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Efficient Synthesis of Substituted 1-Dimethylamino or 1-Methylthio But-3-enylidene-bis-phosphonates, via the [2,3]-Sigmatropic Rearrangement of Related Transient Ammonium or Sulfonium Ylides

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ABSTRACT: *New variously substituted 1-dimethylamino or 1-methylthio but-3-enylidene-bis-phosphonates have been prepared from readily available α-dimethylamino or α-methylthio methylene-bis-phosphonates by postulated [2,3]-Wittig rearrangements of the corresponding N- or S-allylic intermediate ylides.*
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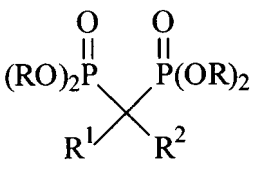
INTRODUCTION

Methylene-bis-phosphonate derivatives **I** (Scheme 1), which are characterized both by a P-C-P bridge inert to hydrolytic cleavage and by a remarkable ability to chelate metallic cations, have found many applications in industrial, chemical, and biological fields. For example, since many years ago, simple methylene-bis-phosphonates (e.g., I, $R^1 = R^2 = H$, R = *n*-Bu) have proved to be powerful chelating extractants for trivalent lanthanides and actinides [1].

Later on, several mono- or disubstituted functional methylene-bis-phosphonic acids [such as: chlodronate (e.g., **I**, R = H, $R^1 = R^2 = Cl$) or alendronate (e.g., **I**, R = H, $R^1 = OH$, $R^2 = (CH_2)_3NH_2$)] have received attention as therapeutic agents for the treatment of bone diseases [2,3]. More recently, allylic substituted derivatives (e.g., **I**, R = H, R^1, R^2 = farnesyl group) have been shown to be potent inhibitors of squalene synthetase [4].

Several methods have been reported for the synthesis of substituted methylene-bis-phosphonates. They can be classified in three groups. In the first one, the P-C-P bridge is directly generated, either from a trialkyl phosphite, by an Arbuzov-type reaction [5–8], or from a dialkyl phosphite, by a Michae-



I

SCHEME 1

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lis–Becker reaction [9,10], or by a Mannich-type reaction [11,12], or also, especially for the synthesis of α-hydroxy bis-phosphonic acid derivatives, from a mixture of phosphorous acid, phosphorus trichloride, and a carboxylic acid [13]. In the second group, the P-C-P bridge is built up, either by phosphonylation of a suitable electrophilic phosphonate [10,14–16], or by phosphonoalkylation of a chlorophosphate [17–19]. Finally, in the third group, a target molecule has been obtained from a pre-existing bis-phosphonate by synthetic adjustments such as halogenation [20], alkylation [21,22], sulphenylation [23], or a Michael addition [24,25].

Pursuing our work on the *[2,3]*-sigmatropic rearrangement that occurs in a phosphonic series [26–30], we report, in this article, on a novel synthesis of methylene-bis-phosphonates **II** bearing, in the α-position, both an allylic substituent and a dimethylamino or a methylthio group. The key step of our method is based on the *[2,3]*-Wittig rearrangement of the transient ylide **III** derived from the readily available α-functional methylene-bis-phosphonate **IV** (Scheme 2).

RESULTS AND DISCUSSION

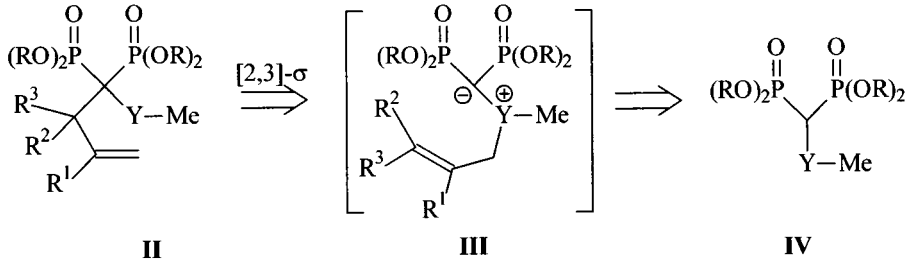
In the Amino Series

The sigmatropic *[2,3]*-Wittig rearrangement of allylic ethers and thioethers is a well-known reaction [31], but the aza analog *[2,3]*-shift appears to be less common [32]. To the best of our knowledge, no example of such a rearrangement in the amino phosphonate series has been reported before our recent article [30]. More recently, the aza *[2,3]*-sigmatropic rearrangement of phosphoramides was described [33].

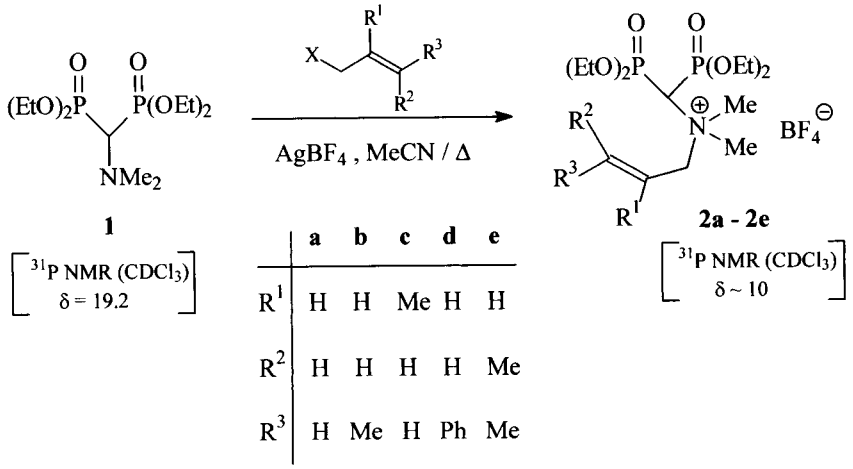
As an extension of our results in the monophosphonate series, we decided to study the rearrangement of the ammonium ylides derived from N-allylic ammonium salts **2** prepared by quaternization of the bis-phosphonate **1**. Thus, when the tetraethyl dimethylaminomethylene-bis-phosphonate **1**, prepared as reported earlier [34], was treated with various allylic halides, in acetonitrile, at 50°C, it was entirely transformed into the expected ammonium salts **2**, provided that the reaction was carried out in the presence of silver tetrafluoroborate (Scheme 3). In the absence of $AgBF_4$, the reaction was often incomplete, due to the competitive deallylation of **2** by the nucleophilic halide anion. After filtering off solids and elimination of the volatile products under reduced pressure, the crude ammonium salts **2** were obtained quantitatively as pale yellow viscous oils, whose purity was determined by ^{31}P NMR spectroscopy.

Crude ammonium salts **2** were then submitted to deprotonation using various bases, the progress of the reaction being monitored by ^{31}P NMR spectroscopy (Scheme 4).

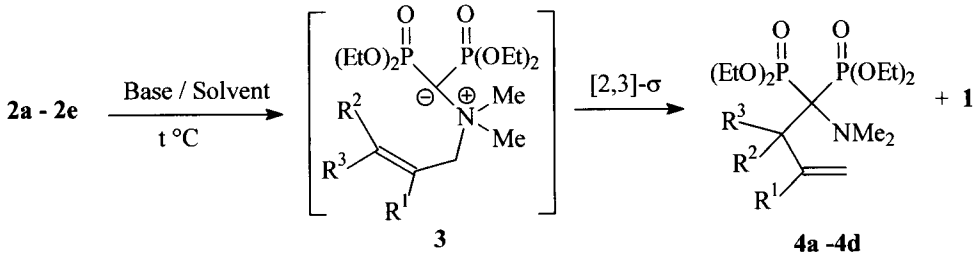
In most cases, the ylide **3** intermediate was not detected (only in the case of salt **2d**, treated with BuLi in THF at -40°C, a transient peak observed near $\delta = 30$ in the ^{31}P NMR spectrum could be assigned to the corresponding ylide **3d**). The rearranged product **4** was formed immediately upon the deprotonation of **2**, the process being completed after a time, depending on the basic system used, namely, BuLi in THF at -40°C (method A), NaH in THF at 20°C (method B), and K_2CO_3 in acetonitrile at 20°C (method C). For example, with the allyl derivative **2a**, the reaction was completed after 1 hour (method A), 1 hour 30 minutes (method B), and 15 hours (method C), and the yields of purified product **4a** were very similar: 86%, 85%, and 82%, respectively. For greater convenience, we have chosen method B for the other attempts. Except for the allyl derivative, in addition to the expected product **4**, we noted the presence of bis-phosphonate **1**, possibly resulting from the nucleophilic attack of the base on the allylic moiety of **2**. In the case of the prenyl derivative **2e**, no rearranged bis-phosphonate **4e** was detected, and the compound **1**, stemming from the foregoing competitive pathway, was the sole product of the reaction (Table 1).



SCHEME 2



SCHEME 3



SCHEME 4

TABLE 1 Rearrangement of bis-Phosphonic Ammonium Salts **2** into bis-Phosphonates **4**[a]

Starting Product	*δ 31P (CDCl3) of* **4** *[2JPP (Hz)]*	*Yield of Pure* **4**[c] *(%)*	*% of* **1** *in the Crude Mixture*[d]
2a	23.7	85	0
2b	23.4	50	20
2c	23.3	76	10
2d	21.0/23.0[b] [36.5]	35	20
2e	—	—	100

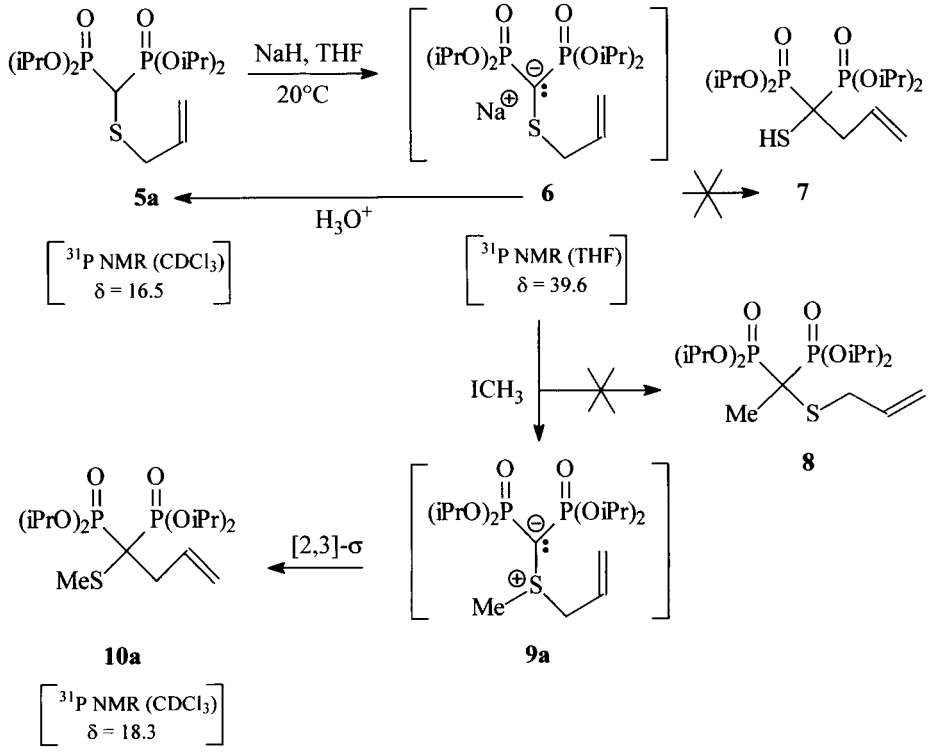
[a]All attempts were realized using method B (see text).
[b]Two diastereotopic coupled 31P nuclei (not separated in the case of **4b**).
[c]Purification by column chromatography over neutral alumine (eluent: hexane/AcOEt: 70/30); purity controlled by 1H and 13C NMR spectroscopy and mass spectrometry.
[d]Determined by 31P NMR integration measurements.

In brief, the *[2,3]*-Wittig rearrangement of metallated ammonium salts **2** proved to be a new and interesting way to prepare quaternary methylene bis-phosphonates, substituted at the α-position both by an amino and an allylic group. However, in contrast with the monophosphonate series, the rearrangement of the bulky and more stabilized intermediate ylide was severely dependent on the steric hindrance at the terminal carbon of the starting allylic chain (**2b, d, e**, compared to **2a, c**, Table 1).

In the Thio Series

We previously described the thia-Wittig rearrangement of the carbanions of (allylthio)methylphosphonates as a convenient route to new 1-mercapto-but-3-enylphosphonates [29]. In order to examine the possibility of extension of this strategy to *S*-allylic α-mercaptomethylene-bis-phosphonates, we first studied the metallation of the readily available [35,36] diisopropyl (allylthio)methylene-bis-phosphonate **5a** (Scheme 5).

When bis-phosphonate **5a** was treated with sodium hydride in THF at room temperature, and after the evolution of hydrogen had ceased, the 31P NMR spectrum of the reaction mixture exhibited a single peak at δ = 39.6 (in THF), which we ascribed to sodium salt **6**. This salt was quite stable, and, after 3 days at room temperature, acidic hydrolysis led to phosphonate **5a** again, without any trace of the rearranged bis-phosphonate **7**. The failure of carban-



SCHEME 5

ion **6** to undergo *[2,3]*-sigmatropic rearrangement could be imputed to its strong stabilization by the two adjacent electron-withdrawing phosphonic groups. Thus, when iodomethane was added to **6**, the expected C-methylated phosphonate **8** was not obtained [37], but instead we isolated the α-methylthio α-allyl methylene-bis-phosphonate **10a**, in moderate yield (45% of purified product), very likely resulting from the *[2,3]*-sigmatropic rearrangement of the transient ylide **9a** (not seen in the NMR spectrum), itself formed by *S*-methylation of salt **6**. The postulated rearrangement of **9a** into **10a** has also been realized by treatment with NaH in THF of the sulfonium salt **12** obtained either from the *S*-methylation of **5a** (1.5 equiv. of methyl iodide, in the presence of silver tetrafluoroborate, Scheme 6, path a) or from the *S*-allylation of the (methylthio) methylene-bis-phosphonate **11**, under similar conditions (path b).

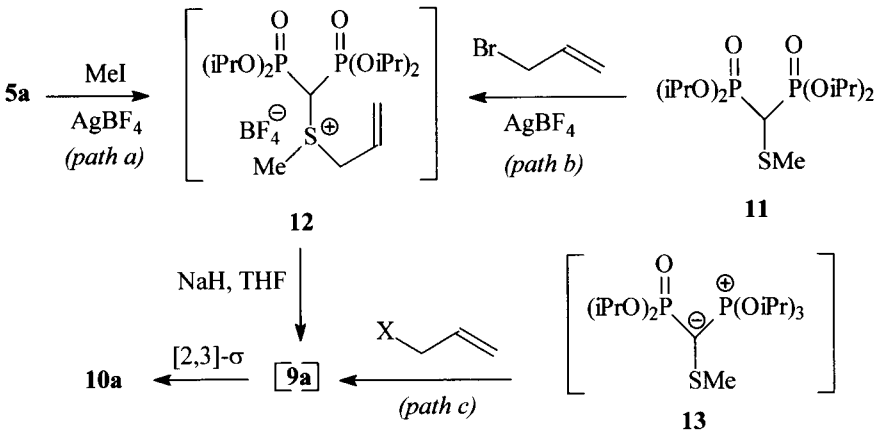
However, interest in the foregoing conversion was limited by the preparation of the sulfonium salt: by path a, **12** was obtained in 50% yield only; by path b, the best experiment (monitored by ^{31}P NMR spectroscopy) gave a 72% yield of **12** (δ = 7.0), 7% of nonreacted **11** (δ = 16.5), and 21% of an unidentified product ($\delta \sim$ 10.6), after 2.5 days at 45°C, while a longer reaction time induced decomposition of **12**. It is noteworthy that an alternative method to generate the sulfonium ylide **9a** is the treatment of the stable phosphonium ylide **13** with an allyl halide (path c, Scheme 6) [35].

Finally, we found that better yields of compounds **10** could be obtained, starting from the carbanion of the bis-phosphonate **11** and an allylic halide (Scheme 7, Table 2). The deprotonation of **11**, as well as the allylation of the resulting sodium salt **14**, occurred smoothly in THF at room temperature, and the expected bis-phosphonates **10a–d** were isolated in very good yields.

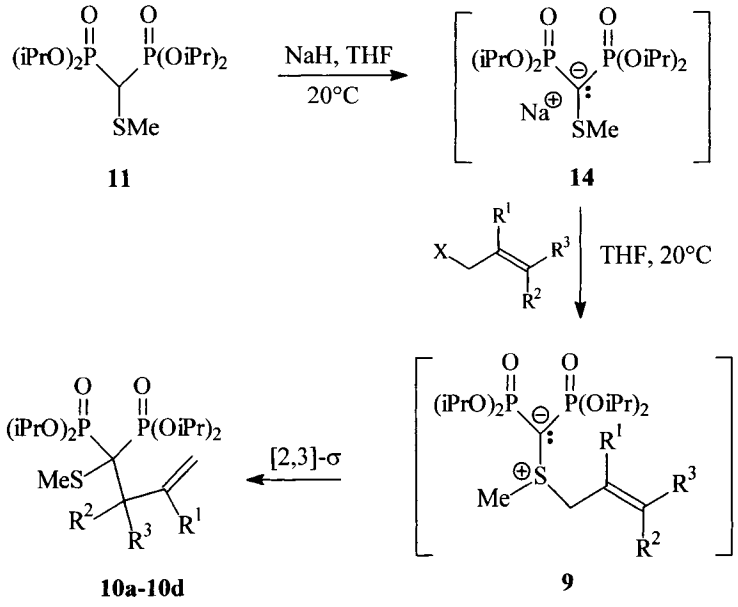
Although it was never detected by NMR spectroscopy, sulfonium ylide **9** can be reasonably suggested to be an intermediate in these reactions; however, the SN_2' allylation of carbanion **14** cannot be definitely excluded. Moreover, when the salt **14** was treated with prenyl bromide, the yield of the reaction product did not exceed a few percent, and mainly the starting bis-phosphonate **11** was recovered after the usual workup. As in the foregoing amino series, steric hindrance might be put forward in order to explain the lack of reactivity of the prenyl halide.

CONCLUSION

This article describes a direct and easy synthesis of new, variously substituted 1-dimethylamino or 1-



SCHEME 6



SCHEME 7

TABLE 2 Synthesis of α-Allylic α-Mercapto Methylene-bis-phosphonates **10**

Product[a]	δ ^{31}P ($CDCl_3$) of **10**	Yield % of Pure **10**[c]
10a	18.3	97
10b	18.1[b]	66
10c	17.9	85
10d	18.3[b]	77

[a]Letters **a** to **d** refer to the table given in Scheme 3.
[b]The two diastereotopic ^{31}P nuclei were not separated.
[c]Purification by column chromatography over silica gel (eluent: cyclohexane/AcOEt: 50/50); purity controlled by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry.

methylthio but-3-enylidene-bis-phosphonates from the realidy available α-dimethylamino or α-methylthio methylene-bis-phosphonates, via the *[2,3]*-Wittig rearrangement of postulated *N*- or *S*-allylic intermediate ylides, in the allyl, crotyl, methallyl, and cinnamyl series.

EXPERIMENTAL

General

All reactions were carried out using standard techniques. Solvents were purified by conventional methods prior to use. The ^{1}H, ^{13}C, and ^{31}P NMR spec-

tra were recorded on a Bruker AC 250 spectrometer at 250, 62.89, and 101.37 MHz respectively, with TMS as internal standard for ^{1}H and ^{13}C NMR spectra and with H_3PO_4 as external standard for ^{31}P NMR spectra. Chemical shifts are expressed as δ values, and coupling constants (J) are given in Hz; coupling multiplicities are reported using conventional abbreviations. The infrared spectra were recorded with a Perkin-Elmer 16 PC, in liquid film deposited on a NaCl plate; ν are given in cm^{-1}, and the following abbreviations are used: (s) strong, (vs) very strong, (m) medium, (w) weak, and (vw) very weak. Elemental microanalyses were performed by «Service de Microanalyse du CNRS, Lyon». Mass spectra under electronic impact were recorded at 70 eV, with a Nermag R 10 10 H spectrometer [m/z and relative abundance (in %) are given], or with a Jeol AX 500 spectrometer (HRMS). Flash chromatography (FC) was performed with Merck 60 silica gel or active neutral aluminium oxide (50–160 μ).

Materials

bis-Phosphonate **1** was prepared following the procedure described in Ref. [34]; bis-phosphonates **11** and **5a** were prepared following the procedure described in Ref. [36]. All other reagents are commercially available and were used without further purification.

Synthesis of Ammonium Salts **2.** *General Procedure*

To a mixture of silver tetrafluoroborate (0.545 g, 2.8 mmol) and bis-phosphonate **1** (0.662 g, 2 mmol) in dry acetonitrile (3 mL) was added, under N_2, a solution of an allylic halide (2.8 mmol) [allyl bromide, crotyl bromide, methallyl iodide (prepared from methallyl chloride [38]), or cinnamyl bromide], in dry acetonitrile (3 mL), and the reaction mixture was stirred for 3 to 5 hours at reflux. The resulting mixture was filtered, at room temperature, over celite, and the filtrate was evaporated under reduced pressure, leading quantitatively to the crude ammonium tetrafluoroborate **2**, as a yellow oil, whose purity was evaluated by ^{31}P NMR spectroscopy only, because of its instability, and which was immediately used in the following step, without further purification. The following chemical shifts were observed in the ^{31}P NMR spectra ($CDCl_3$): 10.5 (**2a**); 10.6 (**2b**); 10.0 (**2c**); 10.2 (**2d**); and 10.6 (**2e**).

Synthesis of bis-Phosphonates **4.** *General Procedure (method B)*

Sodium hydride (0.044 g, 1.8 mmol) and dry THF (15 mL) were introduced under N_2, into a three-necked flask, equipped with a mechanical stirrer, a gas inlet tube, a dropping funnel, and a thermometer. Then, a solution of **2** (1.5 mmol) in THF (20 mL) was dropped in, and the mixture was stirred for about 2 hours at room temperature, the reaction being monitored by ^{31}P NMR spectroscopy. Water (10 mL) and ether (15 mL) were added, and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL), the combined extracts being washed with brine and dried over Na_2SO_4. Evaporation of the solvent led to the crude mixture, as an oily residue, which was analyzed by ^{31}P NMR spectroscopy (Table 1). The crude product was purified by FC over activated alumina (eluent: hexane/ethyl acetate: 70/30), giving the pure bis-phosphonate **4**.

Tetraethyl (*1-Dimethylamino-but-3-enylidene*)*bis-phosphonate* **4a**. Pale yellow oil. ^{1}H NMR ($CDCl_3$): δ (J) = 1.35, t (7), 12H, ($C\underline{H}_3CH_2O)_2P(O)$; 2.63, t (1.5), 6H, ($C\underline{H}_3)_2N$; 2.92, dt (6.7 and 14), 2H, $C\underline{H}_2CH=CH_2$; 4.0–4.4, m, 8H, ($CH_3C\underline{H}_2O)_2P(O)$; 5.04, d (10) and 5.05, d (18), 2H, $CH=C\underline{H}_2$; 6.04, ddt (18, 10 and 6.7), 1H, $C\underline{H}=CH_2$. $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ (J) = 16.5, and 16.6, 2d (3), ($\underline{C}H_3CH_2O)_2P(O)$; 36.1, ~ s, $\underline{C}H_3N$; 41.7, t (4.2), $\underline{C}H_2CH=CH_2$; 62.3, and 62.8, 2d (7), ($CH_3\underline{C}H_2O)_2P(O)$; 68.3, t (135), $P(O)\underline{C}P(O)$; 117.4, s, $CH=\underline{C}H_2$; 133.6, t (9), $\underline{C}H=CH_2$. MS: 371 (0.4); 235 (12); 234 (100); 220 (8); 206 (15); 178 (13); 97 (5); 96 (50); 95 (9); 82 (6); 81 (8); 45 (5); 44 (11); 43 (11); 41 (5). IR: 3076 (w); 2982 (s); 2932 (s); 2908 (s); 2846 (m); 2800 (m); 1638 (w); 1242 (s); 1024 (vs); 968 (vs, br); 806 (m); 790 (m); 732 (m). Anal. calcd for $C_{14}H_{31}NO_6P_2$: C, 45.28; H, 8.41; N, 3.77. Found: C, 44.02; H, 8.47; N, 3.77.

Tetraethyl (*1-Dimethylamino-2-methyl-but-3-enylidene*)*bis-phosphonate* **4b**. Pale yellow oil. ^{1}H NMR ($CDCl_3$): δ (J) = 1.31, d (7), 3H, $C\underline{H}_3$-CH ; 1.33 and 1.34, 2t (7), 12H, ($C\underline{H}_3CH_2O)_2P(O)$; 2.64, t (1.5), 6H, ($C\underline{H}_3)_2N$; ~3.1, m, 1H, CH_3-$C\underline{H}$; 4.0–4.2, m, 8H, ($CH_3C\underline{H}_2O)_2P(O)$; 5.04, d (10) and 5.06, d (18), 2H, $CH=C\underline{H}_2$; 6.4, ddd (18, 10, and 7), 1H, $C\underline{H}=CH_2$. $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ (J) = ~16.6, m, ($\underline{C}H_3CH_2O)_2P(O)$ and $\underline{C}H_3(CH)$; 40.6, t (2), $\underline{C}H_3N$; 41.5, t (3.8), $CH_3(\underline{C}H)$; 63.6, d (4), ($CH_3\underline{C}H_2O)_2P(O)$; 71.8, t (132), $P(O)\underline{C}P(O)$; 114.2, s, $CH=\underline{C}H_2$; 140.3, t (4), $\underline{C}H=CH_2$. MS: 385 (0.6); 331 (20); 248 (100); 220 (19); 192 (14); 110 (9); 55 (10). IR: 3080 (w); 2980 (s); 2932 (s); 2906 (s); 2854 (m); 2808 (m); 1634 (w); 1476 (m); 1456 (m); 1444 (m); 1244 (vs); 1162 (m); 1098 (m); 1028, 964 (vs); 930 (s); 884 (m); 838 (m); 792 (m); 732 (vs).

Tetraethyl (*1-Dimethylamino-3-methyl-but-3-enylidene*)*bis-phosphonate* **4c**. White liquid. ^{1}H NMR

($CDCl_3$): δ (J) = 1.33 and 1.34, 2t (7), 12H, ($C\underline{H}_3CH_2O)_2P(O)$; 1.88, s, 3H, $C\underline{H}_3$-C=; 2.63, t (1.7), 6H, ($C\underline{H}_3)_2N$; 2.78, t (12.8), -$C\underline{H}_2$-C=; 4.05–4.2, m, 8H, ($CH_3C\underline{H}_2O)_2P(O)$; 4.85, 5.02, ~2s, 2H, C=$C\underline{H}_2$. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ (J) = 16.5, 16.6, 2d (2.5), ($\underline{C}H_3CH_2O)_2P(O)$; 24.1, s, $\underline{C}H_3$-C=; 37.7, t (2.5), -$\underline{C}H_2$-C=; 41.7, t (4), ($\underline{C}H_3)_2N$; ~62.3, m, ($CH_3\underline{C}H_2O)_2P(O)$; 69.9, t (132), P(O)$\underline{C}$P(O); 115.2, s, C=$\underline{C}H_2$; 141.6, t (4), $\underline{C}$=CH_2. MS: 385 (0.5); 331 (3); 303 (0.5); 248 (100); 220 (16); 192 (3); 110 (4). IR: 3078 (w); 2980 (s); 2932 (s); 2906 (s); 2870 (s); 2812 (m); 2798 (m); 2360 (w); 1680 (m); 1642 (m); 1540 (w); 1476 (m); 1444 (m); 1390 (m); 1368 (m); 1240 (vs); 1162 (m); 1098 (s); 1044, 968 (vs); 886 (m); 818 (m); 732 (m).

Tetraethyl (*1-Dimethylamino-2-phenyl-but-3-enylidene*)*bis-phosphonate* **4d**. White liquid. ^1H NMR ($CDCl_3$): δ (J) = 0.96, 1.12, 1.23, 1.3, 4t (7), 12H, ($C\underline{H}_3CH_2O)_2P(O)$; 2.65, ~ s, 6H, ($C\underline{H}_3)_2N$; 3.7–4.3, m, 9H, ($CH_3C\underline{H}_2O)_2P(O)$, $C\underline{H}$-C_6H_5; 5.0, dd (17, 1) and 5.15, dd (10, 1), 2H, CH=$C\underline{H}_2$; 6.9, ddd (17, 10, 10), 1H, $C\underline{H}$=CH_2; 7.1–7.4, m, 5H, $C_6\underline{H}_5$. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ (J) = 16.4, d (5.9), 16.5, d (5.6), 16.55, d (2.8), 16.6 d (5.5), ($\underline{C}H_3CH_2O)_2P(O)$; 42.3, 42.4, 2s, ($\underline{C}H_3)_2N$; 50.6, t(4), $\underline{C}$H-C_6H_5; 60.8, d (8), 61.2, d (5), 62.3, d (8), 62.7, d (5), ($CH_3\underline{C}H_2O)_2P(O)$; 73.4, dd (142.7, 117.7), P(O)$\underline{C}$P(O); 118.1, s, CH=$\underline{C}H_2$; 125.9, 126.5, 130.5, 137.7, 4s, $\underline{C}_6H_5$; 140.9, dd (6, 5), $\underline{C}$H=CH_2. MS: 447 (0.2); 403 (0.2); 345 (0.2); 331 (32); 194 (31); 173 (20); 172 (78); 157 (31); 138 (42); 116 (41); 115 (100); 81 (13); 42 (73). IR: 3060 (w); 2980 (s); 2930 (s); 2904 (s); 2854 (m); 2806 (m); 1636 (w); 1600 (w); 1558 (w); 1540 (w); 1496 (m); 1476 (m); 1450 (m); 1390 (m); 1366 (m); 1292 (w); 1244 (vs); 1186 (w); 1162 (m); 1098 (s); 1028, 962 (vs); 846 (m); 784 (m); 770 (m); 732 (s).

Synthesis of the bis-Phosphonate **10a** *from* **5a**, *following Scheme 5*

A solution of **5a** (0.29 g, 0.7 mmol) in dry THF (3 mL) was added to a suspension of NaH (0.017 g, 0.7 mmol, washed with pentane) in THF (6 mL), and the mixture was stirred, under N2, at room temperature for about 1 hour, the progress of the reaction being monitored by ^{31}P NMR spectroscopy. Then a solution of methyl iodide (0.1 g, ~0.7 mmol) in THF (2 mL) was added and allowed to react for 15 hours at room temperature. After filtration, the solution was extracted with ether, and the organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure led to a liquid residue, which had to be purified by successive column chromatographies over silica gel (eluent: cyclohexane/ethyl acetate: 50/50) in order to obtain pure bis-phosphonate **10a** (0.135 g, 45% yield), whose spectra are described later.

Synthesis of the bis-Phosphonate **10a** *from* **11** (*or from* **5a**), *following Scheme 6*

We used the procedure already described for the monophosphonate series [39], starting from 1 equiv. of bis-phosphonate **11** (or **5a**), 1.5 equiv. of $AgBF_4$, and 1.5 equiv. of allyl bromide (or methyl iodide), which were stirred in acetonitrile for 12 hours in the dark at room temperature (path a) or for 2.5 days at 45°C (path b), leading to the sulfonium salt **12** [^{31}P NMR ($CDCl_3$): δ = 7.0; yield ~50% (path a) or 72% (path b), as estimated by NMR integration measurements on the spectra of the reaction mixture]. Then, 1 equiv. of NaH in dry THF was added, and the mixture was stirred at room temperature for 2 hours. After the usual workup, bis-phosphonate **10a** was characterized, in the crude material, by ^{31}P NMR spectroscopy, and the yield (≤40%) was estimated by NMR integration measurements.

Synthesis of the bis-Phosphonates **10** *from* **11**, *following Scheme 7*

A solution of bis-phosphonate **11** (0.273 g, 0.7 mmol) in dry THF (3 mL) was added to a suspension of NaH [0.017 g, 0.7 mmol (washed with pentane)] in THF (6 mL), and the mixture was stirred under N_2 at room temperature for 1 hour. Then the allylic halide [0.7 mmol (namely:allyl bromide, crotyl bromide, methallyl iodide, and cinnamyl bromide)] in THF (3 mL) was added and allowed to react for 15 hours at room temperature. After filtration, the solution was extracted with ether, and the organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure led to a liquid residue, which was purified by column chromatography over silica gel (eluent: cyclohexane/ethyl acetate: 50/50) in order to obtain pure bis-phosphonates **10** as pale yellow liquids, with 66–97% yields (Table 2).

Tetraisopropyl (*1-Methylthio-but-3-enylidene*)*bis-phosphonate* **10a**. ^1H NMR ($CDCl_3$): δ (J) = 1.30, 1.31, 2d (6), 24H, $[C\underline{H}_3)_2CHO]_2P(O)$; 2.37, s, 3H, $C\underline{H}_3S$; 2.70, td (15.0, 6.7), 2H, $C\underline{H}_2CH$=CH_2; ~4.8, m, 4H, $[CH_3)_2C\underline{H}O]_2P(O)$; ~5.1, m, 2H, CH=$C\underline{H}_2$; ~6.1, m, 1H, $C\underline{H}$=CH_2. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ (J) = 14.8, s, $\underline{C}H_3S$; 23.6, d (3.4), 23.7, d (2.8), 23.9, d (2.7), 24.0, d (5.3), $[\underline{C}H_3)_2CHO]_2P(O)$; 37.1, s, $\underline{C}H_2CH$=CH_2; 46.4, t (138.2), P(O)$\underline{C}$P(O); ~72.3, m, $[CH_3)_2\underline{C}HO]_2P(O)$; 117.8, s, CH=$\underline{C}H_2$; 133.3, t (6.7), $\underline{C}$H=CH_2. MS: 430 (1.5); 384 (4); 301 (3); 258 (5);

245 (3); 216 (24); 181 (23); 135 (12); 99 (17); 85 (26); 43 (100). IR: 3078 (w); 2980 (vs); 2932 (m); 2874 (m); 1636 (m); 1556 (m); 1540 (m); 1522 (m); 1506 (m); 1468 (m); 1456 (m); 1386 (s); 1374 (m); 1248 (s); 1178 (s); 1142 (m); 1106 (m); 992 (vs); 886 (m); 860 (m); 788 (m). HRMS required for $C_{17}H_{36}O_6P_2S$: 430.1708 (^{32}S); found: 430.1707.

Tetraisopropyl (*2-Methyl-1-methylthio-but-3-enylidene*)*bis-phosphonate* **10b**. ^1H NMR ($CDCl_3$): δ (J) = ~1.4, m, 27 H, $[C\underline{H}_3)_2CHO]_2P(O)$, $C\underline{H}_3$-CH; 2.45, s, 3H, $C\underline{H}_3S$; ~2.7, m, 1H, $C\underline{H}$-CH_3; 4.83, m (6.2), 4H, $[CH_3)_2C\underline{H}O]_2P(O)$; 4.93, dd, (17.2, 2.4), 4.94, dd (9.8, 1.8), 2H, $CH=C\underline{H}_2$; 6.35, ddd (17.2, 9.5, 9.5), 1H, $C\underline{H}=CH_2$. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ (J) = 14.2, ~s, $\underline{C}H_3S$; 19.1, ~t (2.6), $\underline{C}H_3$-CH; ~23.0, m,; $[\underline{C}H_3)_2CHO]_2P(O)$; 42.3, ~t (3.1), $\underline{C}H$-CH_3; 50.5, t (135.5), P(O)$\underline{C}$P(O); 70.9, m, $[\overline{C}H_3)_2\underline{C}HO]_2P(O)$; 113.6, s, $CH=\underline{C}H_2$; 139.5, t (3.4), $\underline{C}H=CH_2$ [attributions have been confirmed by 2D (^1H-^{13}C) NMR]. MS: 444 (2); 442 (12); 398 (61); 397 (63); 389 (20); 388 (23); 383 (36); 355 (21); 305 (17); 272 (23); 263 (39); 262 (28); 246 (28); 233 (25); 230 (31); 229 (35); 222 (26); 221 (54); 220 (50); 215 (22); 214 (22); 213 (31); 212 (28); 204 (30); 203 (32); 196 (27); 195 (61); 191 (29); 149 (51); 99 (25); 49 (38); 43 (100); 41 (37). IR: 3076 (w); 2978 (s); 2934 (m); 2874 (m); 2362 (w); 1654 (w); 1636 (w); 1560 (w); 1540 (w); 1522 (w); 1508 (w); 1468 (m); 1456 (m); 1418 (m); 1384 (s); 1374 (s); 1246 (vs); 1178 (m); 1142 (m); 1104, 988 (vs); 898 (m); 862 (w); 802 (w); 766 (w). HRMS required for $C_{18}H_{38}O_6P_2S$: 444.1865 (^{32}S); found: 444.1870.

Tetraisopropyl (*3-Methyl-1-methylthio-but-3-enylidene*)*bis-phosphonate* **10c**. ^1H NMR ($CDCl_3$): δ (J) = 1.36, 1.38, 2d (5.9), 24H, $[C\underline{H}_3)_2CHO]_2P(O)$; 1.94, s, $C\underline{H}_3$-C=; 2.5, s, 3H, $C\underline{H}_3S$; 2.74, t (13.8), 2H, C-$C\underline{H}_2$-C=; ~4.8, m, 4H, $[\overline{C}H_3)_2C\underline{H}O]_2P(O)$; 4.9, 5.0, ~2s, 2H, $C=C\underline{H}_2$. $^{13}C\{^1H\}$ NMR ($\overline{C}DCl_3$): δ (J) = 15.7, s, $\underline{C}H_3S$; 24.4, m, $[\underline{C}H_3)_2CHO]_2P(O)$; 25.3, ~s, $\underline{C}H_3$-C=; 40.9, t (4.4), C-$\underline{C}H_2$-C=; 47.8, t (136.4), P(O)$\underline{C}$P(O); 72.0, m, $[\overline{C}H_3)_2\underline{C}HO]_2P(O)$; 117.6, s, $CH=\underline{C}H_2$; 140.6, t (8.2), $\underline{C}=CH_2$. MS: 444 (1.5); 398 (1.5); 315 (1.5); 314 (1.5); 303 (5): 276 (5); 273 (6); 261 (11); 238 (10); 230 (61); 222 (22); 221 (53); 219 (38); 211 (30); 196 (29); 195 (54); 179 (17); 177 (20); 150 (14); 149 (21); 147 (39); 99 (68); 98 (12); 97 (19); 86 (12); 84 (23); 43 (100). IR: 3080 (w); 2978 (s); 2928 (s); 2872 (s); 2732 (w); 1644 (m); 1468 (m); 1452 (m); 1248 (vs); 1178 (m); 1142 (m); 987 (vs); 936 (s); 896 (m); 804 (m); 784 (m); 764 (m); 732 (m). HRMS required for $C_{18}H_{38}O_6P_2S$: 444.1865 (^{32}S); found: 444.1856.

Tetraisopropyl (*1-Methylthio-2-phenyl-but-3-enylidene*)*bis-phosphonate* **10d**. ^1H NMR ($CDCl_3$): δ (J) = 1.28, 1.30, 1.31, 1.34, 4d (5.8), 24H, $[C\underline{H}_3)_2CHO]_2P(O)$; 2.47, s, 3H, $C\underline{H}_3S$; 3.93, m, 1H, $C\underline{H}$-C_6H_5; ~4.7, m, 4H, $[CH_3)_2C\underline{H}O]_2P(O)$; 4.95, ~d (16.8), 5.02, ~d (10.0), 2H, $CH=C\underline{H}_2$; 6.86, m, 1H, $C\underline{H}=CH_2$; 7.0–7.6, m, 5H, $C_6\underline{H}_5$. $^{13}C\{^1H\}$ NMR ($\overline{C}DCl_3$): δ (J) = 15.8, s, $\underline{C}H_3S$; 23.9, m, $[\underline{C}H_3)_2CHO]_2P(O)$; 52.7, t (133.3), P(O)$\underline{C}$P(O); 54.2, t (3), $\underline{C}H$-C_6H_5; 72.2, m, $[CH_3)_2\underline{C}HO]_2P(O)$; 116.3, s, $CH=\underline{C}H_2$; 126.6, 127.2, 128.9, 131.5, 4s, $\underline{C}_6H_5$; 139.0, t (4.2), $\underline{C}H=CH_2$. MS: 506 (2); 460 (0.5); 389 (3); 305 (2); 291 (2); 263 (14); 247 (18); 221 (71); 205 (28); 177 (27); 149 (100); 117 (37); 115 (36); 105 (45); 93 (45); 84 (73); 76 (28); 65 (28); 51 (16); 49 (31); 43 (77). IR: 3062 (w); 3030 (w); 2978 (s); 2930 (s); 2872 (m); 1684 (w); 1636 (w); 1600 (w); 1558 (w); 1540 (w); 1496 (w); 1468 (m); 1454 (m); 1418 (w); 1384 (m); 1372 (m); 1246 (s); 1178 (m); 1140 (m); 1106 (s); 1072 (m); 994 (vs); 928 (m); 908 (m); 770 (m); 732 (m). HRMS required for $C_{23}H_{40}O_6P_2S$: 506.2021 (^{32}S); found: 506.2033.

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