Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 2641–2650

TETRAHEDRON: *ASYMMETRY*

# Enzyme-promoted kinetic resolution of racemic, P-chiral phosphonyl and phosphorylacetates

Piotr Kiełbasiński,[a,*] Piotr Góralczyk,[a] Marian Mikołajczyk,[a] Michał W. Wieczorek[b] and Wiesław R. Majzner[b]

[a]*Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Sienkiewicza 112, 90-363 Łódź, Poland*
[b]*Institute of General Food Chemistry, Technical University, Stefanowskiego 4/10, 90-924 Łódź, Poland*

Received 19 May 1998; accepted 25 June 1998

**Abstract**

A series of racemic methyl phosphonyl- and phosphorylacetates were hydrolyzed in the presence of porcine liver esterase (PLE) under kinetic resolution conditions to give the corresponding P-chiral phosphonyl- and phosphorylacetic acids and recovered esters in moderate to high enantiomeric purity (up to 95% ee). The Jones PLE active site model was applied to explain the enantioselectivity of this reaction. 

## 1. Introduction

Enzymes, the proteins created by nature to catalyze chemical reactions occurring in living organisms, have recently become common reagents for the transformation of man-made organic compounds.[1–3] As enzymes are intrinsically chiral, they have mainly been applied in the synthesis of optically active molecules, using both racemic and prochiral substrates. In addition to hundreds of examples of enzyme-promoted syntheses of non-racemic C-chiral products, in recent years the preparation of several classes of heteroorganic compounds, with a sole center of chirality located on the heteroatom, such, as sulfur, silicon, germanium and phosphorus, has also been achieved.[4]

Within this subject area we have demonstrated the applicability of enzymatic methods in the preparation of optically active sulfoxides[5] and phosphine oxides.[6,7] In the latter case, a series of racemic methyl phosphinylacetates was hydrolyzed in the presence of porcine liver esterase (PLE) under kinetic resolution conditions to give the corresponding P-chiral phosphinylacetic acids and recovered esters in 72–100% enantiomeric purity. Stereoselectivity of this reaction was explained[7] in terms of the Jones' PLE active site model,[8] originally developed for substrates with a stereogenic carbon.

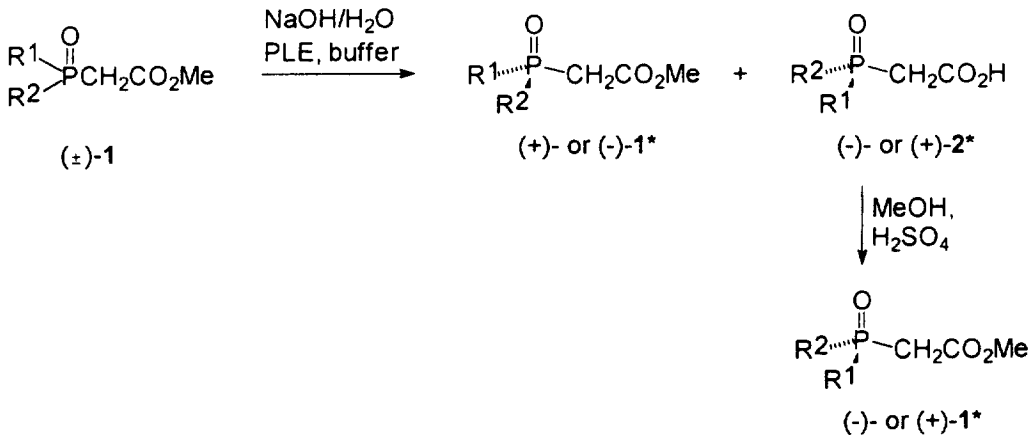
* Corresponding author. E-mail: piokiel@bilbo.cbmm.lodz.pl

0957-4166/98/$ - see front matter 
*PII:* S0957-4166(98)00258-4

The aim of our present study was to determine the scope of the above reaction and to gain more data which would allow a general explanation of the stereoselectivity observed to be formulated. Herein we would like to disclose the detailed results of the investigations on the PLE promoted hydrolysis of phosphonyl- and phosphorylacetates.[9]

## 2. Results and discussion

The racemic phosphonyl- and phosphorylacetates **1a–i** were subjected to hydrolysis in the presence of PLE at 30°C in phosphate buffer, using an automatic titrator to maintain the appropiate pH value. The reaction was generally carried out until 50% conversion was reached, although in some cases, when the hydrolysis was very slow, it was stopped earlier. The reaction was then quenched by additon of excess acetone and cooling the solution to below 0°C for a few hours. The precipitate formed was filtered off and the acetone evaporated. The unreacted ester was extracted with dichloromethane and the aqueous layer acidified with sulfuric acid to pH≈3 and lyophilized. Since the acids **2*** formed were generally difficult to purify, they were reesterified with an excess of methanol in the presence of a catalytic amount of $H_2SO_4$. Both enantiomerically enriched esters thus obtained were purified by column chromatography (Eq. 1, Table 1).




(1)

The enantiomeric excess (ee) values of **1** were determined by means of $^1$H-NMR spectra of their complexes with (−)-(*S*)-*t*-butylphenylphosphinothoic acid which has recently been widely used as a versatile chiral solvating agent.[10] An inspection of Table 1 reveals that the ee values of the products obtained are generally moderate, the exceptions being **1a** and **1i**, where ee exceeds 90%. This is in contrast to the high stereoselectivity observed in the case of phosphinylacetates described previously.[6,7] As the lower stereoselectivity is accompanied by a severe drop in the reaction rate, a competing, non-enzymatic hydrolysis had to be excluded. To this end, a background reaction was conducted under the enzymatic reaction conditions applied (pH up to 7.6) and showed that no hydrolysis of **1c**, used as an example, took place after 140 hours.

Nevertheless, it was necessary to establish the absolute configuration of the products in order to find out whether there is any general relationship between the substrate structure and product configuration. This was achieved for the unreacted esters **1*a–e** and acids **2*a–e**. Thus, the absolute configuration of **2*a** was known from the literature to be (+)-(*R*).[11] The absolute configuration of **2*b** was determined on the basis of chemical correlation, consisting of decarboxylation of (+)-**2*b**, using the conditions described earlier

Table 1
Enzymatic hydrolysis of phosphonyl- and phosphorylacetates **1**

| Substrate | $R^1$ | $R^2$ | pH | Time (h) | Recovered ester 1* | | | | Acid 2* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Yield (%) | $[\alpha]_D$ (MeOH) | e.e. (%) | Abs. conf. | Yield (%) | $[\alpha]_D$ (MeOH) | e.e. (%) | Abs. conf. |
| **1a** | Ph | MeO | 7.5 | 15 | 40 | - 16.1 | ~95 | *S* | 44 | +9.1<br>+10.8[a] | 64 | *R* |
| **1b** | Ph | EtO | 7.2 | 48 | 46 | - 11.3 | 67 | *S* | 40 | +13.8<br>+11.8[a] | 71 | *R* |
| **1c** | Ph | *n*-PrO | 7.2 | 120 | 69 | - 8.7 | 48 | *S* | 30[a] | +13.0<br>+9.1[a] | 50 | *R* |
| **1d** | Ph | *i*-PrO | 7.5 | 120 | 50 | - 5.8 | 26 | *S* | 47[a] | +3.0[a] | 14 | *R* |
| **1e** | Ph | *n*-BuO | 7.4 | 144 | 54 | - 3.0 | 30 | *S* | 33[a] | +4.0[a] | 40 | *R* |
| **1f** | Et | MeO | 7.2 | 1.5 | 50 | +8.5 | 38 | - | 34 | -10[a] | 42 | - |
| **1g** | Et | EtO | 7.2 | 48 | 40 | +1.9 | - | - | 60[a] | - 1.4[a] | - | - |
| **1h** | PhO | EtO | 7.1 | 45 | 66 | - 3.0[b] | 20 | - | 22 | +8.7[b] | 52 | - |
| **1i** | $Et_2N$ | MeO | 7.5 | 7 | 20 | - 21.7 | 90 | - | 58 | +5.8 | ~25 | - |

[a]after reesterification
[b]in $CHCl_3$

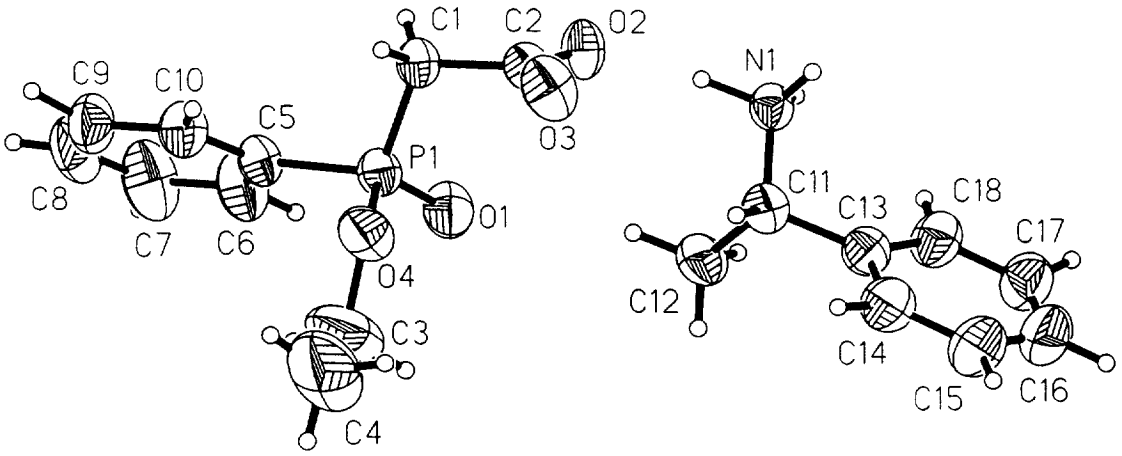
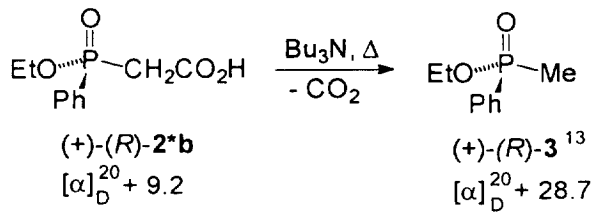



Fig. 1. Thermal ellipsoidal view with the atom numbering scheme of the salt of (+)-**2*b** with (−)-(*S*)-α-phenylethylamine. Ellipsoids are shown with 50% probability

for decarboxylation of α-carboxymethylsulfonium salts,[12] to the corresponding phosphinate **3** of known absolute configuration[13] (Eq. 2), and confirmed by an X-ray analysis performed for the diastereomerically pure salt of (+)-**2*b** with (−)-(*S*)-α-phenylethylamine (Fig. 1, Table 2).



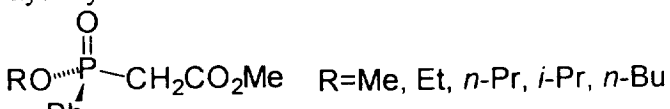

(+)-(*R*)-**2*b**
$[\alpha]_D^{20}$ + 9.2

(+)-(*R*)-**3** [13]
$[\alpha]_D^{20}$ + 28.7

(2)

In turn, the absolute configurations of **1*c**, **d**, **e** were ascribed by comparison of their CD spectra with those of **1*a** and **1*b**. It turned out that the CD curves of all the levorotatory unreacted esters were of the same shape and exhibited the same sign of Cotton effect. The same was valid for all the dextrorotatory esters obtained by re-esterification of acids **2*a–e**, the sign of the Cotton effect being obviously opposite in this case (Fig. 2).

Since all the compounds under discussion are closely related (the phosphorus atom is in each case connected with three identical substituents, the fourth one, i.e. an alkoxy group, differing only by the length or branching of the alkyl chain), one can assume with a high probability that the products exhibiting the same sign of specific rotation have the same absolute configuration at phosphorus. Thus, all the levorotatory esters **1*a–e** have (*S*) and the dextrorotatory ones (*R*) configuration. Moreover, an inspection of Table 1 clearly shows that in all cases the (*R*) enantiomers are recognized by PLE and hence are preferentially hydrolyzed.




(*R*)-**1**

The above regularity makes it possible to consider application of the Jones' model[8] to the phosphonylacetates investigated, as was done previously by us for phosphinylacetates[7] (Fig. 3).

Table 2
Crystal data and experimental details

| | | |
|---|---|---|
| Molecular formula | | $C_{18}H_{24}NO_4P$ |
| Formula weight | | 349.35 |
| Crystallographic system | | orthorhombic |
| Space group | | $P2_12_12_1$ |
| a (Å) | | 7.113(6) |
| b (Å) | | 14.010(7) |
| c (Å) | | 19.290(10) |
| V (Å$^3$) | | 1922(2) |
| Z | | 4 |
| $D_c$ (g/cm$^3$) | | 1.207 |
| $\mu$ [cm$^{-1}$] | | 14.36 |
| Crystal dimensions (mm) | | 0.16x0.16x0.80 |
| Maximum 2θ (°) | | 140 |
| Radiation, λ (Å) | | CuKα, 1.54184 |
| Scan mode | | ω/2θ |
| Scan width (°) | | 0.70+0.14·tanθ |
| *hkl* ranges: | *h* = | -8 0 |
| | *k* = | -17 0 |
| | *l* = | -23 23 |
| DECAY correction: | min. | 1.00005 |
| | max. | 1.02750 |
| | ave. | 1.01375 |
| EAC correction: | min. | 0.9644 |
| | max. | 0.9997 |
| | ave. | 0.9805 |
| No. of reflections: unique | | 3633 |
| with $I>0\sigma(I)$ | | 3419 |
| obs. with $I>2\sigma(I)$ | | 3316 |
| No. of parameters refined | | 304 |
| Largest diff. peak (eÅ$^{-3}$) | | 0.336 |
| Largest diff. hole (eÅ$^{-3}$) | | -0.832 |
| shift/esd max | | 0.000 |
| $R_{obs}$ | | 0.0580 |
| $wR_{obs}$ | | 0.1609 |
| $S_{obs}$ | | 1.122 |
| weighting coeff.* | m | 0.0956 |
| | n | 1.2574 |
| extinction coef.** | k | 0.009(10) |
| Flack χ (Ref. 19) | | -0.02(4) |
| $R_{int}$ | | 0.0361 |
| $T_{meas}$ | | 293(2) |
| F 000 | | 744 |

* weighting scheme $w=[\sigma^2(Fo^2)+(mP)^2+nP]^{-1}$
where $P=(Fo^2+2Fc^2)/3$

** extinction method SHELXL, extinction expression $Fc^*=kFc\,[1+0.001xFc^2\lambda^3/\sin(2\theta)]^{-1/4}$

Thus, the (*R*) enantiomers which undergo hydrolysis faster than the (*S*) ones, should be accommodated in the 'pockets' of the enzyme active site as follows.

The methoxycarbonyl group should be located within the spherical locus of the catalytically active serine function, the large phenyl group in the large hydrophobic pocket ($H_L$), the alkoxy group in the small hydrophobic pocket ($H_S$) and finally the phosphoryl oxygen in the back polar pocket ($P_B$) (Fig. 3a). As far as the location of the three former groups is quite obvious, there is some uncertainty

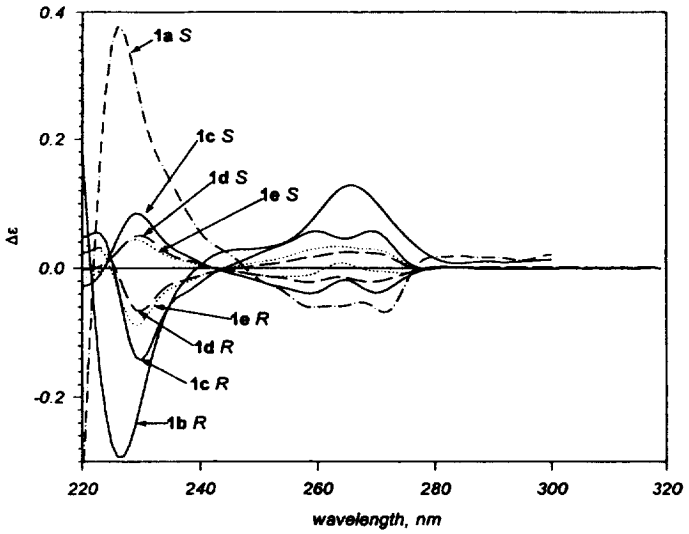



Fig. 2. CD spectra (in MeOH) of chiral esters **1***

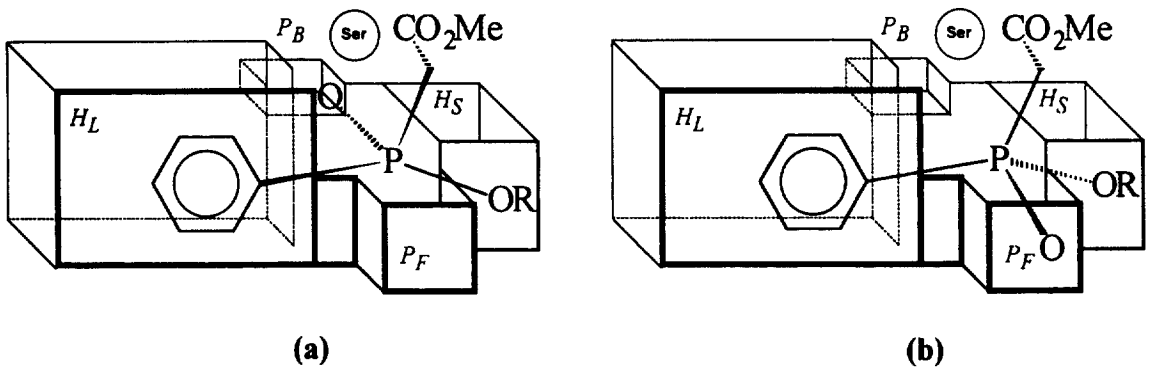



Fig. 3. Binding orientations of **1*a–e** in the active site of PLE: (a) of the enantiomer preferably hydrolyzed; (b) of the enantiomer recovered

as to whether the phosphoryl oxygen may alternatively be accommodated in the front polar pocket $P_F$ (Fig. 3b), which would lead to the preferential hydrolysis of the (*S*) enantiomers, and in the end result in a lower stereoselection. However, in our opinion it is not the case. Thus, according to the Jones' predictions, the $P_F$ pocket is mostly used to bind the second nonhydrolyzed ester function of diester substrates, but it can accept nonpolar groups also. On the other hand, the $P_B$ site interacts well, among others, with carbonyl functions, but is too polar to accept hydrophobic moieties. That is why the strongly polar P=O group should be preferentially accommodated in the $P_B$ pocket, hence favoring the model shown in Fig. 3a. Moreover, since the stereoselectivity is very high for **1a** (R=Me) and becomes lower on passing to the larger alkyl groups, this is rather the decreasing size difference between the 'large' and the 'small' nonpolar substituents which seems responsible for the lower ee values of the products.

## 3. Experimental

### 3.1. General

Phosphate buffer solutions were purchased from Aldrich. An ammonium sulfate suspension of porcine liver esterase was used which was purchased either from FLUKA or SIGMA. A 0.2 M solution of NaOH was used in an automatic titrator to adjust pH. NMR spectra were recorded at 300 MHz or 500 MHz for $^1$H and 121 MHz for $^{31}$P with $CDCl_3$ as a solvent. Optical rotations were measured on a Perkin–Elmer 241 MC polarimeter. Column chromatography was carried out using Merck 60 $F_{254}$ silica gel. TLC was performed on Merck 60 $F_{254}$ silica gel plates.

### 3.2. Synthesis of substrates 1

All the substrates were prepared via the Arbuzov reaction of methyl bromoacetate with the appropriate trivalent phosphorus esters (see below), according to the following general procedure. To methyl bromoacetate (0.1 mol), stirred, heated to 80°C and purged with a continuous stream of argon, the appropriate trivalent phosphorus ester was added very slowly. The reaction was exothermic. After the addition was completed the mixture was heated at 90°C for an additional hour and then submitted to fractional distillation. All products gave satisfactory combustion analysis results (C, H, P ±0.4%).

### 3.3. Methyl methoxy(phenyl)phosphonylacetate 1a

Obtained from dimethyl phenylphosphonite and methyl bromoacetate as a colorless liquid after distillation (bp 140°C/0.2 mmHg) in 74% yield. $^{31}$P NMR: δ 36.0. $^1$H NMR: δ 3.10 (d, $J_{P-H}$=17.7, 2H), 3.61 (d, $J_{P-H}$=0.54, 3H), 3.72 (d, $J_{P-H}$=11.4, 3H), 7.40–7.85 (m, 5H).

### 3.4. Methyl ethoxy(phenyl)phosphonylacetate 1b

Obtained from diethyl phenylphosphonite and methyl bromoacetate as a colorless liquid after distillation (bp 132°C/0.1 mmHg) in 86% yield. $^{31}$P NMR: δ 34.3. $^1$H NMR: δ 1.31 (t, 3H), 3.11 (d, $J_{P-H}$=17.7, 2H), 3.60 (s, 3H), 3.9–4.2 (m, 2H), 7.40–7.80 (m, 5H).

### 3.5. Methyl n-propoxy(phenyl)phosphonylacetate 1c

Obtained from di-*n*-propyl phenylphosphonite and methyl bromoacetate as a colorless oil after bulb-to-bulb distillation (bp 150°C/0.2 mmHg) in 88% yield. $^{31}$P NMR: δ 34.2. $^1$H NMR: δ 0.95 (t, 3H), 1.71 (sxt, 2H), 3.13 (d, $J_{P-H}$=17.7, 2H), 3.63 (d, $J_{P-H}$=0.53, 3H), 3.5–4.2 (m, 2H), 7.45–7.80 (m, 5H).

### 3.6. Methyl isopropoxy(phenyl)phosphonylacetate 1d

Obtained from di-isopropyl phenylphosphonite and methyl bromoacetate as a colorless oil after bulb-to-bulb distillation (bp 150°C/0.2 mmHg) in 75% yield. $^{31}$P NMR: δ 33.0. $^1$H NMR: δ 1.24 (d, 3H), 1.41 (d, 3H), 3.13 (d, $J_{P-H}$=17.7, 2H), 3.63 (s, 3H), 4.55–4.75 (m, 1H), 7.45–7.80 (m, 5H).

### 3.7. *Methyl* n-*butoxy(phenyl)phosphonylacetate* **1e**

Obtained from di-*n*-butyl phenylphosphonite and methyl bromoacetate as a colorless oil after bulb-to-bulb distillation (bp 150°C/0.2 mmHg) in 72% yield. $^{31}$P NMR: δ 34.2. $^{1}$H NMR: δ 0.91 (t, 3H), 1.25–1.50 (m, 2H), 1.55–1.75 (m, 2H), 3.12 (d, $J_{P-H}$=17.7, 2H), 3.63 (s, 3H), 3.85–4.45 (m, 2H), 7.40–7.80 (m, 5H).

### 3.8. *Methyl methoxy(ethyl)phosphonylacetate* **1f**

Obtained from dimethyl ethylphosphonite and methyl bromoacetate as a colorless liquid after fractional distillation (bp 60°C/0.1 mmHg) in 60% yield. $^{31}$P NMR: δ 51.5. $^{1}$H NMR: δ 1.15 (dt, $J_{H-H}$=7.67, $J_{P-H}$=19.6, 3H), 1.75–1.95 (m, 2H), 2.19 (d, $J_{P-H}$=16.9, 2H), 3.68 (s, 3H), 3.70 (d, $J_{P-H}$=10.93, 3H).

### 3.9. *Methyl ethoxy(ethyl)phosphonylacetate* **1g**

Obtained from diethyl ethylphosphonite and methyl bromoacetate as a colorless liquid after fractional distillation (bp 70°C/0.25 mmHg) in 84% yield. $^{31}$P NMR: δ 49.3. $^{1}$H NMR: δ 1.16 (dt, $J_{H-H}$=7.67, $J_{P-H}$=19.43, 3H), 1.29 (t, 3H), 1.8–2.0 (m, 2H), 2.92 (d, $J_{P-H}$=16.9, 2H), 3.70 (s, 3H), 3.95–4.25 (m, 2H).

### 3.10. *Methyl ethoxy(phenoxy)phosphorylacetate* **1h**

Obtained from diethyl phenylphosphite and methyl bromoacetate as a colorless oil after fractional distillation (bp 105°C/0.1 mmHg) in 62% yield. $^{31}$P NMR: δ 17.0. $^{1}$H NMR: δ 1.31 (dt, $J_{H-H}$=7.1, $J_{P-H}$=0.54, 3H), 3.10 (d, $J_{P-H}$=21.6, 2H), 3.73 (d, $J_{P-H}$=0.52, 3H), 4.1–4.4 (m, 2H), 7.1–7.4 (m, 5H).

### 3.11. *Methyl methoxy(diethylamido)phosphorylacetate* **1i**

Obtained from dimethyl diethylamidophosphite and methyl bromoacetate as a colorless liquid after fractional distillation (bp 85°C/0.3 mmHg) in 43% yield. $^{31}$P NMR: δ 26.0. $^{1}$H NMR: δ 1.07 (t, 6H), 2.87 (2×AB, 2H), 2.97–3.10 (m, 4H), 3.59 (d, $J_{P-H}$=11.46, 3H), 3.68 (d, $J_{P-H}$=0.57, 3H).

### 3.12. *General procedure for the enzymatic hydrolysis of* **1**

To a stirred solution of ester **1** (1 mmol) in a phosphate buffer (~20 ml), at 30°C, PLE (~50 μL) was added. The pH was maintained by a continuous addition of 0.2 M aqueous NaOH using an automatic titrator. When 50% conversion was reached (i.e. 2.5 mL of NaOH added dropwise) the reaction was quenched by adding 200 mL of acetone and cooling in a freezer for ca. 3 h (in some cases the reaction was deliberately stopped at different conversions, see Table 1). The mixture was filtered through Celite and the acetone was evaporated. The residue was extracted with $CH_2Cl_2$ (3×10 mL) and the combined organic layers dried over $MgSO_4$. The solvent was evaporated and the crude product purified by silica gel chromatography (AcOEt:hexane gradient as eluent) to give pure unreacted esters **1*** (see Table 1).

The remaining aqueous layer was acidified with $H_2SO_4$ (pH ca. 3.0) and lyophilized. The residue was either extracted with $CHCl_3$, dried and evaporated to give acids **2***, or dissolved in excess methanol and left at room temperature for three days, during which time acids **2*** were re-esterified to the methyl esters **1*** of opposite absolute configuration. Methanol was evaporated, the residue extracted with $CH_2Cl_2$, washed with a small amount of water and dried over $MgSO_4$. After evaporation of the solvent, the residue

was purified by column chromatography (as above) to give the esters **1***. Specfic rotations and the ee values of the products obtained are collected in Table 1.

### 3.13. Decarboxylation of 2*b

Decarboxylation was performed according to the procedure described previously.[12] Thus, **2*b** [0.488 g, 2.1 mmol, $[\alpha]_D^{20}$ +9.2, (c 1.2, MeOH)] was placed in toluene (5 mL) and acetone was added until the solid had dissolved. Then $Bu_3N$ (1 mL) was added and the mixture was refluxed for 5 days. The solvents were evaporated and the residue was separated on preparative TLC (MeOH:$CHCl_3$=1:15). (+)-(*R*)-Ethyl methylphenylphosphinate **3** was obtained (0.1 g, 25%), $[\alpha]_D^{20}$ +28.7, (c 1.15, benzene) [lit.[13] for (+)-(*R*)-**3** $[\alpha]_D^{20}$ +49 (benzene)].

### 3.14. The salt of (+)-2a and (−)-(S)-α-phenylethylamine

The diastereomerically pure salt of (+)-**2a** and (−)-(*S*)-α-phenylethylamine was obtained after repeated crystallization of the appropriate diastereomeric mixture from benzene. Diastereomeric purity was established by $^1$H NMR. The corresponding optical rotation values were as follows: of the diastereomerically pure salt: $[\alpha]_D^{20}$ +11.4 (c 0.43, MeOH); of **2*b** released from the above salt using ion exchange resin: $[\alpha]_D^{20}$ +9.2 (c 0.26, benzene); $[\alpha]_D^{20}$ +19.2 (c 0.26, MeOH); lit.[11]: $[\alpha]_D^{20}$ +9.1 (c 3.0, benzene).

### 3.15. Crystal structure of the salt (+)-2*b with (−)-(S)-α-phenylethylamine

Crystal and molecular structure of the salt of (+)-**2*b** with (−)-(*S*)-α-phenylethylamine was determined using data collected at room temperature on a CAD4 diffractometer with graphite monochromatized CuKα radiation. The compound crystallizes in the orthorhombic system, in space group $P2_12_12_1$ with the unit cell consisting of 4 anions and 4 cations. Crystal data and experimental details are shown in Table 2. The lattice constants were refined by a least-squares fit of 25 reflections in the θ range 20.35–36.08°. The decline in intensities of three control reflections (−2,6,−5; −4,−2,3; −2,6,7) was 5.3% during 46.2 hours of exposure time; the DECAY correction was applied.[14] An empirical absorption correction was applied by the use of the ψ-scan method (EAC program).[14,15] A total of 3419 observed reflections with $I>0\sigma(I)$ were used to solve the structure by direct methods and to refine it[16,17] by full matrix least-squares using $F^2$. Hydrogen atoms were found on a difference Fourier map and were refined isotropically, except hydrogens attached to the C4 that were placed geometrically at idealized positions, set as riding with C–H distance free to refine, and fixed thermal parameters equal to 1.3 times the equivalent isotropic thermal parameter of the parent atom (rotation about the C4–C3 bond was also allowed). Anisotropic thermal parameters were refined for all nonhydrogen atoms. The final refinement converged at $R$=0.0580 for 304 refined parameters and 3316 observed reflections with $I>2\sigma(I)$.

The authors have deposited all crystallographic data for this structure with the Cambridge Crystallographic Data Centre.[18]

## Acknowledgements

Financial support by the Committee of Scientific Research (KBN), Grant No 3T09A 101 10 for P.K., is gratefully acknowledged.

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