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Facile synthesis of 5-hydroxymethylfurfural: A sustainable raw material for synthesis of key intermediates toward 21,23-dioxaporphyrins

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In a simple and conceptually designed method for dehydration of fructose on a solid support, 5-hydroxymethylfurfural (HMF) was synthesized in more than 95% isolated yields from fructose under very mild conditions at room temperature. Loading of fructose on solid support reduced intermolecular interaction between fructose/intermediates, diminished the formation polymeric material (Humin) and increased the selectivity towards HMF formation. The synthesized HMF was readily converted into key intermediates toward the simpler synthesis of 21,23-dioxaporphyrins.

Introduction

Depletion of fossil fuels, its impact on the ecology and increasing demand for raw materials necessitate the smooth transition from fossil fuel era to sustainable era. In this context, various plant derived organic matters have been proposed as energy alternate and sustainable raw materials.[1-8] Among the plant derived matters, 2,5-dimethylfurfural (DMF) best fits by its energy content to meet with present locomotive system,[9] and DMF was obtained from 5-hydroxymethylfurfural (HMF).[10-13] HMF derived 2,5-furandicarboxylic acid is considered as one of the top 12 bio-based building blocks listed by the U.S. Department of Energy.[14-16] Also, HMF has been demonstrated as a promising sustainable raw material and utilized in the synthesis of various interesting molecules.[17-20] Conversion of biomass derived chemicals into value added products is a topic of major interest towards sustainability. Among the value added products, dioxaporphyrins are interesting molecular skeleton capable of forming stable complex with neutral atoms and nanoaggregates with good charge mobility.[21] Current synthesis of 21,23-dioxaporphyrins involves complex synthetic procedures, low yield, and difficulties in isolation.[22] For the first time, we have designed a very simple synthetic methodology to access 21,23-dioxaporphyrins through furanylpyrrolyl carbinols utilizing biomass derived HMF as a starting material (Scheme **1**).

HMF is dehydrated form of fructose obtained in a Bronsted acid catalyzed dehydration of fructose. In the available methods for the dehydration of fructose, fructose was dissolved in a medium and treated with a catalyst under conventional or microwave heating. The reaction medium can be broadly categorized as (i) aqueous,[23-25] (ii) organic,[26-34] (iii) biphasic[35-40] and (iv) ionic liquid.[41-45] The main drawback of using aqueous/biphasic system is rehydration. In the presence of water, the formed HMF was rehydrated to form levulinic acid and formic acid, hence loss in selectivity and yield. Use of organic medium is constrained by limited solubility of fructose. In an exceptional case, fructose is easily soluble in DMSO, but the extraction of HMF becomes very tedious when DMSO is used as a reaction medium.[26-33] Also, the available methods are constrained by many other shortcomings such as humin formation,[46-49] requirement of toxic and environmentally incompatible catalysts,[42] tedious process involved in the preparation of catalysts[50,51] and ionic liquids,[52-55] energy intense conventional/microwave heating[23-45] etc. To expedite our new methodology to access 21,23-dioxaporphyrins, we wanted to develop a simple and selective method for HMF synthesis from fructose by introducing the concept, solid supported dehydration of fructose.

Here in we report a facile synthesis of HMF by dehydration of fructose on solid support under very mild conditions at room temperature. In a foray to utilize HMF as a sustainable starting material in the synthesis of 21,23-dioxaporphyrin, we have demonstrated the synthesis of two types of key intermediates for accessing functionally tuneable 21,23-dioxaporphyrins.

Results and Discussion

Our attempts to use HMF as a starting material in the synthesis of core modified porphyrins were restricted by difficulties in the synthesis of HMF, and the limiting factors were (i) formation of polymeric material (humin) (ii) rehydration of HMF in aqueous medium resulting levulinic acid and formic acid and (iii) difficulties in extraction of HMF. To

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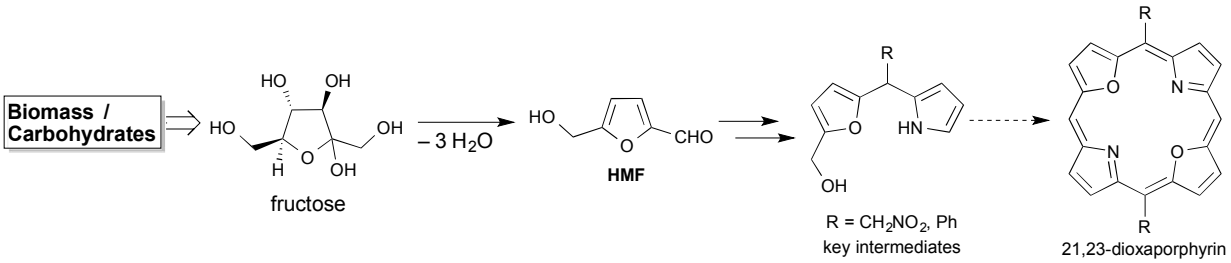


Scheme 1. Synthesis of 21,23-dioxaporphyrin

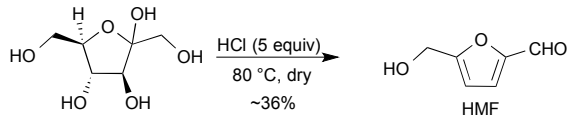
address these issues, we started exploring solid phase synthesis of fructose using readily available simple solid supports (silica gel, celite and neutral alumina).

The initial exploration on solid supported dehydration was carried out under dry condition using silica gel as a solid support (Table 1). Silica gel is incompletely dehydrated polymeric structure with molecular formula $SiO_2 \cdot nH_2O$ and capable of adsorption of water up to 35–40% of its dry mass. Its surface comprises mainly -Si-OH and –Si-O-Si- groups providing intrinsic polarity and absorbs polar adsorbates such as water and alcohol.[56] Fructose by its inherent polarity was adsorbed firmly on the silica gel surfaces. The loading was carried out by mixing fructose and silica gel (1:1, by wt) in a mortar and pestle for 2–3 minutes.

The solid supported fructose was treated with HCl (5 equiv), mixed well by grinding and kept in a hot air oven maintained at specified temperature for stipulated. Keeping at 100 °C for 30 min resulted in the formation of HMF in 32% yield (Table 1, entry 1). The HMF was extracted by washing the treated silica gel with ethyl acetate. Decrease in temperature to 80 °C resulted in slight improvement in HMF yield (36%, Table 1, entry 2). For the experiments carried out at 50 °C, five samples were prepared by mixing silica gel supported fructose with HCl (5 equiv) and the samples were kept in a hot air oven maintained at 50 °C. Samples were removed from oven in a regular time interval as stipulated in Table 1 and washed with EtOAc to obtain HMF. Dehydration of fructose carried out at 50 °C required prolonged heating (Table 1, entry 6) to reach HMF yield of 30%. When the sample was kept at room temperature, very less amount of HMF (5%) was formed even after the period of 48 h (Table 1, entry 7). Formation of HMF, albeit in traces (5%) at room temperature indicated that the dehydration could proceed in room temperature itself and might proceed with better efficiency if the content was stirred at room temperature in the presence of an organic solvent/medium. Also, the use of solvent might facilitate the periodic extraction of HMF from solid support. Hence we designed a set of experiments, treating silica gel supported fructose with HCl (5 equiv) in the presence of dichloromethane as a medium at room temperature (Table 2, Figure 1).

In a wet synthesis using CH_2Cl_2 as a solvent carried out at room temperature for 30 min, HMF was obtained as the only product from solution fraction in very low yield (Table 2, entry 1). Extending time to achieve enhanced yields of HMF did not result in any increase in the HMF yields (Table 2, entries 2-7). But, we noticed the formation of a non-polar compound and its yield was increased with increase in reaction time. The compound was characterized as 5-chloromethylfurfural (CMF). CMF is considered functionally equivalent to HMF and easy to isolate from aqueous/biphasic solvent systems due to its lipophilicity.[57] After 24 h stirring at 30 °C, CMF was obtained in 32% isolated yield. In an experiment carried out using HBr instead of HCl, 5-bromomethylfurfural (BMF) was obtained in 35 % yield (Table 2, entry 7) along with HMF in 10% yield.

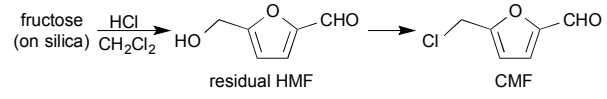
Table 1. Solid supported dry synthesis of HMF[a]



entry	temperature (°C)	time (h)	HMF yield (%)
1	100	0.5	32
2	80	0.5	36
3	50	0.5	<5
4	50	4	10
5	50	12	15
6	50	24	30
7	30	48	5

[a]Fructose (1.8 g) and silica gel (230-400 mesh, 1.8 g) were mixed and treated with HCl (5 equiv) and kept at hot air oven.

Table 2. HMF synthesis on wet silica gel support at room temperature.[a]



entry	time (h)	yield (%)		
		residual HMF	CMF	total
1	0.5	10	--	10
2	3	12	10	22
3	6	11	15	26
4	9	10	18	28
5	12	8	23	31
6	24	5	32	37
7[b]	24	10	35[c]	45

[a]Fructose (1.8 g) and silica gel (230-400 mesh, 1.8 g) were mixed and treated with CH_2Cl_2 (40 mL) and HCl (5 equiv) at room temperature. [b]HBr (5 equiv) was used instead of HCl. [c]Value corresponds to yield of 5-bromomethylfurfural (BMF).

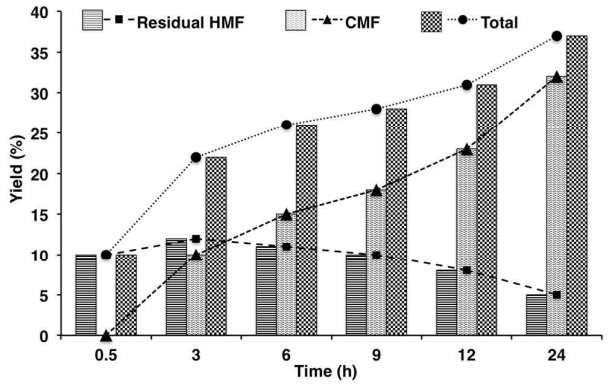


Figure 1. Yield comparison of CMF and residual HMF

Dependence of yield of CMF and residual HMF on reaction time is graphically represented in Figure 1 to provide a clear picture about this transformation. The whole transformation (fructose ➔ CMF/BMF) can be divided in to two steps (i) formation of HMF on solid phase (fructose ➔ HMF) and (ii) conversion of HMF ➔ CMF on liquid phase, leaving CMF and residual HMF in solution. The residual HMF yield increased initially. On prolonged treatment, the residual HMF yield decreased steadily as the transformation HMF ➔ CMF was kinetically faster than the transformation fructose ➔ HMF. The CMF yield steadily increased with time in parallel with total yield. The dehydration mediated by HBr followed similar trend with slight betterment in the overall yield. BMF was obtained as major product and HMF as minor product (Table 2, entry 7).

Diminishing the formation of BMF might be beneficial in developing simpler method of isolation of HMF. The available literature reports on HBr/HCl mediated transformations of HMF to BMF/CMF are utilizing only halogenated solvents (dichloromethane DCM or dichloroethane DCE).[58-60] This implied that use of non-halogenated solvent as reaction medium might stop the dehydration at HMF level. To support this concept and to understand the reactivity of HMF with HBr, we tested HMF ➔ BMF transformation in various solvents. Our study on HMF ➔ BMF transformation mediated by HBr using different solvents concluded that HMF ➔ BMF transformation proceeded quantitatively, only in cases of halogenated solvents (DCM, DCE & $CHCl_3$) being used as a solvent (Table 3, entries 1-3). In non-halogenated solvents (THF, dioxane & acetonitrile), BMF was formed only in traces and unreacted HMF was recovered (Table 3, entries 4-6).

These findings emphasized that HBr mediated dehydration of fructose using non-halogenated solvent might stop at HMF stage and provide HMF selectively. This is very conclusive finding and provided us a crucial lead in tuning fructose dehydration towards HMF selectivity. Accordingly, we proceeded to screening of various solvents broadly categorized as halogenated solvents (DCM, DCE & $CHCl_3$) and non-halogenated solvents (dioxane, THF, acetonitrile & ethyl acetate) for HBr mediated fructose dehydration on solid

Table 3. Screening of solvent for the transformation HMF ➔ BMF[a]

entry	solvent	HMF yield (%)	
		HMF recovered	BMF
1	dichloromethane	-	87
2	chloroform	-	85
3	dichloroethane	-	91
4	acetonitrile	90	<5
5	THF	93	<5
6	dioxane	94	<5

[a]A solution of HMF (1.00 mmol, 126 mg) in solvent (10 mL) was treated with conc. HBr (2.9 mL, 25 mmol, 48% solution in water) for 24 h at 30 °C.

dehydration on solid support. In the dehydration experiments carried out using halogenated solvents, BMF was obtained as the major product (Table 4). All the halogenated solvents tested showed similar trend in terms of yield and selectivity (Table 4, entries 1-4). Reducing the HBr equivalences up to 2 did not show any change in the BMF yield (Table 4, entries 4-6). Using HBr in less than 2 equivalences showed deterioration in the fructose dehydration and BMF was obtained in lower yields (Table 4, entries 7 & 8). Without addition of HBr, the reaction did not proceed as evidenced by the absence of HMF and BMF in the reaction mixture (Table 4, entry 9).

In wet synthesis using non-halogenated solvents (MeCN, dioxane & THF), HMF was obtained as the major product in upto 80% yield (triple extraction) and BMF in traces (Table 5, entries 1-3). This is in accordance with our expectance. In the experiment carried out by treating solid supported fructose

Table 4. Dehydration of fructose in halogenated solvents[a]

entry	solvent	HBr equiv.	BMF yield (%)
1	dichloroethane	5	30
2	chloroform	5	32
3	carbon tetra chloride	5	30
4	dichloromethane	5	35
5	dichloromethane	3	33
6	dichloromethane	2	33
7	dichloromethane	1	22
8	dichloromethane	0.5	11
9	dichloromethane	0	NR

[a]Fructose (1.8 g) and silica gel (230-400 mesh, 1.8 g) were mixed and treated with halogenated solvent (40 mL) and HBr (5 equiv) at 30 °C for 12 h. NR = no reaction

Table 5. HMF synthesis in non-halogenated solvents

entry	solvent	HMF yield (%)	
		single extraction[a]	triple extraction[b]
1	MeCN	36	78
2	dioxane	39	74
3	THF	37	80
4[c]	**THF**	**45**	**95**
5[d]	THF	33	75
6	EtOAc	21	59

[a]Fructose (1.8 g) loaded on silica gel (230-400 mesh, 1.8 g) and solvent (40 mL) were treated with HBr (5 equiv) at rt for 12 h. [b]Stirring time is 3 x 8 h. [c]HBr loaded on silica (1 equiv) was used. [d]Experiment using recovered silica support.

with HBr preloaded on silica, HMF was obtained in 95% yield (Table 5, entry 4). In a multiple extraction process, the solution content of reaction medium was exchanged with fresh solvent in an interval of 8 h, for three cycles. After three extractions, the support was recovered, dried and reused for dehydration and found to be effective in mediating the dehydration of fructose as a fresh support (Table 5, entry 5). With ethyl acetate being used as a solvent, HMF was obtained in slightly lower yield along with formation of BMF and 5-acetoxymethylfurfural (AMF) in traces (Table 5, entry 6).

Our experimental observations concluded that HBr and HCl were effective in mediating dehydration of fructose loaded on solid support at room temperature and HMF was obtained up to 95% isolated yield. In order to test the efficiencies of other acids in mediating the dehydration, we have screened three types of acids (Lewis acids, organic Bronsted acids and inorganic Bronsted acids) and the results are tabulated in Table 6. Lewis acids ($AlCl_3$, $Cu(NO_3)_2$ & $CuCl_2{\cdot}2H_2O$) and organic Bronsted acids (benzoic acid, TsOH & trifluoroacetic acid) are found to be ineffective in mediating the dehydration of fructose. In the H_2SO_4 mediated reaction, the fructose was found to be charred on the support. The screening of various acids suggested the best condition as HBr mediated dehydration of fructose at room temperature with triple extraction procedure using HBr preloaded on silica.

The HMF synthesis was tested by using various readily available solid supports (Table 7). In a parallel experiment carried out using alumina, silica gel of different size, and celite as solid support, alumina did not facilitate HMF formation resulting only trace amount of HMF and BMF. The low yied of HMF and its derivative was due to low conversion of fructose. The absence of humin formation was evidenced by color and TLC analysis of methanol washing of solid support (Table 7, entry 1). In an experiment carried out with out solid support, the fructose was settled in the bottom of reaction flask and polymerization was induced (Table 7, entry 2). HMF selectivity was observed only with celite and silica gel (Table 7, entries 3-7). Better selectivity and yields were obtained using silica gel with fine particle size (230-400 mesh), (Table 7, entries 6 *vs* 7).

Table 6. Screening of acids for dehydration of fructose[a]

entry	acid	HMF yield (%)
1	$Cu(NO_3)_2$	NR
2	$CuCl_2{\cdot}2H_2O$	NR
3	$AlCl_3$	NR
4	p-toluenesulfonic acid	NR
5	4-chlorobenzoic acid	NR
6	trifluoroacetic acid	NR
7	formic acid	NR
8	hydrobromic acid	79[b]
9	hydrochloric acid	64[b]
10	Sulphuric acid	charred

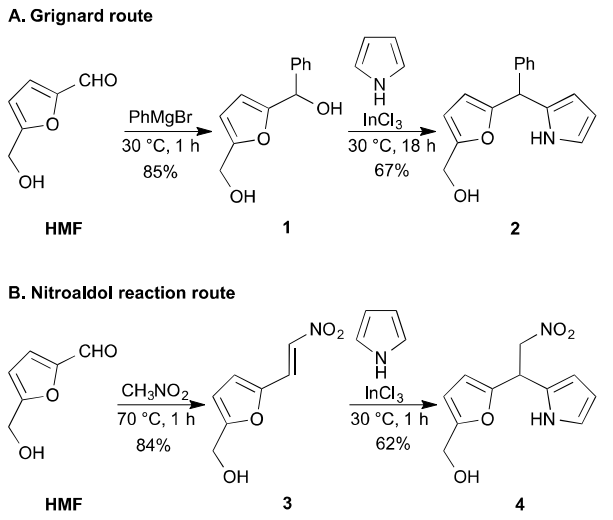
[a]Fructose (1.8 g) and silica gel (230-400 mesh, 1.8 g) were mixed and treated with THF (40 mL) and acid (5 equiv) at 30 °C for 12 h. [b]Triple extraction (3 x 8 h). NR = no reaction.

Table 7. Screening of solid support for HMF synthesis[a]

entry	solid support	HMF yield (%)
1	Alumina	trace
2	-	trace
3	Celite	42
4	Silica gel (230-400 mesh)	45
5	Celite	74[b,c]
6	Silica gel (230-400 mesh)	95[b]
7	Silica gel (100-200 mesh)	78[b]

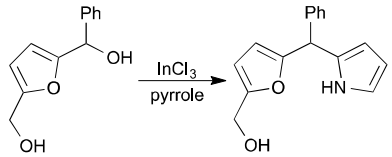
[a]Fructose (1.8 g) and solid support (1.8 g) were mixed and treated THF (40 mL) and silica supported HBr (1 equiv) for 12 h. [b]triple extraction (3 x 8 h). [c]Conc. HBr was used instead of solid supported HBr.

Currently HMF has been utilized in the synthesis of polymers, energy alternatives, solvent etc.[14-20]For the synthesis of 21,23-dioxaporphyrins, we presumed that HMF can be a well suited starting material to begin with. It has one carbonyl group to introduce pyrrole moiety and another carbonyl group in reduced form ($-CH_2OH$) as a handle to build tetra-pyrrole skeleton. In the proposed synthetic strategy (Scheme 2A), HMF was treated with phenylmagnesium bromide to form phenylfuranyldiol **1** in 85% yield. Phenylfuranyldiol was treated with pyrrole (10 equiv) and recyclable $InCl_3$ (Table 8) in a solventless condition to form phenyl-furanylpyrromethanecarbinol **2** in 67% yield, a key intermediate for the synthesis of 21,23-dioxaporphyrin. To study the recyclability of $InCl_3$, the catalyst was loaded on celite to make celite supported $InCl_3$ (10% w/w) by thoroughly mixing required amount of $InCl_3$ and celite. In an experiment to synthesize **2**, after the completion of reaction (either at 30 °C for 18 h or at 70 °C for 30 min), the reaction medium was diluted with dichloromethane and the catalyst was recovered by centrifugation. The recovered catalyst was reused in the synthesis of key intermediate **2** from **1** and found to be effective for upto four cycles (Table 8, entry 6).



Scheme 2. Synthesis of 21,23-dioxaporphyrin

Table 8. Screening of solid support for HMF synthesis[a]



1 2

entry	cycle number	condition	Yield of **2** (%)
1	fresh catalyst	30 °C, 18 h	67
2	I recycle	30 °C, 18 h	65
3	fresh catalyst	70 °C, 30 min	73
4	I recycle	70 °C, 30 min	68
5	II recycle	70 °C, 30 min	70
6	III recycle	70 °C, 30 min	65

[a]Solution of compound **1** (0.25 mmol, 51 mg) in pyrrole (2.5 mmol, 172 μL) was treated with fresh/recovered celite supported $InCl_3$ (25 μmol) under stipulated condition.

In an alternate route (Scheme 2B) to synthesize key intermediate for dioxaporphyrin, HMF was treated with nitromethane at 70 °C in the presence of ammonium acetate yielding 5-(2-nitrovinyl)furan-2-ylmethanol **3** in 84% yield. The treatment of nitroalkene **3** with pyrrole under solvent-less condition in the presence of $InCl_3$ resulted in the formation of 5-(2-nitro-1-(pyrrol-2-yl)ethyl)furan-2-ylmethanol **4** in 62% yield.

Conclusions

We have developed a conceptually designed and simple method for the dehydration of fructose on a solid support addressing several issues like selectivity, easy extraction, diminishing the formation humin and rehydration of HMF. In a solid supported dehydration of fructose mediated by acid (HBr/HCl), HMF was selectively obtained as a major product in >79% yield with other derivatives (BMF/CMF/AMF) in traces. Use of non-halogenated solvent diminished the conversion of HMF to BMF. The solid support and solvent used were recovered and reused. Toward a sustainable era, we have developed new synthetic methodologies to access key intermediates to access functionally tunable 21,23-dioxaporphyrins using plant derived HMF as starting material and recyclable solid supported $InCl_3$. These findings on easy access to HMF and their use in organic synthesis will provide a boost on exploration of HMF as sustainable raw material in various organic syntheses.

Experimental

General information

^{1}H NMR (300 MHz) spectra were recorded on Bruker-300-AVANCE II spectrometer, with chloroform-d as solvent and tetramethylsilane (TMS) as reference (δ = 0 ppm). The chemical shifts are expressed in δ downfield from the signal of internal TMS. Analytical thin layer chromatographic tests were carried out on aluminium sheets coated with silica gel GF provided by Merck. The spots were visualized by UV light or by dipping into sulfuric acid in methanol (5%, v/v) and heated with hot air gun. Column chromatography was carried out using silica gel (230-400 mesh). All yields reported are of isolated materials judged homogeneous by TLC, and NMR spectroscopy. Parallel reactions are carried out in a Heidolph StarFish Hei-End Multi Workstation. HMF produced by the method reported in this article is used in the synthesis of key intermediates **3** and **4**.

Synthetic Procedures

Preparation of solid supported fructose: Fructose (10 mmol, 1.8 g) and solid support (1.8 g) were taken in a mortar and pestle and hand pulverized for 2-3 min. The content was completely transferred to a reaction flask for dehydration studies.

Experimental procedure for HBr mediated synthesis of HMF on silica: Fructose (10 mmol, 1.8 g) loaded on silica gel (230-400 mesh, 1.8 g) was taken in a reaction flask and THF (40 mL) was added. The content was mixed with HBr supported on silica (10 mmol, loaded onto 2.2 g silica) and the content was stirred at 30 °C. After 8 h stirring, the solid matter was allowed to settle down and the organic fraction was transferred to another flask. The settled solid matter was mixed with fresh THF (40 mL) and stirred for another 8 h. The process of stirring and collection of solvent fraction was repeated to a total of 3 cycles. The combined organic fraction was treated with solid sodium bicarbonate and filtered. The filtrate was evaporated under reduced pressure. The resulting crude material was purified by passing through a short silica pad [EtOAc/hexanes (1:4)] to obtain HMF as yellow oily liquid (1.20 g, 95% yield).

Experimental procedure for HBr mediated conversion of HMF to BMF: A solution of HMF (1.00 mmol, 126 mg) in solvent (10 mL) was treated with Conc. HBr (2.9 mL, 25 mmol, 48% solution in water) in a flask, stirred for 24 h at 30 °C and then organic layer was separated, and acidic fraction was extracted with CH_2Cl_2 (for halogenated solvent) or EtOAc (for non-halogenated solvent). Organic fractions were combined, dried with Na_2SO_4. The solvent was removed by rotary evaporation under reduced pressure and purified by passing through a short silica pad.

Synthesis of (5-(hydroxymethyl)furan-2-yl)(phenyl)methanol (1): A solution of HMF (10.0 mmol, 1.26 g) in THF (10 mL) was treated with phenylmagnesium bromide (25 mmol, prepared in a separate flask), stirred for 1 h. The excess Grignard reagent was quenched by adding sat. aq. NH_4Cl solution at 0 °C, extracted with EtOAc. Organic fractions were combined, dried with Na_2SO_4. The solvent was removed by rotary evaporation under reduced pressure and purified by passing through a short silica pad to obtain the title compound as a yellow solid (1.74 g, 85%): mp 90-92 °C; ^{1}H NMR (300 MHz, $CDCl_3$) □ 4.57 (s, 2H), 5.81 (s, 1H), 6.02 (d, *J* = 3.0 Hz, 1H), 6.21 (d, *J* = 3.3 Hz, 1H), 7.29–7.46 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) □ 43.4, 76.6, 110.9, 119.0, 122.0, 129.7, 137.1, 152.6, 155.2, 177.4; ESI-MS obsd 227.0682, calcd 227.0679 (M+Na; M = $C_{12}H_{12}O_3$).

Synthesis of 5-(phenyl(pyrrol-2-yl)methyl)furan-2-ylmethanol (2): A solution of **1** (1.00 mmol, 204 mg) in pyrrole (10.0 mmol, 690 μL) was treated with $InCl_3$ (100 μmol, 221 mg, 10% w/w on celite), stirred for 18 h at 30 °C. The content was diluted with CH_2Cl_2 (10 mL) and the solution fraction was collected. The residue was washed with CH_2Cl_2 (2 x 5 mL). The combined solution fraction and washings was concentrated under reduced pressure. The resulting residue was purified by column chromatography [silica, EtOAc: hexanes (1:19)] to obtain the title compound **2** as a white solid (170 mg, 67%): mp 94-96 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.50 (s, 2H), 5.42 (s, 1H), 5.90–5.92 (m, 1H), 5.98 (d, *J* = 3.3 Hz, 1H), 6.14 (q, *J* = 3.0 Hz, 1H), 6.20 (d, *J* = 3.3 Hz, 1H), 6.67–6.70 (m, 1H), 7.19–7.33 (m, 5H), 8.15 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.4, 57.5, 107.3, 108.2, 108.3, 108.6, 117.5, 127.1, 128.4, 128.6, 131.0, 140.6, 153.5, 155.9; ESI-MS obsd 276.0997, calcd 276.0995 (M+Na; M = $C_{16}H_{15}NO_2$).

Synthesis of 5-(2-nitrovinyl)furan-2-ylmethanol (3): A solution of HMF (10.0 mmol, 1.26 g) in nitromethane (5 mL) was treated with ammonium acetate (2.5 mmol, 190 mg), and the mixture was heated at 70 °C for 1 h. The content was poured into water and extracted with diethyl ether (3 × 20 mL). The extract was washed with brine, dried over MgSO4, filtered and evaporated under reduced pressure. The residue was purified by recrystallization from ethanol to give the title compound **3** as yellow solid (1.42 g, 84 % yield): mp 84-86 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.62 (d, *J* = 4.5 Hz, 2H), 6.42 (d, *J* = 3.3 Hz, 1H), 6.79 (d, *J* = 3.3 Hz, 1H), 7.45 (d, *J* = 13.2 Hz, 1H), 7.68 (d, *J* = 13.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 57.4, 111.0, 121.1, 125.4, 134.5, 146.3, 159.0; ESI-MS obsd 192.0276, calcd 192.0267 (M+Na; M = $C_7H_7NO_4$).

Synthesis of 5-(2-nitro-1-(pyrrol-2-yl)ethyl)furan-2-ylmethanol (4): A solution of **3** (2.00 mmol, 338 mg) in pyrrole (10.0 mmol, 690 μL) was treated with $InCl_3$ (200 μmol, 442 mg, 10% w/w on celite), stirred for 30 min at 30 °C. The content was diluted with CH_2Cl_2 (10 mL) and the solution fraction was collected. The residue was washed with CH_2Cl_2 (2 x 5 mL). The combined solution fraction and washings was concentrated under reduced pressure. The resulting residue was purified by column chromatography [silica, EtOAc: hexanes (1:4)] to obtain the title compound **4** as a light brown liquid (293 mg, 62%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.54 (s, 2H), 4.75–5.00 (m, 3H), 6.07–6.09 (m, 1H), 6.12 (d, *J* = 3.3 Hz, 1H), 6.13–6.16 (m, 1H), 6.21 (d, *J* = 3.3 Hz, 1H), 6.68–6.71 (m, 1H), 8.55 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.0, 56.9, 77.5, 106.5, 108.3, 108.5, 108.9, 118.5, 126.0, 151.0, 153.8; ESI-MS obsd 259.0699, calcd 259.0689 (M+Na; M = $C_{11}H_{12}N_2O_4$).

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Facile synthesis of 5-hydroxymethylfurfural: A sustainable raw material for synthesis of key intermediates toward 21,23-dioxaporphyrins

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