JOC Article

Reactions of Conjugate Phosphinyl- and Phosphonyl-Nitroso Alkenes with Enamines. Preparation of *N*-Hydroxypyrrole Derivatives†

Jesús M. de los Santos, Roberto Ignacio, Domitila Aparicio, and Francisco Palacios*

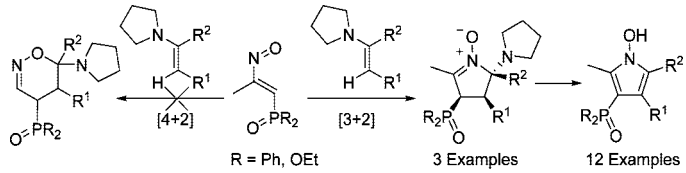
Departamento de Química Orgánica I, Facultad de Farmacia, Universidad del País Vasco, Apartado 450, 01080 Vitoria, Spain

José M. Ezpeleta‡

Departamento de Física Aplicada II, Facultad de Farmacia, Universidad del País Vasco, Apartado 450, 01080 Vitoria, Spain

francisco.palacios@ehu.es

Received March 5, 2009

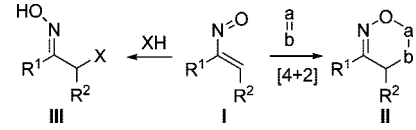


The synthesis of highly functionalized *N*-hydroxypyrrole derivatives by the formal [3+2] cycloaddition reaction of enamines and nitroso alkenes derived from phosphine oxides and phosphonates is reported. Intermediate phosphorylated nitrones, whose formation can be explained by a conjugate addition of enamines to phosphorylated nitroso alkenes and formation of the five-membered heterocycles, are isolated.

Introduction

The chemistry of nitroso compounds has been intensively studied in the past decades, especially due to their applications in the fields of asymmetric synthesis and cycloaddition processes.[1] Likewise, nitroso alkenes are functionalized nitroso derivatives, and the presence of an adjacent double bond in conjugation with the nitroso moiety introduces new reactivity centers in these substrates and then increases the synthetic value of these compounds, especially as heterodienes in Diels−Alder reactions.[2] After pioneering work by Gilchrist's group,[3] cycloaddition reactions in which a nitroso alkene **I** participates as the 4π-electron component in hetero-Diels−Alder reactions[4] with alkenes,[3a,b,5] and enol ethers,[6] for the construction of six-membered heterocycles **II** have been described (see Chart 1). However, to the best of our knowledge, not many examples of

CHART 1. Reactivity Pattern of Nitroso Alkenes I



† Dedicated to Prof. Josep Font on the occasion of his 70th Birthday.

‡ Contact this author regarding the X-ray crystal structure determination.

(1) For recent reviews see: (a) Yamamoto, Y.; Yamamoto, H. *Eur. J. Org. Chem.* **2006**, 2031–2043. (b) Yamamoto, H.; Nimiyama, N. *Chem. Commun.* **2005**, 3514–3525. (c) Gowenlock, B. G.; Richter-Addo, G. B. *Chem. Rev.* **2004**, *104*, 3315–3340. (d) Adam, W.; Krebs, O. *Chem. Rev.* **2003**, *103*, 4131–4146.

(2) For an excellent review see: Gilchrist, T. L. *Chem. Soc. Rev.* **1983**, *12*, 53–73.

(3) (a) Faragher, R.; Gilchrist, T. L. *J. Chem. Soc., Chem. Commun.* **1976**, 581–582. (b) Faragher, R.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1979**, 249–257. (c) Gilchrist, T. L.; Roberts, T. G. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1283–1292. (d) Davies, D. E.; Gilchrist, T. L.; Roberts, T. G. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1275–1281.

(4) Selected reviews: (a) Gilchrist, T. L.; Wood, J. E. *Comprehensive Heterocyclic Chemistry II*; Boulton, A. J., Ed.; Pergamon: Oxford, UK, 1996; Vol. 6, pp 279−299. (b) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1–120.

(5) (a) Gilchrist, T. L.; Roberts, T. G. *J. Chem. Soc., Chem. Commun.* **1978**, 847–849. (b) Iskander, G. M.; Gulta, V. S. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1891–1895. (c) Dennmark, S. E.; Dappen, M. S.; Sternberg, J. A. *J. Org. Chem.* **1984**, *49*, 4741–4743.

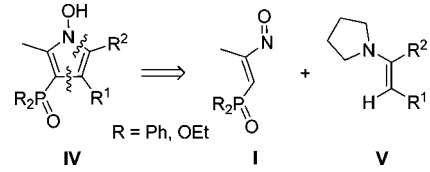
(6) (a) Gilchrist, T. L.; Iskanderl, G. M.; Yagoub, A. K. *J. Chem. Soc., Chem. Commun.* **1981**, 696–698. (b) Hippeli, C.; Reissig, H.-U. *Synthesis* **1987**, 77–79. (c) Gallos, J. K.; Sarli, V. C.; Varvogli, A. C.; Papadoyanni, C. Z.; Papaspyrou, S. D.; Argyropoulos, N. G. *Tetrahedron Lett.* **2003**, *44*, 3905–3909. (d) Arnold, T.; Reissig, H.-U. *Synlett* **1990**, 514–516. (e) Reissig, H.-U.; Hippeli, C.; Arnold, T. *Chem. Ber.* **1990**, *123*, 2403–2411. (f) Arnold, T.; Orschel, B.; Reissig, H.-U. *Angew. Chem., Int. Ed.* **1992**, *31*, 1033–1035. (g) Zimmer, R.; Reissig, H.-U. *Angew. Chem., Int. Ed.* **1988**, *27*, 1518–1519. (h) Zimmer, R.; Reissig, H.-U. *Liebigs Ann. Chem.* **1991**, 553–562. (i) Orschel, B.; Scherer, S.; Reissig, H.-U. *Synthesis* **2002**, *11*, 1553–1563.

10.1021/jo900489j CCC: $40.75
Published on Web 04/03/2009

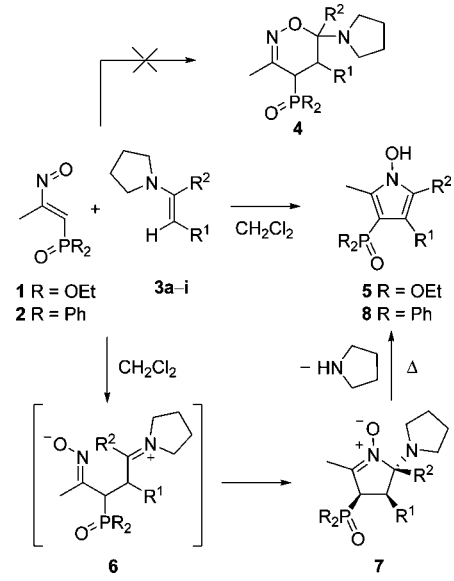
the hetero-Diels−Alder reaction of nitroso alkenes with enamines[7] have been reported. Jorgensen and co-workers[8] recently reported the first catalyzed hetero-Diels−Alder reaction of nitroso alkenes and carbonyl derivatives using pyrrolidine as the organocatalyst, and this hetero-Diels−Alder reaction involves enamine intermediates formed by condensation of the carbonyl compounds with pyrrolidine.

We have previously described the generation of phosphinyl **I** (R^2 = $POPh_2$) and phosphonyl nitroso-alkenes **I** (R^2 = $PO(OEt)_2$) and the conjugate addition of some nucleophiles, such as amines and amino-esters, for the preparation of α-amino phosphonate derivatives **III** (see Chart 1).[9] In this context, we are interested in the preparation of three-,[10] five-,[11] and six-membered[12] nitrogen-containing heterocycles, as well as the synthesis of new amino phosphorus derivatives[13] and their synthetic use for the construction not only of the carbon−carbon double bond[14] but also of the carbon−nitrogen double bond.[15] It is known that phosphorus substituents regulate important biological functions,[16] and the introduction of organophosphorus functionalities in simple synthons may afford the development of new strategies for the preparation of phosphorylated azaheterocycles.[17] For this reason, we wish to describe herein a further and efficient strategy of the regioselective preparation of highly functionalized *N*-hydroxypyrroles with a phosphine oxide (**IV**, R = Ph) or phosphonate group at the 3-position (**IV**, R = OEt), generated through treatment of phosphinyl and phosphonyl-nitroso alkenes **I** with enamines **V** (Chart 2).

CHART 2. Retrosynthetic Pathway for the Preparation of *N*-Hydroxypyrrole Derivatives IV



SCHEME 1. Addition of Enamines 3 to Highly Reactive Phosphorylated Nitroso Alkenes 1 and 2



Results and Discussion

The reaction of 1,2-oxazabuta-1,3-dienes **1** and **2** with enamines **3** was explored. Thus, the addition of enamine **3a** (R^1 = ^{i}Pr, R^2 = H) to the highly reactive 4-phosphonyl-heterodiene **1** (R = OEt), generated in situ from α-bromooximes,[9] in CH_2Cl_2 at room temperature was performed. The highly colored 4-phosphonyl-1,2-oxazabuta-1,3-diene **1** disappeared very fast, showing the end of the reaction with the formation, rather than of the expected six-membered 1,2-oxazine **4**, the hydroxypyrrole-3-phosphonate **5a** in good yield (89%) as a sole product and in a regioselective fashion (Scheme 1, Table 1, entry 1).

The process was extended to the reaction of 4-phosphonyl-1,2-oxazabuta-1,3-diene **1** with other enamines derived from aldehydes **3b−d** and from ketones **3e−g** in CH_2Cl_2 at room temperature to give hydroxypyrrole-3-phosphonates **5** in good yield (Scheme 1, Table 1, entries 2−4 and 5−7, respectively). It was necessary to obtain evidence for structure **5a**, because it is known that nitroso alkenes mainly react with dienophiles according to [4+2]-cycloaddition processes (vide supra). In the latter case, compound **4** could be expected and produced instead of the *N*-hydroxypyrrole **5**. The choice between structures **5** and **4** was based upon the 2D NMR and mass spectral data. Namely, the HMBC spectrum showed a cross signal between the vinylic proton (H−5) with the signal downfield corresponding to the carbon (C−2) of **5a**. This cross signal unambiguously confirms the presence of the *N*-hydroxypyrrole **5a** and not the oxazine ring **4** (four bonds distance between H−6 and C−3 in the oxazine ring). Also two cross signals were observed between the vinylic proton (H−5) with the quaternary carbons C−3 and C−4 of the *N*-hydroxypyrrole **5a**. Moreover, the high resolution

(7) (a) Tahdi, A.; Titouani, S. L.; Soufiaoui, M. *Tetrahedron* **1998**, *54*, 65–70. (b) Henning, R.; Lerch, U.; Urbach, H. *Synthesis* **1989**, 265–268.

(8) Wabnitz, T. C.; Saaby, S.; Jorgensen, K. A. *Org. Biomol. Chem.* **2004**, *2*, 828–834.

(9) de los Santos, J. M.; Ignacio, R.; Aparicio, D.; Palacios, F. *J. Org. Chem.* **2007**, *72*, 5202–5206.

(10) (a) Palacios, F.; Ochoa de Retana, A. M.; Alonso, J. M. *J. Org. Chem.* **2006**, *71*, 6141–6148. (b) Palacios, F.; Aparicio, D.; Ochoa de Retana, A. M.; de los Santos, J. M.; Gil, J. I.; Alonso, J. M. *J. Org. Chem.* **2002**, *67*, 7283–7288.

(11) (a) de los Santos, J. M.; Aparicio, D.; López, Y.; Palacios, F. *J. Org. Chem.* **2008**, *73*, 550–557. (b) Palacios, F.; Alonso, C.; Legido, M.; Rubiales, G.; Villegas, M. *Tetrahedron Lett.* **2006**, *47*, 7815–7818. (c) Palacios, F.; Aparicio, D.; Vicario, J. *Eur. J. Org. Chem.* **2005**, 2843–2850. (d) Palacios, F.; Ochoa de Retana, A. M.; Gil, J. I.; Alonso, J. M. *Tetrahedron* **2004**, *60*, 8937–8947.

(12) (a) Vicario, J.; Aparicio, D.; Palacios, F. *J. Org. Chem.* **2009**, *74*, 452–456. (b) Aparicio, D.; Attanasi, O. A.; Filippone, P.; Ignacio, R.; Lillini, S.; Mantellini, F.; Palacios, F.; de los Santos, J. M. *J. Org. Chem.* **2006**, *71*, 5897–5905. (c) Palacios, F.; Herrán, E.; Alonso, C.; Rubiales, G.; Lecea, B.; Ayerbe, M.; Cossío, F. P. *J. Org. Chem.* **2006**, *71*, 6020–6030. (d) Palacios, F.; Ochoa de Retana, A. M.; Gil, J. I.; López de Munain, R. *Org. Lett.* **2002**, *4*, 2405–2408.

(13) For a recent review of *β*-aminophosphonates see: Palacios, F.; Alonso, C.; de los Santos, J. M. *Chem. Rev.* **2005**, *105*, 899–931.

(14) (a) Palacios, F.; Ochoa de Retana, A. M.; Oyarzabal, J.; Pascual, S.; Fernández de Troconiz, G. *J. Org. Chem.* **2008**, *73*, 4568–4574. (b) Palacios, F.; Vicario, J. *Org. Lett.* **2006**, *8*, 5405–5408. (c) Palacios, F.; Aparicio, D.; López, Y.; de los Santos, J. M.; Ezpeleta, J. M. *Tetrahedron* **2006**, *62*, 1095–1101. (d) Palacios, F.; Ochoa de Retana, A. M.; Pascual, S.; Oyarzabal, J. *J. Org. Chem.* **2004**, *69*, 8767–8774. (e) Palacios, F.; Ochoa de Retana, A. M.; Pascual, S. *Org. Lett.* **2003**, *4*, 769–772.

(15) (a) Palacios, F.; Vicario, J.; Maliszewska, A.; Aparicio, D. *J. Org. Chem.* **2007**, *72*, 2682–2685. (b) Palacios, F.; Aparicio, D.; Vicario, J. *J. Org. Chem.* **2006**, *71*, 7690–7696. (c) Cossío, F. P.; Alonso, C.; Lecea, B.; Ayerbe, M.; Rubiales, G.; Palacios, F. *J. Org. Chem.* **2006**, *71*, 2839–2847. (d) Palacios, F.; Herrán, E.; Alonso, C.; Rubiales, G. *Tetrahedron* **2006**, *62*, 7661–7666. (e) Palacios, F.; Alonso, C.; Amezua, P.; Rubiales, G. *J. Org. Chem.* **2002**, *67*, 1941–1944.

(16) For reviews see: (a) Engel, R. In *Handbook of Organophosphorus Chemistry*; M. Dekker, Inc.: New York, 1992. (b) Kafarski, P.; Lejezak, B. *Phosphorus Sulfur* **1991**, *63*, 193–215. (c) Hoagland, R. E. In *Biologically Active Natural Products*; Culter, H. G., Ed.; ACS Symposium Series 380; American Chemical Society: Washington DC, 1988; p 182. (d) Toy, A. D. F.; Walsh, E. N. In *Phosphorus Chemistry in Everyday Living*; American Chemical Society: Washington DC, 1987; p 333.

(17) For an excellent review see: Moonen, K.; Laureyn, I.; Stevens, C. V. *Chem. Rev.* **2004**, *104*, 6177–6215.

TABLE 1. ***N*-Hydroxypyrrole Phosphonates 5 Obtained through Addition of Enamines 3 to Nitroso Alkene 1**

Entry	Product	3	R^1	R^2	Yield (%)[a,b]
1	**5a**	**3a**	^{i}Pr	H	89
2	**5b**	**3b**	Bn	H	81
3	**5c**	**3c**	Pr	H	(82)[c]
4	**5d**	**3d**	Ph	H	(71)[c]
5	**5e**	**3e**	CO_2Et	Ph	94
6	**5f**	**3f**	$-(CH_2)_3-$		83
7	**5g**	**3g**			93

[a] After chromatography. [b] Yields of pure compounds **5** are based on 1,2-oxazabuta-1,3-diene **1**. [c] Yields of compounds **5** based on isolated nitrones **7**.

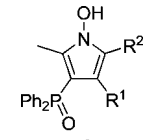
mass spectra for compound **5a** showed an ion peak for the fragment [M^+ − OH] typical loss corresponding to these structures. The X-ray diffraction analysis finally determined the structure of *N*-hydroxypyrrole **5g**. The corresponding ORTEP drawing for compound **5g** is shown in the Supporting Information.

A plausible mechanism for the formation of the *N*-hydroxypyrroles **5** can be explained through initial conjugate addition of enamine **3** at the terminal carbon atom of heterodiene **1** to give adduct **6**, which promptly affords nitrone **7** by ring closure (formally a [3+2] dipolar cycloaddition). Elimination of the pyrrolidine residue in nitrones **7** leads to substituted *N*-hydroxypyrroles **5** isolable by flash chromatography. The electron-withdrawing phosphonate group ($PO(OEt)_2$) on the terminal carbon atom of nitroso alkene **1** may enhance the electrophilic character of this atom and may also favor the initial Michael addition of the enamines on this carbon atom to obtain the five-membered heterocycles **5**. Nitroso alkenes have been shown to add themselves to the C=N double bond of some 1,2-oxazines,[18] 1,3-diazabuta-1,3-dienes,[19] and imines,[20] as well as to the C=C double bond attached to a pyrimidinone ring,[21] with the formation of unusual [3+2] cycloadducts. However, as far as we know, this process represents the first example of a formal [3+2] cycloaddition reaction of nitroso alkenes to electron-rich olefins such as enamines, for the preparation of pyrrole derivatives. In fact, a theoretical study with the DFT method at the B3LYP/G-316* level of the reaction of nitroso alkenes with enamines suggests a polar [4+2] Diels−Alder reaction characterized by a nucleophilic attack of the enamine at the conjugate position of the nitroso alkene with concomitant six-membered-ring closure.[22]

The strategy was extended to 4-phosphinyl-1,2-oxazabuta-1,3-dienes **2** (R = Ph), prepared also through base treatment of bromooximes,[9] with enamines **3a**−**g** to give hydroxypyrrole-3-phosphine oxides **8** in good yields (Scheme 1, Table 2). The scope of the process is not limited to enamines derived from aldehydes **3a**,**b**,**d** (Scheme 1, Table 2, entries 1−3), given that enamines derived from ketones **3e**,**g** (Scheme 1, Table 2, entries 4,5) also led to the regioselective formation of hydroxypyrrole-3-phosphine oxides **8**. NMR data and mass spectrometry are consistent with the assigned structure of compounds **8**, and the X-ray diffraction analysis finally determined the structure of *N*-hydroxypyrrole **8a**. The corresponding ORTEP drawing for compound **8a** is shown in the Supporting Information.

Further evidence for the mechanism of formation of *N*-hydroxypyrroles derived from phosphonates **5** and phosphine oxides **8** is confirmed by the isolation of nitrone intermediates **7**. The nitrones **7** showed a tendency to aromatize and readily occurred in the reaction media to afford the corresponding *N*-hydroxypyrroles **5** and **8**. However, in some cases, when the process was performed at 0 °C, nitrones **7a**,**b** derived from phosphonates (R = OEt) and **7c** derived from phosphine oxides (R = Ph) proved to be stable enough for the reaction conditions and even for flash chromatography and it was possible to isolate them and characterize them on the basis of analytical and spectral data (Scheme 1, Table 3). Thus, the mass spectrum of compound **7a**, for example, analyzed as $C_{16}H_{31}N_2O_4P$, exhibited an intense molecular ion M + 1 peak (*m*/*z* 347). The ^{31}P NMR spectrum of **7a** showed only an absorption at δ 23.1 ppm indicating that the formation of the pentagonal heterocycle takes place in a diastereoselective fashion, while the ^1H NMR

TABLE 2. ***N*-Hydroxypyrrole Phosphine Oxides 8 Obtained through Addition of Enamines 3 to Nitroso Alkene 2**

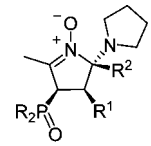


8

Entry	Product	3	R^1	R^2	Yield (%)[a,b]
1	**8a**	**3a**	^{i}Pr	H	89 (81)[c]
2	**8b**	**3b**	Bn	H	88
3	**8c**	**3d**	Ph	H	67
4	**8d**	**3e**	CO_2Et	Ph	89
5	**8e**	**3g**			70

[a] After chromatography. [b] Yields of pure compounds **8** are based on 1,2-oxazabuta-1,3-diene **2**. [c] Yield of compound **8** based on isolated nitrone **7c**.

TABLE 3. Isolated Phosphorylated Nitrones 7



7

entry	product	R	R^1	R^2	yield (%)[a]
1	**7a**	OEt	Pr	H	85
2	**7b**	OEt	Ph	H	87
3	**7c**	Ph	^{i}Pr	H	83

[a] Yield of isolated nitrones after flash chromatography.

(18) (a) Zimmer, R.; Collas, M.; Czerwonka, R.; Hain, U.; Reissig, H.-U. *Synthesis* **2008**, 237–244. (b) Mackay, D.; Watson, K. N. *J. Chem. Soc., Chem. Commun.* **1982**, 775–776.

(19) (a) Sharma, A. K.; Mazumdar, S. N.; Mahajan, M. P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3065–3070. (b) Sharma, A. K.; Hundal, G.; Obrai, S.; Mahajan, M. P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 615–619.

(20) (a) Marwaha, A.; Bharatam, P. V.; Mahajan, M. P. *Tetrahedron Lett.* **2005**, *46*, 8253–8256. (b) Marwaha, A.; Singh, P.; Mahajan, M. P. *Tetrahedron* **2006**, *62*, 5474–5486.

(21) Sharma, A. K.; Mahajan, M. P. *Heterocycles* **1995**, *40*, 787–800.

(22) Domingo, L. R.; Picher, M. T.; Arroyo, P. *Eur. J. Org. Chem.* **2006**, 2570–2580.

spectrum showed absorptions at δ 4.89 ppm as a doublet with coupling constant $^3J_{HH} = 10.4$ Hz for H-5, and H-3 exhibited a doublet of doublet at 2.56 ($^2J_{PH} = 27.8$ and $^3J_{HH} = 4.3$ Hz). This lower coupling constant value than that corresponding to H-5 indicates that H-3 and H-4 protons are *syn* related. The ^{13}C NMR spectra were also in agreement with the nitrone structure assigned above to **7a**. Compounds **7** can be transformed into pyrroles **5** and **8** by thermal treatment in the absence of solvent (1−2 h).

To the best of our knowledge, this novel strategy is the first example of the preparation of *N*-hydroxypyrrole derivatives through reaction of enamines to phosphorylated nitroso alkenes to be reported.[23] Pyrroles are important heterocycles broadly used in material science[24] and can be found in naturally occurring and biologically important molecules.[25] Some of the recently isolated pyrrole containing marine natural products have been found to exhibit considerable cytotoxicity and function as multidrug resistant (MDR) reversal agents.[26] Among them, *N*-hydroxypyrrole containing antibiotic chromoxymycin[27] has shown antitumor activity, and the cyclic depsipeptide hormaomycin,[28] with an interesting spectrum of biological activities, has a unique structure with a side chain terminated with a residue of *N*-hydroxypyrrole-2-carboxylic acid.

Conclusion

In conclusion, the first synthesis of functionalized *N*-hydroxypyrroles containing a phosphine oxide or phosphonate group at the C-3 position of the heterocyclic system by means of a [3+2] formal cycloaddition reaction of phosphorylated nitroso alkenes and enamines is described. In contrast, a theoretical study with the DFT method at the B3LYP/G-316* level of the reaction of nitroso alkenes with enamines suggests a polar [4+2] Diels−Alder reaction with concomitant six-membered-ring closure. Intermediate phosphorylated nitrones have been isolated. Their formation can be explained by a conjugate addition of enamines to phosphorylated nitroso alkenes and formation of the five-membered heterocycles. It also should be emphasized that the use of these very reactive phosphorylated heterodienes opens a novel route to other functionalized cyclic and acyclic phosphorus compounds due to the marked ability of nitroso alkenes to add nucleophiles. These *N*-hydroxypyrrole derivatives may be important synthons in organic synthesis for the preparation of biologically active compounds of interest to medicinal chemistry.[25−28]

(23) A synthesis of *N*-hydroxypyrroles has been described through reaction of enolates with α-halooximes: Haelters, J. P.; Corbel, B.; Sturtz, G. *Phosphorus, Sulfur, Silicon* **1989**, *44*, 53–74.

(24) (a) Butler, M. S. *J. Nat. Prod.* **2004**, *67*, 2141–2153. (b) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*; Blackwell Science: Oxford, UK, 2000. (c) Lee, C.-F.; Yang, L.-M.; Hwu, T.-Y.; Feng, A.-S.; Tseng, J.-C.; Luh, T.-Y. *J. Am. Chem. Soc.* **2000**, *122*, 4992–4993.

(25) (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582–3603. (b) Liu, J.-H.; Yang, Q.-C.; Mark, T. C. W.; Wong, H. N. C. *J. Org. Chem.* **2000**, *65*, 3587–3595. (c) Boger, D. L.; Boyce, C. W.; Labroli, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54–62. (d) Gossauer, A. *Pyrrole*; Houben-Weyl, Thieme: Stuttgart, Germany, 1994; Vol. E6a/1, p 556.

(26) Tao, H.; Hwang, I.; Boger, D. L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5979–5981.

(27) (a) Hori, Y.; Hino, M.; Kawai, Y.; Kiyoto, S.; Terano, H.; Kohsaka, M.; Aoki, H.; Hashimoto, M.; Imanaka, H. *J. Antibiot.* **1986**, *39*, 12–16. (b) Iwami, M.; Kawai, Y.; Kiyoto, S.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1986**, *39*, 6–11. (c) Kawai, Y.; Furihata, K.; Seto, H.; Otake, N. *Tetrahedron Lett.* **1985**, *26*, 3273–3276.

(28) Zlatopolskiy, B. D.; Kroll, H.-P.; Melotto, E.; de Meijere, A. *Eur. J. Org. Chem.* **2004**, 4492–4502.

Experimental Section

General Methods. Reagent and solvent purification, workup procedures, and analyses were performed in general as describe in the Supporting Information.

General Procedure for the Addition of Enamines to Phosphorylated Nitroso Alkenes 1 and 2. To a stirred solution of α-bromooxime[9] (1.0 mmol) in CH_2Cl_2 (5 mL) was added triethylamine (1.2 mmol). Then the corresponding enamine **3a**−**i** (1.2 mmol) was added at once at room temperature and under a nitrogen atmosphere. The reaction was allowed to stir at room temperature for 15−30 min. The solvent was removed by rotary evaporation and the residue was stirred with diethyl ether. The triethylamine hydrobromic salt was filtered through a sintered glass vacuum filtration funnel. The solid was washed twice with ether and the filtrate was concentrated to dryness in vacuum to get stable nitrones **7** or *N*-hydroxypyrroles **5** and **8**. *N*-Hydroxypyrroles **5c**,**d** and **8a** derived from stable nitrones **7a**,**b**,**c**, respectively, were obtained through heating nitrones **7** at 60 °C in the absence of solvent.

Diethyl 1-hydroxy-4-isopropyl-2-methyl-1*H*-pyrrol-3-ylphosphonate (5a): 5a (245 mg, 89%) was obtained as a brown oil from 1-bromo-2-hydroxyiminopropyl phosphonic acid diethyl ester[9] (287 mg, 1.0 mmol), Et_3N (168 μL, 1.2 mmol), and (*E*)-1-(3-methylbut-1-enyl)pyrrolidine **3a** (167 mg, 1.2 mmol) as described in the general procedure at room temperature. The crude product was purified by flash chromatography (SiO_2, AcOEt/pentane 50:50). IR (NaCl) ν_{max} 3423, 2961, 1214, 1031, 963 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.16 (br s, 1H), 6.53 (d, $^4J_{PH} = 6.0$ Hz, 1H), 4.02−3.92 (m, 4H), 3.00 (m, 1H), 1.98 (s, 3H), 1.29 (t, $^3J_{HH} = 7.2$ Hz, 6H), 1.13 (d, $^3J_{PH} = 6.9$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.6 (d, $^2J_{PC} = 26.0$ Hz), 129.8 (d, $^2J_{PC} = 12.5$ Hz), 114.1 (d, $^3J_{PC} = 13.5$ Hz), 94.7 (d, $^1J_{PC} = 218.4$ Hz), 61.3 (d, $^2J_{PC} = 5.6$ Hz), 25.5, 24.5, 16.1 (d, $^3J_{PC} = 7.0$ Hz), 9.2; ^{31}P NMR (120 MHz, $CDCl_3$) δ 21.9; MS (EI) *m*/*z* 275 (M^+, 10), 258 (100), 202 (40); HRMS (EI) *m*/*z* calcd for $C_{12}H_{22}NO_4P$ [M^+] 275.1286, found [M^+] 275.1263.

(2*S,3*R**,4*R**)-4-(Diethoxyphosphoryl)-5-methyl-3-propyl-2-(pyrrolidin-1-yl)-3,4-dihydro-2*H*-pyrrole 1-oxide (7a): 7a** (294 mg, 85%) was obtained as a colorless oil from 1-bromo-2-hydroxyiminopropyl phosphonic acid diethyl ester[9] (287 mg, 1.0 mmol), Et_3N (168 μL, 1.2 mmol), and (*E*)-1(pent-1-enyl)pyrrolidine **3c** (167 mg, 1.2 mmol) as described in the general procedure, when the process was performed at 0 °C. The crude product was purified by flash chromatography (SiO_2, AcOEt/pentane 20:80). IR (NaCl) ν_{max} 2959, 1626, 1447, 1235, 1050, 957 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18−4.04 (m, 4H), 3.89 (d, $^3J_{HH} = 10.4$ Hz, 1H), 3.09−2.95 (m, 4H), 2.77−2.64 (m, 1H), 2.56 (dd, $^2J_{PH} = 27.8$ Hz, $^3J_{HH} = 4.3$ Hz, 1H), 2.16 (d, $^4J_{PH} = 2.8$ Hz, 3H), 1.82−1.76 (m, 4H), 1.49−1.26 (m, 10H), 0.91 (t, $^3J_{HH} = 7.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3 (d, $^2J_{PC} = 8.5$ Hz), 93.5 (d, $^3J_{PC} = 3.4$ Hz), 63.0 (d, $^2J_{PC} = 6.5$ Hz), 62.4 (d, $^2J_{PC} = 7.0$ Hz), 47.2, 43.2 (d, $^1J_{PC} = 131.7$ Hz), 38.5 (d, $^2J_{PC} = 4.0$ Hz), 36.2 (d, $^3J_{PC} = 6.0$ Hz), 24.9, 21.7, 18.9, 16.3 (d, $^3J_{PC} = 5.5$ Hz), 16.3 (d, $^3J_{PC} = 5.5$ Hz), 14.2; ^{31}P NMR (120 MHz, $CDCl_3$) δ 23.1; MS (CI) *m*/*z* 347 ($M^+ + 1$, 100).

Diethyl 1-hydroxy-2-methyl-4-propyl-1*H*-pyrrol-3-ylphosphonate (5c): 5c (226 mg, 82%) was obtained as a colorless oil by heating intermediate phosphorylated nitrone **7a** for 2 h as described in the general procedure. The crude product was purified by flash chromatography (SiO_2, AcOEt/pentane 40:60). IR (NaCl) ν_{max} 3126, 2955, 1442, 1208, 1025, 963 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.07 (br s, 1H), 6.46 (d, $^4J_{PH} = 6.0$ Hz, 1H), 4.07−3.96 (m, 4H), 2.44−2.31 (m, 2H), 1.86 (d, $^4J_{PH} = 1.8$ Hz, 3H), 1.56−1.48 (m, 2H), 1.32 (t, $^3J_{HH} = 7.2$ Hz, 6H), 0.94 (t, $^3J_{HH} = 7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.8 (d, $^2J_{PC} = 26.0$ Hz), 122.1 (d, $^2J_{PC} = 12.0$ Hz), 115.9 (d, $^3J_{PC} = 13.1$ Hz), 95.3 (d, $^1J_{PC} = 218.3$ Hz), 61.4 (d, $^2J_{PC} = 6.0$ Hz), 28.6, 23.6, 16.2 (d, $^3J_{PC} = 7.1$ Hz), 14.1, 9.1; ^{31}P NMR (120 MHz, $CDCl_3$) δ 22.8; HRMS (EI) *m*/*z* calcd for $C_{12}H_{22}NO_4P$ [M^+] 275.1286, found [M^+] 275.1282.

4-Benzyl-3-(diphenylphosphoryl)-2-methyl-1*H*-pyrrol-1-ol (8b): **8b** (341 mg, 88%) was obtained as a colorless solid from 1-bromo-1-(diphenylphosphinoyl) propan-2-one oxime[9] (351 mg, 1.0 mmol), Et_3N (168 μL, 1.2 mmol), and (*E*)-1-(3-phenylprop-1-enyl)pyrrolidine **3b** (224 mg, 1.2 mmol) as described in the general procedure at room temperature. The crude product was purified by flash chromatography (SiO_2, AcOEt/pentane 50:50). Mp 131−134 °C; IR (KBr) ν_{max} 3412, 2921, 1488, 1436, 1157, 1134 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 12.56 (br s, 1H), 7.71−6.80 (m, 15H), 6.23 (d, $^4J_{PH}$ = 4.5 Hz, 1H), 3.02 (s, 2H), 1.41 (d, $^4J_{PH}$ = 0.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.2, 134.6 (d, $^2J_{PC}$ = 19.6 Hz), 134.2, 132.8, 131.7, 131.7, 131.6, 131.6, 128.8, 128.6, 128.5, 128.0, 125.7, 121.2 (d, $^2J_{PC}$ = 10.0 Hz), 118.4 (d, $^3J_{PC}$ = 10.0 Hz), 99.5 (d, $^1J_{PC}$ = 128.2 Hz), 32.6, 9.6; ^{31}P NMR (120 MHz, $CDCl_3$) δ 25.0; HRMS (EI) *m*/*z* calcd for $C_{24}H_{22}NO_2P$ [M^+] 387.1388, found [M^+] 387.1412.

Acknowledgment. This work was financially supported by the Universidad del País Vasco−Departamento de Educación, Universidades e Investigación del Gobierno Vasco (GIU- 07/114; IT-277-07) and Dirección General de Investigación del Ministerio de Ciencia y Tecnología (MCYT, Madrid DGI, CTQ2006-09323).

Supporting Information Available: Full characterization data and procedures for the synthesis of all new compounds, ORTEP diagrams, and X-ray crystallographic data for compounds **5g** and **8a**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO900489J