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Lipase-catalyzed kinetic resolution of α,β-unsaturated α′-acetoxy ketones

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Abstract

The lipase-catalyzed kinetic resolutions of the α,β-unsaturated α′-acetoxy ketones **3a**,**b** have been investigated. Of the lipases examined, CAL-B from *Candida antarctica* (fraction B) has been shown to be an efficient biocatalyst, which may be used effectively in preparative scale reactions.

1. Introduction

In recent years, lipases have been successfully used as efficient biocatalysts for the kinetic resolution of a wide range of chiral compounds.[1] We report here on the lipase-catalyzed hydrolysis of the α,β-unsaturated α′-acetoxy ketones **3a**,**b** in the presence of four different lipases. This reaction provides optically active α-acetoxy ketones **3** and α-hydroxy ketones **4**, highly functionalized molecules with a wide potential (Scheme 1). So far no general procedures for the synthesis of these compounds in enantiomerically pure form have been reported and only a few examples of related cyclic compounds have been resolved with lipases as catalysts.[2]

2. Results and discussion

The racemic enone substrates **3** were prepared by standard acetylation of the corresponding α-hydroxy hydroperoxides[3] **2** by acetic anhydride and triethylamine in dichloromethane with *p*-dimethylaminopyridine (DMAP) as catalyst (Scheme 1). The labile peracetate, which results from acetylation of the hydroperoxy group, dehydrates (Kornblum–de la Mare reaction[4]) to give the racemic enones **3** in 70–75% yield.

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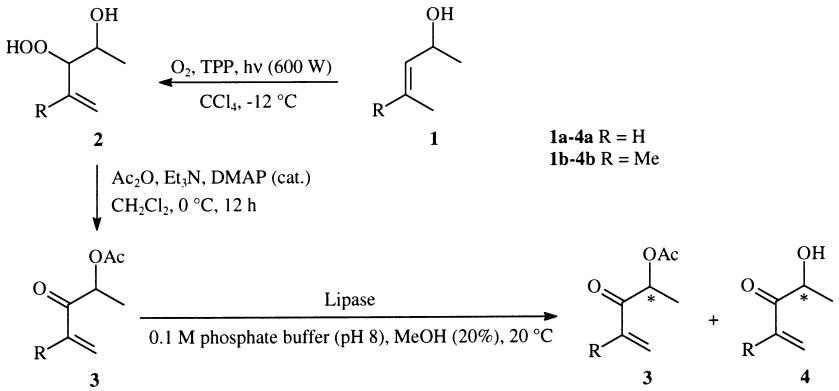


Scheme 1. Synthesis and enzymatic hydrolysis of the enone substrates **3a**,**b**

The enzymatic hydrolyses were carried out in 0.1 M phosphate buffer (pH 8) with 20% methanol as cosolvent. The results are shown in Table 1. Of the lipases tested, the best results for the resolution of the enones **3a**,**b** were obtained with the CAL-B lipase as catalyst (E values, which characterize the efficiency of the resolution, up to 150).

For the substrate **3a**, an ee value of 93% for the acetate and 85% for the alcohol was achieved at 52% conversion (entry 2). In the case of derivative **3b**, an ee value of 92% for the acetate and 96% for the alcohol was obtained at 49% conversion (entry 8), at 52% conversion the acetate reached ee values >98% (entry 10).

The lipase CAL-B exhibited a very pronounced affinity for one of the enantiomers, as evidenced by the low amount of further conversion after the preferred enantiomer had been practically fully consumed. Lipase PSL2 was faster than lipase CAL-B, but the ee values were moderate, even for the acetate at high conversions (entries 6 and 13). Lipases BSL (entries 1 and 7) and PSL1 (entries 5 and 11) showed also only moderate enantiomeric excesses for both the alcohol and acetate.

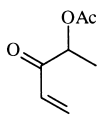
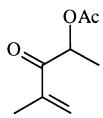
Because of the low ee values obtained for the alcohol in comparison with those for the acetate, we carried out control experiments, which showed that the alcohol, but not the acetate, is partly racemized under the reaction conditions. This may be explained by the equilibrium between the conjugated and the less favored unconjugated tautomers of the hydroxy enone **4** through their enolate intermediate (Scheme 2).

The absolute configurations were assigned by chemical correlation, in which the optically active acetoxy ketones **3** were reduced to the corresponding literature-known 1,2-diols **5** (Scheme 3).[6] Authentic samples of the latter were obtained by horseradish peroxidase (HRP) catalyzed kinetic resolution of the corresponding α-hydroxy hydroperoxides **2** (Scheme 3).

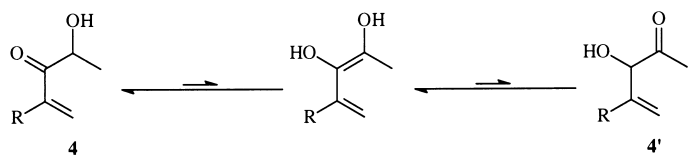
Comparison of the diols **5a** obtained by $NaBH_4$ reduction of the acetoxy ketone **3a** and by Ph_3P reduction of the hydroperoxides **2a**, whose absolute configurations have been previously established,[6] established the *S* configuration of the stereogenic center in the acetoxy ketone **3a**. The *R* configuration deduced in this way for the alcohol **4a** agrees with the reported data.[7] Following the same procedure, comparison of the diols **5b** obtained by $NaBH_4$ reduction of the acetoxy ketone **3b** and by Ph_3P reduction of the hydroperoxides **2b**, established the *R* configuration of the stereogenic center in the acetoxy ketone **3b**. Correspondingly, the absolute configuration of the alcohol **4b** is then assigned as *S*. The acetate **3b** and alcohol **4b** are hitherto unknown and no specific rotation data are available for comparison.

The *R* enantiomer is preferred in the case of acetate **3a**, which fits the empirical model, proposed by Kazlauskas et al.,[8] well for the kinetic resolution of secondary alcohols, based on the size of the substituents at the stereogenic carbon center. However, the lipases examined showed an opposite

Table 1
Lipase-catalyzed kinetic resolution of the unsaturated α-acetoxy ketones **3a**,**b**

Entry	Substrate	Lipase[a] (mg/ mmol of **3**)	Time [h]	Conv[b] [%]	Acetate **3** ee[d] [%]	Acetate **3** Config[e].	Alcohol **4** ee[f] [%]	Alcohol **4** Config[g].	E[c]
1	 **3a**	BSL (50)	7	63	22	*S*	13	*R*	2
2		CAL-B (10)	3	52	93	*S*	85	*R*	44
3		CAL-B (10)	4	53	94	*S*	83	*R*	38
4		CAL-B (10)	5	54	95	*S*	80	*R*	35
5		PSL1 (50)	7	67	54	*S*	27	*R*	3
6		PSL2 (50)	1	64	86	*S*	49	*R*	7
7	 **3b**	BSL (50)	52	49	27	*R*	28	*S*	2
8		CAL-B (10)	4	49	92	*R*	96	*S*	152
9		CAL-B (10)	6	51	97	*R*	93	*S*	119
10		CAL-B (10)	8	52	>98	*R*	91	*S*	>100
11		PSL1 (50)	42	65	83	*R*	44	*S*	6
12		PSL2 (50)	4	55	93	*R*	76	*S*	24
13		PSL2 (50)	6	58	98	*R*	71	*S*	26

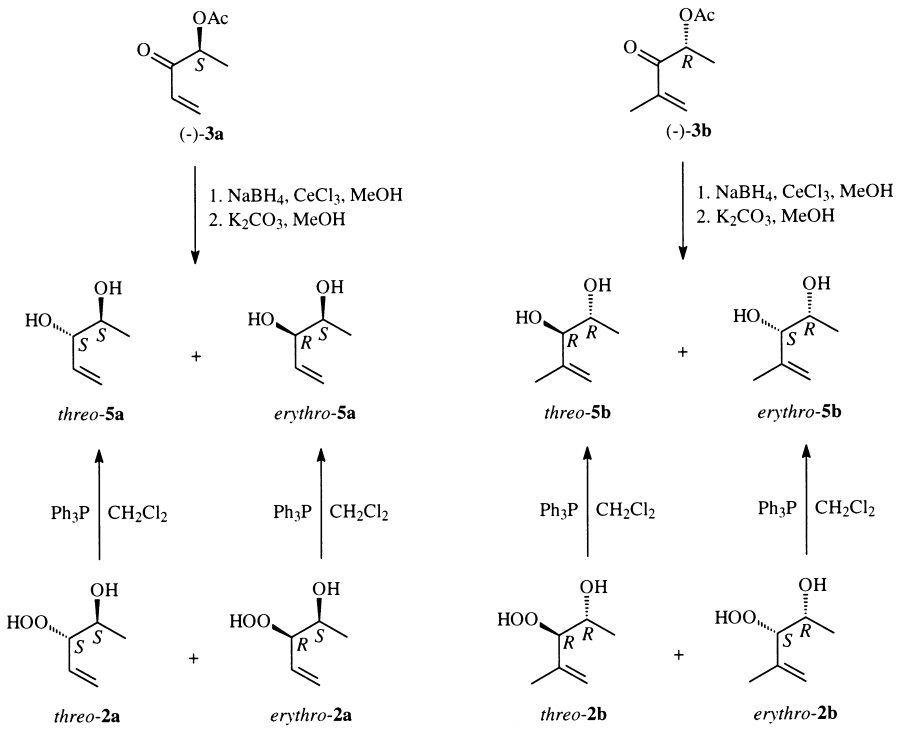
[a]BSL (CHIRAZYME®L1) from *Burkholderia sp.*; CAL-B (CHIRAZYME®L2) from *Candida antarctica*, fraction B; PSL1 (CHIRAZYME®L4) and PSL2 (CHIRAZYME®L6) from *Pseudomonas sp.* (Boehringer Mannheim). [b]Calculated from the expression conv. = ee(acetate)/ee(acetate)+ee(alcohol) (Ref. 5). [c]Enantioselectivity (Ref. 5). [d]Determined by GC analysis on a Fisons-Instruments HRGC Mega Series 2 8560 equipped with a permethylated β-cyclodextrin column packed with OV 1701 (25 m, 0.25-mm ID, 0.25-μm film); conditions: 60 °C, 5 min, then heated at a rate of 1 °C/min to 80 °C; error ≤3%. [e]Assigned by chemical correlation; the product was converted into the corresponding literature-known diol (Ref. 6). [f]Determined by HPLC analysis on a Chiralcel OB-H column with hexane/isopropyl alcohol as eluent (95:5 for entries 1-6, 90:10 for entries 7-13); error ≤3%. [g]In the case of alcohol **4a**, the sign of the specific rotation was compared with literature data (Ref. 7).



Scheme 2. Proposed mechanism for the racemization of the hydroxy enone **4**

preference for the methyl-substituted acetate **3b**. While this behavior is as yet not well understood, similar deviations from the empirical rule have been noted in related compounds.[9]

In conclusion, lipase CAL-B proved to be the most efficient biocatalyst for the kinetic resolution of the compounds **3a**,**b**. The ee values for the alcohol **4** are not as high as expected, which is due to some racemization under the reaction conditions. This lipase was then used for the synthesis of optically active acetates **3** and alcohols **4** on a preparative scale (Table 2).



Scheme 3. Chemical correlation of the optically active α-acetoxy ketones **3** with the corresponding 1,2-diols **5**

Table 2
Preparative-scale lipase-catalyzed kinetic resolution of acetates **3a**,**b**

Entry	Substrate	Time	Conv[a]	Acetate **3**			Alcohol **4**		
				Yield[b]	ee[c]	$[\alpha]_D^{20}$	Yield[b]	ee[d]	$[\alpha]_D^{20}$
		(h)	(%)	(%)	(%)		(%)	(%)	
1	**3a**	4	52	35	94	− 24	16	88	− 51
2	**3b**	7	52	38	98	− 8	25	90	− 30

[a] *cf.* Footnote b in Table 1. [b] Yield of isolated material. [c] *cf.* Footnote c in Table 1. [d] *cf.* Footnote e in Table 1.

3. Experimental

*3.1. General procedure for the lipase-catalyzed hydrolysis of acetates **3a,b***

To a solution of the substrate (0.2 mmol) in 0.4 mL MeOH were added 1.6 mL of 0.1 M phosphate buffer (pH 8) and the lipase powder. The mixture was vigorously stirred at ca 20°C for the time indicated in Table 1 and then the products were extracted with ether (3×10 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ solution and brine and dried over $MgSO_4$. Crude samples were analyzed by GC and HPLC. In preparative-scale experiments (1.0–2.0 mmol) the products were separated by preparative TLC on silica gel 60 F_{254} with n-hexane:ethyl acetate (80:20) as the eluent.

3.2. (S)-(−)-4-Acetoxypent-1-en-3-one [(S)-**3a**]

Colorless oil; $[\alpha]_D^{20}=-24$ ($CHCl_3$, c 0.6, for 98% ee). ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.49 (dd, J=17.4, 10.1 Hz, 1H), 6.35 (dd, J=17.4, 2.1 Hz, 1H), 5.83 (dd, J=10.1, 2.1 Hz, 1H), 5.28 (q, J=7.0 Hz, 1H), 2.11 (s, 3H), 1.40 (d, J=7.0 Hz, 3H); ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 196.3 (s), 170.2 (s), 131.4 (d), 130.1 (t), 73.3 (d), 20.6 (q), 16.2 (q); IR ($CDCl_3$): ν 2991, 2939, 2875, 1740, 1712, 1616, 1457, 1447, 1406, 1373, 1290, 1243, 1048, 982 cm^{-1}. Anal. calcd for $C_7H_{10}O_3$ (142.1): C, 59.13; H, 7.09. Found: C, 58.85; H, 6.77.

3.3. (R)-(−)-4-Acetoxy-2-methylpent-1-en-3-one [(R)-**3b**]

Colorless oil; $[\alpha]_D^{20}=-8$ ($CHCl_3$, c 0.6, for 98% ee). ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.97 (br d, J=0.9 Hz, 1H), 5.87 (q, J=1.5 Hz, 1H), 5.69 (q, J=7.0 Hz, 1H), 2.12 (s, 3H), 1.90 (dd, J=1.5, 0.9 Hz, 3H), 1.44 (d, J=7.0 Hz, 3H); ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 198.1 (s), 170.2 (s), 141.8 (s), 125.3 (t), 70.6 (t), 20.5 (q), 17.7 (q), 17.2 (q); IR ($CDCl_3$): ν 3100, 2990, 2963, 2930, 1735, 1691, 1630, 1450, 1373, 1277, 1246, 1148, 1096, 1049 cm^{-1}. Anal. calcd for $C_8H_{12}O_3$ (156.1): C, 61.51; H, 7.75. Found: C, 61.06; H, 7.35.

3.4. (R)-(−)-4-Hydroxypent-1-en-3-one [(R)-**4a**]

Colorless oil. The spectral characteristics were identical to those reported previously;[7] $[\alpha]_D^{20}=-51$ ($CHCl_3$, c 0.6, for 98% ee).

3.5. (S)-(−)-4-Hydroxy-2-methylpent-1-en-3-one [(S)-**4b**]

Colorless oil; $[\alpha]_D^{20}=-30$ ($CHCl_3$, c 0.3, for 90% ee). ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.92 (br dd, J=1.8, 1.2 Hz, 2H), 4.89 (dq, J=7.0, 6.4 Hz, 1H), 3.56 (d, J=6.4 Hz, 1H), 1.94 (d, J=7.0 Hz, 3H): ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 203.8 (s), 141.1 (s), 126.5 (t), 68.5 (t), 22.6 (q), 17.8 (q); IR ($CDCl_3$): ν 3690, 3487, 2983, 2930, 2860, 1675, 1629, 1602, 1455, 1375, 1315, 1242, 1146, 1058 cm^{-1}.

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References

1. Wong, C. H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*, Pergamon, Oxford, 1994, pp. 41–130.
2. Tanyeli, C.; Demir, A. S.; Dikici, E. *Tetrahedron: Asymmetry* **1996**, *7*, 2399–2402.
3. Adam, W.; Nestler, B. *J. Am. Chem. Soc*. **1992**, *114*, 6549–6550.
4. Kornblum, N.; de la Mare, H. E. *J. Am. Chem. Soc*. **1951**, *73*, 880–881.
5. Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc*. **1982**, *104*, 7294–7299.
6. Hoch, U.; Humpf, H.-U.; Schreier, P.; Saha-Möller, C. R.; Adam, W. *Chirality* **1997**, *9*, 69–74.

7. Stammen, B.; Berlage, U.; Kindermann, M. K.; Günther, B.; Sheldrick, W. S.; Welzel, P.; Roth, W. R. *J. Org. Chem*. **1992**, *57*, 6566–6575.
8. Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. J. *J. Org. Chem*. **1991**, *56*, 2656.
9. Adam, W.; Díaz, M. T.; Saha-Möller, C. R. Lipase-catalyzed kinetic resolution of *threo*-configured 1,2-diols: A comparative study of transesterification versus hydrolysis, in press.