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Quinine as chiral discriminator for determination of enantiomeric excess of diethyl 1,2-dihydroxyalkanephosphonates

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Abstract—Quinine was used as a ^{31}P NMR shift reagent for the determination of the enantiomeric excess of diethyl 1,2-dihydroxyethanephosphonates obtained either by chemical or biocatalytic synthesis. Sharpless asymmetric dihydroxylation of diethyl *trans*-vinylphosphonates enabled differentiation of *threo* and *erythro* isomers of 1,2-dihydroxyphosphonates, and provided standards for the determination of the absolute configuration of each of enantiomeric pair of threo isomers.

1. Introduction

Hydroxyalkanephosphonic acids have received considerable attention in medicinal chemistry because of their interesting, although not fully explored, biological activity. They act as inhibitors of important medicinal enzymes such as renin[1] or human immunodeficiency virus (HIV) protease and polymerase.[2] Hydroxyalkanephosphonates have also been used as haptens for the development of catalytic antibodies.[3]

1,2-Dihydroxyalkanephosphonates constitute a small class of compounds, the preparation of which is still challenging and desirable, with their biological activity awaiting determination. Although the number of literature reports describing their synthesis, including stereocontrolled syntheses, have accumulated in recent years, the availability of these compounds is still limited[4] and the lack of simple and accurate methods for the determination of enantiomeric excess of dihydroxyalkanephosphonates is currently the main limiting factor in designing stereocontrolled syntheses for such as compounds.

^{31}P NMR spectroscopy is a very convenient tool for the determination of the enantiomeric excess of organophosphorus compounds because of the large chemical dispersion and the simplicity of the broad band ^{1}H decoupled spectra.[5] Determination of the enantiomeric excess might be achieved by application of either chiral derivatizing agents or chiral solvating agents. Indeed, these two approaches have been successfully used for the determination of enantiomeric excess of dialkyl 1-hydroxy- and 2-hydroxyalkanephosphonates.[6]

Quinine has been successfully applied as a chiral solvating agent for direct, clean and simple ^{31}P NMR determination of the enantiomeric excess of hydroxyalkanphosphonate esters.[6i] Herein, we report the continuation of this approach and its use for the determination of the diastereomeric and enantiomeric composition of diethyl 1,2-dihydroxyalkanephosphonates obtained either chemically or biocatalytically.

2. Results and discussion

Hydrolysis of *trans*-1,2-epoxyphosphonates **1** afforded a non-equimolar mixture of two pairs of diastereomeric 1,2-dihydroxyethanephosphonates **2** in good yield (Fig. 1 and Table 1), namely the *threo* **2a** and *erythro* **2b** stereoisomers.

Although upon application of quinine, the shift non-equivalences ($\Delta\delta$ values, see Table 2) were quite small, it resulted in a good separation of signals deriving from each pair of enantiomers and base line separation of the signals was observed in each case (see a representative example in Fig. 2).

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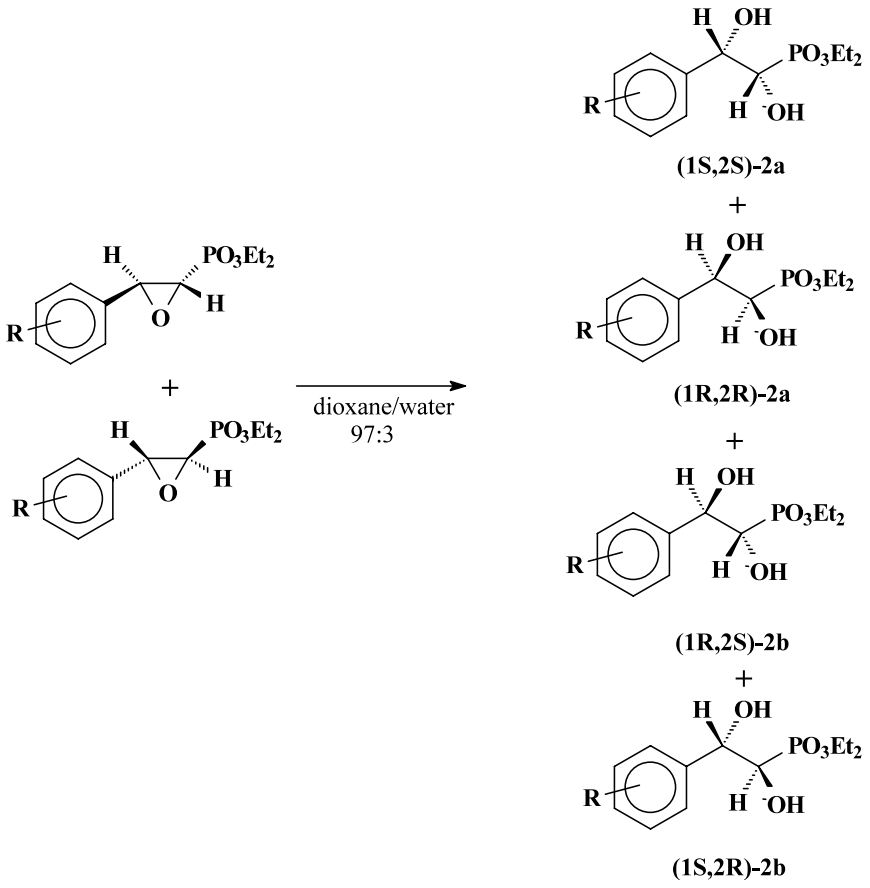

Figure 1. All stereoisomeric diethyl 1,2-dihydroxyethanephosphonates **2** obtained by hydrolysis of *trans*-1,2-epoxyphosphonates **1**.

Table 1. Hydrolysis of diethyl *trans*-1,2-epoxyphosphonates **1** yielding diethyl 1,2-dihydroxyethanephosphonates **2**

R	Reaction time (h)	Total yield (%)	Diastereomeric ratio **2a**:**2b** (*threo*:*erythro*)	^{31}P NMR chemical shift **2a**/**2b** (ppm)
H	48	81	64:36	23.9/24.2
p-CH_3	72	79	85:15	24.4/24.5
o-CH_3	48	66	79:21	24.4/24.5
m-CH_3	72	72	70:30	24.1/24.4
p-Br	24	23	60:40	23.9/24.1
p-Cl	40	73	63:37	23.9/25.1

The quality of separation was strongly dependent on the concentration of the sample, and on the 1,2-dihydroxyalkanephosphonate to quinine molar ratio. The optimal phosphonate to quinine ratio for separation of both pairs of enantiomers is 1:4 if phosphonate was applied at a concentration of 12 mg/ml. A slight increase in this ratio upon increasing the amount of quinine was observed in the case of the *threo* isomer whereas a significant decrease in the separation efficiency for the *erythro* isomer was observed. An increase in the concentration of phosphonate (to 28 mg/ml) resulted in a drop in the separation efficiency and reached saturation limit when a four-fold excess of quinine was applied.

In order to determine which set of signals corresponds to the *threo* isomers they were synthesised independently by the Sharpless approach, using AD-mixes as catalysts for the dihydroxylation of the corresponding *trans*-vinylphosphonates **3** (Fig. 3).[4a]

Table 2. Quinine induced chemical shift non-equivalence ($\Delta\delta$) in ^{31}P NMR spectra for a quinine to phosphonate 4:1 molar ratio

R	$\Delta\delta$ value for isomer *threo*-**2a**	$\Delta\delta$ value for isomer *erythro*-**2b**
H	0.177	0.083
p-CH_3	0.125	0.087
o-CH_3	0.130	0.070
m-CH_3	0.130	0.120
p-Br	0.041	0.031
p-Cl	0.042	0.037

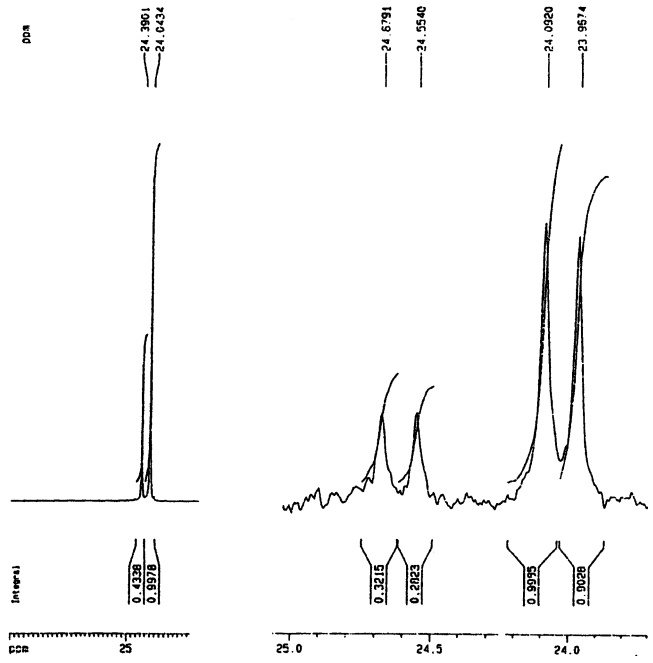

Figure 2. ^{31}P NMR spectra of products of hydrolysis of diethyl (±)-*trans*-1,2-epoxy-2-(*m*-methylphenyl)ethanephosphonate (**1**; R = *m*-CH_3) in the absence (left hand side) and the presence (right hand side) of quinine.

As seen from Table 3 the use of AD-mix-α gave preferentially the (1*S*,2*S*) isomer. Consequently, the use of AD-mix-β resulted in the preferential formation of the isomer (1*R*,2*R*), whose peaks in ^{31}P NMR spectra were shifted downfield in relation to the peaks of (1*S*,2*S*) isomer.

Table 4. Hydrolysis of epoxyphosphonates **1** by whole cells of *Aspergillus niger* yielding **2b** as a major isomer

R	*p*-CH_3	*o*-CH_3	*m*-CH_3	*p*-Br	*p*-Cl
ee (%)	73	100	2	100	<1

Finally, we have used quinine as a chiral selector to determine the course of biocatalytic hydrolysis of *trans*-epoxyethanephosphonates by the action of *Aspergillus niger* (biocatalytic epoxide ring opening by means of various strains of fungi will be the subject of a separate paper) and thus verify the usefulness of this method for the evaluation of the stereospecifity of this process. Contrary to the chemical hydrolysis, biotatalysis gave preferentially *erythro*-1,2-dihydroxylakanephosphonates **2b** (with only trace amounts of the *threo* isomers), which were obtained in good yields and with enantioselectivities strongly dependent on the structure of the substrate used. Preliminary results shown in Table 4 have demonstrated that the quinine method is superior for the analysis of the composition of the products of biocatalytic epoxide hydrolysis. At this moment we are, however, unable to determine, which of the two formed isomers (1*S*,2*R*) or (1*R*,2*S*) is the major one.

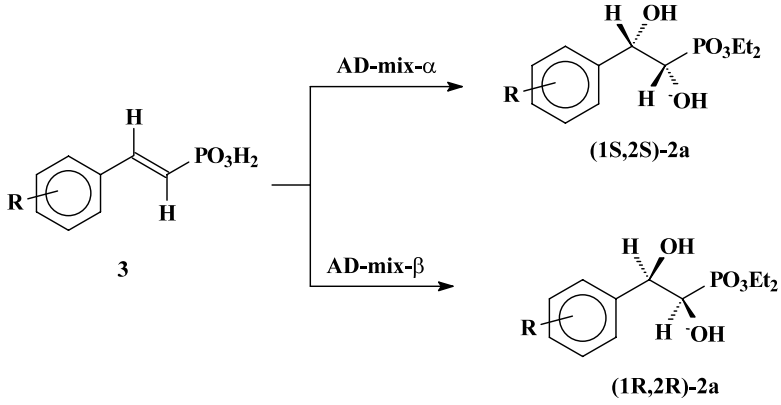

Figure 3. Synthesis of diethyl *threo*-1,2-dihydroxyethanephosphonates **2a** by Sharpless asymmetric dihydroxylation.

Table 3. Asymmetric dihydroxylation of vinylphosphonates **3** by Sharpless asymmetric dihydroxylation

R	Chiral catalyst	Reaction time (h)	Yield of isolated major isomer (%)	^{31}P NMR chemical shift *SS*/*RR* (ppm)	Ee (%)	$[\alpha]^{20}$ (*c* 1, $CHCl_3$)
H	AD-mix-α	48	47	**24.0**[a]	100	+24.7
H	AD-mix-β	96	100	24.18/**24.12**	96	−22.5
p-CH_3	AD-mix-α	55	93	**24.25**/24.12	92	+28.8
o-CH_3	AD-mix-β	48	66	24.24/**24.09**	97	−37.5
m-CH_3	AD-mix-β	50	88	24.19/**24.11**	85	−11.2
p-Br	AD-mix-α	48	50	**23.80**/23.69	96	+20.8
p-Cl	AD-mix-α	72	93	**23.92**/23.80	92	+43.7

[a] Major isomer is shown in bold.

3. Experimental

The course of all reactions and purity of intermediates and the products were checked by means ^{31}P NMR spectroscopy. NMR spectra were recorded on a Bruker Avance DRX 300 or Bruker AV instruments, operating at 300.13 and 200.13 MHz (^{1}H), 121.499 and 81.0 MHz (^{31}P) and 75.46 and 50.32 MHz (^{13}C), respectively. Measurements were made in $CDCl_3$ (99.5 at.% D), CD_3OD (99.5 at.% D) and D_2O (99.8 at.% D) solutions. Optical rotation was measured on an Autopol IV automatic polarimeter (Rudolph) in chloroform; concentrations are denoted in g/100 mL.

3.1. Substrates

Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. Diethyl *trans*-1,2-epoxyphosphonates **1** were synthesized starting from the corresponding diethyl *trans*-vinylphosphonates **3** by the previously described reaction with dioxirane.[7] Compounds **3** were prepared by standard Wittig–Horner reaction of tetraethyl methylenebisphosphonate with aromatic aldehydes in aqueous two-phase system.[8]

3.2. Hydrolysis of *trans*-1,2-epoxyphosphonates 1—general procedure

Epoxyphosphonate **1** (0.5 g) was dissolved in A 97:3 (v/v) dioxane–water mixture (20 mL and several drops of concentrated sulfuric acid was added. The mixture was left at room temperature for 24–72 h (see Table 1) and the reaction was quenched by addition of saturated solution of sodium bicarbonate (20 mL). Crude product was extracted into ethyl ether (3×15 mL) and the crude product was purified by flash chromatography using ethyl acetate–dichloromethane (1:1) as eluent.

3.2.1. Diethyl 1,2-dihydroxy-2-phenylethanephosphonate. 81% yield; ^{31}P NMR ($CDCl_3$), δ: 23.9 (isomer *threo*) and 24.2 (isomer *erythro*); ^{1}H NMR ($CDCl_3$), δ: 1.09 (t, $J=7.05$ Hz, 6H, OCH_2CH_3); 3.61 (bs, 1H, O*H*); 3.89–4.14 (m, OCH_2CH_3, H_α, OH); 4.94 (dd, $J=6.4/17.8$ Hz, H_β of *erythro*); 5.01 (dd, $J=2.7/4.0$ Hz, H_β of *threo*); 7.21–7.40 (m, 5H, aromatic protons); ^{13}C NMR (δ): 15.13 (d, $J=5.9$ Hz, OCH_2CH_3, *eythro*); 15.32 (d, $J=6.0$ Hz, OCH_2CH_3, *erythro*); 15.37 (d, $J=5.6$ Hz, OCH_2CH_3); 15.40 (d, $J=6.5$ Hz, OCH_2CH_3); 61.69 (d, $J=7.05$ Hz, OCH_2CH_3); 61.74 (d, $J=7.28$ Hz, OCH_2CH_3); 71.08 (d, $J=158.2$ Hz, HCP, *threo*); 71.18 (d, $J=155.3$ Hz, HCP, *erythro*); 71.34 (d, $J=3.8$ Hz, PhCH, *threo*); 73.36 (s, PhCH, *erythro*); 125.55, 125.73, 126.85, 126.98, 127.27 (aromatic ring); 139.38 (d, $J=10.6$ Hz, C_{ipso}, *threo*); 138.20 (d, $J=7.2$ Hz, C_{ipso}, *erythro*); elemental analysis was not done because of the instability of the compound.

3.2.2. Diethyl 1,2-dihydroxy-2-(*p*-methylphenyl)ethanephosphonate. 79% yield; ^{31}P NMR ($CDCl_3$), δ: 24.2 (*threo*) and 24.6 (*erythro*); ^{1}H NMR ($CDCl_3$), δ: 1.12–1.26 (m, 6H, OCH_2CH_3); 2.26 (s, 3H, CH_3); 3.63 (dd, $J=2.9/10.5$ Hz, H_α of *threo*), 3.89 (bs, 1H, O*H*); 3.92–4.09 (m, OCH_2CH_3, H_α, *erythro*); 4.93–4.98 (m 1H, H_β); 4.94 (dd, $J=6.4/17.8$ Hz, H_β of *erythro*); 5.01 (dd, $J=2.7/4.0$ Hz, H_β of *threo*); 7.06–7.09 and 7.17–7.27 (m, 4H, aromatic protons); ^{13}C NMR (δ): 16.14 (d, $J=5.8$ Hz, OCH_2CH_3); 20.94 (s, CH_3, *threo*); 20.99 (s, CH_3, *erythro*); 62.50 (d, $J=7.5$ Hz, OCH_2CH_3); 63.14 (d, $J=7.28$ Hz, OCH_2CH_3); 72.14 (d, $J=158.2$ Hz, HCP, *threo*); 72.23 (d, $J=156.6$ Hz, HCP, *erythro*); 72.23 (d, $J=4.4$ Hz, PhCH, *threo*); 74.47 (d, $J=1.8$ Hz, PhCH, *erythro*); 126.51, 126.60, 126.60, 128.66, 128.78, 128.86, 137.05, 137.76 (aromatic ring); 138.07 (d, $J=9.0$ Hz, C_{ipso}, *threo*); 138.56 (d, $J=10.5$ Hz, C_{ipso}, *erythro*); elemental analysis was not done because of the instability of the compound.

3.2.3. Diethyl 1,2-dihydroxy-2-(*o*-methylphenyl)ethanephosphonate. 66% yield; ^{31}P NMR ($CDCl_3$), δ: 24.4 (*threo*) and 24.3 (*erythro*); ^{1}H NMR ($CDCl_3$), δ: 1.29–1.88 (m, 6H, OCH_2CH_3); 2.26 (s, 3H, CH_3, *threo*); 2.30 (s, 3H, *erythro*); 3.50 (bs, 1H, O*H*); 3.89 (dd, $J=2.4/8.4$ Hz, H_α of *threo*); 3.99–4.18 (m, OCH_2CH_3, OH, H_α, *erythro*); 5.13 (dd, $J=6.6/17.4$ Hz, H_β of *eryth o*); 5.28 (dd, $J=2.2/4.6$ Hz, H_β of *threo*); 7.05–7.19 (m, 4H, aromatic protons); ^{13}C NMR (δ): 16.18 (d, $J=5.95$ Hz, OCH_2CH_3, *erythro*); 16.35 (d, $J=5.8$ Hz, OCH_2CH_3, *threo*); 19.02 (s, CH_3, *threo*); 19.35 (s, CH_3, *erythro*); 62.54 (d, $J=7.4$ Hz, OCH_2CH_3, *threo*); 62.95 (d, $J=7.3$ Hz, OCH_2CH_3, *erythro*); 63.33 (d, $J=6.3$ Hz, OCH_2CH_3, *erythro*); 63.60 (d, $J=6.8$ Hz, OCH_2CH_3, *threo*); 68.36 (d, $J=3.7$ Hz, PhCH, *threo*); 70.36 (d, $J=158.9$ Hz, HCP, *threo*); 71.16 (d, $J=157.2$ Hz, HCP, *erythro*); 125.88, 125.94, 126.14, 126.23, 126.37, 126.58, 130.23, 130.28 (aromatic ring); 137.75 (d, $J=9.0$ Hz, C_{ortho}, *erythro*); 137.75 (d, $J=11.3$ Hz, C_{ortho}, *threo*); 139.11 (d, $J=8.3$ Hz, C_{ipso}, *threo*); 138.56 (d, $J=12.0$ Hz, C_{ipso}, *erythro*); elemental analysis was not carried out because of the instability of the compound.

3.2.4. Diethyl 1,2-dihydroxy-2-(*m*-methylphenyl)ethanephosphonate. 72% yield; ^{31}P NMR ($CDCl_3$), δ: 24.0 (*threo*) and 24.4 (*erythro*); ^{1}H NMR ($CDCl_3$), δ: 1.10 (t, $J=7.1$ Hz, 6H, OCH_2CH_3, *erythro*); 1.16–1.25 (m, 6H, OCH_2CH_3, *threo*); 2.27 (s, 3H, CH_3); 3.64 (bs, 1H, O*H*); 3.87–4.13 (bm, 4H, OCH_2, H_α); 4.23 (bs, 1H O*H*); 4.89 (dd, $J=7.2/17.5$ Hz, H_β of *eryth o*); 4.95–4.99 (m, 1H, H_α, *threo*); 7.00–7.11 and 7.13–7.19 (m, 4H, aromatic protons); ^{13}C NMR (δ): 16.08 (d, $J=6.0$ Hz, OCH_2CH_3, *erythro*); 16.25 (d, $J=6.0$ Hz, OCH_2CH_3, *threo*); 16.26 (s, CH_3, *threo*); 16.32 (s, CH_3, *erythro*); 62.62 (d, $J=7.3$ Hz, OCH_2CH_3, *threo*); 62.60 (d, $J=7.3$ Hz, OCH_2CH_3, *erythro*); 63.04 (d, $J=6.5$ Hz, OCH_2CH_3); 72.13 (d, $J=158.1$ Hz, HCP, *threo*); 71.23 (d, $J=156.0$ Hz, HCP, *erythro*); 72.30 (d, $J=3.9$ Hz, PhCH, *threo*); 74.29 (d, $J=1.8$ Hz, PhCH, *erythro*); 127.15, 127.31, 128.08, 128.46, 128.62, 137.73, 137.78 (aromatic ring); 139.51 (d, $J=7.5$ Hz, C_{ipso}, *threo*); 140.00 (d, $J=11.3$ Hz, C_{ipso}, *erythro*); elemental analysis was not carried because of instability of the compound.

3.2.5. Diethyl 1,2-dihydroxy-2-(*p*-chlorophenyl)ethanephosphonate. 73% yield; ^{31}P NMR ($CDCl_3$), δ: 23.9 (*threo*) and 24.1 (*erythro*); ^{1}H NMR ($CDCl_3$), δ: 1.10 (t, $J=6.9$ Hz, 6H, OCH_2CH_3, *erythro*); 1.18–1.31 (m, 6H, OCH_2CH_3, *threo*); 3.64 (bs, 1H, O*H*); 3.82–3.98 (m, 2H, *OH*, H_α); 4.06 (qq, $J=6.8$ Hz, OCH_2CH_3); 4.90–5.20 (m, 1H, H_β); 7.2–7.34 (m, 4H, aromatic protons); ^{13}C NMR (δ): 16.05 (d, $J=6.0$ Hz, OCH_2CH_3, *erythro*); 16.33 (d, $J=5.3$ Hz, OCH_2CH_3, *threo*); 63.24 (d, $J=7.4$ Hz, OCH_2CH_3, *erythro*); 64.16 (d, $J=6.9$ Hz, OCH_2CH_3, *threo*); 72.30 (d, $J=159.0$ Hz, HCP, *threo*); 72.51 (d, $J=156.4$ Hz, HCP, *erythro*); 72.23 (d, $J=1.1$ Hz, PhCH, *threo*); 74.37 (d, $J=1.1$ Hz, PhCH, *erytho*); 128.74, 128.84, 129.09, 129.16, 138.17 (aromatic ring); 138.54 (d, $J=13.5$ Hz, C_{ipso}, *threo*); elemental analysis was not done because of the instability of the compound.

3.2.6. Diethyl 1,2-dihydroxy-2-(*p*-bromophenyl)ethanephosphonate. 23% yield; ^{31}P NMR ($CDCl_3$), δ: 23.9 (*threo*) and 24.0 (*erythro*); ^{1}H NMR ($CDCl_3$), δ: 1.06 (t, $J=7.0$ Hz, 6H, OCH_2CH_3, *erythro*); 1.11–1.27 (m, 6H, OCH_2CH_3, *threo*); 3.66 (bs, 1H, O*H*); 3.37–4.12 (bm, 4H, OCH_2, H_α); 4.90 (d, $J=5.5$ Hz, H_β, *erythro*); 4.94–4.98 (m, 1H, H_β, *threo*); 7.20–7.40 (m, 4H, aromatic protons); ^{13}C NMR (δ): 15.99 (d, $J=6.2$ Hz, OCH_2CH_3, *erythro*); 16.26 (d, $J=3.0$ Hz, OCH_2CH_3, *threo*); 62.50 (d, $J=6.9$ Hz, OCH_2CH_3, *erythro*); 63.53 (d, $J=7.4$ Hz, OCH_2CH_3, *threo*); 72.01 (d, $J=158.4$ Hz, HCP, *threo*); 72.21 (d, $J=155.6$ Hz, HCP, *erythro*); 73.94 (d, $J=1.1$ Hz, PhCH); 121.54, 121.61, 128.36, 131.11, 131.23 (aromatic ring); 140.62 (d, $J=9.0$ Hz, C_{ipso}, *threo*); 141.01 (d, $J=10.5$ Hz, C_{ipso}, *threo*); elemental analysis was not done because of the instability of the compound.

3.3. Asymmetric dihydroxylation of vinylphosphonates 3-synthesis of diethyl erythro-1,2-dihydroxyethanephosphonates 2a

A solution of the reagent was prepared by mixing 5 mL of *t*-butanol, 5 mL of water, 1.4 g appropriate AD-mix and 0.95 g of methanesulphonate. This solution was cooled to 0–5°C in water-ice bath and 1 mmol of vinylphosphonate **3** was added, bath was removed and the mixture allowed to reach room temperature. Then 1.5 g of sodium sulphite was added and stirring continued for additional 30–60 min. Product was extracted with four portions (10 mL) of ethyl acetate, organic layer was washed with 2 M potassium hydroxide solution (2×10 mL) and the organic layer dried over anhydrous magnesium sulphate. Products were purified by means of planar rotary chromatography using mixtures of ethyl acetate–dichloromethane–methanol (3:2:1) or ethyl acetate–chloroform–methanol (3:2:1).

3.3.1. Diethyl (1*S*,2*S*)-dihydroxy-2-phenylethanephosphonate and diethyl (1*R*,2*R*)-dihydroxy-2-phenylethanephosphonate. ^{31}P NMR ($CDCl_3$), δ: 24.0; ^{1}H NMR ($CDCl_3$), δ: 1.17–1.24 (m, 6H, OCH_2CH_3); 1.88 (bs, 1H, O*H*); 3.95 (dd, $J=2.7/8.3$ Hz, H_a); 4.0 (qq, $J=7.2$ Hz, 4H, OCH_2CH_3); 5.03 (bs, 1H, H_β); 7.19–7.36 (m, 5H, aromatic protons); ^{13}C NMR (δ): 16.33 (d, $J=5.5$ Hz, OCH_2CH_3); 16.37 (d, $J=5.7$ Hz, OCH_2CH_3); 62.69 (d, $J=7.3$ Hz, OCH_2CH_3); 63.47 (d, $J=6.8$ Hz, OCH_2CH_3); 72.06 (d, $J=158.2$ Hz, HCP); 72.24 (d, $J=3.6$ Hz, PhCH); 127.31, 186.64, 129.07 (aromatic ring); 140.93 (d, $J=12.0$ Hz, C_{ipso}).

3.3.2. Diethyl (1*S*,2*S*)-dihydroxy-2-(*p*-methylphenyl)-ethanephosphonate. ^{31}P NMR ($CDCl_3$), δ: 24.1; ^{1}H NMR ($CDCl_3$), δ: 1.19 and 1.25 (t, $J=7.0$ Hz, 3H each, OCH_2CH_3); 2.26 (s, 3H, CH_3); 3.94 (dd, $J=3.0/8.6$ Hz, 1H, H_α); 4.00 (qq, $J=7.0$ Hz, 4H, OCH_2CH_3); 4.10 (bs, 1H, O*H*); 5.03 (bs, 1H, H_β); 7.07–7.25 (m, 4H, aromatic protons); ^{13}C NMR (δ): 16.31 and 16.57 (d, $J=5.6$ Hz, OCH_2CH_3); 21.09 (s, CH_3); 62.68 (d, $J=7.2$ Hz, OCH_2CH_3); 63.41 (d, $J=6.8$ Hz, OCH_2CH_3); 72.10 (d, $J=157.8$ Hz, HCP); 72.16 (d, $J=3.6$ Hz, PhCH); 126.44, 128.93, 137.47 (aromatic ring); 137.90 (d, $J=9.0$ Hz, C_{ipso}).

3.3.3. Diethyl (1*R*,2*R*)-dihydroxy-2-(*o*-methylphenyl)-ethanephosphonate. ^{31}P NMR ($CDCl_3$), δ: 24.1; ^{1}H NMR ($CDCl_3$), δ: 1.19–1.41 (m, $J=7.0$ Hz, 6H, OCH_2CH_3); 2.26 (s, 3H, CH_3); 3.47 (bs, 1H, O*H*); 3.97 (dd, $J=2.4/7.2$ Hz, 1.5H, H_α); 4.01–4.26 (m, 6.5H, OCH_2CH_3, OH, H_α); 5.08 (m, 1H, H_β); 7.21–7.41 (m, 4H, aromatic protons); ^{13}C NMR (δ): 16.35 (d, $J=5.9$ Hz, OCH_2CH_3); 18.99 (s, CH_3); 62.57 (d, $J=7.4$ Hz, OCH_2CH_3); 63.60 (d, $J=6.6$ Hz, OCH_2CH_3); 68.29 (d, $J=3.4$ Hz, PhCH); 70.25 (d, $J=158.7$ Hz, HCP); 125.93, 127.66, 129.93, 130.38 (aromatic ring); 137.96 (d, $J=12.0$ Hz, C_{ipso}).

3.3.4. Diethyl (1*R*,2*R*)-dihydroxy-2-(*m*-methylphenyl)-ethanephosphonate. ^{31}P NMR ($CDCl_3$), δ: 24.1 ^{1}H NMR ($CDCl_3$), δ: 1.23 and 1.27 (t, $J=7.1$ Hz, 3H each, OCH_2CH_3); 2.28 (s, 3H, CH_3); 3.90 (dd, $J=3.2/9.0$ Hz, 1H, H_α); 4.00 (qq, $J=7.1$ Hz, 4H, OCH_2). 4.10 (bs, 1H, O*H*); 4.96 (dd, $J=3.4/17.5$ Hz, H_β); 7.19–7.41 (m, 4H, aromatic protons); ^{13}C NMR (δ): 16.38 (d, $J=5.1$ Hz, OCH_2CH_3); 16.41 (d, $J=5.8$ Hz, OCH_2CH_3); 21.46 (s, CH_3, *threo*); 62.62 (d, $J=7.1$ Hz, OCH_2CH_3); 63.58 (d, $J=6.7$ Hz, OCH_2CH_3); 71.97 (d, $J=158.0$ Hz, HCP); 72.07 (d, $J=2.5$ Hz, PhCH); 123.46, 127.02, 128.25, (aromatic ring); 139.82 (d, $J=11.8$ Hz, C_{ipso}).

3.3.5. Diethyl (1*S*,2*S*)-dihydroxy-2-(*p*-chlorophenyl)-ethanephosphonate. ^{31}P NMR ($CDCl_3$), δ: 23.8 ^{1}H NMR ($CDCl_3$), δ: 1.18 and 1.23 (t, $J=7.1$ Hz, 3H each, OCH_2CH_3); 2.35 (bs, 1H, O*H*); 3.90 (dd, $J=3.4/0.2$ Hz, 1H, H_α); 4.00 (qq, $J=7.1$ Hz, OCH_2CH_3); 4.96 (dd, $J=3.7/9.2$ Hz, 1H, H_β); 7.19–7.30 (m, 4H, aromatic protons); ^{13}C NMR (δ): 16.32 and 16.39 (d, $J=5.3$ Hz, OCH_2CH_3); 62.87 (d, $J=7.5$ Hz, OCH_2CH_3); 63.45 (d, $J=6.8$ Hz, OCH_2CH_3); 71.76 (d, $J=1.1$ Hz, PhCH); 72.07 (d, $J=157.5$ Hz, HCP); 127.97, 128.36, 133.53 (aromatic ring); 138.69 (d, $J=12.0$ Hz, C_{ipso}).

3.3.6. Diethyl (1*S*,2*S*)-dihydroxy-2-(*p*-bromophenyl)-ethanephosphonate. ^{31}P NMR ($CDCl_3$), δ: 23.7 ^{1}H NMR ($CDCl_3$), δ: 1.19 and 1.25 (t, $J=7.1$ Hz, 3H each, OCH_2CH_3); 3.90 (dd, $J=3.5/9.2$ Hz, 1H, H_α);

4.00 (qq, $J=7.1$ Hz, 4H, OCH_2); 4.60 (bs, 1H, O*H*); 4.96 (dd, $J=3.7/5.5$ Hz, H_β); 7.19–7.30 (m, 4H, aromatic protons); ^{13}C NMR (δ): 16.33 (d, $J=5.3$ Hz, OCH_2CH_3); 16.39 (d, $J=5.5$ Hz, OCH_2CH_3); 62.80 (d, $J=7.5$ Hz, OCH_2CH_3); 63.59 (d, $J=6.8$ Hz, OCH_2CH_3); 71.94 (Ph*C*H); 71.97 (d, $J=157.5$ Hz, H*C*P); 121.39, 128.31, 131.32 (aromatic ring); 139.19 (d, $J=11.3$ Hz, C_{ipso}).

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