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Differential Effects of Stereochemistry and C-4 Substituents on the Enantioselectivity of PLE and PPL Catalysed Hydrolysis of 3,4-Disubstituted β-lactams

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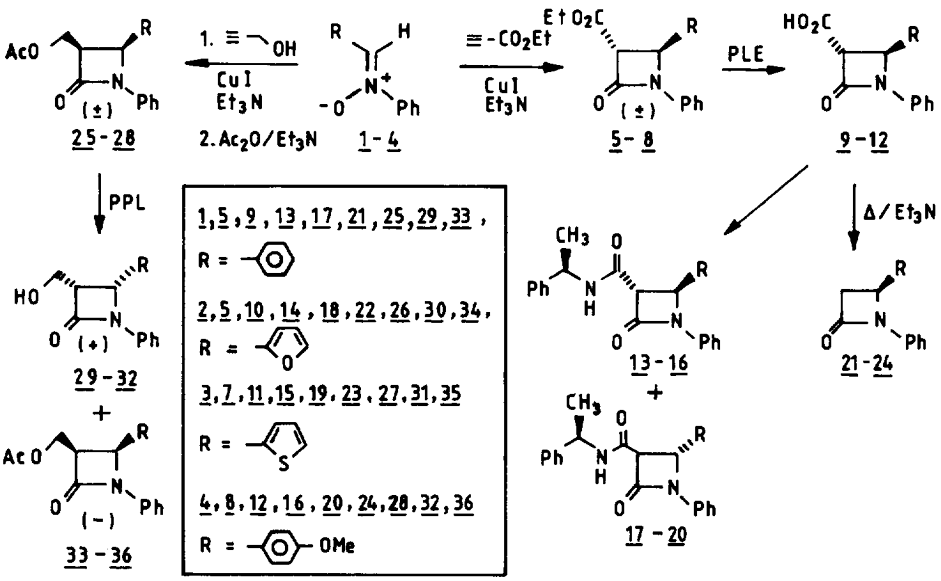
Abstract: Pig Liver Esterase (PLE) and Pig Pancreas Lipase (PPL) catalysed hydrolysis of (±)trans-3-carbethoxy and (±)cis-3-acetoxymethyl 4-substituted β-lactams revealed interesting dependence on C-3, C-4 stereochemistry and nature of C-4 substituents. © 1997, Elsevier Science Ltd. All rights reserved.

Recently β-lactams have been extensively used as synthons for various natural products[1] e.g. the side chain of taxol[2], the anticancer drug and bestatin[3], peptide enzyme inhibitor. We wish to report our own endeavour in the synthesis of functionalized β-lactams in homochiral forms, intended for the construction of new side chain analogues of taxol to study the structure-activity relationship[4].

We adopted the strategy of enantioselective enzyme-catalysed hydrolysis. Two classes of 3,4-disubstituted β-lactams **5-8** and **25-28** having trans-3-carboethoxy and cis-3-acetoxymethyl substituents respectively were prepared[5,6] and then subjected to PLE[7] and PPL[8]-catalysed hydrolysis in phosphate buffer at pH 8.0. The reactions were stopped after about ~50% conversion. In case of 3-carboethoxy β-lactams **5-8** the acids and the unconverted esters were separated by pH adjustments followed by solvent extraction. The enantiomeric excess was determined by converting the free acids to the diastereomeric amides **13-16** and **17-20** and their ratios determined by 200 MHz NMR. The hydrogens at C-3 and C-4 as well as the methyl signals for the amides appeared as separate doublets. The results are shown in Table 1. In all the cases, PPL failed to show any degree of enantioselectivity. However, with PLE moderate enantioselection was observed for esters **6** and **7** substituted at C-4 with small heterocyclic rings like furan or thiophene. Incorporation of conventional aromatic rings like phenyl or *p*-methoxyphenyl at C-4 led to racemic acid during hydrolysis.



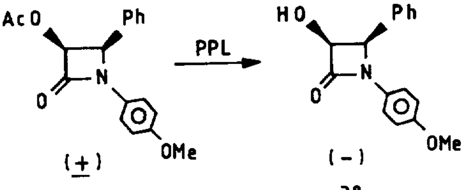
Scheme 1

Table 1

Substrate	Product (yield %)	% ee	Decarboxylated product	[α]D
5	9 (49)	0	21	-
6	10 (47)	50	22	-37.5°
7	11 (50)	50	23	-40.0°
8	12 (51)	0	24	-
25	29 (52)	83	-	+91.4°
26	30 (48)	84	-	+69.5°
27	31 (49)	85	-	+172.2°
28	32 (51)	>98	-	+117.4°

Hydrolysis of the acetates 25-28, on the other hand, showed complete reversal of enzyme selectivity. In these cases, practically no enantioselectivity was observed with PLE as revealed by negligible optical rotation and also by ^{1}H NMR in the presence of chiral shift reagent.[9] However with PPL the enantioselectivity dramatically improved (Table 1). In these cases, the alcohols 29-32 and the unhydrolysed acetates 33-36 were separated by chromatography and then checked for enantiomeric purity.

The absolute configurations of alcohols **29-32** and the acetates **33-36** have been tentatively assigned by comparing their sign of rotation with that of similarly substituted analogues[2]. The configurations of **10** and **11** were assigned from the sign of rotation[10] of their decarboxylated products **22** and **23**. The configurations of the alcohols **29-32** matched with that predicted from the active site model of PPL[11]. Interestingly, Sih et al.[2] in their quest to synthesize taxol side chain, observed preferential hydrolysis of 3S,4R-3-acetoxy-4-phenyl β-lactam **37** with PPL. Thus there is complete reversal of selectivity as a 3-acetoxy group is replaced by an acetoxymethyl.



(±)
37

(-)
38

In conclusion we have demonstrated the highly enantioselective preparation of cis-3-hydroxymethyl-β-lactams with a variety of substituents at C-4 via PPL catalysed hydrolysis of the corresponding acetates. We have also demonstrated an interesting dependence of *ee* on the nature of substituent at C-4 during PLE catalysed hydrolysis of the trans 3-esters.

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