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Lipase-catalyzed Resolution of 5,5-Disubstituted Hydantoins

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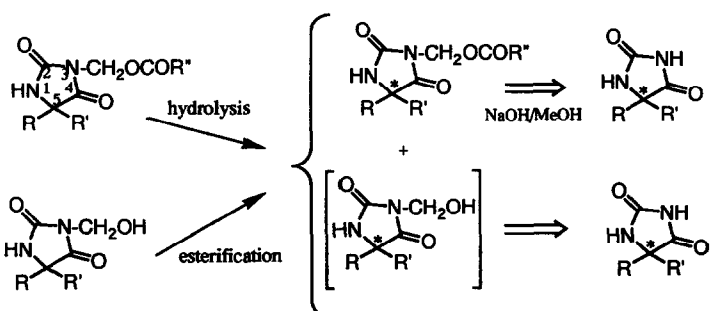
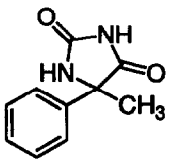
Abstract Chiral non-racemic 5,5-disubstituted hydantoins were prepared by lipase-catalyzed enantioselective hydrolyses of their *N*-acyloxymethyl groups or esterification of their *N*-hydroxymethyl groups.

Hydantoin derivatives have various biological activities and are useful many medicines and agricultural chemicals. Although such derivatives have usually a stereogenic center at the 5-position, most of them have been used as racemates. Therefore, we have started an investigation of the syntheses of optically active hydantoins by enzymatic resolutions. We have reported already that the introduction of an acyloxymethyl group at the terminal position of a target molecule is very useful for lipase-catalyzed hydrolysis[1]. In this paper, we describe the facile synthesis of optically active 5,5-disubstituted hydantoins by lipase-catalyzed hydrolysis of their *N*-acyloxymethyl derivatives and transesterification of their *N*-hydroxymethyl derivatives with vinyl acetate (Scheme1).

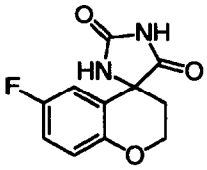


Scheme1

We chose 5-methyl-5-phenylhydantoin(**1**) and sorbinil(**2**) which is attracting attention as an aldose reductase inhibitor[2] as a typical substrates. Preliminary experiments were carried out for 5-methyl-5-phenyl-3-(pivaloyloxymethyl)hydantoin (**1c**) prepared from **1** and commercially available chloromethyl pivalate.



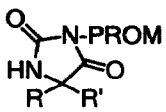
1



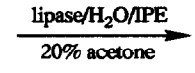
2

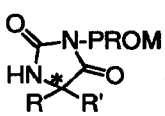
Lipase-catalyzed hydrolysis of **1c** was unsuccessful with several lipases in water-saturated diisopropyl ether(IPE) containing 20% acetone at room temperature. Next, we tested 3-propionyloxymethyl derivative (**1a**) which had a less sterically hindered ester group[3]. The hydrolysis of **1a** under the same conditions was found to proceed enantioselectively and the experimental results are summarized in Table 1. Lipases showed moderate to high enantioselectivity despite the stereogenic carbon atom being remote from the reactive ester site[4].

Table1. *Lipase catalyzed hydrolysis of hydantoin derivatives* [a]



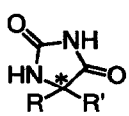
1a or **2a**





recovered ester

+



reacted hydantoin

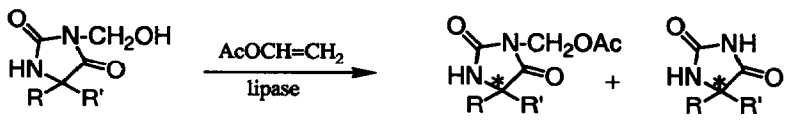
Entry	subst.	lipase[d]	time(h)	recovered ester C.Y.[b]	recovered ester %ee[c]	reacted hydantoin C.Y.[b]	reacted hydantoin %ee
1	**1a**	AY	18	30	11*(R)*	51	2*(S)*
2	**1a**	AH	8	38	99*(S)*	40	90*(R)*
3	**1a**	PS	72	43	99*(S)*	46	88*(R)*
4	**1a**	CE	60	40	14*(R)*	46	19*(S)*
5	**1a**	AL	48	58	15*(S)*	20	26*(R)*
6	**1a**	PL	48	46	6*(S)*	35	5*(R)*
7	**2a**	AY	50	30	4*(R)*	52	48*(S)*
8	**2a**	AH	5	56	32*(R)*	33	75*(S)*
9	**2a**	PS	75	52	1*(R)*	40	2*(S)*
10	**2a**	CE	100	63	8*(R)*	30	24*(S)*
11	**2a**	OF	10	31	76*(S)*	60	38*(R)*

a) All reactions were carried out by stirring a mixture of substrate(100mg), lipase(100mg) in organic solvent(IPE) saturated with water and 20% acetone at 25°c. *b)* Isolated yield. *c)* Enantiomeric purities were determined by HPLC analyses using a column packed with Chiralcel OB-H (2-propanol/hexane =1/10). *d)* lipaseAY*(Candida rugosa)*, lipaseAH*(Pseudomonas sp.)*, lipasePS*(Pseudomonas sp.)*, lipaseCE*(Humicola lanuginosa)*, (Amano); lipaseAL*(Achromobacter sp.)*, lipasePL*(Alcaligenes sp.)*, lipaseOF*(Candida cylindracea)*, (Meito).

Among several lipases tested, lipaseAH and PS showed the highest enantioselectivities(entries 2 and 3)[5,6]. In both cases, the R-isomer was hydrolyzed more rapidly than the S-isomer. On the other hand, LipaseAY and CE catalyzed a little more favorably the hydrolysis of the S-isomer than that of the R-isomer. *(S)*-Isomer of sorbinil which has excellent inhibitory activity toward aldose reductase in animal models, was obtained in 75%ee with lipaseAH and its *N*-propionyloxymethyl derivative[7] in 76%ee with lipase OF. Recrystallization of each of them from ethanol afforded homochiral *(4S)*-(+)-sorbinil[8].

Enantioselective transesterification of 3-(hydroxymethyl)-5-methyl-5-phenyl hydantoin (**1b**) with vinyl acetate was also realized. 1,2-Dimethoxyethane(DME) and acetonitrile were used as solvents on the basis of the preliminary experiments. After screening tests with several lipases, the representative results are listed in Table2. The transesterification with lipase LIP in acetonitrile showed high stereoselectivity (entry 6). However, the enantioselectivity of the transesterification was generally inferior to that of the hydrolysis described above, although the reaction proceeded more rapidly. Lability of the substrate is one of the reasons why this method was not suitable the resolution of *N*-hydroxymethyl derivative of **2b** (entries 7 and 8).

Table2. *Lipase catalyzed esterification of hydantoin derivatives* [a]



					reacted ester		recovered hydantoin	
Entry	subst.	lipase[d]	Sol.	time(h)	C.Y.[b]	%ee[c]	C.Y.[b]	%ee
1	**1b**	PS	DME	24	40	42*(R)*	52	33*(S)*
2	**1b**	PS	CH_3CN	40	35	38*(R)*	54	25*(S)*
3	**1b**	QL	DME	9	30	77*(R)*	55	25*(S)*
4	**1b**	QL	CH_3CN	12	26	63*(R)*	60	20*(S)*
5	**1b**	LIP	DME	5	42	55*(R)*	52	32*(S)*
6	**1b**	LIP	CH_3CN	5	31	80*(R)*	56	43*(S)*
7	**2b**	QL	DME	15	32	14*(R)*	64	6*(S)*
8	**2b**	LIP	CH_3CN	18	28	24*(R)*	76	7*(S)*

a) All reactions were carried out by stirring a mixture of substrate(100mg), vinyl acetate(80mg), and lipase(50mg) in organic solvent at 0°c (20°c in entries 7 and 8). The recovered hydantoin derivative was isolated after treatment with a methanolic solution of 25% ammonium hydroxide.*b)* Isolated yield. *c)* Enantiomeric purities were determined by HPLC analyses using a column packed with Chiralcel OB-H (2-propanol/hexane=1/10) or Chiralcel AS (2-propanol/hexane=3/7 or 1/4). *d)* lipaseQL: *Alcaligenes sp.*(Meito sangyo Co.Ltd.) lipaseLIP:*Pseudomonas sp.*(Toyobo Co.Ltd.)

Thus, kinetic resolution with lipase in organic solvents has been demonstrated to be useful for the syntheses of optically active hydantoins, especially by hydrolysis of the *N*-acyloxymethyl derivative.

Acknowledgement

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3) Propionyloxymethyl ester (**1a**,**2a**) was also prepared by a same method using chloromethyl propionate.

4) Previously, we reported other types of substrate, of which reaction site is fairly remote from the stereogenic carbon atom.
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6) *(S)*-**1a**, >99%ee $[\alpha]_D^{24}$ +61.5 (c=0.46, EtOH).

7) *(S)*-**2a**, 76%ee $[\alpha]_D^{24}$ +35.8 (c=0.50, EtOH).

8) *(4S)*-(+)-sorbinil [*(S)*-**2**] $[\alpha]_D^{23}$ +52.1 (c=0.8, MeOH), mp 243~245°c

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