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Phosphonoallenes for Building Organophosphorus Derivatives

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ABSTRACT: *This review article deals with new approaches to polyfunctional phosphonoallenes as well as synthetically useful reactions of this class of organophosphorus compounds for design of various heterocyclic phosphonates, new phosphonolipids, and phosphononucleotides.* © 2006 Wiley Periodicals, Inc. Heteroatom Chem 17:547–556, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20275

INTRODUCTION

Phosphonoallenes were first obtained in 1962 by Mark through the [2,3]-sigmatropic rearrangement of propargylic phosphites [1]. The unusual structure of these compounds comprising reaction centers that differ in properties and reactivity, their availability, and the wide variety of chemical properties, have for a long time attracted the attention of chemists [2–5]. Further study of phosphonoallenes has continued until today. The results obtained in recent years added much to the general ideas concerning the compounds of this class. First, the range of synthetic reactions based on phosphonoallenes expanded significantly and it became necessary to refine the concept of their reactivity. Secondly, in recent years the structures of certain phosphonoallenes were first investigated by X-ray diffraction methods [6,7] and by gas electron diffraction [8]. In addition, the quantum-chemical calculations and photoelectron spectroscopic data made it possible to reliably characterize for the first time the electronic structure of phosphonoallenes. In connection with the growing interest in the synthesis of promising physiologically active phosphonates, we suggest useful-to-perform systematic collection and analysis of the experimental data accumulated to the moment.

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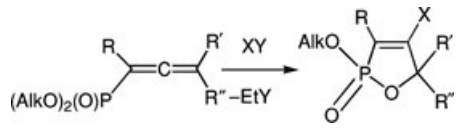
RESULTS AND DISCUSSION

Synthesis of Heterocyclic Phosphonates on the Basis of the Phosphonoallenes

Allenes have been widely used as building blocks in organic chemistry for construction of five- and six-membered carbocyclic and heterocyclic ring systems [9,10]. An impressive number of heterocyclic systems have been prepared from allenic starting materials or via allenes as unstable intermediates [11,12]. Application of new synthetic approaches to phosphonoallenes opened convenient ways to phosphorus-containing heterocyclic compounds.

It is known that phosphonoallenes react with halogens [13], protic acids [14], sulfenyl chlorides [4], and selenenyl chlorides [4] with the formation of 2,5-dihydro-1,2-oxaphospholes (Scheme 1) because of the participation of the phosphoryl oxygen atom as an internal nucleophile in the final step of the addition. In all these reactions, the electrophilic reagents were introduced in a *trans* fashion to the phosphono substituent.

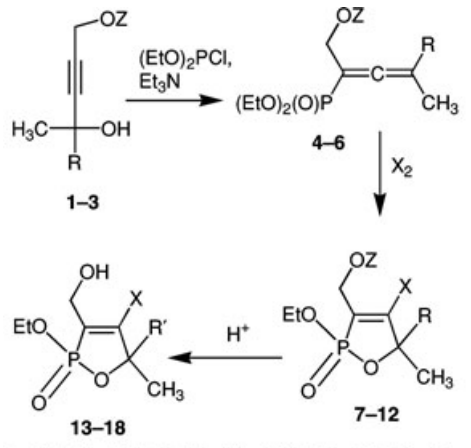


SCHEME 1

Introduction of additional functional groups to the oxaphosphole ring extended considerably their reactivity and applications. 2,5-Dihydro-1,2-oxaphospholes **13–18** possessing $-CH_2OH$ group at C-3 position were synthesized by the sequence shown in Scheme 2 [15]. Phosphorylated allenes **4–6** were prepared directly from alcohols **1–3** in 64–86% yields by Mark through the [2,3]-sigmatropic rearrangement [1]. Reactions of allenes **4–6** with bromine or chlorine were carried out in carbon tetrachloride at low temperature (−25 or −20°C). The hydroxyl group was deprotected by stirring the methanol solution of the reaction mixture in the presence of HCl at room temperature.

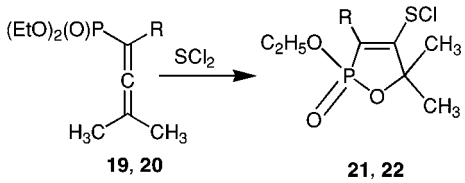
Reaction of phosphoallenes **19, 20** with SCl_2 in an aprotic nonpolar solvent proceeded smoothly and afforded 2-alkoxy-4-chlorothio-5,5-dimethyl-2,5-dihydro-1,2-oxaphosphole-2-oxides **21, 22** in excellent yields [16–19]. Compounds **21** are quite stable and could be stored in a freezer for several weeks.

The sulfenyl chloride **22** (Scheme 3) is less stable; nevertheless, it could be used freshly prepared without isolation for further transformations. Both the sulfenyl chlorides **21** and **22** reacted at S—Cl group with olefins to give additional compounds (Scheme 4); for this reaction Ad_E mechanism was suggested [20]. For example, the reaction of **21, 22**,



R =CH_3 (**1, 4, 7, 10, 13, 16**); $ClCH_2$ (**2, 5, 8, 11, 14, 17**); $-CH_2OCH(CH_3)C_2H_5$ (**3, 6, 9, 12**); R′ = CH_3 (**13, 16**); $ClCH_2$ (**14, 17**); $HOCH_2$ (**15, 18**); X = Cl (**7–9, 13–15**);Br (**10–12,16–18**); Z = $-CH(CH_3)OC_2H_5$.

SCHEME 2



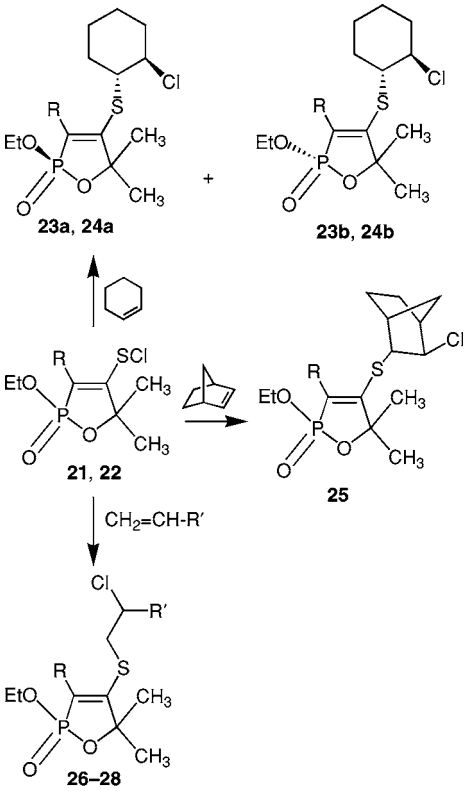
R = H (**19, 21**); CH_2OCH_3 (**20, 22**).

SCHEME 3

and cyclohexene resulted in a mixture of two diastereomeric oxaphospholes **23a, 24a** and **23b, 24b** (2:1 ratio by ^1H and ^{31}P NMR) with a total yield of 95%.

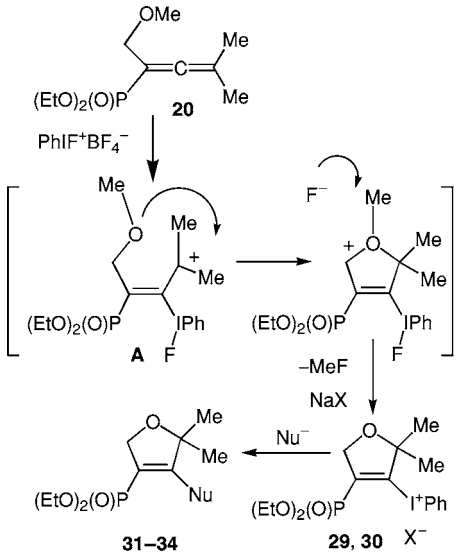
The reaction of **21** with norbornene proceeded analogously to give two diastereomeric products of *trans*-exo-1,2-addition. The reaction of **21, 22** with styrene and 1-hexene proceeded to give Markovnikov products **26–28** exclusively.

The complex of difluoroiodobenzene with boron trifluoride exhibits electrophilic properties and reacts at low temperature with methoxyallene **20** to give cyclic vinyliodonium salts **29, 30** isolated in 63% yield (Scheme 5) [21]. The same compound **29**



R = H (**21**, **23a**, **23b**, **25–27**); CH_2OCH_3 (**22**, **24a**, **24b**, **28**); R′ = C_4H_9 (**26**); C_6H_5 (**27**, **28**).

SCHEME 4



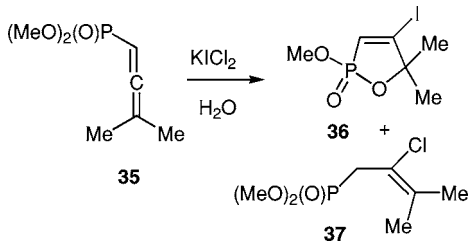
X = BF_4^- (**29**), ClO_4^- (**30**); Nu = N_3 (**31**), OMe (**32**), OEt (**33**), I (**34**).

SCHEME 5

was obtained in the reaction of allene **20** with 2 mol equiv. of iodosobenzene in the presence of boron trifluoride etherate followed by subsequent treatment of the reaction mixture with aqueous saturated solution of sodium tetrafluoroborate. When aqueous solution of lithium perchlorate was used for quenching the reaction mixture, the corresponding perchlorate **30** was formed. Addition of iodonium species generated from difluoroiodobenzene and boron trifluoride to allene **20** proceeds highly regioselectively because of the formation of the stabilized allylic carbanium ion **A**. The participation of the methoxy group as a nucleophile in the final step of the addition proceeds with loss of methyl fluoride and leads via ring closure to the formation of the observed dihydrofuran iodonium salts **29, 30**. The structures of both the iodonium salts were determined by X-ray analysis.

Iodonium salts **29, 30** are highly reactive compounds. Reaction of perchlorate **30** with sodium azide in acetonitrile proceeds smoothly at room temperature to yield the corresponding vinyl azide **31** quantitatively. The high reactivity of the vinyliodonium salts was also demonstrated in the reaction with sodium methoxide and ethoxide in alcohol where 3-methoxy **32** and 3-ethoxy **33** derivatives were obtained. In the reaction of vinyliodonium salts with CuI/KI in DMFA at room temperature, vinyl iodide **34** was isolated in a high yield [21].

The molecule of phosphonoallene contains two double bonds, which differ markedly in reactivity: one reacts readily with electrophiles while another



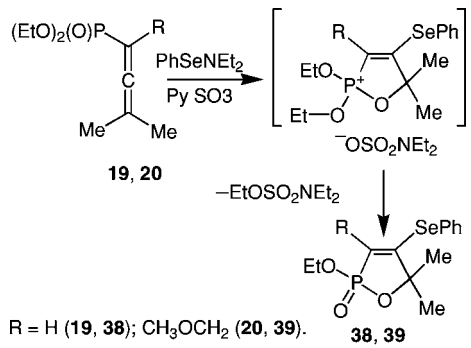
SCHEME 6

with nucleophiles. This made it possible to observe a new type of reaction of potassium dichloroiodate (I) (Scheme 6) [22,23]. The formation of the main products from allene **35** and $KICl_2$ corresponds to the formal addition of iodine chloride via a typical electrophilic mechanism.

The regioselectivity of the chlorine addition points to formation of the acyclic phosphonate **37** as a result of nucleophilic attack by the chloride ion on the α,β-double bond with subsequent protonation of the intermediate.

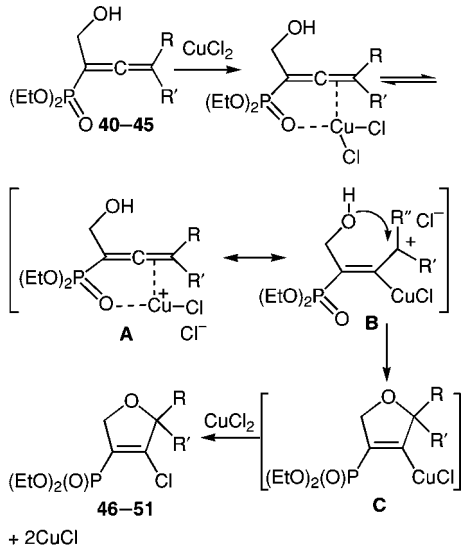
The reaction of benzeneselenenyl *N,N*-diethylamide with the allenephosphonates **19, 20** (Scheme 7) in the presence of an activator (a sulfonate), i.e., under the condition where weakly polar electrophilic species are generated [24] proceeds with the formation of 2,5-dihydro-1,2-oxaphospholes **38, 39** (Scheme 7). As in the case of other weakly polar reagents, *anti*-attack by the electrophilic species relative to the phosphoryl residue is observed. The subsequent cyclization evidently takes place via the formation of a quasi-phosphonium salt with the sulfamate ion as the counterion. Nucleophilicity of the latter is high enough for the rapid dealkylation of the quasi-phosphonium salt.

Application of copper(II) halides for the transformation of organic compounds is widely documented; however, their reaction with

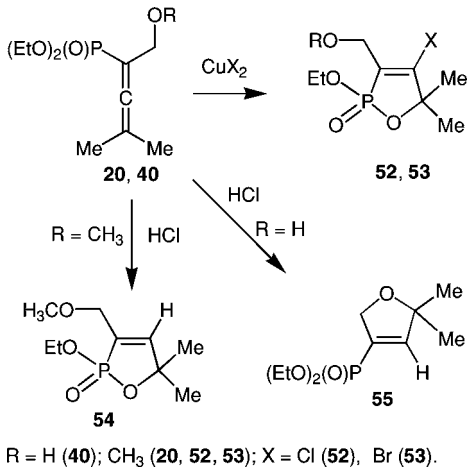


R = H (**19**, **38**); CH_3OCH_2 (**20**, **39**).

SCHEME 7



SCHEME 8



SCHEME 9

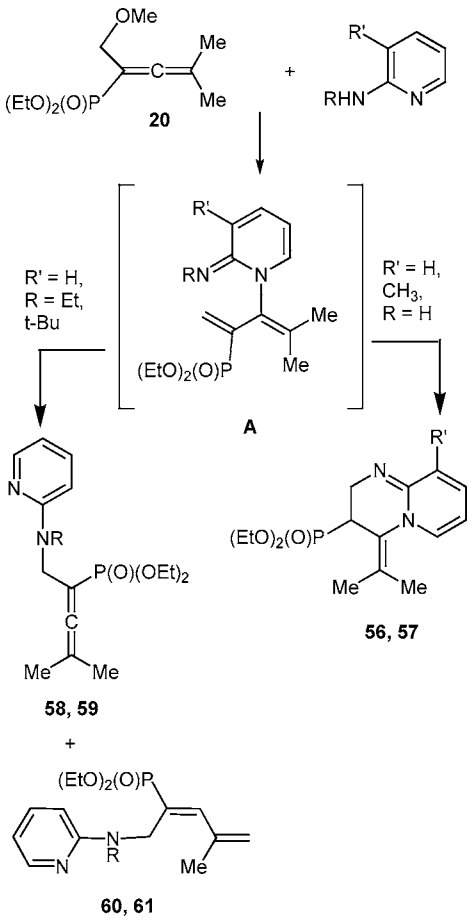
phosphonoallene has not been studied in depth. Recently, a report on the lactonization of allenecarboxylic acids by action of $CuCl_2$ and $CuBr_2$ was published [25]. We carried out the halogenation of 1-(hydroxymethyl)allenephosphonates **40–45**, possessing various substituents that include rings, double bonds, halogens, and hydroxy functions, with $CuCl_2$ [26]. The reaction led to the formation of dihydrofuran ring. The following mechanism can be proposed (Scheme 8). The coordination of $CuCl_2$ with 2,3-π-bond of allenic systems causes its polarization and thus increases the contribution of the resonance structure **B** with the σ-coordinated Cu atom. Intermolecular nucleophilic attack by the hydroxyl group on the C^3 allenic carbon atom allows to "trap" this structure, and the resulting intermediate **C** is rapidly transformed to compounds **46–51** by the oxidative coupling of the ligands. The last process is much faster than the formation of the intermediate **C**, and some amount of $CuCl_2$ is always present in the solution due to the dissociation of the initial complex **A**; therefore, it is impossible to get an intermediate **C** even in solution.

Unlike the alcohols **40–45**, methoxyallene **20** reacts with 2 equiv. of $CuCl_2$ at room temperature in CH_3CN forming 4-chloro-2,5-dihydro-1,2-oxaphospholes **52, 53**. The reaction of compounds **20** with $CuBr_2$ proceeds analogously. The methoxyallene **20** reacts with HCl with formation of 2,5-dihydro-1,2-oxaphosphole **54**, while reaction of allenephosphonate **40** containing OH-group under the same conditions leads to the formation of dihydrofuran **55** (Scheme 9) [27].

The reaction of various bifunctional nucleophilic reagents with phosphonoallene offers wide possibilities for the synthesis of a new type of heterocyclic compounds. Thus, pyridopyrimidines **56, 57** are formed by the reaction of 2-aminopyridines on methoxyallene **20** (Scheme 10). A more detailed study of the reaction with 2-aminopyridines showed that in the first step the intermediate **A** is formed [28,29].

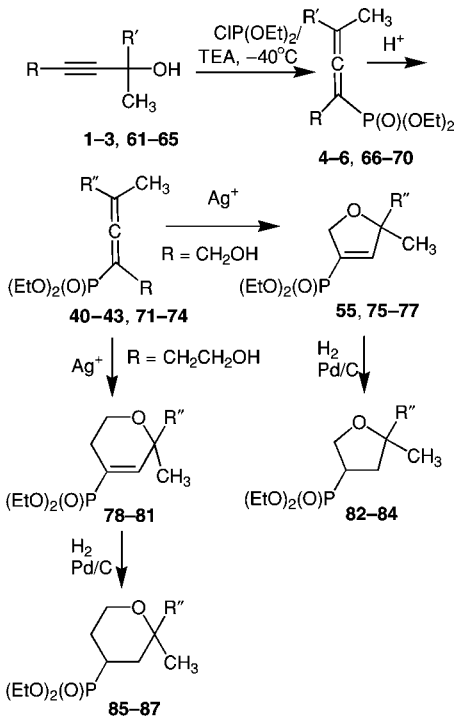
The intermediate **A** is not stable enough and under basic conditions undergoes cyclization to pyridopyrimidines **56, 57** through intramolecular nucleophilic addition of the HN= group to the terminal methylene.

The 4-(diethoxyphosphoryl)-2,5-dihydrofurans **55, 75–77** or 3,6-dihydro-2*H*-pyrans **78–81** were synthesized by a simple procedure (Scheme 11): alkynols **1–3, 61–65** were transformed to the phosphoallenes **4–6, 66–70** and then α-allenic alcohols **40–43, 71–74** were subjected to the ring closure reaction [30]. The propargylic alcohols **1–3, 61–65** were prepared in 60–70% yield by an ordinary procedure starting from propargyl alcohol [31]. Phosphonoallenes **4–6, 66–70** were prepared directly from alcohols **1–3, 61–65** and diethylchlorophosphite in 60–80% yields via the Mark [2,3]-sigmatropic rearrangement of the unstable propargylic phosphites. The latter were generated in situ by the reaction of the alcohols with diethyl chlorophosphite in the presence of triethylamine in diethyl ether at -40°C followed by keeping at 20°C. Compounds **4–6, 66–70** were stable enough to be handled at ambient temperature. The hydroxyl groups in the structures CH_2OZ and CH_2CH_2OZ were deprotected by stirring the methanol solution of the reaction mixture in the



R = Et (**58, 60**), t-Bu (**59, 61**); R' = H (**56**); CH_3 (**57**).

SCHEME 10



Z = $CH(CH_3)OC_2H_5$; R = CH_2OZ (**1–6**, **61**, **66**), CH_2OH (**40–43**), CH_2CH_2OZ (**62–65**, **67–70**), CH_2CH_2OH (**71–74**); R′ = CH_3 (**1**, **4**, **62**, **67**), CH_2Cl (**2**, **5.63**, **68**), CH_2OZ (**3**, **6**, **64**, **69**), $CH{=}CH_2$ (**61**, **65**, **66**, **70**); R″ = CH_3 (**40**, **55**, **71**, **78**, **82**, **85**), CH_2Cl (**41**, **72**, **75**, **79**, **83**, **86**), CH_2OH (**42**, **73**, **76**, **80**, **84**, **87**), $CH_2{=}CH{-}$ (**43**, **74**, **77**, **81**).

SCHEME 11

presence of HCl at room temperature. Analytically, pure phosphorylated allenes **40–43, 71–74** were isolated as colorless or pale yellow oils using column chromatography on silica gel.

Treatment of the γ,γ-disubstituted phosphonoallenic alcohols **40–43, 71–74** with a catalytic amount of silver nitrate in water/acetone led to the complete cyclization, affording the 2,5-dihydrofurans **55, 75–77** or 3,6-dihydro-*H*-pyrans **78–81** within 1–2 h at 50–52°C. Cyclization of the allenephosphonate **42** possessing two $HOCH_2$ groups, in α- and β-positions of the allenic system, was achieved with participation of the α-$HOCH_2$ group exclusively.

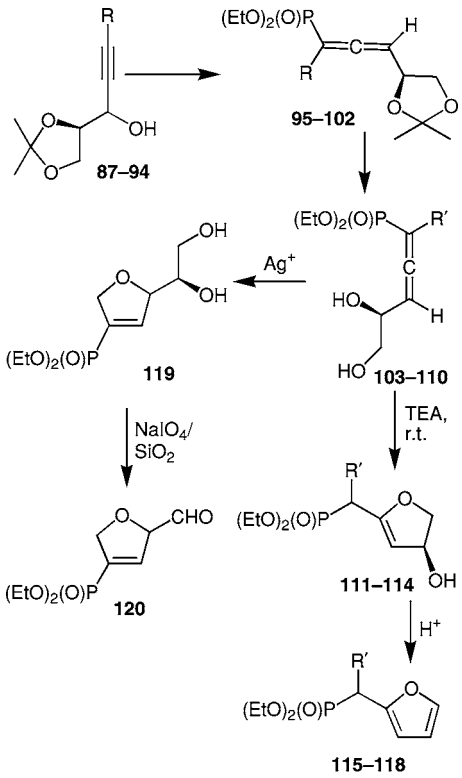
The phosphonoallenic glycols **103–110** were synthesized according to Scheme 12 [32]. These compounds are stable, but under basic conditions, they undergo cyclization to 2,3-dihydrofurans **111–114** by nucleophilic addition of the terminal alkoxide to the central carbon atom of the allenic system.

Reactions were performed in the presence of triethylamine in dry chloroform at 45–50°C for 48 h. When the substituent R was sterically bulky (R = *n*-C_3H_7, *n*-C_4H_9, C_6H_5), attempts of cyclization of the glycol with triethylamine were unsuccessful, and only trace amount of 2,3-dihydrofuran derivative was detected by ^{1}H-NMR analysis. Reaction of 2,3-dihydrofurans **111–114** with a catalytic amount of *p*-toluenesulfonic acid at 40–45°C for 2 h led to furans **115–118** [32].

For the synthesis of allenic aldehydes, compounds **121, 122** were subjected to oxidation with active manganese dioxide in hexane (Scheme 13), but the yield of the target allenic aldehydes **123, 124** was only 10–15% and were isolated by column chromatography.

Exploratory studies to find the conditions for an efficient synthesis of phosphonoallenic aldehydes involved the use of phosphonoallenic glycols. This method was more effective and allenic aldehydes were synthesized with good yields (Scheme 14) [33].

The aldehydes **123, 124, 126–129** are stable compounds and were isolated as colorless oils using column chromatography. In contrast, the



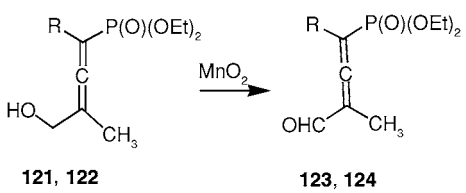
Z = $CH(CH_3)OC_2H_5$; R = H (**87**, **95**); CH_2OZ (**88**, **96**), CH_2OCH_3 (**89**, **97**), $CH(OZ)CH_3$ (**90**, **98**); CH_2CH_2OZ (**91**, **99**); C_3H_7 (**92**, **100**); C_4H_9 (**93**, **101**); C_6H_5 (**94**, **102**); R′ = H (**103**, **111**, **115**); CH_2OH (**104**, **112**, **116**); CH_2OCH_3 (**105**, **113**, **117**); $CH(OH)CH_3$ (**106**, **114**, **118**); CH_2CH_2OH (**107**); C_3H_7 (**108**); C_4H_9 (**109**); C_6H_5 (**110**).

SCHEME 12

phosphonoaldehyde **125** (R = H) is not stable and can be handled only in CH_2Cl_2 solution.

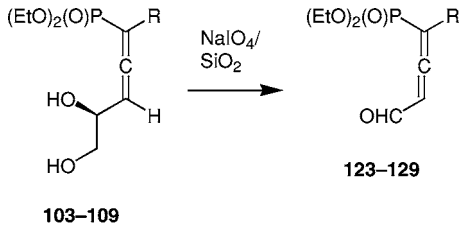
2*H*-Azirines are among the most useful synthetic intermediates toward the synthesis of aziridines, amino acids, indoles, and other biologically active compounds [34]. Recently, we described a convenient and efficient procedure for the preparation of phosphonoallenes **5, 133–135**.

These phosphonoallenes react with sodium azide in methanol to form azidophosphonoallenes



R = *n*-C_3H_7 (**121**, **123**); *n*-C_4H_9 (**122**, **124**).

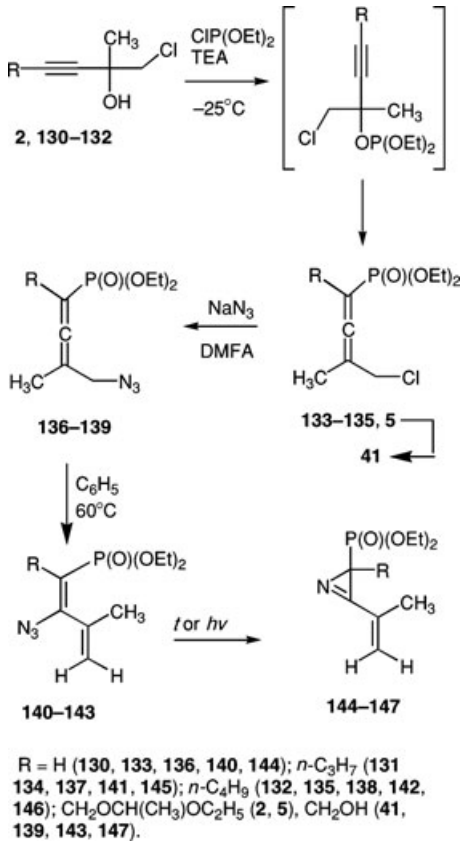
SCHEME 13



R = H (**103**, **125**), $HOCH_2$ (**104**, **126**); CH_3OCH_2 (**105**, **127**); $CH_3(OH)CH$ (**106**, **128**); $HOCH_2CH_2$ (**107**, **129**); *n*-C_3H_7 (**108**, **123**); *n*-C_4H_9 (**109**, **124**).

SCHEME 14

intermediates **136–139** (detected by NMR spectroscopy), which undergo allylic rearrangement giving azido-1,3-alkadienephosphonanes **140–143** (Scheme 15). Compounds **140–143** were not stable and were isolated by flash chromatography only in low yields. Phosphonates **140–143** exposed to ultraviolet light lose two nitrogen atoms and give 2-substituted 2-(diethylphosphono)-2*H*-azirines **144–147** with good yields [35].



R = H (**130**, **133**, **136**, **140**, **144**); *n*-C_3H_7 (**131** **134**, **137**, **141**, **145**); *n*-C_4H_9 (**132**, **135**, **138**, **142**, **146**); $CH_2OCH(CH_3)OC_2H_5$ (**2**, **5**), CH_2OH (**41**, **139**, **143**, **147**).

SCHEME 15

Design of Physiologically Active Compounds on the Basis of the Phosphonoallenes

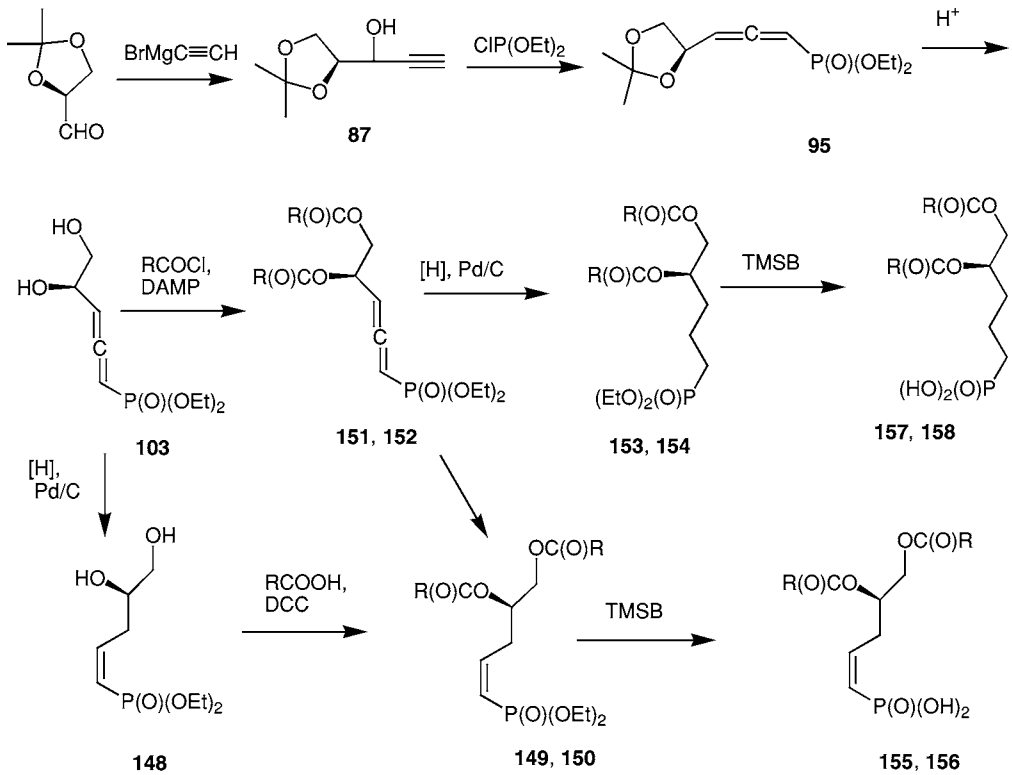
Phospholipids and related structures are major constituents of cell membranes and play an important role in biochemical processes [36]. Structurally modified phospholipids have been widely used for drug delivery in liposomes, and in physical and biochemical studies of membrane structure and function. Recent publications indicate an interest in the preparation of various phosphonolipids [37]. The presence of a phosphonate group—as opposed to a phosphate moiety in natural phospholipids that is less prone to chemical or enzymatic hydrolysis in vivo—increases its therapeutic lifetime and efficacy [38].

Recently, we reported an efficient and stereoselective methodology for the preparation of a new type of phosphonate analog of the natural lipids using phosphonoallenes as starting compounds [39]. The target compounds were prepared by a three-step procedure: synthesis of the propargylic alcohol **87**; synthesis of the phosphorylated diol **103**; and synthesis of the target phosphonates **155–158** (Scheme 16).

When 2,3-*O*-isopropylidene-D-glyceraldehyde was reacted with acetylenemagnesium halide, (1,2-*O*-isopropylidene)-4-pentyn-3-ol **87** was obtained in high yield after purification by column chromatography. Phosphonoallene **95** was synthesized directly from propargylic alcohol **87** in 66% yields by phosphorylation and Mark [2,3]-sigmatropic rearrangement [1]. The isopropylidene protecting group was then easily removed in 1N HCl solution in methanol at room temperature to give 5-(diethoxyphosphoryl)penta-3,4-diene-1,2-diol **103** in quantitative yield.

For preparation of the phosphonate analogs of the lipids with the 3-hydroxyl of the diacylglyceryl moiety substituted by HC=CH, stereospecific hydrogenated of **103** was applied. After purification by column chromatography on silica gel, the pure diol **148** could be acylated with the appropriate fatty acid. The carbodiimide-mediated esterification with palmitic or stearic acid gave (2*R*)-5-(diethoxyphosphoryl)-2-(palmitoyloxy)pent-4-enyl palmitate **149** or (2*R*)-5(diethoxyphosphoryl)-2-(stearoyloxy)pent-4-enyl stearate **150** in satisfactory yields and thus final phosphonic acids **155** and **156** were prepared.

Acylation of both the hydroxyl groups in **103** with palmitoyl or stearoyl chloride was accomplished under normal coupling conditions with



R = $C_{16}H_{33}$ (**149**, **151**, **153**, **155**, **157**), $C_{18}H_{37}$ (**150**, **152**, **154**, **156**, **158**).

SCHEME 16

4-(dimethylamino)pyridine to give (2*R*)-5-(diethoxyphosphoryl)-2-(palmitoyloxy)penta-3,4-dienyl palmitate **151** or (2*R*)-5-(diethoxyphosphoryl)-2-(stearoyloxy)penta-3,4-dienyl stearate **152**. In the next step, a solution of compound **151** or **152** in ethanol was hydrogenated over 5% Pd/C at atmospheric pressure. Hydrolysis of the diethyl esters **153, 154** and **149, 150** using trimethylbromosilane proceeded smoothly to afford phosphonic acids **155–158**, which were obtained as white solids after purification by crystallization [39].

This efficient methodology, based on the use of phosphonoallenes, can be applied to the synthesis of phosphonate analogs of phosphatidyl choline, phosphatidyl ethanolamine, and other phosphatidyl derivatives.

Since the discovery of human immunodeficiency virus (HIV) as the causative agent [40] of acquired immunodeficiency syndrome (AIDS), there has been a considerable effort in the search for new compounds that could inhibit the HIV replication. In the attempts to develop effective, selective, and nontoxic antiviral agents, a variety of strategies has been devised to design nucleotide and nucleoside analogs [41].

Regardless of the synthetic method used, these analogs are the result of modification of natural nucleosides, usually of their carbohydrate moiety. Replacement of the carbohydrate moiety by a cyclic or acyclic unsaturated fragment has been demonstrated to be an effective approach for the creation of antiviral and antitumor agents. For example, 9-(2-(phosphono-methoxy)ethyl)adenine (PMEA **159**, Fig. 1) effectively inhibits a wide array of DNA viruses (herpes, adeno, irido, and poxviruses) [42] and retroviruses (Moloney murine sarcoma virus (MSV) [43], murine acquired immunodeficiency disease [44], hepatitis B [45], and for clinical studies against AIDS [46]).

The modification of the side-chain of PMEA derivatives strongly affects the antiviral selectivity of the compounds [47,48]. *N*-(3-Hydroxy-2-phosphonomethoxypropyl)purine **160** acts solely on DNA viruses [42b] while *N*-(2-phosphonomethoxypropyl)purine **161** [47] and *N*-(3-fluoro-2-phosphonomethoxypropyl)purine **162** exclusively affect retroviruses [47]. 9-[2-(Phosphonofluoromethoxy)ethyl]adenine **163** and its monoester were inactive against HIV-1, but exhibited potent activity against both human cytomegalovirus (HCMV) and Epstein Barr virus (EBV) [48].

In order to better understand the role of the carbon backbone in the analogs of nucleotides **159–163** (Fig. 1), we designed an efficient methodology for the preparation of a new type of phosphonate ana-

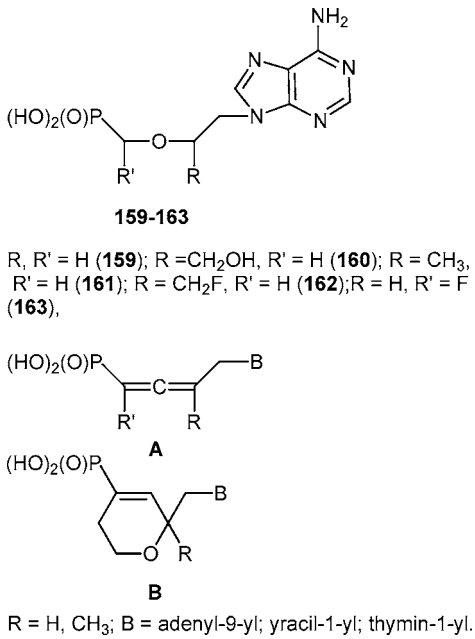
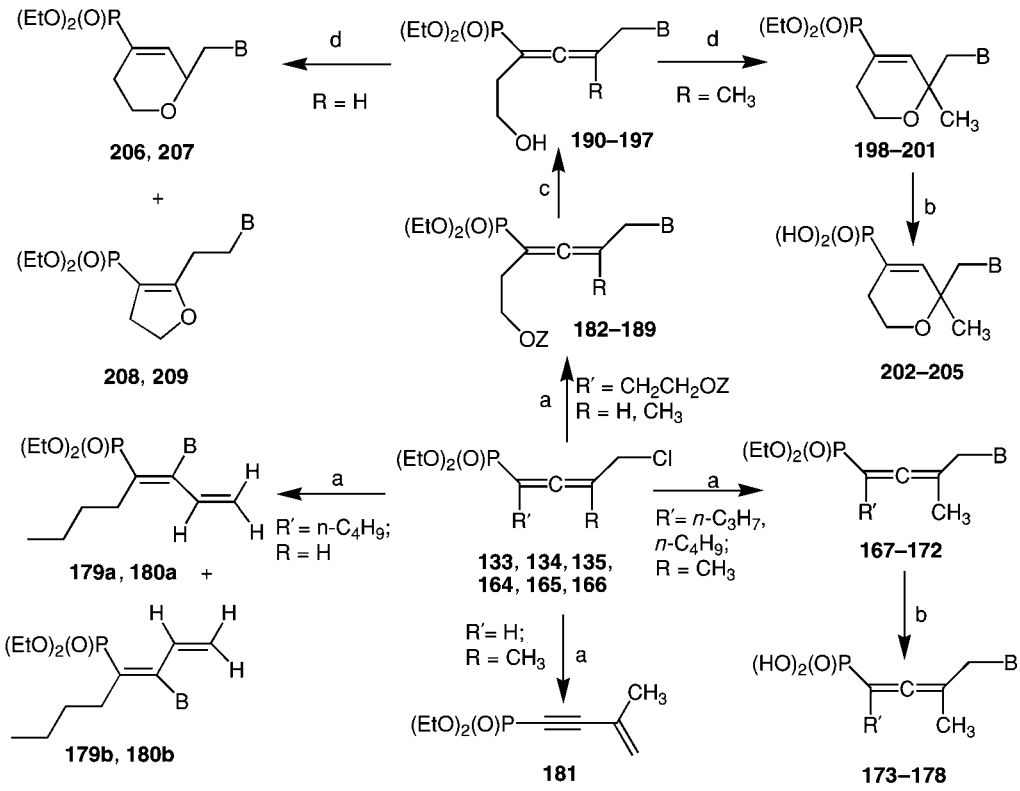


FIGURE 1 Structures of some analogs nucleotides.

log of nucleotides **A** and **B** (Fig. 1) based on phosphonoallenes (Scheme 17). Reaction of 1-chloro-2-methyl-4-(diethylphosphonyl)alka-2,3-dienes **134, 135** with purine and pyrimidine heterocyclic bases in the presence of cesium carbonate resulted in new acyclic analogs of nucleotides containing a 1,2-alkadienic frame **167–172** [49]. Dealkylation of **167–172** yielded phosphonic acids **173–178**. In contrast, alkylation of unsubstituted in 2-position 1-chloro-4-(diethylphosphonyl)octa-2,3-diene **164** led to *Z*- and *E*-1,3-alkadienephosphonates **179a,b** and **180a,b**. A similar reaction with 1-chloro-2-methyl-4-(diethylphosphonyl)buta-2,3-diene **133** led to the elimination of hydrochloride and formation of 4-(diethylphosphonyl)-2-methylbut-1-en-3-yne **181**. Molecular structures of new acyclic nucleotides **169** and **176** were determined by X-ray crystallographic analysis.

Phosphonoallenes **165, 166** were used for synthesis of cyclic analogs of nucleotides [50]. The mixture of heterocyclic base and cesium carbonate in DMF reacted smoothly with chloromethylallenephosphonates to afford the compounds **182–189**. Dialkyl esters **182–189** were isolated in good yield by column chromatography as mixtures of two diastereomers. The treatment with a methanol solution of compounds **182–189** in the presence of *p*-toluenesulfonic acid afforded unprotected allenic alcohols **190–197** with quantitative yields.

The cyclization of γ,γ-disubstituted phosphonoallenic alcohols **190–193** was performed by treatment with a catalytic amount of silver nitrate in



(a) Cs_2CO_3, DMF, BH; (b) TMBS, CH_3CN; (c) 5% HCl; (d) $AgNO_3$, THF.

R = H (**164**, **186–189**, **194–197**); CH_3 (**133–135**, **182–185**, **190–193**); R′= H (**133**); n-C_3H_7 (**134**, **167–169**, **173–175**), n-C_4H_9 (**135**, **170–172**, **176–178**); B = uracil (**167**, **170**, **173**, **176**, **179**, **182**, **186**, **190**, **194**, **198**, **202**, **206**, **208**); thymine (**168**, **171**, **174**, **177**, **180**, **183**, **187**, **191**, **195**, **199**, **203**, **207**, **209**); adenyne (**169**, **172**, **175**, **178**, **184**, **188**, **192**, **196**, **200**, **204**); cytosine (**185**, **189**, **193**, **197**, **201**, **205**), Z = $CH(CH_3)OC_2H_5$ (**192–199**).

SCHEME 17

THF/water (20:0.5) to afford 3,6-dihydropyrans **198–201** within 6 h at 50–52°C. In contrast to allenes **190–193**, compounds **194** and **195** (R = H) formed both dihydropyrans **206, 207** and dihydrofurans **208, 209** under similar reaction conditions. Treatment of the diethyl esters **198–201** with 5 equiv. of trimethylbromosilane (TMSBr) in acetonitrile at room temperature for 12 h under nitrogen yielded the phosphonic acids **202–205** in good yields.

CONCLUSION

This review has illustrated the progress achieved in the chemistry of phosphonoallenes in recent years. The study of the reactivity of new polyfunctional phosphonoallenes in reactions with electrophilic and nucleophilic reagents makes it possible to expand synthetic possibilities of these compounds and to obtain various functionally substituted unsaturated organophosphorus derivatives, which are promising from the standpoint of biological activity and their employment in fine organic synthesis. Further studies on this potentially important synthetic methodology are currently in progress.

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