

## Article

# Synthesis of $\alpha$ -Hydroxyethylphosphonates and $\alpha$ -Hydroxyethylphosphine Oxides: Role of Solvents During Optical Resolution

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**Abstract:** Five chiral, racemic dialkyl  $\alpha$ -hydroxyethylphosphonates and  $\alpha$ -hydroxyethyl-diarylphosphine oxides were prepared in a scalable manner. Possibilities for the optical resolution of the racemic hydroxyphosphine oxides were explored via diastereomeric complex-forming experiments. The acidic calcium salt of *O,O'*-dibenzoyl-(2*R*,3*R*)-tartaric acid and *O,O'*-di-*p*-tolyl-(2*R*,3*R*)-tartaric acid were chosen as the resolving agents. The role of the solvent in the enantiomeric discrimination was investigated. The diastereomeric complex could be obtained in a crystalline form for  $\alpha$ -hydroxyethyl-diphenylphosphine oxide and  $\alpha$ -hydroxyethyl-bis(4-methylphenyl)phosphine oxide. However, in the third case, for  $\alpha$ -hydroxyethyl-bis(3,5-dimethylphenyl)phosphine oxide, there was no chiral discrimination. Decomposition of the recrystallized diastereomeric complex followed by decomposition of the complex yielded the target compounds in 77/90% enantiomeric excess. The absolute configuration of the hydroxyethyl-diphenylphosphine oxide was determined by single-crystal X-ray diffraction measurements. The interactions stabilizing the supramolecular associate were evaluated.

**Keywords:** Pudovik reaction; dialkyl  $\alpha$ -hydroxyethylphosphonates;  $\alpha$ -hydroxyethyl-diarylphosphine oxides; optical resolution; optical isomers; X-ray; crystallography; intermolecular interactions; H-bonding



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## 1. Introduction

The outstanding and broad spectrum of biological properties of  $\alpha$ -hydroxyphosphonates makes them indispensable in the family of enzyme inhibitors [1], herbicides [2], bactericides [3], fungicides [4], antioxidants [5], and cytotoxic agents [6,7]. In the pharmaceutical industry, it is essential to prepare biologically active compounds in an enantiomerically pure form. The enantiomers of racemic compounds may have different biological properties, and therefore, in most cases, the aim is to produce a single enantiomer [8,9]. Typically, this may be achieved by enantioselective syntheses [10–12] or the optical resolution of racemic compounds [13–17]. The most commonly used approach for the synthesis of optically active  $\alpha$ -hydroxyphosphonates is the addition of dialkyl phosphites on the C=O group of the oxo compounds in the presence of a chiral organocatalyst [18–20]. Metal complexes containing chiral ligands may be used as catalysts instead of organocatalysts [21–24]. Another method involves the reaction of an oxo compound and a trialkyl phosphite in an enantioselective Abramov-type condensation [25]. Optically active  $\alpha$ -hydroxyphosphonates may also be obtained by the asymmetric reduction of  $\alpha$ -keto compounds [26–28]. Examples for the enantioselective oxidation of benzylphosphonates to  $\alpha$ -hydroxyphosphonates have been also described [29,30]. As in the case of other hydroxy compounds, enantiomers

of  $\alpha$ -hydroxyphosphonates may also be prepared by enzyme-catalyzed kinetic acylation followed by the separation of the formed ester and the unchanged starting material [31]. This approach usually involves the selective acylation of one of the enantiomers of  $\alpha$ -hydroxyphosphonate in the presence of an enzyme [32,33] or chiral organocatalyst [34]. Another way of resolution is to acylate the hydroxy group of hydroxyphosphonate with an optically active reagent to afford the products as diastereomeric mixtures. The diastereomers are then separated, for example, by chromatography. *O,O'*-dibenzoyl-(2*R*,3*R*)-tartaric acid anhydride is often used as a chiral derivatization agent. After the separation of the esters, the hydroxy compounds may be recovered by hydrolysis [35].

Earlier, we described the synthesis of racemic dialkyl 1-hydroxy-arylmethylphosphonates, whose structure was determined by single-crystal X-ray analysis [36]. In another article, we reported the synthesis and resolution of  $\alpha$ -hydroxy-arylmethylphosphonates [37]. Previously, we successfully resolved cyclic phosphine oxides and phosphinates as related structures. We used the acid calcium salt of *O,O'*-dibenzoyl-(2*R*,3*R*)-tartaric acid [38] and TADDOL [39] as the resolving agents.

In this article, we report the scaled-up preparation of dialkyl- $\alpha$ -hydroxyethylphosphonates and  $\alpha$ -hydroxyethyl-diarylphosphine oxides and the optical resolution of a part of the racemic compounds. Calcium hydrogen *O,O'*-dibenzoyl-(2*R*,3*R*)-tartrate and calcium hydrogen *O,O'*-di-*p*-tolyl-(2*R*,3*R*)-tartaric acid coordination complexes, well suited to our target molecules, were selected as the resolving agents.

## 2. Materials and Methods

### 2.1. General

The  $^{31}\text{P}$ ,  $^{13}\text{C}$ , and  $^1\text{H}$ -NMR spectra were measured on a Bruker DRX-500 (Bruker, Billerica, MA, USA) or Bruker Avance-300 (Bruker, Billerica, MA, USA) spectrometer operating at 202, 126, and 500 MHz or 122, 75, and 300 MHz, respectively. The couplings were given in Hz. LC-MS measurements were performed with an Agilent 1200 liquid chromatography system coupled with a 6130 quadrupole mass spectrometer equipped with an ESI ion source (Agilent Technologies, Palo Alto, CA, USA). High-resolution mass spectrometric measurements were performed using a Thermo Velos Pro Orbitrap Elite (Thermo Fisher Scientific, Waltham, MA, USA) hybrid mass spectrometer in the positive electrospray mode.

The diastereomeric and enantiomeric excess (de and ee) values were determined by chiral HPLC on a Perkin Elmer Series 200 (PerkinElmer, Inc., Shelton, CT, USA) instrument equipped with chiral HPLC using Phenomenex Lux<sup>®</sup> i-Amylose-35 (Phenomenex, Torrance, CA, USA)  $\mu\text{m}$  column (150  $\times$  4.6 mm ID, hexane/isopropyl alcohol 90:10 as an eluent with a flow rate of 1 mL/min,  $T = 25^\circ\text{C}$ , UV detector  $\lambda = 254\text{ nm}$ ). Retention times: 13.6 min for (*S*)-**1c** (for the other enantiomer,  $t_{\text{ret}}$  is 16.8 min); 28.5 min for (*S*)-**1d** (for the other enantiomer,  $t_{\text{ret}}$  is 36.7 min). Resolving agent  $\text{Ca}(\text{H-DBTA})_2$  (**2**) and  $\text{Ca}(\text{H-DpTTA})_2$  (**3**) [40] were prepared according to procedures reported by us.

### 2.2. General Procedure for the Synthesis of Dialkyl $\alpha$ -Hydroxyethylphosphonates (**1a,b**) or $\alpha$ -Hydroxyethyl-Diarylphosphine Oxides (**1c-e**)

A 0.10 mol quantity of acetaldehyde (5.6 mL) and 0.05 mol of dialkyl phosphite (diethyl phosphite 6.4 mL, dibutyl phosphite 9.8 mL) or 0.05 mol of diarylphosphine oxide (diphenylphosphine oxide 10.1 g, bis(4-methylphenyl)phosphine oxide 11.5 g, bis(3,5-dimethylphenyl)phosphine oxide 12.9 g) and 0.05 mmol (7.0 mL) of triethylamine were stirred in 25 mL of ethyl acetate at  $0^\circ\text{C}$  for 12 h.

In the case of **1a**, **1b**, and **1d**, the mixture was evaporated under vacuum, and the crude products were purified by column chromatography (using ethyl acetate as the eluent on silica gel).

Hydroxyphosphine oxides **1c** and **1e** crystallized out from the reaction mixture. They were purified by recrystallization as follows: Crude products **1c** (~12 g) and **1e** (~15 g) were dissolved in toluene (100 mL), 600–750 mg (5%) of charcoal was added, and the mixture was

stirred at the boiling point of toluene for 0.5 h. The mixture was filtered, and the charcoal was washed with toluene (10 mL). The solvent was evaporated so that the remaining mass of the residue should be ~30 g, and then, hexane (100 mL) was added dropwise to the mixture. After stirring for 2 h, the precipitated product was filtered off and washed with hexane (10 mL) to give product **1c** in a yield of 97% (11.9 g) and compound **1e** in a yield of 98% (14.8 g).

Products **1a** and **1b** are pale yellow oils, compound **1d** is a viscous, colorless oil, and hydroxyphosphine oxides **1c** and **1e** are white crystalline compounds.

### 2.2.1. Diethyl $\alpha$ -Hydroxyethylphosphonate (**1a**)

Yield: 8.5 g (93%); pale yellow oil;  $^{31}\text{P}$   $\{^1\text{H}\}$  NMR (122 MHz,  $\text{CDCl}_3$ )  $\delta$  25.9;  $\delta_{\text{P,lit.}}$  [41] 27.9;  $[\text{M} + \text{H}]^+ = 183$ ; HRMS  $m/z$ :  $[\text{M} + \text{Na}]^+$  calculated for  $\text{C}_6\text{H}_{15}\text{O}_4\text{PNa}$  205.0606; found 205.0606.

### 2.2.2. Dibutyl $\alpha$ -Hydroxyethylphosphonate (**1b**)

Yield: 9.0 g (76%); pale yellow oil;  $^{31}\text{P}$   $\{^1\text{H}\}$  NMR (202 MHz,  $\text{CDCl}_3$ )  $\delta$  25.8;  $\delta_{\text{P,lit.}}$  [42] 25.8;  $[\text{M} + \text{H}]^+ = 239$ ; HRMS  $m/z$ :  $[\text{M} + \text{Na}]^+$  calculated for  $\text{C}_{10}\text{H}_{23}\text{O}_4\text{PNa}$  261.1232; found 261.1227.

### 2.2.3. $\alpha$ -Hydroxyethyl-Diphenylphosphine Oxide (**1c**)

Yield: 11.9 g (97%); white crystal; m.p.: 130–131 °C; m.p. [43] 131–132 °C;  $^{31}\text{P}$   $\{^1\text{H}\}$  NMR (202 MHz,  $\text{CDCl}_3$ )  $\delta$  33.5;  $\delta_{\text{P,lit.}}$  [44] 32.9;  $[\text{M} + \text{H}]^+ = 247$ ; HRMS  $m/z$ :  $[\text{M} + \text{Na}]^+$  calculated for  $\text{C}_{14}\text{H}_{15}\text{O}_2\text{PNa}$  269.0707; found 269.0704.  $[\text{M} + \text{H}]^+$  calculated for  $\text{C}_{14}\text{H}_{16}\text{O}_2\text{P}$  247.0888; found 247.0878.

### 2.2.4. $\alpha$ -Hydroxyethyl-Bis(4-Methylphenyl)phosphine Oxide (**1d**)

Yield: 11.5 g (84%); viscous, colorless oil;  $^{31}\text{P}$   $\{^1\text{H}\}$  NMR (202 MHz,  $\text{CDCl}_3$ )  $\delta$  33.8;  $\delta_{\text{P,lit.}}$  [45] 33.3;  $[\text{M} + \text{H}]^+ = 275$ ; HRMS  $m/z$ :  $[\text{M} + \text{Na}]^+$  calculated for  $\text{C}_{16}\text{H}_{19}\text{O}_2\text{PNa}$  297.1020; found 297.1018;  $[\text{M} + \text{H}]^+$  calculated for  $\text{C}_{16}\text{H}_{20}\text{O}_2\text{PNa}$  275.1201; found 275.1198.

### 2.2.5. $\alpha$ -Hydroxyethyl-Bis(3,5-Dimethylphenyl)phosphine Oxide (**1e**)

Yield: 14.8 g (98%); white crystal; m.p.: 192–193 °C;  $^{31}\text{P}$   $\{^1\text{H}\}$  NMR (202 MHz,  $\text{CDCl}_3$ )  $\delta$  35.5;  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  16.7 (d,  $J = 2.7$  Hz,  $\text{CCH}_3$ ), 21.2 (d,  $J = 3.6$  Hz,  $\text{ArCH}_3$ ), 66.2 (d,  $J = 83.4$  Hz, CP), 128.7 (d,  $J = 9.0$  Hz,  $\text{C}_\beta$ ), 129.2 (d,  $J = 8.7$  Hz,  $\text{C}_\beta$ ), 129.4 (d,  $J = 95.2$  Hz,  $\text{C}_\alpha$ ), 130.3 (d,  $J = 92.7$  Hz,  $\text{C}_\alpha$ ), 133.7 (d,  $J = 2.8$  Hz,  $\text{C}_\delta$ ), 133.8 (d,  $J = 2.9$  Hz,  $\text{C}_\delta$ ), 138.1 (d,  $J = 12.2$  Hz,  $\text{C}_\gamma$ ), 138.3 (d,  $J = 11.9$  Hz,  $\text{C}_\gamma$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.48 and 1.51 (d,  $J = 7.1$  Hz, 3H,  $\text{CCH}_3$ ), 2.31 (s, 1H, OH), 2.38 (d,  $J = 3.8$  Hz, 12H,  $\text{ArCH}_3$ ), 4.70–4.75 (m, 1H, CH), 7.23–7.50 (m, 6H, ArH);  $[\text{M} + \text{H}]^+ = 303$ ; HRMS  $m/z$ :  $[\text{M} + \text{Na}]^+$  calculated for  $\text{C}_{18}\text{H}_{23}\text{O}_2\text{PNa}$  325.1333; found 325.1330.

## 2.3. Procedure for the Preparation of Optically Active $\text{Ca}[(S)\text{-1c} \bullet \text{H-DBTA}]_2$ Complex

A mixture of 3.7 mmol (0.92 g) of  $\alpha$ -hydroxyethyl-diphenylphosphine oxide (**1c**) and 0.93 mmol (0.69 g) of  $\text{Ca}(\text{H-DBTA})_2$  was dissolved in 3.0 mL of ethanol and 30 mL of ethyl acetate at reflux. After the solution became clear, it was allowed to cool to 26 °C. After stirring for 24 h at 26 °C, the crystalline diastereomeric complex was filtered, and it was washed with  $3 \times 1.5$  mL of ethyl acetate to give 0.55 g (yield = 48%) of  $\text{Ca}[(S)\text{-1c} \bullet \text{H-DBTA}]_2$ . To 3 mg of  $\text{Ca}[(S)\text{-1c} \bullet \text{H-DBTA}]_2$ , 0.5 mL of ethyl acetate and 0.05 mL of saturated  $\text{Na}_2\text{CO}_3$  solution were added. After intense stirring, the organic phase was dried ( $\text{Na}_2\text{SO}_4$ ), and the solvent was evaporated to afford (S)-**1c** with an enantiomeric excess of 38%.

The diastereomeric complex was purified by recrystallization: 1.4 mL of ethanol and 5.5 mL of ethyl acetate was added to the diastereomeric complex, and the suspension was heated at reflux until it became clear. The solution was allowed to cool to 26 °C, and it was

stirred for 24 h at 26 °C. Filtration of the crystalline diastereomeric complex afforded 0.32 g (yield = 28%) of  $\text{Ca}[(S)\text{-1c} \bullet \text{H-DBTA}]_2$ .

To 3 mg of  $\text{Ca}[(S)\text{-1c} \bullet \text{H-DBTA}]_2$ , 0.5 mL of ethyl acetate and 0.05 mL of saturated  $\text{Na}_2\text{CO}_3$  solution was added. After intense stirring, the organic phase was dried and evaporated to afford (S)-1c with an enantiomeric excess of 77%.

#### 2.4. Procedure for the Preparation of Optically Active $\text{Ca}[(S)\text{-1d} \bullet \text{H-DpTTA}]_2$ Complex and Optically Active (S)-1d

A mixture of 0.55 mmol (0.15 g) of  $\alpha$ -hydroxyethyl-bis(4-methylphenyl)phosphine oxide (1d) and 0.14 mmol (0.11 g) of  $\text{Ca}(\text{H-DpTTA})_2$  was dissolved in 0.75 mL of ethanol and 3 mL of ethyl acetate at reflux. After the solution became clear, it was allowed to cool to 26 °C. After stirring for 24 h at 26 °C, the precipitated crystalline diastereomeric complex was filtered off, and the solid was washed with  $3 \times 0.5$  mL of ethyl acetate to give 0.083 g (yield = 46%) of  $\text{Ca}[(S)\text{-1d} \bullet \text{H-DpTTA}]_2$ . To 3 mg of  $\text{Ca}[(S)\text{-1d} \bullet \text{H-DpTTA}]_2$ , 0.5 mL of ethyl acetate and 0.05 mL of saturated  $\text{Na}_2\text{CO}_3$  solution were added. After intense stirring, the organic phase was dried ( $\text{Na}_2\text{SO}_4$ ), and the solvent was evaporated to afford (S)-1d with an enantiomeric excess of 40%.

The diastereomeric complex was purified by recrystallization: 1 mL of ethanol and 5 mL of ethyl acetate was added to the diastereomeric complex, and the suspension was heated at reflux until it became clear. The solution was allowed to cool to 26 °C, and was stirred for 24 h at 26 °C. The precipitated diastereomeric complex was filtered off, and it was purified by recrystallization using the method described above. Filtration after the second recrystallization of the solid diastereomeric complex afforded 0.016 g (yield = 9%) of  $\text{Ca}[(S)\text{-1d} \bullet \text{H-DpTTA}]_2$ .

To 16 mg of  $\text{Ca}[(S)\text{-1d} \bullet \text{H-DpTTA}]_2$  (de = 90%), 0.5 mL of ethyl acetate and 0.05 mL of saturated  $\text{Na}_2\text{CO}_3$  solution were added. After intense stirring, the organic phase was dried ( $\text{Na}_2\text{SO}_4$ ), and the solvent was evaporated to afford 6 mg (yield = 8%) of (S)-1d with an enantiomeric excess of 90% (S = 0.07).

#### 2.5. Procedure for the Preparation of the Single Crystals of Optically Active (S)-1c

To 0.32 g of  $\text{Ca}[(S)\text{-1c} \bullet \text{H-DBTA}]_2$  (de = 77%) prepared according to the method shown above, 5.0 mL of saturated  $\text{Na}_2\text{CO}_3$  solution was added. The aqueous phase was extracted with  $2 \times 10.0$  mL of dichloromethane to afford 60 mg (yield = 13%) of (S)-1c (S = 0.10). Then, the obtained (S)-1c was dissolved in 0.5 mL of toluene. After stirring for 0.5 h at reflux, the solvent was allowed to evaporate over two weeks to give the single crystals of (S)-1c.

#### 2.6. Single-Crystal X-Ray Diffraction Studies

Single crystals of hydroxyphosphine oxide (S)-1c were prepared by recrystallization of toluene. The crystals were taken up in perfluorinated oil, and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 instrument equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K $\alpha$  radiation ( $\lambda = 0.71071 \text{ \AA}$ ).

Data collection and data reduction were performed with the CrysAlisPro 1.171.40.82a software [46]. Absorption correction using the multiscan method [46] was applied. The structures were solved with SHELXS-97 [47] refined with SHELXL-97 [48] and finally checked using PLATON [49]. Details for data collection and structure refinement are summarized in Table 1.

CCDC-2394035 contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif) (accessed on 26 October 2024).

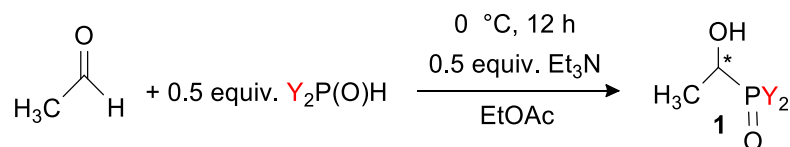
**Table 1.** Details for X-ray data collection and structure refinement for compound (S)-1c.

|                                             | (S)-1c                                           |
|---------------------------------------------|--------------------------------------------------|
| Empirical formula                           | C <sub>14</sub> H <sub>15</sub> O <sub>2</sub> P |
| Formula mass                                | 246.23                                           |
| T [K]                                       | 123 (2)                                          |
| Crystal size [mm]                           | 0.20 × 0.10 × 0.05                               |
| Crystal description                         | colorless rod                                    |
| Crystal system                              | monoclinic                                       |
| Space group                                 | P21                                              |
| a [Å]                                       | 7.0846 (2)                                       |
| b [Å]                                       | 10.8324 (3)                                      |
| c [Å]                                       | 9.1135 (2)                                       |
| α [°]                                       | 90.0                                             |
| β [°]                                       | 105.677 (3)                                      |
| γ [°]                                       | 90.0                                             |
| V [Å <sup>3</sup> ]                         | 673.38 (3)                                       |
| Z                                           | 2                                                |
| ρ <sub>calcd.</sub> [g cm <sup>−3</sup> ]   | 1.214                                            |
| μ [mm <sup>−1</sup> ]                       | 0.192                                            |
| F(000)                                      | 260                                              |
| Θ range [°]                                 | 2.99–25.24                                       |
| Index ranges                                | −10 ≤ h ≤ 10<br>−15 ≤ k ≤ 15<br>−13 ≤ l ≤ 13     |
| Reflns. collected                           | 13284                                            |
| Reflns. obsd.                               | 3755                                             |
| Reflns. unique                              | 4112<br>(R <sub>int</sub> = 0.0309)              |
| R <sub>1</sub> , wR <sub>2</sub> (2σ data)  | 0.0341, 0.0730                                   |
| R <sub>1</sub> , wR <sub>2</sub> (all data) | 0.0402, 0.0763                                   |
| GOOF on F <sup>2</sup>                      | 1.042                                            |
| Peak/hole [e Å <sup>−3</sup> ]              | 0.293/−0.171                                     |

### 3. Results and Discussion

#### 3.1. Preparation of Racemic Compounds

At first, racemic diethyl and dibutyl α-hydroxy-ethylphosphonates (**1a** and **1b**, respectively), as well as diphenyl-, bis(4-methylphenyl)- and bis(3,5-dimethylphenyl)-α-hydroxyethylphosphine oxides (**1c**, **1d** and **1e**, respectively), were synthesized according to the method previously described by Wang et al. [50] and us [51] (Scheme 1).



Y = OEt (a), OBu (b), Ph (c), 4-MePh (d), 3,5-diMePh (e)

**Scheme 1.** Synthesis of racemic diethyl and dibutyl α-hydroxyethylphosphonates (**1a** and **1b**), as well as α-hydroxyethyl-diarylphosphine oxides (**1c–e**).

The acetaldehyde and diethyl or dibutyl phosphite or diarylphosphine oxides were reacted in the presence of triethylamine catalyst in ethyl acetate as the medium. The solvent was evaporated, and the obtained crude products were purified by column chromatography or, in the case of compounds **1c** and **1e**, by recrystallization.

Hydroxyphosphine oxides **1c** and **1e** crystallized out from the reaction mixture. The solid was filtered out; then, it was dissolved in toluene, and charcoal was added. Then,

the mixture was stirred at reflux. Cooling followed by removing the crystals by filtration, afforded the corresponding products.

Hydroxyethylphosphonates **1a** and **1b**, as well as hydroxyethylphosphine oxides **1d** and **1e**, are known compounds. Thus, they were identified by  $^{31}\text{P}$  NMR shifts and HRMS. Their purity was determined by HPLC-MS.  $\alpha$ -Hydroxyethyl-bis(3,5-dimethylphenyl)phosphine oxide (**1e**) is a new compound that was fully characterized by NMR and MS.

### 3.2. Optical Resolution of Hydroxyphosphine Oxides **1c–e**

Dimethyl  $\alpha$ -hydroxy-arylmethylphosphonates were successfully resolved into enantiomers using the acidic calcium salt of *O,O'*-dibenzoyl-(2*R*,3*R*)-tartaric acid ( $\text{Ca}(\text{H-DBTA})_2$ ) (**2**) as the resolving agent [37].  $\text{Ca}(\text{H-DBTA})_2$  (**2**) was prepared by the reaction of *O,O'*-dibenzoyl-(2*R*,3*R*)-tartaric acid monohydrate and calcium oxide according to the procedure reported earlier [40]. The optical resolution of the racemic  $\alpha$ -hydroxyethyl-diarylphosphine oxides (**1c–e**) was attempted using 0.25 equiv. of  $\text{Ca}(\text{H-DBTA})_2$  (**2**) or  $\text{Ca}(\text{H-DpTTA})_2$  (**3**) in various solvents (Table 2).

**Table 2.** Optical resolution experiments for hydroxyphosphine oxides **1c** and **1d** with  $\text{Ca}(\text{H-DBTA})_2$  (**2**) or  $\text{Ca}(\text{H-DpTTA})_2$  (**3**) in various solvents.

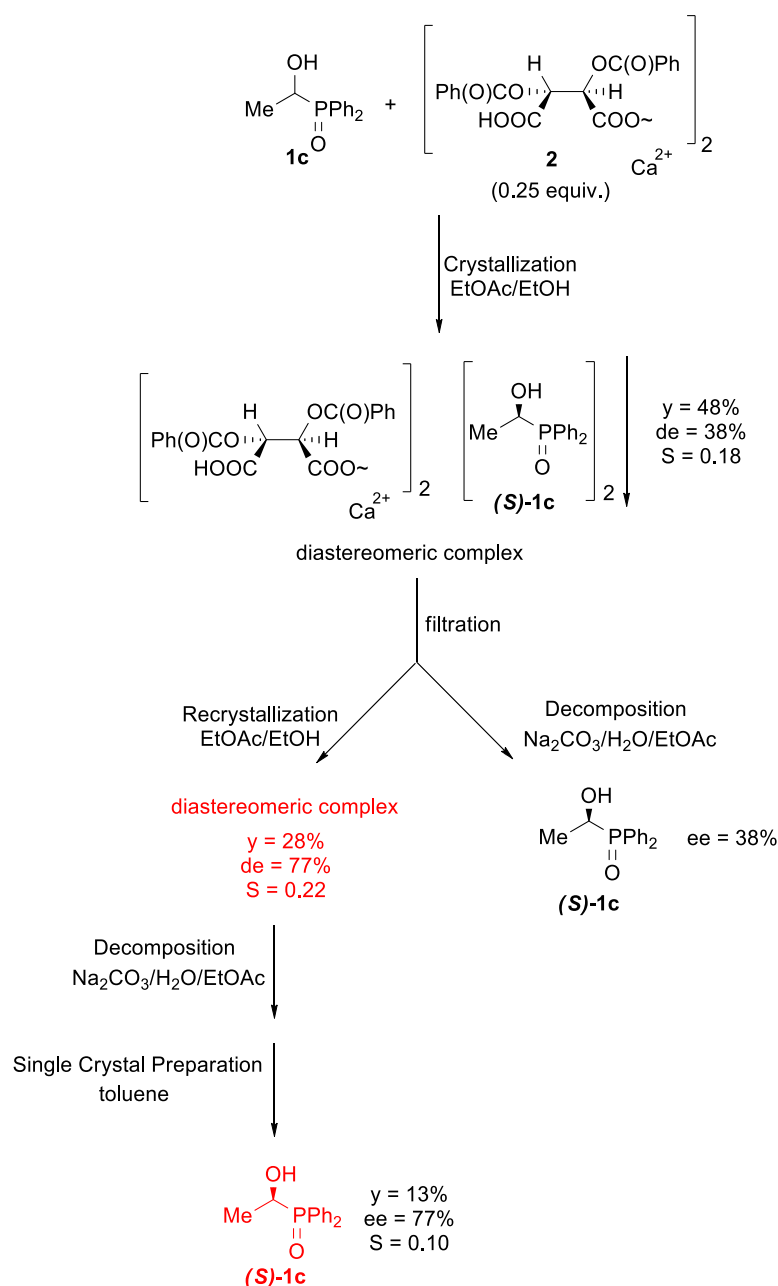
| Compound  | Solvent                                                          | Yield (%)                           | <i>de</i> (%)                        | $S = [de\ (\%)] \times [yield\ (\%)]$    | Remark                               | Entry |
|-----------|------------------------------------------------------------------|-------------------------------------|--------------------------------------|------------------------------------------|--------------------------------------|-------|
| <b>1c</b> | THF                                                              | -                                   | -                                    | -                                        | no diastereomeric complex was formed | 1.    |
|           | MeCN                                                             | -                                   | -                                    | -                                        | no diastereomeric complex was formed | 2.    |
|           | DMSO                                                             | -                                   | -                                    | -                                        | no diastereomeric complex was formed | 3.    |
|           | MEK                                                              | 20                                  | 0                                    | 0                                        | no chiral discrimination             | 4.    |
|           | EtOAc (10 $\times$ ) + MeOH (2.5 $\times$ )                      | 19                                  | 0                                    | 0                                        | no chiral discrimination             | 5.    |
|           | 1,4-dioxane                                                      | 14                                  | 0                                    | 0                                        | no chiral discrimination             | 6.    |
|           | EtOAc (10 $\times$ ) + EtOH (2.5 $\times$ )                      | 48 (28 <sup>a</sup> )               | 38 (77 <sup>a</sup> )                | 0.18 (0.22 <sup>a</sup> )                | -                                    | 7.    |
|           | EtOAc (10 $\times$ ) + <i>Pr</i> OH (2.5 $\times$ )              | 8                                   | 50                                   | 0.04                                     | -                                    | 8.    |
|           | EtOAc (10 $\times$ ) + <sup>i</sup> <i>Pr</i> OH (2.5 $\times$ ) | 16                                  | 45                                   | 0.07                                     | -                                    | 9.    |
|           | EtOAc (10 $\times$ ) + <i>Bu</i> OH (2.5 $\times$ )              | 15                                  | 50                                   | 0.08                                     | -                                    | 10.   |
| <b>1d</b> | EtOAc (10 $\times$ ) + EtOH (2.5 $\times$ )                      | -                                   | -                                    | -                                        | no diastereomeric complex was formed | 11.   |
|           |                                                                  | 46 <sup>b</sup> (9 <sup>b,c</sup> ) | 40 <sup>b</sup> (90 <sup>b,c</sup> ) | 0.18 <sup>b</sup> (0.08 <sup>b,c</sup> ) |                                      | 12.   |

<sup>a</sup> The yield [%], *de* [%], and *S* values refer to the result obtained after recrystallization of the crystalline diastereomer complex. <sup>b</sup> *O,O'*-di-*p*-tolyl-(2*R*,3*R*)-tartaric acid ( $\text{Ca}(\text{H-DpTTA})_2$ ) was used as the resolving agent. <sup>c</sup> The yield [%], *de* [%], and *S* values refer to the result obtained after recrystallization twice of the crystalline diastereomer complex.

The nature of the solvents used for resolution may strongly influence chiral discrimination [52]. The solvent can be incorporated into the diastereomer and thus change the structure of the supramolecule being built [53,54]. Earlier, good results have been obtained with ketone- (e.g., acetone or ethyl-methyl-ketone) and ester- (typically ethyl acetate) type solvent [37]. The role of solvents in chiral discrimination was first studied for racemic  $\alpha$ -hydroxyethyl-diphenylphosphine oxide (**1c**). Three different cases may be distinguished, i.e., (1) there is no diastereomeric complex formation (e.g., in THF, acetonitrile, or DMSO) (Table 2, Entries 1–3), (2) there is complex formation, but without chiral discrimination (e.g., in ethyl-methyl-ketone or EtOAc-MeOH or dioxane) (Table 2, Entries 4–6), or (3) there is a real optical resolution (e.g., in EtOAc-EtOH/<sup>n</sup>*Pr*OH/<sup>i</sup>*Pr*OH/<sup>n</sup>*Bu*OH) (Table 2, Entries 7–10). Ethyl acetate proved to be a suitable solvent, but the solubility of the racemates was limited in it; therefore, there arose a need for different alcohols as co-solvents. It was found that, in the presence of methanol, a diastereomeric complex was formed but without chiral discrimination (Table 2, Entry 6). However, the experiments were successful using EtOH, <sup>n</sup>*Pr*OH, <sup>i</sup>*Pr*OH, or <sup>n</sup>*Bu*OH (Table 2, Entries 7–10). In these cases, the crystalline

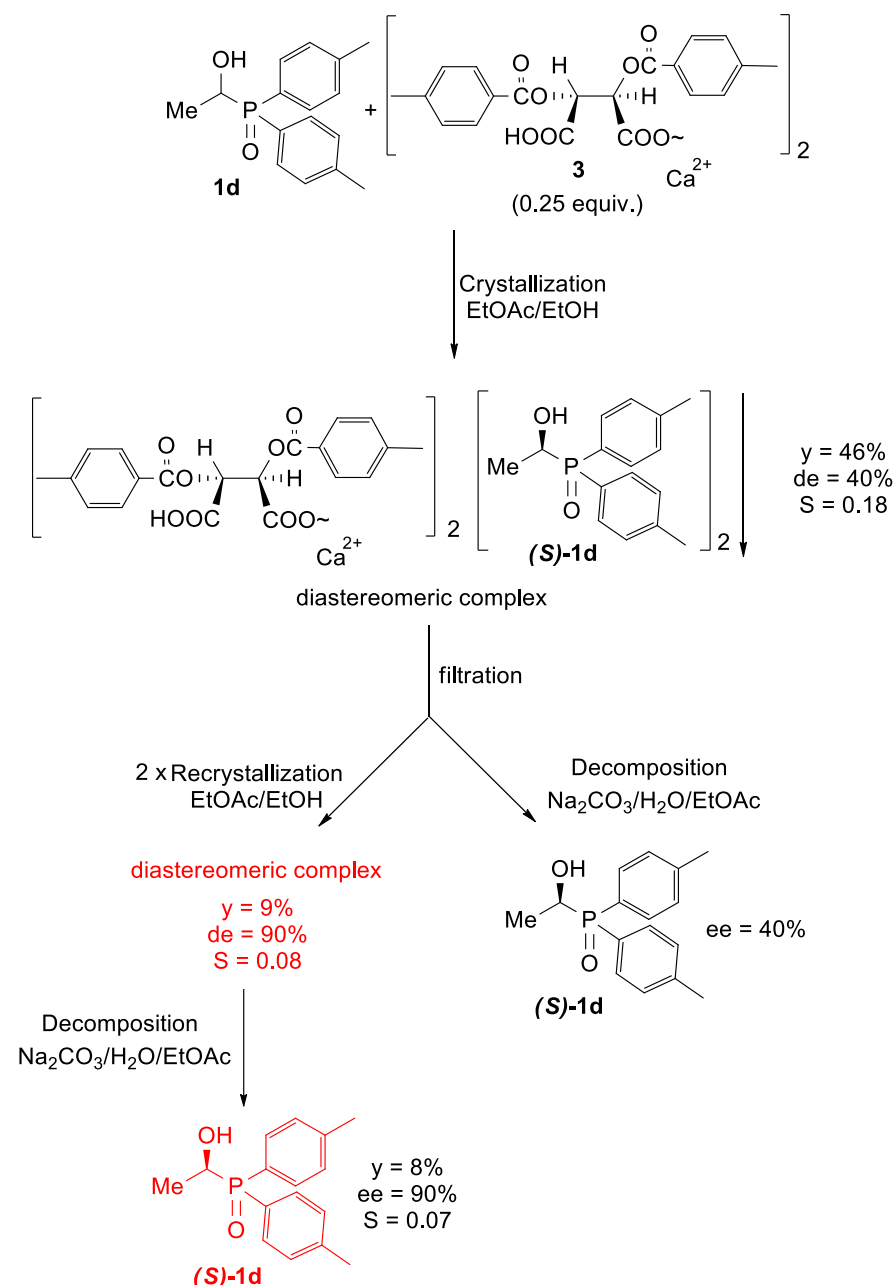
diastereomeric complex with a composition of  $\text{Ca}[(S)\text{-1c} \bullet \text{H-DBTA}]_2$  could be isolated by filtration. (In this phase, the establishment of the absolute configuration was tentative.)

The enantiomeric excess of the crystals was determined by chiral HPLC. Using ethanol as the co-solvent, after the crystallization step, the diastereomer was obtained in a yield of 48%, with a *de* of 38% (Table 2, Entry 7, and Scheme 2). In the case of *PrOH*, *iPrOH*, and *BuOH*, after the crystallization step, the *de* was better (50%, 45%, and 50%, respectively), but the yields were rather low as compared to those obtained using ethanol (8%, 16%, and 15%, respectively) (Table 2, Entries 8–10). For this reason, in these cases, we did not further purify the diastereomeric salt. Considering all results, ethanol gave the best yield and enantiomeric excess among the alcohols tested. The resolvability (*S*) was the best in this case. The diastereomer was purified by recrystallization using the same solvent mixture (*EtOAc-EtOH*), which afforded  $\text{Ca}[(S)\text{-1c} \bullet \text{H-DBTA}]_2$  with a *de* of 77%, in a yield of 28% (Table 2, Entry 7, and Scheme 2).



**Scheme 2.** Optical resolution of **1c** and preparation of  $\alpha$ -hydroxyethyl-diphenylphosphine oxide (*S*)-**1c** single crystals.

For  $\alpha$ -hydroxyethyl-bis(4-methylphenyl)phosphine oxide **1d**, the EtOAc-EtOH solvent system, which worked well for the diphenyl derivative **1c**, was used. In this case, no crystalline precipitation was observed with  $\text{Ca}(\text{H-DBTA})_2$  (Table 2, Entry 11). The optical resolution of  $\alpha$ -hydroxyethyl-bis(4-methylphenyl)phosphine oxide **1d** was also attempted with the calcium salt of *O,O'*-di-*p*-tolyl-(2*R*,3*R*)-tartaric acid ( $\text{Ca}(\text{H-DpTTA})_2$ ) (**3**). In this case, there was precipitation of a diastereomeric salt, characterized by a chiral discrimination of *de* 40%, a yield of 46%, and a *S* value of 0.18. The complex filtered off was recrystallized twice from the EtOAc-EtOH solvent mixture to provide a *de* of 90% (Table 2, Entry 12, and Scheme 3).



**Scheme 3.** Optical resolution of  $\alpha$ -hydroxyethyl-bis(4-methylphenyl)phosphine oxide **1d**.

The optical resolution of  $\alpha$ -hydroxyethyl-bis(3,5-dimethylphenyl)phosphine oxide **1e** with  $\text{Ca}(\text{H-DBTA})_2$  or  $\text{Ca}(\text{H-DpTTA})_2$  was also attempted using the EtOAc-EtOH solvent mixture. In this case, the racemic compound crystallized out; therefore, no chiral discrimination could be observed. Methyl-*i*-butyl-ketone (MIBK) and DMSO were also tried as

solvents for the optical resolution of compound **1e**. Using MIBK, there were crystals, but it included hydroxyphosphine oxide **1e** as its racemate, whereas no crystalline product was formed in DMSO.

Hydroxyphosphine oxide **1e** could not be resolved with either  $\text{Ca}(\text{H-DBTA})_2$  or  $\text{Ca}(\text{H-DpTTA})_2$ . It seems that the racemic species **1e** is much more stable than the corresponding diastereomeric complexes. HPLC-MS analysis confirmed that no diastereomeric complexes were formed, and rather the racemic compound **1e** crystallized out from the mixture.

The crystals of  $\alpha$ -hydroxyethyl-diphenylphosphine oxide **1c** suitable for single-crystal X-ray analysis were obtained from the sample prepared above by dissolving it in toluene and allowing the solvent to evaporate slowly. Decomposition of the  $\text{Ca}[(S)\text{-1c} \bullet \text{H-DBTA}]_2$  complex with saturated  $\text{Na}_2\text{CO}_3$  solution, followed with extraction with dichloromethane, led to an enantiomeric mixture of  $\alpha$ -hydroxyethyl-diphenylphosphine oxide **1c** with an enantiomeric excess of 77% in yield of 13%. Single crystals of  $(S)\text{-1c}$  (with the assumed  $S_C$  configuration) were prepared from this enantiomeric mixture (Scheme 2).

The  $\text{Ca}[(S)\text{-1d} \bullet \text{H-DpTTA}]_2$  complex was decomposed with a saturated  $\text{Na}_2\text{CO}_3$  solution, and the obtained material was then extracted with ethyl acetate. Thus,  $\alpha$ -hydroxyethyl-bis(4-methylphenyl)phosphine oxide (**1d**) was obtained in an ee value of 90% and in a yield of 8%.

The absolute configuration of the major enantiomer of  $\alpha$ -hydroxyethyl-bis(4-methylphenyl)phosphine oxide (**1d**) was substantiated comparing the elution sequences observed for the enantiomers of substrates **1c** and **1d** in chiral HPLC. The  $S_C$  assignment may be regarded as tentative.

Interestingly, in the case of the Ph group-containing hydroxyphosphine oxide (**1c**), the optical resolution was successful using  $\text{Ca}(\text{H-DBTA})_2$ , which also contains a phenyl group. In the case of the 4-MePh-containing derivative (**1d**), the p-tolyl-containing  $\text{Ca}(\text{H-DpTTA})_2$  resolving agent was found to be the suitable resolving agent.

Unfortunately, this method was not suitable for the optical resolution of dialkyl hydroxyethylphosphonates **1a** and **1b**. Neither the application of  $\text{Ca}(\text{H-DBTA})_2$  nor that of  $\text{Ca}(\text{H-DpTTA})_2$  was accompanied by the precipitation of crystals. The reason for the failure may be explained by the lack of aromatic units.

In the course of the formation of coordination complexes of a similar type,  $\pi$ - $\pi$ ,  $\pi$ -ortho aromatic CH, or  $\pi$ -para aromatic CH connections were substantiated [37]. This intermolecular interaction, of course, has an effect on the chiral discriminating ability of the diastereomer complex or salt. The  $\pi$ - $\pi$  stacking may be of utmost importance from the point of view of the stability of the intermolecular associate and its chiral discriminating ability [55–58].

### 3.3. X-Ray Analysis of the Optically Active **1c**

The molecular structure of phosphine oxide **1c** as well as the *S*-configuration of the chiral carbon atom were clearly confirmed by the result of a single-crystal X-ray diffraction study. The compound crystallizes in the monoclinic space group *P*2<sub>1</sub> with two molecules in the unit cell. The molecular structure of  $(S)\text{-1c}$  is displayed in Figure 2. Both phosphorus and the adjacent chiral carbon atom display tetrahedral coordination with a staggered arrangement of the substituents with two oxygen atoms (at phosphorus and of the OH group) in *trans* position to each other. Atom distances and bond angles are as expected (Supplementary Material Tables S1 and S2).

In the crystal,  $(S)\text{-1c}$  forms strong hydrogen bonds involving the oxygen atom of the phosphorus and the OH group at the chiral carbon atom (D-H: 0.844 (31) Å, H...A: 1.763 (29) Å, D...A: 2.594 (2) Å, D-H...A: 168 (3)°). The hydrogen bonding interaction results in the formation of chains along the *b*-axis (Figure 1). This feature corresponds to that observed in the crystal structures of other  $\alpha$ -hydroxyalkylphosphine oxides [59–63] and seems to be a general property of compounds of this type.

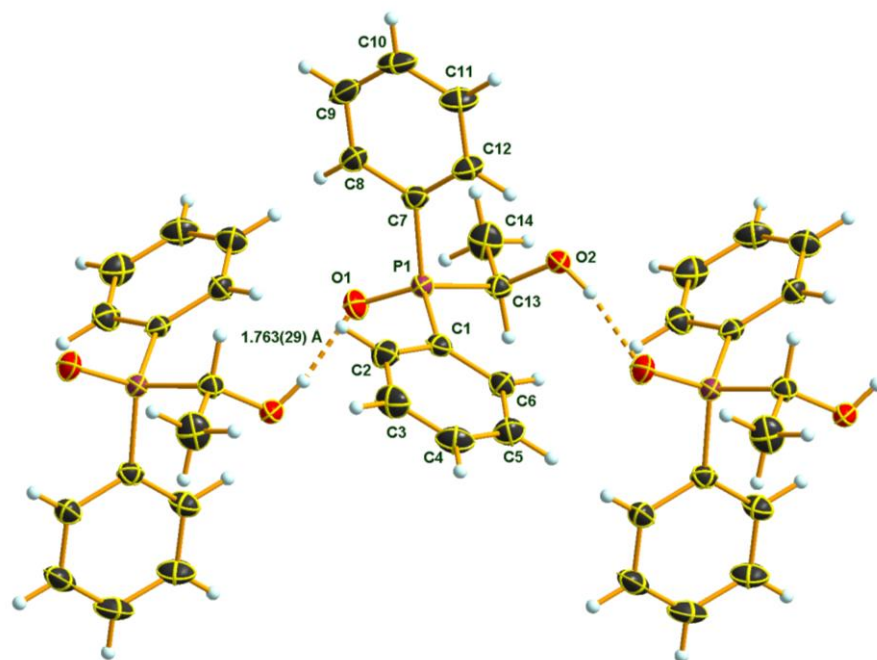


**Figure 1.** Crystal structure of compound (S)-1c; view of the H-bonded chain along the *b*-axis. DIAMOND [64] representation; thermal ellipsoids are drawn at 50% probability level. Symmetry code for the left molecule:  $1 - x, 0.5 + y, -z$ ; symmetry code for the right molecule:  $1 - x, -0.5 + y, -z$ .

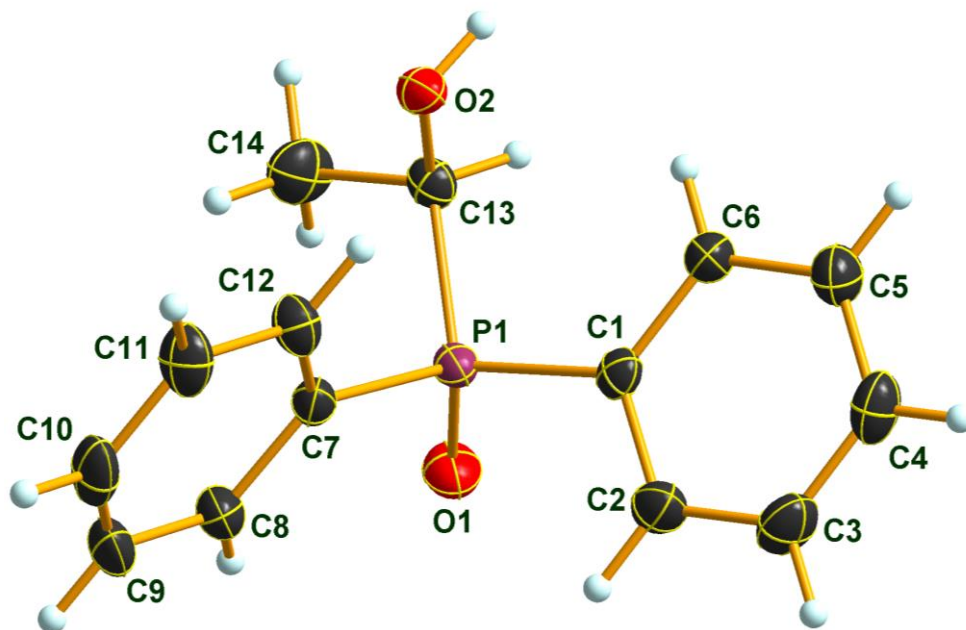


**Figure 2.** Molecular structure of compound (S)-1c in the crystal. DIAMOND [64] representation; thermal ellipsoids are drawn at 50% probability level.

#### 4. Conclusions

Two alkyl  $\alpha$ -hydroxyethylphosphonates and three  $\alpha$ -hydroxyethyl-diarylphosphine oxides were synthesized in the racemic form by the Pudovik reaction of acetaldehyde and diethyl or dibutyl phosphite, as well as diphenylphosphine oxide, bis(4-methylphenyl)phosphine oxide, or bis(3,5-dimethylphenyl)phosphine oxide. The optical resolution of two  $\alpha$ -hydroxyethyl-diarylphosphine oxides (aryl = Ph and 4-MePh) was elaborated via diastereomer complex formation applying the acidic calcium salt of *O,O*-dibenzoyl-(2*R*,3*R*)-tartaric acid and

*O,O'*-di-*p*-tolyl-(2*R*,3*R*)-tartaric acid as the resolving agents. The role of the solvent in the enantiomeric discrimination was also investigated. Among the tested solvents, the ethyl acetate–ethanol solvent mixture proved to be the most effective. After purification by recrystallization and decomposition of the corresponding diastereomers, the  $\alpha$ -hydroxyethyl-diarylphosphine oxides were obtained with an enantiomeric excess of 77% and 90%, respectively.

It was observed that the model compounds containing aryl ring (s) were successful objects for the optical resolution with the acidic calcium salts of *O,O'*-dibenzoyl-(2*R*,3*R*)-tartaric acid derivatives. This underlines the importance of  $\pi$ - $\pi$  stackings and other interactions with the participation of the aromatic ring (s).

The structure of the (*S*)- $\alpha$ -hydroxyethyl-diphenylphosphine oxide was proven by single-crystal X-ray analysis, while the absolute configuration of (*S*)- $\alpha$ -hydroxyethyl-bis(4-methylphenyl)phosphine oxide (**1d**) was substantiated in an empirical way. However, the  $S_C$  assignment may be regarded as tentative.

**Supplementary Materials:** The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/sym16111557/s1>, Geometrical data for (*S*)- $\alpha$ -hydroxyethyl-diphenylphosphine oxide ((*S*)-**1c**) obtained from the X-ray measurements;  $^{31}\text{P}$ ,  $^{13}\text{C}$ , and  $^1\text{H}$  NMR spectra for the hydroxyphosphonate derivatives **1a–e** synthesized.

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**Data Availability Statement:** The data presented in this study are available on request from the corresponding authors.

**Conflicts of Interest:** The authors declare no conflicts of interest.

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