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Synthesis of Amino-L-Lyxose Phosphonates as Fucosyl-Phosphate Mimics

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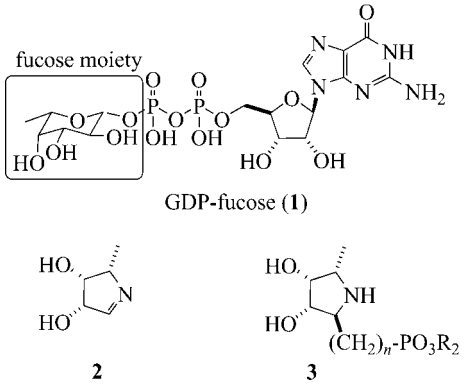
Some reactions of nitrone **4** are described, namely the nucleophilic addition of dialkyl phosphites, $HOP(OR)_2$, **5a–c** or of diethyl methylphosphonate **8** and the dipolar [2+3] cycloaddition of vinylphosphonate **11**. Chemical transformations led to 4-amino-L-fucose derivatives bearing a phosphonate group in the 1α position linked to the pyrrolidine ring through a chain of 0–2 carbon atoms. The target compounds proved to be good-to-excellent α-L-fucosidase inhibitors.

Introduction

The tetrasaccharide sialyl Lewis X is involved in inflammatory processes and more directly in the interaction of leukocytes with the vascular endothelium through diverse adhesion glycoprotein selectins.[1–3] It has been established that the fucosyl moiety of the sialyl Lewis X is essential for these interactions.[2,3] Consequently, inhibition of the biosynthesis of L-fucose, which is believed to be triggered by fucosyltransferases, can be a means to reduce leukocyte recruitment; such inhibition would then be a potential anti-inflammatory treatment.[1–3] One possible way to inhibit the fucosyltransferases is to modify the fucose donator, that is, GDP-fucose (**1**) (Scheme 1). It has been postulated that the transition states of glycosidases and glycosyltransferases are similar.[4,5] As a consequence, replacement of the fucose moiety (shown in the box in Scheme 1) in GDP-fucose with a fucose mimic has been studied by several groups in order to obtain fucosyltransferase inhibitors. Recently, such inhibitors were obtained with K_i values in micromolar range by using as fucose mimics cyclitol,[6] L-fluorofucoses[7] or iminosugars with a 5- or 6-membered ring of the L-xylose,[8,9] D-fucose[10] or L-fucose[6,11] series. It has also been found that the stereochemistry at the anomeric position of the fucose mimic is of variable importance for the inhibition of fucosyltransferases.[7]

We have already shown that the pyrrolidine amino sugar **2** in the L-lyxose series is a potent L-fucosidase inhibitor.[12,13] We describe herein new synthetic ways to synthesise 1-α-phosphonate derivatives **3** of this amino-sugar **2** in which the phosphonate moiety is linked, directly or through a chain of one or two carbon atoms, to the pyrrolidine ring. These compounds can be considered as precursors of GDP-fucose mimics. The nitrone **4**, which we have recently obtained from D-ribose,[12] was used as the starting material. It was substituted either by direct nucleophilic S_N2 addition or by a polar (3+2) cycloaddition reaction. Inversion of the obtained α anomeric isomers into β isomers was attempted but without any success. The inhibition of α-L-fucosidase with these phosphonates is discussed. A partial preliminary communication of these results has already been published.[12,14]



Scheme 1.

Results

Direct Addition of Nucleophiles

Addition of alkyl phosphites to nitrones has been carried out by Lewis acid catalysis,[15,16] with its anion[17,18] or in the absence of solvents.[19] By using this last condition (Scheme 2), the reaction of nitrone **4** with dialkyl esters **5a–c** at 40 °C gave the *N*-hydroxy-phosphonates **6a**,**b** in quantitative yields whereas the bulky dibenzyl derivative **6c** was only obtained in a moderate yield (47%).

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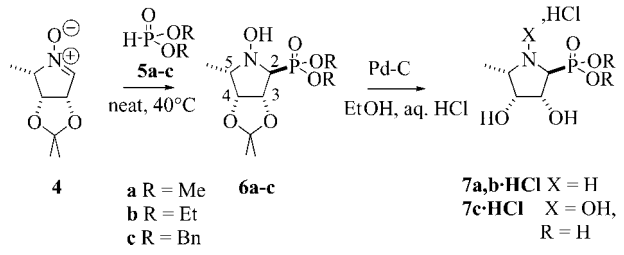
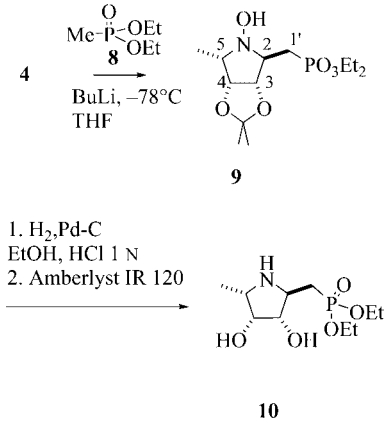


Scheme 2.

The N–OH group is generally reduced by hydrogenolysis over Pd/C,[15,18] and even better in the presence of aqueous HCl.[16,17] We have verified that this reduction also occurred by hydrogenolysis over Raney-nickel[20] but not over 5% Pd/C alone. *O*,*N*-Bis-deprotection of **6a**,**b** was finally carried out by hydrogenolysis with 5% Pd/C in EtOH and aqueous 1 N HCl to give in one step the pyrrolidine-phosphonates **7a**,**b** as hydrochlorides. Reduction of the benzyl derivative **6c** gave the *N*-hydroxy-phosphonic acid **7c**, that is, without reduction of the N–O bond. The ethyl ester **7b** was also obtained in the free amino form after purification over ion-exchange resin [$H^{(+)}$ form].

Addition of the methylphosphonate anion to protected sugars has already been described for the lactone[21,22] and amino ether[23] series. In the case of nitrone **4**, nucleophilic addition of the anion of methylphosphonate **8** readily gave the *N*-hydroxy-phosphonate **9** in near quantitative yield; nevertheless, the reaction temperature (–78 °C) was critical to give good results (Scheme 3). As for **7b**, deprotection of **9** provided the amino-phosphonate **10** in 65% overall yield from the nitrone **4**.

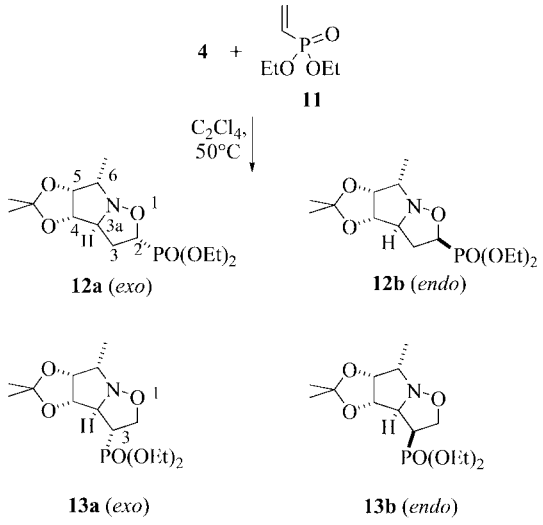


Scheme 3.

In all cases, nucleophilic addition occurred from the less bulky side to provide the α-P anomers **6a**–**c** and the α-C anomer **9**. The small *J*(1,2) values, around 1.2 Hz for **6a**–**c** and 0 Hz for **9**, correspond to a *trans* relationship between the two protons 1-H and 2-H.[24]

Cycloaddition with Vinylphosphonate 11

The [2+3] dipolar cycloaddition reaction of nitrones is a widely used synthetic method.[25] However, vinylphosphonates as the dipolarophile have rarely been used in cycloaddition reactions with nitrones[26] and in those cases a weak regioselectivity was often observed.[26a,26b] Likewise in our case (Scheme 4), the thermal reaction of vinylphosphonate **11** with nitrone **4** in ethylene perchloride was weakly regio- and stereoselective and two pairs of *exo* and *endo* regio-adducts **12a**,**b** and **13a**,**b** were formed in 30:52:13:6 proportions, respectively, the major isomer being the *endo* adduct **12b**. The minor *endo* isomer **13b** was characterised only by ^{1}H NMR spectroscopic data.

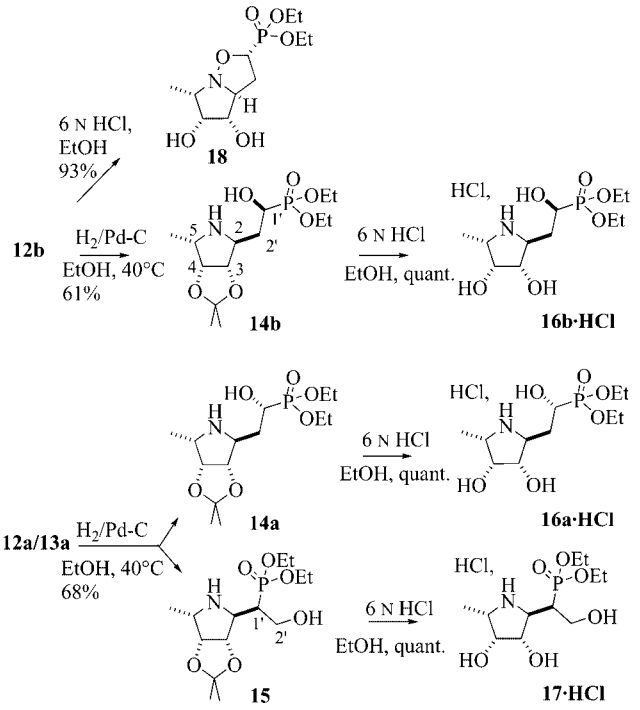


Scheme 4.

The major adduct **12b** (together with **13b**) and a mixture of **12a/13a** were separated by chromatography and their structures ascertained by ^{1}H and ^{13}C NMR spectroscopy. For the regioisomers **12a**,**b** the C-2 atom bearing the phosphonate group is bound to the O-1 atom and appears in the ^{13}C NMR spectrum at 70–75 ppm as a doublet [*J*(2,P) = 170–166 Hz]. For the regioisomer **13a**, the corresponding C-3 atom is strongly shielded at δ = 42 ppm [*J*(3,P) = 150 Hz]. The *exo* stereostructures of **12a** and **13a** were determined by NOESY and NOE experiments: for **12a**, a NOE value of 10% was found for 6-H by irradiation of 2-H, as well as a 5% effect with the near 3a-H; for **13a**, NOE values of 9 and 7%, respectively, were found for 3-H and the nearby 3a-H by irradiation of 4-H. For all adducts, a *trans* relationship between the protons 3a-H and 4-H was ascertained by their very weak coupling [*J*(3a,4) ≈ 0 Hz].

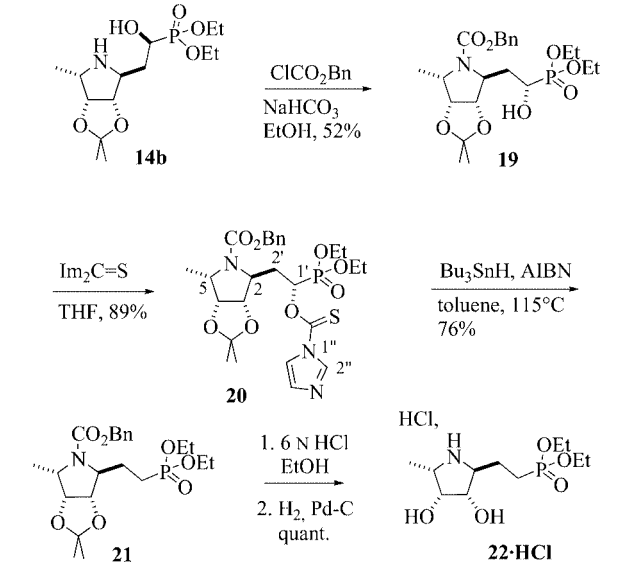
As for 1,2-oxazinanes,[27,28] the N–O bond of the bicyclic adducts was easily hydrogenolysed over Pd/C at 40 °C (Scheme 5). The major adduct **12b** gave the imino-alditol **14b** in 60–70% yield. The mixture of **12a/13a** gave the corresponding mixture of **14a/15** which was resolved by chromatographic separation.

Hydrolysis of the acetonide moiety of **14a**,**b** and **15** with aqueous 6 N HCl in ethanol gave the corresponding triols **16a**,**b** and **17** as hydrochlorides in essentially quantitative yields. Under the same conditions, the major adduct **12b** was hydrolysed to bicyclic diol **18**.



Scheme 5.

In order to obtain a pyrrolidine phosphonate linked through an ethyl chain from the major adduct **12b**, the alcohol function of the opened adduct **14b** was eliminated by a Barton–McCombie[29] radical elimination of a xanthate (see Scheme 6). Preliminary *N*-protection with benzyl chloroformate in ethanol and 2 equiv. of base gave the carbamate alcohol **19** in a moderate yield. Subsequent acylation with thiocarbonyldiimidazole (Im_2CS)[30–33] in THF readily provided xanthate **20**. By heating in toluene with tributylstannane and AIBN as radical initiator, the xanthate **20** underwent reductive radical fragmentation to the ethyl pyrrolidine-phosphonate **21** in good yield. Finally,

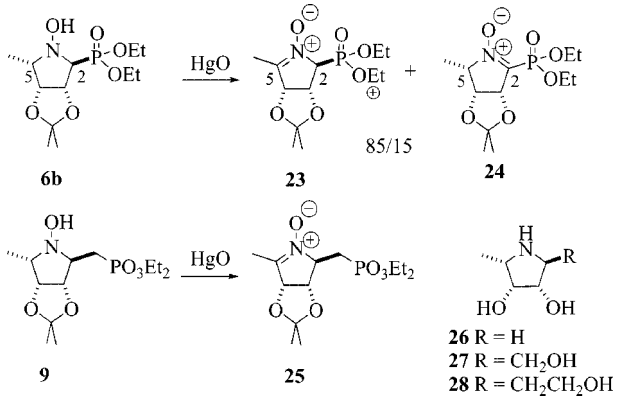


Scheme 6.

quantitative *O*,*N*-deprotection with 6 N HCl followed by hydrogenolysis over Pd/C led to the hydrochloride of the aminolyxitol-phosphonate **22**. This latter pyrrolidine was obtained in 10% overall yield from the nitrone **4**.

Oxidation to Nitrones

We have obtained a diverse range of derivatives of 4-amino-L-lyxose as the 1-α-P or 1-α-C anomers. One possible way to obtain β anomers is to isomerise these α anomers by oxidation of the pseudoanomeric position followed by reduction. We have studied this possibility in the case of the hydroxylamines **6b** and **9**. Unfortunately, these *N*-hydroxypyrrolidines were mainly oxidised (with yellow HgO in $CHCl_3$) at the 5-position. Diethyl phosphonate **6b** led to a 85:15 mixture of nitrones **23** and **24**, respectively, whereas its homologue **9** gave only nitrone **25** (Scheme 7).



Scheme 7.

In the case of **9** the reaction was attempted under other oxidative conditions[34,35] (HgO in EtOH, cyclohexane or AcOH, benzoquinone in $CHCl_3$, potassium ferricyanide in ether, *tert*-butyl hydroperoxide in toluene) in order to change the regioselectivity, but no change in the oxidation process was observed and the nitrone **25** remained the only product formed. Consequently, it would seem that the oxidation was directed by abstraction of the more accessible 5-H.

Pyrrolidine-phosphonates as Glycosidase Inhibitors

All these pyrrolidines are fucosidase inhibitors. Their inhibition data were measured against α-L-fucosidase from bovine kidney and the results are compiled in Table 1.

The pyrrolidines **16a**,**b**, **17** and **22** possessing an alcohol function at the β position of the lateral chain are submicromolar to nanomolar inhibitors, the best one being the 1′*S* isomer **16b**, without reaching the potency of the amino sugar **2**. Comparison between the unsubstituted amino-L-lyxitol **26** (K_i = 0.05 μM[13] or 0.2 μM[36]) and the alcohol-phosphonate **16b** and other good inhibitors, such as the alcohols **27** (K_i = 0.40 μM[36]) and **28** (K_i = 0.008 μM[12]) (see Scheme 7), has led to the conclusion that a hydrophilic in-

Table 1. Inhibition constants (K_i) for pyrrolidine-phosphonates **7a**–**c**, **10**, **16a**,**b**, **17**, **18** and **22** against α-L-fucosidase from bovine kidney and compared with the amino-L-lyxose **2**.

Compounds	**2**[a]	**7a**	**7b**	**7c**	**10**	**16a**	**16b**	**17**	**18**	**22**
K_i [μM]	0.01	2.3	7.3	0.20	4.3	0.20	0.04	0.40	120	0.10

[a] See ref.[13].

teraction in the enzyme's active site occurs near the anomeric position at a two-carbon-chain distance. It is evident that bicyclic adduct **18** interacts unfavourably with this enzyme.

Conclusion

Starting from nitrone **4** we have presented a synthesis of phosphonate derivatives of 4-amino-L-lyxose as 1-α anomers in 40–60% yield for **7a**–**c**, in 65% yield for **10** and in 10% yield for **22**. Some phosphonates, such as **16b** and **22**, are potent nanomolar fucosidase inhibitors. Attempts to inverse the anomeric position in β anomers proved unsuccessful. The synthesis of GDP analogues of these phosphonates and a study of their inhibition against fucosyltransferases are currently under investigation.

Experimental Section

General: Flash chromatography: silica gel (Merck 60, 230–400 mesh). TLC: Al-roll silica gel (Merck 60, F_{254}). Melting points: Kofler hot plate, corrected values. IR spectra: Perkin–Elmer 157 G or Nicolet 405 FT-IR spectrometer; $\tilde{\nu}$ in cm^{-1}. Specific Optical Rotation: Schmidt–Haensch Polartronic Universal or Perkin–Elmer 341 LC polarimeter. ^1H, ^{31}P and ^{13}C NMR (400, 161.9 and 100.6 MHz, respectively) spectra: Bruker Avance 400 or in some cases Bruker AC-F 250 spectrometer; tetramethylsilane (TMS) or natrium [D_4]trimethylsilylpropionate ([D_4]TSP) in D_2O as internal reference (^1H NMR), 80% aqueous H_3PO_4 as external reference (^{31}P NMR) and $CDCl_3$ or (in D_2O) dioxane [$\delta(CDCl_3)$ = 77.0 ppm in D_2O, δ(dioxane) = 67.4 ppm with respect to TMS] as internal reference (^{13}C NMR); δ in ppm and J in Hz. HRMS were measured with a Waters Micromass Q-Tof Ultima API spectrometer at Basilea Pharmaceuticals, Basel. Microanalyses were carried out by the Service Central de Microanalyses du CNRS, 69390 Vernaison, France, or by the Service de microanalyse de l'ICSN-CNRS, 91168 Gif sur Yvette, France.

Reagents and Solvents: Raney nickel (aqueous suspension), tributylstannane and 5% Pd/C were obtained from Fluka, dimethyl, diethyl and dibenzyl phosphite, dimethyl methanephosphonate and diethyl vinylphosphonate from Aldrich. Yellow HgO was purchased from Prolabo, azobis(isobutyronitrile) (AIBN) from Merck and Amberlite IR 120 from Rohm & Haas. Solvents were freshly distilled, dry EtOH and MeOH were distilled over Mg/MgI_2, dry THF over Na and benzophenone, dry Et_2O was distilled and stored over Na, CH_2Cl_2 was distilled over P_2O_5 and kept over Na_2CO_3. NEt_3 and tetrachloroethylene (C_2Cl_4) were distilled before use.

Direct Addition of Nucleophiles

Dimethyl (2*S*,3*R*,4*R*,5*S*)-*N*-Hydroxy-3,4-isopropylidenedioxy-5-methylpyrrolidine-2-phosphonate (6a): Nitrone **4**[12] (200 mg, 1.17 mmol) and dimethyl ester **5a** (160 μL, 1.75 mmol, 1.5 equiv.) were heated for 20 h at 40 °C without any solvent. The crude product was purified by chromatography (diethyl ether/MeOH, 95:5) to give **6a** (328 mg, quant.). Yellowish resin. $[a]_D^{20}$ = +30 (c = 1, $CHCl_3$). R_f = 0.46 (diethyl ether/MeOH, 95:5). ^1H NMR ($CDCl_3$, 295 K): δ = 1.24 (d, 5-Me), 1.30, 1.45 (2 s, CMe_2), 3.66 (quint, 5-H), 3.77, 3.81 (2 d, 2 OMe), 3.85 (d, 2-H), 4.63 (dd, 4-H), 4.95 (ddd, 3-H), ca. 6.0 (s, NOH). J(2,3) = 1.2, J(2,P) = ca. 13, J(3,4) = 6.6, J(3,P) = 8.8, J(4,5) = 4.8, J(5,Me) = 6.6, J(OMe,P) = 11.1 Hz. ^{13}C NMR ($CDCl_3$, 295 K): δ = 11.7 (5-Me), 24.2, 26.0 (CMe_2), 51.9 (d, OMe′), 53.4 (d, OMe′′), 64.2 (C-5), 69.3 (d, C-2), 78.9 (C-3), 79.6 (C-4), 111.6 (*C*Me_2) ppm. J(2,P) = 142.7, J(OMe′,P) = 7.1, J(OMe′′,P) = 5.7 Hz. ^{31}P NMR ($CDCl_3$, 295 K): δ = 26.3 ppm. $C_{10}H_{20}NO_6P$ (281.25): C 42.71, H 7.17, N 4.98, P 11.01; found C 42.8, H 7.3, N 4.7, P 10.3.

Diethyl (2*S*,3*R*,4*R*,5*S*)-*N*-Hydroxy-3,4-isopropylidenedioxy-5-methylpyrrolidine-2-phosphonate (6b): Following the same procedure as used for **6a** with nitrone **4** (200 mg, 1.17 mmol) and diethyl ester **5b** (230 μL 1.75 mmol, 1.5 equiv.) at 40 °C for 30 h. Purification by chromatography (CH_2Cl_2/EtOH, 98:2) gave pure **6b** (361 mg, quant). Yellowish resin. $[a]_D^{20}$ = +22 (c = 1, $CHCl_3$). R_f = 0.18 (CH_2Cl_2/EtOH, 98:2). IR (KBr): $\tilde{\nu}$ = 631, 666, 754, 799, 879, 965, 1045, 1147, 1167, 1212, 1245, 1381, 1448, 2937, 2987, 3290 cm^{-1}. ^1H NMR ($CDCl_3$, 295 K): δ = 1.31 (d, 5-Me), 1.32 (s, C–CH_3), 1.34, 1.36 (2 t, 2 CH_2CH_3), 1.47 (s, C–CH_3), 3.62 (quint, 5-H), 3.86 (dd, 2-H), 4.13–4.23 (m, 2 CH_2CH_3), 4.63 (dd, 4-H), 4.95 (ddd, 3-H), 6.74 (s, NOH) ppm. J(2,3) = 1.3, J(2,P) = 13.0, J(4,3) = 6.5, J(3,P) = 8.5, J(4,5) = 4.8, J(5,Me) = 6.6, J(5,P) = ca. 1.0, J(CH_2CH_3) = 7.0 Hz. ^{13}C NMR ($CDCl_3$, 295 K): δ = 11.7 (5-Me), 16.2, 16.3 (2d, 2 CH_2CH_3), 24.2, 25.9 (CMe_2), 61.3, 62.6 (2 d, 2 CH_2CH_3), 63.9 (C-5), 69.4 (d, C-2), 78.9 (C-4), 79.4 (C-3), 111.3 (*C*Me_2) ppm. J(2,P) = 141.3, J(CH_3CH_2,P) = 6.0, J(CH_2CH_3,P) = 7.2 Hz. ^{31}P NMR ($CDCl_3$, 295 K): δ = 23.9 ppm. $C_{12}H_{24}NO_6P$ (309.30): C 46.60, H 7.82, N 4.53, P 10.01; found C 46.5, H 7.9, N 4.6, P 9.7.

Dibenzyl (2*S*,3*R*,4*R*,5*S*)-*N*-Hydroxy-3,4-isopropylidenedioxy-5-methylpyrrolidine-2-phosphonate (6c): Following the same procedure as used for **6a** with nitrone **4** (150 mg, 0.9 mmol) and dibenzyl ester **5c** (300 μL, 1.3 mmol, 1.5 equiv.) at 45 °C for 30 h. Purification by chromatography (CH_2Cl_2 then CH_2Cl_2/MeOH, 98:2) gave pure **6c** (180 mg, 47%). Colourless crystals. M.p. 78–80 °C (*i*PrOH). $[a]_D^{20}$ = +18.7 (c = 1, $CHCl_3$). R_f = 0.26 (CH_2Cl_2/MeOH, 98:2). IR (KBr): $\tilde{\nu}$ = 697, 735, 749, 874, 1017, 1038, 1056, 1215, 1241, 1370, 1379, 1456, 2934, 2986, 3271 cm^{-1}. ^1H NMR ($CDCl_3$, 295 K): δ = 1.26 (s, C–CH_3), 1.30 (d, 5-Me), 1.44 (s, C–CH_3), 3.68 (m, 5-H), 3.97 (d, 2-H), 4.57 (dd, 4-H), 4.93 (ddd, 3-H), 4.94, 5.03 (2 dd, J = 12.0 and 7.8 Hz, J = 12.0 and 8.8 Hz, CH_2Ph), 5.09, 5.12 (2 dd, J = 12.0 and 9.0 Hz, J = 12.0 and 8.2 ppm, CH_2Ph), 6.62 (s, NOH), 7.33 (m, 10 Har) ppm. J(2,3) = 1.2, J(2,P) = 12.4, J(3,4) = 6.6, J(3,P) = 8.8, J(4,5) = 5.2, J(5,Me) = 6.4 Hz. ^{13}C NMR ($CDCl_3$, 295 K): δ = 11.6 (5-Me), 24.4, 26.2 (CMe_2), 64.4 (d, C-5), 67.0 (d, J(CH_2,P) = 6.8 Hz, *C*H_2Ph), 68.3 [d, J(CH_2,P) = 6.3 Hz, *C*H_2Ph], 70.2 (d, C-2), 79.6 (d, C-3), 80.2 (C-4), 111.8 (*C*Me_2), 128,1, 128.4 128.5, 128.6 (*o*,*m*,*p*-C), 136.4 (*ipso*-C) ppm. J(2,P) = 144.0, J(3,P) = 5.2, J(5,P) = 2.1 Hz. $C_{22}H_{28}NO_6P$ (433.45): C 60.96, H 6.51, N 3.23, P 7.15; found C 60.7, H 6.5, N 3.4, P 6.7.

Diethyl (2*S*,3*R*,4*R*,5*S*)-3,4-Dihydroxy-5-methylpyrrolidine-2-phosphonate (7b): Phosphonate **6b** (135 mg, 0.44 mmol) was hydrogenolysed in EtOH (1.5 mL) and 1 N HCl (2.2 mL) over 5% Pd/C (20 mg) at room temp. for 48 h. The catalyst was then centrifuged off, washed with EtOH (3 × 1 mL) and the combined solvents were evaporated to give crude **7b** (130 mg, quant.) as the hydrochloride. This was purified over Amberlite IR-120 [H^+ form] with successive elution with H_2O, MeOH, NH_4OH, 0.5 N then 1 N. The NH_4OH phases were evaporated to give the amine **7b** (73 mg, 61%).

7b: Brown resin. R_f = 0.63 (EtOH). IR (KBr): $\tilde{\nu}$ = 974, 1033, 1130, 1162, 1226, 1394, 1445, 1640, 2984, 3388 cm^{-1}. ^1H NMR (CD_3OD, 295 K): δ = 1.15 (d, 5-Me), 1.33, 1.34 (2 t, 2 CH_2CH_3), 3.11 (qd, 5-H), 3.33 (t, 2-H), 3.77 (dd, 4-H), 4.16 (m, 2 CH_2CH_3), 4.41 (ddd, 3-H) ppm. J(2,3) = 7.6, J(2,P) = 7.3, J(3,4) = 4.3, J(3,P) = 16.2, J(4,5) = 2.8, J(5,5-Me) = 6.6, J(CH_2CH_3) = 7.1 Hz. ^{13}C NMR (CD_3OD, 295 K): δ = 14.0 (5-Me), 16.7 (d, 2 CH_2CH_3), 57.9 (d, C-5), 59.2 (d, C-2), 63.9, 64.0 (2 d, 2 CH_2CH_3), 75.2 (d, C-4), 76.1 (d, C-3) ppm. J(2,P) = 166.7, J(3,P) = 2.1, J(4,P) = 7.1, J(5,P) = 4.9, J(CH_2CH_3,P) = 5.7, J(CH_2CH_3,P) = 6.7 Hz. ^{31}P NMR ($CDCl_3$, 295 K): δ = 27.1 ppm. MS (TOF ES$^+$): *m*/*z* (%) = 116 (20), 254 (100) $[M + H]^+$, 507 (45) $[2M + H]^+$. HRMS (TOF ES$^+$) for $C_9H_{21}NO_5P$ $[M + H]^+$: calcd. 254.1157; found 254.117.

Hydrochloride 7b·HCl: ^1H NMR (CD_3OD, 295 K): δ = 1.40, 1.41 (2 t, 2 CH_2CH_3), 1.41 (d, 5-Me), 3.63 (t, 2-H), 3.64 (qd, 5-H), 4.04 (dd, 4-H), 4.28 (m, 2 CH_2CH_3), 4.54 (ddd, 3-H) ppm. J(2,3) = 9.2, J(2,P) = 10.6, J(3,4) = 3.6, J(3,P) = 14.9, J(4,5) = 2.4, J(5,5-Me) = 6.8, J(CH_2CH_3) = 7.1 Hz. ^{13}C NMR (CD_3OD, 295 K): δ = 12.0 (5-Me), 16.7 (d, 2 CH_2CH_3), 55.7 (d, C-2), 60.4 (d, C-5), 65.3, 65.6 (2 d, 2 CH_2CH_3), 72.9 (d, C-4), 74.6 (C-3) ppm. J(2,P) = 158.2, J(4,P) = 10.0, J(5,P) = 2.0, J(CH_2CH_3,P) = 7.0, J(CH_2CH_3,P) = 5.7 Hz. ^{31}P NMR (CD_3OD, 295 K): δ = 18.3 ppm.

Dimethyl (2*S*,3*R*,4*R*,5*S*)-3,4-Dihydroxy-5-methylpyrrolidine-2-phosphonate Hydrochloride (7a·HCl): Following the same procedure as used for **7b** with **6a** (88 mg, 0.31 mmol) in EtOH (1 mL), 6 N HCl (1.6 mL) over 5% Pd/C (30 mg) for 30 h to give **7a** as the hydrochloride (30 mg, 43%). Yellowish resin. $[\alpha]_D^{20}$ = –13 (c = 1, MeOH). R_f = 0.69 (MeOH). IR (KBr): $\tilde{\nu}$ = 1042, 1124, 1156, 1187, 1237, 1403, 1452, 1631, 2984, 3417 cm^{-1}. ^1H NMR (CD_3OD, 295 K): δ = 1.41 (d, 5-Me), 3.68 (t, 2-H), 3.69 (m, 5-H), 3.91, 3.92 (2 d, 2 OCH_3), 4.04 (t, 4-H), 4.55 (ddd, 3-H) ppm. J(2,3) = 9.3, J(2,P) = 10.8, J(3,4) = 3.5, J(3,P) = 14.9, J(4,5) = ca. 2.0, J(5,5-Me) = 6.6, J(OCH_3,P) = 11.0 Hz. ^{13}C NMR (CD_3OD, 295 K): δ = 11.9 (5-Me), 54.7, 55.1 (2 d, 2 OCH_3), 55.2 (C-2), 60.4 (C-5), 72.9 (C-4), 74.6 (C-3) ppm. J(2,P) = 158.9, J(4,P) = 9.9, J(5,P) = 2.1, J(OCH_3,P) = 7.1 Hz. ^{31}P NMR (CD_3OD, 295 K): δ = 21.0 ppm. HRMS (ESI-Q-TOF) for $C_7H_{16}NO_5P$ $[M]^+$: calcd. 225.0766; found 225.0747. MS (TOF ES$^+$): *m*/*z* (%) = 116 (15), 212 (10), 226 (100) $[M + H]^+$.

(2*S*,3*R*,4*R*,5*S*)-*N*,3,4-Trihydroxy-5-methylpyrrolidine-2-phosphonic Acid, Hydrochloride (7c·HCl): Following the same procedure as used for **7b** with **6c** (175 mg, 0.4 mmol) in EtOH (1.5 mL), 1 N HCl (4 mL) over 5% Pd/C (50 mg) for 24 h to give **7c** as the hydrochloride (94 mg, quant.). Brown resin. $[\alpha]_D^{20}$ = +20 (c = 1, MeOH). ^1H NMR (D_2O, 295 K): δ = 1.46 (d, 5-Me), 3.82 (br. s, 2-H), 3.95 (br. s, 5-H), 4.31 (m, 4-H), 4.54, 4.74 (2 rotamers, 2 m, 3-H) ppm. J(5,5-Me) = 6.6 Hz. ^{13}C NMR (D_2O, 295 K): 2 rotamers M and m, δ = 8.2 (5-Me m), 9.2 (5-Me M), 66.3 (d, C-2 M), 67.7 (C-5 M), 71.2 (C-5 m, C-4 M + m), 71.9 (C-3 M + m), 74.5 (d, C-2 m) ppm. J(2,P) (M) = 147, J(2,P) (m) = 142 Hz. ^{31}P NMR (D_2O): 8.1 ppm. MS (TOF ES$^+$): 214 (28) $[M + H]^+$, 427 (100) $[2M + H]^+$, 640 (27) $[3M + H]^+$.

Diethyl [2*R*,3*S*,4*R*,5*S*]-(*N*-Hydroxy-3,4-isopropylidenedioxy-5-methylpyrrolidin-2-yl)methanephosphonate (9): A solution of BuLi (1.6 M in hexane) (0.36 mL, 0.58 mmol, 2 equiv.) was added dropwise to a solution of freshly distilled methanephosphonate (**8**) (85 µL, 0.58 mmol, 2 equiv.) in THF (2 mL) at –78 °C. The white mixture was further stirred at –78 °C for 15 min and then added to a solution of nitrone **4**[12] (50 mg, 0.29 mmol) in THF (1 mL) at –78 °C. After stirring at –78 °C for a further 2 h, aqueous 20% NH_4Cl was added and the mixture extracted with AcOEt (3 × 10 mL). The organic phases were dried (Na_2SO_4) and evaporated to give pure **9** (93 mg, 98%). Colourless resin. $[\alpha]_D^{20}$ = +26 (c = 1, $CHCl_3$). R_f = 0.63 (diethyl ether/MeOH, 9:1). ^1H NMR ($CDCl_3$, 295 K): δ = 1.23 (d, 5-Me), 1.29 (s, C-Me), 1.35 (t, 2 CH_2CH_3), 1.45 (s, C-Me), 1.59 (ddd, 1′-Hb), 2.56 (ddd, 1′-Ha), 2.99 (quint, 5-H), 3.68 (td, 2-H), 4.10 (m, 2 CH_2CH_3), 4.53 (t, 4-H), 4.72 (d, 3-H), 6.53 (s, OH) ppm. J(1′a,2) = 2.5, J(1′b,2) = 11.8, J(1′a,1′b) = 15.3, J(1′a,P) = 20.8, J(1′b,P) = 18.3, J(2,3) = 0, J(2,P) = 9.9, J(3,4) = 6.8, J(4,5) = 5.2, J(5,5-Me) = 6.3, J(CH_2CH_3) = 7.0 Hz. ^{13}C NMR ($CDCl_3$, 295 K): δ = 11.9 (5-Me), 16.2 16.3 (2 d, 2 CH_2CH_3), 19.5 (d, C-1′), 24.0, 25.5 (CMe_2), 61.1 (C-5), 61.7, 61.8 (2 d, 2 CH_2CH_3), 63.9 (C-2), 77.3 (C-4), 80.0 (C-3), 110.7 (CMe_2) ppm. J(1′,P) = 140.6, J(CH_2CH_3,P) = 7.0, J(CH_2CH_3,P) = 6.4 Hz. ^{31}P NMR ($CDCl_3$, 295 K): δ = 31.7 ppm. HRMS (ESI-Q-TOF): calcd. for $C_{13}H_{27}NO_6P$ $[M]^+$: 323.1498; found 323.1503.

Diethyl (2*R*,3*S*,4*R*,5*S*)-(3,4-Dihydroxy-5-methylpyrrolidin-2-yl)-methanephosphonate (10): Following the same procedure as used for **7b** with **9** (200 mg, 0.6 mmol) in EtOH (2 mL) and 1 N HCl (3 mL) over 5% Pd/C (50 mg) at room temp. for 24 h. Crude **10** as the hydrochloride was purified on Amberlite IR-120 with successive elution with H_2O, EtOH, 0.5 N NH_4OH and 1 N NH_4OH. Evaporation of the NH_4OH phases gave **10** (113 mg, 68%).

10: Yellowish resin. $[\alpha]_D^{20}$ = –35 (c = 1, MeOH). R_f = 0.53 (EtOH). IR (KBr): $\tilde{\nu}$ = 969, 1026, 1050, 1099, 1162, 1212, 1395, 1445, 1652, 2940, 2986, 3408 cm^{-1}. ^1H NMR (D_2O, 295 K): δ = 1.18 (d, 5-Me), 1.35 (t, 2 CH_2CH_3), 2.12 (td, 1′-Ha), 2.32 (dd, 1′-Hb), 3.42 (m, 2-H, 5-H), 4.00 (m, 3-H, 4-H), 4.18 (m, 2 CH_2CH_3) ppm. ^{13}C NMR (D_2O, 295 K): δ = 13.6 (5-Me), 16.0 (d, 2 CH_2CH_3), 29.0 (C-1′), 55.4 (C-5), 55.8 (C-2), 63.9, 64.0 (2 d, 2 CH_2CH_3), 73.3 (d, C-4), 78.4 (d, C-3) ppm. J(2,P) = 5.7, J(1′,P) = 142.0, J(3,P) = 14.8, J(4,P) = 1.4, J(CH_2CH_3,P) = 6.4, J(CH_2CH_3,P) = 7.2 Hz. ^{31}P NMR (D_2O, 295 K): δ = 32.7 ppm. HRMS (ESI-Q-TOF): calcd. for $C_{10}H_{32}O_5NP$ $[M]^+$: 267.1236; found 267.1239.

10·HCl: ^1H NMR (D_2O, 295 K): δ = 1.32 (d, 5-Me), 1.35 (t, 2 CH_2CH_3), 2.31 (td, 1′-Ha), 2.46 (dd, 1′-Hb), 3.61 (td, 2-H), 3.67 (qd, 5-H), 4.10 (td, 4-H), 4.14 (dd, 3-H), 4.21 (m, 2 CH_2CH_3) ppm. J(1′a,1′b) = 16.0, J(1′a,2) = 10.2, J(1′b,2) = 3.7, J(1′a,P) = 16.0, J(1′b,P) = 19.7, J(2,P) = 8.8, J(2,3) = 8.8, J(3,4) = 3.8, J(4,5) = 2.9, J(5,5-Me) = 6.8, J(CH_2CH_3) = 7.0 Hz. ^{13}C NMR (D_2O, 295 K): δ = 12.1 (CH_3), 15.9 (d, 2 CH_2CH_3), 27.3 (d, C-1′), 55.8 (d, C-2), 56.8 (C-5), 64.2, 64.3 (2 d, 2 CH_2CH_3), 72.8 (C-4), 77.3 (C-3) ppm. ^{31}P NMR (D_2O, 295 K): δ = 31.7 ppm.

1,3-Dipolar Cycloaddition: A solution of nitrone **4**[12] (200 mg, 1.17 mmol) in C_2Cl_4 (1 mL) was stirred at 50 °C with vinylphosphonate **11** (0.360 mL, 2 equiv., 2.34 mmol) for 16 h. The solution was evaporated to give a mixture of cycloadducts **12a**,**b** and **13a**,**b** in the proportions 30:52:13:6 (quant. yield) and resolved by chromatography (diethyl ether/EtOH, 95:5) to give mixture of **12b**,**13b** (200 mg, R_f = 0.49, 51%) and of **12a**,**13a** (190 mg, R_f = 0.34, 48%).

Mixture of Isomers 12b and 13b: Diethyl (2*S*,3a*S*,4*S*,5*R*,6*S*)-4,5-Isopropylidenedioxy-6-methylhexahydropyrrolo[1,2-*b*]isoxazole-2-phosphonate (12b) and Diethyl (3*S*,3a*R*,4*S*,5*R*,6*S*)-4,5-Iso-

propylidenedioxy-6-methylhexahydropyrrolo[1,2-*b*]isoxazole-3-phosphonate (13b)

12b: Colourless resin. $[\alpha]_D^{20}$ = +25 (*c* = 1, $CHCl_3$). R_f = 0.49 (diethyl ether/MeOH, 95:5). IR (CH_2Cl_2): 790, 877, 964, 1026, 1053, 1165, 1211, 1233, 1246, 1373, 1381, 1457, 1630, 1713, 2913, 2936, 2986 cm^{-1}. ^1H NMR ($CDCl_3$, 295 K): δ = 1.28 (d, 6-Me), 1.31 (s, C–CH_3), 1.32, 1.35 (2 t, 2 CH_2CH_3), 1.49 (s, C–CH_3), 2.19 (tdd, 3-Ha), 2.56 (tdd, 3-Hb), 3.38 (quint, 6-H), 3.79 (dd, 3a-H), 4.13 (m, CH_2CH_3), 4.22 (m, CH_2CH_3, 2-H), 4.67 (dd, 5-H), 4.68 (d, 4-H) ppm. *J*(2,3-Ha) = 11.3, *J*(2,3-Hb) = 5.5, *J*(2,P) not determined, *J*(3-Ha,3-Hb) = 12.3, *J*(3-Ha,3a-H) = 10.9, *J*(3-Ha,P) = 20.4, *J*(3-Hb,3a-H) = 7.2, *J*(3-Hb,P) = 7.8, *J*(3a-H,4) = ca. 0, *J*(4,5) = 6.6, *J*(5,6) = 3.8, *J*(6,6-Me) = 6.5, *J*(CH_3CH_2) = 7.1 Hz. ^1H NMR (C_6D_6, 295 K): δ = 1.01, 1.11 (t, CH_2CH_3), 1.19, 1.54 (2 s, CMe_2), 1.54 (d, 6-Me), 1.88 (dddd, 3-Hb), 2.11 (dddd, 3-Ha), 3.54 (qd, 6-H), 3.66 (dd, 3a-H), 3.87 (m, CH_2CH_3), 4.02 (ddd, 2-H), 4.14 (m, CH_2CH_3), 4.24 (dd, 5-H), 4.25 (d, 4-H) ppm. *J*(2,P) = 2.4, *J*(2,3-Ha) = 11.0, *J*(2,3-Hb) = 7.9, *J*(3-Hb,3-Ha) = 12.1, *J*(3-Ha,3a-H) = 11.0, *J*(3-Ha,P) = 21.0, *J*(3-Hb,3a-H) = 7.2, *J*(3-Hb,P) = 5.7, *J*(3a-H,4) = ca. 0, *J*(4,5) = 6.5, *J*(5,6) = 4.5, *J*(6,Me) = 6.4, *J*(CH_3CH_2) = 7.1 Hz. ^{13}C NMR ($CDCl_3$, 295 K): δ = 12.8 (6-Me), 16.3 (2 d, 2 CH_2CH_3), 24.9, 25.9 (CMe_2), 33.7 (C-3), 62.1, 63.4 (2 d, 2 CH_2CH_3), 64.1 (C-6), 70.8 (d, C-3a), 75.2 (d, C-2), 79.5 (C-4), 80.6 (C-5), 111.3 (CMe_2) ppm. *J*(2,P) = 166.7, *J*(3a,P) = 7.1, *J*(CH_2CH_3,P) = 5.7, *J*(CH_2CH_3,P) = 6.7 Hz ^{31}P NMR ($CDCl_3$, 295 K): δ = 23.5 ppm. $C_{14}H_{26}O_6NP$ (335.34): C 50.14, H 7.82, N 4.18, P 9.24; found C 50.2, H 8.0, N 4.1, P 9.2.

13b: ^1H NMR ($CDCl_3$, 295 K), partial data: δ = 1.25 (d, 6-Me), 3.02 (sext, 3-H), 3.20 (quint, 6-H), 3.90 (dd, 3a-H), 4.10 (m, 2-Ha, 2-Hb), 4.64 (dd, 5-H), 5.17 (d, 4-H) ppm. *J*(2a,3) = *J*(2b,3) = 9.8, *J*(3,3a) = 11.0, *J*(3,P) = 17.6, *J*(3a,P) = 15.4, *J*(3a,4) = 0, *J*(4,5) = 6.6, *J*(5,6) = 5.2, *J*(6,6-Me) = 6.6 Hz.

Mixture of Isomers 12a and 13a: Diethyl (2*R*,3a*S*,4*S*,5*R*,6*S*)-4,5-Isopropylidenedioxy-6-methylhexahydropyrrolo[1,2-*b*]isoxazole-2-phosphonate (12a) and Diethyl (3*R*,3a*R*,4*S*,5*R*,6*S*)-4,5-Isopropylidenedioxy-6-methylhexahydropyrrolo[1,2-*b*]isoxazole-3-phosphonate (13a). Mixture of 12a and 13a: Colourless resin. $[\alpha]_D^{20}$ = +70 (*c* = 1, $CHCl_3$). R_f = 0.34 (diethyl ether/MeOH, 95:5). IR (CH_2Cl_2): $\tilde{\nu}$ = 752, 794, 876, 967, 1022, 1054, 1133, 1144, 1164, 1212, 1234, 1378, 1448, 1458, 1652, 2937, 2986 cm^{-1}.

12a: ^1H NMR ($CDCl_3$, 295 K): δ = 1.31 (d, 6-Me), 1.31 (s, C–CH_3), 1.34 (2 t, 2 CH_2CH_3), 1.40 (s, C–CH_3), 2.17 (dddd, 3-Hb), 2.68 (dddd, 3-Ha), 2.88 (m, 6-H), 3.83 (t, 3a-H), 4.15–4.25 (m, 2 CH_2CH_3), 4.47 (ddd, 2-H), 4.64, 4.65 (m, 4-H, 5-H) ppm. *J*(2,3-Ha) = 5.1, *J*(2,3-Hb) = 10.6, *J*(2,P) = 2.0, *J*(3-Ha,3-Hb) = 13.1, *J*(3-Ha,3a-H) = 9.0, *J*(3-Ha,P) = 19.0, *J*(3-Hb,3a-H) = 9.6, *J*(3-Hb,P) = 21.1, *J*(3a-H,4) = ca. 0, *J*(4,5) = 7.3, *J*(5,6) = 4.3, *J*(6,6-Me) = 6.3, *J*(CH_3CH_2) = 7.1 Hz. ^{13}C NMR ($CDCl_3$, 295 K): δ = 12.9 (6-Me), 16.3 (2 d, 2 CH_2CH_3), 24.9, 25.9 (C-Me_2), 33.8 (d, C-3), 61.7 (C-6), 62.8, 62.9 (2 d, 2 CH_2CH_3), 70.3 (C-3a), 72.0 (d, C-2), 80.0 (C-4), 80.3 (C-5), 111.4 (CMe_2) ppm. *J*(2,P) = 170.3, *J*(3,P) = 1.0, *J*(3a,P) = 3.7, *J*(CH_3CH_2,P) = 5.6, *J*(CH_3CH_2,P) = 6.2 Hz. ^{31}P NMR ($CDCl_3$, 295 K): δ = 21.9 ppm.

13a: ^1H NMR ($CDCl_3$, 295 K): δ = 1.30 (d, 6-Me), 1.35, 1,36 (2 t, 2 CH_2CH_3), 1.36, 1.51 (2 s, CMe_2), 2.54 (dtd, 3-H), 2.88 (qd, 6-H), 3.87 (dd, 3a-H), 4.09 (td, 2-Ha), 4.15–4.25 (m, 2 CH_2CH_3), 4.29 (ddd, 2-Hb), 4.64 (dd, 5-H), 4.75 (d, 4-H) ppm. *J*(2a,2b) = 8.7, *J*(2a,3) = 7.9, *J*(2a,P) = 17.0, *J*(2b,3) = 10.2, *J*(2b,P) = 12.3, *J*(3,3a-H) = 10.0, *J*(3,P) = 15.3, *J*(3a-H,P) = 15.1, *J*(3a-H, 4) = 0, *J*(4,5) = 6.5, *J*(5,6) = 5.1, *J*(6,6-Me) = 6.5, *J*(CH_3CH_2) = 7.1 Hz. ^{13}C NMR ($CDCl_3$, 295 K): δ = 12.8 (6-Me), 16.4 (2 d, 2 CH_2CH_3), 24.9, 25.9 (CMe_2), 41.9 (d, C-3), 61.8 (C-6), 62.3, 62.5 (2 d, 2 CH_2CH_3), 67.2 (d, C-2), 72.0 (C-3a), 79.9 (d, C-4), 80.3 (C-5), 111.4 (CMe_2) ppm. *J*(2,P) = 2.1, *J*(3,P) = 150.5, *J*(4,P) = 2.1, *J*(CH_2CH_3,P) = 5.7, *J*(CH_2CH_3,P) = 7.1 Hz. ^{31}P NMR ($CDCl_3$, 295 K): δ = 27.6 ppm.

Diethyl (1′*S*,2*S*,3*S*,4*R*,5*S*)-1′-Hydroxy-2′-(3,4-isopropylidenedioxy-5-methylpyrrolidin-2-yl)ethanephosphonate (14b): A solution of **12b** (200 mg, 0.6 mmol) in EtOH (2 mL) was hydrogenolysed over 5% Pd/C (30 mg) at 40 °C for 48 h. The catalyst was centrifuged off and washed with EtOH. The combined solvents were evaporated and the resulting resin purified by chromatography (diethyl ether/MeOH, 95:5) to give **14b** (120 mg, 61%). Colourless resin. $[\alpha]_D^{20}$ = +15 (*c* = 1, $CHCl_3$). R_f = 0.22 (diethyl ether/MeOH, 95:5). IR (KBr): $\tilde{\nu}$ = 873, 967, 1052, 1083, 1164, 1211, 1249, 1382, 1450, 1625, 2935, 2984, 3253, 3400 cm^{-1}. ^1H NMR ($CDCl_3$, 295 K): δ = 1.19 (d, 5-Me), 1.30 (s, CCH_3), 1.34, 1.35 (2 t, 2 CH_2CH_3), 1.45 (s, CCH_3), 1.65–1.80 (m, CH_2-2′), 3.23 (qd, 5-H), 3.42 (m, 2-H), 4.13–4.25 (m, 2 CH_2CH_3, 1′-H), 4.40 (d, 3-H), 4.50 (dd, 4-H) ppm. *J*(2,CH_2-2′) = 5.4 and 11.0, *J*(2,3) = 0, *J*(3,4) = 5.2, *J*(4,5) = 4.0, *J*(5,5-Me) = 6.6, *J*(CH_3CH_2) = 7.0 Hz. ^{13}C NMR ($CDCl_3$, 295 K): δ = 13.0 (5-Me), 16.5 (2 d, 2 CH_2CH_3), 23.9, 26.0 (CMe_2), 28.7 (d, C-2′), 55.3 (C-5), 62.1, 62.8 (2 d, 2 CH_2CH_3), 66.0 (C-2), 69.1 (d, C-1′), 82.7 (C-4), 87.0 (d, C-3), 111.0 (CMe_2) ppm. *J*(1′,P) = 173.1, *J*(2,P) = 19.1, *J*(2′,P) = 1.4, *J*(3,P) = 5.0, *J*(CH_2CH_3,P) = 5.7, *J*(CH_2CH_3,P) = 7.1 Hz. ^{31}P NMR ($CDCl_3$, 295 K): δ = 24.2 ppm. HRMS (ESI-Q-TOF) for $C_{14}H_{28}NO_6P$ $[M]^+$: calcd. 337.1654; found 337.1656.

Diethyl (1′*R*,2*S*,3*S*,4*R*,5*S*)-1′-Hydroxy-2′-(3,4-isopropylidenedioxy-5-methylpyrrolidin-2-yl)ethanephosphonate (14a) and Diethyl (2′*R*,2*S*,3*S*,4*R*,5*S*)-2′-Hydroxy-1′-(3,4-isopropylidenedioxy-5-methylpyrrolidin-2-yl)ethanephosphonate (15): Following the same procedure as used for **14b** with the mixture of **12a** and **13a** (200 mg, 0.6 mmol). Separation by chromatography (diethyl ether/MeOH, 95:5) gave **14a** (86 mg, 43%) and **15** (52 mg, 25%).

14a: Colourless resin. $[\alpha]_D^{20}$ = +19 (*c* = 1, $CHCl_3$). R_f = 0.33 (diethyl ether/MeOH, 95:5). IR (KBr): $\tilde{\nu}$ = 875, 952, 967, 1024, 1046, 1167, 1211, 1243, 1271, 1373, 1381, 1450, 1620, 2877, 2934, 2986, 3237, 3390, 3499 cm^{-1}. ^1H NMR ($CDCl_3$, 295 K): δ = 1.19 (d, 5-Me), 1.30 (s, C–CH_3), 1.34, 1.35 (2 t, 2 CH_2CH_3), 1.45 (s, C–CH_3), 1.75–1.92 (m, CH_2-2′), 3.19 (qd, 5-H), 3.88 (m, 2-H), 4.12 (m, 1′-H), 4.13–4.25 (m, 2 CH_2CH_3), 4.37 (d, 3-H), 4.50 (dd, 4-H) ppm. *J*(2,CH_2-2′) = ca. 5.0 and 12.0, *J*(2,3) = 0, *J*(3,4) = 5.5, *J*(4,5) = 4.0, *J*(5,5-Me) = 6.6, *J*(CH_3CH_2) = 7.0 Hz. ^{13}C NMR ($CDCl_3$, 295 K): δ = 13.1 (5-Me), 16.4, 16.5 (2 d, 2 CH_2CH_3), 23.9, 26.0 (CMe_2), 28.6 (d, C-2′), 55.3 (C-5), 62.0 (d, CH_2CH_3), 62.3 (d, C-2), 62.8 (d, CH_2CH_3), 67.7 (d, C-1′), 82.9 (C-4), 87.3 (C-3), 110.9 (CMe_2) ppm. *J*(1′,P) = 162.5, *J*(2,P) = 4.9, *J*(2′,P) = 2.8, *J*(CH_2CH_3,P) = 4.9, *J*(CH_2CH_3,P) = 7.1 Hz. ^{31}P NMR ($CDCl_3$, 295 K): δ = 25.6 ppm. HRMS (ESI-Q-TOF) for $C_{14}H_{28}NO_6P$ $[M]^+$: calcd. 337.1654; found 337.1655.

15: Colourless resin. $[\alpha]_D^{20}$ = +22 (*c* = 1, $CHCl_3$). R_f = 0.32 (CH_2Cl_2/EtOH, 98:2). ^1H NMR ($CDCl_3$, 295 K): δ = 1.20 (d, 5-Me), 1.31 (s, C–CH_3), 1.33, 1.34 (2 t, 2 CH_2CH_3), 1.46 (s, C–CH_3), 2.07 (dddd, 1′-H), 3.11 (qd, 5-H), 3.52 (dd, 2-H), 3.86 (ddd, 2′-Ha), 3.97 (ddd, 2′-Hb), 4.08–4.19 (m, 2 CH_2CH_3), 4.50 (dd, 4-H), 5.12 (d, 3-H) ppm. *J*(1′,2) = 12.2, *J*(1′,2′a) = 9.6, *J*(1′,2′b) = 3.0, *J*(1′,P) = 21.0, *J*(2,P) = 7.8, *J*(2′a,2′b) = 11.4, *J*(2′a,P) = 2.7, *J*(2′b,P) = 7.8, *J*(2,3) = 0, *J*(3,4) = 5.4, *J*(4,5) = 3.9, *J*(5,5-Me) = 6.6, *J*(CH_3CH_2) = 7.0 Hz. ^{13}C NMR ($CDCl_3$, 295 K): δ = 13.0 (5-Me), 16.4 (2 d, 2 CH_2CH_3), 24.0, 26.0 (CMe_2), 38.5 (d, C-2′), 55.7 (C-5), 62.0, 62.1 (2 d, 2 CH_2CH_3), 63.0 (C-1′), 66.3 (d, C-2), 82.5 (C-4), 85.9 (C-3), 110.6 (CMe_2) ppm. *J*(1′,P) = 132.1, *J*(2,P) = 2.0, *J*(CH_2CH_3,P) = 5.7, *J*(CH_2CH_3,P) = 7.1 Hz. ^{31}P NMR ($CDCl_3$, 295 K): δ =

28.1 ppm. HRMS (ESI-Q-TOF) for $C_{14}H_{28}O_6NP$ $[M]^+$: calcd. 337.1654; found 337.1660.

Diethyl (1′*S*,2*S*,3*S*,4*R*,5*S*)-2′-(3,4-Dihydroxy-5-methylpyrrolidin-2-yl)-1′-hydroxyethanephosphonate Hydrochloride (16b·HCl): A solution of **14b** (100 mg, 0.29 mmol) was stirred in EtOH (0.1 mL) and 6 N HCl (0.3 mL) at room temp. for 16 h. The solvent was evaporated to give **16b** as the hydrochloride (88 mg, 90%). Yellowish resin. $[\alpha]_D^{20}$ = –13 (*c* = 1, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 980, 1029, 1060, 1130, 1165, 1207, 1395, 1444, 1638, 3000, 3380 cm^{-1}. ^1H NMR (D_2O, 295 K): δ = 1.34, 1.35 (2 t, 2 CH_2CH_3), 1.37 (d, 5-Me), 2.15 (tdd, 2′-Hb), 2.27 (tdd, 2′-Ha), 3.64 (td, 2-H), 3.79 (qd, 5-H), 4.13 (t, 4-H), 4.19 (dd, 3-H), 4.22 (m, 2 CH_2CH_3), 4.28 (ddd, 1′-H) ppm. J(1′,2′a) = 2.8, J(1′,2′b) = 11.6, J(1′,P) = 5.8, J(2,2′a) = 4.8, J(2,2′b) = J(2,3) = 8.8, J(2′a,2′b) = 14.9, J(2′a,P) = 3.8, J(2′b,P) = 8.8, J(3,4) = 3.8, J(4,5) = 2.8, J(5,5-Me) = 6.8, J(CH_3CH_2) = 7.0 Hz. ^{13}C NMR (D_2O, 295 K): δ = 11.6 (5-Me), 16.2, 16.3 (2 d, 2 CH_2CH_3), 32.0 (d, C-2′), 57.5 (C-5), 59.7 (d, C-2), 64.8, 65.1 (2 d, 2 CH_2CH_3), 65.3 (d, C-1′), 71.6 (C-4), 76.4 (C-3) ppm. J(1′,P) = 166.7, J(2,P) = 19.1, J(2′,P) = 3.5, J(CH_2CH_3,P) = 4.2, J(CH_2CH_3,P) = 7.8 Hz. ^{31}P NMR (D_2O, 295 K): δ = 25.9 ppm. HRMS (ESI-Q-TOF) for $C_{11}H_{24}NO_6P$ $[M]^+$: calcd. 297.1341; found 297.1329.

Diethyl (1′*R*,2*S*,3*S*,4*R*,5*S*)-2′-(3,4-Dihydroxy-5-methylpyrrolidin-2-yl)-1′-hydroxyethanephosphonate, hydrochloride (16a·HCl): Following the same procedure as used for **14b** with **14a** (100 mg, 0.29 mmol) in EtOH (0.1 mL) and 6 N HCl (0.3 mL) at room temp. for 16 h to give **16a** as the hydrochloride (88 mg, 90%). Yellowish resin. $[\alpha]_D^{20}$ = –31 (*c* = 1, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 568, 795, 977, 1023, 1040, 1161, 1219, 1395, 1443, 1640, 2942, 2986, 3390 cm^{-1}. ^1H NMR (CD_3OD, 295 K): δ = 1.36 (t, 2 CH_2CH_3), 1.39 (d, 5-Me), 2.17 (tdd, 2′-Hb), 2.23 (tdd, 2′-Ha), 3.72 (qd, 5-H), 3.82 (td, 2-H), 4.00 (t, 4-H), 4.06 (dd, 3-H), 4.15 (ddd, 1′-H), 4.17–4.25 (m, 2 CH_2CH_3) ppm. J(1′,2′a) = 9.0, J(1′,2′b) = 4.3, J(1′,P) = 7.3, J(2,2′a) = 3.4, J(2,2′b) = 9.7, J(2,3) = 9.1, J(2′a,2′b) = 15.3, J(2′a,P) = 9.2, J(2′b,P) = 12.6, J(3,4) = 3.6, J(4,5) = 2.8, J(5,5-Me) = 6.8, J(CH_3CH_2) = 7.0 Hz. ^{13}C NMR (CD_3OD, 295 K): δ = 12.2 (5-Me), 16.8, 16.9 (2 d, 2 CH_2CH_3), 32.7 (d, C-2′), 58.2 (C-5), 59.0 (d, C-2), 64.3, 64.6 (2 d, 2 CH_2CH_3), 65.1 (d, C-1′), 72.8 (C-4), 77.1 (C-3) ppm. J(1′,P) = 168.1, J(2,P) = 12.0, J(2′,P) = 2.8, J(CH_2CH_3,P) = 4.9, J(CH_2CH_3,P) = 7.0 Hz. ^{31}P NMR (CD_3OD, 295 K): δ = 22.7 ppm. HRMS (ESI-QTOF) for $C_{11}H_{24}NO_6P$ $[M]^+$: calcd. 297.1341; found 297.1328.

Diethyl (1′*R*,2*R*,3*S*,4*R*,5*S*)-1′-(3,4-Dihydroxy-5-methylpyrrolidin-2-yl)-2′-hydroxyethanephosphonate, hydrochloride (17·HCl): Following the same procedure as used for **14b** with **15** (35 mg, mmol) in EtOH (0.2 mL) and 6 N HCl (0.3 mL) at room temp. for 16 h to give **17** as the hydrochloride (30 mg, 87%). Orange resin. $[\alpha]_D^{20}$ = –8 (*c* = 1, MeOH). IR (KBr): $\tilde{\nu}$ = 790, 977, 1018, 1039, 1125, 1160, 1224, 1395, 1638, 2987, 3418 cm^{-1}. ^1H NMR (CD_3OD, 295 K): δ = 1.38 (2 t, 2 CH_2CH_3), 1.41 (d, 5-Me), 2.46 (dq, 1′-H), 3.76 (qd, 5-H), 3.88 (ddd, 2-H), 4.03 (m, 4-H), 4.13 (ddd, 2′-Ha), 4.19 (ddd, 2′-Hb), 4.17–4.28 (m, 2 CH_2CH_3), 4.46 (dd, 3-H) ppm. J(1′,2) = 3.0, J(1′,2′a) = 4.5, J(1′,2′b) = 3.6, J(1′,P) = 23.8, J(2′a,2′b) = 11.6, J(2′a,P) = 9.6, J(2′b,P) not determined, J(2,3) = 9.3, J(2,P) = 12.1, J(3,4) = 3.5, J(4,5) = 2.5, J(4,P) = 1.6, J(5,5-Me) = 6.8, J(CH_2CH_3) = 7.0 Hz. ^{13}C NMR (CD_3OD, 295 K): δ = 12.0 (5-Me), 16.7 (2 d, 2 CH_2CH_3), 37.9 (d, C-1′), 58.7 (d, C-2′), 59.1 (C-5), 61.0 (d, C-2), 64.3, 64.4 (2 d, 2 CH_2CH_3), 72.9 (C-4), 74.7 (d, C-3) ppm. J(1′,P) = 140.6, J(2,P) = 4.2, J(2′,P) = 3.0, J(3,P) = 10.6, J(CH_2CH_3,P) = 5.7, J(CH_2CH_3,P) = 7.0 Hz. ^{31}P NMR (CD_3OD, 295 K): δ = 26.2 ppm. HRMS (ESI-Q-TOF) for $C_{11}H_{24}NO_6P$ $[M]^+$: calcd. 297.1341; found 297.1346.

Diethyl (2*S*,3a*S*,4*S*,5*R*,6*S*)-4,5-Dihydroxy-6-methylhexahydropyrrolo[1,2-*b*]isoxazole-2-phosphonate (18): A solution of **12b** (135 mg, 0.4 mmol) in ethanol (1 mL) and 6 N HCl (1 mL) was stirred at room temp. for 16 h. After evaporation of the solvent, the resulting resin was purified by chromatography (AcOEt/EtOH, 7:3) to give **18** (111 mg, 93%). Colourless resin. $[\alpha]_D^{20}$ = +32 (*c* = 1, MeOH). R_f = 0.35 (AcOEt/EtOH, 7:3), R_f = 0.2 (diethyl ether/MeOH, 95:5). IR (KBr): $\tilde{\nu}$ = 544, 592, 655, 773, 789, 976, 1028, 1051, 1161, 1229, 1446, 1652, 2950, 2990, 3386 cm^{-1}. ^1H NMR (D_2O, 295 K): δ = 1.21 (d, 5-Me), 1.35 (2 t, 2 CH_2CH_3), 2.40 (dddd, 3-Ha), 2.90 (dddd, 3-Hb), 3.50 (qd, 6-H), 3.75 (q, 3a-H), 4.19–4.27 (m, 2 CH_2CH_3), 4.25–4.30 (m, 4-H, 5-H), 4.41 (dd, 2-H) ppm. J(2,3-Hb) = 7.4, J(2,3-Ha) = 10.4, J(2,P) = 1.0, J(3-Ha,3-Hb) = 12.6, J(3-Ha,P) = 18.4, J(3-Ha,3a-H) = 7.0, J(3-Hb,3a-H) = 8.2, J(3-Hb,P) = 5.9, J(3a-H,4) = 5.8, J(4,5) not determined, J(5,6) = 4.0, J(6,6-Me) = 6.9, J(CH_2CH_3) = 7.1 Hz. ^{13}C NMR (D_2O, 295 K): δ = 12.8 (6-Me), 16.1 (d, 2 CH_2CH_3), 35.4 (C-3), 65.1, 65.3 (2d, 2 CH_2CH_3), 65.9 (C-6), 69.2 (d, C-3a), 74.4 (d, C-2), 75.6, 75.8 (C-4, C-5) ppm. J(2,P) = 167.4, J(3a,P) = 8.5, J(CH_2CH_3,P) = 4.9, J(CH_2CH_3,P) = 7.1 Hz. ^{31}P NMR (D_2O, 295 K): δ = 23.5 ppm. HRMS (TOF ES^+) for $C_{11}H_{23}NO_6P$ $[M + H]^+$: calcd. 296.1; found 296.2.

Diethyl (1′*S*,2*S*,3*S*,4*R*,5*S*)-2′-(*N*-Benzyloxycarbonyl-3,4-isopropylidenedioxy-5-methylpyrrolidin-2-yl)-1′-hydroxyethanephosphonate (19): A suspension of **14b** (315 mg, 0.93 mmol) in dry EtOH (3.2 mL) under Ar with $NaHCO_3$ (157 mg, 1.87 mmol, 2 equiv.) and benzyl chloroformate (0.145 mL, 1.03 mmol, 1.1 equiv.) was stirred for 8 h at room temp. The solids were centrifuged off and washed with CH_2Cl_2. The combined organic phases were evaporated. The crude product was purified by chromatography (AcOEt) to obtain **19** (230 mg, 52%). Colourless crystals. M.p. 74–75 °C. $[\alpha]_D^{20}$ = +65 (*c* = 1, $CHCl_3$). R_f = 0.63 (diethyl ether/MeOH, 95:5), R_f = 0.27 (AcOEt). IR (KBr): $\tilde{\nu}$ = 981, 1030, 1051, 1102, 1170, 1209, 1242, 1291, 1410, 1712, 2936, 2987, 3302 cm^{-1}. ^1H NMR ($CDCl_3$, 328 K): δ = 1.29, 1.31 (2 t, CH_2CH_3), 1.32 (s, C–CH_3), 1.40 (br. s, 5-Me), 1.47 (s, C–CH_3), 2.00, 2.11 (2 br. s, CH_2-2′), 2.8–3.6 (br. s, 1′-OH), 3.87 (br. s, 1′-H), 3.91 (quint, 5-H), 4.05–4.18 (m, 2 CH_2CH_3), 4.28 (br. d, 2-H), 4.59 (d, 3-H), 4.69 (t, 4-H), 5.12, 5.13 (2 d, CH_2Ph), 7.28–7.35 (m, Ph) ppm. J(2,2′) = 7.2, J(2.3) = 0, J(3,4) = 6.0, J(4,5) = 6.3, J(5,5-Me) = 6.5, J(CH_2Ph) = 12.6, J(CH_2CH_3) = 7.0 Hz. ^{13}C NMR ($CDCl_3$, 295 K): δ = 14.8 (5-Me), 16.5 (d, 2 CH_2CH_3), 24.9, 26.0 (CMe_2), 32.9 (C-2′), 58.1 (C-5), 60.6 (C-2), 62.9 (d, 2 CH_2CH_3), 64.9 (d, C-1′), 66.9 (CH_2Ph), 80.5 (C-4), 83.4 (C-3), 111.4 (CMe_2), 128.1, 128.5 (*o*,*m*,*p*-C), 136.5 (*ipso*-C), ca. 155 (C=O) ppm. J(1′,P) = 163.0, J(CH_2CH_3,P) = 5.3, J(CH_2CH_3,P) = 7.0 Hz. ^{31}P NMR ($CDCl_3$, 295 K): δ = 25.3 ppm. HRMS (ESI-Q-TOF) for $C_{22}H_{34}NO_8P$ $[M]^+$: calcd. 471.2022; found 471.2012.

Diethyl (1′*S*,2*S*,3*S*,4*R*,5*S*)-2′-(*N*-Benzyloxycarbonyl-3,4-isopropylidenedioxy-5-methylpyrrolidin-2-yl)-1′-(imidazole-1′′-thiocarbonyloxy)ethanephosphonate (20): Thiocarbonyldiimidazole (174 mg, 0.98 mmol, 2 equiv.) was added to a solution of **19** (230 mg, 0.49 mmol) in dry THF (3 mL) under Ar at room temp. After stirring for 16 h at room temp., brine was added and the mixture extracted with AcOEt (3×20 mL). The organic phases were dried ($MgSO_4$), evaporated and the crude product was purified by chromatography (AcOEt) to give pure **20** (253 mg, 89%). Colourless resin. $[\alpha]_D^{20}$ = +23 (*c* = 1, $CHCl_3$). This compound is relatively unstable and was only characterised by NMR spectroscopy. ^1H NMR ($CDCl_3$, 328 K) 1.31 (br. s, 2 CH_2CH_3), 1.31, 1.43 (2 s, CMe_2), 1.45 (br. s, 5-Me), 2.10, 2.40, 2.70 (3 br. s, CH_2-2′), 3.87 (quint, *J* = 6.2 Hz, 5-H), 4.07 (br. s, 2-H), 4.15 (br. s, 2 CH_2CH_3), 4.54 (br. s, 3-H), 4.63 (br. s, 4-H), 4.95–5.25 (m, CH_2Ph), 6.19 (dt, *J* = 2 and 10 Hz, 1′-H), 6.96, 7.07 (2 br. s, 4-H′′ imidazole), 7.34

(s, Ph), 7.35, 7.70 (2 br. s, 5-H′′ imidazole), 8.10, 8.40 (2 br. s, 2-H′′ imidazole) ppm. ^{13}C NMR ($CDCl_3$, 295 K): δ = 15.3 (5-Me), 16.4, 16.5 (2 d, CH_2CH_3), 24.9, 25.8 (CMe_2), 31.1 (C-2′), 57.2 (C-5), 59.1 (d, C-2), 63.3, 63.6 (2 d, 2 CH_2CH_3), 67.0 (CH_2Ph), 73.5 (d, C-1′), 80.0 (C-4), 81.6 (C-3), 111.8 (CMe_2), 117.9 (C-5′′ Im), 128.2, 128.6 (Car), 131.2 (C-4′′ Im), 136.3 (*ipso*-C), 137.2 (C-2′′ Im), 154.5 (C=O), 183.3 (C=S) ppm. J(1′,P) = 166.0, J(2,P) = 15.5, J(CH_3CH_2,P) = 5.7, J(CH_2CH_3,P) = 6.4 Hz. ^{31}P NMR ($CDCl_3$, 295 K): δ = 18.5 ppm.

Diethyl (2*S*,3*S*,4*R*,5*S*)-2′-(*N*-Benzyloxycarbonyl-3,4-isopropylidenedioxy-5-methylpyrrolidin-2-yl)ethanephosphonate (21): A solution of **20** (220 mg, 0.38 mmol) was refluxed under Ar for 15 min in dry toluene. Bu_3SnH (0.155 mL, 0.97 mmol, 1.5 equiv.) and AIBN (1.5 mg, 0.008 mmol, 0.02 equiv.) were then added. The solution was refluxed for a further 2 h 45 min and $CHCl_3$ was then added in order to destroy the tin compounds. Evaporation of the solvent and purification by chromatography (AcOEt) gave pure **21** (125 mg, 76%). Colourless resin. $[\alpha]_D^{20}$ = +58 (c = 1, $CHCl_3$). R_f = 0.30 (AcOEt). ^{1}H NMR ($CDCl_3$, 295 K): δ = 1.29 (br. s, 2 CH_2CH_3), 1.32, 1.46 (2 s, CMe_2), 1.46 (br. s, 5-Me), 1.70 (br. s, CH_2-2′), 1.90–2.10 (br. m, CH_2-1′), 3.84 (br. s, 5-H), 4.02 (br. s, 2-H, 2 CH_2CH_3), 4.40 (d, 3-H), 4.61 (t, 4-H), 5.09, 5.14 (2 d, CH_2Ph), 7.29–7.35 (m, Ph) ppm. J(3,4) = 6.0, J(4,5) = 6.0, J(CH_2Ph) = 12.3 Hz. ^{13}C NMR ($CDCl_3$, 295 K), two rotamers: δ = 14.5, 15.9 (2 s, 5-Me), 16.4 (d, 2 CH_2CH_3), 22.1 (d, C-1′), 23.7, 24.7 (C-2′), 24.9, 25.9 (CMe_2), 56.6, 57.0 (C-5), 61.6 (d, 2 CH_2CH_3), 63.3 (C-2), 66.7 (CH_2Ph), 80.4 (C-4), 82.0 (C-3), 111.6 (CMe_2), 127.9, 128.4 (*o*,*m*,*p*-C), 136.4 (*ipso*-C), 154.8 (C=O) ppm. J(1′,P) = 144.0, J(CH_2CH_3,P) = 6.0, J(CH_2CH_3,P) = 6.4 Hz. ^{31}P NMR ($CDCl_3$, 295 K), two rotamers: δ = 31.7, 31.2 ppm. HRMS (ESI-Q-TOF) for $C_{22}H_{34}NO_7P$ $[M]^+$: calcd. 455.2073; found 455.2101.

Diethyl (2*S*,3*S*,4*R*,5*S*)-2′-(3,4-Dihydroxy-5-methylpyrrolidin-2-yl)-ethanephosphonate Hydrochloride (22·HCl): A solution of **21** (104 mg, 0.23 mmol) was stirred in EtOH (0.5 mL) and 6 N HCl (1.5 mL) for 16 h at room temp., then the solvent was evaporated and the crude product hydrogenolysed in EtOH (0.5 mL) and H_2O (0.5 mL) over 5% Pd/C (50 mg) at room temp. for 8 h. The catalyst was centrifuged off, washed with EtOH and H_2O (3 × 1 mL) and the combined solvents were evaporated to give pure **22** as the hydrochloride (66 mg, 91%). Colourless resin. $[\alpha]_D^{20}$ = –19 (c = 1, MeOH). IR (KBr): $\tilde{\nu}$ = 991, 1028, 1161, 1206, 1396, 1445, 1636, 2942, 2987, 3401 cm^{-1}. ^{1}H NMR (D_2O, 295 K): δ = 1.27 (t, 2 CH_2CH_3), 1.32 (d, 5-Me), 1.95–2.10 (m, CH_2-1′, CH_2-2′), 3.46 (q, 2-H), 3.74 (dq, 5-H), 4.07–4.17 (m, 2 CH_2CH_3, 3-H, 4-H) ppm. J(2,3) = J(2,CH_2-2′) = 7.0, J(4,5) = 2.5, J(5,5-Me) = 6.8, J(CH_2CH_3) = 7.0 Hz. ^{13}C NMR (D_2O, 295 K): δ = 11.6 (5-Me), 16.1 (d, 2 CH_2CH_3), 21.5 (d, C-1′), 24.0 (d, C-2′), 57.4 (C-5), 61.0 (d, C-2), 64.1 (d, 2 CH_2CH_3), 72.3 (C-4), 76.1 (C-3) ppm. J(1′,P) = 141.0, J(2,P) = 19.1, J(2′,P) = 4.2, J(CH_2CH_3,P) = 5.7, J(CH_2CH_3,P) = 6.4 Hz. ^{31}P NMR (D_2O, 295 K): δ = 34.3 ppm. HRMS (ESI-Q-TOF) for $C_{11}H_{24}NO_5P$ $[M]^+$: calcd. 281.1392; found 281.1374.

Oxidation into Nitrones

Diethyl (2*S*,3*R*,4*R*)-3,4-Isopropylidenedioxy-5-methyl-1-oxido-5-pyrrolinium-2-phosphonate (23) and Diethyl (3*R*,4*R*,5*S*)-3,4-Isopropylidenedioxy-5-methyl-1-oxido-1-pyrrolinium-2-phosphonate (24): A solution of **6b** (50 mg, 0.16 mmol) in $CHCl_3$ (0.5 mL) was stirred for 24 h with yellow HgO (42 mg, 0.19 mmol, 1.2 equiv.). Solids were centrifuged off and washed with CH_2Cl_2. The combined solvents were evaporated. The crude (85:15) mixture of nitrones **23** and **24** was resolved by TLC (Et_2O/EtOH, 97:3) to give **23** (26 mg, 53%) and **24** (8 mg, 15%).

23: Yellowish resin. $[\alpha]_D^{20}$ = +14 (c = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 295 K): δ = 1. 36 (t, CH_2CH_3), 1.37 (s, C–CH_3), 1.40 (t, CH_2CH_3), 1.40 (s, C–CH_3), 2.10 (dt, 5-Me), 4.21–4.34 (m, 2 CH_2CH_3), 4.44 (dsext, 2-H), 4.96 (dt, 3-H), 5.25 (dsext, 4-H) ppm. J(2,3) = 0.8, J(2,4) = 1.0, J(2,5-Me) = 1.4, J(2,P) = 14.1, J(3,P) = 7.2, J(3,4) = 6.0, J(4,5-Me) = 1.5, J(4,P) = 1.5, J(5-Me,P) = 4.5, J(CH_2CH_3) = 7.1 Hz. ^{13}C NMR ($CDCl_3$, 295 K): δ = 10.7 (d, 5-Me), 16.3, 16.4 (2 d, 2 CH_2CH_3), 26.1, 27.2 (CMe_2), 63.3, 64.6 (2 d, 2 CH_2CH_3), 74.4 (d, C-3), 75.3 (d, C-2), 82.0 (C-4), 112.1 (CMe_2), 143.7 (d, C-5) ppm. J(2,P) = 153.7, J(3,P) = 6.4, J(5,P) = 8.5, J(5-Me,P) = 2.1, J(CH_3CH_2,P) = 6.0, J(CH_3CH_2,P) = 7.1 Hz. ^{31}P NMR ($CDCl_3$, 295 K): δ = 17.0 ppm. $C_{12}H_{22}NO_6P$ (307.29): C 46.91, H 7.22, N 4.56; found C 46.7, H 7.4, N 4.4.

24: Only characterised by ^{1}H NMR ($CDCl_3$, 400 MHz, 295 K): δ = 1.37 (t, 2 CH_2CH_3), 1.41, 1.47 (2 s, CMe_2), 1.50 (d, 5-Me), 4.17 (dquint, 5-H), 4.29 (m, 2 CH_2CH_3), 4.87 (dt, 4-H), 5.46 (d, 3-H) ppm. J(3,4) = 6.0, J(4,5) = 5.6, J(4,P) = 1.0, J(5,5-Me) = 6.8, J(5,P) = 2.6, J(CH_2CH_3) = 7.0 Hz.

Diethyl (2*S*,3*R*,4*R*)-(3,4-Isopropylidenedioxy-5-methyl-1-oxido-5-pyrrolinium-2-yl)methanephosphonate (25): A solution of **9** (200 mg, 0.62 mmol) in EtOH (2 mL) was stirred for 20 h at room temp. with yellow HgO (201 mg, 0.93 mmol, 1.5 equiv.). The solids were centrifuged off, washed with EtOH and the combined solvents evaporated to give nitrone **25** (198 mg, quant.). Colourless resin. $[\alpha]_D^{20}$ = +7 (c = 0.5, $CHCl_3$). R_f = 0.24 (diethyl ether/EtOH, 9:1). IR (KBr): $\tilde{\nu}$ = 972, 1027, 1049, 1161, 1213, 1236, 1384, 1617, 2958, 2987, 3429 cm^{-1}. ^{1}H NMR ($CDCl_3$, 295 K): δ = 1.34, 1.35 (2 t, 2 CH_2CH_3), 1.38 (s, CMe_2), 2.08 (t, 5-Me), 2.15 (ddd, 1′-Hb), 2.65 (ddd, 1′-Ha), 4.13 (m, 2 CH_2CH_3), 4.25 (ddm, 2-H), 4.96 (dt, 3-H), 5.18 (dt, 4-H) ppm. J(1′a,P) = 19.6, J(1′a,1′b) = 15.4, J(1′a,2) = 3.5, J(1′b,2) = 9.8, J(1′b,P) = 16.8, J(2,4) = 1.5, J(2,5-Me) = 1.5, J(2,3) = 1.0, J(2,P) = 20.0, J(3,4) = 6.2, J(3,P) = 1.0, J(4,5-Me) = 1.5, J(CH_3CH_2) = 7.0 Hz. ^{3}C NMR ($CDCl_3$, 295 K): δ = 10.8 (5-Me), 16.4 (d, 2 CH_2CH_3), 25.9 (C*Me*), 26.4 (d, C-1′), 27.1 (C*Me*), 62.2, 62.5 (2 d, 2 CH_2CH_3), 74.4 (d, C-2), 76.0 (C-3), 81.3 (C-4), 112.1 (CMe_2) ppm. J(1′,P) = 142.7, J(2,P) = 1.4, J(CH_2CH_3,P) = 5.6, J(CH_2CH_3,P) = 6.4 Hz. HRMS (ESI-Q-TOF) for $C_{13}H_{24}NO_6P$ $[M]^+$: calcd. 321.1341; found 321.1329.

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