Electronic Supplementary Information

A novel route towards high yield 5-hydroxymethylfurfural from fructose catalyzed by a mixture of Lewis and Brönsted acids

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Contents:

1. Experimental section

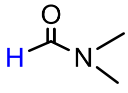
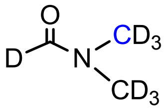
Standard 5-HMF was bought from Tengzhou Runlong Flavors & Fragrances Co. Ltd (>99.9%). Other chemicals, including fructose (purity: 99%), $AlCl_3$, inorganic acids and organic solvents were all analytical pure and bought from Sino-pharm chemical reagent Co. Ltd. All the solvents used in the reactions were treated with 4A molecular sieve and re-boiled to remove water.

The Dehydration of fructose was carried out in a 250 ml magnetically stirred flask at different reaction conditions. In a typical experiment, 5 g of fructose, a preset amount of $AlCl_3$, concentrated sulfuric acid (98 w%) or concentrated H_3PO_4 (98 w%) were successively added into the flask containing a preset amount of the solvent. The mixture was then incubated at 80-130 °C in an oil bath to initiate the reaction. Samples were withdrawn at intervals. Each reaction was repeated more than twice, and presented with average data. For scale-up experiments, the reaction was carried out in a 1 l (5-time scale-up) and 5 l (25-time scale-up) stainless steel autoclaves, respectively. The amount of all the components (substrate, solvent and catalysts) was enlarged accordingly. The reactor tanks were heated with an oil bath instead of heating jacket to ensure a better heat transfer.

After reaction, a given amount of Na_2CO_3 was added to neutralize the reaction solution, and then DMF was completely removed by reduced pressure distillation at 120 °C to achieve brown viscous slurry. For conventional vacuum distillation purification process, the slurry was distillated at 10-100 Pa at raised temperature of 150-180 °C, a final faint yellow liquid was obtained. For our previous developed EIVRD process, a constant flowrate of nitrogen was introduced to the above vacuum distillated system as an entrainer, and a higher recovery of 5-HMF was achieved. For solvent-extraction purification process, 5 g of the brown slurry was separately extracted by 10 ml × 3 times of acetone, ethanol, dichloromethane, ethyl acetate, hexane, and acetate/hexane mixture. After removal of the solvent by simple evaporation, a final faint yellow liquid was obtained.

The analytic method was copied from our previous publication[1] which was listed as follows. Fructose was analyzed by HPLC (Detector: Waters 410 Differential Refractometer; Aminex® HP X-87H column 9 μm, 300 × 7.8 mm), using 5 $mmol \cdot l^{-1}$

H_2SO_4 in ultrapure water as mobile phase at a flow rate of 0.6 ml·min^{-1} and a column temperature of 60 °C. 5-HMF was analyzed by HPLC (UV Detector: Waters 2487; wave length: 284 nm; Sunfire^{TM} C18 column 5 μm; 250 × 4.6 mm), using 70% methanol in ultrapure water as mobile phase at a flow rate of 1 ml·min^{-1} and a column temperature of 35 °C.

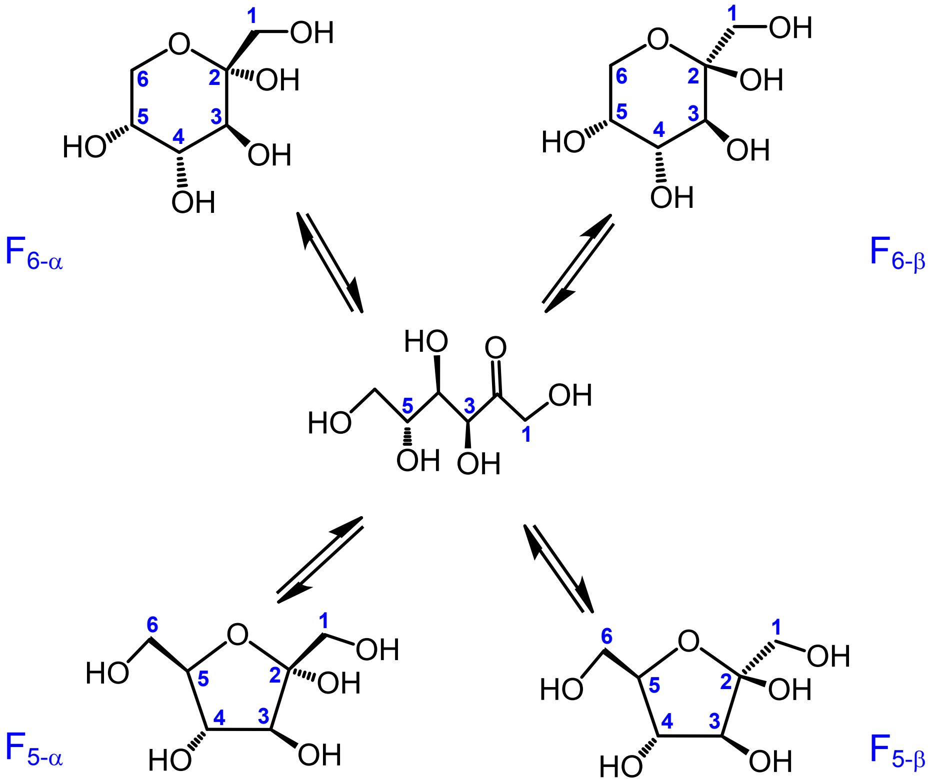
NMR spectra were collected using a Rarian PLUS-400 spectrometer at ambient temperature. All ^{1}H and ^{13}C spectra were carried out with 30 ° flip angles. Quantitative ^{13}C peak heights were obtained using inverse-gated decoupling with recycle delaying 35 s for fructose. Referencing was carried out with respect to 8.21 ppm for residual  for ^{1}H-NMR and 35.8 ppm for ^{13}C-NMR for . The relative contents of the corresponding isomers were approximately calculated by assuming that they are proportional to the ^{13}C peak heights.

2. ^{1}H-NMR and ^{13}C-NMR spectra of the reaction solution

Table S1 Samples for ^{1}H- and ^{13}C-NMR measurements

Sample No.[a]	Components of Sample
1	30 mg Fructose
2	30 mg Fructose + 30 mg H_3PO_4
3	30 mg Fructose + 30 mg H_2SO_4
4	30 mg Fructose + 10 mg $AlCl_3$
5	30 mg Fructose + 30 mg H_3PO_4 + 10 mg $AlCl_3$
6	30 mg Fructose + 30 mg H_3PO_4 + 30 mg H_2SO_4 + 10 mg $AlCl_3$

Note: 0.6 ml of N,N-dimethyl formamide-D_7 was used as solvent.



Scheme S1 Fructose isomers in DMF-d_7

Table S2 Relative content of isomers of D-Fructose[a]

Sample	Relative content of isomers of D-Fructose			
	$F_{5-\alpha}$	$F_{5-\beta}$	$F_{6-\beta}$	$F_{6-\alpha}$
1	0.10	0.27	0.61	0.03
2	0.20	0.47	0.26	0.06
3	0.04	0.32	0.56	0.08
4	0.19	0.49	0.24	0.09
5	0.17	0.39	0.37	0.06
6	0.10	0.24	0.57	0.09

[a] Quantified by the relative peak heights of C-1 carbons in isomers.

Table S3 ^{13}C-NMR chemical shifts of carbon atoms in $F_{5-\beta}$

Sample	Chemical shifts (ppm)[a]					
	C1	C2	C3	C4	C5	C6
1	103.4	77.7	71.7	70.8	69.8	64.4
2	103.2	77.5	71.5	70.6	69.5	64.0
3	103.1	77.4	71.3	70.5	69.4	64.1
4	103.5	77.8	71.7	70.8	69.8	64.4
5	102.5	76.1	70.8	70.0	68.9	63.4
6	102.8	76.3	71.0	70.2	69.0	63.8

[a] Value of the chemical shifts was referenced to references [2, 3].

Table S4 ^{1}H-NMR chemical shifts of carbon atoms in $F_{5-\beta}$

Sample	Chemical shift of $F_{5-\beta}$ (ppm)[a]						
	H-1	H-1’	H-3	H-4	H-5	H-6	H-6’
1	3.66	3.61	4.25	4.24	3.89	3.77	3.72
2	3.65	3.61	4.23	4.23	3.88	3.79	3.71
3	3.61	3.56	4.23	4.21	3.88	3.78	3.71
4	3.61	3.56	4.28	4.27	3.88	3.79	3.67
5	3.61	3.57	4.24	4.23	3.87	3.76	3.71
6	3.43	3.38	4.05	4.03	3.70	3.61	3.53

[a] Value of the chemical shifts was referenced to references [3, 4].

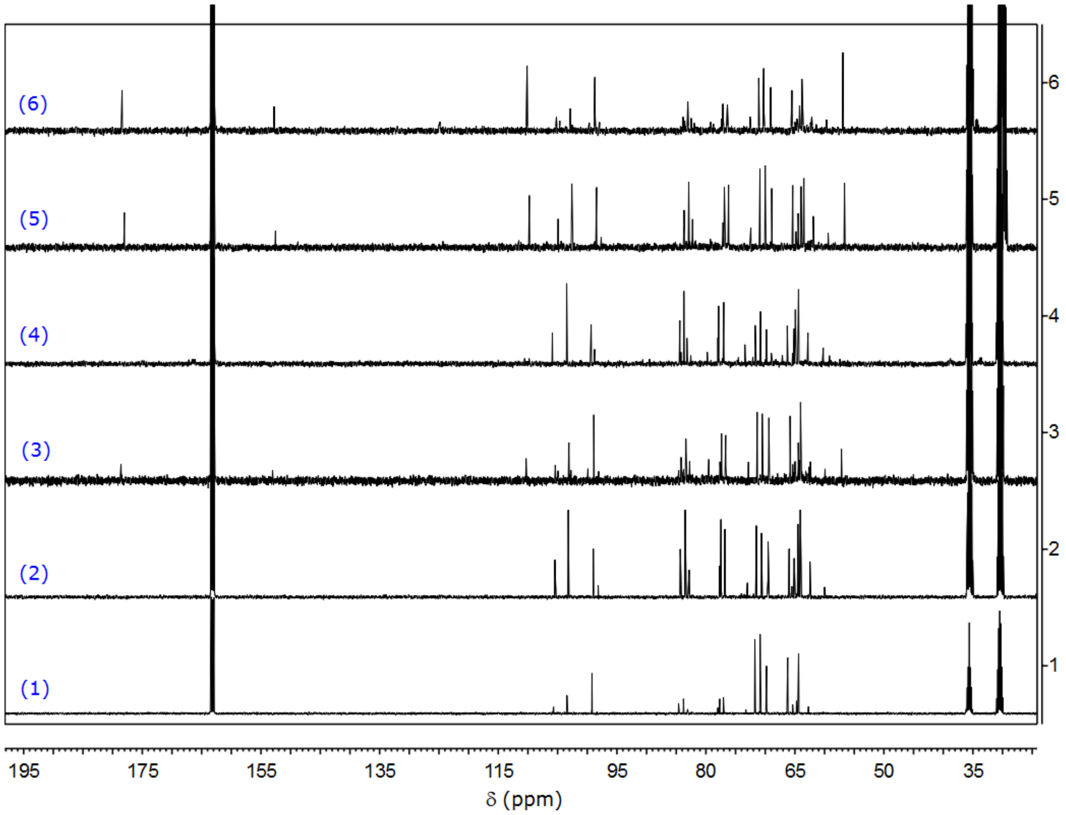
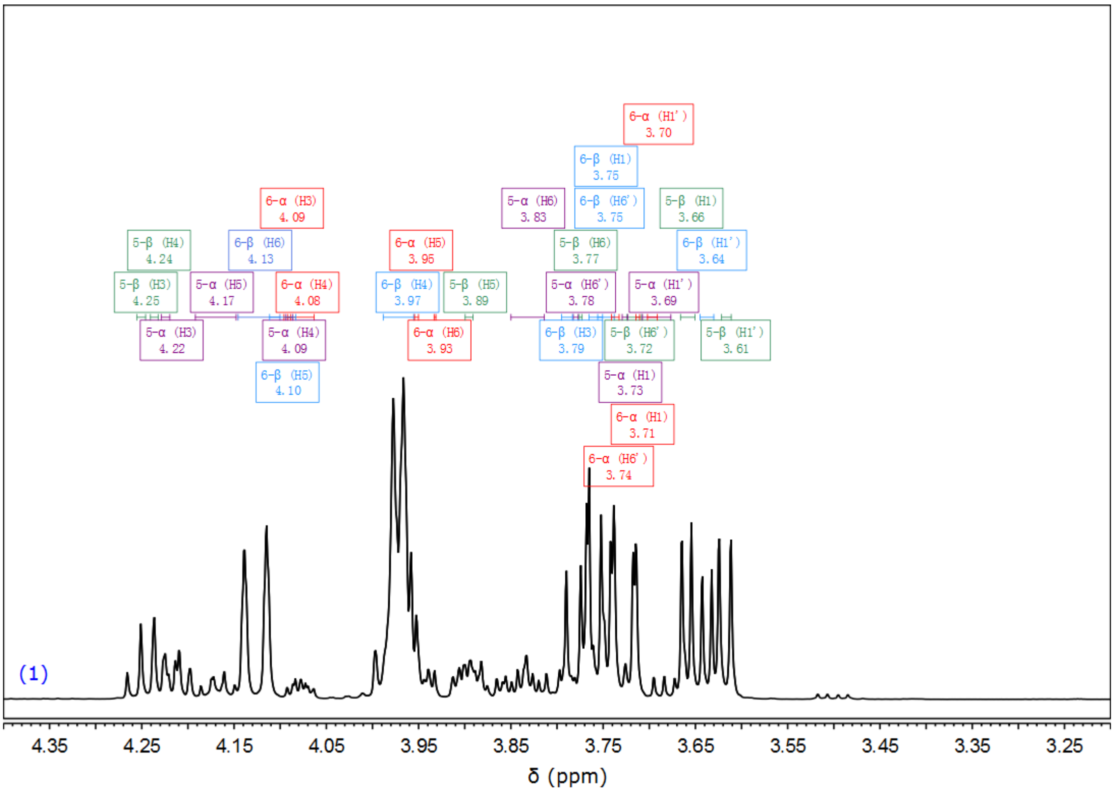
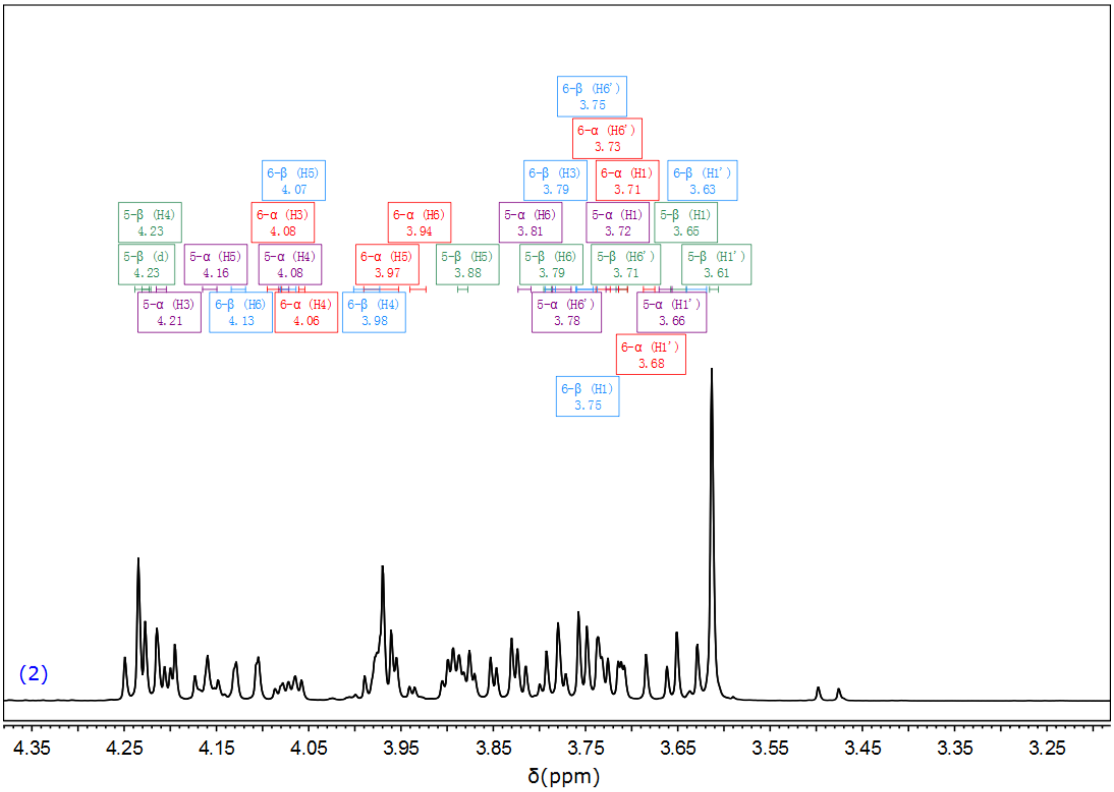
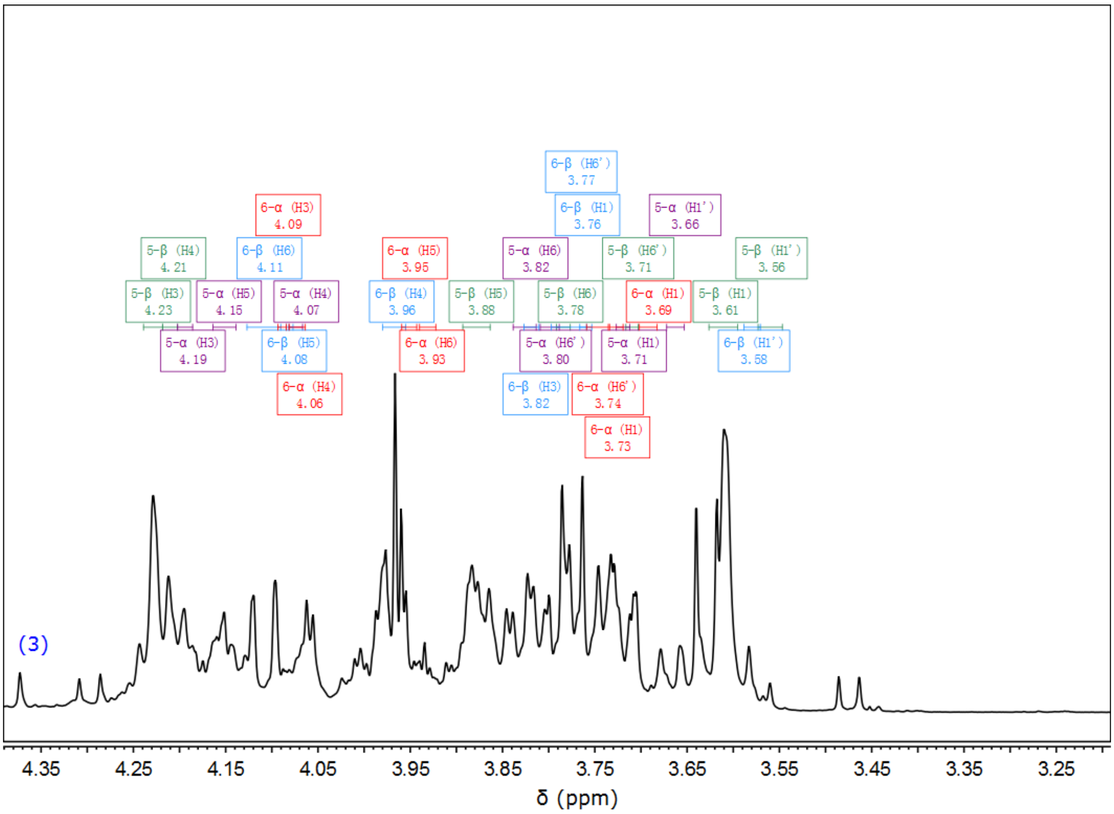
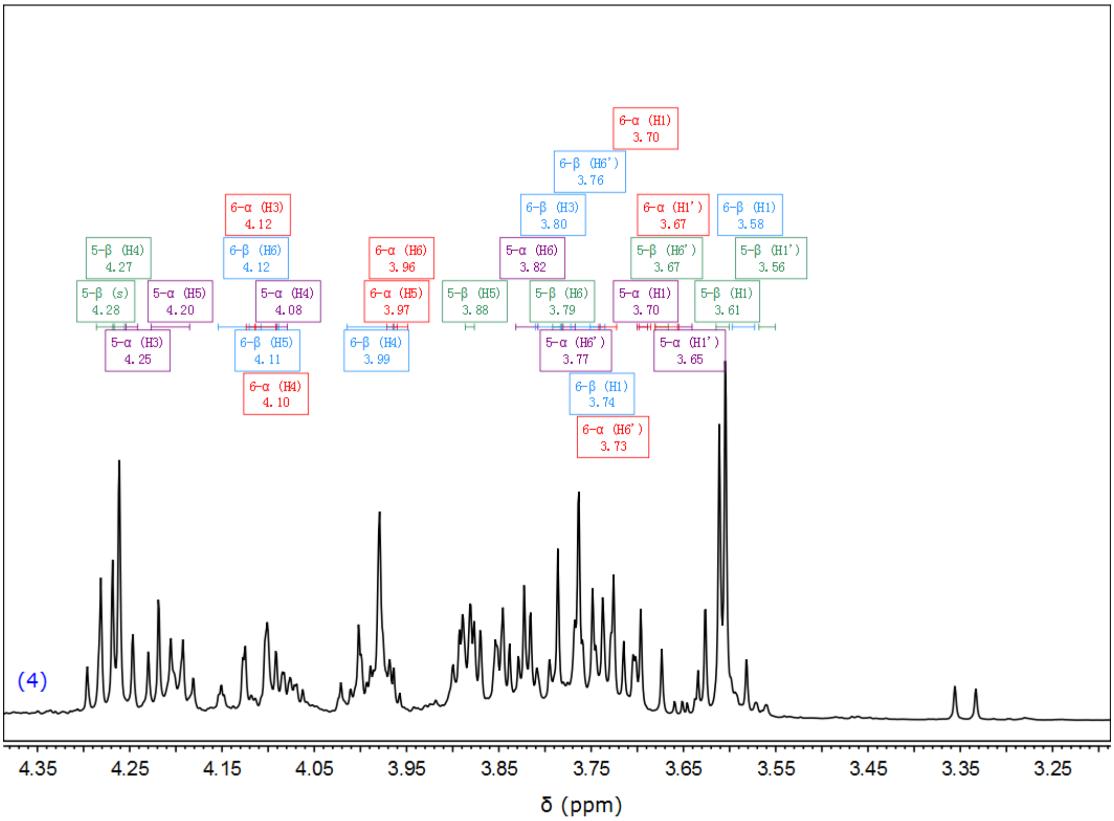


Figure S1 ^{13}C-NMR spectra of fructose in DMF-d_7 in the presence of different combinations of acids.


6-α (H1') 3.70
6-β (H1) 3.75
6-α (H3) 4.09
5-α (H6) 3.83
6-β (H6') 3.75
5-β (H1) 3.66
5-β (H4) 4.24
6-β (H6) 4.13
6-α (H5) 3.95
5-β (H6) 3.77
6-β (H1') 3.64
5-β (H3) 4.25
5-α (H5) 4.17
6-α (H4) 4.08
6-β (H4) 3.97
5-β (H5) 3.89
5-α (H6') 3.78
5-α (H1') 3.69
5-α (H3) 4.22
5-α (H4) 4.09
6-α (H6) 3.93
6-β (H3) 3.79
5-β (H6') 3.72
5-β (H1') 3.61
6-β (H5) 4.10
5-α (H1) 3.73
6-α (H1) 3.71
6-α (H6') 3.74
(1)
4.35
4.25
4.15
4.05
3.95
3.85
3.75
3.65
3.55
3.45
3.35
3.25
δ (ppm)


6-β (H6') 3.75
6-α (H6') 3.73
6-β (H5) 4.07
6-β (H3) 3.79
6-α (H1) 3.71
6-β (H1') 3.63
5-β (H4) 4.23
6-α (H3) 4.08
6-α (H6) 3.94
5-α (H6) 3.81
5-α (H1) 3.72
5-β (H1) 3.65
5-β (d) 4.23
5-α (H5) 4.16
5-α (H4) 4.08
6-α (H5) 3.97
5-β (H5) 3.88
5-β (H6) 3.79
5-β (H6') 3.71
5-β (H1') 3.61
5-α (H3) 4.21
6-β (H6) 4.13
6-α (H4) 4.06
6-β (H4) 3.98
5-α (H6') 3.78
5-α (H1') 3.66
6-α (H1') 3.68
6-β (H1) 3.75
(2)
4.35
4.25
4.15
4.05
3.95
3.85
3.75
3.65
3.55
3.45
3.35
3.25
δ(ppm)


6-β (H6') 3.77
6-α (H3) 4.09
6-β (H1) 3.76
5-α (H1') 3.66
5-β (H4) 4.21
6-β (H6) 4.11
6-α (H5) 3.95
5-α (H6) 3.82
5-β (H6') 3.71
5-β (H1') 3.56
5-β (H3) 4.23
5-α (H5) 4.15
5-α (H4) 4.07
6-β (H4) 3.96
5-β (H5) 3.88
5-β (H6) 3.78
6-α (H1) 3.69
5-β (H1) 3.61
5-α (H3) 4.19
6-β (H5) 4.08
6-α (H6) 3.93
5-α (H6') 3.80
5-α (H1) 3.71
6-β (H1') 3.58
6-α (H4) 4.06
6-β (H3) 3.82
6-α (H6') 3.74
6-α (H1) 3.73
(3)
4.35
4.25
4.15
4.05
3.95
3.85
3.75
3.65
3.55
3.45
3.35
3.25
δ (ppm)


6-α (H1) 3.70
6-β (H6') 3.76
6-α (H3) 4.12
6-β (H3) 3.80
6-α (H1') 3.67
6-β (H1) 3.58
5-β (H4) 4.27
6-β (H6) 4.12
6-α (H6) 3.96
5-α (H6) 3.82
5-β (H6') 3.67
5-β (H1') 3.56
5-β (s) 4.28
5-α (H5) 4.20
5-α (H4) 4.08
6-α (H5) 3.97
5-β (H5) 3.88
5-β (H6) 3.79
5-α (H1) 3.70
5-β (H1) 3.61
5-α (H3) 4.25
6-β (H5) 4.11
6-β (H4) 3.99
5-α (H6') 3.77
5-α (H1') 3.65
6-α (H4) 4.10
6-β (H1) 3.74
6-α (H6') 3.73
(4)
4.35
4.25
4.15
4.05
3.95
3.85
3.75
3.65
3.55
3.45
3.35
3.25
δ (ppm)

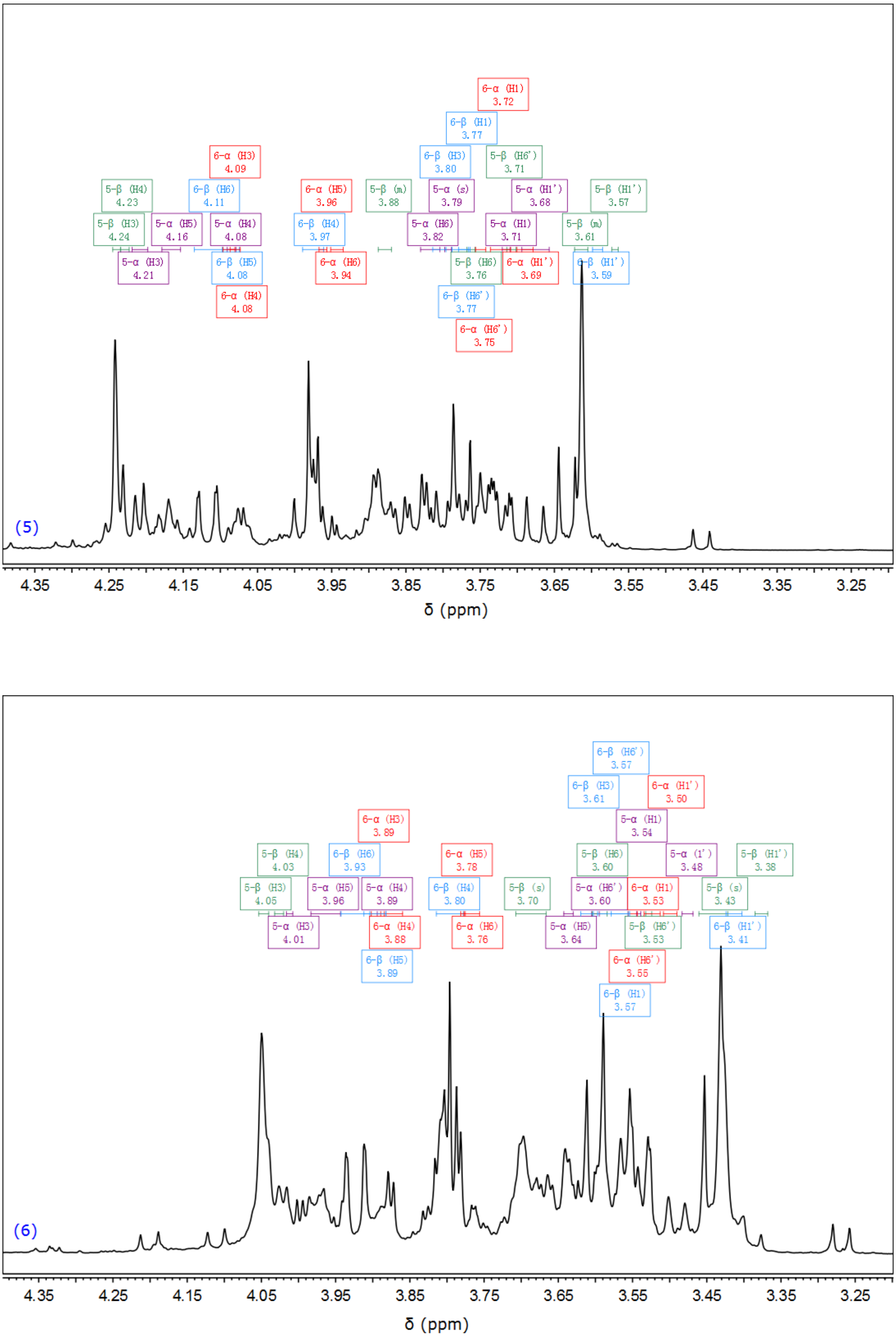


Fig S2 ^{1}H-NMR spectra of fructose in DMF-d_7 in the presence of different combinations of acids

3. Confirmation of the obtained 5-HMF

(1) ^{1}H-NMR

The ^{1}H-NMR (400 MHz, $CDCl_3$, 29 °C) spectrum data for the obtained 5-HMF: δ=9.56 (s, $1H_a$), 7.21 (d, J = 3.5 Hz, $1H_b$), 6.51 (d, J = 3.5 Hz, $1H_c$), 4.71 (s, $2H_d$), 2.73 (s, $1H_e$).

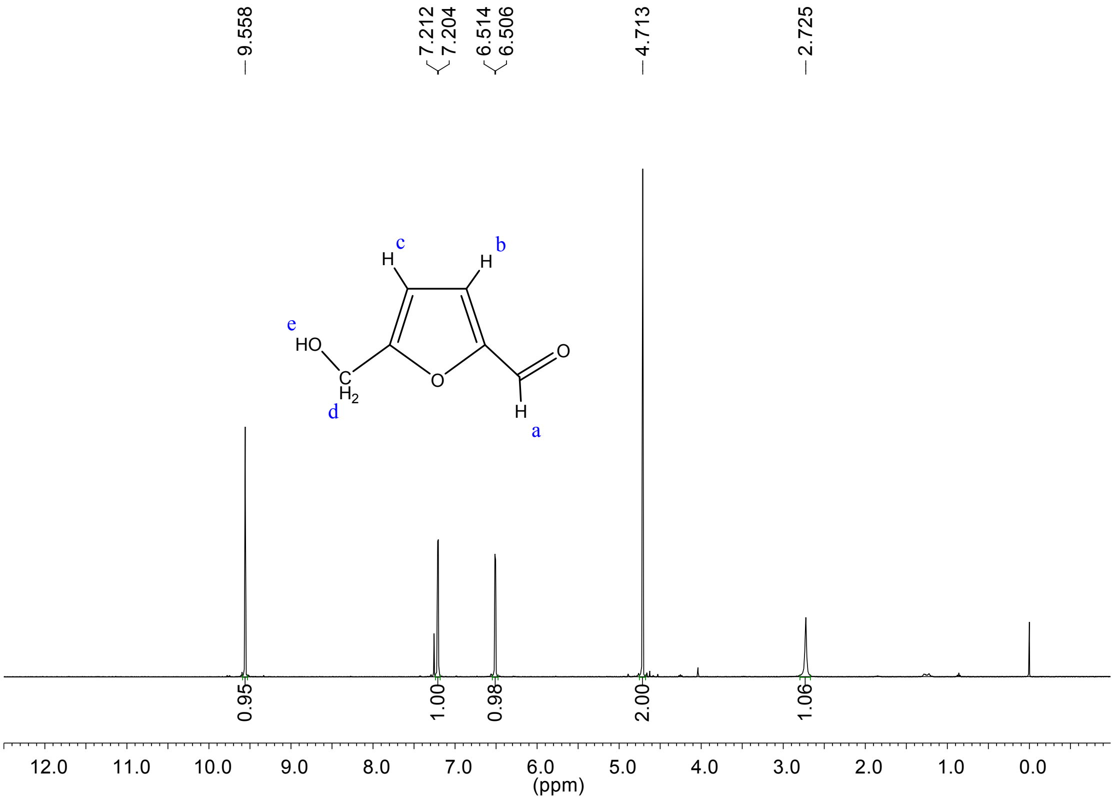


Fig S3 ^{1}H-NMR spectrum of the obtained 5-HMF

(2) ^{13}C-NMR

The ^{13}C-NMR (101 MHz, $CDCl_3$, 29 °C) spectrum data for the obtained 5-HMF: δ_C=177.40 (1C_a), 160.42 (1C_b), 152.12 (1C_c), 122.68 (1C_d), 109.90 (1C_e), 57.62 (1C_f).

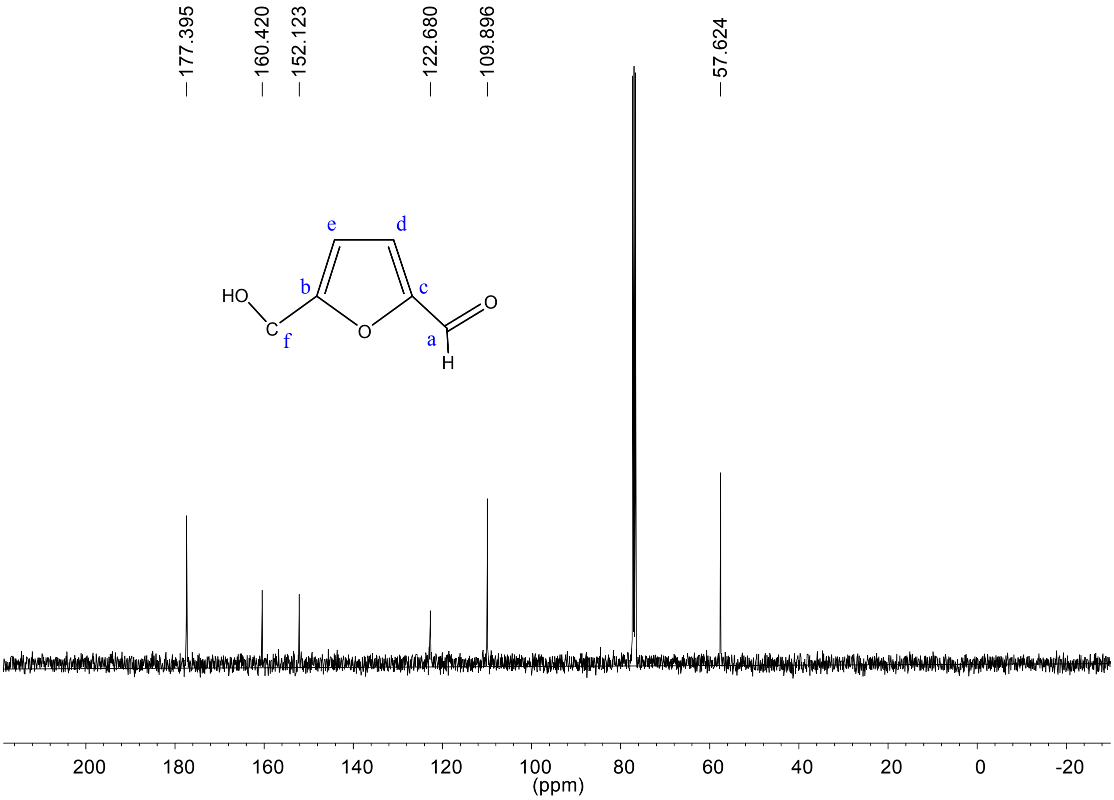


Fig S4 ^{13}C-NMR spectrum of the obtained 5-HMF

(3) Elemental analysis

Elemental analysis for the 5-HMF obtained by vacuum distillation found C: 56.37%; H, 4.87%; O, 38.76% (calculated value C, 57.14%; H, 4.80%; O, 38.06%).

4. HPLC chromatograms for the analysis of the reaction bulks

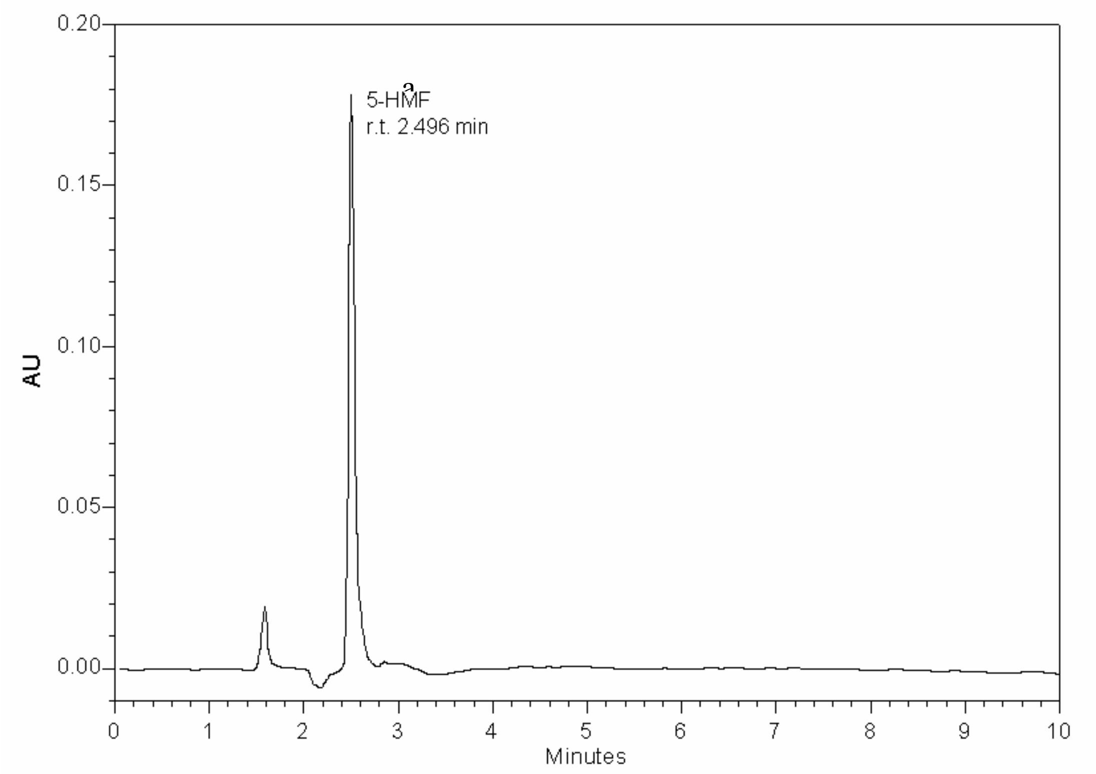


Fig S5 Typical HPLC chromatogram for the analysis of 5-HMF from the reaction bulks.

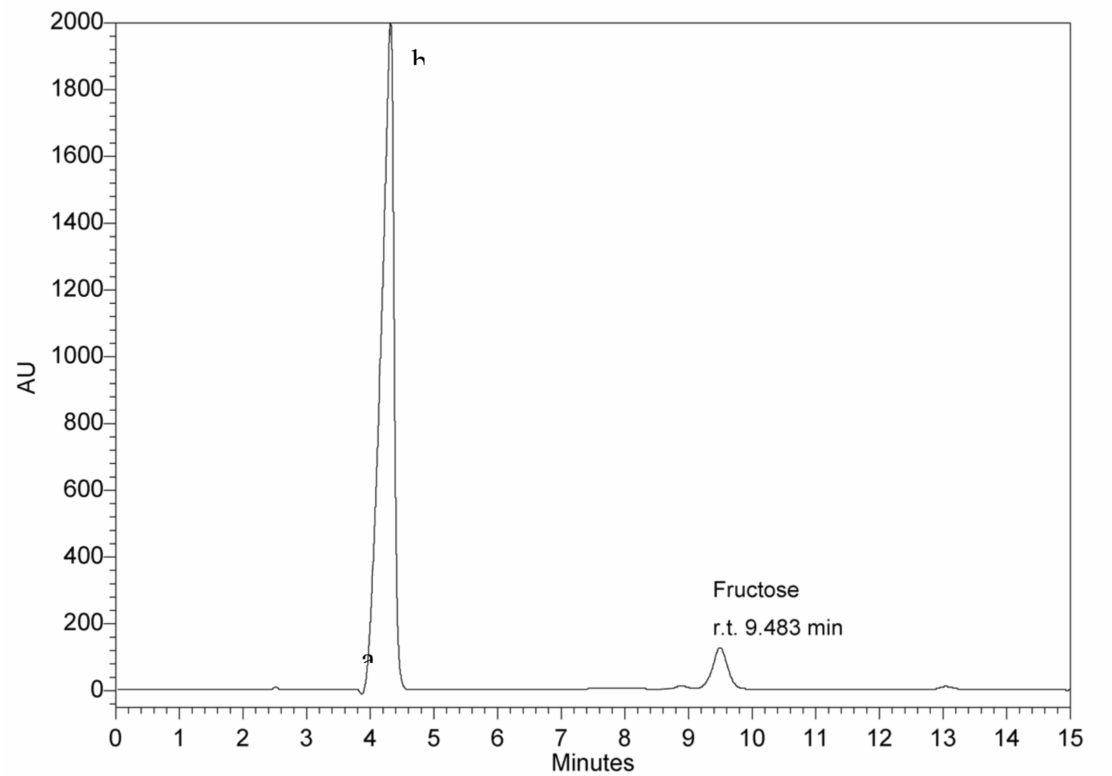


Fig S6 Typical HPLC chromatogram for the analysis of fructose.

5. Raw data for Figure 2

Table S5 Raw data for Figure 2

L/B	Yield of 5-HMF (mol%)			
	S/P=0.5	S/P=1.0	S/P=1.5	S/P=2.0
0	20.0	49.6	36.1	26.7
0.11	60.3	84.0	67.5	53.5
0.22	51.1	92.6	52.4	54.8
0.33	45.3	84.1	43.9	39.7

Note: S/P denotes the molar ratio of H_2SO_4/H_3PO_4; L/B denotes the molar ratio of $AlCl_3/(H_2SO_4 + H_3PO_4)$

6. Impurity analysis and material balance calculation

The main byproducts of the reaction system should be humin derivatives, which is formed by the dehydration, polymerization of 5-HMF and fructose[5]. However, little direct evidences have been reported on the exact structure of these complex macromolecules. Based on the character of vacuum distillation and solvent extraction procedure, we deduce the impurities in the final 5-HMF through vacuum distillation as well as EIVRD process are humin monomers with lower boiling points, trace amount of N,N-dimethyl formamide, catalysts and moisture. For solvent extraction procedure, the impurities should be similar, except that the molecular weight distribution of the humins which are soluble in the extraction solvent and therefore blended in the final product may be much wider.

The detailed material balance for EIVRD purification process is as follows:

Initial material:

Fructose: 25 g; DMF: 500 g;

Catalyst: $AlCl_3$:0.5 g: H_2SO_4: 1.0 g; H_3PO_4: 2.0 g; (i.e. mole ratio of 1: 2.7: 4)

$NaCO_3$: 6.2 g

Conversion of fructose: 100%

Yield to 5-HMF: 92.6 mol% (corresponding to 64.8 wt%)

Brown slurry:

Weight: 37.7 g (contains 5-HMF, humins, neutralized catalysts, $NaCO_3$, trace DMF and water)

Content of 5-HMF: 43.0 wt%

Distillate (final product):

Weight: 15.2 g (faint yellow liquid)

Content of 5-HMF (purity): 94.9%

Recovery: 88.4%

Raffinate

Weight: 21.6 g (Cream like with brown to black in color)

Content of 5-HMF: 7.2%

Balance of material: 37.7-15.2-21.6=0.9 g

Balance of 5-HMF: 37.7×43.0%-15.2×94.9%-21.6×7.2%=0.33 g

i.e., about 0.9/37.7=2.7% of material lost and about 0.33/(37.7×43.0%)=2.1% of 5-HMF decomposed during the purification process.

7. Reference

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2. H. Kimura, M. Nakahara and N. Matubayasi, *The journal of physical chemistry. A*, 2011, **115**, 14013-14021; G. R. Akien, L. Qi and I. T. Horvath, *Chem Commun (Camb)*, 2012, **48**, 5850-5852.
3. T. Barclay, M. Ginic-Markovic, M. R. Johnston, P. Cooper and N. Petrovsky, *Carbohydr Res*, 2012, **347**, 136-141.
4. T. Barclay, M. Ginic-Markovic, M. R. Johnston, P. D. Cooper and N. Petrovsky, *Carbohydr Res*, 2012, **352**, 117-125.
5. G. R. Akien, L. Qi and I. T. Horvath, *Chemical Communications*, 2012, **48**, 5850-5852; M. Zhang, H. Yang, Y. N. Liu, X. D. Sun, D. K. Zhang and D. F. Xue, *Nanoscale Research Letters*, 2012, **7**; R.-J. van Putten, J. C. van der Waal, E. de Jong, C. B. Rasrendra, H. J. Heeres and J. G. de Vries, *Chem. Rev.*, 2013, **113**, 1499-1597; I. van Zandvoort, Y. H. Wang, C. B. Rasrendra, E. R. H. van Eck, P. C. A. Bruijnincx, H. J. Heeres and B. M. Weckhuysen, *Chemsuschem*, 2013, **6**, 1745-1758.