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Letter

Scalable Lipase-Catalyzed Synthesis of (*R*)-4-(Acyloxy)pentanoic Acids from Racemic γ-Valerolactone

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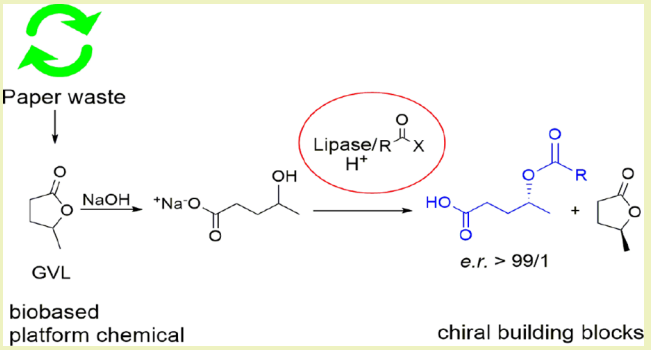
ABSTRACT: Conversion of biobased platform chemicals to enantiopure compounds has become topical. We report a straightforward synthesis of 4-(acyloxy)-pentanoic acids from γ-valerolactone (GVL). An alkaline hydrolysis of GVL is followed by a stereoselective lipase-catalyzed acylation of the sodium salt. Acidic hydrolysis of the acylation product affords (*R*)-4-(acyloxy)-pentanoic acid and relactonized (*S*)-GVL. (*R*)-4-(Propionyloxy)-pentanoic acid and (*R*)-GVL are obtained with *e.r.* > 99/1. An additional enzymatic step following a slightly modified process affords (*S*)-4-(acetyloxy)pentanoic acid with *e.r.* > 99/1. Simple access to enantiopure 4-(acyloxy)pentanoic acids will stimulate the development of their novel applications, including biobased isotactic polymers.



KEYWORDS: *Lipase catalysis, γ-Valerolactone, Stereoselective acylation, 4-Hydroxypentanoic acid salts, Enantiomeric 4-(acyloxy)pentanoic acids*

INTRODUCTION

The chemical industry is undergoing a rapid reorientation from fossil raw materials to renewables. One of the strategies for this is production of levulinic acid (LA) from lignocellulosic biomass.[1] Catalytic hydrogenation of the 4-keto group of LA provides 4-hydroxypentanoic acid that affords γ-valerolactone **1** (GVL) by spontaneous cyclization.[2] GVL is an important chiral platform chemical[3] considered to exhibit many desirable characteristics of an ideal sustainable compound.[4] It can be used as a solvent or raw material in organic synthesis as well as a fuel additive[5] and as a monomer for biobased polymers.[6−8] GVL enantiomers have been used as chiral building blocks in the synthesis of bioactive compounds, such as (*R*)- and (*S*)-sulcatol,[9] geodiamolide A,[10] and (*R*)-(−)- and (*S*)-(+)-phoracantholide.[11]

There are different ways to resolve enantiomers of GVL and other derivatives of 4-hydroxypentanoic acid.[12−25] Attempts to resolve GVL enantiomers in a straightforward manner have been reported, for instance, cocrystallization of GVL with cholic acid[12] and enzymatic hydrolysis of racemic GVL.[13] Although both afford enantiomerically enriched GVL, only modest stereoselectivity was attained. An unsuccessful attempt of transesterification of GVL catalyzed by *Candida antarctica* lipase B (CALB) was explained by high thermodynamic stability of GVL.[14]

Only one stereoselective synthesis of 4-(acyloxy)pentanoic acids is known (Scheme 1A).[15] The product has been applied for the preparation of enantiomerically enriched GVL. This low atom-efficiency synthesis involves three steps, in which the carboxyl group is generated by oxidation of the phenyl group in the final step.[15,16] Large amounts of solvents (including CCl_4 and pyridine) and excess reagents are used which are significant drawbacks regarding scalability of the synthesis and do not adhere to the principles of green chemistry.[26] For instance, process mass intensity (PMI), defined as the total mass in a process/mass of product, is a widely used metric as part of a green chemistry evaluation. (See the Supporting Information for a more detailed critical analysis of Scheme 1A).

A wide range of approaches to the synthesis of individual enantiomers of GVL are known. Several involve stereoselective reduction of levulinic acid to 4-hydroxypentanoic acid[17−19] followed by lactonization. Others employ biocatalytic[20−23] and chemical methods[18,19,24] of stereoselective reduction of the 4-keto group of LA esters and amides, followed by hydrolysis and lactonization of the products. A noteworthy trend is to develop one-pot approaches to the synthesis of enantiomeric GVLs

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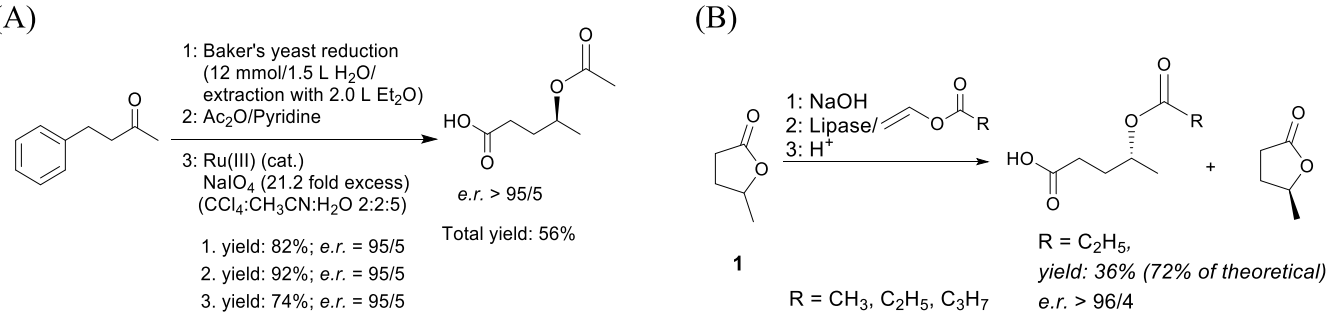
Scheme 1. Synthesis of 4-(Acyloxy)pentanoic Acids: Previously Known Synthesis (A) versus This Work (B)[a]



[a](A) The only previously known example of stereoselective synthesis of a 4-(acyloxy)pentanoic acid, (*S*)-4-(acetyloxy)pentanoic acid.[15] (B) The proposed method for synthesis of (*R*)-4-(acyloxy)pentanoic acids reported in this work; the best stereoselectivity was gained for (*R*)-4-(propionyloxy)pentanoic acid (Table 1).

Table 1. Results of Screening of Reaction Conditions for Lipase-Catalyzed Acylation of 4-Hydroxypentanoic Acid Salts in Organic Solvents and Demonstrations of Scope of the Method

Entry	Nucleophile (mmol)	Solvent (mL)	Substrate[a] (mmol)	N435[b] (mg)	Temperature (°C)	Reaction time (h)	$Conv_{app}$[c] (%)	Product *e.r.*(*R*/*S*)
1	**2** (10)	cyclohexane (20)[k]	vin. ac. (40)	20	20	22	26.5	**10**; 75.8/24.2
2	**2** (10)	toluene (20)[k]	vin. ac. (40)	20	20	22	48.5	**10**; 81.6/18.4
3	**2** (10)	–[k]	vin. ac. (216)[k]	20	20	22	25.6	**10**; 80.9/19.1
4	**2** (10)	CH_3CN (20)[k]	vin. ac. (40)[l]	20	20	22	42.9	**10**; 90.8/9.2
5	**2** (300)	EtOAC (300)[k,n]	vin. ac. (1200)	1200	20	11	45.5	**10**; 83.8/16.2
6	**2** (10)[m]	CH_3CN (20)	vin. prop. (40)[l]	20	20[o]	22	39.8	**11**; 96.1/3.9
7	**2** (5)	CH_3CN (10)	vin. but. (20)[l]	10	20	22	35.9	**12**; 89.3/10.7
8	**3** (10)[m]	CH_3CN (20)	vin. prop. (40)	20	20	22	10.7	**11**; 86.4/13.6
9	**4** (10)[m]	CH_3CN (20)	vin. prop. (40)	20	20	22	9.1	**11**; 93.4/6.6
10	**2** (10)	CH_3CN (20)	vin. prop. (40)	60	−20[o]	120	31.5	**11**; 90.8/9.2
11	**2** (10)	2-Me-THF (20)[o]	vin. prop. (40)	20	20	22	25.9	**11**; 77.8/22.2
12	**2** (10)	–	vin. prop. (184)	20	20	22	20.2	**11**; 68.6/31.4
13	**2** (300)	CH_3CN (270)	vin. prop. (900)	600	20	46	51.2	**11**; 92.0/8.0
14	H_2O (11)	CH_3CN (9.8)	(*R*)-**11** (2.4)[d]	100	20	96	74.6	**1**; 98.4/1.6[e]
15	(*R*)-**2** (90)[f]	CH_3CN (180)	vin. prop. (360)	180	20	22	43.5	**11**; 99.1/0.9
16	**2** (30)	EtOAc (60)	vin. ac. (120)	600	20	120	96.2	**10**; n.d.[g]
17	**2** (30)	MTBE (60)	vin. prop. (120)	600	20	120	98.0	**11**; n.d.[g]
18	H_2O (222)	CH_3CN (96)	(*S*)-**10** (54)[h]	2000	20	144	40.8[i]	(*S*)-**10**[j]; 0.1/99.9

[a]Vinyl acetate, vinyl propionate, vinyl butyrate. [b]Novozym 435. [c]$Conv_{app}$ is *apparent* conversion. [d]Product of entry 13 was used. [e]Parent (*R*)-**11** which is the product of entry 13 contained 1.6% of (*S*)-**1**. [f]Salt (*R*)-**2** was prepared from (*R*)-**1** (*e.r.* = 92/8) obtained from the product (*R*)-**11** of entry 13. [g]Not determined, [h]Prepared from relactonized **1** (*e.r.* = 70/30 (*S*/*R*)) from entry 5 following the procedure of entry 16. [i]Describes formation of (*R*)-**1**. [j]Remaining starting material was targeted. [k]Solvent screen. [l]Test of acyl donors. [m]Comparing alkali metal salts. [n]EtOAc was chosen as a greener alternative to CH_3CN for preliminary preparative synthesis. [o]Test of biomass-derived solvent.

combining different reactions.[25] Methods for the biocatalytic kinetic and dynamic kinetic resolution of enantiomers of 4-hydroxypentanoic acid esters and amides to be further transformed to enantiomeric GVLs have also been reported.[27,28]

Unfortunately, high enantiomeric purity 4-(acyloxy)-pentanoic acids, especially enantiomeric pure GVLs, have so far not been sufficiently accessible to meet the increasing demands of research and development projects. The goal of the current work is to address this challenge.

To attain this goal, we chose to develop a straightforward synthetic approach based on the enzyme-catalyzed acylation of 4-hydroxypentanoic acid salts in organic solvents. Although the investigation is focused on the synthesis of the products with *R* configuration, developing a procedure yielding products with *S* configuration is also an aim.

RESULTS AND DISCUSSION

Our optimization study includes evaluating the influence of the following factors and modifications on the stereoselectivity and the reaction rate: (1) reaction medium (hazardous and highly hazardous solvents were excluded from screening),[29] (2) structure of the substrate, (3) carboxylate counterion, (4) temperature, (5) enzyme loading, (6) solventless process, and (7) use of a sustainable solvent, 2-Me-THF.

The results of all screening syntheses (Table 1) were characterized by analyzing the product after acidic hydrolysis. Analysis was performed with respect to two results: conversion rate and enantiomeric ratio of the product.

The molar ratio of (*R*)-4-(acyloxy)pentanoic acid (**10**–**12**) vs recovered (*S*)-**1** was determined by ^1H NMR spectra by integrating the signals of the carbinyl hydrogen atom at the stereogenic center (Figure S8.1, Supporting Information). The conversion rate was defined as the ratio (molar%) of the

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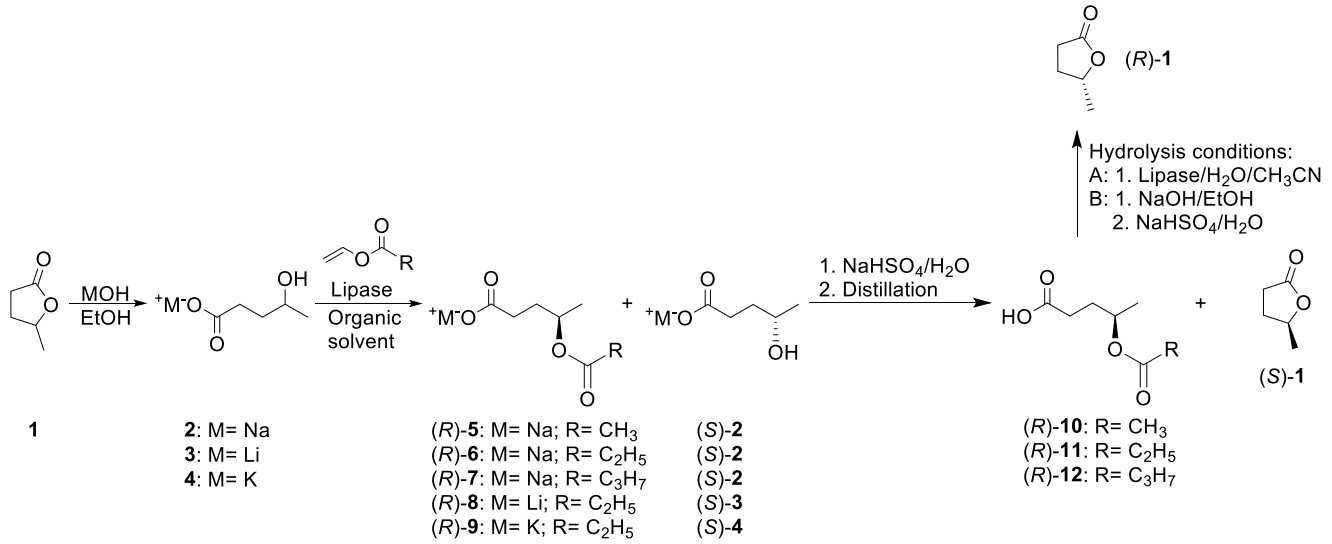
Scheme 2. First Straightforward Synthesis of 4-(Acyloxy)pentanoic Acids, an Approach for Separation of GVL Enantiomers



amount of a product (**10**−**12**) vs the sum of the amounts of the product and recovered (*S*)-**1**.

CALB (Novozym 435) was chosen for the current work as it is a versatile lipase widely applied for the catalysis of ester synthesis, and indeed, the performance of this enzyme was from the start very promising. Acylation of sodium salt **2** with vinyl acetate was performed in different solvents: toluene, cyclohexane, EtOAc, CH_3CN, and solventless (Table 1, entries 1−5). The process in cyclohexane was slower compared to other solvents along with lower stereoselectivity. In EtOAc and toluene, the process occurred at an unexpectedly high rate but with modest stereoselectivity. A solventless synthesis in neat substrate vinyl acetate (Table 1, entry 3) occurred at a low rate and with poor stereoselectivity.

Among the solvents tested, the best result with respect to stereoselectivity was acetonitrile (Table 1, entry 4), although the reaction rate was slightly lower than observed using EtOAc or toluene. In addition to the substrate vinyl acetate (Table 1, entry 4), vinyl propionate (Table 1, entry 6) and vinyl butyrate (Table 1, entry 7) were tested in acetonitrile medium; the best stereoselectivity was observed for vinyl propionate.

The influence of the carboxylate counterion in the 4-hydroxypentanoic acid alkali metal salt was also tested. The best choice was the initially chosen nucleophile−sodium salt **2** (Table 1, entry 6), while lithium salt **3** (Table 1, entry 8) and potassium salt **4** (Table 1, entry 9) were much less active as nucleophiles; reduced stereoselectivity of the reaction was also observed (Table 1; entry 6 vs entries 8 and 9). The nucleofuge is the lipase CALB; more precisely, the OH group of Ser105 of the CALB active site which is partially deprotonated by His224 of the catalytic triad which also involves Asp187. The catalytic performance of the enzyme at room temperature (+20 °C) was satisfactory due to a reasonable reaction time of 22 h (Table 1, entry 6). At a lower temperature of −20 °C (Table 1, entry 10), the stereoselectivity of the reaction was clearly reduced along with a remarkable drop in the reaction rate, with a lower conversion even after 120 h. Efforts were also expended to use greener reaction conditions when using vinyl propionate. An assessment using a green solvent was conducted by performing the synthesis in 2-Me-THF, a solvent prepared from a biorenewable feedstock (Table 1, entry 11); however, this gave the target compound (*R*)-**11** with a low stereoselectivity and velocity. Solventless synthesis occurring in neat substrate vinyl propionate (Table 1, entry 12) was similarly disappointing and in agreement with results using vinyl acetate (Table 1, entry 3).

An optimization of the reaction conditions has resulted in the synthesis of (*R*)-4-(propionyloxy)pentanoic acid ((*R*)-**11**) with *e.r.* up to 96/4 (Table 1, entry 6). In a preparative synthesis (Table 1, entry 13) with prolonged incubation time and higher conversion rate (51.2%), product (*R*)-**11** was gained with *e.r.* = 92/8. The other target compound (*R*)-**1** was obtained with high enantiomeric purity by stereoselective lipase-catalyzed hydrolysis (Table 1, entry 14) of this enantiomerically enriched (*R*)-**11** in one step (Scheme 2; hydrolysis conditions A). In this case, the enantiomeric purity of end product (*R*)-**1** depends greatly on the degree of the trace (*S*)-**1** contamination in the distilled substrate (*R*)-**11**.

In a different reaction sequence focused mainly on the synthesis of (*R*)-**11** with very high enantiomeric purity, chemical hydrolysis (Scheme 2; hydrolysis conditions B) of enriched (*R*)-**11** (*e.r.* = 92/8; the product of Table 1, entry 13) to (*R*)-**1** was performed. The synthetic process was repeated starting from this enriched (*R*)-**1** to afford (*R*)-**11** with enhanced enantiomeric purity (*e.r.* > 99/1; Table 1, entry 15). Product (*R*)-**11** was successfully hydrolyzed to (*R*)-**1** (with *e.r.* > 99/1) (Scheme 2; hydrolysis conditions B).

Our optimal conditions for the synthesis of (*R*)-**11** are described in Table 1, entry 6, and a green chemistry metrics evaluation was perfomed on this procedure (Supporting Information spreadsheet). In our synthesis of (*R*)-**11**, an overall PMI total of 388.5 (step 1 = 12.3; step 2 = 376.2) was calculated. This is a significant improvement compared to the synthesis of (*S*)-**10** (Scheme 1A), with an overall PMI total of 2661.1 (step 1 = 2197.4; step 2 = 93.6; step 3 = 370.1). Analysis of the PMI data shows that future studies should be directed toward reducing or recovery/recycling the solvents used in the workup (step 2, PMI work up solvents = 286.5). The green chemistry metric analysis[29] is available in the Supporting Information spreadsheet.

To demonstrate the scope of the method, analogous racemic material was also synthesized (Table 1, entries 16, 17). Acetonitrile was replaced by greener alternatives (EtOAc and MTBE, respectively), which provided excellent results on the

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first attempt; no further optimization was undertaken. Enzyme loading was increased 10-fold, and the incubation time was 5.5-fold compared to the conditions that provided the 45% conversion intended for the kinetic resolution. Indeed, both 4-(acetyloxy)pentanoic acid as well as 4-(propionyloxy)-pentanoic acid were gained in high chemical purity (>98%) and high yield (>90%). Using this approach on the relactonized (*S*)-**1** fraction (*e.r.* = 70/30) from Table 1, entry 5, followed by lipase-catalyzed hydrolysis (Scheme 2; hydrolysis conditions A) to remove the reactive *R* enantiomer, allowed us to obtain (*S*)-**10** in a 44% yield with *e.r.* > 99/1 (Table 1, entry 18) as the unreacted starting material (Supporting Information; Scheme 4.)

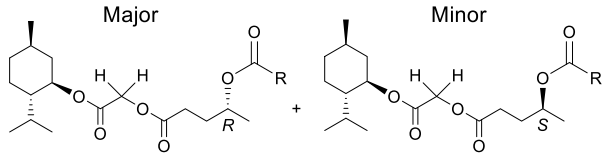
4-Hydroxycarboxylic acids as well as their esters are unstable compounds that under a wide range of conditions lactonize spontaneously. A reverse reaction is alkaline hydrolysis in which after ring opening of a γ-lactone the resulting extended chain moiety bearing an unprotected hydroxyl group is stabilized as a salt. The synthetic approach demonstrated herein is based on a lipase-catalyzed stereoselective acylation of 4-hydroxycarboxylic acid alkali metal salts in organic solvents (Scheme 2). Salts **2**−**4** are prepared by hydrolysis of racemic GVL (**1**) in ethanol. Acidic hydrolysis of the crude product of acylation affords (*R*)-4-(acyloxy)pentanoic acid along with relactonized[27,28] (*S*)-**1** (Scheme 2; protocol 3.1. in the Supporting Information), which are conveniently separated by distillation.

Acylation of 4-hydroxypentanoic acid sodium salt **2** with acetyl, propionyl, or butyryl moieties from vinyl esters catalyzed by Novozym 435 is an unexpectedly intense process in several organic solvents despite the limited solubility of the salt. An enzyme loading of 20 mg of Novozym 435 per 10 mmol of the salt nucleophile affords the desired conversion rate of 40%−45% in 22 h at optimal reaction conditions (Table 1, entry 6). The reaction mixture is a multiphase system consisting of a solvent, which contains dissolved parts of the nucleophile **2** and a product ((*R*)-**5**−(*R*)-**7**), a substrate (vinyl ester), and several solid phases: (1) biocatalyst Novozym 435, (2) starting nucleophile **2** (which dissolves gradually as the synthesis progresses), and (3) a novel solid phase precipitating during the process. The formed solid material, remaining on the filter by the end of the incubation, was hydrolyzed separately and analyzed by NMR. The precipitate was found to contain both reacted and unreacted salts. Thus, quantitative reaction monitoring was considered unfeasible because attempts to obtain representative samples of the reaction mixture during the process failed.

The conversion rate is defined herein as *apparent* (Table 1) because of the following: (1) Formation of minor side products was observed in some screening syntheses. (2) GVL and 4-(acyloxy)pentanoic acid have different solubilities in H_2O solutions, which result in a different loss of these compounds during acidic hydrolysis and workup. (3) The multiphase system observed is substantially different from the model system employed by Chen et al.[30] in creation of the equation linking the conversion rate of the reaction and the enantiomeric excess of the product. Therefore, calculation of E values using this recognized analytical tool for evaluating the results of a kinetic resolution by an irreversible enzyme-catalyzed reaction[30] was considered to be unjustified. More precisely, all fast and slow reacting enantiomers of the starting salt are not equally accessible to the enzyme under the reaction conditions used; enantiomers present in the system in the form of solid materials are probably unable to compete with dissolved ones for the active site of the enzyme. However, the multiphase nature of the system cannot be considered as being a drawback in itself. For instance, analogous systems involving a large amount of solid starting material have reacted smoothly and regioselectively in lipase-catalyzed acylations of isosorbide.[31] Nevertheless, the *apparent* conversion rates measured for the end points of the multiple screening reactions, along with *e.r.* of the products, allowed optimization of the conversion of the preparative syntheses by determination of suitable conditions for the enzyme loading vs the amount and counterion of a nucleophile vs solvent vs substrate vs temperature vs reaction time.[32]

Enantiomeric ratios of the products were determined by ^{1}H NMR measurement of the diastereomeric ratio of the ester conjugates **13**−**15** (Scheme 3) obtained by O-alkylation of the

Scheme 3. Products' (10−12) *e.r.* Determined by ^{1}H NMR Measurement of *d.r.* of Their Derivatives 13−15 by Integrating Signals of Hydrogen Atoms of the Glycolic Acid Moiety (Figure 1)



product with (1*R*)-menthyl bromoacetate,[33] a chiral derivatizing agent.[32,34,35] Diastereomeric ratios were determined by integrating the signals of H atoms of the glycolic acid moiety in the conjugate (Figure 1). Products from the preparative

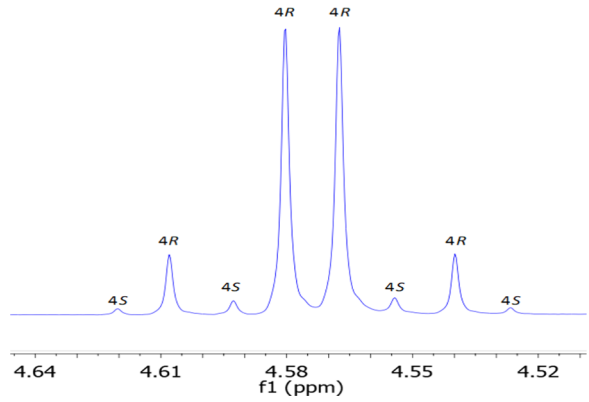


Figure 1. Fragment of ^{1}H NMR spectrum (800 MHz; $CDCl_3$) representing the diastereomeric ratio of (4*R*)-14 (major)/(4*S*)-14 (minor) which was determined by integrating the signals of the hydrogen atoms of the glycolic acid moiety.

syntheses (Table 1, entries 5, 13) were analyzed additionally in the form of *p*-bromophenacyl esters by chiral HPLC (Supporting Information), and results were in good agreement with NMR data analysis. Enantiomeric ratios of the (*R*)-**1** samples prepared by hydrolysis of (*R*)-**11** were measured by GLC using a capillary column with a chiral liquid phase (Supporting Information).[17,36,37]

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CONCLUSIONS

In conclusion, the disclosed approach is the first straightforward synthesis of (*R*)-4-(acyloxy)pentanoic acids. Using racemic GVL, we have disclosed a method for the separation of enantiomers of this important biobased platform chemical. The known syntheses of such compounds are indirect, consume more reagents (e.g., $NaIO_4$) and solvents, use hazardous solvents (e.g., pyridine and CCl_4), and produce greater amounts of waste because several intermediates and/or end products need chromatographic separation. The overall PMI total of 2661.1 of a previously described (Scheme 1A) synthesis was calculated. Our method (Table 1, entry 6) with an overall PMI total of 388.5 represents a significant improvement. The 4-hydroxypentanoic acid sodium salt was found to be an unexpectedly active nucleophile in the lipase-catalyzed transesterification in different organic solvents despite its limited solubility. Acidic hydrolysis of the crude acylation products afforded (*R*)-4-(acyloxy)pentanoic acid along with relactonized (*S*)-GVL, which were readily separated by distillation. The influences of the carboxylate counterion, reaction medium, substrate structure, and temperature on the reaction rate and stereoselectivity were screened, and the influence of all these variables appeared to be equally significant. (*R*)-4-(Propionyloxy)pentanoic acid was obtained with *e.r.* up to 96/4 in one step. An additional lipase-catalyzed treatment of the product afforded (*R*)-4-(propionyloxy)-pentanoic acid and (*R*)-GVL with *e.r.* > 99/1 on a preparative scale. The developed method also allows the synthesis of racemic 4-(acyloxy)pentanoic acids. Use of this approach to fully convert relactonized (*S*)-GVL to (*S*)-4-(acetyloxy)-pentanoic acid, followed by lipase-catalyzed hydrolysis, provided (*S*)-4-(acetyloxy)pentanoic acid with *e.r.* > 99/1. Further optimization of the synthesis as well as extending the scope of the approach involving homologous γ-lactones is in progress.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acssuschemeng.0c07918.

Green chemistry metric workbook (XLSX)

General information, experimental procedures, characterization of products, NMR spectra, HPLC and GLC chromatograms(PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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