Synthesis of α-Fluorovinylphosphonates

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A new general synthesis of α-fluorovinylphosphonates is provided by a Wadsworth-Emmons condensation of tetra-alkyl fluoromethylenebisphosphonates (**1**) with aldehydes and ketones. The reaction shows useful stereoselectivity favouring the less-hindered alkene product (**3**). Catalytic reduction of these alkenic products generally leads to α-fluoroalkylphosphonates (**5**), but hydrogenolysis of the carbon–fluorine bond was observed in the case of β-aryl-α-fluorovinylphosphonates. The free phosphonic acids are readily produced by de-esterification using halogenotrimethylsilanes.

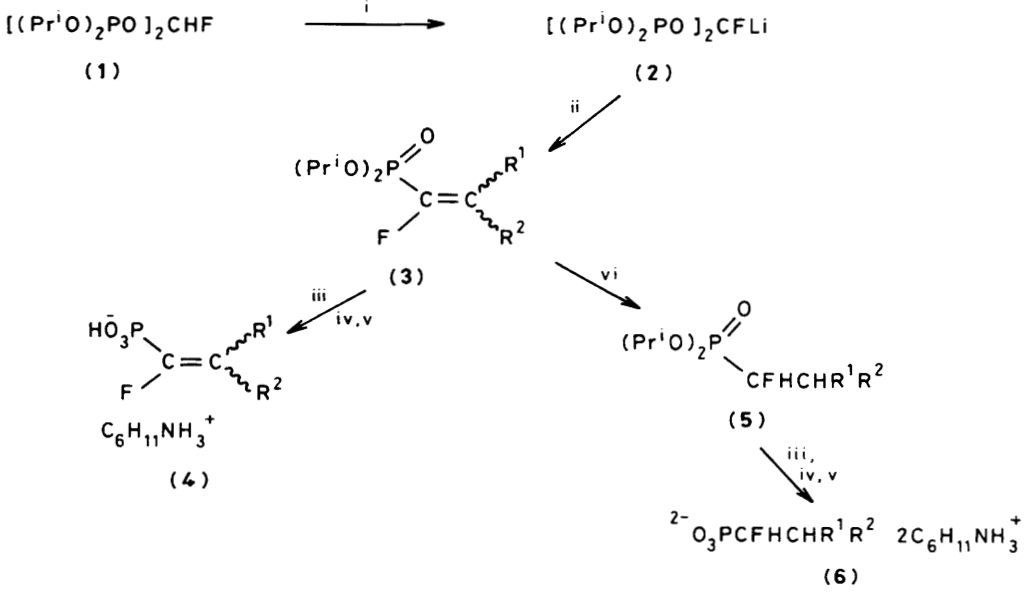
α-Fluorination of phosphonates has been established[1–4] as a successful strategy for the design of phosphonate analogues of phosphate esters. It achieves a useful correlation of significant physical properties of phosphate monoesters and the corresponding alkylphosphonates and hence leads to analogues of biological phosphates which are both isopolar and isosteric.[4] In order to develop the usefulness of this concept, it became necessary to devise new, general methods for the synthesis of α-fluoroalkylphosphonates (**5**). We describe here a new route to these molecules *via* α-fluorovinylphosphonates (**3**).

α-Chlorovinylphosphonates have been synthesized[5] by a Wadsworth-Emmons reaction using the carbanion derived from tetraethyl dichloromethylene-bisphosphonate. We therefore decided to investigate the Wadsworth-Emmons condensations of the carbanion (**2**), derived from tetra-alkyl fluoromethylenebisphosphonate (**1**), with aldehydes and ketones as a general route to α-fluorovinylphosphonates. This initiative gained further support from the fact that ethyl (diethyl phosphono)fluoroacetate has been used similarly to generate α-fluorovinylcarboxylic esters.[6] A preliminary account of this work has been presented.[7]

Results and Discussion

Tetraisopropyl fluoromethylenebisphosphonate[2,8] (**1**) was prepared by direct fluorination of tetraisopropyl methylenebisphosphonate using perchloryl fluoride. The isopropyl ester was used routinely throughout this work although the tetraethyl ester has proved equally satisfactory.[9] Treatment of compound (**1**) with butyl-lithium at −78 °C generates the lithiated carbanion (**2**) (Scheme) which condenses smoothly with aliphatic, aromatic, and α,β-unsaturated aldehydes giving good yields of the α-fluorovinyl-phosphonates (**3a**—**h**) (Table 1).

^{31}P N.m.r. spectroscopy showed the products to be an unequal mixture of the *E*-and *Z*-isomers of the alkenes (**3b**—**e**). Stereochemical assignment could be made by use of the $^{3}J_{PH}$ and $^{3}J_{HF}$ coupling constants for the alkenes (**3b**—**e**) (Table 1) obtained from ^{1}H n.m.r. spectra for the major isomers produced in condensations with aldehydes. These $^{3}J_{PH}$ values range from 7—10 Hz. In compound (**3a**), vinyl hydrogens are present in both *cis* and *trans* relationships to the phosphorus atom and so both $^{3}J_{PH}$ (*cis*) and $^{3}J_{PH}$ (*trans*) can be determined. Comparison with ^{1}H n.m.r. spectra[10–12] for various non-fluorinated vinylphosphonates confirms the assignments $^{3}J_{PH}$ (*cis*) *ca.* 8 Hz



Scheme. *Reagents*: i, BuLi–heptane; ii, R^1COR^2; iii, Me_3SiBr; iv, MeOH; v, $C_6H_{11}NH_2$; vi, H_2–Pd–C–EtOH

Table 1. Yields, isomer ratios, and n.m.r. data for α-fluorovinylphosphonates $(Pr^iO)_2PO–CF=CR'R^2$

Compd. (3)	R^1	R^2	Yield (%)	$E:Z$	δ_P[a] (p.p.m.)		δ_F[b] (p.p.m.)		$^2J_{PF}$ (Hz)		$^3J_{PH}$ (Hz)	$^3J_{HF}$ (Hz)
					E	*Z*	*E*	*Z*	*E*	*Z*		
a	H	H	69		1.3		−115.3		102.2		8(P-H) *cis* 30(P-H) *trans*	50.8(H-F *trans*) 20.5(H-F *cis*)
b	Me_2CH	H	95	5	2.0	3.3			102.2	102.2	8.5(7.5)(*E*)	40.5 (*E*)
c	(*R*)–$\overline{OCMe_2OCH_2}$CH-	H	56	10	1.2	1.2	−125.4		97.6	97.7	7(*E*)	39.7 (*E*)
d	Ph	H	73	6	3.3	4.7	−125.8	−114.0	96.1	109.9	10 (*E*)	43.9 (*E*) 29.3 (*Z*)
e	*trans*-PhCH=CH	H	67	20[c]	3.0[d]	1.2[e]	−133.7[d]	−131.7[e]	93.1[d]	97.6[e]	7 (*E,E*)	36.6 (*E,E*) 35.1 (*E,Z*)
f	Me	Me	73		2.8					105.3		
g	Me_2CH	Me	68	3	4.0	3.6	−126.7	−130.4	108.3	105.3		
h	Ph	Me	66	4	3.5	2.5	−123.6	−120.4	105.3	112.9		3.90 (*E*)[f] 4.76 (*Z*)

[a] Downfield relative to external 85% H_3PO_4. [b] Downfield relative to external $CFCl_3$. [c] (*E,E*):(*E,Z*). [d] (*E,E*)-isomer. [e] (*E,Z*)-isomer. [f] $^4J_{HF}$ values.

Table 2. N.m.r. data for α-fluoroalkylphosphonates, α-fluorovinylphosphonic acid and α-fluoroalkylphosphonic acid

Compd. (5)	Yield (%)	δ_P (p.p.m.)	δ_F (p.p.m.)	$^2J_{PF}$ (Hz)	Compd. (4)	δ_P (p.p.m.) (*E*)-isomer	$^2J_{PF}$ (Hz) (*E*)-isomer	Compd. (6)	δ_P (p.p.m.)	$^2J_{PF}$ (Hz)
a	100	16.6	−201.4	79.3	**a**	0.0	94.6			
b	100	16.9	−208.5	79.3	**b**	1.2	97.7	**b**	13.1	64.1
c	100	15. (minor)	−211.4 (minor)	76.3 (major)	**c**	−1.3	90.0	**c**	11.9	64.1
		15.4 (major)	−206.6 (major)							
d	59[f]	16.6		76.3	**d**	0.0	90.0			
e	51[g]	16.2	−208.6	76.3	**e**	−0.4	90.0	**e**	12.6	64.1
f	33[c]	16.0	−208.5	79.3	**f**	0.6	100.7	**f**	15.5	77.8
g	100	16.7[d]	−218.1[d]	80.9[d]	**g**	2.2	111.4			
		17.1[e]	−206.0[e]	80.9[e]		0.5				
h	59[f]	15.2	−211.6[d]	79.3	**h**		96.1	**h**	12.2[h]	71.7[h]
			−204.0[e]						12.5[h]	71.7[h]

[a] Downfield relative to external 85% H_3PO_4. [b] Downfield relative to external $CFCl_3$. [c] Reaction not complete (isolated yield). [d] (*R,R*)- and (*S,S*)-isomers. [e] (*R,S*)- and (*S,R*)-isomers. [f] H.m.r. yield. [g] Isolated yield. [h] Unassigned isomers.

and $^3J_{PH}$ (*trans*) *ca.* 30 Hz. It is noteworthy that the ^1H n.m.r. chemical shifts and the $^3J_{PH}$ (*cis*) and $^3J_{PH}$) (*trans*) coupling constants of compound (**3a**) fit well onto curves of these physical constants plotted[12] against the electronegativity of the α-halogen substituent for 1-chloro-, 1-bromo-, and 1-iodo-vinylphosphate esters corresponding to (**3a**).

Since all of the α-fluorovinylphosphonates (**3b—e**) show small $^3J_{PH}$ couplings for the major isomers they are therefore the less-hindered *E*-isomers. The $^3J_{HF}$ coupling constants confirm these assignments (Table 1). The major isomers (**3b—e**) have the larger $^3J_{HF}$ coupling (35—45 Hz) consistent with *trans* H–F coupling.[13,14] In the diene (**3e**) the two isomers produced both appear to have the (1*E*,2*E*) configuration while they have different geometries at the 3,4-position. As the starting cinnamaldehyde was exclusively the *E*-isomer it follows that partial isomerization must have occurred in the course of the condensation process to generate the (1*E*, 3*Z*)-product.

The carbanion (**2**) also condenses with a variety of ketones, giving the tetra-substituted alkenes (**3f—h**) in good yields (Table 1). This condensation reaction did, however, show a sensitivity to steric factors and attempts to react the species (**2**) with D-camphor or with 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuran-3-ulose gave only very poor yields of the desired products. Attempts to trap an adduct of (**2**) with acetophenone by rapid quenching of the reaction mixture with dilute acid at 10 °C resulted in the isolation only of the normal product (**3h**). Although the assignment of stereochemistry is more difficult in these cases, the $^4J_{HF}$ couplings of 3.90 Hz and 4.76 Hz for the major and minor isomers respectively of (**3h**) correlate well with the values for the *E*- and *Z*-isomers of analogous fluoroalkenes.[15] The major isomer, having the smaller $^4J_{HF}$ coupling constant, must have the methyl group *trans* to the fluorine atom, hence, as in the reaction with aldehydes, the major product is the *E*-isomer.

The two geometric isomers generally showed different ^{31}P and ^{19}F n.m.r. chemical shifts and sometimes had differing $^2J_{PF}$ coupling constants although analysis of the data (Table 1) showed no consistent trends in behaviour. The values of these physical constants for the novel α-fluorovinylphosphonates (**3a—h**) are very similar to those for di-isopropyl 1,2-difluoro-2-iodoethenylphosphonate[16] and dimethyl 2-chloro-1,3,3,3-tetrafluoroprop-1-enylphosphonate.[17]

Catalytic hydrogenation of the alkenes (**3a—c**), proceeded readily and quantitatively (Table 2) to give the corresponding α-fluoroalkylphosphonates (**5a—c**) (Scheme). Similarly, hydrogenation of compounds (**3f, g**), derived from aliphatic ketones, although requiring more forcing conditions, afforded the α-fluoroalkylphosphonates (**5f, g**) as the sole products (Table 2).

The *E*- and *Z*-isomers of (**3g**) were separated by h.p.l.c. and each was then reduced. Each geometric isomer gave rise solely to a single diastereoisomer of the product (**5g**). The (**5g**) isomer obtained from (*E*)-(**3g**) showed the larger $^3J_{HF}$ coupling constant, indicating[18] a weighted *trans* relationship of fluorine and hydrogen. If it is assumed that the preferred conformation of (**5g**) should have the most bulky β-carbon substituent *trans* to the phosphoryl group, the racemic product from (*E*)- (**3g**) can be assigned (*R,R*) relative stereochemistry arising from *cis*-addition of hydrogen[19] to the *E*-alkene.

The catalytic hydrogenation of the aryl alkenes (**3d,e,h**), did not proceed quantitatively to give the α-fluoroalkylphosphonates (**5d,e,f**). Significant proportions of fluorine-free alkylphosphonates (**7a,b,c**) were formed as a result of catalytic hydrogenolysis of the carbon–fluorine bond[20–22] (Table 2).

$$(Pr^iO)_2\overset{O}{\overset{\|}{P}}CH_2CHR^1R^2$$

(7)

a; R^1 = H, R^2 = Ph
b; R^1 = Me, R^2 = Ph
c; R^1 = H, R^2 = CH=CHPh
d; R^1 = H, R^2 = CH_2CH_2Ph

This loss of fluorine was shown to occur during and not after the hydrogenation step since re-exposure of the pure compound (**5d**) to the reduction conditions produced no further (**7a**). The *E*- and *Z*-isomers of (**3h**) were separated by h.p.l.c. and each reduced. Both isomers gave the same proportion of mixed products, showing that the loss of fluorine is not stereoselective.

Hydrogenation of the diene (**3e**) occurs more rapidly at the 3,4-double bond.[23] An incompletely reduced mixture of partially- and fully-reduced phosphonates was obtained from compound (**5e**). This showed a greater extent of reduction at the 3,4- than the 1,2-double bond and also a small amount of the fluorine-free product (**7d**). The phenyl group is therefore capable of inducing α-fluorine hydrogenolysis, even at long range from the δ-position.

Probably the most valuable result from the catalytic hydrogenation of the substituted vinylphosphonates concerns the reduction of the chiral species (**3c**). This compound comprised at least 90% of the *E*-isomer but hydrogenation gave a 2:1 mixture of isomers (**5c**). It follows that this is caused by stereoface selectivity and that the two products are diastereoisomers with *opposite* chirality at C-1. This approach thus makes feasible the synthesis of α-fluoroalkylphosphonates with a defined absolute configuration at the α-carbon centre.

Table 3. ^{31}P N.m.r. chemical shifts for various phosphonate analogues of phenyl phosphate

Compd.	δ_P (p.p.m.)[a]
$(EtO)_2P(O)CH_2Ph$	27.1
$(Pr^iO)_2P(O)CH{=}CHPh$	17.0[b]
$(Pr^iO)_2P(O)CHFCH_2Ph$ (**5d**)	16.6
$(EtO)_2P(O)CHFPh$	14.7
$(Pr^iO)_2P(O)CF{=}CHPh$ (**3d**)	3.3[b]
$(EtO)_2P(O)OPh$	6.8

[a] Downfield relative to external 85% H_3PO_4. [b] (*E*)-Isomer.

Table 4. P=O I.r. stretching frequency for various α-fluoroalkyl- and α-fluorovinyl-phosphonates

Compd.	$\nu_{P=O}$ (cm^{-1})
$(MeO)_2P(O)Me$	1 241
$(Pr^iO)_2P(O)CHFMe$ (**5a**)	1 250
$(Pr^iO)_2P(O)CHFCH(Me)_2$ (**5f**)	1 254
$(Pr^iO)_2P(O)CH_2F$	1 255
$(Pr^iO)_2P(O)CF{=}CH_2$ (**3a**)	1 265
$(Pr^iO)_2P(O)CF{=}CMe_2$ (**3f**)	1 266
$(MeO)_2P(O)OMe$	1 277

However, in the present study it does not appear possible to assign this configuration for the major and minor isomers.

The α-fluorovinylphosphonates (**3a**—**h**) were conveniently converted into the parent phosphonic acids by treatment with bromotrimethylsilane,[24] followed by methanolysis of the bistrimethylsilyl esters and isolation as their crystalline cyclohexylammonium salts (**4a**—**h**) (Scheme) (Table 2). The only product isolated from each de-esterification was the major, *E*-isomer. Similar treatment of the reduced species (**5b,c,e,f,h**) gave the α-fluoroalkylphosphonic acids as their cyclohexylammonium salts (**6b,c,e,f,h**) (Scheme) (Table 2).

Discussion of the Physical Data.—(*a*) ^{31}P *N.m.r. Chemical Shift.* It has been shown[1] that α-fluorination of alkylphosphonates has an upfield influence on the ^{31}P n.m.r. chemical shift, indicative of a change in the electronic environment around phosphorus towards that of the parent phosphate. The data produced here shows that monofluorination approximately halves the downfield shift of alkylphosphonates by about 50% relative to the parent phosphates (Tables 2, 3). It is known that vinyl phosphonates also have ^{31}P n.m.r. chemical shifts closer to those of the parent phosphates than do simple alkylphosphonates.[25] Therefore the combination of both effects in the α-fluorovinylphosphonates such as (**3d**) should have an upfield effect on the phosphorus resonance to give a ^{31}P n.m.r. chemical shift very close to that of the parent phosphate ester; this is indeed observed (Tables 1 and 3). By the ^{31}P n.m.r. criterion the dialkyl α-fluorostyrylphosphonate (**3d**) is a good isopolar but non-isosteric analogue of a dialkyl phenyl phosphate.

(*b*) P=O *I.r. Stretching Frequency.* As expected,[1] α-fluorination of phosphonates causes an increase in frequency of $\nu_{P=O}$ towards the value typical for the parent phosphates (Table 4). It is also noticeable that the double bond in the α-fluorovinylphosphonates causes an additional enhancement of $\nu_{P=O}$.

Theoretical considerations[26] led to the idea that α-fluorination of alkylphosphonates should produce analogues whose physical properties more closely resemble those of the parent phosphates. The data presented here fully supports this concept. It is clear that α-fluoroalkylphosphonates have physical properties intermediate between those of alkylphosphonates and phosphates. Therefore, the substitution of the ester oxygen atom in a phosphate by a difluoromethylene bridge should produce an even better isopolar, isosteric analogue.

The electronegativity of carbon atoms is dependent upon the state of their hybridisation[27] and increases in the series $sp^3 < sp^2 < sp$. Consequently α,β-unsaturation has a similar electronegativity effect to α-fluorination of phosphonates.[4] α-Fluorovinylphosphonates may therefore prove to be valuable as isopolar but non-isosteric analogues of phosphate esters with a conformational restriction that could be invaluable in certain biological situations. The present study amply demonstrates the generality of a synthesis of such compounds which, moreover, can be adapted to generate chiral α-fluoroalkylphosphonates of pre-determined absolute configuration. Such species should find ready application in development of analogues of nucleotides and of glycolytic phosphates.

Experimental

M.p.s were measured on a Kofler hot stage micro melting point apparatus and are uncorrected. Low resolution mass spectra were run on the Kratos MS25, and accurate masses were obtained on a Kratos MS80 instrument, all data being processed through a Kratos DS55 data system. I.r. spectra were recorded on a Perkin-Elmer 157G grating spectrophotometer as neat oils on sodium chloride plates. ^1H N.m.r. spectra were recorded on a Perkin-Elmer R34 spectrometer at 220 MHz with tetramethylsilane as an internal reference. ^{31}P, ^{19}F, and ^{13}C N.m.r. spectra were recorded in the proton-decoupled mode except as indicated on a Jeol JNM-PS-100 spectrometer at 40.48, 94.08, and 25.14 MHz respectively. Measurement of pK_a was carried out by titration using a Radiometer Autoburette ABU12, Titrator 11, pH Meter 28, and recorded on a Titrograph SBR2c instrument. For all new compounds described, the ^1H n.m.r. spectroscopic data have been deposited and for those marked †, ^{31}P n.m.r. data have also been deposited, as a Supplementary publication [Sup. no. 56564 (15 pp)].*

Di-isopropyl 1-*Fluoroethenylphosphonate* (**3a**).—Treatment of tetraisopropyl fluoromethylenebisphosphonate (1.00 g, 2.76 mmol) at −78 °C with butyl-lithium (2.76 mmol) under dry nitrogen gas followed by paraformaldehyde (0.08 g, 2.76 mmol) added in the solid form with stirring at −78 °C gave a mixture which was rapidly brought to room temperature. Filtration and evaporation under reduced pressure, followed by Kugelrohr distillation gave the *title compound* as a colourless liquid (0.40 g, 69%), b.p. 120—130 °C (oven temperature)/13 mmHg. (Found: $M^+ - Me$, 195.0567. $C_7H_{13}FO_3P$ requires ($M - Me$), 195.0586); $\nu_{P=O}$ 1 265 cm^{-1}; $\delta_P(CDCl_3)$ 1.30 (d, $^2J_{PF}$ 102.23 Hz); δ_F ($CDCl_3$) −115.35 (ddd, $^2J_{PF}$ 102.23, $^3J_{HF(trans)}$ 50.78, $^3J_{HF(cis)}$ 20.52 Hz).

Di-isopropyl 1-*Fluoro*-3-*methylbut*-1-*enylphosphonate* (**3b**).—Treatment of tetraisopropyl fluoromethylenebisphosphonate (0.60 g, 1.72 mmol) with butyl-lithium (1.72 mmol) followed by 2-methylpropanal (0.19 g, 2.58 mmol) under the above conditions produced a crude reaction mixture. Filtration and evaporation under reduced pressure followed by Kugelrohr distillation gave the *title compound* as a colourless liquid (0.40 g, 95%), b.p. 75—85 °C (oven temperature)/0.01 mmHg; $\nu_{P=O}$ 1 261 cm^{-1}; δ_P ($CDCl_3$) 1.98 (83% P, d, *E*, $^2J_{PF}$ 102.23 Hz), and 3.26 (17% P, d, *Z*, $^2J_{PF}$ 102.23 Hz).

* For details of the Supplementary Publications Scheme see 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans. 1*, 1986, Issue 1.

(3S)-*Di-isopropyl* 1-*Fluoro*-3,4-O-*isopropylidene*-3,4-*dihydroxybut*-1-*enylphosphonate* (**3c**).—Treatment of tetraisopropyl fluoromethylenebisphosphonate (0.52 g, 1.44 mmol) with butyl-lithium (1.44 mmol) followed by freshly-prepared 2,3-*O*-isopropylidene-D-glyceraldehyde (0.25 g, 1.92 mmol) under standard conditions produced the crude reaction mixture. Centrifugation and evaporation under reduced pressure, followed by Kugelrohr distillation gave the *title compound* as a colourless, viscous oil (0.25 g, 56%), b.p. 100—130 °C (oven temperature)/0.01 mmHg; $\nu_{P=O}$ 1 265 cm^{-1}; $\delta_P(CDCl_3)$ 1.17 (91% P, d, *E*, $^2J_{PF}$ 97.65 Hz), and 1.21 (9% P, d, *Z*, $^2J_{PF}$ 97.66 Hz); $\delta_F(CDCl_3)$ −125.38 (dd, *E*, $^2J_{PF}$ 97.65, $^3J_{HF}$ 39.67 Hz).

Di-isopropyl α-*Fluorostyrylphosphonate* (**3d**).—To a solution of tetraisopropyl fluoromethylenebisphosphonate (0.50 g, 1.38 mmol) in heptane (12 ml) stirred at −78 °C under dry nitrogen, was added dropwise butyl-lithium (1.00M; 1.38 ml, 1.38 mmol). The mixture was stirred at −78 °C for 10 min then a solution of benzaldehyde (0.15 g, 1.44 mmol) in heptane (2 ml) was added dropwise. The mixture was brought rapidly to 20 °C then heated at reflux for 2 h during which time a white precipitate formed. The mixture was centrifuged and the supernatant liquid evaporated under reduced pressure. Short-path, bulb-to-bulb distillation gave the *title compound* as a colourless viscous oil (0.29 g, 73%), b.p. 120—150 °C (oven temperature)/0.01 mmHg; $\nu_{P=O}$ 1 255 cm^{-1}; $\delta_P(CDCl_3)$ 3.33 (86% P, d, *E*, $^2J_{PF}$ 96.13 Hz), and 4.69 (14% P, d, *Z*, $^2J_{PF}$ 109.87 Hz).

Di-isopropyl 1-*Fluoro*-4-*phenylbuta*-1,3-*dienylphosphonate* (**3e**).—†Treatment of tetraisopropyl fluoromethylenebisphosphonate (0.42 g, 1.15 mmol) with butyl-lithium (1.15 mmol) followed by *trans*-cinnamaldehyde (0.15 g, 1.15 mmol) under standard conditions produced the crude reaction mixture. Filtration and evaporation under reduced pressure, followed by Kugelrohr distillation gave the *title compound* as a colourless, viscous oil which crystallized on standing to give white crystals (0.24 g, 67%), m.p. 51—53 °C, b.p. 180—200 °C (oven temperature)/0.1 mmHg; $\nu_{P=O}$ 1 253 cm^{-1}; $\delta_F(CDCl_3)$ −133.72 [95% F, dd, (*E*,*E*), $^2J_{PF}$ 93.08, $^3J_{HF}$ 36.62 Hz] and −131.75 [5% F, dd, (*E*,*Z*), $^2J_{PF}$ 97.65, $^3J_{HF}$ 35.14 Hz].

Di-isopropyl 1-*Fluoro*-2-*methylprop*-1-*enylphosphonate* (**3f**).—Treatment of tetraisopropyl fluoromethylenebisphosphonate (0.42 g, 1.15 mmol) with butyl-lithium (1.15 mmol) followed by acetone (0.10 g, 1.72 mmol) under standard conditions produced the crude reaction mixture. Filtration and evaporation under reduced pressure, followed by Kugelrohr distillation gave the *title compound* as a colourless liquid (0.20 g, 73%), b.p. 60—80 °C (oven temperature)/0.01 mmHg; $\nu_{P=O}$ 1 266 cm^{-1}; $\delta_P(CDCl_3)$ 2.81 (d, $^2J_{PF}$ 105.29 Hz).

Di-isopropyl 1-*Fluoro*-2,3-*dimethylbut*-1-*enylphosphonate* (**3g**).—†Treatment of tetraisopropyl fluoromethylenebisphosphonate (0.08 g, 2.21 mmol) with butyl-lithium (2.21 mmol) followed by 3-methylbutan-2-one (0.20 g, 2.30 mmol) under standard conditions produced a crude reaction mixture. Centrifugation and evaporation of the supernatant liquid under reduced pressure followed by Kugelrohr distillation of the residue gave the *title compound* as a colourless, viscous oil (0.40 g, 68%), b.p. 80—100 °C (oven temperature)/0.05 mmHg; $\nu_{P=O}$ 1 268 cm^{-1}; $\delta_F(CDCl_3)$ −130.36 (75% F, d, *Z*, $^2J_{PF}$ 108.34 Hz), −126.70 (25% F, d, *E*, $^2J_{PF}$ 105.29 Hz).

The *E*- and *Z*-isomers of di-isopropyl 1-fluoro-2,3-dimethylbut-1-enylphosphonate (0.34 g, 1.28 mmol) were separated by h.p.l.c. (14 μm silica, 1.2 × 25 cm) using light petroleum (b.p. 60—80 °C)–ethyl acetate (1:1) as the eluant. Two fractions were obtained, which were identified as (*Z*)-di-isopropyl 1-fluoro-2,3-dimethylbut-1-enylphosphonate (fraction 1) (0.05 g, 15%), and (*E*)-di-isopropyl 1-fluoro-2,3-dimethylbut-1-enylphosphonate (fraction 2) (0.14 g, 41%).

Di-isopropyl 1-*Fluoro*-2-*phenylprop*-1-*enylphosphonate* (**3h**).—Treatment of tetraisopropyl fluoromethylenebisphosphonate (0.42 g, 1.15 mmol) with butyl-lithium (1.15 mmol) followed by acetophenone (0.14 g, 1.15 mmol) under standard conditions produced the crude reaction mixture. Filtration, evaporation under reduced pressure, and Kugelrohr distillation gave the *title compound* as a colourless, viscous oil (0.23 g, 66%), b.p. 130—140 °C (oven temperature)/0.1 mmHg; *m/z* 300 (M^+); $\nu_{P=O}$ 1 257 cm^{-1}; $\delta_P(CDCl_3)$ 2.52 (20% P, d, *Z*, $^2J_{PF}$ 112.92 Hz) and 3.53 (80% P, d, *E*, $^2J_{PF}$ 105.29 Hz); $\delta_F(CDCl_3)$ −123.59 (80% F, dq, *E*, $^2J_{PF}$ 105.29, $^4J_{HF}$ 3.90 Hz) and −120.45 (20% F, dq, *Z*, $^2J_{PF}$ 112.92, $^4J_{HF}$ 4.76 Hz).

The *E*- and *Z*-isomers of di-isopropyl 1-fluoro-2-phenylprop-1-enylphosphonate (0.40 g, 1.33 mmol) were separated by h.p.l.c. (14 μm silica, 1.2 × 25cm) using light petroleum (b.p. 60—80 °C)–ethyl acetate (2:3) as the eluant. Two fractions were obtained, which were identified as (*Z*)-di-isopropyl-1-fluoro-2-phenylprop-1-enylphosphonate (0.06 g, 15%) (fraction 1), and (*E*)-di-isopropyl-1-fluoro-2-phenylprop-1-enylphosphonate (0.10 g, 25%) (fraction 2).

1-*Fluoroethenylphosphonic Acid Cyclohexylammonium Salt* (**4a**).—Treatment of di-isopropyl 1-fluoroethenylphosphonate (0.20 g, 0.95 mmol) with bromotrimethylsilane (0.32 g, 2.10 mmol) and solvolysis with methanol provided a solution of the free phosphonic acid to which was added cyclohexylamine (0.19 g, 1.90 mmol). The resulting white precipitate was isolated, washed with ether (5 ml), and recrystallized from methanol to give the *title compound* as white crystals (0.15 g, 50%), m.p. 212—215 °C (Found: N, 8.30. $C_{14}H_{30}N_2O_3P$ requires N, 8.64%); $\delta_P(D_2O)$ 0.04 (d, $^2J_{PF}$ 94.59 Hz); $\delta_F(D_2O)$ −116.21 (ddd, $^2J_{PF}$ 94.59, $^3J_{2'\text{-}H\text{-}F}$ 56.45, $^3J_{2''\text{-}H\text{-}F}$ 25.95 Hz).

(E)-1-*Fluoro*-3-*methylbut*-1-*enylphosphonic Acid Cyclohexylammonium Salt* (**4b**).—Treatment of di-isopropyl 1-fluoro-3-methylbut-1-enylphosphonate (0.15 g, 0.60 mmol) with bromotrimethylsilane (0.22 g, 1.43 mmol) and solvolysis as above gave a methanolic solution of the free phosphonic acid to which was added cyclohexylamine (0.14 g, 1.43 mmol). A white solid precipitated immediately and was isolated and washed with ether (5 ml). A second crop was obtained from the mother liquor. Recrystallization of the combined solid product from methanol gave the *title compound* as white crystals (0.15 g, 69%), m.p. 186—189 °C (Found: P, 7.74. $C_{17}H_{36}FN_2O_3$ P·H_2O requires P, 8.05%); $\delta_P(D_2O)$ 1.24 (d, *E*, $^2J_{PF}$ 97.66 Hz).

(3S)-(E)-1-*Fluoro*-3,4-*dihydroxy*-3,4-O-*isopropylidenebut*-1-*enylphosphonic Acid Cyclohexylammonium Salt* (**4c**).—Treatment of di-isopropyl(3*S*)-1-fluoro-3,4-dihydroxy-3,4-*O*-isopropylidenebut-1-enylphosphonate (0.15 g, 0.48 mmol) with bromotrimethylsilane (0.18 g, 1.16 mmol) and solvolysis as above gave a methanolic solution of the free phosphonic acid to which was added cyclohexylamine (0.13 ml, 1.16 mmol). The mixture became warm but no precipitation occurred. Evaporation under reduced pressure left a white residue which was recrystallized from ethanol to give the *title compound* as white crystals (0.08 g, 40%), m.p. 183—185 °C (Found: P, 6.86. $C_{19}H_{38}FN_2O_5P$·H_2O requires P, 6.99%); $\delta_P(CD_3OD)$ −1.26 (d, *E*, $^2J_{PF}$ 90.03 Hz).

(E)-α-*Fluorostyrylphosphonic Acid Cyclohexylammonium Salt* (**4d**).—Bromotrimethylsilane (0.23 g, 1.54 mmol) was added dropwise *via* syringe to di-isopropyl α-fluorostyrylphosphonate (0.20 g, 0.70 mmol) and stirred at ambient temperature under dry nitrogen for 12 h, then evaporated under reduced pressure.

Methanol (2 ml) was added with stirring, followed by the dropwise addition of cyclohexylamine (0.15 g, 1.54 mmol). A white solid precipitated and was isolated and washed with ether (5 ml). A second crop was obtained by slow evaporation of the solvent from the mother liquor. Recrystallization of the combined solid product from methanol gave the *title compound* as white crystals (0.20 g, 71%), m.p. 214—216 °C (Found: C, 57.05; H, 8.5; N, 6.7. $C_{20}H_{34}FN_2O_3P{\cdot}H_2O$ requires C, 57.40; H, 8.67; N, 6.69%); $\delta_P(CD_3OD)$ −0.02 (d, *E*, $^2J_{PF}$ 90.02 Hz).

(1E,3E)-1-*Fluoro*-4-*phenylbuta*-1,3-*dienylphosphonic Acid Cyclohexylammonium Salt* (**4e**).—Treatment of di-isopropyl 1-fluoro-4-phenylbuta-1,3-dienylphosphonate (0.24 g, 0.77 mmol) with bromotrimethylsilane (0.28 g, 1.84 mmol) and solvolysis as above gave a methanolic solution of the free phosphonic acid to which was added cyclohexylamine (0.18 g, 1.85 mmol). The ensuing white precipitate was isolated, washed with ether (5 ml), and recrystallized from methanol to give the *title compound* as white crystals (0.22 g, 66%), m.p. 225—230 °C (Found: P, 7.01, $C_{22}H_{36}FN_2O_3P{\cdot}H_2O$ requires P, 6.97%); $\delta_P(CD_3OD)$ −0.43 [d, (*E*,*E*) $^2J_{PF}$ 90.02 Hz].

1-*Fluoro*-2-*methylprop*-1-*enylphosphonic Acid Cyclohexylammonium Salt* (**4f**).—Treatment of di-isopropyl 1-fluoro-2-methylprop-1-enylphosphonate (0.21 g, 0.88 mmol) with bromotrimethylsilane (0.32 g, 2.12 mmol) and solvolysis as above gave a methanolic solution of the free phosphonic acid to which was added cyclohexylamine (0.21 g, 2.12 mmol). A white precipitate was isolated and washed with ether (5 ml), and a second crop was obtained from the mother liquor. Recrystallization of the combined solid product from methanol gave the *title compound* as white crystals (0.20 g, 64%), m.p. 200—203 °C (Found: P, 8.25. $C_{16}H_{34}FN_2O_3P{\cdot}H_2O$ requires P, 8.36%; $\delta_P(CD_3OD)$ 0.64 (d, $^2J_{PF}$ 100.70 Hz).

(E)-1-*Fluoro*-2,3-*dimethylbut*-1-*enylphosphonic Acid Cyclohexylammonium Salt* (**4g**).—Treatment of di-isopropyl 1-fluoro-2,3-dimethylbut-1-enylphosphonate (0.09 g, 0.34 mmol) with bromotrimethylsilane (0.13 g, 0.83 mmol) and solvolysis as above gave a methanolic solution of the free phosphonic acid to which was added cyclohexylamine (0.7 g, 0.71 mmol). A white solid precipitated immediately and was isolated, washed with ether (2 ml), and recrystallized from methanol to give the *title compound* as white crystals (0.09 g, 70%), m.p. 190—192 °C (Found: P, 7.62. $C_{18}H_{38}FN_2O_3P{\cdot}H_2O$ requires P, 7.79%); $\delta_P(D_2O)$ 2.17 (d, *E*, $^2J_{PF}$ 111.39 Hz).

(E)-1-*Fluoro*-2-*phenylprop*-1-*enylphosphonic Acid Cyclohexylammonium Salt* (**4h**).—Treatment of di-isopropyl 1-fluoro-2-phenylprop-1-enylphosphonate (0.20 g, 0.67 mmol) with bromotrimethylsilane (0.24 g, 1.60 mmol) and solvolysis as above gave a methanolic solution of the free phosphonic acid to which was added cyclohexylamine (0.16 g, 1.60 mmol). A white solid precipitated immediately which was isolated and washed with ether (5 ml) and a second crop was obtained from the mother liquor. Recrystallization of the combined solid product from methanol gave the *title compound* as white crystals (0.20 g, 72%), m.p. 208—210 °C (Found: P, 7.16. $C_{21}H_{36}FN_2O_3P{\cdot}H_2O$ requires P, 7.16%); $\delta_P(CD_3OD)$ 0.55 (d, *E*, $^2J_{PH}$ 96.12 Hz).

Di-isopropyl 1-*Fluoroethylphosphonate* (**5a**).—A solution of di-isopropyl 1-fluoroethenylphosphonate (0.20 g, 0.95 mmol) in absolute ethanol (10 ml) containing 10% Pd–C catalyst (0.01 g) was stirred at ambient temperature under hydrogen (1 atm) until gas uptake ceased (18 h). Filtration and evaporation under reduced pressure gave the *title compound* as a colourless liquid (0.20 g, 99%), (Found: M^+, 212.0987. $C_8H_{18}FO_3P$ requires *M*, 212.0977); $\nu_{P=O}$ 1 250 cm^{-1}; $\delta_P(CDCl_3)$ 16.62 (d, $^2J_{PF}$ 79.35 Hz); $\delta_F(CDCl_3)$ −201.40 (ddq, $^2J_{PF}$ 79.35, $^2J_{HF}$ 46.54, $^3J_{HF}$ 25.94 Hz).

Di-isopropyl 1-*Fluoro*-3-*methylbutylphosphonate* (**5b**).—A solution of di-isopropyl 1-fluoro-3-methylbut-1-enylphosphonate (0.90 g, 3.60 mmol) in absolute ethanol (40 ml) containing 10% Pd–C catalyst (0.05 g) was stirred at ambient temperature under hydrogen at one atmosphere pressure until gas uptake ceased (18 h). The reaction mixture was filtered and evaporated under reduced pressure to give the *title compound* as a colourless liquid (0.90 g, 99%) (Found: MH^+ 255.1494. $C_{11}H_{24}FO_3P{\cdot}H^+$ requires *MH* 255.1525); $\nu_{P=O}$ 1 258 cm^{-1}; $\delta_P(CDCl_3)$ 16.92 (d, $^2J_{PF}$ 79.35 Hz); $\delta_F(CDCl_2)$ − 208.49 (m).

Di-isopropyl 1-*Fluoro*-3,4-*dihydroxy*-3,4-O-*isopropylidenebutylphosphonate* (**5c**).—† A solution of (3*S*)-di-isopropyl 1-fluoro-3,4-dihydroxy-3,4-*O*-isopropylidenebut-1-enylphosphonate (0.40 g, 1.28 mmol) in absolute ethanol (13 ml) containing 10% Pd–C catalyst (0.02 g) was stirred at ambient temperature under hydrogen (1 atm) until gas uptake ceased (18 h). Filtration and evaporation under reduced pressure gave the *title compound* as a colourless viscous liquid (0.40 g, 99%); $\nu_{P=O}$ 1 252 cm^{-1}; $\delta_F(CDCl_3)$ − 211.45 (34% F, m), −206.65 (66% F, dddd, $^2J_{PF}$ 76.30, $^2J_{2'\text{-}H\text{-}F}$ 47.61, $^3J_{2'\text{-}H\text{-}F}$ 30.52, $^3J_{2''\text{-}H\text{-}F}$ 23.30 Hz).

Di-isopropyl 1-*Fluoro*-2-*methylpropylphosphonate* (**5f**).—† A solution of di-isopropyl 1-fluoro-2-methylprop-1-enylphosphonate (0.60 g, 2.52 mmol) in absolute ethanol (20 ml) containing 10% Pd–C catalyst (0.03 g) was stirred at ambient temperature under hydrogen (4 atm) for 17 days. Filtration and evaporation under reduced pressure gave a colourless liquid (0.60 g). ^{31}P n.m.r. analysis showed starting material (40%) to be still present. Purification by column chromatography (Silica H, 1.5 × 25 cm) using dichloromethane–ethyl acetate (4:1) as the eluant gave the *title compound* as a colourless liquid (0.20 g, 33%); $\nu_{P=O}$ 1 254 cm^{-1}; $\delta_C(CDCl_3)$ 17.62 (pseudo-t, *Me*CH, $^3J_{CF}$ 7.63, $^3J_{CP}$ 7.63 Hz), 18.99 (pseudo-t, *Me*$_2$CH, $^3J_{CF}$ 6.48, $^3J_{CP}$ 6.48 Hz), 23.87 (m, *Me*$_2$CHO), 29.51 (dd, Me*C*HCFP $^2J_{CF}$ 19.83, $^2J_{CP}$ 2.00 Hz), 71.04 (d, Me$_2$*C*HO, $^2J_{CP}$ 6.87 Hz), 71.50 (d, Me$_2$*C*HO, $^2J_{CP}$ 7.63 Hz), and 93.29 (dd, $^1J_{CF}$ 182.34, $^1J_{CP}$ 169.37 Hz).

Di-isopropyl 1-*Fluoro*-2,3-*dimethylbutylphosphonate* (**5g**).—A solution of di-isopropyl 1-fluoro-2,3-dimethylbut-1-enylphosphonate (0.30 g, 1.13 mmol) in absolute ethanol (10 ml) containing 10% Pd–C catalyst (0.02 g) was stirred at ambient temperature under hydrogen (4 atm) for 96 h. Filtration, and evaporation under reduced pressure gave the *title compound* as a colourless liquid (0.30 g, 99%) (Found: MH^+ 269.1689. $C_{12}H_{26}FO_3P{\cdot}H^+$ requires *M*H, 269.1682); $\nu_{P=O}$ 1 254 cm^{-1}; $\delta_P(CDCl_3)$ 16.75 [75% P, d, (*R*,*R*) + (*S*,*S*), $^2J_{PF}$ 80.87 Hz] and 17.06 [25% P, d, (*R*,*S*) + (*S*,*R*), $^2J_{PF}$ 80.87 Hz]; $\delta_F(CDCl_3)$ − 218.10 [75% P, ddd, (*R*,*R*) + (*S*,*S*), $^2J_{PF}$ 80.87, $^2J_{HF}$ 45.78, $^3J_{HF}$ 31.28] and −205.98 [25% P, ddd, (*R*,*S*) + (*S*,*R*) $^2J_{PF}$ 80.87, $^2J_{HF}$ 46.54, $^3J_{HF}$ 11.45 Hz].

Pure (*E*)-di-isopropyl 1-fluoro-2,3-dimethylbut-1-enylphosphonate (0.14 g, 0.52 mmol) was hydrogenated under the above conditions for 5 days. Filtration, and evaporation under reduced pressure gave a colourless liquid (0.14 g). ^{19}F N.m.r. analysis showed that starting material (40%) was still present. This analysis also showed, however, that only one of the two possible diastereoisomeric forms of the hydrogenated material had been produced; $\delta_F(CDCl_3)$ − 218.10 [60% F, ddd, (*R*,*R*) + (*S*,*S*), $^2J_{PF}$ 80.87, $^2J_{HF}$ 45.78, $^3J_{HF}$ 31.28 Hz] and −130.36 (40% F, d, *E*, $^2J_{PF}$ 108.34 Hz).

Pure (*Z*)-di-isopropyl 1-fluoro-2,3-dimethylbut-1-enylphosphonate (0.05 g, 0.19 mmol) was hydrogenated under the above conditions for 14 days with several renewals of the catalyst.

After this time ^{19}F n.m.r. analysis showed that only 10% of the starting material had been hydrogenated. This was sufficient to show that only one of the possible diastereoisomeric forms of the hydrogenated material had been produced; $\delta_F(CDCl_3)$ −205.98 [10% F, ddd, (*R*,*S*) + (*S*,*R*), $^2J_{PF}$ 80.87, $^2J_{PF}$ 46.54, $^3J_{HF}$ 11.45 Hz] and −126.70 (90% F, d, *Z*, $^2J_{PF}$ 105.29 Hz).

Di-isopropyl α-Fluorophenethylphosphonate (**5d**).—A solution of di-isopropyl α-fluorophenethylphosphonate (0.90 g, 3.15 mmol) in ethanol (30 ml) containing 10% Pd–C catalyst was stirred at ambient temperature under hydrogen (1 atm) until gas uptake ceased (18 h). Filtration, and evaporation under reduced pressure gave a colourless liquid (0.90 g). ^{31}P N.m.r. analysis showed the presence of two products; a major fluorine-containing one (59%) and a minor, fluorine-free species (41%); $\delta_P(CDCl_3)$ 16.58 (59% P, d, $^2J_{PF}$ 76.29 Hz) and 29.84 (41% P, s). Column chromatography (Silica H, 1.5 × 25 cm) using dichloromethane–ethyl acetate (4:1) as the eluant gave the *title compound* as a colourless liquid (0.30 g, 33%); $\nu_{P=O}$ 1 255 cm^{-1}.

Pure di-isopropyl α-fluorophenethylphosphonate (0.06 g, 0.21 mmol) was subjected to the above hydrogenation conditions for 24 h and worked up as before. ^{31}P N.m.r. analysis showed that no further loss of fluorine had occurred.

Di-isopropyl 1-Fluorophenylpropylphosphonate (**5h**).—A solution of di-isopropyl 1-fluoro-2-phenylprop-1-enylphosphonate (0.50 g, 1.67 mmol) in absolute ethanol containing 10% Pd–C catalyst was stirred at ambient temperature under hydrogen (4 atm) for days when ^{31}P n.m.r. analysis showed that no starting material remained. Filtration and evaporation under reduced pressure gave a colourless liquid (0.50 g). ^{31}P N.m.r. analysis showed the presence of two products; a major fluorine-containing one (59%) and a minor fluorine-free species (41%); $\delta_P(CDCl_3)$ 15.17 (59% P, d, $^2J_{PF}$ 79.35 Hz) and 28.53 (41% P, s). Column chromatography (Silica H, 1.5 × 25 cm) using dichloromethane–ethyl acetate (4:1) as the eluant gave the *title compound* as a colourless liquid (0.10 g, 20%) (Found: MH^+, 303.1530. $C_{15}H_{24}FO_3P{\cdot}H^+$ requires MH 303.1526); $\nu_{P=O}$ 1 250 cm^{-1}; $\delta_F(CDCl_3)$ −211.64 [80% F, ddd, (*R*,*R*) + (*S*,*S*), $^2J_{PF}$ 81.79, $^2J_{HF}$ 45.78, $^3J_{HF}$ 24.42] and −203.97 [20% F, ddd, (*R*,*S*) + (*S*,*R*), $^2J_{PF}$ 78.73, $^2J_{HF}$ 45.78, $^3J_{HF}$ 17.70 Hz].

A second fraction was also obtained which was identified as di-isopropyl 2-phenylpropylphosphonate† (0.10 g, 21%); *m*/*z* 284 (M^+); $\delta_C(CDCl_3)$ 24.06 (s, Me_2CHO), 25.69 (s, *Me*), 35.04 (d, PC*C*Ph, $^2J_{CP}$ 5.50 Hz), 35.74 (d, P*C*CPh, $^1J_{CP}$ 139.62 Hz), 69.92 (d, Me_2CHO, $^2J_{CP}$ 6.10 Hz), 126.32 (s, *p*-C), 126.74 (s, *o*-(*m*)-C), 128.50 (s, *m*-(*o*)-C), and 146.91 (s, *ipso*-C).

The reaction was repeated on the same scale under the same conditions as above using 5% Pd–C catalyst. ^{31}P N.m.r. analysis of the crude product showed the same proportions of fluorine-containing and fluorine-free products as above and ^{19}F n.m.r. analysis showed the same diastereoisomeric ratio as above. The products were separated by h.p.l.c. (14 μm silica gel, 1.2 × 25 cm), using light petroleum (b.p. 60—80 °C)–ethyl acetate (3:2) as the eluant, to give three fractions which were identified as di-isopropyl 2-phenylpropylphosphonate (0.08 g, 17%) (fraction 1) (*R*,*S*)- and (*S*,*R*)-di-isopropyl 1-fluoro-2-phenylpropylphosphonate (0.06 g, 12%) (fraction 2), and (*R*,*R*)- and (*S*,*S*)- di-isopropyl 1-fluoro-2-phenylpropylphosphonate (0.10 g, 20%) (fraction 3).

Pure (*E*)-di-isopropyl-1-fluoro-2-phenylprop-1-enylphosphonate (0.10 g, 0.33 mmol) was hydrogenated under the above conditions (10% Pd–C) for 6 days. Filtration and evaporation under reduced pressure gave a colourless liquid (0.10 g), δ_P 15.17 [d, (*R*,*R*) + (*S*,*S*), $^2J_{PF}$ 81.79 Hz] and 28.53 (s); $\delta_F(CDCl_3)$ −211.64 [ddd, (*R*,*R*) + (*S*,*S*), $^2J_{PF}$ 81.79, $^2J_{HF}$ 45.78, $^3J_{HF}$ 24.42 Hz].

Pure (*Z*)-di-isopropyl 1-fluoro-2-phenylprop-1-enylphosphonate (0.06 g, 0.20 mmol) was hydrogenated under the above conditions (10% Pd–C) for 6 days. Filtration and evaporation under reduced pressure gave a colourless liquid (0.06 g); δ_P 15.17 [d, (*R*,*S*) + (*S*,*R*), $^2J_{PF}$ 78.73 Hz] and 28.53 (s); $\delta_F(CDCl_3)$ −203.97 [ddd, (*R*,*S*) + (*S*,*R*), $^2J_{PF}$ 78.73, $^2J_{HF}$ 45.78, $^3J_{HP}$ 17.70 Hz].

Di-isopropyl 1-Fluoro-4-phenylbutylphosphonate (**5e**).—A solution of di-isopropyl 1-fluoro-4-phenylbuta-1,3-dienylphosphonate (0.25 g, 0.80 mmol) in absolute ethanol (75 ml) containing 10% Pd–C catalyst was stirred at ambient temperature under hydrogen (1 atm) for 18 h. Filtration and evaporation under reduced pressure gave a colourless liquid (0.25 g). ^{31}P N.m.r. analysis showed three products in the proportions 46%, 46%, and 8%. The two major *products* were the partially- and fully-reduced species while the minor product was fluorine-free; $\delta_P(CDCl_3)$ 2.73 (46% P, d, *E*, $^2J_{PF}$ 102.24 Hz), 16.21 (46% P, d, $^2J_{PF}$ 76.29 Hz), and 30.38 (8% P, s); $\delta_F(CDCl_3)$ −208.62 (50% F, m) and −129.63 (50% F, dd, *E*, $^2J_{PF}$ 102.24, $^3J_{HF}$ 39.06 Hz); g.c.–m.s. (column OV225) R_t 8.00 min [*m*/*z*, 314 ($C_{16}H_{24}FO_3P$)] and 9.16 [*m*/*z*, 316. ($C_{16}H_{26}FO_3P$)].

Exposure to the above hydrogenation conditions for a further 7 days followed by column chromatography (Silica H, 1.5 × 25 cm) using dichloromethane–ethyl acetate (4:1) as the eluant gave the *title compound* as a colourless, viscous oil (0.13 g, 51%); $\nu_{P=O}$ 1 250 cm^{-1}; $\delta_P(CDCl_3)$ 16.21 (d, $^2J_{PF}$ 76.29 Hz); $\delta_F(CDCl_3)$ −208.62 (m).

1-*Fluoro*-3-*methylbutylphosphonic Acid Biscyclohexylammonium Salt* (**6b**).—Treatment of di-isopropyl 1-fluoro-3-methylbutylphosphonate (0.30 g, 1.18 mmol) with bromotrimethylsilane (0.40 g, 2.61 mmol) and solvolysis as above gave a methanolic solution of the free phosphonic acid to which was added cyclohexylamine (0.25 g, 2.52 mmol). A white precipitate formed immediately, which was isolated, washed with ether (5 ml), and recrystallized from methanol to give the *title compound* as white crystals (0.30 g, 69%), m.p. 200—202 °C (Found: C, 53.25; H, 10.4; N, 7.5. $C_{17}H_{38}FN_2O_3P{\cdot}H_2O$ requires C, 52.83; H, 10.43; N, 7.25%); $\delta_P(D_2O)$ 13.15 (d, $^2J_{PF}$ 64.09 Hz).

1-*Fluoro*-3,4-*dihydroxy*-3,4-O-*isopropylidenebutylphosphonic Acid Biscyclohexylammonium Salt* (**6c**).—Treatment of di-isopropyl 3(*S*)-1-fluoro-3,4-dihydroxy-3,4-*O*-isopropylidenebutylphosphonate (0.20 g, 0.64 mmol) with bromotrimethylsilane (0.22 g, 1.44 mmol) and solvolysis as above gave a methanolic solution of the free phosphonic acid to which was added cyclohexylamine (0.14 g, 1.41 mmol). The solution was evaporated under reduced pressure to give a white, exceedingly hygroscopic solid (0.20 g), possibly of mixed isomeric composition. (Found: N, 6.25. $C_{19}H_{41}FN_2O_3P$ requires N, 6.56%); $\delta_P(CD_3OD)$ 11.9 (d, $^2J_{PF}$ 64.0 Hz).

1-*Fluoro*-4-*phenylbutylphosphonic Acid Biscyclohexylammonium Salt* (**6e**).—Treatment of di-isopropyl 1-fluoro-4-phenylbutylphosphonate (0.16 g, 0.51 mmol) with bromotrimethylsilane (0.17 g, 1.11 mmol) and solvolysis as above gave a methanolic solution of the free phosphonic acid to which was added cyclohexylamine (0.10 g, 1.02 mmol). The solution was evaporated under reduced pressure to give a solid. Recrystallization from methanol gave the *title compound* as white crystals (0.11 g, 50%), m.p. 192—195 °C, (Found: N, 5.89. $C_{22}H_{40}FN_2O_3P$ requires N, 6.24%); $\delta_P(D_2O)$ 12.59 (d, $^2J_{PF}$ 64.08 Hz).

1-*Fluoro*-2-*methylpropylphosphonic Acid Biscyclohexylammonium Salt* (**6f**).—Treatment of di-isopropyl 1-fluoro-2-methylpropylphosphonate (0.12 g, 0.50 mmol) with bromotrimethylsilane (0.19 g, 1.23 mmol) and solvolysis as above gave

a methanolic solution of the free phosphonic acid to which was added cyclohexylamine (0.10 g, 1.01 mmol). The solution was evaporated under reduced pressure to give a solid. Recrystallization from ethanol gave the *title compound* as white crystals (0.09 g, 51%), m.p. 185—188 °C, (Found: N, 7.49. $C_{17}H_{28}FN_2O_3P$ requires N, 7.60%), $\delta_P(D_2O)$ 15.47 (d, $^2J_{PF}$ 77.82 Hz).

1-*Fluoro*-2-*phenylpropylphosphonic Acid Biscyclohexylammonium Salt* (**6h**).—Bromotrimethylsilane (0.12 g, 0.77 mmol) was added dropwise *via* syringe to di-isopropyl 1-fluoro-2-phenylpropylphosphonate (0.10 g, 0.33 mmol) and stirred under dry nitrogen for 4 h, then evaporated *in vacuo*, and treated with methanol (2 ml). Cyclohexylamine (0.07 g, 0.71 mmol) was then added dropwise with stirring. The solution was evaporated under reduced pressure to give a solid. Recrystallization of this from ethanol gave the *title compound* as white crystals (0.07 g, 51%), m.p. 211—213 °C, (Found: C, 59.95; H, 9.45; N, 6.9. $C_{21}H_{38}FN_2O_3P$ requires C, 60.57; H, 9.13; N, 6.73%); $\delta_P(D_2O$–$CD_3OD)$ 12.23 (50% P, d, $^2J_{PF}$ 71.72 Hz), 12.46 (50% P, d, $^2J_{PF}$ 71.72 Hz); $\delta_F(D_2O)$ −215.42 [50% F, ddd, (*R*,*R*) + (*S*,*S*) $^2J_{PF}$ 71.72, $^2J_{HF}$ 45.77, $^3J_{HF}$ 32.04 Hz] and −195.00 [50% F, ddd, (*R*,*S*) + (*S*,*R*), $^2J_{PF}$ 71.72, $^2J_{HF}$ 45.77, $^3J_{HF}$ 10.68 Hz].

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