

Synthetic methods of cyclic α -aminophosphonic acids and their esters

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Abstract

This review describes the most synthetic methods of cyclic α -aminophosphonic acids and their mono- or di-esters in which at least two atoms of the P–C–N system such as linkage of types C–P, C–N and P–C–N are part of a heterocyclic system.

Keywords: Cyclic α -aminophosphonic acids, Kabachnik-Fields, Pudovik reactions

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1. Introduction

Organophosphorus compounds are important substrates in the study of biochemical processes¹⁻⁴ and compounds of tetracoordinate pentavalent phosphorus are widely used as biologically active compounds. The key role of naturally occurring amino acids in the chemistry of life and as structural units in peptides, proteins, and enzymes has led to intense study on the chemistry and biological activity of synthetic analogues. For a long time the so-called “phosphorus analogues” of the amino acids, in which the carboxylic acid group is replaced by a phosphonic, $-P(O)(OH)_2$, or phosphinic acid group, $-P(O)(OH)R$ (in which R may be H, alkyl, or aryl), as well as a phosphonate group, $-P(O)(OR)_2$ (in which R may be alkyl, or aryl), have attracted particular interest in the preparation of isosteric or bioisosteric analogues of numerous natural products.⁵⁻⁸ In this area, α -aminophosphonic acids, as isosteres of α -amino acids (Figure 1) occupy an

important place and reveal diverse and interesting biological and biochemical properties including antibacterial agents,⁹ enzyme inhibitors,^{10,11} haptens for catalytic antibodies,¹² and anti HIV agents.¹³

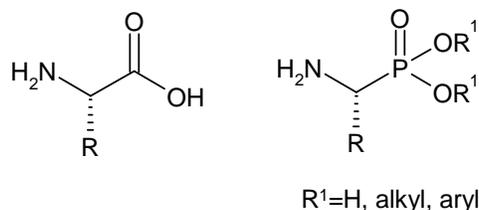
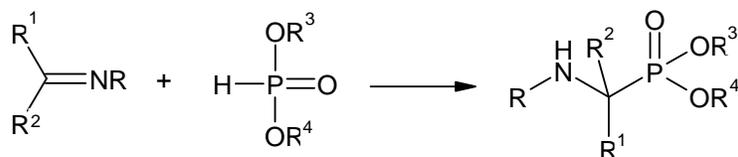
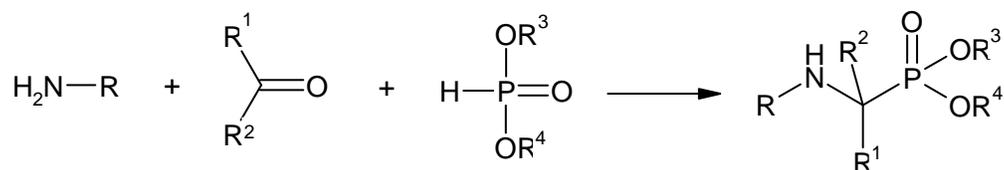


Figure 1

Various synthetic methods for α -aminophosphonic acids and α -aminophosphonates have been reported¹⁴⁻²² and the most straightforward one is the addition of compounds containing a P–H bond to the C=N bond of imines (the Pudovik reaction) (Scheme 1).²³ However, the most useful pathway to the synthesis of α -aminophosphonates is the Kabachnik-Fields reaction,²⁴⁻²⁷ which is a one-pot, three-component procedure using carbonyl compound, amine and dialkyl phosphite (Scheme 2). This process was discovered at a time when multicomponent processes were rather “exotic birds”; from a modern point of view this protocol is obviously very attractive for combinatorial chemistry and has been rarely used for parallel synthesis.²⁸



Scheme 1



Scheme 2

A few reviews have been published to date which are concerned with the synthesis, characterization, stereochemistry and biological activities of acyclic α -aminophosphonate derivatives,²⁹⁻³¹ but none of these focuses solely on the formation of cyclic α -aminophosphonates. Therefore, this review will focus on the synthesis of cyclic α -aminophosphonic acids and their *mono*- or *di*-esters in which at least two atoms of the P–C–N system are part of a

heterocyclic system. Thus, the heterocyclic systems which contain linkage of types C–P (**A**), C–N (**B**) and P–C–N (**C**) (Figure 2) are considered as cyclic α -aminophosphonate derivatives. The review is built up according to the three previous linkage types and starting with the smallest rings in each type.

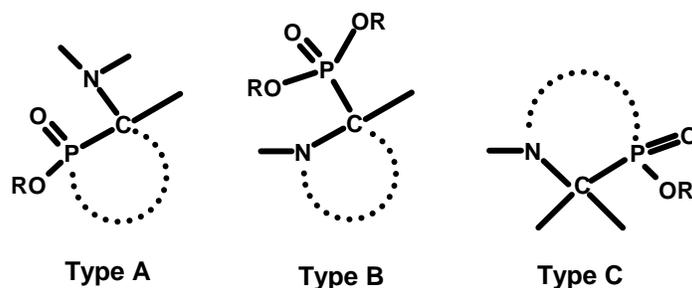


Figure 2

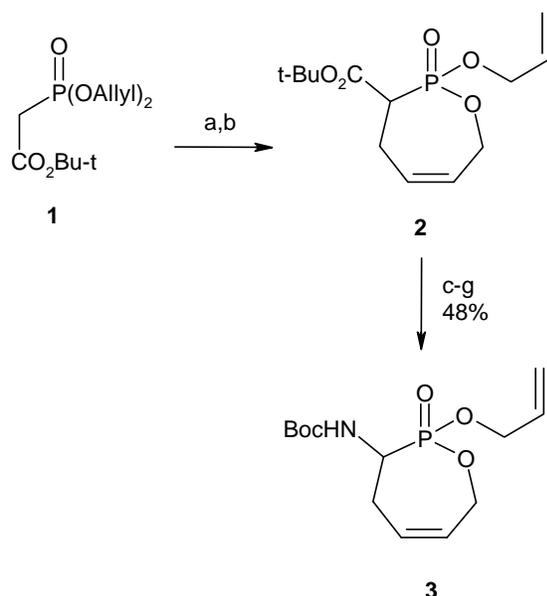
2. Type A: Cyclic α -Aminophosphonic Acid Derivatives Bearing an Exocyclic Amino Group (Heterocycles containing the phosphorus as a ring heteroatom)

This type focuses on the synthesis of heterocyclic systems containing the α -aminophosphonate moiety which contains the P–C linkage as a part of the heterocyclic system (the phosphorus as a ring heteroatom).

2.1. The Curtius rearrangement strategy on phosphorus heterocycles

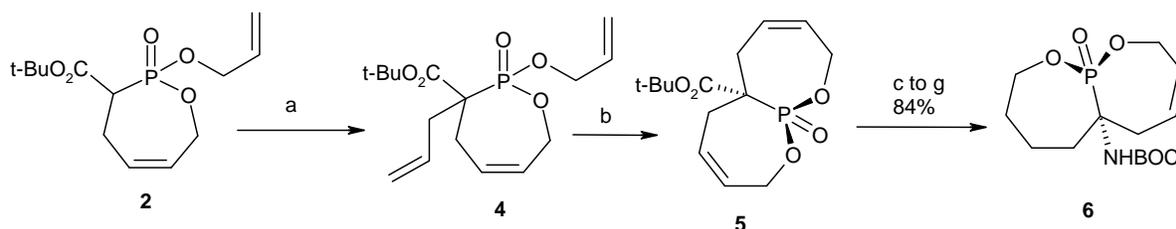
Ring closing metathesis (RCM) strategy was used in synthesis of the seven-membered P-heterocyclic α -aminophosphonate **3**. Thus, monoallylation of *tert*-butyl diallylphosphonoacetate (**1**) using NaH and allyl bromide in THF at 0 °C followed by RCM utilizing the Grubbs benzylidene catalyst generated 1.2:1 mixtures of diastereomeric P-heterocycles **2** in excellent yield. On application of the Curtius rearrangement strategy to **2**, Boc-protected α -aminophosphonate **3** was generated in 48% overall yield as 1.5:1 mixture of separable diastereomers (Scheme 3).³²

Subsequent allylation of an approximate of a 1:1 diastereomeric mixture of **2** produced **4** with 3:1 diastereoselectivity. RCM of the major diastereomer gave the [5,5,0]bicyclic *tert*-butylphosphoacetate **5** as the *cis*-fused diastereomer in excellent yield. This experiment also proved the stereoselectivity (*cis* = major) in the allylation process of **2**. Subjection of **5** to Curtius conditions gave the corresponding α -Boc-bicyclic- α -aminophosphonate **6** in 84% yield (Scheme 4).³²



- (a) NaH, THF, allyl bromide, 0 °C, 85% (b) Grubbs catalyst (5% mol) CH₂Cl₂, 94%
 (c) Formic acid, neat (d) (COCl)₂, CH₂Cl₂, DMF, 0-rt °C
 (e) NaN₃, CH₃CN, H₂O quantitative (three steps) (f) toluene, reflux
 (g) t-BuOH, reflux, 48%

Scheme 3



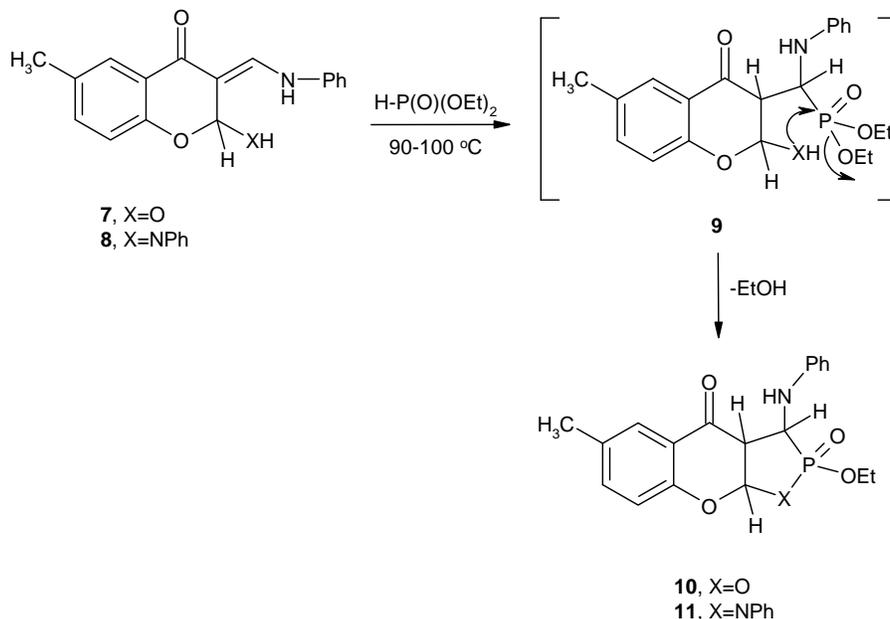
- (a) KOBu-t, THF, allyl bromide, 0-rt °C, 76% (b) Grubbs catalyst (5% mol) CH₂Cl₂, 97%
 (c) Formic acid, neat (d) (COCl)₂, CH₂Cl₂, DMF, 0-rt °C
 (e) NaN₃, CH₃CN, H₂O quantitative (three steps) (f) toluene, reflux
 (g) t-BuOH, reflux, 84%

Scheme 4

2.2. Addition of dialkyl phosphite to double bond (The Pudovik reaction)

Reaction of 3-(phenylaminomethylene)-2-hydroxy/*N*-phenylamino-6-methyl-2,3-dihydro-4*H*-chromen-4-ones (**7**) and (**8**) with diethyl phosphite at 90–100 °C afforded 3-phenylamino-2-ethoxy-6-methyl-2-oxo-2,3,3a,9a-tetrahydro-4*H*-1,2-oxa-phospholo[5,4-*b*]chromen-4-one (**10**) and 3-phenylamino-2-ethoxy-6-methyl-2-oxo-1-phenyl-2,3,3a,9a-tetrahydro-4*H*-1,2-azaphospholo[5,4-*b*]chromen-4-one (**11**), respectively, as cyclic α -aminophosphonate derivatives. Formation of the compounds **10** and **11** may be interpreted as resulting from nucleophilic attack

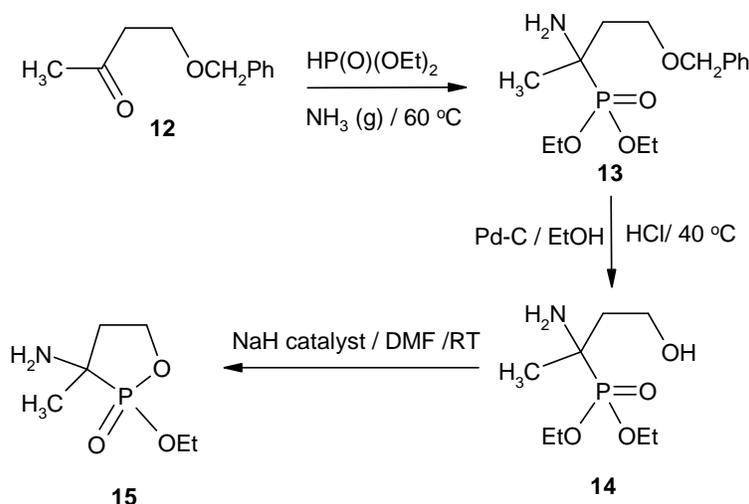
of the phosphorus atom at the α,β -unsaturated moiety of **7** and **8** (Pudovik reaction) to give the nonisolable intermediate **9**. The latter underwent cyclization *via* elimination of one molecule of ethanol to give the final products **10** and **11**, respectively (Scheme 5).³³



Scheme 5

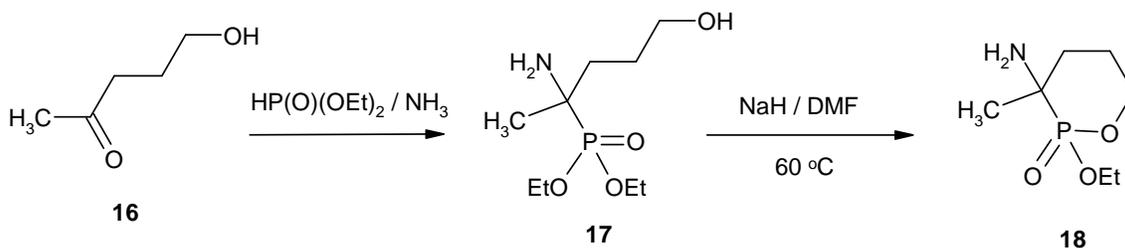
2.3. Multicomponent (Kabachnik-Fields reaction)

Aminophosphonylation of 4-benzyloxy-2-butanone (**12**) was performed with ammonia and diethyl phosphite under mild conditions. The α -aminophosphonic ester **13** was obtained in 65% yield. Its debenylation afforded diethyl 3-hydroxy-1-amino-1-methylpropylphosphonate **14** as a monohydrate. When a solution of the phosphonate **14** in 1,2-dimethoxyethane was treated with a catalytic amount of sodium hydride, 2-ethoxy-2-oxo-1,2-oxaphospholane **15** was obtained as a crude oil (Scheme 6).³⁴



Scheme 6

The synthesis of the phosphorinane analogue **18** was performed by aminophosponylation of the ketone **16** followed by base catalyzed cyclization. Diethyl 4-hydroxy-1-amino-1-methylbutylphosphonate **17** was directly obtained in 45% yield by aminophosponylation of **16**, followed by treatment with a catalytic amount of sodium hydride in anhydrous 1,2-dimethoxyethane, at 60°C for 5 hours (Scheme 7).³⁴



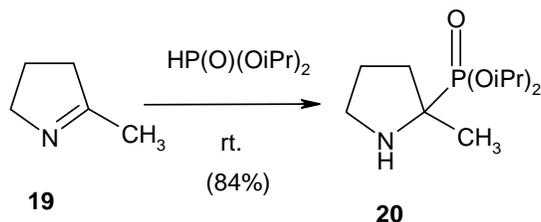
Scheme 7

3. Type B: Cyclic α -Aminophosphonic Acid Derivatives Bearing an Exocyclic Phosphonyl Group (Heterocycles containing the nitrogen as a ring heteroatom)

This section focuses on the synthesis of heterocyclic systems containing the α -aminophosphonate moiety which involves the C-N linkage as a part of the heterocyclic system (the nitrogen as a ring heteroatom).

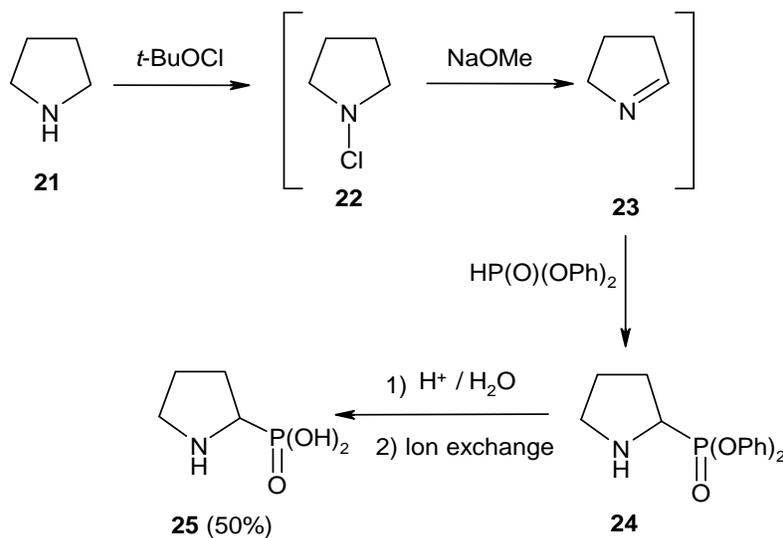
3.1. Addition of dialkyl/trialkyl phosphite to cyclic imines (Pudovik reaction)

Nucleophilic addition of dialkyl phosphite to cyclic C=N imines is one of the most direct ways to synthesize cyclic α -aminophosphonates of this type. Addition of diisopropyl phosphite to the commercially available 2-methyl-1-pyrroline (**19**) produced diisopropyl α -aminophosphonate **20** in 84% yield (Scheme 8).³⁵



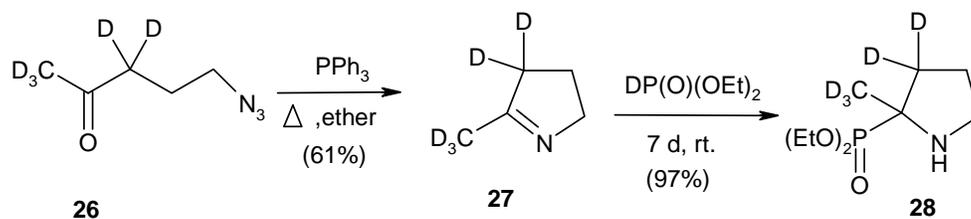
Scheme 8

The pyrrolidinyl phosphonic acid **25** can be formed in 50% overall yield by chlorination of pyrrolidine **21** with *t*-butyl hypochlorite and subsequent elimination followed by reaction with diphenyl phosphite (Scheme 9).^{36,37}

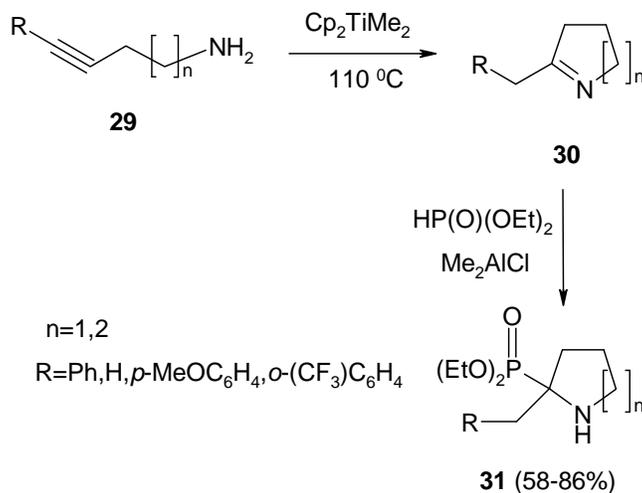


Scheme 9

The D-labelled pyrroline **27** was formed by an aza-Wittig reaction from azide **26**. Addition of diethyl phosphite yielded the pyrrolidinephosphonic acid **28** in 97% yield (Scheme 10).³⁸



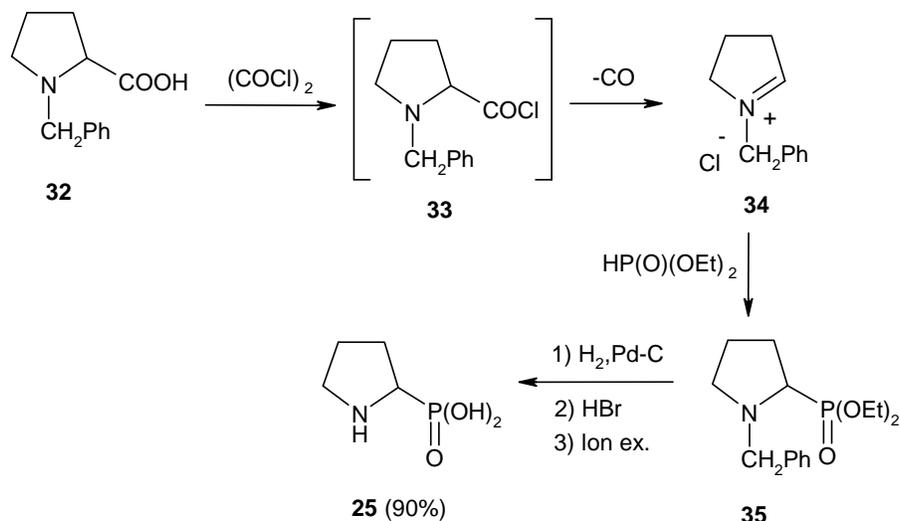
Scheme 10



Scheme 11

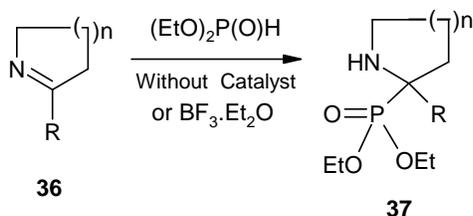
In a one-pot synthesis of 2-phosphonopyrrolidines **31**, the unsaturated 1-azaheterocycles **30** were formed by intramolecular hydroamination of aminoalkynes **29** in the presence of catalytic amounts of Cp₂TiMe₂ at 110 °C (Scheme 11). After addition of diethyl phosphite together with 5 mol % Me₂AlCl, the phosphonylated pyrrolidines **31** were obtained in good overall yields (Scheme 11).³⁹

Treatment of *N*-benzylproline (**32**) with oxalyl chloride followed by decarbonylation led to the formation of the iminium salt **34**. 2-Phosphonopyrrolidine **25** was then obtained by addition of diethyl phosphite followed by debenzoylation and dealkylation, in 90% overall yield (Scheme 12).³⁶



Scheme 12

Addition of diethyl phosphite to α -substituted cyclic imines **36** gave cyclic α -substituted α -aminophosphonates **37**. The reaction proceeded in ether or THF as a solvent at room temperature without any catalyst, but boron trifluoride etherate could be used to accelerate the reaction (Scheme 13).⁴⁰

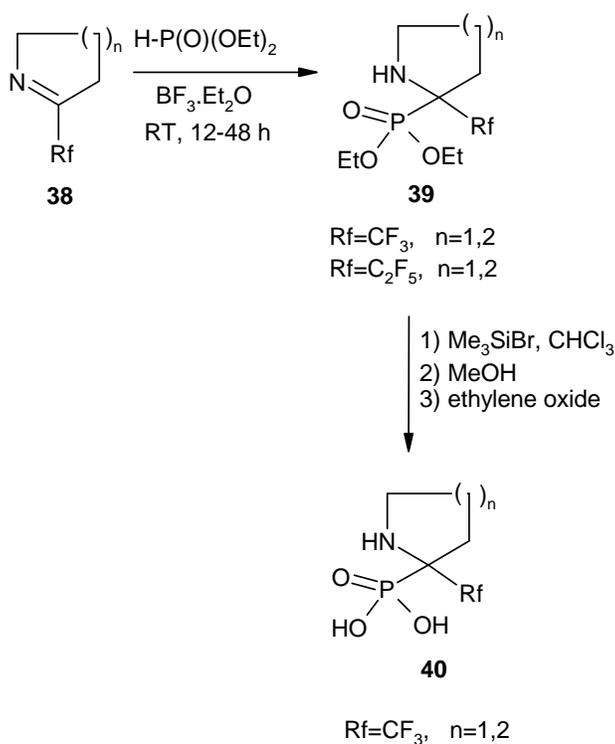


$n=1,2,3$
 $\text{R}=\text{Me}, i\text{Pr}, n\text{-Bu}, \text{Ph}, 4\text{-MeC}_6\text{H}_4, 2\text{-pyridyl}, 2\text{-thienyl}$

Scheme 13

Addition of diethyl phosphite to perfluoroalkyl substituted cyclic imines **38** does not proceed in the absence of catalyst. Under catalysis, α -perfluoroalkyl substituted cyclic α -aminophosphonates **39** were obtained in higher yields than their non-fluorinated analogues mentioned above. As steric hindrances decreases the reaction rate, the formation of five-membered aminophosphonates **39** ($n = 1$) proceed faster comparing to those having a six-membered ring ($n = 2$) and compound **39** bearing a trifluoromethyl group is formed more readily than those having the pentafluoroethyl moiety. In spite of the presence of strong electron withdrawing perfluorinated substituent, α -aminophosphonates **39** ($n = 1,2$) can be converted into the corresponding α -aminophosphonic acids **40** via the reaction with trimethylbromosilane in

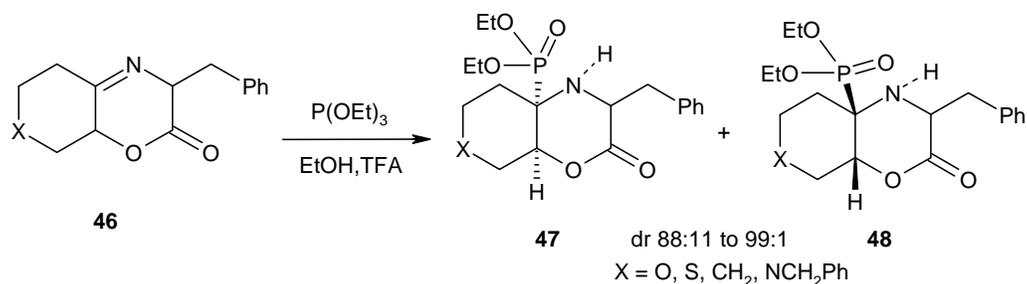
chloroform followed by treatment with aqueous methanol of the intermediate trimethylsilyl ester formed (Scheme 14).⁴⁰



Scheme 14

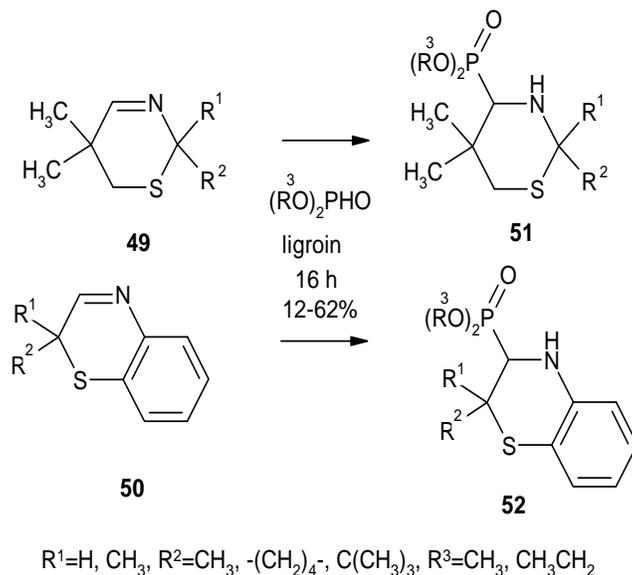
In a similar way, enantioselective hydrophosphonylation of cyclic imines **41** using cyclic phosphites, catalyzed by (*S*)-YbPB (a ytterbium-binolate complex) provided the 4-thiazolidinyl phosphonates (*R*)-**42** in excellent enantiomeric excess and high chemical yields (Scheme 15).⁴¹

Since the chiral auxiliary might be easily removed by hydrolysis of the phosphonic ester, Schlemminger *et al.*⁴² carried out the addition of chiral BINOL-phosphite to achiral 3-thiazolines **41** in the presence of $\text{BF}_3 \cdot \text{OEt}_2$, obtaining the corresponding thiazolidinyl phosphonates **43** in moderate yield and excellent diastereoselectivity. It is noteworthy that the stereoselectivity of the BINOL-phosphite seemed to be independent of the steric demands of the nearby substituents R (Scheme 16).⁴³



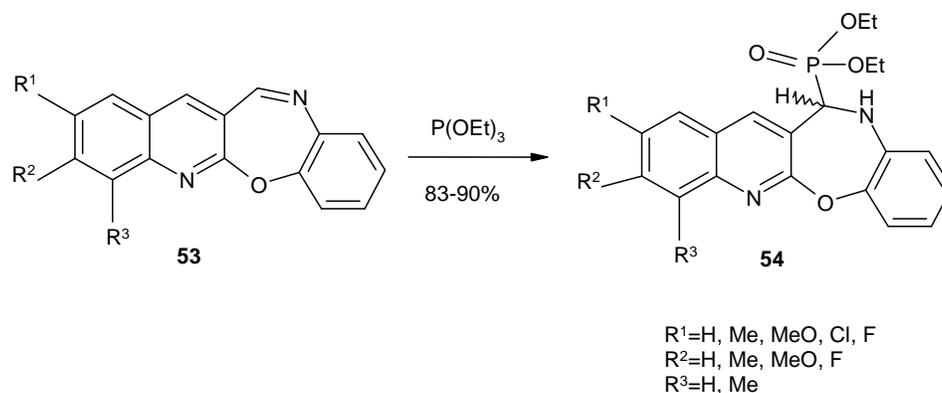
Scheme 18

The synthesis of dialkyl 2-(1,1-dialkyl-5,5-dimethyl-1,3-thiazinan-4-yl)phosphonate (**51**) and 2,2-dimethyl-3,4-dihydro-2*H*-1,4-benzothiazine-3-dialkylphosphonate (**52**) was quite simple, requiring the reflux of a mixture of the cyclic imines **49** or **50**, respectively, with dialkyl phosphite in ligroin for 18 hours (Scheme 19).⁴⁶



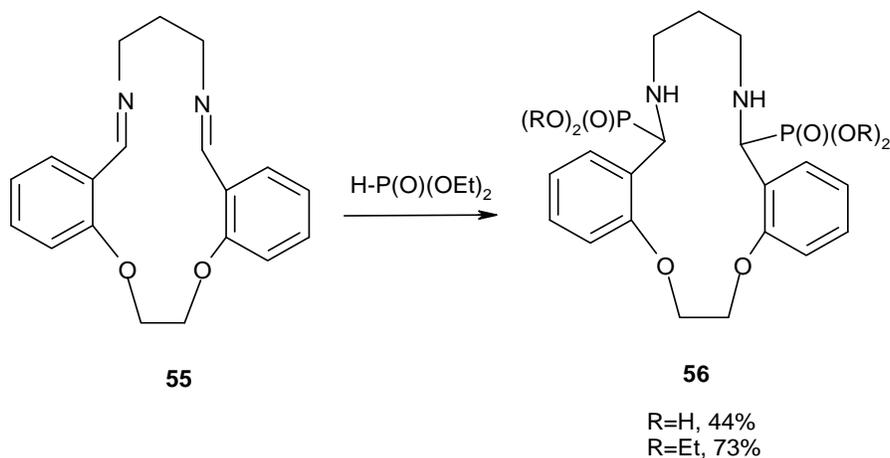
Scheme 19

Quino[2,3-*b*][1,5]benzoxazepine α -aminophosphonates **54** were obtained from the reaction of quino[2,3-*b*][1,5]benzoxazepines **53** with triethyl phosphite at room temperature under solvent-free conditions employing a catalyst such as $\text{KAl}(\text{SO}_4)_2$, FeCl_3 , CaCl_2 , NiCl_2 and *p*-TSA (Scheme 20).^{47,48}



Scheme 20

Oxa-aza mixed macrocycles containing α -aminophosphonate moieties **56** were synthesized by the reaction of diethyl phosphite and the 3,4:9,10-dibenzo-1,12-diaza-5,8-dioxacyclopentadecane (**55**) (Scheme 21).⁴⁹



Scheme 21

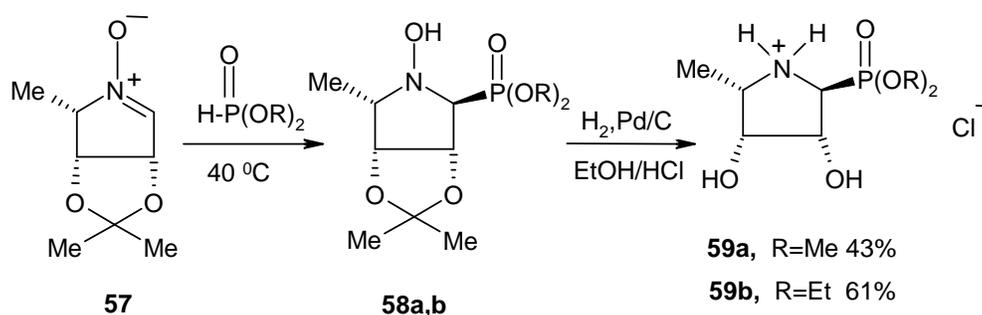
3.2. Addition of dialkyl phosphite to nitrones

Addition of dimethyl or diethyl phosphite to the nitron **57** at 40 °C gave the corresponding *N*-hydroxyphosphonates **58a,b** in quantitative yield. *O,N*-bis-deprotection of **58a,b** by hydrogenolysis over Pd/C in ethanol and aqueous hydrochloric acid afforded the pyrrolidinephosphonates **59a,b** as the hydrochlorides in 43% and 61% yield, respectively (Scheme 22).⁵⁰

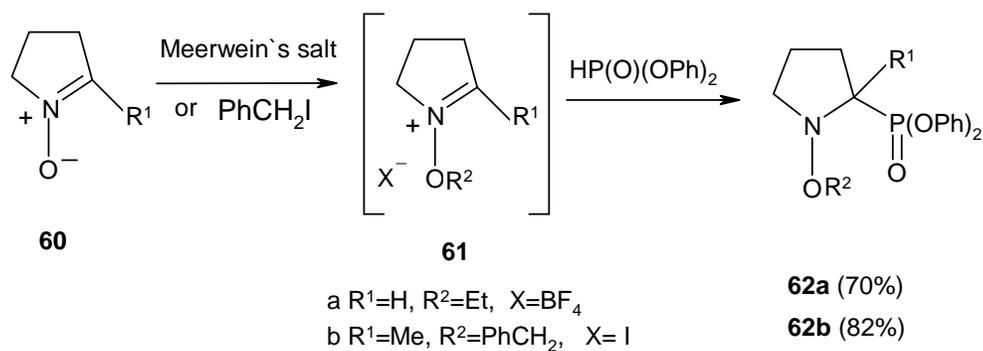
Alkylation of pyrroline *N*-oxides **60** with triethyloxonium tetrafluoroborate (Meerwein's salt) or benzyl iodide followed by reaction with diphenyl phosphite led to the formation of phosphonates **62a,b** in 70% and 82% yield, respectively (Scheme 23).⁵¹

The treatment of nitron **63** with sodium diisopropyl phosphite, gave a complex mixture of products, which were isolated as: starting material **63**, imine **64** and diisopropyl amino-

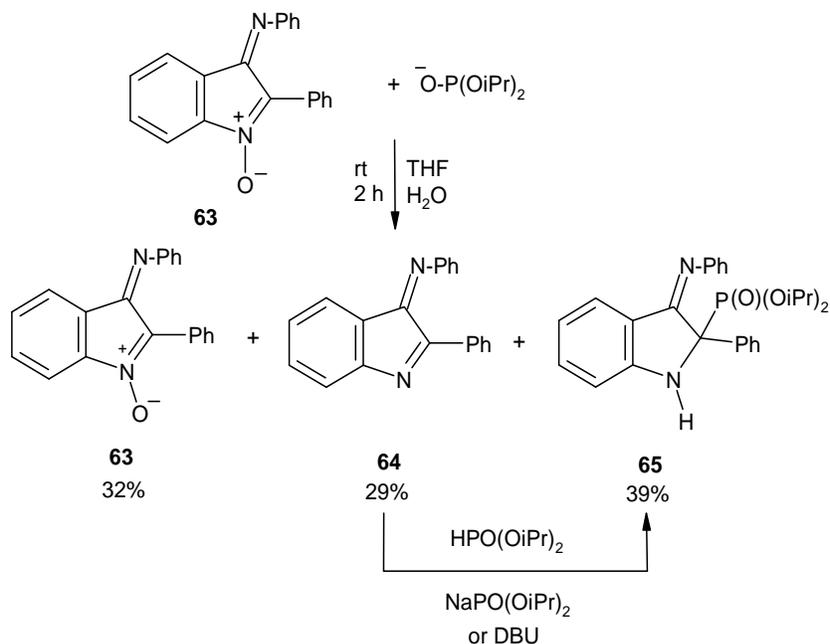
phosphonate **65**. Compound **65** was also obtained from treatment of **64** with diisopropyl phosphite in the presence of sodium diisopropyl phosphite or DBU in THF (Scheme 24).⁵²



Scheme 22

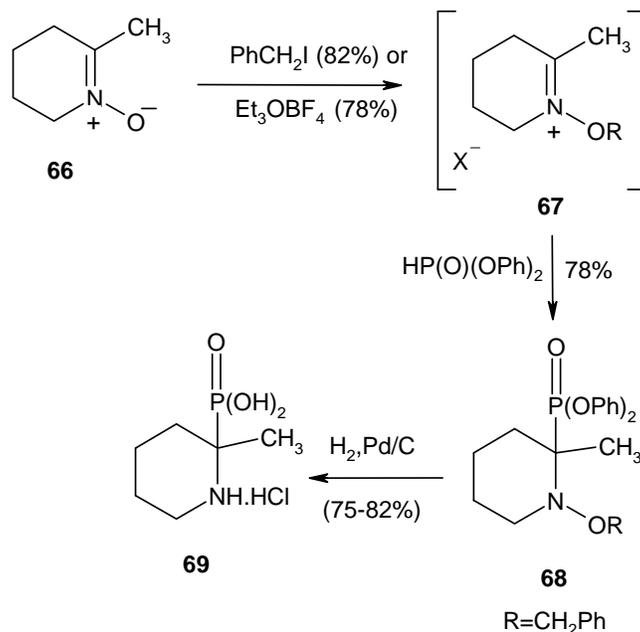


Scheme 23



Scheme 24

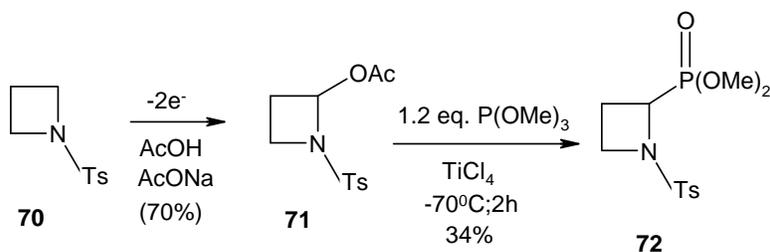
Ethylation of the nitron **66** afforded the oxoiminium salt **67**, which reacted with diphenyl phosphite to yield the corresponding *R*-methyl-*N*-alkoxyphosphonopiperidine **68** in 78% yield. Hydrogenolysis of the N-O bond furnished the phosphonopiperidine **69** in 82% yield (Scheme 25).⁵¹



Scheme 25

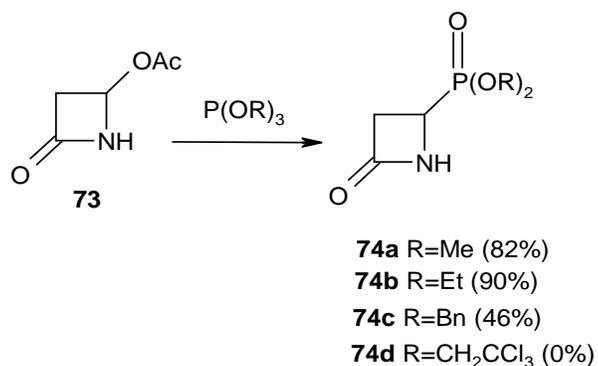
3.3. Nucleophilic phosphorylation

The apparently most obvious method to synthesize cyclic α -aminophosphonates, was started from the desired cyclic compound bearing a suitable leaving group such as acetate (AcO), phenylsulfinyl (PhSO), and benzotriazole (Bt) in the α -position to the N atom, which was then substituted by a phosphonate group. Thus, 1-(*p*-tosyl)-2-acetoxiazetidone (**71**) was synthesized from easily available compound **70** by anodic acetoxylation at the 2-position. Compound **71** was treated with 1.2 equivalents of trimethyl phosphite to obtain the corresponding 2-phosphonoazetidone (**72**) (Scheme 26).⁵³



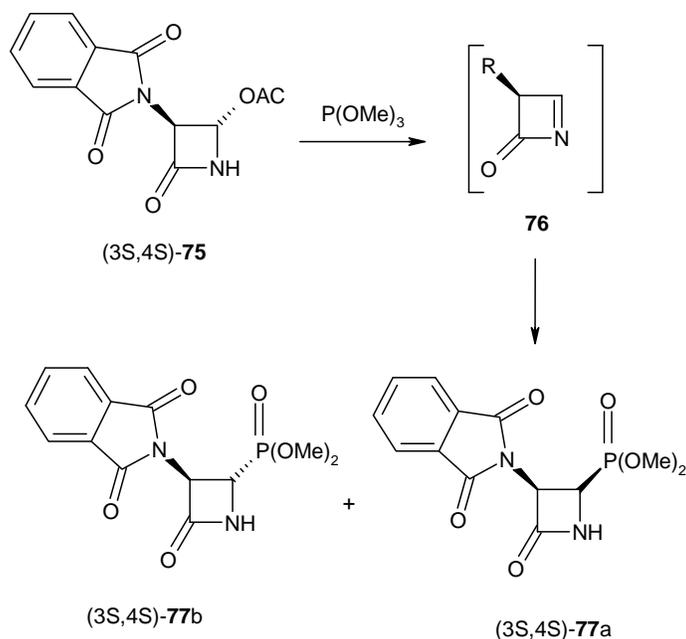
Scheme 26

When 4-acetoxiazetid-2-one (**73**) was treated with trialkyl phosphite, phosphonylated azetidiones **74** were formed *via* an atypical Michaelis-Arbuzov reaction, together with the corresponding alkyl acetate. No reaction occurred with tris(2,2,2-trichloroethyl)phosphite because of its reduced nucleophilicity (Scheme 27).⁵⁴



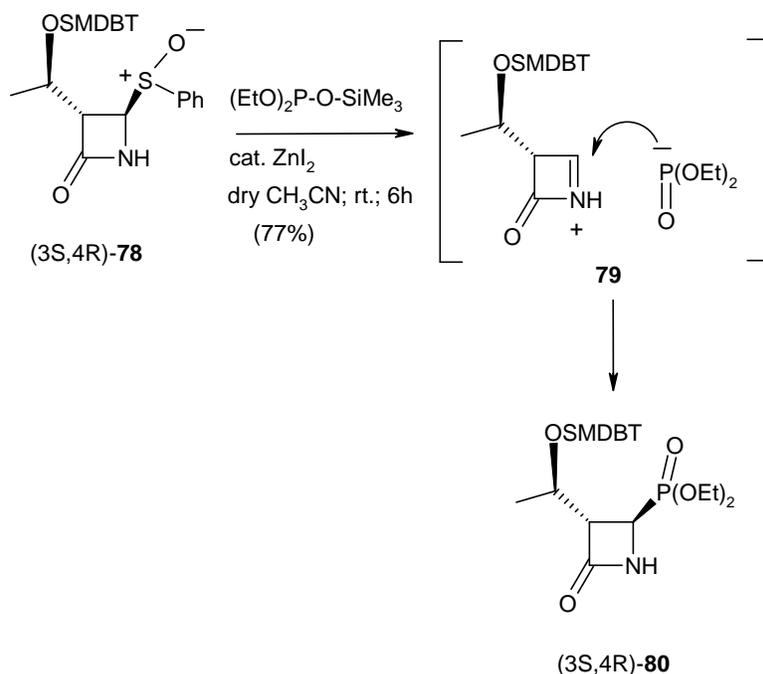
Scheme 27

The phthalimido derivative **75** was evaluated in the reaction with trimethyl phosphite. Campbell and Carruthers stated that the reaction led exclusively to the *cis*-product **77a** (89% yield) (Scheme 28).^{55,56}

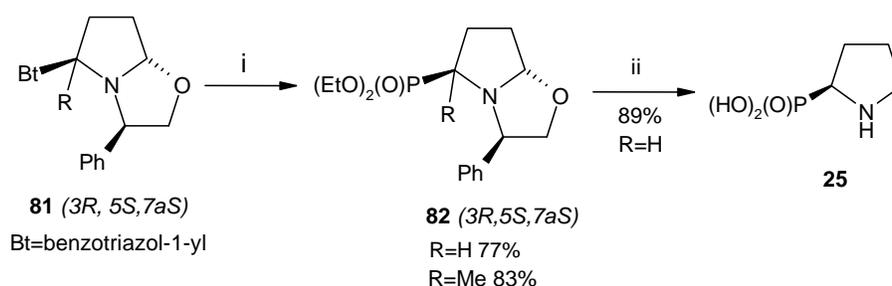


Scheme 28

4-Sulfinylazetid-2-one (**78**) was another substrate with an appropriate leaving group for a substitution reaction with a phosphonate group. Treatment of **78** with silylated phosphite in the presence of ZnI_2 at room temperature for 6 h gave the 4-phosphonoazetid-2-one (**80**) in 77% yield.⁵⁷ Actually, this reaction was not a real substitution reaction, which was indicated by the stereochemistry of the reaction. Due to the action of the Lewis acid, a reactive iminium salt **79** was formed that reacted *in situ* with the trivalent phosphorus nucleophile (Scheme 29).



Scheme 29



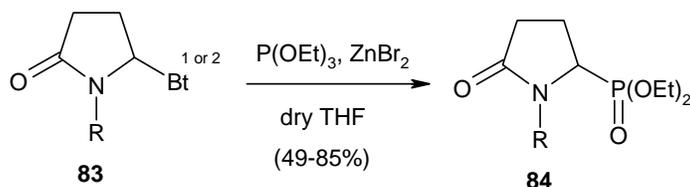
i) $\text{P}(\text{OEt})_3$, ZnCl_2 (0.3 equiv), CH_2Cl_2 , 0 °C, overnight
 ii) a. H_2 , Pd/C, b. 6 M HCl, c. propylene oxide

Scheme 30

Subsequent Arbuzov reaction in the presence of the mild Lewis acid ZnCl_2 or ZnBr_2 , converted **81** into the desired oxazolopyrrolidine phosphonate **82** as the only diastereoisomer.

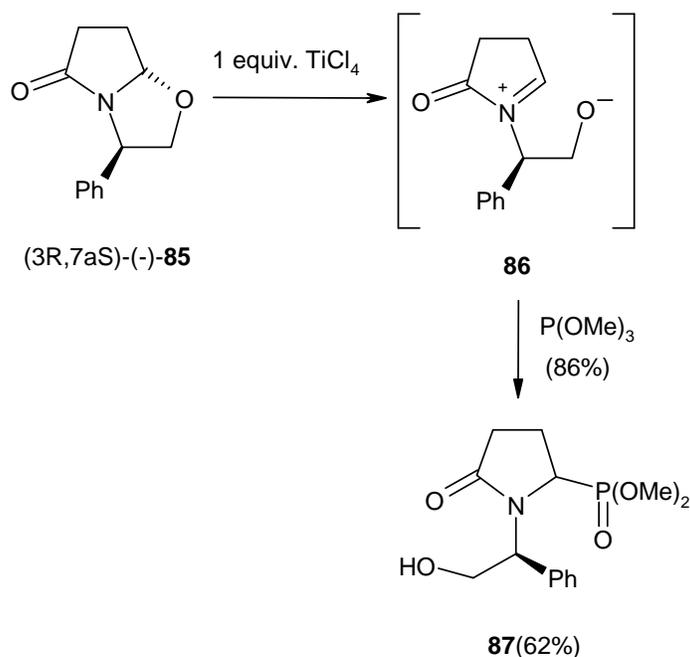
Attempts to obtain **82** directly by replacing benzotriazole with triethyl phosphite in the initial reaction mixture resulted in a mixture of two diastereoisomers.⁵⁸⁻⁶² Hydrogenolysis of **82**, followed by acidic hydrolysis of the phosphonate moiety with 6 M HCl and subsequent treatment with propylene oxide led to (*S*)-phosphopyrrolidine **25** (Scheme 30).⁵⁹

Benzotriazol-1-yl (Bt¹) and benzotriazol-2-yl (Bt²) are good leaving groups and give rise to the iminium cations. Thus, treatment of **83** in dry THF with triethyl phosphite in the presence of one equivalent of ZnBr₂ produced phosphonopyrrolidinones **84** in moderate to good yields (Scheme 31).⁶³



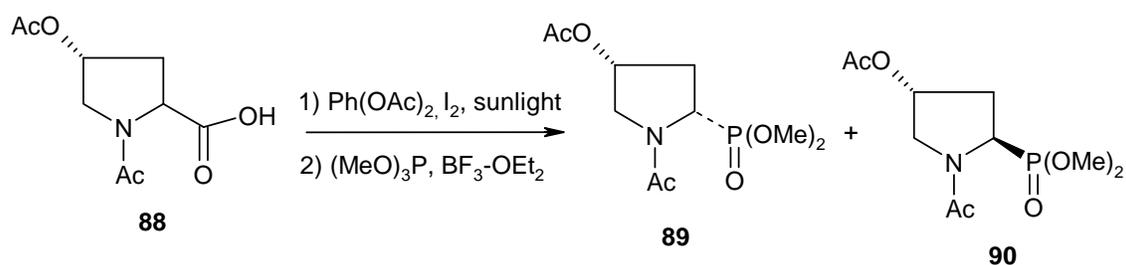
Scheme 31

An asymmetric synthesis of 5-phosphonopyrrolidone **87** was based on a similar principle. Here, the hemiaminal-like C-O bond was cleaved by the action of TiCl₄. The iminium ion **86** was then trapped by trimethyl phosphite with the formation of **87** in 62% diastereomeric excess (Scheme 32).⁶⁴

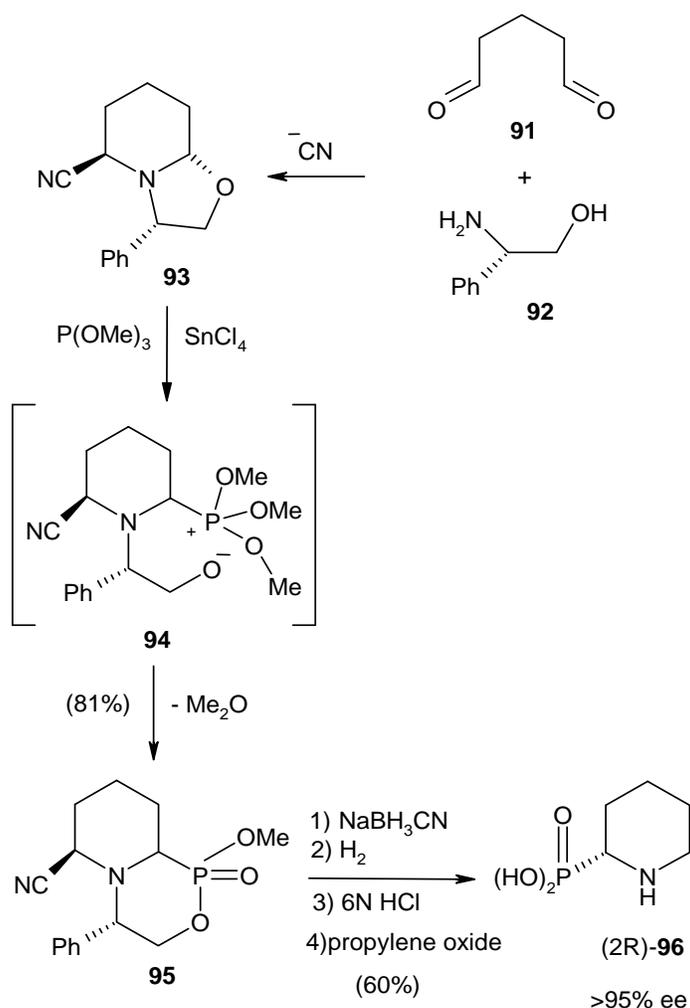


Scheme 32

Decarboxylation–phosphonylation reactions of (4*R*)-acetoxyproline derivative **88** with $\text{PhI}(\text{OAc})_2/\text{I}_2$ under sunlight activation, followed by reaction with trimethyl phosphite in the presence of $\text{BF}_3 \cdot \text{OEt}_2$, afforded the cyclic α -aminophosphonate **89** and its epimer **90** in 64% and 15% yield, respectively (Scheme 33).^{65,66}



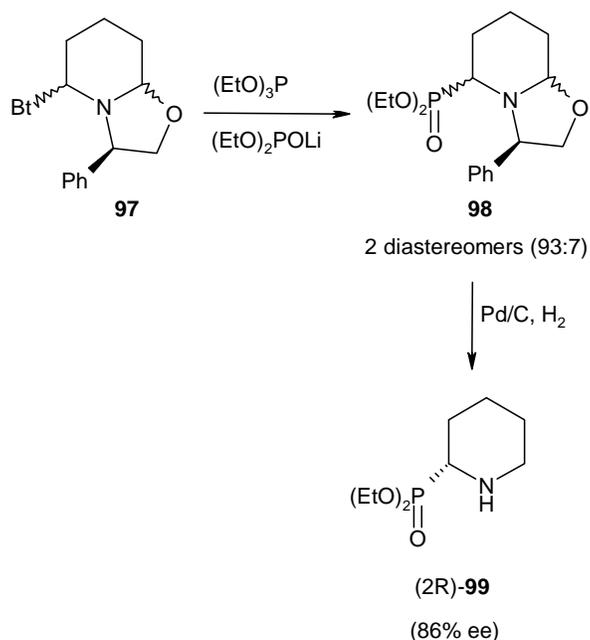
Scheme 33



Scheme 34

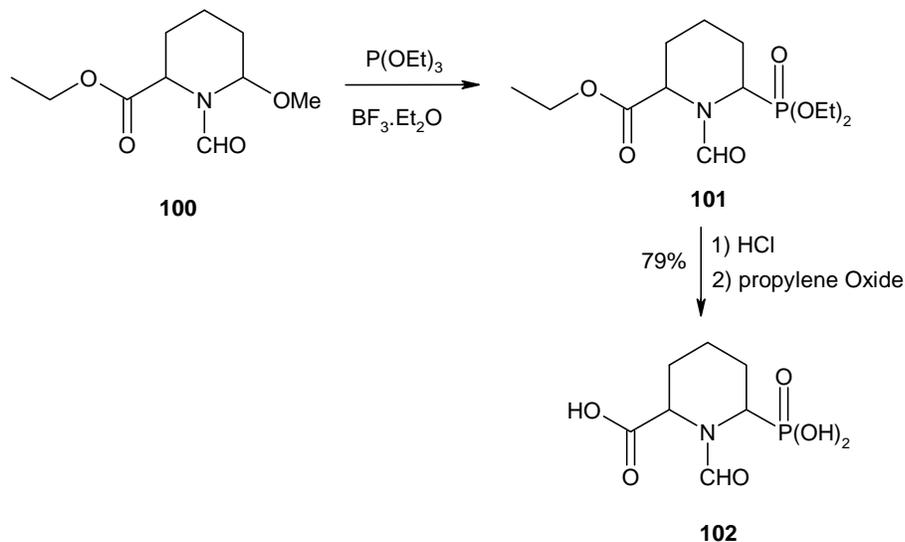
Maury *et al.*⁶⁷ developed a strategy to synthesize both enantiomers of piperidin-2-yl phosphonic acid. The strategy utilized the oxazolopiperidine derivative **93**, which upon treatment with trimethyl phosphite in the presence of SnCl₄ gave the corresponding oxazaphosphorinane derivative **95**, which then led to pure (*R*)-(-)-piperidin-2-ylphosphonic acid (**96**) in good overall yield after reduction and hydrogenolysis (Scheme 34).

The oxazolopiperidine derivative **97** reacted with a triethyl phosphite in the presence of lithium diethyl phosphite to obtain a mixture of two diastereoisomers **98** (93:7, 68% overall yield), which can be hydrogenated to the corresponding 2-phosphonopiperidine **99** in 86% ee (Scheme 35).⁶⁸



Scheme 35

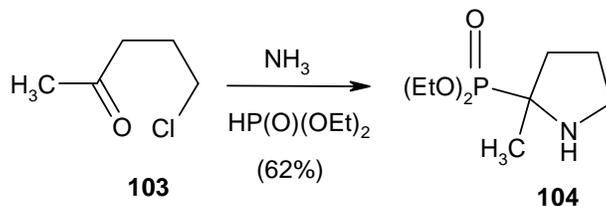
The phosphonate moiety can easily be introduced onto methoxylated piperidines such as **100** in the presence of a Lewis acid by trapping the iminium ion with triethyl phosphite.⁶⁹ This methodology was used to obtain the phosphonopiperidine **102** (Scheme 36).



Scheme 36

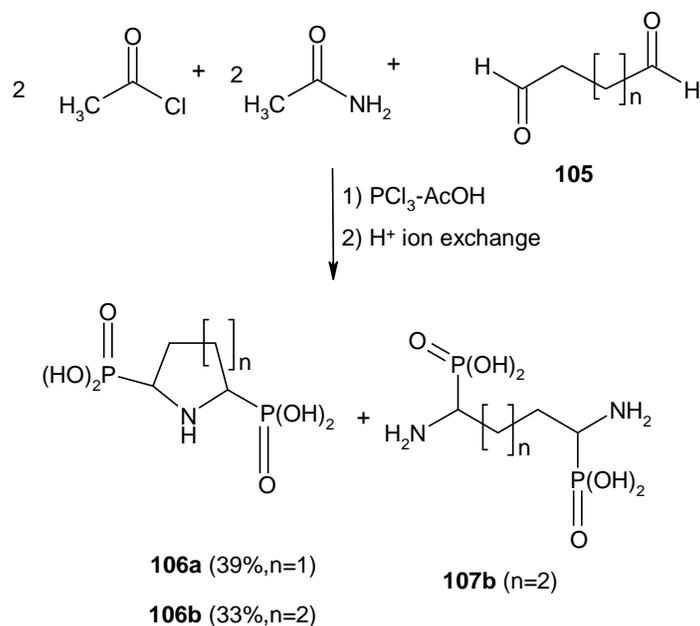
3.4. Multicomponent reaction (Kabachnik-Fields reaction)

2-(Diethylphosphono)-2-methylpyrrolidine (**104**) was obtained in a one-pot reaction by bubbling ammonia into an ethanolic solution of 5-chloropentan-2-one (**103**) and diethyl phosphite (Kabachnik-Fields reaction) (Scheme 37).^{70,71}



Scheme 37

Reaction of alkanedial (**105**), acetamide, and acetyl chloride with PCl_3 in acetic acid exclusively produced the bisphosphonic acid **106a** in 39% yield. When the reaction was performed with pentanedial, the corresponding piperidine **106b** was formed (33%) in a 1:1 mixture with the acyclic bis(aminophosphonic acid) **107b** (Scheme 38).⁷²



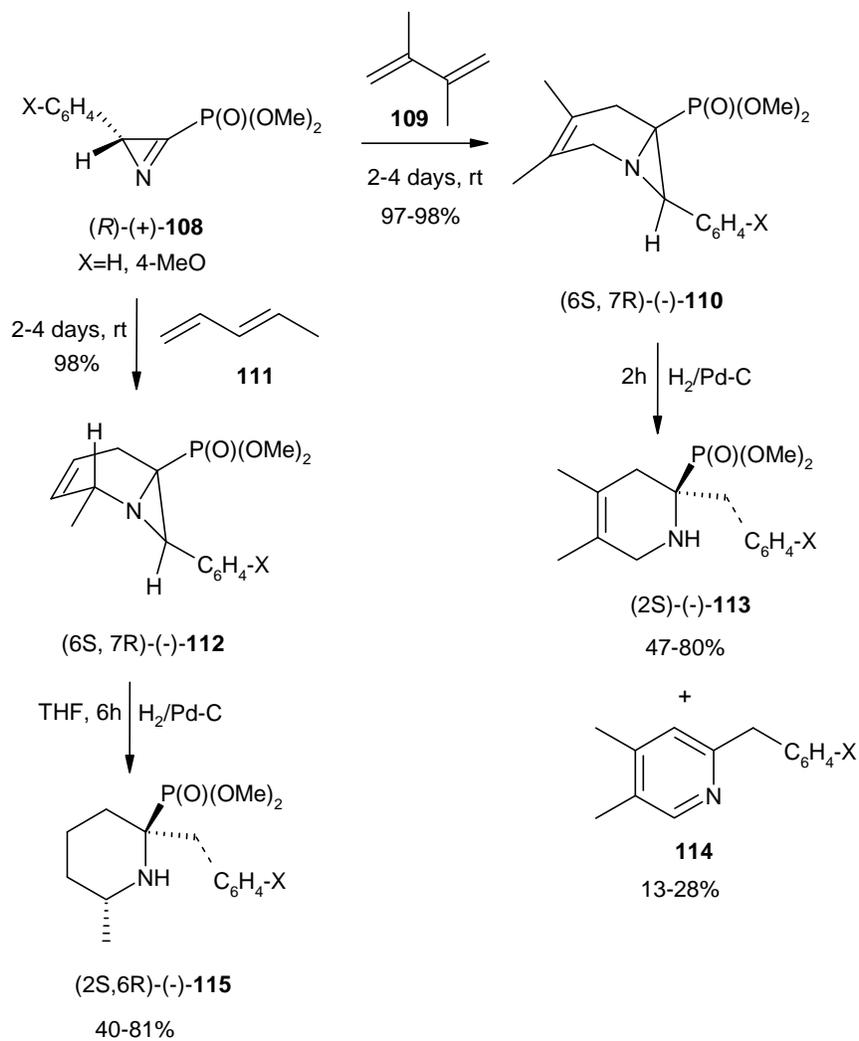
Scheme 38

3.5. Diels-Alder reaction

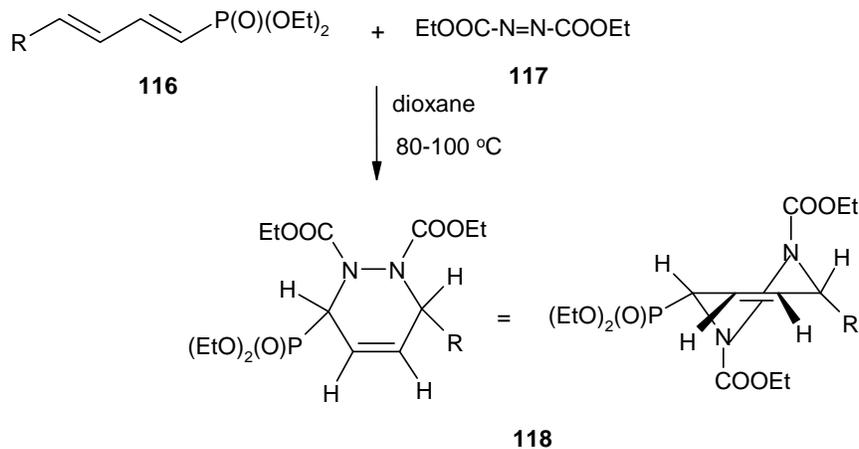
Davis and co-workers⁷³ described [4+2] cycloadditions between azirinylphosphonates **108** with 2,3-dimethylbutadiene (**109**) or *trans*-piperylene **111**. The diene (100 equivalents) was reacted with the phosphonoazirine for 2-4 days at room temperature. Bicyclic aziridines **110** and **112**, respectively were isolated as single stereoisomers by flash chromatography. Catalytic hydrogenation of **110** results in two products. The major products, were identified as quaternary piperidinephosphonates (2*S*)-(-)-**113**, which resulted from the expected cleavage of the C-7-N bond in **110**. The minor products, obtained in 28% and 13% yield, respectively, were identified as pyridines **114**. Controlling the conditions for the hydrogenation of **112** led to the reduction of the C-C double bond, affording the phosphonopiperidine **115** (Scheme 39).

Diethyl 3-(diethoxyphosphoryl)-6-alkylpyridazine-1,2(3*H*,6*H*)-dicarboxylates (**118**) was obtained in 85% yield from cycloaddition reaction of 1,3-dienylphosphonates **116** with diethyl azidodicarboxylate (**117**) in dioxane. Compounds **118** were generally regarded to have a half chair configuration based on the relationship between the vicinal coupling constants and dihedral angles (Scheme 40).⁷⁴

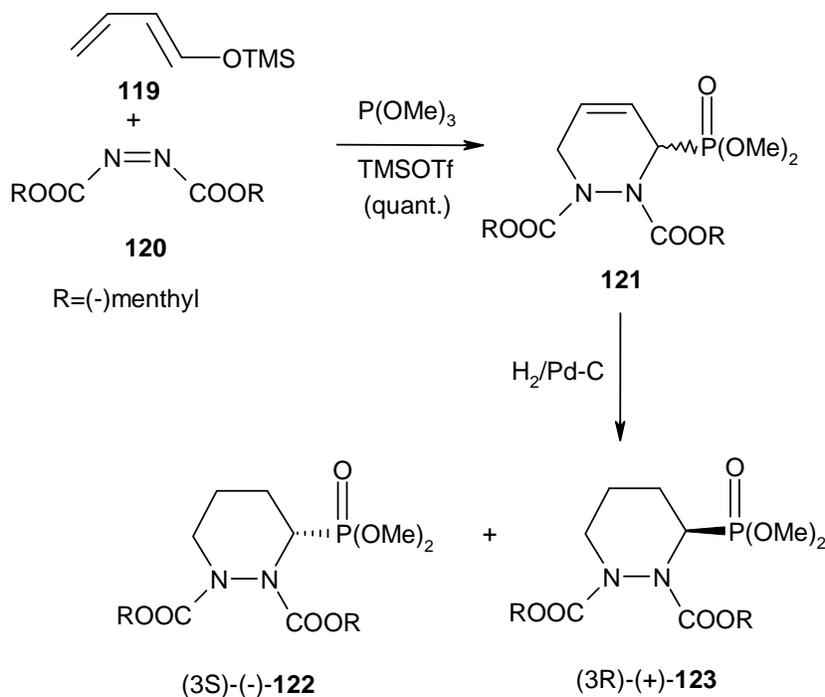
3-(Dimethylphosphino)piperidazine **121** can be synthesized *via* a Diels-Alder reaction of di-(-)-menthyl azodicarboxylate (**120**) and 1-trimethylsilyloxybutadiene (**119**) in the presence of trimethyl phosphite and a Lewis acid, as an inseparable mixture of diastereomers (Scheme 41). However, after hydrogenation of **121**, the phosphonopiperidazines **122** and **123** can easily be separated by column chromatography.⁷⁵



Scheme 39



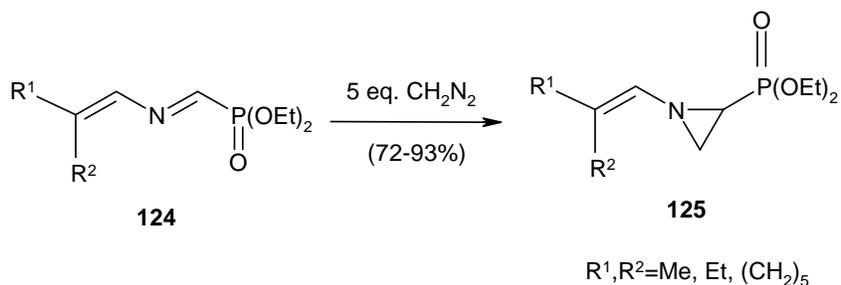
Scheme 40



Scheme 41

3.6. Ring closure of iminophosphonates

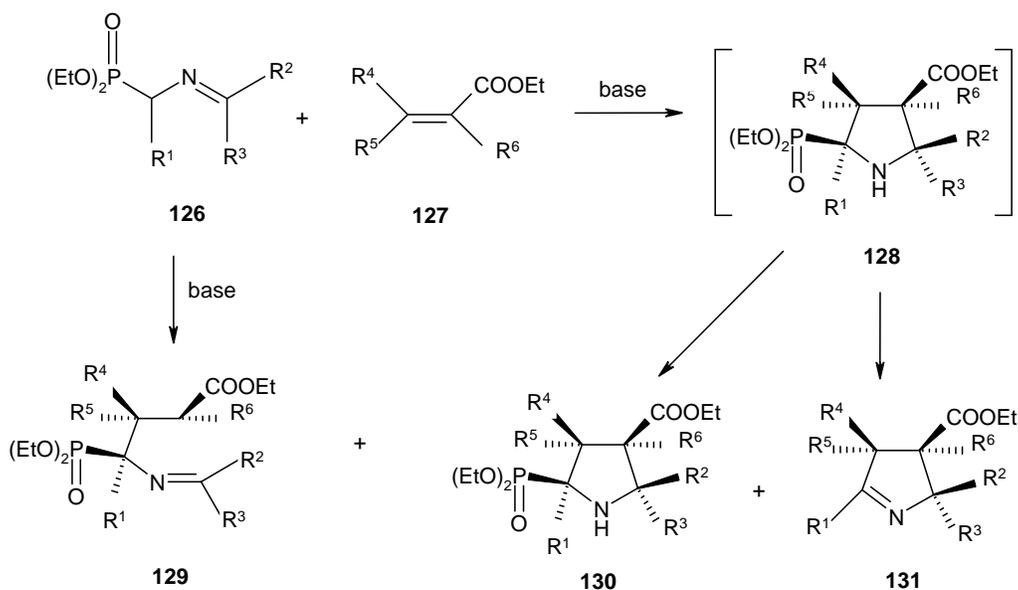
Recently, an initial study was made on the reactivity of 1-phosphono-2-aza-1,3-dienes,^{76,77} which prove to be promising substrates for the synthesis of azaheterocyclic phosphonates. Reaction of the azadienes **124** with an excess of diazomethane led to the clean generation of 1-vinyl-2-phosphonoaziridines **125** in good yields (Scheme 42).



Scheme 42

Reaction of carbanions of *N*-phosphonomethyl imines **126** with α,β -unsaturated esters **127** can lead to three different products: an acyclic adduct **129** due to Michael addition, pyrroline **131** due to cycloaddition and subsequent elimination of the diethyl phosphate anion, or pyrrolidine **130**. When sodium hydride was used as a base at room temperature, pyrrolidines **130** were

formed exclusively in good yields (77-90%) due to the stereospecificity of the reaction related to the concerted mechanism (Scheme 43).⁷⁸⁻⁸⁰

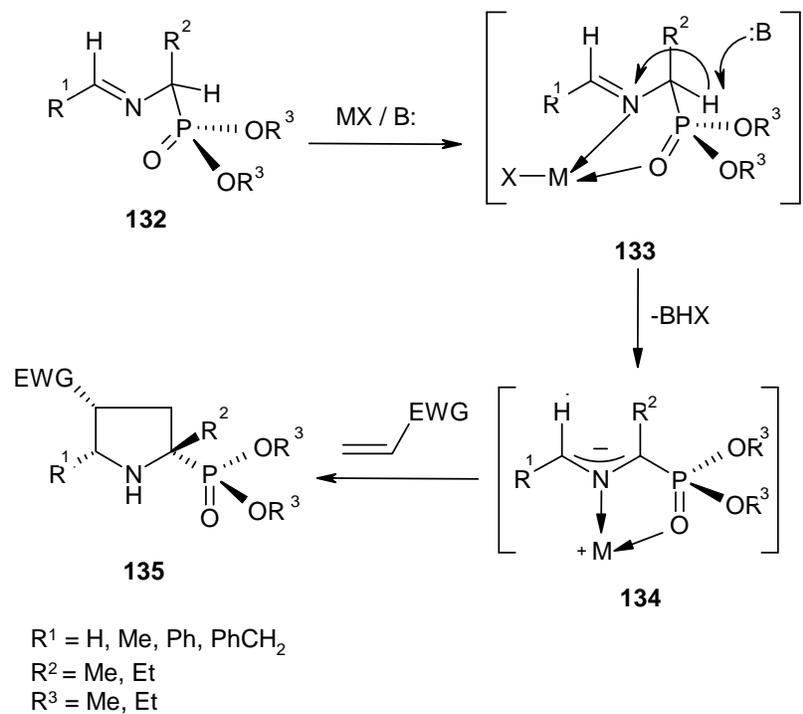


Scheme 43

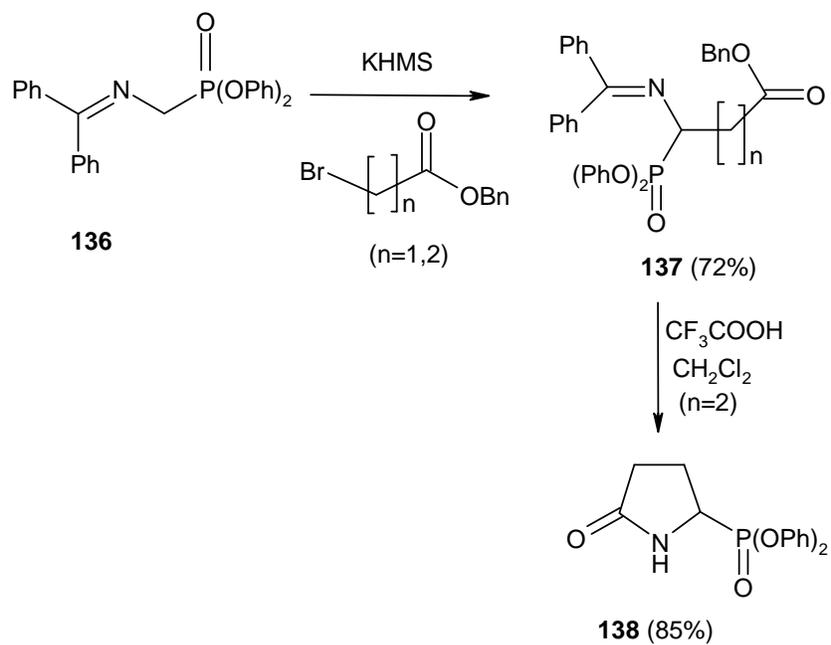
The metal-catalyzed cycloaddition reactions of α -iminophosphonate **132** with various dipolarophiles including chiral menthyloxy furanone with (AgOAc) or (LiBr) and a suitable base [DBU, Et_3N , BTMG (*t*-butyltetramethylguanidine)] afforded a wide variety of conformationally constrained cyclic α -aminophosphonate **135** (Scheme 44).⁸¹

The imine **136** was alkylated, followed by ring closure *via* hydrolysis by trifluoroacetic acid to give the 2-phosphonopyrrolidinone **138** (Scheme 45). When hydrochloric acid was used, no cyclization occurred and the corresponding hydrochloride salt of the acyclic amine was recovered from the reaction mixture.⁸²

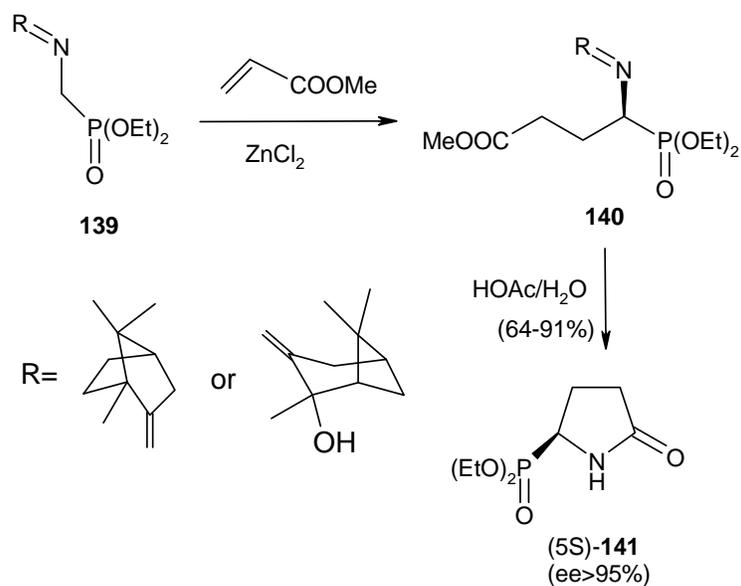
When unsubstituted acrylic esters⁸³⁻⁸⁵ were used in the addition reaction, only ZnCl_2 generated carbanions of **139** were reactive. Iminophosphonate **140** was formed in 66% yield with 71% de. The minor diastereomer was easily removed by flash chromatography on silica gel. After hydrolysis, enantiomerically pure (*5S*)-pyroglutamic acid derivative **141** was isolated. The chiral auxiliary was recovered in 60% yield (Scheme 46).



Scheme 44

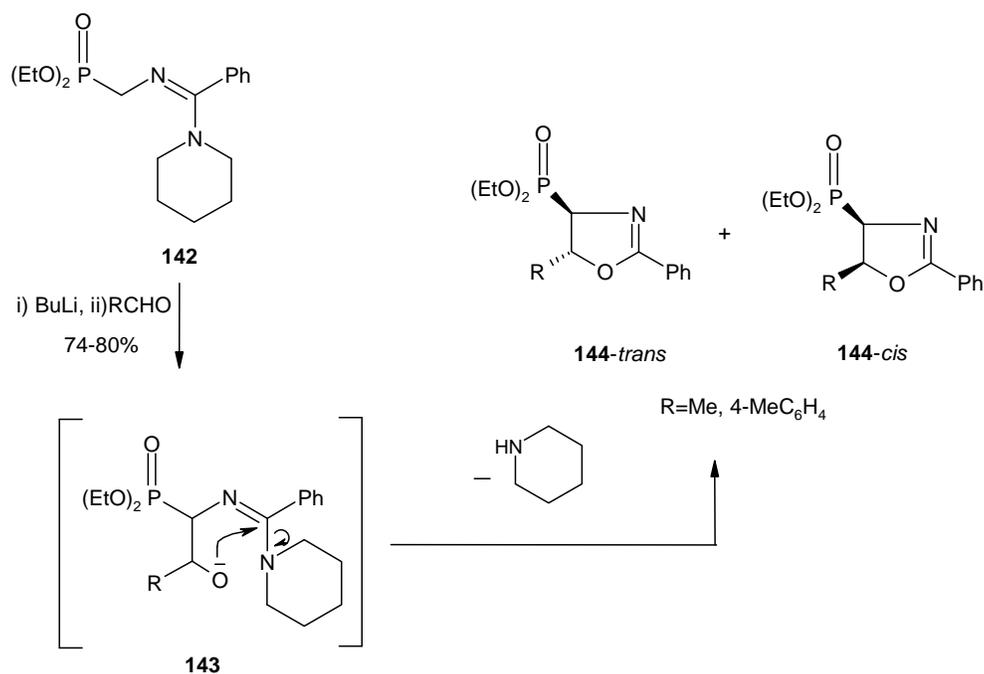


Scheme 45



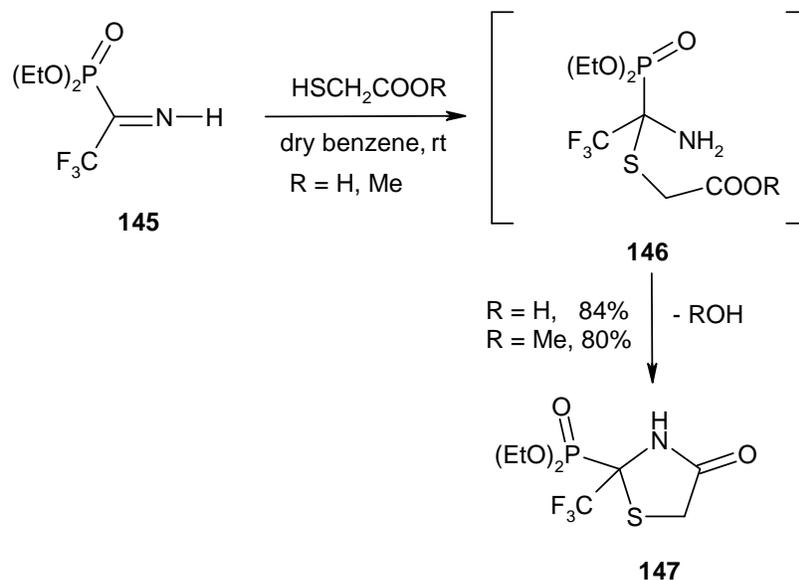
Scheme 46

Treatment of N^1 -(diethoxyphosphorylmethyl)- N^2 -(pentamethylene)benzamide (**142**) with *n*-butyllithium followed by the addition of *p*-tolualdehyde led to the formation of diethyl *trans* and *cis*-2-phenyl-5-alkyl/aryl-oxazolin-4-yl)phosphonates **144** in good yields (Scheme 47).⁸⁶



Scheme 47

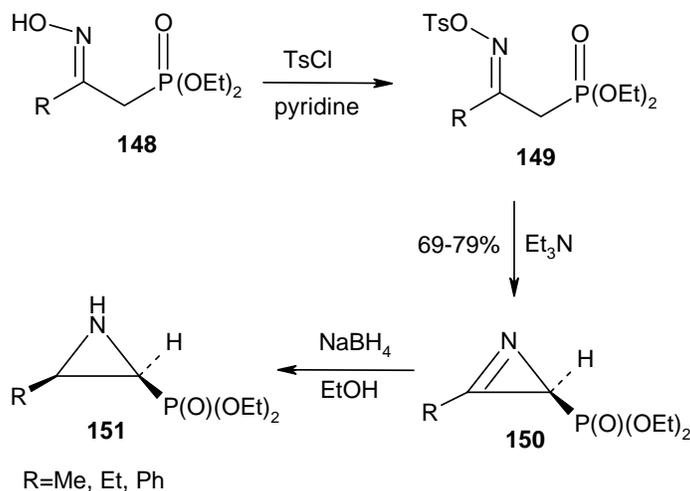
Methyl mercaptoacetate was added to a stirred solution of the diethyl trifluoroacetimidoylphosphonate (**145**) in benzene to give the nonisolable intermediate **146** which was directly cyclized into cyclic α -aminophosphonate **147** (Scheme 48).⁸⁷



Scheme 48

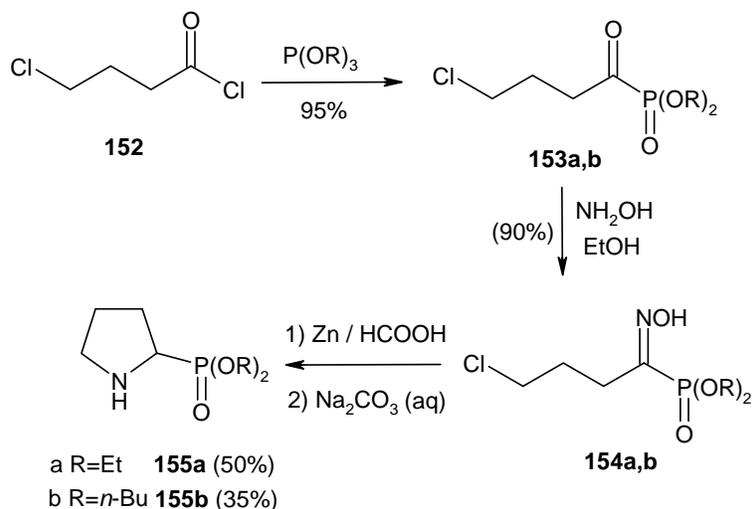
3.7. Ring closure of oximinophosphonates

The preparation of the required functionalized β -tosyl oximes **149** was easily accomplished by simple reaction of β -oximes **148** with tosyl chloride in pyridine. Alkyl and phenyl substituted *2H*-azirines **150** were prepared from β -ketoximes **149** by treatment with triethylamine at room temperature for 8 hours in dry benzene. Reduction of **150** with sodium borohydride in ethanol gave exclusively *cis*-aziridines **151** (Scheme 49).^{88,89}



Scheme 49

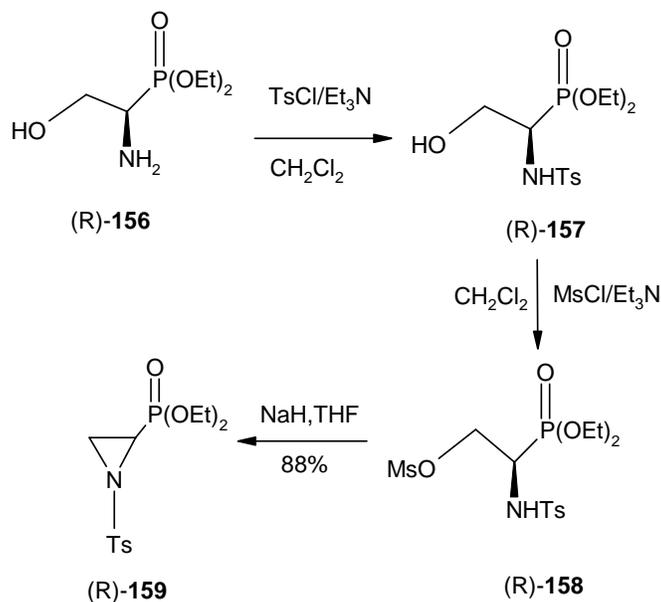
Chlorobutyryl chloride (**152**) was allowed to react with trialkyl phosphite. Then the oxime **154** was formed and ring closure was performed after reduction of the oxime with zinc and formic acid to give the cyclic α -aminophosphonates **155** (Scheme 50).⁹⁰



Scheme 50

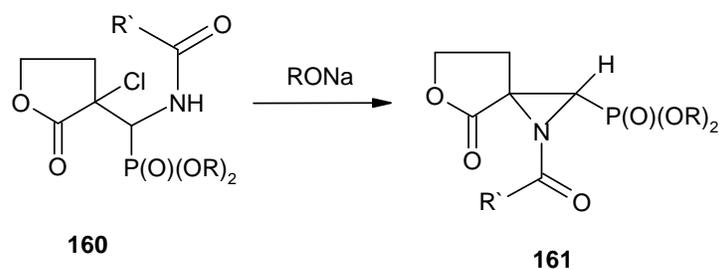
3.8. Ring closure of acyclic α -aminophosphonates

Treatment of phosphoserine diethyl ester (*R*)-**156** with tosyl chloride afforded the corresponding *N*-tosylate (*R*)-**157**, which, by reaction with mesyl chloride, afforded the *O*-mesylate derivative (*R*)-**158**. Reaction of (*R*)-**158** with NaH in THF gave the aziridine-2-phosphonate (*R*)-**159** (Scheme 51).⁹¹



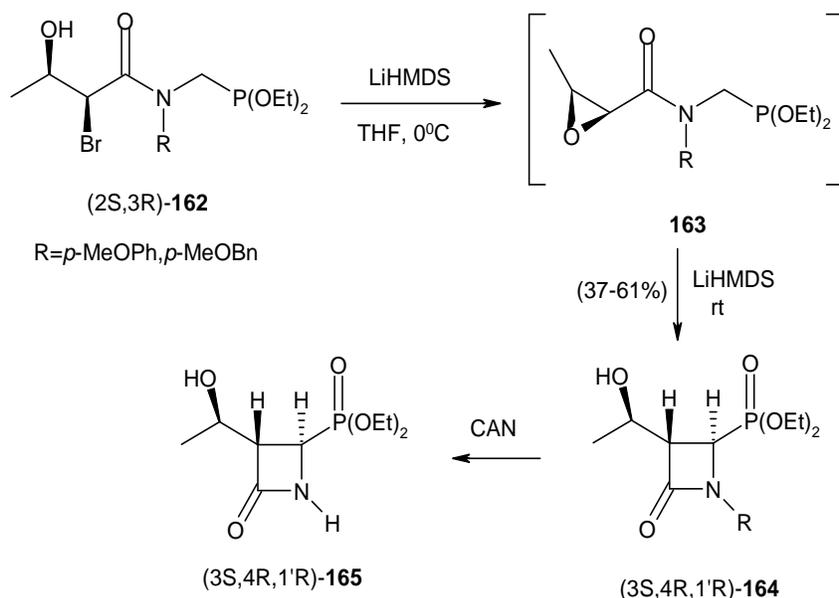
Scheme 51

Similarly, Guseinov *et al.*⁹² reported that acyclic α -aminophosphonate **160** was transformed into phosphonate-containing aziridines **161** by the action of sodium alkoxide (Scheme 52).



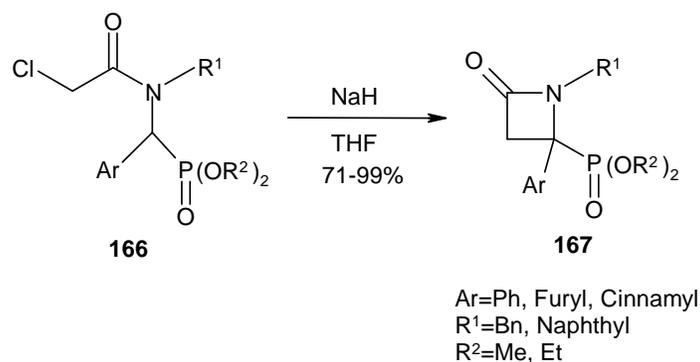
Scheme 52

Ring closure through intramolecular nucleophilic substitution was applied in the synthesis of phosphono- β -lactams. The first example consists of an epoxide ring opening by intramolecular attack of a phosphorus-stabilized carbanion (Scheme 53). The epoxide **163** was formed *in situ* by addition of one equiv of LiHMDS (lithium 1,1,1,3,3,3-hexamethylidisilazane) to amide **162**. A second equivalent was used to form the lactam **164** in a stereospecific manner: only the *trans*- β -lactams were formed. Nitrogen deprotection can then be performed using CAN (cerium ammonium nitrite), and the obtained 4-phosphono- β -lactams **165** are potential precursors for the synthesis of carbapenems.⁹³⁻⁹⁵



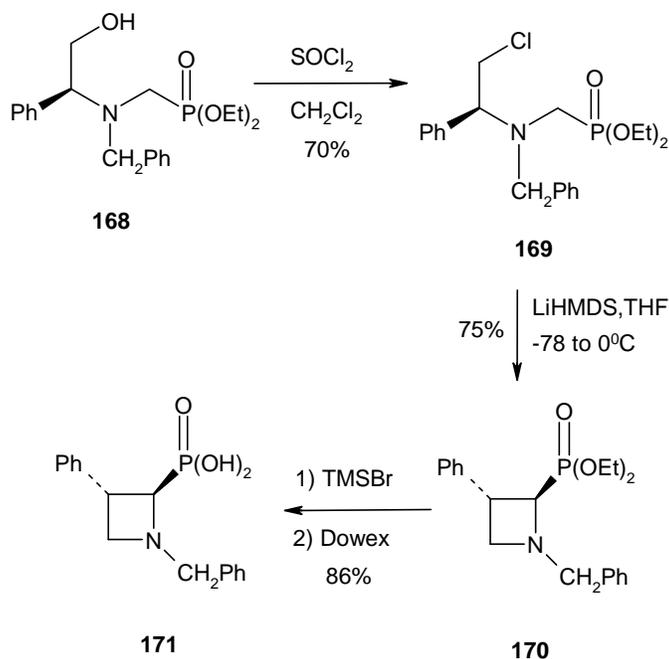
Scheme 53

Chloroamidophosphonates **166** were treated with NaH to involve ring closure to give the cyclic α -aminophosphonates **167** (Scheme 54).^{96,97}



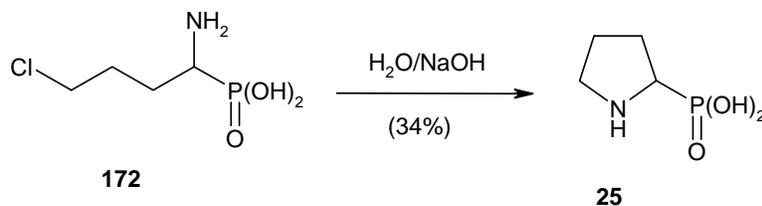
Scheme 54

Treatment of the α -aminophosphonate **168** with thionyl chloride in dichloromethane, followed by the addition of NaHCO₃ gave the chloro derivative **169**. Reaction of **169** with LiHMDS in THF afforded only the 1,3-*trans*-azetidine **170**, which, on hydrolysis of the phosphonate moiety with TMSBr, followed by purification by ion-exchange chromatography, led to azetidion-2-ylphosphonic acid **171** (Scheme 55).⁹⁸



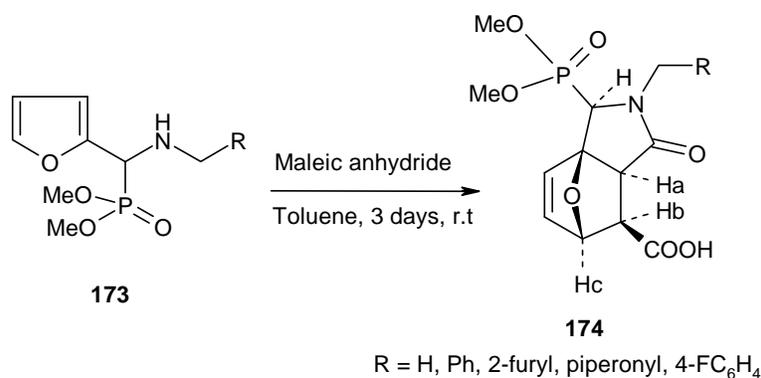
Scheme 55

The cyclization of the δ -chloro- α -aminobutanephosphonic acid (**172**), resulted in the racemic pyrrolidine-2-phosphonic acid **25** which has received some interest as a potential structural mimetic of proline (Scheme 56).⁹⁹



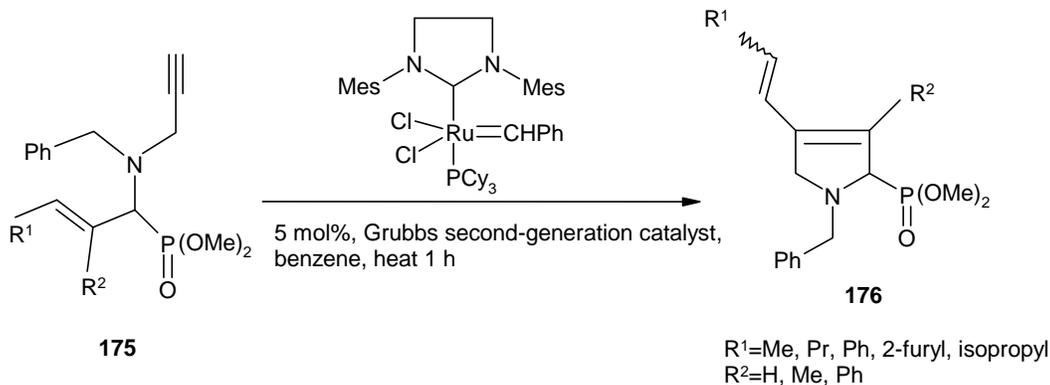
Scheme 56

α -Aminophosphonates **173** underwent tandem acylation and [4+2] cycloaddition with maleic anhydride under stirring in toluene at ambient temperature for 3 days to isolate epoxyisoindolyl phosphonates **174** in good yields (70-90%) as colorless solids (Scheme 57).¹⁰⁰



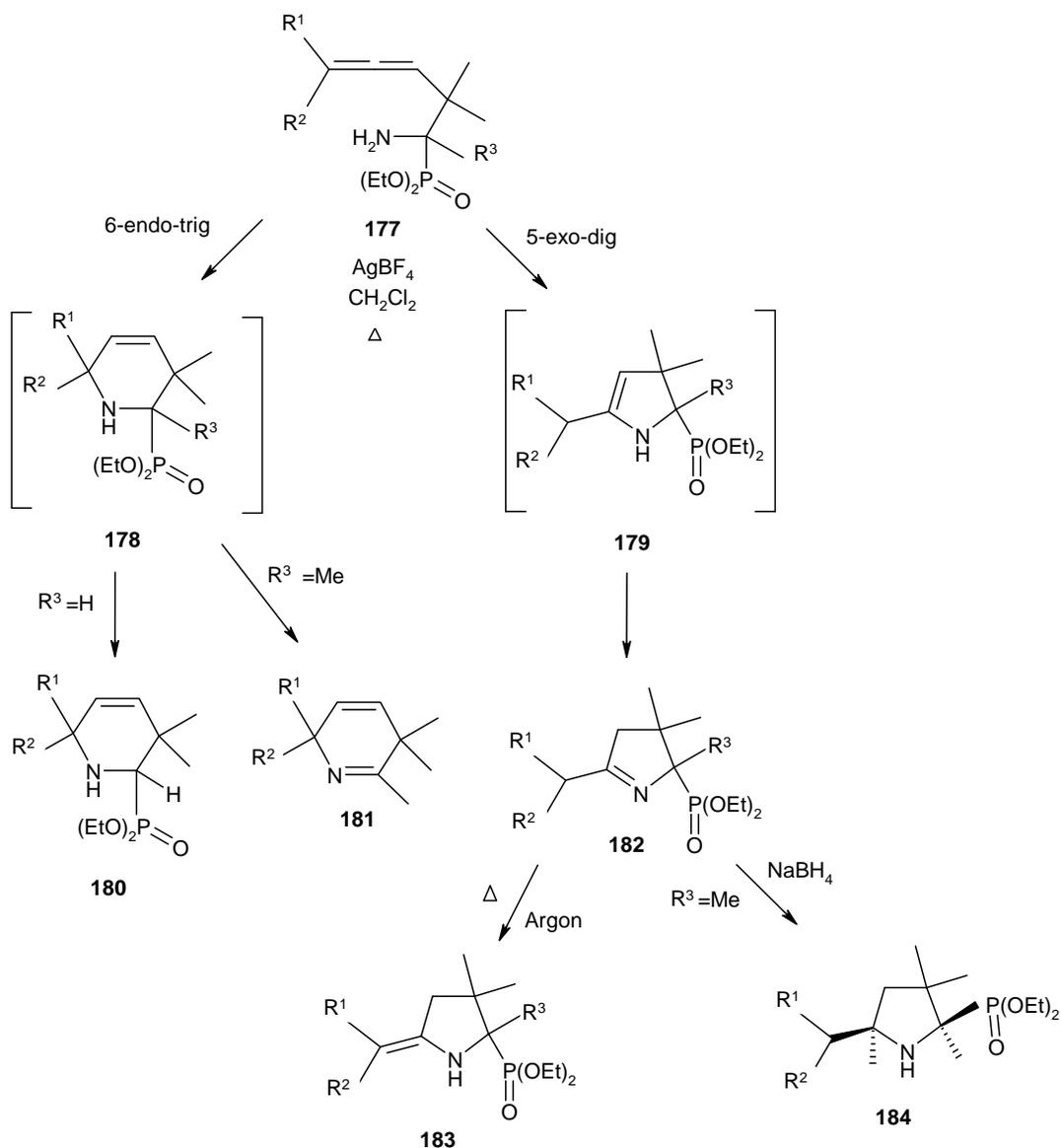
Scheme 57

Adding one equivalent of Grubbs second-generation catalyst to the substrates **175** via ring closure methathesis (RCM) gave the corresponding 2-phosphonopyrrolines **176** (Scheme 58).¹⁰¹



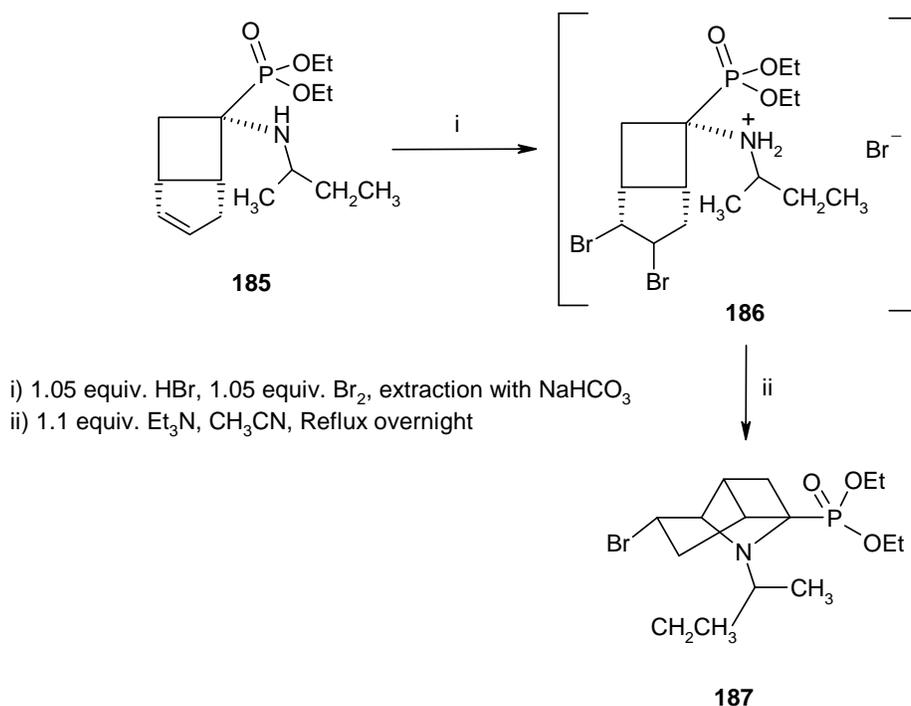
Scheme 58

When β -allenic α -aminophosphonates **177** were heated in the presence of silver salts to activate the allenic moiety, a mixture of five- and six-membered heterocycles was obtained. The ratio of five-membered to six-membered rings was dependent on steric factors. When R^1 and R^2 were more sterically demanding groups, the ratio shifted toward the five-membered ring. The largest effect, however, was observed when R^3 was changed from H to Me; then, only very small amounts of six-membered rings **181** were formed. When the obtained pyrrolines **182** were submitted to high temperatures (80 °C) under an inert atmosphere, the enamines **183** were formed by tautomerization to the more thermodynamically stable compound (Scheme 59).^{102,103}



Scheme 59

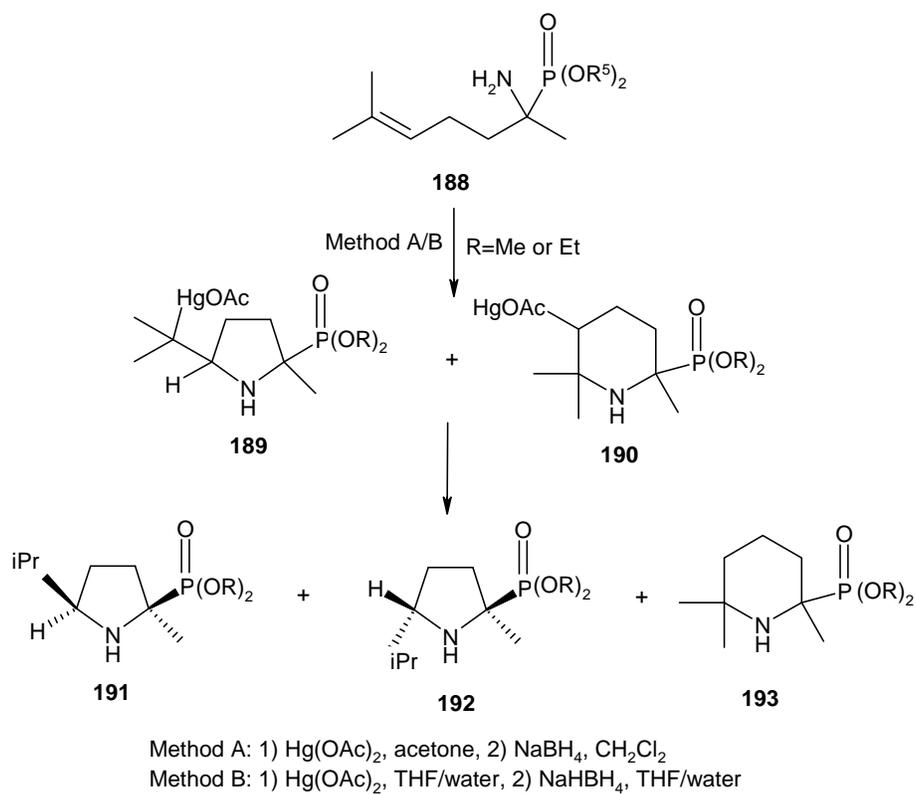
Diethyl (6-isobutylamino)bicyclo[3,2,0]hept-2-en-6-yl phosphonate (**185**) was reacted with HBr and Br₂ to give the hydrobromide salt **186**, which underwent ring closure by addition of triethylamine and heating of the mixture in acetonitrile for 14 hours to give diethyl *endo*-(8-bromo-2-isobutyl-2-azatricyclo[3,3,0,0^{3,6}]oct-3-yl)phosphonate (**187**) (Scheme 60).¹⁰⁴



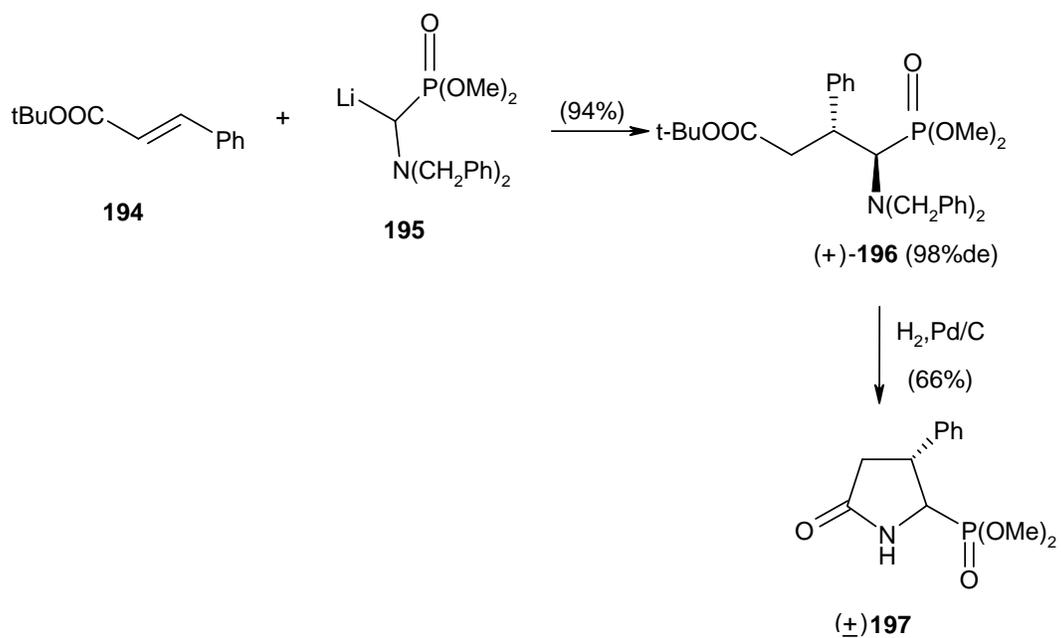
Scheme 60

Cyclization of the R- α -amino- δ -alkenylphosphonates **188** was initiated by addition of Hg(OAc)₂ to the double bond followed by cyclization through intramolecular nucleophilic attack by the free amine. Using α -amino- δ -alkenylphosphonates, it was possible to obtain the five- and six-membered rings containing the α -aminophosphonate moiety (Scheme 61).¹⁰⁵⁻¹⁰⁷

1,4-Addition of lithiated aminomethylphosphonate **195** to α,β -unsaturated ester **194** proceeded to give the dibenzylaminophosphonate **196** in 94% yield and 98% diastereomeric excess. Reductive deprotection of **196** then led to *trans*-phosphonopyrrolidone **197** in 66% yield (Scheme 62).¹⁰⁸

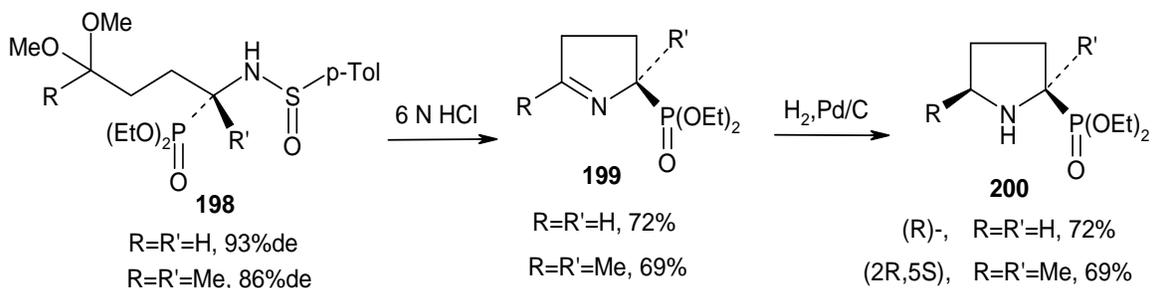


Scheme 61



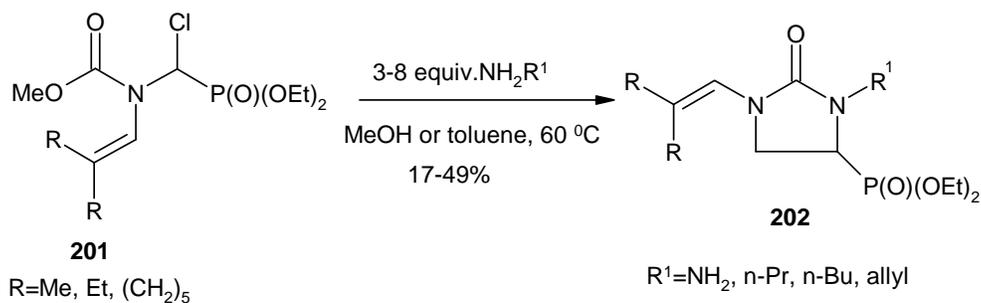
Scheme 62

Cleavage of the sulfinyl group and hydrolysis of the acetal **198** gave the aminocarbonyl derivative, which cyclized to afford the iminophosphonates **199**. Catalytic hydrogenation of **199** led to the cyclic α -aminophosphonates **200** (Scheme 63).¹⁰⁹



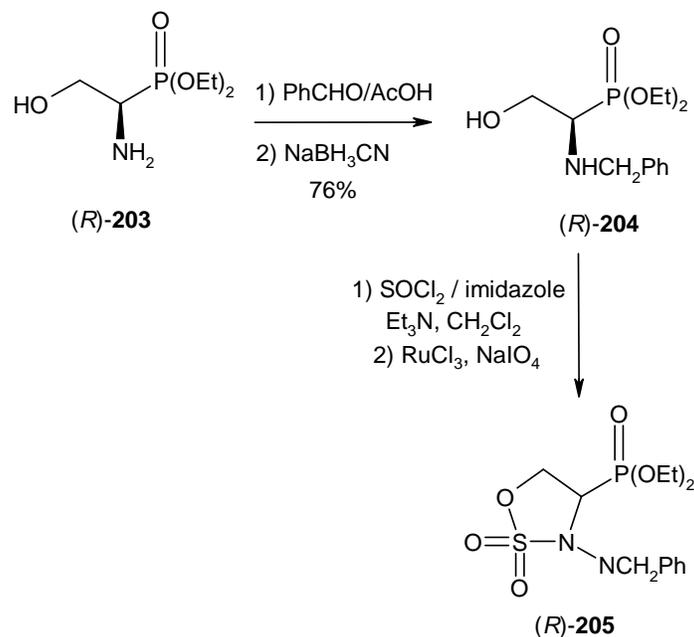
Scheme 63

Addition of three to eight equivalents of amine to the enamide **201** in methanol or toluene afforded the 5-phosphonylated-2-imidazolidinones **202** which could be isolated in moderate yield 17-49% (Scheme 64).¹¹⁰



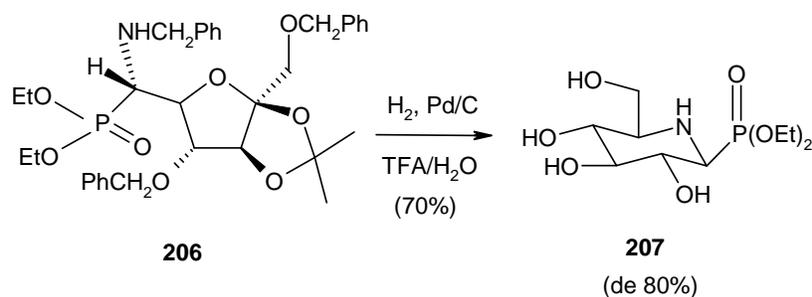
Scheme 64

Reaction of phosphoserinate (*R*)-**203** with benzaldehyde, followed by reduction with sodium cyanoborohydride in acetic acid, afforded the *N*-benzyl α -amino-phosphonate (*R*)-**204** in 76% yield. Treatment of (*R*)-**204** with thionyl chloride and subsequent oxidation with sodium periodate in the presence of ruthenium chloride gave the sulfonamide (*R*)-**205** in 70% yield (Scheme 65).¹¹¹



Scheme 65

The α -aminophosphonate **206** was submitted to a hydrogenolysis-reductive amination, resulting in the polyhydroxylated piperidinylphosphonate **207** (Scheme 66).¹¹²

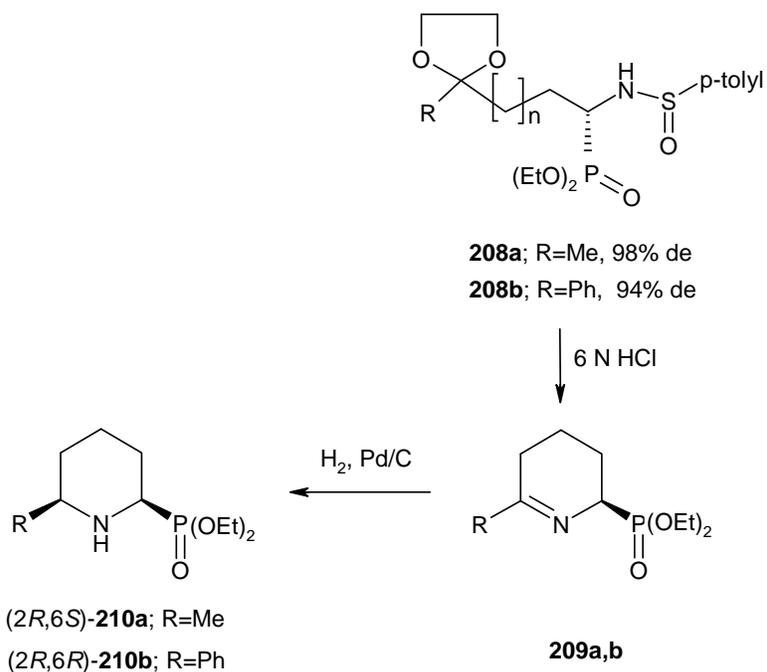


Scheme 66

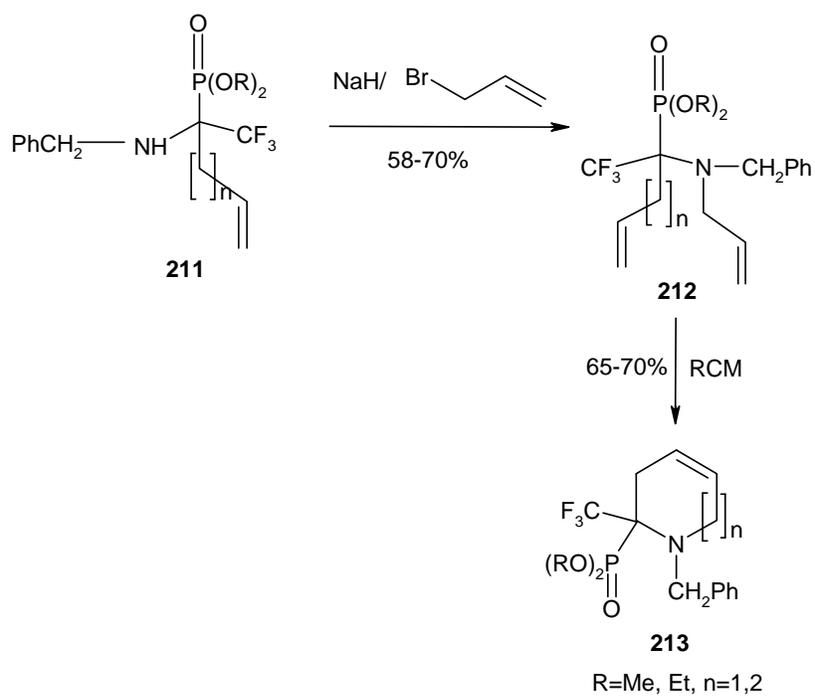
Davis *et al.*¹⁰⁹ described the stereoselective synthesis of piperidin-2-yl-phosphonates **210a,b**. Cleavage of the sulfinyl group and acidic hydrolysis of the ketal in **208a,b** gave an amino-carbonyl derivative, which underwent cyclization to afford the iminophosphonates **209a,b**. Finally, catalytic hydrogenation of **209a,b** led to the cyclic α -aminophosphonates (2*R*,6*S*)-**210a** and (2*R*,6*R*)-**210b**, respectively (Scheme 67).

Ring closing metathesis (RCM) of α -aminophosphonates, bearing two terminal alkene chains, was a convenient strategy to synthesize heterocyclic α -aminophosphonates. Osipov *et al.* succeeded in the synthesis of the cyclic aminophosphonates **213**.^{113,114} Alkylation of the nitrogen

atom of α,β -unsaturated α -aminophosphonates **211** gave rise to the 1,7-dienes **212** which can be ring closed to the 3-piperidines **213** using a Ru catalyst (Scheme 68).

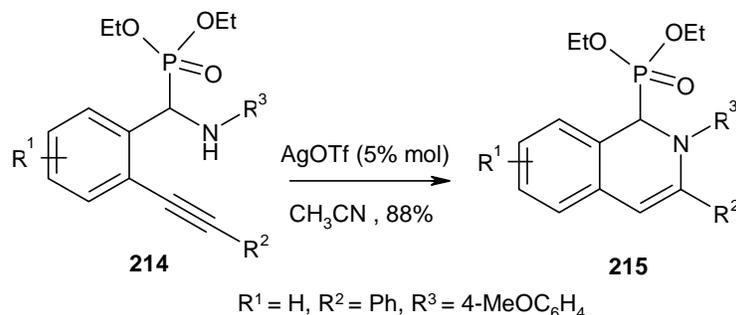


Scheme 67



Scheme 68

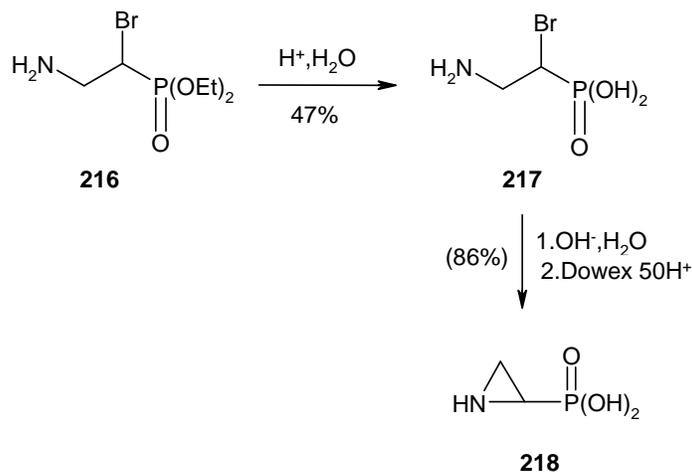
Conversion of α -amino-(2-alkynylphenyl)methylphosphonate **214** to 2,3-disubstituted-1,2-dihydroisoquinolin-1-yl phosphonate **215** was performed through 6-*endo*-cyclization utilizing silver triflate as catalyst (Scheme 69).¹¹⁵



Scheme 69

3.9. Ring closure of acyclic β -aminophosphonates

The hydrolysis of diethyl ester **216** led in a one-pot procedure to the pure β -amino-phosphonic acid **217** (yield: 47%). Cyclization of **217** by boiling in aqueous sodium hydroxide forms within 5 minutes the disodium salt, which gave 86% of pure aziridine **218** after passage through an ion exchange column (Scheme 70).^{116,117}

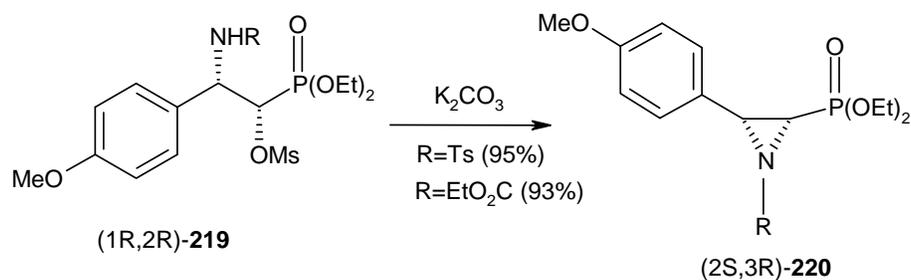


Scheme 70

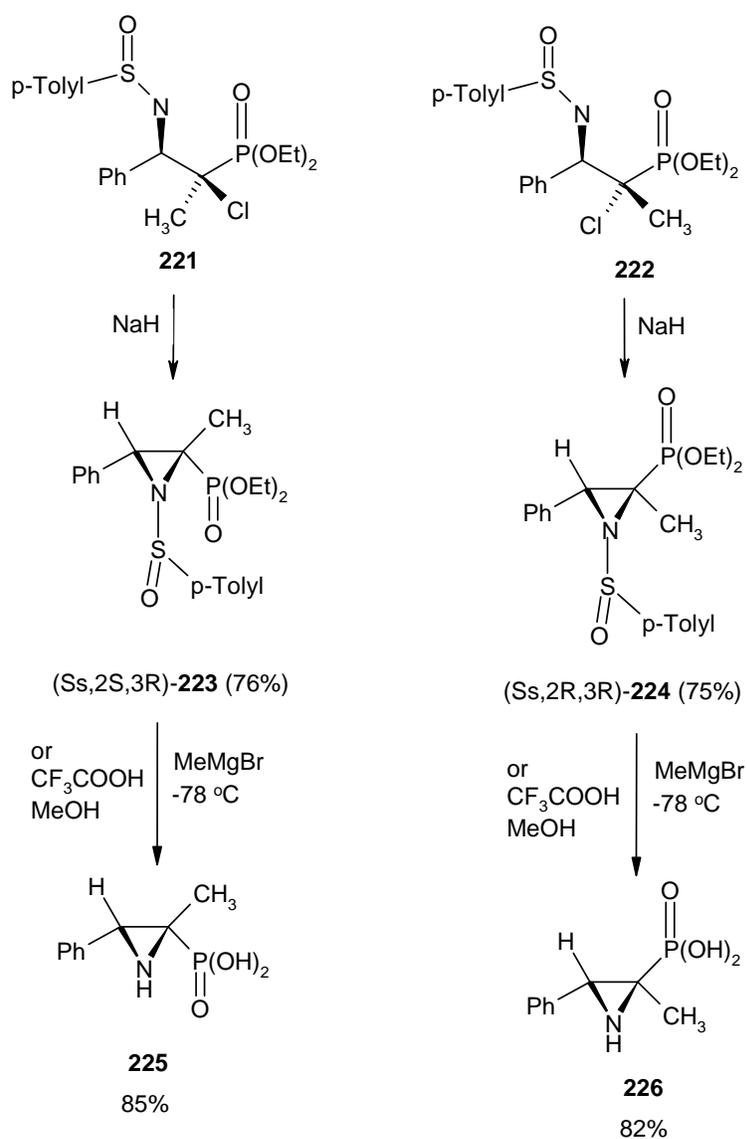
Treatment of the mesylated β -aminophosphonate **219** with K₂CO₃ in DMF resulted in the formation of the *N*-protected aziridines **220** in high yields and purity (>99%) (Scheme 71).¹¹⁸

The diastereoisomers of β -aminophosphonates **221** and **222** were cyclized using NaH, resulting in the diastereoisomers **223** (76%) and **224** (75%), respectively, which were subjected

to hydrolysis conditions (TFA-MeOH) or MeMgBr to give the corresponding acids **225** and **226**, respectively (Scheme 72).^{73,119-120}



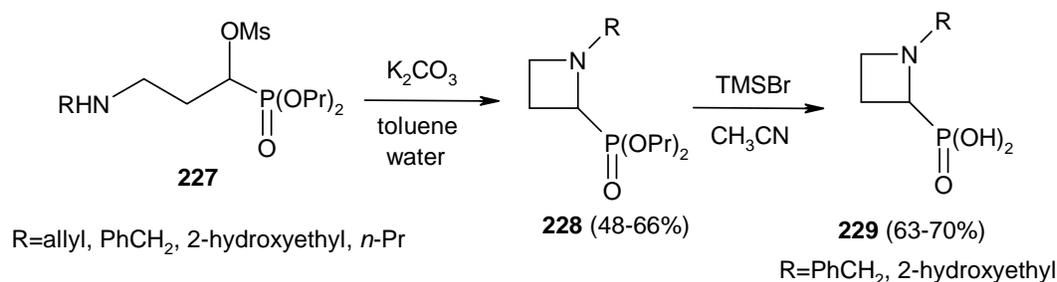
Scheme 71



Scheme 72

3.10. Ring closure of acyclic γ -aminophosphonates

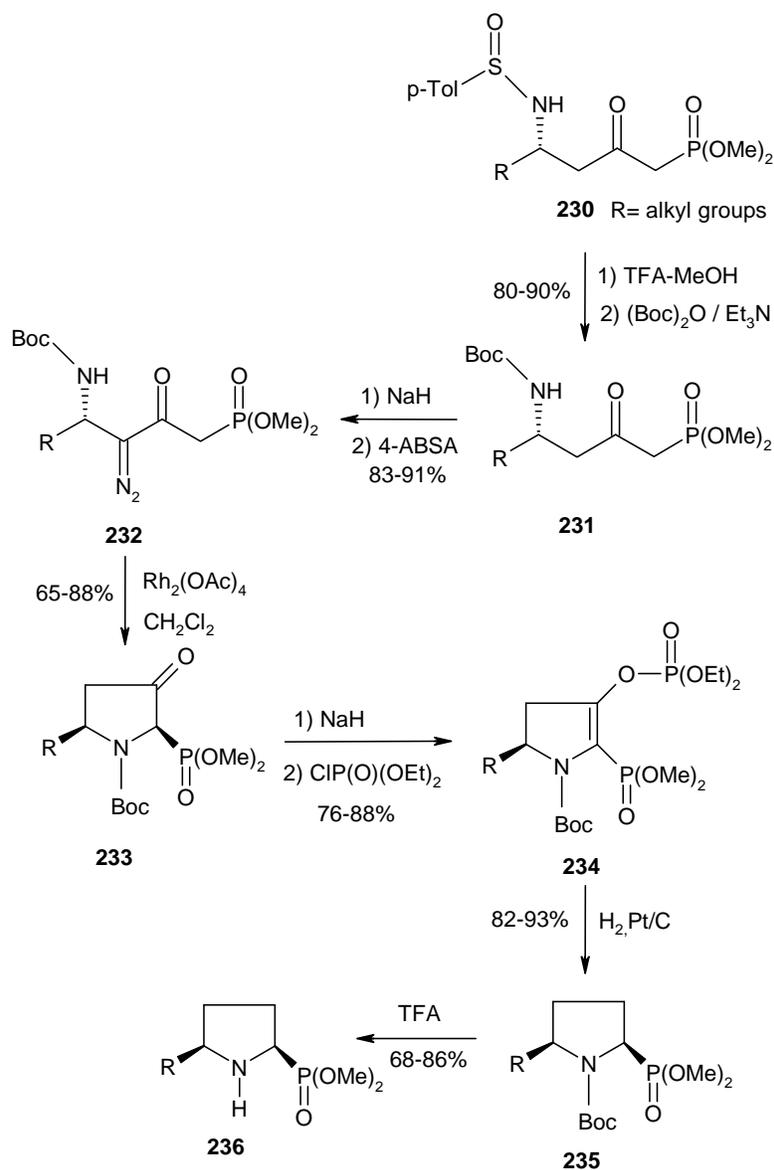
Ring closure of the mesylates **227** in refluxing toluene-water mixture in the presence of K_2CO_3 produced azetidiny-2-phosphonates (**228**), which were hydrolyzed into the corresponding azetidiny-2-phosphonic acids (**229**) (Scheme 73).¹²¹



Scheme 73

3.11. Ring closure of acyclic δ -aminophosphonates

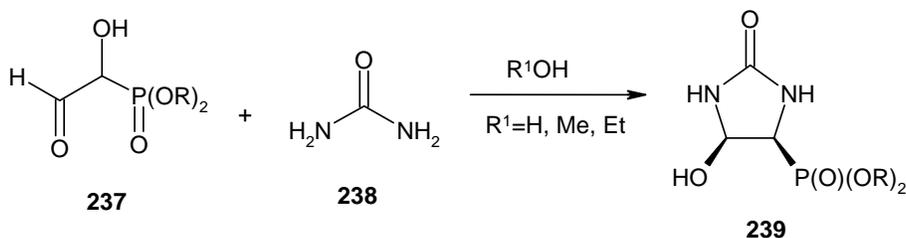
Treatment of δ -amino- β -ketophosphonates **230** with TFA, followed by reaction with $(Boc)_2O$, afforded the derivatives **231** in 80–90% yield. Reaction of **231** with NaH and 4-acetamidobenzenesulfonyl azide (4-ABSA) furnished the diazo derivatives **232** in excellent yield (83–91%), which, by treatment with $Rh_2(OAc)_4$, led to the 3-oxo-pyrrolidine phosphonates **233**. Removal of the 3-oxo group in **233** by treatment with NaH, followed by the addition of diethyl chlorophosphonate, and subsequent hydrogenation of **234** provided the cyclic phosphonates **235** in good yield. Finally, cleavage of the Boc-protective group in **235** with TFA afforded the *cis*-5-substituted pyrrolidine-2-phosphonates **236** in 68–86% yield (Scheme 74).^{81,122-123}



Scheme 74

3.12. Ring closure of acyclic α -hydroxyphosphonates

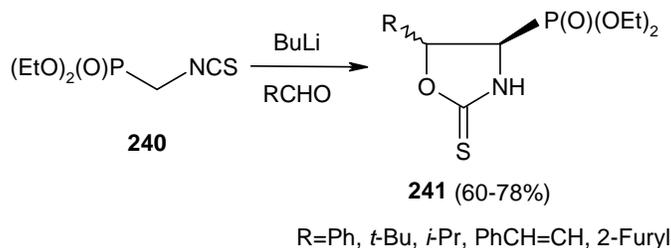
Phosphonylated 2-imidazolidinone **239** was prepared from phosphonylated aldehyde **237** and urea **238** (Scheme 75).^{124,125}



Scheme 75

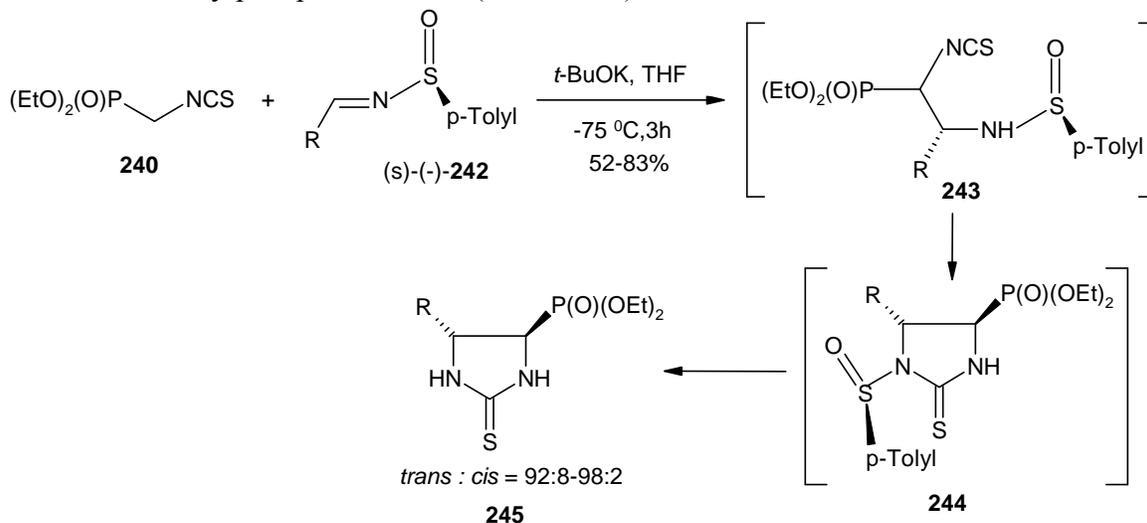
3.13. Ring closure of isothiocyatomethylphosphonates

The lithium derivative of diethyl isothiocyatomethylphosphonate (**240**) was reacted with aldehyde to afford a mixture of *cis*- and *trans*-(2-thioxo)oxazolidin-4-yl)phosphonate (**241**) which were separated by column chromatography (Scheme 76).^{126,127}



Scheme 76

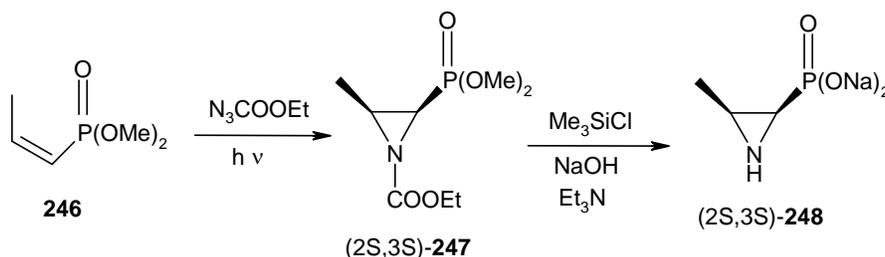
Blaszczyk *et al.*¹²⁸ demonstrated that the diastereoselective addition of diethyl isothiocyatomethylphosphonate (**240**) to various *N*-protected imines **242** afforded the cyclic thioximidazolidinylphosphonates **245** (Scheme 77).



Scheme 77

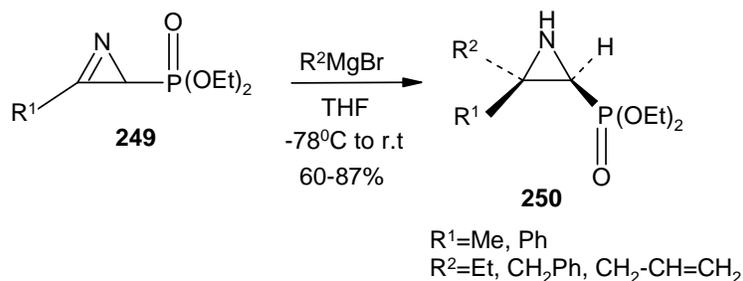
3.14. Miscellaneous

3.14.1. Photocyclization. The antibacterial phosphonoaziridine **247** and a salt of 2H-aziridine **248** were prepared via photocyclization reactions.¹¹⁶ Thus, vinylphosphonate **246** was treated with ethyl azidoacetate by irradiation with UV light (Scheme 78).



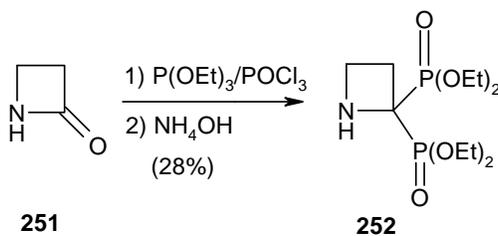
Scheme 78

3.14.2. Reaction of azirine phosphonate with Grignard reagent. Reaction of 2H-azirine phosphonate **249** with ethyl magnesium bromide in THF at -78°C led exclusively to the formation of diethyl *trans*-3-ethyl-3-methylaziridin-2-ylphosphonate (**250**) (Scheme 79).¹²⁹



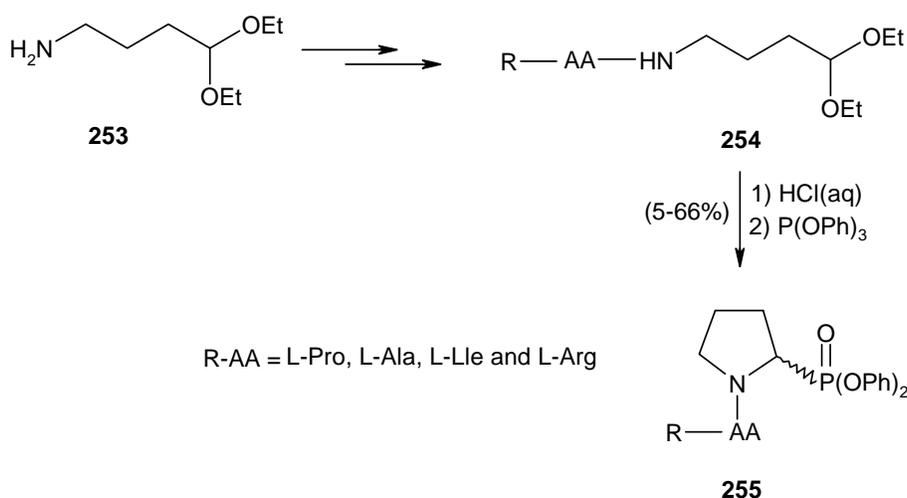
Scheme 79

3.14.3. Phosphonylation of lactams. Lactam **251** was phosphonylated with triethyl phosphite in the presence of phosphorus oxychloride. The 1,1-diphosphonoazetidone **252** was obtained in only low yields (28%) (Scheme 80).¹³⁰



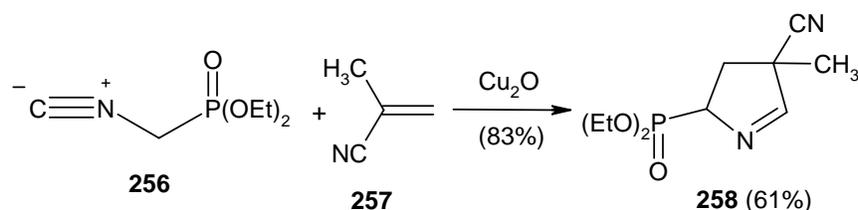
Scheme 80

3.14.4. Hydrolysis of an acetal. The acetal **254** was hydrolyzed in an acidic medium, and the resulting mixture was treated with several triphenyl phosphite reagents in hydrochloric acid to give diastereomeric mixtures of the N-protected diphenyl pyrrolidinephosphonates **255** (Scheme 81).^{131,132}



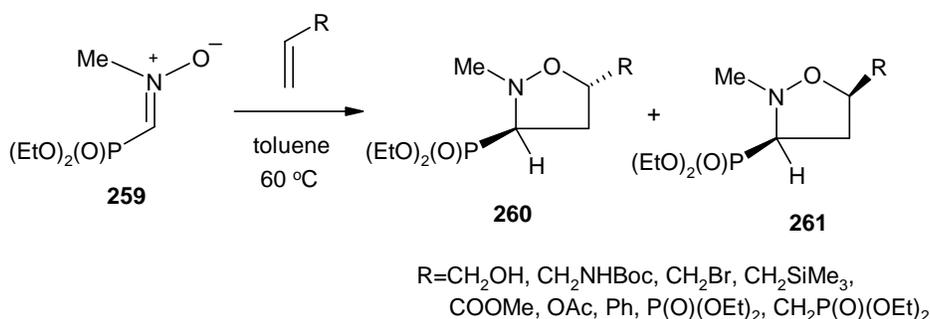
Scheme 81

3.14.5. Cycloaddition to phosphorylated nitrile ylide. Diethyl isocyanomethylphosphonate **256** can be used immediately in a cycloaddition reaction with methacrylonitrile **257** and Cu_2O as a catalyst, producing the pyrroline **258** in 83% yield (Scheme 82).¹³³



Scheme 82

3.14.6. Cycloaddition to phosphorylated nitrene. 1,3-Dipolar cycloaddition of nitrene **259** was first examined with terminal alkenes in toluene at 60 °C. *Cis*- and *trans*-diastereomeric isoxazolidines **260** and **261** were obtained in the ratio 90:10 in yields 23-73% (Scheme 83).¹³⁴

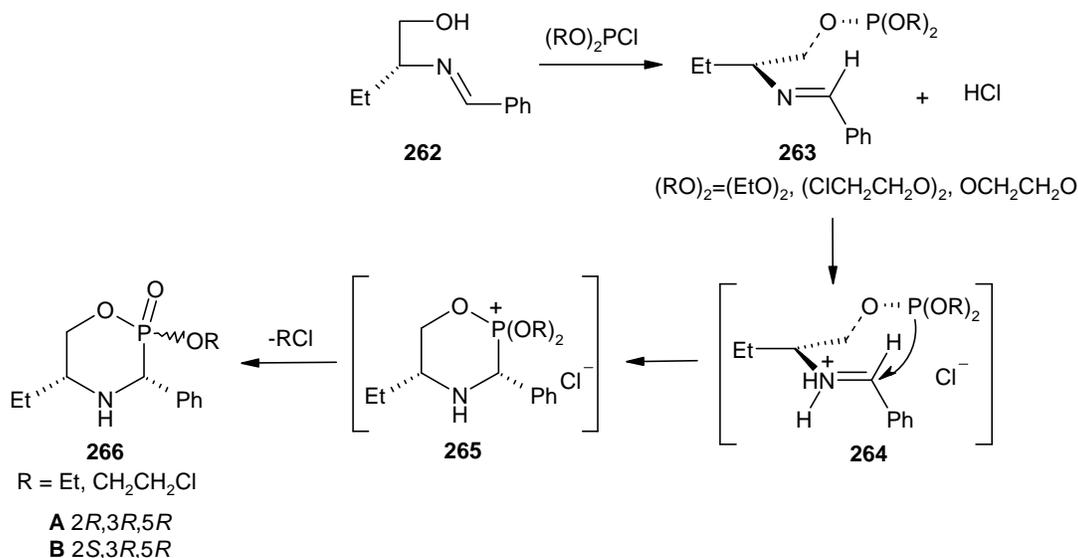


Scheme 83

4. Type C: Cyclic α -Aminophosphonic Acid Derivatives Containing the Phosphorus and Nitrogen as Ring Heteroatoms

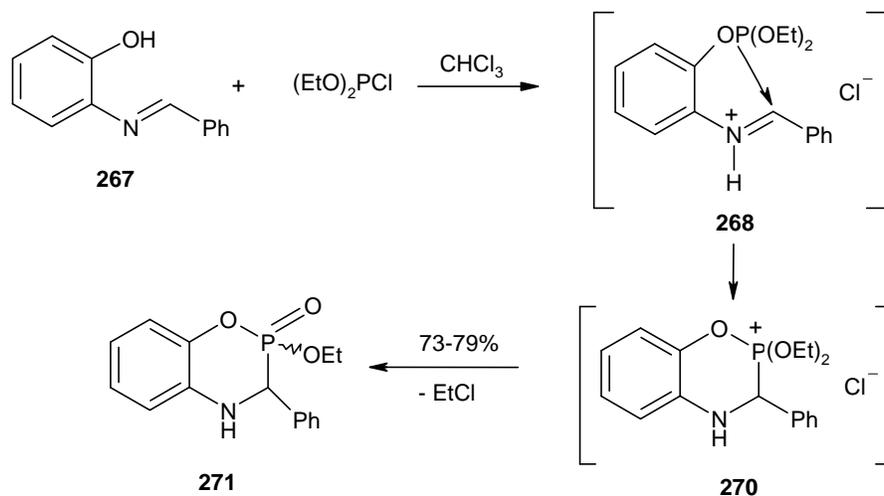
4.1. Addition of phosphorus reagents to acyclic imines

4.1.1. addition of phosphites to acyclic imines (Pudovik reaction). In the reaction of *N*-(benzylidene)-2-aminoethanol (**262**) with diethyl/ethane/bis(β -chloroethyl)chlorophosphite in CHCl₃, 2-(β -chloroethoxy)/ethoxy-2-oxo-3-phenyl-1,4,2-oxazaphosphorines (**266**) were obtained in good yields as diastereomers **A** and **B** (Scheme 84).^{135,136}



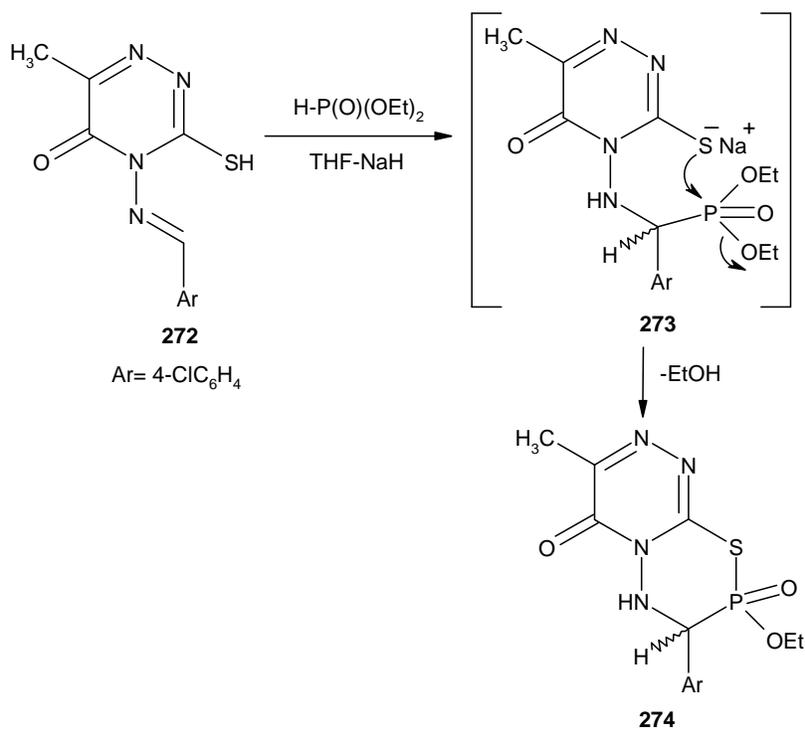
Scheme 84

Reaction of 2-(*N*-benzylidene)aminophenol (**267**) with diethyl chlorophosphite carried out in the absence of an external HCl acceptor resulted in the formation of two diastereomers of 2-(2'-alkoxy)-2-oxo-3-phenyl-1,4,2-benzoxazaphosphorinanes (**271**) (Scheme 85).¹³⁷



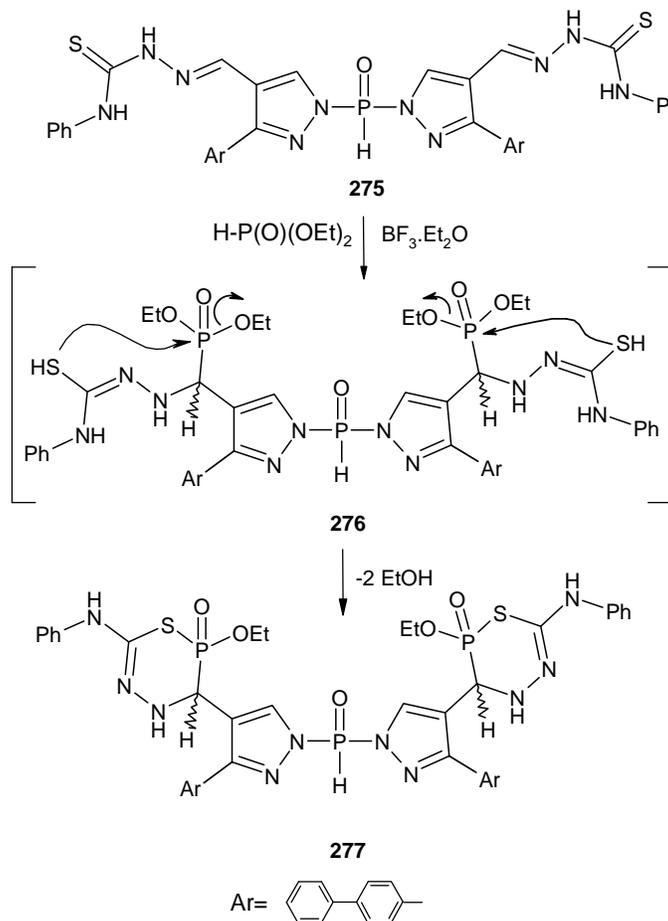
Scheme 85

The Pudovik reaction of hydrazone **272** using diethyl phosphite in boiling THF containing a catalytic amount of sodium hydride produced a cyclic α -aminophosphonate ester **274** as only one isomer (Scheme 86).¹³⁸



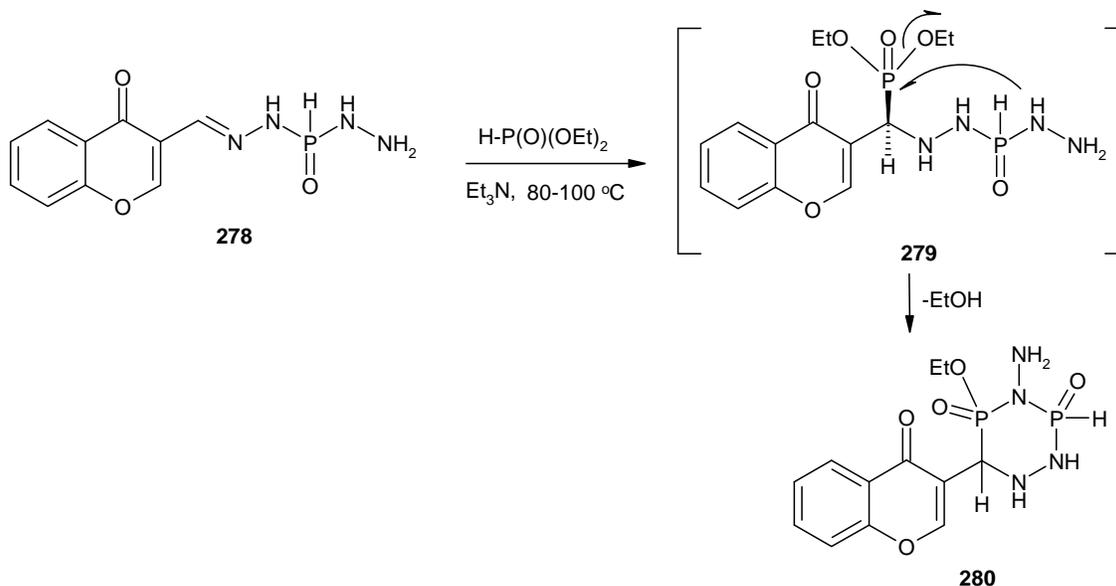
Scheme 86

Heterocyclization of bis-thiosemicarbazone **275** with diethyl phosphite at 80 °C in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ at 80 °C for 10 hours, afforded an interesting type of phosphorus heterocycle, namely *bis*-[3-(4'-biphenyl)-4-[2-ethoxy-6-phenylamino-2-oxo-3,4-dihydro-2*H*-1,4,5,2-thiadiazaphosphinin-3-yl]-1*H*-pyrazol-1-yl}phosphine oxide (**277**) (Scheme 87). The proposed mechanism for formation of **277** may occur *via* addition of the phosphorus atom of diethyl phosphite to the $\text{CH}=\text{N}_{\text{exocyclic}}$ groups to give the nonisolable intermediate **276**, which underwent cyclization by nucleophilic attack of SH groups at the phosphonate to eliminate two molecules of ethanol (Scheme 87).¹³⁹



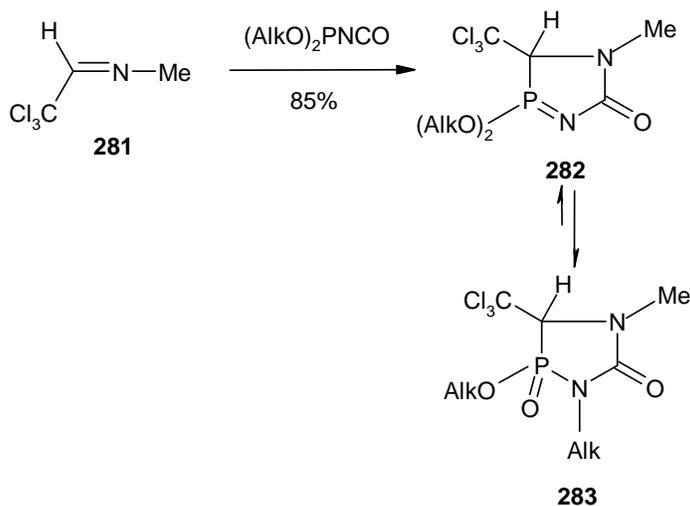
Scheme 87

Addition of diethyl phosphite to the azomethine bond of the hydrazone **278** required heating at 80-100 °C with triethylamine as a catalyst and gave 3-(4-amino-5-ethoxy-3,5-dioxo-1,2,4,3,5-triazadiphosphan-6-yl)-4*H*-chromen-4-one (**280**). Most likely, the addition led to intermediate **279** (not isolated), which underwent intramolecular cyclization *via* elimination of ethanol affording compound **280** (Scheme 88).¹⁴⁰



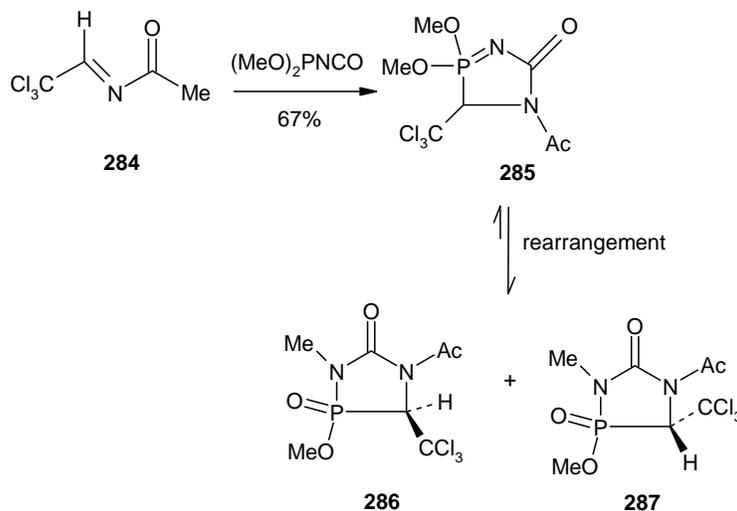
Scheme 88

4.1.2. Addition of isocyanatophosphite to acyclic imines. The phosphorylation pathway for (trichloroethanilydene)-N-methylamine **281** was determined by the nature of the phosphorus reagent. Thus, its reaction with trivalent phosphorus isocyanates as 1,3-dipole gave cyclic C-phosphorylated iminophosphoranes **282** which transformed into α -aminophosphonate **283** as a result of imide-amide rearrangement (Scheme 89).¹⁴¹



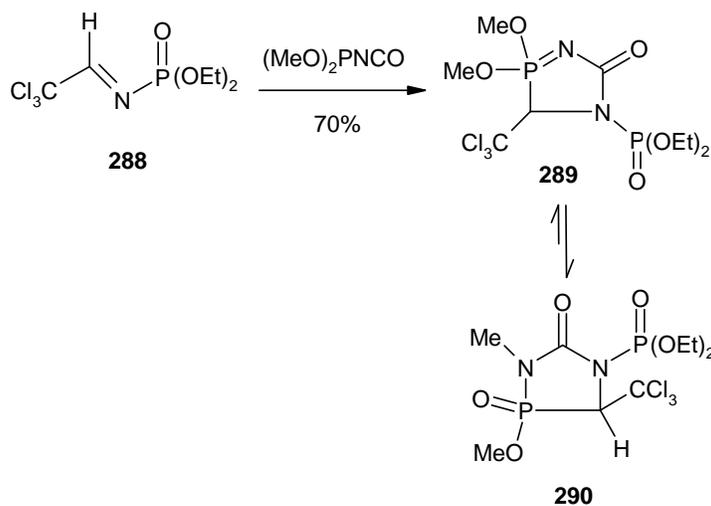
Scheme 89

Reaction of *N*-acetyl compound **284** with dimethyl isocyanatophosphite in benzene at 20-60 °C, gave the cycloadduct **285** which underwent imide-amide rearrangement leading to stereoisomeric diazaphospholanes **286** and **287** (Scheme 90).¹⁴²



Scheme 90

At the same time, dimethyl isocyanatophosphite reacted with imine **288** as a 1,3 dipole giving the diazaphospholanes **290** (Scheme 91).¹⁴²

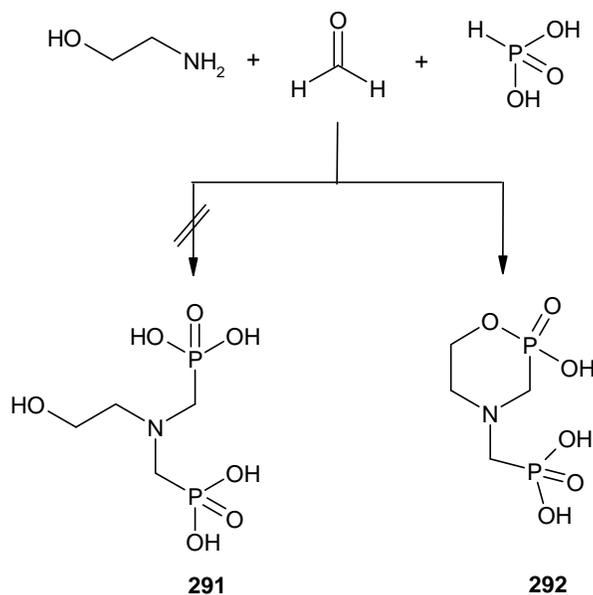


Scheme 91

4.2. Multicomponent reactions

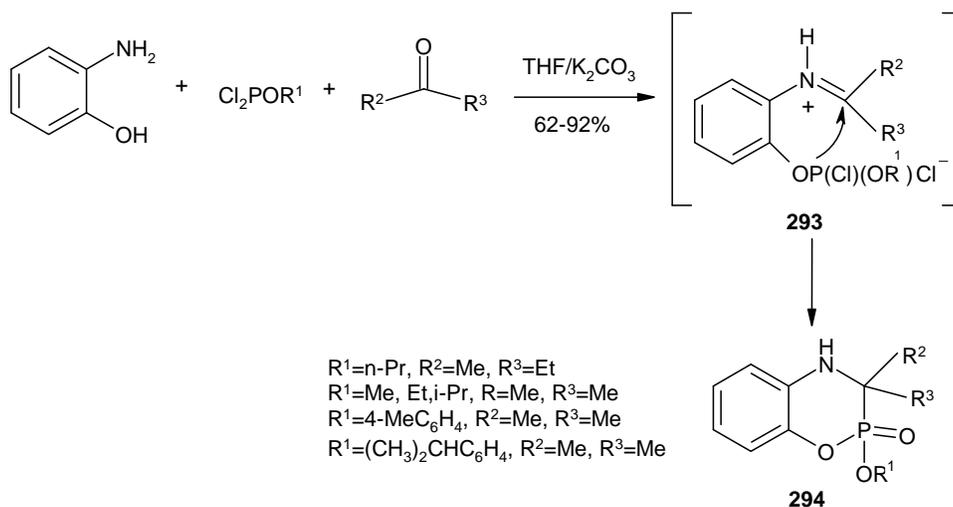
4.2.1. Reaction of carbonyl and aminoalcohols with phosphites (Kabachnik-Fields reaction). The Mannich type reaction between 2-aminoethanol and formaldehyde in an aqueous

solution of phosphorous acid did not result in the expected [(2-hydroxyethyl)imine]bis(methylphosphonic) acid **291** but in [(2-hydroxy-2-oxido-1,4,2-oxazaphosphinan-4-yl)methyl]phosphonic acid (**292**) as a product of an intramolecular condensation (Scheme 92).¹⁴³



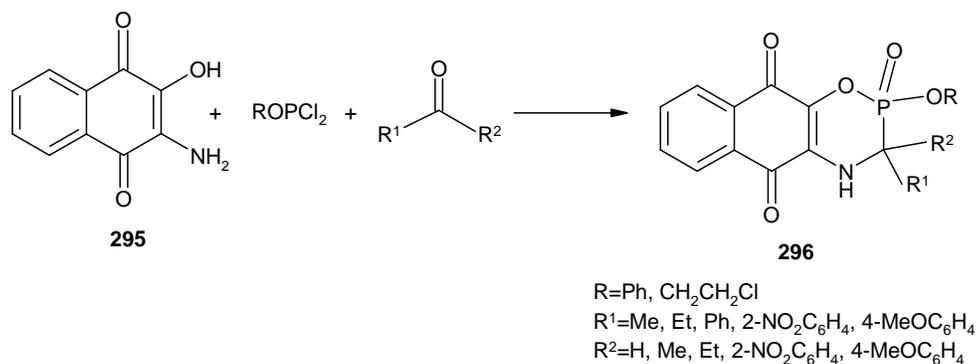
Scheme 92

2-Aminophenol was allowed to react with alkyl dichlorophosphinite and various substituted ketones or benzaldehyde in anhydrous tetrahydrofuran containing a small amount of potassium carbonate to give 2-alkoxy-2-oxo-1,4,2-oxazaphosphinane **294** in good yield. The reaction was carried out using a one pot procedure (Scheme 93).¹⁴⁴⁻¹⁴⁷



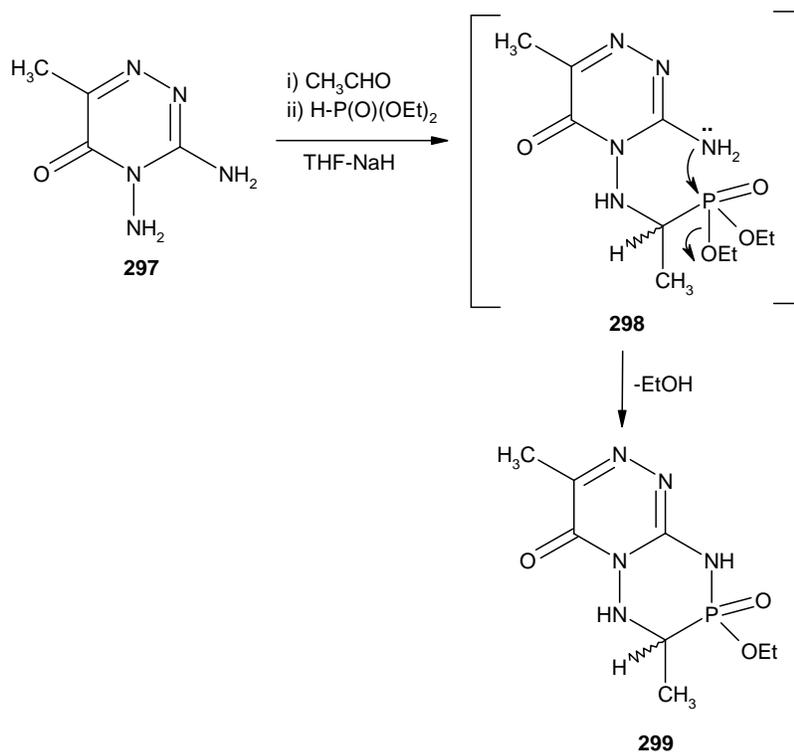
Scheme 93

Similarly, when the starting material 2-amino-3-hydroxy-1,4-naphthoquinone (**295**) reacted with phenyl phosphorodichloridite and ketone or aromatic aldehyde, 2-alkoxy/aryloxy-3,4-dihydro-2*H*-naphtho[2,3-*e*][1,4,2]oxazaphosphinane-5,10-dione 2-oxides (**296**) were obtained in 55-82% yields (Scheme 94).^{148,149}



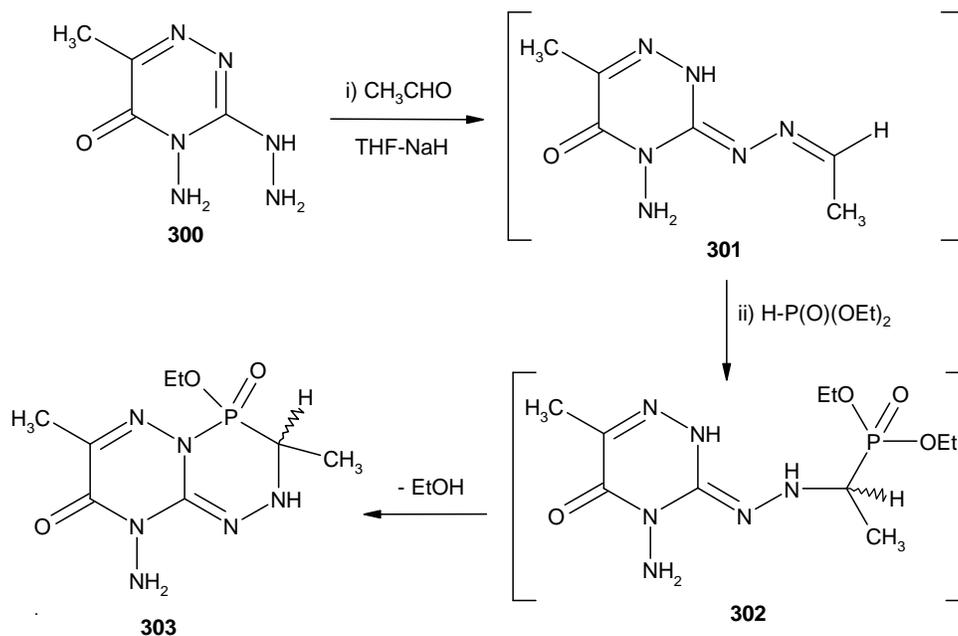
Scheme 94

The Kabachnik-Fields reaction using 3,4-diamino-6-methyl-1,2,4-triazin-5(4*H*)-one (**297**), acetaldehyde and diethyl phosphite in THF in the presence of sodium hydride as a catalyst led to only one isomer of 1,2,4-triazino[4,3-*b*][1,2,4,5]triazaphosphinine derivative **299** (Scheme 95).¹³⁸



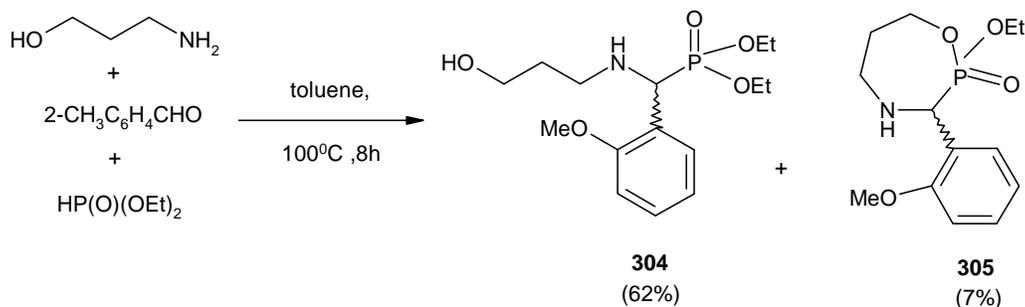
Scheme 95

The one-pot Kabachnik-Fields reaction of compound **300**, acetaldehyde and diethyl phosphite in THF containing sodium hydride as a catalyst produced one isomer of [1,2,4] triazino[3,2-*c*][1,2,4,5]triazaphosphinine **303**, *via* the nonisolable intermediate **302**, which spontaneously was cyclized through *N*-2 of the triazine ring and not the exocyclic *N*-amino, with elimination of a molecule of ethanol (Scheme 96).¹³⁸



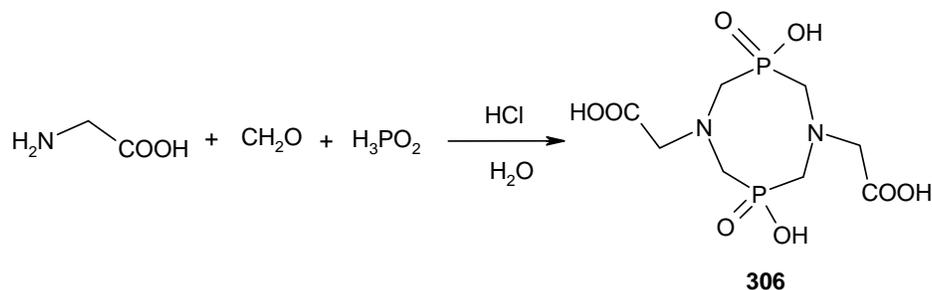
Scheme 96

Diethyl [[(3-hydroxypropyl)amino](aryl)methyl]phosphonate (**304**) and 1,4,2-oxaza-phosphepane derivative **305** were prepared by the Kabachnik-Fields reaction, realizing a three component combination of 3-aminopropanol, *o*-tolualdehyde and diethyl phosphite in toluene (Scheme 97).¹⁵⁰



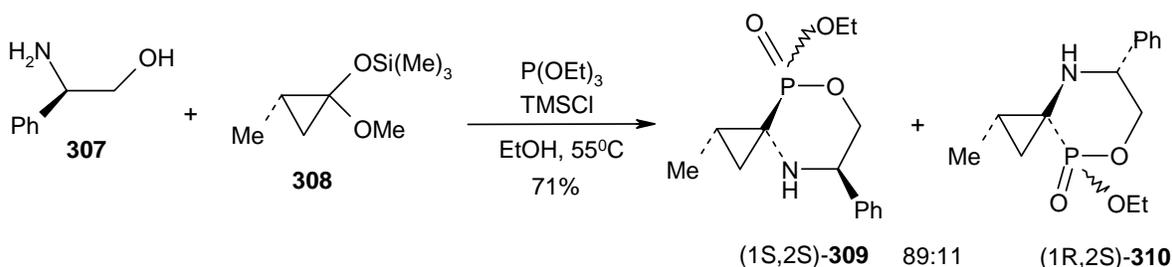
Scheme 97

The eight-membered 3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-diacetic acid (**306**) was obtained with a one step reaction of glycine, formaldehyde and hypophosphorous acid in acidic aqueous medium (Scheme 98).¹⁵¹



Scheme 98

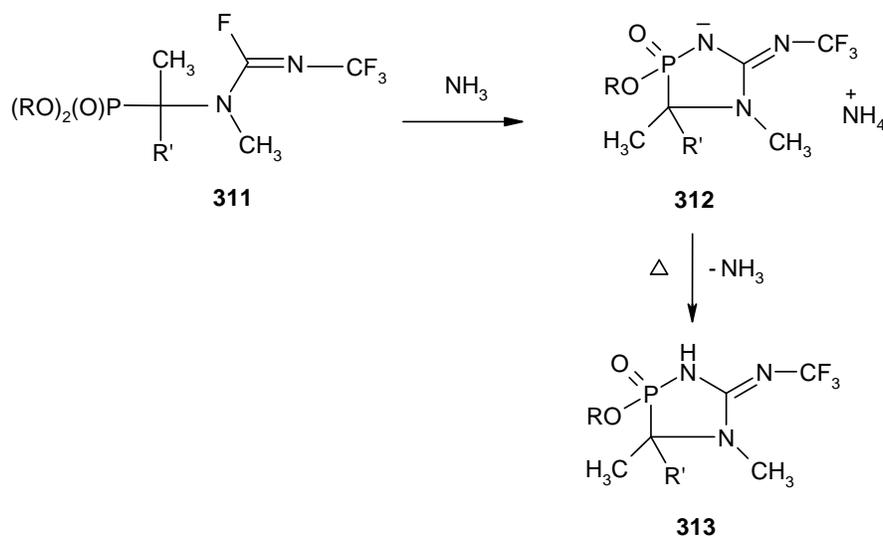
4.2.2. Reaction of cyclopropanone acetal and 1,2-aminoalcohols with phosphites. Reaction of (2*S*)-phenylglycinol (**307**) with cyclopropanone acetal (**308**) and triethyl phosphite gave the spirophosphonates **309** and **310** in low yield and in diastereoisomeric ratio 89:11 (Scheme 99).¹⁵²



Scheme 99

4.3. Ring closure of acyclic α -aminophosphonates

Fluorinated 1-methylaminoalkylphosphonates **311** reacted with NH_3 to form heterocyclic salts **312**, which underwent elimination of ammonia under heating to give the neutral 1,4,2-diazaphospholines **313** (Scheme 100).¹⁵³

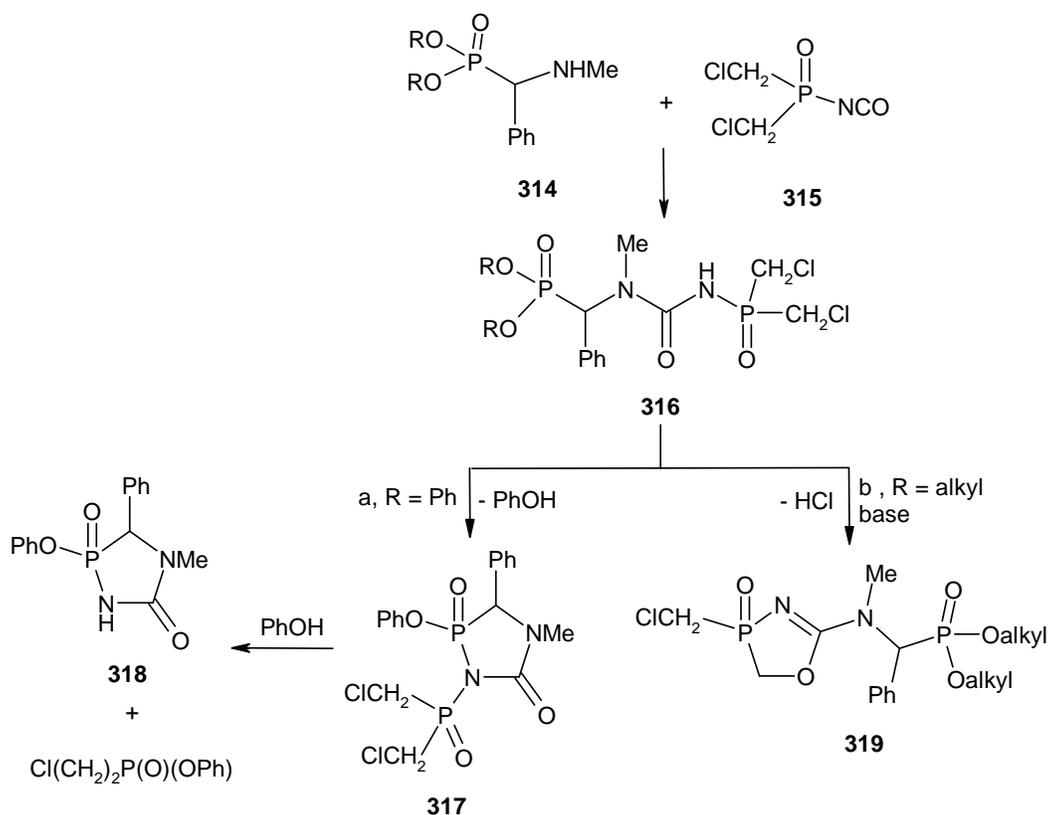


Scheme 100

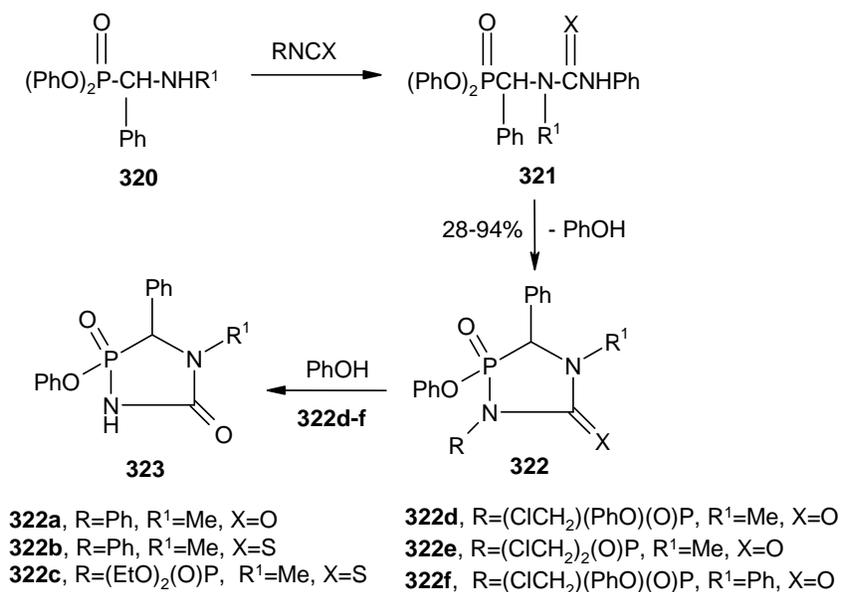
Phosphorylated urea **316** was obtained as the result of addition of α -aminoalkylphosphonates **314** to bis(chloromethyl)isocyanatophosphonate (**315**). Compound **316** can be cyclized in two ways: a) with elimination of phenol and formation of diazaphospholidine **317**, which under the action of phenol was converted into diazaphospholidine **318**. and b) in the presence of a base, intramolecular alkylation of oxygen atoms of carbonyl fragment by chloromethyl group took place with the formation of 1,3,4-oxazaphosphol-2-ines **319** (Scheme 101).¹⁵⁴

It was found that diphenyl (α -methylamino)benzyl phosphonate (**320**) readily underwent addition to different iso(thio)cyanates in the presence of a catalytic amount of triethylamine, yielding 1,3,4-diazaphospholidines **322a-e**. The reaction involved intermediate formation of N,N' -disubstituted (thio)ureas **321** which underwent fast cyclization by elimination of phenol. The labile exocyclic P-N bond of **322d,e** was cleaved upon the action of phenol to give the final product diazaphospholidine **323** (Scheme 102).¹⁵⁵⁻¹⁵⁷

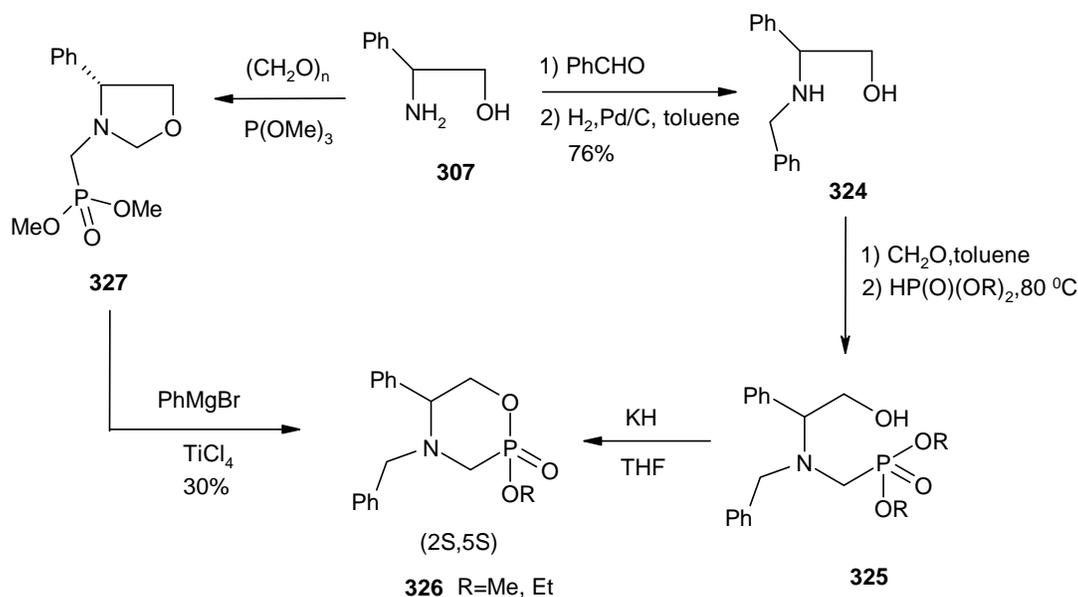
A highly diastereoselective synthetic procedure for the preparation of enantiopure (2*S*,5*S*)-4-benzyl-2-alkoxy-2-oxo-5-phenyl-1,4,2-oxazaphosphinanes [(2*S*, 5*S*)-1] (**326**) from (*S*)-phenylglycinol (**307**) was achieved by its condensation with benzaldehyde followed by palladium catalyzed hydrogenation to give *N*-benzyl-(*S*)-phenylglycinol (**324**). The latter compound was condensed with formaldehyde (toluene solvent) and the resulting imminium salt was immediately treated with dialkyl phosphite to afford Mannich products (*S*)-**325**. Treatment of carbinol (*S*)-**325** with KH in THF solution afforded cyclized products **326** in good yield (Scheme 103).¹⁵⁸ Also, compound **307** was treated with trimethyl phosphite and formaldehyde to give *N*-(phosphonomethyl)oxazolidine **327**. Treatment of **327** with phenyl magnesium bromide and in the presence of TiCl_4 gave directly the expected **326** (R=Me) but in low yield (Scheme 103).¹⁵⁹



Scheme 101



Scheme 102



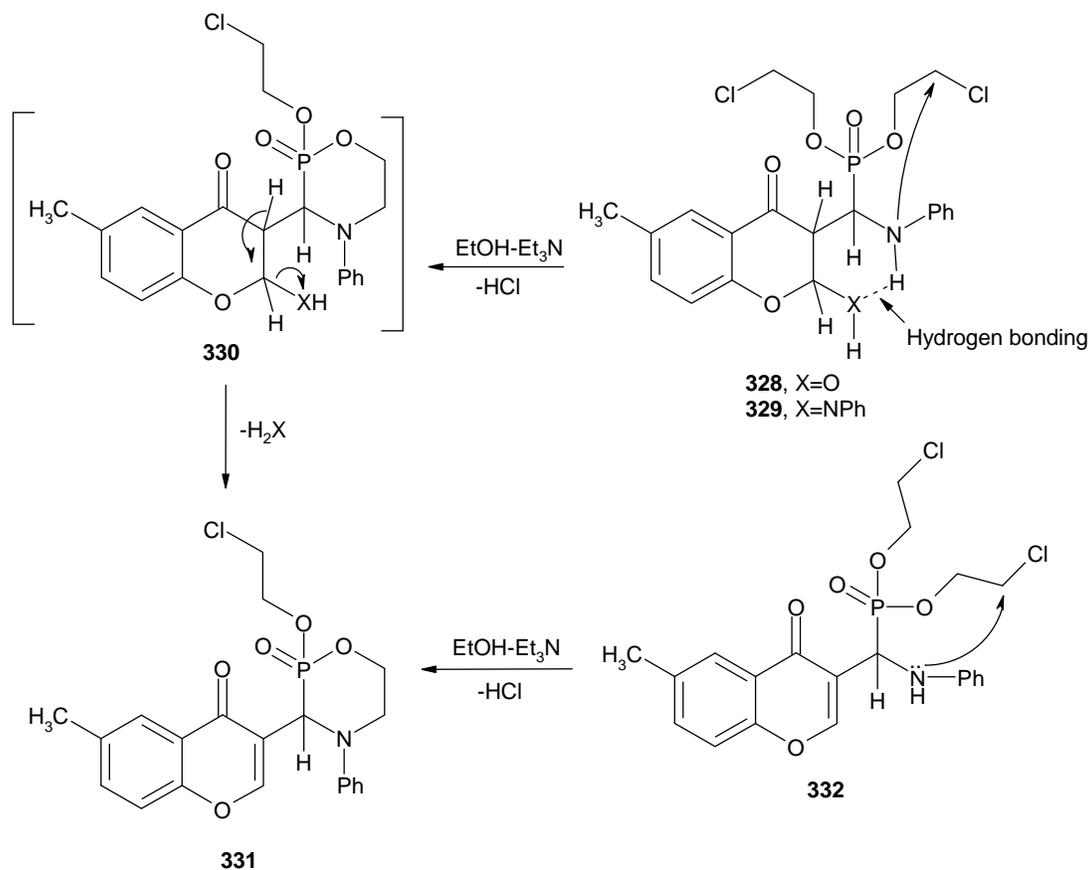
Scheme 103

Compounds **332**, **328** and **329** when heated in absolute ethanol containing a catalytic amount of triethylamine afforded 3-[2-(2-chloroethoxy)-2-oxo-4-phenyl-1,4,2-oxazaphosphan-3-yl]-6-methyl-4-oxo-4*H*-chromen-4-one (**331**). Formation of compound **331** is assumed to take place *via* loss of one HCl molecule from **332**, **328** and **329**, followed by elimination of both water and aniline in the case of **328** and **329**, respectively. Hydrogen bonding between XH and NH groups gives stability to systems **328** and **329**, but destruction of this hydrogen bond, after removing a molecule of HCl, may facilitate elimination of water and aniline (Scheme 104).³³

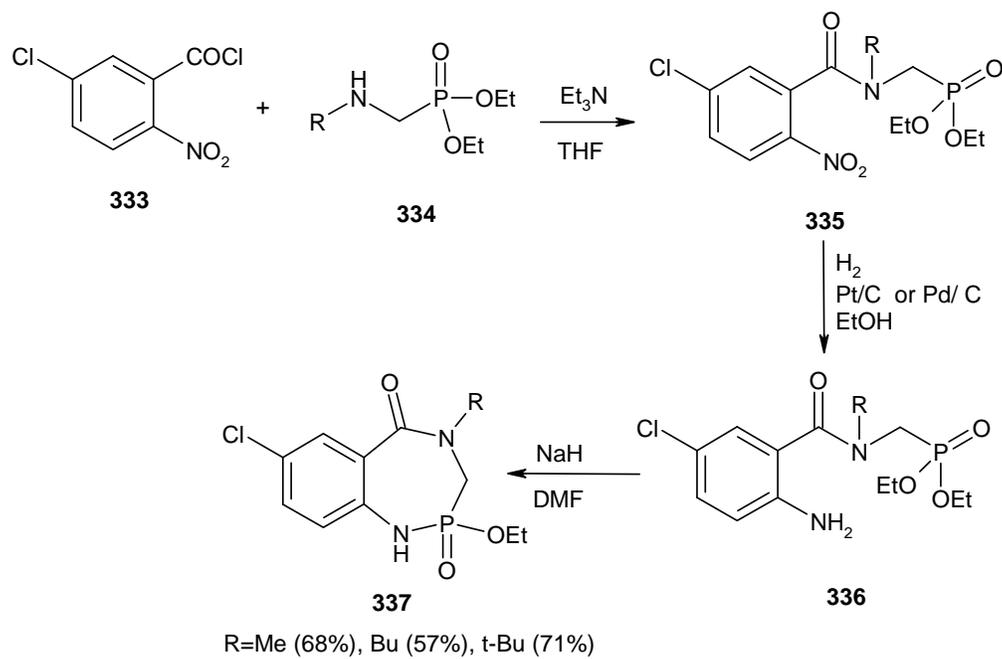
5-Chloro-2-nitrobenzoyl chloride (**333**) was reacted with α -aminophosphonate **334** to afford the nitroamide **335**. Catalytic hydrogenation of **335** gave the cyclization precursor **336**. Reacting a DMF solution of **336** with NaH followed by warming to 60 °C for a few hours, affording 4-alkyl-7-chloro-2-ethoxy-2,3-dihydro-2-oxido-1*H*-1,4,2-benzodiazaphosphepin-5 (*4H*)-ones (**337**) (Scheme 105).¹⁶⁰

4.4. Miscellaneous

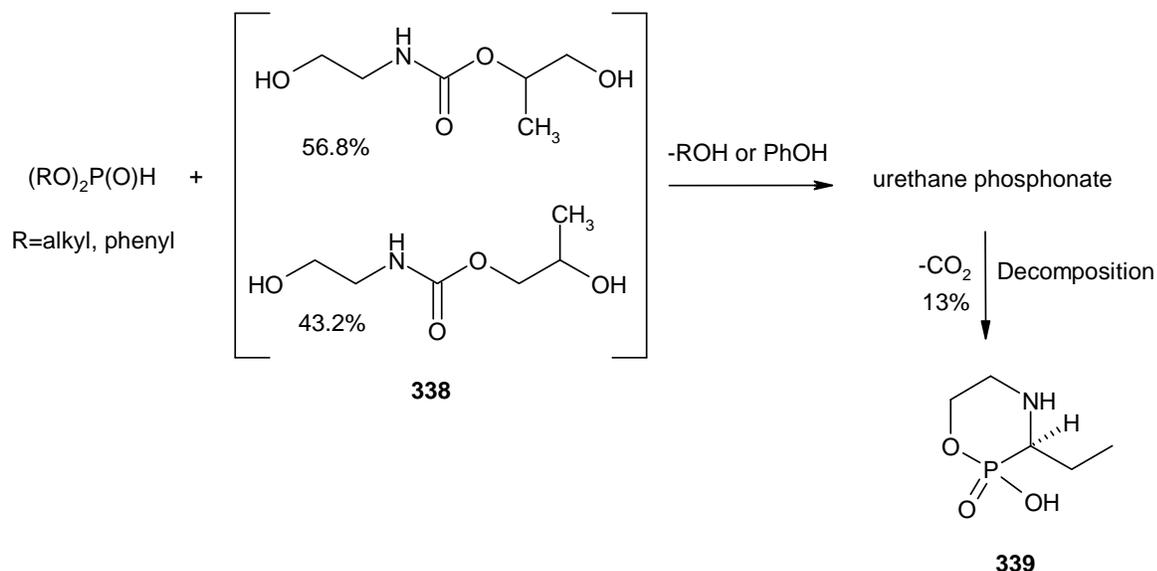
4.4.1. Reaction of dialkyl/diphenyl phosphite with hydroxyl alkyl carbamate. 3-Ethyl-2-hydroxy-2-oxo-1,4,2-oxazaphosphorinane (**339**) was obtained by treating various phosphonic acids diesters with hydroxyl alkyl carbamate mixtures **338**. During the first stage of the reaction at 135 °C, transesterification occurred to give urethane phosphonates. In the second stage of the reaction at 170 °C, thermal decomposition of urethane phosphonate led to selective isolation of (**339**) in low yield (Scheme 106).¹⁶¹⁻¹⁶³



Scheme 104



Scheme 105



Scheme 106

5. Conclusions

This review summarizes most synthetic methods giving rise to cyclic α -aminophosphonates. It focuses on the synthesis of cyclic α -aminophosphonic acids and their esters which contain at least two atoms. *i.e.* C–P, C–N or P–C–N, of the P–C–N system, in the heterocyclic system. The review is built up according to the three linkage types and starting with the smallest rings of each type.

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