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LIPASE CATALYSED HYDROLYSIS OF γ-SUBSTITUTED α-AMINOBUTYROLACTONES

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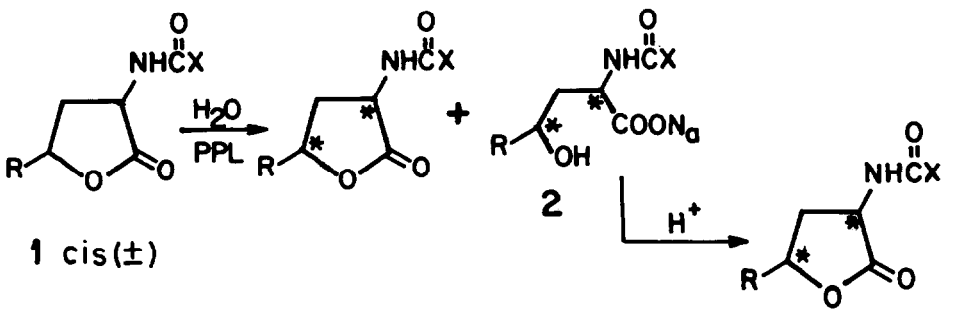
Summary: Porcine pancreatic lipase catalyses stereospecific hydrolysis of N-protected α-aminobutyrolactones and of their γ-substituted derivatives. This provides the first example of lipase catalysed synthesis of chiral disubstituted γ-lactones.

Lipases are often used as catalysts in organic synthesis, because they are easily available, inexpensive, stable, and they require no added cofactors. Recently, a number of reports have appeared on lipase-catalysed resolutions of racemic alcohols and carboxylic acids, either *via* enantioselective hydrolysis of the corresponding esters in aqueous solutions, or *via* enantioselective esterification and transesterification in organic solvents.[1]

We recently found that porcine pancreatic lipase (PPL) is useful for the preparation of chiral lactones. In aqueous solutions PPL catalysed hydrolysis of γ- and δ-lactones into the corresponding hydroxyacids,[2] while in organic solvents, it catalysed lactonisation of γ- and δ-hydroxyesters.[3] In both aqueous and organic media the reactions were stereospecific, which enabled us to carry out preparative synthesis of several optically active γ-substituted γ-lactones or δ-substituted δ-lactones. However, in all of these experiments the lactones were substituted only on the carbon adjacent to the etheric moiety. Often chiral disubstituted γ-lactones are required, in particular the γ-substituted derivatives of α-aminobutyrolactones, which are useful for synthesis of unnatural aminoacids and as building blocks for synthesis of pharmaceuticals. In the present communication we report our results on the PPL catalysed stereospecific hydrolysis of γ-substituted derivatives of α-aminobutyrolactones.

The racemic substrates were prepared by published methods: **1a** and **1b** by a modification of the Schotten-Baumann procedure, while **1c-1e** were prepared following Ben-Ishai's amidoalkylation methodology.[5] Their hydrolysis with PPL proceeded smoothly either on the purified cis isomers (**1c-1d**) or directly on a 65/35 cis/trans diastereomeric mixture (**1e**)[6]. No cis-trans isomerisation was observed under the reaction conditions. In a representative enzymatic experiment 1.5 mmoles of the lactone were added to a suspension containing 1 g crude PPL in 7 ml of distilled water after the pH was adjusted to 7.5. The mixture was stirred at 25 °C, while maintaining the pH at 7.5 with a 0.5M solution of NaOH using an automatic titration system. The unreacted lactone was continuously extracted with ether. The aqueous solution was acidified to pH 2 and the lactone formed from the hydroxyacid product was continuously extracted with ether. In all cases both enantiomers of the lactones were isolated in 60-90% yields by chromatography on preparative silica-gel plates eluting with a mixture of EtOAc:CH_2Cl_2 3:8, and the ee values were determined by NMR in the presence of the chiral shift reagent Eu(tfc)$_3$.

As is seen from the table, PPL-catalysed hydrolysis of monosubstituted α-amino lactones **1a** and **1b** was enantioselective and, as expected, the natural L enantiomer reacted in preference. PPL was also highly enantioselective for the disubstituted lactones **1c-1e**. Since the latter two compounds have not been reported in chiral form their absolute configurations are not known, however the hydrolysed **1c** and **1d** are is assigned the 2R,4S absolute configuration by comparison with literature data.[7] Of particular interest is entry 6, in which the cis isomer of **1e** was hydrolysed with a higher than 90% enantioselectivity. Extension of this method to preparation of other practically useful, chiral disubstituted lactones is under active investigation in both our laboratories.



entry	substrate	time (hrs)	% convers.	ee of unreacted lactone ($[\alpha]_D^{26}$)	ee of lactonised (2) ($[\alpha]_D^{26}$)
1[a]	1a, R=H, X=Ph	30	45	45[c,d] (+10.1°)	54[c,d] (-11.7°)
2[a]	1a, R=H, X=Ph	26	40	43[c,d] (+9.7°)	59[c,d] (-12.8°)
3	1b, R=H, X=OMe	6	50	62[d]	71[d,e] (-5.6°)
4[a]	1c, R=Me, X=Ph	32	34	29[d]	56[d] (+24.4°)
5[a]	1d, R=Ph, X=OMe	27	27	32[d]	86[d] (+31.1°)
6[b]	1e, R=CH=CH_2, X=OMe	10	50	95[d,f]	90[d,f] (+9.7°)

a. 1 ml of acetone was added to the reaction mixture to increase the solubility of the substrate.
b. **1e** was a 65:35 mixture of cis/trans isomers.
c. Compared with reported values of optical rotation in methanol: for L, $[\alpha]_D$=-21.5° and for D, $[\alpha]_D$=+22.5° (ref. 4). All other $[\alpha]_D$ values were determined in CH_2Cl_2 (c=1).
d. Calculated on the basis of NMR in the presence of the chiral shift reagent, following the unequal shifts of Me groups or γ-hydrogens of the two enantiomers.
e. The authentic L isomer of **1b**, prepared from L homoserine lactone, was found to have $[\alpha]_D$=-6.8° in CH_2Cl_2.
f. For the cis isomer. The trans isomer reacted more slowly and with a lower stereospecificity (ee approx. 30%).

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6. Cis-**1c** was obtained by hydrogenolysis of the unsaturated substrate,[5a] and cis-**1d** by recrystallisation of the less soluble cis isomer; **1e** was obtained and submitted to enzymatic hydrolysis as a 65:35 mixture of cis/trans isomers.
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