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Synthesis of (1*R*,2*S*)- and (1*S*,2*S*)-3-(4-carbamoyl-1,2,3-triazol-1-yl)-1,2-dihydroxypropylphosphonates

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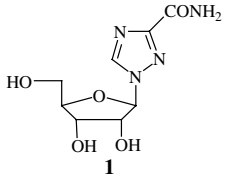
Abstract—Good regioselectivity (86:14 and 80:20) was observed in the 1,3-dipolar cycloaddition of methyl propiolate to diastereoisomeric dimethyl (1*R*,2*S*)- and (1*S*,2*S*)-3-azido-2-benzyloxy-1-hydroxypropylphosphonates. The major 4-methoxycarbonyl regioisomers were transformed into *O*-methyl (1*R*,2*S*)- and (1*S*,2*S*)-3-(4-carbamoyl-1,2,3-triazol-1-yl)-1,2-dihydroxypropylphosphonic acids, structural analogues of ribavirin.

1. Introduction

In the search for more effective antiviral and antitumour agents, various modifications of nucleotides have been proposed.[1] For over three decades, many nucleotide analogues have been studied, in which nucleobases were replaced by heterocyclic moieties of diverse degree of stereo and electronic similarities to those found in Nature. Subsequently, the sugar portion of the nucleotide has also been the subject of intensive studies leading to an array of modified structures having acyclic, carbocyclic and other saturated heterocyclic systems instead of the ribofuranoside ring. These studies led to the discovery of several drugs effective against HIV and other viruses.

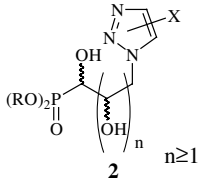
Among these nucleosides mimics, ribavirin **1** plays a special role, since it contains an unusual 3-carbamoyl-1,2,4-triazole group.[2] This compound is a synthetic nucleoside structurally related to inosine and guanosine, which has been used against various viral infections since its approval by FDA in 1986. Detailed studies proved that intracellular conversion of ribavirin into 5′-*O*-triphosphate is required to obtain the active form of the drug.[3] Other 1,2,4-triazole derivatives have recently been shown to act as nonnucleoside reverse transcriptase inhibitors.[4]



1

Substituted 1,2,3-triazoles, easily available from organic azides and acetylenic compounds via [2 + 3] cycloaddition,[5] have enjoyed a continuous interest due to several applications in industry and medicine.[6–22] Syntheses of N-glycosides or other sugar derivatives having substituted 1,2,3-triazole ring instead of nucleobases have been especially an active area of research, since they may act as nucleoside mimics.[6,13–22]

Combining the ideas of unnatural nucleobases, acyclic replacements for the furanose ring and the introduction of a nonhydrolysable C–P bond[23] instead of the O–P phosphate linkage, we designed molecules of general formula **2**.



2 n≥1

Recent papers on 4-(1,2,3-triazole)carboxamide nucleoside analogues **3**[13], **4**[14] and especially **5**[15] (Fig. 1) have

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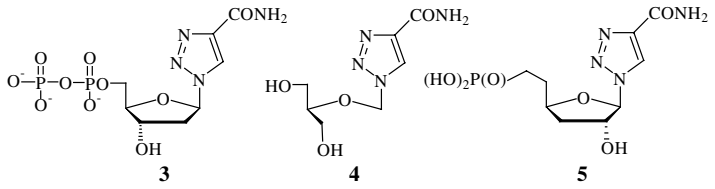
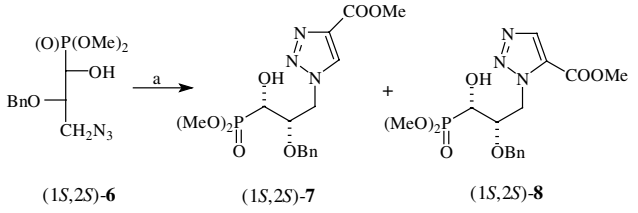


Figure 1. Recent examples of 4-(1,2,3-triazole)carboxamide nucleoside analogues.

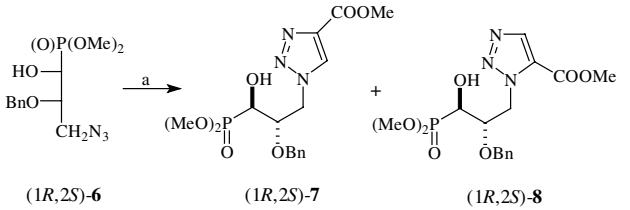
prompted us to report the synthesis of enantiomerically pure 1,2-dihydroxypropylphosphonates substituted at C(3) with a 1,2,3-triazole ring functionalised with the methoxycarbonyl and carbamoyl groups.

2. Results and discussion

A [2 + 3] cycloaddition of 3-azidophosphonates (1*S*,2*S*)-**6** and (1*R*,2*S*)-**6**[24] and methyl propiolate was carried out at 110 °C according to the standard procedure (Schemes 1 and 2).[20] Examination of the crude products by ^{31}P NMR revealed the formation of regioisomeric pairs (1*S*,2*S*)-**7** and (1*S*,2*S*)-**8**, and (1*R*,2*S*)-**7** and (1*R*,2*S*)-**8** in 80:20 and 86:14 ratios, respectively. The mixtures were separated on silica gel to give pure products in good yields.



Scheme 1. Reagents and conditions: (a) HC≡CCOOMe, toluene, 110 °C, 4 h.



Scheme 2. Reagents and conditions: (a) HC≡CCOOMe, toluene, 110 °C, 4 h.

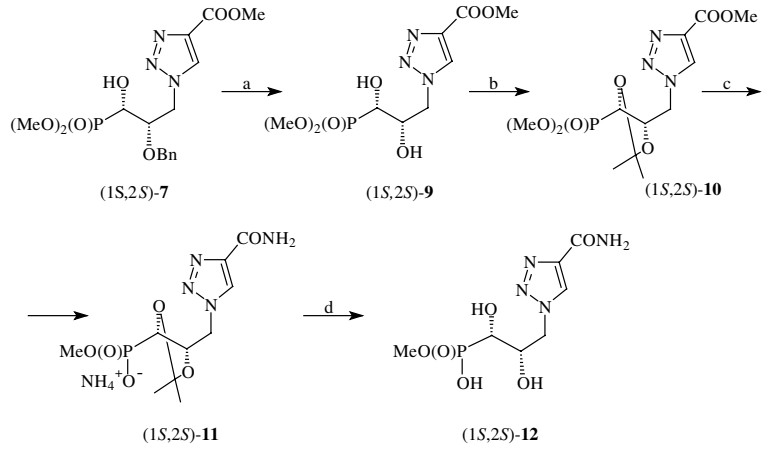
Structural assignment of (1*S*,2*S*)-**8** as a 5-methoxycarbonyl substituted 1,2,3-triazole was based on the deshielding of H_aH_bCN protons in the ^{1}H NMR spectrum of this compound (by ca. 0.4 ppm) in comparison with the 4-methoxycarbonyl isomer (1*S*,2*S*)-**7**. The same relationship was also noticed for (1*R*,2*S*)-**7** and (1*R*,2*S*)-**8** isomers. The deshielding effect of the carbonyl group has frequently been applied to structural studies on the related 1,2,3-triazoles.[20,22,25–29] Furthermore, in [2 + 3] cycloadditions of azides to propiolates, the 4-alkoxycarbonyl-1,2,3-triazoles were always formed as major isomers.[20,22,25–27]

The regioselectivity of the cycloadditions shown on Schemes 1, 2 and 5 was primarily rationalised by the comparison of the steric interactions of alkoxycarbonyl groups of acetylenic compounds and carbon framework of azides[21,27] and later on refined by employing the frontier molecular orbital theory.[12,29,30]

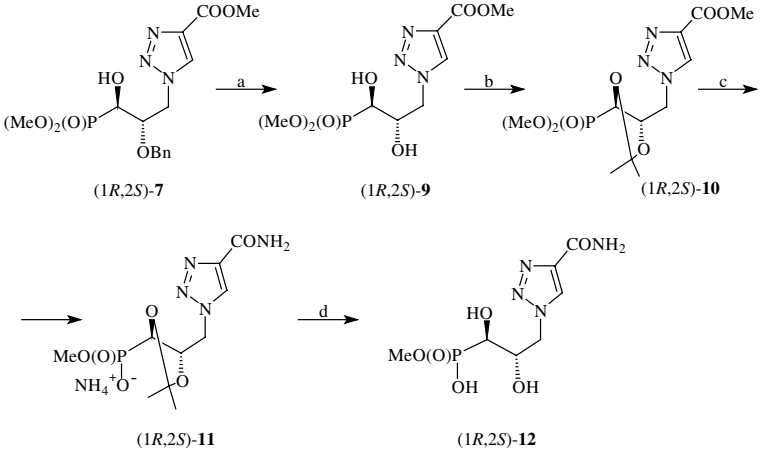
The transformation of the major isomers (1*S*,2*S*)-**7** and (1*R*,2*S*)-**7** into the 4-carbamoyl-1,2,3-triazoles (1*S*,2*S*)-**12** and (1*R*,2*S*)-**12** is illustrated in Schemes 3 and 4, respectively. From the preliminary experiment, we learned that the protection of the C(1) hydroxyl group in phosphonates **7** was necessary. When (1*S*,2*S*)-**7** was treated with 25% aqueous ammonia at room temperature for 5 days, cleavage of the C–P bond occurred. In the ^{1}H and ^{31}P NMR spectra of the crude product, signals (δ^1H = 6.67 ppm; $^1J_{HP}$ = 613 Hz and δ^{31}P = 5.9 ppm) that are characteristic of ammonium *O*-methyl phosphonate (over 60% of the mixture) were found.

Thus, hydrogenolysis of the benzyl protecting groups led to diols (1*S*,2*S*)-**9** and (1*R*,2*S*)-**9** in excellent yields. The 1,2-diols **9** were then treated with 2,2-dimethoxypropane to give the isopropylidene derivatives (1*S*,2*S*)-**10** and (1*R*,2*S*)-**10**. The protected phosphonates **10** were left with 25% aqueous ammonia at room temperature. Under these conditions, quantitative amidation of the methoxycarbonyl group was complete in less than 1 h. As a much slower process hydrolysis of a phosphonate ester took place leading to the formation of monoammonium salts (1*S*,2*S*)-**11** and (1*R*,2*S*)-**11** in about one week. The isopropylidene protecting groups were quantitatively hydrolysed in the presence of a Dowex H^+ resin at 75 °C leaving monoacids (1*R*,2*S*)-**12** and (1*S*,2*S*)-**12** in 86% and 76% yield, respectively, after purification on silanised silica gel.

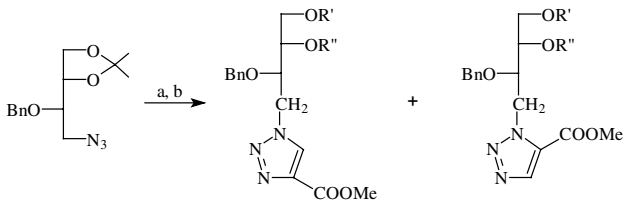
An alternative approach to the synthesis of the phosphonates (1*S*,2*S*)-**7** and (1*R*,2*S*)-**7** is shown in Schemes 5 and 6. The known (2*S*,3*S*)-4-azido-3-benzyloxy-1,2-*O*-isopropylidene-1,2-butanediol **13**[24] was reacted with methyl propiolate under standard conditions[20] to give an 80:20 mixture of (2*S*,3*S*)-**14** and (2*S*,3*S*)-**15** quantitatively. The major product, which was identified as a 4-methoxycarbonyl regioisomer, was separated by crystallisation in 62% yield. After hydrolysis of the isopropylidene group, diol (2*S*,3*S*)-**16** was transformed into the very unstable aldehyde (2*S*)-**18**, quantitatively. Triethylamine-catalysed additions of dimethyl or diethyl



Scheme 3. Reagents and conditions: (a) H_2–Pd/C, rt, 5 days; (b) $Me_2C(OMe)_2$; cat. *p*-TosOH, rt, 20 h; (c) 25% NH_3, 7 days; (d) H_2O, Dowex 50W×4, H^+, 75 °C, 1.5 h.



Scheme 4. Reagents and conditions: (a) H_2–Pd/C, rt, 7 days; (b) $Me_2C(OMe)_2$; cat. *p*-TosOH, rt, 20 h; (c) 25% NH_3, 7 days; (d) H_2O, Dowex 50W×4, H^+, 75 °C, 1.5 h.



Scheme 5. Reagents and conditions: (a) HC≡CCOOMe, toluene, 110 °C, 4 h; (b) 1 M HCl, dioxane, rt, 24 h.

phosphites led to 1:1 mixtures of the respective phosphonates, which could not be separated on silica gel.

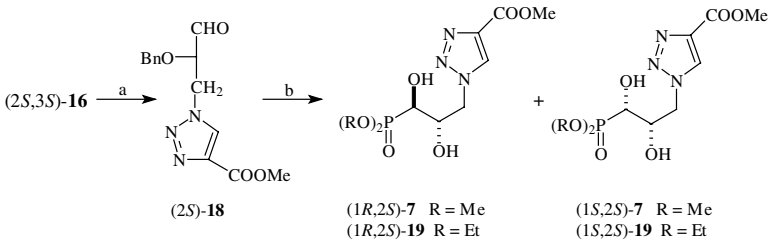
3. Conclusions

Dimethyl (1*R*,2*S*)-3-azido-2-benzyloxy-1-hydroxypropylphosphonate (1*R*,2*S*)-**6** underwent [2 + 3] cycloaddition with methyl propiolate to give an 86:14 mixture of regioisomeric dimethyl 2-benzyloxy-1-hydroxy-3-[4-(and 5-)methoxycarbonyl-1,2,3-triazol-1-yl]propylphosphonates (1*R*,2*S*)-**7** and (1*R*,2*S*)-**8**, respectively. Similarly, from (1*S*,2*S*)-**6** an 80:20 mixture of regioisomers (1*S*,2*S*)-**7** and (1*S*,2*S*)-**8** was obtained. The major 4-methoxycarbonyl isomers (1*R*,2*S*)-**7** and (1*S*,2*S*)-**7** were transformed in a four step reaction sequence into *O*-methyl (1*R*,2*S*)- and (1*S*,2*S*)-3-(4-carbamoyl-1,2,3-triazol-1-yl)-1,2-dihydroxypropylphosphonic acids **12**.

The alternative strategy to phosphonates **7** (cycloaddition proceeds phosphonylation) employing (2*S*,3*S*)-4-azido-3-benzyloxy-1,2-*O*-isopropylidene-1,2-butanediol as a starting material failed, because mixtures of diastereoisomeric phosphonates (1*R*,2*S*)-**7** and (1*S*,2*S*)-**7**, which were formed in a 1:1 ratio, could not be separated.

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



Scheme 6. Reagents and conditions: (a) $NaIO_4$, H_2O, $NaHCO_3$, 40 °C, 3 h; (b) $(RO)_2P(O)H$, NEt_3, rt, 16 h.

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 (1*S*,2*S*)-6 with methyl propiolate

A solution of (1*S*,2*S*)-**6** (213 mg, 0.676 mmol) and methyl propiolate (114 mg, 1.36 mmol) in toluene (2 mL) was refluxed for 4 h. The mixture was concentrated to dryness to leave a white solid (266 mg), which was chromatographed on a silica gel column with chloroform/methanol (100:1, v/v). The appropriate fractions were collected to give (1*S*,2*S*)-**7** (138 mg, 52%), a mixture of (1*S*,2*S*)-**7** and (1*S*,2*S*)-**8** (74 mg, 28%) and (1*S*,2*S*)-**8** (54 mg, 20%).

4.1.1. Dimethyl (1*S*,2*S*)-2-benzyloxy-1-hydroxy-3-(4-methoxycarbonyl-1,2,3-triazol-1-yl)propylphosphonate, (1*S*,2*S*)-7. The material obtained after chromatography was recrystallised from ethyl acetate/hexanes to afford a white amorphous solid (136 mg, 52%). $[\alpha]_D^{20} = -32.1$ (*c* 1.37, $CHCl_3$). Mp 120.5–121.5 °C. IR (KBr): $\nu = 3200$, 2953, 2923, 2853, 1746, 1222, 1204, 1047, 1021 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.57$ (br t, $J = 8.9$ Hz, 1H, OH), 3.82 and 3.83 (2d, $J = 10.5$ Hz, 6H, CH_3OPOCH_3), 3.93 (ddd, $J = 11.9$, 8.9, 3.2 Hz, 1H, *H*CP), 3.95 (s, 3H, CH_3OOC), 4.30 (d, $J = 10.9$ Hz, 1H, H_aCH_bPh), 4.31 (dddd, $J = 7.5$, 7.4, 5.5, 3.2 Hz, 1H, *H*CCP), 4.57 (dd, $J = 11.9$, 7.5 Hz, 1H, H_aCH_bN), 4.69 (d, $J = 10.9$ Hz, 1H, H_aCH_bPh), 4.72 (dd, $J = 11.9$, 5.5 Hz, 1H, H_aCH_bN), 7.20–7.31 (m, 5H, C_6H_5), 8.09 (s, 1H, $HC_{5'}$). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 51.1$ (d, $J = 10.6$ Hz, *C*CCP), 52.3, 53.6 and 53.8 (2d, $J = 7.0$ Hz, CH_3OPOCH_3), 67.6 (d, $J = 163.8$ Hz, *C*P), 74.1, 77.4 (d, $J = 2.3$ Hz, *C*CP), 128.2, 128.4, 128.5, 129.2, 136.7, 139.6, 160.9. ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 24.06$ ppm. Anal. Calcd for $C_{16}H_{22}N_3O_7P$: C, 48.12; H, 5.55; N, 10.52. Found: C, 48.35; H, 5.43; N, 10.68.

4.1.2. Dimethyl (1*S*,2*S*)-2-benzyloxy-1-hydroxy-3-(5-methoxycarbonyl-1,2,3-triazol-1-yl)propylphosphonate, (1*S*,2*S*)-8. Colourless oil. $[\alpha]_D^{20} = -20.1$ (*c* 3.22, $CHCl_3$). IR (film): $\nu = 3277$, 2956, 2922, 2853, 1732, 1454, 1318, 1259, 1054 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.08$ (br s, 1H, OH), 3.77 and 3.79 (2d, $J = 10.7$ Hz, 6H, CH_3OPOCH_3), 3.88 (s, 3H, CH_3OOC), 3.97 (dd, $J = 11.8$, 2.4 Hz, 1H, *H*CP), 4.34 (dddd, $J = 6.5$, 6.2, 5.3, 2.4 Hz, 1H, *H*CCP), 4.43 (d, $J = 10.9$ Hz, 1H, H_aCH_bPh), 4.68 (d, $J = 10.9$ Hz, 1H, H_aCH_bPh), 4.96 (dd, $J = 13.5$, 6.2 Hz, 1H, H_aCH_bN), 5.14 (ddd, $J = 13.5$, 6.5, 1.8 Hz, 1H, H_aCH_bN), 7.23–7.33 (m, 5H, C_6H_5), 8.09 (s, 1H, $HC_{4'}$). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 49.9$ (d, $J = 12.9$ Hz, *C*CCP), 52.8, 53.3 and 53.9 (2d, $J = 7.1$ Hz, CH_3OPOCH_3), 67.9 (d, $J = 162.6$ Hz, *C*P), 73.8, 76.8 (d, $J = 2.3$ Hz, *C*CP), 128.0, 128.3, 128.4, 128.6, 137.0, 137.9, 158.9. ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 24.76$ ppm. Anal. Calcd for $C_{16}H_{22}N_3O_7P$: C, 48.12; H, 5.55; N, 10.52. Found: C, 47.97; H, 5.60; N, 10.21.

4.2. Reaction of (1*R*,2*S*)-6 with methyl propiolate

In a similar manner, from (1*R*,2*S*)-**6** (156 mg, 0.495 mmol) and methyl propiolate (88 μL, 0.99 mmol) in toluene (1 mL), a colourless oil (202 mg) was obtained. After chromatography on a silica gel column with chloroform/methanol (100:1, v/v), (1*R*,2*S*)-**7** (142 mg, 71%), a mixture of (1*R*,2*S*)-**7** and (1*R*,2*S*)-**8** (35 mg, 18%) and (1*R*,2*S*)-**8** (24 mg, 11%) were obtained.

4.2.1. Dimethyl (1*R*,2*S*)-2-benzyloxy-1-hydroxy-3-(4-methoxycarbonyl-1,2,3-triazol-1-yl)propylphosphonate, (1*R*,2*S*)-7. Colourless very thick oil. $[\alpha]_D^{20} = -21.2$ (*c* 1.08, CH_3OH). IR (film): $\nu = 3296$, 2956, 2922, 2854, 1738, 1232, 1042 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.79$ and 3.81 (2d, $J = 10.5$ Hz, 6H, CH_3OPOCH_3), 3.87 (dd, $J = 10.9$, 5.8 Hz, 1H, OH), 3.96 (s, 3H, CH_3OOC), 3.99 (ddd, $J = 9.1$, 5.8, 5.5 Hz, 1H, *H*CP), 4.19 (dddd, $J = 9.1$, 6.9, 5.8, 3.4 Hz, 1H, *H*CCP), 4.41 (d, $J = 11.1$ Hz, 1H, H_aCH_bPh), 4.56 (d, $J = 11.1$ Hz, 1H, H_aCH_bPh), 4.69 (dd, $J = 14.5$, 6.9 Hz, 1H, H_aCH_bN), 4.82 (dd, $J = 14.5$, 3.4 Hz, 1H, H_aCH_bN), 7.18–7.33 (m, 5H, C_6H_5), 8.13 (s, 1H, $HC_{5'}$). ^{13}C NMR

(75.5 MHz, $CDCl_3$): $\delta = 50.7$ (d, $J = 7.6$ Hz, *C*CCP), 52.4, 53.9 and 53.9 (2d, $J = 7.5$ Hz, CH_3OPOCH_3), 67.2 (d, $J = 162.5$ Hz, *C*P), 73.1, 77.5 (d, $J = 5.3$ Hz, *C*CP), 128.3, 128.4, 128.5, 129.4, 136.6, 139.7, 161.1. ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 24.84$ ppm. Anal. Calcd for $C_{16}H_{22}N_3O_7P$: C, 48.12; H, 5.55; N, 10.52. Found: C, 47.81; H, 5.72; N, 10.40.

4.2.2. Dimethyl (1*R*,2*S*)-2-benzyloxy-1-hydroxy-3-(5-methoxycarbonyl-1,2,3-triazol-1-yl)propylphosphonate, (1*R*,2*S*)-8. A white amorphous solid. Mp 119–120 °C. $[\alpha]_D^{20} = -36.3$ (*c* 0.91, $CHCl_3$). IR (KBr): $\nu = 3227$, 3029, 2961, 2855, 1737, 1535, 1454, 1322, 1263, 1208, 1052 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.55$–3.90 (br d, $J = 5.9$ Hz, 1H, OH), 3.76 (s, 3H, CH_3OOC), 3.78 and 3.82 (2d, $J = 10.5$ Hz, 6H, CH_3OPOCH_3), 4.05 (ddd, $J = 9.9$, 6.0, 5.9 Hz, 1H, *H*CP), 4.26 (dddd, $J = 10.2$, 6.6, 6.0, 3.8 Hz, 1H, *H*CCP), 4.36 (d, $J = 10.9$ Hz, 1H, H_aCH_bPh), 4.53 (d, $J = 10.9$ Hz, 1H, H_aCH_bPh), 5.16 (dd, $J = 14.1$, 6.6 Hz, 1H, H_aCH_bN), 5.23 (dd, $J = 14.1$, 3.8 Hz, 1H, H_aCH_bN), 7.10–7.27 (m, 5H, C_6H_5), 8.08 (s, 1H, *H*C$_{4'}$). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 49.5$ (d, $J = 6.9$ Hz, *C*CCP), 52.6, 53.6 and 54.0 (2d, $J = 6.9$ Hz, CH_3OPOCH_3), 67.7 (d, $J = 163.5$ Hz, *C*P), 73.0, 77.7 (d, $J = 4.3$ Hz, *C*CP), 128.0, 128.0, 128.4, 129.0, 137.1, 137.8, 158.9. ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 24.75$ ppm. Anal. Calcd for $C_{16}H_{22}N_3O_7P$: C, 48.12; H, 5.55; N, 10.52. Found: C, 48.24; H, 5.41; N, 10.58.

4.3. Dimethyl (1*S*,2*S*)-1,2-dihydroxy-3-(4-methoxycarbonyl-1,2,3-triazol-1-yl)propylphosphonate, (1*S*,2*S*)-9

A suspension of (1*S*,2*S*)-**7** (114 mg, 0.285 mmol) and Pd–C (10%, 6 mg) in methanol (15 mL) was stirred under hydrogen for 5 days. The catalyst was filtered off through a layer of Celite, the solution concentrated in vacuo and the residue chromatographed on silica gel with methylene chloride/methanol (20:1, v/v) to give (1*S*,2*S*)-**9** as a colourless oil (85 mg, 97%). $[\alpha]_D^{20} = -6.7$ (*c* 1.22, $CHCl_3$). IR (film): $\nu = 3292$, 2959, 2920, 2854, 1732, 1222, 1044 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.81$ and 3.86 (2d, $J = 10.7$ Hz, 6H, CH_3OPOCH_3), 3.93 (ddd, $J = 12.0$, 6.1, 2.3 Hz, 1H, *H*CP), 3.94 (s, 3H, CH_3OOC), 4.34–4.44 (m, 1H, *H*CCP), 4.60 (dd, $J = 14.1$, 7.8 Hz, 1H, H_aCH_bN), 4.69 (dd, $J = 14.1$, 4.8 Hz, 1H, H_aCH_bN), 4.63–4.75 (br s, 2H, O*H*), 8.29 (s, 1H, *H*C$_{5'}$). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 52.4$, 53.0 (d, $J = 14.3$ Hz, *C*CCP), 53.8 and 54.3 (2d, $J = 7.2$ Hz, CH_3OPOCH_3), 68.7 (d, $J = 162.9$ Hz, *C*P), 69.7 (d, $J = 2.6$ Hz, *C*CP), 129.3, 139.5, 161.1. ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 25.21$ ppm. Anal. Calcd for $C_9H_{16}N_3O_7P$: C, 34.96; H, 5.22; N, 13.58. Found: C, 35.19; H, 5.39; N, 13.35.

4.3.1. Dimethyl (1*R*,2*S*)-1,2-dihydroxy-3-(4-methoxycarbonyl-1,2,3-triazol-1-yl)propylphosphonate, (1*R*,2*S*)-9. In a similar way from (1*R*,2*S*)-**7** (464 mg, 1.16 mmol) the crude phosphonate (1*R*,2*S*)-**9** (430 mg) was obtained after 7 days. The purification took place on a silica gel column with chloroform/methanol (50:1 and 25:1, v/v) and gave (1*R*,2*S*)-**9** (328 mg, 91%) as a colourless oil. $[\alpha]_D^{20} = -2.6$ (*c* 2.7, CH_3OH). IR (film): $\nu = 3348$, 2959, 2855, 1729, 1230, 1042 cm^{-1}. ^{1}H NMR (300 MHz, CD_3OD): $\delta = 3.80$ and 3.85 (2d, $J = 10.5$ Hz, 6H, CH_3OPOCH_3), 3.92 (s, 3H, CH_3OOC), 3.93 (dd, $J = 7.9$, 6.5 Hz, 1H, *H*CP), 4.21 (dddd, $J = 8.5$, 8.3, 6.5, 2.9 Hz, 1H, *H*CCP), 4.57 (dd, $J = 14.1$, 8.3 Hz, 1H, H_aCH_bN), 4.74 (dd, $J = 14.1$, 2.9 Hz, 1H, H_aCH_bN), 8.50 (s, 1H, *H*C$_{5'}$). ^{13}C NMR (75.5 MHz, CD_3OD): $\delta = 52.7$, 54.0 and 54.5 (2d, $J = 7.2$ Hz, CH_3OPOCH_3), 54.4 (d, $J = 9.5$ Hz, *C*CCP), 70.5 (d, $J = 163.2$ Hz, *C*P), 71.2 (d, $J = 5.7$ Hz, *C*CP), 130.9, 140.1, 162.4. ^{31}P NMR (121.5 MHz, CD_3OD): $\delta = 26.75$ ppm. Anal. Calcd for $C_9H_{16}N_3O_7P$: C, 34.96; H, 5.22; N, 13.58. Found: C, 35.15; H, 5.23; N, 13.26.

4.4. Dimethyl (1*S*,2*S*)-1,2-dihydroxy-1,2-*O*-isopropylidene-3-(4-methoxycarbonyl-1,2,3-triazol-1-yl)propylphosphonate, (1*S*,2*S*)-10

A mixture of (1*S*,2*S*)-**9** (161 mg, 0.521 mmol) and 2,2-dimethoxypropane (128 μL, 1.04 mmol) in methylene chloride (10 mL) containing *p*-toluenesulfonic acid (1 mg) was left at room temperature for 20 h. The reaction mixture was neutralised with triethylamine and concentrated in vacuo. The residue (198 mg) was chromatographed on a silica gel column with methylene chloride/methanol (50:1, v/v) to give (1*S*,2*S*)-**10** as a white amorphous solid (174 mg, 96%). Mp 61–62.5 °C. $[\alpha]_D^{20} = -26.5$ (*c* 1.09, $CHCl_3$). IR (KBr): $\nu = 3544$, 3476, 3125, 2964, 1733, 1542, 1248, 1020 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.30$ and 1.45 (2s, 6H, CH_3CCH_3), 3.87 and 3.88 (2d, $J = 10.8$ Hz, 6H, CH_3OPOCH_3), 3.90 (dd, $J = 9.1$, 1.1 Hz, 1H, *H*CP), 3.97 (s, 3H, CH_3OOC), 4.55–4.67 (m, 2H, *H*CCP, H_aCH_bN), 4.78–4.87 (m, 1H, H_aCH_bN), 8.26 (s, 1H, *H*C$_{5'}$). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 26.3$ and 26.6 (2s, CH_3CCH_3), 51.0 (d, $J = 3.7$ Hz, *C*CCP), 52.4, 53.9 and 54.2 (2d, $J = 6.9$ Hz, CH_3OPOCH_3), 71.8 (d, $J = 173.2$ Hz, *C*P), 75.3 (d, $J = 4.9$ Hz, *C*CP), 112.5 (d, $J = 10.6$ Hz, CH_3CCH_3), 129.4, 140.0, 161.0. ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 21.37$ ppm. Anal. Calcd for $C_{12}H_{20}N_3O_7P$: C, 41.26; H, 5.77; N, 12.03. Found: C, 41.27; H, 5.80; N, 11.74.

4.4.1. Dimethyl (1*R*,2*S*)-1,2-dihydroxy-1,2-*O*-isopropylidene-3-(4-methoxycarbonyl-1,2,3-triazol-1-yl)propylphosphonate, (1*R*,2*S*)-10. In a similar manner from (1*R*,2*S*)-**9** (287 mg, 0.928 mmol) the phosphonate (1*R*,2*S*)-**10** (281 mg, 87%) was obtained as a white amorphous solid. Mp 88–89 °C. $[\alpha]_D^{20} = -29.6$ (*c* 1.25, $CHCl_3$). IR (KBr): $\nu = 3101$, 3068, 2994, 2960, 1720, 1546, 1255, 1045 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.33$ and 1.61 (2s, 6H, CH_3CCH_3), 3.86 and 3.91 (2d, $J = 10.6$ Hz, 6H, CH_3OPOCH_3), 3.96 (s, 3H, CH_3OOC), 4.48 (dd, $J = 7.1$, 1.9 Hz, 1H, *H*CP), 4.63 (dd, $J = 13.7$, 10.1 Hz, 1H, H_aCH_bN), 4.73 (dddd, $J = 10.1$, 9.9, 7.1, 2.1 Hz, 1H, *H*CCP), 5.01 (dd, $J = 13.7$, 2.1 Hz, 1H, H_aCH_bN), 8.25 (s, 1H, *H*C$_{5'}$). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 24.7$ and 27.0 (2s, CH_3CCH_3), 51.5 (d, $J = 4.0$ Hz, *C*CCP),

52.0, 53.1 and 54.2 (2d, $J = 7.0$ Hz, CH_3OPOCH_3), 71.8 (d, $J = 172.1$ Hz, *C*P), 76.8, 111.7 (d, $J = 8.9$ Hz, CH_3CCH_3), 128.7, 139.6, 160.9. ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 19.82$ ppm. Anal. Calcd for $C_{12}H_{20}N_3O_7P$: C, 41.26; H, 5.77; N, 12.03. Found: C, 41.28; H, 6.00; N, 12.12.

4.5. Ammonium *O*-methyl (1*S*,2*S*)-3-(4-carbamoyl-1,2,3-triazol-1-yl)-1,2-dihydroxy-1,2-*O*-isopropylidene-propylphosphonate, (1*S*,2*S*)-11

A mixture of (1*S*,2*S*)-**10** (360 mg, 1.03 mmol) and aqueous ammonia (25%) (8 mL) was diluted with methanol (2 mL) and left at room temperature for 6 days. Volatiles were removed in vacuo and the residue recrystallised from methanol/diethyl ether to give (1*S*,2*S*)-**11** as a white powder (258 mg, 74%). Mp 141–142 °C. $[\alpha]_D^{20} = -37.7$ (*c* 1.55, CH_3OH). IR (KBr): $\nu = 3439$, 3207, 3103, 2980, 2926, 1632, 1240, 1212, 1047 cm^{-1}. ^{1}H NMR (300 MHz, CD_3OD): $\delta = 1.24$ and 1.40 (2s, 6H, CH_3CCH_3), 3.70 (d, $J = 10.1$ Hz, 3H, CH_3OP), 3.84 (dd, $J = 9.5$, 1.2 Hz, 1H, *H*CP), 4.48 (dddd, $J = 9.5$, 9.4, 6.7, 2.8 Hz, 1H, *H*CCP), 4.67 (dd, $J = 14.3$, 6.7 Hz, 1H, H_aCH_bN), 4.90 (dd, $J = 14.3$, 2.8 Hz, 1H, H_aCH_bN), 8.42 (s, 1H, $HC_{5'}$). ^{13}C NMR (75.5 MHz, CD_3OD): $\delta = 26.9$ and 27.2 (2s, CH_3CCH_3), 53.2 (*C*CCP), 53.4 (d, $J = 6.3$ Hz, CH_3OP), 75.2 (d, $J = 163.1$ Hz, *C*P), 77.9 (d, $J = 7.3$ Hz, *C*CP), 112.0 (d, $J = 10.9$ Hz, CH_3CCH_3), 129.0, 143.5, 164.7. ^{31}P NMR (121.5 MHz, CD_3OD): $\delta = 14.78$ ppm. Anal. Calcd for $C_{10}H_{20}N_5O_6P$: C, 35.61; H, 5.97; N, 20.76. Found: C, 35.71; H, 5.65; N, 21.16.

4.5.1. Ammonium *O*-methyl (1*R*,2*S*)-3-(4-carbamoyl-1,2,3-triazol-1-yl)-1,2-dihydroxy-1,2-*O*-isopropylidenepropylphosphonate, (1*R*,2*S*)-11.

In a similar manner from (1*R*,2*S*)-**10** (57 mg, 0.16 mmol) the phosphonate (1*R*,2*S*)-**11** (40 mg, 73%) was obtained as white plates. Mp 186–188 °C. $[\alpha]_D^{20} = -76.3$ (*c* 1.2, CH_3OH). IR (KBr): $\nu = 3425$, 3274, 3084, 2993, 2953, 2827, 1648, 1210, 1029 cm^{-1}. ^{1}H NMR (300 MHz, CD_3OD): $\delta = 1.31$ and 1.58 (2s, 6H, CH_3CCH_3), 3.73 (d, $J = 10.1$ Hz, 3H, CH_3OP), 4.42 (dd, $J = 6.8$, 5.5 Hz, 1H, *H*CP), 4.58–4.69 (m, 2H, *H*CCP, H_aCH_bN), 4.89–5.00 (m, 1H, H_aCH_bN), 8.41 (s, 1H, $HC_{5'}$). ^{13}C NMR (75.5 MHz, CD_3OD): $\delta = 25.3$ and 28.2 (2s, CH_3CCH_3), 53.3 (d, $J = 6.0$ Hz, CH_3OP), 54.2 (d, $J = 3.0$ Hz, *C*CCP), 74.7 (d, $J = 160.1$ Hz, *C*P), 77.5 (d, $J = 1.5$ Hz, *C*CP), 111.8 (d, $J = 12.6$ Hz, CH_3CCH_3), 128.3, 143.4, 164.8. ^{31}P NMR (121.5 MHz, CD_3OD): $\delta = 13.37$ ppm. Anal. Calcd for $C_{10}H_{20}N_5O_6P$: C, 35.61; H, 5.97; N, 20.76. Found: C, 35.70; H, 6.13; N, 20.40.

4.6. *O*-Methyl (1*S*,2*S*)-3-(4-carbamoyl-1,2,3-triazol-1-yl)-1,2-dihydroxypropylphosphonic acid, (1*S*,2*S*)-12

An aqueous (4 mL) solution of the phosphonate (1*S*,2*S*)-**11** (168 mg, 4.98 mmol) containing Dowex 50W×4 (H^+) (0.95 g) was maintained at 75 °C for 1.5 h. The resin was filtered off and washed with distilled water until washings were neutral. The aqueous solution was concentrated in vacuo to leave a solid (0.125 g), which was chromatographed on a silanised silica gel column with distilled water to give phosphonate (1*S*,2*S*)-**12** (0.105 g, 76%) as a white amorphous solid. Mp 187–189 °C. $[\alpha]_D^{20} = -21.1$ (*c* 1.1, H_2O). IR (KBr): $\nu = 3394$, 3137, 3095, 2958, 2924, 2555, 1619, 1571, 1240, 1197, 1052 cm^{-1}. ^{1}H NMR (300 MHz, D_2O): $\delta = 3.65$ (d, $J = 10.5$ Hz, 3H, CH_3OP), 3.86 (dd, $J = 10.8$, 3.9 Hz, 1H, *H*CP), 4.32 (dddd, $J = 9.6$, 5.4, 3.9, 2.7 Hz, 1H, *H*CCP), 4.58 (dd, $J = 14.1$, 9.6 Hz, 1H, H_aCH_bN), 4.75 (dd, $J = 14.1$, 2.7 Hz, 1H, H_aCH_bN), 8.48 (s, 1H, $HC_{5'}$). ^{13}C NMR (62.9 MHz, D_2O): $\delta = 52.2$ (d, $J = 6.3$ Hz, CH_3OP), 52.9 (d, $J = 11.8$ Hz, *C*CCP), 67.5 (d, $J = 159.6$ Hz, *C*P), 69.2 (d, $J = 3.5$ Hz, *C*CP), 127.7, 141.1, 163.9. ^{31}P NMR (121.5 MHz, D_2O): $\delta = 21.19$ ppm. Anal. Calcd for $C_7H_{13}N_4O_6P \times \frac{1}{4}H_2O$: C, 29.53; H, 4.62; N, 19.68. Found: C, 29.80; H, 4.71; N, 19.43.

4.6.1. *O*-Methyl (1*R*,2*S*)-3-(4-carbamoyl-1,2,3-triazol-1-yl)-1,2-dihydroxypropylphosphonic acid, (1*R*,2*S*)-12.

In a similar manner, from (1*R*,2*S*)-**11** (98 mg, 0.29 mmol) phosphonate (1*R*,2*S*)-**12** (70 mg, 86%) was obtained as a white amorphous solid. Mp 165–167 °C. $[\alpha]_D^{20} = -12.9$ (*c* 1.0, H_2O). IR (KBr): $\nu = 3377$, 2961, 2924, 2853, 1655, 1255, 1051 cm^{-1}. ^{1}H NMR (300 MHz, D_2O): $\delta = 3.66$ (d, $J = 10.3$ Hz, 3H, CH_3OP), 3.93 (dd, $J = 9.8$, 5.8 Hz, 1H, *H*CP), 4.20–4.39 (m, 1H, *H*CCP), 4.59 (dd, $J = 14.2$, 8.8 Hz, 1H, H_aCH_bN), 4.79–4.88 (m, 1H, H_aCH_bN), 8.46 (s, 1H, $HC_{5'}$). ^{13}C NMR (62.9 MHz, D_2O): $\delta = 52.3$ (d, $J = 6.5$ Hz, CH_3OP), 52.4 (d, $J = 6.8$ Hz, *C*CCP), 68.3 (d, $J = 150.1$ Hz, *C*P), 69.6 (d, $J = 1.8$ Hz, *C*CP), 127.8, 141.0, 163.7. ^{31}P NMR (121.5 MHz, D_2O): $\delta = 20.72$ ppm. Anal. Calcd for $C_7H_{13}N_4O_6P \times \frac{1}{4}H_2O$: C, 29.53; H, 4.62; N, 19.68. Found: C, 29.73; H, 4.78; N, 19.35.

4.7. Reaction of (2*S*,3*S*)-13 with methyl propiolate

A solution of azide **13** (2.01 g, 7.24 mmol) and methyl propiolate (1.29 mL, 14.5 mmol) in toluene (10 mL) was refluxed for 4 h. The mixture was concentrated to dryness to leave a white solid (2.62 g), which was recrystallised from ethyl acetate/*n*-heptane to give (2*S*, 3*S*)-**14** (1.535 g) as a white powder. The residue was chromatographed on a silica gel column with methylene chloride/methanol (150:1, v/v). The appropriate fractions were collected to give (2*S*, 3*S*)-**14** (85 mg), a mixture of (2*S*,3*S*)-**14** and (2*S*,3*S*)-**15** (614 mg, 23%) and (2*S*,3*S*)-**15** (386 mg, 15%).

4.7.1. (2*S*,3*S*)-3-Benzyloxy-1,2-*O*-isopropylidene-4-(4-methoxycarbonyl-1,2,3-triazol-1-yl)-1,2-butanediol, (2*S*,3*S*)-14.

Total yield (1.62 g, 62%). Mp 89–90 °C. $[\alpha]_D^{20} = -10.9$ (*c* 1.1, $CHCl_3$). IR (KBr): $\nu = 3121$, 1719, 1238 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.36$ and 1.47 (2s, 6H, CH_3CCH_3), 3.93 (dd, $J = 8.6$, 6.0 Hz, 1H, H_aH_bCO), 3.96 (s, 3H, CH_3OOC), 3.96 (ddd, $J = 8.4$, 5.0, 3.4 Hz, 1H, *H*COBn), 4.07 (dd, $J = 8.6$, 6.5 Hz, 1H,

H_aH_bCO), 4.18 (ddd, $J = 6.5$, 6.0, 5.0 Hz, 1H, HCO), 4.34 (d, $J = 11.7$ Hz, 1H, H_aH_bCPh), 4.37 (dd, $J = 14.1$, 8.4 Hz, 1H, H_aCH_bN), 4.53 (d, $J = 11.7$ Hz, 1H, H_aH_bCPh), 4.63 (dd, $J = 14.1$, 3.4 Hz, 1H, H_aCH_bN), 7.14–7.17 (m, 2H, C_6H_5), 7.27–7.31 (m, 3H, C_6H_5), 8.10 (s, 1H, $HC_{5'}$). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 25.2$, 26.5, 51.4, 52.4, 65.2, 73.9, 75.3, 77.8, 110.1, 128.2, 128.2, 128.6, 129.2, 137.0, 139.8, 161.0. Anal. Calcd for $C_{18}H_{23}N_3O_5$: C, 59.82; H, 6.41; N, 11.62. Found: C, 59.62; H, 6.25; N, 11.59.

4.7.2. (2*S*,3*S*)-3-Benzyloxy-1,2-*O*-isopropylidene-4-(5-methoxycarbonyl-1,2,3-triazol-1-yl)-1,2-butanediol, (2*S*,3*S*)-15. Yellowish oil. $[\alpha]_D^{20} = -43.9$ (c 1.51, $CHCl_3$). IR (film): $\nu = 2987$, 1732, 1261 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.37$ and 1.47 (2s, 6H, CH_3CCH_3), 3.82 (s, 3H, CH_3OOC), 3.98 (dd, $J = 8.7$, 6.0 Hz, 1H, H_aH_bCO), 3.98 (ddd, $J = 9.0$, 5.3, 3.7 Hz, 1H, $HCOBn$), 4.08 (dd, $J = 8.7$, 6.8 Hz, 1H, H_aH_bCO), 4.26 (ddd, $J = 6.8$, 6.0, 5.3 Hz, 1H, HCO), 4.28 (d, $J = 11.7$ Hz, 1H, H_aH_bCPh), 4.45 (d, $J = 11.7$ Hz, 1H, H_aH_bCPh), 4.81 (dd, $J = 13.7$, 3.7 Hz, 1H, H_aCH_bN), 4.95 (dd, $J = 13.7$, 9.0 Hz, 1H, H_aCH_bN), 7.05–7.08 (m, 2H, C_6H_5), 7.22–7.27 (m, 3H, C_6H_5), 8.05 (s, 1H, $HC_{4'}$). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 25.2$, 26.6, 50.4, 52.6, 65.3, 73.4, 75.8, 77.4, 109.9, 127.8, 128.1, 128.4, 128.5, 137.4, 137.8, 158.9. Anal. Calcd for $C_{18}H_{23}N_3O_5$: C, 59.82; H, 6.41; N, 11.62. Found: C, 59.62; H, 6.01; N, 11.55.

4.8. (2*S*,3*S*)-3-Benzyloxy-4-(4-methoxycarbonyl-1,2,3-triazol-1-yl)-1,2-butanediol, (2*S*,3*S*)-16

A solution of (2*S*,3*S*)-**14** (1.477 g, 4.087 mmol) in dioxane (30 mL) containing 1 M HCl (15.7 mL) was left at room temperature for 24 h. The reaction mixture was neutralised by the addition of solid $NaHCO_3$. The volatiles were evaporated in vacuo, the residue dissolved in chloroform (15 mL) and dried over $MgSO_4$. The crude product was chromatographed on a silica gel column with methylene chloride/methanol (100:1, v/v) and the appropriate fractions recrystallised from ethyl acetate/diethyl ether to give (2*S*,3*S*)-**16** (911 mg, 69%) as a white powder. Mp 114–116 °C. $[\alpha]_D^{20} = -39.8$ (c 1.17, CH_3OH). IR (KBr): $\nu = 3369$, 1724, 1218 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.08$ (br t, $J = 5.4$ Hz, 1H, $HOCH_2$), 2.60 (d, $J = 6.3$ Hz, 1H, $HOCH$), 3.58–3.66 (m, 1H, $HCOH$), 3.68–3.78 (m, 2H, H_2COH), 3.98 (s, 3H, CH_3OOC), 4.06 (ddd, $J = 7.1$, 4.8, 3.8 Hz, 1H, $HCOBn$), 4.38 and 4.44 (AB system, $J = 11.3$ Hz, 2H, H_aH_bCPh), 4.58 (dd, $J = 14.1$, 7.1 Hz, 1H, H_aCH_bN), 4.69 (dd, $J = 14.1$, 4.8 Hz, 1H, H_aCH_bN), 7.18–7.23 (m, 2H, C_6H_5), 7.28–7.38 (m, 3H, C_6H_5), 8.13 (s, 1H, $HC_{5'}$). ^{13}C NMR (75.5 MHz, CD_3OD): $\delta = 50.0$, 52.6, 63.5, 72.8, 74.8, 79.7, 128.8, 129.3, 130.8, 138.9, 140.2, 162.2. Anal. Calcd for $C_{15}H_{19}N_3O_5$: C, 56.07; H, 5.96; N, 13.08. Found: C, 56.06; H, 5.74; N, 13.33.

4.8.1. (2*S*,3*S*)-3-Benzyloxy-4-(5-methoxycarbonyl-1,2,3-triazol-1-yl)-1,2-butanediol, (2*S*,3*S*)-17. In a similar way, from (2*S*,3*S*)-**15** (356 mg, 0.985 mmol) diol (2*S*,3*S*)-**17** (159 mg, 50%) was obtained as a yellowish oil. $[\alpha]_D^{20} = -5.25$ (c 2.02, $CHCl_3$). IR (film): $\nu = 3397$, 2927, 1731, 1075 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.22$ (br s, 1H, $HOCH_2$), 2.79 (d, $J = 6.3$ Hz, 1H, $HOCH$), 3.62–3.87 (m, 3H, $HCOH$ and H_2COH), 3.88 (s, 3H, CH_3OOC), 4.01 (ddd, $J = 6.9$, 5.4, 3.4 Hz, 1H, $HCOBn$), 4.40 (s, 2H, H_2CPh), 4.99 (dd, $J = 13.7$, 5.4 Hz, 1H, H_aCH_bN), 5.07 (dd, $J = 13.7$, 6.9 Hz, 1H, H_aCH_bN), 7.17–7.21 (m, 2H, C_6H_5), 7.27–7.34 (m, 3H, C_6H_5), 8.10 (s, 1H, $HC_{4'}$). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 50.4$, 52.8, 63.4, 71.5, 73.5, 77.7, 128.2, 128.3, 128.4, 128.6, 137.1, 137.9, 159.0. Anal. Calcd for $C_{15}H_{19}N_3O_5 \times 0.5H_2O$: C, 55.00; H, 5.91; N, 13.30. Found: C, 55.28; H, 5.96; N, 13.27.

4.9. A mixture of phosphonates (1*R*,2*S*)- and (1*S*,2*S*)-7 from the diol (2*S*,3*S*)-16

Solutions of (2*S*,3*S*)-**16** (400 mg, 1.24 mmol) in chloroform (20 mL) and of $NaIO_4$ (319 mg, 1.49 mmol) in water (10 mL) were vigorously stirred for 5 min and solid $NaHCO_3$ (7.5 mg) then added. After 3 h at 40 °C, the aqueous layer was saturated with NaCl. The organic phase was separated and the aqueous layer extracted with chloroform (5 × 5 mL). The organic extracts were collected, dried over $MgSO_4$ and concentrated in vacuo to leave crude (2*S*)-**18** (360 mg, 100%) as a yellowish oil. IR (film): $\nu = 3427$, 3140, 1714, 1237 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.96$ (s, 3H, H_3COOC), 4.27 (dd, $J = 6.9$, 3.8 Hz, 1H, $HCOBn$), 4.57 (dd, $J = 14.4$, 6.9 Hz, 1H, H_aH_bCN), 4.61 and 4.67 (AB system, $J = 11.7$ Hz, 2H, H_2CPh), 4.83 (dd, $J = 14.4$, 3.8 Hz, 1H, H_aH_bCN), 7.22–7.26 (m, 2H, C_6H_5), 7.27–7.37 (m, 3H, C_6H_5), 8.12 (s, 1H, $HC_{5'}$), 9.67 (s, 1H, CHO).

To a solution of the crude aldehyde, (2*S*)-**18** (360 mg, 1.24 mmol) and dimethyl phosphite (170 μL, 1.86 mmol) in methylene chloride (2 mL) triethylamine (35 μL, 0.25 mmol) was injected. The reaction mixture was left at room temperature for 20 h, diluted with methylene chloride (20 mL), extracted with water (4 × 30 mL) and dried over $MgSO_4$. The volatiles were removed in vacuo to leave a 1:1 mixture of (1*S*,2*S*)-**7** and (1*R*,2*S*)-**7** (447 mg, 90%) as a yellowish oil. ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 24.1$ and 24.8 ppm.

4.9.1. A mixture of phosphonates (1*R*,2*S*)- and (1*S*,2*S*)-19 from the diol (2*S*,3*S*)-16. In a similar manner, from the crude aldehyde (2*S*)-**18** (138 mg, 0.477 mmol) and diethyl phosphite (55 μL, 0.043 mmol) a yellow oil was obtained, which was identified as a 1:1 mixture of (1*S*,2*S*)-**19** and (1*R*,2*S*)-**19**. ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 21.98$ and 22.98 ppm.

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References and notes

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