Supplementary Information

Green and Efficient One-Pot Synthesis of the Bio-Based Platform Molecule 4 Hydroxymethyl-2-Furfural on Multigram Scale

Kubilay Ceyhan, Mattis Rottmann, Harald Gröger*

Chair of Industrial Organic Chemistry and Biotechnology, Faculty of Chemistry, Bielefeld University, Universitätsstraße 25, 33615 Bielefeld, Germany

*To whom correspondence should be addressed

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Determination of the E-factor during the multigram synthesis of 4-HMF.

Table S 1. Substance inputs and outputs during the 100g scale synthesis of 4-HMF.

Reaction Cycle	Input	Output
0	100g dihydroxyaceton 11ml NaOH (1M) 89ml D.I. Water 2ml HCl (1M, neutralization) 1000 ml MTHF (solvent reservoir)	not isolated
1	236.4g HCl (1M) 600 ml H_2O 120g NaCl 750 ml MTHF (3x250 ml for extraction, closed loop distillation)	7.1g 4-HMF (determined by ^{1}H-NMR)
2	11.4g dendroketose 750 ml MTHF (3x250 ml for extraction, closed loop distillation)	8.6g 4-HMF (determined by ^{1}H-NMR)

3	12.4g dendroketose 750 ml MTHF (3x250 ml for extraction, closed loop distillation)	8.6g 4-HMF (determined by ^{1}H-NMR)
4	14.2g dendroketose 750 ml MTHF (3x250 ml for extraction, closed loop distillation)	6.3g 4-HMF (determined by ^{1}H-NMR)
5	10.2g dendroketose 750 ml MTHF (3x250 ml for extraction, closed loop distillation)	8.6g 4-HMF (determined by ^{1}H-NMR)
6	12.0g dendroketose 750 ml MTHF (3x250 ml for extraction, closed loop distillation)	6.8g 4-HMF (determined by ^{1}H-NMR)
7	13.7g dendroketose 750 ml MTHF (3x250 ml for extraction, closed loop distillation)	8.6g 4-HMF (determined by ^{1}H-NMR)

8	11.0g dendroketose	6.9g 4-HMF (determined by ^{1}H-NMR)
9	750 ml MTHF (3x250 ml for extraction, closed loop distillation)	5.7g 4-HMF (determined by ^{1}H-NMR)

$m_{in\ (total\ dendroketose\ Input\ for\ dehydration)}$ = 109g

$m_{in\ (total\ amount\ of\ NaCl/H2O/HCl)}$ = 938.4 g

$m_{out\ (4\text{-}HMF\ determined\ by\ ^{1}H\text{-}NMR\ analysis)}$ = 67.2g (88.1%)

$m_{out\ (4\text{-}HMF\ determined\ by\ balance)}$ = 57.5g (75.5%)

$m_{out\ (solid\ Humin)}$ = 13.7g

$m_{out\ (Water\ after\ the\ 9th\ cycle)}$ = 1026.2g (+87.8g relative to the input)

$m_{out\ (MTHF\ after\ distillation)}$ = 826g (971ml) → Loss of 24.65g (may be dissolved in Water)

In principle, the reaction water is no waste, since it can be used for several reaction cycles as demonstrated in this work for 9 reaction cycles. After the dendroketose concentration is readjusted to 100g/L the next reaction cycle can begin. Under this condition, the E-Factor for this process is determined to be:

E-factor = (13.7g +24.65g) / 57.5 = **0.67**

Determination of energy consumption for the dendroketose preparation.

Total power of the used vacuum pump (vacuumbrand®, RZ 6, S/N: 34810211) = 0.18 kW

Total power of the used heating device (IKA® RCT basic 100091497) = 0.65kW (approximation: 0.1kW to heat up and hold target temperature for the whole use time)

Heat capacity of water = 4.2 kJ/(kg*°C)

Distillation temperature = 40°C

Distillation time = 2h

Equations used:

To calculate the energy amount to heat up the solvent:

(1) $Q = cp\ [J/(kg*°C)] * m[kg] * \Delta T\ [°C]$ and with 1kJ = 0.000278 kWh

To calculate the energy amount for pump and heating device:

(2) Energy = power [kW] * time [h]

Calculation.

Solvent heating for distillation: $Q = 4.2\ [kJ/(kg*°C)]* 0.1\ kg * 15°C = 6.3\ kJ \approx 0.002$ kWh

Heating device for distillation: Energy = 0.1 kWh * 2h = 0.2 kWh = 0.68 kWh

Energy for pump: Energy = 0.18kWh * 2h = 0.36 kWh

Total energy consumption = (0.002 + 0.68 + 0.36) kWh = **1.04 kWh**

Energy cost in Germany (2023) = 0.181 EUR/kWh

CO_2 production per generated kWh in Germany (2023) = 360 g/kWh

With these values we calculate for the production of 100g dendroketose:

Energy cost = 1.04kWh * 0.181 EUR/kWh = 0.188 EUR

CO_2 production = 1.04kWh * 360 g/kWh = 374.4 g

Determination of energy consumption for the multigram synthesis of 4-HMF.

Total power of the used vacuum pump (vacuumbrand®, RZ 6, S/N: 34810211) = 0.18 kW

Total power of the used heating device (IKA® RCT basic 100091497) = 0.65kW (approximation: 0.1kW to heat up and hold target temperature for the whole use time)

Cycle 1: Heating from 25°C to 80°C → $\Delta T = 55°C$

Cycle 2-9: Heating from 60°C to 80°C → $\Delta T = 20°C$

Synthesis temperature = 80°C

Synthesis time = 2h

Heat capacity of sat. NaCl solution = 2.97 kJ/(kg*°C)

Equations used:

To calculate the energy amount to heat up the solvent:

(3) $Q = cp\ [J/(kg*°C)] * m[kg] * \Delta T\ [°C]$ and with 1kJ = 0.000278 kWh

To calculate the Energy amount for pump and heating device:

(4) Energy = power [kW] * time [h]

Calculation.

Solvent heating: Q = 2.97 [kJ/(kg*°C)]* 1 kg * 55°C = 163.35 kJ ≈ 0.05 kWh (cycle 1)

Solvent heating: Q = 2.97 [kJ/(kg*°C)]* 1 kg * 20°C = 59.40 kJ * 8 cycles ≈ 0.13 kWh

Heating device during synthesis: Energy = 0.1kW * 2h = 0.2 kWh * 9 cycles = 1.8 kWh

Heating device for distillation: Energy = 0.1 kWh * 0.25h = 0.025kWh * 9 cycles *3 times extraction per cycle = 0.68 kWh

Energy for pump: Energy **=** 0.18kWh * 0.25h = 0.045kWh * 9 cycles * 3 times extraction per cycle = 1.22 kWh

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Total energy consumption = (0.05 + 0.13 + 1.80 + 0.68+ 1.22) kWh = **3.88 kWh**

3.88 kWh is needed for 58g of 4-HMF. We extrapolate this value for the production of 1kg 4-HMF to be (3.88 kWh * 1000g)/58g = **66.90 kWh**

Energy cost in Germany (2023) = 0.181 EUR/kWh

CO_2 production per generated kWh in Germany (2023) = 360 g/kWh

With these values we calculate to produce 1kg 4-HMF:

Energy cost = 66.90kWh * 0.181 EUR/kWh = 12.1 EUR

CO_2 production = 66.90kWh * 360 g/kWh = 24.1 kg

Determination of energy consumption for a hypothetic scale up of 4-HMF production.

Total power of the used vacuum pump (vacuumbrand®, RZ 6, S/N: 34810211) = 0.18 kW

Total power of the used heating device (IKA® RCT basic 100091497) = 0.65kW (approximation: 0.1kW to heat up and hold target temperature for the whole use time)

Cycle 1: Heating from 25°C to 80°C → $\Delta T = 55°C$

Synthesis temperature = 80°C

Synthesis time = 2h

Heat capacity of sat. NaCl solution = 2.97 kJ/(kg*°C)

Solvent Volume ($NaCl/H_2O$) = 125L

Equations used:

To calculate the energy amount to heat up the solvent:

(1) $Q = cp\ [J/(kg*°C)] * m[kg] * \Delta T\ [°C]$ and with 1kJ = 0.000278 kWh

To calculate the Energy amount for pump and heating device:

(2) Energy = power [kW] * time [h]

Calculation.

Solvent heating: Q = 2.97 [kJ/(kg*°C)]* 125 kg * 55°C = 20.419 kJ ≈ 5.67 kWh (**cycle 1**)

Heating device during synthesis: Energy = 0.1kW * 2h = 0.2 kWh = 1.8 kWh

Heating device for distillation: Energy = 0.1 kWh * 2h = 0.2 kWh *3 times extraction per cycle = 0.6 kWh

Energy for pump: Energy **=** 0.18kW * 1h = 0.18kWh * 3 times extraction per cycle = 0.54 kWh

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Total energy consumption = (5.67 + 1.8 + 0.6 + 0.54) kWh = **8.61 kWh**

Energy cost in Germany (2023) = 0.181 EUR/kWh

CO_2 production per generated kWh in Germany (2023) = 360 g/kWh

With these values we calculate to produce 1kg 4-HMF at a 125L synthesis scale:

Energy cost = 8.61kWh * 0.181 EUR/kWh = 1.56 EUR

CO_2 production = 8.61kWh * 360 g/kWh = 3.1 kg

NMR spectrum of dendroketose.

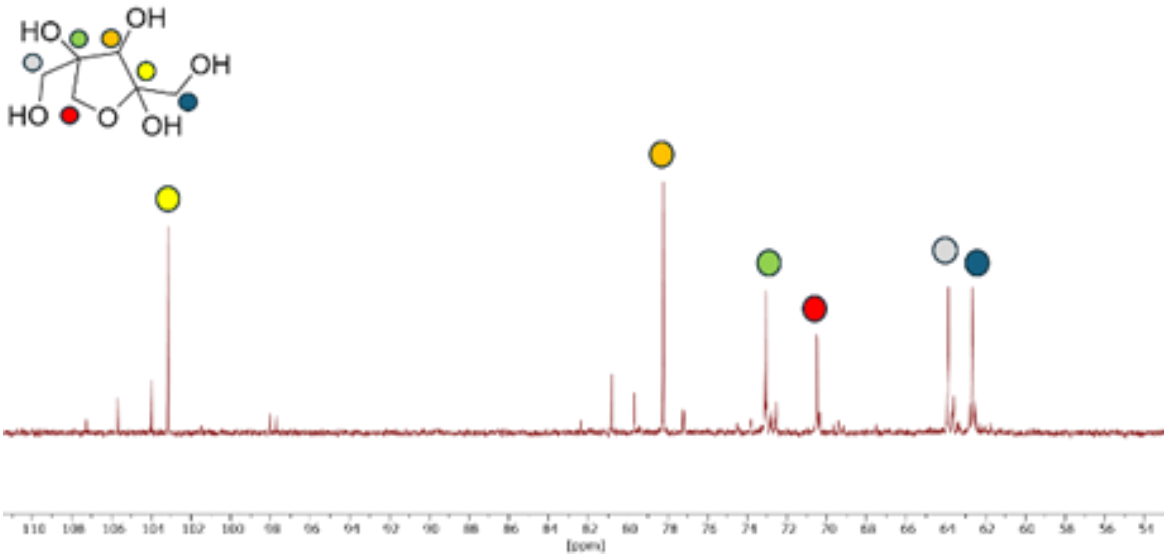


Figure S 1. ^{13}C-NMR spectrum of dendroketose.

Quantification of dendroketose via ^{1}H-NMR analysis

The dendroketose was quantified by using a previously performed calibration line. Aliquot amounts of dendroketose were measured with a fixed and defined amount of potassium formate between 15g/L dendroketose to 180g/L dendroketose concentration in D_2O as solvent. The x-axis represents the set dendroketose concentration, while the y-axis represents the Area-Ratio (A = Area) between the dendroketose ^{1}H-NMR signals between 4.07-3.39 ppm and the KFo ^{1}H-NMR signal at 8.37 ppm.

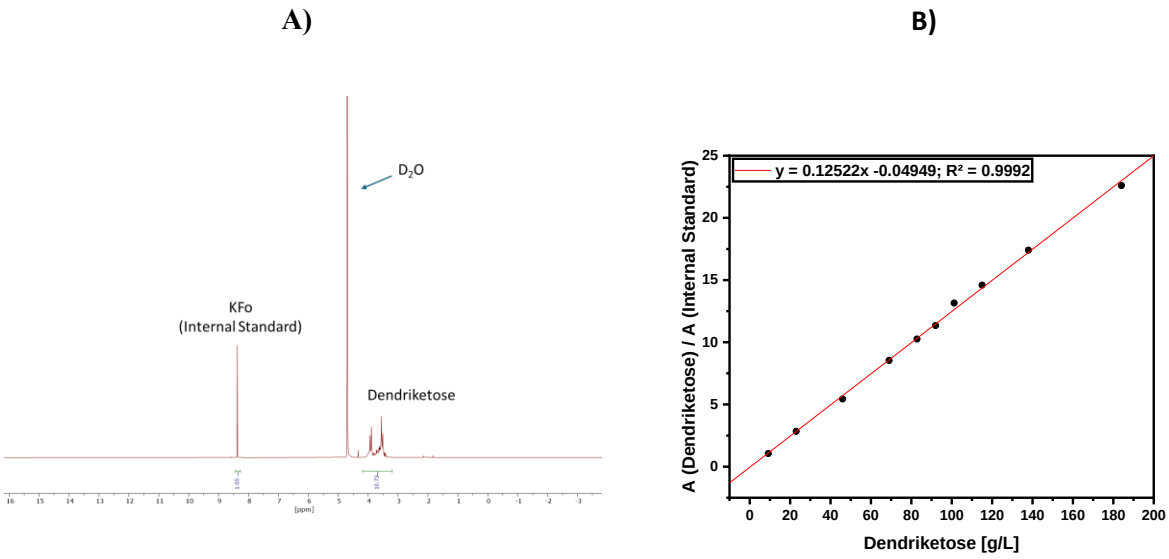


Figure S 2. A) ^{1}H-NMR Spectrum for the dendroketose calibration presented for the datapoint representing 100g/L dendroketose. B) dendroketose calibration line for the quantification of the sugar in aqueous solution. The quantification method has an error of ± 5%.

Screening of Lewis-Acids and Brønsted-Acids for the dendroketose dehydration reaction in NaCl/H_2O

100mg dendroketose and 1mol%, 2.5mol%, 5mol%, 7.5mol%, and 10mol% Metal-triflates were weight into a 2ml Eppendorf tube. 1 ml of saturated NaCl/H_2O solution was added into the tube. The tubes were placed in an Eppendorf-shaker, and were shaked at 800 rpm and 80°C for 2h. After cooling down to room temperature, aliquots of the reaction mixture were diluted in D_2O and the amount of 4-HMF was quantified via ^{1}H-NMR using potassium formate as the internal standard.

Table S 2. Screening of Metal-triflates for the dehydration reaction of dendroketose to 4-HMF.

Metal-Triflates	**Concentration / mol%**	**^{1}H-NMR Yield of 4-HMF / %**
Hf	1	0,9
	2,5	4,7
	5	14,1
	7,5	22,6
	10	21,7
Sc	1	0,0
	2,5	0,0
	5	2,8
	7,5	3,8
	10	4,7

Bi	1	0,0
	2,5	0,0
	5	0,0
	7,5	0,0
	10	3,8
Cu	1-10 mol%	No reaction to 4-HMF
Mn	1-10 mol%	No reaction to 4-HMF
Zr	1-10 mol%	No reaction to 4-HMF
Al	1-10 mol%	No reaction to 4-HMF
Ag	1-10 mol%	No reaction to 4-HMF
Dy	1-10 mol%	No reaction to 4-HMF
Yb	1-10 mol%	No reaction to 4-HMF

100mg dendroketose and 1ml of Sulfuric acid, or trifluormethylsulfonic acid solutions with target concentration prepared in saturated NaCl/H2O were placed into a 2ml Eppendorf tube. The tubes were placed in an Eppendorf-shaker, and were shaked at 800 rpm and 80°C for 2h. After cooling down to room temperature, aliquots of the reaction mixture were diluted in D_2O and the amount of 4-HMF was quantified via ^{1}H-NMR using potassium formate as the internal standard.

Table S 3. Screening of Bronsted acids for the dehydration reaction of dendroketose to 4-HMF.

Bronsted-Acid	Concentration / mol/L	^{1}H-NMR Yield of 4-HMF / %
H_2SO_4	0,05	17,0
	0,125	26,4
	0,25	33,9
	0,375	54,7
	0,5	62,2
TFMS	0,1	0,0
	0,25	8,5
	0,5	0,0
	0,75	39,6
	1	36,8

100mg dendroketose and 10mg to 100mg Amberlyst 15 were placed into a 2ml Eppendorf tube. 1ml of MTHF, MIBK, MEK, or THF were placed into the tube. The tubes were placed in an Eppendorf-shaker, and were shaked at 800 rpm and 80°C for 2h. After cooling down to room temperature, aliquots of the reaction mixture were diluted in $CDCl_3$ and the amount of 4-HMF was quantified via ^{1}H-NMR using trimethoxybenzene as the internal standard.

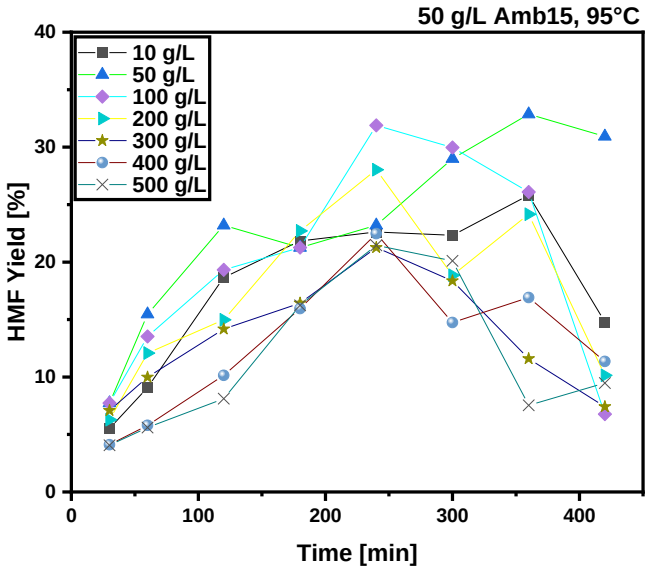
Table S 4. Screening of biphasic reaction medium conditions for the efficient synthesis of 4-HMF

Biphasic System	Resin-Loading/ g/L	^{1}H-NMR Yield of 4-HMF / %
Amb15/dendroketose/MTHF	10	1,8
	25	14,7
	50	25,8
	75	31,3
	100	30,4
Amb15/dendroketose/MIBK	10	0,0
	25	9,2
	50	21,2
	75	23,0
	100	26,7
Amb15/dendroketose/MEK	100	23,9
Amb15/dendroketose/THF	100	6,4

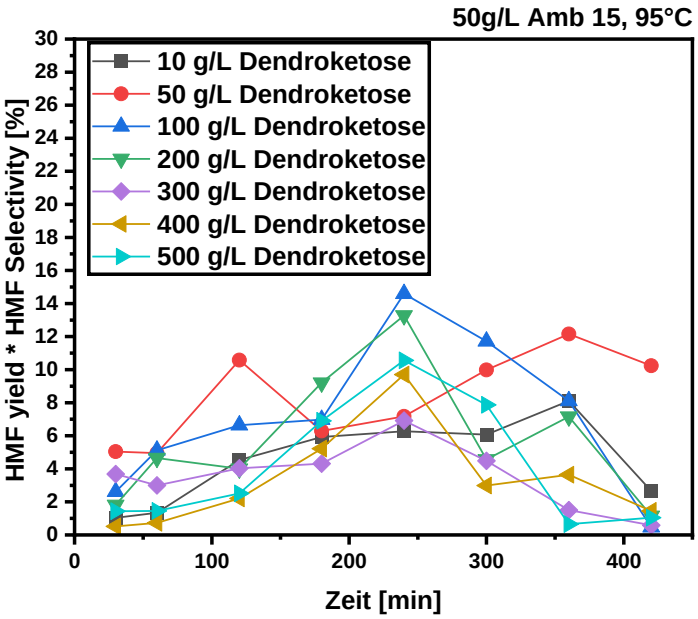
Screening of dendroketose loading

10 mg to 500 mg dendroketose and 50mg Amberlyst 15 were placed into a 2ml Eppendorf tube. 1ml of sat. NaCl/H_2O were placed into the tube. The tubes were placed in an Eppendorf-shaker, and were shaked at 800 rpm and 95°C for 420h. Aliquots of the reaction mixture were diluted in D_2O and the amount of 4-HMF and dendroketose was quantified via ^{1}H-NMR using potassium formate as the internal standard.

A)



B)



C)

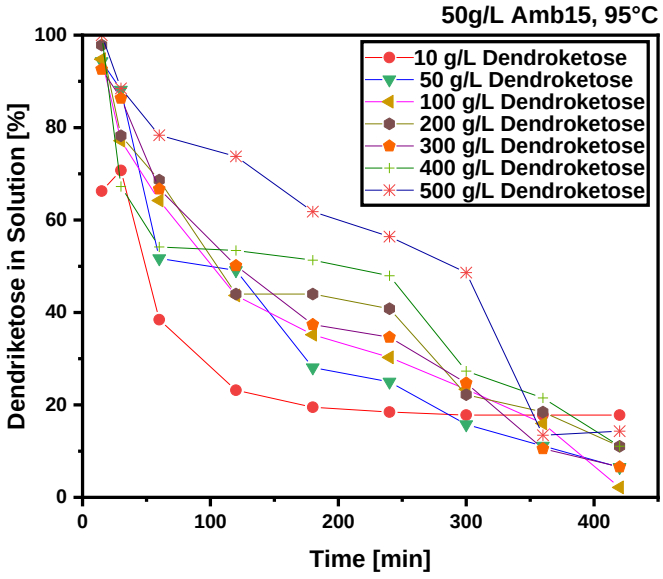


Figure S 3. Screening of dendroketose loading for the efficient dehydration reaction to 4-HMF.

A) 4-HMF yield at dendroketose loadings between 10g/L to 500 g/L, B) HMF yield* HMF

Selectivity at dendroketose loadings between 10g/L to 500 g/L, C) Dendroketose in solution for dendroketose loadings between 10g/L to 500 g/L

Screening of heterogeneous acid catalyst.

100 mg dendroketose and 100 mg of Dowex50, Amberlyst15, Amberlyst16, Fulcat22F, Fulcat22B were placed into a 2ml Eppendorf tube. 1ml of sat. NaCl/H_2O were placed into the tube. The tubes were placed in an Eppendorf-shaker, and were shaked at 800 rpm and 80°C for 120h. Aliquots of the reaction mixture were diluted in D_2O and the amount of 4-HMF and dendroketose was quantified via ^{1}H-NMR using potassium formate as the internal standard.

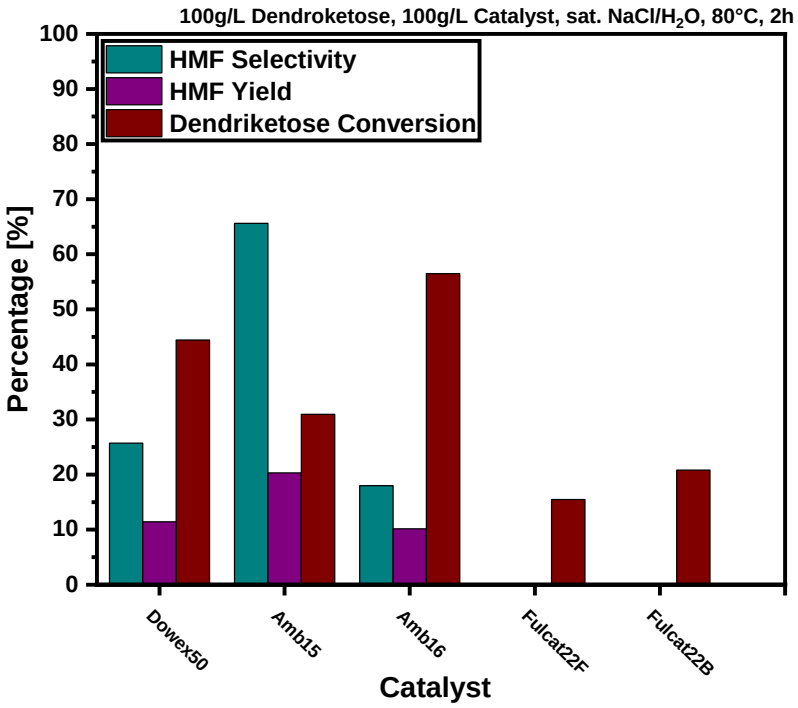


Figure S 4. Screening of heterogeneous acid catalysts for the dendroketose dehydration reaction to 4-HMF.

Recycling studies of heterogeneous acid catalyst

100 mg dendroketose and 100 mg Amberlyst15 were placed into a 2ml Eppendorf tube. 1ml of sat. NaCl/H_2O were placed into the tube. The tubes were placed in an Eppendorf-shaker, and were shaked at 800 rpm and 80°C for 120h. Aliquots of the reaction mixture were diluted in D_2O and the amount of 4-HMF and dendroketose was quantified via ^{1}H-NMR using potassium formate as the internal standard. For the further reaction cycles, the reaction solution was discarded and the catalyst was washed 3 times with sat. NaCl solution. 1 ml of a solution that contains 100 mg dendroketose in total was given to the recycled Amb15 beads and the reaction was conducted at 80°C for 120h using an Eppendorf shaker. Aliquots of the reaction mixture were diluted in D_2O and the amount of 4-HMF and dendroketose was quantified via ^{1}H-NMR using potassium formate as the internal standard.

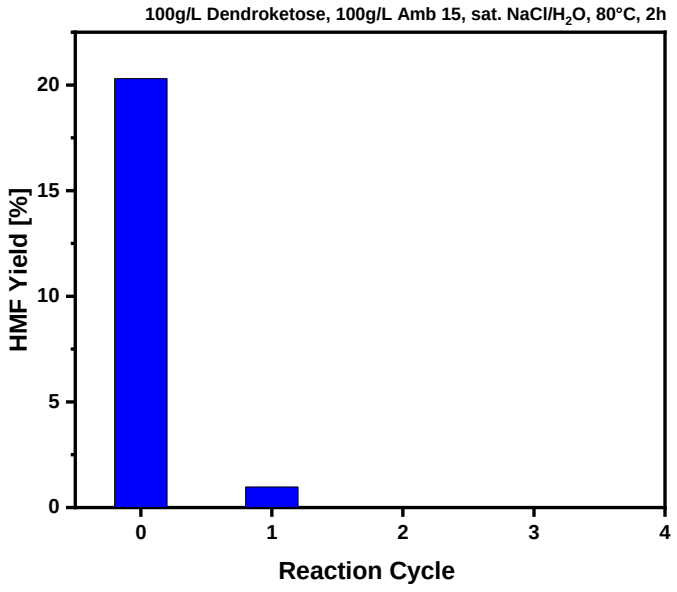


Figure S 5. Recycling of Amb15 beads for dehydration reaction of dendroketose to produce 4-HMF.

For the control experiment, 100 mg Amberlyst15 were placed into a 2ml Eppendorf tube. 1ml of sat. NaCl/H_2O were placed into the tube. The tubes were placed in an Eppendorf-shaker, and were shaked at 800 rpm and 80°C for 120h. 1ml of the reaction solution was removed from the Amb15 beads and 100mg of dendroketose was added to the solution. The tubes were placed in an Eppendorf-shaker, and were shaken at 800 rpm and 80°C for 120h without Amb15 beads.

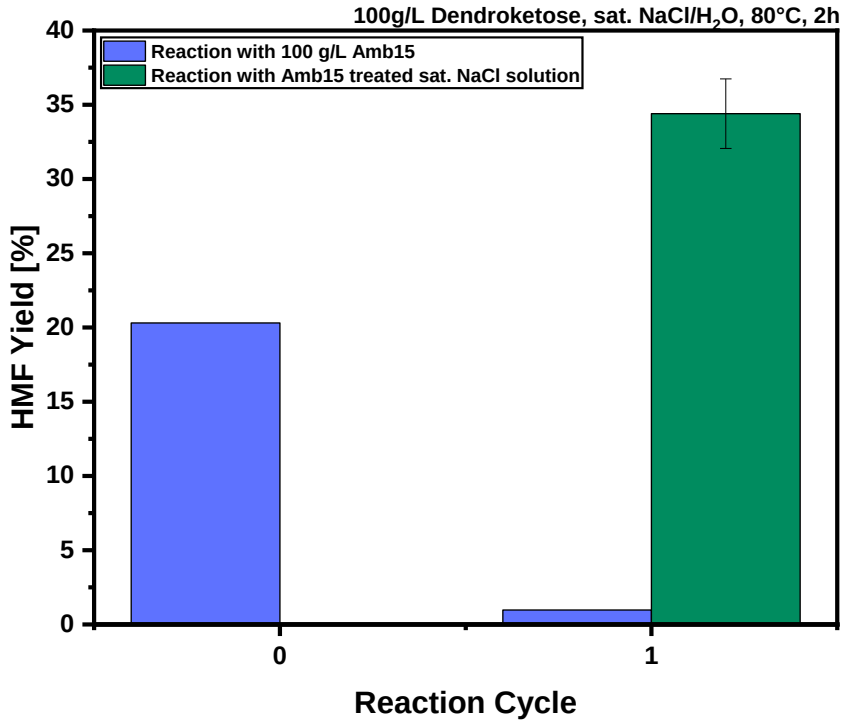


Figure S 6. Recycling of Amb15 beads for dehydration reaction of dendroketose to produce 4-HMF. Control experiment.

Control experiment for the HCl catalyzed dendroketose dehydration

100 mg dendroketose was placed into a 2ml Eppendorf tube. 1ml of sat. NaCl/H_2O including 0.25M HCl, or 1ml of 0.25M HCl in D.I. water were placed into the tube. The tubes were placed in an Eppendorf-shaker, and were shaked at 800 rpm and 80°C for 120h. Aliquots of the reaction mixture were diluted in D_2O and the amount of 4-HMF and dendroketose was quantified via ^{1}H-NMR using potassium formate as the internal standard.

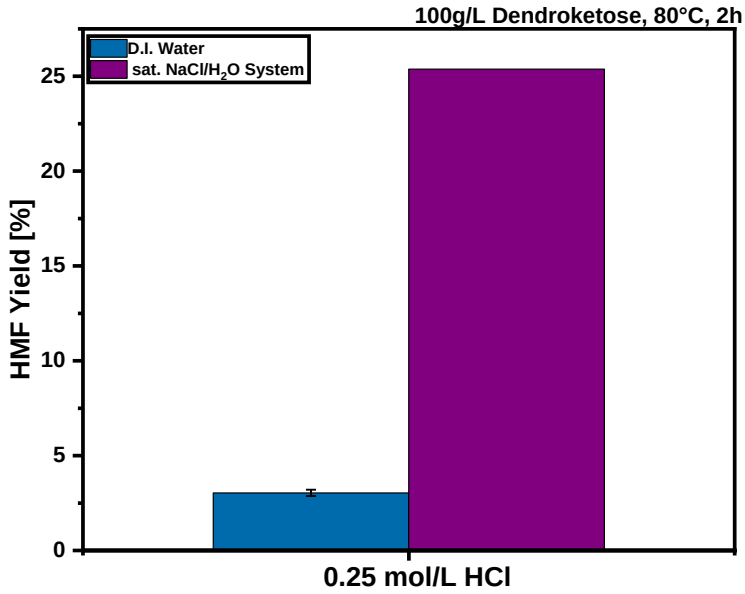


Figure S 7. Dendroketose dehydration reaction in presence of 0.25M HCl in D.I. water and in sat. NaCl solution.