A Practical Method for Optical Resolution of Racemic Alcohols or Esters via Lipase-Catalyzed Transformation and Sulfation

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Optically active esters were conveniently obtained from the corresponding racemic alcohols or esters by lipase-catalyzed transformation, followed by sulfation. Sulfation by sulfurtrioxide pyridine complex enabled facile isolation of optically active esters by extraction instead of laborious column chromatography. The method would be especially advantageous on a large scale.

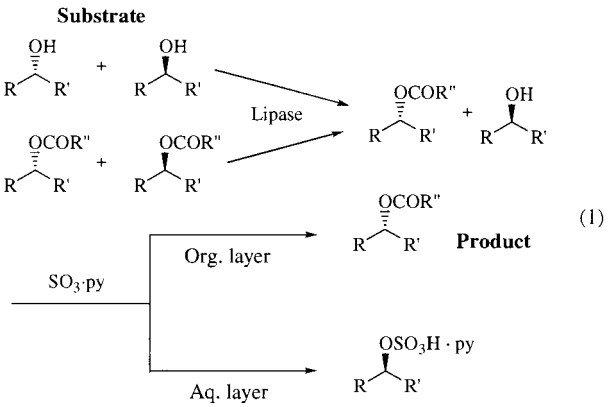
The lipase-catalyzed transformation of racemic alcohols or esters has been recognized to be an indispensable method for synthesis of optically active compounds.[1] The method relies on stereoselectivities accomplished by lipases, and a subsequent skillful trick, which enables physically identical enantiomers to be switched physically distinguishable compounds, alcohols and esters. The separation of alcohols and esters is, in general, carried out by laborious column chromatography, which is extremely difficult and inefficient to carry out on a large scale. In some cases, these difficulties may be avoided by using cyclic acid anhydrides as acyl donors to form a water-soluble monoester of dibasic acid, which is separable with an aqueous alkaline solution.[2] Facile and efficient methods suitable for a large-scale production, however, remain poorly developed.

We wish here to describe a convenient method to separate alcohols and esters by a simple and practical procedure. We assumed that extraction, instead of column chromatography, would be the procedure of choice. To this end, alcohols were converted into water-soluble compounds by simple derivatizations. Among various derivatizations evaluated, sulfation using sulfurtrioxide pyridine complex was found to be the most promising.

Accordingly, as depicted in Eq.1, racemic alcohols or esters were subjected to lipase-catalyzed transformation to give the mixtures consisting of optically active alcohols and esters. The resulting mixtures were treated with sulfurtrioxide pyridine complex to give mixtures consisting of esters and pyridinium salts of monoalkyl sulfates. After dilution with hydrophobic solvents such as diisopropyl ether, the mixtures were washed with water to remove pyridinium salts of monoalkyl sulfates to accomplish substantial separation of esters.[3]

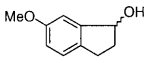
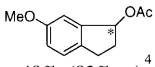
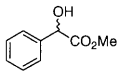
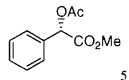
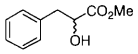
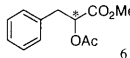
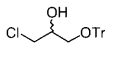
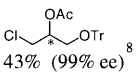
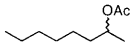
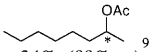
The procedure has proved to be widely applicable (Table 1). High enantiomer excesses, accomplished by the lipase-catalyzed transformation, were not affected by sulfation. The purity of esters was appreciably high and the contents of their counterparts, alcohols, were kept below 1%.

Optically active esters thus obtained from the organic layer could be smoothly converted to the corresponding alcohols by acid- or base-catalyzed hydrolysis under mild conditions. It is noteworthy that pyridinium salts of monoalkyl sulfates thus



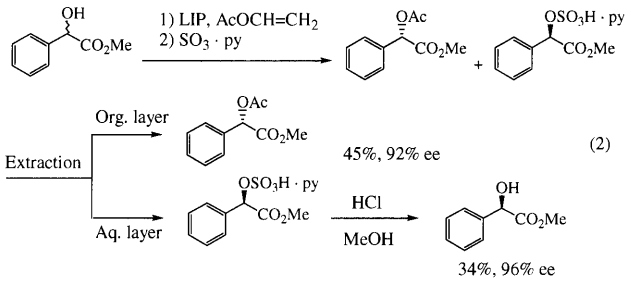
(1)

Table 1. Preparation of optically active esters *via* lipase-catalyzed transformation and sulfation

Substrate	Product	Lipase	Alcohol content
	 48% (82% ee)[4]	LIP (Toyobo Co. Ltd)	0.4%
	 45% (92% ee)[5]	LIP (Toyobo Co. Ltd)	0.2%
	 44% (95% ee)[6]	QL (Meito Sangyo Co., Ltd.)	0.3%
	 42% (99% ee)[7]	PS-C[10] (Amano Pharmaceuitical Co., Ltd.)	0.3%
	 43% (99% ee)[8]	PS-C[11] (Amano Pharmaceuitical Co., Ltd.)	1.0%
	 34% (99% ee)[9]	CHIRAZYME L-2[12] (Roche Diagnostics)	0.2%

Yields were based on racemic substrates. Yields, enantiomer excesses, and alcohol contents (area%) were determined by HPLC or GLC analysis.[4-9] Lipase-catalyzed transformations have been reported.[10-12]

obtained from aqueous layer could be also converted to the corresponding alcohols by acid hydrolysis (Eq.2). Therefore, both enantiomeric alcohols could be obtained readily and effectively by the present procedure. The procedure, thus, will be applicable to the synthesis of a variety of optically active alcohols.



References and Notes

1 a) "Enzymatic Reactions in Organic Media," ed by A. M. P. Koskinen and A. M. Klibanov, Blackie Academic & Professional, Glasgow (1996). b) "Hydrolases in Organic Synthesis," ed by U. T. Bornscheuer and R. J. Kazlauskas, Wiley-VCH, Weinheim (1999).

2 a) Y. Terao, K. Tsuji, M. Murata, K. Achiwa, T. Nishio, N. Watanabe, and K. Seto, *Chem. Pharm. Bull.*, **37**, 1653 (1989). b) A. L. Gutman, D. Bernner, and A. Boltanski, *Tetrahedron: Asymmetry*, **4**, 839 (1993).

3 Preparation of (+)-methyl 2-acetyloxy-2-phenylacetate and (–)-methyl 2-hydroxy-2-phenylacetate was performed as follows: A suspension of lipase (LIP, Toyobo Co. Ltd.) 1.50 g, (±)-methyl 2-hydroxy-2-phenylacetate 1.00 g, Molecular sieves 4A 5.0 g, and vinyl acetate 3.0 ml in diisopropyl ether 100 ml was stirred at 35 °C for 3 h. After the lipase was removed by filtration, the filtrate was concentrated under reduced pressure to give a residue containing methyl (*S*)-(+)-2-(acetyloxy)-2-phenylacetate (93% ee) and methyl (*R*)-(–)-2-hydroxy-2-phenylacetate (99% ee). The residue was dissolved in pyridine 10 ml and DMF 2 ml, and to this solution sulfur trioxide pyridine complex 1.95 g was added. After stirring at room temperature for 1 h, diisopropyl ether 70 ml was added. The mixture was washed with successive water, dilute hydrochloric acid and brine, then dried over sodium sulfate. The filtrate was concentrated under reduced pressure to afford methyl (*S*)-(+)-2-(acetyloxy)-2-phenylacetate 0.559 g (45%, 92% ee) as an oil. The combined aqueous layers were concentrated and treated with 10% methanolic hydrochloric acid. A similar work up afforded methyl (*R*)-(–)-2-hydroxy-2-phenylacetate 0.341 g (34%, 96% ee).

4 The acetate was hydrolyzed to give an alcohol, which was subjected to HPLC analysis. Column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), Mobile phase: hexane/2-propanol (97/3), Flow rate: 1.0 ml/min, Detection: UV (280 nm), Temperature: room temperature.

5 Column: CHIRALCEL OD (Daicel Chemical Industries Ltd.), Mobile phase: hexane/2-propanol (99/1), Flow rate: 1.2 ml/min, Detection: UV (254 nm), Temperature: room temperature.

6 Column: CHIRALCEL OJ (Daicel Chemical Industries, Ltd.), Mobile phase: hexane/2-propanol (98/2), Flow rate: 1.2 ml/min, Detection: UV (220 nm), Temperature: room temperature.

7 Column: CHIRALCEL OB (Daicel Chemical Industries, Ltd.), Mobile phase: hexane/2-propanol (1000/5), Flow rate: 1.0 ml/min, Detection: UV (254 nm), Temperature: room temperature.

8 Column: CHIRALCEL OD two pieces (Daicel Chemical Industries, Ltd.), Mobile phase: hexane/2-propanol (1000/5), Flow rate: 1.0 ml/min, Detection: UV (254 nm), Temperature: room temperature.

9 (GLC) Column: Chirasil Dex-CB (25 m × 0.25 mm I.D., Chrompack), Oven temperature: 80 °C ~ 150 °C, Injection temperature: 200 °C, Detection temperature: 200 °C, Carrier gas: Helium.

10 Y. Hirose, Y. Imada, Y. Yamashita, M. Kamori, H. Ozaki, and J. Takahashi, presented at 9th International Symposium on Chiral Discrimination, Nagoya, 1997, Abstr., PP1-46, p.67.

11 M.-J. Kim and Y. K. Choi, *J.Org.Chem.*, **57**, 1605 (1992).

12 T. Ohtani, H. Nakatsukasa, M. Kamezawa, H. Tachibana, and Y. Naoshima, *J. Mol. Catal. B: Enzymatic*, **4**, 53 (1998).