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New analogues of fosfomycin—synthesis of diethyl (1*R*,2*R*)- and (1*S*,2*R*)-1,2-epoxy-3-hydroxypropylphosphonates

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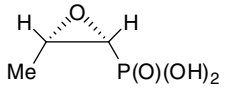
Abstract—The *trans*-configured fosfomycin analogue, diethyl (1*R*,2*R*)-1,2-epoxy-3-hydroxypropylphosphonate, was synthesised via the intramolecular Williamson reaction from 3-*O*-protected (trityl or TBDMS) or even unprotected diethyl (1*S*,2*R*)-2,3-dihydroxy-1-mesyloxypropylphosphonate, which was obtained from the known diethyl (1*S*,2*R*)-2,3-*O*-cyclohexylidene-1,2,3-trihydroxypropylphosphonate. On the other hand, the *cis*-analogue, diethyl (1*S*,2*R*)-1,2-epoxy-3-hydroxypropylphosphonate, could only be prepared from diethyl (1*R*,2*R*)-2-hydroxy-1-mesyloxy-3-trityloxypropylphoshonate.

1. Introduction

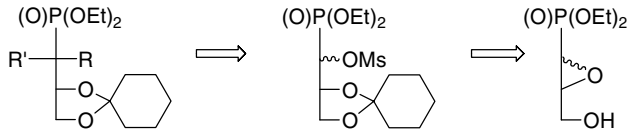
The discovery of the antibiotic properties of fosfomycin [(1*R*,2*S*)-1,2-epoxypropylphosphonic acid] has accelerated the search for new synthetic methods for 1,2-epoxyphosphonates, which have recently been reviewed.[1] The synthetic approaches to fosfomycin fall into two categories: a direct epoxidation of (*Z*)-1-propenylphosphonates and the formation of the oxirane ring by an intramolecular Williamson reaction. These two methods have recently been exemplified by an asymmetric epoxidation[2] and a chemo enzymatic synthesis from 1-chloro-2-hydroxypropylphosphonate.[3]



fosfomycin

A vast number of fosfomycin analogues has been synthesised over the years with the anticipation of novel biological activity. The most prominent examples include compounds in which the methyl group in fosfomycin was replaced by substituted methyl residues (e.g., hydroxymethyl, aminomethyl and their derivatives)[4] or acyl chains.[5] Furthermore, complex fosfomycin analogues, having a 1,2-epoxyphosphonate moiety incorporated into steroids,[6] sugars (cyclic[7,8] or acyclic[9,10]) and nucleosides[11] or their mimetics[9,12] have also been obtained.

Several years ago diethyl (1*R*,2*R*)- and (1*S*,2*R*)-2,3-*O*-cyclohexylidene-1,2,3-trihydroxypropylphosphonates **2** became available[13] and they were later employed in the synthesis of diethyl (1*R*,2*R*)- and (1*S*,2*R*)-2,3-epoxy-1-benzyloxypropylphosphonates.[14] We envisioned the usefulness of phosphonates **2** in the synthesis of enantiomerically pure diethyl (1*R*,2*R*)- and (1*S*,2*R*)-1,2-epoxy-3-hydroxypropylphosphonates **1** (Scheme 1). Herein our efforts to this end are presented.



2
R'=OH, R=H (1*R*,2*R*)
R'=H, R=OH (1*S*,2*R*)

1

Scheme 1. Retrosynthesis of epoxyphosphonates **1**.

2. Results and discussion

A standard mesylation of the HO–C-1 groups in the enantiomerically pure phosphonates (1*R*,2*R*)- and (1*S*,2*R*)-**2** and removal of the cyclohexylidene protecting groups[14]

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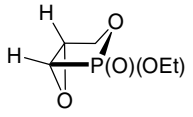
from the respective mesylates (1*R*,2*R*)- and (1*S*,2*R*)-**3** led to diols (1*R*,2*R*)- and (1*S*,2*R*)-**4** in good yields without the formation of any side products (Schemes 2 and 3).

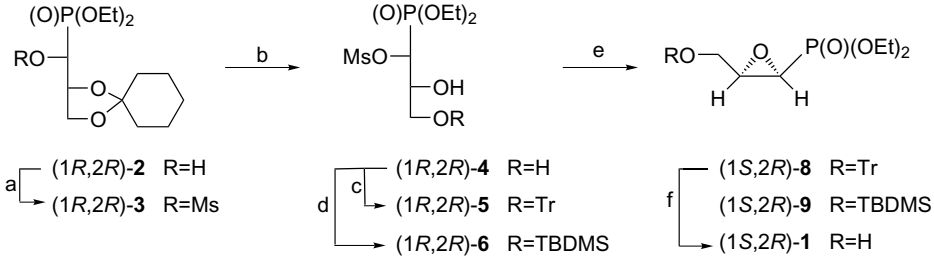
To transform 1-mesyloxy-2-hydroxyalkyl fragments of diols (1*R*,2*R*)-and (1*S*,2*R*)-**4** into the oxirane rings, we first decided to protect the primary HO–C-3 groups as trityl or *tert*-butyldimethylsilyl derivatives.[15] The 3-*O*-protected phosphonates **5** and **6** were selectively obtained in good yields. However, under the basic conditions employed during the tritylation or silylation of diol (1*R*,2*R*)-**4**, the formation of *P*-epimeric 3,4-epoxy-1,2-oxaphospholanes **7** (δ ^{31}P 30.8 and 30.3 ppm) was noticed. In particular, the crude products obtained after tritylations could contain up to 25%, while after silylations up to 5% of the bicyclic compounds **7** were observed, depending on the reaction temperature.



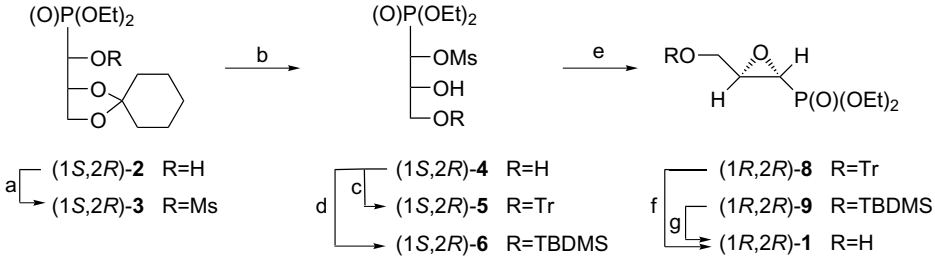
(2*R*/*S*,3*S*,4*R*)-**7**

When diol (1*S*,2*R*)-**4** was subjected to a base-catalysed tritylation or silylation, the crude trityl (1*S*,2*R*)-**5** or *tert*-butyldimethylsilyl (1*S*,2*R*)-**6** derivatives were contaminated with the protected 1,2-epoxyphosphonates (1*R*,2*R*)-**8** (2%) or (1*R*,2*R*)-**9** (8%), respectively. The amounts of the protected 1,2-epoxyphosphonates gradually increased, when the reaction times were extended.

The 3-*O*-protected phosphonates (1*R*,2*R*)- and (1*S*,2*R*)-**5** as well as (1*R*,2*R*)- and (1*S*,2*R*)-**6** were treated with potassium carbonate suspended in anhydrous ethanol–methylene chloride mixtures to produce the respective epoxides in good to excellent yields (Schemes 2 and 3). Diethyl (1*S*,2*R*)-1,2-epoxy-3-trilyloxypropylphosphonate **8** was also formed as a single product upon treatment of phosphonate (1*R*,2*R*)-**5** with potassium carbonate suspended in methanol at room temperature for 24 h. However, under similar conditions from the trityl phosphonate (1*S*,2*R*)-**5**, a mixture of the expected epoxyphosphonate (1*R*,2*R*)-**8** (57%) containing P-epimeric *O*-ethyl-*O*-methyl epoxyphosphonates (1*R*,2*R*,R_P)-**10a** and (1*R*,2*R*,S_P)-**10b** (a 1:1 ratio, total 29%), *O*,*O*-dimethyl epoxyphosphonate (1*R*,2*R*)-**13** (11%) and some unreacted starting material (3%) was formed (Fig. 1). Similar transesterification processes were observed for the silyl derivative (1*R*,2*R*)-**6** leading to a mixture of (1*S*,2*R*)-**9** (45%), (1*S*,2*R*,R_P)-**11a** and (1*S*,2*R*,S_P)-**11b** (a 1:1 ratio, total 30%), (1*S*,2*R*)-**14** (22%) and the unreacted (1*R*,2*R*)-**6** (2%), as judged from the ^{1}H and ^{31}P NMR spectra. Structural assignments in the partially (**10** and **11**) and fully (**13** and **14**) transesterified phosphonates are based on analysis of the ^{1}H NMR spectra of the crude product formed after treating the silylated phosphonate (1*R*,2*R*)-**6** with potassium carbonate in methanol and two chromatographic fractions obtained from this crude product, which contained a 1:1 mixture of (1*S*,2*R*,R_P)-**11a** and (1*S*,2*R*,S_P)-**11b** (ca. 80%) and (1*S*,2*R*)-**14** (ca. 76%) as the major components. When the epoxide ring closure was performed on the silyl derivative (1*S*,2*R*)-**6** at −30 °C for 3 days, the rate of transesterification was significantly slower and the



Scheme 2. Reagents and conditions: (a) MsCl, Et_3N, DMAP, 0 °C to rt, 5 h, 90%; (b) 1 M HCl, dioxane, rt, 24 h, 91%; (c) TrCl, Et_3N, DMAP, 0 °C to rt, 20 h, 87%; (d) TBDMSiCl, Et_3N, DMAP, 0 °C to rt, 5 h, 72%; (e) K_2CO_3, EtOH/CH_2Cl_2, rt, 20 h, 76% **8** and 95% **9**; (f) H_2, Pd–C, EtOH, rt, 24 h, 97% or *p*-TsOH, ethanol, rt, 24 h.



Scheme 3. Reagents and conditions: (a) MsCl, Et_3N, DMAP, 0 °C to rt, 5 h, 93%; (b) 1 M HCl, dioxane, rt, 24 h, 85%; (c) TrCl, Et_3N, DMAP, 0 °C to rt, 20 h, 87%; (d) TBDMSiCl, Et_3N, DMAP, 0 °C to rt, 5 h, 88%; (e) K_2CO_3, EtOH/CH_2Cl_2, rt, 20 h, 70% **8** and 93% **9**; (f) H_2, Pd–C, EtOH, rt, 24 h, 90%; (g) Bu_4NF, THF, rt, 24 h, 90%.

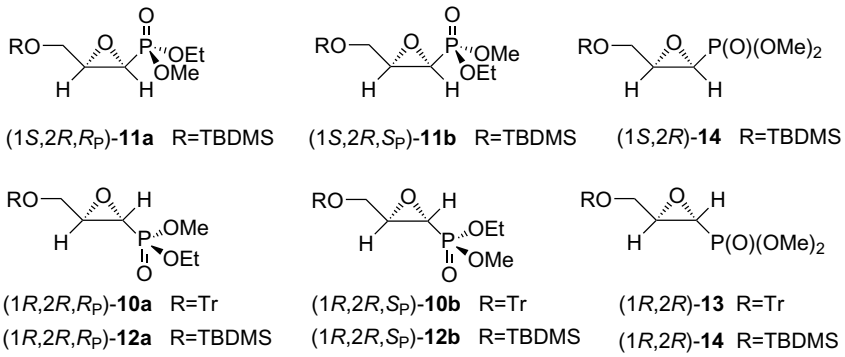


Figure 1. Products of the transesterification of phosphonates **5** and **6** from the epoxide ring formation in methanol.

epoxyphosphonate (1*R*,2*R*)-**9** was the major (88%) component of the crude product, which also contained (1*R*,2*R*,R_P)-**12a** and (1*R*,2*R*,S_P)-**12b** (total 8%), traces of (1*R*,2*R*)-**14** and the unreacted (1*S*,2*R*)-**6** (4%). The clean formation of the *cis*-epoxide (1*S*,2*R*)-**8** in the presence of methanol and significant transesterifications observed in this solvent for other (*cis* and *trans*) phosphonates could be rationalised by shielding the phosphorus atom in this molecule by the trityl group and thus protecting it from nucleophilic attack by methanol.

The hydrogenolysis (10% Pd–C) of the trityl derivatives (1*R*,2*R*)- and (1*S*,2*R*)-**8** gave cleanly the epoxides (1*R*,2*R*)- and (1*S*,2*R*)-**1** in 90% and 97% isolated yields, respectively. On the other hand, cleavage (*p*-TsOH, ethanol) of the trityl group in (1*S*,2*R*)-**8** always led to the contamination of the crude epoxyphosphonate (1*S*,2*R*)-**1** with up to 20% of the P-epimeric 3,4-epoxy-1,2-oxaphospholanes **7**, which could be removed chromatographically. Deprotection of the silyl epoxyphosphonates (1*R*,2*R*)- and (1*S*,2*R*)-**9** was conducted in the presence of tetrabutylammonium fluoride in THF.[16] Pure epoxyphosphonate (1*R*,2*R*)-**1** was obtained in 90% isolated yield from the silyl-derivative (1*R*,2*R*)-**9**. Under the same conditions from the 3-*O*-silylated epoxyphosphonate (1*S*,2*R*)-**9**, a low yield of impure (1*S*,2*R*)-**1** could be isolated. Finally, it appeared that mesylate (1*S*,2*R*)-**4** can be directly transformed into epoxide (1*R*,2*R*)-**1**, when treated with potassium carbonate in ethanol at room temperature for 20 h. However, under similar conditions from the mesylate (1*R*,2*R*)-**4** complex reaction mixtures were formed.

3. Conclusions

The intramolecular Williamson reaction was studied on diethyl (1*R*,2*R*)- and (1*S*,2*R*)-2,3-dihydroxy-1-mesyloxypropylphosphonates **4**, which were obtained from the known diethyl (1*R*,2*R*)- and (1*S*,2*R*)-2,3-*O*-cyclohexylidene-1,2,3-trihydroxypropylphosphonates **2** by mesylation and acetal cleavage. Diethyl (1*R*,2*R*)-1,2-epoxy-3-hydroxypropylphosphonate **1** was formed cleanly from the 3-*O*-trityl, 3-*O*-*tert*-butyldimethylsilyl derivatives of (1*S*,2*R*)-**4** and even from the unprotected phosphonate. However, the synthesis of diethyl (1*S*,2*R*)-1,2-epoxy-3-hydroxypropylphosphonate **1** could only be accomplished from diethyl (1*R*,2*R*)-2-hydroxy-1-mesyloxy-3-trityloxypropylphoshonate **5**. As expected, the formation of the *cis*-analogue of fosfomycin (1*S*,2*R*)-**1** was more difficult than the synthesis of the *trans*-counterpart (1*R*,2*R*)-**1**. Extensive transesterification of the *O*,*O*-diethyl phosphonate group was noticed, when the cyclisation was carried out in methanol.

4. Experimental

^{1}H NMR spectra were recorded with a Varian Mercury-300 spectrometer; chemical shifts δ in ppm with respect to TMS; coupling constants *J* in Hz. ^{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}.

4.1. Diethyl (1*R*,2*R*)-2,3-*O*-cyclohexylidene-2,3-dihydroxy-1-mesyloxypropylphosphonate (1*R*,2*R*)-3

To a solution of the phosphonate (1*R*,2*R*)-**2** (1.92 g, 6.23 mmol) in CH_2Cl_2 (45 mL) containing NEt_3 (2.60 mL, 18.7 mmol) cooled to 0 °C, mesyl chloride (0.98 mL, 12.5 mmol) was added dropwise. After 5 h at room temperature, the reaction mixture was washed with water (3×30 mL), the organic phase was dried over $MgSO_4$, concentrated and the crude product was chromatographed on a silica gel column with chloroform–methanol (100:1, v/v) to give the mesylate (1*R*,2*R*)-**3** (2.14 g, 90%) as a colourless oil. IR (film): $\nu = 2984$, 2937, 2863, 1364, 1261, 1176, 1024 cm^{-1}. $[\alpha]_D^{20} = -12.5$ (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.84$ (dd, $J = 10.8$, 8.2 Hz, 1H, HCP), 4.45 (dddd, $J = 8.2$, 6.6, 6.3, 2.5 Hz, 1H, *H*CCP), 4.31–4.20 (m, 4H, CH_2OP), 4.15 (dd, $J = 9.3$, 6.3 Hz, 1H, H_aCH_bCCP), 4.02 (dd, $J = 9.3$, 6.6 Hz, 1H, H_aCH_bCCP), 3.22 (s, 3H, CH_3SO_2), 1.70–1.60 (m, 2H, CH_2), 1.58–1.40 (m, 8H, $4 \times CH_2$), 1.38 and 1.37 (2td, $J = 7.1$, 0.6 Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 111.0$, 77.6 (d, $J = 161.5$ Hz,

*C*P), 74.0 (d, $J = 9.1$ Hz, *C*CP), 65.6 (d, $J = 2.0$ Hz, *C*CCP), 64.4 and 63.7 (2d, $J = 6.7$ Hz, CH_3CH_2OP), 39.5, 36.1, 35.1, 25.2, 24.1, 24.1, 16.7 and 16.5 (2d, $J = 5.9$ Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 15.27$. Anal. Calcd for $C_{14}H_{27}O_8PS$: C, 43.36; H, 7.06. Found: C, 43.64; H, 6.90.

4.1.1. Diethyl (1*S*,2*R*)-2,3-*O*-cyclohexylidene-2,3-dihydroxy-1-mesyloxypropylphosphonate (1*S*,2*R*)-3. As described in the previous section, from the phosphonate (1*S*,2*R*)-**2** (3.67 g, 11.9 mmol) and mesyl chloride (1.86 mL, 23.8 mmol) in the presence of NEt_3 (4.97 mL, 35.6 mmol), the mesylate (1*S*,2*R*)-**3** (4.30 g, 93%) was obtained as a colourless oil. IR (film): $\nu = 2983$, 2937, 2863, 1366, 1262, 1178, 1028 cm^{-1}. $[\alpha]_D^{20} = +13.8$ (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.14$ (dd, $J = 11.9$, 3.0 Hz, 1H, HCP), 4.50 (dddd, $J = 7.8$, 6.6, 3.0, 1.4 Hz, 1H, *H*CCP), 4.28–4.18 (m, 4H, CH_2OP), 4.11 (dd, $J = 8.5$, 6.6 Hz, 1H, H_aCH_bCCP), 3.98 (dd, $J = 8.5$, 7.8 Hz, 1H, H_aCH_bCCP), 3.19 (s, 3H, CH_3SO_2), 1.64–1.62 (m, 2H, CH_2), 1.60–1.54 (m, 8H, $4 \times CH_2$), 1.38 and 1.37 (2td, $J = 7.1$, 0.6 Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 110.3$, 74.5 (d, $J = 165.8$ Hz, *C*P), 73.4 (d, $J = 12.0$ Hz, *C*CP), 64.3 (d, $J = 1.4$ Hz, *C*CCP), 64.0 and 63.9 (2d, $J = 6.7$ Hz, CH_3CH_2OP), 39.5, 35.9, 34.9, 25.3, 24.1, 24.0, 16.7 and 16.6 (2d, $J = 6.0$ Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 15.45$. Anal. Calcd for $C_{14}H_{27}O_8PS \cdot 1/4H_2O$: C, 43.02; H, 7.09. Found: C, 42.81; H, 6.98.

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

A solution of phosphonate (1*R*,2*R*)-**3** (1.88 g, 4.86 mmol) in dioxane (30 mL) containing 1 M HCl (48.6 mL) was kept at room temperature for 24 h. After neutralisation with solid $NaHCO_3$ all volatiles were removed in vacuo and the crude product was evaporated with dry dioxane (3×20 mL). The residue was suspended in CH_2Cl_2 (30 mL), dried over $MgSO_4$, concentrated and chromatographed on a silica gel column with chloroform–methanol (50:1, v/v) to give the diol (1*R*,2*R*)-**4** (1.21 g, 91%) as a colourless oil. IR (film): $\nu = 3373$, 2986, 2938, 1360, 1245, 1175, 1025 cm^{-1}. $[\alpha]_D^{20} = -15.5$ (*c* 1.25, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.00$ (dd, $J = 11.5$, 4.8 Hz, 1H, HCP), 4.32–4.20 (m, 4H, CH_2OP), 4.13 (dddd, $J = 5.6$, 5.5, 4.8, 4.8 Hz, 1H, *H*CCP), 3.86 (ddd, $J = 11.9$, 4.8, 1.1 Hz, 1H, H_aCH_bCCP), 3.72 (dd, $J = 11.9$, 5.5 Hz, 1H, H_aCH_bCCP), 3.22 (s, 3H, CH_3SO_2), 1.39 and 1.38 (2td, $J = 7.1$, 0.6 Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 76.2$ (d, $J = 164.9$ Hz, *C*P), 70.8 (d, $J = 4.3$ Hz, *C*CP), 64.4 and 63.9 (2d, $J = 6.7$ Hz, CH_3CH_2OP), 62.5 (d, $J = 7.1$ Hz, *C*CCP), 39.2, 16.6 and 16.5 (2d, $J = 6.3$ Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 17.86$. Anal. Calcd for $C_8H_{19}O_8PS$: C, 31.39; H, 6.27. Found: C, 31.65; H, 6.59.

4.2.1. Diethyl (1*S*,2*R*)-2,3-dihydroxy-1-mesyloxypropylphosphonate (1*S*,2*R*)-4. As described in the previous section, from the phosphonate (1*S*,2*R*)-**3** (1.88 g, 4.86 mmol), diol (1*S*,2*R*)-**4** (1.13 g, 85%) was obtained as a colourless oil. IR (film): $\nu = 3376$, 2986, 2938, 1360, 1243, 1177, 1026 cm^{-1}. $[\alpha]_D^{20} = +20.15$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.98$ (dd, $J = 9.5$, 6.7 Hz, 1H, HCP), 4.33–4.20 (m, 4H, CH_2OP), 4.13 (dddd, $J = 6.7$, 4.8, 4.6, 4.5 Hz, 1H, *H*CCP), 3.91 (ddd, $J = 12.1$, 4.8, 1.2 Hz, 1H, H_aCH_bCCP), 3.77 (dd, $J = 12.1$, 4.5 Hz, 1H, H_aCH_bCCP), 3.19 (s, 3H, CH_3SO_2), 1.39 (t, $J = 7.1$ Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 75.7$ (d, $J = 164.3$ Hz, *C*P), 70.8 (d, $J = 5.2$ Hz, *C*CP), 64.5 and 63.9 (2d, $J = 6.6$ Hz, CH_3CH_2OP), 62.1 (d, $J = 5.7$ Hz, *C*CCP), 39.1, 16.6 and 16.5 (2d, $J = 6.0$ Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 17.97$. Anal. Calcd for $C_8H_{19}O_8PS$: C, 31.39; H, 6.27. Found: C, 31.71; H, 6.58.

4.3. Diethyl (1*R*,2*R*)-2-hydroxy-1-mesyloxy-3-trityloxypropylphosphonate (1*R*,2*R*)-5

To a solution of diol (1*R*,2*R*)-**4** (1.30 g, 4.75 mmol) in CH_2Cl_2 (22 mL) cooled to 0 °C, trityl chloride (1.59 g, 5.70 mmol) was added, followed by NEt_3 (1.06 mL, 7.60 mmol) and DMAP (0.06 g, 0.5 mmol). The solution was then stirred at room temperature for 20 h and later treated with cooled saturated NH_4Cl (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3×15 mL), 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 the trityl derivative (1*R*,2*R*)-**5** (2.27 g, 87%), which was crystallised from ethyl acetate to yield a white powder (2.12 g, 81%); mp 125.7–126.5 °C. IR (KBr): $\nu = 3305$, 2941, 2927, 2853, 1354, 1249, 1179, 1043 cm^{-1}. $[\alpha]_D^{20} = -14.4$ (*c* 1.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.43$–7.25 (m, 15H), 5.09 (dd, $J = 10.6$, 3.7 Hz, 1H, HCP), 4.27–4.11 (m, 5H, CH_2OP and *H*CCP), 3.45 (ddd, $J = 9.8$, 6.6, 1.2 Hz, 1H, H_aCH_bCCP), 3.32 (dd, $J = 9.8$, 6.6 Hz, 1H, H_aCH_bCCP), 3.05 (d, $J = 4.5$ Hz, 1H, HO), 2.96 (s, 3H, CH_3SO_2), 1.35 and 1.33 (2t, $J = 7.1$ Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 143.4$, 128.2, 128.1, 127.4, 87.6, 75.6 (d, $J = 166.3$ Hz, *C*P), 69.6 (d, $J = 2.3$ Hz, *C*CP), 64.5 (d, $J = 6.9$ Hz, *C*CCP), 63.5 and 63.4 (2d, $J = 6.8$ Hz, CH_3CH_2OP), 39.1, 16.8 and 16.7 (2d, $J = 5.9$ Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 17.97$. Anal. Calcd for $C_{27}H_{33}O_8PS$: C, 59.11; H, 6.06. Found: C, 59.33; H, 5.96.

4.3.1. Diethyl (1*S*,2*R*)-2-hydroxy-1-mesyloxy-3-trityloxypropylphosphonate (1*S*,2*R*)-5. As described in the previous section, from the phosphonate (1*S*,2*R*)-**4** (1.13 g, 4.12 mmol) and trityl chloride (1.38 g, 4.94 mmol) in the presence of NEt_3 (0.92 mL, 6.6 mmol) and DMAP (0.05 g, 0.4 mmol), the trityl derivative (1*S*,2*R*)-**5** (1.96 g, 87%) was obtained as a white powder after chromatography on a silica gel column with chloroform–methanol–triethylamine (100:1:0.05, v/v) and crystallisation from ethyl acetate; mp 127.7–129 °C. IR (KBr): $\nu = 3414$, 2994, 2929, 1367, 1220, 1180, 1021 cm^{-1}. $[\alpha]_D^{20} = +2.1$ (*c* 1.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.46$–7.21 (m, 15H), 5.08 (dd, $J = 12.0$, 4.2, Hz, 1H, HCP), 4.25 (dddd, $J = 7.8$, 4.2, 4.2, 3.9 Hz, 1H, HCCP), 4.18–4.07 (m, 4H, CH_2OP), 3.58 (dd, $J = 9.9$, 3.9 Hz, 1H, H_aCH_bCCP), 3.38 (dd, $J = 9.9$, 7.8 Hz, 1H, H_aCH_bCCP), 3.18 (dd,

$J = 3.9$, 2.7 Hz, 1H, HO), 2.96 (s, 3H, CH_3SO_2), 1.28 and 1.26 (2t, $J = 7.1$ Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 143.7$, 128.7, 128.0, 127.3, 87.4, 76.4 (d, $J = 164.4$ Hz, *C*P), 70.2 (d, $J = 6.8$ Hz, *C*CP), 64.1 and 63.7 (2d, $J = 6.8$ Hz, CH_3CH_2OP), 63.4 (d, $J = 3.8$ Hz, *C*CCP), 39.1, 16.6 and 16.5 (2d, $J = 5.9$ Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 16.70$. Anal. Calcd for $C_{27}H_{33}O_8PS$: C, 59.11; H, 6.06. Found: C, 59.48; H, 5.82.

4.4. Diethyl (1*R*,2*R*)-3-(*tert*-butyldimethylsilyloxy)-2-hydroxy-1-mesyloxypropylphosphonate (1*R*,2*R*)-6

To a solution of diol (1*R*,2*R*)-**4** (0.54 g, 1.28 mmol) in CH_2Cl_2 (5 mL) cooled to 0 °C, *tert*-butyldimethylsilyl chloride (0.44 g, 2.95 mmol) was added, followed by NEt_3 (0.38 mL, 2.76 mmol) and DMAP (0.01 g, 0.06 mmol). The solution was then stirred at room temperature for 5 h and later treated with water (20 mL). The organic phase was washed with water (2×10 mL), 10% aqueous NH_4Cl (10 mL), dried over $MgSO_4$ and concentrated. The crude product was chromatographed on a silica gel column with chloroform–methanol (100:1, v/v) to give the silyl derivative (1*R*,2*R*)-**6** (0.59 g, 72%) as a slightly yellow oil. IR (film): $\nu = 3368$, 2954, 2931, 2858, 1363, 1254, 1177, 1025 cm^{-1}. $[\alpha]_D^{20} = -19.4$ (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 5.02$ (dd, $J = 10.6$, 4.6 Hz, 1H, HCP), 4.33–4.19 (m, 4H, CH_2OP), 4.10 (dddd, $J = 6.0$, 6.0, 4.6, 1.8 Hz, 1H, *H*CCP), 3.79 (ddd, $J = 10.2$, 6.0, 0.9 Hz, 1H, H_aCH_bCCP), 3.75 (dd, $J = 10.2$, 6.0 Hz, 1H, H_aCH_bCCP), 3.21 (s, 3H, CH_3SO_2), 1.39 (t, $J = 7.2$ Hz, 6H, CH_3CH_2OP), 0.91 (s, 9H), 0.10 (s, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 75.5$ (d, $J = 166.1$ Hz, *C*P), 70.4 (d, $J = 3.8$ Hz, *C*CP), 64.3 and 63.5 (2d, $J = 6.8$ Hz, CH_3CH_2OP), 62.5 (d, $J = 8.3$ Hz, *C*CCP), 39.2, 26.0, 18.4, 16.7 and 16.6 (2d, $J = 5.3$ Hz, CH_3CH_2OP), −5.3. ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 17.25$. Anal. Calcd for $C_{14}H_{33}O_8PSSi$: C, 39.97; H, 7.91. Found: C, 40.01; H, 8.12.

4.4.1. Diethyl (1*S*,2*R*)-3-(*tert*-butyldimethylsilyloxy)-2-hydroxy-1-mesyloxypropylphosphonate (1*S*,2*R*)-6.

As described in the previous section, from phosphonate (1*S*,2*R*)-**4** (0.11 g, 0.39 mmol) and *tert*-butyldimethylsilyl chloride (0.09 g, 0.58 mmol) in the presence of NEt_3 (0.08 mL, 0.55 mmol) and DMAP (0.002 g, 0.02 mmol), the silyl derivative (1*S*,2*R*)-**6** (0.142 g, 88%) was obtained as a yellowish oil after chromatography on a silica gel column with chloroform–methanol (100:1, v/v). IR (film): $\nu = 3370$, 2954, 2932, 2867, 1364, 1253, 1178, 1027 cm^{-1}. $[\alpha]_D^{20} = +9.0$ (*c* 2.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 5.05$ (dd, $J = 10.8$, 5.1, Hz, 1H, HCP), 4.31–4.16 (m, 4H, CH_2OP), 4.10 (dddd, $J = 6.7$, 5.1, 4.0, 2.1 Hz, 1H, HCCP), 3.94 (ddd, $J = 10.8$, 3.9, 0.6 Hz, 1H, H_aCH_bCCP), 3.77 (dd, $J = 10.8$, 6.6 Hz, 1H, H_aCH_bCCP), 3.20 (s, 3H, CH_3SO_2), 1.40 (t, $J = 7.0$ Hz, 6H, CH_3CH_2OP), 0.91 (s, 9H), 0.11 (s, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 75.5$ (d, $J = 165.2$ Hz, *C*P), 70.9 (d, $J = 6.0$ Hz, *C*CP), 64.3 and 63.7 (2d, $J = 7.0$ Hz, CH_3CH_2OP), 62.7 (d, $J = 4.9$ Hz, *C*CCP), 39.3, 26.1, 18.6, 16.7 and 16.6 (2d, $J = 6.5$ Hz, CH_3CH_2OP), −5.0, −5.1. ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 16.82$. Anal. Calcd for $C_{14}H_{33}O_8PSSi$: C, 39.97; H, 7.91. Found: C, 40.01; H, 8.13.

4.5. Diethyl (1*S*,2*R*)-1,2-epoxy-3-trityloxypropylphosphonate (1*S*,2*R*)-8

To a solution of the trityl derivative (1*R*,2*R*)-**5** (2.27 g, 4.14 mmol) in CH_2Cl_2 (13 mL) and anhydrous ethanol (13 mL), anhydrous K_2CO_3 (0.86 g, 6.2 mmol) was added at room temperature and the suspension was vigorously stirred for 20 h. After the addition of CH_2Cl_2 (13 mL) and a saturated solution of NH_4Cl (20 mL), the aqueous phase was extracted with CH_2Cl_2 (3×20 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 the epoxyphosphonate (1*S*,2*R*)-**8** (1.42 g, 76%) as a colourless oil. IR (film): $\nu = 3058$, 2984, 2932, 2910, 1448, 1264, 1161, 1051, 1025 cm^{-1}. $[\alpha]_D^{20} = -10.0$ (*c* 1.15, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.48$–7.20 (m, 15H), 4.11–3.96 (m, 4H, CH_2OP), 3.58–3.50 (m, 2H, H_aCH_bCCP), 3.40 (dddd, $J = 5.6$, 5.4, 4.8, 4.8 Hz, 1H, HCCP), 3.00 (dd, $J = 27.0$, 4.8 Hz, 1H, HCP), 1.22 and 1.19 (2td, $J = 7.0$, 0.6 Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 143.8$, 128.7, 128.2, 127.2, 87.2, 77.4 (s, *C*CCP), 62.9 and 62.8 (2d, $J = 5.6$ Hz, CH_3CH_2OP), 56.6 (d, $J = 2.3$ Hz, *C*CP), 49.0 (d, $J = 203.0$ Hz, *C*P), 16.6 and 16.6 (2d, $J = 5.9$ Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 18.97$. Anal. Calcd for $C_{26}H_{29}O_5P \cdot 1/4H_2O$: C, 68.33; H, 6.51. Found: C, 68.55; H, 6.68.

4.5.1. Diethyl (1*R*,2*R*)-1,2-epoxy-3-trityloxypropylphosphonate (1*R*,2*R*)-8.

As described in the previous section, from trityl derivative (1*S*,2*R*)-**5** (1.65 g, 3.02 mmol), the epoxyphosphonate (1*R*,2*R*)-**8** (0.096 g, 70%) was obtained as a colourless oil after chromatography on a silica gel column with chloroform–methanol–triethylamine (100:1:0.05, v/v). IR (film): $\nu = 3059$, 2984, 2930, 2911, 1448, 1258, 1161, 1054, 1026 cm^{-1}. $[\alpha]_D^{20} = +17.8$ (*c* 1.14, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.44$–7.21 (m, 15H), 4.24–4.13 (m, 4H, CH_2OP), 3.49–3.40 (m, 2H, H_aCH_bCCP and HCCP), 3.19–3.12 (m, 1H, H_aCH_bCCP), 3.07 (dd, $J = 30.6$, 2.7 Hz, 1H, HCP), 1.36 and 1.36 (2td, $J = 7.0$, 0.6 Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 143.5$, 128.6, 128.0, 127.7, 87.0, 63.4 and 63.3 (2d, $J = 6.0$ Hz, CH_3CH_2OP), 63.1 (d, $J = 0.8$ Hz, *C*CCP), 55.7 (d, $J = 1.5$ Hz, *C*CP), 47.8 (d, $J = 201.0$ Hz, *C*P), 16.8 and 16.7 (2d, $J = 6.0$ Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 19.28$. Anal. Calcd for $C_{26}H_{29}O_5P \cdot 1/4H_2O$: C, 68.33; H, 6.51. Found: C, 68.19; H, 6.42.

4.6. Diethyl (1*S*,2*R*)-3-(*tert*-butyldimethylsilyloxy)-1,2-epoxypropylphosphonate (1*S*,2*R*)-9

To a solution of the silyl derivative (1*R*,2*R*)-**6** (0.19 g, 0.45 mmol) in CH_2Cl_2 (5 mL) and anhydrous ethanol (2.5 mL), anhydrous K_2CO_3 (0.09 g, 0.67 mmol) was added at room temperature and the suspension vigorously stirred for 20 h. After the addition of CH_2Cl_2 (5 mL) and a saturated solution of NH_4Cl (10 mL), the aqueous phase was extracted with CH_2Cl_2 (3×5 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 (100:1, v/v) to give the epoxyphosphonate (1*S*,2*R*)-**9** (0.14 g, 95%) as a colourless oil. IR (film): $\nu = 2957$, 2930, 2857, 1669, 1396, 1259, 1094, 1052, 1024 cm^{-1}. $[\alpha]_D^{20} = +2.6$ (*c* 1.3, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 4.23$–4.13 (m, 4H, CH_2OP), 4.12 (dd, $J = 12.3$, 3.6 Hz, 1H, H_aCH_bCCP), 3.98 (ddd, $J = 12.3$, 6.6, 0.9 Hz, 1H, H_aCH_bCCP), 3.36 (dddd, $J = 6.6$, 6.0, 4.8, 3.6 Hz, 1H, HCCP), 3.02 (dd, $J = 26.4$, 4.8 Hz, 1H, HCP), 1.38 and 1.37 (2t, $J = 7.0$ Hz, 6H, CH_3CH_2OP), 0.92 (s, 9H), 0.11 (s, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 63.2$ and 62.8 (2d, $J = 6.2$ Hz, CH_3CH_2OP), 62.0 (s, *C*CCP), 58.3 (d, $J = 1.4$ Hz, *C*CP), 49.2 (d, $J = 203.5$ Hz, *C*P), 26.1, 18.6, 16.8 and 16.7 (2d, $J = 6.0$ Hz, CH_3CH_2OP), −4.8, −5.0. ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 19.40$. Anal. Calcd for $C_{13}H_{29}O_5PSi \cdot 1/4H_2O$: C, 47.47; H, 9.04. Found: C, 47.16; H, 9.14.

4.6.1. Diethyl (1*R*,2*R*)-3-(*tert*-butyldimethylsilyloxy)-1,2-epoxypropylphosphonate (1*R*,2*R*)-9. As described in the previous section, from the silyl derivative (1*S*,2*R*)-**6** (0.12 g, 0.29 mmol), the epoxyphosphonate (1*R*,2*R*)-**9** (0.09 g, 93%) was obtained as a colourless oil after chromatography on a silica gel column with chloroform–methanol (100:1, v/v). IR (film): $\nu = 2956$, 2930, 2858, 1472, 1258, 1100, 1056, 1027 cm^{-1}. $[\alpha]_D^{20} = +16.0$ (*c* 1.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 4.17$–4.07 (m, 4H, CH_2OP), 3.94 (ddd, $J = 12.6$, 2.4, 0.6 Hz, 1H, H_aCH_bCCP), 3.75 (ddd, $J = 12.6$, 3.9, 0.6 Hz, 1H, H_aCH_bCCP), 3.39 (dddd, $J = 5.4$, 3.9, 2.4, 2.4 Hz, 1H, HCCP), 3.03 (dd, $J = 31.2$, 2.4 Hz, 1H, HCP), 1.36 and 1.35 (2td, $J = 7.0$, 0.6 Hz, 6H, CH_3CH_2OP), 0.9 (s, 9H), 0.07 and 0.06 (2 s, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 63.4$ and 63.3 (2d, $J = 6.4$ Hz, CH_3CH_2OP), 61.8 (d, $J = 0.8$ Hz, *C*CCP), 56.9 (d, $J = 0.8$ Hz, *C*CP), 47.3 (d, $J = 202.3$ Hz, *C*P), 26.1, 18.6, 16.7 (d, $J = 5.6$ Hz, CH_3CH_2OP), −5.1. ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 19.63$. Anal. Calcd for $C_{13}H_{29}O_5PSi \cdot 1/4H_2O$: C, 47.47; H, 9.04. Found: C, 47.71; H, 9.39.

4.6.2. *O*-Ethyl-*O*-methyl (1*S*,2*R*,R_P)- and (1*S*,2*R*,S_P)-3-(*tert*-butyldimethylsilyloxy)-1,2-epoxypropylphosphonates (1*S*,2*R*,R_P)-11a and (1*S*,2*R*,S_P)-11b and dimethyl (1*S*,2*R*)-3-(*tert*-butyldimethylsilyloxy)-1,2-epoxypropylphosphonate (1*S*,2*R*)-14. As described in Section 4.6, from the silyl derivative (1*R*,2*R*)-**6** (0.700 g, 1.66 mmol) in the presence of anhydrous K_2CO_3 (0.345 g) in methanol (5.4 mL), a crude product (0.400 g) was obtained as a colourless oil. After chromatography on a silica gel column with chloroform–methanol (100:1, v/v), two fractions were collected. The less polar fraction (0.091 g, a colourless oil) contained a 1:1 mixture of (1*S*,2*R*,R_P)-**11a** and (1*S*,2*R*,S_P)-**11b** (ca. 80%) as major components. In the more polar fraction (0.062 g, a colourless oil) (1*S*,2*R*)-**14** (ca. 76%) predominated.

4.6.2.1. *O*-Ethyl-*O*-methyl (1*S*,2*R*,R_P)- and (1*S*,2*R*,S_P)-3-(*tert*-butyldimethylsilyloxy)-1,2-epoxypropylphosphonates (1*S*,2*R*,R_P)-11a and (1*S*,2*R*,S_P)-11b. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 4.24$–4.09 (m, 3H, $POCH_2$, H_aCH_bCCP), 3.97 (dd, 1H, $J = 12.1$, 6.7 Hz, H_aCH_bCCP), 3.81 (2 × d, 3H, $J = 10.9$ Hz, CH_3OP), 3.36 (dddd, 1H, $J = 6.7$, 4.6, 3.7, 2.2 Hz, PCCH), 3.03 (dd, 1H, $J = 26.8$, 4.6 Hz, PCH), 1.37 (2 × t, 3H, $J = 6.9$ Hz, $POCH_2CH_3$), 0.91 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 20.76$ and 20.57.

4.6.2.2. Dimethyl (1*S*,2*R*)-3-(*tert*-butyldimethylsilyloxy)-1,2-epoxypropylphosphonate (1*S*,2*R*)-14. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 4.10$ (dd, 1H, $J = 12.1$, 3.6 Hz H_aCH_bCCP), 3.96 (ddd 1H, $J = 12.1$, 6.7, 0.8 Hz H_aCH_bCCP), 3.84 and 3.80 (2d, 6H, $J = 10.7$ Hz, CH_3O-$POCH_3$), 3.36 (dddd, $J = 6.7$, 4.8, 3.6, 2.4 Hz, 1H, HCCP), 3.03 (dd, $J = 26.8$, 4.8 Hz, 1H, HCP), 0.91 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 21.89$.

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

4.7.1. By hydrogenolysis of the trityl derivative (1*S*,2*R*)-8. A solution of the trityl derivative (1*S*,2*R*)-**8** (0.13 g, 0,29 mmol) in ethanol (7 mL) was hydrogenated over 10%-Pd/C (3 mg) for 24 h. After removal of the catalyst on a layer of Celite, the residue was chromatographed on silica gel with chloroform–methanol (100:1, v/v) to give the epoxyphosphonate (1*S*,2*R*)-**1** (0.060 g, 97%) as a colourless oil. IR (film): $\nu = 3398$, 2956, 2925, 2870, 1247, 1024 cm^{-1}. $[\alpha]_D^{20} = -10.2$ (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 4.27$–4.10 (m, 4H, CH_2OP), 4.12 (dd 1H, $J = 12.9$, 5.4 Hz H_aCH_bCCP), 3.93 (dd 1H, $J = 12.9$, 5.4 HzH_aCH_bCCP), 3.43 (dddd, $J = 5.4$, 5.4, 4.5, 0.3 Hz, 1H, HCCP), 3.05 (dd, $J = 26.4$, 4.5 Hz, 1H, HCP), 1.38 and 1.37 (2t, $J = 7.2$, Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 63.8$ and 63.0 (2d, $J = 6.3$ Hz, CH_3CH_2OP), 60.7 (s, *C*CCP), 57.4 (d, $J = 0.9$ Hz, *C*CP), 49.4 (d, $J = 203.3$ Hz, *C*P), 16.7 (d, $J = 5.9$ Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 19.59$. Anal. Calcd for $C_7H_{15}O_5P \times 0.1H_2O$: C, 39.66; H, 7.23. Found: C, 39.60; H, 7.04.

4.7.2. By hydrolysis of the trityl derivative (1*S*,2*R*)-8. A solution of the trityl derivative (1*S*,2*R*)-**8** (0.073 g, 0.16 mmol) in ethanol (1 mL) containing a few crystals of *p*-TsOH monohydrate was left at room temperature for 24 h. The acid was neutralised by the addition of the solid sodium bicarbonate, the ethanol was evaporated and the residue was chromatographed on silica gel with chloroform–methanol (100:1, v/v) to give two fractions. A less polar fraction (0.013 g) contained an impure mixture of (2*R*/*S*,3*S*,4*R*)-**7**. In a more polar fraction the epoxyphosphonate (1*S*,2*R*)-**1** (0.029 g, 86%) was collected as a colourless oil in all respects identical with the substance described in the previous Section.

4.7.2.1. (2*R*/*S*,3*S*,4*R*)-3,4-Epoxy-2-ethoxy-2-oxo-1,2-oxaphospholanes 7. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 4.39$–4.22 (m, 4H, CH_2OP-*exo*, CH_2OP-*endo*), 4.00 and 3.93 (2 × ddd, $J = 5.4$, 4.5, 3.6 Hz, 1H, HCCP), 3.53 and 3.44 (2 × dd, $J = 40.0$, 3.6 Hz, 1H, HCP), 1.40 and 1.38 (td, $J = 7.2$, 0.6 Hz, 3H, CH_3). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 30.79$ and 30.57.

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

4.8.1. From trityl derivative (1*R*,2*R*)-8. As described in Section 4.7.1, from the trityl derivative (1*R*,2*R*)-**8** (0.43 g, 0.95 mmol), the epoxyphosphonate (1*R*,2*R*)-**1** (0.18 g, 90%) was obtained as a colourless oil after chromatography on a silica gel column with chloroform–methanol (100:1, v/v). IR (film): $\nu = 3394$, 2988, 2916, 2872, 1244, 1025 cm^{-1}. $[\alpha]_D^{20} = +24.8$ (c 1.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 4.24$–4.14 (m, 4H, CH_2OP), 4.01 (ddd, $J = 13.0$, 1.8, 0.3 Hz, 1H, H_aCH_bCCP), 3.75 (ddd, $J = 13.0$, 3.3, 0.3 Hz, 1H, H_aCH_bCCP), 3.46 (dddd, $J = 5.0$, 3.3, 2.5, 1.8 Hz, 1H, $HCCP$), 3.14 (dd, $J = 30.1$, 2.5 Hz, 1H, HCP), 1.36 and 1.34 (2t, $J = 7.0$ Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 63.3$ and 63.1 (2d, $J = 6.0$ Hz, CH_3CH_2OP), 60.4 (d, $J = 0.7$ Hz, $CCCP$), 56.8 (d, $J = 1.5$ Hz, CCP), 47.1 (d, $J = 202.9$ Hz, CP), 16.5 (d, $J = 5.6$ Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 18.51$. Anal. Calcd for $C_7H_{15}O_5P{\cdot}0.2H_2O$: C, 39.33; H, 7.26. Found: C, 39.47; H, 7.46.

4.8.2. From silyl derivative (1*R*,2*R*)-9. The silyl derivative (1*R*,2*R*)-**9** (0.15 g, 0.46 mmol) was dissolved in THF (10 mL) and TBAF (1 M THF solution, 0.5 mL) was added. After 24 h at room temperature, the mixture was concentrated and the residue was chromatographed on a silica gel column with chloroform–methanol (100:1, v/v) to give the epoxyphosphonate (1*R*,2*R*)-**1** (0.087 g, 90%) as a colourless oil, in all respects identical to the material described in Section 4.7.1.

4.8.3. From diol (1*S*,2*R*)-4. As described in Section 4.5, from diol (1*S*,2*R*)-**4** (0.070 g, 0.17 mmol) dissolved in a mixture of CH_2Cl_2 (0.5 mL) and anhydrous ethanol (0.5 mL) in the presence of K_2CO_3 (0.05 g), the epoxyphosphonate (1*R*,2*R*)-**1** (0.052 g, 92%) was obtained as a colourless oil after chromatography on a silica gel column with chloroform–methanol (100:1, v/v), in all respects identical to the material described in Section 4.8.1.

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