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An improved preparation of levoglucosenone from cellulose

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An improved preparation of levoglucosenone from cellulose

by

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ABSTRACT

Levoglucosenone (**1**) is produced in *ca.* 12% yield from cellulose. The preparation is carried out under reduced pressure and in the presence of soybean oil and 2.5% phosphoric acid based on the cellulose mass. Various factors are investigated to determine the effect they have on the yield of **1** from cellulose, and the optimized procedure is given. Levoglucosenone (**1**) can be made on the gram scale using this process, and the vacuum distillation of the compound results in a purity of greater than 90%. This procedure is the most convenient way to make levoglucosenone on the bench top given to date.

An improved preparation of levoglucosenone from cellulose.

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1. Introduction

Levoglucosenone (**1**) is a chiral bicyclic molecule readily available from cellulose. Only the levorotatory enantiomer is formed in this process[1-5] (eq. 1). Compound **1** has been used in the synthesis of natural products (such as tetrodotoxin[6]) and has been used to make chiral auxiliaries for use in other reactions.[2] Other uses of levoglucosenone (**1**) are given in recent reviews.[2,8]
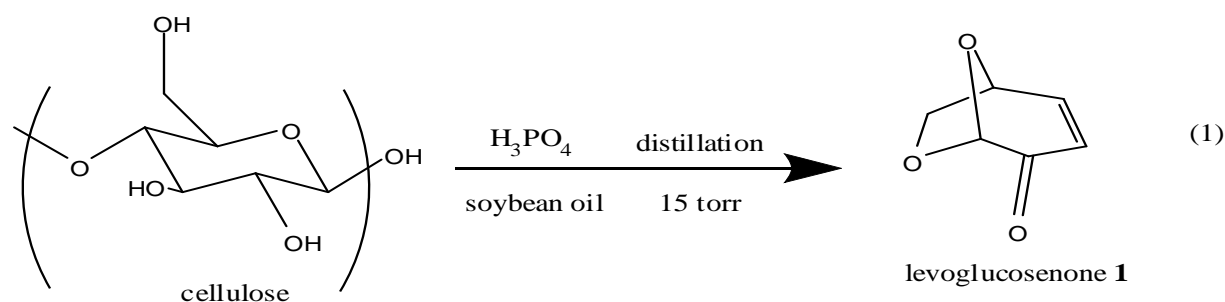
Our research group previously reported the most convenient bench top preparation of **1** from cellulose to date.[9-11] It was noted in this work that the addition of the soybean oil gave an increase in the yield of **1** compared to the same reaction done without the oil.[9-11]

The current studies started from the specific procedure whereby 5 grams of cellulose, 15 grams of soybean oil and 0.025 grams phosphoric acid were heated in a 50-mL 3-necked flask

connected to a short path distillation head under pressure reduced using a water aspirator.[9-11] The levoglucosenone (**1**) would be collected in a round-bottomed flask that was connected to the short path distillation head and cooled in an ice/water bath, and simple extraction with methylene chloride would produce hundreds of milligrams of **1**. This procedure used commonly available glassware and equipment.

The effects of changing some experimental factors were investigated in this earlier work, however, many questions remained unanswered. In this work, we sought to answer these questions in order to increase the convenience of this procedure, and increase the yield of levoglucosenone (**1**) produced in each run. Early in this study, using the original procedure, occasionally the reaction slurry would boil over into the receiver flask. We report here the successful elimination of the boil overs and the answers to several questions regarding variation of the experimental factors.

2. Results and discussion

Levoglucosenone (**1**) is produced from cellulose in the presence of acid. A proposed mechanism has been given for this reaction whereby the acid causes the cellulose to fragment into levoglucosenone.[11a]

2.1 A typical run prior to this study

During a typical run, the mixture of cellulose, soybean oil and phosphoric acid started out as a cloudy yellow mixture. As the temperature was increased by heating with a hemispherical heating mantle, the cellulose would start to react and discolor. The slurry became brown/black by the time the yellow product was seen coating the insides of the flask. The heating mantle was preheated at full power for 10 to 20 min before the run so that it could heat the slurry rapidly.

A clear liquid that is assumed to be water was seen in the collection flask once the oil temperature was over 80 °C. The product could be seen about the time the temperature of the oil reached 225 °C. An aerosol was often seen in these runs once the product was being formed. This aerosol was trapped with liquid nitrogen before it reached the vacuum pump and seemed to contain mostly water. The distillate would be two layers and sometimes there would be a small amount of dark black material present. This dark material appeared to be char and would be filtered out during the extraction procedure. The majority of char and the oil would stay in the reaction flask.

2.2 Boil over problem solved

As mentioned above, the current study was plagued with boil overs in the beginning. This problem was solved by pre-acidification of the cellulose, and by changing the order of reagent addition.

2.2.1 Preacidification of cellulose for levoglucosenone production

Following a literature procedure,[3] cellulose was preacidified by dissolving the required amount of the 85% phosphoric acid solution in methanol and adding the cellulose to that solution while stirring. The slurry was stirred on the order of hours to allow the acid to be evenly distributed throughout the cellulose sample. The slurry was then dried by the removal of the alcohol under reduced pressure on a rotary evaporator. Preacidification was done at the 0.5% phosphoric acid level.

Using the preacidified cellulose in the original procedure eliminated the occurrence of boil over and provided a 5.6% yield of **1** when used shortly after the cellulose was dried. This was an increase in yield compared to the results at the same acid loading level, 4.5% and 3.9%

when the acid was added separately from the cellulose to the oil. If the preacidified cellulose was allowed to sit for a few days at room temperature, however, the yield of **1** from the reaction would fall sharply. The cellulose in these cases would appear to react as if there had been no acid present at all.

The preacidification was attempted to provide a better distribution of the acid in the cellulose phase, and was successful in solving the boil over problem but added an extra set of steps to the procedure. The loss of reactivity on standing was also troubling. The cause of this loss of activity is not known at this time.

2.2.2 Order of reagent addition for levoglucosenone production

The order of reagent addition was not specified in the original procedure and the order was found to be critical for solving the boil over problem. Of several orders of addition tried, the only order that did not lead to boil over was to first add the acid to the 3-necked flask, then add the oil, followed by stirring open to the atmosphere for about 5 minutes. The cellulose was then added to the resulting cloudy slurry.

Combining cellulose and acid directly followed by the addition of the oil was found to produce boil overs. Often, a darkened patch of cellulose was seen later in the process if the acid came into contact the cellulose directly. Adding the oil to the cellulose, or the cellulose to the oil, followed stirring and then by the addition of the acid to the slurry would lead to boil over.

While the proper order of addition could eliminate boil over in most cases, other experimental factors such as the presence of volatile additives in the cellulose, could lead to boil over.

The order of reagent addition could have an effect on the way the acid is distributed in the slurry and on the surface of the cellulose. The more effectively distributed the acid is, the more evenly the reaction would be expected to proceed. In runs in which the order of addition allowed the acid to come into direct contact with the cellulose, it seems that the acid is absorbed by the cellulose, leading to a faster reaction at those spots. Evidence of this can be seen in the appearance of large black chunks of char early in these runs that often matched the shape of the area of acid/cellulose contact.

2.3 Other cellulose sources for levoglucosenone production

After the boil over problem was solved, we were able to investigate the effects of changing some of the experimental variables. We investigated other sources of cellulose to see if they would produce **1** in greater yield than the microcrystalline cellulose that had been used up to that point. Cotton fiber from cloth and from cotton balls gave only traces of compound **1** when used as the cellulose source instead of the microcrystalline cellulose. Copy paper was tried, and worked almost as poorly as cotton.

The cellulose in cotton is crystalline in long chains where as the cellulose in the microcrystalline powders is thicker crystals with a larger number of chain ends than the cotton may have.[12] Some older cotton that had been made into fabric and had been put through many normal wash cycles was tried, in the hope that the history of that material may have made the cellulose in it more accessible and therefore give a higher yield, but no increase was seen over the cotton from a cotton ball.

Cotton was seen to have an apparent density that is much lower than the microcrystalline cellulose particles. It was found that 3 mass equivalents of the vegetable oil would not cover the

cotton. The cotton above the hot oil phase during these runs was condensing the product thereby trapping it in the reaction flask. This was seen as yellow material coating the cotton after the reaction.

Copy paper also had the same low oil coverage problem. Paper, however, was better at trapping the material before it could be removed from the flask. The char in both of these cases had the same general shape as the starting material. The char looked like fibers for the cotton, and small circles or rectangles for the paper case. These materials may prove to be suitable if the particle size can be made to match the particle size of the microcrystalline cellulose.

2.4 Heat pretreatment of cellulose for levoglucosenone production

Cellulose samples were heated prior to reaction in an attempt to produce a greater yield of compound **1**. It was suggested from the literature that heating the cellulose to 220 °C for a certain length of time could drastically reduce the degree of polymerization and the crystallinity.[13] At the time, decreasing the crystallinity and/or the degree of polymerization of the cellulose used was thought to be advantageous with regard to producing **1** from the cellulose.

During the heat pretreatment at 220 °C, the cellulose would discolor rapidly. This did not seem to help the subsequent reaction produce more of compound **1**. In fact, the preheated samples gave significantly less **1** on reaction, compared to reactions where the cellulose had not been pretreated.

Table 1 shows pretreatment conditions varying from open to the atmosphere, under an inert atmosphere and in oil that were tried. None of the heat pretreatments showed any promise of giving a better yield of **1** than the same reaction using cellulose as received. Entry BL in the table is the baseline run, using cellulose as received. Comparing entries 1 through 4, an increase

in yield is noted on increasing the time of the heating pretreatment, however, longer heating

caused a drop off in yield, and none of the heat pretreatment times gave a yield that was higher

than the baseline run where the cellulose was not heat pretreated.

Table 1. Effects of cellulose heat pretreatment on yield of levoglucosenone

Entry	Time	Temp (C°)	Atmosphere	Levoglucosenone Yield, mole %
1	10 min	200	argon	4.6
2	1 hour	200	argon	5.1
3	3 hours	200	argon	7.2
4	5 hours	200	argon	7.4
5	10 hours	200	argon	6.7
6	10 hours	220	argon	4.4
7	10 hours	220	air	5
8	2 hours	200	soybean oil	2.3
9	1hour	200	open flask	2.7
10	3 hours	200	open flask	9.3
11	3 hours	200	open flask	6.8
13	5 hours	200	open flask	5.5
BL[a]	None			9.5

[a]Baseline run without pretreatment, cellulose used as received.

2.5 Cellulose particle size for levoglucosenone production

The particle size of the microcrystalline cellulose was also thought to be important in the

outcome of these decomposition reactions. There were four sizes of microcrystalline cellulose

used to investigate this.

The best result was obtained from the smallest particle size investigated, 20 micron. An

increase in size to 50 micron was accompanied by a reduction in yield, and increasing to 80 and

190 micron caused boil over to occur. Table 2 shows the yields of **1** were 8.7% and 5.8% for the

20 and the 50 micron sized particles, respectively. There were boil overs in the cases with the larger particle sizes, the 90 and 180 micron materials, so no yield is reported.

It may be that the increased surface area in the smaller particles allowed more favorable interactions of the cellulose and the acid. The better yields could also have been due to the larger surface area allowing better access to reactive chain ends.

Table 2. Influence of particle size on the yield of levoglucosenone.

Entry	Cellulose Mass (g)	Acid mass (g)	Oil mass (g)	Particle size	Corrected Acid % [a]	Levoglucosenone Yield, mole %
1	5.1216	0.147	15.0392	180 micron	2.44	Boil over
2	5.0192	0.147	15.0435	90 micron	2.49	Boil over
3	5.0499	0.147	15.0438	50 micron	2.47	5.89
4	5.0840	0.147	15.0551	20 micron	2.46	8.70

[a]Acid % corrected for the purity of the reagent (85% phosphoric acid)

2.6 Amount of acid used for levoglucosenone production from cellulose

There were several runs done where the amount of the acid used was varied, using the same oil and the same amount of oil relative to the amount of the microcrystalline cellulose. The acid amount chosen as best was 2.5 % acid by mass, based on the cellulose mass. This was a compromise between higher yields and higher failure rates at higher acid amounts and lower yields that were more predictable at lower acid amounts. It was seen as impractical to have a procedure that had a greater than 50% chance of failure for an increase of just a few percent yield.

Table 3 shows the results of these runs. When the acid amount is high, in the range of about 8.5% to 8.8% of the cellulose mass, entries 1-4, the yield of **1** was higher in the successful runs, but there was an increased rate of failure. Two of the four runs in this range failed due to boil overs. With the acid amount in the 4.3% to 4.4% range, we see a lower yield, but only one of the four runs boiled over. One of the three successful runs had a higher yield than the other two, but this result was not reproducible (entry 9). The runs around 2.5% acid by cellulose mass seemed to result in more predictable runs, and reasonable yields.

With 0% acid, there were only traces of **1** formed. There was very little distillate in this case as well.

The acid in this process is catalytic and there is evidence that the addition of excess acid leads to the decomposition of the cellulose by other reactions that do not give high yields of **1**, but rather water and char. This could account for the greater occurrence of the boil over condition with the higher acid amounts, since the production of a great deal of water would favor the boil over. It may be that the presence of extra acid would also cause the breakdown of the products at the elevated temperature, thereby lowering yields.

Table 3. Influence of acid amount on yield of levoglucosenone.

Entry	Cellulose Mass (g)	Acid mass (g)	Oil mass (g)	Corrected Acid %[a]	Levoglucosenone Yield, mole %
1	5.042	0.523	15.042	**8.82**	**Boil over**
2	5.033	0.519	15.052	**8.77**	**6.2**
3	5.007	0.506	15.091	**8.59**	**Boil over**
4	4.997	0.499	15.159	**8.49**	**7.5**
5	5.058	0.285	15.009	**4.79**	**Boil over**
6	5.030	0.260	15.070	**4.39**	**5.1**
7	5.032	0.260	15.054	**4.39**	**4.3**
8	5.036	0.258	15.158	**4.35**	**Boil over**
9	4.997	0.252	15.176	**4.29**	**8.2**
10	5.007	0.150	15.278	**2.55**	**Boil over**
11	5.049	0.147	15.032	**2.47**	**6.8**
12	5.006	0.137	15.015	**2.33**	**6.7**
13	5.036	0.091	15.032	**1.54**	**3.3**
14	4.983	0.076	15.003	**1.30**	**4.6**
15	5.094	0.035	15.184	**0.58**	**4.5**
16	5.059	0.033	15.157	**0.55**	**3.9**
17	5.023	0.030	15.092	**0.51**	**4.5**

[a]Acid % corrected for the purity of the reagent (85% phosphoric acid)

2.7 The use of other acids for levoglucosenone production from cellulose

To determine the effect of changing the identity of the acid used in this process, hydrochloric acid, sulfuric acid, and nitric acid were used in place of the phosphoric acid. It was found that on the order of minutes to hours these other acids (sulfuric and nitric in particular) would react with the soybean oil. The use of acid other than phosphoric gave lower yields of **1** in each case. The same molar ratio to the cellulose was used in each of these runs, and was the same amount as used in the base line case so that the results could be compared. When hydrochloric acid was used, only traces of product were seen. The cases where the acid caused a

reaction with the oil, there were boil overs and the investigation was discontinued. In the case of the nitric acid, the soybean oil was seen to turn an orange color within a few minutes. It was also noted however, that the phosphoric acid would react with the soybean oil, but the reaction was only noticed after a period of days.

2.8 Oil to cellulose ratio for levoglucosenone production from cellulose

The optimization of the oil to cellulose ratio was investigated at the 2.5% acid by mass level by varying the amount of cellulose and oil used, keeping the total mass of the slurry as constant as possible (Table 4). It was seen that the 3 to 1 ratio gave the best results (6.7 % yield) where as the 5 to 1 oil to cellulose came in at 5.7%. Ratios of less than 2 to 1 oil to cellulose were seen to not stir well, and at the 2 to 1 level, the yield of levoglucosenone (**1**) was only 2.7%. Higher ratios allowed better stirring, however, the yield at 10 to 1 oil to cellulose had dropped off to 2.6%. The selection was made to continue to investigate other factors, keeping the ratio of oil to cellulose at 3 to 1.

The reaction of cellulose in soybean oil is a heterogeneous reaction. It is important for the reaction to be well heated, and well stirred. The oil is present, in part, to allow the stirring of the cellulose and acid mixtures, thereby allowing more even heating and allowing the products, once formed, to enter the vapor phase and be removed from the hot reaction zone.

Table 4. Influence of oil to cellulose ratio on yield of levoglucosenone.

Entry	Cellulose Mass (g)	Acid Mass (g)	Oil Mass (g)	Oil to cellulose Ratio	Levoglucoseneone Yield, mole %
1	1.998	0.059	19.960	10 to 1	2.6
2	3.523	0.100	17.578	5 to 1	5.7
3	5.006	0.137	15.015	3 to 1	6.7
4	7.061	0.212	14.119	2 to 1	3.5

2.9 Use of other oils for levoglucosenone production from cellulose

Two other vegetable oils, canola and coconut, were used in this study and found to work reasonably well, compared to the soybean oil that was chosen as standard. There were some slight differences between some of the yields of **1** but without large numbers of runs with each of the oils, it would be hard to say if one would always be better than another. In changing from soybean oil to canola oil, it was noted that the canola oil performed better than the soybean oil at lower acid amounts, but not at the conditions that were chosen as standard. The best yield with canola oil was found at an acid amount of about 30 mg for the about 5 grams of cellulose used, when using 15 grams of the canola oil.

Coconut oil gave a slightly lower yield than the baseline soybean oil case at the normal acid loading and oil to cellulose ratio. The best amount of acid to use in each oil was not investigated. The vegetable oils gave similar results, and this is in agreement with some of the previous researchers' work.[10] In that study the following oils were tried peanut, safflower, soybean, corn, olive, sunflower, and canola. Of these, canola gave the best results with 8.5% average and peanut gave the poorest results at 5.1%. Soybean oil in that study gave 5.6% on average of 3 runs.

In this study, canola gave better results than the soybean oil at the acid amount used in the previous study (25 mg acid for 5 g cellulose) but soybean oil have better results at the higher acid amount currently used (125 mg for 5 g cellulose)

There were other non-vegetable derived oils used in this work. Paraffin wax, bee's wax, mineral oil and a poly siloxane oil were tested to see if they would act as efficient heat transfer

agents, and if that alone was sufficient to produce compound **1** from cellulose. The experiment was unsuccessful in most of these cases.

There was evidence that the oils in these latter cases were not interacting with the cellulose and the acid in the same way that the vegetable oils did. The acid added to the waxes and the polysiloxane and mineral oils did not seem to make a stable slurry, but resulted in two separate phases.

Polyethyleneglycol (PEG) was used in place of the oil in some runs. It was thought that the more polar PEG would interact with the cellulose more favorably than the nonpolar vegetable oils. It was found to give a poor yield of **1**, 2.1%, when cellulose was reacted in the presence of acid. PEG was noted to have a favorable effect on the yield of **1** when soluble starch was used in place of the cellulose, this gave an increase in yield (to 1.1%) compared to the starch used in the soybean oil (0.4%). These yields are far too low to be used as a preparative method, and further investigations was not done.

2.10 Influence of reaction pressure on levoglucosenone production from cellulose

The pressure at which the reaction was conducted was varied in a number of experiments to see if that would influence the yield of levoglucosenone. From 2 torr to atmospheric pressure, the highest yields were around the 15 torr pressure mark (table 5). The run at atmospheric pressure produced little collected distillate which was mostly water, as seen during the extraction. The run at 2 to 3 torr was seen to produce less **1** than at a pressure closer to 15 torr, and boil over was seen at this pressure.

At higher pressures it was assumed that the **1** produced was allowed to stay in the hot and acidic oil longer, therefore allowing the breakdown of more of the material before it was

collected. At lower pressures it is supposed that the water, which seems to effect a steam distillation, was not being formed at a rate that would allow for the collection of the maximum amount of **1**.

Table 5. Influence of the reaction pressure on the yield of levoglucosenone.

Entry	Cellulose Mass (g)	Acid mass (g)	Oil mass (g)	Pressure (torr)	Corrected Acid %[a]	Levoglucoseneone Yield, mole %
1	5.0028	0.149	14.985	760	2.52	0.00
2	5.0573	0.146	15.025	45	2.45	6.40
3	5.0501	0.147	15.077	30	2.48	8.32
4	5.0392	0.146	15.038	10	2.46	7.94
5	5.3669	0.148	15.038	5	2.34	7.17
6	5.0076	0.147	15.008	3	2.49	Boil over

[a]Acid % corrected for the purity of the reagent (85% phosphoric acid)

2.11 Influence of salts on levoglucosenone production from cellulose

It has been noted in the literature that the addition of several types of additives can change the results of cellulose decomposition.[14-18] Calcium dihydrogenphosphate seemed to give the best yield of **1** from cellulose. At 2.4 mole % additive, the yield of **1** was 14.6%. This is higher than the baseline of 9.5%. Iron(III)sulfate also increased the yield of **1** from cellulose at 13.25% , as was expected from the literature.[14,17]

It is unclear why the addition of salts would change the yield in this process at this time. Other salts were tried, and some gave very poor yields. A few gave better yields of **1** than the untreated cellulose but the expense of the additives and the availability of cheep cellulose starting material were seen to outweigh the modest gains achieved in the best cases. There may be hazardous waste considerations with some of the salts tried, in addition to the cost of acquiring them. See table 6 for additives tried and the results of those reactions.

Table 6. Effects of additives to cellulose on the yield of levoglucosenone

Entry	Cellulose Mass (g)	Acid mass (g)	Oil mass (g)	Additive	Additive Equivalents	Levoglucosenone Yield , mole %
1	5.023	0.146	15.005	$Ca(H_2PO_4)_2$	0.024	14.60
2	4.990	0.148	15.158	$Cu(SO_4)$	0.024	14.30
3	4.982	0.146	15.149	$MgSO_4$	0.024	13.70
4	5.071	0.146	15.249	$(NH_4)_2HPO_4$	0.024	13.30
5	5.008	0.146	15.000	$Fe_2(SO_4)_3$	0.012	13.25
6	5.036	0.147	15.258	$Fe_2(SO_4)_3$	0.012	13.00
7	5.023	0.146	15.067	$FeCl_3$	0.012	12.80
8	5.000	0.146	15.006	$Fe(SO_4)$	0.048	12.70
9	5.013	0.146	15.082	$Fe_2(SO_4)_3$	0.012	11.12
10	5.019	0.147	15.014	$Fe(SO_4)$	0.012	10.80
11	5.048	0.147	15.027	KCl	0.024	10.60
12	5.249	0.148	15.036	KBr	0.024	9.50
13	4.993	0.147	15.122	$Fe_2(SO_4)_3$	0.012	8.30
14	5.002	0.145	15.072	KI	0.024	7.40
15	5.017	0.000	15.055	$Fe_2(SO_4)_3$	0.012	6.00
16	5.020	0.148	15.269	$FeCl_3$	0.024	5.10
17	5.023	0.146	15.007	NaCl	0.024	4.70
18	5.010	0.146	15.125	$CoCl_2$	0.012	2.50
19	5.054	0.146	15.064	$CuSO_4$	0.048	2.16
20	4.977	0.147	15.027	$CoCl_2$	0.048	1.50
21	4.996	0.147	15.013	NaCl	0.048	0.99

2.12 Influence of scale on levoglucosenone production from cellulose

An investigation into increasing the scale of this reaction was undertaken. Thus, 25 grams of cellulose, without pretreatment, was reacted in the presence of 75 grams soybean oil and 2.5 % acid, based on the mass of the cellulose. It was seen that the increase in the scale was accommodated easily by increasing the flask size from 50 mL to 250 mL. The same short path distillation head was used with this scale and the yield was found to have increased. The yield was roughly 12 mole % **1** based on the amount of cellulose used (table 7).

This increase may be due to a slightly different heating rate, or more material being produced to overcome losses that are inherent in the process, such as hold up in the condenser or on the flask walls. It may also help to have more material in the extraction process, fewer percent are lost to saturate the wash solutions. No major differences were seen when run on the larger scale, with the possible exception of the times that it took to get up to temperature. This took slightly longer with the larger scale reaction.

Table 7. Results of scaled up runs, 25 grams of cellulose.

Entry	Cellulose Mass (g)	Acid mass (g)	Oil mass (g)	Levoglucosenone Yield, mole %
1	24.9861	0.750	75.383	13.20
2	25.2966	0.738	75.163	12.80
3	25.0176	0.745	75.215	12.10
4	25.0474	0.740	75.060	11.70
5	25.2532	0.734	75.057	11.50
6	25.3616	0.735	75.085	11.40
Average				12.12

2.13 Other carbohydrate starting materials used in place of cellulose

Other carbohydrates were investigated to see if they would react in a similar fashion as the cellulose. Soluble starch was found to give 0.43% compound **1** when reacted under conditions that would produce compound **1** from cellulose.

Starch was seen to give very low yields of **1** when reacted. This is not unexpected due to the structure of starch and the presence of the alpha linkages, which are not set up to produce **1** as directly as the beta linkages of cellulose. The highest yield from starch was a little over 1 percent and that was in polyethylene glycol instead of the soybean oil. It is unclear why the PEG would provide more **1** from starch.

Guar gum, methylcellulose, and cellulose acetate gave very low yields of **1** that was contaminated with other products. These yields were so low that no further work was done in our hands with these beyond the initial investigation.

Glucose, sucrose and cellobiose also gave low yields, however, these may have been low due to experimental factors that could be optimized, however we chose not to investigate these as starting materials since they melt during the reaction and form a separate liquid phase in the reaction flask. The char left after these materials were used was seen to be a single chunk of hard material that looked like lava rock, and was hard to remove from the flask.

Inositol was found to give a low yield of some aromatic compounds, but this was not investigated further.

2.14 Purification of crude levoglucosenone produced from cellulose

Simple vacuum distillation of the crude extracted product from the 25 gram scale runs was found to proceed without trouble, and provide material that was between 90 and 97% pure. This is considered quite useable, since the material is an enone and therefore quite reactive. The conditions for the distillation were found to be best at a reduced pressure of 0.10 torr.

Silica gel chromatography was also used to purify some of the material, but the distillation was easier and produced material that was at least as clean as from the chromatography.

2.15 Improved preparation of levoglucosenone from cellulose

We report here an improved preparation of levoglucosenone from cellulose using the results of the current study. It was found that an increase in the amount of acid used in the

preparation would lead to a greater yield of **1**. The correct order of reagent addition is also critical for the reproducibility of the preparation. The addition of some additives increased yield, however, the increased complexity of the preparation and the time needed for each run is increased as well. Therefore, the following procedure is given as the best current preparation of levoglucosenone from cellulose in the presence of acid.

To a 3-necked flask, 2.5% of the cellulose mass of phosphoric acid is added as the 85% reagent. Three times the cellulose mass of soybean oil is added and a magnetic stirring bar is used to stir the resulting suspension. Cellulose is added while the acid and oils suspension is stirring. Slurry temperature monitoring is important, so a temperature probe is fitted into one of the necks of the flask. A short path distillation head was placed in one of the joints, with the receiver flask cooled in ice water. The third joint was plugged with a hollow glass stopper. The pressure was reduced to 15 mmHg and at that point, the slurry was stirred for at least 5 min longer. A preheated heating mantle was used to heat the slurry.

The distillate is collected in an ice/water cooled flask, and is extracted with methylene chloride, neutralized, washed and then dried.

Using 25 grams of cellulose, this procedure yields about 3.4 grams of extracted product, of which 2.4grams is levoglucosenone. The levoglucosenone produced therefore is about 68% pure. The observations in this run were similar to the procedure before the improvements, with the exception of larger distillate volumes. The changes seen and the temperatures seen were very similar. See section 4.6 below for more complete experimental details.

2.16 Comparison to previous levoglucosenone preparations

This procedure seems to overcome some of the problems that are seen in other preparations of levoglucosenone (**1**) in the literature. While some of these procedures report high yields of compound **1**, they suffer from difficulties in isolating the material in a useable form. The procedures that form **1** in a polar aprotic solvent (such as DMF[19,20] or sulfolane[21]) seem to hinder the collection of the desired compound from the solution it is made in.

There are some preparations starting with the acid treated cellulose or acid treated paper and using elevated temperature which allow the formation and the subsequent isolation of that material from the tar that is formed.[3,4]

Our procedure allows for a higher yield without the need of specialized glassware or apparatus, and the advances presented here make our procedure more convenient and more reliable, as well as extending the scale from hundreds of milligrams to a gram or more of levoglucosenone (**1**) for each run.

3. Conclusions

Given here is a better process for making levoglucosenone (**1**) on a bench top scale for further research into its utilization. The process given here surpasses previous preparations in ease and uses commonly available glassware, and surpasses our previously presented preparation in reliability and in scale, as well as having investigated some factors that may have needed optimization. There are many syntheses that have used **1** in the past, and it is hoped that further work will be done using this material that is easy to make from cellulose. The addition of metal salts could be used to increase the yield of levoglucosenone (**1**) but the expense of the additives

and the concerns that arise in the disposal of some of them may outweigh the benefit, given the inexpensive cellulose starting material.

4. Experimental

4.1 General considerations

Microcrystalline cellulose (20 micron particle size) was purchased from Aldrich, phosphoric acid (85%) was from Fisher, soybean oil was from HyVee grocery store and all were used as received. Avicell brand microcrystalline cellulose from FMC biopolymer was used for the particle size experiments. The yields reported are based on NMR data with durene (1,2,4,5-tetramethylbenzene) as internal standard. Varian VXR 400 and VXR 300 MHz NMR spectrometers were used for the collection of NMR data.

4.2 General improved levoglucosenone production from cellulose, 5-gram scale

To a 50-mL 3-necked flask, 85% phosphoric acid (147 mg, 2.5% based on the mass of the cellulose used) was added, then 15 grams of normal soybean oil was added and this was rapidly stirred open to the atmosphere for at least 4 min with a magnetic stirring bar and stirring plate. Cellulose (5 grams) was then added. A short path distillation head was fitted to the 3-necked flask and a thermometer was inserted through an adaptor in the other side neck. The center opening was plugged with a hollow stopper. The slurry was stirred under reduced pressure (15 mmHg) for a minimum of 5 min before the heating mantle was placed under the flask. It was important that the heating mantle was preheated at full power for roughly 10 to 20 min before being placed under the flask. The receiver flask was cooled in an ice water bath. The 3-necked flask was covered with woven glass fiber insulation to reduce the heat loss to the environment. The slurry was heated rapidly to a temperature of 225 °C, (still under reduced pressure) at which

point the power to the heating mantle was reduced to allow the slurry temperature to level off in the range of 260 to 270 °C. The temperature of 225 °C is normally attained within 4 min. Faster heating may reduce rather than increase yields of **1**. Approximately 1.5 mL of material is collected in the receiver flask. This collected material, normally 1.1 mL of water layer on top of a 0.4 mL levoglucosenone layer, was added to 10 mL methylene chloride in a 125 mL separatory funnel. A 5% sodium bicarbonate solution was added until the evolution of gas ceased. The organic layer was washed with water, and then dried with anhydrous magnesium sulfate. The solvent was removed using rotary evaporation. The yield is about 9.6% based on the mass of the cellulose starting material expressed as anhydroglucose units, as found with NMR using durene as internal standard.

4.3 Addition of ferric sulfate to cellulose

Iron(III) sulfate (0.1235 grams) was dissolved in 25 mL deionized water in a 250-mL round-bottomed flask. This gave a clear orange colored solution after approximately 10 min stirring at room temperature. Then 6 grams of cellulose was added and the slurry was stirred for 2 hr at which time about 90 mL of propyl alcohol was added and the slurry was stirred for a few min to allow mixing of the alcohol and the water before the alcohol/water azeotrope was removed using rotary evaporation at reduced pressure (about 1.0 mmHg) at room temperature. The volume of the slurry reduced until most of the alcohol had been removed. Rotation of the evaporator was stopped and the cellulose was allowed to continue to dry under reduced pressure. After the final removal of alcohol/water, the resulting lightly colored cellulose was fluffy and appeared as a dry flowing powder. This was used directly in the place of untreated cellulose in the normal procedure. The mole % yield of levoglucosenone was about 14.75%.

4.4 Other carbohydrate starting materials used in place of cellulose

White copier paper and cotton were used in place of the microcrystalline cellulose in the general procedure as above. These substitutions were made on a gram-per-gram basis.

Starch, guar gum, methylcellulose, cellulose acetate, inositol, glucose, and cellobiose were also used in place of the cellulose in the general procedure, on a gram-per-gram of cellulose basis.

4.5 Preacidification of cellulose used to make levoglucosenone

An acid solution in methanol (150 mL) was made to contain the acid needed to make the desired concentration in 6 grams of cellulose, this solution was stirred briefly and then the cellulose was added. The resulting slurry was allowed to stir for 2 hr and then the alcohol was removed using rotary evaporation.

4.6 General improved levoglucosenone production from cellulose, 25-gram scale

To a 250-mL 3-necked flask, was added 0.7352 grams of 85% phosphoric acid. To this was added 75.0 grams of soybean oil, and a magnetic stirring bar. This was stirred for 10 min to create a milky, slightly yellow colored suspension of the acid in the oil. While this was still stirring, 25.0 grams of cellulose was added to the slurry. The flask was fitted with a temperature probe with a thermometer adaptor to measure the temperature of the oil. A short path distillation head was placed in one of the joints, with the receiver flask cooled in ice water. The third joint was plugged with a hollow glass stopper. The pressure was reduced to 15 mmHg and at that point, the slurry was stirred for at least 5 min longer. A preheated heating mantle was used to heat the slurry to about 225 °C in about 7 min. The power to the heating mantle was controlled

so that the heating continues from 225 °C to about 295 °C in an additional 15 min, at which point no more product is formed.

The distillate (roughly 9 mL) was added to methylene chloride (about 25 mL) and then 5% sodium bicarbonate was added in small portions until there was no further evolution of gas on shaking (10-20 mL). The organic layer was removed and the aqueous layer was washed again with methylene chloride. The combined organic material is dried over magnesium sulfate, and then concentrated on a rotary evaporator.

This procedure yields about 3.4 grams of product, of which 2.4grams is levoglucosenone. The levoglucosenone produced therefore is about 68% pure.

4.7 Levoglucosenone purification by distillation

The distillation of **1** from the crude extract was done using normal vacuum distillation techniques. A pressure of 0.1 torr was found to give **1** at greater than 90% purity and had a boiling point of 65-67°C.

4.8 Levoglucosenone purification by chromatography

Silica gel chromatography was performed on 0.812 grams of the darker orange/yellow crude as extracted **1** using 12.323 grams of silica gel on a fritted glass funnel of about 6.5 cm in diameter. About 500 mL of 4:1 heptane to methylene chloride was used to remove the nonpolar impurities. Then the silica gel was flushed with about 500 mL of methylene chloride to give 0.314 grams of **1** that was 91% pure, as a light yellow oil with a total mass of 0.344 grams.

4.9 NMR-based levoglucosenone yield determination

The reported yields are derived from the 1H NMR of the **1** produced with the addition of durene as an internal standard. The typical procedure for yield calculation is given below, with an example calculation.

General NMR-based yield calculation

$$\text{Mass of internal standard used} \times \left(\frac{1 \text{ mole internal standard}}{\text{formula weight of internal standard}}\right)$$

$$\times \left(\frac{\text{number of protons that give selected signal on internal standard}}{\text{NMR integration of selected internal standard signal}}\right)$$

$$\times \left(\frac{\text{NMR integration of product signal}}{\text{number of protons that give selected product signal}}\right)$$

$$\times \left(\frac{\text{formula weight of product}}{1 \text{ mole product}}\right) = \text{Mass of product in sample}$$

Example NMR-based yield calculation

$$0.1161 \text{ grams durene used} \times \left(\frac{1 \text{ mole durene}}{134.22 \text{ grams durene}}\right)$$

$$\times \left(\frac{2 \text{ moles protons give signal in one mole durene}}{1.000 \text{ integration uints for durene signal}}\right)$$

$$\times \left(\frac{1.70 \text{ integratoin units for levoglucosenone signal}}{1 \text{ mole protons give product signal in one mole levoglucosenone}}\right)$$

$$\times \left(\frac{126.1056 \text{ grams levoglucoenone}}{1 \text{ mole levoglucosenone}}\right)$$

$$= 0.370 \text{ grams levoglucosenone in sample}$$

Signals used are at 6.9 ppm (singlet) for durene internal standard and at 5.0 ppm (triplet) for levoglucosenone.

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APPENDIX Spectra
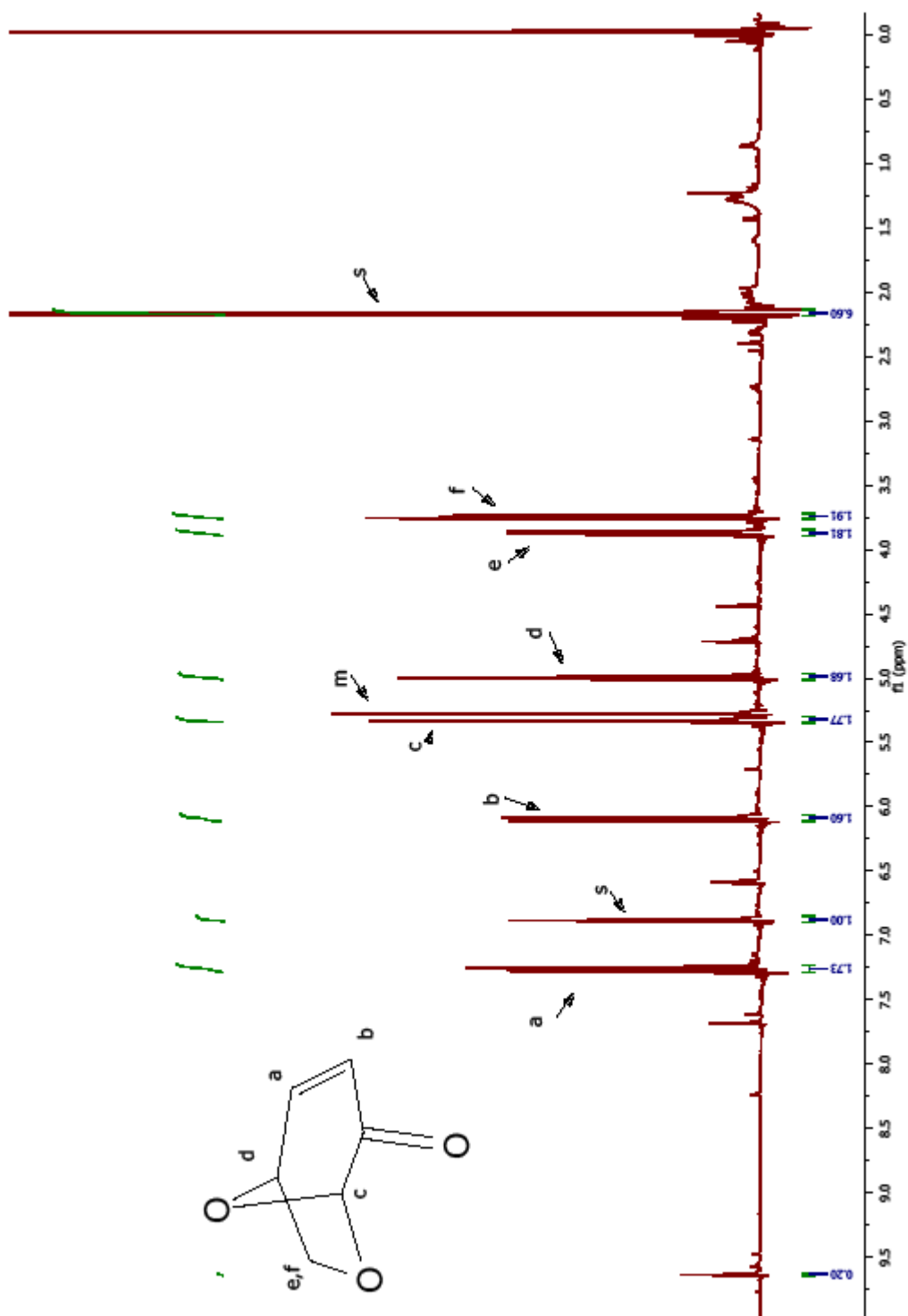
NMR 1. Levoglucosenone from baseline run. 400 MHz in chloroform-d. Peaks from the internal standard durene are labeled s and a-f indicate levoglucosenone peaks. These assignments are given on the structure. Methylene chloride peak is labeled m.
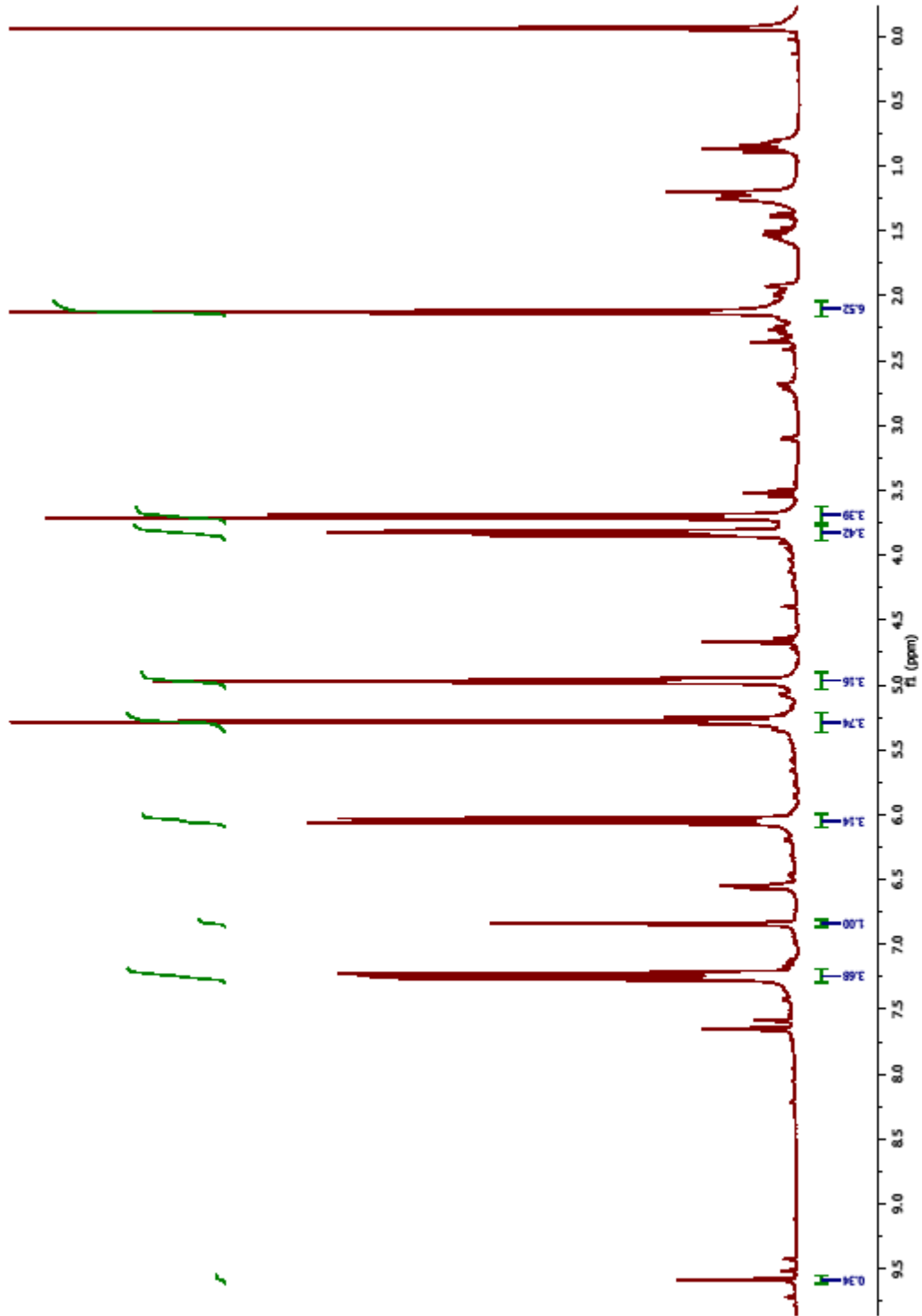
NMR 2. Levoglucosenone from cellulose treated with 0.024 equivalents calcium dihydrogenphosphate.400 MHz in chloroform-d.
Levoglucosenone yield of 14.6% from cellulose.
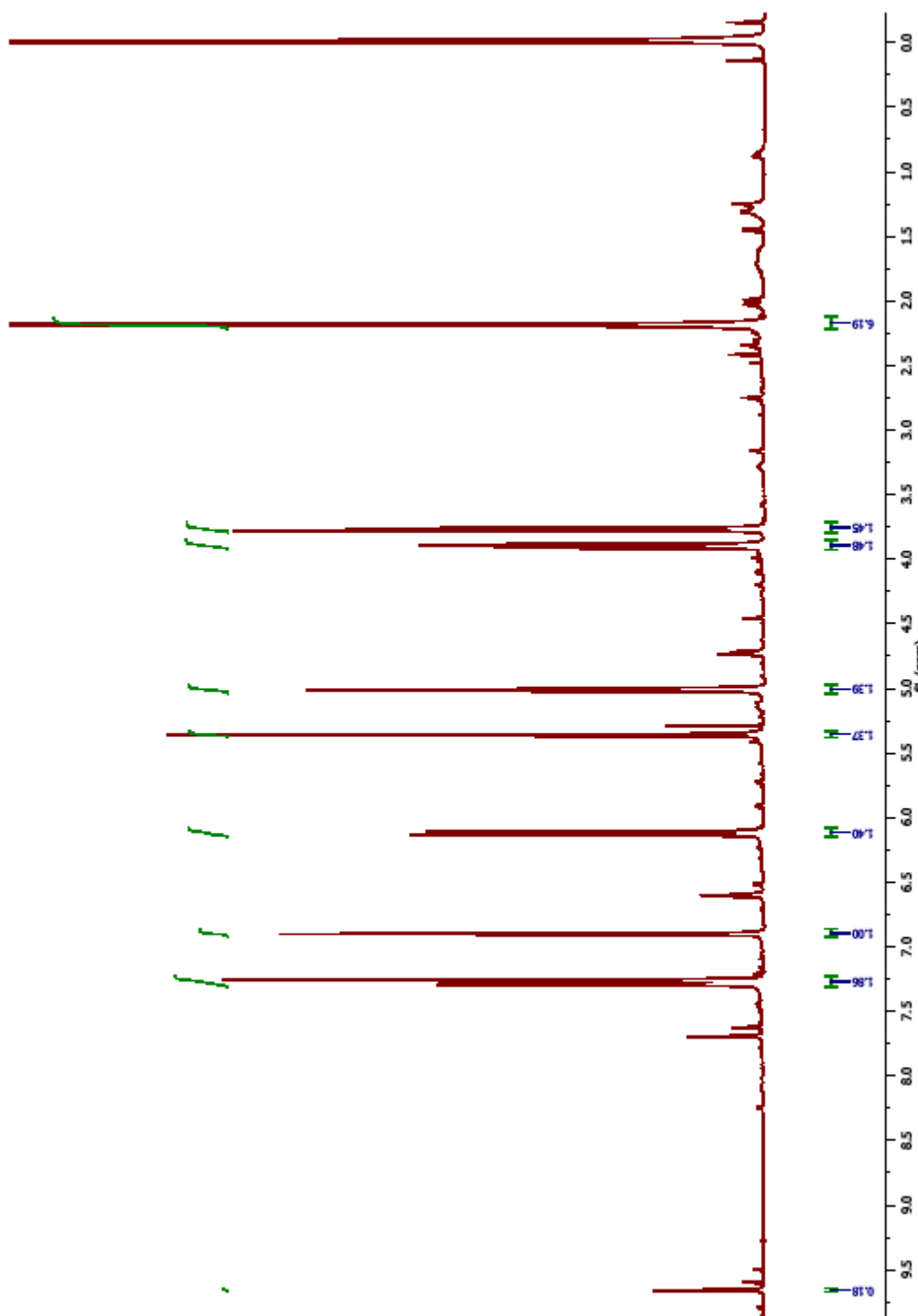
NMR 3. Levoglucosenone from run using 25 grams of cellulose. 400 MHz in chloroform-d, run yield was 12.1% crude as extracted is about 60-70% pure.
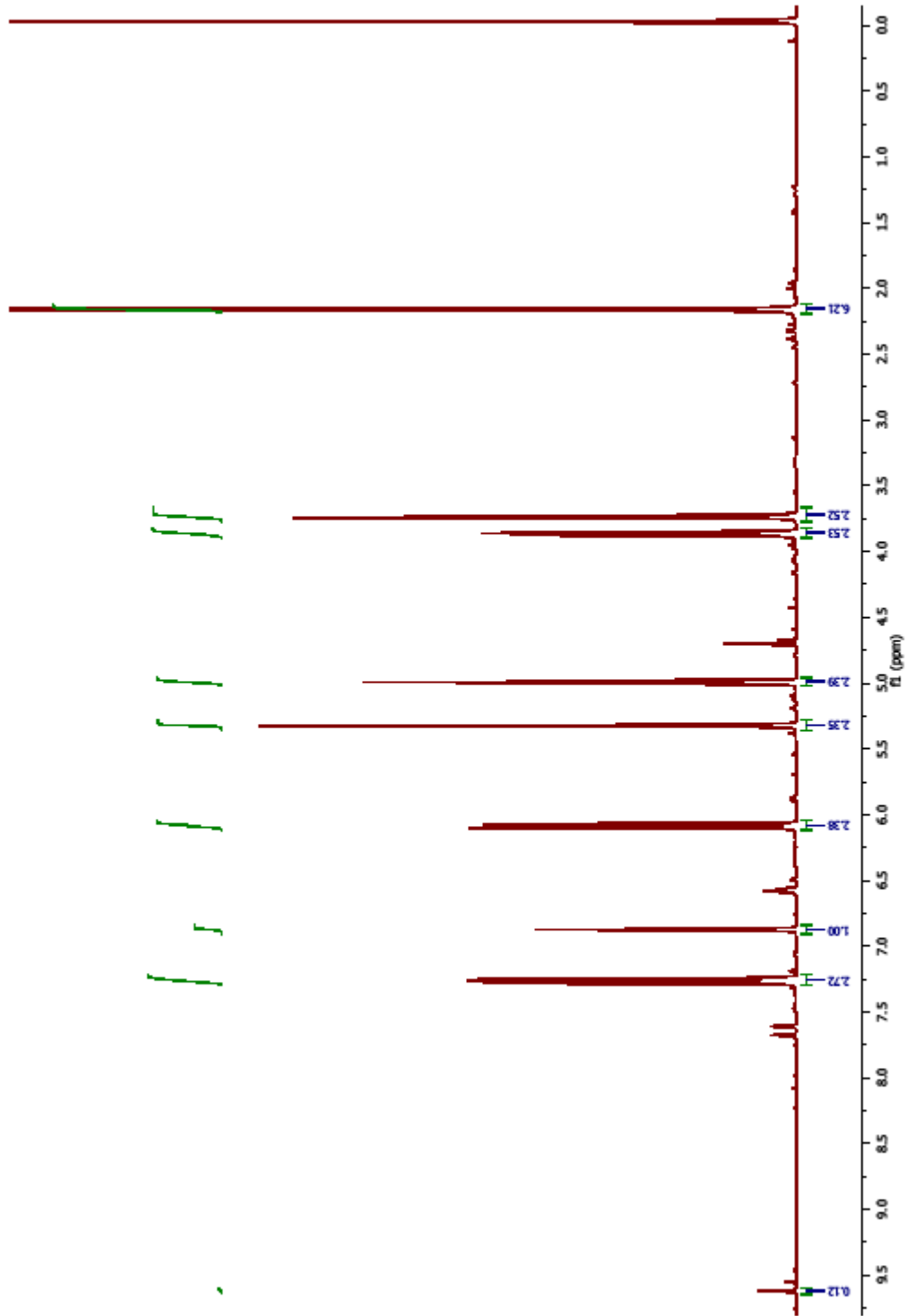
NMR 4. Distilled levoglucosenone from 25-gram run, 97% pure. Distilled at 0.1 torr, b.p. 65-67 ° C. 400 MHz in chloroform-d.