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DIETHOXYMETHYLPHOSPHONITES AND PHOSPHINATES. INTERMEDIATES FOR THE SYNTHESIS OF α,ß- AND ϑ-AMINOALKYLPHOSPHONOUS ACIDS

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New Building blocks for the synthesis of functional alkyl phosphonous acids are described. Diethoxymethylphosphonites and phosphinates are readily prepared and undergo reactions typical of phosphites and phosphonates. The products are stable to chemical transformations, readily handled and purified, and easily transformed to the phosphonous acids.

The replacement of carboxylic acid function in biologically important molecules by a phosphorus acid continues to attract much interest and provide biologically active molecules[1]. We have recently reported[2] the synthesis and biological activity of a range of α-aminoalkylphosphonous acid analogues of the protein amino acids. During the course of this work we became aware of the limitations of hypophosphorous acid and its esters as synthetic intermediates. This paper reports the use of diethoxymethylphosphonites and phosphinates as versatile intermediates for the synthesis of α,ß and ϑ-aminoalkylphosphonous acids.

Our reported synthesis of α-aminoalkylphosphonous acids was based on the addition of hypophosphorous acid to imines. The use of hypophosphorous acid had several limitations which could not satisfactorily be overcome by the use of the corresponding esters. We reasoned that compounds of the general structure (1) and (2) should serve as ideal building blocks for phosphonous acid synthesis. X would represent a protected form of hydrogen, i.e. a functional group which is stable to chemical transformations, but can be removed at the end of the reaction sequence to liberate the desired phosphonous acid.

Typical carbon-phosphorus bond forming reactions of (1) and (2) would lead to phosphinates (3) which after purification by conventional means would yield the phosphonous acids (4) after a final hydrolytic deprotection step.

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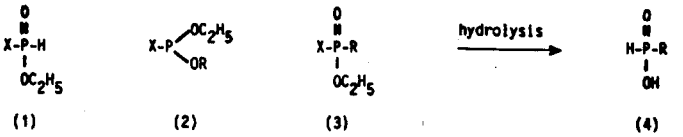
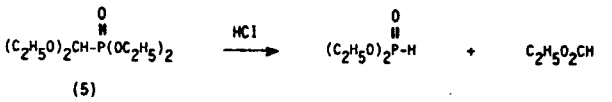


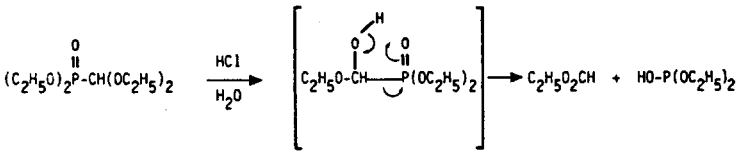
(1) (2) (3) (4)

Of the possible X groups (e.g. CH_3CO-, EtO_2C-) which are known to hydrolyse in the desired sense, we were particularly attracted to the potential of the diethoxymethyl group. Earlier studies[3] had shown that diethoxymethylphosphonates (5) were hydrolysed by acid to give diethylphosphite and ethyl formate.

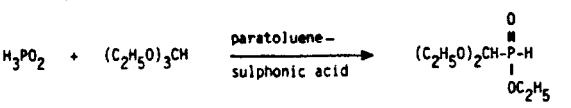


(5)

The following mechanism was proposed for this hydrolysis

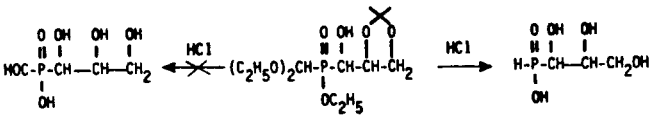


Furthermore, Gallagher[4] in his detailed studies of the reaction of hypophosphorous acid with orthoformates, had reported the preparation of the phosphonite (6) in an acid catalysed reaction.



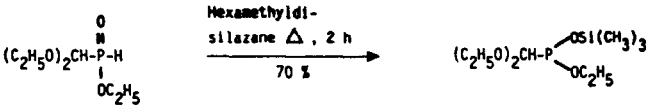
(6)

The same author later[5] reported the use of (6) in an attempted synthesis of a phosphosugar (7). However, the product actually isolated on acid hydrolysis was the phosphonous acid (8).



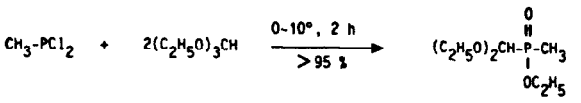
(7) (8)

We have found that phosphonite (6) is an excellent synthon for phosphonous acid synthesis. (6) can be readily deprotonated by bases such as Na, NaH, BuLi, and the anion alkylated with a range of alkylating agents. Acid hydrolysis then generates the substituted phosphonous acids.
Silylation of (6) with hexamethyldisilazane leads to the silyl ester (9)[6] which undergoes reactions typical of P III species, e.g. Arbuzov reactions.



(6) (9)

The ability of a phosphoryl group to stabilize an adjacent carbanion is well known. A reagent (10)[7] which utilizes this property is prepared in quantitative yield by the reaction of methyl dichlorophosphine with two equivalents of triethylorthoformate.

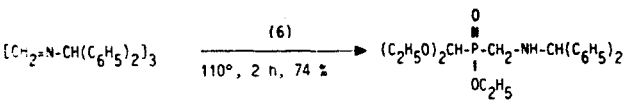


(10)

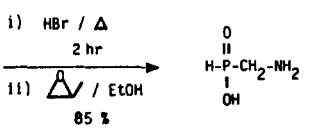
The methyl group in (10) is selectively deprotonated by the use of LDA at low temperatures, and the resulting anion then undergoes reaction with a variety of electrophiles.
The reagents (6), (9) and (10) have been applied to synthesis of several α,β and γ-aminoalkylphosphonous acids.

1. Synthesis of α-aminoalkylphosphonous acids; analogues of glycine, aspartic acid

Our previously reported synthesis of aminomethanephosphonous acid gave an overall yield of only 6%. Aminomethylation of reagent (6) allowed us to adopt one of the most efficient published syntheses of aminomethanephosphonic acid[8].



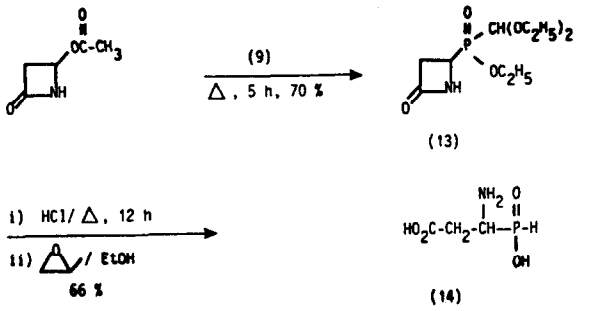
(11)



(12)

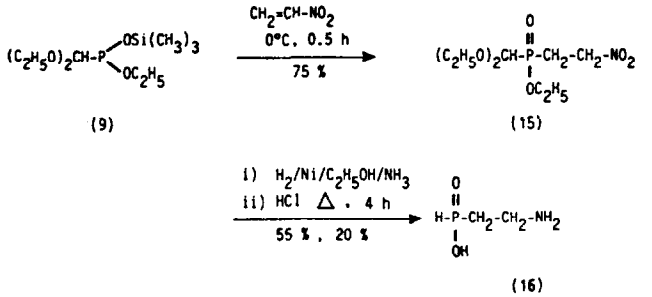
Direct acid hydrolysis of the imine addition product (11) gave the desired glycine analogue in good yield.

Adaptation of a known procedure[9] using (9) gave an efficient two step synthesis of the aspartic acid analogue (14).

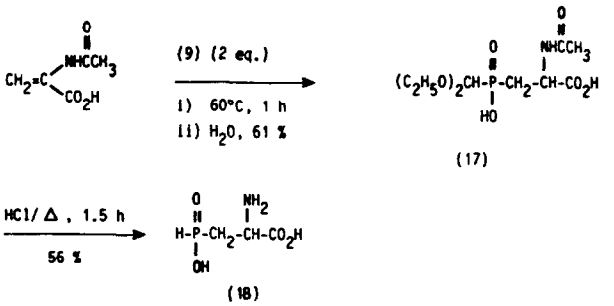


2. Synthesis of ß-aminoalkylphosphonous acid; analogues of ß-alanine, aspartic acid

The phosphonic acid analogue of ß-alanine, ß-aminoethylphosphonic acid (ciliatine) was the first phosphonic acid to be isolated from natural sources[10]. This compound was later found to be present in marine organisms, protozoa and in certain phospholipid extracts from animal tissues. Syntheses of ß-aminoalkylphosphonous acids have not yet been described in the literature. ß-Aminoethylphosphonous acid (16) was readily prepared by addition of (9) to nitroethylene followed by catalytic reduction and hydrolysis.



The aspartic acid analogue (18) could also readily be prepared by the addition of (9) to acetamidoacrylic acid, followed by acid hydrolysis. The second equivalent of (9) is required for silylation of the acrylic acid.



(16) and (18) have recently been isolated[11] from blocked mutants of Streptomyces Hydroscopicus SF-1293, the microorganism which produces the herbicide bialaphos (phosphinothricyl-ala-ala).

3. Synthesis of δ-aminoalkylphosphonous acids

δ-Aminobutyric acid (GABA) is the major inhibitory neutrotransmitter in mammalian central nervous systems. For this reason analogues of GABA have been studied in many laboratories[12]. Apart from one brief patent report[13] δ-aminopropylphosphonous acids have not been described in the literature. The synthesis of a range of δ-aminopropylphosphonous acids[14] using reagents (6), (9) and (10) can be conveniently classified into four main types:

a) Base-catalysed addition of phosphonite (6) to α,β-unsaturated nitriles
b) Alkylation of β-cyanophosphinates
c) Addition of silyl ester (9) to α,β-unsaturated ketones
d) Michael addition of phosphinate (10) to β-nitrostyrenes.

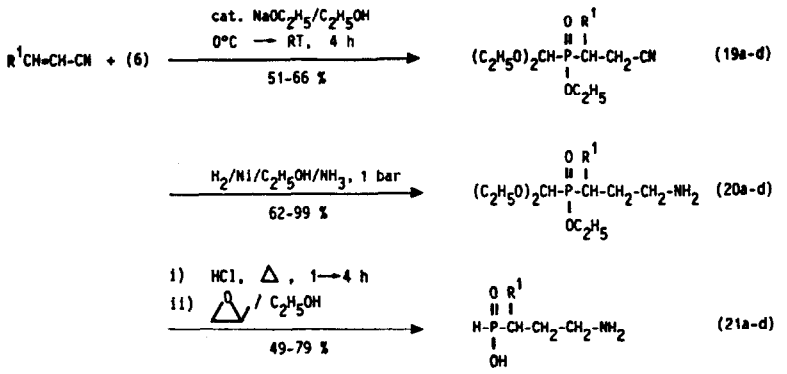
a) Base-catalysed addition of (6) to α,β-unsaturated nitriles (Scheme 1)

The base-catalysed reaction of (6) with α,β-unsaturated nitriles, resulted in a clean addition to give the β-cyanophosphinates (19) which were readily purified by vacuum distillation. Catalytic reduction of these nitriles in the presence of ammonia gave the primary amines (20). The amines (20) could be distilled, however yields were reduced and some decomposition was observed.

Hydrolysis of the primary amines (20) in conc. hydrochloric acid led to complete deprotection of the phosphinate, to give the δ-aminophosphonous acids initially isolated as the hydrochloride salts. Upon treatment with propylene oxide in ethanol the free δ-aminophosphonous acids (21a-d) were obtained. (Table 1).

TABLE I	R^1	Yield % (19)	Bpt	Yield % (20)	Bpt	Yield % (21)	m.p.
a	H	65	114°/0.01 mm	85	150°/0.01 mm	58	209-13
b	CH_3	66	116°/0.01 mm	58	120°/0.01 mm	79	- *
c	C_6H_5	58	170°/0.02 mm	99	-	49	229-34
d	4-ClC_6H_4	51	180-200°/0.01mm	93	90°/0.02 mm	70	210-20

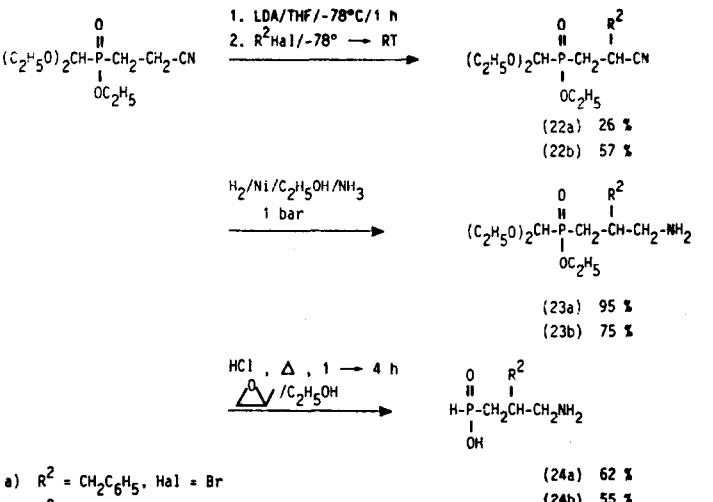
* Product is hygroscopic



Scheme I

b) Alkylation of ß-cyanophosphinates (Scheme II)

The ß-cyanophosphinate (19a, R^1 = H) could be selectively deprotonated with LDA at low temperatures in THF. Formation of the anion is signalled by a characteristic pale-red colouration. Addition of the alkylating agent followed by normal work-up procedures gave the ß-substituted products (22a-b), isolated by chromatography. With benzyl bromide as alkylating agent, some bisalkylated product was also obtained. As in method a) the nitrile function is then catalytically reduced to the primary amine and the phosphinate deprotected by acid hydrolysis to give the 2-substituted ϑ-aminophosphonous acids (24a-b).



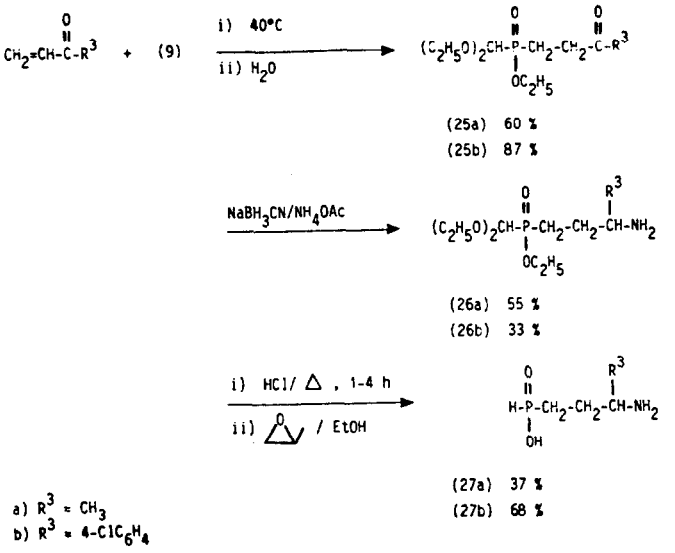
a) $R^2 = CH_2C_6H_5$, Hal = Br

b) $R^2 = CH_3$, Hal = I

Scheme II

c) Reaction of silyl phosphonite (9) with α,β-unsaturated ketones (Scheme III)

To introduce substituents α- to the amino group, the reductive amination route shown in Scheme III was used. Initial attempts to add phosphonite (6) to α,β-unsaturated ketones met with little success, only complicated mixtures resulted. However, by employing the P III ester (9) an extremely clean reaction resulted. The initial products, the silyl enol ethers could either be isolated via distillation or conveniently hydrolysed in situ to give the keto-phosphinates (25a, b). ^{31}P n.m.r. spectroscopy was used to monitor both the nucleophilic addition and the hydrolysis. Reductive amination of the carbonyl group using sodium cyanoborohydride[15] gave the primary amines (26a, b) in fair yield. As in the previous examples, the final products (27a, b) were obtained by acid hydrolysis followed by treatment with propylene oxide.



Scheme III

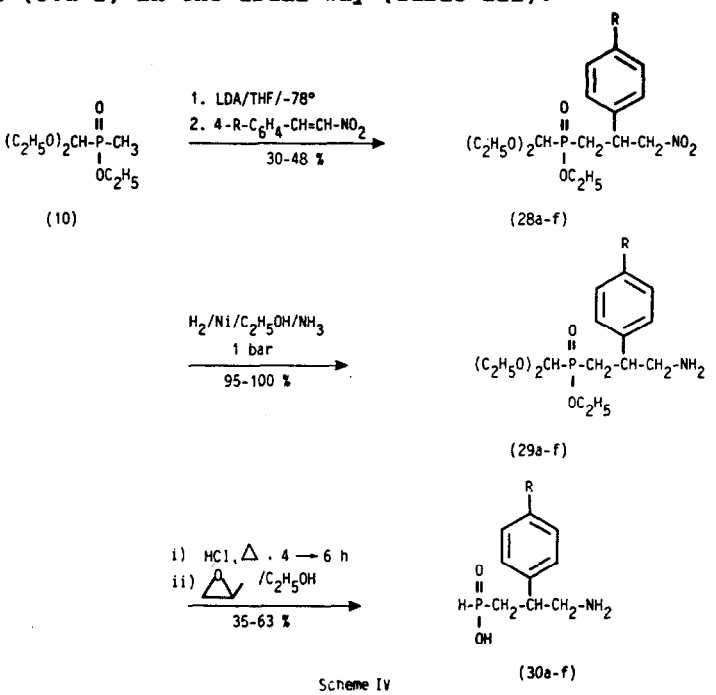
d) Michael reaction of phosphinate (10) with β-nitrostyrenes (Scheme IV)

The introduction of aryl substituents β to the amino group was not easily achieved by method a) or b). We therefore developed an alternative method, whereby a range of functional aryl groups could be introduced in this position.

The anion of (10) was formed over a period of 1 hr. by the action of LDA in THF at low temperature. Addition of 1 equivalent of nitro-styrene in THF resulted in an immediate deep red colouration.

Normal work up gave at best only 50% of product, along with almost 50% starting phosphinate (10). Increasing the amount of nitrostyrene did not improve the yield of product. As we later required large quantities of (30b) for detailed biological investigations we re-examined the reaction of (10) with 4-chloro-β-nitrostyrene and found that inverse addition of the pre-formed anion of (10) to 1.5 equivalents of 4-chloro-β-nitrostyrene at -78° gave a near quantitative yield of the nitrophosphinate (28b).

The products (28a-f) (Table II) were, however, readily purified by chromatography and obtained as mixtures of diastereoisomers. The second step involved a very facile reduction of the nitro group, giving the primary amines (29a-f) in excellent yield. The amines were converted directly to the final products (30a-f) in the usual way (Table III).

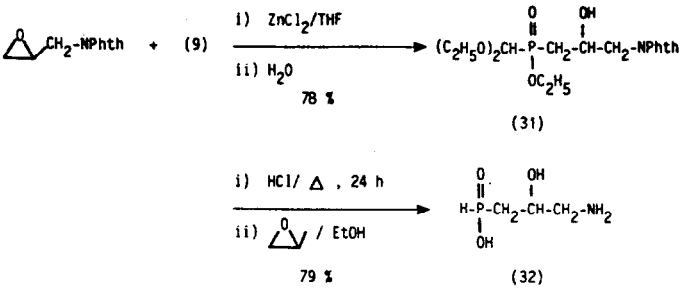


Scheme IV

TABLE II Reaction of phosphinate (10) with β-nitrostyrenes		
Product Number	R	Yield %
28a	H	35
28b	Cl	48
28c	F	35
28d	CH_3	30
28e	OCH_3	30
28f	CF_3	30

TABLE III Hydrolysis of aminophosphinates (29a-f)			
Product Number	R	m.p.	Yield %
30a	H	228-35°	42
30b	Cl	235-40°	63
30c	F	225-35°	60
30d	CH_3	250-55°	61
30e	OCH_3	260-65°	46
30f	CF_3	195-7°	35

An interesting γ-amino acid bearing a hydroxyl group on the β-carbon is γ-amino-β-hydroxybutyric acid (GABOB). This naturally occurring compound is a precursor to the anti-epileptic agent CARNITINE, and itself possesses neuro-activity[16]. The phosphonous acid analogue was prepared in two steps, from the P III silyl ester (9), (Scheme V). Lewis acid catalysed ring opening[17] of 2,3-epoxypropylphthalimide with (9) gave, after aqueous work-up, the β-hydroxyphosphinate (31) in good yield. Simultaneous deprotection of the phosphorus and nitrogen atoms gave the GABOB analogue (32) in 79% yield. Phosphonic and phosphinic acid analogues of GABOB have been previously described[18].



Scheme V

CONCLUSIONS

The diethoxymethylphosphonites and phosphinates described here are easily synthesised intermediates which can be used for the synthesis of a wide range of functional phosphonous acids.

The diethoxymethyl function is stable to base, oxidation and reduction. Intermediates and products containing the diethoxymethyl group are easily handled and purified, and cleaved cleanly under acid conditions. We believe the reagents described here are the reagents of choice for the synthesis of phosphonous acids. Recently reported alternatives, e.g. $EtO_2C\text{-}P(OSiMe_3)_2$[19] and $(Me_3SiO)_2P\text{-}H$[20] suffer the disadvantages of multi-step preparation or difficult handling (spontaneously inflammable).

The biological properties of the γ-aminoalkylphosphonous acids described here will be reported separately.

EXPERIMENTAL

General: Melting points were determined on a Buchi melting point apparatus and are uncorrected. ^{1}H n.m.r. spectra were obtained on either a Varian EM 360A spectrometer operating at 60 MHz or a Jeol FX90 spectrometer operating at 89.55 MHz. Chemical shifts are relative to either TMS or 3-(trimethylsilyl)propionic acid sodium salt references. ^{31}P n.m.r. spectra were obtained on a Jeol FX 90 spectrometer operating at 36.2 MHz with 85% phosphoric acid as external reference. IR spectra were measured on a Perkin-Elmer 457 grating spectrophotometer. Column chromatography was performed on Merck Silica Kieselgel 60 on 70-230 mesh. THF refers to freshly distilled dry tetrahydrofuran; distilled off sodium/benzophenone.

Ethyl trimethylsilyl(diethoxymethyl)phosphonite (9)

Phosphonite (6)[4] (35g. 0.18 mol) was dissolved in hexamethyldisilazane (29.5g ., 0.20 mol) and the mixture heated to reflux under an atmosphere of nitrogen, for a period of 3hr. After cooling to room temperature, excess HMDS was removed under reduced pressure, and the residue distilled to give (9), 33g. (70%) as a liquid b.p. 51°/0.01 mm with an unpleasant odour; ^{31}P = +146.9 ppm ($CDCl_3$); δ ($CDCl_3$) 0.2 (s, 9H); 1.2 (d, t, J = 7Hz, 9H); 3.8 (m, 6H); 4.3 (s, 1H).

Ethyl (diethoxymethyl)methylphosphinate (10)

Triethyl orthoformate (118.0g., 0.8 mol) was placed under nitrogen and cooled to 0°C (internal temperature). Methyl dichlorophosphine[21] (20.8g., 0.18 mol) was added dropwise over a period of 1hr. When the addition was complete, excess ortho ester was removed under reduced pressure to give (10) 35.2g. (93%) as a clear liquid b.p. 75°/0.01 mm ^{31}P = +44.7 ppm ($CDCl_3$); δ ($CDCl_3$) 1.2 (t, J = 16 Hz, 9H); 1.5 (d, J = 15 Hz, 3H); 3.7 (m,. 4H); 4.1 (m, 2H); 4.4 (d, J = 8 Hz, 1H): Found: C 45.71, H 9.09, P 14.02, $C_8H_{19}O_4P$, requires C 45.71, H 9.11, P 14.73.

Ethyl benzhydrylaminomethyl(diethoxymethyl)phosphinate (11)

A mixture of phosphonite (6) (10g. 50.9 mmol) and 1,3,5-tribenzhydryl-hexahydro-s-triazine (9.75g. 16.6 mmol) in toluene (100 ml) was heated to reflux under nitrogen for 2 hr. After cooling to room temperature, the solvent was removed. The residue was dissolved in diethyl ether (100 ml), a small quantity of solid removed by filtration and the solvent evaporated to give (11), 14.7g. (74%) as a viscous oil: ^{31}P = +40.8 ppm ($CDCl_3$); δ ($CDCl_3$) 1.2 (m, 9H); 3.0 (d, J = 12 Hz, 2H); 3.8 (m, 5H); 4.2 (m, 2H); 4.9 (m, 2H); 7.2 (m, 10H).

Aminomethylphosphonous acid (12)

A mixture of phosphinate (11) (11.1g., 28.4 mmol) in 47% aqueous hydrobromic acid (25 ml) was heated to reflux for a period of 2 hr. After cooling to room temperature water (50 ml) was added and the mixture evaporated. This process was repeated, the aqueous then extracted with diethyl ether (25 ml), and the water again evaporated. The crude hydrobromide was dissolved in ethanol (50 ml), propylene oxide added (1 -> 5 ml) and the precipitated product collected by filtration, when free from HBr, to give (12) 2.3g. (85%) as a white solid m.p. 258-60°[2].

Ethyl 4-oxo-azetidin-2-yl(diethoxymethyl) phosphinate (13)

Phosphonite (9) (28.0g. 0.105 mol) was cautiously added to 4-Acetoxy-azetidone[22] (9.6g., 74.4 mmol) under nitrogen and the mixture heated to 100° for 4hr. After cooling the residue was chromatographed using Ethyl Acetate:Isopropyl alcohol 5:1 as eluant. The product was triturated in hexane to give (13) 13.9g. (70%) as a white solid m.p. 57-9°; ^{31}P = +37.4 and +37.0 ppm ($CDCl_3$); δ ($CDCl_3$) 1.2 (m, 9H); 3.2 (m, 2H); 4.5 -> 3.5 (m, 7H); 4.8 (d,d, J = 8 Hz, 1H); 7.3 (broad d, 1H). Found: C 45.36, H 7.44, N 5.18, P 11.88, $C_{16}H_{20}NO_5P$, requires C 45.45, H 7.23, N 5.30, P 11.72.

1-Amino-2-carboxyethylphosphonous acid (14)

Phosphinate (13) (2.7g., 10.2 mmol) was dissolved in 36% aqueous hydrochloric acid (20 ml) and heated to 100°C for a period of 12hr. After cooling and a work up procedure analogous to that described for (12), the title compound (14) was obtained, 1.2g. (77%) as a white solid m.p. 230-1°; ^{31}P = +17.1 ppm (D_2O); δ (D_2O) 3.0 (m, 2H); 3.5 (m, 1H); 4.0 (s, 0.5H); 10.0 (s, 0.5H, JP-H = 555.0 Hz). Found: C 23.68, H 5.28, N 9.09, P 20.41, $C_3H_8NO_4P$, requires C 23.54, H 5.27, N 9.15, P 20.23.

Ethyl 2-nitroethyl(diethoxymethyl)phosphinate (15)

Phosphonite (9) (2.7g., 10.0 mmol) was cooled to 0°C under N_2. Nitroethylene (1.6g., 21.9 mmol) was added cautiously with stirring. After stirring for 30 min., chloroform (50 ml) was added followed by H_2O (20 ml) and the mixture stirred a further 10 mins. The organic layer was separated, dried and evaporated, to give (15) 2.0g. (74%), 31P = +39.7 ppm ($CDCl_3$); δ ($CDCl_3$) 1.3 (m, 9H); 2.6 (m, 2H); 3.8 (m, 4H); 4.2 (q, J = 8Hz, 2H); 4.7 (m, 3H); IR (neat) 3000-2800, 1550, 1480, 1380, 1230 1100-1000, 950 cm^{-1}.

2-Aminoethylphosphonous acid (16)

Phosphinate (15) (2.3g) 8.5 mmol) was dissolved in absolute ethanol (50 ml) and added to a solution of NH_3 in EtOH (8%) containing Raney Nickel (Nicat

Brand 102) (3 mls). This mixture was hydrogenated at 1 bar pressure until uptake of hydrogen ceased. The mixture was filtered, evaporated and the residue passed down a column (SiO_2) eluting first with ethyl acetate and then with 8% NH_3 in EtOH. The product, a brown oil 1.1g. (55%) ^{31}P = +43.0 ppm ($CDCl_3$) was dissolved in concentrated HCl (20 ml) and the mixture refluxed for 4 hr. After evaporation, the residue was co-evaporated with water (3 x 20 ml), washed with ether and the aqueous layer evaporated. The residue was purified by Ion Exchange Chromatography (Dowex 5 OW x 2 200-400 Mesh, BIO-RAD) eluted with water. Ninhydrin positive fractions were combined and evaporated to give (16) O.1g. (20%) as a white solid m.p. 255°C, ^{31}P = +22.3 ppm (D_2O); δ (D_2O) 2.8 (m, 2H); 4.0 (m, 2H); 5.0 (s, 0.5H); 10.7 (s, 0.5H JP-H = 522 Hz). Found: C 22.66, H 7.09, N 12.12, $C_2H_8NO_2P$, requires C 22.02, H 7.39, N 12.84.

2-Acetamido-2-carboxyethyl(diethoxymethyl)phosphinic acid (17)

Phosphonite (9) (11.2g. 41.8 mmol) was added to 2-Acetamidoacrylic acid (2.7g., 20.9 mmol) and the mixture warmed to 60°C with stirring under N_2. After 1 hr. the mixture was heated to 75°C at 0.01 mm to remove phosphonite (6). The residue was dissolved in chloroform (50 ml) washed with water and the aqueous layer stripped to give a gum, which was triturated with ether to give (17) 3.8g. (61%) as a white solid mp. 84-8° 31P = +37.8 ppm (D_2O); δ (D_2O) 1.6 (t, J = 7.2 Hz, 6H); 2.4 (s, 3H); 2.7 (m, 2H); 4.2 (q, J = 8Hz, 4H); 5.0 (m, 2H). Found: C 39.21, H 6.69, N 4.75, $C_{10}H_{20}NO_7P$, requires C 40.41, H 6.78, N 4.71.

2-Amino-2-carboxyethylphosphonous acid (18)

Phosphinate (17) (3.0g. 10 mmol) was dissolved in concentrated HCl (20 ml) and the mixture was heated at 100°C for 1.5 hr. After following the procedure described for (16) the phosphonous acid (18) was obtained 0.75g. (55%) as a hemihydrate m.p. 200°; 31P = +21.9 ppm (D_2O); δ (D_2O) 3.0 (m, 2H); 5.0 (m, 1.5 H); 11.0 (s, 0.5H, JP-H = 524.8Hz). Found: C 22.92, H 5.55, N 8.46, P 18.94, $C_3H_9NO_{4.5}P$, requires C 22.23, H 5.60, N 8.64, P 19.11.

Method A(i) Addition of (6) to α,β-unsaturated nitriles

The following experimental procedure provides details of typical reaction conditions.

Ethyl 2-cyanoethyl(diethoxymethyl)phosphinate (19a)

A solution of phosphonite (6) (130.0g., 0.66 mol) and acrylonitrile (28.1g. 0.53 mol) in absolute ethanol (150 ml) was added dropwise to a cooled (0°C)

solution of sodium hydride (5.6g., 0.14 mol, 60% dispersion in oil) in absolute ethanol (150 ml). After the addition, the reaction mixture was stirred at room temperature for 4 hr. Glacial acetic acid (5 ml) was added and the solvent removed under reduced pressure. The residue was dissolved in ethyl acetate (200 ml), washed with water (50 ml), and the organic phase dried ($MgSO_4$). The solvent was removed and the residue distilled to give the phosphinate (19a) 86.1g. (65%) as a clear liquid b.p. 114°/0.01 mm ^{31}P = +40.8 ppm ($CDCl_3$); δ ($CDCl_3$) 1.3 (m, 9H); 3.2 -> 2.4 (m, 4H); 3.9 (m, 4H); 4.3 (m, 2H); 4.8 (d, J = 8 Hz, 1H). Found: C 47.33, H 8.11, N 5.47, $C_{10}H_{20}NO_4P$, requires C 48.19, H 8.09, N 5.62.

The following compounds were prepared in a similar way:-

Ethyl 2-cyano-1-methylethyl(diethoxymethyl)phosphinate (19b)
From phosphonite (6) (23.5g. 0.12 mol) and crotononitrile (6.7g., 0.1 mol), as a colourless liquid, 17.5g. (66%) b.p. 116°/0.01 mm; ^{31}P = +42.2 and +42.0 ppm ($CDCl_3$); δ ($CDCl_3$) 1.3 (m, 12H); 3.2 -> 2.4 (m, 3H); 3.9 (m, 4H); 4.3 (m, 2H); 4.8 (d,d, J = 8 Hz, 1H).

Ethyl 2-cyano-1-phenylethyl(diethoxymethylphosphinate (19c)
From phosphonite (6) (30.0g., 0.15 mol) and cinnamonitrile (16.5g. 0.13 mol) as a colourless oil, 22.5g. (58%), b.p. 170°/0.02 mm; ^{31}P = +38.4 and 38.3 ppm ($CDCl_3$); δ ($CDCl_3$) 1.3 (m, 9H); 4.2 -> 3.0 (m, 7H); 4.3 (m, 2H); 4.6 (d, J = 8Hz, 1H); 7.4 (s, 5H); Found: C 59.76, H 7.39, N 4.14, P 9.17, $C_{16}H_{24}NO_4P$, requires C 59.07, H 7.44, N 4.31, P 9.52.

Ethyl 1-(4-chlorophenyl)-2-cyanoethyl(diethoxymethyl)phosphinate (19d)
From phosphonite (6) (25.8g. 0.13 mol) and 4-chlorocinnamonitrile (18.0g., 0.11 mol) as a colourless oil, 20.0g. (51%), b.p. 180-200°/0.02 mm (Kugelrohr); ^{31}P = +37.9 and +37.8 ppm ($CDCl_3$); δ ($CDCl_3$) 1.3 (m, 9H); 4.2 -> 3.0 (m, 9H); 4.5 (d,d, J = 8Hz, 12 Hz, 1H); 7.3 (m, 4H). Found: C 53.32, H 6.25, N 4.20, $C_{16}H_{23}ClNO_4P$, requires C 53.41, H 6.44, N 3.89.

(ii) Catalytic reduction of ß-cyanophosphinates (19)
General Procedure: To a solution of ammonia in absolute ethanol ([C] = 8%), a solution of (19) in ethanol was added. To this, Raney Nickel was added and the mixture hydrogenated at a pressure of 1bar until hydrogen uptake ceased. The mixture was filtered, the solvent removed and the residue distilled.

Ethyl 3-aminopropyl(diethoxymethyl)phosphinate (20a)
From phosphinate (19a) (28.0g., 0.11 mol) and Raney Nickel (15.0 ml) in

NH_3/ethanol solution (82.0g.) as a colourless oil, 24.7g. (85%), b.p. 150°/0.01 mm; ^{31}P = +46.4 ppm ($CDCl_3$); δ ($CDCl_3$) 1.2 (m, 15H); 1.7 (m, 2H); 3.7 (m, 4H); 4.2 (m, 2H); 4.6 (d, J = 8Hz, 1H); Found: C 47.37, H 9.54, N 5.45, P 12.17, $C_{10}H_{24}NO_4P$, requires C 47.42, H 9.54, N 5.53, P 12.23.

Ethyl 3-amino-1-methylpropyl(diethoxymethyl)phosphinate (20b)

From phosphinate (19b) (14.6g., 55.5 mmol) and Raney Nickel (9.7 ml) in NH_3/ethanol solution (117.0g.) as a colourless oil, 8.5g. (58%), b.p. 120°/0.01 mm; ^{31}P = +46.4 and +46.7 ppm ($CDCl_3$); δ ($CDCl_3$) 1.2 (m, 16H); 1.8 (m, 1H); 2.6 (m, 2H); 3.6 (m, 4H); 4.1 (m, 2H); 4.6 (d, J = 8 Hz, 1H); Found: C 48.99, H 9.50, N 5.12, $C_{11}H_{26}NO_4P$, requires C 49.42, H 9.80, N 5.24.

Ethyl 3-amino-1-phenylpropyl(diethoxymethyl)phosphinate (20c)

From phosphinate (19c) (22.5g., 69.2 mmol) and Raney Nickel (12.0 ml) in NH_3/ethanol solution (150.0g.) as a colourless oil, 22.5g. (99%). This material was not distilled; ^{31}P = +41.8 ppm ($CDCl_3$) (not resolved); δ ($CDCl_3$) 1.3 (m, 9H); 2.8 -> 2.0 (m, 6H); 4.2 -> 3.2 (m, 7H); 4.5 (d, J = 8 Hz, 1H); 8.4 (broad s, 5H).

Ethyl 3-amino-1-(4-chlorophenyl)propyl(diethoxymethyl)phosphinate (20d)

From phosphinate (19d) (20.0g., 55.6 mmol) and Raney Nickel (8.5 ml) in NH_3/ethanol solution (131.0g.) as a colourless oil, 18.9g. (93%), b.p. 190/0.02 mm; ^{31}P = +41.5 and +41.3 ppm ($CDCl_3$); δ ($CDCl_3$) 1.3 (m, 9H); 2.8 -> 2.0 (m, 6H); 4.2 -> 3.2 (m, 7H); 4.5 (d,d, J = 10 Hz, 12 Hz, 1H); 8.4 (m, 4H).

(iii) Acid hydrolysis of 3-aminophosphinates (20)

General procedure: A solution of (20) in 36% aqueous hydrochloric acid was refluxed under an atmosphere of nitrogen. When the hydrolysis was completed, the mixture was concentrated under reduced pressure and co-evaporated twice with water. The crude hydrochloride salt was dissolved in ethanol, the solution cooled and stirred, and the propylene oxide (1 -> 5 ml) added dropwise. The precipitated product (when free of halogen) was collected by filtration and dried under vacuum.

3-Aminopropylphosphonous acid (21a)

From phosphinate (20a) (5.4g., 21.3 mmol) and 36% aqueous hydrochloric acid (30 ml) as a white powder, 1.5g. (58%) m.p. 209-13°; ^{31}P = +28.2 ppm (D_2O); δ(D_2O) 2.0 (m, 4H); 3.2 (m, 2H); 4.5 (s, 0.5H); 10.2 (s, 0.5H, JP-H = 521.2Hz); Found: C 29.27, H 8.24, N 11.01, P 24.83, $C_3H_{10}NO_2P$, requires C 29.27, H 8.19, N.11.38, P 25.16.

3-Amino-1-methylpropylphosphonous acid (21b)

From phosphinate (20b) (14.1g., 53.2 mmol) and 36% aqueous hydrochloric acid (50 ml) as a hygroscopic solid; ^{31}P = +35.1 ppm (D_2O); δ (D_2O) 0.8 (d,d, J = 20 Hz, 3H); 1.4 (m, 2H); 1.7 (m, 1H); 2.9 (m, 2H); 5.7 (s, 0.5H); 7.5 (s, 0.5H, JP-H = 555.0 Hz); Found: C 34.70, H 9.20, N 9.80, $C_{14}H_{12}NO_2P$, requires C 35.04, H 8.83, N 10.22.

3-Amino-1-phenylpropylphosphonous acid (21c)

From phosphinate (20c) (22.5g., 68.4 mmol) and 36% aqueous hydrochloric acid (75 ml) as a white powder; 6.7g. (49%), m.p. 229-34°; ^{31}P = +35.1 ppm (D_2O) δ 3.2 (m, 2H); 3.8 (m, 3H); 4.8 (s, 0.5H); 8.4 (m, 5H); 10.8 (S, 0.5H, JP-H = 509.0Hz); Found: C 53.86, H 7.09, N 6.77, P 15.41, $C_9H_{14}NO_2P$, requires C 54.27, H 7.09, N 7.03, P 15.55.

3-Amino-1-(4-chlorophenyl)propylphosphonous acid (21d)

From phosphinate (20d) (17.9g., 49.2 mmol) and 36% aqueous hydrochloric acid (200 ml) as a white powder; 7.6g. (70%), m.p. 210-20°; 31P = +29.6 ppm (D_2O); δ(D20) 3.2 (m, 2H); 4.0 (m, 3H); 5.0 (s, 0.5H); 8.4 (m, 4H); 10.8 (s, 0.5H, Jp-H = 522.2Hz); Found C 45.57, H 5.45, N 5.75, P 12.98, $C_9H_{13}ClNO_2P$, requires C 46.27, H 5.61, N 6.00, P 13.26.

METHOD B: Alkylation of Ethyl 2-cyanoethyl(diethoxymethyl)phosphinate

Ethyl 2-cyano-3-phenylpropyl(diethoxymethyl)phosphinate (22a)

n-Butyllithium (30.0 ml, 47.9 mmol, 1.6 M SL_{-}^{n} in Hexane) was added to a solution of diisopropylamine (4.85g., 47.9 mmol) in THF (80 ml) at 0°C under nitrogen, and this was cooled to -78°C. After 10 min, a solution of (19a) (10.0g., 40.1 mmol) in THF (20 ml) was added via a syringe. After stirring for 1 hr. at -78°, a solution of benzyl bromide (7.0g., 40.9 mmol) in THF (10 ml) was introduced. The solution was allowed to warm to room temperature, saturated NH_4Cl solution added (40 ml) , and the product extracted into diethyl ether (200 ml) and dried ($MgSO_4$). Filtration and removal of solvent gave an oil, which on chromatography using ethyl acetate as eluant gave (22a) 3.5g. (26%) as a viscous oil; 31P +40.7 and +40.5 ppm ($CDCl_3$); δ ($CDCl_3$) 1.3 (m, 9H); 2.2 (m, 2H); 3.6 -> 3.0 (m, 3H); 3.8 (m, 4H); 4.2 (m, 2H); 4.7 (d,d, J = 8 Hz, 1H); 7.35 (m, 5H).

Also prepared in a similar way was the following:

Ethyl 2-cyanopropyl(diethoxymethyl)phosphinate (22b)

From phosphinate (19a) (2.0g., 8.0 mmol) and methyl iodide (1.14g ., 8.0 mmol) as a colourless oil, 1.2g. (57%), b.p. 116°/0.02 mm; 31P = +40.4 and 40.3 ppm ($CDCl_3$); δ ($CDCl_3$) 1.4 (m, 12H); 2.3 -> 2.0 (m, 2H); 3.2 (m, 1H); 3.8 (m, 4H); 4.2 (m, 2H) 4.7 (d,d, J = 8 Hz, 1H).

Ethyl 3-amino-2-benzylpropyl(diethoxymethyl)phosphinate (23a)

From phosphinate (22a) (3.5g., 10.3 mmol) analogous to the synthesis of (20a) as a colourless oil, 3.25g. (95%) ^{31}P = +46.3 ppm ($CDCl_3$) (not resolved); δ ($CDCl_3$) 1.3 (t, J = 7.2 Hz, 9H); 1.9 (m, 2H); 3.2 -> 2.0 (m, 5H); 4.0 -> 3.5 (m, 6H); 4.2 (m, 2H); 4.6 (d, J = 8 Hz, 1H); 7.3 (m, 5H).

Ethyl 2-(aminomethyl)propyl(diethoxymethyl)phosphinate (23b)

From phosphinate (22b) (17.0g., 65.0 mmol) analogous to the synthesis of (20a) as a colourless oil, 2.8g. (75%) , b.p. 150°/0.01 mm ^{31}P = +45.8 ppm ($CDCl_3$) (not resolved) ; δ ($CDCl_3$) 1.3 (m, 14H); 2.2 -> 1.4 (m, 3H); 2.7 (d, J = 5 Hz, 2H); 3.8 (m, 4H); 4.2 (m, 2H); 4.3 (d, J = 8 Hz, 1H); Found: C 48.20, H 9.80, N 4.97, $C_{11}H_{26}NO_4P$, requires C 49.42, H 9.80, N 5.24.

2-(Aminomethyl)-3-phenylpropylphosphonous acid (24a)

From phosphinate (23a) (3.5g., 10.2 mmol) and 36% aqueous hydrochloric acid (35 ml) analogous to the synthesis of (21a), as a white powder 1.3g., (62%) m.p. 205-12°; ^{31}P = +26.1 ppm (D_2O); δ (D_2O) 2.5 (m, 2H); 4.0 -> 3.0 (m, 5H); 5.0 (s, 0.5H); 8.3 (s, 5H); 11.0 (s, 0.5H, JP-H = 530.1 Hz).

2-(Aminomethyl)propylphosphonous acid (24b)

From phosphinate (23b) (2.9g., 10.8 mmol) and 36% aqueous hydrochloric acid (25 ml) analogous to the synthesis of (21a), as a monohydrate 0.8g., (55%) m.p. 96-100°; ^{31}P = +25.8 ppm (D20). Found: C 31.25, H 8.78, N 8.86, P 19.63, $C_4H_{14}NO_3P$, requires C 30.97, H 9.10, N 9.03, P 19.97.

METHOD C: Addition of (9) to α,β-unsaturated ketones

Ethyl 3-oxobutyl(diethoxymethyl)phosphinate (25a)

Phosphonite (9) (15.0g., 55.9 mmol) was added dropwise to methyl vinyl ketone (3.9g., 55.7 mmol) under nitrogen at room temperature. After the addition was complete, the mixture was warmed to 50°C for a period of 1 hr. The solution was allowed to cool to room temperature, chloroform (25 ml) added, followed by water (10 ml). This mixture was vigourously stirred for 30 min. The organic phase was separated, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was distilled to give (25a) 9.0g. (60%) as a colourless oil, b.p. 130-5°/0.2 mm; ^{31}P = +40.3 ppm ($CDCl_3$); δ ($CDCl_3$) 1.3 (m, 9H); 2.0 (m, 2H); 2.2 (s, 3H); 2.8 (m, 2H); 3.8 (m, 4H); 4.2 (m, 2H); 4.7 (d, J = 8 Hz, 1H).

Also prepared in a similar way was the following:

Ethyl 2-(4-chlorobenzoyl)ethyl(diethoxymethyl)phosphinate (25b)

From phosphonite (9) (17.7g., 66.0 mmol) and 4-chlorophenyl vinyl ketone[23]

(11.7g., 70.2 mmol) as a viscous oil 20.8g. (87%); ^{31}P = +45.5 ppm ($CDCl_3$); δ ($CDCl_3$) 1.3 (m, 9H); 2.2 (m, 2H); 3.3 (m, 2H); 3.8 (m, 4H); 4.2 (q, J = 8Hz, 2H); 4.7 (d, J = 8 Hz, 1Hz); 8.7 (ABq, 4H).

Ethyl 3-aminobutyl(diethoxymethyl)phosphinate (26a)

This compound was prepared according to the method described by Savignac et al[15] from phosphinate (25a) (13.2g., 49.6 mmol) as a colourless oil, 7.3g. (55%), b.p. 150°/0.01 mm; ^{31}P = +46.1 ppm ($CDCl_3$) (not resolved); δ ($CDCl_3$) 1.1 (m, 14H); 2.0 -> 1.5 (m, 5H); 3.8 (m, 4H); 4.2 (m, 2H); 4.6 (d, J = 8 Hz, 1H).

Also prepared in a similar way was the following:

Ethyl 3-amino-3-(4-chlorophenyl)propyl(diethoxymethyl)-phosphinate (26b)

From phosphinate (25b) (6.0g., 16.5 mmol) as a viscous oil 2.0g. (33%) which decomposed on attempted distillation; ^{31}P = +45.9 ppm ($CDCl_3$) (not resolved); δ ($CDCl_3$) 1.2 (m, 9H); 1.8 (m, 6H); 4.2 -> 3.5 (m, 7H); 4.6 (d, J = 8 Hz, 1H); 8.2 (s, 4H).

3-Aminobutylphosphonous acid (27a)

From phosphinate (26a) (9.8g., 36.7 mmol) and 36% aqueous hydrochloric acid (100 ml) analogous to the synthesis of (21a), as a white powder, 1.8g. (37%), m.p. 195-200°; ^{31}P = +28.1 ppm (D_2O); δ (D_2O) 1.8 (d, J = 2 Hz, 3H); 2.6 -> 1.9 (m, 4H); 3.8 (m, 1H) 4.5 (s, 0.5 H); 10.2 (s, 0.5 H, JP-H = 509.9 Hz).

Also prepared in a similar way was the following:

3-Amino-3-(4-chlorophenyl)propylphosphonous acid (27b)

From phosphinate (26b) (10.5g., 28.8 mmol) and 36% aqueous hydrochloric acid (100 ml) as a white powder, 4.4g. (68%), m.p. 284-6°; ^{31}P = +27.2 ppm (D_2O); δ(D_2O) 1.8 (m, 2H); 2.5 (m, 2H), 4.5 (s, 0.5 H); 4.8 (t, J = 3.6 Hz 1H) 7.8 (m, 4H); 10.2 (s, 0.5 H, JP-H = 514.3 Hz); Found: C 45.50, H 5.45, N 5.82, P 12.82, $C_9H_{13}ClNO_2P$, requires C 46.27, H 5.61, N 6.00, P 13.26.

METHOD D: Michael reaction of Phosphinate (10) with ß-nitrostyrenes

The following experimental procedure provides details of typical reaction conditions.

Ethyl 3-nitro-2-phenylpropyl(diethoxymethyl)phosphinate (28a)

n-Butyllithium (35.7 ml, 57.1 mmol, 1.6 MSl^n in Hexane) was added to a solution of diisopropylamine (5.8g., 57.1 mmol) in THF (80 ml) at O°C under nitrogen, and this stirred solution was cooled to -78°C. After 10 min. a solution of (10) (10.0g., 47.6 mmol) in THF (40 ml) was added via a syringe. After stirring 1 hr at -78°, a solution of ß-nitrostyrene (8.5g., 57.1 mmol)

in THF (40 ml) was added. This caused an immediate deep red colouration. The mixture was allowed to warm to room temperature and saturated NH_4Cl solution (40 ml) was introduced. The organic phase was separated and the aqueous portion extracted with diethyl ether (2 x 25 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated to give an oil which was chromatographed with ethyl acetate as eluant to give (28a) 5.9g. (35%) as an oil; ^{31}P = +42.2 and +41.8 ppm ($CDCl_3$); δ ($CDCl_3$) 1.4 (m, 9H); 2.2 (m, 2H); 4.3 -> 3.5 (m, 7H); 4.8 -> 4.4 (m, 2H); 5.0 (d,d, J = 6Hz, 1H); 7.3 (m, 5H). Found: C 53.55, H 7.08, N 3.76, $C_{16}H_{26}NO_6P$, requires C 53.47, H 7.29, N 3.90.

Also prepared in a similar way were the following:

Ethyl 2-(4-chlorophenyl)-3-nitropropyl(diethoxymethyl)phosphinate (28b)

a) From phosphinate (10) (2.0g., 9.52 mmol) and ß-chloro-nitrostyrene (1.75g., 9.52 mmol) as an oil 1.8g., (48%); ^{31}P = +42.2 ppm and +41.8 ppm ($CDCl_3$); δ ($CDCl_3$) 1.3 (m, 9H); 2.2 (m, 2H); 4.3 -> 3.5 (m, 7H); 4.8 -> 4.5 (m, 2H); 5.2 -> 5.0 (m, 1H); 7.3 (m, 4H); Found: C 48.50, H 6.65, N 3.50, P 7.57, $C_{16}H_{25}ClNO_6P$, requires C 48.80, H 6.40, N 3.56, P 7.87.

b) A solution of LDA (9.52 mmol) in THF (40 ml) was prepared as described previously, and cooled to -78°C. After 10 min. a solution of (10) (2.0g., 9.52 mmol) in THF (20 ml) was added via a syringe, and the mixture stirred 1 hr. This mixture was then transferred, via a canular needle to a stirred solution of 4-chloro-ß-nitrostyrene (2.62g. 14.3 mmol) in THF (60 ml), pre-cooled to -78°C. The mixture was allowed to warm to room temperature and saturated NH_4Cl solution (20 ml) was introduced. Normal work-up gave, after evaporation of solvents, a crude product containing excess 4-chloro-ß-nitrostyrene. This was removed by repeated trituration with hexane and filtration to eventually leave (28b) 3.71g. (97%).

Ethyl 2-(4-fluorophenyl)-3-nitropropyl(diethoxymethyl)phosphinate (28c)

From phosphinate (10) (10.0g., 47.6 mmol) and 4-fluoro-ß-nitrostyrene (7.96g., 47.6 mmol) as an oil 6.1g., (35%); ^{31}P = +42.3 ppm and +41.9 ppm ($CDCl_3$); δ ($CDCl_3$) 1.3 (m, 9H); 2.2 (m, 2H); 4.3 -> 3.5 (m, 7H); 4.8 -> 4.5 (m, 2H); 5.2 -> 5.0 (m, 1H); 7.3 (m, 4H); Found: C 51.03, H 6.61, N 3.58, P 7.95, $C_{16}H_{25}FNO_6P$, requires C 50.93, H 6.68, N 3.71, P 8.21.

Ethyl 2-(4-methylphenyl)-3-nitropropyl(diethoxymethyl)phosphinate (28d)

From phosphinate (10) (15.0g., 71.4 mmol) and 4-methyl-ß-nitrostyrene (11.6g., 71.4 mmol) as an oil 7.7g., (30%); ^{31}P = +42.5 and 42.1ppm ($CDCl_3$); δ($CDCl_3$) 1.3 (m, 9H); 2.1 (m, 2H); 2.3 (s, 3H); 4.2 -> 3.4 (m, 7H); 4.7 ->

4.4 (m, 2H); 4.9 (d,d, J = 6 Hz, 1H); 7.1 (s, 4H); Found: C 54.72, H 7.65, N 3.49, P 8.09, $C_{17}H_{28}NO_6P$, requires C 54.68, H 7.56, N 3.75, P 8.30.

Ethyl 2-(4-methoxyphenyl)-3-nitropropyl(diethoxymethyl)phosphinate (28e)
From phosphinate (10) (15.0g., 71.4 mmol) and 4-methoxy-ß-nitrostyrene (12.8g., 71.4 mmol) as an oil 8.4g., (30%); ^{31}P = +42.4 and 42.1ppm ($CDCl_3$); δ($CDCl_3$) 1.3 (m, 9H); 2.1 (m, 2H); 4.2 -> 3.5 (m, 1OH); 4.6 -> 4.3 (m, 2H); 4.9 (d,d, J = 6 Hz, 1H); 7.0 (m, 4H); Found: C 52.32, H 7.11, N 3.44, P 7.64, $C_{17}H_{28}NO_7P$, requires C 52.43, H 7.25, N 3.60, P 7.95.

Ethyl 3-nitro-2-(4-trifluoromethylphenyl)propyl(diethoxymethyl)phosphinate (28f)
From phosphinate (10) (6.7g., 32.0 mmol) and 4-trifluoromethyl-ß-nitrostyrene (see end Experimental Section) (7.0g., 32.0 mmol) as an oil 3.9g., (29%); ^{31}P = +42.0 and 41.6 ppm ($CDCl_3$); δ ($CDCl_3$) 1.3 (m, 9H); 2.2 (m, 2H); 4.2 -> 3.5 (m, 7H); 4.8 -> 4.5 (m, 2H); 5.2 -> 5.0 (m, 1H); 7.5 (m, 4H); Found: C 48.08, H 5.76, N 3.20, $C_{17}H_{25}F_3NO_6P$, requires C 47.80 H 6.59, N 3.69.

Ethyl 3-amino-2-phenylpropyl(diethoxymethyl)phosphinate (29a)
To a solution of phosphinate (28a) (5.7g., 15.8 mmol) in ethanol (60 ml) was added Raney Nickel (9 ml), and the resulting mixture was hydrogenated at a pressure of 1 bar until hydrogen uptake ceased. The mixture was filtered, and the solvent removed under reduced pressure to give (29a) 5.1g. (98%) as a viscous oil; ^{31}P = +44.4 ppm ($CDCl_3$) (not resolved); IR (Neat) 3400, 3000 -> 2850, 1490, 1450, 1390, 1300, 1220, 1050, 950, 880, 850, 700cm^{-1}.
The following were prepared in a similar manner:-

Ethyl 3-amino-2-(4-chlorophenyl)propyl(diethoxymethyl)phosphinate (29b)
From phosphinate (28b) (1.8g., 4.6 mmol) as a viscous oil 1.4g. (84%) ^{31}P = +44.2 ppm ($CDCl_3$) (not resolved); chromatography gave analytically pure material: Found: C 52.65, H 7.89, N 3.98, P 8.30, $C_{16}H_{27}ClNO_4P$, requires C 52.67, H 7.74, N 3.84, P 8.49.

Ethyl 3-amino-2-(4-fluorophenyl)propyl(diethoxymethyl)phosphinate (29c)
From phosphinate (28c) (5.0g., 13.2 mmol) as a viscous oil 4.4g. (98%); ^{31}P = +44.4 ppm ($CDCl_3$) (not resolved).

Ethyl 3-amino-2-(4-methylphenyl)propyl(diethoxymethyl)phosphinate (29d)
From phosphinate (28d) (6.5g., 17.4 mmol) as a viscous oil 5.7g. (95%); ^{31}P = +44.6 ppm ($CDCl_3$) (not resolved); chromatography gave analytically pure material: Found: C 58.43, H 9.06, N 4.10, P 8.78, $C_{17}H_{32}NO_4P$, requires C 59.11, H 9.34, N 4.06, P 8.97.

Ethyl 3-amino-2-(4-methoxyphenyl)propyl(diethoxymethyl)phosphinate (29e)
From phosphinate (28e) (6.6g., 17.0 mmol) as a viscous oil 6.0g. (100%); ^{31}P = +44.5 ppm ($CDCl_3$) (not resolved); chromatography gave analytically pure material: Found: C 56.61, H 8.34, N 3.85, P 8.61, $C_{17}H_{30}NO_5P$, requires C 56.81, H 8.41, N 3.90, P 8.62.

Ethyl 3-amino-2-(4-trifluoromethylphenyl)propyl(diethoxymethyl)phosphinate (29f)
From phosphinate (28f) (3.7g., 8.6 mmol) as a viscous oil 3.3g. (96%); ^{31}P = +44.0 ppm ($CDCl_3$) (not resolved).

3-Amino-2-phenylpropylphosphonous acid (30a)
From phosphinate (29a) (4.0g., 12.1 mmol) and 36% aqueous hydrochloric acid (40 ml) analogous to the synthesis of (21a), as a white powder 1.4g. (42%), m.p. 228-35°; ^{31}P = +24.3 ppm (D_2O); δ (D_2O) 3.0 (m, 2H); 4.3 (m, 3H); 4.6 (s, 0.5H); 8.3 (s, 5H); 10.4 (s, 0.5 H, JP-H = 519.6 Hz): Found: C 53.58, H 7.08, N 6.96, P 15.25, $C_9H_{14}NO_2P$, requires C 54.27 H 7.09, N 7.03, P 15.95.

3-Amino-2-(4-chlorophenyl)propylphosphonous acid (30b)
From phosphinate (29b) (5.0g., 13.7 mmol) and 36% aqueous hydrochloric acid (60 ml) as a white powder 2.0g. (63%), m.p. 235-40°; ^{31}P = +27.2 ppm (D_2O); δ(D_2O) 2.2 (m, 2H); 3.7 (m, 3H); 4.0 (s, 0.5H); 7.8 (m, 4H); 9.8 (s, 0.5 H, JP-H = 516.0 Hz): Found: C 45.27, H 5.52, N 5.97, P 12.93 $C_9H_{13}ClNO_2P$, requires C 46.27 H 5.61, N 6.00, P 13.26.

3-Amino-2-(4-fluorophenyl)propylphosphonous acid (30c)
From phosphinate (29c) (4.4g., 12.7 mmol) and 36% aqueous hydrochloric acid (40 ml) as a white powder 1.55g. (60%), m.p. 225-35°; ^{31}P = +24.1 ppm (D_2O); δ (D_2O) 2.2 (m, 2H); 3.7 (m, 3H); 4.2 (s, 0.5H); 7.8 (m, 4H); 10.0 (s, 0.5 H, JP-H = 518.4 Hz). Product contained 33% water by microanalysis.

3-Amino-2-(4-methylphenyl)propylphosphonous acid (30d)
From phosphinate (29d) (3.7g., 10.7 mmol) and 36% aqueous hydrochloric acid (40 ml) as a white powder 1.4g. (61%), m.p. 250-5°; ^{31}P = +24.5 ppm (D_2O); δ (D_2O) 3.0 (m, 2H); 3.2 (s, 3H); 4.0 (m, 3H); 4.8 (s, 0.5H); 8.1 (m, 4H); 10.4 (s, 0.5 H, JP-H = 517.8 Hz) . Found: C 56.32, H 7.67, N 6.17, P 14.36, $C_{10}H_{16}NO_2P$, requires C 56.33, H 7.56, N 6.57, P 14.53.

3-Amino-2-(4-methoxyphenyl)propylphosphonous acid (30e)
From phosphinate (29e) (4.6g., 12.8 mmol) and 36% aqueous hydrochloric acid (30 ml) as a white powder 1.33g. (46%), m.p. 260-5°; ^{31}P = +24.5 ppm (D_2O); δ(D_2O) 3.0 (m, 2H); 4.1 (m, 3H); 4.8 (m, 3.5H); 8.0 (m, 4H); 10.3 (s, 0.5 H,

JP-H 516.9 Hz). Satisfactory microanalysis could not be obtained for this compound.

3-Amino-2-(4-trifluoromethylphenyl)propylphosphonous acid (30f)

From phosphinate (29f) (3.5g., 8.8 mmol) and 36% aqueous hydrochloric acid (50 ml) as a white powder 0.8g. (35%), m.p. 195-7°; ^{31}P = +23.6 ppm (D_2O); $\delta(D_2O)$ 3.0 (m, 2H); 4.2 (m, 3.5H) 8.6 (m, 4H); 10.6 (s, 0.5H; JP-H = 515.2 Hz). Found: C 44.25, H 5.12, N 4.74, P 11.33, $C_{10}H_{13}F_3NO_2P$, requires C 44.95, H 4.90, N 5.24; P 11.59.

Ethyl 2-hydroxy-3-phthalimidopropyl(diethoxymethyl)phosphinate (31)

A mixture of phosphonite (9) (25.0g. 93.3 mmol) and 2,3-epoxypropyl-phthalimide (19.2g., 94.5 mmol) in dry THF (200 ml) was stirred under N_2. A catalytic amount of $ZnCl_2$ was added and the mixture refluxed for 2 hrs. After cooling, the solvent was removed, the residue dissolved in chloroform (100 ml) and stirred vigorously with water (50 ml). After separation and drying, the solvent was removed and the residue heated to 100° at 0.05 mm to remove phosphonite (6) formed as by-product. This gave (31) as a viscous oil 29.0g. (78%): ^{31}P +42.0 and +41.6 ppm ($CDCl_3$); δ ($CDCl_3$) 1.4 (m, 9H); 2.2 (m, 2H); 4.5 -> 3.6 (m, 1OH); 4.8 (d,d, J = 8 Hz, 1H); 7.9 (m, 4H).

3-Amino-2-hydroxypropylphosphonous acid (32)

From phosphinate (31) (1.5g., 3.7 mmol) and 36% aqueous hydrochloric acid (10 ml) analogous to the synthesis of (21a), but allowing approx. 24 hr for hydrolysis, as a white powder 0.25g. (63%) m.p. 206-11°; ^{31}P = +28.9 ppm (D_2O); $\delta(D_2O)$ 2.2 (m, 2H); 3.2 (m, 2H); 5.0 (m, 1.5H); 10.6 (s, 0.5H; JP-H = 553.0 Hz). Found: C 26.45, H 7.18, N 9.66, $C_3H_{10}NO3P$, requires C 25.90, H 7.25, N 10.07.

4-Trifluoromethyl-ß-nitrostyrene

Prepared according to the method described for ß-nitrostyrene[24] from nitromethane (17.0g. 0.23 mmol) and 4-trifluoromethylbenzaldehyde (50.0g., 0.29 mmol) as an orange solid 7.0g. (11%) m.p. 89-91°; δ ($CDCl_3$); 7.6(s, 0.5H); 7.7 (s, 4.5H); 8.1 (d, 1H); Found: C 49.36, H 2.71, N 6.38, $C_9H_6F_3NO_4$, requires C 49.78, H 2.79, N 6.45.

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