Enantioselective Hydrolysis of Five-membered-ring Acetates catalysed by *Pseudomonas fluorescens* Lipase

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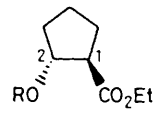
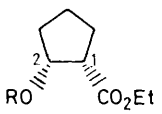
The racemic acetates of five-membered-ring alcohols were successfully resolved into the optically active alcohols with high optical purities by *Pseudomonas fluorescens* lipase.

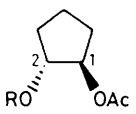
The use of hydrolytic enzymes as chiral catalysts for asymmetric hydrolysis has been well documented.[1] While many enantioselective hydrolyses of esters of racemic acids have been reported,[2] the enzymic hydrolyses of acetates of racemic alcohols have not attracted much attention.[3] Recently, Schneider *et al.*[4] reported the enzymic hydrolysis of (±)-*trans*-1,2-diacetoxy-cycloalkanes with pig liver esterase (PLE), but the hydrolysis of diacetoxy-cyclopentane resulted in low enantioselectivity (63% enantiomeric excess, e.e.), as did that (17% e.e.) of *meso*-1,2-dimethoxycarbonylcyclopentane with PLE.[5] We now report that *Pseudomonas fluorescens* lipase catalyses hydrolyses of (±)-acetoxy-cyclopentanes (**1a**)—(**7a**) to afford the corresponding alcohols with high optical purities. The hydrolyses were performed using *ca.* 100 mg of substrates suspended in 0.1 M-phosphate buffer (20 ml, pH 7.0, 33 °C) in the presence of *P. fluorescens* lipase (50 mg, Amano Pharmaceutical Co.). Optical purities were determined by means of the 400 MHz ^{1}H n.m.r. spectra of the (+)-α-methoxy-α-trifluoromethylphenylacetic acid esters[6] derived from the resulting alcohols (**1b**)—(**7b**), and the absolute configurations



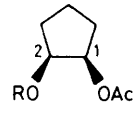
(**1a,b**)



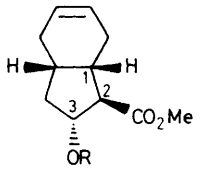
(**2a,b**)



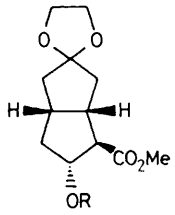
(**3a,b**)



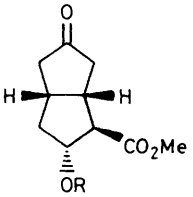
(**4a,b**)



(**5a,b**)



(**6a,b**)



(**7a,b**)

a; R = Ac
b; R = H

Table 1. *P. fluorescens* lipase catalysed hydrolysis of (**1a**)—(**7a**).

		Product		Recovered acetate	
Substrate	Reaction time/h	% Yield (isolated)	% E.e.	% Yield (isolated)	% E.e.
(**1a**)	6	30	>99	65	30
(**2a**)	1.5	42	>99	50	90
(**3a**)	8	43	>99	42	95
(**4a**)	3	39	>99	42	—
(**5a**)	24	50	96	48	87
(**6a**)	56	13	45	76	2
(**7a**)	27	12	77	81	0

were determined by comparison with known compounds.[7] The results are summarized in Table 1. The hydrolyses of the (±)-*trans*- and -*cis*-acetates (**1a**) and (**2a**) afforded exclusively (1*R*,2*R*)-(−)-(**1b**) (>99% e.e.) and (1*S*,2*R*)-(−)-(**2b**) (>99% e.e.), respectively. The (±)-*trans*-diacetate (**3a**) was resolved into (1*R*,2*R*)-(+)-(**3b**) in the enantiomerically pure form (>99% e.e.). It is noteworthy that the *meso*-diacetate (**4a**) was also hydrolysed to the optically pure monoacetate (1*R*,2*S*)-(−)-(**4b**) (>99% e.e.)[8] by *P. fluorescens* lipase, because, according to Schneider,[4] the hydrolyses of the *cis*-1,2-diacetoxy-cycloalkanes (4-, 5-, and 6-membered ring) with PLE resulted in the formation of optically inactive monoacetate. Compound (±)-(**5a**) with its bicyclo[4.3.0]nonene skeleton was resolved into (2*R*,3*R*)-(−)-(**5b**) with high optical purity (96% e.e.). However, the hydrolyses of compounds (±)-(**6a**) and (±)-(**7a**) which contain the bicyclo[3.3.0]octane skeleton resulted in low enantioselectivity to afford (2*R*,3*R*)-(+)-(**6b**) (45% e.e.) and (2*R*,3*R*)-(+)-(**7b**) (77% e.e.), respectively.

From the absolute configuration of the hydrolysis products, we conclude that the alcohol acetates hydrolysed with *P. fluorescens* lipase are usually of the *R*-configuration except for the *meso*-diacetate (**4a**).

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7 For compounds (**1**) and (**2**), see D. Buisson and R. Azerad, *Tetrahedron Lett.*, 1986, **27**, 2631. For compounds (**3**) and (**4**), see B. Helferich and R. Hilton, *Ber. Dtsch. Chem. Ges.*, 1937, **70**, 308. For compounds (**5**)—(**7**), see Z.-F. Xie, K. Funakoshi, H. Suemune, T. Oishi, H. Akita, and K. Sakai, *Chem. Pharm. Bull.*, 1986, **34**, 3058. The absolute configuration of (−)-(**4b**) was determined by conversion of (1*R*,2*R*)-cyclopentene-1,2-diol into (+)-(**4b**) by treatment with a mixture of AcOH, triphenylphosphine, and diethyl azodicarboxylate.

8 The acetyl-migration[4] was not observed under the reaction conditions employed.