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Highly efficient double enantioselection by lipase-catalyzed transesterification of (*R*,*S*)-carboxylic acid vinyl esters with (*RS*)-1-phenylethanol

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Abstract

Transesterification of the title compounds using lipase B from *Candida antarctica* in toluene afforded the corresponding esters in good to excellent diastereomeric excess. (*R*)-2-Phenylpropionic acid-(*R*)-1-phenethyl ester **4** was isolated in 45% yield and 64% *de* after 2.5 h, whereas (*R*)-2-phenylbutyric acid-(*R*)-1-phenethyl ester **5** was obtained in 40% yield and 56% *de* after 35 h. A single recrystallization from *n*-hexane gave **4** with 98% *de*. In all reactions CAL-B showed excellent enantioselectivity (E >100) toward (*RS*)-1-phenylethanol and moderate enantioselectivity ($E \sim 10$) toward both carboxylic acid vinyl esters.

1. Introduction

Hydrolases, especially lipases, have been shown to be versatile enzymes in organic synthesis for kinetic resolution and for the desymmetrization of prostereogenic substrates.[1,2] In the vast majority of publications, lipase-catalyzed reactions were used to obtain products containing only one stereogenic center, i.e. resolution of a racemic secondary alcohol with an achiral acyl donor or hydrolysis of a racemic carboxylic acid methylester. According to Chen and Sih, "double kinetic resolution of appropriate racemic acids with racemic alcohols is an exciting area that warrants systematic exploration in the future".[3] However, in order to achieve an efficient double enantioselection, the following criteria must be fulfilled: (1) the lipase should be highly enantioselective towards both substrates, i.e. both the racemic alcohol and racemic acid; and (2) the reaction equilibrium must be shifted towards ester synthesis in order to obtain high conversion of both enantiomers. The first problem might be solved by testing different lipases and the reaction rate might be enhanced by using activated acyl donors. So far, this approach

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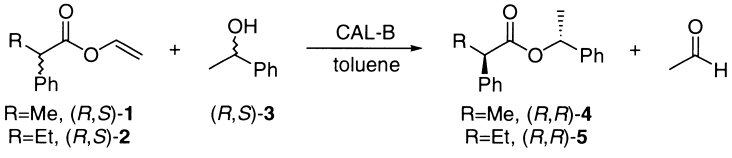
has been investigated only to a limited extent.[4–7] For instance, Theil et al. used *rac*-2,2,2-trifluoroethyl-2-chloropropanoate in the resolution of a *meso*-diol in THF. However, the reaction proceeded only with moderate selectivity and the best results were achieved using a lipase from *Candida* sp. yielding a diastereomeric excess of 52%.[5] The direct esterification of, for example, *rac*-2-phenoxypropionic acid with *rac*-1-phenylethanol in *n*-hexane was much slower (only 15% conversion after 122 h) and enantioselectivity was very low [E=10.4 (alcohol) and E=12.5 (acid)].

Recently, we discovered that an efficient kinetic resolution of α- or β-phenylsubstituted carboxylic acids can be achieved by transesterification of their corresponding vinyl esters with *n*-hexanol in toluene using lipase B from *Candida antarctica* (CAL-B). The reaction was up to 14-fold faster compared to an esterification of the corresponding ethyl esters and the enantioselectivity was greatly enhanced.[8]

In the present paper we report on the double enantioselection by esterification of racemic carboxylic acid vinyl esters with racemic 1-phenylethanol in toluene using CAL-B.

2. Results and discussion

The two 2-phenylsubstituted carboxylic acid vinyl esters **1** and **2** were subjected to CAL-B catalyzed transesterification with (*RS*)-1-phenylethanol **3** yielding the corresponding esters (*R*,*R*)-**4** and (*R*,*R*)-**5** bearing two stereogenic centers (Scheme 1). Due to the use of vinyl esters instead of non-activated esters, the transesterification proceeded with very good reaction rates allowing approximately 50% conversion after 2.5 and 35 h, respectively (Table 1).



Scheme 1.

In both reactions, the lipase showed excellent enantioselectivity (E >100) in the kinetic resolution of **3**: the remaining (*S*)-alcohol as well as the (*R*)-alcohol portion of the ester produced were obtained in excellent enantiomeric excess (>94% *ee* and >99% *ee*, respectively). In contrast, CAL-B was less enantioselective towards the carboxylic acid vinyl esters (E ~10), but still acceptable diastereomeric excesses of esters **4** (64% *de*) and **5** (56% *de*) could be achieved. Other lipases, for example from *Pseudomonas cepacia*, exhibited much lower activity and enantioselectivity. The enantiomeric excess of **4** could be substantially increased to 98% *de* by a single recrystallization from *n*-hexane. Thus, we were able to develop an efficient double enantioselection allowing the synthesis of diastereomeric esters having high diastereomeric excesses at short reaction times.

Table 1

Acid	Time	Enantiomeric excess[a]		Diastereomeric excess[a]
	[h]	(*S*)-acid [%ee]	(*S*)-alcohol [%ee]	[%de]
1	2.5	67 (36)	>98 (41)	98[b] (45)
2	35	58 (41)	94 (39)	75 (40)

[a]values in brackets correspond to isolated yields; [b]after recrystallization

3. Experimental

3.1. Enzymes and chemicals

Immobilized lipase B from *Candida antarctica* (SP435) was a gift from Boehringer Mannheim, Penzberg, Germany. All chemicals were purchased from Fluka, Buchs, Switzerland. All solvents and lipases were dried over an activated 4 Å molecular sieve prior to use.

3.2. General methods

^{1}H NMR spectra were recorded at 250.1 and 500.1 MHz, ^{13}C NMR spectra at 62.9 and 125.7 MHz, in $CDCl_3$ with tetramethylsilane as an internal standard. Signals given below in italics refer to the minor diastereomer. (*RS*)-Carboxylic acid vinyl esters **1** and **2** were synthesized as described previously.[8] To confirm chemical identity, esters **4** and **5** were also synthesized by chemical means.

3.3. General procedure for lipase-catalyzed transesterifications

(*RS*)-2-Phenylpropionic acid vinyl ester **1** or 2-phenylbutyric acid vinyl ester **2** (0.65 mmol) and (*RS*)-1-phenylethanol (0.65 mmol) **3** were dissolved in 6 ml toluene and stirred at 40°C. The reaction was initiated by the addition of 300 mg lipase CAL-B. Samples withdrawn from the solution were diluted with toluene and analyzed by gas chromatography (GC). Reactions were stopped at ~50% conversion by centrifugation of the lipase. Product and non-converted substrate were separated by silica gel column chromatography.

3.4. Determination of the absolute configuration, and the enantiomeric and diastereomeric excess

Enantiomeric excess of vinyl esters **1** and **2** were determined by GC on a heptakis-(2,3-di-*O*-acetyl-6-*O*-TBDMS)-β-cyclodextrin column (25 m×0.25 mm, Prof. W. A. König, University of Hamburg, Germany). The enantiomeric excess of 1-phenylethanol **3** was determined by GC on a heptakis-(2,3,6-tri-*O*-methyl)-β-cyclodextrin column (50 m×0.25 mm, CS-Chromatographie-Service, Langerwehe, Germany). The diastereomeric excesses of esters **4** and **5** and conversions were determined using an Optima 5 column (25 m×0.25 mm; Macherey & Nagel, Düren, Germany). In addition, enantiomeric excesses were also determined for the acid and alcohol portion of the product esters **4** and **5** after chemical hydrolysis. This was performed by dissolving 3 mg of compound **4** or compound **5** in 200 μl heptane followed by addition of 90 μl methanolic potassium hydroxide solution (2 N) and shaking for 1 min. Samples from the organic layer containing (*R*)-1-phenylethanol and methylesters of (*R*)-**1** or **2** were then analyzed by GC using the chiral columns given above. Enantiomeric excesses were verified by optical rotation values, which were determined on a Perkin–Elmer polarimeter 241. Absolute configurations were assigned by comparison with enantiomerically pure samples and sign of the specific rotation values.

3.5. Synthesis of (R)-2-phenylpropionic acid-(R)-1-phenethyl ester *4*

Following the above general procedure, 74 mg (0.29 mmol, 45% yield, >98% *ee* (alcohol), 64% *de* (GC), mp 92–93°C) of (*R*,*R*)-**4** was isolated after 2.5 h reaction time. Recrystallization from *n*-hexane afforded (*R*,*R*)-**4** in 98% *de* (GC; >95% *de*, ^{1}H NMR, $[\alpha]_D^{22}$=+9.9, c= 0.87, $CHCl_3$). Remaining vinyl

ester (*S*)-(+)-**1**: 42 mg, 0.24 mmol, 36% yield, 67% *ee*, $[\alpha]_D^{22}$=+24.9, c=1.19, EtOH); remaining 1-phenylethanol (*S*)-(−)-**3**: 33 mg, 0.27 mmol, 41% yield, >98% *ee*, $[\alpha]_D^{22}$=−40.8, c=1.3, MeOH.

^{1}H NMR (250.1 MHz; $CDCl_3$) **4**: δ 1.48 (3H, d, $J_{1',2'}$=6.6, 2′-H), 1.49 (3H, d, $J_{2,3}$=7.2, 3-H), 3.75 (1H, q, $J_{2,3}$=7.2, 2-H), 5.85 (1H, q, $J_{1',2'}$=6.6, 1′-H), 7.06–7.31 (10H, m, Ph–H); ^{13}C NMR (62.9 MHz; $CDCl_3$): δ 18.47 (3-C), 22.48 (2′-C), 45.86 (2-C), 72.59 (1′-C), 125.80, 127.16, 127.73, 128.42, 128.66, 140.57, 141.81 (Ph–H), 173.67 (1-C); IR (KBr): 2960 m, 1725 s, 1325 m, 1190 s, 1160 s, 1045 m, 740 m, 680 s. Anal. calcd for $C_{17}H_{18}O_2$: C 80.28, H 7.13, found: C 80.21, H 7.21.

*3.6. Synthesis of (*R*)-2-phenylbutyric acid-(*R*)-1-phenethyl ester **5***

Following the above general procedure, 70 mg (0.26 mmol, 40% yield, >98% *ee* (alcohol), 56% *de* (^{1}H NMR, $[\alpha]_D^{22}$=+23.8, c=1.38, $CHCl_3$) of (*R*,*R*)-**5** was isolated as a colorless liquid after 35 h reaction time. Remaining vinyl ester (*S*)-(+)-**2**: 50 mg, 0.26 mmol, 41% yield, 58% *ee*, $[\alpha]_D^{22}$=+14.9, c=1.35, $CHCl_3$); remaining 1-phenylethanol (*S*)-(−)-**3**: 31 mg, 0.25 mmol, 39% yield, 94% *ee*, $[\alpha]_D^{22}$=−36.8, c=1.1, MeOH.

^{1}H NMR (500.1 MHz; $CDCl_3$) **5**: δ *1.06 (3H, t, $J_{3,4}$=7.4, 4-H)*, 1.10 (3H, t, $J_{3,4}$=7.3, 4-H), *1.63 (3H, d, $J_{1',2'}$=6.7, 2′-H)*, 1.71 (3H, d, $J_{1',2'}$=6.5, 2′-H), 1.98–2.34 (2H, m, 3-H), 3.69 (1H, m, 2-H), 6.06 (1H, q, $J_{1',2'}$=6.6), 7.31–7.53 (10H, m, Ph–H); ^{13}C NMR (125.8 MHz; $CDCl_3$): ·12.54 (4-C), *22.36*, 22.75 (2′-C), 26.90, *27.07* (3-C), *54.02*, 54.09 (2-C), 72.78, *72.90* (1′-C), 126.10, 126.42, 127.47, 127.50, 127.95, 128.17, 128.38, 128.46, 128.69, 128.83, 128.86, 128.89, 139.38, 139.51, 142.04, 142.10 (Ph–C), 173.72, 173.72 (1-C); IR (KBr): 2950 m, 2910 m, 1740 s, 1485 m, 1445 m, 1190 s, 1150 s, 1050 s, 1015 m, 740 m, 680 m. Anal. calcd for $C_{18}H_{20}O_2$: C 80.56, H 7.51, found: C 80.42, H 7.53.

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