Dimethyl 3-chloroprop-1-en-2-ylphosphonate. Part 2. Alkylation of amines, phosphines and phosphites

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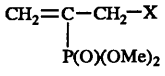
Dimethyl 3-chloroprop-1-en-2-ylphosphonate **1** reacted with secondary amines to give phosphorus-containing allylic amines. Interaction of the phosphonate **1** with triethylamine formed the corresponding ammonium salt which, when heated, was converted into the betaine **15**. The reaction of the phosphonate **1** with triphenylphosphine also led to formation of the corresponding phosphonium salt which, when heated, underwent prototropic isomerisation to give the betaine **17**. The phosphonium salt was utilised in a Wittig reaction with paraformaldehyde to form buta-1,3-dien-2-ylphosphonate. The Michaellis–Arbusov reaction of the phosphonate **1** with trimethyl phosphite led to prop-2-ene-1,2-diyldiphosphonate. Its hydrolysis gave the corresponding diphosphonic acid, which is a hydrolytically stable analogue of phosphoenol pyruvate. Alkylation of *N*-heterocycles, glycine and DL-alanine led to compounds having biological activity potential.

3-Halogenoprop-1-en-2-ylphosphonate esters **1–3** are convenient starting materials for the synthesis of a variety of alk-1-enes with a phosphorus group at the second position of a carbon chain. Whilst several different methods for the synthesis



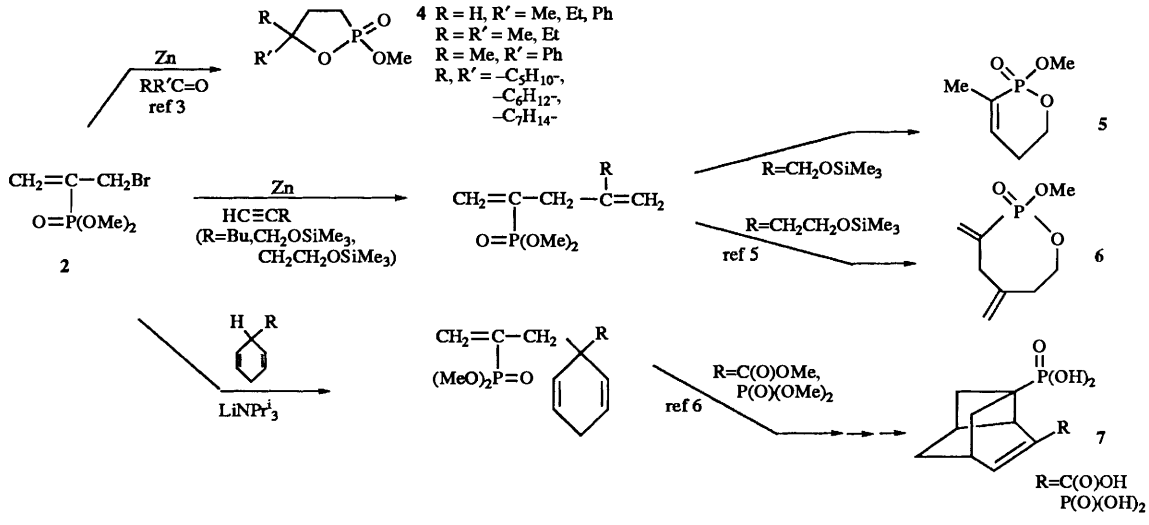
1 X = Cl Refs 1,2
2 X = Br Ref 3
3 X = I Ref 1

of these esters have been reported,[1–4] until recently the esters have been comparatively inaccessible compounds.[2] Dimethyl 3-bromoprop-1-en-2-ylphosphonate **2** has been employed in organozinc synthesis with carbonyl compounds[3] for the synthesis of α-methylene-γ-phostones **4**, and with alk-1-ynes[5] for the synthesis of five- and six-membered heterocycles **5** and **6** (Scheme 1). It has also been used as an alkylating agent in the synthesis of transition-state analogue inhibitors **7** of chorismate mutase.[6] It has been shown that the phosphonate **1** undergoes nucleophilic substitution with highly basic nucleophiles (MeO^-, $HNEt_2$) as well as with low basic nucleophiles (I^-) (Scheme 2). Its reluctance to act as an acid was confirmed by the lack of deuterium exchange for 3-chloroprop-1-en-2-ylphosphonate **1** under the action of NaOMe in CD_3OD.[1] Thus, 3-halogenoprop-1-en-2-ylphosphonates hold much promise as alkylating agents.

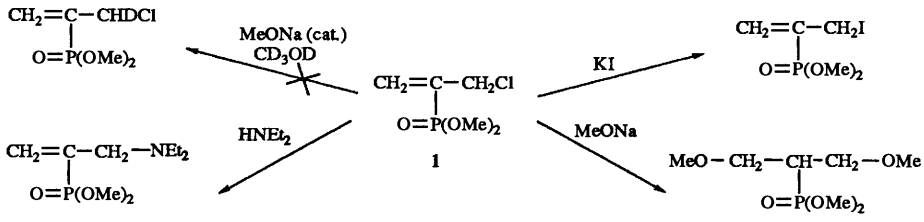
Results and discussion

We have shown that dimethyl 3-chloroprop-1-en-2-ylphosphonate **1** alkylates a variety of amines at room temperature. Secondary amines gave the phosphorus-containing allylic amines **8–13** (Table 1). On the other hand the phosphonate **1** reacted with the tertiary amine triethylamine to form the corresponding ammonium salt **19** which, when heated, was converted into the betaine **20**, Scheme 3. The reaction of phosphonate **1** with triphenylphosphine also led to formation of the corresponding phosphonium salt **21** (Scheme 3). However the phosphonium salt **21** reacted differently when heated and it underwent prototropic isomerisation to give the betaine **22**.

The isomerisation of the salt **21** to betaine **22** is attributed to the higher acidity of the methylene protons in the phosphonium salt **21** and the development of conjugation of the double bond with the phosphorus atom in the isomeric betaine

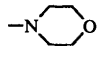
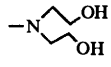
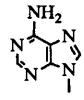


Scheme 1 Reactions of dimethyl ester of 3-bromoprop-1-en-2-ylphosphonic acid



Scheme 2 Reactions of 3-chloroprop-1-en-2-ylphosphonate

Table 1 Allylic amines CH_2=C(CH_2B)-P(O)($OMe)_2$

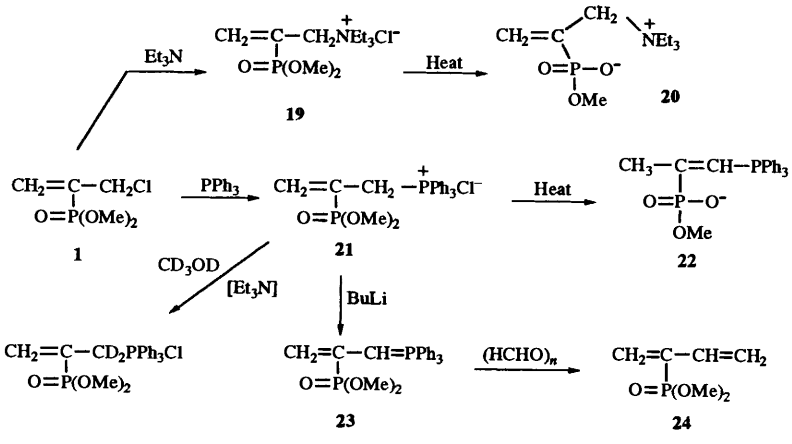
Compound	Substituent B	Yield(%)
8		70
9		79
10		87
11		55
12		59
13		67
14		34
15		17
16		31
17	-HN-CH_2-CO_2Me	93
18	-HN-CH(Me)-CO_2Me	22

22. Similar interconversions have been described for 2-dialkylphosphatoprop-2-enyl(tributyl)phosphonium chloride[7] as well as for phosphorylated *S*-isothiuronium chlorides, which underwent the dealkylation to the corresponding betaines with and without allylic rearrangement.[8]

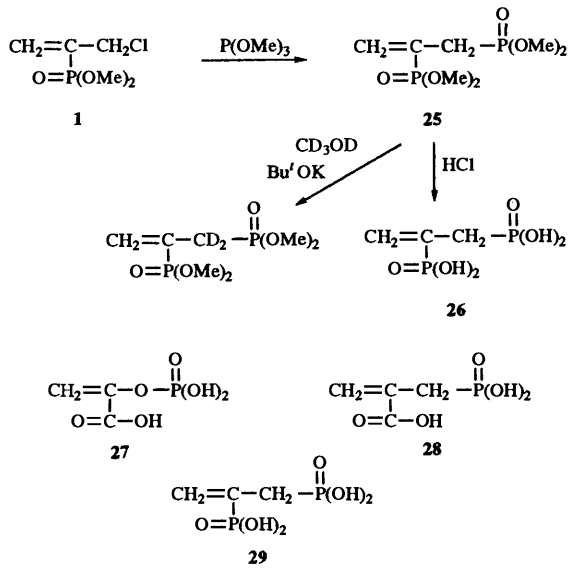
The phosphonium salt **21** separated as white crystals which were stable at room temperature. Investigation of its behaviour in CD_3OD showed that both methylene protons rapidly underwent deuterium exchange in the presence of a catalytic amount of triethylamine. The products of prototropic isomerisation were not observed. Since the observed deuterium exchange indicated that the phosphonium salt **21** might be utilised in a Wittig reaction, it was treated with butyllithium in THF to give the semi-stabilised phosphonium ylide **23**, which interacted with aldehydes to form alka-1,3-dien-2-ylphosphonates (phosphonoprenes). Reaction of the ylide **23** with paraformaldehyde gave buta-1,3-dien-2-ylphosphonate **24**, a compound of theoretical,[9] synthetic[10] and practical interest due to the regioselectivity and stereospecificity of its polymerisation.[11] It should be mentioned, that phosphonylated ylides and diphosphonates have been used in Wittig–Horner–Emmons reactions for the synthesis of a variety of biological active compounds.[12a] However, the number of such ylides and diphosphonates is limited. Thus, the Wittig reagent from the phosphonium salt **21** should have considerable use in organic synthesis and we are continuing our investigations in this direction.

The Michaellis–Arbusov reaction of phosphonate **1** with trimethyl phosphite occurred under mild conditions leading to prop-2-ene-1,2-diyldiphosphonate **25**.[4] The deuterium exchange in CD_3OD for this diphosphonate takes place only in the presence of strong base, such as potassium *tert*-butoxide. Notable was the observation that the degree of deuterium exchange was dependent on the amount of the base added and that exchange occurred only at the α-methylene group.† Hydrolysis of the ester **25** gave the diphosphonic acid **26**. This acid is a hydrolytically stable analogue of phosphoenol acetylphosphonate **29** which is an inhibitor of phosphoenol pyruvate (PEP)-utilizing enzymes.[13] Replacement of the phosphate ester oxygen linkage in PEP **27** with a methylene link is a common strategy in enzyme inhibitor design,[14] for example 2-(dihydroxyphosphinoylmethyl)propenoic acid **28** is a well established inhibitor of PEP-utilising enzymes.[15–17] Another possible application of the diphosphonic acid **26** is as a corrosion inhibitor.[18]

† Exchange with deuteriated methanol was followed by ^{1}H NMR spectroscopy.

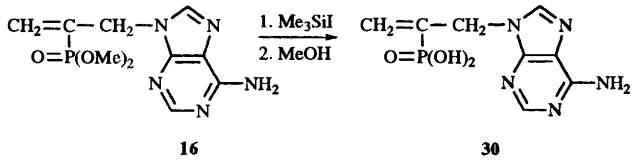


Scheme 3 Formation and some chemical properties of tertiary salts of dimethyl 3-chloroprop-1-en-2-ylphosphonate



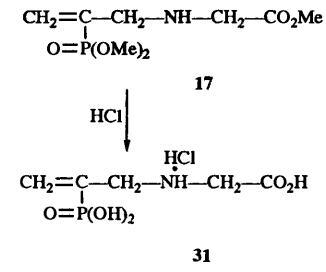
Allylamines are also useful synthetic intermediates.[19,20] Deprotonation of allylamines with bases produce nitrogen-substituted allylic anions which undergo alkylation, trimethylsilylation and reaction with carbonyl compounds and epoxides. Allylamines complexed to palladium(II) undergo facile attack by nucleophiles and the product can be readily liberated from the metal.[21,22] Allylethanolamines have also been used for the formation of the morpholine ring.[23] Thus, the preparation of allylamines has been an area of considerable activity.[19,20,24,25] We have, therefore, investigated the synthetic potential of 3-chloroprop-1-en-2-ylphosphonate **1** for synthesis of the phosphorylated allylamines **8–13**.

Pyrimidines and purines reacted with the 3-chloroprop-1-en-2-ylphosphonate **1** to give 2-phosphonoprop-2-enyl-N^1-pyrimidines **14** and **15** and -1-N^9-purine **16**. The ester **16** was converted into the phosphonic acid **30** by the action of iodotrimethylsilane in $CHCl_3$.[26] Unsaturated and acyclic nucleotide analogues have been investigated as potential antitumour and antiviral agents.[12b,27] Substances containing a reactive chlorine atom in the carbon chain attached to heterocycles have been used as starting materials in Michael–Arbusov and Michael–Becker reactions for the synthesis of such nucleotide analogues.[28] The use of phosphorus-containing alkylating agents is an alternative approach for the synthesis of acyclic analogues of nucleotides with phosphonate moieties.



Alkylation of glycine and DL-alanine methyl esters afforded phosphonates **17** and **18** (see Table 1). They are esters of phosphonaminocarboxylic acids in which alkylphosphonic acid group is bound to alkylcarboxylic group through nitrogen. It is known that such acids are potential antagonists for *N*-methyl-D-aspartate glutamate receptors and strong binding to the receptors was observed for the glycine derivatives.[29] Hydrolysis of the ester **17** gave (2-phosphonoprop-2-enyl)glycine hydrochloride **31**.

Thus, 3-chloroprop-1-en-2-ylphosphonate **1** reacts readily with various neutral nucleophiles providing an effective route to a variety of compounds with potential biological or synthetic interest. Further research is being also performed on the synthetic potential of reactions of phosphonate **1** with variety of anionic nucleophiles.



Experimental

NMR spectra were determined on JEOL FX90Q, GSX270 and Bruker AC200 instruments; the solvent was $CDCl_3$. *J* Values recorded in Hz. GC–MS analysis was performed on a VG Trio 1000 HS linked to a Carlo Erba Mega GC using a DB 17 0.32 mm capillary column. The mass spectroscopy conditions were as follows: electron energy 70 eV, source temperature 200 °C, resolution 1 a.m.u.

Dimethyl 3-chloroprop-1-en-2-ylphosphonate 1. This was prepared as described earlier.[2]

Dimethyl 3-piperidinomethylprop-1-en-2-ylphosphonate 8
To a stirred solution of the ester **1** (1 g) in diethyl ether (20 cm^3), piperidine (1.98 g) was added dropwise. The stirring was continued for 2 h at room temperature after which the precipitate was filtered off and the filtrate evaporated. The residue was vacuum distilled to give the title compound **8** (0.9 g, 70%), bp 90 °C (1 mmHg); δ_H 6.2 (CH_AH_B=, J_{AP} 48, J_{AB} 1.97), 6.17 (CH_AH_B=, J_{BP} 23.5), 2.98 (CH_2, J_{PH} 11.25, J_{HA} 1.97, J_{HB} 1.76), 3.63 (OCH_3, J_{HP} 11), 2.05 (NCH_2, J_{HH} 4.75) and 1.4 (CH_2, J_{HH} 4.75); δ_C, 131.02 (CH_2=, J_{PC} 8), 135.96 [=C(P)–, J_{PC} 173.38], 60.35 (CH_2, J_{PC} 13.58), 52.51 (OCH_3, J_{PC} 5.43), 54.56 (NCH_2), 26.09 ($2CH_2$) and 24.43 (CH_2); δ_P 21; *m/z* (I_{rel}, %) 84 (100) and 233 (5.8, $[C_{10}H_{20}NO_3P]^+$).

Dimethyl 3-pyrrolidin-1-ylmethylprop-1-en-2-ylphosphonate 9
The reaction was carried out in the same manner as for the amine **8**, using the ester **1** (0.9 g) and pyrrolidine (0.74 g) to give the product **9** (0.84 g, 79%), bp 78 °C (1 mmHg); δ_H 6.07 (CH_AH_B=, J_{AP} 48.12, J_{AB} 1.97), 6.14 (CH_AH_B=, J_{BP} 22.41), 3.25 (CH_2, J_{PH} 10.33, J_{HA} 1.97, J_{HB} 1.76), 3.74 (OCH_3, J_{HP} 11), 2.53 (NCH_2, J_{HH} 3.51) and 1.76 (CH_2, J_{HH} 3.51); δ_C 131.07 (CH_2=, J_{PC} 7.69), 136.89 [=C(P)–, J_{PC} 173.59], 57.49 (CH_2, J_{PC} 14.29), 52.84 (OCH_3, J_{PC} 6.6), 54.44 (NCH_2) and 54.02 (CH_2); δ_P 21.6; *m/z* 70 (100%) and 219 (7.7, $[C_9H_{18}NO_3P]^+$).

Dimethyl 3-morpholinomethylprop-1-en-2-ylphosphonate 10
The reaction was carried out in the same manner as for the amine **8**, using the ester **1** (0.86 g) and morpholine (0.81 g) to give the product **10** (0.96 g, 87%), bp 82 °C (1 mmHg); δ_H 6.04 (CH_AH_B=, J_{AP} 45.93, J_{AB} 1.75), 6.14 (CH_AH_B=, J_{BP} 21.97), 3.13 (CH_2, J_{PH} 11.87, J_{HA} 1.75, J_{HB} 1.32), 3.76 (OCH_3, J_{HP} 11.0), 2.46 (NCH_2, J_{HH} 4.73) and 3.7 (OCH_2); δ_C 131.6 (CH_2=, J_{PC} 7.69), 135.43 [=C(P)–, J_{PC} 164.79], 60.05 (CH_2, J_{PC} 13.18), 52.89 (OCH_3, J_{PC} 5.69), 53.47 (NCH_2), 66.88 (OCH_2); δ_P 20.6; *m/z* 126 (100%) and 235 (1.7, $[C_9H_{18}NO_4P]^+$).

Dimethyl 3-bis(2-hydroxyethyl)aminomethylprop-1-en-2-ylphosphonate 11
To a stirred solution of the ester **1** (0.6 g) in dichloromethane (20 cm^3), diethanolamine (0.68 g) was added. The stirring was continued for 2 h at room temperature after which work-up and separation by column chromatography on silica gel afforded the title compound **11** (0.45 g, 55%) as an acetone fraction; δ_H 5.89

(CH_AH_B=, J_{AP} 47.47, J_{AB} 1.31), 5.93 (CH_AH_B=, J_{BP} 21.32), 3.37 (CH_2, J_{PH} 17.79, J_{HA} 1.31, J_{HB} 0.87), 3.79 (OCH_3, J_{HP} 11.0), 2.61 (NCH_2, J_{HH} 4.61) and 3.63 ($HOCH_2$); δ_C 131.87 (CH_2=, J_{PC} 8.79), 136.48 [=C(P)–, J_{PC} 174.69], 57.81 (CH_2, J_{PC} 10.99), 53.18 (OCH_3, J_{PC} 6.6), 55.96 (NCH_2) and 59.51 (HO–CH_2); δ_P 21.6 (Found: C, 42.6; H, 8.0; N, 5.9; P, 12.0. Calc. for $C_9H_{20}NO_5P$: C, 42.69; H, 7.90; N, 5.53; P, 12.25%).

Dimethyl 3-dipropylaminomethylprop-1-en-2-ylphosphonate 12

The reaction was carried out in the same manner as for the amine **8**, using the ester **1** (1 g) and dipropylamine (1.1 g) to give the product **12** (0.8 g, 59%), bp 76 °C (1 mmHg); δ_H 6.15 (CH_AH_B=, J_{AP} 48.34, J_{AB} 2.19), 6.12 (CH_AH_B=, J_{BP} 22.43), 3.15 (CH_2, J_{PH} 9.07, J_{HA} 2.19, J_{HB} 1.54), 3.73 (OCH_3, J_{HP} 11.0), 2.37 (NCH_2, J_{HH} 7.69), 1.45 (CH_2) and 0.86 (CH_3); δ_C 131.02 (CH_2=, J_{PC} 7.71), 137.38 [=C(P)–, J_{PC} 171.38], 56.1 (CH_2, J_{PC} 15.38), 52.76 (OCH_3, J_{PC} 5.5), 56.44 (NCH_2), 20.65 (CH_2) and 12.27 (CH_3); δ_P 21.8; *m/z* 220 (100%) and 249 (2.99, $[C_{11}H_{24}NO_3P]^+$).

Dimethyl 3-diisopropylaminomethylprop-1-en-2-ylphosphonate 13

The reaction was carried out in the same manner as for the amine **8**, using the ester **1** (1 g) and diisopropylamine (1.1 g) to give the product **13** (0.9 g, 67%), bp 68 °C (1 mmHg); δ_H 6.29 (CH_AH_B=, J_{AP} 50.1, J_{AB} 2.42), 6.13 (CH_AH_B=, J_{BP} 21.11), 3.2 (CH_2, J_{PH} 5.93, J_{HA} 2.42, J_{HB} 2.65), 3.73 (OCH_3, J_{HP} 11.0), 3.0 (NCH, J_{HH} 6.6) and 0.98 (CH_3); δ_C 130.8 (CH_2=, J_{PC} 8.79), 139.24 [=C(P)–, J_{PC} 166.99], 46.4 (CH_2, J_{PC} 17.58), 52.5 (OCH_3, J_{PC} 6.59), 48.84 (NCH) and 20.9 (CH_3); δ_P 22.51; *m/z* 206 (100%) and 249 (2.5, $[C_{11}H_{24}NO_3P]^+$).

***N*-(2-Dimethylphosphonoprop-2-enyl)triethylammonium chloride 19**

A solution of the phosphonate **1** (2.9 g) and triethylamine (1.6 g) in $CHCl_3$ (15 cm^3) was stirred for 20 min at room temperature after which the solvent was distilled off *in vacuo* to give the title compound as an oil (4.4 g, 98%); δ_H 6.48 (CH_AH_B=, J_{AP} 43.51), 6.03 (CH_AH_B=, J_{BP} 20.43), 3.91 (CH_2, J_{PH} 15.82), 3.17 (OCH_3, J_{PH} 11.0), 2.93 (NCH_2, J_{HH} 7.25) and 0.83 (CH_3); δ_C 146.01 (CH_2=, J_{PC} 6.59), 126.36 [=C(P)–, J_{PC} 182.38], 57.35 (CH_2, J_{PC} 12.1), 52.79 (OCH_3, J_{PC} 6.6), 52.93 (NCH_2) and 7.69 (CH_3); δ_P 17.5 (Found: C, 46.2; H, 8.8; Cl, 11.9. Calc. for $C_{11}H_{25}ClNO_3P$: C, 46.23; H, 8.76; Cl, 12.43%).

Methyl 3-triethylammonioprop-1-en-2-ylphosphonate 20

A solution of the phosphonate **19** (3.53 g) in $CHCl_3$ (15 cm^3) was refluxed for 20 h after which dilution with ether (200 cm^3) gave a precipitate which when dried *in vacuo* gave the betaine **20** as an oil (2.6 g, 89%); δ_H 5.95 (CH_AH_B=, J_{AP} 33.69, J_{AB} 1.95), 6.3 (CH_AH_B=, J_{BP} 16.11), 4.08 (CH_2, J_{PH} 12.69, J_{HA} 1.95, J_{HB} 1.5), 3.55 (OCH_3, J_{PH} 10.74), 3.58 (NCH_2, J_{HH} 7.33) and 1.4 (CH_3); δ_C 136.02 (CH_2=, J_{PC} 6.59), 136.79 [=C(P)–, J_{PC} 158.2], 62.01 (CH_2, J_{PC} 11), 51.84 (OCH_3, J_{PC} 5.49), 53.32 (NCH_2) and 8.32 (CH_3); δ_P 8.4.

(2-Dimethylphosphonoprop-2-enyl)triphenylphosphonium chloride 21

A mixture of the phosphonate **1** (5 g) and triphenylphosphine (7.05 g) in CH_2Cl_2 (10 cm^3) was stirred for 12 h at room temperature after which work-up and crystallisation from ether afforded the phosphonium salt **21** as white hygroscopic solid (9.5 g, 74%), mp 235 °C; δ_H 6.49 (CH_AH_B=, J_{AP} 45.3, J_{AP} 4.8, J_{AB} 1), 6.26 (CH_AH_B=, J_{BP} 21.5, J_{PB} 5.4), 5.2 (CH_2, J_{PH} 15, J_{PH} 15, J_{HA} 1, J_{HB} 1), 3.48 (OCH_3, J_{PH} 11.3) and 7.5–8.1 (Ph); δ_C 141–130 [Ph, CH_2=, =C(P)–], 27.12 (CH_2, $^2J_{PC}$ 12.09, $^1J_{PC}$ 49.44) and 53.03 (OCH_3, J_{PC} 6.59); δ_P 23 (J_{PP} 9.8) and 18.2 (Found: C, 61.8; H, 5.6; Cl, 7.4; P, 14.0. Calc. for $C_{23}H_{25}ClO_3P_2$: C, 61.81; H, 5.60; Cl, 7.95; P, 13.88%).

Methyl 1-triphenylphosphonioprop-1-en-2-ylphosphonate 22

The phosphonium salt **21** (2.97 g) was refluxed in $CHCl_3$ for 8 h. Work-up and crystallization from ether afforded the betaine **22** as a white solid (2.26 g, 86%), mp 233 °C (decomp.); δ_H 1.98 (CH_3, J_{HP} 10.77, J_{HH} 1.55, J_{HP} 1.76), 3.67 (OCH_3, J_{HP} 11), 7.2 (=CH–, J_{HP} 21.75, J_{HP} 31.27) and 8.2–7.3 (Ph); δ_C 21.09 (CH_3, J_{PC} 7.7, J_{PC} 9.88), 119.27 [–C(P)=, $^1J_{PC}$ 83, $^2J_{PC}$ 5.49], 109.88 (=CH–, $^2J_{PC}$ 14.28, $^1J_{PC}$ 71.44), 51.98 (OCH_3, J_{PC} 5.49) and 135–129 (Ph); δ_P 10.3 (J_{PP} 60) and 6.4 (Found: C, 66.65; H, 5.5. Calc. for $C_{22}H_{22}O_3P$: C, 66.67; H, 5.55%).

Dimethyl buta-1,3-dien-2-ylphosphonate 24[9]

To the phosphonium salt **21** (1.01 g) in THF (20 cm^3) was added BuLi (hexane solution; 0.44 g) at −40 °C. The mixture was stirred at 25 °C for 1 h after which paraformaldehyde (0.1 g) was added to it at −78 °C. After being allowed to warm slowly to room temperature over 1 h and stirred at 25 °C for 24 h, the reaction mixture was diluted with ether (100 cm^3) washed with water (2 × 40 cm^3), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by column chromatography (ether) to give the title compound **24** (0.11 g, 30%).

Tetramethyl prop-2-ene-1,2-diyldiphosphonate 25

The phosphonate **1** (6.12 g) was stirred and heated in trimethyl phosphite (4.5 g) at 110 °C under N_2 for 15 min. After cooling, the mixture was distilled *in vacuo* to give diphosphonate **25** (6.7 g, 78%), bp 140 °C (1 mmHg); δ_H 6.26 (CH_AH_B=, J_{AP} 47.5, J_{AP} 4.4), 6.29 (CH_AH_B=, J_{BP} 22.4, J_{BP} 5.2), 2.79 (CH_2, J_{PH} 13, J_{HP} 21.6) and 3.77 and 3.79 (OCH_3, J_{HP} 11, J_{HP} 0.4); δ_C 133.50 (CH_2=, $^2J_{PC}$ 8.35, $^3J_{PC}$ 8.35), 127.27 [=C(P)–, $^1J_{PC}$ 180.88, $^2J_{PC}$ 9.56], 25.67 (CH_2, $^2J_{PC}$ 11.67, $^1J_{PC}$ 140.24) and 51.49 and 51.36 (P–OCH_3, J_{PC} 7.14); δ_P 29.3 (J_{PP} 29.3) and 20.05; *m/z* 149 (100%), 109 (21.10), 93 (16.40), 79 (15.75), 227 (10.88), 173 (8.85), 150 (6.86), 164 (5.36), 124 (5.24), 135 (5.03) and 258 (1.63, $[C_7H_{16}O_6P_2]^+$).

Dicyclohexylamine salt of prop-2-ene-1,2-diyldiphosphonic acid 26

A solution of the diphosphonate **26** (1.03 g) in 6 mol dm^{-3} HCl (25 cm^3) was refluxed for 5 h after which it was concentrated and the residue dried *in vacuo* to give a colourless oil. This was dissolved in MeOH to which solution cyclohexylamine was added until it reached pH 5.1. The solvent was then distilled off *in vacuo*, and the residue was crystallised from MeOH–acetone (3:1) to give the title salt (0.83 g, 54%), mp 237 °C; δ_H 5.71 (CH_AH_B=, J_{AP} 42.8, J_{AP} 5.2), 5.84 (CH_AH_B=, J_{BP} 19.7, J_{BP} 4.8), 2.67 (CH_2, J_{PH} 8.6, J_{HP} 21.1), 3.14 (NCH) and 1.31 and 1.75 (CH_2, J_{HH} 8.4); δ_C 127.74 (CH_2=, $^2J_{PC}$ 7.68, $^3J_{PC}$ 9.88), 138.48 [=C(P)–, $^1J_{PC}$ 163.69, $^2J_{PC}$ 8.79], 34.72 (CH_2, $^2J_{PC}$ 13.17, $^1J_{PC}$ 125.3), 52.11 (NCH), 32.07, 25.54 and 26.02 (CH_2); δ_P 20 (J_{PP} 10) and 13.61.

***N*^{1}-(2-Dimethylphosphonoprop-2-enyl)cytosine 14**

A mixture of cytosine (0.57 g), the phosphonate **1** (0.96 g) and anhydrous K_2CO_3 (0.71 g) was stirred in DMSO (30 cm^3) at room temperature for 24 h after which it was evaporated (oil pump). The solid residue was washed with CH_2Cl_2–MeOH (4:1, 4 × 50 cm^3) and the combined washings were evaporated, and the crude product was chromatographed on a silica gel column using CH_2Cl_2–MeOH (2:1) as eluent. Evaporation of the appropriate fractions gave a white precipitate, which was crystallized from methanol–ethyl acetate (1:4) to give the pyrimidine **14** (0.46 g, 34%), mp 156 °C; λ_{max}/nm 274 (6700), 238 (5700) and 203 (17 000); δ_H(DMSO) 5.62 (CH_AH_B=, J_{AP} 44.34), 5.99 (CH_AH_B=, J_{BP} 22.0), 4.39 (CH_2, J_{PH} 7.6), 3.63 (OCH_3, J_{HP}

11.0), 5.69 (5-H, J_{HH} 7.4), 7.52 (6-H) and 7.11 (NH_2); δ_C(DMSO) 130.06 (CH_2=, J_{PC} 7.69), 134.42 [=C(P)–, J_{PC} 171.38], 49.02 (CH_2, J_{PC} 16.08), 52.43 (OCH_3, J_{PC} 5.5), 166.06 (C-2), 146.22 (C-6), 93.6 (C-5) and 155.34 (C-4); δ_P 19.25.

N^1-(2-Dimethylphosphonoprop-2-enyl)thymine 15

The method for compound **14** was followed using the phosphonate **1** (1.14 g), thymine (0.77 g) and K_2CO_3 (0.85 g). The crude product was chromatographed on a silica gel column using CH_2Cl_2–MeOH (10:1) as eluent. Evaporation of appropriate fractions gave a white precipitate, which was crystallized from ethyl acetate–cyclohexane (1:1) to give the pyrimidine **15** (0.29 g, 17%), mp 152 °C; λ_{max}/nm 268 (9800) and 206 (9800); δ_H(DMSO) 5.77 (CH_AH_B=, J_{AP} 33.65), 6.0 (CH_AH_B=, J_{BP} 22.0), 4.37 (CH_2, J_{PH} 8), 3.61 (OCH_3, J_{HP} 11.4), 7.42 (6-H), 1.74 (CH_3) and 7.42 (NH); δ_C(DMSO) 131.13 (CH_2=, J_{PC} 7.69), 133.62 [=C(P)–, J_{PC} 172.49], 48.07 (CH_2, J_{PC} 17.58), 52.68 (OCH_3, J_{PC} 5.49), 12.04 (CH_3), 164.45 (C-2), 150.7 (C-4), 141.49 (C-6) and 108.97 (C-5); δ_P 18.7.

N^9-(2-Dimethylphosphonoprop-2-enyl)adenine 16

A mixture of adenine (0.93 g) and the phosphonate **1** (1.28 g) was stirred in 1 mol dm^{-3} tetrabutylammonium fluoride in THF (11 cm^3) for 3 h at room temperature after which it was evaporated. The residue was chromatographed on a silica gel column using CH_2Cl_2–MeOH (10:1) as eluent. Evaporation of the appropriate fractions gave a yellow precipitate, which recrystallized from ethyl acetate–light petroleum (1:3) to give a white precipitate of the purine **16** (0.61 g, 31%), mp 164 °C; λ_{max}/nm 260 (13 000) and 208 (20 000); δ_H(DMSO) 5.59 (CH_AH_B=, J_{AP} 45.1), 6.04 (CH_AH_B=, J_{BP} 21.7), 4.94 (CH_2, J_{PH} 8.5), 3.61 (OCH_3, J_{HP} 11.0), 8.13 (2-H) and 7.26 (8-H); δ_C(DMSO) 131.57 (CH_2=, J_{PC} 7.6), 133.95 [=C(P)–, J_{PC} 174.7], 43.63 (CH_2, J_{PC} 17.6), 52.49 (OCH_3, J_{PC} 5.49), 152.6 (C-2), 141.05 (C-8), 155.9 (C-6), 118.47 (C-5) and 149.39 (C-4); δ_P 20.1; *m/z* 174 (100%), 283 (32.92), 135 (28.25), 282 (21.8), 175 (18.91), 149 (14.06), 109 (14.01), 148 (13.7), 79 (8.17) and 147 (7.31); 283 (32.94, $[C_{10}H_{14}N_5O_3P]^+$).

N^9-(2-Phosphonoprop-2-enyl)adenine 30

A solution of the phosphonate **27** (100 mg) in $CHCl_3$ (15 cm^3) was cooled to −40 °C and solution of iodotrimethylsilane (300 mg) in MeCl (3 cm^3) was added to it. The temperature of the mixture was allowed to rise and, after 1 h at room temperature, it was evaporated. Methanol (10 cm^3) was added to the residue, and the mixture was stirred for 3 h; it was then evaporated. The residue was washed with acetone and crystallized from water–acetone (3:1) to give the free acid **30** (30 mg, 33%), mp 230 °C; δ_H(Na-salt, D_2O) 4.41 (CH_AH_B=, J_{AP} 36.14), 5.47 (CH_AH_B=, J_{BP} 18.55), 4.97 (CH_2, J_{PH} 2), 8.09 (2-H) and 8.07 (8-H); δ_C(Na-salt, D_2O) 119.58 (CH_2=, J_{PC} 13.2), 137 [=C(P)–, J_{PC} 151], 45.73 (CH_2, J_{PC} 19.07), 152.26 (C-2), 142.98 (C-8), 155.39 (C-6), 117.97 (C-5) and 148.9 (C-4); δ_P 8.22.

Methyl *N*-(2-dimethylphosphonoprop-2-enyl)glycinate 17

A solution of the phosphonate **1** (2.05 g) and methyl glycinate hydrochloride (1.53 g) in methanol and triethylamine (2.45 g) was stirred for 2 h at room temperature and then evaporated under reduced pressure. The residue was dissolved in water and extracted with chloroform (3 × 50 cm^3). The combined extracts were dried ($MgSO_4$), filtered and evaporated. The residue was chromatographed on silica gel ($CHCl_3$–MeOH 20:1) to give an oil (2.47 g, 93%); δ_H 5.97 (CH_AH_B=, J_{AP} 47.9, J_{AB} 1.3), 6.07 (CH_AH_B=, J_{BP} 23.3), 3.44 (CH_2, J_{PH} 10.4, J_{HA} 1.3, J_{HB} 1.04), 3.72 (P–OCH_3, J_{PH} 11), 3.4 (NCH_2), 3.4 (OCH_3) and 2.0 (NH); δ_C 130.3 (CH_2=, J_{PC} 8.79), 135.87 [=C(P)–, J_{PC} 173.58], 49.48 (CH_2, J_{PC} 14.29), 52.13 (P–OCH_3, J_{PC} 5.49), 48.93 (NCH_2), 172.04 (C=O) and 51.23 (OCH_3); δ_P 21.

Methyl *N*-(2-dimethylphosphonoprop-2-enyl)-DL-alanine 18

A solution of the phosphonate **1** (2 g) and methyl (±)-alaninate hydrochloride (1.69 g) in methanol and triethylamine (2.45 g) was stirred at room temperature for 24 h after which it was evaporated under reduced pressure. The residue was dissolved in water and extracted with chloroform (3 × 50 cm^3). The combined extracts were dried ($MgSO_4$), filtered and evaporated and the residue was chromatographed on silica gel ($CHCl_3$–MeOH, 20:1) to give an oil (0.6 g, 22%); δ_H 6.04 (CH_AH_B=, J_{AP} 47.9, J_{AB} 1.54), 6.12 (CH_AH_B=, J_{BP} 22.62), 3.32 (CH_2, J_{PH} 9.49, J_{HA} 1.54, J_{HB} 1.32), 3.71 (P–OCH_3, J_{PH} 10.77), 3.36 (N–CH, J_{HH} 7.03), 1.29 (CH_3), 3.71 (OCH_3) and 2.1 (NH); δ_C 130.85 (CH_2=, J_{PC} 6.59), 136.68 [=C(P)–, J_{PC} 174.68], 48.81 (CH_2, J_{PC} 14.28), 52.45 (P–OCH_3, J_{PC} 5.5), 61.1 (NCH), 172 (C=O) and 55.85 (OCH_3).

***N*-(2-Phosphonoprop-2-enyl)glycine hydrochloride 31**

A solution of the glycinate **17** (1 g) in 6 mol dm^{-3} HCl (25 cm^3) was refluxed for 10 h. The solution was concentrated and the residue was dried *in vacuo* to give a white solid which was recrystallised from water to give the product (0.44 g, 45%), mp 191 °C; δ_H 5.91 (CH_AH_B=, J_{AP} 40.2), 6.07 (CH_AH_B=, J_{BP} 19.5), 3.9 (CH_2, J_{PH} 12.7) and 3.9 (NCH_2); δ_P 9.4 (Found: C, 25.9; H, 4.7. Calc. for $C_5H_{11}ClNO_5P$: C, 25.92; H, 4.75%).

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