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RESEARCH ARTICLE

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First practical synthesis of novel 1-phosphonylated pyrrolo[1,2-*a*] pyrazine derivatives

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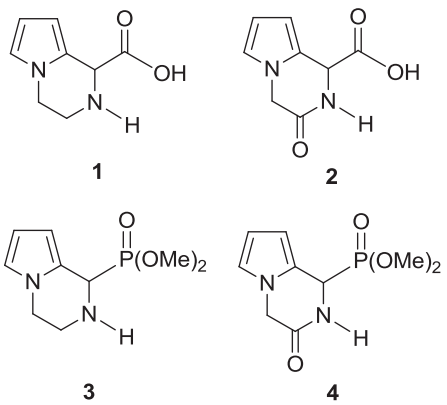
Abstract

We present a convenient synthetic approach to novel 1-phosphonylated pyrrolo[1,2-*a*]pyrazine derivatives based in efficient three-component reactions. According to this method, *N*-functionalized 2-formylpyrrole derivatives are used as bifunctional coupling reagents in the reaction with dialkyl phosphites and amines to access to the target compounds.

1 | INTRODUCTION

Pyrrole derivatives represent a class of singularly interesting heterocyclic compounds.[1] Among these, compounds exhibiting a pyrrole ring sharing a C-N bond with another heterocycles have shown a wide spectrum of biological activities.[2] In this regard, the 1,2,3,4-tetrahydropyrrolo[1,2-*a*] pyrazine core is present in a great number of molecules associated with a wide variety of biological activities, such as antihypoxic,[3] antiarrhythmic,[4] aldose reductase inhibitors,[5] potassium channel ligands,[6] serotonin reuptake inhibitors,[7] and cannabinoid receptor agonists.[8] Particularly, the 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxylic acid **1** and its 3-oxo derivative **2** have been used as key intermediates in the synthesis of bradykinin 1 receptor (B1R) inhibitors[9] and potential physiologically active agents,[10] respectively. Due to the relevant utility exhibited by **1**, **2** and its derivatives, much effort has been dedicated to the synthesis of these compounds.[11],[12] However, to the best of our knowledge, the 1-phosphonylated pyrrolo[1,2-*a*]pyrazine derivatives **3** and **4** represent promising, yet still unexplored synthetic targets, and the development of efficient synthetic approaches to this scaffolds could provide a valuable source of novel pharmacologically active agents, considering the biological profile displayed by the α-aminophosphonic acids and their derivatives.[13]

Considering the high value of these non-proteinogenic amino acids in connection with our current research interest in the synthesis of novel conformationally restricted α-aminophosphonic acids,[14] we report here a convenient synthetic method for the preparation of novel 1-phosphonylated pyrrolo[1,2-*a*]pyrazine derivatives **3** and **4.**



2 | RESULTS AND DISCUSSION

For the synthesis of the target 1-phosphonylated pyrrolo[1,2-*a*]pyrazine derivatives **3** and **4**, and taking in consideration our previous experience in the synthesis of conformationally

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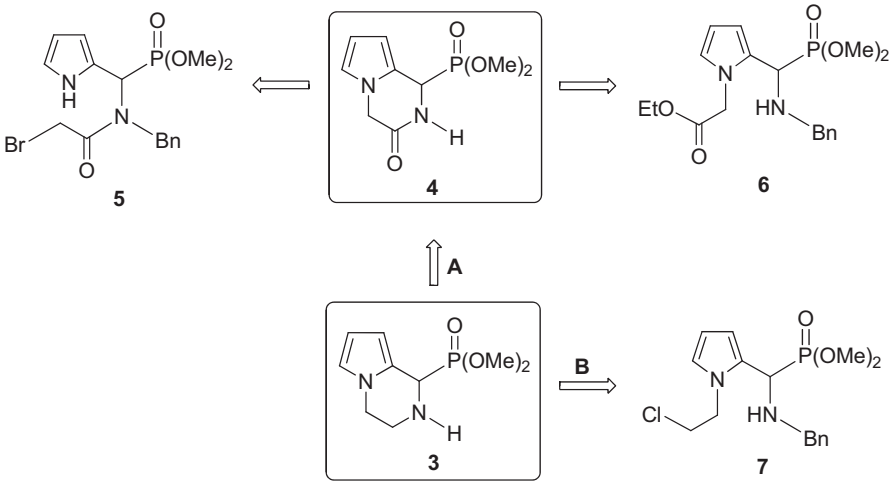
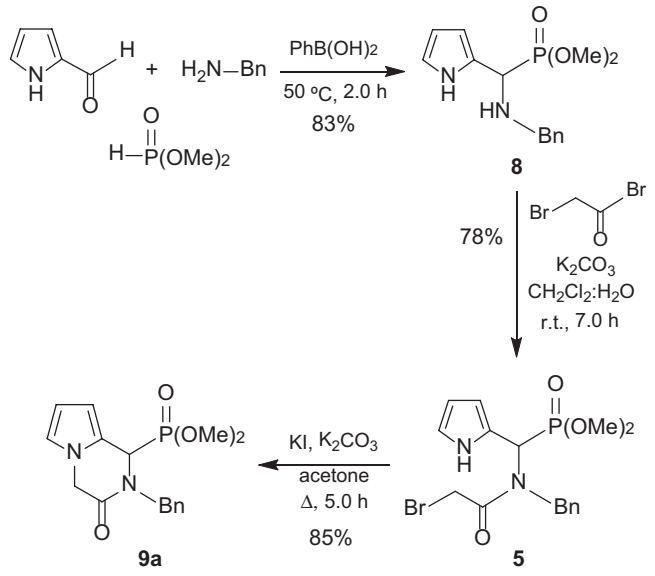


SCHEME 1 Retrosynthetic analysis of phosphopyrrolo[1,2-*a*]pyrazine derivatives **3** and **4**

restricted α-aminophosphonates,[15] we envisaged two synthetic procedures: (1) initially, we proposed that the 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-phosphonate **3** could be obtained by the reduction in the 3-oxo derivative **4** (route A), which in turn could be prepared by *N*-heterocyclization through the pyrrole nitrogen in the α-aminophosphonate **5** or by cyclic amidation of the α-aminophosphonate **6**. Additionally, the compound **3** could also be obtained by intramolecular nucleophilic substitution reaction of the α-aminophosphonate **7** (route B) (Scheme 1).

The synthetic sequence established in the route A began with the reaction of 2-formyl-1*H*-pyrrole with benzylamine and dimethyl phosphite at 50°C in the presence of 10 mol% of phenylboronic acid as catalyst under solvent-free conditions, obtaining the α-aminophosphonate **8** in 83% yield after 2.0 hours,[15b] which was treated with bromoacetyl bromide and K_2CO_3 in a dichloromethane:water mixture, to obtain the corresponding *N*-bromoacetamide **5** in 78% yield.[16] Finally, the treatment of the *N*-bromoacetamide **5** with potassium iodide and K_2CO_3 in acetone at reflux for 5.0 hours,[17] afforded the α-aminophosphonate with the pyrrolo[1,2-*a*]pyrazine core **9a** in 85% yield (Scheme 2).

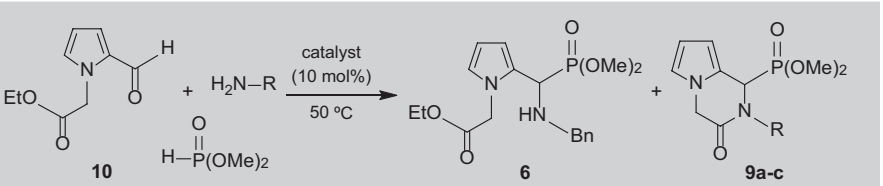


SCHEME 2 Synthesis of the 3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-phosphonate **9a**

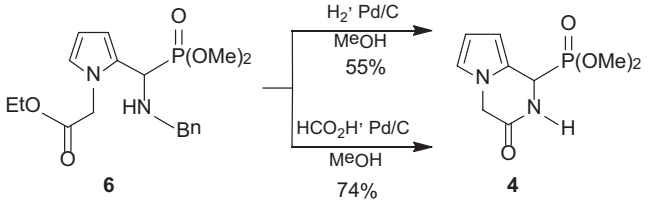
Although this synthetic procedure proved to be a suitable methodology to obtain the target α-aminophosphonate **9a**, we decided to explore an alternative protocol under mild and environmentally friendly reaction conditions. With this purpose in mind, we evaluated the use of ethyl 2-(2-formyl-1*H*-pyrrol-1-yl)acetate **10**[18] as starting material, taking into account the recent application of bifunctional reagents for the synthesis of cyclic α-aminophosphonates.[19] In this context, we carried out the reaction of the dicarbonyl compound **10** with benzylamine and dimethyl phosphite under catalyst and solvent-free conditions at 50°C, to afford only the acyclic α-aminophosphonate **6** in 50% yield after 5.0 hours (Table 1, entry 1). To optimize the reaction conditions, the previously reported phenylphosphonic and phenylboronic acids were tested as catalysts[15b,c] and both promoted the three-component reaction, affording the acyclic α-aminophosphonate **6** in good yield and only traces of cyclic α-aminophosphonate **9a** were isolated (Table 1, entries 2 and 3). This last result encouraged us to carry out the reaction but for a longer period of time. Thus, under the optimized conditions, the dicarbonyl compound **10**, benzylamine, and dimethyl phosphite were reacted in the presence of 10 mol% of phenylboronic acid as catalyst at 50°C for 15.0 hours under solvent-free conditions, obtaining the cyclic α-aminophosphonate **9a** in 65% yield (Table 1, entry 4). Similar results were obtained when other amines, such as allylamine and ethanolamine, were used in this three-component reaction, affording the cyclic α-aminophosphonates **9b** and **9c** in 70 and 62% yield, respectively (Table 1, entries 5 and 6).

With the aim to obtain the cyclic *N*-deprotected α-aminophosphonate **4**, we decided to look back at the acyclic

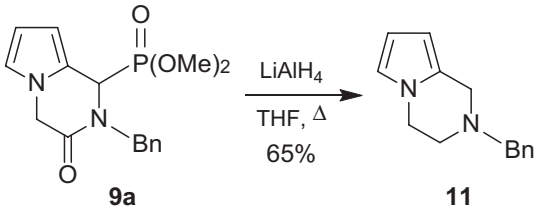
TABLE 1 "One-pot" three-component synthesis of cyclic α-aminophosphonates **9a-c**



Entry	*R*	Catalyst	t (h)	6 (%)	9 (%)
1	**a**; CH_2Ph	—	5	50	—
2	**a**; CH_2Ph	$PhP(O)(OH)_2$	2	65	traces
3	**a**; CH_2Ph	$PhB(OH)_2$	1.5	84	traces
4	**a**; CH_2Ph	$PhB(OH)_2$	15	—	65
5	**b**; $CH_2CH{=}CH_2$	$PhB(OH)_2$	15	—	70
6	**c**; CH_2CH_2OH	$PhB(OH)_2$	15	—	62



SCHEME 3 Synthesis of the 3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-phosphonate **4**



SCHEME 4 Dephosphonation of **9a**

α-aminophosphonate **6**, which by cleavage of the *N*-Bn bond by hydrogenolysis over Pd/C in methanol and subsequent intramolecular cyclization reaction, led to the target molecule **4** in 55% yield. Additionally, when the conditions of the catalytic Leuckart-Wallach-type reaction (HCO_2H, Pd/C) were employed,[20] the α-aminophosphonate **4** was obtained in 74% yield (Scheme 3).

With the cyclic α-aminophosphonate **9a** in hand, the next step consisted in the reduction in the carbonyl group of the lactam ring according to the retrosynthetic analysis showed in the Scheme 1 (route A), which would provide directly the target 1-phosphonated pyrrolo[1,2-*a*]pyrazine **3**. However, when we carried out the reaction of the cyclic α-aminophosphonate **9a** with $LiAlH_4$ in anhydrous THF at reflux, the *C*-dephosphonation also occurred, giving the 2-benzyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine **11** in 65% yield (Scheme 4). These results are in agreement with the results obtained for us, when the isoindolin-1-one-3-phosphonates[21] were reacted under similar reaction conditions.

Therefore, we tested as an alternative route for the synthesis of 1-phosphonated pyrrolo[1,2-*a*]pyrazine **3**, an one-pot reaction using the *N*-(2-chloroethyl)pyrrole derivative **12** as starting material,[22] which would allow access to this heterocyclic core without the need for additional reduction in the amide group. In this context, we initially explored the reaction of *N*-alkylated 2-formylpyrrole **12**, benzylamine, and dimethyl phosphite at reflux in the presence of 10 mol% of phenylboronic acid as catalyst in benzene for 1.5 hours, obtaining the desired α-aminophosphonate **13a** in 60% yield (Table 2, entry 1). To determine the optimal conditions, the reaction was conducted in the presence of an organic base (Et_3N), which produced the α-aminophosphonate **13a** in 68% yield (Table 2, entry 2). Additionally, when the one-pot three-component reaction was carried out in acetonitrile at reflux, the desired cyclic α-aminophosphonate **13a** was obtained in 75% yield (Table 2, entry 3). After optimization of the experimental conditions with benzylamine, we extended this transformation to other aliphatic amines, such as allylamine and *p*-methoxybenzylamine, obtaining the cyclic α-aminophosphonates **13b** and **13c** in 62 and 75% yield, respectively (Table 2, entries 4 and 5).

Once the cyclic α-aminophosphonate **13a** was obtained, it was treated under catalytic hydrogenolysis conditions (H_2, Pd/C), to carried out the cleavage of the *N*-benzyl bond; however, under this conditions, the product of *C*-dephosphonation **11** was also obtained in 68% yield (Scheme 5).

Considering the previous results, we decided to use ammonia as an alternative nitrogen source in order to avoid the removal step of the nitrogen protecting group. Thus, the *N*-(2-chloroethyl)pyrrole derivative **12**, ammonium acetate, and diethyl or dimethyl phosphite were reacted in the presence of anhydrous sodium sulfate at 60°C in nitromethane, obtaining the expected ethyl and methyl phosphonates **14** and **3** in 18 and 36% yield, respectively (Table 3, entries 1 and 2). On the other hand, when we perform the three-component reaction using acetonitrile as solvent, the

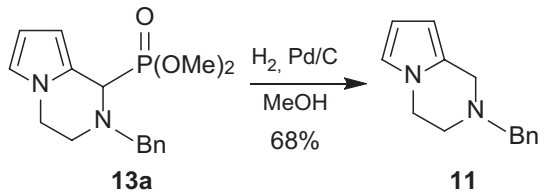
Entry	*R*	Product	Solvent	Base	Yield (%)
1	CH_2Ph	**13a**	PhH	—	60
2	CH_2Ph	**13a**	PhH	Et_3N	68
3	CH_2Ph	**13a**	MeCN	Et_3N	75
4	$CH_2CH{=}CH_2$	**13b**	MeCN	Et_3N	62
5	$CH_2C_6H_4OMe$	**13c**	MeCN	Et_3N	75

TABLE 2 Synthesis of the 1-phosphonated pyrrolo[1,2-*a*]pyrazine **13a-c**

desired cyclic α-aminophosphonates **14** and **3** were obtained in 47% and 52% yield, respectively (Table 3, entries 3 and 4).

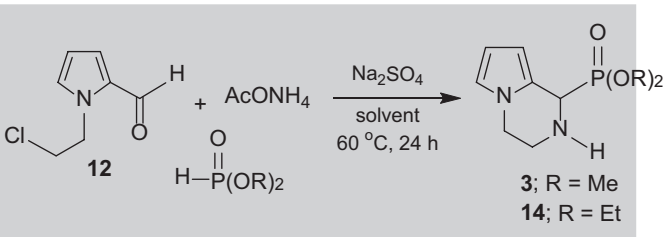
3 | CONCLUSIONS

In summary, we have described a novel and effective method for the synthesis of 1-phosphonated pyrrolo[1,2-*a*]pyrazine derivatives **3** and **4** via highly efficient three-component reactions in both cases. A distinctive feature of these procedures is the use of bifunctional azaheterocyclic reagents **10** and **12** as starting materials. The synthetic approach described in this study may find wide application in the large-scale synthesis of cyclic α-aminophosphonates of biological interest.



SCHEME 5 Dephosphonation of **13a**

TABLE 3 Synthesis of the 1-phosphonated pyrrolo[1,2-*a*] pyrazine derivatives **3** and **14**



Entry	*R*	Product	Solvent	Yield (%)
1	Et	**14**	$MeNO_2$	18
2	Me	**3**	$MeNO_2$	36
3	Et	**14**	MeCN	47
4	Me	**3**	MeCN	52

4 | EXPERIMENTAL

All commercial materials were used as received unless otherwise noted. Flash chromatography was performed with 230- to 400-mesh Silica Flash 60®. Thin layer chromatography was performed with pre-coated TLC sheets of silica gel (60 F_{254}, Merck), and the plates were visualized with UV light, iodine vapors, and ninhydrin. Melting points were determined with a Fisher-Johns apparatus and are uncorrected. NMR spectra were recorded on a Varian instrument (400 MHz for ^1H) or a Mercury instrument (200 MHz for ^1H) and calibrated using the TMS, $P(O)Ph_3$ and the residual solvent signal as internal standards; chemical shifts (δ) are expressed in parts per million (ppm) and coupling constants (*J*) in Hertz. High resolution FAB^+ and CI^+ mass spectra (HRMS) were obtained on a JEOL MStation MS-700.

4.1 | Dimethyl ([benzylamino][1*H*-pyrrol-2-yl]methyl)phosphonate (8)

To a mixture of 2-formyl-1*H*-pyrrole (1.0 g, 10.5 mmol) and benzylamine (1.2 g, 1.2 mL, 11.0 mmol) was added $PhB(OH)_2$ (0.13 g, 1.1 mmol). The reaction mixture was stirred at room temperature for 15 minutes. After this time, dimethyl phosphite (1.2 g, 1.0 mL, 10.5 mmol) was added, and the reaction mixture was stirred at 50°C for 2.0 hours. The crude was purified by flash column chromatography using AcOEt as eluent, to give (2.5 g, 80% yield) of **8** as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ=2.04 (bs, 1H, NH), 3.50 (d, *J*=10.4 Hz, 3H, $[CH_3O]_2P$), 3.61 (AB system, *J*=13.6 Hz, 1H, CH_2Ph), 3.76 (d, *J*=10.4 Hz, 3H, $[CH_3O]_2P$), 3.82 (AB system, *J*=13.6 Hz, 1H, CH_2Ph), 4.10 (d, *J*=19.2 Hz, 1H, CHP), 6.15-6.17 (m, 2H, pyrrole-H), 6.80-6.82 (m, 1H, pyrrole-H), 7.20-7.30 (m, 5H, H_{arom}), 9.10

(bs, 1H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=51.3 (d, *J*=16.2 Hz, CH_2Ph), 52.4 (d, *J*=158.2 Hz, CHP), 53.6 (d, *J*=7.3 Hz, $[CH_3O]_2P$), 54.0 (d, *J*=7.3 Hz, $[CH_3O]_2P$), 108.4 (C4-pyrrole), 109.7 (d, *J*=10.3 Hz, C3-pyrrole), 118.9 (C5-pyrrole), 124.9 (C2-pyrrole), 127.4, 128.5, 128.6, 139.5 ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=20.64 ppm. HRMS (FAB^+): calcd. for $C_{14}H_{20}N_2O_3P$ $[M+H]^+$, *m/z* 295.1212; found for $[M+H]^+$, *m/z* 295.1196.

4.2 | Dimethyl ([*N*-benzyl-2-bromoacetamido][1*H*-pyrrol-2-yl]methyl) phosphonate (5)

To a solution of **8** (1.0 g, 3.4 mmol) in 30 mL of CH_2Cl_2:H_2O (2:1) was added K_2CO_3 (0.5 g, 3.7 mmol). When the addition was complete, the reaction was cooled at 0°C, and bromoacetyl bromide (1.0 g, 0.4 mL, 4.7 mmol) was added dropwise. The reaction mixture was stirred for 6.0 hours at room temperature, filtered, and evaporated under reduced pressure and the crude product was purified by flash column chromatography using Hex:AcOEt (50:50) as eluent, obtaining **5** (1.0 g, 78% yield) as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.66 (d, *J*=10.8 Hz, 3H, $[CH_3O]_2P$), 3.70 (s, 2H, CH_2Br), 3.71 (d, *J*=20.4 Hz, 1H, CHP), 3.78 (d, *J*=10.8 Hz, 3H, $[CH_3O]_2P$), 4.76 (AB system, *J*=17.8 Hz, 1H, CH_2Ph), 5.00 (AB system, *J*=17.8 Hz, 1H, CH_2Ph), 6.07-6.13 (m, 1H, pyrrole-H), 6.30-6.33 (m, 1H, pyrrole-H), 6.70 (m, 1H, pyrrole-H), 6.85-6.90 (m, 2H, H_{arom}), 7.18-7.21 (m, 3H, H_{arom}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=26.8 (CH_2Br), 48.8 (d, *J*=159.5 Hz, CHP), 50.5 (CH_2Ph), 53.5 (d, *J*=5.9 Hz, $[CH_3O]_2P$), 54.0 (d, *J*=5.9 Hz, $[CH_3O]_2P$), 108.8 (C4-pyrrole), 111.7 (d, *J*=10.2 Hz, C3-pyrrole), 119.6 (C5-pyrrole), 121.4 (C2-pyrrole), 125.9, 127.5, 128.8, 136.4, 168.1 (C=O) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=22.06 ppm. HRMS (FAB^+): calcd. for $C_{16}H_{21}BrN_2O_4P$ $[M+H]^+$, *m/z* 415.0422; found for $[M+H]^+$, *m/z* 415.0447.

4.3 | Dimethyl (2-benzyl-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazin-1-yl) phosphonate (9a)

A mixture of potassium iodide (0.7 g, 2.9 mmol), K_2CO_3 (0.4 g, 4.0 mmol), and the compound **5** (1.0 g, 2.6 mmol) in acetone (100 mL) was refluxed for 5.0 hours. The reaction mixture was cooled, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography using Hex:AcOEt (10:90) as eluent, obtaining **9a** (0.9 g, 85% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.60 (d, *J*=10.4 Hz, 3H, $[CH_3O]_2P$), 3.70 (d, *J*=10.4 Hz, 3H, $[CH_3O]_2P$), 4.20 (AB system, *J*=15.4 Hz, 1H, CH_2C=O), 4.70 (dd, *J*=16.6, 2.0 Hz, 1H, CH_2Ph), 4.75 (d, *J*=12.8 Hz, 1H, CHP), 4.87 (dd, *J*=16.6, 3.6 Hz, 1H, CH_2Ph), 5.10 (AB system, *J*=15.4 Hz, 1H, CH_2C=O), 5.99-6.01 (ddd, *J*=3.2, 3.0, 1.6 Hz, 1H, pyrrole-H), 6.20 (dd, *J*=3.2, 2.8 Hz, 1H, pyrrole-H), 6.68 (ddd, *J*=3.0, 2.8, 1.6 Hz, 1H, pyrrole-H), 7.18-7.20 (m, 2H, H_{arom}), 7.27-7.33 (m, 3H, H_{arom}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=48.7 (CH_2C=O), 49.4 (CH_2Ph), 51.5 (d, *J*=158.0 Hz, CHP), 53.1 (d, *J*=7.3 Hz, $[CH_3O]_2P$), 54.3 (d, *J*=7.3 Hz, $[CH_3O]_2P$), 106.1 (d, *J*=7.3 Hz, C3-pyrrole), 109.7 (C4-pyrrole), 118.6 (C5-pyrrole), 119.8 (C2-pyrrole), 127.8, 128.1, 128.8, 135.3, 165.6 (C=O) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=19.37 ppm. HRMS (FAB^+): calcd. for $C_{16}H_{20}N_2O_4P$ $[M+H]^+$, *m/z* 335.1161; found for $[M+H]^+$, *m/z* 335.1143.

4.4 | General procedure for the synthesis of cyclic α-aminophosphonates 9a-c

To a mixture of ethyl 2-(2-formyl-1*H*-pyrrol-1-yl)acetate **10** (1 equiv) and the corresponding amine (1.05 equiv) was added $PhB(OH)_2$ (0.1 equiv). The reaction mixture was stirred at room temperature for 15 minutes. After this time, dimethyl phosphite (1 equiv) was added, and the reaction mixture was stirred at 50°C for 15 hours. Finally, the crude product was purified by flash column chromatography.

4.4.1 | Dimethyl (2-benzyl-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazin-1-yl) phosphonate (9a)

According to the general procedure, ethyl 2-(2-formyl-1*H*-pyrrol-1-yl)acetate **10** (1.5 g, 8.3 mmol), benzylamine (0.9 g, 0.9 mL, 8.7 mmol), $PhB(OH)_2$ (0.1 g, 0.8 mmol), and dimethyl phosphite (0.9 g, 0.8 mL, 8.3 mmol) were reacted, and the crude was purified by flash column chromatography using Hex:AcOEt (10:90) as eluent, to obtain **9a** (1.9 g, 65% yield) as a yellow oil. The spectroscopic data are identical to those describe above.

4.4.2 | Dimethyl (2-allyl-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazin-1-yl) phosphonate (9b)

According to the general procedure, ethyl 2-(2-formyl-1*H*-pyrrol-1-yl)acetate **10** (0.3 g, 2.3 mmol), allylamine (130 mg, 0.2 mL, 2.4 mmol), $PhB(OH)_2$ (30 mg, 0.2 mmol), and dimethyl phosphite (0.3 g, 0.2 mL, 2.3 mmol) were reacted, and the crude was purified by flash column chromatography using Hex:Acetone (70:30) as eluent, to obtain **9b** (0.5 g, 70% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.60 (d, *J*=10.8 Hz, 3H, $[CH_3O]_2P$), 3.61 (dd, *J*=15.6, 8.0 Hz, 1H, CH_2N), 3.70 (d, *J*=10.8 Hz, 3H, $[CH_3O]_2P$), 4.62 (dd, *J*=16.4, 2.0 Hz, 1H, CH_2C=O), 4.79 (dd, *J*=16.4, 4.0 Hz, 1H, CH_2C=O), 4.90 (d, *J*=12.8 Hz,

1H, CHP), 5.00 (dddd, *J*=15.6, 3.6, 2.0, 2.0 Hz, 1H, CH_2N), 5.14-5.23 (m, 2H, CH_2), 5.70 (dddd, *J*=18.8, 8.0, 6.0, 4.0 Hz, 1H, CH), 6.10 (ddd, *J*=3.6, 3.6, 1.6 Hz, 1H, pyrrole-H), 6.20 (dd, *J*=3.6, 3.6 Hz, 1H, pyrrole-H), 6.65 (m, 1H, pyrrole-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=48.3 (CH_2N), 49.6 (CH_2C=O), 51.7 (d, *J*=161.0 Hz, CHP), 53.4 (d, *J*=8.0 Hz, $[CH_3O]_2P$), 54.6 (d, *J*=8.0 Hz, $[CH_3O]_2P$), 106.3 (d, *J*=7.3 Hz, C3-pyrrole), 110.0 (C4-pyrrole), 118.7 (C5-pyrrole), 119.3 (CH_2), 120.1 (C2-pyrrole), 131.6 (CH), 165.5 (C=O) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=21.23 ppm. HRMS (FAB^+): calcd. for $C_{12}H_{18}N_2O_4P$ $[M+H]^+$, *m/z* 285.1004; found for $[M+H]^+$, *m/z* 285.1022.

4.4.3 | Dimethyl (2-[2-hydroxyethyl]-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazin-1-yl) phosphonate (9c)

According to the general procedure, ethyl 2-(2-formyl-1*H*-pyrrol-1-yl)acetate **10** (0.5 g, 4.2 mmol), ethanolamine (0.3 g, 0.3 mL, 4.4 mmol), $PhB(OH)_2$ (50 mg, 0.4 mmol), and dimethyl phosphite (0.5 g, 0.4 mL, 4.2 mmol) were reacted, and the crude was purified by flash column chromatography using CH_2Cl_2:*i*-PrOH (95:5) as eluent, to obtain **9c** (0.8 g, 62% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.40 (ddd, *J*=14.4, 7.2, 4.4 Hz, 1H, CH_2N), 3.60 (d, *J*=10.4 Hz, 3H, $[CH_3O]_2P$), 3.65 (d, *J*=10.4 Hz, 3H, $[CH_3O]_2P$), 3.74-3.77 (m, 2H, CH_2OH), 4.15 (ddd, *J*=14.4, 4.4, 4.4 Hz, 1H, CH_2N), 4.60 (dd, *J*=16.4, 2.0 Hz, 1H, CH_2C=O), 4.74 (dd, *J*=16.4, 4.0 Hz, 1H, CH_2C=O), 5.10 (d, *J*=12.8 Hz, 1H, CHP), 6.10 (ddd, *J*=3.2, 3.2, 1.6 Hz, 1H, pyrrole-H), 6.20 (dd, *J*=3.2, 3.2 Hz, 1H, pyrrole-H), 6.60 (m, 1H, pyrrole-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=49.3 (CH_2C=O), 50.5 (CH_2N), 53.3 (d, *J*=7.4 Hz, $[CH_3O]_2P$), 54.4 (d, *J*=7.4 Hz, $[CH_3O]_2P$), 54.9 (d, *J*=158.2 Hz, CHP), 61.4 (CH_2OH), 106.1 (d, *J*=5.8 Hz, C3-pyrrole), 109.8 (C4-pyrrole), 118.6 (C5-pyrrole), 119.9 (C2-pyrrole), 166.4 (C=O) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=21.04 ppm. HRMS (FAB^+): calcd. for $C_{11}H_{18}N_2O_5P$ $[M+H]^+$, *m/z* 289.0953; found for $[M+H]^+$, *m/z* 289.0963.

4.5 | Ethyl 2-(2-([benzylamino][dimethoxyphosphoryl]methyl)-1*H*-pyrrol-1-yl) acetate (6)

To a mixture of ethyl 2-(2-formyl-1*H*-pyrrol-1-yl)acetate **10** (1.0 g, 5.6 mmol) and benzylamine (1.0 g, 1.0 mL, 5.8 mmol) was added $PhB(OH)_2$ (60 mg, 0.6 mmol). The reaction mixture was stirred at room temperature for 15 minutes. After this time, dimethyl phosphite (0.6 g, 0.50 mL, 5.6 mmol) was added, and the reaction mixture was stirred at 50°C for 1.5 hours. The crude was purified by flash column chromatography using Hex:Acetone (70:30) as eluent, obtaining **6** (1.8 g, 84% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.23 (t, *J*=5.6 Hz, 3H, CH_3), 3.54 (d, *J*=10.0 Hz, 3H, $[CH_3O]_2P$), 3.62 (AB system, *J*=13.6 Hz, 1H, CH_2Ph), 3.71(d, *J*=10.4 Hz, 3H, $[CH_3O]_2P$), 3.73 (AB system, *J*=13.6 Hz, 1H, CH_2Ph), 4.12 (q, *J*=6.8 Hz, 2H, CH_2O), 4.14 (d, *J*=20.4 Hz, 1H, CHP), 4.79 (AB system, *J*=17.8 Hz, 1H, CH_2C=O), 4.95 (AB system, *J*=17.8 Hz, 1H, CH_2C=O), 6.18 (dd, *J* = 3.0, 3.2 Hz, 1H, pyrrole-H), 6.24-6.26 (m, 1H, pyrrole-H), 6.65-6.67 (m, 1H, pyrrole-H), 7.24-7.32 (m, 5H, H_{arom}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (CH_3), 48.8 (CH_2C=O), 51.4 (d, *J*=14.7 Hz, CH_2Ph), 53.0 (d, *J*=169.9 Hz, CHP), 53.4 (d, *J*=7.3 Hz, $[CH_3O]_2P$), 53.6 (d, *J*=7.3 Hz, $[CH_3O]_2P$), 61.3 (CH_2O), 108.3 (C4-pyrrole), 110.7 (d, *J*=7.3 Hz, C3-pyrrole), 124.2 (d, *J*=2.9 Hz, C5-pyrrole), 125.6 (d, *J*=4.4 Hz, C2-pyrrole), 127.2, 128.4, 128.5, 139.5, 169.1 (C=O) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=19.75 ppm. HRMS (FAB^+): calcd. for $C_{18}H_{25}N_2O_5P$ $[M+H]^+$, *m/z* 381.1579; found for $[M+H]^+$, *m/z* 381.1569.

4.6 | Dimethyl (3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-yl) phosphonate (4)

A solution of formic acid (0.5 mL) in methanol (5 mL) was added dropwise to a mixture of **6** (1.0 g, 2.6 mmol) and 10% Pd/C (0.2 g) in methanol (20 mL) under N_2 atmosphere. The reaction mixture was vigorously stirred at room temperature for 10 hours, filtered, and concentrated under reduced pressure and the crude product was purified by flash column chromatography using CH_2Cl_2:MeOH (98:2), to afford the compound **4** (0.5 g, 73% yield) as a yellow oil. ^{1}H NMR (400 MHz, CD_3OD): δ=3.60 (d, *J*=10.8 Hz, 3H, $[CH_3O]_2P$), 3.65 (d, *J*=10.8 Hz, 3H, $[CH_3O]_2P$), 4.54 (dd, *J*=17.6, 2.8 Hz, 1H, CH_2C=O), 4.61 (dd, *J*=17.6, 4.0 Hz, 1H, CH_2C=O), 5.02 (d, *J*=12.4 Hz, 1H, CHP), 6.08 (ddd, *J*=3.6, 3.6, 1.6 Hz, 1H, pyrrole-H), 6.13 (dd, *J*=3.6, 3.6 Hz, 1H, pyrrole-H), 6.68 (ddd, *J*=2.6, 2.6, 1.6 Hz, 1H, pyrrole-H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ=49.1 (d, *J*=161.0 Hz, CHP), 49.2 (CH_2), 54.6 (d, *J*=7.4 Hz, $[CH_3O]_2P$), 55.1 (d, *J*=7.4 Hz, $[CH_3O]_2P$), 107.4 (d, *J*=6.1 Hz, C4-pyrrole), 110.9 (d, *J*=3.0 Hz, C3-pyrrole), 118.3 (C5-pyrrole), 121.3 (C2-pyrrole), 169.7 (C=O) ppm. ^{31}P NMR (81 MHz, CD_3OD): δ=22.31 ppm. HRMS (FAB^+): calcd. for $C_9H_{14}N_2O_4P$ $[M+H]^+$, *m/z* 245.0691; found for $[M+H]^+$, *m/z* 245.0672.

4.7 | 2-Benzyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine (11)

4.7.1 | Method A

To a suspension of $LiAlH_4$ (70 mg, 1.8 mmol) in anhydrous THF (5 mL) at 0°C was added slowly the cyclic α-aminophosphonate **9a** (0.2 g, 0.6 mmol) in anhydrous THF (5 mL). The reaction mixture was allowed to warm to room

temperature and stirred for 30 minutes. After this time, AcOEt (5 mL) and H_2O (5 mL) were added and the resulting mixture was refluxed for 1 hour. The reaction mixture was extracted with AcOEt (3 x 5 mL), and the combined organic layer was washed with H_2O (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography using AcOEt:Hex (1:1) as eluent, obtaining **11** (83 mg, 65% yield) as a yellow oil.

4.7.2 | Method B

10% Pd/C (20 mg) was added to a solution of the cyclic α-aminophosphonate **13a** (100 mg, 0.3 mmol) in MeOH (3 mL). The reaction mixture was vigorously stirred under hydrogen for 24 hours, filtered, and concentrated under reduced pressure and the crude product was purified by flash column chromatography using AcOEt:Hex (1:1) as eluent, to afford compound **11** (45 mg, 68% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.83 (t, *J*=5.4 Hz, 2H, CH_2N), 3.65 (s, 2H, CH_2Ar), 3.67 (s, 2H, CH_2N), 3.97 (t, *J*=5.4 Hz, 2H, NCH_2), 5.79-5.81 (m, 1H, pyrrole-H), 6.13 (dd, *J*=3.6, 2.6 Hz, 1H, pyrrole-H), 6.54 (dd, *J*=2.6, 1.6 Hz, 1H, pyrrole-H), 7.27-7.39 (m, 5H, H_{arom}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=44.9 (NCH_2), 50.7 (CH_2N), 51.5 (CH_2N), 62.6 (CH_2Ar), 102.9 (C4-pyrrole), 108.3 (C3-pyrrole), 118.6 (C5-pyrrole), 127.3 (C2-pyrrole), 127.5, 128.6, 129.3, 138.2 ppm. HRMS (FAB$^+$): calcd. for $C_{14}H_{17}N_2$ $[M+H]^+$, *m/z* 213,1392; found for $[M+H]^+$, *m/z* 213.1387.

4.8 | General procedure for the synthesis of cyclic α-aminophosphonates 13a-c

To a mixture of *N*-(2-chloroethyl)pyrrole derivative **12** (1 equiv) and the corresponding amine (1.05 equiv) in MeCN was added $PhB(OH)_2$ (0.1 equiv). The reaction mixture was stirred at room temperature for 15 minutes. After this time, dimethyl phosphite (1 equiv) and triethylamine (1 equiv) were added, and the reaction mixture was stirred at 90°C for 1.5 hours. The solvent was evaporated under reduced pressure, and the crude was purified by flash column chromatography using AcOEt:Hex (90:10) as eluent.

4.8.1 | Dimethyl (2-benzyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazin-1-yl) phosphonate (13a)

According to the general procedure, *N*-(2-chloroethyl)pyrrole derivative **12** (2.0 g, 12.7 mmol), benzylamine (1.4 g, 1.4 mL, 13.3 mmol), $PhB(OH)_2$ (150 mg, 1.3 mmol), dimethyl phosphite (1.4 g, 1.2 mL, 12.7 mmol), and triethylamine (1.3 g, 1.8 mL, 12.7 mmol) in MeCN (20 mL) were reacted, to obtain **13a** (3.1 g, 75% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.94 (ddd, *J*=14.4, 5.2, 5.2 Hz, 1H, CH_2N), 3.65 (d, *J*=10.4 Hz, 3H, $[CH_3O]_2P$), 3.69 (d, *J*=10.4 Hz, 3H, $[CH_3O]_2P$), 3.75-3.87 (m, 2H, NCH_2), 3.86 (AB system, *J*=12.8 Hz, 1H, CH_2Ph), 3.98 (AB system, *J*=12.8 Hz, 1H, CH_2Ph), 4.00-4.08 (ddd, *J*=12.0, 10.4, 3.2 Hz, 1H, CH_2N), 4.33 (d, *J*=19.2 Hz, 1H, CHP), 6.04-6.07 (m, 1H, pyrrole-H), 6.16 (dd, *J*=3.6, 2.8 Hz, 1H, pyrrole-H), 6.63 (m, 1H, pyrrole-H), 7.25-7.39 (m, 5H, H_{arom}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=40.7 (CH_2N), 45.7 (CH_2N), 53.5 (d, *J*=7.4 Hz, $[CH_3O]_2P$), 55.3 (d, *J*=164.0 Hz, CHP), 59.0 (d, *J*=11.7 Hz, CH_2Ph), 107.0 (d, *J*=5.8 Hz, C3-pyrrole), 108.1 (C4-pyrrole), 119.9 (C5-pyrrole), 120.1 (C2-pyrrole), 127.5, 128.4, 129.0, 138.0 ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=21.58 ppm. HRMS (FAB$^+$): calcd. for $C_{16}H_{22}N_2O_3P$ $[M+H]^+$, *m/z* 321.1368; found for $[M+H]^+$, *m/z* 321.1207.

4.8.2 | Dimethyl (2-allyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazin-1-yl) phosphonate (13b)

According to the general procedure, *N*-(2-chloroethyl)pyrrole derivative **12** (0.8 g, 4.7 mmol), allylamine (0.3 g, 0.4 mL, 5.0 mmol), $PhB(OH)_2$ (60 mg, 0.5 mmol), dimethyl phosphite (0.5 g, 0.4 mL, 4.7 mmol), and triethylamine (0.5 g, 0.7 mL, 4.7 mmol) in MeCN (8 mL) were reacted, to obtain **13b** (0.9 g, 62% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.00 (ddd, *J*=14.4, 4.0, 3.2 Hz, 1H, NCH_2), 3.37-3.40 (m, 2H, NCH_2CH), 3.70 (d, *J*=10.4 Hz, 3H, $[CH_3O]_2P$), 3.75 (d, *J*=10.4 Hz, 3H, $[CH_3O]_2P$), 3.77-3.80 (m, 1H, NCH_2), 3.81-3.86 (m, 1H, CH_2N), 4.00 (ddd, *J*=12.0, 10.4, 3.2 Hz, 1H, CH_2N), 4.35 (d, *J*=20.8 Hz, 1H, CHP), 5.18-5.24 (m, 2H, $CH=CH_2$), 5.83-5.93 (m, 1H, $CH=CH_2$), 6.04-6.06 (m,1H, pyrrole-H), 6.15 (dd, *J*=3.2, 2.4 Hz, 1H, pyrrole-H), 6.61-6.62 (m, 1H, pyrrole-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=40.3 (CH_2N), 46.0 (CH_2N), 53.5 (d, *J*=7.6 Hz, $[CH_3O]_2P$), 53.7 (d, *J*=7.4 Hz, $[CH_3O]_2P$), 54.7 (d, *J*=167.6 Hz, CHP), 57.9 (d, *J*=13.4 Hz, NCH_2CH), 106.9 (d, *J*=5.9 Hz, C3-pyrrole), 108.0 (d, *J*=3.0 Hz, C4-pyrrole), 118.0 (C5-pyrrole), 118.6 ($CH=CH_2$), 120.0 (C2-pyrrole), 135.0 ($CH=CH_2$) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=20.46 ppm. HRMS (FAB$^+$): calcd. for $C_{12}H_{20}N_2O_3P$ $[M+H]^+$, *m/z* 271.1212; found for $[M+H]^+$, *m/z* 271.1140.

4.8.3 | Dimethyl (2-(4-methoxybenzyl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazin-1-yl) phosphonate (13c)

According to the general procedure, *N*-(2-chloroethyl)pyrrole derivative **12** (0.5 g, 3.3 mmol), *p*-methoxybenzylamine (0.5 g, 0.5 mL, 3.5 mmol), $PhB(OH)_2$ (40 mg, 0.3 mmol), dimethyl phosphite (0.4 g, 0.3 mL, 3.3 mmol), and triethylamine (0.3 g, 0.5 mL, 3.3 mmol) in MeCN (5 mL) were reacted to obtain **13c** (1.0 g, 75% yield) as a yellow oil. ^{1}H

NMR (400 MHz, $CDCl_3$): δ=2.90 (ddd, *J*=12.0, 4.0, 4.0 Hz, 1H, CH_2N), 3.65 (d, *J*=10.5 Hz, 3H, $[CH_3O]_2P$), 3.66 (AB system, *J*=12.8 Hz, 1H, CH_2Ar), 3.70 (d, *J*=10.5 Hz, 3H, $[CH_3O]_2P$), 3.75-3.79 (m, 1H, CH_2N), 3.80 (s, 3H, OCH_3), 3.82-3.85 (m, 1H, CH_2N), 3.90 (AB system, *J*=12.8 Hz, 1H, CH_2Ar), 3.99-4.06 (m, 1H, CH_2N), 4.30 (d, *J*=19.6 Hz, 1H, CHP), 6.03-6.05 (m, 1H, pyrrole-H), 6.20 (dd, *J*=3.5, 2.8 Hz, 1H, pyrrole-H), 6.62-6.63 (m, 1H, pyrrole-H), 6.86 (AA'BB', *J*=8.7 Hz, 2H, H_{arom}), 7.30 (AA'BB', *J*=8.7 Hz, 2H, H_{arom}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=40.9 (CH_2N), 45.7 (CH_2N), 53.7 (d, *J*=7.4 Hz, $[CH_3O]_2P$), 55.4 (d, *J*=163.9 Hz, CHP), 55.5 (CH_3O), 58.5 (d, *J*=11.7 Hz, CH_2Ar), 107.2 (d, *J*=5.9 Hz, C3-pyrrole), 108.3 (C4-pyrrole), 114.0, 120.3 (C5-pyrrole), 130.3 (C2-pyrrole), 130.5, 159.3 ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=21.60 ppm. HRMS (FAB^+): calcd. for $C_{17}H_{24}N_2O_4P$ $[M+H]^+$, *m/z* 351.1474; found for $[M+H]^+$, *m/z* 351.1447.

4.9 | Diethyl (1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-yl)phosphonate (14)

To a mixture of *N*-(2-chloroethyl)pyrrole derivative **12** (0.5 g, 3.2 mmol) and ammonium acetate (3.7 g, 47.6 mmol) in MeCN (15 mL) was added dimethyl phosphite (0.5 g, 0.5 mL, 3.4 mmol) and Na_2SO_4 (1.5 g) under N_2 atmosphere, and the reaction mixture was stirred at 60°C for 24 hours. After this time, the reaction mixture was concentrated under reduced pressure and filtered and the crude was purified by flash column chromatography using CH_2Cl_2:MeOH (95:5) as eluent, obtaining **14** (0.4 g, 47% yield) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ=1.21 (t, *J*=7.2 Hz, 3H, CH_3), 1.27 (t, *J*=7.2 Hz, 3H, CH_3), 3.07 (ddd, *J*=12.0, 6.8, 4.4 Hz, 1H, CH_2NH), 3.45 (m, 1H, CH_2NH), 3.88-3.93 (m, 2H, CH_2N), 3.97-4.21 (m, 4H, $[CH_2O]_2P$), 4.50 (d, *J*=14.8 Hz, 1H, CHP), 6.09-6.14 (m, 2H, pyrrole-H), 6.55 (sa, 1H, pyrrole-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=16.6 (d, *J*=5.6 Hz, CH_3), 42.1 (d, *J*=8.9 Hz, CH_2NH), 45.4 (CH_2N), 51.2 (d, *J*=156.8 Hz, CHP), 62.9 (d, *J*=7.4 Hz, $[CH_2O]_2P$), 63.4 (d, *J*=7.4 Hz, $[CH_2O]_2P$), 106.0 (C3-pyrrole), 108.1 (C4-pyrrole), 120.1 (C5-pyrrole), 120.8 (C2-pyrrole) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=21.79 ppm. HRMS (FAB^+): calcd. for $C_{11}H_{20}N_2O_3P$ $[M+H]^+$, *m/z* 259.1212; found for $[M+H]^+$, *m/z* 259.1127.

4.10 | Dimethyl (1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-yl) phosphonate (3)

To a mixture of *N*-(2-chloroethyl)pyrrole derivative **12** (0.5 g, 3.2 mmol) and ammonium acetate (3.7 g, 47.6 mmol) in MeCN (15 mL) was added dimethyl phosphite (0.4 g, 0.2 mL, 3.5 mmol) and Na_2SO_4 (1.5 g) under N_2 atmosphere, and the reaction mixture was stirred at 60°C for 24 hours. After this time, the reaction mixture was concentrated under reduced pressure and filtered and the crude was purified by flash column chromatography using CH_2Cl_2:MeOH (95:5) as eluent, obtaining **3** (0.4 g, 52% yield) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ=3.11 (ddd, *J*=11.6, 6.8, 4.4 Hz, 1H, CH_2NH), 3.50 (m, 1H, CH_2NH), 3.70 (d, *J*=10.4 Hz, 3H, $[CH_3O]_2P$), 3.76 (d, *J*=10.4 Hz, 3H, $[CH_3O]_2P$), 3.86-4.05 (m, 2H, CH_2N), 4.57 (d, *J*=14.8 Hz, 1H, CHP), 6.13-6.24 (m, 2H, pyrrole-H), 6.60 (m, 1H, pyrrole-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=42.0 (d, *J*=8.6 Hz, CH_2N), 45.0 (NCH_2), 50.5 (d, *J*=167.6 Hz, CHP), 53.4 (d, *J*=7.3 Hz, $[CH_3O]_2P$), 53.7 (d, *J*=7.2 Hz, $[CH_3O]_2P$), 105.8 (d, *J*=4.3 Hz, C3-pyrrole), 108.0 (d, *J*=2.6 Hz, C4-pyrrole), 120.0 (d, *J*=2.6 Hz, C5-pyrrole), 120.4 (C2-pyrrole) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ=22.68 ppm. HRMS (FAB^+): calcd. for $C_9H_{16}N_2O_3P$ $[M+H]^+$, *m/z* 231.0899; found for $[M+H]^+$, *m/z* 231.0899.

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