공학석사 학위논문

Efficient synthesis of 5-*O*-acetylhydroxymethylfurfural (AcHMF) as an alternative to HMF

HMF 의 대안으로서 5-*O*-아세틸히드록시메틸푸르푸랄 (AcHMF)의 효과적인 합성법

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Abstract

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In this paper, 5-*O*-acetylhydroxymethylfurfural, AcHMF, an alternative of hydroxymethylfurfural, HMF, was synthesized by eco-friendly way. HMF, a biomass derived furan-based compound, is a promising renewable resource and lots of papers are introducing methods to synthesize HMF effectively. In spite of the high application to various furan-based monomers, HMF has some defects originated from its high reactivity and instability. So in this paper, another furan-based compound called AcHMF (5-*O*-acetylhydroxymethylfurfural) is introduced as an alternative of HMF. Not only AcHMF can compensate the defects of HMF, but also various derivatives

synthesized from HMF previously can be obtained from AcHMF too. To synthesize AcHMF, lipase catalyzed selective acetylation of fructose to obtain 1,6-di-*O*-acetyl fructofuranose followed by dehydration under various acidic conditions was carried out. Previously presented synthetic methods for HMF have troubles because of using DMSO or ionic liquids as solvents, but methods from this paper don't use those solvent. Also, using eco-friendly lipase is also an advantage of this paper.

keywords : AcHMF, HMF, biomass, renewable resource, furanics, ***Green chemistry***
***Student Number* : 2011-21087**

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LIST OF ABBREVIATIONS

Ac_2O	Acetic anhydride
AcOH	Acetic acid
$C_6H_5SO_3H$	Benzenesulfonic acid
CMF	5-Chloromethylfurfural
Conc.	Concentrated or concentration
DHMF	2,5-Dihydroxymethylfuran
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
EDC	Ethylene dichloride
FDCA	2,5-Furandicarboxylic acid
H_2SO_4	Sulfuric acid
HCl	Hydrogen chloride
HMF	5-Hydroxymethylfurfural
HMFA	5-Hydroxymethylfuranoic acid
IL	Ionic liquid
K_2CO_3	Potassium carbonate
LiCl	Lithium chloride
MeCN	Acetonitrile
MeOH	Methanol
$MgCl_2$	Magnesium chloride
$NaBH_4$	Sodium borohydride
$NaHCO_3$	Sodium bicarbonate

NaOH	Sodium hydroxide
Novozym 435	Lipase from *C. Antarctica* B
PET	Polyethylene terephthalate
Pyr.	Pyridine
PivCl	Pivaloyl chloride
Pt/C	Platinum on charcoal
R_f	Retardation factor
$Sc(OTf)_3$	Scandium triflate
TBAA	Tetrabutylammonium acetate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
triflate	Trifluoromethanesulfonate
TsOH	*p*-Toluenesulfonic acid
$Yb(OTf)_3$	Ytterbium triflate
$ZnCl_2$	Zinc chloride

1. Introduction

1.1. The problems of fossil fuel

Human culture has developed with the growth of fossil fuel, such as petroleum, coal and natural gas, and human depends on it more and more. The world's energy market worth around 1.5 trillion dollars was still dominated by fossil fuels in research of 2006.[1] Fossil fuel is not just crucial as energy source, but also an important resource to prepare the compounds that are essential in modern man's life like various plastics. However, the problems of fossil fuels are getting serious as days go by. The defects of fossil fuels can be divided into 2 main aspects.

First, its reserve is limited and getting exhausted. There have been lots of worrying voices saying that thoughtless spending of fossil fuels would cause depletion of energy in few years. But views about world fossil fuel reserved differ and nobody can predict exactly when supplies of fossil fuels will be exhausted.[2] Moreover, the use of fossil fuel has caused environmental problems such as global warming, greenhouse effect, and sea level change. So, in recent years lots of studies about renewable alternative energy and resource have been in progress.

1.2. An alternative for renewable resource, HMF

There are two conditions that a new carbon-based fuel economy should fulfill. First, the carbon source must be originated from atmospheric carbon dioxide, which is formed from the photosynthetic production of cellulose, starch, or simple sugars. Second, these saccharides must be efficiently converted into organic liquids of low volatility and high energy content.[3]

Satisfying those qualifications, a kind of biomass derived organic liquids with high-energy potent, called 'furanics', is illuminated as a promising renewable resource. Furanics include furan rings in their skeletal structures so they are named after furan. The most popular furanic is called HMF, abbreviation of 5-hydroxymethylfurfural, HMF (**1**).

HMF (**1**) is pale yellow oil with high reactivity. HMF can be obtained by dehydration of sugar, not only fructose but also glucose, and even cellulose.[4] HMF is an important intermediate to synthesize furan based monomers like 2,5-dihydroxymethylfuran (**2**), 5-hydroxymethylfuranoic acid (**3**), or 2,5-furandicarboxylic acid (**4**). In spite of the value of HMF, there is still some problems. Storage of HMF is troublesome because of the high reactivity, and isolation during process is difficult because of its hydrophilicity. There already have been

numerous studies synthesizing HMF, but still more studies are needed to compensate the defects of HMF.

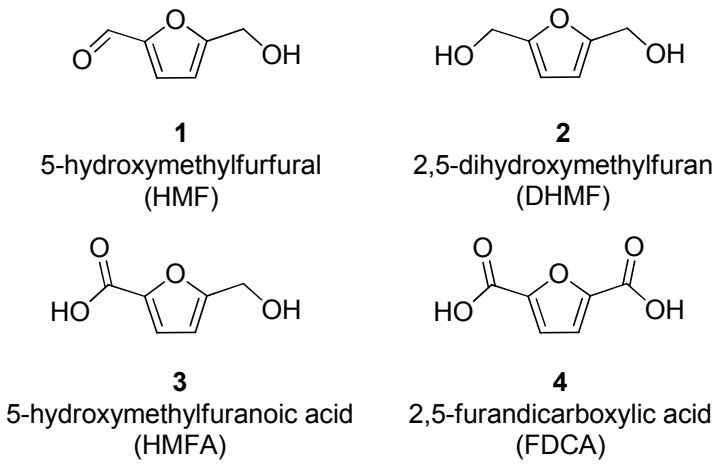


Figure 1. Structures of HMF and its derivatives

1.2.1. Application of HMF

From HMF (**1**), various furan derivatives can be synthesized. By hydrogenation of HMF, 2,5-diol DHMF (**2**) is obtained. DHMF is precursor of 2,5-dimethylfuran, DMF, which is hydrophobic and possesses excellent energy-density and boiling point characteristics to be used as transportation liquid.[5] Also, HMF can be converted into mono acid HMFA (**3**) or 2,5-diacid FDCA (**4**). FDCA is famous as a furan based monomer for PET, replacing terephthalic acid. Above these derivatives, HMF can be converted into various, useful compounds.

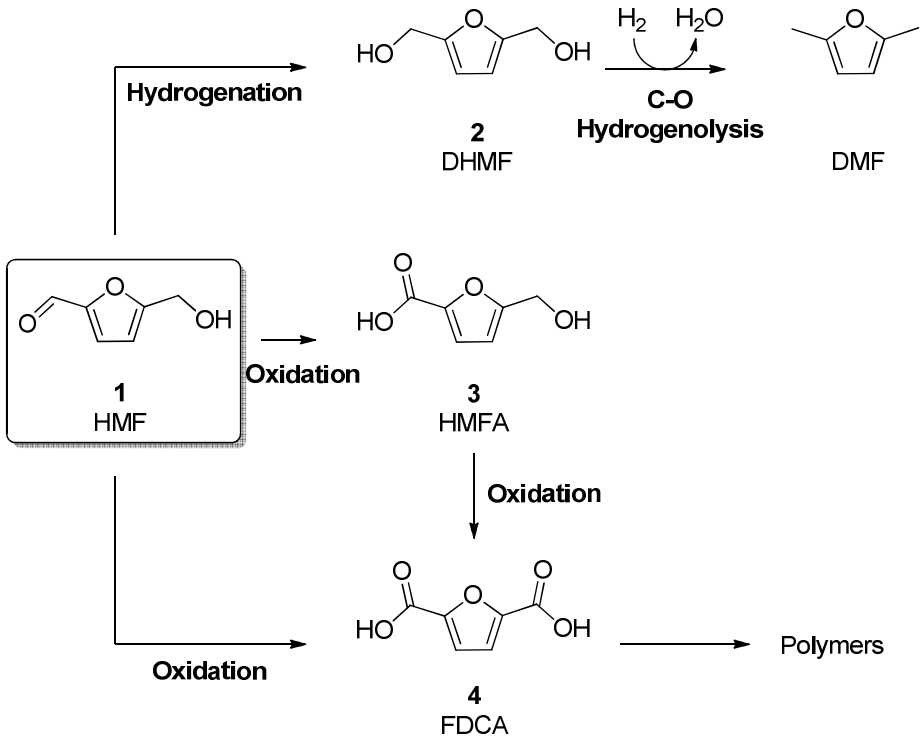


Figure 2. Application of HMF[6]

1.2.2. Previous studies of synthesis of HMF

The synthesis of HMF has been studies a lot, and numerous papers about it had been published already. Also, some papers already reached considerable yields. The methods with high yields usually use solvent like DMSO or ionic liquids.

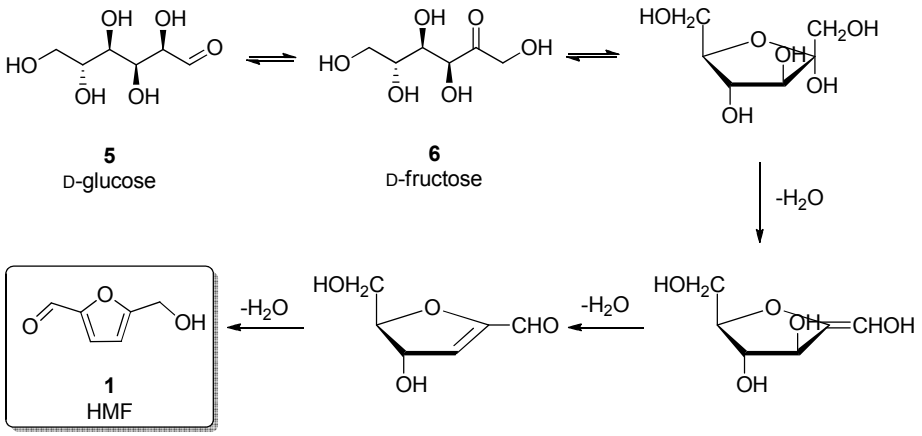


Figure 3. One of the proposed mechanisms of HMF formation[4,6]

There are two types of proposed mechanisms proposed by Antal group and one of them is described in figure 3.[4,6] Referring to this mechanism, driving glucose into fructose, and fructose into furanose form might increase yields. It is very important because the predominant form of D-fructose is pyranose, not furanose. If fructose was used as a starting material, the only problem remained is tautomerization of fructose. A simple way to drive fructose into furanose form is using DMSO as a solvent. Lichtenthaler and Ronninger has examined the distribution of furanose and pyranose forms of D-fructose in water, DMSO and pyridine.[7] They found out furanose form is preferred in DMSO in contrast to water or pyridine. That is because DMSO can stabilize it intramolecular hydrogen-bonding between HO-1 and HO-4.[8] So, lots of papers introducing methods of synthesis of HMF with high

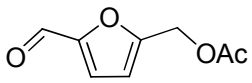
yields use DMSO as solvent.[9,10] Also, ionic liquids are good solvents when synthesizing HMF to get high yields.[11–14] Regardless of solvents, reagents to dehydrate monosaccharides are important too. Usually, using strong acids like hydrogen chloride[12,15], sulfuric acid[16,17], or Lewis acids[18–20] can achieve high yields. Wen-Sheng Dong *et al.* proposed a synthetic method using rare earth metal trifluoromethanesulfonates, like $Sc(OTf)_3$ and $Yb(OTf)_3$ in organic solvents. Those catalysts have nice properties like stability and solubility in organic solvents, less corrosive and lower pollution than conventional mineral acids.[21,22] Using various reagents and solvents explained above, HMF is synthesized up to quantitative yield already.

1.2.3. The defects of HMF and its alternative, AcHMF

Although there are lots of studies synthesizing HMF with high yields, HMF has few defects which has to be considered. First, because of its high hydrophilicity, HMF wouldn't' be isolated easily during the process using polar solvents like DMSO or ionic liquids which are necessary to obtain high yields. So, lots of organic solvents are required to

extract HMF from reaction mixture. It means efficient process to obtain high conversion of HMF causes more pollution. Third, HMF is somewhat unstable under moisture so careful handling in storage is needed. To complement these defects of HMF, an alternative furfural derivative called AcHMF(5-*O*-acetylhydroxymethylfurfural) is proposed in this paper. AcHMF is hydrophobic so that it is isolated easily from the reaction mixture so not that much organic solvents are needed during process. Also, it seems to be more stable than HMF. To be an alternative of HMF, AcHMF should be obtained from biomass efficiently and it should be able to be used as a precursor of variety of furan-based monomers.

In this paper, AcHMF was obtained from fructose using two methods. After that, conversion of AcHMF into various derivatives which were derived from HMF previously was carried out to confirm that AcHMF can be used as an alternative of HMF.



7
5-*O*-acetylhydroxymethylfurfural
(AcHMF)

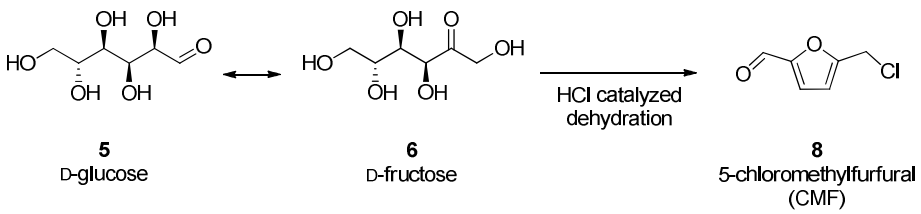
Figure 4. Structure of AcHMF

2. Results and Discussion

2.1. Trials to synthesize AcHMF by one-pot reaction

As mentioned previously, HMF (**1**) can be obtained from D-fructose by one pot reaction. As an alternative of HMF, the best method to synthesize AcHMF (**5**) should be one step too. So, one pot reactions with various conditions were considered and carried out.

2.1.1. Biphasic reaction



5
D-glucose

6
D-fructose

8
5-chloromethylfurfural
(CMF)

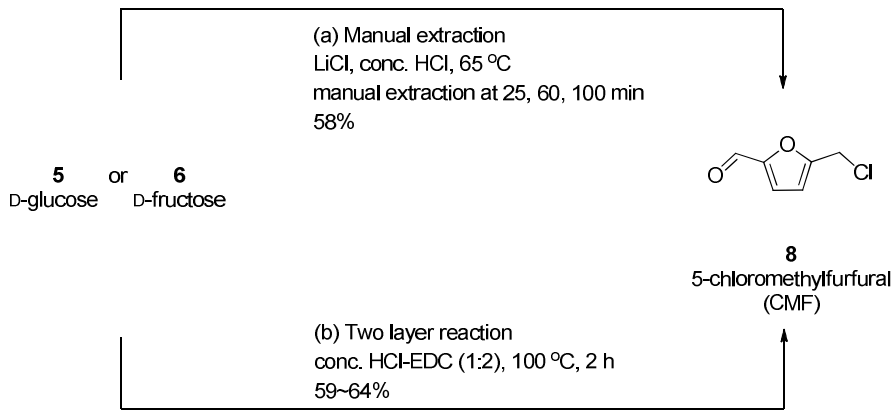
Scheme 1. HCl catalyzed dehydration of sugars to synthesize CMF

There are some published papers introducing methods for synthesis of chloro derivative of HMF, 5-chloro-

methylfurfural, abbreviated to CMF (8) from D-fructose.[3,17,23,24,25] The common thing of those papers is the reaction media is separated into 2 layers, aqueous and organic layer running through flow reactor. The organic layer is not mixed with water like EDC or toluene. The important reagent in these papers is concentrated hydrogen chloride, which is soluble in aqueous layer, catalyzes dehydration of D-fructose and participates in chloride substitution at terminal hydroxyl group of furfural. Reagents including the starting material D-fructose, concentrated hydrogen chloride, and additional options like $MgCl_2$ or LiCl dissolve well in aqueous layer. In contrast, the resulting product CMF would dissolve organic layer rather than aqueous layer, because CMF is too hydrophobic to dissolve in water. Relatively high yields in those methods comparing to those for synthesis of HMF in water solvent[26,27], might be resulted from the high reactivity of concentrated hydrogen chloride and the prevention of further side reaction by transferring CMF into organic layer, where the reaction doesn't occur.

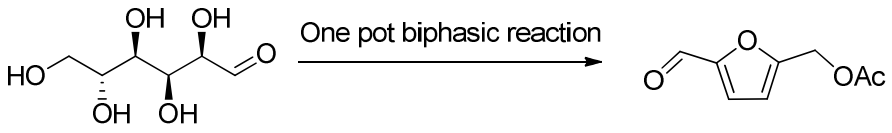
AcHMF (5) is similar with CMF (8) in terms of hydrophobicity. AcHMF and CMF have almost same R_f value. R_f of AcHMF is slightly smaller than that of CMF. So, the concept of the methods for synthesis of CMF (7), the two layer reaction can apply to synthesis of AcHMF (5).

Before application, CMF synthesis was carried out first in order to find out the best condition which is available in usual laboratory. Many of methods with high yields were carried out using flow reactors,[3,4,] which is not available in usual organic chemistry laboratory where most reactions are occurred in round-bottomed flask, so to speak batch reactor. In 2011 Micael Bols *et al.* presented a paper including conversion of fructose into CMF with manual extraction method instead of using flow reactors.[28] Using that method, 58% of CMF was obtained by second extraction, and no CMF was checked by TLC at third extraction. Also, modified process which adopts two-layer condition consisted of concentrated hydrogen chloride and ethylene dichloride was carried out, and with similar and moderate yields, 59-64% of CMF was obtained. Between these two methods, the yield of two layer dehydration is slightly better, so this method was chosen to synthesize AcHMF from D-fructose.



Scheme 2. Synthesis of CMF from D-fructose

To synthesize AcHMF by one pot reaction, an acid to dehydrate D-fructose, and an acetyl donor to substitute hydroxyl group at terminal position should be included in the reaction mixture. Few conditions were screened as described in Table 1. All the entries adopted EDC as an organic layer and the reaction was carried out at 100℃ in oil bath. The reaction mixture was held in pressure tube to avoid losing solvents at high temperature. In entry 1, tetrabutylammonium acetate (TBAA) was used as an acetyl donor, but because TBAA can act as a phase transfer catalyst, two layers were not separated clearly, so only trace amount of CMF was seen by crude NMR. So, acetic acid was used as an acetyl donor instead in next trials. In entry 2, 20% of CMF and only 5% of AcHMF were obtained. When hydrogen chloride was used, CMF rather than AcHMF was synthesized. So, sulfuric acid, which has higher reactivity than hydrogen chloride, was used instead. But through entry 3 to 6, no remarkable results were achieved. So, acetic acid was used instead of sulfuric acid and acetic anhydride was added as an acetyl donor. In entry 7, 9% of AcHMF was obtained. The yield was better than previous entries, but still it was too low. So, in entry 8, two step reaction consisted of dehydration followed by acetylation was conducted, but the result was worse. Only 6% of AcHMF was obtained.



5
D-glucose

7
AcHMF

Entry	Conditions	Results			Others
		AcHMF	CMF	HMF	
1	HCl : EDC = 4 : 10, TBAA 1.1 eq., 100 °C, 2 h	-	trace	-	Conc. of HCl : 37 wt%
2	AcOH : HCl : EDC = 4 : 1 : 10 100 °C, 2 h	5%	20%	trace	
3	AcOH : H_2SO_4 : EDC = 4 : 1 : 10 100 °C, 2 h	-	-	-	Conc. of HCl : 97 wt%
4	AcOH : H_2SO_4 : EDC = 4 : 1 : 10 100 °C, 5 min	Trace	-	-	Conc. of H_2SO_4 : 10 wt%
5	AcOH : H_2SO_4 : EDC = 4 : 1 : 10 100 °C, 10 min	Trace	-	-	
6	AcOH : H_2SO_4 : EDC = 4 : 1 : 10 100 °C, 2 h	Trace	-	trace	
7	AcOH, EDC, Ac_2O, 100 °C, 3 h	9%	-	-	-
8	1. AcOH, EDC, 100 °C, 3 h 2. DMAP, Ac_2O, rt, 4 h	6%	-	-	2 step

Table 1. The screening of biphasic synthesis of AcHMF

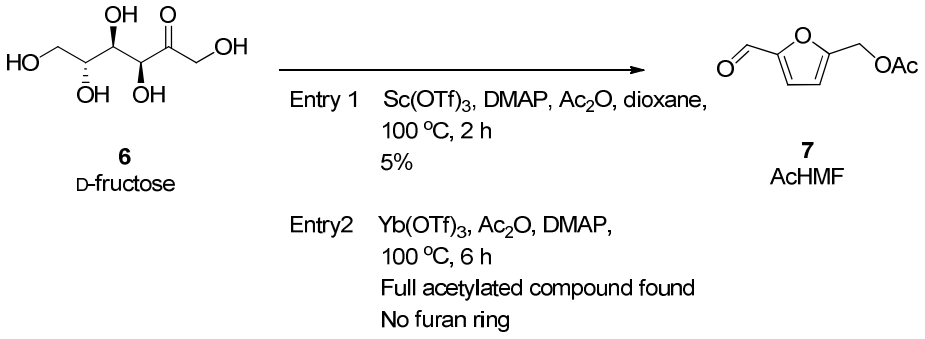
(The concentration of HCl in entry 1,2 is 37 wt%; H_2SO_4 in entry 3 is 97 wt%, H_2SO_4 in entry 4-6 is 10 wt%)

The most important factor of these reactions might be the clear division of two layers. But at this time, contrary to synthesis of CMF, the conditions can't be called biphasic reaction because acetic acid or acetic anhydride can be mixed with both water and organic solvent. So, it was concluded that this concept, biphasic reaction is not proper for synthesis of AcHMF. Also, because D-glucose has to undergo isomerization

into D-fructose in order to form furfural, using D-glucose will be worse. So, starting material should be D-fructose.

2.1.2. Acid catalyzed dehydration

Synthesis of AcHMF was tried by several ways using acids. At first, Lewis acid, especially rare earth metal triflate was considered, but those catalysts work best in DMSO solvent. Because this research has started to compensate the defects of HMF including using DMSO as solvent, dioxane was used instead in entry 1 of Scheme 3. Contrast to synthesis of HMF, DMAP and acetic anhydride were added. But only 5% of AcHMF was obtained. Without using DMSO, no better yield was expected. In entry 2, acetic anhydride was chosen as a solvent, but only acetylation occurred. Rare earth metal triflate might be eco-friendly catalyst for synthesis of HMF, but in that situation, more trials seemed to be useless.

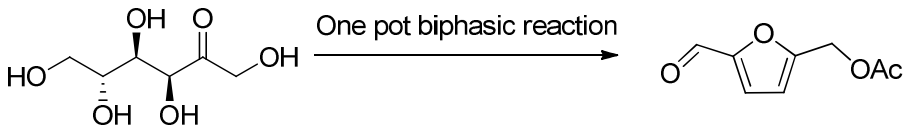


Scheme 3. Synthesis of AcHMF using rare metal triflate

So, strong sulfuric acid was chosen instead. The conditions described in Table 2, are similar with those from Table 1, which were for biphasic process. But this time, EDC was used just as solvent.

The reaction conditions were screened for amount of reagents, temperature and time. Through entry 1 to 7, the amount of sulfuric acid, and the ratio of acetic acid and EDC were kept same. At 80 ℃, the yields increased as the reaction times increased. (Entry 1−3) Entry 3,4 show that the amount of acetic anhydride doesn't affect the result. By increasing reaction temperature up to 100 ℃ (entry 5) the yield declined a little. By decreasing the reaction temperature to 65 ℃ (entry 6,7) the yield declined a lot. The longer reaction time than 3.5 hours (entry 7) didn't affect the yield. In entry 8, only acetic anhydride was used with sulfuric acid without acetic acid or EDC, but no AcHMF was obtained. By changing the ratio of reagents in entry 9 and the amount of sulfuric acid, the yield was higher. In table 2, the highest yield was obtained in entry 9, when using acetic acid−acetic anhydride (7:3) solution and 0.1 equivalent of sulfuric acid at 80 C for 3 hours. But the yield was still disappointing.

With those methods explained above, just screening of conditions would not give us meaningful result. So, a new strategy was needed at that point.



6
D-fructose

7
AcHMF

Entry	Reagents				Temp(°C)	Time (h)	Yield
	AcOH	Ac_2O	H_2SO_4	EDC			
1	8 ml	1 ml	0.3 eq.	8 ml	80	0.5	7%
2						2	12%
3						3.5	21%
4		2 ml					21%
5		1 ml			100	3.5	18%
6					65		6%
7						12	6%
8	-	10 ml		-	80	3	No product
9	7 ml	3 ml	0.1 eq.	-			32%

Table 2. The screening of acidic conditions to synthesize AcHMF

(The reaction was carried out in pressure tube at oil bath)

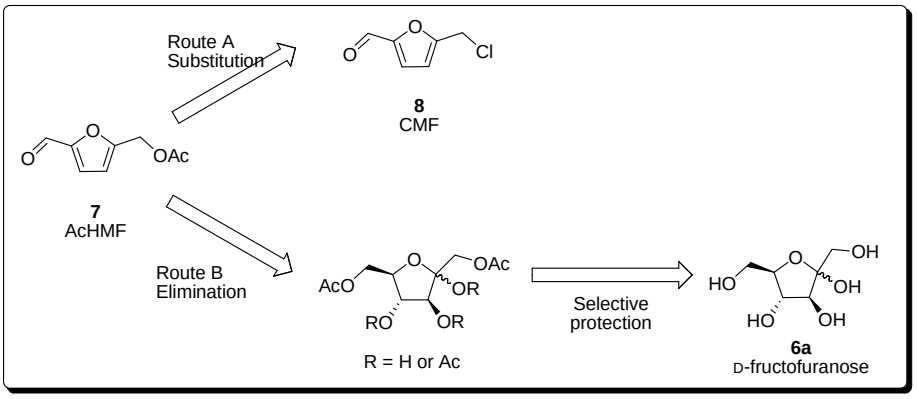
2.2. Designing new strategies

By the mechanism in figure 3, it can be assumed that HMF would be the intermediate of the direct conversion of AcHMF from D-fructose. So, those methods for direct synthesis of AcHMF would never win the previous methods to synthesize HMF in the aspects of efficiency or eco-friendliness. Also, because this research was started to compensate the defects of HMF, if a new method includes formation of HMF, the essence of the research will be same as previous studies and there will be no meaning. So, a new, novel strategy to

obtain AcHMF considering those points explained above should arise.

In this paper, synthesis of AcHMF was conducted by two ways. (Scheme 4) In route A, AcHMF will be converted from CMF (**8**), which is known as an available compound that can be synthesized from fructose or glucose, even from cellulose, by a very efficient method. Also, AcHMF will be synthesized from fructose through 2-step: Selective protection at 1,6-position to fix fructose to furanose-form, followed by elimination.

There are lots of papers introducing methods to synthesize CMF (8) with high yields. Although we don't have proper apparatus to reproduce the yields from references, we could obtain CMF from fructose with moderate yields, 58 to 64 %. (See scheme 2) With obtained CMF, AcHMF was synthesized using very efficient method. (Route A)



Scheme 4. Retro-synthetic schemes of new strategies

The concept of previous trials in this paper was to introduce the furfural base first by dehydration of D-fructose and next change the hydroxyl group to acetyl group by substitution. At this time, pre-protection of D-fructose for fixed furanose state and following elimination (or dehydration) of other functional groups attached directly on the furan ring will be carried out to yield AcHMF. (Route B) Former studies of HMF synthesis have revealed that driving D-fructose into furanose during tautomerization as much as possible would improve the yield. Those researches chose solvents like DMSO or ionic liquids stabilizing the furanose state of D-fructose through intramolecular hydrogen-bonding between HO-1 and HO-4. Avoiding using DMSO or ionic liquids, selective protection was thought to be another way to drive D-fructose into furanose state and following dehydration would complete the synthesis of AcHMF.

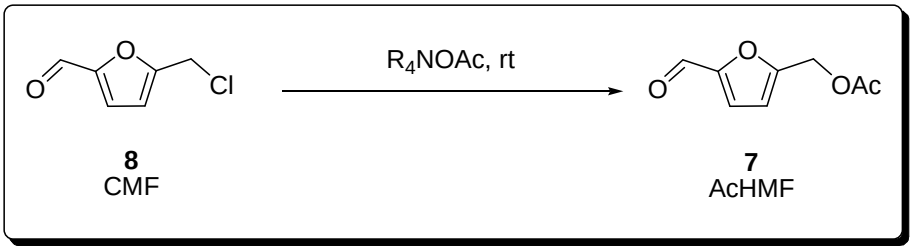
2.3. Effective conversion of AcHMF from CMF

In most of the references introducing methods for synthesis of CMF with high yields, the processes were based on the flow reactor system. But in usual organic chemistry laboratories where most reactions are occurred in round-

bottomed flask, that process is not easy to reproduce. So, we synthesized CMF with yields 58 to 64%, by modified biphasic reaction and manual extraction. (See 2.1.1.) With obtained CMF, various trials to obtain AcHMF were conducted. There is a patent introducing a method converting CMF into AcHMF using acetic acid and potassium carbonate in acetonitrile with 50% yield.[30] That yield is not high enough and not even reproduced easily. Low yield might be resulted from the low reactivity of acetic acid in substitution reaction. Other reagents like sodium acetate or potassium acetate were tried as an acetyl donor, but there was a problem. The acetyl donor like NaOAc, KOAc dissolves in water much more easily than organic solvents, contrary to CMF which is too hydrophobic to be mixed with water. To dissolve all the reagents at once, THF was added to water as a co-solvent, but no better result was obtained. So, tetraaalkylammonium acetate was considered as both a acetyl donor and phase transfer catalyst. Some of solvents and teteraalkylammonium acetate were screened as described in table 3. The best result is more than 95% yield within 5 minutes under room temperature when tetrabutylammonium acetate and acetonitrile were used. When ammonium acetate was used, no reaction occurred (entry1). Using tetramethylammnonium acetate, high yield was obtained, but the reaction time was longer than using tetrabutylammonium acetate (entry 2). When tetraethylammnoium acetate was

used, the yield was much lower because the reagent we used was hydrate form (entry 3). Using DCM as a solvent instead of acetonitrile, the reaction time was still short as entry 4, but the yield was much lower (entry 5).

In short, the best result, 97% of AcHMF within 5 minutes was obtained by using tetrabutylammonium acetate and acetonitrile at room temperature. The yield of CMF from fructose was not that high in this paper, but as mentioned by many papers, CMF can be obtained from fructose with high yield when flow reactor is used. So, using tetraalkylammonium acetate is an efficient method to synthesize AcHMF from CMF, which is available from fructose.



Entry	Reagent	Solvent	Time	Yield
1	AA (H_4NOAc)	MeCN	-	No reaction
2	TMAA (Me_4NOAc)		< 30 min	96%
3	TEAA (Et_4NOAc)		< 30 min	67%
4	TBAA (Bu_4NOAc)		< 5 min	97%
5		DCM	< 5 min	79%

Table 3) The screening of tetraalkylammonium acetate and solvent to convert CMF to AcHMF.

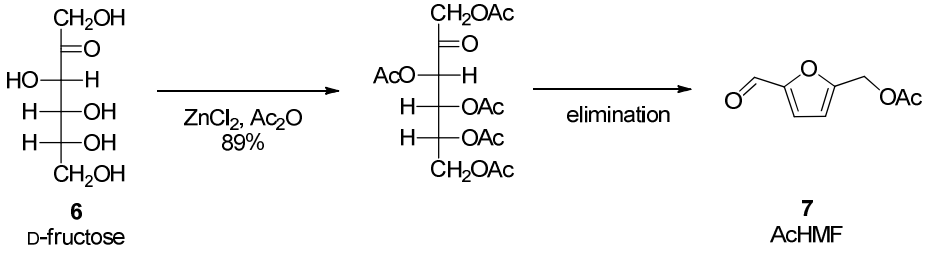
2.4. Synthesis of AcHMF via selective acetylation followed by elimination

2.4.1. Selective protection of D-fructose

Because the target is AcHMF which has acetyl group at the terminal position, selective acetyl protection was considered at first. So, selective acetylation with limited amounts (1-2 eq.) of acetic anhydride with catalyst like DMAP, zinc chloride dissolved in pyridine was tried but D-fructose pentacetate was obtained. (The results were assigned by GC-MS analysis) Remaining D-fructose which didn't react with acetic anhydride was lost during extraction. GC-MS analysis confirmed that the product is pentacetate D-fructose, but it is not certain that the product would be furanose or pyranose. So, elimination step with ytterbium triflate, a lewis acid that is useful for synthesis of HMF. At 120 ℃, D-fructose pentacetate was reacted with ytterbium triflate dissolved in DMSO for overnight (Table 3). But the results were not favorable. Only trace amount of AcHMF was checked by 1H-NMR and 58% of starting material remained. Because more than half of the starting material remained in spite of the long reaction time, next trials adopted higher temperature. Strong acids, sulfuric

acid and oxalic acid were used each in entry 2,3, but the results were disappointing. Trace amount of AcHMF was checked in entry 2, whereas in entry 3, no product or starting material found.

It was concluded that acetyl protection would not take place selectively at terminal positions of D-fructose and would not drive D-fructose into furanose form. So, more bulky protecting groups that can be attached on only primary alcohols should be considered.



6
D-fructose

7
AcHMF

Entry	Acid	Solvent	Temp (^{o}C)	Time (h)	Results
1	$Yb(OTf)_3$	DMSO	120	12	AcHMF trace SM 58% recovered
2	H_2SO_4		150	15	AcHMF trace
3	Oxalic acid				No AcHMF

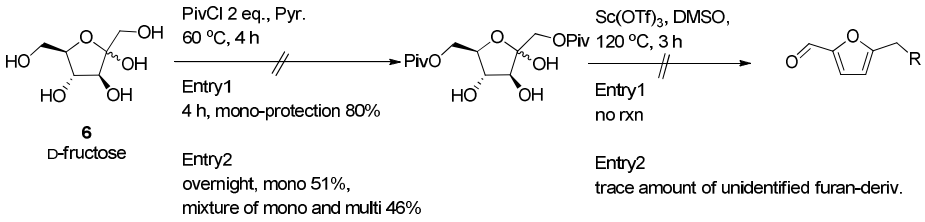
Table 4. Acid screening of elimination reaction of pentacetate fructose
(The product of acetylation of fructose was assigned by GC-MS. The real structure of it, whether it is furanose or pyranose, was not clear)

2.4.1.1. Selective protection with bulky protecting groups

Bulky protecting group was considered for synthesizing 1,6-protected fructofuranose. With bulky protecting groups, protection at the secondary hydroxyl groups on the skeletal of fructose ring whichever furanose or pyranose, would be difficult, so selective protection at primary alcohol could be possible. It there is more than 2 equivalent of protecting reagent and it react with D-fructose entirely, D-fructose should exist as furanose which has 2 primary hydroxyl groups whereas pyranose has only one primary hydroxyl group.

Bulky pivaloyl group was selected and pivaloyl chloride was used to pivaloyl protection. The results of trials were assigned by proton NMR, especially by the ratio of protons of pivaloyl groups and protons on the skeleton of fructose. When only 2 equivalents of pivaloyl chloride were used in 6 hours, 80% of mono protected product was obtained. After that, overnight reaction was carried out too, but the result was so difficult to assign. By column chromatography, the reaction mixture was separated, and 51% of mono protected compound was checked, and mixture of multi protected compounds was found. After that, the reactivity of resulted compound was checked by reaction with scandium triflate in DMSO. But, with both mono protected

one and mixture of multi protected ones, there was almost no reaction. (Scheme 5) Because of the low reactivity of pivaloyl-protected fructose, this trial was stopped.

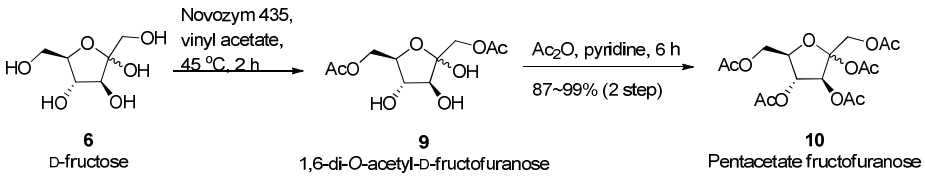


Scheme 5. Pivaloyl protection followed by dehydration

2.4.1.2. Selective protection with lipase

Nicolosi group has presented a paper about the preparation of regio-protected D-fructose derivatives. In this paper, selective acetylation at 1,6-hydroxyl groups of D-fructose was conducted using lipase from *C. antarctica* B in THF. A resin called Novozym 435 (immobilized lipase from *C. antarctica* B) was purchased from Sigma Aldrich. With the same procedure Nicolosi group presented, highly viscous transparent syrup was obtained. In that paper, no further purification was taken place, only filtration to get rid of resin was carried out after reaction. But the analysis of crude product didn't go well because the 1H-NMR of it was not exactly same as the data

from the Nicolosi's paper. So, GC-MS analysis was carried out. Because the result didn't show the mass of the compound, it was confusing that the resulting compounds is whether desired one or mono-acetylated compound. It the compound obtained was mono-acetylated fructose, it can't be said that the product is furanose. To analyze more concisely, further purification by column chromatography was carried out, but because of the instability of the compounds, the amount of the sample diminished and the peaks of 1H-NMR was still too complicated to assign correctly. So, further acetylation was carried out by reaction of unidentified product and acetic anhydride in pyridine at room temperature. The 2-step yield was 80 to 99% and the 1H-NMR of purified compound was matched correctly with the data of the reference.[31] In conclusion, by reaction with lipase from *C. antarctica* B, vinyl acetate in THF, selective acetylation at 1,6-position of fructofuranose was carried out successively. With these fixed furanose derivatives, simple further elimination would synthesize AcHMF.



Scheme 6. Selective acetylation catalyzed by lipase[31]

2.4.2. Elimination step to obtain AcHMF

Early plan to synthesize AcHMF was 2-step reaction, acetylation at 1,6-position followed by dehydration. But as we have obtained pentacetate fructofuranose, 3-step reaction was considered too. Synthesis of AcHMF including lipase-catalyzed selective acetylation was conducted by 2 ways.

2.4.2.1. Elimination from pentacetate fructo-furanose

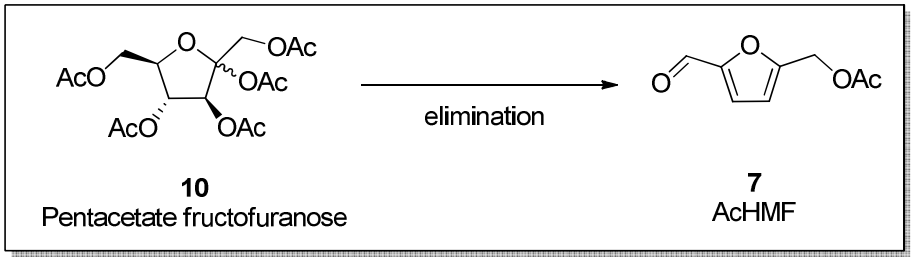
With pentacetate fructofuranose, elimination of acetic acid was tried by few ways. Because acetyl group is a good leaving group when it has adjacent proton, so thermal elimination seemed to be occur easily. Trials for thermal elimination are described in Table 4. Pentacetate fructofuranose was mixed with acetic acid under 100 ℃ and stirred for 1 day, but no reaction occurred. Next, neat conditions under vacuum for removal of acetic acid formed by thermal elimination, were carried out at 120 ℃ and 150 ℃, but still nothing happened. The vacuum was useless because the temperature 150 ℃ might be not enough to eliminate the acetic

acid, so micro wave reactor was used which can heat and give some pressure on the reaction mixture, but nothing happened.

Entry	Conditions	Results
1	AcOH, 100 °C, 24 h	No reaction
2	Neat, 120 °C, vacuum	
3	Neat, 150 °C, vacuum	
4	Microwave, MeCN, 130 °C	

Table 5. Thermal elimination of pentacetate fructofuranose

So, acid catalyzed elimination was tried by several ways. (Table 5) But because of the high stability of pentacetate fructofuranose, starting material remained in most conditions. Using TsOH, only 1% of AcHMF was obtained with 28% of starting material recovered. When sulfuric acid was used, 19% of AcHMF and 17% of starting material were separated. Using TFA no reaction occurred. With Dowex (50W X8), only trace amount of unidentified furan derivative was checked by crude proton NMR and GC-MS. Pentacetate fructofuranose is much stable than 1,6-di-*O*-acetylfructofuranose, but on the other way, its reactivity is too low.



Entry	Acid	Solvent	Temp	Results
1	TsOH	Dioxane	Reflux	SM 28% recovered, AcHMF 1%
2	H_2SO_4			SM 17% recovered, AcHMF 19%
3	TFA			No reaction
4	Dowex	THF		Trace amount of unidentified furan derivatives

Table 6. Acid catalyzed elimination of pentacetate fructofuranose

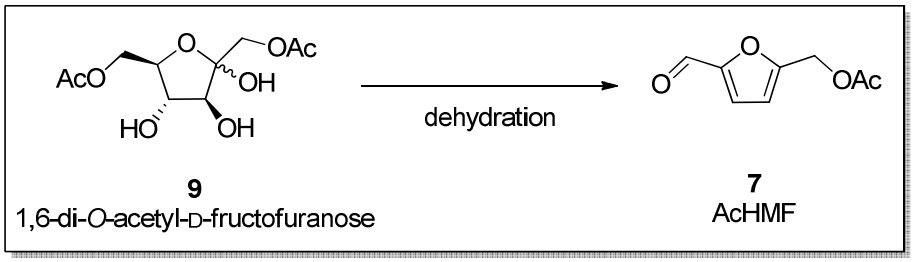
2.4.2.2. Dehydration of 1,6-di-*O*-acetyl-fructofuranose

1,6-di-*O*-acetyl-fructofuranose (**9**) is so unstable that it decomposes in silica gel during column chromatography but which means that its reactivity will be high instead. Dehydration of **9** was tried by various ways. In Entry 1,2, reactions with scandium triflate in dioxane at different temperature was carried out. At 80 ℃, 13% of AcHMF and with trace amount of HMF were obtained, and at 90 ℃, only 23% of HMF was isolated. In entry 3, Dowex (50W X8) was used in

THF and the mixture was stirred for 9 hours. Trace amount of AcHMF and 99% of starting material was isolated. After that, the reaction time was increase to 1 day, and less than 1% of AcHMF and 55% of HMF were obtained. Because AcHMF was the desired product, 2-step reaction, Dowex catalyzed dehydration followed by acetylation was carried out in entry 5, yielding 42% of AcHMF. (Table 6) Using Dowex is very simple and efficient method, but the yields were not that satisfying. So, other acids were used for screening. (Table 7)

In entry 1,2, TFA was used as a solvent or a catalyst, but no reaction occurred. 0.1 or 1.0 equivalent of sulfuric acid was used in dioxane in 5 or 12 hours. Except entry 3 which obtained 17% of AcHMF only, AcHMF and HMF were obtained together. In entry 4, with 1.0 equivalent of sulfuric acid within 12 hours, 36% of AcHMF and 24% of HMF were obtained, and total yield is 60%. Entry 5,6 obtained total yield (sum of yields of AcHMF and HMF) 43 to 48%. In entry 7,8, benzenesulfonic acid was used and AcHMF was obtained with not isolable side compounds. In entry 7, 42% of AcHMF was obtained and the isolated AcHMF was analyzed by GC-MS, showing that the purity is 78%. In entry 8, only 10% of AcHMF was obtained and of the sample, only 86% was AcHMF. In entry 8, 24% of HMF was obtained also. In entry 9,10, 2,4-dinitrotoluene-6-sulfonic acid, which is very acidic, was used but the results were not good. In entry 9, only 20% of AcHMF was obtained

with trace amount of HMF, and in entry 10, trace amount of both were found. Among the results, entry 4 in table 7 is the best result, yielding 36% of AcHMF and 24% of HMF together.



9
1,6-di-*O*-acetyl-D-fructofuranose

7
AcHMF

Entry	Conditions	Results
1	$Sc(OTf)_3$, dioxane, 80 °C	AcHMF 13%, HMF trace
2	$Sc(OTf)_3$, dioxane, 90 °C	HMF 23%
3	Dowex, THF, 9 h, reflux	AcHMF trace, SM 99% recovered
4	Dowex, THF, 12 h, reflux	AcHMF <1%, HMF 55%
5	1. Dowex, THF, 12 h, reflux 2. DMAP, Ac_2O, pyridine, rt, 6 h	AcHMF 42%

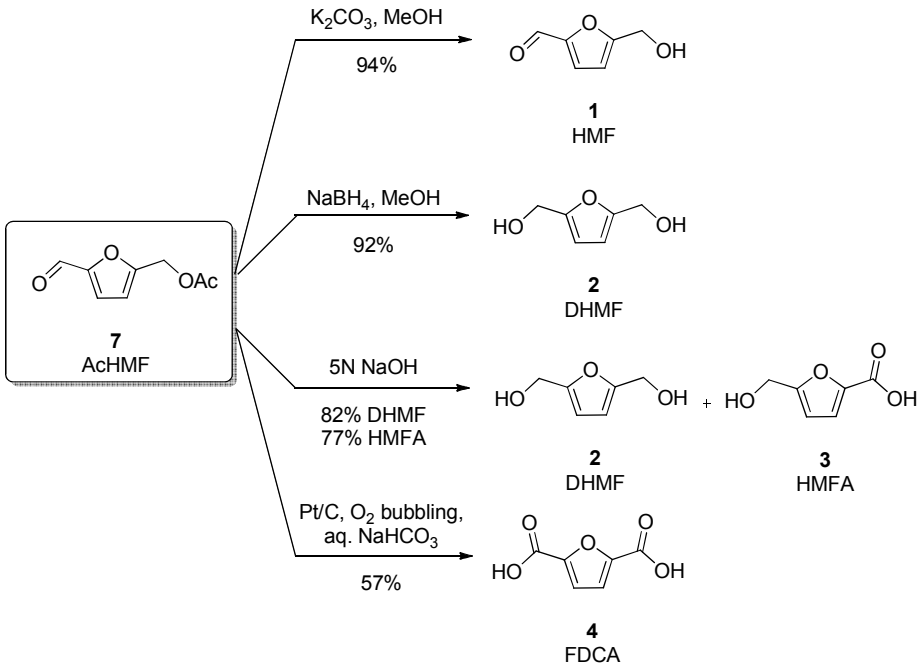
Table 7. Acid screening for dehydration of 1,6-di-*O*-acetyl fructofuranose (**1**)

Entry	Acid		Solvent	Temp.	Time	Results	
	Name	Eq.				AcHMF	HMF
1	TFA	Excess	TFA	Reflux	24 h	No reaction	
2		0.1	Dioxane				
3	H_2SO_4	1.0			5 h	17%	-
4					12 h	36%	24%
5		0.1			5 h	16%	30%
6					12 h	18%	25%
7	$C_6H_5SO_3H$	1.0			24 h	42% (78%GCMS)	-
8		0.1				10% (86%GCMS)	24%
9	2,4-dinitrotoluene-6-sulfonic acid	1.0				20%	trace
10		0.1				trace	trace

Table 8. Acid screening for dehydration of 1,6-di-*O*-acetyl fructofuranose (**2**)

2.5. The application of AcHMF

HMF is useful for synthesizing useful derivatives like DHMF (**2**), HMFA (**3**), or FDCA (**4**). (Scheme 7) To be an alternative of HMF, derivatives should be synthesized from AcHMF with similar conditions. In figure 11, the applications of AcHMF are described. Using potassium carbonate in methanol, AcHMF is converted into HMF with 94% yield. Reduction using sodium borohydride in methanol yields DHMF (**2**) with 92% yield. Cannizzaro reaction of AcHMF using sodium hydroxide yields 41% of DHMF and 38% of HMFA each. (Cannizzaro reaction yields alcohol and acid with 1:1 ratio.)[32] Also, FDCA (**4**) can be obtained from AcHMF by platinum catalyzed oxidation.



Scheme 7. Derivatization of AcHMF

3. Conclusion

HMF (**1**) is a very useful, reactive organic liquid which is regarded as a promising renewable resource. But HMF has some defects because of its high hydrophilicity and instability. So AcHMF (**7**) is recommended as an alternative of HMF in this paper. AcHMF is hydrophobic and more stable than HMF, and also, it can be used as a starting material for useful furan based compounds like DHMF (**2**), HMFA (**3**) and FDCA (**4**). The synthesis of AcHMF can adopt one-pot reaction, but the best yield was only 32%. This paper suggested two methods to obtain AcHMF. First one is to convert a compound called CMF, Cl-derivative of HMF, to AcHMF efficiently. CMF can be synthesized from fructose with high yields but its application was not that high as HMF. But in this paper, the usage of CMF was proved by introducing an efficient method for synthesis of AcHMF from CMF. The method used tetraalkyammonium acetate as both a reagent and a phase transfer catalyst and the reaction time was very short, and the yield was so high. Another new strategy for synthesis of AcHMF is pre-acetylation at 1,6-positions followed by elimination. In this paper, lipase from *C. antarctica* B was used for selective acetylation to get 1,6-di-*O*-acetyl fructofuranose (**9**). Compound **9** was confirmed after further acetylation, yielding pentaceate fructofuranose (**10**), of which proton NMR matched with the proton NMR from reference. The elimination step was

carried out from both **9** and **10**, but because of the low reactivity of **10**, only dehydration from **9** yielded significant results. Using Dowex (50W X8), HMF was obtained with 55% yield, and 43% of AcHMF was synthesized by 2-step reaction: Dowex catalyzed dehydration followed by acetylation of HMF. When sulfuric acid was used as a catalyst, the best results was 36% of AcHMF and 24% of HMF together: the total yield is 60%. The methods introduced in this paper have only moderate yields, but they are meaningful because DMSO or ionic liquids are not used at all, and eco-friendly lipase is used instead. If the yield in dehydration step is enhanced, it will be more meaningful.

4. Experimental Section

5-Chloromethylfurfural, CMF (8)

Method A - Manual extraction: Lithium chloride (2.1 g) was dissolved in concentrated hydrochloric acid (10mL) and fructose (0.43 g, 2.4 mmol) was added to the solution, which was kept at 65 °C. The reaction mixture was manually extracted with dichloromethane (100 mL) after 25, 60, and 100 min. After 100 min, the reaction was stopped and the extracts were concentrated. The residual oil was purified by column chromatography (silica gel; *n*-hexane/ethyl acetate, 2:1) to give pale yellow oil, **8** (58%).

Method B – Biphasic synthesis: Fructose (1.08 g, 10 mmol) was dissolved in concentrated hydrochloric acid (4 ml) and ethylene dichloride (8 ml) was added to the solution, which was kept in pressure tube at 100 °C oil bath. The reaction mixture was stirred for 2 hours, the reaction was stopped and the pressure tube was cooled off at room temperature. The reaction mixture was extracted with dichloromethane (100 ml) and the extracted were dried with sodium sulfate, filtered, and concentrated. The residual oil was purified by column chromatography (silica gel; *n*-hexane/ethyl acetate, 2:1) to give pale yellow oil, **8** (59-64%).

R_f=0.70 (*n*-Hex-EA 1:4). ^{1}H NMR (400MHz, $CDCl_3$) δ 9.647 (s, 1H, H-1), 7.2165 (d, 1H, $J_{2,3}$ 3.6, H-2), 6.5975 (d, 1H, $J_{3,2}$ 3.6, H-3), 4.622 (s, 2H, H-4). ^{13}C NMR (400MHz, $CDCl_3$) δ 177.77 (s, C-1), 156.07 (s, C-5), 152.88 (s, C-2), 121.67 (s, C-3), 111.93 (s, C-4), 36.51 (s, C-6).

1,6-di-O-acetyl fructofuranose (9)

Lipase from *C. antarctica* B (Novozym 435, 40mg) was added to a solution of fructose (**6**) (40mg) in tetrahydrofuran (4mL) containing vinyl acetate (3

equiv.) as acyl donor. The suspension was stirred at 45 °C, and the progress was monitored by TLC (n-Hexane–Ethyl acetate, 1:4). After 2h the reaction was quenched, filtering off the catalyst and the filtrate evaporated to dryness in vacuum to give compound **9** as pale yellow syrup. No further purification was done. The assignment was done after **10** was synthesized.

Pentacetate fructofuranose (10)

1,6-Di-*O*-acetyl fructofuranose **9** (500mg) was dissolved in 10mL of pyridine and 10mL of Ac_2O. The solution was stirred at room temperature for 6h and then evaporated to dryness in vacuo to give compound crude oil. The crude oil was purified by column chromatography (silica gel; *n*-hexane/ethyl acetate, 2:1) to give pale yellow syrup, **10** (87-99% in 2-step from D-fructose) in α/β 1:1.4 mixture. (The ratio is not same all the time) R_f=0.71 (*n*-Hex-EA 1:4). ^{1}H NMR(400MHz, $CDCl_3$) α anomer: 5.85 (d, 1H, $J_{3,4}$ 4.1Hz, H-3), 5.14 (dd, 1H, $J_{4,5}$ 6.3Hz, H-4), 4.62 (d, 1H, $J_{1a,1b}$ 12.0Hz, H-1_a), 4.51 (ddd, 1H, $J_{5,6a}$ 3.6, $J_{5,6b}$ 5.7, H-5), 4.40 (dd, 1H, $J_{6a,6b}$ 12.2Hz, H-6 a), 4.35 (d, 1H, H-1_b), 4.17 (dd, 1H, H-6_b), 2.16 (s, 3H, $COOCH_3$), 2.11 (s, 3H, $COOCH_3$), 2.10 (s, 6H, 2-$COOCH_3$), 2.07 (s, 3H, $COOCH_3$); β anomer: 5.69 (dd, 1H, $J_{4,3}$ 2.2, $J_{4,5}$ 9.0Hz, H-4), 5.50 (d, 1H, H-3), 5.22 (ddd, 1H, $J_{5,6a}$ 2.7, $J_{5,6b}$ 4.9Hz, H-5), 4.92 (d, 1H, $J_{1a,1b}$ 17.3Hz, H-1_a), 4.68 (d, 1H, H-1_b), 4.29 (dd, 1H, $J_{6a,6b}$ 12.6Hz, H-6_a), 4.12 (dd, 1H, H-6_b), 2.20 (s, 3H, $COOCH_3$), 2.11 (s, 3H, $COOCH_3$), 2.10 (s, 6H, 2-$COOCH_3$), 2.08 (s, 3H, $COOCH_3$).

5-*O*-Acetylhydroxymethylfurfural, AcHMF (7)

Method A – Reactions in pressure tube: Lithium chloride (6.23 g) was dissolved in concentrated hydrochloric acid (10 mL) and fructose (1.23 g) was added to the solution, which was kept at 65 °C. The reaction mixture was manually extracted with dichloromethane (100 mL) after 25, 60, and 100 min.

After 100 min, the reaction was stopped and the extracts were concentrated. The residual oil was purified by column chromatography (silica gel; *n*-hexane/ethyl acetate, 2:1) to give pale yellow oil, **8** (58%).

Method B – Reactions with reflux condensor: Fructose (1.08 g, 10 mmol) was dissolved in concentrated hydrochloric acid (4 ml) and ethylene dichloride (8 ml) was added to the solution, which was kept in pressure tube at 100 °C oil bath. The reaction mixture was stirred for 2 hours, the reaction was stopped and the pressure tube was cooled off at room temperature. The reaction mixture was extracted with dichloromethane (100 ml) and the extracted were dried with sodium sulfate, filtered, and concentrated. The residual oil was purified by column chromatography (silica gel; *n*-hexane/ethyl acetate, 2:1) to give pale yellow oil, **8** (59-64%).

Method C – Started from 1,6-di-*O*-acetyl fructofuranose*:* Solvent (dioxane or THF, 10 ml) was added to 1,6-di-*O*-acetyl fructofuranose (0.26 g, 1 mmol) and then acid (Dowex 50W X8, H_2SO_4, TFA, $Sc(OTf)_3$, benzenesulfonic acid, or 2,4-dinitrotoluene-6-sulfonic acid) was added. The reaction mixture was stirred in reflux condition. The progress was checked by TLC. When the spot of starting material disappeared in TLC plate, the reaction mixture was poured into a round-bottomed flask and the solvent was evaporated. The residue was extracted with ethyl acetate (200 ml), dried over with sodium sulfate, filtered off, and concentrated. The residual oil was purified by column chromatography (silica gel; *n*-hexane/ethyl acetate, 2:1) to give pale yellow oil, **7** and **1**. The each yield is written on the Tables in Results and discussion section.

Method D – Started from pentacetate fructofuranose*:* Solvent (dioxane or THF, 10 ml) was added to pentacetate fructofuranose (0.40 g, 1 mmol) and then

acid (Dowex 50W X8, H_2SO_4, TFA, or *p*-toluenesulfonic acid) was added. The reaction mixture was stirred in reflux condition. The progress was checked by TLC. When the spot of starting material disappeared in TLC plate, the reaction mixture was poured into a round-bottomed flask and the solvent was evaporated. The residue was extracted with ethyl acetate (200 ml), dried over with sodium sulfate, filtered off, and concentrated. The residual oil was purified by column chromatography (silica gel; *n*-hexane/ethyl acetate, 2:1) to give pale yellow oil, **7** and **1**. The each yield is written on the Tables in Results and discussion section.

R_f=0.81 (*n*-Hex-EA 1:4). ^{1}H NMR (400MHz, $CDCl_3$) δ 9.644 (s, 1H, H-1), 7.259 (d, 1H, $J_{2,3}$ 3.2, H-2), 6.6305 (d, 1H, $J_{3,2}$ 3.6, H-3), 5.137 (s, 2H, H-4), 2.116 (s, 3H, H-5). ^{13}C NMR (400MHz, $CDCl_3$) δ 177.84 (s, C-1), 170.27 (s, C-7), 155.50 (s, C-5), 152.85 (s, C-2), 121.96 (s, C-3), 112.63 (s, C-4), 57.80(s, C-6), 20.65 (s, C-8).

5-Hydroxymethylfurfural, HMF (1)

K_2CO_3 (0.022 g, 0.16 mmol) was dissolved in methanol (1.5 ml), and then AcHMF (0.188 g, 1 mmol) was added in the solution. The mixture was stirred for one hour at room temperature, and then the solvent was removed using rotary evaporator. The crude mixture was extracted with brine, ethyl acetate (200 ml), dried over with sodium sulfate, filtered off, and concentrated. The residual oil was purified by column chromatography (silica gel; *n*-hexane/ethyl acetate, 2:1) to give pale yellow oil, **1** (94%).

R_f=0.55 (*n*-Hex-EA 1:4). ^{1}H NMR (400MHz, $CDCl_3$) δ 9.618 (s, 1H, H-1), 7.2275 (d, 1H, $J_{2,3}$ 3.6, H-2), 6.5325 (d, 1H, $J_{3,2}$ 3.6, H-3), 4.738 (d, 2H, H-4), 1.976 (t, 1H, OH). ^{13}C NMR (400MHz, $CDCl_3$) δ 177.62 (s, C-1), 160.27 (s, C-5), 152.46 (s, C-2), 122.53 (s, C-3), 110.03 (s, C-4), 57.75 (s, C-6).

Reduction of AcHMF to DHMF (2)

Dissolve sodium borohydride (1.1 eq.) to methanol, and then add AcHMF (0.168 g, 1 mmol). The mixture was stirred at room temperature in one hour, and the solvent was evaporated. The crude oil was extracted with ethyl acetate (200 ml), dried over with sodium sulfate, filtered off, and concentrated. The residual oil was purified by column chromatography (silica gel; *n*-hexane/ethyl acetate, 1:1) to give white solid, **2** (92%).

R_f=0.41 (*n*-Hex-EA 1:4). ^{1}H NMR (400MHz, MeOD-d_4) δ 6.238 (s, 1H), 4.487 (s 2H). ^{13}C NMR (400MHz, MeOD-d_4) δ 154.37(s, C-2), 107.72 (s, C-3), 56.06 (s, C-1).

Cannizzaro reaction of AcHMF to DHMF (2) and HMFA (3)

At 0 ^{o}C ice bath, AcHMF (0.168 g, 1 mmol) was added in 1 mL of 5N NaOH aqueous solution by dropwise. And then, the reaction mixture was warmed up to room temperature and stirred for 1 hour. After that, the mixture was neutralized to pH 7 and extracted with ethyl acetate (200 ml). The organic layer contains DHMF and aqueous layer contains HMFA. And then the aqueous layer at the extraction step was acidified with 1N HCl to pH 2 and extracted with ethyl acetate (400 ml). Both the organic and aqueous layers were dried over sodium sulfate, filtered off, and concentrated. Each residual oil was purified by column chromatography (silica gel; *n*-hexane/ethyl acetate, 2:1) to give white solid, **2** (41% based on starting material) and pale yellow solid, **3** (38.5% based on starting material). The data of DHMF is explained above. Only the data of HMFA is explained here.

R_f=0.81 (*t*-BuOH : AcOH : H_2O = 8:1:1). ^{1}H NMR (300MHz, acetone-d_6) δ 7.16 (d, 1H, $J_{2,3}$ 3.4, H-2), 6.47 (d, 1H, $J_{3,2}$ 3.4, H-3), 4.59 (s, 2H, H-4); ^{13}C

NMR (300MHz, acetone-d_6) δ 160.9, 159.5, 144.9, 119.6, 109.6, 57.3.

Oxidation of AcHMF to FDCA (4)

Dissolve AcHMF (0.18g, 1.07 mmol) in saturated aqueous $NaHCO_3$ solution (11 ml) and then add Pt/C (0.25 g, 1 eq.). The mixture was stirred with oxygen gas bubbling at 75 ^oC oil bath in 3 hours. The reaction mixture was cooled off and acidified with 1N HCl solution. The solvent was removed by rotary evaporator at high temperature. The crude product was purified by precipitation with ether to give white solid, **4** (58%).

R_f=0.21 (*t*-BuOH : H_2O : AcOH = 8:1:1). ^1H NMR (400MHz, MeOD-d_4) δ 7.262 (s, 2H). ^{13}C NMR (400MHz, MeOD-d_4) δ 159.50 (s, C-1), 147.39 (s, C-2), 118.03 (s, C-3).

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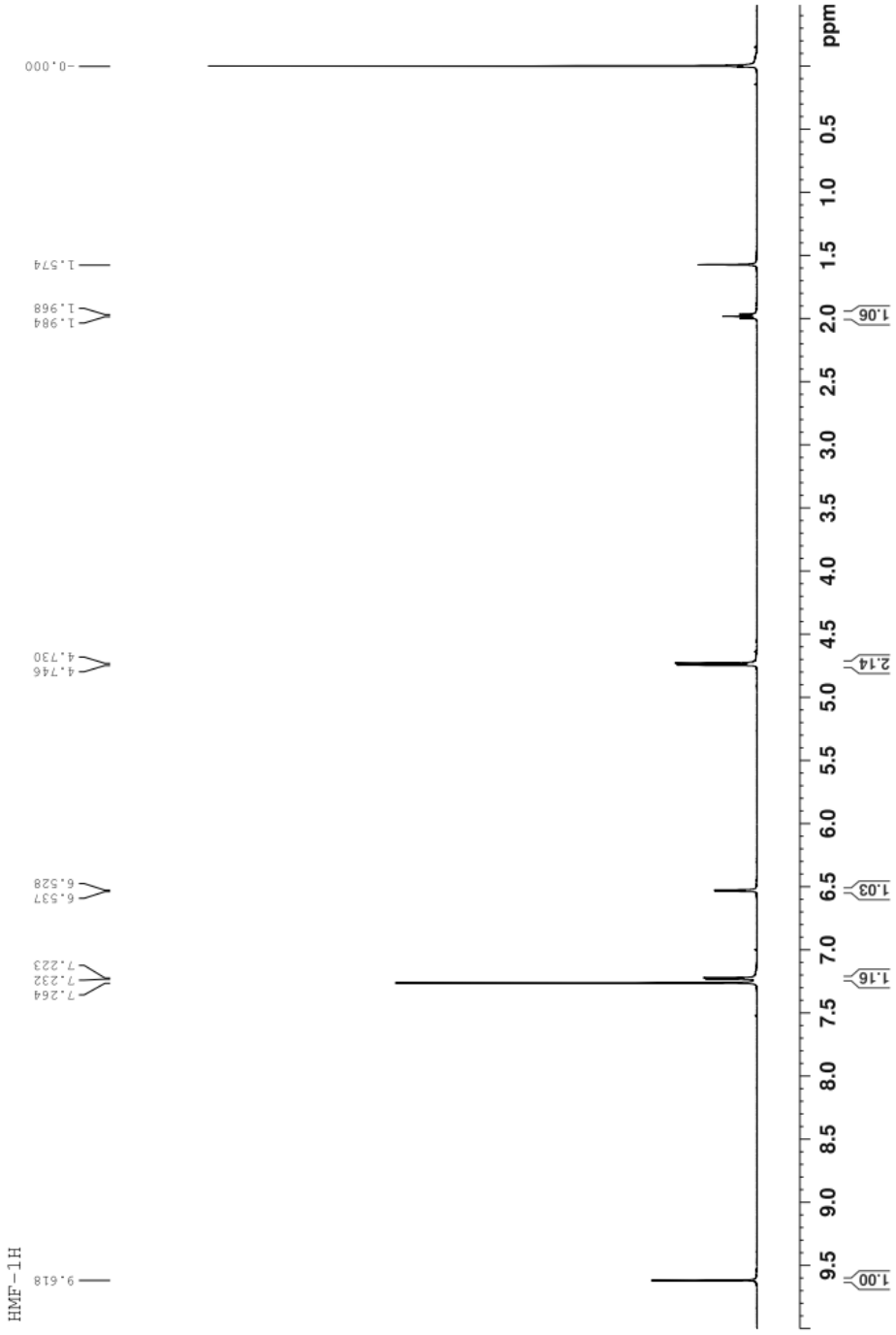
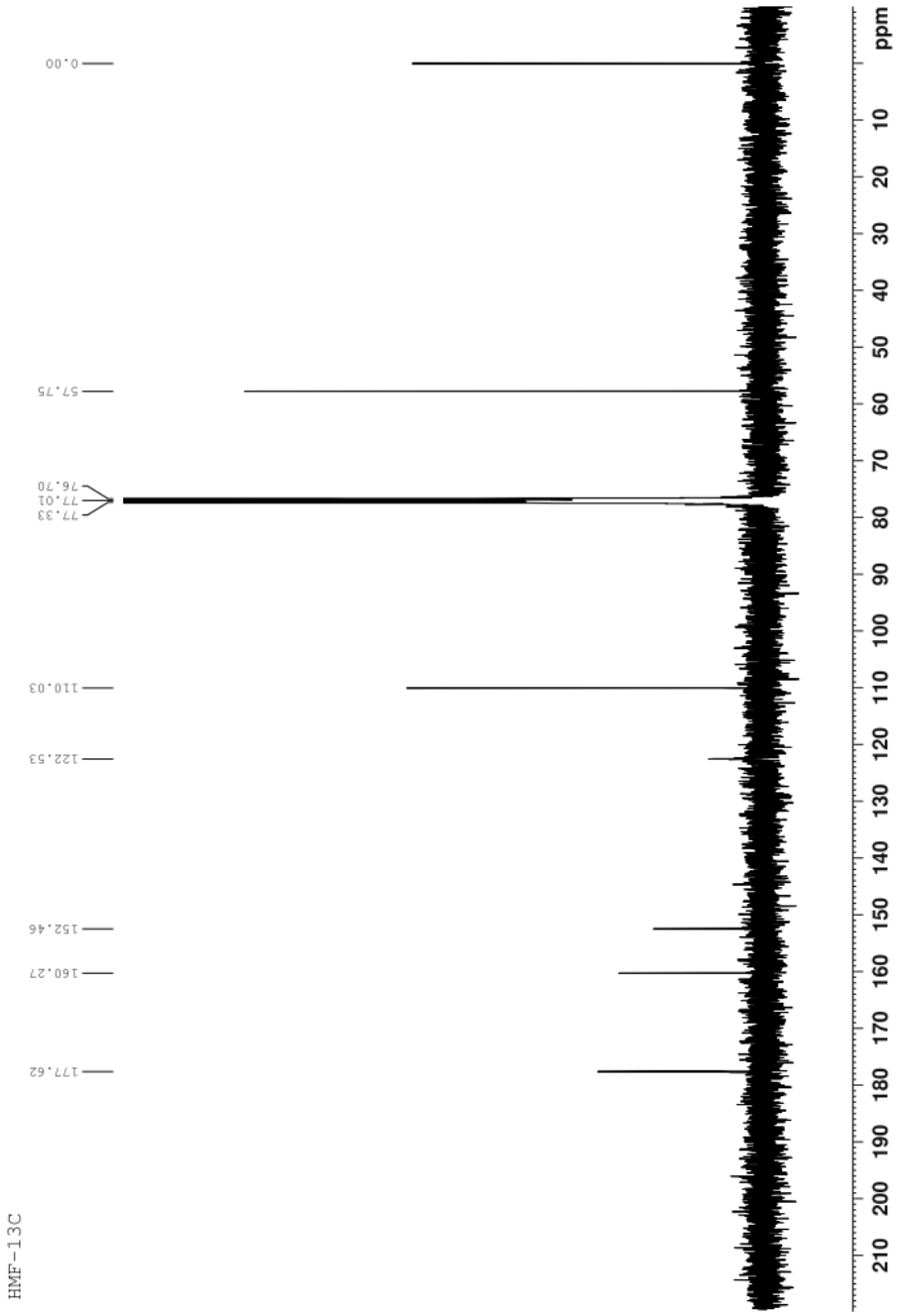
APPENDIX

LIST OF NMR SPECTRUM

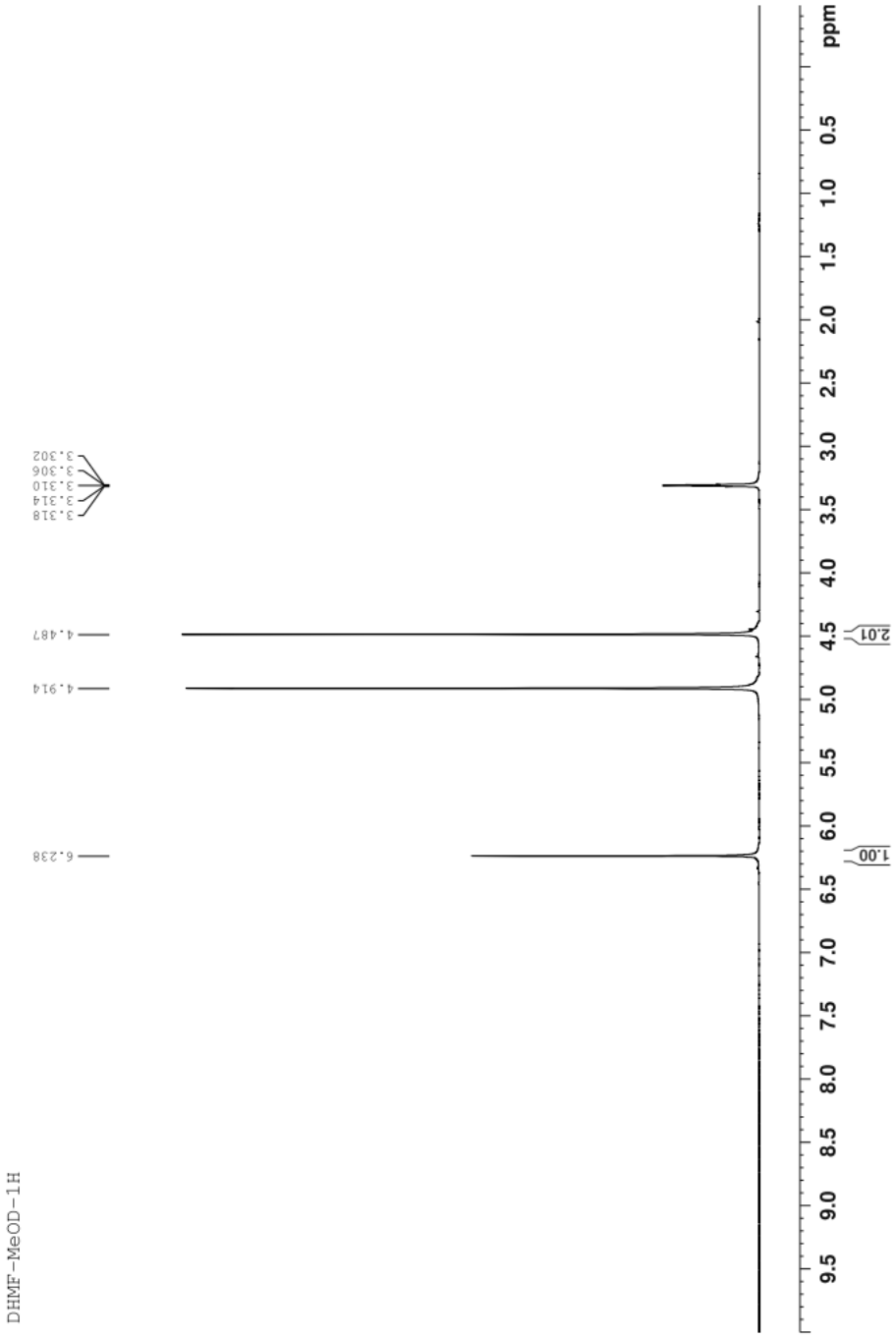
^{1}H-NMR of 5-hydroxmethylfurfural, HMF



^{13}C-NMR of 5-hydroxmethylfurfural, HMF



^{1}H-NMR of 2,5-dihydroxmethylfuran, DHMF



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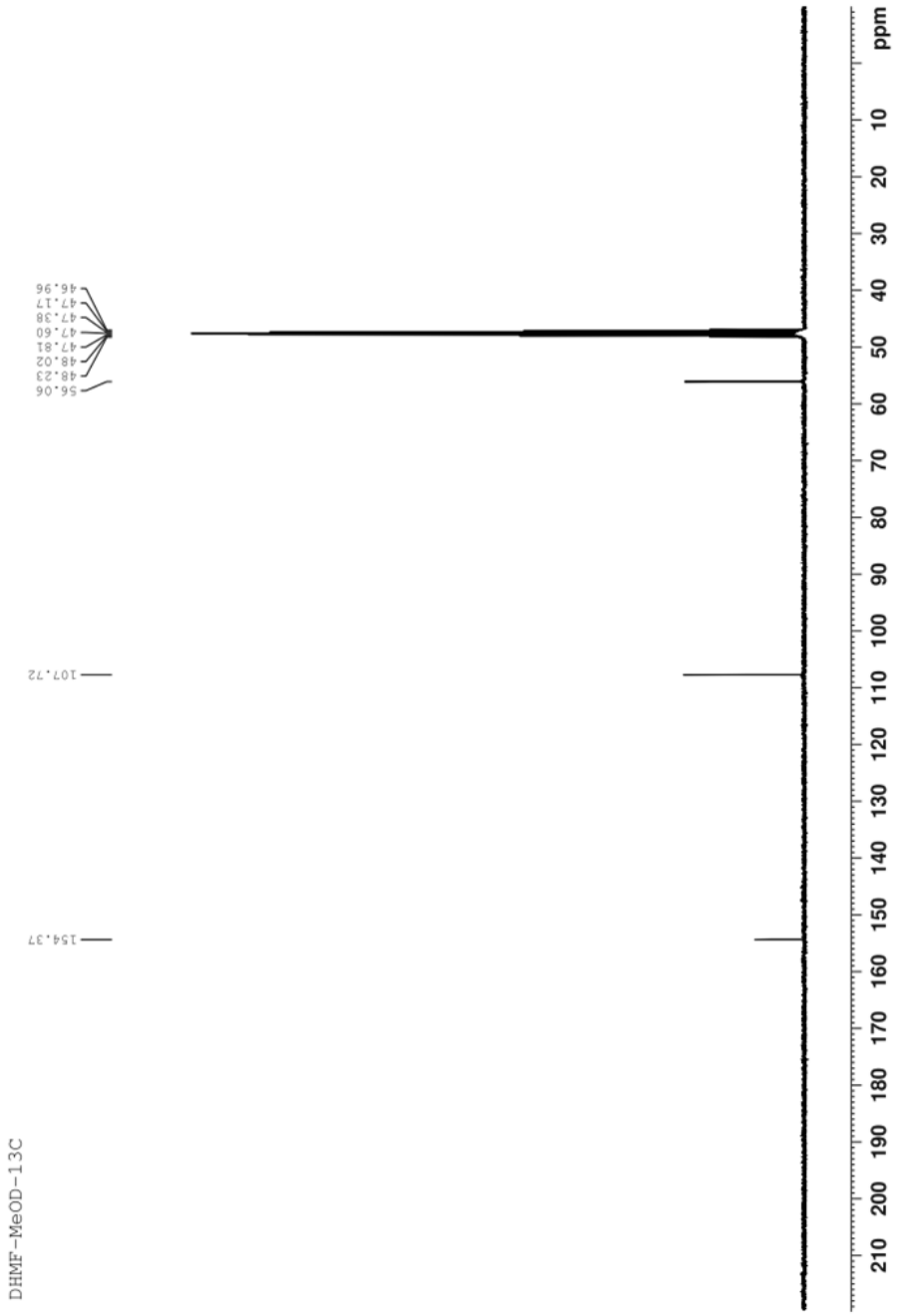
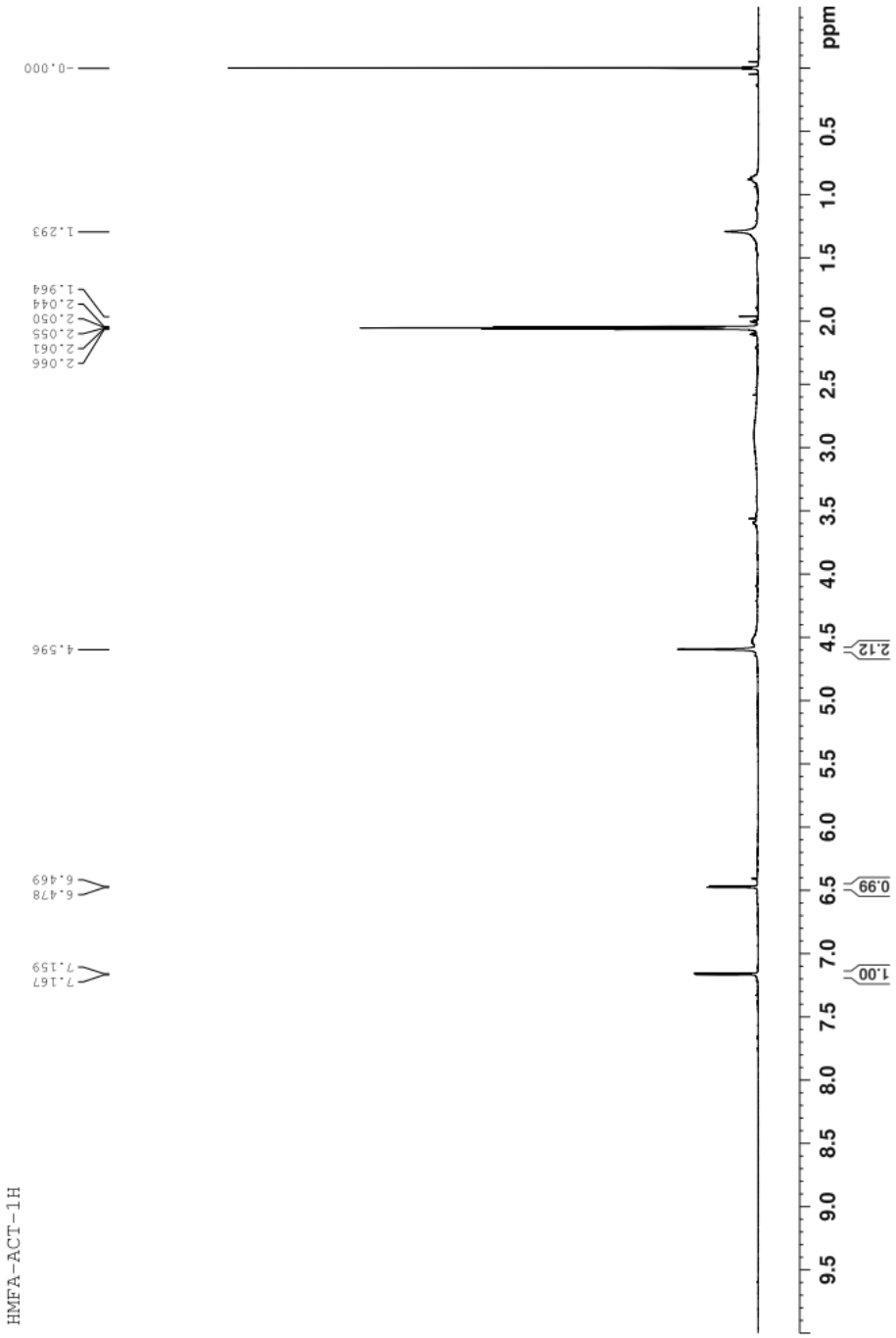


^{1}H-NMR of 5-hydroxymethylfuranoic acid, HMFA



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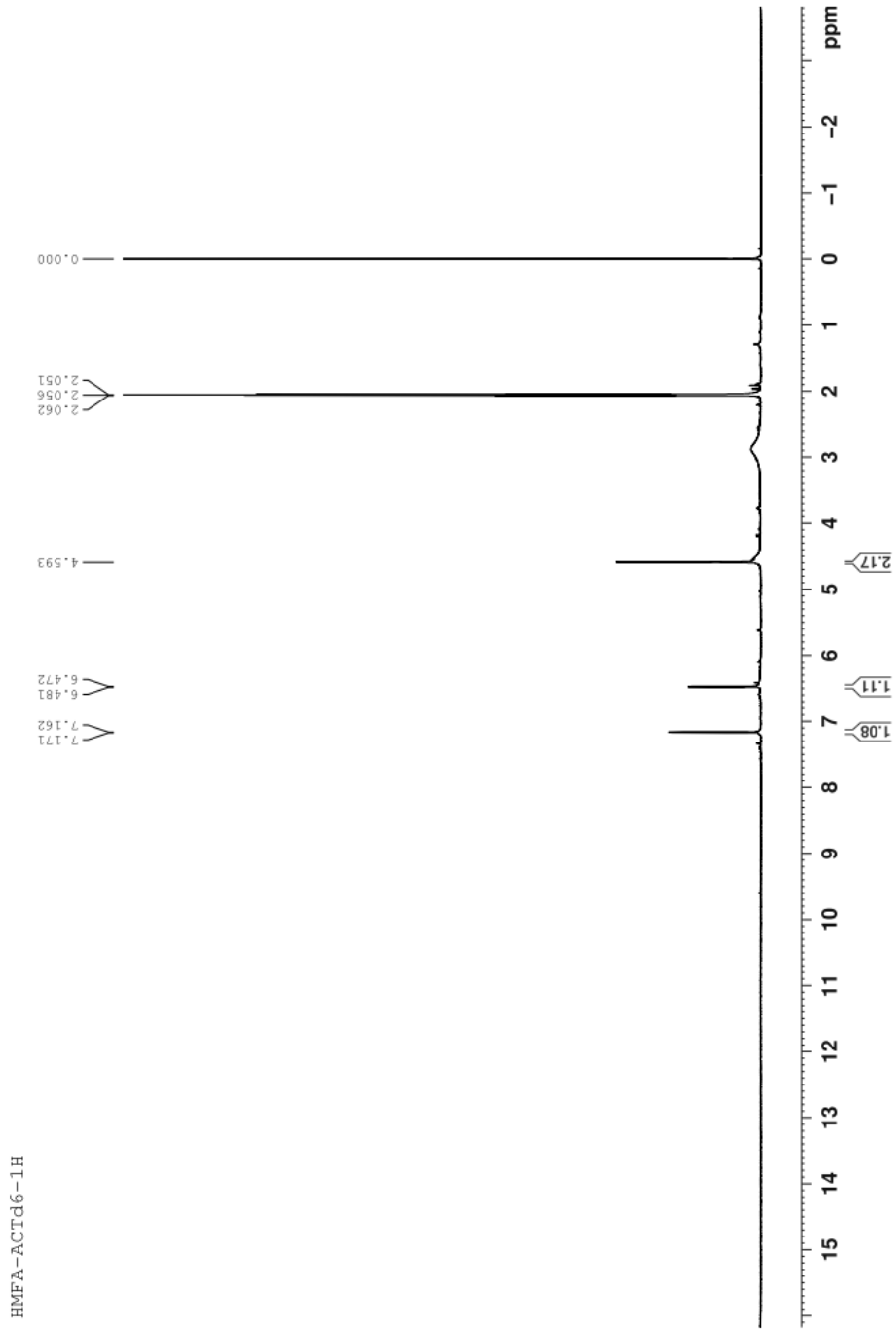
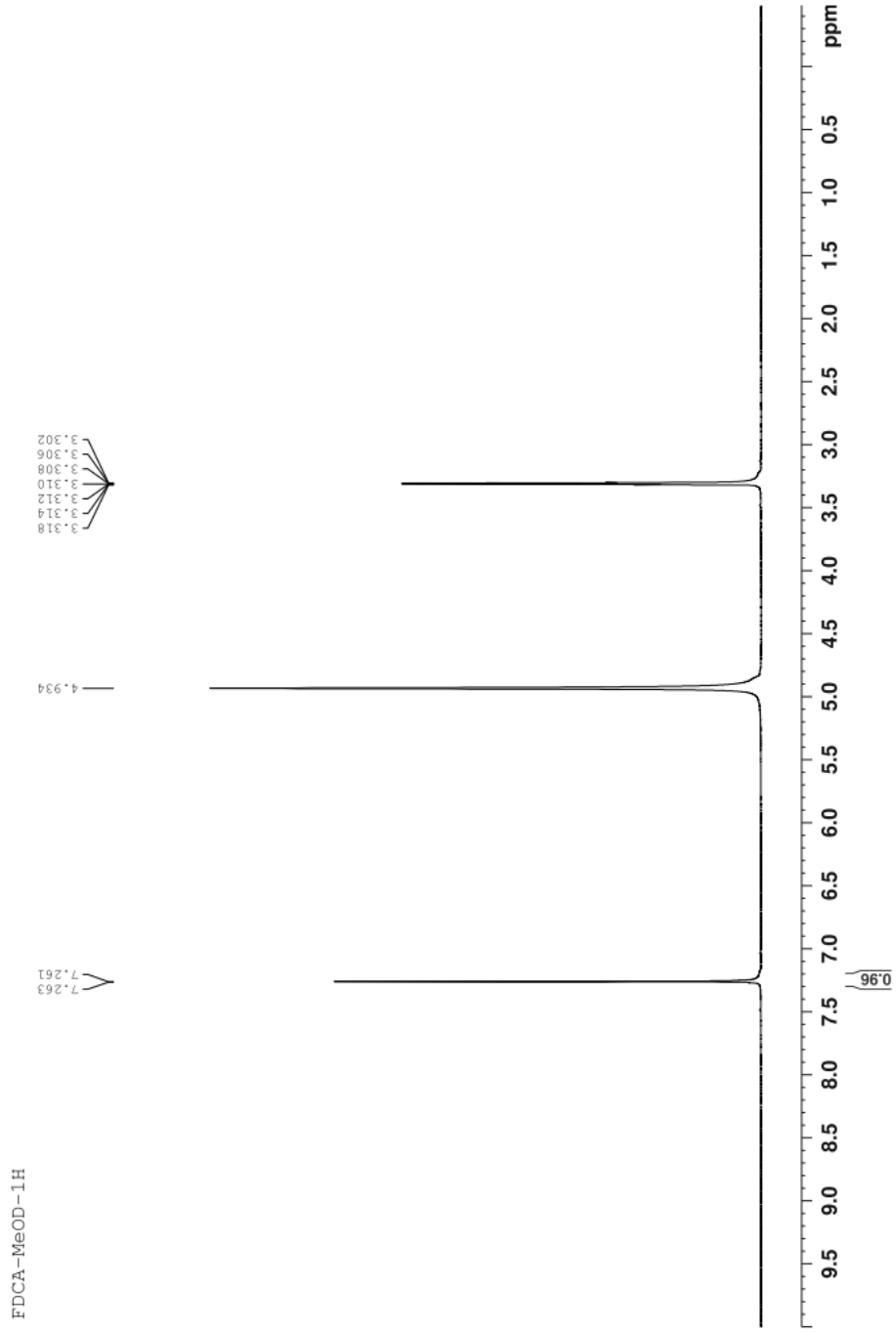
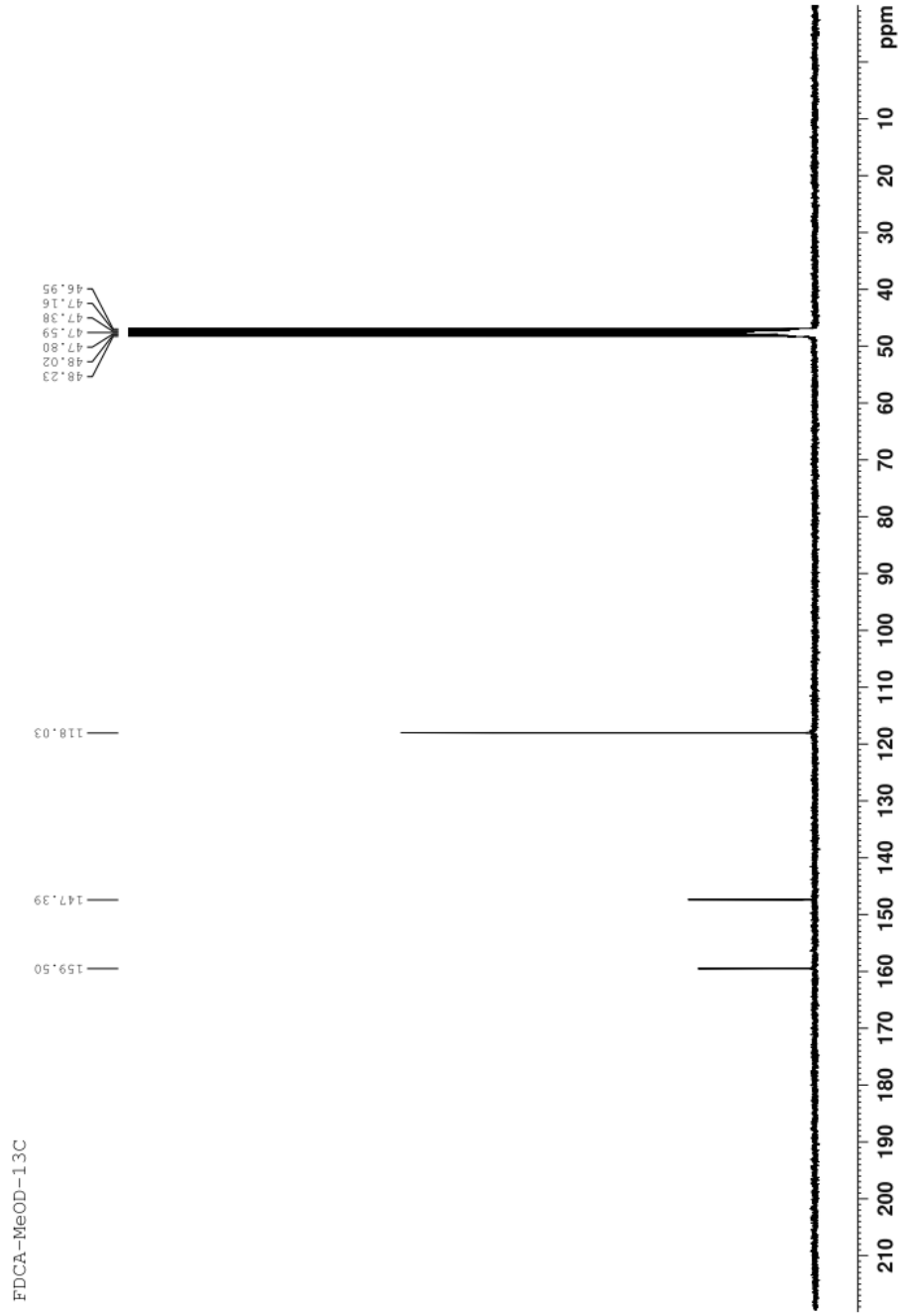


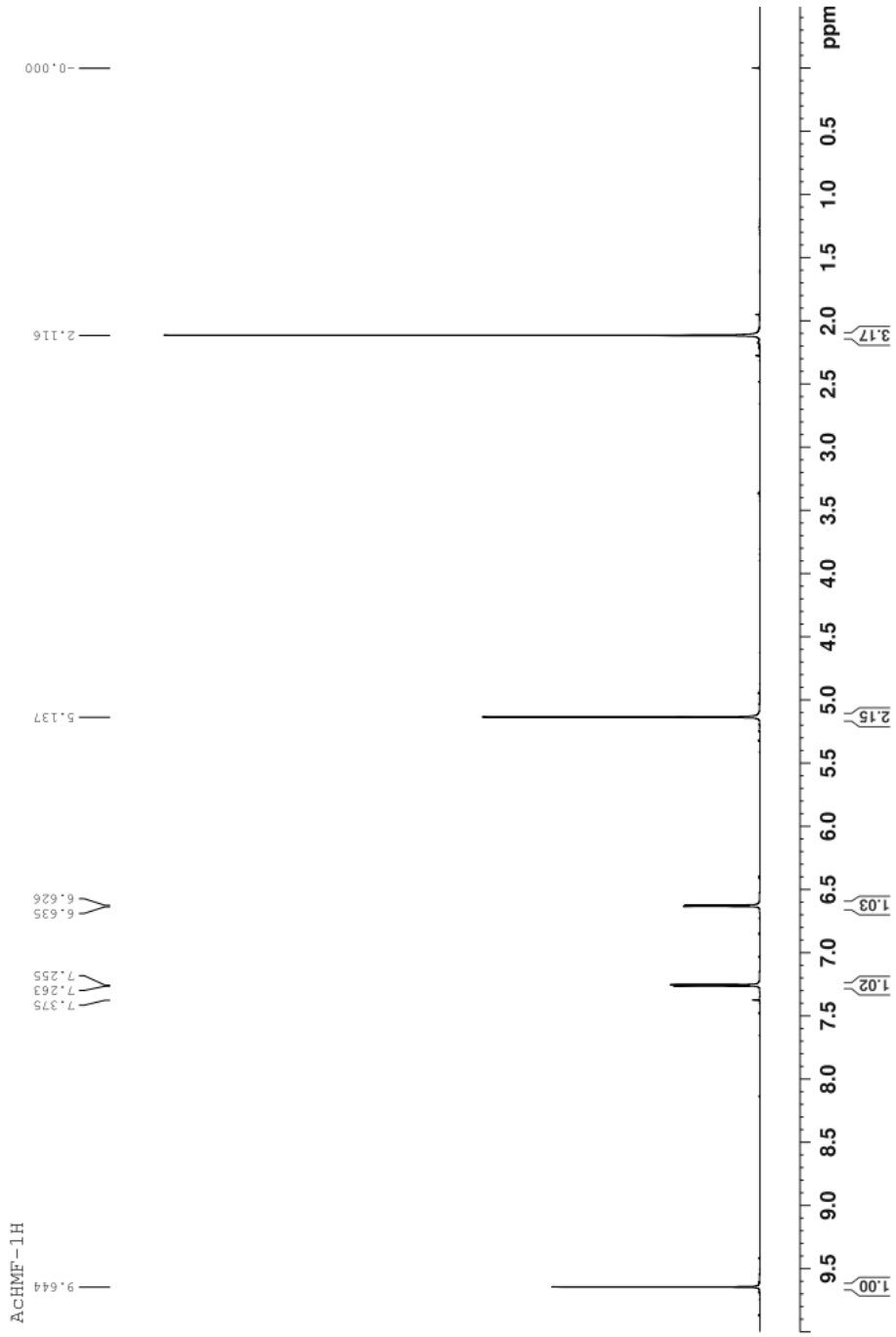
^{1}H-NMR of 2,5-furandicarboxylic acid, FDCA



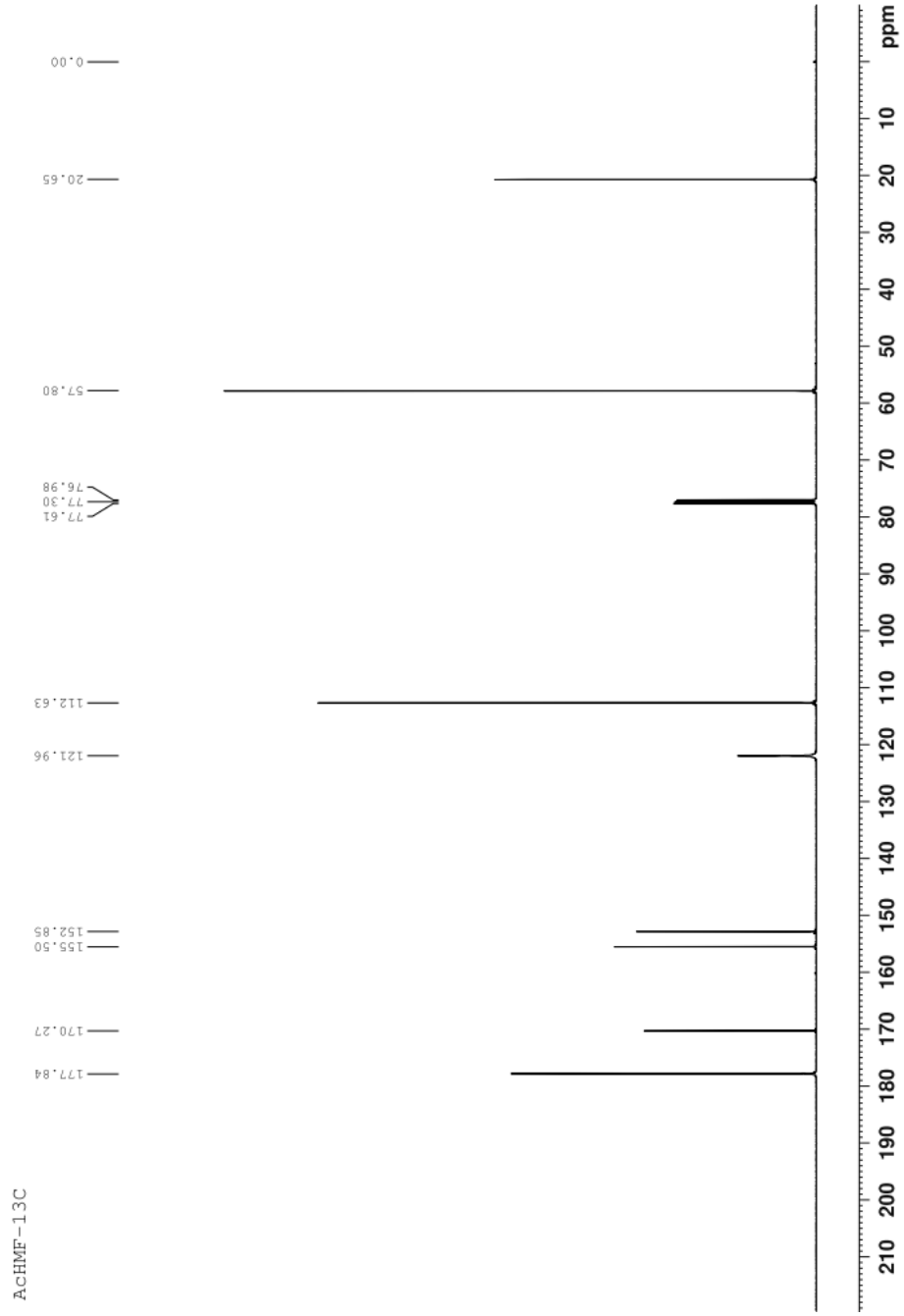
^{13}C-NMR of 2,5-furandicarboxylic acid, FDCA



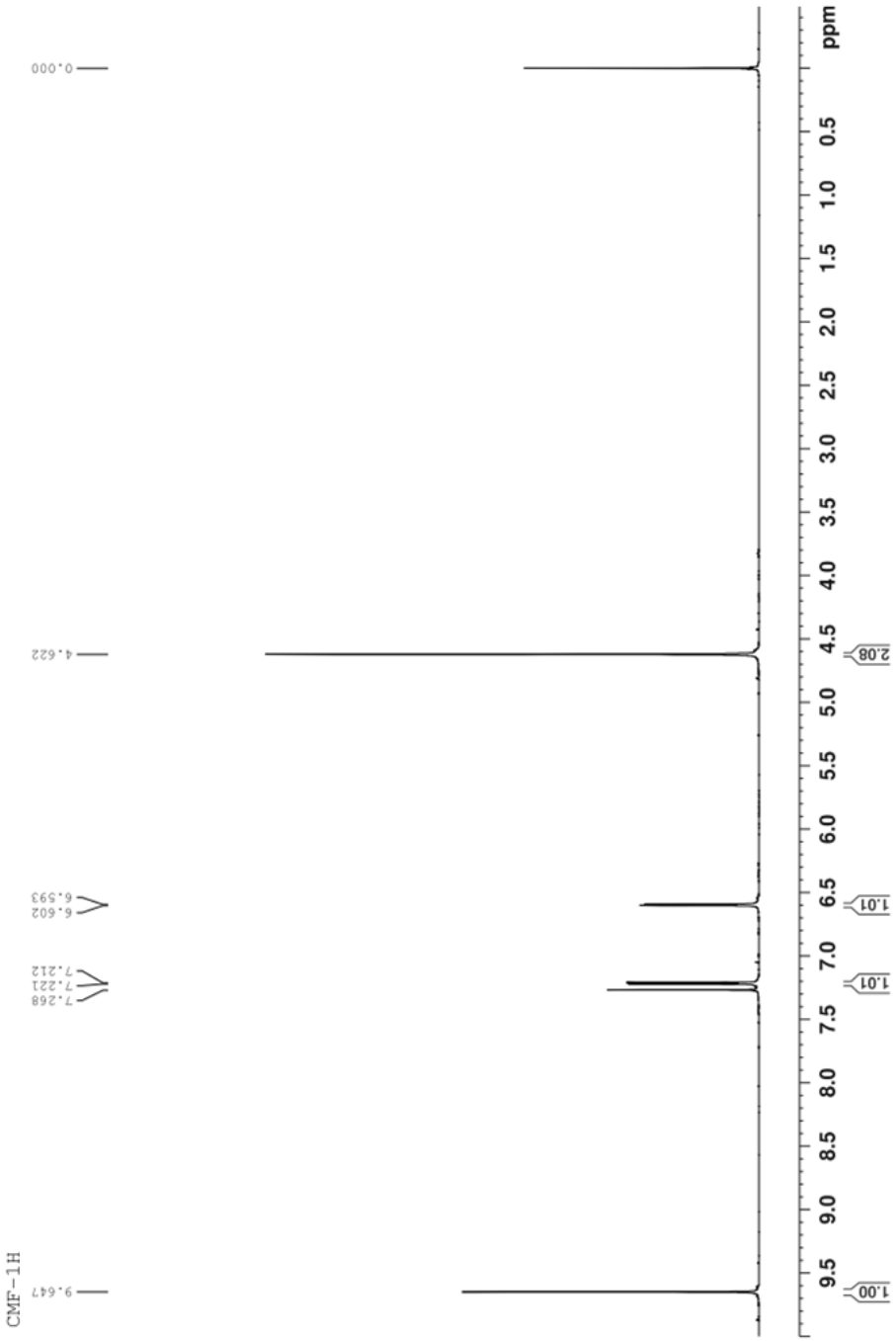
^{1}H-NMR of 5-*O*-acetylhydroxymethylfurfural, AcHMF



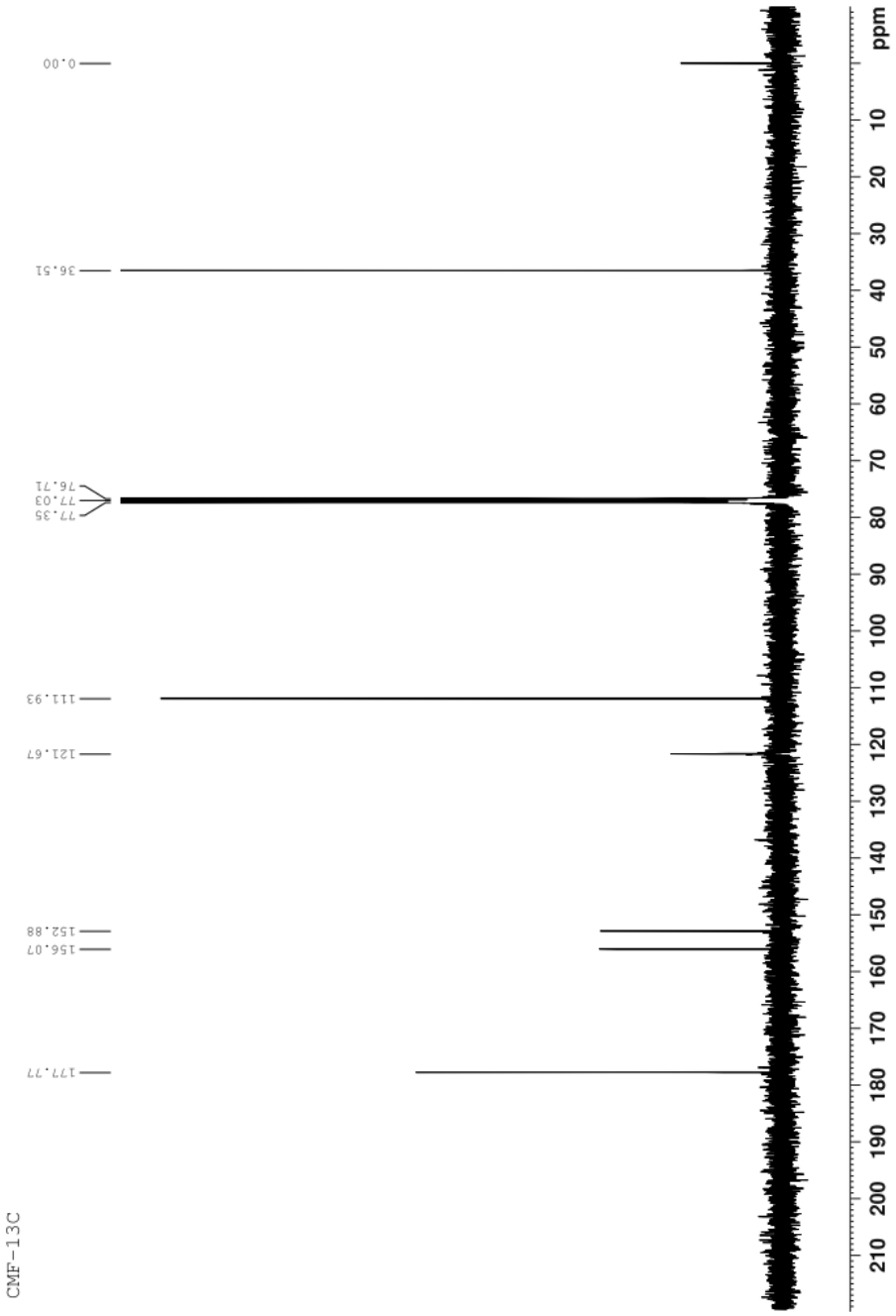
^{13}C-NMR of 5-*O*-acetylhydroxymethylfurfural, AcHMF



^{1}H-NMR of 5-chloromethylfurfural, CMF



^{13}C-NMR of 5-chloromethylfurfural, CMF



요약 (국문초록)

이 논문에서는 대체 자원 중의 하나로서 많은 연구가 진행되어 온 히드록시메틸푸르푸랄 (HMF)이라는 물질의 단점들을 보완하는 해결책으로서, 5-*O*-아세틸히드록시메틸푸르푸랄 (AcHMF)라는 물질을 소개하고, 그 합성법을 제시하였다. 퓨란계 물질인 HMF 는 유망한 차세대 대체 자원으로, 수많은 논문이나 특허에서 HMF 의 효과적인 합성법에 대해 보고한 바 있다. 그러나 HMF 의 유용한 활용성에도 불구하고 HMF 의 높은 반응성과 불안정성 때문에 몇 가지 단점들이 야기되었다. 따라서 이 논문에서는 또 다른 퓨란계 물질인 AcHMF 를 그 대안으로 내세운다. AcHMF 는 HMF 의 단점들을 보완할 수 있을 뿐만 아니라 기존에 HMF 로부터 합성해오던 다양한 유용한 유도체들 또한 AcHMF 로부터 구할 수 있다. AcHMF 를 합성하기 위하여 진행한 반응 경로는 다음과 같다. 프룩토오스로부터 반응을 시작하여 리파아제 촉매를 통한 선택적인 아세틸화를 통해 양 끝 히드록시기에만 아세틸기가 붙은 1,6-*디*-O-아세틸프룩토퓨라노스 를 얻은 후에, 여러가지 산 조건을 적용시켜 탈수 작용을 일으켰다. 기존에 발표되어 있던 HMF 합성법들은 높은 수율을 위하여 DMSO 나 이온성 액체 등을 용매로 사용하였고 그로 인한 문제점들이 있었는데 이 논문에서는 그러한 문제점들을 극복하였다. 또한, 친환경적인 촉매라고 할 수 있는 리파아제를 사용했다는 점도 이 논문의 특징이라고 할 수 있다.

주요어: 5-*O*-아세틸히드록시메틸푸르푸랄, 히드록시메틸푸르푸랄, 바이오매스, 대체 자원, 푸란 유도체, 녹색 화학

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