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Enzymatic Synthesis of 3-Hydroxybutyramides and their Conversion to Optically Active 1,3-Aminoalcohols

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Abstract:. 3-Hydroxybutyramides are obtained in high optical yield from ethyl (±)-3-hydroxybutyrate and aliphatic amines when the reaction is catalyzed by *Candida antarctica* lipase. The chemical reduction of these 3-hydroxybutyramides yields the corresponding 1,3-aminoalcohols.

The resolution of β-hydroxybutyrates is an important task in organic synthesis because these substrates are used as building blocks for the preparation of many bioactive natural products.[1] For this purpose, methods that use biocatalysts have been reported. These methods include the asymmetric reduction of β-ketoesters by baker's yeast[2] and the lipase catalyzed hydrolysis[3] of *tert*-butyl 3-acetoxybutyrate amongst others.[4]

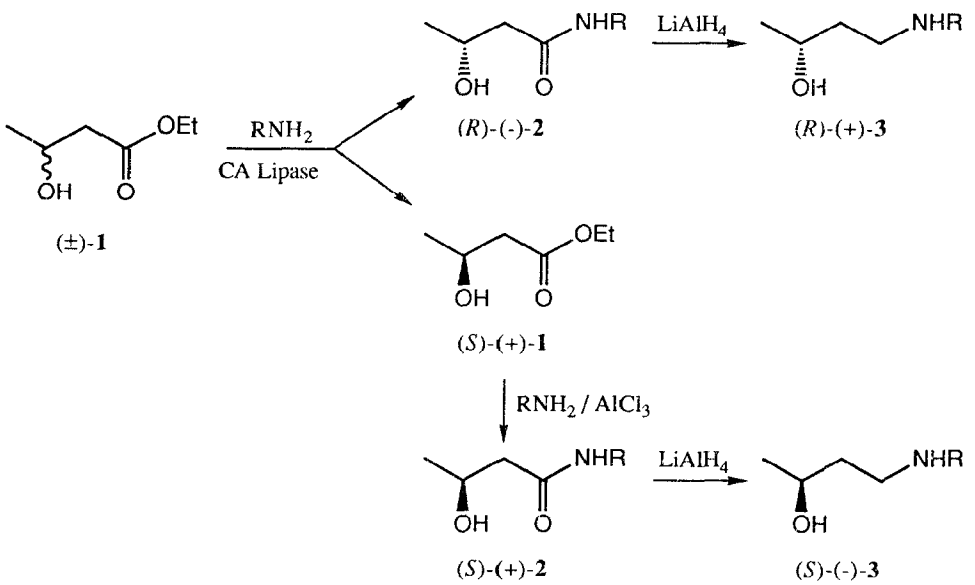
For the resolution of these substrates, we considered that amidation could be an interesting alternative because the resulting β-hydroxyamides are intermediates in the synthesis of 1,3-aminoalcohols, compounds of importance because of their pharmaceutical properties and as starting materials in the synthesis of some antibiotics.[5] We report here a simple and efficient resolution of ethyl 3-hydroxybutyrate through lipase catalyzed amidation. This methodology has previously proved to be of utility for the preparation of optically active amides from racemic esters[6] or amines.[7]

At first, we checked the catalytic potential of different lipases[8] in the amidation of ethyl (±)-3-hydroxybutyrate with butylamine. *Candida cylindracea* lipase exhibited a low catalytic efficiency; large reaction times (6 days) were neccessary to get *ca.* 10% of conversion, and the β-hydroxyamide obtained was racemic. Changes of solvent did not lead to a significative improvement.

More satisfactory results were obtained when *Pseudomonas cepacia* (PS) and *Candida antarctica* (CA) lipases were used as catalysts. Of the different solvents tested, tetrahydrofuran, diisopropylether, hexane, toluene, the best results were obtained when the reactions were carried out in dioxane. In this solvent PS lipase catalyzed the formation of (*S*)-*N*-butyl-3-hydroxybutyramide in moderate optical yield (56% e.e.); however, CA lipase (CAL) displayed a higher and opposite enantioselectivity and the (*R*)-amide was obtained in 79% e.e.

In order to study the influence of the nucleophile on the catalytic activity of the enzyme, we tried the reaction with others amines[9] (The results are collected in Table 1). The lipases tested did not show any catalytic activity when aromatic amines were used as nucleophiles. As it is showed in Table 1, in all cases CAL catalyzed the amidation more efficiently than PSL. Surprisingly, with benzylamine, CAL showed the highest enantioselectivity, and optically pure (*R*)-*N*-benzyl-3-hydroxybutyramide was obtained in high yield (45% of conversion). This enzyme could be repeatedly utilized without loss of catalytic activity.

Scheme



When the reaction with benzylamine and CAL as catalyst was allowed to react until 55% of conversion, (*S*)-(+)-**1** was obtained with an e.e. >99%. By treatment of this optically pure ester with amines in presence of aluminum trichloride,[10] (*S*)-(+)-**2a-c** were obtained (see Scheme). The e.e. of the 3-hydroxybutyramides were determined by ^{1}H-NMR (300 MHz) $CDCl_3$, of their MTPA ester derivatives[11] (for example, for the diastereomeric derivative prepared from (*R*)-**2b**, the signals corresponding to the methyl group were two doublets centered at 1.37 and 1.44 ppm).

Table 1. 3-Hydroxybutyramides (**2**) obtained by enzymatic amidation of (±)-**1**

Entry	R	Lipase	Reaction time, h.	% Conv.[a]	$[\alpha]_D^{22}$ [b]	ee, %	Conf.
2a	*n*-butyl	PS	48	38	+19.4 (c, 0.50)	56	*S*
2a	*n*-butyl	CA	11	46	-27.5 (c, 0.68)	79	*R*
2b	allyl	PS	48	19	+15.3 (c, 0.78)	37	*S*
2b	allyl	CA	14	41	-30.6 (c, 0.75)	75	*R*
2c	benzyl	PS	48	15	+9.3 (c, 0.93)	29	*S*
2c	benzyl	CA	21	45	-33.8 (c, 0.96)	>99	*R*

[a] Determined by the ^{1}H-NMR of the reaction mixture. [b] Measured in $CHCl_3$.

The chemical reduction of compounds (*R*)-(-)-**2** with lithium aluminum hydride yielded the corresponding aminoalcohols (*R*)-(+)-**3**, with little or no racemization. In the case of *N*-allyl-3-hydroxybutyramide (**2b**), the reduction of the C=C double bond also took place. The results are collected in Table 2. The e.e. of compounds **3** were determined by ^{1}H-NMR of their MTPA ester derivatives.[11] In all cases, the ^{1}H-NMR spectrum of the MTPA ester derivative of the corresponding racemic aminoalcohol (obtained from ethyl (±)-3-hydroxybutyrate and the corresponding amine, ref. 10), was used as a reference. For the diastereomeric derivative prepared from (±)-**3c**, the signals corresponding to the C-4 methylene hydrogens were two triplets centered at 2.76 and 2.58 ppm ($CDCl_3$, 300 MHz). For the MTPA ester from (*R*)-(+)-**3c**, the signal was only a triplet centered at 2.76 ppm.

Table 2.- Aminoalcohols (*R*)-(+)-**3** obtained from (*R*)-(-)-**2**

Entry	R	Yield, %	$[\alpha]_D^{22}$ [a]	ee, %
3a	*n*-butyl	86	+12.2 (c, 0.99)	79
3b	*n*-propyl	82	+14.2 (c, 0.89)	75
3c	benzyl	90	+16.3 (c, 0.90)	>99

[a] Measured in $CHCl_3$.

In conclusion, we have described a simple procedure for the preparation of 3-hydroxybutyramides with

moderate to high enantiomeric purity. These amides are useful starting materials for the synthesis of 1,3-aminoalcohols.

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8. *Candida cylindracea* lipase, Type VII crude, was purchased from Sigma Chemical Co. PSL from Amano Pharmaceutical Co. CAL (SP 435 A) was obtained from Novo Nordisk Co.
9. Reaction conditions: 5 mmol of ester, 5 mmol of amine, 20 ml of dioxane. Lipase: PS, 50 mg ml^{-1}; CA (SP 435 A) 15 mg ml^{-1}. When the reaction was terminated, the residue was subjected to flash chromatography on silica using hexane-ethyl acetate (1:1) as eluent.
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