1,3-Dipolar Cycloadditions of the Versatile Intermediate Tetraethyl Vinylidenebisphosphonate

Mariana Ferrer-Casal, Alejandro P. Barboza, Sergio H. Szajnman,* Juan B. Rodriguez*

Departamento de Química Orgánica and UMYMFOR (CONICET–FCEyN), Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Pabellón 2, Ciudad Universitaria, C1428EHA Buenos Aires, Argentina
Fax +54(11)45763346; E-mail: shs@qo.fcen.uba.ar; E-mail: jbr@qo.fcen.uba.ar

Received: 06.05.2013; Accepted after revision: 31.05.2013

Abstract: The use of tetraethyl vinylidenebisphosphonate as a dipolarophile in 1,3-dipolar cycloaddition reactions was investigated. In particular, the cycloaddition reactions between tetraethyl vinylidenebisphosphonate and azides and nitrile oxides, and of tetraethyl vinylidenebisphosphonate in the Grigg azomethine 1,3-dipolar cyclization were studied, affording highly functionalized five-membered rings containing the bisphosphonic unit. These straightforward methods allow the preparation of diverse and fairly complex structures bearing the bisphosphonate moiety, which belong to a group of pharmacologically important compounds.

Key words: bisphosphonates, 1,3-dipolar cycloadditions, azides, nitrile oxides, Grigg azomethine ylides

Bisphosphonates **1** are metabolically stable analogues of naturally occurring pyrophosphates **2** in which a substituted methylene group replaces the oxygen atom bridge between the two phosphorus atoms of the pyrophosphate moiety. Bisphosphonates have become compounds of pharmacological significance as a result of calcification studies performed more than 40 years ago.[1–3] Pamidronate (**3**), alendronate (**4**), risedronate (**5**), and ibandronate (**6**) (here shown in their acid forms) are representative bisphosphonates that are FDA-approved drugs for the long-term treatment and prevention of osteoclast-mediated bone resorption associated with osteoporosis, hypercalcemia, tumor bone metastases, Paget's disease, postmenopausal osteoporosis, and other bone diseases (Figure 1).[4–7] Bisphosphonates are not only important drugs for bone diseases, but also exhibit a wide range of biological properties such as anticancer action,[8] stimulation of γδ T cells,[9] antibacterial action,[10] herbicidal properties,[11] being potent and selective inhibitors of acid sphingomyelinase,[12] and being antiparasitic agents.[13]

Because of the pharmacological importance of 1,1-bisphosphonate derivatives, much attention has been focused on their syntheses. Prospects in the bisphosphonate drug area changed substantially since the development of a reliable and reproducible synthetic approach for obtaining 1-hydroxy-1,1-bisphosphonic acids of formula **7** from carboxylic acids, which can be converted into **7** by treatment with phosphorous acid and phosphorus trichloride in the presence of benzenesulfonic acid, followed by hydrolysis.[14] The 1-hydroxy-*gem*-bisphosphonate derivatives have become the most relevant ones. In addition, 1-amino-1,1-bisphosphonic acids of formula **8** are currently prepared from cyano derivatives[15] or amides,[16] while 1-(substituted amino)methylene-1,1-bisphosphonates **9** are usually synthesized starting from the corresponding amine (Figure 2).[17]

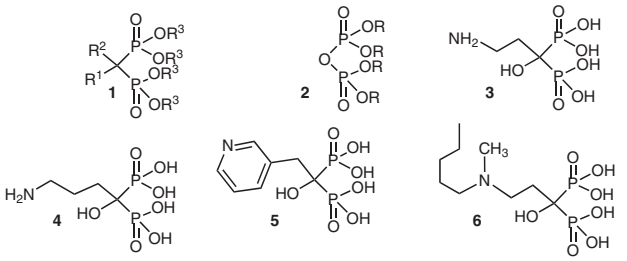


Figure 1 General formulae and chemical structures of representative FDA-approved bisphosphonates clinically employed for long-term treatment of different bone disorders

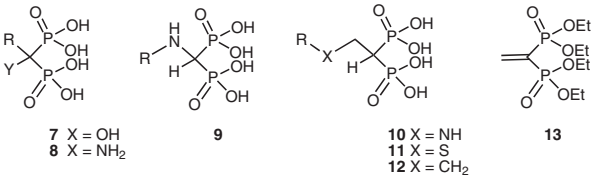
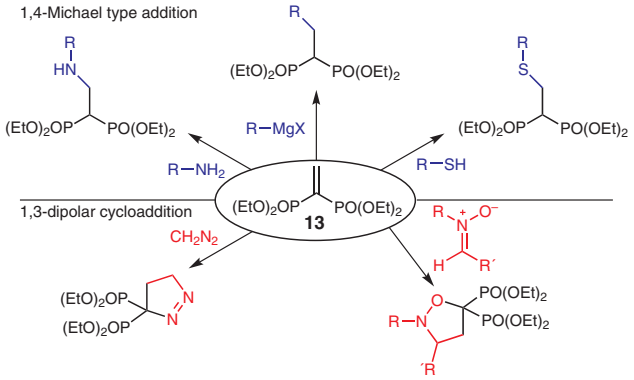


Figure 2 General formulae of a different class of bisphosphonates

Tetraethyl vinylidenebisphosphonate (**13**), which is straightforwardly prepared from commercially available tetraethyl methylenebisphosphonate,[18] is a versatile synthetic intermediate for accessing a variety of compounds bearing the *gem*-bisphosphonate moiety found in **10**–**12**, and others.[19] Compound **13** behaves as a highly activated Michael acceptor, giving rise to 1,4-conjugated adducts, either with strong nucleophiles such as Grignard reagents,[19d,e] or with very mild ones such as amines[19a,b] or mercaptans.[20] In connection with this conjugate addition, **13** and other closely related substituted derivatives have also been used in a number of asymmetric Michael-type additions employing, mostly, enolate species as nucleophiles.[21] The use of pericyclic reactions might have great utility as a synthetic approach to access diverse chemical structures bearing the bisphosphonic moiety. However, there are just a few examples where **13** undergoes cycloaddition reactions, acting either as a dienophile in Diels–

SYNTHESIS 2013, 45, 2397–2404
Advanced online publication: 10.07.2013
DOI: 10.1055/s-0033-1338498; Art ID: SS-2013-M0340-OP

Alder reactions,[22] or as a dipolarophile in 1,3-dipolar cycloadditions.[23–25] Therefore, at present, the use of **13** as a substrate for cycloaddition reactions is definitely an under-explored area of research. The role of **13** in conjugate additions or 1,3-dipolar cycloadditions is summarized in Scheme 1.

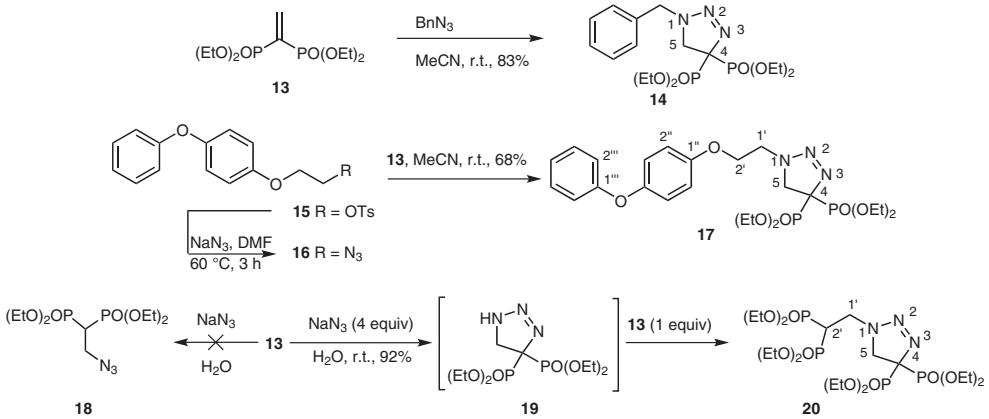


Scheme 1 Conjugate additions and 1,3-dipolar cycloadditions of **13**

In this study, we report on the use of tetraethyl vinylidenebisphosphonate as a valuable intermediate to access putatively relevant bisphosphonate derivatives.

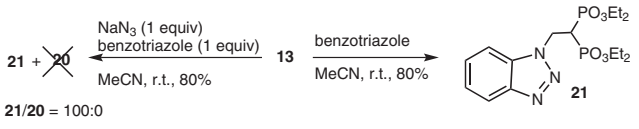
Azide-containing compounds have been widely used in 1,3-dipolar cycloadditions with a number of activated and non-activated alkenes.[26–28] Since we want to access bisphosphonates with diverse chemical structures, it was considered that **13** on treatment with alkyl azides would lead to relatively complex alkyl-4,5-dihydro-1*H*-1,2,3-triazole-4,4-diyl-*gem*-bisphosphonates. Indeed, the reaction between **13** and benzyl azide in acetonitrile at room temperature afforded cycloadduct **14** in 83% yield (Scheme 2). NMR spectroscopy was very helpful to confirm the formation of **14**. In the ^{1}H NMR spectrum, H-5 appeared as a triplet centered at δ = 3.64, coupled with the two adjacent phosphorus atoms ($J_{H–P}$ = 26.7 Hz). This diagnostic signal confirmed that **14** was formed. In the ^{13}C NMR spectrum, the C-4 signal was observed as a triplet centered at δ = 84.3 ($J_{C–P}$ = 151.2 Hz), while the C-5 signal was observed as a triplet centered at δ = 49.1, but with a smaller coupling constant ($J_{C–P}$ = 2.0 Hz). Similarly, a slightly more complex azide such as **16**, prepared from the known tosylate **15**,[29] also gave rise to a 1,2,3-triazole **17** in 68% yield. In this case, similar diagnostic signals were observed in the ^{1}H and ^{13}C NMR data, indicating that this cycloaddition reaction took place (Scheme 2). The corresponding regioisomer could not be observed. Frontier orbital theory provides strong evidence to assume dipole-HO-controlled regiochemistry to yield the molecular targets **14**, **17**, and **20** through **19**.[30]

On the other hand, it has been described that sodium azide can undergo dipolar 1,3-cycloadditions on reaction with α,β-unsaturated carbonyl compounds.[31] It has also been reported that when **13** was reacted with sodium azide in water as solvent, **13** behaved as a Michael acceptor instead of as a dipolarophile, to afford **18**.[32] There have been no spectroscopic NMR data available to support the structure of **18**.[32] Nevertheless, contrary to what was published,[32] reaction of **13** with an excess of sodium azide did not lead to the Michael adduct **18** or to the expected hypothetical cycloaddition product **19**, but to **20** instead (Scheme 2). The ^{1}H NMR spectrum of **20** was in agreement with the proposed structure. A triplet of triplets ($J_{H–P}$ = 24.2 Hz and $J_{H–H}$ = 5.2 Hz) centered at δ = 2.76, assigned to H-2′, clearly indicated the portion of the molecule that, apparently, underwent conjugate addition (Scheme 2). Another diagnostic signal was a triplet centered at δ = 3.81 ($J_{H–P}$ = 26.5 Hz), assigned to H-5, and is typical in these 4,5-dihydro-1*H*-1,2,3-triazole rings. The ^{13}C NMR spectra was also very interesting, showing two different carbon atoms (C-4 and C-2′) bonded to two phosphorus atoms each. Indeed, two indicative signals were observed, one of them as a triplet centered at δ = 37.3 ($J_{C–P}$ = 131.7 Hz; C-4), and the other one as a triplet centered at δ = 85.1 ($J_{C–P}$ = 150.8 Hz; C-2′). The ^{31}P NMR spectrum also supported the presence of two distinct *gem*-bisphosphonic acid units within the molecule showing two well-differentiated signals at δ = 14.44 and 20.84, respectively. The reaction between **13** and sodium azide was carried out in different solvents such as methanol, acetonitrile, and methanol–water (1:1), but afforded, in all cases, **20** exclusively in excellent yields.



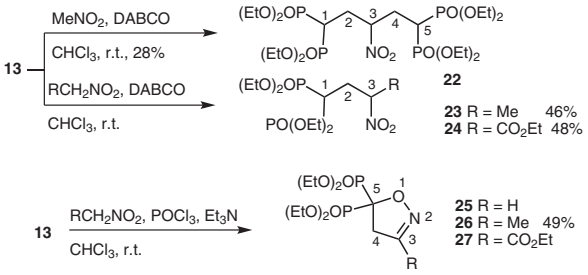
Scheme 2 1,3-Dipolar cycloaddition reactions between **13** and various azides

To rationalize the formation of **20**, the nucleophilicity of a compound containing the 4,5-dihydro-1*H*-1,2,3-triazole unit such as benzotriazole was studied. Reaction of **13** with benzotriazole gave the Michael adduct **21** in 80% yield (Scheme 3). It was therefore postulated that the formation of **20** resulted after a 1,3-dipolar cycloaddition reaction occurred first to give **19**, which, once produced, reacted immediately with another molecule of **13** to undergo a Michael-type reaction yielding **20** (Scheme 2). Competitive reaction studies on **13** reinforced the above idea. When **13** was treated with a solution containing sodium azide (one equivalent) and benzotriazole (one equivalent), only the Michael adduct **21** was formed, while **20** was not detected (Scheme 3). In summary, azides in general act, in these systems, as dipolar compounds rather than as nucleophiles, and the reactions proceed with high regioselectivity.



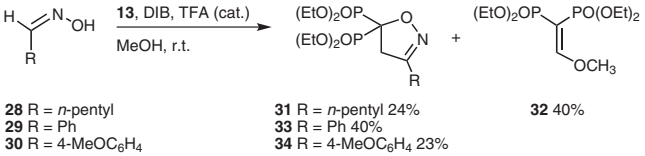
Scheme 3 Competition between Michael addition versus 1,3-dipolar cycloaddition

1,3-Dipolar cycloadditions of **13** with nitrile oxides would afford bisphosphonates bearing the 4,5-dihydroisoxazole ring. To date, only a short communication has reported this type of reaction, by using **13** as a substrate and hydroxamic chlorides as the nitrile oxides source.[25] These reactive intermediates can also be prepared in situ from primary nitro compounds, particularly by dehydration of these compounds by employing a combination of an acetylating agent and a base.[33] The use of a base without an acetylating agent appeared to be an interesting method to study this reaction.[34] Unfortunately, despite this method having been described, in our hands, the use of 1,4-diazabicyclo[2.2.2]octane as a base was not satisfactory to allow 1,3-dipolar cycloaddition reactions of **13**.[34] Only conjugate addition was observed in all cases. For example, an interesting case was the use of nitromethane in the presence of diazabicyclo[2.2.2]octane in chloroform; a double conjugate addition with **13** gave **22** exclusively (Scheme 4). This tendency to form **22** when the reaction is carried out under very mild basic conditions, such as in the presence of diisopropylamine in tetrahydrofuran, has been reported previously.[35] The use of nitroethane or ethyl nitroacetate as substrates gave rise to 1,4-conjugate addition. In these cases, only one molecule of **13** was incorporated to afford **23** and **24**, respectively. On the other hand, nitrile oxides can also be prepared from nitro derivatives by treatment with phosphoryl chloride and triethylamine.[36,37] Therefore, on treatment with nitroethane, **13** was converted into **26** in 49% yield. In the ^{1}H NMR spectrum, the H-4 signal that appeared as a triplet (J_{H-P} = 3.4 Hz) centered at δ = 3.57 confirmed the regioselective formation of **26**. This method was not satisfactory to obtain the hypothetical **25** and **27** starting from nitro compounds (Scheme 4).



Scheme 4 Conjugate addition versus 1,3-dipolar cycloaddition of nitrile oxides by employing nitro compounds as source

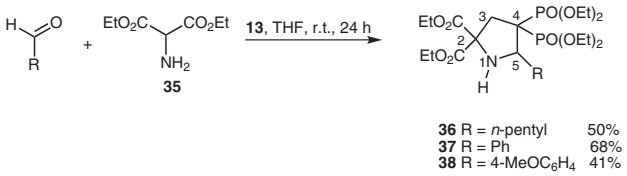
3-Substituted 5-dihydroisoxazole derivatives can also be prepared by employing oximes as a source of nitrile oxides by treatment with (diacetoxyiodo)benzene (DIB) in the presence of trifluoroacetic acid.[38] Oximes **28**–**30** were obtained by following standard procedures.[39] When a methanolic solution of **28** in the presence of (diacetoxyiodo)benzene reacted with **13**, the expected 1,3-cycloadduct **31** was produced in a low but reproducible yield of 24%. The H-4 signal appeared as a triplet (J_{H-P} = 23.7 Hz) centered at δ = 3.56, while the signal assigned to C-5 was observed as a triplet (J_{C-P} = 157.8 Hz) centered at δ = 81.7, indicating that a carbon atom is bonded to two phosphorus atoms and one oxygen atom. The stereochemical course of the reaction can also be explained by dipole-HO-controlled regiochemistry.[30] Unexpectedly, an equivalent amount of the enol ether **32** was formed, probably via conjugate addition of methanol, followed by oxidation. Aromatic oximes of benzaldehyde and *p*-anisaldehyde **29** and **30** gave rise to 1,3-dipolar cycloaddition products **33** (40%) and **34** (23%), respectively, by treatment with diacetoxyiodobenzene and **13** in the presence of trifluoroacetic acid (Scheme 5).



Scheme 5 1,3-Dipolar cycloaddition of nitrile oxides when employing oximes as source

The Grigg azomethine ylide cyclization is an interesting 1,3-dipolar cascade cycloaddition reaction where an in situ imine formation takes place from an aldehyde and an α-amino acid.[40] This imine acts as an azomethine ylide in the presence of a suitable dipolarophile. When **13** was treated with an aldehyde and diethyl aminomalonate (**35**) in tetrahydrofuran,[41] highly functionalized bisphosphonates **36**–**38** with pyrrolidine backbones were produced in 50%, 68%, and 40% yield, respectively (Scheme 6). Once again, the reactions proceeded with high regioselectivity as expected.[30] Taking **37** as an example, the ^{1}H NMR

spectrum confirmed its chemical structure. Bearing in mind that a new stereogenic center (C-5) was formed, the H-5 signal appeared as a doublet of doublets centered at δ = 4.99, coupled with two distinct phosphorus atoms.



Scheme 6 Grigg azomethine ylide 1,3-dipolar cascade cycloaddition

In this article we have described the ability of **13** to behave as a dipolarophile in 1,3-dipolar cycloaddition reactions. This approach allowed us to obtain different polyfunctionalized rings bearing a *gem*-bisphosphonate moiety. In all cases, we were able to obtain nitrogen-containing bisphosphonates in specifically substituted five-membered rings such as triazoles, pyrrolidines, and isoxazoles with high regioselectivity. In summary, **13**, via 1,3-dipolar cycloaddition, could be employed to prepare bisphosphonates of diverse chemical structures that could result in the development of important drugs.

NMR spectra were recorded using a Bruker AM-500 MHz spectrometer. High-resolution mass spectra were obtained using a Bruker micrOTOF-Q II spectrometer, which is a hybrid quadrupole time-of-flight mass spectrometer with MS/MS capability. Melting points were determined using a Fisher-Johns apparatus and are uncorrected. IR spectra were recorded using a Nicolet Magna 550 spectrometer. Column chromatography was performed on silica gel (Merck, Kieselgel 60, 230–400 mesh). Analytical TLC was performed employing 0.2 mm coated commercial silica gel plates (Merck, DC-aluminum sheets, Kieselgel 60 F_{254}).

Tetraethyl Vinylidenebisphosphonate (13)

Tetraethyl 2-Methoxyethylidenebisphosphonate Intermediate
A mixture of paraformaldehyde (3.05 g, 0.1 mol) and Et_2NH (2.08 mL, 1.47 g, 20.1 mmol) in MeOH (50 mL) was refluxed for 2 h until dissolution was complete. Then tetraethyl methylenebisphosphonate (5.0 mL, 5.815 g, 20.2 mmol) was added. The reaction mixture was refluxed for 24 h. The reaction was monitored by ^{1}H NMR until disappearance of the typical peak of the substrate, a triplet centered at δ =2.45 ($J_{H–P}$ = 21.0 Hz). The mixture was allowed to reach r.t., and the solvent was evaporated. Then MeOH (50 mL) was added and the solvent was evaporated. The residue was twice redissolved in toluene (25 mL) and evaporated, to complete elimination of the remaining MeOH. This afforded the corresponding intermediate tetraethyl 2-methoxyethylidenebisphosphonate.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.34 (t, *J* = 7.1 Hz, 12 H, CH_2CH_3), 2.69 (tt, *J* = 23.9, 5.4 Hz, 1 H, H-1), 3.37 (s, 3 H, OCH_3), 3.89 (dt, *J* = 16.1, 5.5 Hz, 2 H, H-2), 4.18 (m, 8 H, CH_2CH_3).

Compound 13
Anhyd toluene (50 mL) was added to this intermediate, and a Dean-Stark trap was attached to the reaction flask. The reaction mixture was refluxed for 48 h. The mixture was concentrated and partitioned between CH_2Cl_2 (70 mL) and H_2O (70 mL). The organic phase was washed with H_2O (2 × 50 mL) and dried ($MgSO_4$), and the solvent was evaporated. The product was purified by column chromatography (silica gel, EtOAc–MeOH, 99:1); this afforded pure **13**.

Yield: 5.785 g (95.5%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.36 (t, *J* = 7.1 Hz, 12 H, CH_2CH_3), 4.16 (m, 8 H, CH_2CH_3), 7.01 (dd, *J* = 37.8, 33.8 Hz, 2 H, H-2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.2 (t, *J* = 3.2 Hz, CH_2CH_3), 62.6 (t, *J* = 2.8 Hz, CH_2CH_3), 132.0 (t, *J* = 167.0 Hz, C-1), 149.2 (C-2).

^{31}P NMR (202 MHz, $CDCl_3$): δ = 13.07.

NMR data were similar to those previously described.[18]

Tetraethyl (1-Benzyl-4,5-dihydro-1*H*-1,2,3-triazole-4,4-diyl)bisphosphonate (14)
A soln of **13** (600 mg, 2.0 mmol) in MeCN (5.0 mL) was added dropwise to a soln of BnN_3 (319 mg, 2.4 mmol) in anhyd MeCN (10 mL). The reaction mixture was stirred at r.t. for 24 h. The mixture was partitioned between CH_2Cl_2 (30 mL) and aq sat. NaCl (30 mL). The layers were separated and the organic soln was dried (Na_2SO_4) and filtered. The solvent was evaporated and the product was purified by column chromatography (silica gel, hexane–EtOAc, 1:1); this afforded pure **14**.

Yield: 370 mg (43%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.1 Hz, 6 H, OCH_2CH_3), 1.34 (t, *J* = 7.0 Hz, 6 H, OCH_2CH_3), 3.64 (t, *J* = 26.7 Hz, 2 H, H-5), 4.21 (m, 8 H, OCH_2CH_3), 4.90 (s, 2 H, $PhCH_2$), 7.28–7.38 (m, 5 H, H_{arom}).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.30 (q, *J* = 2.9 Hz, OCH_2CH_3), 16.33 (q, *J* = 2.9 Hz, OCH_2CH_3), 49.3 ($PhCH_2$), 49.1 (t, *J* = 2.0 Hz, C-5), 63.9 (t, *J* = 3.3 Hz, OCH_2CH_3), 64.2 (t, *J* = 3.4 Hz, OCH_2CH_3), 84.3 (t, *J* = 151.2 Hz, C-4), 128.1 (C-4′), 128.2 (C-2′), 128.8 (C-3′), 134.9 (C-1′).

^{31}P NMR (202 MHz, $CDCl_3$): δ = 14.55.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{29}N_3O_6P_2Na$: 456.1429; found: 456.1441.

(4-Phenoxyphenoxyethyl) Azide (16)
NaN_3 (175.5 mg, 2.7 mmol) was added to a soln of tosylate **15** (350 mg, 0.9 mmol) in anhyd DMF (5 mL) . The reaction mixture was stirred at 80 °C for 5 h. Then the mixture was allowed to cool to r.t. and H_2O (50 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic layers were washed with aq sat. NaCl (5 × 20 mL) and H_2O (2 × 20 mL) and dried ($MgSO_4$). The solvent was evaporated and the product was purified by column chromatography (silica gel, hexane); this afforded pure **16**.

Yield: 150 mg (65%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.59 (t, *J* = 5.0 Hz, 2 H, H-2), 4.14 (t, *J* = 5.0 Hz, 2 H, H-1), 6.90 (d, *J* = 9.2 Hz, 2 H, H-3′), 6.95 (m, 2 H, H_{arom}), 6.98 (d, *J* = 9.2 Hz, 2 H, H-2′), 7.05 (tt, *J* = 7.4, 1.1 Hz, 1 H, H-3′), 7.30 (m, 2 H, H_{arom}).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 50.2 (C-1), 67.5 (C-2), 115.7 (C-2″), 117.8 (C-2′), 120.8 (C-3′), 122.6 (C-4″), 129.6 (C-3″), 150.8 (C-4′), 154.5 (C-1′), 158.3 (C-1″).

Tetraethyl {1-[2-(4-Phenoxyphenoxy)ethyl]-4,5-dihydro-1*H*-1,2,3-triazole-4,4-diyl}bisphosphonate (17)
A soln of azide **16** (90 mg, 0.35 mmol) in anhyd MeCN (5.0 mL) was treated with a soln of **13** (87 mg, 0.29 mmol) in MeCN (3.0 mL) according to the method for the preparation of **14**. The product was purified by column chromatography (silica gel, EtOAc–*i*-Pr, 99:1); this afforded pure **17**.

Yield: 131 mg (68%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.1 Hz, 6 H, OCH_2CH_3), 1.32 (t, *J* = 7.1 Hz, 6 H, OCH_2CH_3), 3.94 (t, *J* = 26.8 Hz, 2 H, H-5), 4.08 (t, *J* = 5.1 Hz, 2 H, H-1′), 4.20 (t, *J* = 5.0 Hz, 2 H, H-2′), 4.24 (m, 8 H, OCH_2CH_3), 6.88 (d, *J* = 9.3 Hz, 2 H, H-2″),

6.94 (m, 2 H, H_{arom}), 6.98 (d, J = 9.3 Hz, 2 H, H-3″), 7.05 (tt, J = 7.4, 1.1 Hz, 1 H, H_{arom}), 7.31 (m, 2 H, H_{arom}).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.3 (q, J = 3.2 Hz, OCH_2CH_3), 49.3 (C-1′), 50.9 (t, J = 1.9 Hz, C-5), 64.0 9 (t, J = 3.3 Hz, OCH_2CH_3), 64.1 9 (t, J = 3.3 Hz, OCH_2CH_3), 67.0 (C-2′), 84.7 (t, J = 151.3 Hz, C-4), 115.6 (C-2‴), 117.7 (C-2″), 120.8 (C-3″), 122.6 (C-4‴), 129.6 (C-3‴), 150.8 (C-4″), 154.4 (C-1′), 158.2 (C-1‴).

^{31}P NMR (202 MHz, $CDCl_3$): δ = 14.51.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{24}H_{35}N_3O_8P_2Na$: 578.1797; found: 578.1772.

Tetraethyl {1-[2,2-Bis(diethoxyphosphoryl)ethyl]-4,5-dihydro-1*H*-1,2,3-triazole-4,4-diyl}bisphosphonate (20)

A soln of NaN_3 (260 mg, 4.0 mmol) in H_2O (10 mL) was treated dropwise with a soln of compound **13** (300 mg, 1.0 mmol) in H_2O (5.0 mL). The reaction mixture was stirred at r.t. for 30 min. The mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried ($MgSO_4$), and the solvent was evaporated. The product was purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 99:1); this afforded pure **20**.

Yield: 306 mg (92%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.32 (t, J = 7.4 Hz, 12 H, OCH_2CH_3), 1.34 (t, J = 7.6 Hz, 12 H, OCH_2CH_3), 2.76 (tt, J = 24.2, 5.2 Hz, 1 H, H-2′), 3.80 (t, J = 26.5 Hz, 2 H, H-5), 4.17 (dt, J = 10.3, 5.6 Hz, 2 H, H-1′), 4.22 (m, 16 H, OCH_2CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.3 (m, OCH_2CH_3), 37.3 (t, J = 131.7 Hz, C-2′), 46.4 (t, J = 3.2 Hz, C-1′), 49.9 (br s, C-5), 62.9 (d, J = 6.7 Hz, OCH_2CH_3), 63.0 (d, J = 6.5 Hz, OCH_2CH_3), 64.0 (p, J = 3.2 Hz, OCH_2CH_3), 85.1 (t, J = 150.8 Hz, C-4).

^{31}P NMR (202 MHz, $CDCl_3$): δ = 14.44, 20.84.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{20}H_{45}N_3O_{12}P_4Na$: 666.1846; found: 666.1878.

Tetraethyl [2-(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)ethane-1,1-diyl]bisphosphonate (21)

Benzotriazole (119 mg, 1 mmol) was added to a soln of **13** (100 mg, 0.33 mmol) in anhyd MeCN (5 mL). The reaction mixture was stirred at r.t. overnight. The mixture was partitioned between H_2O (20 mL) and CH_2Cl_2 (20 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic layers were washed with aq sat. NaCl (2 × 20 mL) and dried ($MgSO_4$), before the solvent was evaporated. The residue was purified by column chromatography (silica gel, EtOAc); this afforded pure **21**.

Yield: 90 mg (65%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.165 (t, J = 7.0 Hz, 6 H, OCH_2CH_3), 1.170 (t, J = 7.0 Hz, 6 H, OCH_2CH_3), 3.51 (tt, J = 23.0, 6.9 Hz, 1 H, H-1), 4.10 (m, 8 H, OCH_2CH_3), 5.21 (ddd, J = 14.2, 12.9, 7.0 Hz, 2 H, H-2), 7.34 (dist t, J = 7.7 Hz, 1 H, H-5′), 7.47 (dist t, J = 7.7 Hz, 1 H, H-4′), 7.66 (dd, J = 8.5, 0.8 Hz, 1 H, H-3′), 8.03 (dd, J = 8.4, 0.8 Hz, 1 H, H-6′).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.07 (d, J = 2.3 Hz, OCH_2CH_3), 16.12 (d, J = 2.3 Hz, OCH_2CH_3), 38.2 (t, J = 131.9 Hz, C-1), 44.2 (t, J = 3.3 Hz, C-2), 62.9 (d, J = 6.7 Hz, OCH_2CH_3), 63.3 (d, J = 6.7 Hz, OCH_2CH_3), 109.9 (C-3′), 119.8 (C-6′), 123.9 (C-5′), 127.3 (C-4′), 133.5 (C-2′), 145.6 (C-1′).

^{31}P NMR (202 MHz, $CDCl_3$): δ = 19.18.

Octaethyl (3-Nitropentane-1,1,5,5-tetrayl)tetrakis(phosphonate) (22)

Compound **13** (300 mg, 1.0 mmol) in $CHCl_3$ (2.0 mL) was added to a soln of $MeNO_2$ (152 mg, 2.5 mmol) in the presence of DABCO (56 mg, 0.5 mmol) in anhyd $CHCl_3$ (5.0 mL) under an argon atmosphere. The reaction mixture was stirred at r.t. for 24 h. The mixture was partitioned between Et_2O (30 mL) and aq sat. NaCl (30 mL). The organic layer was washed with brine (2 × 30 mL) and dried ($MgSO_4$), and the solvent was evaporated. The product was purified by column chromatography (silica gel, EtOAc); this afforded pure **22**.

Yield: 102 mg (28%); colorless oil; R_f = 0.41 (EtOAc–*i*-PrOH–H_2O, 8:1.5:0.5).

^{1}H NMR (500 MHz, $CDCl_3$–CD_3OD): δ = 1.35 (dt, J = 7.0, 2.9 Hz, 12 H, OCH_2CH_3), 1.37 (dt, J = 7.0, 2.2 Hz, 12 H, OCH_2CH_3), 2.28 (m, 2 H, H-1, H-2_a, H-4_a), 2.42 (dddd, J = 25.2, 22.5, 9.0, 2.8 Hz, 2 H, H-1, H-5), 2.54 (dddt, J = 25.0, 15.0, 10.2, 3.3 Hz, 2 H, H-2_b, H-4_b), 5.21 (tt, J = 9.4, 3.6 Hz, 1 H, H-3); 4.18 (m, 16 H, OCH_2CH_3).

^{13}C NMR (125 MHz, $CDCl_3$–CD_3OD): δ = 16.1 (m, OCH_2CH_3), 29.9 (t, J = 4.4 Hz, C-2, C-4), 33.2 (t, J = 135.0 Hz, C-1, C-5), 63.0 (t, J = 6.2 Hz, OCH_2CH_3), 63.3 (d, J = 6.8 Hz, OCH_2CH_3), 84.8 (C-3).

^{31}P NMR (202 MHz, $CDCl_3$–CD_3OD): δ = 21.20, 21.62.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{21}H_{47}O_{14}NP_4Na$: 684.1845; found: 684.1847.

Tetraethyl (3-Nitrobutane-1,1-diyl)bisphosphonate (23)

A soln of $EtNO_2$ (167 mg, 2.5 mmol) and DABCO (56 mg, 0.5 mmol) in anhyd $CHCl_3$ (5 mL) was treated with a soln of compound **13** (300 mg, 1.0 mmol) in $CHCl_3$ (2.0 mL) under an argon atmosphere, as reported for the preparation of compound **22**. After the usual reaction workup, the residue was purified by column chromatography (silica gel, EtOAc); this afforded pure **23**.

Yield: 175 mg (46%); colorless oil; R_f = 0.60 (EtOAc–*i*-PrOH–H_2O, 8:1.5:0.5).

^{1}H NMR (500 MHz, $CDCl_3$–CD_3OD): δ = 1.367 (dt, J = 7.1, 1.4 Hz, 6 H, OCH_2CH_3), 1.367 (dt, J = 7.1, 1.4 Hz, 6 H, OCH_2CH_3), 1.59 (d, J = 6.9 Hz, 1 H, H-4), 2.20 (dddd, J = 23.1, 15.0, 9.4, 3.9 Hz, 1 H, H-2_a), 2.43 (dddd, J = 24.8, 22.9, 9.4, 3.9 Hz, 1 H, H-1), 2.61 (ddddd, J = 26.4, 15.2, 13.6, 9.8, 3.8 Hz, 1 H, H-2_b), 4.19 (m, 8 H, OCH_2CH_3), 4.99 (ddq, J = 9.9, 6.7, 3.6 Hz, 1 H, H-3).

^{13}C NMR (125 MHz, $CDCl_3$–CD_3OD): δ = 15.85 (d, J = 3.9 Hz, OCH_2CH_3), 15.90 (d, J = 3.9 Hz, OCH_2CH_3), 19.5 (C-4), 30.6 (t, J = 4.9 Hz, C-2), 33.3 (t, J = 134.5 Hz, C-1), 62.9 (t, J = 6.9 Hz, OCH_2CH_3), 63.2 (dd, J = 8.8, 6.9 Hz, OCH_2CH_3), 81.3 (dd, 10.8, 3.9 Hz, C-3).

^{31}P NMR (202 MHz, $CDCl_3$–CD_3OD): δ = 21.24, 21.88.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{12}H_{28}O_8NP_2$: 376.1290; found: 376.1292.

Ethyl 4,4-Bis(diethoxyphosphoryl)-2-nitrobutanoate (24)

A soln of ethyl nitroacetate (332 mg, 2.5 mmol) and DABCO (56 mg, 0.5 mmol) in anhyd $CHCl_3$ (5.0 mL) was treated with a soln of **13** (300 mg, 1.0 mmol) in $CHCl_3$ (2.0 mL) according to the method described for the preparation of compound **22**. The product was purified by column chromatography (silica gel, EtOAc); this afforded pure **24**.

Yield: 202 mg (48%); colorless oil: R_f = 0.68 (EtOAc–*i*-PrOH–H_2O, 8:1.5:0.5).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.30 (dt, J = 7.1, 1.1 Hz, 3 H, $C(O)OCH_2CH_3$), 1.339 (dt, J = 7.1, 1.6 Hz, 6 H, $POCH_2CH_3$), 1.341 (dt, J = 7.1, 1.2 Hz, 6 H, $POCH_2CH_3$), 2.44 (ddddd, J = 23.8, 22.7, 9.1, 5.2, 1.1 Hz, 1 H, H-1), 2.65 (m, 1 H, H-2_a), 2.82 (m, 1 H, H-2_a), 4.19 (m, 8 H, OCH_2CH_3), 4.277 (dq, J = 7.1, 2.8 Hz, 1 H, $C(O)OCH_{2a}CH_3$), 4.279 (dq, J = 7.1, 2.8 Hz, 1 H, $C(O)OCH_{2b}CH_3$), 5.74 (dd, J = 9.6, 5.1 Hz, 1 H, H-1).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8 ($C(O)OCH_2CH_3$), 16.24 (d, J = 5.9 Hz, $POCH_2CH_3$), 16.27 (d, J = 5.9 Hz, $POCH_2CH_3$), 26.8 (t, J = 4.4 Hz, C-3), 33.4 (t, J = 133.5 Hz, C-4), 63.0 (dd, J = 6.6, 4.1 Hz, $C(O)OCH_2CH_3$), 63.25 (d, J = 1.8 Hz, $POCH_2CH_3$), 63.31 ($POCH_2CH_3$), 86.02 (dd, 10.3, 5.2 Hz, C-2), 164.1 (C-1).

^{31}P NMR (202 MHz, $CDCl_3$): δ = 20.72, 21.08.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{14}H_{30}O_{10}NP_2$: 434.1345; found: 434.1597.

Tetraethyl (3-Methyl-4,5-dihydroisoxazole-5,5-diyl)bisphosphonate (26)

$POCl_3$ (675 mg, 5.6 mmol) in $CHCl_3$ (1.0 mL) was added dropwise to a soln of **13** (600 mg, 2.0 mmol), $EtNO_2$ (390 mg, 5.2 mmol), and Et_3N (565 mg, 5.6 mmol) in anhyd $CHCl_3$ (10 mL) at 0 °C under an argon atmosphere. The reaction mixture was stirred at r.t. for 3 d. The reaction was quenched by the addition of cold H_2O (20 mL). The organic phase was washed with 10% aq HCl (2 × 20 mL), 5% aq NaOH (2 × 20 mL), and brine (3 × 20 mL). The organic layer was dried ($MgSO_4$) and the solvent was evaporated. The residue was purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 99:1); this afforded pure **26**.

Yield: 350 mg (49%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.35 (t, *J* = 7.1 Hz, 12 H, OCH_2CH_3), 2.02 (s, 3 H, CH_3 at C-3), 3.57 (t, *J* = 23.4 Hz, 2 H, H-5), 4.27 (m, 8 H, OCH_2CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.4 (q, *J* = 2.9 Hz, OCH_2CH_3), 19.9 (CH_3 at C-3), 45.9 (C-5), 64.2 (t, *J* = 3.3 Hz, OCH_2CH_3), 64.5 (t, *J* = 3.4 Hz, OCH_2CH_3), 82.0 (t, *J* = 158.5 Hz, C-4), 154.9 (C-3).

^{31}P NMR (202 MHz, $CDCl_3$): δ = 14.81.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{12}H_{25}O_7NP_2Na$: 380.1004; found: 380.1005.

Tetraethyl (3-Pentyl-4,5-dihydroisoxazole-5,5-diyl)bisphosphonate (31) and Tetraethyl (2-Methoxyethene-1,1-diyl)bisphosphonate (32)

A soln of **13** (200 mg, 0.67 mmol) in MeOH (2.0 mL) was added dropwise to a soln of (diacetoxyiodo)benzene (DIB; 259 mg, 0.80 mmol), hexanal oxime (92 mg, 0.80 mmol), and TFA (15 μL, 0.20 mmol) in MeOH (2 mL) under an argon atmosphere. The reaction mixture was stirred at r.t. for 1 h. The solvent was evaporated and the residue was purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 98:2); this afforded pure **31** and **32**.

Compound 31

Yield: 67 mg (24%); colorless oil; R_f = 0.38 (CH_2Cl_2–MeOH, 9:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.0 Hz, 3 H, H-5′), 1.35 (t, *J* = 7.2 Hz, 12 H, OCH_2CH_3), 1.37 (m, 4 H, H-3′, H-4′), 1.58 (p, *J* = 7.4 Hz, H-2′), 2.36 (t, *J* = 7.6 Hz, H-1′), 3.56 (t, *J* = 23.7 Hz, 2 H, H-4), 4.26 (m, 8 H, OCH_2CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8 (C-5′), 16.33 (q, *J* = 3.3 Hz, OCH_2CH_3), 22.1 (C-4′), 25.8 (C-2′), 26.7 (C-3′), 31.1 (C-1′), 44.4 (t, *J* = 2.1 Hz, C-4), 64.1 (t, *J* = 3.4 Hz, OCH_2CH_3), 64.4 (t, *J* = 3.3 Hz, OCH_2CH_3), 81.7 (t, *J* = 157.8 Hz, C-5), 158.4 (t, *J* = 4.2, C-3).

^{31}P NMR (202 MHz, $CDCl_3$): δ = 14.94.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{16}H_{34}NO_7P_2$: 414.1811; found: 414.1794.

Compound 32

Yield: 89 mg (40%); colorless oil; R_f = 0.32 (CH_2Cl_2–MeOH, 9:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.33 (m, 12 H, OCH_2CH_3), 4.01 (s, 3 H, OCH_3), 4.11 (m, 8 H, OCH_2CH_3), 7.62 (dd, *J* = 33.4, 13.1 Hz, 1 H, H-2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.1 (t, *J* = 5.9 Hz, OCH_2CH_3), 62.0 (d, *J* = 5.0 Hz, OCH_2CH_3), 62.1 (d, *J* = 4.4 Hz, OCH_2CH_3), 63.3 (OCH_3), 93.7 (ddd, *J* = 180.7, 173.6, 2.6 Hz, C-1), 174.2 (dd, *J* = 16.1, 4.4 Hz, C-2).

^{31}P NMR (202 MHz, $CDCl_3$): δ = 12.29 (d, *J* = 31.7 Hz), 17.95 (d, *J* = 30.2 Hz).

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{11}H_{25}O_7P_2$: 331.1076; found: 331.1082.

Tetraethyl (3-Phenyl-4,5-dihydroisoxazole-5,5-diyl)bisphosphonate (33)

A soln of **13** (200 mg, 0.67 mmol) in MeOH (1 mL) was added dropwise to a soln of DIB (259 mg, 0.80 mmol), benzaldehyde oxime (97 mg, 0.80 mmol), and TFA (15 μL, 0.20 mmol) in MeOH (2 mL) under an argon atmosphere. The reaction mixture was stirred at r.t. for 1 h. The solvent was evaporated and the residue was purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 98:2); this afforded pure **33**.

Yield: 112 mg (40%); yellowish oil; R_f = 0.52 (CH_2Cl_2–MeOH, 9:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.34 (t, *J* = 6.9 Hz, 6 H, OCH_2CH_3), 1.35 (t, *J* = 7.0 Hz, 6 H, OCH_2CH_3), 3.99 (t, *J* = 23.4 Hz, 2 H, H-4), 4.31 (m, 8 H, $OCH_{2b}CH_3$), 7.43 m, 3 H, H_{arom}), 7.67 (dd, *J* = 8.0, 1.5 Hz, 2 H, H-2′, H-6′).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.3 (q, *J* = 3.2 Hz, OCH_2CH_3), 42.3 (t, *J* = 2.1 Hz, C-4), 64.1 (t, *J* = 3.4 Hz, OCH_2CH_3), 64.4 (t, *J* = 3.3 Hz, OCH_2CH_3), 83.1 (t, *J* = 157.1 Hz, C-5), 126.9 (C-2′), 127.9 (C-1′), 128.7 (C-3′), 130.6 (C-4′), 156.0 (t, *J* = 4.3 Hz, C-3).

^{31}P NMR (202 MHz, $CDCl_3$): δ = 14.51.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{17}H_{27}O_7NP_2Na$: 442.1161; found: 442.1153.

Tetraethyl [3-(4-Methoxyphenyl)-4,5-dihydroisoxazole-5,5-diyl]bisphosphonate (34)

The same method as that used for the preparation of compound **33** was followed; a soln of DIB (322.9 mg, 0.80 mmol), anisaldehyde oxime (121 mg, 0.80 mmol), and TFA (15 μL, 0.20 mmol) in MeOH (2 mL) was reacted with a soln of **13** (200 mg, 0.67mmol) in MeOH (1 mL). After the usual workup, the product was purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 98:2); this afforded pure **34**.

Yield: 70 mg (23%); yellowish oil; R_f = 0.45 (CH_2Cl_2–MeOH, 9:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 6.9 Hz, 6 H, OCH_2CH_3), 1.35 (t, *J* = 6.9 Hz, 6 H, OCH_2CH_3), 3.85 (s, 3 H, OCH_3), 3.97 (t, *J* = 23.4 Hz, 2 H, H-4), 4.31 (m, 8 H, $OCH_{2b}CH_3$), 6.93 (d, *J* = 8.7 Hz, 2 H, H-3′, H-5′), 7.61 (d, *J* = 8.6 Hz, 2 H, H-2′, H-4′).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.4 (q, *J* = 3.0 Hz, OCH_2CH_3), 42.6 (t, *J* = 2.2 Hz, C-4), 55.3 (OCH_3), 64.2 (t, *J* = 3.4 Hz, OCH_2CH_3), 64.5 (t, *J* = 3.3 Hz, OCH_2CH_3), 82.9 (t, *J* = 157.1 Hz, C-5), 114.2 (C-3′), 120.4 (C-1′), 128.6 (C-2′), 155.6 (t, *J* = 4.3 Hz, C-3), 161.5 (C-4′).

^{31}P NMR (202 MHz, $CDCl_3$): δ = 14.67.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{18}H_{30}O_8NP_2$: 450.1448; found: 450.1457.

Diethyl (±)-4,4-Bis(diethoxyphosphoryl)-5-pentylpyrrolidine-2,2-dicarboxylate (36)

A soln of hexanal (80 mg, 0.80 mmol) and **35** (44 mg, 0.25 mmol) in anhyd THF (4 mL) was treated with a soln of **13** (44 mg, 0.25 mmol) in THF (1.0 mL) under an argon atmosphere. The reaction mixture was stirred at r.t. for 7 d. The solvent was evaporated and the product was purified by column chromatography (silica gel, EtOAc); this afforded pure **36**.

Yield: 72 mg (50%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.0 Hz, 3 H, H-5′), 1.27 (t, *J* = 7.1 Hz, 6 H, $C(O)OCH_2CH_3$), 1.33 (t, *J* = 7.1 Hz, 3 H, $POCH_2CH_3$), 1.34 (t, *J* = 7.1 Hz, 9 H, $POCH_2CH_3$), 2.13 (m, 1 H, H-1′$_a$), 3.98 (ddd, *J* = 20.9, 15.1, 9.1 Hz, 1 H, H-3$_a$), 3.25 (dt, *J* = 20.5, 15.2 Hz, 1 H, H-3$_b$), 3.48 (ddt, *J* = 22.9, 10.4, 2.2 Hz, 1 H, H-5).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.96 ($C(O)OCH_2CH_3$), 13.97 ($C(O)OCH_2CH_3$), 14.1 (C-5′), 16.34 (d, *J* = 4.6 Hz, $POCH_2CH_3$), 16.37 (d, *J* = 4.5 Hz, $POCH_2CH_3$), 16.44 (d, *J* = 4.5 Hz,

POCH$_2$*C*H$_3$), 22.5 (C-4′), 28.4 (C-2′), 31.1 (d, *J* = 3.2 Hz, C-1′), 31.7 (C-4′), 38.7 (dd, *J* = 4.2, 2.4 Hz, C-3), 50.9 (t, *J* = 134.5 Hz, C-4), 62.0 (O*C*H$_2$CH$_3$), 62.1 (O*C*H$_2$CH$_3$), 62.4 (d, *J* = 6.4 Hz, O*C*H$_2$CH$_3$), 62.6 (d, *J* = 6.1 Hz, O*C*H$_2$CH$_3$), 63.1 (d, *J* = 6.1 Hz, O*C*H$_2$CH$_3$), 63.4 (d, *J* = 5.9 Hz, O*C*H$_2$CH$_3$), 65.5 (d, *J* = 2.7 Hz, C-5), 72.4 (dd, *J* = 7.2, 2.0 Hz, C-2), 169.2 (*C*O), 170.6 (*C*O).

^{31}P NMR (202 MHz, CDCl$_3$): δ = 24.17 (d, *J* = 16.8 Hz), 24.29 (d, *J* = 16.8 Hz).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{46}O_{10}NP_2$: 558.2597; found: 558.2602.

Diethyl (±)-4,4-Bis(diethoxyphosphoryl)-5-phenylpyrrolidine-2,2-dicarboxylate (37)

A soln of benzaldehyde (310 mg, 3.0 mmol) and **35** (117 mg, 0.67 mmol) in anhyd THF (4 mL) was treated with a soln of **13** (200 mg, 0.67 mmol) in THF (1.0 mL) under an argon atmosphere. The reaction mixture was stirred at r.t. for 24 h. The solvent was evaporated and the product was purified by column chromatography (silica gel, EtOAc); this afforded pure **37**.

Yield: 257 mg (68%); colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ = 1.07 (t, *J* = 7.1 Hz, 3 H, C(O)OCH$_2$C*H*$_3$), 1.09 (t, *J* = 7.1 Hz, 3 H, C(O)OCH$_2$C*H*$_3$), 1.29 (dt, *J* = 12.2, 7.1 Hz, 6 H, POCH$_2$C*H*$_3$), 1.34 (t, *J* = 7.1 Hz, 6 H, POCH$_2$C*H*$_3$), 3.23 (dd, *J* = 19.3, 15.2 Hz, 1 H, H-3$_a$), 3.32 (ddd, *J* = 22.1, 15.0, 10.4 Hz, 1 H, H-3$_b$), 3.69 (ddt, *J* = 14.3, 9.6, 7.2 Hz, 1 H, C(O)OC*H*$_{2a}$CH$_3$), 3.85 (ddd, *J* = 14.3, 9.6, 7.2 Hz, 1 H, C(O)OC*H*$_{2b}$CH$_3$), 3.92 (p, *J* = 7.3 Hz, 2 H, C(O)OC*H*$_2$CH$_3$), 4.10–4.31 (m. 8 H, POC*H*$_2$CH$_3$), 4.99 (dd, *J* = 30.0, 13.1 Hz, 1 H, H-5), 7.27 (m, 3 H, Ph), 7.67 (m, 2 H, Ph).

^{13}C NMR (125 MHz, CDCl$_3$): δ = 14.01 (C(O)OCH$_2$*C*H$_3$), 14.02 (C(O)OCH$_2$*C*H$_3$), 16.1 (dd, *J* = 6.3, 0.8 Hz, POCH$_2$*C*H$_3$), 16.4 (dd, *J* = 5.8, 1.5 Hz, POCH$_2$*C*H$_3$), 38.3 (t, *J* = 3.8 Hz, C-3), 51.7 (t, *J* = 136.4 Hz, C-4), 62.1 (O*C*H$_2$CH$_3$), 62.2 (d, *J* = 7.3 Hz, O*C*H$_2$CH$_3$), 62.7 (d, *J* = 7.2 Hz, O*C*H$_2$CH$_3$), 63.1 (d, *J* = 7.0 Hz, O*C*H$_2$CH$_3$), 63.2 (d, *J* = 7.0 Hz, O*C*H$_2$CH$_3$), 66.3 (d, *J* = 4.3 Hz, C-5), 71.0 (dd, *J* = 6.9, 1.9 Hz, C-2), 127.1 (C-2′), 127.7 (C-4′), 129.1 (C-3′), 136.6 (d, *J* = 4.7 Hz, C-1′), 169 (*C*O), 171.0 (*C*O).

^{31}P NMR (202 MHz, CDCl$_3$): δ = 22.76 (d, *J* = 13.6 Hz), 23.68 (d, *J* = 13.6 Hz).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{40}O_{10}NP_2$: 564.2122; found: 564.2133.

Diethyl (±)-4,4-Bis(diethoxyphosphoryl)-5-(4-methoxyphenyl)pyrrolidine-2,2-dicarboxylate (38)

A soln of anisaldehyde (224 mg, 1.6 mmol) and **35** (58 mg, 0.25 mmol) in anhyd THF (4 mL) was treated with a soln of **13** (100 mg, 0.33 mmol) in THF (1.0 mL) under an argon atmosphere. The reaction mixture was stirred at r.t. for 24 h. The solvent was evaporated and the product was purified by column chromatography (silica gel, EtOAc); this afforded pure **39**.

Yield: 81 mg (41%); colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ = 1.10 (t, *J* = 7.1 Hz, 3 H, C(O)OCH$_2$C*H*$_3$), 1.14 (t, *J* = 7.1 Hz, 3 H, C(O)OCH$_2$C*H*$_3$), 1.29 (dt, *J* = 10.9, 7.1 Hz, 6 H, POCH$_2$C*H*$_3$), 1.34 (dt, *J* = 7.1, 1.0 Hz, 6 H, POCH$_2$C*H*$_3$), 3.21 (dd, *J* = 19.3, 15.2 Hz, 1 H, H-3$_a$), 3.31 (ddd, *J* = 22.0, 15.2, 10.2 Hz, 1 H, H-3$_b$), 3.72 (ddt, *J* = 14.1, 9.6, 7.2 Hz, 1 H, C(O)OC*H*$_{2a}$CH$_3$), 3.79 (s, 3 H, OC*H*$_3$), 3.85 (ddt, *J* = 14.2, 10.2, 7.1 Hz, 1 H, C(O)OC*H*$_{2b}$CH$_3$), 3.94 (p, *J* = 7.3 Hz, 1 H, C(O)OC*H*$_{2d}$CH$_3$), 3.96 (p, *J* = 7.3 Hz, 1 H, C(O)OC*H*$_{2d}$CH$_3$), 4.11–4.31 (m, 8 H, POC*H*$_2$CH$_3$), 4.95 (dd, *J* = 30.0, 13.0 Hz, 1 H, H-5), 6.82 (d, *J* = 8.9 Hz, 2 H, H-3′), 7.59 (d, *J* = 8.7 Hz, 2 H, H-2′).

^{13}C NMR (125 MHz, CDCl$_3$): δ = 14.02 (C(O)OCH$_2$*C*H$_3$), 14.03 (C(O)OCH$_2$*C*H$_3$), 16.2 (d, *J* = 6.2 Hz, POCH$_2$*C*H$_3$), 16.4 (d, *J* = 5.2, POCH$_2$*C*H$_3$), 38.2 (t, *J* = 3.8 Hz, C-3), 51.6 (dd, *J* = 137.8, 134.9 Hz, C-4), 55.2 (O*C*H$_3$), 62.07 (O*C*H$_2$CH$_3$), 62.08 (O*C*H$_2$CH$_3$), 62.3 (d, *J* = 7.2 Hz, O*C*H$_2$CH$_3$), 62.6 (d, *J* = 7.3 Hz, O*C*H$_2$CH$_3$), 63.06 (d, *J* = 7.0 Hz, O*C*H$_2$CH$_3$), 63.09 (d, *J* = 6.9 Hz, O*C*H$_2$CH$_3$), 65.9 (d, *J* = 4.3 Hz, C-5), 71.0 (dd, *J* = 6.8, 1.9 Hz, C-2), 112.5 (C-3′), 128.8 (d, *J* = 4.9 Hz, C-1′), 130.3 (C-2′), 159.2 (C-4′), 169.0 (*C*O), 171.1 (*C*O).

^{31}P NMR (202 MHz, CDCl$_3$): δ = 22.85 (d, *J* = 13.7 Hz), 23.84 (d, *J* = 13.7 Hz).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{41}O_{11}NP_2Na$: 616.2053; found: 616.2066.

Acknowledgment

This work was supported by grants from the National Research Council of Argentina (PIP 1888), ANPCyT (PICT 2008 #1690), and the Universidad de Buenos Aires (200201001003801) to J.B.R., and from Bunge & Born Foundation to S.H.S.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are experimental procedures for the preparation of oximes **28**–**30**, copies of ^{1}H, ^{13}C, and ^{31}P NMR spectra for all the compounds synthesized, and selected 2D-NMR data.

References

(1) Fleisch, H.; Russell, R. G. G.; Straumann, F. *Nature* **1966**, *212*, 901.
(2) Fleisch, H.; Russell, R. G. G.; Francis, M. D. *Science* **1969**, *165*, 1262.
(3) Francis, M. D.; Russell, R. G. G.; Fleisch, H. *Science* **1969**, *165*, 1264.
(4) Roelofs, A. J.; Thompson, K.; Ebetino, F. H.; Rogers, M. J.; Coxon, F. P. *Curr. Pharm. Des.* **2010**, *16*, 2950.
(5) Reszka, A. A.; Rodan, G. A. *Mini-Rev. Med. Chem.* **2004**, *4*, 711.
(6) Reszka, A. A.; Rodan, G. A. *Curr. Osteoporos. Rep.* **2003**, *1*, 45.
(7) Russell, R. G. G.; Rogers, M. J. *Bone* **1999**, *25*, 97.
(8) (a) Clézardin, P.; Massaia, M. *Curr. Pharm. Des.* **2010**, *16*, 3007. (b) Miller, K.; Erez, R.; Segal, E.; Shabat, D.; Satchi-Fainaro, R. *Angew. Chem. Int. Ed.* **2009**, *48*, 2949. (c) Zhang, Y.; Cao, R.; Yin, F.; Hudock, M. P.; Guo, R.-T.; Krysiak, K.; Mukherjee, S.; Gao, Y.-G.; Robinson, H.; Song, Y.; No, J. H.; Bergan, K.; Leon, A.; Cass, L.; Goddard, A.; Chang, T.-K.; Lin, F.-Y.; Van Beek, E.; Papapoulos, S.; Wang, A. H.-J.; Kubo, T.; Ochi, M.; Mukkamala, D.; Oldfield, E. *J. Am. Chem. Soc.* **2009**, *131*, 5153. (d) Coleman, R. E. *Br. J. Cancer* **2008**, *98*, 1736.
(9) Sanders, J. M.; Ghosh, S.; Chan, J. M. W.; Meints, G.; Wang, H.; Raker, A. M.; Song, Y.; Colantino, A.; Burzynska, A.; Kafarski, P.; Morita, C. T.; Oldfield, E. *J. Med. Chem.* **2004**, *47*, 375.
(10) Reddy, R.; Dietrich, E.; Lafontaine, Y.; Houghton, T. J.; Belanger, O.; Dubois, A.; Arhin, F. F.; Sarmiento, I.; Fadhil, I.; Laquerre, K.; Ostiguy, V.; Lehoux, D.; Moeck, G.; Parr, T. R. Jr.; Far, A. R. *ChemMedChem* **2008**, *3*, 1863.
(11) Forlani, G.; Giberti, S.; Berlicki, Ł.; Petrollino, D.; Kafarski, P. *J. Agric. Food Chem.* **2007**, *55*, 4340.
(12) Roth, A. G.; Drescher, D.; Yang, Y.; Redmer, S.; Uhlig, S.; Arenz, C. *Angew. Chem. Int. Ed.* **2009**, *48*, 7560.
(13) (a) Docampo, R.; Moreno, S. N. J. *Curr. Pharm. Des.* **2008**, *14*, 882. (b) Oldfield, E. *Acc. Chem. Res.* **2010**, *43*, 1216. (c) Rodriguez, J. B.; Szajnman, S. H. *Expert Opin. Ther. Pat.* **2012**, *22*, 311. (d) Szajnman, S. H.; Bailey, B. N.; Docampo, R.; Rodriguez, J. B. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 789. (e) García Liñares, G.; Ravaschino, E. L.; Rodriguez, J. B.

Curr. Med. Chem. **2006**, *13*, 335. (f) Ghosh, S.; Chan, J. M. W.; Lea, C. R.; Meints, G. A.; Lewis, J. C.; Tovian, Z. S.; Flessner, R. M.; Loftus, T. C.; Bruchhaus, I.; Kendrick, H.; Croft, S. L.; Kemp, R. G.; Kobayashi, S.; Nozaki, T.; Oldfield, E. *J. Med. Chem.* **2004**, *47*, 175. (g) Szajnman, S. H.; Ravaschino, E. L.; Docampo, R.; Rodriguez, J. B. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4685. (h) Martin, M. B.; Grimley, J. S.; Lewis, J. C.; Heath, H. T. III.; Bailey, B. N.; Kendrick, H.; Yardley, V.; Caldera, A.; Lira, R.; Urbina, J. A.; Moreno, S. N. J.; Docampo, R.; Croft, S. L.; Oldfield, E. *J. Med. Chem.* **2001**, *44*, 909. (i) Yardley, V.; Khan, A. A.; Martin, M. B.; Slifer, T. R.; Araujo, F. T.; Moreno, S. N. J.; Docampo, R.; Croft, S. L.; Oldfield, E. *Antimicrob. Agents Chemother.* **2002**, *46*, 929.

(14) Kieczykowski, G. R.; Jobson, R. B.; Melillo, D. G.; Reinhold, D. F.; Grenda, V. J.; Shinkai, I. *J. Org. Chem.* **1995**, *60*, 8310.

(15) Widler, L.; Jaeggi, K. A.; Glatt, M.; Müller, K.; Bachman, R.; Bisping, M.; Born, A.-R.; Cortesi, R.; Guiglia, G.; Jeker, H.; Klein, R.; Ramseier, U.; Schmid, J.; Schreiber, G.; Seltenmeyer, Y.; Green, J. R. *J. Med. Chem.* **2002**, *45*, 3721.

(16) (a) Olive, G.; Le Moigne, F.; Mercier, A.; Tordo, P. *Synth. Commun.* **2000**, *34*, 617. (b) Griffiths, D. V.; Hughes, J. M.; Brown, J. W.; Caesar, J. C.; Swetnam, S. P.; Cumming, S. A.; Kelly, J. D. *Tetrahedron* **1997**, *52*, 17815.

(17) Takeuchi, M.; Sakamoto, S.; Yoshida, M.; Abe, T.; Isomura, Y. *Chem. Pharm. Bull.* **1993**, *41*, 688.

(18) (a) Degenhardt, C. R.; Burdsall, D. C. *J. Org. Chem.* **1986**, *51*, 3488. (b) Bulman Page, P. C.; Moore, J. P. G.; Mansfield, I.; McKenzie, M. J.; Bowler, W. B.; Gallagher, J. A. *Tetrahedron* **2001**, *57*, 1837.

(19) (a) Szajnman, S. H.; Rosso, V. S.; Malayil, L.; Smith, A.; Moreno, S. N. J.; Docampo, R.; Rodriguez, J. B. *Org. Biomol. Chem.* **2012**, *10*, 1424. (b) Rosso, V. S.; Szajnman, S. H.; Malayil, L.; Galizzi, M.; Moreno, S. N. J.; Docampo, R.; Rodriguez, J. B. *Bioorg. Med. Chem.* **2011**, *19*, 2211. (c) Szajnman, S. H.; García Liñares, G. E.; Li, Z.-H.; Jiang, C.; Galizzi, M.; Bontempi, E. J.; Ferella, M.; Moreno, S. N. J.; Docampo, R.; Rodriguez, J. B. *Bioorg. Med. Chem.* **2008**, *16*, 3283. (d) Szajnman, S. H.; Montalvetti, A.; Wang, Y.; Docampo, R.; Rodríguez, J. B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3231. (e) Szajnman, S. H.; Liñares, G. G.; Moro, P.; Rodriguez, J. B. *Eur. J. Org. Chem.* **2005**, 3687. (f) Simoni, D.; Gebbia, N.; Invidiata, F. P.; Eleopra, M.; Marchetti, P.; Rondanin, R.; Baruchello, R.; Provera, S.; Marchioro, C.; Tolomeo, M.; Marinelli, L.; Limongelli, V.; Novellino, E.; Kwaasi, A.; Dunford, J.; Buccheri, S.; Caccamo, N.; Dieli, F. *J. Med. Chem.* **2008**, *51*, 6800. (g) Lolli, M. L.; Lazzarato, L.; Di Stilo, A.; Fruttero, R.; Gasco, A. *J. Organomet. Chem.* **2002**, *650*, 77. (h) Houghton, T. J.; Tanaka, K. S. E.; Kang, T.; Dietrich, E.; Lafontaine, Y.; Delorme, D.; Ferreira, S. S.; Viens, F.; Arhin, F. F.; Sarmiento, I.; Lehoux, D.; Fadhil, I.; Laquerre, K.; Liu, J.; Ostiguy, V.; Poirier, H.; Moeck, G.; Parr, T. R. Jr.; Far, A. R. *J. Med. Chem.* **2008**, *51*, 6955. (i) Page, P. C. B.; McKenzie, M. J.; Gallagher, J. A. *J. Org. Chem.* **2001**, *66*, 3704. (j) Sturtz, G.; Guervenou, J. *Synthesis* **1991**, 661. (k) Page, P. C. B.; Moore, J. P. G.; Mansfield, I.; McKenzie, M. J.; Bowler, W. B.; Gallagher, J. A. *Tetrahedron* **2001**, *57*, 1837. (l) Couthon-Gourvès, H.; Simon, G.; Haelters, J.-P.; Corbel, B. *Synthesis* **2006**, 81. (m) Delain-Bioton, L.; Turner, A.; Lejeune, N.; Villemin, D.; Hix, G. B.; Jaffrès, P.-A. *Tetrahedron* **2005**, *61*, 6602. (n) Schlachter, S. T.; Galinet, L. A.; Shields, S. K.; Aspar, D. G.; Dunn, C. J.; Staite, N. D.; Nugent, R. A. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1093. (o) Skarpos, H.; Osipov, S. N.; Vorob'eva, D. V.; Odinets, I. L.; Lork, E.; Röschenthaler, G.-V. *Org. Biomol. Chem.* **2007**, *5*, 2361.

(20) Recher, M.; Barboza, A. P.; Li, Z.-H.; Galizzi, M.; Ferrer-Casal, M.; Szajnman, S. H.; Docampo, R.; Moreno, S. N. J.; Rodriguez, J. B. *Eur. J. Med. Chem.* **2013**, *60*, 431.

(21) (a) Xue, Z.-Y.; Li, Q.-H.; Tao, H.-Y.; Wang, C.-J. *J. Am. Chem. Soc.* **2011**, *133*, 11757. (b) Sulzer-Mossé, S.; Alexakis, A.; Mareda, J.; Bollot, G.; Bernardinelli, G.; Filinchuk, Y. *Chem. Eur. J.* **2009**, *15*, 3204. (c) Sulzer-Mossé, S.; Tissot, M.; Alexakis, A. *Org. Lett.* **2007**, *9*, 3749. (d) Capuzzi, M.; Perdicchia, D.; Jørgensen, K. A. *Chem. Eur. J.* **2008**, *14*, 128. (e) Kato, Y.; Chen, Z.; Matsunaga, S.; Shibasaki, M. *Synlett* **2009**, 1635. (f) Barros, M. T.; Phillips, A. M. F. *Eur. J. Org. Chem.* **2008**, 2525. (g) Barros, M. T.; Phillips, A. M. F. *Org. Biomol. Chem.* **2012**, *10*, 404.

(22) Ruzziconi, R.; Ricci, G.; Gioiello, A.; Couthon-Gourvès, H.; Gourvès, J.-P. *J. Org. Chem.* **2003**, *68*, 736.

(23) Nugent, R. A.; Murphy, M.; Schlachter, S. T.; Dunn, C. J.; Smith, R. J.; Staite, N. D.; Galinet, L. A.; Shields, S. K.; Aspar, D. G.; Richard, K. A.; Rohlofft, N. A. *J. Med. Chem.* **1993**, *36*, 134.

(24) Bortolini, O.; Mulani, I.; De Nino, A.; Maiuolo, L.; Nardi, M.; Russo, B.; Avnet, S. *Tetrahedron* **2011**, *67*, 5635.

(25) Ye, Y.; Xu, G.-Y.; Zheng, Y.; Liu, L.-Z. *Heteroat. Chem.* **2003**, *14*, 309.

(26) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.

(27) Sha, C.-K.; Mohanakrishnan, A. K. *Azides*, In *The Chemistry of Heterocyclic Compounds, Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Vol. 59; Padwa, A.; Pearson, W. H., Eds.; John Wiley & Sons: New York, **2002**, 623–679.

(28) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon: Oxford, **1991**, 269–331.

(29) Cinque, G. M.; Szajnman, S. H.; Zhong, L.; Docampo, R.; Schvartzapel, A. J.; Rodriguez, J. B.; Gros, E. G. *J. Med. Chem.* **1998**, *41*, 1540.

(30) Fleming, I. *Molecular Orbitals and Organic Chemical Reactions*; John Wiley & Sons: New York, **2009**, 242–252.

(31) Chakrasali, R. T.; Ila, H.; Junjappa, H. *Synthesis* **1988**, 453.

(32) Jiang, Q.; Yang, L.; Hai, L.; Wu, Y. *Lett. Org. Chem.* **2008**, *5*, 229.

(33) (a) Harada, K.; Kaji, E.; Sen, S. *Chem. Pharm. Bull.* **1980**, *28*, 3296. (b) Basel, Y.; Hassner, A. *Synthesis* **1997**, 309. (c) Nelson, D.; Kasparian, D. J.; Trager, W. F. *J. Org. Chem.* **1972**, *37*, 2686.

(34) (a) Cecchi, L.; De Sarlo, F.; Machetti, F. *Tetrahedron Lett.* **2005**, *46*, 7877. (b) Cecchi, L.; De Sarlo, F.; Machetti, F. *Eur. J. Org. Chem.* **2006**, 4852.

(35) Winckler, W.; Pieper, T.; Keppler, B. K. *Phosphorus, Sulfur Silicon Relat. Elem.* **1996**, *112*, 137.

(36) (a) Stork, G.; McMurry, J. E. *J. Am. Chem. Soc.* **1967**, *89*, 5461. (b) Stork, G.; McMurry, J. E. *J. Am. Chem. Soc.* **1967**, *89*, 5464.

(37) McMurry, J. E. *Org. Synth. Coll. Vol. VI*; John Wiley & Sons: London, **1988**, 592.

(38) Mendelsohn, B. A.; Lee, S.; Kim, S.; Teyssier, F.; Aulakh, V. S.; Ciufolini, M. A. *Org. Lett.* **2009**, *11*, 1539.

(39) Bousquet, E. W. *Org. Synth. Coll. Vol. II*; John Wiley & Sons: London, **1943**, 313.

(40) (a) Grigg, R.; Kemp, G.; Sheldrick, G.; Trotter, J. *J. Chem. Soc., Chem. Commun.* **1978**, 109. (b) Joucla, M.; Hamelin, J. *Tetrahedron Lett.* **1978**, *19*, 2885.

(41) (a) Garner, P.; Kaniskan, H. Ü. *Tetrahedron Lett.* **2005**, *46*, 5181. (b) Garner, P.; Kaniskan, H. Ü. *J. Org. Chem.* **2005**, *70*, 10868.

