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Lipase Catalyzed Enantioselective Transesterification of 5-Acyloxy-2(5H)-Furanones

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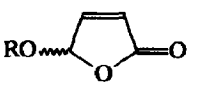
Abstract: Several lipases catalyse the transesterification of γ-acyloxyfuranones in organic solvents with high enantioselectivities. This method has been used for the kinetic resolution of 5-acetoxy-2(5H)-furanone, 5-acetoxy-4-methyl-2(5H)-furanone and 5-propionyloxy-2(5H)-furanone, in e.e.'s ranging from 68-98%.

Enzymes have found widespread application in the enantioselective synthesis of organic compounds.[1] Although in nature they act as catalysts in aqueous solutions, it is well established that various enzymes also function catalytically in organic media.[2] Among the advantages of performing enzymatic transformations in organic solvents are the greater stability of the enzymes and more facile product recovery.

Lipases are the most frequently used enzymes in organic synthesis because of their stability, availability and the fact that they accept a broad range of substrates.[3] Numerous applications have been found in kinetic resolutions, or enantioselective syntheses based on meso compounds, employing transesterifications or ester hydrolyses.[4] Previously we have reported the use of lipases and esterases in the synthesis of optically active α-hydroxy acids[5] and for the resolution of α,α-disubstituted diols.[6]

In this publication we describe the successful application of several lipases in the catalytic transesterification of 5-acyloxy-2(5H)-furanones in organic solvents with high enantioselectivities.



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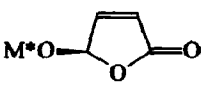
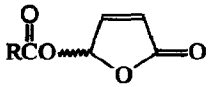


(OM*=l-menthyloxy)

2



3

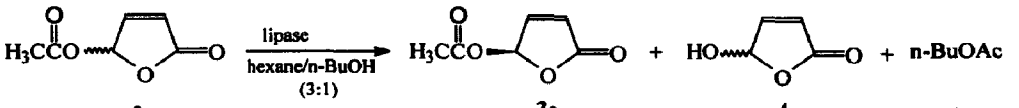
3a) R=CH_3
3b) R=C_2H_5
3c) R=C_6H_5

Optically active butenolides are frequently used in the synthesis of natural products[7]; γ-alkoxybutenolides **1** and **2** are particularly attractive synthons owing to their rich functionality.[8,9] A variety

of stereoselective transformations with these materials has been found, including 1,4-addition, cycloaddition and enolate and acetal chemistry.[8]

Chiefly chiral auxiliary based *l*-menthyloxy-2(5H)-furanone **2** has been employed thus far.[9] γ-Alkoxyfuranones **1** have recently also become available by means of cinchona alkaloid catalyzed thiol addition.[10] With lipase based methodology we hoped to prepare 5-acyloxy-2(5H)-furanones[11] **3** and avoid the use of chiral auxiliaries.

First, fifteen commercially available lipases[12,13] were screened for their activity and stereoselectivity in the transesterification of 5-acyloxy-2(5H)-furanone **3a** (eq.1). Reactions were performed in dry hexane:n-butanol mixtures under ambient conditions.[12] The results obtained with the five most reactive lipases are shown in Table I.



(eq.1) **3a** **3a** **4** **5**

Table I: Lipase Catalyzed Transesterification of 5-Acetoxy-2(5H)-Furanone **3a**

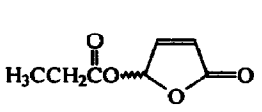
entry	lipase	reaction time (hours)	conversion (%)[a]	e.e. (%)[b] **3a**	enantiomer[c]	E[d]
1	PS	17	61	98	(+)	19
2	R	17	49	85	(+)	44
3	AKG	17	49	87	(+)	57
4	CC	47	55	89	(-)	19
5	AY	52	51	70	(-)	10

a) determined by GC (Hewlet Packard 5890 equipped with a 50m x 0,53mm HP-1 crosslinked methyl silicon gum column) using n-decane as an internal standard. b) determined by chiral GC (Hewlet Packard with a capillary column coated with CP cyclodextrin-B-2,3,6-M-19). c) rotation determined with a Perkin Elmer 241 polarimeter; the absolute configuration has not been determined yet. d) see refs 3 and 14.

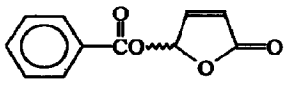
As can be seen from Table I, several of the lipases are highly selective, although excessively long reaction times are found with lipases CC and AY (entries 4 and 5). With lipases PS, R, AKG and CC products **3a** with enantiomeric excess (e.e.) exceeding 99% are obtained at conversions of about 60-63%. Reactions carried out with lipases PS, R and AKG (entries 1, 2 and 3) give the (+)-enantiomer, whereas reactions with lipases CC and AY (entries 4 and 5) yield the (-)-enantiomer of **3a**. It was further established that enantiomerically pure **3a** does not racemize at 130°C (GC analysis), which is of prime importance for application, for instance, in asymmetric cycloaddition reactions. The 5-hydroxy-2(5H)-

furanone **4** undergoes racemization very rapidly, therefore the e.e. of this product could not be determined.

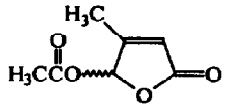
In a preliminary study of the scope of the lipase catalyzed resolution of acylfuranones **3** the enzymatic transesterification reaction was applied to racemic butenolides **3b**, **3c** and **6**.[11] The results obtained with these substrates are shown in Table II. With 5-propionyloxy-2(5H)-furanone **3b** using lipases R and AY (entries 3 and 4) much higher selectivities are obtained than with furanone **3a**. The change from CH_3 to C_2H_5 in the side chain results in a roughly tenfold improvement in E-value.[14]



3b



3c



6

Table II: Lipase Catalyzed Transesterification of Butenolides **3** and **6**

entry	butenolide	solvent[a]	lipase	reaction time (hours)	conversion (%)	e.e. (%)	enantiomer	E[c]
1	**3b**		PS	44	49	74	(+)	19
2	**3b**		AKG	20	42	63	(+)	27
3	**3b**		R	24	51	98	(+)	>130
4	**3b**		AY	22	48	90	(-)	>200
5	**3c**		[b]	-	-	-	-	-
6	**6**		PS	22	61	37	(+)	2
7	**6**		AKG	42	46	68	(+)	18
8	**6**		R	27	44	27	(+)	<1
9	**3a**	$C_6H_5CH_3$	R	24	41	67	(+)	96
10	**3a**	c-C_6H_{12}	R	24	50	92	(+)	76
11	**3a**	CH_3CN	R	48	-	-	-	-
12	**3a**	$(C_2H_5)_2O$	R	24	49	58	(+)	7
13	**3a**	CH_3COCH_3	R	24	<5	-	-	-
14	**3a**	THF	R	24	<5	-	-	-

a) the solvent is mixed with 25% n-BuOH. where no solvent is mentioned hexane:nBuOH (3:1) is used. b) all lipases given in ref. 13 were tested, but gave no reaction. c) see refs 3 and 14.

With 5-benzoyloxy-2(5H)-furanone **3c** no reaction was observed; this is probably due to steric hindrance.[15] Although a 4-methyl substituent on the furanone is tolerated, as in the case of **6**, only modest enantioselectivities have been obtained so far (entries 6-8).

The effect of solvent change was studied in the transesterification of butenolide **3a** using lipase R (entries 9-14). From the results shown in Table II it is clear that the reaction is very slow or does not occur in polar solvents such as acetonitrile, acetone and THF. In these polar solvents the functional

structure of the active site in lipases apparently is disturbed.[3] In apolar solvents lipases are much more reactive. In toluene and cyclohexane the reaction is fast and also very selective, whereas in diethyl ether the E-value is reduced to 7.

The results obtained in these experiments show that enzymatic transesterification of acyloxyfuranones is a good method to obtain these materials in enantiomerically pure form. Both enantiomers of the butenolides can be obtained, depending on the enzyme used. Variation of the acyl group as well as substituents at the 4-position are tolerated. The enzymatic kinetic resolution method described here provides a valuable alternative for the preparation of optically active butenolides **3** since no chiral auxiliary is required.

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11. 5-Acetoxy-2(5H)-furanone **3a** is prepared by treatment of 5-hydroxy-2(5H)-furanone **4** with acetic anhydride in the presence of p-toluenesulfonic acid. 5-Propionyloxy-2(5H)-furanone **3b** and 5-benzoyloxy-2(5H)-furanone **3c** are prepared in the same way using propionic and benzoic anhydride respectively. 5-Acetoxy-4-methyl-2(5H)-furanone **6** is prepared from 5-hydroxy-4-methyl-2(5H)-furanone.
12. A typical procedure is as follows: 10 mg of enzyme is added to 3 ml of a solution of hexane:n-BuOH (3:1) containing 20 mg of substrate and 8 mg of n-decane (internal standard). The suspension is stirred at room temperature for the time indicated (Table I). At given intervals samples of ca. 0.2 ml are taken and filtered over celite (1.0 cm in a pasteur pipet). The celite is washed with CH_2Cl_2 and the crude mixture is analyzed by GC for conversion and e.e..
13. Enzymes used are: Lipase A, AKG, AY, CE, D, G, GC, L, M, N, PS and R from Amano; Hog Pancreatine and *Candida cylindracae* lipase from Sigma; *Candida antarctica* from NOVO.
14. The E value, which is a constant independent of time and substrate concentration (under ideal conditions), can be related to the extent of conversion of the transesterification (c) and the e.e. of the product fraction (ee(P)) or recovered substrate fraction (ee(S)):

$$E = \frac{\ln[1-c(1+ee(P))]}{\ln[1-c(1-ee(P))]} = \frac{\ln[(1-c)(1-ee(S))]}{\ln[(1-c)(1+ee(S))]}$$

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