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Kinetic resolution of racemic secondary aliphatic allylic alcohols in lipase-catalyzed transesterification

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Abstract—Different lipases were screened as biocatalysts in the kinetic resolution process of (±)-hept-1-en-3-ol **1**, (±)-5-methylhex-1-en-3-ol **2**, (±)-6-methylhept-2-en-4-ol **3**, (±)-6,6-dimethylhept-2-en-4-ol **4**, and 1-phenylbut-3-en-2-ol **5** by enantioselective transesterification. The acylation of (±)-**1** and (±)-**2** catalyzed by Novozym 435 (*Candida antarctica*) was very effective and proceeded with good enantioselectivity. After 4–8 h of reactions the esters formed and the alcohols, which remained were obtained with high enantiomeric excess with 97–100% ee and 91–100% ee, respectively. The lipase Amano PS (*Burkholderia cepacia*) was the best catalyst in the asymmetric transesterification of (±)-**5** affording the (*R*)-alcohol with 90–95% ee and the (*S*)-ester with 98–100% ee. Low enantioselectivities were observed in the cases of lipase-catalyzed acylation of (±)-**3** and (±)-**4**.

1. Introduction

In recent years, the application of enzymes as biocatalysts in organic syntheses is quite well known. They ensure the asymmetric course of many chemical transformations and give us the possibility of obtaining chiral compounds in enantiomerically pure forms.[1] Biocatalysts can be used for efficient syntheses of chiral drugs, fragrances, and pheromones.[1–3]

Lipases are the most widely applied enzymes for the regioselective and enantioselective biotransformations, because they are inexpensive, stable, and easy to recycle. They also possess a wide substrate specificity and catalyze many reversible reactions in aqueous and non-aqueous media such as: esterification, transesterification, amidation, and hydrolysis.[4,5] Moreover, conversely to oxidases, lipases do not require cofactors nor catalyze side reactions.[6,7]

Lipase-catalyzed reactions have been applied to solve a number of various synthetic problems, one of which is the kinetic resolution of diastereomeric and enantiomeric mixtures of primary and secondary alcohols.[4,8–11]

We are interested in the kinetic resolution of secondary allylic alcohols for two reasons. The first one is connected with odoriferous properties of allylic alcohols, some of which were obtained by us as racemic mixtures, and possess interesting and valuable odoriferous properties.[12] It would be interesting to evaluate the odors of the pure enantiomers of these alcohols. Recently we have published a paper presenting the lipase-catalyzed kinetic resolution of racemic oct-1-en-3-ol, known as the most important odorant of the mushroom aroma.[13] Sensory analysis indicated that (*R*)-(−)-oct-1-en-3-ol had a fruity, mushroom-like odor, whereas (*S*)-(+)-oct-1-en-3-ol had a moldy grassy note.[14]

The second reason is connected with using pure enantiomers of some allylic alcohols in the first step of the synthesis of the enantiomerically pure hydroxylactones, which exhibited high antifeedant activity against insects.[15,16] The pure enantiomers of starting allylic alcohols used in these syntheses were obtained by kinetic resolution of racemic samples via the Sharpless' epoxidation.[15,17]

Herein we report the results of our attempts to separate the racemic mixtures of several secondary aliphatic allylic alcohols in lipase-catalyzed stereoselective transesterification with various vinyl esters as acyl donors. Different lipases were screened as the biocatalysts in these processes.

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2. Results and discussion

2.1. Synthesis of racemic alcohols

Racemic alcohols: (±)-hept-1-en-3-ol **1**, (±)-5-methylhex-1-en-3-ol **2**, (±)-6-methylhept-2-en-4-ol **3**, (±)-6,6-dimethylhept-2-en-4-ol **4**, and 1-phenylbut-3-en-2-ol **5** were the substrates for enzymatic transesterifications carried out (Scheme 1). The allylic alcohols **2**–**5** were obtained as products of the Grignard reaction of crotonaldehyde or acrolein with the corresponding magnesium bromide. (±)-Hept-1-en-3-ol **1** was obtained in the reaction of acrylaldehyde with *n*-butyllithium. All these alcohols are known compounds **1**,[18] **2**,[19] **3**,[20] **4**,[21] and **5**[22] and one of which, (*E*)-6-methyl-hept-2-en-4-ol **3**, is also named as rhynchophorol. The (*S*)-enantiomer of this alcohol was recognized as the male-produced aggregation pheromone of the American palm weevil (*Rhynchophorus palmarum*).[23]

2.2. Kinetic resolution of racemic alcohols in lipase-catalyzed transesterification

Different lipases were screened when resolving five racemic allylic alcohols **1**–**5** in the enantioselective transesterification with vinyl esters as the acyl donor (Scheme 1).

In our previous report,[24] we presented the results of the studies connecting the influence of different solvents on the enzymatic resolution of racemic allylic alcohols. On the basis of these studies, we applied the diisopropyl ether as a solvent in all processes.

In our current investigations, we checked the influence of the lipase applied and acyl group donor on the effectiveness of the resolution of the studied alcohols in the transesterification process. The results obtained are summarized in Table 1.

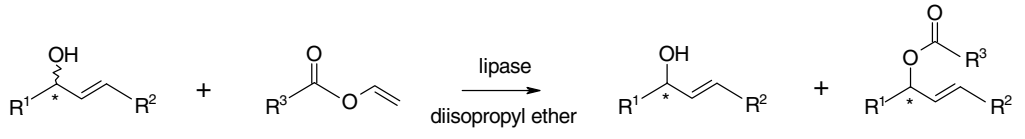
The lipase from *Candida antarctica* (CAL-B) turned out to be the optimal biocatalyst in the resolution of (±)-**1** and (±)-**2**. In both cases, the enantiomeric excesses of the starting alcohols and formed esters were higher than 91%. The lower enantiomeric ratio ($E = 98$) for this enzyme was observed in the transesterification of (±)-**5**, although the ester was obtained in high enantiomeric excess (95% ee). The use of the *Burkholderia cepacia* lipase (Amano PS) allowed us to separate alcohol (±)-**5** with excellent enantioselectivity. After 48 h of transesterification with vinyl butanoate in the presence of the enzyme, the ester was formed with more than 99% ee. The unreacted alcohol possessed also high enantiomeric purity (95% ee).

Transesterification of alcohols (±)-**3** and (±)-**4** was not as effective and enantioselective as for alcohols (±)-**1**, (±)-**2**, and (±)-**5**. The enantiomeric excesses of the esters formed and alcohols which remained did not exceed 50%.

In the lipase-catalyzed transesterification processes of alcohols **1**, **2**, and **5**, the (*S*)-enantiomers were the faster reacting isomers, leaving the (*R*)-enantiomer unreacted. Such a course of transformation can be predicted by Kazlauskas' rule[25] (Scheme 2). These predictions for the two alcohols (±)-**1** and (±)-**5** were confirmed by the comparison of the optical rotation values ($[\alpha]_{589}^{23} = -8.1$ (*c* 1.1, $CHCl_3$) for (*R*)-**1** and $[\alpha]_{589}^{23} = -12.5$ (*c* 0.9, $CHCl_3$) for (*R*)-**5**) with data referred for them in the literature {lit.[26] for (*R*)-**1** $[\alpha]_{589}^{20} = -6.0$ (*c* 0.1, $CHCl_3$), lit.[27] for (*R*)-**5** $[\alpha]_{589}^{27} = -11.4$ (*c* 1.0, $CHCl_3$)}.

Surprisingly, the lipase from *Candida cylindracea* converted alcohols **3** and **4** faster with an (*R*)-configuration at the stereogenic center. The configurations of the remaining alcohols **3** and **4** were determined by comparative GC analysis of samples isolated from the reaction mixture and pure enantiomers of these alcohols obtained earlier via the Sharpless epoxidation.[15] These results seemed not to be consistent with the Kazlauskas' rule (Scheme 2). The small difference between the sizes of the substituents attached to the carbon atom with hydroxy group could be responsible for this.

In the esterification of alcohols (±)-**1**, (±)-**2**, and (±)-**5**, we did not notice any significant influence of the type of the acyl group donor (vinyl propionate and vinyl butanoate) on the progress, as well as the enantioselectivity of the reactions performed. More significant influence of the various vinyl esters tried on the rate of transesterification and the purity of products obtained were observed for alcohols



1-5 **6-15**

1 R^1 = *n*-Bu, R^2 = H
2 R^1 = *i*-Bu, R^2 = H
3 R^1 = *i*-Bu, R^2 = Me
4 R^1 = -$CH_2C(CH_3)_3$, R^2 = Me
5 R^1 = -$CH_2C_6H_5$, R^2 = H

R^3 = Et, n-Pr, -C_9H_{19}, -$C_{11}H_{23}$

6 R^1 = *n*-Bu, R^2 = H, R^3 = Et
8 R^1 = *i*-Bu, R^2 = H, R^3 = Et
10 R^1 = *i*-Bu, R^2 = Me, R^3 = Et
12 R^1 = -$CH_2C(CH_3)_3$, R^2 = Me, R^3 = Et
13 R^1 = -$CH_2C(CH_3)_3$, R^2 = Me, R^3 = *n*-Pr
14 R^1 = -$CH_2C_6H_5$, R^2 = H, R^3 = Et
15 R^1 = -$CH_2C_6H_5$, R^2 = H, R^3 = *n*-Pr

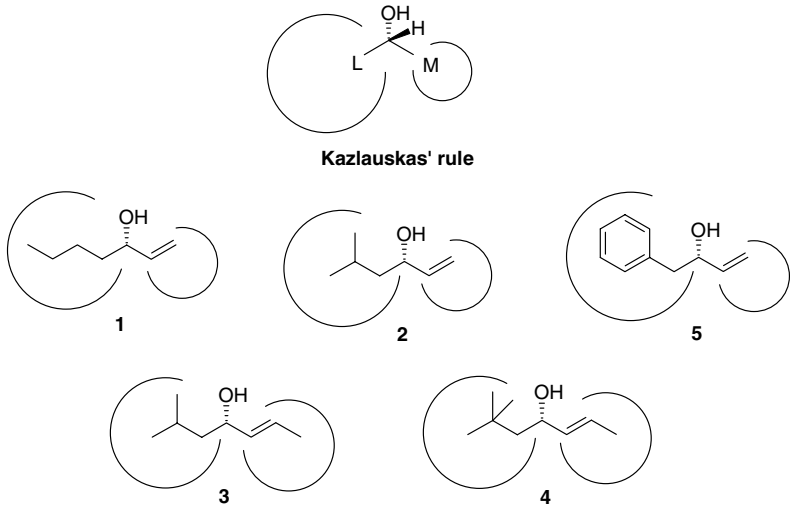
7 R^1 = *n*-Bu, R^2 = H, R^3 = *n*-Pr
9 R^1 = *i*-Bu, R^2 = H, R^3 = *n*-Pr
11 R^1 = *i*-Bu, R^2 = Me, R^3 = *n*-Pr

Scheme 1.

Table 1. Results of the lipase-catalyzed transesterification of alcohols (±)-**1**–**5**

Substrate	Enzyme	Acylating agent[a]	Reaction time	Conversion (%)	ee of formed ester (%)	ee of remaining alcohol (%)	E[b]
(±)-**1**	CAL-B	vp	2 h	49	>**99** (*S*)	**96** (*R*)	>**150**
		vb	4 h	48	**99** (*S*)	**94** (*R*)	>**150**
	CCL	vp	8 h	29	11 (*S*)	4.6 (*R*)	1.3
		vb	6 h	30	24 (*S*)	8.3 (*R*)	1.8
	Amano PS	vp	72 h	62	49 (*S*)	80 (*R*)	6.8
		vb	48 h	41	73 (*S*)	51 (*R*)	10.6
(±)-**2**	CAL-B	vp	8 h	48	>**99** (*S*)	**91** (*R*)	>**150**
		vb	8 h	50	**97** (*S*)	>**99** (*R*)	>**150**
	CCL	vp	24 h	37	18 (*S*)	11 (*R*)	1.6
		vb	8 h	36	30 (*S*)	17 (*R*)	2.2
	Amano PS	vp	14 days	41	**91** (*S*)	62 (*R*)	41
		vb	14 days	34	**91** (*S*)	48 (*R*)	34
(±)-**3**	CAL-B	vp	30 days	58	28 (*S*)	20 (*R*)	1.9
		vb	30 days	57	**49** (*S*)	**37** (*R*)	3.4
	CCL	vp	30 days	44	29 (*R*)	23 (*S*)	2.3
		vb	30 days	41	**45** (*R*)	**31** (*S*)	3.5
	Amano PS	vp	36 days	18	40 (*S*)	9 (*R*)	2.5
		vb	32 days	17	48 (*S*)	10 (*R*)	3.1
(±)-**4**	CAL-B	vp	30 days	22	24 (*S*)	7.3 (*R*)	1.7
		vb	30 days	28	35 (*S*)	14 (*R*)	2.4
	CCL	vp	32 days	18	31 (*R*)	7.8 (*S*)	2.1
		vb	32 days	22	42 (*R*)	12 (*S*)	2.7
	Amano PS	vp	36 days	13	40 (*S*)	6.2 (*R*)	2.5
		vb	36 days	20	42 (*S*)	11 (*R*)	2.7
(±)-**5**	CAL-B	vp	24 h	43	66 (*S*)	86 (*R*)	26
		vb	8 h	46	**95** (*S*)	**81** (*R*)	98
	CCL	vp	7 h	56	5.3 (*S*)	6.9 (*R*)	1.2
		vb	5 h	58	8.7 (*S*)	6.1 (*R*)	1.2
	Amano PS	vp	72 h	48	**98** (*S*)	**90** (*R*)	>**150**
		vb	48 h	49	>**99** (*S*)	**95** (*R*)	>**150**

[a] vp—Vinyl propionate, vb—vinyl butanoate.
[b] The enantiomeric ratio, $E = \ln[(1 - c)(1 - ee_s)]/\ln[(1 - c)(1 + ee_s)] = \ln[1 - c(1 + ee_p)]/\ln[1 - c(1 - ee_p)$, conversion, $c = ee_s/(ee_s + ee_p)$.



Scheme 2.

(±)-**3** and (±)-**4**, where various vinyl esters were attempted. It can be seen that, when the acylation took place using vinyl butanoate as the acyl donor group and Novozyme 435 (CAL-B) or *C. cylindracea* lipase (CCL) as a biocatalyst, the enantiomeric excesses of the formed ester were higher. For this reason, we decided to carry out the experiments with much longer vinyl esters used for transesterification processes of alcohols (±)-**3** and (±)-**4**. The results of these trials are presented in Table 2. Unfortunately, it turned out that when using vinyl decanoate and vinyl laurate, the enantioselectivity decreased in comparison even to that for vinyl propionate. The enantiomeric excesses of the

Table 2. Results of the transesterification of alcohols (±)-**3** and (±)-**4** with different vinyl esters in the presence of *Candida antarctica* lipase B (CAL-B)

Substrate	Acylating agent	Reaction time (days)	Conversion (%)	ee of formed ester (%)	ee of remaining alcohol (%)	E[a]
(±)-**3**	Vinyl propionate (C3)	30	58	28	20	1.9
	Vinyl butanoate (C4)	30	57	**49**	**37**	3.4
	Vinyl decanoate (C10)	10	60	11	7.5	1.7
	Vinyl laurate (C12)	10	48	8.1	7.6	1.2
(±)-**4**	Vinyl propionate (C3)	30	18	24	10	2.5
	Vinyl butanoate (C4)	30	29	35	14	1.8
	Vinyl decanoate (C10)	15	40	8.3	5.5	1.2
	Vinyl laurate (C12)	15	42	6.5	4.7	1.2

[a] The enantiomeric ratio, $E = \ln[(1-c)(1-ee_s)]/\ln[(1-c)(1+ee_s)] = \ln[1-c(1+ee_p)]/\ln[1-c(1-ee_p)$, conversion, $c = ee_s/(ee_s+ee_p)$.

esters formed did not exceed 11% after about 50% of conversion.

Analyzing the results of enzymatic esterification of alcohols (±)-**1**, (±)-**2**, (±)-**3**, (±)-**4**, and (±)-**5**, it can be seen that there is a dependence between the structure of the substrate and the effectiveness and enantioselectivity of enzymatic transesterification. According to the Kazlauskas' rule,[25] the best enantioselectivity of the esterification process was observed for allylic alcohols (±)-**1**, (±)-**2**, and (±)-**5** in which the substituents at the carbon atom with the hydroxy group significantly differ in size. The substitution of the double bond by the methyl group in the compounds (±)-**3** and (±)-**4** led to the reduction of differences in sizes between the relevant substituents, which resulted in decreasing both rate and enantioselectivity of the reaction.

3. Experimental

3.1. General methods

^{1}H NMR Spectra were recorded for $CDCl_3$ solutions on a Bruker AMX 300 spectrometer. IR spectra were recorded on Mattson IR 300 spectrometer (Thermo Nicolet). Optical rotations were measured on the Autopol IV automatic polarimeter (Rudolph) using chloroform solutions at concentrations given in g/100 cm^3. The progress of processes and enantiomeric composition of esters were determined on a Varian Chrompack CP-3380 GC, equipped with a flame ionization detector. A HP-5 column (30 m × 0.32 mm) and a CHIRASIL-DEX CB column (25 m × 0.25 mm × 0.25 μm) were used for the analysis. The following temperature programmes were applied to determinate the enantiomeric excess of the formed esters: for **1**: 60 °C (30 min)/20 °C/min/200 °C (2 min), for **2**: 40 °C (1 min)/0.5 °C/min/65 °C (1 min)/20 °C/min/200 °C (2 min), for (**3**): 80 °C (10 min)/0.3 °C/min/85 °C (1 min)/20 °C/min/200 °C (2 min), for **4**: 77 °C (10 min)/0.3 °C/min/84 °C (1 min)/20 °C/min/200 °C (2 min), and for **5**: 115 °C (1 min)/0.3 °C/min/120 °C (1 min)/20 °C/min/200 °C (2 min). All preparative chromatographic separation and purification of final products were carried out on silica gel columns (Kieselgel 60, 230–400 mesh).

3.2. Chemical and enzymes

Crotonaldehyde, isobutyl bromide, and *n*-butyllithium (1.6 M in hexane) were purchased from Aldrich Chemicals; acrylaldehyde, and vinyl butanoate from Fluka; and vinyl propionate, butyryl chloride, propionyl chloride from Lancaster Synthesis. The biocatalysts were purchased from the following sources: Novozym® 435 (immobilized *C. antarctica* lipase B) from Sigma Chemicals, Amano PS (*Pseudomonas cepacia* lipase) from Aldrich Chemicals, lipase from *C. cylindracea* and Lipozyme IM® (*Rhizomucor miehei* lipase) from Fluka Biochemika.

3.3. Synthesis of racemic alcohols 1–5

3.3.1. (±)-Hept-1-en-3-ol 1. *n*-Butyllithium (100 mL of a 1.6 M solution in hexane, 0.15 mol) was dissolved in 50 mL of dry diethyl ether and cooled to −78 °C. Then acrylaldehyde (0.15 mol) in ether (20 mL) was added slowly in small portions. The reaction mixture was stirred under an argon atmosphere. After warming to room temperature, a saturated aqueous NH_4Cl solution was added. The organic layer was separated, washed with brine, and dried over Na_2SO_4. Removal of the solvent and purification of the residue by column chromatography (silica gel, hexane/diethyl ether 9:1) gave (±)-**1** in 71% yield, as a colorless liquid, $n_D^{20} = 1.4322$ {lit.[28] $n_D^{20} = 1.4330$}. The spectral data (^{1}H NMR and IR) correspond with those referred earlier for **1** {lit.[18]}.

3.3.1.1. Preparation of alcohols 2–5. (±)-5-Methylhex-1-en-3-ol **2** and (±)-6-methylhept-2-en-4-ol **3** and (±)-6,6-dimethylhept-2-en-4-ol **4** were obtained as products of the Grignard reactions of isobutyl magnesium bromide or neopentyl magnesium bromide with acrolein or crotonaldehyde, respectively. (±)-4-Phenylbut-1-en-3-ol **5** was also obtained in the Grignard reaction of acrolein with benzyl magnesium bromide. The reactions were carried out according to the standard procedure.

To a cooled (ice bath) solution of the alkyl or benzyl magnesium bromide (prepared from 0.1 mol bromide and 0.1 mol of magnesium in 40 mL dry diethyl ether), aldehyde (0.09 mol) was very slowly added. The reaction mixture was stirred overnight and then saturated NH_4Cl solution was added. The organic layer was then separated. The aqueous layer was extracted with three portions (50 mL) of ether. The combined ether solutions were washed with brine. After drying over $MgSO_4$, the solvent was evaporated to give a crude product, which was purified by column chromatography (silica gel, hexane–diethyl ether 9:1). All alcohols obtained **2**–**5** are known compounds. Their physical and spectral data correspond with

those referred earlier in the literatures **2**,[19] **3**,[20] **4**,[21] and **5**.[22] Here, only the yields of the reactions and refractive indexes of alcohols obtained are given.

(±)-**5-Methylhex-1-en-3-ol 2**: yield 60%, colorless liquid, $n_D^{20} = 1.4230$ {lit.[29] $n_D^{21} = 1.4251$}.

(±)-**6-Methylhept-2-en-4-ol 3**: yield 62%, colorless liquid, $n_D^{20} = 1.4385$ {lit.[20] $n_D^{21} = 1.4359$}.

(±)-**6,6-Dimethylhept-2-en-4-ol 4**: yield 68%, colorless liquid, $n_D^{20} = 1.4568$ {lit.[21] $n_D^{20} = 1.4576$}.

(±)-**1-Phenylbut-3-en-2-ol 5**: yield 75%, colorless liquid, $n_D^{20} = 1.5162$ {lit.[22] $n_D^{17} = 1.5353$}.

3.4. Preparation of racemic esters 6–15

Propionates and butanoates of alcohols **1**–**5** were obtained as reference compounds for GC analyses in a standard manner (reaction with propionyl chloride or butyryl chloride) according to the following procedure.

To a cooled (0 °C, ice bath) solution of alcohols **1**–**5** (10 mmol) and pyridine (12 mmol) in dry diethyl ether (10 mL), acyl chloride (12 mmol) was added dropwise and the mixture was stirred at room temperature for 24 h. After that time, the reaction mixture was diluted with diethyl ether and washed with 0.1 M aqueous HCl, saturated $NaHCO_3$, and finally with brine. The ether solution was dried over $MgSO_4$. The solvent was evaporated and crude product was purified by column chromatography (silica gel, hexane–ethyl acetate, 22:1).

The yields of the reactions, spectral data, and refractive indexes for the esters obtained are given below.

3.4.1. 1-Vinyl-pentyl propionate 6. Yield 81%, colorless liquid, $n_D^{20} = 1.4241$; IR (film) ν_{max} (cm^{-1}) = 1738 (s, C=O), 1187 (s, C–O), 992 (m, =C–H); ^1H NMR ($CDCl_3$): δ 0.85 (t, $J = 6.8$ Hz, 3H, $-CH_2CH_3$), 1.13 (t, $J = 7.4$ Hz, 3H, $-C(O)CH_2CH_3$), 1.27–1.36 (m, 4H, $CH_3(CH_2)_2-$), 1.47–1.57 (m, 2H, $-CH_2-$), 2.3 (q, $J = 7.4$ Hz, 2H, $-C(O)CH_2CH_3$), 5.07 (ddd, $J = 10.5$, 2.4, 1.4 Hz, 1H, one of $-CH=CH_2$), 5.19 (ddd, $J = 17.3$, 2.6, 1.4 Hz, 1H, one of $-CH=CH_2$), 5.2 (m, 1H, –OCH<), 5.8 (ddd, $J = 17.3$, 10.5, 6.2 Hz, 1H, $-CH=CH_2$).

3.4.2. 1-Vinyl-pentyl butanoate 7. Yield 86%, colorless liquid, $n_D^{20} = 1.4237$ {lit.[30] $n_D^{20} = 1.4241$}; IR (film) ν_{max} (cm^{-1}) = 1742 (s, C=O), 1182 (s, C–O), 996 (m, =C–H); ^1H NMR ($CDCl_3$): δ 0.82 (t, $J = 6.8$ Hz, 3H, $-CH_2CH_3$), 1.15 (t, $J = 7.4$ Hz, 3H, $-C(O)(CH_2)_2CH_3$), 1.25–1.38 (m, 4H, $CH_3(CH_2)_2-$), 1.41–1.53 (m, 2H, $-CH_2-$), 1.57 (m, 2H, $-C(O)CH_2CH_2CH_3$), 2.3 (t, $J = 7.4$ Hz, 2H, $-C(O)CH_2CH_2CH_3$), 5.10 (ddd, $J = 10.5$, 2.4, 1.4 Hz, 1H, one of $-CH=CH_2$), 5.2 (ddd, $J = 17.3$, 2.6, 1.4 Hz, 1H, one of $-CH=CH_2$), 5.22 (m, 1H, –OCH<), 5.8 (ddd, $J = 17.2$, 10.5, 6.2 Hz, 1H, $-CH=CH_2$).

3.4.3. 3-Methyl-1-vinyl-butyl propionate 8. Yield 83%, colorless liquid, $n_D^{20} = 1.4112$; IR (film) ν_{max} (cm^{-1}) = 1745 (s, C=O), 1194 (s, C–O) 989 (m, =C–H); ^1H NMR ($CDCl_3$): δ 0.93 and 0.94 (two d, $J = 6.2$ Hz, 6H, $-CH(CH_3)_2$), 1.16 (t, $J = 7.6$ Hz, 3H, $-C(O)CH_2CH_3$), 1.41 (ddd, $J = 13.2$, 7.3, 5.7 Hz, 1H, one of $-CH_2CH(CH_3)_2$), 1.58–1.70 (m, 2H, $-CH(CH_3)_2$ and one of $-CH_2CH(CH_3)_2$), 2.35 (q, $J = 7.6$ Hz, 2H, $-C(O)CH_2CH_3$), 5.16 (d, $J = 10.5$ Hz, 1H, one of $-CH=CH_2$), 5.25 (d, J = 17.2 Hz, 1H, one of $-CH=CH_2$), 5.35 (m, 1H, –OCH<), 5.79 (ddd, $J = 17.2$, 10.5, 6.4 Hz, 1H, $-CH=CH_2$).

3.4.4. 3-Methyl-1-vinyl-butyl butanoate 9. Yield 79%, colorless liquid, $n_D^{20} = 1.4222$; IR (film) ν_{max} (cm^{-1}) = 1741 (s, C=O), 1178 (s, C–O), 990 (m, =C–H); ^1H NMR ($CDCl_3$): δ 0.89 and 0.92 (two d, $J = 6.5$ Hz, 6H, $-CH(CH_3)_2$), 0.95 (t, $J = 7.4$ Hz, 3H, $-C(O)(CH_2)_2CH_3$), 1.38 (ddd, $J = 13.5$, 7.6, 5.8 Hz, 1H, one of $-CH_2CH(CH_3)_2$), 1.58 (ddd, $J = 13.5$, 7.6, 6.3 Hz, 1H, one of $-CH_2CH(CH_3)_2$), 1.61–1.71 (m, 3H, $-CH(CH_3)_2$ and $-C(O)CH_2CH_2CH_3$), 2.29 (t, $J = 7.4$ Hz, 2H, $-C(O)CH_2CH_2CH_3$), 5.13 (d, $J = 10.5$ Hz, 1H, one of $-CH=CH_2$), 5.22 (d, J = 17.2 Hz, 1H, one of $-CH=CH_2$), 5.32 (m, 1H, –OCH<), 5.76 (ddd, $J = 17.2$, 10.5, 6.4 Hz, 1H, $-CH=CH_2$).

3.4.5. 1-Isobutylbut-2-enyl propionate 10. Yield 78%, colorless liquid $n_D^{20} = 1.4245$; IR (film) ν_{max} (cm^{-1}) = 1737 (s, C=O), 1189 (s, C–O); ^1H NMR: δ 0.88 and 0.90 (two d, $J = 6.3$ Hz, 6H, $-CH(CH_3)_2$), 1.10 (t, $J = 7.6$ Hz, 3H, $-C(O)CH_2CH_3$) 1.28 (m, 1H, one of $-CH_2CH(CH_3)_2$), 1.50–1.60 (m, 2H, one of $-CH_2CH(CH_3)_2$ and $-CH(CH_3)_2$), 1.67 (dd, $J = 6.7$, 1.4 Hz, 3H=CH–CH_3), 2.28 (q, $J = 7.6$ Hz, 2H, $-C(O)CH_2CH_3$), 5.25 (ddd, $J = 7.5$, 7.0, 6.7 Hz, 1H, –OCH<), 5.46 (ddq, $J = 13.6$, 7.5, 1.4 Hz, 1H, $-CH=CHCH_3$), 5.62 (dqd, $J = 13.6$, 6.7, 0.6 Hz, 1H, $=CHCH_3$).

3.4.6. 1-Isobutylbut-2-enyl butanoate 11. Yield 75%, colorless liquid, $n_D^{20} = 1.4321$; IR (film) ν_{max} (cm^{-1}) = 1741 (s, C=O), 1192 (s, C–O), 992 (m, C–H); ^1H NMR: δ 0.89 and 0.92 (two d, $J = 6.2$ Hz, 6H, $-CH(CH_3)_2$), 1.12 (t, $J = 7.5$ Hz, 3H, $-C(O)(CH_2)_2CH_3$), 1.22 (m, 2H, $-C(O)CH_2CH_2CH_3$), 1.30 (m, 1H, one of $-CH_2CH(CH_3)_2$), 1.42–1.55 (m, 2H, one of $-CH_2CH(CH_3)_2$ and $-CH(CH_3)_2$), 1.70 (dd, $J = 6.6$, 1.3 Hz, 3H, =CH–CH_3), 2.30 (t, $J = 6.6$ Hz, 2H, $-C(O)CH_2CH_2CH_3$), 5.42 (ddq, $J = 13.5$, 7.4, 1.3 Hz, 1H, —$CH=CHCH_3$), 5.51 (ddd, $J = 7.4$, 7.0, 6.7 Hz, 1H, –OCH<), 5.60 (dqd, $J = 13.5$, 6.6, 0.6 Hz, 1H, $=CHCH_3$).

3.4.7. 1-(2,2-Dimethylpropyl)but-2-enyl propionate 12. Yield 78%, colorless liquid $n_D^{20} = 1.4425$; IR (film) ν_{max} (cm^{-1}) = 1739 (s, C=O), 1192 (s, C–O), 990 (m, =C–H); ^1H NMR: δ 0.89 (s, 9H, $-C(CH_3)_3$), 1.12 (t, $J = 7.6$ Hz, 3H, $-C(O)CH_2CH_3$), 1.41 (dd, $J = 15.0$, 3.8 Hz, 1H, one of $-CH_2C(CH_3)_3$), 1.60 (dd, $J = 15.0$, 7.9, 1H, one of $-CH_2C(CH_3)_3$), 1.65 (dd, $J = 6.5$, 1.1 Hz, 3H, =CH–CH_3), 2.26 (q, $J = 7.6$ Hz, 2H, $-C(O)CH_2CH_3$), 5.32 (m, 1H, –OCH<), 5.36 (ddq, $J = 13.0$, 8.7, 1.1, 1H, $-CH=CHCH_3$), 5.60 (dq, $J = 13.0$, 6.5 Hz, 1H, $=CHCH_3$).

3.4.8. 1-(2,2-Dimethylpropyl)but-2-enyl butanoate 13. Yield 83%, colorless liquid, $n_D^{20} = 1.4395$; IR (film) ν_{max} (cm^{-1}) = 1741 (s, C=O), 1195 (s, C–O), 986 (m, =C–H); ^1H NMR: δ 0.91 (s, 9H, $-C(CH_3)_3$), 1.1 (t, $J = 7.4$ Hz, 3H, $-C(O)(CH_2)_2CH_3$), 1.26 (m, 2H, $-C(O)CH_2CH_2CH_3$),

1.40 (dd, $J = 15.1$, 3.9 Hz, 1H, one of $-CH_2C(CH_3)_3$), 1.61 (dd, $J = 15.1$, 7.8 Hz, 1H, one of $-CH_2C(CH_3)_3$), 1.62 (dd, $J = 6.2$, 1.0 Hz, 3H, $=CH-CH_3$), 2.26 (t, $J = 7.5$ Hz, 2H, $-C(O)CH_2CH_2CH_3$), 5.31 (m, 1H, $-OCH<$), 5.36 (ddq, $J = 13.2$, 8.7, 1.0 Hz, 1H, $-CH=CHCH_3$), 5.60 (dq, $J = 13.2$, 6.2 Hz, 1H, $=CHCH_3$).

3.4.9. 1-Benzyl-allyl propionate 14. Yield 88%, colorless oil, $n_D^{20} = 1.4902$; IR (film) ν_{max} (cm^{-1}) = 1740 (s, C=O), 1175 (s, C–O), 986 (m, C–H), 760, 700 (m, $C_{ar.}$–H); ^1H NMR ($CDCl_3$): δ 1.11 (t, $J = 7.1$ Hz, 3H, $-C(O)CH_2CH_3$), 2.32 (q, $J = 7.1$ Hz, 2H, $-C(O)CH_2CH_3$), 2.92 (dd, $J = 13.8$, 6.0 Hz, 1H, one of $C_6H_5CH_2-$), 2.99 (dd, $J = 13.8$, 7.8 Hz, 1H, one of $C_6H_5CH_2-$), 5.18 (dd, $J = 10.8$, 1.2 Hz, 1H, one of $-CH=CH_2$), 5.24 (dd, $J = 17.4$, 1.2 Hz, 1H, one of $-CH=CH_2$), 5.50 (m, 1H, $-OCH<$), 5.85 (ddd, $J = 17.4$, 10.8, 6.6 Hz, 1H, $-CH=CH_2$), 7.24–7.32 (m, 5H, $-C_6H_5$).

3.4.10. 1-Benzyl-allyl butanoate 15. Yield 85%, colorless oil, $n_D^{20} = 1.4650$; IR (film) ν_{max} (cm^{-1}) = 1738 (s, C=O), 1181 (s, C–O), 988 (m, C–H), 750, 701 (m, $C_{ar.}$–H); ^1H NMR ($CDCl_3$): δ 1.15 (t, $J = 7.3$ Hz, 3H, $-C(O)(CH_2)_2CH_3$), 1.62 (m, 2H, $-C(O)CH_2CH_2CH_3$), 2.28 (t, $J = 7.5$ Hz, 2H, $-C(O)CH_2CH_2CH_3$), 2.93 (dd, $J = 13.8$, 6.0 Hz, 1H, one of $C_6H_5CH_2-$), 2.98 (dd, $J = 13.8$, 7.6 Hz, 1H, one of $C_6H_5CH_2-$), 5.18 (dd, $J = 10.5$, 0.7 Hz, 1H, one of $-CH=CH_2$), 5.24 (dd, $J = 17.2$, 0.7 Hz, 1H, one of $-CH=CH_2$), 5.52 (m, 1H, $-OCH<$), 5.85 (ddd, $J = 17.2$, 10.5, 6.3 Hz, 1H, $-CH=CH_2$), 7.20–7.31 (m, 5H, $-C_6H_5$).

3.5. General procedure for the lipase-catalyzed tranesterification of racemic alcohols

All racemic allylic alcohols were subjected to the enzymatic transesterification according to the same procedure:

To a stirred mixture of alcohol (100 mg) and vinyl ester (1 mL) in a 10 mL vial in diisopropyl ether (3 mL), 50 mg of lipase was added in one portion and stirring was continued at room temperature. Samples of the reaction mixtures were taken after several time intervals. The enzyme was removed by filtration and the organic layer was diluted with diethyl ether and analyzed by GC. The amount of esters formed during the reactions and their enantiomeric composition were determined by GC, using a chiral column. The alcohols were not separable on the chiral columns being at our disposal. To determine the ee values of the remaining alcohols it was necessary to convert them, after separation from reaction mixtures, into the propanoates by the reaction with propionyl chloride in the presence of pyridine.

3.5.1. Preparative enzymatic resolution of (±)-1. After 2 h of esterification of (±)-**1** with vinyl propionate as an acyl donor and Novozym 435 (*C. antarctica* lipase B) as a biocatalyst, 37.9 mg (yield 38%) of (*R*)-(−)-**1**, ee = 96%, $[\alpha]_{589}^{23} = -8.1$ (*c* 1.1, $CHCl_3$) and 41 mg (yield 32%) of (*S*)-(+)-**6**, ee = 100%, $[\alpha]_{589}^{23} = 6.5$ (*c* 1.9, $CHCl_3$) were obtained.

The configuration of the stereogenic centers of (−)-**1** and (+)-**6** was assigned on the basis of Kazlauskas' rule and by comparison of the specific rotation of alcohol (−)-**1** with the value referred in the literature {lit.[25] for (*R*)-**1** $[\alpha]_{589}^{20} = -6.0$ (*c* 0.1, $CHCl_3$)}.

3.5.2. Preparative enzymatic resolution of (±)-2. After 8 h of esterification of (±)-**2** with vinyl propionate as an acyl donor and Novozym 435 (*C. antarctica* lipase B) as a biocatalyst, there were obtained 41.7 mg (yield 42%) of (*R*)-(+)-**2**, ee = 91%, $[\alpha]_{589}^{23} = 12.0$ (*c* 1.9, $CHCl_3$) and 58 mg (yield 39%) of (*S*)-(−)-**8**, ee = 100%, $[\alpha]_{589}^{23} = -6.9$ (*c* 2.5, $CHCl_3$).

The configuration of the stereogenic centers of (+)-**2** and (−)-**8** were assigned taking into consideration the Kazlauskas' rule (Scheme 2).

3.5.3. Preparative enzymatic resolution of (±)-5. After 48 h of esterification with vinyl butanoate as an acyl donor and Amano PS (*B. cepacia* lipase) as a biocatalyst, 40.5 mg (yield 40%) of (*R*)-(−)-**5**, ee = 95%, $[\alpha]_{589}^{23} = -12.5$ (*c* 1.0, $CHCl_3$) and 58 mg (yield 39%) of (*S*)-(−)-**15**, ee = 100%, $[\alpha]_{589}^{23} = -5.9$ (*c* 1.0, $CHCl_3$) were obtained.

The (*R*)-configuration of the (−)-isomer of alcohol **5** was confirmed by the comparison of the specific rotation of alcohol remained with the value referred in the literature {lit.[26] for (*R*)-**5**, $[\alpha]_{589}^{27} = -11.4$ (*c* 1.0, $CHCl_3$)}.

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