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# Stereochemistry of cycloaddition of (*S*)-*N*-(1-phenylethyl)-*C*-diethoxyphosphorylated nitrone with vinyl acetate. Studies on mutarotation of 3-(*O*,*O*-diethylphosphoryl)-5-hydroxyisoxazolidines

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Received 16 October 2007; accepted 9 January 2008

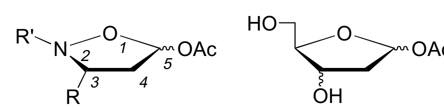
This paper is respectfully dedicated to Professor Maria Michalska

**Abstract**—Three enantiomerically pure diethyl 5-acetoxy-2-[(*S*)-1-phenylethyl]isoxazolidinyl-3-phosphonates were obtained by 1,3-dipolar cycloaddition of the title nitrone and vinyl acetate. Each of them was subsequently transformed into the respective 5-hydroxy derivatives, which exist as equilibrium mixtures of C5-anomers. Detailed mutarotation studies on a 3-(*O*,*O*-diethylphosphoryl)-5-hydroxyisoxazolidine system showed that *trans*-isomer (3*S*,5*R*) is favoured in the solid state, whereas after 48 h in chloroform-*d* solution it epimerises at C5 to an (89:11) equilibrium mixture of (3*S*,5*S*)- and (3*S*,5*R*)-isomer. The major (3*S*,5*S*)-anomer adopts a single $E_3$ conformation, which is stabilised by the C3–P(O)···HO–C5 hydrogen bond. Absolute configurations of the cycloadducts were established based on conformational analysis employing $^{1}$H, $^{13}$C and $^{31}$P NMR data and confirmed by the transformation of the (3*S*,5*R*)-isomer into the known (*S*)-(+)-phosphohomoserine.


## 1. Introduction

The 1,3-dipolar cycloaddition of nitrones with various alkenes has received considerable attention, since substituted isoxazolidines found applications as useful precursors for the construction of important and potentially bioactive compounds, including β-amino acids, β-lactams, amino sugars as well as isoxazolidine nucleosides.[1–4] In most cases the regio- and stereochemistry of the cycloaddition is predictable, although subtle structural differences of the reagents can influence the ratio of the isomers.[1,5] So far, a vast number of the reactions of structurally diversified nitrones and alkenes have been studied, the majority of which were focused on asymmetric transformations.[5,6]

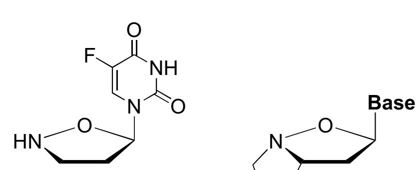
Among various dipolarophiles reacted with nitrones, vinyl acetate is of special interest, since 5-acetoxyisoxazolidine cycloadducts **1** are formed, which can be considered as structural analogues of 1-*O*-acetyl-2-deoxyfuranose **2** (Fig. 1). Several achiral as well as chiral nitrones have been examined in the reaction with vinyl acetate including synthetic,[7–21] as well as theoretical studies.[15,22]




**1** **2**

**Figure 1.** Structural resemblance of 5-acetoxyisoxazolidines **1** and 1-*O*-acetyl-2-deoxyfuranose **2**.

Since 5-acetoxyisoxazolidines could be used as starting materials in the Vorbrüggen reaction,[23] the synthesis of isoxazolidine analogues of nucleosides became apparent. Following this reasoning, various modified nucleosides have been obtained with some of them, for example, **3** and **4** (Fig. 2),[24,25] revealing interesting biological activity.




**3** **4**

**Figure 2.** Isoxazolidinyl nucleoside analogues **3** and **4**.

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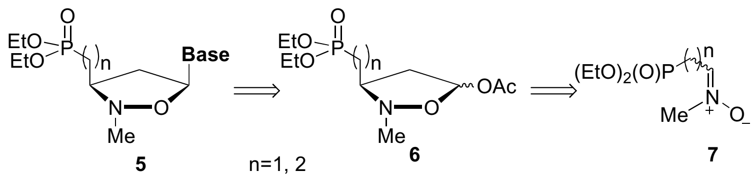
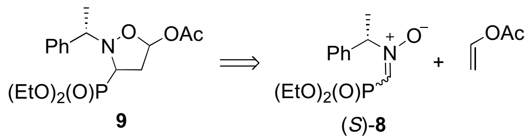
doi:10.1016/j.tetasy.2008.01.009



Scheme 1. Chiacchio's approach to isoxazolidine nucleoside analogues **5**.

For example, Chiacchio et al. have reported the synthesis of phosphonate analogues of isoxazolidinyl nucleosides **5**, which were obtained from nitrones **7** ($n = 1$ or 2) and vinyl acetate following the subsequent coupling with selected nucleobases (Scheme 1).[7,10,11]

Recently, we succeeded in the synthesis of achiral C-phosphorylated nitrone **7** ($n = 0$) and its usefulness in 1,3-dipolar cycloaddition with vinyl acetate was also studied.[26,27] In continuation of these efforts, N-chiral nitrone (*S*)-**8** was reacted with vinyl acetate to obtain enantiomerically pure isoxazolidine cycloadducts **9** (Scheme 2) and to possibly investigate the mutarotation of the respective 5-hydroxyisoxazolidines. Furthermore, isoxazolidines **9** could be considered as useful precursors in the syntheses of isoxazolidine nucleoside analogues **5** ($n = 0$).



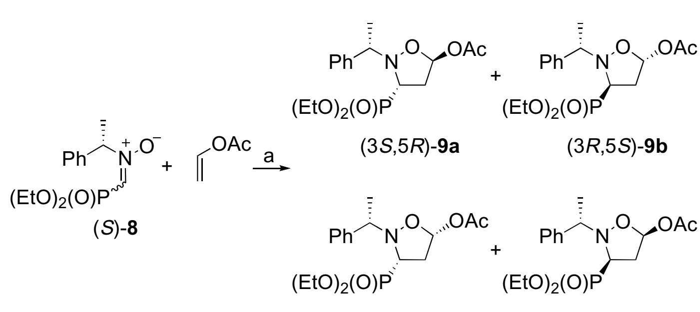
Scheme 2. Retrosynthesis of 5-acetoxyisoxazolidine **9**.

## 2. Results and discussion

Nitrone (*S*)-(+)-**8** was obtained from diethyl formylphosphonate and (*S*)-*N*-(1-phenylethyl)hydroxylamine according to a known procedure and was found to exist in a chloroform-*d* solution as a 7:93 mixture of *E*/*Z* isomers.[28] The reaction of (*S*)-**8** and vinyl acetate gave a 58:34:2:6 mixture of cycloadducts (3*S*,5*R*)-**9a**, (3*R*,5*S*)-**9b**, (3*S*,5*S*)-**9c** and (3*R*,5*R*)-**9d** (Scheme 3). Three pure diastereoisomers (3*S*,5*R*)-**9a**, (3*R*,5*S*)-**9b** and (3*R*,5*R*)-**9d** were separated from this mixture by column chromatography on silica gel in 48%, 18% and 4% yields, respectively.

As reported earlier, the reaction of the racemic C-phosphorylated nitrone with vinyl acetate led to a 90:10 mixture of the corresponding *trans*- and *cis*-isoxazolidines.[26] Based on this observation, *trans*-isoxazolidines (3*S*,5*R*)-**9a** and (3*R*,5*S*)-**9b** are also expected to be formed as the major products in the cycloaddition of (*S*)-**8** to vinyl acetate. To confirm this assumption, detailed conformational analyses of pure isoxazolidines **9** were undertaken based on the vicinal coupling constants (Table 1).[29–35] It appeared that a preferred conformation could only be unambiguously established for the (3*R*,5*S*)-**9b** diastereoisomer only. The isoxazolidine ring in (3*R*,5*S*)-**9b** adopts an $^4E$ conformation having the $P(O)(OEt)_2$ and OAc groups in pseudoequatorial and axial positions, respectively (Fig. 3). The most diagnostic vicinal couplings include: $J(H\text{–}C3C4\text{–}Hb) = 10.8$ Hz, which suggests almost perfect antiperiplanar arrangement of the respective protons, $J(H\text{–}C3C4\text{–}Ha) = 0$ Hz (the respective dihedral angle ~80°) and $J(P\text{–}C3C4\text{–}C5) = 9.2$ Hz (the respective dihedral angle ~150°). Consequently, the second major cycloadduct (3*S*,5*R*)-**9a** also has *trans*-configuration. Additional evidence in support of the *trans*-relative configurations of (3*S*,5*R*)-**9a** and (3*R*,5*S*)-**9b** will be given later. Based on this reasoning the *trans*/*cis* diastereoselectivity of the cycloaddition of (*S*)-**8** and vinyl acetate is 92:8, very close to that observed for the achiral nitrone **7** ($n = 0$).[26] It would be tempting to take advantage of the proximity of an *E*/*Z* ratio (7:93) of the nitrone (*S*)-**8** and the *cis*/*trans* diastereoselectivity of the cycloaddition (8:92) in rationalising the stereochemical outcome of the reaction. However, the possibility of an *E*/*Z* equilibration under the reaction conditions (in our case 60 °C) has recently been raised as a major argument in difficulty in correlating *E*/*Z* ratio of a dipole with ratios of cycloadducts.[6]

The structure of isoxazolidines **9** resembles the 1-*O*-acetyl-2-deoxyfuranose framework, in which the C4 of the furanose ring is replaced with a nitrogen atom. Removal of the acetyl group in **9** would lead to 5-hydroxyisoxazolidine



Scheme 3. Reagents and conditions: (a) toluene, 60 °C, 24 h.

**Table 1.** Stereochemically relevant vicinal couplings and chemical shifts for compounds **9a**, **9b** and **10a**–**10d** and their conformations

| Vicinal coupling constants (Hz) and chemical shifts (ppm) | Compounds | | | | | |
|---|---|---|---|---|---|---|
| | (3*S*,5*R*)-**9a** | (3*R*,5*S*)-**9b** | (3*S*,5*R*)-**10a** | (3*R*,5*S*)-**10b** | (3*S*,5*S*)-**10c** | (3*R*,5*R*)-**10d** |
| *J*(*P*–C3C4–*C5*) | 3.1 | 9.2 | 2.6 | 6.9 | 2.0 | 1.4 |
| *J*(*P*–C3N–*C*) | 14.3 | 6.0 | 16.0 | 9.7 | 17.2 | 14.3 |
| *J*(*H*–C3C4–*Ha*) | 4.8 | 6.3 | 3.9 | 7.5 | 0 | 1.5 |
| *J*(*H*–C3C4–*Hb*) | 8.7 | 10.8 | 9.0 | 9.0 | 9.9 | 10.8 |
| *J*(*H*–C5C4–*Ha*) | 6.6 | 0 | 6.3 | 0.9 | 0 | 0 |
| *J*(*H*–C5C4–*Hb*) | 2.4 | 5.1 | 2.7 | 5.1 | 5.4 | 5.4 |
| *J*(*P*–C3C4–*Ha*) | 18.9 | 5.7 | 18.6 | 9.0 | 13.5 | 15.0 |
| *J*(*P*–C3C4–*Hb*) | 20.4 | 17.1 | 23.4 | 19.2 | 33.9 | 32.7 |
| δ(*H*–C3) | 3.64 | 3.51 | 3.65 | 3.68 | 3.45 | 3.44 |
| δ(*Ha*–C4) | 2.90 | 2.43 | 2.79 | 2.48 | 2.25 | 2.18 |
| δ(*Hb*–C4) | 2.69 | 2.70 | 2.61 | 2.62 | 2.42 | 1.80 |
| δ(*H*–C5) | 6.51 | 6.16 | 5.80 | 5.44 | 5.61 | 5.35 |
| δ($H_3$C–C(O)) | 2.12 | 1.77 | — | — | — | — |
| Conformation | —[a] | $^4E$ | —[a] | —[a] | $E_3$ | $^3E$ |

[a] A preferred conformation cannot be established unambiguously.

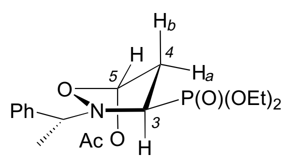
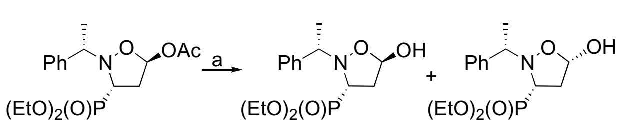



**Figure 3.** Preferred conformation of (3*R*,5*S*)-**9b**.

derivative **10** for which mutarotation is expected, as noticed earlier for structurally similar isoxazolidines,[14,36–41] isoxazolines[42] as well as other compounds possessing cyclic hemiacetal or hemiketal moiety (e.g., hydroxylated oxasilacyclopentane derivatives).[43–47] To this end, the acetyl groups in the enantiomerically pure isoxazolidines **9** were subjected to ammonolysis.

The treatment of (3*S*,5*R*)-**9a** with aqueous ammonia cleanly produced a mixture of 5-hydroxyisoxazolidines (C5-anomers), (3*S*,5*R*)-**10a** and (3*S*,5*S*)-**10c** ($\delta^{31}$P NMR: 23.76 and 26.68 ppm, respectively) (Scheme 4). Chromatographic removal of acetamide followed by crystallisation of the appropriate fractions gave pure (3*S*,5*R*)-**10a** in 59% yield. Similarly, ammonolysis of (3*R*,5*S*)-**9b** led to a mixture of isoxazolidines (3*R*,5*S*)-**10b** and (3*R*,5*R*)-**10d** ($\delta^{31}$P NMR: 23.19 and 26.63 ppm, respectively) (Scheme 5). Furthermore, when (3*R*,5*R*)-**9d** was treated in a similar fashion, the mixture of (3*R*,5*S*)-**10b** and (3*R*,5*R*)-**10d** was obtained (Scheme 5). These experiments prove that the absolute configurations at C3 in the diastereoisomeric pairs (3*R*,5*S*)-**9b** and (3*R*,5*R*)-**9d**, and in (3*S*,5*R*)-**9a** and (3*S*,5*S*)-**9c** are the same.

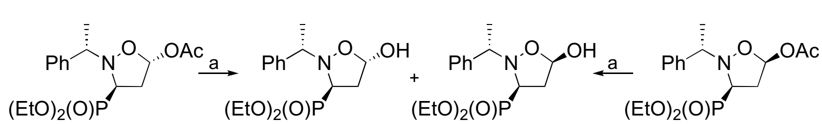



**Scheme 4.** Reagents and conditions: (a) $NH_4OH$, EtOH, rt, 2 h.

The $^1$H NMR spectrum of the chloroform-*d* solution of (3*S*,5*R*)-**10a** recorded immediately after dissolving crystals, exhibited resonance characteristics of the *trans*-isomer (3*S*,5*R*)-**10a** only. In the spectrum of the same solution taken 1 h later, a new set of signals attributed to the *cis*-isomer (3*S*,5*S*)-**10c** (4%) appeared, in addition to resonances of (3*S*,5*R*)-**10a** (96%). After 3 h, an 88:12 mixture of (3*S*,5*R*)-**10a** and (3*S*,5*S*)-**10c** was observed, which changed to 25:75 after 24 h. Finally, an equilibrium mixture (11:89) of two anomers (3*S*,5*R*)-**10a** and (3*S*,5*S*)-**10c** was formed after 48 h at room temperature. When this solution was concentrated to dryness in vacuo at room temperature and the solid obtained was re-dissolved in $CDCl_3$, the $^1$H NMR spectrum showed the presence of (3*S*,5*R*)-**10a** and (3*S*,5*S*)-**10c** in a 80:20 ratio.

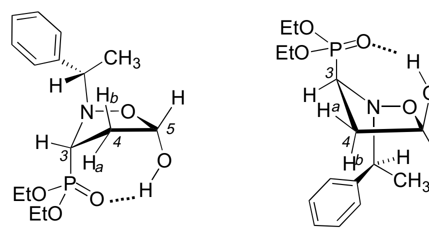
In a similar way, after 24 h at room temperature an equilibrium mixture of (3*R*,5*S*)-**10b** and (3*R*,5*R*)-**10d** (10:90) was produced.

The relative configurations in the diastereoisomers (3*S*,5*R*)-**10a** and (3*S*,5*S*)-**10c**, as well as in (3*R*,5*S*)-**10b** and (3*R*,5*R*)-**10d** were established based on $^1$H, $^{13}$C and $^{31}$P NMR spectroscopic data. Comparison of the respective vicinal couplings in (3*S*,5*R*)-**10a** and (3*S*,5*R*)-**9a** strongly suggests that they both exist in the same conformation or similar conformational equilibrium (Table 1). On the other hand, analysis of vicinal coupling constants for (3*S*,5*S*)-**10c** (Table 1) shows that the isoxazolidine ring exists in a single




**Scheme 5.** Reagents and conditions: (a) $NH_4OH$, EtOH, rt, 2 h.

$E_3$ conformation, in which the $P(O)(OEt)_2$ and hydroxy groups are *cis*-oriented (Fig. 4). The unexpected diaxial orientation of two bulky groups $P(O)(OEt)_2$ and $Ph(CH_3)CH$ can be rationalised by the stabilisation of this conformation by a very strong intramolecular P(O)···H–O hydrogen bond (Fig. 4). Furthermore, a very similar set of couplings has also been found for (3*R*,5*R*)-**10d**, which supports the existence of a single $^3E$ conformation of the isoxazolidine ring again stabilised by the P(O)···H–O hydrogen bond (Table 1, Fig. 4), thereby indicating a *cis*-relationship of the substituents at C3 and C5 in (3*R*,5*R*)-**10d**. As in (3*S*,5*S*)-**10c**, so in (3*R*,5*R*)-**10d** three antiperiplanar arrangements of atoms exist in *H*–C3C4–*Hb*, *P*–C3C4–*Hb* and *P*–C3N–*C* moieties as concluded from the respective vicinal couplings: *J*(*P*–C3C4–*Hb*) = 33.9 and 32.7 Hz, *J*(*H*–C3C4–*Hb*) = 9.9 and 10.8 Hz and *J*(*P*–C3N–*C*) = 17.2 and 14.3 Hz. Close to 90° *H*–C5C4–*Ha* dihedral angles reflect a lack of the respective couplings. These configurational assignments are additionally supported by comparison of the $^{31}$P NMR shifts of the hydrogen-bonded *cis*-isomers (3*S*,5*S*)-**10c** ($\delta$ 26.68 ppm) and (3*R*,5*R*)-**10d** ($\delta$ 26.63 ppm) with non-bonded *trans*-isomers (3*S*,5*R*)-**10a** and (3*R*,5*S*)-**10b** ($\delta$ 23.76 and 23.19 ppm, respectively). Furthermore, significantly downfield shifted signals of O*H* protons in hydrogen-bonded *cis*-phosphonates (3*S*,5*S*)-**10c** and (3*R*,5*R*)-**10d** ($\delta$ 6.17 and 6.05 ppm) were observed, when compared to the corresponding signals of O*H* group in *trans*-isomers (3*S*,5*R*)-**10a** and (3*R*,5*S*)-**10b** ($\delta$ 3.10 and 2.40 ppm).



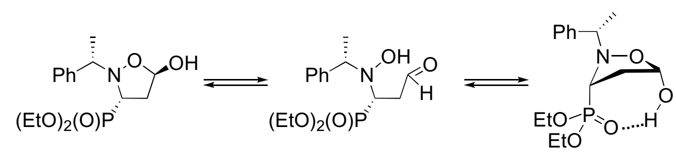
(3*S*,5*S*)-**10c** (3*R*,5*R*)-**10d**

**Figure 4.** The preferred conformations of (3*S*,5*S*)-**10c** and (3*R*,5*R*)-**10d**.

At this stage it became clear that the relative configurations at C3 and C5 are the same in the two diastereoisomeric pairs of the cycloadducts: *trans* in (3*S*,5*R*)-**9a** as well as (3*R*,5*S*)-**9b** and *cis* in (3*S*,5*S*)-**9c** as well as (3*R*,5*R*)-**9d**.

The analysis of stereochemical results described above indicates that isomerisation of 5-hydroxyisoxazolidines **10** involves a ring opening and subsequent re-cyclisation of the corresponding acyclic isomers **11** (Scheme 6). The process is reversible, since the ratio of isomers changed after concentration of an equilibrium mixture. In a solid state the *trans*-diastereoisomer **10** is favoured, whereas the corresponding hydrogen-bonded *cis*-isomer predominates in a chloroform-*d* solution.

When pure 5-hydroxyisoxazolidine (3*S*,5*R*)-**10a** was treated with acetic anhydride in the presence of triethylamine, the *O*-acetates (3*S*,5*R*)-**9a** and (3*S*,5*S*)-**9c** were obtained in a 1:2 ratio. Similarly, acetylation of an equilibrium mixture of (3*S*,5*R*)-**10a** and (3*S*,5*S*)-**10c** (2:8) gave compounds

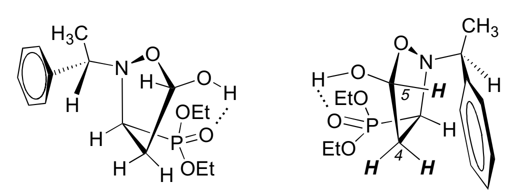


*trans*-**10** **11** *cis*-**10**

**Scheme 6.** Mutarotation of 5-hydroxyisoxazolidine **10**.

(3*S*,5*R*)-**9a** and (3*S*,5*S*)-**9c** in the same 1:2 ratio. Unfortunately, pure (3*S*,5*S*)-**9c** could not be efficiently separated from these mixtures.

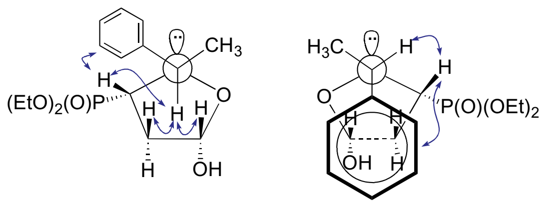
Although significant differences in chemical shifts were observed in the $^1$H NMR spectra of diastereoisomeric cycloadducts (3*S*,5*R*)-**9a** and (3*R*,5*S*)-**9b**, the assignment of their absolute configurations was not possible, since the available data did not allow us to unambiguously establish the conformation of (3*S*,5*R*)-**9a**. However, detailed analyses of $^1$H NMR chemical shifts of (3*S*,5*S*)-**10c** [obtained from (3*S*,5*R*)-**9a**] and (3*R*,5*R*)-**10d** [obtained from (3*R*,5*S*)-**9b**] showed that an already existing 1-phenylethyl functionality produces indicative space-oriented anisotropic effects. First of all, the *C** carbon of 1-phenylethyl group is antiperiplanar to the P atom in both compounds [$^3J_{CNCP}$ = 17.2 and 14.3 Hz for (3*S*,5*S*)-**10c** and (3*R*,5*R*)-**10d**, respectively]. Significant upfield shifts of the $H_b$–C4 ($\delta$ 1.80 ppm), $H_a$–C4 ($\delta$ 2.16 ppm) and *H*–C5 ($\delta$ 5.35 ppm) in (3*R*,5*R*)-**10d**, as compared to the chemical shifts of the same protons in (3*S*,5*S*)-**10c** ($\delta$ 2.25, 2.42 and 5.61 ppm, respectively) are best explained by the shielding of the Ph group in (3*R*,5*R*)-**10d**, which is not possible in the diastereoisomer (3*S*,5*S*)-**10c** (Fig. 5).



(3*S*,5*S*)-**10c** (3*R*,5*R*)-**10d**

**Figure 5.** The preferred conformations of (3*S*,5*S*)-**10c** and (3*R*,5*R*)-**10d**.

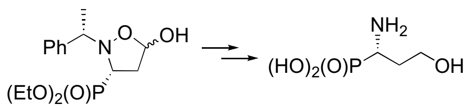
Indeed, examination of the molecular models of both *cis*-diastereoisomers (3*S*,5*S*)-**10c** and (3*R*,5*R*)-**10d** revealed spatial orientations of substituents along the Ph(CH$_3$)H*C*–*N* bond in (3*S*,5*S*)-**10c** and (3*R*,5*R*)-**10d** (Fig. 6). To prove preferred conformations of both isomers, 2D NOE experiments were performed. Positive signals between the *H*CPh–*H*–C5, *H*CPh–*H*–C4 and *H*CPh–*H*–C3 in (3*S*,5*S*)-**10c** indicate spatial proximity of the *H*–C5, *H*–C3, *H*–C4 and *H*C proton of the 1-phenylethyl group. Moreover, a positive signal between the *H*–C3 and *Ph* was observed for this isomer. On the other hand, positive signals for *H*CPh–*H*–C3 and HC*Ph*–*H*–C3 pairs in (3*R*,5*R*)-**10d** support the preferred conformation shown in Figure 6. These observations unambiguously prove the absolute configurations at C3 and C5 in the isoxazolidine ring as (3*S*,5*S*) for isomer **10c** and (3*R*,5*R*) for **10d**.




(3*S*,5*S*)-**10c** (3*R*,5*R*)-**10d**

**Figure 6.** Preferred Newman projections for (3*S*,5*S*)-**10c** and (3*R*,5*R*)-**10d** and major NOESY correlations used to establish the absolute configurations.

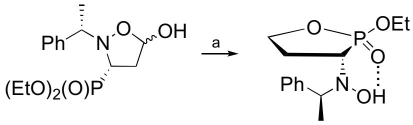
To gather additional evidence for the already established absolute configuration at C3 in isoxazolidine (3*S*,5*R*)-**10a** as well as in (3*S*,5*S*)-**10c** their transformation into the known (*S*)-phosphohomoserine (*S*)-**12** was proposed (Scheme 7).




(3*S*,5*R*)-**10a**
(3*S*,5*S*)-**10c**
(*S*)-**12**

**Scheme 7.** Synthetic approach to phosphohomoserine (*S*)-**12**.

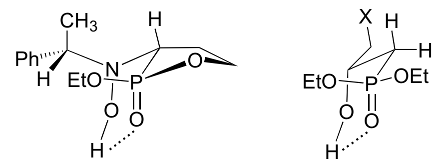
To this end, a crude mixture of 5-hydroxyisoxazolidines (3*S*,5*R*)-**10a** and (3*S*,5*S*)-**10c** was subjected to $NaBH_4$ reduction. The reaction was capricious and led to a complex mixture, from which diastereoisomerically pure 3-hydroxylamino-1,2-oxaphospholane (2*S*,3*S*)-**13** could be isolated in, at best, 66% yield by fast column chromatography on silica gel (Scheme 8). When kept at room temperature, this compound appeared to be unstable undergoing decomposition. The $^{31}$P NMR spectrum of the sample taken one month later showed the presence of signals at 1.01, 0.58 and −10.83 ppm in a 9:29:62 ratio.




(3*S*,5*R*)-**10a**
(3*S*,5*S*)-**10c**
(2*S*,3*S*)-**13**

**Scheme 8.** Reagents and conditions: (a) $NaBH_4$, EtOH, rt, 6 h.

The formation of the 1,2-oxaphospholane ring as well as the configuration of the newly generated stereogenic centre at phosphorus was established on the basis of the NMR spectral data. First of all, the $^{31}$P NMR resonance for (2*S*,3*S*)-**13** appeared at 42.47 ppm, which is characteristic of 1,2-oxaphospholanes.[48] Analysis of vicinal couplings extracted from the $^1$H and $^{13}$C NMR spectra showed that this ring exists in a $^1T_2$ conformation with 1-phenylethyl substituent in the pseudoequatorial position (Table 2). Furthermore, in the $^1$H NMR spectrum, a downfield shifted signal of *H*O was observed ($\delta^1$H = 6.07 ppm), and examination of several NMR spectra of **13** proved that it was practically (±0.1 ppm) concentration independent. This observation clearly proves the presence of a strong P═O···H–O hydrogen bond (Fig. 7) additionally stabilised by the formation of a six-membered ring, which exists in a chair conformation. The other argument supporting the H-bonding in (2*S*,3*S*)-**13** comes from the close resemblance of the H-bonded fragment in (2*S*,3*S*)-**13** with that in a 2-hydroxyalkyl phosphonate system **14**, since the stabilising role of the intramolecular hydrogen bond in 2-hydroxyalkyl phosphonates has been well recognised.[49–52] This clearly demonstrates that the OH and P═O groups are located on the same side of the 1,2-oxaphospholane ring and thus proves the (*S*)-absolute configuration at the phosphorus in (2*S*,3*S*)-**13**.




(2*S*,3*S*)-**13** **14**

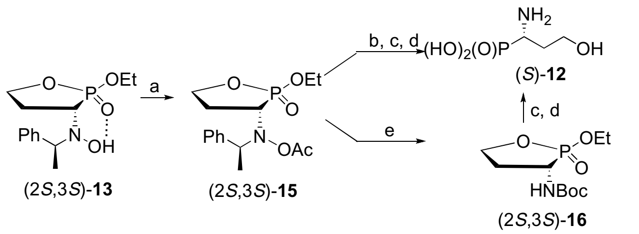
**Figure 7.** The preferred $^1T_2$ conformation of (2*S*,3*S*)-**13** and H-bonding in a 2-hydroxyalkyl phosphonate system **14**.

Finally, a hydroxylamine (2*S*,3*S*)-**13** was subjected to acetylation to give the stable acetate (2*S*,3*S*)-**15**. This derivative was subsequently transformed into the known phosphohomoserine (*S*)-(+)-**12**[53–55] by hydrogenolytic cleavage of the N–O bond and removal of the 1-phenylethyl residue followed by hydrolysis of the phosphonate esters (Scheme 9). Furthermore, it was reasoned that hydrogenolysis of (2*S*,3*S*)-**15** in the presence of $Boc_2O$ would lead to enantiomerically pure 1,2-oxaphospholane (2*S*,3*S*)-**16**, which may be considered as potential QS inhibitor. Indeed, transformation of (2*S*,3*S*)-**15** into (2*S*,3*S*)-**16** was accomplished in 52% yield after column chromatography. Hydrolysis of (2*S*,3*S*)-**16** under acidic conditions again gave (*S*)-(+)-**12**.

Both samples of phosphohomoserine (*S*)-**12** obtained from (2*S*,3*S*)-**13** (Scheme 9) were found to be dextrorotatory. According to the literature data, the levorotatory enantiomer of **12** has the (*R*)-absolute configuration.[53] This earlier finding fully supports our configurational assignments for isoxazolidines (3*S*,5*S*)-**10c** and (3*R*,5*R*)-**10d**, as well as those for the enantiomers of diethyl 5-(hydroxymethyl)-2-[(*S*)-1-phenylethyl]isoxazolidinyl-3-phosphonate and *O*,*O*-

**Table 2.** Stereochemically relevant vicinal couplings for (2*S*,3*S*)-**13**

| Vicinal coupling constants (Hz) | (2*S*,3*S*)-**13** |
|---|---|
| *J*(*P*–C3N–*C*) | 16.6 |
| *J*(*H*β–C5O–*P*) | 16.8 |
| *J*(*H*α–C5O–*P*) | 5.1 |
| *J*(*H*β–C5C4–*H*α) | 7.8 |
| *J*(*H*β–C5C4–*H*β) | 3.6 |
| *J*(*H*α–C5C4–*H*α) | 9.3 |
| *J*(*H*α–C5C4–*H*β) | 6.0 |
| *J*(*H*–C3C4–*H*β) | 8.5 |
| *J*(*H*–C3C4–*H*α) | 8.1 |
| *J*(*H*α–C4C3–*P*) | 7.0 |
| *J*(*H*β–C4C3–*P*) | 22.2 |
| Conformation | $^1T_2$ |



**Scheme 9.** Reactions and conditions: (a) $Ac_2O$, $NEt_3$, DMAP, rt, 3 h; (b) $H_2/Pd(OH)_2$–C, EtOH, rt, 24 h; (c) 6 M HCl, reflux, 6 h; (d) propylene oxide, EtOH; (e) $Boc_2O$, $H_2/Pd(OH)_2$–C, EtOH, rt, 20 h.

diethyl 4-hydroxypyrrolidinyl-2-phosphonate based on advanced conformational and configurational studies presented in this and former papers.[28,55]

## 3. Conclusions

The 1,3-dipolar cycloaddition of nitrone (*S*)-**8** and vinyl acetate led regiospecifically and with high (92:8) *trans*-selectivity to a mixture of four diethyl 5-acetoxy-2-[(*S*)-1-phenylethyl]isoxazolidinyl-3-phosphonates, from which pure isomers (3*S*,5*R*)-**9a**, (3*R*,5*S*)-**9b** and (3*R*,5*R*)-**9d** were isolated. Removal of the *O*-acetyl group from (3*S*,5*R*)-**9a** produced a mixture of 5-hydroxy derivatives (3*S*,5*R*)-**10a** and (3*S*,5*S*)-**10c**.

Mutarotation of 3-(*O*,*O*-diethylphosphoryl)-5-hydroxyisoxazolidines was studied in detail in (3*S*,5*R*)-**10a** revealing the formation of an 11:89 equilibrium mixture of (3*S*,5*R*)-**10a** and (3*S*,5*S*)-**10c** after 48 h at room temperatures in chloroform-*d* solution. In a solid state, the *trans*-isomer (3*S*,5*R*)-**10a** is favoured, whereas in solution, strong intramolecular hydrogen bonds stabilise the *cis*-isomer (3*S*,5*S*)-**10c** in an $E_3$ conformation with axially oriented $P(O)(OEt)_2$ and OH groups.

The absolute configurations of the isoxazolidine cycloadducts have been established based on the conformational analysis of (3*S*,5*S*)-**10c** [obtained from (3*S*,5*R*)-**9a**] and (3*R*,5*R*)-**10d** [obtained from (3*R*,5*S*)-**9b**] taking advantage of the anisotropic effects of aromatic ring present in the (*S*)-1-phenylethyl auxiliary. In addition, by transformation of a mixture of (3*S*,5*R*)-**10a** and (3*S*,5*S*)-**10c** into the known (*S*)-(+)-phosphohomoserine, the absolute configuration was unambiguously correlated with the literature data.

## 4. Experimental

$^1$H, $^{13}$C and $^{31}$P NMR were taken in $CDCl_3$ or $D_2O$ on Varian Mercury-300 spectrometer with TMS as an internal standard at 300, 75.5 and 121.5 MHz, respectively. $^1H\{^{31}P\}$ NMR and $^1$H–$^1$H COSY experiments were applied, when necessary to support spectral assignments. IR spectra were measured on an Infinity MI-60 FT-IR spectrometer. Melting points were determined on an electrothermal apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of this Faculty on Perkin–Elmer PE 2400 CHNS analyser. Polarimetric measurements were conducted on a Perkin–Elmer 241 MC apparatus.

The following adsorbents were used: column chromatography, Merck Silica Gel 60 (70–230 mesh); analytical TLC, Merck TLC plastic sheets Silica Gel 60 $F_{254}$.

### 4.1. Cycloaddition of the nitrone (*S*)-(+)-8 with vinyl acetate

Nitrone (*S*)-**8** (0.784 g, 2.75 mmol) [prepared from (*S*)-*N*-(1-phenylethyl)hydroxylamine and formylphosphonate][28] and vinyl acetate (0.51 mL, 5.5 mmol) were stirred in toluene (5 mL) at 60 °C for 24 h. After the disappearance of the starting nitrone, the mixture was concentrated in vacuo to give a crude product (0.9 g) which was purified by column chromatography on silica gel with toluene–isopropanol (50:1, v/v) to afford (3*R*,5*R*)-**9d** (0.041 g, 4%), (3*R*,5*S*)-**9b** (0.185 g, 18%) and (3*S*,5*R*)-**9a** (0.492 g, 48%) all as colourless oils.

#### 4.1.1. Diethyl (3*S*,5*R*)-5-acetoxy-2-[(*S*)-1-phenylethyl]isoxazolidinyl-3-phosphonate (3*S*,5*R*)-9a.

IR (film): $\nu = 3472$, 2983, 2934, 1751, 1454, 1374, 1233, 1051, 1027, 974 $cm^{-1}$. $[\alpha]_D^{20} = -128.1$ (*c* 1.4, $CHCl_3$). $^1$H NMR ($CDCl_3$): $\delta$ 7.40–7.20 (m, 5H), 6.51 (dd, $J = 6.6$, 2.4 Hz, 1H, *H*–C5), 4.19 (dq, $J = 6.6$, 1.5 Hz, 1H, *H*C–$CH_3$), 4.18–3.95 (m, 3H), 3.95–3.78 (m, 1H), 3.64 (ddd, $J = 9.0$, 8.7, 4.8 Hz, 1H, *H*–C3), 2.90 (dddd, $J = 18.9$, 14.1, 6.6, 4.8 Hz, 1H, *Ha*–C4), 2.69 (dddd, $J = 20.4$, 14.1, 8.7, 2.4 Hz, 1H, *Hb*–C4), 2.12 (s, 3H, C$H_3$–C(O)), 1.46 (d, $J = 6.6$ Hz, 3H, C$H_3$–CH), 1.30 (t, $J = 6.9$ Hz, 3H), 1.22 (t, $J = 6.9$ Hz, 3H). $^{13}$C NMR ($CDCl_3$): $\delta$ 169.98 (C=O), 142.49, 128.73, 128.05, 128.00, 98.63 (d, $^3J_{(CCCP)} = 3.1$ Hz, C5), 67.25 (d, $^3J_{(CNCP)} = 14.3$ Hz, *C*H–Ph), 63.15 (d, $J = 6.9$ Hz, $CH_2$OP), 63.06 (d, $J = 5.7$ Hz, $CH_2$OP), 58.47 (d, $^1J_{(CP)} = 176.1$ Hz, C3), 37.24 (s, C4), 21.61, 20.31, 16.81 (d, $J = 7.2$ Hz), 16.73 (d, $J = 6.0$ Hz). $^{31}$P NMR ($CDCl_3$): $\delta$ 22.11. Anal. Calcd for $C_{17}H_{26}NO_6P$: C, 54.98; H, 7.06; N, 3.77. Found: C, 54.68; H, 7.36; N, 3.73.

#### 4.1.2. Diethyl (3*R*,5*S*)-5-acetoxy-2-[(*S*)-1-phenylethyl]isoxazolidinyl-3-phosphonate (3*R*,5*S*)-9b.

IR (film): $\nu = 3475$, 2982, 1751, 1453, 1375, 1234, 1024, 981 $cm^{-1}$. $[\alpha]_D^{20} = -17.8$ (*c* 1.2, $CHCl_3$). $^1$H NMR ($CDCl_3$): $\delta$ 7.40–7.20 (m, 5H), 6.16 (d, $J = 5.1$ Hz, 1H, *H*–C5), 4.40 (br q, $J = 6.9$ Hz, 1H, *H*C–$CH_3$), 4.35–4.15 (m, 4H), 3.51 (ddd, $J = 10.8$, 6.3, 2.1 Hz, 1H, *H*–C3), 2.70 (dddd, $J = 17.1$, 12.9, 10.8, 5.1 Hz, 1H, *Hb*–C4), 2.43 (ddd, $J = 12.9$, 6.3, 5.7 Hz, 1H, *Ha*–C4), 1.77 (s, 3H, C$H_3$–C(O)), 1.57 (d, $J = 6.9$ Hz, 3H, C$H_3$–CH), 1.39 (t, $J = 7.2$ Hz, 3H), 1.36 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR ($CDCl_3$): $\delta$ 169.71 (C=O), 139.82, 129.29, 127.89, 127.41, 94.72 (d, $^3J_{(CCCP)} = 9.2$ Hz, C5), 65.70 (d, $^3J_{(CNCP)} = 6.0$ Hz, CH–Ph), 63.96 (d, $J = 6.3$ Hz, $CH_2$OP), 62.55 (d, $J = 6.9$ Hz, $CH_2$OP), 56.05 (d, $^1J_{(CP)} = 174.3$ Hz, C3), 39.17 (d, $^2J_{(CCP)} = 2.6$ Hz, C4), 21.38, 21.29, 16.75 (d, $J = 5.4$ Hz), 16.67 (d, $J = 5.7$ Hz). $^{31}$P NMR ($CDCl_3$): $\delta$ 22.42. Anal. Calcd for $C_{17}H_{26}NO_6P$: C, 54.98; H, 7.06; N, 3.77. Found: C, 54.56; H, 7.23; N, 3.86.

**4.1.3. Diethyl (3*R*,5*R*)-5-acetoxy-2-[(*S*)-1-phenylethyl]isoxazolidinyl-3-phosphonate (3*R*,5*R*)-9d.** IR (film): $\nu = 2982$, 1746, 1454, 1375, 1234, 1052, 1023, 967 cm$^{-1}$. $[\alpha]_D^{20} = -107.5$ (*c* 0.9, $CHCl_3$). $^1H$ NMR ($CDCl_3$): $\delta$ 7.45–7.40 (m, 2H), 7.40–7.26 (m, 3H), 6.16 (dd, $J = 3.0$, 1.2 Hz, 1H, *H*–C5), 4.51 (br q, $J = 6.9$ Hz, 1H, *H*C–$CH_3$), 4.36–4.22 (m, 2H), 4.22–4.10 (m, 2H), 2.98 (dt, $J = 8.7$, 2.1 Hz, 1H, *H*–C3), 2.57–2.48 (m, 2H, $H_2$C4), 2.10 (s, 3H, C$H_3$–C(O)), 1.65 (d, $J = 6.9$ Hz, 3H, C$H_3$–CH), 1.41 (t, $J = 7.2$ Hz, 3H), 1.32 (t, $J = 7.2$ Hz, 3H). $^{13}C$ NMR ($CDCl_3$): $\delta$ 170.55 (C=O), 137.65, 130.44, 128.02, 127.85, 93.97 (d, $^3J_{(CCCP)} = 8.3$ Hz, C5), 63.77 (d, $J = 6.9$ Hz), 63.70 (d, $J = 3.1$ Hz), 62.44 (d, $J = 6.9$ Hz), 56.75 (d, $^1J_{(CP)} = 167.7$ Hz, C3), 39.60 (d, $^2J_{(CCP)} = 2.6$ Hz, C4), 21.65, 20.59, 16.77 (d, $J = 6.0$ Hz), 16.73 (d, $J = 5.7$ Hz). $^{31}P$ NMR ($CDCl_3$): $\delta$ 22.28. Anal. Calcd for $C_{17}H_{26}NO_6P$: C, 54.98; H, 7.06; N, 3.77. Found: C, 54.94; H, 7.29; N, 3.75.

### 4.2. Ammonolysis of isoxazolidines 9 (general procedure)

To a solution of isoxazolidine **9** (1.0 mmol) in EtOH (2 mL), concentrated ammonia (25%) was added (5 mL). The reaction mixture was stirred for 2 h at room temperature and then all volatiles were removed under reduced pressure to give a crude product, which was chromatographed on silica gel column with chloroform–methanol (100:1, v/v).

**4.2.1. Diethyl (3*S*,5*R*)- and (3*S*,5*S*)-5-hydroxy-2-((*S*)-1-phenylethyl)isoxazolidinyl-3-phosphonates (3*S*,5*R*)-10a and (3*S*,5*S*)-10c.** As described in Section 4.2, from (3*S*,5*R*)-**9a** (0.215 g, 0.580 mmol), a 1:1 mixture of anomers (3*S*,5*R*)-**10a** and (3*S*,5*S*)-**10c** (0.188 g, 99%) was obtained. Crystallisation of this mixture from ether gave (3*S*,5*R*)-**10a** (0.112 g, 59%) as colourless needles.

**4.2.1.1. Compound (3*S*,5*R*)-10a.** Mp 103–104 °C. IR (KBr): $\nu = 3427$, 3293, 2987, 2931, 1455, 1211, 1055, 1035, 989 cm$^{-1}$. $[\alpha]_D^{20} = -71.5$ (*c* 1.4, $CHCl_3$). $^1H$ NMR ($CDCl_3$): $\delta$ 7.40–7.20 (m, 5H), 5.80 (dd, $J = 6.3$, 2.7 Hz, 1H, *H*–C5), 4.37 (q, $J = 6.6$ Hz, 1H, *H*C–$CH_3$), 4.19–15 (m, 2H), 4.15–3.95 (m, 1H), 3.92–3.80 (m, 1H), 3.65 (ddd, $J = 10.8$, 9.0, 3.9 Hz, 1H, *H*–C3), 3.10 (br s, 1H, O*H*), 2.79 (dddd, $J = 18.6$, 13.8, 6.3, 3.9 Hz, 1H, *Ha*–C4), 2.61 (dddd, $J = 23.4$, 13.8, 9.0, 2.7 Hz, 1H, *Hb*–C4), 1.53 (d, $J = 6.6$, 3H, HC–C$H_3$), 1.29 (t, $J = 7.2$ Hz, 3H), 1.22 (t, $J = 7.2$ Hz, 3H). $^{13}C$ NMR ($CDCl_3$): $\delta$ 143.19, 128.47, 127.96, 127.58, 99.90 (d, $^3J_{(CCCP)} = 2.6$ Hz, C5), 67.24 (d, $^3J_{(CNCP)} = 16.0$ Hz, *C*H–Ph), 62.89 (d, $J = 7.2$ Hz, *C*$H_2$OP), 62.38 (d, $J = 6.6$ Hz, *C*$H_2$OP), 59.01 (d, $^1J_{(CP)} = 175.2$ Hz, C3), 38.00 (s, C4), 21.20 (s, $CH_3$), 16.72 (d, $J = 6.0$ Hz), 16.52 (d, $J = 5.7$ Hz). $^{31}P$ NMR ($CDCl_3$): $\delta$ 23.76. Anal. Calcd for $C_{15}H_{24}NO_5P$: C, 54.71; H, 7.35; N, 4.25. Found: C, 54.85; H, 7.45; N, 4.30.

**4.2.1.2. Compound (3*S*,5*S*)-10c.** (NMR data were extracted from the spectrum of an 11:89 equilibrium mixture of (3*S*,5*R*)-**10a** and (3*S*,5*S*)-**10c**): $^1H$ NMR ($CDCl_3$): $\delta$ 7.40–7.20 (m, 5H), 6.17 (d, $J = 12.5$ Hz, 1H, O*H*), 5.61 (dd, $J = 12.5$, 5.4 Hz, 1H, *H*–C5), 4.40–4.22 (m, 2H), 4.15–3.93 (m, 2H), 3.87 (q, $J = 6.6$ Hz, 1H, *H*C–$CH_3$), 3.45 (dd, $J = 10.8$, 9.9 Hz, 1H, *H*–C3), 2.42 (dddd, $J = 33.9$, 13.5, 9.9, 5.4 Hz, 1H, *Hb*–C4), 2.25 (t, $J = 13.5$, 1H, *Ha*–C4), 1.50 (d, $J = 6.6$ Hz, 3H, HC–C$H_3$), 1.36 (t, $J = 7.1$ Hz, 3H), 1.26 (t, $J = 7.1$ Hz, 3H). $^{13}C$ NMR ($CDCl_3$): $\delta$ 141.31, 128.59, 127.99, 127.84, 98.97 (d, $^3J_{(CCCP)} = 2.0$ Hz, C5), 66.45 (d, $^3J_{(CNCP)} = 17.2$ Hz, *C*H-Ph), 64.88 (d, $J = 6.9$ Hz, *C*$H_2$OP), 62.16 (d, $J = 7.2$ Hz, *C*$H_2$OP), 57.14 (d, $^1J_{(CP)} = 176.6$ Hz, C3), 36.82 (d, $^2J_{(CCP)} = 2.9$ Hz, C4), 20.36 (s, $CH_3$), 16.72 (d, $J = 6.0$ Hz), 16.52 (d, $J = 5.7$ Hz). $^{31}P$ NMR ($CDCl_3$): $\delta$ 26.68.

**4.2.2. Diethyl (3*R*,5*S*)- and (3*R*,5*R*)-5-hydroxy-2-((*S*)-1-phenylethyl)isoxazolidinyl-3-phosphonates (3*R*,5*S*)-10b and (3*R*,5*R*)-10d.** As described in Section 4.2, from (3*R*,5*S*)-**9b** (0.156 g, 0.420 mmol), a 4:6 mixture of anomers (3*R*,5*S*)-**10b** and (3*R*,5*R*)-**10d** (0.103 g, 75%) was obtained as a colourless oil.

**4.2.2.1. Compound (3*R*,5*S*)-10b.** (NMR data were extracted from the spectrum of a 40:60 mixture of (3*R*,5*S*)-**10b** and (3*R*,5*R*)-**10d**): $^1H$ NMR ($CDCl_3$): $\delta$ 7.40–7.26 (m, 5H), 5.44 (dd, $J = 5.1$, 0.9 Hz,1H, *H*–C5), 4.41 (q, $J = 6.9$ Hz, 1H, *H*C–$CH_3$), 4.40–4.05 (m, 4H), 3.69 (ddd, $J = 9.0$, 7.5 Hz, 3.3 Hz, 1H, *H*–C3), 2.61 (dddd, $J = 19.2$, 12.9, 9.0, 5.1 Hz, 1H, *Hb*–C4), 2.50 (dddd, $J = 12.9$, 9.0, 7.5, 0.9 Hz, 1H, *Ha*–C4), 2.40 (s, 1H, O*H*), 1.48 (d, $J = 6.9$ Hz, 3H, HC–C$H_3$), 1.36 (t, $J = 7.2$ Hz, 3H), 1.33 (t, $J = 7.2$ Hz, 3H). $^{13}C$ NMR ($CDCl_3$): $\delta$ 142.50, 128.47, 128.32, 128.23, 97.04 (d, $^3J_{(CCCP)} = 6.9$ Hz, C5), 67.78 (d, $^3J_{(CNCP)} = 9.7$ Hz, *C*H–Ph), 63.65 (d, $J = 6.6$ Hz, *C*$H_2$OP), 62.84 (d, $J = 7.2$ Hz, *C*$H_2$OP), 57.43 (d, $^1J_{(CP)} = 178.4$ Hz, C3), 36.89 (C4), 20.70 (s, $CH_3$), 16.90 (d, $J = 5.7$ Hz,), 16.65 (d, $J = 5.7$ Hz). $^{31}P$ NMR ($CDCl_3$): $\delta$ 23.19.

**4.2.2.2. Compound (3*R*,5*R*)-10d.** (NMR data were extracted from the spectrum of a 10:90 equilibrium mixture of (3*R*,5*S*)-**10b** and (3*R*,5*R*)-**10d**): $^1H$ NMR ($CDCl_3$): $\delta$ 7.40–7.26 (m, 5H), 6.05 (br s, 1H, O*H*), 5.36 (br d, $J = 5.4$ Hz, 1H, *H*–C5), 4.45–4.05 (m, 4H), 3.85 (q, $J = 6.9$ Hz, 1H, *H*C–$CH_3$), 3.44 (ddd, $J = 10.8$, 7.5, 1.5 Hz, 1H, *H*–C3), 2.16 (ddd, $J = 15$, 13.5, 1.5 Hz, 1H, *Ha*–C4), 1.80 (dddd, $J = 32.7$, 13.5, 10.8, 5.4 Hz, 1H, *Hb*–C4), 1.58 (d, $J = 6.9$ Hz, 3H, HC–C$H_3$), 1.40 (t, $J = 7.2$ Hz, 3H), 1.35 (t, $J = 7.1$ Hz, 3H). $^{13}C$ NMR ($CDCl_3$): $\delta$ 139.69, 128.75, 128.37, 127.93, 97.56 (d, $^3J_{(CCCP)} = 1.4$ Hz, C5), 67.00 (d, $^3J_{(CNCP)} = 14.3$ Hz, *C*H–Ph), 65.19 (d, $J = 6.9$ Hz, *C*$H_2$OP), 62.38 (d, $J = 7.4$ Hz, *C*$H_2$OP), 57.43 (d, $^1J_{(CP)} = 178.4$ Hz, C3), 38.20 (s, C4), 20.70 (s, $CH_3$), 16.90 (d, $J = 5.7$ Hz,), 16.65 (d, $J = 5.7$ Hz). $^{31}P$ NMR ($CDCl_3$): $\delta$ 26.63.

**4.2.3. Diethyl (3*R*,5*S*)- and (3*R*,5*R*)-5-hydroxy-2-((*S*)-1-phenylethyl)isoxazolidinyl-3-phosphonates (3*R*,5*S*)-10b and (3*R*,5*R*)-10d.** As described in Section 4.2, from (3*R*,5*R*)-**9d** (0.053 g, 0.153 mmol), a (2:8) mixture of 5-hydroxyisoxazolidines (3*R*,5*S*)-**10b** and (3*R*,5*R*)-**10d** was obtained (34 mg, 68%) as a colourless oil.

### 4.3. (2*S*,3*S*)-2-Ethoxy-2-oxo-3-{*N*-hydroxy-*N*-[(*S*)-1-phenylethyl]amino}-1,2-oxaphospholane (2*S*,3*S*)-13

To a solution of 5-hydroxyisoxazolidines (3*S*,5*R*)-**10a** and (3*S*,5*S*)-**10c** (0.123 g, 0.330 mmol) in ethanol (2 mL), sodium borohydride (0.037 g, 0.99 mmol) was added. The reaction mixture was stirred at room temperature for 6 h and ethanol was removed in vacuo. The residue was suspended in $CH_2Cl_2$ (10 mL) and anhydrous $MgSO_4$ (0.5 g) was added. After filtration and concentration, the solution was evaporated to give a crude product, which was purified by column chromatography with chloroform–methanol (100:1, v/v) to give (2*S*,3*S*)-**13** as a colourless oil (0.059 g, 66%). IR (film): $\nu$ = 3293, 2982, 2932, 1453, 1368, 1247, 1047, 1010, 950, 830, 772, 704 $cm^{-1}$. $[\alpha]_D^{20} = -18.1$ (*c* 1.3 $CHCl_3$). $^1H$ NMR ($CDCl_3$): $\delta$ 7.40–7.25 (m, 5H), 6.07 (s, 1H, N–O*H*), 4.32 (dddd, *J* = 16.8, 9.0, 7.8, 3.6 Hz, 1H, *H*β–C5), 4.17–4.02 (m, 2H, C*H*$_2$OP), 3.88 (dddd, *J* = 9.3, 9.0, 6.0, 5.1 Hz, 1H, *H*α–C5), 3.86 (q, *J* = 6.6 Hz, 1H, C*H*–$CH_3$), 3.17 (ddd, *J* = 12.3, 8.5, 8.1 Hz, 1H, *H*–C3), 2.64 (ddddd, *J* = 13.0, 9.3, 8.1, 7.8, 7.0 Hz, 1H, *H*α–C4), 2.07 (ddddd, *J* = 22.2, 13.0, 8.5, 6.0, 3.6 Hz, 1H, *H*β–C4), 1.54 (d, *J* = 6.6 Hz, 3H, CH–C*H*$_3$), 1.25 (t, *J* = 6.7 Hz, 3H, C*H*$_3$–$CH_2$–OP). $^{13}C$ NMR ($CDCl_3$): $\delta$ 141.17, 128.68, 128.28, 127.88, 64.93 (d, *J* = 16.6 Hz, *C*H–Ph), 64.90 (d, *J* = 9.0 Hz, C5), 62.94 (d, *J* = 6.3 Hz, *C*$H_2$OP), 57.23 (d, *J* = 149.2 Hz, C3), 25.39 (very br s, C4), 20.70 (s, *C*$H_3$–CH), 16.67 (d, *J* = 5.4 Hz, *C*$H_3CH_2$OP). $^{31}P$ NMR ($CDCl_3$): $\delta$ 42.47. Anal. Calcd for $C_{13}H_{20}NO_4P$: C, 54.73; H, 7.07; N, 4.91. Found: C, 54.53; H, 7.34; N, 4.79.

### 4.4. (2*S*,3*S*)-2-Ethoxy-2-oxo-3-{*N*-acetoxy-*N*-[(*S*)-1-phenylethyl]amino}-1,2-oxaphospholane (2*S*,3*S*)-15

A mixture of oxaphospholane (2*S*,3*S*)-**13** (0.08 g, 0.28 mmol), acetic anhydride (0.08 mL, 0.84 mmol) and triethylamine (0.13 mL, 0.92 mmol) containing DMAP (a few crystals) in methylene chloride (2 mL) was stirred at room temperature for 3 h. Afterwards, the reaction mixture was concentrated in vacuo and the residue was chromatographed on silica gel with chloroform–methanol (50:1, v/v) to give (2*S*,3*S*)-**15** (0.074 g, 81%) as a colourless oil. IR (film): $\nu$ = 2983, 1770, 1454, 1364, 1265, 1198, 1042, 1008, 828 $cm^{-1}$. $[\alpha]_D^{20} = -5.2$ (*c* 0.9, $CHCl_3$). $^1H$ NMR ($CDCl_3$): $\delta$ 7.43–7.25 (m, 5H), 4.40 (br s, 1H), 4.32 (br s, 1H), 4.20–4.11 (m, 2H, C*H*$_2$OP), 3.40–3.87 (m, 1H), 3.60–3.40 (br m, 1H), 2.50 (br s, 1H), 2.30 (br s, 1H), 1.98 (s, 3H, C*H*$_3$C(O)), 1.50 (d, *J* = 6.6 Hz, 3H, CH–C*H*$_3$), 1.32 (t, *J* = 6.7 Hz, 3H, C*H*$_3$–$CH_2$–OP). $^{13}C$ NMR ($CDCl_3$): $\delta$ 170.14 (C=O), 140.60, 128.63, 128.13, 128.06, 62.21 (d, *J* = 10.3 Hz, *C*H–Ph), 64.39 (d, *J* = 7.4 Hz, *C*$H_2$OP), 62.87 (d, *J* = 6.3 Hz, C5), 55.88 (d, *J* = 138.1 Hz, C3), 21.03, 19.57, 19.27 (very br s), 16.76 (d, *J* = 5.5 Hz, *C*$H_3CH_2$OP). $^{31}P$ NMR ($CDCl_3$): $\delta$ 37.23. Anal. Calcd for $C_{15}H_{22}NO_5P$: C, 55.04; H, 6.77; N, 4.28. Found: C, 55.07; H, 7.05; N, 4.26.

### 4.5. *tert*-Butyl (2*S*,3*S*)-2-ethoxy-2-oxo-1,2-oxaphospholan-3-ylcarbamate (2*S*,3*S*)-16

A solution of oxaphospholane (2*S*,3*S*)-**15** (0.074 g, 0.23 mmol) and $Boc_2O$ (0.060 g, 0.28 mmol) in ethanol (1 mL) was hydrogenated under atmospheric pressure over 20% $Pd(OH)_2$–C (10 mg) at room temperature for 20 h. The suspension was filtrated through a layer of Celite. The solution was concentrated and the residue was chromatographed on a silica gel column with chloroform–methanol (100:1, v/v) to give (2*S*,3*S*)-**16** (0.031 g, 52%) as a colourless oil. IR (film): $\nu$ = 3268, 2980, 2933, 1741, 1708, 1530, 1455, 1367, 1256, 1167, 1044, 1006, 969, 830 $cm^{-1}$. $[\alpha]_D^{20} = -33.8$ (*c* 0.9, $CHCl_3$). $^1H$ NMR ($CDCl_3$): $\delta$ 5.15 (br s, 1H, N*H*), 4.29 (dddd, *J* = 13.8, 9.6, 6.8, 4.5 Hz, 1H), 4.20 (dq, *J* = 8.7, 7.2 Hz, 2H), 4.07 (dddd, *J* = 9.6, 8.4, 7.5, 5.7 Hz, 1H), 3.98 (br q, *J* = 6.9 Hz, 1H), 2.58 (ddddd, *J* = 24.9, 13.2, 7.5, 5.7, 4.5 Hz, 1H), 2.22 (ddq, *J* = 13.2, 8.4, 6.9 Hz, 1H), 1.45 (s, 9H), 1.37 (t, *J* = 7.2 Hz, 3H). $^{13}C$ NMR ($CDCl_3$): $\delta$ 155.65 (d, *J* = 11.8 Hz), 80.55, 65.11 (d, *J* = 7.8 Hz), 63.85 (d, *J* = 6.6 Hz), 42.81 (d, *J* = 136.9 Hz), 32.69 (d, *J* = 10.9 Hz), 28.53, 16.69 (d, *J* = 5.7 Hz). $^{13}P$ NMR ($CDCl_3$): $\delta$ 41.01. Anal. Calcd for $C_{10}H_{20}NO_5P$: C, 45.28; H, 7.60; N, 5.28. Found: C, 45.38; H, 7.82; N, 5.19.

### 4.6. (*S*)-1-Amino-3-hydroxypropylphosphonic acid (*S*)-12

**4.6.1. Transformation of (2*S*,3*S*)-15 into (*S*)-12.** A solution of oxaphospholane (2*S*,3*S*)-**15** (0.070 g, 0.21 mmol) in ethanol (1 mL) was hydrogenated under atmospheric pressure over 20% $Pd(OH)_2$–C (10 mg) at room temperature for 24 h. The suspension was filtrated through a layer of Celite. The solution was concentrated, the residue dissolved in 6 M HCl (1 mL) and refluxed for 5 h. After that the solution was removed and the residue dissolved in ethanol (0.5 mL) and neutralised with propylene oxide. The solvent was withdrawn, and solid washed with ethanol and dried to afford (*S*)-**12** (0.030 g, 90%) as a white amorphous solid; mp 214–216 °C (lit.[54] mp 214 °C). $[\alpha]_D^{20} = +6.3$ (*c* 1.1, $H_2O$) {lit.[54] $[\alpha]_D = +7.3$ (*c* 1, $H_2O$)}. $^1H$ NMR ($D_2O$): $\delta$ 3.82 (t, *J* = 6.6 Hz, 2H), 3.40 (ddd, *J* = 13.8, 8.7, 4.2 Hz, 1H), 2.24–2.07 (m, 1H), 2.05–1.85 (m, 1H). $^{31}P$ NMR ($D_2O$): $\delta$ 14.09. Anal. Calcd for $C_3H_{10}NO_4P$: C, 23.23; H, 6.50; N, 9.03. Found: C, 23.04; H, 6.65; N, 8.88.

**4.6.2. Hydrolysis of (2*S*,3*S*)-16.** A solution of (2*S*,3*S*)-**16** (0.031 g, 0.12 mmol) in 6 M HCl (1 mL) was refluxed for 6 h. The solution was removed under reduced pressure, and the residue was dissolved in ethanol (0.5 mL) and neutralised with propylene oxide. The solvent was withdrawn, the solid washed with anhydrous ethanol and dried to give (*S*)-**12** (0.018 g, 95%), which was identical in all respects to the compound described in Section 4.6.1.

## Acknowledgements

The author is grateful to Professor Andrzej E. Wróblewski for support and stimulating discussions during preparation of this manuscript. Mrs. Jolanta Płocka is acknowledged for her excellent technical assistance. This work was supported by the Medical University of Łódź internal funds (502-13-332 and 503-3014-1).

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