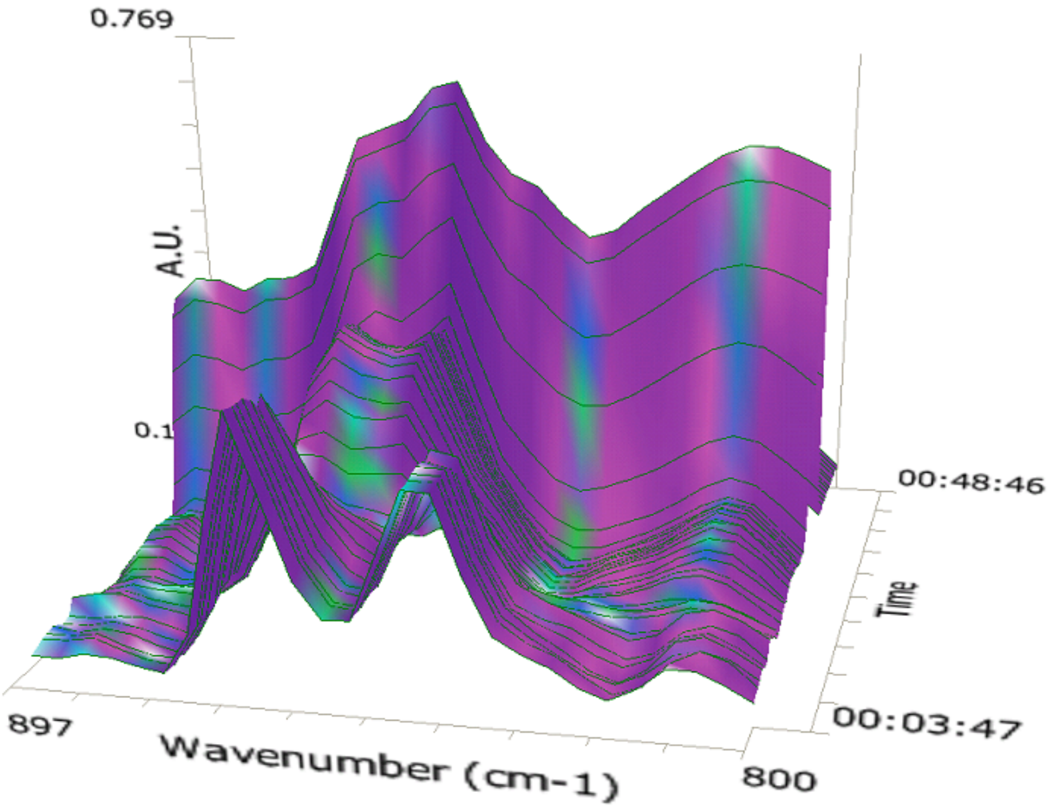
Waterfall representations



Change in IR profile with time from T = 6min 30sec to T = 40min. Spectrum is normalised to nitro peak at 1350 wavenumbers.

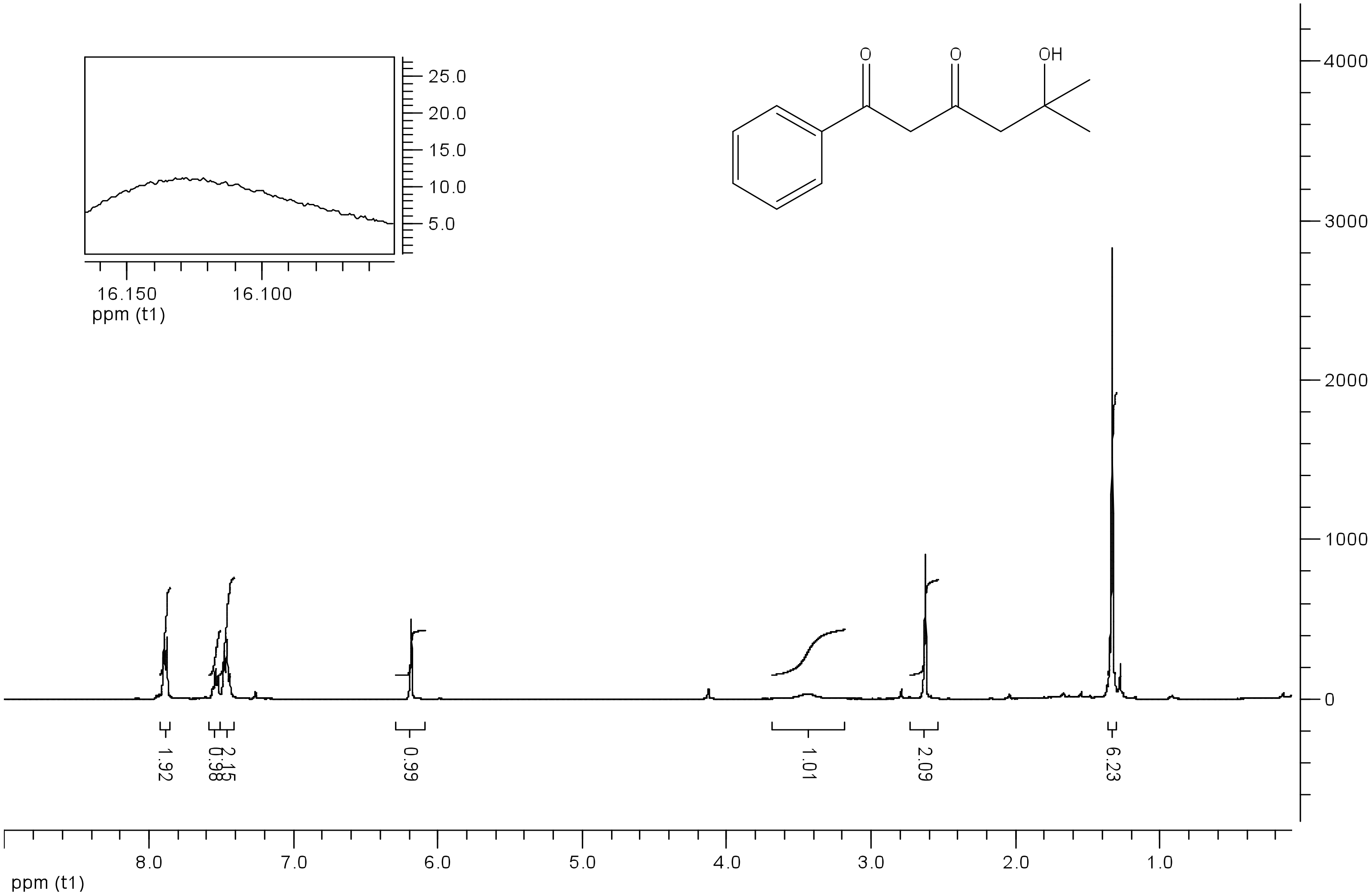


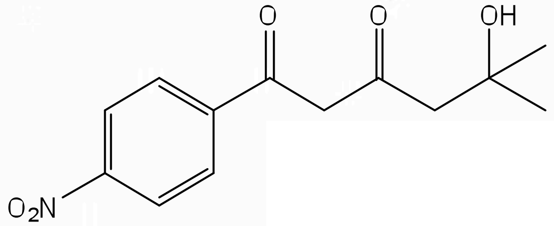
Expansions in region of 1800 to 1400 wavenumbers showing variation in the carbonyl region over the reaction lifetime. T = 6min 30sec to T = 40min. Spectrum is normalised to nitro peak at 1350 wavenumbers.



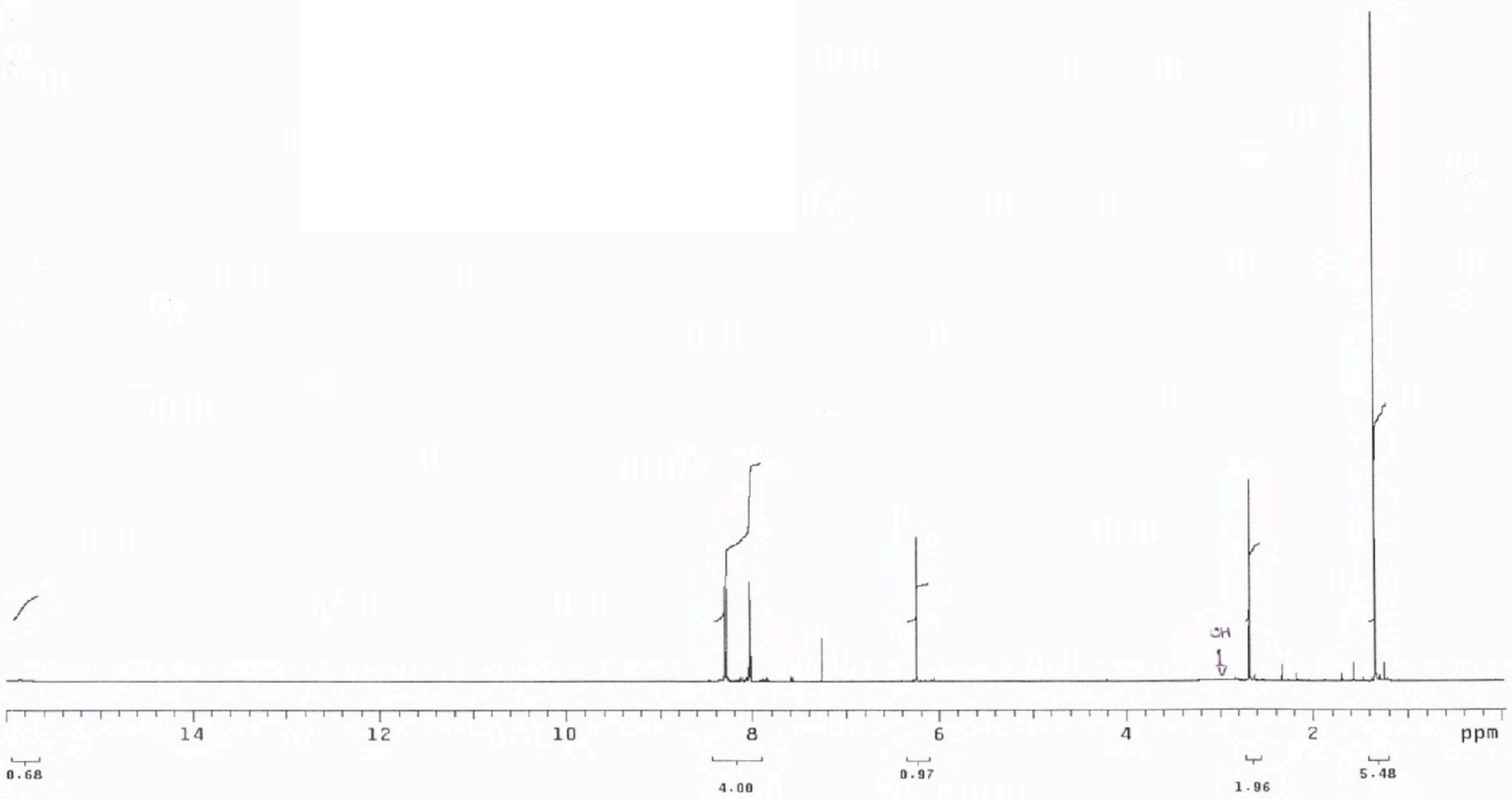
Expansions in region of 900 to 800 wavenumbers showing variation in substituted double bond region over the reaction lifetime. T = 6min 30sec to T = 40min. Spectrum is normalised to nitro peak at 1350 wavenumbers.

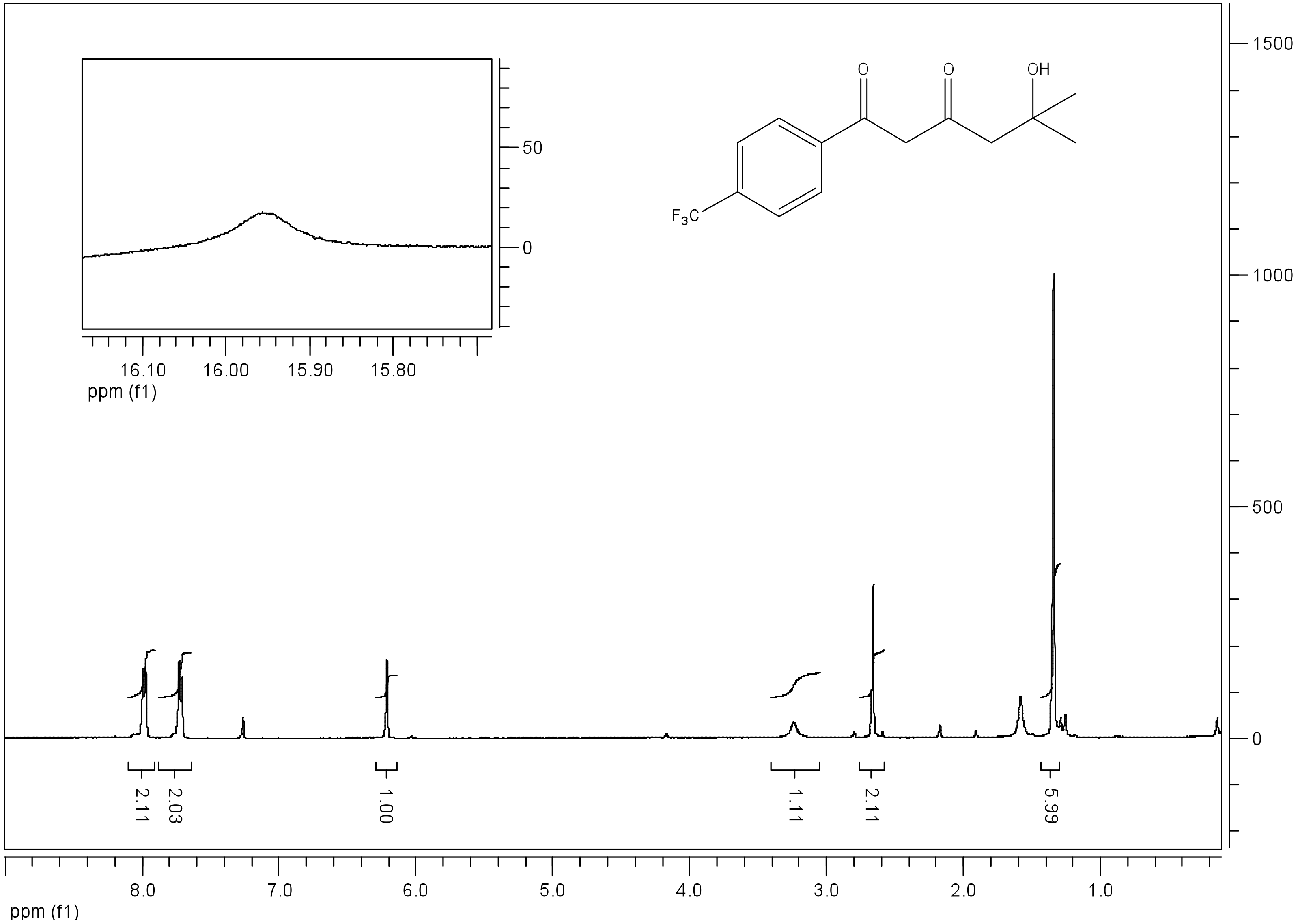
NMR spectra of complexes 1-12





INDEX	FREQUENCY	PPM	HEIGHT
1	4145.220	8.303	15.0
2	4136.255	8.285	15.7
3	4011.032	8.034	16.7
4	4002.067	8.016	13.6
5	3117.411	6.244	24.2
6	1336.533	2.677	33.7
7	669.064	1.340	112.1

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50
0
16.10
16.00
15.90
15.80
ppm (f1)
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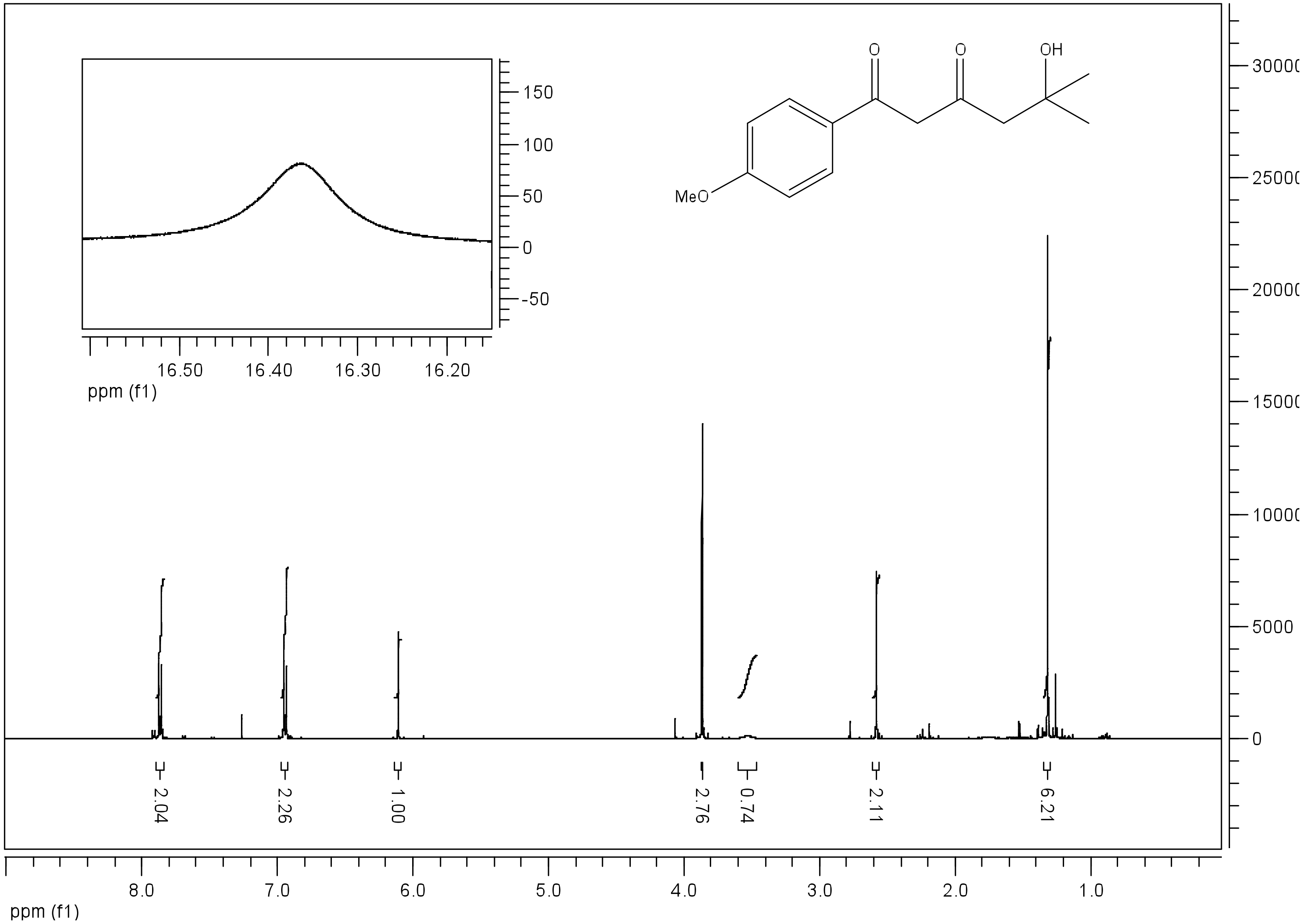
1000
500
0
2.11
2.03
1.00
1.11
2.11
5.99
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)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O
OH
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100
50
0
-50
16.50
16.40
16.30
16.20
ppm (f1)
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25000
20000
15000
10000
5000
0
2.04
2.26
1.00
2.76
0.74
2.11
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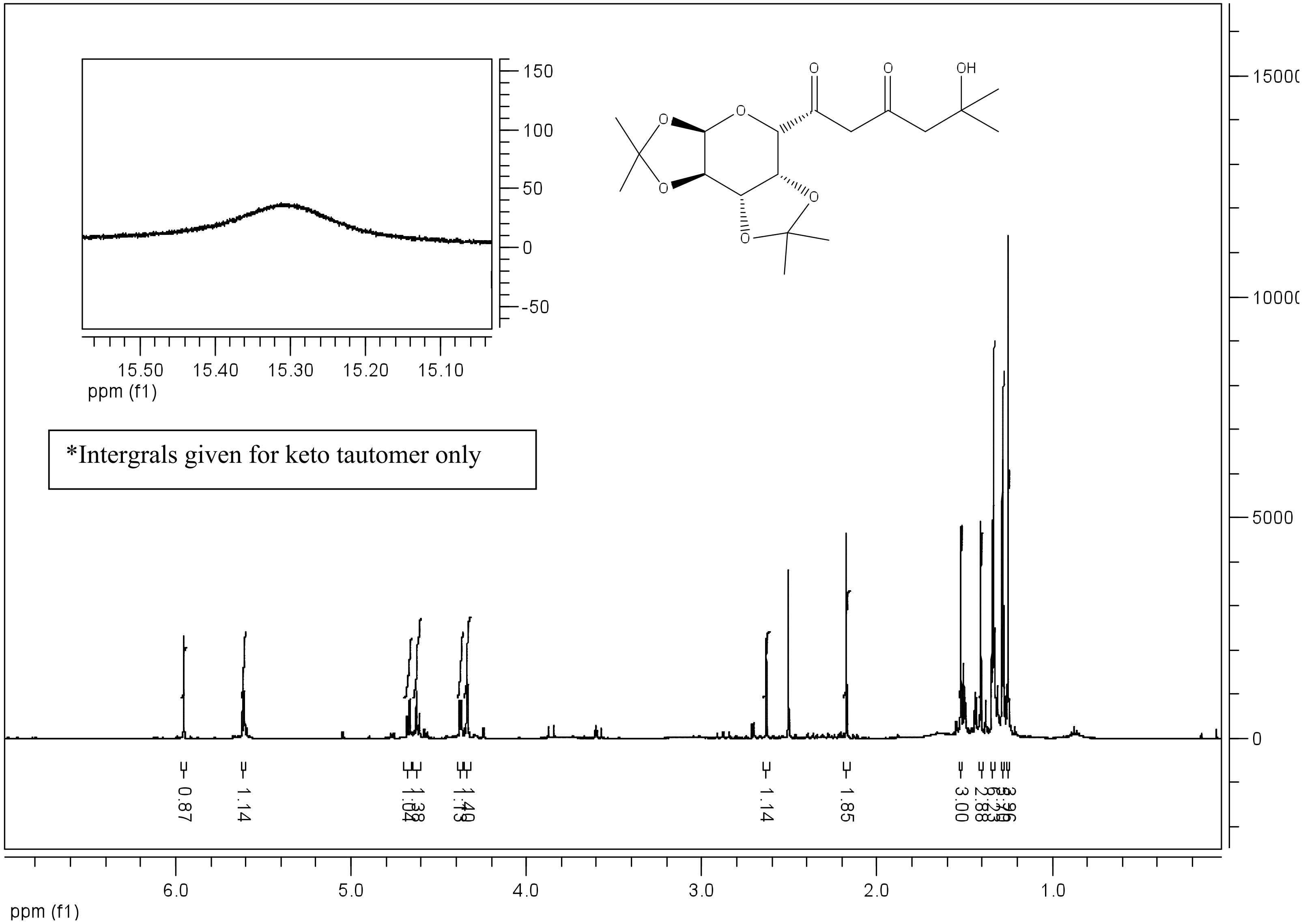
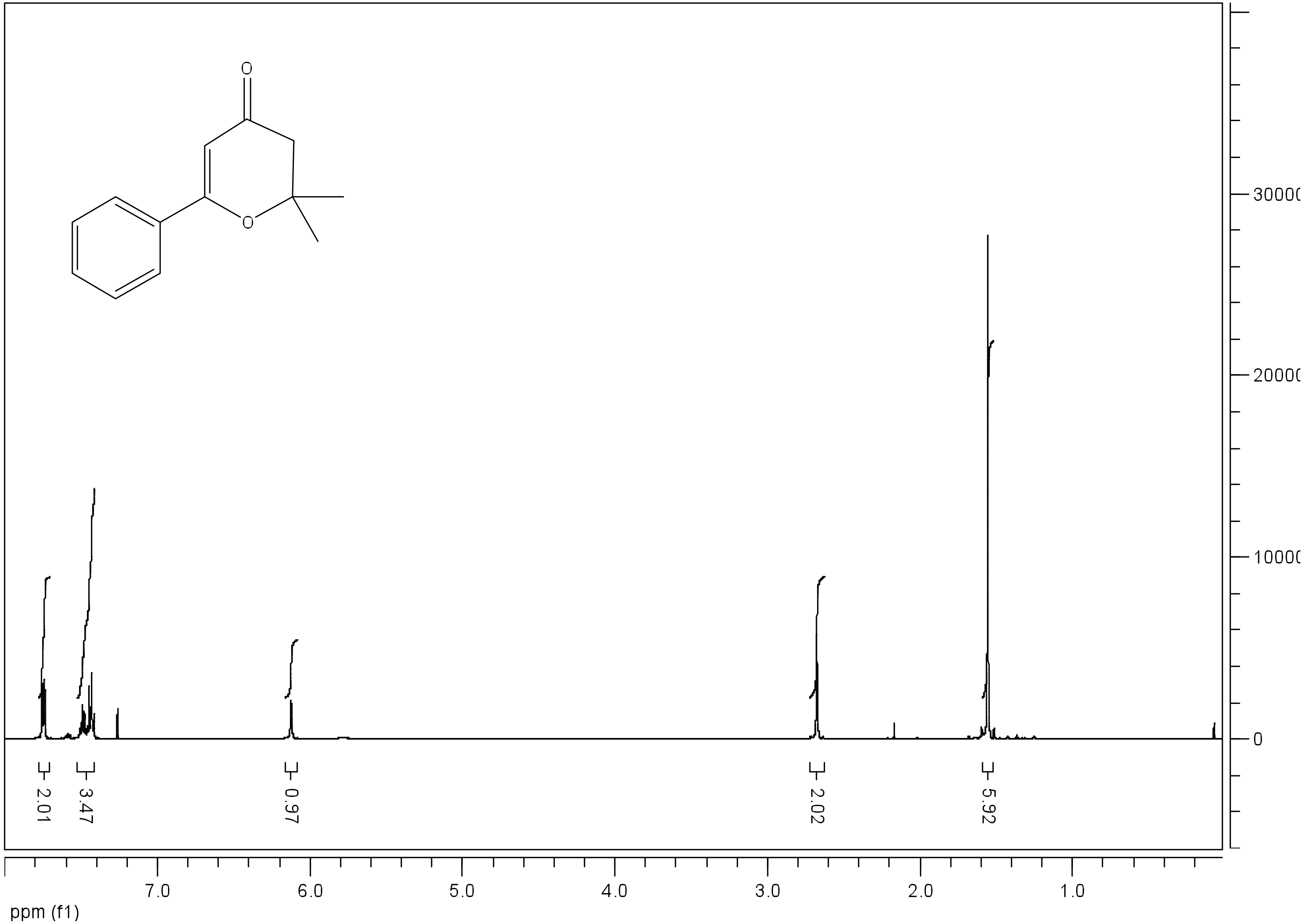
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)



*Intergrals given for keto tautomer only


O
O
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20000
10000
0
2.01
3.47
0.97
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5.92
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6.0
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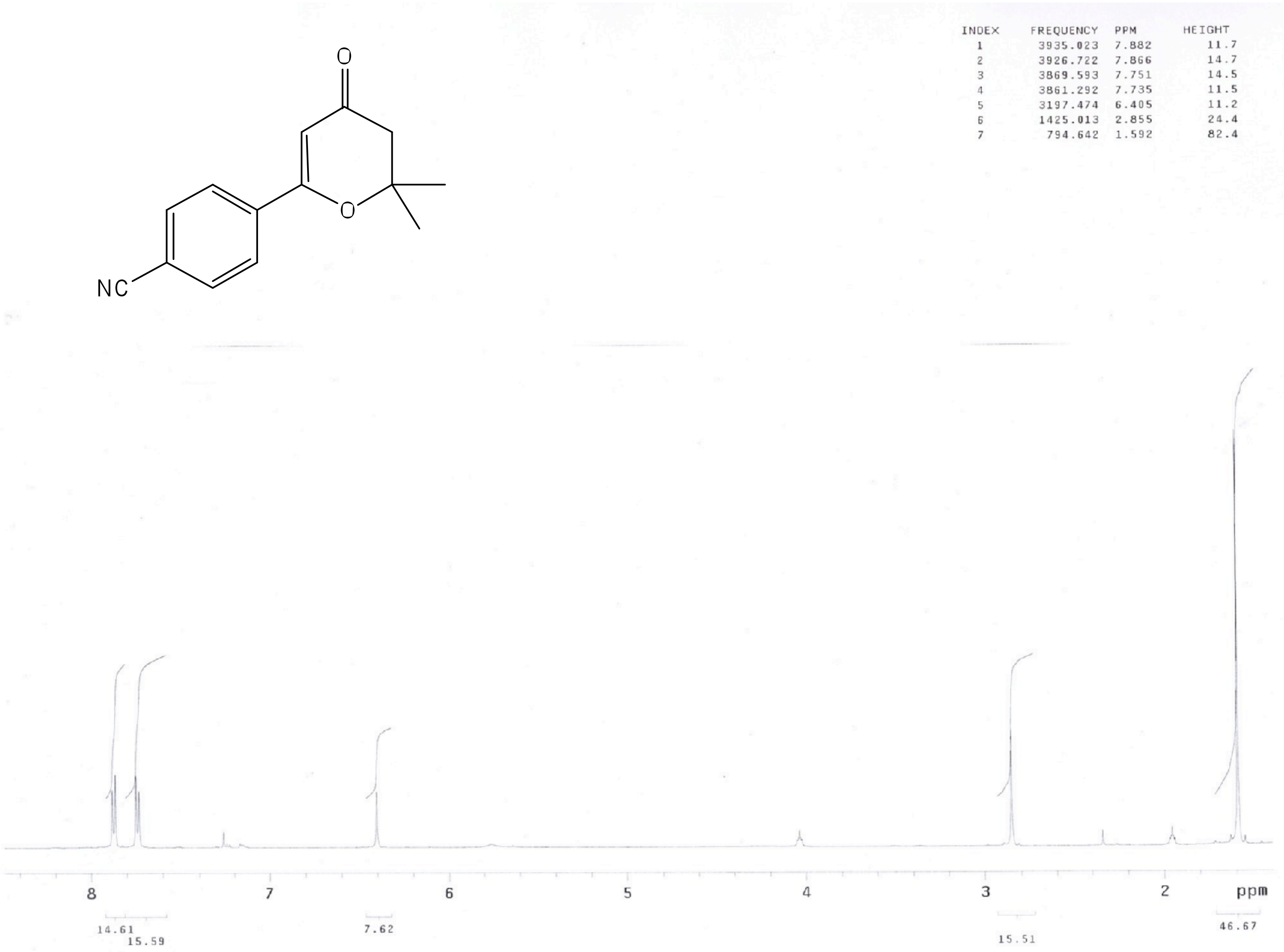
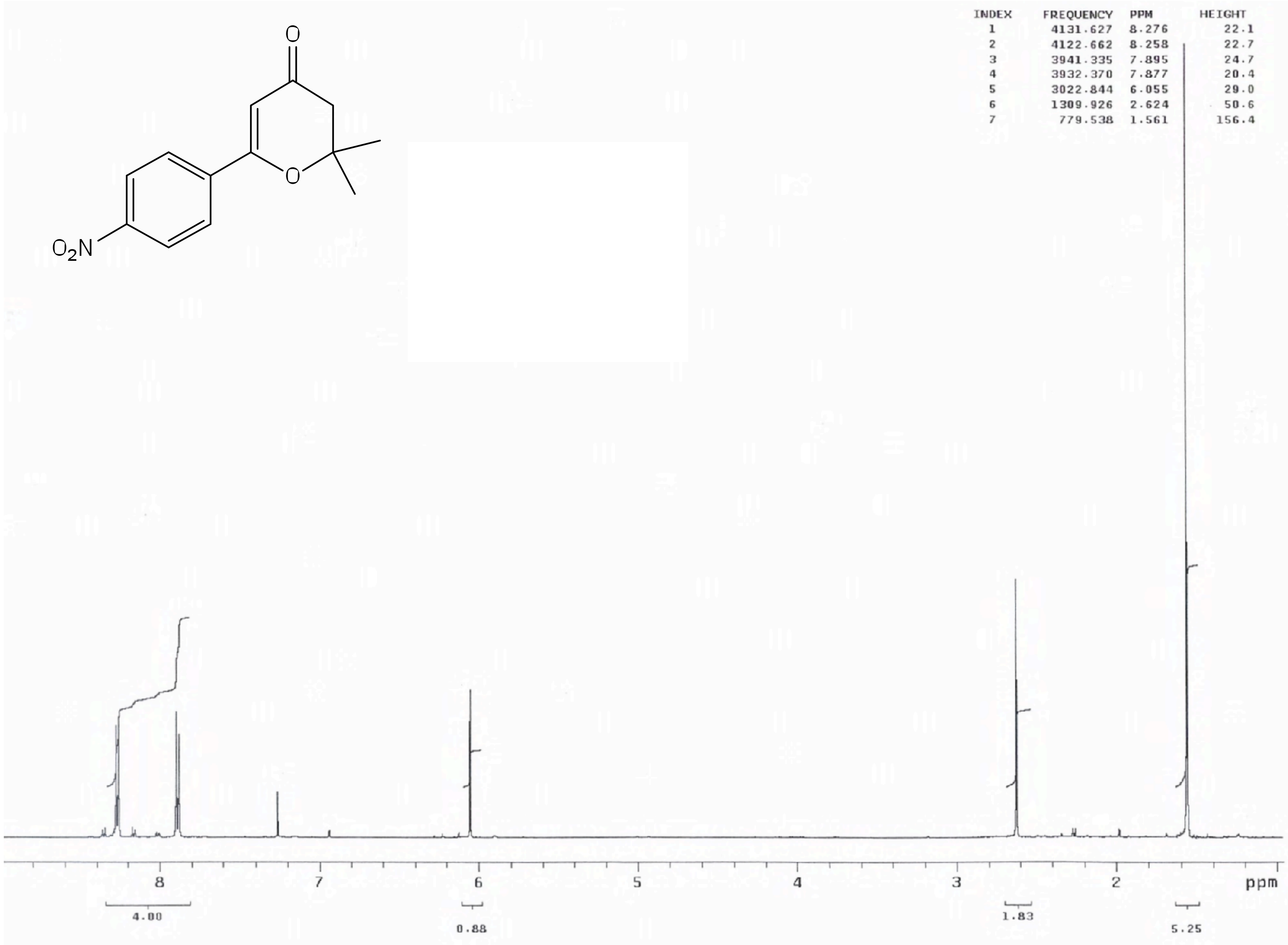
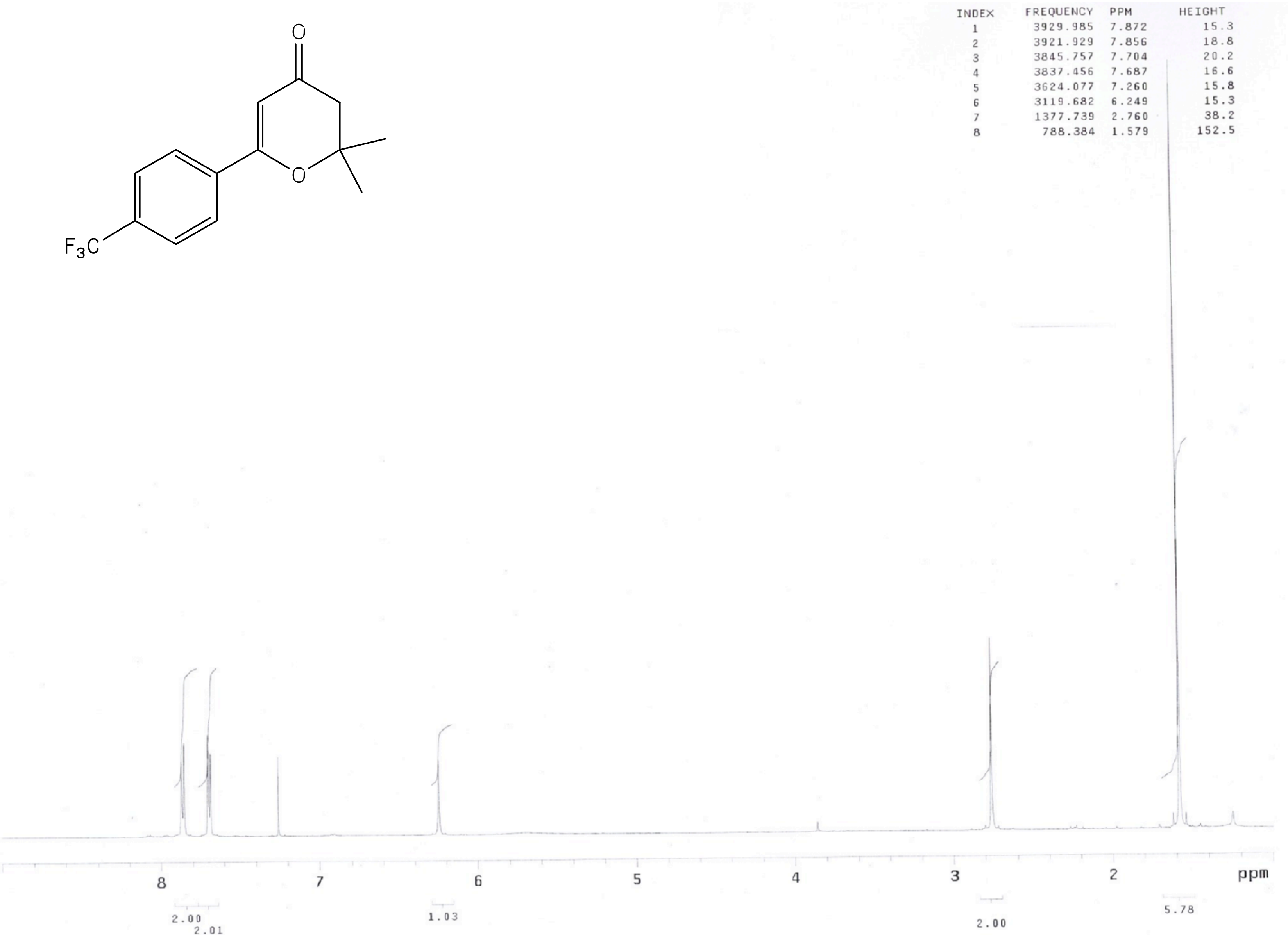
2.0
1.0
ppm (f1)



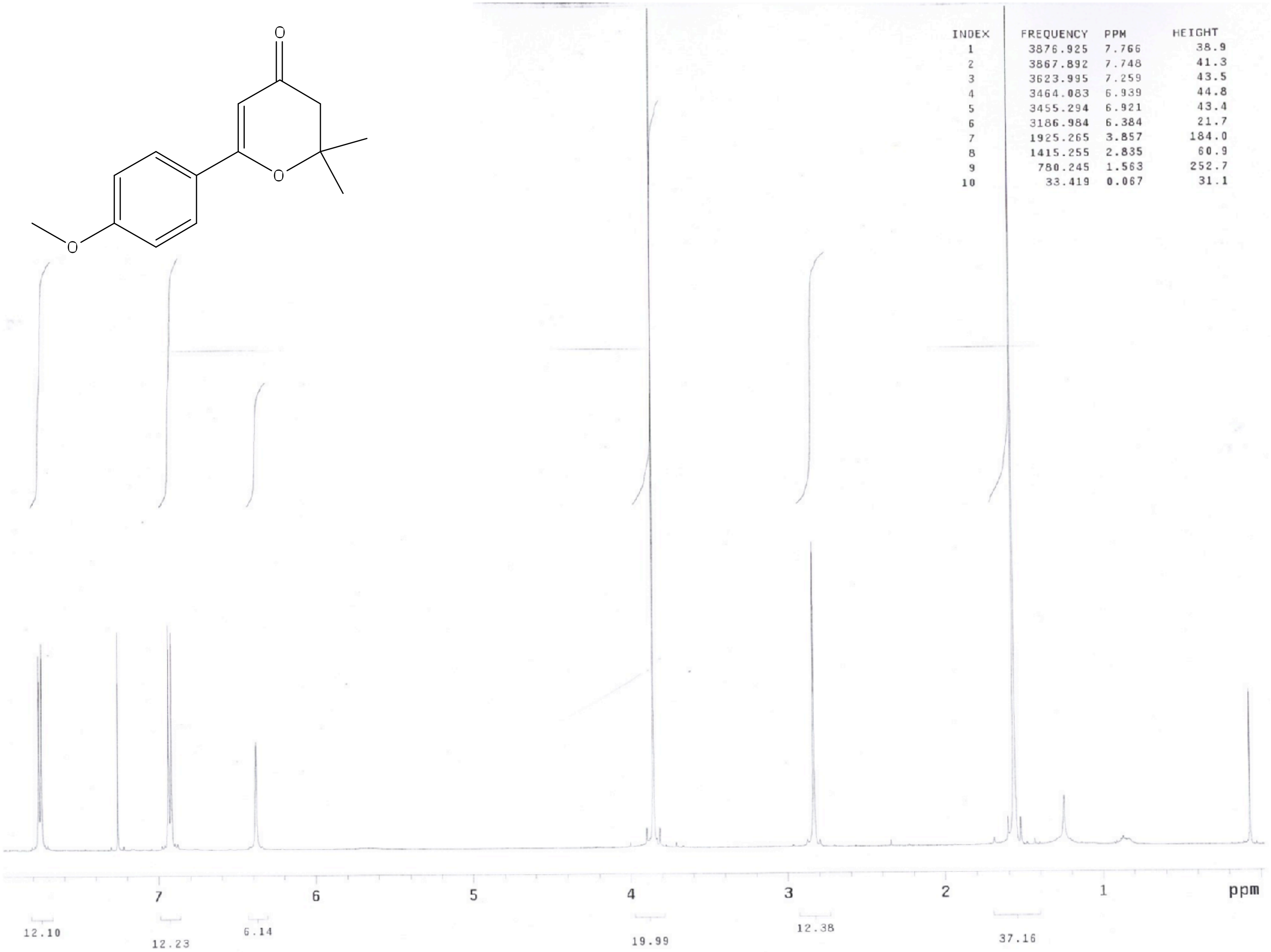
INDEX	FREQUENCY	PPM	HEIGHT
1	3935.023	7.882	11.7
2	3926.722	7.866	14.7
3	3869.593	7.751	14.5
4	3861.292	7.735	11.5
5	3197.474	6.405	11.2
6	1425.013	2.855	24.4
7	794.642	1.592	82.4



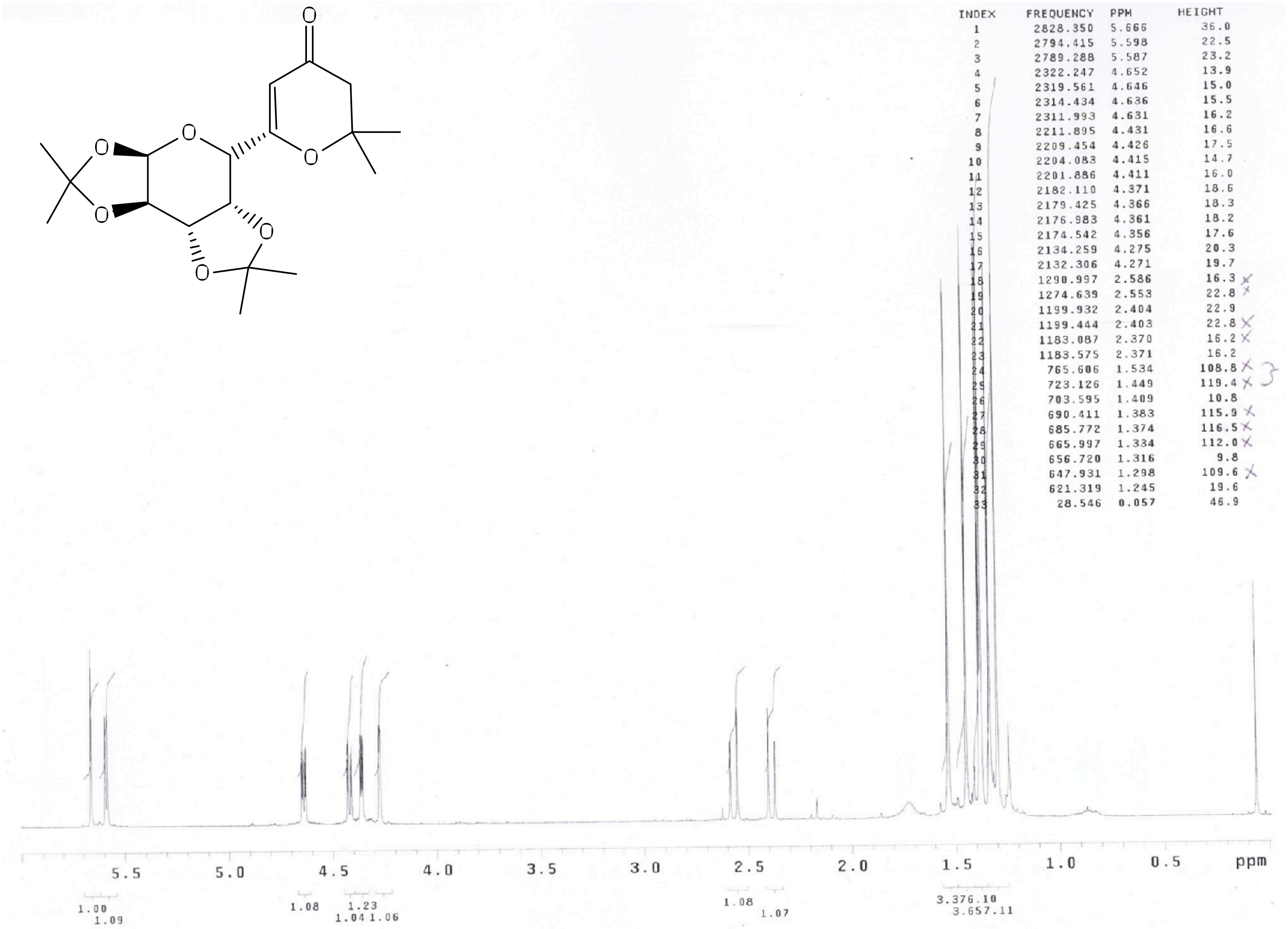
INDEX	FREQUENCY	PPM	HEIGHT
1	4131.627	8.276	22.1
2	4122.662	8.258	22.7
3	3941.335	7.895	24.7
4	3932.370	7.877	20.4
5	3022.844	6.055	29.0
6	1309.926	2.624	50.6
7	779.538	1.561	156.4



INDEX	FREQUENCY	PPM	HEIGHT
1	3929.985	7.872	15.3
2	3921.929	7.856	18.8
3	3845.757	7.704	20.2
4	3837.456	7.687	16.6
5	3624.077	7.260	15.8
6	3119.682	6.249	15.3
7	1377.739	2.760	38.2
8	788.384	1.579	152.5



INDEX	FREQUENCY	PPM	HEIGHT
1	3876.925	7.766	38.9
2	3867.892	7.748	41.3
3	3623.995	7.259	43.5
4	3464.083	6.939	44.8
5	3455.294	6.921	43.4
6	3186.984	6.384	21.7
7	1925.265	3.857	184.0
8	1415.255	2.835	60.9
9	780.245	1.563	252.7
10	33.419	0.067	31.1



INDEX	FREQUENCY	PPM	HEIGHT	
1	2828.350	5.666	36.0	
2	2794.415	5.598	22.5	
3	2789.288	5.587	23.2	
4	2322.247	4.652	13.9	
5	2319.561	4.646	15.0	
6	2314.434	4.636	15.5	
7	2311.993	4.631	16.2	
8	2211.895	4.431	16.6	
9	2209.454	4.426	17.5	
10	2204.083	4.415	14.7	
11	2201.886	4.411	16.0	
12	2182.110	4.371	18.6	
13	2179.425	4.366	18.3	
14	2176.983	4.361	18.2	
15	2174.542	4.356	17.6	
16	2134.259	4.275	20.3	
17	2132.306	4.271	19.7	
18	1290.997	2.586	16.3	x
19	1274.639	2.553	22.8	x
20	1199.932	2.404	22.9	
21	1199.444	2.403	22.8	x
22	1183.087	2.370	16.2	x
23	1183.575	2.371	16.2	
24	765.606	1.534	108.8	x 3
25	723.126	1.449	119.4	x
26	703.595	1.409	10.8	
27	690.411	1.383	115.9	x
28	685.772	1.374	116.5	x
29	665.997	1.334	112.0	x
30	656.720	1.316	9.8	
31	647.931	1.298	109.6	x
32	621.319	1.245	19.6	
33	28.546	0.057	46.9	