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Mechanistic Investigations into the Catalytic Levulinic Acid Hydrogenation, Insight in H/D Exchange Pathways, and a Synthetic Route to d$_8$-γ-Valerolactone

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ABSTRACT: γ-Valerolactone (GVL) is readily accessible by catalytic hydrogenation of carbohydrate-derived levulinic acid (LA) and is an attractive biobased chemical with a wide range of applications in both the chemical (e.g., as biomass-derived solvent) and the transportation fuel sector. In this study, we used isotopic labeling experiments to provide insights into the catalytic hydrogenation pathways involved in the conversion of LA to GVL under different reaction conditions using water as an environmentally benign solvent and Ru/C as a readily available catalyst. ^{2}H NMR experiments combined with quantum chemical calculations revealed that deuterium atoms can be incorporated at different positions as well as the involvement of the different intermediates 4-hydroxypentanoic acid and α-angelica lactone (α-AL). The insight provided by these studies revealed an as of yet unexploited sequential deuteration route to synthesize fully deuterated LA and GVL. The route starts by the conversion of LA to α-AL followed by a selective deuteration of the acidic protons of α-AL by H/D exchange with D$_2$O. Subsequent ring-opening in D$_2$O (d$_2$-AL to d$_3$-LA) and exchange of the remaining protons of d$_3$-LA via a keto-enol tautomerization by heating in D$_2$O under acidic conditions gives d$_8$-LA. Finally, the d$_8$-LA is catalytically reduced at low temperature using Ru/C with D$_2$ in D$_2$O to d$_8$-GVL.

KEYWORDS: deuterium labeling, levulinic acid, γ-valerolactone, ruthenium on carbon, biobased solvent

INTRODUCTION

γ-Valerolactone (GVL) has been identified as a very versatile biobased chemical with a wide range of applications (Scheme 1).[1] It is readily obtained by the hydrogenation of levulinic acid (LA) or its esters,[2−15] which are accessible in good yields from the acid-catalyzed dehydration of carbohydrates.[16] GVL can, similar to ethanol, be directly used as a liquid fuel or as a blend with petroleum fuels.[17] Moreover, GVL can be readily stored and transported safely due to its high boiling point, low volatility, and lack of formation of explosive peroxides in the presence of air. GVL can also be used to produce existing bulk chemicals, for example, ε-caprolactam,[18] and novel building blocks for the polymer industry like α-methylene-γ-valerolactone[19] and methyl pentanoate.[20]

A promising application of GVL is its use as a green solvent. It is miscible with water and has notably low to no toxicity (LD$_{50}$ oral-rat = 8800 mg kg^{-1}) and is readily biodegradable.[21,22] In this respect, deuterated GVL is also of interest and may for instance be used as an NMR solvent, in reactivity studies using NMR spectroscopy, and as a tracer molecule. Routes to d$_{1−6}$-GVL have been reported for this purpose from a variety of substrates.[23−27] However, all of these methods involve complex catalytic systems, harsh operating conditions, and difficult work up procedures or suffer from low yields and impurities. We here propose a novel approach to fully deuterated GVL involving green synthetic steps for deuterium (D) incorporation starting from LA using cheap deuterium reagents (D$_2$ and D$_2$O, Scheme 2).

The most important step in the selective synthesis of GVL is the hydrogenation of LA. A heterogeneous supported-metal catalyst like Ru/C is highly suitable for the hydrogenation of LA to GVL in various reaction media.[2−4] Water is the preferred option as it is green and performs excellently.[2,3,28−30] Two possible mechanisms for the good performance of water as a reaction medium for LA hydrogenation have been proposed. The first assumes that co-adsorbed water on the catalyst surface is essential as it lowers the reaction barriers for substrate hydrogenation by dissociated hydrogen. The second assumes that dissociation of water occurs, leading to an increase of surface hydrogen atoms that facilitate the hydrogenation reaction. As shown in Scheme 1, two pathways
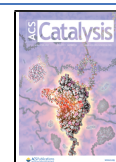
Scheme 1. Reaction Pathways for the Synthesis of γ-Valerolactone (GVL) from Biomass via Levulinic Acid (LA)
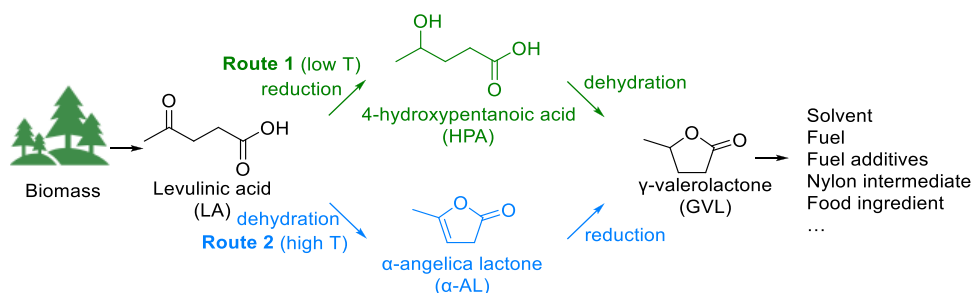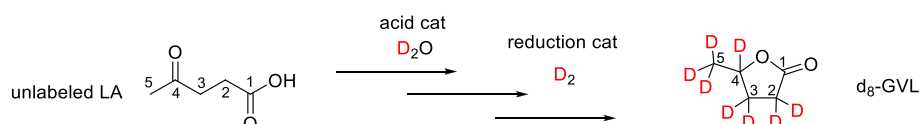

Scheme 2. Targeted Approach for the Synthesis of d₈-GVL from Unlabeled Biobased LA

Table 1. Chemical Structures and Abbreviations for Different Carbon Positions

Chemicals	Carbon numbers used to indicate the site(s) of deuterium incorporation
Levulinic acid (LA)	LA2 LA3 LA5
γ-Valerolactone (GVL)	GVL2 GVL3 GVL4 GVL5
α-Angelica lactone (α-AL)	α-AL2 α-AL3 α-AL5
β-Angelica lactone (β-AL)	β-AL2 β-AL3 β-AL4 β-AL5
Methylene-γ-butyrolactone (MBL)	MBL2 MBL3 MBL5
Valeric acid (VA)	VA2 VA3 VA4 VA5

have been proposed for the aqueous hydrogenation of LA to GVL. The first route starts with the hydrogenation of LA to 4-hydroxypentanoic acid (HPA) followed by lactone formation (Route 1), which is considered more favorable at a lower reaction temperature (<150 °C). This route already has been exploited for stereoselective [4-d]GVL (GVL with a deuterium incorporation at the carbon position 4) synthesis with a chiral homogeneous catalyst.[23] The second route involves the initial dehydration of LA to α-angelica lactone (α-AL, which is also readily obtained from dedicated LA dehydration and a useful biobased compound in its right[31]) followed by C=C double bond hydrogenation to GVL (Route 2), which is reported to

be prevalent in acidic media at elevated temperature.[13] Recently, Tan et al[14] used D_2O as a medium for LA hydrogenation and showed that the thus-obtained GVL was deuterated, which suggested that water also participates in the reaction. However, the level of deuteration was not extensively investigated. Under basic conditions, incorporation of deuterium at the carbon 3 and 5 positions of LA (labeled in this manuscript as LA3 and LA5) by keto-enol tautomerization has been reported to give a [3,3,4,5,5,5-d_6]GVL after hydrogenation (77% purity).[24] However, to the best of our knowledge, the preparation of fully deuterated d₈-GVL has not been accomplished to this date, mainly due to low selectivity

and the lack of a strategy to deuterate the 2 position in both LA and GVL. A green catalytic route from LA requires a new strategy as well as a detailed understanding of both pathways. d_8-LA has also not been reported to date and would be an ideal starting material for this purpose.

To control the extent and positions of the deuterium labels, we aimed to get a deeper understanding of the LA hydrogenation mechanism and the role of water in this reaction. Therefore, we performed a series of isotopic labeling experiments involving D_2O and D_2 and using either LA or α-AL under different reaction conditions over commercially available catalysts with a focus on readily available Ru/C. The different positions and amounts of deuterium incorporation in the final deuterated GVL were investigated. Quantum chemical pK_a calculations were used to explain the observed product distributions and relative H/D exchange rates. These experiments ultimately established various accessible H/D exchange and incorporation pathways that allowed us to develop a catalytic pathway to d_8-LA and d_8-GVL from unlabeled LA using cheap deuterium sources (D_2O and D_2).

■ EXPERIMENTAL SECTION

Materials. D_2O (99.9 atom% D), GVL (98%), α-AL (98%, containing 2% of β-angelica lactone (β-AL) as determined by ^1H NMR in $CDCl_3$ (Figure S1)), H_2SO_4 (98%), D_2 gas (99.8 atom% D), 3 wt % Ru/C, 5 wt % Ru/Al$_2$O$_3$, 5 wt % Pd/C, and 5 wt % Pt/C (powder) were acquired from Sigma-Aldrich. LA (98%) was purchased from Alfa Aesar. Milli-Q water was used for all experiments with unlabeled water. Hydrogen (>99.9%) and nitrogen (>99.9%) gases were supplied by Linde Gas. The structures of the most important compounds and their corresponding abbreviations for different carbon positions are provided in Table 1.

Analytical Equipment and Methods. All the NMR spectra were recorded on a Varian Mercury Plus system (400 MHz) with automatic sampling, locking, shimming, and tuning at room temperature. NMR acquisition parameters pw = 90°, 32 scans, d1 = 20 s (T1 = 17 s), and detailed peak assignments are shown in Table S1. For ^2H NMR samples, the solution was extracted with CH_2Cl_2 and subsequently passed through a $CaCl_2$ tube to remove residual water. $CDCl_3$ was added as a reference. HPLC was performed using an Agilent Technologies 1200 series, a Bio-Rad Aminex HPX-87H 300 mm × 7.8 mm column, T = 60 °C, with 5 mM H_2SO_4 as the eluent, and flow rate 0.55 mL/min. High-resolution mass spectrometry (MS) were performed using a Thermo Fisher LTQ-Orbitrap XL with a Thermo Accela HPLC without column. Injection volume was 4 μL, and different ionization techniques were used based on different compounds, the eluent for electrospray positive (ES$^+$) was acetonitrile with 0.1% formic acid (flow rate 0.15 mL/min), and the eluent for electrospray negative (ES$^-$) was acetonitrile with 0.1% ammonia (flow rate 0.15 mL/min). Average incorporated deuterium atoms and deuteration levels (%) were calculated as shown in eqs 1 and 2:

$$\mathrm{Ave}_D = \mathrm{Pct}_{1d}(\%) \times 1 + \mathrm{Pct}_{2d}(\%) \times 2 +$$
$$\cdots + \mathrm{Pct}_{nd}(\%) \times n \tag{1}$$

$$D_{\mathrm{incorporation}}(\%) = \mathrm{Ave}_D / \mathrm{theory}_D \tag{2}$$

Reaction Procedure and Product Analysis. Hydrogenation reactions were performed in duplicate in a 100 mL stainless-steel batch autoclave equipped with an overhead stirrer and heating/cooling options to maintain a constant temperature. The reactor was typically loaded with a 3 wt % Ru/C catalyst (0.06 g, without pretreatment) and substrate (0.24 mol) dissolved in solvent (40 mL). The reactor was sealed and first purged with N_2 three times and then pressurized either with H_2 or D_2 to 50 bar pressure. The reaction was performed at selected temperatures (90, 150, and 200 °C) for 3 h with a stirring speed of 600 rpm. After the reaction, the reactor was cooled to room temperature and depressurized. The catalyst was separated with a syringe filter (0.45 μm). The solution was analyzed by ^1H NMR, ^2H NMR, HPLC, and MS.

Preparation of [3,3,4,5,5,5-d_6]GVL (d_6-GVL). Typically, LA (2.96 g) and H_2SO_4 (0.1 mL) were dissolved in D_2O (40 mL) and heated at 90 °C for 3 days with a stirring speed of 600 rpm. After this, the solvent was removed by rotary evaporation, and the degree of deuterium incorporation was determined by ^1H and ^2H NMR. A new batch of D_2O (40 mL) was added to the obtained product to increase the deuterium incorporation level. After three cycles, all the possible positions in LA (except LA2) were replaced by D atoms (>99% D incorporation by ^1H NMR). After removal of the solvent by rotary evaporation, the collected deuterated LA was labeled as [1,3,3,5,5,5-d_6]-LA (d_6-LA). Reduction of d_6-LA at 90 °C under 50 bar D_2 pressure for 3 h yielded d_6-GVL (>95% D incorporation by MS).

Preparation of [2,2,3,3,4,5,5,5-d_8]GVL (d_8-GVL). α-AL (2.4 g) was dissolved in D_2O (40 mL) with a stirring speed of 600 rpm at room temperature for 2 weeks. The obtained mixture of LA and α-AL (>97% D incorporation at α-AL2 by ^1H NMR) was extracted by CH_2Cl_2. After removal of the solvent by rotary evaporation, purification was then carried out by flash chromatography (silica gel, 5−20% EtOAc/pentane). Before running the flash chromatography, the silica gel column was eluted with 0.5−1% MeOD/DCM (0.5−1.5 L) and further immersed in the eluent overnight, after which the column was flushed with 0−5% EtOAc/pentane prior to loading the sample. A colorless liquid (66% yield) with 95% deuteration (by ^1H NMR) at the α-AL2 position was collected as [2,2-d_2]α-AL (d_2-AL). Hydrolysis of d_2-AL in D_2O at 90 °C for 2 days continued with the same deuterium incorporation procedure mentioned above for making d_6-LA gave a [1,2,2,3,3,5,5,5-d_8]LA (d_8-LA). Hydrogenation of d_8-LA at 90 °C under 50 bar D_2 pressure for 3 h yielded d_8-GVL (>96% D incorporation by MS).

Quantum Chemical Calculations. Theoretical values for pK_a were obtained using the thermodynamic cycle outlined by Liptak et al. as shown in eq 3.[32]

$$pK_a = [G_{\mathrm{gas}}(A^-) + G_{\mathrm{gas}}(H^+) - G_{\mathrm{gas}}(AH) + \Delta G_{\mathrm{sol}}(A^-)$$
$$+ \Delta G_{\mathrm{sol}}(H^+) - \Delta G_{\mathrm{sol}}(AH)] / [2.303RT] \tag{3}$$

where G_{gas} is the gas-phase free energy, ΔG_{sol} is the free energy of solvation, R is the gas constant, and T is the temperature. Experimental $G_{\mathrm{gas}}(H^+)$ and $\Delta G_{\mathrm{sol}}(H^+)$ values of −6.82 and −265.9 kcal/mol were used, respectively,[33] and therefore, only $G_{\mathrm{gas}}(A^-)$, $G_{\mathrm{gas}}(AH)$, $\Delta G_{\mathrm{sol}}(A^-)$, and $\Delta G_{\mathrm{sol}}(AH)$ were needed to be computed.

G_{gas} values were computed using the complete basis set method CBS-QB3.[34] G_{gas} calculations were done using a reference state of 1 atm, and this was converted to 1 M using eq 4, as also done by Liptak et al.[32]

$$G_{\mathrm{gas}}(1\,\mathrm{M}) = G_{\mathrm{gas}}(1\,\mathrm{atm}) + RT\ln(24.46) \tag{4}$$

ΔG_{sol} values were computed using the M05-2X density functional theory hybrid functional with the 6-31G* basis set using the SMD solvation model.[35] The geometry of the molecules was also optimized with the same method and solvation model. The choice of functional and basis set is based on the same SMD paper where they have shown that the highest accuracy ΔG_{sol} was obtained by this combination of functional and basis sets.[35] All calculations have been done using the Gaussian16[36] software.

The computation of the energy levels for the thermodynamic comparison of the species (Figure S15 and Table S7) in this study was also done with the CBS-QB3 method in the aqueous phase (implicit solvent with the SMD method). The temperature was set to 90 °C and pressure to 50 bar.

■ RESULTS AND DISCUSSION

Aqueous Catalytic Hydrogenation of LA at 90 °C in Different Labeling Environments. Of the many catalysts reported for LA hydrogenation to GVL, noble metal catalysts are known to have excellent catalytic performance. Thus, a set of commercial supported noble catalysts (Pd/C, Pt/C, Ru/Al$_2$O$_3$, and Ru/C) were tested at 90 °C under deuterium labeling conditions (50 bar D$_2$ in D$_2$O for 3 h) (Figure S2). Ruthenium and specifically Ru/C showed the best product yield of the selected catalysts (Table S2). Ru/C performed better than Ru/Al$_2$O$_3$; this can be attributed to the very high surface area of the carbon support leading to more active metallic Ru,[5] and thus, Ru/C was selected for further studies.

Catalytic hydrogenation of LA to GVL in principle allows for control of the deuterium incorporation at positions 3 and 4 in GVL by controlling the route the reaction follows (Scheme 1 and Scheme S1). Previous reports[2,6,13] indicated that when the reaction is performed at 90 °C, HPA is the main intermediate (Route 1), which should lead to [4-d]GVL (GVL with one deuterium at the carbon position 4, GVL4). In contrast, the route via α-AL (Route 2), which was reportedly preferred at higher temperatures,[13] is expected to yield [3,4-d$_2$]GVL, thus also giving GVL with deuterium incorporated at the carbon position 3 (GVL3). To confirm this, LA reduction experiments were performed with H$_2$ and D$_2$ as well as using either H$_2$O or D$_2$O as a solvent in different combinations (Table 2). All of the experiments at 90 °C at fixed batch times of 3 h exhibited a similar conversion (Table 2, entries 1 and 2 compared with Table 2, entries 3 and 4). Interestingly, major differences were observed in the location and amount of deuterium

incorporation as determined by ^{2}H NMR and mass spectroscopy.

The reaction in H$_2$O under D$_2$ gave one distinguishable signal in the ^{2}H NMR corresponding to deuterium incorporation at GVL4 (δ 4.51 ppm, Figure 1, line 1) in line with route 1 via HPA. Quantum chemical calculations, taking into account the reaction conditions, were performed to analyze the reaction pathways (Scheme 3). These indeed showed that thermodynamically the route 1 via HPA should be preferred at low temperature compared to route 2 via α-AL. HPA and GVL are in equilibrium in water. Both theoretically and experimentally, it was shown that the equilibrium between HPA and GVL lies far to the side of the latter, meaning that the former is present in only low amounts and not visible (Figure S3; Scheme 3).[2] Nevertheless, the level of incorporation was lower than the expected 1 deuterium atom per molecule (Table 2, entry 3) suggesting the presence of an exchange mechanism between H$_2$O and D$_2$. This exchange was promoted dramatically by the Ru/C catalyst via Ru-H/Ru-D exchange (Figure S4),[37] which is also observed for related reactions.[38,39] Similar H/D exchange involving water was also observed on other metal surfaces, where it was shown that protonated water clusters (H$_2$O)$_n$H$^+$ are key intermediates.[40] Due to the presence of a higher molar amount of hydrogen atoms from H$_2$O in the reaction (roughly 20 times higher than the deuterium atoms), the levels of deuterium incorporation are relatively low. This H/D exchange mechanism is also evident from the presence of a relatively small HDO signal (1.66 ppm) in the ^{2}H NMR spectra of the undried product mixture (Figure S5). Indeed, deuteration at GVL4 was also observed when the reaction was performed in D$_2$O under H$_2$ (Table 2, entry 2). Combined with the higher level of deuterium incorporation, these results are in line with rapid H/D exchange at the surface of the ruthenium catalyst.

Keto-enol tautomerization of LA also plays a role when performing reactions in water and leads, in the presence of D$_2$O, to the deuteration of GVL3 and GVL5 (Scheme S2; Figure 1). This was confirmed by performing experiments with LA dissolved in D$_2$O for 24 h at 90 °C with and without Ru/C (Table S3, entries 5 and 6). Analyses showed that on average 0.4 D was incorporated at LA3 and LA5 positions (Figure S6, δ 2.65, and δ 2.05 ppm). This confirms the occurrence of H/D exchange via keto-enol tautomerization. This reaction is likely facilitated by the acidity of LA as ethyl levulinate does not undergo exchange with D$_2$O under identical conditions (Figure S7). Additionally, GVL showed no deuteration under neutral or acidic conditions (Table S3; Figure S8), or even under reaction conditions (50 bar gas pressure, 90 °C, 3 h, Figure S9). The LA2 position was not deuterated by such an exchange with D$_2$O. These observations are in alignment with a high theoretical pK_a (25.8) of LA2 compared to LA3 (21.2) and LA5 (22.4) as shown in Table S4.

When unlabeled LA was reduced in D$_2$O with D$_2$ and Ru/C (Table 2, entry 4, Figure 1, line 3), additional deuterium atoms are incorporated in GVL. In this case, GVL3, GVL4, and GVL5 peaks are present in ^{2}H NMR spectra and are from a combination of LA keto-enol tautomerization and ketone reduction with D$_2$ to HPA and subsequent ring closure to GVL. Similar results were also observed for other noble catalysts (Pd/C, Pt/C, and Ru/Al$_2$O$_3$, Figure S2).

Effect of the Solvent Composition (Water/LA Ratio) on the Catalytic Hydrogenation of LA. To control the extent of H/D exchange for both the keto-enol tautomeriza-

Table 2. . Summary of LA Hydrogenation Experiments in Different Deuterium Labeling Environments[a]

entry	solvent	gas	conv. (%)[b]	average D per mol[c]	
				LA	GVL
1	H$_2$O	H$_2$	99.4 ± 0.8	ns[f]	ns
2	D$_2$O	H$_2$	99.8 ± 0.3	ns	0.3
3	H$_2$O	D$_2$	94.5 ± 3	0.5	0.1
4	D$_2$O	D$_2$	96.0 ± 3	0.3	1.2/1.4[d]
5	D$_2$O[e]	D$_2$	99.2 ± 1	ns	2.1

[a]Reaction conditions: 40 mL of 0.6 M LA in the solvent, 60 mg of 3 wt % Ru/C catalyst, 90 °C, 600 rpm, 3 h, 50 bar pressure. [b]Determined by HPLC. [c]Determined by ESI-MS (ES$^+$ GVL, ES$^-$ for LA). [d]Calculated from signal integrations of the ^{2}H NMR (Figure 1, line 3) assuming that the GVL4 peak is fully deuterated. [e]200 °C. [f]ns = not significant.
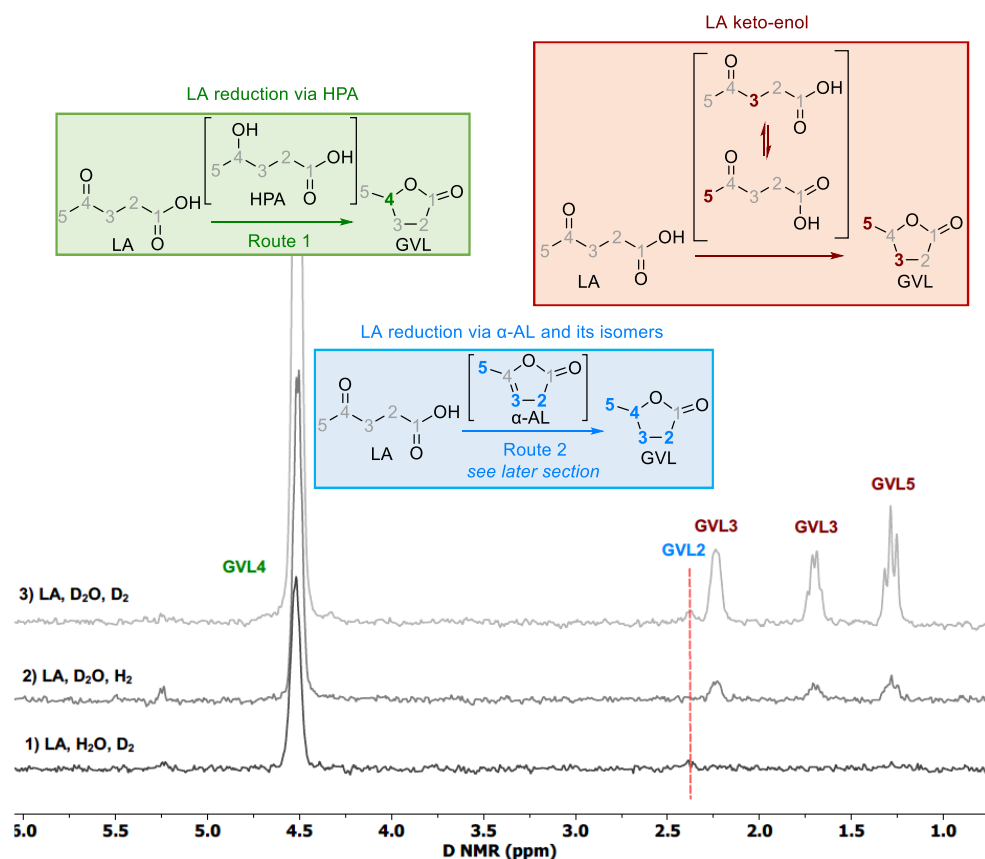
Figure 1. ^{2}H NMR (CH$_2$Cl$_2$) spectra of LA hydrogenation at 90 °C over Ru/C in different isotopic labeling environments with the main labeling pathways responsible for the deuterium incorporation at different positions. Reaction conditions: 40 mL of 0.6 M LA solution, 60 mg of Ru/C catalyst, 600 rpm, 3 h, 50 bar pressure. Bold and colored labels in the insets indicate the main route by which the specific positions are deuterium labeled.

Scheme 3. Calculated Free Energy Values (kcal/mol) of Molecules and Energy Difference for LA Hydrogenation to GVL under Reaction Conditions (Water as the Solvent, 90 °C, 50 bar Gas Pressure), Set Free Energy Value of (GVL + H$_2$O) as Zero (Details in Table S7)
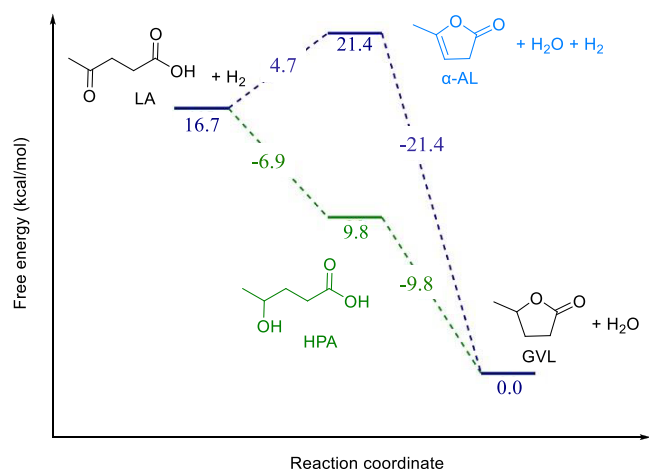
tion and the reduction step, the effect of the solvent composition and particularly the initial water/LA ratio was explored for the reduction of LA with D$_2$ and Ru/C. Neat LA reduction did lead to GVL with GVL4 deuterated (Figure 2a, line 1); however, only a 22% LA conversion (Table S5, entry 1) was achieved. When the D$_2$O/LA molar ratio was increased

to 5, the catalytic conversion of LA nearly doubled (45% conversion, Table S5, entry 2) and further reaction with ratios of 12, 23, and 46 in the reactor all gave full conversion of LA (Table S5, entries 3, 4, and 5), showing the promoting effect of water on this catalytic reaction. A slightly lower conversion (94%, Table S5, entry 6) was observed with a ratio of 93, which is likely due to the relatively lower concentration of LA, thus lowering the reaction rate.

Figure 2b illustrates the ^{2}H NMR integration ratio of GVL4 to (GVL3 + GVL5 + LA3 + LA5) obtained from experiments with different D$_2$O to LA molar ratios for reactions run for 3 h, which can be used to look at the relative rates of catalytic deuteration with D$_2$ (GVL4) and keto-enol tautomerization (GVL3 + GVL5 + LA3 + LA5). The observed volcano-shaped plot indicates that there is an optimum at which the catalytic reduction rate is the highest compared to keto-enol tautomerism, allowing for relatively selective [4-d]GVL synthesis (in this case, a D$_2$O/LA molar ratio of around 23). At shorter reaction times of 10 min and thus lower conversion, similar results are observed but with a larger contribution of the deuterium incorporation in LA3 and LA5 (Figure S10 and Table S6) for the reactions at a lower D$_2$O/LA molar ratio. No significant signals for LA3, LA5, GVL3, and GVL5 are observed while run at a similar conversion to some of the reactions at a higher D$_2$O/LA molar ratio (Figure S10). This result indicates that there is a different rate of keto-enol tautomerism at different ratios, which is likely linked to the
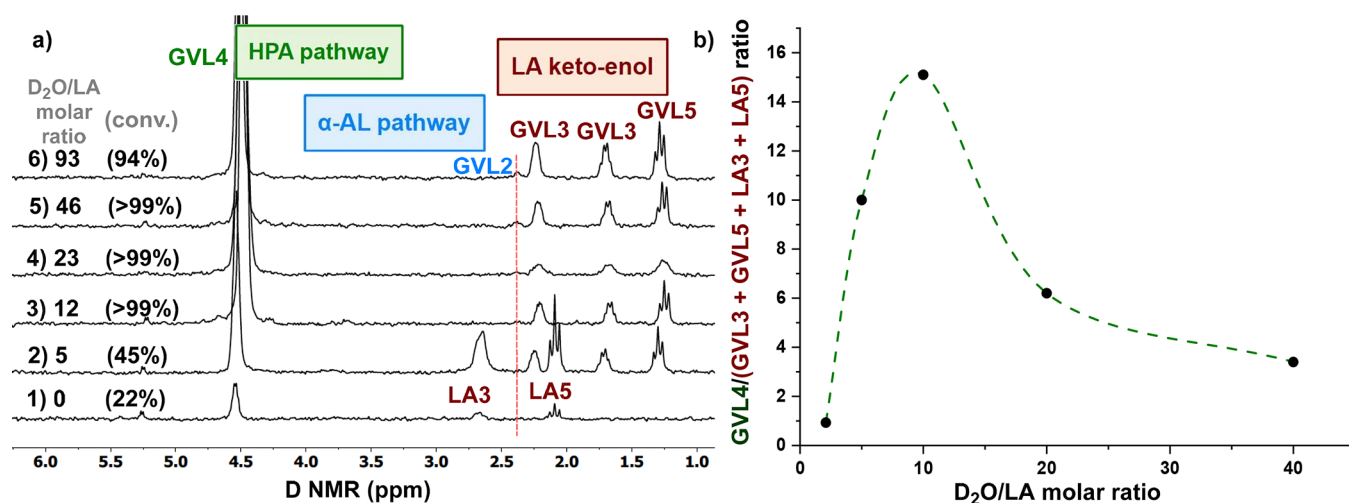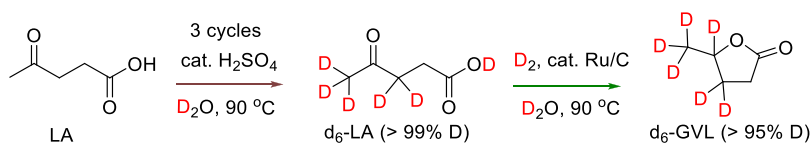
Figure 2. (a) ^{2}H NMR spectra (CH$_2$Cl$_2$) of LA hydrogenation at 90 °C in D$_2$O under D$_2$ with different water/LA molar ratios. Reaction conditions: 2.96 g of LA, 60 mg of Ru/C catalyst, 600 rpm, 3 h, 50 bar pressure; (b) calculated ratios of integrated GVL4 to (GVL3 + GVL5 + LA3 + LA5) from the reactions performed at 3 h.

Scheme 4. Preparation of [3,3,4,5,5,5-d$_6$]GVL (d$_6$-GVL) via [1,3,3,5,5,5-d$_6$]-LA (d$_6$-LA)

lower pH of the solutions with a higher concentration of LA (Table S6).

Overall, the results show that at relatively low temperatures, both D$_2$O and D$_2$ are required for the effective deuteration of GVL4 as water significantly promotes the catalytic hydrogenation reaction. GVL3 and GVL5 can also be deuterated via keto-enol exchange of LA3 and LA5 with D$_2$O. The observed keto-enol exchange with D$_2$O can be used to purposely deuterate LA positions LA3 and LA5, and we demonstrated this by sequential D$_2$O exchange at elevated temperature facilitated by the addition of a catalytic amount of H$_2$SO$_4$ (Scheme 4). Indeed, complete deuteration to d$_6$-LA (>99% D incorporation by ^{1}H NMR, Figure S11) was achieved this way after three cycles. Direct catalytic reduction of the obtained d$_6$-LA (without pretreatment) with Ru/C in D$_2$O under D$_2$ at 90 °C allowed us to selectively prepare d$_6$-GVL (Figure S12, >95% D incorporation by MS).

Effect of Temperature on the Aqueous Catalytic Hydrogenation of LA and Deuteration of GVL2. Surprisingly, in most of the above reactions, in addition to GVL3, GVL4, and GVL5, a weak deuterium signal for GVL2 appeared (δ 2.36 ppm). This was unexpected, and we assumed this had to come from the formation of α-AL and subsequent isomerization to β-angelica lactone (β-AL) even though this was in contrast to a previous literature study that claimed that at temperatures below 100 °C, route 1 via HPA should be exclusive. Quantification of the deuterium signals and taking into account rapid isomerization of α-AL to equimolar mixtures of β-AL and methylene-γ-butyrolactone (MBL, via the blue route in Figure 3) indicated that even at this relatively low reaction temperature of 90 °C, more than 2% of GVL was obtained via route 2 (Figure S13 for spectral overlay confirming the presence of this deuterated GVL2 signal).

This finding is unprecedented and shows that GVL is not exclusively formed via HPA, even at relatively low temperature.

Indeed, by increasing the temperature, higher levels of overall deuteration in GVL could be achieved at 200 °C (Figure 3, and by MS 2.1 D per molecule of GVL, see Table 2 entry 5). However, this also led to the formation of a significant amount of valeric acid (VA) as an undesired side product. VA is proposed to be formed by the isomerization of α-AL to β-AL followed by reduction via pentenoic acid isomers (Scheme S3).[41] VA can also be formed from GVL itself, but a control reaction showed that only a minor amount formed when GVL is converted under our reaction conditions (Figure S14). Additionally, in particular, the intensity of the GVL2 peak increased at 150 °C and dramatically increased at 200 °C (Figure 3, lines 2 and 3 compared with Figure 3, line 1). All the above confirms that the LA hydrogenation pathway through α-AL becomes more dominant at higher T and thus that α-AL formation from LA via lactonization is much faster than the LA ketone hydrogenation to HPA under these conditions. However, the observation of side reactions and the incomplete and random deuterium incorporation does not offer immediate additional benefits to achieve GVL with high levels of deuteration by using higher temperature LA deuteration. The significant increase of the intensity of the GVL2 deuterium signal is however interesting as this position was previously not accessible, and thus, the role α-AL was further evaluated.

The Role of α-AL in the Deuterium Incorporation in GVL. In the previous experiments, deuteration at GVL2 was hypothesized to originate from route 2 via double bond isomerization of α-AL and subsequent reduction with D$_2$. Quantum chemical calculations, taking into account the reaction conditions, showed that indeed isomerization to the thermodynamically more favored β-AL was to be expected (Figure S15 and Table S7). Furthermore, the open forms of
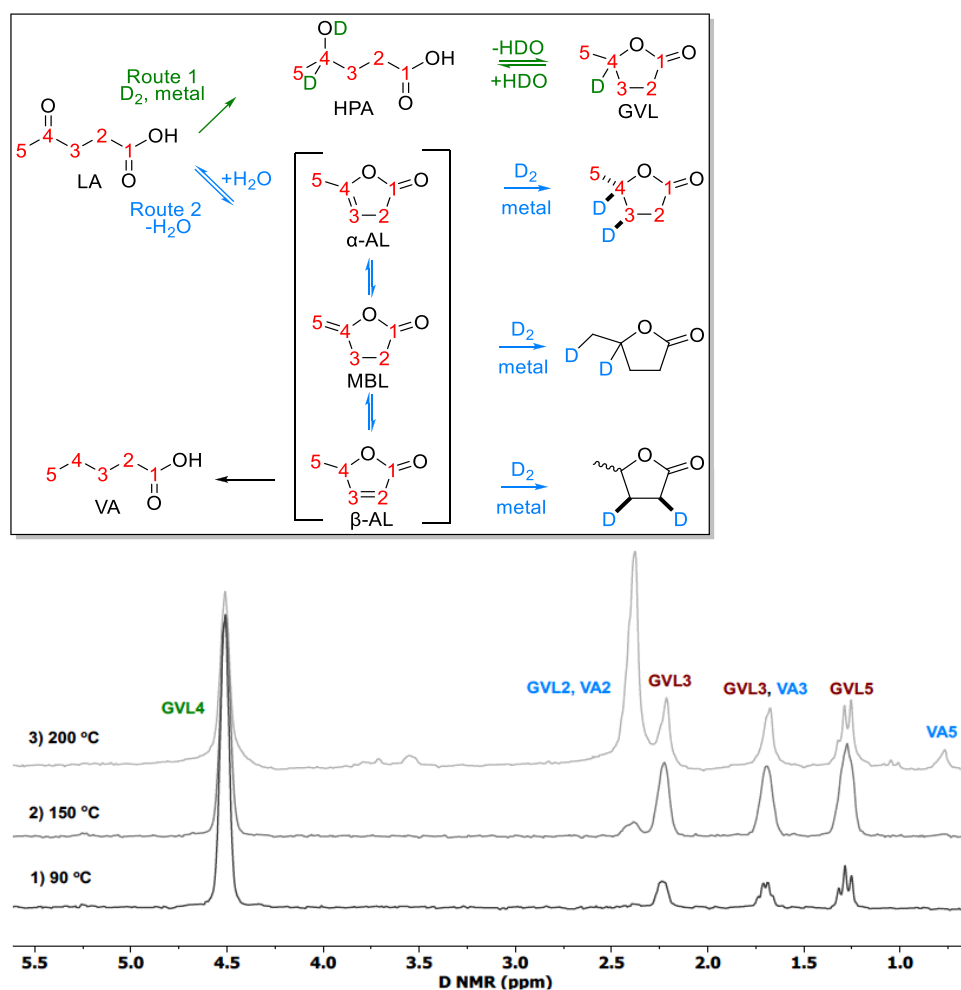
Figure 3. ^{2}H NMR (CH_2Cl_2) of LA reduction in D_2O under D_2 at different temperatures. Reaction conditions: 40 mL of 0.6 M LA in D_2O, 60 mg of Ru/C catalyst, 600 rpm, 3 h, 50 bar pressure.
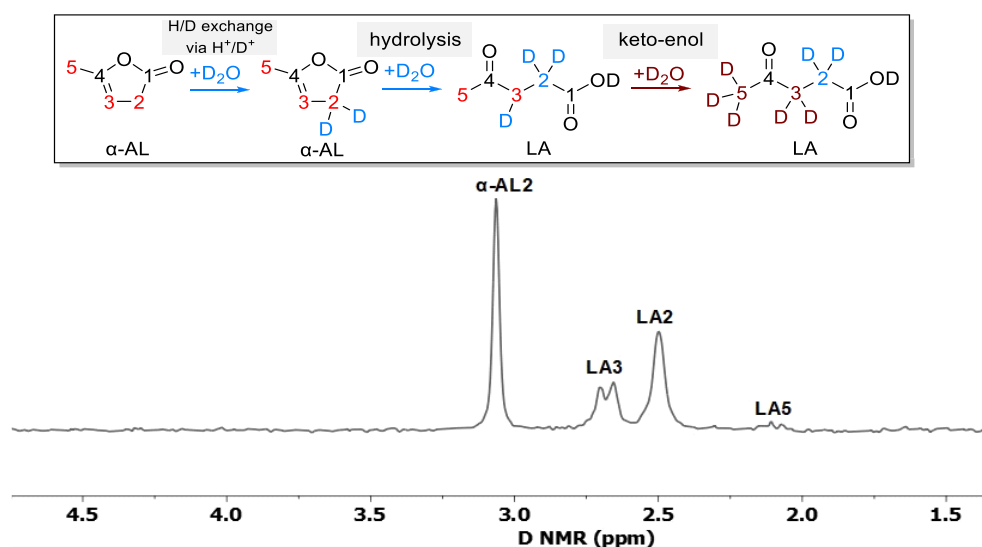

Figure 4. ^{2}H NMR (CH_2Cl_2) of α-AL stirring in D_2O. Reaction conditions: 40 mL of 0.6 M α-AL in D_2O, 90 °C, 600 rpm, 24 h.

the angelica lactones could play a role as their double bond should also be able to similarly undergo isomerization. Nevertheless, quantum chemical calculations showed that their formation should be unfavorable. These potential isomerization routes can lead to direct H/D exchange with the solvent via Ru-H/D. To understand the origin of deuterium incorporation at positions 2−5 from GVL formation from LA reduction via α-AL (route 2), the direct hydrogenation of α-AL under similar conditions to Ru/C was studied. This direct hydrogenation of α-AL to GVL recently

Scheme 5. Overview of the Most Important Deuteration Pathways for LA and α-AL
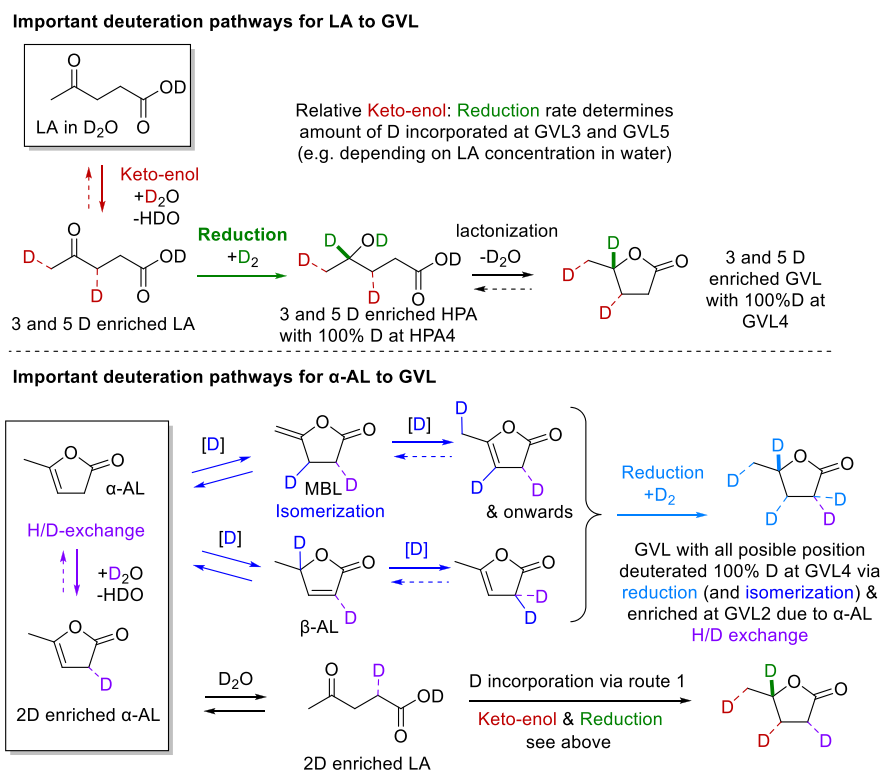
gained a lot of attention,[41−44] but the exact mechanisms and especially the role of double bond isomerization under reaction conditions have not yet been studied.

Neat α-AL reduction with D_2 without the solvent was performed to avoid solvent exchange and hydrolysis to LA. This experiment clearly showed that already at 90 °C, isomerization, likely catalyzed by Ru/C, takes place as all positions in GVL were found to contain deuterium incorporation (Figure S16). Analysis of the respective deuterium incorporation at the different GVL positions by signal integration reveals that incorporation can be traced back to a near equimolar ratio of α-AL, β-AL, and MBL. This indicates rapid interconversion of these isomers under these reaction conditions, which is likely kinetically controlled considering their relative thermodynamic stability (Figure S15 and Table S7). Interestingly, under these conditions, the reaction from α-AL is more effective for GVL formation in comparison to LA and with limited formation of VA. Similarly, aqueous reduction of α-AL with D_2 and Ru/C in D_2O at high temperature was remarkably effective (Table S8, entry 5), but neither is very useful for achieving d_8-GVL selectively.

Aqueous catalytic reduction of α-AL to GVL in combination with different combinations of H_2O or D_2O and H_2 or D_2 at 90 °C (Figure S17; Table S8) indeed yielded GVL deuterated at all the possible positions (and with the formation of VA). But again remarkable high deuterium incorporation at GVL2 was observed, which cannot solely be explained by isomerization. A control experiment in which α-AL was stirred in D_2O at 90 °C without D_2 gas remarkably showed selective deuteration at α-AL2 (δ 3.15 ppm, Figure 4). Under these conditions, hydrolysis of α-AL to LA occurs, which leads to significant deuterium incorporation at LA2 next to expected LA3 and LA5 deuterium incorporation. No significant amount of α-AL isomerization to β-AL and MBL was observed, which indicates

that the Ru/C catalyst is likely involved in this isomerization reaction. These experiments also support that VA formation in reactions starting from LA can indeed be linked to the formation of AL isomers as only the reactions starting from AL did show significant VA formation at 90 °C.

To explain the seemingly selective deuteration at α-AL2, we determined a theoretical pK_a by quantum chemical calculations, which indeed showed a significantly low pK_a of 15.3 that allows for H/D exchange with the solvent (Table S4). The low pK_a can be explained by the stability of the negative charge on α-AL2 after deprotonation due to conjugation stabilization with both the carbon−carbon double bond and the lactone carbon−oxygen double bond. Even though β-AL with the negative charge on the 4 position is a resonance contributor, this does not lead to β-AL4 deuteration due to the lower stability of this carbanion structure. Based on the found pK_a, this H/D exchange should be even more rapid compared to the keto-enol H/D exchange observed for LA. Indeed, even at room temperature, this H/D exchange could be observed without the addition of an acid catalyst.

Overview of the Different Deuteration Pathways and Preparation of d_8-LA and d_8-GVL. Summarizing the results at the low temperature (90 °C) applied in this study, it is evident that route 1 via HPA is the dominant pathway for the hydrogenation of LA to GVL using Ru/C. In a reaction using D_2O and D_2 as deuterium sources, the relative rates of the H/D exchange via keto-enol and the rate of the catalytic reduction of LA will determine the extent of D incorporation in the product (Scheme 5, top). This relative rate can be controlled by the LA concentration in water but only by a certain extent, and even by forcing the keto-enol H/D exchange before reduction, significant deuteration levels at the GVL2 position cannot be attained. However, findings from experiments starting from α-AL indicated that GVL2 deuteration is readily

Scheme 6. Preparation of $[1,2,2,3,3,5,5,5\text{-}d_8]$LA ($d_8$-LA) and $[2,2,3,3,4,5,5,5\text{-}d_8]$GVL ($d_8$-GVL) from LA-Derived α-AL Using D_2O and D_2 as Deuterium Sources
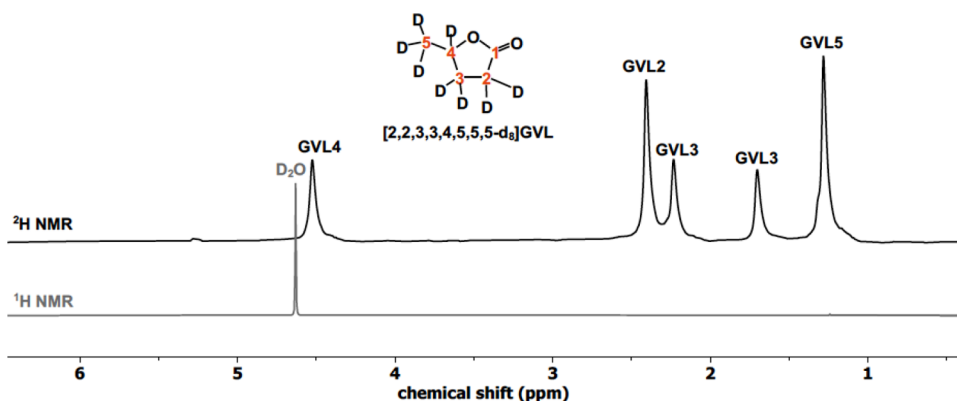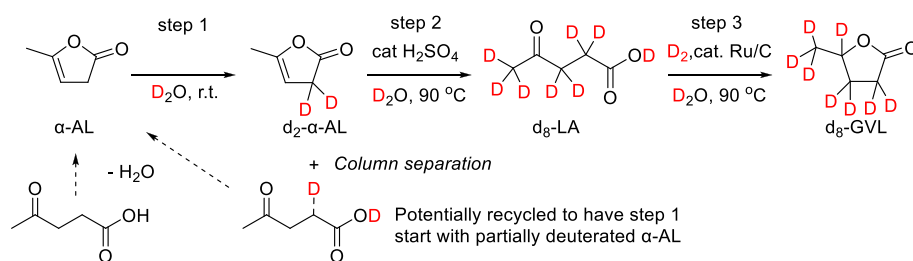
Figure 5. ^{1}H NMR (D_2O) and ^{2}H NMR (CH_2Cl_2) of d_8-GVL.

achieved. Thus, when α-AL is formed by lactonization, by for example increasing the reaction temperature, α-AL isomerization leads to deuterium incorporation at all positions in GVL upon reduction with D_2 gas, and exchange of α-AL2 with D_2O leads to specific enrichment at GVL2 in the product (Scheme 5, bottom). The deuterated α-AL2 can lead to deuterium incorporation of GVL2 by direct reduction or via hydrolysis to LA and subsequent reduction.

Using this knowledge, a synthetic route was designed to obtain d_8-GVL (Scheme 6). In this case, the deuterium incorporation is initiated from α-AL, which is produced from LA by specific dehydration. In α-AL, the α-AL2 position is easily deuterated by D_2O even at room temperature albeit at a low reaction rate. By simply dissolving α-AL in D_2O and leaving it to stand for a couple of weeks, we could obtain a mixture of α-AL and LA (Figure S18) in which the α-AL2 position reached high deuterium enrichment (>97% D incorporation by ^{1}H NMR).

After a separation of α-AL from the LA that was not fully deuterated at the 2-position on a MeOD predeuterated silica column, d_2-AL was obtained with 66% isolated yield and 95% deuterium incorporation (by ^{1}H NMR). The obtained d_2-AL can then be hydrolyzed in D_2O to LA and directly transformed to d_8-LA (Figure S19) by keto-enol tautomerization via step 1 shown in Scheme 4. d_8-LA can then be reduced using Ru/C in D_2O with D_2 at 90 °C according to step 2 described above to obtain d_8-GVL (Figure 5 and Figure S20, >96% D incorporation by MS). The partially deuterated LA (Figure S21) as a byproduct from step 1 from the chromatographic separation can be collected and dehydrated to α-AL, which can again be used as the substrate for subsequent deuteration with D_2O at room temperature. This provides a green route to fully deuterated GVL using cheap deuterium sources. The overall sustainability of this route also relies on the production process

used for obtaining the deuterium sources. D_2O is relatively readily separated from water by distillation or electrolysis, which is then also used as the source for D_2.[45]

■ CONCLUSIONS

A series of isotopic labeling experiments with D_2O and D_2 was performed, and careful analysis of the obtained ^{2}H NMR spectra was used to elucidate the involvement of the solvent in the Ru/C-catalyzed hydrogenation of LA to GVL. At low temperature, solvent H/D exchange was shown to occur mainly with Ru-H and via keto-enol tautomerization of LA; the hydrogenation goes mainly via HPA and subsequent lactonization. At higher temperatures, the pathway through α-AL is more preferred, which itself was shown to be involved in various H/D exchange mechanisms. H/D exchange was shown to occur via acid/base exchange specifically at the 2-position, while isomerization in the presence of Ru/C under reaction conditions leads to incorporation at all positions. Results from the reduction of neat α-AL combined with Ru/C and D_2 suggested that isomerization is rapid under our reaction conditions, and thus, all three double bond isomers α-AL, β-AL, and MBL are in fact present and reduced to GVL. Knowledge of the involvement of all these different pathways can be used to further develop technology for the synthesis of biobased GVL from LA in the presence of water. Additionally, with the understanding of the different H/D exchange pathways leading to different positions in GVL to be deuterated, we developed a simple synthetic route to d_6-GVL and for the first time reported a synthetic route to d_8-LA and d_8-GVL of which the latter can find practical applications, especially in organic and medicinal chemistry as an NMR solvent.

ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c02662.

Assignments of NMR peaks, ^{2}H NMR, ^{1}H NMR, proposed reaction mechanism schemes, summary of labeling experiment results, quantum chemical calculation details, exact mass results, TEM images, Figures S1−S27, Tables S1−S9, and Schemes S1−S3 (PDF)

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Author Contributions

Q.Y. performed the majority of the experimental work under the scientific supervision of H.J.H. and P.J.D. Q.Y. and P.J.D. wrote the manuscript with input from the other authors. A.S.P. and H.H.v.d.B. started the initial experimental work and contributed to design the experiments at this stage. S.S. performed the quantum chemical calculations under supervision of R.W.A.H. Z.Z. helped with the preparation of d$_8$-GVL from α-AL.

Notes

The authors declare no competing financial interest.

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