The Synthesis of α-Fluoroalkylphosphonates

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A general synthesis of functionalized α-fluoroalkylphosphonates is provided by reaction of the dialkyl fluoromethylphosphonate carbanion with aldehydes, ketones, alkyl halides, silyl halides, and acyl halides. Further transformation of the primary products expands the scope of the synthetic method.

The α-fluorination of phosphonates has been shown[1-4] to reduce the disparity in important physical properties between alkylphosphonates and phosphates, leading to isopolar, isoteric analogues of biological phosphates.[4] In our continuing studies on the synthesis of α-fluoroalkylphosphonates we here describe a general synthesis of these molecules from dialkyl fluoromethylphosphonate (**1**).

Recent reports[5,6] have described the elaboration of the phosphonate skeleton of dialkyl difluoromethylphosphonate using carbanion-type chemistry. However no work of this type has been reported using fluoromethylphosphonate esters (**1**). These ought to provide general access to a wide range of α-fluoroalkylphosphonates. At the outset of this study, dialkyl fluoromethylphosphonates were readily available *via* a Michaelis-Becker synthesis using chlorofluoromethane. This Freon has now been withdrawn from commercial production on account of its toxic properties and an alternative source of this phosphonate precursor has been devised. A preliminary account of parts of this work has already appeared.[7]

Results and Discussion

It proved best to employ di-isopropyl fluoromethylphosphonate[8] (**1**) throughout this work because the diethyl ester was less readily available from the Michaelis-Becker reaction of the dialkylphosphite with chlorofluoromethane. Treatment of the phosphonate (**1**) with LDA at low temperature produces the lithiated carbanion (**2**), which is more stable than the lithiated carbanion[6] of difluoromethylphosphonate, and can be used in reactions at temperatures in the range −78—0 °C. The carbanion (**2**) adds to a variety of aldehydes and ketones leading to α-fluoro-β-hydroxyalkylphosphonates (**5**)—(**10**) (Scheme 1). The reaction time and quenching temperature must be carefully controlled since analysis of reaction mixtures by ^{31}P n.m.r. spectroscopy indicated that heating or prolonged stirring at room temperature resulted in the onset and eventual completion of a subsequent Wadsworth-Emmons reaction resulting in a fluoroalkene.

Two new chiral centres are created in the formation of the α-fluoro-β-hydroxyalkylphosphonates (**5**)—(**10**). The diastereoisomers can be easily distinguished by ^{31}P and ^{19}F n.m.r. spectroscopy but are not usually separable by column chromatography (Table). Addition of compound (**2**) to the chiral aldehyde 2,3-*O*-isopropylidene-D-glyceraldehyde to produce (**6**) showed a useful degree of diastereoface selectivity to generate a 5:2 ratio of the C-2 epimers. There appeared to be no discrimination at C-1 where equal amounts of *R* and *S*-epimers were formed. The addition to 1,2:5, 6-di-O-isopropylidene-α-D-*ribo*-hexofuran-3-ulose was diastereoface specific for the ketone from the β-face and resulted in the production of only two of the possible four diastereoisomers of the product (**10**). These can be assigned the *allo*-configuration resulting from addition to the less-hindered *si*-face of the ketone[9] but generating equal amounts of the epimers at the phosphonate α-carbon.†

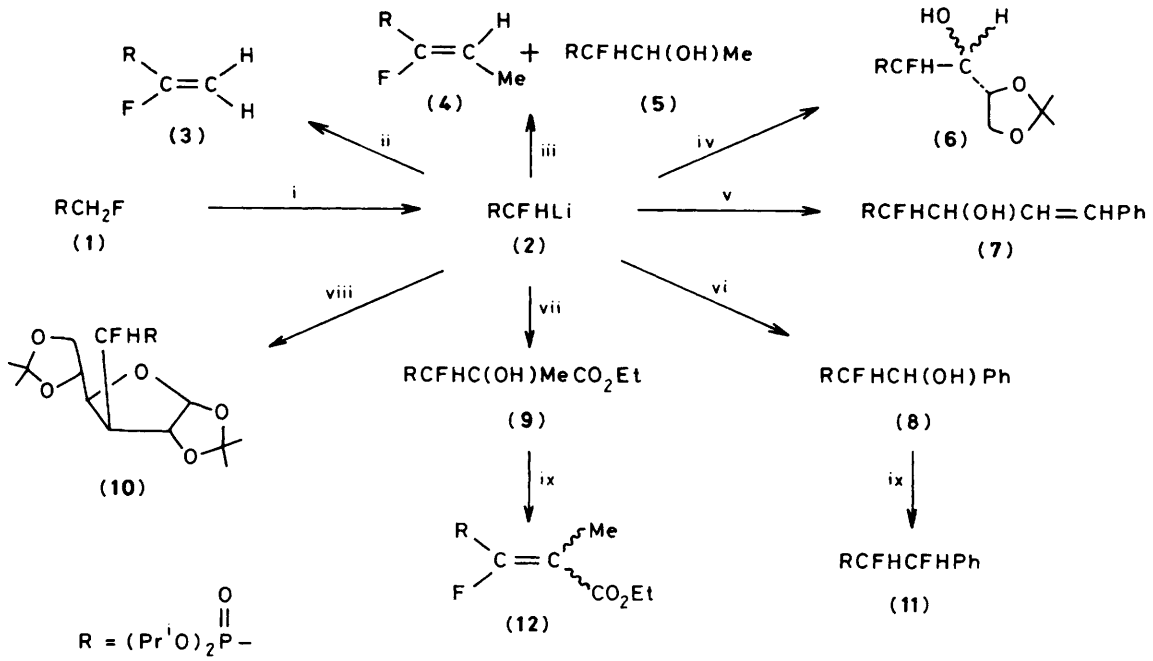
From the reaction of compound (**2**) with paraformaldehyde, none of the expected α-fluoro-β-hydroxyalkylphosphonate, could be isolated and the sole product, was the α-fluorovinylphosphonate (**3**). Similarly, reaction of compound (**2**) with acetaldehyde gave a minor proportion of vinylphosphonate (**4**) together with the expected β-hydroxy product (**5**) (Scheme (1). Since no dehydration was observed to accompany the formation of products (**7**), (**8**), or (**9**), where conjugated double bonds could be formed by dehydration, the size of the β-substituents appears to determine whether or not dehydration occurs. It seems unlikely that this behaviour is under kinetic control of deprotonation at the α-CH group but rather more so that a conformational factor or impedance of stabilization of the β-oxygen by the phosphonate group is responsible.

The carbanion (**2**) can also participate in various substitution reactions. Treatment of (**2**) with 3-chlorobutan-2-one gave the β,γ-epoxy-α-fluoroalkylphosphonate (**13**) by a Darzens-type reaction (Scheme 2). Acylation of (**2**) using benzoyl chloride occurred smoothly to give the α-fluoro-β-oxoalkylphosphonate (**14a**) which, interestingly, exists exclusively as a *E*/*Z* mixture of enol forms (**14b**). Products of this nature may be useful analogues of acyl phosphates, *e.g.* acetyl phosphate. Methylation of the anion (**2**) with dimethyl sulphate gives (**16**) and alkylation with allyl bromide provides the α-fluoro-γ,δ-unsaturated phosphonate (**15**). On treatment of (**2**) with bromo- or chloro-trimethylsilane the silylated species (**17**) is formed initially. This product is now more acidic than compound (**1**), resulting in a facile trans-protonation of the sort which has been encountered elsewhere in this field.[2] The resulting phosphonate silyl carbanion can then undergo further silylation to give compound (**19**). The crude product is thus unavoidably a mixture of compounds (**1**), (**17**), and (**19**) which could not be usefully separated. The results of these addition and substitution reactions are summarized below (Table and Scheme 2).

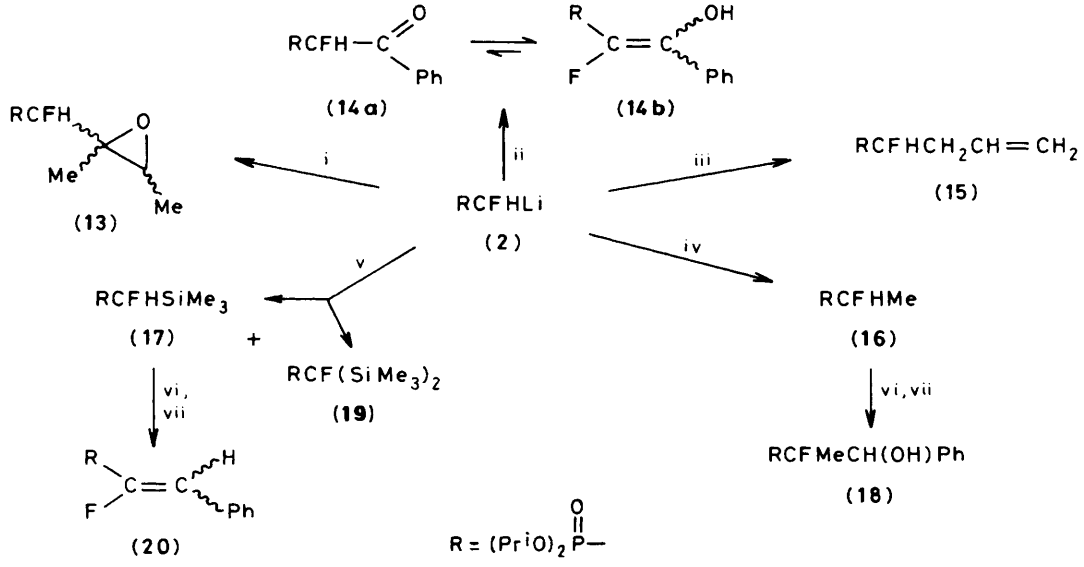
Further elaboration of the primary products was achieved, increasing the range and variety of α-fluoroalkylphosphonates for which (**1**) is a synthon. The silylated derivative (**17**) was employed in a Peterson-type[10] alkenation with benzaldehyde, leading to the α-fluorovinylphosphonate (**20**) (Scheme 2). The product (**20**) from this route usefully contained a higher proportion of the *Z*-isomer than that prepared by Wadsworth-Emmons condensation.[11] The Peterson reaction has previously been used for the separate introduction of the phosphonate group[12,13] or a halogen atom[14] but has not hitherto been used to combine both processes.

The methylated product (**16**) was treated with LDA and the

† The basis for the diastereoisomeric assignments is discussed in the preceding paper.



Scheme 1. *Reagents:* i, LDA–THF, −78 °C; ii, $(CH_2O)_n$; iii, MeCHO; iv, $RCH_2OCMe_2OCHCHO$; v, PhCH=CHCHO; vi, PhCHO; vii, $MeCOCO_2Et$; viii, 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuran-3-ulose; ix, DAST.



Scheme 2. *Reagents:* i, MeCOCHClMe; ii, PhCOCl; iii, CH_2=$CHCH_2Br$; iv Me_2SO_4; v, Me_3SiCl or Me_3SiBr; vi LDA–THF, −78 °C; vii, PhCHO

resulting carbanion reacted with benzaldehyde to give the secondary phosphonate (**18**) (Scheme 2). A small degree of stereoselectivity was observed in this addition (Scheme 2, Table).

As an extension of previous studies in this laboratory,[1] the α-fluoro-β-hydroxyalkylphosphonate (**8**) was treated with diethylaminosulphur trifluoride (DAST) to afford the α,β-difluoroalkylphosphonate (**11**) (Scheme 1). Similar treatment of the tertiary alcohol (**9**) with DAST, however, caused dehydration[15] and gave an *E*/*Z* mixture of the α-fluorovinylphosphonate (**12**) as the sole product (Scheme 1).

This work describes a valuable preparative route to a range of analogues of phosphate esters of biological importance. It demonstrates that diastereoisomeric specificity can be attained for the new chiral centre at C-2 of the phosphonate but it is not capable of any stereoselectivity for the fluorine-bearing C-1 chiral centre. Clearly, novel phosphonates of a chiral nature must be generated to resolve this limitation of the present methodology.

At this point in the investigation, the requisite starting material, chlorofluoromethane (Freon 31) ceased to be commercially available in Europe and in the USA, possibly on account of its toxic properties. In a search for an alternative source of the synthon (1), the di-isopropyl (**21a**) and diethyl (**21b**) esters of chlorofluoromethylphosphonate were prepared from dichlorofluoromethane (Freon 21) in the expectation that these would generate carbanions (**2**) by dechlorination with

Table. Yields, isomer ratios, ^{31}P and ^{19}F n.m.r. chemical shifts, and $^{2}J_{PF}$ coupling constants for various α-fluorophosphonates

Product	Yield (%)	Ratio of diastereoisomers (*E*/*Z* ratio)	δ_P[a] (p.p.m.)	δ_F[b] (p.p.m.)	$^{2}J_{PF}$ (Hz)
(3)	19		1.3	−115.3	102.2
(4)		(1:0)	2.6	−131.6	100.7
(5)		1:1	14.6, 14.9	−147.4, −142.5	79.3, 74.6
(6)	34	5:5:2:2	13.8, 14.9, 13.8, 14.9	−229.5, −213.6, −221.2, −211.9	77.8, 80.9, 76.3, 76.3
(7)	30	1:1	14.0, 14.5	−217.0, −211.0	77.8, 74.8
(8)	46	1:1	14.0, 14.9	−217.1, −208.0	80.9, 73.2
(9)	36	1:1	12.4, 13.2	−219.0, −207.5	74.8, 79.3
(10)	15	1:1:0:0	12.8, 13.9	−216.2, −212.8	77.8, 70.2
(11)	65	1:1	11.4, 11.6	α-F, −216.3;[c] β-F, −183.7, −178.9	74.8, 77.8
(12)	49	(3:2)	−0.1, 1.0	−121.4, −112.1	99.2, 100.7
(13)	46	12:12:3:2	11.8, 11.8, 13.0, 13.4	−146.2, −142.9, −142.8, 136.5	82.4, 82.4, 76.3, 80.9
(14b)	46	(4:3)	0.7, 1.0	−145.5, −132.1	90.0, 91.5
(15)	45		15.5	−208.1	75.5
(15)	45		15.5	−208.1	75.5
(16)	60		16.6	−201.4	79.3
(17)	40,[d] 30[e]		19.3		61.0
(18)	44	5:4	18.9, 17.8	−169.7, −184.2	82.4, 96.1
(19)	30,[d] 40[e]		22.8		65.6
(20)	100[f]	(1:1)	1.5, 3.2	−114.0, −125.8	109.9, 96.1

[a] Downfield relative to external 85% H_3PO_4. [b] Dowfield relative to external $CFCl_3$. [c] Overlapping signals. [d] Spectroscopic yield from Me_3SiBr. [e] Spectroscopic yield from Me_3SiCl. [f] Spectroscopic yield.

butyl-lithium, as has been accomplished for esters of dichloromethylene bisphosphonate.[16] In our hands, the reaction of n-butyl-lithium with the esters (21) at −78 °C resulted in deprotonation only and attempts to trap the carbanion generated did not lead to simple substitution products.[17] At temperatures above −50 °C this carbanion is unstable and fragments, probably by loss of chlorofluorocarbene.[17] It has, however, proved possible to reduce the ester (**21a**) to compound (**1**) by means of tributyltin hydride under radical conditions. The pursuit of this alternative route to (**1**) will be described elsewhere.[18]

Experimental

Chlorofluoromethane was obtained from Fluorochem Ltd, Glossop, and di-isopropyl phosphite from Aldrich Chemicals. Melting points were measured on a Kofler hot stage apparatus and are uncorrected. High resolution mass spectra were run on a Kratos MS80 with data processing on a Kratos DS55 system. I.r. spectra were recorded on a Perkin-Elmer 157G spectrophotometer as neat liquids. ^{1}H N.m.r. spectra were obtained at 220 MHz with a Perkin-Elmer R34 machine; ^{19}F and ^{31}P spectra were recorded on a Jeol JNM-PS-100 n.m.r. spectrometer at 94.08 and 40.48 respectively with ^{31}P spectra run in the proton decoupled mode. Standard solvents and liquid reagents were distilled prior to use.

Di-isopropyl α-Fluoro-β-hydroxyphenethylphosphonate (**8**).—To a solution of di-isopropylamine (0.51 g, 5.04 mmol) in dry tetrahydrofuran (10 ml), stirred at 0 °C under dry nitrogen, was added butyl-lithium (1.69M; 3.40 ml, 5.76 mmol). To the resulting solution of lithium di-isopropylamide stirred at −78 °C under dry nitrogen was added dropwise di-isopropyl-fluoromethylphosphonate[8] (1.00 g, 5.04 mmol). Freshly distilled benzaldehyde (0.54 g, 5.05 mmol) was added dropwise to the stirred mixture at −78 °C. The reaction mixture was brought slowly to ambient temperature and then quenched with water (4 ml). The organic layer was separated and the aqueous layer extracted with ether (3 × 10 ml). The combined organic fractions were dried (anhydrous $MgSO_4$), filtered, and evaporated under reduced pressure to give a pale yellow viscous oil (1.12 g). Kugelrohr distillation gave the *title compound* as a colourless viscous oil (0.70 g, 46%), b.p. 180—200 °C (oven temperature)/0.01 mmHg (Found: M^+, 304.1273. $C_{14}H_{22}FO_4P$ requires *M*, 304.1240); $\nu_{P=O}$ 1 237 and ν_{O-H} 3 320 cm^{-1}; $\delta_H(CDCl_3)$ 1.30 (12 H, m), 4.25 (1 H, br s, OH), 4.52—4.88 (3 H, m), 5.00—5.22 (1 H, m), and 7.40 (5 H, m); $\delta_P(CDCl_3)$ 14.04 [50% P, d, (*R*,*R*) + (*S*,*S*), $^{2}J_{PF}$ 80.87 Hz] and 14.93 [50% P, d, (*R*,*S*) + (*S*,*R*), $^{2}J_{PF}$ 73.24 Hz]; $\delta_F(CDCl_3)$ −217.14 [50% F, ddd, (*R*,*R*) + (*S*,*S*), $^{2}J_{PF}$ 80.87, $^{2}J_{HF}$ 45.01, $^{3}J_{HF}$ 22.89 Hz] and −207.98 [50% F, ddd, (*R*,*S*), + (S,R), $^{2}J_{PF}$ 73.24, $^{2}J_{HF}$ 45.01, $^{3}J_{HF}$ 10.68 Hz].

Di-isopropyl 1-Fluoro-2-hydroxy-4-phenylbut-3-enylphosphonate (**7**).—Lithium di-isopropylamide (5.04 mmol) and di-isopropyl fluoromethylphosphonate (1.0 g, 5.04 mmol) were combined with *trans*-cinnamaldehyde (0.66 g, 5.04 mmol) in dry tetrahydrofuran (12 ml) under the above conditions. Column chromatography (Silica H, 1.5 × 25 cm) of the crude product using dichloromethane–ethyl acetate (4:1) as the eluant gave the *title compound* as a colourless, viscous oil (0.05 g, 30%) (Found: M^+, 330.1392. $C_{16}H_{24}FO_4P$ requires *M*, 330.1397); $\nu_{P=O}$ 1 240 and ν_{O-H} 3 350 cm^{-1}; $\delta_H(CDCl_3)$ 1.43 (12 H, d, $^{3}J_{HH}$ 7 Hz), 4.30 (1 H, br s, OH), 4.65 (1 H, ddd, 1-H, $^{2}J_{HF}$ 44, $^{3}J_{HH}$ 7, $^{2}J_{PH}$ 5 Hz), 4.79 (3 H, m), 6.32 (1 H, d-pseudo-t, 3-H, $^{3}J_{3,4}$ 16, $^{3}J_{2,3}$ 7, $^{4}J_{HF}$ 7 Hz), 6.76 (1 H, d, 4-H, $^{3}J_{3,4}$ 16 Hz), and 7.30 (5 H, m); $\delta_P(CDCl_3)$ 14.00 [50% P, d, (*R*,*R*) + *S*,*S*), $^{2}J_{PF}$ 77.82 Hz] and 14.53 [50% P, d, (*R*,*S*) + (*S*,*R*), $^{2}J_{PF}$ 74.77 Hz]; $\delta_F(CDCl_3)$ − 216.96 [50% F, ddd, (*R*,*R*) + (*S*,*S*), $^{2}J_{PF}$ 77.82, $^{2}J_{HF}$ 43.95, $^{3}J_{HF}$ 21.97 Hz] and −210.99 [50% F, ddd, (*R*,*S*) + (*S*,*R*), $^{2}J_{PF}$ 74.77, $^{2}J_{HF}$ 43.95, $^{3}J_{HF}$ 14.65 Hz].

Ethyl 3-(O,O-Di-isopropylphosphono)-3-fluoro-2-hydroxy-2-methylpropanoate (**9**).—Di-isopropyl fluoromethylphosphonate (1.00 g, 5.04 mmol) was combined with ethyl pyruvate (0.58 g, 5.04 mmol) under the standard conditions. Kugelrohr distillation of the crude organic product gave the title *compound* as a colourless, viscous oil (0.51 g, 36%), b.p. 160—180 °C (oven temperature)/0.1 mmHg (Found: MH^+, 315.1378. $C_{12}H_{24}FO_6P{\cdot}H^+$ requires *M*H, 315.1373); $\nu_{P=O}$ 1 250 and ν_{O-H} 3 320 cm^{-1}; $\delta_H(C_6D_6)$ 1.30 (15 H, m), 1.68 (1.5 H, s), 1.80 (1.5 H, s), 4.13 (1 H, q, $^{3}J_{HH}$ 8 Hz), 4.19 (1 H, q, $^{3}J_{HH}$ 8 Hz), 4.73 (2 H, m),

4.95 (1 H, br s, OH), 5.06 (0.5 H, dd, $^2J_{HF}$ 45, $^2J_{PH}$ 6 Hz), and 5.13 (0.5 H, dd, $^2J_{HF}$ 45, $^2J_{PH}$ 6 Hz); $\delta_P(CDCl_3)$ 12.38 (50% P, d, $^2J_{PF}$ 74.77 Hz) and 13.19 (50% P, d, $^2J_{PF}$ 79.35 Hz); $\delta_F(CDCl_3)$ −219.05 (50% F, dd, $^2J_{PF}$ 79.34, $^2J_{HF}$ 45.77 Hz), −207.55 (50% F, dd, $^2J_{PF}$ 74.76 $^2J_{HF}$ 44.25 Hz).

(3S)-*Di-isopropyl* 1-*Fluoro*-2,3,4-*trihydroxy*-3,4-O-*isopropylidenebutylphosphonate* (**6**).—LDA (5.04 mmol) and di-isopropyl fluoromethylphosphonate (1.00 g, 5.04 mmol) was treated with a solution of 2,3-*O*-isopropylidene-D-glyceraldehyde (0.65 g, 5.04 mmol) in dry tetrahydrofuran (12 ml) under standard conditions. The organic layer was separated and column chromatography (Silica H; 1.5 × 25 cm) of the crude product using dichloromethane–ethyl acetate (4:1) as the eluant gave the *title compound* as two fractions of mixed stereoisomers as colourless, viscous oils.

Fraction 1 (0.81 g, 24%); $\nu_{P=O}$ 1 235, ν_{O-H} 3 350 cm^{-1}; $\delta_H(CDCl_3)$ 1.40 (18 H, m), 3.65—4.30 (4 H, m), 4.42 (1 H, pseudo-q, 3-H, $^3J_{HH}$ 7 Hz), and 4.60—5.13 (3 H, m); $\delta_P(CDCl_3)$ 13.85 (50% P, d, $^2J_{PF}$ 77.82 Hz) and 14.92 (50% P, d, $^2J_{PF}$ 80.87 Hz); $\delta_F(CDCl_3)$ −229.54 (50% F, ddd, $^2J_{PF}$ 80.87, $^2J_{HF}$ 45.77, $^3J_{HF}$ 30.51 Hz) and −213.61 (50% F, ddd, $^2J_{PF}$ 77.82, $^2J_{HF}$ 45.78, $^3J_{HF}$ 21.36 Hz).

Fraction 2 (0.32 g, 10%) (Found: MH^+, 329.1526. $C_{13}H_{26}FO_6P{\cdot}H^+$ requires MH, 329.1529); $\delta_P(CDCl_3)$ 13.79 (50% P, d, $^2J_{PF}$ 76.29 Hz) and 14.87 (50% P, d, $^2J_{PF}$ 76.29 Hz); $\delta_F(CDCl_3)$ −221.24 (50% F, ddd, $^2J_{PF}$ 76.29 Hz, $^2J_{HF}$ 45.77, $^3J_{HF}$ 24.41 Hz) and −211.94 (50% F, ddd, $^2J_{PF}$ 76.29, $^2J_{HF}$ 45.78, $^3J_{HF}$ 4.58 Hz).

3-*Deoxy*-3-(O,O-*di-isopropylphosphono*)*fluoromethyl*-1,2:5,6-*di*-O-*isopropylidene*-α-D-allo-*furanose* (**10**).—Di-isopropyl fluoromethylphosphonate (1.00 g, 5.04 mmol) was treated with a solution of 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuran-3-ulose (1.30 g, 5.04 mmol) in dry tetrahydrofuran (13 ml) under standard conditions. The mixture was allowed to warm slowly to ambient temperature before being quenched with acetic acid (1M; 5 ml, 5 mmol). Column chromatography of the crude oily product (1.40 g) (Silica H; 1.5 × 25 cm) using dichloromethane–ethyl acetate (4:1) as the eluant gave the *title compound* as a colourless viscous oil (0.34 g, 15%) (Found: MH^+, 457.1970. $C_{19}H_{34}FO_9P \cdot H^+$ requires MH, 457.2002); $\nu_{P=O}$ 1 242, ν_{O-H} 3 380 cm^{-1}; $\delta_H(CDCl_3)$ 1.42 (24 H, m), 3.52 (1 H, d, $^3J_{HH}$ 5 Hz), 3.95—4.35 (4 H, m), 4.45—5.00 (3 H, m), 5.18 (1 H, d, $^3J_{HH}$ 5 Hz), and 5.83 (1 H, m); $\delta_P(CDCl_3)$ 12.76 (50% P, d, $^2J_{PF}$ 77.81 Hz) and 13.91 (50% P, d, $^2J_{PF}$ 70.19 Hz); $\delta_F(CDCl_3)$ −216.17 (50% F, dd, $^2J_{PF}$ 70.19, $^2J_{HF}$ 45.78 Hz), −212.85 (50% F, dd, $^2J_{PF}$ 77.81, $^2J_{HF}$ 44.25 Hz).

Di-isopropyl 1-*Fluoro*-2-*hydroxypropylphosphonate* (**5**).—Di-isopropyl fluoromethylphosphonate (1.00 g, 5.04 mmol) was treated with acetaldehyde (0.22 g, 5.04 mmol) under standard conditions. Kugelrohr distillation of the crude yellow oil (0.64 g) gave a colourless, viscous oil (9.5 g), b.p. 100—120 °C (oven temperature)/0.01 mmHg. Spectral analysis showed this to contain the *title compound* together with E-*di-isopropyl* 1-*fluoroprop*-1-*enylphosphonate* (**4**) in the ratio 7:3 respectively. The products were not purified further. $\delta_P(CDCl_3)$ 2.64 (30% P, d, *E*, $^2J_{PF}$ 100.71 Hz), 14.59 [35% P, d, (*R*,*R*) + (*S*,*S*), $^2J_{PF}$ 79.34 Hz], and 14.94 [35% P, d, (*R*,*S*) + (*S*,*R*), $^2J_{PF}$ 74.56 Hz]; $\delta_F(CDCl_3)$ −147.38 [35% F, ddd, (*R*,*S*) + (*S*,*R*), $^2J_{PF}$ 4.56, $^2J_{HF}$ 46.39, $^3J_{HF}$ 12.21 Hz], −142.54 [35% F, ddd, (*R*,*R*) + (*S*,*S*), $^2J_{PF}$ 79.34, $^2J_{HF}$ 46.39, $^3J_{HF}$ 21.97 Hz], and −131.57 (30% F, dd, *E*, $^2J_{PF}$ 100.71, $^3J_{HF}$ 39.07 Hz).

Attempted Synthesis of Di-isopropyl 1-*Fluoro*-2-*hydroxyethylphosphonate*.—To a solution of lithium di-isopropylamide (5.04 mmol) in dry tetrahydrofuran (10 ml) was added di-isopropyl fluoromethylphosphonate (1.00 g, 5.04 mmol) followed by a suspension of paraformaldehyde (0.15 g, 5.04 mmol) in dry tetrahydrofuran (10 ml) under standard conditions. The mixture was brought slowly to ambient temperature, stirred for 0.5 h, then water (5 ml) was added. The organic layer was separated and the aqueous layer extracted with ether (3 × 10 ml). The combined organic extracts were dried (anhydrous $MgSO_4$), filtered, and evaporated under reduced pressure to give a light brown oil (0.45 g). Kugelrohr distillation gave a colourless liquid which spectra analysis showed to be di-isopropyl 1-fluorovinylphosphonate (**3**) (0.20 g, 19%), b.p. 40—60 °C (oven temperature)/0.01 mmHg (Found: MH^+, 211.0894. $C_8H_{16}FO_3P{\cdot}H^+$ requires MH, 211.0899); the spectroscopic properties were identical to those of authentic material prepared by condensation of formaldehyde with tetraisopropyl fluoromethylenebisphosphonate.[19]

Di-isopropyl 2,3-*Epoxy*-1-*fluoro*-2-*methylbutylphosphonate* (**13**).—Di-isopropyl fluoromethylphosphonate (1.00 g, 5.04 mmol) was treated with 3-chlorobutan-2-one (0.53 g, 5.04 mmol) under standard conditions. Kugelrohr distillation of the crude pale yellow oil (0.85 g) gave the *title compound* as a colourless, viscous oil (0.62 g, 46%), b.p. 120—140 °C (oven temperature)/0.01 mmHg (Found: C, 49.5; H, 8.3. $C_{11}H_{22}FO_4P$ requires C, 49.25; H, 8.27%); $\nu_{P=O}$ 1 263 cm^{-1}; $\delta_H(CDCl_3)$ 1.40 (18 H, m), 3.10 (0.5 H, q, 4-H, $^3J_{HH}$ 6 Hz), 3.27 (0.5 H, q, 4-H, $^3J_{HH}$ 6 Hz), 4.27 (0.5 H, dd, 1-H, $^2J_{HF}$ 46, $^2J_{PH}$ 7 Hz), 4.53 (0.5 H, dd, 1-H, $^2J_{HF}$ 46, $^2J_{PH}$ 6 Hz), and 4.84 (2 H, m); $\delta_P(CDCl_3)$ 11.76 (41% P, d, $^2J_{PF}$ 82.40 Hz), 12.97 (11% P, d, $^2J_{PF}$ 76.29 Hz), and 13.44 (7% P, d, $^2J_{PF}$ 80.87 Hz); $\delta_F(CDCl_3)$ −146.18 (41% F, dd, $^2J_{PF}$ 82.40, $^2J_{HF}$ 45.77 Hz), −142.94 (11% F, dd, $^2J_{PF}$ 45.78 Hz), −142.80 (41% F, dd, $^2J_{PF}$ 82.40, $^2J_{HF}$ 45.78 Hz), and −136.52 (7% F, dd, $^2J_{PF}$ 80.87, $^2J_{HF}$ 48.83 Hz).

Di-isopropyl α-*Fluoro*-β-*hydroxystyrylphosphonate* (**14**).—Di-isopropyl fluoromethylphosphonate (1.00 g, 5.04 mmol) was condensed with benzoyl chloride (0.71 g, 5.04 mmol) under standard conditions. Column chromatography (Silica H; 1.5 × 25 cm) of the crude product (1.50 g) using dichloromethane–ethyl acetate (4:1) as the eluant gave the *title compound* as a colourless, viscous oil (0.70 g, 46%) (Found: C, 56.3; H, 6.3. $C_{14}H_{20}FO_4P$ requires C, 55.63; H, 6.67%); $\nu_{P=O}$ 1 275 cm^{-1}; $\delta_H(CDCl_3)$ 1.32 (12 H, m), 3.70 (1 H, br s, OH), 4.80 (2 H, m), and 7.40 (5 H, m); $\delta_P(CDCl_3)$ 0.70 (57% P, d, $^2J_{PF}$ 90.02 Hz), and 1.02 (43% P, d, $^2J_{PF}$ 91.54 Hz); $\delta_F(CDCl_3)$ −145.54 (57% F, d, $^2J_{PF}$ 90.02 Hz), −132.12 (43% F, d, $^2J_{PF}$ 91.54 Hz).

Di-isopropyl 1-*Fluoroethylphosphonate* (**16**).—Di-isopropyl fluoromethylphosphonate (1.00 g, 5.04 mmol) was treated with a solution of lithium di-isopropylamide (5.04 mmol) in dry tetrahydrofuran (10 ml) followed by a solution of dimethyl sulphate (0.63 g, 5.04 mmol) in the same solvent (2 ml) under standard conditions. The reaction was quenched with water (5 ml) at 0 °C and the organic layer separated. The aqueous layer was washed with ether (3 × 10 ml) and the combined organic solutions dried and evaporated. Kugelrohr distillation of the residue gave the *title compound* as a colourless, mobile liquid (0.64 g, 60%), b.p. 140—150 °C (oven temperature)/13 mmHg (Found: C, 45.4; H, 8.9. $C_8H_{18}FO_3P$ requires C, 45.28; H, 8.55%). This material was identical to the product of hydrogenation of di-isopropyl 1-fluorovinylphosphonate.[19]

Di-isopropyl 1-*Fluorobut*-3-*enylphosphonate* (**15**).—Lithium di-isopropylamide (5.04 mmol), di-isopropyl fluoromethylphosphonate (1.00 g, 5.04 mmol), and allyl bromide (0.61 g, 5.0 mmol) were allowed to react in dry tetrahydrofuran (10 ml) under standard conditions and the reaction worked up as above. Kugelrohr distillation of the crude product (1.0 g) gave the *title compound* as a colourless, mobile liquid (0.54 g, 45%),

b.p. 140—160 °C (oven temperature)/13 mmHg (Found: C, 50.35; H, 8.75. $C_{10}H_{20}FO_3P$ requires C, 50.42; H, 8.46%); $\nu_{P=O}$ 1 260 cm^{-1}; $\delta_H(C_6D_6)$ 1.40 (12 H, m), 2.64 (2 H, dm, 2-H_2 $^3J_{HF}$ 23 Hz), 4.80 (3 H, m), 5.20 (1 H, d, 4-H, $^3J_{HHcis}$ 10 Hz), 5.26 (1 H, d, 4″-H, $^3J_{HHtrans}$ 17 Hz), and 5.94 (1 H, m, 3-H); $\delta_P(CDCl_3)$ 15.48 (d, $^2J_{PF}$ 75.54 Hz); $\delta_F(CDCl_3)$ −208.07 (ddt), $^2J_{PF}$ 75.54, $^2J_{HF}$ 46.60, $^3J_{HF}$ 22.88 Hz).

Di-isopropyl Trimethylsilylfluoromethylphosphonate (**17**) *and Di-isopropyl Bis(trimethylsilyl)fluoromethylphosphonate* (**19**).—(*a*) To a solution of lithium di-isopropylamide (10.08 mmol) in dry tetrahydrofuran (20 ml) was added di-isopropyl fluoromethylphosphonate (2.00 g, 10.08 mmol) followed by chlorotrimethylsilane (1.08 g, 10.08 mmol) under standard conditions. The mixture was brought slowly to −6 °C and stirred at this temperature for 48 h. Water (10 ml) was added, the organic layer separated, and the aqueous layer extracted with ether (2 × 10 ml). The combined organic extracts were dried (anhydrous $MgSO_4$), filtered, and evaporated under reduced pressure to give a pale yellow oil (2.20 g). ^{31}P N.m.r. analysis showed the presence of two new *products*; mono- (30%) and bis-trimethylsilylfluoromethylphosphonate (40%) together with some of the starting phosphonate (30%); $\delta_P(CDCl_3)$ 14.17 (30% P, d, $^2J_{PF}$ 64.07 Hz), 19.30 (30% P, d, $^2J_{PF}$ 61.04 Hz), 22.80 (40% P, d, $^2J_{PF}$ 65.62 Hz).

(*b*) To a solution of lithium di-isopropylamide (5.04 mmol) in dry tetrahydrofuran (10 ml) was added di-isopropyl fluoromethylphosphonate (1.00 g, 5.04 mmol) followed by bromotrimethylsilane (0.80 g, 5.04 mmol) under standard conditions. The mixture was brought slowly to ambient temperature and then water (3 ml) was added. The organic layer was separated and the aqueous layer extracted with ether (2 × 5 ml). The combined organic extracts were dried (anhydrous $MgSO_4$), filtered, and evaporated under reduced pressure to give a colourless oil (0.75 g). Kugelrohr distillation gave a colourless, mobile liquid (0.45 g), b.p. 160—190 °C. ^{31}P N.m.r. analysis showed two products; mono- (40%) and bis-trimethylsilylfluoromethylphosphonate (30%), together with some starting phosphonate (30%); $\delta_P(CDCl_3)$ 14.17 (30% P, d, $^2J_{PF}$ 64.07 Hz), 19.30 (40% P, d, $^2J_{PF}$ 61.04 Hz), and 22.80 (30% P, d, $^2J_{PF}$ 65.62 Hz).

Di-isopropyl α-Fluorostyrylphosphonate (**20**).—The above mixture of di-isopropyl fluoromethyl-, trimethylsilyl fluoromethyl-, and bis-trimethylsilylfluoromethylphosphonate (*ca.* 0.25 g, 0.89 mmol) was dissolved in heptane (10 ml). To this solution, stirred at −78 °C under dry nitrogen, butyl-lithium (1.69M; 0.63 ml, 1.07 ml) was added dropwise. The mixture was stirred at −78 °C for 10 min then a solution of benzaldehyde (0.10 g, 0.94 mmol) in heptane (2 ml) was added. The mixture was brought to ambient temperature and stirred for 48 h. Water (5 ml) was added, the organic layer separated, and the aqueous layer extracted with ether (2 × 10 ml). The combined organics were dried (anhydrous $MgSO_4$), filtered, and evaporated under reduced pressure to give a pale yellow, viscous oil (0.60 g). Spectral analysis showed that di-isopropyl trimethylsilylfluoromethylphosphonate had been converted into a 1:1 *E*:*Z*-mixture of α-fluorostyrylphosphonate ester, the other starting phosphonates remaining unchanged; $\delta_P(CDCl_3)$ 1.46 (20% P, d, *Z*, $^2J_{PF}$ 109.87 Hz), 3.22 (20% P, d, *E*, $^2J_{PF}$ 96.13 Hz), 14.17 (30% P, d, J_{PF} 64.07 Hz), and 22.80 (30% P, d, $^2J_{PF}$ 65.62 Hz); $\delta_F(CDCl_3)$ −249.25—−245.36 (60% F, m), −125.77 (20% F, dd, *E*, $^2J_{PF}$ 96.13, $^3J_{HF}$ 43.94 Hz), and −114.00 (20% F, dd, *Z*, $^2J_{PF}$ 109.87, $^3J_{HF}$ 29.30 Hz).

Di-isopropyl α-Fluoro-β-hydroxy-α-methylphenethylphosphonate (**18**).—To a solution of lithium di-isopropylamide (5.04 mmol) in dry tetrahydrofuran (10 ml) was added di-isopropyl 1-fluoroethylphosphonate (1.07 g, 5.04 mmol) followed by a solution of benzaldehyde (0.54 g, 5.04 mmol) in dry tetrahydrofuran (2 ml) under standard conditions. The mixture was brought slowly to 0 °C then quenched with hydrochloric acid (1M; 5 ml, 5 mmol). The organic layer was separated and the aqueous layer extracted with ether (3 × 10 ml). The combined organic fractions were dried (anhydrous $MgSO_4$), filtered, and evaporated under reduced pressure. Kugelrohr distillation of the residue gave the *title compound* as a viscous, colourless oil which crystallized with time to give white crystals (0.71 g, 44%), m.p. 55—58 °C, b.p. 200—210 °C (oven temperature)/0.01 mmHg (Found: MH^+, 319.1449. $C_{15}H_{24}FO_4P{\cdot}H^+$ requires MH, 319.1475); $\nu_{P=O}$ 1 234, ν_{O-H} 3 320 cm^{-1}; $\delta_H(CDCl_3)$ 1.15—1.45 (15 H, m), 4.65 (1 H, br s, OH), 4.80 (2 H, m), 4.97 (0.5 H, dd, $^3J_{HF}$ 24, $^3J_{PH}$ 4 Hz), 5.21 (0.5 H, dd, $^3J_{PH}$ 10, $^3J_{HF}$ 7 Hz), and 7.35 (5 H, m); $\delta_P(CDCl_3)$ 17.81 [44% P, d, (*R*,*R*) + (*S*,*S*), $^2J_{PF}$ 96.13 Hz] and 18.92 [56% P, d, (*R*,*S*) + (*S*,*R*), $^2J_{PF}$ 82.39 Hz]; $\delta_F(CDCl_3)$ −184.24 [44% F, d-pseudo-quintet, (*R*,*R*) + (*S*,*S*), $^2J_{PF}$ 96.13, $^3J_{MeCF}$ 24.42, $^3J_{CHCF}$ 24.42 Hz], −169.70 [56% F, ddq, (*R*,*S*) + (*S*,*R*), $^2J_{PF}$ 82.39, $^3J_{MeCF}$ 24.42 Hz, $^3J_{CHCF}$ 7.33 Hz].

Di-isopropyl α,β-Difluorophenethylphosphonate (**11**).—To a solution of diethylaminosulphur trifluoride (0.15 g, 1.00 mmol) in dichloromethane (3 ml) stirred at −78 °C under dry nitrogen was added dropwise a solution of di-isopropyl 1-fluoro-2-hydroxy-2-phenylethylphosphonate (0.20 g, 0.66 mmol) in dichloromethane (3 ml). The mixture was brought slowly to ambient temperature, stirred for a further 4.5 h then quenched with methanol (5 ml), and evaporated under reduced pressure. The residue was purified by column chromatography (Silica H; 1.5 × 25 cm) using dichloromethane–ethyl acetate (4:1) as the eluant to give the *title compound* as a colourless, viscous oil (0.13 g, 65%) (Found: C, 54.25; H, 6.9. $C_{14}H_{21}F_2O_3P$ requires C, 54.87; H, 6.91%); $\nu_{P=O}$ 1 260 cm^{-1}; $\delta_H(CDCl_3)$ 1.16—1.42 (12 H, m), 4.70 (2 H, m), 4.86 (0.5 H, dddd, 1-H, $^2J_{HF}$ 46, $^3J_{HF}$ 23, $^2J_{PH}$ 8.5, $^3J_{HH}$ 4.5 Hz), 5.02 (0.5 H, dddd, 1-H, $^2J_{HF}$ 46, $^3J_{HF}$ 16, $^3J_{HH}$ 4.5/6.5 Hz, $^2J_{PH}$ 6.5/4.5 Hz), 5.80 (0.5 H, dddd, 2-H, $^2J_{HF}$ 45, $^3J_{HF}$ 19, $^3J_{HH}$ 4.5/6.5, $^3J_{PH}$ 6.5/4.5 Hz), 5.85 (0.5 H, dddd, 2-H, $^2J_{HF}$ 46, $^3J_{HF}$ 22, $^3J_{HH}$ 4.5, $^3J_{PH}$ 2 Hz), and 7.40 (5 H, m); $\delta_P(CDCl_3)$ 11.38 (50% P, dd, $^2J_{PF}$ 74.76, $^3J_{PF}$ 25.94 Hz) and 11.63 (50% P, dd, $^2J_{PF}$ 77.82, $^3J_{PF}$ 23.19 Hz); $\delta_F(CDCl_3)$ −216.3 (1 F, m, 1-F), −183.72 (0.5 F, dd-pseudo-t, 2-F, $^2J_{HF}$ 46.39, $^3J_{PF}$ 23.19, $^3J_{HF}$ 23.19, $^3J_{FF}$ 15.85 Hz), and −178.87 (0.5 F, dd-pseudo-t, 2-F, $^2J_{HF}$ 45.16, $^3J_{PF}$ 25.94, $^3J_{HF}$ 15.87, $^3J_{FF}$ 15.87 Hz).

Ethyl 3-(O,O-*Di-isopropylphosphono*)-3-*fluoro*-2-*methylpropenoate* (**12**).—To a solution of ethyl 3-di-isopropylphosphono-3-fluoro-2-hydroxy-2-methylpropanoate (0.50 g, 1.78 mmol) in dichloromethane (5 ml) stirred at −78 °C under dry nitrogen was added dropwise diethylaminosulphur trifluoride (0.27 g, 1.78 mmol). The mixture was allowed to warm rapidly to ambient temperature, stirred for a further 5 h, quenched with methanol (5 ml), and evaporated under reduced pressure. The residue was purified by column chromatography (Silica H; 1.5 × 25 cm) using dichloromethane–ethyl acetate (4:1) as the eluant to give the *title compound* as a colourless, viscous oil (0.26 g, 49%) (Found: M^+, 296.1187. $C_{12}H_{22}FO_5P$ requires *M*, 296.1189); $\nu_{P=O}$ 1 260 cm^{-1}; $\delta_H(CDCl_3)$ 1.37 (15 H, m), 2.02 (1.2 H, dd, 2-Me, $^4J_{HF}$ 4, $^4J_{PH}$ 3 Hz), 2.21 (1.8 H, pseudo-t, 2-Me, $^4J_{HF}$ 3.5 $^4J_{PH}$ 3.5 Hz), 4.28 (2 H, q, $^3J_{HH}$ 8 Hz), and 4.78 (2 H, m); $\delta_P(CDCl_3)$ −0.06 (60% P, d, $^2J_{PF}$ 99.18 Hz) and 1.05 (40% P, d, $^2J_{PF}$ 100.69 Hz); $\delta_F(CDCl_3)$ −121.40 (60% F, dq, $^2J_{PF}$ 99.18, $^4J_{HF}$ 4.57 Hz), and −112.08 (40% F, dq, $^2J_{PF}$ 100.69, $^4J_{HF}$ 3.05 Hz).

Di-isopropyl Chlorofluoromethylphosphonate.—Sodium (5.75 g, 0.25 mol) was added a solution of di-isopropyl phosphite (41.5

g, 0.25 mmol) in dry toluene (250 ml) and stirred at ambient temperature under dry nitrogen for 18 h. The resulting solution was treated with dichlorofluoromethane (30.9 g, 0.3 mmol) at 0 °C and stirred for 1 h. After carrying out the standard work-up, the crude product was distilled to give the *title compound* as a colourless, mobile liquid (22 g, 38%) b.p. 90—94 °C/0.3 mmHg; $\nu_{P=O}$ 1 265 cm^{-1}; $\delta_H(CDCl_3)$ 1.42 (12 H, pseudo-t, $^3J_{PH}$ 6, $^3J_{HH}$ 6 Hz), 4.89 (2 H, m), and 6.20 (1 H, dd, $^2J_{HF}$ 46, $^2J_{PH}$ 8 Hz); $\delta_P(CDCl_3)$ 6.00 (d, $^2J_{PF}$ 77.82 Hz).

Diethyl Chlorofluoromethylphosphonate.—This was prepared as above from diethyl phosphite (34.5 g, 0.25 mmol) and dichlorofluoromethane (28.0 g, 0.27 mmol) to give the *product* b.p. 88.92 °C (Found: MH^+ 205.0200; $C_5H_{11}{}^{35}ClFO_3P{\cdot}H^+$ requires M, 205.0196); $\nu_{P=H}$ 1 265 cm^{-1}; $\delta_H(CDCl_3)$ 1.40 (6 H, t, $^3J_{HH}$ 8 Hz), 4.35 (4 H, dq, $^3J_{HH}$ 8, $^3J_{PH}$ 8 Hz), and 6.23 (1 H, dd, $^2J_{HF}$ 46, $^2J_{PH}$ 10 Hz); $\delta_P(CDCl_3)$ 7.56 (d, $^2J_{PF}$ 77.86 Hz); $\delta(CDCl_3)$ −159.84 (dd, $^2J_{PF}$ 77.8, $^2J_{HF}$ 47.30 Hz).

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