Facile Synthesis of Optically Active γ-Lactones *via* Lipase-catalyzed Reaction of 4-Substituted 4-Hydroxybutyramides

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Lipase-catalyzed transesterification of racemic 4-substituted 4-hydroxybutyramides with succinic anhydride proceeded enantioselectively to afford (*S*)-succinic acid monoester and unreacted (*R*)-4-hydroxybutyramide derivative, which were separated easily by treatment with an alkaline solution. Both enantiomers were converted easily to optically active γ-substituted γ-butyrolactones.

Key words γ-butyrolactone; lipase; resolution; succinic anhydride

γ-Butyrolactones are widespread in nature; some are flavor compounds existing in plants[1] and others are significant in insect behavior.[2] Many naturally occurring γ-butyrolactones are optically active compounds. It is well established that chiral discrimination is an important principle in odor perception and insect sex pheromones. Therefore development of a convenient synthetic method for chiral γ-butyrolactones has attracted the attention of synthetic chemists.

Recently, several chemists have reported the syntheses of chiral γ-butyrolactones with sufficient optical purity by lipase-catalyzed resolution of 4-substituted 4-hydroxybutyric acid esters.[3] In these cases, however, a mixture of the reaction product and unreacted substrate was separated by a chromatographic method, which is a barrier to industrial-scale preparation. Previously, racemic alcohols were found to be enantioselectively acylated with succinic anhydride using a lipase catalyst in organic solvents, leading to the formation of succinic acid monoester which was easily separable by treatment with an alkaline solution.[4] For the application of this method to the synthesis of chiral γ-lactones *via* lipase-catalyzed resolution, ordinary esters did not appear to be the best substrate because of their lability to alkaline treatment. Our strategy includes the choice of a substrate stable in an alkaline solution, as well as appropriately enantioselective lipases.

We employed 4-substituted 4-hydroxybutyramides as substrates for lipase-catalyzed transesterification with succinic anhydride in organic solvents. A variety of 4-substituted 4-hydroxy-*N*-benzylbutyramides were prepared by aminolysis of racemic γ-lactone derivatives.[5] Several preliminary experiments using various types of lipase indicated that lipase PL (*Alcaligenes* sp.) and lipase PS-C (*Pseudomonas* sp.)[6] were well suited for enantioselective transesterification. Therefore we mainly used those two lipases for resolution of 4-substituted 4-hydroxy-*N*-benzylbutyramides.

The general procedure is as follows: A mixture of 4-substituted 4-hydroxy-*N*-benzylbutyramide 2 mmol, succinic anhydride 2 mmol, and lipase 50 mg in *tert*-butyl methyl ether (MTBE) 25 ml was stirred at 25 °C. After consumption of half the substrate had been confirmed by HPLC analysis, the lipase was removed by filtration and washed with MTBE. The combined organic layer was shaken with sodium carbonate 0.2 M (100 ml×2). The reacted enantiomer passed over into an aqueous layer as a succinic acid monoester, and the unreacted enantiomer remained in the organic layer. The aqueous layer was treated with 10% sodium hydroxide and extracted with MTBE. Both enantiomers isolated were converted into optically active γ-lactones in almost quantitative yields without racemization (Chart 1).

Table 1 shows the results of reactions of six 4-substituted 4-hydroxybutyramides. The results in entries 1—10 demonstrate that these lipases react preferentially with the *S*-enantiomer, and that the chain length of the substrate has little influence on the reaction rate and enantioselectivity. On the other hand, the reaction with lipase PS-C is faster than that with lipase PL, regardless of the alkyl chain length. It is of interest that an unsaturated alkyl group of the substrate is more effective on the enantioselectivity than a saturated one (compare entries 11 and 12 with 5 and 6, respectively). In general, these reactions proceed faster, especially with lipase PS-C, than the reported lactonization or acylation of the 4-hydroxybutyric acid esters with lipases,[3] although the optical yields are comparable.

We successfully converted the resultant chiral 4-hydroxybutyramides to the corresponding γ-butyrolactones, all of which are used as flavors (***R*-1a**—**f**) or a naturally occurring pheromone (***R*-1e**),[7] by hydrolysis with diluted hydrochloric acid without racemization.[8] In addition, the inversion of an enantiomer to a γ-lactone with the opposite configuration was also examined. As shown in Chart 2, the γ-lactonization of mesylated ***S*-2c** and ***S*-2f**, which were prepared from ***S*-3c** and ***S*-3f** purified by recrystallization, gave the corresponding (*R*)-γ-butyrolactones with high optical purity in moderate yields.[9] Optimal conditions for this reaction are under investigation.

Thus the present procedure provides a facile method for the conversion of racemic γ-lactones to only the required enantiomer *via* lipase-catalyzed resolution of 4-hydroxybutyramide derivatives and inversion of the enantiomer not required.

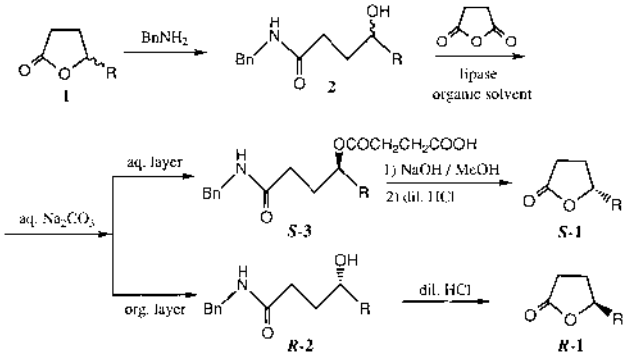

Chart 1

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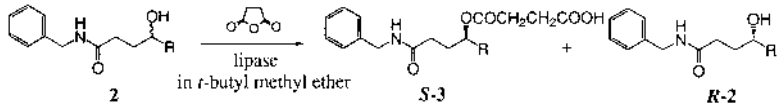
Table 1. Lipase-Catalyzed Transesterification of 4-Substituted 4-Hydroxy-*N*-benzylbutyramides



Entry	Substrate		Lipase	Time (h)	Product ***S*-3**		Unreacted ***R*-2**	
	No.	R			C.Y. (%)[a]	O.Y. (%ee)[b,c]	C.Y. (%)[a]	O.Y. (%ee)[b,c]
1	**2a**	n-C_4H_9	PS-C	5	50	89.7	43	92.2
2	**2a**	n-C_4H_9	PL	24	49	91.7	46	86.4
3	**2b**	n-C_5H_{11}	PS-C	4.5	47	88.9	47	90.5
4	**2b**	n-C_5H_{11}	PL	28.5	46	82.6	44	79.3
5	**2c**	n-C_6H_{13}	PS-C	3	44	85.5	44	86.7
6	**2c**	n-C_6H_{13}	PL	17	46	84.5	46	86.0
7	**2d**	n-C_7H_{15}	PS-C	3.5	47	87.5	43	86.7
8	**2d**	n-C_7H_{15}	PL	17.5	46	88.2	46	88.7
9	**2e**	n-C_8H_{17}	PS-C	5.5	49	80.7	44	85.5
10	**2e**	n-C_8H_{17}	PL	23	46	88.6	46	85.9
11	**2f**		PS-C	9	47	96.9	48	95.1
12	**2f**		PL	29	47	91.2	47	90.0

a) Isolated yield. *b*) Optical yields were determined by HPLC analyses (using Chiralcel OD in entries 1—10, and Chiralcel OD-R in entries 11 and 12) after the hydrolysis. *c*) Absolute configurations were determined by comparison of the optical rotations with those reported, after the lactonization.

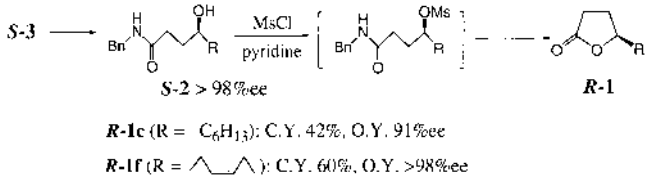


Chart 2

References and Notes

1) *a*) Mosandl A., Gunther C., *J. Agric. Food Chem.*, **37**, 413—418 (1989); *b*) Guichard E. *ACS Symp. Ser.*, **596**, 258—267 (1995); *c*) Guichard E., Kustermann A., Mosandl A., *J. Chromatogr.*, **498**, 396—401 (1990).
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4) Terao Y., Tsuji K., Murata M., Achiwa K., Nishio T., Watanabe N., Seto K., *Chem. Pharm. Bull.*, **37**, 1653—1655 (1989).
5) Preparation of 4-substituted 4-hydroxy-*N*-benzylamides: Racemic γ-substituted γ-lactone **1** 10 mmol and benzylamine 11 mmol were placed in an autoclave, and stirred at 80—90° for 4—12 h to afford the product in 85—95% yield. The structures of products were determined by ^{1}H-NMR, IR, and MS spectral analyses.
6) Lipase PL and lipase PS-C were supplied by Meito Sangyo Co., Ltd., and Amano Pharmaceutical Co., Ltd., respectively.
7) The ^{1}H-NMR spectra of all of chiral γ-alkyl γ-lactones (**1a**—**g**) agreed with those of the starting racemates. The specific rotations of chiral γ-alkyl γ-lactones (**1a**—**g**) were reported previously.[1a] **1f** was determined after conversion to **1c** by catalytic reduction.
8) Recently, a few chiral γ-lactones have been obtained in kilogram amounts using this method in our company.
9) Mesyl chloride 2 mmol was added dropwise to a solution of ***S*-2c** or ***S*-2f** 1.8 mmol in pyridine 5 ml at 0 °C with stirring. The mixture was stirred overnight at room temperature and poured into ice water. The mixture was extracted with hexane. The organic layer was washed with diluted HCl and brine, and dried over $MgSO_4$. Removal of the solvent gave an oily residue, which was chromatographed on a silica gel column using an AcOEt-hexane system to afford an oily product. The optical purity was determined by comparison of the specific rotation of the product with that described in Reference 1a).