

# Studies on the Reactions of Lactone Intermediates Derived from Levulinic Acid: Telescoped Routes to Higher Levulinate Ester Biofuels

Matthew P. Aldred, Thomas E. Davies, Stuart H. Taylor, and Andrew E. Graham\*



Cite This: <https://doi.org/10.1021/acsomega.4c08315>



Read Online

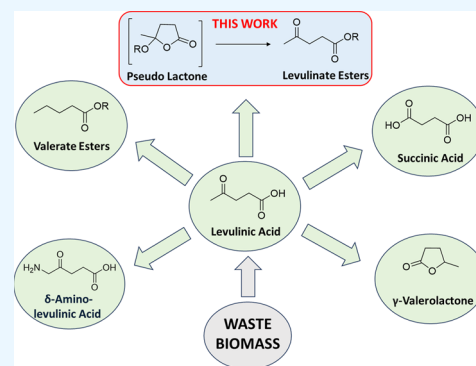
ACCESS |

Metrics & More

Article Recommendations

Supporting Information

**ABSTRACT:** The development of efficient strategies for the synthesis of levulinate esters is of significant current interest due to their potential as biofuels and fuel additives. Herein, we report a novel strategy to access levulinate esters derived from higher alcohols directly from levulinic acid through the in situ generation of lactone intermediates employing commercial heterogeneous catalysts, such as Amberlyst-15. This strategy employs a telescoped approach in which the lactonization/ring-opening reactions are combined into an operationally simple one-pot procedure. This strategy is advantageous as it employs a readily available and inexpensive catalyst and proceeds in short reaction times to produce excellent yields of higher levulinate esters with high selectivity. Furthermore, the Amberlyst-15 catalyst is fully recyclable and can be reused without loss of activity or selectivity.



## 1. INTRODUCTION

The development of strategies for the production of energy, fuels, and feedstock chemicals employing sustainable approaches is crucial to alleviate the current reliance on fossil fuel resources and also offers a potential strategy toward dealing with climate change.<sup>1,2</sup> Biomass valorization, and in particular, the valorization of sustainably sourced inedible lignocellulosic residues, offers a low cost and abundant source of materials for future energy requirements.<sup>3,4</sup> One of the most important of these bioderived materials is levulinic acid 1 (LA), derived from the acid-catalyzed hydrolysis of cellulose, which has been identified as a versatile platform chemical that offers significant opportunities for further structural elucidation into high-value added products (Figure 1).<sup>5–11</sup>

One of the most common strategies for LA upgrading takes advantage of the similar properties of levulinate esters to fatty acid methyl esters (FAMEs), which has led to them being identified as important fuel additives and biofuels due to their low toxicity, high flashpoints, and beneficial flow properties.<sup>12,13</sup> This is typically achieved through LA esterification using homogeneous mineral acid catalysts; however, these catalysts present significant operational difficulties in recyclability, product isolation, and waste stream management. Significantly, commercially available heterogeneous catalysts have been demonstrated to perform poorly, providing disappointing yields of levulinate ester products, particularly in the case of levulinate esters derived from higher alcohols.<sup>14–17</sup> These limitations have led to the development of alternative synthetic approaches employing novel heterogeneous materials that are more efficient and which present fewer

operational complications, which has developed as a vibrant research area in recent years (Table 1).<sup>18–24</sup>

We recently reported a novel synthetic strategy for the production of levulinate esters directly from LA in the presence of dimethyl and diethyl acetals and ketals.<sup>25</sup> This approach proceeds through the efficient formation of a lactone intermediate and provides a simple solution to the limitations typically associated with the Fischer esterification process, and in particular, the low yields of ester products produced due to the formation of equilibrium mixtures, by exploiting the natural tendency of lactones to undergo facile ring-opening reactions.<sup>26–28</sup>

Quantities of lactone products have previously been identified in reaction mixtures during the synthesis of levulinate esters from both levulinic acid and  $\alpha$ -angelica lactone, the amount of which is typically dependent on the nature of the catalyst employed.<sup>29–32</sup> Few studies have systematically investigated the reactivity of these multifunctional lactone intermediates, presumably due to difficulties encountered in their synthesis and isolation, although they have been found to be useful in the development of water-soluble coatings and as prodrugs.<sup>33–35</sup> Our methodology

**Received:** September 13, 2024

**Revised:** December 12, 2024

**Accepted:** December 17, 2024

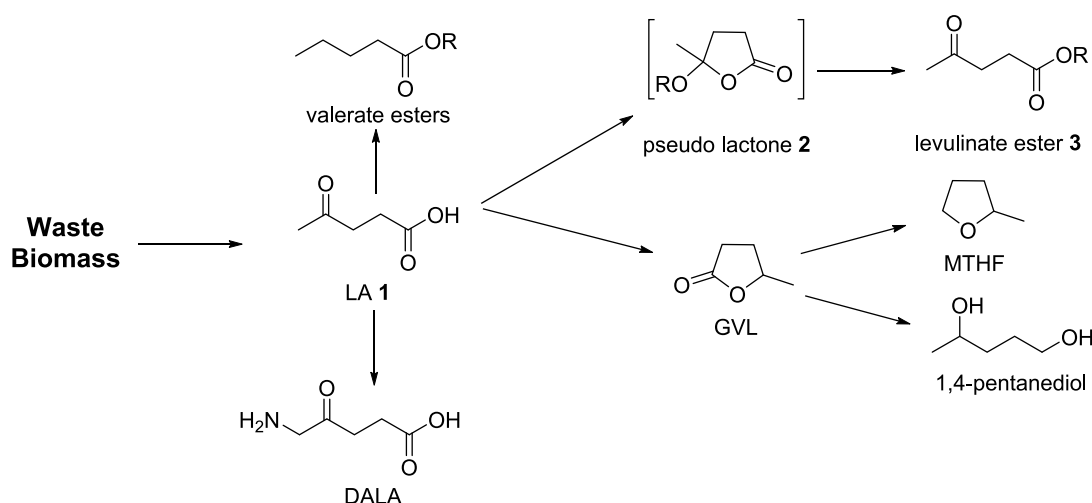


Figure 1. Applications of levulinic acid as a bioderived platform chemical.

Table 1. Previous Levulinic Ester Synthesis Employing Commercial Heterogeneous Catalysts under Fischer Esterification Conditions

	alcohol	catalyst	yield levulinate ester (%)	refs
1	EtOH	H-ZSM-5(100)	15	14
2	EtOH	Keggin HPA	38	15
3	EtOH	Amberlyst-15	55	19
4	PrOH	Amberlyst-15	70	24
5	BuOH	H-ZSM-5	31	16
6	BuOH	H-MOR	30	16
7	BuOH	Amberlyst-15	53	17
8	BuOH	Amberlyst-36	60	17

allows for the efficient and high yielding synthesis of lactones directly from levulinic acid without the requirement for harsh conditions in an operationally simple procedure using inexpensive reagents. We recognized that this might provide an opportunity to exploit the increased reactivity of lactones toward nucleophiles and to develop methodology in which these potentially highly flexible intermediates can be further elaborated into a range of useful consumer products. Herein, we report the successful realization of this strategy, employing alcohol nucleophiles to produce an efficient, high yielding, and flexible strategy to access levulinate esters derived from higher alcohols.

## 2. EXPERIMENTAL SECTION

**2.1. Typical Procedure for the Telescoped Esterification Reactions of LA in 1-Propanol in the Presence of Ketals.** Amberlyst-15 (40 mg) was added to a solution of 2,2-diethoxypropane (DEOP) (1.2 mmol) and levulinic acid (1 mmol) in 1-propanol (2 mL) in a sealed reaction vessel, and the reaction was stirred at 20 °C to affect the lactonization. After 1 h at 20 °C, the reaction mixture was heated to 75 °C for 4 h to affect the ring-opening esterification reaction. Yields of ester and product selectivity were determined by quantitative <sup>1</sup>H NMR spectroscopy analysis of the crude reaction mixture,<sup>33,36,37</sup> and product identities were confirmed by GC–MS analysis.

**2.2. Amberlyst-15 Recycling Studies.** Amberlyst-15 (40 mg) was added to a solution of levulinic acid (1 mmol) and 2,2-diethoxypropane (DEOP) (1.2 equiv) in 1-propanol (2

mL) and stirred at 20 °C for 1 h followed by heating at 75 °C for 4 h to affect esterification. On completion of the esterification reaction, the solvent was removed by aspiration and the catalyst washed with 1-propanol (2 × 1 mL) prior to reuse. Yields of ester and product selectivity were determined by quantitative <sup>1</sup>H NMR spectroscopy analysis of the crude reaction mixture,<sup>33,36,37</sup> and product identities were confirmed by GC–MS analysis.

**2.3. Typical Procedure for the Telescoped Lactonization/Transesterification Reactions of LA with 1-Propanol in DMC in the Presence of Ketals.** Amberlyst-15 (10 mg) was added to a solution of 2,2-diethoxypropane (DEOP) (1.2 mmol) and levulinic acid (1 mmol) in dimethyl carbonate (DMC) (2 mL) in a sealed reaction vessel, and the reaction was stirred at 20 °C. After 1 h, 1-propanol (5 equiv, 5 mmol) and an additional portion of Amberlyst-15 (30 mg) were added, and the reaction was stirred at 20 °C for an additional 1 h. Conversion to higher lactone product 2c was confirmed by GC–MS analysis of the crude reaction mixture.

## 3. RESULTS AND DISCUSSION

**3.1. Catalyst Choice.** The catalytic activity of Amberlyst-15 in esterification reactions has been extensively investigated for a range of substrates and under a variety of reaction conditions in order to determine the kinetic profile of this transformation. In-depth studies have elucidated how the structural and physicochemical characteristics of Amberlyst-15, such as its swelling properties, the degree of cross-linking, and resin morphology, influence its catalytic activity for the formation of butyl levulinate from levulinic acid.<sup>17</sup> Acidic resins, such as Amberlyst-15, have an ideal profile for use in sustainable chemical processes, displaying the desirable features of heterogeneous catalysts, such as easy separation and isolation, high catalytic activity and selectivity, and good reusability. Furthermore, they also display a number of features that are highly desirable for application in industrial processes and are inexpensive and applicable to flow chemistry techniques.

**3.2. Optimization of Lactone Formation.** We have demonstrated that Amberlyst-15 is a highly efficient and selective catalyst for the formation of esters derived from lower alcohols from levulinic acid in the presence of acetals and ketals, such as 2,2-dimethoxypropane (DMOP) and DEOP. In

Table 2. Optimization of Lactone Formation Employing Amberlyst-15<sup>a</sup>

entry	catalyst	loading (mg)	time (h)	ketal	yield 2a (%) <sup>b</sup>	selectivity 2a:3a <sup>b</sup>	conversion (%) <sup>c</sup>
1	A-15	40	1	DMOP	83	80:20	>95
2	A-15	40	2	DMOP	58	65:35	92
3	A-15	20	0.5	DMOP	82	90:10	88
4	A-15	20	1	DMOP	72	80:20	84
5	A-15	10	1	DMOP	92	95:5	92
6	A-15	40	0.5	DMOP	25	55:45	45 <sup>d</sup>

<sup>a</sup>Experimental conditions: Catalyst was added to a solution of levulinic acid (1 mmol) and ketal (1.2 equiv) in DMC (2 mL) in a sealed reaction vessel and stirred at 20 °C for the specified time. <sup>b</sup>Determined by quantitative <sup>1</sup>H NMR spectroscopy of the crude reaction mixture. <sup>c</sup>Sum of levulinate ester and lactone as determined by quantitative <sup>1</sup>H NMR spectroscopy of the crude reaction mixture. <sup>d</sup>Reaction in methanol.

this case, the lactone intermediate is formed as a transient intermediate, which undergoes facile esterification reaction under the high reaction temperatures employed.<sup>25</sup> We envisioned that this chemistry could be adapted and extended to develop a telescoped reaction protocol in which the lactone product is selectively produced in situ and subsequently reacted without the requirement of its isolation. Such telescoped and “one-pot” protocols have proved to be highly effective synthetic strategies that allow for multiple transformations to be carried out sequentially. This approach has a number of benefits, providing substantial savings in time and efficiency as it removes the requirement for tedious isolation and purification steps and significantly reduces solvent usage, waste generation, and energy requirements. Further additional benefits include compatibility with flow chemistry and continuous processing techniques, removal of the requirement to isolate reactive or unstable intermediates, and the potential to enhance and improve the reactivity profile of unreactive functional groups.<sup>38–46</sup> With this strategy in mind, we initially assessed the potential of Amberlyst-15 to selectively catalyze the formation of lactone **2a** in situ employing a combination of low catalyst loadings and reduced reaction temperatures. Our studies initially investigated the reaction of LA in the presence of DMOP and 40 mg Amberlyst-15 at 20 °C in DMC, which provided excellent conversions of LA to lactone **2a** in short reaction times with good selectivity for the lactone product (Table 2, entry 1). Extending reaction times led to the consumption of **2a** and subsequent formation of the ester product **3a** with the expected reduction of selectivity (entry 2). Gratifyingly, reducing the amount of Amberlyst-15 led to a reduction in the amount of ester product **3a** while maintaining high conversions of LA and provided a simple and efficient method for the synthesis of lactone **2a** (entries 2–5). The corresponding reaction employing methanol as a solvent in place of DMC provided only low yields of lactone **2a** with poor overall selectivity (entry 6). No lactone products were observed in reactions of levulinic acid and Amberlyst-15 (10 or 40 mg) in DMC at 20 °C in the absence of ketal. Similarly, no lactone products were observed in reactions of levulinic acid and DMOP in the absence of Amberlyst-15, suggesting that lactone formation by autocatalysis was negligible.

These optimization studies, and our initial observations, clearly demonstrate that the chemistry of levulinic acid can be modified by careful control of the reaction conditions to allow for selective formation of either the lactone **2a** or ester **3a** products with high selectivity. We next extended our studies to

demonstrate that the lactonization reaction can also be achieved employing other macroreticular resins, such as Amberlyst-36, and other ketals, such as DEOP. We were gratified to observe that these reactions provided a similar reaction profile providing high conversions to lactone **2b** with high selectivity (Figure 2).

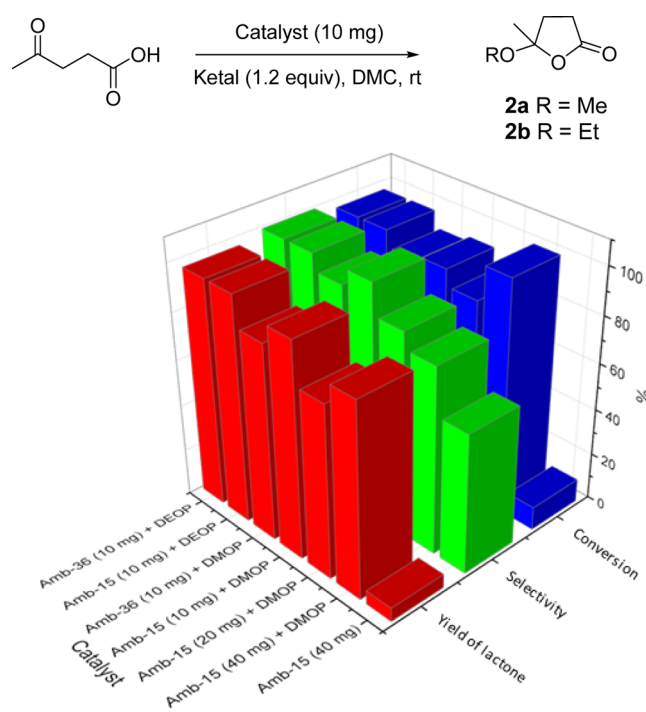


Figure 2. Lactonization reactions of levulinic acid employing macroreticular resin catalysts in the presence of ketals.

To complete these initial investigations, we demonstrated that in contrast to previous studies, the highly reactive lactones **2a** and **2b** can easily be isolated in high purity without the requirement for extended isolation and purification procedures. A benefit of employing DMOP and DEOP is that the only byproducts generated in the lactonization reaction are highly volatile and can be easily removed. Thus, under our optimized conditions, lactone products **2a** and **2b** are realized simply by removal of the catalyst by filtration followed by careful removal of the volatile components under high vacuum (Figures S1–S6, Supporting Information), providing an

## Scheme 1. Telescoped Routes to Higher Levulinate Esters

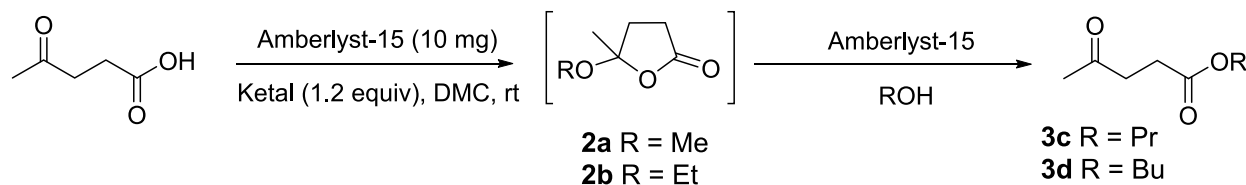
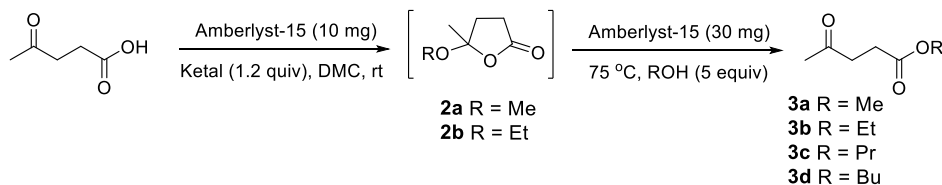


Table 3. Telescoped Protocols to Higher Levulinate Esters in DMC



entry	catalyst	ketal	ROH (5 equiv)	time (h)	selectivity (%) <sup>a</sup>	yield (%) <sup>a</sup>
1	A-15	DMOP	PrOH	3	3c:3a 61:39	59 (3c)
2	A-36	DMOP	PrOH	3	3c:3a 60:40	54 (3c)
3	A-15	DEOP	PrOH	5	3c:3b 88:12	63 (3c)
4	A-15	DEOP	BuOH	5	3d:3b 88:12	63 (3d)

<sup>a</sup>Determined by quantitative <sup>1</sup>H NMR spectroscopy of the crude reaction mixture.

efficient and operationally simple synthesis of these lactone products.

**3.3. Formation of Levulinate Esters from Higher Alcohols.** While this approach allows easy access to lactones and ester products derived from lower alcohols, such as methanol and ethanol, access to lactones derived from higher alcohols is more challenging due to the lack of access to ketals derived from these alcohols. With this in mind, and to further understand the chemistry of these lactones, we next investigated the possibility that this limitation could be addressed by an approach employing DMOP or DEOP to initially produce lactones **2a** or **2b** followed by lactone ring-opening in the presence of an additional nucleophile, in this case higher alcohols, such as 1-propanol or 1-butanol (Scheme 1).

While numerous studies have reported the effectiveness of ethyl levulinate as a biofuel additive, butyl levulinate has received significantly less attention, even though its properties are in a number of respects better suited to this role.<sup>47–49</sup> Indeed it has been demonstrated that in comparison to ethyl levulinate, butyl levulinate has a higher cetane number, a higher calorific value, and better solubility characteristics.<sup>48</sup> High yields of esters derived from higher alcohols, such as 1-propanol and 1-butanol, however, are more difficult to achieve given their reduced nucleophilicity in both Fischer esterification reactions<sup>29</sup> and from the direct alcoholysis of biomass or furfuryl alcohol derivatives.<sup>50</sup> Indeed, in the case of macroreticular resins, yields of higher ester products from reactions employing LA typically do not exceed 60%.<sup>16,17,24,30</sup> Our approach to realize an efficient and flexible route to levulinate esters derived from higher alcohols using lactones as advanced intermediates capitalizes on the higher reactivity of lactones in ring-opening reactions to circumvent these problems. Furthermore, the telescoping of the lactonization/lactone ring-opening esterification process into a one-pot procedure, in which none of the intermediates require isolation or purification, has considerable advantages in efficiency and operational simplicity.

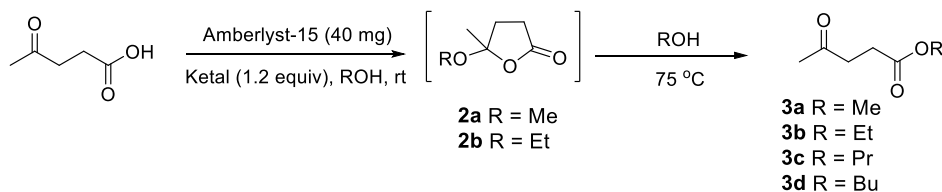
Our initial studies built upon our optimized conditions from our earlier studies employing DMOP in DMC with low loadings of Amberlyst-15 or Amberlyst-36 to initially produce lactone **2a**. On completion of the lactonization reaction, an additional portion of catalyst (30 mg) and 1-propanol (5 equiv) were added, and the reaction was heated to 75 °C to affect the ring-opening esterification. Gratifyingly, good conversions to levulinate ester products were achieved under these conditions; however, the selectivity for the propyl ester **3c** over methyl ester **3a** was only moderate (Table 3, entries 1 and 2).

We reasoned that the moderate selectivity observed here reflected the relative nucleophilicities of the two alcohol components present in the reaction in the final ring-opening esterification step.<sup>29,30</sup> The higher nucleophilicity of methanol in comparison to that of 1-propanol, would ensure that even in the presence of an excess of the less reactive 1-propanol, significant quantities of the methyl ester **3a** would be produced. To test this hypothesis, we next studied the reactions of lactone **2b**, derived from the reaction of LA with DEOP, in the expectation that the similar reactivities of ethanol and 1-propanol might alleviate this problem. Gratifyingly, this proved to be the case, and significant improvements in the quantity of esters **3c** and **3d** produced were observed in the reactions of 1-propanol and 1-butanol, respectively, in good overall yields (entries 3 and 4).

**3.4. Reaction Optimization.** With the poor selectivity issue addressed, we next turned our attention to improving the overall yields of the higher esters **3c** and **3d** by increasing the quantity of the higher alcohol nucleophile present in the reaction mixture by switching the solvent from DMC and carrying out the reaction in the higher alcohol solvent. Given the lower yields of lactone previously observed in the presence of low loadings of Amberlyst-15 in alcohol solvents, an increased amount of catalyst was employed at the start of the reaction. Gratifyingly, the reaction, as previously employing 1-propanol as solvent, gave improved yields of ester product **3c**, providing an operationally simple approach to obtain higher levulinate products (Table 4, entry1).

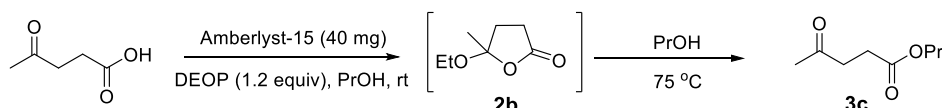


Table 4. Telescoped Protocols to Higher Levulinate Esters in Alcohol Solvents



entry	catalyst	ketal	solvent	time (h)	selectivity (%) <sup>a</sup>	yield (%) <sup>a</sup>
1	A-15	DMOP	PrOH	4	3c:3a 80:20	77 (3c)
2	A-15	DEOP	PrOH	4	3c:3b 92:08	90 (3c)
3	A-15	DEOP	BuOH	5	3d:3b 90:10	94 (3d)
4	A-36	DEOP	PrOH	4	3c:3b 88:12	68 (3c)

<sup>a</sup>Determined by quantitative <sup>1</sup>H NMR spectroscopy analysis of the crude reaction mixture.

Table 5. Amberlyst-15 Recycling in Telescoped Esterification Reactions of Levulinic Acid<sup>a</sup>

entry	ester 3c (%) <sup>a</sup>	selectivity (%) <sup>a</sup>
first cycle	87	90:10
second cycle	84	90:10
third cycle	89	92:08
fourth cycle	91	90:10
fifth cycle	85	88:12

<sup>a</sup>Determined by quantitative <sup>1</sup>H NMR spectroscopy analysis of the crude reaction mixture.

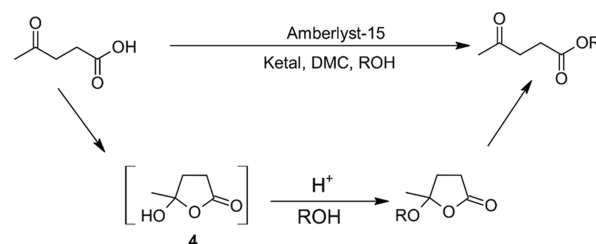
Significant improvements in both yield and selectivity for the higher ester product were successfully achieved by employing DEOP (entries 2 and 3) in place of DMOP, which provided the highest selectivity for ester products 3c and 3d. In this case, slightly lower yields of ester 3c were achieved employing Amberlyst-36 as a catalyst (entry 4).

**3.5. Catalyst Recycling Studies.** To complete our investigations, we carried out recycling and reuse studies to confirm retention of the catalytic activity and selectivity of the Amberlyst-15 catalyst. In agreement with literature reports and our own observations,<sup>18,25</sup> the Amberlyst-15 catalyst was fully recyclable and displayed no significant reduction in its catalytic activity or selectivity over the course of four cycles of reuse (Table 5).

**3.6. Mechanistic Considerations.** While the involvement of lactone intermediates in the formation of levulinate esters is well-established<sup>29–32,34,51</sup> and has been demonstrated to be energetically comparable to the Fischer esterification mechanism when catalyzed by solid acid catalysts,<sup>52</sup> the chemistry of these lactones is less well investigated. It has been demonstrated that the conversion of  $\alpha$ -angelica lactone to levulinate esters by macroreticular resins proceeds efficiently through the lactone intermediate;<sup>29,30</sup> however, it would not be expected that  $\alpha$ -angelica lactone would be formed in our case due to the low temperatures employed. Indeed, no  $\alpha$ -angelica lactone was detected by the <sup>1</sup>H NMR analysis of our crude reaction mixtures.

One plausible alternative mechanism involves the ketal acting as a dehydrating agent to promote the formation of pseudo-levulinic acid 4, which subsequently undergoes an acid-catalyzed transesterification reaction to produce the corresponding lactone intermediates (Scheme 2). Transesterification strategies have attracted considerable attention in a

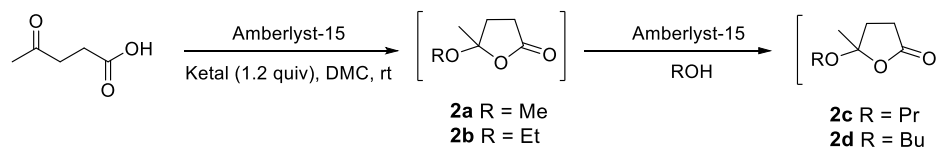
Scheme 2. Plausible Reaction Mechanism for Levulinate Ester Formation



diverse number of research areas as a useful strategy for the formation of carbon–oxygen bonds from a variety of substrates employing both homogeneous and heterogeneous catalysts,<sup>53–55</sup> and indeed, Amberlyst-15 itself has been demonstrated to efficiently catalyze such reactions.<sup>56</sup> We were intrigued as to the possibility that the intermediate lactones 2a and 2b once formed might themselves undergo transesterification reactions under the reaction conditions employed to produce the intermediate lactones 2c and 2d in excess of the higher alcohol solvent (Scheme 3).

With this possibility in mind, we analyzed the crude reaction mixtures derived from the lactonization reactions of LA with DMOP and DEOP in 1-propanol and 1-butanol by GC–MS analysis. This indicated that in all cases, only small quantities of the expected methoxy- or ethoxy lactones 2a or 2b were present in these reaction mixtures with the major product in each case having a longer retention time than 2a and 2b and providing MS data consistent with the propoxy- and butoxy lactone products 2c and 2d (Supporting Information Table S2). Disappointingly, it was not possible to isolate pure samples of these products to further confirm their identity due to the high boiling points of the alcohol solvents, which

## Scheme 3. Potential Transesterification Reactions of Lactones



precluded their removal at low temperature and which also masked the relevant lactone signals in the crude  $^1\text{H}$  NMR spectra. These results suggest that the lactone products undergo in situ transesterification under the reaction conditions and indicate that the site of reaction of the nucleophile can be controlled by careful manipulation of the reaction conditions. We envisage that at low temperatures, the lactone ring-opening reaction is disfavored while the transesterification is rapid and proceeds effectively to provide the lactone product derived from the higher alcohol. At higher temperatures, however, the irreversible ring-opening reactions is rapid and provides the higher ester product. Studies are currently in progress to verify these initial results and to further exploit these intermediates as a potential new opportunity for the valorization of levulinic acid.

#### 4. CONCLUSIONS

In conclusion, we have demonstrated that lactone products **2a** and **2b** are selectively and efficiently synthesized from the reaction of levulinic acid and ketals in the presence of commercially available macroreticular resins, such as Amberlyst-15 and Amberlyst-36. Workup procedures are extremely simple, only requiring the removal of volatile byproducts to provide the lactone products in high yield. To extend this methodology to encompass the synthesis of levulinate esters derived from higher alcohols, we developed a novel telescoped procedure, which does not require the isolation of the intermediate lactone products. In these cases, the lactonization/esterification protocol is achieved in a one-pot reaction sequence in the presence of DMOP or DEOP, a higher alcohol, such as 1-propanol and 1-butanol, and an Amberlyst-15 or Amberlyst-36 catalyst. Heating at moderate temperatures for short reaction times provides excellent conversions to the ester products in high yield with excellent selectivity. Reactions employing DEOP provide higher selectivity for the higher alcohol products in comparison to reactions employing DMOP due to the lower reactivity of the ethanol byproduct present in the reaction mixture. We provide initial evidence that the site of reaction with oxygen nucleophiles can be controlled by careful manipulation of the reaction conditions. Thus, at room temperature, the lactone undergoes a transesterification reaction at the lactol position to provide lactone products **2c** and **2d** in the presence of an excess of the higher alcohols. The Amberlyst-15 catalyst is fully recyclable and displayed no significant reduction in its catalytic activity or selectivity over the course of four cycles of reuse.

#### ■ ASSOCIATED CONTENT

##### SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.4c08315>.

General experimental details, catalyst properties, optimization studies, and NMR and GC–MS data for lactone and ester products (PDF)

#### ■ AUTHOR INFORMATION

##### Corresponding Author

Andrew E. Graham – School of Applied Sciences, University of South Wales, Upper Glyntaff CF37 4AT, U.K.; [orcid.org/0000-0002-2761-5967](https://orcid.org/0000-0002-2761-5967); Email: [andrew.graham@southwales.ac.uk](mailto:andrew.graham@southwales.ac.uk)

##### Authors

Matthew P. Aldred – School of Applied Sciences, University of South Wales, Upper Glyntaff CF37 4AT, U.K.

Thomas E. Davies – Cardiff Catalysis Institute, School of Chemistry, Cardiff University, Cardiff CF10 3AT, U.K.

Stuart H. Taylor – Cardiff Catalysis Institute, School of Chemistry, Cardiff University, Cardiff CF10 3AT, U.K.; [orcid.org/0000-0002-1933-4874](https://orcid.org/0000-0002-1933-4874)

Complete contact information is available at:

<https://pubs.acs.org/10.1021/acsomega.4c08315>

##### Notes

The authors declare no competing financial interest.

#### ■ ACKNOWLEDGMENTS

The authors gratefully acknowledge financial support from the Leverhulme Trust through a Leverhulme Trust Research Project Grant RPG-2020-077.

#### ■ REFERENCES

- Huber, G. W.; Iborra, S.; Corma, A. Synthesis of transportation fuels from biomass: chemistry, catalysis and engineering. *Chem. Rev.* **2006**, *106*, 4044–4098.
- Corma, A.; Iborra, S.; Velty, A. Chemical routes for the transformation of biomass into chemicals. *Chem. Rev.* **2007**, *107*, 2411–2502.
- Delidovich, I.; Hausoul, P. J. C.; Deng, Li.; Pfützenreuter, R.; Rose, M.; Palkovits, R. Alternative monomers based on lignocellulose and their use for polymer production. *Chem. Rev.* **2016**, *116*, 1540–1599.
- Sheldon, R. The road to biorenewables: carbohydrates to commodity chemicals. *ACS Sustain. Chem. Eng.* **2018**, *6*, 4464–4480.
- Pileidis, F. D.; Titirici, M.-M. Levulinic acid biorefineries: new challenges for efficient utilization of biomass. *ChemSusChem* **2016**, *9*, 562–582.
- Yu, Z.; Lu, X.; Xiong, J.; Ji, N. Transformation of levulinic acid to valeric biofuels: a review on heterogeneous bifunctional catalytic systems. *ChemSusChem* **2019**, *12*, 3915–3930.
- Yan, K.; Jarvis, C.; Gu, J.; Yan, Y. Production and catalytic transformation of levulinic acid: A platform for speciality chemicals and fuels. *Renewable Sustainable Energy Rev.* **2015**, *51*, 986–997.
- Gürbüz, E. I.; Alonso, D. M.; Bond, J. Q.; Dumesic, J. A. Reactive extraction of levulinate esters and conversion to  $\gamma$ -valerolactone for production of liquid fuels. *ChemSusChem* **2011**, *4*, 357–361.
- Chaffey, D. R.; Davies, T. E.; Taylor, S. H.; Graham, A. E. Etherification reactions of furfuryl alcohol in the presence of orthoesters and ketals; Application to the synthesis of furfuryl ether bio-fuels. *ACS Sustain. Chem. Eng.* **2018**, *6*, 4996–5002.
- Silva, J. F. L.; Grekin, R.; Mariano, A. P.; Filho, R. M. Making levulinic acid and ethyl levulinate economically viable: a worldwide

technoeconomic and environmental assessment of possible routes. *Energy Technol.* **2018**, *6*, 613–639.

(11) Guo, Y.; Li, K.; Yu, X.; Clark, J. H. Mesoporous H3PW12O40-silica composite: efficient and reusable solid acid catalyst for the synthesis of diphenolic acid from levulinic acid. *Appl. Catal., B* **2008**, *81*, 182–191.

(12) Demirbas, A. Competitive liquid biofuels from biomass. *Appl. Energy* **2011**, *88*, 17–28.

(13) Kean, J. R.; Graham, A. E. Indium (III) triflate promoted synthesis of alkyl levulinates from furyl alcohols and furyl aldehydes. *Catal. Commun.* **2015**, *59*, 175–179.

(14) Nandiwale, K. Y.; Sonar, S. K.; Niphadkar, P. S.; Joshi, P. N.; Deshpande, S. S.; Patil, V. S.; Bokade, V. V. Catalytic upgrading of renewable levulinic acid to ethyl levulinate biodiesel using dodecatungstophosphoric acid supported on desiccated H-ZSM-5 as catalyst. *Appl. Catal., A* **2013**, *460–461*, 90–98.

(15) Pasquale, G.; Vazquez, P.; Romanelli, G.; Baronetti, G. Catalytic upgrading of levulinic acid to ethyl levulinate using reusable silica-included Wells-Dawson heteropolyacid as catalyst. *Catal. Commun.* **2012**, *18*, 115–120.

(16) Cirujano, F. G.; Corma, A.; Llabrés i Xamena, F. X. Conversion of levulinic acid into chemicals: Synthesis of biomass derived levulinate esters over Zr-containing MOFs. *Chem. Eng. Sci.* **2015**, *124*, 52–60.

(17) Tejero, M. A.; Ramírez, E.; Fité, C.; Tejero, J.; Cunill, F. Esterification of levulinic acid with butanol over ion exchange resins. *Appl. Catal., A* **2016**, *517*, 56–66.

(18) Lange, J.-P.; van de Graaf, W.; Haan, R. J. Conversion of furfuryl alcohol into ethyl levulinate using solid acid catalysts. *ChemSusChem* **2009**, *2*, 437–441.

(19) Fernandes, D. R.; Rocha, A. S.; Mai, E. F.; Mota, C. J. A.; Teixeira da Silva, V. Levulinic acid esterification with ethanol to ethyl levulinate production over solid acid catalysts. *Appl. Catal., A* **2012**, *425–426*, 199–204.

(20) Demma Carà, P.; Ciriminna, R.; Shiju, N. R.; Rothenberg, G.; Pagliaro, M. Enhanced heterogeneous catalytic conversion of furfuryl alcohol into butyl levulinate. *ChemSusChem* **2014**, *7*, 835–840.

(21) Démolis, A.; Eternot, M.; Essayem, N.; Rataboul, F. New insights into the reactivity of biomass with butenes for the synthesis of butyl levulinates. *ChemSusChem* **2017**, *10*, 2612–2617.

(22) Song, D.; An, S.; Lu, B.; Guo, Y.; Leng, J. Arylsulfonic acid functionalized hollow mesoporous carbon spheres for efficient conversion of levulinic acid or furfuryl alcohol to ethyl levulinate. *Appl. Catal., B* **2015**, *179*, 445–457.

(23) Melero, J. A.; Molares, G.; Iglesias, J.; Paniagua, M.; Hernández, B.; Penedo, S. Efficient conversion of levulinic acid into alkyl levulinates catalyzed by sulfonic mesostructured silicas. *Appl. Catal., A* **2013**, *466*, 116–122.

(24) Trombettoni, V.; Bianchi, L.; Zupanich, A.; Porciello, A.; Cuomo, M.; Piermatti, O.; Marrocchi, A.; Vaccaro, L. Efficient catalytic upgrading of levulinic acid into alkyl levulinates by resin-supported acids and flow reactors. *Catalysts* **2017**, *7*, 235.

(25) Chaffey, D. R.; Bere, T.; Davies, T. E.; Apperley, D. C.; Taylor, S. H.; Graham, A. E. Conversion of levulinic acid to levulinate ester biofuels by heterogeneous catalysts in the presence of acetals and ketals. *Appl. Catal., B* **2021**, *293*, 120219.

(26) Jin, M.; Hoye, T. R. Lactone ring-opening equilibria in methanol by <sup>1</sup>H NMR analysis: an assessment of the ring-opening polymerizability of lactone monomers. *Macromolecules* **2023**, *56*, 1122–1129.

(27) Phillips, D. J.; Pillinger, K. S.; Li, W.; Taylor, A. E.; Graham, A. E. Desymmetrization of diols by a tandem oxidation/Wittig olefination reaction. *Chem. Commun.* **2006**, 2280–2282.

(28) Phillips, D. J.; Pillinger, K. S.; Li, W.; Taylor, A. E.; Graham, A. E. Diol desymmetrization as an approach to the synthesis of unsymmetrical dienyl diesters. *Tetrahedron* **2007**, *63*, 10528–10533.

(29) Yi, X.; Al-Shaal, M. G.; Ciptonugroho, W.; Delidovich, I.; Wang, X.; Palkovits, R. Synthesis of butyl levulinate based on  $\alpha$ -

angelica lactone in the presence of easily separable heteropoly acid catalysts. *ChemSusChem* **2017**, *10*, 1494–1500.

(30) Al-Shaal, M. G.; Ciptonugroho, W.; Holzhäuser, F. J.; Mensah, J. B.; Hausoul, P. J. C.; Palkovits, R. Catalytic upgrading of  $\alpha$ -angelica lactone to levulinic acid esters under mild conditions over heterogeneous catalysts. *Catal. Sci. Technol.* **2015**, *5*, 5168–5173.

(31) Zhou, S.; Lei, M.; Bai, J.; Liu, X.; Wu, L.; Long, M.; Huang, K.; Yin, D. Titania nanotubes-bonded sulfamic acid as an efficient heterogeneous catalyst for the synthesis of n-butyl levulinate. *Front. Chem.* **2022**, *10*, 894965.

(32) Ciptonugroho, W.; Al-Shaal, M. G.; Mensah, J. B.; Palkovits, R. One pot synthesis of WO<sub>x</sub>/mesoporous-ZrO<sub>2</sub> catalysts for the production of levulinic-acid esters. *J. Catal.* **2016**, *340*, 17–29.

(33) Tristram, C. J.; Mason, J. M.; Williams, D. B. G.; Hinkley, S. F. R. Doubly renewable cellulose polymer for water-based coatings. *ChemSusChem* **2015**, *8*, 63–66.

(34) Shu, C. K.; Lawrence, B. M. Formation of 4-Alkoxy- $\gamma$ -valerolactones from levulinic acid and alcohols during storage at room temperature. *J. Agric. Food Chem.* **1995**, *43*, 782–784.

(35) Schleyer, K.; Halabi, E. A.; Weissleder, R.  $\gamma$ -Butyrolactone derivatives of MSA-2 are STING prodrugs. *ChemMedChem* **2024**, *19*, No. e202400416.

(36) Yamamoto, M.; Yoshitake, M.; Yamada, K. Cyclisation of alkyne-carboxylic acids: a route to an oxaspirolactone. *J. Chem. Soc. Chem. Commun.* **1983**, 991–992.

(37) Yu, F.; Zhong, R.; Chong, H.; Smet, M.; Dehaen, W.; Sels, B. F. Fast catalytic conversion of recalcitrant cellulose into alkyl levulinates and levulinic acid in the presence of soluble and recoverable sulfonated hyperbranched poly(arylene oxindole)s. *Green Chem.* **2017**, *19*, 153–163.

(38) Hayashi, Y. Pot economy and one-pot synthesis. *Chem. Sci.* **2016**, *7*, 866–880.

(39) Hayashi, Y. Time economy in total synthesis. *J. Org. Chem.* **2021**, *86*, 1–23.

(40) Webb, D.; Jamison, T. F. Continuous flow multi-step organic synthesis. *Chem. Sci.* **2010**, *1*, 675–680.

(41) Rogers, L.; Jensen, K. V. Continuous manufacturing—the green chemistry promise. *Green Chem.* **2019**, *21*, 3481–3498.

(42) Phillips, D. J.; Graham, A. E. In situ generation of ylides for tandem oxidation-olefination reactions of unactivated diols. *Synlett* **2008**, *2008*, 649–652.

(43) Graham, A. E.; Taylor, R. J. K. Synthesis of tricholomenyn A and epitricholomenyn A by a palladium-catalysed  $\beta$ -halo enone coupling route. *J. Chem. Soc., Perkin Trans.* **1997**, *1*, 1087–1089.

(44) Bulman Page, P. C.; Graham, A. E.; Park, B. K. A convenient preparation of symmetrical and unsymmetrical 1,2-diketones – application to fluorinated phenytoin synthesis. *Tetrahedron* **1992**, *48*, 7265–7274.

(45) Smith, B. M.; Graham, A. E. Sequential and tandem oxidation/ acetalization procedures for the direct generation of acetals from alcohols. *Tetrahedron Lett.* **2007**, *48*, 4891–4894.

(46) Smith, B. M.; Kubczyk, T. M.; Graham, A. E. Metal triflate catalysed acetal exchange reactions of glycerol under solvent-free conditions. *RSC Adv.* **2012**, *2*, 2702–2706.

(47) Ramírez, E.; Bringué, R.; Fité, C.; Iborra, M.; Tejero, J.; Cunill, F. Role of ion-exchange resins as catalyst in the reaction-network of transformation of biomass into biofuels. *J. Chem. Technol. Biotechnol.* **2017**, *92*, 2775–2786.

(48) Ahmad, K. A.; Siddiqui, M. H.; Pant, K. K.; Nigam, K. D. P.; Shetti, N. P.; Aminabhavi, T. M. A critical review on suitability and catalytic production of butyl levulinate as a blending molecule for green diesel. *Chem. Eng. J.* **2022**, *447*, 137550.

(49) Christensen, E.; Williams, A.; Paul, S.; Burton, S.; McCormick, R. L. Properties and performance of levulinate esters as diesel blend components. *Energy Fuels* **2011**, *25*, 5422–5428.

(50) Raspolli Galletti, A. M.; Antonetti, C.; Fulignati, S.; Licursi, D. Direct alcoholysis of carbohydrate precursors and real cellulosic biomasses to alkyl levulinates: a critical review. *Catalysts* **2020**, *10*, 1221.

(51) Langlois, D. P.; Wolff, H. Pseudoesters of levulinic acid. U.S. Patent 2,493,637 A, 1950.

(52) Ojeda, G. D. R.; Esquenazi, E. N.; Gomes, G. J.; Peruchena, N. M.; Zalazar, M. F. Mechanism insight into esterification of levulinic acid with methanol on H-Beta zeolite: a DFT study. *Catal. Today* **2025**, *445*, 115047.

(53) Evans, D. A.; Beiger, J. J.; Burch, J. D.; Fuller, P. H.; Glorius, F.; Kattnig, E.; Thaisrivongs, D. A.; Trenkle, W. C.; Young, J. M.; Zhang, J. Total synthesis of Aflastatin A. *J. Am. Chem. Soc.* **2022**, *144*, 19953–19972.

(54) Sahoo, P. K.; Gawali, S. S.; Gunanathan, C. Iron-catalyzed selective etherification and transesterification reactions using alcohols. *ACS Omega* **2018**, *3*, 124–136.

(55) Sittiwong, W.; Richardson, M. W.; Schiaffo, C. E.; Fisher, T. J.; Dussault, P. H. Re2O7-catalyzed reaction of hemiacetals and aldehydes with O-, S-, and C-nucleophiles. *Beilstein J. Org. Chem.* **2013**, *9*, 1526–1532.

(56) Mohanta, M.; Chaudhari, M. B.; Digrawal, N. K.; Gnanaprakasam, B. Rapid and multigram synthesis of vinylogous esters under continuous flow: an access to transesterification and reverse reaction of vinylogous esters. *Org. Process Res. Dev.* **2019**, *23*, 1034–1045.