New Insights into the Chemistry of *gem*-Bis(phosphonates): Unexpected Rearrangement of Michael-Type Acceptors

Sergio H. Szajnman,[a] Guadalupe García Liñares,[a] Pablo Moro,[a] and Juan B. Rodriguez*[a]

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The use of tetraethyl ethylidenebis(phosphonate) as a Michael acceptor with different nucleophiles was investigated. It was found that in some cases this compound undergoes phosphate removal, depending on the nature of the nucleophile. The chemical behavior of its epoxy derivative tetraethyl oxiranylidenebis(phosphonate) as an electrophile was also studied. This compound underwent a very attractive and remarkable phosphonate-phosphate rearrangement resulting in the enol phosphate **8** regardless of the nucleophile employed. Different mechanistic studies were conducted in an attempt to explain the mechanisms involved. To the best of our knowledge, this reaction constitutes a remarkable novelty, being the first reported rearrangement reaction of an epoxy derivative of a *gem*-bis(phosphonate). In addition, evidence supporting the involvement of a radical or a polar mechanism, depending on the nature of the nucleophile, is discussed.

Introduction

In recent years much attention has been devoted to the synthesis of phosphonic acids and their corresponding derivatives, since a significant number of these compounds have been employed as useful synthetic intermediates for Diels–Alder reactions, Michael additions, preparation of carbocycles, and other synthetic methods.[1–6] Of special interest are bis(phosphonic acid) derivatives, which exhibit important pharmacological actions. Bis(phosphonates) are compounds structurally related to inorganic pyrophosphate, but with a methylene group replacing the oxygen bridge between the phosphorus atoms. Geminal phosphonates possess greater metabolic stability than pyrophosphate, however, since they are not hydrolyzed by pyrophosphatases and are also stable to hydrolysis under acidic conditions. Pamidronate (**1**), alendronate (**2**), and risedronate (**3**) are representative geminal bis(phosphonates) that act as effective inhibitors of bone resorption and are currently being used for the treatment of several bone disorders such us osteoporosis, Paget's disease, complications associated with bone metastases and multiple myeloma, hypercalcemia caused by malignancy, rheumatoid arthritis, or periodontal disease (Figure 1).[7–12] Bis(phosphonic acid) derivatives also exhibit valuable biological activities other than their antiresorptive properties, it having been found that several bis(phosphonates) are potent growth inhibitors of several pathogenic trypanosomatids such as *Trypanosoma cruzi*, *T. brucei rhodesiense*, and *Leishmania spp.* and apicomplexan parasites such as *Toxoplasma gondii* and *Plasmodium falciparum*.[13–17]

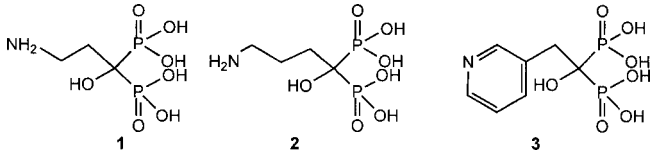

Figure 1. Representative members of bis(phosphonates) clinically in use for bone disorders.

In addition, the molecular target of these drugs has recently been elucidated as farnesyl pyrophosphate synthase.[18,19] In view of the relevance of these compounds not only from the synthetic perspective but also as chemotherapeutic agents, it was decided to study the chemical behavior of tetraethyl ethylidenebis(phosphonate) (**4**) and its epoxy derivative tetraethyl oxiranylidenebis(phosphonate) (**5**) in Michael-type reactions (Figure 2). Such a study should be very important for predicting interactions between these compounds and their molecular targets. Compound **4** is readily prepared from commercially available tetraethyl methylidenebis(phosphonate) (**6**).[4] The chemical study of compounds **4** and **5** was motivated by the biological activity exhibited by 1-hydroxyalkane-1,1-diylbis(phosphonates) derived from fatty acids, a family of drugs from which the

[a] Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires,
Pabellón 2, Ciudad Universitaria, C1428EHA, Buenos Aires, Argentina
Fax: +54-11-4576-3385
E-mail: jbr@qo.fcen.uba.ar

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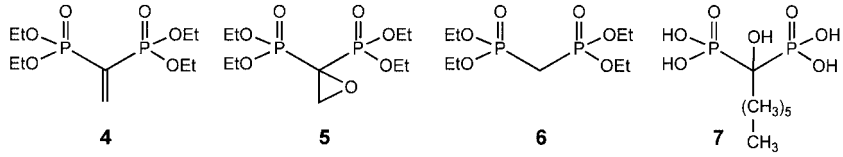


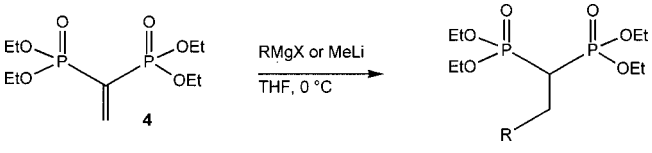
Figure 2. Chemical structures of synthetic intermediates for study of the chemistry of bis(phosphonates).

bis(phosphonic acid) prepared from heptanoic acid (compound **7**) has emerged as the main member.[14,18] Compound **7** can be prepared in good and reproducible yield from the corresponding carboxylic acid under harsh acidic conditions by treatment with an equimolecular mixture of phosphorous acid and phosphorus trichloride in the presence of benzenesulfonic acid, followed by hydrolysis.[20] This approach has become a reliable method to access several bis(phosphonic acids). However, in view of the strongly acidic conditions required to carry out this transformation, this method is restricted to substrates in which no labile groups are present. Bis(phosphonates) can also be prepared from the corresponding acyl halides.[21] In the search for a general methodology to synthesize bis(phosphonates) bearing labile functionalities, it seemed of interest to explore another synthetic approach. Compounds **4** and **5** were therefore, not surprisingly, seen as likely synthetic intermediates with which to carry out either isosteric replacements or structural variations on **7** (Figure 2).

Tetraethyl ethylidenebis(phosphonate) has a certain electrophilic character at the C-2 position and has the ability to react as a Michael acceptor with a variety of nucleophiles.[18,22] The epoxy derivative **5** also possesses an electrophilic center at the C-2 position. For that reason, the putative use of compounds **4** and **5** as entry points for bis(phosphonates) was investigated to obtain a better insight into the predicted reactivities of these compounds.

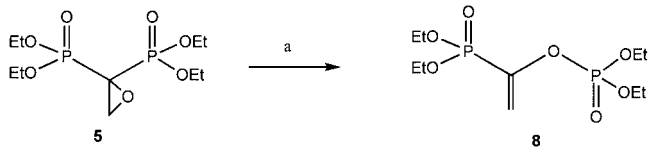
Results and Discussion

We and other groups had previously reported that the Michael acceptor **4** reacted with different Grignard reagents and methyllithium as a general method to prepare alkane-1,1-diylbis(phosphonates) as shown in Scheme 1.[1,18]



Scheme 1. Reactions between **4** and Grignard reagents or methyllithium.

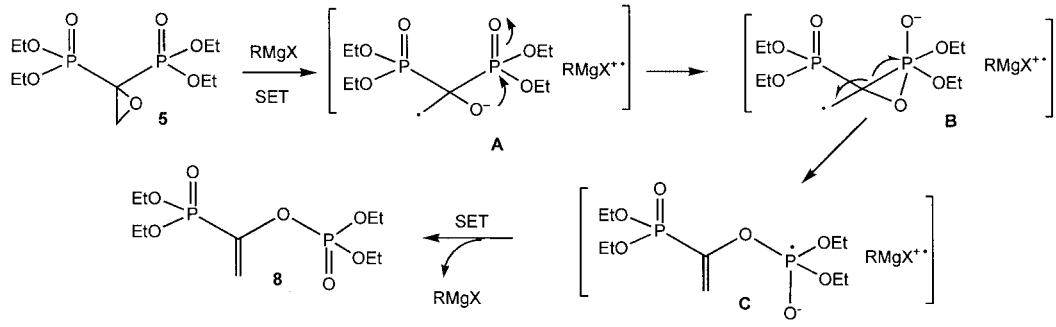
The epoxy derivative **5**, however, behaved quite differently from **4** in this type of reaction. Treatment of **5** with a variety of Grignard reagents afforded the unexpected rearranged product **8** regardless of the nature of the organometallic compound. Accordingly, compound **5** was treated with *n*-butylmagnesium bromide (2 equiv.) in tetrahydrofuran at –78 °C for 1 h to afford **8** in ca. 50% yield (Scheme 2). The same results – in the sense of the same product and similar yields – were obtained when allylmagnesium chloride, *n*-pentylmagnesium bromide or *n*-hexylmagnesium bromide were employed. In addition, the temperature had no influence on the course of the reaction, the same product being obtained at 0 °C or even at room temperature; also, the concentration of the Grignard reagent did not affect the reaction. This phosphonate-phosphate rearrangement involving migration of a diethoxyphosphinyl group from a carbon atom to an oxygen atom under basic conditions has already been described.[23–25]



Scheme 2. Reagents and conditions: a) RMgCl(Br), THF, –78 °C (or 0 °C), 2 h, 42%.

The fact that compound **8** lacks the Grignard reagent's alkyl group suggests that the conversion might occur through paramagnetic species. Single-electron transfer (SET) is an important pathway for a number of organic transformations.[26–28] Although Grignard reactions were initially regarded as simple nucleophilic additions, strong evidence to support SET processes exists in many cases. Ashby et al. suggested a mechanism involving the formation of a radical anion/radical cation pair on the basis of direct EPR evidence of radical formation in the reduction of aromatic ketones with a wide range of Grignard reagents.[29] In addition, it was demonstrated that the rate of electron transfer is a function of the number of β-hydrogen atoms present in the alkyl group of the Grignard reagent rather than of the previously postulated stability of the intermediate alkyl radical.

Most experimental approaches for diagnosing whether electron transfer may be involved in a particular organic transformation exploit the unique properties of the paramagnetic intermediates formed, such as free radicals or ion radicals. In order to gather information relating to radical involvement in the reaction between **5** and allylmagnesium chloride, it was carried out in the presence of a suitable inhibitor of radical formation. Quinhydrone can produce stable radicals by one-electron uptake or donation,[30–33] and so was considered suitable for testing the presence of radicals in this reaction. Complete inhibition of the formation of compound **8** was observed (85% of **5** was recovered), suggesting the partial involvement of electron transfer in the first step. Quinhydrone also inhibited the reaction when *n*-hexylmagnesium bromide and *n*-pentylmagnesium bromide were used. These results were very surprising, be-



Scheme 3. Proposed radical mechanism for the phosphonate-phosphate rearrangement of compound **5**.

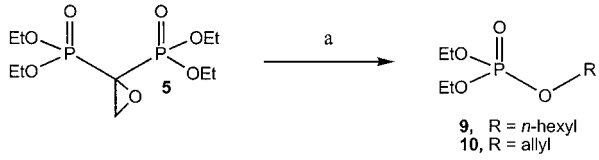
cause it is not likely that primary Grignard reagents would undergo this reaction by a SET process.[34] However, there is evidence to support the possibility that primary Grignard reagents could react by an electron-transfer mechanism:[35] a plausible pathway involving radical ions is outlined in Scheme 3. An electron transfer from the Grignard reagent to **5** would generate the radical cation/radical anion pair **A**, which could then rearrange within the cage to afford the intermediate **C**. Formation of **C** can be interpreted in terms of intramolecular attack of the oxygen atom bearing the negative charge onto the phosphorus atom to give intermediate **B**. This intermediate could cleave the carbon–phosphorus bond homolytically in a concerted way. Intermediate **C** could evolve to regenerate the phosphorus–oxygen π-bond through another SET from **C** to the Grignard reagent to afford **8**. In reinforcement of the concept of the postulated mechanism, the enthalpy of formation of the phosphorus–carbon bond is 65 kcal·mol^{-1}, while the corresponding value for the phosphorus–oxygen bond is 86 kcal·mol^{-1}.[36] Radical anions were recently detected by EPR in reactions between diethoxyphosphoryl dithioformates and Grignard reagents.[37]

To provide further support for the postulated mechanism, as far as the presence of radical intermediates was concerned, the reaction between **5** and allylmagnesium chloride in the presence of 2,2,5,5-tetramethylpiperidin-1-oxyl (TEMPO) was examined in tetrahydrofuran as solvent. The stable radical TEMPO is often used to scavenge free radical pairs that escape the initial solvent cage and appeared applicable to the study of this reaction.[38,39] When this reaction was accordingly conducted in the presence of TEMPO, a significant impairment of formation of **8** was observed, CG-MS analysis showing the presence of TEMPO, TEMPO-H, and a small amount of compound **8**. In addition, no trapping products formed from radical species and TEMPO were detected, but some other random free radical coupling products – such as tetraethyl ethane-1,1-diylbis(phosphonate), tetraethyl 2-hydroxyethane-1,1-diylbis(phosphonate), $[(EtO)_2P(O)]_2$, etc. – were identified. A lack of ability of TEMPO for radical trapping, in spite of producing an inhibitory effect on the course of the reaction, has already been described.[38–40] These findings may be due either to steric hindrance of the TEMPO radical[38] or to thermal instability[39,40] of the coupling products. The addition of TEMPO or quinhydrone retards the formation of compound **8**, which suggests that a radical mechanism was involved in this reaction.

Surprisingly, compound **5** did not act as a Michael acceptor when organolithium compounds were used as nucleophiles; the reactions between **5** and *n*-butyllithium or methyllithium, for example, did not proceed under different reaction conditions including reaction temperatures ranging from –78 °C to 0 °C and different reagent concentrations and addition sequences. When phenyllithium was used as organometallic reagent at 0 °C, however, **8** was obtained as a single product in almost theoretical yield. It is well known that phenyllithium acts as an electron donor while alkyllithium reagents react by polar mechanisms;[32] so these results once more indicated that the reaction was occurring through a radical mechanism.

Moreover, enol phosphates could be prepared through addition reactions between dialkyl phosphite anions and acyl chlorides at low temperature. The potassium anion of diethyl phosphite reacts with 4-bromoacetyl chloride to afford **8** as a rearranged product in good yield.[41]

The reaction times had a marked influence on the reaction product. When the reaction mixture was allowed to react at room temperature for an extended period, the main product was identified as the phosphoric acid diethyl alkyl ester derivative, with the alkyl group corresponding to that from the Grignard reagent. Treatment of epoxy derivative **5** with *n*-hexylmagnesium bromide or allylmagnesium chloride (in different experiments) at room temperature overnight, for example, produced the phosphate esters **9** and **10**, respectively (Scheme 4).

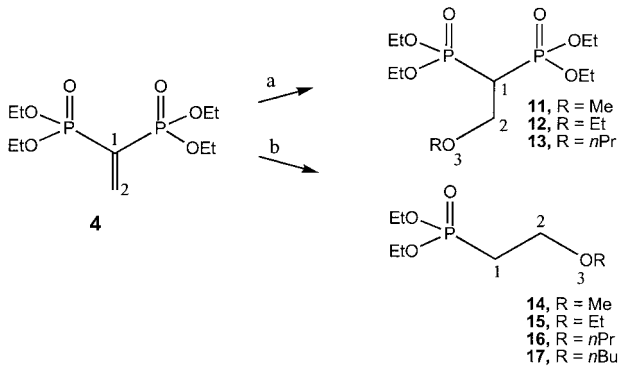


Scheme 4. Reagents and conditions: a) RMgCl(Br), THF, 0 °C, 1 h → room temp., 16 h; 66% for **9**, 57% for **10**.

As demonstrated, **8** was the main product isolated after treatment of **5** with a variety of Grignard reagents at low temperature and short reaction time, through a process involving radicals. When the reaction was conducted at room temperature for a longer period of time, the formation of

compound **8** was also detected, but this compound then smoothly proceeded to form the corresponding alkyl diethyl phosphate, apparently with involvement of radicals, to complete the reaction by a new electron-transfer process.

Treatment of compound **4** with several oxygen and sulfur nucleophiles was explored, with the first series of experiments involving reactions between compound **4** and several sodium alkoxides. Thus, when **4** was treated with sodium methoxide at 0 °C, the expected 1,4-addition product (compound **11**) was obtained (Scheme 5). This compound was unstable in weakly acidic media, such as on silica gel or in solution, reverting to the starting material **4** through loss of the methoxide group. This result was not surprising, since compound **11** is the natural intermediate from which to prepare **4**,[42] and **11** is in fact converted into **4** under acid catalysis.[42] In addition, when **4** was treated with different alkoxides, such as sodium ethoxide and sodium propoxide, the corresponding 1,4-addition derivatives – compounds **12** and **13**, respectively – were formed in moderate yields. Compounds **11–13** also underwent loss of alkoxide to regenerate the starting Michael acceptor **4** in all attempts at product purification either with alumina or with silica gel. It has previously been reported that the adducts formed by treatment of **4** with nitrogen-containing nucleophiles also underwent alkoxide elimination to regenerate the starting material **4**.[2]



Scheme 5. Reagents and conditions: a) RONa, ROH, 0 °C, 1 h; 40% for **11**, 35% for **12**, 20% for **13**. b) RONa, ROH, room temp., 16 h; 40% for **14**, 85% for **15**, 92% for **16**, 30% for **17**.

When the reaction was carried out at room temperature overnight, the 1,4-addition products underwent elimination of one unit of phosphoryl group to produce the corresponding diethyl (2-alkoxyethyl)phosphonate derivatives. Thus, compound **4**, when treated with sodium methoxide, sodium ethoxide, sodium propoxide, and/or sodium butoxide, afforded compounds **14–17**, respectively, in good yields. Remarkably, the loss of the phosphonate unit under these reaction conditions, presumably as a phosphate group, was very unusual. This elimination has been observed in olefination of aldehydes and other related compounds where Wadsworth–Emmons-type conditions are required[43–45] and in nonstabilized β-hydroxyphosphonates.[46] In these cases, the intermediate that generates the corresponding olefin possesses an oxygen atom bearing a negative charge bonded at the β-carbon atom relative to the phosphonate unit. This intermediate forms the common four-membered oxaphosphetane ring, which undergoes fragmentation to afford the olefin and phosphate ion. In our case, however, the elimination of the phosphonate group did not proceed by this mechanism. The carbon bridge accommodated a negative charge after the 1,4-addition of the alkoxy group onto the Michael acceptor. A carbanionic intermediate structurally related to that formed in the course of the reaction has been reported as a stable species in a variety of alkylation reactions of geminal phosphonates.[47,48] Another mechanism of elimination was therefore involved, and this is outlined in Scheme 6.

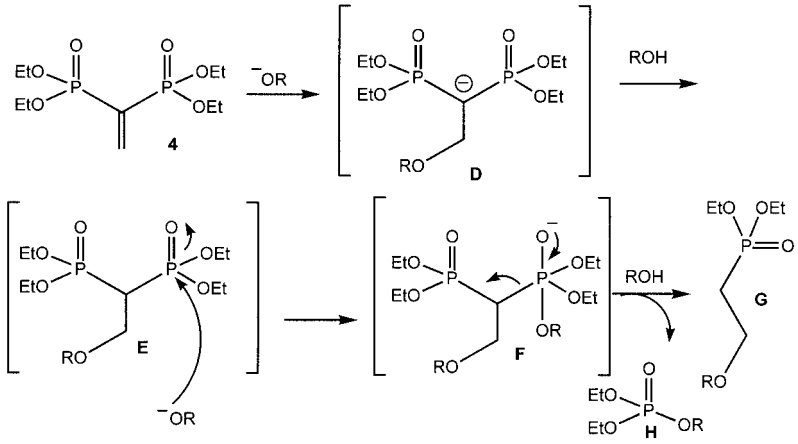
Typical alkoxide 1,4-addition to the Michael acceptor **4** to give the carbanionic species **D** is proposed as the first step. Intermediate **D** could capture a proton from the solvent to give intermediate **E**, which could subsequently be attacked by further alkoxide at one of the phosphorus atoms to generate **F**, in which the negative charge would be supported by the oxygen atom. Elimination of the phosphate ester would yield compounds of general formula **G** (compounds **14–17**).

To verify this hypothesis, the reaction between **4** and sodium [D_3]methoxide in [D_4]MeOH was examined. Analysis of the deuterium content in **14** by ^{1}H NMR spectroscopy showed over 95% deuterium incorporation. The signal assigned to 1-H in **11**, which had appeared as a triplet of triplets centered at δ = 2.69 ppm, was not observed, while the signal corresponding to 2-H, previously observed as a doublet of triplets centered at δ = 3.89 ppm, collapsed to appear as a triplet ($J_{H,P}$ = 16.1 Hz). CG-MS analysis of the reaction mixture after 16 h showed the $[M]^+$ peak (m/z = 201) of the pentadeuterated derivative of the **G** species [$CD_3OCH_2CD_2P(O)(OEt)_2$] together with trideuterated leaving phosphate ester **H** (m/z = 171) [$CD_3OP(O)(OEt)_2$] as diagnostic signals. These results indicated that the incorporation of deuterium at the C-1 position in the **E** and **F** products were in agreement with the proposed reaction mechanism.

The results when compound **5** was employed as a substrate were very surprising. This compound did not react with any of the employed alkoxides – such as methoxide, ethoxide, propoxide, and butoxide ions – as nucleophiles at 0 °C, but when the reaction was carried out at room temperature, diethyl (2-alkoxyethyl)phosphonates were obtained instead, as illustrated in Scheme 7.

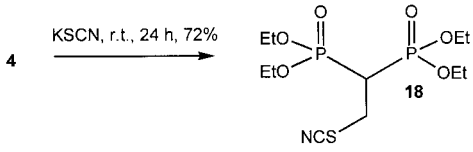
The postulated mechanism of this unusual rearrangement is depicted in Scheme 8. Addition of the alkoxide anion onto epoxide **5** to give the intermediate **J** is suggested as the first step, with **J** then decomposing through a retro-Abramov reaction[23] to give the corresponding acylphosphonate **K** and phosphite ion. The latter species could react as a nucleophile with **5** to generate the intermediate **L**, which could form **4** through a Wittig-type reaction. Finally, compound **4** could proceed as depicted in Scheme 6 to give **G**. The low yields of **G** (compounds **14–17**) support this mechanism.

Compound **4** behaved as a good Michael acceptor for sulfur-containing nucleophiles such as potassium thiocya-



Scheme 6. Postulated mechanism for formation of (2-alkoxyethyl)phosphonates of general formula **G**.

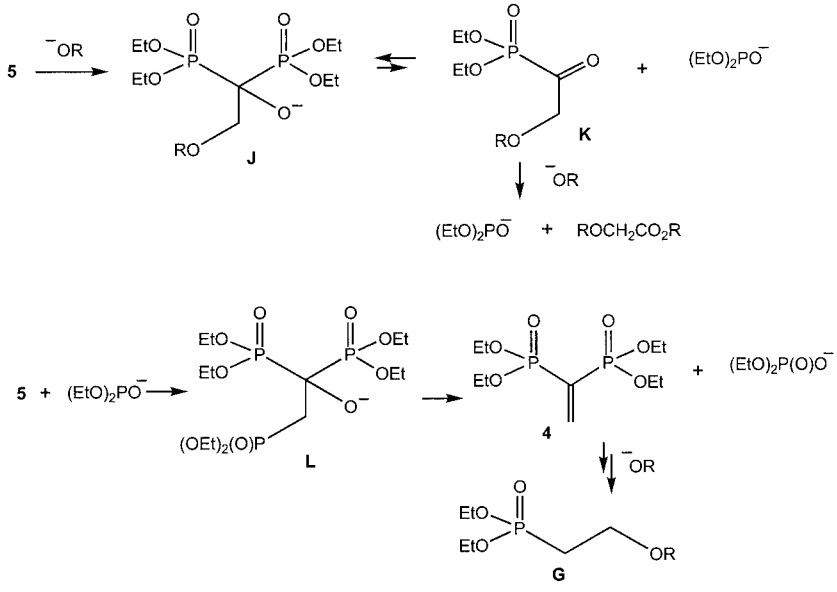
Scheme 7. Reactions between **5** and alkoxides at room temperature overnight.



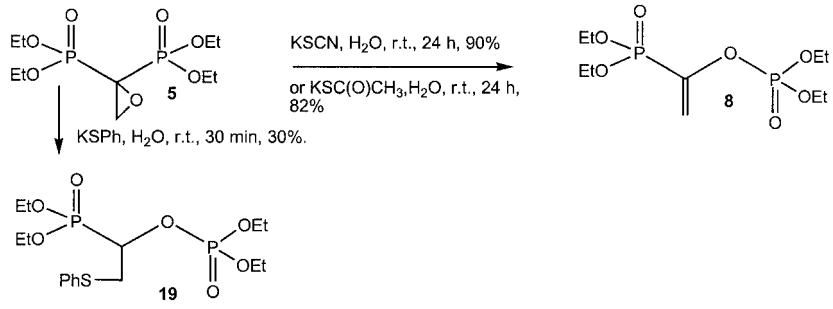
Scheme 9. Michael addition reaction between thiocyanate ion and **4**.

nate. Upon treatment with this reagent, compound **4** was converted into the corresponding 1,4-addition product **18** as expected. These results are fully consistent with those previously reported concerning the use of **4** as a Michael acceptor with negative ions bearing sulfur atoms as nucleophilic centers (Scheme 9).[2]

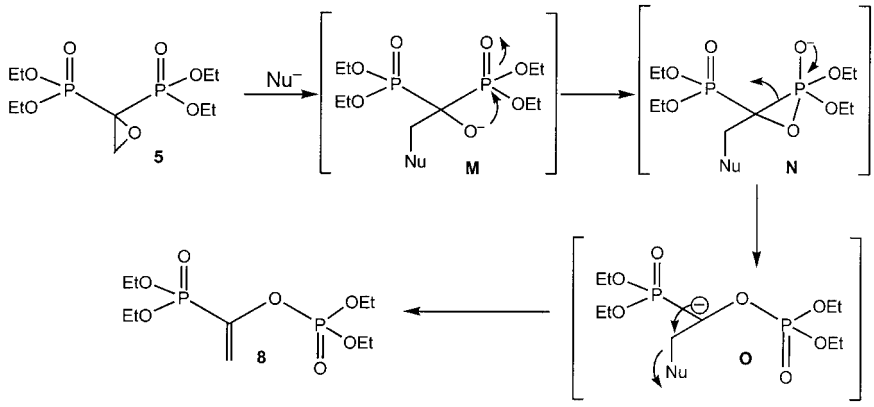
The reactions between the epoxy derivative **5** and sulfur-containing nucleophiles were extremely encouraging. As a rule, the expected product when an epoxy group is treated with potassium thiocyanate is the corresponding episulfide derivative.[49–51] When compound **5** was treated with potassium thiocyanate, however, the main isolated compound was once again the rearranged product **8** instead of the expected thiirane (Scheme 10). In other words, the same compound that had been formed by treatment of **5** with dif-



Scheme 8. Postulated polar mechanism for the formation of 2-alkoxyethane-1,1-diylbis(phosphonates) of general formula **J** starting from **5**.



Scheme 10. Reactions between **5** and sulfur-containing nucleophiles.



Scheme 11. Postulated polar phosphonate-phosphate rearrangement of compound **5**.

ferent Grignard reagents at low temperatures was obtained. In view of this result, the use of other nucleophilic sulfur-containing ions was considered. Treatment with potassium thioacetate transformed the epoxy derivative **5** into **8** in 82% yield, but treatment with potassium thiophenoxide converted compound **5** into **19**. It is worth pointing out that **19** could be obtained irrespective of the number of equivalents of nucleophile. This result was quite unexpected: compound **19** was isolated with a similar reaction yield even if the reaction was carried out with equimolecular amounts of **5** and potassium thiophenoxide.

Reactions between compound **5** and some amines as nucleophiles have been reported.[52] Under these reaction conditions, this compound was converted, as a result of epoxide ring-opening followed by a phosphonate-phosphate rearrangement, into the corresponding diethyl [2-(alkylamino)-1-(diethoxyphosphoryloxy)ethyl]phosphonate derivatives.[52]

In order to acquire information about the mechanism, the reaction was carried out in separate experiments in the presence of quinhydrone and TEMPO. The lack of any effect of these compounds suggested that the reaction was not occurring through an electron-transfer pathway. A mechanism for reactions between **5** and sulfur-containing nucleophiles is illustrated in Scheme 11. Addition of thiocyanate ion or thiophenoxide ion as nucleophiles to **5** could give intermediates **M**, which could undergo phosphonate-phosphate rearrangement with expulsion of thiocyanate ion, but not thiophenoxide ion, which is a much weaker leaving group. In the latter case the carbanion formed (**O**) would be protonated. The tendency of a negative oxygen atom bonded at the α-carbon atom of a specific alkyl phosphonate to produce three-membered oxaphosphirane rings has previously been observed in other reactions involving organophosphorus compounds.[41]

Conclusion

It can be concluded that the epoxy derivative **5** undergoes a very interesting and unusual rearrangement that affords the enol phosphate **8** regardless of the employed nucleophile. In addition, **8** can be transformed into alkyl diethyl phosphate esters (compounds **9** and **10**) by treatment with Grignard reagents but under different reaction conditions. On the other hand, the Michael acceptor tetraethyl ethylidenebis(phosphonate) (**4**) proved to have the ability to react as a typical Michael acceptor with a variety of nucleophiles. In addition, **4** is able to undergo phosphate elimination, depending on the nature of the nucleophile. The different reactivity patterns of **4** and **5** show that the presence of an oxygen atom produces a tendency to form a three-membered oxaphosphirane ring, which is rapidly converted into these unexpected products. Moreover, there is strong evidence to support mechanisms involving radical intermediates in the reactions between **5** and several Grignard reagents. This work sheds some light on the mechanism of an interesting set of reactions reported here for the first time and, to the best of our knowledge, this reaction is a significant novelty relating to phosphonate-phosphate rearrange-

ment reactions of epoxy derivatives of *gem*-bis(phosphonates) to produce enol phosphates.

Experimental Section

General: The glassware used in air- and/or moisture-sensitive reactions was flame-dried and reactions were carried out under dry argon. Unless otherwise noted, chemicals were commercially available and used without further purification. Solvents were distilled before use. Tetrahydrofuran was distilled from sodium/benzophenone ketyl. Nuclear magnetic resonance spectra were recorded with a Bruker AM 500 MHz spectrometer. The ^{1}H NMR spectra are referenced with respect to the residual $CHCl_3$ proton of the solvent $CDCl_3$ at δ = 7.26 ppm. Coupling constants are reported in Hz. ^{13}C NMR spectra were fully decoupled and are referenced to the middle peak of the solvent $CDCl_3$ at δ = 77.0 ppm. ^{31}P NMR spectra are referenced with respect to the peak of 85% H_3PO_4 as external reference. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quadruplet; quint, quintuplet, etc. Assignments were supported by ^{1}H-^{1}H NMR and/or ^{1}H-^{13}C NMR correlation spectra. Melting points were determined with a Fisher–Johns apparatus and are uncorrected. IR spectra were recorded with a Nicolet Magna 550 spectrometer. Low-resolution mass spectra were obtained with a VG TRIO 2 instrument in electron-impact mode at 70 eV (direct inlet). Column chromatography was performed on silica gel 60 (230–240 mesh) and analytical TLC was performed on commercial 0.2 mm aluminium-coated silica gel plates (F_{254}) and visualized by immersion in an aqueous solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (0.04 M), $Ce(SO_4)_2$ (0.003 M), concentrated H_2SO_4 (10%). Elemental analyses were conducted by Atlantic Microlab Inc., Norcross, Georgia.

Tetraethyl Oxirane-2,2-diylbis(phosphonate) (5): A solution of *m*-chloroperoxybenzoic acid (2.27 g, 6.6 mmol) in dichloromethane (10 mL) was added dropwise to a solution of tetraethyl ethane-1,1-diylbis(phosphonate) (compound **4**; 1.00 g, 3.3 mmol) in dichloromethane (15 mL). The mixture was stirred at room temperature overnight. The mixture was extracted with a saturated aqueous solution of sodium hydrogencarbonate (3 × 10 mL) and water (2 × 10 mL). The organic layer was dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) with elution with hexane/EtOAc (1:1) to give pure compound **5** (783.3 mg, 75% yield) as a colorless oil. Literature spectroscopic data agree with our results:[52,53] R_f = 0.30 (EtOAc/*i*PrOH, 9:1). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.37 (t, *J* = 7.1 Hz, 12 H, CH_2CH_3), 3.27 (t, *J* = 5.3 Hz, 2 H, 2-H), 4.24 (m, 8 H, CH_2CH_3) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 16.21 (t, *J* = 3.1 Hz, CH_2CH_3), 47.78 (t, *J* = 182.7 Hz, C-1), 49.81 (t, *J* = 1.7 Hz, C-2), 63.81 (t, *J* = 3.1 Hz, CH_2CH_3) ppm. ^{31}P NMR (D_2O, 202.45 MHz): δ = 12.57 ppm. IR (film): $\tilde{\nu}$ = 2990, 1255, 1179, 1034, 977 cm^{-1}. MS: *m*/*z* (%) = 316 (12) $[M]^+$, 289 (5), 271 (14), 261 (8), 244 (21), 215 (30), 187 (92), 155 (100), 127 (95), 99 (89), 81 (91). $C_{10}H_{22}O_7P_2$: calcd. C 37.98, H 7.01; found C 38.12, H 7.04.

Diethyl [1-(Diethoxyphosphoryloxy)vinyl]phosphonate (8). Method A: Potassium thiocyanate (920 mg, 9.3 mmol) was added to a solution of tetraethyl oxirane-2,2-diylbis(phosphonate) (compound **5**; 300 mg, 0.95 mmol) in water (5 mL). The reaction mixture was stirred at room temperature for 24 h. The mixture was extracted with dichloromethane (3 × 10 mL), the combined organic layers were washed with water (5 mL) and dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) with a mixture of hexane/EtOAc (7:3) as eluent to afford pure compound **8** (270 mg, 90% yield) as a colorless oil. This compound has already been described in the literature:[41,54] R_f = 0.48 (EtOAc/MeOH, 9:1). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.36 (t, *J* = 7.1 Hz, 6 H, CH_2CH_3), 1.37 (dt, *J* = 7.1, 0.9 Hz, 6 H, CH_2CH_3), 4.18 (m, 8 H, CH_2CH_3), 5.80 (dt, *J* = 11.2, 2.5 Hz, 1 H, 2-H^a), 5.86 (ddd, *J* = 35.1, 2.7, 1.1 Hz, 1 H, 2-H^b) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.95 (d, *J* = 5.93 Hz, CH_2CH_3), 16.19 (d, *J* = 5.9 Hz, CH_2CH_3), 63.75 (d, *J* = 5.9 Hz, CH_2CH_3), 64.75 (d, *J* = 5.9 Hz, CH_2CH_3), 114.65 (dd, *J* = 24.6, 4.2 Hz, C-2), 146.00 (dd, *J* = 229.0, 10.1 Hz, C-1) ppm. ^{31}P NMR (D_2O): δ = –6.14 [d, *J* = 24.97 Hz, O–P(O)(OEt)$_2$], 8.27 [d, *J* = 24.97 Hz, C–P(O)(OEt)$_2$] ppm. IR (film): $\tilde{\nu}$ = 2987, 1622, 1394, 1271, 1220, 1164, 1042, 825 cm^{-1}. MS: *m*/*z* (%) = 316 (5) $[M]^+$, 289 (3), 272 (7), 261 (5), 244 (11), 216 (12), 187 (43), 155 (54), 127 (61), 99 (92), 81 (100). $C_{10}H_{22}O_7P_2$: calcd. C 37.98, H 7.01; found C 37.87, H 7.22. **Method B:** Potassium thioacetate (920 mg, 4.74 mmol) was added to a solution of tetraethyl oxirane-2,2-diylbis(phosphonate) (300 mg, 0.95 mmol) in water (5 mL). The reaction was allowed to proceed according to Method A. The residue was purified by column chromatography (silica gel) with a mixture of hexane/EtOAc (7:3) as eluent to afford pure compound **8** (240 mg, 80% yield) as a colorless oil. **Method C:** A solution of allylmagnesium chloride (0.75 mmol) in anhydrous tetrahydrofuran (4 mL) was added under argon at –78 °C to a solution of tetraethyl oxirane-2,2-diylbis(phosphonate) (113 mg, 0.38 mmol) in anhydrous tetrahydrofuran (5 mL). The reaction mixture was stirred at –78 °C (or 0 °C) for 2 h and was then quenched with a saturated aqueous solution of ammonium chloride (1 mL). The mixture was extracted with ethyl acetate (3 × 10 mL), the combined organic layers were washed with water (2 × 10 mL) and dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) with a mixture of hexane/EtOAc (7:3) as eluent to afford pure compound **8** (47 mg, 42% yield) as a colorless oil. Similar yields were obtained with other Grignard reagents such as *n*-hexylmagnesium chloride and *n*-butylmagnesium bromide.

Diethyl *n*-Hexyl Phosphate (9): A solution of freshly prepared *n*-hexylmagnesium bromide (12.6 mmol) in tetrahydrofuran (10 mL) was added under argon at 0 °C to a solution of tetraethyl oxirane-2,2-diylbis(phosphonate) (compound **5**; 400 mg, 1.26 mmol) in anhydrous tetrahydrofuran (5 mL). The reaction mixture was stirred at 0 °C for 1 h, was allowed to warm to room temperature, and was stirred overnight. The reaction was quenched by addition of a saturated aqueous solution of ammonium chloride (5 mL) and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with water (2 × 10 mL) and dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) with a mixture of hexane/EtOAc (9:1) as eluent to afford pure compound **9** (198 mg, 66% yield) as a colorless oil. This compound has already been described in the literature:[55] R_f = 0.78 (EtOAc/MeOH, 95:5). ^{1}H NMR ($CDCl_3$): δ = 0.89 (t, *J* = 6. 9 Hz, 3 H, 6-H), 1.29 (m, 4 H, 4-H, 5-H), 1.34 (dt, *J* = 7.1, 0.8 Hz, 6 H, CH_2CH_3), 1.37 (quint, *J* = 7.1 Hz, 2 H, 3-H), 1.68 (quint, *J* = 6.9 Hz, 2 H, 2-H), 4.03 (q, *J* = 6.9 Hz, 2 H, 1-H), 4.11 (dq, *J* = 8.0, 7.1 Hz, 2 H, CH_2CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.92 (s, C-6), 16.11 (d, *J* = 6.1 Hz, CH_2CH_3), 22.49 (s, C-5); 25.09 (s, C-4), 30.23 (d, *J* = 6.1 Hz, C-2) 31.30 (s, C-3), 63.58 (d, *J* = 5.1 Hz, CH_2CH_3), 67.67 (d, *J* = 6.10 Hz, C-1) ppm. ^{31}P NMR (D_2O): δ = –3.28 ppm. MS: *m*/*z* (%) = 239 (1) $[M + 1]^+$, 211 (3), 195 (3), 155(93), 127 (84), 99 (100). $C_{10}H_{23}O_4P$: calcd. C 50.41, H 9.73; found C 50.25, H 9.70.

Diethyl Prop-2-en-1-yl Phosphate (10): A solution of freshly prepared allylmagnesium chloride (3 mmol) in tetrahydrofuran (10 mL) was added at 0 °C under argon to a solution of tetraethyl oxirane-2,2-diylbis(phosphonate) (compound **5**; 350 mg,

1.10 mmol) in anhydrous tetrahydrofuran (5 mL). The reaction mixture was stirred at 0 °C for 1 h and was then allowed to warm to room temperature and was stirred overnight. The reaction was quenched by addition of an aqueous saturated solution of ammonium chloride (5 mL) and was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with water (2 × 10 mL) and dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) with a mixture of hexane/EtOAc (9:1) as eluent to afford pure compound **10** (114 mg, 57% yield) as a colorless oil: R_f = 0.42 (EtOAc/MeOH, 95:5). ^{1}H NMR ($CDCl_3$): δ = 1.35 (dt, J = 7.1, 1.0 Hz, 3 H, CH_2CH_3), 4.12 (quint, J = 7.2 Hz, 2 H, CH_2CH_3), 4.52 (ddt, J = 8.2, 5.6, 1.3 Hz, 2 H, 1-H), 5.27 (dd, J = 10.2, 1.0 Hz, 1 H, 3-H^a), 5.38 (dq, J = 17.2, 1.4 Hz, 1 H, 3-H^b), 5.95 (m, 1 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.58 (d, J = 7.1 Hz, CH_2CH_3), 63.88 (d, J = 6.1 Hz, CH_2CH_3), 67.89 (d, J = 6.10 Hz, C-1), 117.97 (C-3), 132.00 (d, J = 7.1 Hz, C-2) ppm. ^{31}P NMR (D_2O): δ = –3.90 ppm. MS: m/z (%) = 194 (1) $[M]^+$, 193 (33), 189 (14), 161 (24), 137 (43), 111 (45), 80 (100).

Tetraethyl 2-Methoxyethane-1,1-diylbis(phosphonate) (11): A solution of compound **4** (200 mg, 0.66 mmol) in anhydrous methanol (5 mL) was added under argon to a solution of sodium methoxide, freshly prepared from metallic sodium and anhydrous methanol. The reaction mixture was stirred at 0 °C for 1 h. Then, a saturated aqueous solution of ammonium chloride (1 mL) was added. The mixture was extracted with ethyl acetate (3 × 10 mL), the combined organic layers were washed with water (5 mL) and dried ($MgSO_4$), and the solvent was evaporated. The product was purified by reversed-phase column chromatography (C-18 silica gel) with methanol/H_2O (4:1) as eluent to afford pure compound **11** (50 mg, 40% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ = 1.34 (t, J = 7.1 Hz, 12 H, CH_2CH_3), 2.69 (tt, J = 23.9, 5.4 Hz, 1 H, 1-H), 3.37 (s, 3 H, 4-H), 3.89 (dt, J = 16.1, 5.5 Hz, 2 H, 2-H), 4.18 (m, 8 H, CH_2CH_3) ppm. This ^{1}H NMR spectrum is similar to that depicted in ref.[22]

Tetraethyl 2-Ethoxyethane-1,1-diylbis(phosphonate) (12): A solution of compound **4** (166 mg, 0.55 mmol) in anhydrous ethanol was treated as described for the preparation of **11**. The residue was purified by reversed-phase column chromatography (C-18 silica gel) with methanol/H_2O (4:1) as eluent to afford pure compound **12** (71 mg, 35% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$): δ = 1.20 (t, J = 6.9 Hz, 3 H, 5-H), 1.34 (t, J = 6.9 Hz, 12 H, CH_2CH_3), 2.69 (tt, J = 23.7, 5.4 Hz, 1 H, 1-H), 3.53 (q, J = 6.9 Hz, 2 H, 4-H), 3.92 (dt, J = 16.3, 5.5 Hz, 2 H, 2-H), 4.15 (m, 8 H, CH_2CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.92 (C-5), 16.30 (d, J = 6.1 Hz, CH_2CH_3), 38.89 (t, J = 132.6 Hz, C-1), 61.83 (d, J = 5.1 Hz, CH_2CH_3), 65.97 (t, J = 4.1 Hz, C-2), 66.50 (C-4) ppm. ^{31}P NMR ($CDCl_3$): δ = 20.87 ppm.

Tetraethyl 2-*n*-Propoxyethane-1,1-diylbis(phosphonate) (13): A solution of compound **4** (90 mg, 0.3 mmol) in anhydrous propanol was treated as described for the preparation of **11**. The residue was purified by reversed-phase column chromatography (C-18 silica gel) with methanol/H_2O (4:1) as eluent to afford pure compound **13** (20 mg, 20% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ = 0.92 (t, J = 7.4 Hz, 3 H, 6-H), 1.34 (t, J = 6.9 Hz, 12 H, CH_2CH_3), 1.59 (sext, J = 7.1 Hz, 2 H, 5-H), 2.68 (tt, J = 23.9, 5.4 Hz, 1 H, 1-H), 3.42 (t, J = 6.7 Hz, 2 H, 4-H), 3.92 (dt, J = 16.3, 5.2 Hz, 2 H, 2-H), 4.17 (m, 8 H, CH_2CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 10.46 (C-6), 16.29 (t, J = 7.2 Hz, CH_2CH_3), 22.70 (C-5), 38.88 (t, J = 133.1 Hz, C-1), 72.96 (C-4) ppm. ^{31}P NMR ($CDCl_3$): δ = 20.41 ppm. MS: m/z (%) = 361 (1) $[M + 1]^+$, 302 (9), 223 (100), 165 (74).

Diethyl (2-Methoxyethyl)phosphonate (14). Method A: A solution of compound **4** (200 mg, 0.66 mmol) in anhydrous methanol (5 mL) was added under argon to a freshly prepared solution of sodium methoxide (1.0 M, 10 mL). The reaction mixture was stirred at room temperature overnight, and a saturated aqueous solution of ammonium chloride (1 mL) was then added. The mixture was extracted with ethyl acetate (3 × 10 mL), the combined organic phases were washed with water (5 mL) and dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) with a mixture of hexane/EtOAc (9:1) as eluent to afford pure compound **14** (50 mg, 40% yield) as a colorless oil. R_f = 0.35 (AcOEt). ^{1}H NMR ($CDCl_3$): δ = 1.33 (t, J = 7.1 Hz, 6 H, CH_2CH_3), 2.10 (dt, J = 18.7, 7.5 Hz, 2 H, 1-H), 3.35 (s, 3 H, 4-H), 3.64 (dt, J = 12.1, 7.4 Hz, 2 H, 2-H), 4.10 (m, 4 H, CH_2CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 16.33 (d, J = 6.1 Hz, CH_2CH_3), 26.87 (d, J = 140.4 Hz, C-1), 58.40 (C-4), 61.57 (d, J = 6.1 Hz, CH_2CH_3), 66.37 (C-2) ppm. ^{31}P NMR ($CDCl_3$): δ = 26.07 ppm. MS: m/z (%) = 195 (22) $[M - 1]^+$, 179 (22), 165 (13), 139 (13), 111 (14), 71 (100). **Method B:** A solution of compound **5** (300 mg, 1.0 mmol) in anhydrous methanol (5 mL) was added under argon to a freshly prepared solution of sodium methoxide (1.0 M, 10 mL). The reaction mixture was stirred at room temperature overnight, and a saturated aqueous solution of ammonium chloride (1 mL) was then added. The mixture was extracted with ethyl acetate (3 × 10 mL), the combined organic phases were washed with water (5 mL) and dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) with a mixture of hexane/EtOAc (9:1) as eluent to afford pure compound **14** (60 mg, 31% yield) as a colorless oil.

Diethyl (2-Ethoxyethyl)phosphonate (15). Method A: A solution of compound **4** (200 mg, 0.66 mmol) in anhydrous ethanol (5 mL) was treated with a solution of freshly prepared sodium ethoxide (1.0 m) as described for the preparation of **14**. The residue was purified by column chromatography (silica gel) with a mixture of hexane/EtOAc (9:1) as eluent to afford pure compound **15** (125 mg, 85% yield) as a colorless oil. R_f = 0.32 (AcOEt). ^{1}H NMR ($CDCl_3$): δ = 1.20 (t, J = 7.0, Hz, 3 H, 5-H), 1.32 (t, J = 7.0 Hz, 6 H, CH_2CH_3), 2.10 (dt, J = 18.7, 7.5 Hz, 2 H, 1-H), 3.50 (q, J = 7.0 Hz, 2 H, 4-H), 3.67 (dt, J = 11.6, 7.5 Hz, 2 H, 2-H), 4.10 (m, 4 H, CH_2CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.08 (C-5), 16.40 (d, J = 6.1 Hz, CH_2CH_3), 27.11 (d, J = 139.4 Hz, C-1), 61.59 (d, J = 6.1 Hz, CH_2CH_3), 64.32 (C-4), 66.21 (C-2) ppm. ^{31}P NMR ($CDCl_3$): δ = 26.25 ppm. MS: m/z (%) = 210 (2) $[M]^+$, 195 (21), 179 (20), 165 (17), 71 (100). **Method B:** A solution of sodium ethoxide (1.0 M, 10 mL) was added under argon to a solution of compound **5** (300 mg, 1.0 mmol) in anhydrous ethanol (5 mL). The reaction mixture was treated as described for **14**. The product was purified by column chromatography (silica gel) with a mixture of hexane/EtOAc (9:1) as eluent to afford pure compound **15** (101 mg, 40% yield) as a colorless oil.

Diethyl (2-Propoxyethyl)phosphonate (16). Method A: A solution of compound **4** (200 mg, 0.66 mmol) in anhydrous propanol (5 mL) was treated as described for the preparation of **14**. The residue was purified by column chromatography (silica gel) with a mixture of hexane/EtOAc (9:1) as eluent to afford pure compound **16** (145 mg, 92% yield) as a colorless oil. R_f = 0.38 (AcOEt). ^{1}H NMR ($CDCl_3$): δ = 0.92 (t, J = 7.4, Hz, 3 H, 6-H), 1.32 (t, J = 7.1 Hz, 6 H, CH_2CH_3), 1.59 (sext, J = 7.1 Hz, 2 H, 5-H), 2.10 (dt, J = 18.9, 7.4 Hz, 2 H, 1-H), 3.39 (t, J = 6.2 Hz, 2 H, 4-H), 3.67 (dt, J = 11.6, 7.4 Hz, 2 H, 2-H), 4.10 (m, 4 H, CH_2CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 10.50 (C-6), 16.40 (d, J = 5.9 Hz, CH_2CH_3), 22.82 (C-5), 27.06 (d, J = 139.0 Hz, C-1), 61.60 (d, J = 6.8 Hz, CH_2CH_3), 64.50 (C-2), 72.66 (C-4) ppm. ^{31}P NMR ($CDCl_3$): δ = 26.36 ppm. MS: m/z (%) = 225 (4) $[M + 1]^+$, 195 (7), 181 (73), 166 (40), 138 (66), 125 (100), 109 (77), 81 (42). **Method B:** A solution of sodium

propoxide (1.0 M, 10 mL) was added under argon to a solution of compound **5** (160 mg, 0.51 mmol) in anhydrous propanol (5 mL). The reaction mixture was treated as described for **14**. The product was purified by column chromatography (silica gel) with a mixture of hexane/EtOAc (9:1) as eluent to afford pure compound **16** (58 mg, 51% yield) as a colorless oil.

Diethyl (2-Butoxyethyl)phosphonate (17). Method A: A solution of compound **4** (179 mg, 0.60 mmol) in anhydrous *n*-butanol (5 mL) was treated as described for the preparation of **14**. The product was purified by column chromatography (silica gel) with a mixture of hexane/EtOAc (9:1) as eluent to afford pure compound **17** (25 mg, 30% yield) as a colorless oil. R_f = 0.60 (AcOEt). ^{1}H NMR ($CDCl_3$): δ = 0.92 (t, J = 7.4, Hz, 3 H, 7-H), 1.32 (t, J = 7.0 Hz, 6 H, CH_2CH_3), 1.35 (sext, J = 7.4 Hz, 2 H, 6-H), 1.55 (m, 2 H, 5-H), 2.10 (dt, J = 18.7, 7.5 Hz, 2 H, 1-H), 3.43 (t, J = 6.7 Hz, 2 H, 4-H), 3.67 (dt, J = 11.6, 7.5 Hz, 2 H, 2-H), 4.10 (m, 4 H, CH_2CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.74 (C-7), 16.29 (d, J = 6.1 Hz, CH_2CH_3), 19.17 (C-6), 26.99 (d, J = 139.4 Hz, C-1), 31.61 (C-5), 61.46 (d, J = 6.1 Hz, CH_2CH_3), 64.44 (C-2), 70.64 (C-4) ppm. ^{31}P NMR ($CDCl_3$): δ = 26.26 ppm. MS: *m*/*z* (%) = 239 (6) $[M + 1]^+$, 195 (11), 181(100), 166 (55), 138 (70), 109 (85). **Method B:** A solution of sodium *n*-butoxide (1.0 m, 10 mL) was added under argon to a solution of compound **5** (120 mg, 0.38 mmol) in anhydrous butanol (5 mL). The reaction mixture was treated as described for **14**. The product was purified by column chromatography (silica gel) with a mixture of hexane/EtOAc (9:1) as eluent to afford pure compound **17** (61 mg, 61% yield) as a colorless oil.

Diethyl [1-(Diethoxyphosphoryl)-2-thiocyanatoethyl]phosphonate (18): Potassium thiocyanate (22 mg, 0.22 mmol) was added to a solution of tetraethyl ethane-1,1-diylbis(phosphonate) (**4**; 50 mg, 0.16 mmol) in water (2 mL). The reaction mixture was stirred at room temperature for 24 h. The mixture was extracted with dichloromethane (3 × 5 mL), the combined organic layers were washed with water (5 mL) and dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) with a mixture of hexane/EtOAc (7:3) as eluent to afford pure compound **18** (43 mg, 72% yield) as a colorless oil. R_f = 0.1 (EtOAc/MeOH, 97:3). ^{1}H NMR ($CDCl_3$): δ = 1.35 (t, J = 7 Hz, 12 H, CH_2CH_3), 2.61 (tt, J = 23.2, 5.5 Hz, 1 H, 1-H), 4.08 (dt, J = 17.1, 5.5 Hz, 2 H, 2-H), 4.18 (m, 8 H, CH_2CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 16.30 (d, J = 6.8 Hz, CH_2CH_3), 40.47 (d, J = 131.8 Hz, C-1), 58.59 (t, J = 5.1 Hz, C-2) 62.73 (d, J = 6.8 Hz, CH_2CH_3), 63.03 (d, J = 6.8 Hz, CH_2CH_3), 149.03 (C-3) ppm. ^{31}P NMR (D_2O): δ = 19.10 ppm. IR (film): $\tilde{\nu}$ = 2986, 2357, 1662, 1392, 1242, 1026, 976, 856, 802; 679 cm^{-1}. MS: *m*/*z* (%) = 333 (1) $[M]^+$, 319 (2), 301(6), 288 (12), 261 (20), 195 (45), 181 (100), 171 (43), 163 (58), 125 (43), 109 (73), 81 (65), 65 (72).

Diethyl [1-(Diethoxyphosphoryloxy)-2-(phenylsulfanyl)ethyl]phosphonate (19): Potassium hydroxide (530 mg, 9.5 mmol) was added to a solution of thiophenol (1.04 g, 9.5 mmol) in water (5 mL). The mixture was stirred at room temperature for 5 min, tetraethyl oxirane-2,2-diylbis(phosphonate) (300 mg, 0.94 mmol) was then added, and the reaction mixture was stirred at room temperature for 30 min. The mixture was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride (2 × 10 mL) and dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) with a mixture of hexane/EtOAc (7:3) as eluent to yield pure compound **19** (123 mg, 30% yield) as a colorless oil. R_f = 0.66 (EtOAc/*i*PrOH, 9:1). ^{1}H NMR ($CDCl_3$): δ = 1.328 (t, J = 7.1 Hz, 6 H, CH_2CH_3), 1.329 (dt, J = 7.1, 1.2 Hz, 3 H, CH_2CH_3), 1.335 (dt, J = 7.1, 1.2 Hz, 3 H, CH_2CH_3), 3.27 (dt, J = 14.4, 9.2 Hz, 1 H, 2-H^a), 3.48 (dddd, J = 14.4, 7.1, 3.3, 2.8 Hz, 1 H, 2-H^b), 4.19 (m, 8 H, CH_2CH_3), 4.74 (dddd, J = 10.5, 9.6, 8.3, 3.3 Hz, 1 H, 1-H), 7.23 (tt, J = 7.5, 1.9 Hz, 1 H, aromatic proton), 7.31 (m, 2 H, aromatic protons), 7.46 (m, 2 H, aromatic protons) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.99 (t, J = 6.8 Hz, CH_3), 16.36 (t, J = 5.5 Hz, CH_3), 36.11 (t, J = 3.8 Hz, C-2), 63.19 (dd, J = 6.8, 5.1 Hz, CH_2), 64.27 (dd, J = 37.3, 5.9 Hz, CH_2), 71.46 (dd, J = 165.3, 7.6 Hz, C-1), 126.98 (C-6), 129.12 (C-5), 130.69 (C-4), 134.87 (C-3) ppm. ^{31}P NMR (D_2O): δ = –4.03 [d, J = 16.6 Hz, O–P(O)(OEt)$_2$], 15.45 [d, J = 16.6 Hz, C–P(O)(OEt)$_2$] ppm. IR (film): $\tilde{\nu}$ = 2983, 2931, 1538, 1481, 1440, 1394, 1263, 1164, 792, 746, 534 cm^{-1}. MS: *m*/*z* (%) = 427 (2) $[M + 1^+]$, 272 (57), 195 (18), 163 (100), 135 (23), 109 (24).

Supporting Information (see footnote on the first page of this article): ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra and mass spectra for all compounds described in this work. DEPT spectra, ^{1}H-^{1}H COSY spectra, and ^{1}H-^{13}C 2D correlation spectra for compounds **8** and **19**; ^{1}H-^{31}P HMBC for compound **8**.

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[1] M. L. Lolli, L. Lazzarato, A. Di Stilo, R. Fruttero, A. Gasco, *J. Organomet. Chem.* **2002**, *650*, 77–83.
[2] D. W. Hutchinson, D. M. Thornton, *J. Organomet. Chem.* **1988**, *346*, 341–348.
[3] T. Okauchi, T. Kakiuchi, N. Kitamura, T. Utsunomiya, J. Ichikawa, T. Minami, *J. Org. Chem.* **1997**, *62*, 8419–8424.
[4] T. Minami, J. Motoyoshiya, *Synthesis* **1992**, 333–349.
[5] T. Minami, T. Utsunomiya, S. Nakamura, M. Okubo, N. Kitamura, J. Okada, J. Ichikawa, *J. Org. Chem.* **1994**, *59*, 6717–6727.
[6] Y. Shen, P. Li, *J. Fluorine Chem.* **2003**, *121*, 219–222.
[7] M. J. Rogers, *Curr. Pharm. Des.* **2003**, *9*, 2643–2658.
[8] G. A. Rodan, *Annu. Rev. Pharmacol. Toxicol.* **1998**, *38*, 375–388.
[9] G. A. Rodan, T. J. Martin, *Science* **2000**, *289*, 1508–1514.
[10] A. A. Reszka, G. A. Rodan, *Curr. Rheumatol. Rep.* **2003**, *5*, 65–74.
[11] J. E. Dunford, K. Thompson, F. P. Coxon, S. P. Luckman, F. M. Hahn, C. D. Poulter, F. H. Ebetino, M. J. Rogers, *J. Pharmacol. Exp. Ther.* **2001**, *296*, 235–242.
[12] M. J. Rogers, S. Gordon, H. L. Benford, F. P. Coxon, S. P. Luckman, J. Monkkonen, J. C. Frith, *Cancer (Suppl.)* **2000**, *88*, 2961–2978.
[13] J. A. Urbina, B. Moreno, S. Vierkotter, E. Oldfield, G. Payares, C. Sanoja, B. N. Bailey, W. Yan, D. A. Scott, S. N. J. Moreno, R. Docampo, *J. Biol. Chem.* **1999**, *274*, 33609–33615.
[14] S. H. Szajnman, B. N. Bailey, R. Docampo, J. B. Rodriguez, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 789–792.
[15] M. B. Martin, J. S. Grimley, J. C. Lewis, H. T. Heath, B. N. Bailey, H. Kendrick, V. Yardley, A. Caldera, R. Lira, J. A. Urbina, S. N. J. Moreno, R. Docampo, S. L. Croft, E. Oldfield, *J. Med. Chem.* **2001**, *44*, 909–916.
[16] M. B. Martin, J. M. Sanders, H. Kendrick, K. de Luca-Fradley, J. C. Lewis, J. S. Grimley, E. M. Van Bussel, J. R. Olsen, G. A. Meints, A. Burzynska, P. Kafarski, S. L. Croft, E. Oldfield, *J. Med. Chem.* **2002**, *45*, 2904–2914.
[17] S. Ghosh, J. M. Chan, C. R. Lea, G. A. Meints, J. C. Lewis, Z. S. Tovian, R. M. Flessner, T. C. Loftus, I. Bruchhaus, H. Kendrick, S. L. Croft, R. G. Kemp, S. Kobayashi, T. Nozaki, E. Oldfield, *J. Med. Chem.* **2004**, *47*, 175–187.

[18] S. H. Szajnman, A. Montalvetti, Y. Wang, R. Docampo, J. B. Rodríguez, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3231–3235.
[19] J. M. Sanders, A. O. Gomez, J. Mao, G. A. Meints, E. M. Van Brussel, A. Burzynska, P. Kafarski, D. Gonzalez-Pacanowska, E. Oldfield, *J. Med. Chem.* **2003**, *46*, 5171–5183.
[20] G. R. Kieczykowski, R. B. Jobson, D. G. Melillo, D. F. Reinhold, V. J. Grenda, I. Shinkai, *J. Org. Chem.* **1995**, *60*, 8310–8312.
[21] M. Lecouvey, I. Mallard, T. Bailly, R. Burgada, Y. Leroux, *Tetrahedron Lett.* **2001**, *42*, 8475–8478.
[22] G. Sturtz, J. Guervenou, *Synthesis* **1991**, 661–662.
[23] R. Gancarz, I. Gancarz, A. Deron, *Phosphorus, Sulfur Silicon* **2000**, *161*, 61–69.
[24] E. Y. Spencer, A. Todd, R. F. Webb, *J. Chem. Soc.* **1958**, 2968–2972.
[25] H. Timmler, J. Kurz, *Chem. Ber.* **1971**, *104*, 3740–3749.
[26] E. C. Ashby, B. Park, G. S. Patil, R. Gurumurthy, *J. Org. Chem.* **1993**, *58*, 424–437.
[27] E. C. Ashby, *Acc. Chem. Res.* **1988**, *21*, 414–421.
[28] M. Newcomb, D. P. Curran, *Acc. Chem. Res.* **1988**, *21*, 206–214.
[29] E. C. Ashby, A. B. Goel, *J. Am. Chem. Soc.* **1981**, *103*, 4983–4985.
[30] C. Arnoldi, A. Citterio, F. Minisci, *J. Chem. Soc. Perkin Trans. 2* **1983**, 531–541.
[31] S. F. Rak, L. L. Miller, *J. Am. Chem. Soc.* **1992**, *114*, 1388–1394.
[32] F. Doctorovich, N. S. Nudelman, *Magn. Res. Chem.* **1990**, *28*, 576–579.
[33] G. García Liñares, N. S. Nudelman, *J. Phys. Org. Chem.* **2003**, *16*, 569–576.
[34] T. Holm, I. Crossland, *Acta Chem. Scand.* **1971**, *25*, 59.
[35] E. C. Ashby, J. Bowers, R. Depriest, *Tetrahedron Lett.* **1980**, *21*, 3541–3541.
[36] Quin, L. *A Guide to Organophosphorus Chemistry*, John Wiley & Sons, Inc., New York, **2000**, chapter 2, pp. 11–22.
[37] A. Alberti, M. Benaglia, M. A. Della Bona, D. Macciantelli, B. Heuzé, S. Masson, A. Hudson, *J. Chem. Soc. Perkin Trans. 2* **1996**, 1057–1063.
[38] E. Font-Sanchis, C. Aliaga, E. V. Bejan, R. Cornejo, J. C. Scaiano, *J. Org. Chem.* **2003**, *68*, 3199–3204.
[39] W. Bhanthumnavin, W. G. Bentrude, *J. Org. Chem.* **2001**, *66*, 980–990.
[40] J. A. Howard, J. C. Tait, *J. Org. Chem.* **1978**, *43*, 4279–4283.
[41] R. Ruel, J.-P. Bouvier, R. N. Young, *J. Org. Chem.* **1995**, *60*, 5209–5213.
[42] C. R. Degenhardt, D. C. Burdsall, *J. Org. Chem.* **1986**, *51*, 3488–3490.
[43] M. Prashad, *Tetrahedron Lett.* **1993**, *34*, 1585–1588.
[44] W. F. Gilmore, J. W. Huber III, *J. Org. Chem.* **1973**, *38*, 1423–1424.
[45] W. S. Wadsworth, W. D. Emmons, *J. Am. Chem. Soc.* **1961**, *83*, 1733–1738.
[46] J. F. Reichwein, B. L. Pagenkopf, *J. Am. Chem. Soc.* **2003**, *125*, 1821–1824.
[47] S. A. Holstein, D. M. Cermak, D. F. Wiemer, K. Lewis, R. J. Hohlb, *Bioorg. Med. Chem.* **1998**, *6*, 687–694.
[48] Y. Xu, L. Qian, G. D. Prestwich, *Org. Lett.* **2003**, *5*, 2267–2270.
[49] E. E. van Tamelen, *Organic Syntheses*, Wiley & Sons, New York, **1963**, Collect. Vol. IV, pp. 232–234.
[50] G. M. Cinque, S. H. Szajnman, L. Zhong, R. Docampo, A. J. Schvartzapel, J. B. Rodríguez, E. G. Gros, *J. Med. Chem.* **1998**, *41*, 1540–1554.
[51] E. E. van Tamelen, *J. Am. Chem. Soc.* **1951**, *73*, 3444–3448.
[52] C. E. Burgos-Lepley, S. A. Mizsak, R. A. Nugent, R. A. Johnson, *J. Org. Chem.* **1993**, *58*, 4159–4161.
[53] G. D. Duncan, Z.-M. Li, A. B. Khare, C. E. McKenna, *J. Org. Chem.* **1995**, *60*, 7080–7081.
[54] D. R. Brittelli, *J. Org. Chem.* **1985**, *50*, 1845–1847.
[55] G. Ilia, A. Popa, S. Iliescu, A. Bora, G. Dehelean, A. Pascariu, *Phosphorus, Sulfur Silicon* **2003**, *78*, 1513–1519.

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