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Synthesis of four enantiomers of 2-acetamido-1-hydroxypropylphosphonates

Andrzej E. Wróblewski* and Joanna Drozd

Bioorganic Chemistry Laboratory, Faculty of Pharmacy, Medical University of Łódź, 90-151 Łódź, Muszyńskiego 1, Poland

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Abstract—Enantiomerically pure diethyl 2-acetamido-1-hydroxypropylphosphonates were synthesised from *N*-[(*R*)-(1-phenylethyl)]aziridine-(2*S*)- and *N*-[(*S*)-(1-phenylethyl)]aziridine-(2*R*)-carboxaldehydes via phosphonylation followed by acetylation of the hydroxy groups and the simultaneous hydrogenolytic cleavage of the aziridine rings and the removal of the chiral auxiliaries. In addition, enantiomerically pure diethyl (1*S*,2*R*)- and (1*R*,2*S*)-2-amino-1-hydroxypropylphosphonates (the phosphonate analogues of isothreonine) were separated.

1. Introduction

2-Aminophoshonates can be considered as isosteres of β-amino acids. Although they are less known than 1-aminophoshonates,[1] their chemistry has recently been reviewed.[2–6] Interest in 2-aminophoshonates was stimulated by the isolation of 2-aminoethylphosphonic acid from *Celiate protozoa*[7] and other 2-aminophosphonic acids from diverse species.[8] Furthermore, substituted 2-aminophosphonic acids display an array of biological properties. For example, they act as NMDA[9] or $GABA_B$ receptor[10] antagonists, inhibit aminopeptidase A,[11] glutationylspermidine synthetase,[12] α-L-fucosidase[13] and imidazole glycerol phosphate dehydratase,[14,15] and also show antifungal activity.[16] 2-Amino-3-phosphonopropionic acid (AP3) and its derivatives have been extensively studied and their activity as a metabotropic glutamate receptor antagonist[17] and inhibitors of several enzymes[18,19] was discovered. Tripeptides containing 2-aminophosphonates substituted at C-1 with the hydroxy, oxo or fluorine groups at a C-terminus were found to be inhibitors of human rennin,[20] HIV protease,[21] dipeptidyl peptidase IV,[22] norstatine,[23] human calpain I[24] and cathepsin E.[25] Furthermore, 2-amino-1-hydroxy-3-phenylpropylphosphonic acid showed significant herbicidal activity.[26]

The most straightforward approach to substituted 2-amino-1-hydroxyphosphonates relies on the addition of dialkyl phosphites to N-protected α-amino aldehydes (the Abramov reaction).[27] However, depending on the protective groups at the nitrogen atom and structural features of α-amino aldehydes, the N-protected α-amino aldehydes undergo racemisation in the presence of basic catalysts commonly employed in the Abramov reaction.[28–30] For this reason enantiomerically pure 2-amino-1-hydroxypropylphosphonic acids **1** (phosphonate analogues of isothreonine) were first prepared by different strategies, that is, (1*R*,2*R*)-**1** from fosfomycin,[31] and (1*S*,2*R*)-**1** from diisopropyl (1*S*,2*S*)-2-benzyloxy-1-hydroxypropylphosphonate in a multi step procedure,[32] while only (1*S*,2*S*)-**1** was obtained from *N*-Boc-(*S*)-alaninal in a KF-catalysed addition of dimethyl phosphite followed by hydrolysis.[33] But for the synthesis of diethyl ester (1*S*,2*S*)-**2** catecholborane reduction of diethyl (*S*)-1-oxo-2-(*N*-phthaloyl)aminopropylphosphonate was successfully employed[34] (Fig. 1).

Herein, we report the asymmetric synthesis of all four enantiomerically pure diethyl esters **2** via (aziridin-2-yl)hydroxymethylphosphonates **3** and **4**, employing the esters (2*S*,1′*S*)- and (2*R*,1′*S*)-**5** as the starting materials (Scheme 1). The synthesis and separation of aziridines **5**[35] and their enantiomers[36] were described several years ago. The respective aldehydes **7**[37] are configurationally stable and can serve as synthetic equivalents of serinals in the Abramov reaction.

* Corresponding author. Tel.: +48 42 677 92 33; fax: +48 42 678 83 98; e-mail: aewplld@ich.pharm.am.lodz.pl

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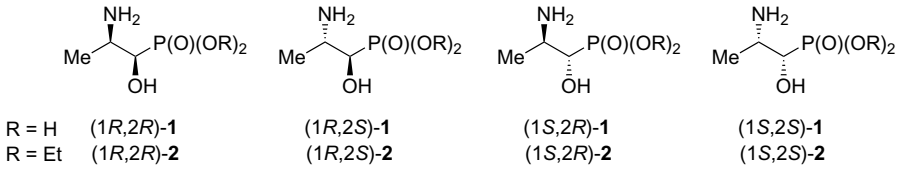
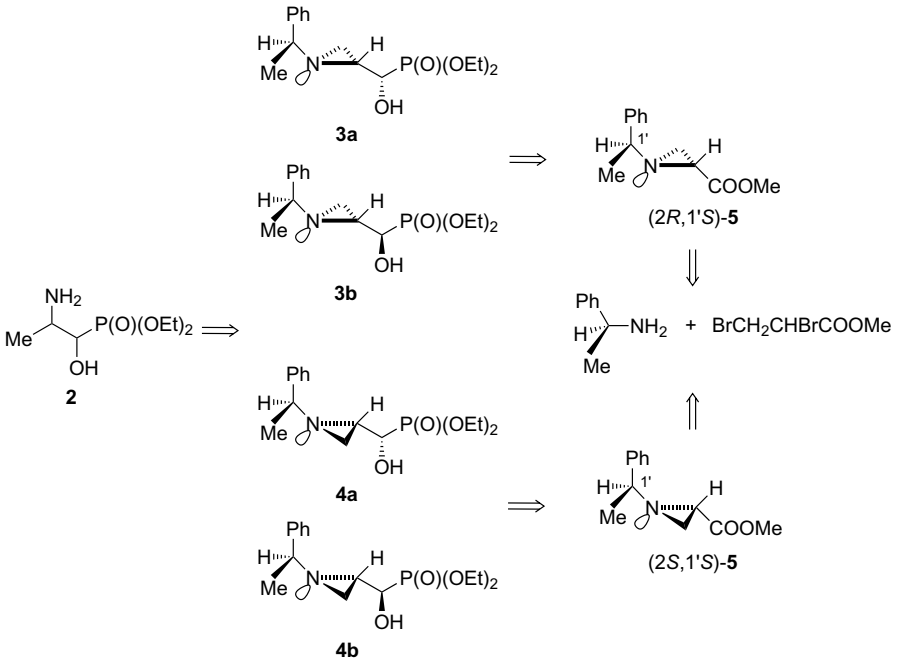


Figure 1. Enantiomers of the phosphonate analogue of isothreonine.

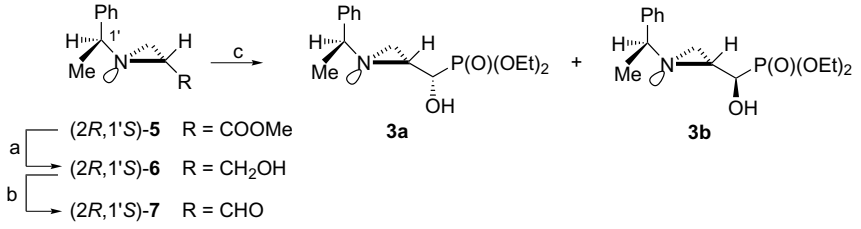


Scheme 1. Retrosynthesis of *P*-isothreonine.

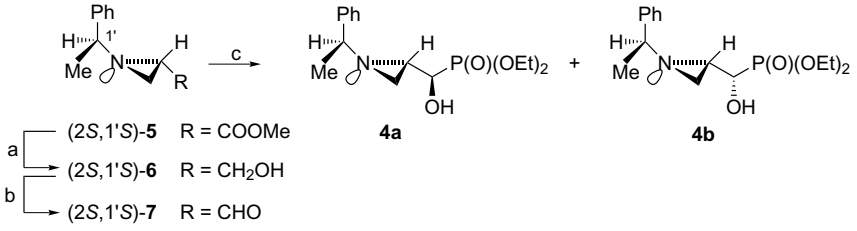
2. Results and discussion

Aziridines (2*S*,1′*S*)- and (2*R*,1′*S*)-**5** were prepared as described in the literature[35] in 42% and 40% yield, respectively. The ester groups were reduced with a sodium borohydride–lithium chloride mixture[38] to provide the corresponding alcohols (2*S*,1′*S*)- and (2*R*,1′*S*)-**6**, both in 87% yield, after column chromatography. Swern oxidation of (2*R*,1′*S*)-**6** gave the respective aldehyde (2*R*,1′*S*)-**7**, which was subjected to the NEt_3-catalysed addition of diethyl phosphite to afford 1-hydroxyphosphonates **3a** and **3b** in a 1:1 ratio (Scheme 2). These were then separated on a silica gel column to afford **3a** and **3b** as slightly yellowish oils in 29% and 37% yield, respectively.

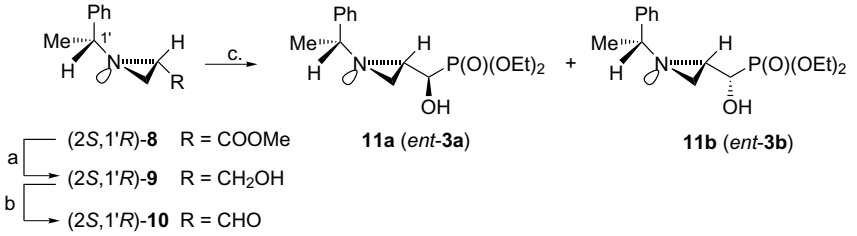
When aldehyde (2*S*,1′*S*)-**7** was subjected to phosphonylation (Scheme 3), a 1:1 mixture of the oily hydroxyphosphonates **4a** and **4b** was produced almost quantitatively, although several attempts at separating them on a silica gel column failed. However, a few fractions partially solidified over 48 h and after recrystallisation, phosphonate **4b** was separated in 14% yield.



Scheme 2. Reagents and conditions: (a) $NaBH_4$–LiCl, 0 °C to rt, 16 h, 87%; (b) DMSO, $(COCl)_2$, −78 °C, 1 h, TEA, −78 °C to rt, 15 min; (c) $(EtO)_2P(O)H$, NEt_3 10 mol %, rt, 3 d.



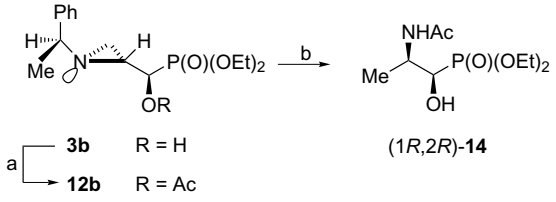
Scheme 3. Reagents and conditions: (a) $NaBH_4$–LiCl, 0 °C to rt, 16 h, 87%; (b) DMSO, $(COCl)_2$, −78 °C, 1 h, TEA, −78 °C to rt, 15 min; (c) $(EtO)_2P(O)H$, NEt_3 10 mol %, rt, 3 d.



Scheme 4. Reagents and conditions: (a) $NaBH_4$–LiCl, 0 °C to rt, 16 h, 78%; (b) DMSO, $(COCl)_2$, −78 °C, 1 h, TEA, −78 °C to rt, 15 min; (c) $(EtO)_2P(O)H$, NEt_3 10 mol %, rt, 3 d.

For this reason, aldehyde (2*S*,1′*R*)-**10** was prepared from aziridine (2*S*,1′*R*)-**8** [via alcohol (2*S*,1′*R*)-**9**] and was reacted with diethyl phosphite to give hydroxyphosphonates **11a** (*ent*-**3a**) and **11b** (*ent*-**3b**) in 43% and 35% yield, respectively (Scheme 4).

The aziridine ring cleavage and removal of the *N*-(1-phenylethyl) group was observed when the respective aziridine alcohols were subjected to hydrogenolysis leading to a variety of chiral amino alcohols.[37,38] Under similar conditions, hydrogenolyses of aziridine hydroxyphosphonates **3a** and **3b** gave complex reaction mixtures. However, after transformation into acetates **12a** and **12b** (Schemes 5 and 6) their hydrogenolyses were accomplished quantitatively. A 1:1 mixture of the 2-acetamidophosphonate (1*S*,2*R*)-**14** and 2-aminophosphonate (1*S*,2*R*)-**2** was formed from **12a**. On the other hand, acetate **12b** furnished the 2-acetamidophosphonate (1*R*,2*R*)-**14** as a single product.

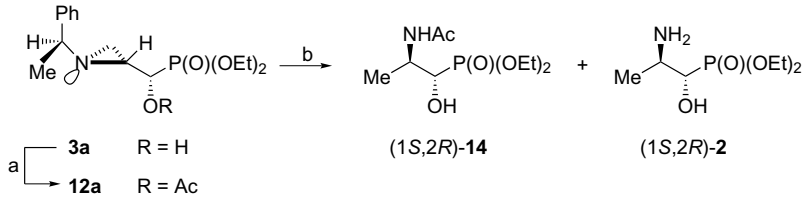


Scheme 6. Reagents and conditions: (a) Ac_2O, NEt_3, DMAP, rt, 16 h, 98%; (b) H_2, 20% $Pd(OH)_2$–C, methanol, 4 d.

In a similar fashion, aziridine phosphonates **11a** (*ent*-**3a**) and **11b** (*ent*-**3b**) were acetylated to give the respective acetates **13a** (*ent*-**12a**) and **13b** (*ent*-**12b**). Catalytic hydrogenation of **13a** led to a 1:1 mixture of (1*R*,2*S*)-**14** and (1*R*,2*S*)-**2**, while from **13b**, only 2-acetamidophosphonate (1*S*,2*S*)-**14** was produced.

The relative configurations of the diastereoisomeric diethyl 2-acetamido-1-hydroxypropylphosphonates have already been established.[28] Based on the comparison of the published NMR spectral data[28] and these described herein, the relative configurations in phosphonates (1*R*,2*R*)-**14** and (1*S*,2*S*)-**14** as well as in (1*R*,2*S*)-**14** and (1*S*,2*R*)-**14** could be assigned. The absolute configurations at C-2 in the 2-acetamidophosphonates (1*R*,2*R*)-**14** and (1*S*,2*R*)-**14** are the same as that in the starting aziridine ester (2*R*,1′*S*)-**5**,[35,36] which without traces of epimerisation, was transformed into the corresponding aldehyde (2*R*,1′*S*)-**7** and later into aziridinephosphonates **3b** and **3a** (Scheme 2), precursors to (1*R*,2*R*)-**14** and (1*S*,2*R*)-**14**, respectively.

In addition, the absolute configuration at C-1 in phosphonate **3a** can be independently assigned, based on the following arguments. The vicinal H1–H2, H2–P and P–C3 couplings, 2.7, 1.2 and 3.1 Hz, respectively, could only be observed, when phosphonate **3a** adopts the antiperiplanar conformation (Fig. 2), which is stabilised by a strong intra-



Scheme 5. Reagents and conditions: (a) Ac_2O, NEt_3, DMAP, rt, 16 h, 89%; (b) H_2, 20% $Pd(OH)_2$–C, methanol, 4 d.

molecular H-bond (N···H–O). This conclusion is further supported by the observation of a large vicinal *PCOH* coupling (22.2 Hz), which arises from the almost antiperiplanar disposition of the hydrogen and phosphorus atoms in the P–C–O–H unit. In this conformation, the bulky diethoxyphosphoryl group is located far away from the 1-phenylethyl moiety. Furthermore, analyses of the vicinal H–H, H–P and C–P coupling constants led us to conclude that (1*R*,2*R*)-**14** and (1*S*,2*R*)-**14** exist in preferred conformations, which are stabilised by strong intramolecular H-bonds (Fig. 2).

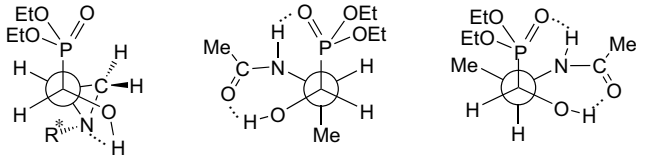
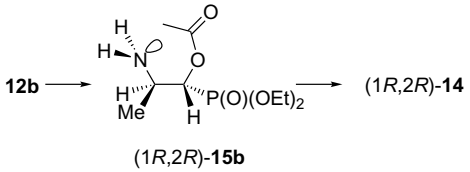
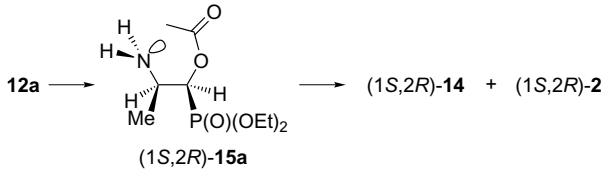


Figure 2. The preferred conformations of phosphonates **3a**, (1*R*,2*R*)-**14** and (1*S*,2*R*)-**14**.

Hydrogenolyses of acetates **12b** or **13b** led exclusively to 2-acetamidophosphonates (1*R*,2*R*)-**14** or (1*S*,2*S*)-**14**. On the other hand, from acetates **12a** or **13a** mixtures of 2-acetamidophosphonates (1*S*,2*R*)-**14** or (1*R*,2*S*)-**14** and 2-aminophosphonates (1*S*,2*R*)-**2** or (1*R*,2*S*)-**2** were formed. Undoubtedly, acetate **12b** was first transformed into *O*-acetate (1*R*,2*R*)-**15b** (Scheme 7), in which the intramolecular acetyl transfer is energetically highly favourable due to lack of spatial interactions of the methyl and *O*,*O*-diethylphosphoryl groups. However, this is not the case for the *O*-acetate (1*S*,2*R*)-**15a** (Scheme 8), in which severe repulsions of the bulky groups are expected to make the intramolecular transacetylation less feasible. The formation of significant amounts of (1*S*,2*R*)-**2** can be explained by assuming that the acetyl group is transferred in an intermolecular process, in which methanol acts as a competing nucleophile.

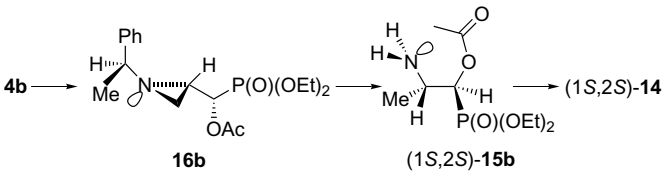


Scheme 7. Intermediate for the intramolecular acetyl transfer in (1*R*,2*R*)-**12b**.



Scheme 8. Intermediate for the intramolecular acetyl transfer in (1*S*,2*R*)-**12a**.

The absolute configuration at C-1 in phosphonate **4b** was assigned in the following way. After acetylation of **4b**, the hydrogenolysis of the crude acetate **16b** gave 2-acetamidophosphonate (1*S*,2*S*)-**14** as a single product (Scheme 9). This could only happen, if acetate (1*S*,2*S*)-**15b** was formed as an intermediate in the intramolecular acetyl transfer.



Scheme 9. Configurational assignment of phosphonate **4b**.

3. Conclusions

The reaction of aziridine aldehyde (2*R*,1′*S*)-**7** with diethyl phosphite led to a separable mixture of the respective aziridine hydroxyphosphonates **3a** and **3b**, while from aldehyde (2*S*,1′*S*)-**7**, only small quantities of the crystalline phosphonate **4b** were isolated. For this reason phosphonylation of the aziridine aldehyde (2*S*,1′*R*)-**10** was undertaken to provide enantiomers of **3a** and **3b**, phosphonates **11a** and **11b**. Acetylation of hydroxyphosphonates **3b** or **11b** furnished the corresponding acetates **12b** or **13b**, which were subjected to hydrogenolysis to give cleanly 2-acetamidophosphonates (1*R*,2*R*)-**14** or (1*S*,2*S*)-**14**. Acetates **12a** or **13a** obtained from hydroxyphosphonates **3a** or **11a** were transformed hydrogenolytically into mixtures of 2-acetamidophosphonates (1*S*,2*R*)-**14** or (1*R*,2*S*)-**14** and 2-aminophosphonates (1*S*,2*R*)-**2** or (1*R*,2*S*)-**2**.

4. Experimental

^{1}H NMR spectra were recorded with a Varian Mercury-300 spectrometer; chemical shifts δ in ppm with respect to TMS; coupling constants J in Hz. ^{13}C and ^{31}P NMR spectra were recorded on a Varian Mercury-300 machine at 75.5 and 121.5 MHz, respectively. IR spectral data were measured on an Infinity MI-60 FT-IR spectrometer. Melting points were determined on a Boetius apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of this Faculty on a Perkin Elmer PE 2400 CHNS 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); analytical TLC, Merck TLC plastic sheets silica gel 60 F_{254}.

4.1. Diethyl (*S*)- and (*R*)-hydroxy{(*R*)-1-[(*S*)-1-phenylethyl]-aziridin-2-yl}methylphosphonates 3a and 3b

A mixture of the crude aldehyde (2*R*,1′*S*)-**6** (0.787 g, 4.49 mmol) and diethyl phosphite (0.550 mL, 4.27 mmol) containing triethylamine (0.063 mL, 0.45 mmol) was left at room temperature for 3 days. The crude product was

chromatographed on a silica gel column with chloroform–methanol (100:1 to 50:1, v/v) to give phosphonates **3a** (0.393 g, 29%) and **3b** (0.499 g, 37%), both as slightly yellowish oils.

4.1.1. Diethyl (*S*)-hydroxy{(*R*)-1-[(*S*)-1-phenylethyl]aziridin-2-yl}methylphosphonate 3a. IR (film): $\nu = 3293$, 3061, 2980, 2930, 1449, 1237, 1027, 756, 702 cm^{-1}. $[\alpha]_D^{20} = -15.2$ (c 1.46, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.35–7.23$ (m, 5H), 4.20–4.08 (m, 4H, CH_2OP), 3.96 (dd, $J = 5.4$, 2.7 Hz, 1H, HCP), 3.56 (br d, $J = 22.2$ Hz, 1H, HO), 2.72 (q, $J = 6.6$ Hz, 1H, $HCCH_3$), 2.18 (d, $J = 3.6$ Hz, 1H, H_aCH_b), 1.97 (dddd, $J = 6.3$, 3.6, 2.7, 1.2 Hz, 1H, HCN), 1.59 (d, $J = 6.3$ Hz, 1H, H_aCH_b), 1.43 (d, $J = 6.6$ Hz, 3H, $HCCH_3$), 1.32 and 1.31 ($2 \times t$, $J = 7.1$ Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 143.8$, 128.6, 127.4, 126.5, 69.0, 64.1 (d, $J = 170.4$ Hz, CP), 63.0 and 62.6 ($2 \times d$, $J = 6.9$ Hz, CH_3CH_2OP), 37.2 (d, $J = 3.7$ Hz, CCP), 29.8 (d, $J = 3.1$ Hz, CCCP), 23.3, 16.8 and 16.7 ($2 \times d$, $J = 6.0$ Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 22.77$. Anal. Calcd for $C_{15}H_{24}NO_4P$: C, 57.50; H, 7.72; N, 4.47. Found: C, 57.21; H, 8.01; N, 4.29.

4.1.2. Diethyl (*R*)-hydroxy{(*R*)-1-[(*S*)-1-phenylethyl]aziridin-2-yl}methylphosphonate 3b. IR (film): $\nu = 3305$, 3059, 2981, 2929, 1449, 1233, 1052, 757, 701 cm^{-1}. $[\alpha]_D^{20} = -42.7$ (c 1.27, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.39–7.23$ (m, 5H), 4.11–3.92 (m, 4H, CH_2OP), 3.47 (ddd, $J = 7.2$, 6.3, 5.1 Hz, 1H, HCP), 2.60 (q, $J = 6.6$ Hz, 1H, $HCCH_3$), 2.15 (dd, $J = 14.7$, 5.1 Hz, 1H, HO), 1.98 (d, $J = 3.3$ Hz, 1H, H_aCH_b), 1.95 (dddd, $J = 6.6$, 6.3, 6.3, 3.3 Hz, 1H, HCN), 1.64 (d, $J = 6.3$ Hz, 1H, H_aCH_b), 1.44 (d, $J = 6.6$ Hz, 3H, $HCCH_3$), 1.26 and 1.23 ($2 \times t$, $J = 7.1$ Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 143.9$, 128.7, 127.6, 127.1, 69.5 (d, $J = 165.3$ Hz, CP), 69.2, 62.8 and 62.6 ($2 \times d$, $J = 6.9$ Hz, CH_3CH_2OP), 38.8 (d, $J = 6.0$ Hz, CCP), 31.9 (d, $J = 3.6$ Hz, CCCP), 23.0, 16.7 (d, $J = 5.4$ Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 22.20$. Anal. Calcd for $C_{15}H_{24}NO_4P$: C, 57.50; H, 7.72; N, 4.47. Found: C, 57.25; H, 8.00; N, 4.35.

4.2. Diethyl (*R*)- and (*S*)-hydroxy{(*S*)-1-[(*S*)-1-phenylethyl]-aziridin-2-yl}methylphosphonates 4a and 4b

A mixture of crude aldehyde (2*S*,1′*S*)-**6** (0.415 g, 2.37 mmol) and diethyl phosphite (0.290 mL, 2.25 mmol) containing triethylamine (0.033 mL, 0.24 mmol) was left at room temperature for 3 days. The crude product was chromatographed on a silica gel column with chloroform–methanol (100:1 to 50:1, v/v) to give several fractions containing various mixtures of phosphonates **4a** and **4b**. The fractions consisting of oil and crystals were collected and recrystallised from methylene chloride–hexanes to give **4b** (0.097 g, 14%) as short white needles; mp 104–105 °C. IR (film): $\nu = 3274$, 3065, 2979, 2931, 1455, 1242, 1017, 758, 706 cm^{-1}. $[\alpha]_D^{20} = -54.7$ (c 1.06, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.37–7.24$ (m, 5H), 4.29–4.19 (m, 4H, CH_2OP), 3.77 (ddd, $J = 7.5$, 6.3, 3.6 Hz, 1H, HCP), 3.24 (dd, $J = 6.9$, 6.3 Hz, 1H, HO), 2.67 (q, $J = 6.6$ Hz, 1H, $HCCH_3$), 2.15 (dddd, $J = 6.6$, 3.6, 3.6, 3.3 Hz, 1H, HCN), 1.78 (dd, $J = 3.6$, 0.9 Hz, 1H, H_aCH_b), 1.50 (d, $J = 6.6$ Hz, 3H, $HCCH_3$), 1.44 (d, $J = 6.6$ Hz, 1H, H_aCH_b), 1.39 and 1.38 ($2 \times t$, $J = 7.1$ Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 144.2$, 128.5, 127.3, 126.8, 69.0, 67.3 (d, $J = 163.8$ Hz, CP), 63.0 and 62.9 ($2 \times d$, $J = 7.6$ Hz, CH_3CH_2OP), 39.0 (d, $J = 5.3$ Hz, CCP), 30.3 (d, $J = 6.8$ Hz, CCCP), 23.7, 16.9 and 16.9 ($2 \times d$, $J = 5.4$ Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 22.54$. Anal. Calcd for $C_{15}H_{24}NO_4P$: C, 57.50; H, 7.72; N, 4.47. Found: C, 57.71; H, 8.00; N, 4.66.

4.3. Diethyl (*R*)- and (*S*)-hydroxy{(*S*)-1-[(*R*)-1-phenylethyl]-aziridin-2-yl}methylphosphonates 11a and 11b

A mixture of crude aldehyde (2*S*,1′*R*)-**6** (1.34 g, 7.66 mmol) and diethyl phosphite (0.938 mL, 7.28 mmol) containing triethylamine (0.107 mL, 0.766 mmol) was left at room temperature for 3 days. The crude product was chromatographed on a silica gel column with chloroform–methanol (100:1 to 50:1, v/v) to give phosphonates **11a** (0.973 g, 43%) and **3 b** (0.790 g, 35%), both as colourless oils.

4.3.1. Diethyl (*R*)-hydroxy{(*S*)-1-[(*R*)-1-phenylethyl]aziridin-2-yl}methylphosphonate 11a. $[\alpha]_D^{20} = +16.5$ (c 1.5, $CHCl_3$). Anal. Calcd for $C_{15}H_{24}NO_4P$: C, 57.50; H, 7.72; N, 4.47. Found: C, 57.28; H, 7.85; N, 4.40.

4.3.2. Diethyl (*S*)-hydroxy{(*S*)-1-[(*R*)-1-phenylethyl]aziridin-2-yl}methylphosphonate 11b. $[\alpha]_D^{20} = +43.8$ (c 1.28, $CHCl_3$). Anal. Calcd for $C_{15}H_{24}NO_4P$: C, 57.50; H, 7.72; N, 4.47. Found: C, 57.21; H, 8.01; N, 4.38.

4.4. Acetylation of phosphonates 3a, 3b, 11a and 11b (general procedure)

A mixture of the phosphonate (0.313 g, 1.00 mmol), acetic anhydride (0.283 mL, 3.00 mmol) and triethylamine (0.460 mL, 3.30 mmol) containing DMAP (0.012 g, 0.1 mmol) was left at room temperature for 16 h. The crude product was diluted with methylene chloride (20 mL). A solution was washed with water (6×10 mL), dried over $MgSO_4$, concentrated in vacuo and the residue was chromatographed on a silica gel column with hexanes–isopropanol (50:1 to 20:1, v/v) to give pure acetates.

4.4.1. Diethyl (*S*)-acetoxy{(*R*)-1-[(*S*)-1-phenylethyl]aziridin-2-yl}methylphosphonate 12a. From phosphonate **3a** (0.343 g, 1.09 mmol), acetate **12a** (0.346 g, 89%) was obtained as a colourless oil. IR (film): $\nu = 2980$, 2928, 1751, 1449, 1220, 1023, 757, 701 cm^{-1}. $[\alpha]_D^{20} = +4.5$ (c 1.3, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.35–7.21$ (m, 5H), 5.25 (dd, $J = 9.9$, 3.9 Hz, 1H, HCP), 4.11–3.91 (m, 4H, CH_2OP), 2.52 (q, $J = 6.6$ Hz, 1H, $HCCH_3$), 2.08 (d, $J = 0.3$ Hz, 3H), 2.05 (d, $J = 3.6$ Hz, 1H, H_aCH_b), 1.89 (dddd, $J = 6.3$, 5.7, 3.9, 3.6 Hz, 1H, HCN), 1.43 (d, $J = 6.3$ Hz, 1H, H_aCH_b), 1.37 (d, $J = 6.6$ Hz, 3H, $HCCH_3$), 1.27 and 1.22 ($2 \times t$, $J = 7.1$ Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 169.4$ (d, $J = 6.8$ Hz, COCP), 143.9, 128.3, 127.1, 127.0, 70.0,

66.8 (d, $J = 167.6$ Hz, *C*P), 63.1 and 62.7 ($2 \times d$, $J = 6.6$ Hz, CH_3CH_2OP), 36.5 (d, $J = 4.5$ Hz, *C*CP), 30.5 (d, $J = 4.5$ Hz, *C*CCP), 23.6, 20.9, 16.7 and 16.6 ($2 \times d$, $J = 5.7$ Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 19.11$. Anal. Calcd for $C_{17}H_{26}NO_5P$: C, 57.46; H, 7.37; N, 3.94. Found: C, 57.17; H, 7.13; N, 3.69.

4.4.2. Diethyl (*R*)-acetoxy{(*R*)-1-[(*S*)-1-phenylethyl]aziridin-2-yl}methylphosphonate 12b. From phosphonate **3b** (0.428 g, 1.37 mmol), acetate **12b** (0.485 g, 98%) was obtained as a colourless oil. IR (film): $\nu = 2980$, 2929, 1745, 1450, 1224, 1029, 759, 702 cm^{-1}. $[\alpha]_D^{20} = -31.2$ (*c* 1.28, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.33$–7.21 (m, 5H), 4.76 (dd, $J = 10.5$, 9.0 Hz, 1H, HCP), 4.15–4.05 (m, 4H, CH_2OP), 2.42 (q, $J = 6.6$ Hz, 1H, *H*CCH$_3$), 2.06 (d, $J = 3.3$ Hz, 1H, H_aCH_b), 1.87 (dddd, $J = 9.0$, 6.6, 3.3, 3.0 Hz, 1H, HCN), 1.69 (s, 3H), 1.67 (d, $J = 6.6$ Hz, 1H, H_aCH_b), 1.40 (d, $J = 6.6$ Hz, 3H, HCC*H*$_3$), 1.29 and 1.28 ($2 \times t$, $J = 7.2$ Hz, 6H, C*H*$_3$CH$_2$OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 169.2$ (d, $J = 5.1$ Hz, *C*OCP), 144.4, 128.4, 127.2, 127.1, 70.9 (d, $J = 167.6$ Hz, *C*P), 70.2 (d, $J = 1.5$ Hz, *C*NCCP), 63.2 and 63.0 ($2 \times d$, $J = 6.8$ Hz, CH_3CH_2OP), 37.8 (d, $J = 7.6$ Hz, *C*CP), 32.2 (s, *C*CCP), 23.2, 20.7, 16.8 and 16.7 ($2 \times d$, $J = 6.0$ Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 18.45$. Anal. Calcd for $C_{17}H_{26}NO_5P$: C, 57.46; H, 7.37; N, 3.94. Found: C, 57.24; H, 7.60; N, 3.73.

4.4.3. Diethyl (*R*)-acetoxy{(*S*)-1-[(*R*)-1-phenylethyl]aziridin-2-yl}methylphosphonate 13a. From phosphonate **11a** (0.553 g, 1.77 mmol), acetate **13a** (0.525 g, 84%) was obtained as a colourless oil. $[\alpha]_D^{20} = -5.7$ (*c* 1.87, $CHCl_3$). Anal. Calcd for $C_{17}H_{26}NO_5P$: C, 57.46; H, 7.37; N, 3.94. Found: C, 57.31; H, 7.59; N, 3.76.

4.4.4. Diethyl (*S*)-acetoxy{(*S*)-1-[(*R*)-1-phenylethyl]aziridin-2-yl}methylphosphonate 13b. From phosphonate **11b** (0.308 g, 0.983 mmol), acetate **13b** (0.299 g, 86%) was obtained as a colourless oil. $[\alpha]_D^{20} = +35.3$ (*c* 2.13, $CHCl_3$). Anal. Calcd for $C_{17}H_{26}NO_5P$: C, 57.46; H, 7.37; N, 3.94. Found: C, 57.74; H, 7.62; N, 3.91.

4.5. Hydrogenolysis of acetates 12a, 12b, 13a and 13b (general procedure)

A solution of acetates **12a**, **12b**, **13a** or **13b** (0.355 g, 1.00 mmol) in methanol (5 mL) was kept under an atmospheric pressure of hydrogen over 20% $Pd(OH)_2$–C (20 mg) at room temperature for 3 days. The suspension was filtered through a layer of Celite. The solution was concentrated and chromatographed on a silica gel column with chloroform–methanol (first, 20:1 and later 3:1, v/v).

4.5.1. Hydrogenolysis of acetate 12a. From acetate **12a** (0.313 g, 0.881 mmol), diethyl (1*S*,2*R*)-2-acetamido-1-hydroxypropylphosphonate (1*S*,2*R*)-**14** (0.077 g, 38%) was separated as a white amorphous solid followed by diethyl (1*S*,2*R*)-2-amino-1-hydroxypropylphosphonate (1*S*,2*R*)-**2** (0.049 g, 24%) as a colourless oil.

4.5.1.1. Diethyl (1*S*,2*R*)-2-acetamido-1-hydroxypropylphosphonate (1*S*,2*R*)-14. Mp 86–87 °C. IR (KBr): $\nu = 3268$, 2986, 2936, 1631, 1557, 1440, 1216, 1053 cm^{-1}. $[\alpha]_D^{20} = +37.8$ (*c* 1.04, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.49$ (d, $J = 7.2$ Hz, 1H, HN), 4.80 (dd, $J = 7.5$, 7.2 Hz, 1H, HO), 4.36 (dddq, $J = 20.7$, 7.2, 2.4, 6.9 Hz, 1H, HCCP), 4.24–4.13 (m, 4H, CH_2OP), 4.00 (ddd, $J = 9.3$, 7.5, 2.4 Hz, 1H, HCP), 2.01 (s, 3H), 1.36 and 1.34 ($2 \times t$, $J = 7.2$ Hz, 6H, C*H*$_3$CH$_2$OP), 1.33 (d, $J = 6.9$ Hz, 3H, C*H*$_3$CH). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 171.4$, 71.6 (d, $J = 158.6$ Hz, *C*P), 63.5 and 62.8 ($2 \times d$, $J = 6.8$ Hz, CH_3CH_2OP), 48.6 (d, $J = 4.5$ Hz, *C*CP), 23.4, 16.7 and 16.7 ($2 \times d$, $J = 6.0$ Hz, CH_3CH_2OP), 16.5 (s, *C*CCP). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 22.18$. Anal. Calcd for $C_9H_{20}NO_5P$: C, 42.69; H, 7.96; N, 5.53. Found: C, 42.41; H, 7.80; N, 5.27.

4.5.1.2. Diethyl (1*S*,2*R*)-2-amino-1-hydroxypropylphosphonate (1*S*,2*R*)-2. IR (film): $\nu = 3322$, 2985, 1625, 1521, 1340, 1222, 1049 cm^{-1}. $[\alpha]_D^{20} = +5.9$ (*c* 1.08, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.2$–4.8 (br s, 7H, H_2N, HO, $2H_2O$), 4.59 (dd, $J = 12.9$, 2.4 Hz, 1H, HCP), 4.28–4.16 (m, 4H, CH_2OP), 3.82 (ddq, $J = 2.4$, 2.1, 6.9 Hz, 1H, HCCP), 1.49 (d, $J = 6.9$ Hz, 3H, C*H*$_3$CH), 1.35 (t, $J = 7.2$ Hz, 6H, C*H*$_3$CH$_2$OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 68.5$ (d, $J = 164.6$ Hz, *C*P), 63.7 and 63.3 ($2 \times d$, $J = 6.8$ Hz, CH_3CH_2OP), 49.3 (d, $J = 9.1$ Hz, *C*CP), 16.7 and 16.7 ($2 \times d$, $J = 6.0$ Hz, CH_3CH_2OP), 15.5 (d, $J = 2.3$ Hz, *C*CCP). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 22.76$. Anal. Calcd for $C_7H_{18}NO_4P{\cdot}2H_2O$: C, 34.01; H, 8.97; N, 5.67. Found: C, 34.30; H, 8.67; N, 5.43.

4.5.2. Hydrogenolysis of acetate 12b. From acetate **12b** (0.476 g, 1.34 mmol), diethyl (1*R*,2*R*)-2-acetamido-1-hydroxypropylphosphonate (1*R*,2*R*)-**14** (0.230 g, 68%) was obtained as an amorphous solid.

4.5.2.1. Diethyl (1*R*,2*R*)-2-acetamido-1-hydroxypropylphosphonate (1*R*,2*R*)-14. Mp 75–76 °C. IR (KBr): $\nu = 3340$, 3239, 2986, 2924, 1648, 1541, 1378, 1221, 1056 cm^{-1}. $[\alpha]_D^{20} = +21.5$ (*c* 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.73$ (d, $J = 7.2$ Hz, 1H, HN), 5.05 (dd, $J = 8.1$, 5.4 Hz, 1H, HO), 4.29 (dddq, $J = 10.5$, 7.2, 3.6, 6.9 Hz, 1H, HCCP), 4.23–4.11 (m, 4H, CH_2OP), 3.90 (ddd, $J = 8.7$, 8.1, 3.6 Hz, 1H, HCP), 1.98 (s, 3H), 1.35 and 1.35 ($2 \times t$, $J = 7.2$ Hz, 6H, C*H*$_3$CH$_2$OP), 1.34 (d, $J = 6.9$ Hz, 3H, C*H*$_3$CH). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 170.4$, 71.0 (d, $J = 161.6$ Hz, *C*P), 63.2 and 63.1 ($2 \times d$, $J = 6.8$ Hz, CH_3CH_2OP), 46.9 (d, $J = 1.5$ Hz, *C*CP), 23.5, 17.9 (d, $J = 11.3$ Hz, *C*CCP), 16.7 (d, $J = 5.3$ Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 22.81$. Anal. Calcd for $C_9H_{20}NO_5P$: C, 42.69; H, 7.96; N, 5.53. Found: C, 42.93; H, 8.20; N, 5.51.

4.5.3. Hydrogenolysis of acetate 13a. From acetate **13a** (0.367 g, 1.03 mmol), diethyl (1*R*,2*S*)-2-acetamido-1-hydroxypropylphosphonate (1*R*,2*S*)-**14** (0.072 g, 31%) was separated as a white amorphous solid followed by diethyl (1*R*,2*S*)-2-amino-1-hydroxypropylphosphonate (1*R*,2*S*)-**2** (0.076 g, 33%) as a colourless oil.

4.5.3.1. Diethyl (1*R*,2*S*)-2-acetamido-1-hydroxypropylphosphonate (1*R*,2*S*)-14. Mp 86–87 °C. $[\alpha]_D^{20} = -38.2$ (*c*

1.12, $CHCl_3$). Anal. Calcd for $C_9H_{20}NO_5P$: C, 42.69; H, 7.96; N, 5.53. Found: C, 42.54; H, 8.22; N, 5.53.

4.5.3.2. Diethyl (1*R*,2*S*)-2-amino-1-hydroxypropylphosphonate (1*R*,2*S*)-2. $[\alpha]_D^{20} = -5.8$ (*c* 1.01, CH_3OH). Anal. Calcd for $C_7H_{18}NO_4P{\cdot}2H_2O$: C, 34.01; H, 8.97; N, 5.67. Found: C, 34.24; H, 9.15; N, 5.59.

4.5.4. Hydrogenolysis of acetate 13b. From acetate **13b** (0.252 g, 0.709 mmol), diethyl (1*S*,2*S*)-2-acetamido-1-hydroxypropylphosphonate (1*S*,2*S*)-**14** (0.128 g, 71%) was obtained as a white amorphous solid.

4.5.4.1. Diethyl (1*S*,2*S*)-2-acetamido-1-hydroxypropylphosphonate (1*S*,2*S*)-14. Mp 75–76 °C. $[\alpha]_D^{20} = -19.4$ (*c* 0.69, $CHCl_3$). Anal. Calcd for $C_9H_{20}NO_5P$: C, 42.69; H, 7.96; N, 5.53. Found: C, 42.83; H, 8.21; N, 5.51.

4.6. Diethyl (1*S*,2*S*)-2-acetamido-1-hydroxypropylphosphonate (1*S*,2*S*)-14

Hydroxyphosphonate **4b** (0.040 g, 0.13 mmol) was acetylated as described in Section 4.4 to give the crude acetate **16b** (0.045 g, 100%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.29$–7.15 (m, 5H), 4.82 (dd, $J = 9.9$, 9.0 Hz, 1H, HCP), 4.17–4.05 (m, 4H, CH_2OP), 2.39 (q, $J = 6.6$ Hz, 1H, $HCCH_3$), 2.12 (s, 3H), 1.93 (dddd, $J = 9.0$, 6.3, 3.6, 2.7 Hz, 1H, HCN), 1.75 (d, $J = 3.6$ Hz, 1H, H_aCH_b), 1.45 (d, $J = 6.3$ Hz, 1H, H_aCH_b), 1.31 (d, $J = 6.6$ Hz, 3H, $HCCH_3$), 1.28 and 1.25 ($2 \times t$, $J = 7.2$ Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 169.3$ (d, $J = 4.6$ Hz, *C*OCP), 144.1, 128.4, 127.2, 126.9, 71.1 (d, $J = 166.1$ Hz, *C*P), 69.4 (s, *C*NCCP), 63.1 and 63.0 ($2 \times d$, $J = 6.9$ Hz, CH_3CH_2OP), 38.6 (d, $J = 6.8$ Hz, *C*CP), 32.0 (s, *C*CCP), 23.5, 21.0, 16.8 and 16.7 ($2 \times d$, $J = 5.4$ Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 18.53$.

Acetate **16b** was hydrogenolysed according to the general procedure (Section 4.5) to afford phosphonate (1*S*,2*S*)-**14** (0.029 g, 91%), which in all respects was identical to the compound described in Section 4.5.4.1.

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