FACILE ENZYMATIC PREPARATION OF ENANTIOMERIC β-LACTAMS

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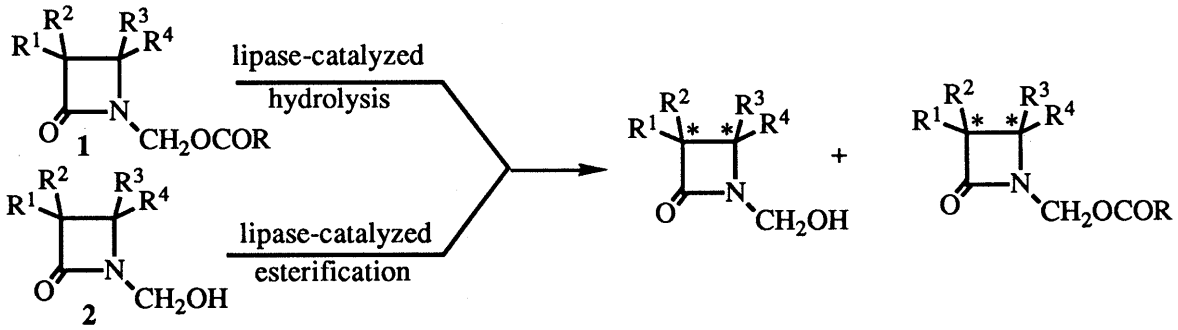
Optically active β-lactams were obtained conveniently by lipase-catalyzed enantioselective hydrolysis of 1-acyloxymethyl-2-azetidinones and esterification of 1-hydroxymethyl-3,3-dimethyl-2-azetidinone with vinyl acetate in organic solvent.

KEYWORDS β-lactam; lipase; resolution; hydrolysis; esterification

One of the difficulties of synthesis of β-lactam antibiotics is due to the presence of asymmetric carbons at the 3 and 4 positions.[1] Much labour has been expended for the creation of optically active β-lactam ring. We describe in this paper how optically pure β-lactams are obtained by convenient lipase-catalyzed resolution. A lipase is a typical enzyme to be accepted into routine use in organic synthesis, because it requires no coenzymes and is commercially available and inexpensive.[2]

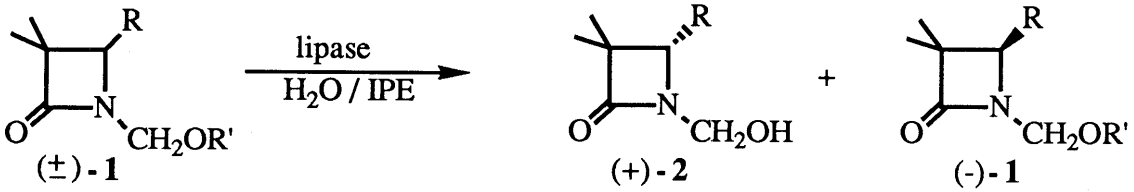
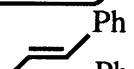
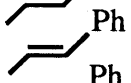
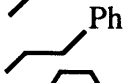
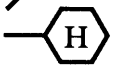
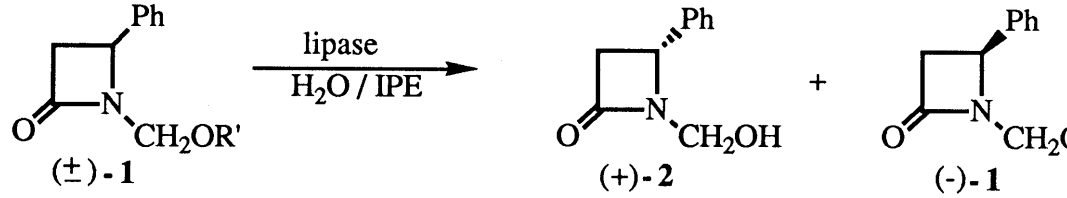
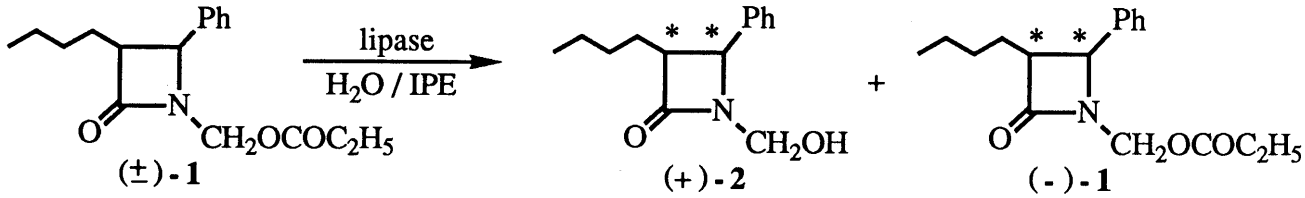
1-Acyloxymethyl-2-azetidinones (**1**) and 1-hydroxymethyl-2-azetidinones (**2**) have been found to be good substrates for lipase-catalyzed hydrolysis and esterification, respectively.[3]



The 1-hydroxymethyl-2-azetidinones (**2**) were prepared by treatment of 1-unsubstituted-2-azetidinones with formaldehyde. Its esters (**1**) were obtained by acylation of **2** with acyl halide in the presence of triethylamine. The general procedure of enantioselective hydrolysis with lipase B[4] is as follows: A solution of 1-acyloxymethyl-2-azetidinone (2 mmol) and lipase B (50 mg) in *iso*-propyl ether (IPE) saturated with H_2O (10 ml) was stirred at room temperature. After checking the consumption of half the amount of substrate by high performance liquid chromatography (HPLC), the enzyme was removed by filtration and the filtrate was condensed to give a clean residue which was subjected to short column chromatography.[5]

High enantioselective hydrolyses proceeded with several carboxylic acid esters of 3,3-dimethyl-1-hydroxymethyl-4-phenyl-2-azetidinone (entries 1-5 in Table I) except for the pivalic acid ester (entry 6), which did not react after several days due to the too bulky moiety. The substrates with some other substituents at the 4-position reacted smoothly to afford almost optically pure 2-azetidinones (entries 7-12). In the case of 4-phenyl-1-propionyloxymethyl-2-azetidinone (entry 11), 1-hydroxymethyl-4-phenyl-2-azetidinone isolated was derived quantitatively to 4-phenyl-2-azetidinone by treatment with aqueous ammonia in methanol at room

Table I. Lipase-Catalyzed Enantioselective Hydrolysis of 1-Acyloxymethyl-2-azetidinones

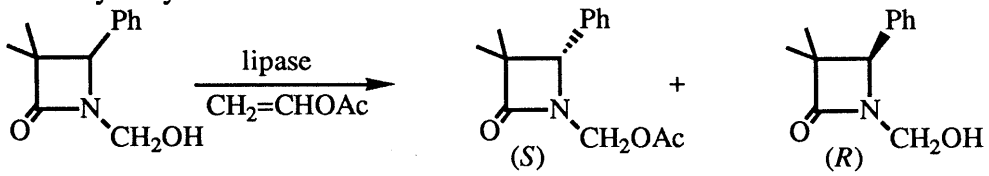
Entry	R or R'	Lipase[a]	Time (h)	Product (+)-2 C.Y. (%)[b]	Product (+)-2 O.Y. (%ee)[c]	Recovery (-)-1 C.Y. (%)[b]	Recovery (-)-1 O.Y. (%ee)[c]
							
	(±)-1			(+)-2		(-)-1	
	R = Ph						
1	R'= $COCH_3$	Lipase B	8	49	98 (*S*)	46	>99 (*R*)
2	R'= $COCH_2CH_3$	Lipase B	5	45	>99 (*S*)	47	98 (*R*)
3	R'= $COCH_2CH_3$	Lipase PS	50	48	98 (*S*)	46	>99 (*R*)
4	R'= $COCH_2(CH_2)_3CH_3$	Lipase B	2	50	98 (*S*)	47	>99 (*R*)
5	R'= COC_6H_5	Lipase B	10 days	44	>99 (*S*)	52	89 (*R*)
6	R'= $COC(CH_3)_3$	Lipase B	>10 days	–	–	–	–
	R'= COC_2H_5						
7	R = 	Lipase B	1	47	>99	50	98
8	R = 	Lipase PS	11	35	>99	42	88
9	R = 	Lipase B	6.5	47	89	46	>99
10	R = 	Lipase B	72	43	97	52	82
							
	(±)-1			(+)-2		(-)-1	
11	R'= $COCH_2CH_3$	Lipase B	2	47	>98 (*R*)	50	93 (*S*)
12	R'= $COC(CH_3)_3$	Lipase B	216	41	91 (*R*)	50	95 (*S*)
							
	(±)-1			(+)-2		(-)-1	
13	3,4-*cis*	Lipase B	13	39	88	32	78
14	3,4-*cis*	Lipase PS	10 days	39	74	45	89
15	3,4-*trans*	Lipase B	1.5	37	98	43	>99

a)Lipase B (*Pseudomonas fragi*), Lipase PS (*Pseudomonas* sp.)
b) Isolated yield.
c) Optical yields were determined by HPLC analyses (Chiralpak AS, IPA / hexane). Absolute configuration (*R*,*S*) of the products in entries 7-10 and 13-15 is unknown.

temperature.[6] Its specific optical rotation was +132° (c =1.0, MeOH), which showed R-configuration.[7]

Kinetic resolution of the 2-azetidinones possessing two asymmetric centers[8] was also demonstrated to give good optical yields (entries 13-15).

On the other hand, the lipase-catalyzed esterification of 1-hydroxymethyl-3,3-dimethyl-4-phenyl-2-azetidinone with vinyl acetate proceeded enantioselectively to afford the optically pure acetate, although the reaction was a little slower.[9] It is of interest that lipase PS was better suited for the esterification than lipase B which acted well for hydrolysis of the ester.



Lipase PS	9h	C.Y. 48%, O.Y. 98%ee	C.Y. 46%, O.Y. >99%ee
Lipase B	24h	C.Y. 47%, O.Y. 96%ee	C.Y. 46%, O.Y. 98%ee

These lipase-catalyzed kinetic resolutions provided a new route to syntheses of not only single-ring β-lactam antibiotics but also chiral synthons for preparation of two-ring ones in view of the ease of obtaining both enantiomers of chiral 1-unsubstituted-2-azetidinones by the convenient procedure.

REFERENCES AND NOTES

1) For recent reviews, see : D. J. Hart and D. C. Ha, *Chem. Rev.*, **89**, 1447 (1989); G. M. Coppola and H. F. Schuster, "*Asymmetric Synthesis*", John Willy & Sons Inc., New York, 1987.

2) For resent reviews on enzymatic reactions, see: W. Boland, C. Frossl, and M. Lorenz, *Synthesis*, **1991**, 1049; A. M. Klibanov, *Acc. Chem. Res.*, **23**, 114 (1990); M.Murata, H. Ebiike, and K.Achiwa, *J.Syn. Org. Chem. Jpn.*, **49**, 1127 (1991).

3) The lipase-catalyzed hydrolyses of acyloxymethyl ester of 4-aryl-1,4-dihydro-3,5-pyridinedicarboxylic acid and barbituric acid derivatives have already been reported: H. Ebiike, Y. Terao, and K. Achiwa, *Tetrahedron Lett.*, **32**, 5805 (1991); M. Murata and K. Achiwa, *ibid.*, **32**, 6763 (1991).

4) Lipase B: T. Nishio, T. Chikano, and M. Kamimura, *Agric. Biol. Chem.*, **51**, 181 (1987). Lipase PS was supplied by Amano Pharmaceutical Co., Ltd.

5) Satisfactory spectral and analytical data were obtained for all new compounds.

6) Although N-hydroxymethyl group is generally labile to acid, alkaline, and elevated temperature, it is not so easy to get the 1-unsubstituted-2-azetidinones quantitatively from 1-hydroxymethyl-2-azetidinones due to the lability of the 2-azetidinone ring to the reaction conditions. After several attempts we realized the quantitative conversion to 1-unsubstituted-2-azetidinone by stirring overnight in aqueous ammonia / methanol. The epimerization was never observed under such reaction conditions.

7) The specific optical rotation of (S)-4-phenyl-2-azetidinone was reported to be $[\alpha]_D^{24}$ - 128° (c=1.0 , MeOH): H. H. Wasserman, G. D. Berger, and K. R. Cho, *Tetrahedron Lett.*, **23**, 465 (1982). The absolute configuration of 3,3-dimethyl-4-phenyl-2-azetidinone was determined by comparison of its HPLC spectrum (Chiralpak AS) with that of the same compound derived from (S)-4-phenyl-2-azetidinone. :S.Hanessian, K.Sumi, B.Vanasse, *Synlett*, **1992**, 33.

8) G. Cainelli, D. Giacomini, M. Panunzio, G. Martelli, and G. Spunta, *Tetrahedron Lett.*, **28**, 5369 (1987).

9) A mixture of 3,3-dimethyl-1-hydroxymethyl-2-azetidinone (2 mmol), vinyl acetate (3 mmol) and lipase PS (100 mg) in dichloromethane (2 ml) was stirred at room temperature for 9 h. The enzyme was filtered off and washed with dichloromethane. The combined solution was condensed to give a residue, which was subjected to column chromatography on silica gel.

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