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# Kinetic resolution of hydroxyalkanephosphonates catalyzed by *Candida antarctica* lipase B in organic media☆

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**Abstract**—A series of hydroxyalkanephosphonates were studied as substrates for CALB catalyzed acetylation with emphasis on enantioselectivity and chemical structure of substrates. Some hydroxyalkanephosphonates could be resolved successfully to give both (*R*)- and (*S*)-isomers with high enantiomeric excess. 

## 1. Introduction

Chiral hydroxyalkanephosphonates have received significant attention due to their potential biological activities as well as their ability to mimic their carboxylic counterparts.[1] Moreover, they also serve as useful precursors for a variety of substituted phosphonates.[2] These compounds can be prepared by $TiCl_4$ catalyzed opening of homochiral 1,3-dioxane acetals with trimethyl phosphite,[3] diastereoselective addition of homochiral phosphorus derivatives to aldehydes,[4] enantioselective reduction of ketophosphonates,[1d,5] enantioselective addition of dialkyl phosphites to aldehydes[6] and even chemical resolutions.[7] The traditional synthetic route leading to such compounds sometimes has drawbacks such as harsh reaction conditions, expensive reagents and low chemical yield. A convenient procedure for the preparation is therefore needed as an alternative method.

Meanwhile, the utility of lipases for efficient resolution of alcohols and related compounds is of great importance in organic synthesis.[8] Hammschmidt has exploited such hydrolases for enantioselective hydrolysis of a series of 1-acyloxyphosphonates in an organic-buffer biphase system at pH 7.0 using an autotitrater.[9]

Klibanov's first report[10] on lipase catalyzed stereoselective esterifications and transesterifications in organic solvents prompted much work on the kinetic resolution of racemic secondary alcohols in organic media, which can overcome the limitations of the traditional method, such as instability of enzymes, time consuming experimental procedures, comparably lower selectivity, etc. Nowadays biocatalysis in non-conventional media is a well-established methodology. To the best of our knowledge, however, few hydroxyalkanephosphonates undergo lipase catalyzed resolution in organic solvents.[11] The effect of the phosphonate moiety on enzymic transesterification is virtually unknown.[12]

Continuing our study on the biotransformations of organophosphorus compounds,[13] and taking into account the scarcity of lipase catalyzed resolution of such molecules in organic solvents, we wish to report the catalytic behavior of *Candida antarctica*. lipase B(CALB), a recently widely used immobilized lipase, for the kinetic resolution of hydroxyalkanephosphonates.

## 2. Results and discussion

The most commonly used method of lipase catalyzed resolution in organic media is transesterification,[14] and our study started with an investigation of CALB catalyzed acylation of diethyl 1-hydroxyethanephosphonate.

The generally used acylating agents include carboxylic acids, various activated and enol esters, or acyclic aliphatic acid anhydrides, 1-ethoxyvinyl acetate etc.[15] The enzymatic reactions amounted to conversion of one enantiomer of the alcohol into an ester with the other one remaining as the unreactived alcohol. Separation of the ester and unreacted alcohol enabled the resolution of racemic mixtures into their enantiomers. Here we chose vinyl acetate as acyl donor (Scheme 1) since it tautomerizes into acetaldehyde making the reaction irreversible.

In many cases, solvent engineering, i.e. careful selection of the most suitable solvent in the light of physicochemical

☆ Studies on organophosphorus compounds 115.

*Keywords*: hydroxyalkanephosphonates; *Candida antarctica* lipase B(CALB); acetylation; optically pure.

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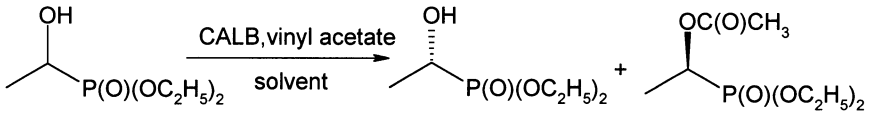



**Scheme 1.**

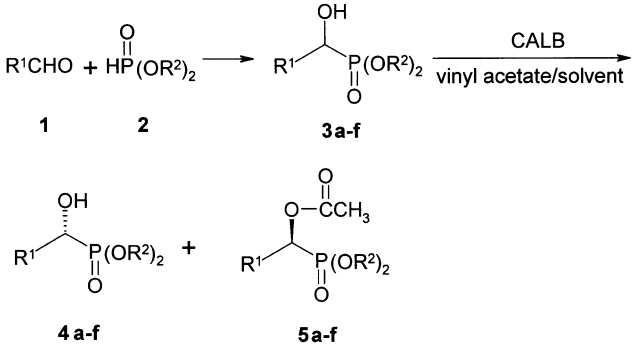
**Table 1.** Effect of solvent on catalytic acetylation of **1** by CALB

| Solvent | $E^a$ | Solvent | $E^a$ |
|---|---|---|---|
| Heptane | 6.4 | Tetrahydrofuran | >100 |
| Toluene | >100 | Vinyl acetate | 5.2 |
| Diisopropyl ether | 11.31 | Acetonitrile | 3.1 |
| Benzene | >100 | Dioxane | >100 |

[a] The enantiomeric ratio, $E=\ln[(1-c)(1-ees)]/\ln[(1-c)(1+ees)]=\ln[1-c(1+eep)]/\ln[1-c(1-eep)]$ $c=ees/(ees+eep)$.[17]

properties and substrate solubility, can contribute to obtaining the highest enantioselectivity.[16] We investigated the effect of solvent on this enzymatic reaction, and the results are listed in Table 1.

Although the acyl transfer reaction catalyzed by CALB in organic media is believed to follow a bi-bi ping-pong mechanism,[18] and solvent effects have been thoroughly studied in many cases, there still seems no obvious correlation between solvent effect and reaction enantioselectivity.[19] As shown in Table 1, solvents of various types work well here. (The case was also true when several other substrates were tested.). Additionally, the observed rate of reaction differed little with the variation of solvent, and it meant choice of solvent did not represent a serious problem concerning the rate of conversion for practical purposes.




**Scheme 2.**

The configuration of the remaining hydroxyethanephosphonate was assigned as (*R*) according to the $^{31}P$ NMR of its ester of (*R*)-Moshers acid.[20] Under optimal conditions, (*S*)-substrate was exclusively acetylated to the corresponding acetate to give both optically pure (*R*)-substrate and (*S*)-acetate in nearly 50% yield, respectively. We also carried out this experiment easily on the gram scale.

We extended the substrates to some other 1-hydroxyalkanephosphonates (Scheme 2) which were conveniently prepared from dialkyl phosphite and aldehyde in the presence of a base.[9] The results were shown in Table 2.

According to the general principle of CALB catalyzed resolution,[22] in most cases, the medium group should not be too large. It is demonstrated by us that other groups such as phenyl and propyl are not suitable. In our continuous effort to introduce the trifluoromethyl group to organophosphorus compounds, we wanted to obtain optically pure 1-hydroxy-2,2,2-trifluoroethanephosphonate via this methdology. But there was no trace of the corresponding acetate detected even after one week. Our attempt to resolve dialkyl 2-chloro-1-hydroxyethanephosphonates also failed. The phenomenon that a halogen atom inhibits CALB catalyzed acetylation of hydroxyalkanephosphonates may be ascribed to two reasons. One is that two electron-withdrawing group are not helpful for acetylation. The second may be the non-steric effect.[23]

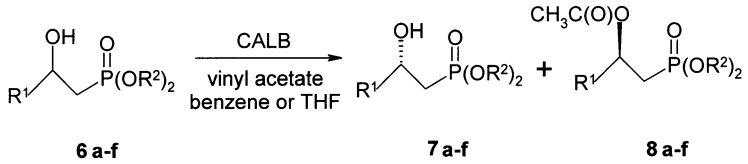
Despite this, CALB shows quite high enantioselectivity in acetylation of (*S*)-hydroxyalkanephosphonates, and this method provides a practical way to prepare optically pure 1-hydroxyalkanephosphonates.

2-Hydroxyalkanephosphonates are also an important class of potential biologically active compounds,[1d] and they are precursors of 2-aminophosphonates.[24] Herein we wish to use CALB catalyzed acetylation for resolution of these compounds (Scheme 3) since few enzymatic resolution routes have been adopted in this field. The results are listed below (Table 3).

**Table 2.** CALB catalyzed enantioselective acetylation of 1-hydroxyalkanephosphonates

| Entry | Substrate | Time (h) | $R^1$ | $R^2$ | **4** | | **5** | | *E* |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Yield (%) | ee (%)[a] | Yield (%) | ee (%)[b] | |
| 1 | **3a** | 30 | Me | Et | 43 | >95 | 44 | >95 | >100 |
| 2 | **3b** | 30 | Me | *i*-Pr | 42 | >95 | 43 | >95 | >100 |
| 3 | **3c** | 48 | Et | Me | 50 | 50.8 | 31 | >95 | >50 |
| 4 | **3d** | 50 | Et | Et | 47 | 79.7 | 41 | >95 | >95 |
| 5 | **3e** | 30 | CH2=CH | Et | 41 | >95 | 40 | >95 | >100 |
| 6 | **3f** | 30 | CH2=CH | *i*-Pr | 43 | >95 | 44 | >95 | >100 |

[a] The ee value was determined by $^{31}P$ NMR using quinine as a solvating agent,[21] a single peak was considered as an ee value of more than 95%.
[b] Ee value was determined by $^{31}P$ NMR after its chemical conversion into alcohols.




**Scheme 3.**

**Table 3.** CALB catalyzed enantioselective acetylation of 2-hydroxyalkanephosphonates

| Entry | Substrate | Time (h) | $R^1$ | $R^2$ | 7 | | 8 | | *E* |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Yield (%) | ee (%) | Yield (%) | ee (%) | |
| 1 | **6a** | 30 | Me | Me | 39 | >95 | 40 | >95 | >100 |
| 2 | **6b** | 30 | Me | Et | 40 | >95 | 39 | >95 | >100 |
| 3 | **6c** | 50 | Et | Et | 43 | 84.7 | 35 | >95 | >100 |
| 4 | **6d** | 28 | Vinyl | Et | 40 | >95 | 40 | >95 | >100 |
| 5[a] | **6e** | 30 | $ClCH_2$ | Et | 40 | 50.2 | 43 | / | <5 |
| 6 | **6f** | 120 | $CF_3$ | Et | | No reaction | | | |

[a] The ee value of **7e** is not determined, and the conversion of the reaction is about 50% according to $^{31}P$ NMR of the mixture.

2-Hydroxy-3-chloropropanephosphonate underwent acetylation smoothly because the electron-withdrawing phosphonate moiety is far away from its chiral center, but its enantioselectivity was quite poor due to the non-steric effect. Compound **6f**, however, still resisted the enzymatic reaction due to the strong electron-withdrawing effect of the trifluoromethyl group.

Obviously, methyl, ethyl, and vinyl groups still serve as suitable medium groups here. We observe that 2-hydroxyalkanephosphonates reacted slightly faster than the corresponding 1-hydroxyalkanephosphonates.

That (*S*)-1- and (*R*)-2-hydroxyalkanephosphonates were preferentially acetylated to acetates by CALB is in accordance with the general rule predicted for CALB catalyzed resolutions (Fig. 1).

It is interesting to note that when diethyl 3-hydroxybutanephosphonate, prepared via reduction of diethtyl 3-oxybutanephosphonate, was subjected to CALB catalyzed acetylation, it disappeared within 50 h under the same conditions (Scheme 4). The comparably lower enantioselectivity may be due to the fact that the enzyme–substrate binding transition state of both enantiomers differs less than that of 1- and 2-hydroxyalkanephosphonates.

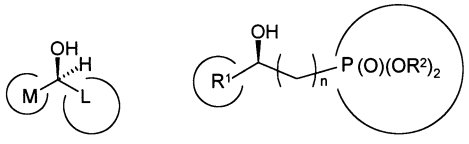
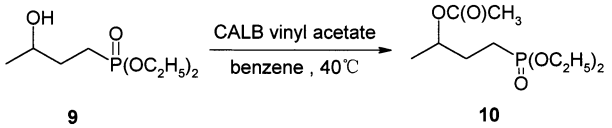



**Figure 1.** Configuration of the preferential enantiomer of hydroxyalkanephosphonate acetylation catalyzed by CALB.




**Scheme 4.**

## 3. Conclusion

In conclusion, some 1-, and 2-hydroxyalkanephosphonates have been successfully resolved by a CALB catalyzed acetylation process. The high enantioselectivity achieved in these reactions as well as the simplicity of the procedure make this strategy a useful alternative for the preparation of optically pure hydroxyalkanephosphonates. The scope and limitations of enzymatic methodology in this field are currently under investigation.

## 4. Experimental

### 4.1. General methods

IR spectra were recorded on a Shimadzu IR-440 spectrometer. EI mass spectra (MS) were run on a HP-5989A mass spectrometer. $^1H$ and $^{31}P$ NMR spectra were recorded on a Bruker AMX-330 (300 MHz) spectrometer in $CDCl_3$ and chemical shifts were reported in ppm downfield relative to TMS (internal standard) and 80% phosphorus acid (external standard) in phosphorus spectra.

CALB (Novozym 435) is a gift from Novo Norvodisk Co. Solvents used for enzymatic reactions were dried by standard methods and stored over 4A sieve before use.

### 4.2. General procedure for CALB catalyzed acetylation of hydroxyalkanephosphonates

To a stirred solution of hydroxyalkanephosphonate (100 mg) in benzene (3 ml) or THF (3 ml) was added vinyl acetate (0.5 ml). The reaction was started by addition of CALB (100 mg). The mixture was maintained at 45°C. When the reaction proceeded to certain conversion, the enzyme was filtered, washed with 3 ml acetone. The volatile solvent was removed under reduced pressure and the residue was subjected to flash chromatography to furnish almost pure hydroxyalkanephosphonates and their acetates.

**4.2.1. (*R*)-Diethyl 1-hydroxyethanephosphonate (4a).**[25] Colorless oil, >95% ee, $[\alpha]_D^{25}=-5.5$ (*c* 0.5, $CH_3OH$); IR (neat) 3317, 2984, 1220, 1053, 1029 $cm^{-1}$; $^1H$ NMR ($\delta$): 4.10–4.17 (4H, m, P(O)($OCH_2CH_3$)$_2$), 4.00 (1H, dq, *J*=3.5, 7.1 Hz, C*H*OH), 3.98 (1H, br, s O*H*), 1.40 (3H, dd, *J*=7.1, 17.5 Hz, $CH_3$CH(OH)), 1.28–1.33 (6H, m, P(O)($OCH_2CH_3$)$_2$); EIMS (*m*/*z*): 183 (M+1), 165, 155, 43, 138, 111, 82, 45.

**4.2.2. (*S*)-Diethyl 1-acetyloxyethanephosphonate (5a).** Colorless oil, >95% ee, $[\alpha]_D^{25}=+26.5$ (*c* 2.0, $CHCl_3$); IR (neat) 2933, 1740, 1237, 1049, 1027 $cm^{-1}$; $^1H$ NMR ($\delta$): 5.27 (1H, dq, *J*=7.2, 8.4 Hz, C*H*P), 4.12–4.23 (4H, m, P(O)($OCH_2CH_3$)$_2$), 2.12 (3H, s, $CH_3$CO), 1.49 (3H, dd, *J*=7.1, 16.9 Hz, $CH_3$CHP), 1.31–1.37 (6H, m, P(O)($OCH_2CH_3$)$_2$); EIMS (*m*/*z*): 225 (M+1), 180, 152, 138, 111, 82, 43; Anal. Calcd for $C_8H_{17}O_5P$: C, 42.86; H, 7.64. Found: C, 42.61; H, 7.41.

**4.2.3. (*R*)-Diisopropyl 1-hydroxyethanephosphonate (4b).**[9] Colorless oil, >95% ee, $[\alpha]_D^{25}=-6.1$ (*c* 1.2, $CHCl_3$); IR (neat) 3317, 2980, 1385, 1220, 1044, 1023 $cm^{-1}$; $^1H$ NMR ($\delta$): 4.70–4.79 (2H, m, P($OCHMe_2$)$_2$), 4.38 (1H, br, s, O*H*), 3.97 (1H, dq, *J*=3.1, 6.9 Hz, $CH_3$C*H*(OH)), 1.42 (3H, dd, *J*=7.1, 17.2 Hz, $CH_3$CH(OH)), 1.33 (12H, overlapping, P($OCHMe_2$)$_2$); EIMS (*m*/*z*): 211 (M+1), 193, 166, 151, 109, 43.

**4.2.4. (*S*)-Diisopropyl 1-acetyloxyethanephosphonate (5b).** Colorless oil, >95% ee, $[\alpha]_D^{25}=+20.10$ (*c* 1.7, $CHCl_3$); IR (neat) 2983, 1752, 1229, 1107, 1044, 1028 $cm^{-1}$; $^1H$ NMR ($\delta$): 5.18 (1H, dq, *J*=7.2, 8.5 Hz), 4.76 (2H, m, P($OCHMe_2$)$_2$), 2.10 (3H, s, $CH_3$CO), 1.44 (3H, dd, *J*=7.0, 8.9 Hz, $CH_3$CH(OH)), 1.30 (12H, dd, *J*=5.9, 11.7 Hz, P($OCHMe_2$)$_2$); EIMS (*m*/*z*): 253 (M+1), 211, 166, 151, 124, 43; Anal. Calcd for $C_{10}H_{21}O_5P$: C, 47.62; H, 8.39. Found: C, 47.61; H, 8.34.

**4.2.5. (*R*)-Dimethyl 1-hydroxypropanephosphonate (4c).**[9] Colorless oil, 50.8% ee, $[\alpha]_D^{25}=-4.3$ (*c* 0.5, $CHCl_3$); IR (neat) 3317, 2962, 1217, 1033 $cm^{-1}$; $^1H$ NMR ($\delta$): 3.79–3.88 (2H, O*H*, CHP), 3.87 (6H, d, *J*=10.3 Hz, P($OCH_3$)$_2$), 1.73–1.84 (2H, m, $CH_3CH_2CH$), 1.10 (3H, t, *J*=7.4 Hz, $CH_3CH_2CH$); EIMS (*m*/*z*): 169 (M+1), 58, 43.

**4.2.6. (*S*)-Dimethyl 1-acetyloxypropanephosphonate (5c).** Colorless oil, >95% ee, $[\alpha]_D^{25}=+44.2$ (*c* 0.25, $CHCl_3$); IR (neat) 2962, 1751, 1228, 1032 $cm^{-1}$; $^1H$ NMR ($\delta$): 5.14–5.21 (1H, m, C*H*P), 3.75 (6H, 2d, *J*=9.3 Hz, P($OCH_3$)$_2$), 2.13 (3H, s, $CH_3$CO), 1.85 (2H, m, $CH_3CH_2$CHP), 0.98 (3H, t, *J*=7.2 Hz, $CH_3CH_2$CHP); EIMS (*m*/*z*): 169, 124, 110, 79, 43; Anal. Calcd for $C_7H_{15}O_5P$: C, 40.01; H, 7.19. Found: C, 40.01; H, 7.19.

**4.2.7. (*R*)-Diethyl 1-hydroxypropanephosphonate (4d).**[5a] Colorless oil, 79.7% ee, $[\alpha]_D^{25}=-4.9$ (*c* 1.5, $CHCl_3$); IR (neat) 3312, 2982, 1213, 1048, 1027 $cm^{-1}$; $^1H$ NMR ($\delta$): 4.12–4.21 (4H, m, P($OCH_2CH_3$)$_2$), 3.89 (1H, br, s, O*H*), 3.74–3.80 (1H, m, $CH_3CH_2$C*H*(OH)), 1.77–1.81 (2H, m, $CH_3CH_2$CH), 1.31–1.36 (6H, m, P(O)($OCH_2CH_3$)$_2$), 1.07 (3H, t, *J*=7.4 Hz, $CH_3CH_2$CH); EIMS (*m*/*z*): 197 (M+1), 179, 138, 111, 82, 65.

**4.2.8. (*S*)-Diethyl 1-acetyloxypropanephosphonate (5d).** Colorless oil, >95% ee, $[\alpha]_D^{25}=+41.3$ (*c* 1.0, $CHCl_3$); IR (neat) 2981, 1751, 1327, 1228, 1023; $^1H$ NMR ($\delta$): 5.07–5.15 (1H, m, C*H*P), 4.01–4.12 (4H, m, P($OCH_2CH_3$)$_2$), 2.06 (3H, s, $CH_3$CO), 1.71–1.87 (2H, m, $CH_3CH_2$CHP), 1.18–1.28 (6H, m, P(O)($OCH_2CH_3$)$_2$), 0.95 (3H, t, *J*=7.4 Hz, $CH_3CH_2$CHP); EIMS (*m*/*z*): 239 (M+1), 180, 152, 138, 111, 82, 43; Anal. Calcd for $C_9H_{19}O_5P$: C, 45.38; H, 8.04. Found: C, 45.11; H, 7.82.

**4.2.9. (*R*)-Diethyl 1-hydroxy-2-propenylphosphonate (4e).**[26] Colorless oil, >95% ee, $[\alpha]_D^{25}=-12.7$ (*c* 0.8, $CHCl_3$); IR (neat): 3293, 2986, 1641, 1238, 1201, 1052, 1028 $cm^{-1}$; $^1H$ NMR ($\delta$): 5.27–6.03 (3H, H of Vinyl), 4.73 (1H, br, s, O*H*), 4.35 (1H, dd, *J*=5.4, 13.7 Hz, C*H*P), 4.13–4.23 (m, 4H, P($OCH_2CH_3$)$_2$), 1.33 (6H, m, P($OCH_2CH_3$)$_2$); EIMS (*m*/*z*): 195 (M+1), 177, 149, 151, 111, 82, 57.

**4.2.10. (*S*)-Diethyl 1-acetyloxy-2-propenylphosphonate (5e).** Colorless oil, >95% ee, $[\alpha]_D^{25}=+23.8$ (*c* 0.9, $CHCl_3$); IR (neat): 2987, 1753, 1643, 1262, 1226, 1052, 1025 $cm^{-1}$; $^1H$ NMR ($\delta$): 5.25–5.90 (4H, H of Vinyl), 5.85 (1H, overlapping, C*H*P), 4.07–4.12 (4H, m, P($OCH_2CH_3$)$_2$), 2.11 (3H, s, $CH_3$CO), 1.23–1.28 (6H, m, P($OCH_2CH_3$)$_2$); EIMS (*m*/*z*): 194, 177, 165, 138, 111, 82, 43; Anal. Calcd for $C_9H_{17}O_5P$: C, 45.77; H, 7.25. Found: C, 45.79; H, 7.36.

**4.2.11. (*R*)-Diisopropyl 1-hydroxy-2-propenylphosphonate (4f).**[27] Colorless oil, >95% ee, $[\alpha]_D^{25}=-14.4$ (*c* 0.7, $CHCl_3$); IR (neat) 3297, 2970, 1645, 1240 $cm^{-1}$; $^1H$ NMR ($\delta$): 5.27–6.01 (3H, H of Vinyl), 4.71–4.79 (2H, m, P($OCHMe_2$)$_2$), 4.43 (1H, dd, *J*=5.4, 13.3 Hz, C*H*P), 3.96 (1H, OH), 1.26–1.44 (m, 12H, overlapping, P($OCHMe_2$)$_2$); EIMS (*m*/*z*): 223 (M+1), 193, 181, 165, 139, 109, 43.

**4.2.12. (*S*)-Diisopropyl 1-acetyloxy-2-propenylphosphonate (5f).** Colorless oil, >95% ee, $[\alpha]_D^{25}=+26.5$ (*c* 1.3, $CHCl_3$); IR: 2984, 1753, 1634, 1261, 1226, 999 $cm^{-1}$; $^1H$ NMR ($\delta$): 5.25–5.90 (4H, H or Vinyl; C*H*P), 4.76 (2H, m, P($OCHMe_2$)$_2$), 3.96 (1H, dd, *J*=5.4, 13.5 Hz), 2.17 (3H, s, $CH_3$CO), 1.33 (12H, dd, *J*=6.3, 7.9 Hz) P($OCHMe_2$)$_2$); EIMS (*m*/*z*): 265 (M+1), 193, 163, 138, 121, 43; Anal. Calcd for $C_{11}H_{21}O_5P$: C, 50.00; H, 8.01. Found: C, 50.06; H, 7.96.

**4.2.13. (*S*)-Dimethyl 2-hydroxypropanephosphonate (7a).**[1d] Colorless oil, >95% ee, $[\alpha]_D^{25}=+13.6$ (*c* 1.1, $CHCl_3$); IR (neat) 3402, 2962, 1227, 1033 $cm^{-1}$; $^1H$ NMR ($\delta$): 4.06–4.21 (1H, m, $CH_3$C*H*OH), 3.72 (6H, 2d, *J*=10.9 Hz, P($OCH_3$)$_2$), 3.34 (1H, s, O*H*), 1.92–2.00 (2H, dd, *J*=6.3, 17.8 Hz, $CH_2$P), 1.19–1.32 (3H, m, $CH_3$CHOH); EIMS (*m*/*z*): 169 (M+1), 151, 124, 109, 94, 79.

**4.2.14. (*R*)-Dimethyl 2-acetyloxypropanephosphonate (8a).** Colorless oil, >95% ee, $[\alpha]_D^{25}=+5.7$ (*c* 1.0, $CHCl_3$); IR (neat): 2960, 1739, 1245, 1033 $cm^{-1}$; $^1H$ NMR ($\delta$): 5.08–5.11 (1H, m, $CH_3$ C*H*$CH_2$P), 3.68 (6H, d, *J*=10.9 Hz, P($OCH_3$)$_2$), 2.1 (3H, s, $CH_3CO$), 1.90–2.15 (2H, m, $CH_2$P), 1.31 (3H, d, *J*=6.4 Hz, $CH_3CHCH_2$P); EIMS (*m*/*z*): 167, 151, 135, 124, 109, 79, 43; Anal. Calcd for $C_7H_{15}O_5P$: C, 40.00; H, 7.19. Found: C, 39.97; H, 7.16.

**4.2.15. (*S*)-Diethyl 2-hydroxypropanephosphonate (7b).**[1d] Colorless oil, >95% ee, $[\alpha]_D^{25}=+15.2$ (*c* 0.25, $CHCl_3$); IR: 3399, 2983, 1234, 1048 $cm^{-1}$; $^1H$ NMR ($\delta$): 4.08–4.23 (5H, m, $CH_3CHOH$; $P(OCH_2CH_3)_2$), 3.66 (1H, br, s, O*H*), 1.96 (2H, dd, *J*=6.3, 17.1 Hz, $CH_2P$), 1.36–1.38 (6H, m, $P(OCH_2CH_3)_2$), 1.31 (3H, dd, *J*=2.4, 5.9 Hz, $CH_3CH$); EIMS (*m*/*z*): 197 (M+1), 179.

**4.2.16. (*R*)-Diethyl 2-acetyloxypropanephosphonate (8b).** Colorless oil, >95% ee, $[\alpha]_D^{25}=+9.7$ (*c* 0.5, $CHCl_3$); IR: 2986, 1740, 1244, 1027, 958 $cm^{-1}$; $^1H$ NMR ($\delta$): 5.13–5.18 (1H, m, $CH_3CHCH_2P$), 4.03–4.13 (4H, m, $P(OCH_2CH_3)_2$), 1.81–2.42 (2H, m, $CH_2P$), 2.08 (3H, s, $CH_3CO$), 1.31 (2H, dd, *J*=3.0, 10.2 Hz, $CH_3CHCH_2P$), 1.22–1.28 (6H, m, $P(OCH_2CH_3)_2$); EIMS (*m*/*z*): 239 (M+1), 195, 179, 151, 43; Anal. Calcd for $C_9H_{19}O_5P$: C, 45.38; H, 8.04. Found: C, 45.20; H, 7.84.

**4.2.17. (*S*)-Diethyl 2-hydroxybutanephosphonate (7c).**[28] Colorless oil, 84.7% ee, $[\alpha]_D^{25}=+13.1$ (*c* 0.21, $CHCl_3$); IR (neat) 3394, 2982, 1225, 1056, 1029, 967 $cm^{-1}$; $^1H$ NMR ($\delta$): 4.11–4.15 (4H, m, $P(OCH_2CH_3)_2$), 3.83 (2H, m, *CHOH*), 1.86–2.03 (2H, m, $CH_2P$), 1.56–1.58 (2H, m, $CH_3CH_2CHOH$), 1.31–1.37 (6H, m, $P(OCH_2CH_3)_2$), 0.95–0.99 (3H, m, $CH_3CH_2CHOH$); EIMS (*m*/*z*): 211 (M+1), 193, 181, 153, 125.

**4.2.18. (*R*)-Diethyl 2-acetyloxybutanephosphonate (8c).** Colorless oil, >95% ee, $[\alpha]_D^{25}=+8.2$ (*c* 0.7, $CHCl_3$); IR (neat) 2980, 1740, 1243, 1055, 1026, 967 $cm^{-1}$; $^1H$ NMR ($\delta$): 5.04 (1H, $CHCH_2P$), 3.99–4.10 (4H, m, $P(OCH_2CH_3)_2$), 2.10 (3H, s, $CH_3CO$), 1.81–2.12 (2H, $CH_2P$), 1.58–2.08 (2H, m, $CH_3CH_2CHCH_2P$), 1.24–1.29 (6H, m, $P(OCH_2CH_3)_2$), 0.98 (3H, t, *J*=7.1 Hz, $CH_3CH_2CHCH_2P$); EIMS (*m*/*z*): 253 (M+1), 211, 193, 43; Anal. Calcd for $C_{10}H_{21}O_5P$: C, 47.62; H, 8.39. Found: C, 47.49; H, 8.39.

**4.2.19. (*S*)-Diethyl 2-hydroxy-3-butenylphosphonate (7d).** Colorless oil, >95% ee, $[\alpha]_D^{25}=+5.6$ (*c* 5.6, $CHCl_3$); IR (neat) 3364, 2985, 1630, 1224, 1058, 1029 $cm^{-1}$; $^1H$ NMR ($\delta$): 5.12–5.96 (3H, H of Vinyl), 4.49–4.56 (1H, m, *CHOH*), 4.06–4.19 (4H, m, $P(OCH_2CH_3)_2$), 3.58 (1H, br, s, O*H*), 2.03 (2H, dd, *J*=6.5, 17.2 Hz, $CH_2P$), 1.32–1.36 (6H, m, $P(OCH_2CH_3)_2$); EIMS (*m*/*z*): 208 (M), 191, 179, 152, 125, 97; Anal. Calcd for $C_8H_{17}O_4P$: C, 46.15; H, 8.23. Found: C, 46.15; H, 8.10.

**4.2.20. (*R*)-Diethyl 2-acetyloxy-3-butenylphosphonate (8d).** Colorless oil, >95% ee, $[\alpha]_D^{25}=+2.5$ (*c* 1.4, $CHCl_3$); IR (neat) 2987, 1743, 1647, 1240, 1025 $cm^{-1}$; $^1H$ NMR ($\delta$): 5.17–5.89 (4H, H of Vinyl; $CHCH_2P$), 4.02–4.11 (4H, m, $P(OCH_2CH_3)_2$), 2.1 (3H, s, $CH_3CO$), 2.00–2.20 (2H, m, $CH_2P$), 1.22–1.31 (6H, m, $P(OCH_2CH_3)_2$); EIMS (*m*/*z*): 251 (M+1), 191, 163, 43; Anal. Calcd for $C_{10}H_{19}O_5P$: C, 48.00; H, 7.65. Found: C, 48.19; H, 7.61.

**4.2.21. (*R*)-Diethyl 3-chloro-2-hydroxypropanephosphonate (7f).**[28] Colorless oil, 50.2% ee, $[\alpha]_D^{25}=+3.5$ (*c* 2.2, $CHCl_3$); IR (neat) 3384, 2965, 1220, 1025 $cm^{-1}$; $^1H$ NMR ($\delta$): 4.14–4.31 (5H, m, *CHOH*; $P(OCH_2CH_3)_2$), 3.85 (1H, br, s, O*H*), 3.61 (2H, d, *J*=5.2 Hz, $ClCH_2$), 2.04–2.17 (2H, m, $CH_2P$), 1.25–1.36 (6H, m, $P(OCH_2CH_3)_2$); EIMS (*m*/*z*): 231 (M+1), 181, 139, 125, 111, 93.

**4.2.22. (*S*)-Diethyl 3-chloro-2-acetyloxypropanephosphonate (8f).** Colorless oil, ee value not determined; IR (neat) 2986, 1747, 1233, 1028, 969 $cm^{-1}$; $^1H$ NMR ($\delta$): 5.30 (1H, m, $ClCH_2CH$), 4.05–4.16 (4H, m, $P(OCH_2CH_3)_2$), 3.67–3.80 (2H, m, $ClCH_2$), 2.11–2.27 (2H, m, $CH_2P$), 2.10 (3H, s, $CH_3CO$), 1.29–1.34 (3H, m, $P(OCH_2CH_3)_2$); EIMS (*m*/*z*): 273 (M), 213, 195, 181, 125, 43; Anal. Calcd for $C_9H_{18}O_5PCl$: C, 39.65; H, 6.65. Found: C, 39.88; H, 6.67.

**4.2.23. Diethyl 3-hydroxybutanephosphonate (9).** Colorless oil, IR (neat) 3397, 1270, 1033 $cm^{-1}$; $^1H$ NMR ($\delta$): 4.00–4.10 (4H, m, $P(OCH_2CH_3)_2$), 3.89 (1H, m, *CHOH*), 2.90 (1H, br, s, O*H*), 1.67–1.87 (4H, $CH_2CH_2P$), 1.26–1.32 (6H, m, $P(OCH_2CH_3)_2$), 1.16 (3H, d, *J*=6.2 Hz, $CH_3CHOH$); EIMS (*m*/*z*): 195, 137, 121, 111, 82, 55; Anal. Calcd for $C_8H_{19}O_4P$: C, 45.71; H, 9.11. Found: C, 45.30; H, 8.89.

**4.2.24. Diethyl 3-acetyloxybutanephosphonate (10).** Colorless oil, IR (neat) 2984, 1737, 1375, 1246, 1057, 1026 $cm^{-1}$; $^1H$ NMR ($\delta$): 4.63 (1H, m, $CH_3CHCH_2CH_2P$), 4.03–4.13 (4H, m, $P(OCH_2CH_3)_2$), 2.02 (3H, s, $CH_3CO$), 1.73–1.85 (4H, $CH_2CH_2P$), 1.29–1.33 (6H, m, $P(OCH_2CH_3)_2$), 1.21 (3H, d, *J*=6.0 Hz, $CH_3CHCH_2CH_2P$); EIMS (*m*/*z*): 209, 193, 43; Anal. Calcd for $C_{10}H_{21}O_5P$: C, 47.62; H, 8.39. Found: C, 47.39; H, 8.38.

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