Pergamon

Tetrahedron 58 (2002) 2569–2575

TETRAHEDRON

Synthesis of 1,2-dihydro-1,3-diaza-2λ^5,4λ^5-2,4-diphosphorine 2-oxides

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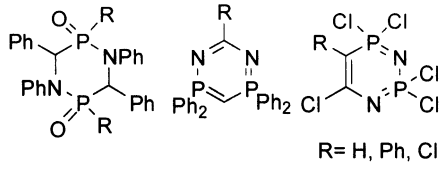
Received 12 September 2001; revised 21 December 2001; accepted 5 February 2002

Abstract—The reaction of lithium (*N*-diphenylphosphoryl)phosphazenes with nitriles afforded 1,2-dihydro-1,3-diaza-2λ^5,4λ^5-2,4-diphosphorine 2-oxides through a *C*-regioselective addition to the cyano linkage followed by in situ cyclocondensation. The new heterocycles were designed to mimic thymine and are promising chemotherapeutic anticancer agents. As an exception, for *p*-nitrobenzonitrile a S_NAr reaction was exclusively observed with the nucleophile entering in the *ortho* position of the nitro substituent in a process directed by the strong electron withdrawing effect of the NO_2 group.

1. Introduction

Phosphorus heterocycles continue attracting a great interest because of the diversity of structures and the biological properties they present.[1,2] In many cases, the phosphorus atom is linked to other heteroatoms such as oxygen or nitrogen and the biological activity of the heterocyclic compound may be associated to the particular arrangement of heteroatoms and size of the ring.[3] As part of an ongoing project devoted to the synthesis of antitumour agents we were interested in the preparation of thymine analogues where the trigonal carbonyl groups are replaced by tetracoordinated phosphorus atoms. Phosphorus-containing anticancer agents are well known. Cyclophosphamide, 2-bis(2-chloroethyl)amino-1,3,2-oxazaphosphorine 2-oxide, an anticancer prodrug in use for over 20 years is the best example. It is a nitrogen mustard with effect as alkylating agent of DNA. In principle, phosphorus analogues of thymine may act as drugs interfering with DNA synthesis either by blocking pyrimidine synthesis or through inhibition of specific enzymes involved in the synthesis of DNA.[4] Phosphonic and phosphinic acid derivatives are known to mimic the transition state of the hydrolysis of a peptide bond and compounds containing these functionalities have been utilized as enzyme inhibitors.[5]

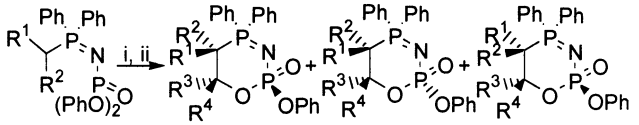
Several synthesis of 1,3,2-[6] and 1,5,2-diazaphosphorines[7] have been described. A literature search revealed that there are very few reports on the preparation of six-membered heterocycles containing two nitrogen and two phosphorus atoms in the ring.[8] The ring structures known include 1,4-diaza-2,5-diphosphorines[9] **1**, 1,5-diaza-2,4-diphosphorines[10] **2**, as well as a series of polychlorinated 1,3-diaza-2,4-diphosphorines **3** obtained by reaction of nitriles with hexachlorodiphosphazonium chloride[11] (Scheme 1). To the best of our knowledge, there are no reports on 1,3-diaza-2,4-diphosphorines with a substituents pattern formed by carbon containing groups which could mimic the thymine system.



1 **2** **3**

We have very recently described the synthesis of 1,2,5,6-tetrahydro 1,3-oxaza-2,4-diphosphorine 2-oxides **5**–**7** through reaction of lithium *N*-phosphorylphosphazenes **4** with aldehydes and ketones (Scheme 1).[12] We reasoned that the target 1,3-diaza-2,4-diphosphorines **8** could be obtained in a similar manner by using nitriles as electrophiles instead of the carbonyl reagents. The retrosynthetic pathway is shown in Scheme 2.

The reaction of nitriles with phosphazenyl stabilized carbanions is precedented. The addition of nitriles to



4 **5** **6** **7**

Scheme 1. (i) Bu^{n}Li, −35°C, THF, 30 min; (ii) R^3R^4CO, −95°C to rt, 8 h.

Keywords: phosphazenes; diphosphorines; carbanions; phosphorus heterocycles; S_NAr.

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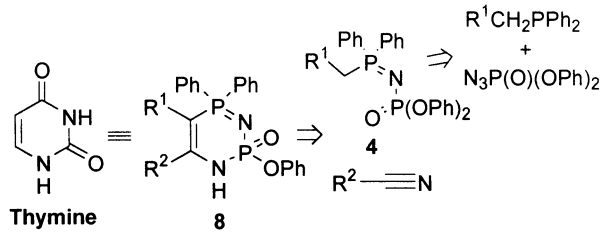
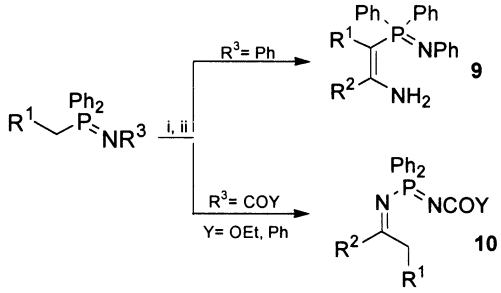


Scheme 2.



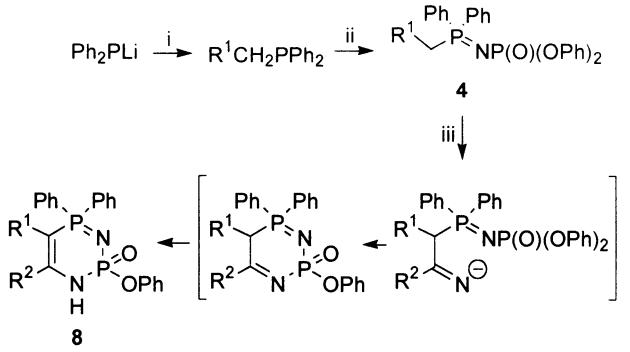
Scheme 3. (i) Bu^{n}Li, −35°C, THF, 30 min; (ii) R^2CN, −70 to 25°C, 12 h.

metalated alkyl(*N*-phenyl)phosphazenes affords *Z*-β-enamino(*N*-phenyl)phosphazenes **9** in reasonable yields.[13] However, in the analogous reaction of phosphazenes with the nitrogen linked to an alkoxycarbonyl and benzoyl group the initial adduct is unstable under the reaction conditions used and rearranges to form iminophosphazenes **10** quantitatively (Scheme 3).[14] A similar behavior has been recently observed in the reaction of lithium phosphonates with amidines.[15] In these processes, the tendency of the phosphazenyl moiety to migrate increases with increasing the electron withdrawing strength of the group bonded to the nitrogen, which produces an increase in the electrophilic character of the phosphorus.[16]

We describe here the reaction of lithium phosphorylphosphazenes with aryl- and alkyl-nitriles. At −80°C the addition proceeds cleanly without the formation of rearranged products affording 1,3-diaza-2,4-diphosphorine 2-oxides **8**. In the particular case of *p*-nitrobenzonitrile the reaction is driven by the NO_2 group and the adducts obtained derived from the addition of the anion to the aromatic ring in β position relative to the nitro substituent. This is the first synthesis of a heterocyclic system with a P–N–P–N structural fragment without halide substituents linked to the phosphorus atoms.

2. Results and discussion

Phosphorylphosphazenes **4** were easily accessible through the Staudinger reaction of diphenylphosphorylazide with the appropriate phosphine.[17] Diphenylphosphorylazide is a commercial compound scarcely used in phosphazene chemistry.[18] Phosphazenes derived from phosphines not available commercially were synthesized by in situ addition of diphenylphosphorylazide to the phosphine prepared by alkylation of diphenylphosphide (generated by reductive lithiation of triphenylphosphine)[19] with the appropriate



Scheme 4. (i) R^1CH_2Br, THF, −70 to 25°C, 3 h; (ii) $N_3P(O)(OPh)_2$, THF, 25°C, 30 min; (iii) (a) 2.5 equiv. Bu^{n}Li, −30°C, THF, 30 min, (b) 2.5 equiv. R^2CN, −85°C, THF, 48 h.

Table 1. $\delta^{31}P$ (ppm), $^2J_{PP}$ (Hz), and melting points (°C) of phosphazenes **4**

Product	R^1	R^2	δ ^{31}P (PN/PO)	$^2J_{PP}$	Mp
4a	H	H	16.17/−5.06	31.2	70–71
4b	CH_3	H	21.77/−5.71	31.2	118–119
4c	$CH_3(CH_2)_2$	H	19.75/−5.74	32.7	85–86
4d	$PhCH_2$	H	18.68/−5.61	32.3	93–94

alkyl halide. Overall yields were generally higher than 80% (Scheme 4). The phosphazenes **4** used in this study and their ^{31}P NMR data are shown in Table 1.

Lithiation of **4** is quantitatively achieved in 30 min by treatment with Bu^{n}Li at −30°C in THF. The first attempts of obtaining 1,3-diaza-2,4-diphosphorine 2-oxides **8** were disappointing. The standard conditions for the reaction of electrophiles with lithium phosphazenes: addition of the nitrile at −80°C, slow increase of the temperature to ambient, and stirring the mixture for 8 h, were unsuccessful and the starting materials were recovered unaltered. New signals, eventually assigned to the adduct, were observed in the ^1H and ^{31}P NMR spectra of crude reactions mixtures when the temperature was maintained at −80°C for a few hours. After some experimentation the best results were obtained when the reaction was stirred at −80°C during 48 h using a stoichiometry phosphorylphosphazene/Bu^{n}Li/nitrile 1:2.5:2.5 (Scheme 4). Aqueous workup afforded the expected heterocycles 1,3-diaza-2,4-diphosphorine 2-oxides **8**. Due to the excess of base and electrophile, the adduct was contaminated with the ketone arising from the addition of Bu^{n}Li to the cyano group of the nitrile. Column chromatography allowed the isolation of the 1,3-diaza-2,4-diphosphorine 2-oxides **8** indicated in Table 2.

The mass spectra of **8** are consistent with a mass balance arising from the addition of one molecule of nitrile to lithiated phosphazenes **4** and the lost of one molecule of phenol from the initial adduct. Formation of heterocycles **8** is clearly detected in the ^{31}P NMR spectra. In all cases, the phosphorus atom of the P═N linkage were shifted down field with respect to phosphazenes **4** (average $\Delta\delta$ (**8**–**4**)=−5.3 ppm, see Tables 1 and 2). The phosphorus of the P═O moiety were less sensitive to the cyclocondensation reaction. Generally, they appeared slightly shifted to higher field ($\Delta\delta$ (**8**–**4**)≈1.2 ppm, see Tables 1 and 2),

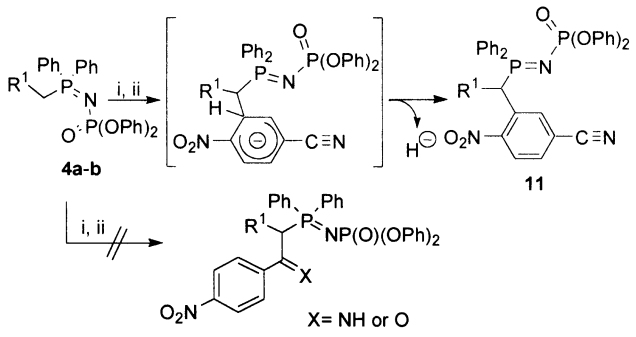
Table 2. ^{31}P NMR data, melting point and yield of the 13-diaza-2λ^5,4λ^5-2,4-diphosphorine 2-oxides **8** and (phosphazenylalkyl)nitriles **11** obtained

Product	R^1	R^2	δ ^{31}P (PN/PO) (ppm)	$^2J_{PP}$ (Hz)	Mp (°C)	Yield[a] (%)
8a	CH_3	C_6H_{11}	26.58/−5.57	8.9	254–255	97
8b	CH_3	C_6H_5	25.57/−6.9	8.9	214–215	40
8c	CH_3	*p*-Cl-C_6H_4	25.43/−6.95	8.9	256–257	63
8d	CH_3	*p*-F-C_6H_4	25.35/−7.01	8.9	253–254	68
8d	$CH_3CH_2CH_2$	C_6H_{11}	25.77/−5.2	8.9	246–247	15
8e	$PhCH_2$	*p*-Cl-C_6H_4	24.82/−7.21	8.9	256–257	13
11a	H		17.58/−5.86	31.1	Oil	26
11b	CH_3		19.65/−7.65	35.6	Oil	63

[a] Isolated yield.

although for **8e** a down field shift of 0.4 ppm was observed. The most dramatic effect is observed on the geminal ^{31}P–^{31}P coupling constant. Its magnitude decreased notably with the cyclization[20] with Δ^2J_{PP} (**8**–**4**) ranging from −22.3 to −23.8 Hz. The presence of the enamino moiety in **8** was easily deduced from the ^{1}H and ^{13}C NMR spectra: the NH of the series of compounds appeared at δ 5.31–5.63[21] as a broad doublet ($^2J_{PH}$=2–4.4 Hz) and the corresponding carbon atoms were assigned according to their chemical shifts and the magnitude of the ^{31}P–^{13}C coupling constants: the carbon α to the phosphorus showed a double doublet in the range δ 80.6–86.57 ppm (average $^1J_{PC}$=89.6 Hz, $^3J_{PC}$=8.9 Hz), while the carbon linked to the nitrogen absorbed at δ 151.78–155.07 and was coupled only to one phosphorus (average $^2J_{PC}$=8.5 Hz).

The formation of heterocycles **8** can be explained by the nucleophilic addition of the metallated phosphazene to the cyano group followed by cyclocondensation with loss of a lithium phenolate. Finally, the imine linkage of the intermediate heterocycle thus obtained stabilized as the corresponding enamine tautomer (Scheme 4). The results in Table 2 indicate that the reaction is very sensitive to relatively small changes in the alkyl substituent of phosphazene **4**. Thus, for cyclohexylcarbonitrile yields dropped from almost quantitative to 15% by increasing the chain length from methyl to *n*-propyl (entries 1, 5). Curiously, no reaction was observed for the simplest phosphazene **4a** (R^1=H). This behavior is analogous to the lack of reaction between lithium *P*-diphenyl(methyl)(*N*-methoxycarbonyl)phosphazene and dimethyl acetylendicarboxylate[22] and may be explained through the lower nucleophilicity of the primary carbanion derived from **4a** compared to the secondary carbanion generated from phosphazenes **4b**–**d**. As expected, yields increased with increasing electrophilic character of the nitrile, cf. benzonitrile with *p*-chlorobenzonitrile or *p*-fluoronitrile (entries 2–4, Table 2). On the contrary, the reaction with *p*-nitrobenzonitrile followed a different course yielding acyclic products **11**. Focusing on **11a**, the ^{1}H, and ^{31}P NMR spectra show that the lithium phosphazene added to the electrophile *C*-regioselectively. This conclusion is supported by the doublet observed for the methylene protons at δ 4.59 ($^2J_{PH}$=14.5 Hz) and the fact that the new compound retained the phosphazene moiety of the starting material, as deduced from the magnitudes of the ^{31}P chemical shifts (cf. entries 1, 2 in Table 1 and entries 6, 7 in Table 2) and homonuclear geminal coupling ($^2J_{PP}$=31.2 Hz). A priori, these data would be consistent with a structure derived from the 1,2 addition of lithium phosphazene to the cyano group of *p*-nitrobenzonitrile, which could lead to either a primary imine (the enamine tautomer was discarded because of the presence of the methylene group) or the corresponding ketone formed by hydrolysis of the C=N moiety (Scheme 5).



Scheme 5. (i) 2.5 equiv. Bu^{n}Li, −30°C, THF, 30 min; (ii) 2.5 equiv. *p*-nitrobenzonitrile, THF, −85°C, 48 h.

However, the ^{13}C NMR spectrum showed no signals in the expected range for a C=X (X=O, N) carbon. Moreover, the IR spectrum showed the C≡N stretching absorption at 2219 cm^{-1}, implying that the cyano group remained unreacted and the attack of the anion had to take place on the aromatic ring of the nitrile. The analysis of the 2D HMBC spectrum confirmed this conclusion and allowed to establish the structure of the compound. The correlation between the methylene protons and the quaternary carbon at δ 150.54 (d, $^3J_{PC}$=5.4 Hz), corresponding to the C-*ipso* bonded to the nitro group, indicated that the phosphazenyl substituent is located *ortho* to the NO_2.[23] The two high field quaternary carbons at δ 116.51 and 116.67 (d, $^4J_{PC}$=3.0 Hz) were assigned to the cyano group and the *ipso*-carbon next to the CN, respectively. The C-*ipso* correlated via $^3J_{CH}$ with the proton *ortho* to the NO_2 group (doublet at δ 7.79), while the cyano group showed correlations with the adjacent protons at δ 7.57 and 8.26. Therefore, the regioselective addition of the lithium phosphazene to the aromatic ring is directed by the strong electron withdrawing effect of the nitro substituent. The addition reaction is followed by a rearomatizing step leading to **11**.

The formal nucleophilic substitution of one hydrogen *ortho* to the nitro group in substituted nitroarenes is precedented.[24–26] The substituents present in the nitroaromatic compound include halogen, nitro, cyano, methoxy, phenoxy dimethylamino, etc. The reaction proceeds by an addition–elimination mechanism, which is the same for the

nucleophilic replacement of either hydrogen or other nucleophugal group located *ortho* or *para* to the nitro group. Hydrogen substitution is the main process if there is a fast step, which transforms the initial adduct into products. This transformation has been carried out through oxidation (with oxidizing substituents[24] or with external oxidants[25]) or via vicarious nucleophilic substitution,[26] a reaction scheme where the rearomatization involves the elimination of a leaving group linked to the carbanion center. In our case, the phosphazenyl moiety may serve as transient hydride acceptor[27] and this hydride is finally converted into molecular hydrogen in the aqueous workup.

Primary dose assays of compound **8c** as anticancer agent against three human tumour cell lines (lung, breast, CNS) showed growth inhibition factors higher than 50% and passed on for further evaluation of additional cell lines.[28]

3. Conclusions

N-(Diphenylphosphoryl)phosphazenes were prepared in high yield through the Staudinger reaction of diphenylphosphoryl azide with a series of phosphines. Metallation of the phosphazenes was easily achieved with Bu^{n}Li in THF at −30°C. The reaction of the lithium phosphazenes with aliphatic and aromatic nitriles afforded 1,2-dihydro-1,3-diaza-2λ^5,4λ^5-2,4-diphosphorine 2-oxides. Yields varied as a function of the reactivity of the nitrile and the steric crowding around the metalated center. Thus, high yields of phosphorus heterocycles were obtained in the reaction of *P*-diphenyl(ethyl)(*N*-diphenylphosphoryl)phosphazene with cyclohexylcarbonitrile and *p*-chlorobenzonitrile, whereas increasing the chain length of the aliphatic moiety of the phosphazene reduced significantly the yield of the heterocycle formed. However, for *p*-nitrobenzonitrile the regioselective alkylation at the *ortho* position of the NO_2 substituent of the aromatic ring was exclusively observed. The S_NAr reaction is promoted by the strong electron withdrawing nature of the nitro group. Preliminary assays as antitumour agents of the new type of heterocycles are promising.

4. Experimental

4.1. General

All reactions were carried out under an atmosphere of nitrogen using dried glassware. Solvents were distilled before use. THF was dried with sodium and distilled under nitrogen. Commercial starting materials were purchased from Aldrich or Química ID Asturias S.L. (methyldiphenyl- and ethyldiphenylphosphine). Liquids, except Bu^{n}Li, were distilled prior to use. Non commercial phosphines were prepared by reacting the appropriate alkyl halide with lithium diphenylphosphide.[18] TLC was performed on Merck plates with aluminum backing and silica gel 60 F_{254}. For column chromatography silica gel 60 (40–63 μm) from Scharlau was used.

Melting points were recorded on a Büchi B-540 apparatus and are uncorrected. Infrared spectra were obtained in KBr pellets using a Mattson Genesis II FT spectrometer. Mass spectra were determined by APCI (Atmospheric Pressure Chemical Ionization) on a Hewlett–Packard 1100. Microanalysis were performed on a Perkin–Elmer 2400. NMR spectra were measured on a Bruker Avance 300 DPX spectrometer. Chemical shifts are referred to internal tetramethylsilane for ^{1}H, the deuterated solvent for ^{13}C, and to external 85% H_3PO_4 for ^{31}P. 2D NMR Correlation spectra (HMQC and HMBC) were acquired using standard Bruker software and processing routines. Anticancer assays were carried by the NCI on 3-cell line panel consisting of MCF7 (breast), NCI-H460 (lung) and SF-268 (CNS). The respective growth inhibition percentages found for a 1.1×10^{-4} M dose were 64, 68 and 53.

4.2. Synthesis of phosphazenes 4

N-(Diphenylphosphoryl)phosphazenes were prepared by addition of diphenylphosphorylazide to the appropriate phosphine following the same methodology previously reported for the synthesis of *N*-(alkoxycarbonyl)phosphazenes.[29] All compounds precipitated from diethyl ether solutions as white solids. They were filtered, dried, and characterized through their spectral data. The purity determined by ^{1}H and ^{31}P NMR was in all cases higher than 95% and the compounds were used without further purification.

4.2.1. *P*,*P*-Diphenyl-*P*-(methyl)(*N*-diphenylphosphoryl)-phosphazene (4a). White solid. Yield: 95%. Mp: 70–71°C. IR (KBr), ν (cm^{-1}): 3053, 1300, 1188. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 2.14 (d, $^2J_{PH}$=13.3 Hz, 3H), 7.08 (m, 2H, H^{ar}), 7.25 (m, 8H, H^{ar}), 7.43 (m, 4H, H^{ar}), 7.54 (m, 2H, H^{ar}), 7.63 (m, 4H, H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 15.37 (d, $^1J_{PC}$=67.9 Hz), 120.67 (d, $^3J_{PC}$=5.4 Hz), 123.67, 128.72 (d, $^3J_{PC}$=12.6 Hz), 129.13, 130.65 (dd, $^3J_{PC}$=6.0 Hz, $^1J_{PC}$ 107.3 Hz), 130.85 (d, $^2J_{PC}$=10.8 Hz), 132.19 (d, $^4J_{PC}$=2.9 Hz), 152.31 (d, $^2J_{PC}$=7.2 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): −5.06 (d, $^2J_{PP}$=31.2 Hz), 16.17 (d, $^2J_{PP}$=31.2 Hz). Anal. Calcd for $C_{25}H_{23}NO_3P_2$ (447.41): C, 67.04; H, 5.13; N, 3.12. Found: C, 66.89; H, 5.01; N, 2.98. MS, *m*/*z* (%): 447 (70).

4.2.2. *P*,*P*-Diphenyl-*P*-(ethyl)(*N*-diphenylphosphoryl)-phosphazene (4b). White solid. Yield: 95%. Mp: 118–119°C. IR (KBr), ν (cm^{-1}): 3061, 1293, 1185. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.14 (dt, $^3J_{HH}$=7.3 Hz, $^3J_{PH}$=18.9 Hz, 3H), 2.48 (dq, $^3J_{HH}$=7.3 Hz, $^2J_{PH}$=13.6 Hz, 2H), 7.08 (m, 2H, H^{ar}), 7.25 (m, 8H, H^{ar}), 7.44 (m, 4H, H^{ar}), 7.55 (m, 2H, H^{ar}), 7.65 (m, 4H, H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 5.70 (d, $^2J_{PC}$=4.8 Hz), 21.92 (d, $^1J_{PC}$=67.9 Hz), 120.64 (d, $^3J_{PC}$=4.8 Hz), 123.56, 128.70 (d, $^3J_{PC}$=12.0 Hz), 129.10, 129.48 (dd, $^3J_{PC}$=5.4 Hz, $^1J_{PC}$=106.5 Hz), 131.32 (d, $^2J_{PC}$=10.2 Hz), 132.14 (d, $^4J_{PC}$=2.4 Hz, C-12), 152.43 (d, $^2J_{PC}$=7.2 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): −5.71 (d, $^2J_{PP}$=32.3 Hz, P-4), 21.77 (d, $^2J_{PP}$=32.3 Hz). Anal. Calcd for $C_{26}H_{25}NO_3P_2$ (461.44): C, 67.60; H, 5.41; N, 3.02. Found: C, 67.44; H, 5.31; N, 2.98. MS, *m*/*z* (%): 461 (70).

4.2.3. *P*,*P*-Diphenyl-*P*-(butyl)(*N*-diphenylphosphoryl)-phosphazene (4c). White solid. Yield: 83%. Mp: 85–86°C. IR (KBr), ν (cm^{-1}): 1203, 1179. ^{1}H NMR

(300.13 MHz, $CDCl_3$), δ (ppm): 0.85 (t, $^3J_{HH}$=7.1 Hz, 3H), 1.39 (m, 2H), 1.46 (m, 2H), 2.42 (m, 2H), 7.08 (m, 2H, H^{ar}), 7.23 (m, 8H, H^{ar}), 7.45 (m, 4H, H^{ar}), 7.54 (m, 2H, H^{ar}), 7.65 (m, 4H, H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 13.51, 23.41 (d, $^3J_{PC}$=3.6 Hz), 23.84 (d, $^2J_{PC}$=16.3 Hz), 28.45 (d, $^1J_{PC}$=68.1 Hz), 120.69 (d, $^3J_{PC}$=5.1 Hz), 123.60, 128.72 (d, $^3J_{PC}$=12.7 Hz), 129.12, 129.68 (dd, $^3J_{PC}$=5.1 Hz, $^1J_{PC}$=103.2 Hz), 131.26 (d, $^2J_{PC}$=10.7 Hz), 132.14 (d, $^4J_{PC}$=2.0 Hz), 152.47 (d, $^2J_{PC}$=7.6 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): −5.74 (d, $^2J_{PP}$=32.7 Hz), 19.75 (d, $^2J_{PP}$=32.7 Hz). Anal. Calcd for $C_{28}H_{29}NO_3P_2$ (489.49): C, 68.64; H, 5.92; N, 2.85. Found: C, 68.44; H, 5.76; N, 2.76. MS, *m/z* (%): 489 (100).

4.2.4. *P,P*-Diphenyl-*P*-(2-phenylethyl)(*N*-diphenylphosphoryl)phosphazene (4d). White solid. Yield: 85%. Mp: 93–94°C. IR (KBr), ν (cm^{-1}): 3053, 1308, 1170. ^1H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 2.8 (m, 4H), 7.15 (m, 5H, H^{ar}), 7.27 (m, 10H, H^{ar}), 7.45 (m, 4H, H^{ar}), 7.54 (m, 2H, H^{ar}), 7.72 (m, 4H, H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 27.47 (d, $^2J_{PC}$=3 Hz), 30.87 (d, $^1J_{PC}$=64.9 Hz), 120.74 (d, $^3J_{PC}$=5 Hz), 123.74 (d, $^4J_{PC}$=1.2 Hz), 126.36, 128.16, 128.54, 128.75 (d, $^3J_{PC}$=12.6 Hz), 129.21, 129.55 (dd, $^3J_{PC}$=5.4, $^1J_{PC}$=107.6 Hz), 131.25 (d, $^2J_{PC}$=10.3 Hz), 132.32 (d, $^4J_{PC}$=3.5 Hz), 140.56 (d, $^3J_{PC}$=16.2 Hz), 152.41 (d, $^2J_{PC}$=7.8 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): −5.61 (d, $^2J_{PP}$=32.3 Hz), 18.68 (d, $^2J_{PP}$=32.3 Hz). Anal. Calcd for $C_{32}H_{29}NO_3P_2$ (537.53): C, 71.44; H, 5.4; N, 2.61. Found: C, 71.31; H, 5.29; N, 2.49. MS, *m/z* (%): 537 (100).

4.3. General procedure for the synthesis of 1,2-dihydro-1,3-diaza-2λ^5,4λ^5-2,4-diphosphinina-2-oxides 8

To a solution of 0.5 mmol of the appropriate phosphazene in THF (25 mL) was added a solution of Bu^{n}Li (0.8 mL of a 1.6 M solution in hexane, 1.25 mmol) at −30°C. After 30 min of metalation, the temperature was lowered to −85°C and the corresponding nitrile (1.25 mmol) was added. The reaction mixture was stirred for 48 h at this temperature. Addition of water (25 mL) followed by extraction with ethyl acetate (3×15 mL) and solvent evaporation under vacuum afforded a crude product, which was purified by precipitation from diethyl ether.

4.3.1. 1,2-Dihydro-*P,P*-diphenyl-6-cyclohexyl-5-methyl-1,3-diaza-2λ^5,4λ^5-2,4-diphosphorine 2-oxide (8a). White solid. Yield: 95%. Mp: 254–255°C. IR (KBr), ν (cm^{-1}): 3170, 1250, 1173. ^1H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.32 (m, 4H), 1.65 (d, $^3J_{PH}$=13.4 Hz, 3H), 1.73 (m, 4H), 1.85 (m, 2H), 2.69 (m, 1H), 5.31 (d, $^2J_{PH}$=2.8 Hz, 1H, NH), 7.03 (m, 3H, H^{ar}), 7.18 (m, 2H, H^{ar}), 7.49 (m, 6H, H^{ar}), 7.76 (m, 4H, H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 12.69 (d, $^2J_{PC}$=10.8 Hz), 25.57, 26.11 (d, $^4J_{PC}$=5.4 Hz), 26.17, 29.5, 30.2, 41.64 (dd, $^3J_{PC}$=7.8, 9.6 Hz), 80.6 (dd, $^3J_{PC}$=9 Hz, $^1J_{PC}$=89.5 Hz), 121.26 (d, $^3J_{PC}$=4.8 Hz), 123.77, 128.54 (d, $^3J_{PC}$=12.5 Hz), 128.58 (d, $^3J_{PC}$=12.5 Hz), 129.06, 129.17 (dd, $^3J_{PC}$=7.2 Hz, $^1J_{PC}$=111.1 Hz), 129.8 (d, $^1J_{PC}$=105.2 Hz), 131.98 (d, $^4J_{PC}$=5.1 Hz), 132.23 (d, $^4J_{PC}$=4.4 Hz), 132.32 (d, $^2J_{PC}$=11 Hz), 151.79 (d, $^2J_{PC}$=8.4 Hz), 161.09 (d, $^2J_{PC}$=4.3 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): −5.57 (d, $^2J_{PP}$=8.9 Hz), 26.58 (d, $^2J_{PP}$=8.9 Hz). Anal. Calcd for $C_{27}H_{30}N_2O_2P_2$ (476.49): C, 67.99; H, 6.29; N, 5.87. Found: C, 67.88; H, 6.21; N, 5.79. MS, *m/z* (%): 477 (90).

4.3.2. 1,2-Dihydro-*P,P*-diphenyl-5-methyl-6-phenyl-1,3-diaza-2λ^5,4λ^5-2,4-diphosphorine 2-oxide (8b). White solid. Yield: 40%. Mp: 214–215°C. IR (KBr), ν (cm^{-1}): 3103, 1266, 1165. ^1H NMR (300.13 MHz, DMSO-d_6), δ (ppm): 1.56 (d, $^3J_{PH}$=13.2 Hz, 3H), 7.08 (m, 2H, H^{ar}), 7.27 (m, 4H, H^{ar}), 7.32 (m, 4H, H^{ar}), 7.52 (m, 3H, H^{ar}), 7.7 (m, 7H, H^{ar}), 8.1 (d, $^2J_{PH}$=4.4 Hz, NH). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 14.6 (d, $^2J_{PC}$=9.8 Hz), 84.79 (dd, $^3J_{PC}$=8.1 Hz, $^1J_{PC}$=89 Hz,), 121.15 (d, $^2J_{PC}$=4.6 Hz), 123.79, 127.69, 128.56 (d, $^4J_{PC}$=2.9 Hz), 128.63 (d, $^3J_{PC}$=13.3 Hz), 128.66 (d, $^3J_{PC}$=12.7 Hz), 128.77 (d, $^1J_{PC}$=113.4 Hz), 128.84, 129.16, 129.43, 132.06 (d, $^2J_{PC}$=11.3 Hz), 132.4 (d, $^4J_{PC}$=3 Hz), 132.41 (d, $^2J_{PC}$=11.1 Hz), 137.82 (dd, $^3J_{PC}$=9.3, 12.7 Hz), 151.99 (d, $^2J_{PC}$=8.1 Hz), 155.91 (d, $^2J_{PC}$= 6.4 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): −6.9 (d, $^2J_{PP}$=8.9 Hz), 25.57 (d, $^2J_{PP}$=8.9 Hz). Anal. Calcd for $C_{27}H_{24}N_2O_2P_2$ (470.44): C, 68.86; H, 5.12; N, 5.95. Found: C, 68.79; H, 5.05; N, 5.83. MS, *m/z* (%): 471 (100).

4.3.3. 1,2-Dihydro-*P,P*-diphenyl-6-(*p*-chlorophenyl)-5-methyl-1,3-diaza-2λ^5,4λ^5-2,4-diphosphorine 2-oxide (8c). White solid. Yield: 63%. Mp: 256–257°C. IR (KBr), ν (cm^{-1}): 3127, 3051, 1263, 1116. ^1H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.56 (d, $^3J_{PH}$=13.7 Hz, 2H), 5.33 (d, $^2J_{PH}$=4.1 Hz, NH), 7.1 (m, 3H, H^{ar}), 7.19 (m, 2H, H^{ar}), 7.25 (m, 2H, H^{ar}), 7.41 (m, 2H, H^{ar}), 7.52 (m, 8H, H^{ar}), 7.85 (m, 2H, H^{ar}). ^{13}C NMR (75.46 MHz, DMSO-d_6), δ (ppm): 14.66 (d, $^2J_{PC}$=10.2 Hz), 83.57 (dd, $^3J_{PC}$=9 Hz, $^1J_{PC}$=89.5 Hz), 121.29 (d, $^3J_{PC}$=4.8 Hz), 123.92, 128.87, 129.24 (d, $^3J_{PC}$=12.6 Hz), 129.44 (d, $^3J_{PC}$=12.6 Hz), 129.63, 129.61, 129.73 (dd, $^3J_{PC}$=3 Hz, $^1J_{PC}$=110.5 Hz), 129.81 (d, $^1J_{PC}$=112.1 Hz), 130.56, 132.14 (d, $^2J_{PC}$=10.8 Hz), 132.19 (d, $^2J_{PC}$=10.8 Hz), 132.77 (d, $^4J_{PC}$=3 Hz), 132.99 (d, $^4J_{PC}$=2.4 Hz), 134.01, 136.13 (dd, $^3J_{PC}$=9.2, 13.8 Hz), 152.5 (d, $^2J_{PC}$=8.4 Hz), 156.47 (d, $^2J_{PC}$=7.2 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): −6.95 (d, $^2J_{PP}$=8.9 Hz), 25.43 (d, $^2J_{PP}$=8.9 Hz). Anal. Calcd for $C_{27}H_{23}N_2O_2P_2Cl$ (504.93): C, 64.16; H, 4.54; N, 5.54. Found: C, 64.01; H, 4.40; N, 5.39. MS, *m/z* (%): 505 (90).

4.3.4. *P,P*-Diphenyl-5-methyl-6-(*p*-fluorophenyl)-1,2-dihydro-1,3-diaza-2λ^5,4λ^5-2,4-diphosphinina-2-oxide (8d). White solid. Yield: 68%. Mp: 253–254°C. IR (KBr), ν (cm^{-1}): 3114, 1169. ^1H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.54 (d, $^3J_{PH}$=13.1 Hz, 3H), 5.63 (d, $^2J_{PH}$=4.4 Hz, 1H, NH), 7.00–7.64 (m, 15H^{ar}), 7.83 (m, 2H^{ar}), 7.86 (m, 2H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 14.59 (d, $^2J_{PC}$=9.6 Hz), 85.65 (dd, $^3J_{PC}$=7.2 Hz, $^1J_{PC}$=89.5 Hz), 114.61 (d, $^2J_{FC}$=22.2 Hz), 116.41 (d, $^2J_{FC}$=21 Hz), 121.15 (d, $^3J_{PC}$=4.2 Hz), 123.55 (d, $^3J_{FC}$=3 Hz), 123.92, 128.46 (dd, $^3J_{PC}$=7.8 Hz, $^1J_{PC}$=109.3 Hz), 128.73 (d, $^3J_{PC}$=12.6 Hz), 128.76 (d, $^3J_{PC}$=13.2 Hz), 129.24 (d, $^4J_{PC}$=1.5 Hz), 130.75 (d, $^3J_{FC}$=7.8 Hz), 132.07 (d, $^2J_{PC}$=11.4 Hz), 132.32 (d, $^4J_{PC}$=2.4 Hz), 132.45 (d, $^2J_{PC}$=10.8 Hz), 132.57 (d, $^4J_{PC}$=3 Hz), 139.62 (ddd, $^4J_{FC}$=7.2 Hz, $^3J_{PC}$=9.0, 13.2 Hz), 151.93 (d, $^2J_{PC}$=8.4 Hz), 154.43 (d, $^2J_{PC}$=7.2 Hz), 162.58 (d, $^1J_{FC}$=248.7 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): −7.01 (d, $^2J_{PP}$=8.9 Hz), 25.35 (d, $^2J_{PP}$=8.9 Hz). Anal. Calcd for $C_{27}H_{23}N_2O_2FP_2$ (488.43): C, 66.39; H, 4.74;

N, 5.73. Found: C, 66.27; H, 4.59; N, 5.67. MS, *m/z* (%): 488 (100).

4.3.5. 1,2-Dihydro-*P*,*P*-diphenyl-6-cyclohexyl-5-propyl-1,3-diaza-2λ^5,4λ^5-2,4-diphosphorine 2-oxide (8e). White solid. Yield: 15%. Mp: 246–247°C. IR (KBr), ν (cm^{-1}): 3167, 1252, 1213. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 0.58 (m, 4H, CH_3+CH), 0.78 (m, 1H), 1.3 (m, 5H), 1.7 (m, 3H), 1.85 (m, 2H), 2.0 (m, 2H), 2.63 (m, 1H), 5.48 (d, $^2J_{PH}$=2.4 Hz, NH), 7.01 (m, 3H, H^{ar}), 7.12 (m, 2H, H^{ar}), 7.48 (m, 8H, H^{ar}), 7.72 (m, 2H, H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 13.85, 23.95 (d, $^3J_{PC}$=1.2 Hz), 25.52, 26.19 (d, $^4J_{PC}$=1.2 Hz), 29.61 (d, $^2J_{PC}$=10.2 Hz), 30.24, 30.7, 41.72 (dd, $^3J_{PC}$=7.2, 10.8 Hz), 86.57 (dd, $^3J_{PC}$=9.6 Hz, $^1J_{PC}$=90.1 Hz), 121.16 (d, $^3J_{PC}$= 4.8 Hz), 123.49, (d, $^5J_{PC}$=1.2 Hz), 128.44 (d, $^3J_{PC}$= 12.6 Hz), 128.48 (d, $^3J_{PC}$=13.2 Hz), 128.91 (d, $^4J_{PC}$= 1.2 Hz), 130.11 (dd, $^3J_{PC}$=7.2 Hz, $^1J_{PC}$=111.7 Hz), 130.53 (dd, $^3J_{PC}$=2.4 Hz, $^1J_{PC}$=105.7 Hz), 131.91 (d, $^4J_{PC}$= 2.2 Hz), 132.07 (d, $^2J_{PC}$=10.8 Hz), 132.1, 132.26 (d, $^2J_{PC}$=11 Hz), 152.05 (d, $^2J_{PC}$=8.4 Hz), 162.1 (d, $^2J_{PC}$= 4.8 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): −5.2 (d, $^2J_{PP}$=8.9 Hz), 25.77 (d, $^2J_{PP}$=8.9 Hz). Anal. Calcd for $C_{29}H_{34}N_2O_2P_2$ (504.54): C, 68.97; H, 6.73; N, 5.55. Found: C, 68.82; H, 6.62; N, 5.39. MS, *m/z* (%): 505 (100).

4.3.6. 1,2-Dihydro-*P*,*P*-diphenyl-5-benzyl-6-(*p*-chlorophenyl)-1,3-diaza-2λ^5,4λ^5-2,4-diphosphorine 2-oxide (8f). White solid. Yield: 13%. Mp: 256–257°C. IR (KBr), ν (cm^{-1}): 3130, 1261, 1094. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 3.38 (dd, $^3J_{PH}$=9.5 Hz, $^2J_{HH}$=17.7 Hz, 1H), 3.46 (dd, $^3J_{PH}$=9.3 Hz, $^2J_{HH}$=17.7 Hz, 1H), 5.52 (1H, $^2J_{PH}$=2 Hz, NH), 6.4 (m, 2H, H^{ar}), 6.82 (m, 3H, H^{ar}), 7.12 (m, 2H, H^{ar}), 7.3 (m, 5H, H^{ar}), 7.47 (m, 6H, H^{ar}), 7.78 (m, 2H, H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 29.58, 80.3 (dd, $^3J_{PC}$=10.2 Hz, $^1J_{PC}$=90 Hz), 121.15 (d, $^3J_{PC}$= 4.8 Hz), 123.89, 125.54, 127.5 (d, $^3J_{PC}$=12.2 Hz), 127.64–132.41 (16C^{ar}), 135.49 (dd, $^3J_{PC}$=9.2, 13.6 Hz), 138.74 (d, $^3J_{PC}$=1.8 Hz), 155.07 (d, $^2J_{PC}$=9.0 Hz), 157.77 (d, $^2J_{PC}$=7.8 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): −7.21 (d, $^2J_{PP}$=8.9 Hz), 24.82 (d, $^2J_{PP}$=8.9 Hz). Anal. Calcd for $C_{33}H_{27}N_2O_2P_2Cl$ (581.02): C, 68.21; H, 4.65; N, 4.82. Found: C, 68.03; H, 4.49; N, 4.72. MS, *m/z* (%): 581 (100).

4.4. Synthesis of nitriles 11

To a solution of 0.5 mmol of the appropiate phosphazene in THF (25 mL) was added a solution of Bu^{n}Li (0.8 mL of a 1.6 M solution in hexane, 1.25 mmol) at −30°C. After 30 min of metallation, the temperature was lowered to −85°C and *p*-nitrobenzonitrile (1.25 mmol) was added. The reaction mixture was stirred for 48 h at this temperature. Addition of water (25 mL) followed by extraction with ethyl acetate (3×15 mL) and solvent evaporation under vacuum afforded a crude product, which was purified by column cromatography using a mixture of ethyl acetate/hexane 1:1.

4.4.1. 3-{[(*P*,*P*-Diphenyl)(*N*-diphenylphosphoryl)phosphazenyl]methyl}-4-nitrobenzonitrile (11a). Oil. Yield: 26%. IR (KBr), ν (cm^{-1}): 2219, 1261, 1023. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 4.59 (d, $^2J_{PH}$=14.5 Hz, 2H), 7.07 (m, 2H, H^{ar}), 7.19 (m, 4H, H^{ar}), 7.25 (m, 5H, H^{ar}), 7.42 (m, 4H, H^{ar}), 7.57 (m, 6H, H^{ar}), 7.79 (d, $^3J_{HH}$=8.9 Hz, 1H^{ar}), 8.26 (t, $^4J_{HH}$=$^4J_{PH}$=1.6 Hz, 1H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 32.79 (d, $^1J_{PC}$= 61.6 Hz), 116.51, 116.67 (d, $^4J_{PC}$=3 Hz), 120.48 (d, $^3J_{PC}$=4.8 Hz), 123.99, 125.74, 126.99 (dd, $^3J_{PC}$=4.2 Hz, $^1J_{PC}$=93 Hz), 127.89 (d, $^2J_{PC}$=9 Hz), 128.97 (d, $^3J_{PC}$= 13.2 Hz), 129.32, 131.68 (d, $^2J_{PC}$=10.3 Hz), 131.89 (d, $^4J_{PC}$=3 Hz), 133.08 (d, $^4J_{PC}$=3 Hz), 137.76 (d, $^3J_{PC}$= 4.2 Hz), 150.54 (d, $^2J_{PC}$=5.4 Hz), 151.97 (d, $^2J_{PC}$= 7.2 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): −5.86 (d, $^2J_{PP}$=31.1 Hz), 17.58 (d, $^2J_{PP}$=31.1 Hz). Anal. Calcd for $C_{32}H_{25}N_3O_5P_2$ (593.53): C, 64.75; H, 4.24; N, 7.07. Found: C, 64.62; H, 4.32; N, 6.98. MS, *m/z* (%): 593 (90).

4.4.2. 3-{[1-[(*P*-Diphenyl)(*N*-diphenylphosphoryl)phosphazenyl]ethyl}-4-nitrobenzonitrile (11b). Oil. Yield: 63%. IR (KBr), ν (cm^{-1}): 2230, 1261, 1022. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.64 (dd, $^3J_{HH}$=7.3, 17.2 Hz, 3H), 4.83 (dq, $^3J_{HH}$=$^2J_{PH}$=7.3 Hz, $^4J_{PH}$=2.6 Hz, 1H), 7.12 (m, 7H, H^{ar}), 7.32 (m, 8H, H^{ar}), 7.63 (m, 5H, H^{ar}), 8.0 (m, 2H, H^{ar}), 8.32 (s, 1H^{ar}). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 15.3 (d, $^2J_{PC}$=3 Hz), 34.08 (dd, $^3J_{PC}$=3.8 Hz, $^1J_{PC}$=68.5 Hz), 116.55, 116.85 (d, $^4J_{PC}$= 2.8 Hz), 120.48 (d, $^3J_{PC}$=5.4 Hz), 120.71 (d, $^3J_{PC}$=4.8 Hz), 124 (d, $^3J_{PC}$=11.1 Hz), 124.98 (d, $^5J_{PC}$=2.1 Hz), 126.56 (d, $^1J_{PC}$=97.1 Hz), 127.56 (dd, $^3J_{PC}$=4.8 Hz, $^1J_{PC}$=104.7 Hz), 129.22, 129.41, 129.44, 130.96 (d, $^2J_{PC}$=10.4 Hz), 131.64 (d, $^4J_{PC}$=2.8 Hz), 132.06 (d, $^2J_{PC}$=9.7 Hz), 132.52 (d, $^4J_{PC}$=3.5 Hz), 133.13 (d, $^4J_{PC}$=2.8 Hz), 133.67 (d, $^4J_{PC}$= 5.6 Hz), 135.35 (d, $^3J_{PC}$=4.2 Hz), 150.98 (d, $^3J_{PC}$=7 Hz), 152.28 (dd, $^2J_{PC}$=7.6 Hz, $^4J_{PC}$=5.5 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): −7.65 (d, $^2J_{PP}$=35.6 Hz), 19.65 (d, $^2J_{PP}$=35.6 Hz). Anal. Calcd for $C_{33}H_{27}N_3O_5P_2$ (607.53): C, 65.24; H, 4.47; N, 6.91. Found: C, 65.1; H, 4.53; N, 6.8. MS, *m/z* (%): 607 (40).

Acknowledgements

Financial support through Dirección General de Enseñanza Superior (project PB97-0587-C02-01) is gratefully acknowledged. C. A. thanks Ministerio de Educación y Cultura for a doctoral fellowship. We thank the NCI for the bioassays performed.

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