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Upgrading of Levulinic Acid with Dimethylcarbonate as Solvent/Reagent

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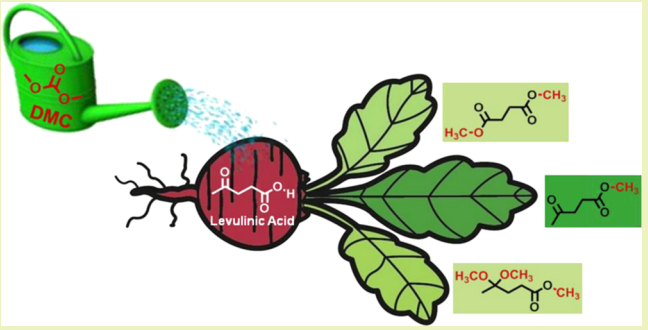
Supporting Information

ABSTRACT: The reactivity of the biobased chemical levulinic acid with dimethylcarbonate as a solvent/reagent under basic conditions is here described. The reaction yields methyl levulinate and dimethyl succinate, along with products that derive from methylation of the aliphatic chain and the dimethylketal of methyl levulinate. A degree of control over selectivity can be achieved by tuning the reaction conditions.



KEYWORDS: *Levulinic acid, Dimethylcarbonate, Upgrading, Ketal*

INTRODUCTION

Levulinic acid (LA) represents a precious biobased C5 feedstock. Its wide availability, low price, and renewable origin, as well as its interesting reactivity, make it a valuable platform molecule for chemical transformations. In particular, it represents an alternative renewable C5 building block that can be used in place of fossil-derived homologues. Unlike succinic acid, which is prepared mainly by biochemical transformations, LA can be synthesized very efficiently by an exclusively chemical sequence starting from biomass. The biofine process reportedly achieves a 50% weight yield of LA based on cellulose as feedstock. It was developed originally in the United States, and a 50 tons/day plant was commissioned in Caserta, Italy, using a mixed lignocellulosic feedstock.[1,2]

LA can be utilized, still in principle, as a platform molecule of renewable origin as an alternative to fossil building blocks. For example, LA can be transformed into butanone,[3] instead of starting from heavy naphta as in the traditional Fischer–Tropsch process.

However, LA represents primarily a self-standing platform for a variety of different molecules, as exemplified in Figure 1.[4,5] With the added advantage that among all these possible products some have already been identified as having the potential for the market, i.e., 2-methyltetrahydrofuran (2-Me-THF), γ-valerolactone (GVL),[5] 1,4-pentadiol, diphenolic acid, δ-aminolevulinic acid (DALA), ethyl levulinate, and succinic acid.[1]

It is apparent that most of the products in Figure 1 can be obtained following a reductive pathway, and in fact, such pathways are described frequently in the scientific literature. We were more interested in a formally oxidative approach to LA upgrading by aiming toward the "oxidized" derivatives of Figure 1. In particular, we focused our attention on succinic acid esters. Traditionally, these are obtained from LA through classical oxidation procedures such as by vanadium-catalyzed oxidation with oxygen[6] or oxidation by *N*-bromoacetamide (NBA) in perchloric acid with mercuric acetate and ruthenium chloride as catalyst,[7] followed by esterification.

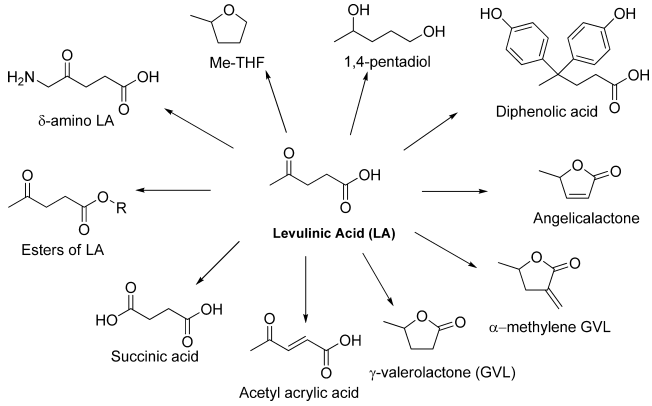


Figure 1. Some products derived from levulinic acid (LA).

On the basis of our experience in the use of dimethylcarbonate as a green reagent,[8] we decided to investigate its reaction with LA to yield LA methyl ester and succinic acid methyl ester. The latter could be approached by applying the reaction of ketones to yield methyl esters previously described

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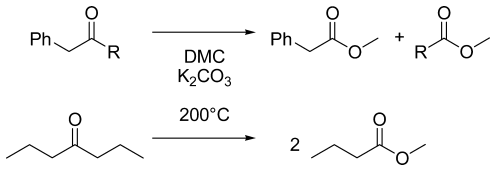
in our group,[9] depicted in Scheme 1. It consists of the formal splitting of a ketone, e.g., a benzyl-alkyl ketone or dialkyl

Scheme 1. Reactions of Ketones with DMC in Presence of K_2CO_3 at 200 °C



ketone, to yield the corresponding benzylic acid methyl ester and alkyl carboxylate methyl ester. Albeit not high yielding and somewhat energy intensive, particularly for aliphatic ketones,[9] this transformation appeared to be a novel interesting strategy to upgrade LA.

Here, we describe the development of a new DMC-based chemical technology to transform LA into target compounds. We did however go one step further and screened our reactions for novel and unexpected outputs by following a more curiosity-driven approach, analogous to a recent work we performed on lignin.[10] Our expectation was that this kind of broad-based method could lead to the discovery of new reactions (selective reductions, oxidations, bond making/breaking processes, catalysis, etc.) that could pave the way to unexpected new compounds. This approach was key in the development of the fossil-based chemical industry that prospered when efficient transformations were discovered which in turn made available a variety of new molecules that successively found multiple applications.[11]

In the present case, by understanding the reaction sequences, the products, and the selectivity that were obtained by the reaction of LA with DMC under alkaline conditions, we were able to pinpoint an uncommon base-promoted acetalyzation reaction that yielded the unexpected compound **5** (methyl levulinate dimethyl-ketal).

EXPERIMENTAL SECTION

Methyl Levulinate (2). Levulinic acid (1.0 g, 8.6 mmol), DMC (14.5 mL, 172.2 mmol), and K_2CO_3 (2.4 g, 17.2 mmol) were loaded in a stainless steel autoclave. After washing with nitrogen, the mixture was heated to 160 °C under stirring for 6 h. The reaction was allowed to cool to room temperature, and the mixture was dried under vacuum and then diluted in diethyl ether and filtered to remove K_2CO_3. The resulting solution was concentrated, and a brown oil was obtained. Distillation under reduced pressure yielded **2** (90%). ^{1}H NMR (400 MHz, CDCl3) δ 3.67 (s, 3H), 2.75 (t, J = 6.6 Hz, 2H), 2.57 (t, J = 6.6 Hz, 2H), 2.18 (s, 3H). Mass spectrum, m/z (I_{rel}, %): 130 (M^+, <1%), 115 (10), 99 (14), 98 (5), 88 (5), 87 (4), 71 (4), 59 (10), 57 (9), 56 (4), 55 (16), 43 (100), 32 (4).

Dimethyl Succinate (3). The same mixture used to synthesize **2** was heated to 200 °C. After the same workup, a brown oil was obtained. Distillation under reduced pressure yielded **3** (18%). ^{1}H NMR (400 MHz, CDCl3) δ 3.68 (s, 6H), 2.62 (s, 4H). Mass spectrum, m/z (I_{rel}, %): 146 (M^+, <1%), 116 (5), 115 (84), 114 (28), 87 (20), 59 (72), 57 (10), 56 (10), 55 (100), 53 (18).

Dimethyl 2-Methylsuccinate (4). The compound was identified by comparison of its GC-MS with a commercial sample. Mass spectrum, m/z (I_{rel}, %): 160 (M^+, <1%), 129 (16), 128 (10), 101 (11), 100 (11), 69 (12), 59 (100), 55 (8).

Methyl 4,4-Dimethoxypentanoate (5). The same mixture used to synthesize **2**, with added methanol (7.0 mL, 172.2 mmol), was heated to 200 °C. After the same workup, a brown oil was obtained. The mixture was purified by flash chromatography on silica gel by eluting with a mixture of 1% of triethylamine, petroleum ether, and diethyl ether (gradient elution: 1:0, 4:1, 2:1). The amine was added to neutralize the acidic centers of silica. The resulting fraction was then distilled under reduced pressure, leading to a yield of **5** of 20%, with a purity ≥95%. ^{1}H NMR (400 MHz, CDCl3) δ 3.67 (s, 3H), 3.17 (s, 6H), 2.35 (m, 2H), 1.95 (m, 2H), 1.24 (s, 3H).Mass spectrum, m/z (I_{rel}, %): 176 (M^+, <1%), 161 (6), 146 (3), 145 (32), 113 (20), 101 (11), 89 (100), 85 (97), 71 (10), 55 (34).

RESULTS

Effect of Temperature. LA **1** and DMC were placed in a stainless steel autoclave with K_2CO_3 (molar ratio K_2CO_3:LA = 2:1) and heated with stirring at temperatures ranging from 160 to 220 °C (depending on the temperature and reactor volume, pressures in a range between 15 and 30 atm were observed). DMC was always used as reagent in a 20-fold excess respect to LA and, thus, also acted as solvent for the reaction. The temperature screening (Table 1) indicated that at 160 °C the

Table 1. Product Distribution of Reaction of LA with DMC in Presence of K_2CO_3 at Different Temperatures

				products (% GC)[b]			
run[a]	temperature (°C)	time (h)	conversion[b] (% GC)	2	3	4	others[c]
1	160	4	100	99	–	–	1
2	180	4	100	12	10	1	77
3	200	4	100	9	16	3	72
4	220	3	100	0	17	5	78

[a]All reactions were performed using a molar ratio of **1**:DMC = 1:20 and **1**:K_2CO_3 = 1:2. [b]Conversion and product percentages in the final mixture were determined by GC/MS analysis. [c]"Others" means all the products whose structures are unknown.

reaction was selective for the formation of methyl levulinate **2**, while at higher temperatures, selectivity decreased. For example, gas-chromatographic (GC) analysis after 4 h at 200 °C indicated the formation of methyl levulinate **2** (9%), dimethyl succinate **3** (16%), and dimethyl-2-methylsuccinate **4** (3%) (Scheme 2), along with a significant amount (>70%) of unidentified byproducts. Above 180 °C, dimethylsuccinate **3** was the major product.

By prolonging the reaction time, the selectivity toward the desired dimethyl succinate **3** increased and went through a maximum (21%) after 6 h and then decreased as the product reacted further. The product dimethyl succinate **3** was isolated through distillation under reduced pressure, achieving an isolated yield of 18%.

Effect of Catalyst. Three strong organic bases were tested in place of K_2CO_3 under the best operative conditions for the reaction of LA **1** with DMC (200 °C, 6 h), including diazabicyclooctane (DABCO), diazabicycloundecene (DBU), and trioctylmethylphosphonium methylcarbonate ($[P_{8,8,8,1}][CH_3OCO_2^-]$).[12] The results are summarized in Table 2. A blank test without catalyst, performed to rule out spontaneous reactions between LA and DMC (run 1, Table 2), indicated only 16% conversion to the methyl ester.

All the bases prompted complete conversion, albeit with poor selectivity and conspicuous amounts of byproducts. The only exception being $[P_{8,8,8,1}][CH_3OCO_2^-]$ (run 5) that, even just in catalytic amounts (2.5% molar respect to **1**), promoted selective conversion to methyl levulinate **2**. DABCO and DBU did not improve on the performance (conversion or selectivity) obtained with potassium carbonate and were not used further.

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Scheme 2. Products of Reaction of LA with DMC in Presence of K_2CO_3 at 200 °C for 4 h

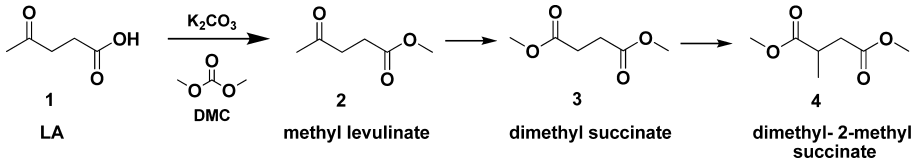


Table 2. Reaction of LA 1 with DMC Using Different Base Catalysts

run[a]	base	base/**1**[b] (mol/mol)	conversion[c] (% GC)	products (% GC)[c]			
				2	**3**	**4**	others[c]
1	none	–	17	16	–	–	1
2	K_2CO_3	2	100	1	21	5	73
3	DABCO	2	100	3	10	2	85
4	DBU	2	100	–	14	26	60
5	$[P_{8,8,8,1}][CH_3OCO_2^-]$	0.025	100	96	–	–	4

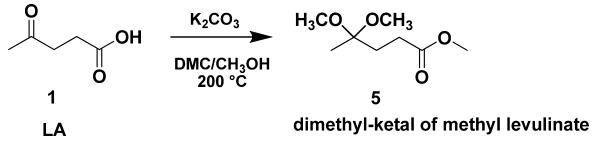
[a]All reactions were performed at 200 °C for a time of 6 h, using a molar ratio of **1**:DMC = 1:20. [b]Molar ratio between base and **1**. [c]Conversion and product percentages in the final mixture were determined by GC/MS analysis. [c]"Others" means all the products whose structures are unknown.

DBU (run 4) showed significant amounts (26%) of dimethyl-2-methyl succinate **4** as the major identifiable product.

Effect of Added Solvent. Further attempts to improve the selectivity toward the desired dimethylsuccinate **3** were made using DMF and methanol as co-solvents at 200 °C. DMF caused an increase in the amounts of unidentified byproducts and was immediately abandoned.

Addition of methanol (molar ratio MeOH:DMC = 1:1) promoted the unexpected formation of the dimethylketal of methyl levulinate **5** (Scheme 3), whose structure was confirmed by isolation and comparison with an independently synthesized sample.[13]

Scheme 3. Product of Reaction of LA with DMC and Methanol in Presence of K_2CO_3



In an attempt to improve the yield of **5**, a set of reactions run with progressively higher amounts of methanol showed the parallel increase in the formation of the ketal (Figure 2), up to 40% by GC at a 1:1 MeOH:DMC ratio.

Pure ketal **5** could be isolated from methyl levulinate **2** and dimethyl succinate **3** (as well as from other higher boiling compounds) by flash column chromatography followed by distillation. Ketal **5** was thus obtained in high purity (≥95%) in a 20% yield with respect to LA.

DISCUSSION

Methods for the synthesis of methyl levulinate are currently of widespread interest. For example, a direct pathway from furfuryl alcohol (Scheme 4) was recently reported.[14] However, the esterification of easily accessible LA **1** to yield methyl levulinate **2** is a more established approach,[15] and it can be carried out under acidic conditions, either by using methanol[16,17] or dialkyldicarbonates as esterification reagents.[18,19]

An alternative esterification reagent for the catalytic synthesis of methyl carboxylates[20] is dimethylcarbonate (DMC), which is

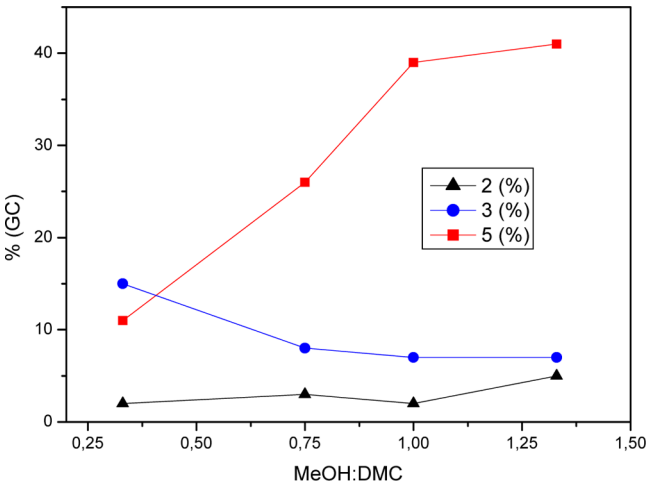
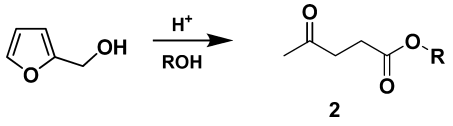


Figure 2. Product distribution vs MeOH:DMC ratio in the reaction of LA with DMC and MeOH after 6 h at 200 °C with K_2CO_3.

Scheme 4. Alkyl Levulinates from Furfuryl Alcohol



considered a green reagent[8] as well as a green solvent.[21] DMC catalysts are usually basic and can be NaY zeolites as well as inorganic bases such as K_2CO_3.

Here, we demonstrated that DMC can be used as a solvent/reagent for the synthesis of methyl levulinate from LA **1** and still in the presence of catalytic amounts of K_2CO_3 (T = 160 °C, t = 4 h, Table 1, line 1). At higher temperature and in the presence of K_2CO_3, the reaction gave instead rise to three main products, methyl levulinate **2**, dimethyl succinate **3**, and 2-methyl dimethyl succinate **4**, accompanied by the formation of sizable amounts of unknown byproducts. On the basis of a previous paper,[8] it was reasonable to assume dimethyl succinate was produced by a mechanism such as the one depicted in scheme 5.

Methyl levulinate **2**, formed by transesterification with DMC, underwent deprotonation by the base, generating a nucleophile

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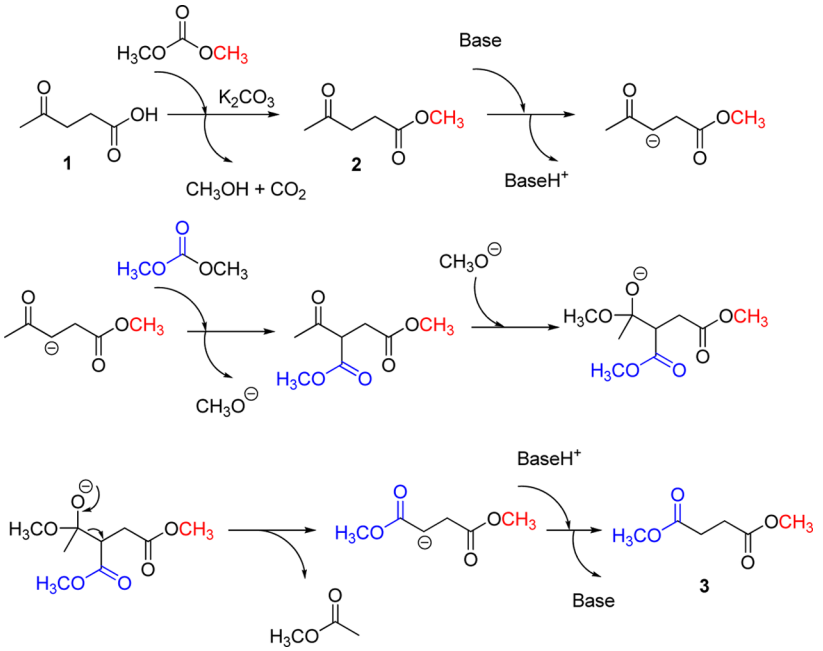
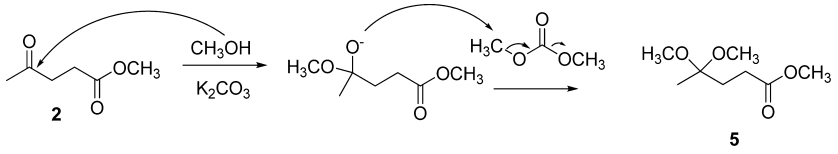
Scheme 5. Mechanism for Formation of Dimethyl Succinate 3 from LA 1 and DMC



Scheme 6. Mechanistic Hypothesis for Formation of Ketal 5 under Basic Conditions



able to add to the carbonyl carbon of DMC. The resulting species was now set up to undergo nucleophilic attack on the ketone carbonyl by methoxide, thereby generating a species able to eliminate methyl acetate, thus yielding dimethyl succinate **3**. Further reaction of **3** with DMC accounted for the formation of 2-methyl dimethyl succinate **4**, likely by a mechanism described elsewhere for the base-promoted methylation of activated CH_2.[22,23] Fine tuning of the reaction conditions followed by vacuum distillation allowed us to obtain pure dimethyl succinate **3** in around 20% yield, a result consistent with previous reports[24] that may serve as benchmark for further developments.

Gaschromatographic analysis showed a discrete number (15−20) of unidentifiable higher boiling byproducts that accounted for up to 70% of the mass balance. The mass spectra of these compounds showed some common features, such as evidence of longer aliphatic chains, as well as the presence of methyl ester groups. These allowed us to presume levulinate oligomeric structures, based on the fact that levulinc esters are prone to aldol-type condensation reactions under the present alkaline conditions. No further attempts to isolate or characterize these compounds were made.

With a view to improve the selectivity of the reaction, three strong organic bases were tested as catalysts. While selectivity with DABCO was far worse than with K_2CO_3, DBU instead appeared to prompt formation of dimethyl succinate **3** and 2-methyl-dimethyl succinate **4** (14% and 26%, respectively, by GC). Both catalysts, however, were poorly selective as well and caused large amounts of byproducts to form. Finally, $[P_{8,8,8,1}][CH_3OCO_2^-]$, that was previously demonstrated by our group to be a strong basic organicatalyst,[25−28] was selective (96%) toward the formation of methyl levulinate **2**, even when used in only 2.5% molar amount respect to LA **1**. It did not, however, catalyze formation of the succinate derivatives **3** and **4** and was therefore not considered further.

A far more interesting result was obtained by attempting to improve selectivity toward dimethyl succinate **3** by means of added solvents. Methanol, in particular, promoted the totally unexpected formation of the dimethyl-ketal of methyl levulinate **5** (Scheme 3). Ketones undergo reversible acid- or base-catalyzed addition of one mole of alcohol to yield the hemiketal. Dehydration followed by addition of a second molecule of alcohol gives a ketal. The second step of the process can be catalyzed only by acids because elimination of water from the intermediate is needed,[29] and in fact, this step often requires a water-scavenging agent such as trimethylorthoformate.[30] To our knowledge, here, we observed a unique case of base-promoted formation of a ketal. A mechanistic hypothesis might involve the excess of methanol acting as a proton source to promote dehydration of the hemiketal as proposed by others,[30] with DMC helping by acting as a dehydrating agent. However, in our opinion, it was more likely that under the harsh conditions (200 °C) here employed a role was played by dimethylcarbonate as a methylating agent of the hemiketal (Scheme 6), as was recently reported in the case of glycerol derivatives.[31] In addition, given that ketal formation is an equilibrium that can be driven forward by removing water to prevent hydrolysis, DMC likely acted as water scavenger in this hypothesis as well, thus preventing the reaction from being reversible.[32]

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CONCLUSIONS

The results presented in this paper indicate that the platform chemical levulinic acid (LA) can produce interesting derivatives when treated by alternative methods with respect to the commonly investigated reductive ones, and that it is possible to establish suitable conditions for its catalytic upgrading. For the time being, the reported reactions are clean and selective only for the synthesis of methyl levulinate **2**, nonetheless access to dimethyl succinate **3** and ketal **5** has been demonstrated as well. In this sense, the investigation is not a target-oriented catalytic study per se, rather the paper wishes to illustrate broad reactivity trends and the most promising avenues that lead to LA-based chemicals.

In the simplest instance, the reaction of LA **1** with DMC in the presence of K_2CO_3 at 160 °C yields selectively levulinic acid methyl ester **2**. Alternatively, **2** could be obtained with high selectivity at 200 °C by using $[P_{8,8,8,1}][CH_3OCO_2^-]$ as a base. At higher temperatures (200 °C), the reaction became less selective but afforded dimethyl succinate **3** in up to 20% isolated yield by a previously described formally "oxidative" mechanism. Addition of methanol to the reaction of LA with K_2CO_3 and DMC at 200 °C prompted the unexpected formation of ketal **5**; this was tentatively rationalized by invoking the harsh conditions that may lead to somewhat unconventional chemistry taking place, as well as to the role of DMC that may act as a sacrificial water scavenger.

Despite the energy intensity required for these reactions, several green aspects can be recognized: (1) DMC is nontoxic and used both as a reagent and solvent. (2) Potassium carbonate used as a catalyst is safe and can be recovered, reactivated, and reused. (3) Methanol and CO_2 are the only byproducts and can be recycled to form DMC. (4) LA is a renewable environmentally friendly feedstock.

Thus, not only have we demonstrated the potential of LA to develop new chemistry by using broad-based technologies to produce multiple outputs, but we have also implemented the use of a green reagent and green solvent (DMC) within these new methodologies.

ASSOCIATED CONTENT

Supporting Information

Spectral (^{1}H NMR and MS) characterization data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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