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Studies towards the synthesis of (1*R*,2*S*)- and (1*S*,2*S*)-1,2-epoxy-3-hydroxypropylphosphonates and (1*S*,2*S*)- and (1*R*,2*S*)-2,3-epoxy-1-hydroxypropylphosphonates

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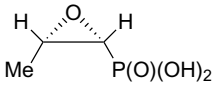
Abstract—The *trans*-configured fosfomycin analogue, diethyl (1*S*,2*S*)-1,2-epoxy-3-hydroxypropylphosphonate, was synthesised by the intramolecular Williamson reaction of diethyl (1*S*,2*R*)-1,3-dihydroxy-2-mesyloxypropylphosphonate. The *cis*-analogue was obtained as *O*-ethyl or *O*,*O*-diethyl (1*R*,2*S*)-1,2-epoxy-3-hydroxypropylphosphonates, when (1*R*,2*R*)-1,3-dihydroxy-2-mesyloxypropylphosphonate or its 3-*O*-trityl derivative were used as starting materials, respectively. The intramolecular Williamson cyclisations of diethyl (1*S*,2*R*)- and (1*R*,2*S*)-1-benzyloxy-3-hydroxy-2-mesyloxypropylphosphonates led to diethyl (1*S*,2*S*)- and (1*R*,2*S*)-2,3-epoxy-1-benzyloxypropylphosphonates, respectively, with the concomitant formation of diethyl (*E*)-1-benzyloxy-3-hydroxyprop-1-en-1-phosphonate. From diethyl (1*S*,2*S*)- and (1*R*,2*S*)-2,3-epoxy-1-benzyloxypropylphosphonates, enantiomerically pure diethyl (1*S*,2*S*)- and (1*R*,2*S*)-1,2-dihydroxypropylphosphonates were obtained by catalytic hydrogenation, while diethyl (1*S*,2*S*)- and (1*R*,2*S*)-3-acetamido-1,2-dihydroxypropylphosphonates were produced after epoxide ring opening with dibenzylamine, acetylation and hydrogenolysis.

1. Introduction

Since the discovery of the antibiotic properties of fosfomycin **1** [(1*R*,2*S*)-1,2-epoxypropylphosphonic acid],[1] several syntheses of its analogues have appeared. Among them compounds of diverse complexity, from those containing a steroid,[2] nucleoside[3–5] or sugar[4,6–8] frameworks to those having a methyl group merely replaced by aminomethyl,[9] hydroxymethyl[9] or acyl[10] fragments, have been obtained.



fosfomycin **1**

In continuation of these efforts, we have recently described the synthesis of enantiomerically pure diethyl (1*R*,2*R*)- and (1*S*,2*R*)-1,2-epoxy-3-hydroxypropylphosphonates **2**.[11] Since the absolute configuration of the natural fosfomycin is (1*R*,2*S*), we were looking for a method to prepare (1*R*,2*S*)-**2**, as well as the *trans*-configured epoxide (1*S*,2*S*)-**2** to complete the syntheses of all four stereoisomers of **2**. In our approach to (1*R*,2*R*)- and (1*S*,2*R*)-**2**, diethyl (1*R*,2*R*)- and (1*S*,2*R*)-2,3-*O*-cyclohexylidene-1,2,3-trihydroxypropylphosphonates **3**[12] were employed as starting materials, and the HO–C-1 were transformed into good leaving groups by mesylation (Scheme 1). To take advantage of the same phosphonates in the synthesis of (1*R*,2*S*)- and (1*S*,2*S*)-**2**, as inversion of configuration at C-2 was necessary, this could, in principle, be accomplished via 2-*O*-mesylates **4** (Scheme 1).

Herein, several new results to this end are presented together with other important and unexpected transformations of the intermediate mesylates **4** and **9**.

2. Results and discussion

The 2,3-dihydroxyphosphonate (1*S*,2*R*)-**6** was synthesised according to the described procedure in 80% overall yield.[13] After standard tritylation followed by mesylation the fully protected phosphonate (1*S*,2*R*)-**8** was obtained (Scheme 2). Hydrogenolysis of this compound led to the formation of the 1,3-dihydroxyphosphonate (1*S*,2*R*)-**4** in

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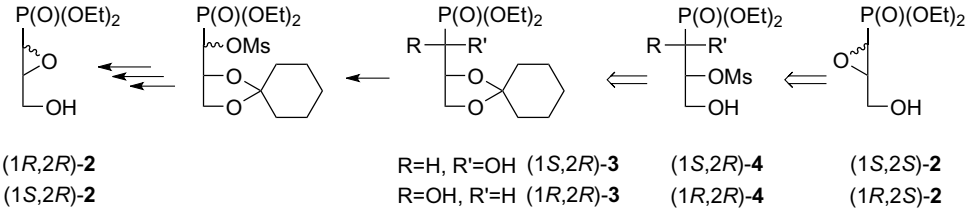
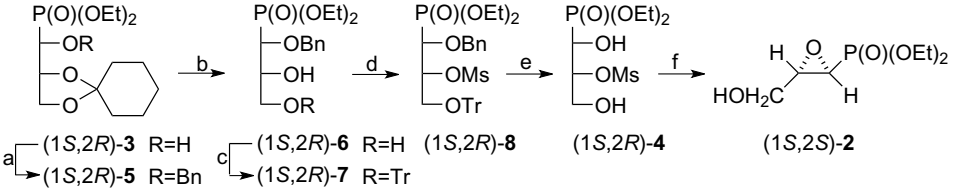


Scheme 1. Synthetic strategy to phosphonates (1*R*,2*R*)- and (1*S*,2*R*)-**2** and retrosynthesis of the phosphonates (1*R*,2*S*)- and (1*S*,2*S*)-**2**.

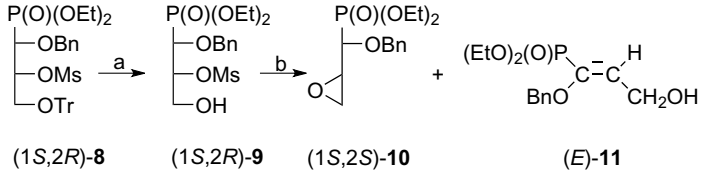


Scheme 2. Reagents and conditions: (a) BnBr, Ag_2O, 4 Å MS, CH_2Cl_2, rt, 24 h, 95%; (b) 70% AcOH, rt, 20 h, 84%; (c) TrCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 20 h, 92%; (d) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 20 h, 80%; (e) H_2, Pd–C, EtOH, rt, 24 h, 88%; (f) K_2CO_3, EtOH, rt, 20 h, 74%.

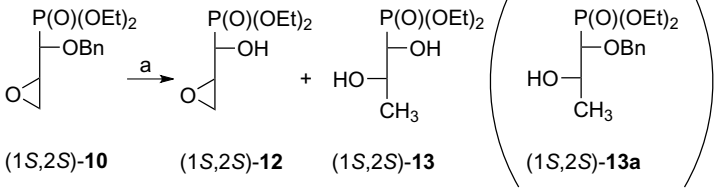
88% yield. Treatment of (1*S*,2*R*)-**4** with anhydrous potassium carbonate in ethanol for 20 h led almost regioselectively to the formation of diethyl (1*S*,2*S*)-1,2-epoxy-3-hydroxypropylphosphonate (1*S*,2*S*)-**2**, which was separated chromatographically in 74% yield. Although the oxirane ring closure in 1,3-dihydroxy-2-mesyloxypropylphosphonate could lead to the formation of 1,2- or 2,3-epoxyphosphonates, only the more substituted epoxide (1*S*,2*S*)-**2** was obtained. As expected, the intramolecular cyclisation in (1*S*,2*R*)-**4** occurred with complete inversion of configuration at C-2 to produce epoxide (1*S*,2*S*)-**2**. Since its enantiomer has recently been synthesised,[11] this conclusion could be proven by comparison of the signs of the specific rotation.

We reasoned that the isomeric (1*S*,2*S*)-2,3-epoxy-1-hydroxypropylphosphonate (1*S*,2*S*)-**12** could be synthesised from (1*S*,2*R*)-**8**, as shown in Schemes 3 and 4. Hydrolytic removal of the trityl group from (1*S*,2*R*)-**8** gave phosphonate (1*S*,2*R*)-**9** in 97% yield. This compound was treated with anhydrous potassium carbonate in ethanol for 20 h to afford the 2,3-epoxide (1*S*,2*S*)-**10** in 89% yield after chromatographic separation of diethyl (*E*)-1-benzyloxy-3-hydroxyprop-1-en-1-phosphonate (*E*)-**11**, which was formed as an impurity (less than 10%). Since the enantiomer of the 2,3-epoxyphosphonate (1*S*,2*S*)-**10** formed in this reaction is known,[13] it can be concluded that the intramolecular cyclisation in (1*S*,2*R*)-**9** took place with complete inversion of configuration at C-2.

When the hydrogenolytic removal of the benzyl group in phosphonate (1*S*,2*S*)-**10** was attempted (Scheme 4), the known[14] diol (1*S*,2*S*)-**13** was obtained instead of the expected diethyl (1*S*,2*S*)-2,3-epoxy-1-hydroxypropylphosphonate (1*S*,2*S*)-**12**. Several catalysts have been tried, but in all instances diol (1*S*,2*S*)-**13** was formed as a single product. When the hydrogenolysis was interrupted after 2 h, the reaction mixture consisted of the unreacted 2,3-epoxyphosphonate (1*S*,2*S*)-**10** and diethyl (1*S*,2*S*)-1-benzyloxy-2-hydroxypropylphosphonate (1*S*,2*S*)-**13a**, as judged



Scheme 3. Reagents and conditions: (a) *p*-TsOH, EtOH, rt, 20 h, 97%; (b) K_2CO_3, EtOH/CH_2Cl_2, rt, 20 h, 89%.



Scheme 4. Reagents and conditions: (a) H_2, Pd–C, EtOH, rt, 20 h, 70%.

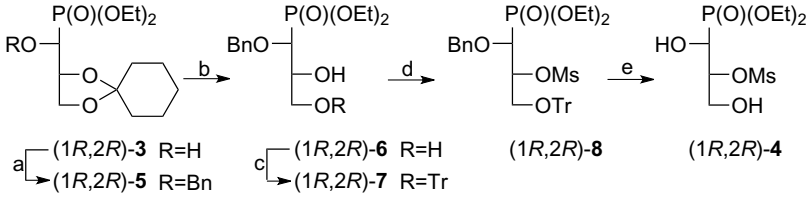
from the ^{1}H and ^{31}P NMR spectra. Thus, the oxirane ring opening in (1*S*,2*S*)-**10** is faster than cleavage of the O–Bn bond.

To synthesise diethyl (1*R*,2*S*)-1,2-epoxy-3-hydroxypropylphosphonate (1*R*,2*S*)-**2**, the 2,3-dihydroxyphosphonate (1*R*,2*R*)-**6** was used as a starting material (Schemes 5 and 6).[13] The protected phosphonate (1*R*,2*R*)-**8** was obtained by tritylation followed by mesylation, in 54% overall yield. It is worth noting that the complete mesylation of phosphonate (1*R*,2*R*)-**7** required the application of 1.1 equiv of DMAP instead of triethylamine in the presence of catalytic amounts of DMAP, as was sufficient for phosphonate (1*S*,2*R*)-**7**. Simultaneous removal of the trityl and benzyl groups gave 1,3-dihydroxyphosphonate (1*R*,2*R*)-**4** in 67% yield, which was further transformed into either the monoester (1*R*,2*S*)-**2a** or the diester (1*R*,2*S*)-**2** (Scheme 6).

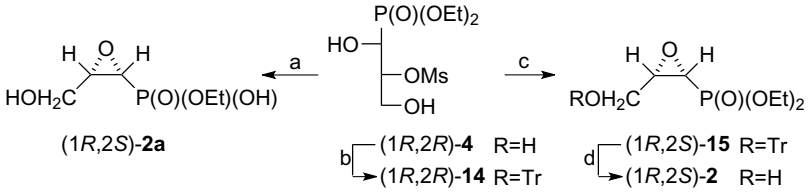
Under basic conditions, mesylate (1*R*,2*R*)-**4** was transformed with the inversion of configuration at C-2 into the monoester (1*R*,2*S*)-**2a**, which was the major component (ca. 85%) of the crude product. After purification on a silica gel column, phosphonate (1*R*,2*S*)-**2a** was obtained in 69% yield. The formation of monoester (1*R*,2*S*)-**2a** instead of the expected diester (1*R*,2*S*)-**2** can be rationalised as follows: initially intramolecular cyclisation leads to the diester (1*R*,2*S*)-**2**. In this compound, the oxirane ring has a *cis*-configuration and this feature brings the hydroxymethyl and diethoxyphosphoryl groups close together. Under basic conditions, the intramolecular cyclisation of (1*R*,2*S*)-**2** to the respective 3,4-epoxy-2-ethoxy-2-oxo-1,2-oxaphospholane occurs rapidly,[11] while its hydrolysis leads to the formation of the monoester (1*R*,2*S*)-**2a**. Since in phosphonate (1*S*,2*S*)-**2**, the oxirane ring has a *trans*-configuration, the intramolecular cyclisation of this compound to the respective 1,2-oxaphospholane is not feasible.

For this reason to prepare the diester (1*R*,2*S*)-**2**, the mesylate (1*R*,2*R*)-**4** had to be subjected to tritylation, since the removal of the *tert*-butyldimethylsilyl protecting group from the structurally similar 1,2-epoxyphosphonates led to severe decomposition.[11] When the trityl derivative (1*R*,2*R*)-**14** was treated with potassium carbonate in ethanol, the expected epoxyphosphonate (1*R*,2*S*)-**15** was produced. Hydrogenolytic deprotection afforded the diester (1*R*,2*S*)-**2** in 68% yield. Since the enantiomers of phosphonates (1*R*,2*S*)-**15** and (1*R*,2*S*)-**2** have already been described,[11] the oxirane ring closure in (1*R*,2*R*)-**14** proceeded with the complete inversion of configuration at C-2. Since the removal of the trityl group from the epoxide (1*R*,2*S*)-**15** was carried out under neutral conditions, the *cis*-configured epoxide could be obtained without traces of the respective 1,2-oxaphospholane.

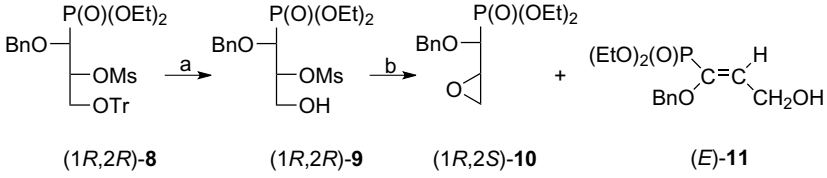
Hydrolysis of the trityl group in phosphonate (1*R*,2*R*)-**8** provided 3-hydroxypropylphosphonate (1*R*,2*R*)-**9** in 87% yield (Scheme 7). When this compound was treated with potassium carbonate in ethanol for 6 h, a 35:65 mixture



Scheme 5. Reagents and conditions: (a) BnBr, Ag_2O, 4 Å MS, CH_2Cl_2, rt, 24 h, 95%; (b) 70% AcOH, rt, 20 h, 86%; (c) TrCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 20 h, 85%; (d) MsCl, DMAP, CH_2Cl_2, 0 °C to rt, 20 h, 77%; (e) H_2, $Pd(OH)_2C$, EtOH, rt, 24 h, 67%.



Scheme 6. Reagents and conditions: (a) K_2CO_3, EtOH, rt, 24 h, 69%; (b) TrCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 20 h, 70%; (c) K_2CO_3, EtOH, rt, 5 h, 69%; (d) H_2, Pd–C, EtOH, rt, 20 h, 68%.



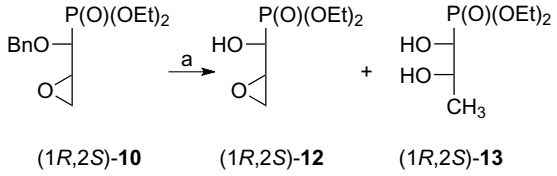
Scheme 7. Reagents and conditions: (a) *p*-TsOH, EtOH, rt, 20 h, 87%; (b) K_2CO_3, EtOH/CH_2Cl_2, rt, 3 h, 30%.

of the epoxide (1*R*,2*S*)-**10** and a vinylphosphonate (*E*)-**11** was obtained. After column chromatography, the epoxyphosphonate (1*R*,2*S*)-**10** was separated in 30% yield.

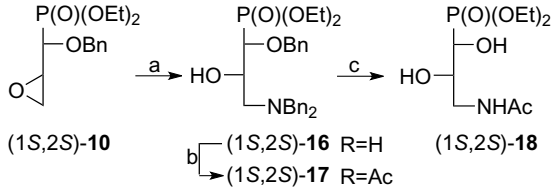
Attempts at synthesising the epoxyphosphonate (1*R*,2*S*)-**12** from (1*R*,2*S*)-**10** by hydrogenolysis led to the formation of complex mixtures. Detailed analyses of ^{1}H and ^{31}P NMR spectra of mixtures obtained after 1 and 2 days suggest that during catalytic hydrogenation of (1*R*,2*S*)-**10**, debenzylation is faster than the opening of the epoxide ring, on the contrary to our observations for phosphonate (1*S*,2*S*)-**10** (vide supra). When the reaction time was extended to 3 days, we were able to separate diol (1*R*,2*S*)-**13** in 61% yield (Scheme 8).

Since the enantiomers of phosphonates (1*S*,2*S*)- and (1*R*,2*S*)-**10** have already been described and proved useful in the preparation of diethyl (1*R*,2*R*)- and (1*S*,2*R*)-3-acetamido-1,2-dihydroxypropylphosphonate,[13] epoxides (1*S*,2*S*)- and (1*R*,2*S*)-**10** were transformed into phosphonates (1*S*,2*S*)- and (1*R*,2*S*)-**18** in 34% and 42% overall yields, respectively, by employing the known reaction sequence (Schemes 9 and 10). Application of catalytic amounts of calcium triflate accelerated the epoxide ring opening and reduced the reaction time from 3 days to 24 h.

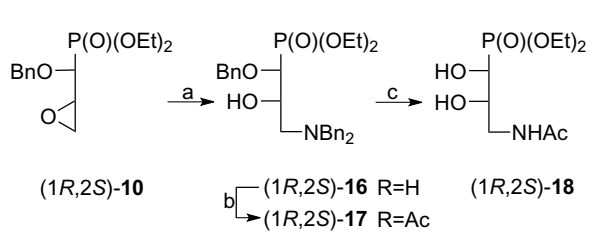
Structural assignments in phosphonate (*E*)-**11** are based on the ^{1}H and ^{13}C NMR spectral data. Thus, the vicinal



Scheme 8. Reagents and conditions: (a) H_2, Pd–C, EtOH, rt, 3 days, 61%.



Scheme 9. Reagents and conditions: (a) Bn_2NH, 5 mol % $Ca(OTf)_2$, CH_2Cl_2, 50 °C, 24 h, 60%; (b) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 20 h, 93%; (c) H_2, Pd–C and $Pd(OH)_2$ (1:1), EtOH, rt, 40 h, 61%.



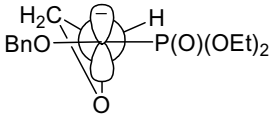
Scheme 10. Reagents and conditions: (a) Bn_2NH, 5 mol % $Ca(OTf)_2$, CH_2Cl_2, 50 °C, 24 h, 74%; (b) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 20 h, 79%; (c) H_2, 20% $Pd(OH)_2C$, EtOH, rt, 3 days, 71%.

HC=CP and CC=CP couplings, 10.5 and 14.3 Hz, respectively, unequivocally support the *cis*-orientation of *HC*=C*P* atoms and the *trans*-configuration of the hydroxymethyl and diethoxyphosphoryl groups.[15] Furthermore, the (*E*)-isomer of phosphonate **11** is energetically more stable than (*Z*)-**11**, because in the former isomer, the bulky diethoxyphosphoryl group and a hydrogen atom are on the same side of the C=C bond, while in the latter severe repulsions with the hydroxymethyl group are expected. Since only one isomeric alkene, (*E*)-**11**, was obtained from either 2-mesyloxyphosphonates (1*S*,2*R*)- and (1*R*,2*R*)-**9** or the respective 2,3-epoxyphosphonates (1*S*,2*S*)- and (1*R*,2*S*)-**10**, we postulate the formation of carbanion **19** as an intermediate. In separate experiments, pure epoxyphosphonates (1*S*,2*S*)- and (1*R*,2*S*)-**10** were cleanly transformed into a vinylphosphonate (*E*)-**11** after stirring with potassium carbonate in ethanol. The reasons, why when starting from the mesylate (1*S*,2*R*)-**9** only minute quantities of (*E*)-**11** were produced, and significant amounts of this alkene always contaminated the epoxide obtained from diastereoisomeric mesylate (1*R*,2*R*)-**9**, remain obscure so far (Fig. 1).

3. Conclusions

Diethyl (1*S*,2*R*)- and (1*R*,2*R*)-1,3-dihydroxy-2-mesyloxypropylphosphonates **4** were obtained from the known diethyl (1*S*,2*R*)- and (1*R*,2*R*)-2,3-*O*-cyclohexylidene-1,2,3-trihydroxypropylphosphonates **3** by benzylation, acetal cleavage, tritylation, mesylation and hydrogenolysis. When the mesylate (1*S*,2*R*)-**4** was subjected to the intramolecular Williamson reaction, diethyl (1*S*,2*S*)-1,2-epoxy-3-hydroxypropylphosphonate **2** was produced almost regioselectively, while under the same conditions from the mesylate (1*R*,2*R*)-**4**, *O*-ethyl (1*R*,2*S*)-1,2-epoxy-3-hydroxypropylphosphonate **2a** was formed. Synthesis of diethyl (1*R*,2*S*)-1,2-epoxy-3-hydroxypropylphosphonate **2** was accomplished via diethyl (1*R*,2*R*)-1-hydroxy-2-mesyloxy-3-trityloxypropylphosphonate **14**.

Syntheses of diethyl (1*S*,2*S*)- and (1*R*,2*S*)-2,3-epoxy-1-benzyloxypropylphosphonates **10** were carried out by employing the intermediate diethyl (1*S*,2*R*)- and (1*R*,2*R*)-1-benzyloxy-3-hydroxy-2-mesyloxypropylphosphonates **9**, respectively. However, the intramolecular cyclisations were accompanied by the formation of various amounts of diethyl (*E*)-1-benzyloxy-3-hydroxyprop-1-en-1-phosphonate (*E*)-**11** [less than 10% when starting from (1*S*,2*R*)-**9** and up to 65% from (1*R*,2*R*)-**9**]. Since under the basic conditions of the Williamson reaction, pure diastereoisomeric epoxides **10** were also transformed into a vinylphosphonate



19

Figure 1. Intermediate carbanion **19**.

11, the P=O stabilised carbanion **19** serves as a common intermediate of the epoxide isomerisation.

The catalytic hydrogenation of diethyl (1*S*,2*S*)- and (1*R*,2*S*)-2,3-epoxy-1-benzyloxypropylphosphonates **10** did not yield the requested diethyl (1*S*,2*S*)- and (1*R*,2*S*)-2,3-epoxy-1-hydroxypropylphosphonates **12**, which could have served as starting materials in studies of Payne rearrangement[16] in the phosphonate series. Instead, diethyl (1*S*,2*S*)- and (1*R*,2*S*)-1,2-dihydroxypropylphosphonates **13** were obtained as pure enantiomers for the first time. In the case of (1*S*,2*S*)-**10** the epoxide ring opening is faster than the removal of the benzyl group, while for (1*R*,2*S*)-**10**, the opposite is true. From diethyl (1*S*,2*S*)- and (1*R*,2*S*)-2,3-epoxy-1-benzyloxypropylphosphonates **10**, diethyl (1*S*,2*S*)- and (1*R*,2*S*)-3-acetamido-1,2-dihydroxypropylphosphonates **18** were obtained according to a known procedure.[13]

4. Experimental

4.1. General

^{1}H NMR spectra were recorded with a Varian Mercury-300 spectrometer; chemical shifts δ in parts per million with respect to TMS; coupling constants J in hertz. ^{13}C and ^{31}P NMR spectra were recorded on a Varian Mercury-300 machine at 75.5 and 121.5 MHz, respectively. IR spectral data were measured on an Infinity MI-60 FT-IR spectrometer. Melting points were determined on a Boetius apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of this Faculty on a Perkin Elmer PE 2400 CHNS analyzer. Polarimetric measurements were conducted on a Perkin Elmer 241 MC apparatus. The following absorbents were used: column chromatography, Merck silica gel 60 (70–230 mesh); analytical TLC, Merck TLC plastic sheets silica gel 60 F_{254}.

4.2. Diethyl (1*S*,2*R*)-1-benzyloxy-2-hydroxy-3-trityloxypropylphosphonate (1*S*,2*R*)-7

To a solution of the diol (1*S*,2*R*)-**6** (0.919 g, 2.89 mmol) in CH_2Cl_2 (30 mL) containing NEt_3 (0.65 mL, 4.6 mmol) cooled to 0 °C, trityl chloride (0.97 g, 3.5 mmol) was added followed by DMAP (0.004 g, 0.03 mmol). The solution was then stirred at room temperature for 20 h and treated with a cold saturated NH_4Cl (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), and the organic phases were combined and dried over $MgSO_4$. After concentration, the crude product was chromatographed on a silica gel column with chloroform–methanol–triethylamine (100:1:0.05, v/v) to give trityl derivative (1*S*,2*R*)-**7** (1.49 g, 92%) as a colourless oil; $[\alpha]_D^{20} = +13.1$ (*c* 1.8, $CHCl_3$). IR (film): $\nu = 3341$, 3059, 3031, 2982, 2930, 2873, 1597, 1491, 1449, 1391, 1225, 1049, 748, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.46$–7.08 (m, 20H), 4.70 (d, $J = 11.1$ Hz, 1H, H_aCH_bPh), 4.44 (d, $J = 11.1$ Hz, 1H, H_aCH_bPh), 4.21–4.03 (m, 5H, CH_2OP and HCCP), 3.99 (dAB, $J_{AB} = 7.3$, $J = 5.6$ Hz, 1H, HCP), 3.50 (ddd, $J = 9.9$, 3.3, 0.6 Hz, 1H, H_aCH_bCCP), 3.38 (d, $J = 3.8$ Hz, 1H, HO), 3.26 (dd, $J = 9.9$, 5.4 Hz, 1H, H_aCH_bCCP), 1.29 and 1.29 (2t, $J = 6.9$ Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 143.9$, 137.2, 128.8, 128.3, 128.2, 128.1, 127.9, 127.1, 86.8, 75.5 (d, $J = 160.7$ Hz, *C*P), 74.8 (d, $J = 3.8$ Hz, O*C*Ph), 71.0 (d, $J = 4.5$ Hz, *C*CP), 64.0 (d, $J = 9.2$ Hz, *C*CCP), 63.3 and 62.7 (2d, $J = 6.7$ Hz, CH_3CH_2OP), 16.8 and 16.8 (2d, $J = 5.6$ Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 24.45$. Anal. Calcd for $C_{33}H_{37}O_6P\cdot H_2O$: C, 68.50; H, 6.74. Found: C, 68.42; H, 6.71.

4.2.1. Diethyl (1*R*,2*R*)-1-benzyloxy-2-hydroxy-3-trityloxypropylphosphonate (1*R*,2*R*)-7.

As described in the previous section, from phosphonate (1*R*,2*R*)-**6** (0.637 g, 2.00 mmol) and trityl chloride (0.660 g, 2.40 mmol) in the presence of NEt_3 (0.35 mL, 3.2 mmol) and DMAP (0.024 g, 0.20 mmol), the trityl derivative (1*R*,2*R*)-**7** (0.953 g, 85%) was obtained as a colourless oil. $[\alpha]_D^{20} = -21.6$ (*c* 3.65, $CHCl_3$). IR (film): $\nu = 3366$, 3059, 3031, 2982, 2930, 2873, 1597, 1491, 1449, 1391, 1225, 1093, 1027, 967, 747, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.47$–7.11 (m, 20H), 4.77 (d, $J = 10.8$ Hz, 1H, H_aCH_bPh), 4.42 (d, $J = 10.8$ Hz, 1H, H_aCH_bPh), 4.23–4.11 (m, 5H, CH_2OP and HCCP), 4.06 (dd, $J = 7.2$, 2.1 Hz, 1H, HCP), 3.39 (ddd, $J = 9.3$, 5.7, 2.1 Hz, 1H, H_aCH_bCCP), 3.14 (dd, $J = 9.3$, 7.5 Hz, 1H, H_aCH_bCCP), 2.78 (br s, 1H, HO), 1.34 and 1.32 (2t, $J = 7.2$ Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, CD_3OD): $\delta = 145.2$, 138.7, 129.8, 129.4, 129.3, 128.9, 128.9, 128.2, 88.3, 77.1 (d, $J = 164.6$ Hz, *C*P), 76.3 (d, $J = 3.1$ Hz, O*C*Ph), 70.9 (d, $J = 0.9$ Hz, *C*CP), 64.9 (d, $J = 11.2$ Hz, *C*CCP), 64.4 and 63.8 (2d, $J = 6.9$ Hz, CH_3CH_2OP), 17.1 and 17.0 (2d, $J = 5.6$ Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 23.85$. Anal. Calcd for $C_{33}H_{37}O_6P\cdot 2H_2O$: C, 66.43; H, 6.93. Found: C, 66.66; H, 6.81.

4.3. Diethyl (1*S*,2*R*)-1-benzyloxy-2-mesyloxy-3-trityloxypropylphosphonate (1*S*,2*R*)-8

To a solution of phosphonate (1*S*,2*R*)-**7** (1.40 g, 2.50 mmol) in CH_2Cl_2 (15 mL) containing NEt_3 (1.04 mL, 7.50 mmol) and DMAP (a few crystals) cooled to 0 °C, mesyl chloride (0.39 mL, 5.0 mmol) was added dropwise. After 20 h at room temperature, the reaction mixture was washed with water (10 mL) and the aqueous phase extracted with CH_2Cl_2 (3 × 15 mL). The organic phases were collected, washed with cold brine (20 mL), dried over $MgSO_4$, concentrated and the crude product was chromatographed on a silica gel column with chloroform–methanol–triethylamine (100:1:0.05, v/v) to give the mesylate (1*S*,2*R*)-**8** (1.28 g, 80%) as a colourless oil; $[\alpha]_D^{20} = +3.2$ (*c* 2.5, $CHCl_3$). IR (film): $\nu = 3061$, 3021, 2936, 2884, 1595, 1490, 1448, 1347, 1245, 1147, 1047, 1018, 751, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.44$–7.18 (m, 20H), 5.10 (dddd, $J = 10.0$, 7.7, 3.2, 2.8 Hz, 1H, HCCP), 4.70 and 4.61 (AB system, $J_{AB} = 11.1$ Hz, 2H, H_aCH_bPh), 4.14 (dd, $J = 12.9$, $J = 3.2$ Hz, 1H, HCP), 4.10–3.94 (m, 4H, CH_2OP), 3.67 (dd, $J = 11.3$, 2.8 Hz, 1H, H_aCH_bCCP), 3.54 (dd, $J = 11.3$, 7.7 Hz, 1H, H_aCH_bCCP), 3.07 (s, 3H, CH_3SO_2), 1.24 and 1.20 (2t, $J = 6.9$ Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 143.4$, 136.7, 128.8, 128.4, 128.4, 128.2, 128.0, 127.3, 87.6, 81.7 (d, $J = 10.0$ Hz, *C*CP), 75.6 (d, $J = 165.2$ Hz, *C*P), 75.2 (d, $J = 6.0$ Hz, O*C*Ph), 63.2 and 63.2 (2d, $J = 7.1$ Hz,

CH_3CH_2OP), 62.6 (d, $J = 1.5$ Hz, $CCCP$), 39.0, 16.7 and 16.7 (2d, $J = 5.3$ Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 18.90$. Anal. Calcd for $C_{34}H_{39}O_8PS \cdot H_2O$: C, 62.18; H, 6.29. Found: C, 62.23; H, 6.06.

4.3.1. Diethyl (1*R*,2*R*)-1-benzyloxy-2-mesyloxy-3-trityloxypropylphosphonate (1*R*,2*R*)-8. As described in the previous section, from phosphonate (1*R*,2*R*)-**7** (0.715 g, 1.28 mmol) and mesyl chloride (0.20 mL, 2.6 mmol) in the presence of DMAP (0.250 g, 2.05 mmol) in CH_2Cl_2 (15 mL), mesylate (1*R*,2*R*)-**8** (0.631 g, 80%) was obtained as a colourless oil; $[\alpha]_D^{20} = -6.2$ (*c* 0.87, $CHCl_3$). IR (film): $\nu = 3060$, 3031, 2986, 2936, 2908, 1597, 1492, 1449, 1363, 1255, 1175, 1048, 1025, 751, 707 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.42$–7.19 (m, 20H), 4.90 (dddd $\approx$ qu, $J = 5.7$ Hz, 1H, HCCP), 4.82 and 4.57 (AB system, $J_{AB} = 10.8$ Hz, 2H, H_aCH_bPh), 4.24–4.02 (m, 5H, CH_2OP and HCP), 3.59 and 3,54 (AB part of ABX, $J_{AB} = 10.5$, $J_{BX} = 5.7$, Hz, 2H, H_aCH_bCCP), 3.00 (s, 3H, CH_3SO_2), 1.27 and 1.25 (2t, $J = 7.1$ Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 143.4$, 136.9, 128.7, 128.4, 128.4, 128.2, 128.1, 127.4, 87.8, 79.9 (d, $J = 5.3$ Hz, CCP), 75.7 (d, $J = 3.0$ Hz, $OCPh$), 74.2 (d, $J = 166.8$ Hz, CP), 63.3 (d, $J = 6.8$ Hz, CH_3CH_2OP), 62.4 (d, $J = 6.0$ Hz, $CCCP$), 38.9, 16.7 and 16.7 (2d, $J = 5.3$ Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 19.42$. Anal. Calcd for $C_{34}H_{39}O_8PS \cdot 2H_2O$: C, 60.52; H, 6.42. Found: C, 60.33; H, 6.16.

4.4. Diethyl (1*S*,2*R*)-1,3-dihydroxy-2-mesyloxypropylphosphonate (1*S*,2*R*)-4

A suspension of 10% Pd–C (10 mg) in a solution of phosphonate (1*S*,2*R*)-**8** (0.169 g, 0.26 mmol) in ethanol (8 mL) was stirred under a hydrogen atmosphere (balloon) for 24 h. The catalyst was removed by filtration through a layer of Celite, a solution was concentrated and the residue was chromatographed on a silica gel column with chloroform–methanol (50:1, v/v) to give the diol (1*S*,2*R*)-**4** (0.070 g, 88%) as a colourless oil; $[\alpha]_D^{20} = +10.9$ (*c* 1.0, $CHCl_3$). IR (film): $\nu = 3376$, 2986, 2938, 1360, 1243, 1177, 1026, 977, 821 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 4.93$ (dddd, $J = 9.0$, 4.8, 4.2, 4.0 Hz, 1H, HCCP), 4.35 (ddd, $J = 11.7$, 5.7, 4.2 Hz, 1H, HCP), 4.29–4.15 (m, 5H, CH_2OP and HO), 4.13–4.05 (m, 2H, H_aCH_bCCP), 3.46–3.35 (br s, 1H, HO), 3.16 (s, 3H, CH_3SO_2), 1.37 (t, $J = 7.1$ Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 82.0$ (d, $J = 10.0$ Hz, CCP), 68.5 (d, $J = 162.3$ Hz, CP), 64.1 and 63.7 (2d, $J = 7.0$ Hz, CH_3CH_2OP), 61.6 (d, $J = 2.9$ Hz, $CCCP$), 38.9, 16.7 and 16.7 (2d, $J = 5.7$ Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 20.34$. Anal. Calcd for $C_8H_{19}O_8PS$: C, 31.37; H, 6.25. Found: C, 31.66; H, 6.50.

4.4.1. Diethyl (1*R*,2*R*)-1,3-dihydroxy-2-mesyloxypropylphosphonate (1*R*,2*R*)-4. As described in the previous section, from phosphonate (1*R*,2*R*)-**8** (0.800 g, 1.25 mmol) dissolved in ethanol (10 mL) in the presence of 10% Pd–C (13 mg) the 1,3-dihydroxypropylphosphonate (1*R*,2*R*)-**4** (0.257 g, 67%) was obtained as a colourless oil; $[\alpha]_D^{20} = +0.8$ (*c* 2.5, $CHCl_3$); $[\alpha]_D^{20} = +4.7$ (*c* 0.97, MeOH). IR (film): $\nu = 3343$, 2985, 2925, 2853, 1342, 1224, 1173, 1047, 1025, 971, 919 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 4.90$ (qu, $J = 4.8$ Hz, 1H, HCCP), 4.31–4.15 (m, 5H, CH_2OP and HCP), 4.00 (dd, $J = 6.6$, 4.8 Hz 2H, CH_2CCP), 3.70 (dd, $J = 9.0$, 8.1 Hz, 1H, HOCP), 3.20 (t, 3.16 $J = 6.6$, 1H, $HOCH_2$), 3.18 (s, 3H, CH_3SO_2), 1.38 and 1.38 (2t, $J = 7.1$ Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 82.1$ (d, $J = 6.6$ Hz, CCP), 66.7 (d, $J = 165.2$ Hz, CP), 63.9 and 63.8 (2d, $J = 7.3$ Hz, CH_3CH_2OP), 61.5 (d, $J = 6.9$ Hz, $CCCP$), 38.9, 16.7 (d, $J = 5.4$ Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 20.20$. Anal. Calcd for $C_8H_{19}O_8PS$: C, 31.37; H, 6.25. Found: C, 31.10; H, 6.10.

4.5. Diethyl (1*S*,2*S*)-1,2-epoxy-3-hydroxypropylphosphonate (1*S*,2*S*)-2

A suspension of anhydrous potassium carbonate (0.127 g, 0.92 mmol) in a solution of phosphonate (0.070 g, 0.23 mmol) in ethanol (1 mL) was stirred at room temperature for 20 h. After filtration through a pad of Celite, a solution was concentrated and chromatographed on silica gel with chloroform–methanol (100:1, v/v) to give epoxyphosphonate (1*S*,2*S*)-**2** (0.035 g, 74%) as a colourless oil; $[\alpha]_D^{20} = -24.7$ (*c* 0.8, $CHCl_3$); lit.[11] $[\alpha]_D^{20} = +24.4$ (*c* 1.5, $CHCl_3$) for (1*R*,2*R*)-**2**. Anal. Calcd for $C_7H_{15}O_5P$: C, 40.00; H, 7.19. Found: C, 40.30; H, 6.90.

4.6. Diethyl (1*S*,2*R*)-1-benzyloxy-3-hydroxy-2-mesyloxypropylphosphonate (1*S*,2*R*)-9

A solution of the trityloxyphosphonate (1*S*,2*R*)-**8** (1.16 g, 1.81 mmol) in ethanol (20 mL) containing enough TsOH to achieve pH 3 was left at room temperature for 20 h. Ethanol was evaporated, the residue dissolved in CH_2Cl_2 (20 mL) and the solution was washed with cold saturated aqueous $NaHCO_3$. After drying over $MgSO_4$ and evaporation of the solvent, the residue was chromatographed on a silica gel column with chloroform–methanol (100:1, v/v) to give phosphonate (1*S*,2*R*)-**9** (0.695 g, 97%) as a colourless oil; IR (film): $\nu = 3381$, 3031, 2985, 2938, 2911, 2878, 1455, 1355, 1233, 1175, 1024, 973, 751, 701 cm^{-1}. $[\alpha]_D^{20} = +23.4$ (*c* 1.3, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.38$–7.32 (m, 5H), 4.98 (dddd, $J = 8.4$, 6.0, 4.2, 3.0 Hz, 1H, HCCP), 4.81 and 4.77 (AB system, $J_{AB} = 11.3$ Hz, 2H, H_aCH_bPh), 4.24–4.12 (m, 5H, CH_2OP and HCP), 4.12 (dd, $J = 12.8$, 4.2 Hz, 1H, H_aCH_bCCP), 3.93 (dd, $J = 12.8$, 6.0 Hz, 1H, H_aCH_bCCP), 3.06 (s, 3H, CH_3SO_2), 2.6–2.4 (br s, 1H, HO), 1.35 and 1.32 (2t, $J = 6.9$ Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 136.6$, 128.6, 128.5, 128.4, 128.0, 82.6 (d, $J = 13.2$ Hz, CCP), 75.7 (d, $J = 164.6$ Hz, CP), 75.5 (d, $J = 6.3$ Hz, $OCPh$), 63.9 and 63.3 (2d, $J = 7.0$ Hz, CH_3CH_2OP), 61.1 (s, $CCCP$), 38.7, 16.7 and 16.6 (2d, $J = 5.7$ Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 19.60$. Anal. Calcd for $C_{15}H_{25}O_8PS$: C, 45.41; H, 6.31. Found: C, 45.17; H, 6.05.

4.6.1. Diethyl (1*R*,2*R*)-1-benzyloxy-3-hydroxy-2-mesyloxypropylphosphonate (1*R*,2*R*)-9. As described in the previous section, from phosphonate (1*R*,2*R*)-**8** (0.631 g, 0.99 mmol) dissolved in ethanol (30 mL) in the presence of TsOH, phosphonate (1*R*,2*R*)-**9** (0.340 g, 87%) was obtained as a colourless oil. $[\alpha]_D^{20} = -14.2$ (*c* 1.5, $CHCl_3$).

IR (film): $\nu = 3368$, 2984, 2938, 2911, 1357, 1232, 1174, 1025, 971, 915, 750, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.38$–7.32 (m, 5H), 4.88 (d, $J = 11.1$ Hz, 1H, H_aCH_bPh), 4.81 (dddd, $J = 7.2$, 6.6, 4.2, 4.2 Hz, 1H, HCCP), 4.65 (d, $J = 11.1$ Hz, 1H, H_aCH_bPh), 4.28–4.17 (m, 4H, CH_2OP), 4.06 (dd, $J = 9.6$, 6.6 Hz, 1H, HCP), 4.01 (ddd, $J = 12.9$, 4.2, 0.3 Hz, 1H, H_aCH_bCCP), 3.91 (ddd, $J = 12.9$, 4.2, 0.6 Hz, 1H, H_aCH_bCCP), 2.98 (s, 3H, CH_3SO_2), 1.9–1.6 (br s, 1H, HO), 1.38 and 1.37 (2t, $J = 7.2$ Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 136.7$, 128.6, 128.5, 128.4, 82.2 (d, $J = 10.6$ Hz, *C*CP), 75.6 (d, $J = 3.0$ Hz, O*C*Ph), 74.3 (d, $J = 163.7$ Hz, *C*P), 63.8 and 63.5 (2d, $J = 6.8$ Hz, CH_3CH_2OP), 61.8 (d, $J = 3.8$ Hz, *C*CCP), 38.7, 16.7 (d, $J = 3.8$ Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 20.28$. Anal. Calcd for $C_{15}H_{25}O_8PS$: C, 45.40; H, 6.31. Found: C, 45.63; H, 6.52.

4.7. Diethyl (1*S*,2*S*)-2,3-epoxy-1-benzyloxypropylphosphonate (1*S*,2*S*)-10

A suspension of anhydrous potassium carbonate (0.274 g, 1.98 mmol) in a solution of phosphonate (1*S*,2*R*)-**9** (0.525 g, 1.32 mmol) in ethanol (20 mL) was stirred at room temperature for 20 h. After filtration through a pad of Celite, a solution was concentrated and chromatographed on silica gel with chloroform–methanol (100:1, v/v) to give the epoxyphosphonate (1*S*,2*S*)-**10** (0.353 g, 89%) as a colourless oil; $[\alpha]_D^{20} = -20.6$ (*c* 4.0, $CHCl_3$) {lit.[13] $[\alpha]_D^{20} = +20.7$ (*c* 1.23, $CHCl_3$)}. ^1H, ^{13}C and ^{31}P NMR spectral data of this compound were identical with those described earlier for its enantiomer.[13] Anal. Calcd for $C_{14}H_{21}O_5P$: C, 55.98; H, 7.06. Found: C, 56.22; H, 7.32.

4.7.1. Diethyl (1*R*,2*S*)-2,3-epoxy-1-benzyloxypropylphosphonate (1*R*,2*S*)-10. As described in the previous section, from phosphonate (1*R*,2*R*)-**9** (0.150 g, 0.380 mmol) dissolved in ethanol (10 mL) in the presence of K_2CO_3 (0.105 g, 0.76 mmol) after 6 h of stirring, the epoxyphosphonate (1*R*,2*S*)-**10** (0.035 g, 30%) was obtained as a colourless oil. $[\alpha]_D^{20} = -19.7$ (*c* 1.0, $CHCl_3$) {lit.[13] $[\alpha]_D^{20} = +22.7$ (*c* 0.997, $CHCl_3$)}. ^1H, ^{13}C and ^{31}P NMR spectral data of this compound were identical with those described earlier for its enantiomer.[13] Anal. Calcd for $C_{14}H_{21}O_5P{\cdot}1/2H_2O$: C, 54.36; H, 7.17. Found: C, 54.31; H, 7.47.

4.8. Diethyl (*E*)-1-benzyloxy-3-hydroxyprop-1-en-1-phosphonate (*E*)-11

Further elution of the silica gel column (Section 4.7.1) gave a vinylphosphonate (*E*)-**11** (0.073 g, 60%) as a colourless oil. IR (film): $\nu = 3396$, 2984, 2931, 287311, 1638, 1455, 1233, 1130, 1023, 973, 740, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.42$–7.26 (m, 5H), 6.12 (dt, $J = 10.5$, 6.0 Hz, 1H, HC=), 5.00 (s, 2H, CH_2Ph), 4.23–4.10 (m, 6H, CH_2OP and CH_2OH), 1.7–1.6 (br s, 3H, HO and H_2O), 1.37 (t, $J = 7.2$ Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 145.8$ (d, $J = 211.3$ Hz, *C*P), 136.8, 131.2 (d, $J = 22.6$ Hz, *C*CP), 128.6, 128.4, 128.3, 74.4 (d, $J = 2.3$ Hz, O*C*Ph), 62.8 (2d, $J = 5.3$ Hz, CH_3CH_2OP), 57.4 (d, $J = 14.3$ Hz, *C*CCP), 16.7 (d, $J = 6.0$ Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 11.00$. Anal. Calcd for $C_{14}H_{21}O_5P{\cdot}H_2O$: C, 52.83; H, 7.28. Found: C, 52.55; H, 6.98.

4.9. Diethyl (1*S*,2*S*)-1,2-dihydroxypropylphosphonate (1*S*,2*S*)-13

A suspension of 10% Pd–C (20 mg) in a solution of phosphonate (1*S*,2*S*)-**10** (0.200 g, 0.670 mmol) in ethanol (10 mL) was stirred under a hydrogen atmosphere (balloon) for 24 h. The catalyst was removed by filtration through a layer of Celite, the solution concentrated and the residue was chromatographed on a silica gel column with chloroform–methanol (100:1, v/v) to give the diol (1*S*,2*S*)-**13** (0.100 g, 70%) as a colourless oil; $[\alpha]_D^{20} = +10.3$ (*c* 1.4, $CHCl_3$) {lit.[14] $[\alpha]_D^{20} = +3.7$ (*c* 1.0, MeOH) for a material of ee = 33%}. IR (film): $\nu = 3368$, 2983, 2913, 1445, 1394, 1218, 1028, 971 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 4.27$–4.12 (m, 5H, CH_2OP and HCCP), 4.0–3.9 (br s, 1H, HO), 3.69 (ddd, $J = 9.0$, 8.2, 3.1 Hz, 1H, HCP), 3.65–3.55 (br s, 1H, HO), 1.36 and 1.35 (2t, $J = 7.2$ Hz, 6H, CH_3CH_2OP), 1.31 (dd, $J = 6.6$, 1.5 Hz, 3H, H_3CCCP). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 72.1$ (d, $J = 158.9$ Hz, *C*P), 66.8 (d, $J = 2.9$ Hz, *C*CP), 63.5 and 62.9 (2d, $J = 7.2$ Hz, CH_3CH_2OP), 19.5 (d, $J = 10.3$ Hz, *C*CCP), 16.7 and 16.7 (2d, $J = 5.6$ Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 24.66$. Anal. Calcd for $C_7H_{17}O_5P{\cdot}1/2H_2O$: C, 38.01; H, 8.20. Found: C, 37.76; H, 8.49.

4.9.1. Diethyl (1*R*,2*S*)-1,2-dihydroxypropylphosphonate (1*R*,2*S*)-13. As described in the previous section, from phosphonate (1*R*,2*S*)-**10** (0.050 g, 0.17 mmol) dissolved in ethanol (2 mL) in the presence 5% Pd–C (0.005 g), after 3 days the diol (1*R*,2*S*)-**13** (0.022 g, 61%) was obtained as a colourless oil; $[\alpha]_D^{20} = -4.4$ (*c* 4.05, $CHCl_3$). IR (film): $\nu = 3368$, 2984, 2917, 2874, 1445, 1394, 1208, 1025, 970 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 4.29$–4.13 (m, 4H, CH_2OP), 4.06 (ddqd, $J = 15.9$, 6.6, 6.3, 5.4 Hz, 1H, HCCP), 3.78 (ddd, $J = 7.8$, 6.6, 5.4 Hz, 1H, HCP), 3.15 (br d, $J = 6.3$ Hz, 1H, HOCCP), 3.01 (dd, $J = 7.8$, 6.6 Hz, 1H, HOCP), 1.38 and 1.37 (2t, $J = 6.9$ Hz, 6H, CH_3CH_2OP), 1.37 (d, $J = 6.6$ Hz, 3H, H_3CCCP). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 72.0$ (d, $J = 154.0$ Hz, *C*P), 68.5 (d, $J = 2.3$ Hz, *C*CP), 63.3 and 62.6 (2d, $J = 7.1$ Hz, CH_3CH_2OP), 19.2 (d, $J = 6.0$ Hz, *C*CCP), 16.5 and 16.5 (2d, $J = 5.5$ Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 24.48$. Anal. Calcd for $C_7H_{17}O_5P{\cdot}1/2H_2O$: C, 38.01; H, 8.20. Found: C, 37.86; H, 8.16.

4.10. *O*-Ethyl (1*R*,2*S*)-1,2-epoxy-3-hydroxypropylphosphonate (1*R*,2*S*)-2a

A suspension of anhydrous potassium carbonate (0.048 g, 0.35 mmol) in a solution of phosphonate (1*R*,2*R*)-**4** (0.050 g, 0.16 mmol) in ethanol (1 mL) was stirred at room temperature for 24 h. After filtration through a pad of Celite, a solution was concentrated and chromatographed on silica gel with chloroform–methanol (5:1, v/v) to give the epoxyphosphonate (1*R*,2*S*)-**2a** (0.020 g, 69%) as a white amorphous solid; the compound did not melt or change its appearance up to 260 °C; $[\alpha]_D^{20} = +12.2$ (*c* 0.8, water); IR (KBr): $\nu = 3600$–3100, 2982, 2932, 1649, 1445, 1370,

1204, 1044, 950 cm^{-1}. ^1H NMR (300 MHz, CD_3OD): $\delta = 4.05$–3.94 (m, 2H, CH_2OP), 3.95 (d, $J = 5.4$ Hz, 1H, HCCCP), 3.24 (dddd, $J = 5.4$, 5.4, 5.1, 4.8 Hz, 1H, HCCP), 2.93 (dd, $J = 22.2$, 5.1 Hz, 1H, HCP), 1.27 (t, $J = 7.2$ Hz, 3H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, CD_3OD): $\delta = 61.9$ (d, $J = 5.1$ Hz, CH_3CH_2OP), 58.4 (*C*CCP), 52.2 (d, $J = 188.1$ Hz, *C*P), 39.5 (*C*CP), 17.3 (d, $J = 6.3$ Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 12.89$. Anal. Calcd for $C_5H_{11}O_5P$: C, 32.98; H, 6.09. Found: C, 33.04; H, 6.05.

4.11. Diethyl (1*R*,2*S*)-1,2-epoxy-3-hydroxypropylphosphonate (1*R*,2*S*)-2

4.11.1. Diethyl (1*R*,2*R*)-1-hydroxy-2-mesyloxy-3-trityloxypropylphosphonate (1*R*,2*R*)-14. To a solution of diol (1*R*,2*R*)-**4** (0.090 g, 0.29 mmol) in CH_2Cl_2 (5 mL) containing NEt_3 (0.12 mL, 0.87 mmol) cooled to 0 °C, trityl chloride (0.13 g, 0.46 mmol) was added followed by DMAP (a few crystals). The solution was then stirred at room temperature for 20 h and treated with cooled, saturated NH_4Cl (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3×2 mL), and the organic phases combined and dried over $MgSO_4$. After concentration, the crude product was chromatographed on a silica gel column with chloroform–methanol–triethylamine (100:1:0.05, v/v) to give the trityl derivative (1*R*,2*R*)-**14** (0.110 g, 70%) as a colourless oil; $[\alpha]_D^{20} = +1.5$ (*c* 1.1, $CHCl_3$). IR (film): $\nu = 3305$, 3061, 3037, 2986, 2941, 2927, 2853, 1597, 1493, 1450, 1354, 1250, 1055, 747, 708 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.45$–7.22 (m, 15H), 4.92 (m, 1H, HCCP), 4.19 (dd, $J = 7.5$, 4.2 Hz, 1H, HCP), 4.17–4.07 (m, 4H, CH_2OP), 3.64 (dd, $J = 10.3$, 5.3 Hz, 1H, H_aCH_bCCP), 3.49 (ddd, $J = 10.3$, 6.0, 1.4 Hz, 1H, H_aCH_bCCP), 3.10 (s, 3H), 1.68 (s, 1H, OH), 1.30 and 1.28 (2t, $J = 7.0$ Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 143.1$, 128.5, 127.8, 127.1, 87.5, 79.8 (d, $J = 4.3$ Hz, *C*CP), 67.2 (d, $J = 163.5$ Hz, *C*P), 63.4 and 63.2 (2d, $J = 7.2$ Hz, CH_3CH_2OP), 62.6 (d, $J = 7.2$ Hz, *C*CCP), 38.8, 16.5 (d, $J = 5.1$ Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 20.81$. Anal. Calcd for $C_{27}H_{33}O_8PS$: C, 59.11; H, 6.06. Found: C, 59.40; H, 6.13.

4.11.2. Diethyl (1*R*,2*S*)-1,2-epoxy-3-trityloxypropylphosphonate (1*R*,2*S*)-15. A suspension of anhydrous potassium carbonate (0.055 g, 0.40 mmol) in a solution of phosphonate (1*R*,2*R*)-**14** (0.11 g, 0.20 mmol) in ethanol (1 mL) was stirred at room temperature for 5 h. After filtration through a pad of Celite, the solution was concentrated and chromatographed on silica gel with chloroform–methanol (50:1, v/v) to give the epoxyphosphonate (1*R*,2*S*)-**15** (0.069 g, 62%) as a colourless oil; $[\alpha]_D^{20} = +9.4$ (*c* 1.6, $CHCl_3$); {lit.[11] $[\alpha]_D^{20} = -10.0$ (*c* 1.15, $CHCl_3$) for its enantiomer}. ^1H, ^{13}C and ^{31}P NMR spectral data of this compound were identical with those described earlier for its enantiomer.[11] Anal. Calcd for $C_{26}H_{29}O_5P \cdot 1/4H_2O$: C, 68.33; H, 6.51. Found: C, 68.50; H, 6.38.

4.11.3. Diethyl (1*R*,2*S*)-1,2-epoxy-3-hydroxypropylphosphonate (1*R*,2*S*)-2. A solution of phosphonate (1*R*,2*S*)-**15** (0.062 g, 0.14 mmol) in ethanol (1 mL) was hydrogenated over Pd–C (10%, 5 mg) at room temperature for 24 h. The catalyst was removed by filtration, the solution was concentrated and the residue chromatographed on a silica gel column with chloroform–methanol (100:1, v/v) to give phosphonate (1*R*,2*S*)-**2** (0.010 g, 68%) as a colourless oil; $[\alpha]_D^{20} = +11.7$ (*c* 0.8, $CHCl_3$) {lit.[11] $[\alpha]_D^{20} = -10.2$ (*c* 1.0, $CHCl_3$) for its enantiomer}. ^1H, ^{13}C and ^{31}P NMR spectral data of this compound were identical with those described earlier for its enantiomer.[11] Anal. Calcd for $C_7H_{15}O_5P \cdot H_2O$: C, 36.85; H, 7.50. Found: C, 37.12; H, 7.74.

4.12. Diethyl (1*S*,2*S*)-3-dibenzyloamino-1-benzyloxy-2-hydroxypropylphosphonate (1*S*,2*S*)-16

A suspension of calcium triflate (0.062 g, 0.18 mmol) in a solution of the epoxyphosphonate (1*S*,2*S*)-**10** (0.110 g, 0.370 mmol) and dibenzylamine (0.078 mL, 0.41 mmol) in acetonitrile (10 mL) was stirred at 50 °C for 20 h. The solvent was evaporated, the residue dissolved in CH_2Cl_2 (15 mL) and the solution washed with water (3×5 mL). After drying with $MgSO_4$ and concentration the crude product was chromatographed on a silica gel column with chloroform–methanol (100:1, v/v). The appropriate fractions were collected and crystallised from ethyl acetate to give phosphonate (1*S*,2*S*)-**14** (0.110 g, 60%) as white needles; $[\alpha]_D^{20} = +4.7$ (*c* 1.2, $CHCl_3$) {lit.[13] $[\alpha]_D^{20} = -4.0$ (*c* 0.73, $CHCl_3$)}. ^1H, ^{13}C and ^{31}P NMR spectral data of this compound were identical with those described earlier for its enantiomer.[13] Anal. Calcd for $C_{28}H_{36}NO_5P$: C, 67.58; H, 7.31; N, 2.81. Found: C, 67.48; H, 7.24; N, 3.08.

4.12.1. Diethyl (1*R*,2*S*)-3-dibenzyloamino-1-benzyloxy-2-hydroxypropylphosphonate (1*R*,2*S*)-16. As described in the previous section, from phosphonate (1*R*,2*S*)-**10** (0.070 g, 0.23 mmol) and dibenzylamine (0.049 mL, 0.25 mmol) dissolved in acetonitrile (3 mL) in the presence of calcium triflate (0.039 g, 0.12 mmol), phosphonate (1*R*,2*S*)-**16** (0.086 g, 74%) was obtained as a white powder after crystallisation from diethyl ether–heptane; mp 63–64 °C (lit.[13] mp 56–57 °C). $[\alpha]_D^{20} = -42.1$ (*c* 1.2, $CHCl_3$) {lit.[13] $[\alpha]_D^{20} = +45.4$ (*c* 0.82, $CHCl_3$)}. ^1H, ^{13}C and ^{31}P NMR spectral data of this compound were identical with those described earlier for its enantiomer.[13] Anal. Calcd for $C_{28}H_{36}NO_5P$: C, 67.58; H, 7.31; N, 2.81. Found: C, 67.64; H, 7.18; N, 3.05.

4.13. Diethyl (1*S*,2*S*)-2-acetyloxy-3-dibenzyloamino-1-benzyloxy-propylphosphonate (1*S*,2*S*)-17

Standard acetylation of (1*S*,2*S*)-**16** (0.080 g, 0.16 mmol) with acetic anhydride (18.0 μL, 0.19 mmol) in the presence of NEt_3 (33.0 μL, 0.24 mmol) and DMAP (two crystals) in CH_2Cl_2 (2.0 mL) gave, after column chromatography on a silica gel column, acetate (1*S*,2*S*)-**17** (0.080 g, 93%) as a colourless oil. $[\alpha]_D^{20} = +11.7$ (*c* 1.0, $CHCl_3$) {lit.[13] $[\alpha]_D^{20} = -11.3$ (*c* 1.42, $CHCl_3$)}. ^1H, ^{13}C and ^{31}P NMR spectral data of this compound were identical with those described earlier for its enantiomer.[13] Anal. Calcd for $C_{30}H_{38}NO_6P$: C, 66.78; H, 7.10; N, 2.60. Found: C, 66.70; H, 6.89; N, 2.88.

4.13.1. Diethyl (1*R*,2*S*)-2-acetyloxy-3-dibenzyloamino-1-benzyloxy-propylphosphonate (1*R*,2*S*)-17. As described in the previous section, from phosphonate (1*R*,2*S*)-**16**

(0.047 g, 0.09 mmol) and acetic anhydride (10.0 μL, 0.11 mmol) in the presence of NEt_3 (12.0 μL, 0.14 mmol) and DMAP (two crystals) in CH_2Cl_2 (1.0 mL), acetate (1*R*,2*S*)-**17** (0.038 g, 79%) was obtained as a colourless oil. $[\alpha]_D^{20} = -38.2$ (*c* 0.9, $CHCl_3$) {lit.[13] $[\alpha]_D^{20} = +37.5$ (*c* 0.84, $CHCl_3$)}. ^1H, ^{13}C and ^{31}P NMR spectral data of this compound were identical with those described earlier for its enantiomer.[13] Anal. Calcd for $C_{30}H_{38}NO_6P$: C, 66.78; H, 7.10; N, 2.60. Found: C, 66.90; H, 7.21; N, 2.65.

4.14. Diethyl (1*S*,2*S*)-3-acetamido-1,2-dihydroxypropylphosphonate (1*S*,2*S*)-18

A solution of phosphonate (1*S*,2*S*)-**17** (0.100 g, 0.18 mmol) in ethanol (5 mL) was hydrogenated over $Pd(OH)_2$–C (20%, 30 mg) and Pd–C (10%, 30 mg) at room temperature for 2 days. The catalyst was removed by filtration, the solution concentrated and the residue chromatographed on a silica gel column with chloroform–methanol (50:1, v/v) to give phosphonate (1*S*,2*S*)-**18** (0.030 g, 61%) as a colourless oil; $[\alpha]_D^{20} = -16.4$ (*c* 1.45, $CHCl_3$) {lit.[13] $[\alpha]_D^{20} = +19.0$ (*c* 0.98, $CHCl_3$) for its enantiomer}. ^1H, ^{13}C and ^{31}P NMR spectral data of this compound were identical with those described earlier for its enantiomer.[13] Anal. Calcd for $C_9H_{20}NO_6P$: C, 40.14; H, 7.50; N, 5.20. Found: C, 40.40; H, 7.26; N, 5.36.

4.14.1. Diethyl (1*R*,2*S*)-3-acetamido-1,2-dihydroxypropylphosphonate (1*R*,2*S*)-18. Phosphonate (1*R*,2*S*)-**17** (0.030 g, 0.060 mmol) was hydrogenated over $Pd(OH)_2$-C (20%, 6 mg) at room temperature for 3 days and worked up as described in the previous section to provide phosphonate (1*R*,2*S*)-**18** (0.011 g, 71%) as a colourless oil; $[\alpha]_D^{20} = +72.2$ (*c* 1.1, $CHCl_3$) {lit.[13] $[\alpha]_D^{20} = -77.2$ (*c* 1.01, $CHCl_3$) for its enantiomer}. ^1H, ^{13}C and ^{31}P NMR spectral data of this compound were identical with those described earlier for its enantiomer.[13] Anal. Calcd for $C_9H_{20}NO_6P$: C, 40.14; H, 7.50; N, 5.20. Found: C, 40.38; H, 7.59; N, 5.26.

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