Synthesis of β-Aminophosphonates and -Phosphinates

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1. Introduction

Organophosphorus compounds are important substrates in the study of biochemical processes,[1] 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 interest in 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.[2,3] In this area, β-aminophosphonic acids **2** ($R^2 = H$, $R^3 = OH$), as isosteres of β-amino acids **1** (Scheme 1) occupy an important place and reveal diverse and interesting biological and biochemical properties: antibacterial agents,[4] enzyme inhibitors,[5] haptens for catalytic antibodies,[6] or anti HIV agents.[7]

In 1959 Horiguchi and Kandatsu[8] first described the isolation of 2-aminoethylphosphonic acid (AEP) **2** ($R = R^1 = R^2 = H$, $R^3 = OH$) (Scheme 1) from *Celiate protozoa*. Biosynthetic reactions creating C−P bonds have been used for the synthesis of 2-amino-

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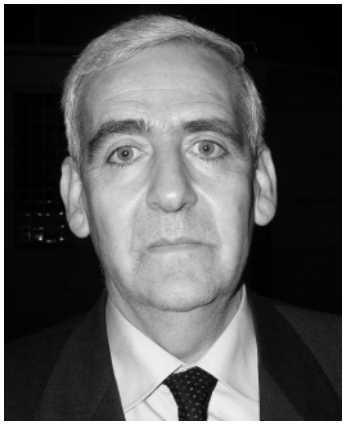


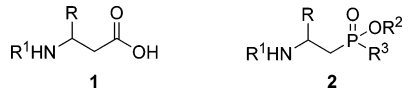
Francisco Palacios was born in Vitoria, Spain (1951). He graduated in Chemistry from the University of Zaragoza and received his Ph.D. degree at the University of Oviedo in 1977 under the supervision of Prof. Dr. José Barluenga. After 2 years (1979–1981) of postdoctoral work with Prof. Dr. Rolf Huisgen at the Organic Chemistry Institute of Ludwig University (Munich, Germany) working on cycloaddition reactions, he came back to the University of Oviedo as Assistant Professor and became Associate Professor in 1983 at the same university. Since 1991 he has been Full Professor of Organic Chemistry at the University of the Basque Country. He has held visiting professorships at the Ecole Nationale Superière de Chimie of Montpellier (2003). His research interests are organic synthesis, organophosphorus chemistry (phosphorus ylides, phosphine oxides, aminophosphonates), heterocyclic chemistry, cycloaddition reactions (azadienes and 1,3-dipoles), and solid-phase synthesis.

Concepción Alonso was born in Vitoria-Gasteiz, Spain, in 1968. She received her B.Sc. degree in Chemistry from the University of Valladolid in 1991 and Ph.D. degree in Chemistry from the University of Basque Country in 1998, the latter under the supervision of Professor Francisco Palacios. From 1998 to 1999 she stayed at the University of California at Davis as a postdoctoral fellow under the supervision of Professor Mark J. Kurth. After her return to Spain she has worked as a postdoctoral fellow with Professor Francisco Palacios at the University of the Basque Country. Her current research interest is focused on development of new reactions and methods for the synthesis of small organophosphorus molecules by solid-phase and combinatorial chemistry.

ethylphosphonates or -phosphinates from biological sources.[9] Since then β-aminophosphonic acid (AEP) has been isolated from various living organisms and a new area of biochemistry has grown up around these compounds, though the biosynthesis of these naturally occurring phosphonates has not yet been fully explained. Hammerschmidt described in several accounts the biosynthesis and transformations of 2-aminoethylphosphonic acid (AEP) and its derivatives from *Acanthamoeba castellanii*[10] and *Thetrahymena thermophila*.[10e]

Jesús M. de los Santos was born in 1966 in Mondragón (Guipúzcoa, Spain). He graduated in Chemistry from the University of the Basque Country in 1990 and received his Ph.D. degree in 1996 under the supervision of Professor F. Palacios. He was awarded with the Ph.D. Extraordinary Prize for his dissertation on the chemistry of β-functionalized phosphorus compounds. He then stayed 2 years at Penn State University with Professor Steven M. Weinreb as a postdoctoral fellow working on the total synthesis of marine alkaloids. He returned to the University of the Basque Country as a Junior Scientist and then became Research Associate in 2003. His current research interest is focused on development of a new synthetic methodology in organic chemistry which includes the chemistry of nitrogen- and phosphorus-containing compounds for the preparation of acyclic and cyclic compounds as well as the solid-phase synthesis of small organic molecules.

Scheme 1

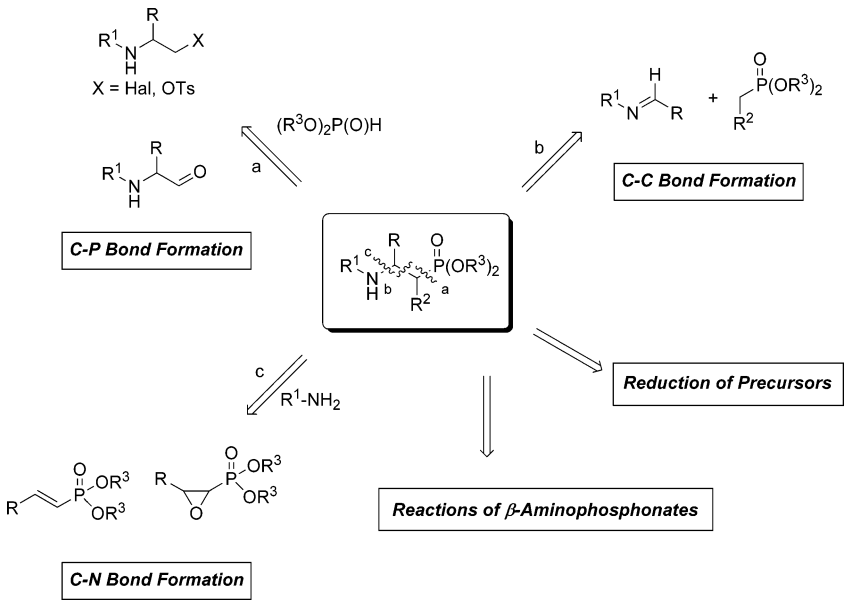


The development of methods for the preparation of aminophosphonic (or phosphinic) acids is important and currently attracting growing interest. A lot of general synthetic methods exist for the preparation of α-aminophosphonic acid derivatives, including efficient asymmetric syntheses.[11] However, β-aminophosphonic acid derivatives have been scarcely described. This review will focus on the synthesis of β-aminophosphonic (R^3 = OH) and β-aminophosphinic acids (R^3 = H, R) and their derivatives **2** (Scheme 1). Depending on the type of bond formed in the reaction, some strategies for the preparation of these derivatives can be highlighted (Scheme 2): section 2 outlines their preparation through carbon−phosphorus bond construction (route a). Sections 3 and 4 deal with their construction through carbon−carbon (route b) and carbon−nitrogen bond formation (route c). Sections 5 and 6 deal with conversion of other nitrogen functional groups present in phosphonates and phosphinates into the amino moiety, and finally in section 7 attention is drawn to reactions of functionalized β-aminophosphonates. At the end of the manuscript a table containing the biological activity of some representative examples of β-aminophosphonates and phosphinates is included.

2. Carbon–Phosphorus Bond-Formation Reactions

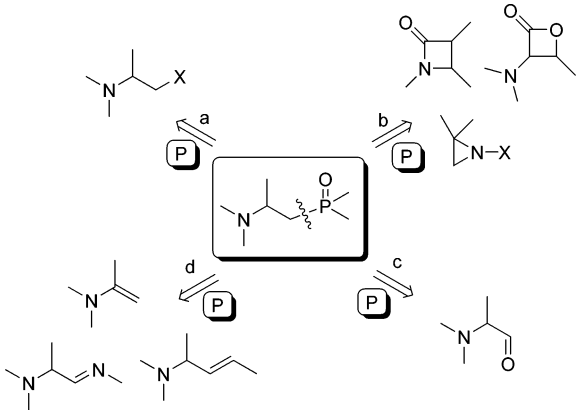
One of the most often used reactions for the synthesis of β-aminophosphonates and -phosphinates is the carbon−phosphorus (C−P) bond-formation

Scheme 2



process (Scheme 2, route a). Several papers have been published on the formation of β-aminoethylphosphonates and -phosphinates through this strategy. This section will concentrate on the most practical routes for the synthesis of target compounds (Scheme 3)

Scheme 3

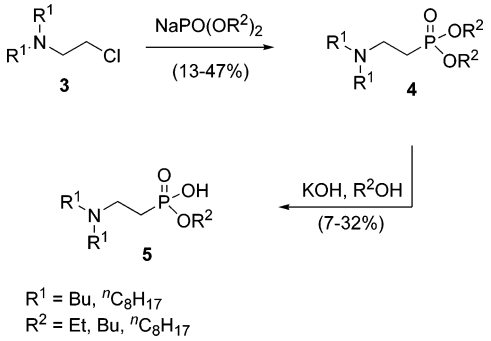


which are as follows: alkylation of phosphorus reagents (route a), nucleophilic addition of phosphorus derivatives to strained heterocycles (route b), hydrophosphinylation of α-amino aldehydes (route c), and addition of phosphorus derivatives to C−C and C−N double bonds (route d).

2.1. Reactions of β-Aminoalkyl Halides with Phosphorus Reagents

Arbuzov reaction of phosphites with alkyl halides[9b] represents a simple route for the preparation of β-aminophosphonic or -phosphinic acid derivatives via a carbon−phosphorus bond-forming process (Scheme 3, route a). This strategy afforded one of the first syntheses of β-aminoethylphosphonic acid (AEP).[12] Likewise, *N*,*N*-disubstituted dialkyl 2-aminoethylphosphonates **4** and their derivatives could be prepared by reaction of dialkyl(2-chloroethyl)-amines **3** with the sodium salt of dialkylphosphonate (Scheme 4). Yields were generally lower than those

Scheme 4

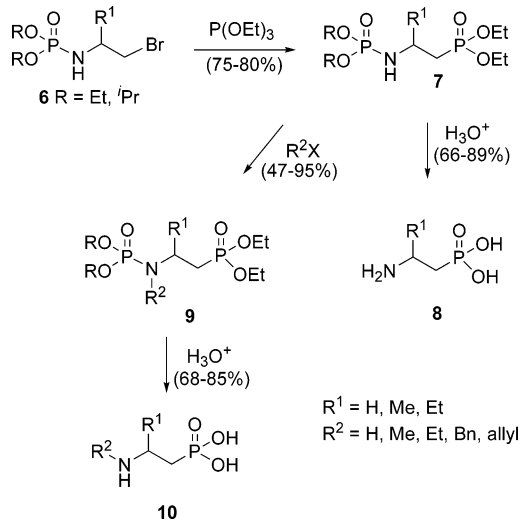


obtained with other methods; however, the starting chloroamines **3** were obtained by known procedures. Hydrolysis of only one of the phosphonate esters can be performed by heating with potassium hydroxide, affording the corresponding phosphonic acid derivatives **5**.[13]

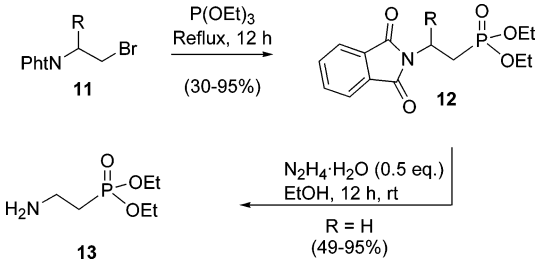
β-Aminoalkylphosphonic acids were also prepared via phosphorus-protected amino alkyl halides. *N*-Phosphonyl haloamines **6** were obtained by phosphorylation of β-bromoalkylamines with diethyl (R = Et)[14] or diisopropyl (R = ^{i}Pr)[15] chlorophosphates. Reaction of the resulting haloalkylphosphoramidates **6** (R = Et, ^{i}Pr) with triethyl phosphite gave a phosphoramidate **7** (Scheme 5). *N*-Deprotection of **7** with acid led to the formation of β-aminophosphonic acid **8**, while the intermediate **7** could be alkylated with alkyl halides, affording *N*-substituted β-aminophosphonates **9** and -phosphonic acids **10**.

Commercially available *N*-protected haloamines such as *N*-(bromoethyl)phthalimides **11** were converted to phthaloylaminophosphonates **12** in near quantitative yields by the well-known Michaelis−Arbuzov[16] reaction by refluxing with triethyl phosphite (Scheme 6). The *N*-substituted phthaloyl-β-aminophosphonate **12** (R = H) was dephthaloylated to β-aminoethylphosphonate **13**.[17] This process has also been used for the synthesis of optically pure 2-substituted diethyl esters of (phthalimidoethyl)-**12**

Scheme 5



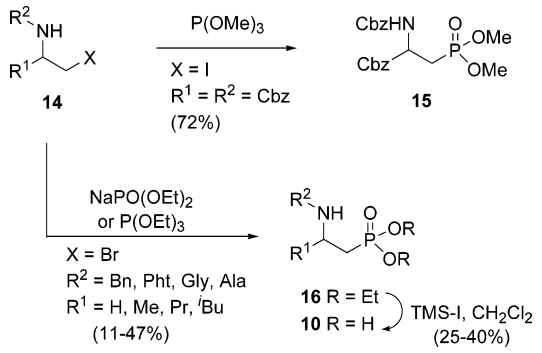
Scheme 6



and 2-aminoethylphosphonic acid (AEP).[18] A nucleophile-assisted ring-opening reaction of phthalimide **12** (R = H) with hydrazide hydrate afforded amide-functionalized novel bis-phosphonates.[17]

On the other hand, the free aminophosphonic acids or their derivatives can be prepared by Arbuzov reaction of *N*-protected aminoalkylhalides. Compound **14** ($R^1 = R^2$ = Cbz, X = I) was converted to the dimethylphosphonate **15** by treatment with trimethyl phosphite under removal of MeI.[19] Bromo derivatives **14** (X = Br) were phosphonated using sodium diethyl phosphite or triethyl phosphite to give functionalized *β*-aminophosphonate **16** (R = Et) (Scheme 7).[20] Afterward, the blocking groups were

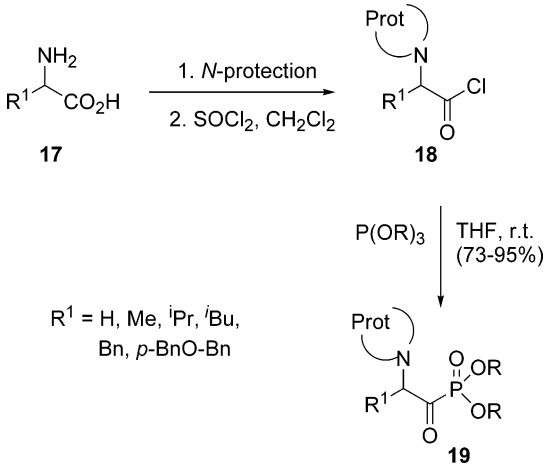
Scheme 7



removed selectively to give the free aminophosphonic acids **10** (R = H). Small phosphonopeptides **10** (R^2 = Gly, Ala) can also be prepared by this route from analogous peptides (Scheme 7).

Extension of the methodology used for alkyl halides to functionalized acyl halides allowed the preparation of *β*-amino-α-ketophosphonates. Treatment of *N*-protected amino acid **17** with thionyl chloride gave the corresponding acid chloride **18,** which on reaction with trialkyl phosphite gave the corresponding α-ketophosphonate **19** (Scheme 8).[21] Also, Arbuzov reac-

Scheme 8

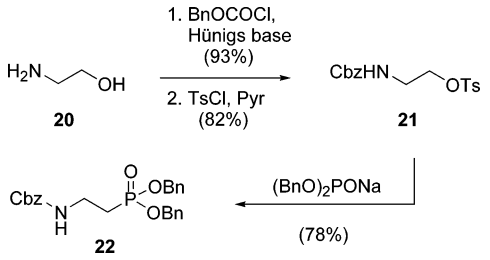


tion of triethyl phosphite with optically active acid chlorides **18** afforded α-ketophosphonates **19**.[22]

2.2. Substitution Reactions

Alkylation of phosphonates or phosphinates can also be performed with *β*-amino alkyl tosylates. Ethanolamine **20** was converted to tosylate **21**; subsequent treatment with sodium dibenzyl phosphinate gave Cbz-*N*-protected dibenzyl (2-aminoethyl)phosphonate **22** in 78% yield (Scheme 9).[23]

Scheme 9



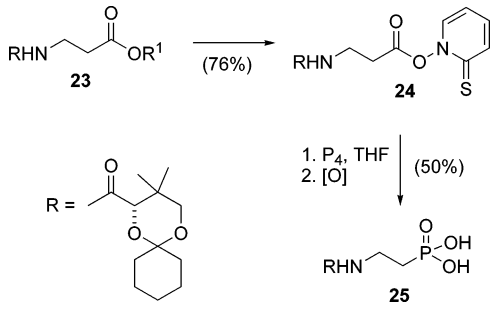
Through a similar process sphingosine can be selectively transformed into sphingosine-1-phosphonate by Michaelis−Arbuzov reaction with trimethyl phosphite and after removal of all protective groups.[24]

A special procedure for the synthesis of phosphonic acids consisted of reaction under inert atmosphere conditions of white phosphorus in tetrahydrofuran with radicals derived from amino acids. Each P_4 molecule can add up to two carbon radicals derived from Barton PTOC esters **24** (Scheme 10) whose posterior oxidation with H_2O_2 gave phosphonic acids **25**.[25] The reaction is initiated by trace amounts of oxygen and strongly inhibited by TEMPO.

2.3. Nucleophilic Addition of Phosphorus Derivatives to Small Heterocycles

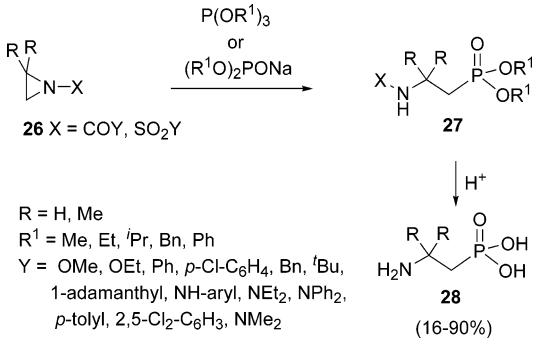
Ring opening of three- or four-membered strained nitrogen heterocycles can also be used for the prepa-

Scheme 10



ration of β-aminophosphorus derivatives (Scheme 3, route b). Nucleophilic addition of phosphites or phosphonates to *N*-acyl or *N*-tosyl aziridines **26**[26] produced dialkyl 2-aminoethylphosphonates **27**[27] via ring opening of the strained aziridine ring. Hydrolysis of esters **27** with concentrated acid gave aminoethylphosphonic acids **28** (Scheme 11). A broad variation

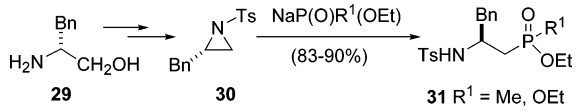
Scheme 11



of *N*-acylated or *N*-sulfonated esters of 2-aminoethylphosphonic acids were also obtained in good yields by reaction of sodium salts of diesters of phosphoric acid with *N*-acylaziridines and *N*-sulfonylaziridines.[28]

Following this strategy the first efficient synthesis of optically active 2-aminoalkylphosphinic and -phosphonic acids from 2-amino alcohols was reported.[29] Optically pure aziridine **30**, easily prepared from 2-amino alcohol **29**, was treated with excess sodium ethyl methylphosphinate (R^1 = Me) or diethyl phosphonate (R^1 = OEt) in THF at room temperature (Scheme 12). *N*-Tosylaminophosphonic or phosphinic

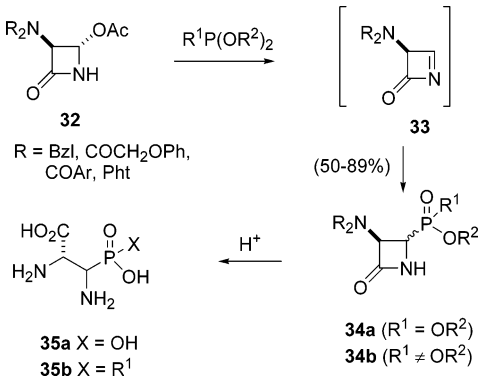
Scheme 12



acid derivatives **31** were obtained in good yields through a nucleophilic attack on the cyclic *N*-tosylaziridine intermediate.

Addition of phosphites or phosphonates to four-membered heterocycles such as β-lactams or β-lactones and subsequent ring opening to afford α,β-diaminophosphonic acids was achieved. Reaction of 4α-acetoxy-3β-phthalimidoazetidin-2-one **32** with a variety of phosphites and phosphinates gave the corresponding *cis*-4-oxoazetidin-2-ylphosphonates and a cis/trans mixture of 4-oxoazetidin-2-ylphosphinates **34** (95:5, cis/trans; R^1 = OR^2, 1:1, cis/trans; R^1 ≠ OR^2)

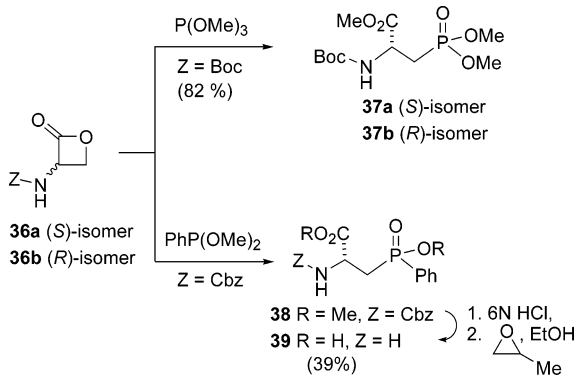
Scheme 13



(Scheme 13).[30] Subsequent hydrolysis provided a new route to α,β-diaminophosphonic and α,β-diaminophosphinic acids **35**. However, for Satoh et al. the major product obtained was the trans isomer.[31] These reactions suggested that displacement reactions of these substrates involve the imine **33** as an intermediate, which may undergo nucleophilic attack by phosphorus reagents preferentially from the less hindered side. Analogously, β-hydroxy azetidinium salts were converted into the corresponding β-amino-α-phosphorus-functionalized phosphonates by reaction with 2 equiv of R$^1_2$P(O)H in the presence of 2.1 equiv of NaH.[32]

In a similar way, β-aminophosphonates and -phosphinates have been synthesized using the β-lactone methodology originally developed by Vederas.[33] Nucleophilic addition of trimethyl phosphite to optically active (*S*)-*N*-Boc-3-amino-2-oxetanone **36a** gave (*S*)-methyl *N*-(*tert*-butoxycarbonyl)-2-amino-3-(dimethylphosphono)propanoate **37a** in excellent yields,[34] while the addition of trimethyl phosphite to (*R*)-enantiomer **36b** afforded the (*R*)-aminophosphonate **37b** (Scheme 14). Likewise, the β-lactone was opened using di-

Scheme 14

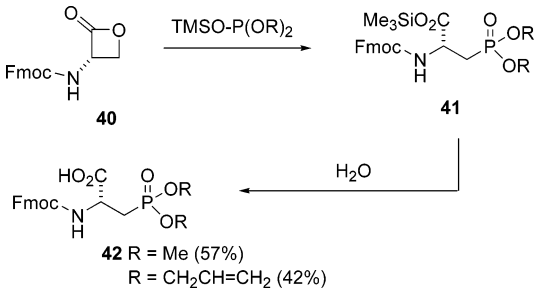


methyl phenyl phosphonite. The methyl ester **38** was obtained due to migration of one of the methyl groups from the phosphonite onto the carboxylate produced on ring opening. Acid hydrolysis gave β-aminophosphinic acid **39** containing an acid group in the β position.[35]

Silyl phosphites are more nucleophilic than alkyl phosphites, and the transfer of a silyl group is favored toward the alkyl groups in the Arbuzov reaction. Therefore, reaction of dimethyl(trimethylsilyl)phosphite (R = Me) with lactone **40** led specifically to

carboxylic trimethylsilyl ester **41** (R = Me) by preferential transfer of the trimethylsilyl group. Subsequent hydrolysis gave the *N*- and *P*-protected free carboxylic acid **42** (R = Me).[36] By a general Fmoc solid-phase peptide synthesis a phosphonic acid isostere of aspartic acid was incorporated into a peptide sequence.[37] Reaction between lactone **40** and neat silylated phosphite (R = $CH_2CH{=}CH_2$) followed by aqueous work up yielded the diallylester **42** (R = $CH_2CH{=}CH_2$) (Scheme 15).

Scheme 15

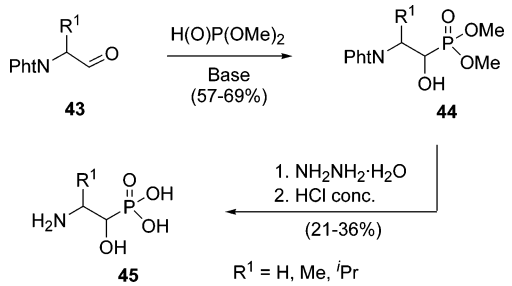


2.4. Hydrophosphinylation of α-Amino Aldehydes

Nucleophilic addition of phosphites and alkyl alkylphosphinates to amino-functionalized aldehydes or ketones in the presence of base[38] or by Lewis-acid-mediated catalysis[39] constitutes an important entry to β-amino-α-hydroxy phosphonic and phosphinic acid derivatives (Scheme 3, route c). Optically active α-aminoaldehydes[40] can be obtained from the respective amino acids. Therefore, stereogenic carbon−phosphorus bond-formation processes of α-aminoaldehydes with phosphorus nucleophiles allow stereoselective introduction of additional bioisosteres (phosphonic and phosphinic functional groups) to the α position in the β-amino alcohol moiety. Following this strategy the synthesis of a potent inhibitor of human renin[41] and HIV protease[42] has been reported. These β-amino-α-hydroxyphosphonates are valuable intermediates for the preparation of *cis*-aziridines[43] or more elaborate compounds as phosphonic acid analogues of norstatine inhibitors.[44]

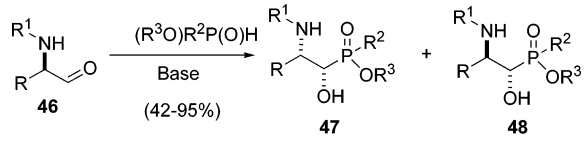
Simple 2-amino-1-hydroxyethylphosphonic acid **45** (R^1 = H) and its alkyl-substituted derivatives were prepared for the first time by the reaction of *N*-(2-oxoethyl)phthalimide **43** and dimethyl phosphite in excess in the presence of base.[45] Subsequent removal of phthaloyl group by treatment with hydrazine hydrate and hydrolysis with concentrated HCl gave the corresponding 2-amino-1-hydroxyethylphosphonic acids **45** (Scheme 16).

Scheme 16



Addition of dialkyl phosphites (R^2 = OR) or phosphinates (R^2 = alkyl or aryl) to racemic aldehydes **46** afforded a mixture of diastereomeric phosphonates and phosphinates **47** and **48**.[38,46] The separation of these diastereomers by means of silica-gel chromatography failed. However, when optically pure *N*-protected-α-aminoaldehydes **46** were used, the corresponding β-amino-α-hydroxyphosphonates or -phosphinates were obtained with high diastereoselectivity (Scheme 17). In some cases, the stereoselectivity of

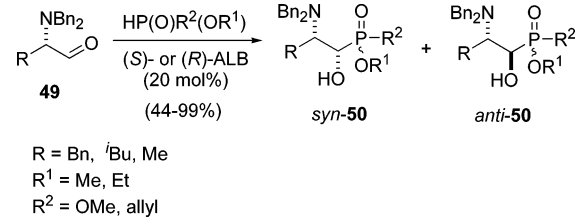
Scheme 17



this process was dependent on the reaction conditions. The use of DBU in dimethyl formamide gave essentially an equimolecular ratio of the syn and anti diastereoisomers.[47] Employing potassium fluoride as a base in DMF[41,48] or Et_3N as a base in benzene[49] favored stereoselection in the formation of *syn*-**47** isomer. β-Amino-α-hydroxyphosphonates and phosphinates, building blocks for the synthesis of novel peptidyl phosphorus derivatives such as inhibitors of Human Calpain I, have also been synthesized through hydrophosphinylation of Boc-Leu-H with dialkyl phosphites employing KF as base.[50]

Several literature reports[51] have noticed the predominance of the anti products in nucleophilic additions to *N*,*N*-disubstituted α-aminoaldehydes unlike to *N*-monosubstituted analogues, which afforded syn isomers as the major products. Moreover, a highly diastereoselective synthesis of β-amino-α-hydroxyphosphonic acid derivatives was achieved by Lewis-acid-mediated hydrophosphinylation.[39c] The stereochemical outcome of the reaction can be controlled in either an anti- or a syn-selective manner by tuning the chirality of catalyst. While the use of ethyl ethylphosphinate ($R^1 = R^2$ = Et)[39a] or ethyl allylphosphinates (R^1 = Et, R^2 = $CH_2CH{=}CH_2$)[39b] in the presence of (*R*)-ALB (AlLi-bis(binaphthoxide)) gave adducts **50** with poor selectivity, (*S*)-ALB gave **50** with anti selectivity (Scheme 18).[39a,39b] Tuning the

Scheme 18

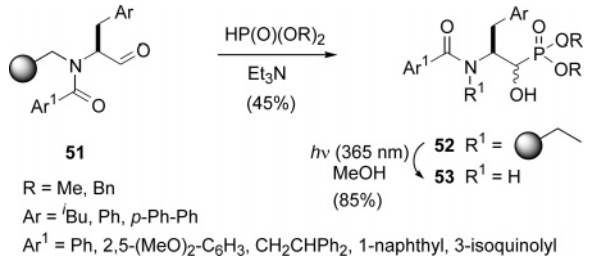


phosphorus nucleophile to ethyl phosphinate (R^1 = Et, R^2 = H) gave rise to high syn selectivity when performing the reaction with (*R*)-ALB.[39a,52] On the other hand, although reactions in the presence of

PhOLi as catalyst have provided moderate anti selectivity compared to the case of ALB, PhOLi possesses sufficient catalytic activity to promote the reaction even at −40 °C.[53] Recently, this reaction was extended to *N*-Boc-prolinal, and both diastereoisomers were obtained in very high yield in a ratio of 2:1 when these optically active aminoaldehydes reacted with dimethylphosphinate in the presence of DBU.[54]

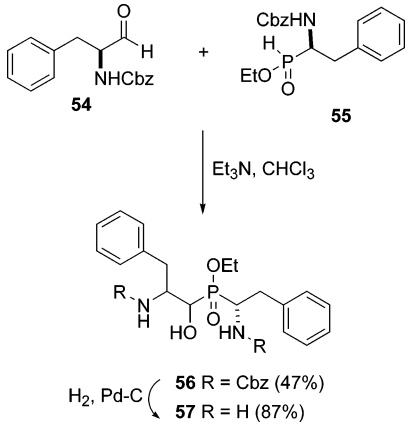
Solid-phase synthesis of β-amino-α-hydroxyphosphonates **53** by hydrophosphinylation of resin-bound *N*-acylated aminoaldehydes **51** has recently been reported.[55] Treatment of resin-bound aldehyde **51** (e.g., alaninal, leucinal, substituted phenylalaninal acylated with electron-rich/deficient aroyls, heteroaroyls, substituted acyls) with commercially available dialkyl and dibenzyl phosphites using Et_3N as base followed by photolysis furnished the α-hydroxydimethylphosphonates **53** with diastereomeric ratios ranging from 1:1 to 3:1 (Scheme 19).

Scheme 19



This strategy has been applied by Stowasser et al.[42] for the synthesis of a powerful inhibitor **57** of HIV protease derived from a β-amino-α-hydroxyphosphinopeptide. This compound was prepared by nucleophilic addition of phosphinic acid derivative **55** to Cbz-protected (*S*)-phenyl alaninal **54** (Scheme 20).

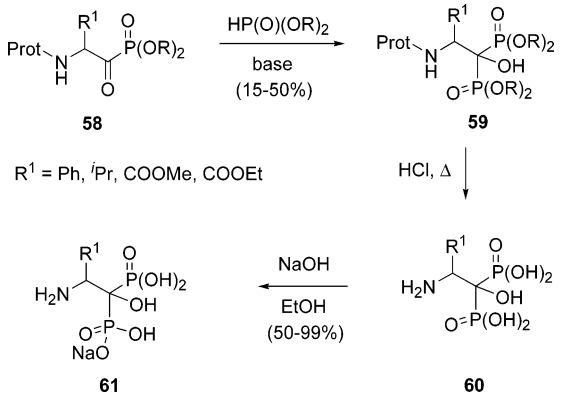
Scheme 20



Base catalysis with Et_3N gave adduct **56** as mixture of three major diastereoisomers in a ratio of 3.4:1.7:1. Deprotection of Cbz group gave β-amino-α-hydroxyphosphinopeptide **57**.

Synthesis of 2-amino-1-hydroxy-substituted ethylene-1,1-bisphosphonic acids **60** has been developed by addition of dialkyl phosphite over α-ketophosphonates **58**, obtained from naturally occurring 1-amino acids, to afford *N*-protected 2-amino-1-hydroxyethylene-1,1-bisphosphonate **59** (Scheme 21).[56] Acid hydrolysis enabled the protecting group and the phosphonate esters, yielding 2-amino-1-hydroxyethylene-1,1-bisphosphonic acid **60**.[21b] Treatment of this acid with sodium hydroxide gave the corresponding sodium salt **61**.

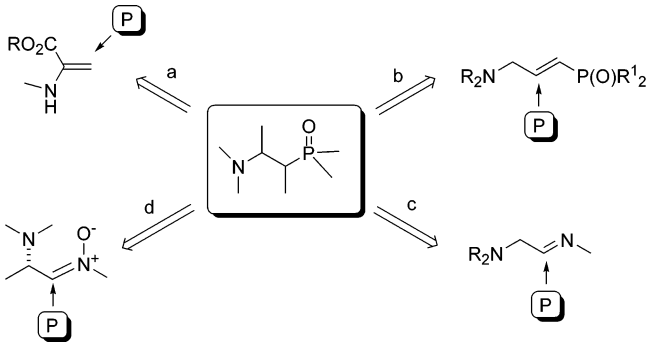
Scheme 21



2.5. Addition of Phosphorus Derivatives to Unsaturated C–C and C–N Double Bonds

The most characteristic reaction involves the C−P bond formation by Michael addition of phosphorus reagents to functionalized acrylic acid derivatives (Scheme 22, route a) or vinyl phosphonates (Scheme

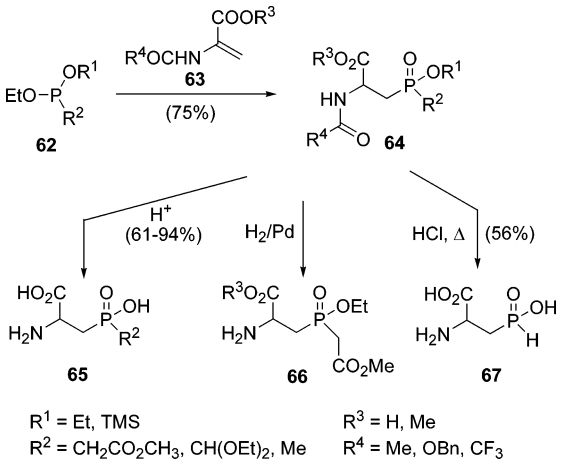
Scheme 22



22, route b). Moreover, reaction of phosphono synthons to the C−N double bond of functionalized imines (Scheme 22, route c) or nitrones (route d) can also be used for this goal.

The first synthesis of 2-amino-3-phosphonopropanoic acid (APPA) **65** (R^2 = OH) (Scheme 23) was accomplished by addition of dimethyl phosphite (HP(O)(OMe)$_2$) to methyl *N*-acetyl-2-aminoacrylate **63** (R^3 = R^4 = Me) followed by acid hydrolysis.[57] Analogously, the phosphonous acid derivative **65** (R^2 = Me) of phosphinothricin was synthesized by reaction of phosphite **62** (R^1 = Et, R^2 = Me) with 2-acetamidoacrylic acid **63** (R^3 = H, R^4 = Me), followed by hydrolysis of phosphinate **64** to give the phosphinic acid **65** (Scheme 23).[58] Also, methyl(diethoxyphosphino)acetate **62** (R^1 = Et, R^2 = CH_2CO_2Me) was added to 2-acetamidoacrylic acid **63** (R^3 = H, R^4 = Me) to give the corresponding phosphinic ester **64** in high yield. Hydrogenolysis of the phosphinic ester in the presence of hydrogen and palladium black gave the aminophosphinate **66**.[59] β-Aminoethylphosphinic acid **67** was prepared by addition of phosphonous acid

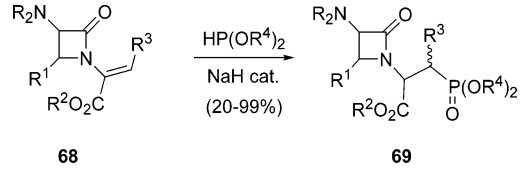
Scheme 23



derivative **62** (R^1 = TMS, R^2 = $CH(OEt)_2$) to acetamidoacrylic acid **63** (R^3 = H, R^4 = Me), followed by acid hydrolysis of the corresponding amide **64**.[60]

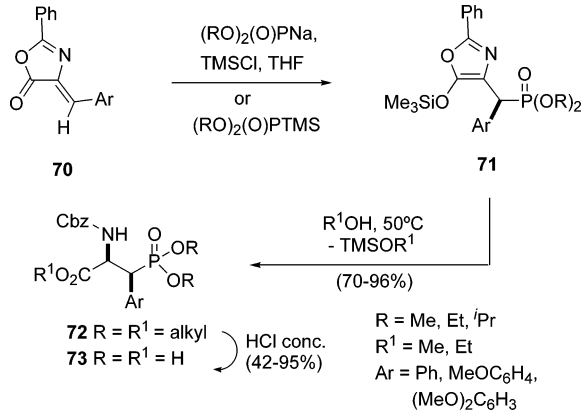
This reaction was extended to the synthesis of novel carbapenem antibiotics containing a β-lactam ring. By simple addition of diethyl phosphite to an α,β-unsaturated double bond, using a catalytic amount of NaH, adduct **69** was obtained in good yield.[61] Acrylate **68** (R^2 = Bn, R^3 = H) and fumarate **68** (R^2 = Bn, R^3 = CO_2Bn) were converted to the corresponding diastereoisomeric phosphonates **69** in 95% and 80% yield, respectively, using diphenyl phosphite and a catalytic amount of NaH (Scheme 24).[62]

Scheme 24



α-Aryl-β-aminophosphonic acid analogues of aspartic acid derivatives can be prepared by an initial attack of trimethyl phosphite at the terminal carbon atom of the conjugated system (α,β-unsaturated) in cyclic synthetic equivalents of α-amino acids **70** (Scheme 25).[63] Reaction with alkali dialkyl phosphi-

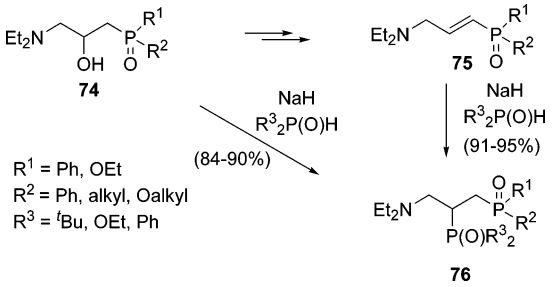
Scheme 25



tes and subsequent silylation afforded 5-silyloxyoxazolones **71**. Alternatively, **71** could be also directly obtained by treatment of **70** with $(RO)_2(O)PTMS$. α-Aryl-β-aminophosphonates **72** (syn and anti) were obtained by ring opening of oxazolones **71** by treatment with alcohols. A remarkably different diastereoselectivity was observed in basic versus acidic media.[64,65] Hydrolysis of **72** was accomplished by heating with HCl to give α-alkyl-β-aminophosphonic acid **73**.

α,β-Unsaturated phosphorus compounds containing an amino group represent a class of compounds which may serve as intermediates in the synthesis of polyfunctional phosphonic acids via Michael addition with a variety of nucleophilic reagents (Scheme 22, route b). In this way, functionalized vinyl phosphonates **75** (R^1 = R^2 = OR) have been employed as electrophilic olefins in Michael addition of $R^3_2P(O)H$ to form compounds **76** (R^1 = R^2 = OR) containing two phosphorus centers (Scheme 26).[32] Alcohol deriva-

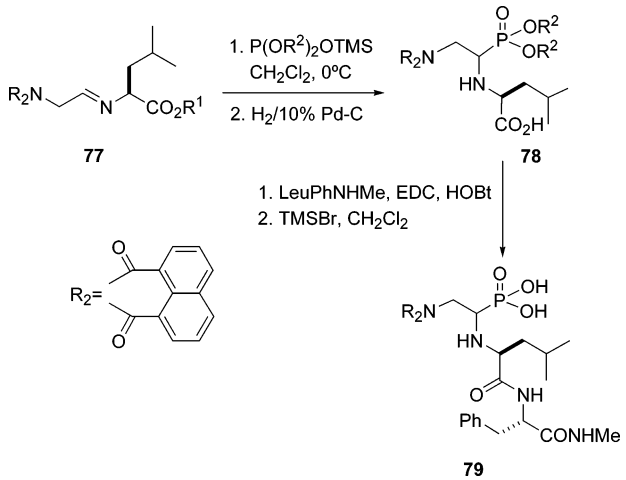
Scheme 26



tives **74**, which can be considered as precursors of functionalized phosphonates (R^1 = R^2 = O-alkyl) and phosphinates (R^1 = OR, R^2 = alkyl) **75**, have been also transformed into compounds **76** by reaction with $R^3_2P(O)H$ in the presence of 1.1 equiv of NaH. Munavalli et al. studied the addition of the various phosphoryl radical intermediates to *N*-(2-propenyl)-phthalimide, observing formation of β-aminoethyl phosphorus derivatives.[66]

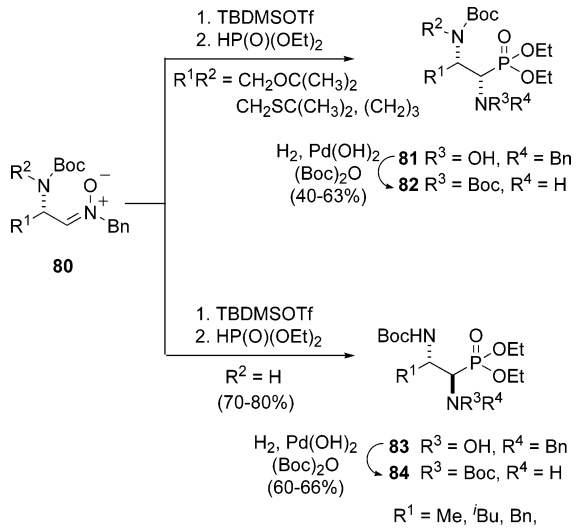
Iminic C−N double bonds of functionalized α-amino aldimines can participate in nucleophilic additions of phosphorus reagents for the synthesis of β-aminophosphonic and -phosphinic acid derivatives (Scheme 22, route c). A peptidomimetic aminophosphonic acid derivative **79**, with an α-amino substitute pattern at the phosphorus atom, was prepared through a phosphite addition to imine **77**[67] (Scheme 27).

Scheme 27



On the other hand, access to chiral α,β-diaminophosphonates with high levels of diastereoselectivity was achieved via a stereoselective carbon−phosphorus bond-forming process through addition of diethyl phosphite to *O*-silylated *N*-benzyl nitrones derived from chiral α-aminoaldehydes (Scheme 22, route d).[68] Treatment of the *N*-diprotected nitrones **80** with diethyl phosphite afforded exclusively the syn adduct **81** (Scheme 28). The diastereoselectivity of the addition reaction to α-aminonitrones can be tuned by monoprotection of the amino group. Thus, the reaction of *N*-monoprotected α-aminonitrones **80** (R^2 = H), whose progenitors were alanine, phenylalanine, and leucine, afforded the corresponding *anti*-*N*-hydroxy α-aminophosphonates **83** in very good yields.[69] The removal of both the benzyl and hydroxy groups from the nitrogen atom of **81** and **83** with concomitant protection of the amino group was carried out in one step by hydrogenation over $Pd(OH)_2$ in the presence of $(Boc)_2O$ to give *N*-Boc-protected α,β-diaminophosphonates **82** and **84**, respectively.

Scheme 28



3. Carbon–Carbon Bond-Formation Reactions

The addition of α-phosphonate carbanions derived from phosphonates and phosphinates to haloamines (route a) and imine derivatives (route b), through carbon−carbon bond-forming process, provides straightforward access to β-aminophosphonates and -phosphinates (Scheme 29). On the other hand, the [4+2] cycloaddition reaction using aminodienes and phosphonodienophiles has been recently used for the preparation of β-aminophosphorus acid derivatives via carbon−carbon bond construction (route c). An extensive description of these strategies is described in the following sections.

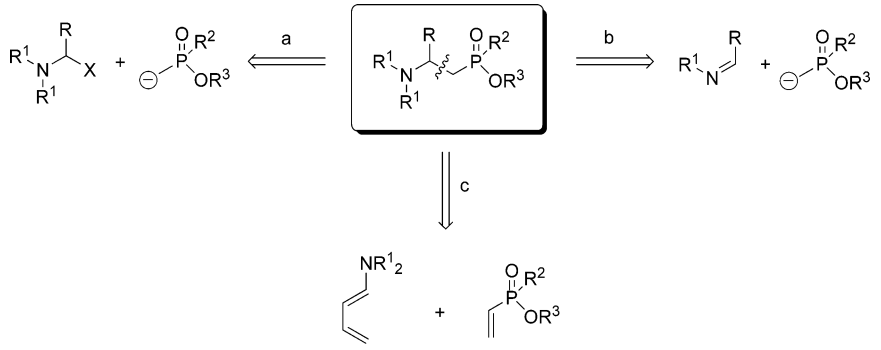
3.1. Addition of Carbanions Derived from Phosphonates to α-Haloamino Derivatives

Addition of carbanions derived from phosphonoacetates **86** (R^1 = Et, R^2 = Ar, R^3 = CO_2Et, R^4 = H) have been employed for the preparation of β-aminophosphonic acids **88**, considered as potential $GABA_B$ receptor antagonists.[70] The synthesis of the required acids was achieved when carbanions derived from phosphonoacetates **86** (R^1 = Et, R^2 = Ar, R^3 = CO_2Et, R^4 = H) were alkylated with *N*-bromomethylphthalimide **85** to give the esters **87**. Alkaline hydrolysis of **87**, under milder conditions than those normally required to hydrolyze a phthalimide, surprisingly resulted in selective hydrolysis and decarboxylation, and subsequent acid hydrolysis led to the formation of β-aminophosphonic acids **88** (Scheme 30). This strategy was applied to the preparation of difluorodiphosphonate **91** (Scheme 30).[71] The binding of diphosphonate **91** to phosphoglycerate kinase has been evaluated, and the synthesis is comprised of reaction of the copper salt derived from phosphonate **86** (R^1 = ^{i}Pr, R^2 = Br, R^3 = R^4 = F) with bromomethylphthalimide **85** followed by deprotection of the amino group to yield β-aminophosphonate **90,** which reacted with chloroacetic anhydride and triethyl phosphite to afford diphosphonate **91**.

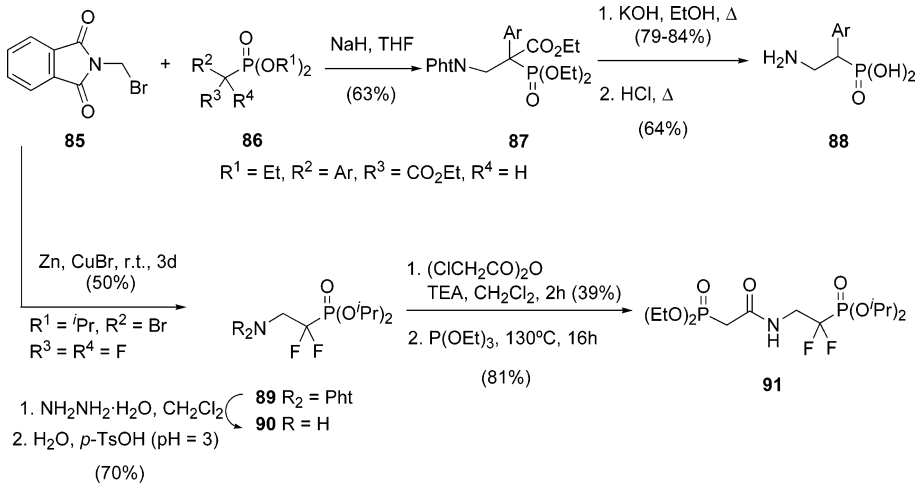
3.2. Addition of Carbanions Derived from Phosphonates and Phosphinates to Imines

Most of the investigations on the synthesis of β-aminophosphonates and derivatives have dealt with the addition of carbanions derived from phosphonates and phosphinates to imines or sulfinimines. For example, Kirilov et al. studied the reaction of carbanions derived from phosphonates and phosphinates for the preparation of α-aryl-substituted β-aminophosphonates[72] and -phosphinates[73] (Scheme 31). Thus, addition of α-phosphonate carbanions, generated from phosphonates **93** (R^1 = OR) using 0.5 equiv of $NaNH_2$, to Schiff's bases **92** in ether or liquid ammonia afforded *syn*-**94** and *anti*-α-aryl-β-aminophosphonates **95** (R^1 = OR) along with small amounts

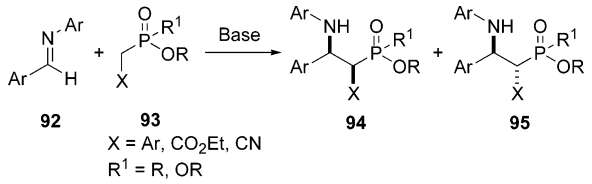
Scheme 29



Scheme 30



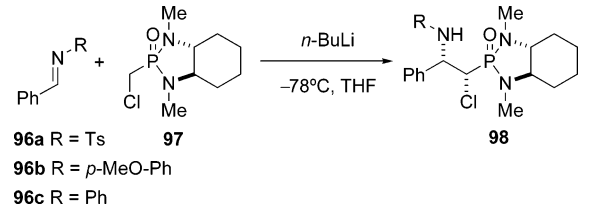
Scheme 31



of trans olefins, particularly in liquid ammonia. The first product of the reaction in ether is the syn adduct, which on increasing the reaction temperature or prolonging the reaction time transforms to the more stable anti isomer. Addition of carbanions derived from phosphonoacetic esters **93** (X = CO_2Et, CN) in the presence of anhydrous $AlCl_3$ has also been reported for the same group[72g] as well as the influence of solvent and metal ion on the reaction of α-phosphonate carbanions with Schiff's bases in the presence of alkaline amides or BuLi.[72a] Ambident lithium allylphosphonic-bis(dimethylamide) also has been investigated as an olefinating reagent in reaction with aromatic Schiff's bases with respect to not only the synthetic scope of the reaction but also the influence of the reaction conditions and the substituents of the Schiff's bases on the regioselectivity.[74]

More recently, Hanessian et al.[75] reported an asymmetric synthesis of *β*-amino-α-chlorophosphonamides **98** as precursor of aziridines, involving the stereoselective addition of carbanions derived from optically pure α-chloromethyl bicyclic phosphonamide **97** to imines **96** (Scheme 32). Attack of the imine

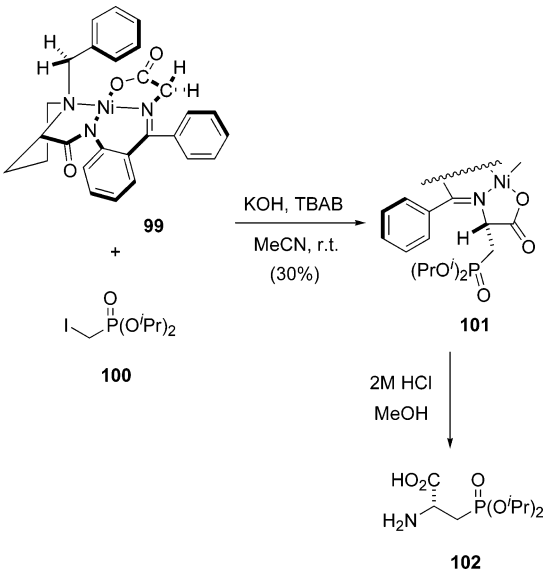
Scheme 32



takes place from the pro *R* side of the planar anion, possibly through a Li-coordinated intermediate. In fact, it was only in the case of R = Ts that the initially formed *β*-amino-α-chloro adduct **98** (R = Ts) could be isolated and transformed into the aziridine by treatment with base.

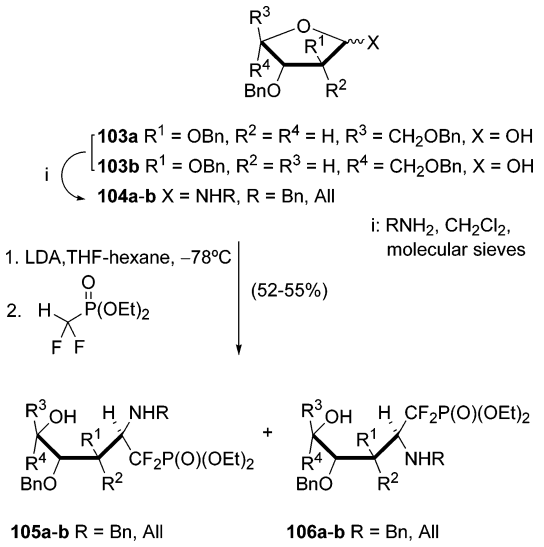
A highly selective procedure for the efficient asymmetric synthesis of (+)-2-amino-3-phosphonopropanoic acid **102** through the alkylation of glycine in its chiral Schiff's base Ni^{II} complex has been developed.[76] Alkylation of complex **99** by diisopropyl iodomethylphosphonate **100** gave the diastereoisomerically pure complex **101**. The mild conditions of the decomposition of the diastereoisomerically pure complex **101** with 2 M HCl furnished amino acid **102,** which has free carboxyl groups and an esterified phosphonic group (Scheme 33).

Scheme 33



β-Amino-α-difluorophosphonates **105** and **106**, intermediates in the synthesis of (difluoromethyl)-phosphonate azadisaccharides, have been designed as inhibitors for glycosyl transferases (Scheme 34).[77,78] Compounds **105** and **106** were prepared by nucleophilic opening of *N*-protected imines derived from carbohydrates **104**, readily available from D-arabinose and from L-xylose by reaction with *N*-allylamine or *N*-Boc amine, with diethyl (lithiodifluoromethyl)-phosphonate. The reaction favored the formation of adduct **105** in a 40−70% de, suggesting that only the stereocenter at the C-2 carbon is controlling the addition process, as previously observed in the reac-

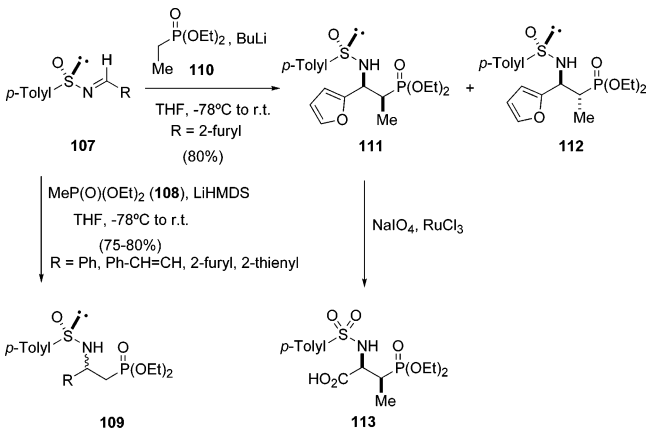
Scheme 34



tion of similar aminofuranosides with Grignard reagents.[79] Compounds **105** and **106** can be separated by column chromatography on silica gel, and the configuration at the newly created stereocenter was firmly assigned after their conversion to the respective pyrrolidines with MsCl.

Chiral enantiopure imines, such as sulfinimines, have also been used in the preparation of β-aminophosphonic acids involving a carbon−carbon bond construction. Addition of α-phosphonate carbanions derived from diethyl methylphosphonate **108** to sulfinimines **107** afforded *N*-sulfinyl-β-aminophosphonates **109** in a diastereomeric ratio arising from 5:1 to 10:1[80] (Scheme 35). Likewise, the addition of

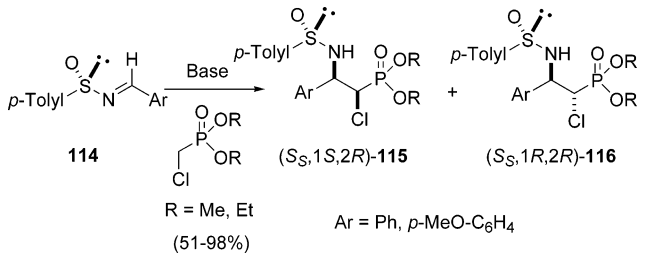
Scheme 35



α-phosphonate carbanion derived from diethyl ethylphosphonate **110** to sulfinimine **107** (R = 2-furyl) proceeded cleanly to give *syn*- and *anti*-*N*-sulfinyl-α-alkyl-β-aminophosphonates **111** and **112**, respectively, in a ratio of 1:1. Treatment of β-aminophosphonate derivative **111** with catalytic amounts of $RuCl_3$ in the presence of $NaIO_4$ led to the formation of β-phosphonylated α-amino acids **113**[81] (Scheme 35).

Davis and co-workers[82] also recently described an approach to the synthesis of β-amino-α-halogenated phosphonates **115** and **116** employed for the asymmetric synthesis of aziridine 2-phosphonates and azirinyl phosphonates. The synthesis of diethyl chlorophosphonates (R = Et) **115** and **116** was achieved by addition of diethyl chloromethylphosphonate (R = Et) to benzaldehyde-derived sulfinimines (*S*)-**114** (Ar = Ph) (Scheme 36). The ratio of (+)-**115**/(+)-**116**

Scheme 36



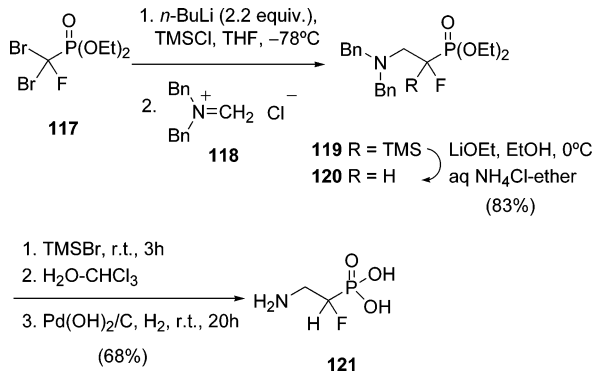
in the crude reaction mixture was 59:41.[82d] Interestingly, the exclusive (*R*)-absolute induction at C-2 in the formation of **115** and **116** is the opposite to that found in the case of the analogous carboxylic ester case[83] and the same as that observed for the addition of phosphites[84] and α-phosphonates carbanions[80] to (*S*)-**114**. The selectivity for metal enolate additions to sulfinimines has been rationalized in terms of chairlike transition states where the metal is coordinated to both the sulfinyl oxygen and imine nitrogen.[83,85] On the other hand, the transition state rationalizes phosphine and α-phosphonate carbanion additions to (*S*)-**114** from the least hindered face, i.e., opposite the *p*-tolylsulfinyl group.[80,84] This difference may reflect the greater steric bulk of metal phosphonate anions compared to enolates as well as their tetrahedral structure. Carbanions derived from dimethyl chloromethylphosphonate (R = Me) in the addition to sulfinimines **114** (Ar = Ph, *p*-MeO−Ph) gave rise to better diastereoselectivities for the β-amino-α-chlorophosphonates **115** and **116** (R = Me) (72:28).[82c] Also, α-alkyl-β-amino-α-chlorophosphonates have been obtained by addition of carbanions derived from diethyl (chloroethyl)phosphonate to sulfinimines **114** (Ar = Ph).[86]

3.3. Addition of Carbanions Derived from Phosphonates to Imminium Salts

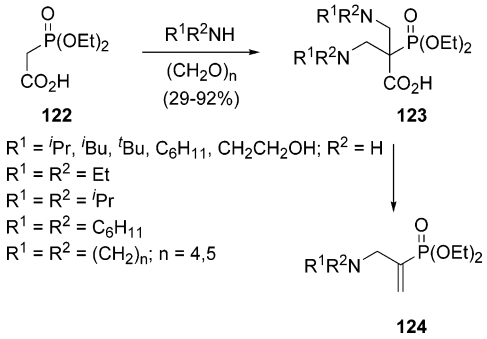
Imminium salts also contain a C−N double bond and therefore can be used for the preparation of β-aminophosphonates. Addition of carbanions derived from diethyl (dibromofluoromethyl)phosphonate to imminium salts has been reported by O'Hagan et al.[87] As Scheme 37 illustrates, α-carbanion derived from diethyl (dibromofluoromethyl)phosphonate **117**, by double halogen exchange with *n*-BuLi in the presence of chlorotrimethylsilane (TMSCl), added to imminium chloride **118** affords adduct **119**. Desilylation of **119** to generate **120**, saponification of the phosphonate ester moiety of **120** with TMSBr and water, followed by hydrogenolysis using palladium hydroxide on carbon gives the β-aminophosphonate **121**.

The preparation of novel β-amino methylvinylphosphonates **124** based on the Mannich reaction between diethyl phosphonoacetic acid **122**, formaldehyde, and primary[88] or secondary aliphatic amines[89] has been reported (Scheme 38). This procedure differs mark-

Scheme 37



Scheme 38

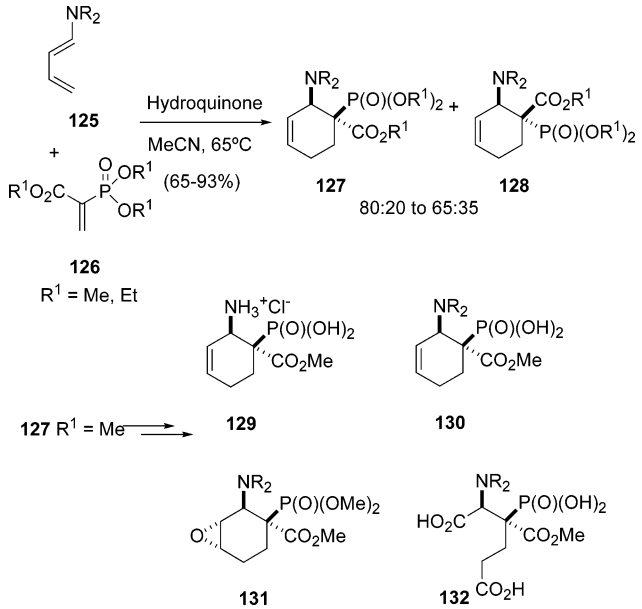


edly from those commonly used for the Mannich condensations. Neither the presence of water nor strongly acidic conditions are needed in this case. Except for amines bearing sterically demanding groups, the yield of phosphonates **124** is quite good.

3.4. [4+2] Cycloaddition Processes

The [4+2] cycloaddition strategy using aminodienes and phosphono-dienophiles has been recently applied for the preparation of β-aminophosphonic acid derivatives (Scheme 39) through carbon−carbon bond formation.[90] The synthesis of β-aminophosphonates **127** and **128** was accomplished by [4+2] cycloaddition of aminodienes **125** to vinylphosphonate dienophiles **126**. The cycloadducts were isolated, after column chromatography, as a mixture of two stereoisomers corresponding exclusively to the β-aminophosphonate regioisomers with a higher proportion of endo isomers.[91,92] The cycloadditions of phosphonodienophiles **126** with 1-aminodienes **125** were practically not affected by the solvent polarity. However, addition of a Lewis acid did not accelerate the cycloaddition but reversed the stereoselectivity in favor of the exo isomer. Other geminal electron-withdrawing substituents could activate the vinyl phosphonate reagent, such as the cyano and sulfonyl groups.[93] Compounds **127** and **128** have been transformed into various β-aminophosphonic acid derivatives. For example, hydrolysis, selective bis-demethylation of the phosphonate group, epoxidation of the C−C double bond of the cyclohexene, and oxidative cleavage of the cyclohexenyl C−C double bond in substrate **127** led to the formation of compounds **129**, **130**, **131**, and **132**, respectively (Scheme 39).[92]

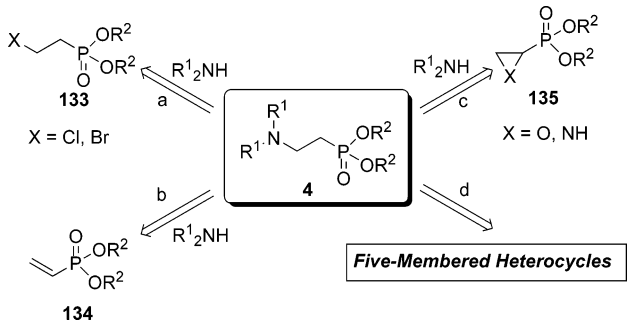
Scheme 39



4. Carbon–Nitrogen Bond-Formation Reactions

Among the various preparation methods for β-aminophosphonates and -phosphinates through carbon−nitrogen bond-forming processes, reaction of haloalkyl phosphorus derivatives **133** with amines (Scheme 40, route a), Michael addition of amines to vinyl phosphonates and phosphinates **134** (route b), ammonolysis of oxiranes **135** (X = O) (route c), addition of amines to aziridines **135** (X = NH) (route c), or ring opening of five-membered heterocycles (route d) constitute entries to β-aminophosphorus derivatives. Moreover, the aminohydroxylation (AA) of vinyl phosphonates **134**, which utilizes Os−(VIII) and the cinchona alkaloid ligands as catalysts, provides a useful strategy for the preparation of these compounds (route b).

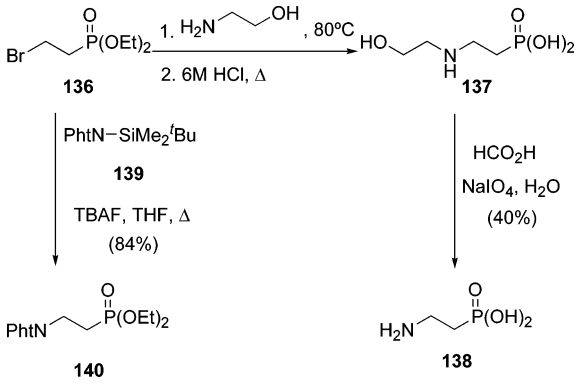
Scheme 40



4.1. Halide Displacement

Several reports described the preparation of β-aminoalkylphosphonic and -phosphinic acids and their esters involving the reaction of haloalkylphosphonates with amines by halide displacement (see general Scheme 40, route a). The simplest example is the synthesis of AEP **138** as shown in Scheme 41. The phosphono group of 2-bromoethylphosphonic acid **136** became masked when this compound was treated

Scheme 41



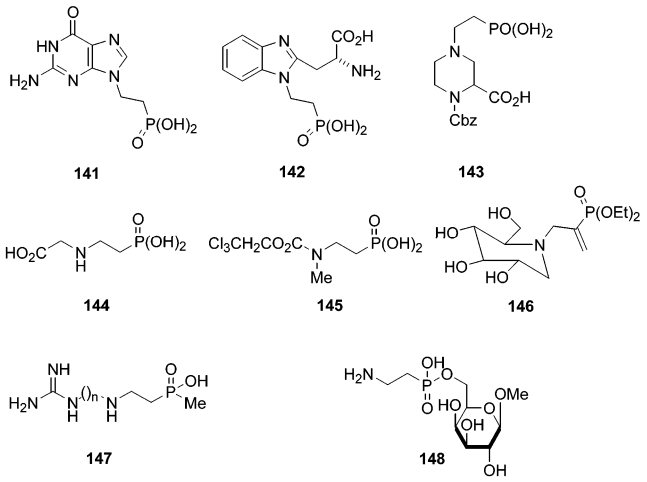
with 2-aminoethanol and de-esterified in the course of the synthesis to afford AEP **138**.[94] The presence of the vinylphosphonate intermediate has been confirmed by some authors. On reacting potassium phthalimide with 2-bromoethylphosphonate **136**, the expected diethyl phthalimidoethylphosphonate **140** was not formed, and diethyl vinylphosphonate was obtained instead by hydrogen bromide elimination.[95] However, preparation of this phthalimidoethylphosphonate **140** could be accomplished by reaction of **136** with silylated phthalimide **139** in the presence of tetrabutylammonium fluoride (TBAF) (Scheme 41).[96] This procedure, which employs the phthalimide **139**/THF system, was easily activated by a naked fluoride ion of TBAF. Catalytic amounts of potassium iodide have also been employed to accelerate the reaction between haloalkylphosphonic acids and amines in a dilute aqueous alkaline solution.[97]

The same synthetic strategy has been widely employed for the preparation of several structurally different compounds derived from AEP. 2-Phosphonoethyl guanine **141**,[98] a very weak inhibitor of human purine nucleoside phosphorylase, phosphonic acids **142**,[99] **143**,[100] and **144**,[101] as *N*-methyl-D-aspartate (NMDA) antagonists, β-aminophosphonic acid **145**,[102] a fragment for the synthesis of a phosphonosphingoglycolipid found in marine organisms, β-aminophosphonate derived from azasugar deoxynojirimycin (DNJ, **146**),[103] *N*-(guanidinoalkyl)-β-aminophosphinic acids **147**,[104] as a potential fungicide, phosphonosphingolipid **148**,[105,106] or phosphonolecithins[107] and phosphinolecithins[108] have been prepared by halide displacement (Scheme 42).

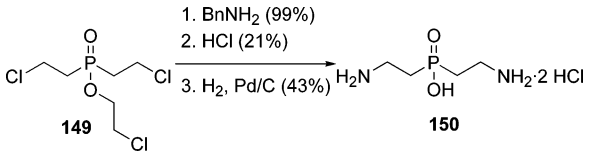
Maier described the preparation of bis(aminoethyl)phosphinic acid **150**, a building block for the preparation of phosphonopeptides, from 2-chloroethyl bis(2-chloroethyl)phosphinate **149** by treatment with benzylamine (Scheme 43).[109] Hydrolysis and debenzylation of phosphinate intermediate over Pd/C as catalyst afforded bis(β-aminoethyl)phosphinate **150** as the dihydrochloride salt.

Gao et al.[110] prepared two dimers **153** and **154** and the convergent synthesis of a tetramer **155** of a nucleotide analogue containing alternating achiral phosphonate and *N*-ethyleneglycosyl amide backbone linkages (Scheme 44). First, the synthesis of both dimers which contain a peptide nucleic acid residue linked with a natural nucleotide was accomplished

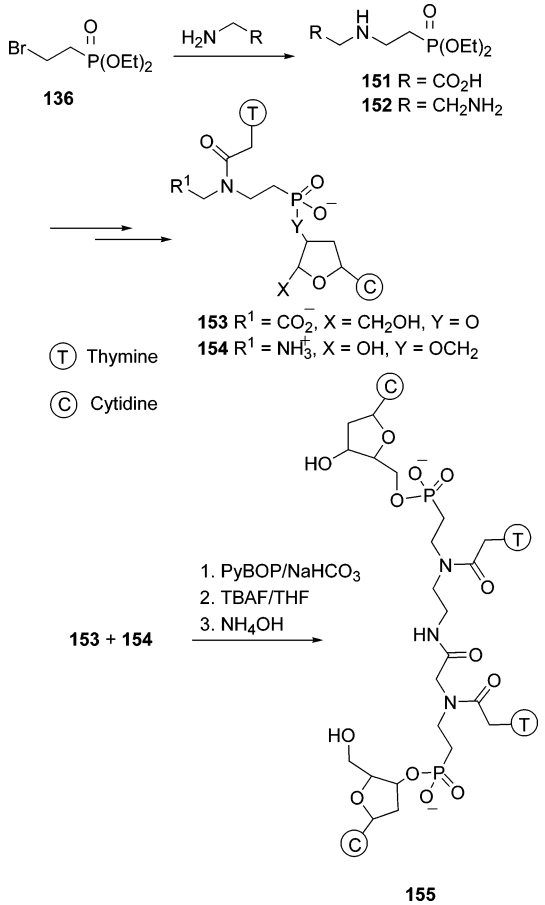
Scheme 42



Scheme 43

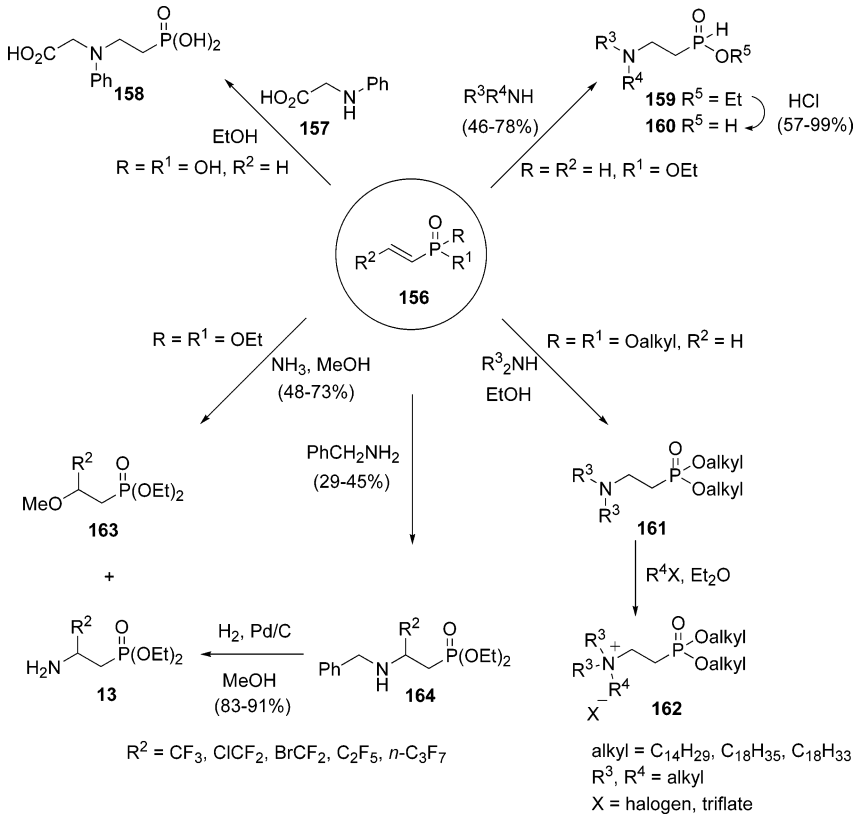


Scheme 44



by nucleophilic Br substitution of diethyl 2-bromoethylphosphonate **136** with glycine for one dimer **151** and with ethylenediamine for the other one **152**. Afterward, a condensation between both dimers through an amide bond construction afforded a new type of tetranucleotide **155**.

Scheme 45



4.2. Michael Addition of Amines to Vinyl Phosphonates and Phosphinates

The conjugate addition of nucleophiles to α,β-unsaturated compounds, commonly known as the Michael reaction, constitutes one of the most important and particularly useful methods for carbon−carbon and carbon−heteroatom bond formation. Several accounts have been reported in the literature for the preparation of β-aminophosphonic[13,111] or -phosphinic[111c,112] acid derivatives through Michael addition of amines to vinylphosphonates and -phosphinates, implying a carbon−nitrogen bond construction (see general Scheme 40, route b).

For example, the synthesis of β-aminophosphonic acid **158** involves the addition of *N*-phenylglycine **157** on the carbon−carbon double bond of vinylphosphonic acid **156** (R = R^1 = OH, R^2 = H) (Scheme 45).[113] Similarly, primary and secondary amines react with vinylphosphinic acid **156** (R = R^2 = H, R^1 = OEt) to give phosphinates **159** in good yields (Scheme 45).[114] Floch et al.[115] reported the preparation of cationic phosphonolipids **162**, quaternary β-ammoniumphosphonates, as synthetic nonviral vector-mediated gene transfer. The synthesis of these quaternary ammonium phosphonates took place through addition of secondary amines to vinylic phosphonate **156** (R = R^1 = Oalkyl, R^2 = H) and subsequent quaternization (Scheme 45). In the same way, the preparation of β-aminophosphonates containing a perfluoroalkyl group has also been reported.[116] Perfluoroalkylated α,β-unsaturated phosphonates **156** (R = R^1 = OEt, R^2 = perfluoroalkyl) reacted with a methanolic ammonia solution to give a mixture of β-alkoxy-**163** and β-aminophosphonate **13,** which could be separated by chromatography in good yields (Scheme 45). Compound **156** also reacted with benzylamine to give 2-benzylamino-2-perfluoroalkylphosphonates **164**, which were smoothly hydrogenated with palladium on carbon at room temperature to afford β-aminophosphonates **13**.

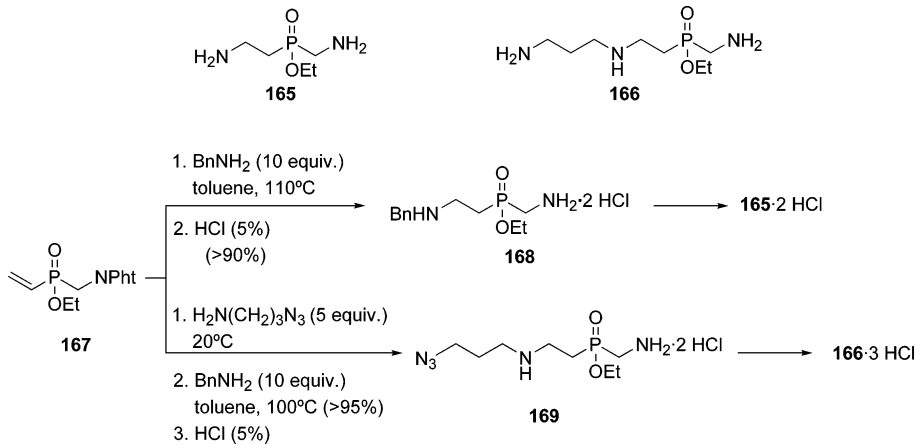
Similarly, this strategy has been used for the synthesis of phosphinates **165** and **166** (Scheme 46), phosphorylated analogues of putrescine and spermidine, respectively.[117] As Scheme 46 illustrates, the synthesis of **165** and **166** could be accomplished from the common precursor ethyl (phthalimidomethyl)-vinylphosphinate **167**. Michael addition of benzylamine or 3-azidopropylamine to vinylphosphinate **167** followed by catalytic hydrogenation (Pd/C) afforded hydrochloride salts of **165** and **166**, respectively, in good overall yields.

Michael reaction of different nitrogen nucleophiles to dicyclohexylammonium vinylphosphonate **170** produced a number of structurally varied β-aminophosphonates **171** in good yields (Scheme 47).[118] Ion-exchange chromatography of the salts **171** provided the corresponding β-aminophosphonates **172** in nearly quantitative yield.

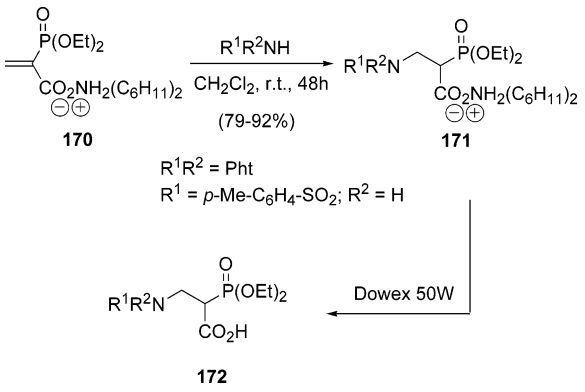
The synthesis of Δ-1 carbopenems **176** based on the Michael addition of *N*-lithio-4-vinyl-azetidin-2-one **173** to several vinylphosphonates **174** has been described (Scheme 48).[119] Ozonolysis of the unmasked β-aminophosphonate **175** followed by an intramolecular Horner−Wittig reaction afforded Δ-1 carbopenems **176**.

As shown in Scheme 49, β-heteroaryl bisphosphonates **179** have been synthesized by Takeuchi et al.[120] by Michael addition of azoles to geminal vinyl bis-

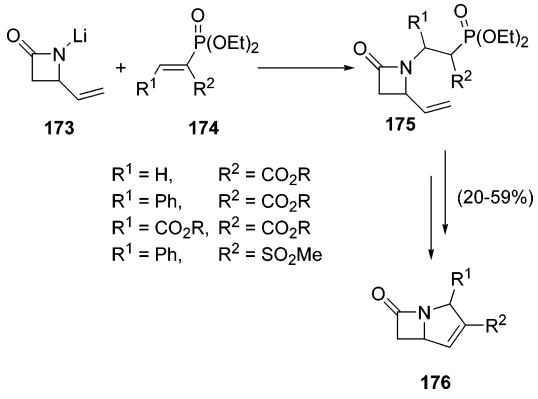
Scheme 46



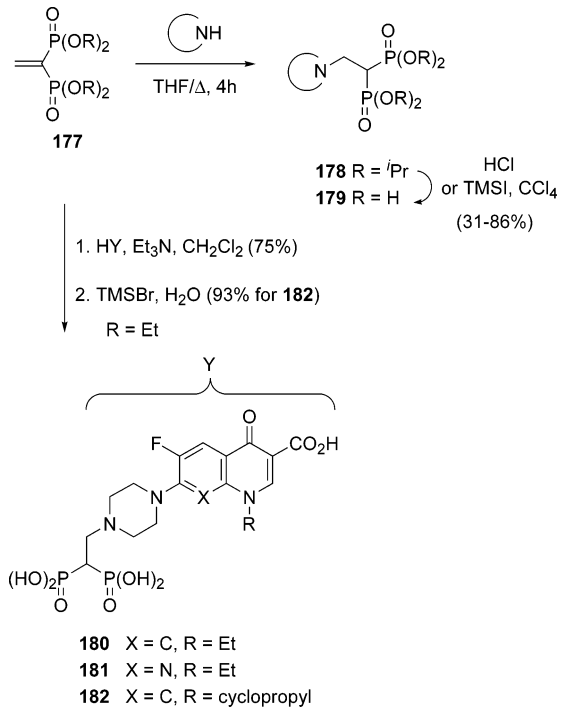
Scheme 47



Scheme 48



Scheme 49



phosphonates **177**. The tetraester of bisphosphonates **178** prepared by this method was saponified with concentrated hydrochloric acid or iodotrimethylsilane to afford bisphosphonic acids **179**. The same strategy has been applied to the preparation of bisphosphonoethyl derivatives **180**−**182** of fluoroquinolone antibacterials: Norfloxacin, Enoxacin, and Ciprofloxacin (Scheme 49). Fluoroquinolone compounds HY were allowed to react with ethenylidenebisphosphonate **177** in CH_2Cl_2 in the presence of Et_3N, resulting in the formation of bis(diethoxyphosphoryl)ethyl derivatives containing the aminoquinolone ring system (Y).[121] The ester groups were then removed by bromotrimethylsilane and subsequent hydrolysis, giving rise to compound **180**, **181**, or **182**, respectively, as hydrobromide salts. The most active derivatives against both Gram-positive and Gram-negative microorganisms were compounds **182** and their *P*-ethyl ester derivative. Tetraalkyl ethenylidenebisphosphonates can undergo straightforward Michael-type addition reaction with nitrogen nucleophiles to give *C*-substituted methylene bisphosphonates.[122] Similarly, 2-(arabinonoylamino)ethylidene-bisphosphonic acid, as weak inhibitor of the *Influenza B* enzyme, has also been synthesized by addition of tetrabenzyloxy-D-arabinoamide to vinyl bisphosphonate **177** (R = Et) in 70% overall yield.[123]

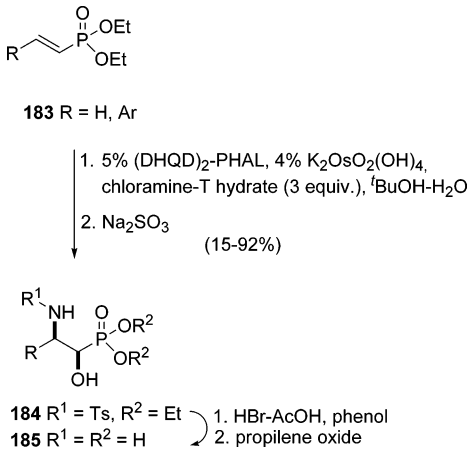
4.3. Sharpless Asymmetric Aminohydroxylation (AA)

The asymmetric aminohydroxylation (AA),[124] which utilizes Os−(VIII) and the cinchona alkaloid ligands as catalysts, provides straightforward access to optically active α-hydroxy-substituted β-aminophosphonate diesters in high ee. Asymmetric aminohydroxylation of dialkyl α,β-unsaturated carbonyls has been thoroughly investigated with a great deal of success; however the study of their phosphonated analogues

still remains undeveloped. Only in the past decade AA[125] reactions have been applied to dialkyl vinylphosphonates to give the corresponding β-amino-α-hydroxyphosphonates.

Diethyl-substituted α,β-unsaturated phosphonates **183** were successfully oxyaminated using Os−(VIII) and the cinchona alkaloid ligand $(DHQD)_2$−PHAL[125b] as the asymmetric inductor and reaction accelerator and chloramine-T hydrate in ^{t}BuOH−H_2O (1:1, v/v) at room temperature (Scheme 50). The reaction

Scheme 50



required about 2−24 h to reach >95% conversion and gave the β-amino-α-hydroxy derivatives **184** with no detectable amounts of the other regioisomer. Although the absolute stereochemistry was not assessed, it seems reasonable to speculate that $(DHQD)_2$−PHAL should direct, as in the case of α,β-unsaturated esters, the addition to the β-face of **183** (*re*, *si* approach), giving rise to a (1*R*,2*R*)-*syn*-configuration. Purification with enantioselectivity enrichment was found possible by recrystallization. β-Amino-α-hydroxyphosphonates **184** (R = Ar) could be hydrolyzed in excellent yields to the corresponding β-amino-α-hydroxyphosphonic acids **185** with HBr in AcOH at 75 °C in the presence of phenol as a scavenger of bromine, followed by neutralization with propylene oxide (Scheme 50).

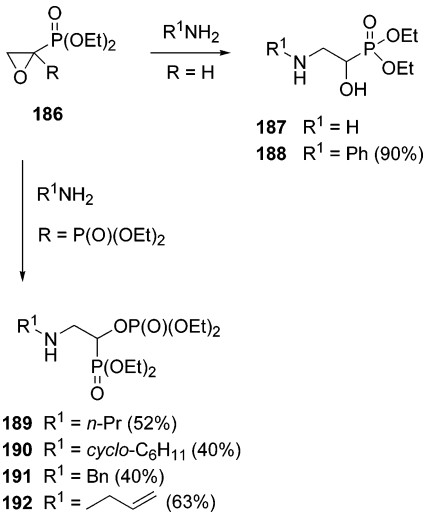
The pseudo-enantiomeric ligand $(DHQ)_2$−PHAL as the asymmetric inductor in AA reaction has also been used employing *N*-chloro-*N*-sodioamides derived from *p*-toluenesulfonyl and ethoxycarbonyl *N*-amino groups, affording *syn*-β-amino-α-hydroxyphosphonates in high ee (ee values from 32 to 99).[125a] The corresponding alkyl-substituted unsaturated phosphonates **183** (R = alkyl) failed to react even upon prolonged heating.

4.4. Three-Membered Heterocycles Ring Opening

4.4.1. Ammonolysis of Oxiranes

Nucleophilic addition of amines to oxiranes constitutes a versatile method for the preparation of β-aminophosphonic esters with a hydroxy group in the α position through carbon−nitrogen bond formation (see general Scheme 40, route c). Addition of nitrogen nucleophiles (ammonia or aniline) to oxirane **186** (R = H) led to the formation of β-aminophosphonates **187** and **188** (Scheme 51).[126] These products

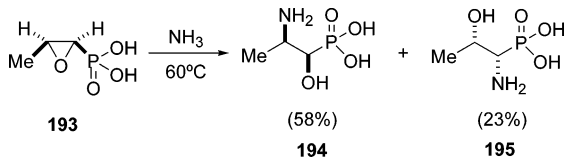
Scheme 51



are formed by attack of nucleophile at the less substituted carbon of the epoxide, and there is no evidence of the formation of the isomeric products resulting from attack of nitrogen nucleophile at the α carbon. Another example of oxiranes opening implies the addition of nitrogen nucleophiles to oxiranylidenebisphosphonate **186** (R = $P(O)(OEt)_2$).[127] Addition of amines to oxirane **186** (R = $P(O)(OEt)_2$), containing two phosphonate groups, gave the phosphinyl phosphate structures **189**−**192** (Scheme 51).

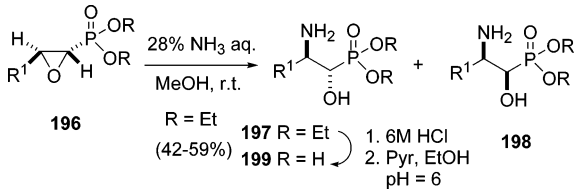
Saturation of optically active fosfomycin **193** with gaseous ammonia has been reported,[128] affording a mixture of regioisomers β-amino-α-hydroxypropylphosphonic acid **194** and α-amino-β-hydroxypropylphosphonic acid **195** (Scheme 52).[129]

Scheme 52



A similar strategy has been achieved for an elegant highly regio- and diastereoselective synthesis of β-amino-α-hydroxyphosphonic esters **197** by opening of *trans*-1,2-epoxy-2-aryl ethylphosphonic esters **196** with aqueous NH_3 (Scheme 53).[130] Reaction of func-

Scheme 53



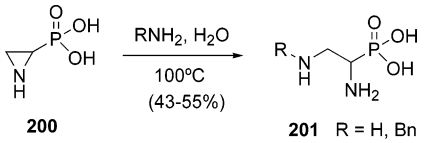
tionalized *trans*-oxirane **196** with a 84-fold excess of ammonia (28% aqueous NH_3) in MeOH gave, practically always, only one diastereoisomer of the desired product **197** in high regioselectivity (Scheme 53). Only in the case of R^1 = *o*-MeO−C_6H_4 was the syn diastereoisomer **198** obtained in a ratio of 90:10. The same procedure applied toward *cis*-1,2-epoxyethylphosphonic esters resulted in poor yields and low

regioselectivity. The phosphonic acids **199** were obtained from their diethyl esters **197** by treatment with 6 M HCl.[131] Preparation of β-amino-α-hydroxyphosphonic acids through hydrolytic kinetic resolution of (±)-oxiranes has also been described.[132] Kinetic resolution of (±)-oxirane **196** (R^1 = H, R = Et) was achieved by using the Jacobsen catalyst. The (*R*)-epoxide **196** reacted with (*S*)- and (*R*)-1-phenylethylamine, giving rise to two single diastereomeric amino alcohols.

4.4.2. Nucleophilic Addition of Amines to Aziridines

The easy synthesis of zwitterionic aziridine-2-phosphonic acid **200** in a two-pot procedure and its good tendency to undergo ring-opening reaction with a series of nucleophiles creates a preparative method for the introduction of suitable chemical function at the 2-position of 1-aminoethylphosphonic acid (Scheme 54).[133] The synthesis of 1,2-diaminoethylphosphonic

Scheme 54



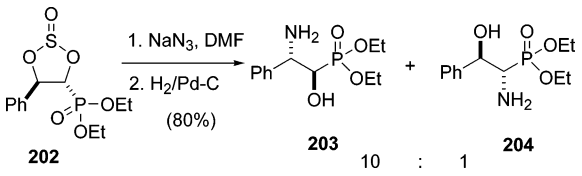
acids **201** was achieved by opening of aziridine ring of **200** by treatment with aqueous solution of ammonia or benzylamine (R = Bn) at 100 °C. The nucleophilic attack is generally directed to the less substituted C-2 carbon of aziridine ring.

4.5. Five-Membered Heterocycles Ring Opening

4.5.1. Nucleophilic Addition of Azides to Cyclic Sulfites

Ring opening of cyclic sulfites **202** upon treatment with NaN_3 afforded the azidohydroxyphosphonates, which were reduced with H_2/Pd−C to give the optically pure hydroxyaminophosphonic acid derivatives **203** and **204** in almost quantitative yield (Scheme 55).[134] The stereochemical assignments were made

Scheme 55

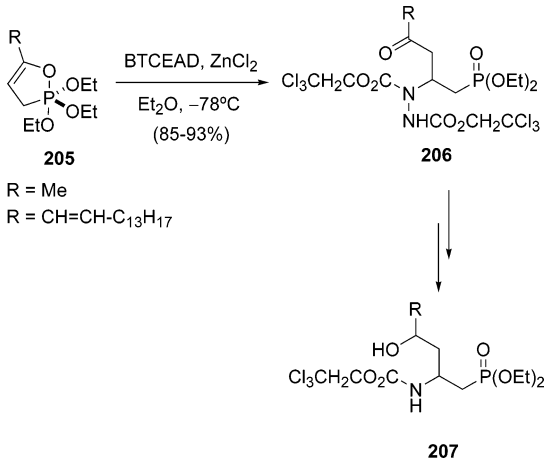


by comparison of the optical rotations of known compounds and also assuming the reaction of cyclic sulfite to proceeds via complete inversion at the reacting stereogenic center.

4.5.2. Condensation of Oxaphospholenes with Nitrogen Electrophiles

Condensation of pentacovalent oxaphospholenes **205**, prepared from the reaction of an enone with a trialkyl phosphite with a variety of electrophiles under very mild conditions produces highly functionalized phosphonates (Scheme 56). This methodology has been applied for the preparation of phosphonate analogues of sphingomyelin, sphingosine 1-phos-

Scheme 56



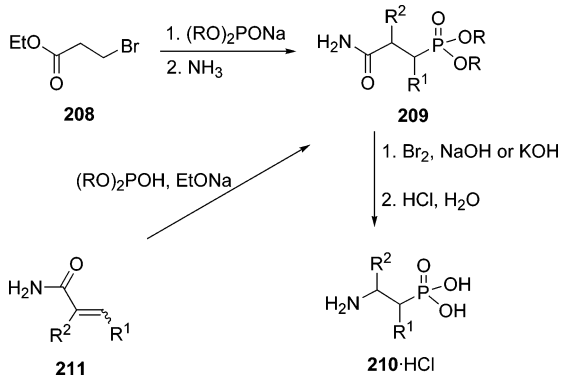
phate, and ceramide 1-phosphate.[135] Thus, condensation of oxaphospholenes **205** with an electrophilic nitrogen source such as bis(2,2,2-trichloroethyl)-azodicarboxylate (BTCEAD) at −78 °C and Lewis-acid activation led to the formation of phosphonates **206** in good yields. Subsequent carbonyl reduction and N−N bond cleavage yielded β-aminophosphonates **207** (Scheme 56).

4.6. Rearrangement Processes

4.6.1. Hofmann Rearrangement

The method of Finkelstein was the first description of the synthesis of β-aminoethylphosphonic acids (AEP) ($R^1 = R^2$ = H) **210** by Hofmann rearrangement of amides **209** ($R^1 = R^2$ = H) obtained by reaction of diethylsodium phosphonate with ethyl 3-bromopropionate **208** (Scheme 57).[136] Analogously, a two-step

Scheme 57



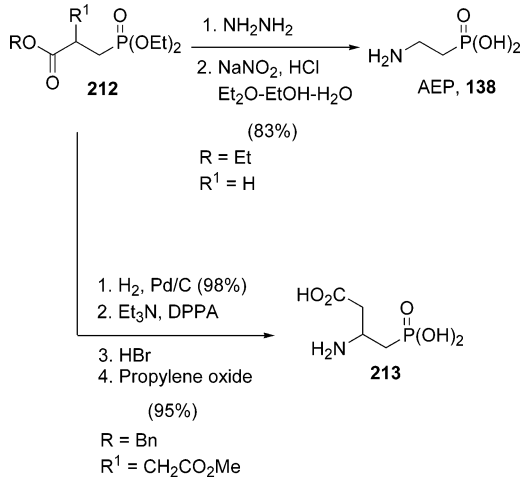
method was developed for the preparation of 2-aminoethylphosphonic acid (AEP) and related compounds from unsaturated amides **211**. The reaction of amides **211** and diethyl phosphite gave phosphonates **209**. The addition was carried out in the presence of sodium ethoxide as catalyst. Hofmann degradation followed by acid hydrolysis yielded the corresponding 2-aminoethylphosphonic acids **210**.[137] In a similar manner, acrylamide **211** ($R^1 = R^2$ = H) was treated with dialkyl phosphite to give the corresponding adduct **209** quantitatively, which was then treated with KOH/Br_2 for the Hofmann degra-

dation reaction to provide the corresponding monoalkyl ester of the phosphonic acid **210** (Scheme 57).[138]

4.6.2. Curtius Rearrangement

Some examples described the preparation of β-aminophosphonic acid derivatives through Curtius rearrangement. The simplest example constitutes the synthesis of 2-aminoethylphosphonic acid (AEP) **138** via triethyl 3-phosphonopropionate **212** (R^1 = H) (Scheme 58).[139] Similarly, the *C*-amino analogue **213**

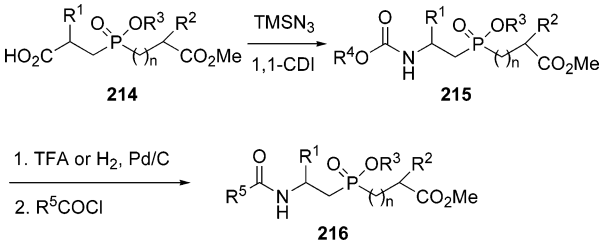
Scheme 58



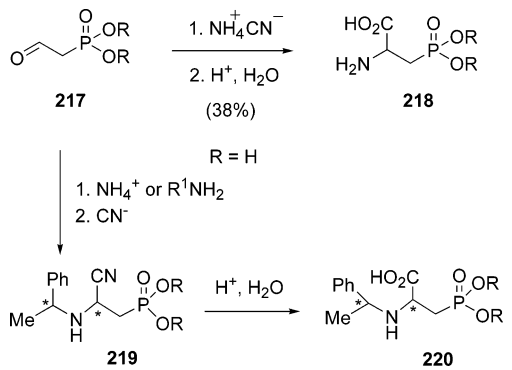
of *N*-aminoglyphosate has been prepared and evaluated for its ability to function as an *E. coli* EPSP synthase inhibitor.[140] Its synthesis was developed from the known addition of phosphonates to itaconate esters and formation of the azide derivative by means of diphenylphosphoryl azide (DPPA) and acid hydrolysis of the phosphonate group (Scheme 58).

Chiral β-phosphono-α-amino acids such as L-2-amino-3-phosphonopropanoic acid (APPA, **218**, R = H, Scheme 60) are known to show potent selective antagonist activities against glutamate receptors as well as antiviral activity. For an enantiocontrolled synthesis of this β-phosphono-α-amino acid, a versatile phosphonic chiron is required and a Curtius rearrangement using diphenylphosphoryl azide (DPPA) and Et_3N of the starting acid has been employed for its synthesis.[141] In the same way, Petrillo et al.[142] reported the preparation of functionalized β-aminophosphinates **216**, useful synthons for the synthesis of phosphonopeptides which possess angiotensin-converting enzyme inhibitory activity and are thus useful as hypertensive agents (Scheme 59). The preparation of such compounds starts from functionalized phosphinate **214**. Compound **214** was subjected to Curtius rearrangement by treatment with $TMSN_3$ and CDI affording, after hydrolysis and treatment with acyl chlorides, β-aminophosphinates **216**.

Scheme 59



Scheme 60



4.7. Strecker Synthesis from Carbonyl Compounds

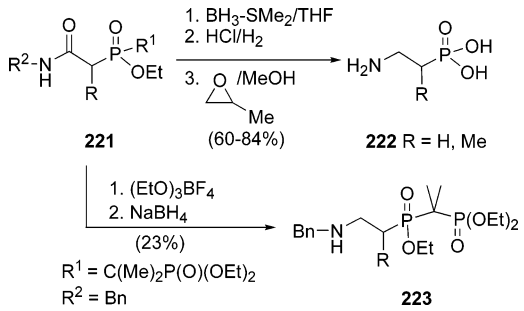
APPA **218** (R = H) has been prepared by the Strecker synthesis from phosphonoacetaldehyde.[143] This synthesis implies the treatment of phosphonoacetaldehyde **217** (R = H) with ammonium cyanide (Scheme 60). Savignac et al.[144] also used the Strecker synthesis but on the diethyl ester of the phosphonoacetaldehyde **217** (R = Et). β-Aminophosphonic acid derivatives can also be prepared by the modified Strecker synthesis starting from formylalkylphosphonates **217** (R = Et) and (*S*)-(−)-α-methyl benzylamine in the presence of hydrogen cyanide. Optically active aminocarboxyethylphosphonic acids **220** were observed in an enantiomeric excess of 50% (Scheme 60).[145]

5. Reduction of Functionalized β-Nitrogen Derivatives

5.1. Amide and Thioamide Reductions

A simple method for the synthesis of aminoalkylphosphonic acids is based on the reduction of dialkyl amidoalkylphosphonates. Selective reduction of amides **221** (R^1 = OEt, R^2 = H) can be accomplished with the borane−dimethyl sulfide complex (Scheme 61).

Scheme 61

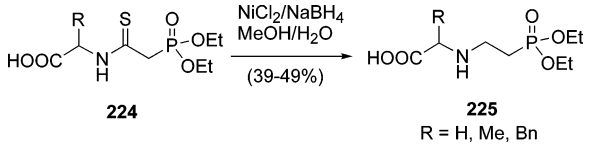


Posterior hydrolysis of the B−N bonds with hydrochloric acid and treatment with methyloxirane gave the corresponding aminoalkylphosphonic acids **222**.[146] The synthesis of squalene synthetase inhibitor was described based on the reduction of an amide diphos-

phonate intermediate.[147] Treatment of amide **221** (R^1 = $C(Me)_2P(O)(OEt)_2$, R^2 = Bn) with triethyloxonium tetrafluoroborate $(EtO)_3BF_4$ followed by the reduction of the intermediate amino ether with sodium borohydride furnished the desired β-amino diphosphorus derivative **223**.

A different method for the synthesis of β-aminoethylphosphonates is carried out through reductive desulfurization with nickel boride of phosphono-substituted thioamides.[148] Starting from the corresponding thiocarbamoylmethyl phosphonates **224** and nickel boride, in the presence of dimethylglyoxime, the corresponding aminoethylphosphonates **225** were obtained in reasonable yields (Scheme 62).

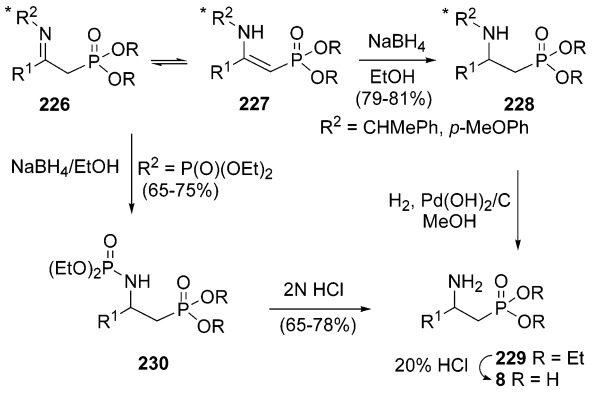
Scheme 62



5.2. Imine–Enamine Reductions

Synthesis of β-aminophosphorylated compounds was accomplished by reduction of enamines and/or imines derived from phosphonates with hydrides.[149] Treatment of chiral and achiral β-enamines derived from phosphonate esters **227** with sodium borohydride led to the formation of β-amino-functionalized derivatives **228** with excellent yields and moderate diastereoselectivity (de = 40−49%) (Scheme 63)

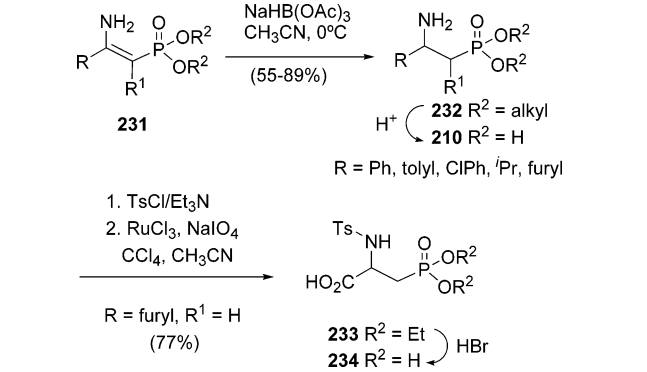
Scheme 63



(favoring the *R* configuration at the newly formed stereogenic center). *N*-Deprotection (R^2 = Bn) by hydrogenolysis gave primary β-aminophosphonates **229**. Modified borohydrides such as aminoborohydrides (LAB) increase the diastereomeric induction of the reduction, giving a diastereomeric excess of 52−65%. *N*-Phosphorylated imines or enamines **226** (R^2 = $P(O)(OEt)_2$),[149a] prepared by reaction of α-oximoalkylphosphonates and chlorophosphite, were reduced with hydride reagents such as $NaBH_4$ to give *N*-phosphorylated β-aminophosphonates **230** in very high yield (Scheme 63). Cleavage of the phosphorus−nitrogen linkage with 2 N HCl afforded β-aminophosphonates **229** (R = Et), whose acid hydrolysis with 20% HCl led to the formation of β-aminoalkylphosphonic acids **8** (R = H) in satisfactory yields. Likewise, reduction of a mixture of *cis*- and *trans*-aminovinylphosphonates with $NaBH_4$/AcOH/THF produced aminoalkylphosphonates in good yield and stereoselectivity (72%), while the reduction with hydrogen in the presence of Pd/C as catalyst gave better selectivity for phosphonates bearing *tert*-butyl substituents (R = ^{t}Bu).[150]

Functionalized primary enamines, easily prepared by addition of *C*α-metalated phosphonates with nitriles,[151] can also be used for the preparation of β-aminophosphonic acids. Addition of carbanions derived from phosphonates to nitriles and in situ reduction with acetoxyborohydride of the obtained primary enamines **231** led to the formation of β-aminophosphonates **232,** which were hydrolyzed to the aminophosphonic acids **210** (Scheme 64).[152,153] Ru-

Scheme 64

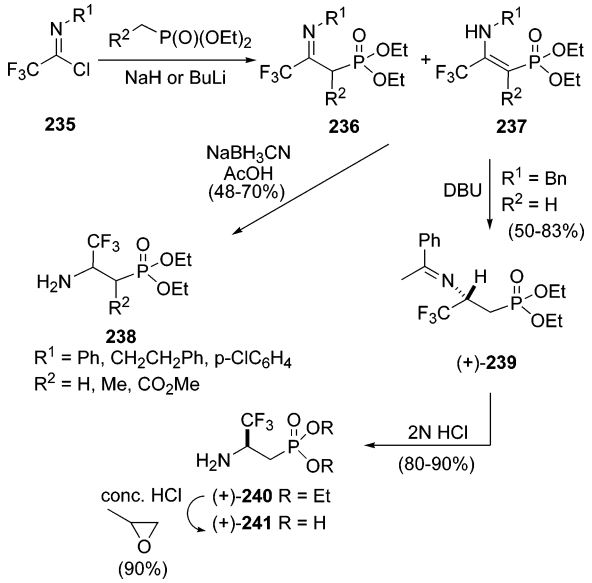


thenium-tetraoxide-catalyzed oxidation of β-*N*-tosylaminophosphonates containing a furyl substituent at the 2-position afforded α-amino acid **233**,[152] given that furan derivatives can be considered as synthetic equivalents of carboxylic groups.[154] Acid hydrolysis (HBr) of phosphonates **233** afforded *N*-tosyl APPA **234**. Through a similar strategy, by using 4-chlorobenzonitrile aminophosphonic acid **210** (R^1 = Me, R = *p*-ClC_6H_4) has been obtained.[155] This lower homologue of phaclofen was evaluated as a specific antagonist of GABA at the $GABA_B$ receptor, being only weakly active.

A similar process has been used for a novel synthetic approach to a new type of trifluoromethylated 2-AEP derivatives containing fluoroalkyl substituents.[156] Sodium borohydride was found to be inert to imine/enamine intermediates **236/237**, and the reduction proceeded very slowly in ethanol even with sodium cyanoborohydride as the reducing reagent (Scheme 65). However, α-substituted 2-amino-3,3,3-trifluoromethylpropylphosphonates **238** were obtained in moderate to good yields when acetic acid was used as solvent. Analogously, 2-amino-3,3,3-trifluoropropylphosphonic acid **241** of high stereochemical purity was successfully achieved.[157] By addition of a strong base such as DBU, a [1,3]-proton shift reaction afforded a 2-imino-3,3,3-trifluoropropylphosphonate intermediate (+)-**239**, whose hydrolysis gave the corresponding phosphonic acid (+)-**241**.

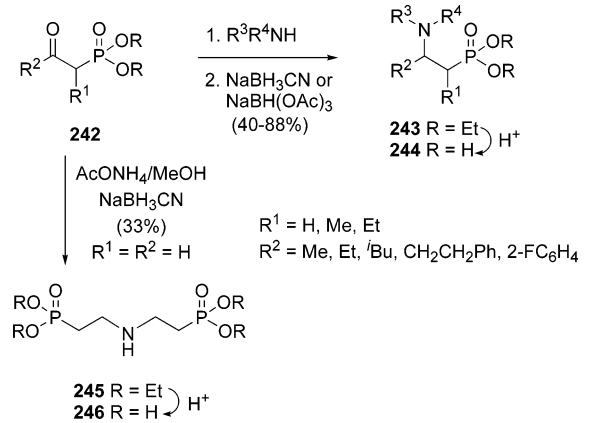
A route to 2-aminoethylphosphonic acids by reductive amination of 2-oxoethylphosphonates **242** has also been described.[158,159] Reductive amination can be carried out with primary or secondary amines,

Scheme 65



aliphatic or aromatic, or ammonium acetate for free amine substitution and $NaBH_3CN$ as reducing agent. Subsequent hydrolysis of 2-aminoethylphosphonates **243** with concentrated hydrochloric acid yielded 2-aminoethylphosphonic acids **244** (Scheme 66). When

Scheme 66



reductive amination of β-formylphosphonates **242** (R^2 = H) was carried out with H_2/Pd, the reduction and debenzylation were observed simultaneously.[160] Reaction of 2-oxoalkylphosphonates **242** with benzylamine (R^3 = H, R^4 = Bn) or benzhydrylamine (R^3 = H, R^4 = $CHPh_2$) followed by reduction with triacetoxyborohydride and acid hydrolysis gave the corresponding aminoalkylphosphonic acids **244** with satisfactory yields,[161] while when optically pure amines were employed no stereoselectivity was observed. However, it was found that the reductive amination of formylalkylphosphonates **242** (R^1 = R^2 = H) with ammonia and $NaBH_3CN$ gave amino bis(ethylphosphonates) **245**.[162] A further reaction of initially formed β-aminoethylphosphonate with another molecule of starting β-formylphosphonates **242** (R^1 = R^2 = H) may have afforded the corresponding amino bis(ethylphosphonate) **245**.

This methodology has been used for the synthesis of [2-(8,9-dioxo-2,6-diazabiciclo[5.2.0]non-1(7)-en-2-yl)ethyl]phosphonic acid **252**, which was identified as a potent NMDA antagonist for the treatment of neurological disorders such as stroke and head trauma.[163] Combining the Cbz-protected diamine **248** with diethyl(2-oxoethyl)phosphonate **247** under reductive amination conditions yielded diamine **249** (Scheme 67). Catalytic transfer hydrogenation afforded **250**, which on reaction with 3,4-diethoxy-3-cyclobutene-1,2-dione followed by deprotection of phosphonate ester with bromotrimethylsilane gave **251** and **252**. This strategy involving reductive amination of β-ketophosphonate also has been used for the design and synthesis of novel phosphonate Ca^{2+} antagonists with $AcONH_4O/NaBH_4$[164] and for β-aminophosphonates in which the P atom is substituted by *n*-ethyl alkoxy groups with butylamine and $NaBH(OAc)_3$.[165]

5.3. Oxime Reductions

Through a simple oxime−amine reduction β-aminophosphonates can also be prepared. Diethyl phosphonoacetaldehyde **217** was converted to the biologically important AEP **138** by addition of hydroxylamine hydrochloride and subsequent hydrogenation with Pd on carbon and acetic anhydride/glacial acetic acid (Scheme 68).[166]

To avoid the use of ketophosphonates, which in some cases are not so readily available, the synthesis of 2-aminophosphonic acid derivatives could be accomplished starting with oxime acetates or ethers.[167] Hydrogenation, using Raney-Ni as a catalyst, of the corresponding 2-oxyimino phosphonates **254**, obtained by Arbuzov reaction of haloalkyl ketoximes with triethyl phosphite, afforded 2-aminoethylphosphonates **255** (Scheme 69). Hydrolysis of 2-aminophosphonates **255** with 20% HCl yielded 2-aminoethylphosphonic acids **256** in good yields.

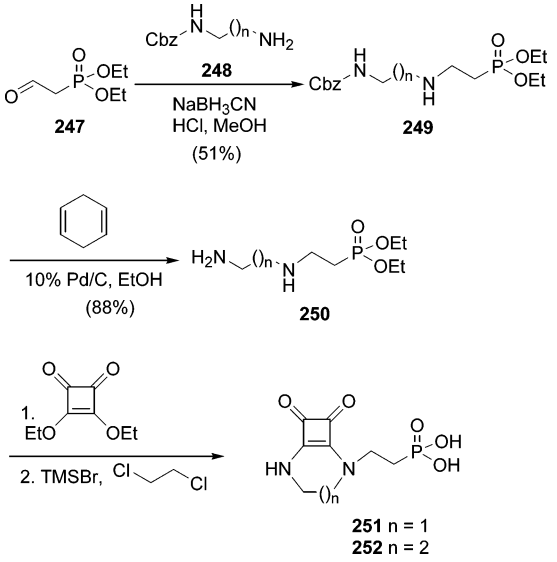
5.4. Nitro Derivative Reductions

The reduction of nitro derivatives represents an interesting tool for the synthesis of β-aminoethylphosphorus derivatives. Hydrogenation reaction over platinum of nitro-derived sugars[168] or over Raney nickel in acidic medium[169] followed by hydrolysis afforded the corresponding aminoethylphosphonic acids **258** (R^1 = OH). In similar processes, β-nitroalkylphosphinic esters were prepared by addition of silylated phosphonous acid derivative to nitroethylene. Catalytic reduction of these nitro compounds **257** and subsequent acid hydrolysis gave β-aminoethylphosphinic acids **258** (R^1 = H) (Scheme 70).[60]

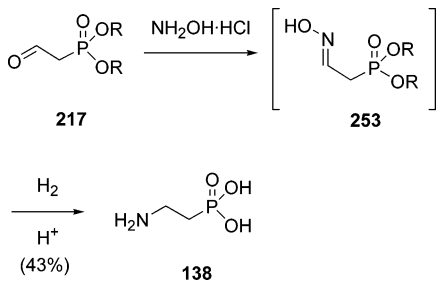
5.5. Nitrile Reductions

The most straightforward example is the reduction of diethyl cyanomethylphosphonate, obtained by Michaelis−Arbuzov reaction of triethyl phosphite and chloroacetonitrile, followed by acidic hydrolysis[139] or hydrogenation using PtO_2 as catalyst[71] to give the corresponding bromohydrate or diester of AEP. α-Cyanoalkylphosphonamides can also be used for the preparation of β-aminophosphorus derivatives. By means of reduction of the nitrile group of bis(dimethylamino)phosphonamides **259** (R = H) and

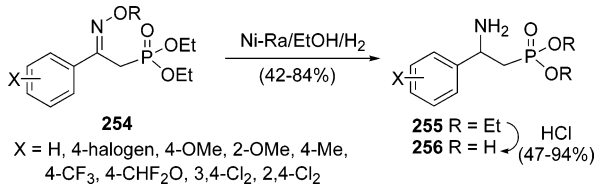
Scheme 67



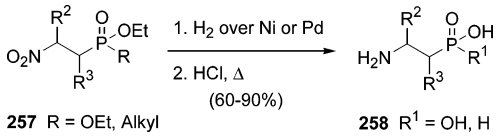
Scheme 68



Scheme 69



Scheme 70



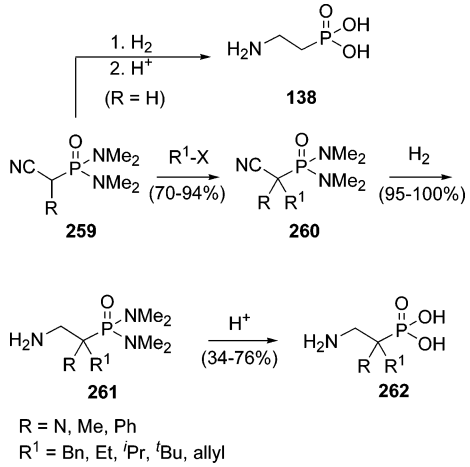
subsequent hydrolysis, AEP **138** can be obtained (Scheme 71).[170] More substituted bis(dimethylamino)-phosphonamides **259** (R ≠ H) could be alkylated using phase-transfer catalysis, affording derivatives **260** whose nitrile group reduction and acid hydrolysis yielded the β-aminophosphonic compounds **262**.[170]

5.6. Azide Reductions

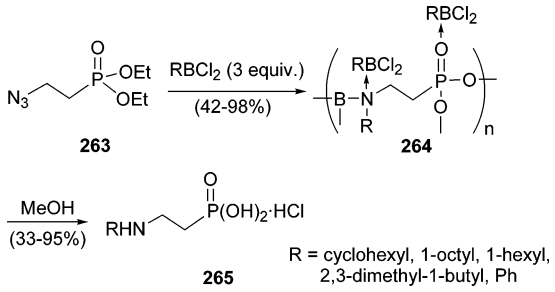
General synthesis of *N*-alkyl/aryl-β-aminoalkylphosphonic acids **265** based on reductive alkylation of β-azidoalkylphosphonates **263** with organodichloroboranes has been carried out by simultaneous dealkylation of the phosphonates via polyborophosphonates **264** (Scheme 72).[171]

An easy method for transformation of the hydroxy group into the amino functionality through an azide

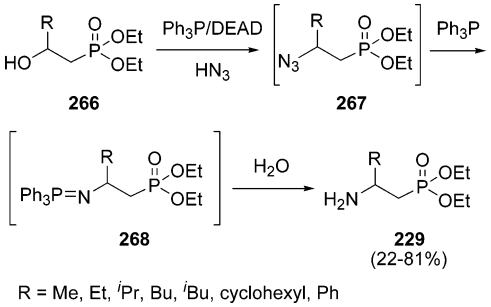
Scheme 71



Scheme 72



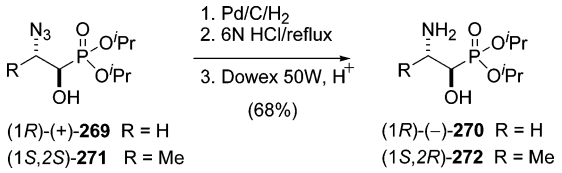
Scheme 73



intermediate can afford diethyl 2-aminoalkylphosphonates **229** with alkyl and aryl substituents at the C-2 carbon in good yields (Scheme 73). Mitsunobu reaction of diethyl 2-hydroxyalkylphosphonates **266** with hydrazoic acid and subsequent treatment of intermediate azides **267** with triphenylphosphine followed by hydrolysis of the iminophosphoranes[172] **268** with water offered a general, convenient, and economic route to diethyl 2-aminoalkylphosphonates **229**.[173]

This process can be extended to β-aminophosphonates containing a hydroxy group in the α position. Optically active (*R*)-(−)-2-amino-1-hydroxyethylphosphonic acid **270** can be prepared by a chemoenzymatic approach with a high enantiomeric excess (Scheme 74).[174] Catalytic reduction of the starting (*R*)-(+)-2-azido-1-hydroxyethylphosphonate **269**, deprotection, and purification furnished l-phosphaisoserine **270** (R = H) in high yield. The same group,[128a] through a similar strategy, also reported the preparation of (1*S*,2*R*)-2-amino-1-hydroxypropylphosphonate **272** (R = Me) with enantiomeric excesses of

Scheme 74



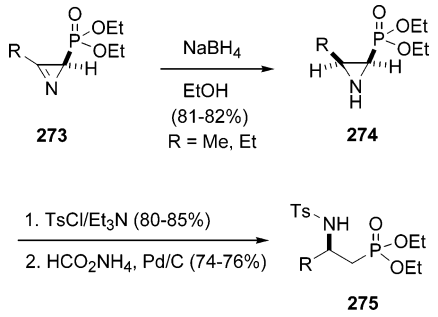
≥98% as well as (*R*)-2-aminophosphonic acid derivative.[175]

6. Heterocyclic Ring Opening

6.1. Aziridines Ring Opening

Simple 2*H*-azirinyl phosphonates **273**, prepared from easily available tosyloximes, served as precursors of *β*-aminophosphonate esters **275**. Reduction of enantiomerically enriched azirines derived from phosphonates **273** with sodium borohydride gave exclusively *cis*-aziridines **274** (Scheme 75). After tosylation

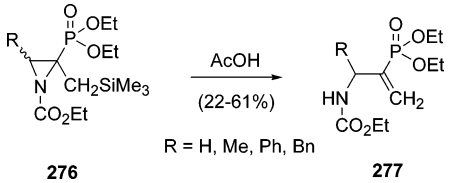
Scheme 75



and hydrogenolysis with ammonium formate (HCO_2NH_4), palladium on carbon gave the corresponding *β*-aminophosphonates **275** with retention of configuration through a regioselective ring opening of the N−C2 single bond of the aziridine ring.[176]

Ring opening of the corresponding *N*-(ethoxycarbonyl)aziridinyl phosphonates **276** in the presence of acetic acid, through a tandem silyl group elimination and selective N−C2 ring opening of aziridine, afforded α-methylene-*β*-(ethoxycarbonyl) aminoalkylphosphonates **277** (Scheme 76).[177]

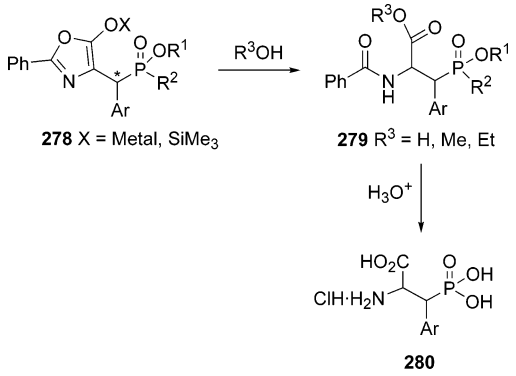
Scheme 76



6.2. Oxazoles Ring Opening

Some oxazoles can be considered as amino acid templates in organic synthesis.[178] For this reason, *β*-aminoethylphosphorus derivatives were also formed by reaction of alkali metal or trialkylsilyl derivatives of 4-(*P*-substituted methyl)-5-hydroxy oxazoles with *O*- or *N*-nucleophiles. Solvolysis of oxazole derivatives **278** with alcohols or water provided 3-aryl-2-(benzoylamino)-3-(dialkoxyphosphoryl)propionic acid esters (R³ = Me, Et) and propionic acids (R³ = H) **279**, respectively (Scheme 77).[64a,179] High diastereoselec-

Scheme 77



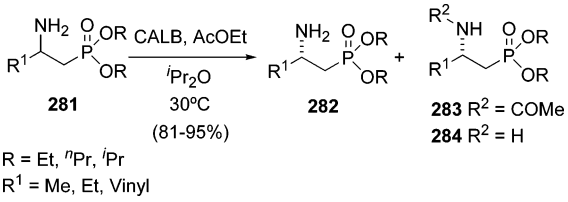
tivity was dependent on the reaction conditions, as there was remarkably different diastereoselectivity in basic versus acid media. A complete hydrolysis of compounds **279** afforded the hydrochloride salt of APPA derivative **280**.

7. Reactions of β-Aminophosphonates

7.1. Enzymatic Resolutions of Racemic Mixtures

Enzymatic synthesis of optically active *β*-aminophosphonates has been recently reported by Yuan et al. (Scheme 78).[180] *Candida antarctica* lipase B

Scheme 78



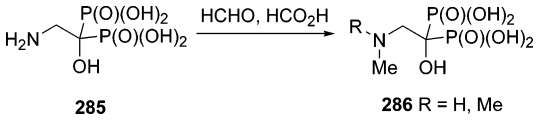
(CALB)-catalyzed acylation of **281** using ethyl acetate as acetylating reagent and diisopropyl ether as the reaction medium led to optically enriched (*S*)-amine-**282** and (*R*)-acyl aminophosphonate **283** with very good enantiomeric excess. The configuration of the resulting 2-aminoalkylphosphonates **282** was assigned as *S* based on the optical rotation of diethyl (*S*)-2-aminopropylphosphonic acid **282** (R = Et).[22b]

7.2. Reactions at the Terminal Nitrogen Atom

Once an aminoethylphosphorus derivative has been prepared, several substituents at the nitrogen atom can be altered or changed. These new compounds obtained by modification of *N*-substituents in the amino group of AEP and derivatives may be of value in studies of the chemical bonds incorporating AEP in macromolecular structures (vide infra, Scheme 88).

Several bisphosphonic acid derivatives **285** have been used for the synthesis of their *N*-methylated derivatives **286** (Scheme 79). *N*-Methylation (**286**, R = H) and *N*,*N*-dimethylation (**286**, R = Me) of this system were achieved with a mixture of formic acid and formaldehyde.[21b]

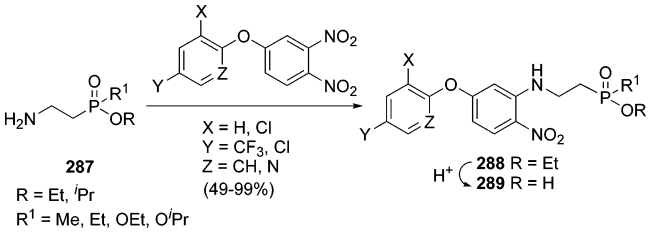
Scheme 79



285 **286** R = H, Me

Interaction of 4-phenoxy- and 4-pyridyloxy-substituted 1,2-dinitrobenzenes and aminoalkylphosphonates (R^1 = OR) and phosphinates (R^1 = alkyl) **287** produced mainly 5-phenoxy- and 5-pyridyloxy-substituted 2-nitrophenylaminoalkylphosphonates (R^1 = OR) and -phosphinates (R^1 = alkyl) **288** in good yields (Scheme 80). Some of them showed herbicidal and

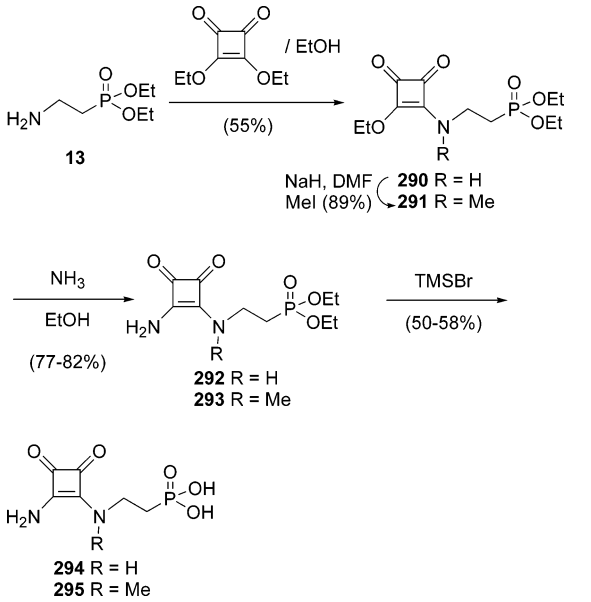
Scheme 80



plant growth regulating activity.[181] Hydrolysis of esters **288** with 6 N HCl under reflux yielded the corresponding acids **289** in nearly quantitative yield.

A new and potent NMDA antagonist was prepared from diethyl (2-aminoethyl)phosphonate **13** when this compound was treated with 3,4-diethoxy-3-cyclobutene-1,2-dione followed by alkylation with iodomethane to afford the phosphonate derivative **291** (Scheme 81). Esters **290** and **291** were treated with

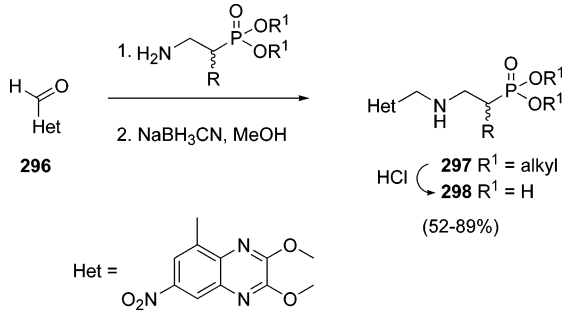
Scheme 81



ethanolic ammonia, delivering compounds **292** and **293**. Deprotection of the phosphonate esters **292** and **293** was achieved in refluxing 1,2-dichloroethane with 6 equiv of bromotrimethylsilane to yield phosphonic acid derivatives **294** and **295**, respectively.[182]

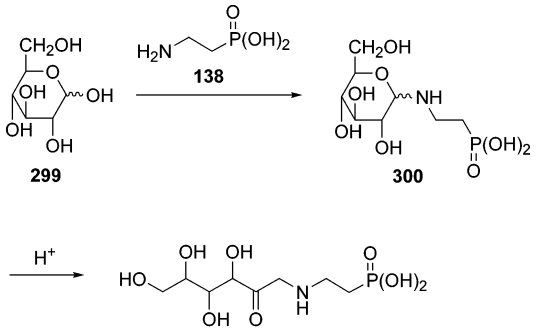
Likewise, *N*-substituted 5-aminomethylquinoxalinediones containing phosphonic acids yielded potent and selective AMPA and/or NMDA (glycine-binding site) antagonists. Heterocyclic aldehydes **296** were coupled to aminophosphonates under reductive amination conditions and deprotected by treatment with concentrated HCl, affording a new β-aminoethylphosphonic acid **298** with a different substitution pattern on the amino group (Scheme 82).[183]

Scheme 82



This simple procedure has been extended to the incorporation of AEP into a sugar structure. Among applications of modification of *N*-substituents in the amino group, AEP **138** has been found to react readily with D-glucose **299**. The D-glucosylamine **300** initially formed underwent Amadori rearrangement, giving an amino ketose as the open-chain form **301** (Scheme 83).[184]

Scheme 83

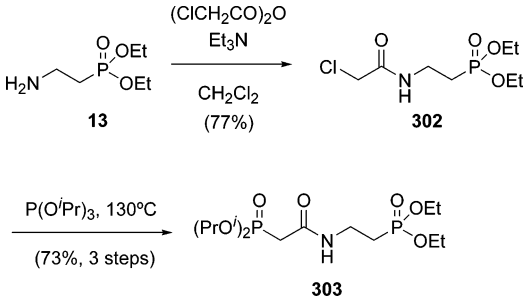


One of the most widely used modification strategies of β-aminophosphonates involves the coupling reaction of the amino group with acylating agents for amide bond formation. Treatment of 3-phosphonoalanine with KOCN gave *N*-carbamoyl-3-phosphonoalanine after *N*-acylation of the amino group.[185] Analogously, phosphonate **13** was treated with chloroacetic anhydride to afford *N*-protected phosphonate **302**, which was then reacted with phosphite, leading to the formation of diphosphonate **303** in 73% overall yield (Scheme 84).[71]

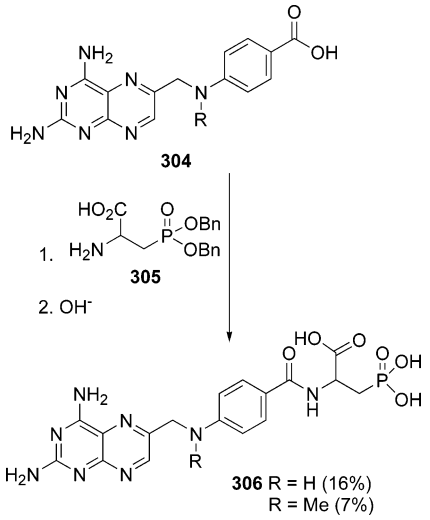
Indeed, an aminophosphonate or -phosphinate unit can be linked to a carboxylic end of an amino acid or a peptide. Treatment of 2-amino-3-(dibenzoxyphosphoryl)propanoic acid **305**, obtained from 2-aminoethylphosphonic acids with benzyl alcohol (BnOH) in the presence of $SOCl_2$, with an equimolar amount of *p*-nitrophenyl 4-deoxy-4-amino-*N*-formylpteroate **304** and excess Et_3N followed by alcaline hydrolysis gave the corresponding amide **306** (Scheme 85).[186]

For the preparation of nonpeptidic inhibitors of farnesyl protein transferase, syntheses of stereochemically pure functionalized acids **310** and **311**

Scheme 84

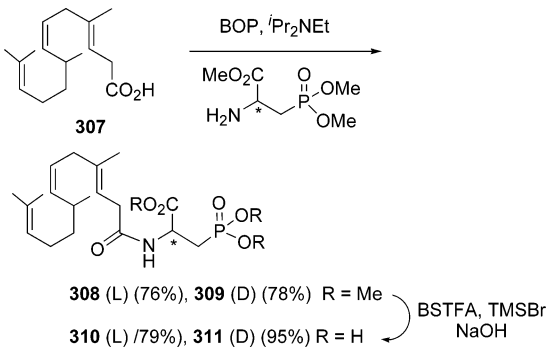


Scheme 85



were needed. These compounds were prepared by coupling of (*E*)-homofarnesoic acids **307** with chiral amino esters derived from D- and L-APPA derivative followed by hydrolysis to give the retro analogues **310** and **311**, respectively, as a 2:1 *E*/*Z* mixture (Scheme 86).[187]

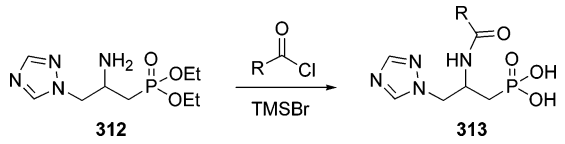
Scheme 86



The synthesis and enzymatic activity of a library of β-carboxamido phosphonic acids as inhibitors of imidazole glycerol phosphate dehydratase (IGPD) have been reported. Starting from the amine phosphonate diester **312**, treatment with a variety of acids or acid chlorides, followed by saponification of the phosphonate diester, the desired carboxamide **313** (Scheme 87) was obtained.[188] Solid-phase-supported scavengers as a diamine resin and succinic anhydride were used for removing unreacted acid chloride and amine.

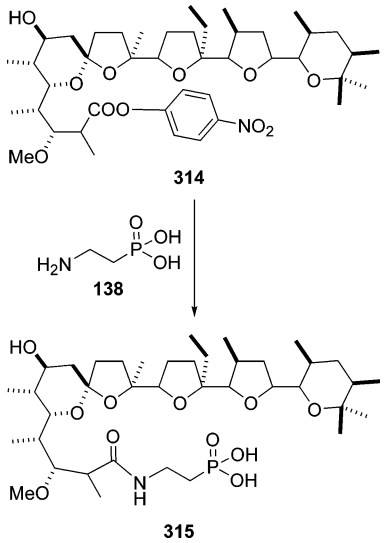
The amide bond formation can also be performed by reaction of ester with β-aminoethylphosphonic acid

Scheme 87



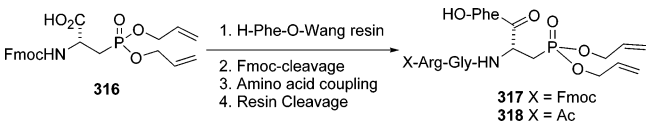
AEP **138** and has been applied for the preparation of several monensin derivatives characterized by different lipophilicities. Among them, monensin ciliatine amide **315** was synthesized by reaction of monensin 4-nitrophenolate **314** with ciliatine (AEP) **138**[189] (Scheme 88).

Scheme 88



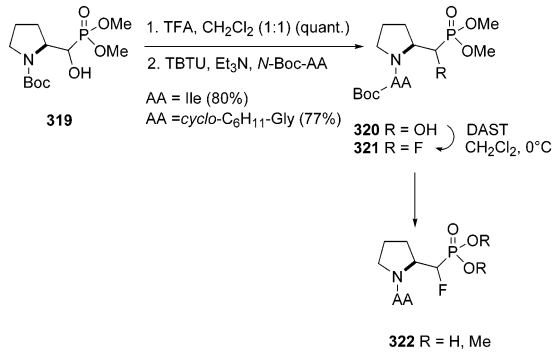
One of the best applications for the amide bond formation of β-aminoethylphosphorus derivatives is attaching of AEP to a peptidic chain through the amino group for the preparation of β-phosphapeptides. Quin[9b] suggested that the naturally occurring aminophosphonic acids are bound to proteins and peptides. Hence, the synthesis and study of phosphonopeptides derived from aminophosphonic acids may be of considerable importance to the understanding of the biological significance of this class of compounds. Among several examples, β-aminophosphonate derivative **316** could be a useful building block for the preparation of phosphorus analogue peptides **317** and **318** with β-carboxylic ester substitution by standard Fmoc-solid-phase synthesis (Scheme 89).[37]

Scheme 89



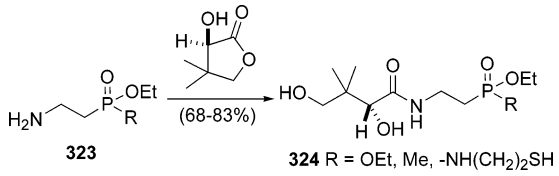
Deprotection of the amino functionality of phosphonate ester **319**, obtained by hydrophosphinylation reaction, and coupling with *N*-Boc-Ile or *N*-Boc-*cyclo*-C_6H_{11}-Gly afforded dipeptides **320**, which were fluorinated with DAST to give β-amino-α-fluorinated phosphonopeptides **321** in moderate yield (Scheme 90).[54] Finally, different deprotecting steps were then used to obtain the deprotected β-amino-α-fluorinated phosphonopeptides **322**.

Scheme 90



Optically active functionalized amides derived from phosphonic or phosphinic esters can also be obtained by reaction with optically active lactones. Likewise, phosphono and phosphino analogues of pantothenic acid ethyl ester **324**, where the β-alanine is replaced by (2-aminoethyl)alkylphosphonic acid, have been prepared (Scheme 91).[190]

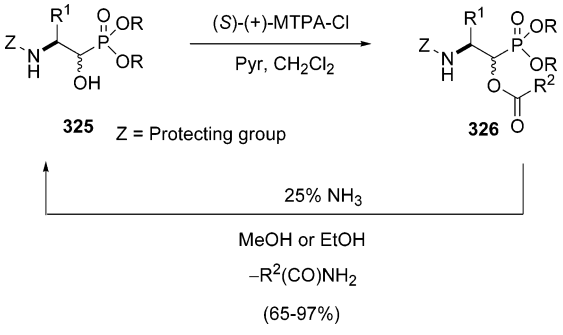
Scheme 91



7.3. Reactions at the α-Carbon Atom and α-Carbon Substituents

Reactions at the α-carbon of the β-aminophosphonates mainly consist in the preparation of esters of α-hydroxyphosphonates and their ammonolysis for recovery of alcohol from carboxylic esters. For example, protection of the free hydroxy group in α-hydroxyphosphonates **325** as Mosher esters (*R*)-MTPA-**326** and their use as protecting groups has been reported by Hammerschmidt et al.[191] (Scheme 92).

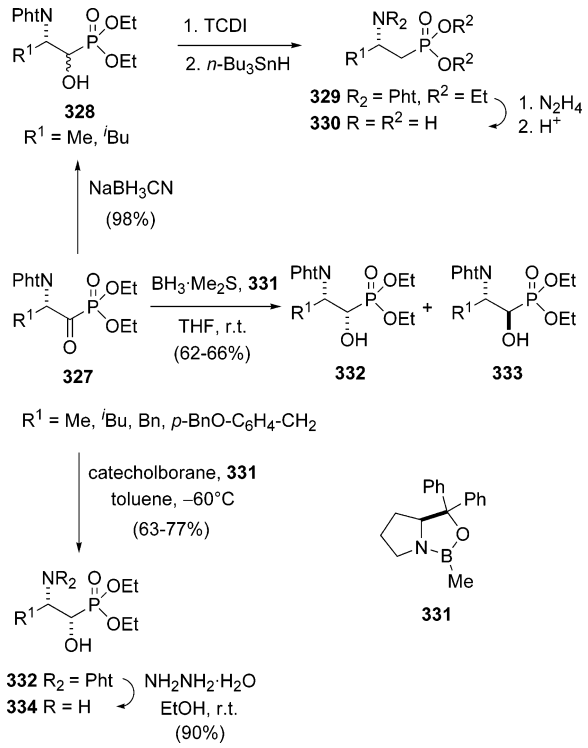
Scheme 92



Ammonolysis of carboxylic esters **326** has also been reported, giving rise to the free α-hydroxyphosphonates **325** with good yields.[192]

Reduction of nitrogen-protected oxoalkylphosphonates **327** represents an easy access to the synthesis of β-aminophosphonates through modification reaction on the *C*α-carbon atom.[21a] Direct synthesis of chiral 2-aminoalkylphosphonic acid derivatives was described from commercially available (*S*)-(+)-alanine and (*S*)-(+)-leucine without racemization of the starting optically active amino acids.[22b] α-Ketophosphonates **327** were converted into α-hydroxylalkylphosphonates **328** by treatment with sodium cyanoborohydride in almost quantitative yield but in low diastereoselectivity (Scheme 93). Following deoxy-

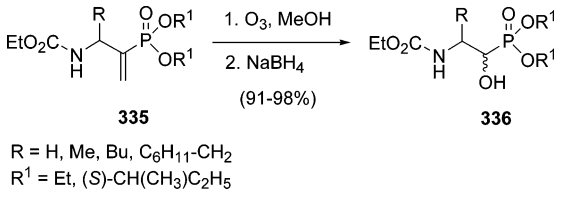
Scheme 93



genation reaction of the hydroxyl group with thiocarbonyl-diimidazole (TCDI), posterior treatment with tributyltin hydride afforded the corresponding phthalimide-protected aminoalkylphosphonates **329** in good yields. Deprotection with hydrazine and acid hydrolysis generated the enantiomerically pure aminophosphonates **330** without racemization of starting amino acids. However, a highly diastereoselective synthesis of β-amino-α-hydroxyphosphonates **332** and **333** by means of oxazaborolidine-catalyzed reduction of β-phthalimido-α-ketophosphonates **327** has been reported (Scheme 93).[22a] Reductions with the borane-dimethyl sulfide complex in the presence of a catalytic amount (12 mol %) of oxazaborolidine **331** afforded mixtures of diastereoisomers **332** and **333** (R = alkyl, aryl) in a ratio from 8:1 to 10:1 in favor of syn diastereoselectivity. On the other hand, the highest diastereoselectivities were achieved when catecholborane was used as the reductant in the presence of a catalytic amount of oxazaborolidine **331**, obtaining exclusively compound **332**.

Oxidative cleavage of C−C double bonds can be performed with ozone. By means of this process it is possible to obtain the interesting α-hydroxy-β-aminophosphonic acid derivatives **336** by ozonization and subsequent reduction with a large excess of $NaBH_4$, of the starting α-methylene-β-aminophosphonic esters **335**.[193] The suitable α-methylene *N*-(ethoxycarbonyl)-β-aminophosphonic esters **335** were prepared from α,β-unsaturated phosphonic esters (Scheme 94).

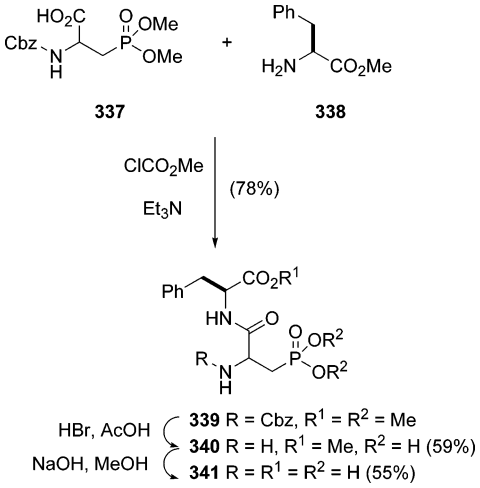
Scheme 94



7.4. Reactions at the β-Carbon Atom and β-Carbon Substituents

Some examples reported modifications at the β-carbon of the β-aminoethylphosphonate skeleton for the preparation of more complex structures. Thus, phosphapeptide **341** was synthesized from (*S*)-phenylalanine methyl ester and the *N*-benzoxycarbonyl derivative of racemic phosphonate **337** (Scheme 95).[194]

Scheme 95



After coupling, the fully blocked peptide **339** ($R^1 = R^2 =$ Me) was partially deblocked to the methyl carboxylate **340** ($R^1 =$ Me, $R^2 =$ H) by treatment with hydrogen bromide in acetic acid. Finally, this ester **340** was converted to the fully deblocked peptide **341** ($R^1 = R^2 =$ H) by treatment with methanolic sodium hydroxide.

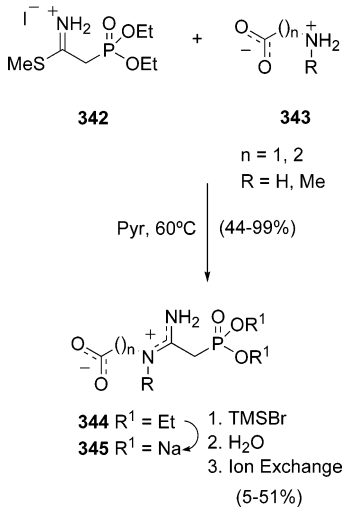
Amidinomethylphosphonate compounds, in which the C−NH−P unit of known phosphocreatine analogues has been replaced by C−CH_2−P unit (compounds **345**, Scheme 96), exhibit antitumor activity. A very concise synthesis was developed for the preparation of this class of compounds starting with 2-(diethylphosphono)-(*S*)-methylthioacetamidinium iodide **342**.[195] This compound was treated with amino acids **343** in pyridine to obtain the protected analogues **344** in good yield (Scheme 96). Subsequent conversion of the diethyl phosphonate to the phosphonic acids was accomplished with bromotrimethylsilane followed by aqueous hydrolysis. Purification of the final compounds with ion-exchange chromatography resulted in isolation of the pure compounds as their disodium salts **345**.

7.5. Reactions at the Phosphorus Atom

7.5.1. Phosphorus–Oxygen Bond Formation

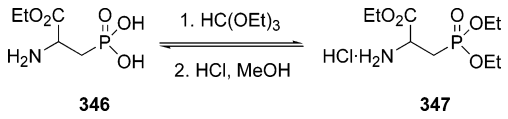
Direct esterification of phosphonic acids with alcohols presents some disadvantages (side reactions).

Scheme 96



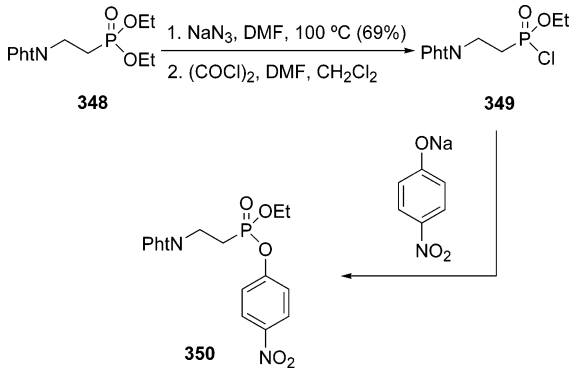
For this reason, an easy strategy has been developed using ethyl orthoformate. When phosphonic acid analogues of aspartic acid **346** were reacted with ethyl orthoformate, the corresponding formyl derivative (major, 90%) and imino derivative (minor, 10%) phosphonates were obtained.[196] Acid hydrolysis of the mixture gave β-amino ester **347** in good yield involving selective esterification of phosphonic acid (Scheme 97).

Scheme 97



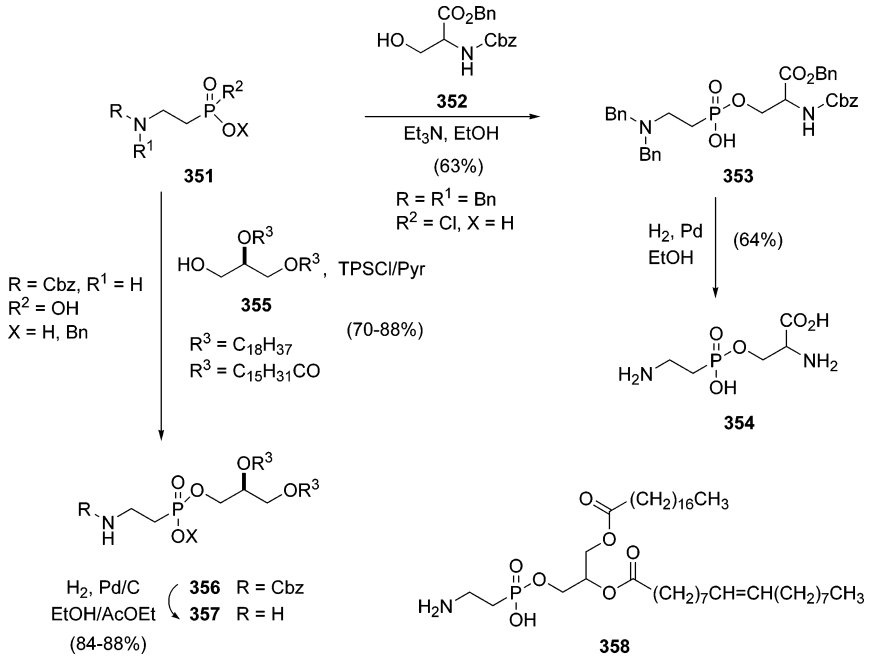
Reactions at the phosphorus atom with phosphorus−oxygen bond formation have been made through the β-aminophosphonic monochloride derivative. Thus, from phthalimide-substituted phosphonates **348**, after selective P−O bond cleavage of phosphonic acid diester with sodium azide to the corresponding monoester, the latter were reacted with oxalyl chloride in the presence of catalytic DMF for the formation of the key intermediate phosphonochloridates **349**. The crude reaction mixture could react with sodium 4-nitrophenolate to form ethyl 4-nitrophenylphosphonate **350** (Scheme 98).[197]

Scheme 98



Baer et al. reported the preparation of phosphonic acid analogues of the naturally occurring phosphate

Scheme 99

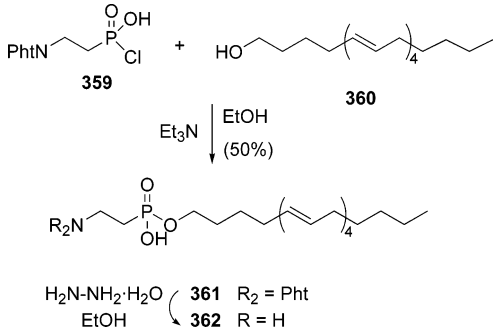


diester derived from L-serine, such as 2-aminoethyl phosphate-L-serine and -D-serine **354**.[198] Phosphonic acid **354** was obtained by the reaction of *N*-diprotected phosphonic acid monochloride **351** and triethylamine with *N*-Cbz-L- or -D-serine benzyl ester **352**, followed by the simultaneous removal of the protective carbobenzoxy (Cbz) and benzyl (Bn) groups of the reaction product **353**, to afford phosphonic acid derivative **354** in an overall yield of about 40% (Scheme 99). Construction of the P−O bond also takes place in the synthesis of glycerophosphonolipids containing aminoalkylphosphonic acids. Thus, phosphonylation reaction of substituted glycerols **355** with phosphonic acids **351** and subsequent hydrogenolysis led to the formation of phosphonolipids **357** (Scheme 99).[199] The same strategy has been used for the preparation of phosphonolipid **358** containing two dissimilar fatty acid substituents (Scheme 99).[200] This mixed-acid L-α-phosphonocephalin **358** was obtained by phosphonylation of the glycerol derivative with the *N*-protected phosphonic acid monochloride.

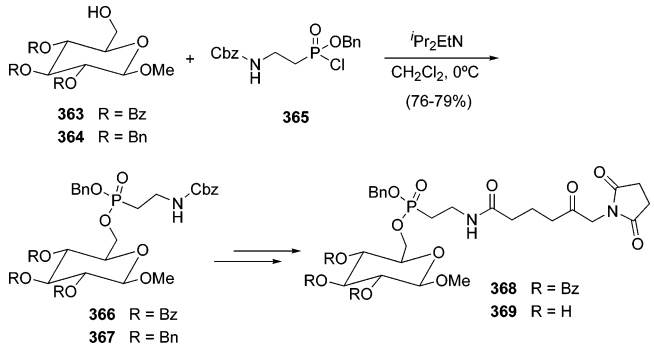
Lysophosphatidylethanolamine analogues have also been reported as effective inhibitors of the renin−renin substrate reaction in vitro.[201] For the preparation of arachidonyl phosphonate **362**, arachidonyl alcohol **360** was subjected to phosphonylation with phosphonic acid monochloride **359** in the presence of triethylamine, providing the intermediate phthalimide **361**, which was converted via hydrazinolysis to arachidonyl phosphonate **362** (Scheme 100).

Two β-aminophosphonate haptens derived from methyl α-D-glucopyranoside **368** and **369** (Scheme 101) have been synthesized to mimic the transition state of a transesterification reaction between methyl α-D-glucopyranoside and 4-nitrophenylester of Boc-β-alanine.[23] A phosphonylation reaction between phosphonochloridate intermediate **365** and glucopyranoside **363** or **364** in the presence of Hünig's base afforded the protected phosphonates **366** and **367** in good yields (Scheme 101). These phosphonates **366**

Scheme 100



Scheme 101

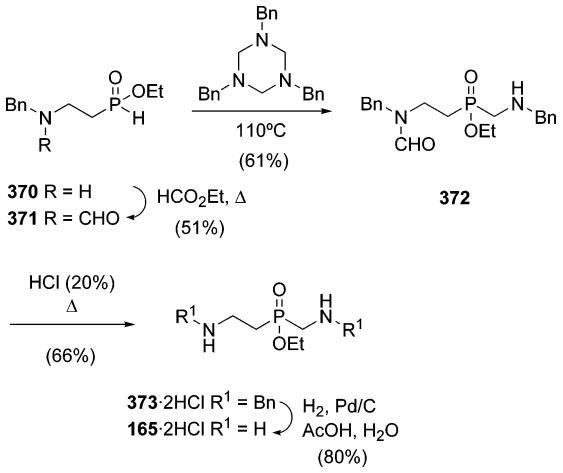


and **367** were subjected to catalytic hydrogenation and subsequent attachment to quinuclidine to afford β-aminophosphonates haptens **368** and **369**.

7.5.2. Additional Carbon–Phosphorus Bond Formation

Reactions of this type are not very often in the chemistry of β-aminophosphorus compounds. However, the addition of phosphinates to imine compounds has been used for the preparation of α-aminophosphorylated derivatives,[202] and a similar strategy has been used for the preparation of phosphinate **165**, phosphorylated analogue of spermidine.[117] The synthesis of **165** could be accomplished starting from

Scheme 102

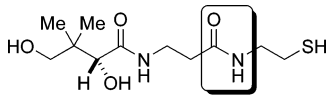


N-protected *β*-aminophosphinate **370** (Scheme 102). Treatment of **370** with ethyl formate as the solvent afforded the (*N*-formyl-*N*-benzyl)aminophosphinate **371**, which was then reacted with tribenzylhexahydrotriazine, the synthetic equivalent of imine derived from formaldehyde, at 110 °C to give phosphinate **372**. The final phosphinate analogue of spermidine **165** was obtained from **372** by hydrolysis of this latter compound and subsequent hydrogenation of the intermediate phosphinate **373**, giving rise to phosphinate **165** with good yield.

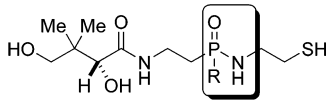
7.5.3. Phosphorus–Nitrogen Bond Formation

Phosphapeptides containing a phosphonamidate bond, where the planar amide of peptides is replaced by the tetrahedral phosphonamide structure, play an interesting role in the design of new enzyme inhibitors because these substrates can mimic the transition state in some reactions, although it is known that P−N linkage is quite easily hydrolyzed in vitro and in vivo.[11] Replacement of the carbonyl group of one of the amide linkage of Pantetheine **374**, an intermediate for the synthesis of the phosphono analogue of coenzyme-A **375**, by a methyl-, ethyl-, or phenylphosphinoyl group as shown in (Scheme 103)[190,203] has been reported.

Scheme 103



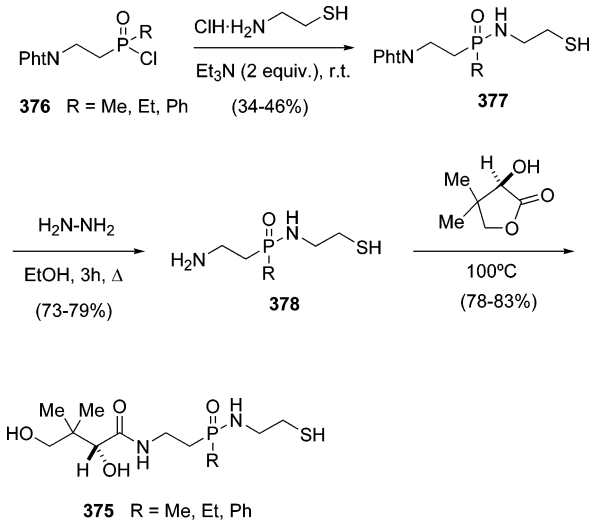
Pantetheine (**374**)



375 R = Me, Et, Ph

The synthesis of **375**, which involves phosphorus−nitrogen bond construction, could be accomplished by reaction of *N*-phthalimidophosphonic acid monochloride **376** and triethylamine with 2-aminoethanethiol hydrochloride followed by removal of the protective phthaloyl (Pht) group of the reaction product **377** to

Scheme 104



afford phosphonic acids analogues **378** (Scheme 104). These analogues **378** reacted with (−)-(*R*)-pantolactone to give phosphonic acid analogues of Pantetheine **375** containing a phosphonamidate bond.

Yamauchi et al. reported the first synthesis of di- and tripeptide aminoethylphosphonic acid analogues.[138,204] The key step in the synthesis of the abnormal peptides is the formation of the phosphonamide bond as well as deprotection of the protecting groups. Since the phosphonamide bond is labile under acidic conditions, it is necessary to select protecting groups which can be removed easily under neutral or alkaline conditions. Phosphono monochloridate **379** was able to condense with various amino acid ethyl esters in the presence of triethylamine to give the corresponding dipeptide analogues **380**. To convert **380** to the tripeptide derivatives **382**, the phthaloyl group was removed by treatment with equimolar hydrazine hydrate, and the resulting dipeptides **381** were subsequently allowed to couple with different amino acids (AA) by means of DCC, giving tripeptides **382** in overall yields of 25−40% (Scheme 105).

Scheme 105

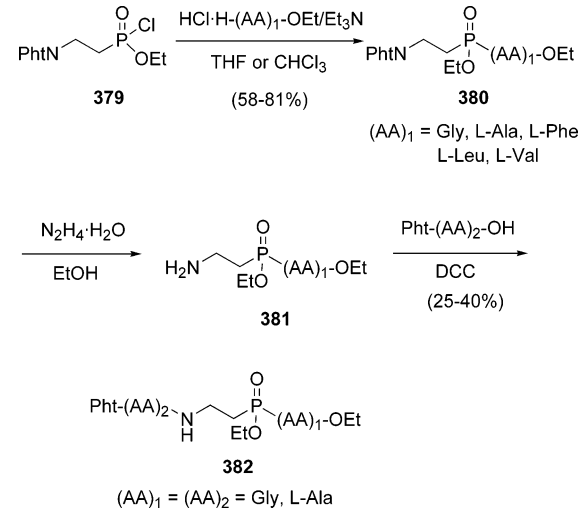


Table 1. Biological Activities of Some Representative β-Aminophosphonates and -Phosphinates

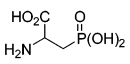
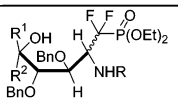
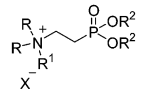
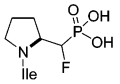
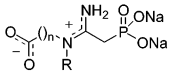
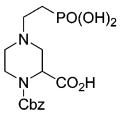
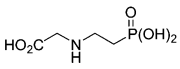
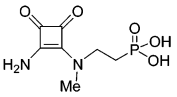
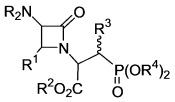
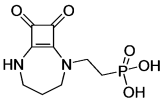
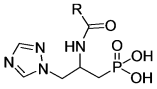
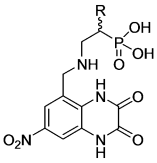
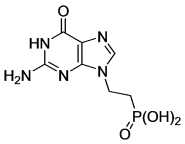
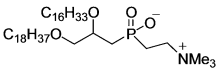
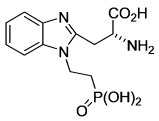
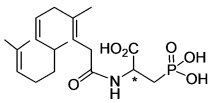
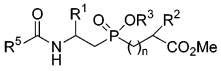
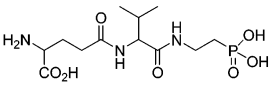
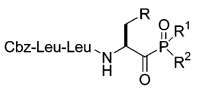
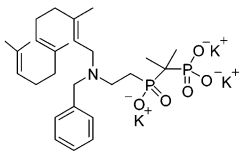
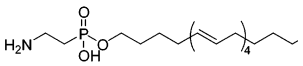
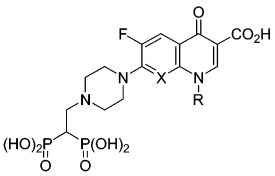
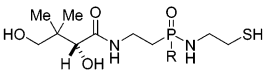
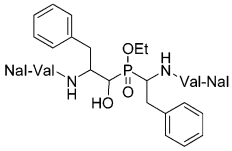
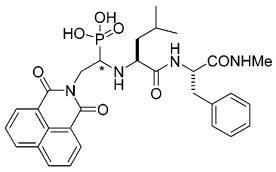
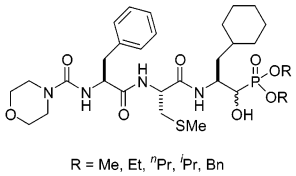
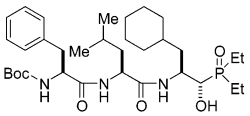
COMPOUND	ACTIVITY	Ref.	COMPOUND	ACTIVITY	Ref.
	- glutamate receptor antagonist - antiviral activity	141	 R = Bn, All R^1 = H, R^2 = CH_2OBn R^1 = CH_2OBn, R^2 = H	glycosyl transferase inhibitors	77,78
 R, R^1, R^2 = $C_{14}H_{29}$, $C_{18}H_{35}$, $C_{18}H_{33}$ X = halogen, triflate	non-viral vector-mediated gene transfer	115		proline selective dipeptidases inhibitor	54
 n = 1, R = H, Me n = 2, R = H	creatine kinase inhibitors	195		NMDA antagonist	100
	*N*-methyl-D-aspartate (NMDA) antagonist	101		NMDA antagonist	182
	carbapenem antibiotics	61		NMDA antagonist (neurological disorders)	163
	imidazole glycerol phosphate dehydratase (IGPD) inhibitors	188	 R = H, Me	α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and/or NMDA antagonists	183
	human purine nucleoside phosphorylase inhibitor	98		*Clostridium welchii* phospholipase C inhibitor	108
	NMDA antagonist	99		farnesyl protein transferase inhibitor	187
	angiotensin converting enzyme inhibitors	142		glutathionyl spermidine inhibitor	205
 R^1 = R^2 = *p*-ClC_6H_4 R^1 = Ph, R^2 = OEt	human calpain I inhibitors	50		squalene synthetase inhibitor	147
	renin inhibitor	201	 X = C, R = Et X = N, R = Et X = C, R = cyclopropyl	antibacterials	121

Table 1 (Continued)

COMPOUND	ACTIVITY	Ref.	COMPOUND	ACTIVITY	Ref.
 R = Me, Et, Ph	phosphono analogues of coenzyme-A	190,203		HIV protease inhibitor	42
	collagenase inhibitor	67	 R = Me, Et, ^{n}Pr, ^{i}Pr, Bn	Norstatine renin inhibitors	44
	human renin inhibitor	41			

8. Conclusions

In summary, it is evident from the results presented in this review that different methodologies have been applied as effective tools for the construction of β-aminophosphonic and -phosphinic acid derivatives. Although carbon−phosphorus, carbon−carbon, or carbon−nitrogen bond-formation reactions have become useful and versatile methods for the synthesis of β-aminophosphonic acid derivatives, other methods, such as ring-opening reaction of heterocycles or reactions of other functionalized β-aminophosphonates, provide straightforward access to β-aminophosphonic acid derivatives. The development of methods for the preparation of β-aminophosphonic or -phosphinic acid derivatives is important and currently attracting growing interest. Therefore, it is reasonable to expect, soon, research into new methodologies for the preparation of asymmetric β-aminophosphonic acid derivatives.

Some works have documented the usefulness of these compounds as biologically active compounds and intermediates for the synthesis of β-aminophosphonopeptides. Because β-aminophosphonopeptides are well-recognized key components for a variety of protease inhibitors, introduction of an aminophosphonate into the peptide molecule offers several structural possibilities. We believe that the growing importance of enantiopure β-aminophosphonic acid derivatives should stimulate further achievements in this area.

Table 1 contains the biological activity of some representative examples of β-aminophosphonates and -phosphinates.

9. Acknowledgments

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