Synthesis of Optically Active α-Hydroxy Acids by Kinetic Resolution Through Lipase-Catalyzed Enantioselective Acetylation

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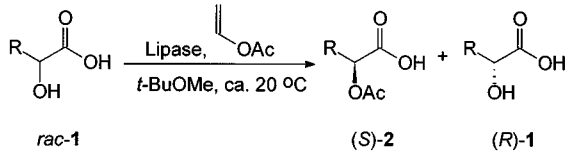
The lipase-catalyzed acetylation of a broad spectrum of racemic 2-hydroxy acids **1** to their 2-acetoxy acids **2** was shown to proceed with high enantioselectivity. Thus, the microbial lipases, in particular from *Candida antarctica* and *Burkholderia species*, are convenient biocatalysts for the synthesis of optically active 2-hydroxy acids in excellent enantioselectivity (ee values up to > 99%). The absolute configurations of the 2-hydroxy acids **1** were assigned by comparison of the gas-chromatographic data with that of literature-known reference compounds, or by means of the exciton-coupled circular dichroism method (ECCD) on their bichromophoric 2-naphthoate 9-anthrylmethyl derivatives **3**. These results establish that (*S*)-2-hydroxy acids **1** were preferentially acetylated by microbial lipases.

Introduction

Optically active 2-hydroxy acids are important building blocks for the asymmetric synthesis of glycols[1a], halo esters[1b] and epoxides[1c]. Several chemical[2] and enzymatic[3][4] methods have been reported previously on the synthesis of optically active α-hydroxy acids. The enzymatic methods employed so far for the synthesis of α-hydroxy-functionalized carboxylic acids are the enantioselective oxidation of 1,2-diols with dehydrogenases[3a], the reduction of α-oxo acids with baker's yeast[3b], the oxynitrilase-catalyzed addition of prussic acid to aldehydes[3c], the reduction of α-oxo acids with lactate dehydrogenases[3d][3e], and the kinetic resolution of methyl α-hydroperoxy esters with horseradish peroxidase[3f]. Recently, we have reported the enzymatic α-oxidation system of young pea leaves[4] as well as the glycolate oxidase from spinach (*Spinacia oleracea*)[5] as biocatalysts for the preparation of enantiomerically pure 2-hydroxy acids.

Lipases have been frequently used as convenient and efficient biocatalysts for the asymmetric synthesis of a wide range of organic compounds[6]. The greatest advantages of these enzymes are that they do not require any expensive and labile cofactors nor the sophisticated technology of recycling. Although the long-chain 2-hydroxytetracosanoic[7a] and 2-hydroxypalmitic acids[7b] as well as the aromatic mandelic[7c] and 2-hydroxy-4-phenylbutanoic acids[7d][7e] have already been resolved by the *Pseudomonas* lipase catalyzed enantioselective acetylation, these are only isolated examples which demonstrate the potential of lipases for the preparation of optically active 2-hydroxy acids. To establish the general scope and applicability of this biocatalytic method, we have undertaken the present detailed study of the kinetic resolution of a broad spectrum of 2-hydroxy acids **1** by microbial lipases through acetylation. For practical reasons (availability of the substrates), we favor this approach (Scheme 1) over the hydrolysis or transesterification of ester derivatives.[7c][7f] Furthermore, we have assigned the absolute configurations of the 2-hydroxy acids by application of the exciton-coupled circular-dichroism method (ECCD) on its bichromophoric 2-naphthoate 9-anthrylmethyl derivatives **3** to establish the preferred transformation of (*S*)-2-hydroxy acids to the corresponding acetates.

Scheme 1. Lipase-catalyzed kinetic resolution of racemic 2-hydroxy acids **1a**−**m**



rac-**1** (*S*)-**2** (*R*)-**1**

a-**e**: R = $CH_3(CH_2)_n$; **a** (n = 1), **b** (n = 2), **c** (n = 4), **d** (n = 7), **e** (n = 13);
f: R = $(CH_3)_2CH$; **g**: R = $PhCH_2$; **h**: R = $CH_3(CH_2)_9O(CH_2)_2$;
i: R = (*Z*)-$CH_3(CH_2)_4CH{=}CHCH_2$; **k**: R = (*E*)-$CH_3(CH_2)_4CH{=}CHCH_2$;
l: R = (*Z*)-$CH_3(CH_2)_7CH{=}CH(CH_2)_6$; **m**: R = (*E*)-$CH_3(CH_2)_7CH{=}CH(CH_2)_6$

Results and Discussion

First the efficiency of different lipases in catalyzing the transesterification of chiral 2-hydroxy acids was investigated. For this purpose, the racemic substrates **1a** and **1b** were taken as model substrates. For all enzymatic kinetic resolutions on the analytical scale, the racemic substrates **1a** and **1b** were treated at room temperature (ca. 20°C) with three equivalents of vinyl acetate in *tert*-butyl methyl ether in the presence of several microbial lipases. The results of the enzyme screening are summarized in Table 1, wherein

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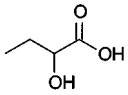
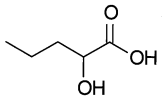
Table 1. Enzyme screening in the enantioselective acetylation of 2-hydroxy acids **1a, b**

Entry	Substrate[a]	Lipase[b]	Time [h]	Conversion[c] (%)	ee (%)[d] (*S*)-**2**	(*R*)-**1**	*E*[e]
1		BSL[f]	24	98	1	51	1.3
2		CAL[g]	24	71	2	5	1.1
3		CAL[h]	48	53	56	62	6.5
4		MML[i]	48	62	47	77	6.1
5	**1a**	PSL[j]	48	51	29	30	2.4
6		BSL[f]	24	93	5	70	1.8
7		BSL[k]	96	41	86	59	24
8		CAL[g]	96	55	80	> 99	46
9		CAL[h]	96	45	95	78	92
10		MML[i]	96	0	–	–	–
11	**1b**	PSL[j]	96	67	48	> 99	13

[a] Substrate (0.1 mmol), vinyl acetate (0.3 mmol), and lipase (10 mg) in methyl *tert*-butyl ether (MTBE). – [b] All enzymes, except PSL (Amano Pharmaceutical Co.), were obtained from Boehringer Mannheim. – [c] By GC analysis (DB-5 column; error limits ± 2%). – [d] Enantiomeric excess by multidimensional, chiral GC analysis (column 1: DB-Wax, column 2: 30% heptakis(2,3-diethyl-6-*tert*-butyldimethylsilyl)-β-cyclodextrin in PS-086; error limits ± 2%). – [e] Enantiomeric ratio (ref.[8]). – [f] Burkholderia species [CHIRAZYME® L-1; approx. 350 U/mg (100 mM tributyrin)]. – [g] Candida antarctica, fraction B [CHIRAZYME® L-2; > 120 U/mg (100 mM tributyrin)]. – [h] Candida antarctica, fraction B [CHIRAZYME® L-2, carrier-fixed; > 500 U/g (100 mM triacetin)]. – [i] Mucor miehei (CHIRAZYME® L-9, carrier-fixed). – [j] Pseudomonas species. – [k] Burkholderia species [CHIRAZYME® L-1, carrier-fixed; 10 kU/g (100 mM tributyrin)].

conversion and the enantiomeric excess of the 2-hydroxy carboxylic acids **1a** and **1b** to their acetates **2a** and **2b** were assessed by chiral gas chromatography. The results in Table 1 (entries 1−5) show that 2-hydroxybutyric acid (**1a**) is transformed by the microbial lipases to the corresponding 2-acetoxybutyric acid (**2a**) in poor enantioselectivity (*E* values 1.1−6.5). Among the lipases tested for the kinetic resolution of 2-hydroxyvaleric acid (**1b**), the lipase from *Candida antarctica* (CAL) exhibits the best results (Table 1, entry 8). Preferrentially the (*S*)-2-hydroxy acid **1b** is converted to (*S*)-2-acetoxy acid **2b** (ee value 80% at 55% conversion) and (*R*)-2-hydroxyvaleric acid (**1b**) is left behind in enantiomerically pure form (ee value 99%).

The results of the enzyme screening reveal that the short-chain 2-hydroxybutyric acid (**1a**) could not be obtained in high enantiomeric purity by the lipase-catalyzed acetylation[9]. In comparison, the lipase-catalyzed kinetic resolution of racemic 2-hydroxyvaleric acid (**1b**) and other homologs proceeds in high enantioselectivity, especially when CAL is used as biocatalyst. The reason for this substrate selectivity may be that in the case of the acid **1a** the relative space requirements for the ethyl substituent and the carboxylic functionality does not differ significantly to facilitate enantiodifferentiation by the enzyme.

The enantioselective acetylation by the CAL enzyme was applied for the kinetic resolution of 2-hydroxyvaleric acid (**1b**) and other 2-hydroxy acids **1c**−**m** on a semi-preparative scale. The results in Table 2 exhibit that the CAL enzyme is a suitable biocatalyst for the preparation of optically active, linear-chain (*R*)-2-hydroxy carboxylic acids **1b**−**d** in high

Table 2. Lipase-catalyzed kinetic resolution of racemic 2-hydroxy acids **1b**−**m**

Entry	Substrate	(mmol)	Lipase (mg)	Time [h]	Conversion[a] (%)	ee (%)[b] (*S*)-**2**	(*R*)-**1**	*E*[c]
1	**1b**	0.5	52[d]	48	55	77[e]	94[e]	26
2	**1c**	0.6	114[d]	48	54	85[e]	> 98[e]	55
3	**1d**	1.1	157[d]	48	57	73[e]	> 98[e]	28
4	**1e**	0.4	123[d]	108	24	65[f]	21[g]	5.8
5	**1e**	0.7	10[h]	3	48	98[f]	91[g]	> 200
6	**1f**	0.9	100[d]	195	51	74[e]	77[e]	15
7	**1f**	0.8	20[h]	13	55	80[e]	> 98[e]	40
8	**1g**	0.6	101[d]	408	17	nd[i]	nd[i]	–
9	**1g**	1.0	21[h]	6	48	98[e]	89[e]	> 200
10	**1h**	0.2	10[h]	2	60	43[f]	65[g]	4.7
11	**1i**	0.6	157[d]	48	60	56[e]	84[e]	9
12	**1k**	0.2	4[h]	2	53	62[e]	70[e]	8.7
13	**1l**	0.4	12[h]	2	57	75[f]	> 99[g]	34
14	**1m**	0.6	7[h]	4	55	80[f]	> 98[g]	40

[a] By GC analysis (DB-5 column); error limits ± 2%. – [b] Enantiomeric excess by GC analysis. – [c] Enantiomeric ratio (ref.[8]). – [d] CAL from *Candida antarctica*, fraction B (CHIRAZYME® L-2). – [e] Multidimensional, chiral GC analysis [column 1: DB-Wax, column 2: 30% heptakis(2,3-diethyl-6-*tert*-butyldimethylsilyl)-β-cyclodextrin in PS-086 or 30% heptakis(2,3-diacetyl-6-*tert*-butyldimethylsilyl)-β-cyclodextrin in OV 1701; error limits ± 2%]. – [f] Deacetylation and esterification with Mosher reagent (DB-5 column; error limits ± 2%). – [g] Esterification with Mosher reagent (DB-5 column; error limits ± 2%). – [h] BSL from *Burkholderia species* (CHIRAZYME® L-1). – [i] Not determined.

enantiomeric purity (ee values 94−99%; cf. Table 2, entries 1−3). In contrast, the reactivity and enantioselectivity of the long-chain 2-hydroxypalmitic acid (**1e**) with CAL has been decreased remarkably (Table 2, entry 4). However, the *Burkholderia* lipase (BSL) catalyzes the kinetic resolution of 2-hydroxypalmitic acid (**1e**) at a high conversion rate and a high degree of enantioselectivity (Table 2; entry 5).

Furthermore, 2-hydroxy-3-methylbutyric acid (**1f**) and phenyllactic acid (**1g**), with substantial steric demand proximate to the α-hydroxy functionality, may be resolved with the BSL to the (*R*)-2-hydroxy acids **1f** and **1g** and (*S*)-2-acetoxy acids **2f** and **2g** with high ee values at ca. 50% conversion (Table 2; entries 7 and 9); however, kinetic resolution could not be achieved in a reasonable time with CAL (Table 2; entries 6 and 8). In case of 4-decyloxy-2-hydroxybutyric acid (**1h**), the preference of the BSL for the (*S*)-2-hydroxy acid **1h** is remarkably decreased, so that the (*R*) enantiomer was obtained in only 65% enantiomeric excess at 60% conversion (Table 2, entry 10). The unsaturated short-chain *cis*- and *trans*-2-hydroxydec-4-enoic acids (**1i** and **1k**) and the long-chain *cis*- and *trans*-2-hydroxyoleic acids (**1l** and **1m**) may also be resolved through enantioselective acetylation with CAL and BSL (Table 2; entries 11−14). As in the case of the 2-hydroxy acid **1h,** also for the *cis*- and *trans*-2-hydroxydec-4-enoic acids (**1i** and **1k**), which possess the double bond in close proximity to the α-hydroxy functionality, a significant decrease in the selectivity of the microbial lipases CAL and BSL was observed (Table 2; entries 11 and 12). In contrast , the remote double bond in the *cis*- and *trans*-acids **1l** and **1m** does not affect the stereoselectivity of the lipase-catalyzed acetylation.

The conversions of the racemic 2-hydroxy carboxylic acids **1b**−**m** were determined by single-column GC analysis, while the enantiomeric excesses of the hydroxy acids were measured either directly by multidimensional gas chromatography (MDGC) on a polar, achiral and a chiral main column in series, or after esterification of their methyl esters with (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (Mosher reagent)[10] by GC analysis. The elution order of the optically active methyl 2-hydroxy esters **1a**−**c** and **1f**−**g** on a chiral stationary phase was ascertained by comparing the gas-chromatographic retention times with those of the authentic literature-kown reference compounds[3f][5].

The gas-chromatographic data display that the (*S*)-2-hydroxy acids **1a**−**c** and **1f**−**g** were transformed by the CAL and BSL enzymes preferentially to the (*S*)-2-acetoxy acids **2a**−**c** and **2f**−**g**. The absolute configurations of the 2-hydroxy acids **1d**−**e** and **1h**−**m** were determined by employing the exciton-coupled circular dichroism (ECCD) method[11].

Recently, we have reported[5][12] that the ECCD analysis is a convenient and reliable chiroptical method for the assignment of the absolute configuration of acyclic α-hydroxy acids. For this method, two chromophores suitable for exciton coupling are required in the substrate. After derivatization (Scheme 2) of the optically active 2-hydroxy acids **1d**−**e** and **1h**−**m** to the corresponding 9′-anthrylmethyl (*R*)-2-(2′′-naphthoyl) esters **3**, the CD and UV[13] spectra of the diesters **3** were recorded. Representative CD and UV spectra are depicted in Figure 1. In the bichromophoric derivatives **3,** the quite intense long-axis ^1B_b transition of the 9-anthryl chromophore couples with the ^1B_b band of the 2-naphthoate chromophore to give a split CD curve with extrema at 254 and 237 nm. The CD data of the diesters **3d**−**e** and **3h**−**m** are presented in Table 3. The positive CD couplet of the diesters **3d**−**e**, **3h** and **3k**−**m** shows that the electric transition dipoles (^1B_b) of the 9-anthryl and the 2-naphthoate chromophore possess a positive chirality, which suggests the (*R*) configuration (Table 3; entries 1−3 and 5−7). After deacetylation of the optically active 2-acetoxy acid **2i** to the corresponding 2-hydroxy acid **1i**[15] and its derivatization to the bichromophoric diester **3i**, a negative CD effect was observed. Thus, the 2-acetoxy acid **2i** that resulted from the lipase-catalyzed kinetic resolution of the racemic *cis*-2-hydroxydec-4-enoic acid (**1i**) is (*S*)-configured.

Scheme 2. Functionalization of the 2-hydroxy acids **1** to the corresponding bichromophoric diester **3**

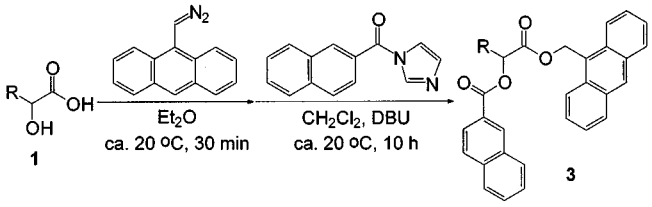
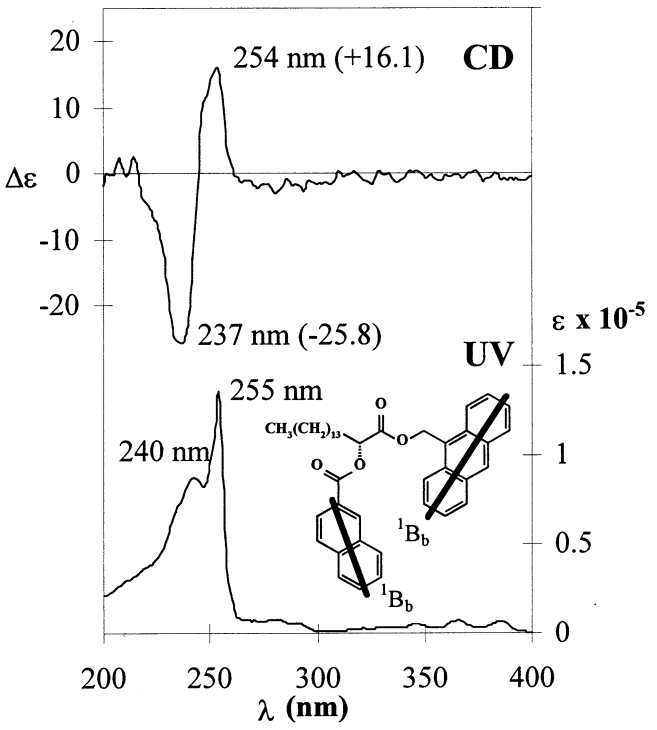


Figure 1. CD and UV spectra of the bichromophoric diester (*R*)-**3e** in acetonitrile (1-cm cell); the bold lines represent the direction of the transition dipoles



The ECCD experiments demonstrate clearly that the employed lipases for the kinetic resolution of the 2-hydroxy

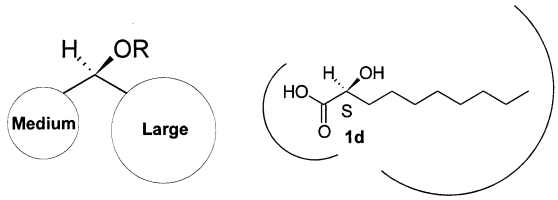
Table 3. CD[a] data, Cotton effects and absolute configurations of the bichromophoric diesters **3**

Entry	Diester **3**	ee (%)	Cotton effects[b] λ_{max} [nm]	1st Δε	λ_{max} [nm]	2nd Δε	*A*	Configuration[c]
1	**3d**[d]	> 99	254	+13.5	237	−16.8	+30.3	(*R*)
2	**3e**[e]	91	254	+16.1	237	−25.8	+41.9	(*R*)
3	**3h**[e]	65	254	+20.0	237	−20.5	+40.5	(*R*)
4	**3i**[f]	56	254	−16.5	237	+12.6	−29.1	(*S*)
5	**3k**[e]	70	254	+16.8	237	−19.6	+36.4	(*R*)
6	**3l**[e]	> 99	254	+18.8	237	−27.3	+46.1	(*R*)
7	**3m**[e]	> 98	254	+23.7	237	−18.2	+41.9	(*R*)

[a] Acetonitrile, JASCO J-600 spectropolarimeter. − [b] Concentrations were determined from the UV extinction coefficients, methylanthryl chromophore: $\varepsilon_{255} = 140000\ M^{-1}\ cm^{-1}$, naphthoate chromophore: $\varepsilon_{240} = 54000\ M^{-1}\ cm^{-1}$. − [c] Absolute configurations (*R*)-[CD(+)254] and (*S*)-[CD(−)254] from CD data (ref.[14]). − [d] Resolution with glycolate oxidase (ref.[5]). − [e] Resolution with lipase. − [f] Deacetylated 2-acetoxy acid **2i** from the kinetic resolution with lipase.

acids **1d−e** and **1h−m** transform enantioselectively the (*S*)-2-hydroxy acid **1** to the corresponding (*S*)-2-acetoxy acid **2**. This is in accord with the empirical rules established in lipase catalysis for acyclic substrates, in which the configuration is predicted on the basis of the relative size of the substituent (Figure 2)[16].

Figure 2. Preferred enantiomer in the lipase-catalyzed transesterification of the representative 2-hydroxy acid **1d**



In summary, our results show that microbial lipases, in particular lipases from *Candida antarctica* and *Burkholderia species*, are efficient and convenient biocatalysts for the synthesis of optically active 2-hydroxy acids through enantioselective acetylation. The saturated 2-hydroxy acids **1b−f**, the unsaturated derivatives **1l−m**, and the aromatic 2-hydroxy acid **1g** may be resolved to afford the (*R*)-2-hydroxy acids and the corresponding (*S*)-2-acetoxy acids in high enantiomeric excess (up to > 99%). However, the 2-hydroxy acids **1h−k** with a hetero atom or a double bond in the close proximity to the α-hydroxy functionality decrease significantly the enantioselectivity of the microbial lipases. The assignment of the absolute configuration of the 2-hydroxy acids by gas-chromatographic and ECCD analysis confirms the high preference of the microbial lipases for the (*S*) enantiomer.

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Experimental Section

General Remarks: All enzymes, except PSL (Amano Pharmaceutical Co.), were obtained as gift samples from Boehringer Mannheim and used without further purification. All commercial chemicals were of analytical-grade quality. All solvents were of high purity at purchase and were redistilled before use. The racemic 2-hydroxy acids **1a−b** and **1e−g** were purchased from Fluka and Sigma. The racemic 2-hydroxy acid **1c−d** and **1i−k** were prepared by the earlier reported procedure[5]. − UV/Vis: Shimadzu UV 2101 PC. − CD: JASCO J-600. − NMR: Bruker AC 250 (250 MHz and 63 MHz, for ^1H and ^{13}C, respectively). For ^1H and ^{13}C NMR, $CDCl_3$ as solvent, TMS as internal standard.

Capillary Gas Chromatography (HRGC): Fisons 8160 and Varian 3400F gas chromatographs with FID were used. Split injection (1:20) was employed. The Fisons 8160 gas chromatograph was equipped with a J & W fused silica DB-Wax capillary column (30 m × 0.25 mm, d_f = 0.25 μm). Helium was used as carrier gas (2.0 ml/min). The temperature program was 3 min isothermal at 50°C and then increased from 50 to 240°C at 4°C/min. The Varian 3400F gas chromatograph was equipped with a J & W fused silica DB-5 capillary column (30 m × 0.25 mm, d_f = 0.25 μm). Helium was used as carrier gas (2.0 ml/min). The temperature program was increased from 60 to 280°C at 5°C/min.

Multidimensional Gas Chromatography (MDGC) with Moving Column-Stream Switching (MCSS): A Fisons Instrument GC 8000 series MDGC system with two gas chromatographs was used. Split injection (1:10) and FIDs on oven 1 and 2 were employed. Preseparation was achieved in the oven 1 on a J & W DB-Wax fused silica capillary column (30 m × 0.25 mm, d_f = 0.25 μm). In oven 2, a chiral MEGA capillary column was connected to the precolumn in oven 1 by a moving column-stream switching system. Helium was used as carrier gas (1.9 ml/min).

General Procedure for the Preparation of Racemic 2-Hydroxy Acids **1h**, **l**, **m** *by Direct Oxidation of Enolates with Molecular Oxygen*[17]: In a typical reaction, anhydrous THF (50 ml) and lithium diisopropylamide (2.2 equiv.) was added to a dry flask flushed with nitrogen gas and cooled to 0°C. The particular acid (0.7−10 mmol), contained in 5 ml of THF was added, followed by HMPA (1 equiv.), while the temperature was maintained at 0°C for 30 min. Dianion formation was completed by warming the solution up to room temp. (ca. 20°C) for 3 h. The solution was oxygenated by direct passage of a vivid stream of oxygen gas at 0°C for 30 min. The reaction mixture was acidified with 6 N hydrochloric acid, extracted with diethyl ether (3 × 50 ml), and the combined organic layers were dried with Na_2SO_4. The solvent was removed (20°C, 17 Torr), the crude product mixture was submitted to chromatography [silica gel, 0.032−0.062 mesh, petroleum ether/ethyl acetate/acetic acid (70:30:1) as eluent].

4-Decyloxy-2-hydroxybutyric Acid (**1h**) was obtained in 42% yield (81 mg, 0.3 mmol). – ^{1}H NMR ($CDCl_3$): δ = 0.87 (t, *J* = 6.4, 7 Hz, 3 H, CH_3), 1.25–1.35 (m, 14 H, CH_2), 1.55 (m, 2 H, CH_2), 2.0 (m, 1 H, CH_2), 2.18 (m, 1 H, CH_2), 3.47 (t, *J* = 6.7 Hz, 2 H, CH_2), 3.68 (t, *J* = 6 Hz, 2 H, CH_2), 4.36 (dd, *J* = 6.7 Hz, 1 H, CH), 6.22 (br. s, 1 H, OH). – ^{13}C NMR ($CDCl_3$): δ = 14.5 (q), 23.1 (t), 26.1 (t), 26.4 (t), 29.3 (t), 29.7 (t), 29.8 (t), 29.9 (t), 32.3 (t), 33.3 (t), 68.7 (t), 70.5 (d), 72. 2 (t), 177.0 (s). – $C_{14}H_{28}O_4$ (260.4): calcd. C 64.58, H 10.84; found C 64.32, H, 10.66.

cis-2-Hydroxyoctadec-9-enoic Acid (**1l**) was obtained in 17% yield (507 mg, 1.7 mmol). – ^{1}H NMR ($CDCl_3$): δ = 0.89 (t, *J* = 6.4, 6.7 Hz, 3 H, CH_3), 1.25–1.35 (m, 18 H, CH_2), 1.45 (m, 2 H, CH_2), 1.68 (m, 1 H, CH_2), 1.83 (m, 1 H, CH_2), 2.0 (m, 4 H, CH_2), 4.22 (dd, *J* = 7.3 Hz, 1 H, CH), 5.34 (dt, *J* = 11, 7.3 Hz, 2 H, CH). – ^{13}C NMR ($CDCl_3$): δ = 14.2 (q), 22.7 (t), 24.8 (t), 26.9 (t), 27.2 (t), 27.3 (t), 29.1 (t), 29.2 (t) 29.4 (t), 29.6 (t), 29.7 (t), 29.8 (t), 31.9 (t), 34.2 (t), 70.3 (d), 129.7 (d), 130. 1 (d), 180.4 (s). – $C_{18}H_{34}O_3$ (298.5): calcd. C 72.44, H 11.48; found C 72.34, H 11.20.

trans-2-Hydroxyoctadec-9-enoic Acid (**1m**) was obtained in 67% yield (700 mg, 2.3 mmol). – ^{1}H NMR ($CDCl_3$): δ = 0.90 (t, *J* = 6.4, 6.7 Hz, 3 H, CH_3), 1.25–1.35 (m, 18 H, CH_2), 1.45 (m, 2 H, CH_2), 1.70 (m, 1 H, CH_2), 1.85 (m, 1 H, CH_2), 1.95 (m, 4 H, CH_2), 4.27 (dd, *J* = 7.3 Hz, 1 H, CH), 5.38 (dt, *J* = 15.3, 6.7 Hz, 2 H, CH). – ^{13}C NMR ($CDCl_3$): δ = 14.5 (q), 23.1 (t), 25.1 (t), 29.3 (t), 29.5 (t), 29.6 (t), 29.7 (t), 29.9 (t) 29.9 (t), 30.1 (t), 32.3 (t), 32.9 (t), 33.0 (t), 34.6 (t), 70.6 (d), 130.5 (d), 131. 0 (d), 179.9 (s). – $C_{18}H_{34}O_3$ (298.5): calcd. C 72.44, H 11.48; found C 72.28, H 11.65.

General Procedure for the Lipase-Catalyzed Irreversible Transesterification: Vinyl acetate (3 equiv.) and lipase powder (cf. Table 2) were added to a solution of the racemic 2-hydroxy acid **1** (cf. Table 2) in *tert*-butyl methyl ether (10 ml/0.1 mmol of the 2-hydroxy acid **1**). The mixture was vigorously stirred at room temperature (ca. 20°C) and after the appropriate time, the enzyme was removed by filtration and the solvent evaporated under reduced pressure (20°C, 17 Torr). Silica gel chromatography afforded the optically active alcohol and acetate in good yields (76–91% based on substrate conversion).

General Procedure for the Functionalization of the (R)-2-Hydroxy Acids **1d–e** *and* **1h–m** *to Their Bichromophoric Derivatives* **3d–e** *and* **3h–m**[12]: To a solution of hydroxy acid **1** (0.04–0.09 mmol) in dry diethyl ether (2.5 ml) was added dropwise a solution of 9-anthryldiazomethane (1.2 equiv.) in dry diethyl ether (2.5 ml). The reaction mixture was stirred at room temp. (ca. 20°C) for 30 min, concentrated (20°C, 17 Torr), and the product purified by preparative TLC (silica gel 60 F_{254}, 2 mm, E. Merck), with a 7:3 petroleum ether/diethyl ether mixture as eluent, yield 80–90%. The 9-anthrylmethyl ester was then treated with 2-naphthoylimidazole (1.2 equiv.) and a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane (1 ml) at room temp. (ca. 20°C) for 10 h. The reaction mixture was concentrated (20°C, 17 Torr) and purified by preparative TLC, as described above, with a 7:3 diethyl ether/pentane mixture as eluent, to afford **3d–e** and **3h–m** in 70–80% yield.

(*R*)-**3d**: ^{1}H NMR ($CDCl_3$): δ = 0.85 (t, *J* = 6.7, 7 Hz, 3 H, CH_3), 1.15–1.45 (m, 12 H, CH_2), 1.90 (m, 2 H, CH_2), 5.32 (dd, *J* = 7 Hz, 1 H, CH), 6.25 (dd, *J* = 49.1, 24.1 Hz, 2 H, CH_2), 7.53 (m, 6 H, Ar), 7.88 (m, 3 H, Ar), 8.04 (m, 3 H, Ar), 8.33 (d, *J* = 8.4 Hz, 2 H, Ar), 8.51 (s, 1 H, Ar), 8.59 (s, 1 H, Ar). – UV (CH_3CN): λ_{max} (lg ε) = 254 nm (5.15), 242 (4.98). – CD (CH_3CN): λ_{ext} (Δε) = 254 nm (+13.5), 237 (–16.8).

(*R*)-**3e**: ^{1}H NMR ($CDCl_3$): δ = 0.88 (t, *J* = 6.1, 7.0 Hz, 3 H, CH_3), 1.10–1.30 (m, 24 H, CH_2), 1.95 (m, 2 H, CH_2), 5.32 (dd, *J* = 6.4 Hz, 1 H, CH), 6.25 (dd, *J* = 48.2, 23.2 Hz, 2 H, CH_2), 7.52 (m, 6 H, Ar), 7.88 (m, 3 H, Ar), 8.05 (m, 3 H, Ar), 8.36 (d, *J* = 8.9 Hz, 2 H, Ar), 8.50 (s, 1 H, Ar), 8.59 (s, 1 H, Ar). – UV (CH_3CN): λ_{max} (lg ε) = 254 nm (5.15), 242 (4.96). – CD (CH_3CN): λ_{ext} (Δε) = 254 nm (+16.1), 237 (–25.8).

(*R*)-**3h**: ^{1}H NMR ($CDCl_3$): δ = 0.89 (t, *J* = 6.7, 3 H, CH_3), 1.10–1.20 (m, 14 H, CH_2), 1.45 (m, 2 H, CH_2), 2.14 (q, *J* = 6.1, 6.4 Hz, 2 H, CH_2), 3.24 (td, *J* = 6.7, 7.0, 1.2 Hz, 2 H, CH_2), 3.53 (m, 2 H, CH_2), 5.47 (t, *J* = 6.1, 6.4 Hz, 1 H, CH), 6.25 (dd, *J* = 32.7, 7.9 Hz, 2 H, CH_2), 7.52 (m, 6 H, Ar), 7.88 (m, 3 H, Ar), 8.05 (m, 3 H, Ar), 8.35 (d, *J* = 8.6 Hz, 2 H, Ar), 8.51 (s, 1 H, Ar), 8.60 (s, 1 H, Ar). – UV (CH_3CN): λ_{max} (lg ε) = 254 nm (5.15), 242 (5.0). – CD (CH_3CN): λ_{ext} (Δε) = 254 nm (+20.0), 237 (–20.5).

(*S*)-**3i**: ^{1}H NMR ($CDCl_3$): δ = 0.82 (t, *J* = 6.7, 7.0 Hz, 3 H, CH_3), 1.14–1.30 (m, 6 H, CH_2), 1.89 (m, 2 H, CH_2), 2.70 (t, *J* = 6.7, 6.4 Hz, 2 H, CH_2), 5.33 (t, *J* = 7.0 Hz, 1 H, CH), 5.37 (dt, *J* = 10, 7 Hz, 2 H, CH), 6.26 (dd, *J* = 38.2, 13.1 Hz, 2 H, CH_2), 7.52 (m, 6 H, Ar), 7.88 (m, 3 H, Ar), 8.04 (m, 3 H, Ar), 8.33 (d, *J* = 8.2 Hz, 2 H, Ar), 8.52 (s, 1 H, Ar), 8.58 (s, 1 H, Ar). – UV (CH_3CN): λ_{max} (lg ε) = 254 nm (5.15), 242 (4.96). – CD (CH_3CN): λ_{ext} (Δε) = 254 nm (–16.5), 237 (+12.6).

(*R*)-**3k**: ^{1}H NMR ($CDCl_3$): δ = 0.81 (t, *J* = 6.7, 7.0 Hz, 3 H, CH_3), 1.12–1.33 (m, 6 H, CH_2), 1.78 (m, 2 H, CH_2), 2.65 (t, *J* = 5.3, 2 H, CH_2), 5.34 (dt, *J* = 15, 7 Hz, 2 H, CH), 5.37 (t, *J* = 7.0 Hz, 1 H, CH), 6.25 (dd, *J* = 48.5, 23.5 Hz, 2 H, CH_2), 7.52 (m, 6 H, Ar), 7.88 (m, 3 H, Ar), 8.03 (m, 3 H, Ar), 8.33 (d, *J* = 8.8 Hz, 2 H, Ar), 8.51 (s, 1 H, Ar), 8.59 (s, 1 H, Ar). – UV (CH_3CN): λ_{max} (lg ε) = 254 nm (5.15), 242 (4.96). – CD (CH_3CN): λ_{ext} (Δε) = 254 nm (+16.8), 237 (–19.6).

(*R*)-**3l**: ^{1}H NMR ($CDCl_3$): δ = 0.86 (t, *J* = 6.4, 6.7, 3 H, CH_3), 1.10–1.38 (m, 20 H, CH_2), 1.88–2.05 (m, 6 H, CH_2), 5.32 (dt, *J* = 11, 6.3 Hz, 2 H, CH), 5.32 (dd, *J* = 7.3, 1 H, CH), 6.26 (dd, *J* = 49.4, 24.4 Hz, 2 H, CH_2), 7.52 (m, 6 H, Ar), 7.88 (m, 3 H, Ar), 8.05 (m, 3 H, Ar), 8.35 (d, *J* = 7.9 Hz, 2 H, Ar), 8.51 (s, 1 H, Ar), 8.58 (s, 1 H, Ar). – UV (CH_3CN): λ_{max} (lg ε) = 254 nm (5.15), 242 (4.96). – CD (CH_3CN): λ_{ext} (Δε) = 254 nm (+18.8), 237 (–27.3).

(*R*)-**3m**: ^{1}H NMR ($CDCl_3$): δ = 0.86 (t, *J* = 6.4, 6.7, 3 H, CH_3), 1.10–1.42 (m, 20 H, CH_2), 1.83–1.98 (m, 6 H, CH_2), 5.32 (dt, *J* = 15, 6.3 Hz, 2 H, CH), 5.33 (dd, *J* = 6.1, 1 H, CH), 6.26 (dd, *J* = 49.4, 24.4 Hz, 2 H, CH_2), 7.52 (m, 6 H, Ar), 7.88 (m, 3 H, Ar), 8.05 (m, 3 H, Ar), 8.35 (d, *J* = 7.9 Hz, 2 H, Ar), 8.51 (s, 1 H, Ar), 8.58 (s, 1 H, Ar). – UV (CH_3CN): λ_{max} (lg ε) = 254 nm (5.15), 242 (4.95). – CD (CH_3CN): λ_{ext} (Δε) = 254 nm (+23.7), 237 (–18.2).

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