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Lipase-catalyzed Enantioselective Hydrolysis of *N*-Acyloxymethyl Groups in Organic Solvent: Syntheses of Chiral 5,5-Disubstituted 1-Methylbarbiturates[1]

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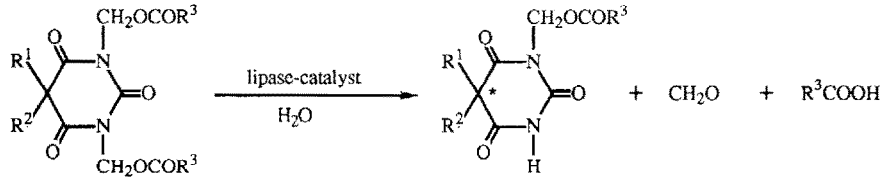
Abstract: Chiral 5,5,-disubstituted *N*-acyloxymethylbarbiturates have been obtained in 40-99% optical yields by lipase-catalyzed hydrolyses of 5,5-disubstituted bisacyloxymethylbarbiturates in H_2O-saturated diisopropyl ether. These chiral barbiturates were readily converted into the corresponding chiral *N*-methylbarbiturates such as (*R*)-(-)-mephobarbital and (*S*)-(+)-hexobarbital.

Some barbiturates such as mephobarbital and hexobarbital have an asymmetric carbon atom at C-5 position due to a dissymmetric *N*-methyl substituent on their 2,4,6(1H,3H,5H)pyrimidinetrione skelton[2] and their optical isomers have pharmacodynamic and pharmacokinetic differences.[3] For example, (*R*)-(-)-5-ethyl-1-methyl-5-phenylbarbiturates (mephobarbital: **3c**) is sedative while its (*S*)-(+)-isomer may cause central nervous system excitation. On the other hand, (*S*)-(+)-5-(cyclohexene-1-yl)-1,5-dimethylbarbiturate (hexobalbital: **3e**) is more anesthetically active than its (*R*)-(-)-antipode. Optically active barbiturates have been synthesized only by resolution of the racemates.[4] Therefore, the lack of efficient synthetic method allowed to use the racemic mixture of chiral barbiturates as drugs. We report here first asymmetric synthesis of optically active barbiturates using enzyme-catalysts. Enzymes are now recognized as substrate-specific and highly enantioselective catalysts for asymmetric syntheses.[5] In particular lipases have been widely used for asymmetric hydrolysis and esterification. As successfully applied to catalytic asymmetric syntheses of chiral 1,4-dihydropyridines in the proceeding paper, the lipase-catalyzed asymmetric synthesis was expected to be applicable to 5,5-disubstituted *N,N*-bisacyloxy-methylbarbiturates (Scheme 1).



1a-f **2a-f**

Scheme 1

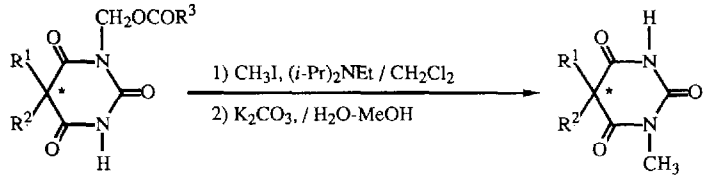
Table 1 shows the results of asymmetric hydrolysis of *N,N*-bisacyloxymethylbalbitals (**1a-f**) which were prepared from chloromethylacylate with sodium barbiturate. Preliminary investigations revealed that lipase AY (from *Candida rugosa*) and CE (from *Humicola lanuginosa*)[6] were effective for the hydrolysis of **1a-f**. The hydrolysis of *N,N*-bispivaloyloxymethylphenobarbital (**1a**) was tested with lipase AY. The reaction was carried out by stirring a suspension of the substrate (0.5mmol) and a crude lipase AY(500mg=25000U) in H_2O-saturated

Table 1. Lipase-catalyzed Asymmetric Syntheses of Chiral Barbituric Acid Derivatives[a]

entry	substrate				lipase	react. time,h	conversn[b],%	product			
	no.	R^1	R^2	R^3				no.	isolated yield,%[c]	%ee[d]	confign
1	**1a**	Ph	Et	*t*-Bu	AY[e]	96	14	**2a**	11	75	***S***
2	**1b**	Ph	Me	Et	AY	1.5	100	**2b**	50	40	***R***
3	**1b**	Ph	Me	Et	CE	4	100	**2b**	49	99	***R***
4	**1c**	Ph	Et	Et	AY	2	100	**2c**	50	92	***S***
5	**1c**	Ph	Et	Et	CE	9	90	**2c**	52	99	***R***
6	**1d**	Ph	Pr	Et	AY	1.5	100	**2d**	62	43	***S***
7	**1d**	Ph	Pr	Et	CE	9	90	**2d**	34	93	***R***
8	**1e**		Me	Et	AY	2.5	100	**2e**	50	43	***S***
9	**1e**		Me	Et	CE	9	80	**2e**	48	95	***R***
10	**1f**		Et	Et	AY	1	100	**2f**	62	90	***S***
11	**1f**		Et	Et	CE	22	77	**2f**	33	81	***R***

[a]All reactions were carried out with substrate(0.5mmol), H_2O-saturated IPE and crude lipase (AY:100mg, CE:500mg) at 20°C unless otherwise cited.
[b]Conversion were determined based on the recovery of substrates. [c]Only accompanied by a fully hydrolyzed barbiturate.
[d]Optical yields were determined by HPLC analyses using the column packed with Chiralcel OJ. [e]lipase(500mg).

diisopropyl ether (20mL) at room temperature. The hydrolysis proceeded to give (-)-*N*-pivaloyloxymethylphenobarbital (**2a**) in 75% optical yield. But the reaction rate was very slow. The successive hydrolysis of *N,N*-bispropionyloxymethylphenobarbital (**1c**) was run with lipase AY (100mg). This hydrolysis proceeded smoothly to give (-)-*N*-propionyloxymethylphenobarbital ((-)-**2c**) in 95% optical yield. When lipase CE (500mg=2500U) was used, the reaction rate was slower than that of lipase AY and the (+)-antipode ((+)-**2c**) was obtained in 99% optical yield. The hydrolyses of the other barbiturates (**1b,d-f**) were run in order to investigate the applicability and stereoselectivity of lipase-catalyzed hydrolysis of barbiturates. The lipase AY-catalyzed hydrolysis of the barbiturates except **1b** gave the *R*-products. On the other hand, the lipase CE-catalyzed hydrolysis gave the *S*-products in high optical yield in every case examined here. The absolute configurations of **2b-f** were determined by conversion of **2b-f** into the corresponding *N*-methylbarbiturates (**3b-f**), respectively.[2] Scheme 2 shows the synthetic routes of chiral *N*-methylbarbiturates (Table 2). Single recrystallization of chiral barbiturates (**3b-3f**) from ethanol-H_2O gave the optically pure products.[7]



2a-f **3b-f**

Scheme 2

Table 2 Synthesis of Optically Active *N*-Methylbarbiturates

starting compound			product			
no.	R^1	R^2	no.	%	%ee[a]	config[b]
(*R*)-**2b**	Ph	Me	**3b**	85	99	***S***
(*S*)-**2c**	Ph	Et	**3c**	90	92	***R***
(*R*)-**2d**	Ph	Pr	**3d**	83	93	***S***
(*R*)-**2e**		Me	**3e**	80	95	***S***
(*S*)-**2f**		Et	**3f**	80	90	***R***

[a]Determined by HPLC analyses using the column packed with Chiralcel OJ. [b]Determined by the sign of the rotation.

The lipase-catalyzed asymmetric hydrolysis of *N,N*-bisacyloxymethylbarbiturates now provides a new method for preparation of chiral barbiturates such as (*R*)-(-)-mephobarbital (**3c**) and (*S*)-(+)-hexobarbital (**3e**) as chiral medicines.[8]

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(1) This work was presented at the 111th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, March 1991, Abstracts of Papers, 29TD3-2.

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(6) Lipases, AY and CE, were kindly supplied by Amano Pharmaceutical Co. Japan.

(7) (a) (*R*)-(-)-mephobarbital: m.p. 100-101°, $[\alpha]^{22}_{D}$-8.5°(*c* 1.0, EtOH); (lit.[4b] m.p.101°, $[\alpha]^{20}_{D}$ -9.03°(EtOH)). (b) (*S*)-(+)-hexobarbital: m.p.153-154°, $[\alpha]^{22}_{D}$+11.5°(*c* 1.0, EtOH); (lit.[4a] m.p.153°, $[\alpha]^{20}_{D}$+12.17°(*c* 3.452,EtOH)).

(8) All new compounds gave satisfactory spectral and analytical data.

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