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Stereochemistry of cycloaddition of (*S*)-*N*-(1-phenylethyl)-*C*-phosphorylated nitrone with cyclopentene and 2,3-dihydrofuran

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ABSTRACT

Cycloaddition of (*S*)-*N*-(1-phenylethyl)-*C*-(diethoxyphosphoryl)nitrone to cyclopentene gave a mixture of diethyl (3*S*,3a*R*,6a*S*)- and (3*R*,3a*S*,6a*R*)-hexahydro-2-[(*S*)-1-phenylethyl]-2*H*-cyclopenta[*d*]isoxazol-3-yl-3-phosphonates with moderate (68:32) diastereoselectivity, while the reaction with 2,3-dihydrofuran led regiospecifically to the formation of an easily separable mixture of diethyl (3*S*,3a*R*,6a*R*)- and (3*R*,3a*S*,6a*S*)-hexahydro-2-[(*S*)-1-phenylethyl]furo[3,2-d]isoxazol-3-yl-3-phosphonates in a 65:35 ratio. Absolute configurations of cycloadducts were established based on conformational analyses employing ^{1}H and ^{13}C NMR data and confirmed by 2D NOE experiments. Diastereoisomeric diethyl (3*S*,3a*R*,6a*S*)- and (3*R*,3a*S*,6a*R*)-hexahydro-2-[(*S*)-1-phenylethyl]-2*H*-cyclopenta[*d*]isoxazol-3-yl-3-phosphonates were transformed into both enantiomers of *tert*-butyl (2*S*,3*S*,3a*R*,6a*S*)- and (2*R*,3*R*,3a*S*,6a*R*)-2-ethoxy-2-oxo-cyclopenta[*d*](1,2-oxaphospholan-3-yl)carbamates in good yields.

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1. Introduction

An α-amino-γ-hydroxy acid moiety is present in many natural and synthetic products. Examples of such compounds containing this moiety and showing important biological activity are collected in Figure 1. Homoserine **1**, the simplest representative of this group, is involved in the biosynthesis of methionine and (*S*)-adenosylomethionine. The lactone of L-*threo*-4-hydroxynorvaline **2** (AL 719Y) was found to possess antimicrobial activity against *Pseudomonas aeruginosa*.[1] Monatin **3** revealed properties such as being an intense sweetener,[2] whereas desihedrine **4**, another naturally occurring amino acid, is an agonist of non-NMDA Glu-receptor.[3] Studies towards the design of glutamate analogues led to the synthesis of conformationally rigid frameworks containing, among others, isoxazoline or isoxazole rings incorporated to the 2-amino-4-hydroxy acid unit.[4] Compounds (*R*)-AMAA **5** and 4-HPCA **9** are known as NMDA receptor agonists,[5,6] while (*R*)-ATAA **6** has been recognised as an AMPA agonist.[7] The presence of a lipophilic side chain at C-4 in **8** increased its activity as a group I antagonist, compared to (*S*)-HIBO **7**.[8,9] Bicyclic analogue (±)-**11** showed a noticeable affinity for NMDA receptors, and at the same time appeared to be an anticonvulsant agent.[10]

Replacement of the carboxyl group with the phosphonate residue has resulted in obtaining isosteric or bioisosteric analogues of a vast number of natural products.[11] Recently, syntheses of N-substituted C-phosphorylated nitrones and their utilisation in cycloaddition reactions with various alkenes have been described.[12,13] It was reasoned that 3-phosphorylated isoxazolidine cycloadducts would have been appropriate substrates for the synthesis of the phosphonate mimetics of α-amino-γ-hydroxyacids. In

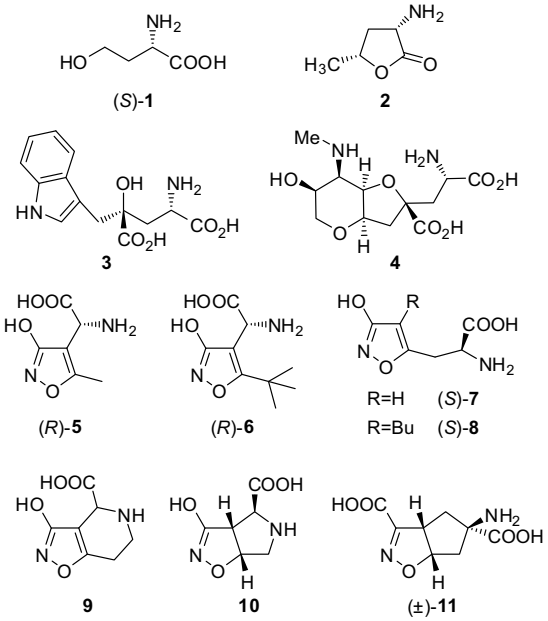

Figure 1.

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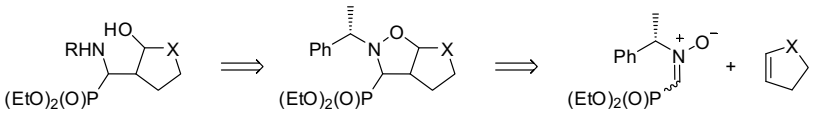


13 X=CH_2 **11** (*S*)-**8** **9**
14 X=O **12** **10**

Scheme 1. Synthetic strategy for phosphonates **13** (X = CH_2) and **14** (X = O).

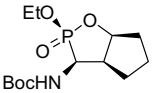
this report, the synthesis of isoxazolidines **11** (X = CH_2) and **12** (X = O) via cycloaddition of (*S*)-*N*-(1-phenylethyl)-*C*-phosphorylated nitrone (*S*)-**8** to cyclopentene **9** and 2,3-dihydrofuran **10**, respectively, is presented (Scheme 1). Subsequent transformation of cycloadducts **11** (X = CH_2) and **12** (X = O) into enantiomerically pure α-amino-γ-hydroxyphosphonates **13** or **14** is expected if hydrogenolytic removal of the 1-phenylethyl group and simultaneous cleavage of the N–O bond in **11** or **12** were to have occurred in good yields.

2. Results and discussion

Thermal cycloaddition of nitrone (*S*)-**8**[14] to cyclopentene produced a 65:35 mixture of isoxazolidines (3*S*,3a*R*,6a*S*,1′*S*)-**11a** and (3*R*,3a*S*,6a*R*,1′*S*)-**11b** (Scheme 2). Both diastereoisomers were separated on a silica gel column, to give (3*S*,3a*R*,6a*S*,1′*S*)-**11a** in 54% and (3*R*,3a*S*,6a*R*,1′*S*)-**11b** in 17% yield, respectively. Similarly, the reaction of (*S*)-**8** with 2,3-dihydrofuran **10** led to the formation of a 68:32 mixture of diastereoisomeric isoxazolidines (3*S*,3a*R*,6a-*R*,1′*S*)-**12a** and (3*R*,3a*S*,6a*S*,1′*S*)-**12b**, which were again isolated by column chromatography in 27% and 29% yield, respectively.

To synthesise an *N*-Boc-aminohydroxyphosphonate (1*S*,2*R*,1′*S*)-**15**, isoxazolidine (3*S*,3a*R*,6a*S*,1′*S*)-**11a** was subjected to catalytic hydrogenolysis in the presence of Boc_2O. In addition to (1*S*,2*R*,1′*S*)-**15** (83%), the crude product contained an 1,2-oxaphospholane (2*S*,3*S*,3a*R*,6a*S*)-**16** (4%) and isoxazolidine (3*S*,3a*R*,6a*S*)-**17** (13%) (Scheme 3). Unfortunately, attempts to purify (1*S*,2*R*,1′*S*)-**15** failed. Instead, when the crude mixture was subjected to chromatography on a silica gel column the 1,2-oxaphospholane (2*S*,3*S*,3a*R*,6a*S*)-**16** was isolated in 38% yield followed by fractions containing impure (1*S*,2*R*,1′*S*)-**15** (10%) and (3*S*,3a*R*,6a*S*)-**17** (4%). This indicates that the transformation of (1*S*,2*R*,1′*S*)-**15** into (2*S*,3*S*,3a*R*,6a*S*)-**16** takes place on silica gel, since (2*S*,3*S*,3a*R*,6a*S*)-**16** was isolated as a major product, whereas only traces of (1*S*,2*R*,1′*S*)-**15** were recovered. The formation of (3*S*,3a*R*,6a*S*)-**17** can be explained by the initial removal of the 1-phenylethyl moiety with the simultaneous introduction of *t*-butoxycarbonyl group at nitrogen atom. This makes cleavage of the N–O bond in isoxazolidine (3*S*,3a*R*,6a*S*)-**17** difficult. After extending the reaction time of the hydrogenolysis to 48 h, 13% of (3*S*,3a*R*,6a*S*)-**17** were again found in the reaction mixture, whereas the amount of (2*S*,3*S*,3a*R*,6a*S*)-**16** increased to 22% at the expense of (1*S*,2*R*,1′*S*)-**15** (65%).

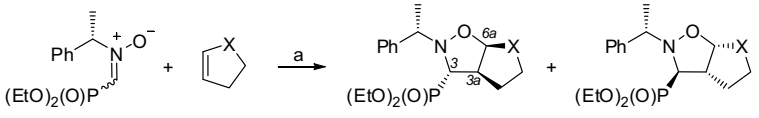
Since attempts at separating pure (1*S*,2*R*,1′*S*)-**15** proved unsuccessful, the crude reaction mixture obtained after hydrogenolysis of (3*S*,3a*R*,6a*S*,1′*S*)-**11a** was treated with DBU (1 equiv). This resulted in a transformation of (1*S*,2*R*,1′*S*)-**15** into a mixture of (2*S*,3*S*,3a*R*,6a*S*)-**16** and its P-epimer (2*R*,3*S*,3a*R*,6a*S*)-**18**, whereas (3*S*,3a*R*,6a*S*)-**17** remained untouched. When a crude reaction mixture containing (2*S*,3*S*,3a*R*,6a*S*)-**16**, (2*R*,3*S*,3a*R*,6a*S*)-**18** and (3*S*,3a*R*,6a*S*)-**17** in a 63:11:26 ratio was chromatographed on a silica gel column, pure (2*S*,3*S*,3a*R*,6a*S*)-**16** was separated in 57% yield followed by fractions of impure 1,2-oxaphospholane (2*R*,3*S*,3a*R*,6a*S*)-**18** (8%) and *N*-Boc-isoxazolidine (3*S*,3a*R*,6a*S*)-**17** (7%).



(2*R*,3*S*,3a*R*,6a*S*)-**18**

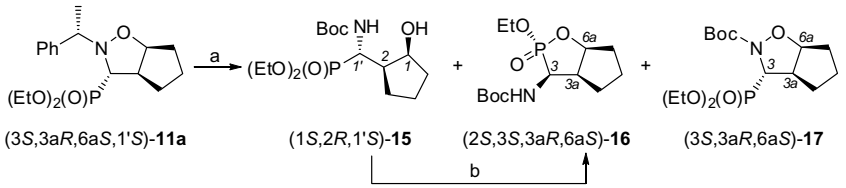
Similarly, isoxazolidine (3*R*,3a*S*,6a*R*,1′*S*)-**11b** was hydrogenated and then treated with DBU (1 equiv) to give 1,2-oxaphospholane (2*R*,3*R*,3a*S*,6a*R*)-**16** in 54% yield after purification on a silica gel column (Scheme 4).

Unfortunately, attempts at transforming isoxazolidines **12** into phosphonates **19** by catalytic hydrogenolysis in the presence of Boc_2O (Scheme 5) led to the formation of complex mixtures of unidentified products.



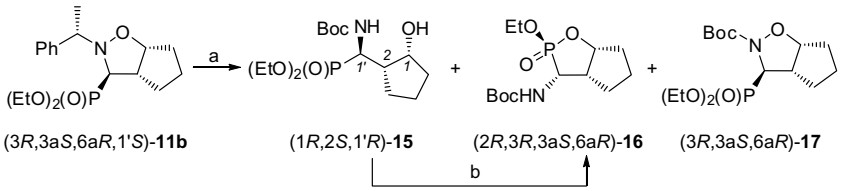
(*S*)-**8** **9** X=CH_2 (3*S*,3a*R*,6a*S*,1′*S*)-**11a** (3*R*,3a*S*,6a*R*,1′*S*)-**11b**
10 X=O (3*S*,3a*R*,6a*R*,1′*S*)-**12a** (3*R*,3a*S*,6a*S*,1′*S*)-**12b**

Scheme 2. Reagents and conditions: (a) toluene, 60 °C, 48 h.



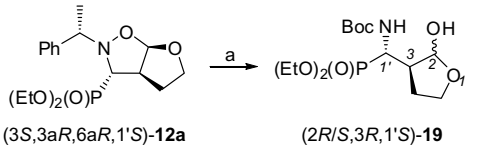
(3*S*,3a*R*,6a*S*,1′*S*)-**11a** (1*S*,2*R*,1′*S*)-**15** (2*S*,3*S*,3a*R*,6a*S*)-**16** (3*S*,3a*R*,6a*S*)-**17**

Scheme 3. Reagents and conditions: (a) Boc_2O, H_2, Pd–C and $Pd(OH)_2$, EtOH, 20 h; (b) DBU, $CDCl_3$, 24 h.



(3*R*,3a*S*,6a*R*,1′*S*)-**11b** (1*R*,2*S*,1′*R*)-**15** (2*R*,3*R*,3a*S*,6a*R*)-**16** (3*R*,3a*S*,6a*R*)-**17**

Scheme 4. Reagents and conditions: (a) Boc_2O, H_2, Pd–C and $Pd(OH)_2$, EtOH, 20 h; (b) DBU, $CDCl_3$, 24 h.



(3*S*,3a*R*,6a*R*,1′*S*)-**12a** (2*R*/*S*,3*R*,1′*S*)-**19**

Scheme 5. Reagents and conditions: (a) Boc_2O, H_2, Pd–C and $Pd(OH)_2$, EtOH, 20 h.

In structural studies on phosphonates (3*S*,3a*R*,6a*S*,1′*S*)-**11a**, (3*R*,3a*S*,6a*R*,1′*S*)-**11b**, (3*S*,3a*R*,6a*R*,1′*S*)-**12a** and (3*R*,3a*S*,6a*S*,1′*S*)-**12b**, we first focused attention on establishing preferred conformation of the fused isoxazolidine and tetrahydrofuran or cyclopentane rings. Thus, the relative configurations of the substituents in the isoxazolidine ring would become available.

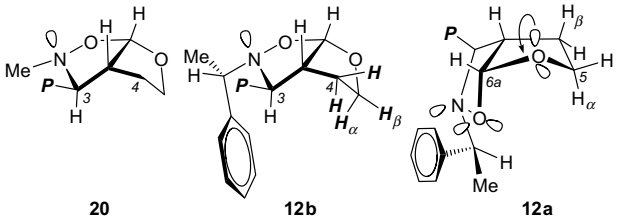
Our previous observations on *N*-methyl isoxazolidine **20** turned out to be useful.[13] Based on analysis of the available vicinal coupling constants (Table 1), it was established that **20** exists in an E_3/E^4 (isoxazolidine/tetrahydrofuran) conformation (Fig. 2),[13] in which bulky diethoxyphosphoryl and tetrahydrofuran rings adopt pseudoequatorial positions regarding the isoxazolidine ring to minimise their steric repulsions. A similar set of vicinal couplings was found for the minor isomer (3*R*,3a*S*,6a*S*,1′*S*)-**12b** (Table 1). This observation allows us to attribute the analogous E_3/E^4 conformation of fused isoxazolidine and tetrahydrofuran rings in **12b**, in which again the diethoxyphosphoryl group at C3 as well as both *H*–C3a and *H*–C6a bridgehead hydrogens are forced to occupy the same side of the molecule (Fig. 2). On the other hand, analysis of vicinal couplings found for the major isomer (3*S*,3a*R*,6a*R*,1′*S*)-**12a** revealed that this compound prefers to adopt E^{6a}/E^6 (isoxazolidine/tetrahydrofuran) conformation, in which the diethoxyphosphoryl group and a fused tetrahydrofuran fragment once again are situated on the opposite sides of the ring junction to minimise their steric interactions. It is worth noting that this conformation was also stabilised by the anomeric effect of the O6–C6a–O1 subunit. In this conformation, the *N*-(1-phenylethyl) residue in **12a** is oriented pseudoaxially, and thus avoids serious repulsion with the diethoxyphosphoryl group.

The assignment of the relative configurations in diastereoisomeric cycloadducts (3*S*,3a*R*,6a*S*,1′*S*)-**11a** and (3*R*,3a*S*,6a*R*,1′*S*)-**11b** seemed to be more difficult since at C6, in a bicyclic skeleton, two additional hydrogen atoms are present, when compared to compounds (3*S*,3a*R*,6a*R*,1′*S*)-**12a** and (3*R*,3a*S*,6a*S*,1′*S*)-**12b**. Based on analysis of the vicinal couplings found in the ^1H and ^{13}C NMR

Table 1
Stereochemically relevant vicinal couplings for compounds **11a**, **11b**, **12a**, **12b**, **20** and **21** and their conformations

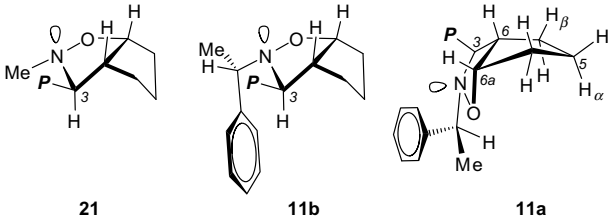
Vicinal coupling constants (Hz)	Compounds					
	(3*S*,3a*R*,6a*S*,1′*S*)-**11a**	(3*R*,3a*S*,6a*R*,1′*S*)-**11b**	**21**	(3*S*,3a*R*,6a*R*,1′*S*)-**12a**	(3*R*,3a*S*,6a*S*,1′*S*)-**12b**	**20**
J(*P*–C3C4–*C6a*)	8.3	9.2	9.8	3.5	8.6	10.0
J(*P*–C3C3a–*C4*)	5.3	4.9	3.4	10.3	4.9	3.8
J(*P*–C3N–*C*)	2.0	0	0	10.6	3.4	0
J(*H*–C3C3a–*H*)	17.7	18.0	16.2	17.1	17.4	17.1
J(*H*–C3C3a–*H*)	6.9	7.5	8.0	4.2	7.8	8.4
J(*H*–C3aC6a–*H*)	5.7	7.5	8.0	5.4	5.7	5.4
J(*H*–C3aC4–*Hα*)	3.6	0	0	2.4	0	0.9
J(*H*–C3aC4–*Hβ*)	6.4	7.5	8.0	9.9	7.8	8.4
J(*H*–C6aC6–*Hα*)	0	0	0	—	—	—
J(*H*–C6aC6–*Hβ*)	5.7	4.0	3.7	—	—	—
J(*Hα*–C6C5–*Hβ*)	0	0	0	—	—	—
J(*Hα*–C6C5–*Hα*)	4.8	6.0	6.0	—	—	—
J(*Hβ*–C4C5–*Hα*)	Overlap	12.1	Overlap	9.0	11.7	11.4
J(*Hα*–C4C5–*Hα*)	Overlap	6.4	Overlap	6.9	5.4	5.4
J(*Hβ*–C4C5–*Hβ*)	Overlap	8.0	Overlap	8.1	7.8	8.4
J(*Hα*–C4C5–*Hβ*)	Overlap	0	Overlap	3.6	0.6	0
Conformation[a]	${}_1T^2/{}^6T_{6a}$	$E_3/{}^4T_5$	E_3/E_5	E^{6a}/E^6	E_3/E^4	E_3/E^4

[a] Isoxazolidine ring/fused ring.



20 **12b** **12a**

Figure 2. The preferred conformation of **20**,[13] **12a** and **12b**; ***P*** = P(O)(OEt)$_2$.



21 **11b** **11a**

Figure 3. The preferred conformation of **21**,[13] **11a** and **11b**; ***P*** = P(O)(OEt)$_2$.

Table 2
Stereochemically relevant chemical shifts (ppm) for compounds **12a**, **12b** and **20**

Compounds	Chemical shifts (ppm)						
	δ(*Hα*–C4)	δ(*Hβ*–C4)	δ(*Hα*–C5)	δ(*Hβ*–C5)	δ(*H*–C3)	δ(*H*–C3a)	δ(*H*–C6a)
(3*R*,3a*S*,6a*S*,1′*S*)-**12b**	1.60	1.87	3.24	3.76	2.74	3.34	5.66
(3*S*,3a*R*,6a*R*,1′*S*)-**12a**	2.01	2.22	4.22	4.05	3.34	3.50	5.80
20	1.89	2.02	3.97	4.04	2.66	3.42	5.71

Table 3
Stereochemically relevant chemical shifts (ppm) for compounds **11a**, **11b** and **21**

Compounds	Chemical shifts (ppm)								
	δ(*Hα*–C4)	δ(*Hβ*–C4)	δ(*Hα*–C5)	δ(*Hβ*–C5)	δ(*Hα*–C6)	δ(*Hβ*–C6)	δ(*H*–C3)	δ(*H*–C3a)	δ(*H*–C6a)
(3*R*,3a*S*,6a*R*,1′*S*)-**11b**	1.28	1.44	1.04	1.35	1.80	1.35	2.42	3.12	4.44
(3*S*,3a*R*,6a*S*,1′*S*)-**11a**	1.70	1.70	1.70	1.60	1.88	1.46	3.06	3.21	4.44
21	Overlap	Overlap	Overlap	Overlap	1.85	Overlap	2.38	3.23	4.47

spectra (Table 1) of the minor isomer (3*R*,3a*S*,6a*R*,1′*S*)-**11b**, it was concluded that this compound exists in a $E_3/{}^4T_5$ (isoxazolidine/cyclopentane) conformation (Fig. 3), which closely resembles the conformation previously established for isoxazolidine **21**, obtained from *N*-methyl nitrone and cyclopentene.[13] A set of vicinal couplings (Table 1) extracted from the spectra of the major isomer (3*S*,3a*R*,6a*S*,1′*S*)-**11a** indicates that this molecule prefers ${}_1T^2/{}^6T_{6a}$ (isoxazolidine/cyclopentane) conformation (Fig. 3), in which spatial interactions of bulky substituents, namely, the diethoxyphosphoryl group and the *N*-(1-phenylethyl) residue are completely avoided.

At this stage, it became evident that the relative configurations of the diethoxyphosphoryl group at C3 and both bridgehead hydrogens at C3a and C6a in the isoxazolidine ring are the same (*cis*) in both diastereoisomeric pairs of the cycloadducts (3*S*,3a*R*,6a*S*,1′*S*)-**11a** and (3*R*,3a*S*,6a*R*,1′*S*)-**11b**, as well as in (3*S*,3a*R*,6a*R*,1′*S*)-**12a** and (3*R*,3a*S*,6a*S*,1′*S*)-**12b**.

Assignments of the absolute configurations in both diastereoisomeric cycloadducts (3*S*,3a*R*,6a*R*,1′*S*)-**12a** and (3*R*,3a*S*,6a*S*,1′*S*)-**12b** could now be undertaken, since significant differences in the chemical shifts were noticed in their ^{1}H NMR spectra (Table 2), which are caused by the space-oriented (*S*)-1-phenylethyl functionality.[15] Large upfield shifts of *Hα*–C4, *Hβ*–C4, *Hα*–C5 and *Hβ*–C5 in the minor isomer (3*R*,3a*S*,6a*S*,1′*S*)-**12b** as compared to the shifts of the same protons in (3*S*,3a*R*,6a*R*,1′*S*)-**12a** ($\Delta\delta$ = 0.41, 0.35, 0.98 and 0.29 ppm, respectively) can only be explained by the shielding of these protons by the phenyl group in (3*R*,3a*S*,6a*S*,1′*S*)-**12b**. This phenomenon was not observed in the diastereoisomer (3*S*,3a*R*,6a*R*,1′*S*)-**12a** as well as in a phenyl lacking *N*-methyl isoxazolidine **20**.[13] The preferred positions of the phenyl groups in (3*S*,3a*R*,6a*R*,1′*S*)-**12a** and (3*R*,3a*S*,6a*S*,1′*S*)-**12b** could be illustrated as shown in Figure 4.

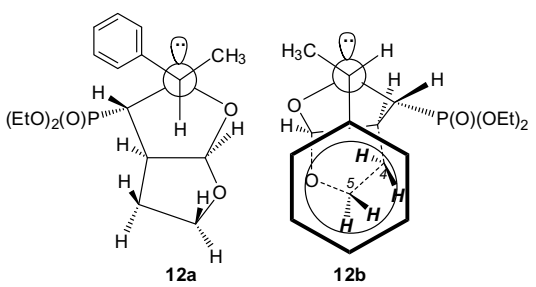


Figure 4. The preferred conformations of (3*S*,3a*R*,6a*R*,1′*S*)-**12a** and (3*R*,3a*S*,6a*S*,1′*S*)-**12b**.

To gather further evidence for different spatial orientations of the Ph(CH$_3$)HC residues in relation to the isoxazolidine skeleton in (3*S*,3a*R*,6a*R*,1′*S*)-**12a** and (3*R*,3a*S*,6a*S*,1′*S*)-**12b**, 2D NOE experiments were performed; the relevant positive signals are depicted in Figure 5. NOE signals between the ortho protons of the aromatic ring in (3*R*,3a*S*,6a*S*,1′*S*)-**12b** and *H*–C3 and *H*–C5 are of special significance, and fully support our previous conclusions based on analysis of the aromatic ring shieldings. On the other hand, NOE signals between *H*–C5 and *Me*–C*, *H*–C* and *H*–C3 in (3*S*,3a*R*,6a*R*,1′*S*)-**12a** clearly point out that the phenyl ring primarily resides outside the molecule. These observations unambiguously prove the absolute configurations at C3, C3a and C6a in the isoxazolidine ring as (3*S*,3a*R*,6a*R*) for isomer **12a** and (3*R*,3a*S*,6a*S*) for **12b**.

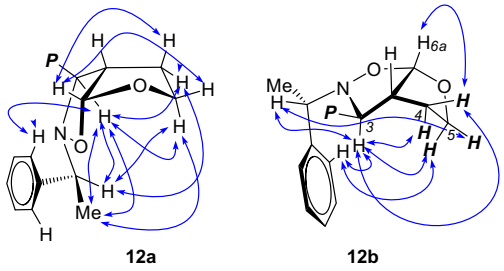


Figure 5. The most important NOESY correlations for (3*S*,3a*R*,6a*R*,1′*S*)-**12a** and (3*R*,3a*S*,6a*S*,1′*S*)-**12b**.

Similarly, significant differences in chemical shifts were also observed in the ^{1}H NMR spectra of (3*S*,3a*R*,6a*S*,1′*S*)-**11a** and (3*R*,3a*S*,6a*R*,1′*S*)-**11b** (Table 3), and were used in establishing their absolute configurations. Upfield shifts of *Hα*–C4, *Hβ*–C4, *Hα*–C5 and *Hβ*–C5 in the minor isomer (3*R*,3a*S*,6a*R*,1′*S*)-**11b** as compared to the shifts of the same protons in (3*S*,3a*R*,6a*S*,1′*S*)-**11a** ($\Delta\delta$ = 0.42, 0.26, 0.66 and 0.25 ppm, respectively) undoubtedly arise due to the shielding effect of the phenyl ring observed in (3*R*,3a*S*,6a*R*,1′*S*)-**11b**. The preferred locations of the phenyl groups in both (3*S*,3a*R*,6a*S*,1′*S*)-**11a** and (3*R*,3a*S*,6a*R*,1′*S*)-**11b** were confirmed by 2D NOE experiments (Fig. 6), and thereby the absolute configurations in diastereoisomeric isoxazolidines (3*S*,3a*R*,6a*S*,1′*S*)-**11a** and (3*R*,3a*S*,6a*R*,1′*S*)-**11b** were proved.

Although our observations of the stereochemistry of the cycloaddition between (*S*)-*N*-(1-phenylethyl)-*C*-(diethoxyphosphoryl)nitrone (*S*)-**8** and alkenes are limited to cyclopentene and 2,3-dihydrofuran, as well as to the earlier reported reactions with allyl alcohol[14] and vinyl acetate,[16] the general tendency for the forma-

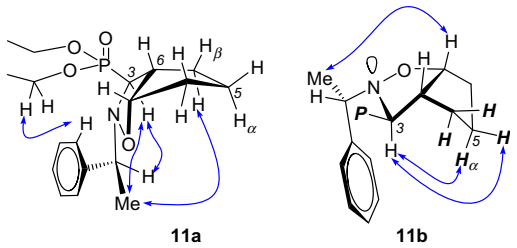


Figure 6. The most important NOESY correlations for (3*S*,3a*R*,6a*S*,1′*S*)-**11a** and (3*R*,3a*S*,6a*R*,1′*S*)-**11b**.

tion of the major isoxazolidines having an (*S*)-configuration at C3 was noticed.

In a two-step transformation of (3*S*,3a*R*,6a*S*,1′*S*)-**11a**, two 1,2-oxaphospholanes (2*S*,3*S*,3a*R*,6a*S*)-**16** (δ^{31}P = 39.80 ppm) and (2*R*,3*S*,3a*R*,6a*S*)-**18** (δ^{31}P = 37.63 ppm) were formed (Scheme 3). By analogy, from (3*R*,3a*S*,6a*R*,1′*S*)-**11b** again two 1,2-oxaphospholanes (2*R*,3*R*,3a*S*,6a*R*)-**16** and (2*S*,3*R*,3a*S*,6a*R*)-**18** were produced. This is because a new stereogenic centre at the phosphorus atom is created, whereas configurations at C3, C3a and C6 in a fused 1,2-oxaphospholane/cyclopentane system remained intact. The ^{31}P NMR chemical shifts of (2*S*,3*S*,3a*R*,6a*S*)-**16** and (2*R*,3*S*,3a*R*,6a*S*)-**18** could be useful in assigning the absolute configurations at the phosphorus atom, since it was previously noticed that ^{31}P NMR signals of hydrogen-bonded isomers of 1,2-oxaphospholanes are shifted downfield, when compared to non-bonded P-epimers.[17–19] Furthermore, in the ^{1}H NMR spectra of the enantiomers of 1,2-oxaphospholanes **16** signals of *H*N were shifted downfield (δ^{1}H = 5.22 ppm), when compared to the same signals for **18** (δ^{1}H = 4.80 ppm). This observation clearly indicates the presence of a strong P═O···H–N hydrogen bond in isomers **16** which means that P═O and NH groups are on the same side of the 1,2-oxaphospholane ring, and thereby the (*S*)-absolute configuration of the newly generated stereogenic centre at the phosphorus in (2*S*,3*S*,3a*R*,6a*S*)-**16** and (*R*) in (2*R*,3*R*,3a*S*,6a*R*)-**16** was established.

Detailed analysis of ^{1}H and ^{13}C NMR spectra of 1,2-oxaphospholane **16** allowed us to unequivocally establish the preferred conformation of this compound. Based on the analysis of vicinal couplings [$J(H_{3a}–H_{6a})$ = 5.4 Hz, $J(H_{3a}–H_3)$ = 8.7 Hz, $J(H_{3a}–H_P)$ = 27.9 Hz, $J(H_{3a}–H_{4\alpha})$ = 8.7 Hz, $J(H_{3a}–H_{4\beta})$ = 8.7 Hz, $J(H_{6a}–H_{6\alpha})$ = 4.8 Hz, $J(H_{6a}–H_{6\beta})$ = 3.0 Hz and J(P–C4) = 0 Hz], the $_3E$ conformation is evident for the 1,2-oxaphospholane ring and a fused cyclopentane ring adopts the $_{3a}E$ conformation. In addition to H-bonding (vide supra) the $_3E$ conformation of the 1,2-oxaphospholane ring is stabilised by the equatorially positioned *N*-Boc group and pseudo-oaxially oriented ethoxy substituent at phosphorus (Fig. 7).

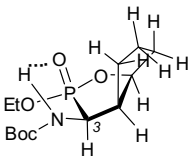


Figure 7. The preferred $_3E/_{3a}E$ conformation of hydrogen-bonded 1,2-oxaphospholane (2*S*,3*S*,3a*R*,6a*S*)-**16**.

3. Conclusions

In the 1,3-dipolar cycloaddition of (*S*)-*N*-(1-phenylethyl)-*C*-(diethoxyphosphoryl)nitrone (*S*)-**8** with 2,3-dihydrofuran, the hexahydrofuro[3,2-*d*]isoxazole framework was formed regiospecifically. The diastereoselectivity of this reaction was moderate since isoxazolidines (3*S*,3a*R*,6a*R*,1′*S*)-**12a** and (3*R*,3a*S*,6a*S*,1′*S*)-**12b** were obtained in a 68:32 ratio. Similarly, reaction of (*S*)-**8** with cyclopentene gave a mixture of two isoxazolidines (3*S*,3a*R*,6a*S*,1′*S*)-**11a** and (3*R*,3a*S*,6a*R*,1′*S*)-**11b** with comparable diastereoselectivity (65:35). Separations of diastereoisomeric isoxazolidines (3*S*,3a*R*,6a*S*,1′*S*)-**11a** and (3*R*,3a*S*,6a*R*,1′*S*)-**11b**, as well as (3*S*,3a*R*,6a*R*,1′*S*)-**12a** and (3*R*,3a*S*,6a*S*,1′*S*)-**12b** were successfully achieved with chromatography.

In the cycloadditions of (*S*)-*N*-(1-phenylethyl)-*C*-(diethoxyphosphoryl)nitrone (*S*)-**8** with cyclopentene and 2,3-dihydrofuran isoxazolidines having an (*S*)-configuration at C3 were formed as the major products. These observations are in agreement with the stereochemistry observed earlier for analogous reactions with allyl alcohol[14] and vinyl acetate.[16]

Catalytic hydrogenolysis of isoxazolidines (3*S*,3a*R*,6a*S*,1′*S*)-**11a** or (3*R*,3a*S*,6a*R*,1′*S*)-**11b** performed in the presence of Boc_2O led to the chromatographically unstable *N*-Boc-protected phosphonates (1*S*,2*R*,1′*S*)-**15** or (1*R*,2*S*,1′*R*)-**15** contaminated with the products of an intramolecular transesterification at phosphorus [(2*S*,3*S*,3a*R*,6a*S*)-**16** and (2*R*,3*R*,3a*S*,6a*R*)-**16**, respectively] and the *N*-Boc-isoxazolidines (3*S*,3a*R*,6a*S*)-**17** or (3*R*,3a*S*,6a*R*)-**17** in which the N–O bond was retained. Phosphonates (1*S*,2*R*,1′*S*)-**15** and (1*R*,2*S*,1′*R*)-**15** were then transformed into mixtures of enantiomerically pure 1,2-oxaphospholanes (2*S*,3*S*,3a*R*,6a*S*)-**16** and (2*R*,3*S*,3a*R*,6a*S*)-**18** or (2*R*,3*R*,3a*S*,6a*R*)-**16** and (2*S*,3*R*,3a*S*,6a*R*)-**18**, respectively, by treatment with DBU. Enantiomerically pure 1,2-oxaphospholanes (2*S*,3*S*,3a*R*,6a*S*)-**16** and (2*R*,3*R*,3a*S*,6a*R*)-**16** were separated by chromatography.

The preferred conformations for diastereoisomeric isoxazolidines (3*S*,3a*R*,6a*S*,1′*S*)-**11a** or (3*R*,3a*S*,6a*R*,1′*S*)-**11b**, as well as for (3*S*,3a*R*,6a*R*,1′*S*)-**12a** and (3*R*,3a*S*,6a*S*,1′*S*)-**12b** were established. Shielding effects observed in the ^{1}H NMR spectra of cycloadducts were employed for assigning the absolute configurations of three new stereogenic centres at C3, C3a and C6 in isoxazolidine rings, which were then confirmed by 2D NOE experiments.

4. Experimental

^{1}H NMR spectra were taken in $CDCl_3$ on the following spectrometers: Bruker Avance II Plus (700 MHz) and Varian Mercury-300 with TMS as an internal standard. ^{13}C and ^{31}P NMR spectra were recorded for $CDCl_3$ solutions on Bruker Avance II Plus spectrometer at 176.2 and 283.5 MHz, or a Varian Mercury-300 machine at 75.5 and 121.5 MHz, respectively. ^{1}H{^{31}P} NMR, ^{1}H–^{1}H COSY and NOESY experiments were applied, when necessary to support spectroscopic assignments. IR spectra 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 Perkin–Elmer PE 2400 CHNS analyser. Polarimetric measurements were conducted on a Optical Activity PolAAr 3001 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. General procedure for the cycloaddition of the nitrone (*S*)-(+)-8 with cyclopentene 9 or 2,3-dihydrofuran 10

Nitrone (*S*)-**8** (1.0 mmol) and cycloalkene **9** or **10** (10 mmol) were stirred in toluene (1–2 mL) at 60 °C, and the disappearance of the starting nitrone was monitored by TLC. All volatiles were removed in vacuo, and the crude product was purified by column chromatography on a silica gel column.

4.1.1. Diethyl (3*S*,3a*R*,6a*S*)- and (3*R*,3a*S*,6a*R*)-hexahydro-2-[(*S*)-1-phenylethyl]-2*H*-cyclopenta[*d*]isoxazol-3-yl-3-phosphonates (3*S*,3a*R*,6a*S*,1′*S*)-11a and (3*R*,3a*S*,6a*R*,1′*S*)-11b

From nitrone (*S*)-**8** (0.856 g, 3.00 mmol) and cyclopentene (2.64 mL, 30.0 mmol), a mixture of phosphonates **11a** and **11b** was obtained. Purification on silica gel column with methylene chloride–MeOH (200:1, v/v) gave isoxazolidine **11a** (0.524 g, 54%) followed by **11b** (0.18 g, 17%).

4.1.1.1. Diethyl (3*S*,3a*R*,6a*S*)-hexahydro-2-[(*S*)-1-phenylethyl]-2*H*-cyclopenta[*d*]isoxazol-3-yl-3-phosphonate (3*S*,3a*R*,6a*S*,1′*S*)-11a. IR (film): ν = 2964, 1686, 1495, 1450, 1252, 1052, 1025, 966 cm^{-1}. $[\alpha]_D^{20} = +69.2$ (*c* 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 700 MHz): δ 7.50–7.40 (m, 2H), 7.38–7.20 (m, 3H), 4.60 (q, *J* = 6.9 Hz, 1H, *H*C–CH_3), 4.44 (t, *J* = 5.7 Hz, 1H, *H*–C6a), 4.22–4.12 (m, 4H), 3.21 (dddd, *J* = 17.7, 6.9, 6.4, 3.6 Hz, 1H, *H*–C3a), 3.06 (dd, *J* = 6.9, 2.1 Hz, 1H, *H*–C3), 1.88 (dd, *J* = 14.7, 4.8 Hz, 1H), 1.75–1.67 (m, 3H), 1.65–1.60 (m, 1H), 1.52–1.42 (m, 1H), 1.46 (d, *J* = 6.9 Hz, 3H, HC–C*H*$_3$), 1.34 (t, *J* = 7.1 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 176.2 MHz): δ 143.68, 128.13, 127.57, 126.74, 82.65 (d, $^3J_{(CCCP)}$ = 8.3 Hz, C6a), 65.63 (d, $^1J_{(CP)}$ = 163.5 Hz, C3), 63.41 (d, *J* = 6.3 Hz), 62.18 (d, *J* = 6.9 Hz), 61.34 (d, *J* = 2.0 Hz, *C*H–CH_3), 50.69 (d, $^2J_{(CCP)}$ = 2.6 Hz, C3a), 32.16 (d, $^3J_{(CCCP)}$ = 5.3 Hz, C4), 32.14, 24.06, 16.80 (d, *J* = 5.7 Hz), 16.76 (d, *J* = 6.0 Hz), 11.80 (s, *C*H_3–CH). ^{31}P NMR ($CDCl_3$, 283.5 MHz): δ 23.93. Anal. Calcd for $C_{18}H_{28}NO_4P$: C, 61.18; H, 7.99; N, 3.96. Found: C, 61.45; H, 8.09; N, 3.82.

4.1.1.2. Diethyl (3*R*,3a*S*,6a*R*)-hexahydro-2-[(*S*)-1-phenylethyl]-2*H*-cyclopenta[*d*]isoxazol-3-yl-3-phosphonate (3*R*,3a*S*,6a*R*,1′*S*)-11b. IR (film): ν = 2976, 1650, 1454, 1246, 1220, 1050, 1024, 964 cm^{-1}. $[\alpha]_D^{20} = -106.8$ (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 700 MHz): δ 7.50–7.40 (m, 2H), 7.38–7.20 (m, 3H), 4.46 (q, *J* = 6.9 Hz, 1H, *H*C–CH_3), 4.44 (br dd, *J* = 7.5, 4.0 Hz, 1H, *H*–C6a), 4.32–4.10 (m, 4H), 3.12 (dq, *J* = 18.0, 7.5 Hz, 1H, *H*–C3a), 2.42 (dd, *J* = 7.5, 1.8 Hz, 1H, *H*–C3), 1.80 (dd, *J* = 12.6, 6.0 Hz, 1H), 1.62 (d, *J* = 6.9 Hz, 3H, HC–C*H*$_3$), 1.45 (dddd, *J* = 13.2, 12.1, 8.0, 7.5 Hz, 1H), 1.39 (t, *J* = 7.2 Hz, 3H), 1.37–1.32 (m, 2H), 1.33 (t, *J* = 7.2 Hz, 3H), 1.27 (dd, *J* = 13.2, 6.4 Hz, 1H), 1.09–0.98 (m, 1H). ^{13}C NMR ($CDCl_3$, 176.2 MHz): δ 138.22, 130.63, 127.54, 127.48, 81.68 (d, $^3J_{(CCCP)}$ = 9.2 Hz, C6a), 65.18 (d, $^1J_{(CP)}$ = 162.6 Hz, C3), 63.28 (d, *J* = 6.3 Hz), 62.18 (d, *J* = 6.9 Hz), 62.72 (s, *C*H–CH_3), 50.72 (d, $^2J_{(CCP)}$ = 2.6 Hz, C3a), 31.90 (d, $^3J_{(CCCP)}$ = 4.9 Hz, C4), 32.10, 23.46, 20.82 (s, *C*H_3–CH), 16.88 (d, *J* = 5.4 Hz), 16.77 (d, *J* = 6.0 Hz). ^{31}P NMR ($CDCl_3$, 283.5 MHz): δ 24.29. Anal. Calcd for $C_{18}H_{28}NO_4P$: C, 61.18; H, 7.99; N, 3.96. Found: C, 61.19; H, 7.98; N, 4.04.

4.1.2. Diethyl (3*S*,3a*R*,6a*R*)- and (3*R*,3a*S*,6a*S*)-hexahydro-2-[(*S*)-1-phenylethyl]furo[3,2-*d*]isoxazol-3-yl-3-phosphonates (3*S*,3a*R*,6a*R*,1′*S*)-12a and (3*R*,3a*S*,6a*S*,1′*S*)-12b

From nitrone (*S*)-**8** (0.856 g, 3.00 mmol) and a 2,3-dihydrofuran (2.26 mL, 30.0 mmol), a mixture of phosphonates **12a** and **12b** was obtained. Purification on silica gel column with toluene–isopropanol (50:1, v/v) gave isoxazolidine **12b** (0.29 g, 27%) followed by **12a** (0.306 g, 29%).

4.1.2.1. Diethyl (3*S*,3a*R*,6a*R*)-hexahydro-2-[(*S*)-1-phenylethyl]-furo[3,2-*d*]isoxazol-3-yl-3-phosphonate (3*S*,3a*R*,6a*R*,1′*S*)-12a. IR (film): ν = 2980, 2934, 1678, 1453, 1247, 1054, 1025, 967 cm^{-1}. $[\alpha]_D^{20} = -17.1$ (*c* 1.2 $CHCl_3$). ^{1}H NMR ($CDCl_3$, 700 MHz): δ 7.40–7.22 (m, 5H), 5.80 (d, *J* = 5.4 Hz, 1H, *H*–C6a), 4.42 (q, *J* = 6.6 Hz, 1H, *H*C–CH_3), 4.22 (dt, *J* = 9.0, 6.9 Hz, 1H, *H*α–C5), 4.20–4.13 (m, 2H), 4.13–4.02 (m, 1H), 4.05 (ddd, *J* = 9.0, 8.1, 3.6 Hz, 1H, *H*β–C5), 4.00–3.88 (m, 1H), 3.50 (ddddd, *J* = 17.1, 9.9, 5.4, 4.2, 2.4 Hz, 1H, *H*–C3a), 3.34 (dd, *J* = 7.2, 4.2 Hz, 1H, *H*–C3), 2.24 (dddd, *J* = 12.9, 9.9, 9.0, 8.1 Hz, 1H, *H*β–C4), 2.01 (dddd, *J* = 12.9, 6.9, 3.6, 2.4 Hz, 1H, *H*α–C4), 1.53 (d, *J* = 6.6 Hz, 1H, HC–C*H*$_3$), 1.32 (t, *J* = 7.2 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 176.2 MHz): δ 142.77, 128.44, 127.89, 127.52, 108.90 (d, $^3J_{(CCCP)}$ = 3.5 Hz, C6a), 67.70 (s, C5), 65.70 (d, $^3J_{(CNCP)}$ = 10.6 Hz, *C*H–CH_3), 64.59 (d, $^1J_{(CP)}$ = 166.3 Hz, C3), 62.95 (d, *J* = 6.3 Hz), 62.90 (d, *J* = 7.4 Hz), 50.33 (s, C3a), 32.08 (d, $^3J_{(CCCP)}$ = 10.3 Hz, C4), 19.54 (s, *C*H_3–CH), 16.71 (d, *J* = 5.4 Hz), 16.64 (d, *J* = 5.2 Hz). ^{31}P NMR ($CDCl_3$, 283.5 MHz): δ 22.08. Anal. Calcd for $C_{17}H_{26}NO_5P$: C, 57.46; H, 7.37; N, 3.94. Found: C, 57.52; H, 7.36; N, 3.98.

4.1.2.2. Diethyl (3*R*,3a*S*,6a*S*)-hexahydro-2-[(*S*)-1-phenylethyl]-furo[3,2-*d*]isoxazol-3-yl-3-phosphonate (3*R*,3a*S*,6a*S*,1′*S*)-12b. IR (film): ν = 2978, 2936, 1638, 1453, 1247, 1098, 1050, 1023, 969 cm^{-1}. $[\alpha]_D^{20} = -91.5$ (*c* 1.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 700 MHz): δ 7.50–7.45 (m, 2H), 7.38–7.26 (m, 3H), 5.66 (d, *J* = 5.7 Hz, 1H, *H*–C6a), 4.46 (q, *J* = 6.9 Hz, 1H, *H*C–CH_3), 4.31–4.11 (m, 4H), 3.76 (dd, *J* = 8.7, 7.8 Hz, 1H, *H*β–C5), 3.34 (ddt, *J* = 17.4, 7.8, 5.7 Hz, 1H, *H*–C3a), 3.24 (ddd, *J* = 11.7, 8.7, 5.4 Hz, 1H, *H*α–C5), 2.74 (dd, *J* = 7.8, 3.3 Hz, 1H, *H*–C3), 1.87 (ddt, *J* = 12.9, 11.7, 7.8 Hz, 1H, *H*β–C4), 1.60 (dd, *J* = 12.9, 5.4 Hz, 1H, *H*α–C4), 1.59 (d, *J* = 6.9 Hz, 1H, HC–C*H*$_3$), 1.39 (t, *J* = 7.2 Hz, 3H), 1.33 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 176.2 MHz): δ 138.71, 129.95, 127.84, 127.64, 105.79 (d, $^3J_{(CCCP)}$ = 8.6 Hz, C6a), 66.47 (s, C5), 63.88 (d, $^3J_{(CNCP)}$ = 3.4 Hz, *C*H–CH_3), 63.68 (d, *J* = 6.6 Hz), 62.70 (d, $^1J_{(CP)}$ = 165.2 Hz, C3), 62.52 (d, *J* = 7.2 Hz), 50.56 (d, $^2J_{(CCP)}$ = 2.3 Hz, C3a), 31.40 (d, $^3J_{(CCCP)}$ = 4.9 Hz, C4), 21.11 (s, *C*H_3–CH), 16.82 (d, *J* = 5.7 Hz), 16.71 (d, *J* = 6.0 Hz). ^{31}P NMR ($CDCl_3$, 283.5 MHz): δ 21.78. Anal. Calcd for $C_{17}H_{26}NO_5P$: C, 57.46; H, 7.37; N, 3.94. Found: C, 57.70; H, 7.32; N, 3.85.

4.2. Hydrogenation of isoxazolidine 11a and 11b (general procedure)

A solution of isoxazolidine **11a** (0.060 g, 0.17 mmol) in ethanol (1.5 mL) was kept under an atmospheric pressure of hydrogen over the mixture of 20% $Pd(OH)_2$–C (10 mg) and 10% Pd–C (10 mg) at room temperature for 15 h. The suspension was filtered through a layer of Celite, and the solution was concentrated to give crude amino alcohol (1*S*,2*R*,1′*S*)-**15** (0.06 g). ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ 39.80 (**16**, 4%), 26.37 (**15**, 83%) and 21.49 (**17**, 13%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.63 (br d, *J* = 10.5 Hz, 1H, NH, **15**), 4.65–4.60 (m, 1H, **15**), 4.40–4.38 (m, 1H, **15**), 4.25–4.05 (m, 6H, **15**), 2.20–2.00 (m, 1H, **15**), 2.00–1.80 (m, 2H, **15**), 1.80–1.60 (m, 4H, **15**), 1.44 (s, 9H, **15**), 1.35 (t, *J* = 7.0 Hz, 3H, **15**), 1.32 (t, *J* = 7.0 Hz, 3H, **15**).

The crude product was purified on a silica gel column with methylene chloride–methanol (100:1, v/v) to give 1,2-oxaphospholane (2*S*,3*S*,3a*R*,6a*S*)-**16** as a white solid (20 mg, 38%), followed by fractions containing impure isoxazolidine (3*S*,3a*R*,6a*S*)-**17** (0.003 g, 4%) and amino alcohol (1*S*,2*R*,1′*S*)-**15** (0.006 g, 10%).

4.2.1. *tert*-Butyl (2*S*,3*S*,3a*R*,6a*S*)-2-ethoxy-2-oxo-cyclopenta[*d*](1,2-oxaphospholan-3-yl)carbamate (2*S*,3*S*,3a*R*,6a*S*)-16

Mp = 90–91 °C. IR (KBr): ν = 3258, 2977, 1706, 1536, 1364, 1280, 1235, 1174, 1054, 969, 895 cm^{-1}. $[\alpha]_D^{20} = -98.4$ (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.22 (br dd, *J* = 8.1, 5.7 Hz, 1H, *H*N), 4.66 (dddd, *J* = 5.4, 4.8, 3.0, 1.8 Hz, 1H, *H*–C6a), 4.21 (ddd, *J* = 16.8, 8.7, 8.1 Hz, 1H, *H*–C3), 4.21–4.11 (m, 2H, C*H*$_2$OP), 3.00 (ddq, *J* = 27.9, 8.7, 5.4 Hz, 1H, *H*–C3a), 2.10–1.85 (m, 3H), 1.84–1.63 (m, 3H), 1.45 (s, 9H), 1.34 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 155.63 (d, *J* = 13.7 Hz, C=O), 83.24 (d, *J* = 6.3 Hz, C6a), 80.38 (s, *C*(CH$_3$)$_3$), 63.47 (d, *J* = 6.3 Hz, *C*H$_2$OP), 46.48 (d, *J* = 132.8 Hz, C3), 46.26 (d, *J* = 10.3 Hz, C3a), 34.26 (d, *J* = 5.2 Hz, C6), 28.52 (s, C(*C*H$_3$)$_3$), 25.70, 23.87, 16.71 (d, *J* = 5.7 Hz, *C*H$_3$CH$_2$OP). ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ 39.80. Anal. Calcd for $C_{13}H_{24}NO_5P$: C, 51.14; H, 7.92; N, 4.59. Found: C, 51.31; H, 8.12; N, 4.76.

4.3. Transformation of (3*S*,3a*R*,6a*S*,1′*S*)-11a and (3*R*,3a*S*,6a*R*,1′*S*)-11b into (2*S*,3*S*,3a*R*,6a*S*)-16 and (2*R*,3*R*,3a*S*,6a*R*)-16 (general procedure)

The crude product obtained after hydrogenation of **11a** or **11b** (0.06 g, 0.17 mmol) was dissolved in $CDCl_3$ (2 mL), and DBU (0.025 mL, 0.17 mmol) was added. After 24 h, the reaction mixture was concentrated and residue was purified on silica gel column with chloroform–methanol (100:1, v/v), and than appropriate fractions were collected and crystallised from ether/hexanes.

4.3.1. Transformation of (3*S*,3a*R*,6a*S*,1′*S*)-11a into (2*S*,3*S*,3a*R*,6a*S*)-16

From isoxazolidine (3*S*,3a*R*,6a*S*,1′*S*)-**11a** (0.184 g, 0.521 mmol), oxaphospholane (2*S*,3*S*,3a*R*,6a*S*)-**16** was obtained as a white solid (0.09 g, 57%) identical in all respects to the compound described in Section 4.2.1, followed by impure 1,2-oxaphospholane (2*R*,3*S*,3a*R*,6a*S*)-**18** (0.012 g, 8%) and isoxazolidine (3*S*,3a*R*,6a*S*)-**17** (0.01 g, 7%).

4.3.1.1. *tert*-Butyl (2*R*,3*S*,3a*R*,6a*S*)-2-ethoxy-2-oxo-cyclopenta[*d*]-(1,2-oxaphospholan-3-yl)carbamate (2*R*,3*S*,3a*R*,6a*S*)-18.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.82–4.75 (m, 2H, N*H* and *H*–C6a), 4.42 (dt, J = 19.2, 8.7 Hz, 1H, *H*–C3), 4.30–4.15 (m, 2H), 3.15–2.90 (m, 1H, *H*–C3a), 2.09–1.90 (m, 2H), 1.90–1.78 (m, 1H), 1.75–1.60 (m, 3H), 1.46 (s, 9H), 1.39 (t, J = 7.0 Hz, 3H). ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ 37.63.

4.3.1.2. *tert*-Butyl (3*S*,3a*R*,6a*S*)-hexahydro-3-diethoxyphosphoryl-cyclopenta[*d*]isoxazolidine-2-carboxylate (3*S*,3a*R*,6a*S*)-17.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.82 (dt, J = 7.2, 2.7 Hz, 1H, *H*–C6), 4.33 (dd, J = 9.0, 1.8 Hz, 1H, *H*–C3), 4.23–4.11 (m, 4H), 3.41–3.28 (m, 1H, *H*–C3a), 2.00–1.75 (m, 3H), 1.75–1.50 (m, 3H), 1.51 (s, 9H), 1.34 (t, J = 7.0 Hz, 3H), 1.33 (t, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 165.93 (d, J = 13.5 HZ, C═O), 87.51, 82.69 (C6a), 63.46 (d, J = 7.2 Hz), 62.98 (d, J = 6.6 Hz), 62.02 (d, J = 170.6 Hz, C3), 48.80 (d, J = 2.0 Hz, C3a), 33.24, 28.71, 28.41, 24.93, 16.75 (d, J = 5.7 Hz), 16.70 (d, J = 6.0 Hz). ^{31}P NMR ($CDCl_3$, 121.5 MHz): δ 21.49.

4.3.2. Transformation of (3*R*,3a*S*,6a*R*,1′*S*)-11b into (2*R*,3*R*,3a*S*,6a*R*)-16

From isoxazolidine (3*R*,3a*S*,6a*R*,1′*S*)-**11b** (0.184 g, 0.521 mmol), oxaphospholane (2*R*,3*R*,3a*S*,6a*R*)-**16** was obtained as a white solid (0.086 g, 54%) followed by impure 1,2-oxaphospholane (2*S*,3*R*,3a-*S*,6a*R*)-**18** (0.006 g, 4%) and isoxazolidine (3*R*,3a*S*,6a*R*)-**17** (0.004 g, 3%).

4.3.2.1. *tert*-Butyl (2*R*,3*R*,3a*S*,6a*R*)-2-ethoxy-2-oxo-cyclopenta[*d*]-(1,2-oxaphospholan-3-yl)carbamate (2*R*,3*R*,3a*S*,6a*R*)-16.

Mp = 90–91 °C. $[\alpha]_D^{20} = +98.8$ (c 1.0, $CHCl_3$). Anal. Calcd for $C_{13}H_{24}NO_5P$: C, 51.14; H, 7.92; N, 4.59. Found: C, 51.23; H, 8.22; N, 4.57.

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References

1. Narayanan, S.; Iyengar, M. R. S.; Ganju, P. L.; Rengaraju, S.; Shomura, T.; Tsuruoka, T.; Inouye, S.; Niida, T. *J. Antibiot.* **1980**, *33*, 1249–1255.
2. Vleggaar, R.; Ackerman, L. G. J.; Steyn, P. S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3095–3098.
3. Sakai, R.; Kamiya, H.; Murata, M.; Shimamoto, K. *J. Am. Chem. Soc.* **1997**, *119*, 4112–4116.
4. Bräuner-Osborne, H.; Egebjerg, J.; Nielsen, E. Ø.; Madsen, U.; Krogsgaard-Larsen, P. *J. Med. Chem.* **2000**, *43*, 2609–2645.
5. Madsen, U.; Frydenvang, K.; Ebert, B.; Johansen, T. N.; Brehm, L.; Krogsgaard-Larsen, P. *J. Med. Chem.* **1996**, *39*, 183–190.
6. Madsen, U.; Ferkany, J. W.; Jones, B. E.; Ebert, B.; Johansen, T. N.; Holm, T.; Krogsgaard-Larsen, P. *Eur. J. Pharmacol.* **1990**, *189*, 381–391.
7. Johansen, T. N.; Frydenvang, K.; Ebert, B.; Madsen, U.; Krogsgaard-Larsen, P. *Chirality* **1997**, *9*, 529–536.
8. Bräuner-Osborne, H.; Nielsen, E. Ø.; Krogsgaard-Larsen, P. *Eur. J. Pharmacol.* **1998**, *350*, 311–316.
9. Johansen, T. N.; Ebert, B.; Bräuner-Osborne, H.; Didriksen, M.; Christensen, I. T.; Søby, K. K.; Madsen, U.; Krogsgaard-Larsen, P.; Brehm, L. *J. Med. Chem.* **1998**, *41*, 930–939.
10. Conti, P.; De Amici, M.; di Ventimiglia, S. J.; Stensbøl, T. B.; Madsen, U.; Bräuner-Osborne, H.; Russo, E.; De Sarro, G.; Bruno, G.; De Michali, C. *J. Med. Chem.* **2003**, *46*, 3102–3108.
11. Hilderbrand, R. L. *The Role of Phosphonates in Living Systems*; CRC Press: Boca Raton, 1983.
12. Piotrowska, D. G. *Tetrahedron Lett.* **2006**, *47*, 5363–5366.
13. Piotrowska, D. G. *Tetrahedron* **2006**, *62*, 12306–12317.
14. Piotrowska, D. G.; Głowacka, I. E. *Tetrahedron: Asymmetry* **2007**, *18*, 1351–1363.
15. Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17–117.
16. Piotrowska, D. G. *Tetrahedron: Asymmetry* **2008**, *19*, 279–287.
17. Wróblewski, A. E. *Tetrahedron* **1983**, *39*, 1809–1816.
18. Wróblewski, A. E.; Konieczko, W. T. *Monatsh. Chem.* **1984**, *115*, 785–791.
19. Wróblewski, A. E. *Liebigs Ann. Chem.* **1986**, 1448–1455.