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Synthesis of four stereoisomers of protected 1,2-epiimino-3-hydroxypropylphosphonates

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ABSTRACT

Enantiomerically pure protected 1,2-epiimino-3-hydroxypropylphosphonates were synthesised from hydroxy-1-{[(*R*)- or (*S*)-1-phenylethyl]aziridin-2-yl}methylphosphonates via regioselective ring opening with acetic acid followed by a stereospecific intramolecular cyclisation of 3-acetoxy-1-mesyloxy-2-(1-phenylethyl)aminopropylphosphonates and hydrogenolytic removal of the 1-phenylethyl group in the presence of Boc_2O. The *trans*-isomers of 3-acetoxy-[*N*-(1-phenylethyl)-1,2-epiimino]propylphosphonates exist as a 2:1 mixture of invertomers, which were fully structurally characterised based on their ^1H and ^{13}C NMR spectroscopic data. Large differences in the $^1J_{C-P}$ values in *N*-(1-phenylethyl)aziridine-2-phosphonates were noticed depending on the spatial arrangement of the nitrogen lone pair and the phosphorus atom (*syn*-periplanar—ca. 215 Hz; *anti*-periplanar—182 Hz).

1. Introduction

Several natural products with an aziridine ring, such as mitomycins, azinomycins and porfiromycins show antitumor activity.[1,2] Other natural aziridines, also known as aziridine alkaloids, display antibacterial and antimicrobial activity against selected microorganisms.[3] Even simple compounds, such as (2*S*,3*S*)-aziridine-2,3-dicarboxylic acid **1**, exhibited antibacterial activity.[4] Peptides containing aziridine-2-carboxylic acid **2** or (2*S*,3*S*)-aziridine-2,3-dicarboxylic acid **1** seem to be inhibitors of various proteases.[5–7] Aziridine-2-phosphonates **3** (R = R′ = R″ = H, alkyl) have been claimed to show antibacterial properties (Fig. 1).[8]

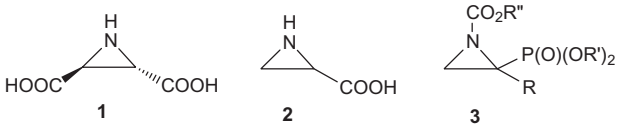

Figure 1. Examples of low-molecular weight bioactive aziridines.

Interest in the chemistry of aziridines has significantly increased in recent years due to numerous applications of these reactive small heterocycles in the synthesis of various natural products,[2,9–14] drugs[15–18] and drug candidates.[19–24] Procedures for the asymmetric synthesis of non-racemic aziridines have been reviewed.[2,25,26] In general, they rely on either asymmetric transformations of either a C=N or C=C bonds or application of the 'chiron approach'.[27]

In comparison to the numerous synthetic approaches to aziridine-2-carboxylates, enantiomerically pure aziridine-2-phosphonates are less accessible.[28] They can be prepared by the intramolecular cyclisation of α-hydroxy-β-aminoalkylphosphonates;[29–31] a Darzens-type condensation of imines with the anion of enantiopure bicyclic chloromethylphosphonamide;[32] the addition of anions of halogenmethylphosphonates to enantiomerically pure *N*-sulfinimines;[33–36] the reduction of homochiral 2*H*-azirinephosphonates;[37] the addition of selected nucleophiles to azirine-3-phosphonates[38–41] or by an aziridination of vinylphosphonates.[42,43]

In a continuation of our studies on the transformations of the readily available hydroxy-1-{[(*R*) or (*S*)-1-phenylethyl]aziridin-2-yl}methylphosphonates **4**[44] into functionalised aminohydroxyphosphonates,[45] we herein report an efficient route to all four enantiomerically pure 1,2-epiiminopropylphosphonates **5** via the corresponding acetates **6** (Scheme 1). Based on the literature data,[46–52] regioselective opening of the aziridine ring in phosphonates **4** was expected to occur at the less substituted carbon atom.

2. Results and discussion

To obtain enantiomerically pure 2,3-disubstituted aziridinephosphonates (2*R*,3*S*)-**11a** and (2*S*,3*R*)-**11b** (cis configured isomers), phosphonates (1*S*,2*S*,1′*R*)-**7a**[44] and (1*R*,2*R*,1′*S*)-**7b**[44] were selected as starting materials. The treatment of these compounds with 3 equiv of glacial acetic acid in methylene chloride at room temperature required 36 h for the reaction to go to completion. However, refluxing the reaction mixture allowed us to shorten the reaction time to 9 h. After chromatographic purification, phosphonate (1*S*,2*S*,1′*R*)-**8a** and its enantiomer (1*R*,2*R*,1′*S*)-**8b** were obtained in 89% and 86% yields, respectively (Scheme 2 and 3).

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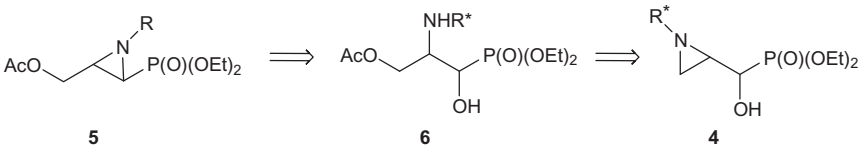
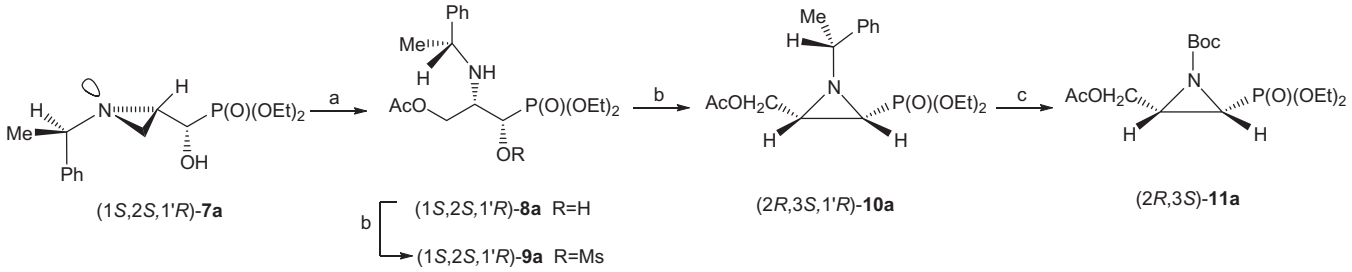
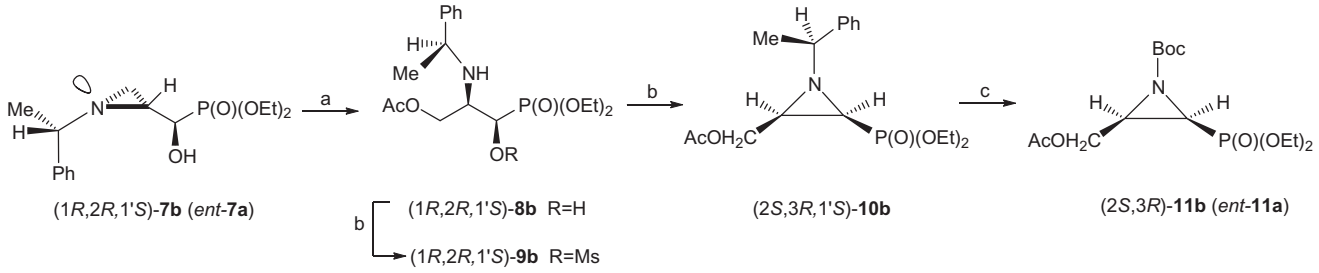


Scheme 1. Retrosynthesis of 1,2-epiiminopropylphosphonates.



Scheme 2. Reagents and conditions: (a) AcOH, CH_2Cl_2, reflux, 9 h, 89%; (b) MsCl, NEt_3, CH_2Cl_2, −70 °C to rt, overnight, 93%; (c) H_2, 10% Pd–C, $(Boc)_2O$, EtOH, rt, 7 h, 89%.



Scheme 3. Reagents and conditions: (a) AcOH, CH_2Cl_2, reflux, 9 h, 86%; (b) MsCl, NEt_3, CH_2Cl_2, −70 °C to rt, overnight, 92%; (c) H_2, 10% Pd–C, $(Boc)_2O$, EtOH, rt, 7 h, 89%.

The cyclisation of 1-hydroxypropylphosphonates **8a** and **8b** to 1,2-epiiminopropylphosphonates **10a** and **10b** was explored next. This was achieved by the mesylation of the hydroxy group at low temperature (−70 °C) followed by warming up the reaction mixture to room temperature to carry out an aziridine ring closure. The *syn*-isomers (1*S*,2*S*,1′*R*)-**8a** and (1*R*,2*R*,1′*S*)-**8b** were readily transformed to *cis*-2,3-disubstituted aziridinephosphonates (2*R*,3*S*,1′*R*)-**10a** and (2*S*,3*R*,1′*S*)-**10b** as single products in 93% and 92% yields, respectively (Scheme 2 and 3). The formation of *cis*-configured aziridines **10a** and **10b** was unequivocally proven by the observation of the vicinal H–H coupling constant (6.3 Hz) characteristic of the *cis*-arrangement within the H–C2–C3–H moiety in aziridines.[49,53,54] The latter reaction proceeded completely *via* intramolecular S_N2 displacement and reflects the ability of the mesylates (1*S*,2*S*,1′*R*)-**9a** and (1*R*,2*R*,1′*S*)-**9b** to adopt a conformation in which the substituted amine as a nucleophile and the leaving group are antiperiplanar (Fig. 2).

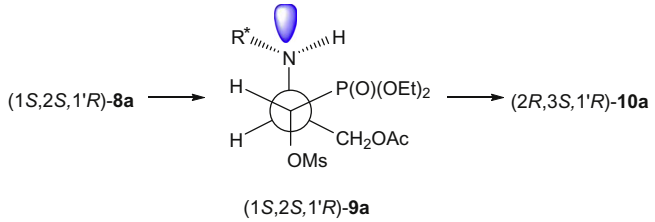


Figure 2. An aziridine ring closure in mesylate (1*S*,2*S*,1′*R*)-**9a**.

During the catalytic hydrogenation of aziridinephosphonates (2*R*,3*S*,1′*R*)-**10a** and (2*S*,3*R*,1′*S*)-**10b** in the presence of Boc_2O the formation of *N*-Boc-aziridine-2-phosphonates (2*R*,3*S*)-**11a** and (2*S*,3*R*)-**11b** is expected. However, under these conditions the aziridine ring opening could also be envisioned.[30] Initially, the reaction was attempted on phosphonate (2*S*,3*R*,1′*S*)-**10b** in the presence of a Pearlman's catalyst in ethanol. After 24 h, a complex reaction mixture was formed. Only small quantities of the impure 2-*N*-Boc-amino-3-acetoxypropylphosphonate (*R*)-**12b** were separated from the reaction mixture (Fig. 3).

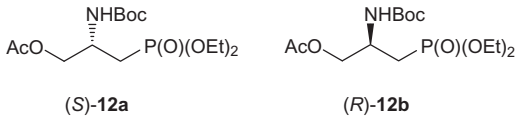


Figure 3. Side products obtained in the hydrogenation of phosphonates (2*R*,3*S*,1′*R*)-**10a** and (2*S*,3*R*,1′*S*)-**10b**.

When the hydrogenation was carried out on phosphonate (2*R*,3*S*,1′*R*)-**10a** in the presence of a 1:1 mixture of $Pd(OH)_2$–C and 10% Pd–C for 72 h, a complex reaction mixture was again obtained. However, the formation of *N*-Boc-aziridinephosphonate (2*R*,3*S*)-**11a** (ca. 50%), phosphonate (*S*)-**12a** (ca. 10%) and several unidentified phosphonates (δ ^{31}P 23.1–23.7 ppm) was confirmed by the ^{31}P NMR spectroscopy. The application of 10% Pd–C alone as a catalyst in the hydrogenation of (2*R*,3*S*,1′*R*)-**10a** afforded a 91:9 mixture of *cis*-aziridinephosphonate (2*R*,3*S*)-**11a** and phosphonate (*S*)-**12a** within 7 h. From this mixture, pure phosphonate (2*R*,3*S*)-**11a** was separated chromatographically in 89% yield. Under the same conditions, from aziridinephosphonate (2*S*,3*R*,1′*S*)-**10b**, *N*-Boc-aziridinephosphonate (2*S*,3*R*)-**11b** was also obtained in 89% yield.

In a conceptually similar manner, the syntheses of *trans*-configured aziridinephosphonates (2*S*,3*S*)-**11c** and (2*R*,3*R*)-**11d** were performed. Refluxing aziridinephosphonate (1*R*,2*S*,1′*R*)-**7c**[44] with 3 equiv of acetic acid in CH_2Cl_2 for 9 h led to the formation of a mixture which contained ca. 50% of phosphonate (1*R*,2*S*,1′*R*)-**8c** together with the starting material (ca. 20%) and several unidentified impurities as judged from the ^{31}P NMR spectrum of the crude product. Extension of the reaction time resulted in complete consumption of the substrate, but led to the formation of significant amounts of unidentified impurities. However, a total conversion of phosphonate (1*R*,2*S*,1′*R*)-**7c** was achieved when the reaction was carried out in neat acetic acid at room temperature for 96 h. After chromatographic purification, phosphonate (1*R*,2*S*,1′*R*)-**8c** was obtained in 61% yield (Scheme 4). In a similar fashion the aziridinephosphonate (1*S*,2*R*,1′*S*)-**7d**[44] was transformed into phosphonate (1*S*,2*R*,1′*S*)-**8d** in 62% yield (Scheme 5).

When the propylphosphonate (1*R*,2*S*,1′*R*)-**8c** was subjected to the standard two-step intramolecular cyclisation, two products in a 2:1 ratio were formed as judged from the ^{31}P NMR spectrum of the crude reaction mixture (δ 23.82 ppm and 22.59 ppm, respectively). The ^{1}H and ^{13}C NMR spectra were also supportive since two sets of signals in the same ratio were observed. None of the compounds formed was identical with the already described cis isomers **10a** and **10b**. Because cyclisation of anti isomer (1*R*,2*S*,1′*R*)-**8c** proceeded again via an intramolecular S_N2 displacement (Fig. 4), only *trans*-1,2-epiiminopropylphosphonate (2*S*,3*S*,1′*R*)-**10c** should be formed. However, 1,2,3-trisubstituted *trans*-aziridines are known to exist as mixtures of invertomers[49,57–61] due to the slow nitrogen inversion on the NMR time scale. A chromatographic purification of the reaction mixture obtained from the propylphosphonate (1*R*,2*S*,1′*R*)-**8c** gave an inseparable 2:1 mixture of *N*-invertomers (2*S*,3*S*,1′*R*)-**10c** in 90% yield (Scheme 4). Their ^{1}H and ^{31}P NMR spectral data perfectly matched those observed for the compounds present in the crude reaction mixture. The values of vicinal H–C2–C3–H couplings found in both invertomers (3.6 and 2.7 Hz, respectively) served as a direct proof of the *trans* configuration.[49,53,54] In a similar manner, the propylphosphonate (1*S*,2*R*,1′*S*)-**8d** was transformed into a 2:1 mixture of *N*-invertomers of *trans*-aziridine-2-phosphonate (2*R*,3*R*,1′*S*)-**10d**, also in 90% yield (Scheme 5).

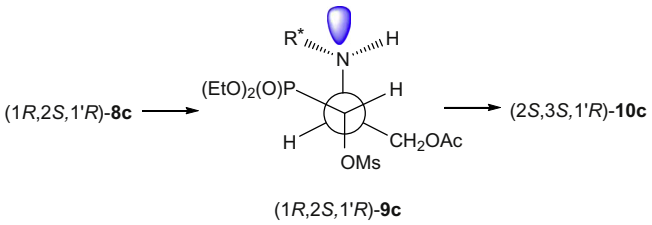
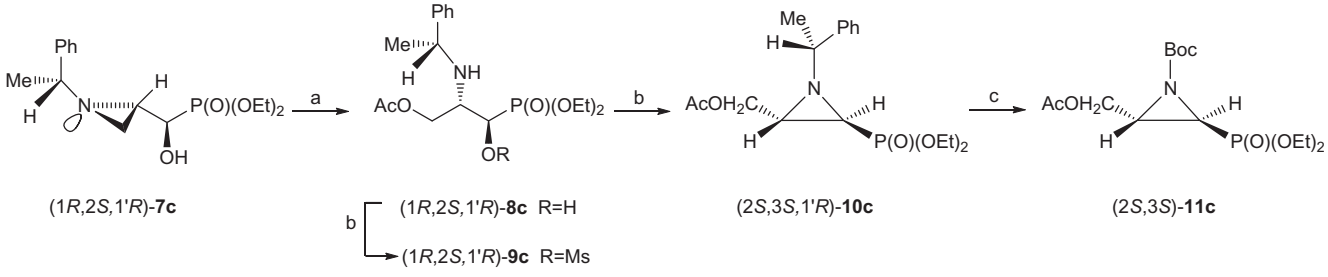


Figure 4. An aziridine ring closure in mesylate (1*R*,2*S*,1′*R*)-**9c**.

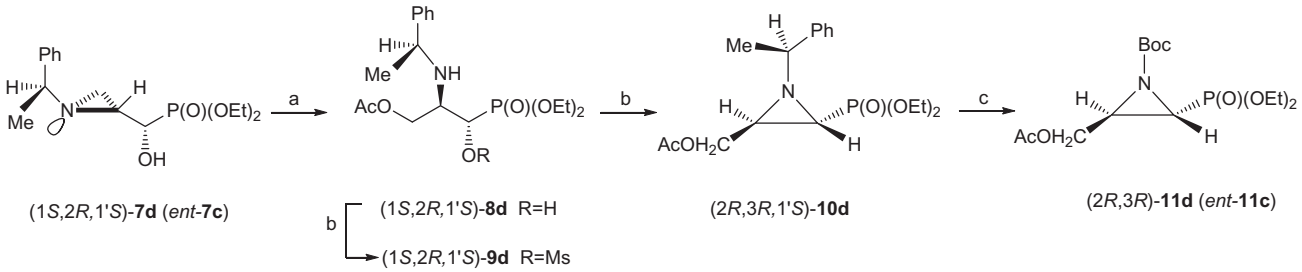
Detailed analysis of the ^{1}H and ^{13}C NMR spectroscopic data of *trans*-1,2-epiiminopropylphosphonate (2*S*,3*S*,1′*R*)-**10c** revealed that structures (1*R*,2*S*,3*S*,1′*R*)-**13c** and (1*S*,2*S*,3*S*,1′*R*)-**13c** can be assigned to the major and minor invertomers, respectively (Fig. 5).

In assigning structures (1*R*,2*S*,3*S*,1′*R*)-**13c** to the major and (1*S*,2*S*,3*S*,1′*R*)-**13c** to the minor invertomer, the ^{13}C NMR data were of primary importance. Since the acetoxymethyl group in the major invertomer does not spatially interact with any other substituent, the chemical shift of CH_2OAc was found in a lower field (δ 66.3 ppm) when compared to chemical shifts of these carbons in the minor invertomer (δ 60.1 ppm) and the *cis*-isomer (2*R*,3*S*,1′*R*)-**10a** (δ 63.7 ppm) where the CH_2OAc groups are close to the 1-phenylethyl and diethoxyphosphoryl groups, respectively (Fig. 5). Furthermore, the resonances of the stereogenic carbons in the 1-phenylethyl groups in the major (δ 60.8 ppm) as well as in the minor (δ 61.8 ppm) invertomers are significantly shifted upfield as a result of the spatial proximity of these groups with the diethoxyphosphoryl and acetoxymethyl groups, respectively, when compared to the chemical shifts of *C**HMePh in the cis isomer **10a** (δ 71.4 ppm) and in the starting phosphonates **7a**–**7d** (δ 69–70 ppm).[44]

The *cis*/*trans* relationships of the substituents in the *trans* [(1*R*,2*S*,3*S*,1′*R*)-**13c** and (1*S*,2*S*,3*S*,1′*R*)-**13c**] and *cis* [(2*R*,3*S*,1′*R*)-**10a**]



Scheme 4. Reagents and conditions: (a) AcOH, rt, 4 d, 61%; (b) MsCl, NEt_3, CH_2Cl_2, −70 °C to rt, overnight, 90%; (c) H_2, 10% Pd–C, $(Boc)_2O$, EtOH, rt, 7 h, 87%.



Scheme 5. Reagents and conditions: (a) AcOH, rt, 4 d, 62%; (b) MsCl, NEt_3, CH_2Cl_2, −70 °C to rt, overnight, 90%; (c) H_2, 10% Pd–C, $(Boc)_2O$, EtOH, rt, 7 h, 86%.

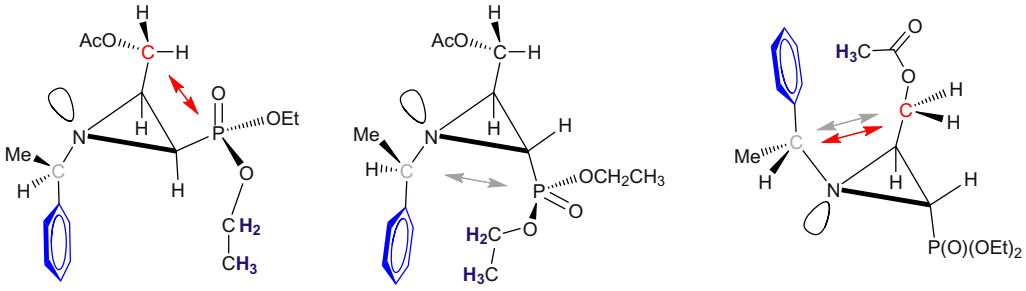


Figure 5. Structures of the invertomers of *cis*- and *trans*-1,2-epiiminopropylphosphonates (2*R*,3*S*,1′*R*)-**10a** and (2*S*,3*S*,1′*R*)-**10c** showing spatial interactions important for stereochemical assignments (in red—upfield shifts of CH_2OAc; in green—upfield shifts of C*HMePh; in blue—upfield shifts induced by aromatic ring currents).

aziridines can also be assigned by taking advantage of the shielding effects that originate from the aromatic ring currents of the phenyl groups in 1-phenylethyl residues.[55,56] Thus, in the major invertomer (1*R*,2*S*,3*S*,1′*R*)-**13c**, the proton resonances of CH_3 (δ 0.84 ppm) and CH_2 (δ 3.36–3.49 ppm and 3.53–3.65 ppm) groups in one of the CH_3CH_2OP residues are significantly shifted upfield in comparison to the other ethoxy group (δ 1.26 ppm and δ 3.96–4.07 ppm) and to the entire diethoxyphosphoryl group in the minor invertomer (1*S*,2*S*,3*S*,1′*R*)-**13c** (δ 1.26 and 1.36 ppm and δ 4.05 and 4.20 ppm). Similar shielding of the ethoxy group is observed in the *cis*-isomer (2*R*,3*S*,1′*R*)-**10a** (δ 1.01 ppm and δ 3.51 and 3.78 ppm). A significant upfield shift of the CH_3CO resonance in the minor invertomer (δ 1.62 ppm) when compared to those in the major one (δ 2.09 ppm) and in the *cis*-isomer **10a** (δ 2.12 ppm) is also configurationally diagnostic and reflects the *cis*- and *trans*-orientations of the acetoxymethyl and 1-phenylethyl groups, respectively (Fig. 5).

The differences of the ^{13}C NMR chemical shifts of *C*–P but especially of the one-bond C–P coupling constants in aziridine-2-phosphonates described herein, are noteworthy. When the nitrogen lone pair is *syn*-periplanar to the phosphorus atom as in the minor invertomer (1*S*,2*S*,3*S*,1′*R*)-**13c** and in the *cis*-isomer (2*R*,3*S*,1′*R*)-**10a**, *C*–P resonates at δ 36.2 and 36.1 ppm and $^1J_{C-P}$ reaches 217.4 and 214.8 Hz, respectively. In the opposite case (*anti*-periplanar orientation of the nitrogen lone pair and the phosphorus atom) as in the major invertomer (1*R*,2*S*,3*S*,1′*R*)-**13c**, *C*–P is shifted upfield (δ 33.7 ppm) and $^1J_{C-P}$ drops down to 182.0 Hz. However, it appeared that in *cis*- and *trans*-*N*-Boc-aziridinephosphonates (2*R*,3*S*)-**11a** and (1*S*,2*S*)-**11c** one-bond C–P coupling constants are less differentiated (207.4 and 197.7 Hz, respectively) and this observation reflects resonance stabilisation of the nitrogen lone pair into the amide bond. Our conclusions regarding dependence of $^1J_{C-P}$ in aziridine-2-phosphonates on the spatial orientation of the phosphorus atom and the nitrogen lone pair gained some support from the literature precedences[29,35,36,38,43] but its full diagnostic value requires further validation.

Finally, the hydrogenolysis (10% Pd–C) of mixtures of *N*-invertomers (2*S*,3*S*,1′*R*)-**10c** and (2*R*,3*R*,1′*S*)-**10d** gave 1,2-epiiminopropylphosphonates (1*S*,2*S*)-**11c** and (1*R*,2*R*)-**11d** in 87% and 86% yields, respectively.

3. Conclusions

An efficient synthetic route to all four enantiomers of diethyl 3-acetoxymethyl-1-[*tert*-butoxycarbonyl]aziridine-2-yl-2-phosphonate has been described. Readily available aziridinephosphonates (1*S*,2*S*,1′*R*)-**7a** and (1*R*,2*S*,1′*R*)-**7c** and their enantiomers (1*R*,2*R*,1′*S*)-**7b** and (1*S*,2*R*,1′*S*)-**7d** were selected as starting materials. The three-step procedure relies on the regioselective aziridine ring opening with acetic acid (in dichloromethane or neat) at the less substituted carbon atom, low temperature mesylation followed by an aziridine ring closure when reaching room temperature and the hydrogenolytic removal of the 1-phenylethyl residue with simultaneous protection of the amino group as an *N*-Boc derivative. The *cis*-isomers of the final *N*-Boc-aziridine-2-phosphonates were obtained in higher overall yields than the respective *trans*-isomers.

As expected, the inversion at the nitrogen atom was not observed for the *cis*-isomers of *N*-(1-phenylethyl)aziridine-2-phosphonates. However, the *trans*-isomers of *N*-(1-phenylethyl)aziridine-2-phosphonates exist as a 2:1 mixture of invertomers, which were fully structurally characterised based on the ^1H and ^{13}C NMR spectroscopic data.

It was noticed that the spatial arrangement of the nitrogen lone pair and the phosphorus atom has a strong influence on the $^1J_{C-P}$ values in *N*-(1-phenylethyl)aziridine-2-phosphonates (for synperiplanar—ca. 215 Hz; for antiperiplanar—182 Hz). To establish a diagnostic value for these observations further studies are under way in this laboratory.

4. Experimental

The ^1H NMR spectra were recorded with a Varian Mercury-300 spectrometer; chemical shifts δ in ppm with respect to TMS; coupling constants *J* in hertz (Hz). ^{13}C and ^{31}P NMR spectra were recorded on a Varian Mercury-300 machine at 75.5 and 121.5 MHz, respectively. The NMR characterisation of a mixture of *N*-invertomers (1*R*,2*S*,3*S*,1′*R*)-**13c** and (1*S*,2*S*,3*S*,1′*R*)-**13c** was supported by ^1H NMR, COSY and HMQC spectra taken on a Bruker Avance III (600 MHz) spectrometer. IR spectral data were measured on an Infinity MI-60 FT-IR spectrometer. 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. Ring opening of aziridinephosphonates 7 with AcOH (general procedure)

A solution of phosphonates **7a** and **7b** (0.313 g, 1.00 mmol) in methylene chloride (4 mL) containing acetic acid (0.172 mL, 3.00 mmol) was refluxed for 9 h or a solution of phosphonates **7c** and **7d** (0.313 g, 1.00 mmol) in neat acetic acid (0.172 mL, 3.00 mmol) was stirred at room temperature for 4 days. The reaction mixtures were then concentrated in vacuo with toluene (3 × 3 mL). Crude products were chromatographed on a silica gel column with methylene chloride–acetone (10:1, v/v) to give the protected 2-amino-1,3-dihydroxypropylphosphonates **8**.

4.1.1. Diethyl (1*S*,2*S*)-3-acetoxy-1-hydroxy-2-[(*R*)-1-phenylethylamino]propylphosphonate 8a

From aziridinephosphonate (1*S*,2*S*,1′*R*)-**7a** (0.228 g, 0.728 mmol) phosphonate (1*S*,2*S*,1′*R*)-**8a** (0.241 g, 89%) was obtained as a colourless oil. IR (film): ν = 3283, 3027, 2980, 2930, 2869, 1740, 1451, 1368, 1233, 1030, 970, 765, 703 cm^{-1}. $[\alpha]_D^{20} = +70.8$ (*c* 1.13, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.21 (m, 5H), 4.31 (dd, *J* = 11.7, 5.7 Hz, 1H, H_aCH_b), 4.23 (ddd, *J* = 11.7, 3.9, 1.2 Hz, 1H, H_aCH_b), 4.13–3.98 (m, 4H, CH_2OP), 3.94 (q, *J* = 6.6 Hz, 1H, $HCCH_3$), 3.80 (dd, *J* = 6.0, 5.7 Hz, 1H, HCP), 2.97 (dtd, *J* = 9.6, 5.7, 5.7, 3.9 Hz, 1H, HCN), 2.06 (s, 3H) 1.38 (d, *J* = 6.6 Hz, 3H, $HCCH_3$), 1.22 and 1.21 (2 × t , *J* = 7.1 Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 170.8, 143.9, 128.6, 127.3, 126.8, 66.1 (d, *J* = 166.7 Hz, *C*P), 63.3 (d, *J* = 7.2 Hz, *C*CCP), 62.5 and 62.3 (2 × d, *J* = 7.2 Hz, CH_3CH_2OP), 55.2, 53.6 (d, *J* = 3.2 Hz, *C*CP), 25.1, 21.1, 16.6 (2 × d, *J* = 5.7 Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 23.65. Anal. Calcd for $C_{17}H_{28}NO_6P$: C, 54.69; H, 7.56; N, 3.75. Found: C, 54.40; H, 7.64; N, 3.66.

4.1.2. Diethyl (1*R*,2*R*)-3-acetoxy-1-hydroxy-2-[(*S*)-1-phenylethylamino]propylphosphonate 8b (*ent*-8a)

From aziridinephosphonate (1*R*,2*R*,1′*S*)-**7b** (0.267 g, 0.852 mmol) phosphonate (1*R*,2*R*,1′*S*)-**8b** (0.273 g, 86%) was obtained as a colourless oil. $[\alpha]_D^{20} = -69.8$ (*c* 1.06, $CHCl_3$). Anal. Calcd for $C_{17}H_{28}NO_6P$: C, 54.69; H, 7.56; N, 3.75. Found: C, 54.67; H, 7.82; N, 3.71.

4.1.3. Diethyl (1*R*,2*S*)-3-acetoxy-1-hydroxy-2-[(*R*)-1-phenylethylamino]propylphosphonate 8c

From aziridinephosphonate (1*R*,2*S*,1′*R*)-**7c** (0.259 g, 0.827 mmol) phosphonate (1*R*,2*S*,1′*R*)-**8c** (0.188 g, 61%) was obtained as a colourless oil. IR (film): ν = 3312, 2980, 2927, 2867, 1739, 1452, 1369, 1234, 1031, 970, 764, 703 cm^{-1}. $[\alpha]_D^{20} = +66.4$ (*c* 1.56, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.24 (m, 5H), 4.31 (d, *J* = 6.0 Hz, 2H, H_aCH_b), 4.25–4.08 (m, 4H, CH_2OP), 4.02 (q, *J* = 6.6 Hz, 1H, $HCCH_3$), 3.82 (dd, *J* = 6.0, 5.7 Hz, 1H, HCP), 3.01 (dtd, *J* = 25.6, 6.0, 6.0, 5.7 Hz, 1H, HCN), 2.07 (s, 3H), 1.38 (d, *J* = 6.6 Hz, 3H, $HCCH_3$), 1.33 and 1.29 (2 × t, *J* = 7.1 Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 170.9, 144.3, 128.8, 127.6, 127.1, 67.3 (d, *J* = 160.1 Hz, *C*P), 63.7 (d, *J* = 6.9 Hz, CH_3CH_2OP), 63.4 (d, *J* = 2.9 Hz, *C*CCP), 62.4 (d, *J* = 7.4 Hz, CH_3CH_2OP), 55.6, 55.5 (d, *J* = 2.6 Hz, *C*CP), 25.3, 21.3, 16.9 and 16.7 (2 × d, *J* = 5.7 Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 23.35. Anal. Calcd for $C_{17}H_{28}NO_6P$: C, 54.69; H, 7.56; N, 3.75. Found: C, 54.41; H, 7.83; N, 3.50.

4.1.4. Diethyl (1*S*,2*R*)-3-acetoxy-1-hydroxy-2-[(*S*)-1-phenylethylamino]propylphosphonate 8d (*ent*-8c)

From aziridinephosphonate (1*S*,2*R*,1′*S*)-**7d** (0.360 g, 1.15 mmol) phosphonate (1*S*,2*R*,1′*S*)-**8d** (0.267 g, 62%) was obtained as a colourless oil. $[\alpha]_D^{20} = -65.5$ (*c* 1.30, $CHCl_3$). Anal. Calcd for $C_{17}H_{28}NO_6P$: C, 54.69; H, 7.56; N, 3.75. Found: C, 54.51; H, 7.60; N, 3.46.

4.2. Intramolecular cyclisation of phosphonates 8 (general procedure)

To a solution of phosphonates **8** (0.373 g, 1.00 mmol) in CH_2Cl_2 (4 mL) under an argon atmosphere at −70 °C was added NEt_3 (0.70 mL, 5.0 mmol). The dark-yellow mixture was stirred for 15 min at −70 °C and then treated with mesyl chloride (0.24 mL, 3.0 mmol). The mixture was allowed to warm to room temperature, stirred overnight and then quenched with 3 mL of saturated $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by silica gel chromatography (CH_2Cl_2/MeOH, 200:1,v/v) gave aziridine-2-phosphonates **10** as slightly yellowish oils.

4.2.1. Diethyl (2*R*,3*S*)-3-acetoxymethyl-1-[(*R*)-1-phenylethyl] aziridin-2-yl-2-phosphonate 10a

From phosphonate (1*S*,2*S*,1′*R*)-**8a** (0.142 g, 0.38 mmol) *cis*-aziridine-2-phosphonate (2*R*,3*S*,1′*R*)-**10a** (0.126 g, 93%) was obtained. IR (film): ν = 2978, 2930, 2869, 1741, 1452, 1372, 1252, 1029, 967, 760, 702 cm^{-1}. $[\alpha]_D^{20} = +16.8$ (*c* 1.55, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.24 (m, 5H), 4.50 (dd, *J* = 12.0, 4.8 Hz, 1H, H_aCH_b), 4.39 (ddd, *J* = 12.0, 7.8, 0.6 Hz, 1H, H_aCH_b), 3.94 (dq, *J* = 7.5, 7.2 Hz, 2H, CH_2OP), 3.78 (ddq, *J* = 10.1, 7.2, 6.9 Hz, 1H, H_aCH_bOP), 3.51 (ddq, *J* = 10.1, 7.2, 7.9 Hz, 1H, H_aCH_bOP), 2.53 (q, *J* = 6.6 Hz, 1H, $HCCH_3$), 2.21 (dtd, *J* = 7.8, 6.9, 6.9, 4.8 Hz, 1H, HCCP), 2.12 (s, 3H), 1.67 (dd, *J* = 15.6, 6.9 Hz, 1H, HCP), 1.49 (d, *J* = 6.6 Hz, 3H, $HCCH_3$), 1.22 and 1.01 (2 × t, *J* = 7.2 Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 170.9, 142.8, 128.5, 127.7, 127.4, 71.4 (d, *J* = 6.0 Hz, CH_3CPh), 63.7 (s, CH_2OAc), 62.5 and 61.9 (2 × d, *J* = 6.0 Hz, CH_3CH_2OP), 42.7 (d, *J* = 5.4 Hz, *C*CP), 36.1 (d, *J* = 214.8 Hz, *C*P), 23.0 (s, CH_3CPh), 21.2 (s, CH_3CO), 16.6 and 16.4 (2 × d, *J* = 6.3 Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 22.25. Anal. Calcd for $C_{17}H_{26}NO_5P$: C, 57.46; H, 7.37; N, 3.94. Found: C, 57.35; H, 7.34; N, 4.12.

4.2.2. Diethyl (2*S*,3*R*)-3-acetoxymethyl-1-[(*S*)-1-phenylethyl] aziridin-2-yl-2-phosphonate 10b (*ent*-10a)

From phosphonate (1*R*,2*R*,1′*S*)-**8b** (0.15 g, 0.40 mmol) *cis*-aziridine-2-phosphonate (2*S*,3*R*,1′*S*)-**10b** (0.131 g, 92%) was obtained. $[\alpha]_D^{20} = -16.4$ (*c* 0.78, $CHCl_3$). Anal. Calcd for $C_{17}H_{26}NO_5P$: C, 57.46; H, 7.37; N, 3.94. Found: C, 57.27; H, 7.55; N, 3.91.

4.2.3. Diethyl (2*S*,3*S*)-3-acetoxymethyl-1-[(*R*)-1-phenylethyl] aziridin-2-yl-2-phosphonate 10c

From phosphonate (1*R*,2*S*,1′*R*)-**8c** (0.210 g, 0.562 mmol) *trans*-aziridine-2-phosphonate (2*S*,3*S*,1′*R*)-**10c** was obtained as a 2:1 mixture of *N*-invertomers (0.180 g, 90%). IR (film): ν = 2979, 2929, 2870, 1743, 1449, 1372, 1236, 1030, 969, 760, 702 cm^{-1}. $[\alpha]_D^{20} = +41.7$ (*c* 1.32, $CHCl_3$). Anal. Calcd for $C_{17}H_{26}NO_5P$: C, 57.46; H, 7.37; N, 3.94. Found: C, 57.61; H, 7.64; N, 3.75.

4.2.3.1. Major invertomer (1*R*,2*S*,3*S*,1′*R*)-13c. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.45–7.18 (m, 5H), 4.31–4.21 (m, 1H, H_aCH_b), 4.07–3.97 (m, 1H, H_aCH_b), 4.02 (q, *J* = 6.3 Hz, 1H, $HCCH_3$), 4.07–3.96 (m, 2H, CH_2OP), 3.65–3.53 (m, 1H, H_aCH_bOP), 3.49–3.36 (m, 1H, H_aCH_bOP), 2.70–2.62 (m, 1H, HCCP), 2.09 (s, 3H), 1.94 (dd, *J* = 15.9, 3.6 Hz, 1H, HCP), 1.37 (d, *J* = 6.3 Hz, 3H, $HCCH_3$), 1.26 and 0.84 (2 × t, *J* = 7.2 Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 170.6, 144.8, 128.1, 126.9, 126.8, 66.3 (s, CH_2OAc), 62.2 and 61.8 (2 × d, *J* = 6.0 Hz, CH_3CH_2OP), 60.8 (d, *J* = 8.3 Hz, CH_3CPh), 40.5 (s, *C*CP), 33.7 (d, *J* = 182.0 Hz, *C*P), 25.3 (s, CH_3CPh), 21.0 (s, CH_3CO), 16.6 and 16.0 (2 × d, *J* = 6.8 Hz, CH_3CH_2OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 23.82.

4.2.3.2. Minor invertomer (1*S*,2*S*,3*S*,1′*R*)-13c. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.45–7.18 (m, 5H), 4.25–4.15 (m, 1H, H_aCH_b), 4.15–4.05 (m, 1H, H_aCH_b), 4.25–4.15 and 4.10–4.00 (m, 4H, CH_2OP), 3.23 (q, *J* = 6.3 Hz, 1H, $HCCH_3$), 2.80–2.72 (m, 1H, HCCP), 1.62 (s, 3H), 1.77 (dd, *J* = 19.5, 2.7 Hz, 1H, HCP), 1.46 (d, *J* = 6.3 Hz, 3H, $HCCH_3$), 1.36 and 1.26 (2 × t, *J* = 7.2 Hz, 6H, CH_3CH_2OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 170.3, 144.2, 128.3, 126.8, 126.3, 63.0 and 62.9 (2 × d, *J* = 6.0 Hz, CH_3CH_2OP), 61.8 (d, *J* = 8.3 Hz, CH_3CPh), 60.1 (d, *J* = 1.5 Hz, CH_2OAc), 39.7 (d, *J* = 6.8 Hz, *C*CP), 36.2 (d,

J = 214.4 Hz, *C*P), 25.3 (s, *C*H_3CPh), 20.4 (s, *C*H_3CO), 16.6 (d, J = 6.8 Hz, *C*$H_3$$CH_2$OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 22.59.

4.2.4. Diethyl (2*R*,3*R*)-3-acetoxymethyl-1-[(*S*)-1-phenylethyl] aziridin-2-yl-2-phosphonate 10d (*ent*-10c)

From phosphonate (1*S*,2*R*,1′*S*)-**8d** (0.342 g, 0.916 mmol) *trans*-aziridine-2-phosphonate (2*R*,3*R*,1′*S*)-**10d** was obtained as a 2:1 mixture of *N*-invertomers (0.294 g, 90%). $[\alpha]_D^{20} = -42.7$ (c 1.24, $CHCl_3$). Anal. Calcd for $C_{17}H_{26}NO_5P$: C, 57.46; H, 7.37; N, 3.94. Found: C, 57.24; H, 7.65; N, 3.85.

4.3. Hydrogenolysis of aziridine-2-phosphonates 10a–d (general procedure)

A solution of aziridine-2-phosphonates **10a–d** (0.178 g, 0.500 mmol) in ethanol (4 mL) containing Boc_2O (0.218 g, 1.00 mmol) was stirred under an atmospheric pressure of hydrogen over 10% Pd–C (50 mg) at room temperature for 7 hours. The suspension was filtered through a layer of Celite, the solution was concentrated and chromatographed on a silica gel column with CH_2Cl_2–MeOH (200:1 and 100:1, v/v).

4.3.1. Diethyl (2*R*,3*S*)-3-acetoxymethyl-1-(*tert*-butoxycarbonyl) aziridin-2-yl-2-phosphonate 11a

From aziridine-2-phosphonate (2*R*,3*S*,1′*R*)-**10a** (0.112 g, 0.315 mmol) *N*-Boc-protected aziridinephosphonate (2*R*,3*S*)-**11a** (0.098 g, 89%) was obtained as a colourless oil. IR (film): ν = 2982, 2935, 1733, 1444, 1370, 1294, 1252, 1159, 1027, 973 cm^{-1}. $[\alpha]_D^{20} = -31.7$ (c 1.26, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.47 (dd, J = 12.0, 5.4 Hz, 1H, $H_a$$CH_b$), 4.42 (dd, J = 12.0, 6.9 Hz, 1H, H_aCH_b), 4.37–4.11 (m, 4H, CH_2OP), 2.97 (dtd, J = 7.5, 6.9, 6.9, 5.4 Hz, 1H, HCCP), 2.59 (dd, J = 15.0, 6.9 Hz, 1H, HCP), 2.11 (s, 3H), 1.46 (s, 9H, (CH_3)$_3$C), 1.38 and 1.36 (2 × t, J = 7.2 Hz, 6H, C$H_3$$CH_2$OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 170.8, 160.5, 82.8, 63.4 and 62.8 (2 × d, J = 6.0 Hz, CH_3*C*H_2OP), 62.5, 39.7 (d, J = 5.1 Hz, *C*CP), 34.4 (d, J = 207.4 Hz, *C*P), 28.1, 21.1, 16.7 (2 × d, J = 6.3 Hz, *C*$H_3$$CH_2$OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 18.17. Anal. Calcd for $C_{14}H_{26}NO_7P$: C, 47.86; H, 7.46; N, 3.99. Found: C, 47.56; H, 7.76; N, 3.89.

4.3.2. Diethyl (2*S*,3*R*)-3-acetoxymethyl-1-(*tert*-butoxycarbonyl) aziridin-2-yl-2-phosphonate 11b (*ent*-11a)

From aziridine-2-phosphonate (2*S*,3*R*,1′*S*)-**10b** (0.126 g, 0.355 mmol) *N*-Boc-protected aziridinephosphonate (2*S*,3*R*)-**11b** (0.112 g, 89%) was obtained as a colourless oil. $[\alpha]_D^{20} = +31.5$ (c 1.15, $CHCl_3$). Anal. Calcd for $C_{14}H_{26}NO_7P$: C, 47.86; H, 7.46; N, 3.99. Found: C, 47.91; H, 7.61; N, 4.06.

4.3.3. Diethyl (2*S*,3*S*)-3-acetoxymethyl-1-(*tert*-butoxycarbonyl) aziridin-2-yl-2-phosphonate 11c

From a mixture of *N*-invertomers of aziridine-2-phosphonate (2*S*,3*S*,1′*R*)-**10c** (0.108 g, 0.289 mmol) *N*-Boc-protected aziridinephosphonate (2*S*,3*S*)-**11c** (0.090 g, 87%) was obtained as a colourless oil. IR (film): ν = 2983, 2934, 1730, 1443, 1370, 1294, 1318, 1233, 1158, 1028, 973 cm^{-1}. $[\alpha]_D^{20} = +37.8$ (c 1.12, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.32–4.27 (m, 2H, H_aCH_b), 4.28–4.14 (m, 4H, CH_2OP), 3.05 (dtd, J = 7.8, 4.2, 4.2, 3.6 Hz, 1H, HCCP), 2.57 (dd, J = 17.7, 3.6 Hz, 1H, HCP), 2.07 (s, 3H), 1.47 (s, 9H, (CH_3)$_3$C), 1.37 (t, J = 7.2 Hz, 6H, C$H_3$$CH_2$OP). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 170.1, 158.4 (d, J = 7.5 Hz, *C*NCP), 82.6, 63.4 and 62.9 (2 × d, J = 6.0 Hz, CH_3*C*H_2OP), 61.6, 38.5 (d, J = 2.3 Hz, *C*CP), 32.9 (d, J = 197.7 Hz, *C*P), 28.1, 21.0, 16.7 and 16.6 (2 × d, J = 6.0 Hz, *C*$H_3$$CH_2$OP). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 19.76. Anal. Calcd for $C_{14}H_{26}NO_7P$: C, 47.86; H, 7.46; N, 3.99. Found: C, 47.61; H, 7.23; N, 3.94.

4.3.4. Diethyl (2*R*,3*R*)-3-acetoxymethyl-1-(*tert*-butoxycarbonyl) aziridin-2-yl-2-phosphonate 11d (*ent*-11c)

From a mixture of *N*-invertomers of aziridine-2-phosphonate (2*R*,3*R*,1′*S*)-**10d** (0.102 g, 0.273 mmol) *N*-Boc-protected aziridinephosphonate (2*R*,3*R*)-**11d** (0.083 g, 86%) was obtained as a colourless oil. $[\alpha]_D^{20} = -38.7$ (c 1.37, $CHCl_3$). Anal. Calcd for $C_{14}H_{26}NO_7P$: C, 47.86; H, 7.46; N, 3.99. Found: C, 47.90; H, 7.68; N, 3.89.

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