Catalytic Synthesis of Methyl 9,10-dihydroxystearate from Technical Feedstocks in Continuous Flow via Epoxidation and Hydrolysis

Johanna Vondran, Tobias Benninghoff, Anahita Irene Emminghaus, and Thomas Seidensticker*

The sequence of the homogeneously Ru-catalyzed epoxidation of methyl oleate and acid-catalyzed hydrolysis of the corresponding epoxide methyl 9,10-epoxy stearate is successfully transferred from batch into flow mode, allowing for the continuous production of methyl 9,10-dihydroxystearate. Thereby, methyl oleate is first converted up to 97% within 14 min at excellent selectivity in the epoxidation using aqueous hydrogen peroxide as the sole oxidant. In the subsequent hydrolysis, a residence time of 10 min is sufficient for quantitative conversion of the epoxide. The desired, pure vicinal diol is isolated upon crystallization from the crude reaction mixture in an integrated process starting from technical grade (91.5%) substrate. The isolated yield is increased upon the addition of water as a green antisolvent from 75% up to 97%. Finally, the concept is transferred to methyl oleate of even lower purity (76%), still obtaining an isolated yield of 66% of the vicinal diol. Thus, the integration of sequential epoxidation and hydrolysis into continuous flow and subsequent crystallization allows for high conversion and selectivities within a total residence time of 27 min, corresponding to a space–time yield of 190 g h^{-1} L^{-1} in the epoxidation and 164 g h^{-1} L^{-1} in the hydrolysis, respectively.

Practical applications: The modular flow setup enables the targeted functionalization toward the epoxide intermediate or the vicinal diol. Both offer versatile applications for the production of polymers, surfactants, or toward further conversion as in oxidative cleavage starting from methyl oleate. The application of flow chemistry offers advantages for the safe handling of hydrogen peroxide even at high temperatures. With fats and oils being natural substances, oleochemicals such as fatty acid methyl esters are typically available in technical purity so that efficient strategies for the isolation of pure products are of need. Crystallization of the product is promising, as additional organic solvents are not required. Thus, using the difference in melting point and solubility behavior of the desired product compared to other compounds is a promising method for the applicability of renewable resource-based substrate mixtures.

1. Introduction

In recent decades, fatty acid methyl esters (FAME), such as methyl oleate, have attracted the interest of the chemical industry and academia far beyond the production of biodiesel.[1] Thereby, the application of technical grade substrates contributes to a sustainable value chain since pure FAME are high-priced and energy-consuming to purify due to their low difference in melting points/boiling points. In contrast, purification of intermediates from chemical conversions seems to be far more promising, assuming an increased difference in physical properties upon functionalization.

Especially oxidative functionalizations, such as epoxidation or oxidative cleavage,[2] offer the potential to produce bio-based high-value chemicals such as epoxides and acids. Although dihydroxylation or epoxidation/ring-opening hydrolysis is less in focus, the products, vicinal diols, also offer versatile applications in hyperbranched polyesters,[3] polyols and polyurethanes,[4,5] sodium sulfate surfactants,[6] or lubricants such as cyclic acetals.[7] Additionally, the vicinal diol can function as a stable intermediate toward oxidative cleavage.[8] The model reaction of two-step epoxidation of methyl oleate and subsequent hydrolysis is shown in **Figure 1**.

Standard synthetic methods toward vicinal diols from olefins are either one-step dihydroxylation or two-step epoxidation followed by ring-opening hydrolysis of the intermediate epoxide. Both have an oxidation step in common, preferably using hydrogen

The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/ejlt.202200041

J. Vondran, T. Benninghoff, A. I. Emminghaus, T. Seidensticker
Laboratory for Industrial Chemistry
Department of Biochemical and Chemical Engineering
TU Dortmund University
Emil-Figge-Straße 66, 44227 Dortmund, Germany
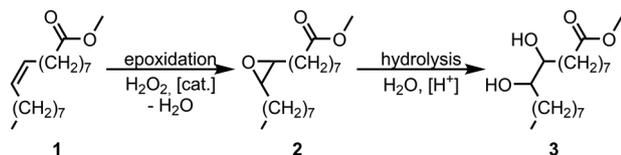E-mail: thomas.seidensticker@tu-dortmund.de

Figure 1. Model synthesis of methyl 9,10-dihydroxystearate (**3**) via two-step epoxidation of methyl oleate (**1**) and hydrolysis of methyl 9,10-epoxystearate (**2**).

peroxide as a green oxidant, whereby water is the only by-product. However, catalysts are required for activation.

Regarding direct dihydroxylation, osmium tetroxide has often been chosen as a catalyst using hydrogen peroxide or *N*-methylmorpholine *n*-oxide as the oxidant,[9] despite its volatility and therefore high toxicity. However, other transition metals such as Mn, Fe, and Ru also serve as catalysts, as reviewed by Bataille and Donohoe.[10] Ru is also applied as tetroxide RuO_4; however, strong inorganic reoxidants such as $NaIO_4$ are of need, resulting in the formation of stoichiometric waste products.[11] In 2003, Sato et al. reported the use of resin-supported sulfonic acid as a catalyst for dihydroxylation of several olefins with hydrogen peroxide. However, only 80% yield of the vicinal diol could be obtained using oleic acid.[12] Recently, De Oliveira Vigier et al. reported a W-catalyzed one-step approach for the selective dihydroxylation of methyl oleate **1** (purity of 96%). In a homogeneous reaction system, 95% methyl 9,10-dihydroxystearate **3** were obtained after a reaction time of 1 h using 2 wt% $H_3PW_{12}O_{40}$ as the catalyst and 1.1 eq. hydrogen peroxide as a green oxidant.[13] For purification of the diol, the organic phase was extracted with ethyl acetate and dried. For separation of product and catalyst, the catalyst was modified toward a heterogeneous species ($Cs_{2.5}H_{0.5}PW_{12}O_{40}$), resulting in a loss of 20% conversion and yield. The catalyst was recyclable three times before catalyst leaching into the product was detected. Moreover, the system is very sensible for the H_2O_2 content.

A two-step method for synthesizing vicinal diols includes epoxidation followed by ring-opening hydrolysis of the epoxide. Therefore, the epoxide is synthesized in advance. Epoxidation is typically carried out via the Prilezhaev reaction.[14,15] Peracids are used as oxidants, formed from hydrogen peroxide and formic or acetic acid in the presence of mineral acids like sulfuric acid. However, the highly acidic conditions provoke corrosion, and the peracids are hazardous in terms of instability. Thus, catalytic systems are considered superior for epoxidation.[16] In our latest work, we further investigated the epoxidation of **1** using a highly selective homogeneous catalyst containing Ru(acac)$_3$ and dipicolinic acid as ligand. This catalyst system yields 99% of the desired epoxide methyl 9,10-epoxystearate **2** within a reaction time of 3 h under mild, non-acidic conditions. We have also shown the catalyst to be recyclable to a certain extent. The same catalyst system had been described by Behr et al. in 2013. The authors investigated the hydrolysis of the epoxide **2** as part of the tandem oxidative cleavage reaction of **1** using sulfuric acid as the catalyst.[17] At a pH of 2.4, 97% of the desired diol **3** were obtained within 4 h in *tert*-butanol as solvent. A major advantage of this approach is the use of similar reaction conditions to the previous epoxidation so that purification of the epoxide was avoided.

Several approaches for the synthesis of vicinal diols deal with direct ring-opening of the pure epoxide. Similarly, Sun et al. developed acid-functionalized iron nanoparticle catalysts for ring-opening of pure methyl 9,10-epoxystearate toward *α*-methoxy-hydroxystearate with 100% selectivity, comparable to sulfuric acid as catalyst.[18] Generally, applying a heterogeneous acid is beneficial in terms of separation and catalyst reusability. Similar approaches had been described using Amberlyst as a heterogeneous catalyst, but methyl 9,10-epoxystearate as substrate had not been investigated.[19] Alumina is also active as a heterogeneous catalyst for hydrolysis of pure methyl 9,10-epoxystearate.[20]

Regarding selectivity, especially the two-step approach suffers from the formation of polyether side-products from the consecutive reaction of the epoxide with the diol, resulting in lowered selectivity.[21] Thus, implementing a continuous flow microreactor is promising due to reduced back mixing. In addition, the spatial separation of the two steps in the microreactor allows optimal reaction conditions for each step separately, rather than choosing a compromise of reaction conditions for both steps. There is no need for purification of the epoxide intermediate, although also the epoxide offers industrial relevant applications. Operating the reaction in continuous flow allows for a modular setup so that the epoxide can also be obtained easily and continuously. Additionally, improved temperature control in microflow facilitates the safe handling of hydrogen peroxide even at higher reaction temperatures. Thus, the reaction rate and, consequently, space–time yield (STY) might be increased. Moreover, combining homogeneous catalysis and the sequential flow setup as an integrated process is very promising for selective syntheses.

Epoxidation of methyl oleate in continuous flow has been investigated before.[22–24] Especially Prilezhaev epoxidation is advantageous in a microflow reactor due to the high surface-to-volume ratio a, therefore, better temperature control. Using cyclohexene as a model substrate, epoxidation and base-catalyzed ring-opening were also transferred into continuous mode. The residence time was thus increased significantly from 120 to 1 min since a higher concentration of hydrogen peroxide could be applied without safety risks.[25] Inspired by this work, the approach was transferred to Prileshaev dihydroxylation of methyl oleate in continuous flow.[26] A yield of 99% methyl 9,10-dihydroxystearate was obtained after a reaction time of 5 min and subsequent batch-wise 45 min treatment with NaOH after removing excess peroxyacetic acid. For purification, neutralization with HCl, extraction with ethyl acetate and subsequent removal of ethyl acetate was necessary to give 82% isolated yield.

As outlined, there are efficient and selective approaches to synthesizing vicinal diols starting from FAME. However, the isolation of the product is usually not considered as an integrated process in the choice of reaction conditions. Thus, the addition of auxiliaries is necessary, resulting in waste production, and often, isolated yields are limited. To improve product isolation, we now integrate downstreaming into the design of the process from scratch, considering reaction conditions and the conditions for product isolation. Especially when using technical grade mixtures as substrate, exploiting differences in physical properties is promising for efficient isolation to avoid the need for prior substrate purification. This is highly relevant when starting from substrates based on renewable resources, such as fatty acids and corresponding methyl esters. Purification is often challenging
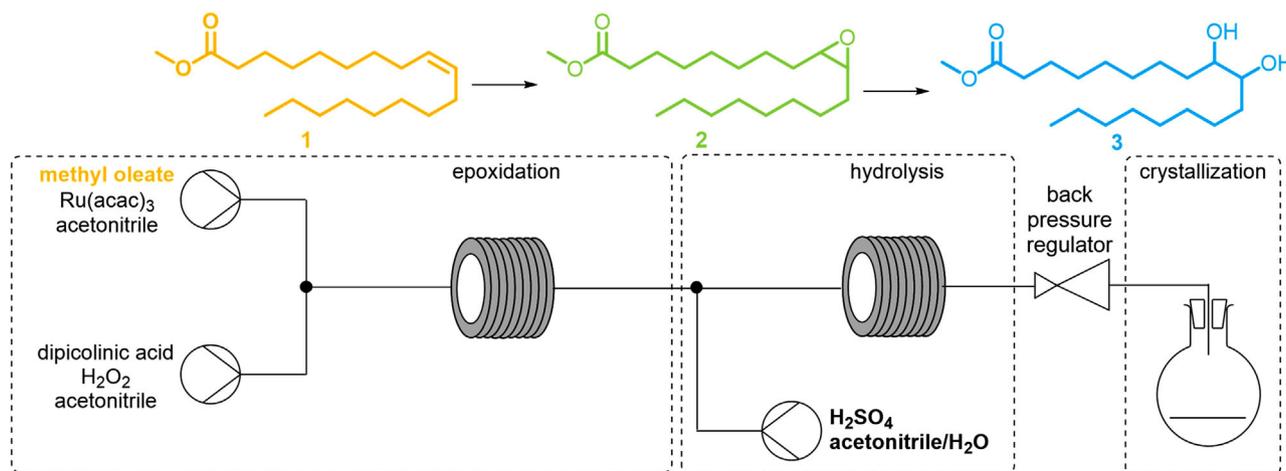
ADVANCED
SCIENCE NEWS
www.advancedsciencenews.com

European Journal of
Lipid Science and Technology
www.ejlst.com

Figure 2. The sequence of epoxidation of methyl oleate (**1**) and subsequent hydrolysis in continuous flow with final crystallization of methyl 9,10-dihydroxystearate (**3**).

due to their high carbon chain length, resulting in a high boiling point and the occurrence of more than just one type of fatty acid in fats and oils.

Thus, we target a method for the selective chemical conversion of a compound from a crude substrate mixture and subsequent purification of the desired product. Our approach is selective crystallization of the product, which depends on the solubility behavior of the target product, making use of the relatively high melting point. Our previous works showed that selective product crystallization is very efficient for purification in the methoxycarbonylation.[27,28] Thereby, auxiliaries are avoided. Regarding this work, methyl 9,10-dihydroxystearate also exhibits a high boiling point of 70 °C[29] and low solubility in suitable solvents, offering the broad potential for purification as a stable intermediate and subsequent application in other reactions, such as oxidative cleavage toward other value products.

Targeting the development of an integrated process, allowing for the modular production of methyl 9,10-epoxystearate or methyl 9,10-dihydroxystearate, we transferred the Ru-catalyzed epoxidation and subsequent acid-catalyzed hydrolysis from batch into the continuous flow (**Figure 2**). Thereby, both reaction steps were optimized individually to maximize selectivity rather than compromise on reaction conditions for each step. Starting from methyl oleate with a technical purity of 91.5% as obtained from high oleic sunflower oil, the desired vicinal diol was isolated, using its solubility behavior. Thus, aiming at an optimized isolated yield of the diol **3**, conversion of methyl oleate toward the epoxide in the first step was required to be quantitative and highly selective. Afterward, hydrolysis was directly following epoxidation under optimized conditions. As aforementioned, we aimed at a high isolated yield of the diol, which depends on first, product yield in the reaction mixture and second solubility therein. Hence, solvent-depending solubility of the diol was considered from scratch to develop an integrated reaction process.

2. Results and Discussion

Before starting investigations in continuous flow, we initially validated our choice of solvent, considering using the solubility be-

havior of the desired product diol **3** for straightforward product isolation by crystallization. As shown in our previous work on the epoxidation of methyl oleate, acetonitrile (ACN) is an efficient solvent for the Ru-catalyzed epoxidation of methyl oleate **1**.[30] However, *tert*-butanol had already been investigated in both epoxidation[31] of methyl oleate and hydrolysis of methyl 9,10-epoxystearate.[17]

The solubility of the diol **3** is much higher in *tert*-butanol than in ACN (250 g L^{-1} vs 20 g L^{-1} at a temperature of 25 °C). Thus, regarding subsequent product isolation via crystallization, ACN as solvent is beneficial. We carried out one batch experiment based on the previously described epoxidation of methyl oleate **1**,[30] followed by the addition of water to reach an ACN:water ratio of 3:1 as previously described in *tert*-butanol.[17] Thereby, assuming quantitative conversion of **1** and the epoxide **2**, the maximum concentration of the diol **3** in the reaction solution is 62 g L^{-1}. Thus, the concentration of the diol **3** after is far below its solubility limit in ACN, resulting in the crystallization of a white-yellowish solid from the crude reaction solution upon storing at 4 °C for 16 h. The solid was identified as the pure diol via ^{1}H and ^{13}C NMR upon centrifugation and drying under high vacuum (see the Supporting Information), corresponding to an isolated yield of 61%. Thus, crystallization is shown to be very efficient and elegant for selective isolation of the diol **3** starting from technical grade methyl oleate. Further purification is unnecessary, as by-compounds from the substrate do not crystallize. Hence, ACN is the key solvent for crystallization and is used for all further investigations.

2.1. Ru-Catalyzed Epoxidation of Methyl Oleate 1 in Continuous Flow

The reaction sequence toward the production of the diol **3** includes the homogeneously Ru-catalyzed epoxidation of **1** and acid-catalyzed hydrolysis of the epoxide **2**. Both steps were transferred into continuous flow and subsequently optimized, starting with the homogeneously Ru-catalyzed epoxidation of **1**.
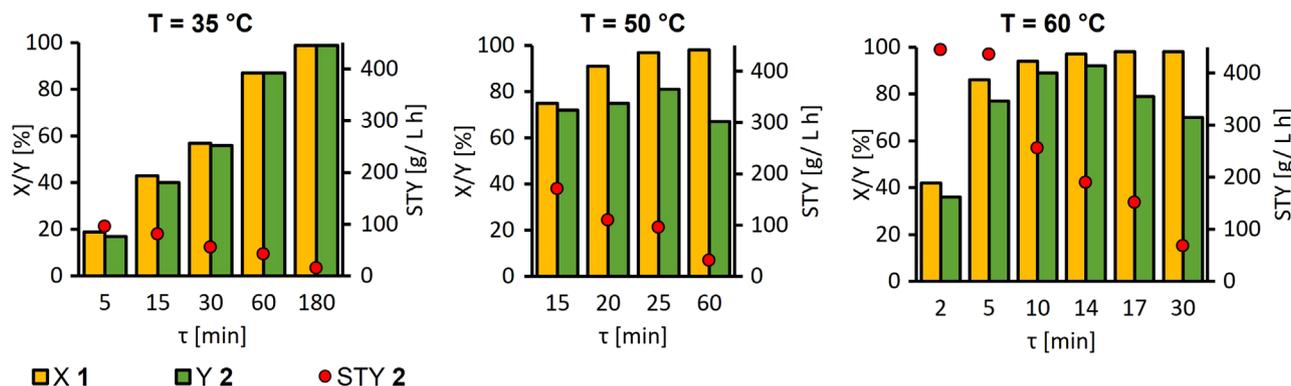
Figure 3. Effect of residence time on epoxidation of **1** in continuous flow at 35 °C (left), 50 °C (middle), and 60 °C (right) and STY of **2**. Reaction conditions: Epoxidation: syringe 1: **1** (0.915 g, 2.8 mmol), Ru(acac)$_3$ (0.375 mol%), ACN (6.3 g), syringe 2: dipicolinic acid (7.5 mol%), H$_2$O$_2$ (50%, 2 eq.), ACN (6.8 g); $l_{\text{epoxidation}}$ = 5.5 m; $V_{\text{epoxidation}}$ = 4.32 mL; $\dot{V}_1 = \dot{V}_2$. Conversion and yield determined via GC-FID analysis with dibutylether as internal standard.

Our aim in the integrated process of epoxidation, hydrolysis and crystallization is to maximize the isolated product yield of the diol **3**. Therefore, quantitative conversion of **1** is required in the first step, aiming at excellent selectivity toward the epoxide **2**, which can, in turn, be converted into the diol **3** through hydrolysis. As previously reported, epoxidation of **1** offers excellent selectivity at 25 °C in batch within 3 h. However, improved temperature control in continuous flow allows for the safe handling of hydrogen peroxide even at higher temperatures, which might result in a higher reaction rate, which is more economical. To obtain high selectivity in the epoxidation at a higher temperature, we assume the residence time τ as the most influencing parameter in the continuous flow, as side-reactions of different reaction rates can occur. Thus, our first investigation in continuous flow is on the effect of τ and T on the epoxidation of **1**, increasing T up to 35, 50, and 60 °C (**Figure 3**). The STY is used to indicate economic efficiency assuming high conversion and selectivity.

At 35 °C, the reaction rate is rather low, and after 3 h, quantitative conversion is obtained. However, side reactions do not occur, resulting in an excellent selectivity toward the epoxide **2**. Increasing the temperature to 50 °C results in a higher reaction rate, as quantitative conversion is obtained within 25 min. However, selectivity is decreased due to side-reactions, especially the longer the residence time. Interestingly, by increasing the temperature further up to 60 °C, the reaction rate of epoxidation is more increased than the rate of side reactions. Hence, an excellent selectivity of 95% is obtained at quantitative conversion of **1** within a residence time of 14 min. Thereby, the STY is increased up to 190 g h^{-1} L^{-1}, which is sevenfold higher compared to the initial batch conditions. Prolonging the residence time by only another 3 min results in a significant loss in selectivity, which probably occurs even faster at the higher reaction temperature. Additionally, the decomposition of hydrogen peroxide should be considered by increasing the temperature even further. Thus, we set the reaction time to 60 °C and the residence time for epoxidation ($\tau_{\text{epoxidation}}$) to 14 min for further experiments.

2.2. Hydrolysis of Methyl 9,10-epoxystearate 2 in Continuous Flow

Motivated by the drastically reduced residence time in the homogeneously Ru-catalyzed epoxidation of 1, still resulting in quantitative conversion and excellent selectivity, we also reduced the residence time in the acid-catalyzed hydrolysis to 13 min, before starting further optimization. A more detailed study on the effect of residence time will be discussed later. All experiments on hydrolysis are carried out directly following epoxidation of methyl oleate **1** as described above to ensure a consistent composition of the reaction solution. Targeting at a high isolated yield of the diol **3** after hydrolysis of the epoxide **2**, we also assume the ACN:water ratio, the concentration of acid and the concentration of diol **3** as important influencing parameters to be optimized.

The diol **3** is less soluble in water, so a higher water content facilitates crystallization. Moreover, high conversion of the epoxide **2** and selectivity toward the diol **3** are required to increase the concentration of the diol **3** and thus maximize the isolated product yield. Depending on the ACN:water ratio, those effects are considered for further optimization (**Figure 4**). As ACN is used as the solvent in epoxidation, the ACN:water ratio in syringe 3 differs from the desired ratio in hydrolysis as outlined in Table S1 (Supporting Information). The maximum concentration of the diol **3** assuming quantitative yield is 3 wt%.

At a low ACN:water ratio of 1:1, the isolated yield of the diol **3** is limited to 47% due to incomplete conversion of the epoxide **2**. At a ratio of 2:1, quantitative conversion is obtained, and the isolated yield is increased to 64%. As the diol **3** is more soluble in ACN than in water, a lower isolated yield would be excepted at a higher ACN:water ratio of 3:1. However, the isolated yield is slightly increased to 67%, indicating increased selectivity. Experiments at even higher ACN:water ratios were not carried out in continuous flow, as a low solubility of the diol **3** is required for crystallization. Hence, the ratio of 3:1 was set as the standard for the following investigations.

As hydrolysis is acid-catalyzed, the concentration of the acid is considered as another influencing parameter (**Figure 5**). Thereby,
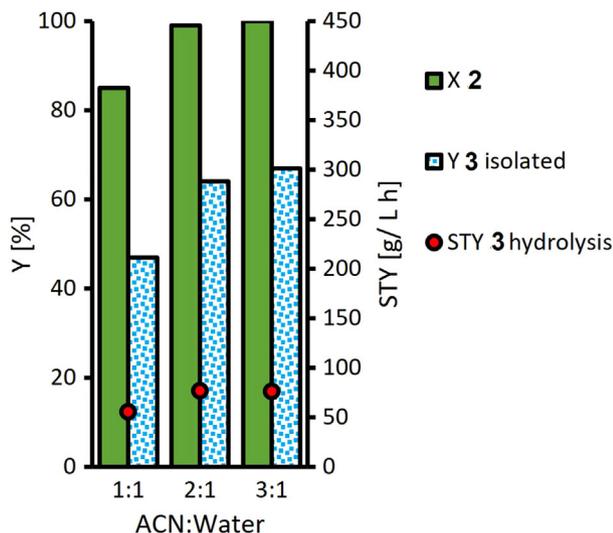
Figure 4. Effect of the acetonitrile:water ratio on acid-catalyzed hydrolysis of the epoxide **2**. Reaction conditions: Epoxidation: Syringe 1: **1** (0.6 g, 1.8 mmol), Ru(acac)$_3$ (0.375 mol%), ACN (4.1 g), syringe 2: dipicolinic acid (7.5 mol%), H$_2$O$_2$ (50%, 2 eq.), ACN (4.4 g); $T_{epoxidation}$ = 60 °C; $l_{epoxidation}$ = 0.65 m; $\tau_{Epoxidation}$ = 14 min; $V_{epoxidation}$ = 0.51 mL; $\dot{V}_1 = \dot{V}_2$ = 0.0183 mL min^{-1}; Hydrolysis: Syringe 3: H$_2$SO$_4$ (1 M, 1 mol%); solvent (11 g; ACN:water, see Table S1, Supporting Information, for detailed ratios), $T_{hydrolysis}$ = 80 °C; $l_{hydrolysis}$ = 1.2 m; $\tau_{hydrolysis}$ = 13 min; $V_{hydrolysis}$ = 0.94 mL; $\dot{V}_3$ = 0.0366 mL min^{-1}. Conversion determined via GC-FID analysis with dibutylether as internal standard; isolated yields are determined upon crystallization and filtration of the samples after storing on ice for 30 min.

a higher acid concentration is expected to result in a faster reaction but might also influence selectivity, as we have shown in our previous work.[8] In addition, hydrolysis of the methyl ester function can occur at high acid concentrations, which also leads to lower selectivity. The isolated diol **3** should be present in high purity and without acid residues. Therefore, we aim for a low acid concentration in the reaction system and, as already mentioned, high conversion of the epoxide **2**.
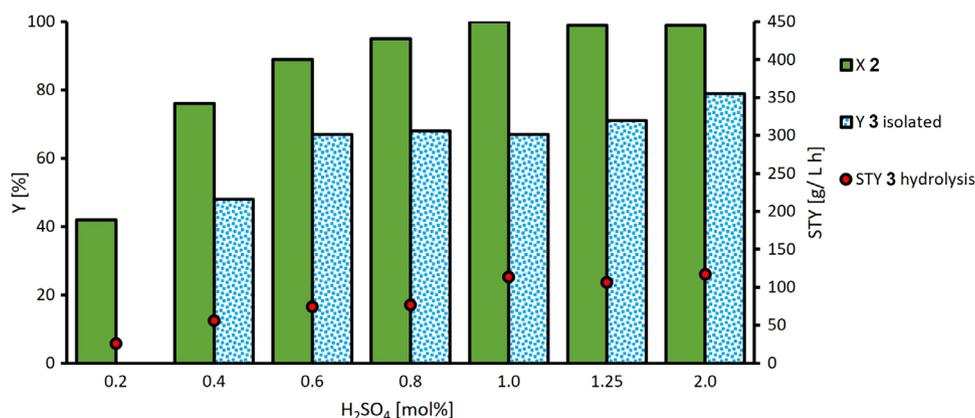
As expected, hydrolysis of the epoxide is limited at a low concentration of acid and a residence time of 13 min. Quantitative conversion is reached at a concentration of 1.0 mol% of sulfuric acid. Interestingly, at a higher concentration of 2.0 mol%, the isolated yield of 3 is slightly increased. From solubility experiments, we have found that the solubility of the diol 3 is decreased from 17 g L^{-1} in an ACN:water mixture to 9 g L^{-1} upon setting the pH to 1. However, we set the acid loading to 1 mol% to keep the acid concentration low and as a quantitative conversion is obtained. Additionally, the STY is only slightly increased at higher acid concentrations.

Consequently, reaction conditions are optimized for both epoxidation and hydrolysis in terms of conversion and selectivity. Toward the target of an optimized isolated yield of the diol **3**, solubility is decreased by increasing the concentration of product in the reaction solution. However, the concentration of substrate and catalyst in the epoxidation is limited due to the solubility of the ligand. Hence, dilution, and concentration of the diol **3**, respectively, can only be adjusted through the addition of water, ACN and acid during hydrolysis. Thus, we increased the maximum concentration of the diol **3** (assuming quantitative conversion of the epoxide **2**) from 3 to 4.6 wt%. A further increase is not possible if the ACN:water is kept at 3:1 and if the dilution in epoxidation is kept constant. Thus, the isolated yield of the diol **3** is increased to 75%. Since the solubility of the diol is reduced in water, we added much more water to the collected reaction solution from the continuous flow up to an ACN:water ratio of 0.2. Thereby, we were able to increase the isolated yield of the diol up to 97%, which is very promising, targeting a high isolated yield. Although water is known as a green solvent, we further investigated the crystallization of the pure vicinal diol **3** without the addition of any auxiliary.

As we have shown that selectivity is reduced under prolonged residence time, we finally investigated the effect of residence time under our optimized conditions (**Figure 6**).

As expected, selectivity is decreased at a prolonged residence time of 17 min. An optimum for the isolated yield of 78% of the

Figure 5. Effect of acid concentration on hydrolysis of the epoxide **2**. Reaction conditions: Epoxidation: Syringe 1: **1** (0.6 g, 1.8 mmol), Ru(acac)$_3$ (0.375 mol%), ACN (4.1 g), syringe 2: dipicolinic acid (7.5 mol%), H$_2$O$_2$ (50%, 2 eq.), ACN (4.4 g); T = 60 °C; $l_{epoxidation}$ = 0.65 m; $\tau_{epoxidation}$ = 14 min; $V_{epoxidation}$ = 0.51 mL; $\dot{V}_1 = \dot{V}_2$ = 0.0183 mL min^{-1}; Hydrolysis: Syringe 3: water (5.8 g); ACN (4.7 g); H$_2$SO$_4$ (1 M); T = 80 °C; $l_{hydrolysis}$ = 1.2 m; $\tau_{hydrolysis}$ = 13 min; $V_{hydrolysis}$ = 0.94 mL; $\dot{V}_3$ = 0.0366 mL min^{-1}. Conversion determined via GC-FID analysis with dibutylether as internal standard; isolated yields are determined upon crystallization and filtration of the samples after storing on ice for 30 min. A product was not isolated due to low conversion.

**ADVANCED
SCIENCE NEWS**

www.advancedsciencenews.com

European Journal of
Lipid Science and Technology

www.ejlst.com

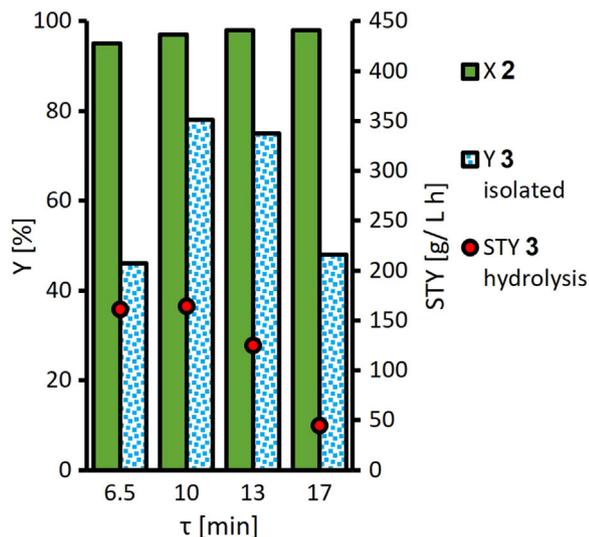**Figure 6.** Effect of residence time on hydrolysis of the epoxide **2**. Reaction conditions: Epoxidation: Syringe 1: 1 (0.6 g, 1.8 mmol), Ru(acac)$_3$ (0.375 mol%), ACN (4.1 g), Hydrolysis: Syringe 2: dipicolinic acid (7.5 mol%), H$_2$O$_2$ (50%, 2 eq.), ACN (4.4 g); $T = 60$ °C; $l_{\text{epoxidation}} = 0.65$ m; $\tau_{\text{epoxidation}} = 14$ min; $V_{\text{epoxidation}} = 0.51$ mL; $\dot{V}_1 = \dot{V}_2 = 0.0183$ mL min^{-1}; Hydrolysis: Syringe 3: water (4.0 g); H$_2$SO$_4$ (1 M, 1 mol%), $T = 80$ °C; $l_{\text{hydrolysis}} = 0.4$–1.05 m; $\dot{V}_3 = 0.012$ mL min^{-1}. Conversion determined via GC-FID-analysis with dibutylether as internal standard; isolated yields are determined upon crystallization and filtration of the samples after storing on ice for 30 min.

diol **3** is found at a residence time of 10 min, reaching a STY of 164 g h^{-1} L^{-1} regarding hydrolysis.

Our aim was now to transfer the continuous process to the epoxidation and hydrolysis of methyl oleate of lower purity and still obtain the pure diol **3** upon crystallization. Therefore, we applied methyl oleate in a technical purity of 76% and were able to isolate 66% of the diol **3** after a residence time of 10 min. In the presence of other FAMEs, such as linoleic acid, the solubility of the diol **3** is decreased, resulting in a slightly lower isolated yield. Finally, we again added more water up to an ACN:water ratio of 0.25 prior to the crystallization of the diol **3** to decrease solubility so that we were able to increase the isolated yield to 88%. Upon collecting the sample directly in cold water, the isolated yield was increased up to 94%. However, solids obtained after using water as antisolvent are slightly yellowish, while the solids obtained from the reaction mixture without the addition of water are white. This might be due to residual catalyst in the product. Investigations on the washing of the solid with organic solvents will be part of future works to further increase product purity.

3. Conclusion

The homogeneously Ru-catalyzed epoxidation of methyl oleate and subsequent acid-catalyzed hydrolysis of the epoxide methyl 9,10-epoxystearate were successfully transferred into continuous flow allowing for the modular, continuous production of those two bio-based value intermediates. Thereby, a residence time of 14 min is sufficient for quantitative epoxidation, reaching a STY of the epoxide of 190 g h^{-1} L^{-1}, which is increased sevenfold compared to our starting point in batch. Hydrolysis is carried

out upon the addition of sulfuric acid and water within a residence time of 10 min, reaching a STY of the diol of 164 g h^{-1} L^{-1} regarding hydrolysis. The pure vicinal diol was isolated through simple crystallization after collecting the reaction mixture on ice. Thereby, we were able to obtain an isolated yield of up to 78% without the addition of any organic auxiliary. However, the addition of water as a green antisolvent seems very promising to further decrease the solubility of the diol since we were able to obtain an isolated yield of 97% of the diol. Using this technique, methyl oleate with a purity of 76% could also be converted, still reaching an isolated yield of up to 94%. Thus, purification of the desired product seems a promising alternative to complex purification of the substrate prior to any conversion. Future works on continuous epoxidation and hydrolysis should cover further detailed investigations on the influence of substrate purity on product quantity and quality, as also washing should be investigated to remove traces of catalyst from the product. Thereby, also catalyst recycling, assuming that the catalyst remains in the reaction solution or can be washed from the product in its active form, will be investigated, opening up the potential for a more sustainable and economical continuous epoxidation and hydrolysis. Finally, the modular setup of the continuous process also allows for other functionalizations following epoxidation and/or hydrolysis to widen the applicability of renewably derived oleochemicals.

4. Experimental Section

Reactants: All reactants were commercially available and were used without further purification: methyl oleate (DAKO AG, 91.5%), Ru(acac)$_3$ (Umicore), dipicolinic acid (TCI chemicals, 99%), hydrogen peroxide (50% as determined from iodometric analysis, Fisher Chemical), acetonitrile (99.9%, Carl Roth).

The composition of methyl oleate, given from the supplier, is as follows:

- 91.5% methyl oleate;
- 3.0% methyl palmitate;
- 2.0% methyl stearate;
- 2.5% methyl linoleate;
- < 0.1 % methyl linolenate; and
- 1% fatty acid methyl esters > C18.

Experimental Procedure: Experiments in continuous flow were carried out using syringe pump modules manufactured by Cetoni. The base module BASE 120 allowed for control of pumps and pressure monitoring using the software Cetoni Elements Pro. Two Nemesys mid pressure syringe pumps were used for dosing reaction solutions, one of which was equipped with a double bracket to hold two syringes (syringes 1 and 2) used for epoxidation. Syringes 1 and 2 were 10 mL glass syringes. The flow rates $\dot{V}_1$ and $\dot{V}_2$ were equal allowing for the application in the double bracket. Syringe 3 was used for dosing water/acid/acetonitrile in the hydrolysis, using a second pump module. The flow rate $\dot{V}_3$ was set individually. The reactor was built from PTFE-tubing with an inner diameter of 1 mm and an outer diameter of 1.6 mm. The reactors were heated individually in two water baths, placed on heating plates and equipped with a magnetic stirrer. A pressure sensor was installed between syringe 1 and the first T-piece to monitor potential blocking and prevent breakage of glass syringes. A backpressure regulator (VICI JOUR BPR-1) was installed at the end of the reactor to ensure a pressure of 3 bar and thus, prevent the formation of gas bubbles in the reactor caused by boiling of solvents or decomposition of hydrogen peroxide.

Syringe 1 was filled with a prepared stock solution of methyl oleate (91.5%, 0.6 g, 1.8 mmol), ruthenium acetyl acetonate (0.375 mol%), and

acetonitrile (4.1 g). Syringe 2 was filled with a prepared stock solution of dipicolinic acid (7.5 mol%), hydrogen peroxide (50%, 2 eq.), and acetonitrile (4.4 g). Both syringes were filled with an equal volume. Syringe 3 was filled with a prepared stock solution of sulfuric acid (1 м, 1 mol%), water (5.8 g) and, if not otherwise stated, acetonitrile (4.8 g). Pumps were started with a flow rate of 0.06 mL min^{-1} to remove gas bubbles. After reaching reaction temperature, the flow rate is set as stated in the authors' conditions, usually 0.0183 mL min^{-1} for epoxidation and 0.0366 mL min^{-1} for hydrolysis. A period of 2× residence time was awaited before collecting samples. Samples were collected in an ice bath. For each experiment, five GC samples and samples for product isolation were collected alternately. GC samples were collected over an 8–15 min period, samples for product isolation were collected over 25–40 min, depending on the flow rates. Samples for GC analysis were homogenized by adding tert-butanol [tert-butanol:reaction solution 1:1 (wt)], and dibutylether was added as an internal standard. The standard deviation of GC results was <2% and can be attributed to slight fluctuations in mass flow due to blockage of the back pressure regulator. Samples for product isolation were cooled on ice for 30 min before the precipitated diol was collected from filter paper upon vacuum filtration using a Buchner funnel and then dried under high vacuum. Isolated product yields varied in a range of 5% within one experiment, which is considered as a systematic error. ^{1}H- and ^{13}C-NMR measurements were conducted on a Bruker Avance III HD NanoBay (400 MHz).

GC analysis of reaction samples was carried out using an Agilent 7890A device, equipped with a flame ionization detector (FID) and an Agilent HP-5 column (30 m × 0.32 mm × 0.25 µm) (5% phenyl methyl siloxan). The injection volume is 1 µL, and the split ratio is 70:1. The heating profile is as follows: start temperature of 50 °C, hold time 3 min; rate of 20 °C min^{-1} up to 290 °C, rate of 45 °C min^{-1} up to 320 °C, hold time 3 min. Dibutyl ether was used as an internal standard for quantification.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

Acknowledgements

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Johanna Vondran: conceptualization, formal analysis, investigation, supervision, validation, visualization, writing – original draft; Tobias Benninghoff: investigation; Anahita Irene Antonia Emminghaus: investigation; Thomas Seidensticker: conceptualization, funding acquisition, resources, supervision, writing – review and editing.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords

crystallization, flow chemistry, homogeneous catalysis, hydrogen peroxide, methyl oleate

[1] L. Meher, D. Vidyasagar, S. Naik, Renewable Sustainable Energy Rev. 2006, 10, 248.
[2] A. E. Kerenkan, F. Béland, T.-O. Do, Catal. Sci. Technol. 2016, 6, 971.
[3] B. Testud, D. Pintori, E. Grau, D. Taton, H. Cramail, Green Chem. 2017, 19, 259.
[4] A. Boyer, C. E. Lingome, O. Condassamy, M. Schappacher, S. Moebs-Sanchez, Y. Queneau, B. Gadenne, C. Alfos, H. Cramail, Polym. Chem. 2013, 4, 296.
[5] G. Lligadas, J. C. Ronda, M. Galià, U. Biermann, J. O. Metzger, J. Polym. Sci., Part A: Polym. Chem. 2006, 44, 634.
[6] M. Dierker, H. J. Schäfer, Eur. J. Lipid Sci. Technol. 2010, 112, 122.
[7] J. Filley, Bioresour. Technol. 2005, 96, 551.
[8] J. Vondran, M. Peters, A. Schnettger, C. Sichelschmidt, T. Seidensticker, Catal. Sci. Technol. 2022, unpublished.
[9] M. Schroeder, Chem. Rev. 1980, 80, 187.
[10] C. J. R. Bataille, T. J. Donohoe, Chem. Soc. Rev. 2011, 40, 114.
[11] B. Plietker, M. Niggemann, Org. Lett. 2003, 5, 3353.
[12] Y. Usui, K. Sato, M. Tanaka, Angew. Chem., Int. Ed. 2003, 42, 5623.
[13] N. Araji, G. Chatel, A. Moores, F. Jérôme, K. de Oliveira Vigier, New J. Chem. 2020, 44, 11507.
[14] S. Warwel, M. Rusch gen Klaas, in Recent Developments in the Synthesis of Fatty Acid Derivates (Eds: G. Knothe, J. T. P. Derksen), AOCS Press, Champaign, IL 1999.
[15] G. Sienel, R. Rieth, K. T. Rowbottom, Ullmann's Encyclopedia of Industrial Chemistry, Wiley-VCH, Weinheim, Germany 2000.
[16] M. M. Cecchini, F. de Angelis, C. Iacobucci, S. Reale, M. Crucianelli, Appl. Catal., A 2016, 517, 120.
[17] A. Behr, N. Tenhumberg, A. Wintzer, RSC Adv. 2013, 3, 172.
[18] B. Kollbe Ahn, H. Wang, S. Robinson, T. B. Shrestha, D. L. Troyer, S. H. Bossmann, X. S. Sun, Green Chem. 2012, 14, 136.
[19] Y.-H. Liu, Q.-S. Liu, Z.-H. Zhang, J. Mol. Catal. A: Chem. 2008, 296, 42.
[20] G. J. Piazza, A. Nunez, T. A. Foglia, J. Am. Oil Chem. 2003, 901.
[21] J. G. Wallace, W. R. Peterson, A. F. Chadwick, D. O. Barlow, J. Am. Oil Chem. 1958, 205.
[22] W. He, P. Kang, Z. Fang, J. Hao, H. Wu, Y. Zhu, K. Guo, Ind. Eng. Chem. Res. 2020, 59, 17513.
[23] L. Vanoye, Z. E. Hamami, J. Wang, C. de Bellefon, P. Fongarland, A. Favre-Réguillon, Eur. J. Lipid Sci. Technol. 2017, 119, 1600281.
[24] F. Pontzen, D. Herzog, D. H. Mueller, M. A. Liauw, L. Greiner, Chem. Ing. Tech. 2007, 79, 1453.
[25] A. Hartung, M. A. Keane, A. Kraft, J. Org. Chem. 2007, 72, 10235.
[26] B. A. M. W. van den Broek, R. Becker, F. Kössl, M. M. E. Delville, P. J. Nieuwland, K. Koch, F. P. J. T. Rutjes, ChemSusChem 2012, 5, 289.
[27] N. Herrmann, K. Köhnke, T. Seidensticker, ACS Sustainable Chem. Eng. 2020, 8, 3913.
[28] J. Vondran, A. I. Seifert, K. Schäfer, A. Laudanski, T. Deysenroth, K. Wohlgemuth, T. Seidensticker, Ind. Eng. Chem. Res. 2022, unpublished.
[29] H. B. Knight, US2613157A, 1952.
[30] J. Vondran, J. Pela, D. Palczewski, M. Skiborowski, T. Seidensticker, ACS Sustainable Chem. Eng. 2021, 9, 11469.
[31] A. Behr, N. Tenhumberg, A. Wintzer, Eur. J. Lipid Sci. Technol. 2012, 114, 905.