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# Lipase-catalyzed kinetic resolution of α-hydroxy-H-phosphinates

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**Abstract**—A chiral synthesis of α-hydroxy-H-phosphinates was achieved via lipase-catalyzed hydrolysis of acetate precursors.


α-Heteroatom substituted phosphinic acids are of much interest due to their usefulness both in the development of catalytic antibodies[1] and pharmacologically active substances.[2] Some α-hydroxyphosphinic acids function as GABA antagonists[3] and significant intermediates for inhibitors of human renin[4] as well as HIV protease.[5] However, very little investigation has been undertaken on a chiral synthesis of this class of compounds.[6] We have previously succeeded in the first chiral synthesis of α-hydroxy-H-phosphinates, useful synthetic intermediates for α-hydroxyphosphinates, through the addition of methyl phosphinate to aldehydes utilizing AlLibis(binaphthoxide) (ALB)[7] as the catalyst.[8] This methodology afforded adducts as a mixture of diastereomers arising from the chirality of the phosphinate group. Enantioselectivity concerning the α-position was moderate (up to 85% ee) in reactions of aromatic aldehydes, whereas low enantiomeric ratio resulted in the case of aliphatic aldehydes. To overcome the limitations of optical purity and generality, we envisioned exploring a new method utilizing an enzymatic procedure for the resolution of α-hydroxy-H-phosphinates. Kielbasinski et al. successfully applied lipase-catalyzed kinetic resolution for a chiral hydroxymethylphosphinate possessing an asymmetric center at phosphorus atom.[9] Quite recently, Shioji et al. accomplished the kinetic resolution of α-hydroxy(phenyl)phosphinates containing two stereogenic centers at the phosphorus and α-carbon atom through lipase-catalyzed acylation.[10] In this letter, we wish to report a new chiral synthesis of α-hydroxy-H-phosphinates having two chiral centers via

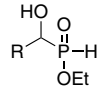


**Figure 1.**

lipase-catalyzed hydrolysis reactions of the corresponding racemic acetates (Fig. 1). The present reactions could provide products as a single diastereomer with high enantio purity starting from not only diastereomerically pure racemic acetates but also a mixture of diastereoisomers.

The requisite α-acetoxy-H-phosphinates **3a**–**e** in the study were prepared as shown in Scheme 1. The hydrophosphinylation of aldehydes with phosphinate **1**[11] in the presence of 20 mol% of PhOLi, according to our previous procedure,[12] provided adducts **2a**–**e** in 61–86% yield. Acetylation of **2a**–**e** followed by treatment with TMSCl and EtOH gave **3a**–**e** as a mixture of diastereomers. Although individual diastereomers of **3a** were not separated by silica gel column chromatography, employing preparative HPLC made it possible to isolate ($R^*$,$R_P^*$)-**3a** and ($R^*$,$S_P^*$)-**3a** in pure states.

To verify the relative stereochemistry of ($R^*$,$S_P^*$)-**3a**, the chemical transformations shown in Scheme 2 were performed. Tanaka and co-workers have recently elucidated that chiral alkenylphosphinates possessing an asymmetric center at phosphorus atom could be prepared via palladium-catalyzed stereospecific hydrophosphinylation of alkynes, which proceeded with retention of configuration at the phosphorus.[13] When the reaction of ($R^*$,$S_P^*$)-**3a** with 4-ethynyltoluene was carried out based upon Tanaka's protocol, alkenylphosphinate **4** was formed in 65% yield without

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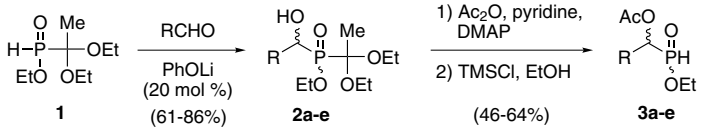
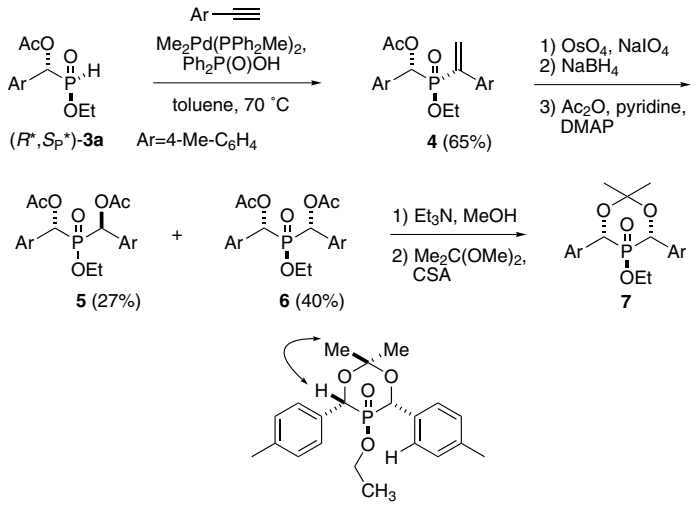



**a**: R=4-Me-$C_6H_4$; **b**: R=Ph; **c**: R=4-Cl-$C_6H_4$; **d**: R=$PhCH_2$; **e**: R=*n*-$C_5H_{11}$

**Scheme 1.**

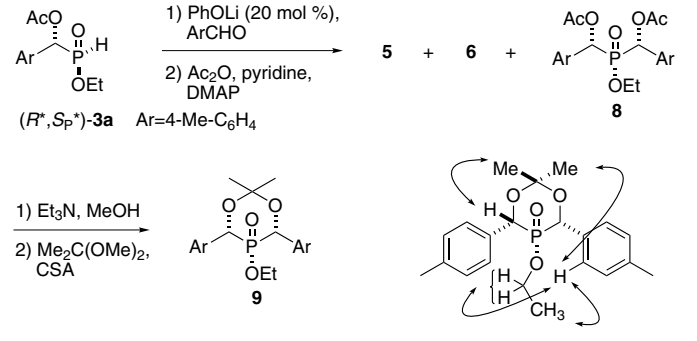



**Scheme 2.**

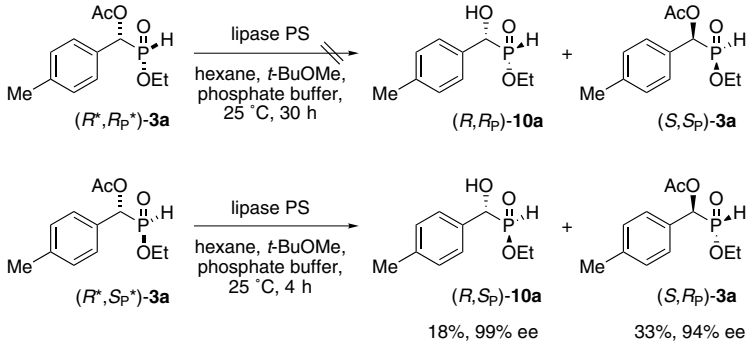
detection of any diastereomer. Sequential oxidative cleavage of the olefin moiety of **4** with $OsO_4$–$NaIO_4$, reduction with $NaBH_4$, and acetylation gave racemic diacetate **5** and *meso* diacetate **6**. Stereochemistry of the *meso* product **6** was determined after converting to the acetonide **7**. The NOESY correlation suggested the relative stereochemistry of **7** to be $R^*,S_P^*,R^*$.

The assignment was further confirmed by spectroscopic comparison with $(R^*,R_P^*,R^*)$-isomer **9**, prepared from $(R^*,S_P^*)$-**3a** (Scheme 3). The PhOLi-catalyzed hydrophosphinylation of *p*-tolualdehyde with $(R^*,S_P^*)$-**3a** and acetylation gave products **5**, **6**, and **8**. After separation, **8** was converted into **9** through removal of the acetyl group with $Et_3N$ in MeOH followed by acetonidation.

Having obtained diastereomerically pure $(R^*,R_P^*)$-**3a** and $(R^*,S_P^*)$-**3a**, enzyme-catalyzed hydrolysis reaction of each isomer was investigated (Scheme 4). Upon treatment of $(R^*,R_P^*)$-**3a** (384 mg, 1.5 mmol) with 75 mg of lipase PS (*Pseudomonas cepacia*) in hexane/*t*-BuOMe in the presence of 0.067 M phosphate buffer (pH 7.0) at 25 °C for 30 h, the desired reaction did not proceed and the crude starting material (76 mg) was recovered.[14] HPLC analysis using a column with a chiral stationary phase (DAICEL CHIRALPAK AS column, hexane–EtOH = 85:15) revealed the recovered $(R^*,R_P^*)$-**3a** was racemate. On the other hand, when $(R^*,S_P^*)$-**3a** was submitted to similar conditions, the reaction was completed within 4 h as verified by TLC monitoring, providing the alcohol $(R,S_P)$-**10a** in 18% yield along with recovered acetate $(S,R_P)$-**3a** in 33% yield.[15] Optical purity of




**Scheme 3.**



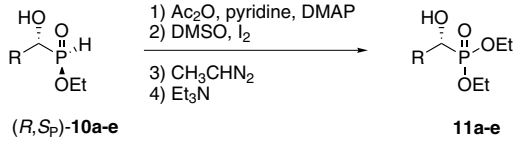

**Scheme 4.**

(*R*,$S_P$)-**10a** and (*S*,$R_P$)-**3a** was determined to be 99% and 94% ee, respectively.[16] The results indicated that lipase PS led to hydrolysis of only one diastereomer (*R**,$S_P$*)-**3a** and highly selective conversion of one enantiomer (*R*,$S_P$)-**3a** into the corresponding alcohol in preference to (*S*,$R_P$)-**3a**.

On the basis of the above results, we next examined lipase-catalyzed hydrolysis of α-acetoxy-H-phosphinates composed of four kinds of stereoisomers. In these reactions, one isomer would be hydrolyzed selectively to give the α-hydroxy-H-phosphinates with high optical purity in 25% maximum yield. The results from these experiments are summarized in Table 1.

The hydrolysis reaction of **3a**, a mixture of diastereomers in a ratio of 1.3:1, in the presence of lipase PS afforded (*R*,$S_P$)-**10a** in 14% yield as a single diastereomer with recovering **3a** (39% yield) as a diastereomixture in a ratio of 2.0:1 (entry 1). The high optical purity of (*R*,$S_P$)-**10a** (>99% ee) demonstrated that only one isomer was reacted selectively among four kinds of stereoisomeric acetates through differentiation of both enantiomer and diastereomer by lipase PS. Similar reactions were carried out using **3b**–**e** for probing the scope of the substrates. Reactions of **3b** and **3c** possessing an aromatic group also gave (*R*,$S_P$)-**10b** and (*R*,$S_P$)-**10c** with high enantiopurity in >99% and 90% ee, respectively (entries 2 and 3). In comparison to using **3a**–**c**, decrease in the optical purity was observed in the reaction of **3d** and **3e** having an aliphatic group (entries 4 and 5). In view of the level of optical purity, the methodology using the lipase-catalyzed hydrolysis proved to be superior to reported ALB-catalyzed hydrophosphinylation of aldehydes (43–85% ee).[17]

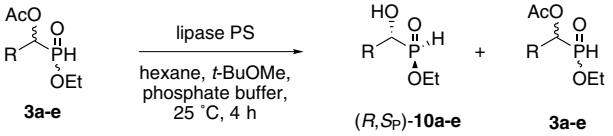
The relative stereochemistry of (*R*,$S_P$)-**10b**–**e** was estimated analogously to (*R*,$S_P$)-**10a**, whose relative configuration has already been determined. The absolute configuration at the α-position of (*R*,$S_P$)-**10a**–**e** was verified after their conversion to known α-hydroxyphosphonates **11a**–**e** through acetylation, oxidation with DMSO and $I_2$,[18] esterfication with diazoethane, and deacetylation (Scheme 5). By comparing the optical rotation of




**a**: R=4-Me-$C_6H_4$; **b**: R=Ph; **c**: R=4-Cl-$C_6H_4$; **d**: R=$PhCH_2$; **e**: R=*n*-$C_5H_{11}$

**Scheme 5.**

**Table 1.** Hydrolysis reactions of α-acetoxy-H-phosphinates in the presence of lipase PS




**a**: R=4-Me-$C_6H_4$; **b**: R=Ph; **c**: R=4-Cl-$C_6H_4$; **d**: R=$PhCH_2$; **e**: R=*n*-$C_5H_{11}$

| Entry | **3** (dr[a]) | (*R*,$S_P$)-**10a**–**e** | | Recovered **3a**–**e** | |
|---|---|---|---|---|---|
| | | Yield (%) | ee (%)[b] | Yield (%) | Dr[a] |
| 1 | **a** (1.3:1) | 14 | >99 | 39 | 2.0:1 |
| 2 | **b** (1.5:1) | 17 | >99 | 45 | 2.8:1 |
| 3 | **c** (1.2:1) | 10 | 90 | 32 | 2.2:1 |
| 4 | **d** (1.3:1) | 14 | 74 | 76 | 1.4:1 |
| 5 | **e** (1.2:1) | 9 | 76 | 54 | 1.5:1 |

[a] Diastereomeric ratio.
[b] Determined by $^{31}P$ NMR (121 MHz, $CDCl_3$) analysis of corresponding MTPA esters.

**11a**–**e** with those reported,[19] the absolute stereochemistry of **11a**–**e** was determined to be *R* configuration.

In conclusion, we have developed a new method for preparing chiral α-hydroxy-H-phosphinates through lipase-catalyzed hydrolysis of the corresponding racemic acetates. From a mixture of four kinds of stereoisomers of α-acetoxy-H-phosphinates, one isomer of α-hydroxy-H-phosphinates was obtained selectively.

## Acknowledgements

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## References and notes

1. (a) Martin, M. T.; Angeles, T. S.; Sugasawara, R.; Aman, N. I.; Napper, A. D.; Darsley, M. J.; Sanchez, R. I.; Booth, P.; Titmas, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 6508; (b) Li, T.; Janda, K. D. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2001.
2. For a review, see: Collinsová, M.; Jirácek, J. *Curr. Med. Chem.* **2000**, *7*, 629.
3. Froestl, W.; Mickel, S. J.; Sprecher, G.; Diel, P. J.; Hall, R. G.; Maier, L.; Strub, D.; Melillo, V.; Baumann, P. A.; Bernasconi, R.; Gentsch, C.; Hauser, K.; Jaekel, J.; Karlsson, G.; Klebs, K.; Maître, L.; Marescaux, C.; Pozza, M. F.; Schmutz, M.; Steinmann, M. W.; Riezen, H.; Vassout, A.; Mondadori, C.; Olpe, H.-R.; Waldmeier, P. C.; Bittiger, H. *J. Med. Chem.* **1995**, *38*, 3313.
4. Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E.; Free, C. A.; Rogers, W. L.; Smith, S. A.; DeForrest, J. M.; Oehl, R. S.; Petrillo, E. W., Jr. *J. Med. Chem.* **1995**, *38*, 4557.
5. Stowasser, B.; Budt, K.-H.; Jian-Qi, L.; Peyman, A.; Ruppert, D. *Tetrahedron Lett.* **1992**, *33*, 6625.
6. (a) Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E. *Tetrahedron Lett.* **1990**, *31*, 5591; (b) Gallagher, M. J.; Ranasinghe, M. G.; Jenkins, I. D. *J. Org. Chem.* **1996**, *61*, 436; (c) Cai, J.; Zhou, Z.; Zhao, G.; Tang, C. *Heteroat. Chem.* **2003**, *14*, 312.
7. (a) Arai, T.; Bougauchi, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1996**, *61*, 2926; (b) Arai, T.; Sasai, H.; Aoe, K.; Okamura, K.; Date, T.; Shibasaki, M. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 104; (c) Yamada, K.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1998**, *63*, 3666; (d) Xu, Y.; Ohori, K.; Ohshima, T.; Shibasaki, M. *Tetrahedron* **2002**, *58*, 2585.
8. Yamagishi, T.; Yokomatsu, T.; Suemune, K.; Shibuya, S. *Tetrahedron* **1999**, *55*, 12125.
9. (a) Kielbasinski, P.; Omelanczuk, J.; Mikolajczyk, M. *Tetrahedron: Asymmetry* **1998**, *9*, 3283; (b) Kielbasinski, P.; Albrycht, M.; Luczak, J.; Mikolajczyk, M. *Tetrahedron: Asymmetry* **2002**, *13*, 735.
10. Shioji, K.; Tashiro, A.; Shibata, S.; Okuma, K. *Tetrahedron Lett.* **2003**, *44*, 1103.
11. Baylis, E. K. *Tetrahedron Lett.* **1995**, *36*, 9385.
12. Yamagishi, T.; Kusano, T.; Kaboudin, B.; Yokomatsu, T.; Sakuma, C.; Shibuya, S. *Tetrahedron* **2003**, *59*, 767.
13. Han, L.-B.; Zhao, C.-Q.; Onozawa, S.; Goto, M.; Tanaka, M. *J. Am. Chem. Soc.* **2002**, *124*, 3842.
14. No by-products were detected by $^{1}H$ and $^{31}P$ NMR analysis of the crude recovered starting materials. Thus, low yield of recovered ($R^*$,$R_P^*$)-**3a** might be associated with partial hydrolysis of their phosphinate moiety in the reaction mixture.
15. Lipase PS-catalyzed hydrolysis reaction of ($R^*$,$S_P^*$)-**3a** (512 mg, 2 mmol) gave the corresponding crude products (378 mg) and performing silica gel column chromatography afforded ($R$,$S_P$)-**10a** (77 mg, 0.36 mmol) and ($S$,$R_P$)-**3a** (171 mg, 0.66 mmol). It was apparent that the amount yield of ($R$,$S_P$)-**10a** and ($S$,$R_P$)-**3a** was relatively low compared to that of crude products. Any by-products were not detected by $^{1}H$ and $^{31}P$ NMR analysis of the corresponding crude materials. Thus, low chemical yields of ($R$,$S_P$)-**10a** and ($S$,$R_P$)-**3a** might be associated with both loss at the purification step and partial hydrolysis of their phosphinate moiety in the reaction mixture.
16. Compound ($R$,$S_P$)-**10a**: an oil; $[\alpha]_D^{20}$ +59.4 (*c* 1.4, $CHCl_3$); $^{1}H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.32–7.30 (2H, m), 7.21–7.19 (2H, m), 6.90 (1H, d, $J$ = 532.6 Hz), 4.92 (1H, s), 4.17–4.10 (2H, m), 2.35 (3H, s), 1.32 (3H, t, $J$ = 7.0 Hz); $^{31}P$ NMR (162 MHz, $CDCl_3$): $\delta$ 33.38; IR (neat) 3227, 1201 $cm^{-1}$; ESIMS *m*/*z* 215 ($MH^+$). HRMS calcd for $C_{10}H_{16}O_3P$ ($MH^+$): 215.0837; found: 215.0833. Compound ($R$,$S_P$)-**3a**: an oil; $[\alpha]_D^{20}$ − 43.0 (*c* 1.4, $CHCl_3$); $^{1}H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.32–7.30 (2H, m), 7.22–7.20 (2H, m), 7.07 (1H, d, $J$ = 571.4 Hz), 6.01 (1H, d, $J$ = 9.0 Hz), 4.13–4.04 (2H, m), 2.35 (3H, s), 1.28 (3H, t, $J$ = 7.0 Hz); $^{31}P$ NMR (162 MHz, $CDCl_3$): $\delta$ 27.58; IR (neat) 1751, 1226 $cm^{-1}$; ESIMS *m*/*z* 279 ($MNa^+$). HRMS calcd for $C_{12}H_{17}O_4NaP$ ($MNa^+$): 279.0762; found: 279.0773.
17. We also examined reactions of **3b** with other enzymes such as lipase AY-30 (*Candida rugosa*), lipase AS (*Aspergillus nieger*), lipase F-AP 15 (*Rhizopus oryzae*). While the desired reaction did not proceed in the presence of lipase AY-30, employing lipase AS gave the hydrolysis product (36% yield) as a mixture of diastereomers (1:2.1). The reaction in the presence of lipase F-AP 15 provided the product as a diastereomixture (1:2.4) in low yield (5%). Thus, lipase PS proved to be the optimum enzyme among those examined for resolving α-hydroxy-H-phosphinates.
18. Albouy, D.; Brun, A.; Munoz, A.; Etemad-Moghadam, G. *J. Org. Chem.* **1995**, *60*, 6656.
19. (a) Drescher, M.; Li, Y.-F.; Hammerschmidt, F. *Tetrahedron* **1995**, *51*, 4933; (b) Drescher, M.; Hammerschmidt, F.; Kählig, H. *Synthesis* **1995**, 1267; (c) Yokomatsu, T.; Yamagishi, T.; Shibuya, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1527; (d) Qian, C.; Huang, T.; Zhu, C.; Sun, J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2097.