Tetraethyl Vinylidenebisphosphonate: A Versatile Synthon for the Preparation of Bisphosphonates

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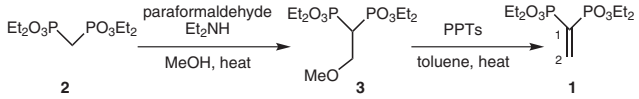
Abstract: Tetraethyl vinylidenebisphosphonate is a versatile synthetic intermediate that allows access to a variety of highly functionalized compounds bearing the bisphosphonic moiety. As an electron-deficient alkene, this compound is able to undergo conjugate addition with a variety of reagents including strong nucleophiles, such as organometallic reagents and enolates, as well as very mild nucleophiles, such as amines, mercaptans and alcohols. The title compound also possesses the ability to behave as a dipolarophile or dienophile in 1,3-dipolar cycloadditions or Diels–Alder reactions, giving rise to five- or six-membered rings containing the bisphosphonic unit. In summary, tetraethyl vinylidenebisphosphonate is a very useful synthon to have at hand for straightforward syntheses of bisphosphonate derivatives of diverse structures. This bisphosphonate moiety has proven to be very important to impart important pharmacological action.

Key words: bisphosphonates, tetraethyl vinylidene bisphosphonate, Michael additions, 1,3-dipolar cycloadditions

1 Introduction

The synthetic intermediate tetraethyl vinylidene bisphosphonate [tetraethyl ethene-1,1-diylbis(phosphonate); **1**] is a very versatile synthetic intermediate used to access a variety of different bisphosphonates of biological importance. Bisphosphonates are metabolically stable analogues of naturally occurring pyrophosphates in which a substituted methylene group replaces the oxygen atom bridge between the two phosphorus atoms of the pyrophosphate moiety.[1] Bisphosphonates have been of pharmacological significance since calcification studies were performed more than 40 years ago.[2–4] Compound **1** is a Michael-type acceptor, which is straightforwardly prepared from commercially available tetraethyl methylenebisphosphonate (**2**) in two steps according to the Degenhardt method via the synthetic intermediate tetraethyl 2-methoxyethyl-1,1-bisphosphonate (**3**) as illustrated in Scheme 1.[5–8] The starting material **2** can also be prepared from triethyl phosphite and methylene dibromide or methylene diiodide.[9]



Scheme 1 Method of preparation of compound **1**

Compound **1** and other 2-alkyl-substituted derivatives such as **10** and **11** can also be prepared from acyl phosphonates via phosphonovinyl nonaflates (nonafluorobutylsulfonates, Nf), which undergo a palladium-catalyzed cross-coupling reaction with dialkyl phosphites to yield the corresponding vinylidenebisphosphonates.[10] Therefore, on treatment with nonylfluoride in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at low temperature, acyl phosphonates **4**–**6** are converted into phosphonovinyl nonaflates **7**–**9**,[11] which are treated with diethyl phosphate (1.1 equiv) in the presence of tetrakis(triphenylphosphine)palladium(0) (0.04 equiv) and ethyl diisopropylamine (1.3 equiv) in *N*,*N*-dimethylformamide to afford the desired *gem*-bis(phosphono)ethylene **1** in an excellent yield of 93%. This reaction is carried out at 110 °C for 40 minutes.[10,11] Compounds **10** and **11** are also obtained in the moderate yields of 63% and 73%, respectively, as shown in Scheme 2.

An efficient method of preparation of 2-alkyl-substituted derivatives of **1** (alkylidene bisphosphonates) is based on a Knoevenagel-type condensation between an aldehyde and tetraethyl methylenebisphosphonate (**2**) in the presence of titanium tetrachloride employing *N*-methylmorpholine as a base as illustrated in Scheme 3.[12] The use of

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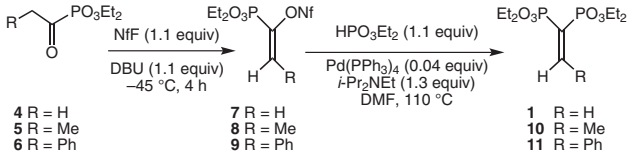
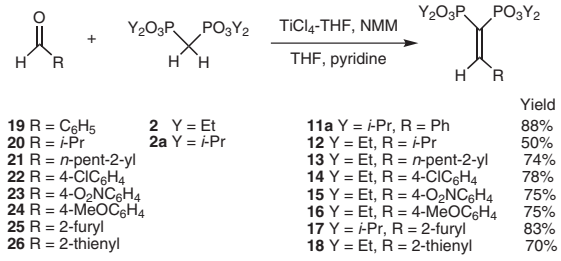
titanium is crucial because coordination with the reactant carbonyl group avoids elimination of one phosphonate moiety via a Wittig-type reaction.[12,13]



Scheme 2 Alternate method of preparation of compound **1** and 2-alkylated derivatives



Scheme 3 Knoevenagel-type condensation to obtain 2-substituted derivatives of **1**

Most of the pharmacologically important bisphosphonates have a hydroxy group at the C-1 position. However, its presence is not necessarily required to warrant an efficient biological activity. The chemical structure of representative bisphosphonates that are in clinical use for the treatment and prevention of osteoclast-mediated bone resorption associated with various bone disorders are presented in Figure 1 and include etidronate (**27**), clodronate (**28**), pamidronate (**29**), alendronate (**30**), risedronate (**31**), tiludronate (**32**), ibandronate (**33**), zoledronate (**34**) and incadronate (**35**).[14–17]

In addition to their use in long-term treatments of bone disorders, bisphosphonates exhibit a broad scope of biological actions, such as anticancer activity,[18–21] antibacterial activity,[22] selective inhibition of the enzymatic activity of acid sphingomyelinase,[23] stimulation of γδ T cells of the immune system,[24] and antiparasitic activity.[25–32]

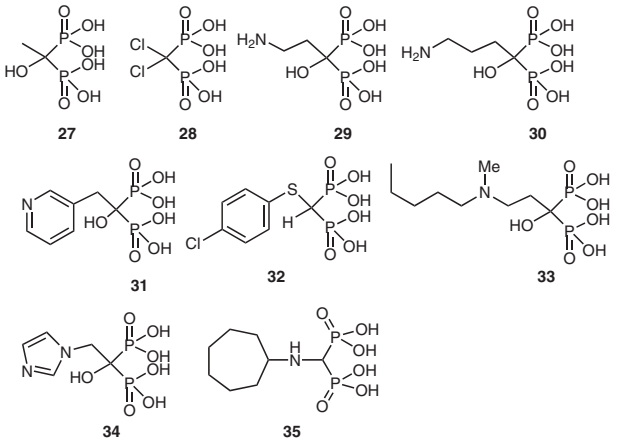


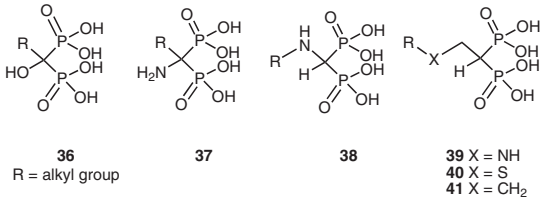
Figure 1 General formula and chemical structure of representative FDA-approved bisphosphonates clinically employed for the treatment of bone disorders

Taking into account the pharmacological importance of 1,1-bisphosphonate derivatives, too much attention has been focused on their methods of preparation. Prospects in bisphosphonate chemistry have changed substantially since the development of a reliable and reproducible method of preparation of 1-hydroxy-1,1-bisphosphonic acids of formula **36** from carboxylic acids, which are converted into the title compounds by treatment with phosphorous acid, and phosphorus trichloride in the presence of benzenesulfonic acid, followed by hydrolysis.[33] These 1-hydroxy-*gem*-bisphosphonates arise, undoubtedly, as the most relevant ones. In addition, 1-amino-1,1-bisphosphonic acids of formula **37** are currently prepared from cyano derivatives[34] or amides,[35,36] while 1-substituted aminoethylidene-1,1-bisphosphonates (**38**) are usually synthesized starting from the corresponding amine (Figure 2).[37]

In addition, as mentioned above, tetraethyl vinylidenebisphosphonate (**1**) is a versatile synthetic intermediate that has been established as a significant synthon for accessing a variety of compounds bearing the *gem*-bisphosphonate moiety of formula **39**–**41**, and others as will be discussed below.

Biographical Sketch

Juan Bautista Rodriguez was born in Buenos Aires. He received his B.Sc. at Universidad de Buenos Aires (1982), his Ph.D. at Universidad de Buenos Aires (1990), and was postdoctoral fellow at the National Institutes of Health under Sanford P. Markey (1992) and Victor E. Marquez (1993). He was appointed Assistant Professor at Universidad de Buenos Aires where he is currently Professor. He is active in the areas of molecular recognition, medicinal chemistry, organophosphorus chemistry, and synthetic organic chemistry. He has made influential contributions to the development of antiparasitic and antiviral agents.



36 R = alkyl group **37** **38** **39** X = NH **40** X = S **41** X = CH_2

Figure 2 General formula of a different class of bisphosphonate

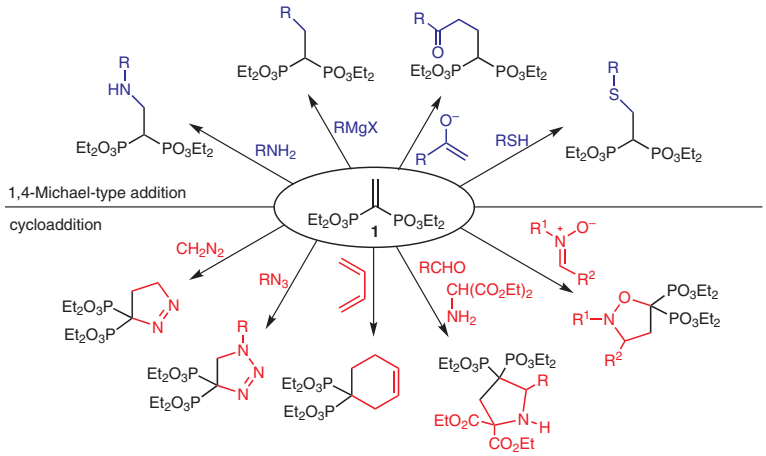
2 General Reactivity

Undoubtedly, compound **1**, as an electron-deficient alkene, behaves as a highly activated Michael-type acceptor, giving rise to 1,4-conjugate addition adducts either with strong nucleophiles such as Grignard reagents[7,38–40] other organometallic compounds,[41] or very mild ones such as amines,[42] including heterocyclic amines such as imidazole, pyrazole and benzimidazole,[43] nucleophilic phosphorus compounds,[44] or mercaptans.[45] In connection with this conjugate addition, the use of **1**, and other closely related substituted derivatives, has also been described for a number of Michael-type additions to form new carbon–carbon bonds involving, mostly, enolate species as nucleophiles.[6,8,46] Pericyclic reactions could be employed as useful tools to access diverse chemical structures bearing a bisphosphonic moiety. At the present time, there are merely a few published examples where **1** experiences cycloaddition reactions behaving either as a dienophile in the Diels–Alder reaction,[47] or as a dipolarophile in 1,3-dipolar cycloadditions.[48–51] The ability of **1** to undergo conjugate additions or cycloadditions is summarized in Scheme 4.

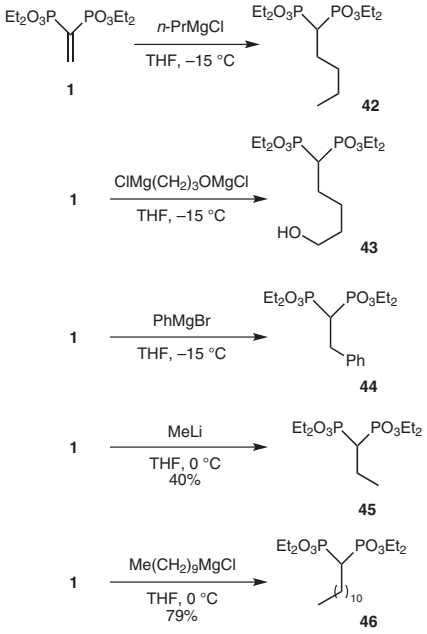
3 Michael Addition Reactions

3.1 Reaction with Organometallic Reagents

The conjugate addition of Grignard reagents on the Michael-type acceptor **1** was first depicted in 1999 by Ebetino and co-workers.[52] Later, different classical and simple Grignard reagents, such as ethylmagnesium chloride, *n*-propylmagnesium chloride, and phenylmagnesium bromide, were described as suitable nucleophiles to carry out 1,4-conjugate additions in reasonable and reproducible yields without affecting the phosphonate moiety (1,2-nucleophilic addition) to yield compounds **42**–**46**.[7] The reaction is usually conducted in the presence of anhydrous tetrahydrofuran as a solvent at –15 °C. Compound **1** is also able to react with functionalized Grignard reagents. An interesting example is the reaction between **1** and the Grignard reagent derived from 3-chloropropanol [$ClMg(CH_2)_3OMgCl$],[53] which affords, in a straightforward manner, the bisphosphonate derivative **43** possessing the hydroxy group at the side chain (Scheme 5). Compound **1** is the committed intermediate in the preparation of long aliphatic chains bearing a bisphosphonate unit. It has been described that it is possible to incorporate up to *n*-decylmagnesium chloride at 0 °C employing tetrahydrofuran as a solvent.[38–40] Interestingly, the shortest member of this series (**45**) could not be prepared via a Grignard reagent but the use of methyllithium in anhydrous tetrahydrofuran at 0 °C was required to produce this compound in 40% yield.[38] Pioneering studies on the ability of **1** to undergo conjugate addition had indicated that the reaction of this compound with butyllithium afforded a complex mixture of products.[54] Although diethyl ethenylphosphonate undergoes 1,4-conjugate addition of alkylcopper and vinylcopper complexes to afford phosphonic esters with the alkyl chain increased by two carbon atoms and γ,δ-unsaturated phosphonic esters, respectively,[55] to date there have been no methodology studies addressing the reaction of **1** with organocopper reagents.



Scheme 4 State of the art for either conjugate addition or 1,3-dipolar cycloaddition of **1**



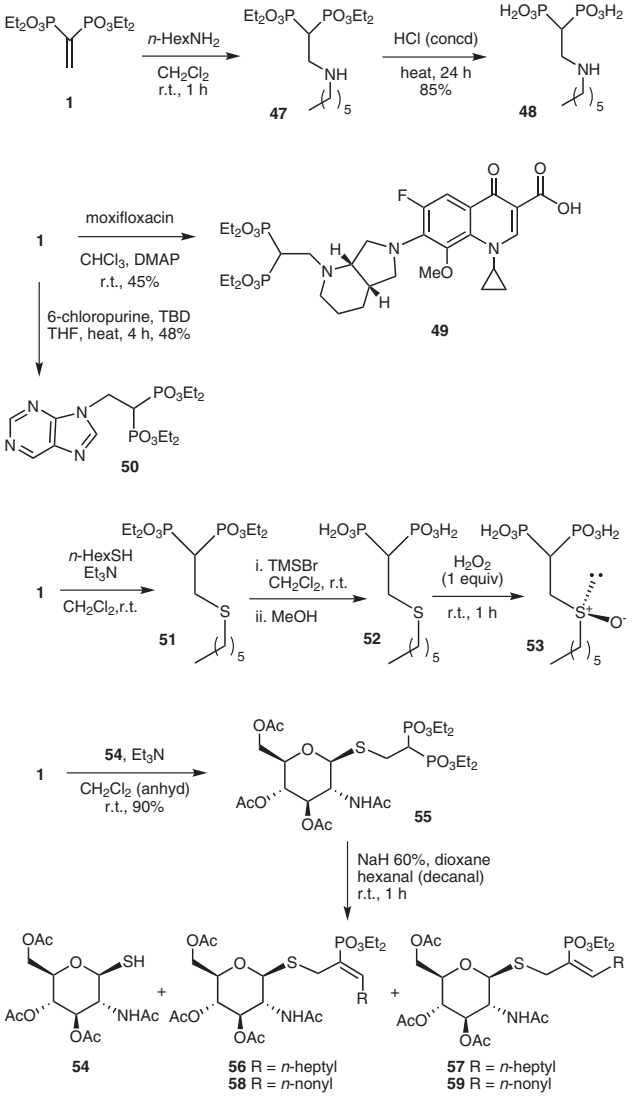
Scheme 5 Reaction of **1** with different Grignard reagents

3.2 Reaction with Mercaptans and Amines

As previously mentioned, compound **1** reacts with a wide variety of mild nucleophilic reagents to give the corresponding Michael adducts (Scheme 6). For example, primary amines reacted smoothly with **1** in anhydrous dichloromethane as solvent, affording the corresponding Michael products such as **47**.[42a,b] This compound had to be purified rapidly due to its tendency to undergo a retro-Michael reaction; however, the free acid **48** was very stable and did not suffer from this retro-Michael reaction.[42a,b] Secondary amines also underwent Michael reactions but the resulting tetraethyl 2-(dialkylamino)ethyl-1,1-bisphosphonates were unstable products that easily underwent the retro-Michael reaction giving rise to the starting materials, that is, the respective dialkylamine and compound **1**.

In addition, different fluoroquinolone antibacterial agents such us norfloxacin, enoxacin, moxifloxacin, gatifloxacin, and ciprofloxacin, all of which are synthetic compounds bearing a secondary amino group, also reacted with **1**.[42c,56] In Scheme 6 is illustrated one example where moxifloxacin reacted with **1** to give rise to **49**, a synthetic intermediate to develop prodrugs for the prevention of osteomyelitis.[42c] Moreover, different heterocyclic compounds also underwent conjugate addition. For example, imidazole, pyrazole, benzimidazole, 1*H*-imidazole-2-thiol, purine, and 6-chloropurine were all nucleophilic enough to undergo conjugate addition on **1** in the presence of 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) as catalyst with tetrahydrofuran as a solvent.[43] The reaction of purine with **1** to produce **50** as shown in Scheme 6 is a representative example.

Moreover, sulfur-containing bisphosphonates are prepared in a straightforward manner via 1,4-conjugate addi-



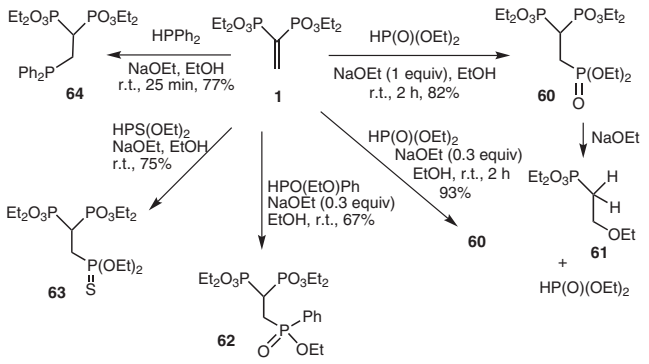
Scheme 6 Reaction of **1** with mild nucleophilic reagents

tion of *n*-alkyl mercaptans to the acceptor **1**, in the presence of triethylamine, in yields ranging from 68 to 94%. However, the production of sulfoxide derivatives at the C-3 position is not so trivial. The controlled oxidation reaction of thioethers is the most widely employed method for the preparation of sulfoxides.[57] In contrast to what has been published for closely related compounds,[58] all the attempts to oxidize sulfides of formula **51** (or other structurally related compounds) by using sodium metaperiodate,[59–60] hydrogen peroxide,[62,63] or *m*-chloroperoxybenzoic acid[64] led to a retro-Michael reaction.[45] It is well known that alkylsulfides bonded at the β-position of aldehydes and ketones undergo a retro-Michael reaction when treated with an oxidizing agent, affording the α,β-unsaturated carbonyl compounds and the corresponding alkylsulfanol.[65–67] However, this effect is more noticeable when alkylsulfides are bonded at the β-position of a bisphosphonate moiety.[45] Tetraalkyl bisphosphonate esters are obligatory intermediates to obtain the pharmacological important free bisphosphonic acids or their sodium

salts; mostly, these esters are devoid of relevant biological activity. Then, **52**, as a free acid, is a good substrate for oxidative reaction, and, on treatment with an appropriate oxidizing agent (one equivalent of hydrogen peroxide), it is transformed into the desired sulfoxide **53**.[45] Thiosugars are also capable of undergoing conjugate addition with the Michael acceptor **1**.[68] In fact, 3,4,6-tri-*O*-acetyl-2-acetamino-2-deoxy-1-thio-β-D-glucopyranose[69] (**54**) reacted with **1** in anhydrous dichloromethane in the presence of triethylamine to afford the respective adduct **55**. On treatment with aliphatic aldehydes such as hexanal or decanal, under Wittig-type conditions, this compound lost a phosphonate group and formed a new carbon–carbon double bond affording, in low but reproducible yields, the pair of geometric isomers **56**–**57**, or **58**–**59**, respectively.[67] Apparently, the retro-Michael addition is the most favorable reaction here, although the authors did not mention it specifically, the fact that the thiosugar **54** is the principal product leads one to believe that a retro-Michael reaction took place (Scheme 6).[67]

3.3 Reaction with Phosphorus-Containing Nucleophiles

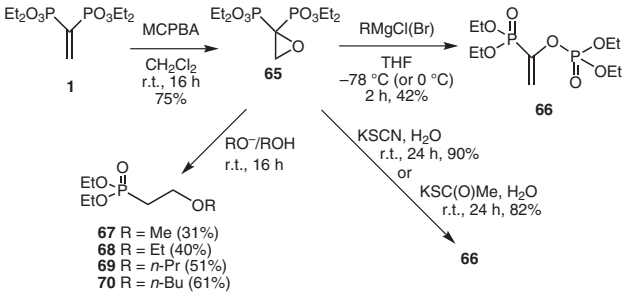
The Michael acceptor **1** also reacts with nucleophilic phosphorus reagents, such as diethyl phosphite, in the presence of a stoichiometric amount of sodium ethoxide in ethanol. This reaction, for example, was complete within 15 minutes and afforded compound **60** in 82% yield. However, longer reaction times led to diethyl 2-ethoxyethylphosphonate (**61**), in which one unit of the bisphosphonate moiety wass lost as triethyl phosphate.[44] Together with diethyl phosphite, other compounds such as dimethyl phosphite, ethyl phenyl phosphonite, diethyl thiophosphite, and diphenylphosphine behaved as phosphorus-containing nucleophilic reagents to produce compounds such as **62**–**64**.[44] The authors have stated that retro-Michael reactions do not occur, but thermal degradation is observed instead. These reactions that use nucleophilic phosphorus were more efficient when carried out in a protic solvent, most often ethanol, in the presence of catalytic sodium ethoxide as illustrated in Scheme 7.



Scheme 7 Michael addition reactions of nucleophilic phosphorus on compound **1**

3.4 Epoxidation, Loss of a Phosphonate Unit and Rearrangement Reactions

In spite of being an electron-deficient alkene, compound **1** easily underwent an epoxidation reaction to afford the corresponding epoxide **65**,[39,70,71] which on treatment with a variety of nucleophilic reagents suffered an interesting phosphonate-phosphate rearrangement that led exclusively to the enol phosphate **66** regardless of the nature of the nucleophile (Scheme 8).[39,70] For example, when **65** reacted with *n*-butylmagnesium bromide (2 equiv) in tetrahydrofuran at –78 °C for one hour, **66** was formed in 50% yield. The same product was obtained with allylmagnesium chloride, *n*-pentylmagnesium bromide and *n*-hexylmagnesium bromide.[39] There is strong evidence to suggest that this reaction involves radical species.[39] When **65** was treated with sulfur-containing nucleophiles, the same rearranged product **66** was obtained via an ionic mechanism. Interestingly, on reaction with various sodium alkoxides, epoxide **65** was converted under the strong basic conditions, losing one unit of the phosphonate functionality to afford compounds **67**–**70**.[39]

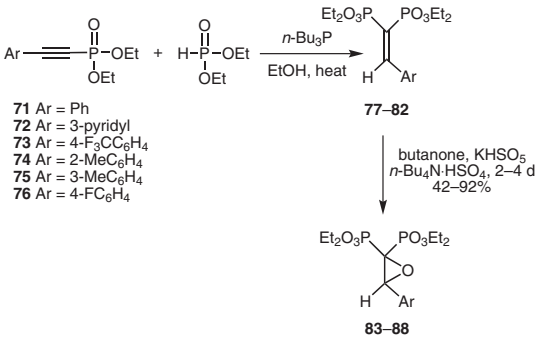


Scheme 8 Phosphonate–phosphate rearrangement experienced by epoxy derivative **65**

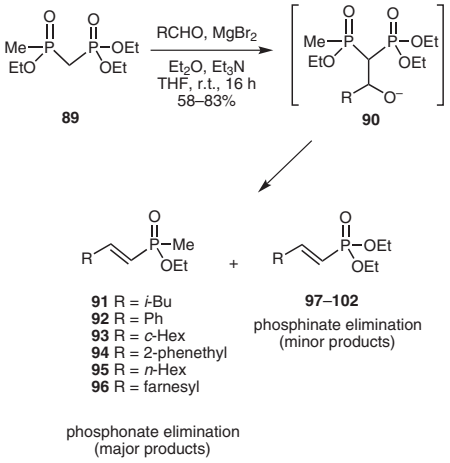
Other structurally related analogues of **1**, such as 2-arylethylidene-1,1-bisphosphonates, underwent epoxidation reactions.[72] These 2-aryl derivatives were converted into the corresponding epoxides **83**–**88** by treatment with dioxirane, which is formed in situ by reaction with potassium hydrogen monopersulfate and methyl ethyl ketone in the presence of tetrabutylammonium bisulfate as phase-transfer catalyst (Scheme 9).[73] The substrates for these reactions (compounds **77**–**82**) were obtained in a straightforward manner from alkynylphosphonates (compounds **71**–**76**) via an α-P-addition of diethylphosphite (Scheme 9).[74]

As discussed previously, the use of alkynyl phosphonates as a bisphosphonate source is an alternative approach to a Wittig-type reaction. The main problem associated with the preparation of 2-substituted derivatives of vinylidene-1,1-bisphosphonates is the phosphonate elimination when carbonyl compounds were used as starting materials.[75] In fact, unless titanium(IV) was present,[12,13] the Wittig-type reaction occurred as described when *O*,*O*,*O*-triethyl methylmethylenephosphonophosphinate (**89**) was allowed to react with a variety of aldehydes, thus undergoing mostly phosphonate elimination (compounds **91**–**96**) over phos-

phinate elimination (compounds **97**–**102**) as shown in Scheme 10.[75]

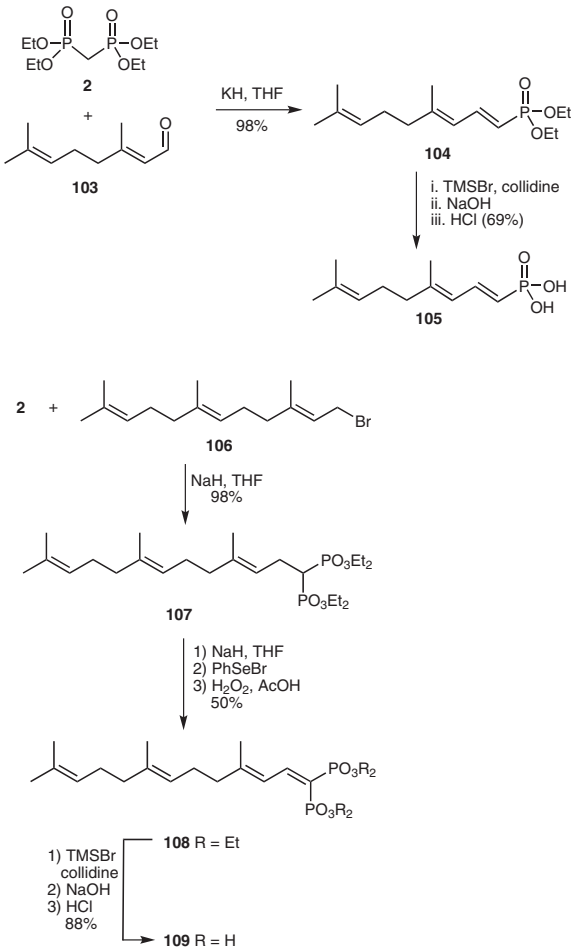


Scheme 9 Synthesis of 1,2-epoxy-1,1-bisphosphonates from alkynylphosphonates



Scheme 10 Phosphonate elimination versus phosphinate elimination in the reaction of **89** with aldehydes

Phosphonate elimination has also been observed in the preparation of vinyl phosphonates derived from farnesol and geraniol. When tetraethyl methylenebisphosphonate (**2**) was treated with geranial (**103**) or farnesal, in a basic medium, a Wittig-type reaction took place with loss of one phosphonate moiety to yield **104** as illustrated in Scheme 11.[76] Therefore, in order to obtain the corresponding vinyl derivatives, phosphonate elimination can be circumvented starting from farnesyl bromide (**106**) as shown in Scheme 11. The double bond at the C-1 position was introduced by treatment with phenylselenyl bromide followed by oxidation with hydrogen peroxide to give **108**, which was further hydrolyzed to produce the corresponding free bisphosphonic acid **109**.[76]



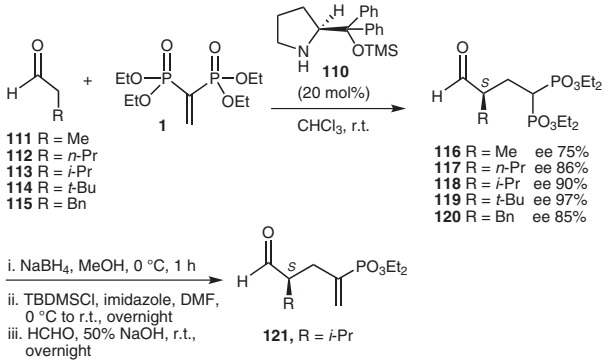
Scheme 11 Preparation of vinyl phosphonate derivatives of farnesol

3.5 Michael Reactions with Enolates

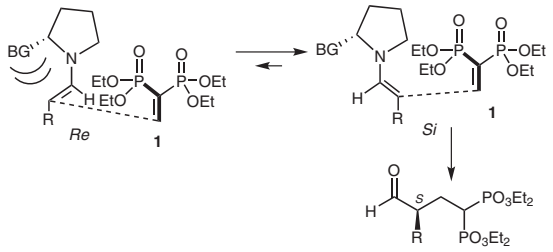
The Michael addition reaction of enolates to alkenyl phosphonates has become a well-established procedure in organic synthesis for the preparation of functionalized phosphonates.[77,78] Enolates of particular interest are those that possess a prochiral carbon at the nucleophilic center.

One of the first examples of asymmetric Michael additions on vinyl phosphonates was the reaction of lithiated SAMP hydrazones with (*E*)-alkenyl phosphonates to give 4-oxo-functionalized phosphonates.[79] In this context, pyrrolidine analogues are very good prospects as catalysts to carry out asymmetric conjugate additions in organocatalysis.[80,81] The trimethylsilyl derivative of (*S*)-2-diphenylprolinol, **110**, first described by Hayashi et al.,[82] is an efficient chiral auxiliary that has been employed in a number of asymmetric Michael additions.[83,84] Compound **1** is able to undergo efficient asymmetric conjugate addition in the presence of **110** as organocatalyst (Scheme 12). Thus, enolates from aldehydes were allowed to react with vinylphosphonate **1** to give rise to conjugate adducts **116**–**120** in good yields and enantiomeric excesses up to 97% as was the case for **119**.[81] These compounds were then converted into β-substituted vinylphosphonates, as exemplified by **121**, without losing enantioselectivity.[81]

This work was extended to other electron-deficient alkenes as substrates, such as vinyl sulfones, and a variety of chiral catalysts derived from proline, and L-proline itself, affording the corresponding Michael adducts with high enantioselectivity and in good reaction yield.[85] A reasonable facial enantioselectivity was proposed to justify the observed stereochemistry (Scheme 13).[84,85]

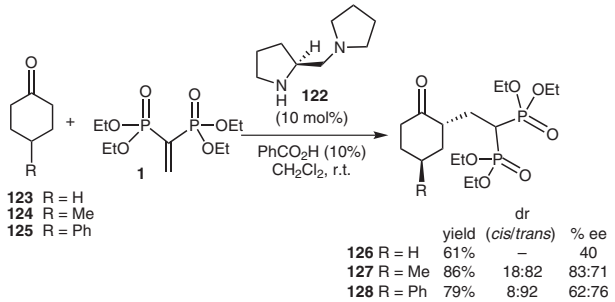


Scheme 12 Organocatalytic Michael additions of aldehydes to **1**, catalyzed by prolinol derivative **110**



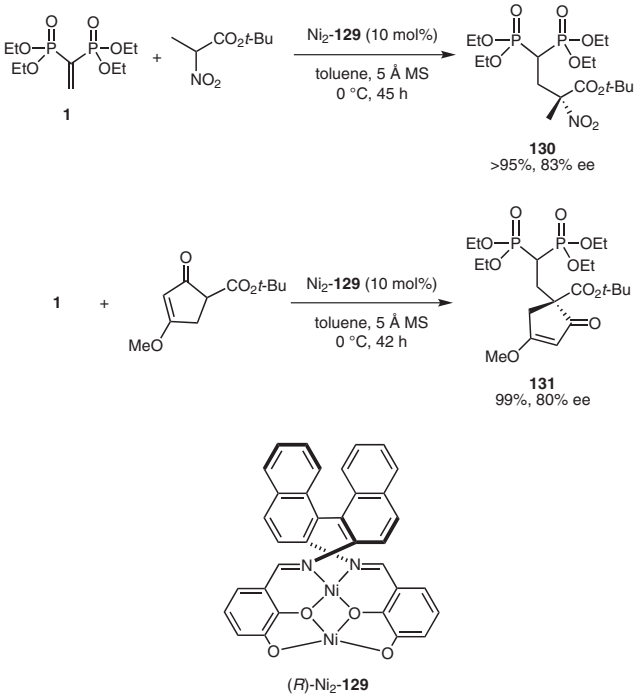
Scheme 13 Postulated approach for organocatalytic asymmetric Michael reactions with **1**; BG = bulky group

(*S*)-(+)-1-(2-Pyrrolidinyl)pyrrolidine (**122**) is an interesting diamine and an organocatalyst derived from proline.[86,87] Cyclic ketones reacted with Michael acceptor **1** in the presence of 10 mol% of catalyst **122**, 10 mol% of benzoic acid as an additive and dichloromethane as solvent to afford cyclic γ-keto *gem*-bisphosphonates with high diastereo- and enantioselectivity. Relevant examples are the compounds **126**–**128**, which are illustrated in Scheme 14.[88,89]



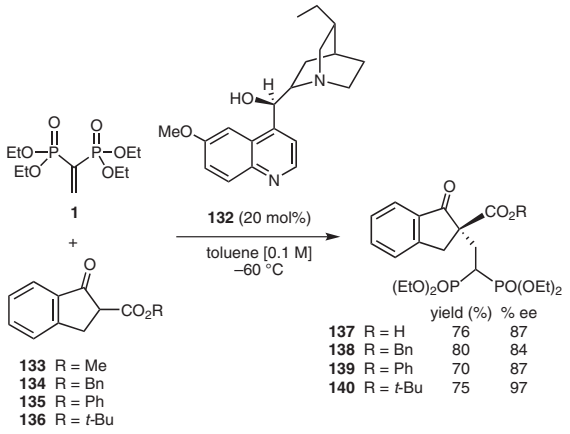
Scheme 14 Organocatalytic Michael additions of cyclic ketones to **1**, catalyzed by **122**

α-Substituted nitroacetates underwent conjugate asymmetric addition on Michael acceptor **1** promoted by the Lewis acid–Brønted base bifunctional homodinuclear nickel–Schiff base complex (*R*)-Ni_2-**129**.[90] For example, *tert*-butyl α-methylnitroacetate underwent an asymmetric 1,4-conjugate addition in the presence of 10 mol% of (*R*)-Ni_2-**129** with high enantioselectivity to afford **130** (Scheme 15). Ethyl α-methylnitroacetate also underwent conjugate addition in very high yield but with modest enantiomeric excess (38% ee).[91] The reaction of *tert*-butyl 4-methoxy-2-oxocyclopent-3-enecarboxylate with **1** is another interesting example of this type of reaction, and it gave rise to **131** with high enantioselectivity.[91] This method is not only relevant to the preparation of highly functionalized nitrogen-containing bisphosphonate derivatives, but also to obtaining unnatural amino acids enantioselectively.



Scheme 15 Catalytic asymmetric Michael addition to **1** with stabilized enolates

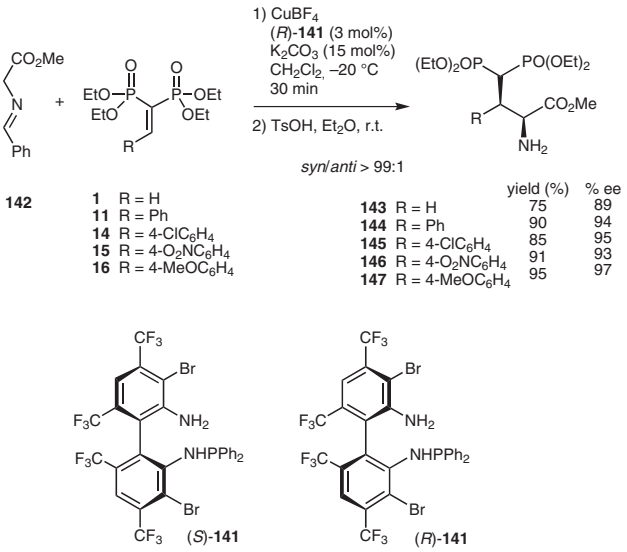
Among several cinchona alkaloids, the commercially available dihydroquinine **132** emerges as an interesting and efficient organocatalyst to be used in Michael-type additions to **1**.[92] For example, cyclic β-keto esters like **133**–**136** were able to undergo asymmetric Michael additions to afford bisphosphonate derivatives bearing a quaternary stereogenic center, such as **137**–**140**, as shown in Scheme 16.[92] The reaction had to be conducted under carefully controlled conditions. A temperature of –60 °C and a substrate concentration of 0.1 M were required in order to obtain high enantioselectivity. Mostly, this reaction took place in short reaction times (less than one hour).[92] Interestingly, it was possible to obtain the enantiomer of **140** by employing dihydroquinidine as a catalyst; a similar level of enantioselectivity was observed.[92]



Scheme 16 Organocatalytic Michael additions of cyclic ketones to **1**, catalyzed by dihydroquinine **132**

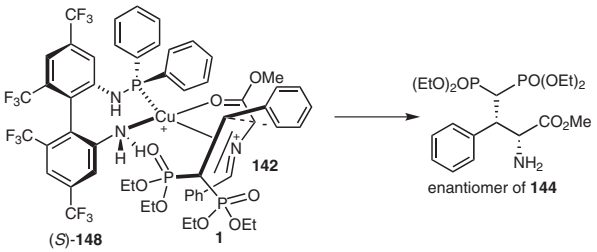
The ligand TF-BiphamPhos [(*S*)-141] when used with silver acetate has proven to be an effective catalyst in asymmetric 1,3-dipolar cycloadditions[93] of alkylidene malonates with an azomethine ylide from methyl 2-(benzylideneamino)acetate (**142**; see Scheme 17) to give *exo*-adducts with high diastereo- and enantioselectivities.[94] From there, the same research group was able to prepare unnatural amino acids bearing the *gem*-bisphosphonate functionality through an asymmetric Michael reaction between methyl 2-(benzylideneamino)acetate and a variety of alkylidene bisphosphonates (Scheme 17).[95] The reaction was conducted by employing the chiral complex copper(I)–TF-BiphamPhos in the presence of potassium carbonate (15% mol) in dichloromethane at –20 °C followed by removal of the corresponding benzaldehyde by treatment with toluenesulfonic acid in diethyl ether.[95] The reaction involved the formation of two new stereogenic centers and occurred with great diastereoselectivity (>99:1, favoring the *syn* isomer) and high enantioselectivity.[95] Representative examples of this interesting reaction are illustrated in Scheme 17.

Interestingly, when the reaction was conducted with (*S*)-**141** on alkylidene bisphosphonate **11**, the resulting product was the corresponding enantiomer of **144** in comparable yield and enantiomeric excess.[95] The authors have tried to explain the resulting stereochemistry through a postulated transition state, but what the authors have actually represented is a facial stereoselectivity rather than a transition state as shown in Scheme 18. At first glance, the appearance of this article seems to indicate that the understanding and controlling of diastereofacial selectivity in carbon–carbon bond-forming Michael additions have been fully resolved. In this context, a question arises regarding the nature of the Michael donor **142**.[95] As drawn, this chemical structure corresponds to a 4π-electron component, that is, a 1,3 dipole,[96] rather than to a nucleophilic species capable of undergoing a nucleophilic addition which is a very interesting observation. The authors of this article did not take advantage of using ^{31}P NMR spectroscopy in all of these phosphorus-containing compounds, which would have been of great utility to confirm the high



Scheme 17 Representative copper(I)-catalyzed asymmetric Michael additions of the imino ester **142** with **1** and some of its β-substituted analogues

diastereoselectivity reported.[95] Only the ^{31}P NMR spectra of the already described **11** and the corresponding synthetic intermediate that led to **144** were included in the article's supporting information. At the present time, it seems difficult to state that the diastereoselectivity is greater than 99:1 based on proton NMR spectra performed at 300 MHz.[95] In the ^{13}C NMR spectra, the multiplicity of the carbon atoms bonded to the two phosphorus atoms should appear as triplets, not as singlets as reported.[95] These signals are very diagnostic of this class of compounds.



Scheme 18 Proposed facial distereoselectivity in the copper(I)-catalyzed asymmetric Michael addition of the azomethine ylide **142** with **11**

4 Cycloaddition Reactions

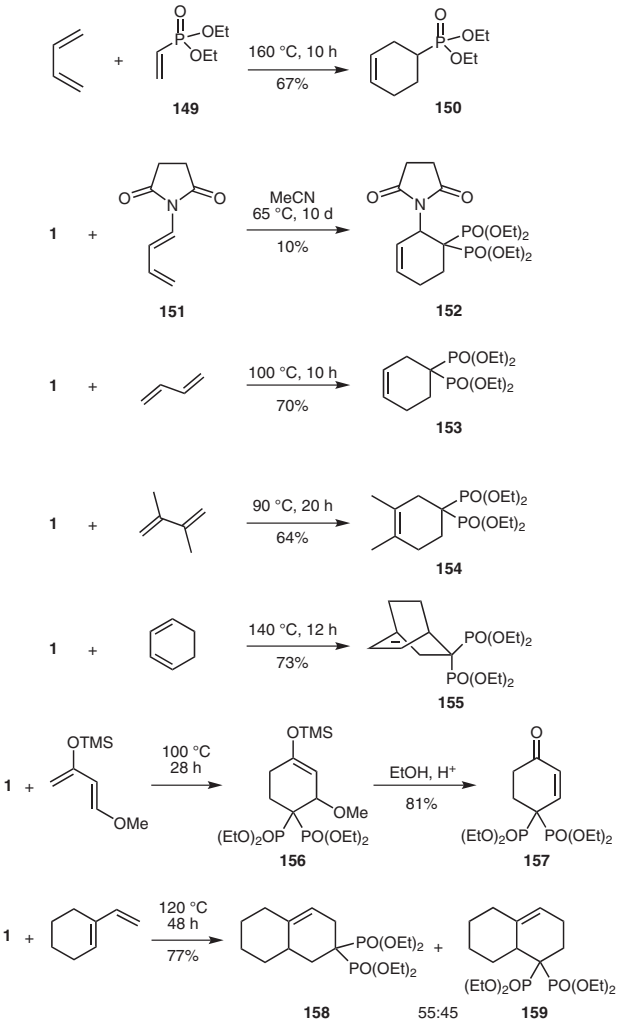
4.1 Diels–Alder Reactions

As an electron-deficient alkene, compound **1** would be able to experience pericyclic reactions. However, in spite of having being used as an efficient Michael-type acceptor, there are just few examples where **1** undergoes cycloaddition reactions, behaving either as a dienophile in Diels–Alder reactions,[47] or as a dipolarophile in 1,3-dipolar cycloadditions.[48–51] Therefore, at the present time, the use of **1** and other β-substituted vinyl bisphosphonates as

substrates for cycloaddition reactions is without doubt an under-explored area of research.

It was reported that the reaction of diethyl vinylphosphonate (compound **149**)[97] with excess buta-1,3-diene at 160 °C for 10 hours gave rise to 3-cyclohexen-1-ylphosphonate **150**.[98] Along these lines, *N*-(1,3-butadienyl)succinimide (**151**) was just barely able to undergo a [4+2] cycloaddition reaction on **1** to afford the corresponding *ortho* cycloadduct **152**; the reaction provided a very low yield of 10%, which is impractical from the synthetic point of view.[99] In fact, as a dienophile, **1** is less reactive than other electron-deficient alkenes such as α,β-unsaturated carbonyl derivatives, or α,β-unsaturated carbonyl nitriles, among others.[99] However, the reactivity of **1** could be improved by the use of Lewis acids as catalysts.[100] Under these conditions, tetraethyl vinylidenebisphosphonate underwent [4+2]-cycloaddition reactions with a variety of very simple dienes. These reactions were carried out at temperatures in the range of 90 to 110 °C, and no solvent was required for the reaction to take place.[47] Unfortunately, with the exception of Danishevsky's diene, regioselectivity was not significant when employed with non-symmetrically substituted dienes.[47] Some representative examples, **153**–**159**, are illustrated in Scheme 19.

Certainly, the [4+2]-cycloaddition reactions on tetraethyl vinydenebisphosphonate **1** and its β-substituted analogues is still an underdeveloped area of research, particularly in terms of enantioselectivity, where it is possible to form putative pharmacologically important cyclohexyl-*gem*-bisphosphonates bearing a maximum of three new stereogenic centers.

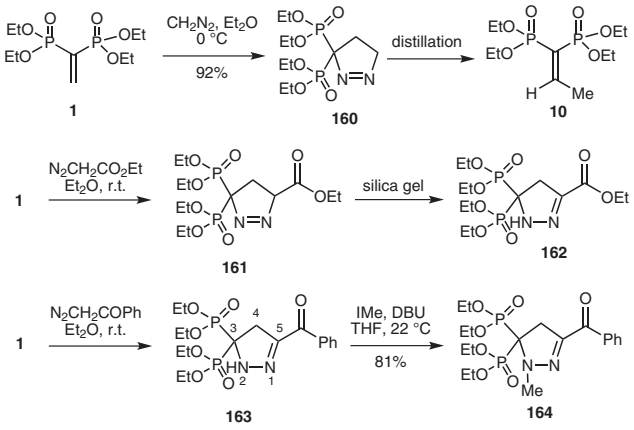


Scheme 19 [4+2]-Cycloaddition reactions of 1,3-dienes with vinylphosphonates

4.2 1,3–Dipolar Cycloadditions

4.2.1 Reaction with Diazo Compounds

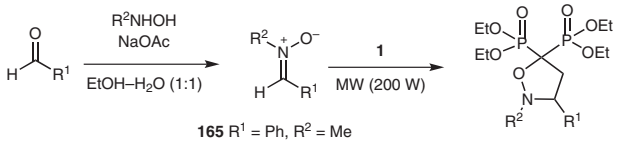
On reaction with diazo ketones, tetraethyl vinylidenebisphosphonate underwent 1,3-dipolar cycloadditions to form pyrazoline bisphosphonate derivatives.[48] In addition, **1** reacted with diazomethane to afford the expected 4,5-dehydro-3*H*-pyrazol-3-ylidene bisphosphonate **160**. This compound was then converted into the β-methyl derivative of **1** by distillation, or simply on standing at room temperature for one week. Ethyl diazoacetate also reacted with **1** to afford the 1,3-cycloaddition product **161**, which underwent shifting of the double bond by treatment with silica gel to yield the α,β-unsaturated carbonyl product **162** that is, without doubt, the more thermodynamically stable product.[48] 5-Keto pyrazines, however, are even more stable than compound **162** and structurally related analogues. On treatment with a diazo ketone in diethyl ether at 22 °C overnight, **1** was converted into **163** in 49% yield. Diazo ketones are easily obtainable from an acyl chloride and diazomethane in the presence of triethylamine,[101] or by treatment of a mixture of the appropriate methyl ketone and ethyl formate with tosyl azide.[102] Moreover, the N-2 position is acidic enough to be alkylated; for instance, **163** reacted with iodomethane, in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), in tetrahydrofuran at 22 °C to afford **164** in 81% yield as shown in Scheme 20.



Scheme 20 1,3-Dipolar cycloaddition reactions of **1** with diazo derivatives

4.2.2 Reaction with Nitrones

Isoxazolidines bearing a *gem*-bisphosphonate moiety are obtained in a straightforward manner through microwave-assisted 1,3-dipolar cycloadditions by treatment of the Michael acceptor **1** with nitrones at 0.1 M concentration, providing reaction yields ranging from 68 to 86%.[49] Nitrones are generally readily prepared by the reaction between an *N*-alkyl hydroxylamine and an aldehyde.[103] In this particular study, the nitrones were prepared by treatment of the corresponding carbonyl compound with *N*-methyl- or *N*-benzylhydroxylamine in the presence of sodium acetate in a mixture of ethanol–water (1:1).[104] The stereochemical course of the reaction occurred as expected and was a dipole-LUMO-controlled reaction leading to the corresponding 5,5-disubstituted isoxazoline derivatives. The preparation of the molecular targets **173**–**180** is illustrated in Scheme 21.[105]



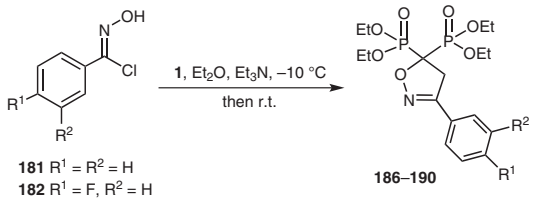
165 R^1 = Ph, R^2 = Me
166 R^1 = 2-ClC_6H_4, R^2 = Me
167 R^1 = 3-pyridyl, R^2 = Me
168 R^1 = 3-furyl, R^2 = Me
169 R^1 = 4-HOC_6H_4, R^2 = Bn
170 R^1 = Ph, R^2 = Bn
171 R^1 = 2-ClC_6H_4, R^2 = Bn
172 R^1 = 2-FC_6H_4, R^2 = Bn

173–180

Scheme 21 Synthesis of isoxazolidine derivatives through a 1,3-dipolar cycloaddition reaction of nitrones

4.2.3 Reaction with Nitrile Oxides

In connection with 1,3-dipolar cycloadditions, the reaction of **1** with nitrile oxides would afford bisphosphonates possessing a 4,5-dihydroisoxazole ring. In fact, it has been depicted that by using **1** as a substrate and hydroxamic chlorides as the nitrile oxide source,[106] it was possible to access these highly functionalized bisphosphonates represented by compounds **186**–**190** (Scheme 22).[50] Frontier orbital theory provides strong evidence to assume dipole-HOMO-controlled regiochemistry to yield these products.[107]

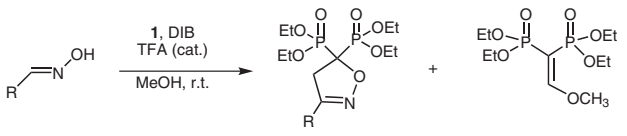


181 R^1 = R^2 = H
182 R^1 = F, R^2 = H
183 R^1 = Cl, R^2 = H
184 R^1 = OMe, R^2 = H
185 R^1 = R^2 = 3,4-OCH_2O

186–190

Scheme 22 Synthesis of 4,5-dihydroisoxazoles bearing a *gem*-bisphosphonate moiety from nitrile oxides generated from hydroxamic chlorides

There is another example of 1,3-dipolar cyclcoaddition of nitrile oxides with **1**. Indeed, substituted 5-dihydroisoxazoles were obtained, starting from the oximes as the nitrile oxide source, by treatment with (diacetoxyiodo)benzene (DIB) in the presence of trifluoroacetic acid.[108] Then, a solution of the decanal oxime in methanol, in the presence of DIB, was allowed to react with **1** to afford the expected 1,3-cycloadduct **194**. Unpredictably, an almost equivalent amount of the enol ether **195** was formed, probably by way of a conjugate addition of methanol, followed by an oxidation.[51] Aromatic oximes **192** and **193** gave rise to 1,3-dipolar cycloaddition products **196** and **197** as shown in Scheme 23.[51]



191 R = *n*-pentyl
192 R = Ph
193 R = 4-$MeOC_6H_4$

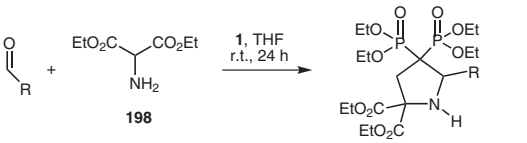
194 R = *n*-pentyl 24%
196 R = Ph 40%
197 R = 4-$MeOC_6H_4$ 23%

195 40%

Scheme 23 Synthesis of 3-substituted 4,5-dihydroisoxazoles via 1,3-dipolar cycloadditon of nitrile oxides generated from oximes

4.2.4 Grigg Azomethine Ylide Cyclizations

Highly functionalized bisphosphonates built on a pyrrolidine backbone, such as **199**–**201**, can be synthesized via the Grigg azomethine ylide cyclization, which is an interesting 1,3-dipolar cascade cycloaddition reaction where an in situ imine formation takes place starting from an aldehyde and an α-amino acid derivative.[109] This imine behaves as an azomethine ylide in the presence of a suitable dipolarophile. For example, when compound **1** was treated with an aldehyde and diethyl aminomalonate (**198**) in tetrahydrofuran,[110] compounds **199**–**201** were produced in 50, 68 and 40% yield, respectively (Scheme 24). Once again, the reactions proceeded with high regioselectivity as expected.[107]



198

199 R = *n*-pentyl 50%
200 R = Ph 68%
201 R = 4-$MeOC_6H_4$ 41%

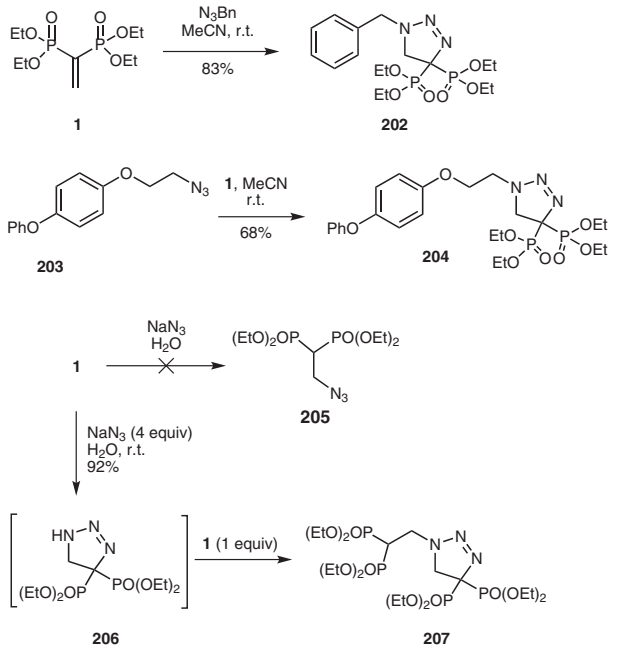
Scheme 24 Bisphosphonates built on a pyrrolidine scaffold via a cascade Grigg azomethine ylide–1,3-dipolar cycloaddition reaction

4.2.5 1,3-Dipolar Cycloaddition with Azides

Of particular interest is the 1,3-dipolar cycloaddition of **1** with azide-containing compounds. Azides have been widely used in 1,3-dipolar cycloadditions on a number of activated and non-activated alkenes.[96,111,112] For example, bisphosphonate **1**, on treatment with alkyl azides, led to

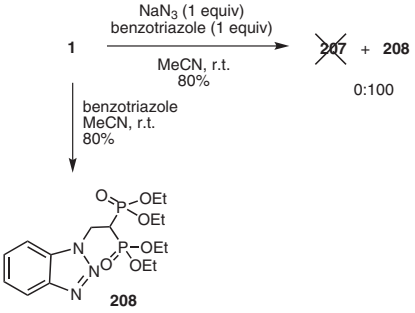
the relatively complex tetraethyl (1-alkyl-4,5-dihydro-1*H*-1,2,3-triazole-4,4-diyl)bisphosphonates **202** and **204** as single regioisomers,[51] and assuming a dipole-HOMO-controlled regiochemistry to yield the molecular targets.[107]

A detailed discussion should be given about the ability of sodium azide to undergo dipolar 1,3-cycloadditions. It is known that sodium azide reacts with α,β-unsaturated carbonyl compounds to produce triazole rings.[113] However, it has also been reported that when **1** is treated with sodium azide in water, it behaves as a Michael acceptor, instead of a dipolarophile, leading to **205**, but there are no NMR spectroscopic data available to support the hypothetical structure of **205**.[114] In addition, formation of the theoretical structure **205** by treatment between sodium azide with **1**, in methanol–water (1:1), was stated to be an intermediate in accessing 1,2,3-triazole-containing bisphosphonates.[115] Once again, with the exception of an upfield shift of the signal assigned to **1** in the corresponding ^{31}P NMR spectrum,[115] no other spectroscopic evidence such as ^{1}H NMR, ^{13}C NMR, accurate mass (HRMS), copies of the spectra, or purification protocol were provided to support the obtainment of **205**.[115] However, contrary to what is published,[112] the reaction of **1** with excess sodium azide does not produce the Michael adduct **205**, nor the expected hypothetical cycloaddition product **206**, but **207** instead, as illustrated in Scheme 25.[51] This reaction can be carried out in solvents such as methanol, acetonitrile, and methanol–water (1:1) giving, in all cases, **207** exclusively, and in excellent yields. The production of **207** is supported by solid spectroscopic evidence.[51]



Scheme 25 1,3-Dipolar cycloaddition reaction between **1** and azides

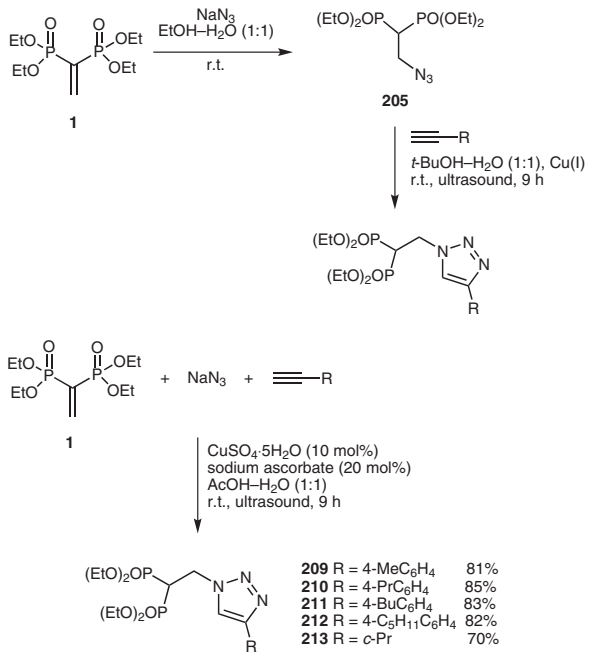
It has been postulated that a 1,3-dipolar cycloaddition reaction would occur first to give **206**, which, once formed, would react immediately with another molecule of **1** to undergo a Michael-type reaction to afford **207**; this would indicate that the 1,2,3-triazole moiety of **206** is a strong nucleophile.[51] Competitive reaction studies showed that when **1** was treated with a solution containing sodium azide and benzotriazole, one equivalent each, only the Michael adduct **208** was formed, while **207** was not observed. These data support the postulated mechanism of the reaction in which, once the 1,2,3-triazole system (**206**) is formed, **206** reacts as a very strong nucleophile, and does so more rapidly than sodium azide, via a conjugate addition on unreacted **1** (Scheme 26).[51]



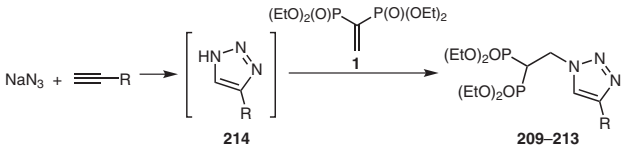
Scheme 26 Competition between Michael addition and 1,3-dipolar cycloaddition

As mentioned before, it has been proposed that the theoretical compound **205** would be a synthetic intermediate to produce tetraethyl 2-(4-substituted 4,5-dihydro-1*H*-1,2,3-triazol-1-yl)ethyl-1,1-bisphosphonates. It was described that these compounds can be prepared sequentially or in a one-pot procedure as shown in Scheme 27, where the preparation of some representative molecular targets (**209**–**213**) is described.[115] In the sequential reaction, the yield reported is less than 20%, while the one-pot procedure was reported to take place in yields ranging from 70 to 85%, depending on the nature of the R substituent at the C-4 position.[115]

Bearing in mind that azides are dipolar compounds and that the one-pot procedure is much more efficient than the sequential one,[115] it is possible to postulate an alternate reaction mechanism to explain the formation of triazole derivatives **209**–**213** (Scheme 28). In fact, alkynes react easily with azides in the presence of copper(II) and sodium ascorbate in water and *tert*-butanol by 'click' methodology to form a triazole ring.[41] The molecule bearing the alkyne group would react with sodium azide to form the intermediate **214**, which is a powerful nucleophile[51] that would then react directly with **1** to form the product compounds **209**–**213**. Sodium azide was used recently to synthesize 1,2,3-triazole-containing bisphosphonates.[116]



Scheme 27 Synthesis of tetraethyl 2-(4-substituted 4,5-dihydro-1*H*-1,2,3-triazol-1-yl)ethyl-1,1-bisphosphonates, with alkynes as intermediates



Scheme 28 An alternate reaction mechanism proposed for the formation of tetraethyl 2-(4-substituted 4,5-dihydro-1*H*-1,2,3-triazol-1-yl)ethyl-1,1-bisphosphonates

5 Concluding Remarks

In this review, the electron-deficient alkene **1** has been described to behave either as a Michael-type acceptor or as dienophile or dipolarophile in [4+2]-cycloaddition or 1,3-dipolar cycloaddition reactions, respectively. All of these approaches allow synthetic organic chemists and medicinal chemists to have at hand a variety of polyfunctionalized *gem*-bisphosphonates of diverse chemical structure. In all cases, it is possible to obtain linear or cyclic (five- or six-membered rings) compounds, such as triazoles, pyrrolidines and isoxazoles, with high regioselectivity. The area of asymmetric bisphosphonate synthesis using pericyclic reactions is still deficient and can be considered as remaining underdeveloped to date.

In summary, **1**, via Michael reactions or pericyclic reactions, is a versatile substrate to prepare bisphosphonates of diverse chemical structure that could lead to the synthesis of important drugs.

Acknowledgement

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