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Lipase mediated sequential resolution of aromatic β-hydroxy esters using fatty acid derivatives

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ABSTRACT

The lipase-catalyzed kinetic resolution of a series of aromatic β-hydroxy esters in organic media has been investigated. Decanoic acid and its esters were successfully used as acyl donors for selective O-acylation. The regio- and enantioselective enzymatic hydrolysis of the decanoate moiety of the diesters was also investigated. The effects of water, reaction temperature, and solvent type, and also the influence of substrates structure on the catalytic behavior of potential commercially available lipases were studied. A novel procedure was developed for the efficient and highly stereoselective synthesis of both enantiomers of both novel and known target compounds.

1. Introduction

Due to their dual functionality, β-hydroxycarboxylic acids, and their esters are versatile chiral synthons in organic synthesis. Optically active β-hydroxycarboxylic acids and their derivatives bearing various aromatic moieties have been used as starting materials for the preparation of enantiopure bioactive compounds, such as vitamins, antibiotics, pheromones, and flavor compounds.[1] For their synthesis, several chiral organometallic or enzymatic procedures are available: (1) enantioselective reduction of the corresponding β-ketoesters; (2) kinetic or dynamic kinetic resolution (KR or DKR) of the racemic β-hydroxycarboxylic acids and their derivatives; (3) deracemization of β-hydroxy esters,[2] and so on.

The enzymatic kinetic resolution of various chiral substrates with fatty acids or their derivatives as acyl donors or the stereoselective enzymatic hydrolysis of long chain fatty acid esters have already been investigated,[3] but to the best of our knowledge, long chain fatty acid derivatives have not been used so far for the kinetic resolution of the herein presented aromatic β-hydroxy esters. The general, eco-friendly biocatalytic procedure presented herein could be a valuable method for the synthesis of enantiomerically pure β-hydroxy esters.

Herein we report a novel, enantioselective O-acylation of various aromatic β-hydroxy esters using fatty acid esters as acyl donors. Importantly, the long acyl chain from the forming diesters proved to be a good leaving group in the reverse reaction. Thus, the hydrolysis of the corresponding diesters proceeded with high regio- and enantioselectivity, yielding deprotection only at the β-position.

2. Results and discussion

The aim of this work was to study the enantioselective lipase-catalyzed O-acylation versus the lipase mediated selective hydrolysis to produce both enantiomeric forms of various β-hydroxy esters and their O-acylated diesters with high enantiomeric purity (Scheme 1).

2.1. Optimization of the enzymatic kinetic resolution of aromatic β-hydroxy esters

Since the enzymatic hydrolysis of β-hydroxy esters generally proceeds with only moderate stereoselectivity,[4] the kinetic resolution via enantioselective lipase-catalyzed O-acylation was first investigated.

2.2. Lipase-catalyzed kinetic resolution by O-acylation

2.2.1. Biocatalyst and solvent screening and the effect of water

To develop a general procedure for the enzymatic kinetic resolution of various aromatic β-hydroxy esters *rac*-**1a**–**m**, first the stereoselective lipase-catalyzed O-acylation of ethyl 3-hydroxy-3-phenylpropanoate *rac*-**1a** was used as the model substrate and tested under various conditions. Commercial lipases (25 mg/mL, each) were screened for the lipase mediated O-acylation of

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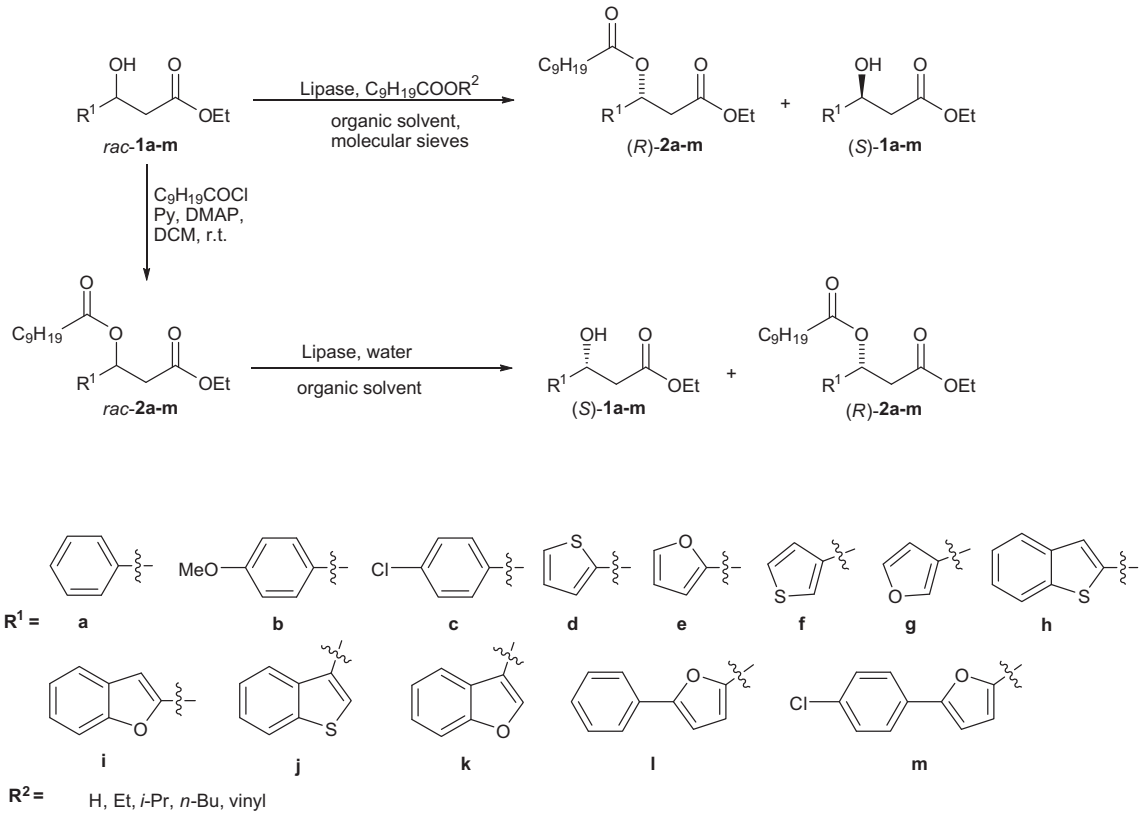


Scheme 1. Kinetic resolution of racemic β-hydroxy esters *rac*-**1a**–**m** and their diesters *rac*-**2a**–**m**.

Table 1
Lipase (25 mg/mL) and solvent (1 mL) screening for the selective O-acylation of *rac*-**1a** (0.025 M) with decanoic acid (0.1 M) at room temperature after 15 h

Entry	Lipase	Solvent	*c* (%)	$ee_{(R)\text{-}\mathbf{2a}}$ (%)	$ee_{(S)\text{-}\mathbf{1a}}$ (%)	*E*
1	CaL-A on Celite	DIPE	27.7	8.6	3.3	1.2
2	CaL-A on Celite	Toluene	21.3	12.6	3.4	1.3
3	CaL-A on Celite	*n*-Octane	19.7	12.6	3.1	1.3
4	CrL[a]-VII	DIPE	4.3	82.7	3.7	11
5	CrL[a]-VII	Toluene	6.9	85.5	6.3	13
6	CrL[a]-VII	*n*-Octane	15.8	97.9	18.4	113
7	CrL[a] (free, AYS Amano)	*n*-Octane	17.0	98.5	20.2	161
8	CrL[a] (immob., T2-150)	*n*-Octane	6.0	97.8	6.2	95

[a] *Candida rugosa* is abbreviated as CrL.

rac-**1a** (0.025 M) with decanoic acid as the acyl donor (0.1 M) in various organic solvents at room temperature. Free and immobilized forms of lipases A and B from *Candida antarctica* (CaL-A and CaL-B), lipase from *Burkholderia cepacia* (formerly *Pseudomonas cepacia*; LPS), lipase from *Pseudomonas fluorescens* (LAK), and lipase from *Candida rugosa* (CrL), were tested as suitable biocatalysts in dry organic solvents. Since even small traces of water could promote hydrolytic reactions, thus yielding undesired by-products, all of the acylation tests were performed in the presence of molecular sieves in the reaction mixture.

Lipases LAK, LPS, and CaL-B were unsatisfactory as biocatalysts for the acylation of *rac*-**1a** in all of the solvents tested; 3-hydroxy-3-phenylpropanoic acid, formed by enzymatic hydrolysis of the carboxyethyl moiety, was detected as the major product. In the control reaction (performed without adding the acyl donor), a quantitative hydrolysis of *rac*-**1a** was observed with all three lipases. Consequently, the high residual water content prohibits the use of these biocatalysts for our main purpose.

A similar control reaction indicated no significant hydrolytic activity with CaL-A and CrL, which renders these enzymes as potential biocatalysts in the stereoselective acylation of *rac*-**1a**; hence further tests were performed only with CaL-A and CrL (Table 1). Among the variations of solvents and enzymes investigated, the best results were achieved in *n*-octane with CrL (free, AYS Amano) (entry 7). Therefore, further tests were performed with this enzyme (CrL, from now on) and solvent.

2.2.2. The effect of the acyl donor

The fast regio- and enantioselective lipase-catalyzed deprotection of various O-acylated β-hydroxy esters could provide a practical and useful method to perform kinetic resolutions. To achieve this goal, an *O*-acyl moiety with a longer carbon chain is required. For this purpose various fatty acids (decanoic acid, lauric acid, and stearic acid) were tested as acyl donors. The preliminary tests indicated that CrL showed catalytic activity only when decanoic acid was used.

Since the nature of the acyl donor could significantly influence the selectivity and activity of CrL in *n*-octane, further the reactions were carried out in the presence of various decanoic acid derivatives (Table 2). With ethyl, isopropyl, and butyl ester as acyl

Table 2
The influence of decanoic acyl donors (0.1 M) upon the selectivity of CrL (25 mg/mL) for the O-acylation of *rac*-**1a** (0.1 M) in *n*-octane at room temperature after 15 h

Entry	Acyl donor	*c* (%)	$ee_{(R)\text{-}\mathbf{2a}}$ (%)	$ee_{(S)\text{-}\mathbf{1a}}$ (%)	*E*
1	Decanoic acid	17.0	98.5	20.2	161
2	Ethyl decanoate	4.0	98.6	4.1	148
3	Isopropyl decanoate	6.1	>99	6.4	>200
4	Butyl decanoate	2.0	>99	2.1	>200
5	Vinyl decanoate	44.8	97.2	78.9	170

donors, CrL showed high stereoselectivity but moderate activity (entries 2–4). When vinyl decanoate was used as the acyl donor, the enantioselectivity decreased slightly, the enzyme activity was considerably enhanced (entry 5). Accordingly, further studies were performed with vinyl decanoate as the acyl donor.

2.2.3. The temperature effect

As the performance of CrL in the acylation of *rac*-**1a** with vinyl decanoate in *n*-octane could strongly depend on the reaction temperature, the temperature effect was also studied (Table 3). While the selectivity increased at higher temperatures, a strong irreversible decrease of the CrL activity was also observed due to its thermal inactivation. Retesting the already used (at 45 °C) CrL catalyst in the same reaction resulted in an acylation with low conversion (*c* <5%). Since the heat treated CrL and the untreated enzyme presented similar enantioselectivity ($E \sim 165$ and $E = 170$ respectively), we supposed that the enhancement of selectivity at the increased temperature ($E \gg 200$) was determined not by the selective denaturation of a less selective component from the crude enzyme, but by an intrinsic feature of the enzyme. Taking both the selectivity and activity into account, the optimal reaction temperature for the acylation of *rac*-**1a** appeared to be 25 °C.

Table 3
The influence of temperature on the selectivity and activity of the CrL (25 mg/mL) mediated selective O-acylation of *rac*-**1a** (0.025 M) with vinyl decanoate (0.1 M) in *n*-octane after 15 h

Entry	*t* (°C)	*c* (%)	$ee_{(R)\text{-}\mathbf{2a}}$ (%)	$ee_{(S)\text{-}\mathbf{1a}}$ (%)	*E*
1	15	36.7	95.8	55.6	82
2	25	44.8	97.2	78.9	170
3	35	32.9	>99	48.5	>200
4	45	10.9	>99	12.2	≫200

2.2.4. The regio- and enantioselective *O*-acylation of racemic aromatic β-hydroxy esters *rac*-1a–m

In order to investigate the biocatalytic behavior of CrL in kinetic resolutions, the O-acylation of other racemic aromatic β-hydroxy esters *rac*-**1b–m** were tested under the optimal conditions previously found for *rac*-**1a** (Table 4). In almost all cases, the reaction proceeded with good selectivity and activity; however, the results were influenced considerably by the nature of the aromatic ring in the substrates *rac*-**1b–m**.

The outcome of the acylation was obviously dependent on several factors, such as the size and charge distribution of the aromatic moiety, or the linear or bent nature of the substrate. In general, the polar and smaller substituents were less beneficial in terms of both activity and selectivity (entries 2 and 6). Whereas the extension of the bulkiness in a linear direction was tolerated and beneficial (entries 1, 7, and 8), the bulky but bent substrates were less tolerated and acylated with lower rates and selectivity (entries 9 and 10). The slightly bent and polarized phenylfuran compound resulted in an acylation with moderate rate and selectivity (entry 11). By further extension of the substituent (the 5-(4-chlorophenyl)furan-2-yl moiety) an excellent substrate, *rac*-**1m**, emerged (entry 12). An additional effect that influenced the overall rate of the acylation might be the low solubility of certain substrates, which was pronounced for benzo[*b*]tiophen-3-yl-hydroxy-propanoate *rac*-**1j**.

Table 4
Selective O-acylation of different aromatic β-hydroxy esters *rac*-**1b–m** (0.025 M) with CrL (25 mg/mL) in *n*-octane with vinyl decanoate (0.1 M) at room temperature after 15 h

Entry	Substrate	*c* (%)	$ee_{(R)\text{-}\mathbf{2a}}$ (%)	$ee_{(S)\text{-}\mathbf{1a}}$ (%)	*E*
1	*rac*-**1b**	49.7	98.3	97.2	>200
2	*rac*-**1c**	22.0	98.5	27.8	174
3	*rac*-**1d**	52.0	92.1	>99	182
4	*rac*-**1e**	50.7	87.3	89.9	45
5	*rac*-**1f**	51.6	91.1	97.1	91
6	*rac*-**1g**	35.2	94.7	51.5	61
7	*rac*-**1h**	47.8	97.2	89.1	>200
8	*rac*-**1i**	41.9	>99	72.1	≫200
9	*rac*-**1j**	20.3	87.7	22.3	19
10	*rac*-**1k**	21.9	97.5	27.4	103
11	*rac*-**1l**	40.7	96.6	66.2	115
12	*rac*-**1m**	51.7	93.3	>99	»200

2.3. Lipase-catalyzed regio- and enantioselective hydrolysis

It is already known that lipases usually retain their enantiopreference in hydrolysis or alcoholysis.[5] Consequently, using the inverse reactions, the opposite enantiomeric forms of the alcohol and ester fractions should result. It was previously reported that CrL is a highly enantioselective catalyst for the hydrolysis of various types of racemic aromatic β-hydroxy-β-arylpropanoates or of their O-acylated derivatives.[6] Therefore, the catalytic performance of CrL in the selective hydrolysis of the decanoate esters *rac*-**2a–m** was also investigated.

2.3.1. Solvent screening for lipase-catalyzed regio- and enantiomer selective hydrolysis

In order to determine the optimal reaction conditions, various organic solvents were used as reaction media for the CrL mediated selective hydrolysis of racemic diester *rac*-**2a** (0.025 M). In the case of water miscible solvents (acetonitrile, THF) and of polar solvents with high water solubility (DCM) the presence of water (10 μL/mL) was not beneficial (data not shown).

The best results in terms of enzyme activity and selectivity were obtained in water-saturated nonpolar solvents (Table 5). In *n*-octane or toluene (Table 5, entries 3 and 4) higher selectivity and lower activity were detected in comparison with those obtained in ethers (Table 5, entries 1 and 2). Due to the better solubility of the substrates and the higher activity of the enzyme in DIPE, this solvent was used as the reaction medium in further experiments.

Table 5
Solvent screening for the hydrolysis of the racemic diacetate, *rac*-**2a** (0.025 M) in presence of CrL (25 mg/mL) at room temperature after 15 h

Entry	Solvent	*c* (%)	$ee_{(R)\text{-}\mathbf{1a}}$ (%)	$ee_{(S)\text{-}\mathbf{2a}}$ (%)	*E*
1	DIPE	17.2	98.8	20.5	>200
2	MTBE	16.4	98.6	19.4	171
3	Toluene	4.3	>99	4.5	≫200
4	*n*-Octane	12.8	99.1	14.6	>200

2.3.2. Selective hydrolysis of aromatic diesters *rac*-2a–m

The CrL-catalyzed hydrolysis of the following substrates *rac*-**2b–m** (Table 6) was investigated under the optimal conditions found for the selective hydrolysis of *rac*-**2a** (Table 5, entry 1). Importantly, no traces of byproducts due to the hydrolysis of the ethoxycarbonylic group were detected in any case. Only the highly hydrophobic phenyl-furan substituted diester *rac*-**2l** was hydrolyzed with higher selectivity (Table 6, entry 11) than that found

for the O-acylation of its parent alcohol *rac*-**1l** (Table 4, entry 11). In all other cases, lower selectivities were detected compared to those found for the enzymatic selective O-acylation. The substituent effects in the selective CrL-catalyzed hydrolysis were almost opposite to those obtained for the enzymatic O-acylation. Lower selectivity was obtained for the methoxylated *rac*-**2b** (Table 6, entry 1) compared to the substrates bearing the stronger electron-withdrawing chlorine (Table 6, entries 2 and 12). The results obtained for the kinetic resolution of the *O*- and *S*-containing heteroaryl diesters *rac*-**2b**–**k**, indicated that the aromatic character had the highest impact upon the enantioselectivity of the enzymatic hydrolysis (Table 6, entries 3–10).

Table 6
CrL (25 mg/mL) mediated regio- and enantioselective hydrolysis of various diesters, *rac*-**2b-m** (0,025 M) in DIPE at room temperature after 15 h

Entry	Substrate	*c* (%)	$ee_{(R)\text{-}1}$ (%)	$ee_{(S)\text{-}2}$ (%)	*E*
1	*rac*-**2b**	42.8	90.6	67.8	41
2	*rac*-**2c**	44.9	97.3	79.3	178
3	*rac*-**2d**	51.7	91.5	97.8	101
4	*rac*-**2e**	53.1	86.9	98.5	69
5	*rac*-**2f**	50.3	86.1	87.1	38
6	*rac*-**2g**	57.0	59.0	78.2	9
7	*rac*-**2h**	51.6	91.8	97.8	105
8	*rac*-**2i**	51.0	92.5	96.2	102
9	*rac*-**2j**	23.3	96	29.2	65
10	*rac*-**2k**	26.7	97.5	35.6	112
11	*rac*-**2l**	51.1	95.3	99.6	>200
12	*rac*-**2m**	44.9	95.7	77.9	108

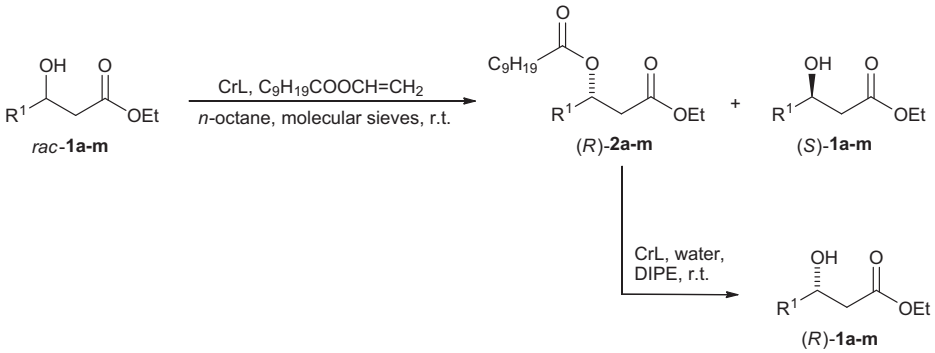
2.4. Preparative scale CrL-catalyzed reactions for the synthesis of both enantiomers of 1a–m

While a relatively high 25 mg/mL enzyme concentration was used on an analytical scale, lower enzyme concentrations (5–25 mg/mL) were first tested for synthetic purposes. The convenient enzyme concentration was found to be 10 mg/mL, offering similar reaction times and selectivity of the enzymatic acylation as those found on an analytical scale. A sequential kinetic resolution process catalyzed by CrL (Scheme 2) resulted in both enantiomers of aromatic β-hydroxy esters (*R*)- and (*S*)-**1a**–**m** with good enantiomeric excesses and yields (Table 7).

First, the selective O-acylation was performed until the conversion slightly exceeded 50%. This first kinetic resolution resulted in the residual substrate fraction (*S*)-**1a**–**m** with good yield and high enantiomeric excess. Next, the enantiomerically enriched O-acylated esters (*R*)-**2a**–**m** were subjected to the CrL mediated hydrolysis to yield the (*R*)-enantiomer of the aromatic β-hydroxy esters (*R*)-**1a**–**m** in high enantiopurity. The absolute configurations of the (*R*)- and (*S*)-**1a**–**k** were determined by comparing the sign of their specific rotations with those existing in the literature. The absolute configurations of the novel compounds (*R*)-and (*S*)-**1l**–**m** were assigned in accordance with Kazlauskas' rule.

3. Conclusion

Herein, a new general method for the lipase mediated kinetic resolution of a series of aromatic β-hydroxy esters has been reported. Using a lipase from *C. rugosa* and a long chain fatty acid



Scheme 2. Preparative scale sequential kinetic resolution of aromatic β-hydroxy esters *rac*-**1a**–**m**.

Table 7
Preparative scale synthesis of both enantiomeric forms of aromatic β-hydroxy esters (*R*)- and (*S*)-**1a-m**

Substrate	Products after acylation				Product after hydrolysis	
	(*S*)-**1a**–**m**		(*R*)-**2a**–**m**		(*R*)-**1a**–**m**	
	Yield[a] (%)	ee (%)	Yield[a] (%)	ee (%)	Yield[a] (%)	ee (%)
rac-**1a**	46	>99	49	90.0	45	>99
rac-**1b**	47	>99	49	98.1	46	>99
rac-**1c**	45	>99	48	90.6	44	>99
rac-**1d**	46	>99	49	90.3	44	>99
rac-**1e**	41	>99	45	71.9	37	>99
rac-**1f**	44	>99	48	83.2	42	>99
rac-**1g**	43	>99	47	77.5	35	81.2
rac-**1h**	49	>99	48	89.5	43	>99
rac-**1i**	48	>99	49	>99	47	>99
rac-1j	38	65.9	42	76.6	35	>99
rac-**1k**	44	>99	46	85.4	42	>99
rac-**1l**	43	>99	45	81.7	41	>99
rac-**1m**	48	>99	48	>99	47	>99

[a] Isolated yields based on the racemic starting material *rac*-**1a**–**m**.

moiety for the selective acylation and hydrolysis, good yields, and stereoselectivities were obtained in organic media under mild conditions. The enantiomeric excess of the products formed were enriched using a sequential kinetic resolution procedure, first by lipase mediated O-acylation with vinyl decanoate and second by the enzymatic hydrolysis of the enantiomerically enriched diesters. In this way, both enantiomers of the aromatic β-hydroxy esters were produced with high enantiopurity.

4. Experimental

4.1. Methods and materials

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker spectrometer operating at 300 MHz and 75 MHz, respectively, at 25 °C using tetramethylsilane (TMS) as internal standard and $CDCl_3$ as the solvent. Mass spectra were recorded on GC–MS Shimadzu QP 2010 Plus spectrometer using direct injection and EI+ ionization at 30–70 eV. The spectroscopic data for **1a** and **1d**–**k** are in accordance with the literature data.[4]

Optical rotations were determined on a Bellingham-Stanley ADP 220 polarimeter using solution with 10 mg/mL concentration and chloroform as solvent, at 25 °C. IR spectra were recorded on a FTIR BRUKER VECTOR 22 spectrometer using a GOLDEN GATE™ system (Singel Reflection Diamond ATR Series MKII). Thin Layer Chromatography (TLC) was carried out using Merck Kieselgel 60F^{254} sheets. Spots were visualized by treatment with 5% ethanolic phosphomolybdic acid solution and heating. Preparative chromatographic separations were performed using column chromatography on Merck Kieselgel 60 Å (63–200 μm).

The enantiomeric separations of **1a**–**m** and **2a**–**m** were performed by high performance liquid chromatography (HPLC) with an Agilent 1200 instrument equipped with the appropriate chiral columns (4.6 × 250 mm) at 25 °C using 1 mL/min flow rate. The enantioselectivity (E) values were calculated with the equation: $E = \ln[(1-c)(1-ee_S)]/\ln[(1-c)(1+ee_S)]$.[7]

All reagents were purchased from Merck or Sigma-Aldrich and used as received. Solvents and acyl donors for the enzymatic reactions were stored over molecular sieves unless otherwise stated. Lipases from *P. fluorescens* (L-AK), *B. cepacia* (BCL), and *C. rugosa* (CrL, free AYS Amano) were products of Amano. Immobilized CrL (immob. T2-150) was purchased from Chiral Vision. Lipase from *C. rugosa* type VII. (CrL-VII) was purchased from Sigma-Aldrich. Lipase A from *C. antarctica* (CAL-A) was the product from Roche (Chirazyme L-5, lyo), and it (5 g) was adsorbed on celite (17 g) in the presence of sucrose (3 g). Lipase B from *C. antarctica* (CAL-B, Novozym 435) was purchased from Novozymes, Denmark.

Racemic β-hydroxy esters were prepared from the corresponding aldehydes using the Reformatsky reaction and the racemic diesters were prepared by chemical acylation.[4]

4.2. Preparative scale lipase mediated kinetic resolution

4.2.1. Selective acylation of *rac*-1a–m

At first, CrL (AYS Amano, 1 g) and 4 Å molecular sieves (100 mg) were added into a solution of the substrate (*rac*-**1a**–**m**, 2.5 mmol) in *n*-octane (100 mL) and the reaction was started by the addition of vinyl decanoate (10 mmol, 1.98 g, 2.23 mL). The reaction mixture was shaken (1350 rpm) at room temperature until the conversion slightly exceeded 50%. The enzyme was removed by filtration and the reaction mixture was concentrated by vacuum distillation. The crude products were separated by column chromatography on silica gel using *n*-hexane/EtOAc (different ratio, depending on the substrate) as eluent to give the enantiomerically enriched product (*R*)-**2a**–**m** and the residual alcohol (*S*)-**1a**–**m** as a semisolid. The yield and enantiomeric excess of the products are listed in Table 7.

4.2.2. Selective hydrolysis of the enantiomerically enriched diesters (*R*)-2a–m

At first, CrL (AYS Amano, 100 mg) was added into a solution of the enantiomerically enriched diester (*R*)-**2a**–**m** (0.25 mmol) in water saturated DIPE (10 mL). The reaction mixture was shaken (1350 rpm) at room temperature until the conversion reached ~85% [based on the amount of added (*R*)-**2a**–**m**]. The enzyme was removed by filtration and the reaction mixture was concentrated in vacuo. The crude product was separated by column chromatography on silica gel using *n*-hexane/EtOAc (different ratio, depending on the substrate) as eluent to give the enantiomerically enriched (*R*)-alcohol (*R*)-**1a**–**m** as a semisolid. The yield and enantiomeric excess data for the products are listed in Table 7.

4.2.2.1. (*S*)-Ethyl 3-hydroxy-3-phenylpropanoate (*S*)-1a. Yield: 46%; clear oil; $[\alpha]_D^{25} = -43.8$ (c 1, $CHCl_3$), ee >99%; lit.[8a] $[\alpha]_D^{25} = -43.6$ (c 1, $CHCl_3$), ee 93%; tandem Chiralpak IA-IB, *n*-hexane/*i*-PrOH = 95:5, 1.0 mL/min, 218 nm, $t_R[(S)/(R)]$ = 22.4/23.1 min.

4.2.2.2. (*R*)-3-Ethoxy-3-oxo-1-phenylpropyl decanoate (*R*)-2a. Yield: 49%; clear oil; $[\alpha]_D^{25} = +22.1$ (c 1, $CHCl_3$), ee 90.0%, tandem Chiralpak IA-IB, *n*-hexane/*i*-PrOH = 95:5, 1.0 mL/min, 218 nm, $t_R[(S)/(R)]$ = 11.5/10.4 min; ^{1}H NMR: (300 MHz, $CDCl_3$) δ = 0.87 (t, J = 6.4 Hz, 3H), 1.19–1.30 (m, 15H), 1.53–1.63 (m, 2H), 2.29 (t, J = 7.5 Hz, 2H), 2.83 (ddd, J = 5.2 Hz, J = 9.0 Hz, J = 15.8 Hz, 2H), 4.12 (q, J = 7.0 Hz, 2H), 6.17 (dd, J = 5.2 Hz, J = 9.0 Hz, 1H), 7.28–7.37 (m, 5H); ^{13}C NMR: (75 MHz, $CDCl_3$): δ = 14.0, 22.6, 24.8, 28.9, 29.1, 29.3, 31.8, 34.3, 41.5, 60.6, 71.8, 126.4, 128.2, 128.5; 139.3, 169.7, 172.5; IR: ν = 3001, 2925, 2860, 2642, 1735, 1464, 1267, 1165, 1111, 755; MS (EI 30 eV) m/z: 348(M, 3), 209(51), 208(48), 206(100), 193(20), 148(20), 119(32), 96(32), 73(33), 43(32).

4.2.2.3. (*R*)-Ethyl 3-hydroxy-3-phenylpropanoate (*R*)-1a. Yield: 45%; clear oil; $[\alpha]_D^{25} = +44.1$ (c 1, $CHCl_3$), ee >99%; lit.[8b] $[\alpha]_D^{20} = +44$ (c 1.015, $CHCl_3$), ee 92%; tandem Chiralpak IA-IB, *n*-hexane/*i*-PrOH = 95:5, 1.0 mL/min, 218 nm, $t_R[(S)/(R)]$ = 22.4/23.1 min.

4.2.2.4. (*S*)-Ethyl 3-hydroxy-3-(4-methoxyphenyl)propanoate (*S*)-1b. Yield: 47%; orange solid; mp: 35–37 °C; $[\alpha]_D^{25} = -29.2$ (c 1, $CHCl_3$), ee >99%; lit.[8a] $[\alpha]_D^{26} = -28.6$ (c 1, $CHCl_3$) ee 94%; tandem Chiralpak IA-AS-H, *n*-hexane/*i*-PrOH = 90:10, 1.0 mL/min, 218 nm, $t_R[(S)/(R)]$ = 42.9/32.3 min; ^{1}H NMR: (300 MHz, $CDCl_3$): δ = 1.28 (t, J = 6.7 Hz, 3H), 2.73 (ddd, J = 3.9 Hz, J = 8.4 Hz, J = 15.9 Hz, 2H), 3.81 (s, 3H), 4.19 (q, J = 7.4 Hz, 2H), 5.10 (dd, J = 3.9 Hz, J = 8.4 Hz, 1H), 6.90 (d, J = 9 Hz, 2H), 7.31 (d, J = 8.7 Hz, 2H); ^{13}C NMR: (75 MHz, $CDCl_3$): δ = 14.1, 43.3, 52.2, 60.8, 69.9, 113.9, 126.9, 134.7, 159.1, 172.4; IR: ν = 2990, 2839, 2796, 1722, 1617, 1510, 1313, 1243, 1186, 1168, 1029, 838; MS (EI 70 eV) m/z: 225(M+1, 16), 224(M, 55), 207(48), 179(30), 150(19), 137(100), 134(68), 94(61), 77(53), 60(15).

4.2.2.5. (*R*)-3-Ethoxy-1-(4-methoxyphenyl)-3-oxopropyl decanoate (*R*)-2b. Yield: 49%; clear oil; $[\alpha]_D^{25} = +36.9$ (c 1, $CHCl_3$), 98.1% ee, tandem Chiralpak IA-AS-H, *n*-hexane/*i*-PrOH = 90:10, 1.0 mL/min, 218 nm, $t_R[(S)/(R)]$ = 13.4/11.3 min; ^{1}H NMR: (300 MHz, $CDCl_3$): δ = 0.86 (t, J = 6.7 Hz, 3H), 1.19–1.30 (m, 15H), 1.51–1.61 (m, 2H), 2.26 (t, J = 7.5 Hz, 2H), 2.83 (ddd, J = 5.2 Hz, J = 9.0 Hz, J = 15.8 Hz, 2H), 4.11 (q, J = 7.0 Hz, 2H), 6.12 (dd, J = 5.2 Hz, J = 9.0 Hz, 1H), 6.86 (d, J = 9.0 Hz, 2H), 7.29 (d, J = 8.3 Hz, 2H); ^{13}C NMR: (75 MHz, $CDCl_3$): δ = 14.0, 22.6, 24.8, 28.9, 29.1, 29.3, 31.8, 34.3, 41.3, 55.1, 60.7, 71.5, 113.7, 113.8,

127.9, 131.4, 159.4, 169.8; IR: ν = 3047, 2926, 2850, 2033, 1732, 1616, 1519, 1282, 1168, 1112, 1032, 837, 786, 730; MS (EI 40 eV) *m/z*: 378(M, 2), 224(14), 223(100), 207(27), 165(21), 150(10), 137(18), 135(66), 71(12), 43(26).

4.2.2.6. (*R*)-Ethyl 3-hydroxy-3-(4-methoxyphenyl)propanoate (*R*)-1b. Yield: 46%; orange solid; mp: 35–37 °C; $[\alpha]_D^{25} = +28.8$ (*c* 1, $CHCl_3$), ee >99%; lit.[8c] $[\alpha]_D^{25} = +25.7$ (*c* 1.4, $CHCl_3$), ee 81%; tandem Chiralpak IA-AS-H, *n*-hexane/*i*-PrOH = 90:10, 1.0 mL/min, 218 nm, $t_R[(S)/(R)]$ = 42.9/32.3 min.

4.2.2.7. (*S*)-Ethyl 3-(4-chlorophenyl)-3-hydroxypropanoate (*S*)-1c. Yield: 45%; clear yellow oil; $[\alpha]_D^{25} = -28.3$ (*c* 1, $CHCl_3$), ee >99%; lit.[8d] $[\alpha]_D^{25} = -43.7$ (*c* 1.38, $CHCl_3$), ee 99%; Chiralpak IA, *n*-hexane/*i*-PrOH = 96:4, 1.0 mL/min, 218 nm, $t_R[(S)/(R)]$ = 18.2/19.3 min; ^{1}H NMR: (300 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7 Hz, 3H), 2.71 (ddd, *J* = 4.1 Hz, *J* = 8.6 Hz, *J* = 16.4 Hz, 2H), 4.19 (q, *J* = 7.3 Hz, 2H), 5.11 (dd, *J* = 4.1 Hz, *J* = 8.6 Hz, 1H), 7.28–7.36 (m, 4H); ^{13}C NMR: (75 MHz, $CDCl_3$): δ = 14.1, 43.2, 61.0, 69.6, 127.0, 128.6, 133.4, 141.0, 172.2; IR: ν = 3343, 3298, 3180, 2982, 1725, 1495, 1270, 1196, 1021, 830, 756; MS (EI 70 eV) *m/z*: 230(M, ^{37}Cl, 4), 228(M, ^{35}Cl, 14), 156(^{37}Cl, 3), 154(^{35}Cl, 10), 143(^{37}Cl, 27), 141(^{35}Cl, 100), 115(^{37}Cl, 5), 113(^{35}Cl, 17), 88(38), 77(32), 60(20).

4.2.2.8. (*R*)-1-(4-Chlorophenyl)-3-ethoxy-3-oxopropyl decanoate (*R*)-2c. Yield: 48%; clear yellow oil; $[\alpha]_D^{25} = +30.4$ (*c* 1, $CHCl_3$), ee 90.6%, Chiralpak IA, *n*-hexane/*i*-PrOH = 96:4, 1.0 mL/min, 218 nm, $t_R[(S)/(R)]$ = 10.4/8.0 min; ^{1}H NMR: (300 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.4 Hz, 3H), 1.19–1.30 (m, 15H), 1.51–1.62 (m, 2H), 2.28 (t, *J* = 7.5 Hz, 2H), 2.83 (ddd, *J* = 5.2 Hz, *J* = 9.0 Hz, *J* = 15.4 Hz, 2H), 4.11 (q, *J* = 7.0 Hz, 2H), 6.12 (dd, *J* = 5.2 Hz, *J* = 9.0 Hz, 1H), 7.30 (s, 4H); ^{13}C NMR: (75 MHz, $CDCl_3$): δ = 14.0, 22.6, 24.8, 28.9, 29.1, 29.3, 31.8, 34.2, 41.3, 60.8, 71.2, 127.9, 128.7, 134.0, 137.9, 169.4, 172.4; IR: ν = 3031, 2667, 2498, 2393, 1910, 1734, 1268, 1018, 752, 708; MS (EI) *m/z*: 382 (M, 0.1), 212(^{37}Cl, 14), 210(^{35}Cl, 44), 172(11), 171(100).

4.2.2.9. (*R*)-Ethyl 3-(4-chlorophenyl)-3-hydroxypropanoate (*R*)-1c. Yield: 45%; clear yellow oil; $[\alpha]_D^{25} = +28.5$ (*c* 1, $CHCl_3$), ee >99%; lit.[8e] $[\alpha]_D^{25} = +41.3$ (*c* 1.5, $CHCl_3$), ee 96%; Chiralpak IA, *n*-hexane/*i*-PrOH = 96:4, 1.0 mL/min, 218 nm, $t_R[(S)/(R)]$ = 18.2/19.3 min.

4.2.2.10. (*S*)-Ethyl 3-hydroxy-3-(thiophen-2-yl)propanoate (*S*)-1d. Yield: 46%; clear yellow oil; $[\alpha]_D^{25} = -17.2$ (*c* 1, $CHCl_3$), ee >99%; lit.[4c] $[\alpha]_D^{25} = -17$ (*c* 1, $CHCl_3$), ee 99%; Chiralpak IB, *n*-hexane/*i*-PrOH = 95:5, 1.0 mL/min, 218 nm, $t_R[(S)/(R)]$ = 7.3/13.6 min.

4.2.2.11. (*R*)-3-Ethoxy-3-oxo-1-(thiophen-2-yl)propyl decanoate (*R*)-2d. Yield: 49%; clear oil; $[\alpha]_D^{25} = +45.8$ (*c* 1, $CHCl_3$), ee 90.3%, Chiralpak IB, *n*-hexane/*i*-PrOH = 95:5, 1.0 mL/min, 218 nm, $t_R[(S)/(R)]$ = 4.7/5.5 min; ^{1}H NMR: (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.4 Hz, 3H), 1.20–1.30 (m, 15H), 1.53–1.63 (m, 2H), 2.28 (t, *J* = 7.5 Hz, 2H), 2.97 (ddd, *J* = 5.2 Hz, *J* = 9.0 Hz, *J* = 15.8 Hz, 2H), 4.13 (q, *J* = 7.0 Hz, 2H), 6.48 (dd, *J* = 5.2 Hz, *J* = 9.0 Hz, 1H), 6.95–6.98 (m, 1H), 7.10 (d, *J* = 3.7 Hz, 1H), 7.28 (d, *J* = 3.7 Hz, 1H); ^{13}C NMR: (75 MHz, $CDCl_3$): δ = 14.0, 22.6, 24.8, 28.9, 29.1, 29.3, 31.8, 34.2, 41.3, 60.8, 67.0, 125.5, 126.0, 126.6, 141.9, 169.2, 172.4; IR: ν = 3070, 2990, 2929, 2864, 2695, 1737, 1460, 1287, 1180, 1153, 754, 710; MS (EI 70 eV) *m/z*: 201(6), 200(21), 199(100), 153(21), 141(7), 115(21), 111(32), 110(10), 71(8), 57(9), 43(9).

4.2.2.12. (*R*)-Ethyl 3-hydroxy-3-(thiophen-2-yl)propanoate (*R*)-1d. Yield: 44%; clear yellow oil; $[\alpha]_D^{25} = +17.4$ (*c* 1, $CHCl_3$), ee >99%; lit.[4c] $[\alpha]_D^{25} = +11$ (*c* 1, $CHCl_3$), ee 68%; Chiralpak IB, *n*-hexane/*i*-PrOH = 95:5, 1.0 mL/min, 218 nm, $t_R[(S)/(R)]$ = 7.3/13.6 min.

4.2.2.13. (*S*)-Ethyl 3-(furan-2-yl)-3-hydroxypropanoate (*S*)-1e. Yield: 41%; clear oil; $[\alpha]_D^{25} = -15.9$ (*c* 1, $CHCl_3$), ee >99%; lit.[4c] $[\alpha]_D^{25} = -16$ (*c* 1, $CHCl_3$), ee 99%; Chiralpak IA, *n*-hexane/*i*-PrOH = 95:5, 1.0 mL/min, 218 nm, $t_R[(S)/(R)]$ = 16.0/16.7 min.

4.2.2.14. (*R*)-3-Ethoxy-1-(furan-2-yl)-3-oxopropyl decanoate (*R*)-2e. Yield: 45%; clear yellow oil; $[\alpha]_D^{25} = +53.6$ (*c* 1, $CHCl_3$), 71.9% ee, Chiralpak IA, *n*-hexane/*i*-PrOH = 95:5, 1.0 mL/min, 218 nm, $t_R[(S)/(R)]$ = 5.9/6.2 min; ^{1}H NMR: (300 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.7 Hz, 3H), 1.19–1.31 (m, 15H), 1.51–1.62 (m, 2H), 2.26 (t, *J* = 7.5 Hz, 2H), 2.96 (ddd, *J* = 6.0 Hz, *J* = 9.0 Hz, *J* = 15.8 Hz, 2H), 4.11 (q, *J* = 7.3 Hz, 2H), 6.24–6.36 (m, 3H), 7.36 (s, 1H); ^{13}C NMR: (75 MHz, $CDCl_3$): δ = 14.0, 22.6, 24.8, 28.9, 29.1, 29.3, 31.7, 34.1, 37.6, 60.7, 64.5, 108.8, 110.3, 142.6, 151.2, 169.3, 172.5; IR: ν = 3082, 2927, 2860, 2367, 1738, 1457, 1371, 1243, 1161, 709; MS (EI 70 eV) *m/z*: 338(M, 0.1), 184(11), 183(100), 167(8), 137(25), 115(18), 110(8), 95(23), 57(10), 43(7).

4.2.2.15. (*R*)-Ethyl 3-(furan-2-yl)-3-hydroxypropanoate (*R*)-1e. Yield: 37%; clear oil; $[\alpha]_D^{25} = +16.0$ (*c* 1, $CHCl_3$), ee >99%; lit.[4c] $[\alpha]_D^{25} = +10$ (*c* 1, $CHCl_3$), ee 63%; Chiralpak IA, *n*-hexane/*i*-PrOH = 95:5, 1.0 mL/min, 218 nm, $t_R[(S)/(R)]$ = 16.0/16.7 min.

4.2.2.16. (*S*)-Ethyl 3-hydroxy-3-(thiophen-3-yl)propanoate (*S*)-1f. Yield: 44%; clear orange oil; $[\alpha]_D^{25} = -44.7$ (*c* 1, $CHCl_3$), ee >99%; lit.[4c] $[\alpha]_D^{25} = -44$ (*c* 1, $CHCl_3$), ee 99%; Chiralpak IB, *n*-hexane/*i*-PrOH = 90:10, 1.0 mL/min, 218 nm, $t_R[(S)/(R)]$ = 7.4/16.3 min.

4.2.2.17. (*R*)-3-Ethoxy-3-oxo-1-(thiophen-3-yl)propyl decanoate (*R*)-2f. Yield: 48%; clear yellow oil; $[\alpha]_D^{25} = +38.9$ (*c* 1, $CHCl_3$), ee 83.2%, Chiralpak IB, *n*-hexane/*i*-PrOH = 90:10, 1.0 mL/min, 218 nm, $t_R[(S)/(R)]$ = 4.9/6.0 min; ^{1}H NMR: (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.4 Hz, 3H), 1.22–1.33 (m, 15H), 1.51–1.65 (m, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 2.90 (ddd, *J* = 5.2 Hz, *J* = 8.3 Hz, *J* = 15.8 Hz, 2H), 4.14 (q, *J* = 7.3 Hz, 2H), 6.33 (dd, *J* = 5.2 Hz, *J* = 8.3 Hz, 1H), 7.08–7.11 (m, 2H), 7.28–7.32 (m, 1H); ^{13}C NMR: (75 MHz, $CDCl_3$): δ = 14.0, 22.6, 24.8, 28.9, 29.1, 29.3, 31.8, 34.3, 40.7, 60.7, 67.5, 122.8, 125.8, 126.1, 140.1, 169.6, 172.5; IR: ν = 2929, 2863, 2749, 1735, 1462, 1380, 1286, 1242, 1165, 1107, 787, 775; MS (EI 70 eV) *m/z*: 355(M+1, 15), 354(M, 0.6), 200(50), 199(38), 111(43), 97(36), 85(34), 71(48), 69(36), 57(100), 55(56), 43(78).

4.2.2.18. (*R*)-Ethyl 3-hydroxy-3-(thiophen-3-yl)propanoate (*R*)-1f. Yield: 42%; clear orange oil; $[\alpha]_D^{25} = +44.4$ (*c* 1, $CHCl_3$), ee >99%; lit.[4c] $[\alpha]_D^{25} = +21$ (*c* 1, $CHCl_3$), ee 51%; Chiralpak IB, *n*-hexane/*i*-PrOH = 90:10, 1.0 mL/min, 218 nm, $t_R[(S)/(R)]$ = 7.4/16.3 min.

4.2.2.19. (*S*)-Ethyl 3-(furan-3-yl)-3-hydroxypropanoate (*S*)-1g. Yield: 43%; clear red oil; $[\alpha]_D^{25} = -29.8$ (*c* 1, $CHCl_3$), ee >99%; lit.[4c] $[\alpha]_D^{25} = -29$ (*c* 1, $CHCl_3$), ee 97%; Chiralpak IB, *n*-hexane/*i*-PrOH = 90:10, 1.0 mL/min, 218 nm, $t_R[(S)/(R)]$ = 6.6/12.1 min.

4.2.2.20. (*R*)-3-Ethoxy-1-(furan-3-yl)-3-oxopropyl decanoate (*R*)-2g. Yield: 47%; clear yellow oil; $[\alpha]_D^{25} = +31.1$ (*c* 1, $CHCl_3$), 77.5% ee, Chiralpak IB, *n*-hexane/*i*-PrOH = 90:10, 1.0 mL/min, 218 nm, $t_R[(S)/(R)]$ = 4.3/5.1 min; ^{1}H NMR: (300 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.7 Hz, 3H), 1.20–1.31 (m, 15H), 1.52–1.64 (m, 2H), 2.26 (t, *J* = 7.5 Hz, 2H), 2.83 (ddd, *J* = 5.2 Hz, *J* = 9.0 Hz, *J* = 15.8 Hz, 2H), 4.12 (q, *J* = 7.0 Hz, 2H), 6.19 (dd, *J* = 5.2 Hz, *J* = 9.0 Hz, 1H), 6.38 (s, 1H), 7.36 (s, 1H), 7.44(s, 1H); ^{13}C NMR: (75 MHz, $CDCl_3$): δ = 14.0, 22.6, 24.8, 28.9, 29.2, 29.3, 31.8, 34.3, 40.0, 60.7, 64.4, 108.7, 123.8, 140.4, 143.3, 169.6, 172.6; IR: ν = 3113, 2971, 2928, 2851, 1734, 1460, 1287, 1167, 1023, 755, 681; MS (EI 70 eV) *m/z*: 339(M+1, 1), 338(M, 3), 184(59), 183(72), 167(14), 155(100), 125(26), 95(69), 71(64), 57(76), 43(35).

4.2.2.21. (*R*)-Ethyl 3-(furan-3-yl)-3-hydroxypropanoate (*R*)-1g. Yield: 35%; clear red oil; $[\alpha]_D^{25} = +23.7$ (*c* 1, $CHCl_3$), ee 81.2%; lit.[4c] $[\alpha]_D^{25} = +16$ (*c* 1, $CHCl_3$), ee 60%; Chiralpak IB, *n*-hexane/*i*-PrOH = 90:10, 1.0 mL/min, 218 nm, $t_R[(S)/(R)]$ = 6.6/12.1 min.

4.2.2.22. (*S*)-Ethyl 3-(benzo[*b*]thiophen-2-yl)-3-hydroxypropanoate (*S*)-1h. Yield: 49%; yellow solid; mp: 30–32 °C; $[\alpha]_D^{25} = -13.3$ (*c* 1, $CHCl_3$), ee >99%; lit.[4a] $[\alpha]_D^{25} = -13.5$ (*c* 1, $CHCl_3$), ee 99%; Chiralpak IA, *n*-hexane/*i*-PrOH = 90:10, 1.0 mL/min, 254 nm, $t_R[(S)/(R)]$ = 14.2/12.7 min.

4.2.2.23. (*R*)-1-(Benzo[*b*]thiophen-2-yl)-3-ethoxy-3-oxopropyl decano-ate (*R*)-2h. Yield: 48%; clear yellow oil; $[\alpha]_D^{25} = +50.2$ (*c* 1, $CHCl_3$), ee 89.5%, Chiralpak IA, *n*-hexane/*i*-PrOH = 90:10, 1.0 mL/min, 254 nm, $t_R[(S)/(R)]$ = 8.1/7.3 min; ^{1}H NMR: (300 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.4 Hz, 3H), 1.20–1.38 (m, 15H), 1.58–1.70 (m, 2H), 2.32 (t, *J* = 7.5 Hz, 2H), 3.02 (ddd, *J* = 5.2 Hz, *J* = 8.3 Hz, *J* = 15.8 Hz, 2H), 4.16 (q, *J* = 7.0 Hz, 2H), 6.56 (dd, *J* = 5.2 Hz, *J* = 8.3 Hz, 1H), 7.31–7.39 (m, 3H), 7.71–7.81 (m, 2H); ^{13}C NMR: (75 MHz, $CDCl_3$): δ = 14.0, 22.5, 24.8, 28.9, 29.1, 29.3, 31.7, 34.2, 41.1, 60.9, 67.7, 122.3, 122.6, 123.8, 124.3, 124.6, 138.9, 139.4, 142.5, 169.1 172.4; IR: ν = 3136, 2959, 2848, 1941, 1739, 1467, 1285, 1146, 1005, 950, 743; MS (EI 70 eV) *m/z*: 404(M, 1), 251(14), 250(77), 249(80), 203(18), 162(27), 161(100), 160(35), 115(34), 57(20), 43(22).

4.2.2.24. (*R*)-Ethyl 3-(benzo[*b*]thiophen-2-yl)-3-hydroxypropanoate (*R*)-1h. Yield: 43%; yellow solid; mp: 30–32 °C; $[\alpha]_D^{25} = +13.3$ (*c* 1, $CHCl_3$), ee;>99% lit.[4a] $[\alpha]_D^{25} = +13.5$ (*c* 1, $CHCl_3$), ee 99%; Chiralpak IA, *n*-hexane/*i*-PrOH = 90:10, 1.0 mL/min, 254 nm, $t_R[(S)/(R)]$ = 14.2/12.7 min.

4.2.2.25. (*S*)-Ethyl 3-(benzofuran-2-yl)-3-hydroxypropanoate (*S*)-1i. Yield: 48%; clear orange oil; $[\alpha]_D^{25} = -24.9$ (*c* 1, $CHCl_3$), ee >99%; lit.[4a] $[\alpha]_D^{25} = -24.3$ (*c* 1, $CHCl_3$), ee 98%; Chiralpak IA, *n*-hexane/*i*-PrOH = 90:10, 1.0 mL/min, 254 nm, $t_R[(S)/(R)]$ = 13.7/11.8 min.

4.2.2.26. (*R*)-1-(Benzofuran-2-yl)-3-ethoxy-3-oxopropyl decanoate (*R*)-2i. Yield: 49%; clear yellow oil; $[\alpha]_D^{25} = +37.6$ (*c* 1, $CHCl_3$), ee >99%, Chiralpak IC, *n*-hexane/*i*-PrOH = 90:10, 1.0 mL/min, 254 nm, $t_R[(S)/(R)]$ = 7.8/7.5 min; ^{1}H NMR: (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.7 Hz, 3H), 1.23–1.34 (m, 15H), 1.56–1.70 (m, 2H), 2.34 (t, *J* = 7.5 Hz, 2H), 3.09 (ddd, *J* = 6.0 Hz, *J* = 9.0 Hz, *J* = 15.8 Hz, 2H), 4.17 (q, *J* = 7.3 Hz, 2H), 6.44 (dd, *J* = 6.0 Hz, *J* = 9.0 Hz, 1H), 6.76 (s, 1H), 7.21–7.33 (m, 2H), 7.48 (d, *J* = 8.3 Hz, 1H), 7.56 (d, *J* = 6.7 Hz, 1H); ^{13}C NMR: (75 MHz, $CDCl_3$): δ = 14.0, 22.5, 24.7, 28.9, 29.1, 29.3, 31.7, 34.1, 37.7, 60.8, 65.0, 105.3, 111.3, 121.3, 122.8, 124.6, 127.6, 153.6, 154.7, 169.2, 172.4; IR: ν = 2926, 2848, 1745, 1684, 1504, 1461, 1267, 1148, 1035, 752; MS (EI 70 eV) *m/z*: 388(M, 1), 234(26), 233(100), 187(24), 160(20), 145(93), 144(56), 115(55), 71(22), 57(47), 43(46), 29(53).

4.2.2.27. (*R*)-Ethyl 3-(benzofuran-2-yl)-3-hydroxypropanoate (*R*)-1i. Yield: 47%; clear orange oil; $[\alpha]_D^{25} = +24.8$ (*c* 1, $CHCl_3$), ee >99%; lit.[4a] $[\alpha]_D^{25} = +24.3$ (*c* 1, $CHCl_3$), ee 98%; Chiralpak IA, *n*-hexane/*i*-PrOH = 90:10, 1.0 mL/min, 254 nm, $t_R[(S)/(R)]$ = 13.7/11.8 min.

4.2.2.28. (*S*)-Ethyl 3-(benzo[*b*]thiophen-3-yl)-3-hydroxypropanoate (*S*)-1j. Yield: 38%; clear yellow oil; $[\alpha]_D^{25} = -30.7$ (*c* 1, $CHCl_3$), ee 65.9%; lit.[4a] $[\alpha]_D^{25} = -42.5$ (*c* 1, $CHCl_3$), ee 94%; Chiralpak IA, *n*-hexane/*i*-PrOH = 96:4, 1.0 mL/min, 254 nm, $t_R[(S)/(R)]$ = 24.0/25.3 min.

4.2.2.29. (*R*)-1-(Benzo[*b*]thiophen-3-yl)-3-ethoxy-3-oxopropyl decano-ate (*R*)-2j. Yield: 42%; clear yellow oil; $[\alpha]_D^{25} = +22.1$ (*c* 1, $CHCl_3$), ee 76.6%; Chiralpak IA, *n*-hexane/*i*-PrOH = 96:4, 1.0 mL/min, 254 nm, $t_R[(S)/(R)]$ = 9.3/9.7 min; ^{1}H NMR: (300 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.7 Hz, 3H), 1.19–1.31 (m, 15H), 1.54–1.64 (m, 2H), 2.32 (t, *J* = 7.5 Hz, 2H), 3.02 (ddd, *J* = 5.2 Hz, *J* = 9.0 Hz, *J* = 15.8 Hz, 2H), 4.13 (q, *J* = 7.3 Hz, 2H), 6.62 (dd, *J* = 5.2 Hz, *J* = 9.0 Hz, 1H), 7.32–7.44 (m, 3H), 7.85 (d, *J* = 6.7 Hz, 1H), 7.94 (d, *J* = 6.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.6, 24.8, 29.0, 29.1, 29.3, 31.8, 34.2, 40.1, 60.8, 67.1, 122.2, 122.8, 124.2, 124.3, 124.5, 134.1, 136.7, 140.6, 169.6, 172.5; IR: ν = 3077, 3012, 2928, 2862, 2338, 1744, 1634, 1528, 1275, 1155, 1058, 753; MS (EI 70 eV) *m/z*: 405(M+1, 1), 404(M, 3), 251(16), 250(100), 249(32), 191(29), 163(23), 162(23), 161(80), 160(35), 135(33), 115(33), 57(38), 43(36).

4.2.2.30. (*R*)-Ethyl 3-(benzo[*b*]thiophen-3-yl)-3-hydroxypropanoate (*R*)-1j. Yield: 35%; clear yellow oil; $[\alpha]_D^{25} = +46.2$ (*c* 1, $CHCl_3$), ee >99%; lit.[4a] $[\alpha]_D^{25} = +42.3$ (*c* 1, $CHCl_3$), ee 94%; Chiralpak IA, *n*-hexane/*i*-PrOH = 96:4, 1.0 mL/min, 254 nm, $t_R[(S)/(R)]$ = 24.0/25.3 min.

4.2.2.31. (*S*)-Ethyl 3-(benzofuran-3-yl)-3-hydroxypropanoate (*S*)-1k. Yield: 44%; clear orange oil; $[\alpha]_D^{25} = -26.2$ (*c* 1, $CHCl_3$), ee >99%; lit.[4a] $[\alpha]_D^{25} = -24.5$ (*c* 1, $CHCl_3$), ee 95%; Chiralpak IA, *n*-hexane/*i*-PrOH = 90:10, 1.0 mL/min, 254 nm, $t_R[(S)/(R)]$ = 13.7/11.8 min.

4.2.2.32. (*R*)-1-(Benzofuran-3-yl)-3-ethoxy-3-oxopropyl decanoate (*R*)-2k. Yield: 46%; clear yellow oil; $[\alpha]_D^{25} = +22.9$ (*c* 1, $CHCl_3$), ee 85.4%, Chiralpak IC, *n-hexane*/*i*-PrOH = 90:10, 1.0 mL/min, 254 nm, $t_R[(S)/(R)]$ = 7.8/7.5 min; ^{1}H NMR: (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.7 Hz, 3H), 1.22–1.33 (m, 15H), 1.56–1.66 (m, 2H), 2.32 (t, *J* = 7.5 Hz, 2H), 3.06 (ddd, *J* = 5.2 Hz, *J* = 8.3 Hz, *J* = 15.8 Hz, 2H), 4.16 (q, *J* = 7.3 Hz, 2H), 6.52 (dd, *J* = 5.2 Hz, *J* = 8.3 Hz, 1H), 7.26–7.36 (m, 2H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.68 (s, 1H), 7.73 (d, *J* = 6.7 Hz, 1H); ^{13}C NMR: (75 MHz, $CDCl_3$): δ = 14.0, 22.5, 24.8, 28.9, 29.1, 29.3, 31.7, 34.2, 39.6, 60.8, 64.5, 111.7, 119.0, 120.3, 122.8, 124.6, 125.4, 142.7, 155.4, 169.5, 172.6; IR: ν = 2929, 2660, 2568, 1742, 1644, 1514, 1463, 1268, 1158, 1108, 756; MS (EI 70 eV) *m/z*: 388(M, 1), 234(32), 233(28), 188(16), 175(10), 145(27), 97(52), 57(100), 43(38).

4.2.2.33. (*R*)-Ethyl 3-(benzofuran-3-yl)-3-hydroxypropanoate (*R*)-1k. Yield: 42%; clear orange oil; $[\alpha]_D^{25} = +25.8$ (*c* 1, $CHCl_3$), ee >99%; lit.[4a] $[\alpha]_D^{25} = +24.7$ (*c* 1, $CHCl_3$), ee 95%; Chiralpak IA, *n*-hexane/*i*-PrOH = 90:10, 1.0 mL/min, 254 nm, $t_R[(S)/(R)]$ = 13.7/11.8 min.

4.2.2.34. (*S*)-Ethyl 3-hydroxy-3-(5-phenylfuran-2-yl)propanoate (*S*)-1l. Yield: 43%; clear red oil; $[\alpha]_D^{25} = -40.7$ (*c* 1, $CHCl_3$), ee >99%, Chiralpak IA, *n*-hexane/*i*-PrOH = 96:4, 1.0 mL/min, 286 nm, $t_R[(S)/(R)]$ = 26.0/30.3 min; ^{1}H NMR: (300 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.1 Hz, 3H), 2.88–3.04 (m, 2H), 3.40 (br s, 1H), 4.22 (q, *J* = 7.3 Hz, 2H), 5.20–5.24 (m, 1H), 6.39 (d, *J* = 3.7 Hz, 1H), 6.61 (d, *J* = 3.0 Hz, 1H), 7.25–7.30 (m, 1H), 7.36–7.43 (m, 2H), 7.65–7.69(m, 2H); ^{13}C NMR: (75 MHz, $CDCl_3$): δ = 14.0, 39.8, 60.9, 64.2, 105.5, 108.4, 123.6, 127.3, 128.5, 130.5, 153.5, 154.2, 171.9; IR: ν = 3131, 2987, 2394, 1727, 1557, 1405, 1285, 1201, 1025, 796; MS (EI 70 eV) *m/z*: 261(M+1, 4), 260(M, 12), 243(25), 242(24), 214(11), 196(16), 173(56), 170(43), 105(100), 57(8), 43(9).

4.2.2.35. (*R*)-3-Ethoxy-3-oxo-1-(5-phenylfuran-2-yl)propyl decanoate (*R*)-2l. Yield: 45%; clear orange oil; $[\alpha]_D^{25} = +21.1$ (*c* 1, $CHCl_3$), ee 81.7%, Chiralpak IA, *n*-hexane/*i*-PrOH = 96:4,

1.0 mL/min, 286 nm, $t_R[(S)/(R)]$ = 8.9/8.4 min; ^{1}H NMR: (300 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.7 Hz, 3H), 1.23–1.35 (m, 15H), 1.54–1.64 (m, 2H), 2.32 (t, J = 7.1 Hz, 2H), 3.07 (ddd, J = 6.0 Hz, J = 9.0 Hz, J = 15.8 Hz, 2H), 4.17 (q, J = 7.3 Hz, 2H), 6.34 (dd, J = 6.0 Hz, J = 9.0 Hz, 1H), 6.47 (d, J = 3.7 Hz, 1H), 6.60 (d, J = 3.0 Hz, 1H), 7.26–7.31 (m, 1H), 7.37–7.42 (m, 2H), 7.66–7.75 (m, 2H); ^{13}C NMR: (75 MHz, $CDCl_3$): δ = 14.0, 22.6, 24.8, 28.9, 29.2, 29.3, 31.8, 34.2, 37.7, 60.8, 64.7, 105.5, 111.0, 123.8, 124.2, 127.5, 128.6, 128.7, 130.3, 150.6, 153.9, 169.4, 172.6; IR: ν = 2927, 2860, 1750, 1737, 1650, 1560, 1539, 1509, 1154, 742; MS (EI 70 eV) m/z: 415(M+1, 1), 414(M, 10), 260(20), 259(100), 244(10), 243(50), 242(15), 171(70), 170(81), 115(45), 57(40), 43(42).

4.2.2.36. (*R*)-Ethyl 3-hydroxy-3-(5-phenylfuran-2-yl)propanoate (*R*)-1l. Yield: 41%; clear red oil; $[\alpha]_D^{25} = +40.5$ (c 1, $CHCl_3$), ee >99%, Chiralpak IA, n-hexane/i-PrOH = 96:4, 1.0 mL/min, 286 nm, $t_R[(S)/(R)]$ = 26.0/30.3 min;

4.2.2.37. (*S*)-Ethyl 3-(5-(4-chlorophenyl)furan-2-yl)-3-hydroxy-propa-noate (*S*)-1m. Yield: 48%; clear red oil; $[\alpha]_D^{25} = -35.2$ (c 1, $CHCl_3$), ee >99%, Chiralpak IC, n-hexane/i-PrOH = 90:10, 1.0 mL/min, 286 nm, $t_R[(S)/(R)]$ = 24.1/16.8 min; ^{1}H NMR: (300 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.1 Hz, 3H), 2.83–2.99 (m, 2H), 3.40(br s, 1H), 4.18 (q, J = 7.0 Hz, 2H), 5.15–5.19 (m, 1H), 6.35 (d, J = 3.7 Hz, 1H), 6.55 (d, J = 3.7 Hz, 1H), 7.31 (d, J = 9.0 Hz, 2H), 7.54 (d, J = 9.0 Hz, 2H); ^{13}C NMR: (75 MHz, $CDCl_3$): δ = 14.0, 39.7, 60.9, 64.1, 106.0, 108.5, 124.8, 128.7, 128.9, 132.9, 152.4, 154.5, 171.8; IR: ν = 3034, 2798, 2026, 1763, 1718, 1474, 1405, 1197, 1090, 1025, 752; MS (EI 70 eV) m/z: 297(M+1, ^{37}Cl, 1), 296(M, ^{37}Cl, 6), 295(M+1, ^{35}Cl, 3), 294(M, ^{35}Cl, 18), 209(^{37}Cl, 31), 207(^{35}Cl, 100), 151(^{37}Cl, 3), 149(^{35}Cl, 10).

4.2.2.38. (*R*)-1-(5-(4-Chlorophenyl)furan-2-yl)-3-ethoxy-3-oxo-propyl decanoate (*R*)-2m. Yield: 48%; clear orange oil; $[\alpha]_D^{25} = +12.0$ (c 1, $CHCl_3$), ee 99%, Chiralpak IC, n-hexane/i-PrOH = 90:10, 1.0 mL/min, 286 nm, $t_R[(S)/(R)]$ = 8.8/10.4 min; ^{1}H NMR: (300 MHz, $CDCl_3$): δ = 0.84 (t, J = 6.7 Hz, 3H), 1.19–1.31 (m, 15H), 1.51–1.61 (m, 2H), 2.28 (t, J = 6.7 Hz, 2H), 3.03 (ddd, J = 6.0 Hz, J = 9.0 Hz, J = 15.8 Hz, 2H), 4.13 (q, J = 7.0 Hz, 2H), 6.30 (dd, J = 6.0 Hz, J = 9.0 Hz, 1H), 6.43 (d, J = 3.0 Hz, 1H), 6.55 (d, J = 3.7 Hz, 1H), 7.31 (d, J = 8.3 Hz, 2H), 7.55 (d, J = 8.3 Hz, 2H); ^{13}C NMR: (75 MHz, $CDCl_3$): δ = 13.9, 22.5, 24.8, 28.9, 29.1, 29.2, 31.7, 34.1, 37.6, 60.7, 64.5, 106.0, 111.0, 124.9, 128.7, 128.8, 128.9, 133.1, 150.9, 152.7, 169.2, 172.4; IR: ν = 2917, 2866, 1741, 1475, 1284, 1241, 1159, 1102, 1016, 838, 787; MS (EI 70 eV) m/z: 450(M, ^{37}Cl, 3), 448(M, ^{35}Cl, 9), 295(^{37}Cl, 29), 293(^{35}Cl, 85), 206(^{37}Cl, 40), 204(^{35}Cl, 100), 151(^{37}Cl, 12), 149(^{35}Cl, 39), 57(60), 43(50).

4.2.2.39. (*R*)-Ethyl 3-(5-(4-chlorophenyl)furan-2-yl)-3-hydroxy-propanoate (*R*)-1m. Yield: 47%; clear red oil; $[\alpha]_D^{25} = +35.1$ (c 1, $CHCl_3$), ee >99%, Chiralpak IC, n-hexane/i-PrOH = 90:10, 1.0 mL/min, 286 nm, $t_R[(S)/(R)]$ = 24.1/16.8 min.

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