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Lipase-catalyzed kinetic resolution of *Z*-configured homoallylic alcohols

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Abstract

Racemic *Z* homoallylic alcohols were prepared by the $BuSnCl_3$-catalyzed addition of aldehydes to 1-(tributylstannyl)-2-butene. These alcohols were resolved for the first time by lipase-catalyzed enantioselective acetylation in up to 98% enantiomeric purity.

1. Introduction

The *Z*-configured homoallylic alcohol functionality is found in numerous natural products and biologically active compounds, a few representatives are given in Fig. 1.[1–4] To date the only known enantio- and *Z*-selective synthesis of optically active homoallylic alcohols utilized the laborious resolution of diastereomeric phosphonium salts by fractional crystallization and subsequent Wittig olefination with appropriate aldehydes.[5] Alternatively, racemic ketene thioacetals with a homoallylic alcohol functionality have been kinetically resolved by lipase-catalyzed hydrolysis of the acetates in high enantiomeric excess.[6]

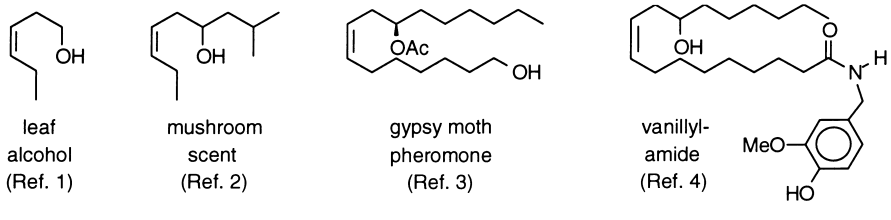

Figure 1. Representative natural products and biologically active compounds with a *Z*-configured homoallylic alcohol functionality

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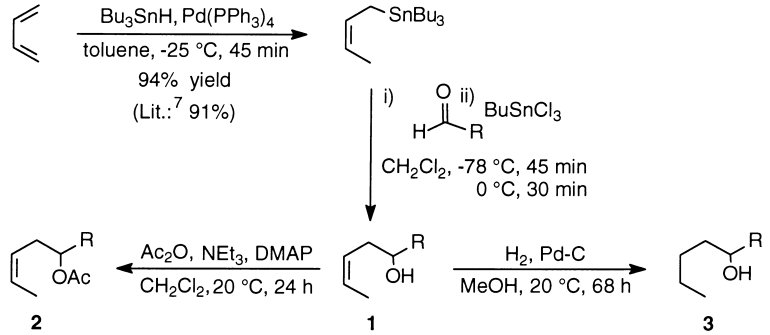
Since simple optically active *Z*-configured homoallylic alcohols should serve as potentially useful building blocks in the asymmetric synthesis and no convenient and efficient preparation is known so far, we have employed the kinetic resolution by lipase-catalyzed transesterification for this purpose. Presently we report that this method is convenient and effective for the preparation of these optically active building blocks.

2. Results and discussion

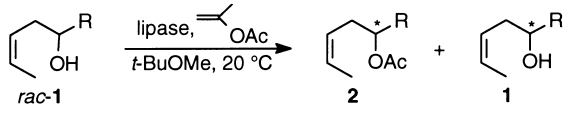
The racemic homoallylic alcohols **1a–d** were prepared in a two-step sequence (Scheme 1). The Pd(0)-catalyzed hydrostannation of butadiene afforded (*Z*)-1-tributylstannyl-2-butene in high yields,[7] the *Z*-selective conversion of this allylic tin derivative with aldehydes under Lewis acid catalysis followed the literature procedure for benzaldehyde.[8] The formation of the regioisomer with a terminal double bond was suppressed (≤5%) by choosing short reaction times and low temperatures.[8] Acetylation gave the acetates **2a–d**, and the catalytic hydrogenation of the homoallylic alcohols **1a**,**d** led to the saturated alcohols **3a**,**d** (Scheme 1).



	2	**1**	**3**
R	Yield [%]	Yield [%]	Yield [%]
Me (**a**)	46	86	39
i-Pr (**b**)	60	51	
t-Bu (**c**)	77	55	
Ph (**d**)	95	60	31

Scheme 1. Synthesis of the homoallylic alcohols **1a–d**, their acetylation and catalytic hydrogenation

The racemic homoallylic alcohols **1a–d** were submitted to enzyme-catalyzed acetylation[9] (Eq. 1), for which a variety of lipases were screened (Boehringer screening set of lipases, L-1 to L-9, E-1 and E-2). The lipases, which gave conversions below 20% within 14 days were not further considered, the others are listed in Table 1. The isopropyl **1b** and *tert*-butyl **1c** derivatives were not acetylated by any of the available lipases and were not further studied. Also the enzymatic hydrolysis of the acetate **2c** failed by all lipases that were used in 0.1 M phosphate buffer (pH 7) with 40% MeOH as cosolvent at 37°C for 4 days.



rac-**1** **2** **1** (1)

The most effective enzyme for the smallest homoallylic alcohol **1a** is lipase CAL-2 (from *Candida antarctica*, fraction B; CHIRAZYME® L-2, Boehringer Mannheim). On the analytical scale (100 μmol), the reaction of alcohol *rac*-**1a** with isopropenyl acetate and CAL-2 gave at ca. 50% conversion an

Table 1
Kinetic resolution of the homoallylic alcohols **1a**,**d** and of the saturated alcohol **3d** by lipase-catalyzed acetylation

Entry	Substrate	Lipase[c)]	Enzyme / Substrate ═<OAc [mg : mmol]	[equiv.]	Time	Convn[a)] [%]	Enantiomeric excess [%][b)] Alcohol	Acetate	E[d)]
1	**1a** (Me)	CAL-2	36	5	3 h	49	94 (*S*)[e)]	>98 (*R*)	>200
2	**1a** (Me)	BSL	36	12	1 h	24	22 (*S*)	70 (*R*)	14
3	**1d** (Ph)	BSL	533	15	9 d	10	10 (*S*)	90 (*R*)	21
4	**1d** (Ph)	BSL	133	5	2 d	47	44 (*S*)	52 (*R*)	5
5	**1d** (Ph)	BSL	133	5	4 d	75	>98 (*S*)[e)]	32 (*R*)	8
6	**1d** (Ph)	BSL	600	20	13 d	67	>98 (*S*)	48 (*R*)	12
7	**1d** (Ph)	PSL	333	15	19 d	39	40 (*S*)	62 (*R*)	6
8	**3d** (Ph)	BSL	157	6	4 d	52	88 (*S*)	80 (*R*)	28

[a)] The conversion was calculated from the enantiomeric excess of the starting material (ee_s) and the product (ee_p) according to % convn = ee_s / (ee_s + ee_p), cf. Ref. 10.

[b)] The enantiomeric excess (ee) was determined by multi-dimensional gas chromatography (MDGC) by employing a achiral OV 1701 column and a permethylated β-cyclodextrin column packed with DB 1701 for **1a** or by HPLC (CHIRACEL OD-H, Daicel Chemical Industries Ltd.) for **1d** and **3d**.

[c)] BSL: *Burkholderia sp.*, CAL-2: *Candida antarctica*, fraction B, PSL: *Pseudomonas sp.*

[d)] The enantioselectivity (E) was calculated from the enantiomeric excess of the starting material (ee_s) and the conversion according to E = ln [(1 − convn) (1 − ee_s)] / ln [(1 − convn) (1 + ee_s)], cf. Ref. 10.

[e)] The absolute configuration was assessed by chemical correlation (see text).

enantiomeric excess (ee) of 94% for the (*S*)-**1a** alcohol and >98% for the (*R*)-**2a** acetate (entry 1). The nearly enantiomerically pure homoallylic derivatives (*S*)-**1a** and (*R*)-**2a** were easily separated by silica gel chromatography. The lipase BSL (*Burkholderia* sp., CHIRAZYME® L-1, Boehringer Mannheim) was also reactive, but much less enantioselective than CAL-2 (entry 2).

The enzyme CAL-2 acetylates the phenyl-substituted homoallylic alcohol **1d** very slowly (in 19 d, only 2% conversion). This substrate, with two relatively large substituents, is not well accepted by this lipase, but good conversions are obtained with BSL (entries 3–6). The best enantiomeric excess (>98%) for the alcohol **1d** was achieved at 67% conversion (entry 6); unfortunately, under these conditions only a moderate ee value (48%) was obtained for the acetate **2d** product. At nearly 50% conversion, the ee values are 44% for the alcohol **1d** and 52% for the acetate **2d** (entry 4). The lipase PSL (*Pseudomonas* sp.; CHIRAZYME® L-6, Boehringer Mannheim) also acetylated the substrate **1d**, but at 39% conversion only moderate enantiomeric excesses were observed for both the alcohol and acetate (entry 7). These

analytical results for the kinetic resolution of the homoallylic alcohols **1a**,**d** are reproducible on the semi-preparative scale (1–3 mmol).

The saturated alcohol **3d** was also enantiomerically acetylated by BSL to compare the efficacy of enantioselection between the *n*-butyl chain and the *Z*-crotyl group. At nearly 50% conversion, the ee values were 88% for the alcohol **3d** and 80% for the corresponding acetate **4d** (entry 8).

As reference samples for the MDGC and HPLC analysis, it was necessary to synthesize the racemic acetates **2** by acetylation of the homoallylic alcohols **1** with acetic anhydride under basic conditions (Scheme 1). All four homoallylic acetates **2a**–**d** are new and have been completely characterized.

To assign the absolute configuration of the homoallylic alcohols (+)-**1a** and (−)-**1d** obtained in the enzymatic resolution, these optically active compounds were hydrogenated[11] on the palladium-on-carbon catalyst to afford the known saturated alcohols (+)-**3a** and (−)-**3d** (Scheme 1).[12] The chemical correlation for both homoallylic substrates **1a**,**d** and the saturated alcohol **3d** revealed that the lipases convert preferentially the (*R*) enantiomer. This sense in the enantioselection is in good accord with the established empirical rule proposed by Kazlauskas et al.[13] for the kinetic resolution of secondary alcohols, which is based on the relative size of the substituents at the stereogenic carbon center (Fig. 2). In the homoallylic alcohol **1a**, the small substituent is methyl and the large one is the *Z*-crotyl group. This small substrate was converted very quickly and highly selectively by CAL-2 (3 h). In the phenyl-substituted alcohol **1d**, the crotyl group takes the place of the small substituent, but this substrate is presumably too large to fit into the active site of the CAL-2 enzyme so that the conversion is very slow (19 days, 2% convn). However, the lipase from *Burkholderia* sp. (BSL) accepts the alcohol **1d** with moderate enantiodifferentiation, which implies that the latter enzyme may possess a bigger enzyme pocket. Unfortunately, this enzyme does not distinguish well between the crotyl and phenyl groups and the enantioselectivity values are only moderate (E≤20, Table 1, entries 3–6).

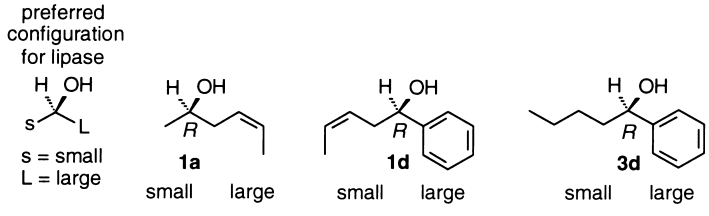


Figure 2. Selected enantiomers in the lipase-catalyzed acetylation of the alcohols **1a**,**d** and **3d**

The lipase-catalyzed kinetic resolution of the saturated alcohol **3d** was much better than that of the homoallylic alcohol **1d** at comparable conversion. The reason for this may be that the more flexible *n*-butyl chain fits better in the active site of the enzyme than the *Z*-crotyl group.

3. Conclusion

The homoallylic alcohols **1a**,**d** and the acetates **2a**,**d** were obtained optically active for the first time by lipase-catalyzed kinetic resolution. This is a convenient and effective preparation of optically active *Z*-configured homoallylic alcohols. By hydrolysis of the optically active acetates **2a**,**d**, which are the products of the lipase-catalyzed acetylation, both enantiomers of these potentially useful building blocks are now available for asymmetric synthesis.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AC 250 (^{1}H: 250 MHz; ^{13}C: 63 MHz), with $CHCl_3$ contained in $CDCl_3$ as reference standard. Multi-dimensional gas chromatography (MDGC) was performed on a HRGC MEGA 2, Series 8560 Fisons Instruments chromatograph, equipped with two columns and two EL 980 detectors from CE Instruments. The stationary phase of the achiral column A was OV 1701 (30 m, 0.25 mm), for the chiral column B it was 30% permethylated β-cyclodextrin on DB 1701 (CYCLODEX-B from J&W, 30 m, 0.25 mm) or dimethylpentyl β-cyclodextrin on OV 1701 (DMEPEBETA from MEGA, 25 m, 0.25 mm). The carrier was hydrogen gas with pressures of 150 kPa (column A) and 100 kPa (column B). The injection temperature was 190°C. HPLC analyses were carried out on Kontron equipment, furnished with a spectrophotometer UVIKON 720 and CHIRALYSER 1.6 from IBZ Messtechnik. The stationary phase was a chiral column (CHIRACEL OD-H from Daicel Chemical Industries Ltd). IR spectra were recorded on a Perkin–Elmer 1420 ratio recording infrared spectrophotometer. The specific rotation $[\alpha]_D^{20}$ was determined on a Perkin–Elmer 241 MC polarimeter by using $CHCl_3$ as solvent. TLC analysis was conducted on precoated silica gel foils Polygram SIL G/UV$_{254}$ from Machery and Nagel. Spots were visualized by phosphomolybdic acid. Silica gel (32–64 μm, Woelm) was used for flash chromatography. The lipases were obtained as gift samples from Boehringer Mannheim and used as received.

4.2. General procedure for the synthesis of the homoallylic alcohols *1a–d*[8]

To a solution of 5.00 g (14.5 mmol) of (*Z*)-tributyltin-2-butene[7] and 15.9 mmol of aldehyde in 30 mL CH_2Cl_2 under a nitrogen atmosphere were added 2.42 mL (14.5 mmol) of butyltin trichloride in 10 mL of CH_2Cl_2 over a period of 45 min at −78°C. After an additional 30 min stirring, the mixture was allowed to warm up to 0°C, stirred at that temperature for 1 h, treated with H_2O (10 mL), and extracted with Et_2O (3×10 mL). The combined organic phases were dried over $MgSO_4$ and purified by distillation to give the homoallylic alcohols **1a–d** as colorless oils, which contained about 5% of the regioisomers with the terminal double bond. Yields are given in Scheme 1. For the lipase-catalyzed kinetic resolution, the homoallylic alcohols were purified by flash chromatography (4:1 petroleum ether:Et_2O).

4.2.1. (Z)-4-Hexen-2-ol *1a*

Colorless oil; bp 52°C/15 torr (lit.[14] 50°C/15 torr); ^{1}H NMR: δ 1.21 (d, 3H, 1-H), 1.59 (br s, 1H, OH), 1.64 (ddt, *J*=5.8, 1.8, 0.9 Hz, 3H, 6-H), 2.22 (dd, *J*=7.6, 0.9 Hz, 2H, 3-H), 3.84 (sext, *J*=6.1 Hz, 1H, 2-H), 5.43 (dtq, *J*=10.7, 7.0, 1.5 Hz, 1H, 4-H), 5.65 (dqt, *J*=10.7, 6.7, 1.5 Hz, 1H, 5-H); ^{13}C NMR: δ 13.0 (q, C-6), 22.7 (q, C-1), 36.7 (t, C-3), 67.7 (d, C-2), 126.0 (d, C-5), 127.3 (d, C-4); GC (CYCLODEX-B): t_R (45°C isothermal)=28.4 (−), 28.8 (+).

4.2.2. (Z)-2-Methyl-5-hepten-3-ol *1b*[15]

Colorless oil; bp 90°C/38 torr; ^{1}H NMR (200 MHz): δ 0.95 (dd, *J*=6.7, 2.3 Hz, 6H, 1-H), 1.55 (br s, 1H, OH), 1.65 (dt, *J*=6.6, 1.2 Hz, 3H, 7-H), 1.70 (m, 1H, 2-H), 2.22 (t, *J*=7.1 Hz, 2H, 4-H), 3.47 (q, 7.1 Hz, 1H, 3-H), 5.44 (dtq, *J*=10.9, 7.2, 1.7 Hz, 1H, 5-H), 5.70 (dqt, *J*=10.9, 6.6, 1.2 Hz, 1H, 6-H); ^{13}C NMR: δ 13.0 (q, C-7), 17.5 (q, C-1), 18.8 (q, C-1), 31.8 (t, C-4), 33.1 (d, C-2), 76.2 (d, C-3), 126.6 (d, C-6), 127.2 (d, C-5); GC (DMEPEBETA): t_R [40°C (25 min) → 70°C (5°C/min)]=41.9, 42.1.

4.2.3. (Z)-2,2-Dimethyl-5-hepten-3-ol ***1c***[15]

Colorless oil, bp 94°C/38 torr; ^{1}H NMR: δ 0.94 (s, 9H, 1-H), 1.58 (br s, 1H, OH), 1.64 (d, *J*=6.7 Hz, 3H, 7-H), 2.19 (m, 2H, 4-H), 3.24 (dd, *J*=9.8, 3.4 Hz, 1H, 3-H), 5.46 (dtq, *J*=10.1, 8.9, 1.8 Hz, 1H, 5-H), 5.67 (dqt, *J*=10.1, 6.7, 1.2 Hz, 1H, 6-H); ^{13}C NMR: δ 13.0 (q, C-7), 25.8 (3×q, C-1), 29.4 (t, C-4), 34.7 (s, C-2), 79.1 (d, C-3), 127.2 (d, C-6), 127.8 (d, C-5); GC (DMEPEBETA): t_R [40°C (25 min) → 70°C (20°C/min)]=38.9, 39.4.

4.2.4. (Z)-1-Phenyl-3-penten-1-ol ***1d***[8]

Colorless oil; R_f (3:1 petroleum ether:Et_2O)=0.33; ^{1}H NMR: δ 1.61 (ddt, *J*=6.70, 1.53, 0.91 Hz, 3H, 5-H), 2.06 (br s, 1H, OH), 2.55 (m, 2H, 2-H), 4.72 (dd, *J*=7.60, 5.50 Hz, 1H, 1-H), 5.43 (dtq, *J*=10.7, 5.40, 1.50 Hz, 1H, 3-H), 5.65 (dqt, *J*=10.7, 6.70, 1.50 Hz, 1H, 4-H), 7.35–7.38 (m, 5H, Ph-H); ^{13}C NMR: δ 13.4 (q, C-5), 37.3 (t, C-2), 74.6 (d, C-1), 126.1 (d, C-4), 126.2 (2×d, Ph-C), 127.9 (d, C-3), 128.0 (d, Ph-C), 128.8 (2×d, Ph-C), 144.5 (s, Ph-C); HPLC (OD-H, 98:2 *n*-Hex:*i*-PrOH, flow 0.35 mL/min): t_R=41.8 (+), 48.3 (−).

4.3. General procedure for the acetylation of the homoallylic alcohols ***1a–d***

To a solution of 2.50 mmol of the homoallylic alcohol **1** in 50 mL of CH_2Cl_2 were added 2.75 mmol of acetic anhydride, 3.75 mmol of triethylamine and 1.00 mg of 4-(dimethylamino)pyridine (DMAP) and stirred at 20°C for 24 h. After concentration (20°C, 15 torr), flash chromatography (100:1 ratio of silica gel to substrate, petroleum ether:Et_2O) gave the esters **2a–d**. Yields are given in Scheme 1.

4.3.1. (Z)-2-Acetoxy-4-hexene ***2a***

Colorless oil; R_f (4:1 petroleum ether:Et_2O)=0.60; ^{1}H NMR: δ 1.21 (d, *J*=6.4 Hz, 3H, 1-H), 1.61 (ddt, *J*=6.7, 1.8, 0.9 Hz, 3H, 6-H), 2.02 (s, 3H, $OCOCH_3$), 2.22–2.35 (m, 2H, 3-H), 4.91 (sext, *J*=6.4 Hz, 1H, 2-H), 5.36 (dtq, *J*=11.0, 7.3, 1.8 Hz, 1H, 4-H), 5.59 (dqt, *J*=11.0, 6.7, 1.5 Hz, 1H, 5-H); ^{13}C NMR: δ 12.9 (q, C-6), 19.4 (q, C-1), 21.3 (q, $OCOCH_3$), 33.2 (t, C-3), 70.6 (d, C-2), 125.1 (d, C-5), 126.7 (d, C-4), 169.3 (s, $OCOCH_3$); IR (CCl_4): ν 1730, 1380 cm^{-1}; GC (CYCLODEX-B): t_R (45°C isothermal)=35.4 (−), 42.9 (+). Anal. calcd for $C_8H_{14}O_2$ (142.2): C, 67.57; H, 9.92. Found: C, 67.15; H, 9.50.

4.3.2. (Z)-3-Acetoxy-2-methyl-4-heptene ***2b***

Colorless oil; R_f (30:1 petroleum ether:Et_2O)=0.38; ^{1}H NMR: δ 0.91 (d, *J*=6.7 Hz, 6H, 1-H), 1.62 (dt, *J*=6.7, 0.9 Hz, 3H, 7-H), 1.83 (sept, *J*=6.7 Hz, 1H, 2-H), 2.04 (s, 3H, $OCOCH_3$), 2.30 (t, *J*=7.3 Hz, 2H, 4-H), 4.75 (dt, *J*=7.0, 5.8 Hz, 1H, 3-H), 5.35 (dqt, *J*=10.7, 7.3, 1.5 Hz, 1H, 5-H), 5.55 (dqt, *J*=10.7, 6.7, 1.5 Hz, 1H, 6-H); ^{13}C NMR: δ 12.9 (q, C-7), 17.6 (q, C-1), 18.7 (q, C-1), 21.1 (q, $OCOCH_3$), 28.9 (t, C-4), 31.0 (d, C-2), 78.1 (d, C-3), 125.5 (d, C-6), 126.3 (d, C-5), 170.9 (s, $OCOCH_3$); IR (neat): ν 1720, 1360, 1020 cm^{-1}; GC (DMEPEBETA): t_R [40°C (25 min) → 70°C (5°C/min)]=42.3, 43.8. Anal. calcd for $C_{10}H_{18}O_2$ (170.3): C, 70.55; H, 10.66. Found: C, 70.73; H, 10.44.

4.3.3. (Z)-3-Acetoxy-2,2-dimethyl-4-heptene ***2c***

Colorless oil; R_f (20:1 petroleum ether:Et_2O)=0.33; ^{1}H NMR: δ 0.92 (s, 9H, 1-H), 1.60 (dt, *J*=6.7, 0.9 Hz, 3H, 7-H), 2.02 (s, 3H, $OCOCH_3$), 2.25 (m, 2H, 4-H), 4.76 (dd, *J*=8.5, 4.6 Hz, 1H, 3-H), 5.33 (dtq, *J*=11.0, 7.6, 1.8 Hz, 1H, 5-H), 5.51 (dqt, *J*=11.0, 6.7, 1.2 Hz, 1H, 6-H); ^{13}C NMR: δ 12.8 (q, C-7), 21.0 (q, $OCOCH_3$), 25.9 (3×q, C-1), 27.3 (t, C-4), 34.5 (s, C-2), 80.2 (d, C-3), 125.9 (d, C-6), 126.7 (d, C-5), 170.9 (s, $OCOCH_3$); IR (neat): ν 1725, 1360, 1230, 1020, 705, 630 cm^{-1}; GC (DMEPEBETA): t_R [40°C

(25 min)→ 70°C (20°C/min)]=43.0, 43.3. Anal. calcd for $C_{11}H_{20}O_2$ (184.3): C, 71.70; H, 10.94. Found: C, 71.11; H, 10.43.

*4.3.4. (Z)-1-Acetoxy-1-phenyl-3-pentene **2d***

Colorless oil; R_f (4:1 petroleum ether:Et_2O)=0.49; ^{1}H NMR: δ 1.55 (ddt, *J*=6.70, 1.83, 0.93 Hz, 3H, 5-H), 2.07 (s, 3H, $OCOCH_3$), 2.44–2.76 (m, 2H, 2-H), 5.30 (dtq, *J*=11.0, 7.33, 1.83 Hz, 1H, 3-H), 5.53 (dqt, *J*=11.0, 6.70, 1.53 Hz, 1H, 4-H), 5.76 (dd, *J*=6.40, 7.33 Hz, 1H, 1-H), 7.30–7.38 (m, 5H, Ph-H); ^{13}C NMR: δ 12.8 (q, C-5), 21.2 (q, $OCOCH_3$), 33.9 (t, C-2), 75.5 (d, C-1), 124.6 (d, C-3), 126.5 (2×d, Ph-C), 127.1 (d, Ph-C), 127.9 (d, C-4), 128.3 (2×d, Ph-C), 140.3 (s, Ph-C), 170.3 (s, $OCOCH_3$); IR (neat): ν=1740, 1495, 1455, 1375, 1240, 1030, 810 cm^{-1}; HPLC (OD-H, 98:2 *n*-Hex:*i*-PrOH, flow 0.35 mL/min): t_R=13.9 (+), 15.0 (−). Anal. calcd for $C_{13}H_{16}O_2$ (204.3): C, 76.44; H, 7.90. Found: C, 76.3; H, 8.06.

4.4. General procedure for the lipase-catalyzed transesterification

To a solution of 100 μmol of the homoallylic alcohol **1a**–**d** in 2.0 mL of *t*-BuOMe was added the appropriate lipase and isopropenyl acetate (5.0 equiv.). The mixture was vigorously stirred at ca. 20°C for the time indicated in Table 1, the enzyme was removed by filtration and the solvent evaporated at reduced pressure (20°C/12 torr). The crude samples were analyzed by gas chromatography or by HPLC. In the case of semi-preparative-scale reactions, the homoallylic alcohols and acetates were separated by flash chromatography (4:1 petroleum ether:Et_2O).

*4.4.1. (S)-(+)-(Z)-4-Hexen-2-ol [(S)-(+)-**1a**]*

$[\alpha]_D^{20}$=+3.48 (*c*=0.71, $CHCl_3$) for 94% ee.

*4.4.2. (R)-(+)-(Z)-2-Acetoxy-4-hexene [(R)-(+)-**2a**]*

$[\alpha]_D^{20}$=+25.7 (*c*=0.80, $CHCl_3$) for >98% ee.

*4.4.3. (S)-(−)-(Z)-1-Phenyl-3-penten-1-ol [(S)-(−)-**1d**]*

$[\alpha]_D^{20}$=−43.2 (*c*=0.50, $CHCl_3$) for >98% ee.

*4.4.4. (R)-(+)-(Z)-1-Acetoxy-1-phenyl-3-pentene [(R)-(+)-**2d**]*

$[\alpha]_D^{20}$=+34.2 (*c*=0.74, $CHCl_3$) for 48% ee.

*4.5. Lipase-catalyzed hydrolysis of the acetate **2c***

The acetate **2c** (100 μmol) was dissolved in 0.1 M phosphate buffer (1 mL, pH 7), which contained 40% methanol as a cosolvent. The lipase powder was added, the mixture was heated to 37°C for 4 days, extracted with Et_2O (5×2 mL), dried over Na_2SO_4, and the solvent evaporated at reduced pressure (20°C/12 torr). The crude samples were analyzed by gas chromatography. No conversion was observed with any of the lipases employed in this work.

*4.6. General procedure for the hydrogenation of **1a**,**d**[11]*

A suspension of 1.00 mmol of homoallylic alcohol **1a**,**d** in 30 mL of methanol and 5.00 mg of palladium-on-carbon catalyst was stirred at room temperature (ca. 20°C) for 68 h under a hydrogen

atmosphere. After filtration over Celite and removal of the solvent (50°C/250 torr), the saturated alcohols **3a**,**d** were obtained as colorless oils. Yields are given in Scheme 1.

*4.7. General procedure for the hydrolysis of the acetates **2***

To a solution of 1.45 mmol of acetate **2** in 30 mL of methanol were added 150 mg (1.08 mmol) of potassium carbonate. After stirring for 6 h, the solvent was removed (40°C/250 torr). The residue was taken up in 5 mL of CH_2Cl_2 and the solid material removed by filtration. Flash chromatography (100:1 ratio of silica gel to substrate, petroleum ether:Et_2O) gave the corresponding alcohol **1**.

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