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Enzymatic preparation of optically active α-methylene β-lactones by lipase-catalyzed kinetic resolution through asymmetric transesterification

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Abstract: The lipase-catalyzed asymmetric transesterification of racemic α-methylene β-lactones **1** with benzyl alcohol in organic media afforded the optically active β-lactones and the corresponding β-hydroxy esters **2** in excellent enantiomeric excess (ee 95–99%).
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Functionalized oxetan-2-ones, in particular α-methylene β-lactones **1**, are versatile building blocks in organic synthesis.[1,2] Therefore, recently several methods[3] have been developed for their preparation. Recently, we have reported[4] on the first synthesis of the optically active α-methylene β-lactones (3*R*)- and (3*S*)-3-methylene-4-(1-methylethyl)-1-oxetan-2-one by topological resolution of the racemic lactone **1b** through a Diels–Alder reaction with an optically active diene. The disadvantage of this method is that stoichiometric amounts of an enantiomerically pure diene are required. Consequently, we have been searching for alternative methods to prepare optically active α-methylene β-lactones.

Lipases have been successfully used as convenient and efficient biocatalysts in the synthesis of a wide range of optically active compounds by kinetic resolution. Recently, lipase-catalyzed kinetic resolution of 4-alkyl-substituted β-lactones has been reported,[5] but to date no α-methylene β-lactones have been optically resolved. We have now achieved this by lipase-catalyzed asymmetric transesterification with benzyl alcohol in organic solvents (Scheme 1).

Lipase, $PhCH_2OH$

rac-**1** → (+)-**1** + (−)-**2** (OCH_2Ph, OH)

1a, **2a**: R = Me
1b, **2b**: R = ^{i}Pr

Scheme 1. Lipase-catalyzed kinetic resolution of α-methylene β-lactones **1**.

The methyl- and isopropyl-substituted α-methylene β-lactones **1a** and **1b** were chosen for this preliminary study of enzymatic kinetic resolution. The racemic β-lactones **1a,b** were synthesized according to the literature procedures,[1,3] and their transesterification conducted with four equivalents of benzyl alcohol under the catalytic action of several lipases. The results are shown in Table 1.

The enzyme screening revealed that the lipase CAL-B (from *Candida antartica*, fraction B; CHIRAZYME® L-2, Boehringer Mannheim) is the most efficient biocatalyst for the resolution of the α-methylene β-lactones **1a,b** (entries 4 and 8). Thus, with this enzyme the racemic α-methylene β-lactone **1a** was enantioselectively transesterified with benzyl alcohol in methyl *tert*-butyl ether, and at ca. 50% conversion, the β-lactone **1a** and the β-hydroxy ester **2a** were obtained in high enantiomeric excess (99 and 95%) (entry 4). CAL-B gave nearly perfect kinetic resolution of the β-lactone **1b** to afford the latter and the hydroxy ester **2b** in 99% ee at 50% conversion (entry 8). In

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Table 1. Lipase-catalyzed kinetic resolution of the racemic α-methylene β-lactones **1**

Entry	Substrate	Lipase	Substrate : Enzyme	Time	Conv.[a]	β-Lactone **1**		Benzyl ester **2**		E[d]
						ee[b]	Config.	ee[c]	Config.	
			mmol : mg	(h)	(%)	(%)		(%)		
1		PS[e]	0.31 : 400	792[f]	54	98	*R*-(+)	83	*S*-(−)	50
2		PFL[g]	0.31 : 400	528[f]	54	99	*R*-(+)	85	*S*-(−)	61
3		BSL[h]	0.19 : 65	11[i]	53	85	*R*-(+)	75	*S*-(−)	19
4		CAL-B[j]	0.19 : 15	11[i]	51	99	*R*-(+)	95	*S*-(−)	>200
5		PS[e]	0.79 : 500	816[f]	44	74	*S*-(+)	93	*R*-(−)	74
6		PFL[g]	0.40 : 400	264[f]	42	67	*S*-(+)	93	*R*-(−)	52
7		BSL[h]	0.24 : 100	72[i]	74	>99	*S*-(+)	34	*R*-(−)	10
8		CAL-B[j]	0.24 : 15	72[i]	50	>99	*S*-(+)	99	*R*-(−)	>200

[a] Calculated (Ref. 6) from c = ee(lactone)/[ee (lactone) + ee(ester)]. [b] HPLC analysis on a Chiralcel OB-H column (9:1 hexane/isopropyl alcohol as eluent for substrate **1a** and 99:1 hexane/isopropyl alcohol for substrate **1b**). [c] HPLC analysis on a Chiralcel OB-H column for the ester **2a** and Chiralcel OD for the ester **2b** with 9:1 hexane/isopropyl alcohol as eluent. [d] Enantiomeric ratio (Ref. 6). [e] From *Pseudomonas cepacia* (Fluka). [f] Acetone as solvent, 40 °C. [g] From *Pseudomonas fluorescens* (Fluka). [h] From *Burkholderia sp.* (CHIRAZYME® L-1, Boehringer Mannnheim). [i] Methyl *tert*-butyl ether as solvent, 20 °C. [j] From *Candida antarctica*, fraction B (CHIRAZYME® L-2, Boehringer Mannnheim).

[a]Calculated (Ref.[6]) from c=ee(lactone)/[ee(lactone) +ee(ester)]. [b]HPLC analysis on a Chiralcel OB-H column (9:1 hexane/isopropyl alcohol as eluent for substrate **1a** and 99:1 hexane/isopropyl alcohol for substrate **1b**). [c]HPLC analysis on a Chiralcel OB-H column for the ester **2a** and Chiralcel OD for the ester **2b** with 9:1 hexane/isopropyl alcohol as eluent. [d]Enantiomeric ratio (Ref.[6]). [e]From *Pseudomonas cepacia* (Fluka). [f]Acetone as solvent, 40°C. [g]From *Pseudomonas fluorescens* (Fluka). [h]From *Burkholderia sp.* (CHIRAZYME® L-1, Boehringer Mannheim). [i]Methyl *tert*-butyl ether as solvent, 20°C. [j]From *Candida antarctica*, fraction B (CHIRAZYME® L-2, Boehringer Mannheim).

contrast, the lipase CCL (from *Candida cylindracea*, Sigma) did not exhibit any activity even after long reaction time (data not shown). With the lipases PS (from *Pseudomonas cepacia*, Fluka) and PFL (from *Pseudomonas fluorescens*, Fluka), the methyl-substituted lactone **1a** was obtained nearly enantiomerically pure at ca. 50% conversion (entries 1 and 2); however, long reaction times and large amounts of enzyme were required. The enzymes PS and PFL were less reactive towards the sterically more encumbered isopropyl-substituted β-lactone **1b**, for which 50% conversion could not be achieved even after 34 and 11 d (entries 5 and 6). The lipase BSL from *Burhholderia sp.* (formerly *Pseudomonas sp.*; CHIRAZYME® L-1, Boehringer Mannheim) was significantly more reactive, but less selective (entries 3 and 7) than the *Pseudomonas* lipases PS and PFL with both β-lactones **1a** and **1b** (entries 1, 2, 5 and 7). Therefore, as much as 74% conversion was required to obtain the lactone **1b** enantiomerically pure with the enzyme BSL (entry 7).

The absolute configuration of the isopropyl-substituted α-methylene β-lactone **1b** was assigned as (+)-(*S*)-**1b** by comparison of the specific rotation data with literature values[4]. The lipases, in particular CAL-B, recognized selectively the (−)-(*R*) enantiomer of the β-lactone **1b**; consequently, the kinetic resolution yielded enantiomerically pure (−)-(*R*)-**2b** ester and (+)-(*S*)-**1b** lactone.

The optically active methyl-substituted β-lactone **1a** is hitherto unknown. The absolute configuration of the enantiomerically pure methyl lactone was determined by chemical correlation. For this purpose the lactone (+)-**1a** was converted to the known[7] ester (+)-(*R*)-**3a**, which was obtained enantiomerically pure by horseradish-peroxidase-catalyzed kinetic resolution of the racemic hydroperoxide **4a** in the presence of guaiacol (Scheme 2).

Scheme 2. Configurational assignment of the β-lactone (+)-**1a** by chemical correlation.

Figure 1. Preferred enantiomer in the lipase-catalyzed transesterification.

The lipase CAL-B accepts selectively the (−)-(*S*) enantiomer of the methyl lactone **1a** to result in the enantiomerically pure (+)-(*R*)-**1a** β-lactone and (−)-(*S*)-**2a** β-hydroxy ester, while for the sterically more demanding isopropyl derivative **1b**, contrarily the β-lactone (+)-(*S*)-**1b** and the ester (−)-(*R*)-**2b** are produced. This opposite sense of stereoselection of the methyl- and isopropyl-substituted α-methylene β-lactones **1a** and **1b** by the lipase may be rationalized in terms of the established empirical rules for acyclic substrates, based on the relative size of the substituents[8] (Figure 1). Thus, for β-lactone **1a**, the α-methylene functionality excercises a larger steric effect around the chirality center than the methyl group, while for derivative **1b** the steric size of the isopropyl substituent exceeds that of the α-methylene unit.

In summary, lipase CAL-B is a very efficient biocatalyst for the kinetic resolution of racemic α-methylene β-lactones **1**, which provides a convenient enzymatic route for the preparation of enantiomerically pure α-methylene β-lactones **1** and 2-hydroxy alkyl-substituted benzyl acrylates **2**.

General procedure for the preparative-scale lipase-catalyzed transesterification

To a solution of 400 mg (3.17 mmol) lactone **1b** in 12 mL methyl *tert*-butyl ether were added 1.31 mL (12.7 mmol) of benzyl alcohol and 110 mg CAL-B lipase powder. The heterogeneous mixture was vigorously stirred at room temperature (ca. 20°C) for 72 h, the enzyme was removed by filtration and the solvent was evaporated (20°C/12 Torr). The residue was distilled (35°C/0.1 Torr) to afford the enantiomerically pure (−)-(*S*)-**1b** in 74% yield (based on 50% substrate conversion).

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