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alpha-substitution in organophosphorus chemistry

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City University of New York, 1991

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alpha-SUBSTITUTION

IN

ORGANOPHOSPHORUS CHEMISTRY

by

SUBIR K. CHAKRABORTY

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York.

1991

This manuscript has been read and accepted for the Graduate Faculty in Chemistry in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

9/23/91
date

Robert Engel
Chairman of Examining Committee

9/23/91
date

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Supervisory Committee

The City University of New York

ABSTRACT

alpha-Substitution

in

ORGANOPHOSPHORUS CHEMISTRY

by

SUBIR K. CHAKRABORTY

ADVISOR: **Professor ROBERT ENGEL**

1. An unique, simple and versatile synthetic scheme has been developed and utilized for the preparation of several *alpha*-aminoalkyl phosphonic acid di-ester analogues. They are analogues of several natural amino acids. The key step in this scheme is the *alpha*-halogenation of the alkyl phosphonates using NBS followed by S_N2 displacement by azido group and subsequent reductive hydrogenolysis.

2. *alpha*-Halogenated alkyl phosphonates (achieved through reaction of Arbuzov products with NBS) are converted to corresponding *alpha*-hydroxy phosphonic acids in two steps by first ester cleavage using BTMS to *alpha*-haloalkyl phosphonic acids and then subsequent hydrolysis with sodium hydroxide solution followed by Dowex treatment and fractional crystallization.

Dedicated to my dear and loving parents and my younger brother.

Acknowledgements

I would like to express my deep sincerity and appreciation to Prof. Robert Engel, my mentor and a friend, who helped me throughout the graduate program and the research projects.

I extend my special thanks to Dr. Hoe Sup Byun not only for his advices and helpful discussions in my research project but also for his encouragement and friendship.

I extend my thanks to all professors including prof. Leonard H. Schwartz, colleagues, friends who provided all the moral boosts and constant encouragement during the research work.

Preface:

Of particular interest in the present work are substituted phosphonate analogues of natural biomolecules. The derivatives with substituents at the α-position relative to phosphorus deserve special treatment because of new chemical properties resulting from close proximity of functional groups and because numerous α-substituted phosphonates have rather interesting biochemical and biological properties. This is particularly true for 1-aminoalkylphosphonates and for phosphonates substituted with a halogen atom or alkoxy/hydroxy groups. In fact, the search for new biologically active compounds has stimulated a substantial part of recent studies on the synthesis of α-substituted phosphonates.

In this light, new approaches to the synthesis of α-substituted phosphonic acids have been the target of the current research.

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Chapter 1

α-Aminoalkyl Phosphonates: Analogues of α-Aminoacids and Peptides

Known natural α-amino acids and their role:

The chemistry of the living organisms is concerned mainly with five major classes of compounds: carbohydrates, lipids, minerals, nucleic acids, and proteins. Among them, exploration of the nature and formation of proteins is greatly pursued in today's chemistry as they are the compounds which help greatly to define the properties we ascribe to life. They determine metabolism, form tissues, provide motion, transport compounds, and protect from deleterious invasion. Even the heredity of an organism is nothing more than an expression of its ability to make various kinds of proteins at different rates.

In operational terms, proteins serve to place reactive chemical groups in particular three-dimensional patterns and to control access of the reagents to these groups. In order to appreciate these functions we must understand the constitution of these patterns and how they interact. In general, the number, chemical nature and sequential order of amino acids in a protein chain determine the distinctive structure and characteristic chemical behavior of each protein.

In chemical terms, a protein is a biologically active macromolecule, or so called polymer, of covalently linked amino acids, that is, 2-amino carboxylic acids, that range in molecular weight from about 6000 (single protein chain) to several million (protein complexes).[1]

Proteins are constructed from approximately 20 different amino acids. Tissues contain substantial amounts of each of these in different individually characteristic combinations. This pool of free amino acids must be present if proteins are to be made, but amino acids also serve other important purposes. Some are used as chemical messengers to transmit impulses between nerves, while others are actively metabolized to form products with important physiological functions. Derangement of amino acid metabolism frequently has severe consequences.[2]

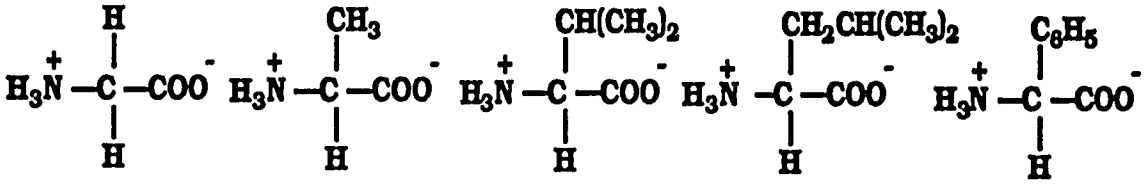
The amino acids have the general structure:

zwitterion

α-amino acid, where R represents a side chain

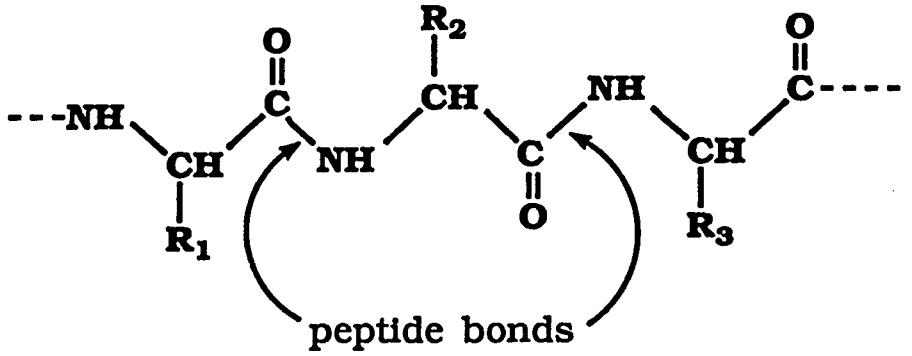
Amino acids, containing both an amino and a carboxylic acid group within the same molecule, and thereby having two groups of opposite charge, draw their properties from a hydrogen

atom and three substituent groups on C-2, the α-carbon atom. It is the nature of the R group that gives character to an individual amino acid, and these groups, usually called side chains, are all important in determining the properties of proteins. More details about each type of amino acid and the side chains can be found in any undergraduate biochemistry text book, but only five amino acids are mentioned here since they are relevant to the thesis work. Except phenylglycine, these are naturally occuring amino acids. The most distinct property of the following α-amino acids, except for glycine, is the asymmetry of their α-carbon site. They thereby exhibit stereoisomerism.



glycine alanine valine leucine phenylglycine

In the above context, it should be mentioned that proteins are simply large peptides. Peptides are biologically important polymers in which α-amino acids are joined into chains through amide bonds, also called peptide bonds. A general peptide structure is given below.



A dipeptide contains two amino acid residues, and a tripeptide contains three amino acid residues. Large peptides of biological importance are known by common names; for example, insulin is an important peptide hormone containing 51 amino acid residues. On the other hand, ribonuclease, an enzyme, is a protein containing 124 amino acid residues and is really a small protein.

Phosphorus analogues: Rationale for such structures.

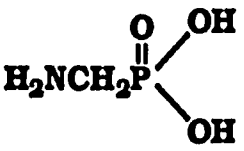
Phosphorus is required for the growth and reproduction of all plants and animals. Organic phosphates are essential biochemical constituents of living organisms, and phosphorylation is one of the most widespread chemical reactions of life. Consequently, organic esters of phosphoric acid play an integral part in the biochemical processes of all living systems.[3]

In recent years a major expansion of efforts in the synthesis of organophosphorus compounds, *i.e.*, those bearing a carbon atom bound directly to a phosphorus atom, has resulted from the recognition of the value of such materials for a variety of industrial, biological and chemical synthetic uses.[4] Their utility for

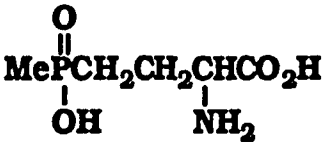
general synthetic organic applications are of particular significance for modern organic chemistry. Industrial uses have been demonstrated as flame-retardants, inhibitors of oxidation in lubricants, surfactants, *etc.* An important biological application of carbon-phosphorus bonded materials is their use as a probe for the investigation of metabolic processes, and has provided valuable information regarding biological mechanisms. Finally, these organophosphorus compounds have widespread popular use as *umpolung* and Wittig reagents.[4]

Since the discovery in 1959 of the first naturally occuring compound containing a covalent C-P bond (aminoethylphosphonic acid, AEP), many phosphonate related compounds have been identified in living organisms. They possess biological activity[5] and thus numerous investigations have been reported about the physical properties and the biological activity affected by the substitution of the carboxyl group with a phosphonyl group moiety.

The study of phosphorus analogues of the natural α-amino acids was started in the 1940's by Chavane,[6] and has accelerated in the past few years due to their useful biological activity. Thus a major area of synthetic interest has been with α-aminoalkylphosphonates and α-aminoalkylphosphonic acids. For example, the glycine analogue **(1)** is a plant growth regulant, the glutamic acid analogue **(2)** is a herbicide, and the dipeptide analogue **(3)** is an antibacterial agent which inhibits bacterial cell wall biosynthesis.[8]



(1)



(2)

(3)

Aminophosphonic acids are of particular interest as analogues of the amino-carboxylic acids and as structural units in phosphonopeptides. They have become increasingly important compounds in recent years due to their interesting biological properties and their applicability to the synthesis of phosphonopeptides of potential biological activity.[9] They are also used as herbicides, insecticides antibiotics and enzyme inhibitors. It is now well established that 1-aminoalkanephosphonic acids act as substrates or inhibitors of several enzymes involved in the metabolism of amino acids. Consequently, these phosphonic analogues of naturally occuring amino acids have received considerable attention in both academic and industrial laboratories. Due to their biological activity a considerable research effort has been directed towards developing suitable synthetic methodologies.

Current interest in 1-aminoalkylphosphonates is reflected by the fact that numerous papers on their synthesis and biological evaluation have been published during the last decade. Much has been published regarding the preparation of

α-aminoalkylphosphonates. Included here are the preparations of analogs of the naturally occuring amino acids, herbicidal agents, antibacterials, reagents for umpolung processes, and a variety of *N*-substituted α-aminoalkylphosphonates.[10] The product materials also have found utility as pharmaceutical agents for bone disorders. While some of them have been of interest as structural analogs of natural amino acids, most of them have been intended for use as herbicides.[11] Very recently, in non-biological chemistry, Pirkle *et.al.* have used optically active α-aminoalkylphosphonic acids diesters bonded to silica gel as a chiral stationary phase to separate many enantiomers and diastereomers.[12] This procedure has been used in our laboratory for the separation and detection of the diastereomers of phenyl menthyl phosphite and phenyl bornyl phosphite.

Chemistry of phosphonates: History, properties, identification and their role.

The study of the chemistry of phosphonates has accelerated in recent years owing to a view of their structures in relationship to the natural phosphates, coupled with the role of natural phosphonates in living systems. The phosphonates which are dealt with in this chapter are derived from alkylphosphonic acids. According to the general usage the term "phosphonate" covers summarily the phosphonic acids as well as their derivatives

with modified phosphonic acid groups. Because of the similarity of properties, it is purposeful to include also the dialkylphosphinic acids with substituents at the α-position.

Particular phosphonates, containing the C-C-P linkage instead of the C-O-P linkage, are considered structural isosteric analogues of natural phosphate esters, and are anticipated to be more stable to natural enzymes. These could be used as probes for metabolic regulation and perturbation since it is anticipated that the carbon-phosphorus bond is incapable of being hydrolyzed by the ordinary enzymes involved in phosphate cleavage.[13] Hence, several mechanistic possibilities are deemed to exist for metabolic regulation by compounds bearing such a linkage in place of the usual phosphate ester linkage. For example, given a phosphate which acts as a metabolite or metabolic regulator using enzymatic reactions at sites distant from the phosphate ester linkage, but by other extraneous routes is hydrolyzed to the inorganic phosphate, the use of a phosphonic acid analogue in its place might be expected to enhance the lifetime, and thereby the integrated activity, of the metabolite or regulator. Also, as a substitute for a natural phosphate metabolite, a phosphonic acid or a phosphonate ester may be capable of inhibiting or perturbing the regular metabolism of an organism simply by nonparticipation in a normal phosphate cleavage process. Finally, the phosphonic acid, substituting for a natural metabolite in its entrance to an organism

and possibly in several consequent steps, might be capable of specific or nonspecific inhibition of one or more enzymatic processes. Thus the use of phosphonic acids or phosphonates as analogues of natural phosphates represents a more systematic approach to metabolic regulation, enhancement or inhibition, than is commonly attributed to 'analogue' study.

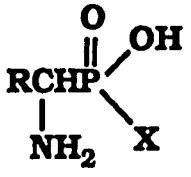
There are several physical and chemical comparisons that should be considered upon the performance of this fundamental structural substitution, aside from the fact that the phosphorus is not liable to hydrolysis by normal routes. For example, there will be a significant decrease in acidity of the phosphorus containing acid function upon the introduction of an electron-donating alkyl group. This could result in the existence of a different state of dissociation for the analogue compared to the natural compound at a particular (physiological) acidity associated with a biological system. Secondly, of even greater significance is the change in physical size and shape which could result in great variation of biochemical or physiological activity.[13]

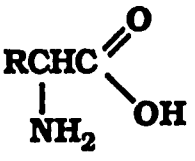
The chemistry of α-aminoalkylphosphonates has developed slowly but has accelerated in the last few years. In the beginning, there were difficulties in the synthesis and the detection of these species. Early studies consist mostly of chromatographic and isolation techniques. More recently, gas-liquid chromatography and mass spectrometry have been employed for aminophosphonate

determination.[14] The use of sophisticated techniques such as NMR (^{1}H & ^{31}P)[14] has made analysis more rapid and sensitive and thereby accelerated the progress in phosphonate chemistry.

Similarities and differences of amino acids and their phosphorus analogues:

Structurally, CO_2^{-1} is less like PO_3^{-2} than PO_2^{-1}. A simple comparison of 1-aminoalkylphosphorus acid types with their carboxylic analogues suggested that the closest parallel in properties would be obtained when the phosphorus acid is monobasic.[15]





X= H, OH

The effects of PO_3^{-2}/CO_2^{-} substitution on the complex forming properties have been extensively investigated in terms of of the differences in basicity, charge, electron-releasing effect, and the size of the phosphonate and the carboxylate groups for alanine, glycine, leucine, phenylalanine, *etc.* Because of the more basic character of the phosphonate group, some interesting results have been reported.[15] For example, some phosphorus analogues of

tyrosine and dopa (3,4-dihydroxyphenylalanine), racemic as well as in optically active forms, exert mixed type of inhibition with an affinity for the enzyme of greater magnitude than that of the natural substrate. It has been suggested that many enzymes do not differentiate between $-CO_2H$ and $-PO_3H_2$ regarding binding to the active sites. This is a rather remarkable finding considering that $-CO_2H$ and $-PO_3H_2$ differ substantially with regard to the size (PO_3H_2 is considerably larger), shape (flat CO_2H versus tetrahedral PO_3H_2) and acidity (pK difference of 3 units). Still these structural differences between phosphonic and carboxylic groups do not prevent aminophosphonates from serving as substrates for enzymes with a much greater affinity than that of carboxylates.[16]

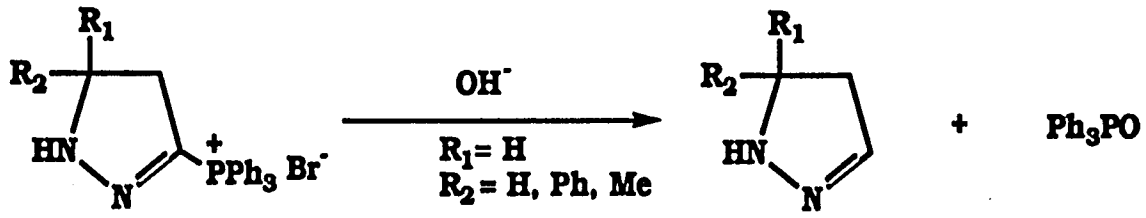
Based on the above factors, chelating properties of α-aminophosphonic acids have been extensively evaluated by studying their complexing behavior and comparing them with that of α-aminocarboxylic acids.[17] The stability constants for a range of combinations of metal ions and phosphonic acids have been determined and it is evident that they are useful chelating agents, although in general, they are less effective than the analogous carboxylic acids. Simple α-aminophosphonic acids possess complexing ability for copper very similar to that observed for glycine. The stability of these copper complexes increases with

alkyl substitution in the phosphonic acid. As might be anticipated, the monophosphonic acids form less stable complexes than diphosphonic acids. Replacement of one carboxyl function in nitrilotriacetic acid (NTA) by a phosphonic acid group yields a more effective reagent for calcium complexation. This result stimulated searches for even more effective compounds bearing combinations of carboxyl and phosphonic functional groups which will not be discussed here.[17]

The phosphorus moiety in P-C-N systems exerts very little influence on the reactions at the nitrogen center, so that most of the familiar transformations in nitrogen chemistry can be accomplished. For example, the α-amino function can be converted to an α-diazo function, which itself is modified in cycloaddition with olefins or acetylenes to yield pyrazolines or pyrazoles.[18]

Many compounds containing P-C-N functions undergo C-P bond cleavage upon treatment with base. C-P Bond cleavages are important steps in the synthesis of a number of nitrogen heterocycles and other unsaturated species. One example is given below in which pyrazolinylphosphonium salts upon treatment with

aqueous sodium hydroxide undergo facile C-P cleavage with the formation of the pyrazolines and triphenyl phosphine oxide.[19]

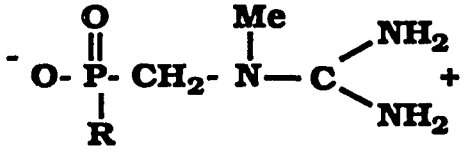


Aside from base-induced chemical cleavage, thermal and photochemical cleavages are reported. Also, several useful syntheses of heterocyclic systems possess nonisolable P-C-N species as labile intermediates, and the chemistry is closely related to that of base-induced cleavage described above. C-N Bond cleavages are common in P-C-N systems and they occur by the loss of a nitrogen molecule from α-diazophosphonates through thermolysis or photolysis.[20]

Biological activities of phosphorus analogues of α-aminocarboxylic acids:

As mentioned earlier, the biological investigation of α-aminophosphonic acids is still in the childhood stages. The fact that α-aminophosphonic acids are phosphorus analogues of

α-aminocaboxylic acids has no doubt spurred investigation into their biological activity. So far, however, no dramatic biological activity has been observed. In general, the α-aminophosphonic acids are toxic in high concentration, they do retard the growth of tobacco mosaic virus but they do not undergo metabolic incorporation into organisms in the manner of the carboxyl counterparts. Various tissues have shown an inability to transform C-P bound phosphorus into phosphate. The α-aminophosphonic acids participate in nonenzymic transamination less readily than α-aminocarboxylic acids, but imine formation with pyridoxal is more rapid. The hydrochlorides of α-aminobenzylphosphonic acid esters inhibit the growth of a number of microorganisms such as *micrococcus rosea.* Some of the α-aminophosphonic acids are quite effective bacteriocides against gram-positive and gram-negative bacteria such as *S. aureus* and *E. coli.* The creatine analogue shows significant activity in the creatine kinase reaction, but the other phosphonates show very low activity.[21]



Creatine analogue

(a) R= H
(b) R= OH
(c) R= OMe

The nitrogen analogue of phosphonomycin, the aziridinyl

phosphonate, possess antibacterial activity. It may not possess the low toxicity associated with phosphonomycin. *N*-Phosphonomethylglycine has revealed herbicidal properties. The peptide analogue, *N*-alanyl-1-aminoethyl phosphonic acid, possesses only weak antibacterial activity.[21]

N-phosphonomethylglycine

peptide analogue
N-alanyl-1-aminoethyl phosphonic acid

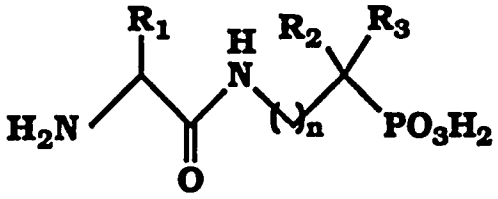
Extensive and intensive biochemical and biological investigations are still underway with a variety of the compounds and might be termed 'medicinal research' although the bulk of the efforts have been mechanistic in nature, that is, attempts to define the biochemical role of the natural analogues by looking at interruptions or modifications of normal processes upon the introduction of the phosphonic acid analogue.

Peptide analogues: Phosphonopeptides

Peptides are of considerable interest because of their biological activity. Many phosphonic acid analogs of dipeptides show significant antibacterial properties, act as enzyme regulators, or display promising antitumor activity. Several phosphono

dipeptides and oligopeptides are known to repress bacterial growth.[22] Phosphonopeptides are compounds in which the amino groups of the phosphonate moiety are substituted with aminoacyl groups. A review article[9] on the synthesis of phosphonopeptides has appeared. *N*-acyl derivatives of aminophosphonic acids are important for the synthesis of phosphonopeptides.

Phosphinothricin is one of the earliest phosphonopeptides isolated from natural cultures. This tripeptide is active as an anti-bacterial, fungicide, and herbicide. It is also known as phosphinothricylalanylalanine and was synthesized in 1972.[23] Since then, a great many efforts have been made to synthesize phosphonopeptides and investigate their biological activities. Among these peptides, those containing *P*-terminal aminoalkanephosphonic acids have received much more attention than other categories of phosphono peptides since they are useful as carriers of aminoalkanephosphonic acids through bacterial cell wall or into plant tissues.[22]



Peptides containing
P-terminal aminoalkanephosphonic acids

This type of peptide has been prepared by condensation of *N*-blocked amino acids with aminoalkanephosphonic acids, as well as with their dialkyl or diphenyl esters.[24] Phosphonopeptides emerged strongly as a new class of synthetic antibacterial agent which act by interfering with the biosynthesis of bacterial cell walls. This is achieved by inhibiting the formation, or subsequent utilization in crosslinking, of the terminal D-Ala-D-Ala units which occur in the peptide chains of the cell-wall peptidoglycans of all pathogenic bacteria so far investigated. One example of such high antibacterial activity is demonstrated by alafosfalin, *N*-(L-alanyl)-L-1-aminoethyl phosphonic acid. This particular diastereoisomer is shown to be most effective as compared to the other diastereoisomers. This indicates that activity also depends on the absolute configuration. This dipeptide alafosfalin has been shown to act by facilitated transport into the bacterial cell wall where it is cleaved enzymatically to L-1-aminoethylphosphonic acid which inhibits alanine racemase and related processes by simulating L-alanine.

Alafosfalin

The analgesic activity of enkephalin analogues containing aminophosphonic acid residues has been reported.[25] Due to this increasing interest in modified peptides, organophosphorus compounds are enjoying a prominent position in today's world of synthetic chemistry. Hence, it is quite understandable that there is an interest in the synthesis of 1-aminoalkylphosphonic acids and their diester derivatives.

Review of contemporary synthetic methods available:

1. Introduction: The main focus of attention here is on the 1-aminoalkylphosphonic acids and their diester derivatives. It is limited to the phosphorus analogues of natural amino acids which are relevant to the thesis work. Few selected synthesis will be mentioned here. There are excellent reviews on the synthesis and chemistry of 1-aminoalkylphosphonic acids and their diester derivatives.[26] Also, there are reports on the preparation of optically active 1-aminoalkylphosphonic acids and their diester derivatives.[27] There are many types of syntheses of 1-aminoalkyl-phosphonic acids and their diester derivatives. Thus this review will be based on each type relevant to the thesis.

2. Syntheses involving the formation of P-C bonds by substitution reactions:

Aminomethylphosphonic acid was first prepared in 1942 from *N*-hydroxymethylamides of carboxylic acids and phosphorus trichloride by M. Engelmann and J. Pikl (US Pat. 2, 304,156). In this synthesis the P-C bond formation took place by substitution of the hydroxyl group by a phosphorus nucleophile whose nature depends on experimental conditions. This original procedure was modified to allow easy preparation of aminomethylphosphonic acid in good yield from the reaction of *N*-hydroxymethylbenzamide with phosphorus trichloride in acetic acid.[28]

$$PhCONHCH_2OH \xrightarrow[2.\ Hydrolysis]{1.\ PCl_3,\ CH_3COOH,\ reflux\ 1hr} H_2NCH_2PO_3H_2$$

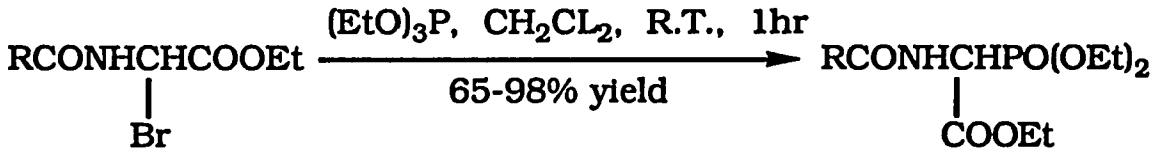
85% yield

The mechanism probably involves the reaction of *N*-acyliminium ions with such phosphorus nucleophiles as may be present in the respective reaction mixtures. Similar procedures were used to synthesize *N*-alkylaminomethylphosphonic and phosphinic acids from alkyldichlorophosphines instead of phosphorus trichloride.[29]

The classical Arbuzov and Michaelis-Becker reactions of P(III) nucleophiles with alkyl halides are not frequently used for the preparation of 1-aminoalkylphosphonates. The usefulness of

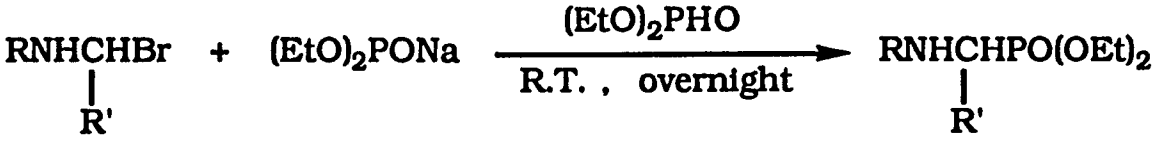
these reactions is limited to the relatively few cases where the required substrates, α-halogenated amine derivatives, are readily available, as has been thoroughly discussed by Redmore.[8a]

More recently the Arbuzov reaction was used in efficient syntheses of 1-amino-2-chloroalkylphosphonates and aminophosphonoacetates. The latter was prepared from *N*-protected bromoglycine derivatives followed by deprotection to triethyl aminophosphonoacetate, a useful synthon for the preparation of the cephalosporin ring system.[30]



R = benzyloxycarbonyl, trichloroethoxycarbonyl

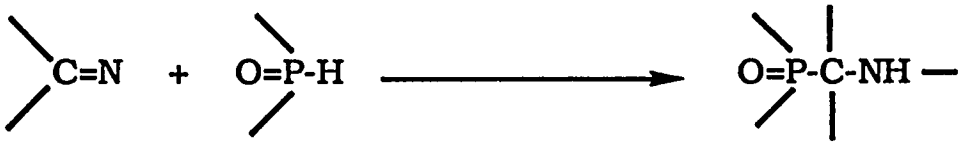
The Michaelis-Becker reaction of *N*-protected α-aminoalkyl bromides was employed to convert amino acids and simple peptides to the corresponding phosphonic acids. The bromides were prepared by Hunsdiecker decarboxylative bromination of silver salts and were reacted without isolation with sodium diethyl phosphonate using excess phosphonate as solvent, but the yields were in the range of only 10 to 20 %.[31]



R = benzoyl, benzyloxycarbonylglycyl, phtalyl
R'= H, alkyl

3. Syntheses involving the formation of P-C bonds by addition of P(III) reagents to carbon-nitrogen double bonds

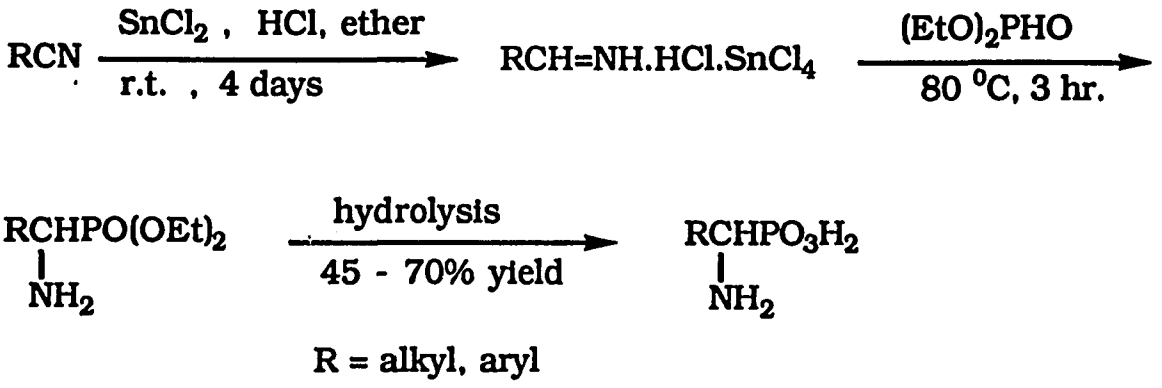
The original method for the preparation of 1-aminoalkyl-phosphonates is based on the addition of dialkyl phosphonates to the double bond of imines. The addition of P-H compounds to imines (Schiff's bases) derived from a very broad spectrum of amines and carbonyl compounds is described in many publications. A detailed review is given by Engel.[32]



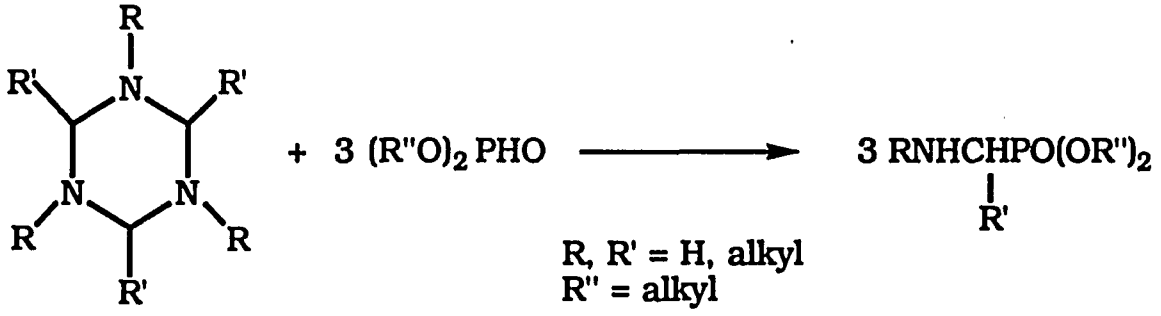
The addition of dialkyl phosphonates to imines derived from ammonia affords directly 1-aminoalkylphosphonates with a free amino group. Unfortunately, the reaction is limited to the few instances where the imines are sufficiently stable to be isolated.[33]

Simple 1-aminoalkylphosphonic acids were prepared from nitriles by a one-pot procedure involving *in situ* addition of diethyl phosphonate to aldimine salts formed by reduction of nitriles with Sn(II) chloride. This procedure is further modified by performing the reduction of nitriles with diisobutyl aluminium

hydride which shortened the reaction time from days to hours.[34]

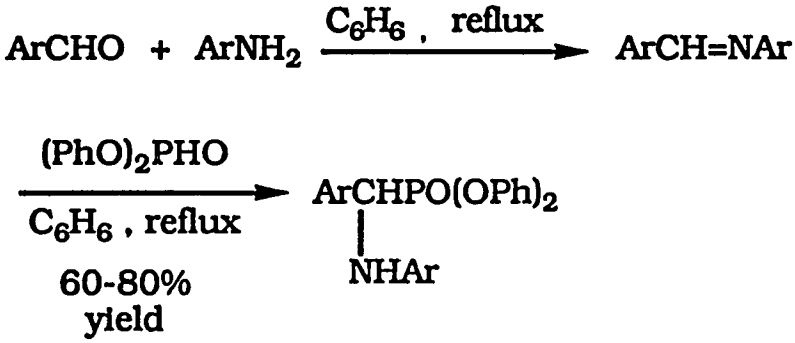


Unlike monomeric aldimines, their trimeric forms, *i.e.*, the hexahydrotriazines, are stable and retain much of the reactivity of their monomers, and were successfully used to prepare 1-aminoalkylphosphonates by ring opening reactions with dialkyl phosphonates and other P-H reagents.[35] The method is applicable to unsubstituted triazines as well as to their derivatives with substituents at the nitrogen and/or carbon atoms and is thus quite versatile.



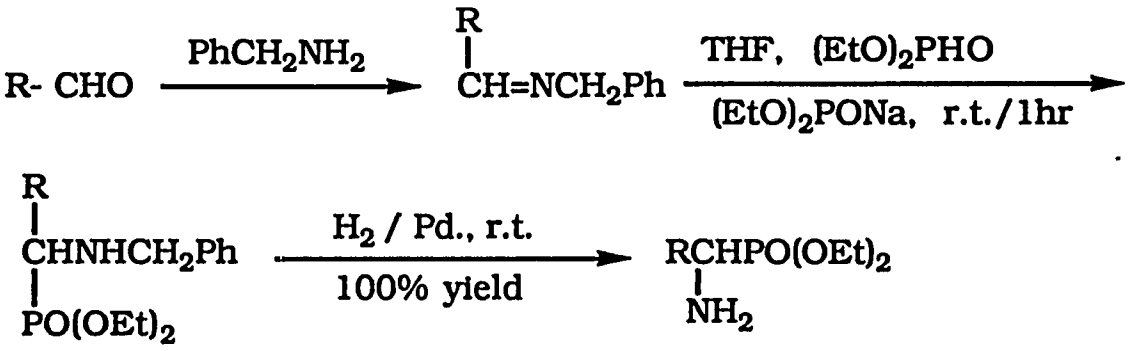
In one-pot procedures it may be convenient to perform the addition in the solvent which was used to prepare the imine,

as in the synthesis of diphenyl 1-(*N*-aryl)-arylmethylphosphonates reported by Smith *et al.*[36]



Ar = phenyl, substituted phenyl

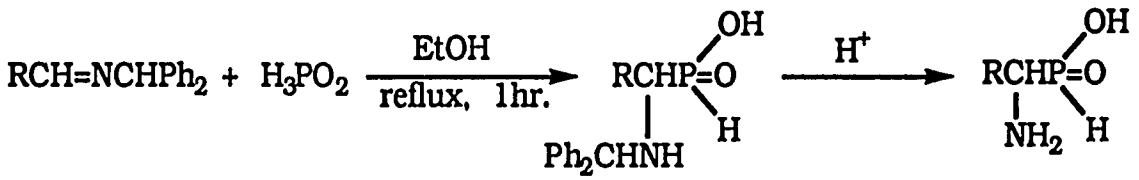
Schiff's bases with readily removable substituents at the nitrogen atom are used in the syntheses of 1-aminoalkylphosphonates containing free amino groups. *N*-Benzylimines were frequently used as they have the advantages of easy preparation and mild removal of benzyl groups by hydrogenolysis.[37]



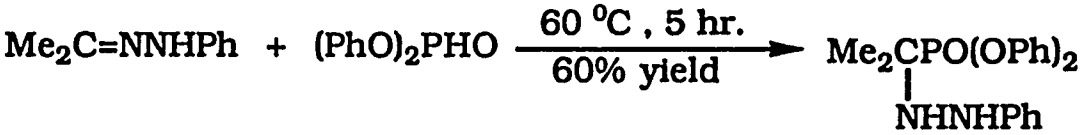
Optically active imines prepared from both enantiomers of

α-methylbenzylamine add to dialkyl phosphonates with some degree of asymmetric induction and were therefore used to synthesize optically active 1-aminoalkylphosphonic acids. This is discussed in the exhaustive review by Dhavan and Redmore.[27]

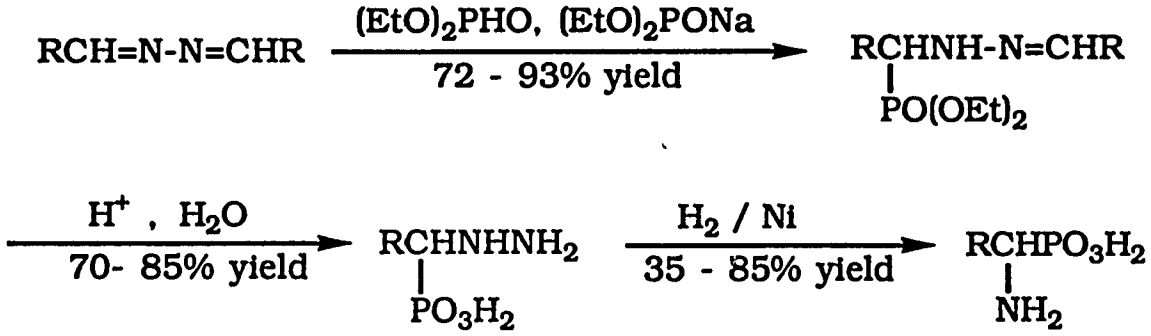
The imines prepared from aldehydes and benzhydrylamine are used to synthesize a series of α-aminoalkylphosphonous acids structurally related to protein amino acids.[38] Oxidation of α-aminoalkylphosphonous acids with bromine or with mercuric chloride yielded the 1-aminoalkylphosphonic acids.



The addition of P-H reagents to simple hydrazones was never systematically examined although it appears to be an obvious approach to the preparation of 1-hydrazinoalkylphosphonates and hence 1-aminoalkylphosphonates (the conversion of hydrazino to amino group is well known). In one of the few studies dealing with such additions the phenylhydrazone of acetone was found to react as expected with diphenyl phosphonate without catalyst.[39]

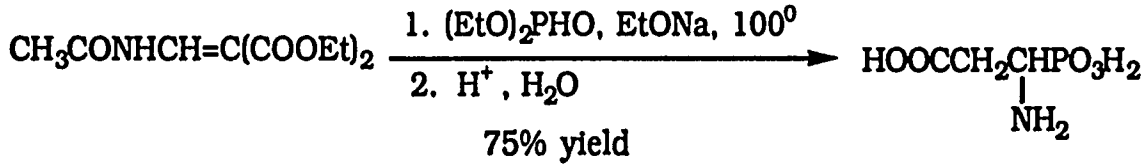


The azines of aliphatic aldehydes react with only one mole of diethyl phosphonate regardless of experimental conditions and the amount of phosphonate. The products, dialkyl 1-(*N*-alkylidene)hydrazinoalkylphosphonates were converted to 1-hydrazinoalkylphosphonic acids by hydrolysis and to 1-aminoalkylphosphonic acids by hydrolysis and reduction.[40]



4. Syntheses involving the formation of P-C bonds by addition of P(III) reagents to carbon-carbon double bonds.

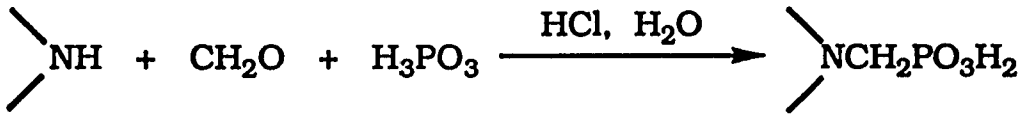
The addition of dialkyl phosphonates to enamines has been known to yield *N*-substituted 1-aminoalkylphosphonates without any need for catalysis, except for for the α-analogue of aspartic acid from diethylacetamidomethylenemalonate where base-catalyzed addition was used.[41]



5. Syntheses by simultaneous formation of P-C and C-N bonds

1-Aminoalkylphosphonates are synthesized in a one-pot overall reaction from amines, carbonyl compounds and phosphorus reactants. The formation of P-C and C-N bonds are not necessarily simultaneous. Most probably, the reactive intermediate is formed first and this is followed by the nucleophilic displacement or addition reactions with the phosphorus species. Unfortunately, no rigorous investigations of reaction mechanism were made.

Many derivatives of aminomethylphosphonic acid were prepared by the Mannich-type procedure of Moedritzer and Irani in which phosphorous acid reacts with formaldehyde and amines in strongly acidic aqueous solution.[8a]



The limitation of this procedure is that, apart from the low pH requirement, only formaldehyde can be used as the carbonyl reagent.[42] But, the procedure is still quite useful because there are no structural requirements concerning the amine component. Syntheses of azamacrocyclic derivatives of aminomethylphosphonic acid illustrated one such application.[43]

The Kabachnik-Fields reaction, similar to the Mannich-type process, produces 1-aminoalkylphosphonates from

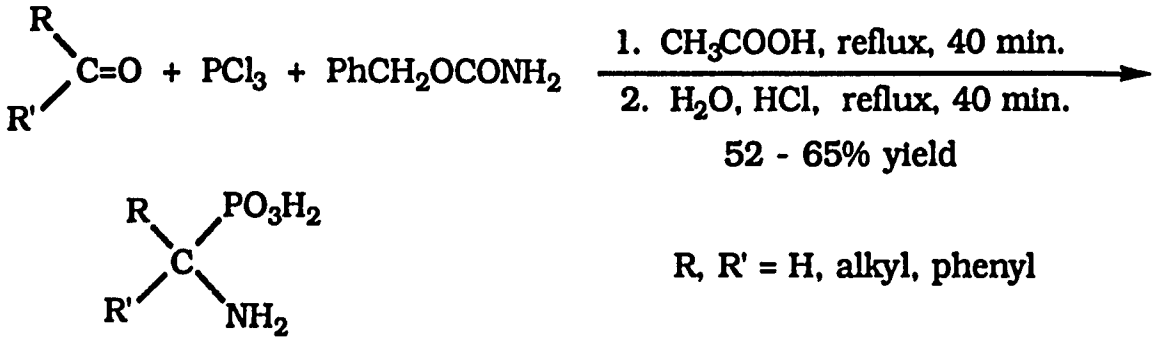
P-H reactants, carbonyl compounds and amines. This reaction is more popular because it is applicable to a wide range of carbonyl compounds. The reactions of dialkyl phosphonates with aldehydes or ketones and primary or secondary amines are strongly exothermic. The following preparation using the Kabachnik-Field reaction having ammonia as the amine component occurred in good yield.[44]

$$CH_3CHO + NH_3 + (EtO)_2PHO \xrightarrow[\text{sealed tube, 3days}]{\text{liquid } NH_3,\ \text{r.t.}} \underset{\text{76\% yield}}{CH_3CHPO(OEt)_2} \quad (NH_2)$$

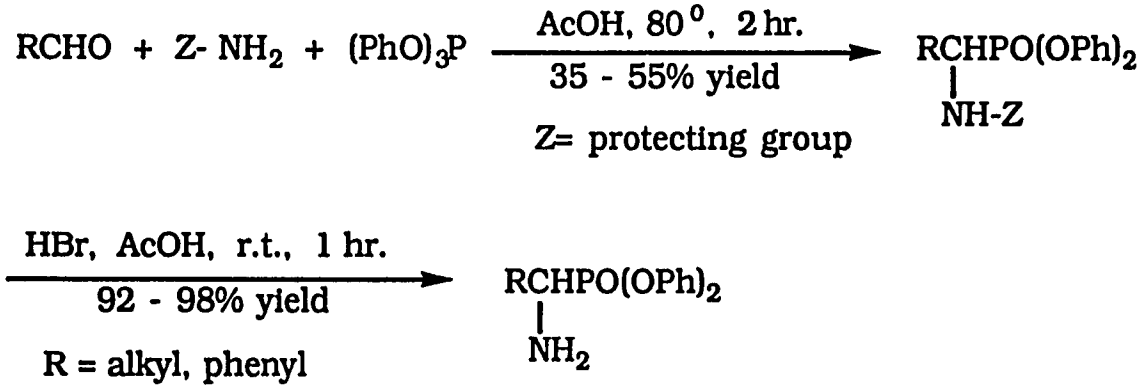
Despite the apparent simplicity in the above reaction, it is still not a general method of preparation of dialkyl 1-amino-alkylphosphonates because of difficulties encountered in the purification of products. This reaction is only good for the preparation of 1-(*N*,*N*-dialkylamino)alkylphosphonates. The most serious competing reaction is the formation of 1-hydroxy-alkylphosphonates.[45]

Several useful syntheses of 1-aminoalkylphosphonates from acid amides including carbamates, aldehydes and P(III) reagents were developed and reported by Birum.[46]

Practical syntheses of 1-aminoalkylphosphonates from aldehydes or ketones, P(III) compounds and benzyl carbamate were developed using carbamates in yields of about 50 per cent.[47]



Another useful procedure is based on the reaction of aldehydes with benzyl carbamate and triphenyl phosphite. The reaction gives about 50 per cent yields of *N*-protected diphenyl esters which are quantitatively deprotected upon treatment with hydrogen bromide in acetic acid. Pure products are isolated as hydrobromide salts. This is an attractive procedure for the preparation of diphenyl 1-aminoalkylphosphonates, compounds which are not readily available by other methods.[48]

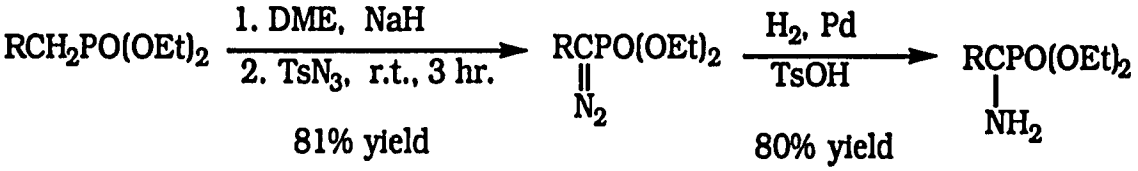


6. Syntheses by formation of C-N bonds

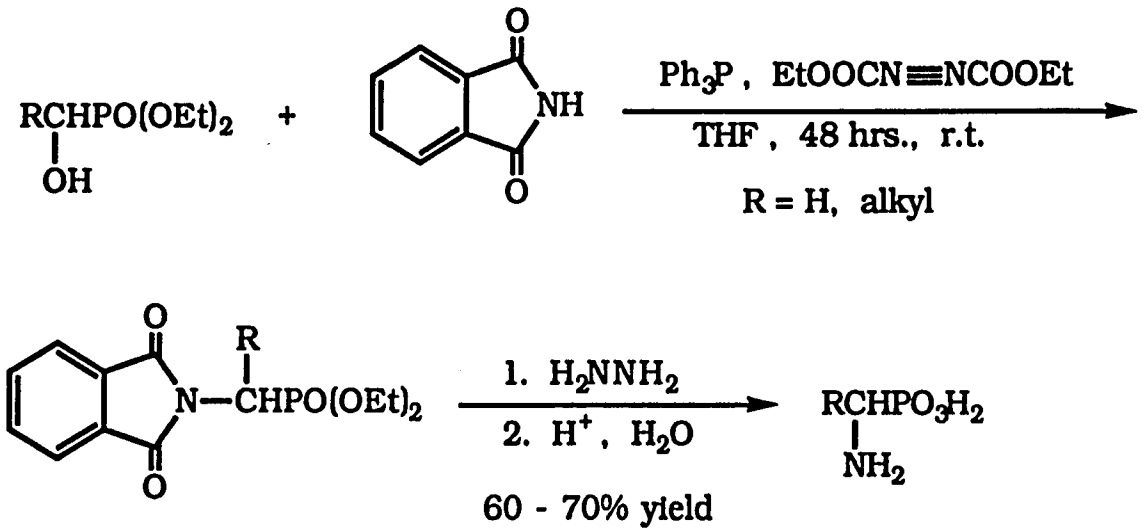
The syntheses classified under this heading will be treated in more detail since they are more closely related to this thesis.

They require that the substituents at the α-position in the phosphonate substrates be replaced with an amino group (direct amination) or with a group which is converted to the amino function by reduction (indirect amination). Many such transformations of amine synthesis are common in general organic chemistry, but only a few are known in the synthesis of 1-aminoalkylphosphonates. For example, direct amination of carbanions with hydroxyalamine derivatives or with chloramine was used in few cases.

α-Aminophosphonoacetates are prepared by indirect amination of trialkyl phosphonoacetates through the formation of diazo derivatives first, followed by the reductive hydrogenation of the diazo group in acid medium.[49]



One general method uses the Mitsunobu reaction to convert 1-hydroxyalkylphosphonates to 1-phthalimido- and hence to 1-aminoalkylphosphonates.[50]



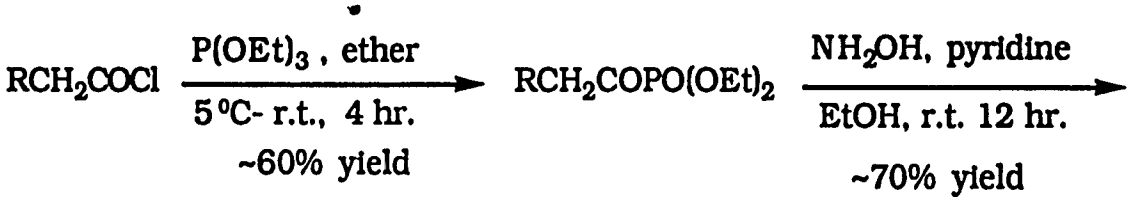
The R(-) enantiomer of the phosphonic analog of serine was obtained from optically active dimethyl 1-hydroxy-2-benzyloxy-ethylphosphonate by the modified Mitsunobu reaction using hydrazoic acid as the nitrogen source.[51] The substitution took place with inversion of configuration.

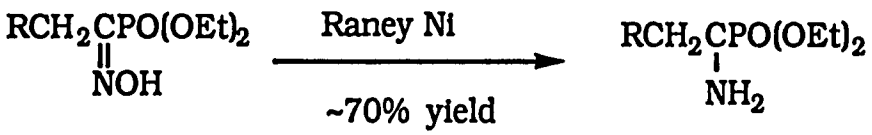
The synthesis of 1-aminoalkylphosphonates by Curtius degradation of carboxylic acids, reported by Isbell in 1964, is interesting despite the low yields. The intermediate acid azides are prepared *via* hydrazides.[52] Recently, the overall yields have been improved considerably by using diphenylphosphoryl azide (DPPA).[53]

The Hofmann degradation of amides to 1-aminoalkylphosphonates was also reported but does not seem to have widespread application.[26c]

Carboxylic acids are converted to 1-aminoalkylphosphonates without degradation of the carbon chain

by a four-step procedure involving the formation of acyl chlorides, their conversion to acylphosphonates, oximation with hydroxylamine and reduction of the oximes.[54] The reduction of oximes is the most troublesome step in this whole synthetic route. Diborane, aluminium amalgam, Raney nickel and recently zinc in formic acid have been used.[55]





The reduction of *N,N*-dimethylhydrazones of acylphosphonates was reported to give 1-aminoalkylphosphonates, but it does not appear to offer any advantages over the oxime route.[56]

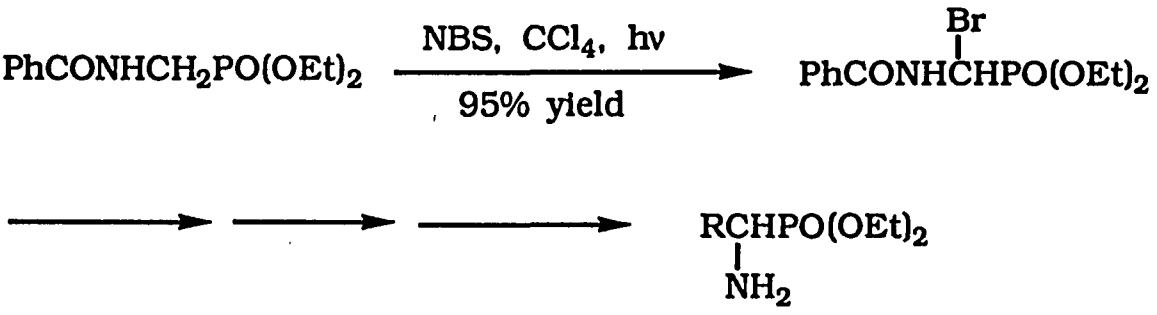
Aminophosphonates were also prepared by reduction of nitroalkylphosphonates, but this approach is not useful because the substrates are rather difficult to prepare.[57]

7. Syntheses by extension of carbon skeleton

Several interesting syntheses of racemic and optically active 1-aminoalkylphosphonic acids are based upon C-alkylation of carbanions derived from suitably derivatized

aminomethylphosphonic acid. Chiral auxiliaries needed for asymmetric syntheses were introduced either by suitable substitution at the nitrogen atom or by modification of the phosphonate function.[58]

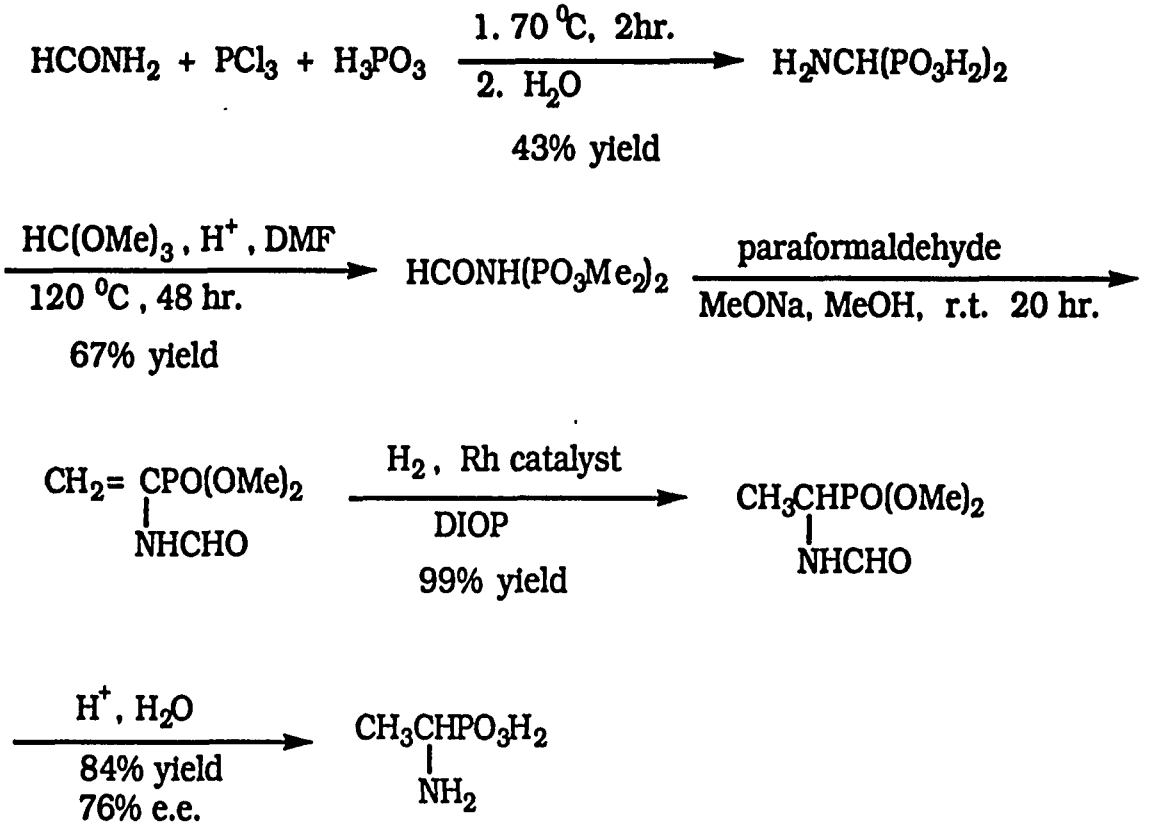
There is a carbocationic route in which *N*-acylaminomethyl-phosphonates are brominated and allowed to react with nucleophilic reagents, including enamines, Grignard reagents and organic cuprates,[59] to form the desired 1-aminoalkylphosphonic acids.



The condensation of isocyanomethylphosphonates with aldehydes proceeds with high diastereo and enantioselectivity in the presence of chiral, ferrocene-based gold(I) catalysts. Hydrogenolysis of the oxazoline intermediates gave optically active phosphonic analogs of phenylalanine.[60]

Optically active α-aminoalkylphosphonic acids are prepared by asymmetric catalytic hydrogenation of *N*-formyl enamines using a rhodium catalyst in the presence of DIOP as the chiral ligand. The starting material is prepared from

aminomethylenebisphosphonic acid by the Wadsworth-Emmons reaction with aldehydes.[61]



Objectives of the Proposal

Much more satisfactory results have been achieved using dialkyl esters of aminoalkanephosphonic acid than with simple aminoalkanephosphonic acids due to the enhanced chemical and enzymatic stability of the phosphonates. Thus, an easy access to the synthesis of O,O-dialkyl 1-aminoalkylphosphonates is of increasing importance in the light of their easy applicability to the synthesis of anti-metabolic phosphonopeptides.[62] Unfortunately, only a few methods are available.

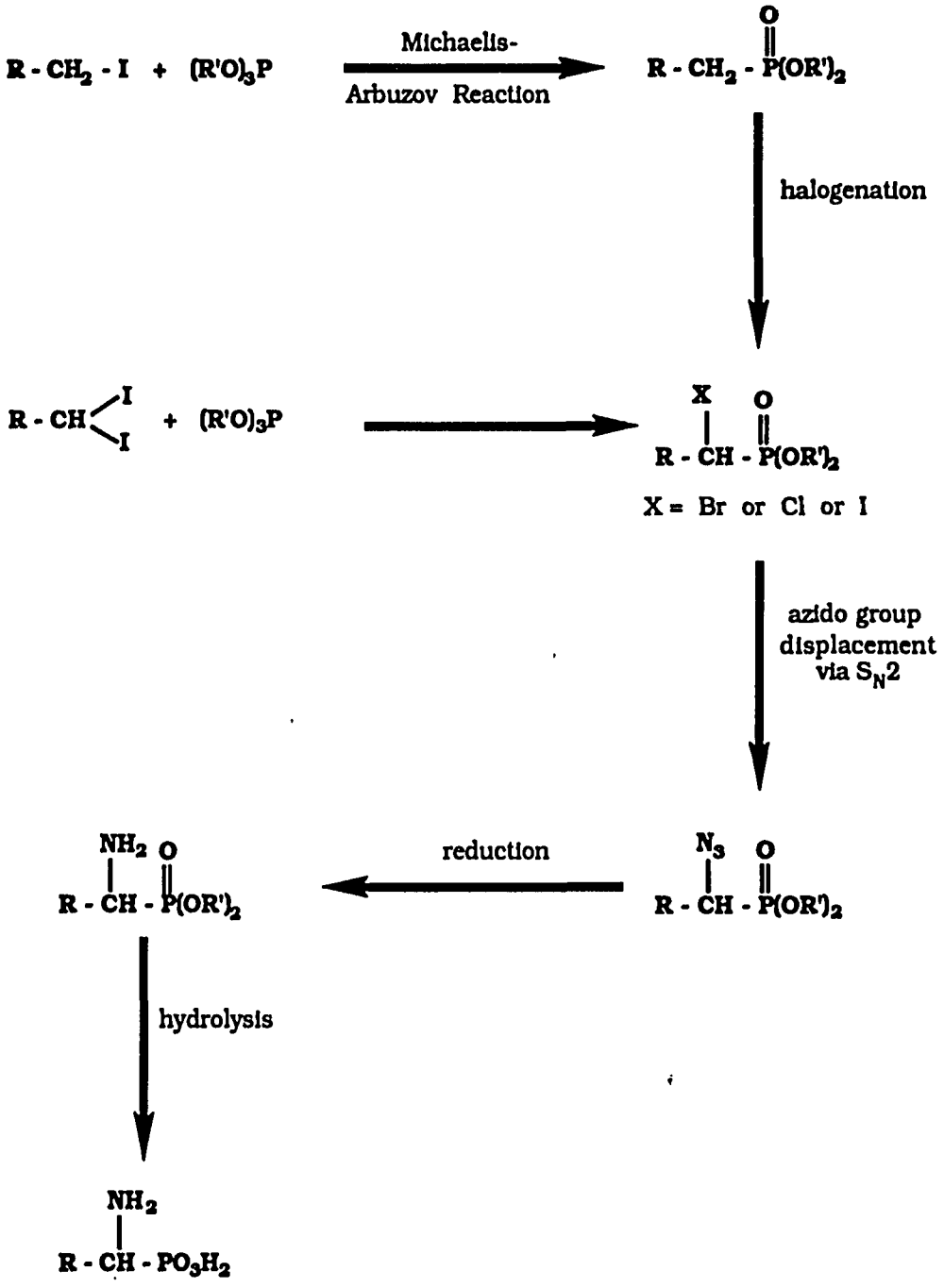
The concern of the present proposal is to develop a unique, but simple, synthetic methodology to produce α-aminoalkylphosphonates in the racemic form. Of particular interest are those materials structurally related to the natural α-amino acids.

Substituted aminomethyl phosphonates were to be prepared by first synthesizing alkyl phosphonates with a halogen atom at the 1-position, as shown below, where X = Br or Cl and R = H, CH_3, $(CH_3)_2CH$, $(CH_3)_2CHCH_2$, C_6H_5 and R' = $CH(CH_3)_2$

These haloalkylphosphonates, once prepared, were to be subjected to S_N2 substitution by azido group and then the final reduction to the desired amino analogues.

Synthetic Design

The fundamental approach toward target materials is shown in the following scheme.



Results and Discussions

As shown in the previously noted scheme, one approach to prepare α-haloalkylphosphonates was through the use of Michaelis-Arbuzov reaction using geminal dihalides.

The approach was tested using methylene iodide to check the feasibility of the S_N2 displacement reaction and subsequent reduction. The Arbuzov reaction of the methylene iodide with triisopropyl phosphite went smoothly, followed by the removal of the excess methylene iodide and the by-product isopropyl iodide under reduced pressure, to yield *O,O*-diisopropyl-iodomethylphosphonate in about 86% yield.

$$CH_2I_2 + P[OCH(CH_3)_2]_3 \xrightarrow[150\ ^{\circ}C,\ 6hr]{reflux} I\text{-}CH_2\overset{O}{\overset{\|}{P}}[OCH(CH_3)_2]_2 + (CH_3)_2CHI$$

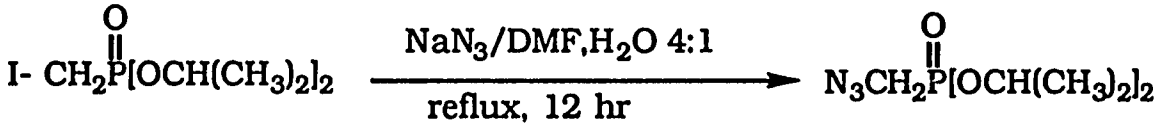
The NMR and the IR spectra perfectly matched and confirmed the structure of the iodomethylphosphonate.

^1H NMR spectra ($CDCl_3$): δ1.00 (d, 12H), δ3.6 (d, 2H), δ4.8(m,2H,).

IR spectra (CCL_4): 1240 cm^{-1}, 1050 cm^{-1}

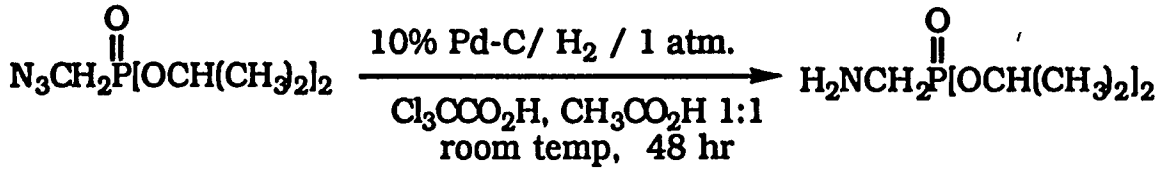
Further purification by distillation or chromatography was not neccesary since the NMR spectra was clean and a single spot was obtained on TLC (R_f = 0.70; hexane:ethyl acetate 4:1). Then, azido group replacement reactions were carried out following

typical procedures of carbon chemistry using sodium and lithium azides and several solvent systems. Both sodium and lithium azides proceeded satisfactorily. DMF and water (4:1 ratio) appeared to be the best solvent system. Methylene chloride and water (two phase solvent system) also worked with the use of a phase transfer catalyst, but a long refluxing time (typically about 48 hours) was required. The yield in these reactions is nearly quantitative, accounting for recovered starting material. The azido group can be detected by its characteristic IR absorption peak[63] around 2200 cm^{-1}, and also a characteristic shift in the α-hydrogen peak in the NMR is noticed.



The final catalytic hydrogenolysis is best achieved at atmospheric pressure with 10% Pd-C in a polar protic solvent such as ethanol or methanol.[64] Strong acid catalysis is required for efficient hydrogenation in quantitative yield. Here, a combination of acetic acid and trifluoroacetic acids has been used. At high pressure using a Parr apparatus, C-N bond decomposition occurred during hydrogenation, yielding *O,O*-diisopropyl-methylphosphonate as indicated by NMR and IR spectra. Many other procedures for the reduction to amino group have been reported in the literature. Triphenylphosphine in water is also

used succesfully, but the work-up is tedious due to the triphenylphosphine-oxide fomation.[65]



The NMR and IR spectra confirm the structure of the amino derivative. The IR spectrum showed a doublet around 3400 cm^{-1} which is characteristic of the primary amino group with the dissappearance of characteristic azido group. It was further confirmed using ninhydrin spray with TLC. Moreover, the above aminomethylphosphonate is hydrolyzed with BTMS (bromotrimethylsilane) to yield crystalline aminomethyl-phosphonic acid, for which the melting point is determined to be 325-326 ^0C, corresponding to the reported melting point.[66]

Overall, the scheme has been tested and optimized to obtain the best possible workable procedure to prepare other α-aminoalkylphosphonates. However, a difficulty is encountered with regard to the preparation and the availability of the four other appropriate α-halogenoalkylphosphonates.

Phosphonates with halogen substituents at the carbon atom adjacent to phosphorus recieved little attention through most of the history of organophosphorus chemistry. This has changed with the recognition that α-halogenated phosphonates

are better mimics of phosphate esters in the biological systems than the simple phosphonates in which the CH_2 group serves as an isosteric but not isopolar replacement of the oxygen or halogen atom.[67]

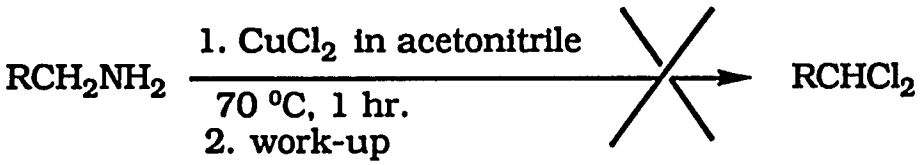
The direct displacement of a suitable leaving group from carbon by a fully esterified trivalent phosphorus acid remains as the most common method for the formation of carbon to phosphorus bonds in quinquevalent organophosphorus compounds. This is the situation due not only to the relative availability of the required starting materials, but also to the relative ease of the performance of the reaction. In most cases, little more than heating the reagents together in the absence of solvent and purification of the product by distillation is required. With this simplicity, even the fact that yields are often only in the fair to moderate range does not cause one to look for other methods.

$$RX + (R'O)_3P \longrightarrow RP(O)(OR')_2 + R'X$$

This Michaelis-Arbuzov approach has been tried to prepare α-halogenoalkylphosphonates by first preparing suitable alkyl *gem*-dihalides of the type $RCHI_2$, where R = H, CH_3, $(CH_3)_2CH$, $(CH_3)_2CHCH_2$, C_6H_5. However, only methylene iodide (CH_2I_2), where R=H, of the materials of interest here, is

commercially available, and has been used successfully to prepare glycine analogue which is described earlier. For the four other *gem*-dihalides, numerous literature procedures were used to prepare them, but unfortunately, extremely poor efficiency in these reactions was encountered. These approaches used, for example, aldehydes of the type RCHO which were treated with PCl_5[68], PCl_3 or $SOCl_2$[69], but the crude product in each instance after work-up gave only a very poor yield of the target material.

A modified approach was then used to convert aldehydes to their respective acetals which were then treated with PCl_5. Again, this attempt was unsuccesful. A rather different approach was taken to convert primary amines to *gem*-dihalides[70], but again all attempts to prepare such *gem*-dihalides were unsuccessful.



At this point, after an extensive literature review, it was decided that the Arbuzov reaction was not generally useful for the direct synthesis of α-halogenated phosphonates, most probably due to the electronic and steric nature of the reaction. In fact, syntheses performed using this type of reaction are limited to derivatives of methylphosphonic acid.[71]

Thus, the fundamental approach for this key step was

changed and modified to achieve the first goal in two steps. The first step was again a Michaelis-Arbuzov reaction to prepare simple *O,O*-dialkyl alkylphosphonates, which were then halogenated at the the α-position. It should be kept in mind that such α-hydrogens are acidic due to the electron withdrawing nature of the phosphoryl group, which is analogous to the carbonyl group although there is pK_a difference of three units. Although the halogenation of the simple Arbuzov products has not been reported before, there are literature procedures reported on the use of NBS and Br_2/HOAC for α-halogenation of similar phosphonate derivatives.[72] This new approach seemed much more reasonable and feasible.

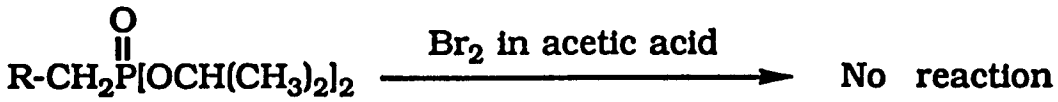
The Michaelis-Arbuzov reaction between appropriate alkyl iodides and triisopropyl phosphite went smoothly to afford all five necessary starting materials, *O,O*-diisopropyl-alkylphosphonates. Here other trialkyl phosphites such as triethyl phosphite could be used. Ethyl groups can, in fact, be cleaved much more easily, but still the use of triisopropyl phosphite was deemed preferable to triethyl or trimethyl phosphite in this synthetic sequence considering the fact that the by-product, isopropyl iodide, would participate only minimally in any extraneous Michaelis-Arbuzov reaction. Although the conversion of phosphorus methyl or ethyl esters to the free acids may be accomplished quite conveniently and selectively, isopropyl esters are not overly difficult to convert

to the free acids and numerous methods are available including treatment with trimethylbromosilane, and by thermolysis. All alkyl halides were bought commercially except isopentyl iodide (3-methylbutyl iodide) which is prepared in the laboratory by reacting isopentyl alcohol with potassium iodide and phosphoric acid in the presence of phosphorus pentoxide. Alkyl iodides worked better than alkyl bromides since the iodide ion is a better leaving group. The refluxing temperatures and times were considerably lower and the yields were generally quite high.

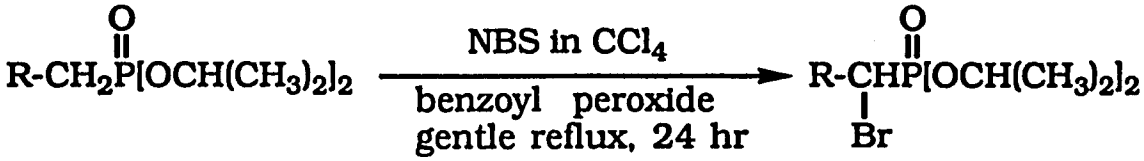
However, the yield for diisopropyl isobutylphosphonate (1c) was quite low. A combination of fractional distillation and column chromatography using hexane:ethyl acetate (20:1) as eluent were used to obtain reasonably pure (96% by GC) diisopropyl isobutylphosphonate 1c. All the Arbuzov products were checked by gas chromatography in order to make sure that they were sufficiently pure for the next step, as halogenation with NBS required high purity.

Thus, all the starting materials, *O,O*-diisopropyl alkylphosphonates, R-CH_2-P(O)[$OCH(CH_3)_2$]$_2$ (**1a-e**) were prepared by Michaelis-Arbuzov reaction of the corresponding alkyl halides, R-CH_2-I and triisopropyl phosphite. The yields of these reactions along with product characterizations are shown in Table 1 in the 'Summary of Results' section. Experimental procedures are given in the 'Experimental' section of this chapter.

With the phosphonates in hand, the next key step was the halogenation. Bromine in acetic acid was tried as it is been used in carbonyl chemistry, but here it was unsuccessful, presumably due to the low pK_a of the phosphoryl group.



There are reports on the use of NBS in phosphonate chemistry[72] but not on the alkyl phosphonates. Thus, NBS was used in this attempt. Highly pure starting alkylphosphonates, as checked by gas chromatography, were used and spectral grade carbon tetrachloride was distilled over sodium hydride prior to its use as solvent. This reaction is carried out in presence of both light and heat. It was noted that the best results were obtained by stirring the mixture of alkylphosphonate and NBS in carbon tetrachloride with gentle heating in the presence of the initiator benzoyl peroxide in catalytic amount. This approach afforded the product in reasonable yield and constituted a new technique for α-halogenation to form P-C-X bonds from simple Arbuzov starting materials.

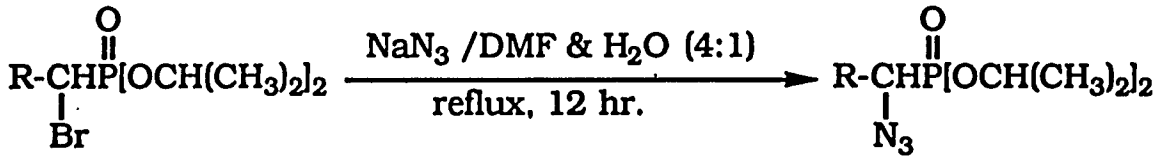


The NMR of the compound, **2e** (*O,O*-diisopropyl-1-bromo-benzylphosphonate) is rather interesting. The two *O*-isopropyl groups are no longer equivalent, owing to the presence of the stereogenic center created at the α-position. The ^1H NMR spectrum of **2e** exhibits a doublet of doublets for the methyl hydrogens of the isopropyl esters; the additional splitting here is presumably due to the stereogenic center providing different positions for these methyl groups relative to the phenyl ring also present. The products were determined to be pure using GC analysis.

Hence the introduction of a bromine at the α-position of the phosphonate diester was accomplished in this key step by treatment with *N*-bromosuccinimide in the presence of a free radical initiator, benzoyl peroxide to obtain products **(2a-e)**. Reactions were performed for 24 hours at the reflux temperature of the solvent system, carbon tetrachloride, using a 10-15% excess of the *N*-bromosuccinimide. The yields for this reaction are corrected for the amount of unconverted starting phosphonate which was recovered. The physical characteristics are listed in Table 2 in the 'Summary of Results', and the experimental procedures are given in the 'Experimental' section.

The remainder of the reaction scheme was accomplished without any problem. The nitrogen of the ultimate α-aminophosphonate, **4**, was introduced by azide ion displacement

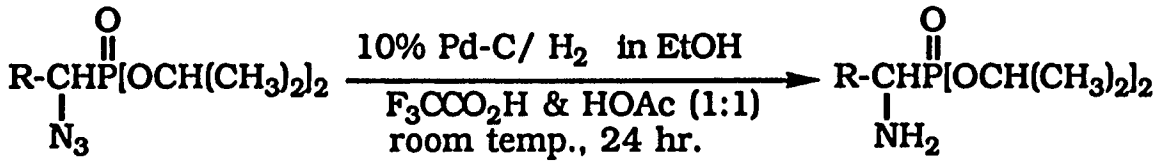
of the bromine in **2** *via* a S_N2 substitution reaction. Two azides, LiN_3 and NaN_3, were tried. The reaction was performed using a mixture of dimethyl formamide and water (4:1) as the solvent as mentioned earlier. Upon removal of the solvent after 12 hours of heating, the progress of the reaction was noted by the shifting of the α-hydrogen signal in the ^{1}NMR spectrum and the presence of the characteristic azide stretching band (2090-2160 cm^{-1}) in the infrared spectrum.[63]



The physical characteristics of the products **3a-e** are given in Table 3 in the 'Summary of Results' section, and the experimental procedures are described in the 'Experimental' section.

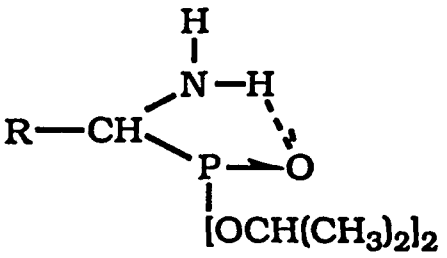
The α-azidophosphonates, **3a-e**, were not purified or subjected to combustion analysis, but immediately hydrogenolyzed using the same procedure described earlier to form the target α-aminoalkylphosphonates, **4a-e**. The progress of this reaction was monitored by TLC and by the observation of the disappearance of the characteristic azide band in the infrared spectrum. The amino

group appears as characteristic doublet in the infrared spectrum around 3400-3200 cm^{-1} together with the disappearence of the characteristic peak for the azido group.



The IR spectra of these amino analogues are uniquely interesting in the sense that the infrared spectra indicates the existence of intramolecularly hydrogen-bonded structures. Also, the NMR analysis of these α-aminoalkylphosphonates indicates the existence of magnetically non-equivalent alkoxy groups as expected from the presence of an chiral center at the α-position.

The infrared spectra showed phosphoryl absorptions of 1210-1240 cm^{-1} for α-aminoalkylphosphonates. In general, phosphoryl absorptions between 1200-1250 cm^{-1} indicate hydrogen-bonded phosphoryl groups, whereas, phosphoryl frequencies from 1250-1300 cm^{-1} represent free phosphoryl functions. In all cases, the phosphoryl absorptions in the amino analogues **4a-e** occured at the longer wavelength than did the phosphoryl absorptions in the corresponding starting materials, alkylphosphonates **1a-e**. The intramolecular hydrogen bonding is shown below.



The yields for the overall conversion of **2** to **4**, and the characteristics of **4a-e** are shown in Table 4 in the 'Summary of Results' section, and all the experimental procedures are given in the 'Experimental section.

Overall, this approach provides a convenient synthesis of α-aminophosphonates starting with alkyl halides and using the convenient Michaelis-Arbuzov reaction.

EXPERIMENTAL

General:

Routine proton spectra were recorded at 60 MHZ on a Varian EM360 instument, and the high field proton spectra were obtained on a Brucker-IBM WP200SY instrument. Proton NMR data are reported in parts per million downfield from TMS used as internal standard (multiplicity s=singlet, d=doublet, t=triplet, dd=doublet of doublets, m=multiplet, bs=broad singlet). Infrared spectra were recorded on a Perkin-Elmer IR598 spectrometer or Perkin-Elmer 1600 series FTIR spectometer, and absorptions are reported in reciprocal centimeters.

Column chromatography was performed in glass columns packed with silica (60-200 mesh, Baker). All thin layer chromatography (TLC) was performed using KODAK Chromatogram Sheet (silica) with fluorescent indicator.

Gas chromatography was performed on a Shimadzu instrument using OV-1 (non-polar phase) column of 1/4" diameter and 10 feet in length.

All the solvents were used without further distillation except carbon tetrachloride which was distilled from sodium hydride and stored over molecular sieves in dried condition and used as soon as possible. Most reagents and solvents were purchased from Aldrich Chemical Co. unless otherwise noted.

Micro-elemental analysis were performed by MicAnal, Tucson, Arizona and Schwarzkopf Microanalytical Lab, Woodside,

New York.

The experimental section is divided into four sections.

Section I: Preparation of *O,O*-diisopropyl-alkylphosphonates

1. Preparation of *O,O*-diisopropyl-methylphosphonate (1a):

In a dried, nitrogen-flushed round-bottomed flask fitted with a magnetic stirrer, heating oil bath, and a reflux condenser with drying tube is placed triisopropyl phosphite (20 g, 0.096 mol) and the methyl iodide (68 g, 0.48 mol, 5 equiv). The mixture is heated at 160° for 8 hr, at which time the solution is cooled and volatile materials are evaporated under reduced pressure. The crude product is vacuum distilled to yield 14.85 g (86%) of the pure product *O,O*-diisopropyl-methylphosphonate **1a** (b.p. 42-44 °C/2.5 torr). The purity was checked by GC (retention time: 4.6 min at 125 °C & 40 mL/min). It exhibited a single spot on TLC, and IR and NMR spectra in accord with the proposed structure. The pertinent data are presented in Table 1 (page 105).

2. Preparation of *O,O*-diisopropyl-ethylphosphonate (1b):

In a dried, nitrogen-flushed round-bottomed flask fitted with a magnetic stirrer, heating oil bath, and a reflux condenser with drying tube is placed triisopropyl phosphite (20 g, 0.096 mol) and the ethyl iodide (74 g, 0.48 mol, 5 equiv). The mixture is heated at 160° for 12 hr, at which time the solution is cooled and volatile

materials are evaporated under reduced pressure. The crude product is vacuum distilled to yield 16.4 g (88%) of the pure product *O,O*-diisopropyl-ethylphosphonate **1b** (b.p. 45-48 ^{0}C/2 torr). It exhibited a single spot on TLC, and IR and NMR spectra in accord with the proposed structure. The purity was checked by GC (retention time: 4.9 min at 125 ^{0}C & 40 mL/min). The pertinent data are presented in Table 1 (page 105).

3. Preparation of *O,O*-diisopropyl-2-methylpropylphosphonate (1c): In a dried, nitrogen-flushed round-bottomed flask fitted with a magnetic stirrer, heating oil bath, and a reflux condenser with drying tube is placed triisopropyl phosphite (15 g, 0.072 mol) and the isobutyl iodide (66.2 g, 0.36 mol, 5 equiv). The mixture is heated at 160^{0} for 12 hr, at which time the solution is cooled and volatile materials are evaporated under reduced pressure. The crude product is vacuum distilled (b.p. 61-65 ^{0}C/2 torr), and this major fraction is subjected to column chromatography on a silica gel column (180 g) eluting with hexane:ethyl acetate (20:1). Solvent is removed from the eluents under reduced pressure to yield 6.7 g (42%) of the pure product *O,O*-diisopropyl-2-methylpropyl-phosphonate **1c**. It exhibited a single spot on TLC, and IR and NMR spectra in accord with the proposed structure. Also the purity was checked by GC (retention time: 5.8 min at 150 ^{0}C & 40 mL/min). The pertinent data are presented in Table 1 (page 105).

4. Preparation of *O,O*-diisopropyl-3-methylbutylphosphonate (1d):

In a dried, nitrogen-flushed round-bottomed flask fitted with a magnetic stirrer, heating oil bath, and a reflux condenser with drying tube is placed triisopropyl phosphite (15 g, 0.072 mol) and the isopentyl iodide (71.3 g, 0.36 mol, 5 equiv). The mixture is heated at 160° for 10 hr, at which time the solution is cooled and volatile materials are evaporated under reduced pressure. The crude product is vacuum distilled (b.p. 68-72 °C/2 torr), under reduced pressure to yield 12.6 g of the pure product *O,O*-diisopropyl-3-methylbutylphosphonate **1d**. It exhibited a single spot on TLC, and IR and NMR spectra in accord with the proposed structure. Also the purity was checked by GC (retention time: 6.1 min at 150 °C & 40 mL/min). The pertinent data are presented in Table 1 (page 105).

5. Preparation of *O,O*-diisopropyl-benzylphosphonate (1e):

In a dried, nitrogen-flushed round-bottomed flask fitted with a magnetic stirrer, heating oil bath, and a reflux condenser with drying tube is placed triisopropyl phosphite (10 g, 0.048 mol) and the benzyl iodide (52.3 g, 0.24 mol, 5 equiv). The mixture is heated at 150° for 8 hr, at which time the solution is cooled and volatile materials are evaporated under reduced pressure. The crude product is vacuum distilled (b.p. 92-95 °C/2 torr), under reduced pressure to yield 8.6 g of the pure product *O,O*-diisopropyl-benzylphosphonate **1e**. It exhibited a single spot on TLC, and IR and

NMR spectra in accord with the proposed structure. The purity was also checked by GC (retention time: 6.8 min at 150 ^{0}C & 40 mL/min). The pertinent data are presented in Table 1 (page 105).

SectionII:Preparation of *O,O*-diisopropyl-1-bromoalkylphosphonates

6. Preparation of *O,O*-diisopropyl-1-bromomethylphosphonate (2a): In a dried round-bottomed flask (250 mL) maintained under a nitrogen atmosphere and fitted with a magnetic stirrer, heating oil bath, and a reflux condenser is dissolved the *O,O*-diisopropyl-methylphosphonate **1a** (3.96 g, 0.022 mol) and *N*-bromosuccinimide (4.4 g, 0.025 mol, 1.1 equiv) in dry and distilled carbon tetrachloride (150 mL). The mixture is stirred for 1 hr, after which time there is added benzoyl peroxide (0.5 g, 0.002 mol, 0.09 equiv), and the reaction mixture is stirred and heated at 60^{0} for a further 24 hr. At this time the insoluble succinimide is removed by filtration and the volatile materials removed by evaporation under reduced pressure. Ethyl acetate (100 mL) is added to the residue and the solution is extracted with saturated aqueous sodium bisulfite solution (50 mL) and water (2 x 50 mL). The organic layer is dried ($MgSO_4$), filtered, and the solvent removed by evaporation under reduced pressure. The crude product is subjected to chromatography on a silica gel column (75 g) eluting with hexane:ethyl acetate (4:1). Solvent is removed from

the eluents to yield 2.4 g of the pure product *O,O*-diisopropyl-1-bromomethylphosphonate **2a.** Elution time on GC: 5.4 min at 125 ^{0}C and 40 mL/min pressure. The compound exhibited spectra and analysis in accordance with the proposed structure. All the physical data are given in Table 2 (page 106).

7. Preparation of *O,O*-diisopropyl-1-bromoethylphosphonate (2b): In a dried round-bottomed flask (250 mL) maintained under a nitrogen atmosphere and fitted with a magnetic stirrer, heating oil bath, and a reflux condenser is dissolved the *O,O*-diisopropyl-ethylphosphonate **1b** (4.3 g, 0.022 mol) and *N*-bromosuccinimide (4.4 g, 0.025 mol, 1.1 equiv) in carbon tetrachloride (150 mL). The mixture is stirred for 1 hr, after which time there is added benzoyl peroxide (0.5 g, 0.002 mol, 0.09 equiv), and the reaction mixture is stirred and heated at 60^{0} for a further 24 hr. At this time the insoluble succinimide is removed by filtration and the volatile materials removed by evaporation under reduced pressure. Ethyl acetate (100 mL) is added to the residue and the solution is extracted with saturated aqueous sodium bisulfite solution (50 mL) and water (2 x 50 mL). The organic layer is dried ($MgSO_4$), filtered, and the solvent removed by evaporation under reduced pressure. The crude product is subjected to chromatography on a silica gel column (75 g) eluting with hexane:ethyl acetate (4:1). Solvent is removed from the eluents to

yield 3.48 g of the pure product *O,O*-diisopropyl-1-bromoethylphosphonate **2b.** Elution time on GC: 5.85 min at 125 °C and 40 mL/min pressure. The compound exhibited spectra and analysis in accordance with the proposed structure. All the physical data are given in Table 2 (page 106).

8. Preparation of *O,O*-diisopropyl-1-bromo-2-methylpropylphosphonate (2c):

In a dried round-bottomed flask (250 mL) maintained under a nitrogen atmosphere and fitted with a magnetic stirrer, heating oil bath, and a reflux condenser is dissolved the *O,O*-diisopropyl-2-methylpropylphosphonate **1c** (4.89 g, 0.022 mol) and *N*-bromosuccinimide (4.4 g, 0.025 mol, 1.1 equiv) in carbon tetrachloride (150 mL). The mixture is stirred for 1 hr, after which time there is added benzoyl peroxide (0.5 g, 0.002 mol, 0.09 equiv), and the reaction mixture is stirred and heated at 60° for a further 24 hr. At this time the insoluble succinimide is removed by filtration and the volatile materials removed by evaporation under reduced pressure. Ethyl acetate (100 mL) is added to the residue and the solution is extracted with saturated aqueous sodium bisulfite solution (50 mL) and water (2 x 50 mL). The organic layer is dried ($MgSO_4$), filtered, and the solvent removed by evaporation under reduced pressure. The crude product is subjected to chromatography on a silica gel column (80 g) eluting with

hexane:ethyl acetate (4:1). Solvent is removed from the eluents to yield 4.9 g of the pure product *O,O*-diisopropyl-1-bromo-2-methylpropylphosphonate **2c.** Elution time on GC: 6.4 min at 125 ^{0}C and 40 mL/min pressure. The compound exhibited spectra and analysis in accordance with the proposed structure. All the pertinent spectral and physical data are given in Table 2 (page 106).

9. Preparation of *O,O*-diisopropyl-1-bromo-3-methylbutyl-phosphonate (2d):

In a dried round-bottomed flask (250 mL) maintained under a nitrogen atmosphere and fitted with a magnetic stirrer, heating oil bath, and a reflux condenser is dissolved the *O,O*-diisopropyl-3-methylbutylphosphonate **1d** (5.2 g, 0.022 mol) and *N*-bromosuccinimide (4.4 g, 0.025 mol, 1.1 equiv) in carbon tetrachloride (150 mL). The mixture is stirred for 1 hr, after which time there is added benzoyl peroxide (0.5 g, 0.002 mol, 0.09 equiv), and the reaction mixture is stirred and heated at 60^{0} for a further 24 hr. At this time the insoluble succinimide is removed by filtration and the volatile materials removed by evaporation under reduced pressure. Ethyl acetate (100 mL) is added to the residue and the solution is extracted with saturated aqueous sodium bisulfite solution (50 mL) and water (2 x 50 mL). The organic layer is dried ($MgSO_4$), filtered, and the solvent removed by evaporation

under reduced pressure. The crude product is subjected to chromatography on a silica gel column (80 g) eluting with hexane:ethyl acetate (4:1). Solvent is removed from the eluents to yield 5.3 g of the pure product *O,O*-diisopropyl-1-bromo-3-methylbutylphosphonate **2d.** Elution time on GC: 6.9 min at 125 ^{0}C and 40 mL/min pressure. The compound exhibited spectra and analysis in accordance with the proposed structure. All the pertinent spectral and physical data are given in Table 2 (page 106).

10. Preparation of *O,O*-diisopropyl-1-bromobenzylphosphonate (2e):

In a dried round-bottomed flask (250 mL) maintained under a nitrogen atmosphere and fitted with a magnetic stirrer, heating oil bath, and a reflux condenser is dissolved the *O,O*-diisopropyl-benzylphosphonate **1e** (5.6 g, 0.022 mol) and *N*-bromosuccinimide (4.4 g, 0.025 mol, 1.1 equiv) in carbon tetrachloride (150 mL). The mixture is stirred for 1 hr, after which time there is added benzoyl peroxide (0.5 g, 0.002 mol, 0.09 equiv), and the reaction mixture is stirred and heated at 60^{0} for a further 24 hr. At this time the insoluble succinimide is removed by filtration and the volatile materials removed by evaporation under reduced pressure. Ethyl acetate (100 mL) is added to the residue and the solution is extracted with saturated aqueous sodium bisulfite solution (50 mL) and water (2 x 50 mL). The organic layer

is dried ($MgSO_4$), filtered, and the solvent removed by evaporation under reduced pressure. The crude product is subjected to chromatography on a silica gel column (80 g) eluting with hexane:ethyl acetate (4:1). Solvent is removed from the eluents to yield 6.05 g of the pure product *O,O*-diisopropyl-1-bromobenzylphosphonate **2e.** Elution time on GC: 7.48 min at 125 ^{0}C and 40 mL/min pressure. The compound exhibited spectra and analysis in accordance with the proposed structure. All the pertinent spectral and physical data are given in Table 2 (page 106).

SectionIII: Preparation of *O,O*-diisopropyl-1-azidoalkylphosphonates

11. Preparation of *O,O*-diisopropyl-1-azidomethylphosphonate (3a):

In a round-bottomed flask (250 mL) fitted with a magnetic stirrer, heating oil bath, and reflux condenser is dissolved the *O,O*-diisopropyl 1-bromomethylphosphonate **2a** (2.25 g, 0.0087 mol) and sodium azide (3.5 g, 0.05 mol, 6 equiv) in a mixture of DMF (150 mL) and water (40 mL). The reaction mixture is refluxed at 140^0 for 12 hr. After cooling, the volatile materials are evaporated under reduced pressure and ethyl acetate (150 mL) is added to the residue. The mixture is washed with water (2 x 100 mL) and the organic component is dried ($MgSO_4$), filtered, and the

solvent is evaporated under reduced pressure. The residual crude *O,O*-diisopropyl-1-azidomethylphosphonate **3a** (1.77 g, 92%) was not purified further. It exhibited IR and NMR spectra in accord with the proposed structure. The pertinent data are presented in Table 3 (page 107).

12. Preparation of *O,O*-diisopropyl-1-azidoethylphosphonate (3b):

In a round-bottomed flask (250 mL) fitted with a magnetic stirrer, heating oil bath, and reflux condenser is dissolved the *O,O*-diisopropyl 1-bromoethylphosphonate **2b** (2.73 g, 0.01 mol) and sodium azide (3.5 g, 0.05 mol, 5 equiv) in a mixture of DMF (150 mL) and water (40 mL). The reaction mixture is heated at 140° for 12 hr. After cooling, the volatile materials are evaporated under reduced pressure and ethyl acetate (150 mL) is added to the residue. The mixture is washed with water (2 x 100 mL) and the organic component is dried ($MgSO_4$), filtered, and the solvent is evaporated under reduced pressure. The residual crude *O,O*-diisopropyl-1-azidoethylphosphonate **3b** (2.2 g, 94%) was not purified further. It exhibited IR and NMR spectra in accord with the proposed structure. The pertinent data are presented in Table 3 (page 107).

13. Preparation of *O,O*-diisopropyl-1-azido-2-methylpropyl-phosphonate (3c):

In a round-bottomed flask (250 mL) fitted with a magnetic stirrer, heating oil bath, and reflux condenser is dissolved the *O,O*-diisopropyl-1-bromo-2-methylpropylphosphonate **2c** (3.01 g, 0.01 mol) and sodium azide (3.5 g, 0.05 mol, 5 equiv) in a mixture of DMF (150 mL) and water (40 mL). The reaction mixture is heated at 140° for 12 hr. After cooling, the volatile materials are evaporated under reduced pressure and ethyl acetate (150 mL) is added to the residue. The mixture is washed with water (2 x 100 mL) and the organic component is dried ($MgSO_4$), filtered, and the solvent is evaporated under reduced pressure. The residual crude *O,O*-diisopropyl-1-azido-2-methylpropylphosphonate **3c** (2.31 g, 88%) was not purified further. It exhibited IR and NMR spectra in accord with the proposed structure. The pertinent data are presented in Table 3 (page 107).

14.Preparation of *O,O*-diisopropyl-1-azido-3-methylbutyl-phosphonate (3d):

In a round-bottomed flask (250 mL) fitted with a magnetic stirrer, heating oil bath, and reflux condenser is dissolved the *O,O*-diisopropyl-1-bromo-3-methylbutylphosphonate **2d** (3.15g, 0.01 mol) and sodium azide (3.5 g, 0.05 mol, 5 equiv) in a mixture of DMF (150 mL) and water (40 mL). The reaction mixture is refluxed at 140° for 14 hr. After cooling, the volatile materials are evaporated under reduced pressure and ethyl acetate (150 mL) is

added to the residue. The mixture is washed with water (2 x 100 mL) and the organic component is dried ($MgSO_4$), filtered, and the solvent is evaporated under reduced pressure. The residual crude *O,O*-diisopropyl-1-azido-3-methylbutylphosphonate **3d** (2.49 g, 90%) was not purified further. It exhibited IR and NMR spectra in accord with the proposed structure. The pertinent data are presented in Table 3 (page 107).

15. Preparation of *O,O*-diisopropyl-1-azidobenzylphosphonate (3e): In a round-bottomed flask (250 mL) fitted with a magnetic stirrer, heating oil bath, and reflux condenser is dissolved the *O,O*-diisopropyl-1-bromobenzylphosphonate **2e** (3.35 g, 0.01 mol) and sodium azide (3.5 g, 0.05 mol, 5 equiv) in a mixture of DMF (150 mL) and water (40 mL). The reaction mixture is heated at 140° for 14 hr. After cooling, the volatile materials are evaporated under reduced pressure and ethyl acetate (150 mL) is added to the residue. The mixture is washed with water (2 x 100 mL) and the organic component is dried ($MgSO_4$), filtered, and the solvent is evaporated under reduced pressure. The residual crude *O,O*-diisopropyl-1-azidobenzylphosphonate **3e** (2.5 g, 84%) was not purified further. It exhibited IR and NMR spectra in accord with the proposed structure. The pertinent data are presented in Table 3 (page 107).

SectionIV: Preparation of *O,O*-diisopropyl-1-aminoalkyl phosphonates

16. Preparation of *O,O*-diisopropyl-1-aminomethylphosphonate (4a):

The crude *O,O*-diisopropyl-1-azidomethylphosphonate **3a** (1.77 g, 0.008 mol) is dissolved in ethanol (50 mL) to which is added 10% Pd/C catalyst (0.25 g), acetic acid (1 mL) and trifluoroacetic acid (1 mL). The mixture is then hydrogenated in a dried, round-bottomed flask (100 mL) fitted with a magnetic stirrer and hydrogen bulb to maintain the pressure of hydrogen at 1 atm. The reaction mixture is stirred at room temperature for 12 hr, after which time it is filtered through a Celite pad, the pad being further washed with 6*M* hydrochloric acid (50 mL). The filtrate is evaporated under reduced pressure to remove ethanol and washed with ether(25 mL). Ethyl acetate (50 mL) is then added to the aqueous solution followed by the addition of aqueous saturated sodium bicarbonate solution (2 x 100 mL). The ethyl acetate layer is washed with water (2 x 50 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to yield the pure *O,O*-diisopropyl-1-aminomethylphosphonate **4a** (1.56 g) in quantitative yield, which exhibited a single spot on TLC, visualized using ninhydrin. IR and NMR spectra were in accord with the proposed structure and the pertinent data are presented in Table 4 (page 108).

17. Preparation of *O,O*-diisopropyl-1-aminoethylphosphonate (4b): The crude *O,O*-diisopropyl-1-azidoethylphosphonate **3b** (2.2 g, 0.00936 mol) is dissolved in ethanol (50 mL) to which is added 10% Pd/C catalyst (0.25 g), acetic acid (1 mL) and trifluoroacetic acid (1 mL). The mixture is then hydrogenated in a dried, round-bottomed flask (100 mL) fitted with a magnetic stirrer and hydrogen bulb to maintain the pressure of hydrogen at 1 atm. The reaction mixture is stirred at room temperature for 12 hr, after which time it is filtered through a Celite pad, the pad being further washed with 6*M* hydrochloric acid (50 mL). The filtrate is evaporated under reduced pressure to remove ethanol and washed with ether (25 mL). Ethyl acetate (50 mL) is then added to the aqueous solution followed by the addition of aqueous saturated sodium bicarbonate solution (2 x 100 mL). The ethyl acetate layer is washed with water (2 x 50 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to yield the pure *O,O*-diisopropyl-1-aminoethylphosphonate **4b** (1.95 g) in quantitative yield, which exhibited a single spot on TLC, visualized using ninhydrin. IR and NMR spectra were in accord with the proposed structure and the pertinent data are presented in Table 4 (page 108).

18. Preparation of *O,O*-diisopropyl-1-amino-2-methylpropyl-phosphonate (4c):

The crude *O,O*-diisopropyl-1-azido-2-methylpropylphosphonate **3c** (2.3 g, 0.0087 mol) is dissolved in ethanol (50 mL) to which is added 10% Pd/C catalyst (0.25 g), acetic acid (1 mL) and trifluoroacetic acid (1 mL). The mixture is then hydrogenated in a dried, round-bottomed flask (100 mL) fitted with a magnetic stirrer and hydrogen bulb to maintain the pressure of hydrogen at 1 atm. The reaction mixture is stirred at room temperature for 12 hr, after which time it is filtered through a Celite pad, the pad being further washed with 6*M* hydrochloric acid (50 mL). The filtrate is evaporated under reduced pressure to remove ethanol and washed with ether(25 mL). Ethyl acetate (50 mL) is then added to the aqueous solution followed by the addition of aqueous saturated sodium bicarbonate solution (2 x 100 mL). The ethyl acetate layer is washed with water (2 x 50 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to yield the pure *O,O*-diisopropyl-1-amino-2-methylpropylphosphonate **4c** (2.06 g) in quantitative yield, which exhibited a single spot on TLC, visualized using ninhydrin. IR and NMR spectra were in accord with the proposed structure and the pertinent data are presented in Table 4 (page 108).

19.Preparation of *O,O*-diisopropyl-1-amino-3-methylbutyl-phosphonate (4d):

The crude *O,O*-diisopropyl-1-azido-3-methylbutylphosphonate **3d** (2.47 g, 0.0089 mol) is dissolved in ethanol (50 mL) to which is added 10% Pd/C catalyst (0.25 g), acetic acid (1 mL) and trifluoroacetic acid (1 mL). The mixture is then hydrogenated in a dried, round-bottomed flask (100 mL) fitted with a magnetic stirrer and hydrogen bulb to maintain the pressure of hydrogen at 1 atm. The reaction mixture is stirred at room temperature for 12 hr, after which time it is filtered through a Celite pad, the pad being further washed with 6*M* hydrochloric acid (50 mL). The filtrate is evaporated under reduced pressure to remove ethanol and washed with ether(25 mL). Ethyl acetate (50 mL) is then added to the aqueous solution followed by the addition of aqueous saturated sodium bicarbonate solution (2 x 100 mL). The ethyl acetate layer is washed with water (2 x 50 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to yield the pure *O,O*-diisopropyl-1-amino-3-methylbutylphosphonate **4d** (2.23 g) in quantitative yield, which exhibited a single spot on TLC, visualized using ninhydrin. IR and NMR spectra were in accord with the proposed structure and the pertinent data are presented in Table 4 (page 108).

20. Preparation of *O,O*-diisopropyl-1-aminobenzylphosphonate (4e):

The crude *O,O*-diisopropyl-1-azidobenzylphosphonate **3e** (2.5 g, 0.0084 mol) is dissolved in ethanol (50 mL) to which is added 10% Pd/C catalyst (0.25 g), acetic acid (1 mL) and trifluoroacetic acid (1 mL). The mixture is then hydrogenated in a dried, round-bottomed flask (100 mL) fitted with a magnetic stirrer and hydrogen bulb to maintain the pressure of hydrogen at 1 atm. The reaction mixture is stirred at room temperature for 12 hr, after which time it is filtered through a Celite pad, the pad being further washed with 6*M* hydrochloric acid (50 mL). The filtrate is evaporated under reduced pressure to remove ethanol and washed with ether(25 mL). Ethyl acetate (50 mL) is then added to the aqueous solution followed by the addition of aqueous saturated sodium bicarbonate solution (2 x 100 mL). The ethyl acetate layer is washed with water (2 x 50 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to yield the pure *O,O*-diisopropyl-1-aminobenzylphosphonate **4e** (2.28 g) in quantitative yield, which exhibited a single spot on TLC, visualized using ninhydrin. IR and NMR spectra were in accord with the proposed structure and the pertinent data are presented in Table 4 (page 108).

Chapter 2

Synthesis of α-hydroxy alkyl phosphonic acids

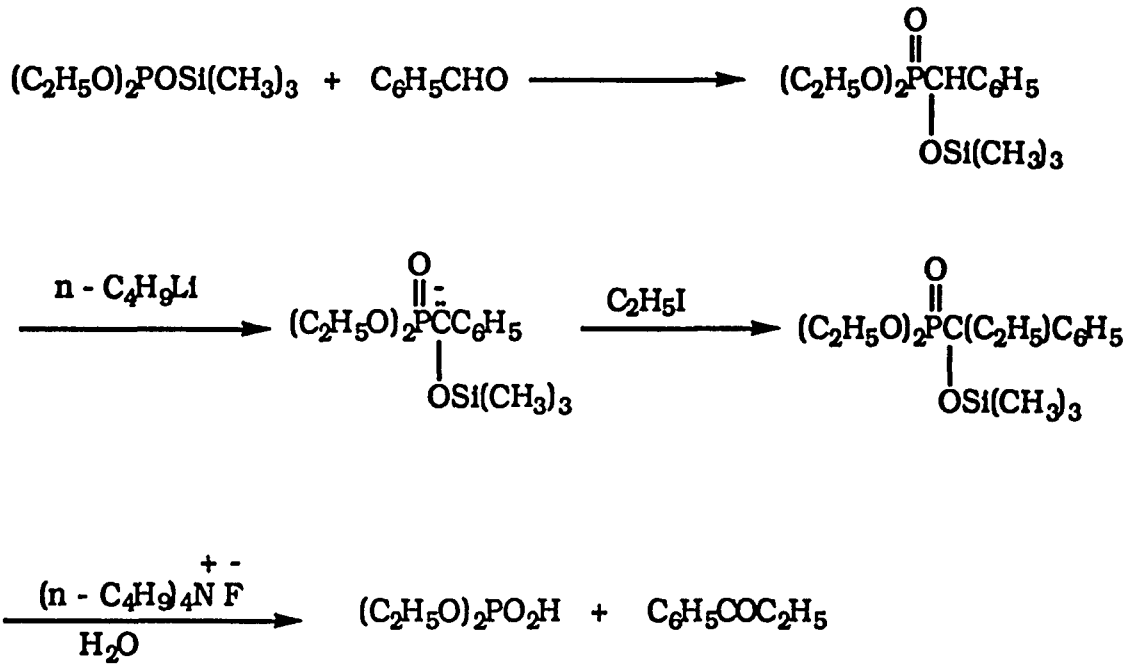
Introduction: History and Background

α-Functionalized phosphonic acids have contributed significantly to research activity in the use of analogs of natural metabolites for the regulation and probing of biological systems. They have utility in a variety of biological applications. These applications include their use as probes of metabolic processes, antibacterial agents, herbicides, pharmaceuticals, insecticides, fungicides, and as analogues of vitamins.[73] Use of these types of materials for non-biological applications such as flame retardants, ion exchange resins, and scale inhibitors has been well reported.[73] With this range of utility for α-functionalized quinquivalent organophosphorus compounds, it is quite understandable that various methods for their synthesis have been explored and investigated.

In this chapter the main emphasis is given on phosphonate compounds containing the P-C-O-H bond system. Of course, the P-C-O bond system also includes ethers, carbonyl derivatives, epoxides, and derivatives of phosphonoformic acids. Because of this structural diversity and the unique chemical properties of each class of materials, they are attractive materials

for study and there is ongoing interest in each field. Reviews are available which cover the literature up to 1982.[74] Here, a brief review with selected examples highlight the most important recent developments of the P-C-O system of 1-hydroxy-alkylphosphonates and 1-hydroxyalkylphosphonic acids.

Two main reaction methodologies, the Abramov and Pudovik reactions are exploited and explored in the syntheses of these materials.[73] The products of these syntheses have utility as *umpolung* reagents for chemical syntheses.[73] The products of trivalent phosphorus addition to carbonyl (or carbonyl related) groups lead directly to quinquevalent phosphorus compounds bearing a hydroxyl group (or related polar functionality) at the carbon attached to phosphorus. Such structural elements facilitate both further functionalization of that carbon and the ultimate cleavage of phosphorus from carbon. Overall, this *umpolung* approach generates a masked carbonyl function capable of reacting with a polarity inverted from the normal pattern, and provides for regeneration of the normal carbonyl group. One significant aspect of this approach lies in the syntheses of various unsymmetrical ketones, and one such example is given below.



Recent developments in the syntheses of 1-hydroxyalkyl-phosphonates and phosphonic acids are accomplished in the following three ways.

Syntheses of the P-C-O Bond System

1. Syntheses by Formation of P-C Bonds (addition of P-H or P-X reagents to carbonyl groups)

The formation of P-C bonds by addition of phosphorus reagents to the carbonyl group of aldehydes and ketones, known for a long time, has been developed into a most general, very efficient synthesis of α-phosphoryl alcohols. The range of phosphorus compounds capable of addition to the carbon-oxygen

double bond includes virtually any species with a P-H or P-X bond. Dialkyl phosphonates were used most frequently, but the additions of other trivalent phosphorus species are also known. The addition of the P-H function represents a simple case of nucleophilic addition to the carbonyl group and follows general rules applying to the reactivity of aldehydes and ketones towards nucleophiles.

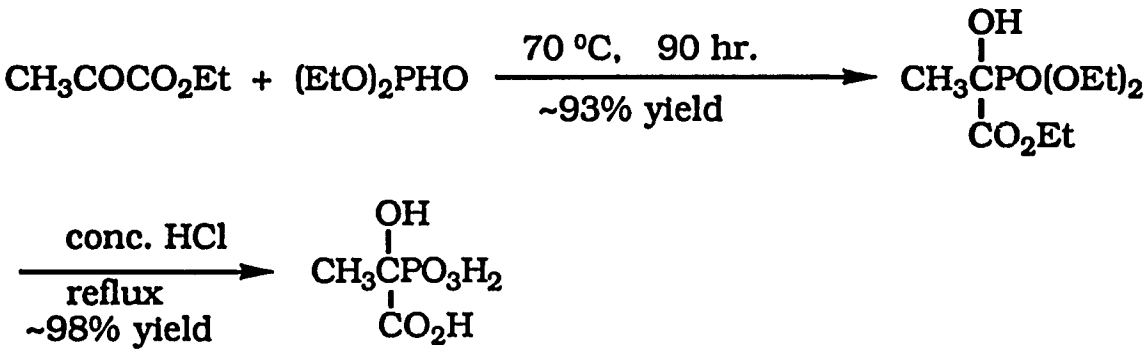
The original work of Abramov involved the heating of an aldehyde with a trialkyl phosphite at 70 to 100 ^{0}C for several hours in a sealed tube. Under these rather stringent conditions α-alkoxyalkylphosphonates could be isolated in variable yield.

Some limitations, *e.g.* those observed with α-halogenoketones or α,β-unsaturated carbonyl compounds are avoided when silylated P(III) reagents are used. The reactions are less straightforward because a desilylation step is necessary to remove the silyl groups from the initially formed silyloxyphosphonates.

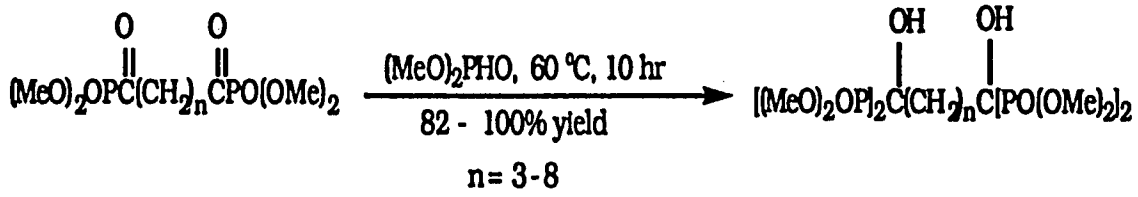
Detailed discussions of the formation of 1-hydroxyalkylphosphonates by addition of P-H compounds to the

carbonyl group are found in older, comprehensive reviews.[75] Recent contributions by Russian workers were also reviewed.[76]

The addition of dialkyl phosphonates to aldehydes and ketones is most frequently performed in the presence of basic catalysts. Acid catalysis was applied rather less frequently and only few examples were described of non-catalyzed additions.[77] The reactions without catalysts are slow but workable and occasionally may provide excellent yields of desired products, as in the following example of the synthesis of 1-hydroxy-1-carboxyethylphosphonic acids from ethyl pyruvate.[78]

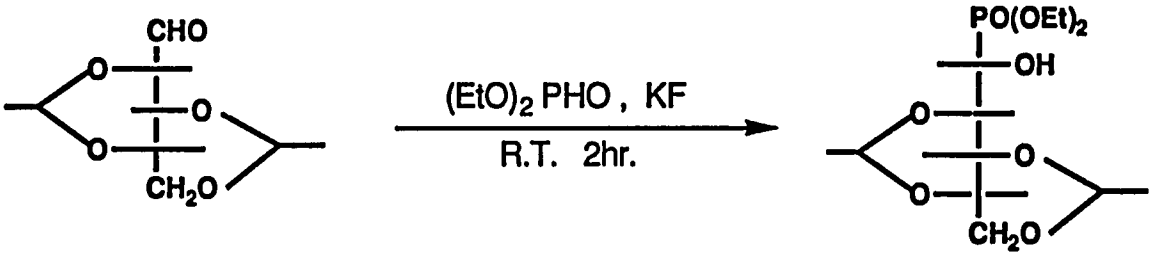


In another example of non-catalyzed addition, dimethyl phosphite was added to each carbonyl group of α,α-dioxobisphosphonates.[79]



Much less efficient (~13%yield) was the addition of dialkyl phosphites to both carbonyl groups of glyoxal.[80] On the other hand, paraformaldehyde and diethyl phosphite gave a 90% yield of diethyl hydroxymethylphosphonate in an exothermic reaction without catalyst.[81]

Very effective catalysis under neutral conditions is provided by alkali metal fluorides, alumina, and potassium fluoride on alumina. The additions of dialkyl phosphites in the presence of these catalysts are performed without solvents and are sufficiently rapid at ambient temperatures. The yields are generally high. Catalysis by potassium fluoride was recently employed in the synthesis of 1-hydroxyalkylphosphonates derived from sugars.[82]

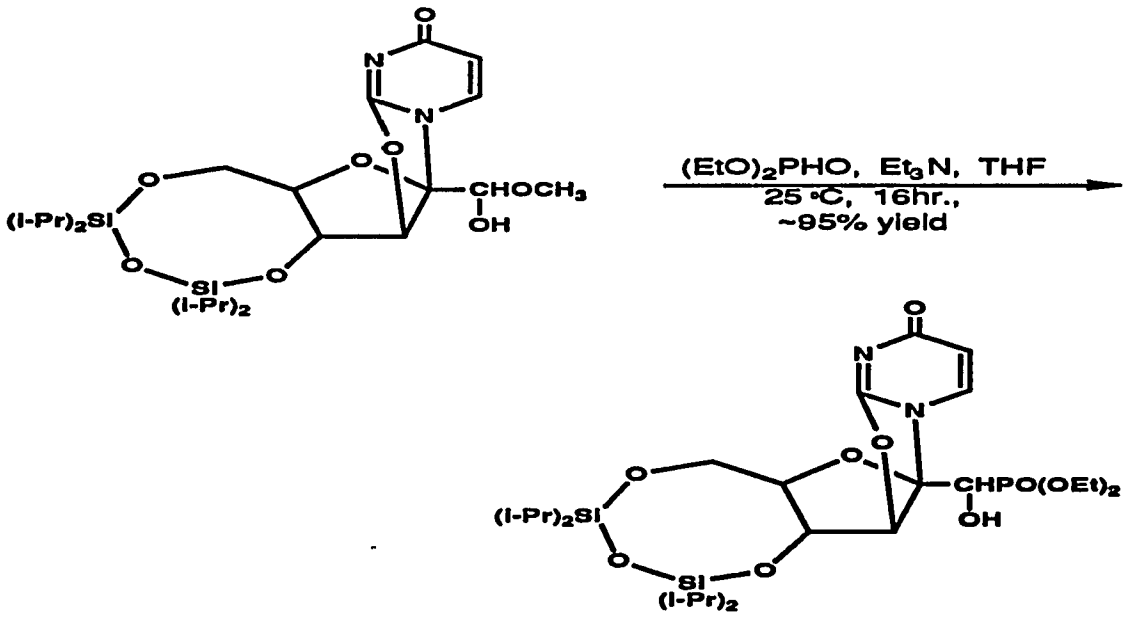


Examples of acid-catalyzed addition of P-H substrates to the carbonyl group are found in older literature. In a more recent work hydrogen chloride was used to promote the formation of α-phosphoryl alcohols from triethyl phosphite and aldehydes.[83] The function of HCl is to assist in the dealkylation step following the initial nucleophilic attack of phosphorus on the carbonyl

carbon atom.

A great number of 1-hydroxyalkylphosphonic acids were prepared from aldehydes and ketones by addition of P-H reagents in the presence of triethylamine followed by subsequent hydrolysis. The yields vary from good to excellent and depend upon the structure of the carbonyl reagents.[84]

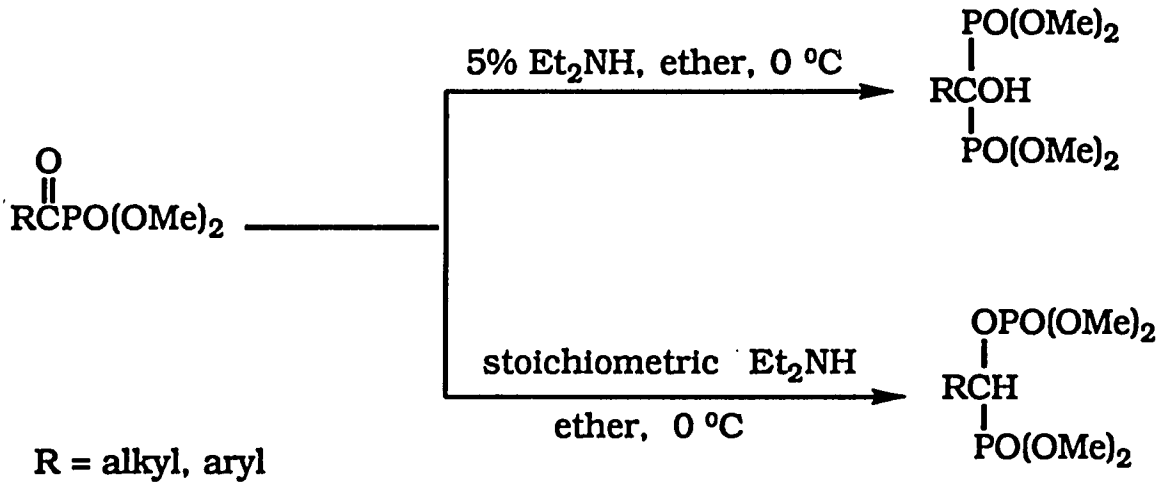
Triethylamine is sufficiently effective under mild conditions to permit its use in synthesis of complex, polyfunctional 1-hydroxyalkylphosphonates. The following example is taken from a reaction sequence performed to synthesize a phosphonic analog of an anhydronucleotide.[85]



More complex organic bases, *e.g.*, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) were also used to catalyze the

addition of P-H reagents to carbonyl groups.[86]

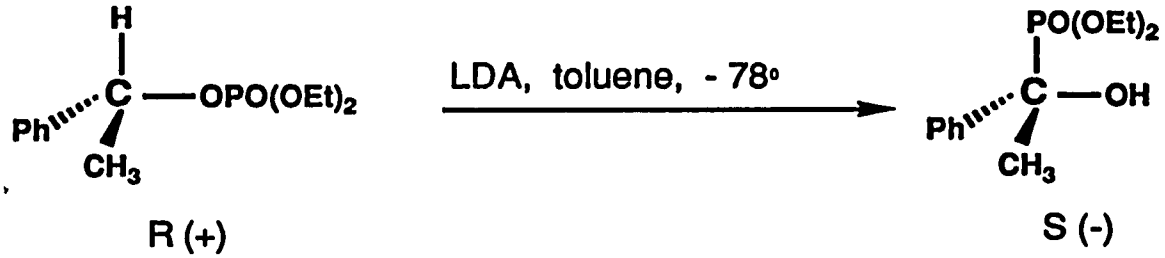
The amount of amine used to catalyze the addition may have dramatic effect upon the reaction course when the addition products readily undergo the phosphonate-phosphate rearrangement. For example, catalytic amounts of diethylamine bring about a smooth addition of dimethyl phosphite to the carbonyl group of acylphosphonates, whereas with stoichiometric amounts of the same catalyst only the rearranged products are obtained under otherwise the same conditions.[87]



1-Hydroxy-1,1-bisphosphonates are rearranged to phosphonate-phosphates at room temperature with catalytic amounts of triethylamine.[88]

The phosphonate-phosphate and other similar rearrangements were reviewed.[89] The reverse process, *i.e.* the formation of 1-hydroxyalkylphosphonates from phosphate esters, is

also known. It is not important in synthetic organophosphorus chemistry but attracts attention because of reaction mechanisms and phosphate-phosphonate rearrangement in the biosynthesis of natural phosphonates. It was found that the base-induced formation of hydroxyphosphonates from phosphates takes place with inversion of configuration at the carbon atom to which the phosphonate group migrates.[90]



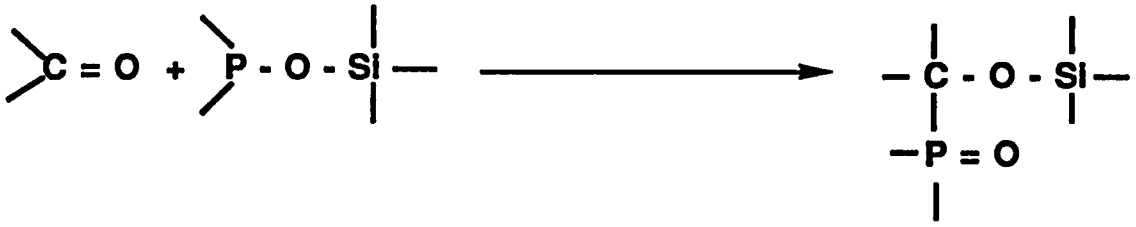
R (+) S (-)

Both enantiomers of hydroxyphosphonates resulting from this rearrangement were obtained also by chemical resolution and their absolute configuration was determined by X-ray crystallography.[90] Several aliphatic and aromatic α-hydroxyalkylphosphonates and phosphonic acids were resolved to pure enantiomers by crystallization of their salts with α-methylbenzylamine or amphetamine and ephedrine.[91]

The synthesis of optically active α-hydroxyalkyl-phosphonates was accomplished also by addition of dialkyl phosphites to aromatic aldehydes in the presence of chiral bases (quinine, quinidine). The degrees of asymmetric induction were

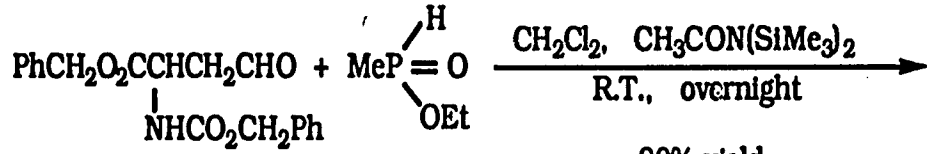
quite high (~85%) and the products were easily crystallized to optical purity.[92] The absolute configuration of dimethyl (*o*-chlorophenyl)hydroxymethylphosphonate was determined by X-ray analysis.[93] The list of optically active 1-hydroxyalkylphosphonates and 1-hydroxyalkylphosphonic acids of known configuration are compiled.[94]

The application of silylated phosphorus reagents in the synthesis of α-hydroxyalkylphosphonic acids was reviewed.[95] In the addition of P(III) silyl esters to the carbonyl group the phosphorus atom forms a bond with the carbonyl carbon and the silyl group is transferred to the carbonyl oxygen.



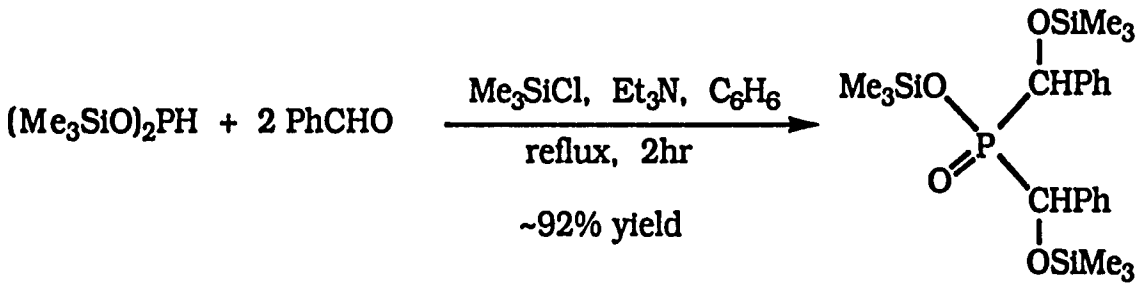
No catalyst is required and the reaction is usually sufficiently rapid at room temperature. The necessity of separate preparation of silylated reagents can be avoided in one-pot procedures where mixtures of P-H substrates with commercially available silylating reagents react with carbonyl substrates. A pertinent example is provided by the synthesis of γ-hydroxyphosphinothricin. The key step in this synthesis is the

reaction of the aldehyde derived from homoserine with a mixture of ethylmethylphosphinate and bis(trimethylsilyl)acetamide.[96]



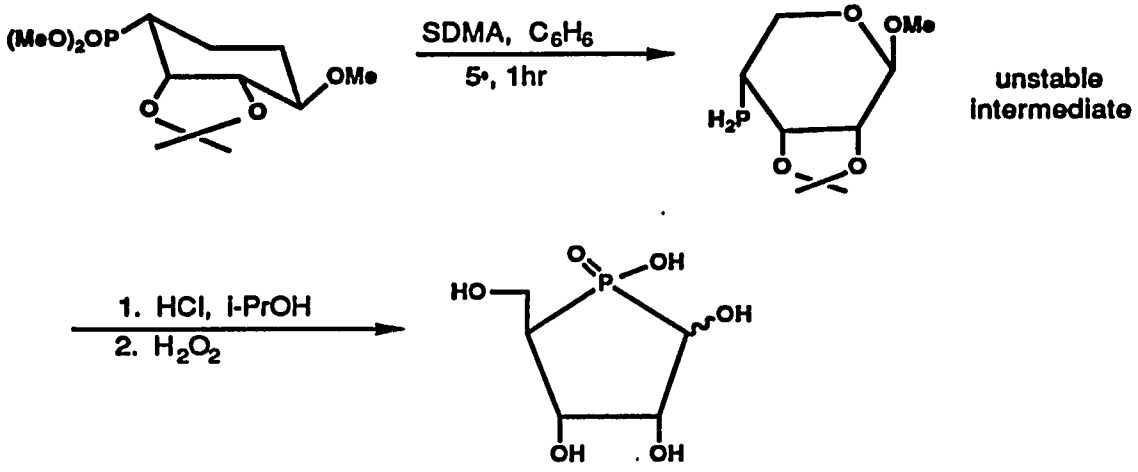
γ - hydroxyphosphinothricin

Phosphorus reagents in which the phosphorus atom is less oxidized than in the P(III) species are capable of multiple additions to the carbonyl group. This property was used in a synthesis of bis(hydroxyalkyl)phosphinic acids from aldehydes and ketones by addition of bis-(trimethylsilyloxy)phosphine.[97]



Examples of primary phosphine addition are also known.

Particularly interesting are the intramolecular additions of the $-PH_2$ function to the carbonyl group in sugar derivatives. Such additions were employed to synthesize sugar analogs with the phosphorus atom in the ring.[98]

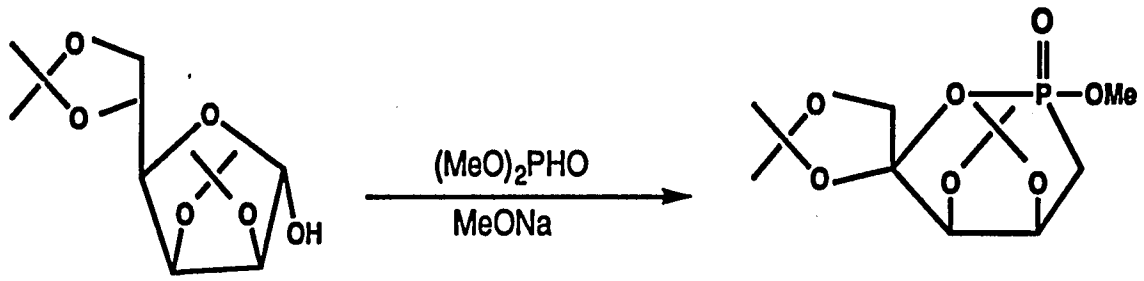


SDMA = sodium dihydrobis(2- methoxyethoxy)aluminate

The syntheses of sugar analogs with the phosphorus atom in the hemiacetal ring were reviewed.[80]

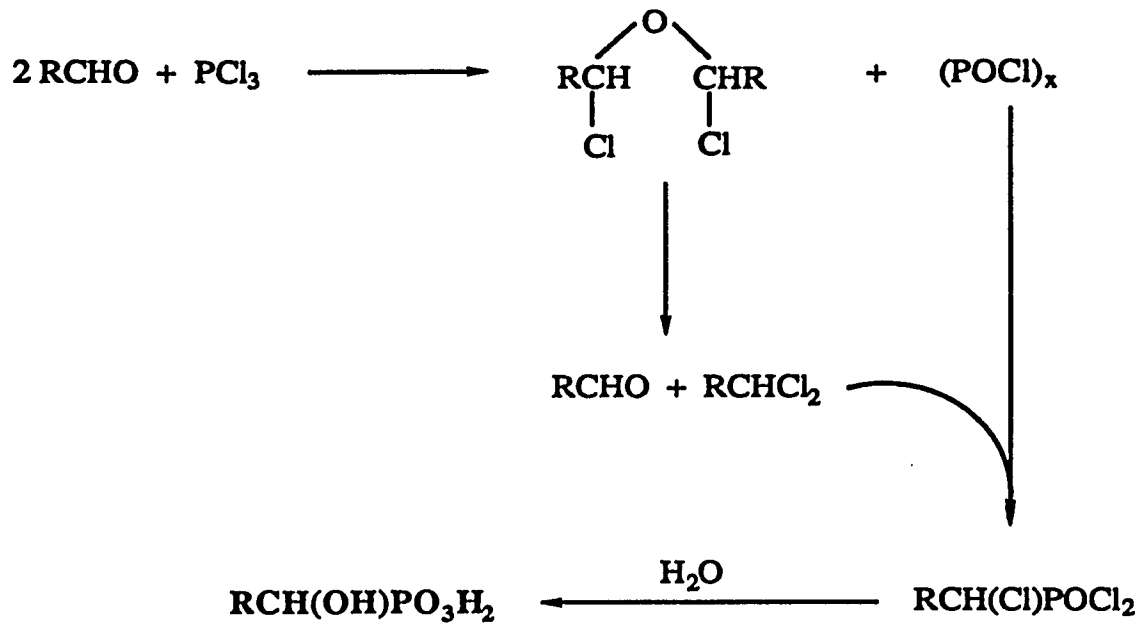
The addition of dialkyl phosphites to the carbonyl groups in sugar molecules was employed also in the syntheses of phosphonate analogues of sugar phosphates. Stereochemical analysis and configuration assignment of products obtained by addition of dimethyl phosphite to threose and erythrose were reported. In some cases the addition is complicated by interaction of the functional groups in the sugar moieties with the introduced phosphonate group. For example, a phostone (intramolecular

phosphonate ester) rather than the expected addition product was formed in base-catalyzed reaction of dimethyl phosphite with diisopropylidene mannofuranose.[99]



The hydroxy group in 1-hydroxyalkylphosphonates and phosphonic acids is readily esterified by standard methods with no interference from the phosphonate and phosphonic acid groups.[100]

The addition of trivalent phosphorus-halogen compounds to the carbonyl carbon of simple aldehydes has been known for quite some time. Phosphorus trichloride reaction with aldehydes followed by water work-up, provides a convenient method for the synthesis of 1-hydroxyalkylphosphonic acids.[101] Mechanistic investigations of these reactions are still unclear. However, it is believed that polymeric phosphorus-halogen material is generated which undergoes Arbuzov-type reactions with organic halides generated *in situ*.

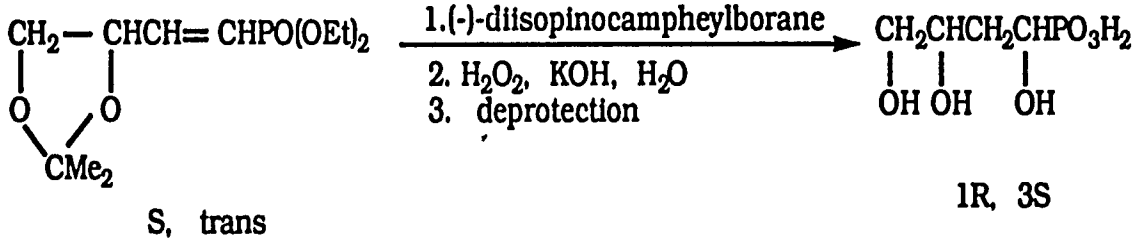


2. Syntheses by Oxidation-Reduction Processes

The reduction of the carbonyl group in acylphosphonates was rather infrequently used to prepare 1-hydroxy-alkylphosphonates. Catalytic hydrogenation works somewhat better than hydride reduction, but complications may arise with more complex substrates. The reduction with borohydride often resulted in very low yields because of the competing P-C bond cleavage typical for 1-hydroxyalkylphosphonates in alkaline media.[102] The reduction of diethyl benzoylphosphonate with a complex chiral borohydride of reduced basicity afforded optically active diethyl (phenyl)hydroxy-methylphosphonate.[100]

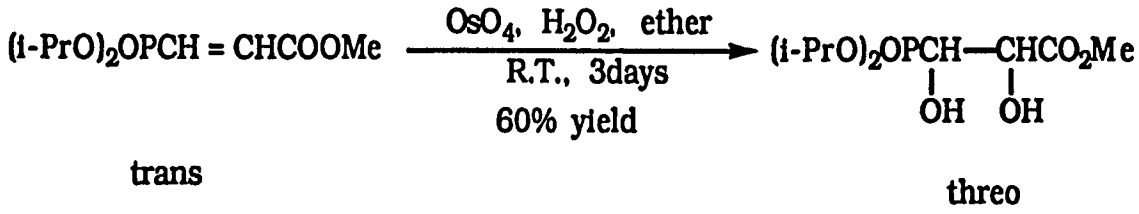
Hydroboration-oxidation of α,β-unsaturated phosphonates appears to be useful for regiospecific introduction of the hydroxyl

group into the α-position. The (1R,3S) and (1S,3S) diastereomers of 1,3,4-trihydroxybutyl-1-phosphonic acid were obtained from a chiral unsaturated substrate using optically active boranes. The (+) enantiomer of diisopinocampheylborane generated the S configuration at the α-position and the (-) enantiomer gave the R configuration.[103]



A different regiospecificity has also been reported. Hydroboration-oxidation of 2-dialkylphosphoryl-1-alkenes gave 1-hydroxyphosphonates.[104]

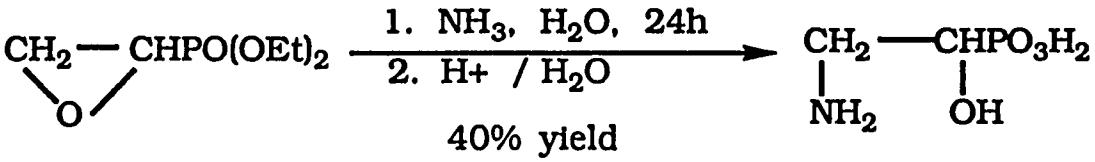
Oxidation of α,β-unsaturated phosphonates was frequently employed to prepare 1,2-dihydroxyphosphonates[105] needed either as analogues of natural products or as substrates for the preparation of other target molecules.[106] The oxidation was carried out with osmium tetroxide in the presence of auxiliary oxidants such as hydrogen peroxide, t-butylhydroperoxide or 4-methylmorpholine-4-oxide.[107] The stereochemistry is governed by the usual rules applying to *syn*-dihydroxylation.



trans

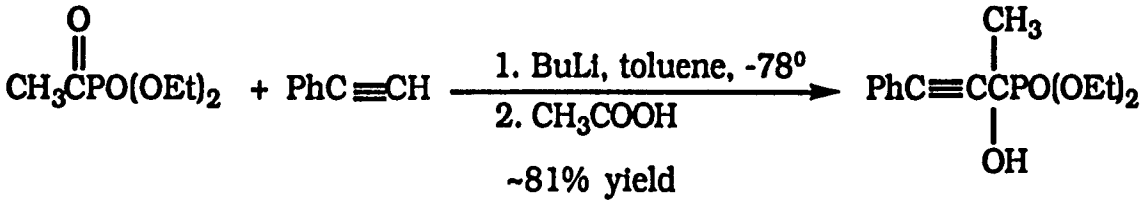
threo

It is also possible to obtain 1,2-dihydroxyphosphonates by hydrolytic ring opening in 1,2-epoxyalkylphosphonates, available directly by oxidation of α,β-unsaturated phosphonates. Epoxide ring opening with ammonia was used to prepare 1-hydroxy-2-aminoalkyl phosphonates.[108]

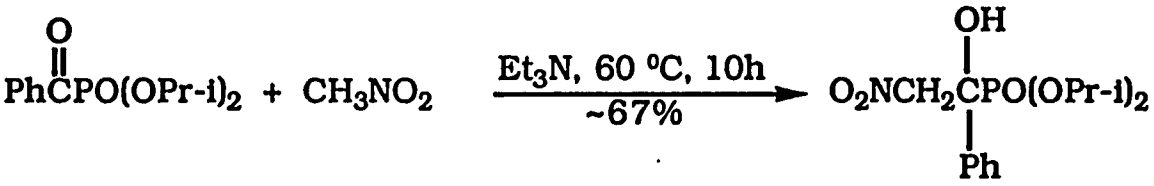


3. Syntheses by Formation of C-C Bonds

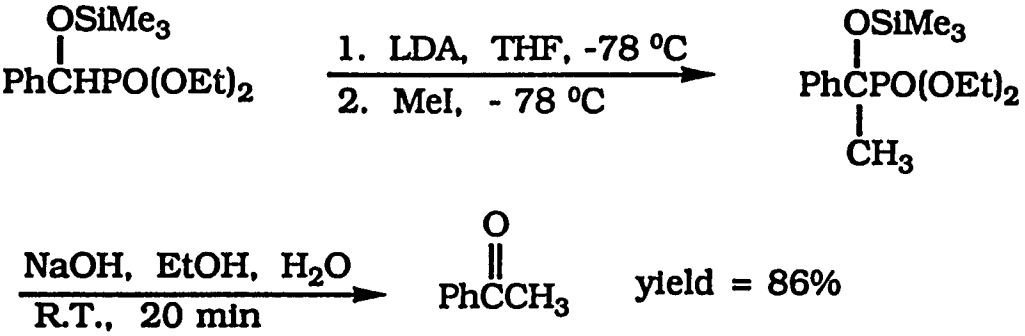
The preparation of 1-hydroxyalkylphosphonates by reactions in which C-C bonds are formed is possible either by addition of carbanions to the carbonyl group of α-ketophosphonates or by alkylation and acylation of α-carbanions obtained by deprotection of silyloxyphosphonates. The first approach was used to prepare several 1-hydroxyalkyl- phosphonates including 1-hydroxy-2-alkynyl derivatives.[109]



Similarly, nitromethane addition yields 1-hydroxy-2-nitroethylphosphonates.[110]



The 1-silyloxyalkylphosphonates serve as acyl anion equivalents in organic synthesis. They are readily C-alkylated and both the phosphoryl and the silyl group are readily removed by alkaline treatment.[111]



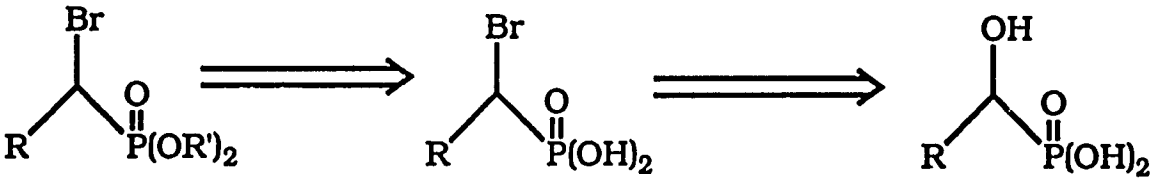
A vast amount of work and literature has been carried out on the biological and non-biological applications of α-hydroxyalkylphosphonates and α-hydroxyalkylphosphonic acids. It is thus highly desirable to prepare α-hydroxyalkylphosphonic acids in the simplest way possible from readily available starting materials, such as Arbuzov reaction with alkyl halides to generate alkylphosphonates which can then be substituted specifically. The α-hydroxyalkylphosphonic acids so produced can serve as synthons or precursors for numerous natural and complex structures since the α-hydroxyl group can be further extended through esterification or functional modification.

A significant achievement has been accomplished regarding α-halogenation of simple Arbuzov products, detailed in Chapter One. This section of the work will consider the possibility of converting α-bromoalkylphosphonates to α-hydroxyalkylphosphonic acids.

In this section, α-bromoalkylphosphonates will be first hydrolyzed to α-bromoalkylphosphonic acids and then S_N2 displacement reactions will be carried out to obtain the target materials, α-hydroxyalkylphosphonic acids.

This scheme is unique in the sense that most

α-hydroxyalkylphosphonic acids are usually prepared directly from the trivalent phosphorus compounds which undergo ready oxidation. The present proposal involved quinquivalent phosphorus which avoids this complication. This scheme is thus quite different from the three conventional and contemporary categories discussed in the introduction. The synthetic design is given below.



R = H, CH_3, $(CH_3)_2CH$, $(CH_3)_2CHCH_2$, C_6H_5

R' = $(CH_3)_2CH$

Approach to the Proposal: Results and Discussions

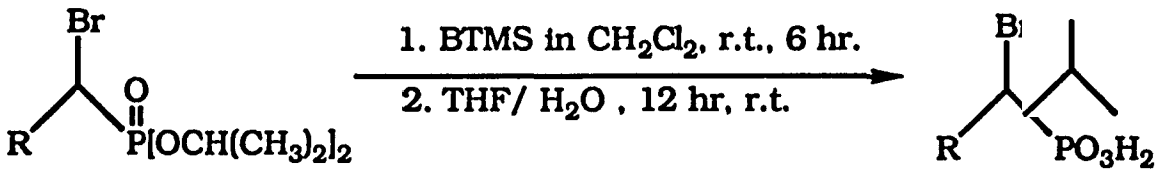
Five systems of α-hydroxyphosphonic acids as mentioned in the previous section with five different **R** groups were prepared. *O,O*-Diisopropyl-1-bromoalkylphosphonates were used as starting materials in this synthetic approach. The preparation of these

starting materials, *O,O*-diisopropyl1-bromoalkylphosphonates, are described in the previous chapter.

The first goal was to cleave the ester *O*-isopropyl groups of the phosphonates to obtain phosphonic acids. There exist procedures reported for ester cleavage. Some difficulty was experienced in accomplishing this with the isopropyl groups. Obviously *O,O*-dimethyl or *O,O*-diethyl esters are easily cleaved but not so with *O,O*-diisopropyl phosphonates.

In the first attempt, conc. HCl was used but no ester cleavage was observed even after stirring for five days with heating with excess conc. HCl.

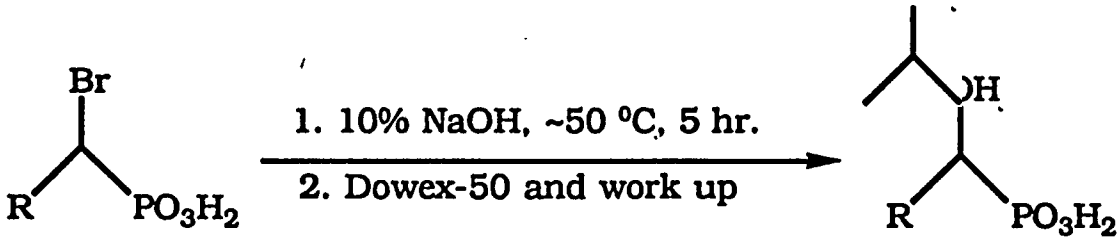
Next, BTMS (bromotrimethylsilane) was tried since it is reported to be highly effective in phosphonate ester dealkylation.[112] BTMS was effective in this ester cleavage. Methylene chloride was used as solvent with stirring (6-8hrs) at room temperature followed by subsequent stirring in THF and water. It should be noted, that cautionary measures should be taken not to apply heat at any stages during stirring and evaporation. Significant decomposition occurs under these conditions. TLC was used to monitor the progress of the reaction. The product bromophosphonic acids were quite hygroscopic and semi-solid.



NMR spectra of the α-bromoalkylphosphonic acids showed an absence of the usual peak due to the isopropyl group in the phosphonic acids. Also, the IR spectra showed the presence of a new peak for acidic P-O-H at around 2200-2300 cm^{-1}. These compounds exhibited spectra and analysis in accordance with the proposed structures. All the partinent data are given in the Table 5 in the 'Summary of Results' section, and the experimental procedures are described in the 'Experimental' section of this Chapter.

The substitution of the bromine atom by the hydroxyl group was explored. There is one reported procedure of alkaline hydrolysis[113] in DMF and this procedure was tried. However, results were very poor, significant decomposition occurring during removal of the DMF. Thus, the experimental procedure was modified to avoid the use of DMF. The bromophosphonic acids were hydrolyzed in aquous hydroxide solution with gentle reflux and then treated with Dowex-50 and filtered. Azeotropic distillation with isopropyl alcohol and finally methylene chloride removed all of the solvent. The materials were recrystallized using methanol/methylene chloride in a 1:1 ratio. It should be noted that the strength of the hydroxide solution is very important in this

hydrolysis reaction, since some elimination reaction also can occur.



All the α-hydroxyalkylphosphonic acids are solid, white, and colorless crystalline products, and their melting points were determined. Their elemental analyses matched perfectly with the molecular composition. They are not soluble in chloroform or any other solvent except water, and thus deuterated water is used for NMR spectra. The phosphoryl IR frequencies are observed to be lower than the normal which indicates that the phosphoryl oxygen to be hydrogen bonded with the hydrogen of the α-hydroxyl group.. This phenomena has been noted in the previous chapter.

These compounds exhibit spectra and analysis in accordance with the proposed structures. All the partinent data are given in the Table 6 in the 'Summary of Results' section and the experimental procedures are described in the 'Experimental' section of this chapter.

Overall, this approach provides a convenient synthesis of the α-hydroxyalkylphosphonic acids.

EXPERIMENTAL:

General:

Routine proton spectra were recorded at 60 MHZ on a Varian EM360 instument and the high field proton spectra were obtained on a Brucker-IBM WP200SY instrument. Proton NMR data are reported in parts per million downfield from TMS used as internal standard (multiplicity s=singlet, d=doublet, t=triplet, dd=doublet of doublets, m=multiplet, bs=broad singlet). Infrared spectra were recorded on Perkin-Elmer IR598 and Perkin Elmer 1600 FTIR spectrometers and absorptions are reported in reciprocal centimeters.

Column chromatography was performed in glass columns packed with silica (60-200 mesh, Baker). All thin layer chromatography (TLC) was performed using a KODAK Chromatogram Sheet (silica) with fluorescent indicator.

All chemicals were of reagent quality and were used without further purification except methylene chloride. Methylene chloride was distilled from calcium hydride and kept over molecular seives. BTMS (bromo-trimethylsilane) and Dowex-50 were obtained from Aldrich Co.

Micro-elemental analysis were performed by MicAnal, Tucson, Arizona and Schwarzkopf Microanalytical Lab, Woodside, New York. All melting points are uncorrected.

The experimental section is divided into two sections: the first section describes the preparation of α-bromoalkylphosphonic acids containing five different alkyl groups from the corresponding α-bromoalkyl-phosphonates, and the second section records all the procedures for the preparation of α-hydroxyalkylphosphonic acids *via* S_N2 displacement reactions.

Section V: Preparation of 1-bromo-alkylphosphonic acids

21. Preparation of 1-bromomethylphosphonic acid (5a):

In a dried round-bottomed flask (50 mL) fitted with a magnetic stirrer is placed *O,O*-diisopropyl-1-bromo-methylphosphonate (1g, 0.0038 mol) in dry methylene chloride (20 mL), distilled just before use. Bromotrimethylsilane (2.9 g, 0.019 mol, 5 equiv) is then added and the mixture is stirred for 6 hours at room temperature under a nitrogen atmosphere. The reaction mixture is evaporated, using a water-aspirator pump, slowly and carefully at room temperature to remove methylene chloride and the excess BTMS which results in a pale yellow, viscous liquid. THF (12 ml) and water (3 mL) are added to the reaction mixture which becomes colorless. It is stirred overnight, then azeotroped under reduced pressure (using a high vacuum pump) with isopropyl alcohol (5 x 20 mL) at room temperature and finally dried in benzene by the freeze-pump-thaw technique under vacuum to afford

bromomethylphosphonic acid **5a** (0.3 g, 44%), a highly hygroscopic, colorless, semi-solid product. The compound exhibited spectra and analysis in accordance with the proposed structure. All the pertinent spectral and physical data are given in Table 5 (page 109).

22. Preparation of 1-bromoethylphosphonic acid (5b):

In a dried round-bottomed flask (50 mL) fitted with a magnetic stirrer is placed *O,O*-diisopropyl-1-bromoethylphosphonate (1.3g, 0.0047 mol) in dry methylene chloride (20 mL), distilled just before use. Bromotrimethylsilane (3.67 g, 0.024 mol, 5 equiv) is then added and the mixture is stirred for 6 hours at room temperature under a nitrogen atmosphere. The reaction mixture is evaporated, using a water-aspirator pump, slowly and carefully at room temperature to remove methylene chloride and the excess BTMS which results in a pale yellow, viscous liquid. THF (12 ml) and water (3 mL) are added to the reaction mixture which becomes colorless. It is stirred overnight, then azeotroped under reduced pressure (using a high vacuum pump) with isopropyl alcohol (5 x 20 mL) at room temperature and finally dried in benzene by the freeze-pump-thaw technique under vacuum to afford 1-bromoethylphosphonic acid **5b** (0.41 g, 47%), a highly hygroscopic, colorless, semi-solid product. The compound exhibited spectra and analysis in accordance with the proposed structure. All the pertinent spectral and physical data are given in

Table 5 (page 109).

23. Preparation of 1-bromo-2-methylpropylphosphonic acid (5c):

In a dried round-bottomed flask (50 mL) fitted with a magnetic stirrer is placed *O,O*-diisopropyl-1-bromo-2-methylpropyl-phosphonate (1.2 g, 0.00398 mol) in dry methylene chloride (20 mL), distilled just before use. Bromotrimethylsilane (3.06 g, 0.02 mol, 5 equiv) is then added and the mixture is stirred for 6 hours at room temperature under a nitrogen atmosphere. The reaction mixture is evaporated, using a water-aspirator pump, slowly and carefully at room temperature to remove methylene chloride and the excess BTMS which results in a pale yellow, viscous liquid. THF (12 ml) and water (3 mL) are added to the reaction mixture which becomes colorless. It is stirred overnight, then azeotroped under reduced pressure (using a high vacuum pump) with isopropyl alcohol (5 x 20 mL) at room temperature and finally dried in benzene by the freeze-pump-thaw technique under vacuum to afford 1-bromo-2-methylpropylphosphonic acid **5c** (0.46 g, 53%), a highly hygroscopic, colorless, semi-solid product. The compound exhibited spectra and analysis in accordance with the proposed structure. All the pertinent spectral and physical data are given in Table 5 (page 109).

24. Preparation of 1-bromo-3-methylbutylphosphonic acid (5d):

In a dried round-bottomed flask (50 mL) fitted with a magnetic

stirrer is placed *O,O*-diisopropyl-1-bromo-3-methylbutyl-phosphonate (1.20g, 0.0038 mol) in dry methylene chloride (20 mL), distilled just before use. Bromotrimethylsilane (2.9 g, 0.019 mol, 5 equiv) is then added and the mixture is stirred for 6 hours at room temperature under a nitrogen atmosphere. The reaction mixture is evaporated, using a water-aspirator pump, slowly and carefully at room temperature to remove methylene chloride and the excess BTMS which results in a pale yellow, viscous liquid. THF (12 ml) and water (3 mL) are added to the reaction mixture which becomes colorless. It is stirred overnight, then azeotroped under reduced pressure (using a high vacuum pump) with isopropyl alcohol (5 x 20 mL) at room temperature and finally dried in benzene by the freeze-pump-thaw technique under vacuum to afford 1-bromo-3-methylbutylphosphonic acid **5d** (0.44 g, 51%), a highly hygroscopic, colorless, semi-solid product. The compound exhibited spectra and analysis in accordance with the proposed structure. All the pertinent spectral and physical data are given in Table 5 (page 109).

25. Preparation of 1-bromobenzylphosphonic acid (5e):

In a dried round-bottomed flask (50 mL) fitted with a magnetic stirrer is placed *O,O*-diisopropyl-1-bromobenzylylphosphonate (140g, 0.004 mol) in dry methylene chloride (20 mL), distilled just before use. Bromotrimethylsilane (3.06 g, 0.02 mol, 5 equiv) is then added and the mixture is stirred for 6 hours at room temperature

under a nitrogen atmosphere. The reaction mixture is evaporated, using a water-aspirator pump, slowly and carefully at room temperature to remove methylene chloride and the excess BTMS which results in a pale yellow, viscous liquid. THF (12 ml) and water (3 mL) are added to the reaction mixture which becomes colorless. It is stirred overnight, then azeotroped under reduced pressure (using a high vacuum pump) with isopropyl alcohol (5 x 20 mL) at room temperature and finally dried in benzene by the freeze-pump-thaw technique under vacuum to afford 1-bromobenzylphosphonic acid **5e** (0.58 g, 58%), a highly hygroscopic, colorless, semi-solid product. The compound exhibited spectra and analysis in accordance with the proposed structure. All the pertinent spectral and physical data are given in Table 5 (page 109).

Section VI: Preparation of 1-hydroxy-alkylphosphonic acids

26. Preparation of 1-hydroxymethylphosphonic acid (6a):

Bromomethylphosphonic acid (0.3 g, 0.0017 mol) is placed in a round-bottomed flask (50mL), 10% aquous sodium hydroxide (15 mL) is introduced and the mixture is stirred with gentle reflux (60 ^{0}C) for about 5 hours. The mixture is then treated with Dowex-50 (5 g) at room temperature, filtered and water (10 mL) is added. It is then azeotroped with isopropyl alcohol (3 x 20 mL) below 40 ^{0}C. The crude product is dissolved in methanol (15 mL),

followed by the addition of methylene chloride (15 mL). The mixture is stored in a refrigerator to induce crystallization. The precipitate is filtered and washed with methylene chloride a few times and then dried under vacuum to obtain hydroxymethylphosphonic acid **6a** (0.1 g, 56%), which is a white crystalline solid insoluble in all solvents except water. The compound exhibited spectra and analysis in accordance with the proposed structure. All the pertinent spectral and physical data are given in Table 6 (page 110).

27. Preparation of 1-hydroxyethylphosphonic acid (6b):

1-Bromoethylphosphonic acid (0.4 g, 0.002 mol) is placed in a round-bottomed flask (50mL), 10% aquous sodium hydroxide (15 mL) is introduced and the mixture is stirred with gentle reflux (60 ^{0}C) for about 5 hours. The mixture is then treated with Dowex-50 (5 g) at room temperature, filtered and water (10 mL) is added. It is then azeotroped with isopropyl alcohol (3 x 20 mL) below 40 ^{0}C. The crude product is dissolved in methanol (15 mL), followed by the addition of methylene chloride (15 mL). The mixture is stored in a refrigerator to induce crystallization. The precipitate is filtered and washed with methylene chloride a few times and then dried under vacuum to obtain 1-hydroxyethylphosphonic acid **6b** (0.13 g, 51%), which is a white crystalline solid insoluble in all solvents except water. The compound exhibited spectra and analysis in accordance with the

proposed structure. All the pertinent spectral and physical data are given in Table 6 (page 110).

28. Preparation of 1-hydroxy-2-methylpropylphosphonic acid (6c): 1-Bromo-2-methylpropylphosphonic acid (0.45 g, 0.002 mol) is placed in a round-bottomed flask (50mL), 10% aquous sodium hydroxide (15 mL) is introduced and the mixture is stirred with gentle reflux (60 ^{0}C) for about 5 hours. The mixture is then treated with Dowex-50 (5 g) at room temperature, filtered and water (10 mL) is added. It is then azeotroped with isopropyl alcohol (3 x 20 mL) below 40 ^{0}C. The crude product is dissolved in methanol (15 mL), followed by the addition of methylene chloride (15 mL). The mixture is stored in a refrigerator to induce crystallization. The precipitate is filtered and washed with methylene chloride a few times and then dried under vacuum to obtain 1-hydroxy-2-methylpropylphosphonic acid **6c** (0.16 g, 54%), which is a white crystalline solid insoluble in all solvents except water. The compound exhibited spectra and analysis in accordance with the proposed structure. All the pertinent spectral and physical data are given in Table 6 (page 110).

29. Preparation of 1-hydroxy-3-methylbutylphosphonic acid (6d): 1-Bromo-3-methylbutylphosphonic acid (0.44 g, 0.0019 mol) is placed in a round-bottomed flask (50mL), 10% aquous sodium hydroxide (15 mL) is introduced and the mixture is stirred with

gentle reflux (60 ^{0}C) for about 5 hours. The mixture is then treated with Dowex-50 (5 g) at room temperature, filtered and water (10 mL) is added. It is then azeotroped with isopropyl alcohol (3 x 20 mL) below 40 ^{0}C. The crude product is dissolved in methanol (15 mL), followed by the addition of methylene chloride (15 mL). The mixture is stored in a refrigerator to induce crystallization. The precipitate is filtered and washed with methylene chloride a few times and then dried under vacuum to obtain 1-hydroxy-3-methylbutylphosphonic acid **6d** (0.16 g, 50%), which is a white crystalline solid insoluble in all solvents except water. The compound exhibited spectra and analysis in accordance with the proposed structure. All the pertinent spectral and physical data are given in Table 6 (page 110).

30. Preparation of 1-hydroxybenzylphosphonic acid (6e):

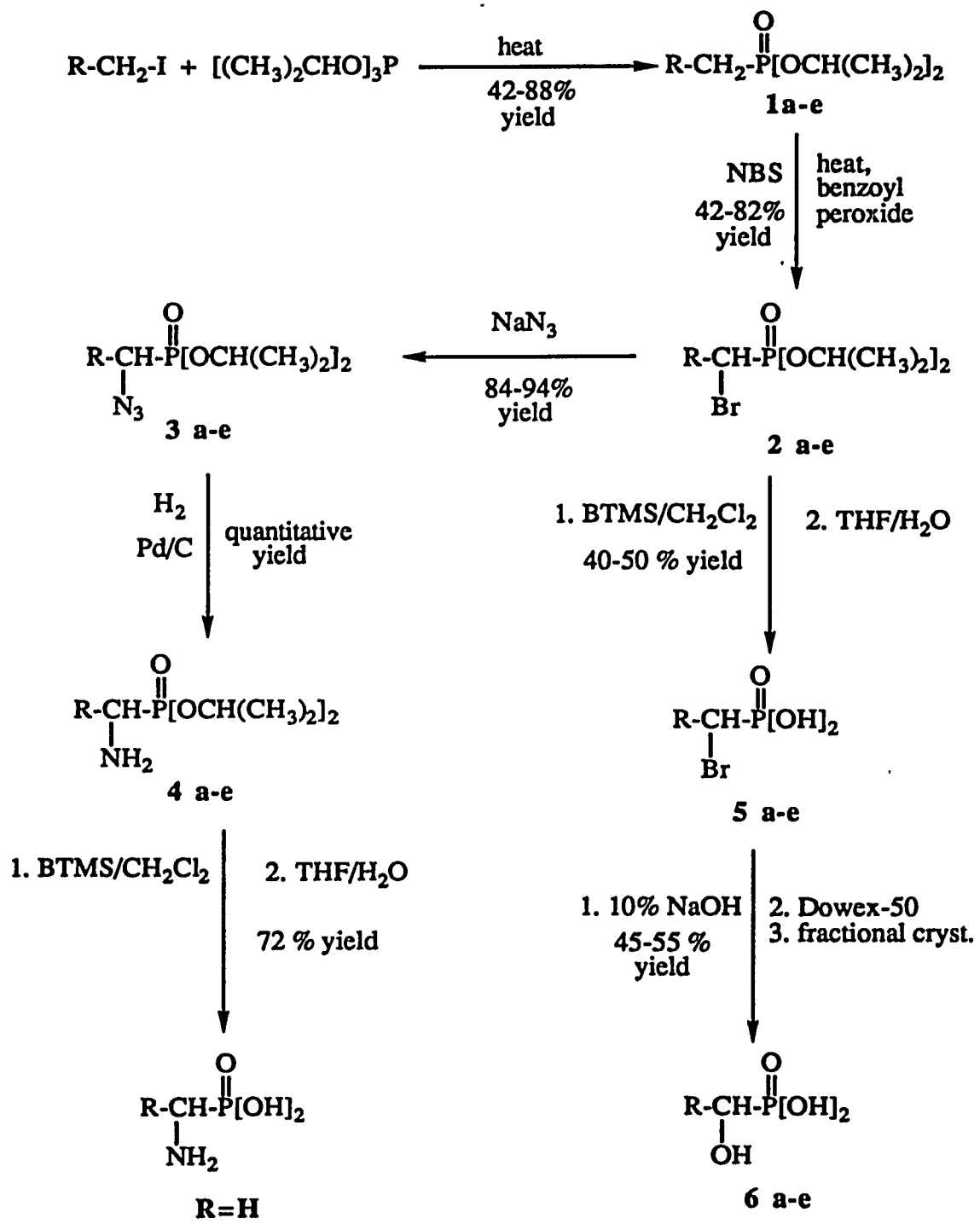
1-Bromobenzylphosphonic acid (0.58 g, 0.0023 mol) is placed in a round-bottomed flask (50mL), 10% aquous sodium hydroxide (15 mL) is introduced and the mixture is stirred with gentle reflux (60 ^{0}C) for about 5 hours. The mixture is then treated with Dowex-50 (5 g) at room temperature, filtered and water (10 mL) is added. It is then azeotroped with isopropyl alcohol (3 x 20 mL) below 40 ^{0}C. The crude product is dissolved in methanol (15 mL), followed by the addition of methylene chloride (15 mL). The mixture is stored in a refrigerator to induce crystallization. The precipitate is filtered and washed with methylene chloride a few

times and then dried under vacuum to obtain 1-hydroxybenzylphosphonic acid **6e** (0.22 g, 52%), which is a white crystalline solid insoluble in all solvents except water. The compound exhibited spectra and analysis in accordance with the proposed structure. All the pertinent spectral and physical data are given in Table 6 (page 110).

Chapter 3

Summary of Results

The synthetic scheme actually worked out is given below. All the pertinent data are given in tables 1-6.



The preparation of the target, Five systems of α-Aminoalkylphosphonates and α-hydroxyalkylphosphonic acids, has been accomplished according to the scheme given above. Various experimental conditions using a variety of reagents were explored in order to work out the best conditions. The general procedures are given below along with six tables containing all the physical characteristics and spectral data.

General Experimental Procedure:

All chemicals were of reagent quality and were used without further purification. All thin layer chromatography (TLC) was performed using a KODAK Chromagram Sheet (silica) with fluorescent indicator. Silica gel, used for preparative chromatography, was from Baker (60-200 mesh). Infrared spectra were measured using a Perkin Elmer 1600 FTIR instrument, and NMR spectra were measured using a Varian EM-360 instrument. Elemental analyses were performed by MicAnal, Tucson, Arizona, and by Schwarzkopf Microanalytical Laboratory, Woodside, New York. All melting points are uncorrected.

Diisopropyl Alkylphosphonates 1; General Procedure:

In a dried, nitrogen-flushed round-bottomed flask fitted with a magnetic stirrer, heating oil bath, and a reflux condenser with drying tube is placed triisopropyl phosphite (20 g, 0.096 mol)

and the alkyl iodide (0.48 mol, 5 equiv). The mixture is heated at 160° for 12 hr, at which time the solution is cooled and volatile materials are evaporated under reduced pressure. The crude product is vacuum distilled, and the major fraction is subjected to chromatography on a silica gel column (180 g) eluting with hexane:ethyl acetate (20:1). Solvent is removed from the eluents under reduced pressure to yield the pure products **1a-e**. All products exhibited a single spot on TLC, and IR and NMR spectra in accord with the proposed structures. The pertinent data are presented in Table 1 (page105).

Diisopropyl 1-Bromoalkylphosphonates 2: General Procedure:

In a dried round-bottomed flask (250 mL) maintained under a nitrogen atmosphere and fitted with a magnetic stirrer, heating oil bath, and a reflux condenser is dissolved the diisopropyl alkylphosphonate **1a-e** (0.022 mol) and *N*-bromosuccinimide (4.4 g, 0.025 mol, 1.1 equiv) in carbon tetrachloride (150 mL). The mixture is stirred for 1 hr, after which time there is added benzoyl peroxide (0.5 g, 0.002 mol, 0.09 equiv), and the reaction mixture is stirred and heated at 60° for a further 24 hr. At this time the insoluble succinimide is removed by filtration and the volatile materials removed by evaporation under reduced pressure. Ethyl acetate (100 mL) is added to the residue and the solution is extracted with saturated aqueous sodium bisulfite solution (50 mL) and water (2 x 50 mL).

The organic layer is dried ($MgSO_4$), filtered, and the solvent removed by evaporation under reduced pressure. The crude product is subjected to chromatography on a silica gel column (75 g) eluting with hexane:ethyl acetate (4:1). Solvent is removed from the eluents to yield the pure products **2a-e**. All products exhibited a single spot on TLC, and IR and NMR spectra in accord with the proposed structures. The pertinent data are presented in Table 2 (page 106).

Diisopropyl 1-Azidoalkylphosphonates 3; General Procedure:

In a round-bottomed flask (250 mL) fitted with a magnetic stirrer, heating oil bath, and reflux condenser is dissolved the diisopropyl 1-bromoalkylphosphonate **2** (0.01 mol) and sodium azide (3.5 g, 0.05 mol, 5 equiv) in a mixture of DMF (150 mL) and water (40 mL). The reaction mixture is heated at 140° for 12 hr. After cooling, the volatile materials are evaporated under reduced pressure and ethyl acetate (150 mL) is added to the residue. The mixture is washed with water (2 x 100 mL) and the organic component is dried ($MgSO_4$), filtered, and the solvent is evaporated under reduced pressure. The residual crude diisopropyl 1-azidophosphonate **3a-e** is not purified further. IR and NMR spectra were in accord with the proposed structures. The pertinent data are presented in Table 3 (page 107).

Diisopropyl 1-Aminoalkylphosphonates 4; General Procedure:

The crude *O,O*-diisopropyl-1-azidoalkylphosphonate **3a-e** (0.004 mol) is dissolved in ethanol (50 mL) to which is added 10% Pd/C catalyst (0.25 g), acetic acid (1 mL) and trifluoroacetic acid (1 mL). The mixture is then hydrogenated in a dried, round-bottomed flask (100 mL) fitted with a magnetic stirrer and hydrogen bulb to maintain the pressure of hydrogen at 1 atm. The reaction mixture is stirred at room temperature for 12 hr, after which time it is filtered through a Celite pad, the pad being further washed with 6*M* hydrochloric acid (50 mL). The filtrate is evaporated under reduced pressure to remove ethanol and washed with ether(25 mL). Ethyl acetate (50 mL) is then added to the aqueous solution followed by the addition of aqueous saturated sodium bicarbonate solution (2 x 100 mL). The ethyl acetate layer is washed with water (2 x 50 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to yield the pure *O,O*-diisopropyl-1-aminoalkylphosphonate **4a-e**, in quantitative yield, which exhibited a single spot on TLC, visualized using ninhydrin. IR and NMR spectra were in accord with the proposed structures and the pertinent data are presented in Table 4 (page 108).

α-Bromoalkyl-phosphonic acids 5; General Procedure:

In a dried round-bottomed flask (50 mL) fitted with a

magnetic stirrer is placed *O,O*-diisopropyl-1-bromoalkyl-phosphonate **2a-e** (0.005 mol) in dry methylene chloride (20 mL), distilled just before use. Bromotrimethylsilane (0.025 mol, 5 equiv) is then added and the mixture is stirred for 4-6 hours at room temperature under a nitrogen atmosphere. The reaction mixture is evaporated, using a water-aspirator pump, slowly and carefully at room temperature to remove methylene chloride and the excess BTMS which results in a pale yellow, viscous liquid. A mixture of THF and water (8:2, 15 mL) is added to the reaction mixture which becomes colorless. It is stirred overnight, then azeotroped under reduced pressure (using a high vacuum pump) with isopropyl alcohol (5 x 20 mL) at room temperature and finally dried in benzene by the freeze-pump-thaw technique under vacuum to afford 1-bromoalkylphosphonic acid **5a-e**, all are highly hygroscopic, colorless, semi-solid products. The compounds exhibited spectra and analysis in accordance with the proposed structures. All the pertinent spectral and physical data are presented in Table 5 (page 109).

α-Hydroxyalkyl-phosphonic acids 6; General Procedure:

1-Bromoalkylphosphonic acid **5a-e** (0.002 mol) is placed in a round-bottomed flask (50mL), 10% aquous sodium hydroxide (15 mL) is introduced and the mixture is stirred with gentle reflux (60 ^{0}C) for about 5 hours. The mixture is then treated with

Dowex-50 (5 g) at room temperature, filtered and water (10 mL) is added. It is then azeotroped with isopropyl alcohol (3 x 20 mL) below 40 ^{0}C. The crude product is dissolved in methanol (15 mL), followed by the addition of methylene chloride (15 mL). The mixture is stored in a refrigerator to induce crystallization. The precipitate is filtered and washed with methylene chloride a few times and then dried under vacuum to obtain 1-hydroxyalkylphosphonic acids **6a-e**, which are white crystalline solids insoluble in all solvents except water. The compounds exhibited spectra and analysis in accordance with the proposed structure. All the pertinent spectral and physical data are given in Table 6 (page 110).

Table 1. Preparation and characterizations of diisopropyl alkylphosphonates (1) R—P(O)(OPr-i)$_2$

Compound	R	Yield (%)	B.P.(°C)/Torr	TLC R_f*	^{1}H NMR (δ 60 MHz)	Formula (M.W.)	C/H Anal.Calcd. (Found)	IR (cm^{-1})
1a	H	86	42-44/2.5	0.67	1.4 [12 H, d, J=6] 1.7 [3 H, d, J=14] 4.8 [2 H, m]	$C_7H_{17}O_3P$ (180.2)	C: 46.66(46.99) H: 9.51(9.52)	1260 (P=O) 1020 (P-O-C)
1b	CH_3	88	45-48/2	0.67	1.4 [12 H, d, J=6] 1.9-2.0 [5 H, br m] 4.8 [2 H, m]	$C_8H_{19}O_3P$ (194.2)	C: 49.48(49.27) H: 9.86(9.81)	1250 (P=O) 1020 (P-O-C)
1c	$(CH_3)_2CH$	42	61-65/2	0.58	1.0 [6H, d, J=8] 1.35 [12H, d, J=6] 1.7 [2H, dd, J=6,12] 2.0 [1H, m] 4.8 [2H, m]	$C_{10}H_{23}O_3P$ (222.3)	C: 54.04(54.07) H: 10.43(10.63)	1230 (P=O) 1010 (P-O-C)
1d	$(CH_3)_2CHCH_2$	74	68-72/2	0.55	1.0 [6H, d, J=6] 1.45 [12H, d, J=5] 1.5-2.1 [5H, m] 4.8 [2H, m]	$C_{11}H_{25}O_3P$ (236.3)	C: 55.91(55.96) H: 10.66(10.71)	1240 (P=O) 1010 (P-O-C)
1e	C_6H_5	70	92-95/2	0.61	1.4 [12H, d, J=7] 3.4 [2H, d, J=22] 5.0 [2H, m] 7.5 [5H, s]	$C_{13}H_{21}O_3P$ (256.3)	C: 60.93(60.93) H: 8.26(8.29)	1210 (P=O) 1000 (P-O-C)

* KODAK Chromagram Sheet (silica) with fluorescent indicator, eluted with hexane:ethyl acetate 4:1

Table 2. Preparation and characterization of diisopropyl 1-bromoalkylphosphonates (2)

Compound	R	Yield(%)	TLC R_f*	^{1}H NMR (δ 60 MHz)	Formula (M.W.)	C/H Anal. Calcd. (Found)	IR (cm^{-1})
2a	H	42	0.72	1.5 [12H, d, J=5] 3.5 [2H, d, J=12] 5.0 [2H, m]	$C_7H_{16}BrO_3P$ (259.1)	C: 32.45(32.72) H: 6.23(6.27)	1210 (P=O) 990 (P-O-C)
2b	CH_3	58	0.71	1.45 [12H, d, J=6] 1.6 [3H, dd, J=7,12] 3.7 [1H, m] 5.0 [2H, m]	$C_8H_{18}BrO_3P$ (273.1)	C: 35.18(34.96) H: 6.64(6.58)	1220 (P=O) 1000 (P-O-C)
2c	$(CH_3)_2CH$	74	0.65	1.1 [6H, d, J=8] 1.4 [12H, d, J=6] 2.1 [1H, m] 3.4 [1H, dd, J=5,5] 5.0 [2H, m]	$C_{10}H_{22}BrO_3P$ (301.2)	C: 37.65(37.48) H: 7.36(7.61)	1215 (P=O) 980 (P-O-C)
2d	$(CH_3)_2CHCH_2$	76	0.65	1.0 [6H, dd, J=3,2] 1.4 [12H, d, J=6] 1.5-2.0 [3H, m] 3.8 [1H, dt, J=4,5] 5.0 [2H, m]	$C_{11}H_{24}BrO_3P$ (315.2)	C: 41.92(42.08) H: 7.68(7.81)	1210 (P=O) 1000 (P-O-C)
2e	C_6H_5	82	0.67	1.35 [12H, dd, J=7,8] 4.9 [2H, m] 5.1 [1H, d, J=12] 7.5 [5H, m]	$C_{13}H_{20}BrO_3P$ (335.2)	C: 46.59(46.90) H: 6.02(6.24)	1200 (P=O) 980 (P-O-C)

* KODAK Chromagram Sheet (silica) with fluorescent indicator, eluted with hexane:ethyl acetate 4:1

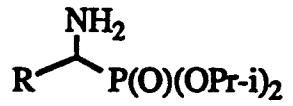
Table 3. Preparation and characterization of diisopropyl 1-azido alkyl phosphonates (3)** 

Compound	R	Yield(%)	TLC R_f*	^{1}H NMR (δ 60 MHz)	Formula (M.W.)	IR (cm^{-1})
3a	H	92	0.42	1.5 [12H, d, J=5] 3.7 [2H, d, J=12] 5.0 [2H, m]	$C_7H_{16}N_3O_3P$ (221.1)	2140 (N_3) 1230 (P=O) 1010 (P-O-C)
3b	CH_3	94	0.41	1.5 [12H, d, J=6] 1.7 [3H, dd, J=7,6] 3.9 [1H, m] 5.0 [2H, m]	$C_8H_{18}N_3O_3P$ (235.1)	2150 (N_3) 1240 (P=O) 1000 (P-O-C)
3c	$(CH_3)_2CH$	88	0.38	1.2 [6H, d, J=8] 1.5 [12H, d, J=5] 2.2 [1H, m] 3.6 [1H, dd, J=7,6] 5.0 [2H, m]	$C_{10}H_{22}N_3O_3P$ (263.2)	2140 (N_3) 1240 (P=O) 1000 (P-O-C)
3d	$(CH_3)_2CHCH_2$	90	0.38	1.1 [6H, d, J=3] 1.4 [12H, d, J=5] 1.6-2.2 [3H, m] 4.0 [1H, dt, J=5,5] 5.0 [2H, m]	$C_{11}H_{24}N_3O_3P$ (277.2)	2140 (N_3) 1220 (P=O) 990 (P-O-C)
3e	C_6H_5	84	0.44	1.45 [12H, dd, J=8,8] 4.9 [2H, m] 5.3 [1H, d, J=13] 7.5 [5H, m]	$C_{13}H_{20}N_3O_3P$ (297.2)	2090 (N_3) 1200 (P=O) 980 (P-O-C)

* KODAK Chromagram Sheet (silica) with fluorescent indicator, eluted with hexane:ethyl acetate 4:1

**Elemental Analyses are not performed since the azides were not subjected to further purification.

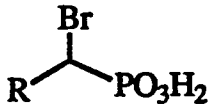
Table 4. Preparation and characterization of disiopropyl 1-aminoalkylphosphonates (4)



Compound	R	TLC R_f*	^{1}NMR (δ 60 MHz)#	Formula (M.W.)	C/H Anal. Calcd. (Found)	IR(cm^{-1}) (CCl_4)
4a	H	0.28	1.5 [12H, d, J=6] 3.3 [2H, d, J=12] 4.9 [2H, m]	$C_7H_{18}NO_3P$ (195.2)	C: 43.07(42.94) H: 9.30(9.14)	3310 (d, NH_2) 1210 (P=O)
4b	CH_3	0.28	1.4 [[12H, d, J=6] 1.9 [3H, dd, J=8,9] 3.4 [1H, m] 4.9 [2H, m]	$C_8H_{20}NO_3P$ (209.2)	C: 45.92(46.06) H: 9.64(9.77)	3330 (d, NH_2) 1200 (P=O)
4c	$(CH_3)_2CH$	0.25	1.3 [6H, d, J=8] 1.4 [12H, d, J=6] 2.1 [1H, m] 3.4 [1H, m] 5.0 [2H, m]	$C_{10}H_{24}NO_3P$ (237.3)	C: 50.62(50.49) H: 10.20(9.95)	3330 (d, NH_2) 1190 (P=O)
4d	$(CH_3)_2CHCH_2$	0.24	1.0 [6H, d, J=4] 1.4 [12H, d, J=6] 2.0-2.6 [3H, m] 3.4 [1H, m] 5.0 [2H, m]	$C_{11}H_{26}NO_3P$ (251.3)	C: 52.57(52.81) H: 10.43(10.07)	3320 (d, NH_2) 1200 (P=O)
4e	C_6H_5	0.36	1.4 [12H, dd, J=5,6] 5.0 [2H, m] 4.9 [1H, d, J=18] 7.6 [5H, m]	$C_{13}H_{22}NO_3P$ (271.3)	C: 57.55(57.40) H: 8.17(8.03)	3290 (d, NH_2) 1180 (P=O)

* KODAK Chromagram Sheet (silica) with fluorescent indicator, eluted with hexane:ethyl acetate 4:1
# D_2O solvent

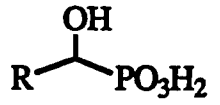
Table 5. Preparation and characterization of 1-bromoalkylphosphonic acids (5)



Compound	R	Yield(%)	TLC R_f*	^{1}H NMR (δ 60 MHz)# (δ ppm, J Hz)	Formula (M.W.)	C/H Anal. Calcd. (Found)	m.p. (°C)	IR (KBr)
5a	H	44	0.14	3.6 [2H, d, J=10]	CH_4BrO_3P (173.91)	C: 6.9(7.42) H: 2.32(2.46)	-	2380 (POH)
5b	CH_3	47	0.10	1.7 [3H, dd, J=7,12] 4.1 [1H, m]	$C_2H_6BrO_3P$ (187.93)	C: 12.77(12.89) H: 3.22(3.26)	-	2380 (POH)
5c	$(CH_3)_2CH$	53	0.12	1.1 [6H, dd, J=4,5] 2.2 [1H, m] 3.5 [1H, dd, J=6,6]	$C_4H_{10}BrO_3P$ (215.96)	C: 22.23(22.58) H: 4.67(4.78)	122-128	2340 (POH)
5d	$(CH_3)_2CHCH_2$	51	0.12	1.0 [6H, dd, J=3,5] 1.6-2.1 [3H, m] 4.0 [1H, dt, J=6,5]	$C_5H_{12}BrO_3P$ (229.97)	C: 26.09(26.24) H: 5.26(5.31)	136-140	2355 (POH)
5e	C_6H_5	58	0.12	5.0 [1H, d, J=14] 7.5 [5H, m]	$C_7H_8BrO_3P$ (249.94)	C: 33.61(33.77) H: 3.23(3.27)	138-143	2340 (POH)

* KODAK Chromagram Sheet (silica) with fluorescent indicator, eluted with hexane:ethyl acetate 4:1
# D_2Osolvent

Table 6. Preparation and characterization of 1-hydroxyalkylphosphonic acids (6)



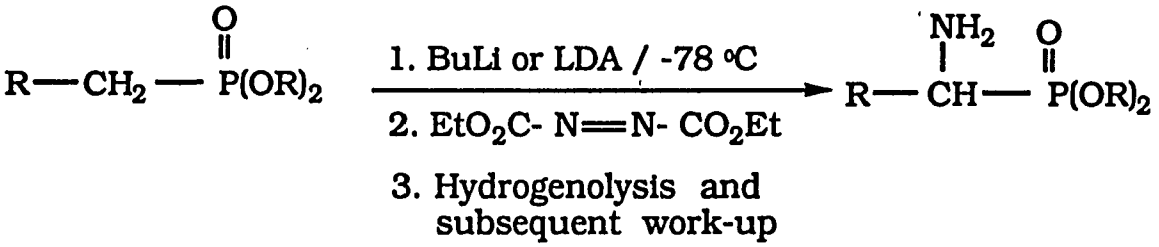
Compound	R	Yield(%)	^{1}H NMR (60 MHz)* (δ ppm, J Hz)	Formula (M.W.)	C/H Anal. Calcd. (Found)	m.p. (°C) (lit.)	IR (KBr) (ν cm^{-1})
6a	H	56	3.9 [2H, d, J=9]	CH_5O_4P (111.99)	C: 10.71 (10.82) H: 4.5 (4.76)	88-90 (87-88)	3410 (OH) 1220 (PO) 2320 (POH)
6b	CH_3	51	1.9 [3H, dd, J=6,8] 4.1 [1H, m]	$C_2H_7O_4P$ (126.01)	C: 19.05 (19.04) H: 5.6 (5.58)	132-136	3410 (OH) 1200 (PO) 2300 (POH)
6c	$(CH_3)_2CH$	54	1.1 [6H, dd, J=3,6] 2.0 [1H, m] 3.7 [1H, dd, J=6,3]	$C_4H_{11}O_4P$ (154.04)	C: 31.16 (31.23) H: 7.2 (7.42)	162-164	3380 (OH) 1200 (PO) 2280 (POH)
6d	$(CH_3)_2CHCH_2$	50	1.0 [6H, dd, J=4,2] 1.4-1.9 [2H+1H, m] 3.9 [1H, dt, J=5,2]	$C_5H_{13}O_4P$ (168.06)	C: 35.7 (35.73) H: 7.8 (7.98)	179-181	3370 (OH) 1215 (PO) 2190 (POH)
6e	C_6H_5	52	5.5 [1H, d, J=10] 7.6 [5H, br]	$C_7H_9O_4P$ (188.02)	C: 44.68 (44.72) H: 4.82 (4.89)	173-175	3350 (OH) 1190 (PO) 2380 (POH)

*D_2O solvent.

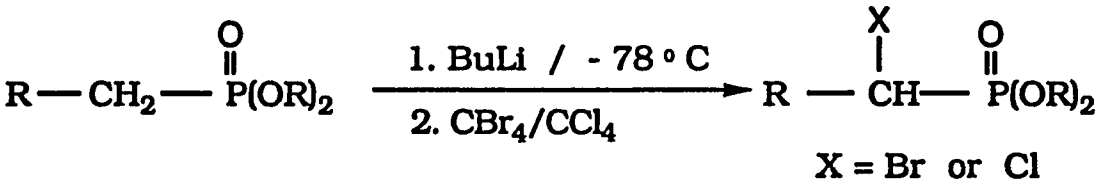
Chapter 4

Suggestions for the Future Scope of Research

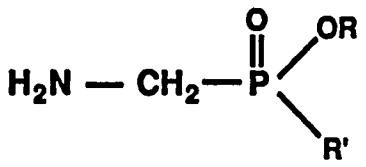
In this thesis, efforts are emphasized on α-halogenation, followed by azido group displacement and subsequent reduction. This is quite simple and versatile. Still, a better versatile system can be visualized with diazo-acetic ester. This can lead to a better one-pot versatile method to prepare several α-aminoalkylphosphonates.



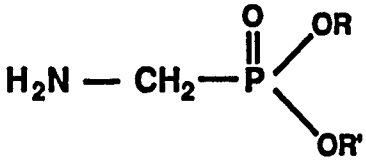
Although α-halogenation was achieved with NBS, it was quite tedious and time-consuming in work-up. α-Functionalization and substitution should also be explored through anion formation with BuLi or LDA. This might result in an easier and more facile substitution with better yield.



Our efforts in the lab have been directed towards the syntheses of symmetric phosphonates followed by α-functionalization. This α-functionalization creates chirality but gives in racemic products. It would be worth investigating the possibility of asymmetric α-functionalization from the unsymmetric phosphonates because the unsymmetric (non-equivalent) phosphonates or phosphinates have a chiral center at phosphorus. Additional chiral centers and the bulkiness of the ester groups might even induce greater asymmetric induction. These unsymmetric 'non-equivalent' phosphonic acid diesters and phosphinic acid monoesters can be prepared to explore/exploit the asymmetric environment created by the chirality at the phosphorus atom. In the case of diester, one of the ester group should be quite bulky like menthyl or bornyl group.



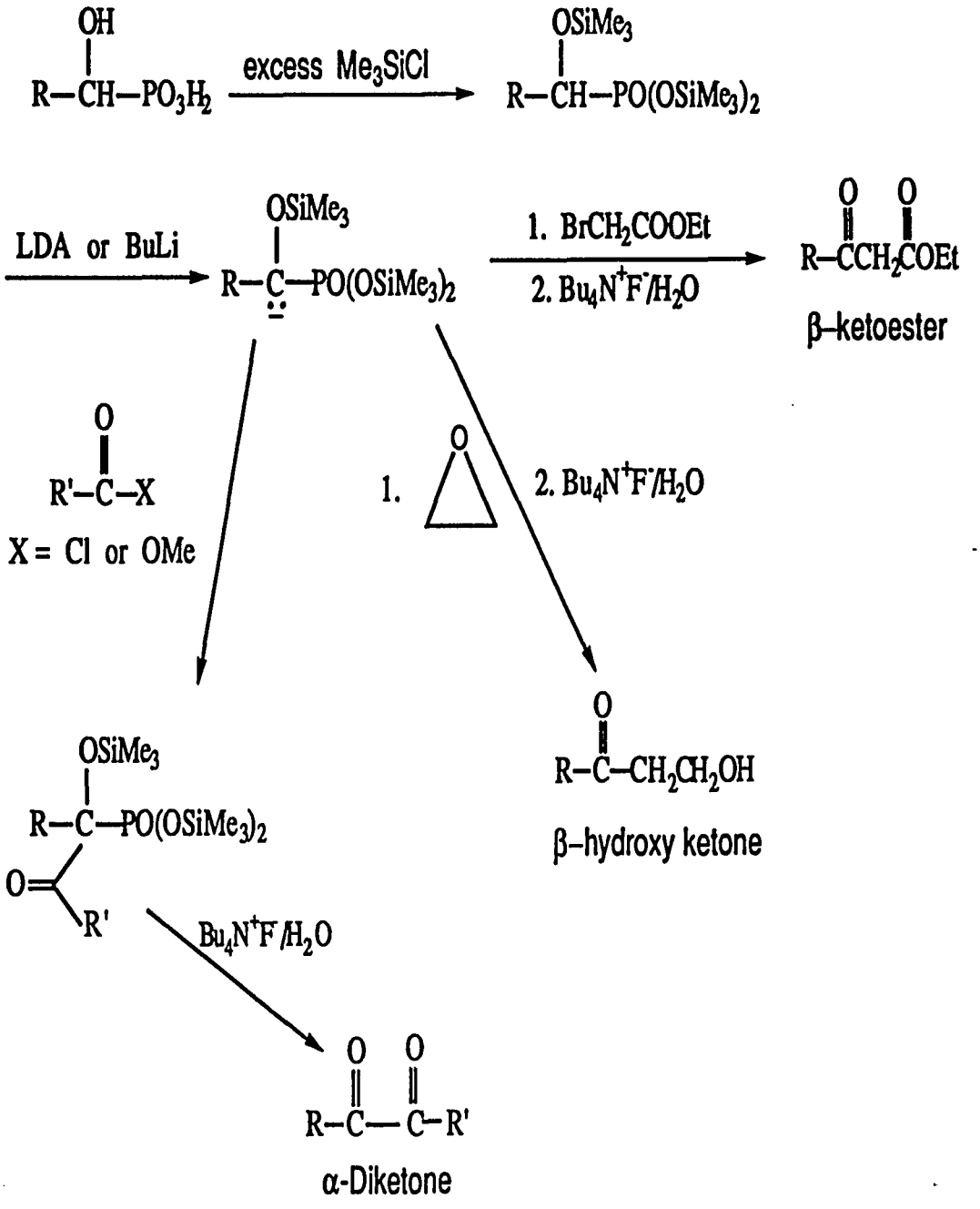
non-equivalent mono-ester



non-equivalent di-ester

In the light of the success of the synthetic scheme for α-hydroxyphosphonic acids, many other functional group incorporations and modifications can be envisioned via S_N2 displacement reactions.

As key intermediates for transformations of aldehydes into diketones, and keto-esters, α-hydroxyalkylphosphonic acids can be treated with chlorotrimethylsilane. An anion could then be generated at the α-position followed by the nucleophilic attack to various electron-deficient species to prepare desired compounds. A general scheme visualizing these applications is given below. The following scheme should lead to some novel procedures for the preparation of α- and β- diketones, β-hydroxyketones and β-ketoesters from the silylated intermediate of α-hydroxyalkyl-phosphonic acids.


OH
R–CH–PO3H2
excess Me3SiCl
OSiMe3
R–CH–PO(OSiMe3)2
LDA or BuLi
OSiMe3
R–C–PO(OSiMe3)2
1. BrCH2COOEt
2. Bu4N+F-/H2O
R–CCH2COEt
β-ketoester
R'–C–X
X = Cl or OMe
1.
2. Bu4N+F-/H2O
OSiMe3
R–C–PO(OSiMe3)2
R'
Bu4N+F/H2O
R–C–CH2CH2OH
β-hydroxy ketone
R–C–C–R'
α-Diketone

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