An Expeditious Route to Novel 1,4,2-Benzodiazaphosphepin-5-one 2-Oxide Analogues

Gary M. Karp

Agricultural Products Research Division, American Cyanamid Company, Princeton, New Jersey 08543-0400

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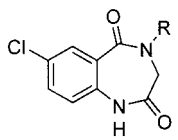
A short and efficient synthesis of the novel 1,4,2-benzodiazaphosphepin-5-one 2-oxide ring system, a phosphonamidate isostere of the 1,4-benzodiazepine-2,5-dione system, has been carried out in good overall yield. The key step is the base-induced cyclization of (2-aminobenzamido)methylphosphonates **6a**−**c** to the 1,4,2-benzodiazaphosphepin-5-one 2-oxides **7a**−**c.** Alkylation of **7b** with methyl iodide gives the expected *N*-methyl analogue **9**. When a tandem one-pot cyclization/alkylation is carried out from **6b** in the presence of excess base, the sole isolable product obtained is the phosphonate **13**, presumably via ethanolysis of a transiently formed **9**. Carrying out the tandem cyclization/alkylation in the absence of excess base, however, affords only **9**. Thionation of **7** with Lawesson's reagent occurs at either the phosphonamidate oxygen (P-2) or the amide carbonyl (C-5) depending on the steric constraint of the N-4 substituent.

During the course of an investigation of the herbicidal properties of 1,4-benzodiazepine-2,5-diones,[1] including homologues[1a] and isosteres,[2] a further understanding of the steric and electronic factors necessary for activity fueled our interest to examine additional related systems. We were intrigued by the idea of incorporating a phosphorus atom into the benzodiazepine skeleton. Organophosphorus compounds are ubiquitous in living systems, comprising a central role in the structure of nucleic acids and cell membranes.[3] The incorporation of phosphorus into organic molecules has found utility as enzyme transition-state inhibitors,[4] antibiotics,[5] and agrochemicals.[6] In light of our continued interest in the preparation of isosteres of benzodiazepinediones **1,** we were interested in the preparation of the 1,4,2-benzodiazaphosphepin-5-one 2-oxide system **2**, where the trigonal C-2 amide carbonyl of **1** is replaced by a tetracoordinate pentavalent phosphorus atom in **2**. Phosphonamidates have been utilized as isosteres for the tetrahedral transition state of protease inhibitors.[7] Despite the existence of numerous examples of cyclic phosphonamidates,[8−10] the target 1,4,2-benzodiazaphosphepin-5-one 2-oxide system **2** appears to be unknown.



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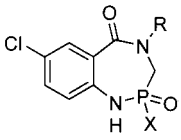

2

It was envisioned that **2** could be constructed in a manner analogous to that of the benzodiazepine-2,5-diones[11] by utilization of the appropriate aminomethylphosphonate.[12] The C-5 amide linkage would be established initially upon reaction of an *o*-nitrobenzoyl chloride with the aminomethylphosphonate followed by formation of the P-2 phosphonamidate center (after nitro reduction and subsequent cyclization). To investigate this approach to **2** (R = *tert*-butyl), 5-chloro-2-nitrobenzoyl chloride **3**[11]

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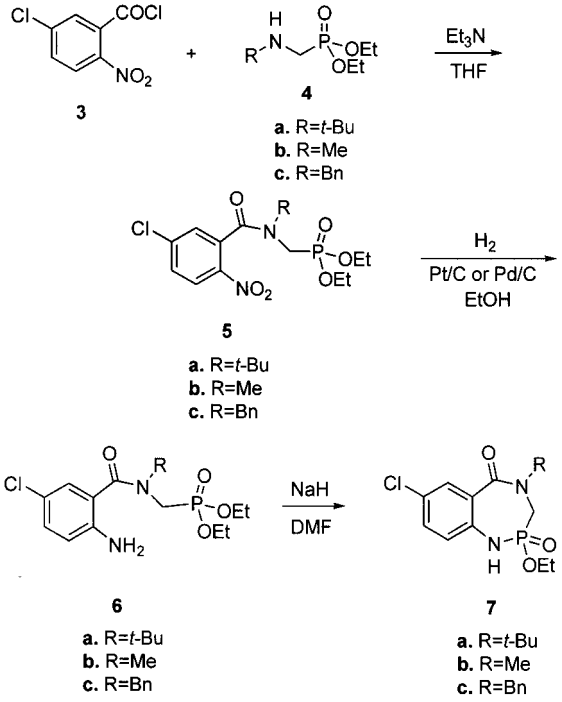
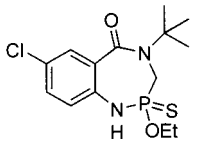
Scheme 1

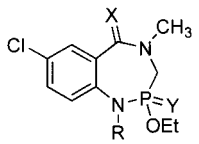


was reacted with *tert*-butylaminophosphonate **4a**[12c] to afford nitroamide **5a** in 68% yield (Scheme 1). Catalytic hydrogenation of **5a** gave the cyclization precursor **6a** in 71% yield. Phosphonate **6a** demonstrated no propensity to cyclize at room temperature,[13] unlike the analogous aminohippurate intermediates that cyclize readily to the benzodiazepinediones on standing.[11] Attempted ring closure of **6a** by heating in aqueous acid or base was unsuccessful, leading primarily to decomposition. Ultimately, cyclization to **7a** could be carried out smoothly by treating a DMF solution of **6a** with NaH followed by warming to 60 °C for a few hours, thereby affording **7a** in 71% yield. The identity of **7a** was established unequivocally by the loss of one ethoxy group and the downfield shift of the exchangeable nitrogen protons in the ^{1}H NMR (two protons at 4.27 ppm to one proton at 7.37 ppm in $CDCl_3$). In addition, the C-3 methylene signal was further complicated by the effects of ^{1}H−^{31}P coupling[14] in the now conformationally restrained system. Also diagnostic was the downfield shift of the phosphorus atom in the ^{31}P NMR from +23.3 to +34.7 ppm upon conversion of the phosphorus atom from a phosphonate to a phosphonamidate linkage.

Thionation of **7a** was then examined. Treatment of **7a** with Lawesson's reagent[15] in toluene at reflux gave a single product (**8**) in 93% yield. The site of thionation could be readily ascertained upon examination of the ^{13}C and ^{31}P NMR. The extreme downfield shift of the phosphorus atom in the ^{31}P NMR from +34.5 to +84.4 ppm and the absence of a significant shift in the ^{13}C NMR of the C-5 amide ($\Delta\delta$ = 0.3 ppm) indicated that thionation took place exclusively on the phosphorus atom.



8



9. X=Y=O, R=Me
10. X=Y=S, R=H
11. X=O, Y=S, R=H
12. X=Y=S, R=Me

To further illustrate the current approach to the benzodiazaphosphepin-5-one 2-oxide system, the 4-methyl (**7b**) and 4-benzyl (**7c**) analogues were prepared. Entry into the 4-methyl series was carried out by initial formation of *N*-benzyl-*N*-methylaminophosphonate via a Mannich-type reaction. Catalytic reduction afforded phosphonate **4b**. Reaction of *o*-nitrobenzoyl chloride **3** with **4b** gave the nitro phosphonate **5b** in 84% yield observed as a 4:1 mixture of amide rotational isomers at room temperature by ^{1}H and ^{31}P NMR in $CDCl_3$. Catalytic reduction of **5b** gave **6b** in 98% yield unencumbered by any mixture of rotamers. Treatment of **6b** with NaH, followed by warming to 60 °C, gave the desired product **7b**, as expected, in 68% yield after chromatography. The ^{31}P NMR exhibited the expected downfield shift (+22.5 to +32.7 ppm) on conversion of **6b** to **7b**. The 4-benzyl series was obtained similarly by reaction of **3** with phosphonate **4c**[12b] to give **5c** in 58% yield. The presence of amide rotamers (3:1 in $CDCl_3$) was again evidenced by ^{1}H and ^{31}P NMR. Nitro reduction gave **6c** in 92% yield and, like **6b**, free of observable rotamers at room temperature. Upon treatment of **6c** with NaH and subsequent warming, **7c** was obtained in 57% yield with the ^{31}P NMR showing the expected downfield shift (+23.4 to +32.8).

The 4-methyl series (**7b**) was then chosen for study to further evaluate alkylation and thionation reactions. Stirring a solution of **7b** with NaH followed by treatment with MeI gave the expected *N*-methyl analogue **9** as the sole product in 52% yield. The presence of the phosphonamidate linkage in **7a**−**c** renders these analogues considerably more polar than the corresponding phosphonate precursors **6a**−**c**. Of the three, **7b** exhibits the greatest degree of polarity toward silica gel. To avoid having to isolate **7b**, the direct conversion of phosphonate **6b** to **9** was examined. Stirring a DMF solution of **6b** with NaH (150 mol %) followed by warming to 60 °C (standard conditions) gave complete conversion to **7b** within 3 h as evinced by HPLC analysis. Treatment of the reaction mixture at room temperature with an additional 150 mol % of NaH (presumably to ensure complete phosphonamidate deprotonation, vide infra) followed by MeI afforded not the expected **9** but the N-methylated phosphonate **13**. No intermediate was observed by HPLC while following the conversion of **7b** to **13**. While initially surprising, this result could be rationalized by ethoxide-induced ring opening of a transiently formed **9** (Scheme 2). The first addition of NaH gives **7b**, as the sodium salt of the phosphonamidate anion along with one molecule of ethanol[16] generated from attack on the phosphonate diester. Following the second addition of NaH and MeI, N-methylated **9** must be formed and then rapidly converted to **13** via ethanolysis. In contrast, upon conversion

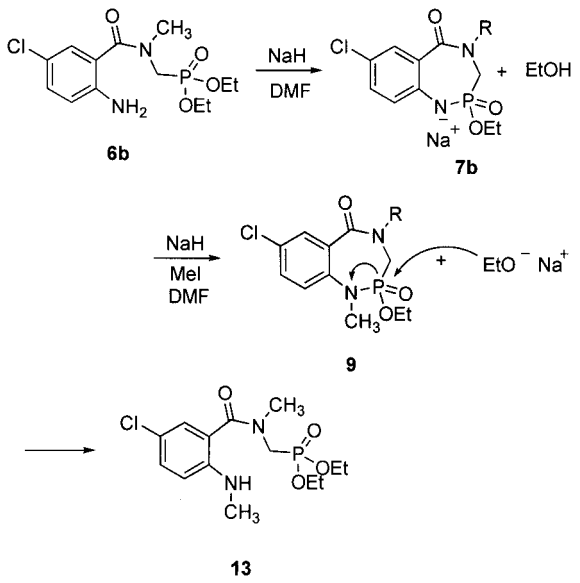
(13) Compound **6a** and related analogues can be stored neat indefinitely at room temperature without change.

(14) Friebolin, H. *Basic One- and Two-Dimensional NMR Spectroscopy;* VCH Publishers: New York, 1991; Chapter 4.

(15) (a) Horner, L.; Lindel, H. *Phosphorous Sulfur* **1982**, *12*, 259. (b) Scheibye, S.; Pedersen, B. S.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 229.

(16) No effort has been made to determine the equilibrium position between the sodium salt of the phosphonamidate + EtOH ↔ phosphonamidate + NaOEt.

Scheme 2



of **6b** to **7b**, the equilibrium lies far to the right as the negative charge on the phosphonamidate nitrogen atom prevents the retro-reaction, i.e., ethanolysis from taking place. When the tandem one-pot cyclization/alkylation of **6b** is carried out with NaH (120 mol %) followed by the addition of excess MeI, the desired **9** was obtained as the sole product.[17]

In contrast to **7a**, heating **7b** in the presence of a small excess of Lawesson's reagent in toluene afforded two thionated products, **10** and **11**. The structures of both **10** (45%) and **11** (16%) were established unequivocally by ^{13}C and ^{31}P NMR. Compound **10**, observed as a mixture of conformers, was identified as a bis-thionated product due to the extreme downfield shifts of both the carbonyl and phosphorus atoms in the ^{13}C NMR (167.9 to 195.3 ppm) and ^{31}P NMR (+32.7 to +93.6 and +80.1 ppm as a mixture of conformers), respectively. In **11**, only the phosphorus atom demonstrated a significant downfield shift (from +32.7 to +83.4 ppm in the ^{31}P NMR). The C-5 carbonyl remained essentially unchanged ($\Delta\delta = 0.5$ ppm), indicating that thionation took place only on the phosphorus atom.

When **10** was treated with NaH and MeI, a single product, **12**, was obtained as a mixture of conformers (ca. 2/1 in $CDCl_3$ and 1/1 in DMSO-d_6). The methyl resonances appeared as a set of doublets in the ^1H NMR ($CDCl_3$) at 3.17 (major) and 2.91 (minor) with $^3J_{HP} = 10.8$ and 10.5 Hz, respectively. The magnitude of the J value, consistent with three-bond coupling, could arise from methylation at either N-1 or the phosphorus-bearing sulfur atom. The observed chemical shift, however, was indicative of N-methylation. The structural assignment was made unambiguously by $^1H-^{13}C$ heteronuclear multiple bond correlation (HMBC) to examine the long-range J couplings. The methyl resonances in question demonstrated strong intensity cross-peaks with the nearest aromatic carbon (three-bond coupling). S-Methylation would require five-bond coupling to the nearest aromatic carbon.

In summary, a novel class of 1,4,2-benzodiazaphosphepin-5-one 2-oxides has been prepared as phosphonamidate isosteres of 1,4-benzodiazepine-2,5-diones as potential herbicidal agents.[18] The expeditious three-step route appears to be general in scope.

Experimental Section

General Methods. All reactions were carried out under an atmosphere of N_2. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Dimethylformamide (DMF), tetrahydrofuran (THF), and toluene were stored over 4A sieves. Mol % (mole percent) refers to the stoichiometry of the reaction components. Organic layers from aqueous extractions were dried over $MgSO_4$ and concentrated in vacuo. Melting points are uncorrected. ^1H (recorded at 400 and 300 MHz), ^{31}P (recorded at 121.4 MHz), and ^{13}C (recorded at 100.6 and 75.4 MHz) NMR spectra were measured in $CDCl_3$ or DMSO-d_6. ^{13}C and ^{31}P spectra (recorded relative to trimethyl phosphite at 140.4 ppm) were run proton decoupled. Coupling constants, J, are reported in hertz and refer to proton−proton coupling unless otherwise indicated. Chemical ionization mass spectra (MS) are recorded in units of m/z. High-resolution mass spectra (HRMS) were carried out by EI techniques. Unless otherwise indicated, flash chromatography was performed on 230−400 mesh silica gel. Reversed-phase C_{18} silica gel was obtained from Supelco. Analytical thin-layer chromatography was done with glass-backed silica plates, 250 μm (Analtech).

Diethyl [(Benzylmethylamino)methyl]phosphonate. To a solution of *N*-benzylmethylamine (12.1 g, 100 mmol) and diethyl phosphite (13.9 g, 100 mmol) was added paraformaldehyde (3.0 g, 100 mmol) portionwise during 5 min. The heterogeneous reaction mixture was then heated to 80 °C and held for 3 h, during which time it became homogeneous. After being cooled to room temperature, the solution was diluted with Et_2O, treated with $MgSO_4$ (10.0 g), and stirred for 30 min. After the solid was filtered, the filtrate was concentrated and the crude product was chromatographed (Et_2O/hexanes, 1/1) to afford 22.06 g (81%) of a clear liquid that was used directly in the next step: ^1H NMR ($CDCl_3$) δ 7.31−7.23 (m, 5H), 4.14−4.04 (m, 4H), 3.63 (s, 2H), 2.79 (d, $^2J_{HP} = 11.4$, 2H), 2.41 (s, 3H), 1.29 (t, $J = 7.2$, 6H); ^{31}P NMR ($CDCl_3$) δ +24.5; MS 272 (MH^+).

Diethyl [(Methylamino)methyl]phosphonate (4b). A solution of diethyl [(benzylmethylamino)methyl]phosphonate prepared above (21.1 g, 78 mmol) in EtOH (200 mL) was hydrogenated over 10% Pd−C (6.35 g, 30 wt %) in a Parr shaker at 55 psi for a total of 17 h. The catalyst was removed, and the filtrate was concentrated and distilled (82 °C, 0.4 mm) to afford 10.6 g (75%) of a clear liquid (lit.[12c] bp 75 °C, 0.3 mm): ^1H NMR ($CDCl_3$) δ 4.12 (dq, $J = 7.4$, $J_{HP} = 7.4$, 4H), 2.92 (d, $^2J_{HP} = 12.3$, 2H), 2.47 (d, $J = 2.1$, 3H), 1.50 (br s, 1H), 1.31 (t, $J = 7.2$, 6H); ^{31}P NMR ($CDCl_3$) δ +25.4; MS 182 (MH^+).

2-Nitrobenzamidophosphonates. General Procedure. A 1.0 M solution of 5-chloro-2-nitrobenzoyl chloride **3**[11] in toluene (110 mol %) was added dropwise to a 0 °C solution of the appropriate aminophosphonate (100 mol %) and triethylamine in THF. The heterogeneous reaction mixture was allowed to reach ambient temperature and then stirred overnight. After dilution with EtOAc, the reaction mixture was washed successively with H_2O, two to three portions of saturated $NaHCO_3$, and brine. The organic phases were dried and concentrated, and the products were purified by the method indicated.

Diethyl [(*N*-*tert*-Butyl-5-chloro-2-nitrobenzamido)-methyl]phosphonate (5a). Reaction of **3** (97 mmol), **4a**[12c] (87.9 mmol), and triethylamine (193.5 mmol) gave 24.2 g (68% yield) of **5a** as yellow needles after recrystallization (EtOAc/

(17) The author would like to thank one of the reviewers for comments concerning the role that additional NaH plays in the tandem cyclization/alkylation of **6b**. Additional experiments indicated that **9** is obtained as the sole product in instances where NaH is kept near stoichiometric so as to avoid the formation of sodium ethoxide.

(18) The 1,4,2-benzodiazaphosphepin-5-one 2-oxides and thioxides reported herein were evaluated for their herbicidal activity both in the whole plant and in vitro and were found to be much less active than the isosteric 1,4-benzodiazepine-2,5-diones.

hexanes): mp 98−99 °C; ^{1}H NMR ($CDCl_3$) δ 8.10 (d, J = 8.7, 1H), 7.61 (d, J = 2.1, 1H), 7.46 (dd, J = 2.1, 8.7, 1H), 4.10−4.00 (m, 4H), 3.71 (dd, J = 8.4, 17.1, 1H), 3.43 (br s, 1H), 1.59 (s, 9H), 1.25 (m, 6H); ^{31}P NMR ($CDCl_3$) δ +21.2; MS 407 (MH^+). Anal. Calcd for $C_{16}H_{24}ClN_2O_6P$: C, 47.24; H, 5.95; N, 6.89; P, 7.61. Found: C, 47.20; H, 6.15; N, 6.76; P, 7.68.

Diethyl [(5-Chloro-*N*-methyl-2-nitrobenzamido)methyl]phosphonate (5b). Reaction of **3** (24.3 mmol), **4b** (22.1 mmol), and triethylamine (27.6 mmol) gave, after chromatography (EtOAc/hexanes, 50−60%), 5.56 g of **5b** as a yellow oil (69%): ^{1}H NMR ($CDCl_3$, rotamers, 4:1) δ (major) 8.11 (d, J = 8.8, 1H), 7.50 (dd, J = 2.4, 8.7, 1H), 7.31 (d, J = 2.2, 1H), 4.18 (dq, J = 7.0, $^3J_{HP}$ =7.0, 4H), 3.98 (br s, 2H), 2.94 (s, 3H), 1.33 (t, J = 7.2, 6H), (minor, partial) 8.10 (d, J = 9.6, 1H), 4.07 (dq, J = 7.2, 8.2, 4H), 3.43−3.38 (m, 2H), 3.23 (s, 3H), 1.28 (t, J = 7.2, 1H); ^{31}P NMR ($CDCl_3$) δ +20.5 (major), +19.3 (minor); MS 365 (MH^+). Anal. Calcd for $C_{13}H_{18}ClN_2O_6P$: C, 42.85; H, 4.97; N, 7.68; P, 8.49. Found: C, 42.62; H, 4.97; N, 7.61; P, 8.44.

Diethyl [(*N*-Benzyl-5-chloro-2-nitrobenzamido)methyl]phosphonate (5c). Reaction of **3** (200 mmol), **4c**[12b] (174 mmol), and triethylamine (400 mmol) gave 44.4 g (58%) of **5c** as an off-white solid after recrystallization (EtOAc/hexanes): mp 108−109 °C; ^{1}H NMR ($CDCl_3$, rotamers, 3:1) δ 8.14 (d, J = 8.7, 1H, major), 8.13 (d, J = 9.0, 1H, minor), 7.64−7.18 (m, 7H), 4.60−4.40 (m, 2H), 4.20 (dq, J = 7.2, $^3J_{HP}$ = 7.2, 4H, major), 4.08 (dq, J = 7.3, $^3J_{HP}$ = 7.3, 4H, minor), 4.20−3.75 (m, 2H), 1.36 (t, J = 6.9, 3H, major), 1.31 (t, J = 6.6, 3H, minor); ^{31}P NMR ($CDCl_3$) δ +21.0 (major), +19.9 (minor); MS 440 (M^+). Anal. Calcd for $C_{19}H_{22}ClN_2O_6P$: C, 51.77; H, 5.03; N, 6.35; P, 7.03. Found: C, 52.03; H, 4.87; N, 6.32; P, 7.00.

2-Aminobenzamidophosphonates. General Procedure. A solution of the 2-nitrobenzamidophosphonates **5a**−**c** was hydrogenated over 5% Pt−C (30 wt %) in a Parr shaker at 50 psi until hydrogen uptake ceased. The catalyst was filtered, and the filtrate was concentrated. The crude product was purified by the method indicated.

Diethyl [(2-Amino-*N*-*tert*-butyl-5-chlorobenzamido)methyl]phosphonate (6a). A solution of **5a** (24.0 g, 59.0 mmol) in EtOH (600 mL) was hydrogenated for 24 h. Recrystallization (EtOAc/hexanes) gave 15.8 g (71%) of **6a** as an off-white solid: mp 123.5−125 °C; ^{1}H NMR ($CDCl_3$) δ 7.04 (m, 2H), 6.52 (d, J = 8.7, 1H), 4.27 (br s, 2H), 4.04−3.94 (m, 4H), 3.85−3.80 (m, 2H), 1.47 (s, 9H), 1.23 (t, J = 7.2, 3H); ^{31}P NMR ($CDCl_3$) δ +23.3; MS 377 (MH^+). Anal. Calcd for $C_{16}H_{26}ClN_2O_4P$: C, 51.00; H, 6.95; N, 7.43; P, 8.22. Found: C, 51.15; H, 7.05; N, 7.43; P, 8.14.

Diethyl [(2-Amino-5-chloro-*N*-methylbenzamido)methyl]phosphonate (6b). A solution of **5b** (4.54 g, 12.5 mmol) in 100 mL of THF/EtOH (1/1, v/v) was hydrogenated for 25 h to afford 4.08 g (98%) of an off-white waxy solid. A small sample (0.6 g) recrystallized from EtOAc/hexanes gave 0.42 g of **6b** as beige needles: mp 110−111.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.11−7.08 (m, 2H), 6.60 (d, J = 9.1, 1H), 4.50−4.25 (m, 2H), 4.17 (dq, J = 7.1, $^3J_{HP}$ = 7.1, 4H), 3.94 (d, $^2J_{HP}$ = 11.3, 2H), 3.11 (s, 3H), 1.34 (t, J = 7.2, 3H); ^{31}P NMR ($CDCl_3$) δ +22.5; MS 335 (MH^+). Anal. Calcd for $C_{13}H_{20}ClN_2O_4P$: C, 46.65; H, 6.02; N, 8.37; P, 9.25. Found: C, 46.49; H, 6.12; N, 8.28; P, 9.23.

Diethyl [(2-Amino-*N*-benzyl-5-chlorobenzamido)methyl]phosphonate (6c). A solution of **5c** (46.6 g, 105 mmol) in 500 mL of THF/EtOH (1/1, v/v) was hydrogenated for 22 h to afford 40.1 g (92%) of a pale yellow oil that was essentially pure: ^{1}H NMR ($CDCl_3$) δ 7.36−7.08 (m, 7H), 6.61 (d, J = 8.5, 1H), 4.65 (br s, 2H), 4.70−4.30 (br s, 2H), 4.23−4.11 (m, 4H), 3.80 (d, $^2J_{HP}$ = 10.7, 2H), 1.34 (t, J = 7.1, 3H); ^{31}P NMR ($CDCl_3$) δ +23.4; MS 410 (M^+). Anal. Calcd for $C_{19}H_{24}ClN_2O_4P$: C, 55.55; H, 5.89; N, 6.82; P, 7.54. Found: C, 55.16; H, 5.98; N, 6.67; P, 7.58.

1,4,2-Benzodiazaphosphepin-5-one 2-oxides. General Procedure. A solution of the aminobenzamidophosphonates **6a**−**c** in DMF (0.25−0.50 M) was treated with NaH (120−130 mol %, 60% oil dispersion) and then warmed to 60 °C and held at this temperature until TLC or HPLC indicated the reaction was complete (ca. 1−5 h). After being cooled to room temperature, the solution was poured into H_2O, acidified to pH 5−6 using HCl, and then extracted with two portions of EtOAc. The organic layer was washed successively with H_2O (two to three portions) and then brine. The organic phases were dried and concentrated, and the products were purified by the method indicated.

4-*tert*-Butyl-7-chloro-2-ethoxy-2,3-dihydro-1*H*-1,4,2-benzodiazaphosphepin-5(4*H*)-one 2-Oxide (7a). Treatment of a solution of **6a** (10.3 g, 27.4 mmol) in DMF (100 mL) with NaH (1.37 g, 34.2 mmol) followed by heating at 60 °C for 5 h gave, after workup, a solid. Trituration of the crude product in EtOAc/hexanes (1/3) afforded 6.45 g (71%) of **7a** as a white solid: mp 225−227 °C; ^{1}H NMR ($CDCl_3$) δ 7.58 (d, J = 2.4, 1H), 7.37 (br s, 1H), 7.25 (dd, J = 2.1, 8.4, 1H), 6.93 (d, J = 8.7, 1H), 4.12−4.04 (m, 2H), 3.76 (dd, J = 17.1, $^2J_{HP}$=12.3, 1H), 3.49 (dd, J = 17.1, $^2J_{HP}$=6.0, 1H), 1.55 (s, 9H), 1.25 (t, J = 7.2, 3H); ^{31}P NMR ($CDCl_3$) δ +34.7; ^{13}C NMR ($CDCl_3$) δ 167.8, 134.6, 134.4, 130.8, 130.1 (d, J_{CP} = 3.5), 130.0, 125.6 (d, J_{CP} = 5.6), 61.0 (d, $^2J_{CP}$ = 7.6), 58.5, 39.5 (d, $^1J_{CP}$ = 144), 28.1, 16.1 (d, $^3J_{CP}$ = 6.0); MS 331 (MH^+). Anal. Calcd for $C_{14}H_{20}ClN_2O_3P$: C, 50.84; H, 6.09; N, 8.47; P, 9.36. Found: C, 51.10; H, 6.14; N, 8.45; P, 9.43.

7-Chloro-2-ethoxy-2,3-dihydro-4-methyl-1*H*-1,4,2-benzodiazaphosphepin-5(4*H*)-one 2-Oxide (7b). Treatment of a solution of **6b** (4.00 g, 13.9 mmol) in DMF (30 mL) with NaH (0.72 g, 18.0 mmol) was followed by heating at 60 °C for 1 h. After the usual workup, the crude product was applied to C_{18} reversed-phase silica gel and eluted with CH_3CN/H_2O (15/85). The fractions containing the product were combined and concentrated and then diluted with $CHCl_3$ and dried. Concentration of the solution gave 2.35 g (68%) of **7b** as a yellow foam: mp 86−94 °C; ^{1}H NMR ($CDCl_3$) δ 7.54 (d, J = 2.5, 1H), 7.48 (br s, 1H), 7.24 (dd, J = 2.5, 8.5, 1H), 6.94 (dd, J = 8.5, $^4J_{HP}$ = 1.1, 1H), 4.10 (dq, J = 7.3, $^3J_{HP}$ = 7.3, 2H), 3.69−3.50 (m, 2H), 3.20 (s, 3H), 1.26 (t, J = 7.1, 3H); ^{31}P NMR ($CDCl_3$) δ +32.7; ^{13}C NMR ($CDCl_3$) δ 167.9, 135.5, 132.0, 131.6, 130.8, 130.7, 126.2 (d, J_{CP} = 5.0), 62.5 (d, $^2J_{CP}$ = 7.1), 45.0 (d, $^1J_{CP}$ = 139), 36.7, 16.7 (d, $^3J_{CP}$ = 5.1); MS 288 (M^+); HRMS calcd for $C_{11}H_{14}ClN_2O_3P$ (M^+) 288.0431, found 288.0430.

4-Benzyl-7-chloro-2-ethoxy-2,3-dihydro-1*H*-1,4,2-benzodiazaphosphepin-5(4*H*)-one 2-Oxide (7c). Treatment of a solution of **6c** (2.10 g, 5.10 mmol) in DMF (20 mL) with NaH (0.27 g, 6.62 mmol) followed by heating at 60 °C for 2 h gave, after workup and trituration with hexanes, 1.06 g (57%) of **7c** as a yellow glass: ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 2.5, 1H), 7.40 (br s, 1H), 7.37−7.25 (m, 6H), 7.01 (dd, J = 8.1, $^4J_{HP}$=1.1, 1H), 5.18 (d, J = 14.7, 1H), 4.56 (d, J = 14.7, 1H), 4.18−4.04 (m, 2H), 3.46 (d, J = 9.0, 2H), 1.28 (t, J = 7.2, 3H); ^{31}P NMR ($CDCl_3$) δ +32.8; ^{13}C NMR ($CDCl_3$) δ 168.2, 136.0, 135.5, 132.3, 131.8, 131.1, 131.0, 129.1, 128.6, 128.3, 126.5 (d, J_{CP} = 5.5), 62.5 (d, $^2J_{CP}$ = 7.0), 51.6, 42.1 (d, $^1J_{CP}$ = 141), 16.8 (d, $^3J_{CP}$ = 6.0); MS 365 (MH^+); HRMS calcd for $C_{17}H_{18}ClN_2O_3P$ (M^+) 364.0743, found 364.0760.

4-*tert*-Butyl-7-chloro-2-ethoxy-2,3-dihydro-1*H*-1,4,2-benzodiazaphosphepin-5(4*H*)-one 2-Thioxide (8). To a suspension of **7a** (1.00 g, 3.03 mmol) in toluene (20 mL) was added Lawesson's reagent (0.67 g, 1.67 mmol, 55 mol %) in one portion. The reaction was heated to reflux for 5 h and then cooled to room temperature. The yellow reaction mixture was then concentrated and chromatographed (EtOAc/hexanes, 15/85) to afford **8** (0.98 g, 93%) as a white solid: mp 150−153 °C; ^{1}H NMR ($CDCl_3$) δ 7.59 (d, J = 2.5, 1H), 7.30 (dd, J = 2.5, 8.2, 1H), 6.87 (dd, J = 2.6, 8.4, 1H), 5.27 (d, J = 4.8, 1H), 4.22−4.08 (m, 2H), 3.94 (dd, J = 17.0, $^2J_{HP}$ = 7.1, 1H), 3.73 (dd, J = 17.0, $^2J_{HP}$ = 8.2, 1H), 1.64 (s, 9H), 1.28 (t, J = 7.1, 3H); ^{31}P NMR ($CDCl_3$) δ +84.4; ^{13}C NMR ($CDCl_3$) δ 167.5, 135.9, 133.1 (d, J_{CP} = 6.0), 131.3, 130.5, 126.2 (d, J_{CP} = 3.5), 126.1, 61.1 (d, $^2J_{CP}$ = 7.0), 58.6, 45.4 (d, $^1J_{CP}$ = 118), 28.3, 15.5 (d, $^3J_{CP}$ = 6.6); MS 347 (MH^+); HRMS calcd for $C_{14}H_{20}ClN_2O_2PS$ (M^+) 346.0672, found 346.0662.

7-Chloro-1,4-dimethyl-2-ethoxy-2,3-dihydro-1*H*-1,4,2-benzodiazaphosphepin-5(4*H*)-one 2-Oxide (9). To a solution of **7b** (1.20 g, 4.16 mmol) in DMF (15 mL) was added NaH (0.25 g, 6.24 mmol, 60% oil dispersion). After the mixture was stirred for 20 min at room temperature, methyl iodide (0.39

mL, 6.24 mmol) was added via syringe and the solution was stirred for an additional 4 h. The yellow solution was then treated with 6 N H_2SO_4 (3 drops) to neutralize the excess NaH. Most of the DMF was removed via distillation on a Kugelrohr apparatus, and the residue was diluted with EtOAc and washed with three portions of H_2O. The combined aqueous phases were back-extracted with additional EtOAc, and the organic layers were combined, washed with brine, and then concentrated. The crude product was applied to C_{18} reversed-phase silica gel and eluted with CH_3CN/H_2O (85/15). The fractions containing the product were combined and concentrated to a pale yellow oil. The oil was dissolved in $CHCl_3$ and dried. Concentration of the solution gave 0.66 g (52% yield) of **9** as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.49 (d, J = 2.5, 1H), 7.35 (dd, J = 2.5, 8.7, 1H), 7.11 (dd, J = 8.7, $^4J_{HP}$ = 1.5, 1H), 4.11 (dq, J = 7.2, 7.7, 2H), 3.59−3.42 (m, 2H), 3.20 (s, 3H), 3.07 (d, $^3J_{HP}$ = 7.8, 3H), 1.28 (t, J = 7.1, 3H); ^{31}P NMR ($CDCl_3$) δ +32.0; ^{13}C NMR ($CDCl_3$) δ 167.6, 139.8 (d, J_{CP} = 3.0), 133.8, 132.0, 131.8 (d, J_{CP} = 2.0), 130.1, 126.0 (d, J_{CP} = 4.1), 62.7 (d, $^2J_{CP}$ = 6.0), 45.7 (d, $^1J_{CP}$ = 142), 36.4, 34.5 ($^2J_{CP}$ = 2.0), 16.8 (d, $^3J_{CP}$ = 6.0); MS 302 (M^+); HRMS calcd for $C_{12}H_{16}ClN_2O_3P$ (M^+) 302.0587, found 302.0583.

7-Chloro-2-ethoxy-2,3-dihydro-4-methyl-2-1*H*-1,4,2-benzodiazaphosphepin-5(4*H*)-thione 2-Thioxide (10) and 7-Chloro-2-ethoxy-2,3-dihydro-4-methyl-1*H*-1,4,2-benzodiazaphosphepin-5(4*H*)-one 2-Thioxide (11). To a suspension of **7b** (2.50 g, 8.67 mmol) in toluene (50 mL) was added Lawesson's reagent (1.93 g, 4.77 mmol, 55 mol %), and the mixture was heated at reflux until TLC indicated that all of **7b** was consumed (ca. 3.5 h). After being cooled to room temperature, the reaction mixture was concentrated to a solid. Addition of a small amount of EtOAc/hexanes (10 mL, 20/80) gave a gummy solid. Upon addition of a small amount of CH_2Cl_2, a finely divided yellow solid precipitated, comprising two major components. The filtrate contained only trace amounts of these components in addition to byproducts generated from Lawesson's reagent. The crude product mixture was chromatographed with CH_2Cl_2 to elute the major, less polar **10**, followed by EtOAc/CH_2Cl_2 (10/90) to elute the minor, more polar **11**.

10: isolated as a yellow solid (1.24 g, 45%); mp 224−225.5 °C; ^{1}H NMR (298 K, DMSO-d_6, rotamers, 2.5:1) δ 8.62 (br s, 1H), 7.62 (br s, 1H), 7.42 (m, 1H), 6.98 (m, 1H), 4.55−4.00 (m, 4H), 3.66 (s, 3H, major), 3.57 (s, 3H, minor), 1.31 (t, J = 6.3, 3H), 1.22 (t, J = 6.9, 3H, major); ^{31}P NMR (298 K, DMSO-d_6, rotamers) δ +93.6 (minor), +80.1 (major); ^{13}C NMR (298 K, DMSO-d_6, partial, major) δ 195.3, 62.1 (d, $^2J_{CP}$ = 7.1), 55.4 (d, $^1J_{CP}$ = 114), 45.4, 16.8 ($^3J_{CP}$ = 6.0); ^{1}H NMR (353 K, DMSO-d_6, coalescence of peaks) δ 8.32 (br s), 7.65 (d, J = 2.4, 1H), 7.38 (dd, J = 2.7, 8.5, 1H), 7.00 (dd, J = 8.5, $^4J_{HP}$ = 1.4), 4.30−4.10 (m, 4H), 3.66 (s, 3H), 1.27 (t, J = 6.9, 3H); MS 321 (MH^+). Anal. Calcd for $C_{11}H_{14}ClN_2OPS_2$: C, 41.19; H, 4.40; N, 8.73; P, 9.66; S, 19.99. Found: C, 41.03; H, 4.37; N, 8.57; P, 9.63; S, 19.91.

11: isolated as a white solid (0.41 g, 16%); mp 169−170 °C; ^{1}H NMR (DMSO-d_6) δ 8.54 (br s, 1H), 7.47−7.43 (m, 2H), 7.04 (d, J = 8.5, 1H), 4.16−3.84 (m, 4H), 3.14 (s, 3H), 1.24 (t, J = 6.9, 3H); ^{31}P NMR (DMSO-d_6) δ +83.4;); ^{13}C NMR (DMSO-d_6) δ 167.4, 137.1 (d, J_{CP} = 6.0), 132.5, 131.9, 130.4, 129.0 (d, J_{CP} = 3.0), 126.3 (d, J_{CP} = 5.0), 62.2 (d, $^2J_{CP}$ = 7.1), 50.6 ($^1J_{CP}$ = 111), 36.7, 16.7 ($^3J_{CP}$ = 6.0); MS 305 (MH^+). Anal. Calcd for $C_{11}H_{14}ClN_2O_2PS$: C, 43.36; H, 4.63; N, 9.19; P, 10.16. Found: C, 42.93; H, 4.63; N, 8.99; P, 9.91.

7-Chloro-1,4-dimethyl-2-ethoxy-2,3-dihydro-2-1*H*-1,4,2-benzodiazaphosphepin-5(4*H*)-thione 2-Thioxide (12). A solution of **10** (0.57 g, 1.78 mmol) in DMF (10 mL) was treated with NaH (0.078 g, 1.96 mmol, 60% oil dispersion) and then stirred at room temperature for 30 min. Methyl iodide was added via syringe at once, and the reaction was stirred for an additional 22 h. The reaction mixture was then diluted with EtOAc and washed with four portions of H_2O. The aqueous layers were then back-extracted with additional EtOAc, and the combined organic phases were washed with brine and then dried and concentrated. The crude product was purified by chromatography (EtOAC/hexanes, 15/85) to afford **12** as an amber glass (0.33 g, 55%): mp 105−108 °C; ^{1}H NMR ($CDCl_3$, conformers, 2:1) δ (major) 7.05 (d, J = 2.4, 1H), 7.32 (dd, J = 2.5, 8.8, 1H), 7.06 (dd, J = 8.3, $^4J_{HP}$ = 1.3, 1H), 4.12−3.75 (m, 4H), 3.73 (s, 3H), 3.17 (d, $^3J_{HP}$ = 10.8, 3H), 1.22 (t, J = 7.2, 3H), (minor) 7.67 (d, J = 2.8, 1H), 7.31 (m, 1H), 7.02 (dd, J = 8.8, $^4J_{HP}$ = 1.9, 1H), 4.35−4.05 (m, 4H), 3.63 (s, 3H), 2.91 (d, $^3J_{HP}$ = 10.5, 3H), 1.38 (t, J = 7.1, 3H); ^{31}P NMR ($CDCl_3$, conformers) δ + 95.8 (minor), +82.1 (major); ^{13}C NMR ($CDCl_3$, conformers) δ 195.8, 195.0, 141.0, 139.2 (2), 136.8, 136.5 (2), 132.2, 132.1, 131.1, 130.9, 130.8 (2), 130.6 (2), 127.2 (2), 123.8 (2), 64.2 (2), 57.0 (d, $^1J_{CP}$ = 100), 56.7 (d, $^1J_{CP}$ = 119), 44.9, 44.4 36.6 (2), 32.4 (2), 16.2 (2), 16.1 (2); MS 334 (M^+); HRMS calcd for $C_{12}H_{16}ClN_2OPS_2$ (M^+) 334.0130, found 334.0141.

Diethyl [(5-Chloro-*N*-methyl-2-(methylamino)benzamido)methyl]phosphonate (13) from 6b via Intermediate 9. A solution of **6b** (2.95 g, 8.82 mmol) in DMF was treated with NaH (0.53 g, 13.2 mmol, 60% oil dispersion), heated to 60 °C, and then held at this temperature for 3 h (at which time HPLC analysis indicated complete consumption of starting material). After the solution was cooled to room temperature, additional NaH (0.35 g, 8.82 mmol) was added, and the resulting solution was stirred for an additional 20 min. Methyl iodide (0.82 mL, 13.2 mmol) was then added, and after being stirred for an additional 2 h at room temperature, the solution was treated with a few drops of 6 N H_2SO_4 to neutralize the excess NaH and the residue was diluted with EtOAc and washed with three portions of H_2O. The combined aqueous phases were back-extracted with additional EtOAc, and the organic layers were combined, washed with brine, and then concentrated. Chromatography (EtOAC/hexanes, 1/1) afforded 1.24 g (40%) of **13** as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.17 (dd, J = 2.5, 8.8, 1H), 7.04 (d, J = 2.2, 1H), 6.51 (d, J = 8.8, 1H), 5.11 (br s, 1H), 4.20−4.10 (m, 4H), 3.92 (d, J = 11.2, 2H), 3.06 (s, 3H), 2.77 (s, 3H), 1.32 (t, J = 7.1, 6H); ^{31}P NMR ($CDCl_3$) δ +22.4; MS 348 (M^+); HRMS calcd for $C_{14}H_{22}ClN_2O_4P$ (M^+) 348.1005, found 348.1015.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of compounds **7a**−**c**, **8**, **9**, **11**, and **12**, ^{1}H NMR spectrum of compound **10**, and ^{1}H−^{13}C HMBC spectrum of compound **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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