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# An Efficient Route to Chiral α- and β-Hydroxyalkanephosphonates

Oscar Pàmies* and Jan-E. Bäckvall*

*Arrhenius Laboratory, Department of Organic Chemistry, Stockholm University, SE-10691 Stockholm, Sweden*

*jeb@organ.su.se; pamies@organ.su.se*

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Enzymatic kinetic resolution of α- and β-hydroxyphosphonates in combination with ruthenium-catalyzed alcohol isomerization led to a successful dynamic kinetic resolution. A variety of racemic hydroxyphosphonates were efficiently transformed to the corresponding enantiomerically pure acetates (ee up to 99% and yield up to 87%).

## Introduction

During recent years, there has been a growing interest in chiral hydroxyalkanephosphonates due to their presence in bioactive molecules (e.g., peptide analogues, haptens of catalytic antibodies, phosphonic acid-based antibiotics, and enzyme inhibitors).[1] Moreover, they are also useful intermediates for a variety of organophosphorus derivatives.[2] The known chemical approaches to these synthetically valuable compounds include the enantio- and diastereoselective addition of dialkyl phosphites to aldehydes,[3] the Lewis acid-catalyzed ring opening of 1,3-dioxane acetals with phosphites,[4] and the asymmetric reduction of ketophosphonates.[5] However, of all these chemical approaches only the asymmetric stoichoimetric boron reduction of ketophosphonates provides access to chiral α-, β-, and γ-hydroxyalkanephosphonates.[5d] Bioconversions also provide access to the required diversity of chiral hydroxyalkanephosphonates. In particular, the microbial and enzymatic reduction of ketophosphonates has been successfully applied.[6] Lipase-catalyzed kinetic resolutions can be useful alternatives, especially because coenzyme regeneration, an inherent problem of enzymatic redox reactions, is not required.[7] Thus, during the past decade, several studies dealing with the kinetic resolution (KR) of hydroxyalkanephosphonates by lipase-catalyzed transesterification[6b,8] and hydrolysis of the corresponding acetates[6b,9] have been reported. The former studies have shown that hydroxyalkanephosphonates are transesterified at good reaction rates and good selectivity.

A major drawback with KR is that the yield is limited to a maximum of 50%. An efficient use of all racemate can be achieved by applying dynamic kinetic resolution (DKR). We and others have recently developed procedures for DKR of alcohols in which the traditional enzymatic kinetic resolution is combined with an in situ racemization of the substrate using a ruthenium hydrogen-transfer catalyst.[10] As a part of our ongoing project on chemoenzymatic DKR of different functionalized alcohols, which would lead to interesting building blocks for the synthesis of high-value compounds (e.g., pharmaceuticals, natural products, etc.),[11] we now report on the synthesis of enantiopure acetoxyalkanephosphonates via DKR (Scheme 1).

## Results and Discussion

**Synthesis of Hydroxyphosphonates.** Two different routes were employed for the synthesis of starting materials (Scheme 2). Thus, α-hydroxyphosphonates **1a**−**h** were prepared efficiently by reaction of the corre-

(1) See for instance: (a) Guiannousis, P. P.; Barlett, P. A. *J. Med. Chem.* **1987**, *30*, 1603. (b) Heilmann, J.; Maier, W. F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 471. (c) Hirschmann, R.; Smith, A. B., III; Taylor, C. M.; Benkovic, P. A.; Taylor, S. D.; Yager, K. M.; Sprengeler, P. A.; Benkovic, S. J. *Science* **1994**, *265*, 234.

(2) See, for example: (a) Dhawm, B.; Redmore, D. *Phosphorus Sulfur* **1987**, *32*, 119. (b) Laschat, H.; Kunz, H. *Synthesis* **1992**, 90.

(3) (a) Gordon; N. G.; Evans, S. A. *J. Org. Chem.* **1993**, *58*, 5293. (b) Rath, N. P.; Spilling, C. D. *Tetrahedron Lett.* **1994**, *35*, 227. (c) Balzis, V. J.; Kobler, K. J.; Spilling, S. *J. Org. Chem.* **1995**, *60*, 931. (d) Arai, T.; Bougauchi, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1996**, *61*, 2926.

(4) Yokomatsu, T.; Shibuya, S. *Tetrahedron: Asymmetry* **1992**, *3*, 377.

(5) For hydrogenation examples, see: (a) Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2931. (b) Gautier, I.; Ratovelomanana-Vidal, V.; Savignac, P.; Genêt, J. P. *Tetrahedron Lett.* **1996**, *43*, 7721. For borane reduction, see, for instance: (c) Gadja, T. *Tetrahedron: Asymmetry* **1994**, *5*, 1965. (d) Meier, C.; Laux, W. H. G. *Tetrahedron* **1996**, *52*, 589.

(6) (a) Zymanczyk-Duda, E.; Lejczak, B.; Kafarski, P.; Grimaud, J.; Fischer, P. *Tetrahedron* **1995**, *51*, 11809. (b) Mikolajczyk, M.; Luczak, J.; Kielbasinski, P. *J. Org. Chem.* **2002**, *67*, 7872.

(7) Engel, K. H.; Boh Nen, M.; Dobe, M. *Enzyme Microb. Technol.* **1991**, *13*, 655.

(8) (a) Zurawinski, R.; Nakamura, K.; Drabowicz, J.; Kielbasinski, P.; Mikolajczyk, M. *Tetrahedron: Asymmetry* **2001**, *12*, 3139. (b) Zhang, Y.; Yuan, C.; Li, Z. *Tetrahedron* **2002**, *58*, 2973.

(9) See, for instance: (a) Li, Y. F.; Hammerschmidt, F. *Tetrahedron: Asymmetry* **1993**, *4*, 109. (b) Drescher, M.; Hammerschmidt, F.; Kählig, H. *Synthesis* **1995**, 1267. (c) Drescher, M.; Hammerschmidt, F. *Tetrahedron* **1997**, *53*, 4627. (d) Hammerschmidt, F.; Wuggenig, F. *Tetrahedron: Asymmetry* **1999**, *10*, 1709.

(10) See, for instance: (a) Larsson, A. L. E.; Persson, B. A.; Bäckvall, J.-E. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1211. (b) Persson, B. A.; Larsson, A. L. E.; LeRay, M.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1999**, *121*, 1645. (c) Choi, J. H.; Kim, Y. H.; Nam, S. H.; Shin, S. T.; Kim, M. J.; Park, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2373. (d) Dijksman, A.; Elzinga, J. M.; Li, Y. X.; Arends, I. W. C. E.; Sheldon, R. A. *Tetrahedron: Asymmetry* **2002**, *13*, 879.

(11) (a) Huerta, F. F.; Laxmi, Y. R. S.; Bäckvall, J.-E. *Org. Lett.* **2000**, *2*, 1037. (b) Huerta, F. F.; Bäckvall, J.-E. *Org. Lett.* **2001**, *3*, 1209. (c) Runmo, A.-B. L.; Pàmies, O.; Fabert, K.; Bäckvall, J.-E. *Tetrahedron Lett.* **2002**, *43*, 2983. (d) Pàmies, O.; Bäckvall, J.-E. *J. Org. Chem.* **2002**, *67*, 1261. (e) Pàmies, O.; Bäckvall, J.-E. *Adv. Synth. Catal.* **2001**, *343*, 726. (f) Pàmies, O.; Bäckvall, J.-E. *J. Org. Chem.* **2001**, 66, 4022.

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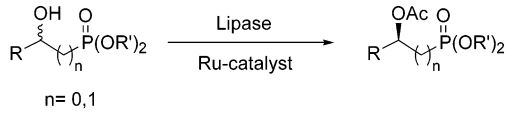
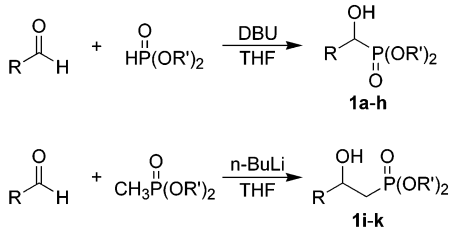
**SCHEME 1**




**SCHEME 2. Preparation of Hydroxyphosphonates 1 (R = Me, Et; R′ = Me, Et)**

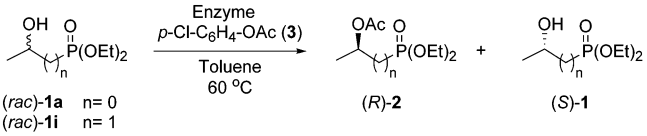



sponding aldehydes with different dialkyl phosphites in the presence of DBU in THF at room temperature. The use of DBU as base turned out to be advantageous compared to other bases used.[12] *β*-Hydroxyphosphonates **1i**−**k** were prepared by reaction of the corresponding lithium salt of dialkyl methyl phosphonate, generated in situ, with different aldehydes.[13]

**Kinetic Resolution and Dynamic Kinetic Resolution of Hydroxyphosphophonates.** A primary requirement for a successful DKR is that the KR conditions are compatible with the racemization process. Therefore, in a first set of experiments, the efficiency of different commercially available lipases to catalyze the transesterification of chiral α- and *β*-hydroxyphosphonates **1** was investigated. For this purpose, racemic diethyl (1-hydroxyethyl)phosphonate (**1a**) and diethyl (2-hydroxypropyl)phosphonate (**1i**) were chosen as model substrates and treated with 3 equiv of 4-chlorophenyl acetate (**3**) in toluene at 60 °C in the presence of different lipases. **3** was used as acyl donor since it is known to be compatible with ruthenium-catalyzed racemization of alcohols.[14] Toluene was chosen as a solvent since the efficiency of the DKR is higher in toluene than in other solvents.[15] The results are summarized in Table 1. In all cases, the enantioselectivity of the acetate was excellent, but the activity varied, and *Candida antarctica* lipase B (CALB, Novozym-435) showed the highest activity (entries 3 and 6). The other lipases examined (lipase from porcine pancreas, *Candida rugosa*, *Candida cylindracea*, and *Aspergillus* sp.) gave either very low conversion (<5%) or no reaction after 48 h.

To investigate how the different substituents affect the lipase-catalyzed transesterification, we extended our study to other substrates. The results are shown in Table 2. The effect of different substituents in the phosphonate moiety was studied using substrates **1a**−**c** with *C. antarctica* lipase B as the enzyme. The results indicate

**TABLE 1. Kinetic Resolution of 1a and 1i[a]**



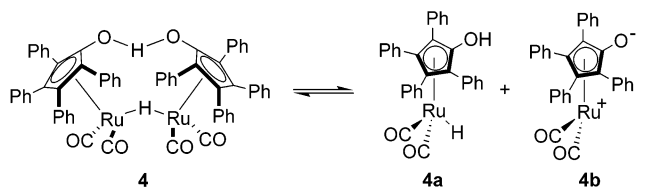

| entry | substrate | lipase[b] | yield of **2**[c] (%) | % ee of **2**[d] | % ee of **1**[d] |
|---|---|---|---|---|---|
| 1 | **1a** | PS-C | 49 | >99 | 96 |
| 2 | **1a** | AK | 45 | >99 | 82 |
| 3 | **1a** | CALB | 50 | >99 | 99 |
| 4 | **1i** | PS-C | 26 | >99 | 35 |
| 5 | **1i** | AK | 5 | >99 | 5 |
| 6 | **1i** | CALB | 49 | >99 | 96 |

[a] Reactions were carried out on a 0.1 mmol scale with 10 mg of enzyme and 3 equiv of **3** in 1 mL of toluene at 60 °C for 5 h. [b] PS-C = *P. cepacia* lipase; CALB = *C. antarctica* lipase B (Novozym-435); AK = *Pseudomonas fluorescens* lipase. [c] Determined by NMR. [d] % ee determined by GC.

that the change of size in the phosphonate substituents does not affect the enantiopreference of the lipase for these substrates (entries 1−3). However, the activity decreases considerably when a bulky diisopropyl phosphonate moiety is present (entry 3). On the other hand, *Pseudomonas cepacia* lipase (PS-C) showed good activity and enantioselecitivity for the ethyl-substituted phosphonate **1d** (entry 4).[16] However, the acylation of diethyl (1-hydroxyallyl)phosphonate (**1e**) proceeded with better enantiopreference with CALB than with PS-C lipase (entry 5 vs entry 6). α-Hydroxyphosphonates containing propyl (**1f**) and 2-propenyl (**1g**) moieties could also be acetylated with good enantiopreference using PS-C lipase (entries 7 and 8).[17] However, the PS-C transesterification of dimethyl (hydroxyphenylmethyl)phosphonate (**1h**) proceeded very slowly (entry 9).

For (2-hydroxypropyl)phosphonates **1i** and **1j** excellent activities and enantioselectivies were obtained using *C. antarctica* lipase B (entries 10 and 11). The transesterification of diethyl (2-hydroxybutyl)phosphonate (**1k**) also proceeded with good enantiomeric ratio, but the reaction rate was low (entry 12).

On the basis of these preliminary results on KR, we next combined the enzymatic KR of hydroxyphosphonates **1** with a ruthenium-catalyzed racemization process via hydrogen transfer employing catalyst **4**.[18] A feature of this catalyst is that no addition of external base is needed as a cocatalyst.[19] This is an important advantage to other potential base-induced ruthenium-catalyzed racemizations.[20]




In a first set of experiments the DKR of different α-hydroxyphosphonates were carried out using 4 mol %

(12) Other bases such as triethylamine, pyridine, and sodium methoxide also gave access to the desired α-hydroxyphosphonates, but either the reaction times were substantially longer or the reactions conditions were less convenient.

(13) Genov, D. G.; Tebby, J. C. *J. Org. Chem.* **1996**, *61*, 2454.

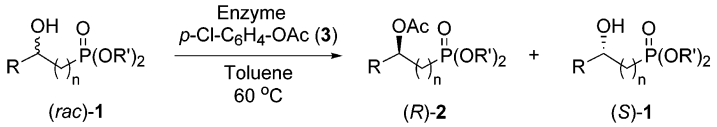
(14) The use of vinyl acetate, commonly used as acyl donor, results in the formation of acetaldehyde after the acyl-transfer process, which interferes with the ruthenium hydrogen-transfer catalysts usually employed in the DKR; see ref 10b.

(15) The solubility of the Ru catalyst **4** in toluene is higher than in ethers and other solvents, and this results in higher racemization rates; see ref 11f.

(16) The KR of **1d** using CALB proceeded with low activity (<5% after 5 h).

(17) Substrates with a medium-sized substituent larger than ethyl are not suitable for CALB-catalyzed transesterification. See, for instance: Rottichi, D.; Halffner, F.; Orrenius, C.; Norin, T.; Hult, K. *J. Mol. Catal. B* **1998**, *5*, 267.

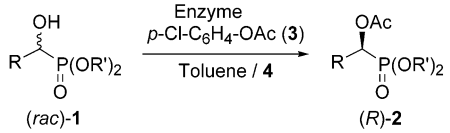
**TABLE 2. Kinetic Resolution of 1**[a]




| entry | substrate | R | n | R′ | lipase[b] | yield of **2**[c] (%) | % ee of **2**[d] | % ee of **1**[d] | E[e] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | Me | 0 | Et | CALB | 50 | >99 (+) | 99 (−) | >500 |
| 2 | **1b** | Me | 0 | Me | CALB | 50 | >99 (+) | 99 (−) | >500 |
| 3 | **1c** | Me | 0 | $^{i}$Pr | CALB | 2 | >95 | 2 | nd[f] |
| 4 | **1d** | Et | 0 | Et | PS-C | 45 | 98 (+) | 90 (−) | 300 |
| 5 | **1e** | $CH_2$=CH | 0 | Et | CALB | 39 | 99 (+) | 65 (−) | 390 |
| 6 | **1e** | $CH_2$=CH | 0 | Et | PS-C | 43 | 84 (+) | 60 (−) | 21 |
| 7 | **1f** | Pr | 0 | Et | PS-C | 16 | 99 (+) | 15 (−) | 230 |
| 8 | **1g** | $CH_3CH$=CH | 0 | Et | PS-C | 15 | nd[f] (−) | 14 (+) | nd[f] |
| 9 | **1h** | Ph | 0 | Me | PS-C | 2 | >95 | 3 | nd[f] |
| 10 | **1i** | Me | 1 | Et | CALB | 49 | 99 (+) | 98 (+) | >500 |
| 11 | **1j** | Me | 1 | Me | CALB | 47 | >99 (+) | 90 (+) | >500 |
| 12[g] | **1k** | Et | 1 | Me | CALB | 12 | >99 (+) | 13 (+) | >225 |

[a] Reactions were carried out on a 0.1 mmol scale with 10 mg of enzyme and 3 equiv of **3** in 1 mL of toluene at 60 °C for 5 h. [b] PS-C = *P. cepacia* lipase; CALB = *C. antarctica* lipase B (Novozym-435). [c] Determined by NMR. [d] % ee determined by GC. Absolute configuration in parentheses. [e] Enantiomeric ratio determined from the ee values of the alcohol and acetate. [f] Not determined. [g] Determined after 24 h.

**TABLE 3. Dynamic Kinetic Resolution of *rac*-α-Hydroxyphosphonates**[a]




| entry | substrate | R | R′ | enzyme | *T* (°C) | yield of **2**[b,c] (%) | % ee[d] |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | Me | Et | CALB | 60 | 70 | >99 |
| 2 | **1a** | Me | Et | CALB | 70 | 76 | >99 |
| 3 | **1a** | Me | Et | CALB | 80 | 86 | >99 |
| 4 | **1a** | Me | Et | PS-C | 60 | 69 | >99 |
| 5 | **1a** | Me | Et | PS-C | 80 | 87 (74)[e] | >99 |
| 6 | **1b** | Me | Me | CALB | 80 | 83 (69)[e] | >99 |
| 7 | **1d** | Et | Et | PS-C | 80 | 85 (73)[e] | 99 |

[a] Conditions: 0.2 mmol of *rac*-**1**, 0.6 mmol of **3**, 4 mol % **4**, 20 mg of lipase and 2 mL of toluene. [b] Yield measured by NMR after 24 h. [c] A high product selectivity for (*R*)-**2** was obtained with <1% of the corresponding ketone as determined by GC. [d] Enantiomeric excess measured by GC. [e] Isolated yields from reactions performed on a 0.6 mmol scale.

**4**, 3 equiv of **3**, and 100 mg of lipase/mmol of **1**. The results are summarized in Table 3. In all cases, traces of the corresponding ketophosphonate (<1%), formed during the hydrogen-transfer process, were observed by GC. A temperature screening indicated that the efficiency of the DKR is higher at 80 °C than at low temperature (entries 1−5). This is due to the faster racemization rates at higher temperature.[11f]

Under these conditions, good yields (~85%) of the corresponding acetoxyphosphonates in excellent enantioselectivities (>99%) were obtained after 24 h for substrates **1a**, **1b**, and **1d** (entries 3 and 5−7).[21] However, longer reaction times did not improve the yields of the acetoxyphosphonates. We believe that this is due to the coordination of the phosphonate to the 16-electron intermediate **4b** at low alcohol concentration, which causes decomposition of the ruthenium catalyst **4**.[22] This hypothesis is based on the following:

(i) No catalyst deactivation was observed when alcohol and **4** were premixed for 24 h.

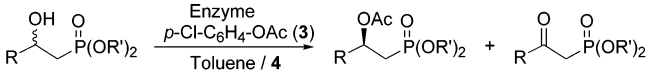
(ii) The addition of 0.5 equiv of 2,4-dimethyl-3-pentanol (**6**), as a bulky competing alcohol that cannot be acetylated, after 10 h, inhibited the catalyst deactivation.[23]

The DKR of β-hydroxyphosphonates was studied under "standard" conditions (i.e., 4 mol % **4**, 3 equiv of **3**, and 100 mg of lipase/mmol of **1**). The results are summarized in Table 4. In contrast to the DKR results on α-hydroxyphosphonates, the formation of large amounts of the corresponding ketone **5**, formed during the hydrogen-transfer process, was observed.[24] Interestingly, the temperature screening indicated that the ratio (*R*)-**2**/**5** was best at 70 °C (entry 2 vs entries 1 and 3).

Several attempts to increase the efficiency of the process by reducing the amount of ketone were done. Thus, hydrogen gas (1 bar) and **6** were tested as hydrogen sources with the aim to push the equilibrium back to the alcohol. The addition of hydrogen gas (1 bar) or 2,4-dimethyl-3-pentanol (0.5 equiv) inhibited the formation of ketone completely (entries 4 and 5). However, the DKR efficiency is highly reduced in both cases. In the former case, this is mainly due to a decrease of the racemization rate under 1 bar of hydrogen. In the latter case, the lower DKR efficiency can be attributed to the competition between alcohols **6** and **1** in the transfer hydrogenation

(18) Menasche, N.; Shvo, Y. *Organometallics* **1991**, *10*, 3885.
(19) Pàmies, O.; Bäckvall, J.-E. *Chem.—Eur. J.* **2001**, *7*, 5052.
(20) The presence of base can cause undesired side reactions in the substrate and/or product. Moreover, the basicity and quantity of base have to be carefully tuned to not affect the enzyme.
(21) Similar results were obtained by adding only 1.2 equiv of acyl donor **3**.
(22) The Ru decomposition triggers, at the same time, the progressive deactivation of the enzyme. Similar behavior has been recently observed when DKR on β-bromo alcohols was attempted; see: Pàmies, O.; Bäckvall, J.-E. *J. Org. Chem.* **2002**, *67*, 9006.
(23) The addition of **6** also reduces the efficiency of the DKR. Thus, the corresponding acetate was obtained in only 53% yield (>99% ee) after 24 h. This is attributed to the competition between alcohols **6** and **1** in the transfer hydrogenation process.
(24) The amount of ketone **5** increased when the amount of acyl donor added was lowered to 1.2 equiv.

**TABLE 4. Dynamic Kinetic Resolution of *rac*-β-Hydroxyphosphonates[a]**




| entry | substrate | R | R′ | H source | *T* (°C) | yield of **2**[b] (%) | yield of **5** (%) | % ee[c] |
|---|---|---|---|---|---|---|---|---|
| 1 | **1i** | Me | Et | | 60 | 54 | 18 | >99 |
| 2 | **1i** | Me | Et | | 70 | 65 | 10 | >99 |
| 3 | **1i** | Me | Et | | 80 | 69 | 19 | >99 |
| 4 | **1i** | Me | Et | $H_2$ | 70 | 53 | 0 | >99 |
| 5 | **1i** | Me | Et | **6** | 70 | 57 | 0 | >99 |
| 6[d] | **1i** | Me | Et | **6** | 70 | 69 | 1 | >99 |
| 7 | **1j** | Me | Me | | 70 | 62 | 16 | >99 |

[a] Conditions: 0.2 mmol of *rac*-**1**, 0.6 mmol of **3**, 4 mol % **4**, 20 mg of CALB, and 2 mL of toluene. [b] Yield measured by NMR after 24 h. [c] Enantiomeric excess measured by GC. [d] **6** (0.5 equiv) added after 24 h. Yield measured after 48 h.

process. To minimize this competitive reaction, we decided to add **6** after 24 h. Despite the fact that ketone **5** was reduced back to the alcohol, the yield of the desired acetate **2i** did not substantially increase (entry 6 vs entry 2).

The DKR of dimethyl (2-hydroxypropyl)phosphonate (**1j**) followed the same trend as observed for substrate **1i**. Thus, a moderate yield but in excellent enantioselectivity (99% ee) was obtained (entry 7).

## Experimental Procedures

**General Experimental Procedures.** All reactions were carried out under a dry argon atmosphere in oven-dried glassware. Solvents were purified by standard procedures. Compounds **1i**−**k** were prepared according to literature procedures.[13] Racemic acetoxyphosphonates **2** were prepared from the corresponding alcohols **1** by reaction with acetic anhydride and pyridine under standard conditions. Acyl donor **3** was prepared according to a literature procedure.[10b] Ruthenium catalyst **4** was synthesized according to a literature procedure[11a] and recrystallized from $CH_2Cl_2$/pentane prior to use. Lipases PS-C and AK were a generous gift from Amano Pharmaceutical Co. Ltd., Japan. All other reagents are commercially available and were used without further purification.

$^1H$, $^{13}C$, and $^{31}P$ NMR spectra were recorded in $CDCl_3$ at 300, 75, and 121 MHz, respectively. Solvents for extraction and chromatography were technical grade and distilled before use. The enantiomeric excess of compounds **1** and **2** was determined by GC analysis on a CP-Chirasil-Dex CB column using racemic compounds as references (Table 5). The oven parameters were 100 °C for 30 min and then 5 °C/min up to 200 °C. The absolute configuration was determined by polarimetry using chloroform as solvent (Table 5).

**General Procedure for the Preparation of *rac*-α-Hydroxyphosphonates 1a−i. *rac*-Diethyl (1-Hydroethyl)-phosphonate (1a).** To a solution of diethyl phosphite (2.58 mL, 20 mmol) and acetaldehyde (1.12 mL, 20 mmol) in THF (20 mL) under an argon atmosphere at 0 °C was added DBU (1.62 mL, 20 mmol). The mixture was stirred for 3 min at 0 °C and then warmed to room temperature. After 10 min, the solvent was removed in vacuo and the residue was dissolved in dichloromethane. The solution was washed with 20 mL of aqueous HCl (2 N), and the organic phase was dried with $Na_2SO_4$ and evaporated.[25] The residue was purified by bulb-to-bulb distillation[26] to yield 3.06 g (84%) of *rac*-**1a** as a colorless liquid.

**TABLE 5. $^{31}P\{^1H\}$ Chemical Shift and Retention Times of Compounds 1 and 2**

| substrate | R | n | R′ | $\delta(^{31}P)$ (ppm) | $t_R$[a] | $t_R$[a] |
|---|---|---|---|---|---|---|
| **1a** | Me | 0 | Et | 26.38 | 33.62 (−) | 33.81 (+) |
| **2a** | Me | 0 | Et | 22.23 | 23.22 (−) | 23.82 (+) |
| **1b** | Me | 0 | Me | 28.35 | 33.74 | 33.74 |
| **2b** | Me | 0 | Me | 24.82 | 16.11 (−) | 16.54 (+) |
| **1c** | Me | 0 | $^i$Pr | 24.34 | 27.52 | 28.46 |
| **2c** | Me | 0 | $^i$Pr | 20.05 | 26.35 | 27.02 |
| **1d** | Et | 0 | Et | 25.72 | 35.59 (−) | 36.42 (+) |
| **2d** | Et | 0 | Et | 21.64 | 29.20 (−) | 30.59 (+) |
| **1e** | $CH_2$=CH | 0 | Me | 22.00 | 35.37 (−) | 36.32 (+) |
| **2e** | $CH_2$=CH | 0 | Me | 18.38 | 29.52 (−) | 20.62 (+) |
| **1f** | Pr | 0 | Et | 26.05 | 38.39 (−) | 39.17 (+) |
| **2f** | Pr | 0 | Et | 21.76 | 35.59 (−) | 35.85 (+) |
| **1g** | $CH_3CH$=CH | 0 | Et | 22.90 | 38.45 (+) | 39.19 (−) |
| **2g** | $CH_3CH$=CH | 0 | Et | 19.43 | 36.23 | 36.23 |
| **1h** | Ph | 0 | Me | 24.07 | 47.51 | 47.92 |
| **2h** | Ph | 0 | Me | 20.66 | 44.67[b] | 44.71[b] |
| **1i** | Me | 1 | Et | 30.80 | 26.94 (+) | 27.52 (−) |
| **2i** | Me | 1 | Et | 27.37 | 36.43 (−) | 36.70 (+) |
| **1j** | Me | 1 | Me | 33.18 | 25.54 (+) | 25.61 (−) |
| **2j** | Me | 1 | Me | 29.72 | 34.34 (−) | 34.97 (+) |
| **1k** | Et | 1 | Me | 34.15 | 33.13 (+) | 33.49 (−) |
| **2k** | Et | 1 | Me | 30.59 | 36.65 (−) | 36.86 (+) |

[a] Absolute configuration in parentheses. [b] No baseline separation.

**General Procedure for the KR of Hydroxyphosphonates. Diethyl (*R*)-(1-Acetoxyethyl)phosphonate ((*R*)-2a).** In a typical experiment, *C. antarctica* lipase B (Novozym-435) (10 mg) was added to a solution of **1a** (15.4 mg, 0.1 mmol) and **3** (51 mg, 0.3 mmol) in dry toluene (1 mL) under argon. The resulting reaction mixture was stirred at 60 °C for 5 h. The enzyme was then filtered off and washed with toluene (3 × 5 mL). The combined toluene phases were evaporated, and the residue was analyzed. The product (*S*)-**2a** was obtained in 50% conversion and in >99% ee.

**General Procedure for the DKR of Hydroxyphosphonates. *(R)-2a*.** In a typical experiment, ruthenium catalyst **4** (30.6 mg, 4 mol %) and *C. antarctica* lipase B (Novozym-435) (60 mg) were placed in a Schlenk flask under argon. A solution of **1a** (109.2 mg, 0.6 mmol) and **3** (306 mg, 1.8 mmol) in dry toluene (6 mL) under argon (2 min of argon bubbling) was transferred to the ruthenium catalyst and the enzyme. The resulting reaction mixture was stirred at 80 °C for 24 h. The enzyme was then filtered off and washed with toluene (3 × 5 mL), the solvent was evaporated, and the product was purified by flash chromatography (ethyl acetate) to yield 99 mg (74%) of (*S*)-**2a** in >99% ee.

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(25) For substrate **1b**, the addition of HCl causes decomposition of the product. Therefore, it was purified by column chromatography using ethyl acetate as eluent and then by bulb-to-bulb distillation.

(26) Alternatively, the product can also be purified by column chromatography using ethyl acetate as eluent with similar yields.