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Stereoselective Synthesis of γ-(Acyloxy)carboxylic Acids and γ-Lactones Featuring the Switch of Stereopreference of *Candida antarctica* Lipase B in Sodium γ-Hydroxycarboxylate Homologues

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Scalable protocols of straightforward synthesis of enantiomeric γ-(acyloxy)carboxylic acids and γ-lactones are presented. The key step is lipase-catalyzed stereoselective acylation of γ-hydroxycarboxylic acid sodium salt in organic solvent followed by acidification of the product, extraction and acidic relactonization of the unreacted enantiomer. The mixture of γ-(acyloxy)carboxylic acid and γ-lactone is separated either by extraction with solution of sodium bicarbonate or by distillation. A switch of enantioinduction of *Candida antarctica* lipase B along homologous nucleophiles from *R* configuration of γ-hydroxyhexanoic acid salt to *S* configuration of the C7 and longer-chain homologues has been disclosed. Both enantiomers of γ-(acyloxy)pentanoic acids; γ-(acetyloxy)octanoic and -nonanoic acids with *S* configuration; [(1*S*,5*R*)-5-(chloroacetyloxy)cyclopent-2-en-1-yl]acetic acid and enantiomeric γ-lactones derived from them were prepared with *e.r.* > 98.5/1.5. The rates of acylation of C5 to C9 homologous salts differ by three orders of magnitude but remain applicable for preparative synthesis by variation of the enzyme loading and reaction time.

Introduction

A considerable reorientation from fossil materials to renewables is happening in different fields of the chemical industry. One of the approaches is the synthesis of levulinic acid (LA) from lignocellulosic biomass.[1] LA affords γ-valerolactone (GVL) upon catalytic hydrogenation of the keto group followed by lactonization. GVL is acknowledged as an important sustainable platform chemical[2] and is of great importance for green chemistry[3] applications. Preliminary results of the study herein regarding a straightforward scalable synthesis of both (*R*)- and (*S*)-4-(acyloxy)pentanoic acids and the corresponding enantiomeric GVLs, starting from racemic GVL, were reported in a previous communication (Supporting Information Scheme S1).[4]

One stereoselective synthesis of 4-(acyloxy)pentanoic acid was known[5] prior to our work. This synthesis involves 3 steps, in which the carboxyl group is generated by oxidation of the phenyl group in the final step.[6] Large amounts of solvents and large excess of reagents are used which are significant drawbacks regarding scalability of the synthesis and do not adhere to the principles of green chemistry.[7] Stereoselective synthesis of some longer-chain homologues of γ-(acyloxy)carboxylic acids using this method[5] has been applied as an approach to the preparation of enantiomerically enriched γ-lactones.[8]

Enantiomeric γ-lactones play significant roles in nature and are involved in numerous applications.[9] For instance, (*R*)-γ-hexalactone is one of the pheromone components of insect *Trogoderma glabrum*.[10] Considering this – the enantiomeric 4-hexanolides have in general been the target compounds in the works proposing novel methods for the synthesis of enantiomeric γ-lactones.[11] Different homologues of γ-lactones have been discovered in fruits and beer,[9c,d] with some used as aroma compounds in food products. Pure enantiomers of γ-lactones are sources of higher quality and intensity aroma compared to racemic mixtures.[12] Enantiomers of GVL have been used as building blocks in the synthesis of biologically active chiral compounds, such as geodiamolide A,[13] (*R*)- and (*S*)-sulcatol,[14] (*R*)-(−)- and (*S*)-(+)-phoracantholide,[15] (+)-patulolide,[16] and cladospolide C.[17]

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Continuous efforts dedicated to the creation of more efficient methodology for the preparation of pure enantiomers of γ-lactones have been expended during decades. Attention has been paid mainly on two approaches – use of asymmetric hydrogenation catalysts based on transition metals and lipases. It is obvious that biocatalysts, being environmentally benign since they are completely degradable, are preferable.[7b] Despite this large body of work, enantiomeric γ-lactones as well as 4-(acyloxy)carboxylic acids have so far not been sufficiently accessible to meet the increasing demands of research and development projects. The approaches studied include:

1) separation of γ-lactone enantiomers, either by preparative liquid chromatography over chiral stationary phase[18] or by co-crystallization with different hosts, like cholic acid[19] or tartaric acid derivatives;[20] or by kinetic resolution using lipase-catalyzed hydrolysis of racemic γ-lactones;[21]
2) separation of γ-lactone enantiomers via diastereomeric derivatives of the corresponding γ-hydroxycarboxylic acids, like amides,[22] or γ-acylates of iso-propyl esters;[16,22]
3) stereoselective catalytic hydrogenation[23] of the γ-keto group of γ-ketocarboxylic acids or their derivatives using biocatalytic reductions – either by yeast[24] or by engineered reductase[25] or using microbial reduction;[26] stereoselective hydrogenation of the γ-keto group based on metal catalysis using either Ru-[27] or Ir-based catalysts,[28] or a tartaric acid and NaBr-modified Ni-catalyst;[29] also, reduction with diisopinocampheylborane has been examined;[30]
4) lipase-catalyzed kinetic resolution of enantiomers of 4-hydroxycarboxylic acid esters and amides;[31] this approach needs extra synthesis of esters and amides and hydrolysis after lipase-catalyzed treatment, therefore requiring an extended list of reagents compared to alkaline hydrolysis/acidification proposed by us;[4]
5) tandem procedures involving isomerization and biocatalytic resolution;[32]
6) biocatalytic oxidation of 1,4-alkanediols and γ-lactols; bacterial oxidation of C5–C20 fatty acids;[33]
7) syntheses starting from γ-ketonitriles;[34]
8) lipase-catalyzed synthesis of enantiomeric γ-lactones from γ-hydroxycarboxylic acid derivatives (see comments in p. 4);[35]
9) miscellaneous multi-step syntheses of enantiomeric γ-lactones starting from a chiral pool, either from amino acids,[36] or carbohydrates[11a,37] or from other materials such as cyclopropane hemimalonates,[38] from chiral propargylic alcohols,[39] via selective epoxide opening[40] or others.[41]

The overall goal of the current work has been to address this stereoselective synthesis challenge. Primarily, the goals of the current work are to broaden the scope of the approach – proposed originally for the stereoselective synthesis of γ-(acyloxy)pentanoic acids[4] – towards longer-chain homologues as well as further development of the synthetic procedure.

Results and Discussion

Preliminary published results[4] of the current research topic considering the synthesis of both (*R*)- and (*S*)-γ-(acyloxy)pentanoic acids and enantiomeric GVLs have been partially revised herein based on the novel results obtained from the development of the synthetic approach involving longer chain homologues. The upgraded protocols of synthesis are presented in Supporting Information of this work.

One of the key results described herein is an unexpected switch of CalB stereopreference along homologous γ-hydroxycarboxylic acid sodium salts which is presented in Scheme 1. In addition, the broad nucleophile scope and high stereoselectivity of the approach are documented in Table 1 and pictured in Schemes 2–4.

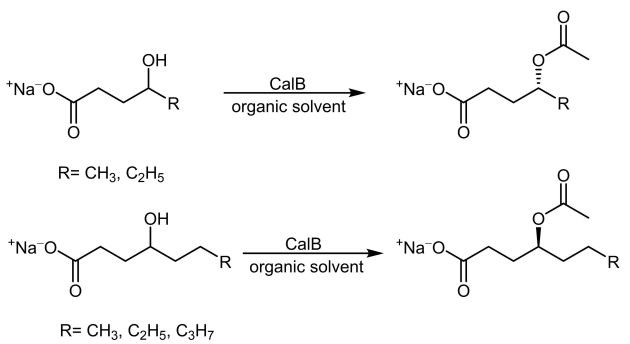
Guidelines drawn from the preliminary work for the current studies were the following.

Firstly, it was found that the metal counterion has significant influence on the stereoselectivity and rate of the reaction (Table 1, entries 1–4). The best choice was sodium salt **3** (Table 1, entry 2) – out of Na (**3**), Li (**3 a**), and K salts (**3 b**) tested (Table 1, entries 2–4; Scheme 2) and as a result – sodium counterion was used exclusively in the current work.

Secondly, results in Entries 1 and 2 (Table 1) show the influence of the structure of the substrate (vinyl acetate vs. vinyl propionate) on reaction stereoselectivity and rate; as a conclusion, different substrates were tested in the screening reactions.

Thirdly, the lipase-catalyzed acylation of 4-hydroxypentanoic acid sodium salt was feasible in a broad spectrum of organic solvents. Lipophilic cyclohexane and toluene through to EtOAc and up to the polar water-miscible acetonitrile were all acceptable solvents, affording target products, albeit with different rates and stereoselectivity. Acetonitrile and also some more lipophilic solvents have been screened[42] in the lipase-catalyzed acylation of longer chain homologous salts.

And finally, the interconversion of an enantiomeric γ-(acyloxy)carboxylic acid to γ-lactone (and the reverse process) occurred without racemization and with quantitative yield. The synthesis of enantiomerically enriched γ-lactones is up to now the only known application of the enantiomeric γ-(acyloxy)carboxylic acids. The obtained γ-lactones can be analyzed by chiral GLC[43] providing an alternative analytical approach for stereochemical analysis of the parent γ-(acyloxy)carboxylic acids.



Scheme 1. The switch of the stereoinduction of CalB from *R* configuration in case of γ-hydroxypentanoic and -hexanoic acid sodium salts to *S* configuration of γ-hydroxyheptanoic, -octanoic, and -nonanoic acid sodium salts.

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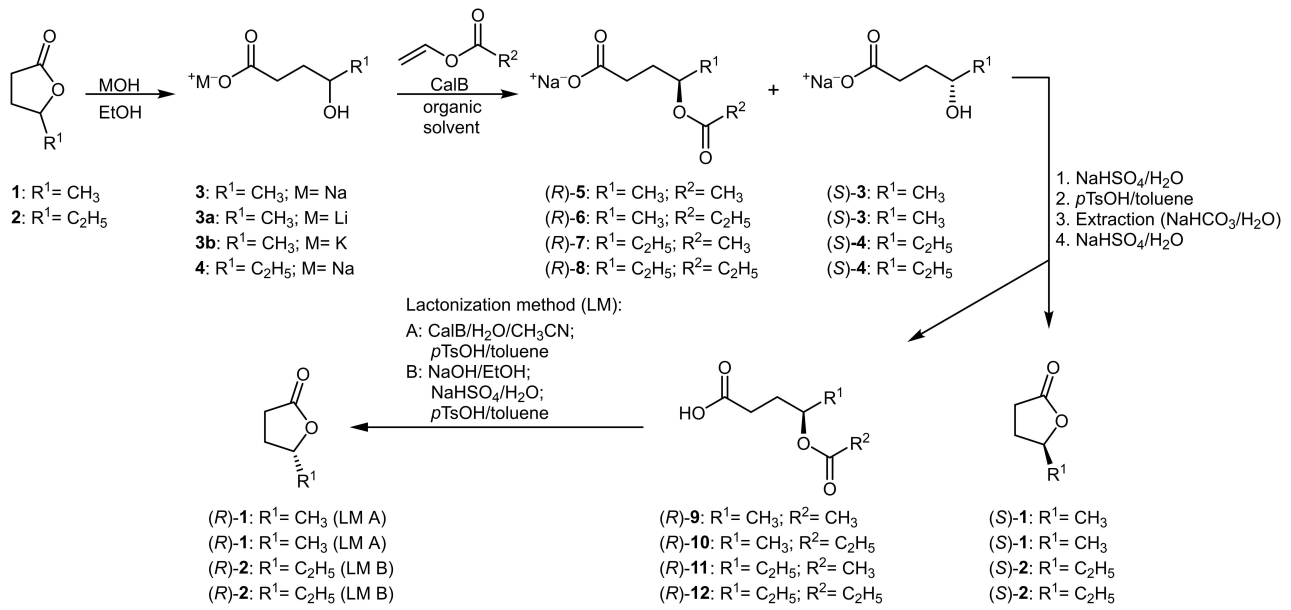
Table 1. Results of the screening of the reaction conditions for the lipase-catalyzed acylation of γ-hydroxycarboxylic acid sodium salts at 20 °C and demonstrations of the scope of the method.

Entry	Nu[a] [mmol]	Solvent [mL]	Substrate[b] [mmol]	N435[c] [mg]	Reaction time [h]	Conv.[d] [%]	Ratio of reaction rates[e]	Product/*e.r.* (*R*/*S*)[f]
1	**3** (10)	CH_3CN (20)	vin. ac. (40)	20	22	42.9	1/0.93	**9**; 90.8/9.2[i]
2	**3** (10)	CH_3CN (20)	vin. prop. (40)	20	22	39.8	1	**10**; 96.1/3.9[i]
3	**3 a** (10)	CH_3CN (20)	vin. prop. (40)	20	22	10.7	1/3.7	**10**; 86.4/13.6[i]
4	**3 b** (10)	CH_3CN (20)	vin. prop. (40)	20	22	9.1	1/4.4	**10**; 93.4/6.6[i]
5	**4** (5)	CH_3CN (10)	vin. ac. (20)	200	22	37.1	1/22	**11**; 78.1/21.9[i]
6	**4** (10)	CH_3CN (20)	vin. prop. (40)	400	22	18.0	1/44	**12**; 86.5/13.5[i]
7	**4** (10)	CH_3CN (20)	vin. prop. (40)	400	44	36.0	1/44	**12**; 85.5/14.5[i] (85.7/14.3)[j]
8	**4** (40)	CH_3CN (80)	vin. prop. (160)	800	93	35.5	1/48	**12**; 85.0/15.0[i]
9	**4**[g] (5.6) *e.r.* 85/15 *R/S*	CH_3CN (12)	vin. prop. (22.4)	112	93	52.1	1/33	**12**; 93.5/6.5[h] (92.5/7.5)[i]
10	**16** (5)	CH_3CN (10)	vin. ac. (20)	500	22	13.8	1/145	**23**; 9.2/90.8[i]
11	**16** (5)	CH_3CN (10)	vin. prop. (20)	500	88	23.6	1/339	**24**; 8.7/91.3[i]
12	**16** (3)	EtOAc (20)	vin. ac. (15)	400	72	45.6	1/191	**23**; 3.8/96.2[i] (3.0/97.0)[j]
13	**16** (10)	$CHCl_3$ (40)	vin. ac. (40)	800	263	37.0	1/515	**23**; 3.6/96.4[i] (2.8/97.2)[h]
14	**17** (5)	CH_3CN (20)	vin. ac. (20)	500	142	23.1	1/559	**25**; 3.4/96.6[i]
15	**17** (5)	EtOAc (20)	vin. ac. (20)	500	54	44.8	1/219	**25**; 3.5/96.5[i]
16	**17** (7)	$CHCl_3$ (30)	vin. ac. (28)	700	167	14.6	1/1040	**25**; 0.5/99.5[i] (1.4/98.6)[j]
17	**18** (5)	CH_3CN (20)	vin. ac. (20)	500	142	31.0	1/417	**26**; 2.2/97.8[i]
18	**18** (5)	EtOAc (20)	vin. ac. (20)	500	54	45.9	1/107	**26**; 1.0/99.0[i] (1.3/98.7)[h]
19	**18** (20)	$CHCl_3$ (60)	vin. ac. (80)	3000	141	34.7	1/554	**26**; 0.9/99.1[i]
20	**28** (5)	EtOAc (20)	vin. ac. (20)	500	120	15.6	1/699	(1*S*,5*R*)-**31**; > 97/3[j]
21	**28** (5)	$CHCl_3$ (20)	vin. Clac. (20)	500	120	18.2	1/599	(1*S*,5*R*)-**32**; > 99.8/0.2[j]

[a] the structures of the nucleophiles are pictured in the Schemes 2, 3 and 4; [b] the substrates (acyl donors) vinyl acetate, vinyl propionate and vinyl chloroacetate were used; [c] N435 – Novozym® 435; [d] „Conv." is final conversion of a nucleophile; [e] ratio of the rates of a screening acylation versus the standard process (entry 2), as calculated by Equation (1); [f] two values of the *e.r.* of the products are given in the cases where different results were obtained using different analytical methods (Δ *e.r.* > 0.2 %); [g] the starting sodium salt **4** was prepared from the product of Entry 8; [h] HPLC over chiral stationary phase was used; [i] ^{1}H NMR of (1*R*)-menthyl glycolic esters was used; [j] chiral GLC was used for determination of *e.r.* of the product.



Scheme 2. Stereoselective synthesis of (*R*)-γ-(acyloxy)pentanoic and (*R*)-γ-(acyloxy)hexanoic acids as well as enantiomerically enriched GVLs and γ-hexalactones.

Estimation of reaction rate; determination of the conversion of nucleophile and enantiomeric ratio of the products

The current work has not involved a reaction kinetics study. However, since it has been fully oriented towards developing the preparative synthesis, the empirical estimation of reaction rates has been necessary for the simultaneous optimization of acylation stereoselectivity and rate. Rates of the screening reactions are given as a ratio (Table 1, column 8) to the rate of the standard process (Table 1, entry 2).

The parameters of the screening reactions were normalized against corresponding parameters of the standard process – the propionylation of γ-hydroxypentanoic acid sodium salt: 1) *10 mmol of the nucleophile* – 4-hydroxypentanoic acid sodium

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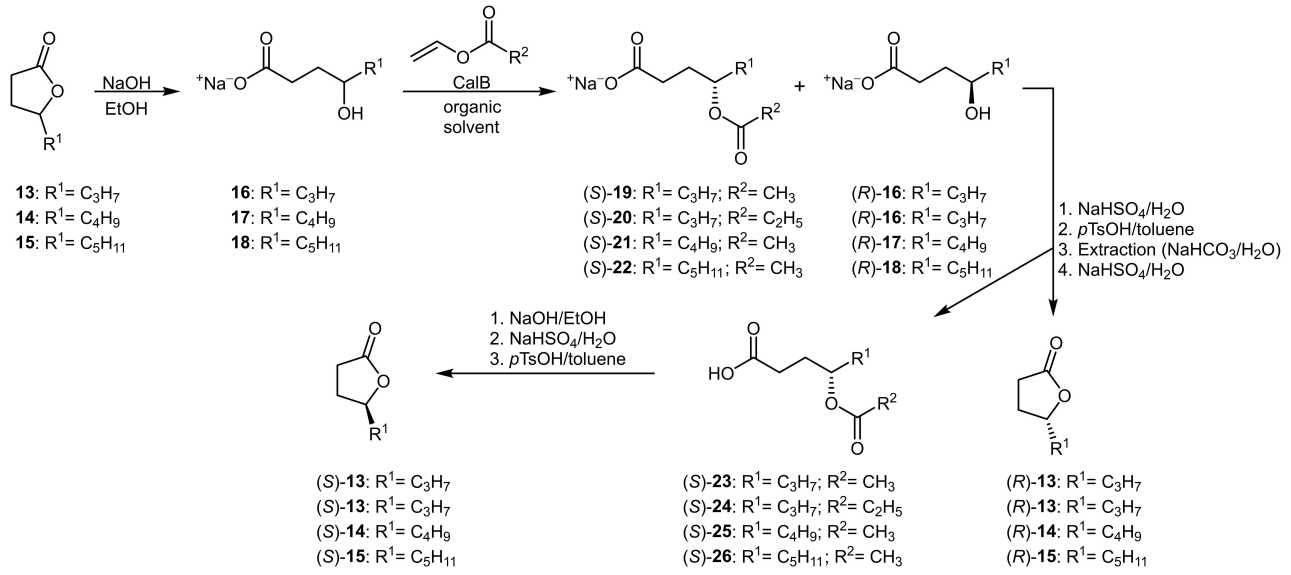
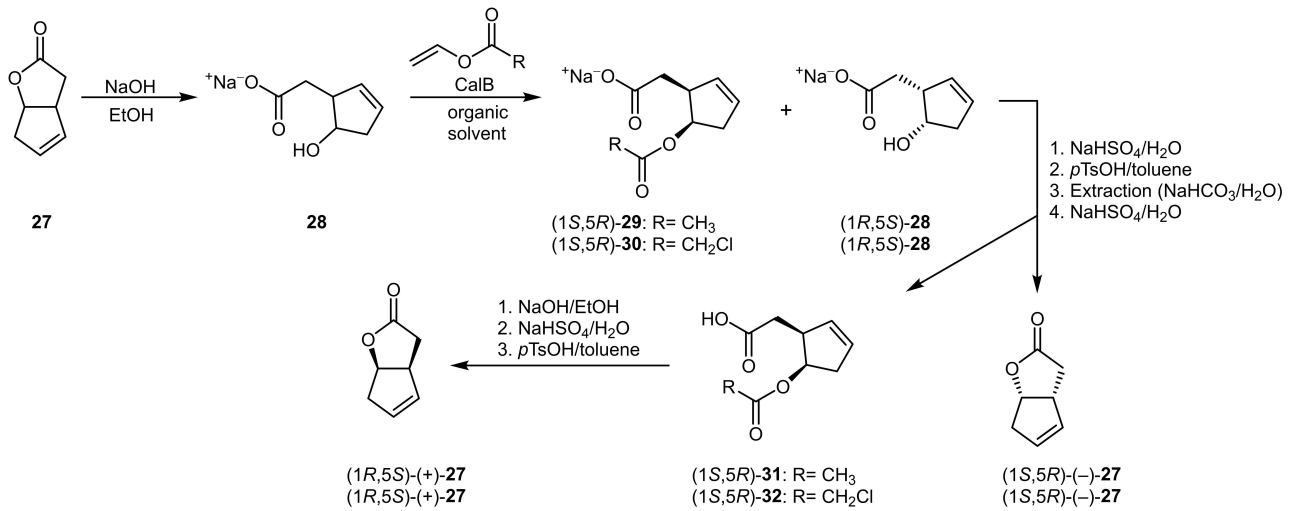


Scheme 3. Stereoselective synthesis of γ-(acetyloxy)- and γ-(propionyloxy)heptanoic, γ-(acetyloxy)octanoic and γ-(acetyloxy)nonanoic acids as well as the corresponding enantiomerically enriched γ-lactones.



Scheme 4. Stereoselective synthesis of [(1*S*,5*R*)-5-(acyloxy)cyclopent-2-en-1-yl]acetic acids (1*S*,5*R*)-**31** and (1*S*,5*R*)-**32**.

salt in 20 mL of acetonitrile (the solvent volume used in the screening reactions was prevailingly proportional to the nucleophile load) was incubated with the biocatalyst – 2) *20 mg of Novozym 435* and the substrate (40 mmol of vinyl propionate; substrate load was mainly proportional to the nucleophile load in the screening experiments, deviations were ignored) for 3) *22 h* at RT affording product with 4) *0.4 (40 %) of final conversion of the nucleophile.* The calculations were performed using Equation (1) which provides comparison of the rates (Table 1, column 8) of the screening reactions (Table 1, entries 1 and 3–21) with the rate of the standard reaction (Table 1, entry 2):

$$\frac{\frac{\textit{nucleophile load [mmol]}}{10} X \frac{\textit{final conversion [0–1]}}{0.4}}{\frac{\textit{N435 load [mg]}}{20} X \frac{}{\textit{reaction time [h]}}{22}} = \frac{\textit{the rate of the screening reaction}}{\textit{the rate of the standard reaction}} \quad (1)$$

Nucleophile load, final conversion, N435 load and reaction time are presented in Table 1. Estimation of the reaction rate based on the final conversion[44] and load of the nucleophile vs. time and biocatalyst load has been used because it was unfeasible to take representative samples from the multiphase reaction mixture to monitor reaction progress.[4] Regarding analysis, and predicting the stereoselectivity of the syntheses depending on conversion, the situations where multiple solid phases are involved[45] (consisting of stereoisomeric mixtures of the starting nucleophile and the products in our case) do not

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match the logic applied for quantitative analyses of biochemical kinetic resolutions of enantiomers using calculation of the „enantioselectivity" (E).[46] In our case, stereoselectivity of the acylation of the salts in organic solvent depends on the apparent conversion,[4] which is based on the real conversion, but depends also on multiple mass-transfer equilibria between liquid phase and the solid phases of the reaction mixture.

In order to render with clarity the connections between reaction rates and certain backgrounds, the rates are given, as mentioned above, as ratio of the normalized value of the „result" (nucleophile loading × conversion) vs. normalized value of the „catalytic impact" (enzyme loading × reaction time) which affords the ratio of the rate of the screening reaction and the rate of the standard reaction. Such a simple estimation of the reaction rates is also justified because of large differences of the reaction rates between homologues that exceed three orders of magnitude.

Conversion of γ-hydroxycarboxylic acid sodium salts (Table 1, column 7) for all screening syntheses was determined by ^{1}H NMR as molar ratio of γ-(acyloxy)carboxylic acid vs. γ-lactone in the final crude product measured after relactonization of the unreacted enantiomer.

Enantiomeric ratios of γ-(acyloxy)carboxylic acids (Table 1, column 9) have been determined by using chiral derivatization[47] with (1*R*)-menthyl bromoacetate to prepare diastereomeric menthyl glycolic ester conjugates[48] for ^{1}H NMR spectroscopic analysis or/and by using HPLC of corresponding *p*-bromophenacyl esters over chiral stationary phase or/and by GLC of γ-lactones over chiral liquid phase (Supporting Information Scheme S5).

Acylation of γ-hydroxyhexanoic acid sodium salt

The rate of acetylation of 4-hydroxyhexanoic acid sodium salt **4** (Table 1, entry 5), performed under identical conditions to those used for 4-hydroxypentanoic acid sodium salt **3** (Table 1, entry 1) occurred at ca. 20-fold lower rate compared to the C5 homologue. Stereoselectivity was lower as well, the reaction afforded γ-(acetyloxy)hexanoic acid with *e.r.* of 78/22 (*R*/*S*) compared to *e.r.* 91/9 obtained for C5 homologue at comparable conversions. When using vinyl propionate (Table 1, entry 6), the reaction rate dropped two-fold compared to acetylation (Table 1, entry 5), however, stereoselectivity was higher for propionylation (Table 1, entries 6–8). The amount of the starting γ-hexalactone **2** used was 10 to 40 mmol, and a substantial difference between reaction rate or *e.r.* of the product depending on the batch size was not observed. Moreover, twofold longer reaction time (other conditions were kept constant) gave exactly twofold higher conversion, an increase from 18% (Table 1, entry 6) to 36% (Table 1, entry 7), difference in the *e.r.* of the products was negligible. Repeating the lipase-catalyzed propionylation process with the enriched lactone – obtained by alkaline hydrolysis of the enantiomerically enriched (*R*)-γ-(propionyloxy)hexanoic acid **12** (Table 1, entry 8) followed by acidic lactonization – afforded acid (*R*)-**12** with improved enantiomeric ratio: *e.r.* 93.5/6.5 (Table 1, entry 9). Attempts to further improve the enantiomeric purity of this enriched product **12** (*e.r.* 85/15 *R*/*S*) by lipase-catalyzed hydrolysis that could afford (*R*)-hexalactone with improved *e.r.* have so far failed because of a too low hydrolysis rate. Such approach has afforded positive results for (*S*)-(acyloxy)pentanoic acid and for (*R*)-GVL.[4]

Acylation of γ-hydroxyheptanoic acid sodium salt; switch of stereopreference of *Candida antarctica* lipase B along homologues

Acetylation of the salt **16** in acetonitrile (Table 1, entry 10) occurred at 156-fold lower rate than the acetylation of the C5 homologue **3** (Table 1, entry 1) but more than two-fold faster compared to propionylation of the same compound under identical conditions (Table 1, entry 11). In these cases (Table 1, entries 10 and 11) the stereoselectivity of acylation was equal, affording products with *e.r.* 9/91 (*R*/*S*).

An important observation is the switch of the stereoinduction of CalB (Scheme 1, Figures 1 and 2) from (*R*)-enantiomer in case of C5 and C6 homologues (Table 1, entries 1–9) to (*S*)-enantiomer for the C7 homologous nucleophile (Table 1, entries 10–13) being also valid for the C8 and C9 homologues (entries 14–16 and 17–19, resp., Table 1).

The switch of enantiopreference of CalB obviously refers to the possibility of realization of two alternative molecular recognition modes between nucleophile and an acyl-enzyme, preceding the formation of the corresponding diastereomeric tetrahedral intermediates.[49] The first mode realizes in accordance with the Kazlauskas rule[50] and leads to formation of the products which include *R* enantiomer (Table 1, entries 1–9).

Realization of the recognition mode which leads to the formation of any of the (*S*)-γ-(acyloxy)carboxylic acid salts as the preferable one leads to a significant drop of the reaction rate compared to the alternative one. The switch has been recognized and characterized by differences in ^{1}H and ^{13}C NMR spectra of the diastereomeric (1*R*)-menthyl glycolic ester conjugates (Figures 1 and 2, resp.) and also by the switch of specific rotation of the products and by the chiral HPLC and GLC data (by the elution order of the enantiomers).

In the case of acylation of γ-hydroxyheptanoic acid sodium salt, the use of lipophilic solvents like EtOAc (Table 1, entry 12) and chloroform (Table 1, entry 13) afforded the product with higher stereoselectivity (Table 1, entries 10–11) compared to acetonitrile. Moreover, the reaction rate for the longer chain homologues (C7–C9) is remarkably higher in EtOAc than in acetonitrile (Table 1, column 8).

Acylation of γ-hydroxyoctanoic and γ-hydroxynonanoic acid sodium salts

Lipase-catalyzed acetylation of the C7 homologue **16** occurred at a higher rate compared to propionylation and with high stereoselectivity (Table 1, entries 10 and 11). Considering this,

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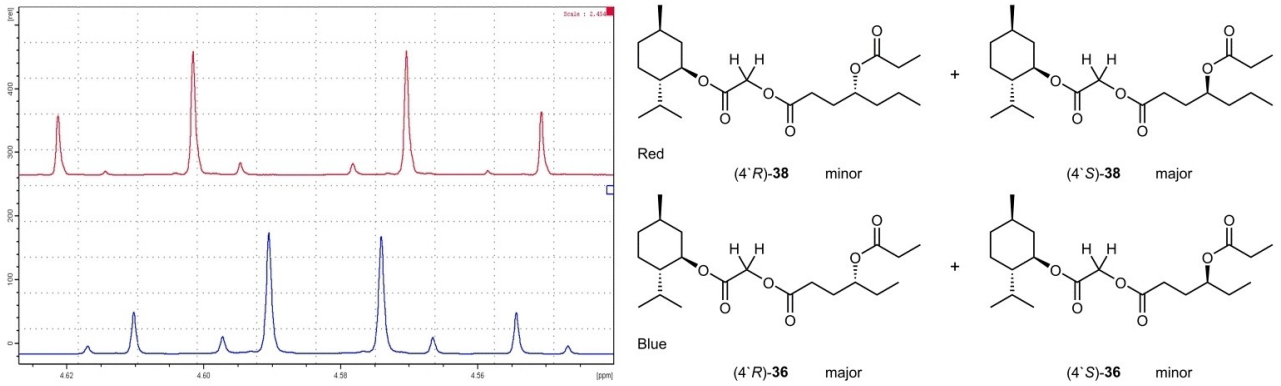

Figure 1. The fragments of ^{1}H NMR spectra and structural formulae of (1*R*)-menthyl glycolic esters of (*R*)-γ-(propionyloxy)hexanoic acid (4′*R*)-**36** (blue line) and (*S*)-γ-(propionyloxy)heptanoic acid (4′*S*)-**38** (red line); *d.r.* of the samples were 85/15 (4′*R*/4′*S;* blue) and 91/9 (4′*S*/4′*R*; red), respectively; the signals belong to the hydrogen atoms of the glycolic acid moiety. The γ-(propionyloxy)carboxylic acid moieties included into the ester conjugates have both been synthesized by propionylation of the corresponding sodium salt catalyzed by CalB in acetonitrile; the switch of the stereopreference of CalB can be observed.

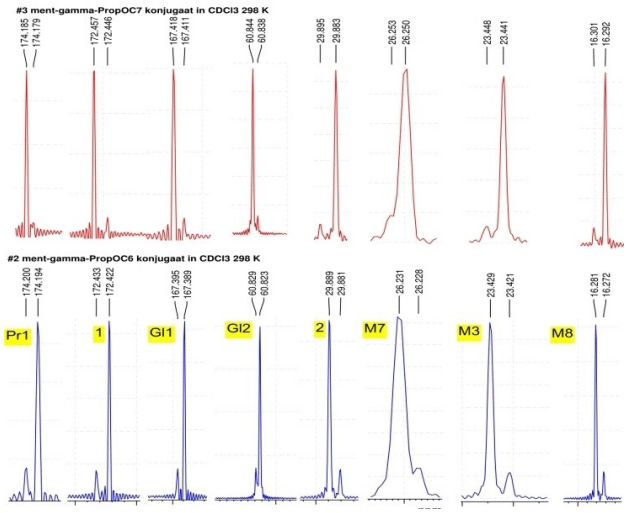

Figure 2. NMR spectral evidence of the switch of the enantiopreference of CalB (the structures are presented in Figure 2). The fragments of ^{13}C NMR spectra of diastereomeric mixtures of (1*R*)-menthyl glycolic esters of (*R*)-γ-(propionyloxy)hexanoic acid (4′*R*)-**36** (blue line; 4′*R*/4′*S* major/minor) and (*S*)-γ-(propionyloxy)heptanoic acid (4′*S*)-**38** (red line; 4′*S*/4′*R* major/minor) involving signals of carbon atoms of: 1) C1 of propionyl (Pr1); 2) C1 and C2 of the γ-substituted carboxylic acid moiety (1 and 2); 3) C1 and C2 of glycolic acid moiety (Gl1 and Gl2); 4) C3 (M3), C7 (M7) and C8 (M8) carbon atoms of the (1*R*)-menthyl moiety of the conjugates.

only acetylation was studied for C8 and C9 homologues **17** and **18**, respectively (Scheme 3).

Reaction rates and stereoselectivities are comparable for **17** and **18** related to each of the three solvents, respectively (Table 1, entries 14 vs. 17, entries 15 vs. 18 and entries 16 vs. 19). Significant differences between the rates of the reactions performed in different solvents with the same nucleophile were observed. For instance, the reaction rate was 1/209 in EtOAc and 1/1040 in $CHCl_3$ for C8 homologue **17** (Table 1, column 8); for the C9 homologue **18** the rates were 1/107 and 1/554, respectively, estimated by comparison with the standard procedure. Stereoselectivity for **17** was comparable in acetonitrile (*e.r.* of the product 96.6/3.4 *S*/*R*; Table 1, entry 14) and in EtOAc (*e.r.* 96.5/3.5 *S*/*R*; Table 1, entry 15) while final conversions were 23.1 % versus 44.8 %, respectively; the reaction rate was at least 4-fold higher in EtOAc giving a preference to EtOAc. When **17** was acetylated in $CHCl_3$, the *e.r.* of the product was higher than in other solvents (> 98.5/1.5, at 15 % of final conversion) while the reaction rate was remarkably lower than in EtOAc. In the case of **18** acetylation afforded the product with *e.r.* > 99.0/1.0 *S*/*R* in both EtOAc (Table 1, entry 18; conversion 45.9 %) and in $CHCl_3$ (Table 1, entry 19; conversion 34.7 %), while the reaction rate was at least 4-fold higher in EtOAc. Acetylation of **18** in acetonitrile (Table 1, entry 17) afforded the product with lower stereoselectivity, *e.r.* of the product was 97.8/2.2 (*S*/*R*) at the conversion rate of 31 %.

Acylation of a cyclic γ-hydroxycarboxylic acid salt

Acylation of the γ-hydroxycarboxylic acid sodium salt derived from a bicyclic γ-lactone – 2-oxa-bicyclo[3.3.0]oct-6-en-3-one **27** (known as *Grieco lactone*, Scheme 4) was feasible, conversion was modest (15–20 %), but the stereoselectivity was high with both substrates, vinyl acetate and vinyl chloroacetate. *E.r.* of the acetate (1*S*,5*R*)-**31** was > 97/3 (Table 1, entry 20), while *e.r.* of the chloroacetate (1*S*,5*R*)-**32** was higher: > 99.8/0.2. Configuration of the nucleophile preferred by lipase was in accordance with the Kazlauskas rule.[50] *E.r.* of **31** and **32** were determined by chiral GLC of the γ-lactone (+)-**27** derived from these products. The *d.r.* of the menthyl glycolic esters of (1*S*,5*R*)-**31** was not possible to determine by ^{1}H NMR because of disadvantageous multiplicity of the signals of the H atoms of the glycolic acid moiety of these structures. The chloroacetylated target compound (1*S*,5*R*)-**32** was prepared essentially enantiomerically pure as determined by GLC analysis of the derived γ-lactone; the minor enantiomer was not detected.

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Development of the synthetic procedure

The synthesis starts from alkaline hydrolysis of racemic γ-lactone in ethanol azeotrope (95.6%) followed by evaporation of ethanol. An organic solvent, substrate and biocatalyst are added and the mixture is stirred on a magnetic stirrer for a suitable time.

Regarding the activity of residual water, there are several probable sources of water in this system: 1) the solvent (HPLC grade solvents were used), 2) ethanol azeotrope, 3) structural water of the enzyme, 4) free residual water on the immobilized enzyme. However, the content of the residual water in the current complex multiphase system was not determined and no measures were taken to maintain artificially the higher level of water activity.[44] It has previously been shown that water accessible to the enzyme reacts under such conditions during the first hour of incubation; there occurs a so-called "water burst," monitored by formation of acetaldehyde using NMR (the reaction was performed in a tightly closed NMR tube).[51a] Moreover, it has been shown by MDS modelling[51b] that a certain number of structural water molecules very probably stayed on their initial locations even in methanol, while the leaving of others is probably one of the factors behind conformational change of the lipase that leads to changes in the selectivities of the lipase-catalyzed reaction. This is one probable mechanism behind improved stereoselectivity when acetonitrile is used instead of lipophilic solvents in our work.

The enzyme is filtered off and washed with ethanol in order to dissolve all solid compounds. The filtrate is evaporated, the residue is acidified with $NaHSO_4$ water solution, all solid material is dissolved by careful shaking of the flask and the products are extracted with EtOAc. In order to avoid the appearance of any amount of the residual unrelactonized 4-hydroxycarboxylic acid, the residue from the extract is dissolved in toluene and treated with acidic catalyst (*p*TsOH) in the presence of anhydrous Na_2SO_4. This separate relactonization procedure was also introduced into the synthetic protocol of the C5 homologue compared to the initial already published one.[4] This was done based on the observation that despite high energetic preference of the cyclic GVL over the open-chain 4-hydroxypentanoic acid there was a small amount (1–3%) of unreacted γ-hydroxypentanoic acid remaining in the crude product. This contaminant relactonizes later, after an extractive separation of GVL and γ-(acyloxy)pentanoic acid or, for instance, during distillation of (*R*)-γ-(acyloxy)pentanoic acid – thus contaminating the distilled product with (*S*)-GVL.[4] Afterwards, the relactonization mixture is filtered, EtOAc is added and the product – γ-(acyloxy)carboxylic acid – is separated by extraction with dilute $NaHCO_3$ solution.[52] The extract is acidified with $NaHSO_4$ water solution and extracted with EtOAc. After drying, filtering, evaporation and further treatment with activated charcoal in ethanol, the method affords the product with high chemical purity and overall yield of up to 45% (90% of theoretical) which is in the case of longer chain homologues almost equal to the conversion of the nucleophile determined by NMR.

Regarding further development of the synthetic approach the conclusions drawn from the results of green metrics calculations should be considered. The mass of the workup solvents needs to be optimized. The green chemistry xcel workbook has been used to calculate *atom economy* (AE), *reaction mass efficiency* (RME) and *process mass intensity* (PMI) values for the best example of the current work, the synthesis of (*S*)-4-(acetyloxy)nonanoic acid. The results of GM calculations are presented in Supporting Information allowing comparison with the same characteristics calculated previously for the synthesis of (*R*)-4-(propionyloxy)pentanoic acid.[4] Two former characteristics are higher (a positive trend) for this work compared to the previous results: AE being 76.6% vs. 72.5% and RME, respectively 17.9% vs. 11.6%. While for step 1 PMI Total = 5 (PMI reaction 5 + PMI workup 0) is almost equal for both variants of the method; for step 2 the PMI total = 703.7 (PMI reaction 38.6 + PMI workup 665.1) vs. 376.2 is higher. This PMI expansion may seem negative; however, it reflects the contribution of extractive separation of the target compounds vs. distillation.[4] It should be stressed that most of the used materials in both cases can be regenerated and reused and almost all wastes (excl. minor amounts of toluene) in both syntheses are benign.[7c] The improved method presented in the current work affords the product with higher yield and quality and is more easily scalable.

The scope and limitations of the approach

It was shown[4] how (*R*)-γ-(propionyloxy)pentanoic acid (*R*)-(**10**), (*S*)-γ-(acetyloxy)pentanoic acid (*S*)-**9** and enantiomeric GVLs can be prepared with *e.r.* > 98.5/1.5. Results of the same level were obtained in the current work by acetylation for the C8 and C9 homologous sodium salts (**17**, **18**) and for the salt **28** derived from racemic *Grieco lactone* **27**. The synthesis of γ-(propionyloxy)hexanoic acid **12** has afforded the product with 35% yield (70% of theoretical) and *e.r.* > 85/15 (*R*/*S*). For the C7 homologue **16** the approach affords the product with up to 45% conversion and with *e.r.* > 97/3 (*S*/*R*).

The limitation of the method is that it does not allow to prepare (*R*)-γ-(acetyloxy)heptanoic, (*R*)-γ-(acetyloxy)octanoic and (*R*)-γ-(acetyloxy)nonanoic acids nor γ-(acyloxy)carboxylic acids corresponding to (−)-Grieco lactone because CalB prefers the antipodes with high selectivity.

Practical significance of the approach

The proposed synthetic approach allows to prepare several highly enantiomerically enriched (*e.r.* > 98.5/1.5) γ-(acyloxy)carboxylic acids and via those also the corresponding enantiomeric γ-lactones. Its practical significance is related to the straightforward character and scalability of the synthesis because of being chromatography-free – all separations of the products are performed either by extraction followed by treatment with activated charcoal or by distillation. A promising example is the propionylation of C5 homologue because of the

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exceptional activity of the sodium salt of γ-hydroxypentanoic acid as a nucleophile in acylations catalyzed by CalB. This is applicable for both the *R* and *S* enantiomer, albeit by different routes (Scheme S1).

Conclusion

A straightforward scalable approach starting from racemic γ-lactones for the synthesis of enantiomerically enriched γ-(acyloxy)carboxylic acids and γ-lactones derived from them has been presented. The key step of the approach is biocatalytic stereoselective acylation of a γ-hydroxycarboxylic acid sodium salt in an organic solvent. The target compounds are separated by extraction with sodium bicarbonate, no column chromatography is needed. Both enantiomers of γ-(acyloxy)pentanoic acid and GVL enantiomers derived from them can be prepared with *e.r.* >98.5/1.5 by using double stereoselective lipase-catalyzed treatment. Switch of CalB enantiopreference from *R* configuration for γ-hydroxypentanoic and -hexanoic acid sodium salts to *S* configuration for the C7 and longer chain homologues has been disclosed. Acetonitrile was the most suitable solvent for the stereoselective synthesis of C5 and C6 homologous products while EtOAc was the most suitable for the treatment of the longer chain homologues. Starting from racemic 2-oxabicyclo[3.3.0]oct-6-en-3-one, the synthesis of [(1*S*,5*R*)-5-(acetyloxy)cyclopent-2-en-1-yl]acetic acid and [(1*S*,5*R*)-5-(chloroacetyloxy)cyclopent-2-en-1-yl]acetic acid was feasible. The rate and yield were modest, the enantioselectivity was high and in accordance with the Kazlauskas' rule. Reliable novel methodology for the stereochemical analysis of the target compounds based on ^{1}H and ^{13}C NMR, HPLC and GLC with proper derivatization of the products was also proposed. The rates of the lipase-catalyzed acylation of the sodium salts vary widely, by up to three orders of magnitude along the five tested homologues. The conditions and results of the screening syntheses presented are useful data for predicting acylation rates and stereoselectivities for different related homologues under varying reaction conditions.

Experimental Section

General experimental information: The syntheses were performed without the use of inert gas atmosphere. The chemicals, solvents, materials (from Sigma, Merck and TCI), and enzyme (from Strem) were purchased from known firms and used without preliminary treatment.

NMR spectra were recorded in $CDCl_3$. Conversions were measured using a 400 MHz spectrometer (Bruker AVANCE III 400 MHz NMR). NMR spectra intended for the determination of the diastereomeric ratios of the menthyl glycolic acid ester conjugates of γ-(acyloxy)carboxylic acids were recorded using a 800 MHz spectrometer (Bruker AVANCE III 800 MHz). All signals were referenced relative to solvent signals (for ^{1}H, $CDCl_3$: $\delta = 7.26$ ppm, for ^{13}C, $CDCl_3$: $\delta = 77.0$ ppm). 2D FT methods were used for the assignment of NMR spectra.

HRMS measurements were performed on an Agilent 6540 UHD Accurate-Mass Q-TOF LC/MS system (Agilent Technologies, Santa Clara, CA, US) equipped with AJS ESI source. The samples were introduced into mass spectrometer by direct injection of the test solutions (injection volume 1 μl). Methanol was used as an eluent, the flow rate was set at 0.1 ml/min. Sample preparations included the preparation of 0.2–1.0 mg/ml solution of test compound in a suitable solvent.

Column chromatography of the derivatives synthesized for stereochemical analysis was performed on Merck silica gel 60 (230–400 mesh). TLC was performed using DC-Alufolien Kieselgel 60 F_{254} (Merck) silica gel plates and the chromatograms were visualised by staining upon heating with anisaldehyde solution (5 mL of anisaldehyde and 10 mL of conc. H_2SO_4 in 150 mL of EtOH) or by UV light. Specific rotation of the compounds was measured using a polarimeter P3002 (A. Krüss, Optronic).

HPLC analysis of *para*-bromophenacyl esters was performed using a set of Agilent Technologies 1200 Series and two columns with a chiral stationary phase: CHIRALPAK®IC and CHIRALPAK®IB (Daicel Chem. Ind-s Ltd.); the conditions used are described in the protocols of syntheses and with the chromatograms. For the derivatives of γ-(acetyloxy)heptanoic, γ-(acetyloxy)octanoic and γ-(acetyloxy)nonanoic acids the use of CHIRALPAK®IB is recommended.

GLC analysis of the enantiomeric purity of γ-lactones was performed using an Agilent Technologies 7890 A GC System and a capillary column with a chiral stationary phase: Supelco Beta Dex™ 325, 30 m×0.25 mm, d_f 0.25 μm. Manual split-splitless injection: 1 μL in hexane. Carrier gas He 1 mL/min. Injector 300 °C. Detector FID, 300 °C, H_2 30 mL/min, Air 400 mL/min, Make-up (N_2) 24.5 mL/min. An example of the temperature program, used for the analysis GVL: 40 °C (2 min hold), ramp (5°/min) to 130 °C (1 min hold), ramp (10°/min) to 180° C (1 min hold). The detailed temperature programs for other compounds are presented in synthetic protocols.

The synthesis of (*S*)-4-(acetyloxy)nonanoic acid (*S*)-26: Racemic γ-nonalactone (0.781 g; 0.81 mL; 5 mmol) was added to NaOH solution in ethanol (1 M; 5 mL) and the solution was stirred at 20 °C (RT) for one hour. The solution was evaporated and the flask evacuated until constant weight of the sodium salt of 4-hydroxy nonanoic acid was reached. Ethyl acetate (20 mL) was added to the salt, followed by the substrate – vinyl acetate (1.722 g; 1.85 mL; 20 mmol; 4 equiv.) and the biocatalyst Novozym 435 (500 mg). The mixture was stirred for 54 h at 20 °C (RT), then the enzyme was filtered off and the filter cake was washed with EtOH (15 mL). The filtrate was evaporated on a rotary evaporator and the residue was acidified by $NaHSO_4$ water solution (1 M; 7.5 mL; 1.5 equiv.). The mixture was thoroughly shaken for 5–10 minutes until total dissolution of the filtrate residue; then EtOAc (50 mL) was added, the mixture was shaken in a separating funnel and the water layer was separated. The organic layer was washed with saturated brine (2×10 mL) and dried over anhydrous sodium sulfate (5 g), filtered and evaporated on a rotary evaporator. Toluene (20 mL) was added to the residue followed by a catalytic amount of *p*TsOH (3 mg) and anhydrous Na_2SO_4 (3 g). The mixture was stirred at RT for 16 h. Then the solution was filtered and a sample (1%) was taken for ^{1}H NMR determination of conversion (conv. = 45.9%). EtOAc (20 mL) was added to the toluene solution and the organic solution was extracted with dilute $NaHCO_3$ water solution (0.125 M; 2× 24 mL; 6 mmol).

The organic solution was washed with saturated brine (2×15 mL), dried over anhydrous sodium sulphate, filtered and evaporated. *n*-Hexane (20 mL) was added followed by activated charcoal (0.1 g).

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The mixture was stirred for 4 h at RT, then filtered through a glass filter equipped with a layer of filter aid Hyflo® Super Cel® and the filtrate evaporated on a rotary evaporator to afford chemically homogeneous enantiomerically enriched (*R*)-γ-nonalactone (412 mg; *e.r.* 89.9/10.1 *R/S*; y.: 52.8%).

The alkaline water extract was washed with EtOAc (2×15 mL), then acidified with $NaHSO_4$ water solution (1 M; 10 mL) and extracted with EtOAc (2×25 mL). The latter EtOAc extract was washed with saturated brine (2×10 mL), dried over anhydrous sodium sulphate (4 g), filtered and evaporated.

The residue was dissolved in ethanol (30 mL) and activated charcoal (0.2 g) was added followed by stirring for 4 h at RT. The solution was filtered through a glass filter equipped with a layer of filter aid Hyflo® Super Cel® and evaporated on a rotary evaporator to afford 485 mg (y.: 44.8%; 89.6% theoretical yield) of the target (*S*)-4-(acetyloxy)nonanoic acid (*S*)-**26** (*e.r.* >99/1 (*S/R*)) of high chemical purity.

Characterization of (*S*)-4-(acetyloxy)nonanoic acid (*S*)-26: ^{1}H NMR (800 MHz, $CDCl_3$) 11.0 (bs, 1H, COOH), 4.92 (dddd, *J*=8.3, 7.3, 5.5, 4.0 Hz, 1H, H-4), 2.39 (m, *J*=16.5, 8.8, 6.6 Hz, 1H, H-2), 2.38 (m, *J*=16.5, 8.8, 7.2 Hz, 1H, H-2), 2.05 (s, 3H, Ac), 1.95 (dddd *J*=14.4, 8.4, 7.1, 4.0 Hz, 1H, H-3), 1.85 (dtd, *J*=14.4, 2×8.3, 6.6 Hz, 1H, H-3), 1.58 (m, 1H, H-5), 1.51 (m, 1H, H-5), 1.32–1.26 (m, 6H, H-6,7,8), 0.89 (t, *J*=7.1 Hz, 3H, H-9). ^{13}C NMR (201 MHz, $CDCl_3$) δ 179.00 (C-1),170.89 (Ac-CO), 73.24 (C-4), 33.97 (C-5), 31.58 (C-7), 30.01 (C-2), 28.84 (C-3), 24.85 (C-6), 22.47 (C-8), 21.08 (Ac C-2), 13.94 (C-9). TLC: R_f=0.30 (eluent: petroleum ether (PE)/EtOAc/EtOH 8/1/1), R_f=0.37 (eluent: $CHCl_3$/MeOH 9/1); $[\alpha]_D^{20}$ +8.3 (c=4.0; EtOAc; *e.r.* 99/1 *S/R*); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{11}H_{20}O_4Na^+$: 239.1254; Found: 239.1250.

Characterization of the rest of the target γ-(acyloxy)carboxylic acids

(*R*)-4-(acetyloxy)pentanoic acid (*R*)-9: ^{1}H NMR (800 MHz, $CDCl_3$) δ 10.8 (bs, 1H, COOH), 4.95 (dqd, *J*=7.5 3×6.3, 5.2 Hz, 1H, H-4), 2.41 and 2.40 (m, 2H, H-2), 2.03 (s, 3H, Ac), 1.90 (m, 2H, H-3), 1.25 (d, *J*=6.3 Hz, 3H, H-5). ^{13}C NMR (201 MHz, $CDCl_3$) δ 179.0 (C-1), 170.7 (Ac C-1), 69.9 (C-4), 30.6 (C-3), 30.1 (C-2), 21.2 (Ac), 19.8 (C-5); $[\alpha]_D^{20}$ −14.0 (c 5.6; EtOAc; e.r. 91/9 *R/S*). IR (neat, cm^{-1}): 480, 808, 868, 1003, 1084, 1134, 1192, 1279, 1338, 1381, 1423, 1463, 1713, 1735, 2983, 3180. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_7H_{12}O_4Na^+$: 183.0628; Found: 183.0623.

(*R*)-4-(propionyloxy)pentanoic acid (*R*)-10: ^{1}H NMR (800 MHz, $CDCl_3$) δ 10.8 (bs, 1H, COOH), 4.95 (dqd, *J*=7.4 3×6.3, 5.3 Hz, 1H, H-4), 2.40 and 2.39 (m, 2H, H-2), 2.31 (qm, *J*=3×7.6 Hz, 2H, Pr H-2), 1.89 (m, 2H, H-3), 1.23 (d, *J*=6.3 Hz, 3H, H-5), 1.12 (t, *J*=7.6 Hz, 3H, Pr H-3). ^{13}C NMR (201 MHz, $CDCl_3$) δ 179.2 (C-1), 174.1 (Pr C-1), 69.7 (C-4), 30.6 (C-3), 30.1 (C-2), 27.8 (Pr C-2), 19.8 (C-5), 9.1 (Pr C-3). $[\alpha]_D^{20}$ −14.5 (c 6.0, EtOAc; *e.r.*=96.0/4.0 *R/S*); IR (neat, cm^{-1}): 457, 649, 808, 869, 905, 931, 1003, 1083, 1134, 1192, 1281, 1338, 1380, 1421, 1463, 1713, 1734, 2983, 3174. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_8H_{14}O_4Na^+$: 197.0784; Found: 197.0781.

(*R*)-4-(acetyloxy)hexanoic acid (*R*)-11: ^{1}H NMR (800 MHz, $CDCl_3$) δ 11.0 (bs, 1H, COOH), 4.84 (dddd, *J*=8.6, 6.9, 5.7, 3.9 Hz, 1H, H-4), 2.39 (ddd, *J*=16.5, 8.6, 6.5 Hz, 1H) and 2.38 (ddd, *J*=16.5, 8.2, 7.1 Hz, 1H), H-2, 1.93 (ddd, *J*=14.5, 8.6, 7.1 Hz, 1H) and 1.84 (ddd, *J*=14.5, 8.5, 6.5 Hz, 1H), H-3, 1.59 and 1.57 (m. 2H, H-5), 0.89 (t, *J*=7.5 Hz, 3H, H-6). ^{13}C NMR (201 MHz, $CDCl_3$) δ 179.3 (C-1), 171.03 (Ac-1), 74.33 (C-4), 30.03 (C-2), 28.27 (C-3), 26.87 (C-5), 21.06 (Ac-2), 9.48 (C-6). TLC: R_f=0.51 (eluent: PE/EtOAc/EtOH 6/4/1); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_8H_{14}O_4Na^+$: 197.0784; Found: 197.0781.

(*R*)-4-(propionyloxy)hexanoic acid (*R*)-12: ^{1}H NMR (800 MHz, $CDCl_3$) 4.87 (dddd, *J*=8.5, 6.9, 5.7, 4.0 Hz, 1H, H-4), 2.39 (m, *J*=16.5, 8.6, 6.6 Hz, 1H, H-2), 2.38 (m, *J*=16.5, 8.2, 7.1 Hz, 1H, H-2), 2.33 (q, *J*=7.6 Hz, 2H, Pr H-2), 1.95 (dddd *J*=14.4, 8.7, 7.1, 4.0 Hz, 1H, H-3), 1.86 (dtd, *J*=14.4, 2×8.4, 6.6 Hz, 1H, H-3), 1.61 (dqd, *J*=14.0, 3×7.5, 6.9 Hz, 1H, H-5), 1.59 (dqd, *J*=14.0, 3×7.5, 5.7 Hz, 1H, H-5), 1.15 (t, *J*=7.6 Hz, 3H, Pr H-3), 0.90 (t, *J*=7.5 Hz, 3H, H-6). ^{13}C NMR (201 MHz, $CDCl_3$) δ 178.71 (C-1),174.32 (Pr-CO), 74.08 (C-4), 29.98 (C-2), 28.45 (C-3), 27.75 (Pr C-2), 26.97 (C-5), 9.48 (C-6), 9.21 (Pr C-3). TLC: R_f=0.54 (eluent: PE/EtOAc/EtOH 6/4/1); $[\alpha]_D^{20}$ −5.6 (c=6.0, EtOAc; *e.r.* 86.5/13.5 *R/S*). HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_9H_{16}O_4Na^+$: 211.0941; Found: 211.0937.

(*S*)-4-(acetyloxy)heptanoic acid (*S*)-23: ^{1}H NMR (800 MHz, $CDCl_3$) δ 11.0 (bs, 1H, COOH), 4.93 (dddd, *J*=8.5, 7.5, 5.3, 3.9 Hz, 1H, H-4), 2.40 and 2.39 (m, 2H, H-2), 2.04 (s, 3H. Ac), 1.94 (dddd, *J*=14.4, 8.6, 7.1, 3.9 Hz, 1H, H-3), 1.84 (dtd, *J*=14.3, 2×8.3, 6.6 Hz, 1H, H-3), 1.58 (m, 1H, H-5), 1.48 (m, 1H, H-5), 1.33 (m, 1H, H-6), 1.32 (m, 1H, H6), 0.91 (t, *J*=7.4 Hz, 3H, H-7). ^{13}C NMR (201 MHz, $CDCl_3$) δ 179.06 (C-1), 170.90 (Ac), 72.98 (C-4), 36.14 (C-5), 30.01 (C-2), 28.87 (C-3), 21.06 (Ac), 18.47 (C-6), 13.87 (C-7). Structure of this compound was also confirmed by 1 *J* CC values from ^{13}C satellites (with 0.55% intensity from main peaks) in proton decoupled ^{13}C NMR spectrum. 1 *J* CC values in Hz from C-1 to C-7: 55.8, 35.5, 39.1, 39.1, 34.5, 34.7 Hz. In Ac 1 *J* CC=59.5 Hz. TLC: R_f=0.24 (eluent: PE/EtOAc/EtOH 4/2/0.1), R_f=0.33 ($CHCl_3$/CH_3OH 9/1); $[\alpha]_D^{20}$ +1.6 (c=10.0, EtOAc; *e.r.* 96.4/3.6 *S/R*). HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_9H_{16}O_4Na^+$: 211.0941; Found: 211.0936.

(*S*)-4-(propionyloxy)heptanoic acid (*S*)-24: ^{1}H NMR (800 MHz, $CDCl_3$) 4.94 (dddd, *J*=8.3, 7.6, 5.3, 4.0 Hz, 1H, H-4), 2.39 and 2.38 (m, 2H, H-2), 2.32 (q, *J*=7.6 Hz, 2H, Pr H-2), 1.95 (dddd *J*=14.4, 8.7, 7.1, 4.0 Hz, 1H, H-3), 1.85 (dtd, *J*=14.4, 2×8.2, 6.6 Hz, 1H, H-3), 1.59 (dddd, *J*=13.8, 9.9, 7.6, 5.5 Hz, 1H, H-5), 1.49 (dddd, *J*=13.8, 9.9, 6.1, 5.3 Hz, 1H, H-5), 1.33 and 1.32 (m, 2H, H-6), 1.14 (t, *J*=7.6 Hz, 3H, Pr H-3), 0.91 (t, *J*=7.4 Hz, 3H, H-7). ^{13}C NMR (201 MHz, $CDCl_3$) δ 179.07 (C-1),174.29 (Pr-CO), 72.72 (C-4), 36.19 (C-5), 30.01 (C-2), 28.91 (C-3), 27.74 (Pr C-2), 18.47 (C-6), 13.86 (C-7), 9.18 (Pr C-3). TLC: R_f=0.35 (eluent: $CHCl_3$/CH_3OH 9/1). $[\alpha]_D^{20}$ +1.9 (c=3.7; EtOAc; *e.r.* 91/9 *S/R*). HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{10}H_{18}O_4Na^+$: 225.1097; Found: 225.1094.

(*S*)-4-(acetyloxy)octanoic acid (*S*)-25: ^{1}H NMR (800 MHz, $CDCl_3$) δ 11.0 (bs, 1H, COOH), 4.90 (dddd, *J*=8.4. 7.4, 5.5, 3.9 Hz, 1H, H-4), 2.39 and 2.38 (m, 2H, H-2), 2.04 (s, 3H, Ac), 1.94 (dddd *J*=14.3, 8.7, 7.1, 3.9 Hz, 1H, H-3), 1.83 (m, 1H, H-3), 1.57 and 1.50 (m, 2H, H-5), 1.27 (m, 2H, H-6), 1.29 (m, 2H, H-7), 0.88 (t, *J*=7.2 Hz, 3H, H-8). ^{13}C NMR (201 MHz, $CDCl_3$) δ 179.43 (C-1), 170.99 (Ac), 73.20 (C-4), 33.66 (C-5), 30.04 (C-2), 28.74 (C-3), 27.29 (C-6), 22.46 (C-7), 21.08 (Ac), 13.91 (C-8). TLC: R_f=0.50 (eluent: PE/EtOAc/MeOH 8/4/1), R_f=0.34 (eluent: $CHCl_3$/MeOH 9/1). $[\alpha]_D^{20}$ +5.2 (c=13; EtOAc; *e.r.* 99/1 *S/R*); HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{10}H_{18}O_4Na^+$: 225.1097; Found: 225.1092.

[(1*S*,5*R*)-5-(acetyloxy)cyclopent-2-en-1-yl]acetic acid (1*S*,5*R*)-31: ^{1}H NMR (800 MHz, $CDCl_3$) δ 11.0 (bs, 1H, COOH), 5.77 (dtd *J*=6.0, 2×2.4, 2.1 Hz, 1H, H-3), 5.69 (dddd, *J*=6.0, 2.3, 2.0, 1.8 Hz, 1H, H-2), 5.45 (td, *J*=2×6.7, 3.3 Hz, 1H, H-5), 3.29 (ddddddd, *J*=8.2, 7.4, 6.7, 2.3, 2.1, 1.7, 1.5 Hz, 1H, H-1), 2.75 (ddddd, *J*=17.5, 6.7, 2.4, 2.0, 1,5 Hz, 1H, H-4), 2.57 (dd, *J*=16.5, 8.2 Hz, 1H, H-6), 2.47 (dd, *J*=16.5, 7.4 Hz, 1H, H-6), 2.36 (ddddd, *J*=17.5, 3.3, 2.4, 1.8, 1.7 Hz, 1H, H-4), 2.03 (s, 3H, Ac). ^{13}C NMR (201 MHz, $CDCl_3$) δ 178.97 (C-7), 170.77 (Ac C-1), 131.65 (C-2), 128.95 (C-3), 74.27 (C-5), 43.88 (C-1), 39.03 (C-4), 33.25 (C-6), 20.89 (Ac C-2). TLC: R_f=0.31 (eluent: petroleum ether/EtOAc/EtOH 8/1/1); R_f=0.27 (eluent: $CHCl_3$/CH_3OH 9/1); $[\alpha]_D^{20}$ +18.8 (c=1.5; EtOAc); IR (neat, cm^{-1}): 717, 849, 952, 1029, 1174, 1244, 1376, 1708, 1735, 3062, 3200. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_9H_{12}O_4Na^+$: 207.0628; Found: 207.0623.

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[(1*S*,5*R*)-5-(chloroacetyloxy)cyclopent-2-en-1-yl]acetic acid (1*S*,5*R*)-32: ^{1}H NMR (800 MHz, $CDCl_3$) δ 11.0 (bs, 1H, COOH), 5.78 (dddd, *J* = 6.0, 2.5, 2.3, 2.2 Hz, 1H, H-3), 5.69 (dddd, *J* = 6.0, 2.5, 2.0, 1.8 Hz, 1H, H-2), 5.55 (td, *J* = 2×6.6, 2.9 Hz, 1H, H-5), 4.05 and 4.03 (2d, *J* = 14.8 Hz, 2H, CH_2Cl), 3.33 (ddddddd, *J* = 8.6, 7.0, 6.6, 2.3, 2.0, 1.6, 1.5 Hz, 1H, H-1), 2.81 (ddddd *J* = 17.7, 6.6, 2.5, 2.2, 1.6 Hz, 1H, H-4), 2.61 (dd, *J* = 16.7, 8.6 Hz, 1H, H-6), 2.52 (dd, *J* = 16.7, 7.0 Hz, 1H, H-6), 2.41 (ddddd *J* = 17.7, 2.9, 2.5, 1.8, 1.5 Hz, 1H, H-4). ^{13}C NMR (201 MHz, $CDCl_3$) δ 178.93 (C-7), 166.95 (ClAc C-1), 131.47 (C-2), 128.84 (C-3), 76.32 (C-5) 44.06 (C-1), 40.85 (CH_2Cl with ^{35}Cl)), 40.84 (CH_2Cl with ^{37}Cl, 39.07 (C-4), 33.05 (C-6). TLC: R_f = 0.33 (eluent: petroleum ether/EtOAc/EtOH 8/1/1), R_f = 0.30 (eluent: $CHCl_3$/MeOH 9/1); $[\alpha]_D^{20}$ −1.2 (c = 8.0; EtOAc; *e.r.* 99.5/0.5); IR (neat, cm^{-1}): 691, 793, 855, 931, 1008, 1171, 1312, 1362, 1412, 1710, 1738, 2957, 3210. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_9H_{11}ClO_4Na^+$: 241.0238; Found: 241.0236.

All detailed synthetic protocols for the target compounds as well as for the derivatives with characterization data and with NMR spectra, GLC and HPLC chromatograms are provided in the Supporting Information.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: acylation · biocatalysis · enantiomeric γ-lactones · γ-(acyloxy)carboxylic acid · γ-hydroxycarboxylic acid sodium salt

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