Tetrahedron: *Asymmetry* 20 (2009) 2240–2246

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Synthesis of four enantiomers of 2,3-di(*N*-Boc-amino)-1-hydroxypropylphosphonates

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ARTICLE INFO

Article history:
Received 24 July 2009
Accepted 27 August 2009
Available online 26 September 2009

ABSTRACT

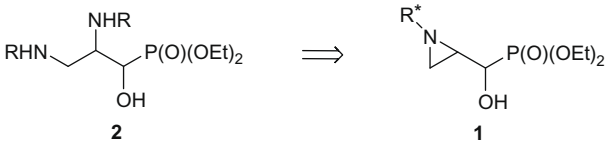
Enantiomerically pure diethyl (1*S*,2*R*)-, (1*S*,2*S*)-, (1*R*,2*R*)- and (1*R*,2*S*)-2,3-di(*tert*-butoxycarbonyl)amino-1-hydroxypropylphosphonates were synthesised from diethyl (1*S*,2*R*,1′*S*)-, (1*S*,2*S*,1′*R*)-, (1*R*,2*R*,1′*S*)- and (1*R*,2*S*,1′*R*)-[*N*-(1-phenylethyl)]-2,3-epimino-1-hydroxypropylphosphonates, respectively, via aziridine ring opening with neat $TMSN_3$ followed by hydrogenolysis in the presence of Boc_2O. A plausible mechanism for the aziridine ring opening in 2,3-epimino-1-hydroxypropylphosphonates involving the intermediate aziridinium ions was proposed. Significant differences in the rates of the aziridine ring opening between diastereoisomeric phosphonates (1*S*,2*R*,1′*S*) and (1*S*,2*S*,1′*R*) were rationalised taking into account different conformations of the 1-phenylethyl group in both diastereoisomers.

1. Introduction

Several diaminoalkylphosphonates are known to exhibit biological activity. 2-N-Substituted 1,2-diaminoethylphosphonates were found to inhibit cytosolic and microsomal aminopeptidases.[1] Peptidomimetics containing substituted 1,2-diaminoethyl- and 1,3-diaminopropylphosphonate fragments appeared to be potent inhibitors of human fibroblast collagenase activity.[2] Analogues of phosphoramidone in which a phosphate residue was replaced by 1,3-diaminopropylphosphonate moiety inhibited endothelin-converting enzyme (ECE).[3] Tripeptides having the diphenyl 1-amino-3-guaninylpropylphosphonate residue at the C-terminus inhibited trypsin-like serine proteases.[4] Analogues of glutathione modified at the C-terminus with 2,3-diaminopropylphosphonate showed modest activity as glutathionylspermidine synthethase inhibitors.[5]

Although a plethora of synthetic methods leading to 1,2-diaminoalkylphosphonates are known,[2,4–16] 1,3- and 2,3-diaminoalkyl phosphonates are much less accessible. Recently, four of the eight possible enantiomers of diethyl hydroxy-1-{[(*R*)- or (*S*)-1-phenylethyl]aziridin-2-yl}methylphosphonate **1** became readily available[17] from the respective aldehydes employing the Abramov reaction.[18] Since aziridines are known to react with various nucleophiles[19] including ammonia,[20] amines[21–33] and azides[24,26,27,34–45] we reasoned that the successful opening of the aziridine ring in **1** with nitrogen nucleophiles would provide a vicinal diamine system and thus the protected 2,3-diamino-1-hydroxypropylphosphonates **2** could be synthesised (Scheme 1). To achieve this goal trimethylsilyl azide was selected as a source of highly nucleophilic azide possibly functioning also as an aziridine nitrogen activator.[45]

The aim of this paper is the synthesis of all four enantiomerically pure diethyl 2,3-[di(*tert*-butoxycarbonyl)amino]-1-hydroxypropylphosphonates **3** (**2** R = Boc) employing the appropriate phosphonates **1** as the starting materials.



Scheme 1. Retrosynthesis of 2,3-diaminophosphonates.

2. Results and discussion

When a dichloromethane solution of aziridinephosphonate (1*S*,2*R*,1′*S*)-**1a** was treated with trimethylsilyl azide at room temperature for 14 days, a 56:44 mixture of 1-trimethylsilyloxyphosphonate (1*S*,2*R*,1′*S*)-**4a** and 1-hydroxyphosphonate (1*S*,2*R*,1′*S*)-**5a** was produced (Scheme 2). Both phosphonates were cleanly separated on a silica gel column to give pure (1*S*,2*R*,1′*S*)-**4a** and (1*S*,2*R*,1′*S*)-**5a** in 31% and 47% yield, respectively. After standard desilylation of (1*S*,2*R*,1′*S*)-**4a** with tetrabutylammonium fluoride, the total yield of (1*S*,2*R*,1′*S*)-**5a** reached 62%. We found that aziridine ring opening in (1*S*,2*R*,1′*S*)-**1a** could be also achieved without solvent to directly give (1*S*,2*R*,1′*S*)-**5a** which was isolated in 85% yield after column chromatography. Catalytic [$Pd(OH)_2$–C] reduction of the azide and hydrogenolysis of the (*S*)-1-phenylethylamino group was performed in the presence of Boc_2O and led to the formation of diethyl (1*S*,2*R*)-2,3-di(*tert*-butoxycarbonylamino)-1-hydroxypropyl phosphonate (1*S*,2*R*)-**3** in 87% yield (Scheme 2).

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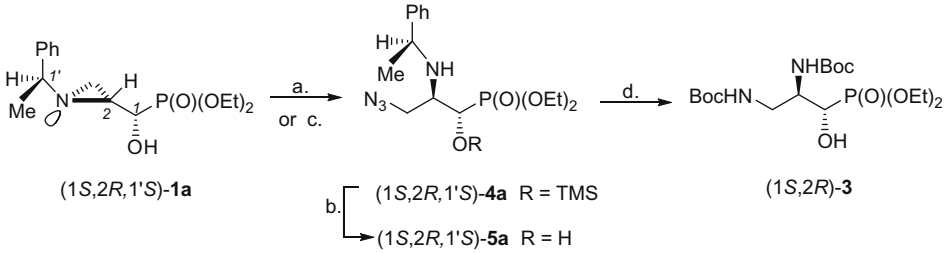
doi:10.1016/j.tetasy.2009.08.032



Scheme 2. Reagents and conditions: (a) $TMSN_3$, CH_2Cl_2, rt, 14 d; (b) Bu_4NF, THF, 2 h, 59%; (c) $TMSN_3$, rt, 14 d, 85% and (d) H_2, 20% $Pd(OH)_2$–C, Boc_2O, ethanol, 3 d, 87%.

To synthesise diaminophosphonate (1*S*,2*S*)-**3** aziridine (1*S*,2*S*,1′*R*)-**1b** was used as a starting material (Scheme 3). Aziridine ring opening of phosphonate (1*S*,2*S*,1′*R*)-**1b** with trimethylsilyl azide in dichloromethane was complete at room temperature after four days providing a 47:53 mixture of *O*-TMS derivative (1*S*,2*S*,1′*R*)-**4b** and 1-hydroxyphosphonate (1*S*,2*S*,1′*R*)-**5b**. Again this mixture was separated on a silica gel column to afford pure (1*S*,2*S*,1′*R*)-**4b** and (1*S*,2*S*,1′*R*)-**5b** in 37% and 46% yield, respectively. Removal of the silyl group from (1*S*,2*S*,1′*R*)-**4b** gave the required 1-hydroxyphosphonate (1*S*,2*S*,1′*R*)-**5b** improving the total yield of (1*S*,2*S*,1′*R*)-**5b** to 80%. When phosphonate (1*S*,2*S*,1′*R*)-**1b** was treated with neat trimethylsilyl azide, (1*S*,2*S*,1′*R*)-**5b** was obtained in one step in 85% yield. Standard transformation of the azide and 1-phenylethylamino groups into *N*-*tert*-butoxycarbonylamino moieties gave di(*N*-Boc-amino)phosphonate (1*S*,2*S*)-**3** in 91% yield.

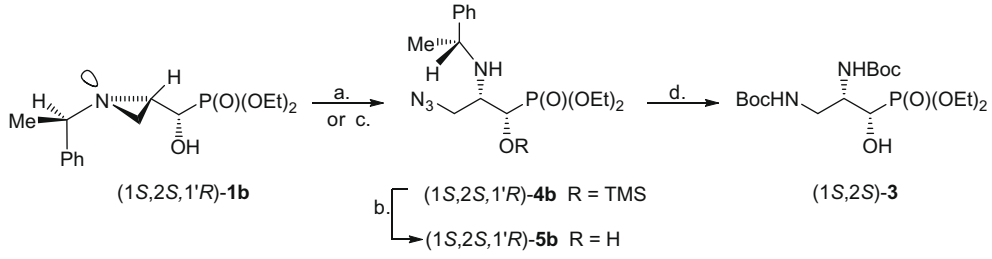
The synthesis of phosphonate (1*R*,2*R*)-**3** could be accomplished using aziridinephosphonate (1*R*,2*R*,1′*S*)-**1c** (*ent*-**1b**) as a starting material. Treatment of (1*R*,2*R*,1′*S*)-**1c** with trimethylsilyl azide without solvent at room temperature for four days cleanly provided 1-hydroxyphosphonate (1*R*,2*R*,1′*S*)-**5c** (*ent*-**5b**) in 85% yield after chromatographic purification (Scheme 4). Catalytic reduction of this product with simultaneous *N*-Boc protection gave diaminophosphonate (1*R*,2*R*)-**3** in 92% yield.

Finally, for the synthesis of diaminophosphonate (1*R*,2*S*)-**3** aziridinephosphonate (1*R*,2*S*,1′*R*)-**1d** (*ent*-**1a**) was selected. Based on our previous experience it was necessary to keep (1*R*,2*S*,1′*R*)-**1d** (*ent*-**1a**) with neat trimethylsilyl azide at room temperature for 14 days to complete the aziridine ring opening. The respective azide (1*R*,2*S*,1′*R*)-**5d** (*ent*-**5a**) was obtained in 85% yield after column chromatography. Its transformation into phosphonate (1*R*,2*S*)-**3** was accomplished in 87% in a standard manner (Scheme 5).

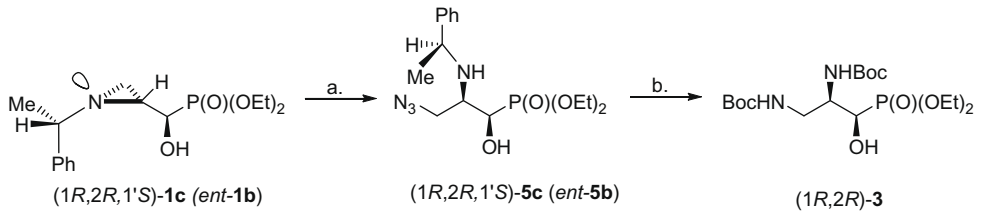
Although the mechanism of the aziridine ring opening in phosphonates (1*S*,2*R*,1′*S*)-**1a** and (1*S*,2*S*,1′*R*)-**1b** was not studied in detail, some comments can be made based on the literature data. It is known that trimethylsilyl azide reacts with alcohols[46–48] (with ethanol even exothermically[49]) to give *O*-TMS ethers and hydrogen azide (pK_a 4.75). Since hydrogen azide readily reacts with aliphatic amines to form stable ammonium salts[49,50] one may envisage it is also able to protonate the less basic nitrogen atom in aziridines **1** (pK_a of the aziridinium ion 7.98) to produce the respective aziridinium ions **7** and thus to activate the three-membered ring for the nucleophilic attack with the azide anion (Scheme 6). On the other hand, in the presence of a residual water trimethylsilyl azide is immediately hydrolysed and phosphonates **1** are transformed into the respective aziridinium ions **8**.

To verify our assumptions reactions of phosphonates (1*S*,2*R*,1′*S*)-**1a** and (1*S*,2*S*,1′*R*)-**1b** with 2 equiv of trimethylsilyl azide were monitored by the ^{31}P NMR spectroscopy. The results of our observations are collected in Tables 1 and 2.

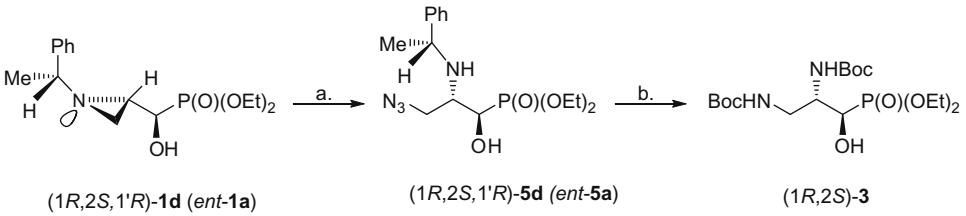
Identification of the particular components of the reaction mixtures was accomplished as follows. Phosphonates (1*S*,2*R*,1′*S*)-**1a** and (1*S*,2*S*,1′*R*)-**1b** are known,[17] the reaction products (1*S*,2*R*,1′*S*)-**4a** and (1*S*,2*R*,1′*S*)-**5a** as well as (1*S*,2*S*,1′*R*)-**4b** and (1*S*,2*S*,1′*R*)-**5b**, respectively, are described in this paper and the formation of *O*-TMS derivatives of the starting materials (1*S*,2*R*,1′*S*)-**6a** and (1*S*,2*S*,1′*R*)-**6b** was proved by the ^{31}P NMR spectroscopy (vide



Scheme 3. Reagents and conditions: (a) $TMSN_3$, CH_2Cl_2, rt, 4 d; (b) Bu_4NF, THF, 2 h, 88%; (c) $TMSN_3$, rt, 4 d, 85% and (d) H_2, 20% $Pd(OH)_2$–C, Boc_2O, ethanol, 3 d, 91%.

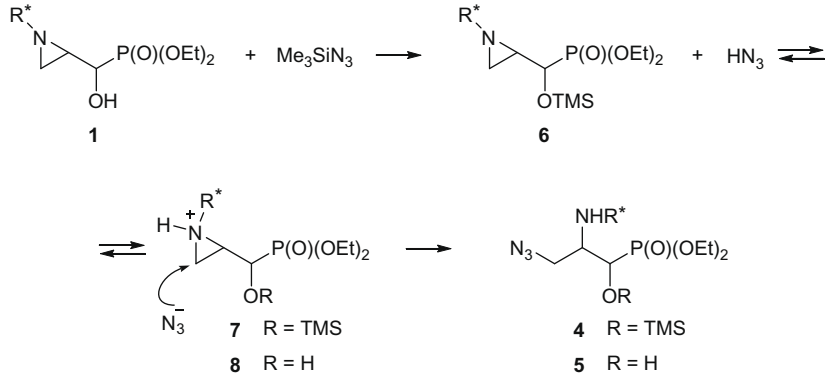


Scheme 4. Reagents and conditions: (a) $TMSN_3$, rt, 4 d; 85% and (b) H_2, 20% $Pd(OH)_2$–C, Boc_2O, ethanol, 3 d, 92%.



(1*R*,2*S*,1′*R*)-**1d** (*ent*-**1a**) (1*R*,2*S*,1′*R*)-**5d** (*ent*-**5a**) (1*R*,2*S*)-**3**

Scheme 5. Reagents and conditions: (a) $TMSN_3$, rt, 14 d; 85% and (b) H_2, 20% $Pd(OH)_2$–C, Boc_2O, ethanol, 3 d, 87%.



Scheme 6. A plausible mechanism of the aziridine ring opening in phosphonates **1**.

Table 1
Monitoring of the reaction of phosphonate (1*S*,2*R*,1′*S*)-**1a** with 2 equiv of trimethylsilyl azide

Time (h)	Compound/δ^{31}P NMR			
	(1*S*,2*R*,1′*S*)-**4a** 23.85	(1*S*,2*R*,1′*S*)-**5a** 23.75	(1*S*,2*R*,1′*S*)-**1a** 23.03	(1*S*,2*R*,1′*S*)-**6a** 22.77
6	3%	5%	81%	11%
24	19%	14%	56%	11%
48	25%	24%	46%	5%
72	25%	33%	39%	2%
96	26%	35%	35%	1%
168	27%	43%	31%	n.d.
264	28%	40%	30%	n.d.
360	51%	29%	18%	n.d.
720	32%	52%	14%	n.d.

n.d.—not detected.

Table 2
Monitoring of the reaction of phosphonate (1*S*,2*S*,1′*R*)-**1b** with 2 equiv of trimethylsilyl azide

Time (h)	Compound/δ^{31}P NMR		
	(1*S*,2*S*,1′*R*)-**4b** and (1*S*,2*S*,1′*R*)-**5b** 23.40	(1*S*,2*S*,1′*R*)-**6b** 22.57	(1*S*,2*S*,1′*R*)-**1b** 22.42
2.5	13%	5%	82%
7.5	28%	8%	62%
23	59%	9%	29%
48	86%	2%	7%
72	94%	n.d.	2%

n.d.—not detected.

infra). It should be noted that some unidentified phosphonates were also formed in both cases and their quantities account for the balance to 100%.

It appeared that silylation of the secondary hydroxy groups in phosphonates (1*S*,2*R*,1′*S*)-**1a** and (1*S*,2*S*,1′*R*)-**1b** with trimethylsilyl azide occurred but amounts of the respective *O*-TMS phosphonates (1*S*,2*R*,1′*S*)-**6a** and (1*S*,2*S*,1′*R*)-**6b** in both cases reached roughly 10% in early stages of the reaction and the respective ^{31}P NMR signals soon collapsed. This observation supports our predictions that besides *O*-TMS phosphonates (1*S*,2*R*,1′*S*)-**6a** and (1*S*,2*S*,1′*R*)-**6b** parent phosphonates (1*S*,2*R*,1′*S*)-**1a** and (1*S*,2*S*,1′*R*)-**1b** can also be transformed into the respective aziridinium ions before they react with azide. The ratios of both products of the azidolysis of phosphonate (1*S*,2*R*,1′*S*)-**1a**, namely 3-azidophosphonate (1*S*,2*R*,1′*S*)-**4a** and its *O*-TMS derivative (1*S*,2*R*,1′*S*)-**5a**, can be readily followed by the ^{31}P NMR spectroscopy and are influenced by several factors including possible hydrolysis of trimethylsilyl ethers during a long-term monitoring. On the other hand, 3-azidophosphonates (1*S*,2*S*,1′*R*)-**4b** and (1*S*,2*S*,1′*R*)-**5b** did not give well separated signals in the ^{31}P NMR spectra at 121.5 MHz but the formation of these compounds was evident from the ^{1}H NMR spectra taken simultaneously. Finally, both monitorings support our observations from the preparative scale experiments proving that phosphonate (1*S*,2*R*,1′*S*)-**1a** reacts with trimethylsilyl azide significantly slower than diastereoisomer (1*S*,2*S*,1′*R*)-**1b**.

To gather NMR spectral data for *O*-TMS phosphonates (1*S*,2*R*,1′*S*)-**6a** and (1*S*,2*S*,1′*R*)-**6b** silylation of phosphonates (1*S*,2*R*,1′*S*)-**1a** and (1*S*,2*S*,1′*R*)-**1b** with 2 equiv of BSA in chloroform-*d* was monitored by the ^{1}H and ^{31}P NMR spectroscopy. Silylation of phosphonate (1*S*,2*S*,1′*R*)-**1b** was almost complete in 26 h giving a 96:4 mixture of phosphonates (1*S*,2*S*,1′*R*)-**6b** and (1*S*,2*S*,1′*R*)-**1b**, respectively. On the other hand, from phosphonate (1*S*,2*R*,1′*S*)-**1a** a 63:37 mixture of phosphonates (1*S*,2*R*,1′*S*)-**6a** and (1*S*,2*R*,1′*S*)-**1a**, respectively, was obtained after 26 h.

In attempts to rationalise different rates of azidolysis of phosphonates (1*S*,2*R*,1′*S*)-**1a** and (1*S*,2*S*,1′*R*)-**1b** structural features of the respective aziridinium ions **9** (R = OH) and **10** (R = TMS) were compared. Since the aziridine ring opening occurs by the S_N2 mechanism, the azide anion approaches the CH_2 carbon atom from the side opposite to the ring nitrogen. Analysis of molecular models of (1*S*,2*R*,1′*S*)-**9a** and (1*S*,2*S*,1′*R*)-**9b** as well as their N-invertomers **11** clearly shows that freely rotating 1-phenylethyl group does

not shield the approach of the nucleophile to the reaction centre. Although phosphonate (1*S*,2*R*,1′*S*)-**1a** exists in a stable antiperiplanar conformation due to a strong intramolecular H-bond (N···H–O), in the respective aziridinium ion (1*S*,2*R*,1′*S*)-**9a**, free rotation of the (*O*,*O*-diethoxyphosphoryl)hydroxymethyl group around C1–C2 is possible and the bulky *O*,*O*-diethoxyphosphoryl group is responsible for the hindrance of the nucleophilic substitution with azide. Furthermore, the approach of the nucleophile in the aziridinium ion (1*S*,2*R*,1′*S*)-**10a** is additionally restricted because of the steric bulkiness of the trimethylsilyl group (Fig. 1).

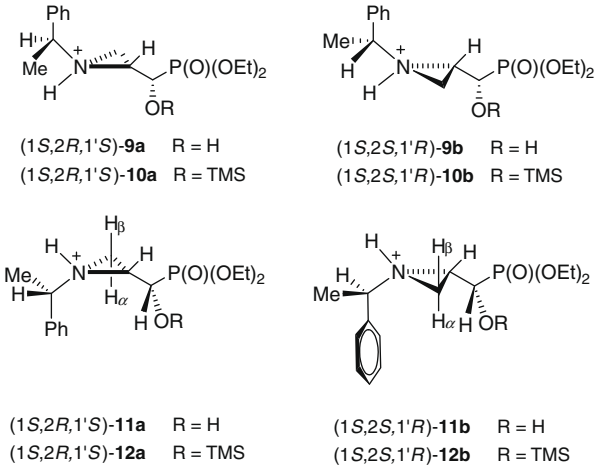


Figure 1. Possible N-invertomers of aziridinium ions formed from phosphonates (1*S*,2*R*,1′*S*)-**1a** and 1(*S*,2*S*,1′*R*)-**1b**.

To investigate why phosphonate (1*S*,2*S*,1′*R*)-**1b** reacts with azide faster than the diastereoisomer (1*S*,2*R*,1′*S*)-**1a** we turned attention to possible structural differences between these phosphonates. It appeared that *H*–CP and H_α–CH_β in (1*S*,2*S*,1′*R*)-**1b** are significantly shifted upfield in comparison to those in (1*S*,2*R*,1′*S*)-**1a** (by 0.49 and 0.20 ppm, respectively). Similar differences in chemical shifts were observed earlier for structurally close aziridine alcohols and together with vicinal coupling constants were employed in configurational assignments.[51] These upfield shifts are obviously a result of shielding by the phenyl ring[52,53] and can only be observed in N-invertomers in which the 1-phenylethyl group is positioned *cis* to the other substituent in the aziridine ring. If one assumes that this configurational relationship is retained in the intermediate aziridinium ions (1*S*,2*S*,1′*R*)-**11b** and (1*S*,2*S*,1′*R*)-**12b** the 1-phenylethyl group again has no influence on the incoming nucleophile. However, the trajectory of the approaching azide is now significantly less hindered by the *O*,*O*-diethoxyphosphoryl group when compared to that of the aziridinium ions (1*S*,2*R*,1′*S*)-**9a** and (1*S*,2*R*,1′*S*)-**10a**. This is because the (*O*,*O*-diethoxyphosphoryl)hydroxymethyl group in (1*S*,2*S*,1′*R*)-**11b** and (*O*,*O*-diethoxyphosphoryl)(trimethylsilyloxy)methyl group in (1*S*,2*S*,1′*R*)-**12b** are no longer able to freely rotate around the C1–C2 bond due to *cis*-configuration of substituents in the three-membered ring.

3. Conclusions

An efficient synthetic strategy to all four enantiomers of diethyl 2,3-di(*N*-Boc-amino)-1-hydroxypropylphosphonates has been elaborated. Readily available aziridinephosphonates (1*S*,2*R*,1′*S*)-**1a** and (1*S*,2*S*,1′*R*)-**1b** and their enantiomers (1*R*,2*S*,1′*R*)-**1d** and (1*R*,2*R*,1′*S*)-**1c**, respectively were selected as starting materials. A two-step procedure included the aziridine ring opening with neat trimethylsilyl azide followed by the reduction of the azido group and hydrogenolytic removal of the 1-phenylethyl residue with simultaneous protection of the amino groups as Boc derivatives. Reaction with azide was regiospecific and less substituted carbon in the aziridine ring was attacked. An application of neat trimethylsilyl azide cleanly gave 3-azido-1-hydroxyphosphonates, while reactions performed in dichloromethane led to ca. 1:1 mixtures of 3-azido-1-hydroxyphosphonates and their *O*-TMS derivatives.

A mechanism of the aziridine ring opening with trimethylsilyl azide in 2,3-aziridine-1-hydroxyphosphonates was proposed based on the monitoring of reactions by the ^{1}H and ^{31}P NMR spectroscopy and the literature data. Silylation of the hydroxy group in phosphonates or hydrolysis of trimethylsilyl azide with a residual water produce hydrogen azide which transforms the aziridine ring nitrogen into the intermediate aziridinium ion. Under these conditions regiospecific ring opening with azide takes place at room temperature.

Attempts at rationalising reasons why phosphonate (1*S*,2*S*,1′*R*)-**1b** reacts with trimethylsilyl azide faster than phosphonate (1*S*,2*R*,1′*S*)-**1a** were undertaken based on the comparison of the structural features of the starting phosphonates. Phosphonate (1*S*,2*R*,1′*S*)-**1a** is less reactive because the approach of the nucleophile is shielded due to free rotation of the bulky (*O*,*O*-diethoxyphosphoryl)hydroxymethyl group in the respective aziridinium ions (1*S*,2*R*,1′*S*)-**9a**. Since phosphonate (1*S*,2*S*,1′*R*)-**1b** exists as N-invertomer having the 1-phenylethyl and the (*O*,*O*-diethoxyphosphoryl)hydroxymethyl groups in the *cis*-configuration, in the respective aziridinium ions (1*S*,2*S*,1′*R*)-**11b** and (1*S*,2*S*,1′*R*)-**12b** rotation of the substituent around the C1–C2 bond is restricted and thus trajectory of the incoming azide anion is less hindered.

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 hertz. ^{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 Optical Activity PolAAr 3001 apparatus. The following absorbents were used: column chromatography, Merck Silica Gel 60 (70–230 mesh); analytical TLC, Merck TLC plastic sheets Silica Gel 60 F_{254}.

4.1. Reaction of phosphonates 1 with trimethylsilyl azide in CH_2Cl_2 (general procedure)

To a solution of phosphonates **1** (0.313 g, 1.00 mmol) in methylene chloride (2 mL) $TMSN_3$ (0.265 mL, 2.00 mmol) was added at room temperature. The mixture was stirred at ambient temperature for 14 days (for **1a**) or four days (for **1b**) and then was chromatographed on a silica gel column with hexanes/ethyl acetate (2:1, v/v) to give *O*-TMS derivatives **4** (first eluted) and 1-hydroxyphosphonates **5**.

4.1.1. Reaction of phosphonate (1*S*,2*R*,1′*S*)-1a with trimethylsilyl azide

From aziridinephosphonate (1*S*,2*R*,1′*S*)-**1a** (0.356 g, 1.14 mmol), *O*-TMS derivative (1*S*,2*R*,1′*S*)-**4a** (0.170 g, 31%) was obtained followed by 1-hydroxyphosphonate (1*S*,2*R*,1′*S*)-**5a** (0.168 g, 47%), both as colourless oils.

4.1.1.1. Diethyl (1*S*,2*R*)-3-azido-2-[(*S*)-1-phenylethyl]amino-1-trimethylsilyloxypropylphosphonate (1*S*,2*R*,1′*S*)-4a. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.18 (m, 5H), 4.16–3.97 (m, 5H, CH_2OP, HCP), 3.90 (q, *J* = 6.6 Hz, 1H, $HCCH_3$), 3.63 (ddd, *J* = 12.6, 3.9, 1.2 Hz,

1H, H_aCH_b), 3.32 (dd, J = 12.6, 3.9 Hz, 1H, H_aCH_b), 2.90 (dddd, J = 12.3, 6.0, 3.9, 3.9 Hz, 1H, HC-2), 1.37 (d, J = 6.6 Hz, 3H, HCCH_3), 1.30 and 1.26 (2 × t, J = 7.1 Hz, 6H, CH_3CH_2OP), 0.13 (s, 9H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 144.7, 128.4, 127.0, 126.8, 69.6 (d, J = 165.0 Hz, *C*P), 62.7 and 62.4 (2 × d, J = 7.2 Hz, CH_3CH_2OP), 56.4 (d, J = 5.7 Hz, *C*CP), 55.4, 49.7 (d, J = 6.6 Hz, *C*CCP), 24.5, 16.6 (d, J = 5.7 Hz, CH_3CH_2OP), 0.25. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 23.22.

4.1.1.2. Diethyl (1*S*,2*R*)-3-azido-2-[(*S*)-1-phenylethyl]amino-1-hydroxypropylphosphonate (1*S*,2*R*,1′*S*)-5a. IR (film): ν = 3307, 2980, 2930, 2101, 1451, 1219, 1027, 763, 703 cm^{-1}. $[\alpha]_D^{20} = -65.1$ (*c* 3.07, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.22 (m, 5H), 4.22–4.07 (m, 4H, CH_2OP), 3.98 (q, J = 6.6 Hz, 1H, *H*CCH$_3$), 3.86 (dd, J = 6.6, 5.7 Hz, 1H, HCP), 3.68 (dd, J = 12.9, 5.7 Hz, 1H, H_aCH_b), 3.61 (dd, J = 12.9, 5.4 Hz, 1H, H_aCH_b), 2.93 (dddd, J = 18.0, 5.7, 5.7, 5.4 Hz, 1H, HCN), 1.41 (d, J = 6.6 Hz, 3H, HCCH_3), 1.32 and 1.30 (2 × t, J = 7.1 Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 144.1, 128.8, 127.6, 127.0, 67.5 (d, J = 159.8 Hz, *C*P), 63.4 and 62.7 (2 × d, J = 7.2 Hz, CH_3CH_2OP), 56.0 (d, J = 4.0 Hz, *C*CP), 55.8, 50.8 (d, J = 4.0 Hz, *C*CCP), 24.7, 16.8 and 16.7 (2 × d, J = 5.2 Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 23.01. Anal. Calcd for $C_{15}H_{25}N_4O_4P$: C, 50.56; H, 7.07; N, 15.72. Found: C, 50.42; H, 7.18; N, 15.78.

4.1.2. Reaction of phosphonate (1*S*,2*S*,1′*R*)-1b with trimethylsilyl azide

From aziridinephosphonate (1*S*,2*S*,1′*R*)-**1b** (0.132 g, 0.408 mmol), *O*-TMS derivative (1*S*,2*S*,1′*R*)-**4b** (0.063 g, 37%) and 1-hydroxyphosphonate (1*S*,2*S*,1′*R*)-**5b** (0.074 g, 46%) were obtained, both as colourless oils.

4.1.2.1. Diethyl (1*S*,2*S*)-3-azido-2-[(*R*)-1-phenylethyl]amino-1-trimethylsilyloxypropylphosphonate (1*S*,2*S*,1′*R*)-4b. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.11 (m, 5H), 4.11–3.95 (m, 4H, CH_2OP), 3.88 (q, J = 6.6 Hz, 1H, *H*CCH$_3$), 3.88 (dd, J = 7.8, 4.5 Hz, 1H, HCP), 3.39 (ddd, J = 12.3, 6.3, 1.2 Hz, 1H, H_aCH_b), 3.28 (dd, J = 12.3, 6.0 Hz, 1H, H_aCH_b), 2.81 (dddd, J = 18.6, 6.3, 6.0, 4.5 Hz, 1H, HC-2), 1.26 (d, J = 6.6 Hz, 3H, HCCH_3), 1.19 and 1.19 (2 × t, J = 7.2 Hz, 6H, CH_3CH_2OP), 0.00 (s, 9H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 145.5, 128.8, 127.5, 126.9, 69.6 (d, J = 167.8 Hz, *C*P), 63.0 and 62.3 (2 × d, J = 7.2 Hz, CH_3CH_2OP), 57.1 (d, J = 3.1 Hz, *C*CP), 56.4, 51.7 (d, J = 8.0 Hz, *C*CCP), 25.0, 16.8 and 16.7 (2 × d, J = 6.0 Hz, CH_3CH_2OP), 0.25. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 22.77.

4.1.2.2. Diethyl (1*S*,2*S*)-3-azido-2-[(*R*)-1-phenylethyl]amino-1-hydroxypropylphosphonate (1*S*,2*S*,1′*R*)-5b. IR (film): ν = 3274, 2980, 2929, 2102, 1452, 1224, 1028, 764, 703 cm^{-1}. $[\alpha]_D^{20} = +92.8$ (*c* 0.75, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.31 (m, 5H), 4.23–4.10 (m, 4H, CH_2OP), 4.02 (q, J = 6.6 Hz, 1H, *H*CCH$_3$), 3.85 (dd, J = 6.9, 5.1 Hz, 1H, HCP), 3.79 (dd, J = 12.9, 5.1 Hz, 1H, H_aCH_b), 3.74 (dd, J = 12.9, 3.9 Hz, 1H, H_aCH_b), 2.94 (dddd, J = 9.9, 6.9, 5.1, 3.9 Hz, 1H, HCN), 1.50 (d, J = 6.6 Hz, 3H, HCCH_3), 1.35 and 1.29 (2 × t, J = 7.1 Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 143.8, 128.8, 127.5, 126.9, 66.3 (d, J = 166.2 Hz, *C*P), 63.5 and 62.6 (2 × d, J = 6.8 Hz, CH_3CH_2OP), 55.1, 54.1 (d, J = 3.4 Hz, *C*CP), 50.6, (d, J = 6.3 Hz, *C*CCP), 25.1, 16.6 (d, J = 5.7 Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 22.73. Anal. Calcd for $C_{15}H_{25}N_4O_4P$: C, 50.56; H, 7.07; N, 15.72. Found: C, 50.84; H, 7.24; N, 15.62.

4.2. Reaction of phosphonates 1 with neat trimethylsilyl azide (general procedure)

A mixture of phosphonates **1** (0.313 g, 1.00 mmol) and $TMSN_3$ (0.265 mL, 2.00 mmol) was stirred at room temperature for 14 days (for **1a** and **1d**—*ent*-**1a**) or four days (for **1b** and **1c**—*ent*-**1b**). Crude products were chromatographed on a silica gel column with hexanes/ethyl acetate (2:1, v/v) to give 1-hydroxyphosphonates **5**.

4.2.1. Reaction of phosphonate (1*S*,2*R*,1′*S*)-1a with neat trimethylsilyl azide

From aziridinephosphonate (1*S*,2*R*,1′*S*)-**1a** (0.200 g, 0.638 mmol), 1-hydroxyphosphonate (1*S*,2*R*,1′*S*)-**5a** (0.193 g, 85%) was obtained as a colourless oil in all respects identical with a sample described in Section 4.1.1.2.

4.2.2. Reaction of phosphonate (1*S*,2*S*,1′*R*)-1b with neat trimethylsilyl azide

From aziridinephosphonate (1*S*,2*S*,1′*R*)-**1b** (0.203 g, 0.648 mmol), 1-hydroxyphosphonate (1*S*,2*S*,1′*R*)-**5b** (0.196 g, 85%) was obtained as a colourless oil in all respects identical with a sample described in Section 4.1.2.2.

4.2.3. Diethyl (1*R*,2*R*)-3-azido-2-[(*S*)-1-phenylethyl]amino-1-hydroxypropylphosphonate (1*R*,2*R*,1′*S*)-5c

From aziridinephosphonate (1*R*,2*R*,1′*S*)-**1c** (0.207 g, 0.661 mmol), 1-hydroxyphosphonate (1*R*,2*R*,1′*S*)-**5c**—*ent*-**5b** (0.199 g, 85%) was obtained as a colourless oil. $[\alpha]_D^{20} = -92.2$ (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{15}H_{25}N_4O_4P$: C, 50.56; H, 7.07; N, 15.72. Found: C, 50.61; H, 7.29; N, 15.71.

4.2.4. Diethyl (1*R*,2*S*)-3-azido-2-[(*R*)-1-phenylethyl]amino-1-hydroxypropylphosphonate (1*R*,2*S*,1′*R*)-5d

From aziridinephosphonate (1*R*,2*S*,1′*R*)-**1d** (0.198 g, 0.632 mmol), 1-hydroxyphosphonate (1*R*,2*S*,1′*R*)-**5d** (0.192 g, 85%) was obtained as a colourless oil. $[\alpha]_D^{20} = +64.6$ (*c* 1.98, $CHCl_3$). Anal. Calcd for $C_{15}H_{25}N_4O_4P$: C, 50.56; H, 7.07; N, 15.72. Found: C, 50.26; H, 7.31; N, 15.75.

4.3. Hydrogenolysis of 1-hydroxyphosphonates 5a, 5b, 5c and 5d (general procedure)

A solution of 1-hydroxyphosphonates **5a**, **5b**, **5c** and **5d** (0.426 g, 1.00 mmol) in ethanol (5 mL) containing Boc_2O (0.546 g, 2.50 mmol) was stirred under atmospheric pressure of hydrogen over 20% $Pd(OH)_2$–C (50 mg) at room temperature for three days. The suspension was filtered through a layer of Celite, the solution was concentrated and chromatographed on a silica gel column with chloroform/methanol (100:1 and 50:1, v/v).

4.3.1. Diethyl (1*S*,2*R*)-2,3-di(*tert*-butoxycarbonylamino)-1-hydroxypropylphosphonate (1*S*,2*R*)-3

From 1-hydroxyphosphonate (1*S*,2*R*,1′*S*)-**5a** (0.143 g, 0.401 mmol), diaminophosphonate (1*S*,2*R*)-**3** (0.149 g, 87%) was obtained as a white amorphous solid. Mp 60–61 °C. IR (KBr): ν = 3395, 2978, 2932, 1702, 1537, 1249, 1039 cm^{-1}. $[\alpha]_D^{20} = -33.7$ (*c* 1.07, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.41 (d, J = 6.0 Hz, 1H, *H*NC-2), 5.17 (br m, 1H, *H*NC-3), 4.73 (dd, J = 13.2, 7.2 Hz, 1H, *H*OC-1), 4.26–4.14 (m, 4H, CH_2OP), 4.04–3.87 (br m, 2H, *H*C-1, *H*C-2), 3.65–3.52 (br m, 1H, H_aCH_b), 3.48–3.36 (br m, 1H, H_aCH_b), 1.44 [s, 18H, $(CH_3)_3$], 1.36 and 1.35 (2 × t, J = 7.1 Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 157.3, 156.1, 80.0, 68.7 (d, J = 164.1 Hz, *C*P), 63.3 and 63.2 (2 × d, J = 6.9 Hz, CH_3CH_2OP), 53.0, 41.1, 28.6, 16.8 (d, J = 4.3 Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 22.77. Anal. Calcd for $C_{17}H_{35}N_2O_8P$: C, 47.88; H, 8.27; N, 6.57. Found: C, 47.60; H, 7.98; N, 6.87.

4.3.2. Diethyl (1*S*,2*S*)-2,3-di(*tert*-butoxycarbonylamino)-1-hydroxypropylphosphonate (1*S*,2*S*)-3

From 1-hydroxyphosphonate (1*S*,2*S*,1′*R*)-**5b** (0.176 g, 0.494 mmol) diaminophosphonate (1*S*,2*S*)-**3** (0.191 g, 91%) was obtained as a colourless oil. IR (film): ν = 3346, 2979, 2933, 1711, 1515, 1248, 1027 cm^{-1}. $[\alpha]_D^{20} = -13.9$ (*c* 2.25, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.52 (d, J = 8.1 Hz, 1H, *H*NC-2), 5.35 (t, J = 7.8 Hz 1H, *H*NC-3), 5.06 (dd, J = 17.4, 6.0 Hz, 1H, *H*OC-1),

4.23–4.13 (m, 4H, CH_2OP), 4.03 (ddd, J = 12.0, 6.0, 2.4 Hz, 1H, *H*C-1), 3.99–3.87 (m, 1H, *H*C-2), 3.45–3.21 (br m, 2H, H_aCH_b), 1.43 [s, 18H, $(CH_3)_3$], 1.34 (t, J = 7.1 Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 157.6, 156.0, 80.3, 79.8, 67.2 (d, J = 169.3 Hz, *C*P), 63.1 and 63.0 (2 × d, J = 6.9 Hz, CH_3CH_2OP), 52.0, 41.4, (d, J = 12.6 Hz, C-3), 28.6, 16.8 and 16.7 (2 × d, J = 5.7 Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 22.74. Anal. Calcd for $C_{17}H_{35}N_2O_8P$: C, 47.88; H, 8.27; N, 6.57. Found: C, 47.85; H, 8.43; N, 6.38.

4.3.3. Diethyl (1*R*,2*R*)-2,3-di(*tert*-butoxycarbonylamino)-1-hydroxypropylphosphonate (1*R*,2*R*)-3

From 1-hydroxyphosphonate (1*R*,2*R*,1′*S*)-**5c** (0.140 g, 0.393 mmol), diaminophosphonate (1*R*,2*R*)-**3** (0.155 g, 92%) was obtained as a colourless oil. $[\alpha]_D^{20} = +13.5$ (*c* 0.44, $CHCl_3$). Anal. Calcd for $C_{17}H_{35}N_2O_8P$: C, 47.88; H, 8.27; N, 6.57. Found: C, 47.62; H, 8.03; N, 6.67.

4.3.4. Diethyl (1*R*,2*S*)-2,3-di(*tert*-butoxycarbonylamino)-1-hydroxypropylphosphonate (1*R*,2*S*)-3

From 1-hydroxyphosphonate (1*R*,2*S*,1′*R*)-**5d** (0.138 g, 0.387 mmol), diaminophosphonate (1*R*,2*S*)-**3** (0.143 g, 87%) was obtained as a white amorphous solid. Mp 60–61 °C. $[\alpha]_D^{20} = +33.8$ (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{17}H_{35}N_2O_8P$: C, 47.88; H, 8.27; N, 6.57. Found: C, 47.66; H, 8.53; N, 6.39.

4.4. Monitoring of the reaction of phosphonates (1*S*,2*R*,1′*S*)-1a and (1*S*,2*S*,1′*R*)-1b with 2 equiv of trimethylsilyl azide

To a solution of phosphonate (1*S*,2*R*,1′*S*)-**1a** or (1*S*,2*S*,1′*R*)-**1b** (10.0 mg, 0.032 mmol) in chloroform-*d* (0.7 mL) trimethylsilyl azide (9.0 μL, 0.064 mmol) was injected and the progress of the reaction was observed by the ^1H and ^{31}P NMR spectroscopy (Tables 1 and 2).

4.5. Monitoring of the reaction of phosphonates (1*S*,2*R*,1′*S*)-1a and (1*S*,2*S*,1′*R*)-1b with 2 equiv of *N*,*O*-bis(trimethylsilyl)acetamide (BSA)

To a solution of phosphonate (1*S*,2*R*,1′*S*)-**1a** or (1*S*,2*S*,1′*R*)-**1b** (6.2 mg, 0.020 mmol) in chloroform-*d* (0.7 mL) BSA (10.0 μL, 0.040 mmol) was injected and the progress of the reaction was observed by the ^1H and ^{31}P NMR spectroscopy.

4.5.1. Diethyl (*S*)-{(*R*)-1-[(*S*)-1-phenylethyl]aziridin-2-yl}(trimethylsilyloxy)methylphosphonate (1*S*,2*R*,1′*S*)-6a

[Spectral data were calculated from a spectrum of a 63:37 mixture of phosphonates (1*S*,2*R*,1′*S*)-**6a** and (1*S*,2*R*,1′*S*)-**1a**]. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.23 (m, 5H), 4.13–4.01 (m, 4H, CH_2OP), 3.83 (dd, J = 8.7, 3.3 Hz, 1H, HCP), 2.50 (q, J = 6.6 Hz, 1H, *H*CCH$_3$), 1.98 (d, J = 3.3 Hz, 1H, H_aCH_b), 1.87 (dddd, J = 6.3, 3.3, 3.3, 2.7 Hz, 1H, HCN), 1.43 (d, J = 6.3 Hz, 1H, H_aCH_b), 1.40 (d, J = 6.6 Hz, 3H, HCC*H*$_3$), 1.24 and 1.24 (2 × t, J = 7.1 Hz, 6H, CH_3CH_2OP), 0.12 [s, 9H, $Si(CH_3)_3$]. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 22.78.

4.5.2. Diethyl (*S*)-{(*S*)-1-[(*R*)-1-phenylethyl]aziridin-2-yl}-(trimethylsilyloxy)methylphosphonate 6b

[Spectral data were calculated from a spectrum of a 96:4 mixture of phosphonates (1*S*,2*S*,1′*R*)-**6b** and (1*S*,2*S*,1′*R*)-**1b**]. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.21 (m, 5H), 4.18–4.01 (m, 4H, CH_2OP), 3.37 (dd, J = 8.1, 8.1 Hz, 1H, HCP), 2.48 (q, J = 6.6 Hz, 1H, *H*CCH$_3$), 1.92–1.84 (m, 2H, H_aCH_b and HCN), 1.55 (d, J = 6.3 Hz, 1H, H_aCH_b), 1.43 (d, J = 6.6 Hz, 3H, HCC*H*$_3$), 1.31 (t, J = 7.1 Hz, 6H, CH_3CH_2OP), −0.10 [s, 9H, $Si(CH_3)_3$]. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 22.61.

Acknowledgments

Financial support from the Medical University of Łódź (502-13-772) is gratefully acknowledged. The authors wish to express their gratitude to Mrs. Edyta Grzelewska and Mrs. Agata Lasota for excellent technical assistance. A part of this project was conducted by Mr. Paweł Szuberski.

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