Enzymatic Kinetic Resolution and Chemoenzymatic Dynamic Kinetic Resolution of δ-Hydroxy Esters. An Efficient Route to Chiral δ-Lactones

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A successful kinetic resolution of a racemic mixture of δ-hydroxy esters **1** was obtained via lipase-catalyzed transesterification (*E* value up to 360). The combination of the enzymatic kinetic resolution with a ruthenium-catalyzed alcohol racemization led to an efficient dynamic kinetic resolution (ee up to 99% and conversion up to 92%). The synthetic utility of this procedure was illustrated by the practical syntheses of δ-lactones (*R*)-6-methyl- and (*R*)-6-ethyl-tetrahydropyran-2-one and (*S*)-5-(*tert*-butyldimethylsiloxy)heptanal. The former are important building blocks in the synthesis of natural products and biologically active compounds, and the latter is a key intermediate in the synthesis of widely used commercial insecticide Spinosyn A.

Introduction

The importance of enantiopure δ-hydroxy esters as precursors of versatile building blocks in asymmetric synthesis is well established. Perhaps the most important building blocks that can be easily synthesized from δ-hydroxy esters are the δ-lactones. The interest in chiral δ-lactones is due to the fact that they are present in a variety of natural products isolated from insects, plants, fungi, and marine organisms, especially in attractants and pheromones.[1] In addition, lactones are important building blocks for the synthesis of natural products, such as alkaloids and terpenoids,[2] and biologically active compounds (e.g., antitumor and antiviral agents).[3]

Many approaches for the preparation of enantiomerically pure δ-lactones have been developed.[4] Among these methods, the reduction of the corresponding keto esters via microbial or enzymatic reduction followed by chemical lactonization has had a dominant role.[5] Lipase-catalyzed kinetic resolutions of racemic substrates can be useful alternatives, especially because coenzyme regeneration, an inherent problem of processes based on enzymatic reductions, is not required.[6]

In the last few years, only a few studies dealing with the lipase-catalyzed kinetic resolution (KR) of δ-hydroxy esters by either intramolecular esterification or transesterification have been reported.[6,7] The efficiency of the KR for this type of substrate is usually rather low due to the competition with the enzyme-catalyzed esterification and transesterification.[6] Moreover, a major drawback with KR is that the yield is limited to a maximum of 50%. By applying dynamic kinetic resolution (DKR), this limitation can be overcome. With DKR the unreactive enantiomer, is continuously racemized and the product can be obtained optically pure in 100% yield (Scheme 1). To the best of our knowledge the only example of the use of DKR for obtaining δ-hydroxy esters was carried out using a special class of substrates, the γ-alkylated β-δ-keto esters, and alcohol dehydrogenase from *Lactobacillusa brevis* (refLBADH).[8]

Following our investigations dealing with bioconversions,[9] we now report on the efficient kinetic resolution

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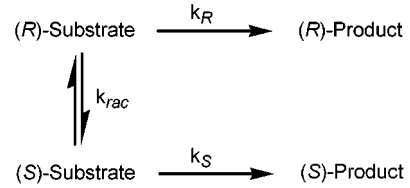
Scheme 1. Dynamic Kinetic Resolution



of *tert*-butyl *δ*-hydroxy esters **1** via lipase-catalyzed esterification. We also report on the combination of the enzymatic kinetic resolution with ruthenium-catalyzed alcohol isomerization that results in an efficient dynamic kinetic resolution. The viability of this strategy is illustrated by the practical syntheses of (*R*)-6-methyltetrahydropyran-2-one, widely used as a building block (e.g., in the preparation of antiviral and antitumoral agent mycalamide A),[3] the naturally occurring fragrance (*R*)-6-ethyltetrahydropyran-2-one,[10] and (*S*)-5-(*tert*-butyldimethylsiloxy)heptanal, a building block used in the synthesis of widely used commercial insecticide Spinosyn A.[11]

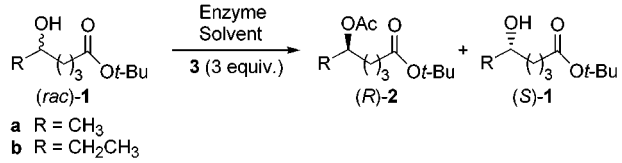
Results and Discussion

In the first set of experiments, the efficiency of different commercially available lipases to catalyze the transesterification of chiral *δ*-hydroxy esters was investigated. For this purpose, racemic *δ*-hydroxy *tert*-butyl esters **1** were chosen as models to avoid the competition with the enzyme-catalyzed intramolecular esterification.[6] A necessary condition for a successful DKR is that the KR conditions should be compatible with the racemization process.[9] Therefore, we screened different lipases in the kinetic resolution of **1** under different reaction conditions, using *p*-chlorophenyl acetate (**3**) as acyl donor. The latter is known to be compatible with Ru-catalyzed racemization of alcohols.[9] The results are summarized in Table 1. In a control experiment, it was shown that the reaction did not proceed in the absence of enzyme. Moreover, the formation of six-membered lactones via either thermal lactonization or enzyme-catalyzed esterification was not observed.

Although the enzyme *Candida antarctica* lipase B (Novozyme 435, N-435) showed the highest activity (entry 2), the enantiomeric ratio was better using *Pseudomonas cepacia* lipase (PS-C) ($E > 360$, entry 3). Lipase *Pseudomonas fluorescens* (AK) showed low activity (entry 1). The other examined lipases (lipase from porcine pancreas, *Candida rugosa*, and *Aspergillus* sp.) showed either very low conversion or no reaction after 24 h. Thus, from all the lipases tested, the optimum result with respect to both enantioselectivity and reaction rate was achieved using lipase PS-C.

It is well-known that enantioselectivity and reaction rates in the kinetic resolutions by lipases can be greatly

Table 1. Kinetic Resolution of 1[a]



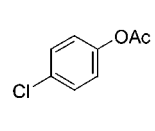
a R = CH_3
b R = CH_2CH_3

entry	substrate	enzyme[b]	solvent	rate[c]	% convn (t/h)[d]	% ee[e]	E[f]
1	**1a**	AK	toluene	7	38 (8)	98	182
2	**1a**	N-435	toluene	56	47 (1)	98	282
3	**1a**	PS-C	toluene	21	37 (2.5)	>99[g]	>360
4	**1a**	PS-C	cyclohexane	45	36 (1)	99	349
5	**1a**	PS-C	*t*-BuOMe	46	37 (1)	99	360
6	**1a**	PS-C	$(i\text{-Pr})_2O$	32	32 (1)	99	315
7	**1a**	PS-C	$(n\text{-Bu})_2O$	28	47 (2.5)	98	282
8	**1b**	PS-C	toluene	27	41 (2.5)	98	202

[a] Reactions were performed on a 0.1 mmol scale with 5 mg of enzyme and 3 equiv of **3** in 1 mL of solvent at 60 °C. [b] AK = *P. fluorescens* lipase, N-435 = *C. antarctica* lipase B, PS-C = *P. cepacia* lipase. [c] Initial rate (μmol × h^{-1}). [d] Determined by NMR. [e] % ee of **2** determined by GC. [f] Enantiomeric ratio. [g] The other enantiomer was not observed.

influenced by variation of solvent.[12] We therefore screened the acetylation of *rac*-**1a** with **3** at 60 °C in the presence of lipase PS-C in various nonpolar solvents (entries 4−8). The results showed that the reaction rates are very dependent on the solvent. However, the variation of solvent did not considerably affect the enantioselectivity.

On the basis of our preliminary results on KR, we combined the KR of *δ*-hydroxy esters **1** using PS-C and the acyl donor **3** with a ruthenium-catalyzed racemization process via hydrogen transfer with the so-called Shvo catalyst **4** in toluene.[13] Despite the fact that the KR was



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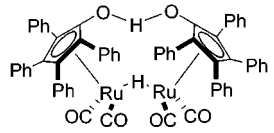

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faster in ether solvents, i.e., *tert*-butyl methyl ether, than in toluene (Table 1), the latter was chosen as a solvent to perform DKR due to the higher solubility of the Ru catalyst **4** in toluene than in ethers, and this results in higher racemization rates.[9f] The results are summarized in Table 2.

Under "standard" conditions (i.e., 60 °C, 5 mg of PS-C, and 4 mol % **4**), the formation of large amounts of the corresponding ketone **5**, formed during the hydrogen-transfer process, was observed (entry 1). Moreover, the racemization proceeded slowly, resulting in a slightly lower enantioselectivity than the maximum observed in the KR (99%). In previous studies we have shown that increasing the temperature leads to a significantly higher racemization rate.[9f,g] Therefore, we performed the DKR at 70 °C.[14] At 70 °C, the activity and enantioselectivity were better; however, high amounts of ketone **5a** were also formed.

Several attempts to increase the efficiency of the process by reducing the amount of ketone have been

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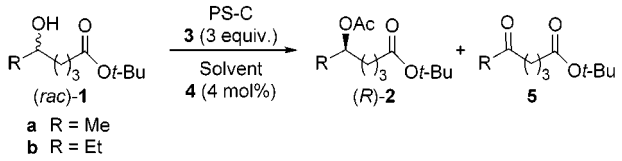
(14) PS-C lipase is thermostable up to 70−80 °C.

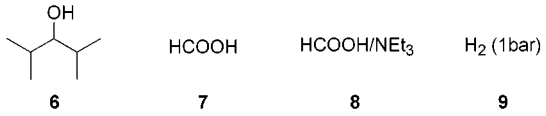
Table 2. Dynamic Kinetic Resolution[a]



entry	substrate	H-donor	*T*/°C	*t*/h	% **2**[b]	% **5**[b]	% ee[c]
1	**1a**		60	48	59	37	97
2	**1a**		70	24	52	38	99
3	**1a**		70	48	66	34	99
4	**1a**	**6**[d]	70	48	65	25	98
5[e]	**1a**	**6**[d]	70	48	86	13	98
6[e]	**1a**	**6**[d]	70	72	92	7	98
7[e]	**1a**	**6**[f]	70	48	63	25	99
8[e]	**1a**	**7**[f]	70	48	50[g]	2	99
9[e]	**1a**	**8**[f]	70	48	54	4	96
10	**1a**	**9**	70	48	78		89
11[h]	**1a**	**9**	70	48	65		99
12[h,i]	**1a**	**9**	70	48	71		99
13[h,i]	**1a**	**9**	70	92	89 (80)[j]		98
14[e]	**1b**	**6**[d]	70	72	91	8	95
15[k]	**1b**	**9**	70	92	87 (81)[j]		98

[a] Reactions were performed on a 0.1 mmol scale with 5 mg of PS-C, 4 mol % **4**, and 3 equiv of acyl donor in 1 mL of toluene. [b] Determined by ^{1}H NMR. [c] % ee of **2a** determined by HPLC. [d] 0.5 equiv of H-donor used. [e] H-donor added after 24 h. [f] 1 equiv of H-donor used. [g] 27% lactone formed. [h] 1 mg of PS-C used. [i] 6 mol % **4**. [j] Reaction performed on a 0.6 mmol scale. Isolated yield in parentheses. [k] 0.75 mg of PS-C and 6 mol % **4** used.

carried out. Thus, several hydrogen sources, **6**−**9**, were tested with the aim to push the equilibrium back to the alcohol **1**.



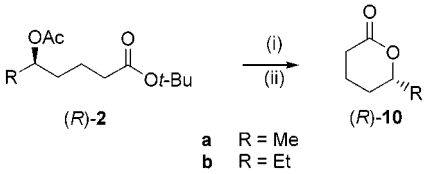
The addition of 0.5 equiv of 2,4-dimethyl-3-pentanol (**6**) to the reaction mixture reduced the amount of ketone **5a** considerably (25%), but did not show an improvement in the formation of acetate **2a** (entry 4). This can be attributed to the competition between alcohols **6** and **1** in the transfer hydrogenation process. To minimize this competitive reaction, we decided to add **6** (0.5 equiv) after 24 h, when almost no alcohol **1** is present in the reaction mixture (entries 5 and 6). This significantly increases the efficiency of the process, and the desired acetate **2a** was formed in 92% yield after 72 h of reaction in almost enantiomerically pure form (98% ee, entry 6). The addition of larger amounts of **6** had a negative effect on the activity (entry 7).

The use of formic acid (**7**) inhibited the formation of undesired ketone **5a**, but catalyzed the lactone formation via acid-catalyzed reaction (27% lactone after 48 h, entry 8).

The use of a mixture of formic acid/triethylamine, which has been successfully used in DKR involving hydrogen-transfer racemization,[15] inhibited both ketone and lactone formation, however, the activity and enantioselectivity was low (entry 9).

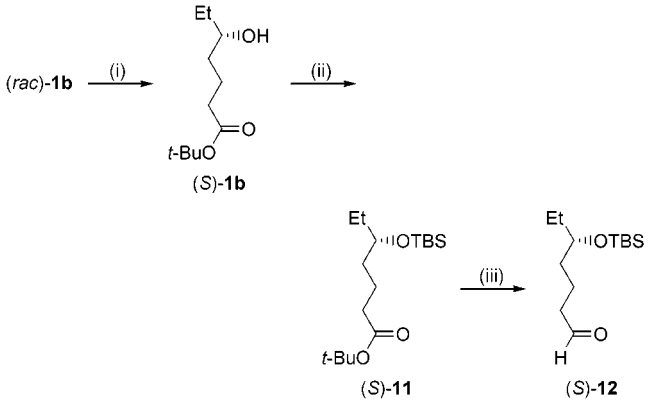
The use of hydrogen gas (1 bar) inhibited the formation of ketone completely. However, the DKR under these conditions gave the acetate in lower enantioselectivity

Scheme 2. Synthesis of (*R*)-Lactones 10[a]



[a] Reagents and conditions: (i) LiOH, toluene/MeOH; (ii) HCl (pH 1).

Scheme 3. Synthesis of Compound (*S*)-12[a]



[a] Reagents and conditions: (i) PS-C, **3**, toluene (8 h, 41%); (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2 (91%); (iii) DIBALH, CH_2Cl_2 (88%).

(89% ee, entry 10) than in the kinetic resolution experiments (see Table 1). This is mainly due to a decrease of the racemization rate under 1 bar of hydrogen gas. To obtain better enantioselectivity, one has to take full advantage of the DKR by increasing the ratio of the rate of racemization and rate of enzymatic acetylation. Thus, by reducing the enzyme/ruthenium catalyst ratio, the relative rate of enzymatic acylation toward racemization decreased and the enantioselectivity was substantially improved (entries 11−13). Comparing these results with those using **6**, we can conclude that, although longer reaction times were needed, the use of molecular hydrogen is advantageous since no byproducts are formed.[16]

The DKR of δ-hydroxy ester **1b** followed the same trend as observed for substrate **1a**. Thus, both good yields and excellent enantioselectivity (98% ee) were obtained using molecular hydrogen (entry 15).

A wide range of synthetic applications of this dynamic kinetic resolution procedure can be envisaged. One example is the practical synthesis of the versatile intermediates (*R*)-6-methyl- and (*R*)-6-ethyltetrahydropyran-2-one ((*R*)-**10a** and (*R*)-**10b**) (Scheme 2). Dynamic kinetic resolution of the racemic δ-hydroxy esters **1a** and **1b** afforded the corresponding acetates (*R*)-**2a** and (*R*)-**2b** in 98% ee (entries 13 and 15, Table 2). The transformation of the latter to (*R*)-lactones (*R*)-**10a** and (*R*)-**10b**, respectively, was performed in a one-pot two-step procedure involving hydrolysis with LiOH in toluene/methanol (1/1) followed by acid-catalyzed lactone formation.

The lipase-catalyzed transesterification was applied to the practical synthesis of (*S*)-5-(*tert*-butyldimethylsiloxy)-heptanal ((*S*)-**12**), which is a key intermediate in the

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(16) The separation of 2,4-dimethylpentan-3-one was difficult in the purification of acetates **2**.

synthesis of Spinosyn A, a commercially important insecticidal macrocyclic lactone (Scheme 3).[11] The kinetic resolution of *rac*-**1b** afforded (*S*)-**1b** in 41% yield and in essentially enantiomerically pure form (99% ee). The protection of secondary carbinol (*S*)-**1b** as the silyl ether (*S*)-**11** followed by reduction of the ester group by DIBALH in THF at −78 °C afforded (*S*)-**12** in good yield. The enantiomer (*R*)-**12** can be obtained more efficiently by using the new DKR procedure disclosed here since the in situ hydrolysis of acetate (*R*)-**2b** with LiOH gave quantitatively *tert*-butyl (*R*)-5-hydroxyheptanoate in essentially enantiomerically pure form (98% ee).

Conclusion

We have described a highly selective kinetic resolution of racemic δ-hydroxy esters **1** via inexpensive lipase PS-C catalyzed transesterification (*E* values >360). This enzymatic kinetic resolution combined with ruthenium-catalyzed alcohol isomerization led to an efficient dynamic kinetic resolution. The efficiency of the process together with the easy transformation of these δ-acetoxy esters to δ-lactones makes the present method an attractive alternative to existing methods for obtaining δ-lactones in enantiomerically pure form.

Experimental Procedures

General Experimental Procedures. All reactions were carried out under a dry argon atmosphere in oven-dried glassware. Solvents were purified by standard procedures. All other reagents are commercially available and were used without further purification. Acyl donor **3** was prepared according to a literature procedure.[9b] Ruthenium catalyst **4** was synthesized according to a literature procedure[9d] and recrystallized from CH_2Cl_2/pentane prior to use. Novozym-435 was a generous gift from Novo Nordisk A/S, Denmark. Lipases PS-C and AK were a generous gift from Amano Pharmaceutical Co. Ltd., Japan. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 and 100 MHz, respectively. Solvents for extraction and chromatography were technical grade and distilled before use. Column chromatography was performed with Merck 60 silica gel. The enantiomeric excess of **2** was determined by analytical GLC employing a CP-Chirasil-Dex CB column using racemic compounds as references. The oven temperature was 110 °C for 30 min and then was increased 5 °C/min to 200 °C.

General Procedure for the Synthesis of δ-Keto Esters. *tert*-Butyl 5-Ketohexanoate (5a). To a solution of 5-ketohexanoic acid (1.30 g, 10 mmol) in CH_2Cl_2 (100 mL) under an argon atmosphere were added DCC (2.64 g, 10 mmol), *tert*-butyl alcohol (5 mL), and 4-DMAP (12.2 mg, 0.1 mmol). After 40 h, the reaction was quenched with saturated $NaHCO_3$ (100 mL). The mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined ether phases were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (pentane/ethyl acetate, 4/1) to give 1.07 g (58%) of ketone **5a** as a colorless oil. ^{1}H NMR: δ 1.43 (s, 9H, CH_3, *t*-Bu), 1.84 (q, 2H, CH_2, $^3J_{H-H}$ = 7.2 Hz), 2.23 (t, 2H, CH_2, $^3J_{H-H}$ = 7.2 Hz), 2.47 (t, 2H, CH_2, $^3J_{H-H}$ = 7.2 Hz). ^{13}C NMR: δ 19.3 (CH_2), 28.3 (CH_3, *t*-Bu), 30.1 (CH_3), 34.7 (CH_2), 42.8 (CH_2), 80.5 (C, *t*-Bu), 172.7 (CO), 208.4 (CO).

***tert*-Butyl 5-Ketoheptanoate (5b).** Treatment of 5-ketoheptanoic acid[17] (1.44 g, 10 mmol) as described for compound **5a** afforded δ-keto ester **5b**, which was purified by flash chromatography (pentane/ethyl acetate, 4/1) to give 0.98 g (49%) as a colorless oil. ^{1}H NMR: δ 1.04 (t, 3H, CH_3, $^3J_{H-H}$ = 7.2 Hz), 1.42 (s, 9H, CH_3, *t*-Bu), 1.84 (q, 2H, CH_2, $^3J_{H-H}$ = 7.6 Hz), 2.22 (t, 2H, CH_2, $^3J_{H-H}$ = 7.6 Hz), 2.39 (t, 1H, CH_2Me, $^3J_{H-H}$ = 7.2 Hz), 2.45 (t, 1H, CH_2, $^3J_{H-H}$ = 7.6 Hz). ^{13}C NMR: δ 8.0 (CH_3), 19.4 (CH_2), 28.3 (CH_3, *t*-Bu), 34.8 (CH_2), 36.1 (CH_2-Me), 41.4 (CH_2), 80.5 (C, *t*-Bu), 172.8 (CO), 211.1 (CO).

General Procedure for the Preparation of δ-Hydroxy Esters. *tert*-Butyl 5-Hydroxyhexanoate (1a). To a solution of **5a** (0.93 g, 5 mmol) in methanol (25 mL) was added $NaBH_4$ (94.6 mg, 2.5 mmol) at 0 °C. The reaction mixture was stirred for 2 h. The mixture was then quenched with saturated NH_4-Cl (25 mL), and the methanol was evaporated. The mixture was extracted with CH_2Cl_2 (3 × 25 mL), and the combined ether phases were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography to give 0.86 g (92%) of alcohol **1a** as a colorless oil. ^{1}H NMR: δ 1.19 (d, 3H, CH_3, $^3J_{H-H}$ = 6.4 Hz), 1.43 (s, 9H, CH_3, *t*-Bu), 1.46 (m, 2H, CH_2), 1.65 (m, 2H, CH_2), 2.24 (dt, 2H, CH_2, $^3J_{H-H}$ = 7.2 Hz, $^3J_{H-H}$ = 1.2 Hz), 3.80 (m, 1H, CH). ^{13}C NMR: δ 21.3 (CH_2), 23.7 (CH_2), 28.3 (CH_3, *t*-Bu), 35.5 (CH_3), 38.5 (CH_2), 67.8 (CH), 80.4 (C, *t*-Bu), 173.4 (CO). GC retention times: 20.9 (*S*), 20.9 (*R*).

***tert*-Butyl 5-Hydroxyheptanoate (1b).** Yield: 0.92 g (91%). ^{1}H NMR: δ 0.93 (t, 3H, CH_3, $^3J_{H-H}$= 7.6 Hz), 1.45 (s, 9H, CH_3, *t*-Bu), 1.48 (m, 4H, CH_2, CH_2Me), 1.68 (m, 2H, CH_2), 2.24 (t, 2H, CH_2, $^3J_{H-H}$ = 6.8 Hz), 3.51 (m, 1H, CH). ^{13}C NMR: δ 10.1 (CH_3), 21.3 (CH_2), 28.3 (CH_3, *t*-Bu), 30.5 (CH_2Me), 35.6 (CH_2), 36.5 (CH_2), 72.9 (CH), 80.4 (C, *t*-Bu), 173.4 (CO). GC retention times: 33.8 (*S*), 34.0 (*R*).

General Procedure for the Preparation of δ-Acetoxy Esters. *tert*-Butyl 5-Acetoxyhexanoate (2a). To a solution of **1a** (0.19 g, 1 mmol) in dichloromethane (5 mL) were added triethylamine (1 mL) and acetic anhydride (5 mmol) at 0 °C. The reaction was then stirred at room temperature overnight. The mixture was then evaporated and the residue purified by chromatography to give 207 mg (90%) of acetate **2a** as a colorless oil. ^{1}H NMR: δ 1.20 (d, 3H, CH_3, $^3J_{H-H}$ = 6.4 Hz), 1.43 (s, 9H, CH_3, *t*-Bu), 1.57 (m, 4H, CH_2), 2.01 (s, 3H, CH_3-CO), 2.21 (t, 2H, CH_2, $^3J_{H-H}$ = 7.2 Hz), 4.89 (m, 1H, CH). ^{13}C NMR: δ 20.1 (CH_3), 21.1 (CH_2), 21.6 (CH_3CO), 28.3 (CH_3, *t*-Bu), 35.4 (2C, CH_2), 70.7 (CH), 80.4 (C, *t*-Bu), 170.9 (CO), 172.9 (CO). GC retention times: 39.2 (*S*), 39.5 (*R*).

***tert*-Butyl 5-Acetoxyheptanoate (2b).** Yield: 232 mg (95%). ^{1}H NMR: δ 0.86 (t, 3H, CH_3, $^3J_{H-H}$ = 7.6 Hz), 1.42 (s, 9H, CH_3, *t*-Bu), 1.56 (m, 6H, 2 × CH_2, CH_2Me), 2.03 (s, 3H, CH_3CO), 2.20 (t, 2H, CH_2, $^3J_{H-H}$ = 7.2 Hz), 4.78 (m, 1H, CH). ^{13}C NMR: δ 9.74 (CH_3), 21.0 (CH_2), 21.4 (CH_3CO), 27.0 (CH_2-Me), 28.3 (CH_3, *t*-Bu), 33.0 (CH_2), 35.4 (CH_2), 75.2 (CH), 80.3 (C, *t*-Bu), 171.1 (CO), 172.9 (CO). GC retention times: 23.8 (*S*), 30.5 (*R*).

General Procedure for the Kinetic Resolution of δ-Hydroxy Esters. *tert*-Butyl (*R*)-5-Acetoxyhexanoate ((*R*)-2a). To a solution of *rac*-**1a** (18.8 mg, 0.1 mmol) and **3** (66 mg, 0.3 mmol) in dry toluene (1 mL) under argon (5 min of argon bubbling) was added the lipase PS-C (5 mg). The resulting reaction mixture was stirred at 60 °C for 2.5 h. The enzyme was then filtered off and washed with toluene (3 × 5 mL). The combined toluene phases were evaporated, and the residue was analyzed. The product (*R*)-**2a** was obtained in 37% conversion and in >99% ee.

General Procedure for the DKR of δ-Hydroxy Esters. *tert*-Butyl (*R*)-5-Acetoxyhexanoate ((*R*)-2a). To a solution of *rac*-**1a** (112.8 mg, 0.6 mmol) and **3** (336 mg, 1.8 mmol) in dry toluene (6 mL) under argon were added ruthenium catalyst **4** (48.7 mg, 6 mol %) and lipase PS-C (6 mg). The resulting reaction mixture was bubbled with H_2 for 5 min, and the reaction mixture was stirred at 70 °C for 72 h under a hydrogen atmosphere. The enzyme was then filtered off and washed with toluene (3 × 5 mL). The combined toluene phases were evaporated, and the product was purified by flash chromatography (pentane/ethyl acetate, 15/1) to yield 110.4 mg (80%) of (*R*)-**2a** in 98% ee.

General Procedure for the Synthesis of (*R*)-Lactones 10. (*R*)-6-Methyltetrahydropyran-2-one ((*R*)-10a). To a solution of δ-acetoxy ester (*R*)-**2a** (92.1 mg, 0.4 mmol) in toluene/methanol (4 mL) was added LiOH (12 mg, 0.5 mmol). The solution was allowed to stir at room temperature for 12 h. Then the solution was acidified (pH 1) with HCl. The

(17) Prepared by hydrolysis of methyl 5-ketoheptanoate.

reaction was allowed to stir for 2 h at 60 °C. The mixture was then evaporated, the residue was extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic phases were dried over Na_2SO_4 and evaporated to afford lactone **10a** as a colorless oil (44 mg, 96%). The characterization data are in agreement with those previously reported for (*R*)-**10a**[18] ($[\alpha]_D^{20}$ +36.9 (*c* 1.82, EtOH) [lit.[19] $[\alpha]_D^{20}$ +37.2 (*c* 1.82, EtOH)]) and (*R*)-**10b**[5a] ($[\alpha]_D^{20}$ +54.1 (*c* 1.13, THF) [lit.[5a] $[\alpha]_D^{20}$ +55.0 (*c* 1.13, THF]).

Synthesis of *tert*-Butyl (*S*)-5-(*tert*-Butyldimethylsiloxy)heptanoate ((*S*)-11). *tert*-Butyldimethylsilyl triflate (114 μL, 0.5 mmol) was added to a solution of (*S*)-**1b** (94 mg, 0.46 mmol) and 2,6-lutidine (235 μL, 2 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The solution was then stirred at room temperature for 90 min and quenched with a 10% aqueous citric acid solution (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic phases were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (pentane/ethyl acetate, 10/1) to give 132 mg (91%) of **11** as a colorless oil. ^{1}H NMR: δ 0.03 (s, 6H, CH_3Si), 0.84 (m, 3H, CH_3), 0.88 (s, 9H, CH_3, *t*-BuSi), 1.42 (m, 13H, CH_2, CH_2Me, CH_3, *t*-Bu), 1.60 (m, 2H, CH_2), 2.19 (t, 1H, CH_2, $^3J_{H-H}$= 7.6 Hz), 3.57 (m, 1H, CH). ^{13}C NMR: δ −4.3 (CH_3Si), −4.2 (CH_3Si), 9.68 (CH_3), 18.3 (CSi), 21.3 (CH_2), 26.1 (CH_3, *t*-BuSi), 28.3 (CH_3, *t*-Bu), 29.8 (CH_2Me), 36.0 (2C, CH_2), 73.3 (CH), 80.1 (C, *t*-Bu), 173.3 (CO).

Synthesis of (*S*)-5-(*tert*-Butyldimethylsiloxy)heptanal ((*S*)-12). To a solution of (*S*)-**11** (100 mg, 0.32 mmol) in CH_2Cl_2 (2 mL) was added dropwise DIBALH (0.33 mL of a 1 M solution in hexanes, 0.33 mmol) at −78 °C. The solution was then stirred for 1 h and quenched with MeOH (0.25 mL) and saturated Rochelle's salt solution (5 mL). The mixture was extracted with ethyl acetate (5 × 10 mL), and the combined organic phases were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (pentane/ethyl acetate, 15/1) to give 69 mg (88%) of **12** as a colorless oil. The characterization data are in agreement with those previously reported for (*S*)-**12**.[11]

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