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Synthesis of Levulinic Acids From Muconic Acids in Hot Water

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Abstract: Levulinic acid is a key biorenewable platform molecule. Its current chemical production from sugars is plagued by limited yields, char formation and difficult separations. An alternative and selective route starting from muconic acid *via* simple heating in water at high temperature (180 °C) has been developed. Muconic acid can be obtained from sugars or catechol fermentation. Chemical oxidation of catechol is another possibility which advantageously can also be applied on substituted catechols, hereby providing substituted muconic acids. When applying the disclosed hydrothermal protocol on these substrates hitherto unknown substituted levulinic acids were accessed. In particular, 3-propyllevulinic acid has been synthesized from 4-propylcatechol, prepared from pine wood. This propylated derivative has been used for the synthesis of a 3-propyllevulinate diester, i.e. butane-1,4-diyl bis(4-oxo-3-propylpentanoate), *via* esterification with 1,4-butanediol. The diester showed superior performance as plasticizer in comparison to the corresponding levulinate diester in both PVC (polyvinyl chloride) and PLA (polylactic acid). It plasticizes equally effective as the notorious commercial phthalate-based benchmark DEHP (di-2-ethylhexyl phthalate) in PVC.

Levulinic acid (**2a**) is considered one of the key biobased platform molecules of the renewable chemical industry of the future.[1] It can be converted into products spanning various application fields (pharmaceuticals, agrochemicals, cosmetics, plastics & additives, solvents, fuels) (Figure 1).[1-2] The market is estimated to reach 2400 ton p.a. in 2025, with an annual growth of up to 3%.[3] Currently **2a** is produced from sugar biomass.[4] Both hexoses (cellulose/glucose) (Segetis and Biofine processes) and pentoses (xylan/xylose) (Westpro-modified Huaxia process) can serve as a feedstock (Scheme 1A).[2a, 5] These processes are however plagued with extensive char (humins) formation and the need for expensive, corrosion-resistant reactor equipment because of the mineral acid used at high temperature.[6] In addition, separation of **2a** from the dilute aqueous stream containing side products is energy intensive. The hexose routes involve 5-hydroxymethylfurfural (**5-HMF**) as intermediate and produce formic acid as a by-product, further complicating the separation and purification. In accordance with this, the downstream processing is responsible for a large part of the total production cost from cellulosic feedstock.[7] The pentose routes are more expensive than the hexose routes as they require more process

steps, involving expensive furfural (**FF**) and furfuryl alcohol (**FA**) as intermediates.[1]

In search for improved processes, levulinic acid (**2a**) synthesis from hexoses involving various heterogeneous catalysts,[8] microwave heating,[9] ionic liquids,[10] or biphasic systems[11] have been disclosed.[6, 12] However, though advances were made none of these provided the necessary breakthrough to resolve all the limitations of the existing processes. Clearly, there is a need for a novel approach embracing alternative biorenewable substrates derived from 2nd generation (2G) biomass.
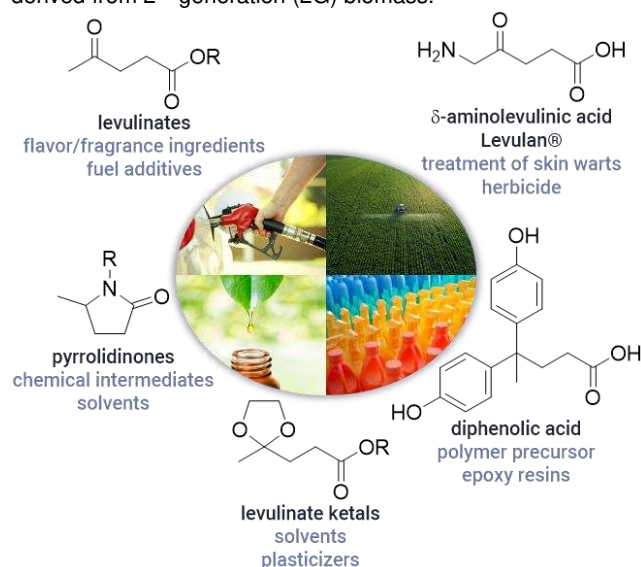

Figure 1. Selected levulinic acid (**2a**) derivatives.

We envisioned a novel route involving reaction of *cis,cis*-muconic acid (***cis,cis*-1a**) with water, used as reactant and solvent (Scheme 1B). This tandem reaction should only require heating and no additional reagents or catalysts. Furthermore, CO_2 is the only by-product expected, which spontaneously separates from the reaction mixture and can be captured for further use. ***cis,cis*-1a** has attracted considerable attention as a biorenewable platform molecule towards industrially important monomers for plastics, such as adipic acid, terephthalic acid and caprolactam.[13] It can be synthesized by two major routes.[13] The first one is the fermentation of glucose or catechol (**6a**). The highest titers obtained to date are 59.2 g/L from glucose (using *E. coli*)[14] and 85 g/L from **6a** (using *C. glutamicum*).[15] Techno-economic

analysis of *cis,cis*-**1a** production by fermentation from 2G sugars indicates future availability at a price below 3 EUR/kg when state-of-the art metabolic yields (30-40%) of the fermentation can be combined with an improved productivity (0.5 g/L/h).[16] Considering a levulinic acid prize of 6.4-7.5 EUR/kg in 2019[3] this leaves enough margin to use *cis,cis*-**1a** as a novel starting material for levulinic acid production.

An alternative second route is the chemical, Fenton-like[17] oxidative cleavage of **6a**.[18] Biorefinery of lignocellulose provides cellulose pulp and lignin oil rich in guaiacols (**5**), i.e. guaiacol (**5a**) or alkylguaiacols [e.g. 4-methyl- (**5b**), 4-ethyl- (**5c**) and 4-

propylguaiacol (**5d**)], depending on the feedstock and the cleavage process.[19] The cellulose of the pulp can be transformed in glucose and **5a** in the lignin oil into **6a** by *O*-demethylation, and in case of **5b-d** with additional *C*-dealkylation, hereby providing the substrate to produce *cis,cis*-**1a**.[20] Furthermore, oxidative cleavage of alkylcatechols **6b-d**, obtained *via O*-demethylation of **5b-d**,[20e] yields alkyl-substituted muconic acids (**1b-d**) which provide access to hitherto unknown alkyl-substituted levulinic acids (**2b-d**) through our solvolysis method. These novel derivatives potentially allow to get superior performance versus parent levulinic acid (**2a**) or explore completely novel applications.
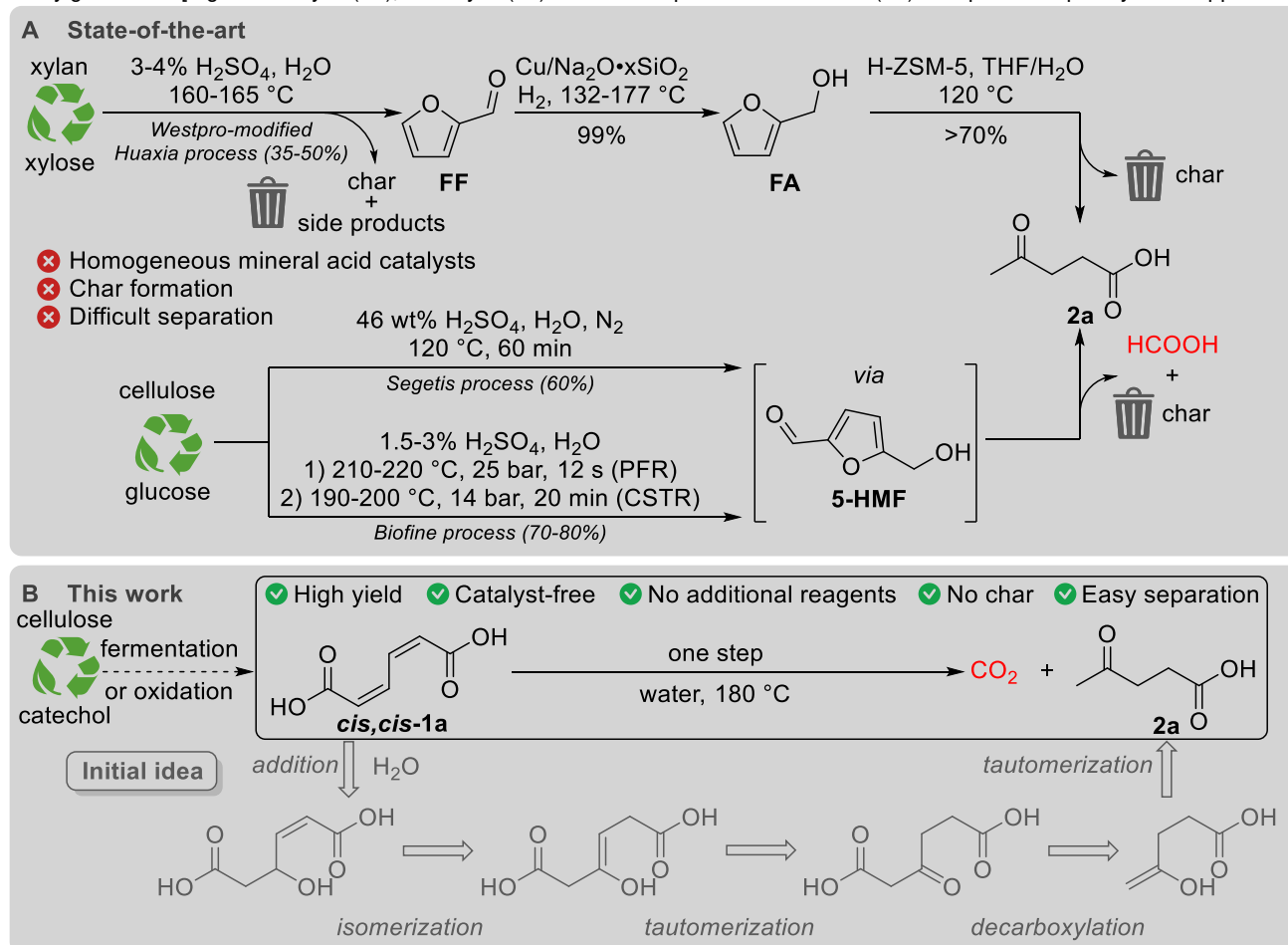
Scheme 1. (**A**) Hexose and pentose routes towards levulinic acid (**2a**).[1, 5, 21] (**B**) New synthesis of **2a**. GVL = γ-valerolactone, THF = tetrahydrofuran, PFR = plug flow reactor, CSTR = continuous stirred tank reactor.

Our study of the levulinic acid (**2a**) synthesis from *cis,cis*-muconic acid (*cis,cis*-**1a**) and water started with a reaction temperature screening in water (Scheme 2A). Levulinic acid (**2a**) formation was observed at 110 °C, while at a lower temperature only

isomerization of *cis,cis*-**1a** into *cis,trans*-**1a** was observed.[22] Furthermore muconolactone (**3a**) and -dilactone (**4a**) were formed *via* lactonization of *cis,trans*-**1a** (see Scheme 3).[22] Complete conversion of *cis,cis*-**1a** into **2a** was achieved at 200 °C in 3 h.
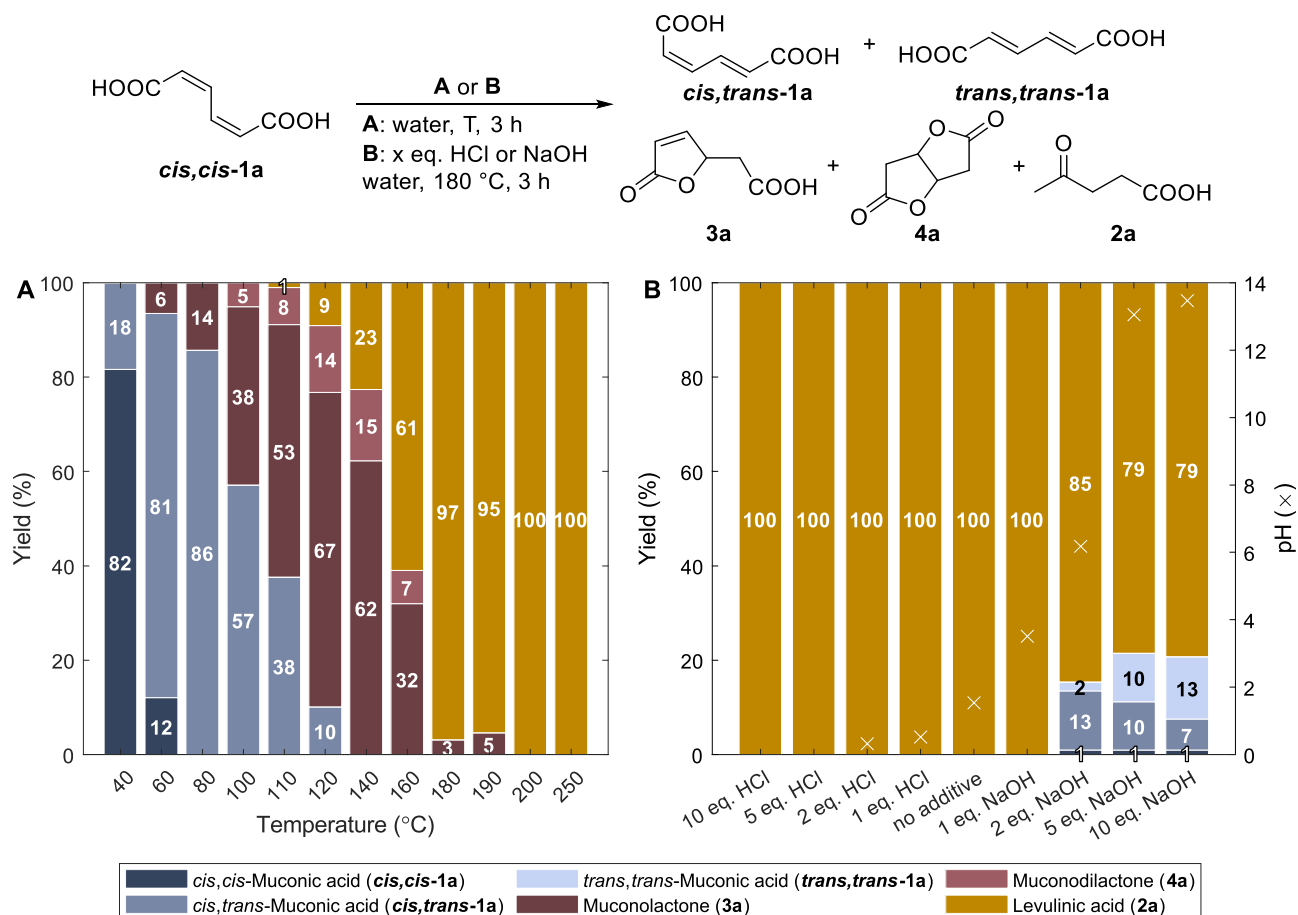
Scheme 2. Temperature and additive screening of the levulinic acid (**2a**) synthesis. **A**: *cis,cis*-muconic acid (***cis,cis*-1a**, 0.3 mmol) in water (3 mL), N_2 (50 bar), T, 3 h, 25 mL Parr reactor. **B**: *cis,cis*-muconic acid (***cis,cis*-1a**, 0.3 mmol) and additive (x eq.) in water (3 mL), N_2 (15 bar), 180 °C, 3 h, 300 mL Parr reactor. All yields are normalized to 100% mass balance.

Concentration had little influence on the **2a** yield (see Supporting Information Table S5). The reaction requires mildly acidic conditions to work well, which are provided by the inherent acidity of the substrate (see Supporting Information Table S7). At a 0.1 M concentration of ***cis,cis*-1a**, a pH of 1.54 is obtained. Lower pH did not interfere while at pH > 3.5 a decrease in yield was observed (Scheme 2B). Optimal conditions at 0.1 M ***cis,cis*-1a** in water are heating at 180 °C for 3 h. In small scale experiments glass vials of 4 mL were placed inside reactors of 25-300 mL volume and a backpressure of N_2 was applied to keep the solvent liquid in the vial. A simple extraction of the reaction mixture with isopropanol/ethyl acetate (15:85 vol.) was sufficient for the isolation, providing 87% **2a** (Scheme 4A). Reactions on larger scale were performed in the glass-liner of the reactor under the autogenic pressure generated by the boiling solvent without initial N_2 backpressure. On 75 mmol (10.7 g) scale 90% isolated yield (8.3 g) of **2a** with 94 wt% purity was obtained (Scheme 4A). The purity could be increased to 98 wt% by vacuum distillation without significant product loss (see Supporting Information Section 10.2.1). No column chromatography was required, reflecting the selectivity of the new transformation.

In order to elucidate the reaction mechanism of the transformation of ***cis,cis*-1a** into **2a** in water, reaction profiles were measured at 180 °C by sampling the reaction mixture in function of time (Figure 2A). Most of the *cis,cis*-muconic acid (***cis,cis*-1a**) had already been converted into ***cis,trans*-1a** within 30 min. Muconolactone (**3a**) formed after 45 min before any levulinic acid (**2a**) appeared. Muconodilactone (**4a**) was also detected in low concentrations and had a similar profile to **3a**. Levulinic acid (**2a**) formation started after about 60 min of heating and its concentration then steadily increased throughout the reaction. Full conversion towards **2a** was achieved within 200 min. Next, the experiment was repeated using the observed intermediate lactones **3a** and **4a** as the substrate (Figure 2C and Figure 2D). Neither monolactone **3a** nor dilactone **4a** reopened to form ***cis,trans*-1a**, only yielding **2a** instead. With **4a** as the starting material (Figure 2D) a 1:1 ratio of di- **4a** and monolactone **3a** was formed within one hour, but at this point no levulinic acid (**2a**) was generated yet. The concentration of both lactones then decreased while **2a** was steadily formed, pointing towards reversible dilactone **4a** formation from monolactone **3a**. When ***cis,trans*-1a** was used as substrate a similar picture as for ***cis,cis*-1a** was observed (Figure 2B) due to the rapid isomerization of ***cis,cis*-1a** into ***cis*,trans-1a** (Figure 2A). *trans,trans*-Muconic acid (***trans,trans*-1a**) did not react under these reaction conditions (Supporting Information Table S9, entry 1) and was never observed in the experiments using ***cis,cis*-1a** or ***cis,trans*-1a** (Figure 2A and 2B).
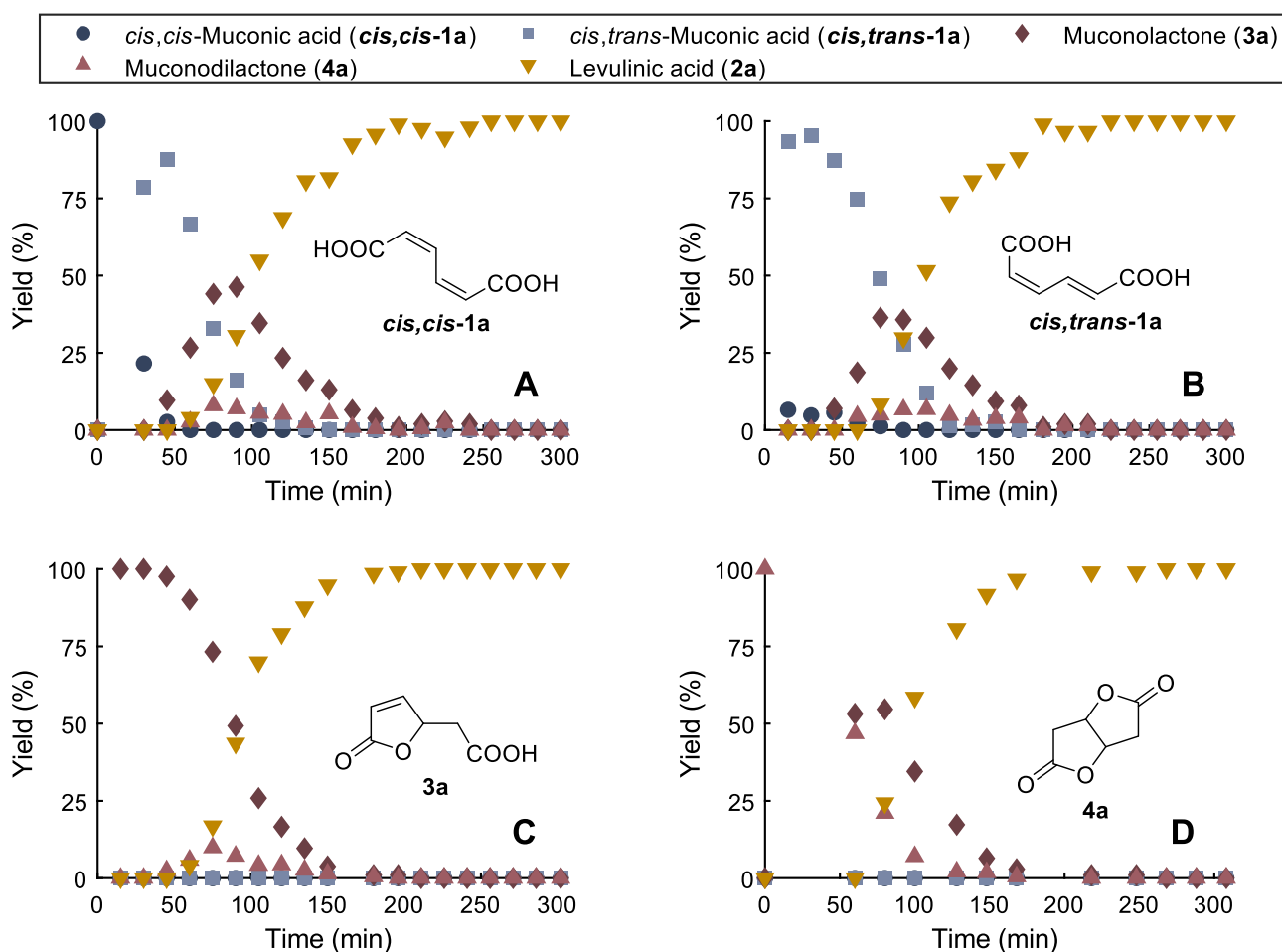
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Figure 2. Product distribution in function of time for the levulinic acid (**2a**) formation from (**A**) *cis,cis*-muconic acid (**cis,cis-1a**); (**B**) *cis,trans*-muconic acid (**cis,trans-1a**); (**C**) muconolactone (**3a**); (**D**) muconodilactone (**4a**). Reaction conditions: substrate (15 mmol) in water (150 mL), N_2 (15 bar), 180 °C, 300 mL Parr reactor. In each case, a stable internal temperature of 180 °C was reached after about 60 min of heating.

Based on the reaction profiles a reaction mechanism can be proposed (Scheme 3). In accordance with the literature,[22] *cis,cis*-muconic acid (**cis,cis-1a**) initially undergoes rapid isomerization into **cis,trans-1a**,[13] which *via* intramolecular addition provides muconolactone (**3a**). The latter exists in equilibrium with muconodilactone (**4a**), formed *via* a second lactonization. Hydrolysis of **3a** is the rate-limiting step, producing 4-hydroxyhex-2-enedioc acid (**A**). Isomerization of the allylic alcohol of **A** into enol provides 3-hydroxy-3-hexenedioc acid (**B**), and enol-keto tautomerization of **B** yields 4-oxo-hexanedioc acid (**C**). This *β*-ketoacid **C** spontaneously decarboxylates[23] under the reaction conditions providing levulinic acid (**2a**). The involvement of **3a** as an intermediate was revealed from the sampling experiments. This is further supported by the inability of *trans,trans*-muconic acid (**trans,trans-1a**) to provide levulinic acid (**2a**) under the reaction conditions (Scheme 4A, Supporting Information Figure S13 and Table S9, entry 1). The spatial configuration of the double bonds in **trans,trans-1a** does not allow a direct lactonization reaction.[13] Only upon addition of 10 eq. HCl or NaOH, or when increasing the reaction temperature to 250 °C **2a** was formed, indicating that under these harsher reaction conditions either the isomerization of **trans,trans-1a** into **cis,trans-1a** or the direct addition of water to **trans,trans-1a** is possible (Supporting Information Table S9, entries 2-4). The formation of CO_2 in our reaction was confirmed by a capturing experiment with (2-ethylamino)ethanol, where CO_2 was recovered from the Parr reactor in 84% yield (Supporting Information section 10.2.1). Supplementary to this experimental work, density functional theory (DFT) calculations revealed that the conversion of **cis,cis-1a** into **2a** is energetically favorable with a reaction free energy (ΔG) of -27.9 kcal/mol (Figure 3, Supporting Information section 14).
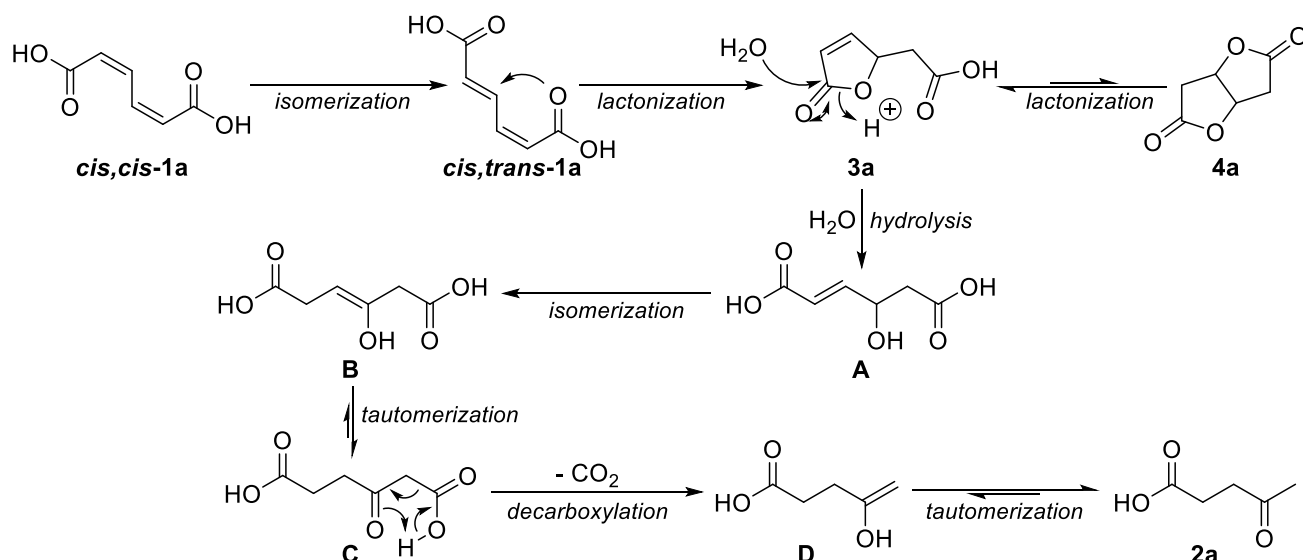
Scheme 3. Proposed mechanism of the transformation of *cis,cis*-muconic acid (*cis,cis*-**1a**) into levulinic acid (**2a**) involving water as reactant and solvent.
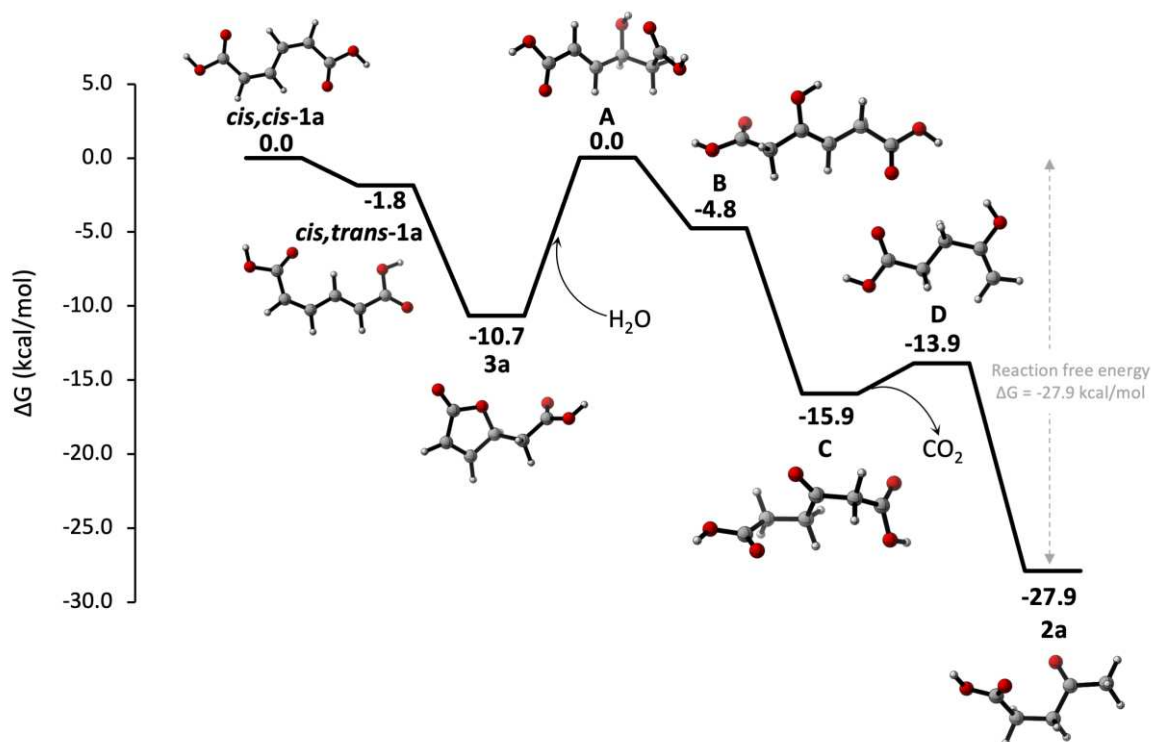

Figure 3. Free energy diagram (180 °C) of the transformation of *cis,cis*-muconic acid (*cis,cis*-**1a**) into levulinic acid (**2a**), following the mechanism proposed in Scheme 3.

Next, the scope of the method was studied (Scheme 4). Substituted muconic acids (**1**) and their corresponding lactones (**3**) can be easily obtained *via* oxidative cleavage of the corresponding catechols (**6**) with hydrogen peroxide in formic acid and 0.1 mol% $(NH_4)_2Fe(SO_4)_2$ catalyst.[18] This method provides either **1**, **3** or a mixture of both depending on the substituent. A preliminary screening on the sterically hindered 3-*tert*-butylmuconolactone (**3e**) revealed that a reaction temperature of 250 °C was required to obtain full conversion in 3 h (see Supporting Information Table S10). This was then applied as standard reaction temperature for other substituted muconic acid derivatives. Several muconic acids (**1**) and muconolactones (**3**) featuring 3-alkyl [Me (**1b**, **3b**), Et (**1c**, **3c**), Pr (**3d**), *t*-Bu (**3e**)] and

a 3-phenyl (**3h**) group provided high yields of the corresponding 3-substituted levulinic acids (**2**) (Scheme 4B). Notably, **3f** (derived from biorenewable protocatechuic acid) and **3g** (derived from biorenewable caffeic acid) lost their side chains *via* respectively decarboxylation and retro-aldol condensation under the reaction conditions,[24] both yielding levulinic acid (**2a**). 2-Substituted muconic acids (**1'**) and muconolactones (**3'**) provided a mixture of the corresponding 2- (**2'**) and 5-substituted (**2''**) levulinic acids, as major and minor product, respectively (Scheme 4C). Only muconolactone **3'e** with a bulky 2-*tert*-butyl substituent yielded a single product, i.e. 2-*tert*-butyllevulinic acid (**2'e**).

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A   Muconic acids, muconolactone and muconodilactone
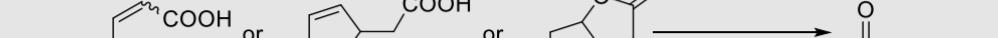
water
180 °C, 3 h

1a   **3a**   **4a**   **2a**

cis,cis-**1a**: 99%
(87%, 90%[a]) **2a**

cis,trans-**1a**: quant. (93%) **2a**

trans,trans-**1a**: 0% **2a**
(50% **1a** recovered)

3a: 99% (89%) **2a**

4a: 96% (79%) **2a**

B   C3-substituted muconic acids and muconolactones

water
250 °C, 3 h

1   **3**   **2**

1b: 91% (90%) **2b**
[R² = Me]

3b: quant. (82%) **2b**
[R² = Me]

1c: quant. **2c**
[R² = Et]

3c: 73% (82%) **2c**
[R² = Et]

3d: 82% (77%) **2d**
[R² = Pr]

3e: quant. (75%) **2e**
[R² = tBu]

3f: quant. (92%) **2a**
[R² = H]

3g: 96% (63%) **2a**
[R² = H]

3h: 96% (71%)[b] **2h**
[R² = Ph]

C   C2-substituted muconic acids and muconolactones

water
250 °C, 3 h

1'   **3'**   **2'**   **2''**

1'b: 85% (74%)[c] **2'b**
+ 22% (15%)[c] **2''b**

3'b: 75% (83%)[c] **2'b**
+ 18% (21%)[c] **2''b**

1'd: (81%)[b] **2'd**
+ (5%)[b] **2''d**

3'd: (82%)[b] **2'd**
+ (5%)[b] **2''d**

3'e: quant. (81%) **2'e**
+ 0% (0%) **2''e**

D   Synthesis of 3-propyllevulinic acid from pine sawdust

pine sawdust

5% Ru/C
MeOH, 35 bar H₂
250 °C, 16 h

work-up

lignin oil
81 wt% **5d**

0.2 eq. HCl
water
250 °C, 3 h

work-up

93%
80 wt% **6d**

4.5 eq. H₂O₂
0.1 mol% (NH₄)₂Fe(SO₄)₂·6H₂O
HCOOH/water, air
RT, 20 h

work-up

54%
69 wt% **3d**

water
250 °C, 3 h

work-up

61%
82 wt% **2d**

6

To demonstrate the application of our synthetic method we applied it on lignin oil rich in 4-propylguaiacol (**5d**) obtained *via* reductive catalytic fractionation of pine wood.[20a, 25] *O*-demethylation[20e] of **5d** and oxidative cleavage[18] of the resulting 4-propylcatechol (**6d**) provided 3-propylmuconolactone (**3d**) (Scheme 4D). Gratifyingly, when the crude **3d** (69 wt%) was heated in water for 3 h at 250 °C, 3-propyllevulinic acid (**2d**) was obtained in 61% yield (82 wt%). A similar yield and purity was obtained from petrochemical **5d** (see Supporting Information section 8.3). Only filtration, extraction and vacuum distillation were used to purify the products of each step. This indicates the robustness of the process and its compatibility with products of wood biorefineries (featuring mixtures of components). Moreover, this opens up the possibility to access new biorenewable 3-propyllevulinic acid (**2d**) derived products.

The increasing restrictions on the use of the notorious and fossil derived phthalate plasticizers stimulated the transition towards new biobased replacements.[26] The diester of levulinic acid and 1,4-butanediol **11a**, has been identified as a promising plasticizer.[27] We therefore compared the plasticizing properties of **11a** with its propyl-substituted derivative **11d**, synthesized from 3-propyllevulinic acid (**2d**) and 1,4-butanediol (Supporting Information section 9). **2d** contains a flexible propyl chain potentially beneficial for the plasticizing properties and is directly obtainable from wood (Scheme 4D). To evaluate the plasticizing properties the glass transition temperature (T$_g$) of the blended polymer films was measured (Figure 4). Both polyvinyl chloride (PVC) and polylactic acid (PLA) were used as polymer matrices. **11a** showed a significant T$_g$ decrease in both blended polymers compared to unplasticized PVC and PLA. In accordance with our hypothesis propyl substituted derivative **11d** showed a further T$_g$ decrease, confirming the beneficial effect of the propyl side chain on the plasticizing properties. Gratifyingly, **11d** performs equally well as and even outperforms the commercial benchmark plasticizer di-2-ethylhexyl phthalate (DEHP) in PVC and PLA, respectively.
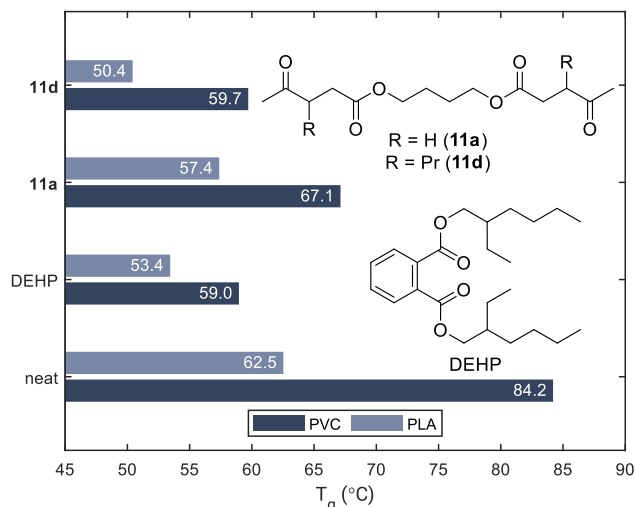

Figure 4. T$_g$ values for unplasticized (neat) and plasticized (10 wt% of **11a,d** or DEHP) PVC and PLA films. T$_g$ values are indicated in the bar. DEHP (di-2-ethylhexyl phthalate) is a commercial benchmark plasticizer.

In conclusion, we reported that muconic acids (**1**) and muconolactones (**3**,**4**) can be transformed into levulinic acids (**2**) in a catalyst- and reagent-free process by simply heating in water at high temperature under autogenic pressure. The high selectivity of the tandem reaction and gaseous nature of the CO$_2$ by-product allowed to use simple extraction for the isolation, providing **2** in high purity and yield. This robust method could be applied on crude streams of alkylcatechols (**6**), obtained from reductive catalytic fractionation of pine wood providing alkylguaiacols (**5**) and subsequent *O*-demethylation of **5**, as illustrated for the synthesis of 3-propyllevulinic acid (**2d**). These novel substituted biorenewable levulinic acids, not accessible *via* the classical hexose and pentose routes, will allow to get superior performance versus parent levulinic acid (**2a**) in specific applications or explore completely novel ones. The diester of **2d** and 1,4-butanediol provided a biorenewable plasticizer that outperformed the corresponding diester synthesized from parent **2a** and 1,4-butanediol, both in PVC and PLA. Remarkably, it performed equally well as the commercial phthalate-based benchmark DEHP.

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