Preparation of New Wittig Reagents and Their Application to the Synthesis of α,β-Unsaturated Phosphonates

Yibo Xu, Michael T. Flavin, and Ze-Qi Xu*

MediChem Research, Inc., 12305 South New Avenue, Lemont, Illinois 60439

Received May 6, 1996[⊗]

The Wittig reagent [(diethoxyphosphinyl)methylidene]triphenylphosphorane (**1b**) has been successfully synthesized for the first time *via* its phosphonium triflate salt (**4a**), by treating (diethoxyphosphinyl)methyl triflate with triphenylphosphine. The procedure has been applied to the synthesis of other phosphoranes and phosphonium salts. The new Wittig reagents thus synthesized were treated with various aldehydes and an activated ketone, affording the corresponding α,β-unsaturated phosphonates. Triphenylphosphorane **1b** and triphenylphosphonium **4a** led to both *cis* and *trans* isomers with the latter being predominant, while *trans* isomers were almost exclusively formed when tributyl reagents (**1c** and **4d**) were used.

Phosphonic acids have been frequently used as suitable isosteric and isoelectronic replacements for biologically important phosphates such as nucleotides, phospholipids, nucleoside polyphosphates, and sugar phosphates.[1,2] Also, phosphonic acids containing an amino group in the α-, β-, or γ-position have attracted considerable interest as replacements for natural amino acids.[3,4] These phosphonic acid analogues can exert their biological activity as regulators, mediators, or enzyme inhibitors.[1−4] In addition, phosphonates have found wide application in general organic synthesis.[5−7] For example, phosphonate-stabilized carbanions undergo Horner−Wadsworth−Emmons condensation with aldehydes and ketones to afford olefins;[5,6] vinyl phosphonates have been used in Diels−Alder reactions and Michael additions, and they are also versatile intermediates for the synthesis of hetero- and carbocyclic compounds.[7]

Numerous methods have been reported in the literature for the synthesis of phosphonates, the best known of which are the Arbuzov and Michaelis−Becker reactions.[8] The Wittig reagent, [(diphenoxyphosphinyl)-methylidene]triphenylphosphorane (**1a**), developed by Moffatt et al. in 1968,[9] has been applied to the synthesis of various diphenyl phosphonates.[5,6,10−15] However, the subsequent removal of the phenyl groups is difficult and requires either transesterification of the diphenyl ester into the dibenzyl ester followed by hydrogenolysis or alkaline hydrolysis to remove one phenyl group followed by enzymatic treatment with *Crotalus atrox* phosphodiesterase to remove the second one.[10−15] Tetraethyl methylenebis(phosphonate) (**2**) has been used in Horner−Wadsworth−Emmons condensations to provide diethyl phosphonates,[5,6] which can be readily hydrolyzed by using Me_3SiBr. Strongly basic reagents are generally required for such condensations and, therefore, may not be suitable for base-sensitive aldehydes and ketones, resulting in poor yield and the formation of side products.[16]

As part of our research program, it has been of interest to prepare phosphonate esters under less basic conditions and execute the subsequent hydrolysis under mild conditions. One reagent which meets such requirements is [(diethoxyphosphinyl)methylidene]triphenylphosphorane (**1b**). Moffat et al. attempted to prepare the reagent **1b** by reaction of triphenylphosphine with diethyl (iodomethyl)phosphonate, but were not successful.[9] Even though **1b** has been mentioned in review articles concerning the Wittig reaction,[5,6] reference to Moffat's paper[9] for synthesis and reactions of **1b** has always been made.

$(RO)_2P(O)CH{=}PPh_3$ $(EtO)_2P(O)CH_2P(O)(OEt)_2$

1a, R = Ph **2**

b, R = Et

Trifluoromethanesulfonate (triflate) is an excellent leaving group and has been widely used in organic synthesis.[17] Since (diethoxyphosphinyl)methyl triflate (**3a**) has been synthesized and demonstrated to react with nucleophiles,[18] it was anticipated that **3a** would readily react with triphenylphosphine to form the phosphonium triflate salt **4a**, which, in turn, would yield the ylide **1b** after treatment with a base. Herein, we would like to communicate our method for preparation of **4a** and **1b** and their analogues, as well as their application to the synthesis of α,β-unsaturated phosphonates.

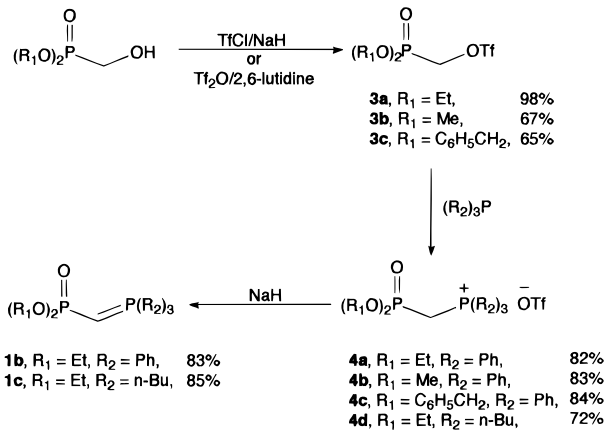
Two methods have been published for the synthesis of (diethoxyphosphinyl)methyl triflate (**3a**) from diethyl (hydroxymethyl)phosphonate, one of which used triflic

[⊗] Abstract published in *Advance ACS Abstracts,* October 1, 1996.

(1) Engel, R. *Chem. Rev.* **1977**, *77*, 349.
(2) Klachburn, G. M.; Perree, T. D.; Rashid, A.; Bisbal, C.; Lebleu, B. *Chem. Scr.* **1986**, *26*, 21.
(3) Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *63*, 193.
(4) O'Donnell, M. J.; Lawley, L. K.; Pushpavanam, P. B.; Burger, A.; Bordwell, F. G.; Zhang, X.-M. *Tetrahedron Lett.* **1994**, *35*, 6421 and references cited therein.
(5) Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73.
(6) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.
(7) Minami, T.; Motoyoshiya, J. *Synthesis* **1992**, 333.
(8) Bhattacharya, A.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415.
(9) Jones, G. H.; Hamamura, E. K.; Moffatt, J. G. *Tetrahedron Lett.* **1968**, 5731.
(10) Jones, G. H.; Moffatt, J. G. *J. Am. Chem. Soc.* **1968**, *90*, 5337.
(11) Fuertes, M.; Witkowski, J. T.; Streeter, D. G.; Robins, R. K. *J. Med. Chem.* **1974**, *17*, 642.
(12) Kappler, F.; Hai, T. T.; Cotter, R. J.; Hyver, K. J.; Hampton, A. *J. Med. Chem.* **1986**, *29*, 1030.
(13) Martin, J. C.; Verheyden, J. P. H. *Nucleosides Nucleotides* **1988**, *7*, 365.
(14) Secrist, J. A., III; Riggs, R. M.; Comber, R. N.; Montgomery, J. A. *Nucleosides Nucleotides* **1992**, *11*, 947.
(15) Freeman, G. A.; Rideout, J. L.; Miller, W. H.; Reardon, J. E. *J. Med. Chem.* **1992**, *35*, 3192.
(16) Gupta, A.; Sacks, K.; Khan, S.; Tropp, B. E.; Engel, R. *Synth. Commun.* **1980**, *10*, 299.
(17) Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85.
(18) Phillion, D. P.; Andrew, S. S. *Tetrahedron Lett.* **1986**, *27*, 1477.

S0022-3263(96)00827-4 CCC: $12.00

Scheme 1



chloride in the presence of sodium hydride,[18] while the other employed triflic anhydride and lutidine.[19] The second procedure was chosen for the preparation of **3a** because triflic anhydride is less volatile than triflic chloride and, thus, is relatively easier to handle. (Dimethoxyphosphinyl)methyl and [bis(benzyloxy)phosphinyl]methyl triflate (**3b** and **3c**) were also prepared by the same procedure from the corresponding hydroxyl compounds (Scheme 1).

As designed, all the triflates (**3a**−**c**) reacted readily with triphenylphosphine in CH_2Cl_2 at rt to afford phosphonium triflate salts **4a**−**c** in ca. 80% yield (Scheme 1). Tributylphosphine has also been demonstrated to react with **3a**, leading to the formation of **4d**. Not surprisingly, (diethoxyphosphinyl)methyl tosylate[20,21] failed to react with triphenylphosphine.

Treatment of **4a** with aqueous NaOH led only to the isolation of triphenylphosphine oxide; however, treatment of **4a** and **4d** with sodium hydride in THF followed by nonaqueous workup afforded the desired ylides **1b** and **1c** (Scheme 1). All the phosphonium triflate salts (**4a**−**d**), as well as the ylides (**1b** and **1c**), yielded satisfactory analytical and spectral data and were determined to be stable upon storage at rt.

The triphenylphosphonium triflate salt **4a** and ylide **1b** both proved to react smoothly with a variety of aromatic and aliphatic aldehydes at about 100 °C to generate α,*β*-unsaturated phosphonates (**5a**−**f**). These results are presented in Table 1. In the reactions with triphenylphosphonium triflate salt **4a**, triethylamine was added as a base and ylide **1b** was assumed to be generated *in situ*. As expected, electron-withdrawing groups accelerated the reaction and electron-donating substituents slowed the reaction (entries 2 and 6, Table 1).

In contrast to the reaction of diphenyl phosphonate ylide **1a**, in which only *trans* α,*β*-unsaturated phosphonates were observed,[9] a mixture of *cis* and *trans* isomers were formed with both phosphonium triflate salt **4a** and ylide **1b**, and the ratios of *trans*/*cis* varied from 60:40 to 80:20. However, when suitably protected nucleoside aldehydes such as the 2′,3′-isopropylideneadenosine derivative[10] were treated with ylide **1b** at rt, only *trans* isomer **6** was formed (Scheme 2). This result was similar to that observed for the diphenyl phosphonate ylide **1a**.[10] Similarly, tributylphosphonium triflate salt **4d** and the corresponding ylide **1c** also reacted with aldehydes (entries 4 and 5, Table 1), but they appeared to be more reactive when compared with **4a** and **1b**, thereby requiring mild reaction conditions and resulting in formation of a higher percentage of *trans* isomer. For example, in the reaction of tributylphosphorane **1c** with 4-chlorobenzaldehyde (entry 5, Table 1), the *trans* isomer of **5b** was exclusively produced.

Reaction with ordinary ketones such as acetophenone was very slow under similar conditions with both phosphonium triflate salts (**4a** and **4d**) and ylides (**1b** and **1c**). However, activated ketones such as 4-chloro-2,2,2-trifluoroacetophenone reacted with both phosphonium triflate salts (**4a** and **4d**) to afford the corresponding α,*β*-unsaturated phosphonate **5g**, with the two isomers being formed in approximately a 75:25 ratio (entries 11 and 12, Table 1).

The structural assignments of the *trans* and *cis* isomers of **5a**−**f** were made by analysis of ^{1}H NMR data. It is well established that the coupling constants between the olefinic protons and phosphorus in α,*β*-unsaturated phosphonates are within the following ranges: $J_{cis-H,H} = 8-15$ Hz, $J_{trans-H,H} = 14-18$ Hz, $J_{cis-H,P} = 10-30$ Hz, $J_{trans-H,P} = 30-50$ Hz, and $J_{gem-H,P} = 12-20$ Hz.[22-24] In the cases of **5a**−**c**, the signals due to the olefinic protons *β* to phosphorus overlapped with the phenolic protons, while the olefinic protons α to phosphorus had $J_{cis-H,H} = J_{gem-H,P}$ = ca. 15 Hz and $J_{trans-H,H} = J_{gem-H,P} = 17-18$ Hz.

For compound **5d**, derived from *trans*-cinnamaldehyde, the two isomers (*trans* and *cis* in terms of the newly formed double bond) were separated by silica gel column chromatography and the *cis* isomer was unambiguously assigned due to its $J_{trans-H,P} = 50.7$ Hz, and hence $J_{cis-H,H}$ being 12.5 Hz and $J_{gem-H,P}$ being 17.4 Hz. Also, the two olefinic protons for both isomers of **5f** were clearly assigned, since there was no interference with the phenolic protons. Thus, $J_{cis-H,H} = 13.0$ Hz, $J_{trans-H,P} = 53.0$ Hz, and $J_{gem-H,P} = 19.9$ Hz were observed for the *cis* isomer, while $J_{trans-H,H} = 17.1$ Hz, $J_{cis-H,P} = 22.0$ Hz, and $J_{gem-H,P} = 21.2$ Hz were found for the *trans* isomer.

Interestingly, compound **5e**, the pure *trans* isomer, was the double-bond-migrated product, in which the double bond was conjugated with the phenyl ring (*β*,*γ*-unsaturated phosphonate), instead of the normal α,*β*-unsaturated phosphonate. It might be hypothesized that the latter compound was originally formed in the reaction but then rearranged to **5e** under the reaction conditions (Scheme 3), suggesting that **5e** is more thermodynamically stable. In the ^{1}H NMR spectrum of **5e**, neither geminal nor vicinal coupling between the two olefinic protons and phosphorus was observed. Instead, only long-range coupling of the two olefinic protons from phosphorus was recorded, with the *J* values being 7.2 and 5.1 Hz, respectively. However, a typical geminal splitting by phosphorus was observed for the methylene group ($J_{gem-H,P}$ = 22.2 Hz in ^{1}H NMR and $^1J_{C,P} = 140.9$ Hz in ^{13}C NMR), confirming that the CH_2 group was attached to phosphorus. Hydrogenation of **5e** led to the saturated phosphonate **7a** (Scheme 3).

The resulting α,*β*-unsaturated phosphonate esters (**5a**−**d**,**f**) can be hydrogenated to afford the saturated phosphonate esters or be easily hydrolyzed by Me_3SiBr

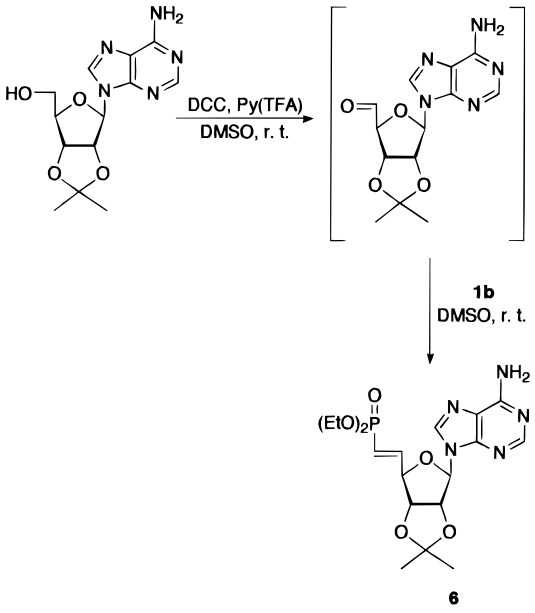
(19) Creary, X.; Underiner, T. L. *J. Org. Chem.* **1985**, *50*, 2165.
(20) Holy, A.; Rosenberg, I. *Collect. Czech. Chem. Commun.* **1982**, *47*, 3447.
(21) Krecmerova, M.; Hrebabecky, H.; Holy, A. *Collect. Czech. Chem. Commun.* **1990**, *55*, 2521.
(22) Kenyon, G. L.; Westheimer, F. H. *J. Am. Chem. Soc.* **1966**, *88*, 3557.
(23) Petrov, A. A.; Ionin, B. I.; Ignatyev, V. M. *Tetrahedron Lett.* **1968**, 15.
(24) Tavs, P.; Weitkamp, H. *Tetrahedron* **1970**, *26*, 5529.

Table 1. Reaction of Phosphonium Triflate Salts and Ylides with Carbonyl Compounds[a]

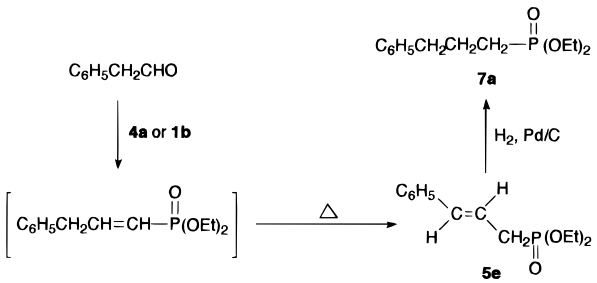
entry no.	Wittig reagents	aldehyde	time (h)	yield[b] (%)	product (*trans*:*cis*[c])
1	**4a**	PhCHO	20	75	PhCH=CHP(O)(OEt)$_2$ (**5a**) (70:30)
2	**4a**	4-ClC$_6$H$_4$CHO	18	78	4-ClC$_6$H$_4$CH=CHP(O)(OEt)$_2$ (**5b**) (70:30)
3	**1b**	4-ClC$_6$H$_4$CHO	4	68	**5b** (86:14)
4	**4d**	4-ClC$_6$H$_4$CHO	6	72	**5b** (96:4)
5	**1c**	4-ClC$_6$H$_4$CHO	6	78	**5b** (100:0)
6	**4a**	4-MeOC$_6$H$_4$CHO	40	50	4-MeOC$_6$H$_4$CH=CHP(O)(OEt)$_2$ (**5c**) (80:20)
7	**4a**	*trans*-PhCH=CHCHO	20	57[d]	PhCH=CHCH=CHP(O)(OEt)$_2$ (**5d**) (60:40)
8	**4a**	PhCH$_2$CHO	6	78	PhCH=CHCH$_2$P(O)(OEt)$_2$ (**5e**) (100:0)
9	**1b**	PhCH$_2$CHO	4	68	**5e** (100:0)
10	**4a**	CH$_3$(CH$_2$)$_3$CHO	6	31[e]	CH$_3$(CH$_2$)$_3$CH=CHP(O)(OEt)$_2$ (**5f**) (75:25)
11	**4a**	4-ClC$_6$H$_4$COCF$_3$	20	34	4-ClC$_6$H$_4$C(CF$_3$)=CHP(O)(OEt)$_2$ (**5g**) (75:25)[f]
12	**4d**	4-ClC$_6$H$_4$COCF$_3$	16	34	**5g** (75:25)[f]

[a] See the Experimental Section for detailed reaction conditions. [b] In all the reactions, the starting aldehydes had not been completely consumed and were recovered. [c] The isomers refer to the newly formed double bond and were determined by ^{1}H NMR. [d] The two isomers (*trans* and *cis*) were separated by silica gel column chromatography, and the yield was the combined one. [e] Some products might be lost during the purification. [f] The ratio was *Z*/*E* isomers.

Scheme 2



Scheme 3



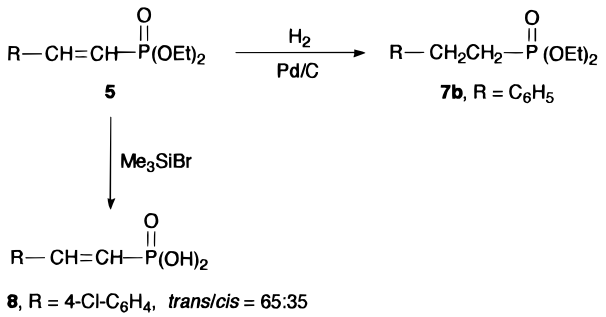
to the corresponding phosphonic acids, examples of which are depicted in Scheme 4. The phosphonic acid **8** was a mixture of *trans* and *cis* isomers, and the ratio was determined to be ca. 65:35 by ^{1}H NMR, which was very similar to that of the starting ester **5b** (70:30).

In conclusion, various phosphonate Wittig reagents have been successfully synthesized and demonstrated to react with aldehydes and activated ketones under mild conditions. These reagents will find general application to the synthesis of α,β-unsaturated as well as saturated phosphonates and the corresponding phosphonic acids.

Experimental Section

Chemical shifts are reported in parts per million (δ ppm) downfield from TMS, which was used as an internal standard.

Scheme 4



Analytical TLC was carried out on precoated plates (silica gel 60 F_{254} from EM Science), and components were visualized with UV light and/or stained with iodine. Column chromatography was performed with silica gel 60 (70−230 mesh from EM Science). All chemical reagents and anhydrous solvents were purchased from Aldrich Chemical Co.

General Procedures for Synthesis of (Dialkoxyphosphinyl)methyl Triflates 3a−c. To a stirred solution of dialkyl (hydroxymethyl)phosphonate (30.6 mmol) and 2,6-lutidine (37.6 mmol) in anhydrous CH_2Cl_2 (50 mL) at −50 °C under N_2 was added trifluoromethanesulfonic anhydride (35.5 mmol) dropwise. The resulting mixture was allowed to warm to 0 °C over a period of 1.5 h, whereupon the dark brown solution was diluted with ether (300 mL). The precipitates formed were removed by filtration. The ethereal solution was successively washed with water, 1 N HCl, and brine and then dried over Na_2SO_4. After concentration, a yellow oil was obtained, which was used in the next step without further purification.

(Diethoxyphosphinyl)methyl triflate (3a):[18] 9.0 g (98% yield); ^{1}H NMR ($CDCl_3$) δ 1.39 (t, J = 7.1 Hz, 6 H), 4.27−4.24 (m, 4 H), 4.64 (d, J = 8.8 Hz, 2 H).

(Dimethoxyphosphinyl)methyl triflate (3b): 4.9 g (67% yield). ^{1}H NMR ($CDCl_3$) δ 3.89 (d, J = 8.3 Hz, 6 H), 4.65 (d, J = 8.8 Hz, 2 H).

[Bis(benzyloxy)phosphinyl]methyl triflate (3c): 8.3 g (65% yield); ^{1}H NMR ($CDCl_3$) δ 4.45 (d, J = 9.0 Hz, 2 H), 5.10 (m, 4 H), 7.34−7.39 (m, 10 H).

General Procedure for Synthesis of [(Dialkoxyphosphinyl)methyl]triphenylphosphonium Triflates 4a−c: To a stirred solution of triphenylphosphine (34.4 mmol) in anhydrous CH_2Cl_2 (50 mL) was added (dialkoxyphosphinyl)-methyl triflate (**3a−c**) (30 mmol) in anhydrous CH_2Cl_2 (15 mL) dropwise at 0 °C under N_2. The mixture was allowed to warm to rt and then stirred overnight (~16 h). The solvent was removed under reduced pressure to about one-third of the volume and the remaining oil triturated with ether (200 mL). A white solid was formed and collected by filtration. After being washed with ether (50 mL × 2), [(dialkoxyphosphinyl)-methyl]triphenylphosphonium triflates (**4a−c**) were obtained as white solids. The analytical samples were obtained by recrystallization from ethyl acetate/hexane.

[(Diethoxyphosphinyl)methyl]triphenylphosphonium triflate (4a): 13.7 g (82% yield). mp 98−100 °C; ^{1}H NMR ($CDCl_3$) δ 1.16 (t, J = 7.1 Hz, 6 H), 3.90−4.10 (m, 4 H), 4.20 (dd, J = 19.6, 16.1 Hz, 2 H), 7.65−7.90 (m, 15 H); MS (CI) 414 (26.1, M − CF_3SO_3H + 2), 413 (100, M − CF_3SO_3H + 1), 367 (26.1, M − CF_3SO_3H-C_2H_5O); IR (KBr, cm^{-1}) 1589, 1443, 1277, 1154, 1032. Anal. Calcd for $C_{24}H_{27}F_3O_6P_2S$: C, 51.25; H, 4.84; P, 11.01; S, 5.70. Found: C, 50.89; H, 4.84; P, 10.67; S, 6.38.

[(Dimethoxyphosphinyl)methyl]triphenylphosphonium triflate (4b): 13.3 g (83% yield); mp 149−151 °C; ^{1}H NMR ($CDCl_3$) δ 3.62 (d, J = 11.6 Hz, 6 H), 4.26 (dd, J = 19.9, 16.1 Hz, 2 H), 7.65−7.88 (m, 15 H); IR (KBr, cm^{-1}) 1589, 1443, 1273, 1154, 1038; MS (CI) 386 (21.7, M − CF_3SO_3H+2), 385 (100, M − CF_3SO_3H + 1), 353 (35.7, M − CF_3SO_3H − CH_3O). Anal. Calcd for $C_{22}H_{23}F_3O_6P_2S$: C, 49.44; H, 4.34; P, 11.59; S, 6.00. Found: C, 49.06; H, 4.23; P, 11.29; S, 6.19.

[[Bis(benzyloxy)phosphinyl]methyl]triphenylphosphonium triflate (4c): 17.3 g (84% yield); mp 78−81 °C; ^{1}H NMR ($CDCl_3$) δ 4.30 (dd, J = 20.1, 16.1 Hz, 2 H), 4.88 (m, 4 H), 7.17−7.79 (m, 25 H); IR (KBr, cm^{-1}) 1732, 1589, 1439, 1366, 1275, 1217, 1155, 1034; MS (FAB) 537 (100, M − CF_3SO_3H + 1). Anal. Calcd for $C_{34}H_{31}F_3O_6P_2S$: C, 59.48; H, 4.55; P, 9.02; S, 4.67. Found: C, 59.48; H, 4.53; P, 8.59; S, 4.87.

[(Diethoxyphosphinyl)methyl]tributylphosphonium Triflate (4d). The compound **4d** was synthesized by a procedure similar to that described above. Tri-*n*-butylphosphine, instead of triphenylphosphine, was used. From 1 g (33.3 mmol) of **3a** and 0.8 g (40 mmol) of tri-*n*-butylphosphine was obtained 1.1 g (72% yield) of a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.98 (t, J = 7.0 Hz, 9 H), 1.38 (t, J = 7.0 Hz, 6 H), 1.52 (m, 12 H), 2.37 (m, 6 H), 3.09 (dd, J = 19.5, 15.7 Hz, 2 H), 4.21 (apparent quintet, J = 7.2 Hz, 4 H); IR (KBr, cm^{-1}) 1467, 1395, 1262, 1155, 1022; MS(CI) 354 (30.2, M − CF_3SO_3H + 2), 353 (100, M − CF_3SO_3H + 1).

[(Diethoxyphosphinyl)methylidene]triphenylphosphorane (1b). To a stirred suspension of NaH (50 mg, 1.25 mmol, washed with hexane) in anhydrous THF (2 mL) was added triphenylphosphonium triflate salt **4a** (300 mg, 0.53 mmol) in anhydrous THF (2 mL) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 0.5 h. The solvent was then removed at reduced pressure and the residue extracted with anhydrous CH_2Cl_2. After concentration of the extracts, a colorless oil was obtained, which was then triturated with hexane to yield an off-white solid (180 mg, 83% yield). An analytical sample was obtained by repetitive trituration with hexane: mp 73−75 °C; ^{1}H NMR ($CDCl_3$) δ 1.12 (t, J = 7.1 Hz, 6 H), 1.27 (d, J = 7.5 Hz, 1 H), 3.86 (apparent quintet, J = 10.5 Hz, 4 H), 7.40−7.74 (m, 15 H); MS (CI) 414 (27.2, M + 2), 413 (100, M + 1), 412 (32.9, M$^+$), 367 (38.9, M − C_2H_5O); IR (KBr, cm^{-1}) 1587, 1483, 1433, 1204, 1101, 976. Anal. Calcd for $C_{23}H_{26}O_3P_2$: C, 66.99; H, 6.35; P, 15.02. Found: C, 67.25; H, 6.57; P, 14.75.

[(Diethoxyphosphinyl)methylidene]tributylphosphorane (1c). The procedure used for preparation of **1b** decribed above was followed for synthesis of **1c**. Thus, from tributylphosphonium triflate salt **4d** (100 mg, 0.20 mmol) and NaH (20 mg, 0.40 mmol, washed with hexane) in anhydrous THF (2 mL) was obtained 60 mg (85% yield) of crude product, which was used in the reaction with aldehydes without further purification: ^{1}H NMR ($CDCl_3$) δ 0.93 (t, J = 7.0 Hz, 9 H), 1.30 (m, 7 H), 1.38 (m, 12 H), 1.78 (m, 6 H), 4.21 (m, 4 H).

General Procedures for Synthesis of α,β-Unsaturated Phosphonates. Procedure A: Using Phosphonium Triflate Salt 4a or 4d. To a stirred solution of aldehyde (1.20 mmol) in anhydrous toluene (5 mL) and DMF (1 mL) was added [(diethoxyphosphinyl)methyl]triphenylphosphonium triflate (**4a**) or **4d** (1.80 mmol) at rt under N_2, followed by addition of triethylamine (7.20 mmol). The resulting mixture was slowly heated to 100 °C (for **4a**) and 70 °C (for **4d**). The reaction was monitored by TLC analysis. After the mixture was stirred at that temperature for a period of time indicated in Table 1, the solvents were removed under reduced pressure and the residue was chromatographed on a silica gel column, eluting with ethyl acetate/hexane (1:1) to afford the product. The ratio of *cis* and *trans* isomers was determined by ^{1}H NMR.

Procedure B: Using Ylide 1b or 1c. The reaction was carried out using a procedure similar to that described above. However, toluene was used as the solvent without addition of triethylamine.

Diethyl (2-phenylethenyl)phosphonate (5a): colorless liquid; ^{1}H NMR ($CDCl_3$) δ for *cis* isomer (minor) 1.18 (t, J = 7.1 Hz, 6 H), 4.00 (apparent quintet, J = 7.2 Hz, 4 H), 5.81 (dd, J = 15.8, 12.3 Hz, 1 H), 7.15−7.75 (m, 6 H); δ for *trans* isomer (major)[25] 1.36 (t, J = 7.1 Hz, 6 H), 4.14 (apparent quintet, J = 7.3 Hz, 4 H), 6.26 (apparent t, J = 17.5 Hz, 1 H), 7.15−7.75 (m, 6 H); IR (neat, cm^{-1}) 1617, 1246, 1053, 1028; MS (CI) 242 (12.0, M + 2), 241 (100, M$^+$).

Diethyl [2-(4-chlorophenyl)ethenyl]phosphonate (5b): colorless liquid; ^{1}H NMR ($CDCl_3$) δ for *cis* isomer (minor) 1.20 (t, J = 7.0 Hz, 6 H), 4.00 (apparent quintet, J = 7.1 Hz, 4 H), 5.81 (apparent t, J = 15.2 Hz, 1 H), 7.10−7.65 (m, 5 H); δ for *trans* isomer (major) 1.34 (t, J = 7.2 Hz, 6 H), 4.12 (apparent quintet, J = 7.0 Hz, 4 H), 6.22 (apparent t, J = 17.3 Hz, 1 H), 7.10−7.65 (m, 5 H); IR (neat, cm^{-1}) 1618, 1246, 1053, 1028; MS (CI) 277 and 275 (31.4, 100, M + 1), 276 and 274 (4.8, 13.4, M$^+$).

Diethyl [2-(4-methoxyphenyl)ethenyl]phosphonate (5c): colorless liquid; ^{1}H NMR ($CDCl_3$) δ for *cis* isomer (minor) 1.23 (t, J = 7.1 Hz, 6 H), 3.83 (s, 3 H), 4.03 (apparent quintet, J = 7.3 Hz, 4 H), 5.65 (apparent t, J = 14.9 Hz, 1 H), 6.90−7.55 (m, 5 H); δ for *trans* isomer (major)[22] 1.35 (t, J = 7.1 Hz, 6 H), 3.83 (s, 3 H), 4.13 (apparent quintet, J = 7.1 Hz, 4 H), 6.09 (apparent t, J = 18.2 Hz, 1 H), 6.90−7.55 (m, 5); IR (neat, cm^{-1}) 1605, 1258, 1175, 1030; MS (CI) 272 (26.2, M + 2), 271 (100, M + 1), 270 (19.0, M$^+$).

Diethyl (1,2-*cis*-3,4-*trans*-4-phenylbuta-1,3-dienyl)phosphonate (*cis*-5d): pale yellow liquid; ^{1}H NMR ($CDCl_3$) δ 1.36 (t, J = 7.1 Hz, 6 H), 4.13 (apparent quintet, J = 7.1 Hz, 4 H), 5.58 (dd, J = 17.4, 12.5 Hz, 1 H), 6.78 (d, J = 15.4 Hz, 1 H), 7.02 (dt, J = 50.7, 12.2 Hz, 1 H), 7.3−7.5 (m, 5 H), 7.82 (ddt, J = 15.0, 11.9, 1.5 Hz, 1 H); UV (MeOH) λ_{max} 297 (38,800) nm; IR (neat, cm^{-1}) 1626, 1584, 1244, 1051, 1026; MS (CI) 268 (18.8, M + 2), 267 (100, M + 1), 266 (9.0, M$^+$).

Diethyl (1,2:3,4-*trans*,*trans*-4-phenylbuta-1,3-dienyl)-phosphonate (*trans*-5d): pale yellow liquid; ^{1}H NMR ($CDCl_3$) δ 1.35 (t, J = 7.1 Hz, 6 H), 4.12 (apparent quintet, J = 7.2 Hz, 4 H), 5.80 (dd, J = 18.9, 16.7 Hz, 1 H), 6.84 (m, 2 H), 7.16−7.46 (m, 6 H); UV (MeOH) λ_{max} 294 (43,400) nm; IR (neat, cm^{-1}) 1626, 1589, 1244, 1054, 1022; MS (CI) 268 (34.2, M + 2), 267 (100, M + 1), 266 (29.1, M$^+$).

Diethyl (*trans*-3-phenyl-2-propenyl)phosphonate (5e): colorless liquid; ^{1}H NMR ($CDCl_3$) δ 1.32 (t, J = 7.1 Hz, 6 H), 2.77 (ddd, J = 22.2, 7.6, 1.1 Hz, 2 H,), 4.12 (apparent quintet, J = 7.3 Hz, 4 H), 6.15 (apparent dq, J = 14.9, 7.2 Hz, 1 H), 6.53 (dd, J = 15.8, 5.1 Hz, 1 H), 7.22−7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 16.3 (d, $^3J_{C,P}$ = 5.7 Hz), 31.0 (d, $^1J_{C,P}$ = 140.9 Hz), 62.0 (d, $^2J_{C,P}$ = 6.9 Hz), 118.8 (d, $^2J_{C,P}$ = 12.6 Hz), 127.6 and 128.6 (2 s), 134.7 (d, $^3J_{C,P}$ = 14.9 Hz), 136.9 (d, $^4J_{C,P}$ = 3.4 Hz); IR (neat, cm^{-1}) 1651, 1599, 1250, 1024; MS (CI) 256 (13.7, M + 2), 255 (100, M + 1), 254 (29.1, M$^+$).

Diethyl 1-hexenylphosphonate (5f): colorless liquid; ^{1}H NMR ($CDCl_3$) δ for *cis* isomer (minor) 0.91 (t, J = 7.0 Hz, 3 H), 1.31 (t, J = 7.1 Hz, 6 H), 1.24−1.45 (m, 4 H), 2.52 (m, 2 H), 4.07 (apparent quintet, J = 7.3 Hz, 4 H), 5.58 (dd, J = 19.9, 13.0 Hz, 1 H), 6.47 (ddt, J = 53.0, 13.0, 7.6 Hz, 1 H); δ for *trans* isomer (major) 0.89 (t, J = 7.0 Hz, 3 H), 1.31 (t, J = 7.1 Hz, 6 H), 1.24−1.45 (m, 4 H), 2.21 (m, 2 H), 4.06 (apparent quintet, J = 7.3 Hz, 4 H), 5.63 (dd, J = 21.2, 17.1 Hz, 1 H), 6.78 (ddt, J = 22.0, 17.1, 6.7 Hz, 1 H); IR (neat, cm^{-1}) 1632, 1248, 1028; MS (CI) 222 (13.2, M + 2), 221 (100, M + 1).

Diethyl [2-(4-chlorophenyl)-3,3,3-trifluoro-1-propenyl]-phosphonate (5g): colorless liquid; ^{1}H NMR ($CDCl_3$) δ for *Z*-isomer (major) 1.17 (t, J = 7.1 Hz, 6 H), 3.78−4.01 (m, 4 H), 6.55 (dq, J = 12.3, 1.2 Hz, 1 H), 7.36, 7.40 (AB type, J_{AB} = 8.6 Hz, 4 H); δ for *E*-isomer (minor) 1.38 (t, J = 7.1 Hz, 6 H), 4.22

(25) Xu, Y.; Jin, X.; Huang, G.; Huang, Y. *Synthesis* **1983**, 556.

(dq, J = 7.2, 7.4 Hz, 4 H), 6.27 (d, J = 8.4 Hz, 1 H), 7.35, 7.37 (AB type, J_{AB} = 8.4 Hz, 4 H); IR (neat, cm^{-1}) 1643, 1595, 1256, 1134, 1024; MS (CI) 345 and 343 (33.3, 100, M + 1).

9-[5,6-Dideoxy-6-(diethoxyphosphinyl)-2,3-*O*-isopropylidene-*β*-D-*ribo*-hex-5-enofuranosyl]adenine (6). To a stirred solution of 2′,3′-isopropylideneadenosine (200 mg, 0.65 mmol) and pyridinium trifluoroacetate (62 mg, 0.32 mmol) in dry DMSO (5 mL) at rt under N_2 was added a solution of DCC (400 mg, 1.95 mmol) in dry DMSO (1 mL). The reaction mixture was stirred at rt for 8 h, and then additional DCC (300 mg, 1.46 mmol) and pyridinium trifluoroacetate (38 mg, 0.20 mmol) were added. The reaction mixture was stirred overnight, and TLC analysis indicated the completion of the reaction. After removal of the resulting DCU by filtration, crude **1b** (400 mg, 0.98 mmol) was added into the filtrate. The resulting mixture was stirred at rt for 36 h, then diluted with ethyl acetate (50 mL), washed with water (3 × 30 mL), and dried over Na_2SO_4. A pale brown solid (71 mg, 25% yield) was obtained after silica gel column chromatography and elution with 5% methanol in CH_2Cl_2: mp 85−89 °C, ^{1}H NMR (DMSO-d_6) δ 1.15 (t, J = 6.9 Hz, 3 H), 1.16 (t, J = 7.1 Hz, 3 H), 1.35 (s, 3 H), 1.56 (s, 3 H), 3.82 (apparent quintet, J = 7.8 Hz, 4 H), 4.81 (br, 1 H), 5.19 (dd, J = 6.3 Hz, J = 3.3 Hz, 1 H), 5.56 (d, J = 5.7 Hz, 1 H), 5.72 (t, J = 18.6 Hz, 1 H), 6.28 (s, 1 H), 6.65 (ddd, J = 22.2 Hz, J = 16.7 Hz, J = 5.6 Hz, 1 H), 7.35 (s, 2 H), 8.15 and 8.30 (2 s, 2 H); IR (KBr, cm^{-1}) 3337 (m, NH_2), 1642, 1597, 1211, 1028; MS (CI) 441 (21.3, M + 2), 440 (100, M + 1), 439 (2.5, M^+).

Diethyl (3-Phenylpropyl)phosphonate (7a). A solution of compound **5e** (30 mg) in ethanol (5 mL) was hydrogenated over 10% Pd/C (5 mg) at atmospheric pressure. The mixture was vigorously stirred at rt for 3 h, whereupon the catalyst was removed by filtration and the filtrate concentrated under reduced pressure to afford **7a** as a colorless oil (30 mg, 99% yield): ^{1}H NMR ($CDCl_3$) δ 1.30 (t, J = 7.1 Hz, 6 H), 1.69−1.77 (m, 2 H), 1.91−1.94 (m, 2 H), 2.69 (t, J = 7.5 Hz, 2 H), 4.04−4.10 (m, 4 H), 7.16−7.30 (m, 5 H).

Diethyl (2-Phenylethyl)phosphonate (7b). Compound **5a** (30 mg) was hydrogenated using the same procedure described above to afford **7b** quantitatively: ^{1}H NMR ($CDCl_3$) δ 1.32 (t, J = 7.1 Hz, 6 H), 2.11 (m, 2 H), 2.85 (m, 2 H), 4.09 (apparent quintet, J = 7.4 Hz, 4 H), 7.21−7.29 (m, 5 H).

[2-(4-Chlorophenyl)ethenyl]phosphonic acid (8). To a stirred solution of **5b** (50 mg, 0.18 mmol) in dry CH_2Cl_2 (5 mL) at rt under N_2 was added bromotrimethylsilane (280 mg, 1.8 mmol) dropwise. The reaction mixture was stirred for 2 h. The volatile materials were then removed under vacuum, and the residue was dissolved in water (5 mL) and stirred for 10 min. The aqueous solution was washed with ether and coevaporated with MeOH to dryness, affording a white solid (42 mg, 94% yield): mp >300 °C; ^{1}H NMR (D_2O) δ for *cis* isomer (minor) 6.03 (dd, J = 14.4, 10.5 Hz, 1 H), 6.81 (dd, J = 40.5, 14.4 Hz, 1 H), 7.38, 7.79 (AB type, J_{AB} = 8.7 Hz, 4 H); δ for *trans* isomer (major) 6.54 (dd, J = 17.7, 13.5 Hz, 1 H), 6.99 (t, J = 18.2 Hz, 1 H), 7.41, 7.53 (AB type, J_{AB} = 8.7 Hz, 4 H); IR (KBr, cm^{-1}) 3424, 1665, 1491, 1368, 1090, 978; MS (FAB) 219 and 217 (39.0, 100, M^+).

Acknowledgment. The work described herein was financially supported by a Phase I Small Business Innovation Research (SBIR) Grant (1R43 AI38205) from the National Institutes of Health.

Supporting Information Available: ^{1}H NMR spectra for all new compounds and known compounds where NMR data were not available, as well as ^{13}C NMR spectrum for **5e** (26 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9608275