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Lipase-promoted kinetic resolution of racemic, P-chiral hydroxymethylphosphonates and phosphinates

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Abstract

Lipase-mediated acetylation of racemic P-chiral hydroxymethylphosphonates and phosphinates, and hydrolysis of their *O*-acetyl derivatives have been conducted under kinetic resolution conditions to give the enantiomerically enriched title products with up to 92% ee. Their absolute configuration has been determined by means of chemical correlation and CD measurements.

1. Introduction

α-Hydroxyalkanephosphonates and phosphinates are gaining increasing attention due to their interesting biological activity.[1–4] Some of their derivatives have been found to exhibit antibacterial and antiviral properties,[1] and others to act as effective inhibitors of certain enzymes, e.g. renin[2] or HIV protease.[3] As there is a continuously growing demand that every stereoisomer of a newly introduced pharmaceutical should be pharmacologically (in general — biologically) examined, it is necessary to develop efficient and general methods for the synthesis of enantiopure compounds. In this context, it should be noted that some *O*-sulfonyl derivatives of enantiomeric hydroxymethylphosphinates exhibit a distinctly different herbicidal activity.[4]

So far, P-chiral α-hydroxyalkanephosphonates and related derivatives have been synthesized in the Abramov and Pudovik reactions of carbonyl compounds with appropriate chiral H-phosphonates or H-phosphinates,[5] the main limitation being poor accessibility of the latter. As a continuation of our studies[6] on the use of enzymes in the preparation of non-racemic sulphinyl[7] and phosphoryl[8,9] compounds, we have undertaken investigations on the possibility of using enzymatic procedures for the resolution of racemic title derivatives **1**.

We have chosen a lipase-mediated acetylation of **1** and a reverse hydrolysis of the appropriate *O*-acetyl derivatives **2**, since these types of compounds are known to be good substrates for enzymatic

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Table 1
Enzyme-promoted resolution of racemic **1** and **2**

No	R^1	R^2	*Lipase*[a] Solvent[b-e]	Proced.	1*				2*			
					Yield [%]	$[\alpha]_D^f$	ee [%]	Abs. conf.	Yield [%]	$[\alpha]_D^f$	ee [%]	Abs. conf.
a	Ph	MeO	*PFL*[b]	A	44	- 24.7	80	*R*	39	+53.5	89	*S*
a	Ph	MeO	*AM*[c]	A	42	- 29.7	92	*R*	44	+51.4	86	*S*
b	Ph	EtO	*PFL*[b]	A	42	- 17.3	54	*R*	53	+35.5	47	*S*
b	Ph	EtO	*PFL*[d]	A	25	- 18.5	58	*R*	54	+27.2	36	*S*
b	Ph	EtO	*AM*[c]	A	30	- 17.2	54	*R*	68	+14.9	21	*S*
c	Ph	i-PrO	*PFL*[b]	A	37	- 46.6	80	*R*	46	+27.1	21	*S*
c	Ph	i-PrO	*PFL*[b]	A	52	- 20.6	36	*R*	45	+31.0	24	*S*
d	i-PrO	MeO	*PFL*[e]	B	55	+0.5	16	*S*	45	- 0.93[g]	34	*R*
						+3.0[h]	92[h]			- 2.3[g,h]	92[h]	

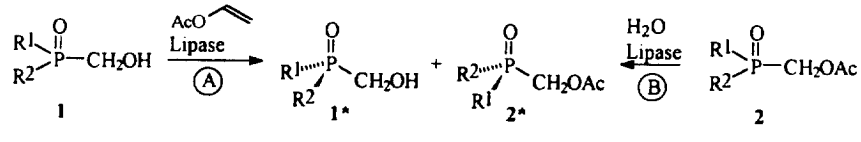
a) PFL - Pseudomonas fluorescence lipase (FLUKA), AM - AMANO PS lipase; b) in i-Pr_2O; c) in CH_2Cl_2; d) in t-BuOMe; e) in i-Pr_2O saturated with a phosphate buffer; f) in $CHCl_3$; g) neat; h)see text

transformations.[10] Moreover, it is noteworthy that the above procedures have recently been used in the resolution of C-chiral α-hydroxyalkanephosphonates.[11,12] This paper describes a successful lipase-mediated resolution of P-chiral α-hydroxyalkanephosphinates and phosphonates, in which the phosphorus atom is the sole stereogenic centre.

2. Results and discussion

The racemic hydroxymethylphosphinates **1a–c** were acetylated using vinyl acetate in the presence of lipases of *Pseudomonas cepacia*. The reaction was carried out under kinetic resolution conditions, i.e. it was stopped at ca. 50% conversion, which was determined by ^{31}P-NMR. The unconsumed substrate **1*** was then separated from the acetylated product **2*** by column chromatography using a $CHCl_3$/acetone gradient to elute **2*** and a $CHCl_3$/MeOH gradient to elute **1***.

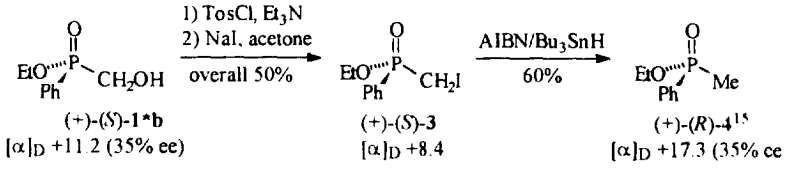
In the case of hydroxymethylphosphinate **1d**, a reverse procedure, i.e. hydrolysis of its *O*-acetyl derivative **2d**, proved to be more efficient. Separation and isolation of the unreacted **2d*** and the hydrolysis product **1d*** were performed as above. However, it is noteworthy that a threefold, repetitive hydrolysis of the enantiomerically enriched substrate enabled us to increase the ee values of both **1d*** and **2d*** to >92%. The results are summarized in Eq. 1 and collected in Table 1.



(1)

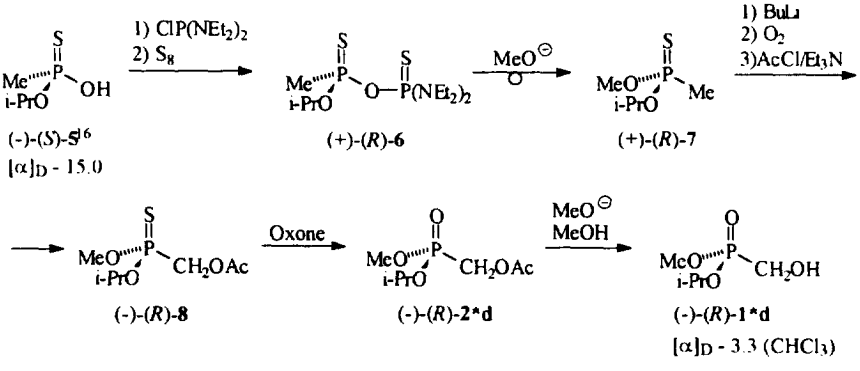
The enantiomeric excess (ee) values were determined either by means of ^{1}H-NMR spectroscopy (using (−)-(*S*)-*t*-butylphenylphosphinothioic acid as a chiral solvating agent[13]), for **1a**, **1c** and **1d**, or from chemical correlation, as for **1b** (see below).

To investigate whether there is any general relationship between the substrate structure and configuration of the enantiomer preferentially recognized by the enzyme, we determined the absolute configuration of the products. Thus, the absolute configuration of (+)-**1b** was established by the chemical correlation shown in Eq. 2. The substrate **1b** was first transformed into the *O*-tosyl derivative and then into the iodomethylphenylphosphinate **3**. The latter was reduced using the conditions developed by Bałczewski[14] to give ethyl methylphenylphosphinate **4** of known absolute configuration.[15] As none of the transformations involved the phosphorus stereogenic centre, the whole sequence did not result in a change of its absolute configuration and proceeded with full stereoselectivity. Hence, (+)-**1b** has (*S*) configuration and the same ee as (+)-(*R*)-**4** obtained in this reaction. In turn, the absolute configurations of **1a** and **1c** were ascribed by comparison of their CD spectra with that of **1b**. It turned out that the CD curves of all the unreacted levorotatory hydroxymethylphosphinates **1** were of the same shape and exhibited the same sign of the Cotton effect (Fig. 1). Since all the compounds are closely related (the phosphorus atom is in each case linked to three identical substitutents, and the fourth one, i.e. the alkoxy group, differs only by the length or branching of the alkyl group), it seems very reasonable to asssume that the absolute configuration of the compounds exhibiting the same sign of optical rotation is identical. Thus, all the levorotatory hydroxymethylphosphinates **1** have (*R*) configuration which means that, within the series investigated, in all cases this is the (*S*) enantiomer which is recognized by the lipases and hence is preferentially acetylated.



(2)

The absolute configuration of **1d** was determined by the chemical correlation presented in Eq. 3. In this case, unlike the reactions shown in Eq. 2, some reactions take place at the phosphorous stereogenic centre.



(3)

As a configurational standard, (−)-(*S*)-*O*-isopropyl methylphosphonothioic acid **5** was used,[16] whose *O*-phosphitylation by bis-(diethylamino)chlorophosphine, followed by sulfuration, afforded the mixed dithioanhydride **6**. Methanolysis of this compound proceeded exclusively at the thiophosphonyl centre and resulted in a full inversion of configuration at phosphorus[17] to give (+)-(*R*)-**7**. The carbanion of the latter was subjected to oxidation[18] followed by acetylation to give the phosphonothioate **8**. Its transform-

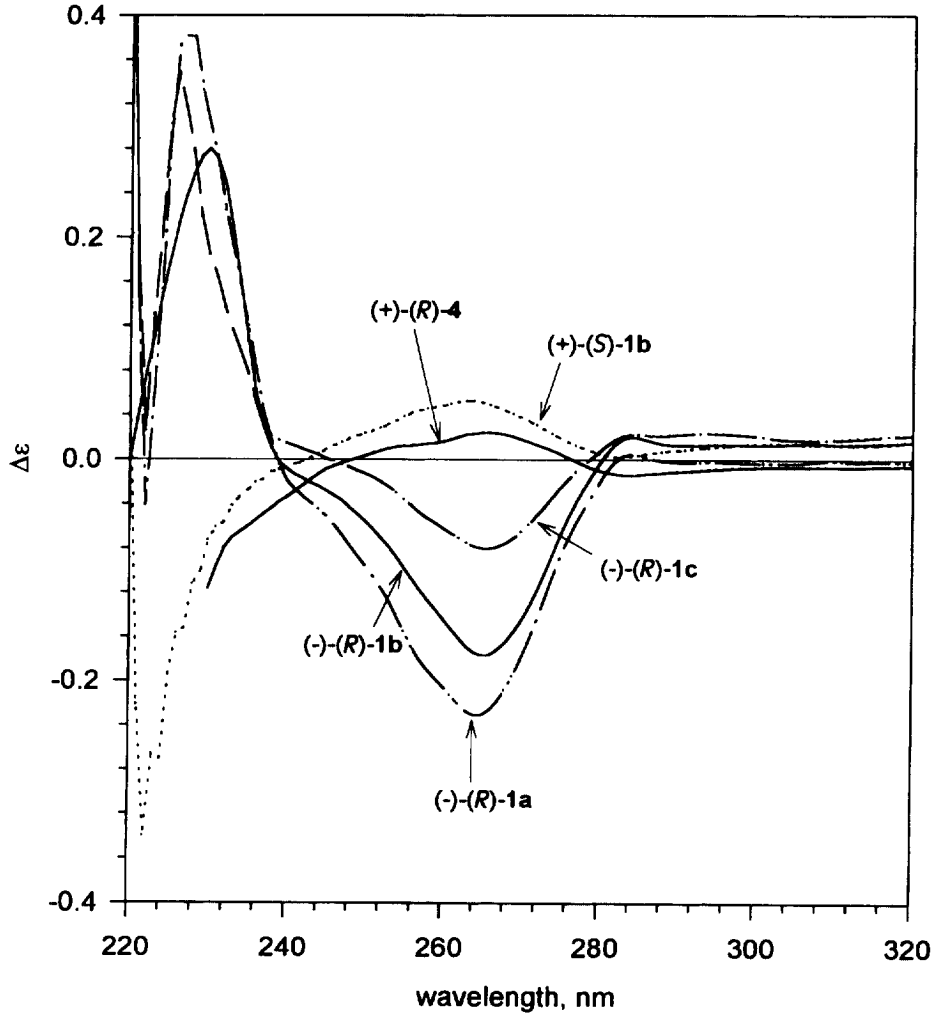


Fig. 1. CD spectra (in MeOH) of chiral hydroxymethylphosphinates **1a–c** and phosphinate **4**

ation into **2*d** was performed using Oxone as an oxidizing agent. Assuming that this reaction proceeds with retention of configuration at phosphorus, as found for other types of phosphonothioate oxidations,[19] we could ascribe (*R*) configuration to (−)-**2*d**. Hence, (−)-**1*d** also has an (*R*) configuration.

In conclusion, the methodology described above enabled us to obtain non-racemic P-chiral hydroxymethylphosphinates and phosphonates. Apart from their possible practical use,[4] they serve as new examples for attempts to find a general model of the lipase active site which could be applied to heteroorganic substrates bearing an active hydroxy group (for other examples see Serreqi and Kazlauskas[20]). The models which have been developed thus far for C-chiral substrates[21] do not allow an unequivocal explanation for the stereoselectivities observed in the cases described above.

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References

1. Sum, V.; Kee, T. P., *J. Chem. Soc., Perkin Trans. 1*, **1993**, 2701.
2. Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E., *Tetrahedron Lett.*, **1990**, *31*, 5587.
3. Stowasser, B.; Budt, K.-H.; Jian-Qi, L.; Peyman, A.; Ruppert, D., *Tetrahedron Lett.*, **1992**, *33*, 6625.
4. Spangler, L. A.; Mikołajczyk, M.; Burdge, E. L.; Kiełbasiński, P.; Smith, H. C.; Łyżwa, P.; Fisher, J. D.; Omelańczuk, J., *J. Agr. Food Chem.*, in press.
5. For recent reviews see: Mikołajczyk, M.; Drabowicz, J.; Kiełbasiński, P. In *Methods of Organic Chemistry, Houben–Weyl*; Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds; G. Thieme Verlag: Stuttgart, 1995; Vol. 21e, pp. 5701–5731. Kolodiazhnyi, O. I., *Tetrahedron: Asymmetry*, **1998**, *9*, 1279.
6. Kiełbasiński, P.; Mikołajczyk, M., *Main Group Chem. News*, **1997**, *5*(4), 7.
7. Mikołajczyk, M.; Kiełbasiński, P.; Żurawiński, R.; Wieczorek, M. W.; Błaszczyk, J., *Synlett*, **1994**, 127.
8. Kiełbasiński, P.; Żurawiński, R.; Pietrusiewicz, K. M.; Zabłocka, M.; Mikołajczyk, M., *Tetrahedron Lett.*, **1994**, *35*, 7081; *Polish J. Chem.*, **1998**, *72*, 564.
9. Kiełbasiński, P.; Góralczyk, P.; Mikołajczyk, M.; Wieczorek, M. W.; Majzner, W. R., *Tetrahedron: Asymmetry*, **1998**, *9*, 2641.
10. For recent books see: *Enzymatic Reactions in Organic Media*; Koskinen, A. M. P.; Klibanov, A. M., Eds; Blackie Academic & Professional: Glasgow, 1996; Faber, K., *Biotransformations in Organic Chemistry*, 3rd edn; Springer Verlag: Berlin, 1996.
11. Li, Y.-F.; Hammerschmidt, F., *Tetrahedron: Asymmetry*, **1993**, *4*, 109.
12. Khushi, T.; O'Toole, K. J.; Sime, J. T., *Tetrahedron Lett.*, **1993**, *34*, 2375.
13. Drabowicz, J.; Dudziński, B.; Mikołajczyk, M.; Colonna, S.; Gaggero, N., *Tetrahedron: Asymmetry*, **1997**, *8*, 2267 and references therein.
14. Bałczewski, P., *Phosphorus, Sulfur, Silicon*, **1995**, *104*, 113.
15. DeBruin, K. E.; Mislow, K., *J. Am. Chem. Soc.*, **1969**, *91*, 7393.
16. Denohue, J.; Mandel, N.; Farnham, W. B.; Murray, R. K.; Mislow, K.; Benschop, H. P., *J. Am. Chem. Soc.*, **1971**, *93*, 3792.
17. For an analogous transformation see: Mikołajczyk, M.; Omelańczuk, J.; Para, M., *Tetrahedron*, **1972**, *28*, 3855.
18. Mikołajczyk, M.; Grzejszczak, S.; Midura, W. H.; Popielarczyk, M.; Omelańczuk, J. In *Phosphorus Chemistry: Proceedings of the 1981 International Conference*; Quin, L. D.; Verkade, J. G., Eds. ACS Symposium Series, **1981**, *171*, 55–58.
19. Stec, W. J.; Woźniak, L. A.; Pyzowski, J.; Niewiarowski, W., *Antisense & Nucl. Acid Drug Development*, **1997**, *7*, 381.
20. Serreqi, A. N.; Kazlauskas, R. J., *J. Org. Chem.*, **1994**, *59*, 7604; *Can. J. Chem.*, **1995**, *73*, 1357.
21. Weissfloch, A. N. E.; Kazlauskas, R. J., *J. Org. Chem.*, **1995**, *60*, 6959.