# Single-Step Preparation of 1-Hydroxybisphosphonates via Addition of Dialkyl Phosphite Potassium Anions to Acid Chlorides

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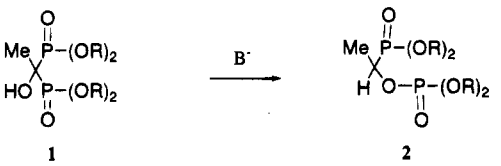
The addition reaction between the potassium anion of dialkyl phosphites and acid chlorides at low temperature produced tetraalkyl 1-hydroxybisphosphonates, whereas the corresponding lithium anion gave mostly the rearranged products tetraalkyl phosphono phosphates. The rate of rearrangement was found to be dramatically accelerated by the presence of bulky substituents at the α-position of the acid chloride. Intermediates arising from the addition of dibenzyl phosphite anion rearranged more readily than those obtained from diethyl phosphite anion, but again less so for the potassium anion reagent.

## Introduction

Bisphosphonates are used in the treatment of diseases of bone and calcium metabolism of which osteoporosis is the most common form.[1,2] The central core of geminal bisphosphonates (P–C–P) and 1-hydroxybisphosphonates (P–C(OH)–P) is characterized by two carbon–phosphorus bonds. They are therefore carbon analogues of pyrophosphates (P–O–P) and are metabolically more stable since the latter are hydrolyzed by phosphatases.[1] Bisphosphonates are targeted to bone and adsorbed onto hydroxyapatite surfaces[3] where they inhibit bone resorption through the mediation of osteoclastic activity.[4]

Several methods have been reported for the preparation of bisphosphonates[5] and hydroxybisphosphonates.[6,7] Most of the reported methods describe the preparation of the free bisphosphonic acid under rather harsh acidic reaction conditions.[7] For example, the most common method involves the reaction of a carboxylic acid, phosphorous acid, and phosphorus trichloride[7a] or phosphorus oxychloride.[7b] Comparatively few reports deal with the preparation of 1-hydroxybisphosphonates under basic conditions. McConnell and Coover[8] first described the synthesis of 1-hydroxybisphosphonates **1** from base-catalyzed addition of dialkyl phosphites to acylphosphonates which were obtained from Michaelis–Arbuzov reaction of trialkyl phosphite and an acid chloride.[9] Fitch and Moedritzer[10] later showed that McConnell and Coover had erroneously assigned the 1-hydroxybisphosphonate structure **1** to tetraalkyl phosphono phosphate **2**.




**1** **2**

During the course of another study, we were required to prepare tetraalkyl ester analogues of compound **1** under *basic* conditions. We then undertook a study of the addition reaction of a dialkyl phosphite anion to acid chlorides at low temperature. This report describes the results of the study and shows how the base-induced rearrangement of hydroxybisphosphonates to tetraalkyl phosphono phosphate (**1** → **2**) can be supressed. The effect of the alkoxide metal counterion and the nature of phosphonic ester alkyl groups on the outcome of the reaction is reported.

## Results and Discussion

We have prepared several 1-hydroxybisphosphonates under mild reaction conditions as shown in Table 1. Two equivalents of a dialkyl phosphite anion were added to an acid chloride at low temperature. The reaction is somewhat similar to that of McConnell and Coover[8] since the electrophile acylphosphonate (used in their study as starting material) is a likely intermediate in the addition of dialkyl phosphite anion to acid chlorides. We had hoped to control the rearrangement (**1** → **2**) by carrying

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(1) For a comprehensive review on the physiology and pharmacology of bone see: Fleisch, H. In *Handbook of Experimental Pharmacology*; Mundy, G. R., Martin, T. J., Eds.; Springer-Verlag: Berlin, Heidelberg, 1993; pp 377–418.

(2) Raisz, L. G. *N. Engl. J. Med.* **1988**, *318*, 818–828.

(3) Jung, A.; Bisaz, S.; Fleisch, H. *Calc. Tiss. Res.* **1973**, *11*, 269–280.

(4) Sahni, M.; Guenther, H. L.; Fleisch, H.; Collin, P.; Martin, T. J. *J. Clin. Invest.* **1993**, *91*(5), 2004–2011.

(5) For selected references, see: (a) Nicholson, D. A.; Cilley, W. A. *J. Org. Chem.* **1970**, *35*, 3149–3150. (b) Teulade, M.-P.; Savignac, P. *J. Organomet. Chem.* **1986**, *304*, 283–300. (c) Degenhardt, C. R.; Burdsall, D. C. *J. Org. Chem.* **1986**, *51*, 3488–3490. (d) Takeuchi, M.; Sakamoto, S.; Yoshida, M.; Abe, T.; Isomura, Y. *Chem. Pharm. Bull.* **1993**, *41*(4), 688–693. (e) Sturtz, G.; Guervenou, J. *Synthesis* **1991**, 661–662 and references therein. (f) Hutchinson, D. W.; Thornton, D. M. *J. Organomet. Chem.* **1988**, *346*, 341–348. (g) Jouko, V.; Heikki, N.; Esko, P. *J. Labelled Cmpds Radiopharm.* **1991**, *29*(11), 1191–1196. (h) Neidlein, R.; Eichinger, T. *Synthesis* **1991**, 1228–1230. (i) Vepsäläinen, J.; Nupponen, H.; Pohjala, E.; Ahlgren, M.; Vainiotalo, P. *J. Chem. Soc., Perkin Trans. 2* **1992**, 835–842.

(6) (a) Nicholson, D. A.; Vaughn, H. *J. Org. Chem.* **1971**, *36*, 3843–3845. (b) Nguyen, L. M.; Niesor, E.; Bentzen, C. L. *J. Med. Chem.* **1987**, *30*, 1426–1433.

(7) For selected references, see: (a) Kaas, S. M.; Ebetino, F. H.; Francis, M.D. WO 93/24496 1993 and references therein. (b) Bauss, F.; Mühlbauer, R. C. *Drugs Future* **1994**, *19*(1), 13 and references therein. (c) Jaeggi, K. A.; Widler, L. U.S. patent 4,939,130, 1990.

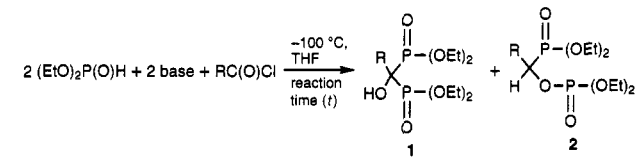
(8) McConnell, R. L.; Coover, H. W., Jr. *J. Am. Chem. Soc.* **1956**, *78*, 4450–4452.

(9) (a) Arbuzow, B. A. *Pure Appl. Chem.* **1964**, *9*, 307–335. (b) See also: Bhattacharya, A. K.; Thyagarjan, G. *Chem. Rev.* **1981**, *81*, 415–430. (c) Tam, C. C.; Mattocks, K. L.; Tishler, M. *Proc. Natl Acad. Sci. U.S.A.* **1981**, *78*, 3301–3304.

(10) Fitch, S. J.; Moedritzer, K. *J. Am. Chem. Soc.* **1962**, *84*, 1876–1879.

0022-3263/95/1960-5209$09.00/0 

**Table 1. Addition of Diethyl Phosphite Anions to Acid Chlorides**




| entry | base | R | $t$ (s) | products | ratio[a] 1:2 | yield[b] (%) |
|---|---|---|---|---|---|---|
| 1 | LiHMDS | $PhCH_2CH_2$ | 10 | **1a:2a** | 1:25 | 85 |
| 2 | KHMDS | $PhCH_2CH_2$ | 10 | **1a**[c]:**2a** | 7:1 | 72 |
| 3 | LiHMDS | $PhCH_2$ | 10 | **1b:2b** | nd[d]:1 | 92 |
| 4 | KHMDS | $PhCH_2$ | 10 | **1b:2b** | 6:1 | 93 |
| 5 | LiHMDS | $CH_3(CH_2)_4$ | 10 | **1c**:2c | 1:nd | 72 |
| 6 | LiHMDS | $CH_3(CH_2)_4$ | 150 | **1c:2c** | 1:5 | 70 |
| 7 | KHMDS | $CH_3(CH_2)_4$ | 150 | **1c**[c]:**2c** | 6:1 | 68 |
| 8 | NaHMDS | $CH_3(CH_2)_4$ | 150 | **1c:2c** | 2:1 | 71 |
| 9 | LiHMDS | $(CH_3)_3C$ | <2 | **1d:2d** | nd:1 | 84 |
| 10 | KHMDS | $(CH_3)_3C$ | <2 | **1d:2d** | nd:1 | 70 |
| 11 | LiHMDS | Ph | <2 | **1e:2e** | nd:1 | 84 |
| 12 | KHMDS | Ph | <2 | **1e:2e** | nd:1 | 78 |

[a] Ratios were determined from $^1H$ nmr of the crude reaction mixture. [b] Yield refers to combined yields of isolated pure compounds. [c] Small amounts (< 10%) of the corresponding ester $RC(OCOR)(P(O)(OEt)_2)_2$ **3** was also isolated. [d] nd: not detected.

out the reaction at lower temperature (−100 °C) than that of McConnell and Coover (+70 °C).[8] However, the lithium anion of diethyl phosphite reacted with hydrocinnamoyl chloride in THF at −100 °C to give only trace amounts of hydroxybisphosphonate **1a** and provided a high yield of the rearranged product **2a** (entry 1). Interestingly, the rearrangement was much slower with the potassium anion of diethyl phosphite, and under similar reaction conditions, hydroxybisphosphonate **1a** was isolated in good yield. We also isolated small amounts of ester **3a** (see Table 1) as a result of acylation of the alkoxide anion of **1a** (entry 2). Similar ratios of hydroxybisphosphonate:phosphinyl phosphate were obtained in the reactions with phenylacetyl chloride (entries 3−4). The reaction with hexanoyl chloride provided hydroxybisphosphonate **1c** for which the corresponding lithium anion rearranged to lesser extent (entry 5) than those of compounds **1a** and **1b** (entries 1 and 3). When reacted for a longer time, however, the lithium salt (entry 6) provided rearranged product **2c** more readily than did the potassium salt (entry 7). Use of sodium bis(trimethylsilyl)amide (entry 8) gave a mixture of hydroxybisphosphonate **1c** and phosphate **2c** with moderate selectivity (2:1). The reactions with pivaloyl chloride and benzoyl chloride, however, provided only phosphates **2d** and **2e**,[9] respectively, regardless of the nature of the base used (entries 9−12). These results suggested that the rearrangement of **1** to phosphinyl phosphate **2** might be facilitated, for a given counterion, by α-substitution on the alkyl group (R). Hence, hydroxybisphosphonates **1d** and **1e** could not be isolated, whereas, for example, the corresponding *n*-hexyl compound **1c** was isolated in good yield. More rapid rearrangement was also observed with bulkier dialkyl phosphites. As exemplified by reaction with hexanoyl chloride, intermediates arising from addition of dibenzyl phosphite anion rearranged more readily, for a given counterion, than those obtained from diethyl phosphite (compare Table 2, entry 1, with Table 1, entry 5).

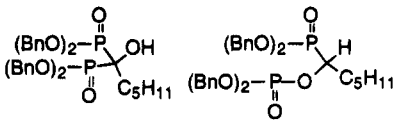
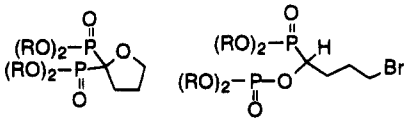
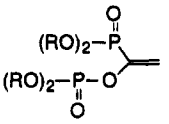
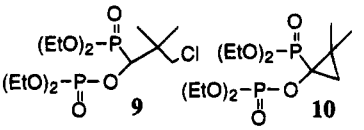
Bearing this in mind, we then studied the reactivity of *n*-bromoalkanoyl chlorides as a means to trap the intermediate 1-hydroxybisphosphonate anion. The lithium anion of diethyl phosphite was reacted with 4-bromobutyryl chloride and the intermediate alkoxide anion rapidly cyclized at −100 °C to give cyclic ether **6a** in 91% yield (Table 2, entry 3). Consistent with the result reported for hexanoyl chloride (Table 1, entry 5), we detected no evidence of rearranged bromide **7a**. On the other hand, the reaction of dibenzyl phosphite lithium anion with 4-bromobutyryl chloride gave rise to more of the rearranged phosphate **7b**. In fact, under similar reaction conditions, the lithium anion of dibenzyl phosphite (Table 2, entry 4) gave predominantly bromide **7b** (1.7:1/ **7b:6b**) whereas the corresponding potassium anion gave none of the rearranged product **7b** but exclusively cyclic ether **6b** (Table 2, entry 5). Clearly, the use of potassium bis(trimethylsilyl)amide once again inhibited the rearrangement. On the other hand, the reaction with bromoacetyl chloride or chloroacetyl chloride only provided enol phosphates **8a** and **8b** in good yield regardless of the nature of base and dialkyl phosphite used (entries 6−8). We were unable to detect or isolate any epoxide resulting from cyclization. This class of (dialkoxyphosphinyl)enol phosphate has been previously reported via an alternative route on related fluorine-containing compounds.[11]

All of the hydroxybisphosphonates reported above were stable in chloroform solution at room temperature for several weeks. We were particularly intrigued by those cases where hydroxybisphosphonates (Table 1, entries 10 and 12) or any of the corresponding cyclized derivatives (Table 2, entries 6−8) could not be isolated. Common to each of these cases is the presence of a relatively bulky substituent at the α-position of the acid chloride. Whether the influence of these substituents is steric and/or electronic in nature is not known, but the following experiment suggests that rearrangement occurred in the reaction mixture and not during workup or purification as a result of intrinsic instability of the corresponding hydroxybisphosphonates. For example, we had previously seen that the reaction of diethyl phosphite potassium anion with pivaloyl chloride afforded only the rearranged phosphate **2d** even after extremely short reaction time at −100 °C (Table 1, entry 10). The possibility that "unstable" hydroxybisphosphonate **1d** was indeed formed but later decomposed to phosphate **2d** upon subsequent handling might be precluded on the basis of the following experiment with chloropivaloyl chloride (Table 2, entry 9). In this case, the reaction of diethyl phosphite potassium anion and 3-chloro-2,2-dimethylpropanoyl chloride provided a (3:1) mixture of chloropropyl phosphate **9** and cyclopropyl phosphate **10**. The cyclopropyl compound was the sole product when the reaction was allowed to run for a longer time (10 min), and its formation might be explained by cyclization of anion **10c** (Scheme 1). It seems rather unlikely considering the above observations that the formation of compounds **9** and **10** be the result of decomposition during workup or purification of the (hypothetical) precursor 3-chloro-2,2-dimethyl-1-hydroxybisphosphonate (the neutral form of **10a**). By extension, it also seems unlikely that hydroxybisphosphonates **1d** and **1e** were formed after quenching the reaction mixture *but* could not be isolated because of instability imparted by bulky sub-

(11) (a) Ishihara, T.; Maekawa, T.; Yamasaki, Y.; Ando. *J. Fluorine Chem.* **1986**, *34*(5), 271−274; (b) *Tetrahedron Lett.* **1983**, *24*, 4229−4232.

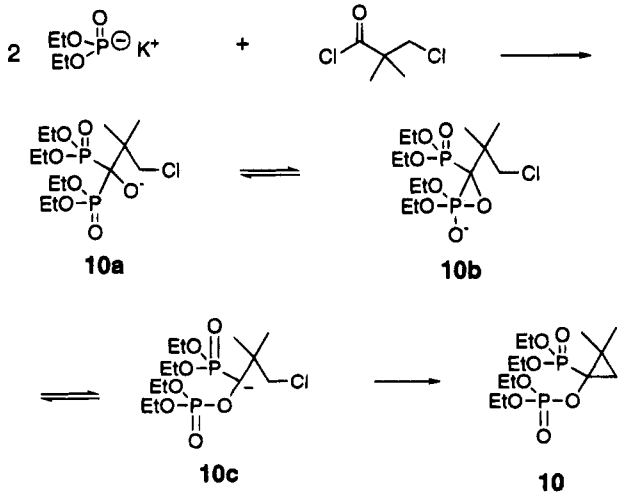
**Table 2. Addition of Dialkyl Phosphite Anions to Acid Chlorides and *n*-Haloalkanoyl Chlorides**

$$2(RO)_2P(O)H + 2\ base + X(CH_2)_nC(O)Cl \xrightarrow[\text{reaction time } (t)]{-100\ ^\circ C,\ THF} products$$

| Entry | Base | R | Acid chloride | t(s) | Products | ratio | yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | LiHMDS | Bn | X=H n=5 | 10 |  **4a** **5a** | 1: 25 | 90 |
| 2 | KHMDS | Bn | X=H n=5 | 10 | **4a** **5a** | 3: 1 | 75 |
| 3 | LiHMDS | Et | X=Br n=3 | 5 |  **6a** **7a** | 1: 0 | 91 |
| 4 | LiHMDS | Bn | X=Br n=3 | 5 | **6b** **7b** | 1: 1.7 | 90 |
| 5 | KHMDS | Bn | X=Br n=3 | 5 | **6b** **7b** | 1: 0 | 87 |
| 6 | KHMDS | Et | X=Br n=1 | 5 |  **8a** | - | 72 |
| 7 | KHMDS | Et | X=Cl n=1 | 5 | **8a** | - | 66 |
| 8 | KHMDS | Bn | X=Br n=1 | 5 | **8b** | - | 71 |
| 9 | KHMDS | Et | X=Cl n=1 H=$CH_3$ | 5 |  **9** **10** | 3: 1 | 76 |

[a] Ratios were determined from $^1H$ nmr of the crude reaction mixture. [b] Yield refers to combined yield isolated pure compounds.

**Scheme 1**




stituents. Substitutiton at the 2-position of the intermediate potassium (and lithium) 1-alkoxide bisphosphonates apparently enhances the rate of rearrangement yielding the dialkyl phosphinyl phosphates.

Dialkyl acylphosphonate ($(RC(O)P(O)(OR)_2$) is a likely intermediate of the reactions leading to tetraalkyl 1-hydroxybisphosphonates **1** and tetraalkyl phosphono phosphate **2**. When diethyl phosphite, potassium bis(trimethylsilyl)amide, and hexanoyl chloride were used in stochiometric amounts diethyl hexanoylphosphonate (**11**) could not be isolated and the reaction provided a low yield of hydroxybisphosphonate **1c** along with trace of the corresponding ester **3c**. The intermediate acylphosphonate **11**[9] could, however, be obtained from the Michaelis–Arbuzov reaction of triethyl phosphite and hexanoyl chloride at 0 °C. When acylphosphonate **11** was treated with potassium bis(trimethylsilyl)amide in THF at −100 °C *without any added diethyl phosphite*, hydroxybisphosphonate **1c** was obtained in 21% yield (based on a 50% theoretical yield). It is possible that the base-catalyzed fragmentation of acylphosphonate[12] generated the corresponding ketene and diethyl phosphite potassium anion which then reacted with another molecule of acylphosphonate **11** to provide hydroxybisphosphonate **1c** and a trace of ester **3c**. The latter compound was most likely

(12) Breuer, E.; Karaman, R.; Goldblum. A. *Phosphorus Sulfur* **1984**, *21*, 119–120.

formed via acylation[13-15] of the potassium anion of **1c** with acylphosphonate **11**.

In conclusion, we have showed that several 1-hydroxybisphosphonates could be synthesized under mild basic reaction conditions via a general one-step procedure. The reaction between dialkyl phosphite potassium anions and acid chlorides described herein represents an advantageous alternative for the synthesis of 1-hydroxybisphosphonates for which reported preparations[6,7] have hitherto used fairly drastic reaction conditions or more complex multistep protocol. We have also described the limitation of the reaction with acid chlorides bearing substitution at the α-position and showed the effect of the posphite alkyl groups on the outcome of the reaction.

## Experimental Section

**General.** $^1H$, $^{13}C$, and $^{31}P$ NMR spectra were recorded at 400, 100, and 121.5 MHz, respectively, unless otherwise specified. The spectra were recorded in $CDCl_3$ with tetramethylsilane ($^1H$ and $^{13}C$) and 85% $H_3PO_4$ ($^{31}P$) as internal and external references, respectively. All $^1H$, $^{13}C$, and $^{31}P$ NMR spectra are included in the supplementary material. MS data are *m/z* (relative intensity compared to that of largest peak). Column and thin layer chromatography were performed on silica gel with the indicated solvent system. Diethyl phosphite was distilled prior to use. All reactions were carried out under a positive pressure of nitrogen.

**Typical Procedure.** A 0.5 M solution of potassium bis(trimethylsilyl)amide (14.5 mL, 3.9 mmol) was added at −78 °C to a solution of diethyl phosphite (1.0 g, 7.3 mmol) in THF (36 mL). The mixture was stirred at −78 °C for 30 min and cooled to −100 °C, and hydrocinnamoyl chloride (536 uL, 3.6 mmol) was added. The mixture was stirred at −100 °C for 10 s, and a saturated solution of ammonium chloride (40 mL) was added. The mixture was concentrated under reduced pressure until all THF evaporated, and ethyl acetate (50 mL) was added. The separated aqueous layer was extracted with ethyl acetate (4 × 50 mL), and the combined organic layers were washed (brine), dried ($MgSO_4$ anhyd), filtered, and evaporated to give 1.5 g of an oil. Flash chromatography (ethyl alcohol: ethyl acetate/1:99−1:9) of the residue gave 887 mg (60%) of **1a** as an oil along with phosphate **2a** (126 mg, 9%) and ester **3a** (59 mg, 3%): $R_f$ (ethyl alcohol:ethyl acetate/1:99) **1a**, 0.10; **2a**, 0.55; **3a**, 0.25.

**(1-(Diethoxyphosphinyl)-1-hydroxy-3-phenylpropyl)-phosphonic acid diethyl ester (1a)**: IR (neat) 3240, 1245 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.26−7.13 (5H, m), 4.25−4.13 (8H, m), 3.74 (1H, br. s), 2.92 (2H, m), 2.26 (2H, m), 1.33 (12H, t, *J* = 7.1 Hz); $^{13}C$ NMR ($CDCl_3$) δ 142.0, 128.4, 125.9, 74.5 (t, *J* = 150.0 Hz), 63.7 (m), 36.2, 29.7 (t, *J* = 5.6 Hz), 16.5 (d, *J* = 2.6 Hz).; $^{31}P$ NMR ($CDCl_3$) δ 20.34 (s) MS (FAB) *m/z* (relative intensity) 839 ($2M^+$ + Na, 15), 431 ($M^+$ + Na, 100), 409 ($MH^+$, 59), 293 (43); HRMS calcd for $C_{17}H_{31}P_2O_7$ ($MH^+$) 409.1545, found 409.1547.

**Diethyl 1-(diethoxyphosphinyl)-3-phenylpropyl phosphate (2a)**: IR (neat) 1260 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.28−7.15 (5H, m), 4.66 (1H, m), 4.22−4.10 (8H, m), 2.92 (1H, m), 2.77 (1H, m), 2.18 (2H, m), 1.33 (12 H, m); $^{13}C$ NMR ($CDCl_3$) δ 140.9, 128.4, 126.1, 72.1 (dd, *J* = 170.0, 7.2 Hz), 64.0 (d, *J* = 5.9 Hz), 62.8 (d, *J* = 5.8 Hz), 32.9, 31.6 (d, *J* = 10.7 Hz), 16.4 (t, *J* = 4.6 Hz), 16.0 (t, *J* = 6.6 Hz).; $^{31}P$ NMR ($CDCl_3$) δ 19.95 (d, *J* = 22.0 Hz), −0.79 (d, *J* = 22.0 Hz); MS (FAB) *m/z* (relative intensity) 409 ($MH^+$, 100), 255 (27); HRMS calcd for $C_{17}H_{31}P_2O_7$ ($MH^+$) 409.1545, found 409.1547.

**3-Phenylpropionic acid 1,1-bis(diethoxyphosphinyl)-3-phenylpropyl ester (3a)**: IR (neat) 1755, 1260 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.25−7.12 (10H, m), 4.22 (8H, m), 2.96 (2H, t, *J* = 8.0 Hz), 2.68 (6H, m), 1.32 (12H, m); $^{13}C$ NMR ($CDCl_3$) δ 170.7 (t, *J* = 7.4 Hz), 141.6, 128.3 (m), 82.3 (t, *J* = 150.6 Hz), 63.7 (d, *J* = 23.7 Hz), 35.8, 34.0, 30.7, 30.3 (t, *J* = 6.3 Hz), 16.5 (d, *J* = 2.8 Hz); $^{31}P$ NMR ($CDCl_3$) δ 16.82 (s); MS (FAB) *m/z* (relative intensity) 1103 ($2M^+$ + Na, 1), 563 ($M^+$ + Na, 22), 541 ($MH^+$, 53), 495 (30), 409 (81), 363 (100); HRMS calcd for $C_{26}H_{39}P_2O_8$ ($MH^+$) 541.2120, found 541.2120.

**(1-(Diethoxyphosphinyl)-1-hydroxy-2-phenylethyl)-phosphonic acid diethyl ester (1b)**: IR (neat) 3200, 1245 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.35−7.21 (5H, m), 4.17−4.06 (8H, m), 3.33 (2H, t, *J* = 13.7 Hz), 1.22 (12H, m); $^{13}C$ NMR ($CDCl_3$) δ 134.6 (t, *J* = 8.3 Hz), 131.4, 129.7, 128.4, 127.8, 126.9, 75.0 (t, *J* = 151.2 Hz), 63.4 (m), 39.0, 16.3 (m); $^{31}P$ NMR ($CDCl_3$) δ 19.11 (s); MS (FAB) *m/z* (relative intensity) 395 (100), 241 (24); HRMS calcd for $C_{16}H_{29}P_2O_7$ ($MH^+$) 395.1389, found 395.1388.

**Diethyl 1-(diethoxyphosphinyl)-2-phenylethyl phosphate (2b)**: IR (neat) 1260 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.33−7.17 (5H, m), 4.91 (1H, m), 4.24−4.00 (6H, m), 3.68−2.98 (4H, m), 1.28 (9H, m), 1.05 (3H, m); $^{13}C$ NMR ($CDCl_3$) δ 136.1 (d, *J* = 12.4 Hz), 129.7, 128.4, 126.9, 74.4 (dd, *J* = 167.9, 7.1 Hz), 63.5 (m), 37.1, 16.0 (m), 16.0 (d, *J* = 6.6 Hz); $^{31}P$ NMR ($CDCl_3$) δ 19.59 (d, *J* = 17.0 Hz), −1.34 (d, *J* = 17.0 Hz); MS (FAB) *m/z* (relative intensity) 395 (100), 241 (27); HRMS calcd for $C_{16}H_{29}P_2O_7$ ($MH^+$) 395.1389, found 395.1388.

**(1-(Diethoxyphosphinyl)-1-hydroxyhexyl)phosphonic acid diethyl ester (1c)**: IR (neat) 3250, 1245 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 4.06 (8H, m), 1.83 (2H, m), 1.46 (2H, m), 1.17 (16H, m), 0.71 (3H, t, *J* = 6.8 Hz); $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 74.6 (t, *J* = 152.1 Hz), 63.2 (m), 34.2, 32.2, 22.6 (t, *J* = 5.3 Hz), 22.2, 16.2 (m), 13.8; $^{31}P$ NMR ($CDCl_3$) δ 20.63 (s); MS (FAB) *m/z* (relative intensity) 771 ($2M^+$ + Na, 16), 397 ($M^+$ + Na, 63), 375 ($MH^+$, 100), 259 (20); HRMS calcd for $C_{14}H_{33}P_2O_7$ ($MH^+$) 375.1701, found 375.1702.

**Diethyl 1-(diethoxyphosphinyl)hexyl phosphate (2c)**: IR (neat) 1260 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 4.62 (1H, m), 4.26−4.05 (8H, m), 1.90 (2H, m), 1.50 (2H, m), 1.33 (16H, m), 0.88 (3H, m); $^{13}C$ NMR ($CDCl_3$) δ 73.2 (dd, *J* = 169.6, 7.3 Hz), 62.8 (m), 31.4, 31.0 (d, *J* = 2.0 Hz), 25.0 (d, *J* = 10.4 Hz), 16.3 (m), 16.2,13.9; $^{31}P$ NMR ($CDCl_3$) δ 20.62 (d, *J* = 18.0 Hz), −0.63 (d, *J* = 18.0 Hz); MS (FAB) *m/z* (relative intensity) 375 (100), 221 (27), 165 (20); HRMS calcd for $C_{14}H_{33}P_2O_7$ ($MH^+$) 375.1702, found 375.1700.

**Hexanoic acid 1,1-bis(diethoxyphosphinyl)hexyl ester (3c)**: IR (neat) 1755, 1260 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 4.27 (8H, m), 2.37 (4H, m), 1.33 (24H, m), 0.87 (6H, m); $^{13}C$ NMR ($CDCl_3$) δ 171.3 (t, *J* = 7.5 Hz), 82.3 (t, *J* = 150.9 Hz), 63.3 (m), 34.2, 31.9, 31.7, 31.1, 24.5, 23.2 (t, *J* = 6.1 Hz), 22.2, 22.1, 16.3 (d, *J* = 2.9 Hz), 13.8, 13.7; $^{31}P$ NMR ($CDCl_3$) δ 17.34 (s); MS (FAB) *m/z* (relative intensity) 967 ($2M^+$ + Na, 8), 495 ($M^+$ + Na, 91), 473 ($MH^+$, 89), 427 (31), 375 (36), 357 (20), 329 (58), 121 (100); HRMS calcd for $C_{20}H_{43}P_2O_8$ ($MH^+$) 473.2433, found 473.2434.

**Diethyl 1-(diethoxyphospinyl)-2,2-dimethylpropyl phosphate (2d)**: IR (neat) 1260 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 4.45 (1H, dd, *J* = 11.7, 8.5 Hz), 4.27−4.06 (8H, m), 1.34 (12 H, m), 1.14 (9H, s); $^{13}C$ NMR ($CDCl_3$) δ 74.6 (dd, *J* = 150.0, 7.0 Hz), 63.6 (m), 35.1, 26.7 (d, *J* = 6.0 Hz), 16.0 (m); $^{31}P$ NMR ($CDCl_3$) δ 19.62 (d, *J* = 15.2 Hz), −0.84 (d, *J* = 15.2 Hz); MS (FAB) *m/z* (relative intensity) 361 (100), 207 (70); HRMS calcd for $C_{13}H_{31}P_2O_7$ ($MH^+$) 361.1545, found 361.1546.

**Diethyl 1-(diethoxyphosphinyl)benzyl phosphate (2e)**: IR (neat) 1260 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.48 (2H, m), 7.32 (3H, m), 5.52 (1H, dd, *J* = 13.5, 10.6 Hz), 4.13−3.81 (8H, m), 1.33−1.07 (12 H, m); $^{13}C$ NMR ($CDCl_3$) δ 133.6, 128.4 (m), 74.6 (dd, *J* = 172.0, 7.0 Hz), 63.6 (m), 16.1 (m); $^{31}P$ NMR ($CDCl_3$) δ 16.87 (d, *J* = 34.9 Hz), −0.95 (d, *J* = 34.9 Hz). MS (FAB) *m/z* (relative intensity) 381 (100), 227 (46); HRMS calcd for $C_{15}H_{27}P_2O_7$ ($MH^+$) 381.1232, found 381.1234.

**(1-Bis((benzyloxy)phosphinyl)-1-hydroxyhexyl)phosphonic acid dibenzyl ester (4a)**: IR (neat) 3250, 1245 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 7.27 (20H, m), 5.06 (8H, m), 2.10 (2H, m), 1.63 (2H, m), 1.18 (4H, m), 0.79 (3H, m); $^{13}C$ NMR ($CDCl_3$) δ 136.2 (m), 128.3 (m), 75.4 (t, *J* = 151.6 Hz), 68.8 (m), 34.5, 32.3, 22.9 (t, *J* = 5.4 Hz), 22.3, 14.0; $^{31}P$ NMR ($CDCl_3$)

(13) Pashinkin, A. P.; Gazizov, T. K.; Pudovik, A. N. *Zh. Obshch. Khim.* **1970**, *40*, 28; *Chem. Abstr.* **1970**, *72*, 100827.

(14) Terauchi, K.; Sakurai, H. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 883−890.

(15) (a) Sekine, M.; Satoh, M.; Yamagata, H.; Hata, T. *J. Org. Chem.* **1980**, *45*, 4162−4167. (b) Sekine, M.; Kume, A.; Hata, T. *Tetrahedron Lett.* **1981**, *22*, 3617−3620.

δ 21.33 (s); MS (FAB) *m/z* (relative intensity) 645 ($M^+$ + Na, 14), 623 ($MH^+$, 76), 271 (12), 181 (100) HRMS calcd for $C_{34}H_{41}P_2O_7$ ($MH^+$) 623.2328, found 623.2325.

**Dibenzyl 1-bis((benzyloxy)phosphinyl)hexyl phosphate (5a)**: IR (neat) 1265 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 4.62 (1H, m), 4.26–4.05 (8H, m), 1.90 (2H, m), 1.50 (2H, m), 1.33 (16H, m), 0.88 (3H, m); $^{13}C$ NMR ($CDCl_3$) δ 136.0 (m), 128.5 (m), 73.8 (dd, $J$ = 169.4, 7.2 Hz), 68.3 (m), 31.3, 30.9, 25.1 (d, $J$ = 10.8 Hz), 22.3, 14.0; $^{31}P$ NMR ($CDCl_3$) δ 21.13 (d, $J$ = 21.7 Hz), −0.73 (d, $J$ = 21.7 Hz); MS (FAB) *m/z* (relative intensity) 623 (100), 375 (41), 221 (12); HRMS calcd for $C_{34}H_{41}P_2O_7$ ($MH^+$) 623.2328, found 623.2326.

**(2-(Diethoxyphosphinyl)tetrahydrofuran-2-yl)phosphonic acid diethyl ester (6a)**: IR (neat) 1250 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 4.24 (8H, m), 4.01 (2H, t, $J$ = 6.6 Hz), 2.50 (2H, m), 2.06 (2H, m), 1.34 (12H, t, $J$ = 7.1 Hz); $^{13}C$ NMR ($CDCl_3$) δ 80.9 (t, $J$ = 162.2 Hz), 71.0 (t, $J$ = 3.3 Hz), 63.4 (m), 31.3, 26.5 (t, $J$ = 5.0 Hz), 16.5; $^{31}P$ NMR ($CDCl_3$) δ 20.16 (s); MS (FAB) *m/z* (relative intensity) 711 ($2M^+$ + Na, 11), 367 ($M^+$ + Na, 100), 345 ($MH^+$, 67), 229 (11), 207 (51); HRMS calcd for $C_{12}H_{27}P_2O_7$ ($MH^+$) 345.1231, found 345.1232.

**Diethyl 1-(diethoxyphosphinyl)-4-bromobutyl phosphate (7a)**: IR (neat) 1260 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 4.63 (1H, m), 4.20 (8H, m), 3.46 (2H, m), 2.10 (4H, m), 1.35 (m); $^{13}C$ NMR ($CDCl_3$) δ 72.1 (dd, $J$ = 171.4, 7.3 Hz), 64.2 (d, $J$ = 6.0 Hz), 63.0 (d, $J$ = 6.5 Hz), 32.8, 29.7, 28.3 (d, $J$ = 10.5 Hz), 16.2 (m); $^{31}P$ NMR ($CDCl_3$) δ 19.54 (d, $J$ = 22.6 Hz), −0.78 (d, $J$ = 22.6 Hz); MS (FAB) *m/z* (relative intensity) 425 ($MH^+$, 100), 345 (22), 273 (16), 271 (16); HRMS calcd for $C_{12}H_{28}P_2BrO_7$ ($MH^+$) 425.0495, found 425.0494.

**(2-Bis((benzyloxy)phosphinyl)tetrahydrofuran-2-yl)-phosphonic acid dibenzyl ester (6b)**: IR (neat) 1250 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.26 (20H, m), 5.06 (8H, m), 3.97 (2H, t, $J$ = 6.6 Hz), 2.53 (2H, m), 1.98 (2H, m); $^{13}C$ NMR ($CDCl_3$) δ 136.3 (d, $J$ = 9.8 Hz), 128.3 (m), 81.3 (t, $J$ = 162.4 Hz), 71.4 (t, $J$ = 2.3 Hz), 68.7 (m), 31.5; $^{31}P$ NMR ($CDCl_3$) δ 20.36 (s); MS (FAB) *m/z* (relative intensity) 593 (96), 331 (16), 241 (55), 181 (100); HRMS calcd for $C_{32}H_{35}P_2O_7$ ($MH^+$) 593.1858, found 593.1859.

**Dibenzyl 1-bis((benzyloxy)phosphinyl)-4-bromobutyl phosphate (7b)**: IR (neat) 1260 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.27 (20H, m), 5.02 (8H, m), 4.71 (1H, m), 4.20 (8H, m), 3.39 (2H, m), 2.00 (4H, m); $^{13}C$ NMR ($CDCl_3$) 135.6 (m), 128.6 (m), 72.8 (dd, $J$ = 171.3, 7.3 Hz), 68.4 (m), 32.7, 29.6, 28.3 (d, $J$ = 10.9 Hz); $^{31}P$ NMR ($CDCl_3$) δ 20.23 (d, $J$ = 22.4 Hz), −0.70 (d, $J$ = 22.4 Hz); MS (FAB) *m/z* (relative intensity) 675 (54), 673 (51), 181 (100); HRMS calcd for $C_{32}H_{36}P_2BrO_7$ ($MH^+$) 593.1858, found 593.1859.

**Diethyl 1-(diethoxyphosphinyl)ethenyl phosphate (8a)**: IR (neat) 1620, 1270, 1220 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 5.78 (2H, m), 4.14 (8H, m), 1.32 (12H, m); $^{13}C$ NMR ($CDCl_3$) 145.9 (dd, $J$ = 229.7, 10.7 Hz), 114.6 (dd, $J$ = 24.6, 3.8 Hz), 64.7 (d, $J$ = 6.2 Hz), 62.9 (d, $J$ = 5.3 Hz), 16.1 (d, $J$ = 6.3 Hz), 15.9 (d, $J$ = 6.7 Hz); $^{31}P$ NMR ($CDCl_3$) δ 7.29 (d, $J$ = 27.4 Hz), −6.34 (d, $J$ = 27.4 Hz); MS (FAB) *m/z* (relative intensity) 317 (100), 187 (9); HRMS calcd for $C_{10}H_{23}P_2O_7$ ($MH^+$) 317.0919, found 317. 0919.

**Dibenzyl 1-bis((benzyloxy)phosphinyl)ethenyl phosphate (8b)**: IR (neat) 1620, 1275, 1220 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.29 (20H, m), 5.82 (2H, m), 5.00 (8H, m); $^{13}C$ NMR ($CDCl_3$) 144.6 (dd, $J$ = 232.3, 10.8 Hz), 114.6 (dd, $J$ = 24.6, 3.8 Hz), 64.7 (d, $J$ = 6.2 Hz), 62.9 (d, $J$ = 5.3 Hz), 16.1 (d, $J$ = 6.3 Hz), 15.9 (d, $J$ = 6.7 Hz); $^{31}P$ NMR ($CDCl_3$) δ 7.68 (d, $J$ = 26.9 Hz), −6.38 (d, $J$ = 26.9 Hz); MS (FAB) *m/z* (relative intensity) 565 (75), 375 (10), 313 (10), 181 (100); HRMS calcd for $C_{30}H_{31}P_2O_7$ ($MH^+$) 565.1545, found 565. 1544.

**Diethyl 1-(diethoxyphosphinyl)-3-chloro-2,2-dimethylpropyl phosphate (9)**: IR (neat) 1260 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 4.71 (1H, dd, $J$ = 11.7, 9.2 Hz), 4.17 (8H, m), 3.59 (2H, m), 1.30 (12H, m), 1.19, 1.17 (6H, 2s); $^{13}C$ NMR ($CDCl_3$) 76.8 (dd, $J$ = 164.9, 8.1 Hz), 64.0 (m), 52.9 (d, $J$ = 9.5 Hz), 39.8 (m), 22.2 (m), 16.4 (m), 16.1 (m); $^{31}P$ NMR ($CDCl_3$) δ 18.75 (d, $J$ = 13.7 Hz), −1.22 (d, $J$ = 13.7 Hz); MS (FAB) *m/z* (relative intensity) 397 (41), 395 (100), 304 (7), 241 (33); HRMS calcd for $C_{13}H_{30}P_2ClO_7$ ($MH^+$) 395.1156, found 395.1155.

**Diethyl 1-(diethoxyphosphinyl)-2,2-dimethylcyclopropyl phosphate (10)**: IR (neat) 1250 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 4.25, 4.10 (8H, 2m), 1.30 (20H, m); $^{13}C$ NMR ($CDCl_3$) 62.8 (dd, $J$ = 175.1, 9.3 Hz), 62.1 (m), 24.6 (br. s), 22.9 (br. s), 21.1 (br. s), 20.8, 16.2 (m); $^{31}P$ NMR ($CDCl_3$) δ 20.66 (d, $J$ = 4.2 Hz), −2.97 (d, $J$ = 4.2 Hz); MS (FAB) *m/z* (relative intensity) 359 (81), 181 (100); HRMS calcd for $C_{13}H_{29}P_2O_7$ ($MH^+$) 359.1388, found 359.1389.

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**Supporting Information Available:** $^1H$, $^{13}C$, and $^{31}P$ NMR spectra for all compounds (61 pages). This material is contained in librairies 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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