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Enantioselective Reduction of 2-Keto-3-Haloalkane Phosphonates by Baker's Yeast*

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ABSTRACT: *Bioreduction of 3-substituted-2-oxoalkanephosphonates by baker's yeast afforded 3-substituted-2-hydroxy-alkanephosphonates in moderate to good yields and ee value. These compounds could serve as useful chirons for the stereoselective synthesis of phosphorus analogs of biologically active molecules including R-(−)-3-trimethylammonium-2-hydroxypropanoic acid and R-(−)-3-trimethylammonium-2-hydroxypropanoic acid.* © 2001 John Wiley & Sons, Inc. Heteroatom Chem 12:551–556, 2001

INTRODUCTION

Baker's yeast (*Saccharomyces cerevisiae*) is now well recognized as a valuable stereoselective reagent in biotransformations of organic compounds [1–3]. The asymmetric reduction of carbonyl groups with this microbiological substance has been studied extensively, but little is known about its activity toward ketophosphonates [4]. On the other hand, chiral β-hydroxyalkanephosphonic acids have received much attention because of their unique physiological activities as well as their ability to mimic the corresponding hydroxy- or amino-alkanecarboxylic acids [5]. As important illustrative examples, (*R*)-(−)-3-amino-2-hydroxybutyric acid (GABOB) and (*R*)-(−)-3-trimethylammonium-2-hydroxypropanoic acid [(*R*)-(−)-Carnitine] can be cited, since the former has been used as an antiepileptic and hypotensive drug, while the latter is a vitamin-like compound that is responsible for the metabolism of long-chain fatty acids by regulating their transport through mitochondrial membranes. It is most important to note that the corresponding (*S*)-enantiomer of Carnitine acts as a competitive inhibitor of carnitine acyltransferase, causing depletion of the (*R*)-Carnitine level in heart tissue. Consequently, synthetic study of the phosphorus analogs of GABOB and Carnitine, particularly their stereoisomers, aroused our interest. In this article, a stereoselective synthesis of 3-halo (or azido)-2-hydroxypropanephosphonates by bioreduction with baker's yeast is discussed. In addition to phosphorus analogues, the target molecules can be regarded as useful phosphonate chirons for the preparation of optically active polyfunctional phosphonates with biological significance.

RESULTS AND DISCUSSION

The 3-halo-2-oxopropanephosphonates **1a–g** were prepared according to the literature [6], while the corresponding azido derivative **1h** was obtained by reaction of **1e** with sodium azide in DMF. We found that 3-iodo-2-oxopropanephosphonates were not suitable substrates in this case due to their instability.

*Studies on organophosphorus compounds 110.

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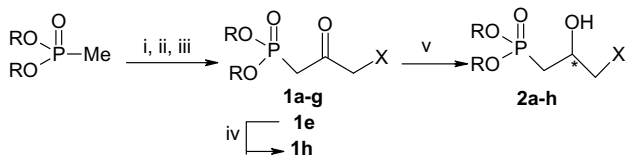


SCHEME 1 Reagents and conditions: (i) n-C_4H_9Li; (ii) CuCl or CuBr; (iii) $ClCOCH_2Cl$ or $BrCOCH_2Br$; (iv) NaN_3/DMF, 0°C; (v) baker's yeast, 30°C

The substrates **1a–h** thus obtained are stable in aqueous medium and undergo bioreduction with baker's yeast as illustrated in Scheme 1. The biotransformation was performed by shaking an aqueous (50 mL) suspension of dried baker's yeast (5 g) and substrate (0.5 mmol) at 30°C until the disappearance of the substrate was observed, as monitored by thin-layer chromatography (TLC).

As shown in Table 1, all 2-keto-3-halo/azido propanephosphonates (**1a–h**) can be transformed conveniently into the corresponding 2-hydroxypropanephosphonates (**2a–h**) in moderate to good yields and enantiomeric excess (ee) value. The enatioselectivity of the reaction was determined by means of ^{31}P NMR spectroscopy using quinine as a chiral discriminating agent, and this method may be applied for the tentative estimation of their configuration [7, 8]. In the meantime, the absolute configurations of the 3-substituted-2-hydroxypropanephosphonates were preliminarily assigned on the basis of two features: (1) the measurement of $\Delta\delta$ values in ^1H NMR spectra of their α-methoxy-α-trifluoromethylphenyl acetic acid (MTPA) esters using the modified Mosher's method [9], and (2) according to the general experimental observation, bioreduction of ketones by baker's yeast usually obeys Prelog's rule [10]. In our case, the phosphonate group is the larger substituent, while the chloromethyl moiety is the smaller one. Furthermore, under the same conditions, stereoselectivity of the reduction is strongly dependent on the chemical structure of 3-substituted 2-oxopropanephosphonates. As shown in Table 1, the ee values of the 3-bromo-2-hydroxypropanephosphonates are much larger than those of the corresponding chloro-counterparts (**e,f,g** vs. **b,c,d**). The ee value of 3-azido-2-hydroxypropanephosphonate **2h** was found to be up to 92%. These data demonstrated that the electron-withdrawing ability of the substituent on position 3 plays the dominating factor in governing the magnitude of the ee value of these reaction systems. Furthermore, the ee value of this bioreduction is also influenced significantly by the steric effect. Data in Table 1 show that the diisopropyl 3-halo-2-keto-propanephosphonates **1e** and **f** gave only 13 and 52% ee values, respectively. It seems that the keto-phosphonates with bulky diisopropyl groups hindered the bioreduction process.

TABLE 1 Reduction of **1a–e** with Baker's Yeast

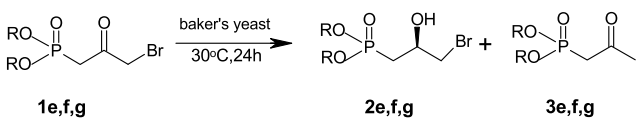
Substrate	*R*	*X*	*Time (h)*	*Yield (%)*	*ee (%)*[a]	*Config*[b]
1a	Me	Cl	24	74	70	*R*
1b	Et	Cl	12	82	72	*R*
1c	iPr	Cl	24	57	13	—
1d	nBu	Cl	24	88	70	*R*
1e	Et	Br	24	35[c]	83	*R*
1f	iPr	Br	24	41[c]	52	—
1g	nBu	Br	24	55[c]	87	*R*
1h	Ets	N_3	12	77	92	*S*

[a]The ee(%) was determined by the use of quinine as a chiral solvating agent [7, 8].
[b]The absolute configuration was determined according to Mosher's methods [9].
[c]The 2-oxopropanephosphonate was isolated as a by-product.

For the purpose of improving the enantioselectivity of the reduction, we introduced several experimental modifications. Either by adding dehydrogenase inhibitors, such as allyl alcohol, methyl vinylketone, and L-cysteine, or by the variation of ratio between the substrates **1a–g** and cosolvents, however, no significant improvement was observed; trials on the increase of the enatioselectivity of the microbial reduction are being carried on in our laboratory.

The unexpected experimental data in Table 1, that is, the low yield of bioreduction of **1e, f**, and **g**, attracted our attention. By careful study of the reaction products, in addition to 3-bromo-2-hydroxypropanephosphonates **2e,f**, and **g**, a significant amount (30–35%) of 2-keto-propanephosphonates **3e,f**, and **g** were isolated as by-products of the reaction (Scheme 2).

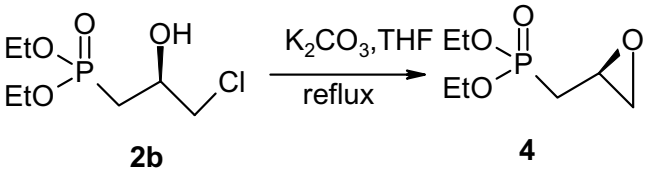
However, no dechlorinated products could be detected from the corresponding 3-chloro-2-oxopropanephosphonates. On the other hand, as found by Hamdani et al. [11], a free-radical reductive dehalogentation had taken place in the treatment of ethyl 2-chloro-3-oxobutanoate with baker's yeast in aqueous medium. Such an explanation is not applicable to our case, due to the different chemical environment of the halogen atom in the molecule. Consequently, the reaction mechanism for the



1e,f,g **2e,f,g** **3e,f,g**

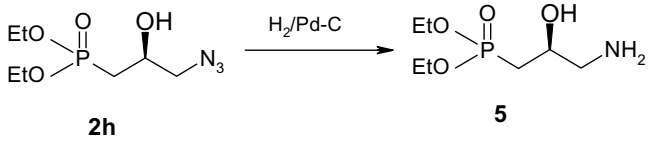
R = Et,iPr,nBu

SCHEME 2



2b **4**

SCHEME 3



2h **5**

SCHEME 4

formation of debrominated compounds (**3e,f,g**) is not yet clear. It should be pointed out that when **3e, 3f**, and **3g** were treated with baker's yeast, even for several days, no ^{31}P NMR signal for 2-hydroxypropanephosphonate was detected, even when the starting substrates had completely disappeared, as monitored by TLC. It is reasonable to conclude that 3-halo-2-oxo propanphosphonates undergo reduction mediated by baker's yeast much faster than does 2-oxopropanephosphonates.

As shown by our scaled-up experiments, 10 mmol of compounds **1a, 1b, 1d**, and **1h** can efficiently be reduced to the corresponding hydroxypropanephosphonates with 25 g baker's yeast without the loss of yield and optical purity of the products. Consequently, the bioreduction method described by us has potential application for large-scale preparations.

3-Halo-2-hydroxypropanephosphonates **2a–g** could readily be converted to 2,3-epoxypropanephosphonates in the presence of potassium carbonate; for example, diethyl 2,3-epoxypropanephosphonate (**4**) was prepared from diethyl 3-chloro-2-hydroxypropanephosphonate (**2b**) (Scheme 3). The enationmetric 2,3-epoxypropane phosphonates thus obtained are useful three-carbon phosphonate chirons for the synthesis of Fosfomycin derivatives [12,13,14].

Diethyl 3-azido-2-hydroxypropanephosphonate (**2h**), on hydrogenation using palladium on carbon as catalyst, provided diethyl 3-amino-2-hydroxypropane phosphonate (**5**), which is the phosphorus analog of (R)-GABOB (Scheme 4).

Therefore, reduction of 3-substituted-2-oxoalkanephosphonates by baker's yeast afforded the corresponding hydroxyalkanephosphonates in moderate to good yields and ee values. Stereoseletivity of the reduction was heavily dependent on the chemical structure of the 3-substituted-alkanephosphonate chirons for the stereospecific synthesis of polyfunctional phosphonates, which display promising or potential biological activities.

EXPERIMENTAL

IR spectra were recorded on a Shimadzu IR-440 spectrometer. EI-MS were run on an Hp-5989A mass spectrometer. ^1H and ^{13}P NMR spectra were recorded on a Bruker AMX-330 (300 MHz) spectrometer in $CDCl_3$ solutions, and chemical shifts (δ) were reported in ppm downfield relative to TMS (internal standard) and 80% phosphoric acid (external standard) in phosphorus spectra.

Baker's yeast was purchased from Sigma Co. Int. Spots in TLC monitoring were visualized by dipping the plate into a solution of 24 g of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ and 1 g of $Ce(SO_4)_2\cdot 4H_2O$ in 500 mL of 10% H_2SO_4 in water, followed by heating with a hot gun.

*3-Substituted-2-oxopropanephosphonates (***1***)*

Under a nitrogen atmosphere, butyllithium (0.05 mol) was added at −78°C to tetrahydrofuran (30 mL), followed by addition of the dialkylalkanephosphonate (0.05 mol), after 30 minutes of stirring, CuCl(or CuBr) (0.05 mol) was added, and the reaction mixture allowed to warm to −30°C during an hour. The acyl chloride (0.055 mol) in ether (50 mL) was added, and the mixture was allowed to warm to room temperature. Water (50 mL) was added, and the solution was filtered and washed with dichloromethane. The combined organic layers were dried with $MgSO_4$, and the product was purified by column chromatography (hexane/acetone as eluent, v/v = 2/1).

*Dimethy 3-chloro-2-oxopropanephosphonate (***1a***).* Colorless oil; R_f = 0.30; 7.30 g (yield 73%); IR (υ): 2980, 1735 (C=O), 1250, 1028 cm^{-1}, ^1H NMR (δ): 4.37(s, 2H, $\underline{CH_2}Cl$), 3.88 (d, 6H, J = 11 Hz, PO$\underline{Me}$), 3.37 (d, 2H, J = 23 Hz, P$\underline{CH_2}$). MS (*m/e*, %): 201(M + 1), 183, 151(base), 109, 79. Anal Calcd for $C_5H_{10}ClO_4P$: C, 29.94; H, 5.03; P, 15.44. Found: C, 29.90; H, 5.08; P, 15.13.

*Diethyl 3-chloro-2-oxoproanephosphonate (***1b).** Colorless oil; R_f = 0.45; 6.31 g (yield 55%); IR(υ): 2985, 1736 (C=O), 1396, 1252, 1025 cm^{-1},^1H NMR (δ): 4.25(s, 2H, $\underline{CH_2}Cl$), 4.15 (m, 4H, P$\underline{CH_2}CH_3$), 3.28 (d, 2H, J = 22 Hz, P$\underline{CH_2}$), 1.32 (m, 6H, PCH$_2\underline{CH_3}$). MS (*m/e*, %): 229 (M + 1), 179, 151, 137, 109, 81. Anal.

Calcd for $C_7H_{14}ClO_4P$ (228.61): C, 36.78; H, 6.17; P 13.55. Found: C, 36.81; H, 6.20; P, 13.49.

*Diisopropyl 3-chloro-2-oxoproanephosphonate (***1c***).* Colorless oil; $R_f = 0.50$; 9.73 g (yield 76%); IR(υ): 2984, 1736 (C=O), 1388, 1252, 992 cm^{-1}, ^1H NMR (δ): 4.70 (m, 2H, P(O)OCH$(CH_3)_2$), 4.26 (s, 2H, CH_2Cl), 3.16 (d, $J = 21$ Hz, PCH_2), 1.32 (12H, d, POCH $(CH_3)_2$). MS (*m/e*, %): 257 (M + 1), 215, 165, 123, 43. Anal. Calcd for $C_9H_{18}ClO_4P$ (256.66): C, 42.12; H, 7.07. Found: C, 42.23; H, 7.14.

*Dibutyl 3-chloro-2-oxoproanephosphonate (***1d***).* Colorless oil; $R_f = 0.65$; 7.67 g (yield 54%); IR(υ): 2963, 1737(C=O), 1256, 1026 cm^{-1}. ^1H NMR (δ): 4.35 (s, 2H, CH_2Cl),4.15 (m, 4H, $POCH_2C_3H_7$), 3.31 (d, 2H, $J = 22$ Hz, PCH_2), 1.70 (m, 4H, $POCH_2$ $CH_2CH_2CH_3$), 1.45(m, 4H, $POCH_2CH_2$ CH_2CH_3), 0.97 (m, 6H, $POCH_2$ $CH_2CH_2CH_3$). MS (*m/e*, %): 285 (M + 1), 229, 173,123 (base), 105, 57. Anal Calcd for $C_{11}H_{22}$ ClO_4P (284.72): C, 46.40; H, 7.79; P, 10.88. Found: C, 46.62; H, 7.56; P, 10.78.

*Diethyl 3-bromo-2-oxoproanephosphonate (***1e***).* Colorless oil; $R_f = 0.46$; 8.19 g (yield 60%); IR(υ): 2986, 1733(C=O), 1394, 1253, 1025 cm^{-1}. ^1H NMR (δ): 4.15 (m, 6H, $POCH_2CH_3$ + CH_2Br), 3.35 (d, 2H, $J = 23$ Hz, PCH_2), 1.40 (6H, $POCH_2CH_3$). MS (*m/e*, %): 274 (M + 1), 193, 179 (base), 165, 123, 109. Anal Calcd for $C_7H_{14}BrO_4P$ (273.06): C, 30.79; H, 5.17; P, 11.34. Found: C, 30.94; H, 5.15; P, 11.04.

*Diisopropyl 3-bromo-2-oxoproanephosphonate (***1f***).* Colorless oil; $R_f = 0.55$; 6.77 g (yield 45%); IR(υ): 2987, 1773(C=O), 1280, 1254 cm^{-1}. ^1H NMR (δ): 4.76(m, 2H, $POCH(CH_3)_2$),4.34 (s, 2H, CH_2Br), 3.23(d, 2H, $J = 23$ Hz, PCH_2), 1.36 (12H, d, $POCH(CH_3)2$). MS (*m/e*, %): 302 (M + 1),165. Anal Calcd for $C_9H_{18}BrO_4P$ (301.12): C, 35.90; H, 6.03. Found: C, 35.97; H, 6.15.

*Dibutyl 3-bromo-2-oxoproanephosphonate (***1g***).* Yellow oil; $R_f = 0.65$; 9.04 g (yield 55%); IR(υ): 2963, 1734(C=O), 1255, 1025 cm^{-1}. ^1H NMR (δ): 4.07(s, 2H, CH_2Br), 4.02 (m, 4H, $POCH_2$), 3.27 (d, 2H, $J = 22$ Hz, PCH_2), 1.62 (4H, m, $POCH_2CH_2CH_2CH_3$), 1.35 (4H, m, $POCH_2CH_2CH_2CH_3$), 0.89 (6H, m, $POCH_2CH_2CH_2$ CH_3). ^{31}P NMR (δ): 19.8. MS (*m/e*, %): 331 (M + 2), 329, 275, 273, 137, 123 (base), 57, 41. Anal Calcd for $C_{11}H_{22}BrO_4P$ (329.17): C, 40.13; H, 6.74. Found: C, 40.34; H, 6.77.

*Diethyl 3-azido-2-oxo-proanephosphonate (***1h***).* To a stirred solution of diethyl 3-bromo-2-oxoproanephosphonate (**1e**) (0.273 g, 1.1 mmol) in DMF (10 mL) was added NaN_3 (0.071 g) at 0°C, and the resulting mixture was stirred while being monitored by TLC. After 4–6 hours, water (50 mL) was added, and the solution was washed with dichloromethane (20 mL × 4). The product was purified by column chromatography (hexane/acetone = 2/1).

Colorless oil; $R_f = 0.55$; yield 85%; IR(υ): 2987, 2913, 2109(s), 1730(C=O), 1256, 1025 cm^{-1}. ^1H NMR (δ): 4.15(m, 6H, $POCH_2CH_3$ + CH_2N_3), 3.10 (d, 2H, $J = 19$ Hz, PCH_2), 1.35 (m, 6H, $POCH_2CH_3$). MS (*m/e*, %): 236 (M + 1), 208, 179, 151, 123, 109, 81. Anal Calcd for $C_7H_{14}N_3O_4P$ (235.18): C, 35.75; H, 6.00; N, 17.54. Found: C, 35.93; H, 6.10; N, 17.62.

General Procedure for the Reaction of Baker's Yeast with **1a–1h**

Baker's yeast (5 g) was suspended in water (50 mL), then each phosphonate **1a–h** (0.5 mmol) was added and the mixture was shaken at 30°C, while being monitored by TLC. The biomass was removed and extracted with ethyl ether and with chloroform (20 mL×3). The combined organic layers were dried over anhydrous $MgSO_4$, and the solvents were removed under reduced pressure. The product was separated by column chromatography(hexane/acetone = 3/2).

*Conversion of 3-Substituted-2-hydroxyproanephosphonates (***2***) to the Corresponding α-Methoxy-α-trifluoromethylphenyl-Acetic Acid (MT-PA) Esters*

To a stirred solution of 0.1 mmol (*R*)[or (*S*)]-α-methoxy-α-trifluoromethylphenyl acetic acid (MTPA) in 1 mL anhydrous CH_2Cl_2 was added 0.1 mmol of hydroxypropanephosphonates (**2**) and 2–3 mg of DMAP. The dicyclohexlcarbodiimide (DCC) (0.1 mmol) was added to the reaction mixture at 0°C, which was then stirred for 8 hours at 0°C. Precipitated urea was then filtered off. CH_2Cl_2 (20 mL) was added, and the solution was washed twice with saturated $NaHCO_3$ solution and then dried with $MgSO_4$. The solvent was removed by evaporation, and the ester was purified by column chromatography (hexane/acetone = 3/2).

*(***R***)-Dimethyl 3-chloro-2-hydroxypropanephosphonate (***2a***).* Colorless oil; $R_f = 0.35$; 74 mg (yield = 74%), ee 72%; IR(υ): 3340(OH), 1228(P=O) cm^{-1}. ^1H NMR (δ): 4.25(1H, -OH); 3.80 (d, 6H, $2CH_3OP$); 3.55 (d, 2H, CH_2Cl); 3.50 (m,CHOH); 2.10 (m, 2H, CH_2P); ^{31}P NMR (δ): 31.8; MS (*m/e*, %): 203 (M + 1, base), 185, 153, 109, 79; Anal. Calcd for $C_5H_{12}ClO_4P$

(202.57): C, 29.63; H, 5.93; P, 15.29. Found: C, 29.39; H, 5.79; P, 15.18.

*(R)-Diethyl 3-chloro-2-hydroxypropanephosphonate (***2b***).* Colorless oil; $R_f = 0.50$; 94 mg (yield 82%), ee 70%; IR(υ): 3337, 2962, 1222 (P=O) cm^{-1}. ^1H NMR (δ): 4.35(1H, -OH); 4.10 (m, 4H, OCH_2CH3); 3.65 (d, 2H, CH_2Cl); 3.30 (m, 1H, CHOH); 2.10 (m, 2H, CH_2P); 1.65 (m, 2H, CH_2); 1.40 (m, 2H, CH_2); 0.95 (m, 6H, CH_3CH_2O–P); ^{31}P NMR (δ): 28.9 ppm; MS (*m/e*, %): 231(M + 1), 181, 153, 125 (base), 107, 81; Anal. Calcd for $C_7H_{16}ClO_4P$ (230.60): C, 36.52; H, 6.96; P, 13.43; Found: C, 36.56; H, 7.16; P, 12.95.

(*R*)-MTPA-(*R*)-(**2b**): ^1H NMR (δ): 7.55 (2H, Ph), 7.42 (3H, Ph), 5.52 (1H, HCO), 4.13 (m, 4H, $POCH_2$), 3.87 (m, 2H, CH_2Cl), 3.56 (s, 3H, OCH_3), 2.21 (m, 2H, PCH_2), 1.31 (m, 6H, $POCH_2CH_3$).

(*S*)-MTPA-(*R*)-(**2b**): ^1HNMR (δ): 7.55 (2H, Ph), 7.42 (3H, Ph), 5.52 (1H, HCO), 4.13 (m, 4H, $POCH_2$), 3.82 (m, 2H, CH_2Cl), 3.56 (s, 3H, OCH_3), 2.28 (m, 2H, PCH_2), 1.31 (m, 6H, $POCH_2CH_3$).

*Diisopropyl 3-chloro-2-hydroxypropanephosphonate (***2c***).* Colorless oil; $R_f = 0.55$; 73 mg(yield 57%), ee 13%; IR(υ):3285(-OH), 2983, 1387, 1377, 1216 (P=O), 1021 cm^{-1}, ^1H NMR (δ): 4.72(m, 2H, $POCH(CH_3)_2$), 4.24(1H, -OH); 3.61 (d, 2H, CH_2Cl), 2.05 (m, 2H, CH_2P), 1.34(d, 12H, $POCH(CH_3)_2$); ^{31}P NMR (δ): 29.2, MS (*m/e*, %): 259(M + 1, base), 217, 175, 139, 125, 43; Anal. Calcd for $C_9H_{20}ClO_4P$ (258.68): C, 41.70; H, 7.73; P, 11.97; Found: C, 41.70; H, 7.81; P, 11.79.

*(R)-Dibutyl 3-chloro-2-hydroxypropanephosphonate (***2d***)* . Colorless oil; $R_f = 0.58$; 118 mg (yield 88%), ee 70%; IR(υ):3337(-OH), 2962, 1222 (P=O) cm^{-1}. ^1H NMR (δ): 4.35 (1H, -OH), 4.10 (m, 4H, $OCH_2C_3H_7$), 3.65 (d, 2H, CH_2Cl), 3.30 (m, 1H, CH), 2.10 (m, 2H, CH_2P), 1.65 (m, 2H, CH_2), 1.40 (m, 2H, CH_2), 0.95 (m, 6H, CH_3). ^{31}P NMR (δ): 28.5. MS (*m/e*, %): 287 (m + 1), 237, 175, 157, 125 (base), 107. Anal. Calcd for $C_{11}H_{24}ClO_4P$ (286.73): C, 46.03; H, 8.37; P, 10.80; Found: C, 45.67; H, 8.46; P, 10.97.

(*R*)-MTPA-(*R*)-(**2d**): 7.59 (2H, Ph), 7.47 (3H, Ph), 5.38 (1H, HCO), 4.10 (m, 4H, $OCH_2C_3H_7$); 3.65 (d, 2H, CH_2Cl); 3.64 (s, 3H, OCH_3), 2.10 (m, 2H,CH_2P); 1.65 (m, 2H, CH_2); 1.40 (m, 2H, CH_2); 0.95 (m, 6H, CH_3).

(*S*)-MTPA-(*R*)-(**2d**): 7.59 (2H, Ph), 7.47 (3H, Ph), 5.38 (1H, HCO), 4.10 (m, 4H, $OCH_2C_3H_7$); 3.60 (d, 2H, CH_2Cl); 3.64 (s, 3H, OCH_3), 2.17 (m, 2H,CH_2P); 1.65 (m, 2H, CH_2); 1.40 (m, 2H, CH_2); 0.95 (m, 6H, CH_3).

*(R)-Diethyl 3-bromo- 2-hydroxypropanephosphonate (***2e***).* Colorless oil; $R_f = 0.50$; 48 mg (yield 35%), ee 83%; IR(υ): 3339 (-OH), 1226 (P=O), 1055 (P-OC_2H_5) cm^{-1}, ^1H NMR (δ): 4.15 (m, 4H, OCH_2CH_3), 3.52 (d, 2H, CH_2Br), 3.10 (1H, OH), 2.10 (m, 2H, CH_2P), 1.36 (m, 6H, OCH_2CH_3). $^{31}PNMR$ (δ): 29.2. MS (*m/e*, %):277 (M + 2, base), 275, 259, 181, 125, 107; Anal. Calcd for $C_7H_{16}BrO_4P$ (275.08): C, 30.54; H, 5.82; Found: C, 30.60; H, 5.91.

(*R*)-MTPA-(*R*)-(**2e**): ^1H NMR (δ): 7.56 (2H, Ph), 7.42 (3H, Ph), 5.49 (1H, HCO), 4.12 (m, 4H, $POCH_2$), 3.73(m, CH_2Br), 3.64 (s, 3H, OCH_3), 2.25 (m, 2H, PCH_2), 1.30 (m, 6H, $POCH_2CH_3$).

(*S*)-MTPA-(*S*)-(**2e**): ^1H NMR (δ): 7.56 (2H, Ph), 7.42 (3H, Ph), 5.49 (1H, HCO), 4.12 (m, 4H, $POCH_2$), 3.68(m, CH_2Br), 3.64 (s, 3H, OCH_3), 2.34 (m, 2H, PCH_2), 1.30 (m, 6H, $POCH_2CH_3$).

*Diisopropyl 3-bromo-2-hydroxypropanephosphonate(***2f***)*

Colorless oil; $R_f = 0.55$; 62 mg (yield 41%), ee 52%; IR(υ): 3300 (-OH), 1375, 1380, 1233 (P=O) cm^{-1}. ^1H NMR (δ): 4.78 (2H, $POCH(CH_3)_2$), 4.18 (1H, m, CH_1OH), 3.55 (d, 2H, CH_2Br), 1.62 (m, 2H, PCH_2), 1.33 (12H, d, $POCH(CH_3)_2$). ^{31}P NMR (δ): 29.0 ppm. MS (*m/e*, %): 302 (M + 1), 221, 219, 201, 203, 167, 139, 125 (base), 43. Calcd for $C_9H_{20}BrO_4P$ (303.12): C, 35.66; H, 6.65. Found: C, 35.79; H, 6.55.

*(R)-Dibutyl 3-bromo-2-hydroxypropanephosphonate (***2g***)*

Colorless oil; $R_f = 0.60$; 78 mg (yield 55%), ee 87%; IR(cm^{-1}): 3337(-OH), 2962, 1222 (P=O); ^1H NMR (δ): 4.11 (1H, -OH); 4.07 (m, 4H, $POCH_2C_3H_7$); 3.51 (d, 2H, CH_2Br); 2.20 (m, 2H, CH_2P); 1.67 (m, 2H, CH_2); 1.39 (m, 2H, CH_2); 0.94 (m, 6H, CH_3) ppm. ^{31}P NMR (δ): 29.0. MS (*m/e*, %): 333 (M + 2), 331, 251, 221, 219, 125 (base), 97; Anal Calcd for $C_{11}H_{24}BrO_4P$ (331.18): C, 39.89; H, 7.30. Found: C, 40.04; H, 7.47.

*(S)-Diethyl 3-azido-2-hydroxypropanephosphonate (***2h***)*

Colorless oil; $R_f = 0.60$; 90 mg (yield 77%), ee 92%; IR(υ): 3343(-OH), 2986, 2105(vs), 1225 (P=O), 1050 (P-OC_2H_3) cm^{-1}. ^1H NMR (δ): 4.20(1H, OH), 4.13 (m, 6H, OCH_2CH_3), 3.37 (d, 2H, CH_2N_3), 2.01(m, 2H, CH_2P), 1.35 (m, 6H, OCH_2CH_3). ^{31}P NMR (δ): 29.1. MS (*m/e*, %): 238 (M, base), 181, 153, 125, 107, 72; Anal. Calcd for $C_7H_{16}N_3O_4P$ (238.17): C, 35.30; H, 6.35; N, 17.64; Found: C, 35.22; H, 6.75; N, 17.29.

(*R*)-MTPA-(*S*)-(**2h**): ^{1}H NMR (δ): 7.54 (2H, Ph), 7.41 (3H, Ph), 5.39 (m, 1H, HCO), 4.10 (m, 4H, $PO\underline{CH_2}$), 3.72 (m, 2H, CH_2N_3), 3.57 (s, 3H, OCH_3), 2.16 (m, 2H, CH_2P), 1.32(m, 6H, $POCH_2\underline{CH_3}$).

(*S*)-MTPA-(*S*)-(**2h**): ^{1}H NMR (δ): 7.54 (2H, Ph), 7.41 (3H, Ph), 5.39 (m, 1H, HCO), 4.13 (m, 4H, $PO\underline{CH_2}$), 3.62 (m, 2H, CH_2N_3), 3.57 (s, 3H, OCH_3), 2.23 (m, 2H, $\underline{CH_2}P$), 1.34(m, 6H, $POCH_2\underline{CH_3}$).

*Diethyl 2-oxopropanephonate (***3e***)*. Colorless oil; $R_f = 0.25$; yield 35%; ^{1}H NMR (δ): 4.07 (m, 4H, $PO\underline{CH_2}CH_3$), 3.20 (d, 2H, $J = 22$ Hz, $P\underline{CH_2}$), 2.30 (s, 3H, $\underline{CO}CH_3$), 1.30 (m, 6H, $POCH_2\underline{CH_3}$). MS (*m/e*, %): 195 (M + 1), 179, 167, 152, 125, 97, 81.

*Diisopropyl 2-oxopropanephonate (***3f***)*. Colorless oil; $R_f = 0.45$; yield 35%; ^{1}H NMR (δ): 4.72 (m, 2H, $PO\underline{CH}(CH_3)_2$), 3.09 (d, 2H, $P\underline{CH_2}$), 2.32(s, 3H, $COCH_3$), 1.33 (d, 12H, $POCH(\underline{CH_3})_2$). MS (*m/e*, %): 223 (M + 1), 180,153,125,97.

*Dibutyl 2-oxopropanephonate (***3g***)*. Colorless oil; $R_f = 0.40$; yield 30%; ^{1}H NMR (δ): 4.05(m, 4H, $POCH_2$), 3.16(d, 2H, $J_{PH} = 23$ Hz, PCH_2), 2.32 (s, 3H, $COCH_3$),1.66 (4H, $POCH_2CH_2CH_2CH_3$), 1.40 (m, 4H, $POCH_2CH_2CH_2CH_3$), 0.93 (6H, $POCH_2CH_2CH_2CH_3$). MS (*m/e*, %): 251 (M + 1), 153, 139, 125, 97, 58.

*Conversion of (R)-Diethyl-3-chloro-2-hydroxypropanephosphonate (***2b***) to (S)-Diethyloxiranylmethylphosphonate (***4***)*

To a stirred solution of compound (*R*)-diethyl-3-chloro-2-hydroxypropane phosphonate **2b** (0.228 g,1 mmol) in tetrahydrofuran (20 mL), K_2CO_3 (0.138 g, 2 mmol) was added at room temperature, the resulting mixture was refluxed while monitored by TLC, and the product was purified by column chromatography (hexane/acetone, v/v = 3/2) to afford 0.178 g of (*S*)-diethyl oxiranylmethyl phosphonate (4).

Colorless oil; $R_f = 0.33$,yield 92%. IR(υ): 1250 (P=O),1158 (P-OC_2H_5), 1020 cm^{-1}. ^{1}H NMR (δ): 4.05 (m, 4H, $PO\underline{CH_2}CH_3$), 3.20 (m, 1H, CHO), 2.55 (m, 2H,$\underline{CH_2}O$), 1.83 (m, PCH_2), 1.28 (m, 6H, $POCH_2CH_3$). MS (*m/e*, %): 195(M + 1), 167, 149, 139, 121, 109, 81.

Anal Calcd for $C_7H_{15}O_4P$ (194.17): C, 43.30; H, 7.78; Found: C, 43.28; H, 7.75.

*Conversion of (S)-Diethyl-3-azido-2-hydroxypropanephosphonate (***2h***) to (S)-diethyl-3-amino-2-hydroxypropanephosphonate (***5***)*

The mixture of (*S*)-diethyl 3-azido-2-hydroxypropanephosphonate (**2h**) (200 mg) and palladium (10%) on carbon (10 mg in 20 mL MeOH) was stirred for 4 hours under hydrogen gas at 25°C. The mixture was filtered, and the solvents were removed under reduced pressure. The product was purified to afford 167 mg of (*S*)-diethyl 3-amino-2- hydroxypropanephosphonate (**5**), yield 95%.

^{1}H NMR (δ):4.70 (3H, NH_2 + OH), 4.05 (m, 4H, $PO\underline{CH_2}CH_3$), 2.75 (d, 2H, $\underline{CH_2}NH_2$), 1.30 (m, 2H, $PO\underline{CH_2}$), 1.28 (m, 6H, $POCH_2\underline{CH_3}$). MS (*m/e*, %):212 (M + 1), 181, 138, 125, 96, 70; Anal Calcd for $C_7H_{18}NO_4P$ (211.20): C, 39.80; H, 8.59; Found: C, 39.56; H, 8.50.

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