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Application of pig liver esterase catalyzed transesterification in organic media to the kinetic resolution of glycerol derivatives

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Abstract

The PLE/MPEG catalyzed transesterification of the glycerol ketals *rac*-**1a** and *rac*-**1d–f** with vinyl propionate in toluene proceeded with good selectivities (E=24–34) and gave the enantiomerically enriched *S*-alcohols **1a** and **1d–f**, and the *S*-esters **2a** and **2d–f**. High selectivities (E=99 and E≥200) were observed in the transesterification of the glycerol ether *rac*-**3** and its desoxy analog *rac*-**5**, both having a secondary hydroxy group, with PLE/MPEG. In transesterifications in organic media PLE exhibited a much higher enantioselectivity than in hydrolysis in water.

1. Introduction

Pig liver esterase (PLE) is one of the most valuable catalysts for the enantioselective hydrolysis of esters in aqueous solution.[1–4] However, unlike lipases PLE exhibits only very low activity in organic media, which renders its application as such to the enantioselective acylation of alcohols practically impossible. Initial attempts to convey activity to PLE in organic media by entrapment in water-filled porous supports[5,6] or by the covalent attachment of hydrated methoxypolyethylene glycol (MPEG) residues[7] were less successful. We have found recently that this problem can be overcome, at least in part, by simply using a colyophilisate of PLE and MPEG (termed as PLE/MPEG) in toluene of a low water content.[8] We now describe the application of the PLE/MPEG catalyzed transesterification in organic media to the kinetic resolution of glycerol ketals. Enantiomerically enriched glycerol ketals are important starting materials for the synthesis of biologically active compounds.[9–12] Resolution of 1,2-ketals of glycerol is synthetically especially attractive because of the possibility of a complete conversion of the racemate to a given enantiomer via an acid catalyzed racemization of the unwanted enantiomer.

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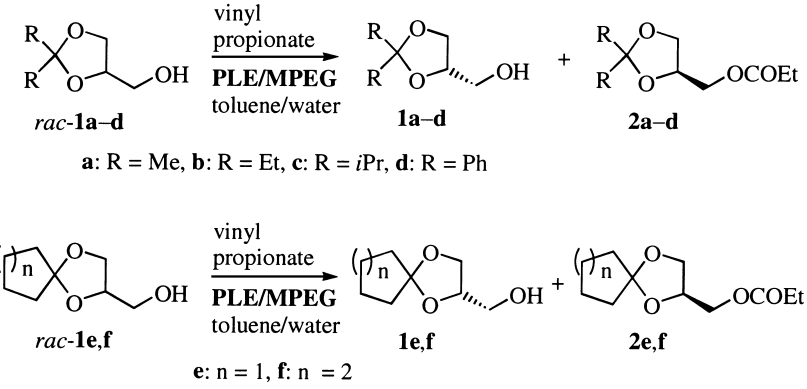
Previously, the kinetic resolution of glycerol ketals and esters of glycerol ketals had been accomplished with various degrees of success when mainly lipases were used.[13–38]

2. Results and discussion

The racemic glycerol ketals *rac*-**1a–f**[39–44] (Scheme 1) were selected for the present study because of the possibility of a structure-based optimization of the enantioselectivity of the PLE/MPE catalyzed transesterification.[1–3] PLE/MPEG containing 0.8% water was prepared by colyophilization of desalted PLE (30 mg, 160 U/mg) with MPEG (MW 5000, 1 g). The PLE/MPEG catalyzed acylations of *rac*-**1a–f** were run on a 4–21 mmol scale by using 2900–6300 U of PLE, 3.6–5.0 equiv. of vinyl propionate as the acyl donor and toluene as the solvent. The reaction mixtures consisted in most cases of two phases. The progress of the reactions and the selectivities were determined by GC on achiral and chiral stationary phases or by HPLC on a chiral stationary phase directly from samples of the reaction mixtures without prior[27] derivatization.



Scheme 1.

All ketals were substrates for PLE under the conditions employed (Table 1). Preparatively useful enantioselectivities, as expressed in enantiomeric ratios (E),[45,46] were observed in the case of the dimethyl, diphenyl, cyclopentylidene and cyclohexylidene derivatives *rac*-**1a**, *rac*-**1d**, *rac*-**1e** and *rac*-**1f**, respectively. In all the cases investigated the *R*-enantiomer of the racemic glycerol ketals reacted faster.[47] The selectivities of the PLE/MPEG catalyzed transesterification of *rac*-**1a** and *rac*-**1d–f** are generally higher than those recorded with lipases (cf. Table 1).

We had previously observed that in PLE/MPEG catalyzed transesterification of racemic alcohols in toluene the activity of the enzyme and the enantioselectivity were crucially dependent on the water content of the reaction mixture.[8] While the maximum of the selectivity was reached with an initial water content of 1%, the maximum of the activity was attained with an initial water content of 0.2%. In the case of the transesterification of *rac*-**1a–f** the reaction mixtures initially contained 0.4% water. A study of the resolution of *rac*-**1f** in toluene in the presence of varying amounts of water revealed similar dependencies of the enantioselectivity and the activity on the initial water content (Table 2). The highest E value was recorded with an initial water content of 1%. Changing the acyl donor from vinyl propionate to isopropenyl propionate in the transesterification of *rac*-**1f** did not alter the selectivity but led to a decrease of the activity of PLE.

Finally, the influence of the solvent upon the activity and the selectivity of PLE in the transesterification of *rac*-**1f** was studied (Table 3). The results obtained show that the activity and selectivity of PLE in

Table 1
PLE/MPEG catalyzed acylation of the glycerol derivatives *rac*-**1a–f** with vinyl propionate in toluene (initial water content: 0.4%)[a]

Substrate	t (d)	convn (%)	alcohol			ester			E[b]
			ee (%)	y (%)	confn	ee (%)	y (%)	confn	
rac-**1a**	5	58	92	31	*S*	77	45	*S*	24 (13-27[c])
rac-**1b**	6	35	41	50	*S*	75	31	*S*	10 (6[d])
rac-**1c**	5	7	3	80	*S*	30	7	*S*	2 (23[d])
rac-**1d**	4	20	35	71	*S*	91	18	*S*	29 (8[d])
rac-**1e**	12	39	43	52	*S*	88	31	*S*	24 (6[e])
rac-**1f**	5	36	51	53	*S*	89	30	*S*	28 (7[e])
1f[f]	12	28	91	65	*S*	45	24	*S*	-

[a] Yields (y) are based on *rac*-**1a–f**. [b] Values in parenthesis refer to the highest enantiomer selectivities recorded in the transesterification of this substrates by using lipases. [c] See ref 31-33. [d] See ref 16. [e] See ref 32. [f] 51% ee.

Table 2
PLE/MPEG catalyzed transesterification of *rac*-**1f** in toluene in the presence of varying amounts of water and additives

acyl donor	water[a] (%)	additive	t (h)	convn (%)	alcohol ee (%)	ester ee (%)	E
vinyl propionate	≤0.1	-	24	18	11	49	3
vinyl propionate	0.4	-	48	31	41	90	28
vinyl propionate	1.0	-	48	28	36	91	30
vinyl propionate	0.4	Me_2CO[b]	48	11	11	89	20
vinyl propionate	0.4	MeCHO[c]	>100	0	0	-	-
isopropenyl prop.	0.4	-	48	16	18	93	34

[a] Initial water content. [b] 8 equiv. [c] 9 equiv.

transesterification in organic solvents are generally the highest in solvents of low polarity[8] as judged by their E_T values[48] or log *P* values.[49]

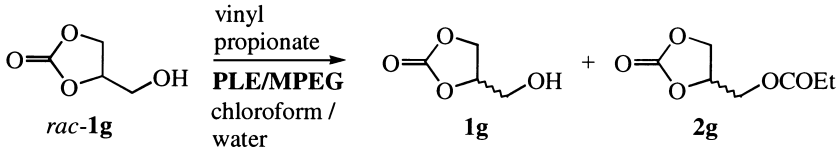
Acetaldehyde and acetone are formed as by-products in the above PLE/MPEG catalyzed transesterifications with vinyl propionate and isopropenyl propionate, respectively. It has recently been demonstrated that in lipase catalyzed transesterifications with vinyl acetate the acetaldehyde liberated can lead to a deactivation of the enzyme.[50] Thus, the influence of acetaldehyde and acetone upon the activity and enantioselectivity of PLE in the transesterification of *rac*-**1f** with vinyl propionate in toluene was studied. While the addition of 9 equiv. of acetaldehyde resulted in a complete loss of the activity of PLE, that of 8 equiv. of acetone decreased the activity of the enzyme but left the selectivity practically unchanged.

In addition to the ketals *rac*-**1a–f** the carbonate *rac*-**1g**[22,41] was investigated because of its different structure (Scheme 2). The PLE/MPEG catalyzed acylation of *rac*-**1g**[51] with vinyl propionate in chloroform (0.4% water), which had to be used as solvent because of the low solubility of *rac*-**1g** in toluene, proceeded rather slowly with a similar selectivity (E=14) to that of the diethyl ketal *rac*-**1b** in toluene.

Finally, we studied the PLE/MPEG catalyzed transesterification of the glycerol ether *rac*-**3**[19] which carries a secondary hydroxy group (Scheme 3). Although the activity of PLE/MPEG towards *rac*-**3** was

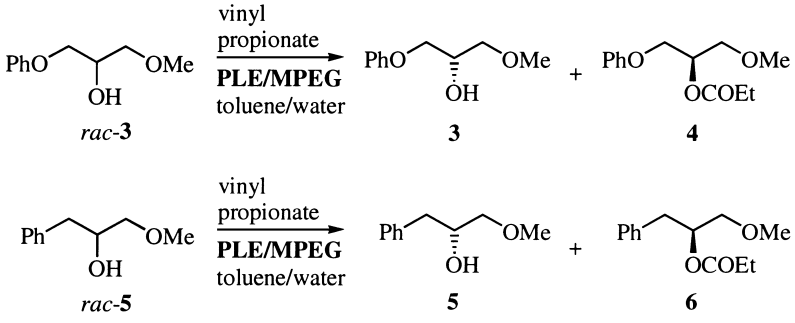
Table 3
PLE/MPEG catalyzed transesterification of *rac*-**1f** in different solvents

solvent	water (%)	t (h)	conv. (%)	alcohol ee (%)	ester ee (%)	E
n-decane	0.4	48	34	44	89	26
toluene	0.4	48	31	41	90	28
benzene	0.4	48	13	14	93	31
*t*BuOMe	0.4	48	47	51	51	5
vinyl propionate	0.4	48	64	79	43	6
CH_2Cl_2	0.4	48	3	2	71	6
$CHCl_3$	0.4	48	1	1	82	10
$MeO(CH_2)_2OMe$	0.4	48	2	3	67	5



Scheme 2.

relatively low under the conditions employed, the selectivity of the transesterification (E=99) was much higher than in the case of *rac*-**1a**–**f**. At 28% conversion (10 d) the *S*-alcohol **3**[18,52] was obtained with 42% ee in 56% yield and the *R*-ester **4** with 97% ee in 27% yield. Similar selectivities had been reported for the transesterification of other racemic secondary alcohols of type **3** by using lipases.[38a,c,d]



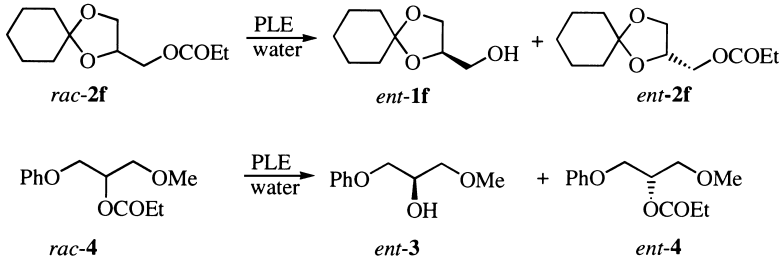
Scheme 3.

Having obtained these results, we were wondering whether the high enantioselectivity would be retained in the case of the secondary alcohol *rac*-**5**[53] which carries, at the stereogenic center, a benzyl group instead of a phenoxymethyl group. The PLE/MPEG catalyzed transesterification of *rac*-**5** with vinyl propionate in toluene (0.4% water) proceeded with high selectivity (E≥200) and led after 47% conversion (5 days) to the isolation of the *R*-alcohol **5**[54,55] with 90% ee in 41% yield and of the *S*-ester **6** with 97% ee in 39% yield. Thus, it seems as if the PLE/MPEG catalyzed transesterification is especially appropriate for the resolution of secondary alcohols, carrying a phenoxymethyl or a benzyl group at the stereogenic center, as exemplified by *rac*-**3**, *rac*-**5** and racemic 1-phenyl-2-propanol.[8]

In all of the above described transesterifications with MPEG/PLE the enzyme was discharged during work-up. However, we have shown previously that PLE can conveniently be immobilized in transesterifications simply by the placement of a polyaramide ultrafiltration membrane in the flask, containing

PLE/MPEG, the substrate and the acyl donor in toluene.[8] Within a short time a spontaneous and complete adsorption of PLE together with MPEG and water occurs on the membrane. Thus, after the completion of the transesterification the liquid phase is removed and the immobilized PLE can be reused several times without significant loss of activity.[56]

For comparison we studied the hydrolysis of the propionates *rac*-**2f** and *rac*-**4** with PLE in aqueous solution (Scheme 4). Most surprisingly, the hydrolysis of *rac*-**2f** proceeded only with a low enantioselectivity (E=2) and that of *rac*-**4** was almost unselective. A similar low enantioselectivity (E=2–5) had been reported previously for the PLE catalyzed hydrolysis of the butyrate of *rac*-**1a** in aqueous solution.[34] In contrast, the lipase catalyzed hydrolyses of esters of *rac*-**1a**–**f** proceed with somewhat higher selectivities (E values up to 13).[18,33,57]



Scheme 4.

3. Conclusion

The PLE/MPEG catalyzed transesterification in organic media allows for the attainment of enantiomerically enriched glycerol ketals and their esters on a g-scale. In the case of solketal (*rac*-**1a**) PLE/MPEG should permit a larger scale resolution. Interestingly, the PLE/MPEG catalyzed transesterification of *rac*-**1a** and *rac*-**5** in organic media proceeded with much higher enantioselectivities than the PLE catalyzed hydrolysis of the corresponding esters *rac*-**2f** and *rac*-**4** in water. The activity of PLE/MPEG in transesterification with vinyl acetate in toluene is lower than that of most lipases in organic media. However, the activity of PLE under these conditions can perhaps be significantly increased by the removal of the acetaldehyde liberated during the transesterification.

4. Experimental

4.1. General remarks

Chemical shifts are given in ppm relative to Me_4Si: δ 0.00 as internal standard. J values are reported in hertz. Peaks in the ^{13}C NMR spectra are denoted as 'u' for carbons with zero or two attached protons or 'd' for carbons with one or three attached protons, as determined from the ATP pulse sequence. Specific rotations are given in grad mL/dm g (*c* in g/100 mL). The enzymatic transesterifications, which were run at ca. 22°C, were monitored by GC analysis on a CP-Sil-8 column. PLE (EC 3.1.1.1, 150 U/mg) was purchased from Boehringer Mannheim as a suspension in 3.2 M NH_4SO_4. The activity of PLE was determined by hydrolysis of ethyl butyrate in aqueous buffer solution (pH 8.0, 25°C). PLE/MPEG was prepared as previously described from MPEG and PLE which was first desalted by ultrafiltration (cut-off 30 kDa) under ice cooling.[8] Enantiomeric ratios were determined by GC analysis on an octakis-(2,3-*O*-dipentyl-6-*O*-methyl)-γ-cyclodextrin column (25 m×0.25 mm) (Lipodex γ-6-Me) (Macherey

Nagel), a permethylated β-cyclodextrin column (25 m×0.25 mm) (CP-Chirasil-Dex-CB) (Chrompack), and on an octakis-(2,6-di-*O*-pentyl-3-*O*-butyl)-ɣ-cyclodextrin column (25 m×0.25 mm) (Lipodex E) (Macherey–Nagel). Hydrogen was used as the carrier gas at 100 kPa. Column chromatography was done on a Merck silica gel 60 (230–400 mesh). $MPEG_{5000}$ was purchased from Sigma. The water content of PLE/MPEG was determined by Karl–Fischer titration with Karl–Fischer solutions from Merck and Riedel–de Haën. Correct C,H analyses were obtained for all enantiomerically enriched compounds described.

4.2. Determination of enantiomeric ratios

GC: *rac*-**1a** and *rac*-**2a**: Lipodex ɣ-6-Me, split 1:40, 50°C (15 min)→80°C (10°C/min) (5 min)→140°C (10°C/min) (5 min): t_R (**1a**)=17.6 min, t_R (*ent*-**1a**)=18.2 min, t_R (**2a**)=22.4 min, t_R (*ent*-**2a**)=21.9 min. *rac*-**1b** and *rac*-**2b**: CP-Chirasil-Dex-CB, split 1:40, 50°C (10 min)→100°C (10°C/min), (2 min)→150°C (10°C/min) (2 min): t_R (**1b**)=20.9 min, t_R (*ent*-**1b**)=21.0 min, t_R (**2b**)=22.3 min, t_R (*ent*-**2b**)=22.6 min. *rac*-**1c** and *rac*-**2c**: CP-Chirasil-Dex-CB, split 1:40, 100°C (5 min)→130°C (10°C/min) (5 min)→160°C (10°C/min) (5 min): t_R (**1c**)=11.6 min, t_R (*ent*-**1c**)=12.0 min, t_R (**2c**)=14.6 min, t_R (*ent*-**2c**)=14.8 min. *rac*-**1e** and *rac*-**2e**: CP-Chirasil-Dex-CB, split 1:40, 80°C (5 min)→120°C (10°C/min) (5 min)→160°C (10°C/min) (5 min): t_R (**1e**)=15.0 min, t_R (*ent*-**1e**)=14.7 min, t_R (**2e**)=17.7 min, t_R (*ent*-**2e**)=18.1 min. *rac*-**1f** and *rac*-**2f**: CP-Chirasil-Dex-CB, split 1:40, 60°C (5 min)→100°C (10°C/min) (5 min)→140°C (10°C/min) (5 min): t_R (**1f**)=19.4 min, t_R (*ent*-**1f**)=19.3 min, t_R (**2f**)=23.5 min, t_R (*ent*-**2f**)=23.8 min. *rac*-**1g**: Lipodex E, split 1: 40, 50°C (10 min)→80°C (10°C/min) (5 min)→120°C (10°C/min) (5 min): t_R (**1g**)=31.0 min, t_R (*ent*-**1g**)=31.1 min. *rac*-**2g**: CP-Chirasil-Dex-CB, split 1:40, 50°C (60 min)→80°C (10°C/min) (5 min)→140°C (10°C/min) (5 min): t_R (**2g**)=81.1 min, t_R (*ent*-**2g**)=81.3 min. *rac*-**3** and *rac*-**4**: CP-Chirasil-Dex-CB, split 1:40, 120°C (10 min)→140°C (10°C/min) (5 min)→160°C (10°C/min) (5 min): t_R (**3**)=14.3 min, t_R (*ent*-**3**)=14.5 min, t_R (**4**)=18.9 min, t_R (*ent*-**4**)=18.8 min. *rac*-**6**: CP-Chirasil-Dex-CB, split 1:40, 80°C (5 min)→120°C (10°C/min) (5 min)→160°C (10°C/min) (5 min): t_R (**6**)=17.5 min, t_R (*ent*-**4**)=17.4 min.

HPLC: *rac*-**1d** and *rac*-**2d**: Baker–Daicel Chiralcel OD/OD-H column, *n*-hexane:*i*PrOH, 9:1, flow rate: 0.5 mL/min: t_R (**1d**)=19.2 min, t_R (*ent*-**1d**)=18.6 min, t_R (**2d**)=13.6 min, t_R (*ent*-**2d**)=14.6 min. *rac*-**5**: Baker–Daicel Chiralcel OD/OD-H column, *n*-hexane:*i*PrOH, 18:1, flow rate: 0.5 mL/min: t_R (**5**)=22.0 min, t_R (*ent*-**5**)=23.4 min.

4.3. Transesterification of rac-***1a***

Vinyl propionate (5.0 g, 50 mmol) and alcohol *rac*-**1a** (1.4 g, 10 mmol) were dissolved in toluene (60 mL, saturated with water) and water (0.5 mL) was added to the solution. After stirring the mixture for 30 min at room temperature, PLE/MPEG (0.80 g, 4900 U) and toluene (60 mL, water saturated) were added. The reaction mixture was stirred at room temperature for 5 days (58% conversion). Subsequently, $MgSO_4$ (10 g) and $NaHCO_3$ (5 g) were added. After stirring the suspension for 5 min, it was filtered through Celite. The filtrate was concentrated in vacuo, and the residue was purified by kugelrohr distillation (0.4 mbar, 100°C). Chromatography (cyclohexane:*i*PrOH, 8:1) gave alcohol **1a**[43,58] (0.43 g, 31%) with 92% ee, $[\alpha]_D^{25}$ +9.1 (*c* 1.48, MeOH) and ester **2a** (0.89 g, 45%) with 77% ee, $[\alpha]_D^{25}$ +1.1 (*c* 1.48, MeOH), as colorless oils.

Compound **1a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.24 (m, 1H), 4.04 (dd, *J*=6.7, *J*=8.4, 1H), 3.78 (dd, *J*=6.3, *J*=8.0, 1H), 3.72 (m, 1H), 3.60 (m, 1H), 2.27 (s, 1H), 1.44 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.3 (d), 26.7 (d), 63.0 (u), 65.8 (u), 76.2 (d), 109.4 (u).

Compound **2a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.31 (m, 1H), 4.04–4.21 (m, 3H), 3.74 (dd, *J*=6.0, *J*=8.0, 1H), 2.39 (q, *J*=7.6, 2H), 1.43 (s, 3H), 1.37 (s, 3H), 1.15 (t, *J*=7.6, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.1 (d), 25.4 (d), 26.7 (d), 27.4 (u), 64.6 (u), 66.4 (u), 73.7 (d), 109.8 (u), 174.2 (u).

4.4. Transesterification of rac-***1b***

Vinyl propionate (7.8 g, 78 mmol) and alcohol *rac*-**1b** (3.25 g, 20 mmol) were dissolved in toluene (100 mL, saturated with water) and water (0.8 mL) was added to the solution. After stirring the mixture for 30 min at room temperature, PLE/MPEG (1.39 g, 5700 U) and toluene (100 mL, water saturated) were added. The reaction mixture was stirred at room temperature (25°C) for 6 days (35% conversion). Subsequently, $MgSO_4$ (20 g) and $NaHCO_3$ (10 g) were added. After stirring the suspension for 5 min, it was filtered through Celite. The filtrate was concentrated in vacuo, and the residue was purified by kugelrohr distillation (0.4 mbar, 110°C). Chromatography (cyclohexane:EtOAc, 1:1) gave alcohol **1b**[18] (1.61 g, 50%) with 41% ee, $[\alpha]_D^{25}$ +5.8 (*c* 1.89, MeOH) and ester **2b** (1.34 g, 31%) with 75% ee, $[\alpha]_D^{25}$ −3.4 (*c* 1.34, MeOH), as colorless oils.

Compound **1b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.23 (m, 1H), 4.04 (dd, *J*=6.4, *J*=8.1, 1H), 3.75 (dd, *J*=7.0, *J*=7.7, 1H), 3.72 (m, 1H), 3.60 (m, 1H), 2.17 (t, *J*=6.0, 1H), 1.65 (m, 4H), 0.91 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.0 (d), 8.3 (d), 29.2 (u), 29.6 (u), 63.1 (u), 66.2 (u), 76.4 (d), 113.3 (u).

Compound **2b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (m, 1H), 4.07–4.22 (m, 3H), 3.70 (dd, *J*=7.1, *J*=8.3, 1H), 2.37 (q, *J*=7.3, 2H), 1.65 (m, 4H), 1.43 (s, 3H), 1.37 (s, 3H), 1.15 (t, *J*=7.5, 3H), 0.91 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.9 (d), 8.2 (d), 9.1 (d), 27.4 (u), 29.4 (u), 29.6 (u), 64.4 (u), 66.9 (u), 73.9 (d), 113.7 (u), 174.3 (u).

4.5. Transesterification of rac-***1c***

Vinyl propionate (4.0 g, 40 mmol) and alcohol *rac*-**1c** (2.04 g, 11 mmol) were dissolved in toluene (50 mL, saturated with water) and water (0.4 mL) was added. After stirring the mixture for 30 min at room temperature, PLE/MPEG (0.69 g, 2900 U) and toluene (50 mL, water saturated) were added. The reaction mixture was stirred at room temperature for 5 days (7% conversion). Subsequently, $MgSO_4$ (10 g) and $NaHCO_3$ (5 g) were added. After stirring the suspension for 5 min, it was filtered through Celite. The filtrate was concentrated in vacuo, and the residue was purified by kugelrohr distillation (0.4 mbar, 110°C). Chromatography (cyclohexane:EtOAc, 1:1) gave alcohol **1c**[24–27] (1.64 g, 80%) with 3% ee, $[\alpha]_D^{20}$ +0.4 (*c* 1.50, MeOH) and ester **2c** (0.18 g, 7%) with 30% ee, $[\alpha]_D^{20}$ −5.2 (*c* 1.75, MeOH).

Compound **1c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33 (m, 1H), 4.12 (t, *J*=7.4, 1H), 3.70 (m, 2H), 3.63 dd, *J*=7.4, *J*=8.8, 1H), 2.16 (m, 2H), 2.08 (m, 1H), 0.94 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4 (d), 17.5 (d), 17.5 (d), 17.5 (d), 33.6 (d), 34.7 (d), 63.5 (u), 68.5 (u), 78.2 (d), 117.0 (u).

Compound **2c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40 (m, 1H), 4.13–4.21 (m, 3H), 3.64 (dd, *J*=7.7, *J*=8.7, 1H), 2.36 (q, *J*=7.5, 2H), 2.09 (sept, *J*=6.9, 1H), 1.15 (t, *J*=7.5, 3H), 0.93 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.0 (d), 17.3 (d), 17.4 (d), 17.4 (d), 17.5 (d), 27.4 (u), 33.7 (d), 34.7 (d), 64.3 (u), 69.1 (u), 75.4 (d), 117.4 (u), 174.3 (u).

4.6. Transesterification of rac-***1d***

Vinyl propionate (1.9 g, 19 mmol) and alcohol *rac*-**1d** (1.1 g, 4 mmol) were dissolved in toluene (50 mL, saturated with water) and water (0.4 mL) was added. After stirring the mixture for 30 min at room temperature, PLE/MPEG (0.73 g, 3600 U) and toluene (50 mL, water saturated) were added. The

reaction mixture was stirred at room temperature for 4 days (20% conversion). Subsequently, $MgSO_4$ (10 g) and $NaHCO_3$ (5 g) were added. After stirring the suspension for 5 min, it was filtered through Celite. The filtrate was concentrated in vacuo, and the residue was purified by kugelrohr distillation (0.001 mbar, 110°C). Chromatography (cyclohexane:EtOAc, 1:1) gave alcohol **1d**[18] (0.78 g, 71%) with 35% ee, $[\alpha]_D^{22}$ +8.1 (*c* 1.10, MeOH), mp 53°C, and ester **2d** (0.24 g, 18%) with 91% ee, $[\alpha]_D^{22}$ −14.0 (*c* 1.86, MeOH), mp 44°C.

Compound **1d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (m, 4H), 7.30 (m, 6H), 4.32 (m, 1H), 4.00 (m, 2H), 3.78 (m, 1H), 3.64 (m, 1H), 1.87 (t, *J*=6.3, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 63.1 (u), 66.2 (u), 76.9 (d), 110.0 (u), 126.0 (d), 126.2 (d), 128.2 (d), 128.2 (d), 128.2 (d), 128.3 (d), 141.9 (u), 142.0 (u).

Compound **2d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 4H), 7.30 (m, 6H), 4.41 (m, 1H), 4.22 (m, 2H), 4.10 (dd, *J*=6.9, *J*=8.2, 1H), 3.91 (dd, *J*=6.9, *J*=8.2, 1H), 2.31 (q, *J*=7.4, 2H), 1.11 (t, *J*=7.5, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.0 (d), 27.4 (u), 64.2 (u), 67.0 (u), 74.3 (d), 110.2 (u), 126.3 (d), 126.3 (d), 128.1 (d), 128.2 (d), 128.2 (d), 128.3 (d), 141.8 (u), 141.9 (u), 174.2 (u).

4.7. Transesterification of rac-***1e***

Vinyl propionate (8.1 g, 81 mmol) and alcohol *rac*-**1e** (3.1 g, 20 mmol) were dissolved in toluene (100 mL, saturated with water) and water (0.8 mL) was added. After stirring the mixture 30 min at room temperature, PLE/MPEG (1.72 g, 6300 U) and toluene (100 mL, water saturated) were added. The reaction mixture was stirred at room temperature for 12 days (39% conversion). Subsequently, $MgSO_4$ (15 g) and $NaHCO_3$ (5 g) were added. After stirring the suspension for 5 min, it was filtered through Celite. The filtrate was concentrated in vacuo, and the residue was purified by kugelrohr distillation (0.4 mbar, 110°C). Chromatography (cyclohexane:EtOAc, 1:1) gave alcohol **1e**[24–27,59] (1.60 g, 52%) with 43% ee, $[\alpha]_D^{22}$ +4.1 (*c* 1.35, MeOH) and ester **2e** (1.29 g, 31%) with 88% ee, $[\alpha]_D^{22}$ +0.2 (*c* 1.64, MeOH).

Compound **1e**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (m, 1H), 3.98 (dd, *J*=6.7, *J*=8.4, 1H), 3.74 (dd, *J*=6.0, *J*=8.1, 1H), 3.70 (m, 1H), 3.60 (m, 1H), 2.38 (s, 1H), 1.64–1.90 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3 (u), 23.7 (u), 36.0 (u), 36.5 (u), 63.2 (u), 65.7 (u), 75.9 (d), 119.4 (u).

Compound **2e**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26 (m, 1H), 4.16 (m, 1H), 4.10 (m, 1H), 4.01 (dd, *J*=6.6, *J*=8.5, 1H), 3.73 (dd, *J*=5.8, *J*=8.5, 1H), 2.37 (q, *J*=7.7, 2H), 1.65–1.88 (m, 8H), 1.15 (t, *J*=7.3, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.1 (d), 23.4 (u), 23.7 (u), 27.4 (u), 36.2 (u), 36.6 (u), 64.6 (u), 66.3 (u), 73.4 (d), 119.7 (u), 174.3 (u).

4.8. Transesterification of rac-***1f***

Vinyl propionate (7.9 g, 79 mmol) and alcohol *rac*-**1f** (3.6 g, 21 mmol) were dissolved in toluene (100 mL, saturated with water) and water (0.8 mL) was added. After stirring the mixture for 30 min at room temperature, PLE/MPEG (1.38 g, 5900 U) and toluene (100 mL, water saturated) were added. The reaction mixture was stirred at room temperature for 5 days (36% conversion). Subsequently, $MgSO_4$ (10 g) and $NaHCO_3$ (5 g) were added. After stirring the suspension for 5 min, it was filtered through Celite. The filtrate was concentrated in vacuo, and the residue was purified by kugelrohr distillation (0.0004 mbar, 100°C). Chromatography (cyclohexane:EtOAc, 1:1) gave alcohol **1f**[18,59] (1.88 g, 53%) with 51% ee, $[\alpha]_D^{20}$ +3.9 (*c* 2.10, MeOH) and ester **2f** (1.40 g, 30%) with 89% ee, $[\alpha]_D^{20}$ +1.2 (*c* 1.30, MeOH). Alcohol **1f** (0.75 g, 4 mmol, 51% ee) and vinyl propionate (1.74 g, 17 mmol) were dissolved in toluene (37.5 mL, saturated with water) and water (0.3 mL) was added. After stirring the mixture for 30 min at room temperature, PLE/MPEG (0.55 g, 2300 U) and toluene (37.5 mL, water saturated) were added. The

reaction mixture was stirred at room temperature for 12 days (28% conversion). Subsequently, $MgSO_4$ (5 g) and $NaHCO_3$ (2 g) were added. After stirring the suspension for 5 min, it was filtered through Celite. The filtrate was concentrated in vacuo, and the residue was purified by kugelrohr distillation (0.4 mbar, 130°C). Chromatography (cyclohexane:EtOAc, 1:1) gave alcohol **1f** (0.49 g, 65%) with 91% ee, $[\alpha]_D^{23}$ +6.0 (*c* 1.08, MeOH) and ester **2f** (0.24 g, 24%) with 45% ee, $[\alpha]_D^{23}$ +0.7 (*c* 1.35, MeOH).

Compound **1f**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.23 (m, 1H), 4.03 (dd, *J*=6.4, *J*=8.1, 1H), 3.78 (dd, *J*=6.4, *J*=8.1, 1H), 3.70 (m, 1H), 3.59 (m, 1H), 2.33 (t, *J*=6.4, 1H), 1.35–1.66 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8 (u), 24.0 (u), 25.1 (u), 35.0 (u), 36.4 (u), 63.1 (u), 65.4 (u), 75.8 (d), 110.0 (u).

Compound **2f**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.31 (m, 1H), 4.13 (m, 1H), 4.11 (m, 1H), 4.06 (m, 1H), 3.77 (dd, *J*=6.0, *J*=8.4, 1H), 2.37 (q, *J*=7.4, 2H), 1.30–1.66 (m, 8H), 1.15 (t, *J*=7.4, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.1 (d), 23.8 (u), 24.0 (u), 25.1 (u), 27.4 (u), 35.0 (u), 36.4 (u), 64.7 (u), 66.1 (u), 73.3 (d), 110.4 (u), 174.2 (u).

4.9. Transesterification of rac-***1f*** *under variation of the initial water content*

Vinyl propionate or isopropenyl propionate (4 mmol) and alcohol *rac*-**1f** (1 mmol) were dissolved in toluene (5 mL, saturated with water). After the addition of the calculated amount of water, the mixture was stirred for 30 min at room temperature. Subsequently, PLE/MPEG (75 mg, 300–400 U) and toluene (5 mL, water saturated) were added. The reaction mixture was stirred at room temperature. Alternatively, dry acetone (8 equiv.) or freshly distilled acetaldehyde (9 equiv.) was added following the addition of PLE/MPEG.

4.10. Transesterification of rac-***1f*** *under variation of the solvent*

Vinyl propionate (4 mmol, except when used as solvent) and alcohol *rac*-**1f** (1 mmol) were dissolved in dry toluene, benzene, *n*-decane, chloroform, methylene chloride, dimethoxyethane, vinyl propionate or methyl *tert*-butyl ether (5 mL). After the addition of water (43 μL), the mixture was stirred for 30 min at room temperature. Subsequently, PLE/MPEG (65 mg, 350 U) and an additional amount of solvent (5 mL) were added. The reaction mixture was stirred at room temperature.

4.11. Transesterification of rac-***1g***

Vinyl propionate (483 mg, 4.8 mmol) and alcohol *rac*-**1g** (170 mg, 1.4 mmol) were dissolved in chloroform (5 mL) (the alcohol was not completely dissolved) and water (0.43 μL) was added. After stirring the mixture for 30 min at room temperature, PLE/MPEG (74.8 mg, 300 U) and chloroform (5 mL) were added. The reaction mixture was stirred at room temperature for 5 days (61% conversion). Subsequently, $MgSO_4$ (1 g) was added. After stirring the suspension for 5 min, the mixture was filtered through Celite.

4.12. Transesterification of rac-***3***

Vinyl propionate (3.9 g, 39 mmol) and alcohol *rac*-**3** (1.8 g, 10 mmol) were dissolved in toluene (75 mL, saturated with water) and water (0.6 mL) was added. After stirring the mixture for 30 min at room temperature, PLE/MPEG (1.07 g, 6300 U) and toluene (75 mL, water saturated) were added. The reaction mixture was stirred at room temperature for 10 days (28% conversion). Subsequently, $MgSO_4$ (10 g) and $NaHCO_3$ (5 g) were added. After stirring the suspension for 5 min, it was filtered through

Celite. The filtrate was concentrated in vacuo, and the residue was purified by kugelrohr distillation (0.4 mbar, 110°C). Chromatography (cyclohexane:EtOAc, 1:1) gave alcohol **3**[18,52] (1.02 g, 56%) with 42% ee, $[\alpha]_D^{25}$ −1.7 (*c* 1.02, EtOH) and ester **4** (0.63 g, 96%) with 97% ee, $[\alpha]_D^{20}$ +27.0 (*c* 2.14, MeOH).

Compound **3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 2H), 6.94 (m, 3H), 4.17 (m, 1H), 4.02 (m, 2H), 3.56 (m, 2H), 3.41 (s, 3H), 2.72 (d, *J*=5.2, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 59.3 (d), 68.9 (u), 69.0 (d), 73.5 (u), 114.5 (d), 121.1 (d), 129.5 (d), 158.5 (u).

Compound **4**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 2H), 6.93 (m, 3H), 5.32 (m, 1H), 4.13 (m, 2H), 3.65 (m, 2H), 3.38 (s, 3H), 2.37 (q, *J*=7.7, 2H), 1.14 (t, *J*=7.4, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.0 (d), 27.6 (u), 59.3 (d), 66.2 (u), 70.7 (d), 71.0 (u), 114.6 (d), 121.1 (d), 129.5 (d), 158.5 (u), 174.0 (u).

4.13. *Transesterification of* rac-***5***

Vinyl propionate (9.2 g, 92 mmol) and alcohol *rac*-**5** (3.4 g, 21 mmol) were dissolved in toluene (100 mL, saturated with water) and water (0.8 mL) was added. After stirring the mixture for 30 min at room temperature, PLE/MPEG (1.32 g, 5800 U) and toluene (100 mL, water saturated) were added. The reaction mixture was stirred at room temperature for 5 days (49% conversion). Subsequently, $MgSO_4$ (10 g) and $NaHCO_3$ (5 g) were added. After stirring the suspension for 5 min, it was filtered through Celite. The filtrate was concentrated in vacuo, and the residue was purified by kugelrohr distillation (0.8 mbar, 100°C). Chromatography (cyclohexane:EtOAc, 1:1) gave alcohol **5**[58,59] (1.41 g, 41%) with 90% ee, $[\alpha]_D^{22}$ +9.3 (*c* 1.20, EtOH), $[\alpha]_D^{22}$ +7.6 (*c* 1.10, MeOH), $[\alpha]_D^{22}$ −0.7 (*c* 1.21, $CHCl_3$), and ester **6** (1.79 g, 39%) with 97% ee, $[\alpha]_D^{22}$ −4.1 (*c* 1.71, MeOH).

Compound **5**: ^{1}H NMR (300 MHz $CDCl_3$) δ 7.29 (m, 2H), 7.22 (m, 3H), 4.00 (m, 1H), 3.40 (m, 1H), 3.38 (s, 3H), 3.30 (m, 1H), 2.79 (m, 2H), 2.48 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.9 (u), 59.1 (d), 71.3 (d), 76.0 (u), 126.5 (d), 128.5 (d), 129.4 (d), 138.0 (u).

Compound **6**: ^{1}H NMR (300 MHz $CDCl_3$) δ 7.28 (m, 2H), 7.22 (m, 3H), 5.20 (m, 1H), 3.43 (m, 2H), 3.37 (s, 3H), 2.93 (m, 2H), 2.31 (q, *J*=7.7, 2H), 1.09 (t, *J*=7.4, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.1 (d), 27.7 (u), 37.0 (u), 59.1 (d), 72.6 (u), 73.1 (d), 126.6 (d), 128.4 (d), 129.5 (d), 137.2 (u), 174.0 (u).

4.14. *Hydrolysis of* rac-***2f***

Ester *rac*-**2f** (0.55 g, 2 mmol) was dissolved in aqueous phosphate buffer solution (36 mL, pH 8) and acetone (4 mL). After stirring the mixture for 5 min at room temperature, PLE (1 mg, 180 U) (NH_4Cl suspension) was added and a pH value of 8.0 was maintained by the addition of 1N NaOH via pH-STAT-autotitration. The hydrolysis was terminated after 50 min (45% conversion) by the extraction of the aqueous solution with CH_2Cl_2 in a perforator overnight. The organic phase was dried ($MgSO_4$) and concentrated in vacuo to give a 45:55 mixture (0.46 g) of alcohol *ent*-**1f** with 31% ee and of ester *ent*-**2f** with 12% ee.

4.15. *Hydrolysis of* rac-***4***

Ester *rac*-**4** (0.40 g, 1.7 mmol) was added to an aqueous phosphate buffer solution (60 mL, pH 7.2). After stirring the mixture for 5 min at room temperature, PLE (1 mg, 180 U) (NH_4Cl suspension) was added and a pH value of 7.2 was maintained by the addition of 0.1N NaOH via pH-STAT-autotitration. The hydrolysis was terminated after 30 min (95% conversion) by the extraction of the aqueous solution with ether. The organic phase was dried ($MgSO_4$) and concentrated in vacuo to give a 96:4 mixture (0.34 g) of alcohol *ent*-**3** with 2% ee and ester *ent*-**4** with 5% ee.

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46. The E values were calculated according to Ref. 45 by using the equations for irreversible reactions although reversibility of the transesterifications under the conditions employed cannot be rigorously excluded. However, we observed only a minor dependency of the calculated E values on the extent of conversion of the substrate.
47. Note that acylation of the *R*-alcohol gives the *S*-ester due to a change in the priority sequence of the substituents.
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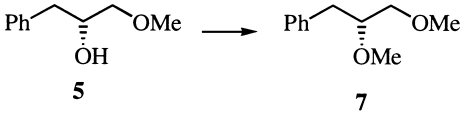
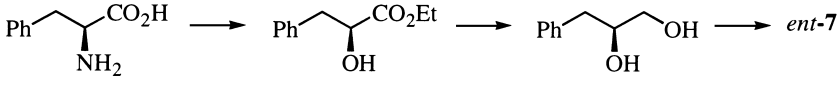
55. Determination of the absolute configuration of **5** was accomplished by chemical correlation with L-phenylalanine according to the scheme below:



5 **7**



8 **9**

Thus, treatment of **5** (90% ee) with NaH and MeI afforded **7** (Ref. 54) ($[\alpha]_D^{23}$ −9.1 (*c* 1.76, $CHCl_3$); $[\alpha]_D^{23}$ −4.1 (*c* 1.37, EtOH); $[\alpha]_{546}^{23}$ −7.2 (*c* 1.37, EtOH)). L-Phenylalanine was converted via diazotization, hydrolysis and esterification to the *S*-ester **8** [Cohen, S. G.; Weinstein, S. Y. *J. Am. Chem. Soc*. **1964**, *86*, 5326 and McKenzie, A.; Barrow, F. *J. Chem. Soc*. **1911**, *99*, 1910] ($[\alpha]_D^{23}$ +4.2 (*c* 1.27, EtOH)) which, upon reduction with $LiAlH_4$, delivered the *S*-diol **9** [Bergstein, W.; Kleemann, A.; Martens, J. *Synthesis* **1981**, 76] ($[\alpha]_D^{23}$ −24.7 (*c* 1.37, EtOH)). Treatment of **9** with NaH and MeI furnished the *S*-dimethyl ether *ent*-**7** (Ref. 54). $[\alpha]_D^{25}$ +7.1 (*c* 1.50, $CHCl_3$); $[\alpha]_D^{25}$ +3.5 (*c* 1.25, EtOH); $[\alpha]_{546}^{25}$ +5.8 (*c* 1.25, EtOH) with 81% ee (GC: Lipodex E, split 1:40, 70°C (5 min)→100°C (10°C/min) (5 min)→140°C (10°C/min) (5 min): t_R (*ent*-**7**)=9.2 min, t_R (**7**)=9.3 min).
56. Following this procedure PLE has been used repeatedly in the batch-wise resolution of *rac*-**1a** without a decrease of the E value: Gais, H.-J.; Jadhav, V., unpublished results.
57. However, recently the isolation and purification of a carboxylesterase from *Bacillus coagulans* has been described, which exhibited a high selectivity (E=55) in the hydrolysis of the caprylate of *rac*-**1a**, see: Ref. 29.
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