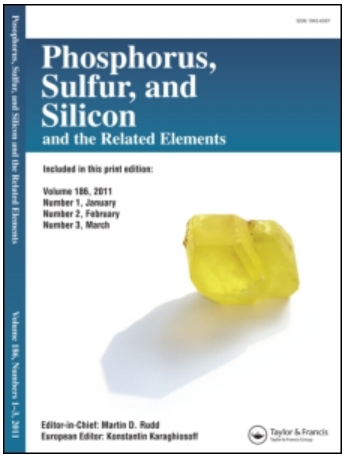

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ENZYMATIC SYNTHESIS OF CHIRAL, NON-RACEMIC PHOSPHORYL COMPOUNDS

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Abstract: A series of phosphinyl-, phosphonyl- and phosphorylacetates was hydrolyzed in the presence of Pig Liver Esterase (PLE) to give the corresponding P-chiral phosphoroacetic acids and unreacted esters in a high enantiomeric purity (up to 100% ee).

Chiral phosphine oxides constitute a very important class of chiral phosphorus compounds which are widely used in synthetic and stereochemical studies. Chiral phosphine oxides are used as chiral auxiliaries in stoichiometric reactions[1] and they are the best precursors of chiral phosphines which, in turn, are usually applied as chiral ligands in transition metal catalyzed reactions.[2] Therefore, a search for new, efficient and general methods of the synthesis of chiral phosphine oxides continues.

Recently, the enzyme-mediated hydrolysis reactions have been proven to be suitable for the generation of chiral heteroatomic centers. This approach was successfully applied to the synthesis of chiral sulfinyl carboxylates[3], hydroxymethylsilanes[4,5] and hydroxymethylgermanes.[6] Our recent work has demonstrated that enzyme-promoted hydrolysis of prochiral sulfinyldiacetate $(MeO_2CCH_2)_2SO$, is also very effective (ee up to 92%) in the preparation of both enantiomers of the corresponding carboxy-sulfoxide.[7]

These results prompted us to extend our investigations to phosphorus compounds having a stereogenic phosphinyl group. In the first instance, we decided to study the enzymatic hydrolysis of prochiral phosphinyldiacetates **1**. These compounds were obtained by a Reformatsky-type reaction of dichlorophosphines with alkyl bromoacetates.[8]

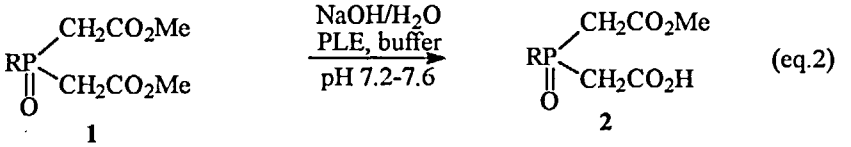
$$RPCl_2 + 2BrCH_2CO_2R^1 \xrightarrow[45\text{-}64\%]{\begin{array}{c}1.\ Zn\\ 2.\ [O]\end{array}} \underset{\underset{O}{\|}}{RP}(CH_2CO_2R^1)_2 \quad \text{(eq.1)}$$

1

R=Ph,Et,BuO

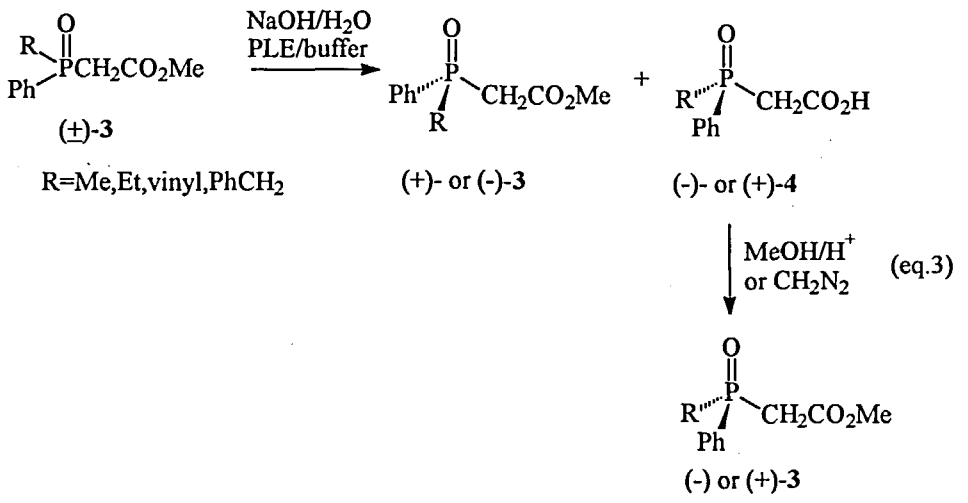
R^1=Me,Et

However, in contrast to prochiral sulfinyldiacetates, the PLE-catalyzed hydrolysis of prochiral phosphinyldiacetates **1** was found to proceed slowly and with very low enantioselectivity affording the products **2** with enantiomeric excess values not exceeding 10%.



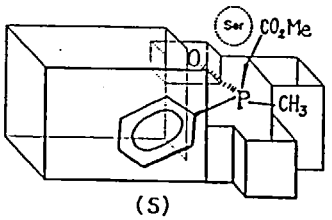
1 2 (eq.2)

Therefore, we turned our attention to a different type of phosphinyl substrates, namely racemic phosphinylacetates **3**. In this case, the enzymatic hydrolysis was performed under kinetic resolution conditions, that is it was stopped after ca. 50% conversion. It was gratifying to find that the PLE-promoted hydrolysis of **3** proceeded smoothly and gave both the unreacted ester **3** and the corresponding acid **4** in good yields and with high enantioselectivity (ee up. to 100%).[9]



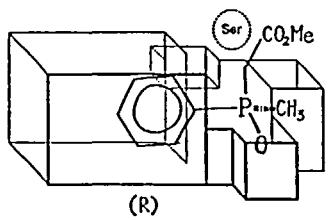
By means of chemical correlation and circular dichroism (CD) spectra we were able to determine absolute configuration of the chiral products **3** and **4**. It turned out that all the recovered esters **3** have the same spatial arrangement of substituents around chiral phosphorus (as depicted in equation 3). This means that within the series of substrates investigated, enantiomers of the same spatial structure are recognized by PLE.[9]

Although the X-ray crystal structure of PLE is not known, extensive studies of Jones and his coworkers[10] on the PLE-catalyzed reactions of chiral and prochiral substrates led them to propose the active-site model of Pig Liver Esterase. Application of this model to our case requires that the methoxycarbonyl group should be located within the spherical locus of the catalytically active serine function (Fig.1). Taking into account the chirality at phosphorus in the ester **3**, which undergoes hydrolysis, the phenyl group should be accommodated in the large hydrophobic pocket (H_L), the alkyl group in the small hydrophobic pocket (H_S) and the phosphoryl oxygen in the back polar pocket (P_B) (Fig.1a). The alternative binding mode (Fig.1b) required for hydrolysis of the ester **3** with opposite configuration at phosphorus would change the position of the phosphoryl oxygen from the H_B- to H_F-pocket. The reason why the first binding mode is strongly preferred is not clear now.



(S)

Fig 1a

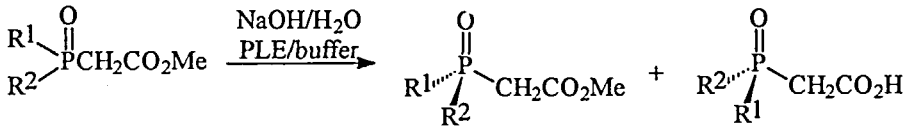


(R)

Fig 1b

To broaden the spectrum of chiral phosphorus substrates, our investigations were extended to phosphonyl- and phosphorylacetates **5**. It was found that in the majority of cases the PLE-mediated hydrolysis is enantioselective and affords the products in good yields.

However, enantiomeric excess values of the chiral products **5** and **6** are generally lower, an exception being **5a** (ee~95%). Determination of the chirality at phosphorus in these compounds is under way.



(±)-5 (+)- or (-)-5* (-)- or (+)-6*

Substrate	R^1	R^2	pH	Time [h]	Ester 5*			Acid 6*		
					Yield [%]	$[\alpha]_D$ (MeOH)	ee [%]	Yield [%]	$[\alpha]_D$ (MeOH)	ee [%]
5a	Ph	MeO	7.5	15	40	-16.1	~95	44	+9.1 +10.8[a]	~64
5b	Ph	EtO	7.2	48	46	-11.3	~67	40	+13.1 +11.8[a]	~71
5c	Et	MeO	7.2	1.5	50	+8.5	~38	34[a]	-10[a]	42
5d	Et	EtO	7.2	48	40	+1.9	-	60[a]	-14[a]	-
5e	Et_2N	MeOH	7.5	7	20	-21.7	~90	58	+5.8	-
5f	PhO	EtO	7.1	45	66	-3.0[b]	~20	22	+8.7[b]	52

a) after reesterification
b) in $CHCl_3$

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