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TETRAHEDRON

An Efficient Strategy for the Regioselective Synthesis of 3-Phosphorylated-1-Aminopyrroles from β-Hydrazono Phosphine Oxides and Phosphonates

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Abstract: An easy strategy for the synthesis of 1-aminopyrroles substituted with a phosphine oxide or phosphonate group in the 3-position is described. The key step is the 1,4-conjugate addition of the enamine to the 4-phosphorylated 1,2-diazabuta-1,3-diene **3** and heterocyclisation to give substituted 1-aminopyrroles **9**. Basic hydrolysis of pyrroles **9** afforded 3-phosphinoyl-1-aminopyrroles **11**. Similarly, substituted 3-phosphinoyl-1-aminopyrroles **10**, can also be obtained from acetylacetone and 1,2-diazabuta-1,3-diene **3**.

Pyrrole ring systems are important in organic chemistry because they constitute the skeleton of natural products, alkaloids, antibiotics and polymers.[1] 1-Aminopyrrole derivatives have been used in the preparation of polypyrrole-silica nanocomposites,[2a] pyrrolo[1,2-*b*][1,2,4]triazines,[2b,c] phytochromes,[2d] analgesics,[2e] as well as NMDA receptor[2f] and angiotensin II antagonists.[2g] Despite these applications, the limited presence of 1-aminopyrroles in the literature can be ascribed to the few procedures which exist for their preparation.[3,4] Synthetic routes to 1-aminopyrroles are relatively few, [3,4] and these derivatives seem to be difficult to prepare by Knorr and its modified procedures, since the condensation of hydrazine with 1,4-dicarbonyl compounds provides only low yields of 1-aminopyrroles, and dihydropyrazines or bispyrroles are formed as byproducts. The presence of different functional groups in many positions of these systems has been especially emphasized since such compounds have, in turn, potential for further interesting structural modifications, making them suitable as intermediates for more complex compounds. However, pyrroles, directly substituted with phosphorus containing functional groups, have received scant attention. To the best of our knowledge, only one example of phosphorus substituted aminopyrroles,[5] namely 1-amino-4-triphenyl-phosphoranylidene-5-pyrrolones, has been described, from azoalkenes[6] and phosphorus ylides.

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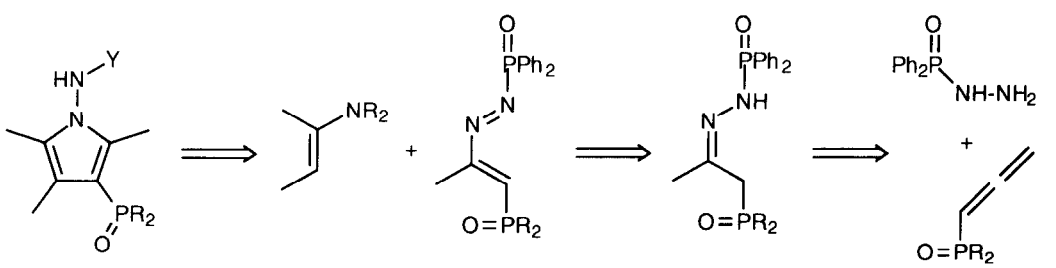
We are interested in the design of new 1-aminopyrrole derivatives bearing a phosphine oxide or phosphonate moiety in the 3-position of the heterocyclic system. This substituent could regulate important biological functions and increase the biological activity of these compounds, in a similar way to that reported for other pharmaceuticals.[7] In this context and in connection with our interest in the synthesis of five[8] and six[9] membered phosphorylated nitrogen heterocycles, we have used β-functionalized enamines and hydrazones derived from phosphazenes, phosphonium salts, phosphine oxides and phosphonates as intermediates in the synthesis of acyclic derivatives such as oximes[10a] allylamines,[10b] hydrazones,[10c] and β-amino functionalized compounds[10d] as well as of phosphorus containing heterocycles.[11] Continuing with our interest in the synthesis of new phosphorus substituted heterocycles, we report here an easy and high yielding synthesis of phosphorylated 1-aminopyrrole derivatives (**1**) from 1-phosphinoylaminopyrrole derivatives (**2**) prepared from enamines or β-diketones and 1,2-diazabuta-1,3-dienes containing a phosphine oxide (**3**, R = Ph) or a phosphonate group (**3**, R = OEt). Conjugated azoalkenes have been previously used as versatile precursors in organic chemistry.[6,12,13] Nevertheless, the preparation and synthetic use of 1,2-diazabuta-1,3-dienes with a phosphorus containing group has not, to the best of our knowledge, been studied. Retrosynthetically, the required 4-phosphorylated azoalkenes (**3**) (Scheme 1) could be prepared by addition of phosphinoylhydrazides to allenes, in a similar way to that previously reported for aryl and alkyl hydrazines[10c] or for hydroxylamines.[10a] Subsequent introduction of a leaving group (chlorine) at the carbon atom adjacent to the hydrazono function of functionalized hydrazone (**4**) followed by 1,4-elimination of HCl could give 4-phosphorylated azoalkenes (**3**).



1 Y = H **3** **4**

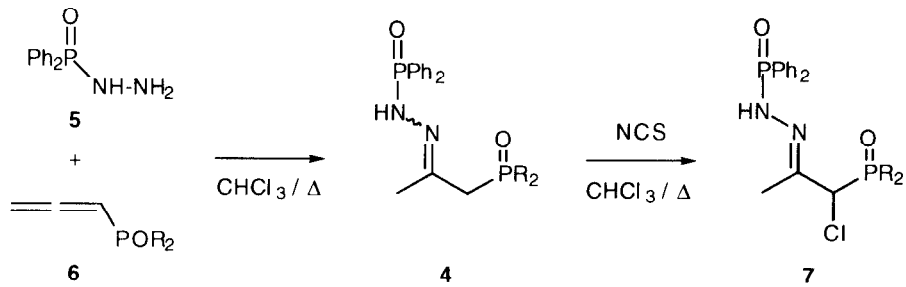
2 Y = $POPh_2$

Scheme 1

RESULTS AND DISCUSSION

Functionalized β-hydrazones **4** (R = Ph, OEt) were prepared by the reaction of allenic phosphine oxide **6a** (R = Ph) or phosphonate **6b** (R = OEt) with easily removable monoprotected hydrazide, in a similar way to that previously reported for simple hydrazines[10c] or for hydroxylamines.[10a] Addition of diphenylphosphinoylhydrazide **5** to allene **6a** in refluxing chloroform (*TLC* control) led to the formation of β-

hydrazono phosphine oxide **4a** (Scheme 2, Table 1, entry 1). This compound **4a** was characterized by its spectroscopic data, which indicate that it is isolated as a mixture of the *syn* and *anti* hydrazone **4a** (R = Ph), although, for our purposes, the separation of both isomers was not necessary for subsequent reactions. ^{31}P-NMR spectrum of **4a** showed four absorptions at δ_P 23.0 and 23.5 (*syn* and *anti* $NHPOPh_2$) and 28.8 and 32.2 (*syn* and *anti* $POPh_2$). Likewise, the ^{1}H and ^{13}C-NMR spectra gave well resolved doublets for the methylene proton (δ_H 3.30 and 3.38) and carbon (δ_C 35.4 and 41.0) of **4a**.[10c] Similarly, the allene **6b** (R = OEt) reacted with hydrazide **5** and gave β-functionalized phosphonate **4b** in high yield (Scheme 2, Table 1, entry 2). Chlorohydrazones **7** are prepared from β-hydrazones **4** by treatment with one equivalent of *N*-chlorosuccinimide (NCS) in refluxing chloroform (Scheme 2, Table 1, entries 3-4).



a R = Ph
b R = OEt

Scheme 2

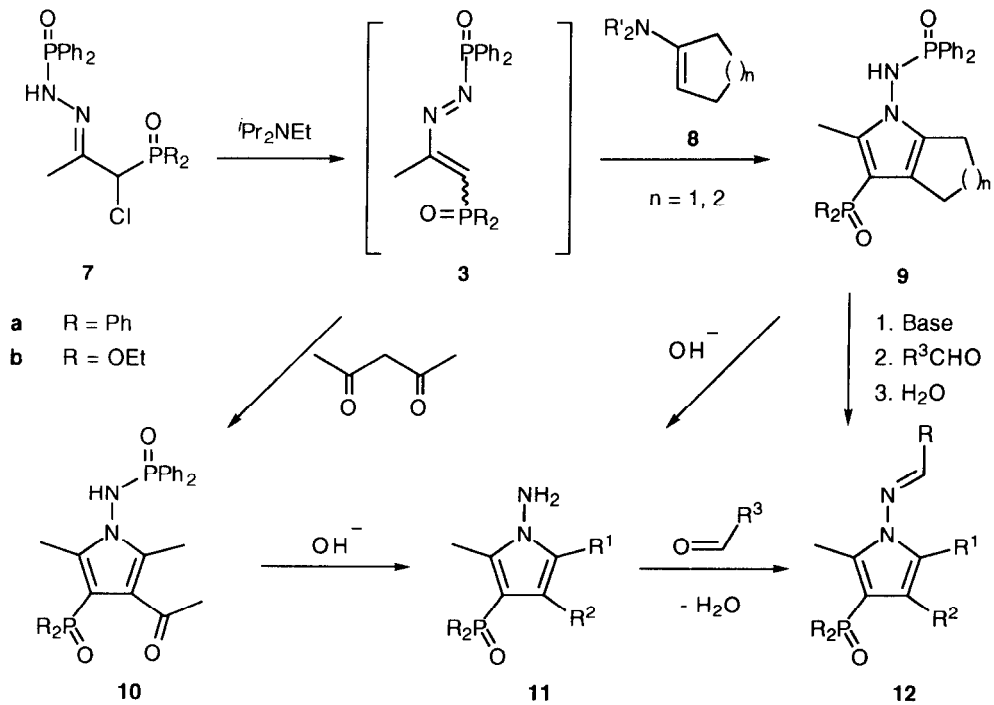
Table 1. Hydrazones **4** and **7** obtained.

Entry	Compound	R	Yield (%)	mp (°C)
1	**4a**	Ph	72[a]	187-189
2	**4b**	OEt	79[b]	131-133
3	**7a**	Ph	64[c]	134-136 (dec)
4	**7b**	OEt	96[d]	149-151 (dec)

[a] Yield of isolated purified hydrazone **4a** from allenediphenylphosphine oxide **6a**. [b] Yield of isolated purified hydrazone **4b** from allenic phosphonate ester **6b**. [c] Yield of isolated purified chlorohydrazone **7a** from hydrazone **4a**. [d] Yield of isolated purified chlorohydrazone **7b** from hydrazone **4b**.

Highly coloured 1,2-diazabuta-1,3-dienes derived from phosphine oxide **3a** (R = Ph) or phosphonate **3b** (R = OEt) were generated *in situ* by treatment of chlorohydrazones **7a-b** with Hünig's base[13b] (^{i}Pr$_2$NEt) in

chloroform at reflux. These compounds underwent 1,4-elimination of HCl and azo-alkenes **3** were trapped in the presence of enamines such as **8a** [n = 1, $R'_2 = (CH_2)_2O(CH_2)_2$] and **8b** [n = 2, $R'_2 = (CH_2)_4$] to give, exclusively, 3-phosphorylated 1-phosphinoylaminopyrroles derived from phosphine oxide **9a-b** (R = Ph) or phosphonate **9c** (R = OEt) in moderate yields and in a regioselective fashion (see Scheme 3, Table 2, entries 1-3). Spectroscopic data were in agreement with the assigned structure of compounds **9**. High resolution mass spectrometry of **9a** showed the (M^++1) peak (*m/z* 537.2, 100%), while in the ^{31}P-NMR spectrum of compound **9a** phosphinoyl groups resonated at δ_P 22.8 and 24.1. The ^{13}C-NMR spectrum of this compound **9a** showed absorption at δ_C 101.6 as a doublet ($^1J_{PC}$ 127.4 Hz) for the carbon atom directly bonded to the phosphinoyl moiety (C-3), as well as doublets at δ_C 125.7 ($^2J_{PC}$ 10.6 Hz), 138.6 ($^3J_{PC}$ 11.1 Hz) and 140.8 ($^2J_{PC}$ 19.2 Hz) for the heterocyclic carbon atoms C-4, C-5 and C-2. The formation of these heterocycles **9** could be explained by initial 1,4-conjugate addition of the enamines to the azo-ene systems, and heterocyclisation. The use of monoprotected hydrazones containing a diphenylphosphinoyl group seems to play an important role in avoiding the formation of byproducts such as pyridazines.[3,4d]



Scheme 3

This methodology for the preparation of bicyclic phosphorylated 1-aminopyrroles **9** can be applied to the synthesis of other functionalized pyrroles, when compounds containing active methylene groups are used.

Thus, 1,2-diazabuta-1,3-dienes **3a** or **3b**, generated *in situ* from the chlorohydrazone derived from phosphine oxide **7a** (R = Ph) or phosphonate **7b** (R = OEt) and Hünig's base, reacted with acetylacetone in chloroform at reflux to give phosphorylated 1-phosphinoylaminopyrroles **10a** and **10b** (see Table 2, entries 4-5). Formation of these compounds can be explained by a nucleophilic attack on the heterodiene system of conjugated azoalkene **3** by the carbanion of the acetylacetone, in a similar way to that previously reported for other β-diketones.[4a,6a] Phosphorylated pyrroles **9** and **10** underwent phosphinoyl cleavage by basic hydrolysis with 5 eq. of KOH to give the corresponding bicyclic 1-aminopyrroles **11a** ($R^1R^2 = (CH_2)_3$), **11b** ($R^1R^2 = (CH_2)_4$) and functionalized 1-aminopyrroles **11c** ($R^1 = CH_3$, $R^2 = COCH_3$) substituted with a carbonyl and a phosphine oxide group, in excellent yields (Scheme 3, Table 2, entries 6-8). 3-Phosphinoyl 1-aminopyrrole derivatives **11** were condensed with aldehydes to give imines **12** (Scheme 3, Table 2, entries 9-10). The synthesis of phosphorylated pyrroles **12** does not require the isolation and purification of compounds **11** and they can be obtained from 1-phosphorylaminopyrrole **9** when this compound is directly treated with base followed by addition of aldehydes and aqueous work-up (Table 2, entry 11).

Table 2. Pyrroles **9**, **10**, **11** and **12** obtained.

Entry	Compound	R^1	R^2	R^3	R	Yield (%)	mp (°C)
1	**9a**	n = 1			Ph	60[a]	246-247
2	**9b**	n = 2			Ph	54[a]	290-291
3	**9c**	n = 1			OEt	45[b]	oil
4	**10a**				Ph	45[a]	286-287
5	**10b**				OEt	33[b]	oil
6	**11a**	$(CH_2)_3$			Ph	99[c]	193-194
7	**11b**	$(CH_2)_4$			Ph	83[c]	234-235
8	**11c**	Me	COMe		Ph	99[c]	190-191
9	**12a**	$(CH_2)_3$		Ph	Ph	79[d]	240-241
10	**12b**	$(CH_2)_4$		*p*-MePh	Ph	84[d]	188-189
11	**12c**	$(CH_2)_3$		*p*-NO_2Ph	Ph	50[e]	254-255

[a] Yield of isolated purified pyrroles **9a**, **9b**, **10a** from 1,2-diazabuta-1,3-diene **3a** derived from phosphine oxides (R = Ph). [b] Yield of isolated purified pyrroles **9c**, **10b** from 1,2-diazabuta-1,3-diene **3b** derived from phosphonates (R = OEt). [c] Yield of isolated purified 1-aminopyrroles **11a-11c** from pyrroles **9** and **10**. [d] Yield of isolated purified compounds **12a**, **12b** from 1-aminopyrroles **11a**, **11b**. [e] Yield of isolated purified compound **12c** in one-pot reaction from pyrrole **9a**.

In conclusion, we have developed a simple, mild, and convenient strategy for the regioselective synthesis of polysubstituted 1-aminopyrroles **9**, **10**, **11** and **12**, substituted with a phosphine oxide or phosphonate group in the 3-position, from readily available starting materials. These heterocycles could serve as precursors for organic materials,[1,2a] and for the preparation of a large variety of molecules that may be useful in the synthesis of biologically active compounds of interest as agrochemicals and in medicinal chemistry.[1,2d-g]

ACKNOWLEDGEMENTS

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EXPERIMENTAL SECTION

General. Chemicals were purchased from Aldrich Chemical Company. Solvents for extraction and chromatography were technical grade. All solvents used in reactions were freshly distilled from appropriate drying agents before use. All other reagents were recrystallized or distilled as necessary. All reactions were performed under an atmosphere of dry nitrogen. Analytical TLC was performed with Merck silica gel 60 F_{254} plates. Visualization was accomplished by UV light and $KMnO_4$ solution. Flash chromatography was carried out using Merck silica gel 60 (230-400 mesh ASTM). Melting points were determined with a Electrothermal IA9100 Digital Melting Point Apparatus and are uncorrected. ^1H (300 MHz), ^{13}C (75 MHz) and ^{31}P-NMR (120 MHz) spectra were recorded on a Varian VXR 300 MHz spectrometer using $CHCl_3$ solutions with TMS as an internal reference for ^1H and ^{13}C-NMR spectra and phosphoric acid (85%) for ^{31}P-NMR spectra. Coupling constants (*J*) are reported in Hertz. Low-resolution mass spectra (MS) were obtained at 50-70 eV by electron impact (EIMS) on a Hewlett Packard 5971 or Hewlett Packard 5973 spectrometers. High-resolution mass spectra (HRMS) were obtained by using an APCI source on a Hewlett Packard 1100 MSD spectrometer. Data are reported in the form *m/z* (intensity relative to base = 100). Infrared spectra (IR) were recorded on a Nicolet IRFT Magna 550 spectrometer for solids in KBr or for neat oils; peaks are reported in cm^{-1}. Elemental analyses were performed in a LECO CHNS-932 apparatus. Diphenylphosphinoyl hydrazide **5** was synthesized according to the literature procedure.[14]

General procedure for the preparation of β-hydrazone phosphine oxide (4a) and β-hydrazone phosphonate (4b). To a solution of allenediphenylphosphine oxide or diethyl 1,2-propadienylphosphonate (15 mmol) in $CHCl_3$ (50 mL) was added diphenylphosphinoyl hydrazide (3.48 g, 15 mmol) at rt. The mixture was stirred and heated at reflux for 12 h and then concentrated. The crude residue was recrystallized from CH_2Cl_2 / hexanes.

***Syn*- and *anti*-2-(*N*-diphenylphosphinoylhydrazono)propyldiphenylphosphine oxide (4a)**. 5.10 g (72 %) of **4a** as a white solid, mp 187-189 °C; ^1H-NMR (300 MHz) 1.48 and 1.93 (s, 3 H, *anti* and *syn* CH_3), 3.30 (d, 2 H, $^2J_{PH}$ = 13.8 Hz, *syn* CH_2), 3.38 (d, 2 H, $^2J_{PH}$ = 14.7 Hz, *anti* CH_2), 6.32 (d, 1 H, $^2J_{PH}$ = 17.4 Hz, *syn* NH), 7.20-7.96 (m, 20 H, arom), 9.33 (d, 1 H, $^2J_{PH}$ = 20.4 Hz, *anti* NH); ^{13}C-NMR (75 MHz) 15.9 and 25.8 (*anti* and *syn* CH_3), 35.4 (d, $^1J_{PC}$ = 63.6 Hz, *syn* CH_2), 41.0 (d, $^1J_{PC}$ = 65.6 Hz, *anti* CH_2), 128.2-133.2 (C-arom), 146.4 and 146.5 (C=N); ^{31}P-NMR (120 MHz) 23.0 and 23.5 (*syn* and *anti* N-$POPh_2$), 28.8 and 32.2 (*syn* and *anti* $POPh_2$); IR (KBr) 3214, 3057, 1435, 1206, 1182 cm^{-1}; EIMS *m/z* 472 (M^+, 56), 201 ($POPh_2^+$, 100). Anal. Calcd for $C_{27}H_{26}N_2O_2P_2$: C, 68.62; H, 5.55; N, 5.93. Found: C, 68.44; H, 5.53; N, 5.94.

***Syn*- and *anti*-2-(*N*-diphenylphosphinoylhydrazono)propylphosphonate (4b).** 4.84 g (79 %) of **4b** as a white solid, mp 131-133 °C; ^{1}H-NMR (300 MHz) 1.15 (t, 3 H, $^3J_{HH}$ = 7.0 Hz, *anti* CH_3), 1.23 (t, 3 H, $^3J_{HH}$ = 7.2 Hz, *syn* CH_3), 1.90 and 1.95 (s, 3 H, *anti* and *syn* CH_3), 2.75 (d, 2 H, $^2J_{PH}$ = 21.8 Hz, *anti* CH_2), 2.83 (d, 2 H, $^2J_{PH}$ = 22.9 Hz, *syn* CH_2), 3.86-3.96 (m, 2 H, *anti* OCH_2), 4.00-4.10 (m, 2 H, *syn* OCH_2), 6.50 (d, 1 H, $^2J_{PH}$ = 17.1 Hz, NH), 7.35-7.96 (m, 10 H, arom); ^{13}C-NMR (75 MHz) 15.2 and 25.2 (*anti* and *syn* CH_3), 16.2 (*syn* and *anti* CH_3), 30.2 (d, $^1J_{PC}$ = 135.5 Hz, *syn* CH_2), 36.6 (d, $^1J_{PC}$ = 135.5 Hz, *anti* CH_2), 62.0 (*anti* OCH_2), 62.7 (*syn* OCH_2), 128.2-132.4 (C-arom), 145.3 (dd, $^2J_{PC}$ = 15.6 Hz, $^3J_{PC}$ = 9.6 Hz, *anti* C=N), 145.7 (dd, $^2J_{PC}$ = 16.6 Hz, $^3J_{PC}$ = 11.6 Hz, *syn* C=N); ^{31}P-NMR (120 MHz) 23.6, 23.6, 23.9 and 24.4; IR (KBr) 3450, 3157, 1436, 1236, 1211, 1053 cm^{-1}; HRMS *m/z* 409.0 (M^++1, 100). Anal. Calcd for $C_{19}H_{26}N_2O_4P_2$: C, 55.88; H, 6.42; N, 6.86. Found: C, 55.66; H, 6.44; N, 6.84.

General procedure for the synthesis of chlorohydrazones 7. To a solution of β-hydrazono phosphine oxide **4a** or β-hydrazono phosphonate **4b** (10 mmol) in $CHCl_3$ (80 mL) was added *N*-chlorosuccinimide (1.36 g, 10 mmol) at rt. The mixture was stirred and heated at reflux (3-4 days) and then diluted with water (30 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with water, dried over $MgSO_4$, and concentrated. The crude residue was crystallized from Et_2O and used without further purification.

2-(*N*-diphenylphosphinoylhydrazono)-1-chloropropyldiphenylphosphine oxide (7a). 3.24 g (64 %) of **7a** as a pale yellow solid, mp 134-136 °C (dec); ^{1}H-NMR (300 MHz) 2.00 (s, 3 H, CH_3), 3.39 (d, 1 H, $^2J_{PH}$ = 14.7 Hz, CH), 6.62 (d, 1 H, $^2J_{PH}$ = 18.3 Hz, NH), 7.20-7.76 (m, 20 H, arom); ^{13}C-NMR (75 MHz) 12.3 (CH_3), 59.2 (d, $^1J_{PC}$ = 69.5 Hz, CH), 128.2-132.6 (C-arom), 146.4 (d, $^2J_{PC}$ = 15.0 Hz, C=N); ^{31}P-NMR (120 MHz) 24.0 and 28.2; IR (KBr) 3417, 1434, 1196, 1123 cm^{-1}; HRMS *m/z* 507.1 (M^++1, 34), 201.0 ($POPh_2^+$, 100). Anal. Calcd for $C_{27}H_{25}ClN_2O_2P_2$: C, 63.98; H, 4.97; N, 5.53. Found: C, 63.74; H, 4.98; N, 5.51.

2-(*N*-diphenylphosphinoylhydrazono)-1-chloropropylphosphonate (7b). 4.25 g (96 %) of **7b** as a pale yellow solid, mp 149-151 °C (dec); ^{1}H-NMR (300 MHz) 1.16-1.25 (m, 3 H, CH_3), 2.01 (s, 3 H, CH_3), 2.77 (d, 1 H, $^2J_{PH}$ = 21.7 Hz, CH), 3.91-4.16 (m, 2 H, OCH_2), 7.13 (d, 1 H, $^2J_{PH}$ = 18.0 Hz, NH), 7.25-7.93 (m, 10 H, arom); ^{13}C-NMR (75 MHz) 11.6 (CH_3), 15.9 (CH_3), 55.8 (d, $^1J_{PC}$ = 158.1 Hz, CH), 63.3 (OCH_2), 127.7-132.3 (C-arom), 145.2 (d, $^2J_{PC}$ = 15.1 Hz, C=N); ^{31}P-NMR (120 MHz) 15.7 and 24.8; IR (KBr) 3430, 2986, 1713, 1640, 1434, 1196, 1023 cm^{-1}; HRMS *m/z* 443.0 (M^++1, 36), 408.0 [(M^+-1)-Cl, 100]. Anal. Calcd for $C_{19}H_{25}ClN_2O_4P_2$: C, 51.54; H, 5.69; N, 6.33. Found: C, 51.72; H, 5.67; N, 6.34.

General procedure for the synthesis of phosphorylated 1-phosphinoylaminopyrroles 9 and 10. To a mixture of chlorohydrazono phosphine oxide **7a** or chlorohydrazono phosphonate **7b** (3 mmol) and cyclic enamine or pentane-2,4-dione (3.6 mmol) in $CHCl_3$ (18 mL) was added a solution of Hünig's base (^{i}Pr$_2$NEt) (0.63 mL, 3.6 mmol) in $CHCl_3$ (2 mL) at rt. The mixture was stirred and heated at reflux (36-48 h) and then diluted with water (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with water, dried over $MgSO_4$, and concentrated. The crude residue was recrystallized from the appropriate solvent or purified by flash chromatography eluting with the appropriate solvent.

3-Diphenylphosphinoyl-1-diphenylphosphinoylamino-2-methylcyclopenta[*b*]pyrrole (9a). Chlorohydrazono phosphine oxide **7a** and a solution of freshly distilled 4-(1-cyclopenten-1-yl)morpholine **8a** were used. The crude residue was recrystallized from Et_2O / CH_2Cl_2 to afford 965 mg (60

%) of **9a** as a white solid, mp 246-247 °C; ^{1}H-NMR (300 MHz) 1.47-1.51 (m, 2 H, CH_2), 1.62 (s, 3 H, CH_3), 1.86-1.90 (m, 2 H, CH_2), 2.51-2.55 (m, 2 H, CH_2), 7.20-7.86 (m, 20 H, arom), 8.83 (d, 1 H, $^2J_{PH}$ = 19.5 Hz, NH); ^{13}C-NMR (75 MHz) 11.6 (CH_3), 25.4 (CH_2), 25.8 (CH_2), 27.7 (CH_2), 101.6 (d, $^1J_{PC}$ = 127.4 Hz, C-3), 125.7 (d, $^2J_{PC}$ = 10.6 Hz, C-4), 128.0-135.0 (C-arom), 138.6 (d, $^3J_{PC}$ = 11.1 Hz, C-5), 140.8 (d, $^2J_{PC}$ = 19.2 Hz, C-2); ^{31}P-NMR (120 MHz) 22.8 and 24.1; IR (KBr) 3417, 3059, 2860, 1481, 1434, 1208, 1169, 1116 cm^{-1}; HRMS *m/z* 537.2 (M^++1, 100). Anal. Calcd for $C_{32}H_{30}N_2O_2P_2$: C, 71.63; H, 5.64; N, 5.22. Found: C, 71.34; H, 5.66; N, 5.20.

3-Diphenylphosphinoyl-1-diphenylphosphinoylamino-2-methyl-4,5,6,7-tetrahydroindole (9b). Chlorohydrazono phosphine oxide **7a** and a solution of freshly distilled 1-(1-cyclohexen-1-yl)pyrrolidine **8b** were used. The crude residue was recrystallized from CH_2Cl_2 / hexanes to afford 891 mg (54 %) of **9b** as a white solid, mp 290-291 °C; ^{1}H-NMR (300 MHz) 1.37-1.40 (m, 2 H, CH_2), 1.53-1.59 (m, 2 H, CH_2), 1.61 (s, 3 H, CH_3), 1.63-1.65 (m, 2 H, CH_2), 2.62-2.65 (m, 2 H, CH_2), 7.26-7.85 (m, 21 H, arom and NH); ^{13}C-NMR (75 MHz) 11.2 (CH_3), 22.0 (CH_2), 22.5 (CH_2), 22.9 (CH_2), 23.4 (CH_2), 103.2 (d, $^1J_{PC}$ = 127.4 Hz, C-3), 117.1 (d, $^2J_{PC}$ = 10.6 Hz, C-4), 128.1-135.7 (C-arom), 130.3 (d, $^3J_{PC}$ = 10.1 Hz, C-5), 137.3 (d, $^2J_{PC}$ = 18.6 Hz, C-2); ^{31}P-NMR (120 MHz) 22.6 and 24.5; IR (KBr) 3417, 3059, 2926, 1434, 1202, 1176, 1109 cm^{-1}; HRMS *m/z* 551.2 (M^++1, 100). Anal. Calcd for $C_{33}H_{32}N_2O_2P_2$: C, 71.99; H, 5.86; N, 5.09. Found: C, 71.84; H, 5.86; N, 5.11.

3-Diethoxyphosphoryl-1-diphenylphosphinoylamino-2-methylcyclopenta[*b*]pyrrole (9c). Chlorohydrazono phosphonate **7b** and a solution of freshly distilled 4-(1-cyclopenten-1-yl)morpholine **8a** were used. The crude residue was purified by flash chromatography eluting with AcOEt to yield 637 mg (45 %) of **9c** as a pale yellow oil; ^{1}H-NMR (300 MHz) 1.06 (t, 6 H, $^3J_{HH}$ = 7.0 Hz, CH_3), 1.97 (s, 3 H, CH_3), 1.97-2.03 (m, 2 H, CH_2), 2.37-2.39 (m, 4 H, CH_2), 3.56-3.75 (m, 4 H, OCH_2), 7.23-7.69 (m, 10 H, arom), 8.61 (d, 1 H, $^2J_{PH}$ = 20.6 Hz, NH); ^{13}C-NMR (75 MHz) 10.9 (CH_3), 15.9 (CH_3), 25.3 (CH_2), 26.0 (CH_2), 27.5 (CH_2), 60.5 (OCH_2), 97.2 (d, $^1J_{PC}$ = 216.1 Hz, C-3), 125.9 (d, $^2J_{PC}$ = 9.6 Hz, C-4), 127.9-131.9 (C-arom), 137.9 (d, $^3J_{PC}$ = 13.6 Hz, C-5), 140.8 (d, $^2J_{PC}$ = 27.2 Hz, C-2); ^{31}P-NMR (120 MHz) 19.5 and 24.1; IR (NaCl) 3423, 3072, 1434, 1215, 1043 cm^{-1}; HRMS *m/z* 473.1 (M^++1, 100). Anal. Calcd for $C_{24}H_{30}N_2O_4P_2$: C, 61.01; H, 6.40; N, 5.93. Found: C, 60.79; H, 6.42; N, 5.95.

3-Acetyl-4-diphenylphosphinoyl-1-diphenylphosphinoylamino-2,5-dimethylpyrrole (10a). Chlorohydrazono phosphine oxide **7a** and a solution of freshly distilled pentane-2,4-dione were used. The crude residue was recrystallized from CH_2Cl_2 / hexanes to afford 745 mg (45 %) of **10a** as a white solid, mp 286-287 °C; ^{1}H-NMR (300 MHz) 0.92 (s, 3 H, CH_3), 1.90 (s, 3 H, CH_3), 2.43 (s, 3 H, CH_3), 7.20-7.86 (m, 20 H, arom), 10.34 (d, 1 H, $^2J_{PH}$ = 22.8 Hz, NH); ^{13}C-NMR (75 MHz) 12.1 (CH_3), 12.8 (CH_3), 30.4 (CH_3), 104.4 (d, $^1J_{PC}$ = 126.4 Hz, C-4), 123.3 (d, $^2J_{PC}$ = 8.1 Hz, C-3), 128.1-136.2 (C-arom), 137.1 (d, $^3J_{PC}$ = 7.6 Hz, C-2), 141.2 (d, $^2J_{PC}$ = 18.2 Hz, C-5), 194.1 (C=O); ^{31}P-NMR (120 MHz) 18.6 and 23.8; IR (KBr) 3431, 3054, 2802, 1657, 1435, 1162, 1109 cm^{-1}; HRMS *m/z* 553.2 (M^++1, 100). Anal. Calcd for $C_{32}H_{30}N_2O_3P_2$: C, 69.56; H, 5.47; N, 5.07. Found: C, 69.29; H, 5.45; N, 5.09.

3-Acetyl-4-diethoxyphosphoryl-1-diphenylphosphinoylamino-2,5-dimethylpyrrole (10b). Chlorohydrazono phosphonate **7b** and a solution of freshly distilled pentane-2,4-dione were used. The crude residue was purified by flash chromatography eluting with AcOEt to yield 483 mg (33 %) of **10b** as a pale yellow oil: ^{1}H-NMR (300 MHz) 1.11 (t, 6 H, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.94 (s, 3 H, CH_3), 2.05 (s, 3 H, CH_3), 2.29 (s, 3 H, CH_3), 3.72-3.79 (m, 4 H, OCH_2), 7.27-7.63 (m, 10 H, arom), 9.10 (d, 1 H, $^2J_{PH}$ =

22.9 Hz, NH); ^{13}C-NMR (75 MHz) 11.5 (CH_3), 16.0 (CH_3), 16.1 (CH_3), 31.1 (CH_3), 61.5 (OCH_2), 100.4 (d, $^1J_{PC}$ = 217.6 Hz, C-4), 122.4 (d, $^2J_{PC}$ = 11.1 Hz, C-3), 128.2-132.4 (C-arom), 135.9 (d, $^3J_{PC}$ = 10.5 Hz, C-2), 140.3 (d, $^2J_{PC}$ = 23.7 Hz, C-5), 196.9 (C=O); ^{31}P-NMR (120 MHz) 17.5 and 23.9; IR (NaCl) 3436, 3078, 1660, 1441, 1023 cm^{-1}; HRMS *m/z* 489.1 (M^++1, 100). Anal. Calcd for $C_{24}H_{30}N_2O_5P_2$: C, 59.01; H, 6.19; N, 5.74. Found: C, 59.16; H, 6.17; N, 5.76.

General procedure for the basic hydrolysis of phosphorylated 1-phosphinoylaminopyrroles 9 and 10. Synthesis of 1-aminopyrroles 11. To a solution of phosphorylated 1-phosphinoylaminopyrrole **9** or **10** (1 mmol) in EtOH (10 mL) was added KOH (281 mg, 5 mmol). The mixture was stirred and heated at reflux for 12 h. The mixture was concentrated, diluted with CH_2Cl_2 (10 mL), and washed with water (3 x 4 mL). The combined organic layers were washed with water, dried over $MgSO_4$, and concentrated. The crude residue was recrystallized from CH_2Cl_2 /hexanes.

1-Amino-3-diphenylphosphinoyl-2-methylcyclopenta[*b*]pyrrole (11a). 333 mg (99 %) of **11a** as a white solid, mp 193-194 °C; ^{1}H-NMR (300 MHz) 1.67-1.72 (m, 2 H, CH_2), 2.02-2.12 (m, 2 H, CH_2), 2.16 (s, 3 H, CH_3), 2.57-2.61 (m, 2 H, CH_2), 4.61 (s, 2 H, NH_2), 7.38-7.70 (m, 10 H, arom); ^{13}C-NMR (75 MHz) 11.5 (CH_3), 24.2 (CH_2), 26.0 (CH_2), 27.7 (CH_2), 101.6 (d, $^1J_{PC}$ = 127.9 Hz, C-3), 125.5 (d, $^2J_{PC}$ = 11.5 Hz, C-4), 128.1-135.7 (C-arom), 137.4 (d, $^3J_{PC}$ = 11.6 Hz, C-5), 139.5 (d, $^2J_{PC}$ = 18.2 Hz, C-2); ^{31}P-NMR (120 MHz) 23.9; IR (KBr) 3443, 1434, 1169, 1116 cm^{-1}; EIMS *m/z* 336 (M^+, 24), 320 (M^+-NH_2, 100). Anal. Calcd for $C_{20}H_{21}N_2OP$: C, 71.41; H, 6.29; N, 8.33. Found: C, 71.13; H, 6.27; N, 8.30.

1-Amino-3-diphenylphosphinoyl-2-methyl-4,5,6,7-tetrahydroindole (11b). 291 mg (83 %) of **11b** as a white solid, mp 234-235 °C; ^{1}H-NMR (300 MHz) 1.40-1.43 (m, 2 H, CH_2), 1.59-1.65 (m, 2 H, CH_2), 1.71-1.75 (m, 2 H, CH_2), 2.10 (s, 3 H, CH_3), 2.47-2.51 (m, 2 H, CH_2), 4.19 (s, 2 H, NH_2), 7.24-7.71 (m, 10 H, arom); ^{13}C-NMR (75 MHz) 10.7 (CH_3), 21.4 (CH_2), 22.5 (CH_2), 22.9 (CH_2), 23.5 (CH_2), 102.6 (d, $^1J_{PC}$ = 128.4 Hz, C-3), 117.2 (d, $^2J_{PC}$ = 11.1 Hz, C-4), 128.2-136.1 (C-arom), 128.7 (d, $^3J_{PC}$ = 11.1 Hz, C-5), 136.1 (d, $^2J_{PC}$ = 18.6 Hz, C-2); ^{31}P-NMR (120 MHz) 24.1; IR (KBr) 3430, 3291, 3178, 2919, 1494, 1434, 1149 cm^{-1}; EIMS *m/z* 350 (M^+, 50), 334 (M^+-NH_2, 100); HRMS *m/z* 351.1 (M^++1, 100). Anal. Calcd for $C_{21}H_{23}N_2OP$: C, 71.98; H, 6.62; N, 7.99. Found: C, 70.69; H, 6.59; N, 7.95.

3-Acetyl-1-amino-4-diphenylphosphinoyl-2,5-dimethylpyrrole (11c). 348 mg (99 %) of **11c** as a white solid, mp 190-191 °C; ^{1}H-NMR (300 MHz) 2.00 (s, 3 H, CH_3), 2.09 (s, 3 H, CH_3), 2.41 (s, 3 H, CH_3), 4.54 (s, 2 H, NH_2), 7.28-7.70 (m, 10 H, arom); ^{13}C-NMR (75 MHz) 11.3 (CH_3), 11.7 (CH_3), 30.8 (CH_3), 104.7 (d, $^1J_{PC}$ = 124.4 Hz, C-4), 122.8 (d, $^2J_{PC}$ = 8.1 Hz, C-3), 127.9-136.2 (C-arom), 135.3 (d, $^3J_{PC}$ = 7.6 Hz, C-2), 140.0 (d, $^2J_{PC}$ = 17.1 Hz, C-5), 194.4 (C=O); ^{31}P-NMR (120 MHz) 25.6; IR (KBr) 3284, 3158, 1653, 1408, 1136, 1076 cm^{-1}; EIMS *m/z* 352 (M^+, 100); HRMS *m/z* 353.1 (M^++1, 100). Anal. Calcd for $C_{20}H_{21}N_2O_2P$: C, 68.17; H, 6.01; N, 7.95. Found: C, 67.90; H, 5.99; N, 7.97.

General procedure for reaction of 1-aminopyrroles 11 with aldehydes. To a solution of 1-aminopyrrole **11** (0.5 mmol) in MeOH (6 mL) was added a solution of aldehyde (1 mmol) in MeOH (2 mL). The mixture was stirred and heated at reflux for 2 h. The mixture was concentrated and the crude product was recrystallized from the appropriate solvent.

1-Benzylidenamino-3-diphenylphosphinoyl-2-methylcyclopenta[*b*]pyrrole (12a). The crude residue was recrystallized from MeOH to afford 167 mg (79 %) of **12a** as a white solid, mp 240-241 °C; ^{1}H-NMR (300 MHz) 1.70-1.71 (m, 2 H, CH_2), 2.06-2.20 (m, 2 H, CH_2), 2.36 (s, 3 H, CH_3), 2.83-2.97 (m,

2 H, CH_2), 7.35-7.72 (m, 15 H, arom), 8.37 (s, 1 H, =CH); ^{13}C-NMR (75 MHz) 12.4 (CH_3), 24.6 (CH_2), 28.1 (CH_2), 28.4 (CH_2), 103.7 (d, $^1J_{PC}$ = 128.0 Hz, C-3), 127.6-135.4 (C-arom, C-4 and C-5), 141.7 (d, $^2J_{PC}$ = 18.6 Hz, C-2), 148.5 (=CH); ^{31}P-NMR (120 MHz) 23.6; IR (KBr) 3430, 3045, 2939, 1501, 1394, 1176, 1123 cm^{-1}; HRMS *m/z* 425.1 (M^++1, 100). Anal. Calcd for $C_{27}H_{25}N_2OP$: C, 76.40; H, 5.94; N, 6.60. Found: C, 76.10; H, 5.92; N, 6.58.

3-Diphenylphosphinoyl-2-methyl-1-(*p*-methylbenzylidenamino)-4,5,6,7-tetrahydroindole (12b). The crude residue was recrystallized from CH_2Cl_2 / hexanes to afford 190 mg (84 %) of **12b** as a white solid, mp 188-189 °C; ^{1}H-NMR (300 MHz) 1.45-1.48 (m, 2 H, CH_2), 1.57-1.69 (m, 2 H, CH_2), 1.79-1.87 (m, 2 H, CH_2), 2.10 (s, 3 H, CH_3), 2.35 (s, 3 H, CH_3), 2.50-2.59 (m, 2 H, CH_2), 7.19-7.72 (m, 14 H, arom), 8.23 (s, 1H, =CH); ^{13}C-NMR (75 MHz) 11.8 (CH_3), 21.6 (CH_3), 23.0 (CH_2), 23.1 (CH_2), 23.1 (CH_2), 23.9 (CH_2), 104.4 (d, $^1J_{PC}$ = 127.4 Hz, C-3), 120.0 (d, $^2J_{PC}$ = 10.6 Hz, C-4), 124.8 (d, $^3J_{PC}$ = 11.1 Hz, C-5), 128.1-135.9 (C-arom), 142.2 (C-2), 158.1 (=CH); ^{31}P-NMR (120 MHz) 24.3; IR (KBr) 3044, 3059, 2922, 1603, 1502, 1180, 1119 cm^{-1}; HRMS *m/z* 453.2 (M^++1, 100). Anal. Calcd for $C_{29}H_{29}N_2OP$: C, 76.97; H, 6.46; N, 6.19. Found: C, 76.67; H, 6.44; N, 6.20.

Synthesis of 3-diphenylphosphinoyl-2-methyl-1-(*p*-nitrobenzylidenamino)cyclopenta[*b*]pyrrole (12c). Pyrroles **12** can be obtained in one-pot reaction from phosphorylated 1-phosphinoylaminopyrroles **9**. To a solution of compound **9a** (268 mg, 0.5 mmol) in THF (8 mL) at 0 °C was added a 1.6 M solution of MeLi in Et_2O (0.38 mL, 0.6 mmol). The mixture was allowed to stir at this temperature for 1 h and a solution of *p*-nitrobenzaldehyde (770 mg, 0.5 mmol) in THF (2 mL) was then added at the same temperature. After the mixture was allowed to warm to rt, the reaction mixture was stirred and refluxed for 12 h. The mixture was diluted with water and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with water, dried over $MgSO_4$, and concentrated. The crude residue was recrystallized from CH_2Cl_2 / hexanes to afford 117 mg (50 %) of **12c** as a pale yellow solid, mp 254-255 °C; ^{1}H-NMR (300 MHz) 1.70-1.75 (m, 2 H, CH_2), 2.16-2.22 (m, 2 H, CH_2), 2.39 (s, 3 H, CH_3), 2.90-2.97 (m, 2 H, CH_2), 7.36-8.24 (m, 14 H, arom), 8.42 (s, 1 H, =CH); ^{13}C-NMR (75 MHz) 12.3 (CH_3), 24.6 (CH_2), 28.4 (CH_2), 28.5 (CH_2), 105.3 (d, $^1J_{PC}$ = 126.4 Hz, C-3), 124.1-135.2 (C-arom), 130.2 (d, $^2J_{PC}$ = 10.6 Hz, C-4), 139.9 (C-5), 142.7 (d, $^2J_{PC}$ = 18.1 Hz, C-2), 144.4 (=CH), 148.8; ^{31}P-NMR (120 MHz) 23.4; IR (KBr) 1587, 1341, 1257, 1176, 1109 cm^{-1}; HRMS *m/z* 470.1 (M^++1, 100). Anal. Calcd for $C_{27}H_{24}N_3O_3P$: C, 69.08; H, 5.15; N, 8.95. Found: C, 68.88; H, 5.17; N, 8.97.

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