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"Double Enantioselection" by a Lipase-Catalyzed Transesterification of a meso-Diol with a Racemic Carboxylic Ester[1]

Fritz Theil*, Annamarie Kunath, and Hans Schick

Centre of Selective Organic Synthesis, Rudower Chaussee 5, D(O)-1199 Berlin-Adlershof, Federal Republic of Germany

Abstract: The doubly enantioselective lipase-catalyzed transesterification of the *meso*-diol **1** with *rac*-2,2,2-trifluoroethyl 2-chloropropanoate (**2**) afforded mainly the diastereomers **3a** and **3c** in a ratio depending on the origin of the lipase. Both compounds were obtained with very high e.e.'s.

Enzymes have been widely used as chiral catalysts in organic synthesis for kinetic resolutions of racemates and for asymmetrizations of prochiral compounds[2-9]. Many papers in this field deal with lipase-catalyzed esterifications, transesterifications, and interesterifications[4]. It was expected by Chen and Sih[4] that "the matching of appropriate racemic acids with racemic alcohols in a double kinetic resolution experiment is an exciting area that warrants systematic exploration in the future."

To our knowledge, only two papers have been published so far dealing with enzyme-catalyzed double kinetic resolutions. Synthesis of carboxylic amides[10] and carboxylic esters[11] with two newly generated chiral centres by reaction of *rac*-ethyl 2-chloropropanoate with racemic amines and by esterification or interesterification of *rac*-2-(4-chlorophenoxy)propanoic acid with a racemic bicycloheptenol derivative has been described.

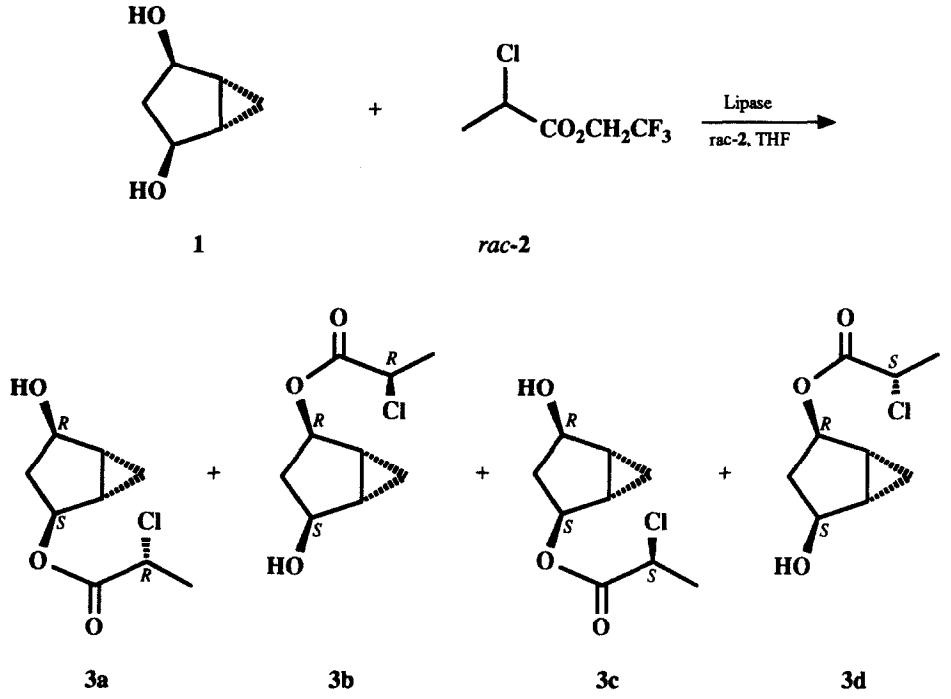
In this paper we describe the first lipase-catalyzed "doubly enantioselective" transesterification between a *meso*-diol and a racemic carboxylic ester. Reaction[12] of the *meso*-diol **1**[13] with *rac*-2,2,2-trifluoroethyl 2-chloropropanoate (**2**) in organic solvents in the presence of lipases[14] of different origin (Scheme 1) gave the four stereoisomers **3a** - **3d**[15] in distinct ratios[16] (Table 1). In general, the stereoisomers **3a** and **3c** are predominating over **3b** and **3d**. Among the lipases tested the highest selectivities were achieved with the lipase from *Candida Sp. 382* (entry 1) and with pancreatin (entry 2).

The analysis of these results in consideration of the reaction pathway for lipase-catalyzed acylations[4] shows that the selectivity for the first step of this transformation – the enantioselection between the enantiomers of *rac*-**2** – is moderate (entry 1 and 2); or there is even no enantioselection (entry 3). Remarkably, pancreatin and the lipase from *Candida Sp. 382* show opposite enantioselectivity in this step. The second step in this transformation, the acyl transfer from the acyl enzyme to the enantiotopic groups of the prochiral diol **1** is for three of the lipases (entry 1, 2, and 3) very high to afford **3a** and **3c** in high enantiomeric purity.

Variation of the solvent (tert-butyl methyl ether, diisopropyl ether, or toluene) has no significant influence on the selectivity of the reaction.

The described process combines the asymmetrization of a prochiral diol with the kinetic resolution of a carboxylic ester to give a chiral molecule with at least three asymmetric centres in one step. These preliminary results clearly demonstrate the potential of lipases to catalyze a "doubly enantioselective" transesterification between a *meso*-diol and a racemic carboxylic ester.

We are continuing these investigations to improve and broaden the scope of this reaction by testing further enzymes, changing the reaction conditions, and by finding matching partners for this "doubly enantioselective" process.



Scheme 1

Table 1: Lipase-Catalyzed Doubly Enantioselective Transesterification of **1** with *rac*-**2**

entry	lipase	reaction time (h)	yield of **3a - 3d** (%)	ratio of **3a : 3b : 3c : 3d** (%)	e.e. of **3a** (%)	e.e. of **3c** (%)	ratio of **(3a + 3d) : (3b + 3c)** (%)
1	SP 382	2.5	95	69.1 : 0 : 28.4 : 2.5	93	100	71.6 : 28.4
2	Pancreatin	28	76[a]	23.7 : 1.5 : 74.4 : 0.4	97	96	24.1 : 75.9
3	Amano PS	23	92	47.1 : 1.9 : 49.9 : 1.1	96	93	48.2 : 51.8
4	CCL	4.5	68[b]	47.7 : 9.0 : 33.7 : 9.6	66	62	57.3 : 42.7

[a] 23 % of unchanged **1** were isolated, [b] 19 % of unchanged **1** were isolated

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12. Reaction conditions: 1 mmol of **1** in 2.5 ml of THF was treated with 7 mmol of *rac*-**2** and 50 mg of lipase (500 mg of CCL were used.) and stirred at room temperature for the given time. After removing the enzyme by filtration and subsequent evaporation of the solvents under reduced pressure the residue was purified by flash chromatogaphy with hexane/ethyl acetate (67 : 33, v : v) to yield a mixture of **3a** - **3d** as a colourless oil.

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14. The following lipases were used: Pancreatin 6 × NF: Fa. Belger, Kleinmachnow, FRG; Amano PS: Amano Pharmaceutical Co. Ltd., Nagoya, Japan; lipase from *Candida Sp. 382*: Novo Industri A/S, Copenhagen, Denmark, and lipase from *Candida cylindracea* type VII (CCL): Sigma.

15. **3a** - **3d**: ^{1}H NMR (200 MHz, $CDCl_3$): -0.08 (m, 1H, cycloPr), 0.60 (dt, J 15 and 8 Hz, 1H, cycloPr), 1.60 - 1.73 (d, J 7 Hz, 3H, CH_3 and m, 4H, CH_2 and 2 × CH), 2.55 (br s, 1H, OH), 4.16 (d, J 3 Hz, 1H, CHOH), 4.33 (q, J 7 Hz, 1H, CHCl), 5.20 (d, J 3 Hz, 1H, CH-OAcyl); ^{13}C NMR (75 MHz, $CDCl_3$): 6.49, 20.86, 21.07 + 21.16, 24.56 + 24.61, 37.85 + 37.89, 52.46 + 52.58, 73.27 + 73.31, 78.85, 169.35 + 169.44 [doubling of most of the signals reflects the ratio of (**3a** + **3d**) : (**3b** + **3c**)].

16. This ratio has been determined by separation of the mixture by HPLC on silica gel with hexane/2-propanol (97 : 3, v : v) into two fractions which contained the enantiomeric pairs **3a** + **3d** and **3b** + **3c**. The enantiomeric excess (e.e.) of these two fractions has been determined by HPLC on amylose tris-3,5-dimethylphenyl carbamate coated on silica gel (Chiralpak AD) with hexane/2-propanol (80 : 20, v : v). The structures of **3a** - **3d** have been determined by comparing the chromatographic behaviour with that of independently synthesized **3a** - **3d**.

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