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Synthesis of 1-Hydroxypyrrolidin-2,5-dione Derivatives of the Phosphonic–Hydroxamic Acid Antibiotic SF-2312

Wamuyu Owotoki,^A Detlef Geffken,^A and Thomas Kurz^{A,B}

^A Institute of Pharmacy, University of Hamburg, 20146 Hamburg, Germany. ^B Corresponding author. Email: kurz@chemie.uni-hamburg.de

Analogues of the antibiotic SF-2312 with a 3-substituted 1-hydroxypyrrolidine moiety have been prepared from 1-benzyloxy-3-bromopyrrolidin-2,5-dione (1) through Michaelis–Arbusov reaction with various trialkyl phosphites and subsequent alkylation of ring position 3. Cleavage of phosphonic esters **3** by TMSBr afforded the corresponding phosphonic acids **7**, which were treated with ethanolamine to give the monosalts **8**. Finally, hydrogenolysis furnished 1-hydroxypyrrolidin-2,5-diones **9**.

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Introduction

Compounds containing both the hydroxamic acid and phosphonic acid functions have attracted growing interest in medicinal chemistry because of their broad antimicrobial spectra.^[1,2] In 1986, Watabe et al. reported the isolation of the novel broad spectrum antibiotic SF-2312 from *Micromonospora* sp.,^[3] which is characterized by a cyclic *N*-hydroxyimide and a phosphonic acid functionality.^[4] In a formal sense SF-2312 might be regarded as a rigid analogue of the open-chain antibiotic Fosmidomycin (Fig. 1) which displays its antimicrobial activity through the inhibition of the non-mevalonate synthesis of isoprenoids by blocking the DOXP-reductoisomerase.^[5–9]

On account of the good antibacterial activities of SF-2312 and Fosmidomycin, we became interested in investigating the structure–activity relationship of SF-2312. We report herein the synthesis and properties of 3-substituted 1-hydroxypyrrolidin-2,5-dione analogues of SF-2312.

Results and Discussion

The starting material 1-benzyloxy-3-bromopyrrolidin-2,5dione (1) was prepared by bromination of *N*-benzyloxyisomaleimide^[10] according to the literature procedure.^[11]





Michaelis–Arbusov reaction of 1 with various alkyl phosphites provided the phosphonic esters 2a-2c in 63-77% yields.

Alkylation of compounds $2\mathbf{a}-2\mathbf{c}$ with alkyl(benzyl) halides in presence of sodium hydride afforded 3-substituted 1-benzyloxypyrrolidin-2,5-diones $(3\mathbf{a}-3\mathbf{j})$ in 51–91% yields.^[12] Catalytic hydrogenation of $3\mathbf{a}-3\mathbf{f}$ provided *N*-hydroxyimides $(4\mathbf{a}-4\mathbf{f})$ in yields of 52–85% as solid compounds.

Treatment of **4f** with 4-methoxyphenyl-isocyanate led to the carbamate **5** in 84% yield (Scheme 1, Table 1).

Functionalization of the pyrrolidin-2,5-dione nucleus was also achieved through Mannich reaction of **2a** with formalin and piperidine in acetic acid.^[13] The Mannich base was isolated as a crystalline hydrogen chloride salt (**6**; Scheme 2) which has also been characterized by X-ray crystallography.

Cleavage of the phosphonic acid esters 3f-3i by trimethylsilyl bromide led to the phosphonic acids 7a-7e as highly hygroscopic compounds that did not furnish satisfactory elemental analysis data.^[14] With regard to the reported stability of phosphonic acid ethanolamine salts,^[15] we treated 7a-7e with ethanolamine in a molar ratio of 1:0.9 in dry tetrahydrofuran. After subsequent cooling at -18°C for two days, the monosalts 8a-8e were obtained as analytically pure compounds in yields of 57-68% (Scheme 3, Table 2). Finally, catalytic hydrogenation of 8a-8e provided 9a-9e in high yields of 90-96% as stable compounds. The IR spectra of compounds 8 show two carbonyl bands at 1706–1724 and $1782-1786 \text{ cm}^{-1}$ whereas the 1-hydroxypyrrolidin-2,5diones 9 exhibit the carbonyl bands bathochromically shifted to 1697–1718 and 1774–1782 cm⁻¹. All compounds were characterized by elemental analysis and IR, ¹H NMR, and ¹³C NMR spectroscopy.



Scheme 1. Synthesis of 3-substituted 1-hydroxypyrrolidin-2,5-diones 4. (a) $P(OEt)_3$, $P(OMe)_3$, or $P(OPr^i)_3$; (b) NaH, R^1Br or R^1I ; (c) H_2/Pd -C; (d) 4-MeO-PhNCO.

Table 1. Synthesis of compounds 3 and 4

3, 4	R	R ¹	Yields [%]	
			3	4
a	Me	Bn	91	82
b	\mathbf{Pr}^{i}	4-F-Bn	78	85
c	\mathbf{Pr}^{i}	Bn	70	85
d	Et	Me	60	76
e	Et	3-PhO-Bn	68	52
f	Et	Bn	80	69
g	Et	4-F-Bn	64	-
ĥ	Et	4-Me-Bn	78	-
i	Et	$CH_2 = CH - CH_2$	71	-
j	Et	4-MeO-Bn	51	-



Conclusions

This paper describes a simple and effective synthetic route for the preparation of novel 1-hydroxy-pyrrolidin-2,5-dione analogues of the phosphonic acid antibiotic SF-2312. Due to their hygroscopicity the phosphonic acids have been converted into stable, non-hygroscopic ethanolamine monosalts. In the course of further investigations the selective reduction of the carbonyl groups of the pyrrolidin-2,5-dione nucleus is intended. The results of the biological studies will be reported in due course.



Scheme 3. Synthesis of compounds **7–9**. (a) (1) TMSBr, (2) H₂O; (b) H₂NCH₂CH₂OH/THF or MeOH; (c) H₂/Pd-C.

 Table 2.
 Synthesis of compounds 8 and 9

8, 9	\mathbb{R}^1	Yields [%]	
		8	9
a	Bn	57	96
b	4-F-Bn	68	90
c	4-Me-Bn	65	90
d	CH ₂ =CH-CH ₂	64	92 ^A
e	4-MeO-Bn	66	96

^A $\mathbb{R}^1 = n - \mathbb{C}_3 \mathbb{H}_7$.

Experimental

General

Melting points were determined on a Mettler FP 62 apparatus and are uncorrected. Elemental analyses were carried out with a Heraeus CHN-O-Rapid instrument. IR spectra were recorded on a Shimadzu FT-IR 8300 or a Perkin–Elmer Series 1600 FT-IR. ¹H NMR (400.14 MHz) and ¹³C NMR (100.61 MHz) spectra were recorded on a Bruker AMX 400 spectrometer using tetramethylsilane (δ 0.00) as the internal standard and [D₆]DMSO, D₂O, or CDCl₃ as solvents. Coupling constants are reported in Hertz. Column chromatography was conducted on silica gel (ICN silica 100–200, active 60 Å).

General Procedure for the Preparation of 2a-2c

1-Benzyloxy-3-bromopyrrolidin-2,5-dione (1; 0.57 g, 2 mmol) was refluxed at 140°C with the respective trialkyl phosphite (12 mmol) for 2 h. Excess of trialkyl phosphite was removed in vacuo and the oily residue was purified by column chromatography. Elution with EtOAc/n-hexane (4/1) afforded oily compounds, which in the case of **2a** and **2b** furnished solids compounds after drying for 5 min in vacuo.

Diethyl (1-Benzyloxy-2,5-dioxopyrrolidin-3-yl)phosphonate 2a

Light green solid (77%), mp 88°C. (Found: C 52.97, H 5.99, N 4.09%. C₁₅H₂₀NO₆P requires C 52.79, H 5.91, N 4.10%.) ν_{max} (KBr)/cm⁻¹ 1782, 1724 (C=O), 1251 (P=O), 1016 (POC). $\delta_{\rm H}$ (CDCl₃) 7.49–7.40 (m, 5H, ArH), 5.00 (s, 2H, CH₂Ph), 4.13–4.05 (m, 4H, POCH₂), 3.74–3.65 (m, 1H, PCH), 3.08–2.99 (m, 1H, CH₂), 2.69–2.66 (m, 1H, CH₂), 1.23–1.27 (m, 6H, (CH₃)₂). $\delta_{\rm C}$ (CDCl₃) 169.1, 166.6 (C=O), 133.2 (ArC_{quart.}), 128.6, 129.5, 129.9 (ArC_{tert.}), 78.9 (CH₂Ph), 63.4 (d, ²*J*_{C,P} 6.61, POC), 63.9 (d, ²*J*_{C,P} 7.12, POC), 36.9 (d, ¹*J*_{C,P} 142.9, PCH), 27.9 (CH₂), 16.4 (t, ³*J*_{C,P} 5.10, CH₃).

Dimethyl (1-Benzyloxy-2,5-dioxopyrrolidin-3-yl)phosphonate 2b

White solid (64%), mp 85°C. (Found: C 49.51, H 5.20, N 4.48%. C₁₃H₁₆NO₆P requires C 49.85, H 5.15, N 4.47%.) ν_{max} (KBr)/cm⁻¹ 1787, 1728 (C=O), 1257 (P=O), 1031 (POC). δ_{H} ([D₆]DMSO) 7.49– 7.40 (m, 5H, ArH), 5.01 (s, 2H, CH₂Ph), 3.70–3.62 (m, 4H, POCH₂), 3.08–2.98 (m, 1H, PCH), 2.76–2.74 (m, 1H, CH₂), 3.81–3.76 (m, 1H, CH₂). δ_{C} ([D₆]DMSO) 169.9, 167.3 (C=O), 134.1 (ArC_{quart.}), 129.9, 129.5, 128.8 (ArC_{tert.}), 78.5 (CH₂Ph), 54.0 (d, ²J_{C.P} 6.61, POC), 53.7 (d, ²J_{C.P} 6.62, POC), 35.9 (d, ¹J_{C.P} 140.39, PC), 27.9 (CH₂).

Diisopropyl (1-Benzyloxy-2,5-dioxopyrrolidin-3-yl)phosphonate 2c

Yellow oil (63%). (Found: C 55.26, H 6.57, N 3.50%. $C_{17}H_{24}NO_6P$ requires C 55.28, H 6.55, N 3.79%.) ν_{max} (film)/cm⁻¹ 1799, 1739 (C=O), 1261 (P=O), 999 (POC). $\delta_{\rm H}$ (CDCl₃) 7.52–7.37 (m, 5H, ArH), 5.08 (s, 2H, CH₂Ph), 4.82–4.74 (m, 2H, POCH), 3.21–3.12 (m, 1H, CH), 2.99–2.81 (m, 2H, CH₂), 1.38–1.33 (m, 12H, CH₃). $\delta_{\rm C}$ (CDCl₃) 169.7, 167.1 (C=O), 133.6 (ArCquart.), 130.7, 130.3, 129.8, 128.9 (ArCtert.), 79.3 (CH₂Ph), 73.2 (d, ²J_{C,P} 6.61, POC), 72.8 (d, ²J_{C,P} 6.61, POC), 37.7 (d, ¹J_{C,P} 142.42, PC), 28.3 (CH₂), 24.5 (d, ³J_{C,P} 3.07, CH₃), 24.4 (d, ³J_{C,P} 4.07, CH₃), 24.2 (t, ³J_{C,P} 5.83, CH₃).

General Procedure for the Preparation of 3a-3j

To a stirred solution of 2a-2c (2 mmol) in dry THF (5 mL) under N₂ atmosphere was added sodium hydride (0.05 g, 2 mmol) portionwise over a period of 10 min. After stirring for 10 min, a solution of the appropriate alkyl(benzyl) halide (2 mmol) in dry THF (2 mL) was added dropwise. The reaction mixture was stirred for 90 min, poured into ice-cold 1 M HCl solution and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO₄, and evaporated. The oily residues were purified by column chromatography (3/2 EtOAc/*n*-hexane elution) to give 3a-3j as oily or solid compounds. Compounds 3a, 3b, 3d, 3f-3h were crystallized from EtOAc/*n*-hexane.

Dimethyl (3-Benzyl-1-benzyloxy-2,5-dioxopyrrolidin-3-yl)phosphonate **3a**

White solid (91%), mp 78.8°C. (Found: C 59.53, H 5.52, N 3.30%. C₂₀H₂₂NO₆P requires C 59.55, H 5.50, N 3.47%.) ν_{max} (KBr)/cm⁻¹ 1789, 1724 (C=O), 1258 (P=O), 1014 (POC). $\delta_{\rm H}$ (CDCl₃) 7.41–7.13 (m, 10H, ArH), 4.83 (ABs, *J* 14.00, CH₂Ph), 3.89 (t, *J* 10.93, 6H, CH₃), 3.69–3.66 (m, 1H, CH₂), 3.05–2.93 (m, 2H, CH₂), 2.65–2.63 (m, 1H, CH₂). $\delta_{\rm C}$ (CDCl₃) 170.4, 168.9 (C=O), 133.9, 133.7 (ArC_{quart.}), 130.7, 130.2, 129.7, 129.5, 128.9, 128.5 (ArC_{tert.}), 79.4 (CH₂Ph), 55.6 (d, ²*J*_{C,P} 7.12, POC), 55.7 (d, ²*J*_{C,P} 7.12, POC), 48.1 (d, ¹*J*_{C,P} 140.89, PC), 36.6 (CH₂), 31.8 (CH₂).

Diisopropyl [3-(4-Flurobenzyl)-1-benzyloxy-2,5-dioxopyrrolidin-3-yl]phosphonate **3b**

Rod-like crystals (78%), mp 83.8°C. (Found: C 60.33, H 6.26, N 2.91%. C₂₄H₂₉NO₆P requires C 60.37, H 6.12, N 2.93%.) ν_{max} (KBr)/cm⁻¹ 1787, 1731 (C=O), 1249 (P=O), 975 (POC). $\delta_{\rm H}$ (CDCl₃) 7.42–6.95 (m, 9H, ArH), 4.92–4.86 (m, 2H, CH₂Ph), 4.85–4.77 (m, 2H, POCH), 3.65–3.63 (m, 1H, CH₂), 3.03–2.87 (m, 2H, CH₂), 2.56–2.64 (m, 1H, CH₂), 1.41–1.35 (m, 12H, CH₃). $\delta_{\rm C}$ 170.4, 169.3 (C=O), 162.7 (d, $J_{\rm C,F}$ 247.19, CF), 133.6 (ArCquart.), 132.3, 130.1, 129.70, 128.9, 116.5 (ArCtert.), 79.3 (CH₂Ph), 73.6 (d, $^2J_{\rm C,P}$ 7.12, POC), 73.2 (d, $^2J_{\rm C,P}$ 7.63, POC), 48.2 (d, $^1J_{\rm C,P}$ 139.87, PC), 35.6 (CH₂), 31.9 (CH₂), 24.6 (d, $^3J_{\rm C,P}$ 3.05, CH₃), 24.5 (d, $^3J_{\rm C,P}$ 4.07, CH₃), 24.3 (d, $^3J_{\rm C,P}$ 5.09, CH₃), 24.1 (d, $^3J_{\rm C,P}$ 6.10, CH₃).

Diisopropyl (3-Benzyl-1-benzyloxy-2,5-dioxopyrrolidin-3-yl)phosphonate **3c**

Colourless oil (70%). (Found: C 62.63, H 6.78, N 2.97%. $C_{24}H_{30}NO_6P$ requires C 62.74, H 6.58, N 3.05%.) ν_{max} (film)/cm⁻¹ 1789, 1728 (C=O), 1261 (P=O), 989 (POC). δ_H (CDCl₃) 7.40–7.13 (m, 10H, ArH), 4.87–4.77 (m, 2H, POCH), 3.70–3.69 (m, 1H, CH₂), 3.02–2.89 (m, 2H, CH₂), 2.62–2.60 (m, 1H, CH₂), 1.42–1.35 (m, 12H, CH₃). δ_C

(CDCl₃) 170.6, 169.5 (C=O), 134.3, 133.8 (ArC_{quart.}), 130.7, 130.1, 129.7, 129.5, 128.9, 128.8 (ArC_{tert.}), 79.4 (CH₂Ph), 73.5 (d, ${}^{2}J_{C,P}$ 7.12, POC), 73.1 (d, ${}^{2}J_{C,P}$ 7.63, POC), 48.2 (d, ${}^{1}J_{C,P}$ 139.88, PC), 36.5 (CH₂), 31.9 (CH₂), 24.6 (d, ${}^{3}J_{C,P}$ 3.05, CH₃), 24.5 (d, ${}^{3}J_{C,P}$ 4.07, CH₃), 24.2 (d, ${}^{3}J_{C,P}$ 5.59, CH₃), 24.1 (d, ${}^{3}J_{C,P}$ 6.11, CH₃).

Diethyl (1-Benzyloxy-3-methyl-2,5-dioxopyrrolidin-3-yl)phosphonate **3d**

White solid (60%), mp 54°C. (Found: C 53.76, H 6.30, N 3.90%. C₁₆H₂₂NO₆P requires C 54.08, H 6.24, N 3.94%.) ν_{max} (KBr)/cm⁻¹ 1784, 1732 (C=O), 1247 (P=O), 1020 (POC). $\delta_{\rm H}$ (CDCl₃) 7.42–7.38 (m, 5H, ArH), 5.01 (ABs, 2H, CH₂Ph), 4.04 (m, 4H, POCH₂), 2.76–2.71 (m, 2H, CH₂), 1.25–1.23 (m, 6H, (CH₃)₂), 1.44 (d, *J* 16.53, 3H, CH₃). $\delta_{\rm C}$ (CDCl₃) 170.6, 168.9 (C=O), 133.7 (ArC_{quart.}), 129.4, 129.0, 128.4 (ArC_{tert.}), 78.0 (OCH₂Ph), 63.3 (d, ²*J*_{C,P} 7.12, POC), 63.5 (d, ²*J*_{C,P} 6.61, POC), 41.7 (d, ¹*J*_{C,P} 139.90, PC), 35.5 (CH₂), 17.6 (d, ²*J*_{C,P} 4.07, CH₃), 16.3 (d, ³*J*_{C,P} 5.09, CH₃).

Diethyl [1-Benzyloxy-3-(3-phenoxybenzyl)-2,5-dioxopyrrolidin-3-yl]phosphonate **3e**

Colourless oil (68%). (Found: C 64.35, H 6.13, N 2.44%. $C_{28}H_{30}NO_7P$ requires C 64.24, H 5.78, N 2.68%.) ν_{max} (film)/cm⁻¹ 1789, 1724 (C=O), 1252 (P=O), 1018 (POC). δ_H ([D₆]DMSO) 7.37–6.93 (m, 14H, ArH), 4.75 (ABs, *J* 4.83, CH₂Ph), 4.17–4.10 (m, 4H, POCH₂), 3.45–3.39 (m, 1H, CH₂), 3.03–2.80 (m, 3H, CH₂), 1.25 (t, *J* 7.42, 6H, CH₃). δ_C ([D₆]DMSO) 170.0, 168.9 (C=O), 156.9, 136.4, 133.8 (ArC_{quart.}), 130.7, 130.4, 129.9, 128.8, 125.9, 123.3, 120.9, 118.9 (ArC_{tert.}), 78.7 (CH₂Ph), 63.5 (d, ²*J*_{C,P} 7.12, POC), 63.8 (d, ²*J*_{C,P} 7.12, POC), 47.5 (d, ¹*J*_{C,P} 139.90, PC), 35.9 (CH₂), 31.9 (CH₂), 16.6 (d, ³*J*_{C,P} 5.30, CH₃).

Diethyl (3-Benzyl-1-benzyloxy-2,5-dioxopyrrolidin-3-yl)phosphonate 3f

Yellow oil (80%). (Found: C 61.06, H 6.22, N 3.08%. $C_{22}H_{26}NO_6P$ requires C 61.25, H 6.07, N 3.25%.) v_{max} (film)/cm⁻¹ 1787, 1726 (C=O), 1249 (P=O), 1018 (POC). $\delta_{\rm H}$ (CDCl₃) 7.38–7.23 (m, 10H, ArH), 4.64 (ABs, *J* 46.36, 2H, CH₂Ph), 4.20–4.12 (m, 4H, POCH₂), 3.49–3.44 (m, 1H, CH₂), 3.01–2.77 (m, 3H, CH₂), 1.28 (dt, *J* 1.78, *J* 7.09, 6H, (CH₃)₂). $\delta_{\rm C}$ (CDCl₃) 170.0, 168.8 (C=O), 134.2, 133.8 (ArC_{quart.}), 130.7, 129.9, 129.5, 129.1, 128.8, 128.0 (ArC_{tert.}), 78.6 (CH₂Ph), 64.0 (d, ²*J*_{C,P} 7.12, POC), 63.8 (d, ²*J*_{C,P} 6.61, POC), 47.6 (d, ¹*J*_{C,P} 139.88, PC), 36.1 (CH₂), 31.7 (CH₂), 16.6 (d, ³*J*_{C,P} 5.08, CH₃).

Diethyl [1-Benzyloxy-3-(4-fluorobenzyl)-2,5-dioxopyrrolidin-3-yl]phosphonate **3g**

White solid (64%), mp 66°C. (Found: C 58.90, H 5.61, N 3.19%. C₂₂H₂₅FNO₆P requires C 58.80, H 5.61, N 3.12%.) ν_{max} (KBr)/cm⁻¹ 1786, 1726 (C=O), 1251 (P=O), 1018 (POC). $\delta_{\rm H}$ (CDCl₃) 7.40–6.97 (m, 9H, ArH), 4.92–4.85 (m, 2H, CH₂Ph), 4.26–4.24 (m, 4H, POCH₂), 3.68–3.63 (m, 1H, CH₂), 3.06–2.93 (m, 2H, CH₂), 2.62–2.54 (m, 1H, CH₂), 1.36 (t, *J* 6.94, 6H, (CH₃)₂). $\delta_{\rm C}$ (CDCl₃) 170.0, 168.6 (C=O), 162.2 (d, *J*_{C,F} 247.60, CF), 133.2, 129.5 (ArC_{quart.}), 131.9, 129.7, 128.5, 116.1 (ArC_{tert.}), 78.93 (CH₂Ph), 64.3 (d, ²*J*_{C,P} 6.61, POC), 64.0 (d, ²*J*_{C,P} 7.63, POC), 47.8 (d, ¹*J*_{C,P} 141.47, PC), 35.2 (CH₂), 31.4 (CH₂), 16.5 (t, ³*J*_{C,P} 5.85, CH₃).

Diethyl [1-Benzyloxy-3-(4-methylbenzyl)-2,5-dioxopyrrolidin-3-yl]phosphonate **3h**

White solid (78%), mp 54°C. (Found C 61.85, H 6.35, N 3.20%. C₂₃H₂₈NO₆P requires C 62.02, H 6.34, N 3.14%.) ν_{max} (KBr)/cm⁻¹ 1782, 1720 (C=O), 1257 (P=O), 1020 (POC). $\delta_{\rm H}$ (CDCl₃) 7.40–7.01 (m, 9H, ArH), 4.87 (ABs, *J* 27.15, 2H, CH₂Ph), 4.28–4.17 (m, 4H, POCH₂), 3.69–2.64 (m, 1H, CH₂), 3.03–2.88 (m, 2H, CH₂), 2.67–2.60 (m, 1H, CH₂), 2.29 (s, 3H, CH₃), 1.42–1.34 (m, 6H, (CH₃)₂). $\delta_{\rm C}$ (CDCl₃) 170.2, 168.9 (C=O), 137.7, 133.4 (ArC_{quart.}), 130.1, 129.7, 129.3, 128.5 (ArC_{tert.}), 78.92 (CH₂Ph), 133.7 (ArC_{quart.}), 129.4, 129.0, 128.4 (ArC_{tert.}), 78.0 (OCH₂Ph), 63.9 (d, ²*J*_{C,P} 7.12, POC), 64.1 (d, ²*J*_{C,P} 6.61, POC), 47.6 (d, ¹*J*_{C,P} 139.37, PC), 35.7 (CH₂), 31.4 (CH₂), 21.0 (CH₃), 16.4 (t, ³*J*_{C,P} 5.85, CH₃).

Diethyl (3-Allyl-1-benzyloxy-2,5-dioxopyrrolidin-3-yl)phosphonate **3i**

Colourless oil (71%). (Found: C 56.76, H 6.54, N 3.72%. $C_{18}H_{24}NO_6P$ requires C 56.69, H 6.50, N 3.67%.) ν_{max} (KBr)/cm⁻¹ 1789, 1728 (C=O), 1249 (P=O), 1018 (POC). $\delta_{\rm H}$ (CDCl₃) 7.51–7.37 (m, 5H, ArH), 5.38–5.28 (m, 1H, CH₂CH), 5.19–5.15 (m, 2H, CH₂CH), 5.10 (ABs, *J* 12.86, 2H, CH₂Ph), 4.22–4.16 (m, 4H, POCH₂), 3.04–2.87 (m, 2H, CH₂), 2.65–2.58 (m, 1H, CH₂), 2.46–2.39 (m, 1H, CH₂), 1.38–1.31 (m, 6H, (CH₃)₂). $\delta_{\rm C}$ (CDCl₃) 169.9, 169.2 (C=O), 133.3 (ArCquart.), 129.7, 129.4, 128.5 (ArC_{tert.}), 122.1 (CH₂), 78.7 (OCH₂Ph), 63.7 (d, ²*J*_{C,P} 6.61, POC), 64.0 (d, ²*J*_{C,P} 7.12, POC), 45.6 (d, ¹*J*_{C,P} 139.96, PC), 35.4 (CH₂), 31.9 (CH₂), 16.4 (d, ³*J*_{C,P} 5.08, CH₃), 16.5 (d, ³*J*_{C,P} 6.11, CH₃).

Diethyl [1-Benzyloxy-3-(4-methoxybenzyl)-2,5-dioxopyrrolidin-3-yl]phosphonate **3**j

Yellow oil (51%). (Found: C 59.52, H 6.34, N 2.95%. $C_{23}H_{28}NO_6P$ requires C 59.87, H 6.12, N 3.04%.) ν_{max} (KBr)/cm⁻¹ 1791, 1726, (C=O), 1251 (P=O), 1018 (POC). $\delta_{\rm H}$ (CDCl₃) 7.41–6.79 (m, 9H, ArH), 4.85 (ABs, *J* 23.46, 2H, CH₂Ph), 4.28–4.17 (m, 4H, POCH₂), 3.75 (s, 3H, OCH₃), 3.67–3.62 (m, 1H, CH₂), 3.03–2.86 (m, 2H, CH₂), 2.67–2.60 (m, 1H, CH₂), 1.45–1.34 (m, 6H, (CH₃)₂). $\delta_{\rm C}$ (CDCl₃) 170.4, 168.9 (C=O), 159.3, 133.4, 125.5 (ArC_{quart.}), 131.3, 129.8, 129.3, 128.5, 114.4 (ArC_{tert.}), 78.9 (CH₂Ph), 63.9 (d, ²*J*_{C,P} 7.12, POC), 64.1 (d, ²*J*_{C,P} 6.61, POC), 55.3 (OCH₃), 35.7 (CH₂), 31.4 (CH₂), 16.5 (t, ³*J*_{C,P} 5.85, CH₃).

General Procedure for the Preparation of 4a-4f

Compounds 3a-3f (5 mmol) were dissolved in MeOH (100 mL), Pd-C 10% (300 mg) was added and the resulting mixture was hydrogenated for 90 min. The suspension was filtered through an SPE tube RP-18. The solvent was evaporated and the residue crystallized from EtOAc/ *n*-hexane to give 4a-4f.

Dimethyl (3-Benzyl-1-hydroxy-2,5-dioxopyrrolidin-3-yl)phosphonate **4a**

White solid (82%), mp 198.8°C. (Found: C 49.55, H 5.13, N 4.46%. C₁₃H₁₆NO₆P requires C 49.85, H 5.15, N 4.47%.) ν_{max} (KBr)/cm⁻¹ 1783, 1724 (C=O), 1227 (P=O), 1039 (POC). $\delta_{\rm H}$ (CDCl₃) 9.58 (s, 1H, OH), 7.28–7.08 (m, 5H, ArH), 3.99 (d, *J* 10.93, OCH₃), 3.85 (d, *J* 10.93, 3H, OCH₃), 3.65–3.62 (m, 1H, CH₂), 2.98–2.96 (m, 1H, CH₂), 2.89–2.85 (m, 1H, CH₂), 2.59–2.54 (m, 1H, CH₂). $\delta_{\rm C}$ 170.7, 169.5 (C=O), 133.5 (ArC_{quart.}), 130.4, 129.5, 128.4 (ArC_{tert.}), 56.3 (d, ²*J*_{C,P} 6.62, POC), 54.1 (d, ²*J*_{C,P} 7.63, POC), 48.7 (PC), 31.3 (CH₂), 30.1 (CH₂).

Diisopropyl [3-(4-Flurobenzyl)-1-hydroxy-2,5-dioxopyrrolidin-3-yl]phosphonate **4b**

White solid (85%), mp 180.2°C. (Found: C 51.82, H 5.92, N 3.58%. C₁₇H₂₃FNO₆P·1/2H₂O requires C 51.52, H 6.10, N 3.53%.) ν_{max} (KBr)/cm⁻¹ 1790, 1724 (C=O), 1245 (P=O), 990 (POC). $\delta_{\rm H}$ (CDCl₃) 9.91 (s, 1H, OH), 7.08–6.94 (m, 4H, ArH), 4.90–4.76 (m, 2H, POCH), 3.59–3.57 (m, 1H, CH₂), 2.98–2.95 (m, 1H, CH₂), 2.81–2.78 (m, 1H, CH₂), 3.50–3.47 (m, 1H, CH₂), 1.38–1.49 (m, 12H, (CH₃)4). $\delta_{\rm C}$ (CDCl₃) 170.8, 169.7 (C=O), 162.7 (d, $J_{\rm CF}$ 247.70, CF), 132.1, 116.4, 116.2 (ArC_{tert.}), 75.4 (d, ² $J_{\rm C,P}$ 7.12, POC), 73.3 (d, ² $J_{\rm C,P}$ 7.63, POC), 47.9 (d, ¹ $J_{\rm C,P}$ 149.9, PC), 36.5 (CH₂), 31.3 (CH₂), 24.9 (d, ³ $J_{\rm C,P}$ 1.53, CH₃), 24.3 (d, ³ $J_{\rm C,P}$ 3.56, CH₃), 24.1 (d, ³ $J_{\rm C,P}$ 5.09, CH₃), 23.7 (d, ³ $J_{\rm C,P}$ 6.61, CH₃).

Diisopropyl (3-Benzyl-1-hydroxy-2,5-dioxopyrrolidin-3-yl)phosphonate **4**c

White solid (85%), mp 180.2°C. (Found: C 54.90, H 6.55, N 3.82%. C₁₇H₂₄NO₆P requires C 55.28, H 6.55, N 3.79%.) ν_{max} (KBr)/cm⁻¹ 1785, 1724 (C=O), 1243 (P=O), 1001 (POC). $\delta_{\rm H}$ (CDCl₃) 9.69 (s, 1H, OH), 7.28–7.08 (m, 5H, ArH), 4.91–4.76 (m, 2H, POCH), 3.85–3.82 (m, 1H, CH₂), 2.96–2.91 (m, 1H, CH₂), 2.82–2.79 (m, 1H, CH₂), 2.54–2.51 (m, 1H, CH₂), 1.50–1.36 (m, 12H, (CH₃)₄). $\delta_{\rm C}$ (CDCl₃) 170.9,

169.5 (C=O), 134.2 (ArC_{quart.}), 130.5, 129.3, 128.2 (ArC_{tert.}), 75.3 (d, ${}^{2}J_{C,P}$ 7.12, POC), 73.3 (d, ${}^{2}J_{C,P}$ 7.63, POC), 47.9 (d, ${}^{1}J_{C,P}$ 144.45, PC), 37.3 (CH₂), 31.4 (CH₂), 24.9 (d, ${}^{3}J_{C,P}$ 1.52, CH₃), 24.3 (d, ${}^{3}J_{C,P}$ 3.56, CH₃), 24.2 (d, ${}^{3}J_{C,P}$ 5.08, CH₃), 23.8 (d, ${}^{3}J_{C,P}$ 7.12, CH₃).

Diethyl (1-Hydroxy-3-methyl-2,5-dioxopyrrolidin-3-yl)phosphonate 4d

White solid (76%), mp 118°C. (Found: C 40.76, H 6.08, N 5.25%. C₉H₁₆NO₆P requires C 40.76, H 6.08, N 5.28%.) ν_{max} (KBr)/cm⁻¹ 1782, 1720 (C=O), 1230 (P=O), 1014 (POC). $\delta_{\rm H}$ (CDCl₃) 4.26–4.18 (m, 4H, POCH₂), 3.20–2.47 (m, 2H, CH₂), 1.44 (d, *J* 16.53, 3H, CH₃)/ 1.23–1.26 (m, 6H, (CH₃)₂). $\delta_{\rm C}$ (CDCl₃) 171.4, 169.7 (C=O), 65.4 (d, ²J_{C,P} 6.61, POC), 63.6 (d, ²J_{C,P} 7.63, POC), 41.9 (d, ¹J_{C,P} 147.50, PC), 35.9 (CH₂), 31.9 (CH₂), 19.7 (d, ³J_{C,P} 4.98, CH₃), 16.3 (d, ³J_{C,P} 5.93, CH₃).

Diethyl [1-Hydroxy-3-(3-phenoxybenzyl)-2,5-dioxopyrrolidin-3-yl]phosphonate **4e**

White solid (52%), mp 174.4°C. (Found: C 57.85, H 5.76, N 3.17%. C₂₁H₂₄NO₇P requires C 58.20, H 5.58, N 3.23%.) ν_{max} (KBr)/cm⁻¹ 1787, 1723 (C=O), 1254 (P=O), 971 (POC). $\delta_{\rm H}$ (CDCl₃) 9.37 (s, 1H, OH), 7.35–6.76 (m, 9H, ArH), 4.36–4.19 (m, 4H, POCH₂), 3.63–3.60 (m, 1H, CH₂), 2.99–2.93 (m, 1H, CH₂), 2.82–2.79 (m, 1H, CH₂), 2.58–2.55 (m, 1H, CH₂), 1.39–1.36 (m, 6H, (CH₃)₂). $\delta_{\rm C}$ (CDCl₃) 171.6, 169.6 (C=O), 158.1, 152.3 (ArC_{quart.}), 125.1, 123.9, 120.8, 119.4, 118.6 (ArC_{tert.}), 65.9 (d, ²J_{C,P} 6.61, POC), 64.0 (d, ²J_{C,P} 7.63, POC), 47.8 (d, ¹J_{C,P} 142.42, PC), 36.8 (CH₂), 31.3 (CH₂), 16.7 (q, ³J_{C,P} 5.76, CH₃).

Diethyl (1-Hydroxy-3-benzyl-2,5-dioxopyrrolidin-3-yl)phosphonate **4**f

White solid (69%), mp 162°C. (Found: C 52.37, H 5.97, N 3.91%. C₁₅H₂₀NO₆P requires C 52.79, H 5.91, N 4.10%.) v_{max} (KBr)/cm⁻¹ 1786, 1724 (C=O), 1242 (P=O), 1026 (POC). $\delta_{\rm H}$ (CDCl₃) 7.11–7.04 (m, 5H, ArH), 4.22–4.19 (m, 4H, POCH₂), 3.64–3.61 (m, 2H, CH₂), 2.96–2.86 (m, 2H, CH₂), 2.58–2.56 (m, 2H, CH₂), 1.38 (m, 6H, (CH₃)₂). $\delta_{\rm C}$ (CDCl₃) 170.9, 169.8 (C=O), 133.9 (ArC_{quart.}), 130.5, 129.4, 128.3 (ArC_{tert.}), 66.1 (d, ²*J*_{C,P} 7.12, POC), 64.1 (d, ²*J*_{C,P} 7.63, POC), 47.8 (d, ¹*J*_{C,P} 143.4, PC), 37.1 (CH₂), 31.3 (CH₂), 16.8 (q, ³*J*_{C,P} 6.60, CH₃).

Diethyl [3-Benzyl-1-({[(4-methyoxyphenyl)amino]carbonyl}oxy)-2,5-dioxopyrrolidin-3-yl]phosphonate 5

To a solution of **4a** (0.11 g, 0.32 mmol) in dry DCM (3 mL) was added 4-methoxy-phenylisocyanate (0.48 g, 0.32 mmol). After stirring for 48 h, the solvent was evaporated and the crude product crystallized in Et₂O/*n*-hexane to yield compound **5** as short, white needles (0.138 g, 84%), mp 153.5°C. (Found: C 56.30, H 5.42, N 5.83%. C₂₃H₂₇N₂O₈P requires C 56.33, H 5.55, N 5.71%.) ν_{max} (KBr)/cm⁻¹ 1779, 1739 (C=O), 1248 (P=O), 1017 (POC). $\delta_{\rm H}$ (CDCl₃) 7.32–7.16 (m, 7H, ArH), 7.00 (s, 1H, NH), 6.87–6.85 (m, 2H, ArH), 4.31–4.25 (m, 4H, OCH₂), 3.79 (m, 1H, OCH₃), 3.78–3.73 (m, 1H, CH₂), 3.17–3.02 (m, 1H, CH₂), 2.79–2.72 (m, 1H, CH₂), 1.41 (t, *J* 7.01, 3H, CH₃), 1.37 (t, *J* 3.76, 3H, CH₃). $\delta_{\rm C}$ (CDCl₃) 169.5, 167.9, 148.7 (C=O), 133.9, 133.8 (ArC_{quart.}), 130.6, 129.4, 128.4, 121.6, 114.8 (ArC_{tert.}), 64.8 (d, ²*J*_{C,P} 7.12, POC), 64.6 (d, ²*J*_{C,P} 7.12, POC), 55.9 (OCH₃), 48.4 (d, ¹*J*_{C,P} 140.40, PC), 36.7 (CH₂), 31.9 (CH₂), 1.68 (q, ³*J*_{C,P} 5.43, CH₃).

1-{[1-Benzyloxy-3-(diethoxyphosphoryl)-2,5-dioxopyrrolidin-3-yl]methyl}piperidinum Chloride 6

Piperidine (1.02 g, 12 mmol) was added dropwise to a stirred solution of **2a** (0.68 g, 2 mmol) in glacial acetic acid (4.6 mL), the mixture was cooled to 30°C and 35% formaldehyde (0.5 g, 16 mmol) was added. The solution was stirred for 1h and then poured onto 12 g crushed ice. The resulting mixture was made alkaline by slow addition of 30% NaOH (5 mL) and then extracted with Et_2O (3 × 10 mL). The solvent was evaporated and 1 M HCl (3 mL) was used to lower the pH to 2. This acidic mixture was washed with EtOAc (2 × 5 mL). 30% NaOH (2 mL) was used to raise the pH of the aqueous solution to 9. The crude base was

extracted with EtOAc (3 × 5 mL). Dry HCl gas was passed through this solution which was then cooled for 24 h at 4°C, affording crystalline **6** (0.28 g, 21%). (Found: C 53.00 H 6.84 N 5.92%. C₂₁H₃₂ClN₂O₆P requires C 53.11, H 6.79, N 5.90%.) ν_{max} (KBr)/cm⁻¹ 1793, 1720 (C= O), 1245 (P=O), 1010 (POC). $\delta_{\rm H}$ ([D₆]DMSO) 10.49 (s, 1H, NH), 7.50–7.41 (m, 5H, ArH), 5.08 (s, 2H, CH₂Ph), 4.16–4.12 (m, 4H, POCH₂), 3.60–1.63 (m, 14H, CH₂), 1.29–1.23 (m, 6H, CH₃). $\delta_{\rm C}$ ([D₆]DMSO) 170.0, 168.6 (C=O), 134.9 (ArC_{quart.}), 129.9, 129.5, 128.8 (ArC_{tert.}), 78.7 (CH₂Ph), 55.9 (d, ²*J*_{C,P} 4.07, POC), 48.1 (CH₂), 35.2 (CH₂), 28.1 (CH₂), 22.4 (CH₂), 21.9 (CH₂), 16.5 (g, ³*J*_{C,P} 5.59, CH₃).

General Procedure for the Preparation of Ethanolamine Monosalt Derivatives **8a–8j**

To a solution of compounds **3** (3 mmol) in dry CH₂Cl₂ (5 mL) was added trimethylsilyl bromide (0.92 g, 6 mmol) and the reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated and the remaining oil was dissolved in MeOH (3 mL), treated with water (0.1 mL), and stirred for 10 min. The solvents were removed under reduced pressure and the residue dried in vacuo for 12 h. The resulting phosphonic acids **7** were dissolved in dry THF (5 mL), and ethanolamine (0.17 g, 2.7 mmol) dissolved in 2 mL dry THF was added dropwise. The solution was stirred for 1 h at RT and then kept at -18° C for 2 days. The solids formed were filtered and recrystallized from MeOH/Et₂O to give **8a–8e** as white solids.

2-Hydroxyethanaminium Hydrogen(3-benzyl-1-benzyloxy-2,5-dioxopyrrolidin-3-yl)phosphonate **8a**

White solid (57%), mp 175°C. (Found: C 54.51, H 6.30, N 5.79%. C₂₀H₂₅N₂O₇P requires C 55.05, H 5.77, N 6.42%.) ν_{max} (KBr)/cm⁻¹ 1784, 1710 (C=O). $\delta_{\rm H}$ (D₂O) 7.27–6.95 (m, 10H, ArH), 4.74–4.55 (m, 2H, CH₂Ph), 3.66 (t, *J* 6.49, 2H, CH₂NH₃), 3.53 (CH₂), 2.98 (t, *J* 6.48, 2H, CH₂OH), 2.86–2.76 (m, 2H, CH₂), 2.60 (q, 1H, CH₂). $\delta_{\rm C}$ (D₂O) 175.2, 173.6 (C=O), 135.7, 133.4 (ArC_{quart.}), 130.7, 129.4, 129.1, 128.1 (ArC_{tert.}), 79.7 (CH₂Ph), 57.9 (CH₂OH), 41.6 (CH₂NH₃), 48.2 (d, ¹*J*_{C,P} 142.92, PC), 36.9 (CH₂), 32.4 (CH₂).

2-Hydroxyethanaminium Hydrogen[1-benzyloxy-3-(4-fluorobenzyl)-2,5-dioxopyrrolidin-3-yl]phosphonate **8b**

White solid (68%), mp 172°C. (Found: C 52.52, H 6.01, N 5.29%. C₂₀H₂₄FN₂O₇P requires C 52.87, H 5.32, N 6.17%.) ν_{max} (KBr)/cm⁻¹ 1786, 1712 (C=O). $\delta_{\rm H}$ (D₂O) 7.39–7.18 (m, 9H, ArH), 4.94–4.70 (m, 2H, CH₂Ph), 3.83 (t, *J* 6.35, 2H, CH₂NH₃), 3.75–3.60 (m, 1H, CH₂), 3.17 (t, *J* 6.38, 2H, CH₂OH), 3.05–2.90 (m, 2H, CH₂), 2.70–2.60 (m, 1H, CH₂). $\delta_{\rm C}$ (D₂O) 175.1, 173.5 (C=O), 162.5 (d, *J*_{C,F} 243.13, CF), 133.4 (ArC_{quart.}), 132.4, 130.6, 129.1, 116.2, 115.9 (ArC_{tert.}), 79.7 (CH₂Ph), 57.9 (CH₂OH), 49.6 (d, ¹*J*_{C,P} 122.58, PC), 41.6 (CH₂NH₃), 35.9 (CH₂), 32.3 (CH₂).

2-Hydroxyethanaminium Hydrogen[1-benzyloxy-3-(4-methylbenzyl)-2,5-dioxopyrrolidin-3-yl]phosphonate **8c**

White solid (65%), mp 187°C. (Found: C 55.68, H 6.05, N 6.19%. C₂₁H₂₂N₂O₇P requires C 56.00, H 6.04, N 6.22%.) ν_{max} (KBr)/cm⁻¹ 1786, 1712 (C=O). $\delta_{\rm H}$ (D₂O) 7.91–6.93 (m, 9H, ArH), 4.81–4.58 (m, 2H, CH₂Ph), 3.72 (t, *J* 6.09, 2H, CH₂NH₃), 3.54–3.50 (m, 1H, CH₂), 3.04 (t, *J* 6.47, 2H, CH₂OH), 2.87–2.79 (m, 2H, CH₂), 2.65–2.58 (m, 1H, CH₂), 2.21 (s, 3H, CH₃). $\delta_{\rm C}$ (D₂O) 173.7, 173.6 (C=O), 138.3, 130.7 (ArC_{quart.}), 130.6, 130.1, 130.0, 129.1 (ArC_{tert.}), 79.7 (CH₂Ph), 57.9 (CH₂OH), 49.6 (d, ¹*J*_{C,P} 123.60, PC), 41.6 (CH₂NH₃), 36.4 (CH₂), 32.3 (CH₂), 20.5 (CH₃).

2-Hydroxyethanaminium Hydrogen(3-allyl-1-benzyloxy-2,5dioxopyrrolidin-3-yl)phosphonate **8d**

White solid (64%), mp 169°C. (Found: C 49.73, H 6.13, N 7.15%. C₁₆H₂₃N₂O₇P requires C 49.74, H 6.00, N 7.25%.) ν_{max} (KBr)/cm⁻¹ 1786, 1706 (C=O). $\delta_{\rm H}$ (D₂O) 7.47–7.45 (m, 5H, ArH), 5.38–5.28 (m, 1H, CHCH₂), 5.17–5.13 (m, 2H, CHCH₂), 5.10 (s, 2H, CH₂Ph), 3.78 (t, *J* 5.12, 2H, CH₂NH₃), 3.10 (t, *J* 5.12, 2H, CH₂OH), 2.92–2.67 (m,

3H, CH₂), 2.40–2.33 (m, 1H, CH₂). δ_{C} (D₂O) 174.1, 174.0 (C=O), 133.4 (ArC_{quart.}), 131.4, 130.3, 129.2 (ArC_{tert.}), 121.4 (CH₂), 79.5 (CH₂PH), 57.9 (CH₂OH), 47.7 (d, ¹*J*_{C,P} 125.12, PC), 41.6 (CH₂NH₃), 35.7 (CH₂CH), 32.7 (CH₂).

2-Hydroxyethanaminium Hydrogen[1-benzyloxy-3-(4-methoxybenzyl)-2,5-dioxopyrrolidin-3-yl]phosphonate **8e**

White solid (66%), mp 205°C. (Found: C 53.27, H 5.91, N 5.77%. C₂₁H₂₇N₂O₈P·1/2H₂O requires C 53.04, H 5.93, N 5.89%.) ν_{max} (KBr)/cm⁻¹ 1784, 1712 (C=O). $\delta_{\rm H}$ (D₂O) 7.52–7.11 (m, 9H, ArH), 5.01–4.79 (m, 2H, CH₂Ph), 3.91 (s, 3H, OCH₃), 3.93–3.90 (m, 2H, CH₂NH₃), 3.72–3.68 (m, 1H, CH₂), 3.23 (t, *J* 5.30, 2H, CH₂OH), 3.07–2.98 (m, 2H, CH₂), 2.84–2.76 (m, 1H, CH₂). $\delta_{\rm C}$ (D₂O) 174.5, 173.7 (C=O), 158.7, 133.5 (ArC_{quart.}), 132.1, 130.6, 130.1, 129.0, 114.8 (ArC_{tert.}), 79.7 (CH₂Ph), 57.9 (CH₂OH), 55.8 (OCH₃), 41.6 (CH₂NH₃), 36.0 (CH₂), 32.3 (CH₂).

General Procedure for the Preparation of Compounds 9a-9e

Compounds **8a–8e** (5 mmol) were dissolved in MeOH (100 mL), Pd-C 10% (300 mg) was added and the resulting mixture was hydrogenated for 90 min. The suspension was filtered through an SPE tube RP-18. The solvent was evaporated and the residue crystallized from MeOH/Et₂O to give **9a–9e**.

2-Hydroxyethanaminium Hydrogen(3-benzyl-1-hydroxy-2,5-dioxopyrrolidin-3-yl)phosphonate **9a**

White solid (96%), mp 232°C. (Found: C 44.83, H 5.36, N 7.92%. C₁₃H₁₉N₂O₇P requires C 45.09, H 5.53, N 8.09%.) ν_{max} (KBr)/cm⁻¹ 1780, 1697 (C=O). $\delta_{\rm H}$ (D₂O) 7.38–7.21 (m, 5H, ArH), 3.82 (t, *J* 5.92, 2H, CH₂NH₃), 3.67–3.62 (m, 1H, CH₂), 3.14 (t, *J* 6.30, 2H, CH₂OH), 3.05–2.97 (m, 2H, CH₂), 2.96–2.75 (m, 1H, CH₂). $\delta_{\rm C}$ (D₂O) 176.1, 174.3 (C=O), 135.5 (ArC_{quart.}), 130.0, 129.2, 127.9 (ArC_{tert.}), 57.9 (CH₂OH), 49.0 (d, ¹*J*_{C,P} 126.65, PC), 41.6 (CH₂NH₃), 37.2 (CH₂), 32.3 (CH₂).

2-Hydroxyethanaminium Hydrogen[3-(4-fluorobenzyl)-1-hydroxy-2,5-dioxopyrrolidin-3-yl]phosphonate **9b**

White solid (90%), mp 160°C. (Found: C 41.91, H 5.04, N 7.39%. C₁₃H₁₈FN₂O₇P·1/2H₂O requires C 41.81, H 5.13, N 7.51%.) ν_{max} (KBr)/cm⁻¹ 1782, 1697 (C=O). $\delta_{\rm H}$ (D₂O) 7.09–7.06 (m, 4H, ArH), 3.82 (t, *J* 7.75, 2H, CH₂NH₃), 3.64–3.59 (m, 1H, CH₂), 3.14 (t, *J* 7.74, 2H, CH₂OH), 3.06–2.90 (m, 2H, CH₂), 2.74–2.67 (m, 1H, CH₂). $\delta_{\rm C}$ (D₂O) 176.0, 174.2 (C=O), 162.4 (d, *J*_{C,F} 243.13, CF), 131.8, 115.7 (ArC_{tert.}), 57.9 (CH₂OH), 48.9 (d, ¹*J*_{C,P} 126.65, PC), 41.6 (CH₂NH₃), 36.4 (CH₂), 32.2 (CH₂).

2-Hydroxyethanaminium Hydrogen[1-hydroxy-3-(4-methylbenzyl)-2,5-dioxopyrrolidin-3-yl]phosphonate **9c**

White solid (90%), mp 214°C. (Found: C 45.83, H 5.87, N 7.60%. C₁₄H₂₁N₂O₇P·1/2H₂O requires C 45.51, H 6.01, N 7.59%.) ν_{max} (KBr)/cm⁻¹ 1780, 1701 (C=O). $\delta_{\rm H}$ (D₂O) 6.95–6.83 (m, 4H, ArH), 3.56 (m, *J* 6.52, 2H, CH₂NH₃), 3.36–3.32 (m, 1H, CH₂), 2.88 (t, *J* 8.14, 2H, CH₂OH), 2.78–2.67 (m, 2H, CH₂), 2.48–2.41 (m, 1H, CH₂), 2.03 (s, 3H, CH₃). $\delta_{\rm C}$ (D₂O) 174.5, 174.3 (C=O), 138.1, 132.3 (ArC_{quart.}), 130.2, 129.8 (ArC_{tert.}), 57.9 (CH₂OH), 48.0 (d, ¹*J*_{C,P} 127.05, PC), 41.6 (CH₂NH₃), 36.8 (CH₂), 32.3 (CH₂), 20.4 (CH₃).

2-Hydroxyethanaminium Hydrogen(1-hydroxy-3-propyl-2,5-dioxopyrrolidin-3-yl)phosphonate **9d**

White solid (92%), mp 168°C. (Found: C 35.94, H 6.45, N 9.28%. C₉H₁₉N₂O₇P requires C 36.25, H 9.39, N 6.42%.) ν_{max} (KBr)/cm⁻¹ 1780, 1701 (C=O). $\delta_{\rm H}$ (D₂O) 3.82 (t, *J* 5.06, 2H, CH₂NH₃), 3.14 (t, *J* 5.29, 2H, CH₂OH), 3.07–2.81 (m, 2H, CH₂), 2.15–2.05 (m, 1H, CH₂), 1.83–1.74 (m, 1H, CH₂), 1.41–1.33 (m, 1H, CH₂), 1.19–1.06 (m, 1H, CH₂), 0.92 (t, *J* 7.40, 3H, CH₃). $\delta_{\rm C}$ (D₂O) 176.9, 175.8 (C=O), 57.9 (CH₂OH), 48.0 (d, ¹*J*_{C,P} 127.16, PC), 41.6 (CH₂NH₃), 33.8 (d, ²*J*_{C,P} 2.55, CCH₂), 33.3 (CH₂), 17.4 (d, ³*J*_{C,P} 10.69, CH₂CH₃), 13.8 (CH₃).

2-Hydroxyethanaminium Hydrogen[1-hydroxy-3-(4-methoxybenzyl)-2,5-dioxopyrrolidin-3-yl]phosphonate **9e**

White solid (96%), mp 214°C. (Found: C 44.49, H 5.67, N 7.37%. C₁₄H₂₁N₂O₈P requires C 44.69, H 5.62, N 7.44%.) ν_{max} (KBr)/cm⁻¹ 1780, 1716 (C=O). $\delta_{\rm H}$ (D₂O) 7.17–6.95 (m, 4H, ArH), 3.84–3.82 (m, 2H, CH₂NH₃), 3.81 (s, 3H, OCH₃), 3.61–3.56 (m, 1H, CH₂), 3.15 (t, J 5.16, 2H, CH₂OH), 3.05–2.92 (m, 2H, CH₂), 2.74–2.68 (m, 1H, CH₂). $\delta_{\rm C}$ (D₂O) 176.2, 174.4 (C=O), 158.5, 127.9 (ArC_{quart.}), 132.5, 114.6 (ArC_{tert.}), 49.1 (d, ¹J_{C,P} 124.62, PC), 57.9 (CH₂OH), 55.7 (OCH₃), 41.6 (CH₂NH₃), 36.5 (CH₂), 32.3 (CH₂).

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References

- T. Kamiya, K. Hemmi, H. Takeno, M. Hashimoto, *Tetrahedron Lett.* 1980, 21, 95. doi:10.1016/S0040-4039(00)93633-5
- [2] C. E. Mackenna, L. A. Khawli, W. Y. Ahmad, P. Pham, J. P. Bongartz, *Phosphorus Sulfur* 1988, 37, 1.
- [3] H. Watabe, J. Yoshida, E. Tanaka, M. Itoh, S. Miyadoh, T. Shomura, Sci. Rep. Meiji Seika Kaisha 1986, 25, 12.
- [4] K. Ohba, Y. Sato, T. Sasaki, M. Sezaki, Sci. Rep. Meiji Seika Kaisha 1986, 25, 18.

- [5] E. Eguchi, M. Okuhara, M. Kohsaka, H. Aoki, H. Imanaka, J. Antibiot. 1980, 33, 18.
- [6] H. Jomaa, J. Wiesner, S. Sanderbrand, B. Altincicek, C. Weidemeyer, M. Hintz, I. Türbachova, M. Eberl, J. Zeidler, K. H. Lichtenahler, D. Soldati, E. Beck, *Science* 1999, 285, 1573. doi:10.1126/SCIENCE.285.5433.1573
- [7] A. Reichner, J. Wiesner, C. Weidemeyer, E. Dreiseidler, S. Sanderbrand, B. Altincicek, E. Beck, M. Schlitzer, H. Jomaa, *Bioorg. Med. Chem. Lett.* 2001, 11, 833. doi:10.1016/S0960-894X(01)00075-0
- [8] T. Kamiya, K. Hemmi, H. Takeno, M. Hashimoto, *Tetrahedron Lett.* 1980, 21, 95. doi:10.1016/S0040-4039(00)93633-5
- [9] K. Hemmi, H. Takeno, M. Hashimoto, T. Kamiya, Chem. Pharm. Bull. (Tokyo) 1982, 30, 111.
- [10] D. E. Ames, T. Grey, J. Chem. Soc. 1955, 631. doi:10.1039/ JR9550000631
- [11] M. Narita, M. Akiyama, M. Okawara, Bull. Chem. Soc. Jpn. 1971, 44, 437.
- B. M. Trost, L. S. Kallander, J. Org. Chem. 1999, 64, 5427. doi:10.1021/JO990195X
- [13] L. M. Harwood, C. J. Moody, J. M. Percy, in *Experimental Organic Chemistry, 2nd edn* 1999, Ch. 8, pp. 542–544 (Blackwell: Oxford).
- [14] T. Kurz, D. Geffken, C. Wackendorff, Z. Naturforsch. B 2003, 58, 106.
- [15] F. J. Harris, H. L. Brown, D. L. Hobson, R. N. Eckersall (Scottish Agricultural Industries Ltd.), *Brit. Patent* 1347009 1974.