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SYNTHESIS OF POTENTIAL ORGANOPHOSPHORUS METABOLIC REGULATORS

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SYNTHESIS OF POTENTIAL ORGANOPHOSPHORUS METABOLIC REGULATORS

by

SHYAMAL C BANERJEE

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.

1985

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.

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George Michael
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ABSTRACT

SYNTHESIS OF POTENTIAL ORGANOPHOSPHORUS METABOLIC REGULATORS

by

SHYAMAL C BANERJEE

Advisor: Professor Robert Engel

The present thesis program has been concerned with two related areas of organophosphorus chemistry. These involve new methods of generating carbon-phosphorus bonds and the application of organophosphorus chemistry to metabolic regulation. Specifically, a method for the generation of vinylic carbon-phosphorus bonds has been applied to the synthesis of cylic vinyl phosphonates, and a series of potential organophosphorus antimetabolites conjugated with chemical vectors has been synthesized.

The purpose of the oligopeptide is to enable transport of the potential organophosphorus agents into intact cells. Several phosphonic acids have been used, including 4-hydroxy-3-oxobutyl-1-phosphonic acid, 3,4-dihydroxybutyl-1-phosphonic acid, and 5-carboxy-4-hydroxy-4-methylpentyl-1-phosphonic acid.

ACKNOWLEDGEMENT

I wish to express my deepest gratitude and sincere appreciation to my mentor Professor Robert Engel for his precious guidance and excellent advice on my entire research project and his untiring efforts in directing and assisting me through various aspects of academic life throughout my graduate study.

I would like to thank the members of my doctoral committee, Professors G. Axelrad, K. Grohmann, and T. Strekas for helpful suggestions.

I also thank Professors David C. Locke and W.F. Berkowitz for their kind assistance and advisement during my study.

Finally, I find it hard to express adequately my indebtedness to my wife Putul, for her unfailing patience, endless love, and staunch support; to my sons Raju and Papu for their remarkable understanding, awareness, and affection without which the completion of my dissertation would not have been possible.

DEDICATION

This thesis is dedicated

To my late father Debendra Nath Banerjee, and my mother Smt. Sabitri Banerjee for their love and faith.

To my father-in-law and mother-in-law Sj. Arunoday Chakraborty and Smt. Gita Chakraborty for their spiritual support.

To my elder brother Sri Nirmal Chandra Banerjee who has been a constant source of inspiration and guidance, as a result of which this thesis has become a reality. I am fortunate to have a brother like him.

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BACKGROUND

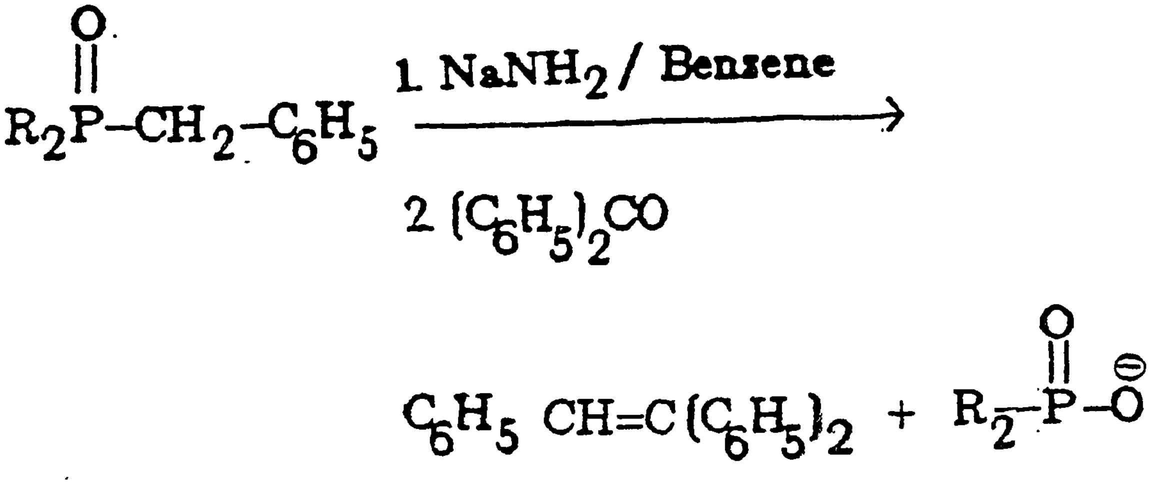
I. General:

The present work has been concerned with two casually related areas of interest involving organophosphorus chemistry and its application to metabolic regulation. These are: (1) methods for the generation of vinylic carbon-phosphorus bonds with their application to the synthesis of cyclic vinyl phosphonates; (2) the synthesis of potential organophosphorus antimetabolites conjugated with specific chemical vectors for the purpose of "illicit transport".

The design and synthesis of such specific vectors for transport of organophosphorus antimetabolites into intact cells or to a specific site in a complex organism involves the use of oligopeptides, known to be capable of providing such "illicit transport" into bacteria, yeast, and intestinal cells.

II. 1-Cycloalkenyl phosphonates:

In the twenty five years since the original report by Horner and Wippel (1) of the use of phosphoryl stabilized carbanions in olefin synthesis (Eq.1), the reaction has come to challenge the Wittig reaction as the synthetic method of choice when a specific alkene is required.

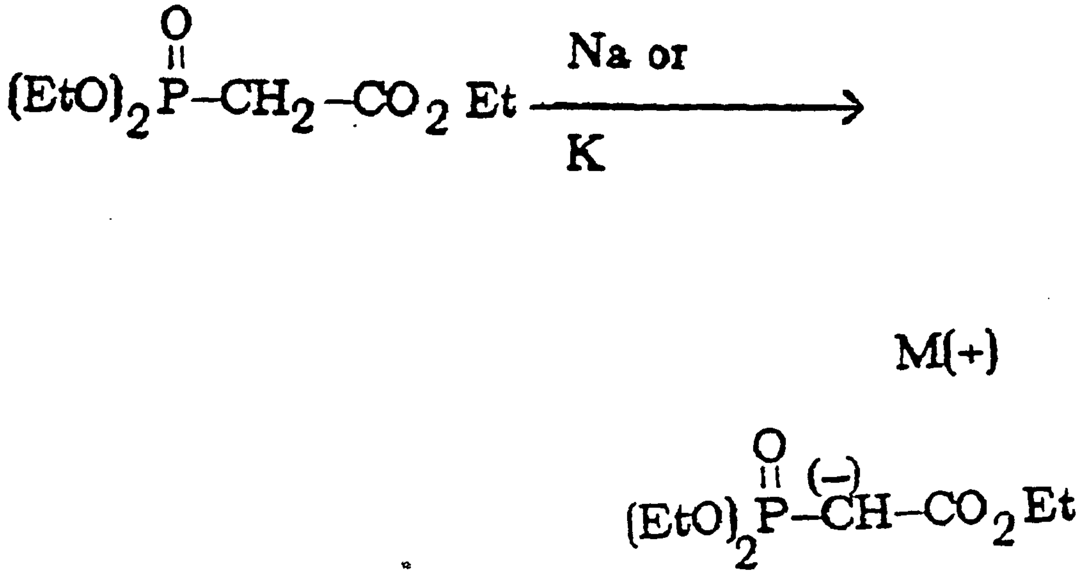


$$\mathrm{R_2\overset{O}{\overset{\|}{P}}-CH_2-C_6H_5} \xrightarrow[\mathrm{2.\ (C_6H_5)_2CO}]{\mathrm{1.\ NaNH_2\,/\ Benzene}} \mathrm{C_6H_5\ CH{=}C(C_6H_5)_2} + \mathrm{R_2-\overset{O}{\overset{\|}{P}}-O^{\ominus}}$$

$R = C_6H_5$; OEt

Equation 1

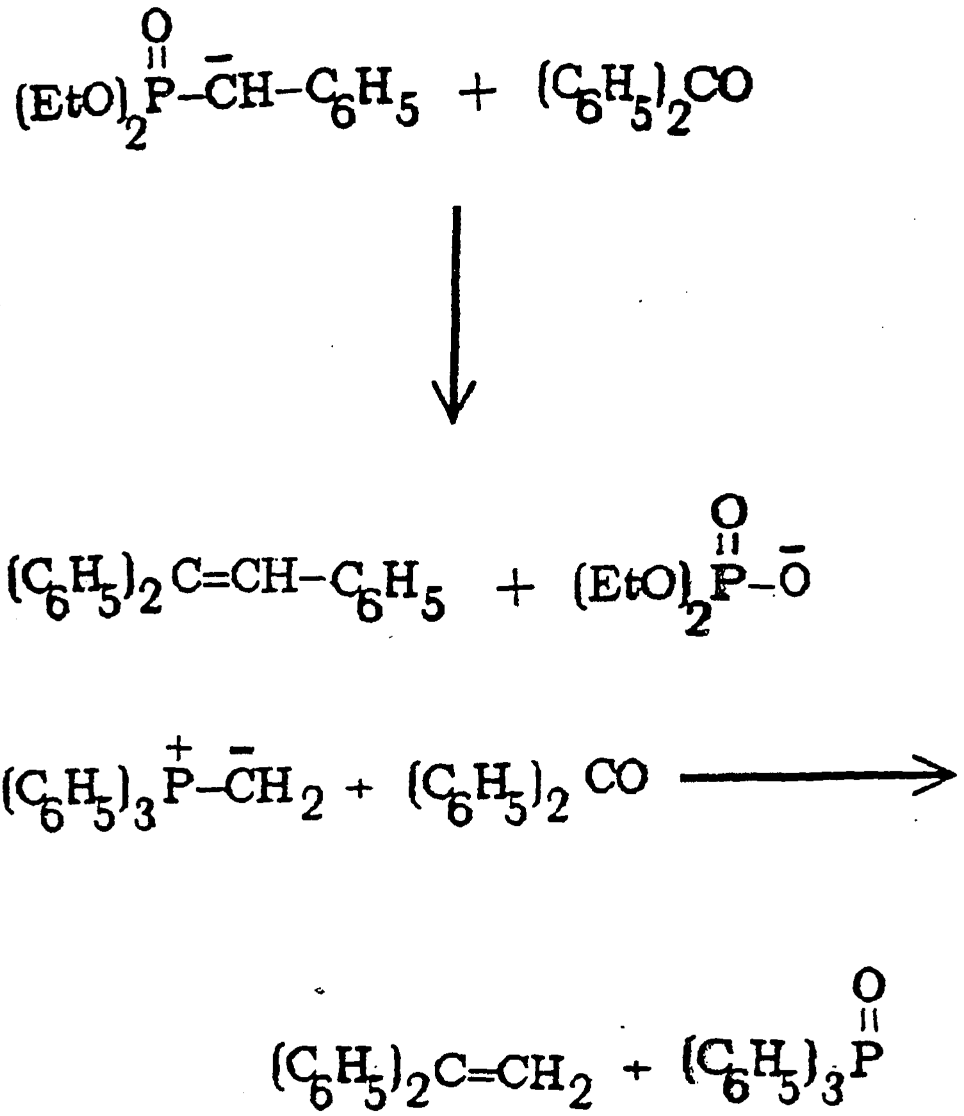
The possibility of a phosphoryl activated olefin synthesis can be traced back to 1927 when Arbusov (2) demonstrated that the phosphoryl linkage would stabilize an adjacent carbanion which in turn could be alkylated using a variety of reagents (Eq. 2).



$$(EtO)_2\overset{\overset{O}{\|}}{P}-CH_2-CO_2Et \xrightarrow[K]{Na\ or} \overset{M(+)}{(EtO)_2\overset{\overset{O}{\|}}{P}-\overset{(-)}{C}H-CO_2Et}$$

Equation 2

The original observations of Horner, Hoffman and Wippel (1,3,4) of the olefin formation reaction involved the treatment of a phosphonate or a phosphoryl stabilized carbanion with benzophenone to give the corresponding olefins accompanied by elimination of dialkylphosphate or diarylphosphinate respectively (Eq. 3).

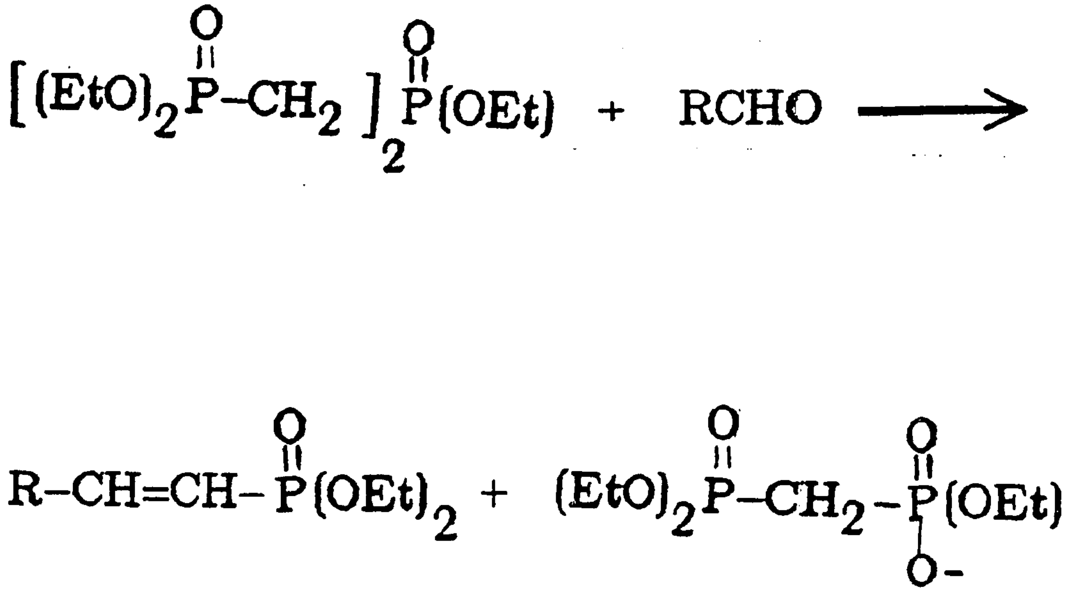


$$(EtO)_2\overset{O}{\overset{\|}{P}}-\bar{C}H-C_6H_5 + (C_6H_5)_2CO \longrightarrow (C_6H_5)_2C=CH-C_6H_5 + (EtO)_2\overset{O}{\overset{\|}{P}}-\bar{O}$$

$$(C_6H_5)_3\overset{+}{P}-\bar{C}H_2 + (C_6H_5)_2CO \longrightarrow (C_6H_5)_2C=CH_2 + (C_6H_5)_3\overset{O}{\overset{\|}{P}}$$

Equation 3

Patai and Schwartz (5) also observed olefin formation from an ester phosphonate with aldehydes, (Eq. 4), but failed to appreciate the significance of their results, mainly owing to a competing condensation reaction to give vinyl phosphonates.

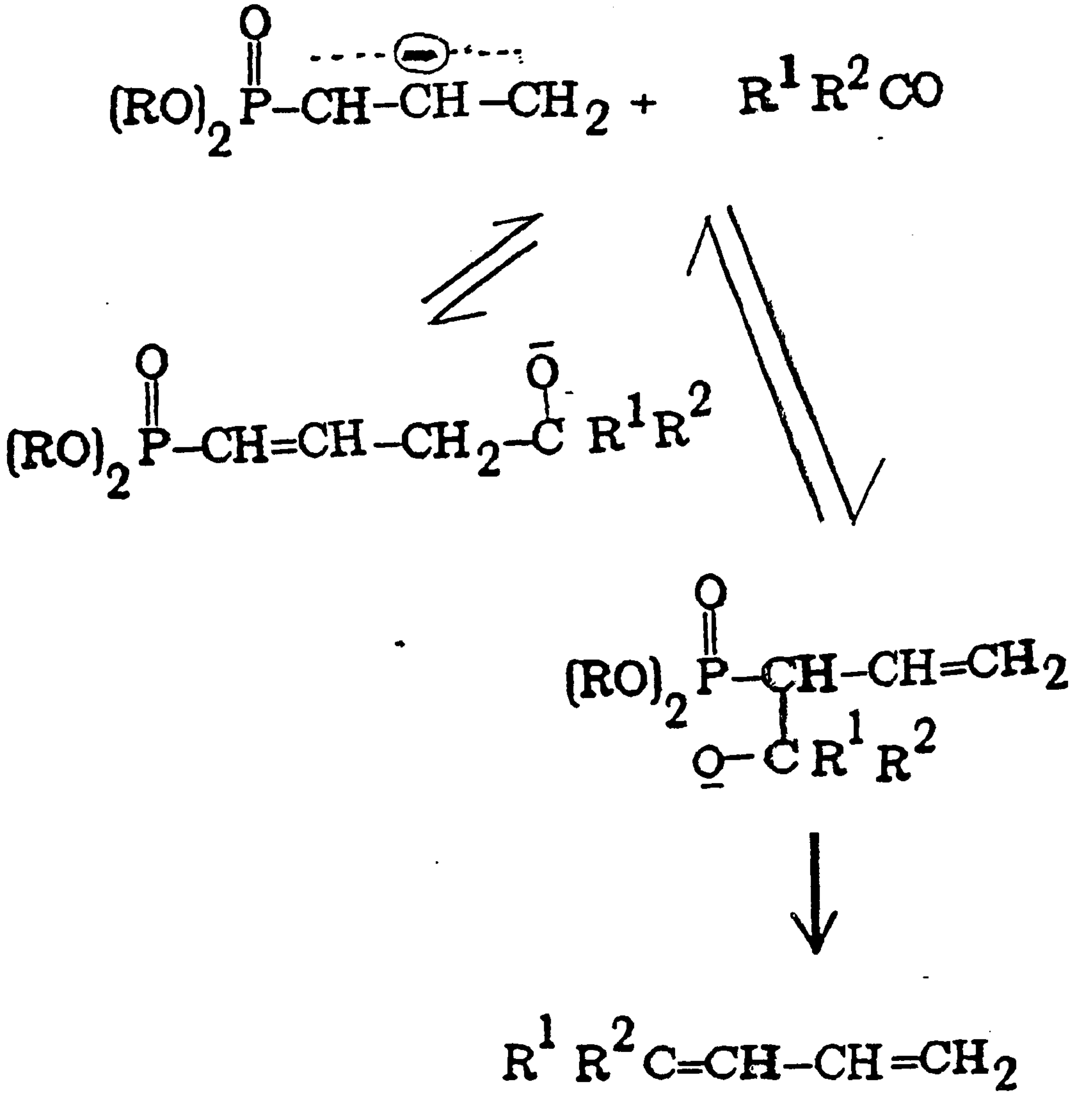


$$\left[(EtO)_2\overset{O}{\overset{\|}{P}}{-}CH_2\right]_2\overset{O}{\overset{\|}{P}}(OEt) + RCHO \longrightarrow$$

$$R{-}CH{=}CH{-}\overset{O}{\overset{\|}{P}}(OEt)_2 + (EtO)_2\overset{O}{\overset{\|}{P}}{-}CH_2{-}\underset{O^-}{\overset{O}{\overset{\|}{P}}}(OEt)$$

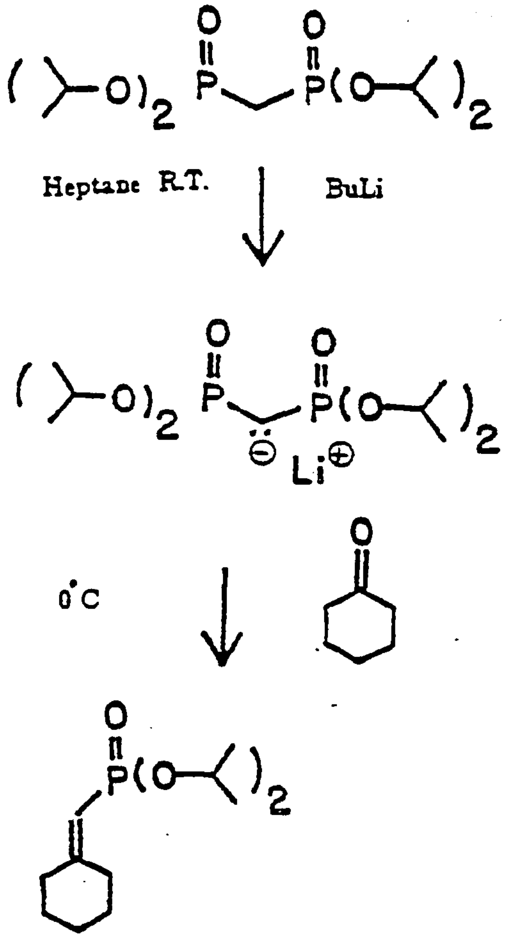
Equation 4

This now represents a significantly useful method for vinylic carbon-phosphorus bond formation. With α, β-unsaturated aldehydes and ketones, Michael addition competes with olefin formation (6,7), and in the case of ketones, often predominates (8), although this depends to some extent on the reaction conditions (9). Allylic phosphonates often react normally to give dienes, but γ -addition can compete depending on the substituents present. It seems that γ-addition, as shown in (Eq. 5), commonly occurs. However, if the reaction is reversible, the alkene is the final product.



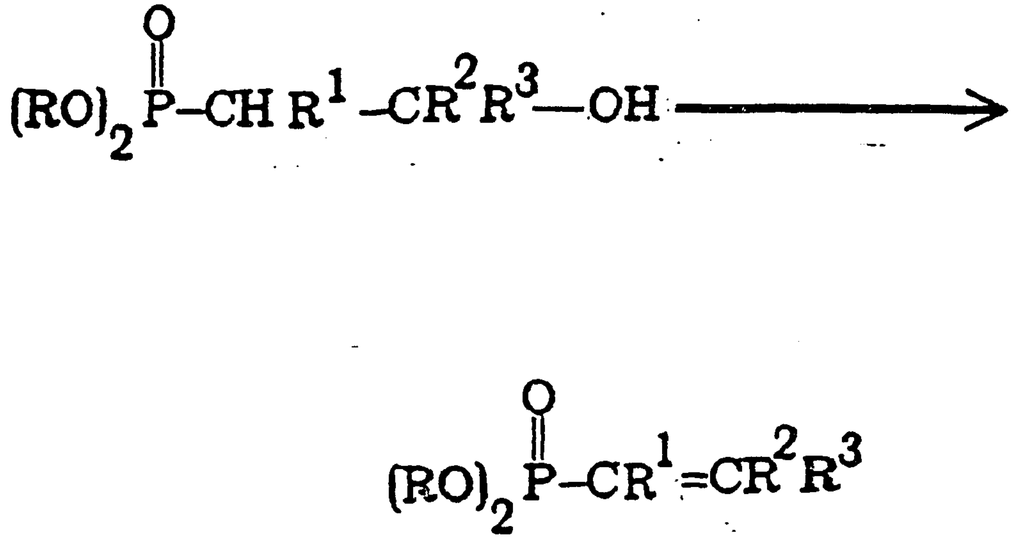
Equation 5

A modification (10) of the Wittig-reagent - method for synthesis of vinylic phosphonates is shown in (Eq. 6). Tetraisopropyl methylenebisphosphonate was dissolved in heptane and the corresponding phosphonate carbanion was generated by using one equivalent of butyl lithium as the base. Addition of an equivalent of the carbonyl compound formed the vinylphosphonate in good yield.



Equation 6

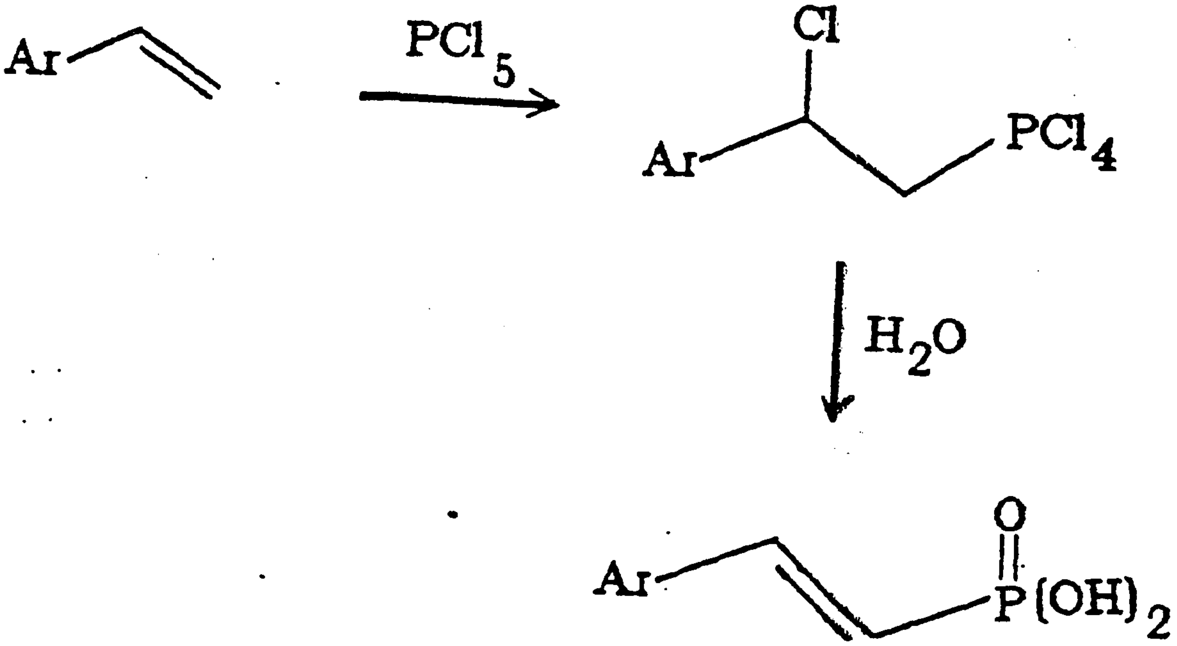
Other routes for the synthesis of vinylic carbon-phosphorus linkages should be noted. Vinylic phosphonates can be generated through the dehydation of β-hydroxyphosphonates as shown in (Eq. 7). A variety of condensation products are formed when the phosphonate bears more than one highly acidic site (11).



$$(RO)_2\overset{O}{\overset{\|}{P}}-CHR^1-CR^2R^3-OH \longrightarrow (RO)_2\overset{O}{\overset{\|}{P}}-CR^1=CR^2R^3$$

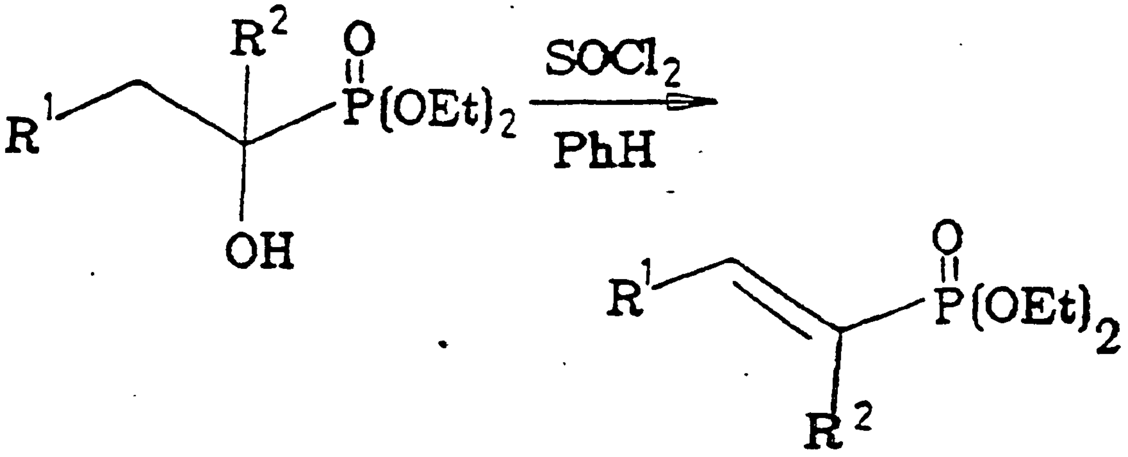
Equation 7

A number of multi-step synthetic methods are also available. An early report on the synthesis of vinylic phosphonic acids by the addition of phosphorus pentachloride to unsymmetrical olefins followed by hydrolysis was made by J. Thiele (12) and was reinvestigated by Bergmann and Bondi (13) (Eq. 8).



Equation 8

This reaction has been shown to proceed in a Markovnikov manner (13-16). The yields from this reaction are quite good and it has been used for the synthesis from olefins of a variety of phosphonate derivatives. Similarly, a number of diolefinic phosphonates (17,18,19-20) which are of use for the synthesis of rubber-like polymers (17,18) have been prepared from phosphorus pentachloride and 1,3-diolefinic compounds. A series of vinylic phosphonates have also been prepared in good yield by the dehydration of α-hydroxyphosphonates (21) (Eq. 9).

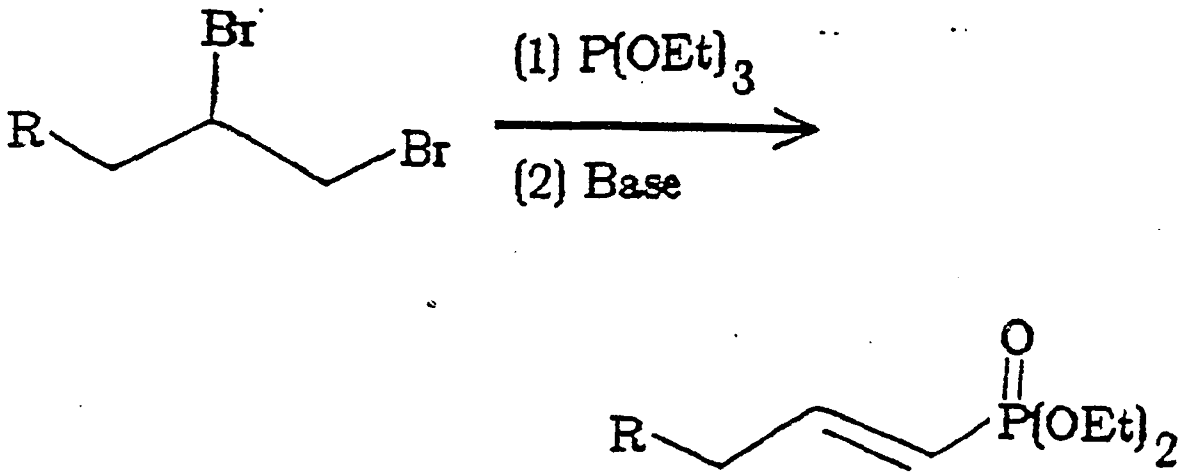


(a) $R^1 = H$, $R^2 = Me$
(b) $R^1 = R^2 = Me$
(c) $R^1 R^2 = -(CH_2)_4-$
(d) $R^1 R^2 = -(CH_2)_4-$
(e) $R^1 = iPr$, $R^2 = Me$

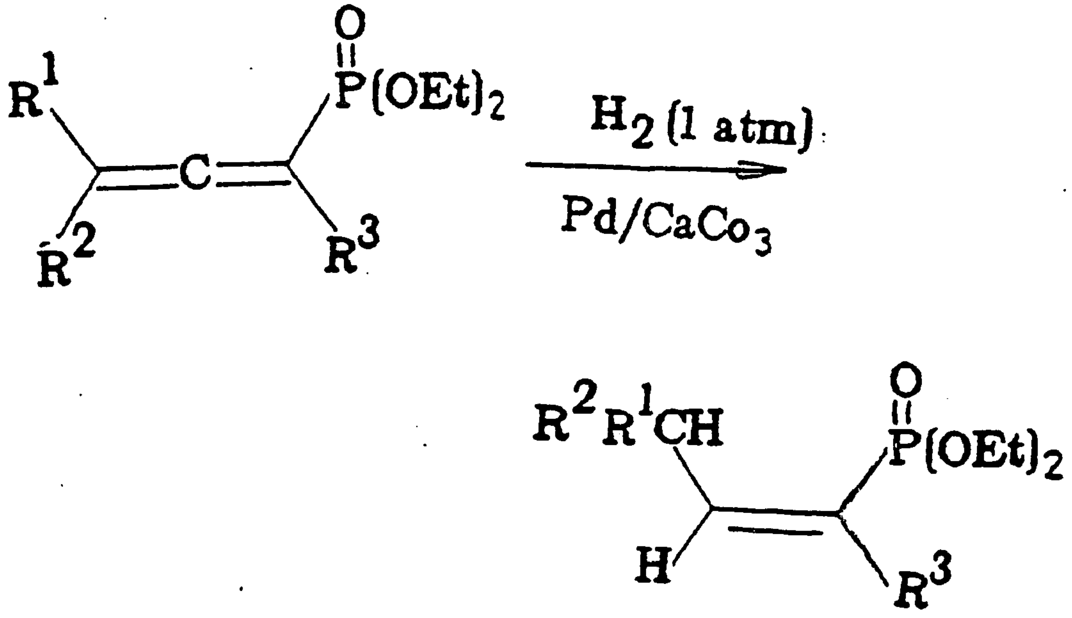
63-82 %

Equation 9

The Michaelis-Arbuzov reaction (22,23) of 1,2-dihalopropanes with trialkyl phosphites followed by dehydrohalogenation has been found to be useful for the synthesis of vinylic phosphonates (24) (Eq. 10). However, the cis-isomers of vinylic phosphonates, which are considerably less available (25,26) than the trans-isomers, could best be obtained by the catalytic hydrogenation (27,28) of either 1,2-dienyl (27) or 1-acetylenic phosphonates (29,30) (Eq. 11,12).

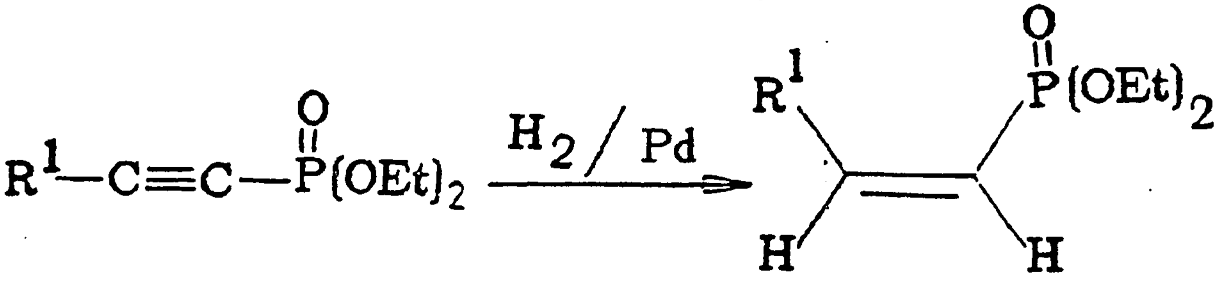


Equation 10



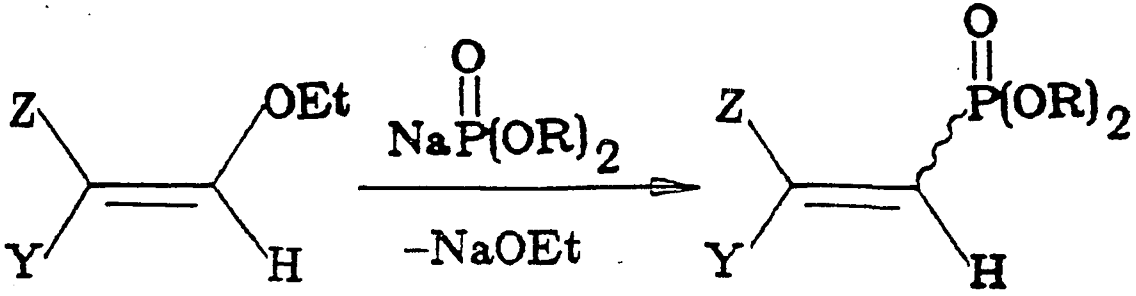
(a) $R^{I} = R^{2} = R^{3} = H$
(b) $R^{I} = Me, R^{2} = R^{3} = H$
(c) $R^{I} = R^{2} = Me, R^{3} = H$
(d) $R^{I} = R^{2} = R^{3} = Me$

Equation 11



Equation 12

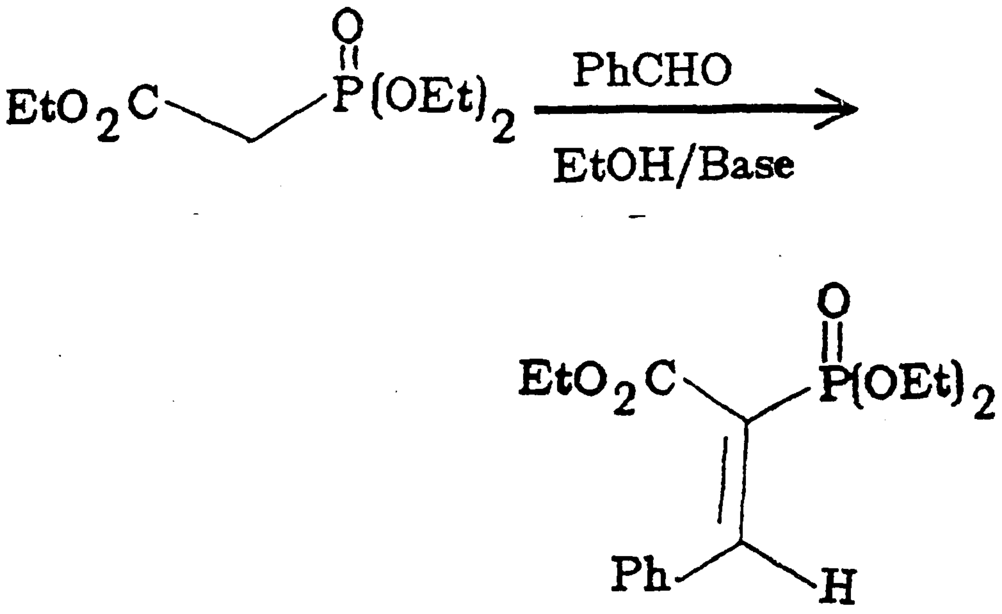
Sodium dialkylphosphites react readily with ethoxymethylene derivatives of β-dicarbonyl compounds. The initial reaction is followed by an elimination of sodium ethoxide to give α, β-unsaturated dicarbonyl phosphonates in good yield (31) (Eq. 13).



(a) Y = Z = MeCO, R= Et
(b) Y = Z = MeCo, R = n-Bu
(c) Y = MeCO, Z = CO Et, R = Et
(d) Y = CO Et, Z = CN, R = Et
(e) Y = EtO CCO, Z = CO Et, R = Et

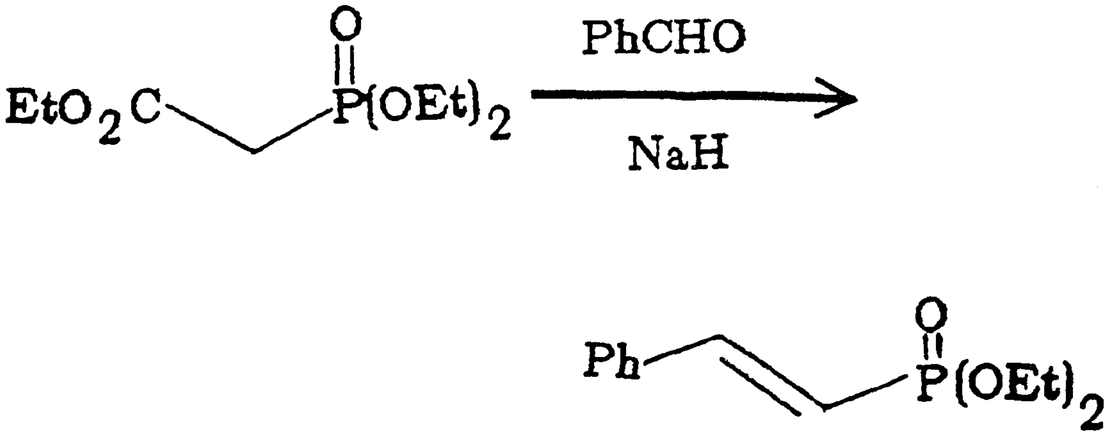
Equation 13

It is interesting to note that the reaction between triethyl phosphonoacetate and benzaldehyde has been reported to give triethyl benzylidenephosphonoacetate in the presence of a base and a protic solvent (32,33) (Eq. 14).



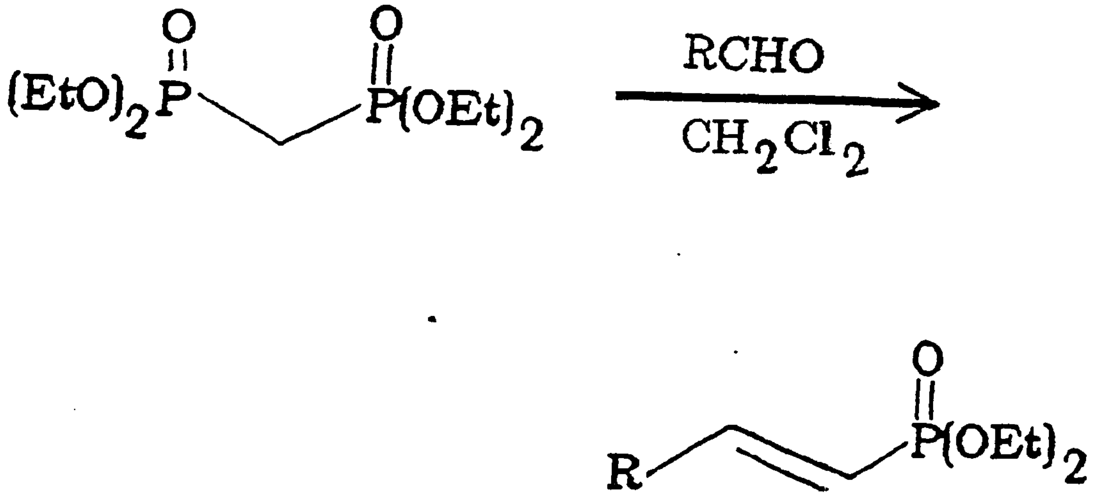
Equation 14

However, this procedure usually gives poor yields due to the formation of cinnamic acid. High yields of the vinylic phosphonates could be obtained by the reaction of triethyl phosphonoacetate and benzaldehyde in the presence of sodium hydride (34) (Eq. 15).



Equation 15

Recentaly, Mikolajczyk et. al. (35) have used the Horner-Wittig reaction in a two-phase system to synthesize the vinylic phosphonates from tetraethyl methylenebisphosphonate and aldehydes. It should be noted that the reaction can proceed even in the absence of a typical phase-transfer catalyst since the starting phosphonate contains two basic centers in the molecule as well as the relatively acidic methylene protons and acts in an autocatalytic mannar (36) (Eq. 16). Moreover, this reaction is convenient to perform and gives good yields of the pure E-isomers.



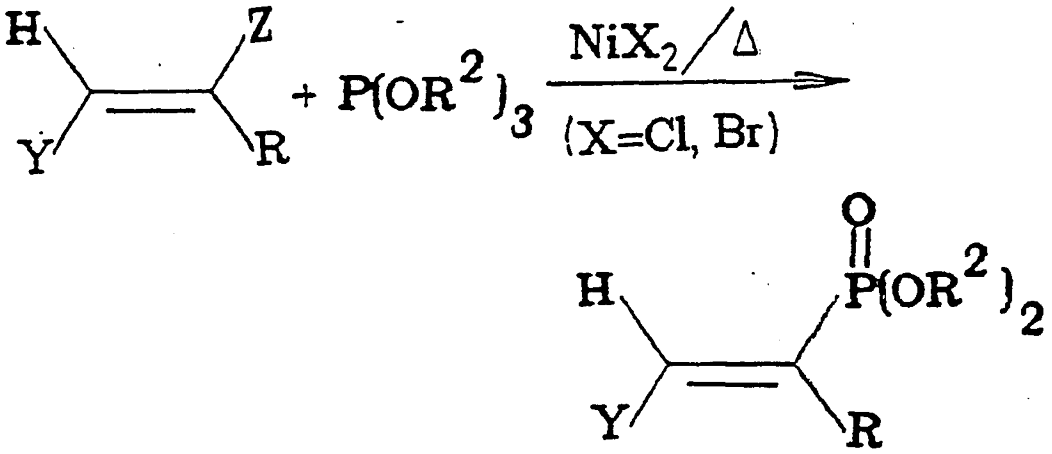
70-79 %

50% aq. NaOH

R = Ph, 4-BrC_6H_4 , p-$Me_2NC_6H_4$, PhCH=CH

Equation 16

There are very few methods involving the *direct* synthesis of the vinylic phosphonates. These compounds can not be obtained easily by the typical Michaelis-Arbuzov reaction (22,23). The first direct synthesis of these vinylic phosphonates was reported by Tavs and Weitkamp (37). On heating the mixture of a vinylic halide and trialkyl phosphite in the presence of a nickel halide complex at 150-190^{o} C the vinylic phosphonates could be obtained in yields of 21-94% (Eq. 17). However, the *typical* yield of product from this reaction is low and the stereochemistry of the products still has not been clarified.



(a) R = H, Y = H, Z = Cl

(b) R = Ph, Y = H, Z =Br

(c) R = H, Y = Z = Cl

(d) R = H, Y = Ph, Z = Br

(a) R = Y = H, R = Et, iPr

(b) R = Ph, Y = H, R^2 = Et

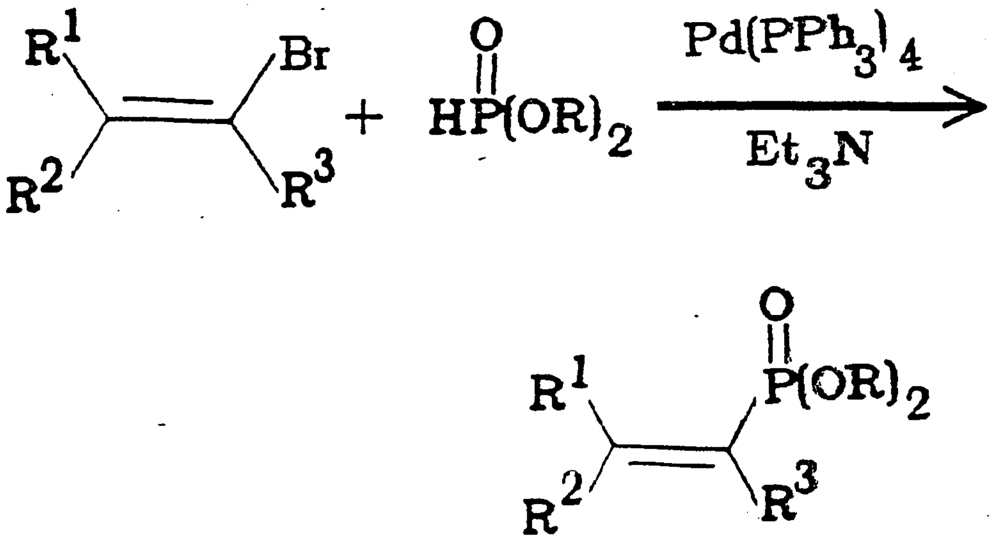
(c) R = H, Y = PO(OR) ,
R^2 = Me, Et

(d) R = H, Y = Cl, R^2 = Et

(e) R = H, Y = Ph, R^2 = Et

Equation 17

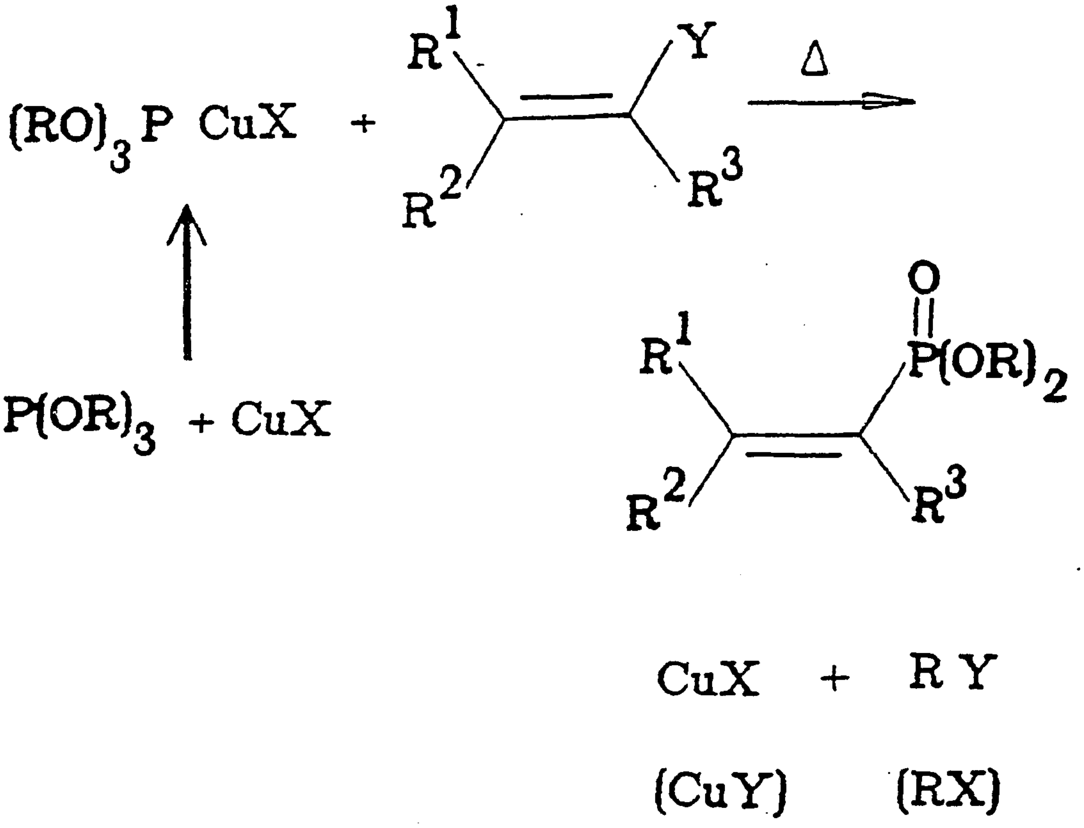
Recently, Hirao et. al. (38) have found that the reaction of vinylic bromides with dialkylphosphites in the presence of tetrakis (triphenylphosphine)palladium afforded the corresponding vinylic phosphonates in 66-98% yields. This reaction was also found to be stereoselective (Eq. 18). The reaction has been shown to work well only with the vinylic bromides.



(a) R^1 = Ph, R^2 = R^3 = H, R^4 = Et
(b) R^1 = R^2 = H, R^3 = Ph, R^4 = Et, iPr, n-Bu
(c) R^1 = R^2 = H, R^3 = Ph, R^4 = Et
(d) R^1 = R^2 = H, R^3 = Me, R^4 = Et, iPr
(e) R^1R^2 = $-(CH_2)_4-$, R^3 = H, R^4 = Et

<u>Equation 18</u>

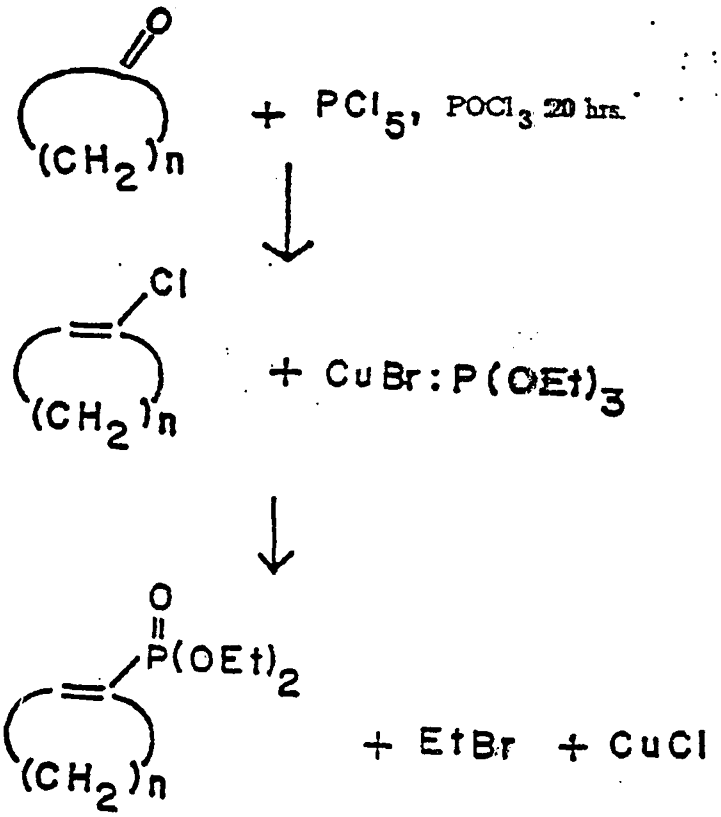
Thus until recently direct phosphonation of vinylic halides by the use of transition metals as catalysts had found only limited success. However, direct phosphonation of aryl iodides by trialkyl phosphites has been reported to be effected by the use of CuCl (39), $NiCl_2$ (40), $PdCl_2$ (39), Bronze (41) or photolysis (42). These results led to investigations in this laboratory regarding the possibility of using trialkyl phosphite-copper(I) halide complexes (43-53) as reagents for the direct displacement of vinylic halides as shown in (Eq. 19).



Equation 19

The use of such copper(I) complexes allows the phosphonation to be performed in a homogeneous system. Copper(I) complexes are soluble in many organic solvents as well as are the vinylic halides.

Of the routes available for vinylic carbon-phosphorus bond generation, only this last one is readily ameanable to the synthesis of those structures wherein the vinylic linkage is part of a ring system (54). The required 1-chlorocycloalkenes are readily available from the corresponding ketones in reasonable yield by reaction with phosphorus pentachloride and phosphorus oxychloride (Eq. 20).



Equation 20

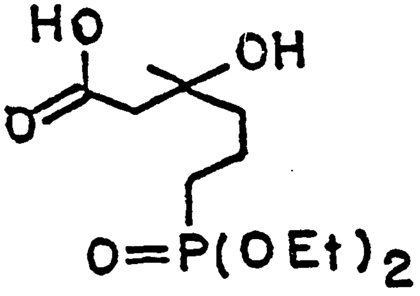
There are several reasons for the search for new and better routes for vinylic carbon-phosphorus bond generation. Analogues of biological phosphates in which a C-O-P linkage is replaced with a direct C-C-P linkage have significant utility. A wide variety of such systems have been investigated to date, and the overall problem has been throughly reviewed (55,56). As related vinylic carbon-phosphorus compounds may be converted readily to these analogues by reduction, and provide a possibility for the introduction of further functionality, the synthesis of such materials is of general importance for the generation of bioactive agents.

A second area in which vinylic carbon-phosphorus compounds are of value is that of flame retardants. The flame retardation of textiles is important for improvement of the safety characteristics of a wide variety of apparel, household goods, and industrial textiles. Of the various chemical agents used for the flame retardant treatment of textiles, phosphonates have been among the more successful. Vinyl phosphonates undergo homopolymerization, or copolymerization with N-hydroxy methyl acrylamide, in the presence of a free radical catalyst like potassium persulfate, to generate materials with high flame retardant characteristics.

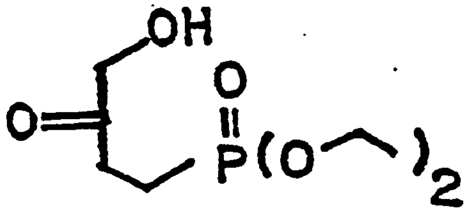
III: The Synthesis of Peptides as Chemical Vectors for phosphonates:

Phosphonic acid analogues of natural phosphates have been shown to be important probes for studing intermediary metabolism (55). Unfortunately, as many are charged organic compounds, they cannot enter intact cells by normal routes. It is therefore necessary to devise methods that will permit these materials to enter intact cells.

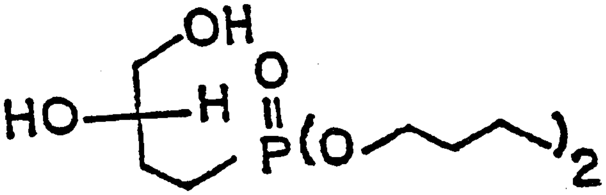
In the present work several oligopeptides were synthesized for use as chemical vectors. The tripeptides, alanyl-seryl-alanine, aspartyl-alanyl-alanine, and glutamyl-alanyl-alanine were synthesized and conjugated with four phosphonates. These phosphonates are: (I) diethyl 5-carboxy-4-hydroxy-4-methylpentyl-1-phosphonate; (II) diethyl 4-hydroxy-3-oxobutyl-1-phosphonate; and (III) dibutyl (S)-3,4-dihydroxybutyl-1-phosphonate; (IV) diisopropyl (S)-3.4-dihydroxybutyl-1-phosphonate.



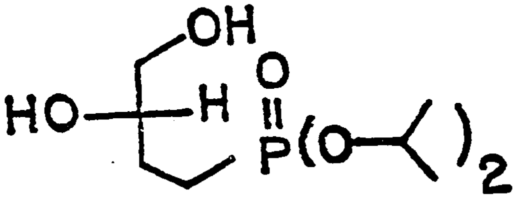
[I]



[II]



[III]



[IV]

The significance of phosphonic acids as analogues of natural phosphates for use as metabolic regulators has been discussed extensively (56). The fundamental value of these materials as bioactive materials is a result of the carbon-phosphorus bond being resistant to hydrolysis by the "ordinary" enzymes involved in phosphate cleavage. With this presumption, several mechanistic possibilities may be envisioned for metabolic regulation by such compounds. As a substitute for a natural phosphate metabolite, a phosphonic acid may be capable of perturbing the regular metabolism of a biological system simply by non-participation in a normal phosphate ester cleavage process. Also, the phosphonic acid, substituting for a natural metabolite, might be capable of specific or nonspecific inhibition of one or more enzymatic processes. Those of interest in the present work have been demonstrated to have *in vitro* enzymatic biological activity, by one route or another. However, they exhibit difficulties in the expression of these activities *in vivo* due to an inability to be transported into intact cells (57).

To overcome this problem a chemical vector is needed which will facilitate transport of these potential chemotherapeutic agents into the appropriate cells or to particular sites in a complex organism. This involves linking the non-penetrating substances covalently to a molecule that is actually transported by a pre-existing transport system. This method maintains the structural integrity of the substance and takes advantage of existing metabolic processes.

It is known that bacteria are capable of taking up certain types of molecules even from very dilute solutions. For some time the uptake of oligopeptides by Escherichia coli has been studied. This has been shown to occur when the N-terminal amino group of the peptide is unacylated. This has been demonatrated by performing comparative studies on the growth response of E. Coli lysine auxotroph to lysine (58,59), oligolysine peptides and -N-acetyl-derivatives of oligolysine. It was observed that the lysine auxotroph could use di-, tri-, and tetralysine as sources of lysine, while -N-acetylated derivatives were inactive. This conclusion was further substantiated by the results with acetylated arginine oligopeptides. The importance of the C-terminal carboxyl group in peptide transport was also studied by Gilvarg and Payne (62). They concluded that the free C-terminal carboxyl group is not necessary for the uptake of oligopeptide, but is desirable for maximum efficiency.

AIMS AND SUMMARY OF ACCOMPLISHMENTS.

1. Development of a general route for the synthesis of 1-cycloalkenyl phosphonates:

The feasibility of synthesizing directly a series of 1-cycloalkenyl phosphonate diesters starting with the appropriate vinylic chlorides has been investigated. This has been accomplished using the copper(I) bromide complex of triethyl phosphite in a direct reaction with the vinylic chlorides. The chlorides used contain rings of six, seven, eight or twelve carbons, several with ring substitution or further unsaturation in the ring. All of the 1-chlorocycloalkenes are readily available from the corresponding ketones in reasonable yields by reaction with phosphorus petachloride and phosphorus oxychloride.

II. The synthesis of potential phosphonic acid antimetabolites linked with oligopeptides:

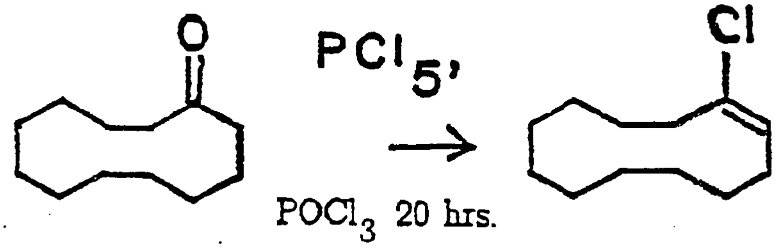
Phosphonic acids conjugated with oligopeptides are designed with the intent of facilitation of their transport into specific organisms or to sites within an organism. The synthesis of the three tripeptides, alanylserylalanine, aspartylalanylalanine, and glutamylalanylalanine , and their conjugation with four phosphonates has been accomplished. These phosphonates are: (a) diethyl 5-carboxy-4-hydroxy-4-methyl-pentyl-1-phosphonate; (b) diethyl 4-hydroxy-3-oxobutyl-1-phosphonate: (c) dibutyl (S)-3,4-dihydroxybutyl-1-phosphonate; (d) diisopropyl (S)-3,4-dihydroxybutyl-1-phosphonate.

RESULTS AND DISCUSSION

Part I : Direct Synthesis of Vinylic Phosphonates.

A series of 1-chlorocycloalkenes has been investigated in reaction with the copper(I) chloride complexes of triethyl phosphites as illustrated in (Eq. 1) The chlorides used contain rings of six, seven, eight or twelve carbons, several with ring substitution or further unsaturation in the ring. All of the 1-chlorocycloalkenes are readily available from the corresponding ketones in reasonable yield by reaction with phosphorus pentachloride and phosphorus oxychloride. The yields for the preparation of these chlorides are summarized in Table 1.

1



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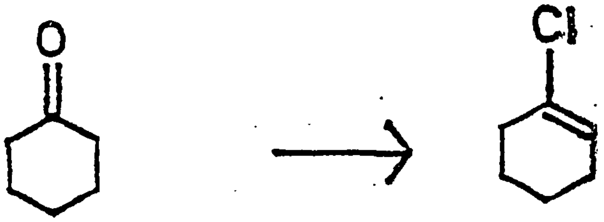

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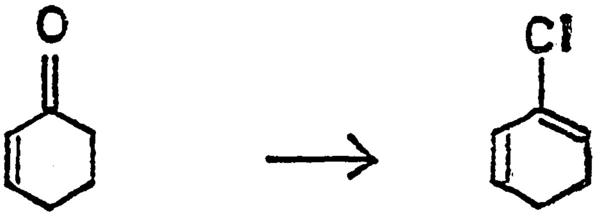
3



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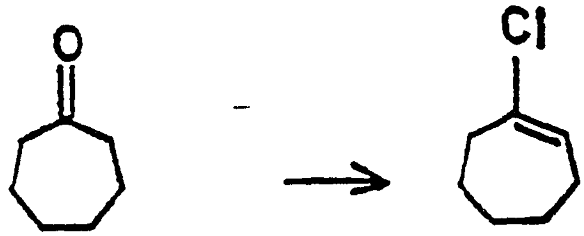
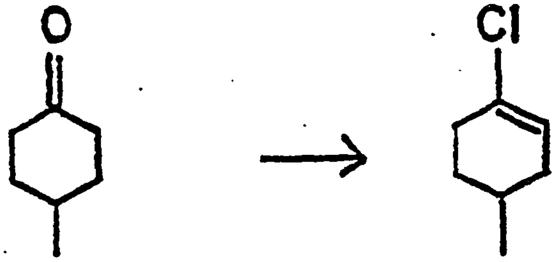
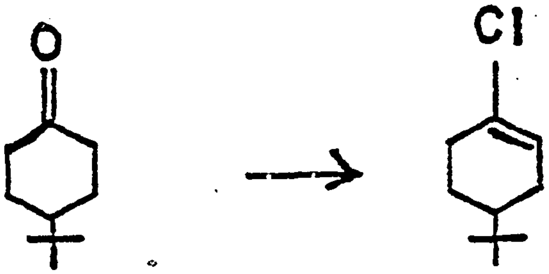
	PREPARATION OF 1-CHLOROCYCLOALKENES	% Yield
4		78
5		79
6		97
7		64

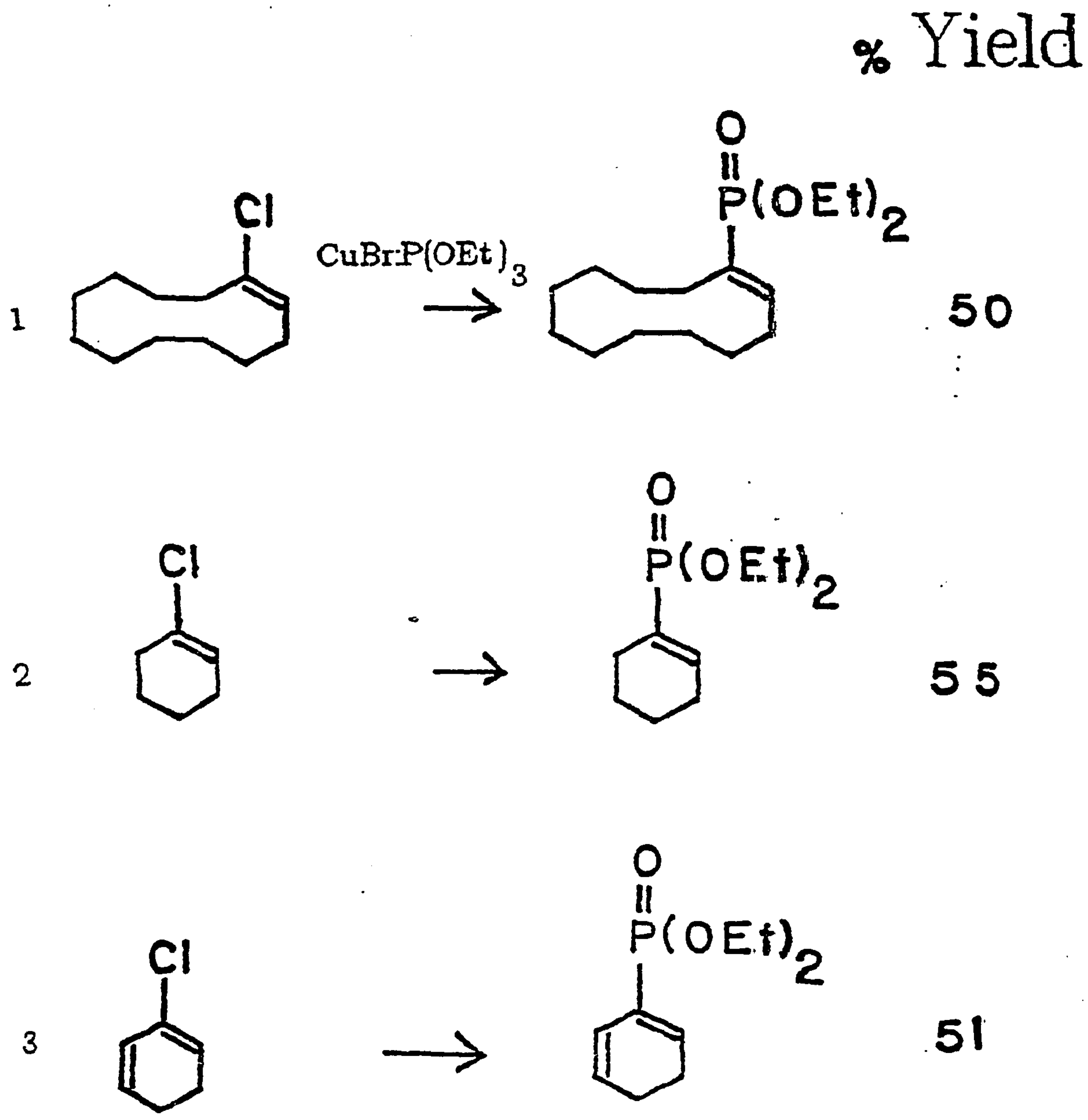
Table 1

For the phosphonation reactions, cuprous bromide was prepeared fresh by a standard method (62) and used to generate the triethyl phosphite complex according to the method of Wulfmann, et. al. (63) immediately prior to its use in the phosphonation reaction.

In practice, the reaction proceeded smoothly when a copper(I) bromide complex of triethyl phosphite was heated with a vinylic chloride under a nitrogen atmosphere at 200-205° C (external oil bath) for 1-2 hours. The resultant ethyl chloride liberated was removed and monitored by the use of a Dean-Stark trap. For isolation of the desired vinylic phosphonates it was found that removal of copper salts was necessary prior to product isolation. This was concluded after (a) all attempts at distillation were found difficult to perform and there was a considerable amount of copper salt remaining after each distillation; (b) the distillate upon injection into a gas liquid chromatographic column (2mx3mm. column, silicone SE-30, oven temprature 180° C) resulted in the formation only of obvious decomposition materials; and (c) any material isolated using these methods always exhibited a blue color as a tail on thin layer chromatography.

Thus, the vinylic phosphonate complex was treated with ethylenediamine in toluene or pentane to form a copper-amine complex (64,65) which was filtered leaving the free vinylic phosphonate. The phosphonate so obtained could be purified by using the standard methods as described above. By these procedures it was possible to obtain the pure vinylic phosphonates in high yields as shown in Table 2.

PREPARATION OF 1-CYCLOALKENYLPHOSPHONATES



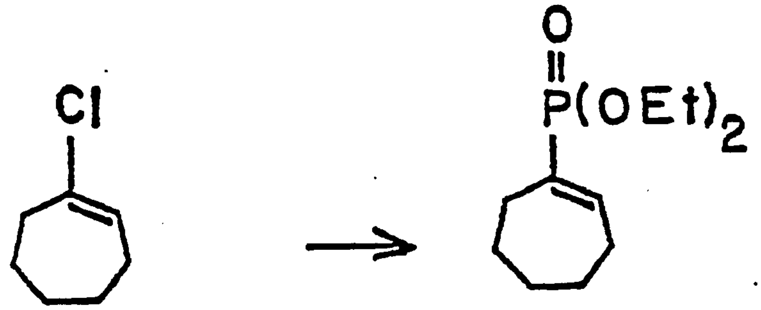
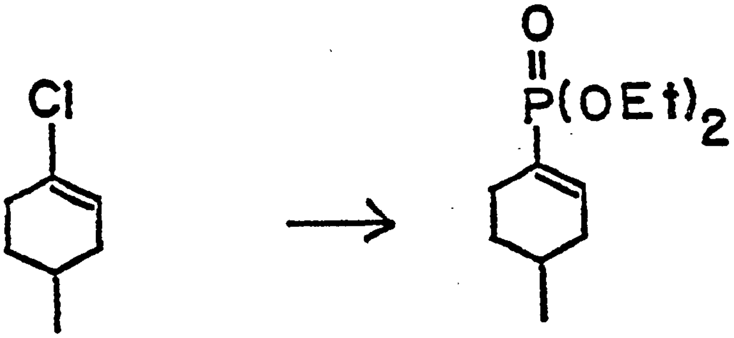
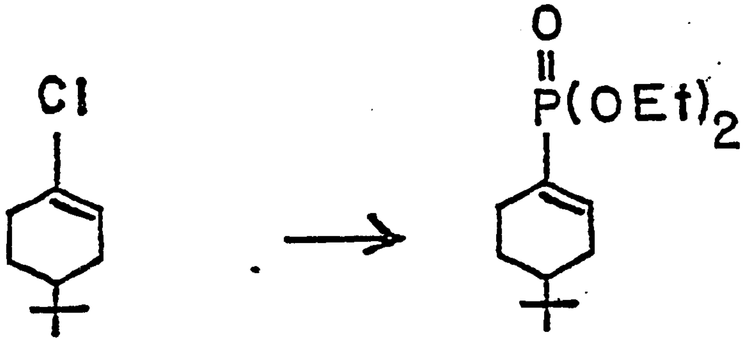
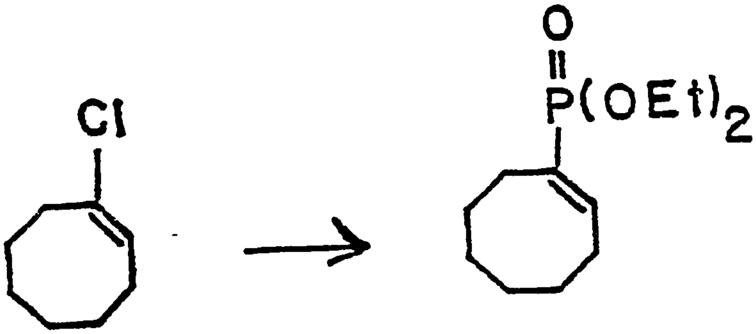
		% Yield
4		64
5		60
6		55
7		71

Table 2

A rather important feature of this reaction is its stereoselectivity, as the stereochemistry of the vinylic halides was observed to be principally retained during the course of the reaction. Determination of the stereochemistry of all compounds was based on proton-NMR analysis. The spin coupling constants of trans and cis protons have been observed to be that J_{HH} trans are greater than J_{HH} cis; J_{HP} trans are greater than J_{HP} cis. Typical values for J_{HH} trans are 14-18 Hz., and J_{HH} cis are 8-12 Hz.(66), J_{HP} trans are 20-50 Hz., J_{HP} cis are 10-30 Hz. (37,67,68). All chemical shifts of the vinylic phosphonates were assigned according to the previous work (35,38,69) and by using additive increments (68) compared to the starting vinylic halides.

Several notes should be made regarding the reaction conditions and course of the reactions. Only the vinylic chlorides were used in this study. It is likely that higher yields would be obtained by the use of the vinylic bromides rather than the vinylic chlorides. However, for general utility, the chlorides are of greater significance due to the relative difficulty encountered in obtaining the vinylic bromides. As observed previously in the studies with phenyl-substituted vinylic halides (70), no halogen exchange is observed in the use of the vinylic chloride in reaction with the copper(I) bromide complex(71). Nor has any reaction been observed by the use of the copper(I) chloride complex of the phosphite.

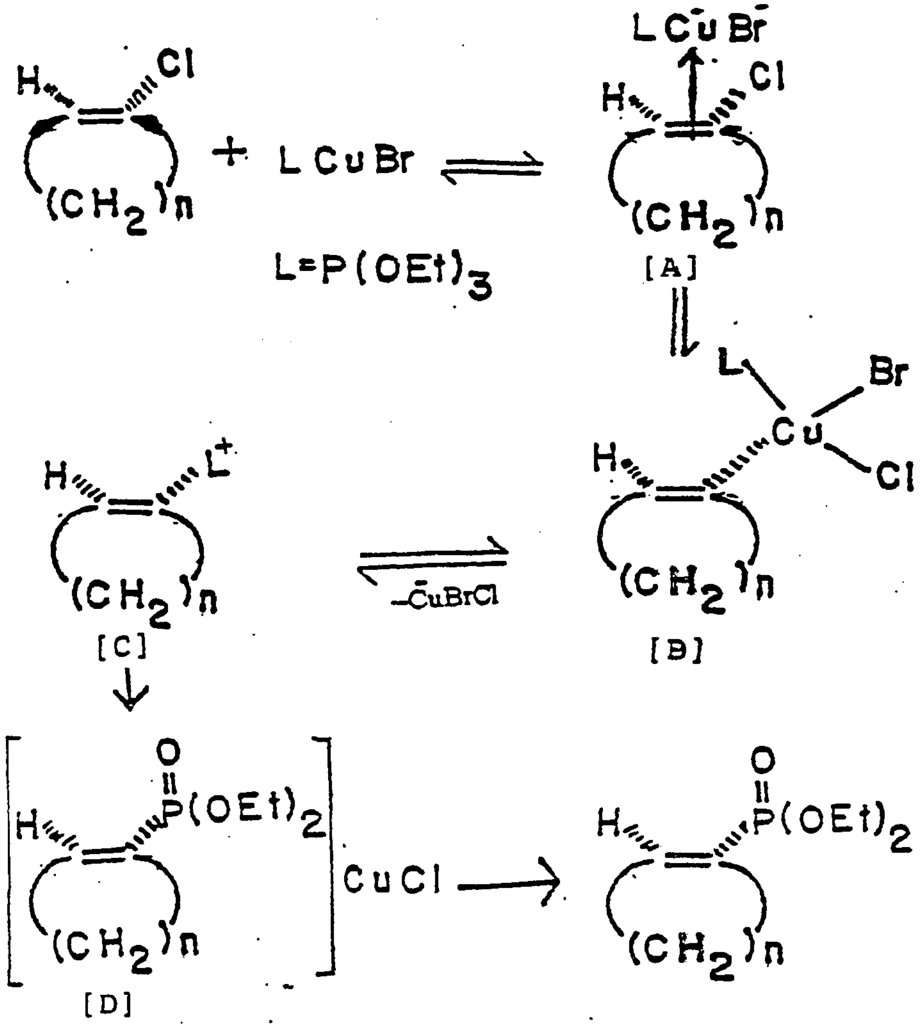
Overall, the method presented here for the synthesis of 1-cycloalkenylphosphonates represents a facile and efficient method for the preparation of these materials which were hitherto available only with great difficulty.

Prior mechanistic investigations on this type of reaction have been performed (72). Copper(I) reagents have been known to catalyze many replacement reactions of aromatic and vinylic halides. Of particular note are those reactions involving copper(I) halides which are related to the well known Ullmann reaction (73-83). In recent years the mechanism of the Ullmann reaction has been reviewed (79-85) and interpreted in different ways. In general, a concerted reaction involving a four-center transition states has been considered as the mechanism for a copper-assisted nucleophilic displacement reaction (83,86,87). An alternative stepwise reaction involving a radical species as an intermediate has also been proposed (73,81,83, 88,89). Cohen et.al.(82,90). have proposed organocopper compounds as intermediates in this reactions. However, all the mechanisms which have been proposed so far give no definitive answers.

The phosphonation and halide exchange reactions of vinylic halides as observed in the present systems have a close relationship to the Ullmann reaction in many respects. Firstly, these reactions are usually performed at high temperature (73-78). Secondly, these reactions usually proceed with high stereospecificity when applied to the vinylic halides (9,91). Finally, the Ullmann reaction can also be performed in a homogeneous system by using a copper(I) salt in a complexing solvent (84).

Recently, a few copper(III) complexes have been proposed as intermediates in several related reaction systems (92-95). Such copper(III) species are also believed to be intermediate in many copper(I)-assistated replacement reactions (84,96,97,98). Thus, copper(III) would also be a resonable intermediate species for consideration in the present system. These copper(III) species presumably result from the so called oxidative addition (99). This type of reaction requires nonbonding electron density on the metal and is in agreement with the present observations and many others (84,96,99-101). A mechanistic scheme which could accommodate the present experimental data is shown in <u>Scheme 1</u>.

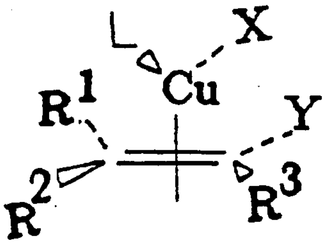
Mechanism of Cu(1) Complex Catalysed
Reaction of Vinylic Halide

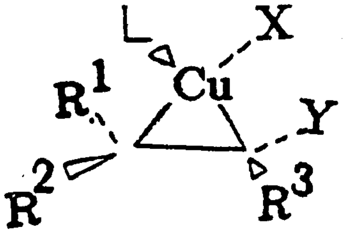


Scheme-1

The first step would involve a nucleophilic attack of the π-complex [A] (100,101) by a LCuBr at the sp^2 carbon bearing the halogen (102,103). This nucleophile approaches perpendicularly to the plane of the olefin as shown in structure [A]. The leaving group Cl leaves perpendicularly to the plane of the olefin while the entering group now is on the same plane as the olefin, as is shown in structure [B]. The organocopper(III) species [B] so formed would then collapse to give the phosphonium intermediate [C] which further undergoes the second stage of the Arbuzov reaction to give the phosphonate, which is complexed then with copper(I).

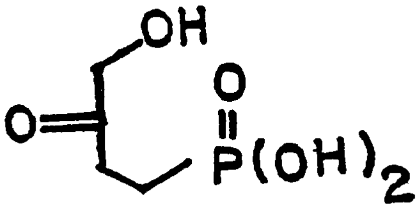
By analogy with other organocuprates(104-108), these complexes LCuBr would act as nucleophiles(100-101) rather than Lewis acids by forming π-complexes [E] (109-117). Although some copper(I) halides are known to form complexes with a few normal olefins (118-120), it is noted in the present work that no π-complexes could be observed forming from vinylic halides with either copper(I) halides or copper(I) halide complexes. Alternatively, oxidative addition of a vinylic halide to LCuBr across the π-bond [F] (100-101) would be unlikely for copper(I) halide complexes. Only a few organometallic compounds of this type are known, and only those with Pt(O) (104) and Pd(O) (100-101). This type of complex would be subjected to nucleophilic attack at the carbon bearing the halogen by another LCuX. This could lead to several possible products and retention of the configuration of the expected products would not be expected.


[E]

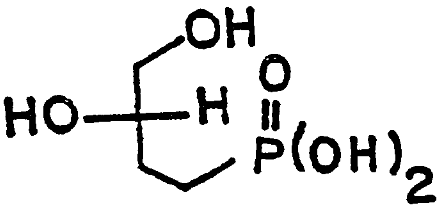

[F]

II. Synthesis of Oligopeptide Chemical Vector Species.

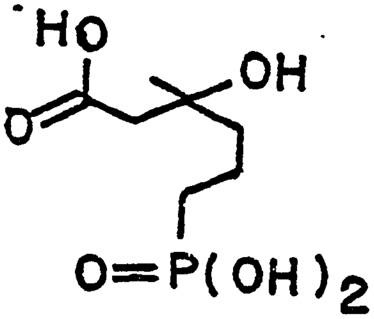
The isosteric analogues of a series of natural phosphonate esters have been synthesized previously in this laboratory (121,122,123). These include the analogues of dihydroxyacetone phosphate (4-hydroxy-3-oxobutyl-1-phosphonic acid [G]), sn-glycerol-3-phosphate ([S]-3,4-dihydroxybutyl-1-phosphonic acid [H]) and 5-phosphomevalonate (5-carboxy-4-hydroxy-4-methylpentyl-1-phosphonic acid [K]).



[G]

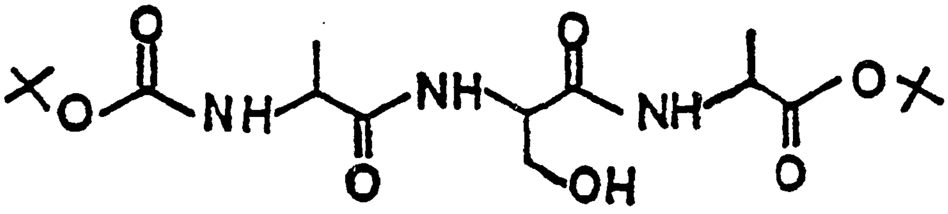


[H]

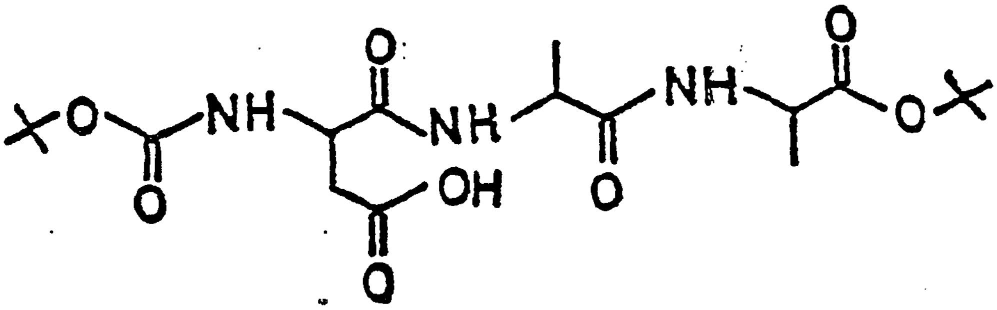


[K]

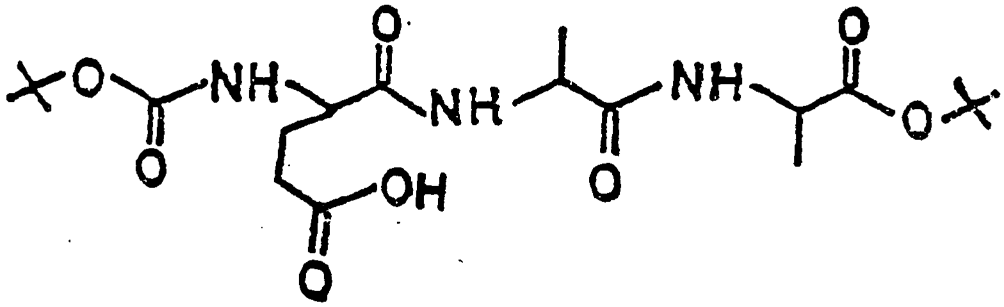
These analogue materials were coupled to oligopeptides for the facilitation of their transport into intact bacterial cells from which they would normally be excluded. The tripeptide conjugates to be generated were specifically alanylserylalanine [XX], aspartylalanylalanine [XXVII], and glutamylalanylalanine [XXXIII].



[XX]



[XXVII]



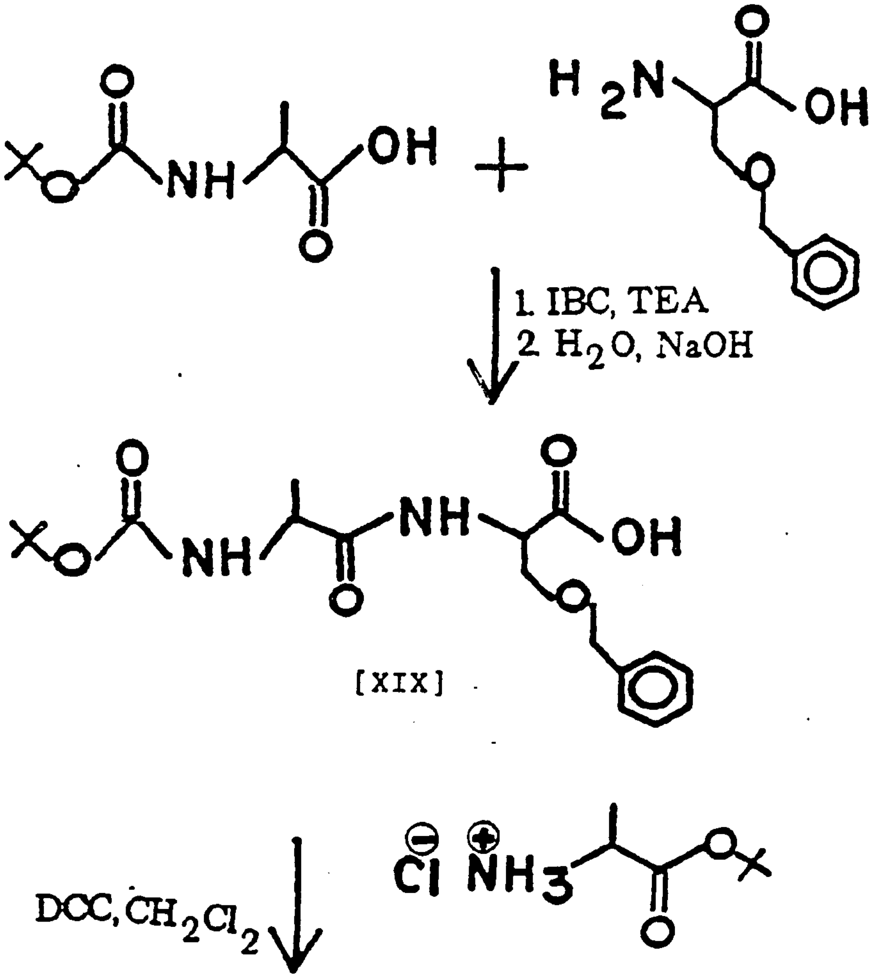
[XXXIII]

For these syntheses of tripeptides linked to the phosphonate analogues, the carbobenzyloxy group was used initially for the protection of the amino termini (124) and t-butyl esters were used for the protection of carboxyl termini (125). In the later efforts the butyloxycarbonyl group (126) was used as the amino termini protecting function instead of the carbobenzoxy group since its use and deprotection (along with t-butoxy group) eliminates an additional step. The deprotection of BOC- and t-Bu groups can be performed together, and also the preparation of the BOC-amino acid is more facile and proceeds in higher yield.

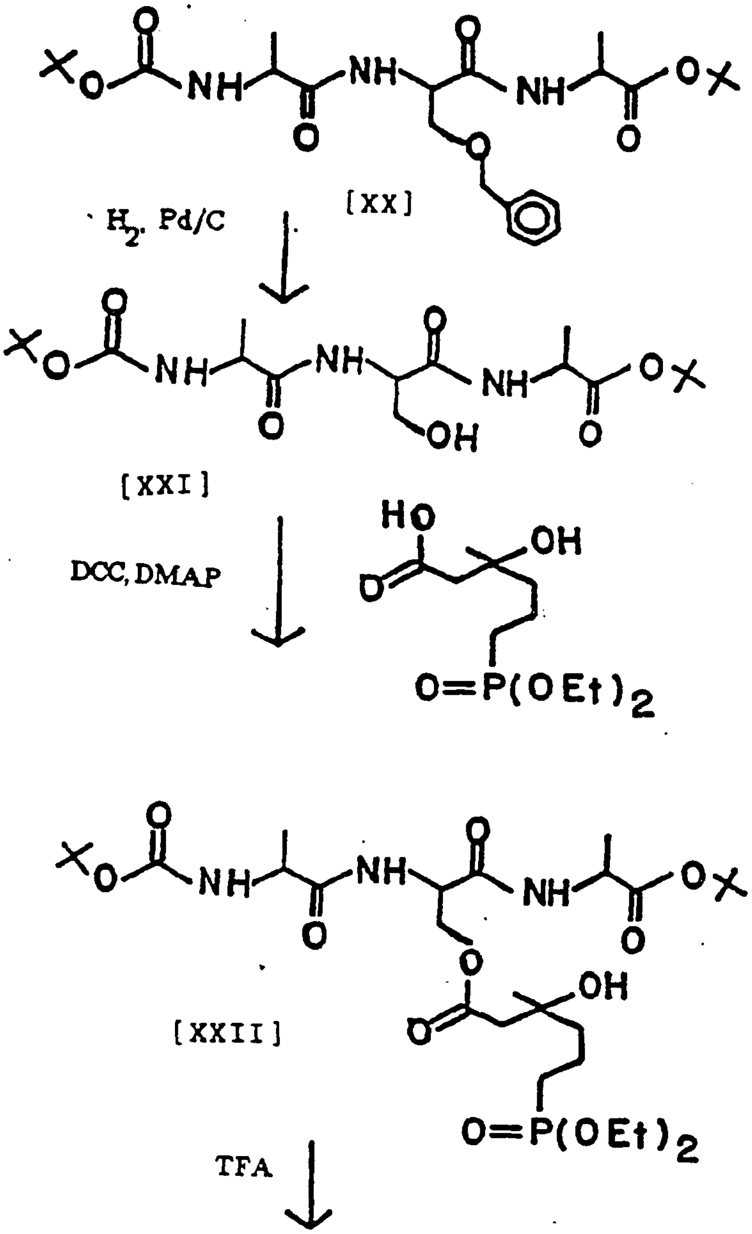
The first chemical vector, the tripeptide (BOC-alanylserylalanine-O-t-butyl ester), [XXI] was synthesized as follows. Using the mixed anhydride method, the dipeptide (BOC-alanyl(O-benzyl)serine) [XIX] was obtained in 60% yield. This dipeptide [XIX] was coupled with alanine-O-t-butyl ester hydrochloride using DCC in dichloromethane in 60% yield. The benzyl group was removed through catalytic hydrogenation (127) over palladium on carbon at atmospheric pressure giving the tripeptide [XXI] in 91% yield.

The tripeptide [XXI] was allowed to react with diethyl 5-carboxy-4-hydroxy-4-methylpentyl-1-phosphonate in methylene chloride using N,N-dicyclohexylcarbodiimide at 0 C giving the coupled compound [XXII] in 52% yield.

The protecting groups, butyloxycarbonyl and t-butyl, were **cleaved by the treatment with trifluoroacetic acid (TFA)** as shown in Scheme 2. The phosphonate esters were cleaved to the free phosphonic acid by reaction with bromotrimethylsilane under a nitrogen atmosphere and with subsequent hydrolysis under mild conditions of the resulting bis(trimethylsilyl) phosphonate (128,129).



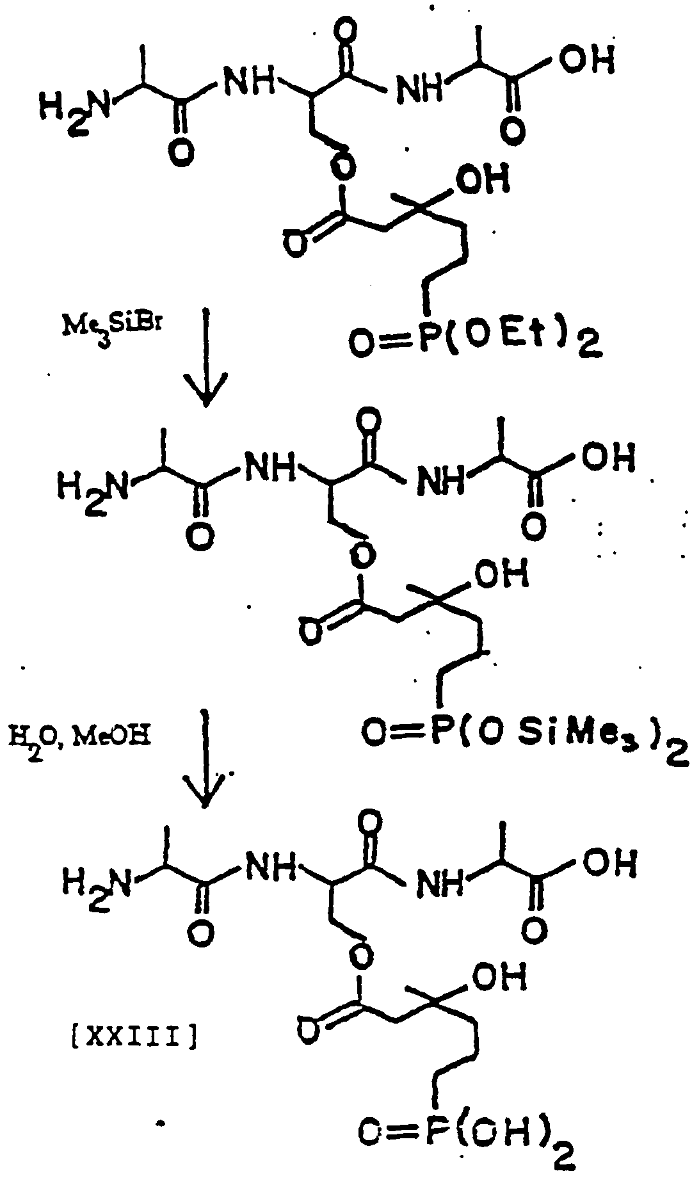
[XIX]



[XX]

[XXI]

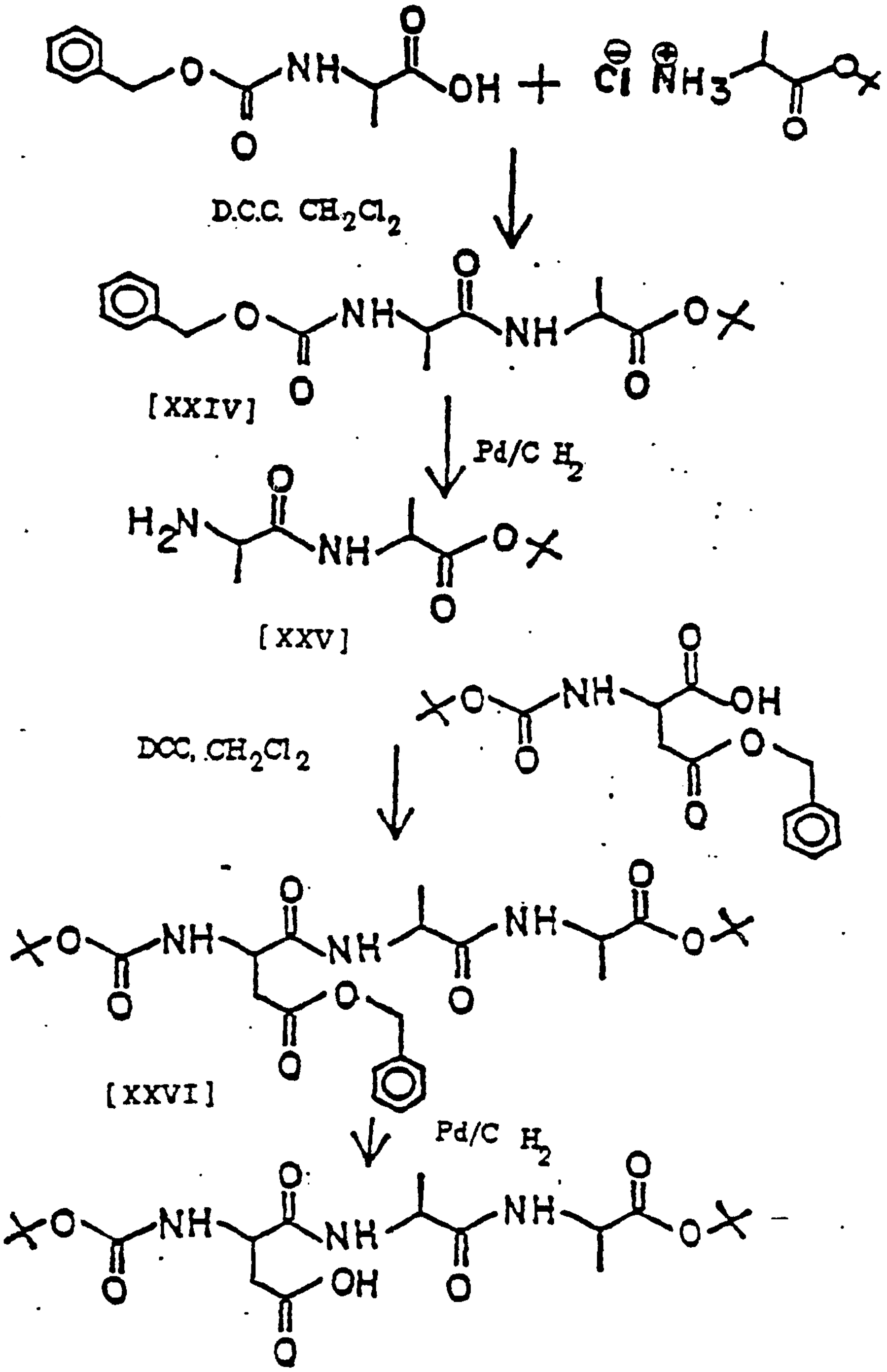
[XXII]



Scheme 2

For the synthesis of the second chemical vector, the tripeptide aspartylalanylalanine, the starting point was the trifunctional amino acid, aspartic acid. The amino function was protected with the BOC group using BOC-anhydride. The β-carboxyl function was protected as the benzyl ester. The dipeptide [XXV], alanylalanine, was synthesized by the coupling of carbobenzoxyalanine and **alanine-t-butyl ester hydrochloride by the carbodiimide** method in 87% yield. The dipeptide was subjected to catalytic hydrogenation (127) over palladium on carbon at atmospheric pressure. This catalytic hydrogenation cleaves the benzyloxycarbonyl group in almost quantitative yield without affecting the t-butyl ester. Butyloxycabonyl-β-benzyl aspartate and alanylalanine-t-butyl ester were allowed to react in dichloromethane by the carbodiimide method in 87% yield. The choice of solvent was made keeping in mind that with DCC racemization increases with the temprature (130) and is more pronounced in polar solvents such as dimethylformamide than methylene chloride. The tripeptide derivative [XXVI], BOC-(β-benzyl)-aspartylalanylalanine-t-butyl ester, was hydrogenated catalytically to cleave the β-benzyl group on the aspartate unit. The product was obtained in quantiative yield.

The tripeptide [XXVII] was allowed to react with dibutyl 3,4-dihydroxybutyl-1-phosphonate in methylene chloride using N,N-dicyclohexylcarbodiimide at 0^0 C giving the coupled compound [XXVIII] in 60% yield. The protecting groups, butyloxycarbonyl and t-butyl groups were cleaved by the treatment with trifluoroacetic acid (TFA) as shown in Scheme 3. The phosphonate esters were cleaved to the free phosphonic acid by reaction with bromotrimethylsilane under a nitrogen atmosphere and with the subsequent hydrolysis under mild conditions of the resulting bis(trimethylsilyl) phosphonate.

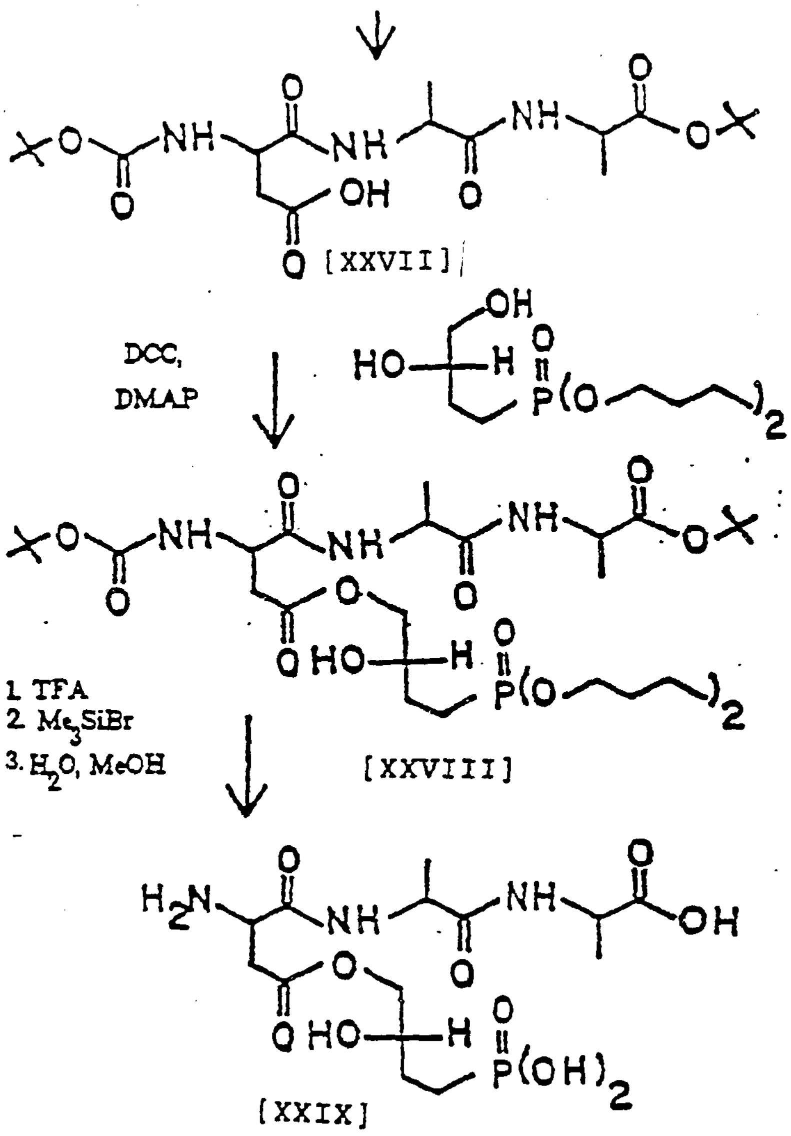


[XXIV]

[XXV]

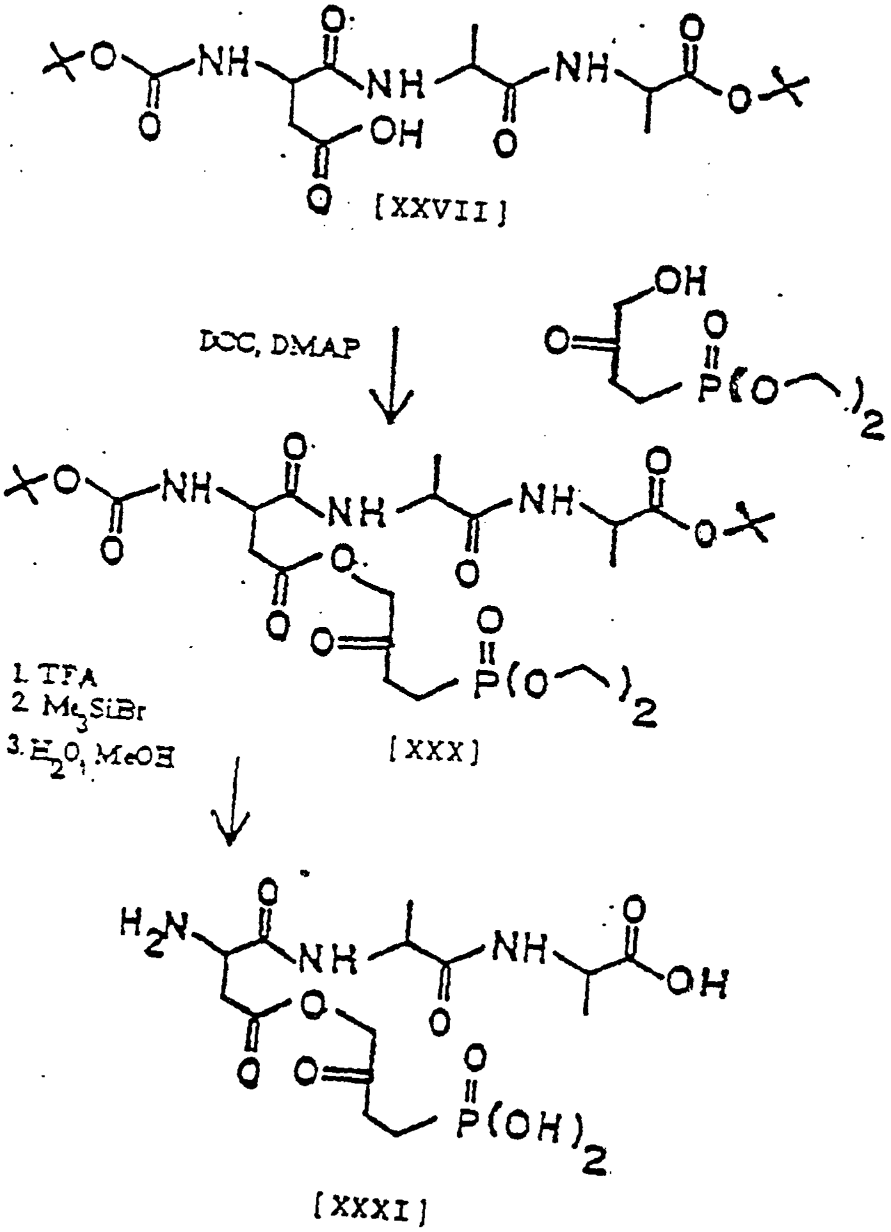
[XXVI]

[XXVII]



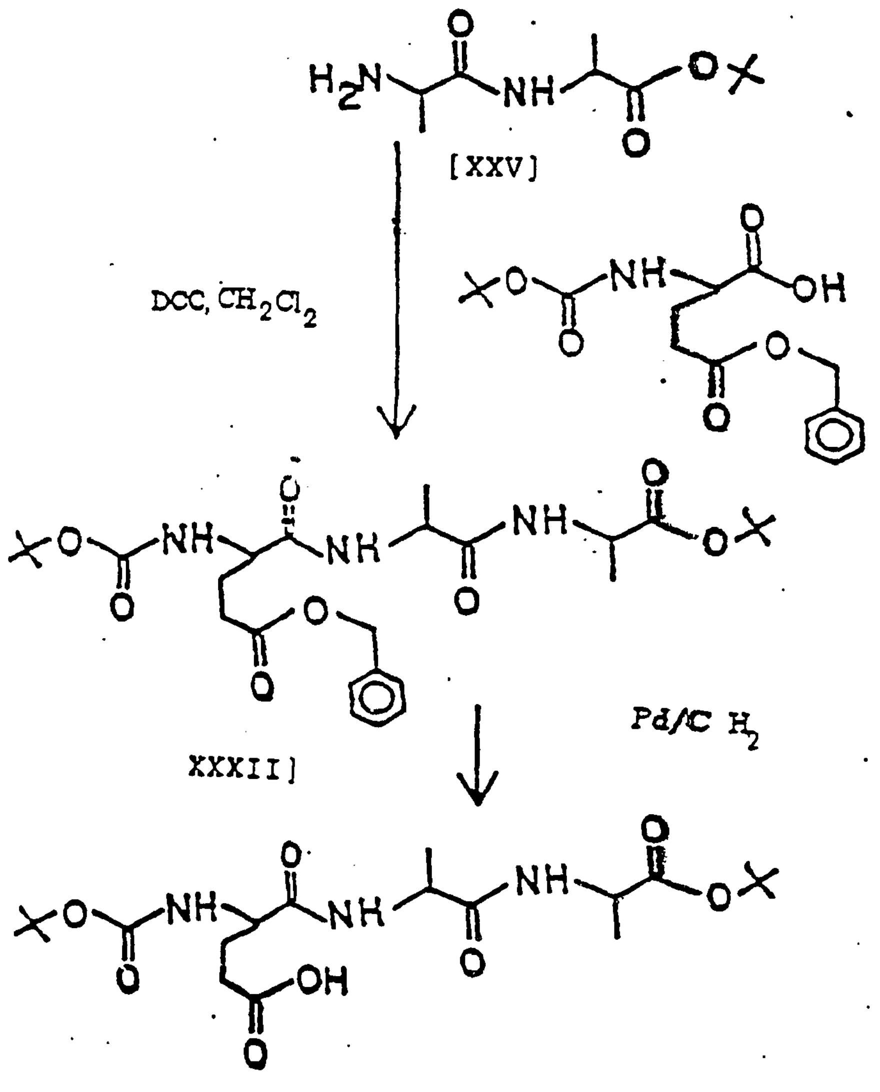
Scheme 3

The coupling of the tripeptide [XXVII] with diethyl 4-hydroxy-3-oxobutyl-1-phosphonate was performed in anhydrous dichloromethane using DCC in the presence of N,N-dimethylaminopyridine (DMAP) as a catalyst (131) for esterification. The favorable catalytic action of pyridine in such reactions (132) suggested that the 10^4-fold more effective acylation catalyst, 4-dimethylaminopyridine, might prove to be a useful agent in our present studies on the esterification. We found that the addition of 3-10 mole % DMAP accelerates the DCC-activated esterification of the caroxylic group in [XXVI] with the hydroxyl group in diethyl 4-hydroxy-3-oxobutyl-1-phosphonate to such an extent that the formation of side products is suppressed and even the strictly demanding ester [XXX] is formed in good yield (59 %) at 0^0 C. The BOC- and t-Bu ester were removed in the usual way as mentioned earlier. The protecting groups on the phosphonate ester were removed to yield the free phosphonic acid using trimethylsilyl bromide under a nitrogen atmosphere. The silyl ester formed here is also easily hydrolyzed by treatment with water and methanol to give the corresponding acid [XXXI] as shown in Scheme 4.

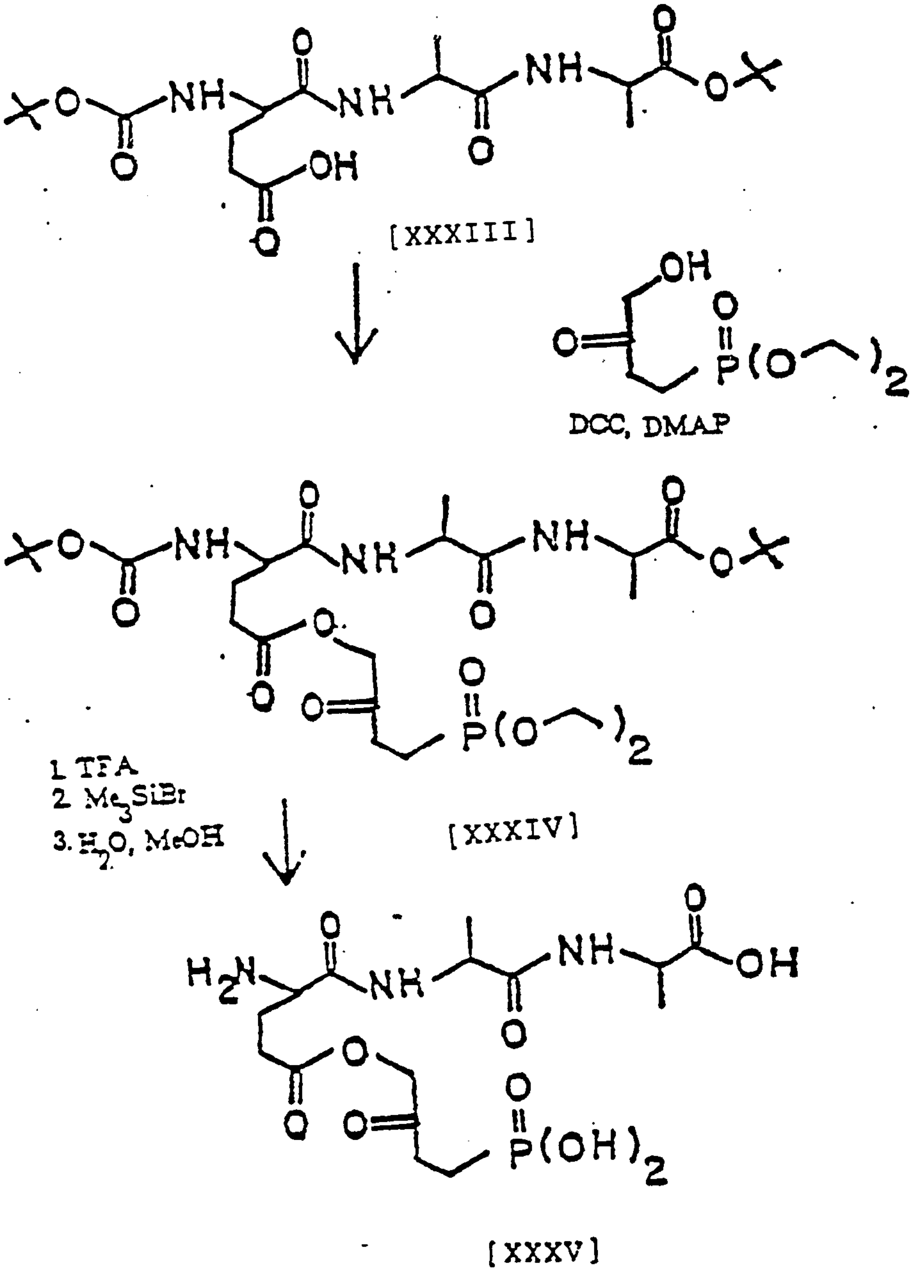


Scheme 4

The third chemical vector, glutamylalanylalanine was synthesized by using the mixed anhydride method. Butyloxycabonyl-γ-benzyl glutamate and alanylalanine-t-butyl ester [XXV] were allowed to react in dichloromethane by the carbodiimide method to give the desired product [XXXII] in 87% yield using DCC method. The BOC-(γ -benzyl)-glutamylalanylalanine-t-butyl ester was hydrogenolyzed catalytically to cleave the γ-benzyl group on the glutamate unit. The product [XXXIII] was obtained in quantitative yield.



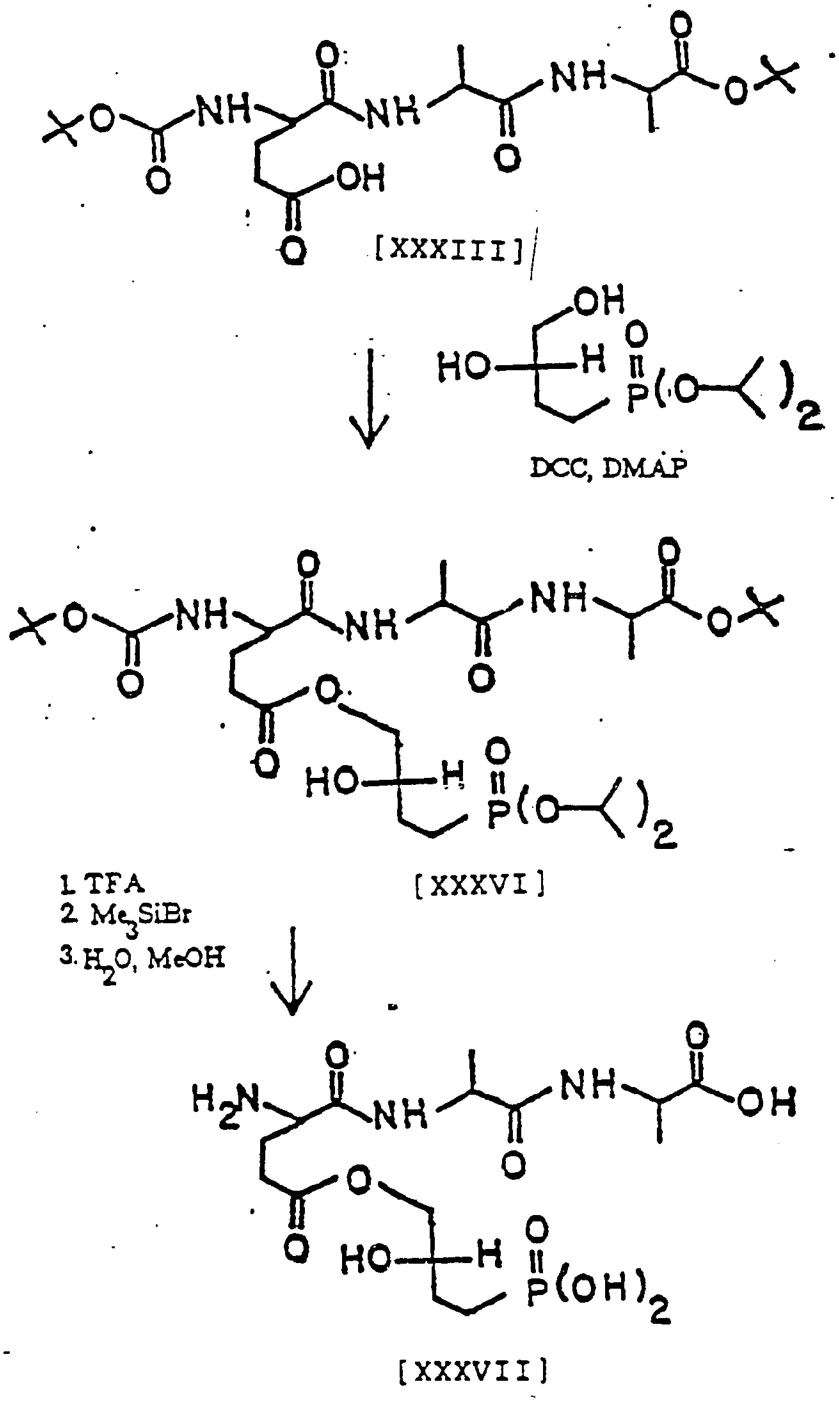
[XXXIII]



Scheme 5

The coupling of the tripeptide [XXXIII] with diethyl 4-hydroxy-3-oxobutyl-1-phosphonate was performed in anhydrous acetonitrile using DCC in the presence of N,N-dimethylaminopyridine (DMAP) as a catalyst for esterification giving the coupled compound [XXXIV]. The protecting groups, butyloxycarbonyl and t-butyl groups were cleaved by the treatment with trifluoroacetic acid (TFA) as shown in Scheme 5. The phosphonate esters were cleaved to the free phosphonic acid by reaction with bromotrimethylsilane under a nitrogen atmosphere and with subsequent hydrolysis under mild conditions of the resulting bis(trimethylsilyl) phosphonate.

Again the tripeptide [XXXIII] was allowed to react with diisopropyl 3,4-dihydroxybutyl-1-phosphonate in methylene chloride using N,N-dicyclohexylcarbodiimide at 0^{o} C giving the coupled compound [XXXVI] in 58% yield. The protecting groups, butyloxycarbonyl and t-butyl groups were cleaved by the treatment with trifluoroacetic acid (TFA) as shown in Scheme 6. The phosphonate esters were cleaved to the phosphonic acid by reaction with bromotrimethylsilane under a nitrogen atmosphere and with subsequent hydrolysis under mild conditions of the resulting bis(trimethylsilyl) phosphonate.



[XXXIII]

[XXXVI]

[XXXVII]

Scheme-6

EXPERIMENTAL

GENERAL

All chemicals were of reagent quality and used without further purification with the following exceptions: benzene, pentane and hexanes were dried over sodium ribbon; acetonitrile and pyridine were distilled over calcium hydride; tetrahydrofuran was distilled over lithium aluminum hydride; dimethylformamide (DMF), dioxan, and methylene chloride were distilled immediately prior to use and stored over molecular sieves.

Thin layer chromatography was performed using polygram Sil-N-HR silica gel sheets purchased from Brinkmann Instruments, Inc., and paper chromatography was performed using Whatmann filter paper No.3. Palladium on carbon (10%) was purchased from Colonial Metals Inc., Maryland.

Infra-red spectra were measured using a Perkin Elmer 237-B spectrophotometer; NMR spectra were measured using either a Varian EM-360 (60 MHz), or IBM-Brucker WP-200SY (200 MHz) instrument. Melting points were obtained on a Meltemp instrument and were uncorrected. The elemental analysis of the compounds were performed by Mic Anal of Tucson, Arizona. The optical rotations of the compounds were measured on a JASCO Digital Polarimeter (DIP-140).

SYNTHESIS OF COPPER(I) BROMIDE-TRIETHYL PHOSPHITE COMPLEX:

In a 250 mL, one-necked flask equipped with a Claisen head, a rubber septum, and a gas inlet tube was placed 7.2 g (0.05 mol) of freshly prepared copper(I) bromide and 80 mL of dry pentane. Triethyl phosphite (8.3 g, 0.05 mole) was added dropwise to the suspension at room temperature and the resulting reaction mixture was stirred for 1 hr. After stirring, the trace of unreacted material was filtered off and the solution concentrated. The thick, colorless liquid was dried in vacuo to give the pure complex (15.0 g 96% yield).

NMR ($CDCl_3$) : δ 1.30 (t, J =7.0 Hz, 9H); 4.09 (dq,J =7.0 Hz, J =10.0 Hz, 6H).

I.R.(neat) cm^{-1}: 2980; 2930; 2900; 1025(broad); 940(broad); 800-714.

SYNTHESIS OF 1-CYCLODODECENYL CHLORIDE: [V]

Into a three necked flask equipped with a mechanical stirrer, a drying tube, and an addition funnel was placed 56.12 g (0.25 moles) of phosphorus pentachloride and 32 mL (0.25 moles) of phosphorus oxychloride. The mixture was stirred at 0 °C, and 45.57 g (0.25 moles) of cyclododecanone was added dropwise. The mixture was allowed to stir for 20 hours. After this time the reaction mixture was heated under reduced pressure to remove any phosphorus oxychloride and was then poured into ice-water with vigorous stirring. The resultant mixture was extracted with ether and the extracts washed with 30 mL of 2% sodium bicarbonate solution and water. The extracts were then dried over magnesium sulfate and evaporated to give the crude vinylic chloride. The product was purified by chromatography on a silica gel column eluting with 1:1 hexane : ethyl acetate followed by distillation to yield 47.16 g, (94% yield) of the desired product.

b.p. 85°C/ 0.15 Torr.

Rf. : 0.57 (1:1 hexane : ethyl acetate).

IR:(CCl_4) cm^{-1}: 2900-2960 (broad), 2850, 1710, 1650 (C=C), 1470, 1348, 985, 975.

NMR($CDCl_3$):δ 1.2-2.7 (m,20 H), 5.45-5.8 (dq, 1H)

Elemental Analysis:

[C(12)H(21)Cl]

	Calculated	Found
C%	71.79	71.85
H%	10.54	10.67

SYNTHESIS OF 1-CYCLOHEXENYL CHLORIDE: [VI]

Into a three necked flask equipped with a mechanical stirrer, a drying tube, and an addition funnel was placed 56.12 g (0.25 moles) of phosphorus pentachloride and 32 mL (0.25 moles) of phosphorus oxychloride. The mixture was stirred at 0°C and 24.53 g (0.25 moles) of cyclohexanone was added dropwise. The mixture was allowed to stir for 20 hours. After this time the reaction mixture was heated under reduced pressure to remove any phosphorus oxychloride and was then poured into ice-water with vigorous stirring. The resultant mixture was extracted with ether and the extracts washed with 30 mL each of 2% sodium bicarbonate solution and water. The extracts were then dried over magnesium sulfate and evaporated to give the crude vinylic chloride. The product was purified by chromatography on a silica gel column eluting with 1:1 hexane:ethyl acetate followed by distillation to yield 14.0 g (94% yield) of the desired product.

b.p. 60-61 °C / 0.4 Torr.

Rf: 0.60 (1:1 hexane : ethyl acetate).

IR:(CCl_4) cm^{-I}: 2922, 2845, 1550(C=C), 1440, 1240, 1120, 1000, 892, 860, 570.

NMR($CDCl_3$):δ 1.2-2.5 (b,8H), 5.5-6.1 (m,1H)

Elemental Analysis:

[C(6)H(9)Cl]

	Calculated	Found
C%	61.81	61.92
H%	7.78	7.84

SYNTHESIS OF 2-CHLORO-1,3-CYCLOHEXADIENE: [VII]

Into a three necked flask equipped with a mechanical stirrer, a drying tube, and an addition funnel was placed 56.12 g (0.25 moles) of phosphorus pentachloride and 32 mL

(0.25 moles) of phosphorus oxychloride. The mixture was stirred at 0°C and 24.04 g (0.25 moles) of 2-cyclohexen-1-one was added dropwise. The mixture was allowed to stir for 20 hours. After this time the reaction mixture was heated under reduced pressure to remove any phosphorus oxychloride and was then poured into ice-water with vigorous stirring. The resultant mixture was extracted with ether and the extracts washed with 30 mL each of 2% sodium bicarbonate solution and water. The extracts were then dried over magnesium sulfate and evaporated to give the crude vinylic chloride. The product was purified by chromatography on a silica gel column eluting with 1:1 hexane:ethyl acetate followed by distillation to yield 29.8 g (98% yield) of the desired product.

b.p. 80°C / 0.1 Torr.

Rf: 0.54 (1:1 hexane : ethyl acetate).

IR(CCl_4) cm^{-1}: 2935, 1640, (C=C) 1540, 1420, 1348, 1315, 1250, 1218, 1050, 915, 870, 590.

NMR($CDCl_3$): δ 1.6-2.7 (m,4H), 4.6-4.8 (m,2H), 5.9-6.1 (d,1H)

Elemental Analysis:

[C(6)H(7)Cl]		Calculated	Found
	C%	62.89	62.80
	H%	6.59	6.65

SYNTHESIS OF 1-CYCLOHEPTENYL CHLORIDE: [VIII]

Into a three necked flask equipped with a mechanical stirrer, a drying tube, and an addition funnel was placed 22.45 g (0.10 moles) of phosphorus pentachloride and 12.5 mL (0.10 moles) of phosphorus oxychloride. The mixture was stirred at 0°C and 11.21 g (0.1 moles) of cycloheptanone was added dropwise. The mixture was allowed to stir for 20 hours. After this time the reaction mixture was heated under reduced pressure to remove any phosphorus oxychloride and was then poured into ice-water with vigorous stirring. The resultant mixture was extracted with ether and the extracts washed with 20 mL each of 2% sodium bicarbonate solution and water. The extracts were then dried over magnesium sulfate and evaporated to give the crude vinylic chloride. The product was purified by chromatography on a silica gel column eluting with 1:1 hexane:ethyl acetate followed by distillation to yield 10.2 g (78% yield) of the desired product.

b.p. 60°C / 2.5 Torr.

Rf: 0.61 (1:1 hexane : ethyl acetate).

IR (CCl_4) cm^{-1}: 2920, 2850, 1705, 1640 (C=C), 1440, 1350, 1270, 1210, 960, 920, 840, 670.

NMR($CDCl_3$): 1.4-2.7 (m,10H), 5.8-6.1 (t,1H)

Elemental Analysis:

[C(7)H(11)Cl]

	Calculated	Found
C%	64.37	64.45
H%	8.48	8.35

SYNTHESIS OF 4-METHYL-1-CYCLOHEXENYL CHLORIDE: [IX]

Into a three necked flask equipped with a mechanical stirrer, a drying tube, and an addition funnel was placed 56.12 g (0.25 moles) of phosphorus pentachloride and 32 mL (0.25 moles) of phosphorus oxychloride. The mixture was stirred at 0 °C and 28.04 g (0.25 moles) of 4-methyl cyclohexanone was added dropwise. The mixture was allowed to stir for 20 hours. After this time the reaction mixture was heated under reduced pressure to remove any phosphorus oxychloride and was then poured into ice-water with vigorous stirring. The resultant mixture was extracted with ether and the extracts washed with 30 mL each of 2% sodium bicarbonate solution and water. The extracts were then dried over magnesium sulfate and evaporated to give the crude vinylic chloride. The product was purified by chromatography on a silica gel column eluting with 1:1 hexane:ethyl acetate followed by distillation to yield 25.7 g (79% yield) of the desired product.

b.p. 77 °C / 1.1 Torr.

Rf: 0.46 (1:1 hexane : ethyl acetate).

IR(CCl_4) cm^{-1}: 2940, 2910, 1650 (C=C), 1540, 1450, 1435, 1370, 1240, 1130, 1075, 1010, 960, 890, 570.

NMR($CDCl_3$): δ: 0.9 (s,3H), 1.2-2.6 (m,7H), 5.8 (m,1H)

Elemental Analysis:

[C(7)H(1)1Cl]

	Calculated	Found
C%	64.65	64.75
H%	8.42	8.50

SYNTHESIS OF 4-t-BUTYL-1-CYCLOHEXENYL CHLORIDE: [X]

Into a three necked flask equipped with a mechanical stirrer, a drying tube, and an addition funnel was placed 56.12 g (0.25 moles) of phosphorus pentachloride and 32 mL (0.25 moles) of phosphorus oxychloride. The mixture was stirred at 0° C and 38.56 g (0.25 moles) of 4-t-butyl cyclohexanone was added dropwise. The mixture was allowed to stir for 20 hours. After this time the reaction mixture was heated under reduced pressure to remove any phosphorus oxychloride and was then poured into ice-water with vigorous stirring. The resultant mixture was extracted with ether and the extracts washed with 30 mL each of 2% sodium bicarbonate solution and water. The extracts were then dried over magnesium sulfate and evaporated to give the crude vinylic chloride. The product was purified by chromatography on a silica gel column eluting with 1:1 hexane:ethyl acetate followed by distillation to yield 42 g (97% yield) of the desired product.

b.p. 70 °C / 0.4 Torr.

Rf: 0.64 (1:1 hexane : ethyl acetate).

IR:(CCl4) cm^{-1}: 2940, 1652 (C=C), 1460, 1390, 1360, 1240, 1100, 1045, 1020, 975, 905, 830, 575.

NMR($CDCl_3$): δ 0.87(s, 9H), 1.08-2.65 (m,7H); 5.78(m, 1H)

Elemental Analysis:

[C(10)H(17)Cl]

	Calculated	Found
C%	69.55	69.60
H%	9.92	9.97

SYNTHESIS OF 1-CYCLOOCTENYL CHLORIDE: [XI]

Into a three necked flask equipped with a mechanical stirrer, a drying tube, and an addition funnel was placed 56.12 g (0.25 moles) of phosphorus pentachloride and 32 mL (0.25 moles) of phosphorus oxychloride. The mixture was stirred at 0 °C and 31.55 g (0.25 mole) of cyclooctanone was added dropwise. The mixture was allowed to stir for 20 hours. After this time the reaction mixture was heated under reduced pressure to remove any phosphorus oxychloride and was then poured into ice-water with vigorous stirring. The resultant mixture was extracted with ether and the extracts washed with 30 mL each of 2% sodium bicarbonate solution and water. The extracts were then dried over magnesium sulfate and evaporated to give the crude vinylic chloride. The product was purified by chromatography on a silica gel column eluting with 1:1 hexane:ethyl acetate followed by distillation to yield 23.0 g (64% yield) of the desired product.

b.p. 56 °C / 1.9 Torr.

Rf: 0.48 (1:1 hexane : ethyl acetate).

IR:(CCl_4) cm^{-I}: 2920, 2850, 1695 (C=C), 1643, 1540, 1460, 1240, 1210, 1115, 995, 885, 650.

NMR ($CDCl_3$): δ 0.72-2.86 (b,12H); 5.68 (t, 9H)

Elemental Analysis:

[C(8)H(13)Cl]

	Calculated	Found
C%	66.43	66.05
H%	9.06	9.18

SYNTHESIS OF DIETHYL 1-CYCLODODECENYLPHOSPHONATE: [XII]

To a 50 mL, one-necked flask equipped with a short Vigreaux column, a Dean-Stark trap, a condenser, and topped with a nitrogen inlet tube was placed copper(I) bromide-triethyl phosphite complex (16.60 g, 0.052 mole) and 1-cyclododecenyl chloride (7.02 g, 0.035 mole). The mixture was then heated under a nitrogen atmosphere at 200-205 °C (external oil bath) and the volatile materials were collected in the Dean-Stark trap. The heating was performed until no more volitiles were distilled. After cooling to room temperature the reaction mixture was poured into 60 mL of toluene. Then ethylenediamine (6.7 mL) was added to the solution dropwise while stirring. The solids formed were filtered off and washed well with toluene. The filtrate was acidified with 10% hydrochloric acid and extracted with ether. The organic phase was washed with water. The aqueous phase was extracted with ether. The combined organic phase was dried over magnesium sulfate and the solvent evaporated under reduced pressure. The crude product thus isolated was chromatographed on silica gel eluting with 1:1 hexane ethyl acetate mixtures, followed by distillation, to give the pure desired product (5.32 g, 50% yield).

b.p. 84^{o}C/ 0.2 Torr.

Rf. :0.39 (1:1 hexane : ethyl acetate).

IR(CCl_4) cm^{-I}: 3680; 3400 (broad); 2920; 2860; 1620(C=C); 1548; 1465; 1440; 1390; 1248(P=O); 1060;-1020(broad); 960; 555.

NMR($CDCl_3$): δ 1.15-2.68 (b, 12H); 4.02 (dq, J=10 Hz, J=7Hz, 4H); 6.50 (dt, J=26 Hz, J=8 Hz, 1H).

Elemental Analysis:

[C(16)H(31)O(3)P]

	Calculated	Found
C%	63.55	63.24
H%	10.33	10.69

SYNTHESIS OF DIETHYL 1-CYCLOHEXENYLPHOSPHONATE: [XIII]

To a 50 mL, one-necked flask equipped with a short Vigreaux column, a Dean-Stark trap, a condenser, and topped with a nitrogen inlet tube was placed copper(I) bromide-triethyl phosphite complex (16.60 g, 0.052 mole) and 1-cyclohexenyl chloride (4.08 g, 0.035 mole). The mixture was then heated under a nitrogen atmosphere at 200-205 °C (external oil bath) and the volatile materials were collected in the Dean-Stark trap. The heating was performed until no more volitiles were distilled. After cooling to room temperature the reaction mixture was poured into 60 mL of toluene. Then ethylenediamine (6.7 mL) was added to the solution dropwise while stirring. The solids formed were filtered off and washed well with toluene. The filtrate was acidified with 10% hydrochloric acid and extracted with ether. The organic phase was washed with water. The aqueous phase was extracted with ether. The combined organic phase was dried over magnesium sulfate and the solvent evaporated under reduced pressure. The crude product thus isolated was chromatographed on silica gel eluting with 1:1 hexane:ethyl acetate mixtures, followed by distillation, to give the pure desired product (4.21 g, 55.2% yield).

b.p. 82 °C / 0.5 Torr.

Rf. : 0.39 (1:1 hexane : ethyl acetate).

IR(CCl_4) cm^{-1}: 3670; 3420(broad); 2970; 2920; 1627(C=C);

1540; 1430; 1385; 1241(P=O); 1160; 1080; 1050-1020; 960; 600.

NMR($CDCl_3$): δ 1.31 (t, J=7 Hz, 6H); 1.40-2.51 (m,8H); 4.10 (dq, J=8 Hz, J= 7 Hz, 4H);6.72 (dm,J= 22 Hz, 1H).

Elemental Analysis:

[C(10)H(19)O(3)P]

	Calculated	Found
C%	55.03	55.21
H%	8.78	9.04

SYNTHESIS OF DIETHYL 2-(1,3-CYCLOHEXADIENYL)PHOSPHONATE: [XIV]

To a 50 mL, one-necked flask equipped with a short Vigreaux column, a Dean-Stark trap, a condenser, and topped with a nitrogen inlet tube was placed copper(I) bromide-triethyl phosphite complex (16.60 g, 0.052 mole) and 2-chloro-1,3-cyclohexadiene (4.0 g, 0.035 mole). The mixture was then heated under a nitrogen atmosphere at 200-205° C (external oil bath) and the volatile materials were collected in the Dean-Stark trap. The heating was performed until no more volitiles were distilled. After cooling to room temperature the reaction mixture was poured into 60 mL of toluene. Then ethylenediamine (6.7 mL) was added to the solution dropwise while stirring. The solids formed were filtered off and washed well with toluene. The filtrate was acidified with 10% hydrochloric acid and extracted with ether. The organic phase was washed with water. The aqueous phase was extracted with ether. The combined organic phase was dried over magnesium sulfate and the solvent evaporated under reduced pressure. The crude product thus isolated was chromatographed on silica gel eluting with 1:1 hexane:ethyl acetate mixtures, followed by distillation, to give the pure desired product (3.85 g, 51.4% yield).

b.p. 71^{o}C / 0.55 Torr.

Rf. :0.42 (1:1 hexane : ethyl acetate).

IR(CCl_4) cm^{-1}: 3670; 3420(broad); 2965; 2910; 2890; 2420; 1711(C=C); 1540; 1470; 1435; 1385; 1360; 1249(P=O); 1158; 1050; 1015; 980-950; 540.

NMR($CDCl_3$): δ 1.32 (t, J=8 Hz,6H); 1.75-3.00 (m, 4H); 4.03 (dq, J=8 Hz, J=8 Hz, 4H); 5.55-6.14 (m, 2H); 6.74 (dm, J=22 Hz, 1H).

Elemental Analysis:

[C(10)H(17)O(3)P]

	Calculated	Found
C%	55.55	55.24
H%	7.92	8.28

SYNTHESIS OF DIETHYL 1-CYCLOHEPTENYLPHOSPHONATE: [XV]

To a 50 mL, one-necked flask equipped with a short Vigreaux column, a Dean-Stark trap, a condenser, and topped with a nitrogen inlet tube was placed copper(I) bromide-triethyl phosphite complex (16.60 g, 0.052 mole) and 1-cycloheptenyl chloride (4.57 g, 0.035 mole). The mixture was then heated under a nitrogen atmosphere at 200-205° C (external oil bath) and the volatile materials were collected in the Dean-Stark trap. The heating was performed until no more volitiles were distilled. After cooling to room temperature the reaction mixture was poured into 60 mL of toluene. Then ethylenediamine (6.7 mL) was added to the solution dropwise while stirring. The solids formed were filtered off and washed well with toluene. The filtrate was acidified with 10% hydrochloric acid and extracted with ether. The organic phase was washed with water. The aqueous phase was extracted with ether. The combined organic phase was dried over magnesium sulfate and the solvent evaporated under reduced pressure. The crude product thus isolated was chromatographed on silica gel eluting with 1:1 hexane:ethyl acetate mixtures, followed by distillation, to give the pure desired product (5.23 g, 64.5% yield).

b.p. 80° C / 0.2 Torr.

Rf. :0.28 (1:1 hexane : ethyl acetate).

IR(CCl_4) cm^{-I}: 3670; 3400; 2970; 2910; 2840; 1625(C=C); 1540; 1440; 1385; 1240(P=O); 1158; 1090; 1055; 1025; 950; 590; 550.

NMR($CDCl_3$): δ 1.27 (t, J= 7 Hz, 6H); 1.35-2.90 (m, 10 H); 4.00 (dq, J= 8 Hz, J= 7Hz); 6.93 (dt, J= 24 Hz, J= 6 Hz, 1H).

Elemental Analysis:

[$C_{11}H_{21}O_3P$]

	Calculated	Found
C%	56.88	56.86
H%	9.11	9.17

SYNTHESIS OF DIETHYL 4-METHYL-1-CYCLOHEXENYLPHOSPHONATE: [XVI]

To a 50 mL, one-necked flask equipped with a short Vigreaux column, a Dean-Stark trap, a condenser, and topped with a nitrogen inlet tube was placed copper(I) bromide-triethyl phosphite complex (16.60 g, 0.052 mole) and 4-methyl-1-cyclohexenyl chloride (4.56 g, 0.035 mole). The mixture was then heated under a nitrogen atmosphere at 200-205 °C (external oil bath) and the volatile materials were collected in the Dean-Stark trap. The heating was performed until no more volitiles were distilled. After cooling to room temperature the reaction mixture was poured into 60 mL of toluene. Then ethylenediamine (6.7 mL) was added to the solution dropwise while stirring. The solids formed were filtered off and washed well with toluene. The filtrate was acidified with 10% hydrochloric acid and extracted with ether. The organic phase was washed with water. The aqueous phase was extracted with ether. The combined organic phase was dried over magnesium sulfate and the solvent evaporated under reduced pressure. The crude product thus isolated was chromatographed on silica gel eluting with 1:1 hexane ethyl acetate mixtures, followed by distillation, to give the pure desired product (4.87 g, 60% yield).

b.p. 102 ^{o}C/ 0.55 Torr.

Rf. : 0.26 (1:1 hexane : ethyl acetate).

IR(CCl_4) cm^{-I}: 3665; 3410; 297; 2900; 1630(C=C); 1540; 1430; 1385; 1240)P=O); 1160; 1095; 1060-1010; 960; 610.

NMR($CDCl_3$): δ 1.00 (d, J= 5 Hz, 3H); 1.32 (t, J= 7Hz, 6H); 1.18-2.72 (m, 7H); 4.05 (dq, J= 7 Hz, J= Hz, 4H); 6.74 (dm, J= 23 Hz, 1H).

Elemental Analysis:

[C(11)H(21)O(3)P]

	Calculated	Found
C%	56.88	56.53
H%	9.11	9.37

SYNTHESIS OF DIETHYL 4-t-BUTYL-1-CYCLOHEXENYLPHOSPHONATE: [XVII]

To a 50 mL, one-necked flask equipped with a short Vigreaux column, a Dean-Stark trap, a condenser, and topped with a nitrogen inlet tube was placed copper(I) bromide-triethyl phosphite complex (16.60 g, 0.052 mole) and 4-t-butyl-1-cyclohexenyl chloride (6.04 g, 0.035 mole). The mixture was then heated under a nitrogen atmosphere at $200-205^{0}$ C (external oil bath) and the volatile materials were collected in the Dean-Stark trap. The heating was performed until no more volitiles were distilled. After cooling to room temperature the reaction mixture was poured into 60 mL of toluene. Then ethylenediamine (6.7 mL) was added to the solution dropwise while stirring. The solids formed were filtered off and washed well with toluene. The filtrate was acidified with 10% hydrochloric acid and extracted with ether. The organic phase was washed with water. The aqueous phase was extracted with ether. The combined organic phase was dried over magnesium sulfate and the solvent evaporated under reduced pressure. The crude product thus isolated was chromatographed on silica gel eluting with 1:1 hexane ethyl:acetate mixtures, followed by distillation, to give the pure desired product (5.26 g, 55% yield).

b.p. 121^{o}C/ 0.4 Torr.

Rf. : 0.42 (1:1 hexane : ethyl acetate).

IR(CCl$_4$) cm^{-I}: 3675; 3420(broad); 2960; 1632(C=C); 1540; 1460; 1385; 1360; 1240(P=O); 1155; 1030; 950; 600.

NMR(CDCl$_3$): δ 0.88 (s, 9H); 1.32 (t, J= 7 Hz, 6H); 1.25-2.76 (m, 7H); 4.03 (dq, J= 7 Hz, J= 7 Hz, 4H); 6.78 (dm, J= 22 Hz, 1H).

Elemental Analysis:

[C(1)4H(27)O(3)P]

	Calculated	Found
C%	61.21	61.31
H%	9.92	9.98

SYNTHESIS OF DIETHYL 1-CYCLOOCTENYLPHOSPHONATE: [XVIII]

To a 50 mL, one-necked flask equipped with a short Vigreaux column, a Dean-Stark trap, a condenser, and topped with a nitrogen inlet tube was placed copper(I) bromide-triethyl phosphite complex (16.60 g, 0.052 mole) and 1-cyclooctenyl chloride (5.06 g, 0.035 mole). The mixture was then heated under a nitrogen atmosphere at 200-205 °C (external oil bath) and the volatile materials were collected in the Dean-Stark trap. The heating was performed until no more volitiles were distilled. After cooling to room temperature the reaction mixture was poured into 60 mL of toluene. Then ethylenediamine (6.7 mL) was added to the solution dropwise while stirring. The solids formed were filtered off and washed well with toluene. The filtrate was acidified with 10% hydrochloric acid and extracted with ether. The organic phase was washed with water. The aqueous phase was extracted with ether. The combined organic phase was dried over magnesium sulfate and the solvent evaporated under reduced pressure. The crude product thus isolated was chromatographed on silica gel eluting with 1:1 hexane:ethyl acetate mixtures, followed by distillation, to give the pure desired product (6.03 g, 71.4% yield).

b.p. 95 °C/ 0.65 Torr.

Rf.: 0.28 (1:1 hexane : ethyl acetate).

IR(CCl_4) cm^{-I}: 3675; 3420(broad); 2970; 2928; 1628(C=C); 1540; 1435; 1253(P=O); 1160; 1090; 1030; 970; 540.

NMR($CDCl_3$): δ 1.28 (t, J= 7 Hz, 6H); 1.35-2.62 (m, 12H); 3.97 (dq, J= 7 Hz, J= 7 Hz, 4H); 6.68 (dq, J= 23 Hz, J= 9 Hz, 1H).

Elemental Analysis:

[C(12)H(23)O(3)P]

	Calculated	Found
C%	58.52	58.15
H%	9.41	9.73

SYNTHESIS OF BOC-ALANYL-SERYL-O-BENZYL ESTER [XIX]

BOC-Alanine (10 g, 52.8 mmole) was dissolved in 160 mL THF and TEA (7.34 mL, 52.8 mmole). The solution was cooled in an ice-acetone bath. Isobutylchloroformate (7.28 mL, 52.8 mmole) was dissolved in 30 mL THF. This solution was added to the solution of BOC-alanine in 1 mL portions with colling and swirling. O-benzyl serine (10.3 g, 52.8 mmole) was dissolved in 52 mL of 1.15 N sodium hydroxide and 160 mL dioxane. This mixture was cooled in ice and then added to the anhydride solution. The reaction mixture was left in the cold for 4 hours and then overnight at room temp. The reaction mixture was freed from the solvent by evaporation under vacuum. The residue was treated with 150 mL hot ethyl acetate and the resulting solution was treated with 150 mL of 1 N hydrochloric acid. The aqueous layer was drawn off and the ethyl acetate layer was washed with two 100 mL portion of water. The ethyl acetate layer was extracted with three 40 mL portions of aqueous sodium bicarbonate solution which were combined and acidified with 1 N hydrochloric acid. The acidified suspension was extracted with 100 mL portions of ethyl acetate which were washed three times with 70 mL water and dried over anhydrous sodium sulfate. Evaporation of the solvent left an oil which was crystallized with ethyl acetate and petroleum ether (11 g, 60% yield).

Rf.= 0.77 (BuOH:H_2O:Acetic acid; 4:1:1)

Melting Point: 156°C

NMR($CDCl_3$) δ 0.9-1.2 (d, 3H, CH_3); 1.6-1.9 (s, 9H, $C[CH_3]_3$); 2.0-2.2 (d.2H, CH_3); 4-0-4.3 (m, 2H, CH); 4.4-4.7 (s, 2H, $CH_2C_6H_5$); 5.1-5.3 (broad, 1H, NH); 5.5-5.8 (broad, 1H, NH); 7.4 (s, 5H, C_6H_5); 11.0 (s, 1H, COOH).

Elemental Analysis:

[C(18)H(26)O(6)N(2)]

	Calculated	Found
C%	59.00	58.82
H%	7.15	7.37

SYNTHESIS OF BOC-ALANYL-(β-BENZYL)-SERYL-ALANINE-O-t-BUTYL ESTER: [XX]

A solution of the dipeptide (18) (11 g, 30.0 mmoles) and 5.4 g, 30 mmoles) alanine-t-butyl ester hydrochloride in 200 mL dichloromethane was cooled to -10 C. Triethylamine (4.00 mL, 30 mmoles), DCC (10.00 g, 48 mmoles) and DMAP (40 mg.) were added to the stirred mixture which was maintained at -10°C for 2 hr. After warming to room temperature overnight, a few drops of glacial acetic acid were added and after a further 1 hr. the DCU ppt were removed by filtration. The organic layer was washed with 5% sodium bicarbonate solution, water, cold 1 N hydrochloric acid and water and then evaporated to yield 9.3 g, 60% yield of the tripeptide [XX].

Rf. 0.88 (BuOH:H_2O:AcOH ::6:1:1)

Melting Point: 124^{o} C

NMR ($CDCl_3$): δ 0.8-1.4 (m, CH_3, $C[CH_3]_3$); 1.8-2.0 (d, 2H,CH_2); 3.8-4.1 (m,2H, CH); 4.4-4.6(s, 2H, $CH_2C_6H_5$); 5.0-5.2 (broad, 1H, NH); 5.9-6.1 (broad, 1H, NH); 7.4 (s, 5H, C_6H_5).

IR($CHCl_3$) cm^{-I}: 3570, 2990, 2940, 1720, 1670, 1500, 1370, 1300, 1100, 1050, 850.

Elemental Analysis:

[C(25)H(39)O(7)N(3)]

	Calculated	Found
C%	60.83	60.78
H%	7.96	7.79

SYNTHESIS OF BOC-ALANYL-SERYL-ALANINE-O-t-BUTYL ESTER [XXI]

A suspension of 0.2 g, of Pd-C catalyst (10%) in absolute ethyl alcohol with a few drops of glacial acetic acid and 8.00 g, (16.6 mmoles) of BOC-Alanyl-(-benxyl)-seryl-alanine-O-t-butyl ester was hydrogenated at atmospheric pressure until no further uptake of hydrogen occured. The reaction mixture was filtered free from the catalyst and the filtrate was evaporated under reduced pressure. The residue was crystallized from ethyl acetate-petroleum ether yielding 6.00 g, (91%) of pure [XXI].

M.P. 104^{o} C

Rf. 0.76 (BuOH:H_2O:AcOH ::6:1:1)

$[\alpha]_D^{25}$= -17 (c 0.3, MeOH)

TLC indicated a small portion of starting material remaining which could not be separated easily. This was confirmed by the elemental analysis. However, the material was deemed to be of sufficient purity for continuing the reaction sequence. As noted below, the further product could be properly purified.

NMR ($CDCl_3$): δ 0.9-1.2 (d, 6H, CH_2); 1.4-1.8 (s, 18H, $C[CH_3]_3$); 3.9-4.1 (m, 3H, CH); 4.7-4.9 (broad, 1H, NH).

IR ($CHCl_3$) cm^{-I}: 3400, 2980, 2920, 1710, 1660, 1450, 1380, 1250, 1050.

SYNTHESIS OF BOC-ALANYL-SERYL-(O-3-HYDROXY-3-METHYL-6-DIETHOXYPHOSPHINYL HEXANOYL)-ALANINE-t-BUTYL ESTER [XXII]

To a stirred solution of 1.8 g, (6.60 mmoles) diethyl 5-carboxy-4-hydroxy-4-methylpentyl-1-phosphonate in 20 mL anhydrous dichloromethane was added 1.0 gm. DMAP and 3.4 g, (5.09 mmoles) of the tripeptide, [XXI]. DCC (3.0 g,) was added to the reaction mixture at 0°C which was then stirred for 35 min. at 0°C and 3 hr at 25°C. Precipitated DCU was then filtered off and the filtrate evaporated under vacuum. The residue was then taken up in ethyl acetate and filtered free of any further precipitated DCU. The ethyl acetate layer was washed twice with 0.5 N hydrochloric acid, twice with 5% sodium bicarbonate solution and then dried over sodium sulfate. The solvent was removed by evaporation and the ester [XXII] was isolated by crystallization from ethyl acetate-petroleum ether and further purified on a short silica gel column to yield 2.4 g, (52%) of product.

Rf.= 0.88 (BuOH:H_2O:AcOH::6:1:1)

TLC showed one spot both in ninhydrin & phosphorus spray.

NMR.($CDCl_3$) δ 0.7-0.8 (s, 3H, CH_3); 0.9-1.1 (d, 6H, CH_3); 1.3-1.6 (m, 31H, 3CH_2, C[CH_3]$_3$); 2.4-2.6 (q, 4H. CH_2); 3.8-4.0 (m, 2H, CH); 5.4-5.6 (broad, 1H, NH); 6.0-6.2 (broad, 1H, NH).

IR:($CHCl_3$) cm^{-I}: 3400, 2900, 1710, 1675, 1500, 1250, 1150.

Elemental Analysis:

[C(24)H(54)O(12)N(3)P]

	Calculated	Found
C%	52.16	52.35
H%	8.15	8.30

SYNTHESIS OF ALANYL-SERYL-(O-3-HYDROXY-3-METHYL-6-DIHYDROXYPHOSPHINYL HEXANOYL)-ALANINE: [XXIII]

Boc-alanyl-seryl (O-3-hydroxy-3-methyl-6-diethoxyphosphinyl hexanoyl)alanine-t-butyl ester (1.0 g. 16.47 mmoles) was dissolved in THF and 15 mL TFA was added and stirred for 15 minutes at room temperature. The solvent was evaporated under vacuum and the residue was washed six times with hexane. The product was dried and dissolved in dry acetonitrile and bromotrimethylsilane (10.8 mL, 82.2 mmoles) was added dropwise under a nitrogen atmosphere . The mixture was stirred at room temperature for 48 hours. The resulting solution was filtered off rapidly and washed with dry ether. Upon removing low boiling material from the filtrate with an evaporator, the corresponding silyl ester was obtained as an oily residue. This was dissolved in methanol and the mixture was concentrated to dryness to the free phosphonic acid.

Rf. 0.50 (BuOH:H_2O:AcOH::6:1:1). TLC showed single spot both in ninhydrin and phosphorus spray.

NMR ($CDCl_3$): δ 0.7-0.9 (s, 3H, CH_3); 1.0-1.2 (d, 6H, CH_2); 1.4-1.7 (m, 6H, CH_2); 4.0-4.3 (m, 2H, CH); 6.0-6.2 (broad, 2H, NH)

IR.($CHCl_3$) cm^{-1}: 3320-3600 (broad); 2980; 1750; 1650; 1500; 1240; 1150.

Elemental Analysis

[C(16)H(30)O(10)P]

	Calculated	Found
C%	42.19	41.90
H%	6.59	6.70

SYNTHESIS OF CARBOBENZOXY-ALANYL-ALANINE-O-t-BUTYL ESTER: [XXIV]

A solution of carbobenzoxy-alanine (10.45 g, 50.0 mmoles) and alanine-O-t-butyl ester hydrochloride (9.08 g, 50.0

mmoles) was cooled to -10^{o} C. Triethyamine (6.96 mL, 50.0 mmole) and DCC (16.50 g, 80.0 mmoles) and DMAP (40 mg.) were added successively to the stirred mixture which was maintained at -10^{o} C for 2 hours. After warming to room temperature overnight, a few drops of glacial acetic acid were added and after a further 1 hour , the DCU precipitate was removed by filtration. The organic layer was washed with 5% sodium bicarbonate solution, cold 1 N hydrochloric acid and water and then evaporated. The residue was crystallized from ethyl acetate-petroleum ether (B.P. 60-90^{o}C) to yield 16 g, (87%) of dipeptide as white crystals.

Rf.=0.77 (BuOH:H_2O:AcOH::4:1:1)

$[\alpha]_D^{25}$ = -10 (c 0.5, MeOH)

M.P. 202^{o}C

NMR($CDCl_3$): δ 1.2-1.4 (d,d, 6H, 2 CH_3); 1.5-1.8 (s, 9H, $C[CH_3]_3$); 4.1-4.7 (m, 2H, CH_2); 5.5-5.8 (d, 1H, NH); 7.4 (s, 5H, C_6H_5).

IR($CHCl_3$):cm^{-1}: 3420, 2900, 2940, 1720, 1670, 1500, 1380.

Elemental Analysis:

[C(18)H(26)O(5)N(2)]

	Calculated	Found
C%	61.69	61.80
H%	7.47	7.65

SYNTHESIS OF ALANYL-ALANINE-O-t-BUTYL ESTER: [XXV]

A suspension of 0.2 g of Pd-C catalyst (10%) in absolute ethyl alcohol with a few drops of glacial acetic acid, and 16.00 g (45.65 mmoles) of N-carbobenzoxy-alanyl-alanine-t-butyl ester was hydrogenated at atmospheric pressure until no further uptake of hydrogen occured. The reaction mixture was filtered free from the catalyst through celite and the filtrate was evaporated under reduced pressure. The residue was crystallized from ethyl acetate-petroleum ether yielding 9.50 g, (96.5%) of [XXV].

M.P. 104^{o} C Rf.= 0.78 (BuOH:H_2O:AcOH ::4:1:1)

$[\alpha]_D^{25}$= -4.5 (c 0.18, MeOH).

NMR ($CDCl_3$): δ 1.3-1.5 (d, 6H, 2 CH_3); 1.5-1.6 (s, 9H, $C[CH_3]_3$); 2.0-2.1 (m, 2H, NH); 3.6-3.9 (m, 1H, CH); 4.1-4.4 (m, 1H, CH); 7.7-7.8 (d, 1H, NH).

IR ($CHCl_3$) cm^{-1}: 3340, 2980, 2920, 1740-1650 (broad), 1380, 1160.

Elemental Analysis:

[C(10)H(20)O(3)N(2)]

	Calculated	Found
C%	55.53	55.37
H%	9.32	9.24

SYNTHESIS OF t-BOC-β-BENZYL-ASPARTYL-ALANYL-ALANINE-t-BUTYL ESTER: [XXVI]

t-BOC-L-aspartate-β-benzyl ester (16.4 g, 51.22 mmoles) and alanyl-alnine-O-t-butyl ester (11.0 g, 51.22 mmoles) were dissolved in 100 mL of dry methylene chloride. The solution was cooled in an ice-acetone bath and treated with 20 g, (96.0 mmoles) of DCC in 25 mL of methylene chloride. The reaction mixture was left at 0^{o} C for 2 hours and then at room temperature for overnight. The excess DCC was decomposed by the addition of glacial acetic acid. The reaction mixture was filtered to remove the precipitate of DCU and the filtrate was evaporated under reduced pressure and the residue was dissolved in ethyl acetate . The organic layer was washed twice with 5% sodium bicarbonate and water. The solution was dried with anhydrous magnesium sulfate, filtered and evaporated under vacuum. The residual oil was crystallized in ethyl acetate-petroleum ether and washed with ether, dried in a dessicator over phosphorus pentoxide yielding 23 g, (87%) of [XXVI].

Rf.= 0.92 (BuOH:H_2O:AcOH::4:1:1)

$[\alpha]_D^{25}$=-6.8 (c 0.3, MeOH).

NMR($CDCl_3$) δ : 1.3-1.4 (d, 6H,2CH_3); 1.4-1.7 (s, 18 H, $C[CH_3]_3$); 2.2-2.3 (d, H, CH); 3.0-3.2 (m, 2H, CH); 4.1-4.3 (d, 2H, CH_2); 4.9 9broad, 1H,NH); 5.2-5.3(s, 2H, CH_2); 5.3-5.5 (broad, 1H, NH); 7.4 (s, 5H, C_6H_5).

IR(CHCl$_3$) cm^{-1}: 3400, 2910, 1750, 1650, 1500, 1380.

Elemental Analysis:

[C(26)H(39)O(8)N(3)]

	Calculated	Found
C%	59.87	59.95
H%	7.53	7.65

SYNTHESIS OF t-BOC-ASPARATYL-ALANYL-ALANINE-t-BUTYL ESTER [XXVII]

A suspension of 0.2 g of Pd-C catalyst (10%) in absolute ethyl alcohol with a few drops of glacial acetic acid and 11.00 g (21.08 mmoles) of N-butyloxycarbonyl-β-benzoxyl-asparatyl-alanyl-alanine-t-butyl ester was hydrogenated at atmospheric pressure until no further uptake of hydrogen occured. The reaction mixture was filtered free from the catalyst through celite and the filtrate was evaporated under reduced pressure. The residue was crystallized from ethyl acetate-petroleum ether yielding 7.50 g (82.45%) of [XXVII].

Rf.= 0.70 (BuOH:H$_2$O:AcOH ::4:1:1)

$[\alpha]_D^{25} = -47$ (c 0.34, MeOH).

NMR (CDCl$_3$): δ 1.3-1.4 (d, 6H, 2 CH$_3$); 1.5-1.7 (s, 18 H, 2 C[CH$_3$]$_3$); 2.1-2.2 (m, 2H, CH); 2.9-3.2 (m, 1H, CH); 4.1-4.4 (d, 2H, CH$_2$); 6.2 (broad, 1H,NH); 7.3-7.6 (broad, 2H, NH); 10.3-10.4 (s, 1H, COOH)

IR (CHCl$_3$) cm^{-1}: 3350-3200 (broad), 2900, 1500, 1380, 1160.

Elemental Analysis:

[C(19)H(33)O(8)N(3)]

	Calculated	Found
C%	52.88	52.77
H%	7.70	7.54

SYNTHESIS OF BUTYLOXYCARBONYL-ASPARTYL-[β-(S)-2-HYDROXY-4-BUTOXYPHOSPHINYL-1-BUTYL ESTER)-ALANYL-ALANINE-O-t-BUTYL ESTER: [XXVIII]

A solution of 0.77 g (1.78 mmoles) BOC-asparatyl-L-alanyl-L-alanine-O-t-butyl ester in 20 mL anhydrous dichloromethane was cooled to 0°C, and to this solution was added successively 114 mg DMAP and 0.68 g (3.46 mmoles) of DCC and 0.5 g (1.78 mmoles) of dibutyl-(S)-3,4-dihydroxybutyl-1-phosphonate. The solution was stirred in the cold for 3 hours and then overnight at room temperature. Precipitated DCU was then filtered off and the filtrate evaporated under vacuum. The residue was then taken up in ethyl acetate and filtered free of any further precipitated DCU. The ethyl acetate layer was washed twice with 5% citric acid, once with water, twice with 10% sodium bicarbonate solution and once again with water. The solution was dried with magnesium sulfate, filtered and evaporated under reduced pressure. The residual oil was dissolved in ethyl acetate, filtered to remove any remaning DCU, and crystallized by the addition of cold petroleum ether. This was purified by passing through a short silica gel column using chloroform and ethanol(1:1) as eluents. The product was dried under high vacuum over phosphorus pentoxide yielding 0.71 g (60%) of pure [XXVIII]. TLC showed a single spot both with ninhydrin and molybdate spray.

Rf.=0.85 (BuOH:$H_2$0:AcOH::4:1:1)

NMR.($CDCl_3$) δ 0.8-2.0 (m, 36H, CH_3); 0.9-1.1 (d, 6H, CH3), $C[CH_3]_3)CH_2CH_2CH_3)$; 2.1-2.2 (s, 2H. CH_2); 2.7-2.9 (m, 2H); 3.9-4.4 (m, 4H, CH); 7.4-7.7 (broad, 3H, NH).

IR:($CHCl_3$) cm^{-1}: 3400, 2900, 1710, 1675, 1500, 1380, 1250, 1150.

Elemental Analysis:

[C(31)H(49)O(12)N(3)P]

	Calculated	Found
C%	54.22	54.00
H%	7.19	7.30

SYNTHESIS OF ASPARATYL-[β -(S)-2-HYDROXY-4-DIHYDROXYPHOSPHINYL-1-BUTYL ESTER)-ALANYL-ALANINE: [XXIX]

The ester [XXVIII] (0.5 g 0.72 mmoles) was dissolved in THF and 15 mL TFA was added and stirred for 15 minutes at room temprature. The liquid was evaporated under vacuum and the residue was washed six times with hexane. The product was dried and dissolved in dry acetonitrile and bromotrimethylsilane (3.5 mL, 3.6 mmoles) was added dropwise under a nitrogen atmosphere . The mixture was stirred at room temperature for 48 hours . The resulting solution was filtered off rapidly and washed with dry ether . Upon removing low boiling material from the filtrate with an evaporator, the corresponding silyl ester was obtained as an oily residue. This was dissolved in methanol and the mixture was concentrated to dryness to yield the free phosphonic acid [XXIX] (81%, 2.5 g).

Rf.= 0.51 (BuOH:H_2O:AcOH::1:1:1)

TLC showed single spot both in ninhydrin and phosphorus spray.

$[\alpha]_D^{32}$ =-2.5 (c 0.165, MeOH)

NMR($CDCl_3$): δ 0.9-1.3 (d, 6H, $2CH_3$); 1.4-1.6 (m, 6H, CH_2); 3.9-4.2 (m, 4H, CH); 7.0-7.3 (broad, 3H, NH); 8.5 (s, 1H, COOH).

IR.($CHCl_3$) cm^{-I} : 3300-3600 (broad), 2970, 1750, 1660, 1500, 1250, 1150.

Elemental Analysis:

[C(14)H(26)O(10)N(3)P]

	Calculated	Found
C%	39.35	39.80
H%	6.13	6.50

SYNTHESIS OF BOC-ASPARATYL-[β -2-OXO-4-DIETHOXYPHOSPHINYL-1-BUTYL ESTER]-ALANYL-ALANINE-t-BUTYL ESTER: [XXX]

A solution of 0.868 g (2.03 mmoles) BOC-asparatyl-alanyl-alanine-O-t-butyl ester phosphonate in 20 mL anhydrous dichloro methane was cooled to $0^{\circ}C$, and to this solution was added successively 50 mg. DMAP and 0.95 g (4.6 mmoles) of DCC and 0.458 g (2.03 mmoles) of diethyl 4-hydroxy-3-oxobutyl-1-phosphonate. The solution was stirred in the cold for 3 hours and then overnight at room temperature. Precipitated DCU was then filtered off and the filtrate evaporated under vacuum. The residue was then taken up in ethyl acetate and filtered free of any further precipitated DCU. The ethyl acetate layer was washed twice with 5% citric acid, once with water, twice with 10% sodium bicarbonate solution and once again with water. The solution was dried with magnesium sulfate, filtered and evaporated under reduced pressure. The residual oil was dissolved in ethyl acetate, filtered to remove any remaning DCU and crystallized by the addition of cold petroleum ether. This was purified by passing through a short silica gel column using chloroform and ethanol(1:1) as eluents. The product was dried under high vacuum over phosphorus pentoxide yielding 0.71 g (59%) of pure [XXX]. TLC showed a single spot both with ninhydrin and molybdate spray.

Rf.= 0.89 ($BuOH:H_2O:AcOH::6:1:1$)

NMR ($CDCl_3$)δ 0.9-2.1 (m, 30H, CH_3, $C(CH_3)_3$; 2.1-2.2 (d, 2H, CH_2); 2.7-3.2 (q, 4H, CH_2); 3.8-4.4 (m, 4H, CH, CH_2); 7.0-7.2 (broad, 3H, NH).

IR:($CHCl_3$) cm^{-I}: 3400, 2920, 1710, 1675, 1500, 1380, 1250, 1150.

Elemental Analysis:

[C(27)H(48)O(12)N(3)P]

	Calculated	Found
C%	50.85	51.00
H%	7.58	7.40

SYNTHESIS OF ASPARATYL-(β-2-OXO-4-DIHYDROXYPHOSPHINYL-1-BUTYL ESTER)-ALANYL-ALANINE: [XXXI]

THe ester [XXX] (0.5 g, 0.71 mmoles) was dissolved in THF and 15 mL TFA was added and stirred for 15 minutes at room temprature. The liquid was evaporated under vacuum and the residue was washed six times with hexane. The product was dried and dissolved in dry acetonitrile and bromotrimethylsilane (3.5 mL, 3.6 mmoles) was added dropwise under a nitrogen atmosphere . The mixture was stirred at room temperature for 48 hours . The resulting solution was filtered rapidly and washed with dry ether. Upon removing low boiling material from the filtrate with an evaporator, the corresponding silyl ester was obtained as an oily residue. This was dissolved in methanol and the mixture was concentrated to dryness to yield the free phosphonic acid [XXXI] (0.25 g, 82%).

Rf.= 0.48 (BuOH:H_2O:AcOH::6:1:1)

TLC showed single spot both in ninhydrin and phosphorus spray.

$[\alpha]_D^{32}$=-4 (c 0.116, MeOH)

NMR.($CDCl_3$) δ 0.9-1.3 (d, 6H, $2CH_3$); 1.4-1.7 (m, 6H, CH_2); 3.9-4.2 (m, 3H, CH); 7.0-7.3 (broad, 3H, NH); 8.2 (s, 1H, COOH).

IR.($CHCl_3$) cm^{-1}: 3300-3600 (broad), 2970, 1720, 1660, 1500, 1250, 1150.

Elemental Analysis:

[C(14)H(24)O(10)N(3)P]

	Calculated	Found
C%	39.55	39.40
H%	6.65	6.70

SYNTHESIS OF t-BOC-γ-BENZYL-L-GLUTAMYL-L-ALANYL-L-ALANINE-t-BUTYL ESTER: [XXXII]

t-BOC-Glutamate-γ-benzyl ester (8.64 g, 25.61 mmoles) and alanyl-alanine-O-t-butyl ester (5.51 g, 25.61 mmoles) were dissolved in 50 mL of dry methylene chloride. The solution was cooled in an ice-acetone bath and treated with 10 gm.(48.0 mmoles) of DCC in 25 mL of methylene chloride. The reaction mixture was left at 0 C for 2 hours and then at room temperature for overnight. The excess DCC was decomposed by the addition of glacial acetic acid. The recation mixture was filtered to remove the precipitate of DCU and the filtrate was evaporated under reduced pressure and the residue was dissolved in ethyl acetate . The organic layer was washed twice with 5% sodium bicarbonate and water. The solution was dried with anhydrous magnesium sulfate, filtered and evaporated under vacuum. The residual oil was crystallized in ethyl acetate-petroleum ether and washed with ether and dried in a dessicator over phosphorus pentoxide yielding 11.9 g (87%) of [XXXII].

Rf.=0.59 (BuOH:H_2O:AcOH::4:1:1)

$[\alpha]_D^{32}$= +25.5 (c 0.51, MeOH).

NMR($CDCl_3$) δ: 1.3-1.4 (d, 6H, $2CH_3$); 1..4-1.7 (s, 18 H, $C[CH_3]_3$); 2.2-2.3 (d, H, CH); 3.0-3.2 (m, 2H, CH); 4.1-4.3 (d, 2H, CH_2); 4.99(broad), 1H,NH); 5.2-5.3 (s, 2H, CH_2); 5.3-5.5 (broad, 1H, NH); 7.4 (s, 5H, C_6H_5).

IR($CHCl_3$) cm^{-I}: 3400, 2910, 1750, 1650, 1500, 1380.

Elemental Analysis:

[C(27)H(41)O(8)N(3)]

	Calculated	Found
C%	60.54	60.75
H%	7.84	8.07

SYNTHESIS OF t-BOC-GLUTAMYL-ALANYL-ALANINE-t-BUTYL ESTER: [XXXIII]

A suspension of 0.2 g of Pd-C catalyst (10%) in absolute ethyl alcohol with a few drops of glacial acetic acid and 11.00 g (20.53 mmoles) of of t-BOC γ-benzoxyl-glutamyl-alanyl-alanine-t-butyl ester [XXXII] was hydrogenated at atmospheric pressure until no further uptake of hydrogen occured. The reaction mixture was filtered free from the catalyst through celite and the filtrate was evaporated under reduced pressure. The residue was crystallized from ethyl acetate-petroleum ether yielding 8.4 g (91.90%) of pure [XXXIII].

Rf.= 0.90 (BuOH:H_2O:AcOH ::4:1:1)

$[\alpha]_D^{32}$= -28.36 (c 0.14, MeOH).

NMR ($CDCl_3$): δ 1.3-1.4 (d, 6H, 2 CH_3); 1.5-1.7 (s, 18 H, 2 $C[CH_3]_3$); 2.1-2.2 (m, 2H, CH); 2.9-3.2 (m, 1H, CH); 4.1-4.4 (d, 2H, CH_2); 6.2 (broad, 1H,NH); 7.3-7.6 (broad, 2H, NH); 10.3-10.4 (s, 1H, COOH)

IR ($CHCl_3$) cm^{-1}: 3350-3200 (broad), 2900, 1500, 1380, 1160.

Elemental Analysis:

[C(20)H(35)O(8)N(3)]

	Calculated	Found
C%	53.92	54.17
H%	7.92	8.04

SYNTHESIS OF BOC-GLUTAMYL-[γ-2-OXO-4-DIETHOXYPHOSPHINYL-1-BUTYL ESTER]-ALANYL-ALANINE-t-BUTYL ESTER: [XXXIV]

A solution of 1.14 g (2.54 mmoles) BOC-glutamylyl-alanyl-alanine-O-t-butyl ester [XXXIII] in 20 mL anhydrous dichloromethane was cooled to 0^{o}C, and to this solution was added successively 125 mg. DMAP, 1.19 g (5.75 mmoles) of DCC, and 0.57 g (2.54 mmoles) of diethyl-4-hydroxy-3-oxobutyl-1-phosphonate. The solution was stirred in the cold for 3 hours and then overnight at room temperature. Precipitated DCU was then filtered off and the filtrate evaporated under vacuum. The residue was then taken up in ethyl acetate and filtered free of any further precipitated DCU. The ethyl acetate layer was washed twice with 5% citric acid, once with water, twice with 10% sodium bicarbonate solution and once again with water. The solution was dried with magnesium sulfate, filtered and evaporated under reduced pressure. The residual oil was dissolved in ethyl acetate, filtered to remove any remaning DCU and crystallized by the addition of cold petroleum ether. This was purified by passing through a short silica gel column using chloroform and ethanol(1:1) as eluents. The product was dried under high vacuum over phosphorus pentoxide yielding 0.85 g (51%) of pure [XXXIV].

TLC showed a single spot both with ninhydrin and molybdate spray. Rf.=0.89 (BuOH:$H_2$0:AcOH::6:1:1)

$[\alpha]_D^{32} = -8$ (c 0.14, MeOH)

NMR.($CDCl_3$)δ 0.9-2.1 [m, 30H, CH_3) $C(CH_3)_3$]; 2.1-2.2 (d, 2H, CH_2); 2.7-3.2 (q, 4H, CH_2); 3.8-4.4 (m, 4H, CH, CH_2); 7.0-7.2 (broad, 3H, NH).

IR:($CHCl_3$) cm^{-I}: 3400, 2920, 1710, 1675, 1500, 1380, 1250, 1150.

Elemental Analysis:

[C(28)H(50)O(12)N(3)]

	Calculated	Found
C%	51.61	51.90
H%	7.73	8.00

SYNTHESIS OF GLUTAMYL-(γ -2-OXO-4-DIHYDROXYPHOSPHINYL-1-BUTYL ESTER)-ALANYL-ALANINE: [XXXV]

The ester [XXXIV] (0.5 g, 0.76 mmoles) was dissolved in THF and 15 mL TFA was added and stirred for 15 minutes at room temperature. The solvent was evaporated under vacuum and the residue was washed with six times with hexane. The product was dried and dissolved in dry acetonitrile and bromotrimethylsilane (3.5 mL, 3.6 mmoles) was added dropwise in the nitrogen atmoshphere . The mixture was stirred at room temperature for 48 hours . The resulting solution was filtered off rapidly and washed with dry ether . Upon removing low boiling material from the filtrate with an evaporator, the corresponding silyl ester was obtained as an oily residue. This was dissolved in methanol and the mixture was concentrated to dryness to yield the free phosphonic acid [XXXV] (0.3 g, 89.9%).

Rf. 0.48 (BuOH:H_2O:AcOH::6:1:1). Although the TLC showed a single spot with both in ninhydrin and phosphorus spray, and the spectra were in accord with the proposed structure, the elemental analysis indicate the presence (6.5%) of silicate which could not be removed.

$[\alpha]_D^{32}$ = -1.3 (c 0.23, MeOH)

NMR.($CDCl_3$) δ 0.9-1.3 (d, 6H, $2CH_3$); 1.4-1.7 (m, 8H, $4CH_2$); 3.9-4.2 (m, 3H, CH); 7.0-7.3 (broad, 3H, NH); 8.2 (s, 1H, COOH).

IR.($CHCl_3$) cm^{-1}: 3300-3600 (broad), 2970, 1720, 1660, 1500, 1250, 1150.

Elemental Analysis:

[C(15)H(27)O(10)N(3)P]

	Calculated	Found
C%	41.01	35.73
H%	5.97	5.89

SYNTHESIS OF t-BOC-GLUTAMYL-[γ -(S)-2-HYDROXY-4-BUTOXYPHOSPHINYL-1-ISOPROPYL ESTER)-ALANYL-ALANINE-O-t-BUTYL ESTER: [XXXVI]

A solution of 0.79 g (1.78 mmoles) BOC-glutamyl-alanyl-alanine-O-t-butyl ester in 20 mL anhydrous dichloromethane was cooled to 0°C, and to this solution was added successively 114 mg. DMAP, 0.68 g (3.46 mmoles) of DCC, and 0.46 g (1.78 mmoles) of diisopropyl (S)-3,4-dihydroxy-1-butyl-1-phosphonate. The solution mixture was stirred in cold for 3 hours and then overnight at room temperature. Precipitated DCU was then filtered off and the filtrate evaporated under vacuum. The residue was then taken up in ethyl acetate and filtered free of any further precipitated DCU. The ethyl acetate layer was washed twice with 5% citric acid, once with water, twice with 10% sodium bicarbonate solution and once again with water. The solution was dried with magnesium sulfate, filtered and evaporated under reduced pressure. The residual oil was dissolved in ethyl acetate, filtered to remove any remaning DCU, and crystallized by the addition of cold petroleum ether. This was purified by passing through a short silica gel column using chloroform and ethanol(1:1) as eluents. The product was dried under high vacuum over phosphorus pentoxide yielding 0.7 g (58%) of pure [XXXVI]. TLC showed a single spot both with ninhydrine and molybdate spray. Rf.= 0.75 (BuOH:H_2O:AcOH::4:1:1).

NMR.($CDCl_3$): δ 0.8-2.0 (m, 6H, CH_3); 0.9-1.1 (d, 36H, CH ,$C[CH_3]_3$) $(CH_3)_2$CH); 2.1-2.2 (s, 2H. CH_2); 2.7-2.9 (m, 2H); 3.9-4.4 (m, 4H, CH_2); 7.4-7.7 (broad, 3H, NH).

IR:($CHCl_3$) cm^{-1}: 3400, 2900, 1710, 1675, 1500, 1380, 1250, 1150.

Elemental Analysis:

[C(30)H(49)O(12)N(3)P]

	Calculated	Found
C%	53.48	53.27
H%	7.33	7.51

SYNTHESIS OF GLUTAMYL-[γ-(S)-2-HYDROXY-4-DIHYDROXYPHOSPHINYL-1-BUTYL ESTER)-ALANYL-ALANINE: [XXXVII]

The ester [XXXVI] (0.5 g, 0.74 mmoles) was dissolved in THF and 15 mL TFA was added and stirred for 15 minutes at room temperature. The liquid was evaporated under vacuum and the residue was washed six times with hexane. The product was dried and dissolved in dry acetonitrile and bromotrimethylsilane (3.5 mL, 3.6 mmoles) was added dropwise under a nitrogen atmosphere . The mixture was stirred at room temperature for 48 hours . The resulting solution was filtered rapidly and washed with dry ether . Upon removing low boiling material from the filtrate with an evaporator, the corresponding silyl ester was obtained as an oily residue. This was dissolved in methanol and the mixture was concentrated to dryness to yield the free phosphonic acid [XXXVII] (0.25 g, 77%).

Rf.= 0.48 (BuOH:H_2O:AcOH::1:1:1). Although the TLC showed a single spot with both ninhydrin and phosphorus spray, and the spectra were in accord with the proposed structure, the elemental analysis indicated the presence (5.5%) of silicate which could not be removed.

$[\alpha]^{32}_{D} = -2.5$ (c 0.165, MeOH)

NMR.($CDCL_3$): δ 0.9-1.3 (d, 6H, $2CH_3$); 1.4-1.6 (m, 8H, CH_2); 3.9-4.2 (m, 4H, CH); 7.0-7.3 (broad, 3H, NH); 8.4 (s, 1H, COOH).

IR.($CHCL_3$) cm^{-I}: 3300-3600 (broad), 2970, 1750, 1660, 1500, 1250, 1150.

Elemental Analysis:

[C(15)H(27)O(10)N(3)P]

	Calculated	Found
C%	41.02	36.54
H%	6.19	6.27

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