The Use of Vinyl Esters Significantly Enhanced Enantioselectivities and Reaction Rates in Lipase-Catalyzed Resolutions of Arylaliphatic Carboxylic Acids

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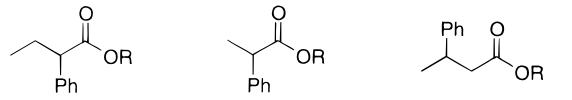
Introduction

Lipases and esterases accept a wide range of substrates, which are usually converted with high enantioselectivity. These enzymes also exhibit high stability in nonaqueous solvents.[1] In most cases, optically pure alcohols were prepared starting from racemic or prostereogenic precursors and reactions are often performed via transesterification in organic solvents. To increase the reaction rate and to shift the equilibrium toward product synthesis, activated esters such as vinyl acetate are routinely employed.[2] This takes advantages of the tautomerization of the vinyl alcohol generated during the esterification to the highly volatile acetaldehyde; thus, the undesired back reaction is suppressed.

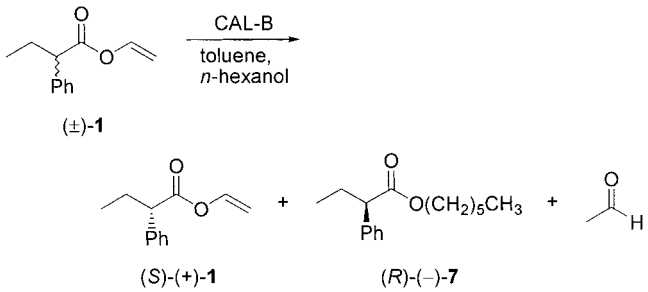
In contrast, the enzymatic synthesis of optically pure carboxylic acids is normally performed as hydrolysis of simple esters, e.g., methyl or ethyl esters. Unfortunately, hydrolysis cannot be performed with water-labile substrates and a partial racemization in aqueous media can lead to a decrease in the optical purity. The alternative transesterification using nonactivated esters is hampered by an unfavored equilibrium causing extremely long reaction times. To circumvent this problem, we investigated the transesterification of vinyl esters of racemic carboxylic acids. As model compounds three arylaliphatic carboxylic acids were chosen, which can be used as chiral building blocks[3] or as chiral derivatizating agents.[4] The corresponding vinyl esters (±)-**1**−**3** (Scheme 1) were synthesized using a known procedure[2b] and then subjected to lipase-catalyzed transesterifications with *n*-hexanol in toluene yielding *n*-hexyl esters (*R*)-(−)-**7**−**9** (Schemes 1 and 2).

Scheme 1



1 R = $CH{=}CH_2$ **2** R = $CH{=}CH_2$ **3** R = $CH{=}CH_2$
4 R = CH_2CH_3 **5** R = CH_2CH_3 **6** R = CH_2CH_3
7 R = $(CH_2)_5CH_3$ **8** R = $(CH_2)_5CH_3$ **9** R = $(CH_2)_5CH_3$
10 R = H **11** R = H **12** R = H

Scheme 2



For comparison of enantioselectivities and reaction rates, the corresponding arylaliphatic carboxylic acid ethyl esters (±)-**4**−**6** (Scheme 1) were synthesized and transesterified with *n*-hexanol in toluene to afford *n*-hexyl esters (*R*)-(−)-**7**−**9** (Scheme 2) or subjected to hydrolysis in sodium phosphate buffer leading to acids (*R*)-(−)-**10**−**12** (Schemes 1 and 3).

Results and Discussion

Vinyl esters of arylaliphatic carboxylic acids were prepared in acceptable yields around 50% and subjected to hydrolase-catalyzed transesterification with *n*-hexanol in toluene. A preliminary study[5] revealed, that only lipase B from *Candida antarctica* exhibited sufficient rates and enantioselectivities (Table 1).

The most interesting observation was the increase in enantioselectivity found when using vinyl esters instead of ethyl esters. The highest enantioselectivity was determined for the transesterification of 2-phenylbutyric acid vinyl esters (±)-**1** (E >100), whereas in reactions using ethyl ester (±)-**4**, only E = 6.5 (transesterification with *n*-hexanol in toluene) or E = 3.7 (hydrolysis in sodium phosphate buffer) were achieved. Figure 1 shows the time course of the conversion of vinyl ester (±)-**1** compared to the reaction of ethyl ester (±)-**4** at 60 °C. It is obvious that the reaction employing the vinyl ester proceeded with much higher enantioselectivity and reaction rate and after ca. 50 h the enantiomeric excess of remaining (*S*)-(+)-**1** was >99%ee. Enantioselectivities were also significantly increased in the resolution of 2-phenylpropionic acid vinyl ester (±)-**2** (E = 26) compared to the reactions using ethyl ester (±)-**5**. For 3-phenylbutyric acid vinyl ester (±)-**3**, the highest value

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(1) For reviews and books, see: (a) Schoffers, E.; Golebiowski, A.; Johnson, C. R. *Tetrahedron* **1996**, *52*, 3769. (b) Kazlauskas, R. J.; Bornscheuer, U. T. In *Biotechnology-Series*; Rehm, H. J., Reed, G., Pühler, A., Stadler, P. J. W., Kelly, D. R., Eds.; VCH: Weinheim, 1998; Vol. 8, p 37. (c) Schmid, R. D.; Verger, R. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1608. (d) Wong, C.-H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Pergamon Press: Oxford, 1994. (e) Faber, K. *Biotransformations in Organic Chemistry*, 3rd ed.; Springer: Berlin, 1997.

(2) For first publications on the use of vinyl esters, see: (a) Degueil-Castaing, M.; de Jeso, B.; Drouillard, S.; Maillard, B. *Tetrahedron Lett.* **1987**, *28*, 953. (b) Wang, Y. F.; Lalonde, J. J.; Momongan, M.; Bergbreiter, D. E.; Wong, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 7200. (c) Laumen, K.; Breitgoff, D.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1988**, 1459.

(3) Kogure, T.; Eliel, E. L. *J. Org. Chem.* **1984**, *49*, 576.

(4) (a) Helmchen, G.; Völter, H.; Schühle, W. *Tetrahedron Lett.* **1977**, 1417. (b) Bravo, P.; Piovosi, E.; Resnati, G.; Fronza, G. *J. Org. Chem.* **1989**, *54*, 5171.

(5) The following enzymes were used: recombinant esterase from *Pseudomonas fluorescens* (Krebsfänger, N.; Schierholz, K.; Bornscheuer, U. T. *J. Biotechnol.* **1998**, *60*, 105); recombinant esterase from *Bacillus stearothermophilus* (Amaki, Y.; Nakano, H.; Yamane, T. *Appl. Microbiol. Biotechnol.* **1994**, *40*, 664); pig liver esterase (Sigma, Deisenhofen, Germany); lipase B from *C. antarctica* (SP435, Boehringer Mannheim, Penzberg, Germany); lipase from *Pseudomonas cepacia* (PS, Amano Pharmaceutical Co., Nagoya, Japan).

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Scheme 3

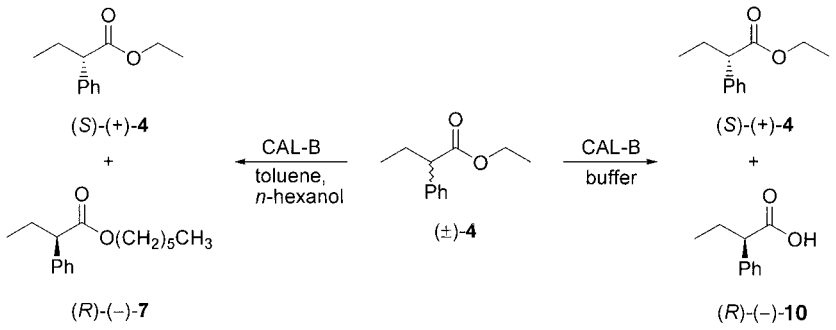

Table 1. Resolution of Arylaliphatic Carboxylic Acids (±)-1−6 with Lipase B from *C. antarctica*

compd	reactn[a]	reactn time[b] [h]	convn [%]	enantiomeric excess [% ee$_S$][d]	enantiomeric excess [% ee$_P$][e]	E[c]
(±)-**1**	T	68	43	74 (**1**)[f]	99 (**7**)	>100
(±)-**4**	T	304	18	14 (**4**)[f]	66 (**7**)	6.5 (0.37)[g]
(±)-**4**	H	1	43	34 (**4**)[f]	22 (**10**)	3.7
(±)-**2**	T	1.3	47	75 (**2**)[f]	53 (**8**)	26
(±)-**5**	T	44	44	41 (**5**)	68 (**8**)	17 (0.79)[g]
(±)-**5**	H	0.3	47	38 (**5**)	28 (**11**)	3.5
(±)-**3**	T	68	56	86 (**3**)	31 (**9**)	13 (23)[h]
(±)-**6**	T	720	19	22 (**6**)	60 (**9**)	13 (0.53)[g]
(±)-**6**	H	3	56	93 (**6**)	13 (**12**)	9

[a] T, transesterification; H, hydrolysis. [b]At 40 °C. [c]Calculated according to ref 9 using the equation $E = [\ln\{(1 - c)(1 - ee_S)\}]/[\ln\{(1 - c)(1 + ee_S)\}]$. [d]All remaining substrates had (*S*)-(+) configuration. [e]All products had (*R*)-(−) configuration. [f]Determined by GC using a chiral column. [g]Values in parentheses correspond to the equilibrium constant calculated according to ref 10 using the computer program available at http://bendik.mnfak.unit.no. [h]Values in parentheses corresponds to reaction at room temperature.

was $E = 13$ ($E = 23$ when the reaction was performed at room temperature) and slightly higher compared to values determined for the hydrolysis of ethyl ester (±)-**6** (Table 1).

Furthermore, the transesterification of the activated vinyl esters (±)-**1**−**3** proceeded with significantly higher reaction rates. For instance, the resolution of 2-phenylbutyric acid vinyl ester (±)-**1** gave 43% conversion after 68 h, but only 18% conversion after more than 300 h when using ethyl ester (±)-**4**. With the other ethyl esters, maximum conversions were less than half and reaction times were significantly prolonged, making this approach synthetically useless. However, hydrolysis in sodium phosphate buffer proceeded faster in all cases studied.

Changes in the enantioselectivity in lipase-catalyzed biotransformations have been published already, and E was influenced by temperature,[6] solvent,[7] enzyme,[8a] and variation of the substrate structure.[8] The latter approach was based on changes in the size of substituents[8a] or protecting group strategies.[8b] In contrast, in the examples shown here, the only structural change is from an ethyl to a vinyl group, which corresponds only to a neglectible change in the size of the substrates. One explanation could be that the increase in enantioselectivity is due to an electronic effect, presumably based on the interaction of the π-electrons of the vinyl double bond with amino acid residues in the active site of CAL-B. A related example was found in the literature, where the resolution of 3-nonanol with CAL-B proceeded with high enantioselectivity ($E > 300$)[8c] but the resolution of 1-bromo-2-octanol with low enantioselectivity ($E = 7.6$)[8d] under similar conditions. Both an ethyl and a CH_2Br group are similar in size, so the difference in E suggests that an electronic effect lowered the enantioselectivity there too. One might also speculate that the use of vinyl esters promotes acylation of the active-site serine and deacylation becomes the rate-determining step. However, this implies that the rate of deacylation must be different for each enantiomer.

Although our method requires the extra synthesis of vinyl esters of racemic carboxylic acids, it might be especially useful for the resolution of (i) acids which are only converted with low enantioselectivity in hydrolysis reactions, (ii) water-labile compounds, and/or (iii) reactions where the exclusive use of organic solvents fits best into a synthetic route.

Experimental Section

General Methods. ^{1}H NMR spectra were recorded at 250.1 and 500.1 MHz and ^{13}C NMR spectra at 62.9 and 125.7 MHz, in $CDCl_3$ with tetramethylsilane as internal standard. Substrates and products were also synthesized in optically pure form by chemical synthesis from commercially available optically pure carboxylic acids **10**−**12** to determine the enantiomeric excess (based on optical rotation or chiral GC, see below) and to assign the absolute configurations of biotransformation products. In cases where both racemic and enantiomerically pure compounds were synthesized, the racemates were used for full characterization including IR spectra (data not shown). Purity of optically pure compounds was verified by NMR and GC analysis and matched that of racemates. Gas chromatographic analyses were conducted using an Optima 5 column (25 m × 0.25 mm; Macherey & Nagel, Düren, Germany) for the determination of conversion and purity and using a heptakis(2,3-di-*O*-acetyl-6-*O*-TBDMS)-β-cyclodextrin column (25 m × 0.25 mm, Prof. W.

(6) Sakai, T.; Kawabata, I.; Kishimoto, T.; Ema, T.; Utaka, M. *J. Org. Chem.* **1997**, *62*, 4906.

(7) See, for instance: (a) Orrenius, C.; Norin, T.; Hult, K.; Carrea, G. *Tetrahedron: Asymmetry* **1995**, *6*, 3023. (b) Bornscheuer, U.; Herar, A.; Kreye, L.; Wendel, V.; Capewell, A.; Meyer, H. H.; Scheper, T.; Kolisis, F. N. *Tetrahedron: Asymmetry* **1993**, *4*, 1007. Even reverse stereoselectivities were found, for the most drastic example, see: (b) Hirose, Y.; Kariya, K.; Sasaki, I.; Kurono, Y.; Ebiike, H.; Achiwa, K. *Tetrahedron Lett.* **1992**, *33*, 7157.

(8) (a) Numerous examples can be found in Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656. (b) Lampe, T. F. J.; Hoffmann, H. M. R.; Bornscheuer, U. T. *Tetrahedron: Asymmetry* **1996**, *7*, 2889. (c) Orrenius, C.; Öhrner, N.; Rotticci, D.; Mattson, A.; Hult, K.; Norin, T. *Tetrahedron: Asymmetry* **1995**, *6*, 1217. (d) Kim, M. J.; Choi, G. B.; Kim, J. Y.; Kim, H. J. *Tetrahedron Lett.* **1995**, *36*, 6253.

(9) Chen, C. S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.

(10) Anthonsen, H. W.; Hoff, B. H.; Anthonsen, T. *Tetrahedron: Asymmetry* **1996**, *7*, 2633. Note that the example used there is based on the resolution of a chiral alcohol using an excess of an achiral acyl donor, whereas we used a chiral acyl donor and an excess of an achiral alcohol.

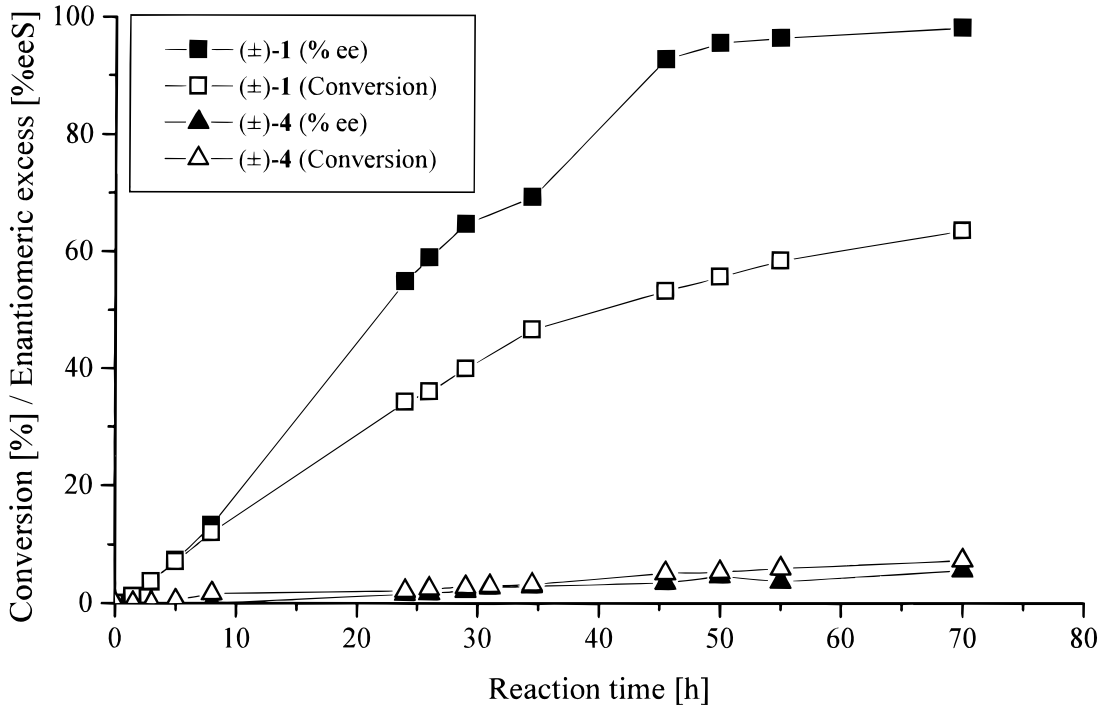

Figure 1. Time course of the resolution of vinyl ester (±)-**1** and ethyl ester (±)-**4** by transesterification with *n*-hexanol in toluene catalyzed by lipase B from *C. antarctica* at 60 °C.

A. König, University of Hamburg, Germany) for the determination of enantiomeric excesses in the case of compounds **1**, **2**, and **4**. Immobilized lipase B from *C. antarctica* (Chirazyme L-2, c.-f., C2; 5000 U/g) was donated by Boehringer Mannheim, Penzberg, Germany.

General Procedure for Preparation of Vinyl Esters 1−3. Vinyl esters were synthesized according to a known method.[2b] Carboxylic acid (500 mg) and $HgOAc_2$ (70 mg, 0.22 mmol) were dissolved in 10 mL of vinyl acetate. After stirring the mixture for 30 min at room temperature, 0.1 mL of concentrated H_2SO_4 was added and the solution was refluxed for 6 h. Then the mixture was allowed to cool to room temperature, and NaOAc (400 mg) was added to quench the catalyst. The solution was filtered and concentrated. The crude products were purified by silica gel column chromatography (petroleum ether:Et_2O 20:1). All vinyl esters were obtained as colorless liquids needing no further purification. Optically pure vinyl esters were synthesized in smaller amounts using about 60−120 mg of carboxylic acid.

(±)-2-Phenylbutyric Acid Vinyl Ester (±)-1. Preparation following the general procedure starting with 500 mg of (±)-**10** (3.05 mmol) yielded 290 mg of (±)-**1** (1.52 mmol, 50%): ^{1}H NMR (500.1 MHz; $CDCl_3$) δ 0.91 (t, J = 7.4, 3H), 1.80−2.16 (m, 2H), 3.51 (t, J = 7.7, 1H), 4.54 (dd, J = 6.32, 1.6, 1H), 4.85 (dd, J = 14.0, 1.7, 1H), 7.23−7.34 (m, 6H); ^{13}C NMR (125.8 MHz; $CDCl_3$) δ 12.08, 26.62, 53.17, 97.90, 127.41, 128.00, 128.67, 138.28, 141.32, 171.12. Anal. Found: C, 75.80; H, 7.41. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42;

(*R*)-(−)-2-Phenylbutyric acid vinyl ester (*R*)-(−)-1: 120 μL of (*R*)-(−)-**10** (126.6 mg, 0.77 mmol) yielded 44 mg (*R*)-(−)-**1** (0.23 mmol, 30%); $[\alpha]^{22}_D$ = −23.9 (*c* 0.664, $CHCl_3$).

(±)-2-Phenylpropionic acid vinyl ester (±)-2: 420 μL of (±)-**11** (460.7 mg, 3.07 mmol) yielded 210 mg of (±)-**2** (1.19 mmol, 39%): ^{1}H NMR (500.1 MHz; $CDCl_3$) δ 1.53 (d, J = 7.2, 3H), 3.79 (q, J = 7.1, 1H), 4.54 (d, J = 6.18, 1H), 4.77 (d, J = 14.0, 1H), 7.23−7.35 (m, 6H); ^{13}C NMR (125.7 MHz; $CDCl_3$) δ 18.41, 45.26, 97.92, 127.36, 127.52, 128.73, 139.71, 141.36, 171.59. Anal. Found: C, 74.73; H, 6.93. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86.

(*R*)-(−)-2-Phenylpropionic acid vinyl ester (*R*)-(−)-2: 60 μL of (*R*)-(−)-**11** (65.8 mg, 0.44 mmol) yielded 18 mg of (*R*)-(−)-**2** (0.10 mmol, 23%); $[\alpha]^{22}_D$ = −34.6 (*c* 0.9, EtOH).

(±)-3-Phenylbutyric acid vinyl ester (±)-3: 500 mg of (±)-**12** (3.05 mmol) yielded 300 mg of (±)-**3** (1.58 mmol, 52%): ^{1}H NMR (250.1 MHz; $CDCl_3$) δ 1.25 (d, J = 7.0, 3H), 2.59 (m, 2H), 3.24 (m, 1H), 4.47 (dd, J = 6.3, 1.5, 1H), 4.77 (dd, J = 14.0, 1.5, 1H), 7.13−7.27 (m, 6H); ^{13}C NMR (62.9 MHz; $CDCl_3$) δ 21.82, 36.27, 42.60, 97.76, 126.63, 126.78, 128.66, 141.18, 145.41, 169.48. Anal. Found: C, 75.63; H, 7.68. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42.

(*R*)-(−)-3-Phenylbutyric acid vinyl ester (*R*)-(−)-3: 120 μL of (*R*)-(−)-**12** (128.3 mg, 0.78 mmol) yielded 29 mg of (*R*)-(−)-**3** (0.15 mmol, 19%); $[\alpha]^{22}_D$ = −21.2 (*c* 1.543, 1,4-dioxane).

General Procedure for Preparation of Ethyl Esters 4−6. The carboxylic acid was dissolved in a mixture of EtOH (15 mL) and toluene (100 mL) and 0.5 mL of concentrated H_2SO_4 was added. Then the flask was equipped with a condenser and a Dean−Stark trap and the mixture was refluxed until the formation of water stopped. The solution was allowed to cool to room temperature and was washed with ice water (100 mL), a saturated solution of Na_2CO_3 (100 mL), and 100 mL of H_2O successively. After drying the organic layer over Na_2SO_4 and removal of solvent, the crude product was purified by silica gel column chromatography (petroleum ether:Et_2O 15:1). Optically pure vinyl esters were synthesized in smaller amounts using about 60−120 mg of carboxylic acid.

(±)-2-Phenylbutyric Acid Ethyl Ester (±)-4. Following the general procedure 5.0 g of (±)-**10** (30.5 mmol) yielded 3.1 g of (±)-**4** (16.1 mmol, 53%) as a colorless oil: ^{1}H NMR (250.1 MHz; $CDCl_3$) δ 0.82 (t, J = 7.4, 3H), 1.13 (t, J = 7.1, 3H), 1.66−2.08 (m, 2H), 3.36 (t, J = 7.7, 1H), 4.04 (m, 2H), 7.23 (m, 5H); ^{13}C NMR (62.9 MHz; $CDCl_3$) δ 12.24, 14.22, 26.88, 53.63, 60.66, 127.16, 128.02, 128.58, 139.34, 174.14. Anal. Found: C, 74.96; H, 8.54. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39.

(*R*)-(−)-2-Phenylbutyric acid ethyl ester (*R*)-(−)-4: 120 μL of (*R*)-(−)-**10** (126.6 mg, 0.77 mmol) yielded 80 mg of (*R*)-(−)-**4** (0.42 mmol, 55%); $[\alpha]^{22}_D$ = −65.7 (*c* 1.508, Et_2O).

(±)-2-Phenylpropionic acid ethyl ester (±)-5: 2.0 g of (±)-**11** (13.3 mmol) yielded 1.1 g of (±)-**5** (6.2 mmol, 47%) as a colorless oil: ^{1}H NMR (250.1 MHz; $CDCl_3$) δ 1.21 (t, J = 7.1, 3H), 1.51 (d, J = 7.2, 3H), 3.72 (q, J = 7.2, 1H), 4.13 (m, 2H), 7.23−7.34 (m, 5H); ^{1}C NMR (62.9 MHz; $CDCl_3$; Me_4Si) δ 14.19, 18.68, 45.64, 60.79, 127.13, 127.54, 128.65, 140.78, 174.63. Anal. Found: C, 74.08; H, 8.01. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92.

(*R*)-(−)-2-Phenylpropionic acid ethyl ester (*R*)-(−)-5: 60 μL of (*R*)-(−)-**11** (65.8 mg, 0.44 mmol) yielded 38 mg of (*R*)-(−)-**5** (0.21 mmol, 48%); $[\alpha]^{22}_D$ = −60.0 (*c* 1.63, $CHCl_3$).

(±)-3-Phenylbutyric acid ethyl ester (±)-6: 5.0 g of (±)-**12** (30.5 mmol) yielded 3.1 g of (±)-**6** (16.1 mmol, 53%) as a colorless oil: ^{1}H NMR (250.1 MHz; $CDCl_3$) δ 1.19 (t, J = 7.1,

3H), 1.32 (d, J = 7.0, 3H), 2.58 (m, 2H), 3.30 (m, 1H), 4.09 (q, J = 7.1, 2H), 7.17−7.36 (m, 5H); ^{13}C NMR (62.9 MHz; $CDCl_3$) δ 14.24, 21.88, 36.60, 43.08, 60.31, 126.45, 126.84, 128.54, 145.83, 172.46. Anal. Found: C, 74.89; H, 8.52. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39.

(*S*)-(+)-3-Phenylbutyric acid ethyl ester (*S*)-(+)-6: 120 μL of (*S*)-(+)-**12** (128.3 mg, 0.78 mmol) yielded 60 mg of (*S*)-(+)-**6** (0.31 mmol, 40%); $[\alpha]^{22}_D$ = +21.4 (*c* 1.538, Et_2O).

General Procedure for Synthesis of Hexyl Esters 7−9. The carboxylic acid and toluene-4-sulfonic acid (20 mg) were dissolved in a mixture of *n*-hexanol (3.5 mL) and toluene (50 mL) in a round-bottom flask. The flask was equipped with a Dean−Stark trap and a condenser before the mixture was refluxed. Reaction was continued until formation of water stopped. The mixture was washed with ice water (30 mL), a saturated Na_2CO_3 solution (30 mL), and water (30 mL). After drying over Na_2SO_4 and evaporation of the solvent, the crude product was purified by silica gel column chromatography (petroleum ether:Et_2O 40:1) and obtained as a colorless oil.

(±)-2-Phenylbutyric acid hexyl ester (±)-7: 500 mg of (±)-**10** (3.05 mmol) yielded 510 mg of (±)-**7** (2.05 mmol, 67%); ^{1}H NMR (250.1 MHz; $CDCl_3$) δ 0.76−0.85 (m, 6H), 1.17 (m, 6H), 1.49 (t, J = 6.7, 2H), 1.66−2.09 (m, 2H), 3.36 (t, J = 7.7, 1H), 3.98 (dt, J = 6.6, 1.8, 2H), 7.16−7.25 (m, 5H);^{13}C NMR (62.9 MHz; $CDCl_3$) δ 12.25, 14.02, 22.53, 25.52, 26.73, 28.59, 31.40, 53.70, 64.82, 127.15, 128.02, 128.56, 139.36, 141.32, 174.20. Anal. Found: C, 77.54; H, 9.78. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74.

(*R*)-(−)-2-Phenylbutyric acid hexyl ester (*R*)-(−)-7: 120 μL of (*R*)-(−)-**10** (126.6 mg, 0.77 mmol) yielded 61 mg of (*R*)-(−)-**7** (0.25 mmol, 32%); $[\alpha]^{22}_D$ = −29.3 (*c* 1.438, $CHCl_3$).

(±)-2-Phenylpropionic acid hexyl ester (±)-8: 100 μL of (±)-**11** (109.7 mg, 0.73 mmol) yielded 91 mg of (±)-**8** (0.39 mmol, 53%); ^{1}H NMR (250.1 MHz; $CDCl_3$) δ 0.78 (t, J = 6.6, 3H), 1.14−1.22 (m, 6H), 1.42 (d, J = 7.2, 3H), 1.48 (t, J = 6.8, 2H), 3.63 (q, J = 7.2, 1H), 3.97 (t, J = 6.7, 2H), 7.15−7.25 (m, 5H); ^{13}C NMR (62.9 MHz; $CDCl_3$) 14.00, 21.88, 22.52, 25.54, 28.55, 31.41, 36.56, 43.01, 64.50, 126.37, 126.75, 128.47, 145.75, 172.50. Anal. Found: C, 76.93; H, 9.56. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46.

(*R*)-(−)-2-Phenylpropionic acid hexyl ester (*R*)-(−)-8: 60 μL of (*R*)-(−)-**11** (65.8 mg, 0.44 mmol) yielded 39 mg of (*R*)-(−)-**8** (0.17 mmol, 39%); $[\alpha]^{22}_D$ = −35.8 (*c* 1.58, $CHCl_3$).

(±)-3-Phenylbutyric acid hexyl ester (±)-9: 130 mg of (±)-**12** (0.79 mmol) yielded 98 mg of (±)-**9** (0.39 mmol, 49%); ^{1}H NMR (250.1 MHz; $CDCl_3$) δ 0.81 (t, J = 6.7, 3H), 1.18−1.26 (m, 9H), 1.46 (t, J = 6.8, 2H), 2.51 (m, 2H), 5.80 (m, 1H), 3.93 (t, J = 6.7, 2H), 7.11−7.25 (m, 5H); ^{13}C NMR (62.9 MHz; $CDCl_3$) δ 14.00, 21.88, 22.52, 25.54, 28.55, 31.41, 36.56, 43.01, 64.50, 126.37, 126.75, 128.47, 145.75, 172.50. Anal. Found: C, 77.42; H, 9.80. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74.

(*R*)-(−)-3-Phenyl-butyric Acid Hexyl Ester (*R*)-(−)-9: 120 μL of (*R*)-(−)-**12** (128.3 mg, 0.78 mmol) gave 78 mg of (*R*)-(−)-**9** (0.31 mmol, 40%); $[\alpha]^{22}_D$ = −21.6 (*c* 2.73, $CHCl_3$).

Lipase-Catalyzed Transesterification. A total of 0.52 mmol of the substrate ((±)-**1**−**6**) was dissolved in 5 mL of toluene, 560 μL of *n*-hexanol (4.49 mmol) was added, and the reaction was started by addition of 100 mg (500 U) of CAL-B. The reaction mixture was stirred, and the temperature was adjusted by use of an oil bath. Samples withdrawn from the solution were diluted with toluene, lipase was removed by centrifugation, and conversion was determined by GC using the Optima 5 column. After termination of the reaction by filtration, product and nonconverted substrate were separated by flash column chromatography. Enantiomeric purities were calculated from optical rotation values. In case of substrates (±)-**1**, (±)-**2**, and (±)-**4** determination of optical purity was also feasible by means of chiral column GC.

Transesterification of (±)-1: 98.9 mg of (±)-**1** (0.52 mmol) yielded after 68 h 49.7 mg of (*R*)-(−)-**7** (0.20 mmol, 38%, 99% ee ($[\alpha]^{22}_D$ = −29.0 (*c* 0.78, $CHCl_3$))) and 43.8 mg of (*S*)-(+)-**1** (0.23 mmol, 45%, 74% ee (GC)).

Transesterification of (±)-4: 100 mg of (±)-**4** (0.52 mmol) yielded after 304 h 19.4 mg of (*R*)-(−)-**7** (0.08 mmol, 15%, 66% ee ($[\alpha]^{22}_D$ = −19.4 (*c* 0.680, $CHCl_3$))) and 73.1 mg of (*S*)-(+)-**4** (0.38 mmol, 74%, 14% ee (GC)).

Transesterification of (±)-2: 91.6 mg of (±)-**2** (0.52 mmol) yielded after 1.3 h 51.7 mg of (*R*)-(−)-**8** (0.21 mmol, 40%, 53% ee ($[\alpha]^{22}_D$ = −19.0 (*c* 0.435, $CHCl_3$))) and 40.3 mg of (*S*)-(+)-**2** (0.23 mmol, 44%, 75%ee (GC)).

Transesterification of (±)-5: 92.7 mg of **(±)-5** (0.52 mmol) yielded after 44 h 36.6 mg of (*R*)-(−)-**8** (0.16 mmol, 30%, 68% ee ($[\alpha]^{22}_D$ = −24.2 (*c* 1.3, $CHCl_3$))) and 44.5 mg of (*S*)-(+)-**5** (0.25 mmol, 48%, 41% ee ($[\alpha]^{22}_D$ = +24.6 (*c* 0.35, $CHCl_3$)).

Transesterification of (±)-3: 98.9 mg of (±)-**3** (0.52 mmol) yielded after 68 h 65.1 mg of (*R*)-(−)-**9** (0.26 mmol, 50%, 31% ee ($[\alpha]^{22}_D$ = −6.6 (*c* 2.39, $CHCl_3$))) and 34.6 mg of (*S*)-(+)-**3** (0.18 mmol, 35%, 86% ee ($[\alpha]^{22}_D$ = +18.2 (*c* 0.372, $CHCl_3$)).

Transesterification of (±)-6: 100 mg of **(±)-6** (0.52 mmol) yielded after 720 h 13.0 mg of (*R*)-(−)-**9** (0.05 mmol, 10%, 60% ee ($[\alpha]^{22}_D$ = −13.0 (*c* 0.680, $CHCl_3$))) and 71.0 mg of (*S*)-(+)-**6** (0.37 mmol, 71%, 22% ee ($[\alpha]^{22}_D$ = +4.7 (*c* 0.458, $CHCl_3$)).

Hydrolysis of Ethyl Esters (±)-4−6. Hydrolysis reactions were performed in a pH-stat system. In general 1 mmol of substrate ((±)-**4**−**6**) was added to 20 mL of sodium phosphate buffer (50 mM, pH 7.5) at 40 °C. Then 200 mg (1000 U) of CAL-B was added to start the reaction and the pH was kept constant automatically with 0.1 N NaOH. After consumption of base indicated the desired conversion, nonreacted substrate was extracted from the mixture with heptane. Subsequently the aqueous layer was saturated with NaCl and the pH was adjusted to 3 by adding H_2SO_4 before it was extracted again three times with EtOAc to obtain the free carboxylic acids (**10**−**12**). The organic layers were dried over Na_2SO_4, and the enantiomeric excess was determined by optical rotation and by chiral column GC for compound (±)-**4**.

Hydrolysis of (±)-4: 192.3 mg of (±)-**4** (1.00 mmol) yielded after 1 h 55.8 mg of (*R*)-(−)-**10** (0.34 mmol, 34%, 22% ee ($[\alpha]^{22}_D$ = −20.5 (*c* 1.005, toluene; lit. $[\alpha]^{22}_D$ = +93.0 (*c* 0.900, toluene))) and 76.9 mg of (*S*)-(+)-**4** (0.40 mmol, 40%, 34% ee (GC)).

Hydrolysis of (±)-5: 178.2 mg of (±)-**5** (1.00 mmol) yielded after 0.3 h 63.1 mg of (*R*)-(−)-**11** (0.42 mmol, 42%, 28% ee ($[\alpha]^{22}_D$ = −20.4 (*c* 2.39, $CHCl_3$; lit. $[\alpha]^{22}_D$ = −72 (*c* 1.6; $CHCl_3$)) and 92.7 mg of (*S*)-(+)-**5** (0.52 mmol, 52%, 38% ee ($[\alpha]^{22}_D$ = +22.8 (*c* 0.54, $CHCl_3$)).

Hydrolysis of (±)-6: 192.1 mg of (±)-**6** (1.00 mmol) yielded after 3 h 83.7 mg of (*R*)-(−)-**12** (0.51 mmol, 51%, 13% ee ($[\alpha]^{22}_D$ = −9.2 (*c* 3.74, C_6H_6; lit. $[\alpha]^{22}_D$ = −57 (*c* 1.0; C_6H_6)) and 57.7 mg of (*S*)-(+)-**6** (0.30 mmol, 30%, 93% ee ($[\alpha]^{22}_D$ = +20.0 (*c* 0.5, Et_2O)).

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