Synthesis of activated alkenes bearing the difluoromethylenephosphonate group: a range of building blocks for the synthesis of secondary difluorophosphonates

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Active methylene compounds reacted readily with stable hydrate 2-diethoxyphosphoryl-2,2-difluoroethane-1,1-diol to afford a range of activated alkenes bearing the difluoromethylenephosphonate group, a useful motif in the synthesis of phosphate ester mimics of biological interest. Wadsworth–Horner–Emmons reactions were employed using modified Rathke conditions for the syntheses of alkenoates, an alkenoic acid and a vinyl sulfone, while a Henry reaction followed by E1$_c$B dehydration afforded an enedioate and a nitroalkene. A vinyl sulfoxide was less straightforward to synthesise and dephosphorylation to a difluoromethyl congener accompanied attempts to force the reaction to completion.

The synthesis of phosphonate analogues of naturally-occurring phosphate esters remains an active field of endeavour. For example, recent publications have described syntheses of phosphonate inhibitors of enzymes of the shikimate pathway,[1] while routes to phosphonate analogues of seconucleotides,[2] and 2-deoxyribose 3-phosphate[3,4] and analogues of sugar phosphates[5,6] have also been described. Where sensible comparisons are possible, the α,α-difluorophosphonates appear to mimic phosphate esters more effectively than non-halogenated analogues (though recent work appears to be showing that the des-halo congeners also have a significant role to play[7–9]). The studies of the Burke group offer the best documented applications of this mimicry and much has been learnt about the interactions between peptides containing phosphotyrosine surrogates and target enzymes.[10] Other compounds of interest include non-tyrosyl phosphoamino acid analogues,[11] conformationally-restricted amino acid analogues,[12] protein phosphatase 1B inhibitors,[13] difluorophosphonate analogues of FTC[14] and other nucleotides,[15] and ligands for glycerol[16] and phosphoglycerate[17] kinases though less is known about the modes of action of these systems. Also, despite significant advances in synthetic methodology which have been made recently, enabling aryl and vinyl difluorophosphonates to be prepared *via* copper(I) mediated coupling reactions of the zinc reagent **2** (prepared from the bromodifluoromethyl phosphonate **1**) with aryl[18] and vinyl[19] halides, there remain very few

$XCF_2PO(OEt)_2$

1, X = Br
2, X = ZnBr
3, X = H
4, X = Li

reports of efficient syntheses of building blocks which bear the difluoromethylenephosphonate group and possess the potential for exploitation in key technologies such as cycloaddition reactions (Scheme 1).[20–24] α,α-Difluoro-β-ketophosphonates are available routinely from **3** and esters *via* our own cerium-mediated chemistry of **4**,[25] or as described by Berkowitz.[26] In the latter case, *in situ* trapping with a Grignard or organo-

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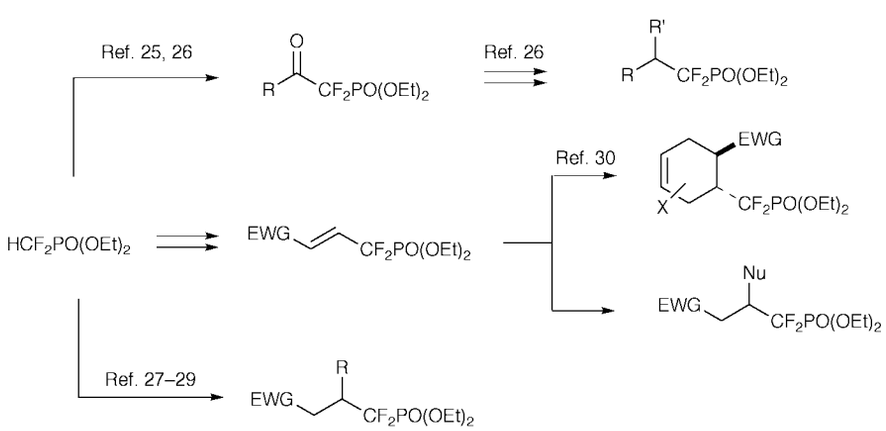
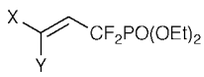


Scheme 1 Routes to secondary difluorophosphonates.

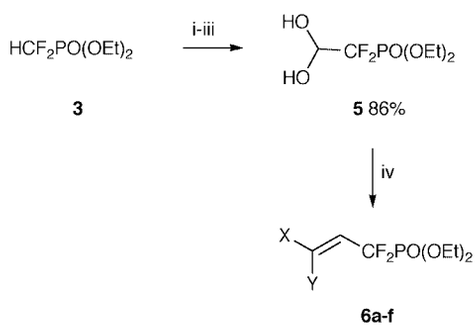
Table 1

Entry	HCXYZ	Product	Conditions	Yield (%)
1	X = CO_2Et, Y = H, Z = $PO(OEt)_2$		**6a**, X = CO_2Et, Y = H	*a*	65
2	X = CO_2allyl, Y = H, Z = $PO(OEt)_2$		**6b**, X = CO_2H, Y = H	*a*, *b*	78[f]
3	X = Y = CO_2Et, Z = H		**6c**, X = Y = CO_2Et	*c*, *d*	60
4	X = SO_2Ph, Y = H, Z = $PO(OEt)_2$		**6d**, X = SO_2Ph, Y = H	*a*	60
5	X = SOPh, Y = H, Z = $PO(OEt)_2$		**6e**, X = SOPh, Y = H	*e*	43
6	X = NO_2, Y = Z = H		**6f**, X = NO_2, Y = H	*c*, *d*	75

[a] LiBr, Et_3N, THF, RT. [b] Morpholine, $Pd(AOc)_2$, PPh_3, THF (see Scheme 3). [c] KF, propan-2-ol, RT. [d] MsCl then Et_3N, DCM. [e] K_2CO_3. 18-crown-6, PhMe, 60 °C, reflux. [f] For 3 steps from **6**.

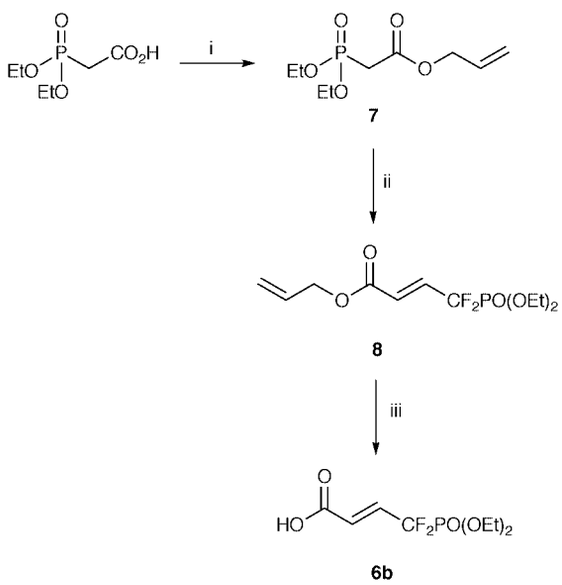
lithium reagent set the stage for Dolan–MacMillan deoxygenation affording phosphothreonine analogues in a rare example of a reaction forming a compound in which the difluorophosphonate was attached to a secondary sp^3 carbon atom. The location of the phosphate mimic at a centre of this type represents a problem of strategic importance, limiting the range of targets accessible by convenient and flexible methods. We have explored solutions to this latter problem *via* cerium-mediated conjugate addition of **3** to nitroalkenes,[27] vinyl sulfones,[28] and vinyl sulfoxides,[29] and have published, in preliminary form, our attempts to develop Diels–Alder based routes to carbocycles that bear the difluorophosphonate group.[30] Our reasons for initiating this investigation lay in the possibility of preparing stable (non-scissile) analogues of the cyclitol phosphates[31] as potential inhibitors or probes in the second messenger signalling cascade, an area in which significant progress has been made concerning the molecular recognition of phosphate esters providing a rigorous testing ground for the (often orthogonal) theories propounded to explain phosphate ester mimicry.[32,33] In this paper, we wish to describe fully the synthesis of a range of activated alkenes that can deliver the difluoromethylenephosphonate group through cycloaddition or potentially conjugate addition reactions. While our chemistry does rely on chlorodifluoromethane as a starting material, the construction of activated alkenes of *E*-configuration that contain a range of electron-withdrawing groups is facile and general and uses readily-available active methylene compounds as reaction partners.

We were able to synthesise dienophiles **6a**–**f** from masked aldehyde **5**, obtained *via* the cerium(III)-mediated addition of [(diethoxyphosphoryl)difluoromethyl]lithium **4** to DMF (Scheme 2), a reaction which we have performed reproducibly



Scheme 2 *Reagents and conditions*: i, 1.0 equiv. LDA, $CeCl_3$, THF, −78 °C; ii, DMF; iii, aq. HCl; iv HCXYZ, see Table 1.

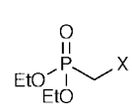
to make 30 g batches of **5** in high yield. In all cases bar one, reaction of active methylene compounds with **5** proved facile (Table 1); for example, under the conditions described by Rathke, alkenoate **6a** was formed as the *E* isomer exclusively in high yield from ethyl diethylphosphonoacetate and **5**. Similar compounds were prepared by Campbell and Kawamoto[34] *via* an organozinc route from the corresponding 2-haloacrylic acids, though the reported yields were low. Instead, we prepared the *E*-alkenoic acid **6b** in good yield from allyl diethylphosphonoacetate **7**, prepared under conventional conditions from the commercial diethylphosphonoacetic acid according to Scheme 3. Olefination under Rathke conditions[35] afforded **8**, then Pd(0)-catalysed deallylation[36,37] afforded the acid.



Scheme 3 *Reagents and conditions*: i, $H_2C{=}CHCH_2OH$, DCC, DMAP, DCM, rt, 18 h, 100%; ii, LiBr, TEA, THF, 0 °C, 1 h, then 4, warm to rt, 18 h, 79%; iii, morpholine, $Pd(OAc)_2$, Ph_3P, THF, rt, 18 h, 99%.

Two step procedures were employed for the production of alkenedioate **6c** and nitroalkene **6f**. Fluoride-mediated addition of either diethyl malonate or nitromethane to **5** followed by mesylation and elimination *in situ* completed the conversions to **6c** and **6f** respectively.

The Rathke conditions also allowed the synthesis of sulfone **6d** in good yield by using diethyl (phenylsulfonyl)methylphosphonate **9** as the carbon nucleophile.



9, X = SO_2Ph
10, X = SOPh

Presumably, the addition of carbon nucleophiles to **5** proceeded according to Scheme 4, in which pre-equilibrium between **5** and the aldehyde and water was followed by reaction with the conjugate base of the active methylene compound. If the pK_a of the active methylene compound is too high, deprotonation of **5** or water destroys the nucleophile terminating the reaction. This effect was demonstrated clearly when we attempted to synthesise sulfinylalkene **6e**; no alkene was obtained under the Rathke conditions when diethyl (phenylsulfinyl)methylphosphonate **10** was exposed to hydrate **5**. Unambiguous deprotonation of the phenylsulfinyl phosphon-

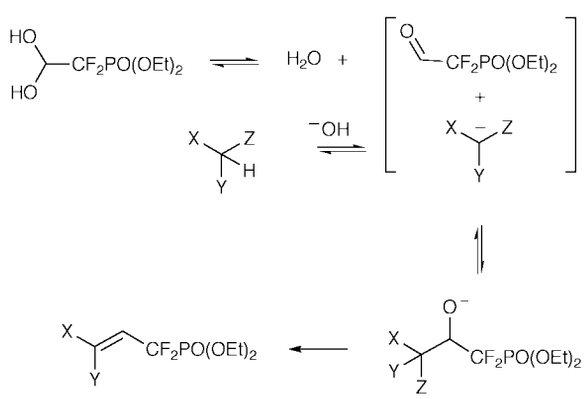
ate with *n*-butyllithium (1.0–5.0 equivalents) failed to improve the situation, and stronger amine bases such as DBU were ineffective. The barium hydroxide·hydrate mediated conditions reported by Patterson[38] were ineffective also; however, the combination of potassium carbonate as base and refluxing acetonitrile as solvent afforded **6e**,[39] albeit in poor yield after 5 days. Shortening the reaction time to 1.5 hours failed to change the product ratio; in both cases, the major product was the difluoromethyl alkene **11**, formed presumably *via* hydroxide ion attack at phosphorus followed by phosphorane collapse with elimination of a difluoroallylic sulfinyl anion **12**, analogous to the sequence described by Piettre[40] (Scheme 5). Finally, we were able to obtain an expedient (43%) yield of **6e** under the conditions described by Ermolenko (K_2CO_3, 18-crown-6, toluene, 60 °C, 2 hours).[41]

Activated alkenes bearing the difluoromethylenephosphonate group have been synthesised *via* a direct procedure (three or four steps from chlorodifluoromethane) and in good yield. All species display considerable potential for use in the construction of mimetics of structurally complex phosphate esters. Studies describing conjugate and cycloaddition reactions of our activated alkenes and cycloadduct elaboration to cyclitol analogues will be reported elsewhere.

Experimental

All NMR spectra were obtained in $CDCl_3$ and were recorded relative to tetramethylsilane as the internal standard. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300 (300.13 and 75.47 MHz respectively) spectrometer and *J* values are given in Hz. ^{13}C NMR spectra were recorded using the PENDANT pulse sequence. ^{31}P NMR spectra were also recorded on a Bruker AC-300 (121.50 MHz) spectrometer using *ortho*-phosphoric acid as the internal standard. ^{19}F NMR spectra were recorded on a Bruker AC-300 (282.41 MHz) relative to chlorotrifluoromethane as the internal standard. Chemical Ionisation (CI) and Electron Impact (EI) mass spectra were recorded on a VG ProSpec mass spectrometer, Kratos Profile mass spectrometer or a VG Zabspec mass spectrometer. Chemical ionisation (CI) methods used ammonia as the reagent gas. Elemental analyses were performed at the University of North London. For TLC, precoated aluminium-backed silica gel plates were supplied by E. Merck, A.G. Darmstadt, Germany (Silica gel 60 F254, thickness 0.2 mm, Art. 5554). Visualisation was achieved by UV light and/or an anisaldehyde–sulfuric acid or potassium permanganate stain. Flash column chromatography was performed using an air compressor on silica gel (E. Merck A.G. Kieselgel 60, Art. 9385). THF was dried by refluxing with benzophenone over sodium wire until a deep purple colour developed, then distilled and collected by dry syringe as required. Dichloromethane was dried by distillation with calcium hydride and subsequent distillation and collection by dry syringe as required. *n*-Butyllithium was titrated before use against 1,3-diphenylpropan-2-one *p*-tolylsulfonylhydrazone. Cerium(III) chloride was dried according to our published procedure.[25] The heptahydrate was obtained from the Aldrich Chemical Company, as was diethylphosphonoacetic acid. Diisopropylamine and triethylamine were distilled from calcium hydride and each stored under an atmosphere of nitrogen over calcium hydride. *N*,*N*-Dimethylformamide was distilled from calcium hydride under high vacuum and stored over activated 4 Å molecular sieves under an atmosphere of nitrogen.

2-Diethoxyphosphoryl-2,2-difluoroethane-1,1-diol **5** was prepared according to our published procedure.[25]



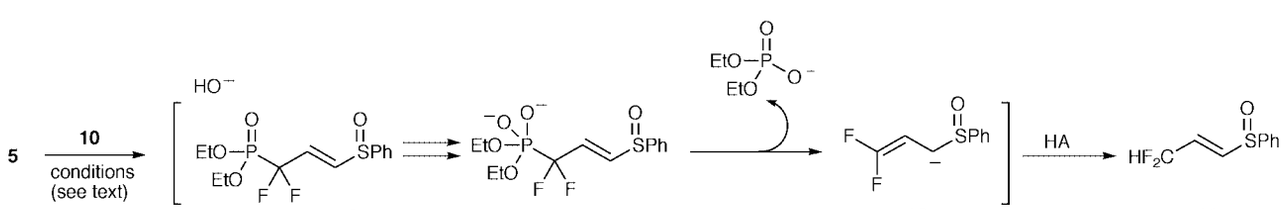
Scheme 4

Ethyl (2*E*)-4-(diethoxyphosphoryl)-4,4-difluorobut-2-enoate 6a

Freshly distilled triethylamine (0.56 ml, 4.0 mmol) was added slowly to a solution of anhydrous lithium bromide (0.38 g, 4.3 mmol) and triethyl phosphonoacetate (0.71 ml, 3.6 mmol) in THF (10 ml) under nitrogen at 0 °C over a 10 minute period. The resulting white suspension was stirred for 30 minutes then **5** (0.85 g, 3.6 mmol) was added slowly to the reaction mixture. The yellow solution was stirred at 0 °C for 1 hour, then at room temperature overnight, then quenched with dilute HCl (0.1 M, 15 ml), and extracted with diethyl ether (3 × 30 ml). The combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo* to afford a yellow oil. Column chromatography (40% ethyl acetate in light petroleum) afforded the enoate **6a** (0.66 g, 65%) as a pale yellow oil; R_f (40% ethyl acetate in light petroleum) 0.24 (Found: C, 41.9; H, 5.9; $C_{10}H_{17}F_2O_5P$ requires: C, 42.0; H, 6.0%); ν_{max}(film)/cm^{-1} 2986s, 1728vs (C=O), 1652w; δ_H (300 MHz; $CDCl_3$) 6.75 (1H, tdd, *J* 15.5, $^3J_{H-F}$ 12.5, $^3J_{H-P}$ 2.5, H-3), 6.30 (1H, tdd, *J* 15.5, $^4J_{H-F}$ 2.5, $^4J_{H-P}$ 2.5, H-2), 4.25–4.18 (4H, m, POCH_2CH$_3$), 4.15 (2H, q, *J* 7.2, CO$_2$CH_2CH$_3$), 1.25 (6H, t, *J* 7.3, POCH$_2$CH_3), 1.20 (3H, t, *J* 7.2, CO$_2$CH$_2$CH_3); δ_C (75 MHz; $CDCl_3$) 164.0, 134.9 (dt, $^2J_{C-F}$ 22.0, $^2J_{C-P}$ 13.0), 127.7, 117.3 (dt, $^1J_{C-F}$ 260, $^1J_{C-P}$ 216), 64.7, 61.0, 16.1, 13.8; δ_F (282 MHz; $CDCl_3$) −112.5 (ddd, $^2J_{F-P}$ 107, $^3J_{F-H}$ 12.5, $^4J_{F-H}$ 2.5); δ_P (121 MHz; $CDCl_3$) 4.8 (t, $^2J_{P-F}$ 107); *m*/*z* (CI) 304 (100%, M[NH$_4$]$^+$), 287 (100, M + 1).

Allyl diethylphosphonoacetate 7

Diethylphosphonoacetic acid (1.0 mmol, 0.16 cm^3) was added dropwise under nitrogen to a stirred solution of allyl alcohol (1.0 mmol, 0.07 cm^3), DCC (1.00 mmol, 0.21 g) and DMAP (0.1 mmol, 0.01 g) in DCM (5 cm^3). The white suspension was stirred overnight at ambient temperature, then filtered and the filtrate washed with a saturated solution of $NaHCO_3$ (2 cm^3), dried ($MgSO_4$) and concentrated *in vacuo* to leave a white solid. The solid was suspended in diethyl ether (5 cm^3), then the



Scheme 5

suspension was filtered and the filtrate concentrated *in vacuo* to leave a yellow oil (0.24 g) which was purified by column chromatography (silica gel, 40% ethyl acetate–light petroleum) to afford the ester **7** (0.24 g, 100%) as a colourless oil; R_f (40% ethyl acetate–light petroleum) 0.11; δ_H (300 MHz; $CDCl_3$) 5.85 (1H, tdd, *J* 17.3, 10.7, 5.5, *H*-2′), 5.29 (1H, d, *J* 17.3, H-3′$_a$), 5.18 (1H, d, *J* 10.7, H-3′$_b$), 4.56 (2H, d, *J* 5.5, H-1′), 4.16–4.04 (4H, m, OC*H*$_2$CH$_3$), 2.93 (2H, d, $^2J_{H-P}$ 21.7, H-1), 1.27 (6H, t, *J* 7.0, OCH$_2$C*H*$_3$); δ_C (75 MHz; $CDCl_3$) 165.3, 131.5, 118.6, 66.0, 62.6 (d, $^2J_{C-P}$ 5.7), 32.4 (d, $^1J_{C-P}$ 134), 16.2; δ_P (121 MHz; $CDCl_3$) 19.8 (s).

Allyl (2*E*)-4-(diethoxyphosphoryl)-4,4-difluorobut-2-enoate 8

The allyl ester was prepared in an identical manner to **6a** from triethylamine (1.12 mmol, 0.16 cm^3), **7** (1.02 mmol, 0.24 g), LiBr (1.22 mmol, 0.11 g) and **5** (1.12 mmol, 0.26 g) in THF (5 cm^3). The yellow oil (0.28 g) was purified by column chromatography (silica gel, 40% ethyl acetate in light petroleum) to afford the allyl ester (0.24 g, 79%) as a colourless oil; R_f (40% ethyl acetate in light petroleum) 0.13 (Found: C, 44.6; H, 5.7. $C_{11}H_{17}F_2O_5P$ requires: C, 44.3; H, 5.8%); δ_H (300 MHz; $CDCl_3$) 6.89 (1H, dt, *J* 12.9, $^3J_{H-F}$ 12.7, H-3), 6.40 (1H, dd, *J* 12.9, $^4J_{H-F}$ 2.2, H-2), 5.91 (1H, tdd, *J* 17.3, 10.7, 5.5, H-2′), 5.32 (1H, d, *J* 17.3, H-3′$_a$), 5.25 (1H, d, *J* 10.7, H-3′$_b$), 4.66 (2H, d, *J* 5.5, H-1′), 4.30–4.13 (4H, m, OC*H*$_2$CH$_3$), 1.35 (6H, t, *J* 7.0, OCH$_2$C*H*$_3$); δ_C (75 MHz; $CDCl_3$) 164.0, 135.7 (dt, $^2J_{C-F}$ 22.0, $^2J_{C-P}$ 13.0), 131.5, 127.6 (dt, $^3J_{C-F}$ 14.7, $^3J_{C-P}$ 5.7), 118.9, 116.1 (dt, $^1J_{C-F}$ 260.0, $^1J_{C-P}$ 217.0), 65.9, 65.1 (d, $^2J_{C-P}$ 6.5), 16.2; δ_F (282 MHz; $CDCl_3$) −112.0 (ddd, $^2J_{F-P}$ 109.1, $^3J_{F-H}$ 12.7, $^4J_{F-H}$ 2.2); δ_P (121 MHz; $CDCl_3$) 5.27 (t, $^2J_{F-P}$ 109.1) [HRMS (CI, M + 1) Found: 299.086839. Calc. for $C_{11}H_{18}F_2O_5P$ 299.085994]; *m*/*z* (CI) 316 (20%, M + 18), 299 (30, M + 1), 174 (50), 157 (64), 70 (100).

(2*E*)-4-(Diethoxyphosphoryl)-4,4-difluorobut-2-enoic acid 6b

Triphenylphosphine (3.38 mmol, 0.89 g) was added to a stirred solution of the allyl butenoate (2.11 mmol, 0.63 g), palladium acetate (0.10 mmol, 0.02 g) and morpholine (2.54 mmol, 0.22 cm^3) in THF (6 cm^3) under an atmosphere of nitrogen. After stirring overnight the solvent was concentrated *in vacuo*. The residue was redissolved in DCM (20 cm^3), washed with HCl (2 × 2 cm^3 of a 3.0 M aqueous solution), dried ($MgSO_4$) and concentrated *in vacuo* to leave a golden oil (1.03 g) which was purified by column chromatography (silica gel, 1% acetic acid and 4% methanol in chloroform) to afford acid **6b** (0.54 g, 99%) as a clear oil; R_f (1% acetic acid and 4% methanol in chloroform) 0.20; δ_H (300 MHz; $CDCl_3$) 10.42 (br s, CO_2H), 6.92 (1H, tdd, *J* 15.8, $^3J_{H-F}$ 12.7, $^3J_{H-P}$ 1.9, H-3), 6.40 (1H, tdd, J_{H-H} 15.8, $^4J_{H-P}$ 5.3, $^4J_{H-F}$ 2.5, H-2), 4.36–4.23 (4H, m, OC*H*$_2$CH$_3$), 1.38 (6H, t, J_{H-H} 7.0, OCH$_2$C*H*$_3$); δ_C (75 MHz; $CDCl_3$) 166.9, 135.8 (dt, $^2J_{C-F}$ 21.5, $^2J_{C-P}$ 13.0), 128.3 (dt, $^3J_{C-F}$ 7.0, $^3J_{C-P}$ 7.0), 116.2 (dt, $^1J_{C-F}$ 260.3, $^1J_{C-P}$ 218.2), 65.7 (d, $^2J_{C-P}$ 6.6), 16.4; δ_F (282 MHz; $CDCl_3$) −112.1 (ddd, $^2J_{F-P}$ 108.7, $^3J_{F-H}$ 12.7, $^4J_{F-H}$ 2.5); δ_P (121 MHz; $CDCl_3$) 5.19 (t, $^2J_{F-P}$ 108.7). These spectroscopic data were in agreement with those reported by Kawamoto and Campbell.[34]

(2*E*)-3-Diethoxyphosphoryl-3,3-difluoro-1-phenylsulfonylprop-1-ene 6d

Vinyl sulfone **6d** was prepared in an identical manner to **6a** from anhydrous lithium bromide (1.40 g, 16.32 mmol), **9**[42] (4.39 g, 15.00 mmol), triethylamine (2.05 ml, 15.00 mmol) and **5** (3.00 g, 13.6 mmol) in THF (25 ml). Column chromatography (40% ethyl acetate in light petroleum) afforded vinyl sulfone **6d** (3.01 g, 66%) as a pale yellow oil; R_f (40% ethyl acetate in light petroleum) 0.24 (Found: C, 44.1; H, 4.9; $C_{13}H_{17}F_2O_5PS$ requires: C, 44.0; H, 4.8%); δ_H (300 MHz; $CDCl_3$) 7.82 (2H, d, *J* 8.0, ArH), 7.61 (1H, t, *J* 8.0, ArH), 7.58 (2H, t, *J* 8.0, ArH), 6.90–6.86 (2H, m, H-1, H-2), 4.38–4.12 (4H, m, OC*H*$_2$CH$_3$), 1.25 (6H, t, *J* 7.3, OCH$_2$C*H*$_3$); δ_C (75 MHz; $CDCl_3$) 138.4, 137.8, 134.4, 132.2 (dt, $^2J_{C-P}$ 13.8, $^2J_{C-F}$ 23.1), 129.6, 128.1, 115.4 (dt, $^1J_{C-P}$ 215, $^1J_{C-F}$ 262), 65.3, 16.2; δ_F (282 MHz; $CDCl_3$) −112.1 (dd, $^3J_{F-H}$ 9.1, $^2J_{F-P}$ 106); δ_P (121 MHz; $CDCl_3$) 12.7 (t, $^2J_{P-F}$ 106); *m*/*z* (CI) 372 (100%, M[NH$_4$]$^+$), 355 (80, M + 1).

Ethyl 4-diethoxyphosphoryl-4,4-difluoro-2-ethoxycarbonyl-3-hydroxybutanoate

Potassium fluoride (0.1 g, 2.0 mmol) was added to a cool (0 °C) solution of **5** (1.00 g, 4.3 mmol) and diethyl malonate (1.94 ml, 12.82 mmol) in propan-2-ol (25 ml). The reaction mixture was stirred at 0 °C for 1 hour before being warmed to room temperature and stirred for a further 18 hours. The resulting yellow solution was diluted with diethyl ether (30 ml), washed with brine (30 ml) and re-extracted with diethyl ether (3 × 40 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to afford a yellow oil. Column chromatography (40% ethyl acetate in light petroleum) afforded the alcohol adduct (1.41 g, 88%) as a slightly yellow oil; R_f (40% ethyl acetate in light petroleum) 0.43 (Found: C, 41.9; H, 6.2; $C_{13}H_{23}F_2O_8P$ requires: C, 41.5; H, 6.1%); δ_H (300 MHz; $CDCl_3$) 4.88 (1H, br s, O*H*), 4.71–4.59 (1H, m, H-3), 4.25–4.04 (8H, m, POC*H*$_2$CH$_3$, CO$_2$C*H*$_2$CH$_3$), 3.73 (1H, d, *J* 6.0, H-2), 1.25 (6H, t, *J* 7.3, OCH$_2$C*H*$_3$), 1.17 (3H, t, *J* 7.3, CO$_2$CH$_2$C*H*$_3$), 1.15 (3H, t, *J* 7.3, CO$_2$CH$_2$C*H*$_3$); δ_C (75 MHz; $CDCl_3$) 168.0, 166.1, 118.6 (dt, $^1J_{C-P}$ 209, $^1J_{C-F}$ 266), 70.6 (dt, $^2J_{C-P}$ 17.1, $^2J_{C-F}$ 25.3), 64.8, 62.1, 50.4, 16.2, 13.8; δ_F (282 MHz; $CDCl_3$) −114.5 (1F, dd, $^2J_{F-P}$ 97.6, $^2J_{F-F}$ 305), −125.95 (1F, ddd, $^3J_{F-H}$ 21.0, $^2J_{F-P}$ 97.6, $^2J_{F-F}$ 305); δ_P (121 MHz; $CDCl_3$) 5.38 (t, $^2J_{P-F}$ 97.6); *m*/*z* (CI) 394 (55%, M[NH$_4$]$^+$), 377 (90, M + 1).

Ethyl 4-diethoxyphosphoryl-4,4-difluoro-2-ethoxycarbonylbut-2-enoate 6c

Methanesulfonyl chloride (0.86 ml, 11.17 mmol) was added in one portion to a cooled (0 °C) solution of the alcohol (1.40 g, 3.72 mmol) in DCM (25 ml) under a nitrogen atmosphere. The mixture was stirred for 30 minutes at 0 °C, before the addition of freshly distilled triethylamine (1.53 ml, 11.17 mmol). After stirring for 1 hour, water (20 ml) was added. The mixture was extracted with diethyl ether (3 × 25 ml), washed with brine (15 ml) and re-extracted with diethyl ether (3 × 25 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil. Purification by column chromatography (40% ethyl acetate in light petroleum) afforded the enedioate **6c** (0.91 g, 68%) as a clear oil; R_f (40% ethyl acetate in light petroleum) 0.35 (Found: C, 48.2; H, 6.5; $C_{13}H_{21}F_2O_7P$ requires: C, 47.9; H, 6.4%); ν_{max}/cm^{-1} 2986s, 1738vs (C=O), 1666w; δ_H (300 MHz; $CDCl_3$) 6.76 (1H, dt, $^3J_{H-P}$ 2.5, $^3J_{H-F}$ 15.0, H-3), 4.38–4.12 (8H, m, POC*H*$_2$CH$_3$, CO$_2$C*H*$_2$CH$_3$), 1.37–1.33 (12H, m, POCH$_2$C*H*$_3$, CO$_2$CH$_2$C*H*$_3$); δ_C (75 MHz; $CDCl_3$) 163.5, 161.9, 135.9, 130.9 (dt, $^2J_{C-P}$ 14.1, $^2J_{C-F}$ 21.0), 116.0 (dt, $^1J_{C-P}$ 216, $^1J_{C-F}$ 261), 65.3, 62.5, 62.0, 16.3, 13.8; δ_F (282 MHz; $CDCl_3$) −112.1 (dd, $^3J_{F-H}$ 15.0, $^2J_{F-P}$ 103); δ_P (121 MHz; $CDCl_3$) 3.6 (t, $^2J_{P-F}$ 103); *m*/*z* (CI) 376 (100%, M[NH$_4$]$^+$), 359 (80, M + 1), 174 (38).

3-Diethoxyphosphoryl-3,3-difluoro-1-nitropropan-2-ol

Prepared as for **6c** from potassium fluoride (0.5 g, 10 mmol), **5** (6.00 g, 25.6 mmol) and nitromethane (4.16 ml, 77.0 mmol) in propan-2-ol (100 ml). Column chromatography (40% ethyl acetate in light petroleum) afforded pure nitroalcohol (6.00 g, 84%) as a slightly yellow oil; R_f (40% ethyl acetate in light petroleum) 0.44 (Found: C, 30.4; H, 5.1; N, 5.1; $C_7H_{14}F_2NO_6P$ requires C, 30.3; H, 5.1; N, 5.1%); δ_H (300 MHz; $CDCl_3$) 5.30 (1H, br s, O*H*), 4.95–4.75 (1H, m, H-2), 4.63 (1H, dd, *J* 14.0, 2.5, H-1$_a$), 4.55 (1H, dd, *J* 14.0, 9.2, H-1$_b$), 4.28 (2H, q, *J* 7.3, OC*H*$_2$CH$_3$), 4.26 (2H, q, *J* 7.3, OC*H*$_2$CH$_3$), 1.36 (6H, t, $^3J_{H-H}$

7.3, OCH_2CH_3); δ_C (75 MHz; $CDCl_3$) 118.5 (dt, $^1J_{C-P}$ 211, $^1J_{C-F}$ 267), 74.9, 69.0 (dt, $^2J_{C-P}$ 7.1, $^2J_{C-F}$ 23.0), 65.6, 16.3; δ_F (282 MHz; $CDCl_3$) −115.7 (1F, ddd, $^3J_{F-H}$ 6.2, $^2J_{F-P}$ 98.3, $^2J_{F-F}$ 308), −124.1 (1F, ddd, $^3J_{F-H}$ 16.4, $^2J_{F-P}$ 98.3, $^2J_{F-F}$ 308); δ_P (121 MHz; $CDCl_3$) 4.6 (t, $^2J_{P-F}$ 98.3); *m/z* (CI) 295 (100%, $M[NH_4]^+$), 278 (36, M + 1), 248 (17).

(1*E*)-3-Diethoxyphosphoryl-3,3-difluoro-1-nitroprop-1-ene 6f

Prepared as for **6c** from methanesulfonyl chloride (5.00 ml, 65.0 mmol), nitroalcohol (6.00 g, 21.0 mmol) and freshly distilled triethylamine (8.92 ml, 65.0 mmol) in DCM (100 ml). Purification by column chromatography (20% ethyl acetate in light petroleum) afforded the nitroalkene **6f** (4.50 g, 83%) as a clear oil; R_f (20% ethyl acetate in light petroleum) 0.19; ν_{max}(film)/cm^{-1} 2987s, 1547s; δ_H (300 MHz; $CDCl_3$) 7.28 (1H, tdd, *J* 13.5, $^4J_{H-F}$ 2.5, $^4J_{H-P}$ 2.5, H-1), 7.07 (1H, tdd, *J* 13.5, $^3J_{H-F}$ 12.0, $^3J_{H-P}$ 2.5, H-2), 4.25 (4H, m, OCH_2CH_3), 1.35 (6H, t, *J* 7.3, OCH_2CH_3); δ_C (75 MHz; $CDCl_3$) 144.2, 129.9 (dt, $^2J_{C-P}$ 14.3, $^2J_{C-F}$ 23.0), 115.1 (dt, $^1J_{C-P}$ 217, $^1J_{C-F}$ 261), 65.6, 16.2; δ_F (282 MHz; $CDCl_3$) −112.1 (ddd, $^4J_{F-H}$ 2.5, $^3J_{F-H}$ 12.0, $^2J_{F-P}$ 103); δ_P (121 MHz; $CDCl_3$) 3.6 (t, $^2J_{P-F}$ 103); *m/z* (CI) 277 (100%, $M[NH_4]^+$), 260 (20, M + 1), 210 (85) [HRMS (CI, $M[NH_4]^+$) Found: 277.076492. Calc. for $C_7H_{16}F_2N_2O_5P$: 277.076983].

(1*E*)-3-Diethoxyphosphoryl-3,3-difluoro-1-phenylsulfinylprop-1-ene 6e

A mixture of **10**[43] (1.09 mmol, 0.30 g), **5** (1.09 mmol, 0.25 g), 18-crown-6 (4.35 mmol, 1.15 g) and K_2CO_3 (2.17 mmol, 0.30 g) in toluene (20 ml) was heated at 60 °C under an atmosphere of nitrogen for 2 hours. After cooling, the mixture was diluted with HCl (20 ml of a 0.1 M solution) and extracted with diethyl ether (3 × 20 ml). The combined organic extracts were washed with $NaHCO_3$ (10 ml) and brine (10 ml), dried ($MgSO_4$) and concentrated *in vacuo* to leave a yellow oil (0.57 g) which was purified by column chromatography (60% ethyl acetate in light petroleum) to afford vinyl sulfoxide **6e** (0.16 g, 43%) as a clear oil; R_f (60% ethyl acetate in light petroleum) 0.29 (Found: C, 45.9; H, 5.2; $C_{13}H_{17}F_2O_4PS$ requires: C, 46.2; H, 5.1%); ν_{max}(film)/cm^{-1} 2985s, 1632w; δ_H (300 MHz; $CDCl_3$) 7.57–7.47 (5H, m, Ar*H*), 6.95 (1H, dd, *J* 15.1, $^4J_{F-H}$ 1.8, H-1), 6.64 (1H, dd, *J* 15.1, $^3J_{F-H}$ 12.8, H-2), 4.26–4.10 (4H, m, OCH_2CH_3), 1.25 (6H, t, *J* 7.3, OCH_2CH_3); δ_C (75 MHz; $CDCl_3$) 143.8 (dt, $^3J_{C-F}$ 17.0, $^3J_{C-P}$ 6.2), 141.7, 131.9, 129.8, 125.3 (dt, $^2J_{C-F}$ 23.1, $^2J_{C-P}$ 14.1), 124.9, 116.4 (dt, $^1J_{C-F}$ 260, $^1J_{C-P}$ 218), 65.0 (d, $^2J_{C-P}$ 6.8), 16.3; δ_F (282 MHz; $CDCl_3$) −109.3 (ddd, $^2J_{F-P}$ 108, $^3J_{F-H}$ 12.8, $^4J_{F-H}$ 1.84); δ_P (121 MHz; $CDCl_3$) 5.33 (t, $^2J_{F-P}$ 108) [HRMS (CI, M + 1) Found: 339.062108. Calc. for $C_{13}H_{18}F_2O_4PS$ 339.063151]; *m/z* (CI) 339 (52%, M + 1), 322 (8), 290 (10), 274 (15), 260 (75), 153 (100).

(1*E*)-3,3-Difluoro-1-phenylsulfinylprop-1-ene 11

A mixture of sulfoxide **10** (2.14 mmol, 0.59 g), **5** (4.28 mmol, 1.00 g) and K_2CO_3 (8.55 mmol, 1.18 g) in MeCN (25 ml) was refluxed for 90 minutes under an atmosphere of nitrogen. The residual cloudy brown solution was cooled to room temperature and diluted with HCl (25 ml of a 0.1 M solution). The mixture was extracted with diethyl ether (3 × 25 ml) and the combined organic extracts were washed with $NaHCO_3$ (10 ml) and brine (10 ml), dried ($MgSO_4$) and concentrated *in vacuo* to leave a brown oil (0.65 g) which was purified by column chromatography (40% ethyl acetate in light petroleum) to afford sulfoxide **11** (0.31 g, 72%) as a white solid; mp 52–54 °C (from diethyl ether–hexane); R_f (40% ethyl acetate in light petroleum) 0.48 (Found: C, 53.6; H, 3.8; $C_9H_8F_2OS$ requires: C, 53.5; H, 4.0%); δ_H (300 MHz; $CDCl_3$) 7.66–7.59 (2H, m, Ar*H*), 7.57–7.50 (3H, m, Ar*H*), 6.85 (1H, dt, *J* 15.1, $^4J_{H-F}$ 2.6, H-1), 6.62 (1H, dtd, *J* 15.1, 3.3, $^3J_{H-F}$ 10.2, H-2), 6.27 (1H, dt, $^2J_{H-F}$ 56.0, *J* 3.3, H-3); δ_C (75 MHz; $CDCl_3$) 143.0 (t, $^3J_{C-F}$ 9.4), 141.3, 132.0, 129.9, 126.8 (t, $^2J_{C-F}$ 24.7), 124.9, 112.3 (t, $^1J_{C-F}$ 238); δ_F (282 MHz; $CDCl_3$) −114.8 (ddd, $^2J_{F-H}$ 56.0, $^3J_{F-H}$ 10.2, $^4J_{F-H}$ 2.6) [HRMS (CI, M + 1) Found 203.033381. Calc. for $C_9H_9F_2OS$ 203.034218]; *m/z* (CI) 220 (40%, $M[NH_4]^+$), 203 (100, M + 1).

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