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Enzymatic Resolution of Racemic Phosphinoylacetates Having a Stereogenic Phosphorus Atom[1]

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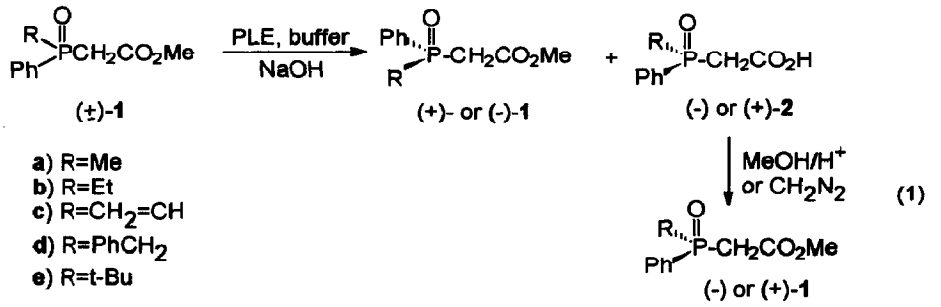
Abstract: A series of racemic methyl alkylphenylphosphinoylacetates was hydrolyzed in the presence of pig liver esterase (PLE) to give the corresponding P-chiral phosphinoylacetic acids and unreacted esters in a high enantiomeric purity (72-100% ee).

Enzyme mediated hydrolytic reactions are of great synthetic value because they have been used for the preparation of a large number of chiral carbon compounds.[2] Recently, this approach has also been successful with heteroorganic substrates having stereogenic sulfur and silicon atoms. Thus, racemic sulfinylacetates[3,4] and 2-sulfinylbenzoates[5] as well as silylmethanols[6] were efficiently resolved into enantiomers using various hydrolytic enzymes under kinetic resolution conditions. Chiral silylmethanols were also obtained via enzymatic acetylation of prochiral di(hydroxymethyl)silanes.[7] Our recent work[1] has demonstrated that enzyme-promoted hydrolysis of prochiral dimethyl sulfinyldiacetate is very effective in the preparation of both enantiomers of the corresponding carboxy-sulfoxide.

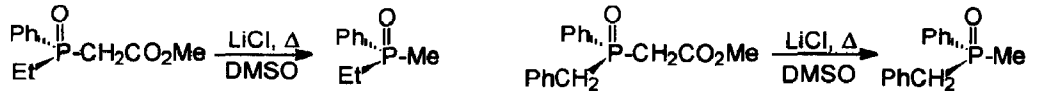
The above results prompted us to extend our studies to phosphorus compounds and to investigate a series of racemic phosphinoylacetates **1** having a stereogenic phosphine oxide group with respect to substrate behaviour and enantioselectivity in an enzyme-catalyzed hydrolytic reaction. In this context, it should be noted that chiral phosphine oxides constitute a very important class of chiral phosphorus compounds, particularly as precursors of chiral phosphines[8] which, in turn, are widely used as chiral ligands in the transition metal catalysts.[8,9] Therefore, a search for efficient and general methods of the synthesis of chiral phosphine oxides continues.[10]

The racemic methyl phosphinoylacetates **1a-e**[11] were hydrolyzed in the presence of pig liver esterase (PLE) at room temperature in phosphate buffer ($NaOH$-KH_2PO_4) solutions using automatic titrator to control the pH stability. In some cases the reaction was carried out in the presence of toluene as a co-solvent. It should be noted that no hydrolysis was observed under these conditions in the case of the phosphinoylacetate **1e**. After completion of the reaction (ca.50% conversion) the unreacted esters **1** were extracted with chloroform, dried over $MgSO_4$ and purified by column chromatography. The remaining aqueous layers were acidified with H_2SO_4 to pH≈ 2 and either extracted with chloroform or lyophylized. The acids **2** obtained were purified by column chromatography and esterified either by the reaction with diazomethane or with an excess of methanol in the presence of a catalytic amount of sulfuric acid. The methyl esters **1** thus obtained were again purified by column chromatography.



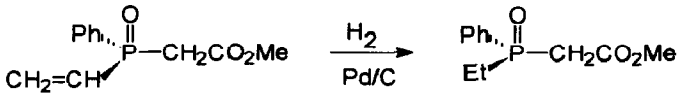
The enantiomeric excess (ee) values of the recovered chiral phosphinoylacetates **1a-d** were determined by means of ^{1}H-NMR spectra (300 MHz, $CDCl_3$) of their complexes formed with (-)-(*S*)-t-butylphenylphosphinothioic acid.[14] The results obtained are summarized in the Table.

In order to establish the absolute configuration of the products, the chiral phosphinoyl acetate (+)-**1b** obtained from the enzymatic hydrolysis was subjected to decarboxylation[15] to give ethylmethylphenylphosphine oxide (-)-**3**. Since the absolute configuration of the latter is known to be (*S*),[16] the (*R*) chirality at phosphorus can be ascribed to the investigated enantiomer (+)-**1b**. In a similar way the absolute configuration of **1d** was determined as (-)-(*R*)[16]



(+)-(*R*)-**1b**, $[\alpha]_D$ +7.3 (-)-(*S*)-**3**, $[\alpha]_D$ -12.2 (-)-(*R*)-**1d**, $[\alpha]_D$ -27.8 (-)-(*S*), $[\alpha]_D$ -41.4

Reduction of (-)-**1c** gave, in turn, (+)-**1b** which allowed to ascribe the (*S*) chirality to (-)-**1c**.



(-)-(*S*)-**1c**, $[\alpha]_D$ -54 (+)-(*R*)-**1b**, $[\alpha]_D$ +10.2

Moreover, we have recorded circular dichroism (CD) spectra of the chiral acetates **1a-d** (Figure). Since the CD spectra of the structurally closely related phosphine oxides (+)-**1a** and (+)-**1b** are practically identical and show the same sign of the Cotton effect, it is reasonable to propose that the absolute configuration at phosphorus in (+)-**1a** is also (*R*).

It is interesting to note that the arrangement of substituents around chiral phosphorus in all recovered esters is the same although the signs of the Cotton effect and optical rotation for **1a** and **1b** are opposite to those of **1c** and **1d**. This means that within the series of substrates investigated, enantiomers of the same spatial structure are recognized by PLE.

In conclusion, it has been demonstrated that enzymatic hydrolysis of racemic phosphinoylacetates

TABLE: Enzymatic hydrolysis of Phosphinoylacetates 1

Phos-phine oxide	Reaction conditions			Recovered Ester 1				Acid 2			
	pH	Conc. of enzyme [µl/mmol]	Time [h]	Yield [%]	$[\alpha]_D$ MeOH	e.e. [%]	Abs. conf. [c]	Yield [%]	$[\alpha]_D$ MeOH	e.e. [%]	Abs. conf.[e]
1a	7.5	120	139	50	+20.2	73.6[b]	R[f]	41.7[a]	-22.2[a]	82.0[a,c]	S[f]
1a	7.5	110	140	45	+22	81.7[b]	R[f]	-	-	-	
1b	7.0	56	6	50.8	+7.3	71.6[b]	R	18	-22.1		S
1b	7.0	50	8	45	+9.7	>96[b,c]	R	41[a]	-8.2[a]	81[a,c]	S
1c	7.0	35	4	35.7	-51.8	>96[b]	S	22.4	+54.5		R
1c	7.1	45	4	40.1	-54	~100	S	18	+36		R
1d	7.0[d]	40	8	46	-23.3	80[b]	R	43	+19.6 +21.7[a]	78.8[a,b]	S

a) The acid transformed into ester; data concern the ester; b) from ^{1}H-NMR using (-) *t*-BuPhP(S)OH as a chiral agent; c) calculated on the basis of the rotation predicted for the pure enantiomer; d) a mixture of a buffer and toluene; pH is an apparent value shown by the titrator; e) see the text, f) assigned from CD comparison alone.

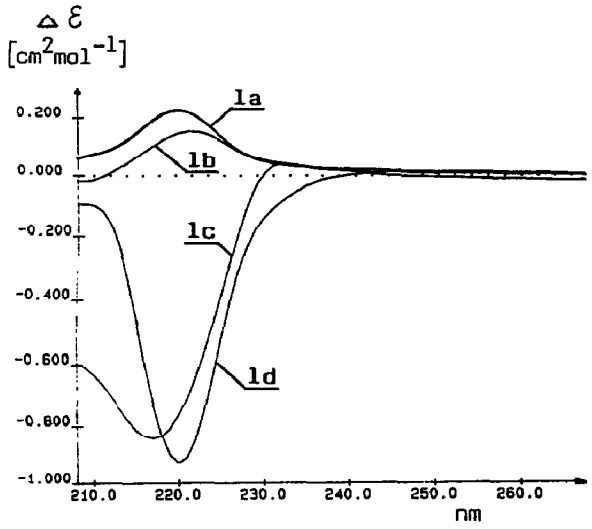


Figure. CD spectra (in MeOH) of the recovered esters: (+)-**1a**, (+)-**1b**, (-)-**1c** and (-)-**1d**.

provides a convenient access to the resolved esters as well as to the corresponding acids, both in a high enantiomeric purity. In the P^{III} forms, these compounds should find immediate utility in homogeneous catalysis as P-chiral hemilabile P,O-ligands.[17] To the best of our knowledge, this is the first report on the enzymatic resolution of phosphorus compounds having a stereogenic phosphine oxide group.

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REFERENCES AND NOTES

1. Part II in the series: Enzymatic Heteroatom Chemistry; for part I see: Mikołajczyk,M.; Kiełbasiński,P.; Żurawiński,R.; Wieczorek,M.W. and Błaszczyk,J. *Synlett* **1994**, 127.
2. For recent reviews see: Faber,K.; "Biotransformations in Organic Chemistry", Springer Verlag, Berlin 1992; Santaniello,E.; Ferraboschi,P.; Grisenti,P. and Manzocchi,A. *Chem.Rev.* **1992**, *92*, 1071.
3. Ohta,H.; Kato,Y.; and Tsuchihashi,G. *Chem.Lett.* **1986**, 217.
4. Burgess,K., Henderson,J. and Ho,K.K. *J.Org.Chem.* **1992**, *57*, 1290; Burgess,K. and Henderson,I.; *Tetrahedron Letters* **1989**, *30*, 3633.
5. Allenmark,S. and Andersson,A.C. *Tetrahedron: Asymmetry* **1993**, *4*, 2371.
6. Fukui,T., Kawamoto,T. and Tanaka,A. *Tetrahedron: Asymmetry* **1994**, *5*, 73.
7 Djerourou,A.H. and Blanco,L. *Tetrahedron Letters* **1991**, *32*, 6325.
8. Kagan,H.B. and Sasaki,M. in "The Chemistry of Organophosphorus Compounds", vol. 1., F.R.Hartley (Ed.); Patai,S. (series Ed.), J.Wiley & Sons, 1990, p.51.
9. Noyori,R. Kitamura,M.; in "Modern Synthetic Methods 1989", vol.5, Scheffold,R.; (Ed.), Springer Verlag, Berlin 1989, p.115.
10 For a recent review see: Gallagher,M.J.; in "The Chemistry of Organophosphorus Compounds", Hartley,F.R ; (Ed.), J.Wiley & Sons, 1992, chapter 2; Pietrusiewicz,K.M. and Zabłocka,M. *Chem.Rev.* in press.
11 For the synthesis of racemic **1a** and **1c** a procedure developed earlier for **1c** was employed.[12] Phosphinoylacetate **1b** was obtained by hydrogenation of **1c** over Pd/C.[12] Phosphinoylacetates **1d** and **1e** were prepared from the corresponding secondary phosphine oxides by the Michaelis-Becker reaction with methyl chloroacetate.[13]
12. Bodalski,R.; Rutkowska-Olma,E. and Pietrusiewicz,K.M. *Tetrahedron* **1980**, *36*, 2353.
13. Imamoto,T.; Sato,K ; and Johnson,C.R. *Tetrahedron Letters* **1985**, *26*, 783.
14. For recent applications of optically active *t*-butylphenylphosphinothioic acid as a chiral agent in the NMR determination of enantiomeric excess see: Mikołajczyk,M.; Omelańczuk,J.; Perlikowska,W.; Markovski,L.N.; Romanenko,V.D.; Ruban,A.V. and Drapailo,A.B. *Phosphorus Sulfur* **1988**, *36*; Drabowicz,J.; Dudziński,B. and Mikołajczyk,M. *Tetrahedron: Asymmetry* **1992**, *3*, 1231.
15 Pietrusiewicz,K.M.; Zabłocka,M. and Monkiewicz,J. *J.Org.Chem.* **1984**, *49*, 1522; Krapcho,P.A.; Weimaster,J.F.; Eldridge,J.M.; Jahngen, Jr.,E.G.E.; Lovey,A.J. and Stephens,W.P. *J.Org.Chem.* **1978**, *43*, 138.
16. Korpiun,O.; Lewis,R.A.; Chickos,J. and Mislow,K. *J.Am.Chem.Soc.* **1968**, *90*, 4842.
17. For leading references on the use of achiral phosphinoacetate ligands see: Britovsek,G.J.P.; Keim,W.; Mecking,S.; Sainz,D. and Wagner,T. *J.Chem.Soc., Chem.Commun.* **1993**, 1632; Keim,W.; *Angew.Chem., Int.Ed.Engl.* **1990**, *29*, 235; Braunstein,P.; Matt,D.; Nobel,D.; Bouaoud,S.-E. and Grandjean,D. *J.Organomet.Chem.* **1986**, *301*, 401.

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