

**Synthesis of Polyfunctionalized 1-Aminobuta-1,3-dienes by Addition of Dimethyl Acetylenedicarboxylate to (Z)- $\beta$ -Enamino- $\lambda^5$ -Phosphazenes. Configurational and Conformational Analysis Based on NOE Data,  $^nJ_{\text{PX}}$  Coupling Constant, X-ray Structures, and Semiempirical Calculations**

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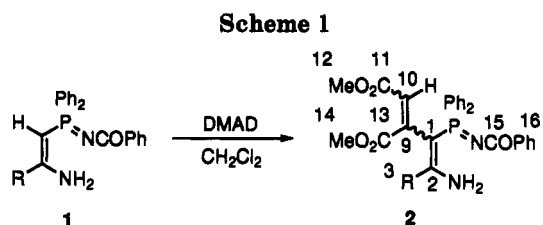
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DMAD adds regioselectively to *N*-acyl-(*Z*)- $\beta$ -enamino-phosphazenes through the  $\beta$  position with high stereoselectivity. The stereochemistry and conformation of the products 2 and 4 in solution have been elucidated based upon NOE experiments and  $^nJ_{\text{PX}}$  ( $n = 1-4$ , X = C, H) data. Large negative  $^4J_{\text{PH}}$  coupling constants from a predominant  $\pi$  contribution were observed from which conformational information could be derived.  $^3J_{\text{PC}}$  values are positive and follow the expected Karplus model, and values  $^2J_{\text{PC}}$  show a large stereochemical dependence. The activation energies for the isomerization of the C=C double bond as well as for the rotation around the C-N single bond of the enamine linkage have been calculated. The crystal structures of (*Z*)-1-benzoyl-3-[(*Z*)-1,2-bis(methoxycarbonyl)vinyl]-2,2-diphenyl-4-(*p*-tolyl)-1,5-diaza-2 $\lambda^5$ -phosphapenta-1,3-diene (2a) [ $P2_1/c$ ,  $a = 15.332(6)$  Å,  $b = 17.154(4)$  Å,  $c = 12.127(3)$  Å,  $\beta = 101.40(3)^\circ$ ,  $Z = 4$ ] and (*E*)-1-benzoyl-3-[(*Z*)-1,2-bis(methoxycarbonyl)vinyl]-2,2-diphenyl-4-cyclohexyl-1,5-diaza-2 $\lambda^5$ -phosphapenta-1,3-diene (2d) [ $P2_1/c$ ,  $a = 12.167(7)$  Å,  $b = 21.14(4)$  Å,  $c = 12.845(7)$  Å,  $\beta = 108.77(6)^\circ$ ,  $Z = 4$ ] have been elucidated by single-crystal X-ray diffraction. Calculated conformations by MM and PM3 methods were in good agreement with the experimental observations.

Enamines are important starting materials for the preparation of a large variety of heterocyclic compounds<sup>1</sup> as well as useful intermediates for the synthesis of biologically active molecules.<sup>2</sup> During the last few years, we have developed a new methodology based on the use of phosphorylated enamines<sup>3</sup> which allows the introduction of both nitrogen and phosphorus heteroatoms into a heterocyclic framework.<sup>4</sup> The incorporation of a side chain containing various specific functionalities would broaden the synthetic scope of these intermediates. We have recently reported the reaction between (*N*-acylamidophosphazenes 1 and dimethyl acetylenedicarboxylate<sup>5</sup> (DMAD). On the basis of the analysis of the phosphorus coupling constants of the isolated product, a *trans* addition of the enamine C-H bond to the acetylenic triple bond was assumed to occur (Scheme 1).

The use of vicinal and long-range phosphorus coupling constants is a well-established criterion for stereochemical assignment.<sup>6</sup> Thus, a value of  $^3J_{\text{PC3}}$  of 11.9 Hz in 2a can be taken as a steady indication<sup>7</sup> for the retention of the *Z*-configuration around the enamino structure of 2. On the other hand, the value for  $^4J_{\text{PH}}$  (2.7 Hz) for the vinylic



2	R	Configuration <sup>a</sup>	$\delta_{\text{P}}$ (ppm)
a	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	ZZ	19.0
b	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	ZE	13.3
c	C <sub>6</sub> H <sub>11</sub>	ZZ	19.0
d	C <sub>6</sub> H <sub>11</sub>	EZ	20.2

<sup>a</sup>The first letter refers to the C1C2 double bond and the second to the C9C10 one. The same numeration as in the X-ray studies has been used.

proton at C10 in 2a could be consistent with a *W* relationship between both nuclei.<sup>8</sup> This arrangement is met *a priori* when the new C9-C10 double bond possesses an *E*-stereochemistry and the molecule adopts predom-

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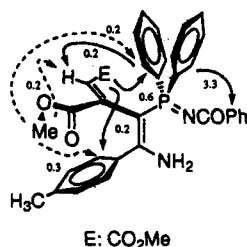
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**Figure 2.** Selected NOEs for compound **2b** measured at 400.13 MHz in  $\text{CDCl}_3$ .

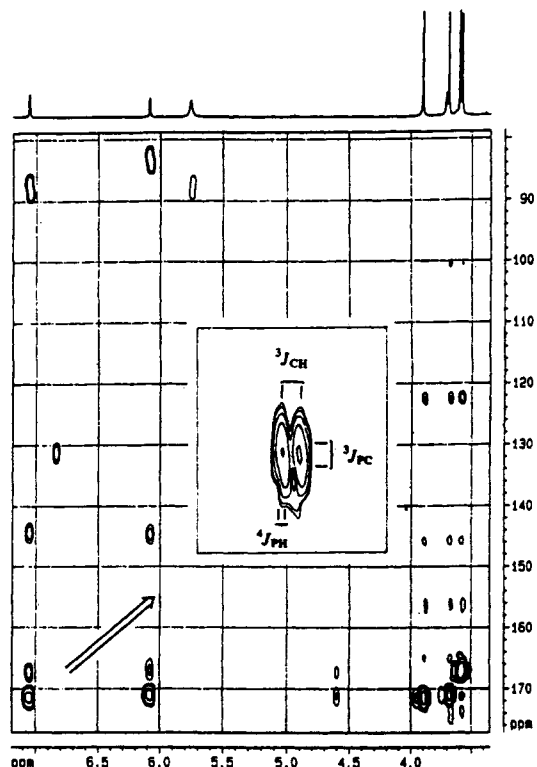
**Table 1.** Solvent Dependence of the Ratio **2c**:**2d**<sup>a</sup>

solvent	<b>2c</b>	<b>2d</b>
DMSO- <i>d</i> <sub>6</sub>	25	75
CD <sub>3</sub> CN	30	70
THF- <i>d</i> <sub>8</sub>	45	55
CDCl <sub>3</sub>	60	40

<sup>a</sup> In percent, by integration of the <sup>1</sup>H-NMR spectra, 0.05 M solutions, room temperature.

data are interpreted to mean that the rotation of these rings is now restricted, possibly due to an increase in their steric interactions, as expected for an *E* stereochemistry for the C9–C10 double bond. The *Z* configuration of the enaminic moiety is readily assignable from the <sup>3</sup>J<sub>PC3</sub> coupling constant, <sup>3</sup>J<sub>PC3</sub> = 11.4 Hz. This picture is fully confirmed by NOE experiments. The enhancements observed demonstrate the conformation of **2b**. Thus, both methoxy protons afford positive NOEs with H10 as well as the *ortho* protons of the *p*-tolyl and phosphazanyl substituents; however, the intensity of the enhancements for these last protons depends most notably on the presaturated methoxy group (Figure 2), and only the most deshielded one is dipolarly related with the *N*-benzoyl group. These differences are clearly incompatible with a free rotation around the C1–C9 and the C1–P single bonds; in that case, the NOEs between the vinylic proton H10 and the *p*-tolyl substituent can only be explained assuming a large dihedral angle for the aminodiene system of **2b**, according to the conformation depicted in Figure 2. From the <sup>3</sup>J<sub>PC</sub> values found for C10 and C13 it can be concluded that the magnitude of this angle must be similar to that for **2a**. Therefore, compound **2b** is the result of a *trans* addition of the enaminophosphazene to the DMAD, and interestingly, a similar <sup>4</sup>J<sub>PH</sub> = 2.4 Hz to that for **2a** is obtained, which clearly shows the impossibility of using the absolute value of this coupling for stereochemical assignments (see below).

As already mentioned, a mixture of two compounds **2c** and **2d** was found in solution for R = C<sub>6</sub>H<sub>11</sub>. They produce a unique molecular ion on the IE mass spectrum (*M*<sup>+</sup> = 556) and an analogous group of signals in the NMR spectra; *i.e.*, they are isomers. Their ratio, determined by <sup>1</sup>H-NMR, is solvent dependent in the sense that more polar solvents<sup>16</sup> tend to favor **2c** over **2b** (Table 1). The <sup>1</sup>H-NMR spectrum measured in CDCl<sub>3</sub> shows two overlapped methoxy groups which are resolved into two separated signals when THF-*d*<sub>8</sub> is used as solvent; their <sup>1</sup>H- and <sup>13</sup>C-NMR spectra have been assigned by 2D heteronuclear correlation spectroscopy. Thus, the 2D HMQC spectrum<sup>17</sup> allows the identification of all the protonated carbon atoms, even though



**Figure 3.** Expansion plot of the HMBC spectrum of the mixture **2c/2d** recorded at 400.13 MHz in THF-*d*<sub>8</sub>, showing the connectivities of the methinic and methoxy protons. The negative slope of the cross peak between H10 and C1 is clearly seen. The inset corresponds to the cross peak of H10 with the carbonyl carbon C13, obtained from a second HMBC spectrum acquired with higher resolution (final matrix of 4K x 1K, sweep width of 3000 Hz in F2 and of 2000 Hz in F1, magnitude mode). From its negative slope the positive sign of <sup>3</sup>J<sub>PC</sub> is identified.

there is a severe overlap in the aromatic region of the <sup>1</sup>H-NMR (see Experimental Section). On the other hand, the assignment of the quaternary carbon atoms has been deduced from the long-range correlations observed in the 2D HMBC spectrum.<sup>18</sup> The key entries are the two doublets of H10 at 7.06 ppm for the major and 6.09 ppm for the minor component. Each of them shows four cross peaks corresponding to the connections with C1, C9, C11, and C13 (Figure 3); the higher intensity obtained for the cross peaks of H10 with C1 and C13 is a result of the increased efficiency in the coherence transfer<sup>19</sup> through <sup>3</sup>J<sub>CH</sub> over that of <sup>2</sup>J<sub>CH</sub>. Moreover, the negative slope of the pairs of cross peaks between H10 and C1 derives from the passive coupling to the phosphorus-31 nucleus. This slope is a consequence<sup>20</sup> of the opposite sign of <sup>1</sup>J<sub>PC</sub> vs <sup>4</sup>J<sub>PH</sub>; since a positive sign<sup>21</sup> can be assumed for <sup>1</sup>J<sub>PC</sub>, a negative sign is obtained for <sup>4</sup>J<sub>PH</sub>. Once the identity of each carbonyl linkage is established, the corresponding methoxy groups are easily assigned by their respective <sup>3</sup>J<sub>CH</sub> correlations in the HMBC spectrum.

The above discussion does not show whether **2c** and **2d** are conformational or configurational isomers. However, the analysis of the PC couplings reveals that the isomerization occurred at the enaminic moiety: <sup>3</sup>J<sub>PC3</sub> = 8.9 Hz for **2c** and <sup>3</sup>J<sub>PC3</sub> = 5.2 Hz for **2d** are consistent with a *Z* and *E* stereochemistry for this double bond, respectively.

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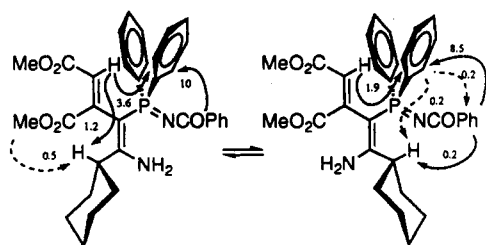


Figure 4. Selected NOEs for compounds 2c and 2d measured at 400.13 MHz in THF-*d*<sub>8</sub>.

Table 2. Energy Barrier (kcal mol<sup>-1</sup>) for Rotation around the C2-N Bond in Compounds 2 and 4

compd <sup>a</sup>	<i>T</i> <sub>coal</sub> (K)	Δ <i>G</i> <sup>‡</sup>
2a	261	11.2
2b <sup>b</sup>	269	11.4
2c	286	12.4
2d	256	11.5
4a	277	12.1

<sup>a</sup> 0.05 M solutions in THF-*d*<sub>8</sub>. <sup>b</sup> In Et<sub>2</sub>O-*d*<sub>10</sub>.

Steady-state NOE experiments confirm the assignment made. The key points are the dipolar connectivities established for each methyne proton of the cyclohexyl substituent and those of the methoxy protons (Figure 4). It is interesting to note that the couplings to phosphorus for C10 and C13 are very similar for both isomers and lie in the range 5.0–6.7 Hz. Also noteworthy is the increase observed in <sup>2</sup>*J*<sub>PC2</sub> due to the isomerization of the enaminic double bond: 4.4 Hz in 2c vs 17.7 Hz in 2d. Following the same argument outlined above a similar conformation to that of 2a can be assumed for 2c and 2d (Figure 4).

The NOE spectra also showed the existence of a magnetization transfer process<sup>22</sup> between 2c and 2d, the rate of which is of the order of the longitudinal relaxation rate. We have quantified<sup>23</sup> the process for each vinylic proton and calculated a Δ*G*<sup>‡</sup> for the isomerization reaction of Δ*G*<sup>‡</sup><sub>ZE</sub> = 17.8 kcal mol<sup>-1</sup> and Δ*G*<sup>‡</sup><sub>EZ</sub> = 17.7 kcal mol<sup>-1</sup>, in good agreement to reported values for similar push-pull olefins.<sup>24</sup>

Lowering the temperature produces a broadening of the more shielded methoxy protons in the <sup>1</sup>H-NMR spectra as well as a decrease in the rotation rate around the C-N single bond. In that way the two protons of the amino group can be distinguished, and their rate of exchange has been calculated at the coalescence temperature<sup>25</sup> (Table 2). The biggest chemical shift difference is encountered for the NH protons in the *Z*-configuration, which could be ascribed to the presence of an intramolecular hydrogen bond,<sup>26</sup> which explains the higher Δ*G*<sup>‡</sup> for the NH<sub>2</sub> rotation<sup>27</sup> in 2c relative to 2d. Whether the P=N or the C=O linkages of the *N*-benzoylphosphazenyli moiety are involved in this bond cannot be decided by the <sup>1</sup>H-NMR spectrum itself, it must be analyzed together with the conformation of the group around the C15-N single bond. The large <sup>3</sup>*J*<sub>PC16</sub> = 21.2 Hz indicates an *anti* orientation

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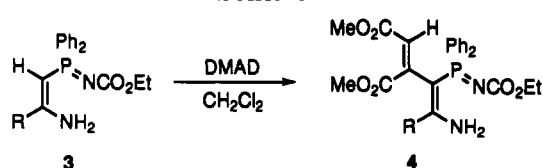
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Scheme 2



4	R	Configuration <sup>a</sup>	δ <sub>p</sub> (ppm)
a	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	<i>ZZ</i>	22.8
b	C <sub>6</sub> H <sub>11</sub>	<i>ZZ</i>	23.4
c	C <sub>6</sub> H <sub>11</sub>	<i>EZ</i>	19.9

a) The first letter refers to the enaminic double bond

between both atoms with a planar arrangement of the P=N and C=O double bonds, and the NOE enhancement observed for the *ortho* protons of the *P*-phenyl rings after presaturation of the corresponding *ortho* protons of the *N*-benzoyl group is consistent with a preferred *s-cis* conformation for the *N*-benzoylphosphazenyli substituent, in which the carbonyl double bond faces the NH<sub>2</sub> group and, therefore, both P=N and C=O double bonds are available for hydrogen bonding.<sup>28</sup>

Two consequences can be drawn from the discussion above: (i) a reduced mobility for the *N*-benzoyl group is expected, in good agreement with the absence of conformer exchange at very low temperatures, and (ii) steric interactions would impose a nonplanar arrangement of the molecular fragment defined by the enamine, P=N and C=O linkages; therefore, the phosphazenyli group will be rotated in relation to the enaminic moiety, which would favor the observation of NOE between their phenyl protons and those of the *p*-tolyl substituent, as experimentally detected.

The same study has been carried out for compounds 4 (Scheme 2). Once again, a single product is isolated for 4a, whereas a mixture of the *Z* and *E* isomers of the enaminic double bond results for 4b. Both compounds are very sensitive to traces of acid. Even during the acquisition of the NMR spectra of freshly prepared samples, they transform very rapidly into a cyclic compound whose structure is currently under study. In fact, all attempts to purify 4b failed, and its identification was carried out over the reaction crude.

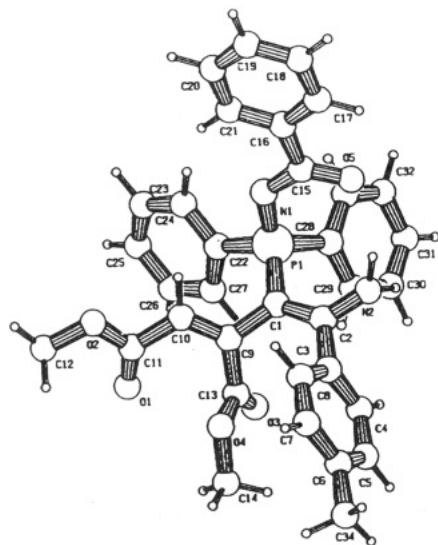
The <sup>1</sup>H-NMR spectra show the characteristic doublets for the methyne proton due to the <sup>4</sup>*J*<sub>PH</sub> coupling constant. On the other hand, similar deshielding<sup>29</sup> of the <sup>31</sup>P resonances is observed in the adducts 2 and 4 in relation to those of the starting materials 1 and 2. The analysis of the P-C couplings together with the steady-state NOEs observed indicates that changing a benzoyl for an ethoxy-carbonyl group in 1 increases their reactivity<sup>30</sup> toward the DMAD but does not significantly modify the configuration and conformation for the reaction products.

**Single-Crystal X-ray Studies and Computational Calculations.** To clarify the structural assignments made above, a crystallographic study was carried out. Single

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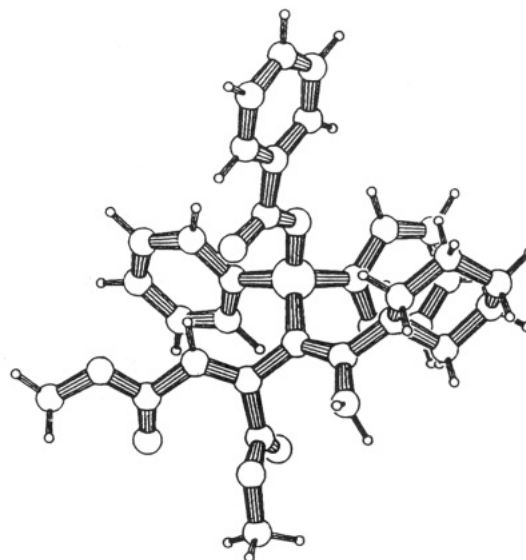
**Figure 5.** Molecular structure of compound **2a** in the crystal and crystallographic numbering scheme used.

**Table 3.** Selected Bond Lengths (Å) and Angles (deg) for Compounds **2a** and **2d**

distance	<b>2a</b>	<b>2d</b>	angle	<b>2a</b>	<b>2d</b>
P1–N1	1.603(5)	1.607(3)	C1–P1–N1	115.6(3)	118.6(2)
P1–C1	1.786(6)	1.793(3)	C15–N1–P1	125.1(4)	121.1(2)
O1–C11	1.202(8)	1.191(5)	C2–C1–P1	120.7(5)	120.4(2)
O2–C11	1.336(8)	1.336(5)	C9–C1–P1	119.0(4)	117.9(2)
O3–C13	1.191(7)	1.193(5)	C9–C1–C2	120.3(6)	121.7(3)
O4–C13	1.333(8)	1.351(5)	C1–C2–N2	125.2(6)	121.9(3)
O5–C15	1.263(6)	1.247(4)	C3–C2–N2	112.8(5)	114.7(3)
N1–C15	1.326(7)	1.350(4)	C3–C2–C1	122.0(6)	123.4(3)
N2–C2	1.359(7)	1.357(4)	C4–C3–C2	120.1(7)	112.8(3)
C1–C2	1.382(7)	1.375(4)	C10–C9–C1	120.3(6)	123.0(3)
C1–C9	1.489(8)	1.479(4)	C13–C9–C1	117.0(6)	116.4(3)
C2–C3	1.496(8)	1.517(4)	C13–C9–C10	121.9(6)	120.3(3)
C9–C10	1.345(8)	1.342(5)	C11–C10–C9	122.3(7)	122.3(3)
C9–C13	1.506(9)	1.498(5)	C10–C11–O1	126.7(8)	127.5(4)
C10–C11	1.489(9)	1.479(5)	C10–C11–O2	108.7(7)	109.3(4)
C15–C16	1.499(8)	1.508(5)	C9–C13–O3	122.8(7)	124.4(4)
			C9–C13–O4	111.4(7)	110.7(4)
			C16–C15–N1	115.9(6)	114.4(3)

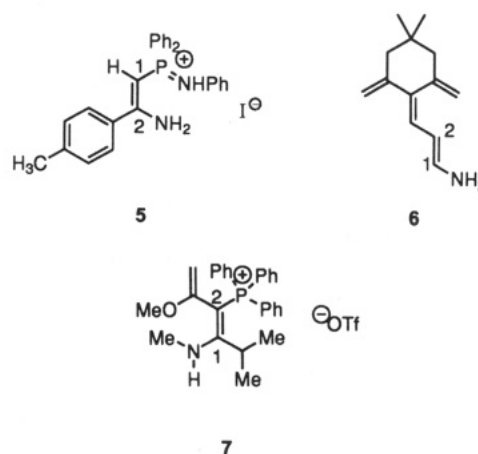
crystals of **2a** and **2d** were obtained from a solution of hexane–CH<sub>2</sub>Cl<sub>2</sub> and toluene, respectively, at room temperature. Crystallographic data including fractional coordinates, molecular distances, and angles are given as supplementary material; a summary of the most relevant molecular distances and angles discussed in the text is collected in Table 3.

The X-ray data show only one solid-state configuration for each compound **2a** and **2d**, corresponding to a *ZZ* stereochemistry for the dienic system in **2a** (Figure 5), whereas a *EZ* configuration was found for **2d** (Figure 6). It is worth mentioning that both compounds have in common the lack of planarity for the dienic systems defined by C2C1C9C10 and C2C1P1N1, the dihedral angles being 136.7(7)° and –79.8(6)° for **2a** and 129.7(5)° and –59.8(5)° for **2d**, respectively. Moreover, only the methoxycarbonyl group C11O1 is coplanar with the C9–C10 double bond, while the carbonyl group C13O3 forms a dihedral angle close to 115° with that bond, in good agreement with the values found for similar subunits in the literature.<sup>31</sup> Also, the *p*-tolyl substituent in **2a** lies *quasi* perpendicular to the enaminic linkage (the dihedral angle C1C2C3C4 is 109.4(7)°); on the other hand, the *E* stereochemistry of



**Figure 6.** Molecular structure of compound **2d** determined by X-ray diffraction.

the enamine in **2d** allows the allocation of the carbonyl group of the *N*-benzoyl moiety antiperiplanar to the phenyl rings bonded to the phosphorus. Therefore, both compounds adopt a highly distorted conformation in the crystal most probably imposed by the bulky substituents around the double bonds, in contrast to similar conjugated systems with less steric demand.<sup>32</sup> The overcrowding is also reflected in the significant decrease of the bond angles connecting the N2C2C3 and P1C1C9 atoms (Table 3). The primary amino group is coplanar with the C1C2 double bond, which in turn is longer [1.382(7) Å in **2a** and 1.375(4) Å in **2d**] than a formal double bond (1.337 Å),<sup>33</sup> owing to the delocalization of the lone-pair on nitrogen atom with this group,<sup>34</sup> as expected for a typical push-pull ethylene. However, the conjugation along the aminodienic system of **2a/2d** must be very much reduced, as deduced from the comparison with the data for some related systems. Thus, the C1C2 bond distance in **2a** (1.382 Å) is comparable<sup>35</sup> to the one found in compound **5**, but it is shorter than that observed<sup>32</sup> for the corresponding



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Table 4. Bond Lengths (Å) and Angles (deg) for Compounds 2a and 2d<sup>a</sup>

donor-H	donor...acceptor	H...acceptor	angle
Compound 2a			
N2-H202, 1.08(1)	N2...O5, 2.857(7)	H202...O5, 2.161(7)	N2-H202...O5, 119.9(5)
N2-H202 (i), 1.08(1)	N2...O5 (i), 2.995(6)	H202...O5 (i), 2.690(7)	N2-H202...O5, 93.3(4)
Compound 2d			
N2-H202 (i), 1.08(1)	N2...O5 (i), 3.014(4)	H202...O5 (i), 2.192(4)	N2-H202...O5, 131.1(4)

<sup>a</sup> Symmetry code: (i) -X, -Y, -Z.

bond in **6** [1.397(8) Å] and in the trifluorosulfonate<sup>36</sup> **7** [1.440 Å]; the same happens when the analogous C9C10 double bonds of **2a** [1.345(8) Å] and **6** [1.409(8) Å] are compared. Consequently, the C1C9 bond distance is markedly longer [1.489(8) Å in **2a** and 1.385(8) Å in **6**] even when compared with the standard C<sub>sp<sup>2</sup></sub>-C<sub>sp<sup>2</sup></sub> distance.<sup>37</sup> The same argument applies to the lack of conjugation through the system involving the methoxycarbonyl groups, as well as the *p*-tolyl substituent of **2a** in relation to the enaminic linkage.

Comparing the crystal packing of both compounds shows that they present a dimeric structure through intermolecular hydrogen bond formation, linking together the *N*-benzoyl and the amino groups; however, in the case of **2a** these groups also participate in an intramolecular hydrogen bond (Table 4).

The solid-state structures reported here were directly used as input for the conformational analysis of all the possible stereoisomers of compounds **2** (*ZZ*, *ZE*, *EZ*, and *EE*) based on the semiempirical PM3 method,<sup>38</sup> in all other cases a geometry preoptimization via MM was performed.<sup>39</sup> The heats of formation obtained for the minimal energy conformation of each isomer are depicted in Figure 7, and the computed structures for **2a** and **2d** are represented in Figure 8; additional data are given as supplementary material. To a good approximation, the changes in the entropy of the isomerization process can be neglected for comparison in each series of compounds, so that these heats of formation can be treated as free energy values in the gas phase. The predicted stabilities are in good agreement with the experimental results. Thus, for R = *p*-tolyl the two more stable isomers are **2a** (*ZZ*) and **2b** (*ZE*), the first being favored by 0.33 kcal mol<sup>-1</sup>, while for R = C<sub>6</sub>H<sub>11</sub> the two isomers around the enaminic double bond **2c** (*EZ*) and **2d** (*ZZ*) are now preferred. Conformationally speaking, all isomers show a very twisted arrangement for the aminodiene system, with dihedral angles close to 90° for the segments P1C1C9C10 and P1C1C9C13 (Table 5). The enaminic linkage is planar, but the R substituent lies nearly perpendicular to the C1C2 double bond, while the phosphazanyl group is slightly counterclockwise rotated relative to that bond; as expected, only one of the methoxycarbonyl groups is found in the plane of the C9C10 double bond. On the other hand, the *N*-benzoylphosphazanyl moiety adopts an *s-cis* conformation with the carbonyl group *syn* to the enamine, in sharp contrast with the transoid arrangement encountered with CNDO/2 calculations carried out with *N*-vinylphosphazenes.<sup>40</sup>

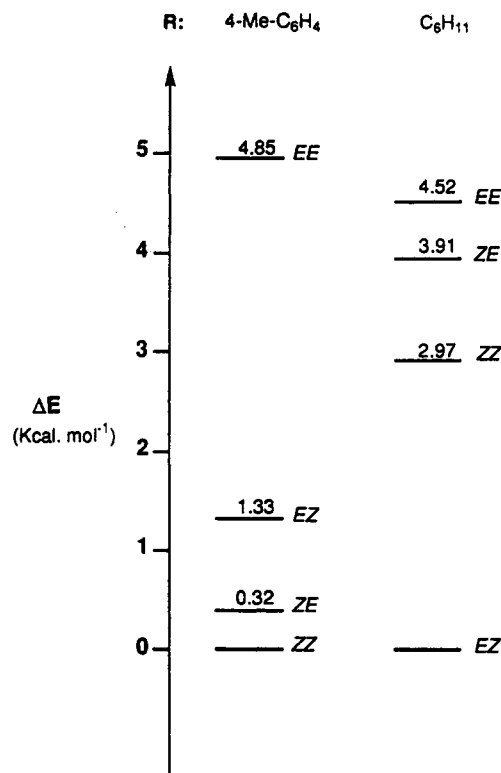


Figure 7. Relative energies among all configurational isomers of compounds **2** derived from the heats of formation calculated by MNDO-PM3 method.

## Discussion

The experimental results and theoretical calculations show very similar results regarding probable conformations for compounds **2** and **4** both in solution and in the solid state, in which the aminodiene framework may be described as enaminic and the vinylic subunits are very poorly conjugated owing to the large deviation from planarity of the double bonding system. This distortion can be ascribed to the bulkiness of the substituents around the butadienic moiety, which at the same time imposes a high degree of rigidity according with the observed NOEs and coupling constants.

It is interesting to note that although a higher energy difference has been calculated for the *ZZ*/*ZE* isomers when R = C<sub>6</sub>H<sub>11</sub> (2.97 kcal mol<sup>-1</sup>) than when R = *p*-tolyl (1.33 kcal mol<sup>-1</sup>), which are found to interconvert in solution even when low polar solvents are used ( $\Delta G^*_{ZE} = 17.8$  kcal mol<sup>-1</sup>, see above), the *p*-tolyl derivatives do not. Moreover, by dissolving a small portion of the crystals used in the X-ray analysis of **2d** in CDCl<sub>3</sub>, the same ratio of **2c**/**2d** is found in their NMR spectra as when the crude reaction product is measured. This means that the enamino-phosphazenes **1** add regio- and stereoselectively to the DMAD, but an inversion of the configuration of the enaminic moiety is observed depending on the R substituent used. The difference in the isomerization rates of the enaminic moiety in compounds **2** could be in principle attributed

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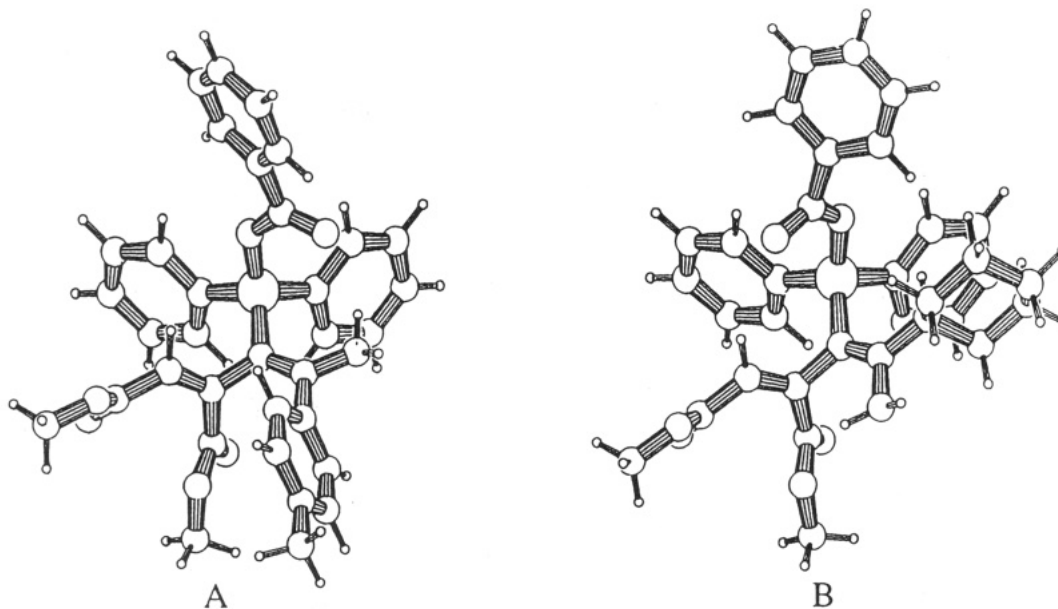
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**Figure 8.** Conformers showing minimal energy using PM3 method: (A) for compound **2a** and (B) for compound **2d**. See Figure 5 for labeling.

**Table 5.** Selected Torsion Angles (deg) for the MNDO-PM3 Calculated Structures along with Their Corresponding Heats of Formation (kcal mol<sup>-1</sup>)

	R = 4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>				R = C <sub>6</sub> H <sub>11</sub>			
	EE	ZE ( <b>2b</b> ) <sup>a</sup>	EZ	ZZ <sup>b</sup> ( <b>2a</b> ) <sup>a</sup>	EE	ZE	EZ <sup>b</sup> ( <b>2d</b> ) <sup>a</sup>	ZZ ( <b>2c</b> ) <sup>a</sup>
C2-C1-C9-C10	79.11	91.79	-90.33	105.96	-80.63	86.25	99.45	-85.87
C1-P1-N1-C15	120.91	81.26	-50.17	61.29	-52.95	48.77	-49.04	100.57
N1-P1-C1-C2	-66.33	-74.14	-46.87	-75.94	-52.62	-71.47	-50.81	-44.38
C10-C9-C13-O3	45.35	-7.45	66.77	128.97	-66.01	18.51	120.74	-65.03
C9-C10-C11-O1	-68.75	-68.99	-48.40	-48.19	-55.98	-71.38	-51.03	-50.61
H <sub>f</sub>	-42.10	-46.63	-45.62	-46.95	-86.04	-86.65	-90.56	-87.59

<sup>a</sup> Compounds experimentally observed and identified by NMR. <sup>b</sup> Configuration for compounds determined by X-ray diffraction.

to a stronger intramolecular hydrogen bond<sup>41</sup> in **2a** vs **2c**. However, a lower energy for the rotation of the amino group has been measured for **2a** than for **2c** (Table 2); therefore, the isomerization process must be controlled by the energy gap necessary to overtake the transition state.

Another interesting structural feature in the enamines **2** and **4** is the set of couplings to the phosphorus-31 nucleus found. No significant fluctuations of <sup>1</sup>J<sub>PC</sub> were observed, and the values obtained are in the expected range<sup>6</sup> for C<sub>sp</sub><sup>2</sup> carbons bonded to phosphorus (IV), however, <sup>2</sup>J<sub>PC</sub> coupling were very sensitive to the stereochemistry of the enaminic double bond; for C2 in **2c/2d** they differ by 1 order of magnitude. Changes in <sup>2</sup>J<sub>PC</sub> within isomer pairs of P(IV) compounds have been noted by various authors<sup>6b</sup>. Steric interactions<sup>42</sup> as well as stereochemical dependence from the orientation of the P=O group<sup>43</sup> have been invoked to explain the values observed. However, in **2c** and **2d** the orientation of the phosphazanyl group remains almost unchanged, so that the increase of <sup>2</sup>J<sub>PC</sub> in **2d** could be a consequence of several factors involving a higher *s* character of C2 as well as an increase in bond angles.<sup>44</sup> One may note that the calculated geometries for **2c** and

**2d** predict a decrease in the bond angles C1C2N2 and C1C2C3 on going from **2c** to **2d**, which can be related with an increase in the *s* character between C2 and C1 in **2d**, and hence, a larger <sup>2</sup>J<sub>PC</sub> coupling should result.<sup>15,45</sup>

Greater confidence can be placed in the stereochemical assignments based on <sup>3</sup>J<sub>PC</sub> because of the large body of data showing the dihedral angle ( $\varphi$ ) dependence of the vicinal <sup>13</sup>C-<sup>31</sup>P coupling constants<sup>6</sup> for P(IV) compounds;<sup>7</sup> the resulting Karplus curve shows maxima for *J* at  $\varphi = 0$  and 180° with <sup>3</sup>J<sub>PC-trans</sub> > <sup>3</sup>J<sub>PC-cis</sub> and the usual minimum at  $\varphi = 90^\circ$  (*J* ≈ 0 Hz). Accordingly, large <sup>3</sup>J<sub>PC3</sub> (>9 Hz) have been measured for the *Z* enaminic moiety in compounds **2** and **4**, whereas intermediate values (<6 Hz) are found in the *E* configuration. Nonetheless, lower efficiency is obtained in the determination of the conformation around C1-C9; mean <sup>3</sup>J<sub>PC</sub> values of 6 Hz are measured for C10 and C13, while both NOE experiments and semiempirical calculations predict a  $\varphi$  close to 90° relating the P-C10 and P-C13 nuclei so that, a very small vicinal coupling should be expected. Considering the fact that a positive sign is obtained from the HMBC (Figure 3) spectra for <sup>3</sup>J<sub>PC13</sub>, a displacement from the 90° position to lower dihedral angles of the minimum of the vicinal <sup>13</sup>C-<sup>31</sup>P coupling seems a reasonable expectation for the phosphazenes studied here; however, more work is necessary on compounds of fixed conformation and of known orientation of the P=N linkage<sup>46</sup> to calculate a Karplus curve for this coupling constant.

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Finally, large values of  ${}^4J_{\text{PH}}$  have been found relating both nuclei (2.7/2.4 Hz for H10 in compounds **2a/2b**, respectively) independently of the geometry, so that no conformational information could be obtained *a priori*. It is well known that  ${}^nJ_{\text{HH}}$ ,  ${}^nJ_{\text{CH}}$ , and  ${}^nJ_{\text{CC}}$  ( $n = 1-9$ ) couplings involving  $\pi$  electrons may be considered as the sum of two contributions,<sup>47</sup>  $J^\sigma$  and  $J^\pi$ , and that a sign alternation characterizes  $J^\pi$  depending on the number of intervening bonds, the even numbers of bonds corresponding to negative  $J^\pi$  couplings.<sup>48</sup> Moreover, valence bond calculations for allylic fragments<sup>49</sup> have shown a  $\cos^2 \phi$  dependence for  ${}^4J_{\text{HH}}$ ,  $\phi$  being the angle formed between the  $\text{sp}^3$  hybridized C-H bond and the axis of the adjacent  $2p\pi$  orbital; therefore, a maximum negative value is expected for  $\phi = 0^\circ$  and  $180^\circ$  and vanishes for  $\phi = 90^\circ$ ; in acyclic molecules a weighted average of the conformer populations must be considered.<sup>50</sup> In our case the experimental and theoretical evidence are in agreement with such conformations for compounds **2** and **4** in which the torsion angle between the phosphorus atom and the  $2p\pi$  orbitals of the C9C10 double bond is very close to  $0^\circ$ ; this implies that the  $\pi$  component must predominate in  ${}^4J_{\text{PH}}$ , and therefore, a negative sign for this coupling should be obtained. Indeed, this proved to be the case because from the HMBC spectra of these compounds a negative sign for  ${}^4J_{\text{PH10}}$  has been measured (see explanation above, Figure 3). These facts allow us to state that *valuable conformational information can be obtained from  ${}^4J_{\text{PH}}$  in phosphorylated allylic fragments when the magnitude and sign of this coupling is known.*

In summary, *N*-acyl  $\beta$ -enaminophosphazenes add to the DMAD through the  $\beta$ -enaminic carbon with a *Z*-stereoselectivity higher than 90% in the new double bond formed; the stereochemistry of the enamine is retained or inverted depending on the substituent on the  $\alpha$ -carbon. The 1-amino-1,3-butadiene derivatives formed exhibit a preferred conformation in which the dihedral angle formed by the dienic system is close to  $90^\circ$ , so that a very poor conjugation is expected. The predicted stabilities and conformations of the possible stereoisomers as derived from semiempirical calculations are in good agreement with the experimental observations and with the olefinic push-pull character of these compounds.

Precise stereochemical information has been obtained from NOE enhancements and coupling constants. Both geminal and vicinal carbon-phosphorus couplings can be used to assign the configuration of phosphazeryl-substituted double bonds, whereas the vicinal coupling constant has also been shown to be sensitive to conformational changes according to the Karplus model. On the other hand, the large  ${}^4J_{\text{PH}}$  values found in compounds **2** and **4** arise from a predominantly  $\pi$  contribution according to the negative sign measured and have been ascribed to a torsion angle close to  $0^\circ$  between the phosphorus atom and the axis of the  $2p\pi$  orbital of C9, in analogy with the known model for proton-proton long-range couplings in allylic systems. Therefore, long-range coupling constants to the phosphorus involving allylic type frameworks can

be used as a tool for conformational analysis whenever its absolute sign is known.

Further work is in progress to calculate the energy barriers of rotation around all the double bonds of the aminodiene system of **2** and **4** in order to promote the selective formation of different phosphazeryl-substituted heterocyclic systems under the appropriate reaction conditions.

## Experimental Section

**Materials and General Methods.** The DMAD used was reagent grade and distilled prior to use. The solvents were dried and distilled prior to use following standard procedures.<sup>51</sup> Compounds **1** and **4** were prepared according to the literature methods.<sup>4b,5</sup> Column chromatography was performed using 230-400-mesh silica gel. Melting points were measured in a Büchi-Tottoli apparatus and are uncorrected. Microanalyses were performed on a Perkin-Elmer 240 B instrument. Infrared spectra were recorded on a FTIR Mattson 3020 spectrophotometer. Mass spectra were obtained on a Hewlett-Packard 5987 A. NMR spectra were recorded on a Bruker AC300 or AMX400 spectrometer. Details about their configuration and pulse performance have been published elsewhere.<sup>52</sup> Perdeuterated solvents were used (see text) throughout the study with a sample concentration ranging between 0.1 and 0.2 mmol. Spectra were referred to internal  $\text{SiMe}_4$  ( ${}^1\text{H}$ ,  ${}^{13}\text{C}$ ) or external 85%  $\text{H}_3\text{PO}_4$  ( ${}^{31}\text{P}$ ). Temperature calibrations were performed according to the method of van Get<sup>53</sup> using a sample of 4% methanol in  $\text{CD}_3\text{OD}$  and are considered to be accurate to  $\pm 1$  K. Couplings constants are accurate to  $\pm 0.15$  Hz. Standard experimental parameters for the acquisition of NOE difference were used<sup>54</sup>. The proton detected heteronuclear 2D correlation experiments<sup>17,18</sup> were acquired with 256 time increments and zero filled to give a final  $2048 \times 1024$  data matrix. For the magnetization transfer experiment a low power irradiation was applied during 0.7 s, and the transfer of magnetization was monitored over a 10-s time range at a temperature of  $22^\circ\text{C}$ . A least-squares fitting was carried out, and the repetition time was set to 25 s, which was greater than  $5T_1$  of the more slowly relaxing proton, according to standard inversion-recovery  $T_1$  measurements.<sup>54</sup>

**Theoretical Calculations.** Solid-state geometries obtained by X-ray diffraction for compounds **2a** and **2d** were used as starting points for all other isomers of **2**, whose geometry was then derived by simple rotation of  $180^\circ$  around C1-C2 and/or C9-C10 bonds. Once the respective family of compounds was built, the conformational analysis was carried out for each one under the same conditions. Considering the large size of the target molecules, an empirical method based on molecular mechanics (CHEMX program at the MME level) was applied first to calculate the conformer populations for each configuration. The system was allowed to rotate  $360^\circ$  around the bonds C1-C9, P1-N1, P1-C1, C9-C13, and C10-C11 in steps of  $5^\circ$ . For each compound, the conformer showing the lowest MM energy was selected, and in a second step, its geometry was full-optimized using a semiempirical procedure (MNDO-PM3, MOPAC package<sup>55</sup>). Final results are summarized in Table 5 and Figures 7 and 8; all other computed structures are included as supplementary material.

**Single-Crystal X-ray Data Acquisition and Processing.** Relevant crystal and refinement data for compounds **2a** and **2d** are supplied as supplementary material. Mo  $K\alpha$  radiation, graphite crystal monochromator, Enraf-Nonius CAD4 single crystal diffractometer. Unit cell dimensions were determined from the angular settings of 25 reflections. Space group was determined from systematic absences;  $\omega - 2\theta$  scan technique with a maximum scan time of 60 s per reflection. Intensity was checked throughout data collection by monitoring three standard reflections

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every 60 min. A profile analysis performed on all reflections.<sup>55</sup> Semiempirical absorption corrections,  $\psi$ -scans based, were applied.<sup>56</sup> Some double-measured reflections were averaged,  $R_{\text{int}} = (|I - \langle I \rangle|)/I$ . Lorentz and polarization correction applied and data reduced to  $|F_o|$ -values. Structure solved by Direct Methods using the program SHELXS86<sup>57</sup> and completed by the phase-expansion procedure of DIRDIF.<sup>58</sup> Isotropic least-squares refinement, using SHELX76,<sup>59</sup> was carried out until convergence. Empirical absorption correction was applied.<sup>60</sup> Further refinements included anisotropic thermal parameters for all non-hydrogen atoms. All hydrogen atoms were isotropically refined with a common thermal parameter and riding on their parent atoms. Function-minimized  $W(F_o - F_c)^2$ ,  $W = 1/(\sigma^2(F_o) + gF_o^2)$ , with  $\sigma(F_o)$  from counting statistics.

Atomic scattering factors were from the *International Tables for X-ray Crystallography*.<sup>61</sup> Plots were made with the EUCLID program.<sup>61</sup> Geometrical calculations were made with PARST.<sup>62</sup> All calculations were made on a MicroVax-3400 at the Scientific Computer Center, University of Oviedo. A list of structure amplitudes, anisotropic thermal parameters, H-atom parameters, distances and angles involving H atoms, distances, angles, and least-squares-planes-lines data and torsion angles have been deposited at the Cambridge Crystallographic Data Centre.<sup>63</sup>

**Reaction of *N*-Acyl- $\beta$ -enamino- $\lambda^5$ -phosphazenes (1) and (3) with DMAD.** DMAD (5 mmol) was added to a solution of compound 1 or 3 (5 mmol) in  $\text{CH}_2\text{Cl}_2$ , dried, and freshly distilled under *N,N*-diethylaniline. The mixture was stirred at room temperature during 36 h, and then *in vacuo* solvent evaporation afforded a yellow oil, from which compound 2 or 4 was isolated by recrystallization in hexane-methylene chloride.

**(Z)-1-Benzoyl-3-[(Z)-1,2-bis(methoxycarbonyl)vinyl]-2,2-diphenyl-4-(*p*-tolyl)-1,5-diaza-2 $\lambda^5$ -phosphapenta-1,3-diene (2a)** (75%):  $\text{C}_{33}\text{H}_{31}\text{N}_2\text{O}_5\text{P}$ ; mp 168 °C; IR 3318, 3119 (NH), 1724, 1669 (C=O), 1366 (P=N); MS (rel intensity)  $m/z$  546 (16), 384 (32), 103 (10);  $^1\text{H}$  NMR (300.13 MHz,  $\text{CDCl}_3$ )  $\delta$  2.38 (s, 3H), 3.15 (s, 3H), 3.46 (s, 3H), 5.74 (d, 1H,  $^4J_{\text{PH}} = 2.7$  Hz), 7.15–8.40 (m, 21H, Ar and  $\text{NH}_2$ );  $^{13}\text{C}$  NMR (100.61 MHz,  $\text{THF-}d_6$ )  $\delta$  21.29, 51.34–51.81, 84.76 (d,  $^3J_{\text{PC}} = 101.3$  Hz), 126.99 (d,  $^3J_{\text{PC}} = 6.2$  Hz), 127.67–132.82 (21 Car + C10), 134.99 (d,  $^3J_{\text{PC}} = 11.9$  Hz), 138.65 (d,  $^3J_{\text{PC}} = 19.3$  Hz), 139.95, 142.54 (d,  $^2J_{\text{PC}} = 9.1$  Hz), 164.71 (d,  $^2J_{\text{PC}} = 6.7$  Hz), 165.23 (d,  $^4J_{\text{PC}} = 1.4$  Hz), 168.44 (d,  $^3J_{\text{PC}} = 4.2$  Hz), 175.69 (d,  $^2J_{\text{PC}} = 8.4$  Hz);  $^{31}\text{P}$  NMR (121.4 MHz,  $\text{CDCl}_3$ )  $\delta$  19.0.

Column chromatography of the resulting crude after separation of compound 2a, using a mixture of ethyl acetate and methanol (1:1) as eluent ( $R_f = 0.58$ ), yielded compound 2b (15%). **(Z)-1-Benzoyl-3-[(E)-1,2-bis(methoxycarbonyl)vinyl]-2,2-diphenyl-4-(*p*-tolyl)-1,5-diaza-2 $\lambda^5$ -phosphapenta-1,3-diene (2b)**:  $\text{C}_{34}\text{H}_{31}\text{N}_2\text{O}_5\text{P}$ ; mp 105 °C; IR 3400 (NH), 1719, 1617 (C=O), 1555 (NH), 1375 (P=N); MS (rel intensity)  $m/z$  578 ( $\text{M}^+$ , <1), 519 (9), 384 (39), 201 (100);  $^1\text{H}$  NMR (400.13 MHz,  $\text{CDCl}_3$ )  $\delta$  2.24 (s, 3H), 3.41 (s, 3H), 3.61 (s, 3H), 6.31 (d,  $^4J_{\text{PH}} = 2.4$  Hz), 7.05–8.40 (m, 21H, Ar and  $\text{NH}_2$ );  $^{13}\text{C}$  NMR (100.61 MHz,  $\text{CDCl}_3$ )  $\delta$  21.8, 51.91, 52.24, 82.70 (d,  $^1J_{\text{PC}} = 99.3$  Hz), 126.99 (d,  $^1J_{\text{PC}} = 94.4$  Hz), 127.69–133.25 (21 Car + C10), 136.06 (d,  $^3J_{\text{PC}} = 11.4$  Hz), 138.91 (d,  $^3J_{\text{PC}} = 20.3$  Hz), 139.58, 142.08 (d,  $^2J_{\text{PC}} = 8.0$  Hz), 162.73 (d,  $^2J_{\text{PC}} = 5.4$  Hz), 165.68 (d,  $^4J_{\text{PC}} = 2.1$  Hz), 168.03 (d,  $^3J_{\text{PC}} = 1.6$  Hz), 175.29 (d,  $^2J_{\text{PC}} = 8.2$  Hz);  $^{31}\text{P}$  NMR (121.4 MHz,  $\text{CDCl}_3$ )  $\delta$  13.3.

**(Z)-1-Benzoyl-4-cyclohexyl-2,2-diphenyl-3-[(Z)-1,2-bis(methoxycarbonyl)vinyl]-1,5-diaza-2 $\lambda^5$ -phosphapenta-1,3-diene (2c).** This compound has been characterized in solution from the mixture 2c/2d (see Table 1);  $\text{C}_{33}\text{H}_{35}\text{N}_2\text{O}_5\text{P}$ ;  $^1\text{H}$  NMR (400.13 MHz,  $\text{THF-}d_6$ )  $\delta$  0.7–1.9 (m, 10H), 2.77 (m, 1H), 3.57 (s, 3H), 3.68 (s, 3H), 6.1 (d, 1H,  $^4J_{\text{PH}} = 3.4$  Hz), 7.35 (s, 2H,  $\text{NH}_2$ ), 7.40–8.40 (m, 15H, Ar);  $^{13}\text{C}$  NMR (100.61 MHz,  $\text{THF-}d_6$ )  $\delta$  27.70, 28.32, 31.62, 45.76 (d,  $^3J_{\text{PC}} = 8.9$  Hz), 52.57, 53.36, 87.58 (d,  $^1J_{\text{PC}} = 107.9$  Hz), 129.25–141.48 (18 Car + C10), 144.34 (d,  $^2J_{\text{PC}} = 8.5$  Hz), 166.65 (d,  $^4J_{\text{PC}} = 2.1$  Hz), 170.89 (d,  $^2J_{\text{PC}} = 4.4$  Hz), 171.11 (d,  $^3J_{\text{PC}} = 5.0$  Hz), 176.43 (d,  $^2J_{\text{PC}} = 8.1$  Hz);  $^{31}\text{P}$ -RMN (121.4 MHz,  $\text{CDCl}_3$ )  $\delta$  19.0.

**(E)-1-Benzoyl-4-cyclohexyl-2,2-diphenyl-3-[(Z)-1,2-bis(methoxycarbonyl)vinyl]-1,5-diaza-2 $\lambda^5$ -phosphapenta-1,3-diene (2d)** (80%):  $\text{C}_{33}\text{H}_{35}\text{N}_2\text{O}_5\text{P}$ ; mp 165 °C; IR 3455, 3351 (NH), 1738, 1719 (C=O), 1647 (C=O), 1344 (P=N); MS (rel intensity)  $m/z$  570 ( $\text{M}^+$ , 1), 511 (26), 408 (22), 376 (56), 201 (97). The NMR data were obtained from the mixture 2c/2d in solution:  $^1\text{H}$  NMR (400.13 MHz,  $\text{THF-}d_6$ )  $\delta$  0.7–1.9 (m, 10H), 2.95 (m, 1H), 3.59 (s, 3H), 3.89 (s, 3H), 5.80 (s, 2H,  $\text{NH}_2$ ), 7.06 (d, 1H,  $^4J_{\text{PH}} = 2.8$  Hz), 7.40–8.50 (m, 15H, Ar);  $^{13}\text{C}$ -NMR (100.61 MHz,  $\text{THF-}d_6$ )  $\delta$  27.91, 27.98, 32.58, 44.80 (d,  $^3J_{\text{PC}} = 5.2$  Hz), 52.48, 53.60, 83.09 (d,  $^1J_{\text{PC}} = 101.0$  Hz), 129.08–142.11 (18 Car + C10), 144.06 (d,  $^2J_{\text{PC}} = 7.9$  Hz), 167.14 (d,  $^4J_{\text{PC}} = 2.0$  Hz), 168.82 (d,  $^2J_{\text{PC}} = 17.7$  Hz), 171.29 (d,  $^3J_{\text{PC}} = 5.3$  Hz), 176.78 (d,  $^2J_{\text{PC}} = 7.9$  Hz);  $^{31}\text{P}$  NMR (121.4 MHz,  $\text{CDCl}_3$ )  $\delta$  20.2.

**(Z)-1-(Ethoxycarbonyl)-3-[(Z)-1,2-bis(methoxycarbonyl)vinyl]-2,2-diphenyl-4-(*p*-tolyl)-1,5-diaza-2 $\lambda^5$ -phosphapenta-1,3-diene (4a)** (70%):  $\text{C}_{30}\text{H}_{31}\text{N}_2\text{O}_6\text{P}$ ; mp 182 °C; IR 3393, 3308 (NH), 1723, 1609 (C=O), 1289 (P=N); MS (rel intensity) 545 (2), 499 (5), 487 (18), 441 (100);  $^1\text{H}$  NMR (400.13 MHz,  $\text{CDCl}_3$ )  $\delta$  1.26 (t, 3H,  $^3J_{\text{HH}} = 7.2$  Hz), 2.34 (s, 3H), 3.09 (s, 3H), 3.42 (s, 3H), 4.09 (q, 2H,  $^3J_{\text{HH}} = 7.2$  Hz), 5.67 (d, 1H,  $^4J_{\text{PH}} = 2.9$  Hz), 6.60 (2H,  $\text{NH}_2$ ), 7.15–7.95 (m, 16H, Ar and  $\text{NH}_2$ );  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  14.72, 21.27, 51.32, 51.74, 61.22, 85.04 (d,  $^1J_{\text{PC}} = 108.4$  Hz), 127.36 (d,  $^3J_{\text{PC}} = 6.4$  Hz), 128.24–132.92 (14 Car), 134.97 (d,  $^3J_{\text{PC}} = 11.6$  Hz), 140.08, 142.26 (d,  $^2J_{\text{PC}} = 9.11$  Hz), 162.03, 164.51 (d,  $^2J_{\text{PC}} = 5.7$  Hz), 165.23, 168.20 (d,  $^3J_{\text{PC}} = 4.0$  Hz);  $^{31}\text{P}$  NMR (121.4 MHz,  $\text{CDCl}_3$ )  $\delta$  22.8.

**(Z)- and (E)-1-(Ethoxycarbonyl)-2,2-diphenyl-3-[(Z)-1,2-bis(methoxycarbonyl)vinyl]-4-cyclohexyl-1,5-diaza-2 $\lambda^5$ -phosphapenta-1,3-diene (4b and 4c).** Spectroscopic data were obtained from the reaction crude (50%);  $\text{C}_{29}\text{H}_{35}\text{N}_2\text{O}_6\text{P}$ ;  $^1\text{H}$  NMR (400.13 MHz,  $\text{CDCl}_3$ )  $\delta$  1.23 (t, 3H,  $^3J_{\text{HH}} = 8.9$  Hz), 0.9–2.0 (m, 20H), 2.66 (m, 1H), 2.81 (m, 1H), 4.1 (q, 2H,  $^3J_{\text{HH}} = 8.9$  Hz), 5.04 (2H,  $\text{NH}_2$ , 4b) 5.80 (d, 1H,  $^4J_{\text{PH}} = 3.5$  Hz, 4c), 6.04 (1H, NH, 4c), 6.33 (1H, NH, 4c), 6.47 (1H, d,  $^4J_{\text{PH}} = 2.9$  Hz, 4b), 7.30–7.90 (m, 10H, Ar);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  14.37, 14.95, 24.94, 25.58, 26.12, 26.35, 30.05, 30.90, 42.29 (d,  $^3J_{\text{PC}} = 4.6$ , 4c), 43.37 (d,  $^3J_{\text{PC}} = 9.2$ , 4b), 51.36, 51.51, 51.67, 53.07, 92.38 (d,  $^1J_{\text{PC}} = 106.1$ ) 98.35 (d,  $^1J_{\text{PC}} = 114.6$ ), 126.22–133.23 (12 Car), 142.60 (d,  $^2J_{\text{PC}} = 9.8$  Hz), 143.85 (d,  $^2J_{\text{PC}} = 9.9$  Hz), 161.12, 161.73, 166.31, 166.01, 168.11, 168.97 (d,  $^2J_{\text{PC}} = 6.3$  Hz), 172.50, 170.98;  $^{31}\text{P}$  NMR (121.4 MHz,  $\text{CDCl}_3$ )  $\delta$  19.9 (4c), 23.4 (4b).

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**Supplementary Material Available:** Full assignment of the  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR spectra for compounds 2 and 4, NOE spectra of 2a and 2c/2d, HMQC and HMBC spectra of 2c/2d, plots derived from the magnetization transfer study between 2c and 2d, and plots showing the minimal energy conformation for all configurations of 2 as obtained from the PM3 calculations (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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