Lipase-catalyzed transesterification of primary alcohols: resolution of 2-ethylhexan-1-ol and 2-ethylhex-5-en-1-ol

Krystyna Baczko and Chantal Larpent *

Université de Versailles-Saint Quentin en Yvelines, SIRCOB CNRS ESA 8086, 45 Avenue des Etats Unis, 78035 Versailles Cédex, France. E-mail: chantal.larpent@chimie.uvsq.fr; Tel: (33) 1.39254413; Fax: (33) 1.39254452

Received (in Cambridge, UK) 4th October 1999, Accepted 24th December 1999

Both the (*R*) and (*S*) enantiomers of 2-ethylhex-5-en-1-ol (*R*)-(−)-**1**, (*S*)-(+)-**1** and 2-ethylhexan-1-ol (*R*)-(−)-**2**, (*S*)-(+)-**2** were prepared in good yields and in high enantiomeric excess *via* lipase-catalyzed transacetylation of racemic alcohols **1** and **2** with vinyl acetate. Various experimental conditions (lipase PSL or PLF, solvent and temperature ranging from 30 to −30 °C) are used and their influence on the enantioselectivity and on the reaction rate is evaluated. The (*S*) unsaturated alcohol **1** is specifically esterified by lipase PS in CH_2Cl_2 at 0 °C with a very high enantiomeric ratio ($E \sim 750$) thus allowing the production of both enantiomers (*R*)-(−)-**1** and (*S*)-(+)-**1** with fairly good yields from the same enzymatic transformation. The comparison of unsaturated and saturated primary alcohols **1** and **2** shows that, for a similar atomic framework, the enantioselectivity of PSL is greatly enhanced by the presence of a terminal double bond. On the other hand, an enhancement of PSL enantioselectivity without loss of catalytic activity is achieved by decreasing the temperature to −30 °C thus giving access to both enantiomers.

Introduction

In the course of our studies to develop new chiral surfactants with multiple stereocenters, we are involved in the synthesis of sulfosuccinic diesters, analogs of the well-known Aerosol OT®, with various enantiopure branched alkyl chains. To achieve this goal, we needed efficient and general methods to produce enantiomerically pure, saturated or unsaturated, primary alcohols. We turned to enzymatic reactions since during the last decade lipase-catalyzed transformations have proved successful for kinetic resolutions of numerous secondary alcohols. Nevertheless, the methodologies devised for secondary alcohols are usually less efficient for primary ones[1] since the stereogenic center is far from the reacting group.[2] Mechanistic studies of active site models[3–5] and substrate mapping[2,4,5] indicate that the enantioselectivity toward primary alcohols requires a significant difference in the size and the shape of β-substituents and depends on the favored conformations along the C1–C2 bond.[1] Accordingly, from previous studies of enzymatic transformation of unsaturated substrates,[3a,6,7] it turns out that the presence of a double bond in the substrate usually increases the selectivity. Some improvements of lipase-catalyzed resolutions of primary alcohols have been achieved by optimizing the experimental conditions *e.g.* the proper choice of the solvent,[7,8] of the acylating reagent[8a,9] or the introduction of additives.[4b,10] Although scarcely studied, it has been found that for a given enzymatic reaction the enantioselectivity also depends on physical parameters such as pressure[11] and temperature.[12]

In this paper we describe our studies of the lipase-catalyzed transesterification of 2-ethyl-substituted primary alcohols **1** (2-ethylhex-5-en-1-ol) and **2** (2-ethylhexan-1-ol) with the aim of producing both (*R*) and (*S*) enantiomers from the same enzymatic transformation. Indeed, the preparation of (*R*)-**1** has recently been described *via* asymmetric alkylation of dihydrofuran followed by hydrovinylation (51% yield, ee > 0.99)[13] and *via* Evans' method in several steps (50% yield, ee > 0.98).[14] Nevertheless, to our knowledge, neither the synthesis of (*S*)-**1** or *rac*-**1** nor the enzymatic resolution of *rac*-**1** have ever been reported.

On the other hand, there are some papers reporting enzymatic transformations of **2** but none of them affords both enantiomers with acceptable yields and enantiomeric purities. Thus the (*S*)-rich acetate of **2** has been obtained in 60% yield (ee 0.75) by porcine pancreatic lipase-catalyzed transesterification with oxime acetate[15] while lipase from *Penicillium camembertii* preferentially acylates the (*R*)-enantiomer affording (*S*)-rich-**2** (23% yield, ee 0.47).[16] Lipase from *Pseudomonas species* (PSL) in butanol catalyzes the hydrolysis of 2-ethylhexyl butyrate in butanol leading to (*S*)-**2** (15% yield, ee 0.61).[16] We obtained optically pure (*R*)-**2** (21% yield, ee > 0.99) by vinyl acetate transesterification catalyzed by lipase from *Pseudomonas fluorescens* (PLF) in THF, but the optical purity of the (*S*)-acetate was still low (ee 0.32).[17] Similar results have been obtained with the lipase from *Pseudomonas species* in CH_2Cl_2.[7] Otherwise, (*R*)- and (*S*)-**2** have been prepared using chemical processes respectively from hexene[18] and from (*S*)-2-ethylhexanoic acid.[19]

The results reported in this paper show that by optimizing the experimental conditions (lipase, solvent, temperature) both the (*R*) and (*S*) enantiomers of **1** and **2** can be efficiently prepared from the racemic material.

Results and discussion

Preparation of 1 and determination of the enantiomeric excess

Synthesis of 2-ethylhex-5-en-1-ol 1. Various synthetic approaches including malonic ester synthesis, oxy-Cope rearrangement and alkylation of carboxylic acid have been tested to prepare the racemic unsaturated alcohol **1**.[20] Among them the alkylation of hexenoic acid followed by reduction has been found to be the most efficient (Scheme 1). Thus, hex-5-enoic acid was treated with lithium diisopropylamide and the resulting dianion alkylated with iodoethane to furnish the ethylated hexenoic acid **3** (95%) accompanied by small amounts of dialkylated product and unreacted acid. This crude mixture was reduced with $LiAlH_4$ in ether and chromatographic purification gave 2-ethylhex-5-en-1-ol **1** in 60% overall yield from hex-5-enoic acid.

DOI: 10.1039/a907987d

Table 1 Enzymatic transacetylation of 2-ethylhex-5-en-1-ol **1** and 2-ethylhexan-1-ol **2**

Entry	Substrate	Lipase (conc./mg mmol^{-1})	Reaction conditions: Solv.	*T*/°C	*t*/h	τ[a] (%)	Alcohol (*R*): Yield (%)[c]	$[\alpha]_D$[d]/10^{-1} deg cm^2 g^{-1}	ee[e]	Acetate (*S*): Yield (%)[c]	$[\alpha]_D$[f]/10^{-1} deg cm^2 g^{-1}	ee[g]	*E*[b]
1	*rac*-**1**	PSL (10)	CH_2Cl_2	30	48	61	27	−4.5[h,i]	0.96[j]	43	+6.4[h]	0.82	40
2	*rac*-**1**	PSL (15)	CH_2Cl_2	0	48	51	32	−4.5[h]	0.96[j]	45	+7.4[h]	0.99[j]	>750
3	*rac*-**2**	PLF (3.5)	THF	40	33	74	20	−3.4[k]	0.99[j]	69	+1.3[k]	0.30	8
4	(*S*)-**2** (0.30)[l]	PLF (3.5)	THF	40	18	78	20	−3.2	0.95	58	+2.5	0.62	10[m]
5	(*S*)-**2** (0.62)[l]	PLF (3.5)	THF	40	48	88	not isol[n]	—	—	80	+3.7	0.90	—
6	*rac*-**2**	PSL (10)	CH_2Cl_2	30	48	80	19	−3.1	0.92	68	+1.4	0.32	6
7	(*S*)-**2** (0.32)[l]	PSL (10)	CH_2Cl_2	30	48	78	19	−3.4	0.99[j]	75	+3.4	0.84	31[m]
8	(*S*)-**2** (0.84)[l]	PSL (10)	CH_2Cl_2	30	24	84	14	−2.9	0.85	77	+3.8	0.94	11[m]
9	*rac*-**2**	PSL (15)	CH_2Cl_2	0	48	66	31	−3.4	0.99[j]	61	+3.0	0.73	31
10	(*S*)-**2** (0.73)[l]	PSL (10)	CH_2Cl_2	30	24	90	8	−2.8	0.82	85	+4.0	0.97[j]	42[m]
11	*rac*-**2**	PSL (10)	CH_2Cl_2	−30	185	44	51	−3.0	0.86	41	+3.2	0.79	23
12	*rac*-**2**	PSL (15)	CH_2Cl_2	−30	78	58	40	−2.9	0.86	57	+3.5	0.86	37
13	*rac*-**2**	PSL (15)	CH_2Cl_2	−30	305	63	29	−3.4	0.99[j]	62	+3.2	0.78	41
14	*rac*-**2**	PSL (20)	CH_2Cl_2	−30	140	68	26	−3.4	0.99[j]	67	+3.0	0.72	31

[a] % Conversion determined by ^{1}H NMR spectroscopy. [b] $E = \ln [1 - c(1 + ee_S)]/\ln [1 - c(1 - ee_S)]$, $c = ee_R/ee_R + ee_S$.[25] [c] Isolated product. [d] (*c* 5.3, $CHCl_3$). [e] ee determined by ^{19}F NMR of the (*R*)-(+)-Mosher's ester and $[\alpha]_D$. [f] (*c* 4.4, $CHCl_3$). [g] ee determined by ^{19}F NMR after saponification and conversion of the resulting alcohol to the (*R*)-(+)-Mosher's ester and $[\alpha]_D$. [h] (*c* 1.2, $CHCl_3$). [i] Lit.,[14] (−4.7°). [j] Calculated from $[\alpha]_D$, NMR: ee > 0.95. [k] Lit.,[17] (−3.4°). [l] (*S*)-Rich alcohol **2** isolated by saponification of acetate **5** resulting from the previous transesterification. [m] $E = \ln [1 - c(1 + ee_S)/(1 + ee_o)]/\ln [1 - c(1 - ee_S)/(1 - ee_o)]$, $c = ee_o + ee_R/ee_R + ee_S$.[25] [n] Not isolated.

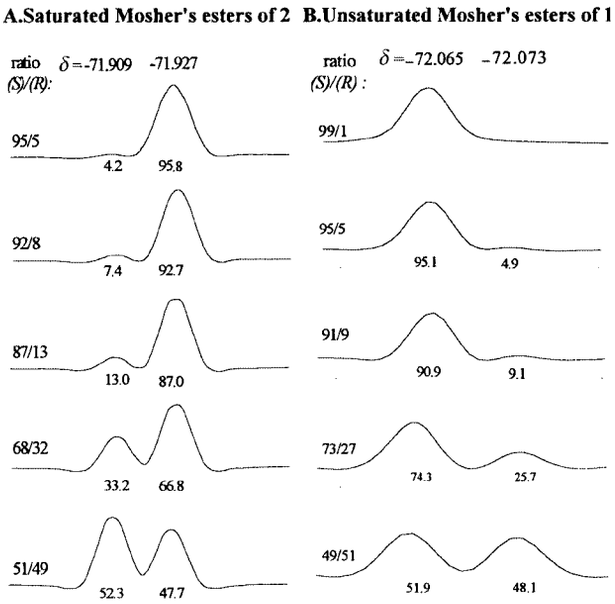
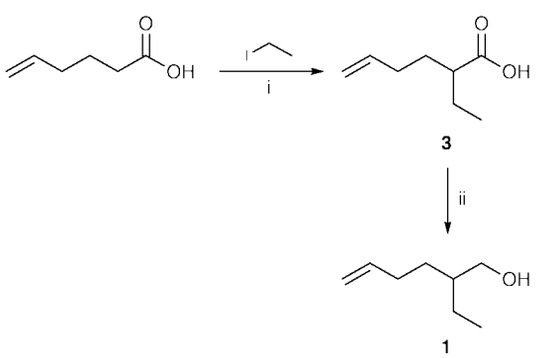


Fig. 1 ^{19}F NMR spectra of mixtures of diastereomeric Mosher's esters **6** and **7**.



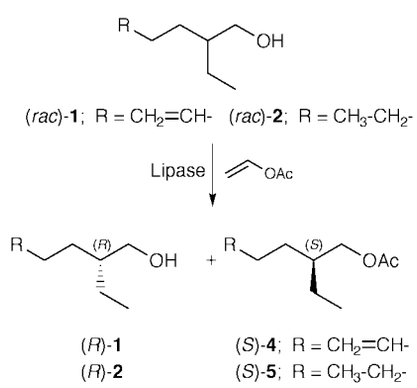
Scheme 1 *Reagents*: i, C_2H_5I (1.5 eq.), LDA in THF–heptane (2.5 eq.); ii, $LiAlH_4$ (2.5 eq.).

Determination of the enantiomeric purity of alcohols 1 and 2 by ^{19}F NMR. NMR methods involving chiral derivatizing agents such as the well known Mosher's acid (α-methoxy-trifluoromethylphenylacetic acid, MTPA)[21] have been developed for the determination of the enantiomeric purity of alcohols.[22] Nevertheless in the case of primary alcohols like **1** and **2**, the diastereomeric protons of the Mosher's esters are not sufficiently discriminated to allow a quantitative determination of the enantiomeric purity by ^{1}H NMR, even in the presence of europium shift reagents.[19,22a,23]

On the other hand, the two diastereomeric CF_3 signals of their (*R*)-MTPA esters **6** and **7** are clearly detected by ^{19}F NMR analysis[24] thus affording a useful direct method for the determination of enantiomeric excess of primary alcohols **1** and **2**. As shown in Fig. 1, the chemical shift difference between the two diastereomeric CF_3 signals ($\Delta\delta = 0.018$ ppm for **2** and 0.008 ppm for **1**) is large enough to permit a direct determination of the enantiomeric excess with a detection limit of up to 0.95. The enantiomeric excesses determined by this NMR method are in good agreement with GC analysis on a chiral column as well as with the specific rotations.[14,17] Similar results were obtained with α-fluorophenylacetic acid ($\Delta\delta = 0.02$ ppm) but this compound is not commercially available.

Enzymatic transesterifications of 1 and 2

The lipase-catalyzed transesterification of alcohols **1** and **2** with vinyl acetate has been performed under various conditions (Scheme 2 and Table 1). The conversion was monitored by ^{1}H NMR and the reaction was stopped by filtration of the lipase. The effects of lipase, substrate, solvent and temperature on the enantioselectivity of the enzymatic reaction were evaluated by the enantiomeric ratio *E*.[25]



Scheme 2

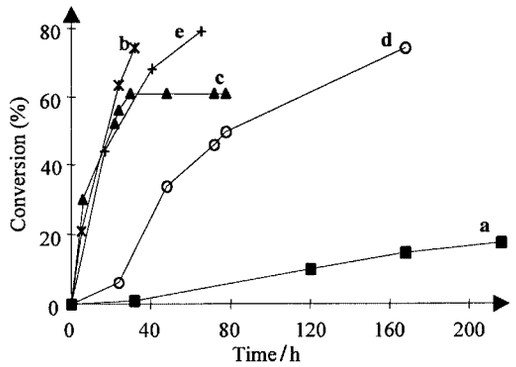


Fig. 2 Conversion *vs.* time for PLF and PSL catalyzed transesterification of **1** and **2** at 30 °C: –■– **a**, PLF–THF, **1**; –✳– **b**, PLF–THF, **2**; –▲– **c**, PSL–CH_2Cl_2, **1**; –○– **d**, PSL–THF, **1**; –+– **e**, PSL–CH_2Cl_2, **2**.

Lipase from *Pseudomonas fluorescens* (PLF) catalyzed transesterification. The transesterification using PLF as catalyst and vinyl acetate as acylating reagent at 40 °C in THF has been performed according to the previously described conditions.[19] As reported before, the saturated alcohol **2** is readily converted and (*R*)-(−)-**2** was obtained with high ee and good yield (Fig. 2b; entry 3 in Table 1). The other enantiomer (*S*)-(+)-**2**, isolated after saponification of the (*S*)-rich acetate **5**, was submitted to a second transesterification under the same conditions to give (*S*)-**2** with 62% enantiomeric excess after saponification. Finally, (*S*)-**2** with an ee of 0.90 was obtained by three times PLF-catalyzed esterification with an overall yield 19% (entries 3–5 in Table 1).

On the other hand, as can be seen from the conversion *versus* time curves (a and b) in Fig. 2, the presence of the terminal double bond in **1** almost inhibits the PLF activity in THF: after 9 days the conversion of 2-ethylhex-5-en-1-ol **1** was very low and did not exceed 18% (Fig. 2a).

Lipase Amano PS (PSL) catalyzed transesterification. In order to improve the enzymatic conversion of **1**, PLF was substituted by lipase Amano PS (PSL), according to its previously reported activity for other unsaturated substrates.[3a,7] Acceptable conversions were obtained both in THF and CH_2Cl_2 but the reaction was much faster in CH_2Cl_2 than in THF (Fig. 2, c–d). Moreover in CH_2Cl_2 the conversion reaches a plateau at 61%, thus demonstrating that PSL selectively acylates the enantiomer (*S*)-**1** with an enantiomeric ratio $E = 40$ (Table 1, entry 1). These results are in agreement with the reported proposal that a linear solvent can exert higher enantioselectivity than a cyclic solvent.[10b] Pure unreacted enantiomer (*R*)-**1** was thus isolated at 61% conversion in CH_2Cl_2 (ee 0.96, 27% yield) accompanied by (*S*)-rich acetate **4** affording (*S*)-**1** with an ee of 0.82 in 40% overall yield after saponification (Table 1, entry 1). For the saturated alcohol **2**, the *E* value in CH_2Cl_2 is much lower (Fig. 2e; entry 6 in Table 1) and (*R*)-**2** is isolated in 19% yield and ee 0.92 at 80% conversion. The other enantiomer (*S*)-**2** with 94% enantiomeric excess was obtained as described above after three successive transesterifications with an overall yield of 29% (entries 6–8 in Table 1). These results clearly illustrate that for a similar atomic framework, the selectivity of PSL is greatly increased by the presence of a terminal double bond. This enhanced selectivity may result from favourable dipolar interactions with the enzymatic active site or from conformational changes favouring a conformation which fits in the active site.

Effect of the temperature on the PSL catalyzed transesterification of alcohols 1 and 2. Sakai *et al.*[12b] have recently reported that the selectivity of PSL for substrates like azirine-2-methanol is significantly increased by lowering the temperature to −40 °C. Consequently, in order to get valuable preparative access to (*S*)-**1** and (*S*)-**2**, we have investigated the PSL catalyzed transacetylation of **1** and **2** in CH_2Cl_2 at various temperatures ranging from 30 to −30 °C (entries 2, 9–14 in Table 1).

The conversion *versus* time curves depicted in Fig. 3 show that lipase PS remains active even at very low temperatures (−30 °C) for both alcohols. Moreover, for both substrates, the enantioselectivity significantly increases upon cooling (Fig. 3B and D). The lowering of the temperature to 0 °C only slightly influences the initial rate and increases the lipase selectivity since the conversion reaches a plateau at about 50% for **1** and 66% for **2**. Further cooling to −30 °C gives rise to a significant decrease of the reaction rate and acceptable reaction times are obtained at −30 °C by increasing the amount of lipase (Fig. 3C and D e,f,g; entries 9 and 14 in Table 1).

In the case of the unsaturated alcohol **1**, a simple cooling of the reaction medium from 30 to 0 °C substantially improved the enantioselectivity ($E > 750$ at 0 °C compared to $E = 40$ at 30 °C) as well as the enantiomeric excess of (*S*)-**4** affording, after saponification, (*S*)-**2** with ee 0.99 compared to ee 0.82 at 30 °C (Fig. 3A–B, entry 2 in Table 1). The remarkable enantioselectivity of this PSL-catalyzed transesterification thus permitted the isolation of both enantiomers of 2-ethylhex-5-en-1-ol **1** in good yields [(*R*)-**1**: ee 0.96, 32% yield; (*S*)-**1**: ee 0.99, 42% overall yield after saponification]. Moreover, it is worth noticing that simultaneous preparations of both enantiomers from the same enzymatic transformation have only been reported in the literature for secondary alcohols, when the enantioselectivity resulted from an effect of the acyl donor group,[9b,c] of the substrate[26] or of an additive such as a thiacrown ether.[10c]

On the other hand, the enantiomeric ratio for the acylation of **2** was weakly improved at 0 °C ($E = 31$ at 0 °C compared with $E = 6$ at 30 °C). Further lowering of the temperature to −30 °C slightly decreased the enantiomeric excess towards (*R*)-**2** ($E = 37$, ee 0.86) with a small enhancement of the optical purity of (*S*)-**5** leading to (*S*)-**2** with an ee of 0.86 after saponification (entry 12, Table 1). The lengthening of the reaction time did not improve the efficiency since after 13 days the enzymatic transformation affords (*R*)-**2** with a good enantioselectivity ($E = 41$, ee 0.99, yield 29%; entry 13 in Table 1) but results in a loss of purity of the *S* enantiomer ((*S*)-**2**: ee 0.78 after saponification).

From these experiments it turns out that a temperature of 0 °C is the best compromise for achieving the preparation of both (*R*) and (*S*)-**2**. Thus, PSL-catalyzed acetylation of **2** in CH_2Cl_2 at 0 °C provides, after 48 h, (*R*)-**2** with an ee of 0.99 in 31% yield and (*S*)-rich **2** (ee 0.73) isolated after saponification of the acetate. Pure (*S*)-**2** (ee 0.97) is then isolated with an overall yield of 46% after a second enzymatic transesterification at 30 °C for 24 h (τ 90%) followed by saponification (Scheme 3, entries 9 and 10 in Table 1).

Conclusion

This study of the lipase-catalyzed esterification of primary alcohols **1** and **2** shows that, for a similar atomic framework, the selectivity of the enzyme PSL is enhanced by the presence of the terminal double bond, while the same unsaturation almost inhibits the activity of PLF. Both lipase PSL and PLF exhibit the highest activity for esterification of the saturated alcohol **2** though to the detriment of the selectivity. The conformational flexibility of the saturated chain may account for these results. Our results demonstrate that, in such a case, a decrease in temperature is highly profitable since it gives rise to a substantial enhancement of the enantioselectivity for the (*S*) enantiomer. Thus, lipase PS specifically acetylates (*S*)-2-ethylhex-5-en-1-ol (*S*)-**1** in CH_2Cl_2 at 0 °C and allows the preparation of both (*R*) and (*S*) enantiomers from the same enzymatic transformation of the racemic alcohol with good yields and high enantiomeric excess.

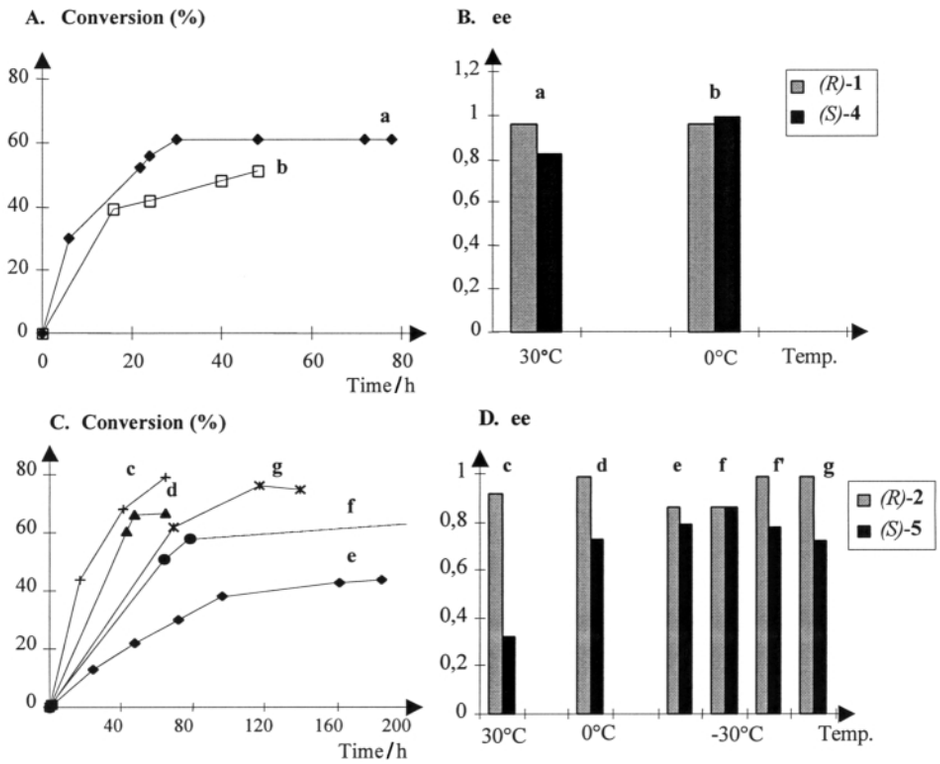
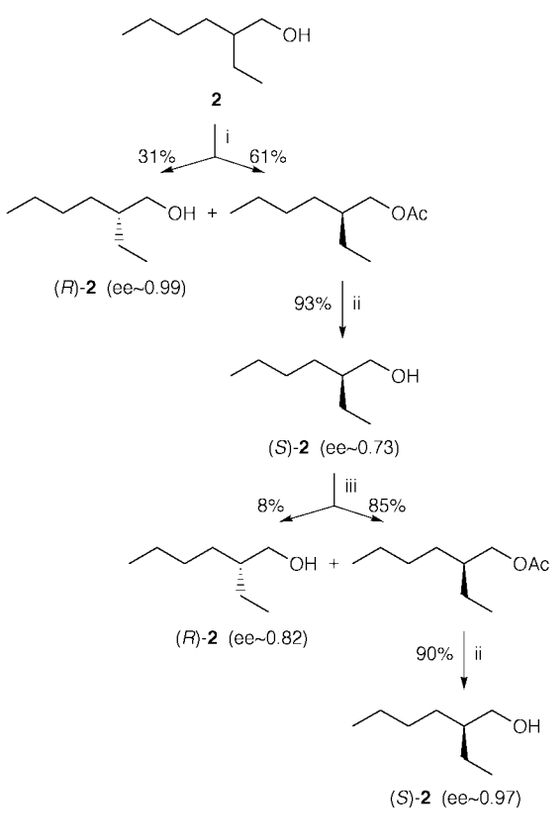


Fig. 3 Effect of temperature on PSL-catalyzed transacetylation in CH_2Cl_2: **A** Conversion *vs*. time of *rac*-**1**; **B** Enantiomeric excess *vs*. temperature of *rac*-**1**; –◆– **a**: 30 °C, 10 mgPSL mmol^{-1}, 78 h; –□– **b**: 0 °C, 15 mgPSL mmol^{-1}, 48 h; **C** Conversion *vs*. time of *rac*-**2**; **D** Enantiomeric excess *vs*. temperature of *rac*-**2**; –+– **c**: 30 °C, 10 mgPSL mmol^{-1}, 48 h; –▲– **d**: 0 °C, 15 mgPSL mmol^{-1}, 48 h, **2**; –◆– **e**: −30 °C, 10 mgPSL mmol^{-1}, 185 h; –●– **f**: −30 °C, 15 mgPSL mmol^{-1}, 78 h; **f′**: 305 h; –✳– **g**: −30 °C, 20 mgPSL mmol^{-1}, 140 h.



Scheme 3 *Reagents and conditions*: i, Lipase PS, CH_2Cl_2 anhydrous, CH_2=CHOAc, 48 h at 0 °C; ii, KOH–EtOH; iii, Lipase PS, CH_2Cl_2 anhydrous, CH_2=CHOAc, 24 h, 30 °C.

On the other hand, both (*R*) and (*S*) enantiomers of 2-ethylhexan-1-ol **2** have been obtained by performing the PSL-catalyzed transesterification at 0 °C respectively in one and two steps with acceptable yields and high enantiomeric purity.

Experimental

Lipase from *Pseudomonas fluorescens* (PLF) was purchased from Fluka (activity 31.5 U mg^{-1}) and Lipase Amano PS from Amano Pharmaceutical Co., Ltd. (activity 39.4 U mg^{-1}). All starting materials were purchased from Acros Organics except 2-ethylhexan-1-ol and (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid from Fluka and hex-5-enoic acid from Lancaster. Solvents were distilled by conventional methods. Petroleum ether has bp 40–60 °C. NMR spectra were recorded on a Bruker AC 300 (^{1}H at 300 MHz, ^{13}C at 75 MHz, ^{19}F at 282 MHz). IR spectra were obtained on a Magna-IR Spectrometer 550 (KBr pellets or films). Mass spectra were obtained on a GC-MS Engine HP-5989 Spectrometer using chemical ionization (CI, reactant gas: CH_4) and electronic impact (EI, 70 eV). Optical rotations were measured on a Perkin-Elmer Model 241 polarimeter at 25 °C. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Melting points and boiling points are uncorrected. Elemental analyses were obtained from the Service Central d'Analyse (CNRS, Vernaison).

Synthesis of 2-ethylhex-5-en-1-ol 1

Synthesis of 2-ethylhex-5-enoic acid 3. To a cooled solution (0 °C) of lithium diisopropylamide (31.0 mL of a 2 M solution in THF–*n*-heptane, 62 mM) was added, under nitrogen, hex-5-enoic acid (2.8 g, 24 mM) in anhydrous THF (28 mL). After stirring at room temperature for 30 min and subsequent cooling to 0 °C, iodoethane (5.7 g, 36 mM) was added. The mixture was stirred for 3 h at room temperature and the reaction was then quenched with 3 M HCl (100 mL). After removal of THF, the reaction mixture was extracted with Et_2O and the combined organic phases were washed with 1 M NaOH. The aqueous basic layer was acidified to pH ~ 1 with conc. HCl and then extracted with Et_2O. The crude acid **3**, isolated after drying over Na_2SO_4 and removal of the solvent, was used without further purification in the next step (colorless oil, 3.30 g, 96%); R_f (Et_2O–*n*-hexane 1 : 1, I_2) 0.47; δ_H ($CDCl_3$) 0.94 (3H, t, *J* 7.4 Hz,

CH_3), 1.55–1.81 (4H, m, CH_2), 2.12 (2H, m, CH_2-CH=CH_2), 2.38 (H, m, CH), 5.02 (2H, m, =CH_2), 5.80 (H, ddt, *J* 16.9, 10.1, 6.9 Hz, CH=).

Synthesis of 2-ethylhex-5-en-1-ol 1. To a solution of **3** (3.25 g, 23 mM) in dry Et_2O (65 mL) at 0 °C was slowly added $LiAlH_4$ (2.15 g, 57 mM). After stirring at room temperature for 2 h, the mixture was quenched with H_2O (200 mL) and conc. HCl was added until the solution became clear. The resulting mixture was extracted with Et_2O. The combined organic phases were washed with brine and dried over Na_2SO_4, followed by column chromatography on silica gel with Et_2O–petroleum ether 1:5, then Et_2O–petroleum ether 1:2 as eluent to give **1** (1.8 g, 64%); (Found: C, 75.19; H, 12.42; $C_8H_{16}O$ requires C, 74.95; H, 12.58%); bp 40–41 °C (2–3 mbar); R_f (Et_2O–petroleum ether 1:5, H_2SO_4) 0.20; ν_{max}(film)/cm^{-1} 3340 (OH), 1640 (C=C), 1040 (C–O); δ_H ($CDCl_3$) 0.91 (3H, t, *J* 7.4 Hz, CH_3), 1.26–1.60 (6H, m, CH_2, CH, OH), 2.09 (2H, m, CH_2-CH=CH_2), 3.57 (2H, d, *J* 4.4 Hz, OCH_2), 4.96 (H, dm, *J* 10, 2 Hz, =CH_2), 5.03 (H, dm, *J* 17 Hz, =CH_2), 5.38 (H, ddt, *J* 17, 10.2, 6.6 Hz, CH=); δ_C ($CDCl_3$) 11.03 (CH_3), 23.25, 29.66, 30.86 (CH_2), 39.12 (CH), 67.35 (OCH_2), 114.0 (CH_2=), 139.0 (CH=); *m*/*z* (EI) 128 (M^+, 0.1%), 110 ($M^+ - H_2O$, 6), 95 (32), 81 (62), 55 (100); *m*/*z* (CI) 129 (MH^+, 47%), 111 ($MH^+ - H_2O$, 100).

Lipase catalyzed transesterification of 1 and 2

Vinyl acetate (40 mM) and racemic alcohol (10 mM) were added to a suspension of lipase PLF (3.5 mg per mM alcohol) in anhydrous THF (10 mL) at 40 °C or lipase Amano PS (10 to 20 mg per mM alcohol) in anhydrous solvent (THF, 10 mL or CH_2Cl_2, 15 mL). The experimental conditions and the reaction temperatures are detailed in Table 1. The conversion was followed by ^{1}H NMR (OCH_2 signals). The enzyme was filtered through a Celite pad and the filtrate was evaporated under reduced pressure, chromatographed on a silica gel column with Et_2O–petroleum ether 1:8, then Et_2O–petroleum ether 1:5 (for alcohol **1**) or Et_2O–*n*-hexane 1:25, then Et_2O–*n*-hexane 1:8 (for alcohol **2**) as eluent. For each reaction, the $[\alpha]_D$ and ee, determined from ^{19}F NMR and specific rotation, are given in Table 1.

(*R*)-(−)-2-Ethylhex-5-en-1-ol (*R*)-(−)-1. (Experimental conditions: entry 1 in Table 1, 350 mg, 27%); $[\alpha]_D$ −4.5, $[\alpha]_{436\ nm}$ −7.5, $[\alpha]_{365\ nm}$ −13.4 (*c* 1.2, $CHCl_3$) for ee 0.96 (lit.,[14] $[\alpha]_D = -4.7$); same spectroscopic data as racemic alcohol **1** (*vide supra*).

(*R*)-(−)-2-Ethylhexan-1-ol (*R*)-(−)-2. (Experimental conditions: entry 3 in Table 1, 260 mg, 20%); bp 39–40 °C (2–3 mbar); R_f (Et_2O–*n*-hexane 1:8, H_2SO_4) 0.33; δ_H ($CDCl_3$) 0.89 (3H, t, *J* 7.4 Hz, CH_3), 0.90 (3H, t, *J* 7.0 Hz, CH_3), 1.28–1.44 (9H, m, CH_2, CH), 1.70 (H, s, OH), 3.54 (2H, d, *J* 4.8 Hz, OCH_2); δ_C ($CDCl_3$) 11.01, 13.99 (CH_3), 23.06, 25.35, 29.11, 30.15 (CH_2), 41.99 (CH), 65.1 (CH_2O); *m*/*z* (EI) M^+ not observed, 112 ($M^+ - H_2O$, 4%), 98 ($M^+ - CH_3OH$, 6), 83 (23), 70 (26), 57 (100); *m*/*z* (CI) 129 ($M^+ - H$, 34%), 113 ($M^+ - H_2O$, 100); $[\alpha]_D$ −3.4 (lit.,[17] −3.4), $[\alpha]_{436}$ −5.8, $[\alpha]_{365}$ −7.7 (*c* 5.3, $CHCl_3$).

(*S*)-2-Ethylhex-5-enyl acetate (*S*)-4. (Experimental conditions: entry 2 in Table 1, 750 mg, 45%); R_f (Et_2O–petroleum ether 1:8, H_2SO_4) 0.57; ν_{max}(film)/cm^{-1} 1750 (C=O), 1640 (C=C), 1040 (C–O); δ_H ($CDCl_3$) 0.90 (3H, t, *J* 7.4 Hz, CH_3), 1.33–1.45 (4H, m, CH_2), 1.60 (H, m, CH), 2.06 (5H, m, CH_2-CH=CH_2 and OCH_3), 4.00 (2H, d, *J* 5.9 Hz, OCH_2), 4.96 (H, dm, *J* 10.3 Hz, =CH_2), 5.03 (H, dm, *J* 17.3 Hz, =CH_2), 5.38 (H, ddt, *J* 17.3, 10.3, 6.6 Hz, CH=); δ_C ($CDCl_3$) 10.90 (CH_3), 20.97 (CH_3CO), 23.62, 28.95, 30.93 (CH_2), 38.13 (CH), 66.63 (OCH_2), 114.52 (CH_2=), 139.69 (CH=), 171.33 (C=O); *m*/*z* (EI) M^+ not observed, 140 ($M^+ - CH_3O$, 2%), 128 ($M^+ - COCH_3$, 8), 110 ($M^+ - HCO_2CH_3$, 40), 95 (47), 81 (100); *m*/*z* (CI) 171 (MH^+, 32%), 129 ($MH^+ - COCH_3$, 11), 111 ($MH^+ - OCOCH_3$, 100); $[\alpha]_D$ +7.4, $[\alpha]_{436}$ +9.7, $[\alpha]_{365}$ +14.0 (*c* 1.2, $CHCl_3$).

(*S*)-2-Ethylhexyl acetate (*S*)-5. (Experimental conditions: entry 10 in Table 1) prepared starting from 960 mg of (*S*)-rich alcohol **2** (ee = 0.73, entry 9 in Table after saponification) (1.08 g, 85%); bp 83–85 °C (20–23 mbar); R_f (Et_2O–*n*-hexane 1:25, H_2SO_4) 0.45; ν_{max}(film)/cm^{-1} 1750 (C=O), 1040 (C–O); δ_H ($CDCl_3$) 0.89 (3H, t, *J* 7.4 Hz, CH_3), 0.90 (3H, t, *J* 7.0 Hz, CH_3), 1.29–1.41 (8H, m, CH_2), 1.56 (H, m, CH), 2.06 (3H, s, $COCH_3$), 3.98 (2H, dd, *J* 1.5, 5.9 Hz, OCH_2); δ_C ($CDCl_3$) 10.79, 13.82 (CH_3), 20.65 (CH_3CO), 22.87, 23.71, 28.86, 30.35 (CH_2), 38.72 (CH), 66.73 (OCH_2), 170.85 (C=O); $[\alpha]_D$ +4.0 (*c* 5.3, $CHCl_3$).

Saponification of acetates 4 and 5

To a solution of KOH (7.5 mM) in water (0.6 mL) was added acetate **4** or **5** (5 mM) dissolved in ethanol 95% (8 mL). The reaction mixture was stirred overnight at room temperature and the solvent was removed. The residue was partitioned between Et_2O and H_2O, the organic layer was then washed with H_2O (pH ~ 7) and dried over Na_2SO_4. The crude alcohol isolated after concentration under vacuum was then distilled under reduced pressure through a Vigreux column to provide pure alcohol.

(*S*)-(+)-2-Ethylhex-5-en-1-ol (*S*)-(+)-1. Obtained by saponification of (*S*)-**4** (entry 2 in Table 1, 520 mg, 93%); $[\alpha]_D$ +4.7 (*c* 1.2, $CHCl_3$); same spectroscopic data as racemic alcohol **1**.

(*S*)-(+)-2-Ethylhexan-1-ol (*S*)-(+)-2. Obtained by saponification of (*S*)-**5** (Table 1, entry 10, 730 mg, 90%); $[\alpha]_D$ +3.3 (*c* 5.3, $CHCl_3$); same spectroscopic data as alcohol (*R*)-**2**.

Synthesis of esters (*R*)-α-methoxy-α-trifluoromethylphenylacetic acid 6 and 7

Diastereomeric Mosher's (*R*,*R*) or (*S*,*R*) esters have been prepared by reacting (*R*)-(+)-MTPA (125 mg, 0.5 mM) with the alcohol (0.5 mM) in the presence of APTS (10 mg, 0.05 mM) and 4 Å molecular sieve in toluene (1 mL). After refluxing the reaction for 48 h and removal of the solvent, the crude mixture was dissolved in Et_2O (5 mL) and filtered through a Celite pad. The Mosher ester was isolated by column chromatography on silica gel with Et_2O–petroleum ether 1:40 as eluent. It is worth noticing that, whatever the enantiomeric excess of the starting alcohol, complete conversion of both enantiomers was achieved thus demonstrating that no kinetic resolution occurred during the reaction. Moreover, it has been checked that the composition of the diastereoisomeric mixture of Mosher esters remains unchanged after the chromatographic purification.

(*R*)-2-Ethylhex-5-enyl (*R*)-α-methoxy-α-trifluoromethylphenylacetate (*R*,*R*)-6. Prepared starting from (*R*)-**1** (entry 2 in Table 1); (colorless oil, 148 mg, 86%); R_f (Et_2O–petroleum ether 1:40, H_2SO_4) 0.29; δ_H ($CDCl_3$) 0.89 (3H, t, *J* 7.8 Hz, CH_3), 1.31–1.44 (4H, m, CH_2), 1.68 (H, m, CH), 2.05 (2H, m, CH_2-CH=CH_2), 3.56 (3H, q, $J_{H\text{-}F}$ 1.1 Hz, OCH_3), 4.21 (H, dd, *J* 5.1, 11.0 Hz, OCH_2), 4.31 (H, dd, *J* 5.5, 11.0 Hz, OCH_2), 4.96 (2H, m, =CH_2), 5.74 (H, ddt, *J* 16.9, 10.3, 6.6 Hz, CH=), 7.42 (3H, m, $H_{arom.}$), 7.52 (2H, m, $H_{arom.}$); δ_C ($CDCl_3$) 10.79 (CH_3), 23.55, 29.77, 30.75 (CH_2), 38.05 (CH), 55.38 (OCH_3), 68.19 (OCH_2), 114.7 (CH_2=), 123.35 (q, $J_{C\text{-}F}$ 288 Hz, CF_3), 127.32 (C_{para}), 128.37 (C_{ortho}), 129.55 (C_{meta}), 132.35 (C_{ipso}), 138.32 (CH=), 166.70 (C=O); δ_F ($CDCl_3$–$CFCl_3$) −72.065 (3F, s, CF_3).

(*S*)-2-Ethylhex-5-enyl (*R*)-α-methoxy-α-trifluoromethylphenylacetate (*S*,*R*)-6. Prepared starting from (*S*)-**1** (entry 2 in Table 1) (colorless oil, 134 mg, 78%); same spectroscopic data as **(*R*,*R*)-6**; δ_F ($CDCl_3$–$CFCl_3$) −72.073 (3F, s, CF_3).

(*R*)-2-Ethylhexyl (*R*)-α-methoxy-α-trifluoromethylphenylacetate (*R*,*R*)-7. Prepared starting from (*R*)-**2** (entry 3 in Table 1) (colorless oil, 149 mg, 86%); R_f (Et_2O–petroleum ether 1 : 40, H_2SO_4) 0.5; δ_H ($CDCl_3$) 0.87 (3H, t, *J* 7.4 Hz, CH_3), 0.88 (3H, t, *J* 7.0 Hz, CH_3), 1.25–1.44 (8H, m, CH_2), 1.63 (H, m, CH), 3.56 (3H, q, $J_{H\text{-}F}$ 1.1 Hz, OCH_3), 4.20 (H, dd, *J* 5.5, 11.0 Hz, OCH_2), 4.29 (H, dd, *J* 5.5, 11.0 Hz, OCH_2), 7.42 (3H, m, H_{arom}), 7.52 (2H, m, H_{arom}); δ_C ($CDCl_3$) 10.85 (CH_3), 13.96 (CH_3), 22.87, 23.57, 28.75, 30.20 (CH_2), 38.61 (CH), 55.38 (d, $J_{C\text{-}F}$ 1.7 Hz, OCH_3), 68.55 (OCH_2), 127.33 (C_{para}), 123.35 (q, $J_{C\text{-}F}$ 288 Hz, CF_3), 128.36 (C_{ortho}), 129.54 (C_{meta}), 132.39 (C_{ipso}), 166.73 (C=O); δ_F ($CDCl_3$–$CFCl_3$) −71.927 (s, 3F, CF_3).

(*S*)-2-Ethylhexyl (*R*)-α-methoxy-α-trifluoromethylphenylacetate (*S*,*R*)-7. Prepared starting from (*S*)-**2** (entry 10 in Table 1) (colorless oil, 137 mg, 79%); same spectroscopic data as **(*R*,*R*)-7**; δ_F ($CDCl_3$–$CFCl_3$) −71.909 (3F, s, CF_3).

Determination of the optical purity of the alcohols 1 and 2

The enantiomeric purities of (*R*) or (*S*) alcohols were determined from the ^{19}F NMR spectra of their (*R*)-α-methoxy-α-trifluoromethylphenylacetyl esters. The following mixtures were prepared for determination of the detection limit: for **1** of mixtures (*R*,*R*)-**6** and (*S*,*R*)-**6**: 19 μL/1 μL, 18 μL/2 μL, 14 μL/6 μL, 10 μL/10 μL in 0.5 mL $CDCl_3$ and for **2** of mixtures (*R*,*R*)-**7** and (*S*,*R*)-**7**: 19.5 μL/0.5 μL, 19 μL/1 μL, 18 μL/2 μL, 14 μL/6 μL, 10 μL/10 μL in 0.5 mL $CDCl_3$ (Fig. 1).

The enantiomeric excess of alcohol **2** has also been determined by GC analysis on a chiral Cydex B column (25 m × 0.25 μm, isotherm 65 °C, 0.7 mbar): the ee values are in very good agreement with the ee values deduced from NMR spectra.

Acknowledgements

We gratefully acknowledge SEPPIC (Société d'Exploitation de Produits Pour les Industries Chimiques) for the generous gift of lipase Amano from *Pseudomonas species.*

References

1 A. N. E. Weissfloch and R. J. Kazlauskas, *J. Org. Chem.*, 1995, **60**, 6959.
2 P. Grisenti, P. Ferraboschi, S. Casati and E. Santaniello, *Tetrahedron: Asymmetry*, 1993, **4**, 997; P. Ferraboshi, S. Casati, A. Manzocchi and E. Santaniello, *Tetrahedron: Asymmetry*, 1995, **6**, 1521.
3 (*a*) K. Burgess and L. D. Jennings, *J. Am. Chem. Soc.*, 1991, **113**, 6129; (*b*) K. Naemura, R. Fukuda, M. Konishi, K. Hirose and Y. Tobe, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1253; (*c*) K. Lemke, M. Lemke and F. Theil, *J. Org. Chem.*, 1997, **62**, 6268.
4 (*a*) M. Cygler, P. Grochulski, R. J. Kazlauskas, J. D. Schrag, F. Bouthillier, B. Rubin, A. N. Serreqi and A. K. Gupta, *J. Am. Chem. Soc.*, 1994, **116**, 3180; (*b*) K. Nishizawa, Y. Ohgami, N. Matsuo, H. Kisida and H. Hirohara, *J. Chem. Soc., Perkin Trans. 2*, 1997, 1293; (*c*) G. Colombo, S. Toba and K. Merz, *J. Am. Chem. Soc.*, 1999, **121**, 3486.
5 A. K. Saikia, G. Bez, M. S. Bezbarua and N. C. Barua, *J. Indian Chem. Soc.*, 1997, **74**, 937; Z.-H. Li, A. Bulychev, L. P. Kotra, I. Massova and S. Mobashery, *J. Am. Chem. Soc.*, 1998, **120**, 13003.
6 Y. Naoshima, M. Kamezawa, H. Tachibana, Y. Munakata, T. Fujita, K. Kihara and T. Raku, *J. Chem. Soc., Perkin Trans. 1*, 1993, 557.
7 S. Barth and F. Effenberger, *Tetrahedron: Asymmetry*, 1993, **4**, 823.
8 (*a*) T. Ke, Ch. R. Wescott and A. M. Klibanov, *J. Am. Chem. Soc.*, 1996, **118**, 3366; (*b*) M. Peter, J. Van der Eycken, G. Bernath and F. Fulop, *Tetrahedron: Asymmetry*, 1998, **9**, 2339.
9 (*a*) T. Miyazawa, S. Kurita, S. Ueji and T. Yamada, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2253; (*b*) T. Ema, S. Maeno, Y. Takaya, T. Sakai and M. Utaka, *J. Org. Chem.*, 1996, **61**, 8610; (*c*) Y. Kita, Y. Takebe, K. Murata, T. Naka and S. Akai, *Tetrahedron Lett.*, 1996, **37**, 7369; (*d*) M. Schudok and G. Kretzschmar, *Tetrahedron Lett.*, 1997, **38**, 387; (*e*) C. C. Akoh and L. N. Yee, *J. Mol. Catal. B Enzym.*, 1998, **4**, 149; (*f*) B. Das and P. Madhusufhan, *Tetrahedron*, 1999, **55**, 7875; M. Kawasaki, M. Goto, S. Kawabata, T. Kodama and T. Kometani, *Tetrahedron Lett.*, 1999, **40**, 5223.
10 (*a*) Ch. R. Wescott and A. M. Klibanov, *J. Am. Chem. Soc.*, 1993, **115**, 1629; (*b*) K. Nakamura, M. Kinoshita and A. Ohno, *Tetrahedron*, 1995, **51**, 8799; (*c*) Y. Takagi, J. Teramoto, H. Kihara, T. Itoh and H. Tsukube, *Tetrahedron Lett.*, 1996, **37**, 4991; (*d*) T. Itoh, Y. Takagi, T. Murakami, Y. Hiyama and H. Tsukube, *J. Org. Chem.*, 1996, **61**, 2158; (*e*) A. Fishman and M. Zviely, *Tetrahedron: Asymmetry*, 1998, **9**, 107; (*f*) S. Backlund, F. Eriksson, R. Friman, G. Hedstrom and S. Karlsson, *J. Dispersion Sci. Technol.*, 1999, **20**, 767; (*g*) K. Mitsukura, H. Choraku, S. Da and T. Itoh, *Bull. Chem. Soc. Jpn.*, 1999, **72**, 1589.
11 S. V. Kamat, J. Barrera, E. J. Beckman and A. J. Russell, *Biotechnol. Bioeng.*, 1992, **40**, 158; S. Kamat, E. J. Beckman and A. J. Russell, *J. Am. Chem. Soc.*, 1993, **115**, 8845.
12 (*a*) J. W. Thuring, A. J. H. Klunder, G. H. L. Nefkens, M. A. Wegman and B. Zwanenburg, *Tetrahedron Lett.*, 1996, **37**, 4759; (*b*) T. Sakai, I. Kawabata, T. Kishimoto, T. Ema and M. Utaka, *J. Org. Chem.*, 1997, **62**, 4906.
13 A. F. Houri, Z. Xu, D. A. Cogan and A. H. Hoveyda, *J. Am. Chem. Soc.*, 1995, **117**, 2943.
14 L. F. Tietz and Ch. Schneider, *J. Org. Chem.*, 1991, **56**, 2476.
15 A. Ghogare and S. Kumar, *J. Chem. Soc., Chem. Commun.*, 1989, 1533.
16 M. Majeric and V. Sunjic, *Tetrahedron: Asymmetry*, 1996, **7**, 815.
17 Ch. Larpent and X. Chasseray, *New J. Chem.*, 1993, **17**, 851.
18 D. Y. Kondakov and E. Negishi, *J. Am. Chem. Soc.*, 1996, **118**, 1577.
19 Ch. Larpent and X. Chasseray, *Tetrahedron*, 1992, **48**, 3903.
20 X. Chasseray, Ph.D. Thesis, Université de Rennes (France), January 1994.
21 J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, 1973, **95**, 512.
22 (*a*) F. Yasuhara and S. Yamaguchi, *Tetrahedron Lett.*, 1977, **47**, 4085; (*b*) S. Hammon, *J. Fluorine Chem.*, 1993, **60**, 225; (*c*) S. P. Khanapure, N. Najafi, S. Manna, J.-J. Yang and J. Rokach, *J. Org. Chem.*, 1995, **60**, 7548; (*d*) M. Barelle and S. Hamman, *J. Chem. Res.* (*S*), 1995, 316; (*e*) M. J. Ferreiro, Sh. K. Latypov, E. Quinoa and R. Riguera, *Tetrahedron: Asymmetry*, 1996, **7**, 2195; (*f*) J. Omelanczuk and M. Mikolajczyk, *Tetrahedron: Asymmetry*, 1996, **7**, 2687; (*g*) M. Barelle, L. Boyer, J. Chang-Fong and S. Hamman, *Tetrahedron: Asymmetry*, 1996, **7**, 1961.
23 M. D. McCreary, D. W. Lewis, D. L. Wernick and G. M. Whitesides, *J. Am. Chem. Soc.*, 1974, **96**, 1038.
24 R. Baudouy and Ph. Prince, *Tetrahedron*, 1989, **45**, 2067; Y. Takeuchi, N. Itoh, T. Satoh, T. Koizumi and K. Yamaguchi, *J. Org. Chem.*, 1993, **58**, 1812.
25 C.-S. Chen, Y. Fujimoto, G. Girdaukas and C. J. Sih, *J. Am. Chem. Soc.*, 1982, **104**, 7294; C.-S. Chen, S. Wu, G. Girdaukas and C. J. Sih, *J. Am. Chem. Soc.*, 1987, **109**, 2812.
26 F. Theil and S. Ballschuh, *Tetrahedron: Asymmetry*, 1996, **7**, 3565.

Paper a907987d