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Synthesis of enantiomerically pure diethyl (*R*)- and (*S*)-2-hydroxy-3-(1,2,3-triazol-1-yl)propylphosphonates

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ABSTRACT

The synthesis and ee determination of diethyl 3-azido-2-hydroxypropylphosphonates from 2,3-epoxypropylphosphonates have been optimised. Enantiomerically enriched diethyl (*R*)- and (*S*)-2-hydroxy-3-(1,2,3-triazol-1-yl)propylphosphonates (*R*)-**3a–j** and (*S*)-**3a–h** as well as (*S*)-**3j** were synthesised from diethyl (*R*)- and (*S*)-2,3-epoxypropylphosphonates in a reaction sequence including azidolysis followed by 1,3-dipolar cycloaddition with selected alkynes.

1. Introduction

1,2,3-Triazoles are an important class of heterocycle which display a large range of biological activities and are widely employed as pharmaceuticals and agrochemicals. Compounds containing the 1,2,3-triazole moiety are known to exhibit antibacterial,[1–3] antifungal,[4,5] anticancer[6,7] and antiviral activity.[8,9] They have also been found to act as β3 adrenergic receptor agonists[10] as well as GABA α5 subtype inverse agonists.[11] These molecules have also found industrial applications as corrosion inhibitors, photostabilisers[12] and herbicides.[13]

In 2001, Sharpless defined the concept of 'click chemistry' and the criteria for a transformation to be considered as a 'click'.[14] The conventional route to 1,2,3-triazoles relies on the Huisgen [3+2] cycloaddition between alkynes and organic azides and is qualified as a 'click reaction'. Under thermal conditions, this process usually affords a mixture of 1,4- and 1,5-disubstitued regioisomers.[15,16] Since copper(I) has recently been found to be an efficient and regiospecific catalyst for this transformation,[17,18] it now represents a general and mild approach to the preparation of 1,4-disubstituted 1,2,3-triazole derivatives.

Herein we report a short synthesis of highly enantiomerically enriched diethyl (*R*)- and (*S*)-2-hydroxy-3-(1,2,3-triazol-1-yl)propylphosphonates (*R*)-**3a–j** and (*S*)-**3a–h** as well as (*S*)-**3j**; the strategy is outlined in Scheme 1.

2. Results and discussion

Jacobsen has reported (salen)Cr–Cl complex **4a** (Fig. 1) as an effective catalyst for the enantioselective ring opening of racemic epoxides with trimethylsilyl azide ($TMSN_3$).[19,20] It was reasoned out that the application of this methodology to the opening of epoxide **1** could lead efficiently to diethyl (*R*)- and (*S*)-3-azido-2-hydroxypropylphosphonate (*R*)- and (*S*)-**2**, respectively, in one step from the racemic starting material. To this end racemic diethyl 2,3-epoxypropylphosphonate **1** was treated with 1 equiv of $TMSN_3$ in the presence of 2 mol % (salen)Cr–Cl (*R*,*R*)-**4a** complex at room temperature for 7 h to afford a 47:45 mixture of (*S*)-**5** and (*R*)-**1**, respectively, as judged by the ^{31}P NMR spectroscopic analysis of the crude reaction product (Scheme 2). The mixture of azidosilyl ether (*S*)-**5** and the epoxide (*R*)-**1** was subjected to chromatography on a silica gel column. The epoxide (*R*)-**1** and a more polar diethyl (*S*)-3-azido-2-hydroxypropylphosphonate (*S*)-**2** were separated cleanly in 40% and 41% yield, respectively. This means that on the surface of silica gel in the presence of methanol desilylation of the trimethylsilyl group in (*S*)-**5** occurred to afford azidoalcohol (*S*)-**2**. Searching for a quick and reliable way to determine the enantiomeric excesses of diethyl 3-azido-2-hydroxypropylphosphonates, it was found that the application of quinine as an enantiodifferentiating reagent is the method of choice, while the ee of (*S*)-**2** was determined based on analysis of the ^{31}P NMR spectra. The ee of the azidophosphonate (*S*)-**2** obtained in the presence of (*R*,*R*)-**4a** was established as only 28%.

The epoxide (*R*)-**1** from the same kinetic resolution experiment was reacted with sodium azide in the presence of ammonium sulfate to provide diethyl (*R*)-3-azido-2-hydroxypropylphosphonate (*R*)-**2** in 84% yield. The ee of this material was estimated to be 26% by the same method. The kinetic resolution of the racemic epoxide **1** with $TMSN_3$ at 4 °C did not improve the enantiomeric excesses of the azide (*S*)-**2** as well as of the epoxide (*R*)-**1**.

For this reason, another approach to 3-azidophosphonates with high enantiomeric purities was considered. Based on the procedure described in the literature, enantiomerically enriched diethyl

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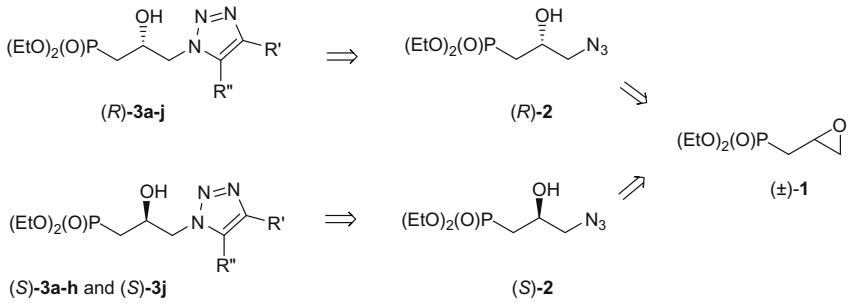
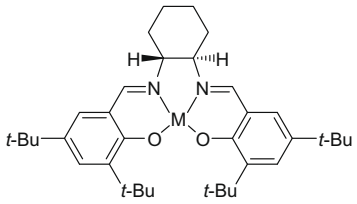


Scheme 1. Retrosynthesis of diethyl (*R*)- and (*S*)-2-hydroxy-3-(1,2,3-triazol-1-yl)propylphosphonates.

(*R*)- and (*S*)-2,3-epoxypropylphosphonate (*R*)-**1** and (*S*)-**1** (ee of both was 93%) were obtained in 42% and 35% yields, respectively, via the hydrolytic kinetic resolution (HKR) of the racemic epoxide **1** using (*S*,*S*)-**4b** and (*R*,*R*)-**4b** as catalysts (Fig. 1).[21] In preliminary studies, the epoxide ring opening in (*R*)-**1** was performed with sodium azide in the presence of ammonium chloride in refluxing methanol as described in the literature.[22] However, this procedure led to the formation of a 94:6 mixture of diethyl (*R*)-3-azido-2-hydroxypropylphosphonate (*R*)-**2** and diethyl (*R*)-3-chloro-2-hydroxypropylphosphonate (*R*)-**6**[21] in ca. 92% total yield (Scheme 3). As expected, the enantiomeric purity of (*R*)-**2** in the crude product remained unchanged (93%). Several attempts at separating 3-chlorophosphonate (*R*)-**6** from 3-azidophosphonate (*R*)-**2** on silica gel columns failed. However, chromatography allowed us to improve the ee of (*R*)-**2** to 96%.

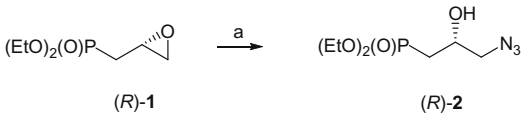


(*R*,*R*)-**4a** M = Cr-Cl

(*R*,*R*)-**4b** M = Co-OAc

Figure 1.

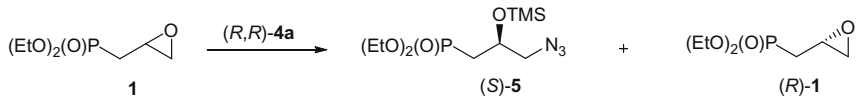
To avoid the formation of 3-chlorophosphonate (*R*)-**6,** ammonium chloride was replaced with non-nucleophilic ammonium sulfate. Thus, the treatment of epoxide (*R*)-**1** (ee 93%) with sodium azide in the presence of ammonium sulfate (1.8 equiv) in refluxing methanol for 4 h (Scheme 4) produced diethyl (*R*)-3-azido-2-hydroxypropylphosphonate (*R*)-**2** as a single product. After removal of the inorganic salts by filtration through a pad of Celite, (*R*)-**2** (ee 96%) was obtained in 80% yield and used in the next step without further purification.



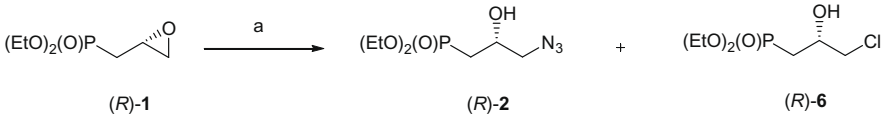
Scheme 4. Reagents and conditions: (a) NaN_3, $(NH_4)_2SO_4$, MeOH, reflux, 4 h, 80%.

Under the same conditions, diethyl (*S*)-3-azido-2-hydroxypropylphosphonate (*S*)-**2** was obtained from epoxide (*S*)-**1**. The reaction of (*S*)-**1** with sodium azide in the presence of ammonium chloride in refluxing methanol again led to an inseparable 94:6 mixture of diethyl (*S*)-3-azido-2-hydroxypropylphosphonate (*S*)-**2** and diethyl (*S*)-3-chloro-2-hydroxypropylphosphonate (*S*)-**6**[21] in ca. 89% yield. However, treatment of epoxide (*S*)-**1** (ee 93%) with sodium azide in the presence of ammonium sulfate in refluxing methanol for 4 h afforded diethyl (*S*)-3-azido-2-hydroxypropylphosphonate (*S*)-**2** (ee 96%) in 83% yield.

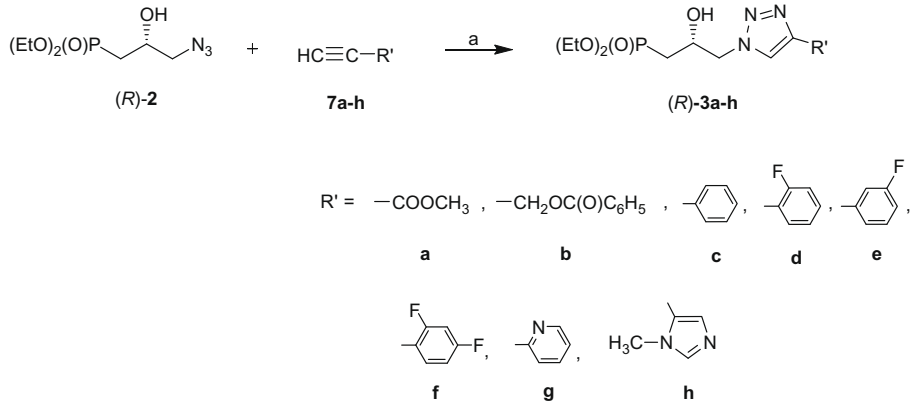
To check the reactivity of the diethyl 3-azido-2-hydroxypropylphosphonate framework compound (*R*)-**2** (ee 96%) was reacted with 8 different terminal alkynes **7a**–**h** (**7a**–methyl propiolate, **7b**–propargyl benzoate, **7c**–phenylacetylene, **7d**–1-ethynyl-2-fluorobenzene, **7e**–1-ethynyl-3-fluorobenzene, **7f**–1-ethynyl-2,4-difluorobenzene, **7g**–1-ethynyl-2-pyridine and **7h**–5-ethynyl-1-methyl-1*H*-imidazole) according to a standard protocol employing Cu(I) as a catalyst which was generated in situ from $CuSO_4$ and sodium ascorbate.[18,23] The corresponding 1,2,3-triazoles **3a**–**h** (ee 92–96%) were formed in moderate to excellent yields and were finally purified either by column chromatography on silica gel or by crystallisation (Scheme 5 and Table 1).



Scheme 2.

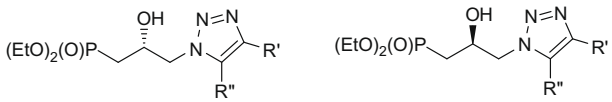


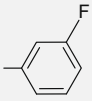
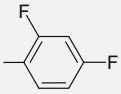
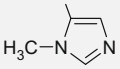
Scheme 3. Reagents and conditions: (a) NaN_3, NH_4Cl, MeOH, reflux, 4 h.



Scheme 5. Reagents and conditions: (a) $CuSO_4{\cdot}5H_2O$ (0.1 equiv), sodium ascorbate (0.2 equiv), H_2O–*t*-BuOH (2:1), rt, 48–72 h.

Table 1



Compounds	R′	R″	Yield (%)	ee (%)	δ ^{31}P NMR[a]
(*R*)-**3a**	–$COOCH_3$	H	95	96	28.44
(*S*)-**3a**			95	97	29.07
(*R*)-**3b**	–$CH_2OC(O)Ph$	H	75	95	28.66
(*S*)-**3b**			70	96	28.79
(*R*)-**3c**		H	95	96	29.03
(*S*)-**3c**			86	95	29.30
(*R*)-**3d**		H	88	92	28.70
(*S*)-**3d**			95	91	28.90
(*R*)-**3e**		H	91	96	28.41
(*S*)-**3e**			86	96	28.95
(*R*)-**3f**		H	90	96	28.73
(*S*)-**3f**			95	96	28.90
(*R*)-**3g**		H	88	94	29.21
(*S*)-**3g**			91	94	28.44
(*R*)-**3h**		H	75	92	28.60
(*S*)-**3h**			80	94	29.19
(*R*)-**3i**	–$C(O)NH_2$	NH_2	70	96	29.02
(*S*)-**3i**			—	—	29.11
(*R*)-**3j**	–$COOCH_3$	–$COOCH_3$	95	100	29.48
(*S*)-**3j**			80	100	29.98

[a] The ^{31}P NMR chemical shifts observed with 1 equiv of quinine.

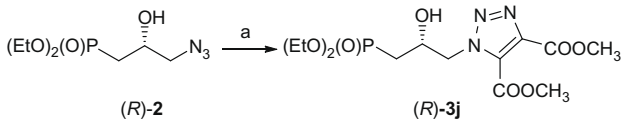
Conversely, the cycloaddition of (*R*)-3-azidophosphonate (*R*)-**2** (ee 96%) and dimethyl acetylenedicarboxylate **7j** was carried out at 110 °C according to the standard procedure[24] to give crude (*R*)-**3j** (ee 96%) in quantitative yield (Scheme 6). After crystallisation from an ethyl acetate–petroleum ether mixture enantiomerically pure (*R*)-**3j** (ee 100%) was obtained in 95% yield.

To prepare phosphonate (*R*)-**3i**, the cycloaddition of azidophosphonate (*R*)-**2** and 2-cyanoacetamide should be carried out. However, this reaction is usually performed in the presence of potassium carbonate and DMSO.[25] To avoid possible dehydration of diethyl (*R*)-3-azido-2-hydroxypropylphosphonate (*R*)-**2** to diethyl 3-azido-1-propenylphosphonate the protection of the hydroxy group was deemed necessary. To this end, (*R*)-2-hydroxyphosphonate (*R*)-**2** (ee 96%) was transformed into 2-*O*-benzyl derivative (*R*)-**8** which was next subjected to cycloaddition with 2-cyanoacetamide.[25] After removal of the benzyl group by hydrogenolysis a crude (*R*)-**3i** (ee 94%) was obtained (Scheme 7). Chromatographic purification on silica gel column followed by crystallisation of the appropriate fractions gave pure (*R*)-**3i** (ee 96%) in 56% overall yield after three steps.

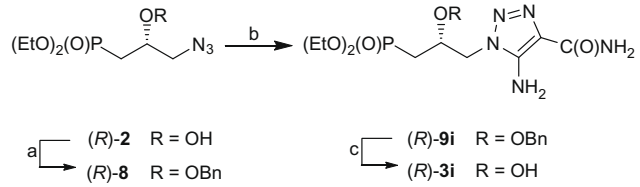
It appeared that phosphonate (*R*)-**3i** could also be obtained without protection of the hydroxy group in (*R*)-**2**. Cycloaddition of diethyl (*R*)-3-azidophosphonate (*R*)-**2** and 2-cyanoacetamide performed in the presence of potassium carbonate and DMSO[25] gave phosphonate (*R*)-**3i** (ee 96%) in 70% yield after column chromatography and crystallisation (Scheme 8).

Under the same conditions, from azidophosphonate (*S*)-**2** 1,2,3-triazoles (*S*)-**3a**–**h** and (*S*)-**3j** were obtained (Scheme 9 and Table 1).

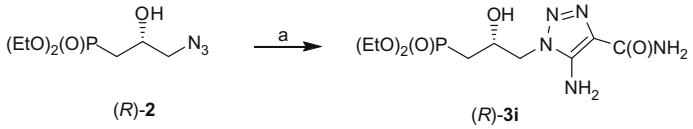
The determination of the enantiomeric excesses of all the phosphonates obtained in this paper deserves comment. For 3-azido- and 3-(1,2,3-triazol-1-yl)-2-hydroxypropylphosphonates, ^{31}P NMR spectroscopy using quinine was found most efficient. To optimise the molar 3-azidoalcohol or 1,2,3-triazole to quinine ratio, the ^{31}P NMR spectra for 1:1, 1:2, 1:3, 1:4 and 1:5 mixtures of racemic compounds with quinine were recorded. In the case of azidoalcohol **2** the best separation of the ^{31}P NMR signals of (*R*)- and (*S*)-**2** was observed for a 4:1 quinine to azidoalcohol ratio. However, for 1,2,3-triazole derivatives (*R*)- and (*S*)-**3a-j** addition of 1 equiv of quinine was found to be sufficient. This methodology was extended to establish ee of (*R*)- and (*S*)-2,3-epoxypropylphosphonates obtained by HKR to simplify the methodology already described in the literature,[21] which relied on a two-step procedure [the epoxide ring opening with dibenzylamine and esterification with (*S*)-*O*-methylmandelic acid] and was time consuming (at least four days to complete both steps). Since the epoxide ring opening in **1** with azides is complete in 4 h, this new approach is fast and simple.



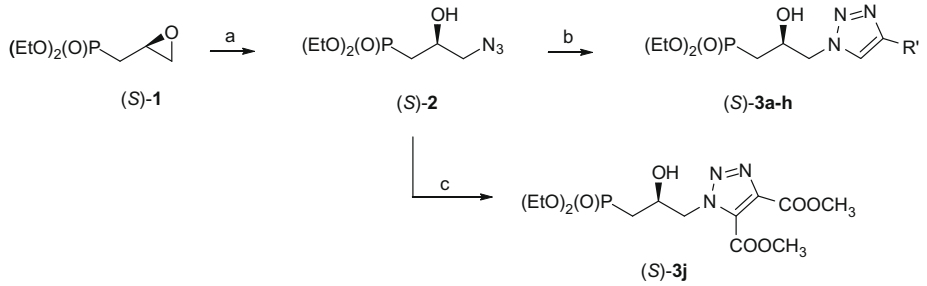
Scheme 6. Reagents and conditions: (a) $H_3COOCC{\equiv}CCOOCH_3$ **7j**, toluene, 110 °C, 4 h, 95%.



Scheme 7. Reagents and conditions: (a) BnBr, Ag_2O, CH_2Cl_2, rt, 24 h, 87%; (b) 2-cyanoacetamide, DMSO, K_2CO_3, 5 h, 50 °C, 70%; (c) H_2, 10% Pd–C, EtOH, rt, 24 h, 92%.



Scheme 8. Reagents and conditions: (a) 2-cyanoacetamide, DMSO, K_2CO_3, 5 h, 50 °C, 70%.



Scheme 9. Reagents and conditions: (a) NaN_3, $(NH_4)_2SO_4$, MeOH, reflux, 4 h, 83%; (b) alkynes **7a–h**, $CuSO_4{\cdot}5H_2O$ (0.1 equiv), sodium ascorbate (0.2 equiv), H_2O–*t*-BuOH (2:1), rt, 48–72 h; (c) $H_3COOCC{\equiv}CCOOCH_3$ **7j**, toluene, 110 °C, 4 h, 80%.

3. Conclusions

The opening of the epoxide ring in racemic 2,3-epoxypropylphosphonate **1** with $TMSN_3$ in the presence of (salen)Cr–Cl as a catalyst gave (*S*)-3-azido-2-hydroxyphosphonate (*S*)-**2** and (*R*)-2,3-epoxypropylphosphonate (*R*)-**1** in good chemical yields but the products had low enantiomeric purities (ee 28% and 26%, respectively).

The clean transformation of epoxide (*R*)- and (*S*)-**1** (ee 93%) to (*R*)- and (*S*)-3-azido-2-hydroxypropylphosphonate (*R*)- and (*S*)-**2** (ee 96%) was accomplished using sodium azide and ammonium sulfate because in the presence of ammonium chloride, 3-chloro-2-hydroxyphosphonate **5** (6%) was formed as a by-product.

3-Azidopropylphosphonates **2** easily react with terminal alkynes **7a–h** in the presence of Cu(I) as a catalyst, withstood refluxing in toluene when treated with dimethyl acetylenedicarboxylate **7j** and underwent cycloaddition with 2-cyjanoacetamide in strongly basic medium.

The enantiomeric excesses of the (*R*)- and (*S*)-epoxide **1**, diethyl (*R*)- and (*S*)-3-azido-2-hydroxypropylphosphonates (*R*)- and (*S*)-**2** and diethyl (*R*)- and (*S*)-2-hydroxy(1,2,3-triazol-1-yl)propylphosphonate (*R*)- and (*S*)-**3** were efficiently determined by ^{31}P NMR spectroscopy using quinine as an enantiodifferentiating reagent.

4. Experimental

^1H 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 an Optical Activity PolAAr 3001 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}. TLC plates were developed in chloroform–methanol solvent systems. Visualisation of spots was effected with iodine vapours. All solvents were purified by methods described in the literature.

4.1. Dynamic kinetic resolution of racemic epoxide 1 at room temperature

To racemic epoxide **1** (0.104 g, 0.536 mmol) was added catalyst (*R*,*R*)-**4** (6.76 mg, 0.011 mmol, 0.02 equiv). After 5 min. the solution was cooled to 0 °C and $TMSN_3$ (0.074 mL, 0.56 mmol, 1.05 equiv) was injected. The reaction mixture was stirred at room temperature for 7 h, concentrated and purified on a silica gel column with chloroform-methanol (100:1, v/v) to give azidoalcohol (*S*)-**2** (0.052 g, 41%; ee 28%) and epoxide (*R*)-**1** (0.042 g, 40%; ee 26%). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 26.65$ for (*R*)-**1** and 29.54 for (*S*)-**2** (fully characterised in 4.4.2).

4.2. Dynamic kinetic resolution of racemic epoxide 1 at 4 °C

To racemic epoxide **1** (0.104 g, 0.536 mmol) was added catalyst (*R*,*R*)-**4** (6.76 mg, 0.011 mmol, 0.02 equiv). After 5 min. the solution was cooled to 0 °C and $TMSN_3$ (0.074 mL, 0.562 mmol, 1.05 equiv) was injected. The solution was stirred at 4 °C for 7 h, concentrated and purification on a silica gel column with chloroform-methanol (100:1, v/v) gave azidoalcohol (*S*)-**2** (0.049 g, 39%; ee 28%) and epoxide (*R*)-**1** (0.040 g, 40%; ee 26%).

4.3. Hydrolytic kinetic resolution of racemic epoxide 1

A mixture of (*S*,*S*)-Salen Co^{II} (0.024 g, 0.040 mmol), toluene (0.4 mL) and acetic acid (4.6 μL, 0.074 mmol) was stirred in air at room temperature for 1 h. After removal of the solvent, the brown residue was vacuum dried. The racemic epoxide (3.601 g, 18.6 mmol) was added to the catalyst in one portion and the mixture was cooled in an ice-water bath. Water (0.200 mL, 11.0 mmol, 0.55 equiv) was added over 10 min. After 1 h, the bath was removed and the reaction mixture was stirred at room temperature for 72 h. Ethyl acetate (6 mL) was added followed by $MgSO_4$ (0.5 g). After removal of the drying agent and the solvent, the crude product was subjected to distillation to give (*R*)-**1** (1.532 g, 42%) as a colourless oil (bp 80–82 °C/0.2 mmHg). $[\alpha]_D^{20} = +3.1$ (*c* 2.01, ethanol); ee 93%. ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 26.82$.

4.4. Reaction of epoxide (*R*)-1 with sodium azide

4.4.1. Reaction of epoxide (*R*)-1 with sodium azide in the presence of NH_4Cl

A mixture of epoxide (*R*)-**1** (1.53 g, 7.26 mmol), sodium azide (1.23 g, 18.7 mmol) and ammonium chloride (0.757 g, 14.2 mmol) in methanol (5 mL) was stirred at 65 °C for 4 h. After evaporation of solvents the residue was suspended in ethyl acetate (15 mL) and filtered through a layer of Celite. The solution was concentrated in vacuo to give a 94:6 mixture of diethyl (*R*)-3-azido-2-hydroxypropylphosphonate (*R*)-**2** (ee 93%) and diethyl (*R*)-3-chloro-2-hydroxypropylphosphonate (*R*)-**6** (1.74 g) in 92% yield. The crude product was chromatographed on a silica gel column with chloroform-methanol mixtures (100:1, v/v) to give a 94:6 mixture of (*R*)-**2** (ee 96%) and (*R*)-**6** (1.68 g, 90%). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 30.18$ for **2** and 29.81 for **6**.

4.4.2. Reaction of epoxide (*R*)-1 with sodium azide in the presence of $(NH_4)_2SO_4$

A mixture of the epoxide (*R*)-**1** (0.200 g, 1.03 mmol), sodium azide (0.161 g, 2.47 mmol) and ammonium sulfate (0.245 g, 1.85 mmol) in methanol (2 mL) was stirred at 65 °C for 4 h. After evaporation of solvents the residue was suspended in ethyl acetate (5 mL) and filtered through a layer of Celite. The solution was concentrated in vacuo to give diethyl (*R*)-3-azido-2-hydroxypropylphosphonate (*R*)-**2** (0.198 g, 80%; ee 96%) as a yellowish oil. $[\alpha]_D^{20} = -4.4$ (*c* 1.45, $CHCl_3$), IR (film): $\nu = 3339, 2985, 2931, 2911, 2105, 1225, 1029\ cm^{-1}$; ^1H NMR (300 MHz, C_6D_6): $\delta = 0.87$ and 0.89 (2t, $J = 6.8$ Hz, 6H, 2 × $POCH_2CH_3$), 1.60 (ddd, $J = 19.2$ Hz, $J = 15.0$ Hz, $J = 3.3$ Hz, 1H, H-1b), 1.81 (ddd, $J = 16.5$ Hz, $J = 15.0$ Hz, $J = 9.6$ Hz, 1H, H-1a), 2.02 (br s, 1H, OH), 2.87–2.82 (m, 2H, H-3a, H-3b), 3.91–3.72 (m, 4H, 2 × $POCH_2CH_3$), 4.16–4.03 (m, 1H, H-2); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 16.2$ (d, $J = 6.3$ Hz, POC*C*), 30.7 (d, $J = 139.4$ Hz, C-1), 56.5 (d, $J = 14.3$ Hz, C-3), 61.7 and 61.9 (2d, $J = 6.6$ Hz, POC), 65.7 (d, $J = 2.9$ Hz, C-2); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 30.18$. Anal. Calcd for $C_7H_{16}N_3O_4P$: C, 35.45; H, 6.80; N, 17.72. Found: C, 35.26; H, 6.60; N, 17.62.

4.5. Synthesis of phosphonates (*R*)-3a–h, general procedure

To a solution of (*R*)-**2** (1 mmol) in *t*-BuOH (0.5 mL) and H_2O (1 mL) were added $CuSO_4{\cdot}5H_2O$ (0.1 mmol), sodium ascorbate (0.2 mmol) and selected alkynes **7a–h** (1 mmol). This suspension was stirred vigorously at room temperature for 48–72 h. The reaction mixture was extracted with chloroform (3 × 5 mL), dried over $MgSO_4$, filtered through a layer of Celite and evaporated. The crude product was purified by column chromatography on the silica gel or was crystallised to give (*R*)-**3a–h**.

4.5.1. Diethyl (*R*)-2-hydroxy-3-(4-methoxycarbonyl-1,2,3-triazol-1-yl)propylphosphonate (*R*)-3a

From (*R*)-**2** (0.266 g, 1.120 mmol), methyl propiolate **7a** (0.100 mL, 1.120 mmol), $CuSO_4{\cdot}5H_2O$ (0.028 g), sodium ascorbate (0.044 g) in a mixture of *t*-BuOH (0.5 mL)–H_2O (1 mL), phosphonate (*R*)-**3a** (0.343 g, 95%; ee 96%) was obtained as a white solid after crystallisation from ethyl acetate–petroleum ether. Mp 103–104 °C. $[\alpha]_D^{20} = -3.7$ (*c* 5.20, $CHCl_3$), ee 96%; IR (KBr): $\nu = 3424, 3287, 2986, 2958, 1725, 1548, 1437, 1237, 1029, 965\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.32$ and 1.34 (2t, $J = 7.2$ Hz, 6H, 2 × $POCH_2CH_3$), 1.78 (ddd, $J = 16.8$ Hz, $J = 15.3$, $J = 3.0$ Hz, 1H, H-1b), 2.00 (ddd, $J = 19.2$ Hz, $J = 15.3$, $J = 9.3$ Hz, 1H, H-1a), 2.45 (br s, 1H, OH), 3.93 (s, 3H, $COOCH_3$), 4.04–4.19 (m, 4H, 2 × $POCH_2CH_3$), 4.36–4.51 (m, 2H, H-3b, H-2), 4.59–4.67 (m, 1H, H-3a), 8.31 (s, 1H, $HC_{5'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 16.5$ and 16.6 (2d, $J = 6.0$ Hz, POC*C*), 30.8 (d, $J = 140.4$ Hz, C-1), 52.3 (s, $COOCH_3$), 56.3 (d, $J = 17.8$ Hz, C-3), 62.2 and 62.4 (2d, $J = 6.6$ Hz, 2 × POC), 65.3 (d, $J = 3.8$ Hz, C-2), 129.4 (s, HC≡C), 139.7 (s, HC≡*C*), 161.1 (s, C=O); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 29.24$. Anal. Calcd for $C_{11}H_{20}N_3O_6P$:C, 41.12; H, 6.28; N, 13.08. Found: C, 41.08; H, 6.17; N, 12.80.

4.5.2. Diethyl (*R*)-3-(4-benzoyloxymethyl-1,2,3-triazol-1-yl)-2-hydroxypropylphosphonate (*R*)-3b

From (*R*)-**2** (0.103 g, 0.430 mmol), propargyl benzoate **7a** (0.063 mL, 0.430 mmol), $CuSO_4{\cdot}5H_2O$ (0.011 g), sodium ascorbate (0.017 g) in a mixture of *t*-BuOH (0.5 mL)–H_2O (1 mL), phosphonate (*R*)-**3b** (0.129 g, 75%; ee 95%) was obtained as a colourless oil after purification on a silica gel with chloroform–methanol (50:1, v/v). $[\alpha]_D^{20} = -1.3$ (*c* 2.15, $CHCl_3$), ee 95%; IR (film): $\nu = 3338, 2984, 2910, 1720, 1272, 1027, 836, 714\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.32$ and 1.33 (2t, $J = 7.2$ Hz, 6H, 2 × $POCH_2CH_3$), 1.82 (ddd, $J = 16.8$ Hz, $J = 15.3$ Hz, $J = 9.0$ Hz, 1H, H-1b), 2.01 (ddd, $J = 19.5$ Hz, $J = 15.3$ Hz, $J = 2.7$ Hz, 1H, H-1a), 2.70 (br s, 1H, OH), 4.05–4.20 (m, 4H, 2 × $POCH_2CH_3$), 4.36–4.47 (m, 2H, H-3b, H-2), 4.54–4.61 (m, 1H, H-3a), 5.49 (s, 2H, $CH_2OC(O)Ph$), 7.40–7.45 (m, 2H, Ar-H), 7.50–7.60 (m, 1H, Ar-H), 7.92 (s, 1H, $HC_{5'}$), 8.03–8.07 (m, 2H, Ar-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 16.5$ and 16.6 (2d, $J = 6.0$ Hz, POC*C*), 30.8 (d, $J = 140.4$ Hz, C-1), 56.0 (d, $J = 17.4$ Hz, C-3), 58.1 (s, $CH_2OC(O)Ph$), 62.3 and 62.4 (2d, $J = 7.3$ Hz, 2 × POC), 65.5 (d, $J = 3.8$ Hz, C-2), 123.0 (s, HC≡*C*) 128.3, 129.6 ($C_{arom.}$), 133.1 (s, HC≡C), 142.0 (C_{ipso}), 166.2 (s, C=O); ^{31}P-NMR (121.5 MHz, $CDCl_3$): $\delta = 28.85$. Anal. Calcd for $C_{17}H_{24}N_3O_6P$: C, 51.39; H, 6.09; N, 10.57. Found: C, 51.26; H, 6.08; N, 10.50.

4.5.3. Diethyl (*R*)-2-hydroxy-3-(4-phenyl-1,2,3-triazol-1-yl)propylphosphonate (*R*)-3c

From (*R*)-**2** (0.116 g, 0.491 mmol), phenylacetylene **7c** (0.054 mL, 0.491 mmol), $CuSO_4{\cdot}5H_2O$ (0.012 g), sodium ascorbate (0.019 g) in a mixture of *t*-BuOH (0.5 mL)–H_2O (1 mL), phosphonate (*R*)-**3c** (0.158 g, 95%; ee 96%) was obtained as a white solid after purification on a silica gel with chloroform–methanol (100:1, v/v) and crystallisation from ethyl acetate–petroleum ether. Mp 87–89 °C. $[\alpha]_D^{20} = +0.7$ (*c* 2.02, $CHCl_3$), ee 96%; IR (KBr): $\nu = 3327, 2984, 2908, 1227, 1029, 965\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.30$ and 1.31 (2t, $J = 7.2$ Hz, 6H, 2 × $POCH_2CH_3$), 1.85 (ddd, $J = 17.1$ Hz, $J = 15.3$ Hz, $J = 9.3$ Hz, 1H, H-1b), 2.02 (ddd, $J = 18.6$ Hz, $J = 15.3$ Hz, $J = 3.3$ Hz, 1H, H-1a), 4.02–4.17 (m, 5H, 2 × $POCH_2CH_3$, OH), 4.38–4.50 (m, 2H, H-3b, H-2), 4.56–4.63 (m, 1H, H-3a), 7.29–7.34 (m, 1H, Ar-H), 7.37–7.43 (m, 2H, Ar-H),

7.79–7.83 (m, 2H, Ar-H), 7.99 (s, 1H, *H*C$_{5'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 16.4 and 16.5 (2d, *J* = 6.0 Hz, POC*C*), 30.8 (d, *J* = 139.7 Hz, C-1), 56.1 (d, *J* = 15.9 Hz, C-3), 62.2 and 62.3 (2d, *J* = 7.3 Hz, 2 × POC), 65.5 (d, *J* = 3.8 Hz, C-2), 121.5 (s, HC=*C*), 125.5, 128.0, 128.6 ($C_{arom.}$), 130.4 (s, C_{ipso}), 147.3 (HC=C); ^{31}PNMR (121.5 MHz, $CDCl_3$): δ = 28.89. Anal. Calcd for $C_{15}H_{22}N_3O_4P$: C, 53.09; H, 6.53; N, 12.38. Found: C, 53.19; H, 6.60; N, 12.42.

4.5.4. Diethyl (*R*)-3-[4-(2-fluorophenyl)-1,2,3-triazol-1-yl]-2-hydroxypropylphosphonate (*R*)-3d

From (*R*)-**2** (0.149 g, 0.628 mmol), 1-ethynyl-2-fluorobenzene **7d** (0.071 mL, 0.628 mmol), $CuSO_4{\cdot}5H_2O$ (0.016 g), sodium ascorbate (0.025 g) in a mixture of *t*-BuOH (0.5 mL)–H_2O (1 mL), phosphonate (*R*)-**3d** (0.196 g, 88%) was obtained as a colourless oil after purification on a silica gel with chloroform–methanol (100:1, v/v). $[\alpha]_D^{20} = +0.6$ (*c* 1.48, $CHCl_3$), ee 92%; IR (film): *v* = 3339, 2984, 2911, 1478, 1221, 1028, 967, 818, 762 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 and 1.34 (2t, *J* = 6.9 Hz, 6H, 2 × $POCH_2CH_3$), 1.83 (ddd, *J* = 16.5 Hz, *J* = 15.3 Hz, *J* = 9.3 Hz, 1H, H-1b), 1.80 (br s, 1H, OH), 2.03 (ddd, *J* = 18.6 Hz, *J* = 15.3 Hz, *J* = 3.3 Hz, 1H, H-1a), 4.06–4.21 (m, 4H, 2 × CH_3CH_2OP), 4.41–4.66 (m, 3H, H-2, H-3a, H-3b), 7.14 (ddd, *J* = 10.8 Hz, *J* = 7.8 Hz, *J* = 1.2 Hz, 1H, Ar-H), 7.22–7.35 (m, 2H, Ar-H), 8.14 (d, *J* = 3.6 Hz, *H*C$_{5'}$), 8.28 (dt, *J* = 7.5 Hz, *J* = 1.8 Hz, 1H, Ar-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 16.4 and 16.5 (2d, *J* = 6.8 Hz, POC*C*), 31.0 (d, *J* = 140.3 Hz, C-1), 56.2 (d, *J* = 16.9 Hz, C-3), 62.3 and 62.4 (2d, *J* = 6.6 Hz, POC), 65.6 (d, *J* = 3.1 Hz C-2), 115.7 (d, *J* = 21.8 Hz, C-3$_{arom.}$), 118.5 (d, *J* = 12.9 Hz, C-1$_{arom.}$), 124.6 (d, *J* = 12.6 Hz, $C_{arom.}$), 124.6 (d, *J* = 3.4 Hz, $C_{arom.}$), 127.6 (d, *J* = 3.4 Hz, HC=C), 129.2 (d, *J* = 8.6 Hz, C-4$_{arom.}$), 141.0 (s, *C*=CH), 159.1 (d, *J* = 247.6 Hz, C–F); ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 28.91. Anal. Calcd for $C_{15}H_{21}FN_3O_4P$: C, 50.42; H, 5.92; N, 11.76. Found: C, 50.44; H, 5.96; N, 11.62.

4.5.5. Diethyl (*R*)-3-[4-(3-fluorophenyl)-1,2,3-triazol-1-yl]-2-hydroxypropylphosphonate (*R*)-3e

From (*R*)-**2** (0.239 g, 1.01 mmol), 1-ethynyl-3-fluorobenzene **7e** (0.116 mL, 1.01 mmol), $CuSO_4{\cdot}5H_2O$ (0.025 g), sodium ascorbate (0.040 g) in a mixture of *t*-BuOH (0.5 mL)–H_2O (1 mL), phosphonate (*R*)-**3e** (0.328 g, 91%) was obtained as a colourless oil after purification on a silica gel with chloroform–methanol (100:1, v/v). $[\alpha]_D^{20} = +0.6$ (*c* 2.06, $CHCl_3$), ee 96%; IR (film): *v* = 3326, 3141, 2985, 2911, 1466, 1229, 1030, 967, 866, 787 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 and 1.35 (2t, *J* = 6.9 Hz, 6H, 2 × $POCH_2CH_3$), 1.80 (ddd, *J* = 16.8 Hz, *J* = 15.3 Hz, *J* = 9.6 Hz, 1H, H-1b), 1.85 (br s, 1H, OH), 1.97–2.09 (m, 1H, H-1a), 4.05–4.21 (m, 4H, 2 × $POCH_2CH_3$), 4.39–4.51 (m, 2H, H-2, H-3b), 4.56–4.66 (m, 1H, H-3b), 6.99–7.06 (m, 1H, Ar-H), 7.35–7.42 (m, 1H, Ar-H), 7.55–7.62 (m, 2H, Ar-H), 8.01 (s, 1H, *H*C$_{5'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 16.5 and 16.6 (2d, *J* = 6.0 Hz, POC*C*), 30.9 (d, *J* = 140.0 Hz, C-1), 56.2 (d, *J* = 17.2 Hz, C-3), 62.4 and 62.5 (2d, *J* = 6.9 Hz, POC), 65.6 (d, *J* = 3.7 Hz C-2), 112.7 (d, *J* = 22.9 Hz, C-2$_{arom.}$), 114.9 (d, *J* = 21.2 Hz, $C_{arom.}$), 121.3 (d, *J* = 2.9 Hz, $C_{arom.}$), 122.1 (s, HC=C) 130.5 (d, *J* = 8.3 Hz, $C_{arom.}$), 146.4 (s, *C*=CH), 163.1 (d, *J* = 245.1 Hz, C–F); ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 28.93. Anal. Calcd for $C_{15}H_{21}FN_3O_4P$: C, 50.42; H, 5.92; N, 11.76. Found: C, 50.28; H, 5.89; N, 11.64.

4.5.6. Diethyl (*R*)-3-[4-(2,4-difluorophenyl)-1,2,3-triazol-1-yl]-2-hydroxypropylphosphonate (*R*)-3f

From (*R*)-**2** (0.250 g, 1.05 mmol), 1-ethynyl-2,4-difluorobenzene **7f** (0.145 g, 1.05 mmol), $CuSO_4{\cdot}5H_2O$ (0.026 g), sodium ascorbate (0.040 g) in a mixture of *t*-BuOH (0.5 mL)–H_2O (1 mL), phosphonate (*R*)-**3f** (0.356 g, 90%) was obtained as a white solid after crystallisation from ethyl acetate–petroleum ether. Mp 93–94 °C. $[\alpha]_D^{20} = -1.0$ (*c* 3.51, $CHCl_3$), ee 96%; IR (KBr): *v* = 3286, 3136, 2988, 2907, 1628, 1600, 1561, 1493, 1196, 1072, 1036, 979, 826 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 and 1.34 (2t, *J* = 6.9 Hz, 6H, 2x $POCH_2CH_3$), 1.80 (br s, 1H, OH), 1.83 (ddd, *J* = 16.8 Hz, *J* = 15.3 Hz, *J* = 9.3 Hz, 1H, H-1b), 2.03 (ddd, *J* = 19.2 Hz, *J* = 15.3 Hz, *J* = 3.0 Hz, 1H, H-1a), 4.06–4.21 (m, 4H, 2 × $POCH_2CH_3$), 4.40–4.66 (m, 3H, H-2, H-3a, H-3b), 6.87–7.03 (m, 2H, Ar-H), 7.35–7.42 (m, 1H, Ar-H), 8.09 (d, *J* = 3.9 Hz, *H*C$_{5'}$), 8.26 (dt, *J* = 8.4 Hz, *J* = 6.3 Hz, 1H, Ar-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 16.5 and 16.6 (2d, *J* = 6.0 Hz, POC*C*), 30.9 (d, *J* = 140.4 Hz, C-1), 56.2 (d, *J* = 17,4 Hz, C-3), 62.3 and 62.5 (2d, *J* = 6.8 Hz, POC), 65.6 (d, *J* = 3.8 Hz, C-2), 104.1 (t, *J* = 30.2 Hz, C-3$_{arom.}$), 112.0 (dd, *J* = 21.2 Hz, *J* = 3.4 Hz, C-1$_{arom.}$), 115.0 (dd, *J* = 13.2 Hz, *J* = 3.7 Hz, C-5$_{arom.}$), 124.1 (d, *J* = 12.0 Hz, C-6$_{arom.}$), 128.6 (dd, *J* = 9.7 Hz, *J* = 5.2 Hz, HC=C), 140.4 (s, C=*C*–Ph), 159.2 (dd, *J* = 249.2 Hz, *J* = 12.3 Hz, C-2$_{arom.}$), 162.4 (dd, *J* = 249.2 Hz, *J* = 12.6 Hz, C-4$_{arom.}$); ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 29.65. Anal. Calcd for $C_{15}H_{20}F_2N_3O_4P$: C, 48.00; H, 5.37; N, 11.20. Found: C, 48.25; H, 5.06; N, 11.14.

4.5.7. Diethyl (*R*)-2-hydroxy-3-[4-(2-pyridinyl)-1,2,3-triazol-1-yl]propylphosphonate (*R*)-3g

From (*R*)-**2** (0.225 g, 0.95 mmol), 1-ethynyl-2-pyridine **7g** (0.096 mL, 0.95 mmol), $CuSO_4{\cdot}5H_2O$ (0.024 g), sodium ascorbate (0.038 g) in a mixture of *t*-BuOH (0.5 mL)–H_2O (1 mL), phosphonate (*R*)-**3e** (0.285 g, 88%) was obtained as a yellowish oil after purification on a silica gel with chloroform–methanol (100:1, v/v). $[\alpha]_D^{20} = -2.3$ (*c* 1.82, $CHCl_3$), ee 94%; IR (film): *v* = 3339, 3104, 2925, 2851, 1636, 1612, 1226, 1163, 1080, 786 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 and 1.37 (2t, *J* = 7.0 Hz, 6H, 2 × $POCH_2CH_3$), 1.91–2.22 (m, 2H, H-1b, H-1a), 4.05–4.21 (m, 4H, 2 × $POCH_2CH_3$), 4.21–4.59 (m, 3H, H-2, H-3b, OH), 4.61 (dd, *J* = 14.2 Hz, *J* = 4.0 Hz, 1H, H-3a), 7.22–7.26 (m, 1H, Ar-H), 7.80 (dt, *J* = 7.8 Hz, *J* = 1.8 Hz, 1H, Ar-H), 8.16 (d, *J* = 7.8 Hz, 1H, Ar-H), 8.38 (s, 1H, *H*C$_{5'}$), 8.37–8.60 (m 1H, Ar-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 16.6 and 16.7 (2d, *J* = 6.0 Hz, POC*C*), 31.0 (d, *J* = 140.4 Hz, C-1), 56.3 (d, *J* = 17.4 Hz, C-3), 62.3 and 62.5 (2d, *J* = 6.0 Hz, POC), 65.7 (d, *J* = 3.7 Hz C-2), 120.4 (s, $C_{arom.}$), 123.0 (s, HC=C), 124.0, 137.2 (s, $C_{arom.}$), 147.9 (s, *C*=CH), 149.2, 150.1 (s, $C_{arom.}$); ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 29.52. Anal. Calcd for $C_{14}H_{21}N_4O_4P$: C, 49.41; H, 6.22; N, 16.46. Found: C, 49.26; H, 6.34; N, 16.41.

4.5.8. Diethyl (*R*)-2-hydroxy-3-[4-(1-methyl-1*H*-imidazol-5-yl)-1,2,3-triazol-1-yl]propylphosphonate (*R*)-3h

From (*R*)-**2** (0.206 g, 0.87 mmol), 5-ethynyl-1-methyl-1*H*-imidazole **7h** (0.088 mL, 0.87 mmol), $CuSO_4{\cdot}5H_2O$ (0.022 g), sodium ascorbate (0.034 g) in a mixture of *t*-BuOH (0.5 mL)–H_2O (1 mL), phosphonate (*R*)-**3h** (0.225 g, 75%) was obtained as a white solid after purification on a silica gel with chloroform–methanol (100:1, v/v). $[\alpha]_D^{20} = -2.4$ (*c* 1.82, $CHCl_3$), ee 92%; IR (KBr): *v* = 3392, 2985, 2911, 1656, 1629, 1510, 1230, 1029, 966, 833 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 and 1.35 (2t, *J* = 6.9 Hz, 6H, 2 × $POCH_2CH_3$), 1.84–2.12 (m, 2H, H-1a, H-1b), 3.05 (br s, 1H, OH), 3.91 (s, 3H, CH_3–N), 4.07–4.21 (m, 4H, 2 × $POCH_2CH_3$), 4.39–4.51 (m, 2H, H-2, H-3b), 4.60–4.68 (m, 1H, H-3a), 7.20 (br s, 1H, H_{imid}), 7.56 (br s, 1H, H_{imid}), 7.94 (s, 1H, *H*C$_{5'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 16.5 and 16.6 (2d, *J* = 6.0 Hz, POC*C*), 31.3 (d, *J* = 140.0 Hz, C-1), 33.8 (s, CH_3–N), 56.4 (d, *J* = 16.0 Hz, C-3), 62.2 and 62.4 (2d, *J* = 6.6 Hz, POC), 65.4 (d, *J* = 3.1 Hz C-2), 122.7, 123.6, 127.8 (s, HC=C), 137.9 (s, HC=*C*), 139.1 (s, N–CH–N); ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 28.70. Anal. Calcd for $C_{13}H_{22}N_5O_4P$: C, 45.48; H, 6.46; N, 20.40. Found: C, 45.64; H, 6.54; N, 20.48.

4.6. Diethyl (*R*)-3-(5-amino-4-carbamoyl-1,2,3-triazol-1-yl) 2-hydroxypropylphosphonate (*R*)-3i

4.6.1. Synthesis of diethyl (*R*)-3-azido-2-benzyloxypropylphosphonate (*R*)-8

A suspension of (*R*)-**2** (0.645 g, 2.72 mmol), benzyl bromide (0.502 mL, 4.35 mmol), Ag_2O (1.01 g, 4.35 mmol) and powdered

molecular sieves 4 Å was stirred at room temperature for 4 h. After filtration through a pad of Celite, the solvent was evaporated and the crude product was purified on a silica gel column with chloroform–methanol (100:1, v/v) to give (*R*)-**8** (0.773 g, 87%) as a colourless oil. $[\alpha]_D^{20} = -6.6$ (*c* 3.07, $CHCl_3$); IR (film): ν = 3429, 2983, 2930, 2871, 2104, 1245, 1052, 964, 740, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.28 and 1.31 (2t, *J* = 6.8 Hz, 6H, 2 × $POCH_2CH_3$), 2.07 (ddd, *J* = 18.2 Hz, *J* = 15.6 Hz, *J* = 7.5 Hz, 1H, H-1b), 2.18 (ddd, *J* = 19.5 Hz, *J* = 15.6 Hz, *J* = 5.7 Hz, 1H, H-1a), 3.38 (dd, *J* = 13.2 Hz, *J* = 5.7 Hz, 1H, H-3b), 3.54 (dd, *J* = 13.2 Hz, *J* = 3.6 Hz, 1H, H-3a), 3.91–4.00 (m, 1H, H-2), 4.03–4.16 (m, 4H, 2 × $POCH_2CH_3$), 4.64 (AB, J_{AB} = 12.9 Hz, 2H, *Ha*H*b*C–Ph), 7.25–7.42 (m, 5H, Ar-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 16.5 (d, *J* = 6.3 Hz, POC*C*), 29.1 (d, *J* = 139.2 Hz, C-1), 54.1 (d, *J* = 7.7 Hz, C-3), 61.8 and 61.9 (2d, *J* = 6.6 Hz, POC), 71.9 (s, CH_2Ph), 73.7 (s, C-2), 127.8, 127.8, 128.3 ($C_{arom.}$); ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 27.64. Anal. Calcd for $C_{14}H_{22}N_3O_4P$:C, 51.37; H, 6.77; N, 12.84. Found: C, 51.16; H, 6.64; N, 11.94.

4.6.2. Synthesis of diethyl (*R*)-3-(5-amino-4-carbamoyl-1,2,3-triazol-1-yl)-2-benzyloxypropylphosphonate (*R*)-9i

To a solution of 2-cyanoacetamide (0.227 g, 2.68 mmol) in DMSO (2 mL) was added K_2CO_3 (0.371 g, 2.68 mmol) at room temperature under an argon atmosphere. The mixture was stirred at the same temperature for 30 min. After the addition of diethyl (*R*)-2-benzyloxy-3-azidopropylphosphonate (*R*)-**8** (0.439 g, 1.34 mmol) in DMSO (1 mL), the stirring was continued for 5 h at 50 °C. After evaporation of the solvent, the residue was purified by silica gel column chromatography with chloroform–methanol (200:1, v/v) to give (*R*)-**9i** (0.386 g, 70%) as a colourless oil. $[\alpha]_D^{20} = -3.2$ (*c* 2.01, $CHCl_3$); IR (film): ν = 3414, 3319, 3180, 2986, 2922, 2864, 1658, 1244, 1025, 966, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 6.9 Hz, 6H, 2 × $POCH_2CH_3$), 2.02–2.16 (m, 2H, H-1a, H-1b), 4.06–4.25 (m, 5H, 2 × $POCH_2CH_3$, H-2), 4.38 (dd, *J* = 14.7 Hz, *J* = 6.6 Hz, 1H, H-3b), 4.55 (AB, J_{AB} = 11.4 Hz, 2H, *Ha*H*b*C–Ph), 4.58 (dd, *J* = 14.7 Hz, *J* = 3.6 Hz, 1H, H-3a), 5.69 (br s, 2H, C(O)NH_2), 5.46 and 6.84 (2 × br s, 2H, NH_2), 7.22–7.46 (m, 5H, Ar-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 16.6 (d, *J* = 6.0 Hz, POC*C*), 28.3 (d, *J* = 138.2 Hz, C-1), 50.2 (d, *J* = 5.4 Hz, C-3), 62.2 and 62.4 (2d, *J* = 6.0 Hz, 2 × POC), 72.1 (s, CH_2Ph), 73.5 (s, C-2), 122.3 (s, *C*–NH_2), 128.0, 128.2, 128.5, 136.5 ($C_{arom.}$), 145.7, 164.8 (s, C=O); ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 27.97. Anal. Calcd for $C_{17}H_{26}N_5O_5P$: C, 49.63; H, 6.37; N, 17.02. Found: C, 49.44; H, 6.18; N, 17.08.

4.6.3. Diethyl (*R*)-3-(5-amino-4-carbamoyl-1,2,3-triazol-1-yl)-2-hydroxypropylphosphonate (*R*)-3i

A solution of (*R*)-**9i** (0.317 g, 0.77 mmol) in ethanol (3 mL) was kept under a hydrogen atmosphere over palladium catalyst [20% $Pd(OH)_2$] (10 mg) at room temperature for 24 h. The suspension was filtered through a pad of Celite and washed with methanol. After evaporation of the solvent, the residue was chromatographed on a silica gel column with chloroform–methanol (20:1, v/v) and the appropriate fractions were crystallised from methanol–diethyl ether to give (*R*)-**3i** (0.229 g, 92%) as a white amorphous solid. Mp 153–154 °C. $[\alpha]_D^{20} = -1.0$ (*c* 3.52, CH_3OH), ee 96%; IR (KBr): ν = 3486, 3366, 3193, 2956, 2911, 1665, 1638, 1239, 1030, 949 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.33 and 1.35 (2t, *J* = 6.9 Hz, 6H, 2 × $POCH_2CH_3$), 1.81 (ddd, *J* = 16.2 Hz, *J* = 15.3 Hz, *J* = 10.5 Hz, 1H, H-1b), 2.02 (ddd, *J* = 19.2 Hz, *J* = 15.3 Hz, *J* = 3.0 Hz, 1H, H-1a), 2.70 (br s, 1H, OH), 4.05–4.42 (m, 4H, 2 × $POCH_2CH_3$), 4.26 (dd, *J* = 14.4 Hz, *J* = 5.1 Hz, H-3b), 4.35–4.50 (m, 2H, H-2, H-3a), 5.79 (br s, 2H, C(O)NH_2), 5.48 and 6.74 (2 × br s, 2H, NH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 16.6 and 16.7 (2d, *J* = 6.0 Hz, POC*C*), 30.3 (d, *J* = 139.7 Hz, C-1), 52.6 (d, *J* = 17.4 Hz, C-3), 62.7 and 62.8 (2d, *J* = 6.8 Hz, 2 × POC), 67.0 (d, *J* = 3.0 Hz, C-2), 123.0 (s, HC=C), 146.5 (s, HC=*C*), 164.6 (s, C=O); ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 29.87. Anal. Calcd for $C_{10}H_{20}N_5O_5P$: C, 37.39; H, 6.28; N, 21.80. Found: C, 37.44; H, 6.33; N, 21.88.

4.6.4. Diethyl (*R*)-3-(5-amino-4-carbamoyl-1,2,3-triazol-1-yl)-2-hydroxypropylphosphonate (*R*)-3i

To a solution of 2-cyanoacetamide (0.102 g, 1.21 mmol) in DMSO (0.5 mL) was added K_2CO_3 (0.167 g, 1.21 mmol) at room temperature under an argon atmosphere. The mixture was stirred at the same temperature for 30 min. After the addition of diethyl (*R*)-3-azido-2-hydroxypropylphosphonate (*R*)-**2** (0.143 g, 0.603 mmol) in DMSO (0.5 mL), stirring was continued for 5 h at 50 °C. After evaporation of the solvent, the residue was purified by silica gel column chromatography with chloroform–methanol (200:1, 100:1, 50:1, 20:1 v/v) and the appropriate fractions were crystallised from methanol–diethyl ether to give (*R*)-**3i** (0.136 g, 70%) as a white amorphous solid. Mp 153–154 °C. $[\alpha]_D^{20} = -1.0$ (*c* 3.52, CH_3OH), ee 96%; IR (KBr): ν = 3486, 3366, 3193, 2956, 2911, 1665, 1638, 1239, 1030, 949 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.33 and 1.35 (2t, *J* = 6.9 Hz, 6H, 2 × $POCH_2CH_3$), 1.81 (ddd, *J* = 16.2 Hz, *J* = 15.3 Hz, *J* = 10.5 Hz, 1H, H-1b), 2.02 (ddd, *J* = 19.2 Hz, *J* = 15.3 Hz, *J* = 3.0 Hz, 1H, H-1a), 2.70 (br s, 1H, OH), 4.05–4.42 (m, 4H, 2 × $POCH_2CH_3$), 4.26 (dd, *J* = 14.4 Hz, *J* = 5.1 Hz, H-3b), 4.35–4.50 (m, 2H, H-2, H-3a), 5.79 (br s, 2H, C(O)NH_2), 5.48 and 6.74 (2 × br s, 2H, NH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 16.6 and 16.7 (2d, *J* = 6.0 Hz, POC*C*), 30.3 (d, *J* = 139.7 Hz, C-1), 52.6 (d, *J* = 17.4 Hz, C-3), 62.7 and 62.8 (2d, *J* = 6.8 Hz, 2 × POC), 67.0 (d, *J* = 3.0 Hz, C-2), 123.0 (s, HC=C), 146.5 (s, HC=*C*), 164.6 (s, C=O); ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 29.87. Anal. Calcd for $C_{10}H_{20}N_5O_5P$: C, 37.39; H, 6.28; N, 21.80. Found: C, 37.44; H, 6.33; N, 21.88.

4.7. Diethyl (*R*)-2-hydroxy-3-(4,5-dimetoxycarbonyl-1,2,3-triazol-1-yl)propylphosphonate (*R*)-3j

A solution of azide (*R*)-**2** (0.346 g, 1.46 mmol) and dimethyl acetylenedicarboxylate **7j** (0.179 mL, 1.46 mmol) in toluene (2 mL) was refluxed for 4 h. The mixture was concentrated to dryness to leave a yellow solid (0.549 g), which was chromatographed on a silica gel column with chloroform–methanol (100:1, v/v) and was later crystallised from ethyl acetate–petroleum ether to give enantiomerically pure (*R*)-**3j** (0.523 g, 95%) as a white solid. Mp 76–78 °C. $[\alpha]_D^{20} = -3.7$ (*c* 1.82, $CHCl_3$); IR (KBr): ν = 3302, 2986, 2957, 2911, 1737, 1468, 1440, 1224, 1025, 963, 826, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.33 and 1.34 (2t, *J* = 7.2 Hz, 6H, 2 × $POCH_2CH_3$), 1.80 (ddd, *J* = 16.5 Hz, *J* = 15.3 Hz, *J* = 9.9 Hz, 1H, H-1a), 2.04 (ddd, *J* = 19.8 Hz, *J* = 15.3 Hz, *J* = 3.0 Hz, 1H, H-1b), 2.15 (br s, 1H, OH), 3.98 (s, 3H, $COOCH_3$), 3.99 (s, 3H, $COOCH_3$), 4.05–4.24 (m, 4H, 2 × $POCH_2CH_3$), 4.39 (ddddd, *J* = 11.4 Hz, *J* = 9.9 Hz, *J* = 6.3 Hz, *J* = 3.9 Hz, *J* = 3.0 Hz, 1H, H-2), 4.70 (d, *J* = 13.8 Hz, *J* = 6.3 Hz, 1H, H-3a), 4.82 (ddd, *J* = 13.8 Hz, *J* = 3.9, *J* = 1.5 Hz, 1H, H-3b); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 16.5 and 16.6 (2d, *J* = 6.0 Hz, POC*C*), 30.9 (d, *J* = 140.4 Hz, C-1), 52.8 (s, $COOCH_3$), 56.3 (s, $COOCH_3$), 55.3 (d, *J* = 18.9 Hz, C-3), 62.4 and 62.6 (2d, *J* = 6.8 Hz, 2 × POC), 65.6 (d, *J* = 3.8 Hz, C-2), 132.1 (s, HC=C), 139.2 (s, HC=*C*), 159.3 (s, C=O), 160.3 (s, C=O); ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 29.21. Anal. Calcd for $C_{13}H_{22}N_3O_8P$: C, 41.16; H, 5.84; N, 11.08. Found: C, 41.41; H, 5.76; N, 10.93.

4.8. Hydrolytic kinetic resolution of racemic 1

A mixture of (*R,R*)-Salen Co^{II} (0.024 g, 0.040 mmol), toluene (0.4 mL) and acetic acid (4.6 μl, 0.074 mmol) was stirred in air at room temperature for 1 h. After removal of the solvent, the brown residue was vacuum dried. The racemic epoxide (3.601 g, 18.6 mmol) was added to the catalyst in one portion and the mixture was cooled in an ice-water bath. Water (0.200 mL, 11.0 mmol, 0.55 equiv) was added over 10 min. After 1 h, the bath was re-

moved and the reaction mixture was stirred at room temperature for 72 h. Ethyl acetate (6 mL) was added followed by $MgSO_4$ (0.5 g). After removal of the drying agent and the solvent, the crude product was subjected to distillation to give (*S*)-**1** (1.266 g, 35%) as a colourless oil (bp 79–84 °C/0.3 mmHg). $[\alpha]_D = -3.0$ (*c* 1.25, ethanol) ee 93%. ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 26.82$.

4.9. Reaction of epoxide (*S*)-1 with sodium azide

4.9.1. Reaction of epoxide (*S*)-1 with sodium azide in the presence of NH_4Cl

A mixture of epoxide (*S*)-**1** (0.868 g, 4.47 mmol), sodium azide (0.697 g, 10.7 mmol) and ammonium chloride (0.359 g, 6.71 mmol) in methanol (5 mL) was stirred at 65 °C for 4 h. After evaporation of solvents, the residue was suspended in ethyl acetate (10 mL) and filtered through a layer of Celite. The solution was concentrated in vacuo to give a 94:6 mixture of diethyl (*S*)-3-azido-2-hydroxypropylphosphonate (*S*)-**2** (ee 93%) and diethyl (*S*)-3-chloro-2-hydroxypropylphosphonate (*S*)-**6** (1.043 g) in 98% yield. The crude product was chromatographed on a silica gel column with chloroform-methanol (100:1, v/v) to give a 96:4 mixture of (*S*)-**2** (ee 96%) and (*S*)-**6** (0.943 g, 89%). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 30.18$ for (*S*)-**2** and 29.81 for (*S*)-**6**.

4.9.2. Reaction of epoxide (*S*)-1 with sodium azide in the presence of $(NH_4)_2SO_4$

A mixture of the epoxide (*S*)-**1** (0.200 g, 1.03 mmol), sodium azide (0.161 g, 2.47 mmol) and ammonium sulfate (0.245 g, 1.85 mmol) in methanol (2 mL) was stirred at 65 °C for 4 h. After evaporation of solvents the residue was suspended of ethyl acetate (5 mL) and filtered through a layer of Celite. The solution was concentrated in vacuo to give of diethyl (*S*)-3-azido-2-hydroxypropylphosphonate (*S*)-**2** (0.206 g, 83%; ee 96%) as a yellowish oil. $[\alpha]_D^{20} = +4.1$ (*c* 1.63, $CHCl_3$).

4.10. Synthesis of phosphonates (*S*)-3a–h, general procedure

To a solution of (*S*)-**2** (1 mmol) in *t*-BuOH (0.5 mL) and H_2O (1 mL) were added $CuSO_4{\cdot}5H_2O$ (0.1 mmol), sodium ascorbate (0.2 mmol) and selected alkynes **7a–h** (1 mmol). This suspension was stirred vigorously at room temperature for 48–72 h. The reaction mixture was extracted with chloroform (3 × 5 mL), dried over $MgSO_4$, filtered through Celite and evaporated. The crude product was purified by column chromatography on silica gel or crystallised to give (*S*)-**3a–h**.

4.10.1. Diethyl (*S*)-2-hydroxy-3-(4-methoxycarbonyl-1,2,3-triazol-1-yl)propylphosphonate (*S*)-3a

From (*R*)-**2** (0.191 g, 0.81 mmol), methyl propiolate **7a** (0.072 mL, 0.81 mmol), $CuSO_4{\cdot}5H_2O$ (0.020 g), sodium ascorbate (0.032 g) in a mixture of *t*-BuOH (0.5 mL)–H_2O (1 mL), phosphonate (*S*)-**3a** (0.247 g, 95%) was obtained as a white solid after crystallisation from ethyl acetate–diethyl ether. Mp 103–104 °C. $[\alpha]_D^{20} = +3.9$ (*c* 2.35, $CHCl_3$), ee 97%. Anal. Calcd for $C_{11}H_{20}N_3O_6P$: C, 41.12; H, 6.28; N, 13.08. Found: C, 41.20; H, 6.46; N, 13.28.

4.10.2. Diethyl (*S*)-3-(4-benzoyloxymethyl-1,2,3-triazol-1-yl)-2-hydroxypropylphosphonate (*S*)-3b

From (*S*)-**2** (0.169 g, 0.713 mmol), propargyl benzoate **7b** (0.103 mL, 0.713 mmol), $CuSO_4{\cdot}5H_2O$ (0.018 g), sodium ascorbate (0.028 g) in a mixture of *t*-BuOH (0.5 mL)–H_2O (1 mL), phosphonate (*S*)-**3b** (0.196 g, 70%) was obtained as a colourless oil after purification on a silica gel with chloroform–methanol (100:1, 50:1, 20:1 v/v). $[\alpha]_D^{20} = +1.5$ (*c* 2.30, $CHCl_3$), ee 96%. Anal. Calcd for $C_{17}H_{24}N_3O_6P$: C, 51.39; H, 6.09; N, 10.57. Found: C, 51.16; H, 6.18; N, 10.48.

4.10.3. Diethyl (*S*)-2-hydroxy-3-(4-phenyl-1,2,3-triazol-1-yl)propylphosphonate (*S*)-3c

From (*S*)-**2** (0.160 g, 0.675 mmol), phenylacetylene **7c** (0.074 mL, 0.675 mmol), $CuSO_4{\cdot}5H_2O$ (0.017 g), sodium ascorbate (0.027 g) in a mixture of *t*-BuOH (0.5 mL)–H_2O (1 mL), phosphonate (*S*)-**3c** (0.198 g, 86%) was obtained as a colourless oil after purification on a silica gel with chloroform–methanol (100:1, v/v). $[\alpha]_D^{20} = -0.8$ (*c* 1.93, $CHCl_3$), ee 95%. Anal. Calcd for $C_{15}H_{22}N_3O_4P$: C, 53.09; H, 6.53; N, 12.38. Found: C, 53.16; H, 6.70; N, 12.28.

4.10.4. Diethyl (*S*)-3-[4-(2-fluorophenyl)-1,2,3-triazol-1-yl]-2-hydroxypropylphosphonate (*S*)-3d

From (*S*)-**2** (0.195 g, 0.822 mmol), 1-ethynyl-2-fluorobenzene **7d** (0.093 mL, 0.822 mmol), $CuSO_4{\cdot}5H_2O$ (0.021 g), sodium ascorbate (0.033 g) in a mixture of *t*-BuOH (0.5 mL)–H_2O (1 mL), phosphonate (*S*)-**3d** (0.281 g, 95%) was obtained as a white solid after purification on silica gel with chloroform–methanol (100:1, v/v) and crystallisation from diethyl ether–petroleum ether. $[\alpha]_D^{20} = 0.6$ (*c* 2.08, $CHCl_3$), ee 91%. Anal. Calcd for $C_{15}H_{21}FN_3O_4P$: C, 50.42; H, 5.92; N, 11.76. Found: C, 50.51; H, 6.04; N, 11.52.

4.10.5. Diethyl (*S*)-3-[4-(3-fluorophenyl)-1,2,3-triazol-1-yl]-2-hydroxypropylphosphonate (*S*)-3e

From (*S*)-**2** (0.201 g, 0.847 mmol), 1-ethynyl-3-fluorobenzene **7e** (0.098 mL, 0.847 mmol), $CuSO_4{\cdot}5H_2O$ (0.021 g), sodium ascorbate (0.034 g) in a mixture of *t*-BuOH (0.5 mL)–H_2O (1 mL), phosphonate (*S*)-**3e** (0.262 g, 86%) was obtained as a colourless oil after purification on silica gel with chloroform–methanol (100:1, 50:1 v/v). $[\alpha]_D^{20} = -0.7$ (*c* 2.22, $CHCl_3$), ee 96%. Anal. Calcd for $C_{15}H_{21}FN_3O_4P$: $C_{15}H_{21}FN_3O_4P$: C, 50.42; H, 5.92; N, 11.76. Found: C, 50.61; H, 6.10; N, 11.84.

4.10.6. Diethyl (*S*)-3-[4-(2,4-difluorophenyl)-1,2,3-triazol-1-yl]-2-hydroxypropylphosphonate (*S*)-3f

From (*S*)-**2** (0.190 g, 0.801 mmol), 1-ethynyl-2,4-difluorobenzene **7f** (0.111 g, 0.801 mmol), $CuSO_4{\cdot}5H_2O$ (0.020 g), sodium ascorbate (0.032 g) in a mixture of *t*-BuOH (0.5 mL)–H_2O (1 mL), phosphonate (*S*)-**3f** (0.286 g, 95%) was obtained as a white solid after crystallisation from ethyl acetate–petroleum ether. Mp 92–93 °C. $[\alpha]_D^{20} = +1.0$ (*c* 4.23, $CHCl_3$), ee 96%. Anal. Calcd for $C_{15}H_{20}F_2N_3O_4P$: C, 48.00; H, 5.37; N, 11.20. Found: C, 48.11; H, 5.40; N, 11.31.

4.10.7. Diethyl (*S*)-2-hydroxy-3-[4-(2-pyridinyl)-1,2,3-triazol-1-yl]propylphosphonate (*S*)-3g

From (*S*)-**2** (0.170 g, 0.717 mmol), 1-ethynyl-2-pyridine **7g** (0.072 mL, 0.717 mmol), $CuSO_4{\cdot}5H_2O$ (0.018 g), sodium ascorbate (0.028 g) in a mixture of *t*-BuOH (0.5 mL)–H_2O (1 mL), phosphonate (*S*)-**3e** (0.223 g, 91%) was obtained as a yellowish oil after purification on a silica gel with chloroform–methanol (50:1, v/v). $[\alpha]_D^{20} = +2.2$ (*c* 2.01, $CHCl_3$), ee 94%. Anal. Calcd for $C_{14}H_{21}N_4O_4P \times H_2O$: C, 46.92; H, 6.47; N, 15.64. Found: C, 47.06; H, 6.54; N, 15.77.

4.10.8. Diethyl (*S*)-2-hydroxy-3-[4-(1-methyl-1*H*-imidazol-5-yl)-1,2,3-triazol-1-yl]propylphosphonate (*S*)-3h

From (*S*)-**2** (0.154 g, 0.649 mmol), 5-ethynyl-1-methyl-1*H*-imidazole **7h** (0.066 mL, 0.649 mmol), $CuSO_4{\cdot}5H_2O$ (0.016 g), sodium ascorbate (0.026 g) in a mixture of *t*-BuOH (0.5 mL)–H_2O (1 mL), phosphonate (*S*)-**3h** (0.179 g, 80%) was obtained as a colourless oil after purification on a silica gel with chloroform–methanol (20:1, v/v). $[\alpha]_D^{20} = +2.5$ (*c* 2.15, $CHCl_3$), ee 94%. Anal. Calcd for $C_{13}H_{22}N_5O_4P$: C, 45.48; H, 6.46; N, 20.40. Found: C, 45.44; H, 6.21; N, 20.61.

4.11. Diethyl (*S*)-2-hydroxy-3-(4,5-dimetoxycarbonyl-1,2,3-triazol-1-yl)propylphosphonate (*S*)-3j

A solution of azide (*S*)-**2** (0.153 g, 0.649 mmol) and dimethyl acetylenedicarboxylate **7j** (0.080 mL, 0.649 mmol) in toluene (3 mL) was refluxed for 4 h. The mixture was concentrated to dryness to leave a yellow solid (0.240 g), which was chromatographed on a silica gel column with chloroform–methanol (100:1, v/v) and was crystallised from ethyl acetate–petroleum ether to give enantiomerically pure (*S*)-**3j** (0.196 g, 80%) as a white solid. Mp 75–77 °C. $[\alpha]_D^{20} = +3.6$ (*c* 4.53, $CHCl_3$). Anal. Calcd for $C_{13}H_{22}N_3O_8P$: C, 41.16; H, 5.84; N, 11.08. Found: C, 28.25; H, 5.96; N, 11.14.

4.12. Determination of enantiomeric excesses using quinine

4.12.1. Diethyl (*R*)-3-azido-2-hydroxypropylphosphonate (*R*)-2

A solution of (*R*)-**2** (0.020 mg, 0.084 mmol) in $CDCl_3$ (0.7 mL) containing quinine (0.096 mg, 0.253 mmol) was analysed by the ^{31}P NMR spectroscopy; $\delta = 30.94$ [(*S*)-**2**], 29.86 [(*R*)-**2**].

4.12.2. Diethyl (*S*)-3-azido-2-hydroxypropylphosphonate (*S*)-2

A solution of (*S*)-**2** (0.010 mg, 0.042 mmol) in $CDCl_3$ (0.7 mL) containing quinine (0.048 mg, 0.126 mmol) was analysed by the ^{31}P NMR spectroscopy; $\delta = 30.94$ [(*S*)-**2**], 29.86 [(*R*)-**2**].

4.12.3. Diethyl 2-hydroxy-3-(1,2,3-triazol-1-yl)propylphosphonate (general procedure)

A solution of **3** (0.025 mmol) in $CDCl_3$ (0.7 mL) containing quinine (0.011 mg) was analysed by the^{31}P NMR ^{31}P NMR spectroscopy. The ^{31}P NMR chemical shifts are collected in Table 1.

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