Enantioselective Hydrolysis of Racemic Diesters by Porcine Pancreatic Lipase

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Porcine pancreatic lipase catalysed hydrolysis of dimethyl succinates, aspartates, and glutamate provides (*R*) and (*S*) methyl esters enantioselectively.

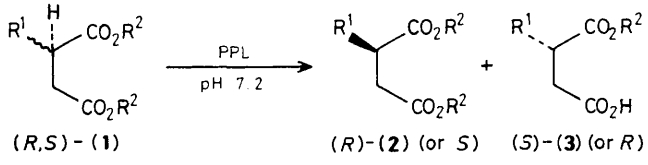
Utilization of enzymes in organic synthesis to prepare chiral compounds of synthetic value is well documented.[1] It has been recently reported that the inexpensive commercially available porcine pancreatic lipase (PPL; E.C.3.1.1.3) catalyses specifically the hydrolysis of esters of racemic alcohols[2] and *meso* diols.[3] In contrast with α-chymotrypsin,[4] liver esterase,[1] and microbial lipases,[5] PPL hydrolyses α-substituted carboxylic esters with low chemical and optical yields.[5,6]

We now report that PPL can catalyse the regio- and enantio-selective hydrolysis of some racemic dimethyl

Table 1. Chiral esters from PPL hydrolysis.

	Substrate		Reaction conditions[c] Conc. of (**1**)/ mol dm^{-3}	Lipase ratio/[d] g mmol^{-1} (**1**)	$t_{1/2}$/h	Yields (**2**)/%	E.e./%[e]
	R^1	R^2					
(**1a**)	Me	Me	0.62	0.04	7.5	93	95
(**1b**)	Me	Et	0.53	0.06	14	78	75
(**1c**)	Me	Bu	0.55	0.07	32	96	21
(**1d**)	Benzyl	Me	0.33	0.15	13	90	98
(**1e**)	Allyl	Me	0.33	0.15	7	80	5[f]
(**1f**)	n-Butyl	Me	0.33	0.15	17	85	40[f]
(**1g**)	NHZ[a]	Me	0.33	0.15	4	90	100
(**1h**)	NHAc	Me	0.33	0.07	0.13	90	100
(**4**)	AcGlu(OMe)$_2$[b]		0.33	0.06	2	90	100

[a] Z = benzyloxycarbonyl. [b] AcGlu(OMe)$_2$ = dimethyl *N*-acetyl glutamate. [c] All hydrolysis performed in 0.1 M KH_2PO_4 at room temp. (18—20 °C); 100—200 mmol [(**1a**—**c**)] or 10 mmol scales [(**1d**—**h**), (**4**)] at pH 7.2 (maintained by an automatic burette). The reaction was stopped when 0.50—0.55 equiv. of 2 M NaOH was consumed, and worked-up under standard conditions. [d] PPL was purchased from Sigma. [e] Determined by ^{1}H n.m.r. spectroscopy (250 MHz) in the presence of tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]-europium(III), Eu(hfc)$_3$ (20—30% mol/mol) on the purified product, or by comparison of the optical rotations of (**2b**), (**2c**) unequivocally prepared following the procedure in ref. 7. [f] The hydrolysis was also non-regioselective.



alkylsuccinic, *N*-protected aspartic, and glutamic esters.

We have obtained from (*R*,*S*)-dimethyl methylsuccinate (**1a**) the unhydrolysed ester (*R*)-(**2a**)[8] (93%) with an enantioselectivity higher than 95%† ([α]$_D$ +4.75, *c* 2.9, $CHCl_3$) and, after acidification of the aqueous phase, the half ester (*S*)-(**3a**)[9] (76%). Esterification of (*S*)-(**3a**) by diazomethane gave the dimethyl methylsuccinate (*S*)-(**2a**).[10] The optical purity [73% enantiomeric excess (e.e.)] was improved by a second PPL hydrolysis, which led to (*S*)-(**3a**) (>96% e.e.) ([α]$_D$ = −10.04, *c* 2.5, $CHCl_3$; lit.[9] [α]$_D$ −9.3, *c* 17.5, $CHCl_3$). Treatment with diazomethane gave the diester (*S*)-(**2a**) with ≥96% e.e. ([α]$_D$ −4.90, *c* 2.9, $CHCl_3$). Hydrolysis of (**1a**) by α-chymotrypsin has been reported previously, providing (*R*)-(**2a**) (76% e.e.) and a regioisomeric half-ester, *i.e.*, the β-methyl α-methylsuccinate (70% e.e.).[4]

However, (*R*,*S*)-diethyl (**1b**) and dibutyl methylsuccinate (**1c**) underwent PPL hydrolysis more slowly than (**1a**), providing (*R*)-(**2b**) and -(**2c**) with 75 and 21% e.e. respectively (see Table 1). The rate and the enantioselectivity of the PPL hydrolysis was also influenced by the nature of the substituent R^1 of the diester (**1**). Thus, while dimethyl benzylsuccinate (**1d**) appeared to be an excellent substrate leading to (*S*)-(**2d**) (≥98% e.e., 90% yield) ([α]$_D$ −27.3, *c* 4.5, $CHCl_3$)[4] the dimethyl allyl- (**1e**) and butyl-succinate (**1f**) were hydrolysed with low selectivity.

Only L-amino acid derivatives were hydrolysed, but in the α-position. A bulky *N*-protecting group reduced the hydrolysis rate [compare *N*-benzyloxycarbonyl (**1g**) and *N*-acetyl-aspartate (**1h**)] but did not affect its enantioselectivity. An identical result was observed with a γ-diester: *i.e.*, the dimethyl *N*-acetylglutamate (**4**). However unprotected dimethyl aspartate and glutamate underwent the hydrolysis without selectivity and β-methyl aspartate was not a substrate for PPL.

In conclusion, we have carried out for the first time PPL enantioselective carboxylate hydrolysis at a β chiral centre, and the resolution of α-amino esters by means of a cheap and convenient reagent.‡ Synthetic applications of these useful chiral blocks and the results of PPL transesterification will be published elsewhere.

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† See footnote e in Table 1.

‡ PPL is respectively 10^6 and 10^4 times less expensive than pig liver esterase (PLE) and α-chymotrypsin for a standard enzymatic activity (see ref. 1a).