PHOSPHINIC ACID SYNTHESIS

by

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University of Kent at Canterbury

A dissertation submitted in partial fulfilment of the requirement for the degree of Doctor of Philosophy in the University of Kent

1990

To Alison

Preface

The work described in this thesis was undertaken at the University of Kent at Canterbury between October 1986 and December 1989, with a period between August and December 1988 spent at Pfizer Central Research, Sandwich. It is original except where otherwise stated and includes nothing which is the outcome of work in collaboration or which has been submitted for any other qualification at this or any other university.

ABSTRACT

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Chapter 1 gives a background to the importance of phosphinic acids, and a description of their physical propeties and chemical reactivity. A review of the more useful methods towards synthesis is given. At the end of the chapter, trivalent silyl phosphonite esters are introduced as potentially useful synthetic reagents. However, only limited work has performed using these species.

Chapter 2 introduces the novel addition of bis(trimethylsilyl) phosphonite to α,β-unsaturated esters under basic silylating conditions. This reaction is optimised and transformed into a useful synthetic method for the preparation of phosphinic acids, named the "triethylammonium phosphinate reaction." Various other electrophiles were used as substrates in this reaction, little success was obtained. Theories are provided to explain side reactions and products, some additional reactions were performed to give evidence to support these theories. A novel reaction between a Mannich base and silyl phosphonite esters, yielding a phosphinic acid, is introduced. The problems of phosphinic acid purification by physical and chemical methods are discussed.

Chapter 3 is concerned with the development of the "triethylammonium reaction" to allow addition of silyl phosphonite esters to α,β-unsaturated ketones. The novel "sodium phosphinate" reaction was developed but little success was achieved, however excellent yields of phosphinic acids were obtained when α,β-unsaturated esters were used as substrates.

Chapter 4 is about developing a new reaction to allow phosphinic acid synthesis using vinyl ketones as substrates, under controlled conditions. This mild reaction was then combined with a novel method of purification forming adamantanammonium phosphinate esters. This flexible methodology was established by the preparation of a variety of substituted phosphinic acids and phosphinate esters.

In chapter 5 adaption of the reaction discovered in chapter 4 was undertaken which, allows the synthesis of phosphinic acids using alkyl iodides. A useful reaction was developed which gives similar products to the Arbuzov reaction, however it is demonstrated that this new reaction does not proceed by the same mechanism.

Chapter 6 gives an account of work undertaken to the phosphinate analogue of platelet activating factor. The original route was unsuccessful, reasons for this are discussed. A shorter alternative route is given, which relies on chemistry developed in this thesis. I have made an attempt to show the utility of the novel methodology contained in this thesis, by giving my ideas on proposed routes to the synthesis of some interesting phosphinate analogues. I consider some of these analogues to be useful biochemical tools.

Acknowledgements

Many thanks to my University supervisor, Dr. A. C. Regan for his helpful advice and enthusiasm, thanks also to Dr. K. James my industrial supervisor. I would also like to thank my fellow chemists in the ACR research group particually Richard Greenhalgh, Paul Mitchell, Alan Smith, John Andrews, Steve Lloyd and Ambo Mahal for there stimulating and enjoyable company throughout this work and thanks also to fellow chemists within Discovery Chemistry at Pfizer Central Research who gave me the opportunity and help in carrying out research within a fine and successful research department.

I am grateful to the staff of the University Chemical Laboratory whose technical assistance helped make this work possible, particular thanks to Ms. M. Williamson and Dr. D. O. Smith.

I am grateful for the partial funding by the Science and Engineering Council and many thanks for the financial support by Pfizer Central Research for the CASE award and also for the generous support while at Sandwich.

Many thanks to John, Zi and Francis for making life more bearable, while writing this thesis.

Special thanks to Alison for the tolerance and support shown until early 1990.

Contents

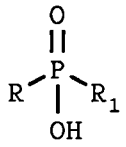
CHAPTER 1.

INTRODUCTION

1.1. Introduction.

The phosphinic acids are a group of phosphorus containing molecules based on the parent, phosphinic acid, (Figure 1.1).

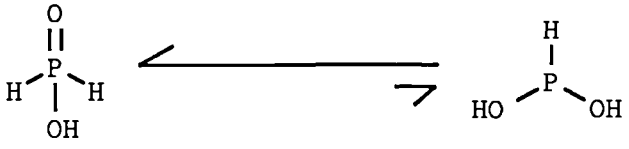
Figure 1.1.



Phosphinic acid, R = R_1 = H

Phosphinic acids are tetrahedral molecules with the exception of the parent phosphinic acid (1) which is in equilibrium with the tautomeric trivalent phosphonous acid (2) (Figure 1.2); however due to the strength of the phosphoryl group the equilibrium is to the left. Phosphinic acid is a relatively strong acid with a pK_a of 1.1.

Figure 1.2.



(1) (2)

Nomenclature within phosphorus chemistry, especially phosphorus oxy-acids, is very confused because chemists have referred to phosphorus containing reagents by different names, and standardising names within a particular group has generally been illogical. One of the main reasons for this is because phosphorus chemistry has been undertaken by both organic and inorganic chemists who have both devised naming systems; biochemists also have an "alternative" nomenclature.

Phosphinic acids were initially called secondary phosphonates, with the parent being called phosphonous or hypophosphorous acid. In this thesis we have been consistent in naming the derivatives of the phosphorus oxy-acids following the recommendations of the American and British chemistry societies in 1952.[1] However even today unconventional names are used so when referring to the oxy-acids cited from the literature to avoid confusion they have been renamed according to these recommendations. A table summarising these recommendations is shown in Table 1.1. Organophosphorus compounds can be envisaged as formed by replacement of the hydrogen atoms in the phosphorus oxy-acids of Table 1.1, by organic groups. If the organic group is directly attached to phosphorus then the name is prefixed, but if the organic group is substituted at an acidic proton site then the organic group is written as a separate word.

e.g. $Et_2P(O)OH$ = diethylphosphinic acid.

$H_2P(O)OEt$ = ethyl phosphinate.

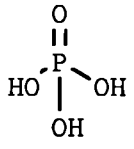
$Et_2P(O)OEt$ = ethyl diethylphosphinate.

All phosphorus acids containing a phosphoryl group end with the suffix "ic", whereas trivalent isomers have the suffix "ous". The corresponding esters are "ates" and "ites" respectively. Compounds with three hydroxy or alkoxy groups on phosphorus have the generic name "phosphor", compounds with two hydroxy and one hydrogen or alkyl/aryl group attached are named "phosphon", and di-substituted compounds with one hydroxy group are called "phosphin".

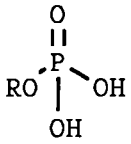
The first naturally occurring phosphinic acid was isolated from cultures of *Streptomyces viridochromogenes*[2] and *Streptomyces hydroscopicus*[3] as the tripeptide phosphinotricyl-L-alanyl-L-alanine (3), (Bialaphos) (Figure

Table 1.1.

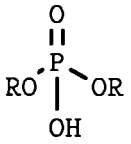
Nomenclature of phosphorus oxy-acids.



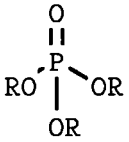
phosphoric acid



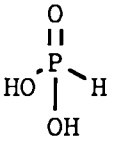
alkyl phosphate



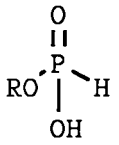
dialkyl phosphate



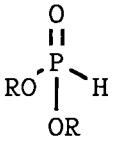
trialkyl phosphate



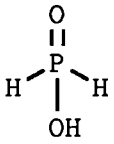
phosphonic acid



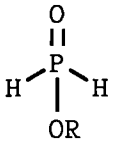
O-alkyl phosphonate



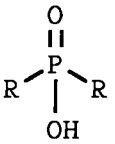
O,O-dialkyl phosphonate



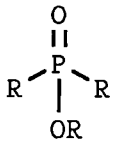
phosphinic acid



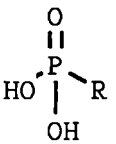
O-alkyl phosphinate



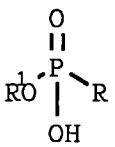
dialkyl phosphinic acid



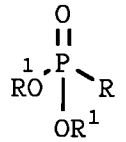
O-alkyl dialkyl-phosphinate



alkyl phosphonic acid



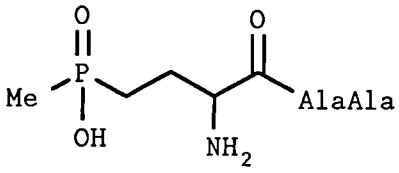
O-alkyl alkyl-phosphonate



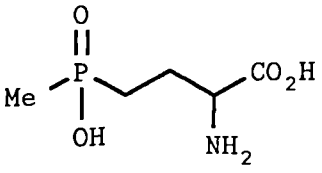
O,O-dialkyl alkyl-phosphonate

1.3). This tripeptide contains a novel amino acid phosphinothricin (4), (2-amino-4-(methylphosphino)butanoic acid) which was found to be highly active against gram positive and negative bacteria. Phosphinothricin is a phosphinate analogue of glutamic acid and has strong herbicidal activity,[4] and is an active glutamine synthase inhibitor.

Figure 1.3.



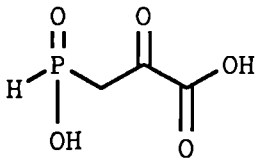
(3) Bialaphos



(4) Phosphinothricin

Recently Seto *et al.*[5] have shown that phosphinopyruvate (5) is a naturally occurring phosphinate intermediate produced by *S. viridochromogenes* in the biosynthesis of bialaphos (Figure 1.4).

Figure 1.4.



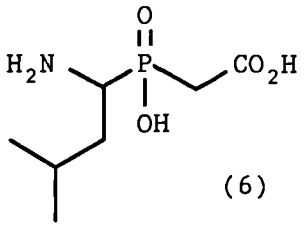
Phosphinopyruvate.

(5)

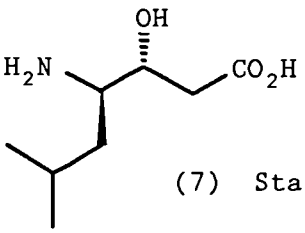
To our knowledge these are the only examples of naturally occurring phosphinic acids. Phosphinothricin highlights the profound biological effect exerted by phosphinate ester analogues of naturally occurring amino acids.[6]

In recent years phosphinate analogues of dipeptides and tripeptide have been synthesised and shown to have enzyme inhibitory properties. Bartlett *et al.*[7] synthesised a phosphinate analogue (6) of the amino acid statine (7), (Figure 1.5), and showed that the incorporation into the appropriate oligopeptide sequence gave a very tight slow binding inhibitor of aspartic peptidase.

Figure 1.5.



(6)



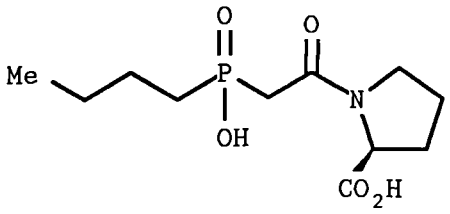
(7) Statine.

Parsons *et al.*[8] synthesised phosphinate analogues of D-Alanyl-D-alanine ligase and showed that the most active analogues are tight binding inhibitors of the enzyme. The mechanism of inhibition by these compounds was proposed to involve an adenosine triphosphate dependent formation of phosphorylated inhibitor at the enzyme's active site.

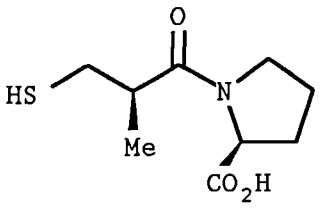
A series of phosphinate analogues of dipeptides and tripeptide analogues were synthesized at the Squibb institute for medical research[9] as possible Angiotensin converting enzyme (ACE) inhibitors, the rational being that the hydroxyphosphoryl of the inhibitor had been shown to bind to the zinc site on the enzyme, resulting in inhibition.[10] Some very potent inhibitors were synthesised, the most potent (8) had an I_{50} of 0.18 μM, (Figure 1.6); this compares favourably with the actual marketed drug developed by Squibb, Captopril (9) (I_{50} = 0.023 μM), which was the first orally active ACE inhibitor and the first specific antihypertensive agent

resulting in it becoming one of the highest selling ethical drugs. Indeed the potential importance of these phosphinic acids and esters can be seen by the fact that many were patented.[11]

Figure 1.6.



(8)



(9) Captopril.

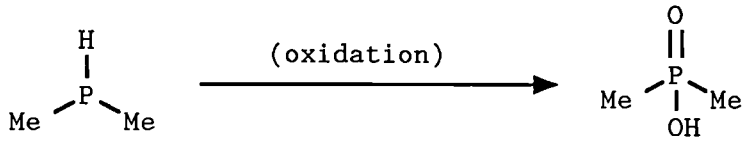
Phosphinic acids can constitute stable mimics of the unstable tetrahedral transition states involved in amide bond formation or hydrolysis, hence they can function as stable transition state analogue enzyme inhibitors. The examples above show that phosphinic acids are of growing importance in understanding and modulating biological processes, therefore novel routes to substituted phosphinic acids are of interest.

1.2 Phosphinic acid synthesis: background.

This section gives a background to the previous syntheses of phosphinic acids, and outlines the more important methods.

A. W. Hoffmann in 1872 synthesized and isolated the first recorded phosphinic acid[12] by fuming nitric acid oxidation of dimethylphosphine (10), to yield crystalline dimethylphosphinic acid (11) (Figure 1.7). The oxidation of secondary phosphines has been little used due to the unstable nature and inaccessibility of the starting phosphines.

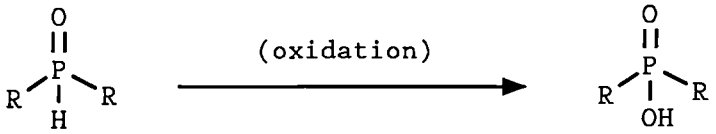
Figure 1.7.



(10) (11)

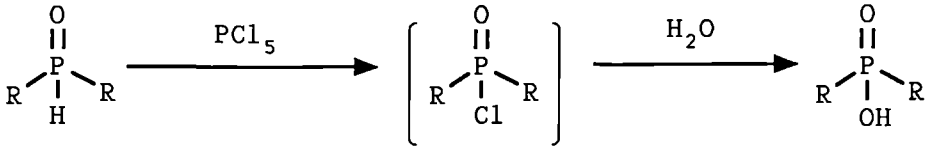
An improvement on the above method of synthesis is oxidation of secondary phosphine oxides (Figure 1.8), prepared from the reaction between dialkyl phosphites[13] or mono alkyl phosphonites[14] and Grignard reagents. The secondary phosphine oxides are much more stable than the corresponding phosphines. The first oxidants used were air or oxygen,[15] but hydrogen peroxide is now preferred.

Figure 1.8.



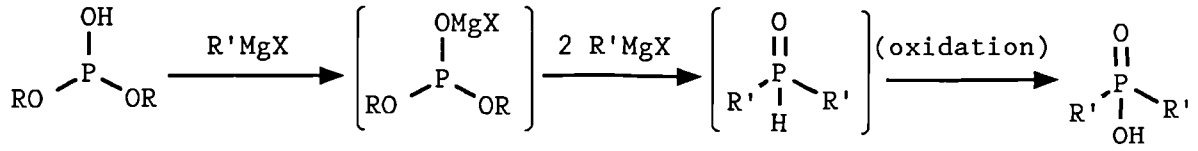
An alternative method of oxidation is chlorination of a phosphine oxide using phosphorus pentachloride to give the phosphinic acid chloride which is not isolated but directly hydrolysed to give the phosphinic acid (Figure 1.9). This method[16] is reported to be more efficient for preparation of higher molecular weight phosphinic acids.

Figure 1.9.



The starting alkyl phosphites can be reacted with a variety of primary,[17] secondary[18] and aryl[19]-magnesium halides, to yield crude dialkylphosphine oxides which can be directly oxidized to the phosphinic acid, (Figure 1.10). The sodium salt of the dialkyl phosphite has been used to overcome excessive use of Grignard reagent.[20] This general method has been used to synthesize many simple symmetrical di-substituted phosphinic acids, owing to the relative accessibility of the starting material. However this method is not suitable towards unsymmetrical di-substituted phosphinic acids.

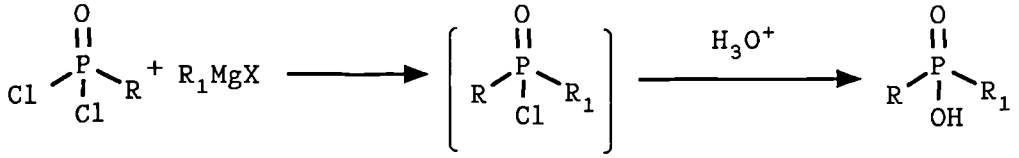
Figure 1.10.



Grignard reagent addition to phosphoryl chloride[21] and chlorophosphonates[22] (Figure 1.11), followed by acidic work-up has been used to prepare phosphinic acids. Generally low yields are achieved using Grignard addition to phosphoryl chloride due to extra Grignard reagent addition taking place, resulting in contamination with tri-substituted phosphine oxide; however this is not observed if sterically bulky phosphonic dichlorides are used.[18,23] Slow reversed addition of Grignard reagent to the substrate has also been reported to be effective against extra addition taking place. Organometallic addition to chlorophosphonates[22,24] is also competitive because Grignard reagents are known to nucleophilicly displace alkoxy[17,18] and aryloxy[19] groups; however if medium sized alkoxy (*e.g.* butyl, isopentyl) groups

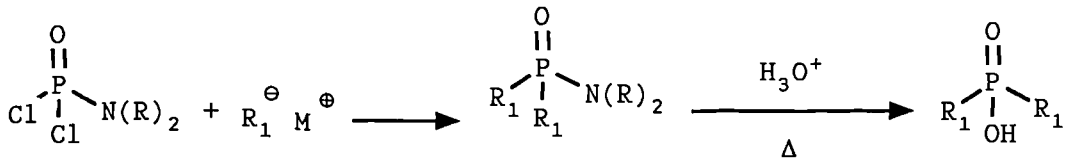
are used only the halide is displaced and hence competitive substitution is avoided.

Figure 1.11.



Phosphinic acids have been synthesized by nucleophilic organometallic attack on phosphonamidic chlorides, followed by acidic hydrolysis, (Figure 1.12). This reaction, analogous to addition to chlorophophonates above has the advantage that the dialkylamide group is more stable to Grignard attack, and hence more controlled addition is achieved. The first recorded example of this reaction was by A. Michaelis[25] in 1903, by the reaction of sodium on N,N-diethylphosphoramidic dichloride and bromobenzene, to synthesize diphenyl phosphinic acid. In all other examples preformed aliphatic[23,26,27] or aromatic[26,27,28] Grignard solutions have been used, and the use of difunctional Grignard reagents resulted in di(phosphinic acids) being prepared. Aryl lithiates have been used for linear phosphinic acid,[29,30] and also cyclic phosphinic acid synthesis.[31]

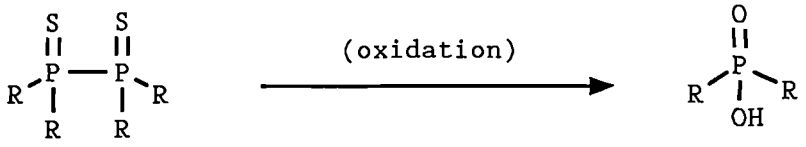
Figure 1.12.



Oxidation of biphosphine disulphides (Figure 1.13), prepared from phosphonyl chloride or phosphonthioic dihalides

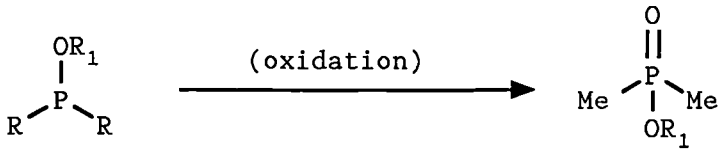
and Grignard reagents to yield phosphinic acids has proved useful for lower molecular weight symmetrical,[32] unsymmetrical[33] and cyclic dialkylphosphinic acids.[34] Oxidation has been achieved using nitric acid and hydrogen peroxide. This method has been particually useful in preparation of dimethylphosphinic acid,[35] which is difficult to synthesize by other methods.

Figure 1.13.



Oxidation of phosphinites to phosphinates, (Figure 1.14) has been achieved using nitrogen oxides[36] and oxygen;[37] if the product is stable to hydrolysis hydrogen peroxide[38] can also be used. The limitation of the method is difficult accessibility of the starting phosphinite, however esters of some acid sensitive alcohols have been obtained by transesterification reactions.[37] The free phosphinic acids can be isolated by acidic hydrolysis.

Figure 1.14.

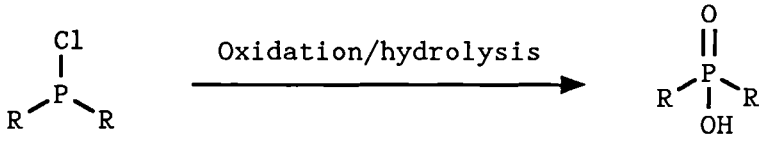


Diphenylphosphinic acid was first prepared by A. Michaelis[39] in 1897 by dilute nitric oxidative hydrolysis of chloro(diphenyl)phosphine. This method, (Figure 1.15) of oxidatively hydrolysing chloro-di-substituted phosphines has

been used to synthesize many phosphinic acids; however non-oxidative hydrolysis has been found to cause disproportionation.[40] Oxidative hydrolysis has been effected by chlorination and hydrolysis,[41] and alkaline hydrolysis.[42] The main drawback of this method is accessibility of functionalised starting materials.

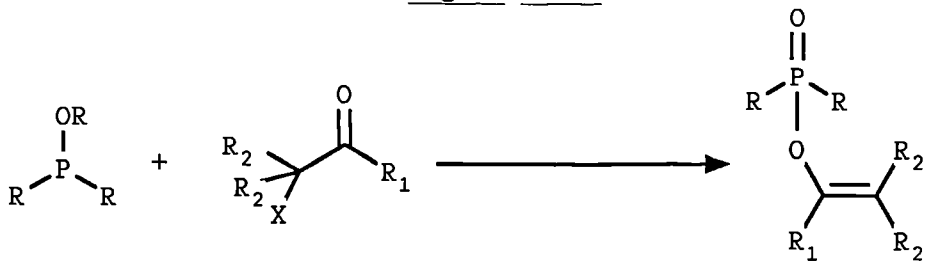
Phosphinic acids have also been synthesized by organometallic addition to trichlorophosphine[43] or substituted chlorophosphines;[22] the resulting crude chloro-di-substituted phosphine is then oxidatively hydrolysed. This method has been little used owing to low yields.

Figure 1.15.



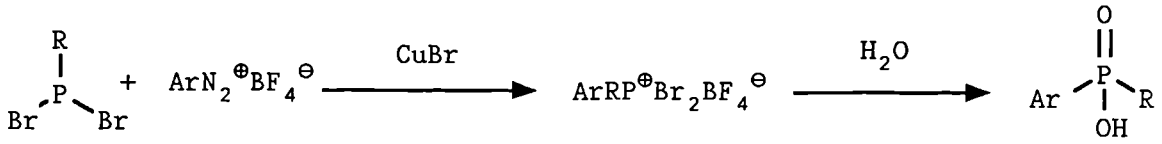
Phosphinate esters have been prepared by the reaction of dialkyl or diaryl phosphinites[44,45] and α-halo carbonyl compounds (Figure 1.16), following the Perkov reaction. These exothermic reactions have to be moderated because high temperatures facilitate the Arbuzov reaction, forming tertiary phosphine oxides.[45]

Figure 1.16.



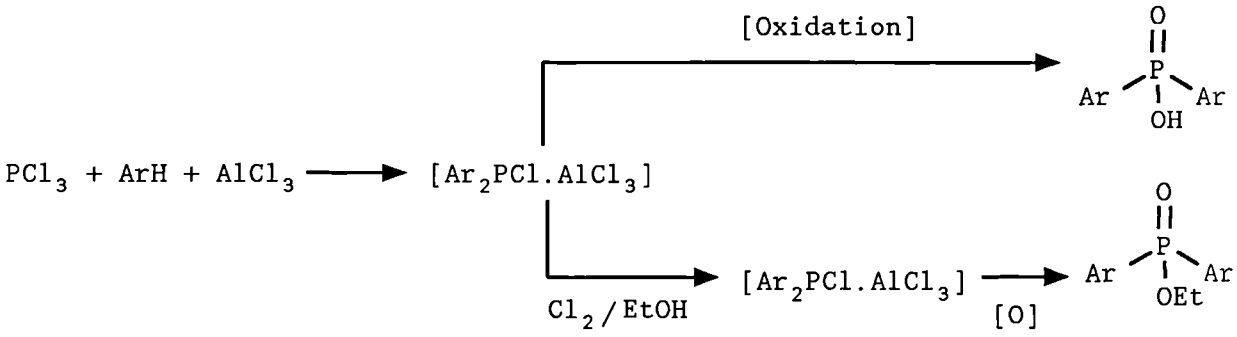
Phosphinic acids can be prepared by the reaction between substituted dihalophosphines or trihalophosphines and aryldiazonium fluoroborates (Figure 1.17). Although initial work used trichlorophosphine,[46] chlorides are not used now owing to very low yields. Use of tribromophosphine and catalytic copper (I) bromide[47] gave higher yields of unsymmetrical dialkylphosphinic acids[48] and alkylarylphosphinic acids.[48,49] This method, although giving variable yields of phosphinic acids, has been reported to be useful in the preparation of diphenylphosphinic acid,[13,49] and gave higher yields than preparation using the Grignard addition to dialkyl phosphites discussed earlier (Figure 1.10).

Figure 1.17.



Diarylphosphinic acids have been synthesized by Friedel-Crafts arylation of trichlorophosphines using aluminium trichloride as the Lewis acid (Figure 1.18). The first preparation[51] used hydrolysis followed by atmospheric oxidation of the aluminium trichloride-arylchlorophosphine complex to isolate the phosphinic acid. An improvement on this method is the preparation of the ethyl phosphinates by chlorination and subsequent ethanolysis of the crude chlorophosphoranes.[52] However if phosphoryl chloride is used instead of trichlorophosphine the reaction fails due to formation of a stable aluminium chloride complex.

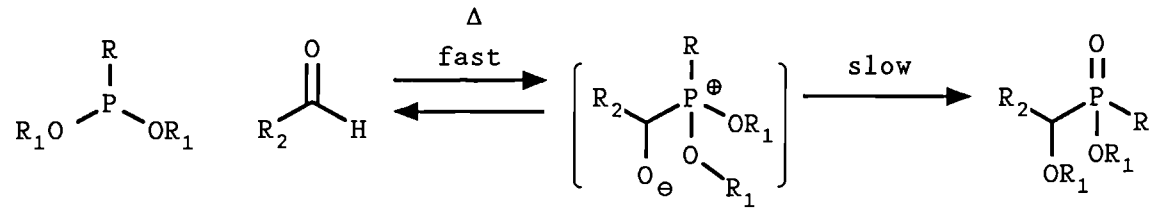
Figure 1.18.



Phosphinic acids have been synthesized by two closely related reactions, which both consist of nucleophilic 1,2-addition at unsaturated electrophilic centres, for example carbonyl and imine groups. Both reactions involve tervalent addition by phosphinic acid or mono-substituted-phosphonites. The Pudovik reaction[53] is catalysed by base however no base is used in the Abramov reaction.[54]

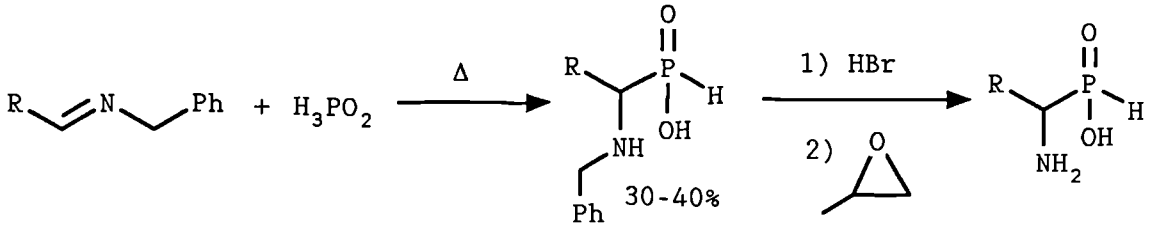
In the Abramov reaction, (Figure 1.19) initial 1,2 nucleophilic attack occurs readily, however the intermediate zwitterionic species is unfavourably orientated for intramolecular dealkylation because rear side attack to carbon by the α-oxy-anion is sterically prohibited, and front side attack is electronically disfavoured.[55] However intermolecular dealkylation is achieved if conditions are used to favour high concentrations of initial adduct.

Figure 1.19.



The Abramov reaction has been used to synthesize phosphinic acids using ketones and aldehydes,[56] and more recently using imines.[57] Starting with phosphinic acid seventeen 1-aminoalkylphosphinic acid isosteres of the protein amino acids have been synthesized by nucleophilic addition to benzyl imines, (Figure 1.20).

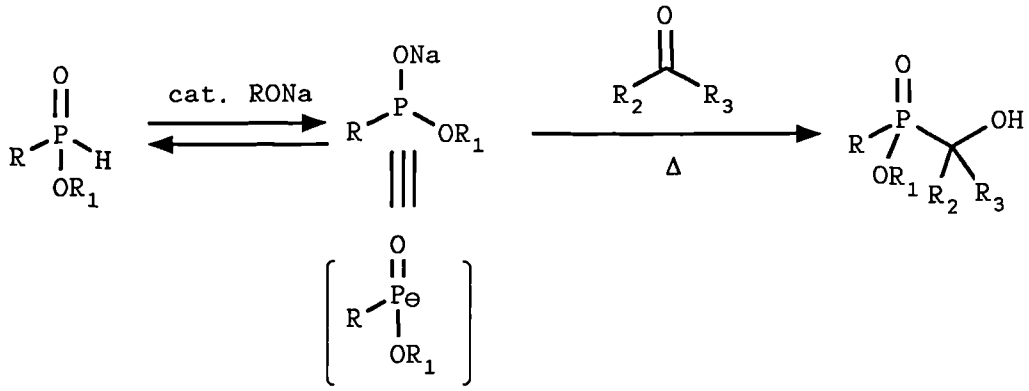
Figure 1.20.



The use of silylating agents has greatly increased the utility of the Abramov reaction. If silyl esters of alkylphosphonites are used, intramolecular desilylation and α-oxy-anion charge neutralization is no longer sterically prohibited. Although much work has recently been directed towards phosphonate synthesis facilitated by silyl esterification very little relevant work has been directed towards phosphinate synthesis.

The Pudovik reaction, (Figure 1.21) consists of anionic nucleophilic addition of a trivalent mono-basic phosphinic acid or substituted phosphonite to a suitable unsaturated electrophilic centre. These species are usually formed from the pentavalent parent phosphinic acids by base catalysed isomerization. Phosphinic acid has been successfully added to carbonyl compounds[58,59] and imines;[60] substituted phosphonites have also been added to carbonyl compounds[59,61] and imines,[62,63,64] and Michael acceptors.[65]

Figure 1.21.



Comparable yields are obtained by both Abramov and Pudovik reactions, however the Pudovik route is usually taken due to the relative ease of obtaining the starting phosphonite, which is catalytically formed from a phosphinate. In contrast the Abramov reaction actually requires the phosphonite as the starting material.

Di-substituted phosphinic acids have been prepared by 1,4 Michael-type addition to α,β-unsaturated Michael acceptors by mono-substituted phosphinates, catalysed by sodium alkoxides. α,β-Unsaturated ketones,[66] esters,[64,67,68] nitriles,[67,69] sulphones[70] and α,β-unsaturated nitroalkanes[70] have all been used to synthesize phosphinic acids (Figure 1.22). If α,β-unsaturated aldehydes or α,β-acetylenic carbonyl[61] reagents are used, 1,2 addition predominates. The free phosphinic acids are prepared from their phosphinate esters by acidic hydrolysis.

Trichlorophosphines undergo cheleotropic 1,4-cycloaddition reactions with 1,3-dienes to yield trichloro-3-phospholenes,[71] which on hydrolysis give cyclic five membered phosphinic acids (3-phospholenes) (12) (Figure 1.23).

Figure 1.22.

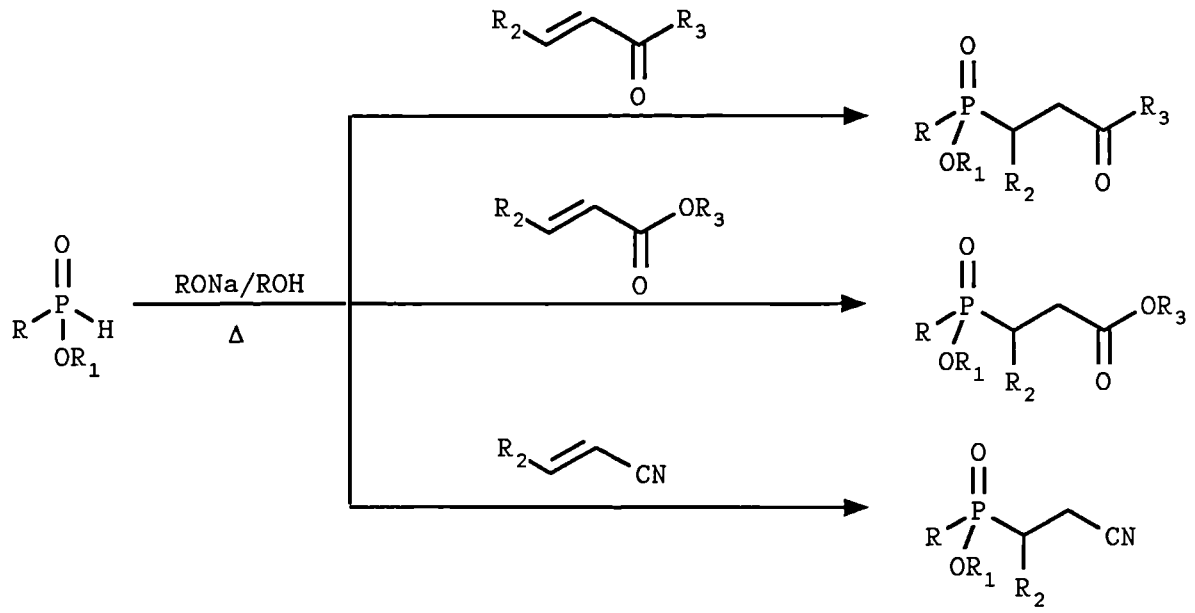
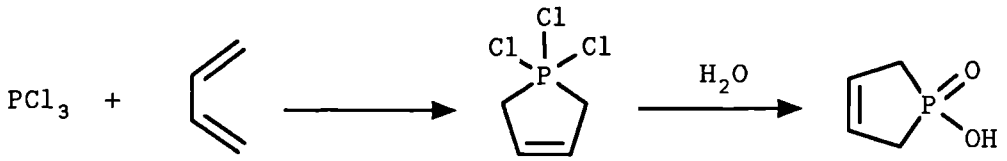


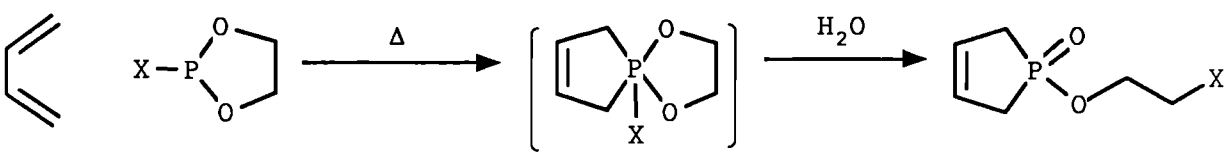
Figure 1.23.



(12)

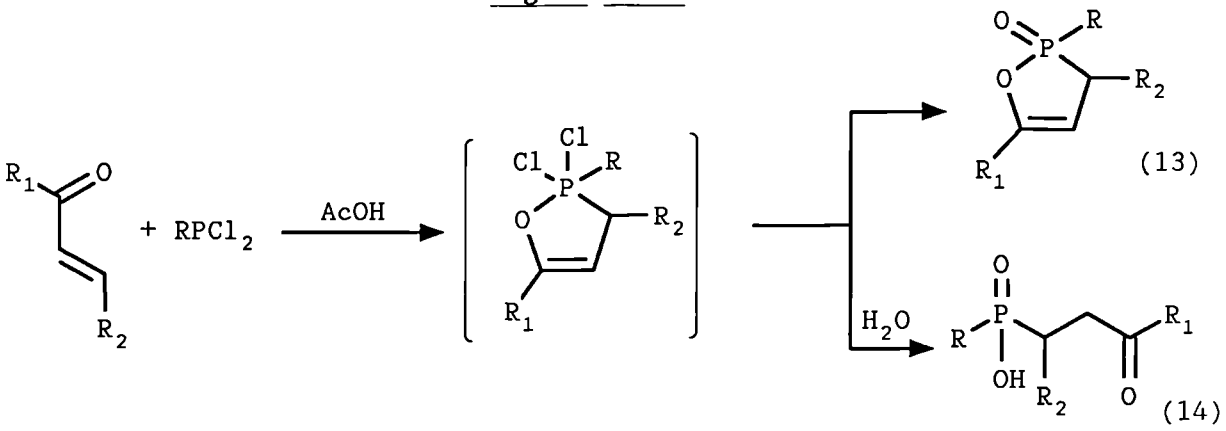
P-(halo)-1,3,2-dioxaphospholane undergoes a similar cheleotropic reaction to yield cyclic phosphinates[72] (Figure 1.24). Heating with water is sometimes necessary to convert the bicyclic phospholenes into the phosphinate esters.[73] The phospholenes are useful phosphinic acid intermediates because of the additional functionality they posses which enables interconversion or modification.

Figure 1.24.



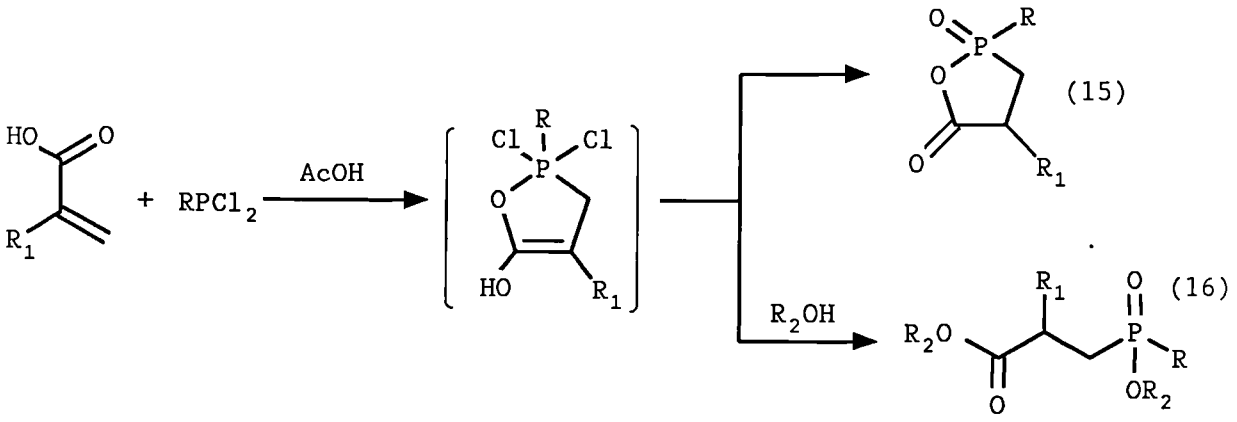
Substituted dichlorophosphines undergo Michael-type cheleotropic reactions with α,β-unsaturated carbonyl compounds, (Figure 1.25) to yield either functionalised cyclic enol ethers (13),[74] or upon hydrolysis the free substituted phosphinic acid (14).[75]

Figure 1.25.



Analogous reactions to those above take place between α,β-unsaturated carboxylic acids and substituted dichlorophosphines,[76] to yield cyclic phosphinic-carboxylic anhydrides (15) or phosphinate esters (16) upon alcoholylsis (Figure 1.26).

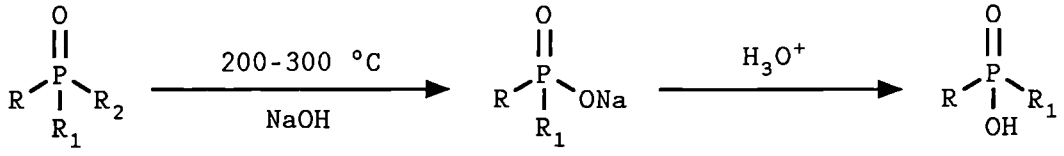
Figure 1.26.



Phosphinic acids have been prepared from tertiary phosphine oxides by fusion at 200-300 °C with potassium or

sodium hydroxide.[77,78] If a substituted phosphine oxide is used the product results from expulsion of the most electronegative leaving group (the most stable carbanion is expelled), resulting in only a single phosphinic acid being synthesized[78,79] (Figure 1.27). The free phosphinic acid is isolated by an acidic work-up. Sodium hydride has also been used in fusion at 160 °C to yield phosphinic acids,[36] following an analogous reaction.

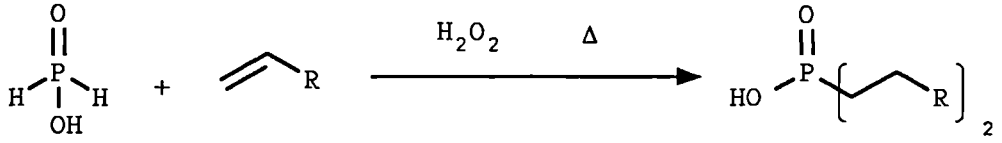
Figure 1.27.



(carbanion stability $R_2 > R_1 = R$)

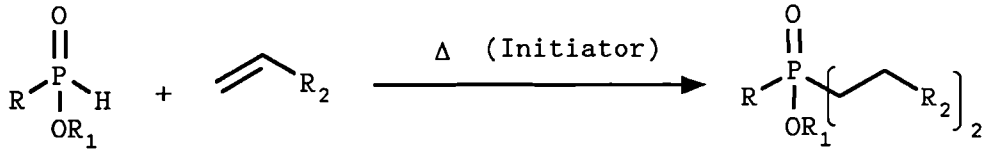
Phosphinic acids have been synthesized by radical initiated terminal alkene addition to 50% aqueous phosphinic acid, [16,81,82] using hydrogen peroxide as the initiator, at elevated temperatures, (Figure 1.28). Di-substituted phosphinic acids have also been prepared from mono-substituted phosphinic acids by analogous radical addition.[82] Phosphinic acids have also been synthesised by the addition of sodium phosphinate[83] to alkenes in an analogous manner to above, however this method was only suitable for higher molecular weight alkenes.

Figure 1.28.



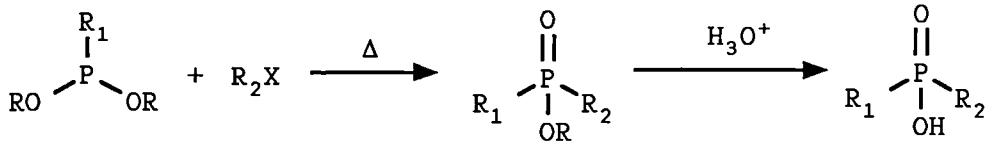
Mono-substituted phosphinates can be converted to di-substituted phosphinates by analogous radical addition, initiated by ultra violet light or dibenzoyl peroxide at elevated temperatures,[84] (Figure 1.29). If acetylenes are used instead of alkenes, mono addition occurs at 80-95 °C[85] and a second addition to the vinyl phosphinate to yield di(phosphinates) at 140-180 °C.[86]

Figure 1.29.



The Arbuzov,[87] (or Michaelis-Arbuzov[88]) reaction is the single most used method to date for the preparation of phosphinate esters of phosphinic acids. The reaction involves the direct nucleophilic displacement of a suitable leaving group, usually halide from carbon by a substituted phosphonite ester (Figure 1.30). This yields a phosphinate ester which upon acidic hydrolysis yields the free phosphinic acid.

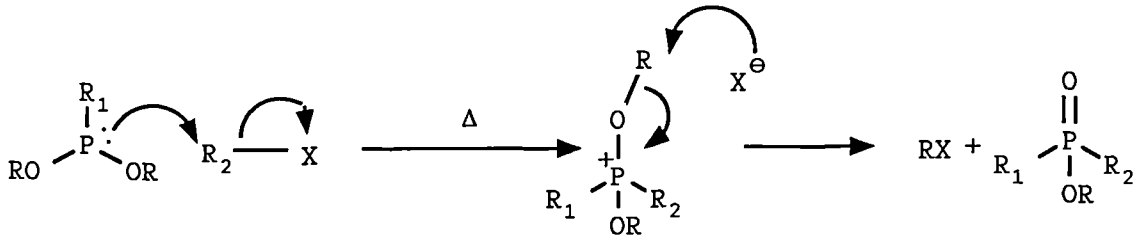
Figure 1.30



The mechanism of reaction has been extensively studied[89] and is classically S_N2, where the substituted halide permits, (Figure 1.31).

The reaction method generally consists of mixing the phosphonite with the substituted halide at room temperature then gradual controlled heating to 120-160 °C for several to

Figure 1.31.



many hours. At the end of reaction the product is isolated as the crude phosphinate ester which can generally be purified by distillation. However some phosphinates are very high boiling and decomposition results on distillation, hence acidic hydrolysis is used to yield the crystalline free phosphinic acids, which can be further purified by recrystallisation.[90,91]

The advantage of the Arbuzov method of phosphinate synthesis is that additional functionality in the phosphinate side chains can be achieved by the appropriate choice of halide, provided the structure of the halide allows S_N2 reaction. For example acyloxy-ethers,[92] alkoxy,[92,93,94] carboxylic esters[94,95,96] tertiary amides,[94,97,98] tertiary amines[94] and nitrile[67] halides have been successfully used for phosphinate ester and free phosphinic acid preparation. Activated halides such as benzyl, allyl, and acyl halides[99] are much more reactive towards phosphonites, and hence the reactions can be performed at lower temperatures. Cyclic phosphinates[100] have been prepared from ω-halo-alkylphosphonites by intramolecular reaction. The use of dihalides results in either halo-alkylphospinates[101] or diphosphinates.[102]

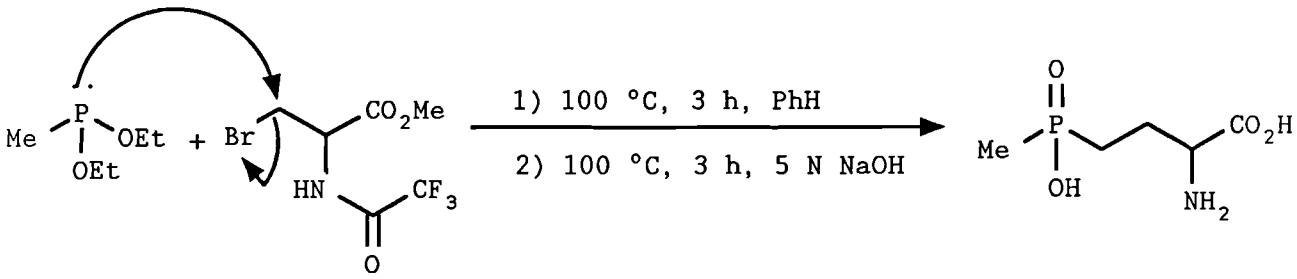
The Arbuzov reaction has a number of limitations, namely restricted starting phosphonite structure, reactivity

of the phosphonite towards other functionality, the use of secondary and tertiary halides and the temperature at which the reaction is performed. Firstly, the substituted phosphonite structure is dependant on the required phosphinate. Before the early 1970's the major substituents in the phosphonite esters were dialkylamino-aryl,[103] aryl,[104] ester[105] and ketone[105] containing groups, which obviously limited the structure of the final phosphinate; however in 1971 silylated phosphonite esters[106] were prepared and subsequently used in the synthesis of phosphinic acids, representing a major advance in synthetic approach. Additional functionality contained in the halide is critical because phosphonite esters will competitively react with for example, primary or secondary amines, carboxylic acids, hydroxy or thiol groups. If secondary and in particular tertiary halides are used elimination reactions predominate, however low yields using secondary halides have been reported in rare cases. The high temperatures at which the Arbuzov reaction is performed causes limitations. If the isomerization is not catalysed, temperatures of at least 240 °C are required,[107] however impurities contained in the phosphonite have been reported to catalyse the reaction.[108] The thermal stability of the phosphonite, halide and product has therefore to be good if they are to withstand these harsh conditions.

Although the Arbuzov reaction has limitations in synthesis it has been successfully used in phosphinate ester and free phosphinic acid preparation. The main area of synthesis has been towards isosteric analogues of biological molecules. Phosphinothricin was originally synthesized by this method,[2] (Figure 1.32); alternative shorter routes using

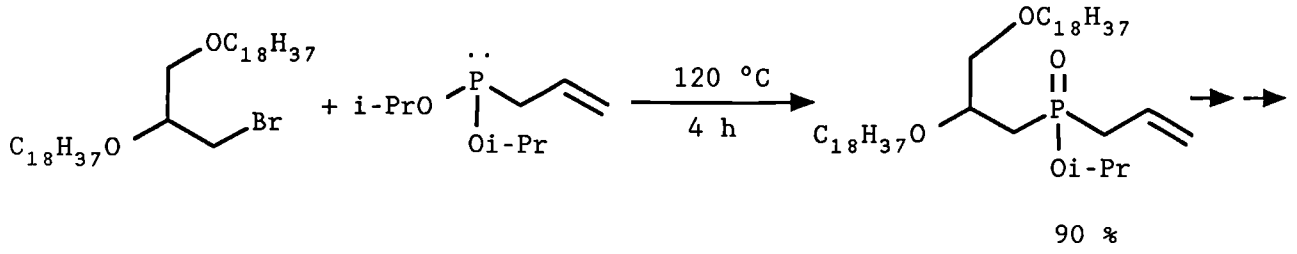
analogous Arbuzov chemistry have also been reported.[109] Various analogues of phosphinothricin have been prepared using benzyl halides and diethyl 2-chloroethylphosphonite;[110] the extra reactivity of the benzyl halide ensures negligible displacement of internal halide.

Figure 1.32.



Various phosphinate analogues of the phospholipid lecithin have been synthesized[111] using the Arbuzov reaction to synthesize a key intermediate suitable for further modification (Figure 1.33). Various other phosphinolipids[112] have been synthesized by Arbuzov methods.

Figure 1.33.

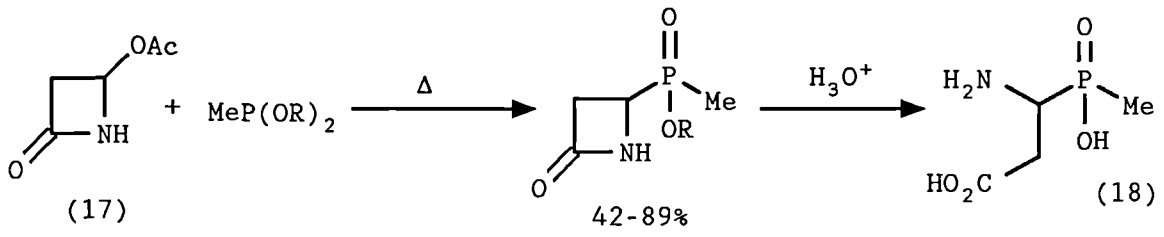


90 %

Phosphinate analogues of pyranose sugars,[113,114] in particular 5-(alkylphosphinyl)-5-deoxy-D-xylopyranoses[114] have been synthesized in high yield using Arbuzov chemistry. In the synthesis of macrocyclic di(phosphine) transition metal chelating ligands,[115] Arbuzov chemistry was used to prepare the key intermediate di(phosphinates).

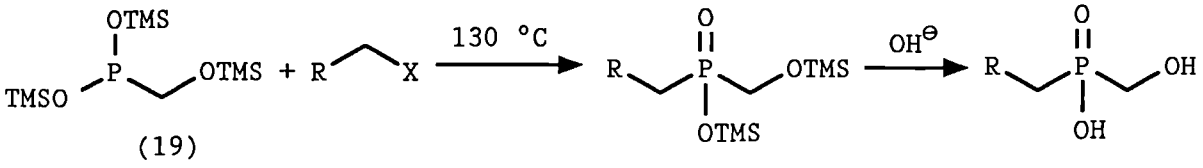
Synthesis of α-amino phosphinic acids and dipetide analogues from 4-acetoxyazetidin-2-ones[116] (17) has been achieved using Arbuzov chemistry by nucleophilic displacement of the acetoxy group to form the new carbon-phosphorus bond. This chemistry is utilized in synthesis of a phosphinic acid analogue of aspartic acid (18) (Figure 1.34).

Figure 1.34.



Rosenthal *et al.*[117] have synthesized bis(trimethylsilyl) trimethylsiloxymethylphosphonite (19) which is a useful reagent for the introduction of the hydroxymethylphosphinate group, an α-functionalised phosphinate (Figure 1.35).

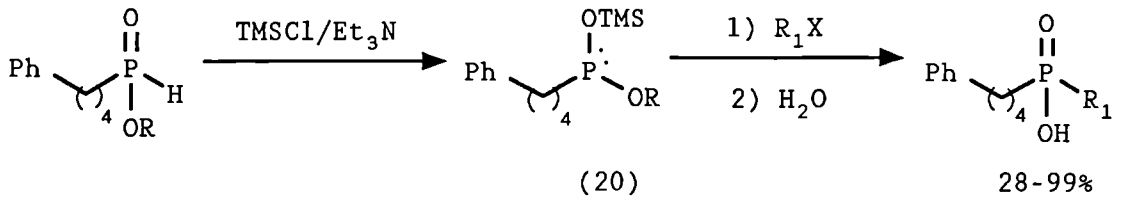
Figure 1.35.



The use of silyl phosphonite esters has greatly expanded the utility of the Arbuzov reaction. Once silyl groups are removed on isomerization an advantage they possess is their inertness to compete with the substrate. Previously the phosphonite ester of choice was the methyl ester, because it was extremely easy to remove. However on isomerization methyl

halide by-products are liberated which are generally more reactive than other alkyl halides and hence they compete with the substrate causing undesired phosphinate ester formation and contamination. This problem is alleviated using trimethylsilyl phosphonites because de-esterification occurs exclusively at the silyl ester site. The free phosphinic acid is easily liberated, often by simple hydrolysis, which means sensitive additional functionality can be incorporated into the electrophilic substrate. In 1984 Thottathil *et al.*[118] synthesized phosphinic acids using silyl alkylphosphonites (20), generated *in situ* from mono-substituted phosphinic acids, and α-bromoesters; these reactions occur readily under very mild conditions at room temperature (Figure 1.36).

Figure 1.36.



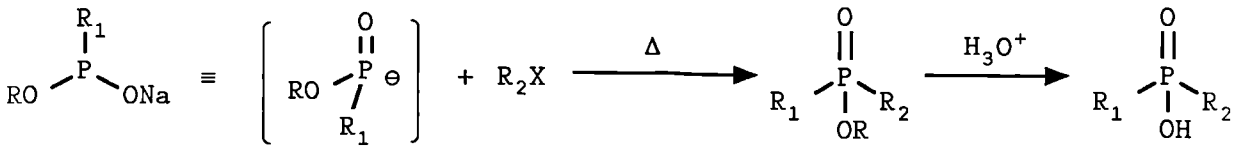
(20) 28-99%

Di-substituted phosphinic acids were also prepared[119] from mono-substituted phosphinic acids in high yield by 1,4 Michael-type addition of (20) to a variety of activated conjugated systems; however addition to crotonaldehyde resulted in 1,2 addition. This very mild Michael type addition avoids the use of metal alkoxide bases in alcoholic solvents which has previously been used.[120]

The Michaelis-Becker reaction[121] involves reaction between salts of mono-substituted phosphonites and alkyl[97,122] and aryl[123] halides to synthesize phosphinate

esters by anionic nucleophilic displacement of a halide ion, for example using the sodium salt (Figure 1.37). Metalation of the mono-substituted-phosphonites increases the relative stability of the reagent and hence is a useful advantage over the Arbuzov preparation, however the need for a reaction solvent can be a disadvantage, because metal salts of phosphonites have limited solubility in the necessary aprotic solvents, and even the use of the free phosphonite as a solvent has had very little success. The sodium salts of mono-substituted phosphonite esters were originally generated by sodium metal reduction of the phosphonite ester, but sodium hydride is a cleaner and more rapid reagent. The lack of solubility of the metallated salts has led to the use of tertiary amines as bases for generation of the anionic phosphonites, the ammonium salts being very much more soluble than their metallated analogues. If the free phosphinic acid is required the crude phosphinate ester can be directly hydrolysed without isolation at the end of reaction.[124]

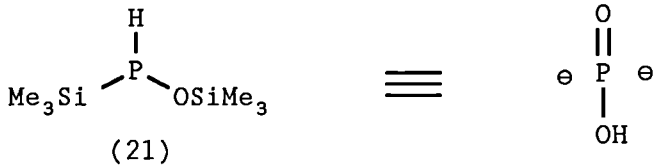
Figure 1.37.



Voronkov[125] in 1971 reported the preparation of bis(trimethylsilyl) phosphonite (21) and showed addition to acrylonitrile at 150 °C in a yield of 49%. However reaction with alkyl bromides resulted in disproportionation instead of the expected phosphinic acid products. Bis(trimethylsilyl)

phosphonite constitutes an equivalent to the synthon (22) (Figure 1.38), and has been used to synthesise phosphinic acids by nucleophilic attack at electron deficient sites.

Figure 1.38.



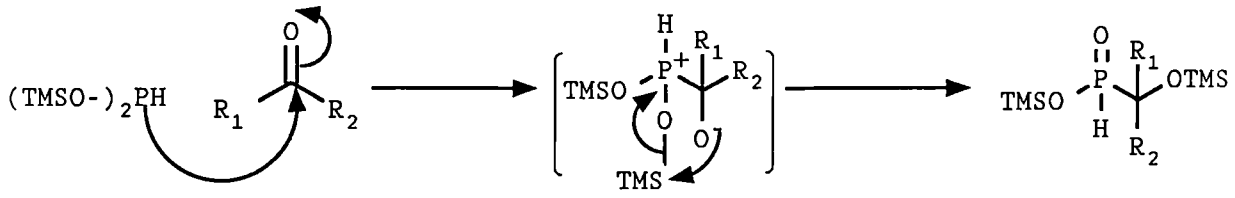
(21)

Bis(trimethylsilyl) phosphonite.

(22)

1,2 addition of bis(trimethylsilyl) phosphonite to carbonyl compounds,[126,127] (Figure 1.39) results in intermediates (23) which have been proposed to undergo intramolecular silyl transfer to give phosphinate derivatives (24). This synthesis is useful for the preparation of α-hydroxyphosphinic acids which are obtained by hydrolysis of (24). Bis addition[128] has been effected by using addition of chlorotrimethylsilane and triethylamine to form substituted silyl phosphonites after initial carbonyl attack by bis(trimethylsilyl) phosphonite. These substituted silyl phosphonites react with a further equivalent of carbonyl compound and on hydrolysis yield di-substituted (α-hydroxyalkyl)phosphinic acids.

Figure 1.39.



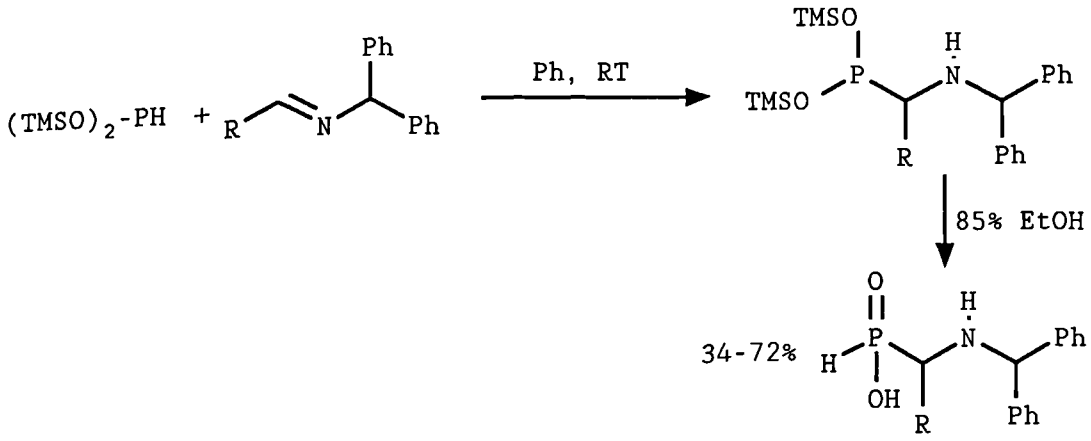
(23)

(24)

In situ generation of bis(trimethylsilyl) phosphonite was found to be convenient and was achieved by the action of trimethylchlorosilane and triethylamine or bis(trimethylsilyl)acetamide on phosphinic acid. This method had the advantage that bis(trimethylsilyl) phosphonite was not isolated and hence eliminated the problems of manipulating and purifying such a reactive reagent. Phosphinic acid synthesis involved addition of the appropriate electrophile to an *in situ* generated solution of bis(trimethylsilyl) phosphonite, followed by hydrolysis of the resulting phosphinate ester to yield the α-hydroxyphosphinic acids in fair yield.

α-Aminoalkylphosphinic acids have been prepared[129] by direct addition of bis(trimethylsilyl) phosphonite to diphenylmethylimines (Figure 1.40). However addition to the imine at the nitrogen atom was observed unless an appropriate imine was used. α-Aminoalkylphosphinic acids have often been prepared by addition of phosphinic acids to N-(diphenylmethyl)imines (see earlier), followed by hydrolysis of the secondary amine; however this generally gave low yields probably due to the use of elevated temperatures. Hence the use of bis(trimethylsilyl) phosphonite for the synthesis of aminophosphinic acids is advantageous.

Figure 1.40.



1.3. Conclusions.

Most of the early methods for the synthesis of phosphinic acids allow only a small group to be synthesised and are not general methods. Many of these methods allow competing reactions producing side products which are often similar in structure to the desired product and hence purification is problematical. For example Grignard addition to phosphoryl chloride can result, after hydrolysis, in a mixture of phosphonic and phosphinic acid, and tertiary phosphine oxide.

Use of functionalised starting materials is important for most methods, however this detracts from the synthetic utility of the reaction for two main reasons. Firstly many methods involve harsh reaction conditions which cannot tolerate sensitive functionality, and secondly these starting reagents may be difficult to synthesise.

The most generally useful synthetic method for phosphinic acids is via the Arbuzov reaction, but often this is not ideal. Although the Arbuzov reaction has been widely used it has some major disadvantages which limit the overall usefulness. The starting halide has to be primary because with most secondary and all tertiary halides elimination reactions predominate. High temperatures (100-200 °C) are generally required which means that starting materials and products must be stable at this temperature.

Most synthetic methods for phosphinic acids start by having functionality in the starting phosphorus reagent. This can be a disadvantage because these reagents have to be synthesised and then transformed. In certain rare cases substituted phosphinic acids have been built up from phosphinic acid, for example the radical initiated addition to alkenes. Recently bis(trimethylsilyl) phosphonite has been shown to be useful in synthesis of phosphinic acids;[127,128,129,130] the use of this reactive species along with phosphinic acid is fundamentally different from the usual methods of preparation, because the only funtionality these starting materials contribute to the final phosphinic acid is the hydroxyphosphoryl group. This is obviously advantageous because simple, standard starting reagents are used which do not limit the final structure of the phosphinic acid.

In section 1.1. the rapidly growing importance of phosphinic acids was established, however there are no standard reactions for the synthesis of phosphinic acids, particually when complicated products are required. In recent years the use of silylated phosphorus reagents has expanded the utility of some methods for the synthesis of phosphinic

acids, however relatively little work has been done in this field. The limited use of bis(trimethylsilyl) phosphonite suggests that this may be a useful general reagent for the synthesis of phosphinic acids; its reactivity towards a small number of electrophiles has been reported but some results are not consistent.[125,130] Little useful synthetic work has been achieved using this species. The work described in this thesis involves the investigation of the reactivity of bis(trimethylsilyl) phosphonite towards a range of electrophiles with the aim to manipulate this reactive species towards a standard versatile methodology, allowing novel and previously inaccessible phosphinic acids to be synthesised conveniently.

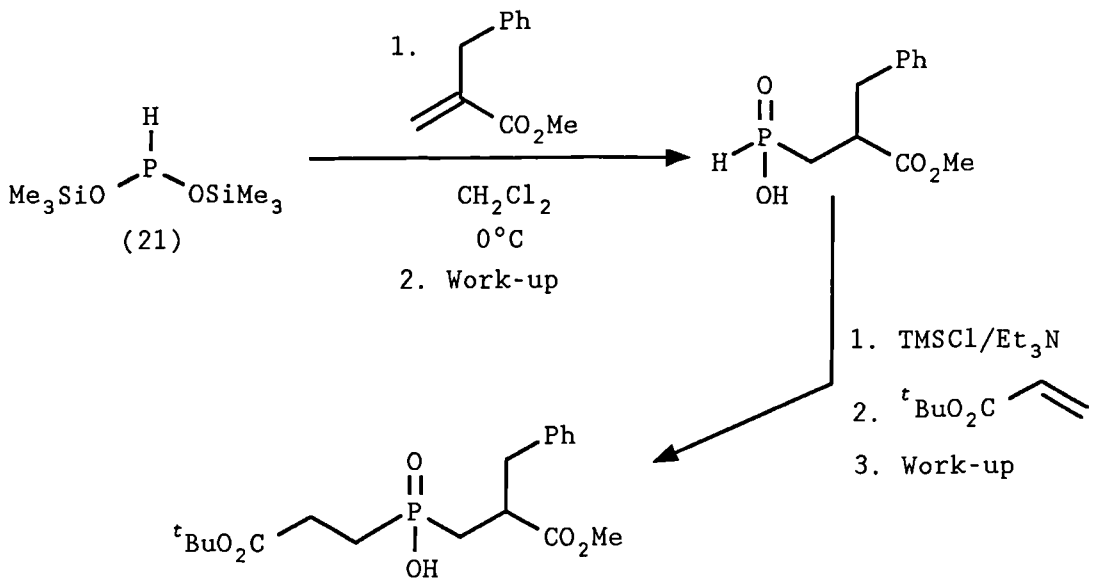
CHAPTER 2.

A NEW SYNTHESIS OF PHOSPHINIC ACIDS

2.1. Introduction.

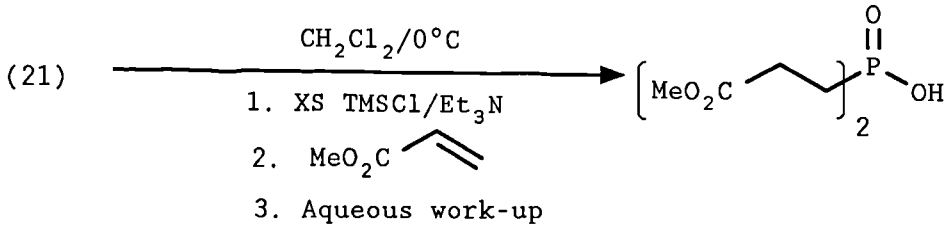
In preliminary investigations in the field of phosphinic acid synthesis, James and Corless at Pfizer Central Research found that bis(trimethylsilyl) phosphonite (21) could be reacted in a 1,4 Michael-type addition to various acrylates, yielding mono-substituted phosphinic acids upon work-up. These mono-substituted phosphinic acids could subsequently be reacted with a second acrylate under chlorotrimethylsilane and triethylamine conditions to yield di-substituted phosphinic acids after work-up (Figure 2.1). Monitoring of the reactions by TLC showed that an excess of both triethylamine and chlorotrimethylsilane were required to push the reaction to completion.

Figure 2.1.



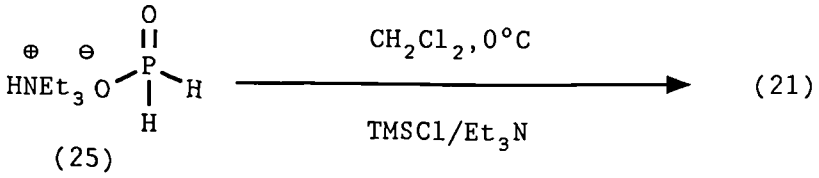
Alternatively, symmetrical di-substituted phosphinic acids were prepared in one step by treatment of (21) with an excess of the chosen acrylate and chlorotrimethylsilane/triethylamine (Figure 2.2).

Figure 2.2.



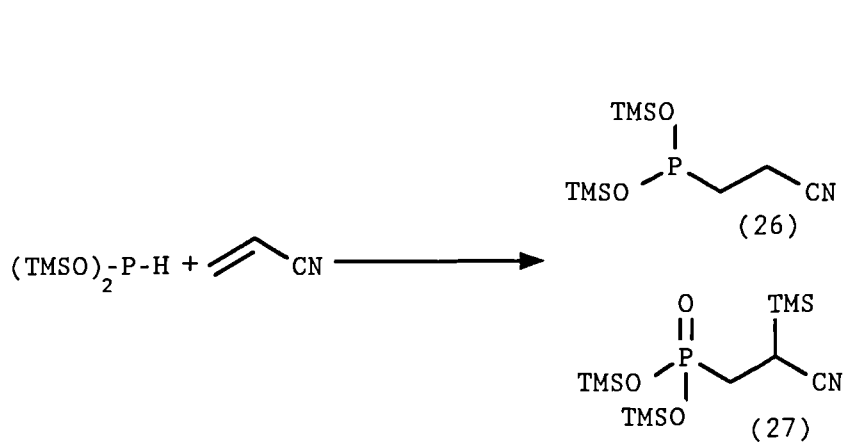
In situ generation and use of (21), from the action of excess triethylamine and chlorotrimethylsilane on triethylammonium phosphinate (25), (Figure 2.3) overcame the need for separate preparation of (21) and the problems associated with isolating and handling this highly reactive and pyrophoric reagent.

Figure 2.3.



This was the first example of bis(trimethylsilyl) phosphonite addition to an α,β-unsaturated ester and preliminary results suggested that this had potential synthetic use towards substituted phosphinic acids. The only 1,4 Michael-type addition by bis(trimethylsilyl) phosphonite to an α,β-unsaturated system reported was by addition to acrylonitrile,[106,130] where Voronkov reported 49% yield of 1,4 Michael-type product (26), and Issleib reported a 36% yield of (26) and a 5% yield of product (27) resulting from 3,4 addition to the vinyl functionality of acrylonitrile (Figure 2.4).

Figure 2.4.



Voronkov	Issleib
Yield (%)	Yield (%)
49	36
0	5

Michael-type addition to a variety of α,β-unsaturated species by a substituted phosphonite, (20) (Figure 1.36) has been reported by Thottathil.[118] Although this transformation is useful there is the drawback that only di-substituted phosphinic acids are synthesised from mono-substituted phosphinic acids, which first have to be prepared by other means. However good yields were generally obtained by this addition. Thottathil[118] reported that on addition to unsaturated aldehydes 1,2 addition to the carbonyl group occurred, and addition to mesityl oxide resulted in a mixture of 1,2 and 1,4 addition products.

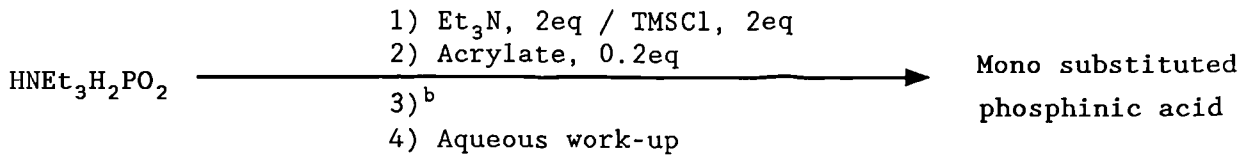
2.2 Phosphinic acids synthesized at Pfizer Central Research.

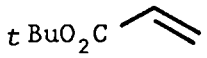
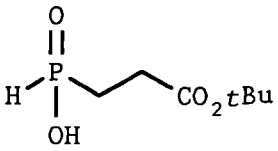
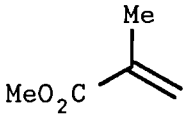
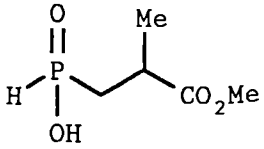
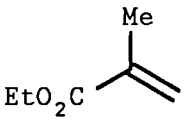
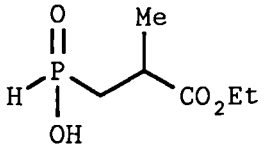
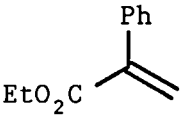
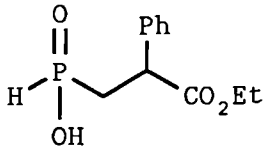
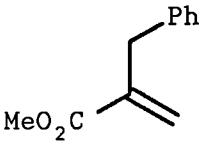
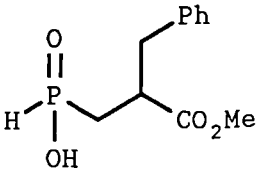
Results obtained at Pfizer Central Research are shown in Table 2.1 for the preparation of mono-substituted phosphinic acids, in Table 2.2 for symmetrical di-substituted phosphinic acids, and in Table 2.3 for unsymmetrical di-substituted phosphinic acids.

Mono-substituted phosphinic acids were synthesized in moderate to good yields and isolated as oils. From the 300

Table 2.1

Mono addition.



Acrylate	Phosphinic acid	Yield (%)
		51[a]
		21[a]
		64[a]
		50[a]
		80

[a] The 300 MHz ^1H spectrum showed trimethylsilyl contamination.

[b] An extra half equivalent of Et_3N/TMSCl was often required to drive the reaction to completion.

MHz ^{1}H NMR spectra the products showed contamination from trimethylsilyl groups, probably resulting from incomplete hydrolysis of the silyl ethers. Although no triethylammonium resonances were observed they may be masked by other resonances. Contamination from symmetrical di-substituted phosphinic acid formation resulting from second addition to acrylate may have occurred, and ^{31}P NMR spectra could be used to elucidate this contamination, (if they had been available).

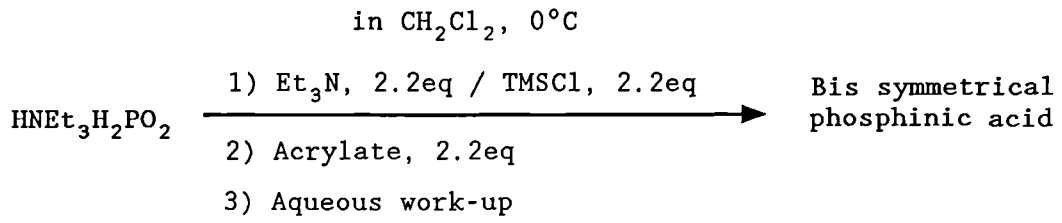
Symmetrical di-substituted phosphinic acids were synthesized in good to excellent yields (apart from when methyl methacrylate was used; the reason for failure in this reaction is unclear). The use of unsubstituted acrylates, gave crystalline phosphinic acids, however the use of ethyl crotonate resulted in an oil which was a mixture of mono- and di-substituted phosphinic acids as seen by the P-H resonance from a very contaminated 300 MHz ^{1}H NMR spectrum.

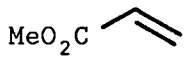
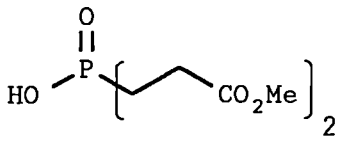
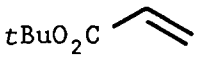
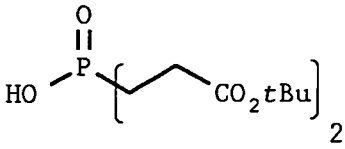
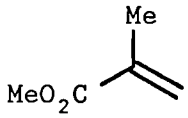
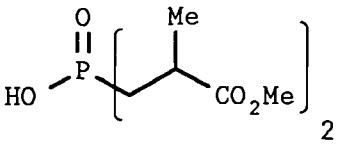
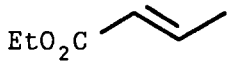
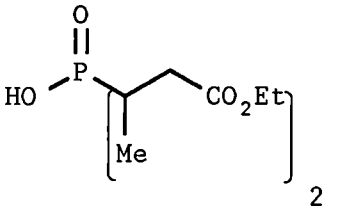
The unsymmetrical di-substituted phosphinic acids were synthesized in good yields after mono-substituted phosphinic acid had been treated with triethylamine and chlorotrimethylsilane followed by addition of the appropriate acrylate and subsequent acidic work-up.

The results obtained at Pfizer Central Research suggested that a new route to mono-, symmetrical and unsymmetrical di-substituted phosphinic acids had been achieved, by 1,4 addition of bis(trimethylsilyl) phosphonite to α,β-unsaturated esters. These reactions were performed under mild conditions at 0 °C to room temperature. The controlled synthesis of relatively complicated unsymmetrical phosphinic acids starting with phosphinic acid itself was particularly useful due to the simplicity of starting

Table 2.2

Bis symmetrical addition.



Acrylate	Phosphinic acid	Yield (%)
		90[a]
		83[b]
		Reaction failed
		77[a,c]

[a] Extra Et_3N (1 eq) and TMSCl (1 eq) were injected after 24h if the TLC showed substantialstarting material present.

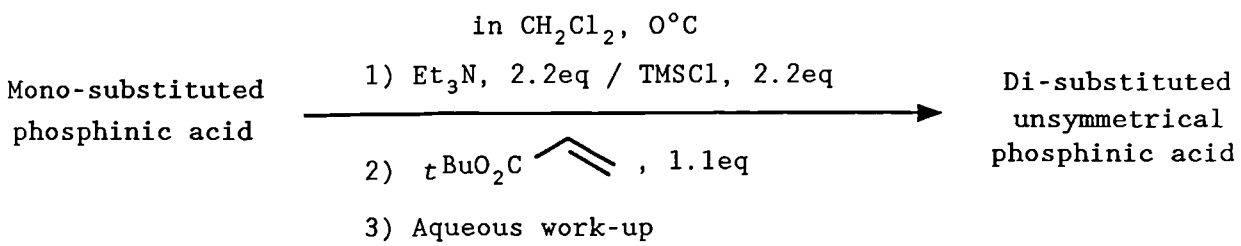
[b] This was an attempted mono addition using excess Et_3N/TMSCl, the yield was calculated on available acrylate.

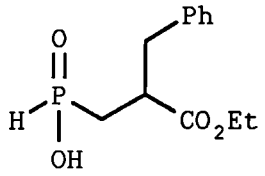
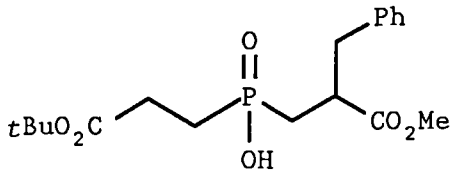
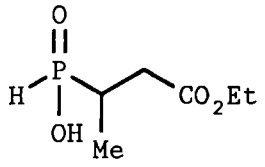
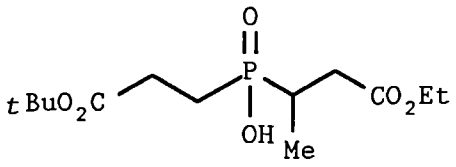
[c] The 300 MHz ^1H NMR spectrum showed triethylammonium contamination and also P-H resonance due to incomplete reaction.

materials and conditions. These phosphinic acids would be extremely difficult to synthesize by other methods (Chapter 1). The phosphinic acids synthesized have additional functionality γ to phosphorus and hence could allow further transformations to even more complicated phosphinic acids.

Table 2.3

Bis unsymmetrical addition.



Mono-substituted phosphinic acid	Di-substituted unsymmetrical phosphinic acid	Yield (%)
		64[a]
		77[b]

[a] The 300 MHz ^1H NMR spectrum showed triethylammonium contamination.

[b] The 300 MHz ^1H NMR spectrum showed trimethylsilyl contamination.

The preliminary results obtained from Pfizer Central Research provided a good starting point for a new synthetic route towards phosphinic acids, and there was good evidence

for phosphinic acid formation. However from spectral evidence many of the products were inadequately purified and consequently our initial research strategy was directed towards fully examining this new reaction using α,β-unsaturated esters. The preliminary results showed products obtained by 1,4 Michael-type addition; however both 1,2-carbonyl[118] or 3,4 vinyl[130] addition in analogous reactions have been reported, and so synthesis of a series of phosphinic acids using this addition reaction would allow a study of the selectivity of addition. After trying to establish an efficient standard reaction a study of the reactivity of bis(trimethylsilyl) phosphonite towards a variety of electrophiles was undertaken.

2.3.1. Investigation of the symmetrical bis addition using α,β-unsaturated esters.

Satisfactory duplication of the symmetrical bis-addition reaction using methyl acrylate was achieved using the conditions and precautions described below which were as a result of extensive optimization.

It was found that triethylammonium phosphinate was very hygroscopic and due care had to be taken to ensure rigorous azeotropic drying and careful handling. All the reagents and glassware were dried before use and a dry oxygen-free atmosphere of nitrogen or argon was used because the reaction was found to be very sensitive to both moisture and oxygen. It was found that redistilled chlorotrimethylsilane hydrolysed on standing, liberating hydrogen chloride which dissolved in the reagent and competed for the triethylamine in this reaction. This problem was reduced by premixing triethylamine and chlorotrimethylsilane (an extra equivalent

of silylating agent over base is required in this reaction), centrifuging the mixture and removing the supernatant from the copious triethylammonium chloride under nitrogen, and storing the mixture in a septum capped bottle over 4Å molecular sieves. This method was found to be practically very convenient because it allowed clean triethylamine and chlorotrimethylsilane to be introduced in one operation.

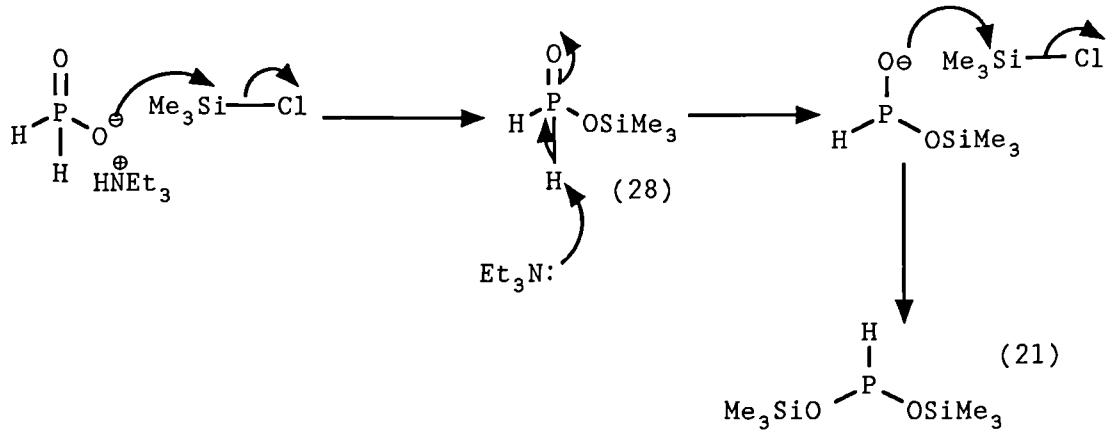
Isolation of the free phosphinic acids in the preliminary work was achieved by a simple aqueous wash, however we found it necessary to use a 2M hydrochloric acid wash, because from NMR and mass spectral analysis isolation of a mixture of the triethylammonium salt and the free acid was observed on aqueous work-up. Triethylammonium contaminated phosphinates could easily be converted to the free acid by simple dilute acid washing.

A reasonable mechanism for generation of bis(trimethylsilyl) phosphinate from triethylammonium phosphinate is shown in Figure 2.5. It is proposed that triethylammonium phosphinate is readily silylated to form trimethylsilyl phosphinate (28) which under basic conditions is deprotonated to form an anionic phosphorus(III) species which is readily silylated to form bis(trimethylsilyl) phosphonate (21).

Table 2.4 shows the results obtained for symmetrical bis-addition of (21) to α,β-unsaturated esters, and (Figure 2.6) shows a reasonable mechanism for the reaction with methyl acrylate. The first step in the reaction involves 1,4 Michael-type addition to methyl acrylate by bis(trimethylsilyl) phosphonite, to form the zwitterionic adduct (34) which undergoes proton transfer to yield the substituted phosphonite (35). The proton source could be by

Figure 2.5.

Mechanism of generation of bis(trimethylsilyl) phosphonite from triethylammonium phosphinate.

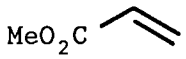
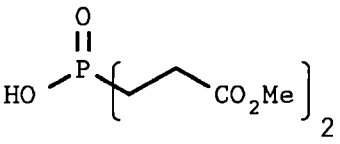
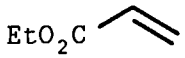
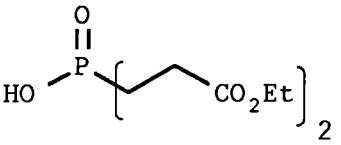
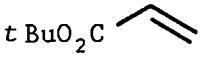
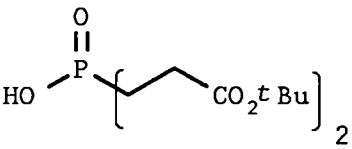
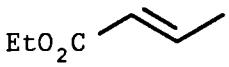
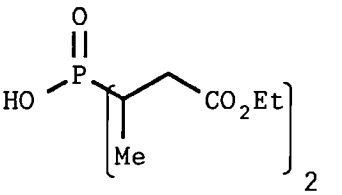
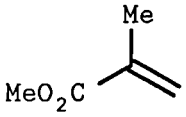
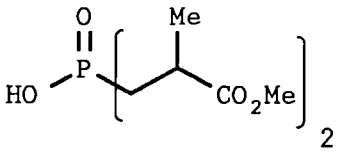
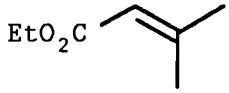
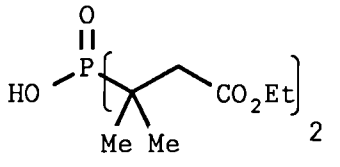


abstraction from another molecule of (34) or from triethylammonium chloride which is formed during *in situ* preparation of bis(trimethylsilyl) phosphonite and has appreciable solubility in dichloromethane. The substituted phosphonite (35) reacts with a second molecule of methyl acrylate yielding (36) which probably reforms the ester group by proton abstraction but stays as the phosphonium salt (37) until acidic hydrolysis liberates the free acid.

Using unsubstituted acrylates generally gave crystalline di-substituted phosphinic acids in high yield. Due to their lack of solubility in most organic solvents, they could be washed with either hexane or diethyl ether to yield analytically pure solids. However as the amount of acrylate substitution increased the yields and overall purity of phosphinic acids decreased. Substitution either α or β to the carbonyl group, generally resulted in some mono-substituted phosphinic acid contamination. This is probably due to steric hindrance being more pronounced with β-substituents; indeed this resulted in lower yields with β-substituents than with analogous α-substituents. An increase in reaction time was

Table 2.4

Bis-symmetrical addition.

α,β-Unsaturated ester	Phosphinic acid	Yield (%)
	(28) 	70
	(29) 	82
	(30) 	78
	(31) 	62[a]
	(32) 	56[a]
	(33) 	44[a]

[a]The 109 Mhz ^{31}P NMR spectrum showed mono phosphinic acid contamination.

found to be useful to drive these substituted acrylate reactions towards di-substituted phosphinic acid products. Yields of phosphinic acids from substituted acrylates could generally be increased by increasing reaction times by 24-48 hours.

2.3.2. Mono addition.

Mono-substituted phosphinic acids were synthesized using different relative proportions of reagents to try to optimise purity and yields. It was found that if triethylammonium phosphinate (25) and acrylate were mixed in one to one proportions, contamination by di-substituted phosphinic acid formation (resulting from a second addition to acrylate), was greater than thirty percent. Even when 2.5 equivalents of (25) were used, 109 MHz ^{31}P NMR spectra showed the product was still contaminated with di-substituted phosphinic acid. Pure mono-substituted phosphinic acids (one peak in the 109 MHz ^{31}P NMR spectra) could be synthesized starting with a five-equivalent excess of (25) over acrylate. The results obtained using a five equivalents excess of (25) are shown in Table 2.5; the products were isolated as colourless oils.

2.3.3. Unsymmetrical second addition.

These phosphinic acids were prepared by subjecting a mono-substituted phosphinic acid to the silylating conditions, (chlorotrimethylsilane/triethylamine) followed by acrylate addition. The crystalline phosphinic acids were isolated after acidic work-up, and the results are shown in Table 2.6.

Figure 2.6.

Proposed mechanism of bis(trimethylsilyl) phosphonite addition to methyl acrylate. Symmetrical bis addition.

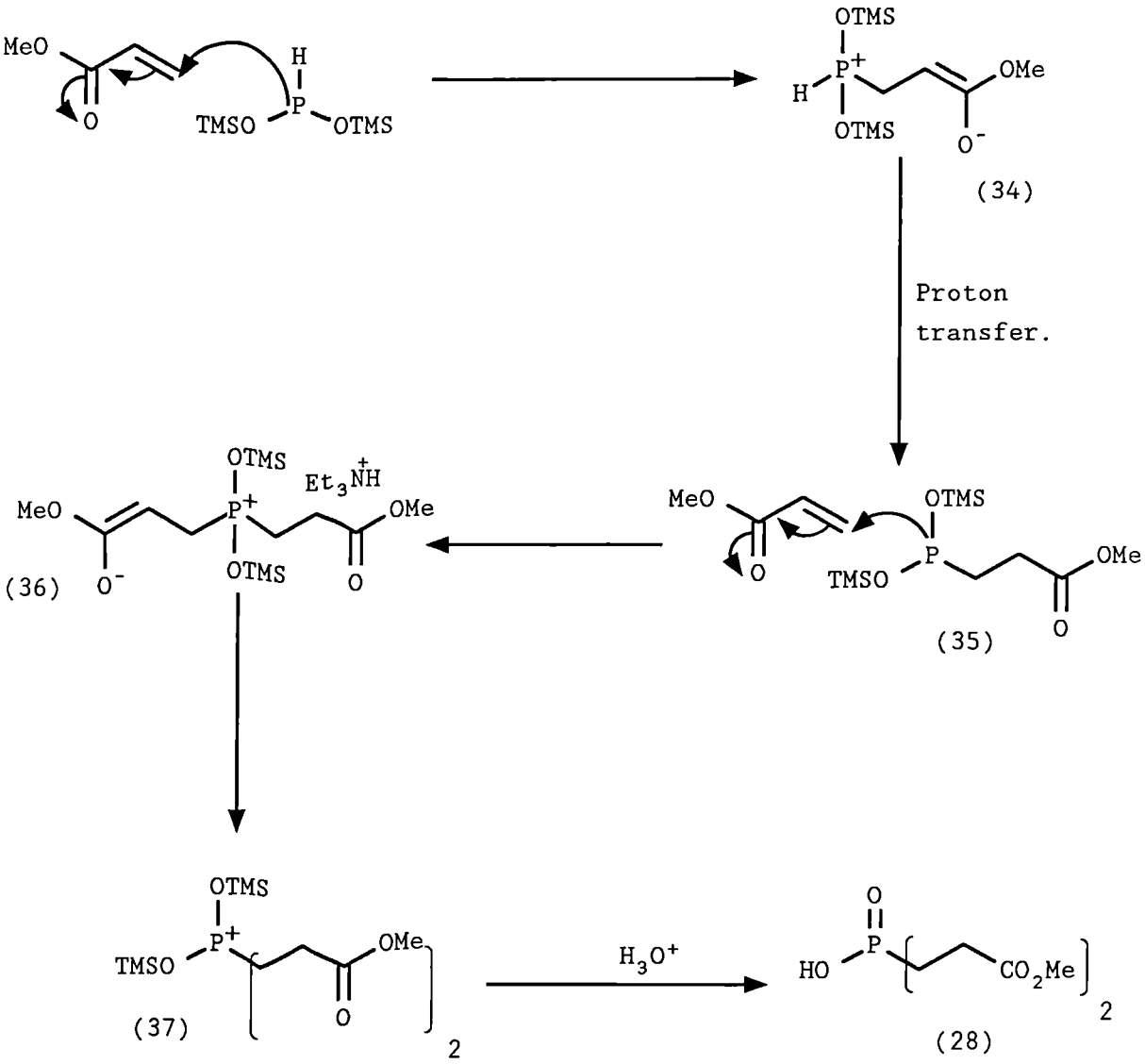


Table 2.5

Mono addition.

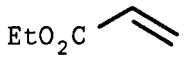
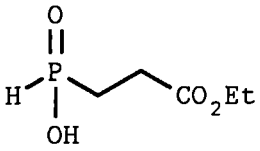
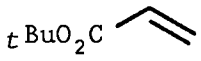
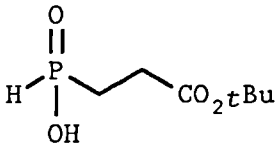
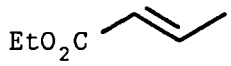
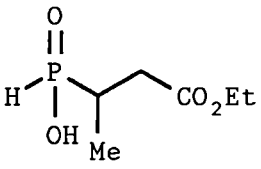
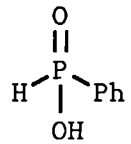
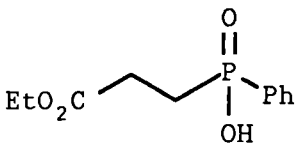
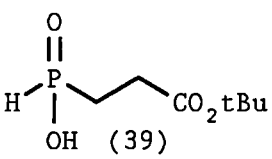
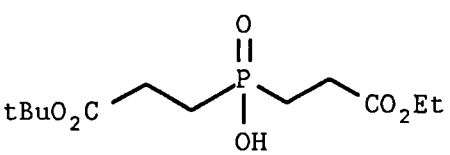
Acrylate	Phosphinic acid	Yield (%)
	(38) 	90
	(39) 	85
	(40) 	74

Table 2.6

Di-substituted unsymmetrical phosphinic acids.

Mono-substituted phosphinic acid	Di-substituted unsymmetrical phosphinic acid	Yield (%)
	 (41)	38
 (39)	 (42)	75

2.3.4. Discussion.

The results we obtained using this modified method of synthesis, (now referred to as the "triethylammonium phosphinate" method or reaction) were very encouraging. Generally high yields of phosphinic acids were achieved using acrylates, if the previously described precautions were followed. It was decided to test the general utility of the reaction using other electrophilic reagents.

2.4.1. Vinyl ketones in the "triethylammonium phosphinate" reaction.

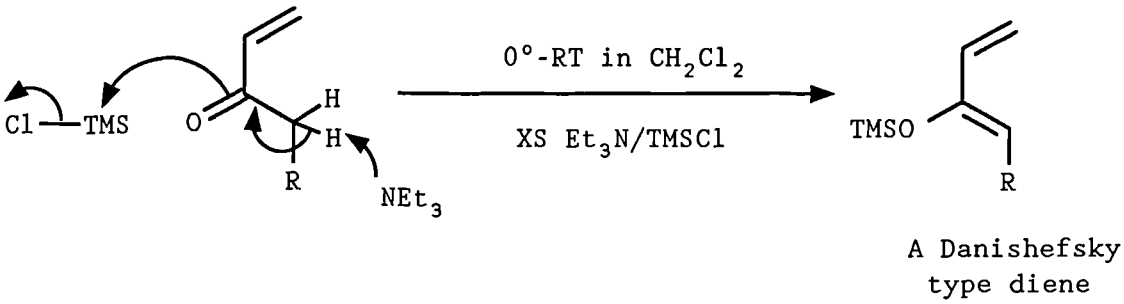
A synthetic target in the original plan was the phosphinic acid analogue of platelet activating factor. Our initial strategy towards this natural product isostere required either the addition of bis(trimethylsilyl) phosphonite or addition of a chlorotrimethylsilyl / triethylamine treated mono-substituted phosphinic acid to a vinyl ketone. For this reason a study of the reactivity of (21) towards vinyl ketones was undertaken *with initial work* being directed towards symmetrical bis-addition.

Substituting vinyl ketones for acrylates in the "triethylammonium phosphinate" reaction generally produced a less than thirty percent yield of phosphinic acid as very contaminated dark brown oils using methyl and ethyl vinyl ketones and 3-penten-2-one. The use of mesityl oxide and benzylideneacetophenone resulted only in recovery of the starting material. From 270 MHz ^{1}H and 109 MHz ^{31}P NMR spectra it was clear that both mono- and di-substituted phosphinic acids had been produced, (generally more of the di-substituted phosphinic acid could be identified); however both ^{1}H and ^{13}C NMR spectra were extremely contaminated.

Using 2-cyclohexenone gave, as judged by 109 MHz ^{31}P NMR spectra, a mixture of mono- and di-substituted phosphinic acids in 32% yield, (as calculated for di-substituted phosphinic acid).

We rationalised these relatively low yields and contaminated products as follows; if excess base and silylating agents are added to vinyl ketones which possess acidic enolizable protons α to the carbonyl then deprotonation and silylation can occur to form Danishefsky-type dienes[131,132] (Figure 2.7). Indeed under these basic silylating reaction conditions methyl vinyl ketone reacts to form 2-trimethylsilyloxybutadiene which has been used in many Diels-Alder reactions.[131] It was predicted that these reactive dienes could undergo further different competing side reactions and hence cause the relatively low and contaminated yields.

Figure 2.7.



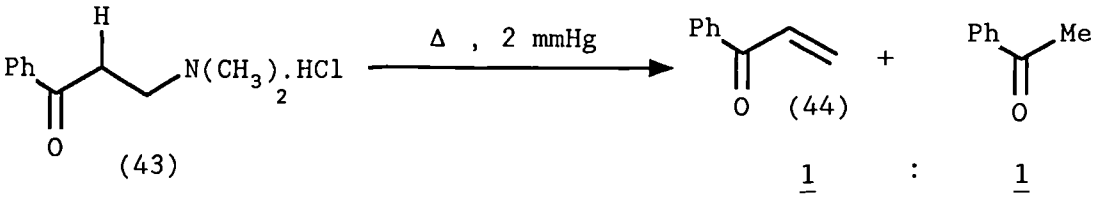
A Danishefsky type diene

2.4.2. Synthesis of vinyl ketones.

To elucidate whether enolizable protons α to the carbonyl were the cause of the relative failure of this reaction when vinyl ketones were used, or whether the cause was inherent lack of reactivity of bis(trimethylsilyl) phosphonite towards vinyl ketones, two vinyl ketones were

synthesized which did not posses enolizable protons: *t*-butyl and phenyl vinyl ketone. Phenyl vinyl ketone was first prepared by the method of Vogel,[133] by the direct pyrolysis of the Mannich base (43), (Figure 2.8). This pyrolysis generally gives phenyl vinyl ketone contaminated with acetophenone resulting from the retro Mannich reaction. However, this was not noted in the original preparation because both products boil within 10 °C of each other, and also the synthesis was performed before the advent of NMR which would have clearly revealed the contaminant. Hence it is thought that the yield quoted for the redistilled "pure ketone" of 51% actually represents as much as a fifty percent mixture of the two products. A literature search of phenyl vinyl ketone revealed that retro-Mannich products had been observed by other chemists[134] who reported approximately 30% acetophenone contamination. However by careful distillation phenyl vinyl ketone was obtained in 82% purity by G.C. analysis.

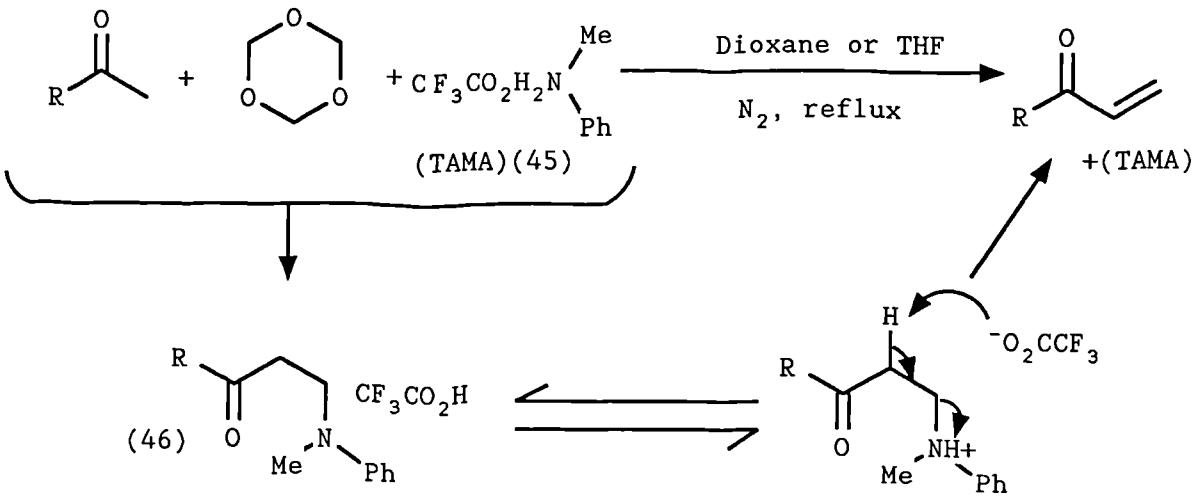
Figure 2.8.



Work by J-L. Gras[135] suggested that a new efficient way to vinyl ketones was by an analogous Mannich type reaction using 1,3,5-trioxane as a source of formaldehyde, N-methylanilinium trifluoroacetate (TAMA) (45) and the appropriate ketone (Figure 2.9). This general method is reported as a "direct methylene" transfer reaction involving

firstly formation of the Mannich base (46) by the TAMA induced condensation of formaldehyde and the appropriate ketone, then β-elimination after protonation of the amine by trifluoroacetic acid to form the vinyl ketone. The use of TAMA is thus catalytic, and Gras claims that the use of 0.1 equivalents of TAMA merely slows the reaction down. Using trioxane (dried over P_2O_5) gave negligible amounts of extremely contaminated vinyl ketone (<5%) so paraformaldehyde was used instead, this failure using trioxane has been reported by other chemists.[136] Gras claimed a pure yield of 82% for *t*-butyl vinyl ketone and 91% for phenyl vinyl ketone.

Figure 2.9.

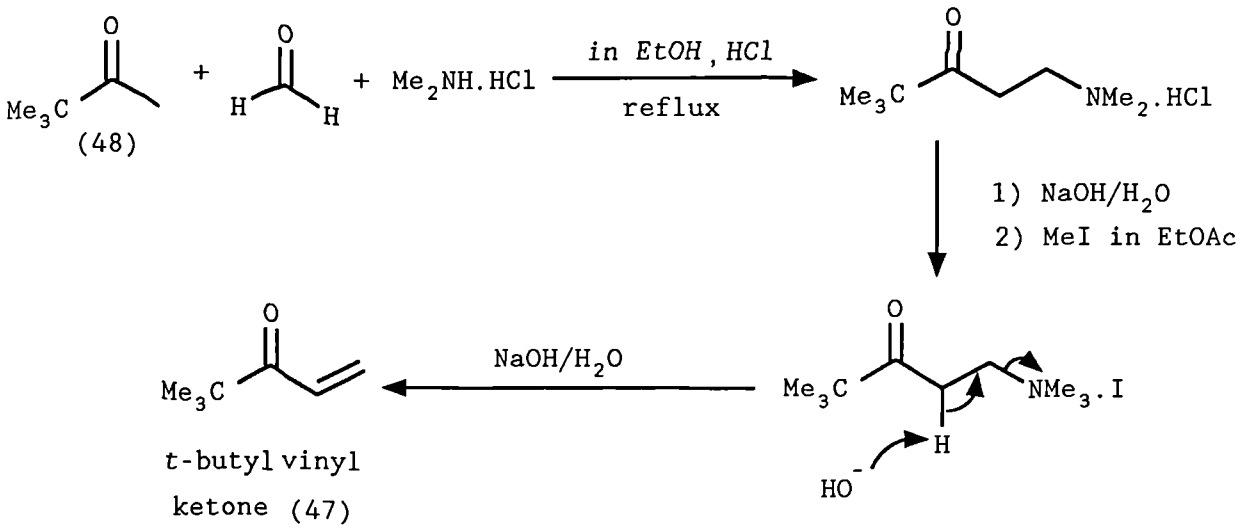


Using paraformaldehyde gave some limited success but yields were very low and impure, and excesses of TAMA and paraformaldehyde were required to push the reaction towards the vinyl ketone. This reaction using pinacalone (*t*-butyl methyl ketone) and acetophenone was extensively studied and monitored by GC analysis. The proportions of reagents, sequential addition of excess reagents, solvent, and reaction times were varied to try to optimize yields. Tetrahydrofuran gave the highest yields of contaminated vinyl ketones and

also had the advantage of less precipitation occurring during reaction. The best result achieved for phenyl vinyl ketone was a total crude yield of 59%, this consisting of 56% (44) and the remainder mostly starting acetophenone. For *t*-butyl vinyl ketone (47) a total crude yield of 31%, being 64% (47) and the remainder mostly pinacalone (48). After much experimentation it was decided that this synthetic method was actually less satisfactory than existing methods for preparation of phenyl and *t*-butyl vinyl ketones. Indeed this relatively complicated reaction gave (44) with approximately the same amount of acetophenone contamination as the simple pyrolysis. *t*-Butyl vinyl ketone was finally synthesized using standard Mannich chemistry[137] in good yield (Figure 2.10). Due to the commercial availability of (43) direct pyrolysis and purification of the phenyl vinyl ketone/acetophenone mixture by distillation proved adequate. However if phenyl vinyl ketone without traces of acetophenone contamination is necessary, the Mannich base of acetophenone could be liberated as the free base, methylated and subsequent Hoffmann elimination would liberate phenyl vinyl ketone in an analogous manner to the synthesis of (47), (Figure 2.10), without the possibility of the retro Mannich reaction taking place.

When *t*-butyl and phenyl vinyl ketones were used under the conditions of the "triethylammonium phosphinate" reaction, crystalline phosphinic acids resulted, which were purified by a hexane wash to yield white solids. A yield of 80% bis phosphinic acid from (44) and 83% from *t*-butyl vinyl ketone were obtained. These results were good evidence that α,β-unsaturated ketones have suitable reactivity as electrophiles, and that Danishefsky "type" dienes were

Figure 2.10.



probably being formed, which were competing with the desired reaction in the case of enolisable ketones.

2.5 The use of other electrophiles in the "triethylammoniumphosphinate" reaction.

Due to the lack of general success using vinyl ketones it was decided to use other electrophiles in this reaction to see if they might be synthetically more useful than vinyl ketones.

2.5.1. α-Bromo esters.

Various α-bromo esters were used in the triethylammonium phosphinate reaction to elucidate whether they are useful for the synthesis of symmetrical di-substituted phosphinic acids: Table 2.7 gives the results.

Although these results were more promising than using vinyl ketones they were much worse than using acrylates to synthesize phosphinic acids. The reason for this is probably alkylation of triethylamine by nucleophilic displacement of

Table 2.7

Symmetrical bis addition using α-bromo esters.

α-Bromo ester	Phosphinic acid	Yield (%)
EtO_2C Br	(49) HO P(O) [CO_2Et]$_2$	38
Me, EtO_2C Br	(50) HO P(O) [CO_2Et, Me]$_2$	30[a]
Me Me, EtO_2C Br	(51) HO P(O) H, CO_2Et, Me Me	29[b]

[a] The ^1H and ^{31}P NMR showed a mixture of mono and di-substituted phosphinic acid, the yield is calculated for di-substituted phosphinic acid.

[b] The ^1H and ^{31}P NMR showed only mono-substituted phosphinic acid had been prepared and the yield shown reflects this.

bromide to form the corresponding quaternary ammonium salt. Indeed using identical reaction conditions, but no triethylammonium phosphinate resulted in isolation of (1-methylethoxycarbonyl)triethyl ammonium bromide (52), (Figure 2.11).

Figure 2.11.

$$EtO_2C\text{-}Br \xrightarrow[\text{in } CH_2Cl_2,\ RT]{Et_3N/TMSCl} EtO_2C\text{-}\overset{+}{N}Et_3\ \overset{-}{Br}$$

(52)

The use of α substituted bromo esters resulted in contamination with mono-substituted phosphinic acid. When ethyl-2-bromoisobutyrate was used no di-substituted phosphinic acid was observed. This is probably because the second addition is sterically unfavourable and hence there is competition for the bromo ester by the triethylamine resulting in loss of bromo ester and hence no di-substituted phosphinic acid is able to form.

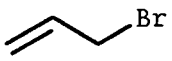
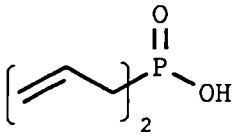
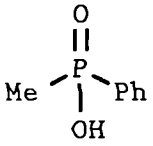
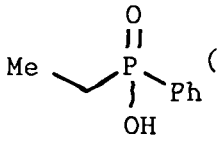
Competition for bromo ester by triethylamine would result in depletion of both base and electrophile, hence more base and electrophile addition might be beneficial. For this reason an identical reaction to the attempted bis-substitution using ethyl bromo acetate shown in Table 2.7 was performed. However after 18 hours extra chlorotrimethylsilane/triethylamine (1.8 eq.) were injected at 0° C and stirred for two hours, followed by addition of ethylbromoacetate (1.7 eq.). After work-up the product was isolated as an oil in 41% yield. Although the yield has increased slightly the product was impure and hence this result is of little help or significance.

Second addition to a mono-substituted phosphinic acid was achieved in 71% yield by treatment of phenyl phosphinic acid with excess chlorotrimethylsilane/triethylamine followed by addition of ethyl bromo acetate, giving a crystalline solid. This gives evidence of competition by triethylamine for the bromo ester.

2.5.2. Alkyl and benzyl halides.

Relatively reactive alkyl and benzyl halides were used as electrophiles in the "triethylammonium phosphinate" reaction to elucidate whether any were synthetically useful, Table 2.8 shows the results.

Table 2.8

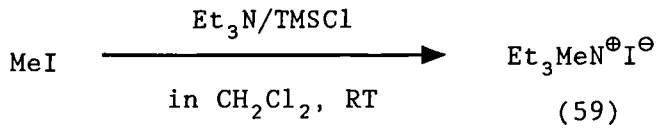
Starting reagent	Electrophile	Phosphinic acid	Yield (%)
$HNEt_3H_2PO_2$	MeI	Me_2PO_2H (53)	9
$HNEt_3H_2PO_2$	EtBr	Et_2PO_2H (54)	8
$HNEt_3H_2PO_2$	BnBr	Bn_2PO_2H (55)	44
$HNEt_3H_2PO_2$		 (56)	16
$PhPO_2H_2$	MeI	 (57)	48[a]
$PhPO_2H_2$	EtBr	 (58)	55[a]

[a]The ^{31}P NMR shows starting phenyl phosphinic acid contamination.

The reaction between triethylammonium phosphinate and benzyl bromide was the only synthetically useful reaction giving a moderate yield of crystalline di-substituted phosphinic acid which was clean by NMR spectra. All the other phosphinic acids were very impure as judged by NMR spectra. Bis alkylation using methyl iodide and ethyl bromide was unsatisfactory because low yields of extremely contaminated products were produced, but addition to (mono)

phenylphosphinic acid gave improved yields of relatively clean products (57) and (58) as oily solids, which were slightly contaminated by starting phenylphosphinic acid. It was thought that as in the case of α-bromo esters base competes for the electrophile, and so methyl iodide was used in the same bis-addition reaction conditions, omitting triethylammonium phosphinate, and an almost quantitative yield of triethylmethylammoniun iodide (59) was obtained (Figure 2.12).

Figure 2.12.

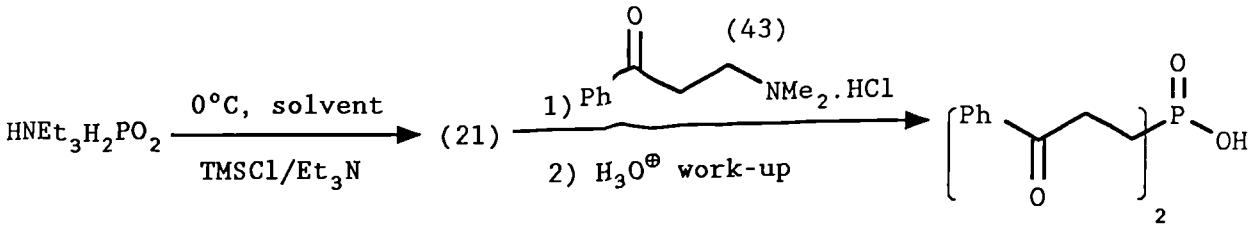


2.6. Preparation of phosphinic acids using the "triethylammonium phosphinate" reaction with a Mannich base.

Due to the success in phosphinic acid synthesis using phenyl vinyl ketone it was decided to investigate whether under these conditions β-dimethylaminopropiophenone hydrochloride (43) could be forced to eliminate dimethylamine and liberate phenyl vinyl ketone which could react with bis(trimethylsilyl) phosphinate to yield a phosphinic acid. Initial results were promising (Table 2.9). By using standard "triethylammonium phosphinate" reaction conditions and working up after 115h, crude di-substituted phosphinic acid could be detected by ^{31}P NMR. Refluxing dichloromethane gave an increased yield, however the product was also very contaminated. Refluxing in chloroform did not yield the

desired product, the extra acidity of chloroform over dichloromethane may influence the reaction towards another pathway. White crystalline di-substituted phosphinic acid was prepared in high yield in refluxing 1,2-dichloroethane.

Table 2.9



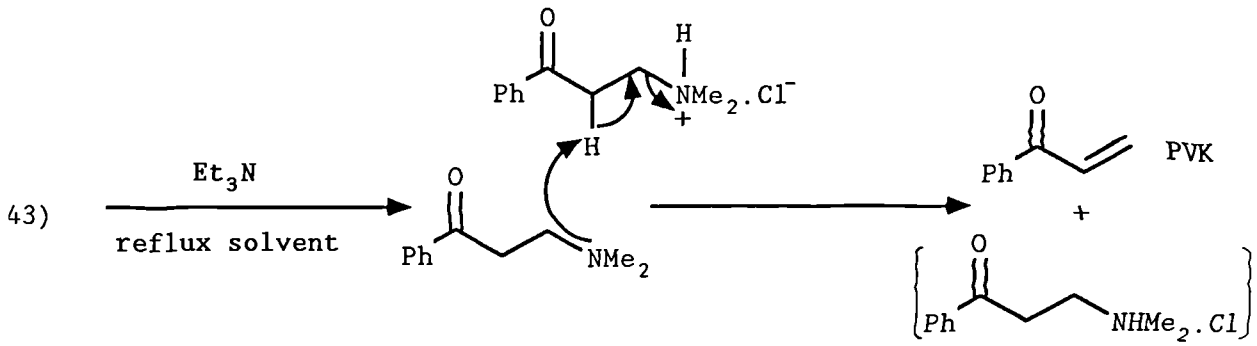
Solvent	Temperature (°C)	Yield (%)
CH_2Cl_2	RT, 24	11
CH_2Cl_2	reflux, 40	37
$CHCl_3$	reflux, 62	reaction failed[a]
CH_2ClCH_2Cl	reflux, 83	76

[a] Unidentified product, not phosphinic acid

On addition of (43) to the reaction the triethylamine removes the hydrochloride to leave the free base. The resulting dimethylaminopropiophenone can eliminate dimethylamine by an intermolecular mechanism after abstracting a proton from another molecule of (43) or from triethylammonium chloride, (Figure 2.13). The mechanism shown shows dimethylaminopropiophenone acting as a base, however if triethylamine is in excess then there would be competition for β-proton which is abstracted. Although the mechanism is not fully elucidated the result is *in situ* liberation of

phenyl vinyl ketone (observed by TLC), which undergoes 1,4 addition to yield di-substituted phosphinic acid.

Figure 2.13.



2.7. Esterification of phosphinic acids.

The phosphinic acids synthesized in this chapter were generally insoluble in aprotic solvents, however most of the oils were soluble in dichloromethane and to a lesser degree in other halogenated solvents. Most of the crystalline phosphinic acids were only partially soluble or were very insoluble. This provided a useful method of analytical purification of crystalline phosphinic acids by simply washing them with cyclohexane or diethyl ether, however this lack of solubility was a distinct disadvantage for purification of phosphinic acids isolated as oils.

One fairly general method for purification of organic products is by flash chromatography.[141] The only relatively good solvent found for the phosphinic acids was methanol which results in much silicic acid formation by direct solution of the flash silica by methanol when used as a solvent using this purification method. When using high concentrations of methanol this becomes a problem because silicic acid is soluble in methanol and hence contaminates

the products. This can be overcome if the product is soluble in acetone or another differentiating solvent system because silicic acid is not soluble in acetone and hence separation can be achieved. However we found no phosphinic acids to be soluble in acetone effectively ruling out flash chromatography as a purification method for the free acids.

Esterification of phosphinic acids to give phosphinate esters is known to increase their solubility in aprotic solvents and to increase volatility. Exploiting these characteristics could be utilized for their purification.

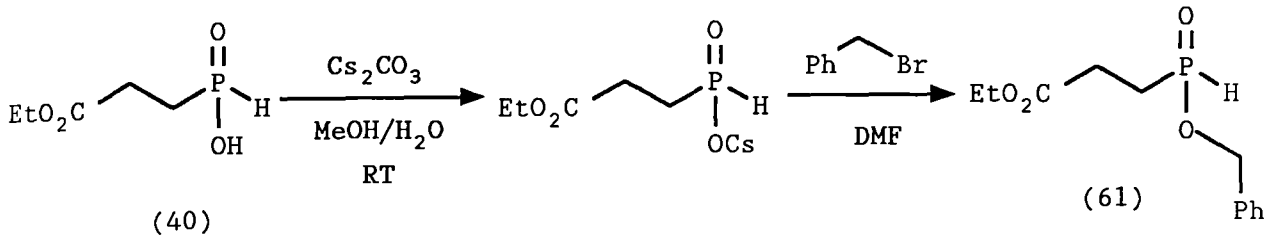
2.7.1. Benzyl esterification of phosphinic acids.

This method of benzyl esterification was adapted from a general esterification procedure for amino acid derivatives.[138] Figure 2.14 shows esterification of the mono-substituted phosphinic acid (40), obtained from bis(trimethylsilyl) phosphonite addition to ethyl acrylate. Unfortunately this method resulted in phosphinate esters which were much more contaminated than their parent phosphinic acids; a viscous brown oil resulted from a mobile colourless oil. From the NMR spectra it was observed that incomplete benzylation had occurred; and complete benzylation was never achieved. For these reasons this method of purification was not pursued.

2.7.2. Methyl esterification of phosphinic acids.

Quantitative methylation[139] of phosphinic acids was achieved using diazomethane easily liberated from N-methyl-N-nitro-*p*-toluenesulphonamide (Figure 2.15). A

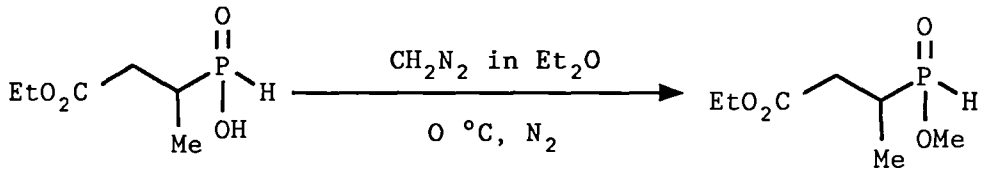
Figure 2.15.



(40) (61)

solution of diazomethane in ether was added to the appropriate phosphinic acid in methanol, and removal of the solvents resulted in methyl phosphinate formation. However it was found that methanol was still required in the solvent system for TLC, and for this reason the esterification had little utility for purification. However using this procedure methyl phosphinates of (29) and (31) were prepared.

Figure 2.15.



(40) (62)

2.9. Conclusion.

The "triethylammonium phosphinate" reaction has been shown to be a useful synthetic method for the synthesis of functionalised phosphinic acids from α,β-unsaturated esters. Development and expansion of the preliminary work performed has led to a series of reactions to give mono-substituted phosphinic acids, symmetrical di-substituted and unsymmetrical di-substituted phosphinic acids in good to

excellent yield. This new mild and flexible method for phosphinic acid synthesis has many useful advantages over previous synthetic methods, discussed in chapter 1. The desired substituted phosphinic acid can readily and conveniently be made from simple starting materials. Under these mild reaction conditions sensitive functionality can be tolerated within the α,β-unsaturated ester, leading to the possibility of complex phosphinic acid synthesis. This method is particually useful for the synthesis of phosphinic acids that are alkyl or aryl substituted α to the hydroxyphosphoryl group, these compounds are difficult to prepare by conventional methods. If the Arbuzov reaction is used to gain functionality α to the hydroxyphosphoryl group then this requires the use of a secondary or tertiary substituted halide which will undergo elimination under Arbuzov conditions and are thus useless.

The use of other types of electrophilic reagent in the reaction generally led to disappointingly low and contaminated yields. The addition of bis(trimethylsilyl) phosphonite to vinyl ketones is unreported in the literature, and under these conditions other competitive reactions occurred. Although the "triethylammonium phosphinate" method was unsuitable for phosphinic acid synthesis using vinyl ketones there was strong evidence that this was due to undesired side reactions rather than lack of electrophilic reactivity of the vinyl ketones.

Addition of a substituted phosphonite to ethyl bromoacetate has been reported in good yield[119] if the phosphinic acid was first protected as an alkyl phosphinate. Bis(trimethylsilyl) substituted phosphonite addition was reported in lower yields. Our results on addition of a

mono-substituted bis(trimethylsilyl) phosphonite to ethyl bromoacetate were also good but the use of bis(trimethylsilyl) phosphonite to generate di-substituted symmetrical phosphinic acids was not satisfactory for the reasons discussed.

Some methods of overcoming these problems are discussed but were not tested because it was felt that with the difficulty in purifying phosphinic acids anyway, a clean method of synthesis, (*i.e.* where the starting materials do not preferentially perform side reactions) was necessary if any chance of analytically pure phosphinic acid preparation was to be achieved.

The reason the Mannich base method for formation and introduction of vinyl ketones was explored was that this might allow a more controlled liberation of vinyl ketone to the bis(trimethylsilyl) phosphonite which might decrease the likelihood of "Danishefsky type" dienes being formed. This novel method of vinyl ketone liberation showed success after the appropriate conditions were optimised. It was envisaged that the appropriate Mannich base could be methylated before use which would allow, under appropriate conditions at room temperature, facile Hoffmann elimination to liberate the appropriate vinyl ketone, without the need for forcing reaction conditions.

Competition by base for starting electrophiles was found to be a severe problem. A proposed method for overcoming this was a second introduction of base and electrophile, however introduction of more base and electrophile after 18 hours had little effect in the case of ethyl bromoacetate. Another proposed solution to this problem would be controlled introduction of the electrophile over a long period, probably

24 hours and could be practically achieved using a syringe pump set-up. This method would rely on the silylphosphonite esters being more reactive than the base towards the electrophile.

Results on speed of addition suggests that second addition by mono-substituted phosphinates occur faster than first addition by bis(trimethylsilyl) phosphonite to the appropriate electrophile. Evidence for this comes, for example from bis(trimethylsilyl) phosphonite addition to α-bromoacetates. Although base is competing with the α-bromoacetate, no mono-substituted phosphinic acid is observed from the ^{31}P NMR spectrum. This was also found to be true for vinyl ketones, the NMR spectra although being very contaminated, showed no sign of mono-substituted phosphinic acid. Evidence to dispute this comes from the use of substituted electrophiles which show mono-substituted phosphinic acid contamination when di-substituted phosphinic acids are desired. The reason for this is probably due to steric hindrance, second addition is unfavourable which allows substrate competition by base to predominate.

At the outset of this work we were concerned about the direction of addition of bis(trimethylsilyl) phosphonite to α,β-unsaturated species. Conclusive evidence of addition is only available from addition to unsaturated esters which were exclusively observed to proceed by 1,4 Michael-type addition.

CHAPTER 3.

DEVELOPMENT OF PHOSPHINIC ACID REACTIONS

3.1. Introduction.

The "Triethylammonium phosphinate" reaction of Chapter 2 has proved useful in the synthesis of symmetrical and unsymmetrical mono- and di-substituted phosphinic acids by bis(trimethylsilyl) phosphonite addition to α,β-unsaturated esters. However, using vinyl ketones and some other electrophilic reagents in this reaction results in very impure products in generally low yield. This Chapter is concerned with developing the synthetic methodology used in Chapter 2 towards a reaction which can tolerate sensitive electrophilic reagents, with particular emphasis on vinyl ketones.

3.2. The use of sodium phosphinate.

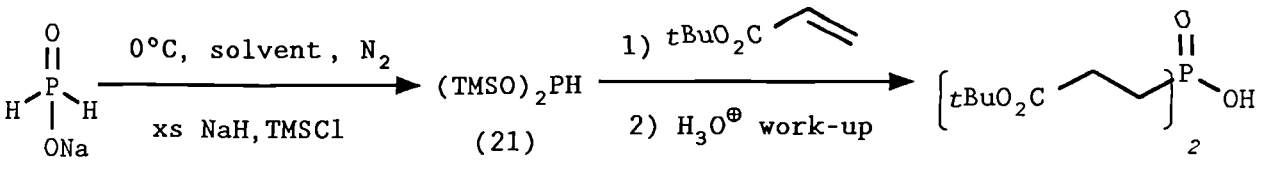
Sodium phosphinate was substituted for triethylammonium phosphinate in a series of reactions to ascertain its synthetic usefulness. Sodium phosphinate was easily prepared by the controlled addition of sodium hydroxide to a 50% solution of phosphinic acid. Triethylammonium phosphinate, being a viscous hygroscopic oil, was relatively difficult to handle and to keep anhydrous. However sodium phosphinate being a crystalline solid overcame these problems. Triethylammonium phosphinate contamination was observed in early attempts at mono- and di-substituted phosphinic acid synthesis; the use of sodium phosphinate would reduce the likelihood of this and also the general volume of precipitation; this was predicted to make the reaction more efficient. The substitution of sodium phosphinate for triethylammonium phosphinate in the "triethylammonium phosphinate" reaction resulted in a 92% analytically pure yield of di-substituted phosphinic acid (30) from t-butyl

acrylate, (*cf.* standard "triethylammonium phosphinate" conditions gave 78%).

3.3. The use of sodium hydride as a base.

It was envisaged that a much more efficient reaction would occur if sodium hydride was used as a base instead of triethylamine. The product of deprotonation would be volatile hydrogen instead of triethylammonium chloride hence resulting in irreversible deprotonation and a cleaner reaction. The use of sodium phosphinate and sodium hydride would eliminate any undesirable triethylammonium contamination. A study was undertaken using *t*-butyl acrylate as the electrophile to find an appropriate reaction medium, results are shown in Table 3.1. A 10% excess of *t*-butyl acrylate over sodium phosphinate was used.

Table 3.1



Solvent	Temperature (°C)	Yield (%)
CH_2Cl_2	RT, 25	7
CH_2ClCH_2Cl	reflux, 83	19
DMF	RT, 25	86

The reason for low yields of di-substituted phosphinic acid formed in chlorinated "non polar" solvents is probably due to the lack of solubility of sodium hydride and sodium phosphinate, however the use of polar dimethylformamide resulted in good yields of phosphinic acid of high purity.

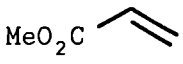
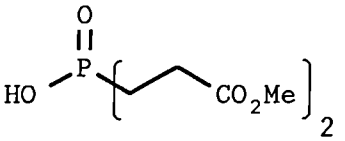
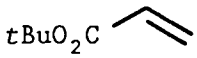
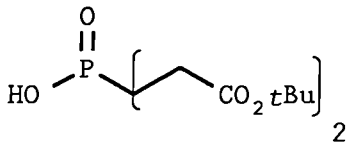
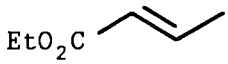
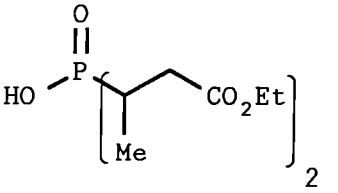
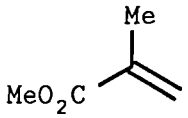
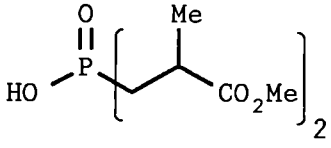
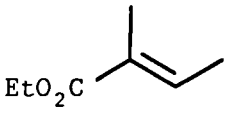
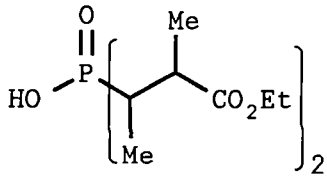
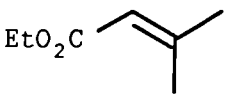
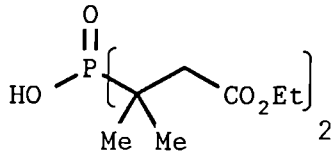
3.4. The "sodium phosphinate" method of phosphinic acid synthesis.

The results obtained using sodium phosphinate as a source of hydroxyphosphoryl functionality seemed to be an improvement over triethylammonium phosphinate, also using sodium hydride seemed to have advantages over triethylamine, hence these modifications were combined. The use of sodium phosphinate under excess chlorotrimethylsilane and sodium hydride conditions in dimethylformamide to generate bis(trimethylsilyl) phosphonite, followed by addition of excess *t*-butyl acrylate to synthesize the di-substituted phosphinic acid gave a higher yield than using the "triethylammonium phosphinate" method. This new method of phosphinic acid synthesis is referred to as the "sodium phosphinate" reaction or method. For this reason a series of di-substituted symmetrical phosphinic acids were synthesized to test the new method. The results are shown in Table 3.2.

Generally, higher yields were obtained using this method, especially from addition to substituted acrylates. The purity of products was also generally higher. However non-crystalline phosphinic acids still could not be isolated in analytically pure form.

Table 3.2

Symmetrical bis addition using the "sodium phosphinate" method.

Acrylate	Phosphinic acid	Yield (%)
	(28) 	95
	(30) 	86
	(31) 	74
	(32) 	54
	(63) 	73
	(33) 	59[a]

[a] The 109 MHz ^{31}P NMR spectrum showed mono-substituted phoshinic acid contamination.

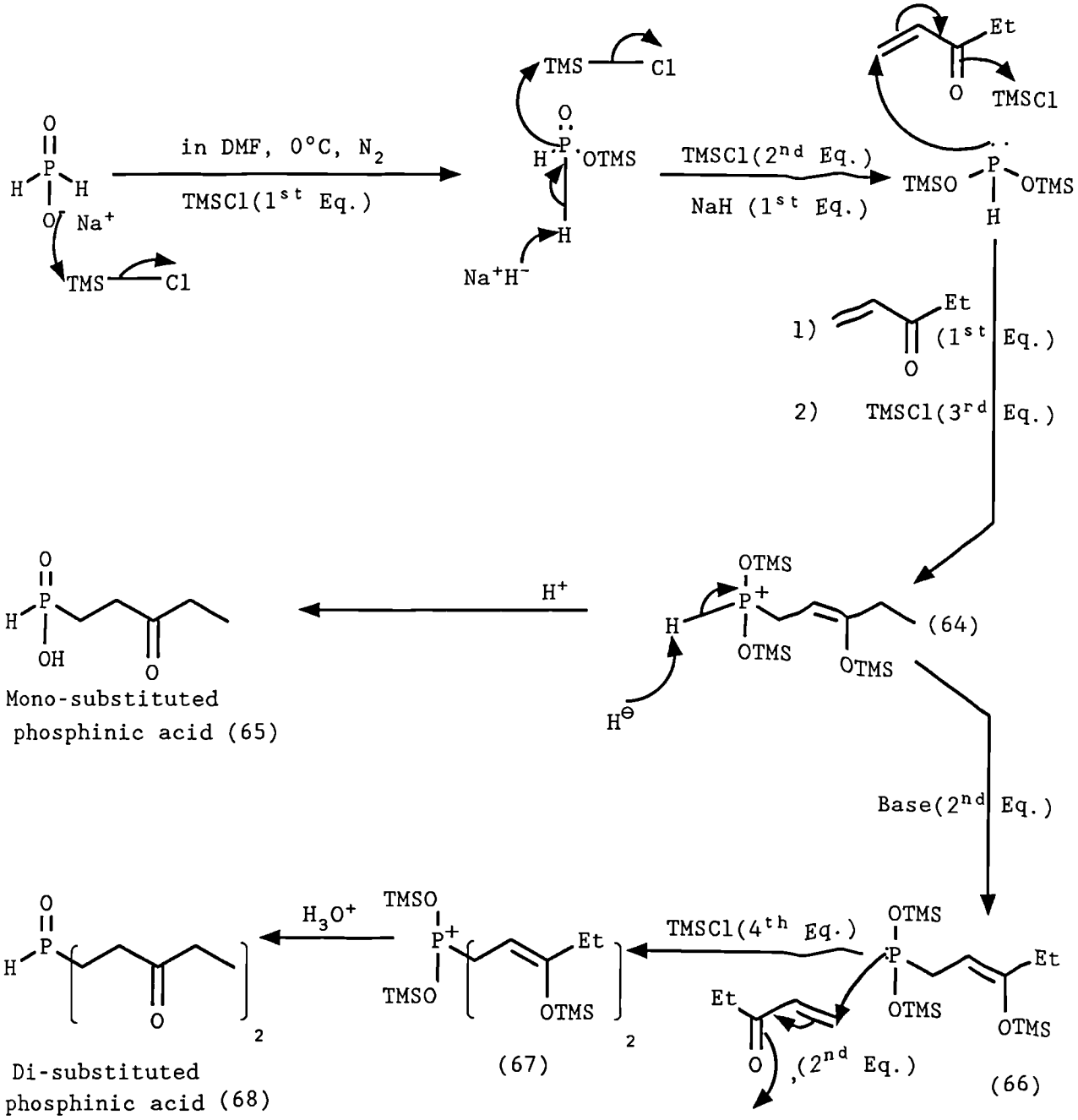
3.5. The "sodium phosphinate" reaction using vinyl ketones.

Due to the success of the "sodium phosphinate" reaction using acrylates it was decided to substitute vinyl ketones as the electrophiles. Figure 3.1 shows the proposed mechanism of bis(trimethylsilyl) phosphonite formation and addition to ethyl vinyl ketone for mono- and di-substituted phosphinic acid formation. 1,4 Michael-type addition by bis(trimethylsilyl) phosphonite to ethyl vinyl ketone forms the trimethylsilyl enol ether phosphonium salt (64) which can be hydrolysed to form mono-substituted phosphinic acid (65). However if base is present abstraction of a proton from (64) results in the substituted phosphonite (66) which can undergo further addition to ethyl vinyl ketone to form phosphonium salt (67), which on hydrolysis yields the di-substituted phosphinic acid (68). This mechanism of addition to vinyl ketones differs from that of addition to α,β-unsaturated esters in respect that the silyl enol ethers form[140] and probably remain throughout the reaction using vinyl ketones, whereas the ester carbonyl is thought to be regenerated after addition to acrylates, (if a proton source is present *e.g.* triethylammonium salts).

Bis addition was attempted using one equivalent of sodium hydride and two equivalents of chlorotrimethylsilane, (redistilled from calcium hydride and stored under argon) to form bis(trimethylsilyl) phosphonite, this was followed by addition of one equivalent of vinyl ketone. A second equivalent of base, (triethylamine was used for convenience) was injected followed by two further equivalents of chlorotrimethylsilane and one equivalent of vinyl ketone. Using this controlled base addition led to a 31% yield of

Figure 3.1.

Bis(trimethylsilyl) phosphonite generation and addition to ethyl vinyl ketone to generate mono- and di-substituted phosphinic acids using the "sodium phosphinate" method.



predominantly di-substituted phosphinic acid from ethyl vinyl ketone and a 19% yield from methyl vinyl ketone, which were impure from ^{1}H, ^{31}P and ^{13}C NMR spectra. The use of four equivalents of sodium hydride and four and a half equivalents of chlorotrimethylsilane at the start of the reaction resulted in a 50% crude isolated yield for ethyl vinyl ketone and 14% for methyl vinyl ketone. It is uncertain why the yield from ethyl vinyl ketone was relatively so high when excess base was used. This could be a result of unidentified contamination, because NMR and mass spectra showed the products to be very contaminated. As a control, *t*-butyl vinyl ketone was used under these excess conditions yielding an oil which was crystallised out and washed with hexane in 86% yield.

Due to the lack of success in synthesizing di-substituted phosphinic acids, attention was turned to mono addition, which was extensively studied using varying equivalents of sodium hydride in an attempt to limit side reactions. Numerous reactions using methyl vinyl ketone were undertaken, varying the amount of sodium hydride from 0.8 equivalents to two and a half equivalents and also a vast excess; however the highest crude yield of 10% was achieved using two and a half equivalents of base. *t*-Butyl vinyl ketone gave the mono-substituted phosphinic acid as an oil in 87% yield using 2.5 equivalents of sodium hydride, giving evidence of deprotonation of α-carbonyl protons with other ketones, to give diene side-products, (as discussed in chapter 2).

3.6. Conclusion.

Due to poor results obtained from addition to vinyl ketones in the "sodium phosphinate" reaction ethyl bromoacetate was used as an electrophile in an attempted bis addition using excess sodium hydride and chlorotrimethylsilane. This yielded an oil in 47% which showed some spectral contamination, (a small amount of mono-substituted phosphinic acid was observed in the ^{31}P NMR spectrum). Although this result was higher than that using the "triethylammonium phosphinate" method, (*cf.* yield of 38%) it was not thought sufficiently high or pure to warrant a thorough investigation into the accessibility of phosphinic acids using α-bromo esters under "sodium phosphinate" reaction conditions. Extensive studies on limiting the amount of base still resulted in low yields of contaminated products when vinyl ketones were used. We believe that a synthesis of phosphinic acids using vinyl ketones would require that base and vinyl ketone should never be present at the same time, as a prerequisite for success. Vinyl ketones are well known to be very susceptible to polymerization, which can be base catalysed, hence although these are relatively very mild reaction conditions, depletion of starting electrophilic substrate may be serious. The studies on limiting base were performed mostly using methyl vinyl ketone which was chosen because it is very reactive, and hence if we could achieve bis(trimethylsilyl) phosphonite addition to methyl vinyl ketone without polymerization or Danishefsky-type diene formation then we would be more likely to succeed using less reactive vinyl ketones.

This method of phosphinic acid synthesis is a useful alternative to the "triethylammonium phosphinate" reaction;

generally higher yields of di-substituted phosphinic acid are obtained which in most cases appeared from spectral evidence to be less contaminated. Mono addition to *t*-butyl acrylate resulted in a yield of 78% of phosphinic acid (39). This is comparable to using the "triethylammonium phosphinate" method and hence was not pursued. This method appears better than the "triethylammonium phosphinate" method for phosphinic acids with alkyl substitution α or β to the hydroxyphosphoryl group; this can be seen by the absence of mono-substituted phosphinic acid contamination when di-substituted phosphinic acids are synthesised, with the exception of (33). Unfortunately it has not proved a good method for phosphinic acid preparation from vinyl ketones; although it is somewhat better than the "triethylammonium phosphinate" method it is still no use as a general synthetic method.

At this stage of research we were very concerned about the purity of the phosphinic acid products. Crystalline products could be purified to analytical standard by washing with suitable solvents but the products isolated as oils, (which includes all mono-substituted phosphinic acids synthesized) were generally not analytically pure and, we had no efficient method of purification. Although many methods had been tried they were all unsuitable. It was found that the mono-substituted phosphinic acids were extremely hygroscopic, and this was revealed on weighing prior to combustion analysis. The weights of these samples rapidly increased on weighing due to absorption of atmospheric moisture, and this was confirmed by infra red spectral studies. Although the two new methods for phosphinic acid synthesis described in Chapters 2 and 3 are excellent when acrylates were used, we felt that a conceptual change of

approach was required if bis(trimethylsilyl) phosphonite was going to be useful in synthesis with vinyl ketones if pure products were to be gained, especially in view of the difficulties already encountered in their purification.

CHAPTER 4.

PHOSPHINIC ACID SYNTHESIS FROM VINYL KETONES

4.1. Introduction.

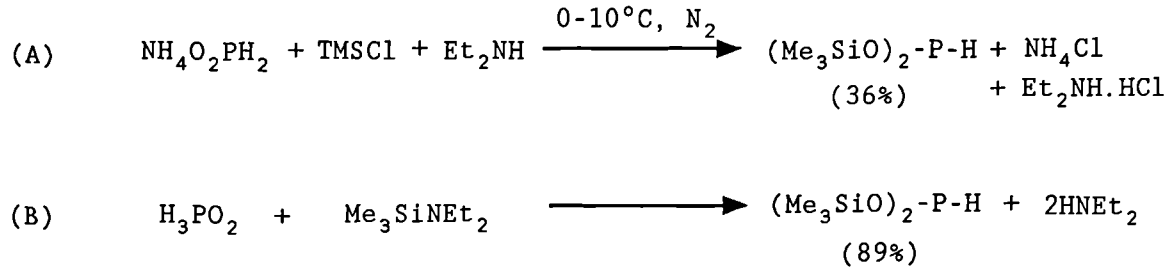
In chapters 2 and 3, substituted phosphinic acids have been prepared and isolated in good yield after *in situ* generation of bis(trimethylsilyl) phosphonite and addition to a variety of acrylates. However variation of starting reagents and reaction conditions did little to improve the yield and purity of phosphinic acids from other electrophiles, particually vinyl ketones, for reasons discussed previously. It was proposed that reactions were failing not due to the lack of inherent reactivity of bis(trimethylsilyl) phosphonite towards electrophiles, but due to competing side reactions. Hence the preparation, isolation and characterisation of bis(trimethylsilyl) phosphonite was thought necessary for the purposes of establishing direct reactivity of bis(trimethylsilyl) phosphonite towards a range of electrophiles.

4.2. Preparation of bis(trimethylsilyl) phosphonite.

The first literature preparion[106] of bis(trimethylsilyl) phosphonite gave two methods for its synthesis and isolation, (Figure 4.1). The first (A) involved the action of diethylamine and chlorotrimethylsilane on ammonium phosphinate, giving a 36% yield. The second method (B) involved the reaction between anhydrous phosphinic acid and N,N-diethyl-trimethylsilylamine to give an 89% yield.

Our initial approach to generation and direct isolation of bis(trimethylsilyl) phosphonite was to use analogous conditions to those used in chapter 2, which gave di-substituted phosphinic acids in high yields, but with isolation of the bis(trimethylsilyl) phosphonite before electrophile addition, (*i.e.* by the action of triethylamine

Figure 4.1.

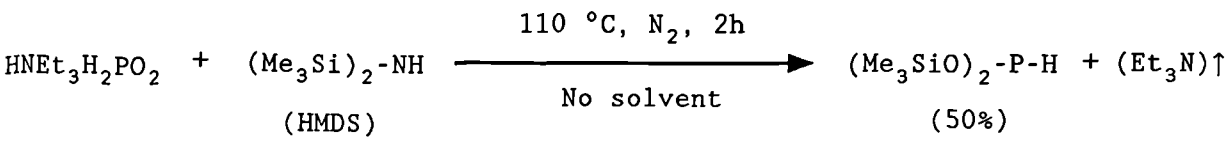


and chlorotrimethylsilane on triethylammonium phosphinate in dichloromethane followed by filtration of triethylammonium chloride and removal of solvents). This method was practically difficult to execute due firstly to copious precipitation of triethylammonium chloride which was difficult to remove efficiently, and secondly purification of the bis(trimethylsilyl) phosphonite by distillation to remove unreacted starting materials proved troublesome. Yields by this method were generally less than 30%, the low yields were probably due to the reasons discussed above, and hence an alternative method was sought.

A more efficient method of generation of bis(trimethylsilyl) phosphonite was achieved using hexamethyldisilazane as a combined base and silylating agent, as used by Isslieb.[130] We achieved generation of bis(trimethylsilyl) phosphonite by the action of hexamethyl disilazane on triethylammonium phosphinate, (Figure 4.2). The triethylamine formed was removed by distillation because the reaction temperature was slowly raised to and maintained at 110 °C. After approximately two hours no further triethylamine distilled out and the temperature was gradually raised to allow purification of the bis(trimethylsilyl) phosphonite by distillation at 159-165 °C in a yield of 50%.

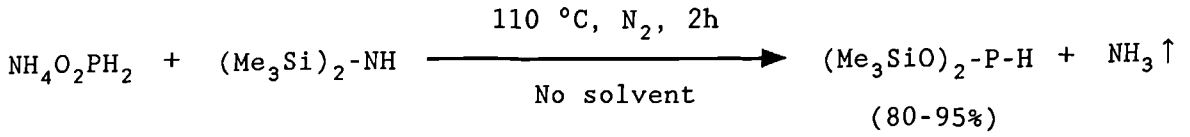
It is thought that depletion of hexamethyldisilazane may have occurred due to azeotroping with triethylamine, resulting in a lower yield of bis(trimethylsilyl) phosphonite.

Figure 4.2.



The most convenient preparation of bis(trimethylsilyl) phosphonite was by the action of hexamethyl disilazane on ammonium phosphinate giving yields of 80-95%, (figure 4.3). This reaction was much cleaner than other reactions towards bis(trimethylsilyl) phosphonite because the "by-product" was volatile ammonia which was conveniently vented from the reaction. Other methods towards bis(trimethylsilyl) phosphonite required removal of by-products by distillation. Ammonium phosphinate was conveniently prepared by controlled addition of concentrated ammonium hydroxide to a 50% solution of phosphinic acid followed by rigorous azeotropic drying. Hexamethyl disilazane was used in 5-10% excess because gradual evaporation of hexamethyl disilazane could be detected by condensation in the distillation flask, due to use of relatively high reaction temperatures, (hexamethyldisilazane bpt. 125 °C). A useful feature of this reaction is that its progress could be monitored by detection of ammonia liberated, the end of reaction being signalled by cessation of ammonia evolution.

Figure 4.3.



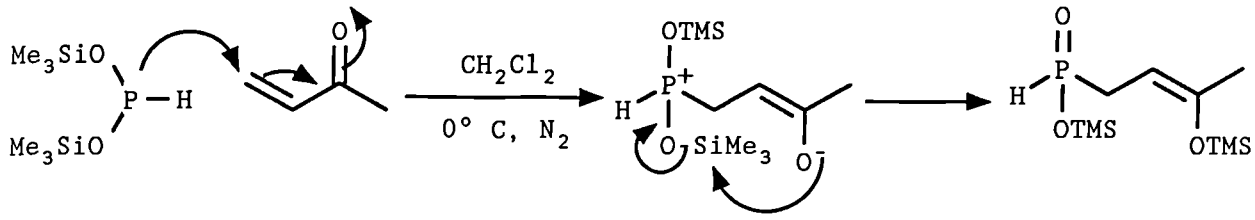
Bis(trimethylsilyl) phosphonite is a colourless mobile liquid with a boiling point of 164 °C.[125] It is highly sensitive to oxygen or moisture but is thermally stable in an inert atmosphere of nitrogen or argon, even on refluxing. Care had to be taken in directly handling of bis(trimethylsilyl) phosphonite due to the extreme pyrophoric nature exhibited on exposure to air or moisture. Bis(trimethylsilyl) phosphonite was stored refrigerated under nitrogen or argon in a flask equipped with a three way tap adaptor fitted with a septum. This way small aliquots of bis(trimethylsilyl) phosphonite could easily and conveniently be removed maintaining an inert atmosphere. Long refrigerated storage of bis(trimethylsilyl) phosphonite resulted in slight browning and white precipitation (of bis(trimethylsilyl) phosphinate) occurring, however use of this stored reagent in standardised reactions still gave reproducible results and yields.

4.3.1. Direct phosphinic acid synthesis using bis(trimethylsilyl) phosphonite: mono addition.

Bis(trimethylsilyl) phosphonite was dissolved in dichloromethane at 0° C and a variety of electrophiles were added. After approximately twelve hours the reactions were worked up to yield the phosphinic acids as oils: the results are shown in Table 4.1.a. for addition to vinyl ketones and

Table 4.1.b. for addition to other electrophiles. The predicted mechanism of addition of bis(trimethylsilyl) phosphonite to methyl vinyl ketone is shown in Figure 4.4; intramolecular silyl transfer is shown however intermolecular silyl transfer is probably more likely.

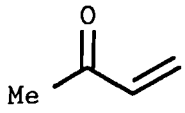
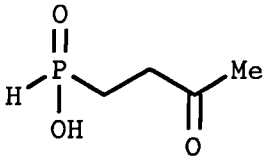
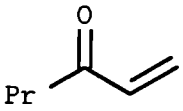
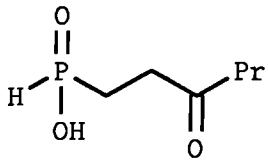
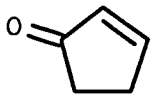
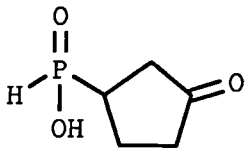
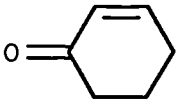
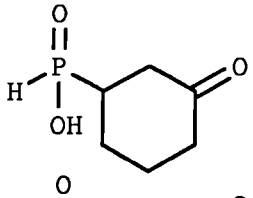
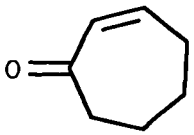
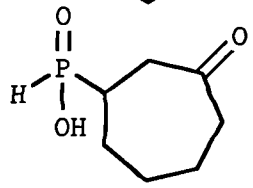
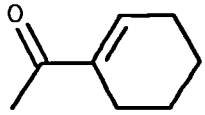
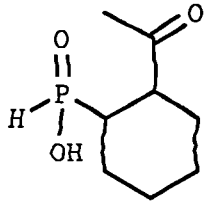
Figure 4.4.



Mono-substituted products from methyl and propyl vinyl ketones were isolated as colourless oils which showed no contamination by NMR, mass spectral analysis. These were extremely encouraging results because this was the first time a clean product had been isolated from addition to a vinyl ketone, and also relatively good yields were achieved. This gave strong evidence that Danishefsky type dienes were being formed in the presence of base because when no base is present then yields of phosphinic acid are good and generally pure.

Table 4.1.a.

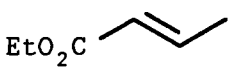
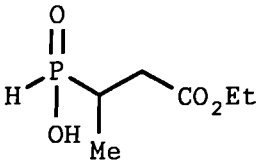
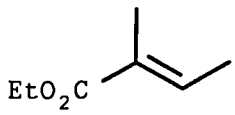
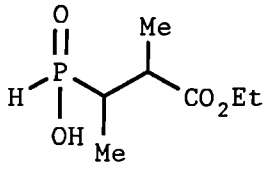
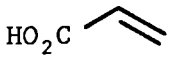
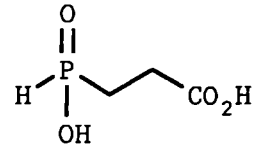
Addition to vinyl ketones.

Electrophile	Phosphinic acid	Yield. (%)
	(69) 	51
	(70) 	66
	(71) 	77[a]
	(72) 	94[a]
	(73) 	86[a]
	(74) 	76[a]

a) Impure from NMR spectra.

Table 4.1.b.

Addition to other electrophiles.

Electrophile	phosphinic acid	yield. (%)
	(40) 	74
	(75) 	28
	(76) 	68

Although the yields obtained from addition to 1-acetyl--1-cyclohexene, 2-cyclopentene-1-one, 2-cyclohexene-1-one and 2-cycloheptene-1-one were high the products were impure as judged from NMR spectra, and it is uncertain why addition to cyclo-enones gave contamination.

The direct addition of bis(trimethylsilyl) phosphonite to acrylates provided a more efficient route than using the "triethylammonium phosphinate" method for the syntheses of mono-substituted phosphinic acids. This is because a five to one ratio of bis(trimethylsilyl) phosphonite to acrylate was required in the "triethylammonium phosphinate" reaction, however in the above reactions bis(trimethylsilyl) phosphonite is used in a one to one manner. The clean

spectral data and the fact that the phosphinic acids generated above were colourless oils showed that this method allowed the isolation of cleaner purer products than the "triethylammonium phosphinate" or "sodium phosphinate" methods.

An important consequence of the direct use of bis(trimethylsilyl) phosphonite to synthesise mono-substituted phosphinic acids is that there is no chance of contamination from di-substituted phosphinic acid formation, this was found to result if other methods of phosphinic acid synthesis were used. However care needed to be taken to remove any unreacted hexamethyldisilazane from the ammonium phosphinate/hexamethyldisilazane reaction mixture, and this was achieved by distillation of the "crude" bis(trimethylsilyl) phosphonite. Di-substituted phosphinic acid contamination was actually observed if these precautions were not followed.

Two identical reactions involving bis(trimethylsilyl) phosphonite addition to methyl vinyl ketone were undertaken to elucidate whether extra reaction time could be used to increase yields. The first was worked up after sixteen hours giving a yield of 51%, the second was worked up after five days giving a 53% yield of mono-substituted phosphinic acid. Allowing for experimental error this gives evidence that extra reaction time has little or no effect on yield or purity of phosphinic acid.

Care had to be taken during the isolation of some of the mono-substituted phosphinic acids from vinyl ketones, due to appreciable solubility in water. This was particularly true for lower homologues. An alternative method for hydrolysing the silyl phosphinate esters resulting from addition of

bis(trimethylsilyl) phosphonite to an electrophile, was to inject a solution of dilute hydrochloric acid in tetrahydrofuran at 0°C to the reaction mixture. Excess acid could be conveniently removed on the rotary evaporator followed by pumping (< 0.01 mbar) to yield mono-substituted phosphinic acids generally, as colourless oils.

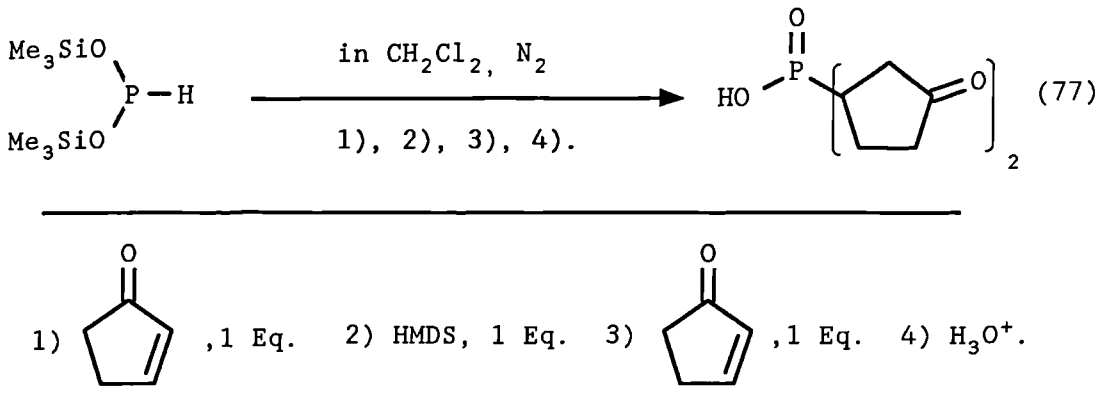
4.3.2. Direct phosphinic acid synthesis using bis(trimethylsilyl) phosphonite, bis addition.

The aim of these reactions was to extend the reaction developed in section 4.3.1. to allow preparation of di-substituted phosphinic acids which were inaccessible using other methods. Addition of bis(trimethylsilyl) phosphonite to vinyl ketones resulted in a silyl phosphinate after rearrangement, however if hexamethyldisilazane was added a trivalent substituted bis(trimethylsilyl) phosphonite resulted which could add to another equivalent of vinyl ketone. Figure 4.5 shows the addition to cyclopentenone, the mechanism of this reaction is discussed later. Using these conditions cyclopentenone gave 49% and cyclohexenone gave 22% as impure oils. Due to the lack of purity of these products and techniques for purifying them it was decided to direct research towards purification of the crude phosphinic acids.

4.4. Purification of phosphinic acids, the adamantanamine method

Many methods for the purification of phosphinic acids isolated as impure oils were undertaken as discussed previously. Direct distillation of phosphinic acids was not found to be useful for purification of either mono- or di-substituted phosphinic acids due to the lack of volatility

Figure 4.5.



even at high temperatures and low pressure. However the silyl phosphinates produced after addition of bis(trimethylsilyl) phosphonite to α,β-unsaturated carbonyl compounds were found to be relatively much more volatile than the free phosphinic acids themselves. The crude silyl phosphinates were isolated by removal of dichloromethane and direct Kugelrohr distillation of the reaction products; distilled by this method were the silyl phosphinates from 2-cycloheptene-1-one and ethyl crotonate. After hydrolysis and isolation of the free phosphinic acids the products were found to be not quite analytically pure. It was thought that this method, although allowing partial purification of phosphinic acids, was not suitable as a general method of purification, and hence was not further developed.

Having used many physical methods for phosphinic acid purification with little success it was decided to utilise chemical methods. We rationalised that if crystalline phosphinic acid derivatives could be prepared these could be purified by washing or recrystallisation. The precedent for purification by washing came from the fact that crystalline di-substituted phosphinic acids from simple acrylates had

utilized this method, yielding analytically pure products, in chapters 2 and 3. The first chemical method for phosphinic acid purification was to synthesise methyl and benzyl phosphinate esters; this was used in chapter 2. A proposed second method was in some respects the opposite of what esterification was trying to achieve: the formation of salts of phosphinic acids was undertaken. The effects of salt formation can be seen from the following phenomenon, the sodium salt of phosphinic acid decomposes on heating above 150 °C, whereas the free phosphinic acid has a melting point of 27 °C. This concept of derivatisation to form crystalline solids from oils or glasses, enabling purification and easier handling, has been utilized in amino acid chemistry which suffers from similar purification problems. In this area dicyclohexylammonium salts of N-protected amino acids have often been used.

D.S.Karanewsky[142] has recently isolated phosphonic acids as their 1-adamantanammonium salts by adding an ethereal solution of adamantanamine to a phosphonic mono ester, and the resulting salt was obtained by filtration. This direct approach was thought to be unsuitable for phosphinic acids, due to their lack of solubility in diethyl ether or similar solvents. However the use of adamantanamine, being such a highly crystalline compound, was attractive because it was predicted that adamantanammonium phosphinates should be crystalline.

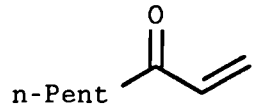
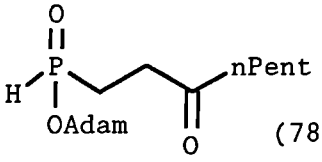
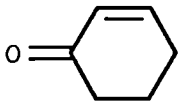
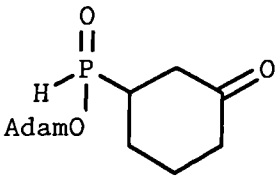
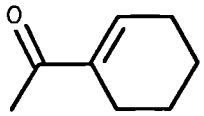
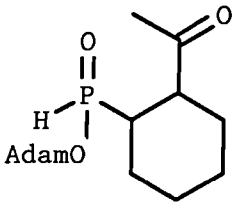
Direct addition of a solution of adamantanamine in diethyl ether to a dispersion of phosphinic acid resulted in high yields of adamantanammonium phosphinates, which however were not analytically pure even on washing. This was probably due to contamination of the product by unreacted free

phosphinic acid, which being oily and insoluble in ether coated some of the products. Little success was achieved by changing the solvent system; many mixtures were evaluated but analytically reproducible results were not obtained. However the fact that the first crystalline derivatives of mono-substituted phosphinic acids had been prepared was extremely encouraging.

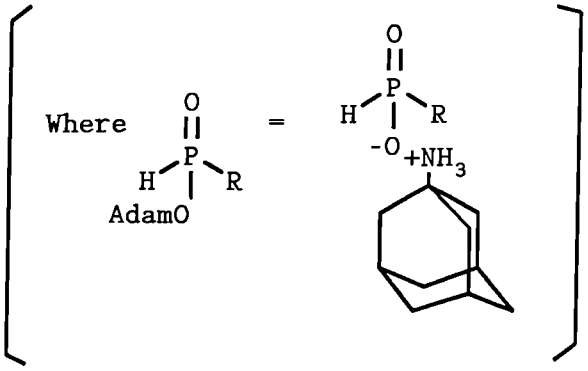
Instead of trying to form the adamantanammonium phosphinate salts by direct addition of adamantanamine to phosphinic acids, it was proposed to try to slowly hydrolyse the silyl phosphonites which result after bis(trimethylsilyl) phosphonite addition to electrophiles. The silylated phosphinates were found to be much more soluble in diethyl ether than the corresponding free acids, and it was hoped that residual amount of water in diethyl ether would hydrolyse the silylated phosphinates. The results are shown in Table 4.2. Yields shown are based on starting amounts of bis(trimethylsilyl) phosphonite. The results show that only the mono-substituted phosphinic acid from 1-octen-3-one was analytically pure, and this was rationalised from ^{1}H and ^{13}C NMR spectra, which revealed silyl functionality still present contaminating the desired adamantanammonium phosphinate due to incomplete hydrolysis of the silylated phosphinates, even after twenty four hours of reaction.

Many different solvent systems were tried to find a suitable medium for controlled desilylation. A solution of methanol in tetrahydrofuran (approximately 1:7) was found to be optimal for the formation of analytically pure adamantanammonium phosphinate products. Methanol seemed to give more controlled and effective hydrolysis of the silyl phosphinates than direct use of water which was observed to

Table 4.2.

Vinyl ketone	Adamantanammonium phosphinate	yield. (%)
	 (78)	70[a]
	 (79)	92
	 (80)	89

[a] Analytically pure.



cause the free phosphinic acids to precipitate out.

It should be noted that commercially available adamantanamine (Aldrich) contained a small amount of impurity (probably by reaction with atmospheric carbon dioxide) which was easily removed by filtration of an ethereal solution of adamantanamine prior to use. Analytically pure products were difficult to reproduce if this precaution was not followed.

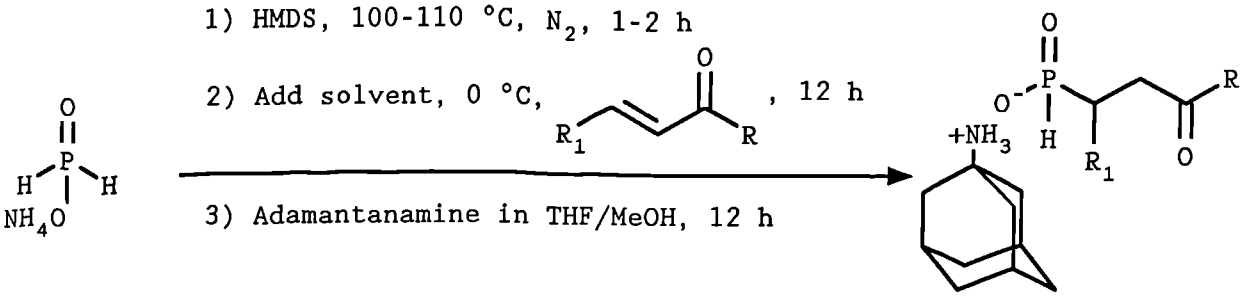
Adamantanammonium phosphinate formation provided a necessary breakthrough in the purification of phosphinic

acids. Analytically pure products have been isolated by salt formation, which allowed removal of impurities by crystallisation from ether, with the impurities remaining in solution. This method has been utilized successfully in the direct hydrolysis/quaternization of silyl phosphinates to yield, under appropriate conditions, pure phosphinate products in very high yield.

4.5. One pot sequential adamantanammonium mono-substituted phosphinate preparation.

The fact that bis(trimethylsilyl) phosphonite could be conveniently prepared by the reaction of hexamethyldisilazane on ammonium phosphinate led to the idea of utilizing this reaction *in situ*, without isolation of bis(trimethylsilyl) phosphonite. This method was combined with the adamantanamine method to form a novel one pot synthesis of mono-substituted phosphinic acids, which were isolated as the crystalline adamantanammonium phosphinates, (Figure 4.6). The reaction consisted of *in situ* bis(trimethylsilyl) phosphonite generation, followed by addition of dichloromethane solvent after cooling. The appropriate α,β-unsaturated carbonyl electrophile was injected followed by room temperature stirring for approximately twelve hours. Removal of the solvents yielded silyl phosphinates, generally as viscous oils to which was added a solution of adamantanamine in tetrahydrofuran/methanol with stirring for twelve hours. The adamantanammonium phosphinate was isolated by filtration and washed with ether which generally yield analytically pure white crystalline products.

Figure 4.6.



The results for *in situ* one pot addition of bis(trimethylsilyl) phosphonite to vinyl ketones is shown in Table 4.3.1. and addition to acrylates is shown in Table 4.3.2.

Some adamantanammonium phosphinates were slightly soluble in the tetrahydrofuran/methanol solution used for the controlled hydrolysis of the silylated phosphinates, and a second crop of product could conveniently be obtained by concentration of the filtrate followed by dispersion in diethyl ether. Filtering after twelve hours resulted in crystalline adamantanammonium phosphinates of good purity; the yields given represent combined yields where applicable.

The results obtained showed this to be an excellent method for preparation of analytically pure adamantanamine salts of phosphinic acids in very good to excellent yields. A general trend was observed which showed that yields decreased with double bond substitution; hence α,β-unsaturated carbonyl compounds with no substitution on the double bond gave higher yields than those which did possess substitution, as observed for bis alkylation in chapter 2. The reason for the modest yield of phosphinic acid from methyl vinyl ketone (74%) was probably due to polymerization which occurs much more readily for methyl vinyl ketone than other vinyl ketones.

Table 4.3.1.

One pot preparation of mono-substituted adamantanammonium phosphinate

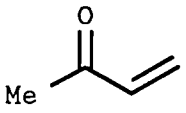
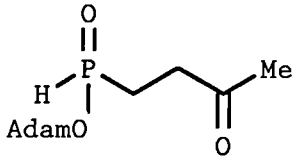
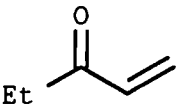
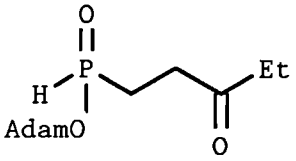
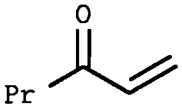
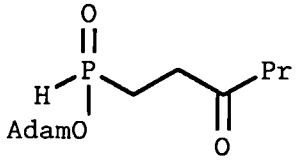
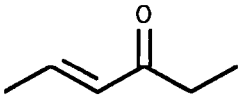
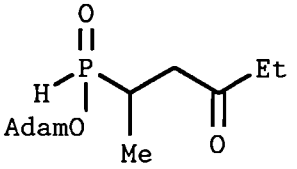
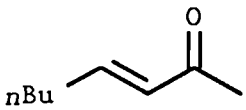
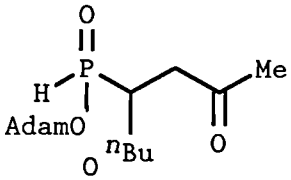
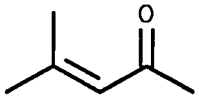
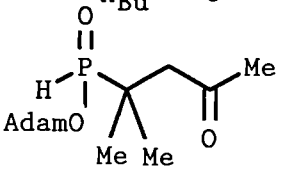
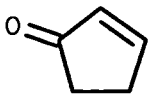
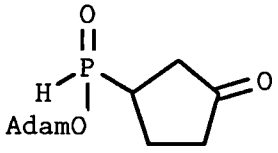
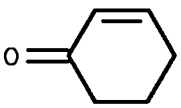
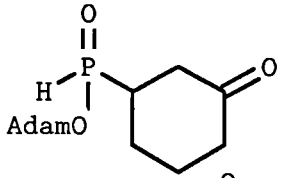
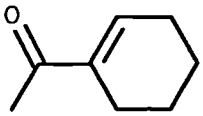
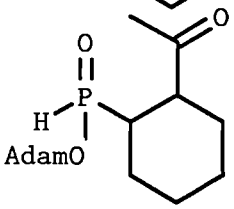
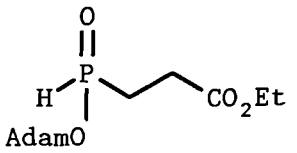
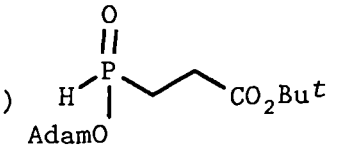
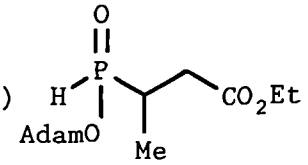
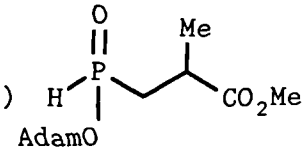
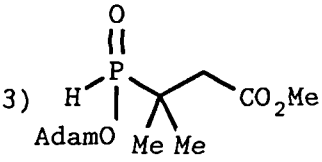
Vinyl ketone	Adamantammonium phosphinate	Yield (%)
	(81) 	74
	(82) 	89
	(83) 	87
	(84) 	80
	(85) 	77
	(86) 	80
	(87) 	91
	(79) 	87
	(88) 	79

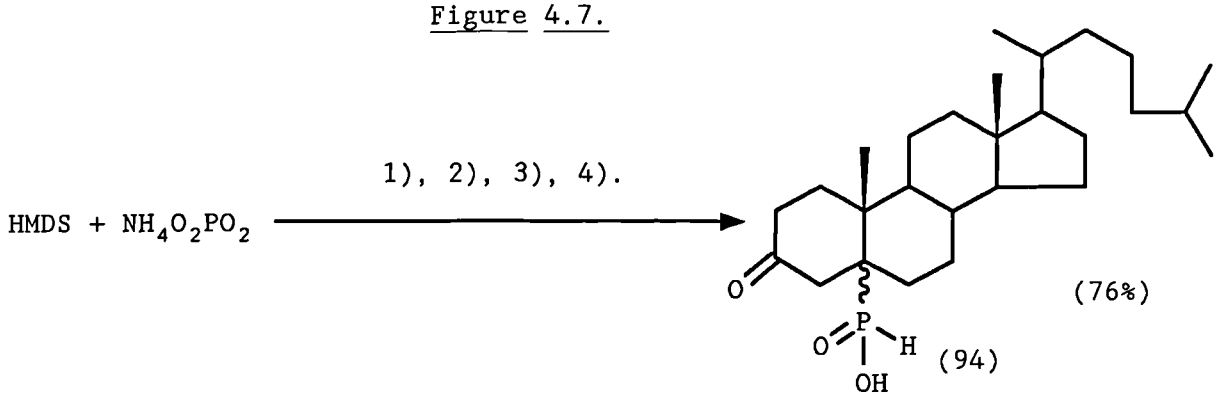
Table 4.3.2.

One pot prepartion of mono-substituted adamantanammonium phosphinate.

Unsaturated ester	Adamantanammonium phosphinate	Yield (%)
EtO_2C	(89) 	99
$tBuO_2C$	(90) 	93
EtO_2C	(91) 	92
MeO_2C	(92) 	78
EtO_2C	(93) 	67

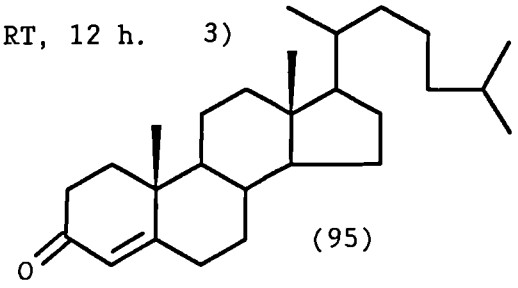
To illustrate the potential of this reaction preparation of the phosphinic acid obtained by the addition of bis(trimethylsilyl) phosphonite to 4-cholesten-3-one (95) was attempted, (Figure 4.7). Preparation of the free acid (94) was achieved in 76% and isolated as a solid foam, however attempts at synthesis of the adamantanammonium phosphinate resulted in a mixture of free acid and ammonium salt isolated as an oily solid. This was probably due to the large size of both adamantanamine and the steroidal phosphinate, making reaction sterically unfavourable.

Figure 4.7.



1) 100 °C, 2 h, N_2. 2) CH_2Cl_2, 0 °C - RT, 12 h. 3)

4) Methanolic work-up .



An adaptation of this method involved dividing the silylated phosphinates after the solvent had been removed into two portions. The first portion was used for adamantanammonium phosphinate formation and the second portion was hydrolysed at 0 °C by dissolving in methanol. This led to isolation of free phosphinic acids as oils, some of which were analytically pure.

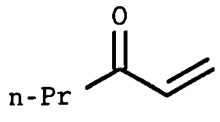
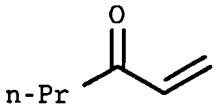
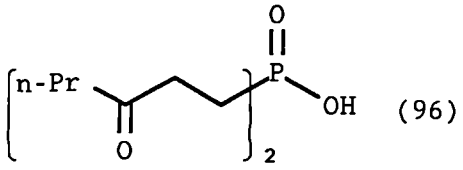
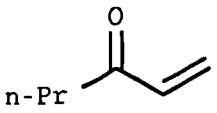
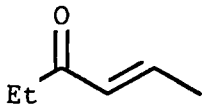
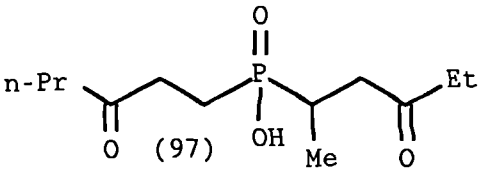
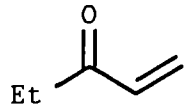
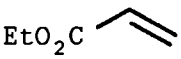
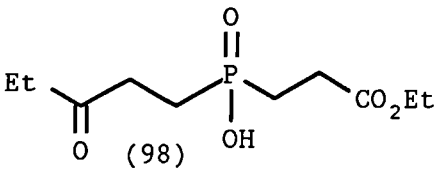
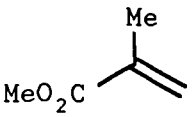
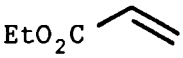
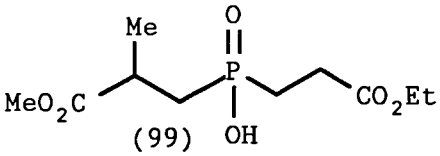
4.6. One pot sequential di-substituted phosphinic acid formation.

In section 4.5. a sequential one pot synthesis of mono-substituted phosphinic acids and their adamantanamine salts was achieved and successfully utilized. We proposed to extend this methodology towards the synthesis of symmetrical and unsymmetrical di-substituted phosphinic acids. The reaction was the same as for mono addition, however after generation of the silyl phosphinate after first addition to

an electrophile another equivalent of hexamethyldisilazane was injected which formed a substituted phosphonite. Addition of another equivalent of α,β-unsaturated carbonyl reagent resulted in addition by the substituted phosphonite, and upon protic work-up the free di-substituted phosphinic acid resulted. Some adamantanamine salts of di-substituted phosphinic acids were isolated in an analogous manner to mono-substituted adamantanammonium phosphinate formation by directly hydrolysing the silyl phosphinates resulting at the end of reaction with a solution of adamantanamine in tetrahydrofuran/methanol. However formation of sticky oily solids resulted on analogous adamantanammonium phosphinate formation. We proposed that due to steric bulk, reaction of adamantanamine and silyl phosphinates is slow and unfavourable.

The results are shown in Table 4.4, and a possible mechanism of addition to methyl vinyl ketone is shown in Figure 4.8. The mechanism follows the same route as for mono addition, however addition of an extra equivalent of hexamethyldisilazane results in generation of substituted phosphonite (101) which reacts with a further equivalent of methyl vinyl ketone after injection, to form the phosphonium salt (102). (102) probably rearranges by silyl transfer to form the trimethylsilyl di-substituted-phosphinic acid, which on acidic methanolysis or aqueous work-up yields di-substituted phosphinic acid. To demonstrate the flexibility and hence utility of this reaction combinations of α,β-unsaturated esters and ketones were used.

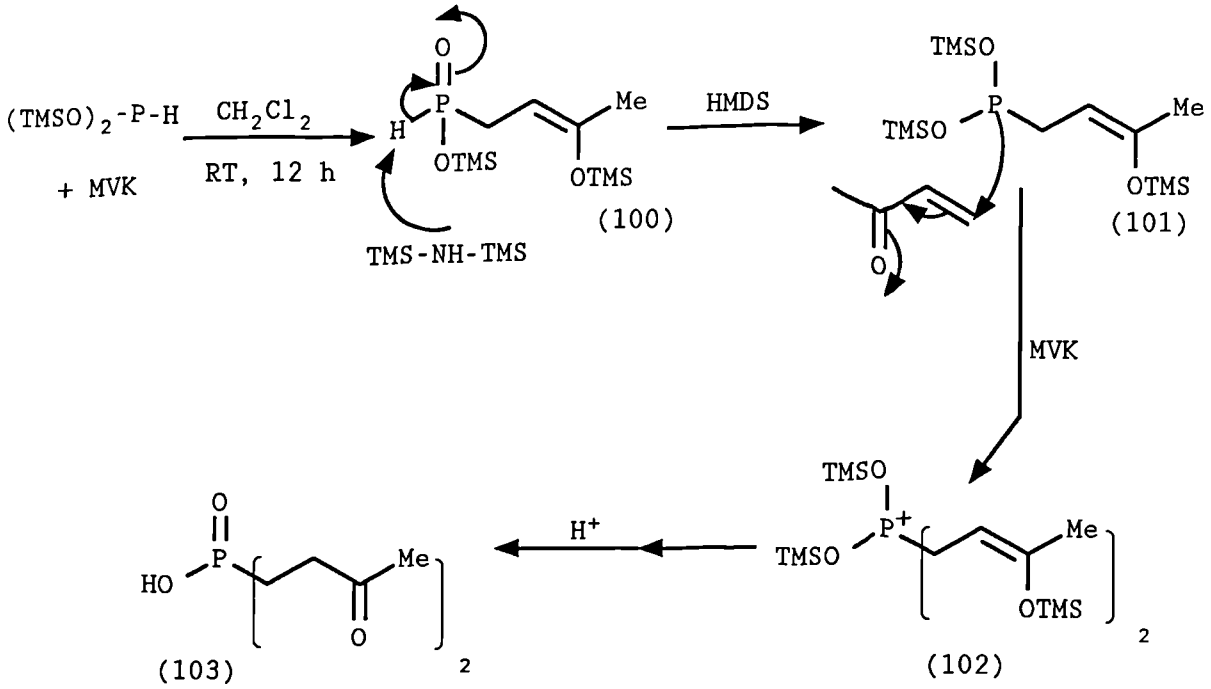
Table 4.4.

First Electrophile	Second Electrophile	Di-substituted unsymmetrical phosphinic acid	Yield (%)
		 (96)	87
		 (97)	83
		 (98)	79
		 (99)	77

4.7. Conclusion.

The research described in this chapter has successfully allowed synthesis of phosphinic acids from vinyl ketones, which had not previously been possible for reasons discussed above. Extremely flexible methodology has been formulated and developed to allow a one pot preparation of mono-substituted, symmetrical and unsymmetrical di-substituted phosphinic acids in very high yields and of good purity by sequential controlled addition of appropriate reagents. A large number of novel phosphinic acids have been synthesized to demonstrate the utility of this method. This methodology

Figure 4.8.



allows the synthesis of relatively complex substituted phosphinic acids from simple starting materials.

The analytical purity of products from mono addition has been ensured by the novel use of *in situ* adamantanammonium phosphinate formation to yield crystalline products from oils. This method of purification is probably general to phosphinic acids and hence is potentially very useful for characterisation.

This chapter has revealed that bis(trimethylsilyl) phosphonite is a very reactive nucleophilic species in Michael-type addition to vinyl ketones and other electrophiles. The controlled addition of reagents stops the need to have base or silylating agent in contact with the electrophile thus reducing side-reactions and hence greatly increasing the scope of this synthetic method. The flexibility of this methodology can be seen by the use of acrylic acid as an electrophile; by other methods of

phosphinic acid synthesis this would not have been possible. This has been demonstrated to be a very clean synthetic method. Some of the mono-substituted phosphinic acids were directly isolated after reaction, without further purification and were found to be analytically pure.

All products were as result of 1,4 Michael-type addition by bis(trimethylsilyl) phosphonite to the α,β-unsaturated carbonyl electrophiles, and there was no evidence of any 1,2 addition which has been reported to occur on addition to α,β-unsaturated aldehydes.[118]

CHAPTER 5.

A NEW GENERAL METHOD FOR PHOSPHINIC ACID SYNTHESIS

5.1. Introduction.

Due to the success in being able to synthesise phosphinic acids using vinyl ketones (Chapter 4), it was predicted that under the appropriate reaction conditions alkyl halides would also be useful as electrophiles. Due to ready availability of alkyl halides this would be extremely useful if it could be achieved.

The aim of this chapter was to develop methodology to allow alkyl phosphinic acid synthesis from alkyl halides under mild conditions using bis(trimethylsilyl) phosphonite as the source of hydroxyphosphoryl functionality.

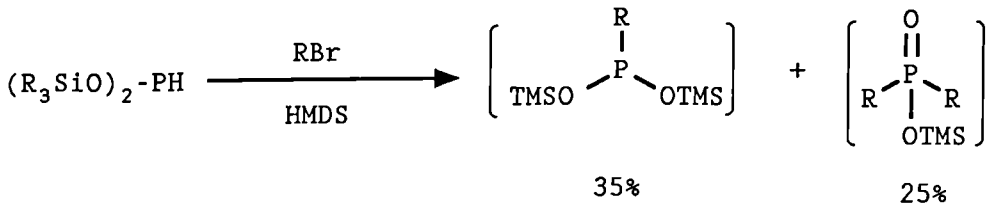
The first recorded addition of bis(trimethylsilyl) phosphonite to alkyl halides was by Voronkov *et al.*[125] who claimed that additions to alkyl bromides at 100 °C resulted in practically complete disproportionation instead of the expected Arbuzov products, (Figure 5.1).

Figure 5.1.

$$6\ (R_3SiO)_2\text{-}PH \xrightarrow[100\ ^\circ C,\ Ar]{RBr} 3\ (R_3SiO)_2\text{-}PHO + 3\ R_3SiOSiR_3 + PH_3 + 2\ P$$

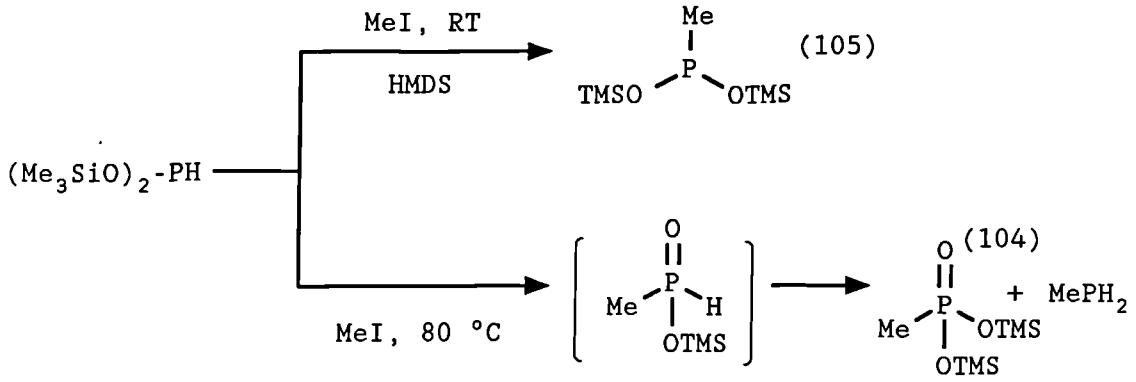
Issleib *et al.*[130] reported that certain alkyl halides undergo substitution by bis(trimethylsilyl) phosphonite. They reported that alkyl chlorides were inactive towards substitution but alkyl bromides underwent substitution in the presence of hexamethyldisilazane to yield a mixture of bis(trimethylsilyl) alkylphosphonite and trimethylsilyl di-alkyl phosphinate, (Figure 5.2) which rapidly underwent disproportionation to phosphine and phosphonate.

Figure 5.2.



They also reported that direct addition of methyl iodide to bis(trimethylsilyl) phosphonite resulted in an exothermic reaction which is claimed first to form the phosphinate which under these conditions immediately breaks down to form methyl phosphine and bis(trimethylsilyl) methylphosphonate (104), (Figure 5.3). However if methyl iodide was added to a solution of bis(trimethylsilyl) phosphonite and hexamethyldisilazane then bis(trimethylsilyl) methylphosphonite (105)(58%) resulted (Figure 5.3).

Figure 5.3.

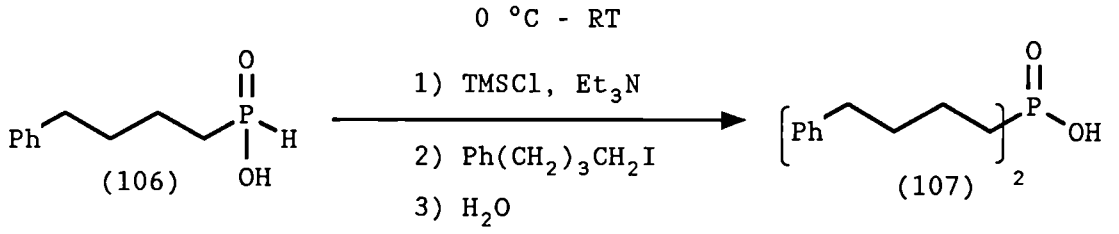


These results suggest that reaction of bis(trimethylsilyl) phosphonite with reactive alkyl halides could be achieved, however the alkylated products were susceptible to disproportionation reactions.

Thottathil *et al.*[119] reported that a substituted trimethylsilyl phosphonite (106) underwent substitution with

1-iodo-4-phenyl butane, and the resulting di-substituted phosphinic acid (107) was isolated in a 48% crude yield after aqueous work-up (Figure 5.4). Although evidence suggests that substitution by a substituted bis(trimethylsilyl) phosphonite is quicker than for the bis(trimethylsilyl) phosphonite, (*i.e.* second substitution is more facile than the first substitution) this gave evidence that direct alkylation might be viable under suitable reaction conditions.

Figure 5.4.



Due to the mildness and flexibility of the methodology for the synthesis of phosphinic acids developed in Chapter 4 it was decided to direct further research towards adapting this new chemistry towards phosphinic acids from alkyl halides *i.e.* a modified "Arbuzov type" reaction under very mild conditions.

5.2. Mono alkylation.

Due to the ease and convenience of *in situ* generation and use of bis(trimethylsilyl) phosphonite developed in Chapter 4 we decided firstly in an attempt to synthesize mono-alkylated phosphinic acids to use the same conditions with alkyl iodides as with the other electrophiles. Alkyl iodides were chosen due to the general increase in electrophilicity compared to bromides or chlorides. At the end of the reaction we proposed to hydrolyse any silyl

phosphinates with controlled methanolysis to yield free acids, or isolate them as adamantanammonium phosphinates by addition of a methanolic tetrahydrofuran solution of adamantanamine, as this methodology had proved successful and very useful in chapter four.

Initial results using methyl iodide gave a colourless oil in yields of greater than 90% which was clean as judged by ^{31}P, ^{13}C and ^{1}H NMR spectra. No disproportionation was detected as observed in analogous reactions by Voronkov and Issleib. Due to the apparent cleanness of this reaction a series of mono alkyl phosphinic acids were synthesized; Table 5.1 shows the results.

The results obtained for mono alkylation showed that we had developed a simple route to mono alkyl phosphinic acids in high yields, and this had been achieved by adaptation of the *in situ* one pot addition reaction. We initially thought that direct use of this method might result in the disproportionation observed by Issleib and Voronkov, however this was not the case. We proposed that alkylation addition by bis(trimethylsilyl) phosphonite a tetravalent phosphonium iodide results, which upon methanolysis results in the free phosphinic acid (Figure 5.5).

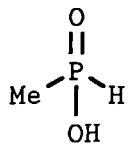
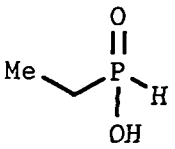
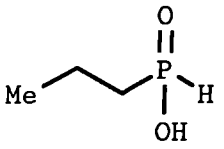
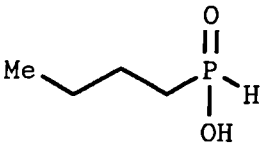
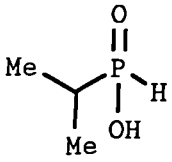
5.3. Bis alkylation.

Due to the success of mono alkylation of bis(trimethylsilyl) phosphonite by alkyl iodides, we tested the synthetic utility by synthesizing a series of symmetrical di-alkyl phosphinic acids. This was achieved by adaptation of the *in situ* one pot phosphinic acid reaction; the results are shown in Table 5.2.

^{1}H, ^{13}C and ^{31}P NMR spectra for the dialkyl symmetrical

Table 5.1.

Mono alkylation

Alkyl iodide	Phosphinic acid	yield (%)
MeI	(108) 	94 97[a]
EtI	(109) 	95
n-PrI	(110) 	81[a]
n-BuI	(111) 	88[b]
i-PrI	(112) 	58[a]

[a] Isolated as free acid and adamantanammonium phosphinate.
[b] Isolated as the adamantanammonium phosphinate.

Figure 5.5.

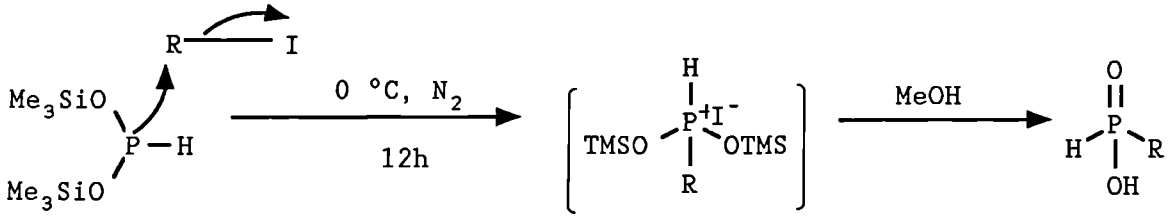
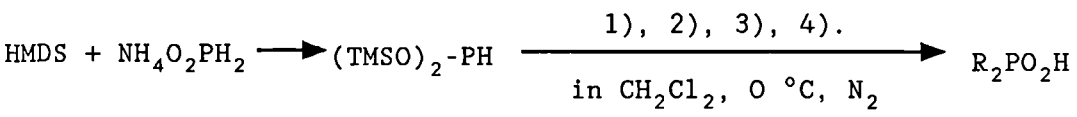
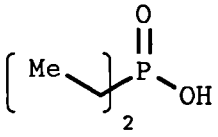
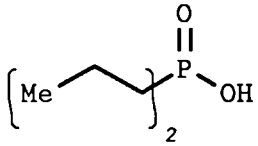
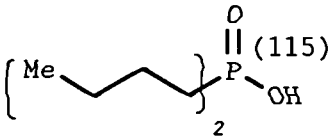
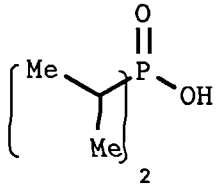


Table 5.2.
Bis alkylation



1) RI, 2) HMDS, 3) RI, 4) MeOH.

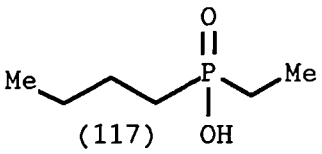
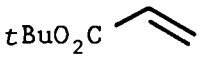
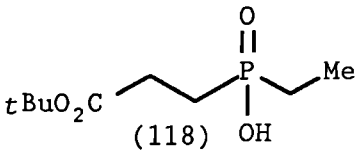
Results

Alkyl iodide	Phosphinic acid	yield (%)
EtI	(113) 	75
n-PrI	(114) 	87
n-BuI	 (115)	82
i-PrI	(116) 	67

phosphinic acids showed clean compounds: diethyl phosphinic acid was isolated as a colourless oil, di-*n*-propyl and di-*n*-butyl phosphinic acids were also isolated as oils but crystallised out on standing. Due to the success towards synthesising symmetrical di-alkylphosphinic acids using this method, some unsymmetrical phosphinic acids were synthesised to demonstrate the synthetic utility and flexibility; Table 5.3 shows the results.

Table 5.3.

Unsmmetrical di-alkylphosphinic acids.

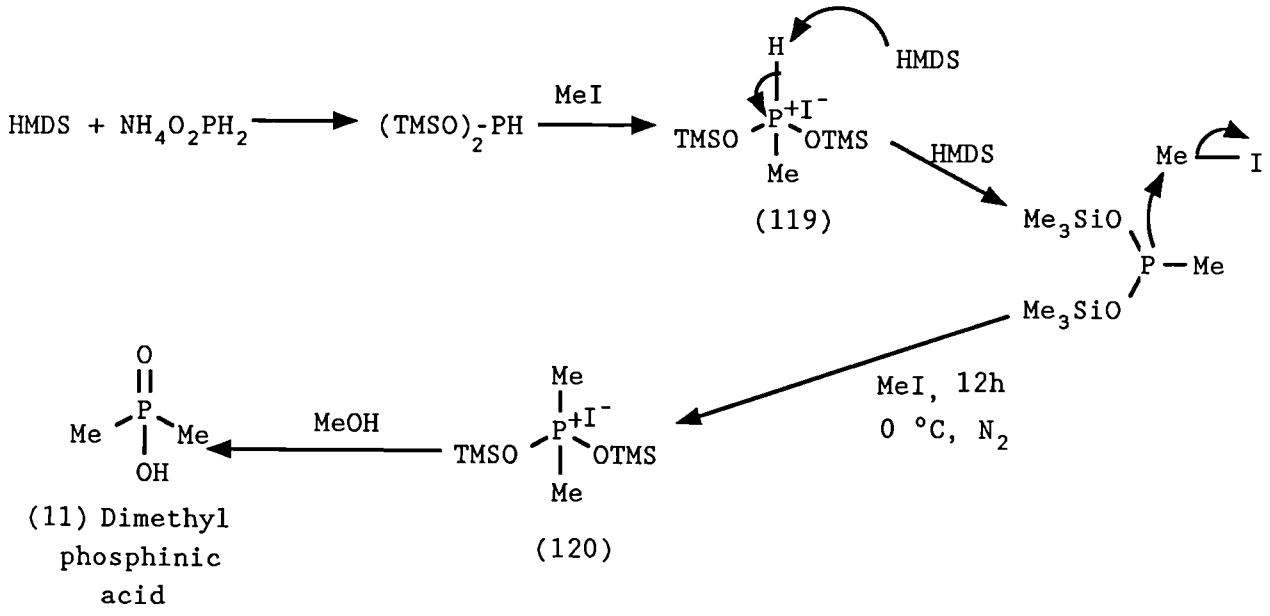
First electrophile	second electrophile	Phosphinic acid	Yield (%)
n-BuI	EtI	 (117)	87
EtI		 (118)	88

Attempts at synthesis of dimethyl phosphinic acid gave a brown oil in almost quantitative yield which was almost pure from NMR spectra, however conventional attempts at crystallising this oil failed. The phosphinic acid could be Kugelrohr distilled at approximately 0.1 mbar/ 200 °C to yield a viscous brown oil which crystallised on standing. The crystalline dimethylphosphinic acid could conveniently be separated from the oil by washing with an ethereal ethyl acetate(20%) solution, to yield the phosphinic acid as colourless crystalline plates. Analytically pure samples were obtained by this method in greater than 50% yield, (calculated from ammonium phosphinate), and impure crystalline products were recrystallised from benzene.

A probable mechanism for di-alkylation of bis(trimethylsilyl) phosphonite is shown in Figure 5.6, using methyl iodide. Evidence for this mechanism came from isolation of intermediate (120) by the removal of the solvent twelve hours after the second addition of methyl iodide in an

attempted dimethylphosphinic acid preparation. The product was a yellow crystalline solid which rapidly decomposed on atmospheric exposure, but could be stored under nitrogen. The mass spectrum showed the product to be intermediate (120). This we found surprising because iodide was expected to cleave the silyl ether bond which would result in reformation of the phosphoryl bond, a process which in most analogous systems is very facile due to it being energetically favourable. The fact the product was crystalline probably reduced the possibility of decomposition.

Figure 5.6.



5.4. Conclusion.

In this chapter synthesis of mono- and di-substituted symmetrical and unsymmetrical alkylphosphinic acids have been synthesized in high yield in a relatively simple one pot reaction, involving generation of bis(trimethylsilyl) phosphonite *in situ*. No problems were encountered due to disproportionation, as reported by Issleib and Voronkov; this

probably results and is facilitated by the fact that they used no solvents and high temperatures. Issleib reported mono alkylation of bis(trimethylsilyl) phosphonite by methyl iodide in the presence of hexamethyldisilazane, yielding bis(trimethylsilyl) methylphosphonite(58%), however using these conditions we found predominantly di-alkylation products. Evidence that bis(trimethylsilyl) methylphosphonite was not the "only" product synthesised, (under these conditions we expect it to be a contaminant with di-alkylation predominating) comes from the analytical analysis. The calculated phosphorus content for the proposed structure is 10.60%, however Issleib quotes a phosphorus content of 13.80% as measured by elemental analysis. However the lack of spectral data means that we cannot be totally sure that a dialkylated phosphorus product actually resulted.

The studies were not extended to alkyl chlorides or bromides because iodides are generally readily available and tend to be electrophilically more reactive. However if only bromides or chlorides are available these can conveniently be transformed to the iodide by using the Finkelstein reaction.

This new methodology is very flexible and can allow very simple to very complex phosphinic acid synthesis. For example dimethyl phosphinic acid can conveniently be synthesised using this methodology, whereas previous methods of synthesis, (see chapter 1) are long, expensive and hazardous, and this is reflected in the commercial price of over fifty pounds per gram! (Aldrich). However, just as easily, larger chains can be incorporated containing additional functionality, and hence more complicated phosphinic acids are accessible.

The mechanism of alkylation of bis(trimethylsilyl)

phosphonite by alkyl iodides for the synthesis of bis phosphinic acids differs from the Arbuzov reaction, which is catalysed by a halide induced isomerization to yield a phosphinate from a phosphonium salt. There is no isomerization in our new reaction and only phosphonium salts (120) are isolated, however on atmospheric exposure these products rapidly desilylate, going through the isomerised phosphinate intermediates to phosphinic acid. Evidence for this came from mass spectral analysis.

This new synthetic method has general flexibility and does not rely on the availability of the appropriately substituted phosphorus containing reagent, as do other approaches. This reaction can tolerate substitution in the alkyl chains, secondary halides give phosphinic acid products rather than elimination side products which predominate under usual Arbuzov reaction conditions. The fact that these reactions are facile at room temperature or below means that more sensitive functionality can be incorporated into the phosphinic acids with less chance of decomposition due to pyrolysis or disproportionation reactions.

CHAPTER 6.

PHOSPHINIC ACID ANALOGUES OF NATURAL PRODUCTS AND IDEAS AND FUTURE SYNTHESIS

6.1. Introduction.

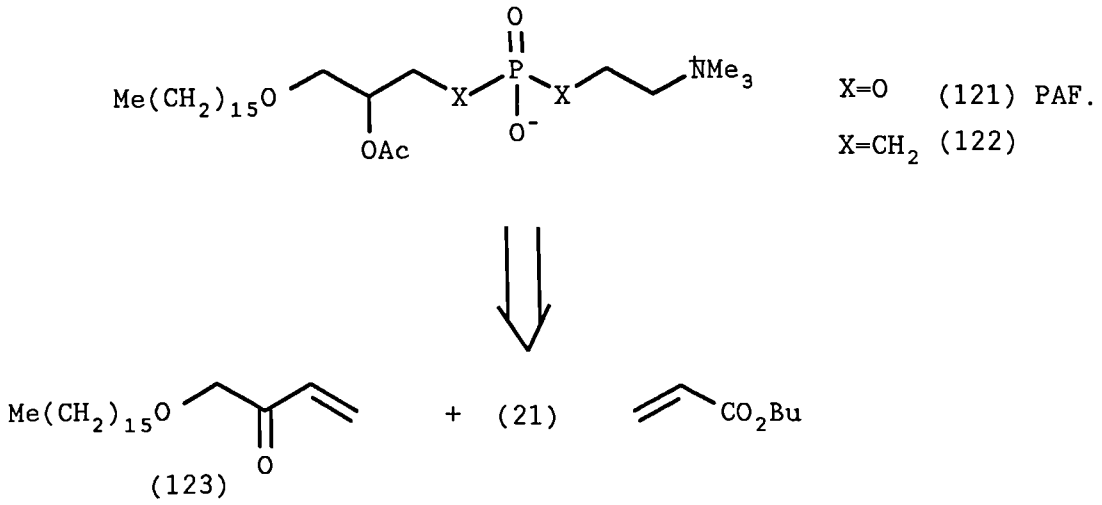
One of the most important reasons for undertaking this research project was to allow phosphinate analogues of naturally occurring phosphorus containing compounds to be synthesized. The methylene phosphinic acid group can act as a non-hydrolysable isosteric analogue of the P-O-C bonds of phosphate esters or the P-O-P bond of phosphoric anhydrides. In this chapter preliminary work has been undertaken towards a phosphinate analogue of platelet activating factor, section 6.2. Due to the development of the mild Arbuzov reaction of chapter 5 only limited time was spent towards synthesis of analogues. However interesting results have been achieved which are useful for synthesis of phosphinate analogues and for novel phosphinic acid synthesis. Section 6.3 describes some preliminary work in this area, with my ideas on other phosphinate analogues and gives examples of the predicted synthesis and use of these reagents.

6.2. Platelet activating factor.

The first analogue attempted was the phosphinate analogue of platelet activating factor (PAF)(121),[143] a 1-O-alkyl-2-acetyl glyceryl-3-phosphorylcholine, (Figure 6.1). Platelet activating factor is a phosphate diester, and we proposed to substitute the two P-O-C bonds with isosteric P-C bonds. Platelet activating factor (121) was the first bioactive phospholipid discovered and has a complex role of physiological and biochemical functions; of particular interest is that it exhibits antihypertensive propeties.

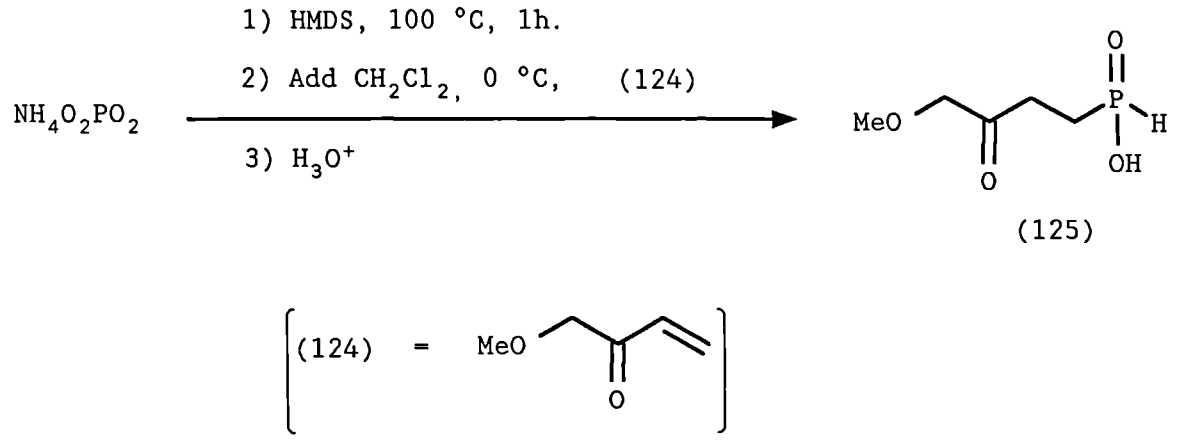
We envisaged the key step in synthesis of (122) as the addition of bis(trimethylsilyl) phosphonite to an α-alkoxy vinyl ketone (123). A simple model study was undertaken using

Figure 6.1.



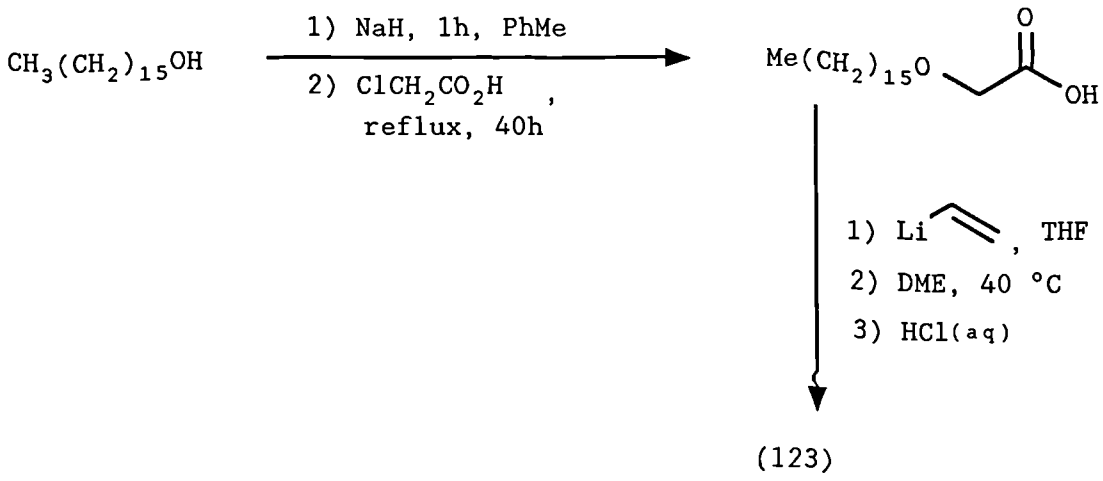
methoxymethyl vinyl ketone[144] as the electrophile (Figure 6.2). Mono addition resulted in the desired phosphinic acid (125) in 84% yield as a colourless oil. Methoxymethyl vinyl ketone was prepared by methylation of 1,4-butynediol using dimethyl sulphate followed by methanolysis using mercuric chloride to yield 1,4-dimethoxy-2-butanone which eliminates methanol under acid catalysed conditions, to give (124).

Figure 6.2.



Due to the success of the model study we attempted to synthesize (123), which has been reported[145] in a crude yield of 30% but it was not characterised, no spectral data was provided either. Figure 6.3 shows the synthetic sequence reported.

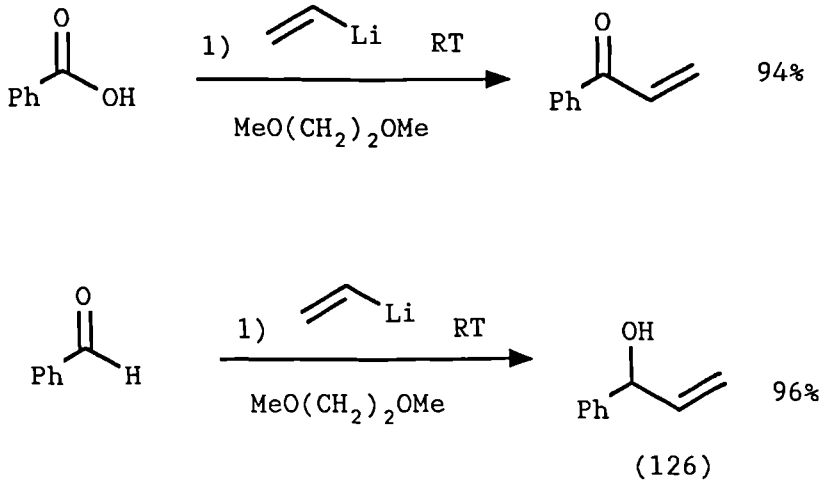
Figure 6.3.



Hexadecyloxyacetic acid was prepared according to the literature;[145] it is difficult to handle in solution due to the surfactant like properties exhibited. However all attempts at addition of vinyl lithium to hexadecyloxyacetic acid failed. The reaction time was extended, elevated temperatures were used, extra equivalents of vinyl lithium were added over the course of the reaction, and the reaction was performed under sonication conditions, however none of these changes effected reaction. Attempts at preparing the lithium carboxylate salt[146] of hexadecyloxyacetic acid (127) resulted in incomplete salt formation and the contaminated product was not used towards synthesis of (123). The reason that the reaction was failing is thought to be due to the lack of solubility of hexadecyloxy acetic acid in dimethoxyethane, even at 40 ^{o}C it appears only sparingly

soluble. Vinyl lithium was conveniently prepared[147] by addition of *n*-butyllithium to tetravinyl tin followed by removal of the hexane in which the *n*-butyllithium was supplied. After washing, the vinyllithium was dissolved in tetrahydrofuran and titrated.[148] Due to the lack of reaction between vinyl lithium and hexadecyloxyacetic acid the reactivity of vinyl lithium was assessed by reaction with benzaldehyde and benzoic acid (Figure 6.4). Both reactions proceeded to give the desired products in excellent yield. A solution of vinyl lithium was made up in dimethoxyethane because hexadecyloxyacetic acid was found to be insoluble in tetrahydrofuran. This vinyl lithium solution had to be used quickly because it rapidly decolourised and went brown on standing for a day.

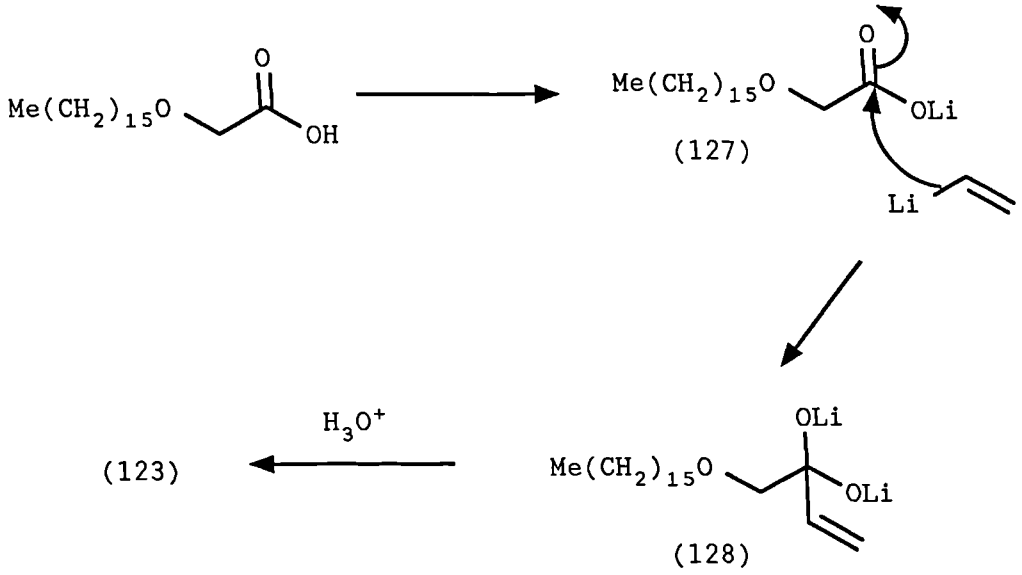
Figure 6.4.



(126)

The proposed mechanism of addition of vinyllithium to hexadecyloxyacetic acid is shown in figure 6.5 and involves a dilithio ketal intermediate (128).

Figure 6.5.



Repetition of the literature procedure towards (123) (using addition of 2.2 equivalents of vinyl lithium) yielded none of the desired vinyl ketone. However a crude oil was isolated at the end of reaction and from thin layer chromatography it was found to consist of two major products. These two products were separated and purified, mass spectral analysis and NMR spectra revealed the products to be hexadecanol and divinyl carbinol (129), (Figure 6.6). The mechanism of this reaction is uncertain, however formation of any hexadecanol would facilitate breakdown of the dilithio derivative (128) into vinyl ketone (123) which could undergo further vinyl lithium addition to give (129) after hydrolysis (Figure 6.7).

Figure 6.6.

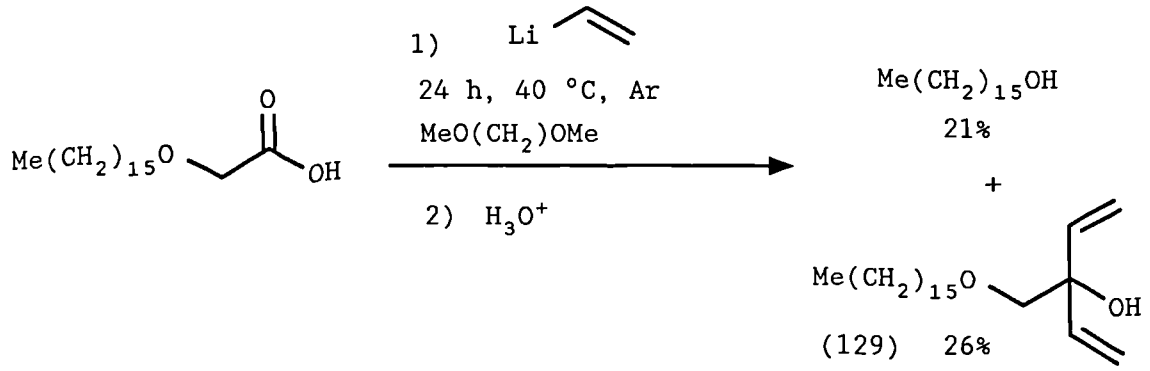
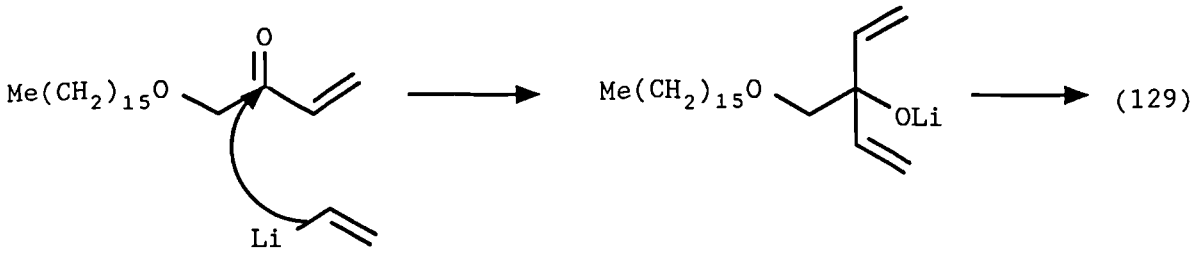


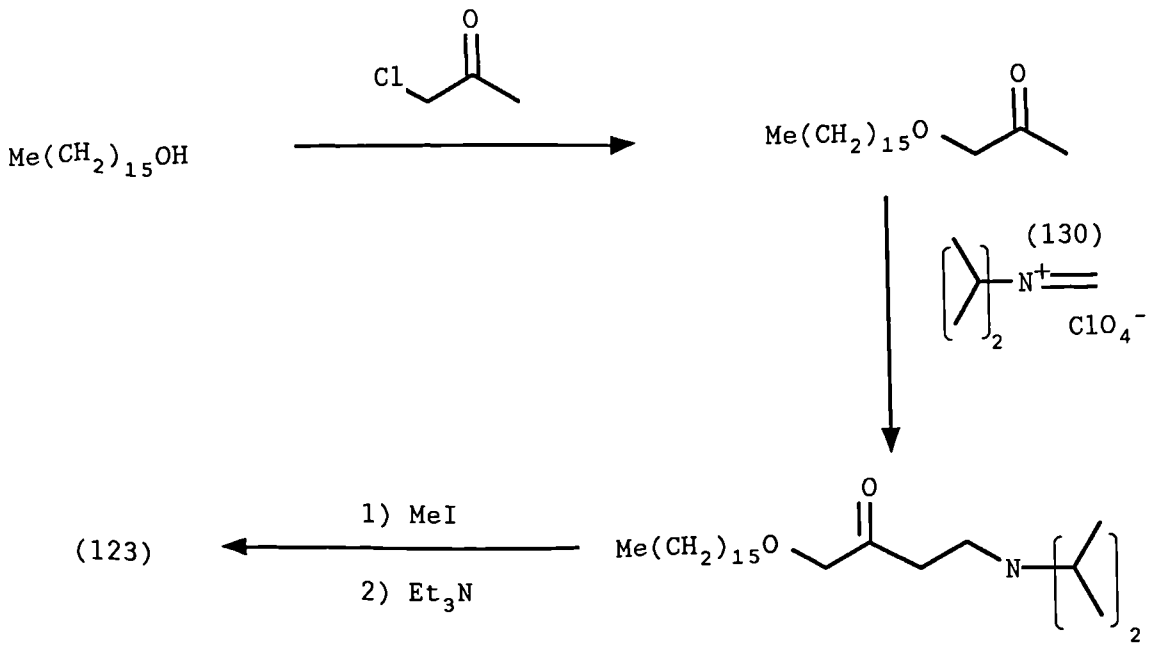
Figure 6.7.



All attempts at preparation of (123) using the claimed literature method,[145] failed. For this reason I proposed an alternative synthesis, (Figure 6.8). The key step in this synthesis involves a regioselective Mannich type reaction[149] using diisopropyl(methylene)ammonium perchlorate (130) to ensure reaction at the least substituted carbon atom relative to the carbonyl. Quaternization followed by base induced elimination of diisopropylmethylamine is predicted to result in (123).

The synthetic sequence above (Figure 6.8) was not adopted because attention was focused on an alternative strategy for synthesis of the PAF analogue (122). Due to the practical difficulty in the synthesis of (123) it was decided to try to construct (122) starting with the more simple

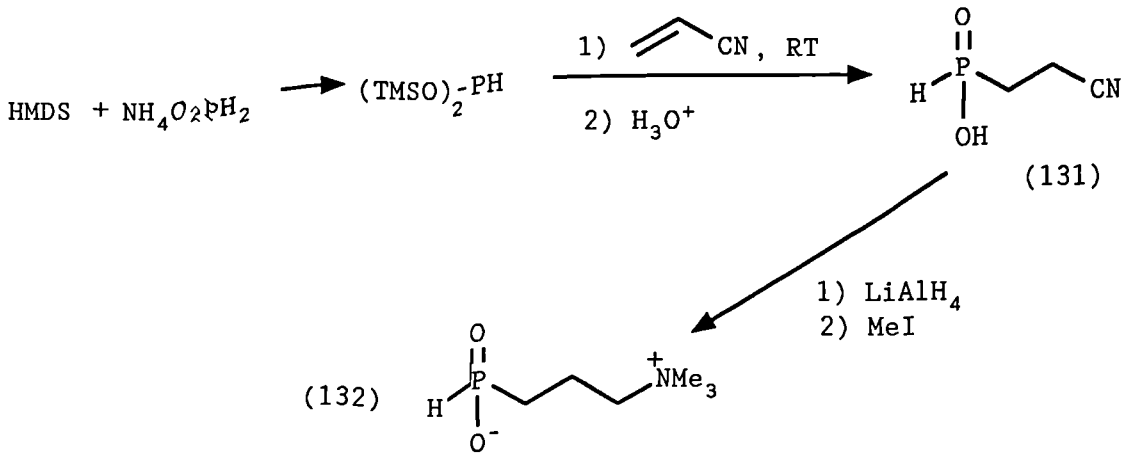
Figure 6.8.



propylammonium fragment. This has the advantage that it is more easy to disconnect and synthesise, and the large non polar alkyl chain could be introduced late in the synthesis by second addition to a substituted phosphonite, thus avoiding solubility and reactivity problems which plagued the synthesis of key precursor (123). My proposed route to the propylammonium fragment is shown in Figure 6.9, and involves bis(trimethylsilyl) phosphonite addition to acrylonitrile.

The reaction between bis(trimethylsilyl) phosphonite and acrylonitrile has been reported twice[100,130] but the products of addition were isolated as trivalent phosphonites in low yield. Using the methodology developed in previous chapters (131) was isolated in a 99% yield as a colourless oil after bis(trimethylsilyl) phosphonite addition to acrylonitrile, and work-up. Unfortunately time considerations meant that synthesis of (122) was abandoned, this was due to time spent developing the mild general phosphinic acid reaction of

Figure 6.9.

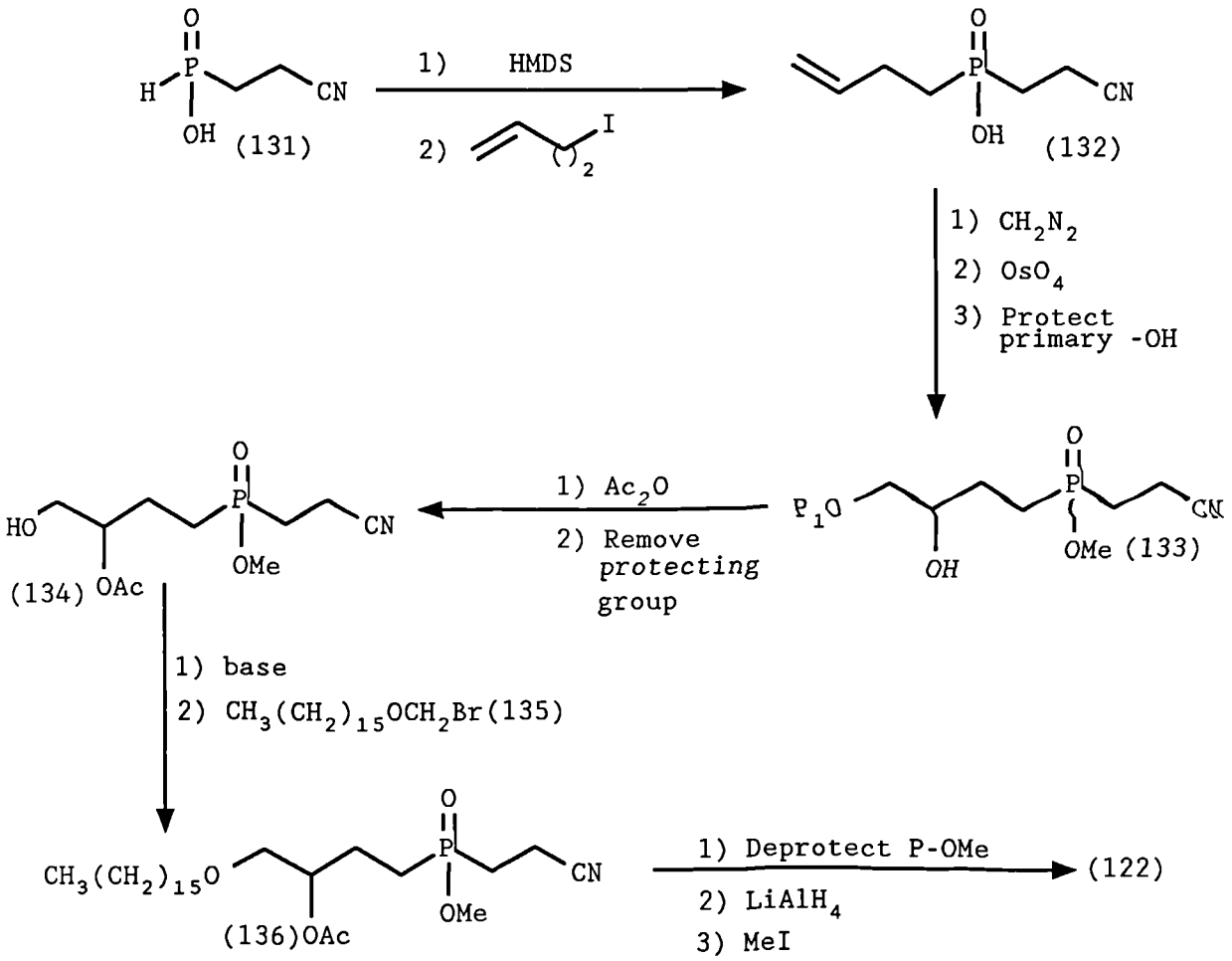


chapter 5. However (131) was synthesised in excellent yield and is a useful precursor for synthesis of (122).

The synthesis of (122) above relies on isolation of vinyl ketone (123) which was found problematical. I devised a synthesis designed to alleviate the need for vinyl ketone (123). The non polar hydrocarbon chain which was contained in (123) was probably responsible for practical difficulties, *e.g.* solubility; hence the new synthesis was designed to incorporate this chain as a last step in the synthesis. My proposed synthesis is shown in Figure 6.10.

I proposed to react intermediate (131) with 4-iodobutene under the conditions formulated in chapter 5 to yield intermediate (132). Methylation of (132) using diazomethane could be achieved using conditions in chapter 2. Dihydroxylation of the methyl ester of (132) using osmium tetroxide followed by protection of the primary hydroxyl group with a suitable protecting group is predicted to result in (133). Acetylation of the secondary hydroxyl group of (133) followed by removal of the appropriate protecting group from the primary hydroxyl is predicted to result in (134). Base induced deprotonation of (134) followed by reaction of

Figure 6.10



P_1 = suitable protecting group.

intermediate (135) is thought to result in (136). Reduction of (136) to the primary amine followed by exhaustive methylation using methyl iodide should result in platelet activating factor analogue (122). However, it would be elegant if under appropriate conditions the hexadecyloxy-methyl group could be incorporated instead of the protecting group, hence drastically reducing the number of steps in the synthesis. Obviously further research would try this possibility first.

Although the methyl phosphinate is shown in Figure 6.10, practical undertakings would reveal the most suitable and effective protectant of (132). The protecting group should allow facile de-esterification at the end of synthesis without the disruption of the secondary acetate group. Starting material could be easily synthesised using known reactions, but access to this reagent may be effected by reaction of hexadecanol with formaldehyde and hydrogen bromide in one step. The nitrile is reduced to the primary amine in the step because amines (particually) zwitterionic amino acids are difficult to practically manipulate and purify.

6.3.

This section includes preliminary studies and my ideas for synthesis of novel phosphinic acid reagents, and analogues.

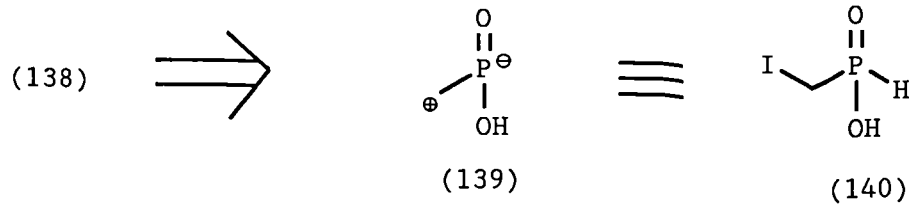
6.3.1. NMR reagents.

Polyphosphate or trimetaphosphate[150] (137) has been used to bind dysprosium as the dysprosium(III)bis-(tripolyphosphate), $Dy(PPP)_2^{7-}$, and is used as a cationic shift reagent for sodium NMR.[151] $Dy(PPP)_2^{7-}$ possesses the largest paramagnetic shift of any known complex for sodium or potassium ions per concentration of shift reagent. The reason that dysprosium is required as a shift reagent is that sodium has almost the same chemical shift in any physiological environment. The $Dy(PPP)_2^{7-}$ complex is used to shift the NMR signal of the extracellular sodium and because it is not taken up by living cells; the sodium NMR spectra can then be used to measure the sodium concentrations inside as well as

under previously discussed basic silylating reaction conditions. Formaldehyde or diiodomethane would probably serve as suitable electrophiles. Although this route would allow quick access to (138) I thought that the final cyclisation would be difficult due to many competing reactions. For this reason I also proposed a second synthesis of (138) which involves a more controlled sequential approach.

In my second disconnection of (138) the synthon (139) is required,(Figure 6.12). Iodomethylphosphinic acid is a synthetic equivalent of synthon (140) and attempts at synthesis were undertaken. (140) was isolated in a 91% crude yield as a viscous translucent oil using iodomethane as the electrophile under the general phosphinic acid reaction conditions developed in Chapter 5 (Figure 6.13.).

Figure 6.12.

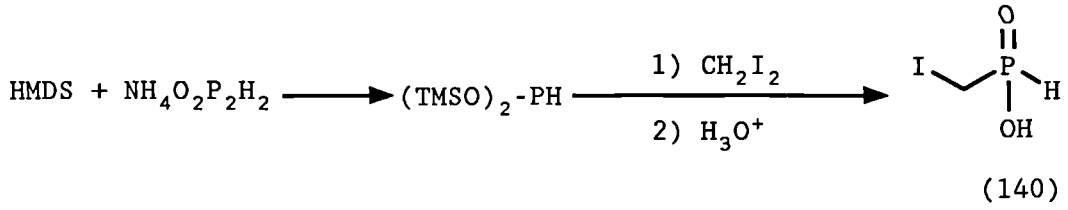


(139) (140)

Due to the success in preparation of (140) I devised a synthesis of (138) (Figure 6.14).

The key step in this reaction is between (141) and the silylated trivalent phosphonite (142) formed from reaction of (140) and hexamethyl disilazane. Intramolecular cyclisation of (143) would probably be facilitated over intermolecular

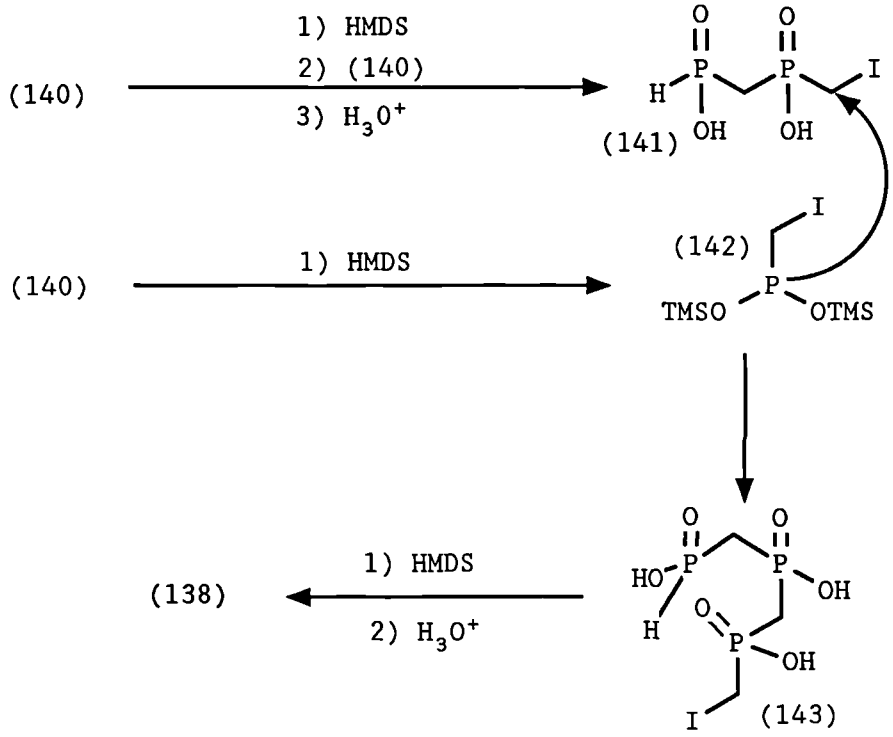
Figure 6.13.



(140)

addition if high dilution conditions are used. This synthesis is elegant in the respect that it uses simple starting materials, whether it is iodomethylphosphinic acid or the trivalent phosphonite (142) which is generated from it.

Figure 6.14.



6.3.2. Future synthesis.

The amount of work published using phosphinic acids is very small and methods for their preparation are very limited. However with the chemistry contained in this thesis it should make preparation and transformation of phosphinic acids a much more convenient and simple process. It was felt more important when undertaking the research in this thesis to concentrate on developing new methods for phosphinic acid synthesis, rather than making interesting analogues after I had developed the first reaction. However the subsequent chemistry developed will enable phosphinate analogues of for example, cyclic adenosine monophosphate,[155] and other analogues of adenosine phosphates *e.g.* ATP, Nicotinamide adenine dinucleotides, Coenzyme A and other biologically important molecules. It is thought that this chemistry could allow sequences of nucleosides joined using P-C-P bonds rather than P-O-P bonds which are analogues of DNA/RNA. These structures are predicted to be much more stable than their natural analogues and hence may be of use for genetic engineering. Indeed all the above phosphinate analogues can now be disconnected by known chemical transformations in combination with the chemistry contained in this thesis, relatively simply.

EXPERIMENTAL

GENERAL

Equipment used in phosphinic acid synthesis was thoroughly cleaned and dried in an oven at greater than 150 °C, or at 80 °C/60 mmHg and cooled in a desiccator prior to use. These reactions were performed under an atmosphere of nitrogen or argon. Organic solutions which had come into contact with water were dried over anhydrous magnesium sulphate. Evaporation under reduced pressure was achieved using a rotary evaporator at approximately 20 mmHg.

PHYSICAL MEASUREMENTS

Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. Boiling points were determined at atmospheric pressure unless otherwise stated.

Infrared spectra were obtained on a Perkin-Elmer 297 or a Perkin-Elmer 983, solid reagents were mixed with potassium bromide and ground up and compressed to make discs, liquid reagents were run as thin films between sodium chloride or potassium bromide plates.

^{1}H N.M.R. spectra were recorded using a Jeol PMX 60si, PX 100 or GX 270 or a Bruker 250 or a General Electric GE QE-300 spectrometer. ^{13}C N.M.R. spectra were recorded using a Jeol GX 270 or a General Electric GE QE-300 spectrometer. Chemical shifts are reported in parts per million on the δ scale relative to tetramethylsilane internal standard for continuous wave mode and spectra recorded using the Jeol GX 270 spectrometer. The solvent peak was used as the reference for other spectra recorded in pulsed Fourier transform mode. ^{31}P spectra were recorded using a Jeol GX 270 spectrometer,

chemical shifts are reported in parts per million on the δ scale relative to phosphoric acid external standard. Unless otherwise stated, all samples were dissolved in deuterated chloroform. In N.M.R. descriptions the following abbreviations are used: s=singlet, d=doublet t=triplet, q=quartet, br=broad, and *J*=signal splitting due to non-equivalence. It should be noted that spin splitting due to non-equivalence can only be accurately presented if the frequency of resonance was supplied accurately. Some spectra were not supplied with this information and hence resonances shown as singlets may be split, however the majority of the experimental data records signal splitting.

Mass spectra were recorded on a VG Analytical MS 9 instrument or were obtained via the SERC Mass Spectrometry Service at Swansea.

Analytical thin layer chromatography was performed using commercially prepared plates coated with Merck Kieselgel 60 F_{254} (0.2 mm thickness). Visualisation of spots was achieved using U.V. or various staining reagents. Analytical gas chromatography was performed using a Pye-Unicam PU 4500 gas chromatograph using S.G.E. BP1, BP10 and Carbowax 20 bonded phase capillary columns of 25 m length. Helium was used as the carrier gas and detection was by flame ionisation.

Elemental analyses were carried out within the University Chemical Department and at Pfizer Central Research.

SOLVENT AND REAGENT PURIFICATION

Solvents and reagents were purified as follows:

Benzene: dried over sodium wire.

Chloroform: dried by running through a column of alumina and used immeadiately.

1,2-Dichloroethane: refluxed over calcium hydride, distilled and stored under nitrogen over 4Å molecular sieves.

Dichloromethane: refluxed over phosphorus pentoxide and distilled.

Diethylether: refluxed over sodium wire then distilled from sodium benzophenone ketyl.

1,2-Dimethoxyethane: refluxed over sodium then distilled.

N,N-Dimethylformamide: refluxed over barium oxide and distilled under nitrogen and stored over 4Å molecular sieves, under nitrogen.

Pentane: dried over sodium wire.

Tetrahydrofuran: refluxed over potassium then distilled from potassium benzophenone ketyl.

Toluene: refluxed over phosphorus pentoxide and distilled.

Triethylamine: dried over potassium hydroxide.

Other commercially available reagents and solvents were used as received unless otherwise stated.

The following abbreviations are used:

Et_3N:	Triethylamine.
GC:	Gas/liquid chromatography.
HMDS:	Hexamethyl disilazane.
NMR:	Nuclear magnetic resonance.
PAF:	Platelet activating factor.
TAMA:	*N*-methylanilinium trifluoroacetate.
TLC:	Thin layer chromatography.
TMSCl:	Chlorotrimethylsilane.

Triethylammonium phosphinate (25):- Triethylamine (139 ml, 1.0 mol) was cautiously added to phosphinic acid (109 ml of a 50% solution, 1.0 mol), below 35 °C. Water was removed under reduced pressure followed by azeotroping with cyclohexane; final solvent traces were removed at 40 °C/0.02 mm Hg to yield the product as an oil in quantitative yield, δ_H (100 MHz, DMSO-d^6) 1.1-1.3 (9 H, t, J_{HH} 7.1 Hz, CH_2) and 4.6-9.5 (2 H, d, J_{PH} 490 Hz); δ_P (109 MHz, solvent DMSO-d^6), 2.48 (s).

Symmetrical di-substituted phosphinic acid synthesis, the "Triethylammonium Phosphinate Method":-

General procedure.

To a stirred solution of triethylammonium phosphinate (1.0 g, 5.99 mmol) in dry dichloromethane (30 ml) at 0 °C under dry nitrogen was added TMSCl/Et_3N (an equimolar, filtered mixture) (6.0 ml, 20 mmol) at less than 5 °C. After 1-2 h the acrylate (13.2 mmol) was added at 0 °C, stirred for 0.5 h, allowed to warm to room temperature and stirred overnight. The reaction was filtered, and washed with 2M hydrochloric acid (2 x 15 ml). The organic extract was dried and evaporated under reduced pressure to yield the phosphinic acid. Crystallization of some phosphinic acids was achieved by trituration with diethylether or hexane, the crystalline phosphinic acids were purified by washing with diethylether/hexane.

By this procedure the following di-substituted phosphinic acids were prepared.

Bis[2-(methoxycarbonyl)ethyl]phosphinic acid (28), (1.0 g, 70%) as a solid, m.p. 116-117 °C (from hexane); (Found: C, 40.24; H, 6.44; $(M+H)^+$, 239.069. $C_8H_{15}O_6P$ requires C, 40.34; H, 6.35%; *M*, 238.176); $\upsilon_{max.}$ 1 745 C=O, 1 250 P=O; δ_H (270 MHz) 2.00-2.11 (4 H, br m, $-CH_2-CO$), 2.59-2.70 (4 H, br m, $P-CH_2$), 3.71 (6 H, s, Me), 11.07 (1 H, br s, P-OH); δ_C 23.56-24.95 (d, J_{PC} 94.7 Hz P-C), 26.58-26.63 (d, J_{PC} 3.3 Hz), 48.62 (s, OMe), 172.26-172.48 (d, J_{PC} 15.8 Hz, CO); (δ_P (109 MHz) 52.39 (s); *m/z* 239 (M^+, 100%).

Bis[2-(ethoxycarbonyl)ethyl]phosphinic acid (29), (1.3 g, 82%) as a solid, m.p. 63-64 °C (from hexane) (Found: C, 45.20; H, 7.11; N, nil. $C_{10}H_{19}O_6P$ requires C, 45.12; H, 7.19; N, nil%); $\upsilon_{max.}$ 1 740 C=O, 1 235 P=O; δ_H (270 MHz) 1.24-1.29 (6 H, t, J_{HH} 7.14 Hz, Me), 2.01-2.11 (4 H, br m, CH_2-CO), 2.58-2.68 (4 H, br m, $P-CH_2$), 4.12-4.20 (4 H, q, J_{HH} 7.14 Hz, $CO-O-CH_2$), 11.89 (1 H, br s, P-OH); δ_C (68 MHz) 14.19 (s, Me), 23.34-24.73 (d, J_{PC} 94.7 Hz, P-C), 26.53-26.58 (d, J_{PC} 3.3 Hz, CO-*C*), 60.98 (s, O-C), 172.07-172.30 (d, J_{PC} 15.4 Hz, CO); δ_P (109 MHz) 55.07 (s); *m/z* 267.27 (M^+, 100%).

Bis[2-(t-butoxycarbonyl)ethyl]phosphinic acid (30), (1.51 g, 78%) as a solid, m.p. 111-114 °C (from hexane); (Found; C, 51.84; H, 8.53; $(M+H)^+$, 323.1618. $C_{14}H_{27}O_6P$ requires C, 52.17; H, 8.44%; *M*, 322.338; $\upsilon_{max.}$ 1 725 C=O, 1 255 P=O; δ_H (270 MHz) 1.38 (18 H, s, Me), 1.94-2.05 (4 H, br m, CH_2-CO), 2.50-2.60 (4 H, br m, $P-CH_2$), 12.09 (1 H, br s, P-OH); δ_C (68 MHz) 23.52-24.91 (d, J_{PC} 94.7 Hz, P-C), 27.55-27.59 (d, J_{PC} 2.2 Hz, CO-*C*), 28.04 (s, $C\{C\}_3$), 80.99 (s, O-C), 171.24-171.49 (1d, J_{PC} 16.6 Hz, CO); δ_p (109 MHz) 56.86 (s); *m/z* 323 (M^+, 100%)

Bis[2-(ethoxycarbonyl)-1-methyl-ethyl]phosphinic acid (31), (1.09 g, 62%) as an oil; (Found: $(M+H)^+$, 267.201. $C_{14}H_{15}O_2P$ requires *M*, 266.230); $\upsilon_{max.}$ 1 730 C=O, 1 225 P=O; δ_H 1.16-1.18 1.23-1.26 (6 H, d d, J_{HH} 7.14 Hz J_{PH} 16.76 Hz, P-CH-CH_3, 1.24-1.30 6 H, t, J_{HH} 7.14 Hz, Me), 2.27-2.44 (4 H, br m, CO-CH_2), 4.13-4.21 (4 H, q, J_{HH} 7.14 Hz, O-CH_2), 11.63 (1 H, s, P-OH); δ_C (68 MHz) 18.62-18.68 (d, J_{PC} 4.1 Hz, CH-*Me*), 33.56-33.59 (d, J_{PC} 2.0 Hz, Me-*C*H), 33.82-35.09 (d, J_{PC} 86.0 Hz, P-C), 52.12 (s, OMe), 175.29-175.15 (d, J_{PC} 9.5 Hz, CO); δ_P 59.63 (s), 60.00 (s); *m/z* 295 ($[M+H]^+$, 100%).

Bis[2-(methoxycarbonyl)propyl]phosphinic acid (32), (0.90 g, 56%) as an oil; (Found: $(M+H)^+$, 267.107. $C_{10}H_{19}O_6P$ requires *M*, 266.230); $\upsilon_{max.}$ 1 740 C=O, 1 240 P=O; δ_H (270 MHz) 1.31-1.34 (6 H, d, J_{HH} *6.87 Hz, CO-CH-CH*$_3$), *1.72-2.33 (4* H, d m, P-CH_2), 2.85-3.75 (2 H, br m, CH), 11.93 (1 H, s, P-OH); δ_C (68 MHz) δ_P (109 MHz) 53.47 (s) and 53.57 (s); *m/z* 267 ($[M+H]^+$, 100%).

Bis[2-(ethoxycarbonyl)-1,1-dimethyl-ethyl]phosphinic acid (33), (0.51 g, 44%) as an oil; (Found: $(M+H)^+$, 323.336. $C_{14}H_{27}O_6P$ requires *M*, 322.338); $\upsilon_{max.}$ 1 730 C=O, 1 210 P=O; δ_H (270 MHz) 1.12 (12 H, s, CH[C*H*$_3$]), 1.24-1.29 (6 H, t, J_{HH} 7.15 Hz, CH_2-C*H*$_3$), 2.49-2.54 (4 H, d, J_{PH} 13.5 Hz, CO-CH_2), 4.10-4.15 (4 H, q, J_{HH} 7.14 Hz, CO-O-CH_2), 13.05 (1 H, brs,P-OH); δ_C (68MHz) 14 (s, CH_2CH_3), 20 (s, C(CH_3)$_2$), 33-34 (d, P-C), 41 (d, OCO-*C*) 61 (s, O-C), 171 (d, CO); δ_P 44.94 (s); *m/z* 323.21 ($[M+H]^+$, 100%).

The above general procedure, the "triethylammonium phosphinate" reaction, was also used to synthesize di-substituted phosphinic acids using vinyl ketones in place of α,β-unsaturated esters.

Bis(3-oxocyclohexyl)phosphinic acid (0.49 g, 32%) as an oil; (Found: $(M+H)^+$, 259.110. $C_{12}H_{19}O_4P$ requires *M*, 258.121); $\upsilon_{max.}$ 1 705 C=O, 1 195 P=O; δ_H (100 MHz) 1.8-2.5 (12 H, br m, CH-CH_2), 8.8-9.0 (1 H, br s, P-OH); δ_P (109 MHz) 44.20 (s); *m/z* 239 ($[M+H]^+$, 41%).

Bis(3-oxo-3-phenylpropyl)phosphinic acid (1.58 g, 80%) as a solid, m.p. 91-93 °C (from hexane); (Found: $(M+H)^+$, 331.1091. $C_{18}H_{19}O_4P$ requires *M*, 330.32); $\upsilon_{max.}$ 1 695 C=O, 1 190 P=O; δ_H (270 MHz) 2.17-2.22 (4 H, br m, CH_2-CO), 3.33-3.38 (4 H, br m, P-CH_2) 7.47-8.02 (10 H, br m, Ph); δ_C (68 MHz) 22.92-24-29 (d, J_{PC} 93.7 Hz, P-C), 31.58-31.38 (d, J_{PC} 2.2 Hz, CO-*C*), 128.49-134.02 (br m, Ph), 198.89-199.09 (d, J_{PC} 16.6 Hz, CO); δ_P (109 MHz) 59.00 (s); *m/z* 331 ([*M+H*]$^+$, 42%).

Bis(4,4-dimethyl-3-oxopentyl)phosphinic acid (1.74 g, 83%) as a solid, m.p. 163-167 °C (from cyclohexane); (Found: $(M+H)^+$, 291.351. $C_{14}H_{27}O_4P$ requires *M*, 290.350); $\upsilon_{max.}$ 1 710 C=O, 1 235 P=O; δ_H (270 MHz) 0.72 (9 H, s, Me), 1.79-2.00 (4 H, br m, P-CH_2), 2.72-2.92 (4 H, br m, CH_2CO); δ_C (75.5 MHz) 16.87 (s, Me), 21.23-22.38 (d, J_{PC} 86.8 Hz, P-C), 34.72 (s, P-C-*C*), 50.42 (s, CMe_3), 207.13 (s, CO); δ_P 55.76 (s); *m/z* 291 ($[M+H]^+$, 100%).

The above general procedure, the "triethylammonium phosphinate" method, was also used to synthesize di-substitued phosphinic acids using α-bromoesters in place of unsaturated esters. The use of ethyl 2-bromoisobutyrate resulted in predominantly mono-substituted phosphinic acid.

Bis(ethoxycarbonyl)methylphosphinic acid (49), (0.54 g, 38%) as an oil; (Found: $(M+H)^+$, 239.059. $C_8H_{15}O_6P$ requires *M*, 238.176); $\upsilon_{max.}$ 1 740 C=O, 1 235 P=O; δ_H (270 MHz) 1.26-1.31 (6 H, t, J_{HH} 7.14 Hz, Me), 3.15-3.22 (4 H, d, J_{PH} 18.4 Hz, P-CH_2), 4.16-4.23 (4 H, q, J_{HH} 7.14 Hz, O-CH_2), 12.18-12.22 (1 H, s, P-OH); δ_C (68 MHz) 14.08 (s, Me), 36.25-37.59 (d, J_{PC} 91.5 Hz, P-C), 61.50 (2*s*, O-C), 166.26-166.33 (d, J_{PC} 4.4 Hz, CO); δ_P (109 MHz) 39.51 (s); *m/z* 239 ($[M+H]^+$, 78%). .

Bis(ethoxycarbonyl)-1-methyl-methylphosphinic acid (50), (0.48 g, 30%) as an oil; (Found: $(M+H)^+$, 267.307. $C_{10}H_{19}O_6P$ requires *M*, 266.230); $\upsilon_{max.}$ 1 740 C=O, 1 210 P=O; δ_H (270 MHz) 1.20-1.26 (6 H, t, J_{HH} 7.14 Hz, CH_2CH_3), 1.27-1.47 (6 H, br m, CH-CH_3), 2.80-3.40 (2 H, br m, CH), 4.11-4.19 (4 H, q, J_{HH} 7.14 Hz, CH_2), 6.04-8.19 (1 H, d, J_{PH} 579.86 Hz, mono alkyl-phosphinic acid P-H), 11.45-11.46 (1 H, br s, P-OH); δ_C (68 MHz) 7.74-7.56 (d, J_{PH} 12.2 Hz P-C-*C*), 13.06 (s, O-C-*C*), 38.78-39.96 (, d, J_{PC} 80.4 Hz, P-C), 168.58-168.40 (d, J_{PC} 12.2 Hz, CO); δ_P (109 MHz) 33.04 (s, mono-substituted phosphinic acid), 48.09 (s); *m/z* 267 ($[M+H]^+$, 56%).

Ethoxycarbonyl)-1,1-dimethyl-methylphosphinic acid (51), (0.31 g, 29%) as an oil; $\upsilon_{max.}$ 2 350 P-H, 1 730 C=O, 1 205 P=O; δ_H (270 Mz) 1.26-1.32 (6 H, t, J_{HH} 7.14 Hz, CH_2CH_3), 1.43 (6 H, s, $C[CH_3]_2$), 4.19-4.23 (4 H, q, J_{HH} 7.14, CH_2), 6.0-8.1 (1 H, d, 565 Hz, mono-substituted phosphinic acid P-H), 11.10 (1 H, s, P-OH); δ_P (109 MHz) 34.92 (s)

The above general procedure, the "triethylammonium phosphinate" reaction was also used to synthesize di-substituted phosphinic acids using alkyl and benzyl halides. Phosphinic acids resulting from alkylation by methyl iodide (53) and ethyl bromide (54) were very impure and were not fully characterised. However characterisation of these compounds is included later when clean methods to their synthesis are used.

Dibenzylphosphinic acid (55),[156] (0.64 g, 44%) as a solid, m.p. 178-182 °C from hexane (lit.,[154] 194 °C); (Found: $(M+H)^+$, 247.0891. $C_{14}H_{15}O_2P$ requires *M*, 246.246); $\upsilon_{max.}$ 1 130 P=O; δ_H (270 MHz) 2.90-3.02 (4 H, br m, $P-CH_2$), 7.17-7.24 (10 H, br m, Ph), 10.96-11.01 (1 H, br s, P-OH); δ_C (68 MHz) 35.18-36.96 (2 C, d, J_{PC} 89.3 Hz, P-C), 126.40-131.38 (12 C, br m, Ph); *m/z* 247 ($[M+H]^+$, 100%).

Bis(2-propenyl)phosphinic acid (56), (0.19 g, 16%) as an oil; (Found: $(M+H)^+$, 143.101. $C_6H_7O_2P$ requires *M*, 142.094); $\upsilon_{max.}$ 1 170 P=O; δ_H (270 MHz) 2.62-2.70 (4 H, br m, $P-CH_2$), 5.21-5.31 (4 H, br m, $CH=CH_2$), 5.81-5.85 (2 H, br m, CH); δ_P (109 MHz) 42.82 (s).

Unsymmetrical di-substituted phosphinic acid synthesis from phenylphosphinic acid:- General procedure.

To a stirred solution of pheylphosphinic acid (1.14 g, 8.00 mmol) in dry dichloromethane (30 ml) at 0 °C under dry nitrogen was added $TMSCl/Et_3N$ (7.0 ml, 28 mmol) at less than 5 °C. After 1 h the appropriate electrophile (8.8 mmol) was added at 0 °C, stirred for 0.5 h, allowed to warm to room temperature and stirred overnight. The reaction was filtered, and washed with 2M hydrochloric acid (2 x 15 ml). The organic extract was dried and evaporated under reduced pressure to yield the phosphinic acid.

By this procedure the following di-substituted phosphinic acids were prepared.

[(Ethoxycarbonyl)ethyl]phenylphosphinic acid (41), (from ethyl acrylate), as an oily solid (0.75 g, 38%); $\upsilon_{max.}$ 1 730 C=O, 1 140 P-Ph, 1 150 P=O; δ_H (270 MHz) 1.16 (3 H, t, J_{HH} 7.14 Hz Me), 2.09-2.19 (2 H, br m, $P-CH_2$), 2.41-2.51 (2 H, br m, $CO-CH_2$), 4.00-4.08 (2 H, q, J_{HH} 7.14 Hz), 7.36-7.76 (5 H, br m, Ph), 11.96 (1 H, s, P-OH); δ_P (109 MHz) 42.77 (s); *m/z* 243.4 ($[M+H]^+$, 67%).

[(Ethoxycarbonyl)methyl]phenylphosphinic acid, (from ethyl bromoacetate), as an oil which crystallized out on freezing and was washed with hexane (1.30 g, 71%); δ_H (270 MHz) 1.02-1.07(3 H, t, J_{HH} 7.14 Hz), 3.06-3.13(2 H, d, J_{PH} 17.86 Hz, $P-CH_2$), 3.94-4.02(2 H, q, J_{HH} 7.14 Hz, $O-CH_2$), 7.33-7.80(5 H, br m, Ph), 9.82(1 H, br s, P-OH); δ_C (68 MHz) 13.83(1 C, s, Me), 38.60-39.91(1 C, d, J_{PC} 89.2 Hz, P-C),

61.37(1 C, s, O-C), 128.02-132.60(6 C, br m, Ph), 169.00-169.09(1 C, d, J_{PC} 4.5 Hz, CO) ; δ_P (109 MHz) 34.45 (s); *m/z* 231 ($[M+H]^+$, 100%).

Methylphenylphosphinic acid (57),[124] (from methyl iodide) as an oil (0.61 g, 48%); δ_H (270 MHz) 1.62-1.67 (3 H, d, J_{PH} 14.84 Hz, Me), 7.56-7.82 (5 H, br m, Ph), 12.18 (1 H, s, P-OH); δ_C (69 MHz) 15.18-17.35 (d, J_{PC} 100.2 Hz, Me), 128.40-132.74 (m, Ph); δ_P (109 MHz) 42.39.

Ethylphenylphosphinic acid (58),[77] (from ethyl bromide) as an oil (0.75 g, 55%); δ_H (270 MHz) 1.01-1.07(3 H, m, Me), 1.84-1.93(2 H, m, CH_2), 7.37-7.80 (5 H, br m, Ph), 12.98 (1 H, s, P-OH); δ_C (69 MHz) 5.90-5.97 (d, J_{PC} 4.4 Hz, Me), 22.49-23.97 (d, J_{PC} 100.2 Hz, CH_2), 128.35-132.71 (m, Ph); δ_P (109 MHz) 46.03 (s).

Mono-substituted phosphinic acid synthesis from triethylammonium phosphinate:- General procedure.

To a stirred solution of *triethylammonium phosphinate* (5.0 g, 29.9 mmol) in dry dichloromethane (100 ml) at 0 °C under dry nitrogen was added TMSCl/Et_3N (an equimolar, filtered mixture) (20 ml, 65 mmol) at less than 5 °C. After 1-2 h the acrylate (5.9 mMol) was added at 0 °C, stirred for 0.5 h, allowed to warm to room temperature and stirred overnight. The reaction was filtered, and washed with 2M hydrochloric acid (2 x 40 ml). The organic extract was dried and evaporated under reduced pressure to yield the phosphinic acid.

By this procedure the following mono-substituted phosphinic acids were prepared.

2-(Ethoxycarbonyl)ethylphosphinic acid (38), (0.89 g, 90%) as an oil; $\upsilon_{max.}$ 2 320 P-H, 1 740 C=O, 1 240 P=O; δ_H (270 MHz) 1.16 (3 H, t, J_{HH} 7.14 Hz Me), 2.09-2.19 (2 H, br m, P-CH_2), 2.41-2.51 (2 H, br m, CO-CH_2), 4.00-4.08 (2 H, q, J_{HH} 7.14 Hz), 7.36-7.76 (5 H, br m, Ph), 11.96 (1 H, s, P-OH); δ_P (109 MHz) 40.72 (s); *m/z* 167.07 ($[M+H]^+$, 100%).

2-(t-Butoxycarbonyl)ethylphosphinic acid (39), (0.99 g, 85%) as an oil; (Found: $(M+H)^+$, 195.171. $C_7H_{14}O_4P$ requires *M*, 194.167); $\upsilon_{max.}$ 2 260 P-H, 1 730 C=O, 1 245 P=O; δ_H (100 MHz) 1.4-1.5 (9 H, s, Me), 1.9-2.2 (2 H, br m, CO-CH_2), 2.3-2.7 (2 H, br m, P-CH_2), 4.4-10.0 (1 H, d, J_{PH} 558 Hz, P-H); δ_P (109 MHz) 41.28 (s).

2-(Ethoxycarbonyl)-1-methyl-ethylphosphinic acid (40), (0.79 g, 74%) as an oil; $\upsilon_{max.}$ 2 310 P-H, 1 725 C=O, 1 225 P=O; (Found: $(M+H)^+$, 181.0630. $C_6H_{13}O_4P$ requires *M*, 180.140); δ_H (270 MHz) 1.16-1.18 1.23-1.26 (3 H, dd, J_{PH} 16.76 J_{HH} 7.14 Hz, CH-CH_3), 1.24-1.30 (3 H, t, J_{HH} 7.14 Hz, CH_2CH_3) 2.27-2.44 (2 H, br m, CO-CH_2) 4.13-4.21 (1 H, br m, CH) 6.01-8.05 (1 H, d, J_{PH} 551 Hz, P-H) 11.63 (1 H, s, P-OH); δ_P (109 MHz) 41.28 (s) ; *m/z* 181 ($[M+H]^+$, 68%).

Unsymmetrical phosphinic acid synthesis from triethylammonium phosphinate.

[2-(Ethoxycarbonyl)ethyl][2-(t-butoxycarbonyl)ethyl]phos-phinic acid (42). 2-(*t*-Butoxycarbonyl)ethylphosphinic acid (0.75 g, 4.07 mmol) was cooled to 0 °C in dichloromethane (30 ml) with stirring. TMS-Cl/Et_3N (7 ml, 18 mmol) was injected and stirred at this temperature for 1 h, followed by ethyl acrylate (0.45 g, 4.50 mmol). After 0.5 h, the temperature was allowed to rise to room temperature. After stirring overnight the flask was filtered and washed with 2*M* hydrochloric acid (2 x 15 ml). The organic extract was dried and the solvent removed under reduced pressure to yield the product as an oil which solidified on rotary oil pumping (<0.01 mmHg), (1.02 g, 85%). *The solid product was washed by* dispersion in hexane (35 ml), filtering yielded the crystalline product (0.90 g, 75%), (Found: C, 48.68; H, 7.80; N, nil. $C_{12}H_{23}O_6P$ requires *C*, 48.98; *H*, 7.88; *N*, *nil*); $\upsilon_{max.}$ 1 735 and 1 730 C=O, 1 240 P=O; δ_H (270 MHz) 1.24-1.29 (3 H, t, J_{HH} 7.15 Hz, CH_2-C*H*$_3$), 1.45 (9 H, s, *t*-Bu), 2.00-2.10 (4 H, br m, P-CH_2), 2.50-2.68 (4 H, br m, CO-CH_2), 4.15-4.20 (2 H, q, J_{HH} 7.14 Hz, O-CH_2), 10.98 (1 H, s, P-OH); δ_C (68 MHz) 14.19 (s, Me of Et), 23.45-24.52 (d, J_{PC} 94.7 Hz, P-C of *t*-Bu) 23.52-24.93 (d, J_{PC} 95.8 Hz, P-C of Et), 26.50-26.53 (d, J_{PC} 3.3 Hz, CO-*C* of Et), 27.55-27.60 (d, J_{PC} 2.2 Hz, CO-*C* of *t*-Bu), 28.04 (s, C{*C*}$_3$), 60.95 (s, O-C of Et) 81.07 (s, O-C of *t*-Bu), 171.23-171.45 (d, J_{PC} 15.5 Hz, CO of *t*-Bu), 172.07-172.30 (1 C, d, J_{PC} 15.4 Hz, CO of Et); δ_P (109 MHz) 56.46 (s); *m/z* 295.39 ($[M+H]^+$, 18.5%).

Preparation of vinyl ketones.

Acetylmethylenetriphenylphosphonium chloride.[158] Triphenyl phosphine (20.0 g, 76 mmol) and redistilled chloroacetone (7.0 g, 76 mmol) were refluxed in chloroform for 0.75 h. On cooling the solution was filtered into diethylether (500 ml), and the precipitated solid removed by filtration to give the phosphonium chloride as plates (18.7 g, 69%), m.p. 225-228 °C; δ_H (100 MHz) 2.5-2.6 (3 H, m, Me), 6.1-6.3 (2 H, d, J_{PH} 16.0 Hz, CH_2), 7.4-8.1 (15 H, m, Ph)

Acetylmethylenetriphenylphosphorane.[158] Sodium hydroxide solution (200 ml, 8% w/v) was slowly added to acetylmethylenetriphenylphosphonium chloride (18 g, 51 mmol) in water (50 ml). After 0.5 h of stirring the phosphorane was filtered as a solid (14.2 g, 88%), m.p. 207-210 °C (lit.,[158] 209-210 °C).

3-Penten-2-one.[158] Redistilled acetaldehyde (6.9 g, 157 mmol) in dichloromethane (15 ml) was added to a solution of acetylmethylenetriphenylphosphorane (19.5 g, 61 mmol) in dichloromethane (65 ml). The solution was refluxed for 6 h then allowed to stand for 6 h. The solution was distilled into pentane (45 ml), filtered, and the solvents removed under reduced pressure to yield the ketone (4.9 g, 95%) as an oil. Fractional distillation yielded the ketone (3.4 g, 66%), b.p. 114-118 °C (Lit.,[158] 121-122.5 °C); δ_H 1.8-2.0 (3 H, m, CH_3=CH), 2.2 (3H, s, CO-CH_3), 6.0-6.3 (1 H, br m, CH-CO), 6.7 7.0 (1 H, br m, C*H*=CH_3).

Phenyl vinyl ketone (44).[133] An intimate mixture of β-dimethylaminopropiophenone hydrochloride (30.0 g, 0.14 mol), (dried over phosphorus pentoxide at 0.1 mm Hg) and hydroquinone (0.2 g) are pyrolysed at (65-90 °C/3 mm Hg) under nitrogen, and collected by distillation to yield a mobile slurry, (12.3 g, 66%). Fractional distillation 83-85 °C/11mm Hg (lit.,[133] 115 °C/18mm Hg) gave the product as a liquid (5.1 g, 28%); δ_H (60 MHz) 5.4-5.7 (1 H, m, CH), 6.1-7.0 (2 H, m, CH_2), 7.2-8.1 (5 H, br m, Ph).

4,4-Dimethyl-1-(dimethylamino)-pentan-2-one hydrochloride.[137] Dimethylamine hydrochloride (53.0 g, 0.65mol), paraformaldehyde (20.0 g, 0.66 mol), pinacalone (49.5 g, 0.49 mol) and concentrated hydrochloric acid (1 ml) in ethanol (40 ml) were refluxed for 6 h with vigorous mechanical stirring. Acetone (250 ml) was added to the cooled solution and left to stand at 4 °C overnight. Filtering of the solution followed by drying over phosphorus pentoxide *in vacuo*, resulted in the Mannich base (56.9 g, 60%) as a crystalline solid; (Found: C, 55.40; H, 10.81; N, 7.26. $C_9H_{20}ClNO$ requires C, 55.80; H, 10.41; N, 7.23); δ_H (60 MHz) 1.2(9 H, s, *t*-Bu), 2.8(6 H, s, $N\{Me\}_2$), 3.2(2 H, s, CH_2CO), 3.4(2 H, s, CH_2-N); δ_C 26.34(s, $C\{C\}_3$), 31.94(s, CO-*C*), 43.22(s, $N\{C\}_2$), 44.26(s, $C\{C\}_3$), 52.79(s, CH_2N), 212.02(s, CO).

4,4-Dimethyl-1-(dimethylamino)-pentan-2-one.[137] 4,4-dimethyl-1-(dimethylamino)-pentan-2-one hydrochloride (153.8 g, 0.79 mol) was added to 3M sodium hydroxide (700 ml) with vigorous stirring for 2 h. The reaction mixture was extracted with diethylether (4x75 ml). The organic layers

combined, dried and the solvents removed under reduced pressure to yield the amine as an oil (119.0 g, 95%); δ_H (100 MHz) 1.2 (9 H, s, *t*-Bu), 2.3 (6 H, s, Me), 2.6-2.9 (4 H, br m, CH_2CH_2).

2,2-Dimethyl-3-oxopentyl-5-trimethylammonium iodide.[137] Methyl iodide (113.0 g, 0.80 mol) in ethyl acetate (200 ml) was slowly added to a solution of 4,4-dimethyl-1-(dimethylamino)-pentan-2-one (119.0 g, 0.76 mol) in ethyl acetate (500 ml) with vigorous stirring. After 2 h the precipitated product was filtered, washed with ethyl acetate (2 x 150 ml, 0 °C) and dried *in vacuo* over silica gel, yielding the ammonium iodide (212.0 g, 93%) as plates.

t-Butyl vinyl ketone(47).[137] 2,2-Dimethyl-3-oxopentyl--5-trimethylammonium iodide (212.0 g, 0.71 mol) was dissolved in 2.5 M sodium hydroxide (900 ml) at 0 °C, with vigorous stirring. After 2 h the reaction was extracted with 30-40 petroleum ether (4 x 250 ml). The combined organic layers were washed with 2 M hydrochloric (2 x 130 ml), water (2 x 100 ml) and dried. Removal of solvent under reduced pressure resulted in the product (46.5 g, 60%) as an oil; δ_H (100 MHz) 1.1 (9 H, s, *t*-Bu), 5.4-5.7 (1 H, br m, CH), 6.0-7.1 (2 H, br m, CH_2); G.C. (B.P.1, 72 °C, 84%).

Fractional distillation of the crude vinyl ketone (40-42 °C/14 mm Hg) gave an oil (29.7 g,38%); ^{1}H NMR as above; G.C. (B.P.1, 71 °C, >99.5%).

2-Butyne-1,4-diol dimethylether.[144] Dimethyl sulphate (460 g, 3.65 mol) was added to a solution of 2-Butyne-1,4-diol (129.1 g, 1.5 mol) in water (340 ml) with mechanical stirring over 6 h, from a dropping funnel. Sodium hydoxide (150 g, 3.75 mol) in (15 g) portions was also added to the solution over 5 h. The reaction was refluxed for 2.5 h, cooled to room temperature and water (100 ml) added. The organic layer was separated and the aqueous layer extacted with diethylether (2 x 75 ml, 1 x 100 ml). The organic extracts were dried and solvent removed under reduced pressure to yield the dimethylether as an oil (156.9 g, 92%) δ_H (60 MHz) 5.6 (6 H, s, Me), 6.8 (4 H, s, CH_2); G.C. (B.P.1, 105 °C, >96.3%).

1,4-Dimethoxybutan-2-one.[144] A solution of 2-butyne-1,4-diol dimethylether (97.0, 0.85 mol) in methanol (50 g) was added dropwise over 15 min to a stirred solution of mercury (II) oxide (3.2 g, 14.8 mmol) and concentrated sulphuric acid (3 g) in 70% aqueous methanol (150 ml), the temperature was allowed to rise to 70 °C before being cooled to 35 °C by means of an ice bath. After 1 h of stirring mercury (II) oxide (1.0 g, 4.6 mmol) was added, followed by a futher hour of stirring. The reaction was allowed to settle over two days followed by filtration. The solvents were removed under reduced pressure to yield the crude ketone (93.2 g, 83%) as an oil. Fractional distilation (98-104 °C/46 mmHg) gave the pure ketone (71.0 g, 63%) δ_H (60 MHz) 2.5-2.8 (2 H, t, CO-C*H*$_2$-CH$_2$), 3.3 (3 H, s, CO-CH$_2$-CH$_2$-OC*H*$_3$), 3.4 (3 H, s, C*H*$_3$O-CH$_2$CO), 3.5-3.8 (2 H, t, CO-CH-C*H*$_2$), 4.0 (2 H, s, O-CH$_2$CO).

Methoxymethyl vinyl ketone (124).[144] 1,4-Dimethoxybutan--2-one (71 g, 0.54 mol) and *p*-toluene sulphonic acid (33.4 mg, 1.8 mmol) were repeatedly distilled using a 0.1 m fractionating column to yield the product as an oil, most pure fraction, (14.3 g, 27%) as an oil; δ_H (60 MHz) 3.4 (3 H, s, Me), 4.2 (2 H, s, O-CH_2), 5.6-6.0 (1 H, br m, CH), 6.1-6.6 (2 H, br m, CH-CH_2).

N-methylanilinium trifluoroacetate (45).[135] To a solution of *N*-methylaniline (28.2 g, 263 mmol) in diethylether (400 ml), is added trifluoroacetic acid (30.0 g, 263 mmol) over 0.5 h, temperature below 0 °C. The reaction is stirred at this temperature for 1.5 h followed by filtration. The product is washed with diethylether (2 x 50 ml) and dried *in vacuo* to give (50.4 g, 87%) as a crystalline solid, m.p. 65-66 ° C (lit.,[135] 65-66 °C).

Attempted direct synthesis of α-methylene ketones,

e.g. phenyl vinyl ketone (44).[135] Paraformaldehyde (1.4 g, 45 mmol) and *N-methylanilinium trifluoroacetate (3.5 g, 16* mmol) were purged in a flask with nitrogen. Acetophenone (1.2 g, 10 mmol) in dioxane (12 ml) was injected and the temperature raised to 100 °C for 5 h, constant GC monitoring was used throughout the reaction. On cooling two layers separate out, diethylether (20 ml) and water (20 ml) were added followed by separation. The aqueous layer was futher extracted with diethylether (2 x 10 ml). The organic extracts were combined, and washed with half saturaed sodium bicarbonate (20 ml) and water (2 x 10 ml), dried, and evaporated under reduced pressure to yield the product (1.4

g, 59% calculated from GC spectra, however this was only 56% phenyl vinyl ketone); δ_H (100 MHz) 2.7(3 H, s, acetophenone starting matetial) 5.5-5.7 (1 H, m, CH), 6.3-6.9 (2 H, m, CH_2), 7.3-8.0 (5 H, br m, Ph); G.C.(B.P.1, 140 °C, ketone 56%).

Symmetrical di-substituted phosphinic acid synthesis, use of a Mannich base in the "Triethylammonium phosphinate" reaction.

Bis(3-oxo-3-phenylpropyl)phosphinic acid. To a stirred solution of triethylammonium phosphinate (1.0 g, 5.99 mmol) in dry 1,2-dichloroethane (30 ml) at 0 °C under dry nitrogen was added TMSCl/Et_3N (an equimolar, filtered mixture) (6.0 ml, 20 mmol) at less than 5 °C. After 1 h the solution was transfered by aid of a canula to a flask containing β-dimethylaminopropiophenone hydrochloride (2.82 g, 13.2 mmol). After addition of triethylamine (1.83 ml, 13.2 mmol) to the reaction the temperature was raised to reflux for 48 h. The reaction was *susequently cooled and washed with* hydrochloric acid (2 x 18 ml). The organic phase was dried and evaporated under reduced pressure to yield the crude *phosphinic acid* which was washed with diethyl ether to yield the product as a crystalline solid, (1.51 g, 76 %), m.p. 90-91 °C. All other physical data identical to previous preparation.

Esterification of phosphinic acids.

Diazomethane.[139] A solution of potassium hydroxide (0.40 g) in ethanol (10 ml) was cautiously added to a solution of *N*-methyl-*N*-nitrosotoluene-*p*-sulphonamide (2.14 g, 10 mmol) in diethylether (30 ml) at 0 °C. The precipitate which formed was dissolved by adding ethanol, followed by stirring for 10 min. The ethereal solution of diazomethane was collected by distillation and used directly without analysis.

Methylation of phosphinic acids using diazomethane, General procedure:-

To a solution of the phosphinic acid (2.5 mol) in absolute methanol (10 ml) at 0 °C was added a solution of diazomethane in diethylether (approx. 1.1 eq.). After stirring for 15 mins the solvents were removed under reduced pressure, followed by rotary oil pumping (<0.01 mmHg) for 1 h, to yield the product.

By this procedure the following *methylated phosphinic* acids were synthesized.

Methyl bis[2-(ethoxycarbonyl)ethyl]phosphinic acid (62), 0.70 g, 100%) as a oil; δ_H (100 MHz) 1.10-1.40 (6 H, t, CH_3CH_2), 1.94-2.30 (4 H, br m, P-CH_2), 2.50-2.80 (4 H, br m, CO-CH_2), 3.70-3.86 (3 H, d, J_{PH} 16 Hz, P-OMe), 4.04-4.30 (4 H, q, O-CH_2); δ_C (68 MHz) 14.21 (s, O-C-*C*), 23.32-23.68 (d, J_{PC} 92.5 Hz, P-C), 26.73-26.82 (d, J_{PC} 3.3 Hz, CO-*C*), 51.17-51.26 (d, J_{PC} 6.6 Hz, OMe), 60.96 (s, O-C), 171.96-172.17 (d, J_{PC} 15.4 Hz, CO); δ_P (109 MHz) 55.76 (s).

Methyl bis[2-(ethoxycarbonyl)-1-methyl-ethyl]phosphinic acid, (0.77 g, 99%) as an oil; δ_H (100 MHz) 1.1-1.4 (12 H, br m, P-CH-CH_3 Me), 2.2-2.8 (6 H, br m, CO-CH_2-CH), 3.6-3.7 (3 H, d, P-OMe), 4.1-4.3 (4 H, q, O-CH_2), 10.0-10.1 (1 H, br s, P-OH); δ_P (109 MHz) 60.00 (s), 60.52 (s).

Sodium phosphinate.[159] Sodium hydroxide 6M was cautiously added to phosphinic acid (50 ml of a 50% solution, 1.0 mol) at 0 °C over thirty minutes, until the solution was neutral pH. Water was removed under reduced pressure followed by azeotroping with cyclohexane, final solvent traces were removed at 100 °C/ <0.01 mm Hg to give the product as a crystalline solid in quantitative yield, which was stored over phosphorus pentoxide.

Symmetrical di-substituted phosphinic acid synthesis, the "Sodium Phosphinate" Method:- General procedure. Sodium phosphinate (0.75 g, 8.5 mmol) was purged under dry nitrogen in a flask containg sodium hydride (60% dispersion in mineral oil) (1.36 g, 24 mmol), the mineral oil was removed by washing with dry toluene or pentane and decanting with a syringe, the final solvent traces were removed under vacuum (< 0.05 mmHg). Dimethylformamide (30 ml) was injected with cooling to 0° C, chlorotrimethylsilane (3.24 g, 29.8 mmol) was injected with stirring at this temperature for 1-2 h. The appropriate α,β-unsaturated ester (18.7 mmol, 2.2 eq.) was injected and stirred at this temperature for 1-2 h, followed by room temperature overnight. The reaction was filtered and the solvent removed under reduced pressure to

yield an oily residue which was taken up in dichloromethane (50 ml). The organic solution was washed with 2*M* hydrochloric acid (2 x 15 ml), dried and the solvent removed under reduced pressure to yield the *product*.

By this procedure the following di-substituted phosphinic acids were prepared.

Bis[2-(methoxycarbonyl)ethyl]phosphinic acid (28), as a solid (1.73 g, 85%), m.p. 115-117 °C (from hexane); physical data identical to previous synthesis.

Bis[2-(t-butoxycarbonyl)ethyl]phosphinic acid (30), as a solid, m.p. 113-114 °C (from diethylether); (Found; C, 52.25; H, 8.69; N, nil. $C_{14}H_{27}O_6P$ requires C, 52.17; H, 8.44; N, nil%), physical data identical to previous synthesis.

Bis[2-(ethoxycarbonyl)ethyl]1-methylphosphinic acid (31), as an oil (1.86 g, 74%), physical data identical to previous synthesis.

Bis[2-(ethoxycarbonyl)propyl]phosphinic acid (32), as an oil (1.20 g, 54%), physical data identical to previous synthesis.

Bis[2-(ethoxycarbonyl)-1,2-dimethyl-ethyl]phosphinic acid (63), as an oil (2.0 g, 73%), (Found: $(M+H)^+$, 323.341. $C_{14}H_{27}O_6P$ requires *M*, 322.338); $\upsilon_{max.}$ 1 730 C=O, 1 130 P=O; δ_P (109 MHz) 41.60 (s); *m/z* 322. M^+, 11%). This product was isolated in a crude form making ^1H and ^{13}C spectral analysis uncertain.

Bis[2-(ethoxycarbonyl)-1,1-dimethyl-ethyl]phosphinic acid (33), as an oil (1.62 g, 59%), physical data identical to previous preparation.

t-Butyl vinyl ketone was substituted for α,β-unsaturated esters in the "sodium phosphinate" reaction.

Bis(4,4-dimethyl-3-oxopentyl) phosphinic acid, as a solid, (1.93 g, 78%), physical data identical to previous synthesis.

Ethyl bromo acetate was substituted for α,β-unsaturated esters in the "sodium phosphinate" reaction.

Bis(ethoxycarbonyl)methylphosphinic acid (49), as an oil (0.95 g, 47%), physical data identical to previous synthesis.

Mono-substituted phosphinic acid using the "Sodium phosphinate" method.

2-(t-Butoxycarbonyl)ethyl]phosphinic acid (39). Sodium phosphinate (1.0 g, 11.36 mmol) was purged under dry nitrogen in a flask containg sodium hydride (60% dispersion in mineral oil) (1.36 g, 24 mmol), the mineral oil was removed by washing with dry toluene and decanting with a syringe, the final solvent traces were removed under vacuum (< 0.01 mmHg). Dimethylforamide (30 ml) was injected with cooling to 0° C, chlorotrimethylsilane (3.70 g, 34.1 mmol) was injected with stirring at this temperature for 1 h. *t*-Butyl acrylate (1.31 g, 10.23 mmol, 0.9 eq.) was injected and stirred at this temperature for 1 h, followed by room temperature overnight.

The reaction was filtered and the solvent removed under reduced pressure to yield an oily residue which was taken up in dichloromethane (50 ml). The organic solution was washed with 2*M* hydrochloric acid (1 x 25 ml, 1 x 20 ml) dried and the solvent removed under reduced pressure to yield the *phosphinic acid* as an oil (1.48 g, 78%); physical data identical to previous synthesis.

Ammonium Phosphinate.- Ammonia solution (d=0.880; 58.6 ml, 1.1 mol) was cautiously added to phosphinic acid (109 ml of a 50% solution, 1.0 mol) at 0 °C over 2h. Water was removed under reduced pressure followed by azeotroping with cyclohexane, final solvent traces were removed at 60 °C/0.01 mm Hg to give the product as a crystalline solid in quantitative yield, which was stored over phosphorus pentoxide, (Found: C, nil; H, 7.22; N, 16.90. H_6NO_2P requires C, nil; H, 7.28; N, 16.87%).

Bis(trimethylsilyl) phosphonite (21). Triethylammonium phosphinate (25.05 g, 0.15 mol) and anti-bumping granules were purged in a flask with argon. Hexamethyldisilazane (24.21 g, 0.15 mol) was injected and the temperature was gradually raised to 95 °C. After 2 h hexamethyldisilazane (12.5 g, 75 mmol) was injected, and after a further 1 h the reaction was fractionally distilled to yield the *phosphonite*, (12.4 g, 50%) as an oil, b.p. 159-165 °C (Lit.,[130] 164 °C); δ_H (60 MHz) 0.1-0.3 (18 H, br s, Me), 5.8-8.8 (1 H, d, P-H).

Bis(trimethylsilyl) phosphonite (21).[130] Ammonium Phosphinate (12.45 g, 0.15 mol) was purged in a flask with argon and hexamethyldisilazane (24.21 g, 0.15 mol) injected. The temperature was raised to 100-105 °C with light stirring for 2 h. Ammonia evolution from the reaction was monitored with moist pH paper at a bubbler on the vacuum line and after 2 h evolution had ceased, and the reaction was fractionally distilled to yield the product as an oil (21.3 g, 85%), b.p. 159-161 °C (Lit.,[130] 164 °C); δ_H (300 MHz) 0.15 (18 H, br s, Me), 7.1-7.7 (1 H, d, J_{PH} 180 Hz, P-H).

Mono-substituted phosphinic acid synthesis directly from bis(trimethylsilyl) phosphonite, General procedure:- Dichloromethane (30 ml) was cooled to 0 °C in a flask purged with dry nitrogen. Bis(trimethylsilyl) phosphonite (4.48 g, 21.3 mmol) followed by the appropriate vinyl ketone (23.4 mmol, 1.1 eq.) were injected and maintained at this temperature with stirring for 1-2 h, followed by a return to room temperature with stirring overnight. The reaction was filtered and cooled to 0 °C, tetrahydrofuran (10 ml) and 4 *M* hydrochloric acid (15 ml) were added with stirring for 1 h. The solvents were removed under reduced pressure and the resulting oil dissolved in dichloromethane (50 ml), filtered, and washed with water (2 x 15 ml). The organic extract was dried, and the solvent removed under reduced pressure to yield the product as an oil.

By this procedure the following mono-substituted phosphinic acids were prepared.

3-Oxo-butylphosphinic acid (69), was water soluble and was isolated by removal of solvent from the washings under reduced pressure, and taking the product up in dichloromethane/methanol and drying, followed by rotary oil pumping (<0.01 mm Hg, 45 °C, 24 h, over phosphorus pentoxide) to give the *phosphinic acid* as an oil (2.43 g, 51%); δ_H (100 MHz, CD_3OD) 1.9-2.2 (2 H, br m, P-CH_2), 2.2 (3 H, s, Me), 2.7-3.0 (2 H, br m, CO-CH_2), 4.4-10.1 (1 H, d, P-H); δ_P (109 MHz, CD_3OD) 33.71 (s); *m/z* 136.80 M^+, 31%).

3-Oxo-hexylphosphinic acid (70), as an oil (2.29 g, 66%),(Found: $(M+H)^+$, 165.0665. $C_6H_{13}O_3P$ requires *M*, 164.0602); δ_H (250 MHz) 0.8-0.9 (3 H, t, Me), 1.4-1.6 (2 H, sextet, CH_2CH_3), 1.8-2.0 (2 H, br m, P-CH_2), 2.3-2.4 (2 H, t, $CH_3CH_2CH_2$), 2.6-2.8 (2 H, br m, P-CH_2CH_2), 5.9-8.2 (1 H, d, P-H), 11.5 (1 H, s, P-OH); δ_C (75.5 MHz) 13.29 *(s, Me), 16.89* (s, Me-*C*), 21.51-22.77 (d, J_{PC} 95.1 Hz, P-C), 34.10 (s, P-C-*C*), 44.04 (s, Me-C-*C*), 207.61-207.77 (d, J_{PC} 12.1 Hz, CO); δ_P (109 MHz, CD_3OD) 35.39; *m/z* 164.77 ($[M+H]^+$, 100%).

3-Oxo-cyclopentylphosphinic acid (71), was water soluble and was isolated by removal of solvent from the washings under reduced pressure followed by rotary oil pumping (<0.05 mm Hg, 40 °C, 16 h, over phosphorus pentoxide) to give the *phosphinic acid* as an oil (2.42 g, 77%); δ_H (300 MHz, CD_3OD) 1.8-2.4 (7 H, br m, cyclopentyl), 6.1-7.8 (1 H, d, P-H); δ_P (109 MHz, CD_3OD) 39.78.

3-Oxo-cyclohexylphosphinic acid (72), was water soluble and was isolated by removal of solvent from the washings under reduced pressure followed by rotary oil pumping (<0.01

mm Hg, 40 °C, 14 h, over phosphorus pentoxide) to give the *phosphinic acid* as an oil (3.24 g, 94%); (Found: $(M+H)^+$, 163.0524. $C_6H_{11}O_3P$ requires *M*, 162.0046); δ_H (300 MHz, CD_3OD) 1.2-2.2(9 H, br m, cyclohexyl) 6.0-7.8 (1 H, d, P-H), *m/z* 180.04 ($[M+NH_4]^+$, 55%).

3-Oxo-cycloheptylphosphinic acid (73), as an oil (5.92 g, 86%); *m/z* 177 ($[M+H]^+$, 8%). The spectral data was contaminated making spectral assignment uncertain.

(2-Acetylcyclohexyl)phosphinic acid (74), as an oil (3.08 g, 76%). This compound was synthesised in purer form later and is characterised.

The above general procedure was used to synthesize mono-substituted phosphinic acids using α,β-unsaturated esters instead of vinyl ketones.

2-(Ethoxycarbonyl)-1-methyl-ethylphosphinic acid (40), as an oil (1.46, 74%); δ_H (300 MHz) 1.2-1.3 (6 H, m, Me Me), 2.2-2.5 (2 H, br m, $COCH_2$), 2.6-2.9 (1 H, br m, CH), 4.1-4.2 (2 H, q, CH_3CH_2), 6.1-8.0 (1 H, d, P-H); δ_C (75.5 MHz) 11.62 (s, CH-CH_3), 14.22 (s, CH_2CH_3), 29.19-30.46 (d, J_{PC} 96 Hz), 33.85 (s, CO-CH_2), 61.04 (s, O-CH_2), 171.00 (s, CO); δ_P (109 MHz, CD_3OD) 41.26 (s); *m/z* 181.05 ($[M+H]^+$, 18%).

2-(Ethoxycarbonyl)-1-methyl-propylphosphinic acid (75), as an oil (1.14, 28%); δ_H (60 MHz) 1.0-1.2 (3 H, t, J_{HH} 7.14 Hz), 1.3 and 1.4 (6 H, 2 s, Me), 1.7-2.4 (1 H, br m, P-CH), 2.6-3.2 (2 H, br m, CO-CH), 4.0-4.4 (2 H, q, J_{HH} 7.14 Hz,

OCH_2), 2.5-10.5 (1 H, d, J_{HH} 480 Hz),2.6-10.6 (1 H, d, J_{HH} 480 Hz); (*m/z* 195 ($[M+H]^+$, 12%).

The above general procedure was used to synthesize a mono-substituted phosphinic acid using acrylic acid instead of vinyl ketone.

(3-Carboxypropyl)phosphinic acid (76), was very water soluble and was isolated by removal of solvent from the washings followed by rotary oil pumping (<0.01 mm Hg, 40 °C, 12 h, over phosphorus pentoxide) to give the *phosphinic acid* as an oil (1.90 g, 68%); δ_H (500 MHz, DMSO-d^6) 1.8-1.9 (2 H, m,P-CH_2), 2.3-2.4 (2 H, m, CO-CH_2), 6.4-6.5 (1 H, d, P-H); *m/z* 138.68 ($[M+H]^+$, 100%).

Formation of adamantanammonium phosphinates.

Synthesis of adamantanammonium phosphinates was developed and utilised to allow full characteration of the free phosphinic acids previously synthesised, because the salts were generally pure by elemental analysis. However the ^1H and ^{13}C adamantanammonium nuclear magnetic resonances were very strong compared to the phosphinate resonances, which they generally masked. This yielded little useful imfomation. For this reason, although a full set of ^1H and ^{13}C NMR spectra were obtained for the adamantanammonium phosphinates, the data has not been included. From NMR spectral information, formation of adamantanammonium phosphinates has little effect on the frequency of the ^1H and ^{13}C magnetic resonances of the phosphinates relative to the free phosphinic acid resonances, which are included.

Formation of adamantanammonium phosphinates had negligible effect on the frequency of P=O, C=O and P-H infrared absorptions, relative to the free phosphinic acids. Generally the infrared spectra were overcomplicated by the presence of strong absorptions resulting from the adamantanammonium fragment, hence although all the infrared spectra were recorded the information is not included, however the infrared spectra of the free phosphinic acids is included.

N-(1-adamantanammonium) 3-oxo-octylphosphinic acid (78), the phosphinic acid was isolated as the (1-adamatanamino) salt by taking the product after first filtration and filtering a solution of adamantamine (3.54 g, 23.4 mmol) in diethylether (50 ml) at 0 °C into it and stirring at this temperature for 1 h. The reaction was left stirring overnight at room temperature. The reaction was filtered and the product washed with diethylether (2 x 20 ml) and dried *in vacuo* over phosphorus pentoxide, (5.12 g, 70%) as a crystalline solid; (Found; *C, 62.64; H, 10.05; N, 3.97.* $C_{18}H_{34}O_3NP$ requires C, 62.95; H, 9.98; N, 4.08); δ_P (109 MHz, TFA d^6) 25.82 (s); *m/z* 344.15 ($[M+H]^+$, 35%).

N-(1-adamantanammonium) 3-oxocyclohexylphosphinic acid (79), (3.24 g, 92%) as a solid; δ_P (109 MHz, TFA d^6); *m/z* 314. ($[M+H]^+$, 100%)

N-(1-adamantanammonium) (2-acetylcyclohexyl)phosphinic acid (80), the phosphinic acid was isolated as the (1-adamatanammonium) salt by taking the product after first

filtration and filtering a solution of adamantammonium (3.54 g, 23.4 mmol) in diethylether (60 ml) at 0 °C into it and stirring at this temperature for 1 h. The reaction was left stirring overnight at room temperature then filtered and the product washed with diethylether (2 x 30 ml) and dried *in vacuo* over phosphorus pentoxide, (5.40 g, 74%) as a crystalline solid; δ_P (109 MHz, TFA d^6) 39.23; *m/z* 342 ($[M+H]^+$, 100%)

Substituted phenylphosphinic acid synthesis from phenylphosphinic acid:- General procedure. Phenylphosphinic acid (2.13 g, 15 mmol) *and hexamethyl*-disilazane (4.84 ml, 30 mmol in dichloromethane (40 ml) at 0 °C were stirred for 2 h. Vinyl ketone (16.5 mmol, 1.1 equivalents) was injected and after 0.5 h the temperature was allowed to return to room temperature. After stirring overnight the solvent was removed under reduced pressure, and methanol (40 ml) at 0 °C was added with stirring for 1 h. The mixture was evaporated under reduced pressure, followed by rotary oil pumping (35 °C/0.01 mmHg) to yield the product.

By this procedure the following substituted phenylphosphinic acids were prepared.

(3-Oxopentyl)phenylphosphinic acid, (3.03 g, 89%) as a foam; δ_H (300 MHz) 0.8-0.9 (3 H, t, Me), 1.9-2.0 (2 H, br m, P-CH_2), 2.2-2.3 (2 H, q, CH_3CH_2), 2.2-2.4 (2 H, br m, CO-CH_2-CH_2), 7.2-7.7 (5 H, br m, Ph); δ_C (75.5 MHz) 7(s, Me), 24-26 (d, P-C), 35 (s, CO{C}$_2$, 127-133 (br m, Ph); δ_p (109 MHz) 35.83; *m/z* 227.47 ($[M+H]^+$, 87%).

(3-Oxohexyl)phenylphosphinic acid, as an oil (2.56 g, 71%); δ_H (300 MHz) 0.8-0.9 (3 H, t, Me); 1.4-1.6 (2 H, sextet, $CH_2CH_2CH_2$), 2.0-2.2 (2 H, br m, P-CH_2), 2.2-2.3 (2 H, t, $CH_3CH_2CH_2$), 2.5-2.7 (2 H, br m, P-CH_2CH_2), 7.4-7.8 (5 H, br m, Ph), 12.7-12.9 (1 H, br s, P-OH); δ_C (75.5 MHz) 13.78 (1 C, s, Me), 17.35 (1 C, s, Me-CH_2), 23.79-25.13 (1 C, d, J_{PC} 101.2 Hz, P-CH_2), 34.83 (1 C, s, C{4}), 44.53 (1 C, s, C{2}), 128.47-132.38 (6 C, br m, Ph), 208.20-208.38 (1 C, d, J_{PC} 13.6 Hz, CO); *m/z* 240.88 M^+, 100%).

The above general procedure was used to synthesize substituted phenylphosphinic acids using ethyl acrylate instead of a vinyl ketone.

[2-(Ethoxycarbonyl)ethyl]phenylphosphinic acid, (3.10 g, 60%) as a foam; (Found: $(M+H)^+$, 243.0791. $C_{12}H_{15}O_4P$ requires *M*, 242.071); δ_H (300 MHz, CD_3OD) 1.2-1.3 (3 H, t, Me), 1.9-2.1 (2 H, br m, P-CH_2), 2.5-2.6 (2 H, br m, CH_2CO), 4.0-4.1 (2 H, q, O-CH_2), 7.4-7.9 (5 H, br m, Ph); δ_p (109 MHz, CD_3OD) 31.97; *m/z* 243.02 ($[M+H]^+$, 100%).

N-(1-adamantanammonium) mono-substituted phosphinate synthesis from ammonium phosphinate:-

General procedure.

Ammonium phosphinate (2.5 g, 30.1 mmol) and hexamethyldisilazane (5.1 g, 31.6 mmol) were heated together under a dry nitrogen atmosphere at 100-110 °C for 1.5-2.5 h, until no further ammonia was evolved. The system was cooled to 0 °C and dichloromethane (30 ml) was injected, followed by the appropriate vinyl ketone (31.6 mmol). The reaction was

stirred overnight, filtered and the solvent removed under reduced pressure to yield an oil, a small portion of which was removed for free substituted phosphinic acid formation, the rest dissolved in tetrahydrofuran (10 ml). Adamantanamine (1.05 equivalents) dissolved in tetrahydrofuran(40 ml)/methanol(15 ml) was filtered into the above solution at 0 °C. The reaction was left stirring overnight, filtered and the precipitate washed with diethylether (2 x 25 ml), dried *in vacuo* (over phosphorus pentoxide) to yield the product as a crystalline solid. The solvents were removed from the filtrate to yield a residue which was *dispersed* in diethylether (50 ml), aided by sonication. The suspension was stirred overnight, yielding a precipitate which was filtered, washed with diethylether (2 x 25 ml) and dried *in vacuo* (over phosphorus pentoxide) to yield a second crop of the product as a crystalline solid.

Free mono-substituted phosphinic acid formation:-

General procedure. Methanol (25 ml) at 0 °C was slowly added to the above removed product at 0 °C, and stirred for 2 h. The solvent was removed to yield the product as an oil, which was dried *in vacuo* (over phosphorus pentoxide).

By this procedure the following N-(1-adamantanammonium) mono-substituted and free mono-substituted phosphinic acids were prepared.

N-(1-adamantanammonium) 3-oxobutylphosphinic acid (81), no product precipitated out in tetrahydrofuran/methanol. From diethylether, (4.68 g, 74%) as a crystalline solid; (Found;

C, 58.25; H, 9.23; N, 5.01. $C_{14}H_{26}NO_3P$ requires C, 58.52, H, 9.12; N, 4.88); δ_P (109 MHz, TFA d^6) 44.31 (s); *m/z* 287.34 ($[M+H]^+$, 7%).

3-Oxobutylphosphinic acid (69),(0.88 g, 79%) as an oil; $\upsilon_{max.}$ 2 350 P-H, 1 715 C=O, 1 230 P=O; δ_H (300 MHz, CD_3OD) 1.86-2.08 (2 H, br m, P-CH_2), 2.22 (3 H, s, Me), 2.77-2.88 (2 H, br m, CO-CH_2), 6.22-8.02 (1 H, d, J_{PH} 540 Hz, P-H); δ_C (75.5 MHz CD_3OD) 21.59-22.85 (d, J_{PC} 95 Hz, P-C), 26.10 (s, Me) 34.10 (s, P-C-*C*), 207-208 (d, J_{PC} CO); δ_p (109 MHz, CD_3OD) 33.88 (s); *m\z* 136 (M^+, 40%).

N-(1-adamantanammonium) 3-oxopentylphosphinic acid (82), after the dichloromethane was removed, adamantanamine (1.05 equivalents) in diethylether (50 ml)/methanol (5 ml) was added. Filtration followed by washing gave (82) (4.60 g, 89%) as a crystalline solid; (Found; C, 59.69; H, 9.41; N, 4.70. $C_{15}H_{28}NO_3P$ requires C, 59.78; H, 9.37; N, 4.65)

3-Oxopentylphosphinic acid (70), (1.72 g, 92%) as an oil; $\upsilon_{max.}$ 2 340 P-H, 1 710 C=O, 1 210 P=O; δ_H (300 MHz, CD_3OD) 1.84-2.38 (7 H, br m, CH and CH_2), 6.00-7.79 (1 H, d, J_{PH} 537 Hz, P-H); δ_C (75.5 MHz CD_3OD) 21.43-23.00 and 32.28-37.79 (br m, CH and CH_2), 217.16 (CO); δ_P (109 MHz CD_3OD) 40.15; *m/z* 148.95 M^+, 13.2.

N-(1-adamantanammonium) 3-oxohexylphosphinic acid (83), after the dichloromethane was removed, adamantanamine (1.05 equivalents) in diethylether (60 ml)/methanol (5 ml) was

added. Filtration followed by washing with ether gave (83) (4.9 g, 87%) as a crystalline solid; (Found; C, 59.89; H, 9.55; N, 4.24. $C_{16}H_{30}NO_3P$ requires C, 60.93; H, 9.59; N, 4.44); *m/z* 316 ($[M+H]^+$, 100%).

3-Oxohexylphosphinic acid (70), as an oil (1.78 g, 88%); (Found C, 44.06; H, 7.81; N, nil. $C_6H_{13}O_3P$ requires C, 43.91; H, 7.98;N, nil); $\upsilon_{max.}$ 2 300 P-H, 1 710 C=O, 1 210 P=O; δ_H (300 MHz) 0.8-0.9 (3 H, t, Me), 1.5-1.7 (2 H, sextet, CH_2-CH_3), 1.9-2.0 (2 H, br m, P-CH_2) 2.3-2.4 (2 H, t, $CH_3CH_2CH_2$) 2.6-2.8 (2 H, br m, P-CH_2CH_2) 6.2-8.1 (1 H, d, P-H), 11.8 (1 H, br s, P-OH); δ_C (75 MHz) 13.73 (s, Me), 17.38 (s, Me-*C*), 22.71-23.98 (d, J_{PC} 96 Hz ,P-C), 34.17-34.21 (d, J_{PC} 3 Hz), 44.36 (s, P-C-*C*), 208.02-208.08 (d, J_{PC} 4.5, CO); δ_P (109 MHz) 40.85 (s); *m/z* 165 ($[M+H]^+$, 100%).

N-(1-adamantanammonium) (1-methyl)-3-oxopentylphosphinic acid (84), first crop (4.76 g, 50%), second crop (2.82 g, 30%) as crystalline solids; (Found C, 60.73; H, 9.35; N, 4.53. $C_{16}H_{30}NO_3P$ requires C, 60.93; H, 9.59; N, 4.44); δ_P (109 MHz, TFA d^6) 49.28 (s); *m\z 315.96 (M^+, 24%).*

(1-Methyl)-3-oxopentylphosphinic acid, as an oil (0.48 g, 83%); (Found C, 43.75; H, 7.98; N, nil. $C_6H_{13}O_3P$ requires C, 43.91; H, 7.98; N, nil); $\upsilon_{max.}$ 2 360 P-H, 1 715 C=O, 1 180 P=O; δ_H (300 MHz) 1.02-1.16 (6 H, br, Me Me), 2.27-2.58 (4 H, br, CH_2 CH_2), 2.72-2.87 (1 H, br m, CH), 6.07-7.91 (1 H, d, J_{PH} 552 Hz, P-H), 10.35 (1 H, br s, P-OH); δ_C (75 MHz) 8 (s, P-C-*Me*), 12 (s, Me-*C*-CO), 27-28 (d, J_{PC} 75 Hz, P-C), 35 (s, P-C-*C*), 40 (s, Me-*C*-CO); δ_P (109 MHz) 41.31. *m/z* 165 ($[M+H]^+$, 100%)

N-(1-adamantanammonium) (1-butyl)-3-oxobutylphosphinic acid (85), first crop (0.46 g, 7%), second crop (5.10 g, 77%) as crystalline solids; (Found C, 63.27; H, 10.27; N, 4.09. $C_{18}H_{34}NO_3P$ requires C, 62.95; H, 9.98; N, 4.08);

(1-butyl)-3-oxobutylphosphinic acid, as an oil; (Found C, 50.10; H, 8.94; N, nil. $C_8H_{17}O_3P$ requires C, 50.00; H, 8.92; N, nil); $\upsilon_{max.}$ 2 360 P-H, 1 720 C=O, 1 200 P=O; δ_P 0.75-0.85 (3 H, t, J_{HH} 7.14 Hz, CH_2-*Me*), 1.20-1.40 (6 H, br m, Me-*C*-*C*-*C*), 2.15 (3 H, s, CO-*Me*), 6.10-7.90 (1 H, d, J_{PH} 540 Hz, P-H), 11.90-12.10 (1 H, br s, P-OH); δ_P (109 MHz) 39.96 (s); *m/z* 344 ($[M+H]^+$, 100%)

N-(1-adamantanammonium) (1,1-dimethyl)-3-oxobutylphosphinic acid (86), first crop (3.11 g, 50%), second crop (1.98 g, 30%) as crystalline solids; δ_P (109 MHz, TFA d^6) 53.54 (s); *m/z* 316.01 ($[M+H]^+$, 29%).

(1,1-dimethyl)-3-oxobutylphosphinic acid, as an oil (1.38 g, 81%); $\upsilon_{max.}$ 2 330 P-H, 1 715 C=O, 1 190 P=O; δ_H (300 MHz) 1.02-1.05 (6 H, d, J_{PH} 9 Hz, $C[Me]_2$) 2.03 (3 H, s, CO-Me), 2.56-2.61 (2 H, d, J_{PH} 15 Hz, CH_2), 6.01-7.88 (1 H, d, J_{PH} 561 Hz, P-H), 11.15 (1 H, s, P-OH); δ_P (109 MHz) 45.9; *m/z* 182.39 ($[M+NH_4]^+$, 85%).

N-(1-adamantanammonium) 3-oxocyclopentylphosphinic acid (87), first crop (3.70 g, 61%), second crop (1.82 g, 30%) as crystalline solids; (Found C, 60.10; H, 9.01; N, 4.68. $C_{15}H_{26}NO_3P$ requires C, 60.19; H, 8.76; N, 4.68); δ_P (109 MHz, TFA d^6) 44.76; *m/z* 300.12 ($[M+H]^+$, 34%).

3-oxocyclopentylphosphinic acid (71), as an oil (1.28 g, 87%); $\upsilon_{max.}$ 2 350 P-H, 1 740 C=O, 1 170 P=O; δ_H (300 MHz, CD_3OD) 1.84-2.38 (7 H, br m, cyclopropanyl), 5.99-7.78 (1 H, d, J_{PH} 537 Hz); δ_C (75 MHz, CD_3OD) 21.43-23.00 and 32.28-37.79 (br m, CH and CH_2), 217.00-217.16 (d, J_{PC} 12.1 Hz); δ_P (109 MHz, CD_3OD) 40.34; *m/z* 148.95 (M^+, 13%).

N-(1-adamantanammonium) 3-oxocyclohexylphosphinic acid (79), first crop (1.4 g, 23%), second crop (3.8 g, 64%) as crystalline solids; δ_P (109 MHz, TFA d^6) 42.43; *m/z* 314.29 ($[M+H]^+$, 11%).

3-oxocyclohexylphosphinic acid (72), as an oil (1.48 g, 87%); $\upsilon_{max.}$ 2 360 P-H, 1 710 C=O, 1 190 P=O; δ_H (300 MHz, CD_3OD) 1.2-2.3 (9 H, br m, cyclohexyl), 6.0-7.7 (1 H, d, P-OH); δ_P (109 MHz) 39.15; *m\z* 161.96 (M^+, 21%).

N-(1-adamantanammonium) (2-acetylcyclohexyl)phosphinic acid (88), first crop (4.19 g, 57%), second crop (1.64 g, 22%) as crystalline solids; (Found C, 63.43; H, 9.39; N, 4.18. $C_{18}H_{32}NO_3P$ requires C, 63.32; H, 9.45; N, 4.10); *m/z* ($[M+H]^+$, 100 %); δ_P (109 MHz, TFA d^6) 39.36 (s).

(2-Acetylcyclohexyl)phosphinic acid (74), as an oil (1.32 g, 83%); $\upsilon_{max.}$ 2 400 P-H, 1 705 C=O, 1 200 P=O; δ_H (300 MHz, CD_3OD) 1.45-2.27 (13 H, br m, cyclohexyl), 1.5 (3 H, s, Me), 5.72-7.58 (1 H, d, J_{PH} 558 Hz), 8.39 (1 H, br s, P-OH); δ_P (109 MHz) 38.46 (s); *m\z* 190.92 (M^+, 63%)

5-Cholestanylphosphinic acid (94), as a foam (3.25 g, 76%); (Found: $(M-H_2O)^+$, 433.32426. $C_{27}H_{47}O_3P$ requires *M*, 450.644); (note: this accurate mass measurement was performed at Pfizer Central Research and is the only molecule that they have observed to lose H_2O in the FAB mass spectrum); *m/z* 473.48 ($[M+Na]^+$, 9.2%). The proton and carbon spectra were complex)

The above general procedure was also used to synthesize mono-substituted phosphinic acids using α,β-unsaturated esters instead of vinyl ketones.

N-(1-adamantanammonium) 2-(ethoxycarbonyl)ethyl-phosphinic acid (89), first crop (4.44 g, 53%), second crop (3.88 g, 46%) as crystalline solids; (Found C, 57.05; H, 9.00; N, 4.41. $C_{15}H_{28}NO_4P$ requires C, 56.77; H, 8.89, N, 4.41); δ_p (109 MHz, TFA d^6) 41.66; *m/z* 318.12 ($[M+H]^+$, 37%).

2-(ethoxycarbonyl)ethylphosphinic acid (38), (0.57 g, 98%) as an oil; $\upsilon_{max.}$ 2 350 P-H, 1 735 C=O, 1 245 P=O; δ_H (300 MHz) 1.1-1.3 (3 H, t, Me), 1.9-2.1 (2 H, br m, P-CH_2), 2.5-2.7 (2 H, br m, CH_2CO), 4.1-4.2 (2 H, q, O-CH_2), 6.2-8.1 (1 H, d, P-H), 11.3 (1 H, br s, P-OH); δ_C (109 Mz) 22-25 (m, Me P-C-C), 60 (s, OMe), 172 (d, CO); *m/z* 167.06 ($[M+H]^+$, 100%).

N-(1-adamantanammonium) 2-(t-butoxycarbonyl)ethyl-phosphinic acid (90), first crop (5.51 g, 53%), second crop (4.12 g, 40%) as crystalline solids; (Found C, 59.11; H, 9.14; N, 4.14. $C_{17}H_{32}NO_4P$ requires C, 59.11; H, 9.34, N, 4.06); $\upsilon_{max.}$ 2 250 P-H, 1 730 C=O, 1 240 P=O; δ_P (109 MHz, TFA d^6) 42.87; *m/z* 167.06 ($[M+H]^+$, 100%).

N-(1-adamantanammonium) 2-(ethoxycarbonyl)-1-methyl-ethyl phosphinic acid (91), first crop (2.82 g, 28%), second crop (6.34 g, 64%) as crystalline solids; (Found C, 57.59; H, 9.18, N, 4.05. $C_{16}H_{30}NO_4P$ requires C, 57.99; H, 9.13; N, 4.23); δ_P (109 MHz, TFA d^6) 32.83; *m/z* 184.35 ($[M+NH]^+$, 100%).

N-(1-adamantanammonium) 2-(methoxycarbonyl)-propyl-phosphinic acid (92) no product precipitated out in tetrahydrofuran/ methanol. From diethylether, (5.24 g, 78%) as a crystalline solid; (Found; C, 56.44; H, 8.68; N, 4.54. $C_{15}H_{28}NO_4P$ requires C, 56.77, H, 8.89; N, 4.41); δ_P (109 MHz TFA d^6) 41.97 (s); *m/z* 318.12 ($[M+H]^+$, 100%).

2-(methoxycarbonyl)propylphosphinic acid, as an oil (1.25 g, 83%); (Found C, 36.15; H, 6.72; N, nil. $C_5H_{11}O_4P$ requires C, 36.15; H, 6.68; N, nil); $\upsilon_{max.}$ 2 400 P-H, 1 735 C=O, 1 230 P=O; δ_H (300 MHz) 1.29-1.31 (3 H, d, J_{PH} 6 Hz, CH-CH_3), 1.77-2.25 (2 H, br m, P-CH_2), 2.83-2.92 (1 H, br m, CH), 3.68 (3 H, s, O-Me), 6.23-8.09 (1 H, d, J_{PH} 558 Hz, P-H), 10.44 (1 H, br s, P-OH); δ_C (75.5 MHz) 18.41-18.54 (d, J_{PC} 10 Hz, CH-CH_3), 32.39-33.65 (d, J_{PH} 95 Hz, CH_2),

33.53-33.55 (d, J_{PH} 2 Hz, CH), 51.99 (s, O-Me), 175.16-175.28 (d, J_{PC} 9 Hz, CO); δ_P (109 MHz) 32.83; *m/z* 184.35 ($[M+NH_4]^+$, 100%).

N-(1-adamantanammonium) 2-(ethoxycarbonyl)-(1,1-dimethyl)-ethylphosphinic acid (93), first crop (1.62 g, 28%), second crop (2.30 g, 39%) as crystalline solids; (Found C, 59.11; H, 9.34, N, 4.06. $C_{17}H_{32}NO_4P$ requires C, 59.11; H, 9.34; N, 4.06); δ_p (109 MHz, TFA d^6); *m/z* 346 ($[M+H]^+$, 28%).

2-(ethoxycarbonyl)-(1,1-dimethyl)ethylphosphinic acid, (1.96 g, 77%) as an oil; $\upsilon_{max.}$ 2 420 P-H, 1 730 C=O, 1 230 P=O; 1.1-1.3 (12 H, m, Me), 2.5-2.6 (2 H, d, CH_2CO), 4.1-4.2 (2 H, q, O-CH_2), 6.0-7.9 (1 H, d, P-H), 11.9 (1 H, s, P-OH); δ_C (75.5 MHz) 14 (CH_2CH_3), 20 ($C\{CH_3\}_2$), 33-35 (d, CH), 41 (1 C, CO-CH_2), 62 (1 C, CH_3CH_2), 171 (1 C, CO); δ_p (109 MHz) 45.28 (s); *m/z* 195 $[M+H]^+$, 100%.

The above general procedure was used to synthesise mono-substituted phosphinic acids using other reagents.

2-Cyanoethylphosphinic acid (131) as an oil (2.10 g, 99%), (Found: $(M+H)^+$, 120.082. $C_3H_6NO_2P$ requires *M*, 238.176); δ_H (270 MHz CD_3OD) 1.95-2.40 (2 H, br m, P-CH_2), 2.60-2.90 (2 H, br m, NC-CH_2); δ_C (75 MHz CD_3OD) 11.02-12.21 (d, J_{PC} 81.5 Hz); 25.32 (s, CN-*C*); 120.34-120.42 (d, J_{PC} 3.4 Hz, CN); δ_P (109 MHz CD_3OD) 24.78; *m/z* 120 $[M+H]^+$, 100%

Di-substituted N-(1-adamantanammonium) phosphinate synthesis from ammonium phosphinate:-

General procedure.

Ammonium phosphinate (2.5 g, 30.1 mmol) and hexamethyl-1disilazane (5.1 g, 31.6 mmol) were heated together under a dry nitrogen atmosphere at 100-110 °C for 1.5-2.5 h, until no further ammonia was evolved. The system was cooled to 0 °C and dichloromethane (40 ml) was injected, followed by the appropriate vinyl ketone or α,β-unsaturated ester (30.1 mmol). The reaction was stirred overnight, cooled to 0° C, and hexamethyldisilazane (5.3 g, 33.1 mmol) injected and stirred for 2 h. The appropriate vinyl ketone or α,β-unsaturated ester (30.1 mmol) was injected and stirred for 1-2 h at 0 °C, followed by stirring overnight at room temperature. The system was filtered and the solvent removed under reduced pressure to yield a viscous oil, a small portion of which was removed for free bis substituted phosphinic acid formation, the rest was dissolved in tetrahydrofuran (10 ml). Adamantanamine (1.05 equivalents) dissolved in tetrahydrofuran(40 ml)/methanol(15 ml) was filtered into the above solution at 0 °C. The reaction was left stirring overnight, filtered and the precipitate washed with diethylether (3 x 20 ml), dried *in vacuo* (over phosphorus pentoxide) to yield the product as a crystalline solid. The solvents were removed from the filtrate to yield a residue which was dispersed in diethylether (50 ml), aided by sonication. The suspension was stirred overnight, yielding a precipitate which was filtered, washed with diethylether (3 x 20 ml) and dried *in vacuo* (over phosphorus pentoxide) to yield a second crop of the product as a crystalline solid.

Free di-substituted phosphinic acid formation:-

General procedure. Methanol (50 ml) at 0 °C was slowly added to the above removed product at 0 °C, and stirred for 2 h. The solvent was removed to yield the product which was dried *in vacuo* (over phosphorus pentoxide).

By this procedure the following N-(1-adamantanammonium) di-substituted and free di-substituted phosphinic acids were prepared.

Bis(3-oxohexyl)phosphinic acid (96), all of the *reaction* was worked up as the free acid, the product was obtained as a crystalline solid (6.68 g, 87%), $\upsilon_{max.}$ 1 710 C=O, 1 215 P=O; m.p. 132.5-133.5 °C (Found C,54.77; H, 8.95; N, nil. $C_{12}H_{23}O_4P$ requires C, 54.95; H, 8.84, N, nil); δ_H (300 MHz) 0.8-0.9 (6 H, t, Me), 1.6-1.7 (4 H, sextet, CH_2-CH_3), 1.9-2.1 (4 H, br m, P-CH_2) 2.4-2.5 (4 H, t, $CH_3CH_2C\underline{H}_2$) 2.7-2.8 (2 H, br m, P-CH_2CH_2), 6.7 (1 H, s, P-OH); δ_C (75.5 MHz) 13.29 (s, Me), 16.89 (s, Me-CH_2), 21.51-22.77 (d, J_{PC} 95.1 Hz, P-CH_2), 34.11 (s, C{4}), 44.04 (2 C, s, C{2}), 207.61-207.77 (d, J_{PC} 12 Hz, CO); *m/z* 263.09 $[M+H]^+$, 100%).

N-(1-adamantanammonium) bis(3-oxohexyl)-(1-methyl-3-oxopentyl)phosphinic acid, first crop (3.75 g, 39%), second crop (4.03 g, 42%) as solids which were impure; *m/z* 404.52 $[M+H]^+$, 100%).

Bis(3-oxohexyl)(1-methyl-3-oxopentyl)phosphinic acid (97), (1.40 g, 83%) as a foam; (Found: $(M+H)^+$, 263.1396. $C_{12}H_{23}O_4P$ requires *M*, 265.286); δ_H (300 MHz) 0.9-1.1(12 H, br m, Me), 1.5-1.6(4 H, sextet, $CH_3CH_2CH_2$), 1.8-2.0(2 H, br m,

P-CH_2), 2.3-2.4(2 H, t, $CH_3CH_2CH_2$), 2.6-2.8 (3 H, br m, CH P-CH_2CH_2), 11.7-11.9(1 H, br s, P-OH); δ_p (109 MHz, $CDCL_3/CD_3OD$) 53.48; *m/z* 263.65 $[M+H]^+$, 83%)

N-(1-adamantanammonium) [2-(ethoxycarbonyl)-ethyl](3-oxopentyl)phospinic acid, first crop (1.74 g, 19%), second crop (3.56 g, 38%) as oily solids, which were impure.

[2-(Ethoxycarbonyl)ethyl](3-oxopentyl)phospinic acid (98), (1.39 g, 79%) as a viscous oil/glass. A small sample was induced to crystallise with diethyether to yield a solid, (Found C, 48.38; H, 7.92; N, nil. $C_{10}H_{19}O_5P$ requires C, 48.38; H, 7.92; N, nil)δ_H (300 MHz) 1.0-1.1 (3 H, t, CO-CH_2CH_3), 1.2-1.3 (3 H, t, O-CH_2-CH_3), 1.9-2.1 (4 H, br m, CH_2-P-CH_2), 2.4-2.5 (2 H, q, $CO\{CH_2\}_2$), 2.6-2.8 (4 H, br m, $P\{CH_2CH_2\}_2$) 4.1-4.2 (2 H, q, CO-O-CH_2), 9.1-9.3 (1 H, br s,P-OH); *m/z* 251.26 ($[M+H]^+$,18%).

N-(1-adamantanammonium) [2-(ethoxycarbonyl)ethyl]-(2-(methoxycarbonyl)propylphospinic acid, first crop (0.38 g, 6%) as a crystalline solid, second crop (2.11 g, 33%) as an oily solid which was impure.

[2-(Ethoxycarbonyl)ethyl](2-(methoxycarbonyl)propylphosp inic acid (99), (3.05 g, 77%) as an oil; δ_H (300 MHz) 1.1-1.2(6 H, d t, CH_3CH CH_3CH_2), 1.4-2.2(4 H, br m, CH_2-P-CH_2), 2.4-2.5(2 H, br m, O-CO-CH_2), 2.7-2.8(1 H, br m, CH), 3.6(3 H, s, O-Me), 13.1(1 H, br s, P-OH); δ_p(109 MHz, CD_3OD)50.48; *m/z* 267.14 $[M+H]^+$, 100%.

Mono-alkylphosphinic acid synthesis from ammonium phosphinate:- General procedure.

Ammonium phosphinate (2.5 g, 30.1 mmol) and hexamethyldisilazane (5.1 g, 31.6 mmol) were heated together under a dry nitrogen atmosphere at 100-110 °C for 1.5-2.5 h, until no further ammonia was evolved. The system was cooled to 0 °C and dichloromethane (30 ml) was injected, followed by the appropriate alkyl iodide (31.6 mmol). The reaction was stirred overnight, filtered and the solvent removed under reduced pressure to yield an oil which was taken up in dichloromethane (aided by a minimum of methanol), refiltered and the solvents removed, to yield the oil which was dried over phosphorus penoxide at 40 °C and >0.1 mmHg overnight.

By this procedure the following mono-alkylphosphinic acids were prepared.

Methylphosphinic acid (108), as an oil (1.82 g, 94%), δ_H (270 MHz, $CDCl_3/CD_3OD$) 1.46-1.59 (3 H, br m, Me), 6.18-8.22 (1 H, d, J_{PH} 550 Hz); δ_C (68 MHz, $CDCl_3/CD_3OD$) 15.44-16.83 (d, J_{PC} 94.8 Hz); δ_P (109 MHz, $CDCl_3/CD_3OD$) 30.38 (s); *m/z* 65 $[M+H]^+$, 82%).

Ethylphosphinic acid (109), as an oil (2.68 g, 95%), δ_H (100 MHz) 1.0-1.5 (3 H, br m, Me), 1.7-2.0 (2 H, br m, CH_2), 4.4-9.8 (1 H, d, P-H); δ_C (68 MHz) 4.49-4.54 (1 C, d, J_{PC} 3.3 Hz, Me), 21.55-22.71 (1 C, d, J_{PC} 93.6 Hz); δ_P (109 MHz) 39.95 (s); *m/z* 95 $[M+H]^+$, 71%).

1-Propylphosphinic acid (110), as an oil (3.73 g, 81%); δ_H (270 MHz) 1.00-1.08 (3 H, m, Me), 1.40-1.76 (4 H, br m, CH_2), 5.59-8.04 (1 H, P-H); δ_C (75 MHz) 15.29-17.30 (m, C); δ_P (109 MHz) 30.92.

1-Butylphosphinic acid (111), as an oil (2.60 g, 71%), δ_H (100 MHz) 0.8-1.0 (3 H, t, J_{HH} 7.14 Hz), 1.2-2.0 (6 H, br m, CH_2), 4.4-9.8 (1 H, d, J_{PH} 540 Hz, P-H), 12.2 (1 H, br s, P-OH); δ_C (68 MHz) 13.57 (s, Me), 22.67-22.71 (d, J_{PC} 2.2 Hz, P-CH_2-*CH_2*), 23.63 (s, Me-*CH_2*), 28.01-29.39 (d, J_{PC} 93.6 Hz, P-CH_2); δ_P (109 MHz) 37.84.

2-Propylphosphinic acid (112), as an oil (2.49 g; 58%); δ_H (270 MHz CD_3OD) 1.12-1.15 and 1.19-1.21 (6 H, d of d, J_{HH} 7.14 J_{PH} 18.13), 3.62-3.66 (m, CH); δ_C (75 MHz CD_3OD), 16.64-16.70 (d, J_{PC} 4.4 Hz, Me), 26.44-28.49 (d, J_{PC} 139.9 Hz, CH); δ_P (109 MHz CD_3OD) 34.74; *m/z* 109 $[M+H]^+$, 8%).

Iodomethylphosphinic acid (140), as an oil (5.63 g, 91%), δ_H (100 MHz CD_3OD) 2.4-2.7 (d); δ_C (75 MHz CD_3OD) 15.62-16.98 (d, J_{PC} 102 Hz); δ_P (109 MHz CD_3OD) 21.55.

N-(1-adamantanammonium) mono-alkylphosphinic acid:-

General procedure.

Ammonium phosphinate (2.5 g, 30.1 mmol) and hexamethyldisilazane (5.1 g, 31.6 mmol) were heated together under a dry nitrogen atmosphere at 100-110 °C for 1.5-2.5 h, until no further ammonia was evolved. The system was cooled to 0 °C and dichloromethane (30 ml) was injected, followed by the

appropriate alkyl iodide (31.6 mmol). The reaction was stirred overnight, filtered and the solvent removed under reduced pressure to yield an oil which was cooled to 0 °C in tetrahydrofuran (10 ml) and a solution of adamantanamine (4.8 g, 31.6 mmol) in tetrahydrofuran (45 ml)/methanol (15 ml) was added with stirring. The reaction was stirred overnight, filtered and the crystalline product washed with diethylether (2 x 20 ml) and dried over phosphorus penoxide at 40 °C and >0.1 mmHg overnight. A second crop of product was obtained by condensing the tetrahydrofuran/methanol filtrate and dispersing the resulting residue in diethylether (50 ml) aided by sonocation with stirring overnight. The solution was filtered and the product was washed with diethylether (3 x 20 ml) and dried over phosphorus penoxide at 40 °C and >0.1 mmHg overnight to yield the product.

By this procedure the following N-(1-adamantanammonium) mono-alkylphosphinic acids were prepared.

N-(1-adamantanammonium) methylphosphinic acid, as a solid (0.77 g, 11%), from diethylether as a solid, (6.0 g, 86%) which was not analytically pure.

N-(1-adamantanammonium) butylphosphinic acid, as a solid (3.90 g, 48%), from diethylether (3.67 g, 45%) which was not analytically pure.

Di-alkylphosphinic acid synthesis

from ammonium phosphinate:-

General procedure.

Ammonium phosphinate (2.5 g, 30.1 mmol) and hexamethyl-disilazane (5.1 g, 31.6 mmol) were heated together under a dry nitrogen atmosphere at 100-110 °C for 1.5-2.5 h, until no further ammonia was evolved. The system was cooled to 0 °C and dichloromethane (30 ml) was injected, followed by the appropriate alkyl iodide (31.6 mmol). The reaction was stirred overnight, cooled to 0 °C, and hexamethyldisilazane (4.9 g, 30.1 mmol) injected with stirring for 2 h. The appropriate alkyl iodide (or *t*-butyl acrylate for product 118), (30.1 mmol) was injected and stirred overnight at room temperature. The reaction was fitered and the solvents removed under reduced pressure and the resulting residue was taken up in dichloromethane (50 ml), (aided by a minimum of methanol and sonocation) filtered, and the solvents removed under reduced pressure to yield the product which was dried over phosphorus penoxide at 40 °C and <0.1 mmHg overnight.

By this procedure the following di-alkyl-phosphinic acids were prepared.

Dimethylphosphinic acid (11),[18] as oil (1.82 g, 94%) which was Kugelrohr distilled (0.08 mmHg/163-192 °C) to yield a partially crystallised oil which further crystallised on standing. The oily solid was washed with diethyl ether/ethyl acetate (80:20) (2 x 15 ml) to give colourless plates, (1.00 g, 52%), (Found C, 25.50; H, 7.61; N, nil. $C_2H_7O_2P$ requires C, 25.54; H, 7.50; N, nil); δ_H (100 MHz CD_3OD) 1.5-1.7 (6 H, Me).

Diethylphosphinic acid (113), as an oil (2.68 g, 95%), δ_H (100 MHz CD_3OD) 1.0-1.4 (4 H, br m, P-CH_2), 1.6-2.0 (4 H, br m, NC-CH_2); 3.4-10.2 (1 H, d, J_{PH} 680 Hz, P-H).

Di-(1-Propyl)phosphinic acid (114), as an oil which crystallised slowly on standing (3.9 g, 87%), δ_H (100 MHz CD_3OD) 0.9-1.2 (6 H, m, Me), 1.5-1.9 (8 H, br m, CH_2).

Di-(2-Propyl)phosphinic acid (116), as an oil (3.02 g, 67%), this product was impure from NMR spectra.

Di-(1-Butyl)phosphinic acid (115), as an oil which crystallized on standing, (2.60 g, 71%); δ_H (100 MHz CD_3OD) 1.0-1.2 (6 H, m, Me), 1.1-1.9 (8 H, br m, CH_2).

Unsymmetrical di-substituted phosphinic acids.

Butyl(ethyl)phosphinic acid (117) as an oil (3.90 g, 87); (Found: $(M+H)^+$, 151.089. $C_6H_{15}O_2P$ requires *M*, 150.158); δ_H (270 MHz) 0.90-0.95 (3 H, m, *Bu*); 1.12-1.70 (9 H, br m, CH_2 and CH_3 of alkyl chain); 12.45 (s, br, P-OH); δ_C (75 MHz) 5.79-5.85 (d, J_{PC} 4.4 Hz, P-C-*Me*), 13.64 (s, Me of *Bu*) 20-21 (d, P-C); 23.29-24.11 (m, Me-*C*-*C*); δ_P (109 MHz) 58.72; *m/z* 151 $[M+H]^+$, 100%).

(2-(t-butoxycarbonyl)ethyl)ethylphosphinic acid (118) as an oil (5.90 g, 88%) (Found: $(M+H)^+$, 223.1099 $C_9H_{19}O_4P$ requires *M*, 222.221); δ_H (270 MHz) 0.95-1.08 (2 H, br m, P-*C*-C-CO), 1.32 (9 H, s, Me of ester) 1.53-1.59 (2 H, br m, P-CH_2 of ester), 1.77-1.88 (2 H, br m, P-C*H*$_2$-Me), 7.36 (1 H, s, P-OH); δ_P (109 MHz) 35.85; *m/z* 223 $[M+H]^+$, 14%)

Bis(trimethylsilyl) dimethylphosphonium iodide (120):- Ammonium phosphinate (10.0 g, 121 mmol) and hexamethyldisilazane (25.2 ml, 121 mmol) were heated together under a dry nitrogen atmosphere at 100-110 °C for 3 h. The system was cooled to 0 °C and dichloromethane (150 ml) was injected, followed by the methyl iodide (7.5 ml, 121 mmol). The reaction was stirred for 48 h, cooled to 0 °C, and hexamethyldisilazane (25.2 ml, 121 mmol) injected with stirring for 5 h. Methyl iodide (7.9 ml, 127 mmol) was injected and stirred for 48 h at room temperature. The reaction was filtered and the solvents removed under reduced pressure yielding the *phosphonium iodide* as a pale yellow solid (44.1g, 100%); (Found: $(M\text{-}I)^+$ 239.1052. $C_8H_{24}O_2PSi_2$ requires $(M\text{-}I)^+$, 239.424).

This is the first example of silyl stabilisation of a phosphonium iodide, this orbital interaction allowing a the cationic stabilisation is probably the reason this species exists in an isolatable form rather than as a reactive intermediate. However on exposure to air the *phosphonium iodide* quickly oxidises and gives a brown oily solid which was characterised. The main component was *Trimethylsilyl dimethylphosphinate;* (Found: $(M+H)^+$ 167.066. $C_5H_{15}O_2PSi$ requires *M*, 166.233).

REFERENCES

1. J. Emsley and D. Hall, "The Chemistry of Phosphorus", Butterworth, London, 1976, p. 512; a useful tabular summary is shown on p. 514.

2. E. Bayer, K.H. Grugel, K. Hägelt, H.Hayenmaier, S. Jessipow, W.A. König and H. Zähaer, *Helv. Chim. Acta.*, 1972, **55**, 224.

3. Y. Kondo, T. Shomura, Y. Ogawa, T. Suzuki, C.Moriyama, J. Yoshida, S. Inonye and T. Niida, *Science Reports of Meiji Seika Kaisha.*, 1973, **13**, 34.

4. K. Weissermel, H.J. Kleiner, M. Finke and U.H. *Felcht*, *Angew. Chem., Int. Ed. Engl.*, 1981, **20**, 223.

5. H. Seto and T. Hidaka, *J. Am. Chem. Soc.*, 1989, **111**, 8012.

6. L. Maier, *Phosphorus Sulphur*, 1983, **14**, 295.

7. P.A. Bartlett and W.B. Kezer., *J. Am. Chem. Soc.*, 1984, **106**, 4282.

8. W.H. Parsons, A.A. Patchett, H.G. Bull, W.R. Schoen, D. Taub, J. Davidson, P.L. Combs, J.P. Springer, H. Gadebusch, B. Weissberger, M.A. Valiant, T.N. Mellin and R.D. Buschl., *J. Med. Chem.*, 1988, **31**, 1772.

9. E. Petrillo and M.A. Ondetti, *Medicinal Research Reviews*, 1982, **2**, 1, 1.

10. W.R. Kester and B.W. Matthews, *Biochemistry*, 1977, **16**, 2506.

11. EP 0 138 403 A2, EP 0 138 403 A3

12. A.W. Hoffmann, *Chem. Ber.*, 1872, **5**, 104.

13. B.B. Hunt and B.C. Saunders, *J. Chem. Soc.*, 1957, 2413.

14. T.L. Emmick and R.L. Letsinger, *J. Am. Chem. Soc.*, 1968, **90**, 3459.

15. M. Bourneuf, *Bull. Soc. Chim. Fr.*, 1923, **33**, 1808.

16. R.H. Williams and L.A. Hamilton, *J. Am. Chem. Soc.*, 1955, **77**, 3411, 1952, **74**, 5418.

17. G.M. Kosolapoff and R.M. Watson, *J. Am. Chem. Soc.*, 1951, **73**, 4101.

18. P.C. Crofts and G.M. Kosolapoff, *J. Am. Chem. Soc.*, 1953, **75**, 3379.

19. G.M. Kosolapoff and R.F. Struck, *J. Chem. Soc.*, 1959, 3950.

20. K.A. Petrov, N.K. Bliznyuk and T.N. Lysenko, *Zh. Obshch. Khim.*, 1960, **30**, 1964 (*Chem. Abs.*, 1961, **55**, 6362).

21. K.C. Firsch and H. Lyons *J. Am. Chem. Soc.*, 1953, **75**, 4078.

22. G.M. Kosolapoff, *J. Am. Chem. Soc.*, 1950, **72**, 5508; F.F. Blicke and S. Raines, *J. Org. Chem.*, 1964, **29**, 204, K.A. Petrov, N.K. Bliznyuk and V.P. Korotkova, *Zh. Obshch. Khim.*, 1960, **30**, 2995 (*Chem. Abs.*, 1961, **55**, 18561).

23. P.C. Crofts and I.S. Fox, *J. Chem. Soc.*, 1958, 2995.

24. R.S. Edmundson and J.O.L. Wrigley, *Tetrahedron*, 1967, **23**, 283.

25. A. Michaelis, *Liebigs Annalen*, 1903, **326**, 129.

26. A. Michaelis and F. Wegner, *Chem. Ber.*, 1915, **48**, 316.

27. G.M. Kosolapoff, *J. Am. Chem. Soc.*, 1949, **71**, 369.

28. B.E. Smith and A. Burger, *J. Am. Chem. Soc.*, 1953, **75**, 5891.

29. R.A. Baldwin and M.T. Cheng, *J. Org. Chem.*, 1967, **32**, 1572.

30. R.A. Baldwin, M.T. Cheng and D.G. Homer, *J. Org. Chem.*, 1967, **32**, 2176.

31. R.A. Baldwin and C.O. Wilson Jr and R.I. Wagner, *J.*

Org. Chem., 1967, **32**, 217, G.M. Kosolapoff, *J. Am. Chem. Soc.*, 1955, **77**, 6658; G.M. Kosolapoff and R.F. Struck, *J. Chem. Soc.*, 1957, 3739.

32. W. Kuchen, K. Strolenberg and H. Buchwald, *Chem. Ber.*, 1962, **95**, 1703.

33. L. Maier, *Chem. Ber.*, 1961, **94**, 3051.

34. R. Schmutzler, Inorg. Chem. 1964, **3**, 421.

35. G.M. Kosolapoff and R.M. Watson, *J. Am. Chem. Soc.*, 1951, **73**, 5466, H. Reinharde, D. Bianchi and D. Mölle, *Chem. Ber.*,1957, **90**, 1656.

36. K.A. Petrov, E.E. Nifant'ev and L.V. Khorkhoyanu, *Zh. Obshch. Khim.*, 1961, **31**, 2899 (*Chem. Abs.*, 1962, **57**, 860).

37. K.A. Petrov, E.E. Nifant'ev and R.G. Gol'tsova, *Zh. Obshch. Khim.*, 1962, **32**, 3716 (*Chem. Abs.*, 1963, **58**, 12596).

38. K.D. Berlin, T.H. Austin and K.L. Stone, *J. Am. Chem. Soc.*, 1964, **86**, 1787, C. Stuebe, W.M. LeSuer and G.R. Norman, *J. Am. Chem. Soc.*, 1955, **77**, 3526.

39. A. Michaelis and F. Graeff, *Chem. Ber.*, 1875, **8**, 1304.

40. L.R. Ocone and C.W. Schaumann, *Inorg. Synth.*, 1966, **8**, 71.

41. A. Michaelis, *Chem. Ber.*, 1877, **10**, 627.

42. G.O. Doak and L.D. Freeman, *J. Org. Chem.*, 1964, **29**, 2382.

43. P.C. Crofts and D.M. Parker *J. Chem. Soc. (C).*, 1970, 2529; G.T. Morgan and W.R. Moore, *J. Chem. Soc.*, 1910, **97**, 1697.

44. F.M. Kharrasova and G. Kamai, *Zh. Obshch. Khim.*, 1964, **34**, 2195 (*Chem. Abs.*, 1964, **61**, 10705); G. Kamai, F.M. Kharrasova, G.I. Rakhimova and R.B. Sultanova, *Zh.*

Obshch. Khim., 1969, **39**, 625 (*Chem. Abs.*, 1969, **71**, 50104).

45. V.S. Abramov and N.I. Dyakonova, *Zh. Obshch. Khim.*, 1968, **38**, 1502 (*Chem. Abs.*, 1968, **69**, 106805).

46. G.O. Doak and L.D. Freeman, *J. Am. Chem. Soc.*, 1951, **73**, 5658.

47. G.O. Doak and L.D. Freeman, *J. Am. Chem. Soc.*, 1952, **74**, 753; *J. Org. Chem.*, 1959, **24**, 638; L.D. Freeman, H. Tauber, G.O. Doak and H.J. Magnuson, *J. Am. Chem. Soc.*, 1953, **75**, 1379.

48. G.O. Doak and L.D. Freeman, *J. Am. Chem. Soc.*, 1952, **74**, 2884.

49. R.C. Hinton,F.G. Mann and D. Todd, *J. Chem. Soc.*, 1961, 5454.

50. K.B. Mallion and F.G. Mann, *J. Chem. Soc.*, 1964, 6121.

51. A. Michaelis, *Liebigs Annalen*, 1896, **294**, 1.

52. G.M. Kosolapoff, *J. Am. Chem. Soc.*, 1948, **70**, 3465.

53. A.N. Pudovik and B.A. Arbuzov, *Zh. Obshch. Khim.*, 1951, **21**, 382.

54. V.S. Abramov, *Dokl. Akad. Nauk. SSSR.*, 1954, **95**, 991.

55. Y.A. Stepikheev, L.V. Kovalenko, A.V. Batalina and A.I. Livshits, *Zh. Obshch. Khim.*, 1976, **46**, 2364.

56. V.S. Abramov and V.I. Barabanov, *Zh. Obshch. Khim.*, 1966, **36**, 3056 (*Chem. Abs.*, 1967, **66**, 55554); V.S. Abramov and M.I. Kashirskii, *Zh. Obshch. Khim.*, 1958, **28**, 1830 (*Chem. Abs.*, 1959, **53**, 10091); V.S. Abramov and V.K. Khairullin, *Zh. Obshch. Khim.*, 1957, **27**, 2387 (*Chem. Abs.*, 1958, **52**, 7125).

57. E.K. Baylis, C.D. Campbell and J.G. Dingwall, *J. Chem. Soc., Perkin Trans. 1.*, 1984, 2845.

58. C. Marie, *Ann. Chim. Phys.*, 1904, **3**, 335.

59. A.N. Pudovik, I.V. Gur'yanova and G.V. Romonov, *Zh. Obshch. Khim.*, 1969, **39**, 2418.

60. L. Maier, *Helv. Chim. Acta.*, 1969, **50**, 827.

61. A.N. Pudoik and O.S. Durova, *Zh. Obshch. Khim.*, 1966, **36**, 1460 (*Chem. Abs.*, 1967, **66**, 11009).

62. V.S. Abramov and V.I. Barabanov, *Zh. Obshch. Khim.*, 1966, **36**, 1830 (*Chem. Abs.*, 1967, **66**, 55554).

63. A.N. Pudovik, L.V. Spirina, M.A. Pudovik, Y.M. Kargin and L.S. Andeeva, *Zh. Obshch. Khim.*, 1969, **39**, 1715 (*Chem. Abs.*, 1969, **71**, 124597).

64. A.N. Pudovik and M.A. Pudovik, *Zh. Obshch. Khim.*, 1966, **36**, 1467 (*Chem. Abs.*, 1967, **66**, 11001).

65. L. Maier, *Helv. Chim. Acta.*, 1973, **56**, 489.

66. A.N. Pudovik, R.D. Sabirova and T.A. Tener, *Zh. Obshch. Khim.*, 1954, **24**, 1026 (*Chem. Abs.*, 1955, **49**, 8790).

67. B. Bochwic and J. Michalski, *Roczniki Chem.*, 1952, **26**, 593 (*Chem. Abs.*, 1955, **49**, 2345).

68. A.N. Pudovik and D.Kh. Yarmukhametova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk.*, 1952, 902; 1954, 636 (*Chem. Abs.*, 1953, **47**, 10469; 1955, **49**, 8789).

69. A.N. Pudovik and N.G. Poloznova, *Zh. Obshch. Khim.*, 1955, **25**, 778 (*Chem. Abs.*, 1956, **50**, 2417).

70. A.N. Pudovik and F.N. Sitdikova, *Dolk. Akad. Nauk SSSR.*, 1959, **125**, 826 (*Chem. Abs.*, 1959, **53**, 19850).

71. H. Hasserodt, K. Hunger and F. Korte, *Tetrahedron*, 1964, **20**,1593; 1963, **19**, 1563.

72. L.S. Kovolev, N.A. Razumova and A.A. Petrov, *Zh. Obshch. Khim.*,1968, **38**, 2277 (*Chem. Abs.*, 1969, **71**, 13171). N.A. Razumova and A.A. Petrov, *Zh. Obshch. Khim.*, 1964, **34**, 1886 (*Chem. Abs.*, 1964, **61**, 8336). A.

Kh. Voznesenskaya and N.A. Razumova, *Zh. Obshch. Khim.*,1969, **39**, 387 (*Chem. Abs.*, 1969, **70**, 115231).

73. N.A. Razumova, Zh.L. Evtikhov, A. Kh. Voznesenskaya and A.A. Petrov, *Zh. Obshch. Khim.*, 1969, **39**, 176 (*Chem. Abs.*, 1969, **70**, 106608).

74. J.B. Conant, A.H. Bump and H.S. Holt, *J. Am. Chem. Soc.*, 1921, **43**, 1677; 1921, **43**, 1665.

75. L.R. Drake and C.S. Marvel, *J. Org. Chem.*, 1937, **2**, 387.

76. V.K. Khairullin, V.N. Eliseenkov and A.N. Pudovik, *Zh. Obshch. Khim.*, 1967, **37**, 871 (*Chem. Abs.*, 1968, **68**, 105302); V.K. Khairullin, R. Kondrat'eva and R.M. Pudovik, *Zh. Obshch. Khim.*, 1968, **38**, 288 (Chem. Abs., 1968, **69**, 106816).

77. L. Horner, H. Hoffman and H.G. Wippel, *Chem. Ber.*, 1958, **91**, 64.

78. L.P. Zhuravleva, M.I. Zola, M.G. Suleimanova and A.V. Kirsanov, *Zh. Obshch. Khim.*, 1968, **38**, 342 (*Chem. Abs.*, 1969, **69**, 27484).

79. B.R. Ezzel and L.D. Freedman, *J. Org. Chem.*, 1964, **34**, 1317.

80. L. Horner, P. Beck and V.G. Toscano, *Chem. Ber.*, 1961, **94**, 1317.

81. D.F. Peppard, G.W. Mason and S. Lewey, *J. Inorg. Nucl. Chem.*, 1965, **27**, 2065.

82. D.F. Peppard, G.W. Mason and S. Lewey, *J. Inorg. Nucl. Chem.*, 1965, **27**, 697.

83. È.E. Nifant'ev and M.P. Koroteev *Zh. Obshch. Khim.*, 1966, **37**, 1366.

84. A.N. Pudovik and I.V. Konovalova, *Zh. Obshch. Khim.*, 1960, **30**, 2348 (*Chem. Abs.*, 1961, **55**, 61493).

85. A.N. Pudovik, I.V. Konovalova and O.S. Durova, *Zh. Obshch. Khim.*, 1961, **31**, 2656 (*Chem. Abs.*, 1962, **56**, 12925).

86. A.N. Pudovik and O.S. Shulyndina, *Zh. Obshch. Khim.*, 1969, **39**, 1014 (*Chem. Abs.*, 1969, **71**, 61493).

87. A. Michaelis and R. Kaehne, *Chem. Ber.*, 1898, **31**, 1048.

88. A.E. Arbuzov, *Russ. J. Phys. Chem. (Engl. Transl.)*, 1906, **38**, 687.

89. R.G. Harvey and E.R. de Sombre, "Topics in Phosphorus Chemistry", John Wiley and Sons, New York, 1964, **1**, 57, M. Grayson and E.J. Griffith (eds.).

90. E. Steininger, *Chem. Ber.*, 1963, **96**, 3184.

91. A.W. Frank, *J. Org. Chem.*, 1966, **31**, 1917; E. Cherbulitz, A. Buchs, S. Jaccard, D. Janjic and J. Rabinowitz, *Helv. Chim. Acta.*, 1966, **49**, 2395.

92. B.A. Arbuzov and D.Kh. Yarmukhametova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk.*, 1960, 1767 (*Chem. Abs.*, 1961, **55**, 15507).

93. A.E. Arbuzov and A.I. Razumov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk.*, 1945, 167 (*Chem. Abs.*, 1946, **40**, 3411).

94. H. Gross, G. Engelhardt, J. Freiberg, W. Bürger and B. Costisella, *Liebigs Ann. Chem.*, 1967, *707*, 35.

95. A.E. Arbuzov and B.A. Arbuzov, *Russ. J. Phys. Chem. (Engl. Transl.).*, 1929, **61**, 1599 (*Chem. Abs.*, 1930, **24**, 5289).

96. H.G. Henning and G. Hilgetag, *J. Prakt. Chem.*, 1965, **29**, 86.

97. B.A. Arbuzov and N.I. Rizpolozhenskii, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk.*, 1952, 854 (*Chem. Abs.*, 1953,

47, 9903).

98. J.R. Falbe, R. Paatz and F. Korte, **Chem. Ber.**, 1964, **97**, 2544.

99. M.I. Iliopulus, *Chem. Ber.*, 1966, **99**, 2410; A.I. Razumov and M.B. Gazizov, *Zh. Obshch. Khim.*, 1967, **37**, 3738 (*Chem. Abs.*, 1968, **69**, 19263).

100. G. Aksnes and K. Bergesen, *Acta Chem. Scand.*, 1966, **20**, 2508; B. Helferich and E. Aufderhaar, *Liebigs Ann. Chem.*, 1962, **658**, 100.

101. H.G. Hennings, *J. Prakt. Chem.*, 1965, **29**, 93.

102. P. Mastalerz, *Rocz. Chem.*, 1959, **33**, 985; G.H. Dahl and B.P. Block, *Inorg. Chem.*, 1966, **5**, 1394.

103. D.M. Coyne, W.E. McEwen and C.A. Vanderwerf, *J. Am. Chem. Soc.*, 1956, **78**, 3061.

104. A.A. Neimysheva, V.I. Sauchuk and I.L. Knunyants, *Zh. Obshch. Khim.*, 1966, **36**, 500 (*Chem. Abs.*, 1966, **65**, 2103).

105. W.G. Bentrude and E.R. White, *J. Am. Chem. Soc.*, 1963, **85**, 2522.

106. M.G. Voronkov, L.Z. Marmur, O.N. Dolgov, V.A. Pestunovich, E.I. Pokrovskii and Yu.I. Popel, *J. Gen. Chem. USSR. (Engl. Tranl.)*, 1971, **41**, 2005.

107. A.N. Pudovik and V.K. Krapnov, *Zh. Obshch. Khim.*, 1968, **38**, 1287 (*Chem. Abs.*, 1968, **69**, 77340).

108. A.E. Arbuzov, *Zh. Obshch. Khim.*, 1934, **4**, 898 (*Chem. Abs.*, 1935, **29**, 2146).

109. C. Wasielewski and K. Antczak, *Synthesis*, 1981, 540; E. Gruszecka, P. Mustalerz and M. Soroka, *Rocz. Chem.*, 1975, **49**, 2127.

110. L. Maier and P.J. Lea, *Phosphorus Sulfur*, 1983, **17**, 1.

111. A.F. Rosenthal and S.V. Chodsky, *J. Lipid Res.*, 1971,

12, 277; A.F. Rosenthal, L.Vargas and C.H. Han, *Biochim. Biophys. Acta.*, 1972, **260**, 369.

112. M.C. Moschichs, *Chem. Phys. Lipids.*, 1985, **36**, 343.

113. K. Seo and S. Inokawa, *Bull. Chem. Soc. Jpn.*, 1973, **46**, 3301; S. Inokawa, Y. Tsuchiya, K. Seo, H. Yishida and T. Ogata, *Bull. Chem. Soc. Jpn.*, 1971, **44**, 2279.

114. K. Seo and S. Inokawa, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 1237.

115. T.H. Chan and B.S. Ong, *J. Org. Chem.*, 1974, **39**, 1748.

116. M.M. Campbell and N. Carruthers, *J. C. S. Chem. Comm.*, 1980, 730.

117. A.F. Rosenthal, A. Grinrauz and L.A. Vargas, *J. C. S. Chem. Comm.*, 1976, 384.

118. J.K. Thottathil, D.E. Ryono, C.A. Przybyla and J.L. Moniot and R. Neubeck, *Tettrahedron Lett.*, 1984, **25**, 4741.

119. J.K. Thottathil, C.A. Przybyla and J.L. Moniot, *Tettrahedron Lett.*, 1984, **25**, 4737.

120. M.J. Gallagher and J. Sussman, *Phosphorus*, 1975, **5**, 91.

121. A. Michaelis and T. Becker, *Chem. Ber.*, 1897, **30**, 1003.

122. B.A. Arbuzov, N.I. Rizpolozhenskii, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk.*, 1954, 631 (*Chem. Abs.*, 1955, **49**, 11541).

123. E.N. Tsvetkov, R.A. Malevannaya and M.I. Kabacknik *Zh. Obshch. Khim.*, 1967, **37**, 695 (*Chem. Abs.*, 1967, **67**, 21971); D.J. Cram, R.D. Trepku and P.St. Janiek,*J. Am. Chem. Soc.*, 1966, **88**, 2749; V.S. Abramov, L.A. Tarasov and F.G. Farykhova, *Zh. Obshch. Khim.*, 1968, **38**, 1794 (*Chem. Abs.*, 1969, **70**, 4224).

124. G.M. Kosolapoff, *J. Am. Chem. Soc.*, 1950, **72**, 4292.

125. M.G. Voronkov, L.Z. Marmur, O.N. Dolgov, V.A. Pestunovich, E.I. Pokrovskii and Y.I. Popel, *Zh. Obshch. Khim.*, 1971, **41**, 1987.

126. A.N. Pudovik, I.V. Konovalova, G.V. Romanov, R.Y. Nazmutdinor, *Phosphorus*, 1975, **5**, 2, 105.

127. T. Hata, H. Mori and M. Sekine, *Chemistry Letters*, 1977, **12**, 1431.

128. P. Majewski, *Synthesis*, 1987, 557.

129. D. Grobelny, *Synthesis*, 1987, 942.

130. K. Issleib, W. Mögelin and A. Balszuweit, *Z. Anorg. Allg. Chem.*, 1985, **16**, 530.

131. M.E. Jung, C.A. McCombs, Y. Takeda and Y-G. Pan, *J. Am. Chem. Soc.*, 1981, **103**, 6677.

132. S. Danishefsky, T. Kitahara, C.F. Yan and J. Morris, *J. Am. Chem. Soc.*, 1974, **96**, 7807; 1979, **101**, 6996.

133. A. Vogel, "Textbook of Practical Organic Chemistry", Longman, London, 4th Edt., 816.

134. G. Dienys and J. Steponavicius, *Zh. Obshch. Khim.*, 1968, **38**, 1391 (*Chem. Abs.*, 1968, **69**, 86551).

135. J-L. Gras, *Tettrahedron Lett.*, 1978, **24**, 2111; **32**, 2955.

136. W.H. Kruizinga and R.M. Kellogg, *J. Am. Chem. Soc.*, 1981, **103**, 5183.

137. D. Beke and C. Szántay, *Chem. Ber.*, 1962, **95**, 2132.

138. S. Wang, B.F. Gisin, D.P. Winter, R. Makofske, J.D. Kulesha, C. Tsougraki and J. Meienhofer, *J. Org. Chem.*, 1977, **42**, 8, 1288.

139. A.Vogel, "Textbook of Practical Organic Chemistry", Longman, London, 4th Edt., 291, method 2.

140. D.A. Evans, K.M. Hurst and J.M. Takais, *J. Am. Chem.*

Soc., 1978, **100**, 3467.

141. W.C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.

142. D.S. Karanewsky and M.C. Badia, *Tettrahedron Lett.*, 1986, **27**, 1751.

143. M.C. Venuti, *Annu. Rep. Med. Chem.*, 1985, **20**, 71 and 193, and references cited therin.

144. G.F. Hennion and F.P. Kupiecki, *J. Org. Chem.*, 1953, **18**, 1601.

145. B.M. Goldstein, C.A. Kohler and A.Wissner , *J. Med. Chem.*, 1985, **28**, 1365.

146. R. Levine, M.J. Karten and W.M. Kadunce, *J. Org. Chem.*, 1975, **40**, 1770; M.J. Jorgenson, *Org. React.*, 1970, **18**, 52.

147. B. Wakefield, "Organolithium Methods", Academic Press, London, 1988, p. 46.

148. W. Kofron and L.M. Baclawski, *J. Org. Chem.*, 1976, **41**, 1879.

149. Y. Jasor, M-J. Luche, M.Gaudry, A. Marquet, *J. Chem. Soc., Chem. Commun.*, 1974, 253; *Org. Synth.*, **59**, 155.

150. D.B. Trowbridge, D.M. Yamamoto and L.Kenyon, *J. Am. Chem. Soc.*, 1972, **94**, 3816.

151. A.D. Sherry, C.R. Malloy, F.M.H. Jeffrey, W.P. Cacheris and C.F.G.C. Geraldes, *Journal of Magnetic Resonance*, 1988, **76**, 528, and references cited therin.

152. N.A. Matwiyoff, C. Gasparovic, R. Wenk, J.D. Wickes and A. Rath, *Magnetic Resonance Methods*, 1986, **3**, 164.

153. D.V. Bowen, personal communication.

154. P. Majewski, *Synthesis*, 1987, 555.

155. "Advances in Cyclic Nucleotide Research", ed. P. Greengard, R. Paeoletti and G.A. Robinson, Raven

Press, New york, 1972, Vol 2 and 3.

156. R.C. Miller, J.S. Bradley and L.A. Hamilton, *J. Am. Chem. Soc.*, 1956, **78**, 5299.

157. E.A. Letts and R.F. Blake, *Trans. Roy. Soc. Edinburgh.*, 1889, **35**, 527.

158. H.O. House, W.L.Repass and G.M. Whiteside, *J. Org. Chem.*, 1966, **31**, 3128.

159. S.R. Palit, *J. Am. Chem. Soc.*, 1947, **69**, 3120.

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A VERSATILE ROUTE TO SUBSTITUTED PHOSPHINIC ACIDS

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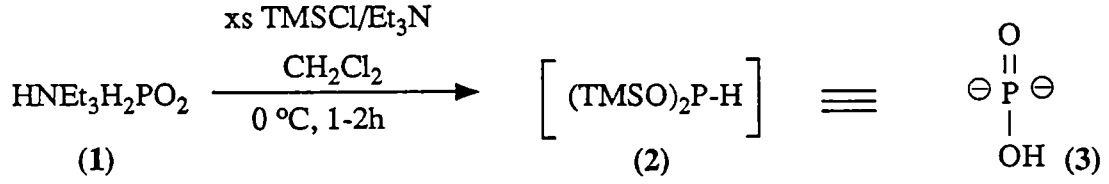
Abstract: *Mono-substituted phosphinic acids, symmetrical and unsymmetrical disubstituted phosphinic acids have been conveniently synthesized by 1,4 addition to α,β-unsaturated esters of bis(trimethylsilyl)phosphonite generated in situ, under very mild conditions.*

Phosphinic acids are of growing importance in understanding and modulating biological processes.[1] For example, they constitute stable mimics of the tetrahedral transition states involved in amide bond formation[1d] or hydrolysis, and can thus function as transition state analogue enzyme inhibitors. Novel routes to substituted phosphinic acids are therefore of considerable interest.[2]

Classical methods for phosphinic acid synthesis utilizing the Arbuzov reaction,[3] involving dialkyl phosphonites and an appropriate alkylating agent, often involve harsh reaction conditions. Recently a mild procedure has appeared for the conversion of mono-substituted phosphinic acids to disubstituted phosphinic acids, *via* addition of an intermediate silyl phosphonite to activated conjugated systems.[4]

We wish to report a synthesis of both symmetrical and unsymmetrical substituted phosphinic acids involving sequential 1,4 addition of bis(trimethylsilyl)phosphonite[5] to α,β-unsaturated esters. Bis(trimethylsilyl)phosphonite (**2**), which was easily prepared *in situ* from triethylammonium phosphinate (**1**), constitutes an equivalent to the synthon (**3**). Preparation, isolation and use of bis(trimethylsilyl)phosphonite[5,6] was found to be undesirable due to the extreme pyrophoric nature of (**2**), and so *in situ* generation[7] was used as shown in Scheme 1, and found to be much more convenient.

Scheme 1.



For the synthesis of symmetrical disubstituted phosphinic acids (**4**) the appropriate acrylate was added to a solution of bis(trimethylsilyl)phosphonite (**2**) prepared *in situ* from (**1**) using an excess of chlorotrimethylsilane (TMSCl)/triethylamine[8] solution in dichloromethane at 0 °C, and stirred overnight at room temperature, followed by simple acidic work-up. The results for symmetrical bis-addition are shown in Table 1, and the reaction in Scheme 2.

Synthesis of mono-substituted phosphinic acids was achieved by starting with a five-equivalent excess of (**2**) over the acrylate. The large excess of bis(trimethylsilyl)phosphonite had only a limited

Scheme 2.

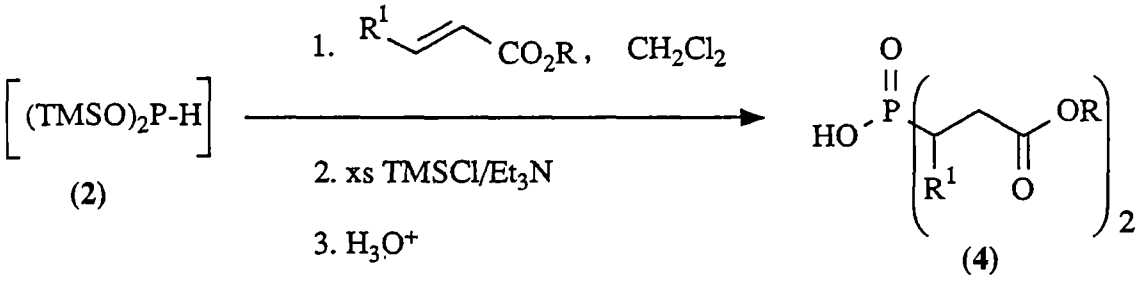
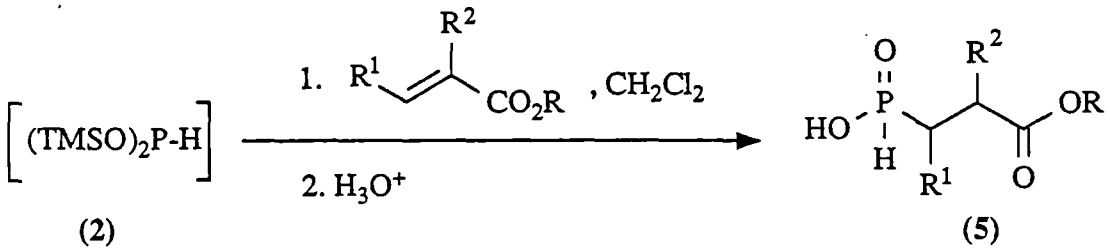


Table 1

Acrylate	R	R^1	Yield[9] (%)
MeO_2C	Me	H	90
EtO_2C	Et	H	82
t-BuO_2C	t-Bu	H	78
EtO_2C	Et	Et	77

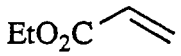
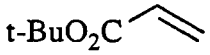
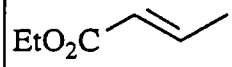
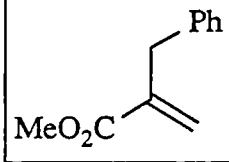
amount of acrylate with which to react, hence no contamination with disubstituted phosphinic acid resulting from a second addition to acrylate was observed. Simple acidic work-up resulted in mono-substituted phosphinic acids (**5**) as viscous, colourless oils. The reaction is shown in Scheme 3, and examples in Table 2.

Scheme 3.



Synthesis of unsymmetrical disubstituted phosphinic acids was achieved by taking a previously synthesized mono-substituted phosphinic acid (**5**), and subjecting it to the silylating conditions ($TMSCl/NEt_3$)[8] to form the probable intermediate (**6**), followed by addition of the chosen acrylate and acidic work-up, to give the appropriate disubstituted phosphinic acid (**7**) (Scheme 4). Examples are shown in Table 3.

Table 2

Acrylate	R	R^1	R^2	Yield[9] (%)
	Et	H	H	85
	t-Bu	H	H	78
	Et	Me	H	74
	Me	H	Bn	81

Scheme 4.

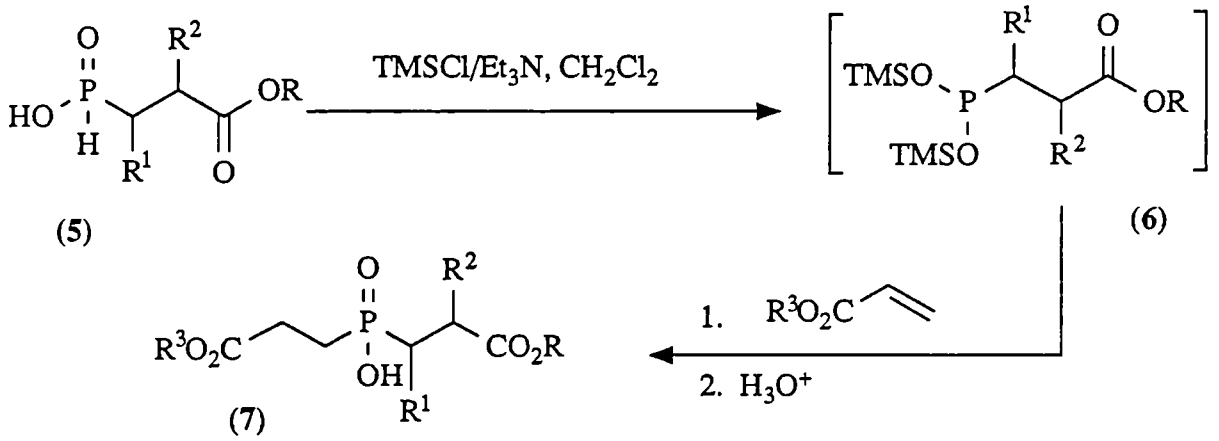
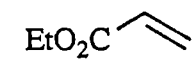
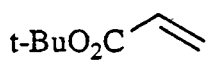
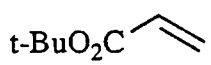


Table 3

Mono-substituted Phosphinic acid (**5**)			acrylate	Disubstituted Phosphinic acid (**7**)	yield[9] (%)
R	R^1	R^2		R^3	
t-Bu	H	H		Et	75
Me	H	Bn		t-Bu	63
Et	Me	H		t-Bu	77

Typical Experimental Procedure.[9,10]

1. Symmetrical disubstituted phosphinic acids (**4**).
To a stirred solution of (**1**) (1.0 g, 5.99 mmol) in dry CH_2Cl_2 (30 ml) at 0 °C, was added a 1:1 mixture of chlorotrimethylsilane and triethylamine ($TMSCl/Et_3N$)[8] (6.0 ml, 18 mmol, 3.5 eq. of each), at less than 5 °C. After 1-2 h the acrylate (2.2 eq.) was added at 0 °C, stirred for 0.5 h, allowed to warm to room temperature and stirred overnight. The reaction was filtered, dilute hydrochloric acid added, and extracted with CH_2Cl_2 to give the crystalline disubstituted phosphinic acid (**4**) which was purified by trituration with hexane/ether.

2. Mono-substituted phosphinic acids (**5**).
To a stirred solution of (**1**) (5.0 g, 29.9 mmol, 5 eq.) in dry CH_2Cl_2 (100 ml) at 0 °C, was added a 1:1 mixture of chlorotrimethylsilane and triethylamine (20 ml, 12 eq.). The acrylate (1.0 eq.) was added at 0 °C, stirred for 0.5 h, then allowed to warm to room temperature overnight. The reaction was filtered and dilute hydrochloric acid work-up followed by dichloromethane extraction yielded the phosphinic acid (**5**) as an oil.

3. Unsymmetrical disubstituted phosphinic acids (**7**).
To a solution of the appropriate mono-substituted phosphinic acid (**5**) (4.0 mmol, 1 eq.) in dry CH_2Cl_2 (30 ml) was added a 1:1 mixture of chlorotrimethylsilane and triethylamine (7 ml, 4 eq.) at 0 °C. After stirring for 1 h the appropriate acrylate (4.4 mmol, 1.1 eq.) was added, the reaction allowed to warm to room temperature, and stirred overnight. Filtration followed by acidic work-up and dichloromethane extraction yielded the disubstituted phosphinic acid (**7**) which was purified by trituration with hexane/ether.

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REFERENCES AND NOTES.

1. (a) L. Maier, *Phosphorus and Sulfur*, 1983, **14**, 295.
(b) E.W. Petrillo, and M.A. Ondetti, *Med. Res. Rev.*, 1982, **2**, 1.
(c) W.H. Parsons, A.A. Patchett, H.G. Bull, W.R. Schoen, D. Taub, J. Davidson, P.L. Combs, J.P. Springer, H. Gadebusch, B. Weissberger, M.A. Valiant, T.N. Mellin and R.D. Buschl., *J. Med. Chem.* 1988, **31**, 1772.
(d) P.A. Bartlett and W.B. Kezer, *J. Am. Chem. Soc.*, 1984, **106**, 4282.
2. J.K. Thottatil, C.A. Przybyla and J.L. Moniot, *Tetrahedron Lett.*, 1984, **25**, 4737.
3. G.M. Kosolapoff and L. Maier, "Organic Phosphorus Compounds", Wiley-Interscience, New York, 1973, **6**, p 14.
4. J.K. Thottathil, D.E. Ryono, C.A. Przybyla, J.L. Moniot and R. Neubeck, *Tetrahedron Lett.*, 1984, **25**, 4741.
5. M.G. Voronkov, L.Z. Marmur, O.N. Dolgov, V.A. Pestunovich, E.I. Pokrovskii, and Y.I. Popel, *J. Gen. Chem. USSR (Engl. Trans.)*, 1971, **41**, 2005.
6. (a) D. Grobelny, *Synthesis*, 1987, 942.
(b) P. Majewski, *Synthesis*, 1987, 555.
7. T. Hata, H. Mori and M. Sekine, *Chemistry Letters*, 1977, 1431.
8. $TMSCl/Et_3N$, equivalent molar amounts, were mixed under nitrogen and centrifuged to allow removal of the supernatant, leaving behind a (copious) triethylammonium chloride precipitate.
9. Satisfactory IR, NMR (^1H, ^{13}C, and ^{31}P), MS and/or elemental analysis were obtained for all new compounds.
10. All the apparatus was meticulously dry and clean. All reactions were carried out under a dry nitrogen atmosphere.