High-yield conversion of plant biomass into the key value-added feedstocks 5-(hydroxymethyl)furfural, levulinic acid, and levulinic esters *via* 5-(chloromethyl)furfural

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5-(Hydroxymethyl)furfural, levulinic acid, ethyl levulinate and butyl levulinate are produced by the solvolysis of 5-(chloromethyl)furfural (CMF). Since CMF can be derived in high yield from sugars, cellulose, or lignocellulosic feedstocks, the process described here presents an efficient entry into the value-added manifold of biomass-derived products of relevance to the organic materials and fuel industries.

As and when the global petroleum economy draws to a close, the portfolio of derived products from biomass will need to diversify in order to satisfy feedstock requirements across a range of markets. Bioethanol and biobutanol, for example, have primarily uses as fuel oxygenates, and can be used in the production of biodiesel from vegetable oil, but they can also be dehydrated to give the major industrial feedstocks ethylene and 1-butene. Similarly, biogenic methane can be catalytically converted into methanol which, like ethanol and butanol, can be used to prepare biodiesel, but can also be submitted to oxidative coupling processes to give ethylene and higher olefins.¹⁻³ Yet as versatile as these mainstream biomass derivatives are, they

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cannot cover the breadth of chemical feedstock classes available from petroleum.

Recently, we described the digestion of sugars, cellulose, or cellulosic biomass with hydrochloric acid in a biphasic reactor which resulted in the isolation of a mixture of 5-(chloromethyl)furfural 1 (CMF) and levulinic acid 2 in up to 95% combined yield (Scheme 1).⁴ The major product of the reaction is by far CMF 1, which accounts for between 70 and 90% of the organic material isolated, depending on the feedstock loading, while levulinic acid comprises less than 10% of the product mixture.

While our earlier work focused on CMF 1 as a precursor to the new generation biofuels 5-(ethoxymethyl)furfural 3 and 5-methylfurfural 4 by reaction of 1 with ethanol and hydrogen, respectively,⁵ in this report we describe the efficient conversion of CMF 1 into the value-added products 5-(hydroxymethyl)furfural 5 (HMF), levulinic acid 2 (LA), ethyl levulinate **6a** (EL) and n-butyl levulinate **6b** (BL) by reaction with water or alcohols at elevated temperatures.

HMF **5** is a versatile platform chemical for the synthesis of a wide range of industrially important materials, including biofuels.⁶ For example, **5** is a starting material in Dumesic's approach to the production of biomass-derived hydrocarbons.⁷ It can also be reduced to 2,5-dimethylfuran **7** or 2,5-dimethyltetrahydrofuran **8**, both high energy liquids which have been proposed as fuel additives.⁸ HMF **5** is also





a precursor to the polyester monomer furan-2,5-dicarboxylic acid **9**, a molecule that has the distinction of appearing on the list of Top Value-Added Chemicals From Biomass published by the US Department of Energy's National Renewable Energy Laboratory (NREL). This list of twelve, mainly sugar-derived products was assembled in order to identify major opportunities for "the production of value-added chemicals from biomass that would economically and technically support the production of fuels and power in an integrated biorefinery, and identify the common challenges and barriers of associated production technologies."⁹ Finally, the core structure of **5** also appears in the blockbuster antiulcer drug Ranitidine (Zantac®) **10**.

Although HMF 5 can be prepared from fructose in good yield,10 fructose itself is sourced from the food chain, and it would be far too expensive to produce 5 on an industrial scale in this manner. Interestingly, a report as far back as 1912 describes the hydrolysis of 1 to 5 in unspecified yield.¹¹ This paper was cited by Haworth and Jones in 1944 in their repetition of the procedure,12 which again lacked experimental detail. We thus undertook a careful study of this conversion with the benefit of modern analytical techniques. The results are quantified as shown in Scheme 2. Thus, under optimized conditions (hydrolysis in boiling water for 30 s), HMF 5 is produced in 86% yield from 1 alongside 10% LA 2. Formation of the latter product 2, observed across a range of conditions, appears to be unavoidable in this reaction. In the case, however, where LA 2 is actually the desired product, it can be produced with high efficiency (see below).

LA 2, like furan-2,5-carboxylic acid 9, also appears on the NREL Top 12 Value-Added Chemical list.⁹ In its candidate summary biography, LA 2 is referred to as "one of the more recognized building blocks available from carbohydrates," the derivatives of which "address a number of large volume chemical markets." These derivatives include levulinate esters and 2-methyltetrahydrofuran (fuel additives), δ -aminolevulinic acid (herbicide), and β -acetylacrylic acid, diphenolic acid and 1,4-pentanediol (polymer building blocks).⁹ The technical barrier to development of an LA-based chemical intermediate trade is indicated to be the moderate selectivity of the process used to derive LA 2 from biomass.

When CMF 1 is heated for longer periods in water, the amount of LA 2 grows at the expense of HMF 5, but even after 15 h reflux the reaction is not complete, and increasing amounts of decomposition products (dark solids) are seen to accumulate. The addition of acid to the reaction mixture increases the initial rate of the conversion, such that after only 30 s heating in dilute HCl the ratio of LA to HMF approaches 1:1. However, sampling the reaction mixture at subsequent intervals shows little in the way of further progress over the course of the next hour. Heating CMF in water at temperatures >100 °C in a closed vessel was also shown to accelerate the reaction, and it was by a combination of higher temperature and acid catalysis that a high yielding route to **2** was first developed. Thus, heating **1** in dilute HCl at 150 °C for 5 h gave a 94% isolated yield of LA. In an attempt to further shorten the reaction time, the temperature was raised to 190 °C, which resulted in the complete conversion of **1** into **2** within 20 minutes without the need for additional acid (Scheme 3).



When CMF 1 is stirred with ethanol at room temperature, 5-(ethoxymethyl)furfural 3 is produced in high yield.⁵ As was the case with the CMF 1 to HMF 5 conversion, more severe conditions shift the product distribution from the substituted furan toward the levulinate. Thus, heating CMF 1 in ethanol at 160 °C for 30 min gave EL 6a in 85% isolated yield (Scheme 4).



The analogous reaction of **1** with n-butanol at 110 °C for 2 h likewise gave BL **6b** (Scheme 5). In the conversion of C_6 furfurals to levulinates, there is a loss of a one-carbon fragment at the formate oxidation state, *i.e.* formic acid in the hydrolysis of CMF **1** or the corresponding formate ester in the alcoholysis. In the reactions in Schemes 3 and 4, no attempt was made to recover the formic acid or ethyl formate by-products. In the reaction with n-butanol, however, n-butyl formate **11** (BF) was isolated in approximately equal amounts to that of butyl levulinate **6b**, although it could not be completely separated from the excess butanol by distillation.¹³



Table 1	Yields	of	value-added	products	from	carbohydra	ate	and
biomass	feedstoo	cks	determined a	s the follo	wing e	xpression: (yiel	d of
CMF 1	and LA	Α2	from either	glucose, s	ucrose,	cellulose,	or	corn
stover)4 >	× (yield o	of H	MF 5, LA 2,	EL 6a, BL	6b , or 1	BF 11 from	CM	F1)

	feedstock							
derivative	glucose	sucrose	cellulose	corn stover				
HMF 5 $(LA 2)^a$ LA 2^a EL $6a^b$	70.0 (12.6) 78.7 72.7	77.3 (14.2) 87.1 80.5	72.0 (13.6) 81.5 75.2	69.1 (15.8) 81.0 74.6				
BL 6b °(BF 11)	72.4 (70.4)	80.2 (77.8)	74.9 (72.4)	74.4 (69.5)				

^{*a*} The LA **2** yield is a combination of that produced by both reactions. ^{*b*} Assumes conversion of both CMF **1** and LA **2** into EL **6a** in the same percent yield. ^{*c*} Assumes conversion of both CMF **1** and LA **2** into BL **6b** in the same percent yield.

If the results in Scheme 2–5 are superimposed upon the high yields of CMF 1 and LA 2 from glucose, sucrose, cellulose, and corn stover recently described by our group,⁴ the overall yield of value-added products from these substrates can be reckoned as shown in Table 1. To our knowledge, these levels of conversion from carbohydrate feedstocks are largely unrivalled in the literature.

While a comprehensive review of developments in the area of biomass conversion cannot be given here, the results given in Table 1 can be shown to compare favorably to approaches to LA 2 and HMF 5 at the forefront of the field. Thus, a recent report by Yong and co-workers described the conversion of glucose into HMF 5 in up to 81% yield (by GC and NMR analysis) using a chromium(II) catalyst and N-heterocyclic carbene ligand system.¹⁴ However, the method requires the use of expensive 1-butyl-3-methylimidazolium chloride ([BMIM]Cl) ionic liquid as the solvent. Practical questions remain about this process, not least of which being the activity of the catalytic system after multiple cycles. Along the same lines, Dumesic and coworkers have published a study in which HMF 5 is derived from glucose with 53% selectivity at high conversion in 60% aqueous DMSO in a biphasic reactor.¹⁵ While promising, the separation of DMSO from the HMF product remains an issue. Most recently, Binder and Raines have shown that corn stover can be processed directly into HMF 5 in 48% yield (by HPLC analysis) in a medium loaded with 10 mol% CrCl₃, 10 mol% HCl, and 60 wt% [EMIM]Cl in N,N-dimethylacetamide-LiCl solution.16

As concerns LA **2**, although a multitude of routes have been described over the years, the highest yields to date from biomass are claimed for the "Biofine Process," a two-stage protocol involving high pressures and temperatures, for which yields of between 70-80% of **2** are reported.¹⁷ The technology we have developed, however, operates under substantially milder conditions and is more versatile with respect to product output, *i.e.* includes furfurals such as **3**, **4**, and **5** and their derivatives.

In conclusion, we have described a simple, efficient processes for the conversion of biomass-derived 5-(chloromethyl)furfural **1** into the mainstream value-added products 5-(hydroxymethyl) furfural **5**, levulinic acid **2**, ethyl levulinate **6a** and butyl levulinate **6b**, which may be applied to a variety of purposes in the materials and fuel industries that would otherwise involve the expenditure of petroleum. We foresee a time when CMF **1** may emerge as a central organic platform chemical, and biphasic acid/solvent carbohydrate digesters as the method of choice for exploiting cellulosic biomass.

Experimental

Hydrolysis of CMF 1 to HMF 5

CMF 1 (0.9490 g, 6.565 mmol) was added in a single portion to boiling water (900 mL) in a 2 L round-bottomed flask with fast stirring. After 30 s the reaction was quickly cooled to room temperature in an ice/water bath. The mixture was extracted with ethyl acetate (5 × 100 mL), the aqueous layer was saturated with sodium chloride, and extraction with ethyl acetate was continued (5 × 100 mL). The combined organic extracts were dried (MgSO₄) and the solvent was evaporated. Column chromatography (silica, 1 : 1 Et₂O–CH₂Cl₂) gave HMF **5** (0.7137 g, 86.2%) and LA **2** (0.0751 g, 9.9%).

Hydrolysis of CMF 1 to LA 2

A 150 mL sealed glass vessel was charged with CMF (0.9889 g, 6.84 mmol) and water (30 mL) and the mixture was heated in an oil bath at 190 °C with stirring for 20 min. The reaction was allowed to cool to room temperature and filtered. The filtrate was extracted with ethyl acetate (5×100 mL), the aqueous layer was saturated with sodium chloride, and extraction with ethyl acetate was continued (5×100 mL). The combined organic extracts were dried (MgSO₄) and the solvent was evaporated to give LA **2** (0.7248 g, 91.2 %).

Ethanolysis of CMF 1 to EL 6a

A 150 mL sealed glass vessel was charged with CMF (3.1662 g, 21.90 mmol) and absolute EtOH (80 mL) and the mixture was heated in an oil bath at 160 °C with stirring for 30 min. The reaction was allowed to cool to room temperature and the excess ethanol was evaporated. Chromatography (silica, 1:1 hexane–ethyl acetate) gave EL **6a** (2.6746 g, 84.7%).

Butanolysis of CMF 1 to BL 6b and BF 11

A solution of CMF (9.2211 g, 63.79 mmol) in n-BuOH (50 mL) was heated at 110 °C with stirring for 2 h. Distillation gave a mixture of BF 11 (5.65 g, 86.7%) and n-BuOH (16.40 g) (by NMR integration) between 104–110 °C and BL **6b** (9.2770 g, 84.4%) between 90–91 °C at 2 Torr.

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- 13 It should be pointed out here that the solvolytic reactions described in Schemes 2–5 involve the liberation of a molecule of hydrogen chloride into the reaction medium, *i.e.* water (Schemes 2 and 3), ethanol (Scheme 4), or butanol (Scheme 5). In terms of atom economy, the hydrogen chloride produced can be recovered for recycling back into the acid/solvent digestion reaction wherein the biomass was first processed into CMF 1. Industrial HCl recovery modules may be based on distillation,¹⁸ pervaporation,¹⁹ acid–base-couple extraction,²⁰ solvent extraction,^{21,22} or electrodialysis.²³ In the reactions where alcohols were both reagent and solvent, small quantities of the corresponding chloroalkane substitution products could be detected in the reaction mixture (by NMR and GC-MS). Chloroethane (bp 12 °C) is much more volatile than the desired product **6a** (204 °C) and the ethanol solvent (78 °C). Likewise, chlorobutane (bp 78 °C) is more volatile than the desired products
- **6b** (238 °C) and **11** (107 °C), and the butanol solvent (117 °C). Hence, separation of these minor products, which are themselves commercially traded organic intermediates, would be uncomplicated. If desired, the occurrence of haloalkanes could be avoided altogether by practicing the hydrolysis of **1** to levulinic acid **2** (Scheme 3) followed by standard esterification of **2** with ethanol or butanol using a non halogen-containing catalyst.
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