Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 18 (2007) 1351–1363

Enantiomerically pure phosphonate analogues of *cis*- and *trans*-4-hydroxyprolines

Dorota G. Piotrowska* and Iwona E. Głowacka

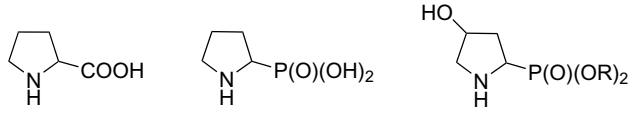
Bioorganic Chemistry Laboratory, Faculty of Pharmacy, Medical University of Łódź, 90-151 Łódź, Muszyńskiego 1, Poland

Received 25 April 2007; accepted 5 June 2007

Abstract—All the enantiomers of *O*,*O*-diethyl 4-hydroxypyrrolidinyl-2-phosphonates, phosphonate analogues of *cis*- and *trans*-4-hydroxyprolines, have been obtained for the first time. The synthetic strategy involved 1,3-dipolar cycloaddition of (*R*)- and (*S*)-*N*-(1-phenylethyl)-*C*-(diethoxyphosphoryl)nitrones to allyl alcohol and separation of the corresponding *O*,*O*-diethyl 5-(hydroxymethyl)-2-(1-phenylethyl)isoxazolidinyl-3-phosphonates, which were subsequently mesylated and hydrogenated to undergo intramolecular cyclisation. Absolute configurations of the enantiomeric proline phosphonates were established after *N*- and *O*-derivatization with (*S*)-*O*-methylmandelic acid employing the Trost model.

1. Introduction

Proline **1** and its hydroxylated analogues are important amino acids present in many natural and synthetic products.[1–3] They received considerable attention due to their biological activity, among others, as antibiotics[4] and antiparasites[5,6] or enzyme inhibitors.[7,8] The structural framework of proline has also been employed as an important building block for organic synthesis.[9] Moreover, proline and its derivatives have been applied as extremely useful enantioselective catalysts in asymmetric induction, for example, aldol,[10–16] Diels–Alder,[16–18] Baylis–Hillman,[19,20] Michael,[21–25] Mannich reactions[25–27] and Robinson annulation.[28] Among the various proline derivatives, phosphonate proline analogue **2**, as well as its diethyl ester, were also found to serve as an efficient chiral catalyst for the aldol reaction.[29]



1 **2** **3** R=H **4** R=Et

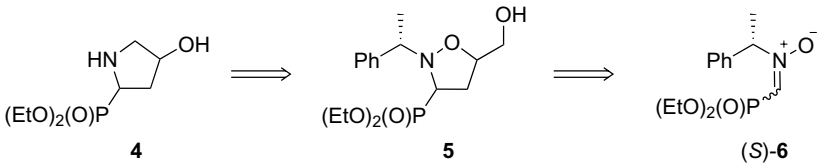
Since the synthesis of racemic **2**,[30] several attempts have been made to prepare various phosphoproline derivatives,[31] including 3-[32] and 4-hydroxylated,[33–35] as well as 3,4-dihydroxylated analogues,[36] some of which have exhibited promising biological activities.[37–41]

In 1986, Seebach and Renaud obtained the pure enantiomer of phosphonic acid **3** via the electrochemical oxidative decarboxylation of 4-hydroxy-L-proline followed by $TiCl_4$-catalysed phosphonylation, but the absolute configuration at C2 was not unambiguously assigned.[33] Although the synthesis of two isomers of racemic phosphonates **4** has been reported, no attempts were made to establish their relative (*cis* or *trans*) configuration.[34] Very recently, enantiomerically pure *N*,*O*-diacetyl derivatives of *O*,*O*-dimethyl (2*S*,4*R*)- and (2*R*,4*R*)-4-hydroxypyrrolidinyl-2-phosphonates have also been synthesised from *N*,*O*-diacetyl L-hydroxyproline via a free radical decarboxylation–phosphorylation reaction.[35]

Our recent achievements in application of the *N*-substituted *C*-phosphorylated nitrone[42,43] prompted us to design a new approach to enantiomerically pure phosphonate analogues of 4-hydroxyproline **4**, which, for the first time, would have given all four enantiomerically pure compounds (Scheme 1). Transformation of the hydroxy function in **5** into a good leaving group led to an intermediate, which was expected to cyclise to aminophosphonate **4**, after hydrogenolytic cleavage of the N–O bond and the removal of the chiral auxiliary.

* Corresponding author. Tel.: +48 42 677 92 35; fax: +48 42 678 83 98; e-mail: dorota@ich.pharm.am.lodz.pl

0957-4166/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2007.06.006



Scheme 1. Retrosynthesis of 4-hydroxypyrrolidinyl-2-phosphonates **4**.

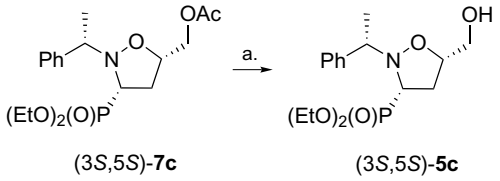
2. Results and discussion

1,3-Dipolar cycloaddition of *N*-(1-phenylethyl)-*C*-phosphorylated nitrone (*S*)-**6** and allyl alcohol led to a mixture of isoxazolidines (3*S*,5*R*)-**5a**, (3*R*,5*S*)-**5b**, (3*S*,5*S*)-**5c** and (3*R*,5*R*)-**5d** in a 25:16:36:23 ratio (Scheme 2). The reaction appeared to be completely regioselective, but negligible stereoselectivity was noticed. From this mixture two pure diastereoisomers, (3*S*,5*R*)-**5a** (up to 25%) and (3*S*,5*S*)-**5c** (up to 15%), could be isolated by column chromatography on silica gel.

$ZnCl_2$ or $MgBr_2$-catalysed reaction of nitrone (*S*)-**6** with allyl alcohol gave an inseparable mixture of *cis*-isomers (3*S*,5*S*)-**5c** and (3*R*,5*R*)-**5d** in a 1:1 ratio with no concomitant *trans*-isomers (3*S*,5*R*)-**5a** and (3*R*,5*S*)-**5b** (Scheme 2). However, a mixture of the corresponding acetates was cleanly separated by column chromatography to give pure (3*S*,5*S*)-**7c** and (3*R*,5*R*)-**7d** in 47% and 37% yield, respectively (Scheme 3).

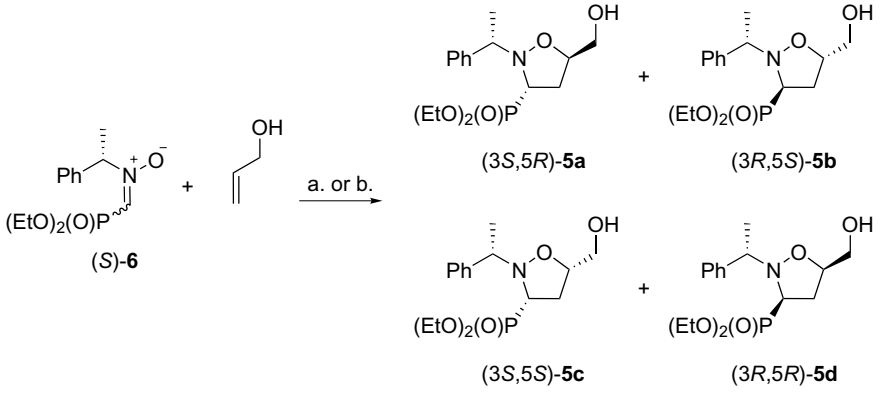
After ammonolysis, isoxazolidine (3*S*,5*S*)-**5c** was recovered from *O*-acetate (3*S*,5*S*)-**7c** in 87% yield (Scheme 4).[44] In a similar fashion, (3*R*,5*R*)-**7d** was transformed into (3*R*,5*R*)-**5d** in 88% yield.

Since the pure isomer (3*R*,5*S*)-**5b** could not be separated from the mixture of isoxazolidines obtained from nitrone (*S*)-**6**, another approach was proposed. The application of nitrone (*R*)-**6** would have led to a mixture of isoxazolidines (3*S*,5*R*)-**8a**, (3*R*,5*S*)-**8b**, (3*S*,5*S*)-**8c** and (3*R*,5*R*)-**8d** from which (3*R*,5*S*)-**8b** should be easily separable, since it is a mirror image of (3*S*,5*R*)-**5a**. Indeed, from (*R*)-**6** and allyl alcohol, a 13:30:21:36 mixture of the respective isoxazolidines was formed and (3*R*,5*S*)-**8b** was separated chromatographically in 22% yield (Scheme 5). In addition, (3*R*,5*R*)-**8d** was isolated in 10% yield.

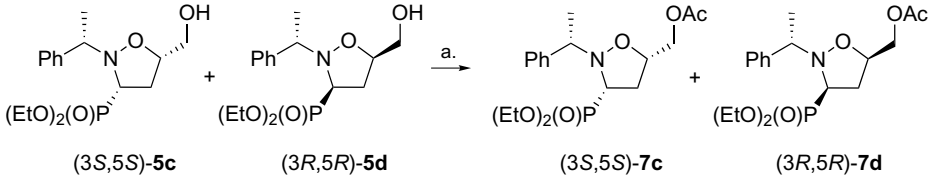


Scheme 4. Reagents and conditions: (a) NH_4OH, EtOH, rt, 4 h, 87%.

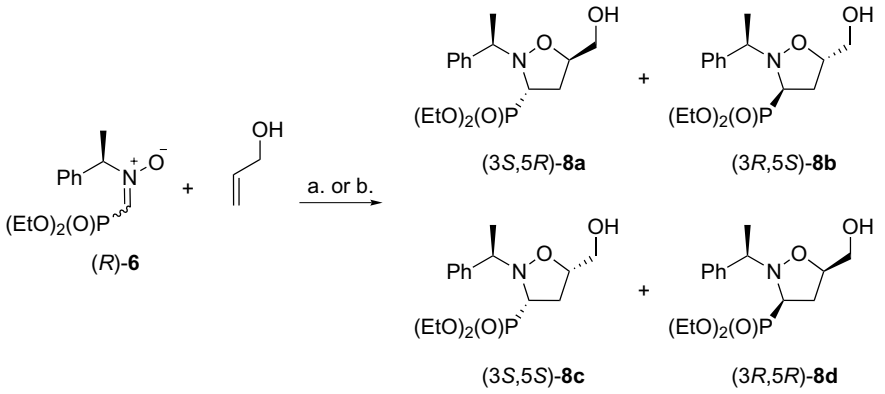
As expected, the reaction of (*R*)-**6** with allyl alcohol in the presence of $MgBr_2$ gave a mixture of *cis*-isoxazolidines (3*S*,5*S*)-**8c** and (3*R*,5*R*)-**8d** in a 1:1 ratio, which again was



Scheme 2. Reagents and conditions: (a) toluene, 60 °C, 48 h; (b) CH_2Cl_2, $ZnCl_2$, rt, 9 days or $MgBr_2$-etherate, 24 h, rt.



Scheme 3. Reagents and conditions: (a) Ac_2O, NEt_3, DMAP, rt, 24 h, 47% **7c** and 37% **7d**.



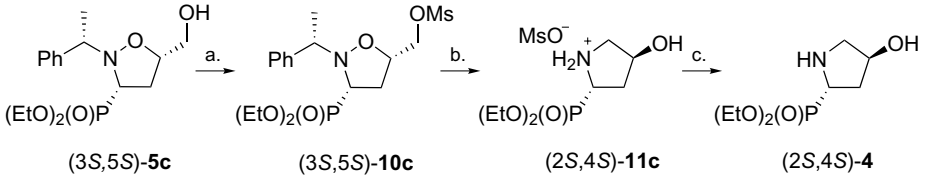
Scheme 5. Reagents and conditions: (a) toluene, 60 °C, 48 h; (b) CH_2Cl_2, $MgBr_2$-etherate, rt, 24 h.

separated as *O*-acetyl derivatives (3*S*,5*S*)-**9c** and (3*R*,5*R*)-**9d**.

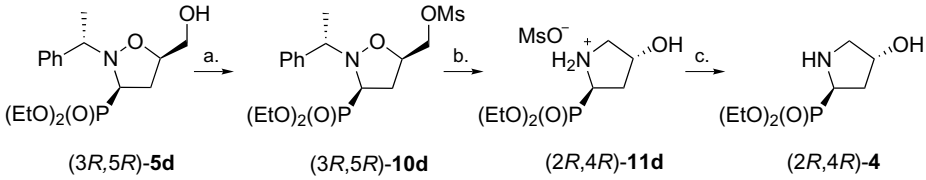
In order to convert *cis*-isoxazolidines (3*S*,5*S*)-**5c** and (3*R*,5*R*)-**5d** into *trans*-4-hydroxypyrrolidinyl-2-phosphonates (2*S*,4*S*)-**4** and (2*R*,4*R*)-**4**, they were first mesylated under standard reaction conditions to form (3*S*,5*S*)-**10c** and (3*R*,5*R*)-**10d** in 96% and 88% yield, respectively. *O*-Mesylates (3*S*,5*S*)-**10c** and (3*R*,5*R*)-**10d** were then subjected to hydrogenolysis to execute the following transformations: cleavage of the N–O bond, removal of 1-phenylethyl group and intramolecular S_N2 substitution of the mesyl group. The resulting ammonium mesylates (3*S*,5*S*)-**11c** and (3*R*,5*R*)-**11d** were neutralised with potassium carbonate in chloroform to provide 4-hydroxyproline analogues (2*S*,4*S*)-**4** and (2*R*,4*R*)-**4** in 75% and 57% yield, respectively, after column chromatography (Schemes 6 and 7).

Similarly, *trans*-isoxazolidines (3*S*,5*R*)-**5a** and (3*R*,5*S*)-**8b** were mesylated to give (3*S*,5*R*)-**10a** and (3*R*,5*S*)-**12b** in 91% and 81% yield, respectively, and the corresponding *O*-mesylates were transformed into *cis*-proline phosphonates (2*S*,4*R*)-**4** and (2*R*,4*S*)-**4** in 72% and 69% yield (Schemes 8 and 9).

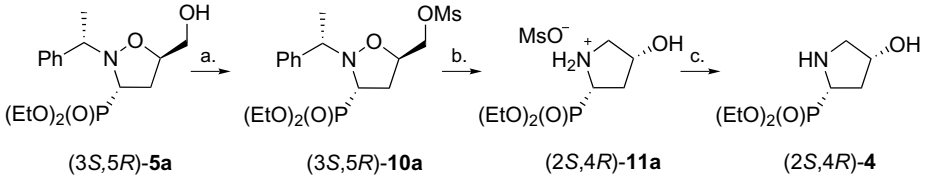
Aminophosphonates **4** appeared to be stable enough to survive purification on a silica gel column. However, they underwent slow decomposition to *N*-alkylated products. For example, when a sample of pure (2*S*,4*S*)-**4** was left at



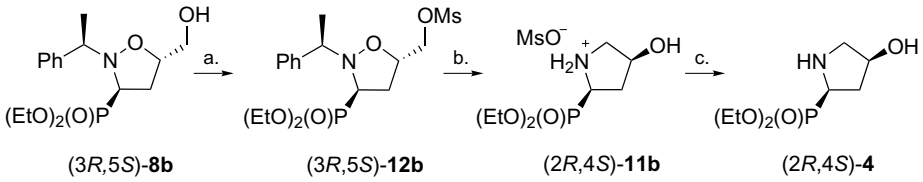
Scheme 6. Reagents and conditions: (a) MsCl, NEt_3, 0 °C, 2 h, 96%; (b) H_2/$Pd(OH)_2$–C, EtOH, 7 days; (c) K_2CO_3, $CHCl_3$, rt, 3 h, 75%.



Scheme 7. Reagents and conditions: (a) MsCl, NEt_3, 0 °C, 2 h, 88%; (b) H_2/$Pd(OH)_2$–C, EtOH, 7 days; (c) K_2CO_3, $CHCl_3$, rt, 3 h, 57%.

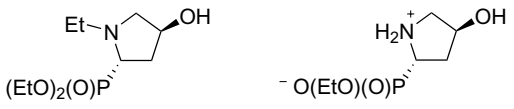


Scheme 8. Reagents and conditions: (a) MsCl, NEt_3, 0 °C, 2 h, 91%; (b) H_2/$Pd(OH)_2$–C, EtOH, 7 days; (c) K_2CO_3, $CHCl_3$, rt, 3 h, 72%.



Scheme 9. Reagents and conditions: (a) MsCl, NEt_3, 0 °C, 2 h, 81%; (b) $H_2/Pd(OH)_2$–C, EtOH, 7 days; (c) K_2CO_3, $CHCl_3$, rt, 3 h, 69%.

+5 °C for 7 days a less polar phosphonate was isolated and identified as *N*-ethyl derivative (2*S*,4*S*)-**13**. Furthermore, impure (2*S*,4*S*)-**14** was eluted from the same column in the most polar fractions.



As reported earlier, the thermal (60 °C) cycloaddition of the racemic *C*-phosphorylated nitrone to allyl alcohol proceeded with low diastereoselectivity and led to a 6:4 mixture of the corresponding *trans* and *cis*-isoxazolidines, whereas in the presence of $ZnCl_2$ or $MgBr_2$ the *cis*-isomer was formed as a major product.[42] Based on these observations, a similar reactivity was expected for the chiral nitrones (*R*)- and (*S*)-**6**. Indeed, a negligible stereoselectivity was observed when the cycloaddition was performed at 60 °C. On the other hand, the $ZnCl_2$ or $MgBr_2$-catalysed reactions of (*R*)- and (*S*)-**6** with allyl alcohol are diastereospecific only providing the *cis*-isoxazolidines, while they again lack enantioselectivity.

To additionally prove the relative stereochemistry (at C3 and C5) of the cycloadducts **5a**–**5d**, detailed conformational analyses of pure isoxazolidines were undertaken. Fortunately, it was possible to unequivocally establish the preferred conformations of both *cis*-isoxazolidines (3*S*,5*S*)-**5c** and (3*R*,5*R*)-**5d**. Based on the vicinal couplings [J(C–NC–P) = 18.3 Hz, J(C5–CC–P) = 0 Hz, $J(H_3–H_{4\alpha})$ = 3.3 Hz, $J(H_3–H_{4\beta})$ = 9.3 Hz, $J(H_{4\alpha}–P)$ = 20.7 Hz, $J(H_{4\beta}–P)$ = 27.0 Hz, $J(H_{4\alpha}–H_5)$ = 6.6 Hz and $J(H_{4\beta}–H_5)$ = 9.3 Hz] found in the ^1H and ^{13}C NMR spectra of (3*S*,5*S*)-**5c**, it was concluded that the isoxazolidine ring exists in an $_2E$-conformation, in which 1-phenylethyl and diethoxyphosphoryl groups occupy axial positions (Fig. 1). From the couplings found for (3*R*,5*R*)-**5d** [J(C–NC–P) = 13.2 Hz, J(C5–CC–P) = 4.0 Hz, $J(H_3–H_{4\alpha})$ = 9.3 Hz, $J(H_3–H_{4\beta})$ = 5.4 Hz, $J(H_{4\alpha}–P)$ = 19.5 Hz, $J(H_{4\beta}–P)$ = 19.8 Hz, $J(H_{4\alpha}–H_5)$ = 8.1 Hz and $J(H_{4\beta}–H_5)$ = 6.6 Hz], a $_1E$-conformation of the isoxazolidine ring is proposed for this isomer (Fig. 1). These findings prove the *cis*-relative configurations between substituents at C3 and C5 in the diastereoisomeric pair (3*S*,5*S*)-**5c** and (3*R*,5*R*)-**5d**, and as a consequence the *trans*-relationship in both isomers (3*S*,5*R*)-**5a** and (3*R*,5*S*)-**5b**.

Transformations of isoxazolidines **5** into the proline analogues **4** proceed via an intramolecular S_N2 reaction. Consequently, from *cis*-isoxazolidines (3*S*,5*S*)-**5c** and (3*R*,5*R*)-**5d**, *trans*-proline analogues (2*S*,4*S*)-**4** and (2*R*,4*R*)-**4** are produced, whereas *trans*-isoxazolidines (3*S*,5*R*)-**5a** and (3*R*,5*S*)-**8b** are transformed into the corresponding *cis*-4-hydroxypyrrolidinyl-2-phosphonates (2*S*,4*R*)-**4** and (2*R*,4*S*)-**4**. Moreover, the *cis*-relative configuration of the phosphonate (2*R*,4*S*)-**4** or its enantiomer (2*S*,4*R*)-**4** is additionally proven by the analysis of vicinal couplings [J(C5–NC–P) = 8.9 Hz, J(C4–CC–P) = 3.7 Hz, $J(H_2–H_{3\alpha})$ = 3.6 Hz, $J(H_2–H_{3\beta})$ = 10.5 Hz, $J(H_{3\alpha}–P)$ = 15.0 Hz, $J(H_{3\beta}–P)$ = 25.2 Hz, $J(H_{3\alpha}–H_4)$ = 0 Hz and $J(H_{3\beta}–H_4)$ = 5.7 Hz] extracted from the ^1H and ^{13}C NMR spectra. In a preferred $_5E$-conformation, which is stabilised by an intramolecular P(O)···H–O hydrogen bond, the diethoxyphosphoryl and hydroxyl groups occupy pseudoaxial positions (Fig. 1).

In order to establish the absolute configurations, both enantiomers of *trans*-phosphonates (2*S*,4*S*)-**4** and (2*R*,4*R*)-**4** were transformed into the respective *N*,*O*-bismandelic acid derivatives (2*S*,4*S*)-**15c** and (2*R*,4*R*)-**15d** with (*S*)-*O*-methylmandelic acid in the presence of DCC (Scheme 10).

Analyses of the ^1H NMR spectra of (2*S*,4*S*)-**15c** and (2*R*,4*R*)-**15d** show significant shielding effects on some pyrrolidine ring protons originating from the *O*-mandelate fragment (Fig. 2). Thus, the phenyl ring of mandelic ester in (2*R*,4*R*)-**15d** shifts the *H*–C(3) proton upfield to 1.85 ppm, when compared to the same proton in the isomeric (2*S*,4*S*)-**15c** (δ = 2.19 ppm), as well as in the starting *trans*-phosphonate (2*S*,4*S*)-**4** (δ = 2.10 ppm). On the other hand, resonances of both $H_2C(5)$ in (2*S*,4*S*)-**15c** are only

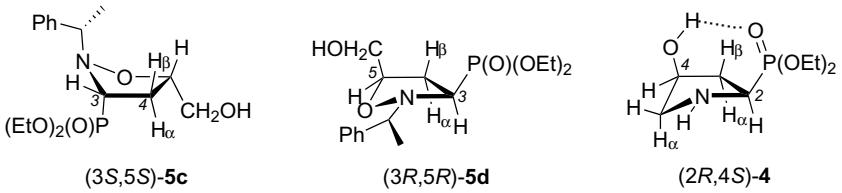
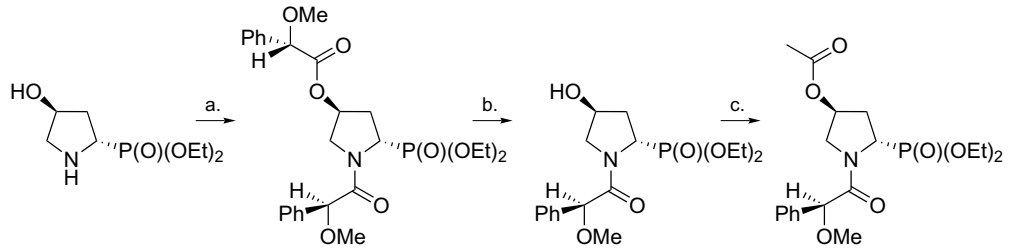


Figure 1. Preferred conformations of isoxazolidines (3*S*,5*S*)-**5c** and (3*R*,5*R*)-**5d** and *cis*-proline (2*S*,4*R*)-**4**.



Scheme 10. Reagents and conditions: (a) (*S*)-PhCH(OMe)COOH, DCC, DMAP, rt, 24 h; (b) NH_4OH, EtOH, rt, 3 h; (c) Ac_2O, NEt_3, DMAP, rt, 24 h.

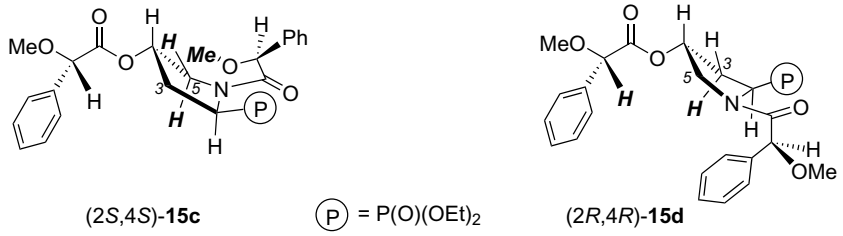


Figure 2. Preferred conformations of *N*,*O*-bismandelates (2*S*,4*S*)-**15c** and (2*R*,4*R*)-**15d**.

slightly shifted upfield (to 3.80 and 3.41 ppm), as compared to those in (2*R*,4*R*)-**15d** ($\delta = 3.90$ and 3.52 ppm). Although *N*-mandelamide residues in (2*S*,4*S*)-**15c** and (2*R*,4*R*)-**15d** cause a negligible influence on the pyrrolidine ring hydrogens, the shielding effects of the phenyl rings of this moiety are observed. A signal of the methine proton of the PhC*H*(OMe)–C(O)O grouping in (2*R*,4*R*)-**15d** is shifted to 4.29 ppm from a normal region (~4.5–4.8 ppm), as a result of the shielding by the phenyl ring from the mandelamide function. Moreover, the CH_3O protons of the mandelamide residue in (2*S*,4*S*)-**15c** are shielded ($\delta =$ 3.33 ppm), when compared to the same protons in (2*R*,4*R*)-**15d**, which resonate at 3.50 ppm. Moreover, all these observations comply very well with the Trost model, which allows us to assign the absolute configurations in the enantiomerically pure *trans* proline phosphonates (2*S*,4*S*)-**4** and (2*R*,4*R*)-**4** (Fig. 2).

To ensure that the phenyl ring of *N*-mandelamide residue does not shield the pyrrolidine ring protons, *O*-acetyl-*N*-mandelates (2*S*,4*S*)-**17c** and (2*R*,4*R*)-**17d** were synthesised (Scheme 10). Indeed, the ^{1}H NMR spectra of (2*S*,4*S*)-**17c** and (2*R*,4*R*)-**17d** were almost identical and no significant differences in chemical shifts were noticed. This conclusion proves that only the *O*-mandelate fragment is responsible for diagnostic upfield shifts observed for the pyrrolidine ring protons. Furthermore, based on these data, a preferred configuration around N–C(O) bond can be assigned, in which a mandelic acid residue is *trans*-oriented to the CHP(O)$(OEt)_2$ moiety. This is in agreement with the general tendency of amides derived from chiral acids and cyclic secondary amines having stereogenic carbon atoms at the α-position, to predominantly exist as an *anti*-rotamer around the N–C(O) bond.[45]

The same methodology was attempted in assigning the absolute configurations of both enantiomers of *cis* phosphonates (2*S*,4*R*)-**4** and (2*R*,4*S*)-**4**. Comparison of the ^{1}H NMR spectra of the corresponding *N*,*O*-bismandelic acid derivatives (2*S*,4*R*)-**15a** and (2*R*,4*S*)-**15b** shows two diagnostic shielding effects: one of the *H*–C(3) protons in (2*S*,4*R*)-**15a** is shifted upfield to 2.15 ppm when compared to the same proton in (2*R*,4*S*)-**15b** ($\delta = 2.30$ ppm), while the signal of the *H*–C(5) proton in (2*R*,4*S*)-**15b** appeared at 3.90 ppm, in contrast to *H*–C(5) in (2*S*,4*R*)-**15a** ($\delta = 4.21$ ppm). These differences can be explained by assuming that (2*S*,4*R*)-**15a** and (2*R*,4*S*)-**15b** exist in the conformations shown in Figure 3.

To further prove these assignments and at the same time to discriminate between the shielding effects of the phenyl rings of the *O*- and *N*-mandelic acid residues, *N*-acetyl-*O*-mandelate derivatives (2*S*,4*R*)-**20a** and (2*R*,4*S*)-**20b** were synthesised from (2*S*,4*R*)-**4** and (2*R*,4*S*)-**4** (Scheme 11).

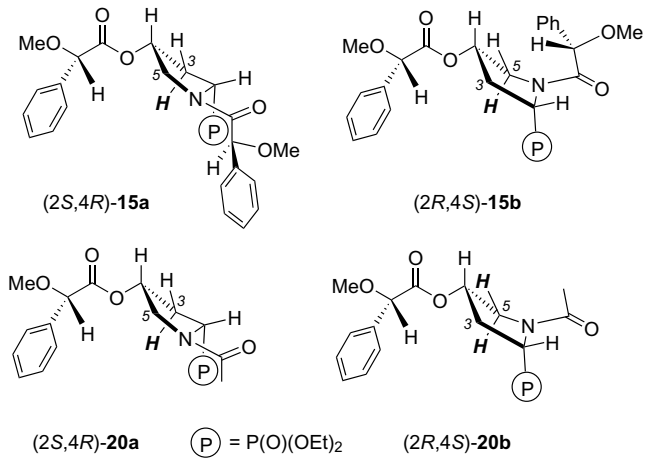
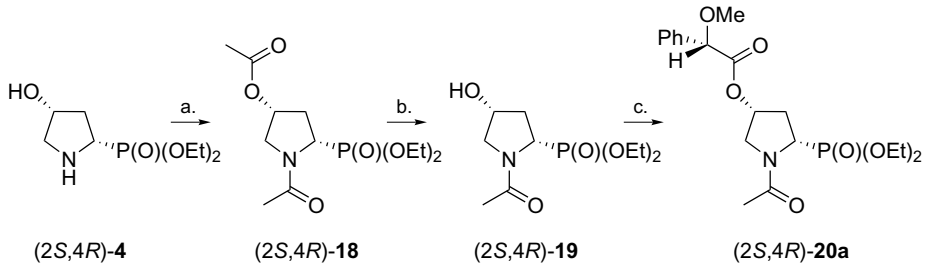


Figure 3. Preferred conformations of *N*,*O*-bismandelates (2*S*,4*R*)-**15a** and (2*R*,4*S*)-**15b** and *N*-acetyl-*O*-mandelates (2*S*,4*R*)-**20a** and (2*R*,4*S*)-**20b**.



Scheme 11. Reagents and conditions: (a) Ac_2O, NEt_3, DMAP, rt, 2 h; (b) NH_4OH, EtOH, rt, 4 h; (c) (*S*)-PhCH(OMe)COOH, DCC, DMAP, rt, 24 h.

The ^1H and ^{31}P NMR spectra showed that the derivatives (2*S*,4*R*)-**20a** and (2*R*,4*S*)-**20b** exist as mixtures of *Z*- and *E*-rotamers in a 7:3 ratio, respectively. Taking into consideration the spectra of both the major (*Z*) isomers of (2*S*,4*R*)-**20a** and (2*R*,4*S*)-**20b**, again the upfield shift of one of the *H*–C(3) protons in (2*S*,4*R*)-**20a** ($\delta = 2.20$ ppm) was observed, as compared to the same proton in (2*R*,4*S*)-**20b** ($\delta = 2.50$ ppm). Moreover, resonances of the $H_2C(5)$ protons in (2*R*,4*S*)-**20b** are shifted upfield to 3.90 and 3.33 ppm, when compared to the same protons in (2*S*,4*R*)-**20a** ($\delta = 4.10$ and 3.53 ppm) (Fig. 3). These observations are in full agreement with the Trost model and further support the absolute configurations of both *cis*-proline phosphonates (2*S*,4*R*)-**4** and (2*R*,4*S*)-**4** established earlier by employing the *N*,*O*-bismandelic acid derivatives.

3. Conclusions

At 60 °C, the 1,3-dipolar cycloaddition of nitrone (*S*)-**6** with allyl alcohol led regiospecifically to a mixture of four 3-diethoxyphosphoryl-5-(hydroxymethyl)isoxazolidines **5a**–**5d** with low stereoselectivity, from which pure phosphonates (3*S*,5*R*)-**5a** and (3*S*,5*S*)-**5c** were isolated. In a $ZnCl_2$-catalysed cycloaddition, a 1:1 mixture of the *cis*-isoxazolidines (3*S*,5*S*)-**5c** and (3*R*,5*R*)-**5d** was formed, which was efficiently separated as *O*-acetyl derivatives. In order to obtain the isomeric isoxazolidine with the (3*R*,5*S*) configuration, the thermal cycloaddition of nitrone (*R*)-**6** to allyl alcohol was performed and isoxazolidine (3*R*,5*S*)-**8b** was isolated efficiently.

The reaction sequence used in the transformation of each of 3-diethoxyphosphoryl-5-(hydroxymethyl)isoxazolidines (3*S*,5*R*)-**5a**, (3*R*,5*S*)-**8b**, (3*S*,5*S*)-**5c** and (3*R*,5*R*)-**5d** into 4-hydroxyproline phosphonates (2*S*,4*R*)-**4**, (2*R*,4*S*)-**4**, (2*S*,4*S*)-**4** and (2*R*,4*R*)-**4**, respectively, consisted of a standard *O*-mesylation, a hydrogenolytic cleavage of the N–O bond and the removal of the chiral auxiliary, which triggered the formation of the pyrrolidine ring by an intramolecular S_N2 reaction.

4. Experimental

^1H NMR spectra were recorded with a Varian Mercury-300 spectrometer; chemical shifts δ in ppm with respect to TMS; coupling constants *J* in Hz. ^{13}C and ^{31}P NMR spectra were recorded on a Mercury-300 machine at 75.5 and 121.5 MHz, respectively. IR spectra data were measured on an Infinity MI-60 FT-IR spectrometer. Melting points were determined on a Boetius apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of this Faculty on a Perkin Elmer PE 2400 CHNS analyzer. Polarimetric measurements were conducted on a Perkin–Elmer 241 MC apparatus. The following absorbents were used: column chromatography, Merck silica gel 60 (70–230 mesh); analytical TLC plastic sheets silica gel 60 F_{254}.

4.1. Synthesis of nitrones (*R*)- and (*S*)-6

Nitrones (*R*)- and (*S*)-**6** have been obtained from in situ generated formylphosphonate (1.0 mmol)[41] and the corresponding (*R*)- or (*S*)-1-phenylethylhydroxylamine (1.0 mmol) and were purified by column chromatography followed by crystallisation.

4.1.1. *N*-[(*R*)-1-Phenylethyl]-*C*-(diethoxyphosphoryl)nitrone (*R*)-6. Mp 59–61 °C. IR (KBr): $\nu = 3044$, 2984, 1546, 1449, 1239, 1171, 1064, 1028, 962 cm^{-1}. $[\alpha]_D^{20} = -6.6$ (*c* 1.7, $CHCl_3$). ^1H NMR ($CDCl_3$): $\delta = 7.45$–7.32 (m, 5H), 6.87 (d, $J = 24.0$ Hz, $0.07 \times 1H$, C*H*–P), 6.80 (d, $J = 26.1$ Hz, $0.93 \times 1H$, C*H*–P), 5.12 (q, $J = 6.9$ Hz, 1H, C*H*–CH_3), 4.28–4.12 (m, 4H), 1.82 (d, $J = 6.9$ Hz, $0.93 \times 3H$, CH–C*H*$_3$), 1.77 (d, $J = 6.9$ Hz, $0.07 \times 3H$, CH–C*H*$_3$), 1.30 (t, $J = 7.2$ Hz, 3H), 1.28 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 137.43$, 129.22, 128.98, 127.27, 124.38 ($J = 208.4$ Hz, P–*C*H), 76.89 (d, $J = 12.0$ Hz, *C*H–Ph), 63.46 (d, $J = 5.7$ Hz), 63.34 (d, $J = 6.0$ Hz), 19.43 (s, *C*H$_3$CHN), 16.58 (d, $J = 6.0$ Hz), 15.54 (d, $J = 6.0$ Hz). ^{31}P NMR ($CDCl_3$): $\delta = 6.66$ (93%) and 5.83 (7%). Anal. Calcd for $C_{13}H_{20}NO_4P$: C, 54.73; H, 7.07; N, 4.91. Found: C, 54.86; H, 7.18; N, 5.14.

4.1.2. *N*-[(*S*)-1-Phenylethyl]-*C*-(diethoxyphosphoryl)nitrone (*S*)-6. Mp 59–60 °C. $[\alpha]_D^{20} = +7.5$ (*c* 1.9, $CHCl_3$). Anal. Calcd for $C_{13}H_{20}NO_4P$: C, 54.73; H, 7.07; N, 4.91. Found: C, 54.47; H, 7.34; N, 5.11.

4.2. Diethyl (3*S*,5*R*)-, (3*R*,5*S*)-, (3*S*,5*S*)- and (3*R*,5*R*)-5-(hydroxymethyl)-2-[(*S*)-1-phenylethyl]isoxazolidinyl-3-phosphonates (3*S*,5*R*)-5a, (3*R*,5*S*)-5b, (3*S*,5*S*)-5c and (3*R*,5*R*)-5d

4.2.1. Cycloaddition of the nitrone (*S*)-6 to allyl alcohol. A solution of nitrone (*S*)-**6** (0.982 g, 3.44 mmol) and allyl alcohol (0.60 mL, 6.88 mmol) in toluene (3 mL) was stirred

at 60 °C for 48 h. All volatiles were removed in vacuo and the crude product was purified by chromatography on silica gel with chloroform–methanol (100:1, v/v) to give pure phosphonates (3*S*,5*R*)-**5a** (0.267 g, 23%) and (3*S*,5*S*)-**5c** (0.177 g, 15%) both as colourless oils.

4.2.1.1. Diethyl (3*S*,5*R*)-5-(hydroxymethyl)-2-[(*S*)-1-phenylethyl]isoxazolidinyl-3-phosphonate (3*S*,5*R*)-5a. IR (film): $\nu = 3392$, 2982, 2932, 1454, 1233, 1055, 1028, 970 cm^{-1}. $[\alpha]_D^{20} = -3.8$ (*c* 1.1, $CHCl_3$). ^1H NMR ($CDCl_3$): $\delta = 7.40$–7.20 (m, 5H), 4.38 (dddd, $J = 9.3$, 7.5, 5.1, 3.6 Hz, 1H, *H*–C5), 4.23–4.11 (m, 2H), 4.10–3.90 (m, 3H), 3.85 (br d, $J = 12.5$ Hz, 1H, *H*–C1′), 3.65 (br d, $J = 12.5$ Hz, 1H, *H*–C1′), 3.54 (dt, $J = 9.3$, 2.4 Hz, 1H, *H*–C3), 2.48 (dddd, $J = 15.6$, 12.9, 7.5, 2.4 Hz, 1H, *H*–C4), 2.32 (ddt, $J = 26.7$, 12.9, 9.3 Hz, 1H, *H*–C4), 1.95 (br s, 1H, O*H*), 1.50 (d, $J = 6.5$ Hz, 3H, CH–CH_3), 1.32 (t, $J = 7.2$ Hz, 3H), 1.25 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 142.52$, 128.56, 127.93, 127.76, 80.24 (d, $J = 2.0$ Hz, C5), 66.33 (d, $J = 14.3$ Hz, *C*H–Ph), 64.08 (s, C1′), 63.02 (d, $J = 7.2$ Hz), 62.62 (d, $J = 6.6$ Hz), 59.55 (d, $J = 174.3$ Hz, C3), 31.21 (s, C4), 19.63 (s, CH–*C*H_3), 16.80 (d, $J = 5.7$ Hz), 16.69 (d, $J = 6.3$ Hz). ^{31}P NMR ($CDCl_3$): $\delta = 24.14$. Anal. Calcd for $C_{16}H_{26}NO_5P$: C, 55.97; H, 7.63; N, 4.08. Found: C, 55.92; H, 7.72; N, 4.00.

4.2.1.2. Diethyl (3*S*,5*S*)-5-(hydroxymethyl)-2-[(*S*)-1-phenylethyl]isoxazolidinyl-3-phosphonate (3*S*,5*S*)-5c. IR (film): $\nu = 3387$, 2982, 2908, 1455, 1233, 1054, 1028, 971 cm^{-1}. $[\alpha]_D^{20} = -2.6$ (*c* 1.4, $CHCl_3$). ^1H NMR ($CDCl_3$): $\delta = 7.40$–7.25 (m, 5H), 4.48 (dddd, $J = 9.3$, 6.6, 3.0, 1.2 Hz, 1H, *H*–C5), 4.25–4.10 (m, 2H), 4.08–3.95 (m, 4H, CH_2OP, *H*–C1′ and O*H*), 3.81 (dq, $J = 6.3$, 1.8 Hz, 1H, *H*C–N), 3.67 (ddd, $J = 13.2$, 10.5, 3.0 Hz, 1H, *H*–C1′), 3.41 (ddd, $J = 13.5$, 9.6, 3.3 Hz, 1H, *H*–C3), 2.62 (dddd, $J = 20.7$, 13.2, 6.6, 3.3 Hz, 1H, *H*–C4), 2.54 (ddt, $J = 27.0$, 13.2, 9.3 Hz, 1H, *H*–C4), 1.49 (d, $J = 6.3$ Hz, 3H, CH–CH_3), 1.29 (t, $J = 7.2$ Hz, 3H), 1.23 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 141.75$, 128.44, 127.83, 127.69, 77.63 (s, C5), 64.00 (d, $J = 18.3$ Hz, *C*H–Ph), 63.51 (d, $J = 7.2$ Hz), 61.96 (d, $J = 7.2$ Hz), 61.30 (s, C1′), 59.70 (d, $J = 178.1$ Hz, C3), 28.17 (s, C4), 21.12 (s, CH–*C*H_3), 16.44 (d, $J = 6.2$ Hz), 16.33 (d, $J = 6.0$ Hz). ^{31}P NMR ($CDCl_3$): $\delta = 25.27$. Anal. Calcd for $C_{16}H_{26}NO_5P$: C, 55.97; H, 7.63; N, 4.08. Found: C, 55.73; H, 7.82; N, 4.08.

4.2.2. Cycloaddition of the nitrone (*S*)-6 to allyl alcohol in the presence of $MgBr_2$. To a freshly prepared solution of $MgBr_2$ (10 mmol) in Et_2O, nitrone (*S*)-**6** (0.576 g, 2.02 mmol) in methylene chloride (3 mL) was added followed by allyl alcohol (0.687 mL, 10.1 mmol). The reaction mixture was stirred at room temperature for 24 h. After removal of the volatiles, the crude product was purified by column chromatography on silica gel to give an inseparable mixture of (3*S*,5*S*)-**5c** and (3*R*,5*R*)-**5d** (0.587 g, 85%).

4.2.3. Cycloaddition of the nitrone (*S*)-6 to allyl alcohol in the presence of $ZnCl_2$. A solution of nitrone (*S*)-**6** (0.143 g, 0.501 mmol) and allyl alcohol (0.034 mL, 0.502 mmol) in methylene chloride (2 mL) $ZnCl_2$ (0.068 g, 0.501 mmol) was added. The reaction mixture was stirred at room temperature for 9 days. After removal of the volatiles, the crude product was purified by column chromatography on silica gel to give an inseparable mixture of (3*S*,5*S*)-**5c** and (3*R*,5*R*)-**5d** (0.153 g, 89%).

4.3. Diethyl (3*S*,5*R*)-, (3*R*,5*S*)-, (3*S*,5*S*)- and (3*R*,5*R*)-5-(hydroxymethyl)-2-[(*R*)-1-phenylethyl]isoxazolidinyl-3-phosphonate (3*S*,5*R*)-8a, (3*R*,5*S*)-8b, (3*S*,5*S*)-8c and (3*R*,5*R*)-8d

4.3.1. Cycloaddition of the nitrone (*R*)-6 to allyl alcohol. A solution of nitrone (*R*)-**6** (1.11 g, 3.89 mmol) and allyl alcohol (0.793 mL, 11.7 mmol) in toluene (3 mL) was stirred at 60 °C for 48 h. All volatiles were removed in vacuo and the crude product was purified by chromatography on silica gel with chloroform–methanol (100:1, v/v) to give phosphonates (3*R*,5*S*)-**8b** (0.297 g, 22%) and (3*R*,5*R*)-**8d** (0.137 g, 10%).

4.3.1.1. Diethyl (3*R*,5*S*)-5-(hydroxymethyl)-2-[(*R*)-1-phenylethyl]isoxazolidinyl-3-phosphonate (3*R*,5*S*)-8b (*ent*-5a). $[\alpha]_D^{20} = +4.1$ (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{16}H_{26}NO_5P$: C, 55.97; H, 7.63; N, 4.08. Found: C, 55.95; H, 7.76; N, 4.07.

4.3.1.2. Diethyl (3*R*,5*R*)-5-(hydroxymethyl)-2-[(*R*)-1-phenylethyl]isoxazolidinyl-3-phosphonate (3*R*,5*R*)-8d (*ent*-5c). $[\alpha]_D^{20} = +1.6$ (*c* 1.3, $CHCl_3$). Anal. Calcd for $C_{16}H_{26}NO_5P$: C, 55.97; H, 7.63; N, 4.08. Found: C, 55.85; H, 7.87; N, 4.01.

4.3.2. Cycloaddition of the nitrone (*R*)-6 to allyl alcohol in the presence of $MgBr_2$. To a freshly prepared solution of $MgBr_2$ (10 mmol) in Et_2O, nitrone (*R*)-**6** (0.725 g, 2.54 mmol) in methylene chloride (3 mL) was added followed by allyl alcohol (0.864 mL, 12.7 mmol). The reaction mixture was stirred at room temperature for 24 h. The crude product was purified by column chromatography on silica gel to give an inseparable mixture of (3*S*,5*S*)-**8c** and (3*R*,5*R*)-**8d** (0.792 g, 90%).

4.4. Acetylation of isoxazolidines (3*S*,5*S*)-5c and (3*R*,5*R*)-5d

A mixture of isoxazolidines (3*S*,5*S*)-**5c** and (3*R*,5*R*)-**5d** (0.958 g, 2.79 mmol), acetic anhydride (0.791 mL, 8.37 mmol) and triethylamine (1.28 mL, 9.21 mmol) containing DMAP (0.034 g, 0.279 mmol) in methylene chloride (10 mL) was stirred at room temperature for 24 h. The reaction mixture was washed with water (3×5 mL), dried over $MgSO_4$, concentrated in vacuo and the residue chromatographed on silica gel with hexane–isopropanol (50:1, v/v) to give phosphonates (3*S*,5*S*)-**7c** (0.507 g, 47%) and (3*R*,5*R*)-**7d** (0.399 g, 37%).

4.4.1. Diethyl (3*S*,5*S*)-5-(acetoxymethyl)-2-[(*S*)-1-phenylethyl]isoxazolidinyl-3-phosphonate (3*S*,5*S*)-7c. IR (film): $\nu = 3463$, 2983, 2934, 1743, 1454, 1371, 1240, 1049, 968 cm^{-1}. $[\alpha]_D^{20} = -12.2$ (*c* 1.9, $CHCl_3$). ^1H NMR ($CDCl_3$): $\delta = 7.40$–7.20 (m, 5H), 4.47 (ddt, $J = 8.4$, 7.2, 4.2 Hz, 1H, *H*–C5), 4.31 (dAB, $J_{AB} = 11.4$ Hz, $J = 4.2$ Hz, 1H, *H*–C1′), 4.24 (dAB, $J_{AB} = 11.4$ Hz, $J = 7.2$ Hz, 1H, *H*–C1′), 4.16 (q, $J = 7.2$ Hz, 1H), 4.07–3.93 (m, 1H), 3.90–3.75 (m, 2H), 3.47 (ddd, $J = 10.8$, 10.0, 3.6 Hz, 1H, *H*–C3),

2.67 (dddd, $J = 21.0$, 12.9, 10.0, 8.4 Hz, 1H, *H*–C4), 2.22 (dddd, $J = 20.7$, 12.9, 7.2, 3.6 Hz, 1H, *H*–C4), 2.10 (s, 3H, CH_3C(O)), 1.47 (d, $J = 6.6$ Hz, 3H, CH–CH_3), 1.31 (t, $J = 7.2$ Hz, 3H), 1.21 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 170.88$, 142.08, 128.67, 128.09, 127.98, 74.71 (d, $J = 1.7$ Hz, C5), 65.04 (d, $J = 16.6$ Hz, *C*H–Ph), 65.06, 63.11 (d, $J = 7.5$ Hz), 62.56 (d, $J = 6.6$ Hz), 59.35 (d, $J = 176.6$ Hz, C3), 32.43 (s, C4), 21.16, 20.89, 16.79 (d, $J = 6.0$ Hz), 16.67 (d, $J = 6.0$ Hz). ^{31}P NMR ($CDCl_3$): $\delta = 24.38$. Anal. Calcd for $C_{18}H_{28}NO_6P$: C, 56.10; H, 7.32; N, 3.64. Found: C, 56.01; H, 7.59; N, 3.68.

4.4.2. Diethyl (3*R*,5*R*)-5-(acetoxymethyl)-2-[(*S*)-1-phenylethyl]isoxazolidinyl-3-phosphonate (3*R*,5*R*)-7d. IR (film): $\nu = 3464$, 2982, 2936, 1743, 1236, 1048, 1027, 968 cm^{-1}. $[\alpha]_D^{20} = -74.4$ (*c* 1.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$): $\delta = 7.42$–7.22 (m, 5H), 4.31–4.13 (m, 5H), 4.11 (dAB, $J_{AB} = 11.4$ Hz, $J = 5.4$ Hz, 1H, *H*–C1′), 4.08 (dAB, $J_{AB} = 11.4$ Hz, $J = 4.5$ Hz, 1H, *H*–C1′), 3.92 (dddd, $J = 8.1$, 6.9, 5.4, 4.5 Hz, 1H, *H*–C5), 3.35 (ddd, $J = 8.4$, 8.1, 4.2 Hz, 1H, *H*–C3), 2.37 (dddd, $J = 12.6$, 9.0, 8.4, 6.9, 1H, *H*–C4), 2.17 (ddt, $J = 18.9$, 12.6, 8.1 Hz, 1H, *H*–C4), 2.04 (s, 3H, CH_3C(O)), 1.56 (d, $J = 6.9$ Hz, 3H, CH–CH_3), 1.37 (t, $J = 7.2$ Hz, 3H), 1.34 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 170.79$, 139.79, 129.26, 128.20, 127.66, 73.98 (d, $J = 6.9$ Hz, C5), 64.72, 64.66 (d, $J = 8.6$ Hz, *C*H–Ph), 63.59 (d, $J = 6.6$ Hz), 62.67 (d, $J = 7.2$ Hz), 58.34 (d, $J = 173.5$ Hz, C3), 34.62 (d, $J = 1.7$ Hz, C4), 21.20, 21.10, 16.87 (d, $J = 5.4$ Hz), 16.79 (d, $J = 5.7$ Hz). ^{31}P NMR ($CDCl_3$): $\delta = 23.71$. Anal. Calcd for $C_{18}H_{28}NO_6P$: C, 56.10; H, 7.32; N, 3.64. Found: C, 55.89; H, 7.33; N, 3.59.

4.5. Acetylation of isoxazolidines (3*S*,5*S*)-8c and (3*R*,5*R*)-8d

A mixture of isoxazolidines (3*S*,5*S*)-**8c** and (3*R*,5*R*)-**8d** (0.692 g, 2.02 mmol) was acetylated as described in Section 4.4 to give phosphonates (3*S*,5*S*)-**9c** (0.272 g, 35%) and (3*R*,5*R*)-**9d** (0.163 g, 21%).

4.5.1. Diethyl (3*S*,5*S*)-5-(acetoxymethyl)-2-[(*R*)-1-phenylethyl]isoxazolidinyl-3-phosphonate (3*S*,5*S*)-9c (*ent*-7d). $[\alpha]_D^{20} = +76.3$ (*c* 1.8, $CHCl_3$). Anal. Calcd for $C_{18}H_{28}NO_6P$: C, 56.10; H, 7.32; N, 3.64. Found: C, 55.95; H, 7.56; N, 3.55.

4.5.2. Diethyl (3*R*,5*R*)-5-(acetoxymethyl)-2-[(*R*)-1-phenylethyl]isoxazolidinyl-3-phosphonate (3*R*,5*R*)-9d (*ent*-7c). Anal. Calcd for $C_{18}H_{28}NO_6P$: C, 56.10; H, 7.32; N, 3.64. Found: C, 55.85; H, 7.13; N, 3.67.

4.6. Ammonolysis of (3*S*,5*S*)-7c and (3*R*,5*R*)-7d (general procedure)

A solution of phosphonate (3*S*,5*S*)-**7c** or (3*R*,5*R*)-**7d** (0.385 g, 1.00 mmol) in ethanol (10 mL) containing aqueous NH_3 (25%, 15 mL) was left at room temperature for 4 h. The volatiles were removed and the residue was evaporated with anhydrous ethanol (3 × 10 mL), chloroform (3 × 10 mL) and finally chromatographed on silica gel with chloroform–methanol (50:1, v/v).

4.6.1. Ammonolysis of (3*S*,5*S*)-7c. From acetate (3*S*,5*S*)-**7c** (0.507 g, 1.32 mmol), phosphonate (3*S*,5*S*)-**5c** (0.397 g, 87%) was obtained as a colourless oil identical in all respects with the material described in Section 4.2.1.2.

4.6.2. Ammonolysis of (3*R*,5*R*)-7d. From acetate (3*R*,5*R*)-**7d** (0.399 g, 1.04 mmol), phosphonate (3*R*,5*R*)-**5d** (0.314 g, 88%) was obtained as a colourless oil.

4.6.2.1. Diethyl (3*R*,5*R*)-5-(hydroxymethyl)-2-((*S*)-1-phenylethyl)isoxazolidinyl-3-phosphonate (3*R*,5*R*)-5d. IR (film): $\nu = 3399$, 2981, 1454, 1230, 1053, 1029, 969 cm^{-1}. $[\alpha]_D^{20} = -63.6$ (*c* 1.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$): $\delta = 7.40$–7.20 (m, 5H), 4.36–4.15 (m, 4H, 2 × CH_2OP), 4.09 (dddd, $J = 8.1$, 6.6, 3.6, 2.1 Hz, 1H, *H*–C5), 4.02 (dq, $J = 6.3$, 1.5 Hz, 1H, *H*C–N), 3.71 (dd, $J = 12.3$, 2.1 Hz, 1H, *H*–C1′), 3.56 (dt, $J = 9.3$, 5.4 Hz, 1H, *H*–C3), 3.53 (dd, $J = 12.3$, 3.6 Hz, 1H, *H*–C1′), 3.20 (br s, 1H, O*H*), 2.62 (dddd, $J = 19.8$, 12.9, 6.6, 5.4 Hz, 1H, *H*–C4), 2.43 (dddd, $J = 19.5$, 12.9, 9.3, 8.1 Hz, 1H, *H*–C4), 1.47 (d, $J = 6.3$ Hz, 3H, CH–CH_3), 1.38 (t, $J = 6.9$ Hz, 3H), 1.36 (t, $J = 6.9$ Hz, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 141.13$, 128.31, 128.25, 127.53, 77.35 (d, $J = 4.0$ Hz, C5), 64.10 (d, $J = 13.2$ Hz, *C*H–Ph), 63.73 (d, $J = 6.9$ Hz), 62.77 (d, $J = 6.9$ Hz), 62.23 (s, C1′), 59.20 (d, $J = 176.1$ Hz, C3), 30.91 (s, C4), 21.74 (s, CH–*C*H$_3$), 16.87 (d, $J = 5.7$ Hz), 16.75 (d, $J = 5.7$ Hz). ^{31}P NMR ($CDCl_3$): $\delta = 24.36$. Anal. Calcd for $C_{16}H_{26}NO_5P$: C, 55.97; H, 7.63; N, 4.08. Found: C, 55.70; H, 7.86; N, 3.89.

4.7. Mesylation of (3*S*,5*R*)-5a, (3*S*,5*S*)-5c, (3*R*,5*R*)-5d and (3*R*,5*S*)-8b (general procedure)

To a solution of phosphonate (3*S*,5*R*)-**5a**, (3*S*,5*S*)-**5c**, (3*R*,5*R*)-**5d** or (3*R*,5*S*)-**8d** (0.343 g, 1.00 mmol) in methylene chloride (10 mL), triethylamine (0.418 mL, 3.00 mmol) was added at 0 °C followed by mesyl chloride (0.116 mL, 1.50 mmol). The reaction mixture was stirred at this temperature for 2 h, washed with water (3 × 5 mL), dried over $MgSO_4$, concentrated in vacuo and the residue was chromatographed on silica gel with chloroform–methanol (100:1, v/v).

4.7.1. Diethyl (3*S*,5*R*)-5-(mesyloxymethyl)-2-[(*S*)-1-phenylethyl]isoxazolidinyl-3-phosphonate (3*S*,5*R*)-10a. From phosphonate (3*S*,5*R*)-**5a** (0.267 g, 0.776 mmol), mesylate (3*S*,5*R*)-**10a** (0.30 g, 91%) was obtained as a colourless oil. IR (film): $\nu = 2984$, 2935, 1454, 1355, 1241, 1175, 1053, 1027, 965 cm^{-1}. $[\alpha]_D^{20} = -19.0$ (*c* 3.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): $\delta = 7.40$–7.20 (m, 5H), 4.54 (ddt, $J = 9.0$, 6.9, 5.1, 1H, *H*–C5), 4.34 (d, $J = 5.1$ Hz, 2H, H_2C-1′), 4.23–4.12 (m, 2H), 4.10–3.92 (m, 3H), 3.55 (ddd, $J = 9.6$, 9.3, 1.8 Hz, 1H, *H*–C3), 3.05 (s, 3H), 2.58 (dddd, $J = 14.7$, 13.2, 6.9, 1.8 Hz, 1H, *H*–C4), 2.32 (dddd, $J = 29.4$, 13.2, 9.3, 9.0 Hz, 1H, *H*–C4), 1.50 (d, $J = 6.5$ Hz, 3H, CH–CH_3), 1.32 (t, $J = 7.2$ Hz, 3H), 1.26 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 142.29$, 128.62, 127.90, 127.87, 77.10 (d, $J = 2.0$ Hz, C5), 69.82, 66.42 (d, $J = 14.0$ Hz, *C*H–Ph), 63.15 (d, $J = 7.2$ Hz), 62.71 (d, $J = 6.9$ Hz), 59.37 (d, $J = 174.3$ Hz, C3), 37.99, 31.82, 19.54, 16.77 (d, $J = 6.6$ Hz), 16.68 (d, $J = 6.3$ Hz). ^{31}P NMR ($CDCl_3$): $\delta = 22.74$. Anal. Calcd for $C_{17}H_{28}NO_7SP$:

C, 48.45; H, 6.70; N, 3.32. Found: C, 48.19; H, 6.67; N, 3.36.

4.7.2. Diethyl (3*S*,5*S*)-5-(mesyloxymethyl)-2-[(*S*)-1-phenylethyl]isoxazolidinyl-3-phosphonate (3*S*,5*S*)-10c. From phosphonate (3*S*,5*S*)-**5c** (0.095 g, 0.277 mmol), mesylate (3*S*,5*S*)-**10c** (0.112 g, 96%) was obtained as a colourless oil. IR (film): $\nu = 3463$, 2984, 2935, 1455, 1356, 1243, 1175, 1052, 1028, 965 cm^{-1}. $[\alpha]_D^{20} = +2.8$ (*c* 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$): $\delta = 7.40$–7.20 (m, 5H), 4.55 (dddd, $J = 8.4$, 7.2, 6.0, 3.6 Hz, 1H, *H*–C5), 4.46 (dAB, $J_{AB} = 10.8$ Hz, $J = 7.2$ Hz, 1H, *H*–C1′), 4.35 (dAB, $J_{AB} = 10.8$ Hz, $J = 3.6$ Hz, 1H, *H*–C1′), 4.23–4.08 (m, 2H), 4.07–3.84 (m, 3H), 3.48 (ddd, $J = 10.8$, 9.6, 3.6 Hz, 1H, *H*–C3), 3.01 (s, 3H), 2.69 (dddd, $J = 21.9$, 13.2, 9.6, 8.4 Hz, 1H, *H*–C4), 2.22 (dddd, $J = 19.5$, 13.2, 6.0, 3.6 Hz, 1H, *H*–C4), 1.48 (d, $J = 6.3$ Hz, 3H, CH–CH_3), 1.32 (t, $J = 7.2$ Hz, 3H), 1.24 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 141.88$, 128.70, 128.03, 127.99, 74.72 (d, $J = 2.3$ Hz, C5), 70.09, 64.74 (d, $J = 15.5$ Hz, *C*H–Ph), 63.22 (d, $J = 7.2$ Hz), 62.54 (d, $J = 6.6$ Hz), 58.96 (d, $J = 176.6$ Hz, C3), 37.63, 31.95, 19.88, 16.76 (d, $J = 6.3$ Hz), 16.67 (d, $J = 6.3$ Hz). ^{31}P NMR ($CDCl_3$): $\delta = 23.57$. Anal. Calcd for $C_{17}H_{28}NO_7SP$: C, 48.45; H, 6.70; N, 3.32. Found: C, 48.20; H, 6.77; N, 3.30.

4.7.3. Diethyl (3*R*,5*R*)-5-(mesyloxymethyl)-2-[(*S*)-1-phenylethyl]isoxazolidinyl-3-phosphonate (3*R*,5*R*)-10d. From phosphonate (3*R*,5*R*)-**5d** (0.266 g, 0.775 mmol), mesylate (3*R*,5*R*)-**10d** (0.286 g, 88%) was obtained as a colourless oil. IR (film): $\nu = 3460$, 2982, 1454, 1355, 1246, 1175, 1051, 1025, 963 cm^{-1}. $[\alpha]_D^{20} = -54.3$ (*c* 2.1, $CHCl_3$). ^1H NMR ($CDCl_3$): $\delta = 7.41$–7.25 (m, 5H), 4.38–4.08 (m, 8H, $2 \times CH_2OP$, CH_2–OMs, *H*–C5 and C*H*–CH_3), 3.34 (ddd, $J = 9.0$, 7.5, 5.1, 1H, *H*–C3), 2.91 (s, 3H), 2.43 (dddd, $J = 12.9$, 12.0, 9.0, 7.5 Hz, 1H, *H*–C4), 2.19 (dddd, $J = 18.9$, 12.0, 7.5, 7.2 Hz, 1H, *H*–C4), 1.54 (d, $J = 6.9$ Hz, 3H, CH–CH_3), 1.38 (t, $J = 7.2$ Hz, 3H), 1.35 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 139.75$, 129.05, 128.26, 127.73, 73.91 (d, $J = 6.0$ Hz, C5), 70.09, 64.62 (d, $J = 8.3$ Hz, *C*H–Ph), 63.40 (d, $J = 6.9$ Hz), 62.86 (d, $J = 6.9$ Hz), 58.09 (d, $J = 174.1$ Hz, C3), 37.75, 33.80, 21.27, 16.84 (d, $J = 4.6$ Hz), 16.77 (d, $J = 5.4$ Hz). ^{31}P NMR ($CDCl_3$): $\delta = 22.93$. Anal. Calcd for $C_{17}H_{28}NO_7SP$: C, 48.45; H, 6.70; N, 3.32. Found: C, 48.44; H, 6.66; N, 3.41.

4.7.4. Diethyl (3*R*,5*S*)-5-(mesyloxymethyl)-2-[(*R*)-1-phenylethyl]isoxazolidinyl-3-phosphonate (3*R*,5*S*)-12b (*ent*-10a). From phosphonate (3*R*,5*S*)-**8b** (0.210 g, 0.611 mmol), mesylate (3*R*,5*S*)-**12b** (0.208 g, 81%) was obtained as a colourless oil. $[\alpha]_D^{20} = +19.6$ (*c* 1.4, $CHCl_3$). Anal. Calcd for $C_{17}H_{28}NO_7SP$: C, 48.45; H, 6.70; N, 3.32. Found: C, 48.47; H, 6.62; N, 3.09.

4.8. Synthesis of the proline phosphonates 4 from the mesylates (3*S*,5*R*)-10a, (3*S*,5*S*)-10c, (3*R*,5*R*)-10d and (3*R*,5*S*)-12b (general procedure)

A solution of *O*-mesylate (0.422 g, 1.00 mmol) in ethanol (5 mL) was kept under an atmospheric pressure of hydrogen over 20% $Pd(OH)_2$–C (10 mg) at room temperature for 7 days. The suspension was filtered through a layer of Celite and the solution was concentrated to give pure ammonium mesylate [(3*S*,5*R*)-**10a**, (3*S*,5*S*)-**10c**, (3*R*,5*R*)-**10d** or (3*R*,5*S*)-**12b**], which was dissolved in chloroform (5 mL) and stirred with potassium carbonate (0.276 g, 2.00 mmol) at room temperature for 3 h. Then anhydrous $MgSO_4$ was added and the suspension was filtered through a pad of Celite. The solution was concentrated and the residue chromatographed on a silica gel column with chloroform–methanol (first 50:1 and later 10:1, v/v).

4.8.1. Diethyl (2*S*,4*R*)-4-hydroxypyrrolidinyl-2-phosphonate (2*S*,4*R*)-4. From mesylate (3*S*,5*R*)-**10a** (0.222 g, 0.527 mmol), phosphonate (2*S*,4*R*)-**4** (0.084 g, 72%) was obtained as a colourless oil. IR (film): $\nu = 3400$, 2983, 1657, 1444, 1393, 1217, 1026, 969 cm^{-1}. $[\alpha]_D^{20} = +10.7$ (*c* 1.1, MeOH). ^1H NMR ($CDCl_3$): $\delta = 4.36$ (br m, 1H, *H*–C4), 4.30–4.10 (m, 4H, $2 \times CH_2OP$), 3.47 (ddd, $J_{(2-3\beta)} = 10.5$ Hz, $J_{(2-P)} = 5.1$ Hz, $J_{(2-3\alpha)} = 3.6$ Hz, 1H, *H*–C2), 3.12 (br tAB, $J_{AB} = 10.5$ Hz, $J_{(5\text{-}4)} = J_{(5\text{-}NH)} = 1.2$ Hz, 1H, *H*–C5), 4.35 (dAB, $J_{AB} = 10.8$ Hz, $J_{(5\text{-}4)} = 4.2$ Hz, 1H, *H*–C5), 3.28 (dddd, $J_{(3\beta-P)} = 25.2$ Hz, $J_{(3\alpha-3\beta)} = 14.7$ Hz, $J_{(3\beta-2)} = 10.5$ Hz, $J_{(3\beta-4)} = 5.7$ Hz, 1H, *H*β–C3), 3.11 (ddd, $J_{(3\alpha-P)} = 15.0$ Hz, $J_{(3\alpha-3\beta)} = 14.7$ Hz, $J_{(3\alpha-2)} = 3.6$ Hz, 1H, *H*α–C3), 1.80 (br s, 2H, O*H* and N*H*), 1.36 (t, $J = 7.2$ Hz, 3H), 1.35 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 72.32$ (d, $J = 3.7$ Hz, C4), 63.40 (d, $J = 7.2$ Hz), 62.64 (d, $J = 7.2$ Hz), 56.64 (d, $J = 8.9$ Hz, C5), 52.84 (d, $J = 162.3$ Hz, C2), 36.51 (s, C3), 16.84 (d, $J = 5.7$ Hz), 16.81 (d, $J = 5.7$ Hz). ^{31}P NMR ($CDCl_3$): $\delta = 29.96$. Anal. Calcd for $C_8H_{18}NO_4P$: C, 43.05; H, 8.13; N, 6.28. Found: C, 43.06; H, 8.27; N, 6.01.

4.8.2. Diethyl (2*R*,4*S*)-4-hydroxypyrrolidinyl-2-phosphonate (2*R*,4*S*)-4. From mesylate (3*R*,5*S*)-**12b** (0.160 g, 0.378 mmol), phosphonate (2*R*,4*S*)-**4** (0.059 g, 69%) was obtained as a colourless oil. $[\alpha]_D^{20} = -9.8$ (*c* 1.6, MeOH). Anal. Calcd for $C_8H_{18}NO_4P$: C, 43.05; H, 8.13; N, 6.28. Found: C, 43.26; H, 8.26; N, 6.01.

4.8.3. Diethyl (2*S*,4*S*)-4-hydroxypyrrolidinyl-2-phosphonate (2*S*,4*S*)-4. From mesylate (3*S*,5*S*)-**10c** (0.285 g, 0.676 mmol), phosphonate (2*S*,4*S*)-**4** (0.112 g, 75%) was obtained as a colourless oil. IR (film): $\nu = 3349$, 2982, 2936, 2910, 1442, 1392, 1224, 1052, 1029, 965 cm^{-1}. $[\alpha]_D^{20} = -4.6$ (*c* 1.0, MeOH). ^1H NMR ($CDCl_3$): $\delta = 4.52$–4.47 (br m, 1H, *H*–C4), 4.24–4.10 (m, 4H, $2 \times CH_2OP$), 3.64 (ddd, $J = 8.7$, 8.4, 5.7 Hz, 1H, *H*–C2), 3.07 (dAB, $J_{AB} = 12.0$ Hz, $J_{(5\text{-}4)} = 3.9$ Hz, 1H, *H*–C5), 4.35 (tAB, $J_{AB} = 10.8$ Hz, $J = 1.5$ Hz, 1H, *H*–C5), 2.20–2.00 (m, 2H, H_2C-3), 1.73 (br s, 2H, N*H* and O*H*), 1.34 (t, $J = 7.2$ Hz, 3H), 1.33 (t, $J = 7.2$ Hz, 3H). ^1H NMR (C_6D_6): $\delta = 4.20$–3.95 (m, 5H, $2 \times CH_2OP$ and *H*–C4), 3.61 (ddd, $J = 9.0$, 8.1, 5.4 Hz, 1H, *H*–C2), 2.88 (dAB, $J_{AB} = 11.7$ Hz, $J = 3.9$ Hz, 1H, *H*–C5), 2.72 (tAB, $J_{AB} = 11.7$ Hz, $J = 1.5$ Hz, 1H, *H*–C5), 2.08 (dddd, $J = 19.2$, 13.2, 9.0, 4.8 Hz, 1H, *H*–C3), 2.00–1.90 (m, 1H, *H*–C3), 1.30 (br s, 2H, N*H* and O*H*), 1.08 (t, $J = 7.2$ Hz, 3H), 1.06 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 72.10$ (d, $J = 7.4$ Hz, C4), 62.56 (d, $J = 6.9$ Hz), 55.84 (d, $J = 7.7$ Hz,

C5), 52.47 (d, $J = 170.6$ Hz, C2), 36.63 (s, C3), 16.73 (d, $J = 5.4$ Hz). ^{31}P NMR ($CDCl_3$): $\delta = 28.92$. Anal. Calcd for $C_8H_{18}NO_4P$: C, 43.05; H, 8.13; N, 6.28. Found: C, 42.91; H, 8.37; N, 6.12.

4.8.4. Diethyl (2*R*,4*R*)-4-hydroxypyrrolidinyl-2-phosphonate (2*R*,4*R*)-4. From mesylate (3*R*,5*R*)-**10d** (0.264 g, 0.626 mmol), phosphonate (2*R*,4*R*)-**4** (0.192 g, 57%) was obtained as a colourless oil. $[\alpha]_D^{20} = +3.8$ (*c* 7.0, MeOH). Anal. Calcd for $C_8H_{18}NO_4P$: C, 43.05; H, 8.13; N, 6.28. Found: C, 43.39; H, 8.36; N, 5.96.

4.8.5. Decomposition products of (2*S*,4*S*)-4. A sample (0.159 g) of phosphonate (2*S*,4*S*)-**4**, which was left at +5 °C for 7 days, was chromatographed on silica gel with chloroform–methanol (50:1, v/v) to give phosphonate (2*S*,4*S*)-**13** (0.028 g, 18%) and (2*S*,4*S*)-**4** (0.139 g, 87%). Further elution with methanol gave impure (2*S*,4*S*)-**14** (0.013 g, 8%).

4.8.5.1. *O*,*O*-Diethyl (2*S*,4*S*)-1-ethyl-4-hydroxypyrrolidinyl-2-phosphonate (2*S*,4*S*)-13. IR (film): $\nu = 3389$, 2978, 2934, 1445, 1222, 1026, 964 cm^{-1}. $[\alpha]_D^{20} = +37.4$ (*c* 1.65, $CHCl_3$). ^{1}H NMR ($CDCl_3$): $\delta = 4.50$–4.22 (m, 1H, *H*–C4), 4.21–4.10 (m, 4H), 3.36 (dd, $J = 9.9$, 5.1 Hz, 1H, *H*–C5), 3.19–3.07 (m, 2H), 2.62–2.51 (m, 2H), 2.42 (ddd, $J = 9.9$, 4.8, 0.9 Hz, 1H, *H*–C5), 2.26 (dddd, $J = 17.1$, 13.8, 8.1, 6.0 Hz, 1H, *H*–C3), 2.01 (ddddd, $J = 13.8$, 12.3, 8.7, 4.2, 0.9 Hz, 1H, *H*–C3), 1.32 (t, $J = 7.2$ Hz, 6H), 1.08 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 70.68$ (d, $J = 7.5$ Hz, C4), 62.70 (d, $J = 6.8$ Hz), 62.32 (d, $J = 7.5$ Hz), 61.16 (d, $J = 13.6$ Hz), 58.96 (d, $J = 175.1$ Hz, C2), 50.77 (d, $J = 2.3$ Hz), 36.83 (d, $J = 1.5$ Hz, C3), 16.85 (d, $J = 5.3$ Hz), 13.86. ^{31}P NMR ($CDCl_3$): $\delta = 27.44$. Anal. Calcd for $C_{10}H_{22}NO_4P$: C, 47.80; H, 8.82; N, 5.58. Found: C, 47.63; H, 8.89; N, 5.37.

4.8.5.2. *O*-Ethyl (2*S*,4*S*)-4-hydroxypyrrolidinyl-2-phosphonate (2*S*,4*S*)-14. ^{1}H NMR (CD_3OD): $\delta = 4.58$–4.55 (br m, 1H), 3.98 (qu, $J = 7.1$ Hz, 2H), 3.78–3.60 (m, 1H), 3.34 (dd, $J = 12.0$, $J = 4.0$ Hz, 1H), 3.15 (d, $J = 12.0$ Hz, 1H), 2.21–2.05 (m, 2H), 1.29 (t, $J = 7.1$ Hz, 3H). ^{31}P NMR (CD_3OD): $\delta = 15.13$.

4.9. Synthesis of *N*,*O*-bismandelic acid derivatives 15 (general procedure)

To a solution of the phosphonate **4** (0.018 g, 0.080 mmol) and (*S*)-*O*-methylmandelic acid (0.033 g, 0.202 mmol) in methylene chloride (2 mL) containing DMAP (two crystals) DCC (0.045 g, 0.218 mmol) was added. After stirring for 24 h at room temperature DCU was filtered off, the residue was concentrated and filtered though a pad of silica gel. A crude product was dissolved in chloroform-*D* and ^{1}H, ^{13}C and ^{31}P NMR spectra were taken.

4.9.1. Diethyl (2*S*,4*R*)-4-[(*S*)-2-methoxy-2-phenylacetoyloxy]-1-[(*S*)-2-methoxy-2-phenylacetyl]pyrrolidinyl-2-phosphonate (2*S*,4*R*)-15a. From (2*S*,4*R*)-**4** (0.018 g, 0.080 mmol) the phosphonate (2*S*,4*R*)-**15a** (0.02 g, 50%) was obtained as a colourless oil.

^{1}H NMR ($CDCl_3$): $\delta = 7.43$–7.26 (m, 10H), 5.00–4.89 (br m, 1H, *H*–C4), 4.87 (s, 1H, C*H*C(O)N), 4.74 (s, 1H, C*H*C(O)O), 4.65–4.53 (br m, 1H, *H*–C2), 4.21 (dd, $J = 11.4$, 7.2 Hz, 1H, *H*–C5), 4.20–4.03 (m, 4H), 3.43 (s, 3H, H_3CO–CH–C(O)N), 3.36 (s, 3H, H_3CO–CH–C(O)O), 3.28 (dd, $J = 11.7$, 6.3 Hz, 1H, *H*–C5), 2.58–2.30 (m, 1H, *H*–C3), 2.15 (ddt, $J = 17.7$, 14.4, 4.8 Hz, 1H, *H*–C3), 1.29 (t, $J = 7.2$ Hz, 3H), 1.27 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 170.37$, 168.59 (d, $J = 1.6$ Hz), 135.72, 135.60, 128.99, 128.85, 128.80, 128.75, 127.38, 127.36, 84.05, 82.29, 72.53, 63.01 (d, $J = 6.8$ Hz), 62.61 (d, $J = 5.3$ Hz), 57.85, 57.47, 51.71 (d, $J = 156.0$ Hz, C2), 50.68, 31.17, 16.78 (d, $J = 6.0$ Hz), 16.65 (d, $J = 6.9$ Hz). ^{31}P NMR ($CDCl_3$): $\delta = 23.83$.

4.9.2. Diethyl (2*R*,4*S*)-4-[(*S*)-2-methoxy-2-phenylacetoyloxy]-1-[(*S*)-2-methoxy-2-phenylacetyl]pyrrolidinyl-2-phosphonate (2*R*,4*S*)-15b. From (2*R*,4*S*)-**4** (0.045 g, 0.202 mmol), phosphonate (2*R*,4*S*)-**15b** (0.086 g, 82%) was obtained as a colourless oil. ^{1}H NMR ($CDCl_3$): $\delta = 7.41$–7.26 (m, 10H), 5.38 (s, 0.13×1H), 5.00 (dddd, $J = 9.9$, 6.6, 5.7, 4.8 Hz, 1H, *H*–C4), 4.94 (s, 0.87×1H, C*H*C(O)N), 4.76 (s, 0.13×1H), 4.74 (s, 0.87×1H, C*H*C(O)O), 4.65 (ddd, $J = 10.5$, 7.5, 4.8 Hz, 1H, *H*–C2), 4.25–3.98 (m, 4H), 3.90 (dd, $J = 12.0$, 6.6 Hz, 1H, *H*–C5), 3.47 (s, 0.87×3H, H_3CO–CH–C(O)N), 3.42 (s, 0.13×3H), 3.39 (s, 0.13×3H), 3.37 (s, 0.87×3H, H_3CO–CH–C(O)O), 3.20 (dd, $J = 12.0$, 5.7 Hz, 1H, *H*–C5), 2.50 (dddd, $J = 20.4$, 14.4, 9.9, 7.5 Hz, 1H, *H*–C3), 2.30 (ddt, $J = 19.8$, 14.4, 4.8 Hz, 1H, *H*–C3), 1.33 (t, $J = 7.2$ Hz, 3H), 1.18 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 170.14$ (major), 169.56 (minor), 169.12 (d, $J = 1.4$ Hz), 135.77, 135.45, 129.35 (minor), 129.20, 129.00, 128.86 (minor), 128.78 (minor), 128.70, 128.66, 128.41, 128.37 (minor), 127.28, 126.53, 83.78 (major), 82.33 (minor), 82.24 (major), 81.10 (minor), 72.67 (major), 70.89 (minor), 63.15 (d, $J = 6.6$ Hz, minor), 62.63 (d, $J = 6.8$ Hz, major), 62.57 (d, $J = 6.0$ Hz, major), 57.53, 57.45, 51.59 (d, $J = 159.2$ Hz, C2), 50.63, 33.82 (minor), 31.20 (major), 16.65 (d, $J = 6.4$ Hz), 16.58 (d, $J = 6.0$ Hz). ^{31}P NMR ($CDCl_3$): $\delta = 24.09$ (87%) and 23.25 (13%).

4.9.3. Diethyl (2*S*,4*S*)-4-[(*S*)-2-methoxy-2-phenylacetoyloxy]-1-[(*S*)-2-methoxy-2-phenylacetyl]pyrrolidinyl-2-phosphonate (2*S*,4*S*)-15c. From (2*S*,4*S*)-**4** (0.020 g, 0.090 mmol), phosphonate (2*S*,4*S*)-**15c** (0.33 g, 72%) was obtained as a colourless oil. ^{1}H NMR ($CDCl_3$): $\delta = 7.40$–7.25 (m, 10H), 5.30 (br m, 1H, *H*–C4), 4.75 (s, 1H, C*H*C(O)N), 4.67 (dt, $J = 9.3$, 5.4 Hz, 1H, *H*–C2), 4.62 (s, 1H, C*H*C(O)O), 4.22–3.96 (m, 4H), 3.80 (br dt, $J = 12.3$, 1.2 Hz, 1H, *H*–C5), 3.41 (dd, $J = 12.3$, 5.1 Hz, 1H, *H*–C5), 3.33 (s, 3H, H_3CO–CH–C(O)N), 3.29 (s, 3H, H_3CO–CH–C(O)O), 2.57 (dddd, $J = 18.3$, 15.0, 5.7, 5.4 Hz, 1H, *H*–C3), 2.19 (dddd, $J = 19.5$, 15.0, 9.3, 3.9 Hz, 1H, *H*–C3), 1.30 (t, $J = 7.2$ Hz, 3H), 1.23 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 170.15$, 168.76 (d, $J = 1.6$ Hz), 135.85, 135.76, 129.05, 128.85, 128.62, 128.48, 127.34, 127.25, 127.00, 84.60, 82.54, 74.31 (d, $J = 2.3$ Hz, C4), 62.97 (d, $J = 7.2$ Hz), 62.87 (d, $J = 6.9$ Hz), 57.55, 57.50, 51.56 (d, $J = 160.6$ Hz, C2), 51.41, 32.24, 16.68 (d, $J = 5.3$ Hz), 16.57 (d, $J = 5.3$ Hz). ^{31}P NMR ($CDCl_3$): $\delta = 24.27$.

4.9.4. Diethyl (2*R*,4*R*)-4-[(*S*)-2-methoxy-2-phenylacetoyloxy]-1-[(*S*)-2-methoxy-2-phenylacetyl]pyrrolidinyl-2-phosphonate (2*R*,4*R*)-15d. From (2*R*,4*R*)-**4** (0.030 g, 0.130 mmol) phosphonate (2*R*,4*R*)-**15d** (0.052 g, 74%) was obtained as a colourless oil. ^{1}H NMR ($CDCl_3$): $\delta = 7.55$–7.20 (m, 10H), 5.51 (s, 0.12×1H), 5.35–5.26 (br m, 0.12×1H), 5.25–5.17 (br m, 0.88×1H, *H*–C4), 4.98 (s, 0.88×1H, C*H*C(O)N), 4.56 (dt, $J = 9.6$, 6.6 Hz, 1H, *H*–C2), 4.44 (s, 0.12×1H), 4.29 (s, 0.88×1H, C*H*C(O)O), 4.25–3.98 (m, 4H), 3.90 (br d, $J = 12.9$ Hz, 1H, *H*–C5), 3.52 (dd, $J = 12.9$, 4.5 Hz, 1H, *H*–C5), 3.50 (s, 0.88×3H, H_3CO–CH–C(O)N), 3.45 (s, 0.12×3H), 3.35 (s, 0.12×3H), 3.28 (s, 0.88×3H, H_3CO–CH–C(O)O), 2.36 (ddt, $J = 19.5$, 14.7, 6.6 Hz, 1H, *H*–C3), 1.85 (dddt, $J = 18.6$, 14.7, 9.6, 1.8 Hz, 1H, *H*–C3), 1.30 (t, $J = 7.2$ Hz, 3H), 1.23 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$): $\delta = 169.76$, 169.64 (d, $J = 1.6$ Hz), 136.02, 135.60, 129.17, 128.96, 128.81, 128.65, 128.32, 127.01, 126.39, 84.03, 81.89, 73.91 (d, $J = 3.4$ Hz, C4), 62.78 (d, $J = 6.0$ Hz), 62.66 (d, $J = 7.2$ Hz), 57.61, 57.31, 52.23, 50.74 (d, $J = 161.8$ Hz, C2), 31.70, 16.67 (d, $J = 6.0$ Hz), 16.64 (d, $J = 6.0$ Hz). ^{31}P NMR ($CDCl_3$): $\delta = 24.58$ (88%) and 23.08 (12%).

4.10. Ammonolysis of *N*,*O*-bismandelic acid derivatives 15 (general procedure)

A solution of phosphonate **15** (0.028 g, 0.054 mmol) in ethanol (1.5 mL), containing aqueous NH_3 (25%, 2 mL) was left for 3 h. Volatiles were removed and the residue was evaporated with anhydrous ethanol (3×5 mL), chloroform (3×5 mL) and filtered though a pad of silica gel. Crude products **16** were dissolved in chloroform-*D* and ^{1}H and ^{31}P NMR spectra were taken.

4.10.1. Diethyl (2*S*,4*R*)-4-hydroxy-1-[(*S*)-2-methoxy-2-phenylacetyl]pyrrolidinyl-2-phosphonate (2*S*,4*R*)-16a. From (2*S*,4*R*)-**15a** (0.031 g, 0.060 mmol) phosphonate (2*S*,4*R*)-**16a** (0.01 g, 50%) was obtained as a colourless oil. ^{1}H NMR ($CDCl_3$): $\delta = 7.42$–7.25 (m, 5H), 5.69 (br d, $J = 10.8$ Hz, 1H, O*H*), 4.82 (s, 1H, C*H*C(O)N), 4.71 (t, $J = 9.6$ Hz, 1H, *H*–C2), 4.42–4.32 (br m, 1H, *H*–C4), 4.32–4.00 (m, 4H), 3.73 (dd, $J = 11.7$, 5.7 Hz, 1H, *H*–C5), 3.61 (d, $J = 11.7$ Hz, 1H, *H*–C5), 3.39 (s, 3H, H_3CO–CH–C(O)N), 2.34–2.22 (m, 1H, *H*–C3), 2.22–2.05 (m, 1H, *H*–C3), 1.36 (t, $J = 7.2$ Hz, 3H), 1.33 (t, $J = 7.2$ Hz, 3H). ^{31}P NMR ($CDCl_3$): $\delta = 26.34$.

4.10.2. Diethyl (2*R*,4*S*)-4-hydroxy-1-[(*S*)-2-methoxy-2-phenylacetyl]pyrrolidinyl-2-phosphonate (2*R*,4*S*)-16b. From (2*R*,4*S*)-**15b** (0.067 g, 0.129 mmol) phosphonate (2*R*,4*S*)-**16b** (0.037 g, 48%) was obtained as a colourless oil. ^{1}H NMR ($CDCl_3$): $\delta = 7.41$–7.26 (m, 5H), 5.56 (br d, $J = 11.1$ Hz, 1H, O*H*), 5.10 (s, 0.1×1H), 4.93 (s, 0.9×1H, C*H*C(O)N), 4.85–4.77 (m, 1H, *H*–C2), 4.47–4.36 (br m, 1H, *H*–C4), 4.30–4.00 (m, 3H), 3.90–3.75 (m, 2H), 3.59 (d, $J = 12.0$ Hz, 1H, *H*–C5), 3.44 (s, 0.9×3H, H_3CO–CH–C(O)N), 3.40 (s, 0.1×3H), 2.30–2.05 (m, 2H, H_2C-3), 1.43 (t, $J = 7.2$ Hz, 0.1×3H), 1.40 (t, $J = 7.2$ Hz, 0.1×3H), 1.35 (t, $J = 7.2$ Hz, 0.9×3H), 1.22 (t, $J = 7.2$ Hz, 0.9×3H). ^{31}P NMR ($CDCl_3$): $\delta = 26.83$ (10%) and 26.24 (90%).

4.10.3. Diethyl (2*S*,4*S*)-4-hydroxy-1-[(*S*)-2-methoxy-2-phenylacetyl]pyrrolidinyl-2-phosphonate (2*S*,4*S*)-16c. From (2*S*,4*S*)-**15c** (0.028 g, 0.054 mmol) phosphonate (2*S*,4*S*)-**16c** (0.016 g, 80%) was obtained as a colourless oil. ^{1}H NMR ($CDCl_3$): $\delta = 7.50$–7.40 (m, 2H), 7.40–7.30 (m, 3H), 4.92 (s, 1H, C*H*C(O)N), 4.77–4.68 (m, 1H, *H*–C2), 4.55–4.47 (br m, 1H, *H*–C4), 4.25–4.00 (m, 4H), 3.70 (br d, $J = 11.7$ Hz, 1H, *H*–C5), 3.46 (s, 3H, H_3CO–CH–C(O)N), 3.40 (dd, $J = 11.7$, 4.8 Hz, 1H, *H*–C5), 2.50–2.30 (m, 1H, *H*–C3), 2.15–1.95 (m, 1H, *H*–C3), 1.70 (br s, 1H, O*H*), 1.33 (t, $J = 7.2$ Hz, 3H), 1.26 (t, $J = 7.2$ Hz, 3H). ^{31}P NMR ($CDCl_3$): $\delta = 24.81$.

4.10.4. Diethyl (2*R*,4*R*)-4-hydroxy-1-[(*S*)-2-methoxy-2-phenylacetyl]pyrrolidinyl-2-phosphonate (2*R*,4*R*)-16d. From (2*R*,4*R*)-**15d** (0.033 g, 0.064 mmol), phosphonate (2*R*,4*R*)-**16d** (0.024 g, 99%) was obtained as a colourless oil. ^{1}H NMR ($CDCl_3$): $\delta = 7.50$–7.40 (m, 2H), 7.40–7.30 (m, 3H), 5.51 (s, 0.17×1H), 5.00 (s, 0.83×1H, C*H*C(O)N), 4.80 (dt, $J = 9.6$, 6.0 Hz, 1H, *H*–C2), 4.50–4.40 (br m, 1H, *H*–C4), 4.30–3.90 (m, 4H), 3.61 (dt, $J = 12.0$, 1.5 Hz, 1H, *H*–C5), 3.50 (s, 0.83×3H, H_3CO–CH–C(O)N), 3.46 (s, 0.17×3H), 3.44 (dd, $J = 12.0$, 4.5 Hz, 1H, *H*–C5), 2.39 (ddt, $J = 19.5$, 13.8, 5.7 Hz, 1H, *H*–C3), 2.08 (ddddd, $J = 17.4$, 13.8, 9.6, 3.6, 1.5 Hz, 1H, *H*–C3), 1.60 (br s, 1H, O*H*), 1.33 (t, $J = 7.2$ Hz, 3H), 1.21 (t, $J = 7.2$ Hz, 3H). ^{31}P NMR ($CDCl_3$): $\delta = 25.06$ (83%) and 23.92 (17%).

4.11. Acetylation of 16

Phosphonates **16** were acetylated as described in Section 4.4 to give crude products **17**, which were dissolved in chloroform-*D* and ^{1}H and ^{31}P NMR spectra were taken.

4.11.1. Diethyl (2*S*,4*R*)-4-acetoxy-1-[(*S*)-2-methoxy-2-phenylacetyl]pyrrolidinyl-2-phosphonate (2*S*,4*R*)-17a. From (2*S*,4*R*)-**16a** (0.010 g, 0.027 mmol) phosphonate (2*S*,4*R*)-**17a** (0.011 g, 100%) was obtained as a colourless oil. ^{1}H NMR ($CDCl_3$): $\delta = 7.42$–7.25 (m, 5H), 5.04–4.90 (br m, 1H, *H*–C4), 4.88 (s, 1H, C*H*C(O)N), 4.66–4.55 (m, 1H, *H*–C2), 4.25–4.10 (m, 4H), 4.07 (dd, $J = 11.7$, 6.6 Hz, 1H, *H*–C5), 3.45 (s, 3H, H_3CO–CH–C(O)N), 3.33 (dd, $J = 11.7$, 5.4 Hz, 1H, *H*–C5), 2.52–2.30 (m, 2H, H_2C-3), 2.04 (s, 3H, H_3CC(O)), 1.34 (t, $J = 6.9$ Hz, 3H), 1.29 (t, $J = 6.9$ Hz, 3H). ^{31}P NMR ($CDCl_3$): $\delta = 24.07$.

4.11.2. Diethyl (2*R*,4*S*)-4-acetoxy-1-[(*S*)-2-methoxy-2-phenylacetyl]pyrrolidinyl-2-phosphonate (2*R*,4*S*)-17b. From (2*R*,4*S*)-**16b** (0.037 g, 0.100 mmol), phosphonate (2*R*,4*S*)-**17b** (0.040 g, 99%) was obtained as a colourless oil. ^{1}H NMR ($CDCl_3$): $\delta = 7.41$–7.26 (m, 5H), 5.38 (s, 0.15×1H), 4.97 (s, 0.85×1H, C*H*C(O)N), 4.95 (dddd, $J = 10.2$, 6.9, 6.0, 4.8 Hz, 1H, *H*–C4), 4.68 (ddd, $J = 10.5$, 7.5, 4.8 Hz, 1H, *H*–C2), 4.26–4.12 (m, 2H), 4.12–4.00 (m, 2H), 4.02 (dd, $J = 12.0$, 6.9 Hz, 1H, *H*–C5), 3.50 (s, 0.85×3H, H_3CO–CH–C(O)N), 3.44 (s, 0.15×3H), 3.32 (dd, $J = 12.0$, 6.0 Hz, 1H, *H*–C5), 2.48 (dddd, $J = 21.0$, 14.4, 10.2, 7.5 Hz, 1H, *H*–C3), 2.30 (ddt, $J = 18.0$, 14.4, 4.8 Hz, 1H, *H*–C3), 2.06 (s, 0.15×3H, H_3CC(O)), 2.03 (s, 0.85×3H, H_3CC(O)), 1.42 (t, $J = 7.2$ Hz, 0.15×3H), 1.38 (t, $J = 7.2$ Hz, 0.15×3H), 1.33 (t, $J = 7.2$ Hz, 0.85×3H), 1.23 (t, $J = 7.2$ Hz,

0.85 × 3H). ^{31}P NMR ($CDCl_3$): $\delta = 24.23$ (85%) and 23.47 (15%).

4.11.3. Diethyl (2*S*,4*S*)-4-acetoxy-1-[(*S*)-2-methoxy-2-phenylacetyl]pyrrolidinyl-2-phosphonate (2*S*,4*S*)-17c. From (2*S*,4*S*)-**16c** (0.016 g, 0.043 mmol) phosphonate (2*S*,4*S*)-**17c** (0.017 g, 99%) was obtained as a colourless oil. ^{1}H NMR ($CDCl_3$): $\delta = 7.50$–7.30 (m, 5H), 5.20–5.12 (br m, 1H, *H*–C4), 4.86 (s, 1H, C*H*C(O)N), 4.75 (dt, $J = 9.6$, 6.3 Hz, 1H, *H*–C2), 4.30–4.05 (br m, 4H), 3.94 (br d, $J = 12.3$ Hz, 1H, *H*–C5), 3.44 (s, 3H, H_3CO–CH–C(O)N), 3.43 (dd, $J = 12.3$, 4.5 Hz, 1H, *H*–C5), 2.51 (ddt, $J = 18.9$, 14.7, 6.3 Hz, 1H, *H*–C3), 2.27–2.12 (m, 1H, *H*–C3), 1.76 (s, 3H, H_3CC(O)), 1.34 (t, $J = 7.2$ Hz, 3H), 1.28 (t, $J = 7.2$ Hz, 3H). ^{31}P NMR ($CDCl_3$): $\delta = 24.63$.

4.11.4. Diethyl (2*R*,4*R*)-4-acetoxy-1-[(*S*)-2-methoxy-2-phenylacetyl]pyrrolidinyl-2-phosphonate (2*R*,4*R*)-17d. From (2*R*,4*R*)-**16d** (0.024 g, 0.070 mmol) phosphonate (2*R*,4*R*)-**17d** (0.023 g, 79%) was obtained as a colourless oil. ^{1}H NMR ($CDCl_3$): $\delta = 7.50$–7.40 (m, 2H), 7.40–7.30 (m, 3H), 5.52 (s, 0.1 × 1H), 5.25–5.16 (br m, 0.1 × 1H), 5.16–5.10 (br m, 0.9 × 1H, *H*–C4), 5.01 (s, 0.9 × 1H, C*H*C(O)N), 4.79 (dt, $J = 9.6$, 6.3 Hz, 1H, *H*–C2), 4.30–4.00 (m, 4H), 3.86 (dt, $J = 12.9$, 1.5 Hz, 1H, *H*–C5), 3.51 (s, 0.9 × 3H, H_3CO–CH–C(O)N), 3.49 (dd, $J = 12.9$, 4.5 Hz, 1H, *H*–C5), 3.47 (s, 0.1 × 3H), 2.48 (ddt, $J = 19.5$, 12.3, 6.3 Hz, 1H, *H*–C3), 2.19 (dddt, $J = 17.5$, 12.3, 9.6, 1.5 Hz, 1H, *H*–C3), 1.84 (s, 0.1 × 3H), 1.69 (s, 0.9 × 3H, H_3CC(O)), 1.34 (t, $J = 6.9$ Hz, 3H), 1.27 (t, $J = 6.9$ Hz, 3H). ^{31}P NMR ($CDCl_3$): $\delta = 24.91$ (90%) and 23.37 (10%).

4.12. Synthesis of *N*-acetyl-*O*-mandelates (2*S*,4*R*)-20a and (2*R*,4*S*)-20b (general procedure)

A solution of phosphonate (2*S*,4*R*)-**4** or (2*R*,4*S*)-**4** (0.029 g, 0.130 mmol), acetic anhydride (0.037 mL, 0.390 mmol) and triethylamine (0.060 mL, 0.430 mmol) containing DMAP (two crystals) in methylene chloride (2 mL) was stirred at room temperature for 2 h. The reaction mixture was filtered though a pad of silica gel to give crude products (2*S*,4*R*)-**18** or (2*R*,4*S*)-**18** (0.027 g) as colourless oils. ^{1}H NMR ($CDCl_3$) $\delta = 5.21$–5.13 (m, 1H, *H*–C4), 4.59 (ddd, $J = 9.0$, 7.2, 5.1 Hz, 1H, *H*–C2), 4.33 (dd, $J = 12.9$, 7.2 Hz, 0.31 × 1H, *H*–C5), 4.23–4.01 (m, 4H), 4.00 (dd, $J = 11.4$, 6.6 Hz, 0.69 × 1H, *H*–C5), 3.54 (dd, $J = 11.4$, 5.1 Hz, 0.69 × 1H, *H*–C5), 3.32 (dd, $J = 12.9$, 5.1 Hz, 0.31 × 1H, *H*–C5), 2.75–2.39 (m, 2H, H_2C-3), 2.21 (s, 0.31 × 6H, 2 × H_3CC(O)), 2.09 (s, 0.69 × 6H, 2 × H_3CC(O)), 1.35 (t, $J = 7.2$ Hz, 0.31 × 6H), 1.33 (t, $J = 7.2$ Hz, 0.69 × 6H). ^{31}P NMR ($CDCl_3$) $\delta = 24.42$ (69%) and 23.51 (31%).

A solution of phosphonate (2*S*,4*R*)-**18** or (2*R*,4*S*)-**18** (0.027 g, 0.080 mmol) in ethanol (0.7 mL) containing aqueous NH_3 (25%, 4 mL) was left at room temperature for 4 h. Volatiles were removed and the residues evaporated with anhydrous ethanol (3 × 5 mL), chloroform (3 × 5 mL) and filtered though a pad of silica gel to give crude products (2*S*,4*R*)-**19** or (2*R*,4*S*)-**19** (0.021 g) as colourless oils. ^{1}H NMR ($CDCl_3$) $\delta = 5.82$ (d, $J = 11.7$ Hz, 0.7 × 1H, O*H*), 5.29 (d, $J = 12.0$ Hz, 0.3 × 1H), 4.72–4.65 (m, 1H), 4.56–4.44 (m, 1H), 4.30–4.3 (m, 4H), 3.83 (ddd, $J = 11.4$, 6.0, 1.2 Hz, 1H, *H*–C5), 3.64 (br d, $J = 11.4$ Hz, 0.7 × 1H, *H*–C5), 3.43 (br d, $J = 11.4$ Hz, 0.3 × 1H, *H*–C5), 2.40–2.22 (m, 2H, H_2C-3), 2.17 (s, 0.3 × 3H, H_3CC(O)), 2.09 (s, 0.7 × 3H, H_3CC(O)), 1.38 (t, $J = 7.2$ Hz, 0.3 × 3H), 1.37 (t, $J = 7.2$ Hz, 0.7 × 3H), 1.36 (t, $J = 7.2$ Hz, 0.3 × 3H), 1.33 (t, $J = 7.2$ Hz, 0.7 × 3H). ^{31}P NMR ($CDCl_3$) $\delta = 26.85$ (30%) and 26.79 (70%).

To a solution of phosphonate (2*S*,4*R*)-**19** or (2*R*,4*S*)-**19** (0.021 g, 0.080 mmol) and (*S*)-*O*-methylmandelic acid (0.022 g, 0.130 mmol) in methylene chloride (2 mL) containing DMAP (two crystals) DCC (0.031 g, 0.150 mmol) was added. After stirring for 24 h at room temperature, the DCU was filtered off, and the residue was concentrated and filtered though a pad of silica gel. Crude products (2*S*,4*R*)-**20a** or (2*R*,4*S*)-**20b** were dissolved in chloroform-*D* and ^{1}H and ^{31}P NMR spectra were taken.

4.12.1. Diethyl (2*S*,4*R*)-4-[(*S*)-2-methoxy-2-phenylacetoyloxy]-1-acetylpyrrolidinyl-2-phosphonate (2*S*,4*R*)-20a. From (2*S*,4*R*)-**4** (0.029 g, 0.130 mmol) phosphonate (2*S*,4*R*)-**20a** (0.036 g) was obtained as a colourless oil. ^{1}H NMR ($CDCl_3$): $\delta = 7.50$–7.30 (m, 5H), 5.24–5.15 (m, 1H, *H*–C4), 4.81 (s, 0.71 × 1H, C*H*C(O)N), 4.78 (s, 0.29 × 1H), 4.61–4.48 (m, 1H, *H*–C2), 4.20–4.00 (m, 5H, 2 × CH_2OP and *H*–C5), 3.53 (dd, $J = 11.4$, 6.3 Hz, 0.71 × 1H, *H*–C5), 3.40 (s, 3H, H_3CO–CH–C(O)N), 3.22 (dd, $J = 12.9$, 5.7 Hz, 0.29 × 1H, *H*–C5), 2.60–2.40 (m, 1H, *H*–C3), 2.38–2.10 (m, 1H, *H*–C3), 2.19 (s, 0.29 × 3H), 2.09 (s, 0.71 × 3H, H_3CC(O)), 1.33 (t, $J = 7.2$ Hz, 3H), 1.30 (t, $J = 7.2$ Hz, 3H). ^{31}P NMR ($CDCl_3$): $\delta = 24.22$ (71%) and 23.09 (29%).

4.12.2. Diethyl (2*R*,4*S*)-4-[(*S*)-2-methoxy-2-phenylacetoyloxy]-1-acetylpyrrolidinyl-2-phosphonate (2*R*,4*S*)-20b. From (2*R*,4*S*)-**4** (0.023 g, 0.100 mmol) phosphonate (2*R*,4*S*)-**20b** (0.043 g) was obtained as a colourless oil.

^{1}H NMR ($CDCl_3$): $\delta = 7.50$–7.30 (m, 5H), 5.24–5.15 (m, 1H, *H*–C4), 4.81 (s, 0.69 × 1H, C*H*C(O)N), 4.79 (s, 0.31 × 1H), 4.57 (ddd, $J = 10.2$, 7.5, 4.8 Hz, 1H, *H*–C2), 4.29 (dd, $J = 12.9$, 6.9 Hz, 0.31 × 1H, *H*–C5), 4.20–4.06 (m, 4H), 3.90 (dd, $J = 12.0$, 6.9 Hz, 0.69 × 1H, *H*–C5), 3.43 (s, 0.31 × 3H), 3.41 (s, 0.69 × 3H, H_3CO–CH–C(O)N), 3.33 (dd, $J = 12.0$, 5.7 Hz, 0.69 × 1H, *H*–C5), 3.14 (dd, $J = 12.9$, 4.2 Hz, 0.31 × 1H), 2.80–2.40 (m, 2H, H_2C-3), 2.19 (s, 0.31 × 3H), 2.05 (s, 0.69 × 3H, H_3CC(O)), 1.33 (t, $J = 7.2$ Hz, 3H), 1.30 (t, $J = 7.2$ Hz, 3H). ^{31}P NMR ($CDCl_3$): $\delta = 24.29$ (69%) and 23.32 (31%).

Acknowledgements

The authors are grateful to Professor Andrzej E. Wróblewski for support and stimulating discussions. Mrs. Małgorzata Pluskota is acknowledged for her technical assistance. This work was supported by the Medical University of Łódź internal funds (502-13-332, 502-13-487 and 503-3014-1).

References

1. Tamaki, M.; Okitsu, T.; Araki, M.; Sakamoto, H.; Takimoto, M.; Muramatsu, I. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 531–535.
2. Mauger, A. B. *J. Nat. Prod.* **1996**, *59*, 1205–1211.
3. Eriksson, M.; Myllyharju, J.; Tu, H.; Hellman, M.; Kivirikko, K. I. *J. Biol. Chem.* **1999**, *274*, 22131–22134.
4. Keller-Juslén, C.; Kuhn, M.; Loosli, H. R.; Petcher, T. J.; Weber, H. P.; von Wartburg, A. *Tetrahedron Lett.* **1976**, *17*, 4147–4150.
5. Wehner, V.; Jäger, V. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1169–1171.
6. Benz, F.; Knüsel, F.; Nüesch, J.; Treichler, H.; Voser, W.; Nyfeler, R.; Keller-Schierlein, W. *Helv. Chim. Acta* **1974**, *57*, 2459–2477.
7. Ondetti, M. A.; Rubin, B.; Cushman, D. W. *Science* **1977**, *196*, 441–444.
8. Patchett, A. A.; Harris, E.; Tristram, E. W.; Wyvratt, M. J.; Wu, M. T.; Taub, D.; Peterson, E. R.; Ikeler, T. J.; Tenbroeke, J.; Payne, L. G.; Ondeyka, D. L.; Thorseu, E. D.; Greenlee, W. J.; Lohr, N. S.; Hoffsommer, R. D.; Joshua, H.; Ruyle, W. V.; Rothrock, J. W.; Aster, S. D.; Maycock, A. L.; Robinson, F. M.; Hirschmann, R.; Sweet, C. S.; Ulm, E. H.; Gross, D. M.; Vassil, T. C.; Stone, C. A. *Nature* **1980**, *288*, 280–283.
9. Remuzon, P. *Tetrahedron* **1996**, *52*, 13803–13835.
10. Mestres, R. *Green Chem.* **2004**, *6*, 583–5603.
11. Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65–75.
12. Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352–1375.
13. Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357–389.
14. Wang, Y.; Wei, S.; Sun, J. *Synlett* **2006**, 3319–3323.
15. Gu, L.; Yu, M.; Wu, X.; Zhang, Y.; Zhao, G. *Adv. Synth. Catal.* **2006**, *348*, 2223–2228.
16. Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580–591.
17. Thayumanavan, R.; Dhevalapally, B.; Sakthivel, K.; Tanaka, F.; Barbas, C. F., III. *Tetrahedron Lett.* **2002**, *43*, 3817–3820.
18. Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F., III. *Tetrahedron Lett.* **2002**, *43*, 6743–6746.
19. Shi, M.; Jiang, J.-K.; Li, C.-Q. *Tetrahedron Lett.* **2002**, *43*, 127–130.
20. Chen, S.-H.; Hong, B.-C.; Su, C.-F.; Sarshar, S. *Tetrahedron Lett.* **2005**, *46*, 8899–8903.
21. Enders, D.; Seki, A. *Synlett* **2002**, 26–28.
22. Betancort, J. M.; Barbas, C. F., III. *Org. Lett.* **2001**, *3*, 3737–3740.
23. List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423–2425.
24. Reyes, E.; Vicario, J. L.; Badia, D.; Carrillo, L. *Org. Lett.* **2006**, *8*, 6135–6138.
25. Hong, B.-C.; Nimje, R. Y.; Yang, C.-Y. *Tetrahedron* **2007**, *48*, 1121–1125.
26. Chowdari, N. S.; Ramachary, D. B.; Barbas, C. F., III. *Synlett* **2003**, 1906–1909.
27. Notz, W.; Tanaka, F.; Watanabe, S.; Chowdari, N. S.; Turner, J. M.; Thayumanavan, R.; Barbas, C. F., III. *J. Org. Chem.* **2003**, *68*, 9624–9634.
28. Bui, T.; Barbas, C. F., III. *Tetrahedron Lett.* **2000**, *41*, 6951–6954.
29. Dinér, P.; Amedjkouh, M. *Org. Biomol. Chem.* **2006**, *4*, 2091–2096.
30. Denhel, A.; Lavielle, G. *Bull. Soc. Chim. Fr.* **1978**, *II*, 95–96.
31. Moonen, K.; Laureyn, I.; Stevens, C. V. *Chem. Rev.* **2004**, *104*, 6177–6215.
32. Davis, F. A.; Wu, Y.; Xu, H.; Zhang, J. *Org. Lett.* **2004**, *6*, 4523–4526.
33. Renaud, Ph.; Seebach, D. *Helv. Chem. Acta* **1986**, *69*, 1704–1710.
34. El Khalabi, R.; El Hallaoui, A.; Ouazzani, F.; Elachqar, A.; Atmani, A.; Roumestant, M. L.; Viallefont, Ph.; Martinez, J. *Prep. Biochem. Biotechnol.* **2000**, *30*, 295–304.
35. Boto, A.; Gallardo, J. A.; Hernández, R.; Saavedra, C. J. *Tetrahedron Lett.* **2005**, *46*, 7807–7811.
36. Chevrier, C.; Le Nouen, D.; Defoin, A.; Tarnus, C. *Eur. J. Org. Chem.* **2006**, 2384–2392.
37. Boduszek, B.; Oleksyszyn, J.; Kam, C.-M.; Selzler, J.; Smith, R. E.; Powers, J. C. *J. Med. Chem.* **1994**, *37*, 3969–3976.
38. Belyaev, A.; Zhang, X.; Augustyns, K.; Lambeir, A.-M.; De Meester, I.; Vedernikova, I.; Scharpe, S.; Haemers, A. *J. Med. Chem.* **1999**, *42*, 1041–1052.
39. Lambeir, A.-M.; Durinx, C.; Scharpe, S.; De Meester, I. *Crit. Rev. Clin. Lab. Sci.* **2003**, *40*, 209–294.
40. Powers, J. C.; Boduszek, B.; Oleksyszyn, J. PCT Int. Appl., WO 9529691, 1995; *Chem. Abstr.* **1996**, *124*, 203102.
41. Augustyns, K. J.; Vanhoof, G. C.; Borloo, M. J.; De Meester, I. A.; Goossens, F. J.; Haemers, A. Hendriks, D. F.; Lambeir, A. M.; Scharpe, S. L. PCT Int. Appl., WO 9534538, 1995; *Chem. Abstr.* **1996**, *124*, 261758.
42. Piotrowska, D. G. *Tetrahedron Lett.* **2006**, *47*, 5363–5366.
43. Piotrowska, D. G. *Tetrahedron* **2006**, *62*, 12306–12317.
44. Greene, T. W.; Wuts, P. G. M. *Protecting Groups on Organic Chemistry*; Wiley: New York, 1991.
45. Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17–117.