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Synthesis of four enantiomerically pure 4-(4-carbamoyl-1,2,3-triazol-1-yl)-2,3-dihydroxy-1-methoxybutylphosphonic acids

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Abstract—CuCl-catalysed cycloaddition of methyl propiolate to *O*,*O*-diisopropyl (1*S*,2*R*,3*S*)- and (1*R*,2*R*,3*S*)-, or *O*,*O*-dibenzyl (1*S*,2*R*,3*S*)-, (1*R*,2*R*,3*S*)-, (1*S*,2*R*,3*R*)- and (1*R*,2*R*,3*R*)-4-azido-1,2,3-trihydroxy-2,3-*O*-isopropylidenebutylphosphonates followed by methylation of HO–C-1, ammonolysis of methoxycarbonyl groups and hydrolysis of isopropylidene acetals led to diisopropyl (1*S*,2*R*,3*S*)- and (1*R*,2*R*,3*S*)-4-(4-carbamoyl-1,2,3-triazol-1-yl)-2,3-dihydroxy-1-methoxybutylphosphonates or, after hydrogenolytic removal of benzyl groups, to (1*S*,2*R*,3*S*)-, (1*R*,2*R*,3*S*)-, (1*S*,2*R*,3*R*)- and (1*R*,2*R*,3*R*)-4-(4-carbamoyl-1,2,3-triazol-1-yl)-2,3-dihydroxy-1-methoxybutylphosphonic acids.

1. Introduction

Recent interest in 1,3-dipolar cycloadditions of azides and alkynes was stimulated by the discovery of the catalytic properties of Cu(I) salts, which allows complete control of regioselectivity in the synthesis of 1,2,3-triazoles from unsymmetrical alkynes.[1,2] This regioselective and quantitative transformation, classified among click reactions,[3] has found numerous applications in the synthesis of novel compounds, for example, water-soluble calixarenes,[4] triazole-linked glycoconjugates,[5] neoglycoconjugate[6] and glycopeptides,[7,8] peptides[1] and cyclic peptides,[9] enzyme inhibitors,[10–12] 1,2,3-triazole-modified nucleic acids,[13] vitamin D analogues,[14,15] 1,2,3-triazole dendrimers,[16,17] nucleoside analogues[18,19] and fluorescence coumarin dyes.[20] Several compounds containing a 1,2,3-triazole moiety have exhibited biological activities including anti-allergic,[21] anti-bacterial,[22,23] anti-HIV[24,25] and anti-epileptic.[26] They were also found acting as β_3 selective adrenergic receptor agonists[27] as well as GABA-A α5 subtype inverse agonists.[28]

In our recent contribution to this area, the synthesis of (1*R*,2*S*)- and (1*S*,2*S*)-3-(4-carbamoyl-1,2,3-triazol-1-yl)-1,2-dihydroxypropylphosphonates **1** as acyclic analogues of ribavirin[29] **2** was described.[30] In the meantime several 4-(1,2,3-triazole)carboxamide nucleoside analogues (Fig. 1) have been prepared.[31–33]

As the spatial separation of the 1,2,3-triazole ring mimicking a nucleobase and the phosphonate group as well as absolute stereochemistries at secondary hydroxyl functions may have played an important role in the biological activity, we extended our studies to include a functionalised butylphosphonate scaffold. Herein, we report on the synthesis of enantiomerically pure (1*S*,2*R*,3*S*)-, (1*R*,2*R*,3*S*)-, (1*S*,2*R*,3*R*)- and (1*R*,2*R*,3*R*)-4-(4-carbamoyl-1,2,3-triazol-1-yl)-2,3-dihydroxy-1-methoxybutylphosphonic acids.

2. Results and discussion

A thermal cycloaddition of methyl propiolate and diisopropyl 4-azido-1,2,3-trihydroxy-2,3-*O*-isopropylidenebutylphosphonates,[34] (1*S*,2*R*,3*S*)-**3** or (1*R*,2*R*,3*S*)-**5** led to the formation of mixtures of regioisomeric 1,2,3-trihydroxy-2,3-*O*-isopropylidene-4-[(4- and 5-methoxycarbonyl)-1,2,3-triazol-1-yl]butylphosphonates (1*S*,2*R*,3*S*)-**4a** and (1*S*,2*R*,3*S*)-**4b** (Scheme 1) and phosphonates (1*R*,2*R*,3*S*)-**6a** and (1*R*,2*R*,3*S*)-**6b** (Scheme 2) in both cases in a 4:1 ratio (Table 1). The same ratios of the regioisomers were observed for the dibenzyl esters

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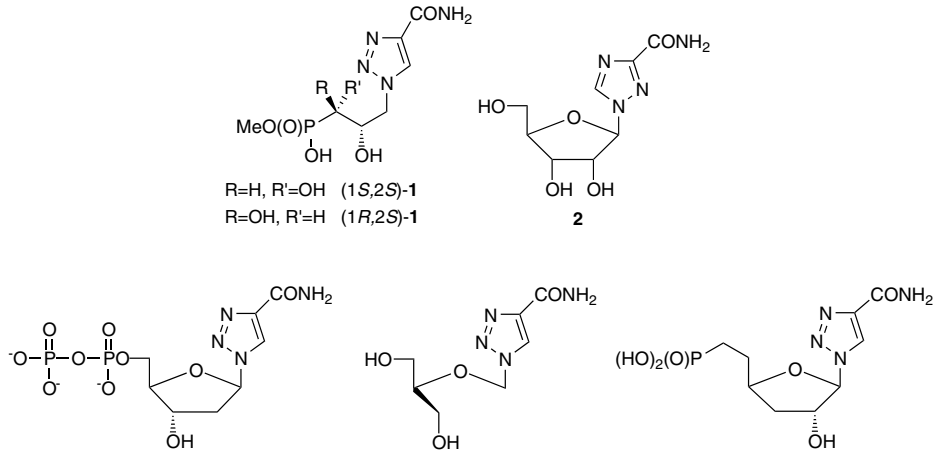
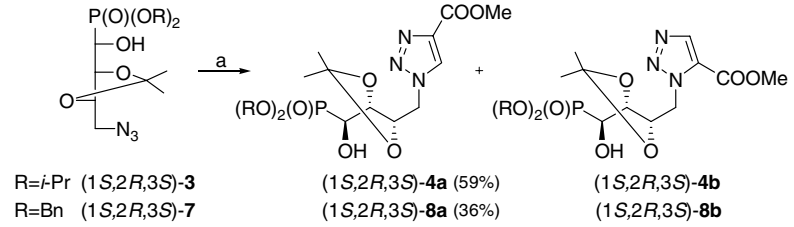
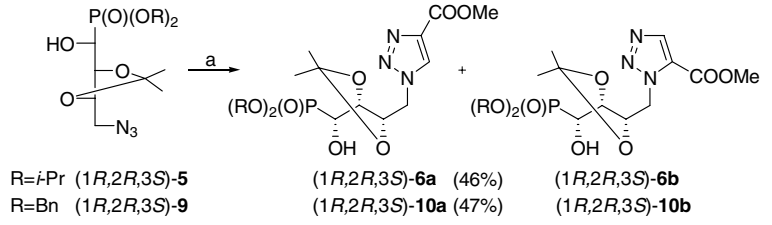


Figure 1.



Scheme 1. Reagents and conditions: (a) HC≡CCOOMe, toluene, reflux, 4 h.



Scheme 2. Reagents and conditions: (a) HC≡CCOOMe, toluene, reflux, 4 h.

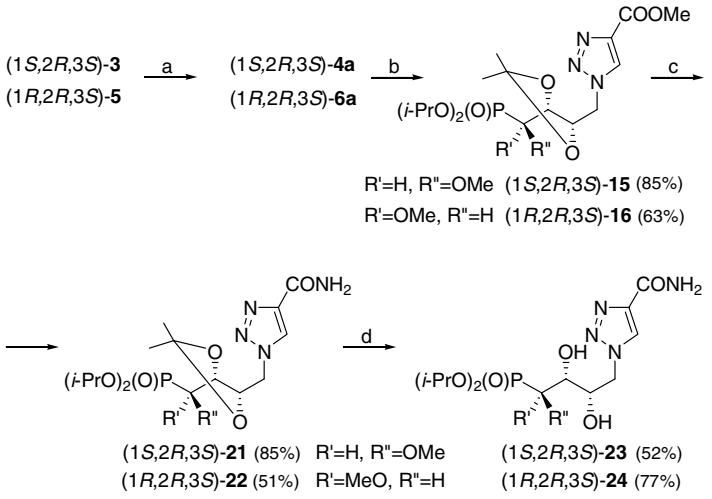
Table 1. Thermal versus CuCl-catalysed [2+3] cycloadditions of methyl propiolate and the azides **3**, **5**, **7**, **9**, **11** and **12**

Entry	Azide	CuCl (mol %)	1,2,3-Triazoles		Yield (%)
			4-COOMe	5-COOMe	
1	**3**	0[a]	**4a** (75)	**4b** (25)	**4a** (59)
		10[b]	**4a** (100)	**4b** (0)	**4a** (94)
2	**5**	0[a]	**6a** (75)	**6b** (25)	**6a** (46)
		10[b]	**6a** (100)	**6b** (0)	**6a** (99)
3	**7**	0[a]	**8a** (75)	**8b** (25)	**8a** (36)
		10[b]	**8a** (100)	**8b** (0)	**8a** (94)
4	**9**	0[a]	**10a** (75)	**10b** (25)	**10a** (47)
		10[b]	**10a** (100)	**10b** (0)	**10a** (99)
5	**11**	10[b]	**13** (100)		**13** (98)
6	**12**	10[b]	**14** (100)		**14** (92)

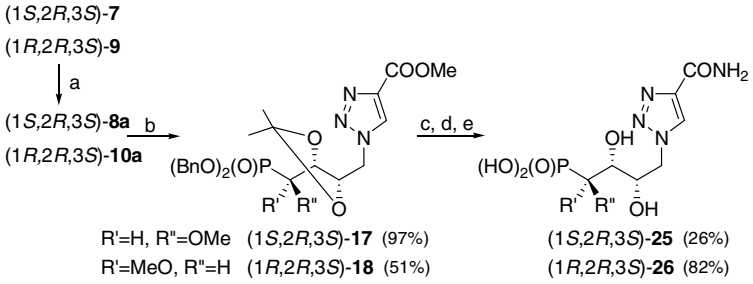
[a] In toluene at reflux, 4 h.
[b] In water at room temperature, 4 days.

(1*S*,2*R*,3*S*)-**8a** and (1*S*,2*R*,3*S*)-**8b** (Scheme 1) and (1*R*,2*R*,3*S*)-**10a** and (1*R*,2*R*,3*S*)-**10b** (Scheme 2). Attempts at separating mixtures of regioisomeric 1,2,3-triazoles **a** and **b** proved unsuccessful in all four cases. However, pure major products **4a**, **6a**, **8a** and **10a** were isolated by crystallisation. Structural assignments in regioisomers **a** are based on the observation that in thermal [2+3] cycloadditions of azides and propiolates, the 4-alkoxycarbonyl-1,2,3-triazoles were always formed as major isomers,[35–39] but primarily on our results in CuCl-catalysed cycloadditions, when 4-methoxycarbonyl-1,2,3-triazoles (1*S*,2*R*,3*S*)-**4a** or (1*R*,2*R*,3*S*)-**6a** (Scheme 3) and (1*S*,2*R*,3*S*)-**8a** or (1*R*,2*R*,3*S*)-**10a** (Scheme 4) were produced as single isomers. Yields (Table 1) of the purified products obtained in the catalysed reactions were significantly higher (94–99%) in comparison to yields of the major isomers from thermal processes (36–59%).

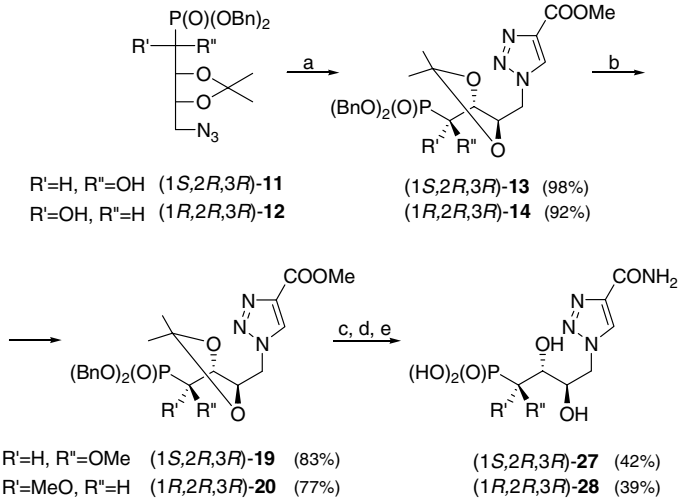
Dibenzyl 4-azido-1,2,3-trihydroxy-2,3-*O*-isopropylidene-butylphosphonates[34] (1*S*,2*R*,3*R*)-**11** and (1*R*,2*R*,3*R*)-**12** cleanly reacted with methyl propiolate in CuCl-catalysed reactions to produce only the respective 4-methoxycarbonyl-1,2,3-triazoles (1*S*,2*R*,3*R*)-**13** and (1*R*,2*R*,3*R*)-**14**, which were separated in very high yields (Scheme 5).



Scheme 3. Reagents and conditions: (a) HC≡CCOOMe, CuCl, water, rt, 4 days, yields: (1*S*,2*R*,3*S*)-**4a**—94% and (1*R*,2*R*,3*S*)-**6a**—99%; (b) MeI, Ag_2O, rt, 4 days; (c) 25% ammonia, rt, 5 days; (d) H_2O, Dowex 50W × 8 H^+, 75 °C, 2.5 h.



Scheme 4. Reagents and conditions: (a) HC≡CCOOMe, CuCl, water, rt, 4 days, yields: (1*S*,2*R*,3*S*)-**8a**—94% and (1*R*,2*R*,3*S*)-**10a**—99%; (b) MeI, Ag_2O, rt, 4 days; (c) 25% ammonia, rt, 5 days; (d) H_2O, Dowex 50W × 8 H^+, 75 °C, 2.5 h; (e) H_2, 10 % Pd–C, aqueous methanol, 48 h.

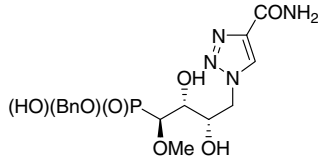


Scheme 5. Reagents and conditions: (a) HC≡CCOOMe, CuCl, water, rt, 4 days; (b) MeI, Ag_2O, rt, 4 days; (c) 25% ammonia, rt, 5 days; (d) H_2O, Dowex 50W × 8 H^+, 75 °C, 2.5 h; (e) H_2, 10% Pd–C, aqueous methanol, 48 h.

Due to our previous experience in the decomposition of α-hydroxyphosphonates during ammonolysis of alkoxycarbonyl groups,[30] the protection of HO–C-1 groups in phosphonates **4a**, **6a**, **8a 10a**, **13** and **14** was necessary. We were disappointed with the failure of benzylation and unsuccessful attempts at introducing the methoxyethoxymethyl (MEM) group. However, acetylation of HO–C-1 went smoothly and we concluded that the steric

bulkiness of the *O*,*O*-diisopropyl(dibenzyl)phosphoryl and isopropylidene groups prevented benzylation at HO–C-1. Finally, methylation of this group was accomplished in satisfactory yields to provide 1-methoxyphosphonates (1*S*,2*R*,3*S*)-**15** and (1*R*,2*R*,3*S*)-**16** (Scheme 3), (1*S*,2*R*,3*S*)-**17** and (1*R*,2*R*,3*S*)-**18** (Scheme 4) as well as (1*S*,2*R*,3*R*)-**19** and (1*R*,2*R*,3*R*)-**20** (Scheme 5).

The ammonolysis of the 4-methoxycarbonyl group in diisopropyl esters **15** and **16** was carried out in the presence of 25% ammonia and led to the formation of *O*,*O*-diisopropyl 4-(4-carbamoyl-1,2,3-triazole)phoshonates (1*S*,2*R*,3*S*)-**21** and (1*R*,2*R*,3*S*)-**22** in good yields (Scheme 3). When *O*,*O*-dibenzyl esters (1*S*,2*R*,3*S*)-**17** and (1*R*,2*R*,3*S*)-**18** (Scheme 4) and (1*S*,2*R*,3*R*)-**19** and (1*R*,2*R*,3*R*)-**20** (Scheme 5) were similarly treated with ammonia, complex reaction mixtures were produced as judged from ^{31}P NMR spectra. However, the ammonolysis was complete as evidenced by disappearance of the *Me*OOC resonances in ^{1}H NMR spectra. Opposite to *O*,*O*-diisopropyl esters **15** and **16**, but similar to *O*,*O*-dimethyl esters[30] in the presence of 25% ammonia, partial debenzylation of *O*,*O*-dibenzyl esters **17**–**20** took place. We were able to isolate *O*-benzyl (1*S*,2*R*,3*S*)-4-(4-carbamoyl-1,2,3-triazol-1-yl)-2,3-dihydroxy-1-methoxybutylphosphonic acid **29** by treating the crude product after the ammonolysis of (1*S*,2*R*,3*S*)-**17** with Dowex (H^+).



(1*S*,2*R*,3*S*)-**29**

Removal of the isopropylidene protecting groups from phosphonates **21** and **22** cleanly gave pure diisopropyl 4-(4-carbamoyl-1,2,3-triazol-1-yl)-2,3-dihydroxy-1-methoxybutylphosphonates (1*S*,2*R*,3*S*)-**23** and (1*R*,2*R*,3*S*)-**24** (Scheme 3).

The crude products obtained after ammonolysis of *O*,*O*-dibenzyl esters **17**–**20** (Schemes 4 and 5) were subjected to hydrolysis followed by catalytic hydrogenolysis of the benzyl groups to afford 4-(4-carbamoyl-1,2,3-triazol-1-yl)-2,3-dihydroxy-1-methoxybutylphosphonic acids (1*S*,2*R*,3*S*)-**25** and (1*R*,2*R*,3*S*)-**26** (Scheme 4), as well as (1*S*,2*R*,3*R*)-**27** and (1*R*,2*R*,3*R*)-**28** (Scheme 5).

3. Conclusions

Enantiomerically pure 4-(4-carbamoyl-1,2,3-triazol-1-yl)-2,3-dihydroxy-1-methoxybutylphosphonic acids (1*S*,2*R*,3*S*)-**25**, (1*R*,2*R*,3*S*)-**26**, (1*S*,2*R*,3*R*)-**27** and (1*R*,2*R*,3*R*)-**28** were synthesised from the respective dibenzyl 4-azido-1,2,3-trihydroxy-2,3-*O*-isopropylidenebutylphosphonates **7**, **9**, **11** and **12** in a sequence of reactions involving the CuCl-catalysed cycloaddition of methyl propiolate followed by a methylation of the HO–C-1 groups, ammonolysis and the removal of the protective groups by hydrolysis and hydrogenolysis.

Diisopropyl 4-(4-carbamoyl-1,2,3-triazol-1-yl)-2,3-dihydroxy-1-methoxybutylphosphonates (1*S*,2*R*,3*S*)-**23** and (1*R*,2*R*,3*S*)-**24** were obtained from diisopropyl 4-azido-1,2,3-trihydroxy-2,3-*O*-isopropylidenebutylphosphonates **3** and **5** by a similar sequence of reactions.

4. Experimental

^{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. However, ^{13}C NMR spectra in D_2O were taken on a Bruker DPX spectrometer at 62.9 MHz. 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 analyser. 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) or Kieselgel 60 silanisiert (70–230 mesh) (Merck Art. 7719); analytical TLC, Merck TLC plastic sheets silica gel 60 F_{254}.

4.1. Reaction of diisopropyl and dibenzyl 4-azido-1,2,3-trihydroxy-2,3-*O*-isopropylidenebutylphosphonates (1*S*,2*R*,3*S*)-3 and (1*R*,2*R*,3*S*)-5, and (1*S*,2*R*,3*S*)-7 and (1*R*,2*R*,3*S*)-9 with methyl propiolate in refluxing toluene (general procedure)

A solution of azidophosphonate (1.00 mmol) and methyl propiolate (2.00 mmol) in toluene (10 mL) was refluxed for 4 h. The reaction mixture was concentrated in vacuo and the residue was crystallised to give pure major regioisomers.

4.1.1. Diisopropyl (1*S*,2*R*,3*S*)-1,2,3-trihydroxy-2,3-*O*-isopropylidene-4-[(4-methoxycarbonyl)-1,2,3-triazol-1-yl]butylphosphonate, (1*S*,2*R*,3*S*)-4a. From (1*S*,2*R*,3*S*)-**3** (0.301 g, 0.860 mmol) and methyl propiolate (0.163 mL, 1.72 mmol) in toluene (2.0 mL), phosphonate (1*S*,2*R*,3*S*)-**4a** (0.221 g, 59%) was obtained as a white amorphous solid after crystallisation from ethyl acetate–chloroform, mp 212–213 °C; $[\alpha]_D^{20} = -29.6$ (c 1.06, $CHCl_3$). IR (KBr): $\nu = 3274$, 2980, 2953, 1732, 1245, 1220, 1001 cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta = 8.31$ (s, 1H), 4.92 (dd, $J = 14.4$, 2.7 Hz, 1H), 4.90–4.76 (m, 2H), 4.72 (dd, $J = 14.4$, 6.0 Hz, 1H), 4.54 (ddd, $J = 7.2$, 6.0, 2.7 Hz, 1H), 4.13–4.03 (m, 2H), 3.96 (s, 3H), 1.42–1.35 (m, 15H), 1.28 (s, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 161.3$, 139.9, 129.4, 110.4, 77.0 (d, $J = 6.6$ Hz), 75.7 (d, $J = 6.0$ Hz), 72.8 and 72.5 (2d, $J = 7.0$ Hz), 68.3 (d, $J = 163.8$ Hz), 52.6, 52.4, 27.3, 27.1, 24.5 and 24.4 and 24.3 and 24.2 (4d, $J = 5.3$ Hz). ^{31}P NMR ($CDCl_3$):

$\delta = 19.55$. Anal. Calcd for $C_{17}H_{30}N_3O_8P$: C, 46.89; H, 6.95; N, 9.65. Found: C, 46.83; H, 6.99; N, 9.42.

4.1.2. Diisopropyl (1*R*,2*R*,3*S*)-1,2,3-trihydroxy-2,3-*O*-isopropylidene-4-[(4-methoxycarbonyl)-1,2,3-triazol-1-yl]-butylphosphonate, (1*R*,2*R*,3*S*)-6a. From (1*R*,2*R*,3*S*)-**5** (0.171 g, 0.492 mmol) and methyl propiolate (0.097 mL, 0.98 mmol) in toluene (2.0 mL), phosphonate (1*R*,2*R*,3*S*)-**6a** (0.098 g, 46%) was obtained as a white amorphous solid after crystallisation from chloroform–hexane, mp 157–158 °C; $[\alpha]_D^{20} = -29.7$ (*c* 1.23, $CHCl_3$). IR (KBr): $\nu = 3227$, 2986, 2937, 1725, 1236, 1032, 1009 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 8.29$ (s, 1H), 4.90–4.70 (m, 2H), 4.79 (dd, $J = 14.4$, 2.7 Hz, 1H), 4.61 (dd, $J = 14.4$, 6.3 Hz, 1H), 4.45 (ddd, $J = 7.5$, 6.3, 2.7 Hz, 1H), 4.08 (ddd, $J = 7.5$, 4.5, 4.2 Hz, 1H), 3.96 (s, 3H), 3.84 (dd, $J = 11.4$, 4.2 Hz, 1H), 2.5–1.7 (br s, 1H) 1.42 (s, 3H), 1.39–1.35 (m, 12H), 1.33 (s, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 161.2$, 140.0, 129.2, 110.8, 77.3, 75.2 (d, $J = 9.2$ Hz), 72.6 and 72.3 (2d, $J = 7.0$ Hz), 67.5 (d, $J = 163.2$ Hz), 52.4, 51.8, 27.3, 27.1, 24.5 and 24.4 (2d, $J = 9.0$ Hz), 24.2 and 24.1 (2d, $J = 6.0$ Hz). ^{31}P NMR ($CDCl_3$): $\delta = 19.14$. Anal. Calcd for $C_{17}H_{30}N_3O_8P$: C, 46.89; H, 6.95; N, 9.65. Found: C, 46.70; H, 6.85; N, 9.47.

4.1.3. Dibenzyl (1*S*,2*R*,3*S*)-1,2,3-trihydroxy-2,3-*O*-isopropylidene-4-[(4-methoxycarbonyl)-1,2,3-triazol-1-yl]-butylphosphonate, (1*S*,2*R*,3*S*)-8a. From (1*S*,2*R*,3*S*)-**7** (1.346 g, 3.008 mmol) and methyl propiolate (0.535 mL, 6.02 mmol) in toluene (10.0 mL), phosphonate (1*S*,2*R*,3*S*)-**8a** (0.575 g, 36%) was obtained as a white amorphous solid after crystallisation from methanol, mp 186.5–187 °C; $[\alpha]_D^{20} = -16.7$ (*c* 1.08, $CHCl_3$). IR (KBr): $\nu = 3266$, 2986, 2980, 1725, 1237, 1056, 1039 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 8.21$ (s, 1H), 7.39–7.26 (m, 10H), 5.19–5.02 (m, 4H), 4.81 (dd, $J = 14.1$, 2.4 Hz, 1H), 4.59 (dd, $J = 14.1$, 6.6 Hz, 1H), 4.48 (ddd, $J = 7.5$, 6.6, 2.4 Hz, 1H), 4.14 (dd, $J = 8.1$, 5.4 Hz, 1H), 4.03 (ddd, $J = 7.5$, 5.4, 4.5 Hz, 1H), 3.95 (s, 3H), 3.7–3.5 (br s, 1H), 1.35 (s, 3H), 1.27 (s, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 161.3$, 139.9, 135.9, 135.8, 129.2, 128.8, 128.8, 128.7 128.4, 128.2, 110.7, 76.7, 76.4 (d, $J = 8.6$ Hz), 69.0 and 68.9 (2d, $J = 7.2$ Hz), 68.6 (d, $J = 161.9$ Hz), 52.6, 52.4, 27.3, 27.0. ^{31}P NMR ($CDCl_3$): $\delta = 22.48$. Anal. Calcd for $C_{25}H_{30}N_3O_8P$: C, 56.50; H, 5.69; N, 7.91. Found: C, 56.48; H, 5.53; N, 7.85.

4.1.4. Dibenzyl (1*R*,2*R*,3*S*)-1,2,3-trihydroxy-2,3-*O*-isopropylidene-4-[(4-methoxycarbonyl)-1,2,3-triazol-1-yl]-butylphosphonate, (1*R*,2*R*,3*S*)-10a. From (1*R*,2*R*,3*S*)-**9** (0.343 g, 0.767 mmol) and methyl propiolate (0.136 mL, 1.53 mmol) in toluene (5.0 mL), phosphonate (1*R*,2*R*,3*S*)-**10a** (0.193 g, 47%) was obtained as a white amorphous solid after crystallisation from ethyl acetate, mp 152.7–153.9 °C; $[\alpha]_D^{20} = -27.7$ (*c* 2.33, $CHCl_3$). IR (KBr): $\nu = 3262$, 3126, 2986, 1726, 1237, 1055, 1040 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 8.23$ (s, 1H), 7.38–7.26 (m, 10H), 5.18–5.03 (m, 4H), 4.69 (dd, $J = 14.1$, 2.4 Hz, 1H), 4.49 (dd, $J = 14.1$, 6.6 Hz, 1H), 4.42 (ddd, $J = 7.8$, 6.6, 2.4 Hz, 1H), 4.08 (ddd, $J = 7.8$, 4.4, 3.6 Hz, 1H), 3.96 (s, 3H), 3.94 (dd, $J = 11.0$, 3.6 Hz, 1H), 3.3–2.5 (br s, 1H), 1.36 (s, 3H), 1.32 (s, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 160.9$, 139.7, 136.0 and 135.9 (2d, $J = 7.6$ Hz), 129.0, 128.5, 128.5, 128.4 128.4, 128.0, 127.9, 110.8, 77.2, 74.7 (d, $J = 10.6$ Hz), 68.7 and 68.4 (2d, $J = 7.2$ Hz), 66.7 (d, $J = 163.1$ Hz), 52.3, 51.8, 27.2, 26.9. ^{31}P NMR ($CDCl_3$): $\delta = 22.08$. Anal. Calcd for $C_{25}H_{30}N_3O_8P$: C, 56.50; H, 5.69; N, 7.91. Found: C, 56.49; H, 5.75; N, 7.98.

4.2. Reaction of diisopropyl and dibenzyl 4-azido-1,2,3-trihydroxy-2,3-*O*-isopropylidenebutylphosphonates (1*S*,2*R*,3*S*)-3 and (1*R*,2*R*,3*S*)-5, and (1*S*,2*R*,3*S*)-7 and (1*R*,2*R*,3*S*)-9 with methyl propiolate in the presence of CuCl (general procedure)

A suspension of azidophosphonate (1.00 mmol), methyl propiolate (1.00 mmol) and CuCl (0.10 mmol) in water (10 mL) was stirred vigorously at room temperature for 4 days. The reaction mixture was extracted with methylene chloride (3×10 mL), dried over $MgSO_4$, filtered through a layer of Celite or short pad of silica gel, concentrated and the residue was crystallised to give pure products.

4.2.1. Diisopropyl (1*S*,2*R*,3*S*)-1,2,3-trihydroxy-2,3-*O*-isopropylidene-4-[(4-methoxycarbonyl)-1,2,3-triazol-1-yl]-butylphosphonate, (1*S*,2*R*,3*S*)-4a. From (1*S*,2*R*,3*S*)-**3** (0.100 g, 0.281 mmol), methyl propiolate (0.023 g, 0.28 mmol) and CuCl (3 mg, 0.03 mmol) in water (2.5 mL), phosphonate (1*S*,2*R*,3*S*)-**4a** (0.116 g, 94%) was obtained after crystallisation from ethyl acetate–chloroform.

4.2.2. Diisopropyl (1*R*,2*R*,3*S*)-1,2,3-trihydroxy-2,3-*O*-isopropylidene-4-[(4-methoxycarbonyl)-1,2,3-triazol-1-yl]-butylphosphonate, (1*R*,2*R*,3*S*)-6a. From (1*R*,2*R*,3*S*)-**5** (0.285 g, 0.811 mmol), methyl propiolate (0.068 g, 0.81 mmol) and CuCl (8 mg, 0.08 mmol) in water (6.0 mL), phosphonate (1*R*,2*R*,3*S*)-**6a** (0.348 g, 99%) was obtained after crystallisation from chloroform–hexane.

4.2.3. Dibenzyl (1*S*,2*R*,3*S*)-1,2,3-trihydroxy-2,3-*O*-isopropylidene-4-[(4-methoxycarbonyl)-1,2,3-triazol-1-yl]-butylphosphonate, (1*S*,2*R*,3*S*)-8a. From (1*S*,2*R*,3*S*)-**7** (0.220 g, 0.501 mmol), methyl propiolate (0.045 mL, 0.50 mmol) and CuCl (5 mg, 0.05 mmol) in water (2.0 mL), phosphonate (1*S*,2*R*,3*S*)-**8a** (0.246 g, 94%) was obtained after crystallisation from ethyl acetate–petroleum ether.

4.2.4. Dibenzyl (1*R*,2*R*,3*S*)-1,2,3-trihydroxy-2,3-*O*-isopropylidene-4-[(4-methoxycarbonyl)-1,2,3-triazol-1-yl]-butylphosphonate, (1*R*,2*R*,3*S*)-10a. From (1*R*,2*R*,3*S*)-**9** (0.138 g, 0.308 mmol), methyl propiolate (0.027 mL, 0.31 mmol) and CuCl (3 mg, 0.03 mmol) in water (1.0 mL), phosphonate (1*R*,2*R*,3*S*)-**10a** (0.162 g, 99%) was obtained after crystallisation from ethyl acetate.

4.2.5. Dibenzyl (1*S*,2*R*,3*R*)-1,2,3-trihydroxy-2,3-*O*-isopropylidene-4-[(4-methoxycarbonyl)-1,2,3-triazol-1-yl]-butylphosphonate, (1*S*,2*R*,3*R*)-13. From (1*S*,2*R*,3*R*)-**11** (0.316 g, 0.706 mmol), methyl propiolate (0.063 mL, 0.71 mmol) and CuCl (7 mg, 0.07 mmol) in water

(6.0 mL), phosphonate (1*S*,2*R*,3*R*)-**13** (0.368 g, 98%) was obtained as a white amorphous solid after crystallisation from ethyl acetate, mp 178–179 °C; $[\alpha]_D^{20} = +31.2$ (*c* 1.26, $CHCl_3$). IR (KBr): $\nu = 3282, 3110, 2992, 1730, 1225, 1034, 992\ cm^{-1}$. ^1H NMR ($CDCl_3$): $\delta = 8.16$ (s, 1H), 7.38–7.26 (m, 10H), 5.18–5.00 (m, 5H), 4.56–4.45 (m, 2H), 4.37 (dd, $J = 14.1$, 9.6 Hz, 1H), 4.12 (dd, $J = 8.7$, 5.7, Hz, 1H), 3.95 (s, 3H), 1.43 (s, 3H), 1.28 (s, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 161.3$, 139.9, 136.0 and 136.0 (2d, $J = 7.6$, Hz), 128.8, 128.7, 128.7 128.6, 128.1, 128.0, 110.3, 76.4 (d, $J = 12.1$ Hz), 75.6 (d, $J = 2.3$ Hz), 68.9 and 68.7 (2d, $J = 7.6$ Hz), 66.6 (d, $J = 162.3$ Hz), 52.3, 51.2, 28.2, 25.7. ^{31}P NMR ($CDCl_3$): $\delta = 23.56$. Anal. Calcd for $C_{25}H_{30}N_3O_8P$: C, 56.50; H, 5.69; N, 7.91. Found: C, 56.44; H, 5.57; N, 7.87.

4.2.6. Dibenzyl (1*R*,2*R*,3*R*)-1,2,3-trihydroxy-2,3-*O*-isopropylidene-4-[(4-methoxycarbonyl)-1,2,3-triazol-1-yl]-butylphosphonate, (1*R*,2*R*,3*R*)-14. From (1*R*,2*R*,3*R*)-**12** (0.248 g, 0.554 mmol), methyl propiolate (0.049 mL, 0.55 mmol) and CuCl (6 mg, 0.06 mmol) in water (5.0 mL), phosphonate (1*R*,2*R*,3*R*)-**14** (0.271 g, 92%) was obtained as a white amorphous solid after crystallisation from chloroform–petroleum ether, mp 171.6–173 °C; $[\alpha]_D^{20} = +15.3$ (*c* 1.65, $CHCl_3$). IR (KBr): $\nu = 3288, 3109, 2989, 1728, 1222, 1038, 994\ cm^{-1}$. ^1H NMR ($CDCl_3$): $\delta = 8.18$ (s, 1H), 7.39–7.26 (m, 10H), 5.19–5.03 (m, 4H), 4.74 (dd, $J = 13.5$, 1.8 Hz, 1H), 4.66–4.46 (m, 3H), 4.03 (ddd, $J = 13.5$, 9.9, 1.8 Hz, 1H), 3.95 (s, 3H), 2.96 (dd, $J = 9.9$, 4.8 Hz, 1H), 1.52 (s, 3H), 1.31 (s, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 161.2$, 140.0, 136.1 and 135.8 (2d, $J = 5.7$ Hz), 128.7, 128.2, 110.0, 76.2 (d, $J = 14.0$ Hz), 74.9, 68.9 and 68.6 (2d, $J = 7.1$ Hz), 66.8 (d, $J = 160.9$ Hz), 52.4, 52.0, 27.3, 24.9. ^{31}P NMR ($CDCl_3$): $\delta = 22.05$. Anal. Calcd for $C_{25}H_{30}N_3O_8P$: C, 56.50; H, 5.69; N, 7.91. Found: C, 56.77; H, 5.49; N, 7.90.

4.3. Methylation of 1-hydroxyphosphonates with MeI in the presence of Ag_2O (general procedure)

A suspension of 1-hydroxyphosphonates (1.00 mmol), methyl iodide (10 mmol) and silver(I) oxide (1.60 mmol) in chloroform (6 mL) was stirred vigorously at room temperature for 4 days. The reaction mixture was filtered through a layer of Celite, concentrated and the crude product was chromatographed on silica gel.

4.3.1. Diisopropyl (1*S*,2*R*,3*S*)-2,3-dihydroxy-2,3-*O*-isopropylidene-1-methoxy-4-[(4-methoxycarbonyl)-1,2,3-triazol-1-yl]butylphosphonate, (1*S*,2*R*,3*S*)-15. From (1*S*,2*R*,3*S*)-**4a** (0.822 g, 1.89 mmol), phosphonate (1*S*,2*R*,3*S*)-**15** (0.724 g, 85%) was obtained as a white amorphous solid after chromatography with chloroform–methanol (150:1, v/v), mp 96–97.5 °C; $[\alpha]_D^{20} = -28.4$ (*c* 1.43, $CHCl_3$). IR (KBr): $\nu = 3133, 2982, 2928, 1723, 1241, 997\ cm^{-1}$. ^1H NMR ($CDCl_3$): $\delta = 8.30$ (s, 1H), 4.89 (dd, $J = 14.4$, 2.7 Hz, 1H), 4.89–4.78 (m, 2H), 4.78 (dd, $J = 14.4$, 5.7 Hz, 1H), 4.59 (ddd, $J = 7.8$, 5.7, 2.7 Hz, 1H), 4.10 (ddd, $J = 7.8$, 2.6, 1.1 Hz, 1H), 3.95 (s, 3H), 3.74 (dd, $J = 13.2$, 2.6 Hz, 1H), 3.62 (d, $J = 0.8$ Hz, 3H), 1.42 (s, 3H), 1.40–1.36 (m, 12H), 1.27 (s, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 161.3$, 139.7, 129.4, 110.0, 77.6 (d, $J = 13.6$ Hz), 77.5 (d, $J = 166.9$ Hz), 74.2 (d, $J = 1.4$ Hz), 72.4 and 72.3 (2d, $J = 7.5$ Hz), 62.9 (d, $J = 4.3$ Hz), 52.3, 52.1, 27.3, 26.7, 24.5 (d, $J = 3.8$ Hz), 24.2 and 24.2 (2d, $J = 4.5$ Hz). ^{31}P NMR ($CDCl_3$): $\delta = 17.75$. Anal. Calcd for $C_{18}H_{32}N_3O_8P$: C, 48.10; H, 7.18; N, 9.35. Found: C, 48.35; H, 7.23; N, 9.16.

4.3.2. Diisopropyl (1*R*,2*R*,3*S*)-2,3-dihydroxy-2,3-*O*-isopropylidene-1-methoxy-4-[(4-methoxycarbonyl)-1,2,3-triazol-1-yl]butylphosphonate, (1*R*,2*R*,3*S*)-16. From (1*R*,2*R*,3*S*)-**6a** (0.186 g, 0.432 mmol), phosphonate (1*R*,2*R*,3*S*)-**16** (0.120 g, 63%) was obtained as a white amorphous solid after chromatography with chloroform–methanol (150:1, v/v), mp 75–76 °C; $[\alpha]_D^{20} = -26.5$ (*c* 1.40, $CHCl_3$). IR (KBr): $\nu = 3136, 2984, 2926, 1731, 1237, 998\ cm^{-1}$. ^1H NMR ($CDCl_3$): $\delta = 8.31$ (s, 1H), 4.87 (dd, $J = 14.4$, 2.7 Hz, 1H), 4.91–4.78 (m, 2H), 4.60 (dd, $J = 14.4$, 6.3 Hz, 1H), 4.49 (ddd, $J = 7.5$, 6.3, 2.7 Hz, 1H), 4.06 (ddd, $J = 7.5$, 6.6, 6.6 Hz, 1H), 3.96 (s, 3H), 3.61 (s, 3H), 3.47 (dd, $J = 9.9$, 6.6 Hz, 1H), 1.41 (s, 3H), 1.40–1.35 (m, 12H), 1.34 (s, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 161.2$, 139.9, 129.2, 110.8, 79.1 (d, $J = 158.6$ Hz), 77.9 (d, $J = 2.6$ Hz), 75.6 (d, $J = 3.0$ Hz), 72.6 and 72.2 (2d, $J = 6.8$ Hz), 61.8 (d, $J = 4.5$ Hz), 52.5, 52.4, 27.3, 27.1, 24.5 (d, $J = 3.0$ Hz), 24.3 (d, $J = 4.5$ Hz), 24.2 (d, $J = 5.3$ Hz). ^{31}P NMR ($CDCl_3$): $\delta = 18.24$. Anal. Calcd for $C_{18}H_{32}N_3O_8P$: C, 48.10; H, 7.18; N, 9.35. Found: C, 48.27; H, 7.25; N, 9.53.

4.3.3. Dibenzyl (1*S*,2*R*,3*S*)-2,3-dihydroxy-2,3-*O*-isopropylidene-1-methoxy-4-[(4-methoxycarbonyl)-1,2,3-triazol-1-yl]butylphosphonate, (1*S*,2*R*,3*S*)-17. From (1*S*,2*R*,3*S*)-**8a** (0.119 g, 0.224 mmol), phosphonate (1*S*,2*R*,3*S*)-**17** (0.118 g, 97%) was obtained as a colourless oil after chromatography with chloroform–methanol (100:1, v/v); $[\alpha]_D^{20} = -13.4$ (*c* 2.68, $CHCl_3$). IR (film): $\nu = 3129, 2989, 2952, 1723, 1240, 1009\ cm^{-1}$. ^1H NMR ($CDCl_3$): $\delta = 8.18$ (s, 1H), 7.39–7.26 (m, 10H), 5.19–5.01 (m, 4H), 4.74 (dd, $J = 14.4$, 3.6 Hz, 1H), 4.70 (dd, $J = 14.4$, 5.1 Hz, 1H), 4.54 (ddd, $J = 7.8$, 5.1, 3.6 Hz, 1H), 4.04 (ddd, $J = 7.8$, 3.0, 2.4 Hz, 1H), 3.96 (s, 3H), 3.78 (dd, $J = 12.0$, 3.0 Hz, 1H), 3.55 (d, $J = 1.0$ Hz, 3H), 1.38 (s, 3H), 1.25 (s, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 161.2$, 139.7, 135.9 (d, $J = 5.7$ Hz), 135.8 (d, $J = 5.4$ Hz), 129.2, 128.8, 128.7, 128.7, 128.5, 128.3, 110.2, 77.6 (d, $J = 166.1$ Hz), 77.2 (d, $J = 13.6$ Hz), 74.5 (d, $J = 3.0$ Hz), 68.8 and 68.7 (2d, $J = 6.8$ Hz), 62.7 (d, $J = 4.5$ Hz), 52.3, 52.0, 27.2, 26.7. ^{31}P NMR ($CDCl_3$): $\delta = 21.13$. Anal. Calcd for $C_{26}H_{32}N_3O_8P$: C, 57.25; H, 5.91; N, 7.70. Found: C, 57.38; H, 5.70; N, 7.71.

4.3.4. Dibenzyl (1*R*,2*R*,3*S*)-2,3-dihydroxy-2,3-*O*-isopropylidene-1-methoxy-4-[(4-methoxycarbonyl)-1,2,3-triazol-1-yl]butylphosphonate, (1*R*,2*R*,3*S*)-18. From (1*R*,2*R*,3*S*)-**10a** (0.235 g, 0.442 mmol), phosphonate (1*R*,2*R*,3*S*)-**18** (0.122 g, 51%) was obtained as a colourless oil after chromatography with chloroform–methanol (100:1, v/v); $[\alpha]_D^{20} = -8.3$ (*c* 1.53, $CHCl_3$). IR (film): $\nu = 3138, 2988, 2950, 1730, 1236, 1017\ cm^{-1}$. ^1H NMR ($CDCl_3$): $\delta = 8.21$ (s, 1H), 7.39–7.31 (m, 10H), 5.16–5.01 (m, 4H), 4.79–4.68 (m, 1H), 4.56–4.43 (m, 2H),

4.12–4.02 (m, 1H), 3.96 (s, 3H), 3.55 (dd, $J = 9.6$, 6.0 Hz, 1H), 3.54 (d, $J = 0.6$ Hz, 3H), 1.35 (s, 3H), 1.31 (s, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 161.2$, 140.0, 136.0 (d, $J = 5.4$ Hz), 135.9 (d, $J = 5.7$ Hz), 129.1, 128.7, 128.4, 128.3, 110.6, 78.6 (d, $J = 158.0$ Hz), 77.5 (d, $J = 11.3$ Hz), 75.3 (d, $J = 4.5$ Hz), 69.0 and 68.3 (2d, $J = 6.9$ Hz), 61.8 (d, $J = 4.0$ Hz), 52.4, 52.3, 27.3, 27.0. ^{31}P NMR ($CDCl_3$): $\delta = 21.14$. Anal. Calcd for $C_{26}H_{32}N_3O_8P \times 0.5H_2O$: C, 56.32; H, 6.00; N, 7.58. Found: C, 56.51; H, 6.04; N, 7.56.

4.3.5. Dibenzyl (1*S*,2*R*,3*R*)-2,3-dihydroxy-2,3-*O*-isopropylidene-1-methoxy-4-[(4-methoxycarbonyl)-1,2,3-triazol-1-yl]butylphosphonate, (1*S*,2*R*,3*R*)-19. From (1*S*,2*R*,3*R*)-**13** (0.368 g, 0.692 mmol), phosphonate (1*S*,2*R*,3*R*)-**19** (0.316 g, 83%) was obtained as a white powder after chromatography with chloroform–methanol (50/1, v/v) followed by crystallisation from ethyl acetate–petroleum ether, mp 106.4–106.6 °C; $[\alpha]_D^{20} = +54.4$ (*c* 1.19, $CHCl_3$). IR (KBr): $\nu = 3131$, 2990, 2952, 1726, 1230, 1010 cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta = 8.01$ (s, 1H), 7.40–7.26 (m, 10H), 5.18–4.92 (m, 5H), 4.46–4.32 (m, 3H), 3.95 (s, 3H), 3.90 (dd, $J = 12.0$, 3.9 Hz, 1H), 3.55 (d, $J = 1.0$ Hz, 3H), 1.50 (s, 3H), 1.26 (s, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 161.3$, 139.9, 135.8 (d, $J = 5.3$ Hz), 128.9, 128.8, 128.8, 128.5, 128.5, 128.3, 109.3, 76.9 (d, $J = 165.2$ Hz), 76.3 (d, $J = 3.7$ Hz), 76.1 (d, $J = 12.3$ Hz), 68.7 and 68.6 (2d, $J = 7.2$ Hz), 62.1 (d, $J = 4.5$ Hz), 52.3, 52.3, 28.3, 25.7. ^{31}P NMR ($CDCl_3$): $\delta = 21.81$. Anal. Calcd for $C_{26}H_{32}N_3O_8P$: C, 57.25; H, 5.91; N, 7.70. Found: C, 57.09; H, 5.76; N, 7.78.

4.3.6. Dibenzyl (1*R*,2*R*,3*R*)-2,3-dihydroxy-2,3-*O*-isopropylidene-1-methoxy-4-[(4-methoxycarbonyl)-1,2,3-triazol-1-yl]butylphosphonate, (1*R*,2*R*,3*R*)-20. From (1*R*,2*R*,3*R*)-**14** (0.204 g, 0.384 mmol), phosphonate (1*R*,2*R*,3*R*)-**20** (0.162 g, 77%) was obtained as a colourless oil after chromatography with chloroform–methanol (100:1, v/v); $[\alpha]_D^{20} = +27.3$ (*c* 3.8, $CHCl_3$). IR (film): $\nu = 3201$, 2992, 2954, 1734, 1241, 1008 cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta = 8.08$ (s, 1H), 7.42–7.26 (m, 10H), 5.20–5.04 (m, 4H), 4.67 (dd, $J = 12.6$, 1.5 Hz, 1H), 4.57 (ddd, $J = 10.2$, 5.7, 4.5Hz, 1H), 4.47 (dd, $J = 12.6$, 9.6 Hz, 1H), 4.40 (ddd, $J = 9.6$, 4.5, 1.5 Hz, 1H), 3.96 (s, 3H), 3.72 (dd, $J = 8.4$, 5.7 Hz, 1H), 3.58 (d, $J = 1.2$ Hz, 3H), 1.53 (s, 3H), 1.31 (s, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 161.2$, 140.0, 135.9 (d, $J = 5.3$ Hz), 135.8 (d, $J = 5.7$ Hz), 128.8, 128.7, 128.5, 128.4, 128.3, 110.0, 76.5 (d, $J = 160.9$ Hz), 76.1 (d, $J = 6.9$ Hz), 75.8 (d, $J = 7.7$ Hz), 68.9 and 68.5 (2d, $J = 6.9$ Hz), 60.9 (d, $J = 2.6$ Hz), 52.3, 51.7, 27.9, 25.6. ^{31}P NMR ($CDCl_3$): $\delta = 21.40$. Anal. Calcd for $C_{26}H_{32}N_3O_8P$: C, 57.25; H, 5.91; N, 7.70. Found: C, 57.04; H, 5.90; N, 7.47.

4.4. Diisopropyl (1*S*,2*R*,3*S*)-4-(4-carbamoyl-1,2,3-triazol-1-yl)-2,3-dihydroxy-2,3-*O*-isopropylidene-1-methoxybutylphosphonate, (1*S*,2*R*,3*S*)-21

A solution of phosphonate (1*S*,2*R*,3*S*)-**15** (0.750 g, 1.67 mmol) in methanol (3 mL) containing 25% ammonia (10 mL) was left at room temperature for 5 days. All volatiles were removed in vacuo and the residue chromatographed on a silica gel column with chloroform–methanol (50:1, v/v) to give (1*S*,2*R*,3*S*)-**21** (0.489 g, 85%) as a white powder after crystallisation from ethyl acetate–hexane, mp 106–107 °C; $[\alpha]_D^{20} = -26.3$ (*c* 2.51, $CHCl_3$). IR (KBr): $\nu = 3437$, 3245, 3199, 2987, 2933, 1692, 1657, 1248, 1006, 979 cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta = 8.31$ (s, 1H), 7.07 and 5.70 (2 × br s, 2H), 4.94 (dd, $J = 13.8$, 2.4 Hz, 1H), 4.91–4.79 (m, 2H), 4.66 (dd, $J = 13.8$, 6.6 Hz, 1H), 4.58 (ddd, $J = 7.5$, 6.6, 2.4 Hz, 1H), 4.12 (ddd, $J = 7.5$, 2.4, 1.2 Hz, 1H), 3.74 (dd, $J = 12.6$, 2.4 Hz, 1H), 3.63 (d, $J = 1.0$ Hz, 3H), 1.41 (s, 3H), 1.41–1.36 (m, 12H), 1.31 (s, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 162.4$, 142.5, 127.5, 110.1, 77.8 (d, $J = 15.8$ Hz), 77.5 (d, $J = 166.9$ Hz), 74.4 (d, $J = 2.0$ Hz), 72.3 and 72.2 (2d, $J = 7.6$ Hz), 62.7 (d, $J = 5.3$ Hz), 52.5, 27.3, 26.7, 24.5 (d, $J = 3.8$ Hz), 24.4 (d, $J = 3.5$ Hz), 24.2 and 24.1 (2 × d, $J = 5.4$ Hz). ^{31}P NMR ($CDCl_3$): $\delta = 18.41$. Anal. Calcd for $C_{17}H_{31}N_4O_7P$: C, 46.99; H, 7.20; N, 12.90. Found: C, 46.82; H, 7.23; N, 13.06.

4.4.1. Diisopropyl (1*R*,2*R*,3*S*)-4-(4-carbamoyl-1,2,3-triazol-1-yl)-2,3-dihydroxy-2,3-*O*-isopropylidene-1-methoxybutylphosphonate, (1*R*,2*R*,3*S*)-22. In a similar method as described in Section 4.4. from (1*R*,2*R*,3*S*)-**16** (0.120 g, 0.270 mmol) dissolved in methanol (4 mL) containing ammonia (6 mL), phosphonate (1*R*,2*R*,3*S*)-**22** (0.059 g, 51%) was obtained as a white powder after crystallisation from ethyl acetate–hexane, mp 140–141 °C; $[\alpha]_D^{20} = -34.0$ (*c* 1.1, $CHCl_3$). IR (KBr): $\nu = 3443$, 3197, 3098, 2982, 2936, 1631, 1242, 1027, 996 cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta = 8.31$ (s, 1H), 7.06 and 5.68 (2 × br s, 2H), 4.88 (dd, $J = 13.8$, 2.1 Hz, 1H), 4.85–4.77 (m, 2H), 4.55 (dd, $J = 13.8$, 6.9 Hz, 1H), 4.48 (ddd, $J = 7.5$, 6.9, 1.8 Hz, 1H), 4.08 (ddd, $J = 7.5$, 6.6, 6.3 Hz, 1H), 3.62 (d, $J = 1.0$ Hz, 3H), 3.47 (dd, $J = 9.6$, 6.6 Hz, 1H), 1.41 (s, 3H), 1.40–1.35 (m, 12H), 1.35 (s, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 162.2$, 142.7, 127.4, 110.4, 78.9 (d, $J = 163.8$ Hz), 78.1 (d, $J = 9.1$ Hz), 75.5 (d, $J = 3.8$ Hz), 72.4 and 72.0 (2 × d, $J = 7.2$ Hz), 61.7 (d, $J = 4.5$ Hz), 52.6, 27.3, 27.1, 24.4 (d, $J = 3.0$ Hz), 24.3 (d, $J = 4.5$ Hz), 24.1 (d, $J = 5.3$ Hz). ^{31}P NMR ($CDCl_3$): $\delta = 18.29$. Anal. Calcd for $C_{17}H_{31}N_4O_7P$: C, 46.99; H, 7.20; N, 12.90. Found: C, 46.79; H, 6.89; N, 12.76.

4.5. Diisopropyl (1*S*,2*R*,3*S*)-4-(4-carbamoyl-1,2,3-triazol-1-yl)-2,3-dihydroxy-1-methoxybutylphosphonate, (1*S*,2*R*,3*S*)-23

A solution of phosphonate (1*S*,2*R*,3*S*)-**21** (0.229 g, 0.987 mmol) in aqueous dioxane (20 mL, 3:1, v/v) was stirred with Dowex 50W × 8 H^+ (1.0 g) at 75 °C for 1.5 h. After filtration, the solution was concentrated in vacuo and the residue chromatographed on a silica gel column with chloroform–methanol (25:1, v/v) to give (1*S*,2*R*,3*S*)-**23** (0.109 g, 52%) as a white amorphous solid, mp 169–170 °C; $[\alpha]_D^{20} = +6.8$ (*c* 1.1, CH_3OH). IR (KBr): $\nu = 3484$, 3299, 3093, 2984, 2939, 1649, 1620, 1223, 998 cm^{-1}. ^{1}H NMR (CD_3OD): $\delta = 8.41$ (s, 1H), 4.82–4.70 (m, 2H), 4.62 (dd, $J = 13.8$, 4.8 Hz, 1H), 4.54 (dd, $J = 13.8$, 8.7 Hz, 1H), 4.20 (ddd, $J = 8.7$, 4.8, 1.5 Hz, 1H), 3.75 (ddd, $J = 9.0$, 9.0, 1.5 Hz, 1H), 3.59 (dd, $J = 9.0$, 3.9 Hz, 1H), 3.52 (d, $J = 1.0$ Hz, 3H),

1.36 (d, $J = 6.9$ Hz, 9H), 1.33 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (CD_3OD): $\delta = 164.7$, 143.5, 128.7, 79.0 (d, $J = 166.6$ Hz), 73.2 and 73.2 (2 × d, $J = 7.2$ Hz), 71.7 (d, $J = 4.5$ Hz), 70.2 (d, $J = 10.6$ Hz), 61.6 (d, $J = 2.3$ Hz), 54.9, 24.7 and 24.7 (2 × d, $J = 3.8$ Hz), 24.4 and 24.4 (2 × d, $J = 3.0$ Hz). ^{31}P NMR (CD_3OD): $\delta = 22.47$. Anal. Calcd for $C_{14}H_{27}N_4O_7P \times 0.25\ H_2O$: C, 42.16; H, 6.95; N, 14.05. Found: C, 42.30; H, 6.93; N, 13.83.

4.5.1. Diisopropyl (1*R*,2*R*,3*S*)-4-(4-carbamoyl-1,2,3-triazol-1-yl)-2,3-dihydroxy-1-methoxybutylphosphonate, (1*R*,2*R*,3*S*)-24. In a similar method as described in Section 4.5. from (1*R*,2*R*,3*S*)-**22** (0.127 g, 0.290 mmol), phosphonate (1*R*,2*R*,3*S*)-**24** (0.088 g, 77%) was obtained as a white powder, mp 163–164 °C; $[\alpha]_D^{20} = -1.1$ (*c* 1.8, $CHCl_3$). IR (KBr): $\nu = 3405$, 3205, 2978, 2928, 1636, 1212, 1108, 993 cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta = 8.30$ (s, 1H), 7.05 and 5.96 (2 × br s, 2H), 4.85–4.72 (m, 2H), 4.66 (dd, $J = 13.8$, 3.9 Hz, 1H), 4.54 (dd, $J = 13.8$, 8.1 Hz, 1H), 4.36 (ddd, $J = 8.1$, 3.6, 2.4 Hz, 1H), 3.83 (ddd, $J = 15.3$, 6.0, 2.4 Hz, 1H), 3.65 (dd, $J = 8.1$, 6.0 Hz, 1H), 3.58 (s, 3H), 3.2–2.8 (br s, 2H), 1.36 (d, $J = 6.3$ Hz, 9H), 1.34 (d, $J = 6.3$ Hz, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 168.3$, 143.3, 127.6, 78.8 (d, $J = 163.1$ Hz), 72.7 and 72.2 (2 × d, $J = 7.6$ Hz), 70.7 (d, $J = 6.0$ Hz), 69.6 (d, $J = 5.3$ Hz), 61.3 (d, $J = 3.8$ Hz), 53.8, 24.5 and 24.4 and 24.3 and 24.2 (4 × d, $J = 4.9$ Hz). ^{31}P NMR ($CDCl_3$): $\delta = 20.55$. Anal. Calcd for $C_{14}H_{27}N_4O_7P$: C, 42.64; H, 6.90; N, 14.21. Found: C, 42.80; H, 6.62; N, 13.93.

4.6. 4-(4-Carbamoyl-1,2,3-triazol-1-yl)-2,3-dihydroxy-1-methoxybutylphosphonic acids 25, 26, 27 and 28 (general procedure)

A solution of phosphonate (**17**–**20**, 1.00 mmol) in methanol (2 mL) containing 25% ammonia (7 mL) was left at room temperature for 5 days. All volatiles were removed in vacuo and the residue dissolved in aqueous methanol (20 mL, 1:3, v/v) and stirred with Dowex 50W × 8 H^+ (1.0 g) at 75 °C for 1.5 h. After filtration, the solution was concentrated in vacuo and the residue was dissolved in methanol (30 mL). After addition of water (15 mL) and 10% Pd–C (12 mg) the suspension was stirred under hydrogen atmosphere for 24 h. Removal of the catalyst by filtration through a layer of Celite and concentration of the solution gave crude products, which were chromatographed on silanised silica gel using water and finally crystallised.

4.6.1. (1*S*,2*R*,3*S*)-4-(4-Carbamoyl-1,2,3-triazol-1-yl)-2,3-dihydroxy-1-methoxybutylphosphonic acid, (1*S*,2*R*,3*S*)-25. From (1*S*,2*R*,3*S*)-**17** (0.337 g, 0.618 mmol), phosphonic acid (1*S*,2*R*,3*S*)-**25** (0.050 g, 26%) was obtained as a white powder after crystallisation from aqueous ethanol, which decomposed above 230 °C; $[\alpha]_D^{20} = -64.6$ (*c* 0.89, water). IR (KBr): $\nu = 3365$, 2967, 2923, 1653, 1233, 1050 cm^{-1}. ^{1}H NMR (D_2O): $\delta = 8.46$ (s, 1H), 4.80–4.60 (m, 2H), 4.35–4.25 (m, 1H), 3.90–3.80 (m, 1H), 3.60–3.45 (m, 1H), 3.50 (s, 3H). ^{13}C NMR (69.5 MHz, D_2O): $\delta = 162.5$, 139.6, 126.2, 76.4 (d, $J = 154.9$ Hz), 68.6, 67.1, 58.6, 52.1. ^{31}P NMR (D_2O): $\delta = 18.64$. Anal. Calcd for $C_8H_{15}N_4O_7P \times 3\ H_2O$: C, 26.39; H, 5.81; N, 15.38. Found: C, 26.21; H, 5.90; N, 15.09.

4.6.2. (1*R*,2*R*,3*S*)-4-(4-Carbamoyl-1,2,3-triazol-1-yl)-2,3-dihydroxy-1-methoxybutylphosphonic acid, (1*R*,2*R*,3*S*)-26. From (1*R*,2*R*,3*S*)-**18** (0.113 g, 0.207 mmol), phosphonic acid (1*R*,2*R*,3*S*)-**26** (0.053 g, 82%) was obtained as a white powder after crystallisation from aqueous ethanol, which decomposed above 230 °C; $[\alpha]_D^{20} = -19.6$ (*c* 1.01, water). IR (KBr): $\nu = 3358$, 2961, 2914, 1647, 1239, 1045 cm^{-1}. ^{1}H NMR (D_2O): $\delta = 8.46$ (s, 1H), 4.80–4.50 (m, 2H), 4.45–4.30 (m, 1H), 3.95–3.80 (m, 1H), 3.60–3.45 (m, 1H), 3.54 (s, 3H). ^{13}C NMR (69.5 MHz, D_2O): $\delta = 162.5$, 139.6, 126.2, 77.3 (d, $J = 150.8$ Hz), 69.7, 68.3, 58.6, 51.6. ^{31}P NMR (D_2O): $\delta = 17.60$. Anal. Calcd for $C_8H_{15}N_4O_7P \times 3\ H_2O$: C, 26.39; H, 5.81; N, 15.38. Found: C, 26.29; H, 6.01; N, 15.13.

4.6.3. (1*S*,2*R*,3*R*)-4-(4-Carbamoyl-1,2,3-triazol-1-yl)-2,3-dihydroxy-1-methoxybutylphosphonic acid, (1*S*,2*R*,3*R*)-27. From (1*S*,2*R*,3*R*)-**19** (0.501 g, 0.918 mmol), phosphonic acid (1*S*,2*R*,3*R*)-**27** (0.119 g, 42%) was obtained as a white powder after crystallisation from aqueous ethanol, which decomposed above 230 °C; $[\alpha]_D^{20} = +12.4$ (*c* 0.84, water). IR (KBr): $\nu = 3363$, 2958, 2927, 1655, 1242, 1054 cm^{-1}. ^{1}H NMR (D_2O): $\delta = 8.42$ (s, 1H), 4.85–4.75 (m, 1H), 4.55 (dd, $J = 14.3$, 8.6 Hz, 1H), 4.34 (ddd, $J = 8.6$, 5.7, 3.4 Hz, 1H), 3.92 (ddd, $J = 9.9$, 5.7, 4.4 Hz, 1H), 3.58 (dd, $J = 10.9$, 4.4 Hz, 1H), 3.51 (s, 3H). ^{13}C NMR (69.5 MHz, D_2O): $\delta = 162.6$, 139.6, 126.3, 78.2 (d, $J = 151.7$ Hz), 70.5 (d, $J = 6.4$ Hz), 68.3, 58.5, 51.2. ^{31}P NMR (D_2O): $\delta = 16.52$. Anal. Calcd for $C_8H_{15}N_4O_7P \times H_2O$: C, 29.27; H, 5.22; N, 17.07. Found: C, 29.10; H, 5.27; N, 17.36.

4.6.4. (1*R*,2*R*,3*R*)-4-(4-Carbamoyl-1,2,3-triazol-1-yl)-2,3-dihydroxy-1-methoxybutylphosphonic acid, (1*R*,2*R*,3*R*)-28. From (1*R*,2*R*,3*R*)-**20** (0.162 g, 0.297 mmol), phosphonic acid (1*R*,2*R*,3*R*)-**28** (0.036 g, 39%) was obtained as a white powder after crystallisation from aqueous acetone, which decomposed above 230 °C; $[\alpha]_D^{20} = +7.7$ (*c* 0.83, water). IR (KBr): $\nu = 3360$, 2973, 2920, 1659, 1228, 1049 cm^{-1}. ^{1}H NMR (D_2O): $\delta = 8.46$ (s, 1H), 4.90–4.75 (m, 1H), 4.56 (dd, $J = 14.2$, 7.8 Hz, 1H), 4.12 (dd, $J = 8.4$, 7.8 Hz, 1H), 3.79 (d, $J = 8.4$, Hz, 1H), 3.68 (d, $J = 9.3$, Hz, 1H), 3.53 (s, 3H). ^{13}C NMR (69.5 MHz, D_2O): $\delta = 162.6$, 139.6, 126.4, 75.3 (d, $J = 151.0$ Hz), 70.2, 67.3 (d, $J = 9.4$ Hz), 59.0, 51.8. ^{31}P NMR (D_2O): $\delta = 18.76$. Anal. Calcd for $C_8H_{15}N_4O_7P \times 1.25\ H_2O$: C, 28.89; H, 5.45; N, 16.83. Found: C, 28.95; H, 5.16; N, 16.82.

4.7. *O*-Benzyl (1*S*,2*R*,3*S*)-4-(4-carbamoyl-1,2,3-triazol-1-yl)-2,3-dihydroxy-1-methoxybutylphosphonic acid, (1*S*,2*R*,3*S*)-29

Phosphonate (1*S*,2*R*,3*S*)-**17** (0.337 g, 0.579 mmol) was treated with 25% ammonia (4 mL) as described in Section 4.6. After hydrolysis of the isopropylidene group

(Section 4.6.), the crude product was crystallised from methanol–chloroform to give (1*S*,2*R*,3*S*)-**29** (0.108 g, 48%) as a white amorphous solid, mp 170.6–171.5 °C; $[\alpha]_D^{20} = -8.5$ (*c* 1.01, DMSO). IR (KBr): $\nu = 3413$, 3210, 2958, 2921, 1654, 1108, 996 cm^{-1}. ^1H NMR (CD_3OD): $\delta = 8.40$ (s, 1H), 7.44–7.27 (m, 5H), 5.12 (d, $J = 7.2$ Hz, 2H), 4.62 (dd, $J = 13.8$, 4.8 Hz, 1H), 4.56 (dd, $J = 13.8$, 8.4 Hz, 1H), 4.22 (dd, $J = 8.4$, 4.8 Hz, 1H), 3.80 (dd, $J = 9.0$, 9.0 Hz, 1H), 3.65 (dd, $J = 9.0$, 3.9 Hz, 1H), 3.51 (s, 3H). ^{13}C NMR (CD_3SOCD_3): $\delta = 161.5$, 142.4, 137.6 (d, $J = 6.3$ Hz), 128.1, 127.5, 127.2, 127.2, 76.9 (d, $J = 158.3$ Hz), 70.1 (d, $J = 3.0$ Hz), 68.7 (d, $J = 10.3$ Hz), 66.2 (d, $J = 6.0$ Hz), 59.9 (d, $J = 2.3$ Hz), 53.3. ^{31}P NMR (CD_3OD): $\delta = 23.53$. Anal. Calcd for $C_{15}H_{21}N_4O_7P \times 0.5\ H_2O$: C, 44.01; H, 5.41; N, 13.69. Found: C, 43.80; H, 5.12; N, 13.41.

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