LIPASE-CATALYZED OPTICAL RESOLUTION OF 2-OXAZOLIDINONES

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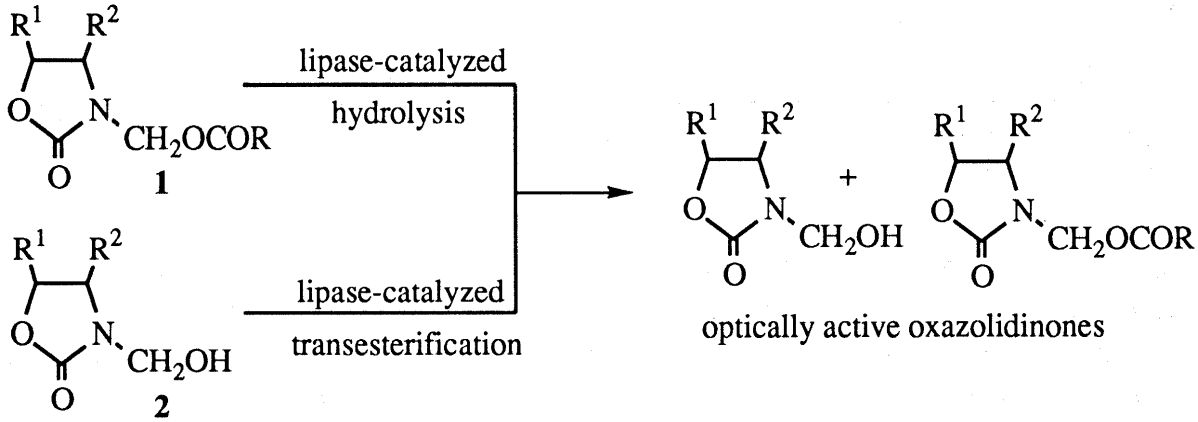
Optically active 4- or 5-substituted 2-oxazolidinones were obtained by lipase-catalyzed enantioselective hydrolysis of the 3-acyloxymethyl-2-oxazolidinones and transesterification of the 3-hydroxymethyl-2-oxazolidinones with vinyl propionate in organic solvents.

KEY WORDS oxazolidinone; lipase; chiral auxiliary; optical resolution

Optically active 2-oxazolidinones are excellent chiral auxiliaries for the enantioselective α-alkylation or α-acylation of carboxylic acids and aldol condensation known as the Evans method.[1] Recently, it has been found that various 3,5-disubstituted-2-oxazolidinones have antibacterial activity, where only one enantiomer was reported to show the activity.[2] In this paper, we describe a convenient synthetic method for both enantiomers of 4- or 5-substituted 2-oxazolidinones by lipase-catalyzed resolution in organic solvents.

A lipase is a typical enzyme for routine use in organic synthesis, because it requires no coenzyme and is commercially available and inexpensive.[3] We have already demonstrated that an acyloxymethyl and a hydroxymethyl group attached at the oxygen or nitrogen atom of various molecules are useful for lipase-catalyzed enantioselective reactions.[4] We designed 3-acyloxymethyl-2-oxazolidinones (**1**) and 3-hydroxymethyl-2-oxazolidinones (**2**) as the substrates for lipase-catalyzed enantioselective hydrolysis and esterification, respectively.



3-Hydroxymethyl-2-oxazolidinones (**2**) were prepared by treatment of *N*-unsubstituted-2-oxazolidinones with formaldehyde. Its esters were obtained by *N*-acyloxymethylation of 2-oxazolidinones with acyloxymethyl chloride or acylation of **2**. Enantioselective hydrolysis with lipase was carried out as follows: A mixture of ester (**1**) (2mmol) and lipase (50-100mg) in *iso*-propyl ether (IPE) (5 ml) saturated with water was stirred at room temperature. The lipase was removed by filtration when about 50% of the substrate was consumed. The filtrate was condensed to give a clean residue which was subjected to short column chromatography or preparative thin-layer

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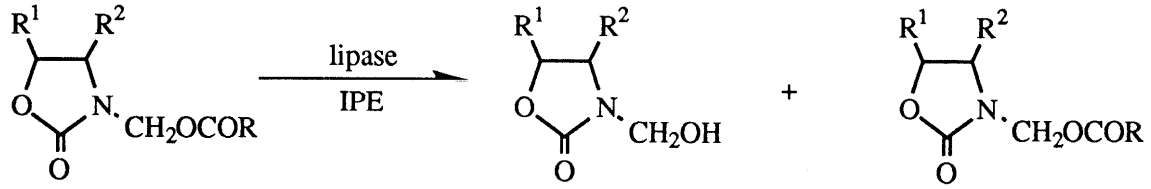
chromatography (PTLC), and optical purities of the both enantiomers were determined by HPLC analysis using a chiral column. [5] The transesterification of **2** was carried out by almost the same method using vinyl propionate (equimolar amount to the substrate).

Table 1. Lipase-Catalyzed Hydrolysis



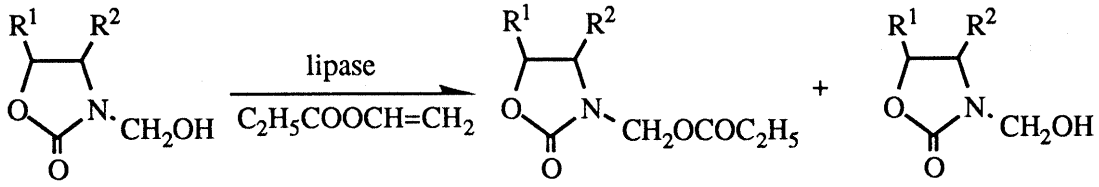
						Reacted oxazolidinones		Recovered oxazolidinones	
Entry	R	R^1	R^2	Lipase	Time (h)	c.y.(%)[a]	o.y.(%ee)[b]	c.y.(%)[a]	o.y.(%ee)[b]
1	C_2H_5	Ph	H	PS	3	42	75(*S*)	46	70(*R*)
2	*t*-C_4H_9	Ph	H	PS	240	50	62(*S*)	47	67(*R*)
3	C_2H_5	H	Ph	PS	70	51	89(*S*)	42	93(*R*)
4	C_2H_5	H	Ph	AH	50	42	87(*S*)	46	90(*R*)
5	*n*-C_5H_{11}	H	Ph	PS	24	44	97(*S*)	50	92(*R*)
6	C_2H_5	H	$PhCH_2$	PS	12	43	94(*S*)	46	91(*R*)
7	C_2H_5	H	$PhCH_2$	AH	3	46	72(*S*)	44	76(*R*)
8	C_2H_5	H	C_2H_5	PS	8	52	69(*S*)	40	98(*R*)
9	C_2H_5	H	C_2H_5	PS	14 [c]	50	97(*S*)	47	87(*R*)

a) Isolated yield. b) Determined by HPLC analysis (absolute configuration).[6]
c) This reaction was carried out at 0°C.

The lipase-catalyzed hydrolysis of 3-acyloxymethyl-2-oxazolidinones (**1**) was found to proceed enantioselectivity, and the experimental results are summarized in Table 1. Based on the results of our preliminary experiments, lipases PS and AH (from *pseudomonas sp.*)[7] were demonstrated to be well suited for these reactions. Lipase PS showed higher enantioselectivity than lipase AH (entries 3, 4, 6 and 7), and gave higher optical purity for 4-substituted 2-oxazolidinone than for 5-substituted one (entries 1 and 3). As shown in entries 3 and 5, conversion of propionyl group to hexanoyl made the reaction time shorter.

Enantioselective transesterification of 3-hydroxymethyl-2-oxazolidinones (**2**) with vinyl propionate was also realized, and the experimental results are summarized in Table 2.
Esterification also proceeded enantioselectively, although the optical purity of each enantiomer was slightly lower.

Table 2. Lipase-Catalyzed Transesterification



						Reacted oxazolidinones		Recovered oxazolidinones	
Entry	R^1	R^2	Lipase	Solvent	Time (h)	c.y.(%)[a]	o.y.(%ee)[b]	c.y.(%)[a]	o.y.(%ee)[b]
1	Ph	H	PS	CH_2Cl_2	4	47	73(*S*)	42	78(*R*)
2	H	Ph	PS	CH_2Cl_2	30	43	92(*S*)	48	81(*R*)
3	H	Ph	PS	Toluene	13	44	99(*S*)	51	74(*R*)
4	H	$PhCH_2$	PS	CH_2Cl_2	15	52	71(*S*)	43	87(*R*)

a) Isolated yield. b) Determined by HPLC analysis (absolute configuration).[6]

Both *N*-acyloxymethyl and *N*-hydroxymethyl groups of optically active 2-oxazolidinone obtained were hydrolyzed without racemization by treatment with ammonium hydroxide in methanol at room temperature to afford corresponding *N*-unsubstituted 2-oxazolidinones. These results provide useful tools for synthesis of such chiral auxiliaries and synthons as 2-oxazolidinone derivatives.

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5) Chiralcel OB & OD (Daicel Chemical Industry, Ltd.).

6) The structures of all unknown compounds in literature were determined by NMR, IR and mass spectra. Their absolute configurations were determined by conversion to corresponding 4 - substituted 2-oxazolidinone or 2-aminoethanol derivatives, the single enantiomers of which are commercially available.

7) Lipases PS and AH were obtained from Amano Pharmaceutical Co., Ltd.

(Received October 20, 1995; accepted November 20, 1995)