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"Triple Enantioselection" by an Enzyme-Catalyzed Transacylation Reaction

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Abstract: The triply enantioselective enzyme-catalyzed transacylation of *rac*-1-indanol with *rac*-1,1'-bi-2-naphthyl-2,2'-dibutyrate afforded *(S)*-1-indanol, *(R)*-1-indanylbutyrate, *(S)*-1,1'-bi-2-naphthyl-2,2'-diol, and *(R)*-1,1'-bi-2-naphthyl-2,2'-dibutyrate.

The recent development of enzyme catalysis in organic synthesis for kinetic resolutions of racemates has attracted the attention of organic chemists because of their synthetic utility.[1-5] The lipase-catalyzed acylations and transacylations have become popular methods in asymmetric synthesis.[3] It was expected by Chen and Sih[3] that "the matching of appropriate racemic alcohols in a double kinetic resolution experiment is an exciting area that warrants systematic exploration in the future."

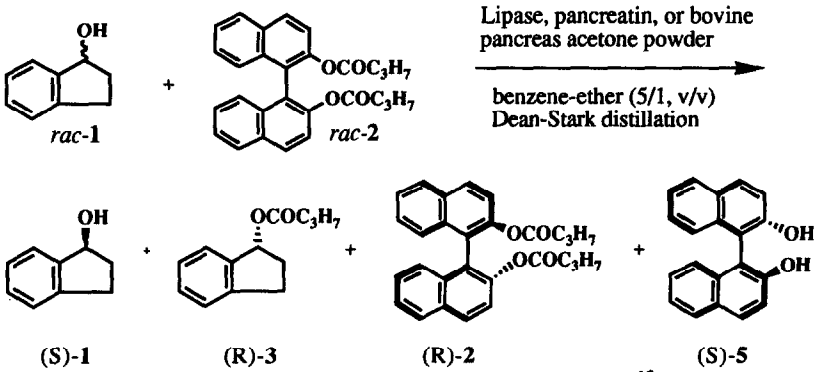
Three papers have been published so far dealing with enzyme-catalyzed double kinetic resolution.[6-8] Enzymatic synthesis of amides with two newly generated chiral centers by reaction of *rac*-2-ethyl 2-chloropropanoic acid with racemic amines has been described first.[6] Fowler et al.[7] reported highly diastereoselective transacylation reactions involving a racemic acetate and a racemic carboxylic acid catalyzed by lipase enzymes. With the low enantioselection of the second compound, Theil et al.[8] reported the "double enantioselection" by a lipase-catalyzed transacylation of a meso-diols with a racemic carboxylic ester. To the best of our knowledge, no publication about triple enantioselection has been found so far.

In this paper, we describe the first enzyme-catalyzed "triply enantioselective" transacylation between a *rac*-1-indanol (*rac*-**1**) and *rac*-1,1'-bi-2-naphthyl-2,2'-dibutyrate (*rac*-**2**) (Table and Scheme). The first enantioselection is the acylation of (*R*)-1-indanol ((*R*)-**1**) from *rac*-**1** with an acyl donor **2** or 1,1'-bi-2-naphthyl-2-ol-2'-butyrate (**4**), and the product is (*R*)-1-indanylbutyrate ((*R*)-**3**). The second enantioselection occurs in the hydrolysis of the first acyl donor (*S*)-**2** from its racemic mixture. This hydrolysis product is the second acyl donor (*S*)-**4** which undergoes the second enzyme-catalyzed hydrolysis (the third enantioselection) to give (*S*)-1,1'-bi-2-naphthyl-2,2'-diol ((*S*)-**5**).[9]

Among many enzymes we tested, porcine pancreatic lipase (PPL) showed the best results in both chemical yield and enantioselectivity. Both porcine pancreatin (PN) and crude cholesterol esterase from bovine pancreatic acetone powder (PAP) had moderate reaction rates and enantioselectivities. The catalysis rates for both lipase from *Candida cylindracea* (Sigma L9767) and lipase from *Pseudomonas species* (Sigma L9518) were too slow to measure. The enzyme enantioselectivity on (*R*)-**1** from *rac*-**1** can be fit into Burgess' model[10] for lipase from *Pseudomonas species*. The enzyme stereospecificity on the *rac*-**2** site is the same as Kazlauskas reported[11] for cholesterol esterase.

We are continuing these investigations to elucidate the mechanism for this triple enantioselection.

Scheme



(S)-1 (R)-3 (R)-2 (S)-5

Table. Enzymes-Catalyzed Triply Enantioselective Transacylation[12] of *rac*-Indanol (**1**) with *rac*-1,1'-Bi-2-naphthyl-2,2'-dibutyrate (**2**)

Enzymes[a]	relative rate	yield ratio (%) of (*S*)-**1**:(*R*)-**3**:(*R*)-**2**:(*S*)-**5**	% OP of (*S*)-**1**[c]	% OP of (*R*)-**3**[d]	% OP of (*R*)-**2**[d]	% OP of (*S*)-**5**[c]
PPL	1[b]	24:23:23:23	>99	>99	98	98
PN	0.3	21:23:21:23	99	>99	97	98
PAP	0.5	23:22:21:22	98	97	95	95

a. PPL: lipase from porcine pancreas (Sigma L0382); PN: pancreatin from porcine pancreas (Sigma P1750); PAP: bovine pancreas acetone powder (Sigma P3006). b. As a standard: 0.6 nmol/min mg enzyme c. Optical purity of alcohols was calculated by OP = $[\alpha]_{D\ exp.}$ / $[\alpha]_{D\ lit.}$· $[\alpha]_{D\ exp.}$ values for (*S*)-**1** and (*S*)-**5** were measured from a polarimeter at 25°C, c2 $CHCl_3$ and c1 THF, respectively. $[\alpha]_{D\ lit.}$ values for (*S*)-**1** (+30°, c2, $CHCl_3$) and (*S*)-**5** (+34°, c1, THF) were obtained from Aldrich Catalog 1992-1993. d. These values were obtained indirectly from the % OP values of (*R*)-alcohols from the basic hydrolysis of the corresponding esters. The basic hydrolysis products ((*R*)-**1** and (*R*)-**5**) were obtained from basic hydrolysis (0.1 N KOH, EtOH, 25°C, 18h, 92%) of esters and their % OP values were determined as note c.

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9. We also found that the PPL or PAP catalyzed hydrolysis of *rac*-**4** to (*S*)-**5** is also enantioselective ((*S*)-**4** is a substrate but (*R*)-**4** is not). Thus, these two enzymes catalyze both the hydrolysis of (*S*)-**4** (from *rac*-**4**) to (*S*)-**5** with %OP>98 and the acylation of (*R*)-**1** (from *rac*-**1**) to (*R*)-**3** with %OP>97.
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12. General procedures: To *rac*-**1** (200 mg) in 150 mL of benzene-ether (5/1, v/v), 2 g of an enzyme (PPL, PN, or PAP), 500 mg of bovine albumin (fraction V), and 0.5 mole eq. of *rac*-**2** (prepared by the condensation of 2 mole eq. of butyryl chloride with *rac*-**5** in the presence of pyridine) were added. The reaction was stirred slowly under reflux with Dean-Stark trap for 24-48h. After removing the enzyme by filtration and subsequent evaporation of the solvents under reduced pressure, the residue was purified by medium pressure liquid chromatography (MPLC) on silica gel eluted with hexane-ethyl acetate solvent gradient (5/1, v/v to 2/1, v/v) to afford (*S*)-**1**, (*R*)-**3**, (*R*)-**2**, and (*S*)-**5** with R_f values (hexane/ethyl acetate, 3/1, v/v) 0.33, 0.83, 0.67, and 0.32, respectively. All products were characterized by ^1H NMR and ^{13}C NMR spectra. Relative rates of these reactions were estimated by UV and ^1H NMR in small scale experiments.

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