Novel class of difluorovinylphosphonate analogues of PEP

Aparecida M. Kawamoto *,[a] and Malcolm M. Campbell[b]

[a] *Chemistry Division, Space Activity Institute, São Jose dos Campos, SP, Brazil*
[b] *School of Chemistry, University of Bath, UK*

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A new class of difluorovinylphosphonate analogues of PEP, 4,4-difluoro-4-(diethoxyphosphinoyl)-2-methylenebutanoic acid 15, methyl 4,4-difluoro-4-(diethoxyphosphinoyl)-2-methylenebutanoate 17, (*E*)- and (*Z*)-4,4-difluoro-4-(diethoxyphosphinoyl)but-2-enoic acid 14 and 4,4-difluoro-4-phosphono-2-methylenebutanoic acid 16 have been synthesized. Methyl 3,3-difluoro-3-(diethoxyphosphinoyl)-2-hydroxy-2-methylpropionate 21 and the corresponding acid 3,3-difluoro-3-phosphono-2-hydroxy-2-methylpropionic acid 23, have also been synthesized. These compounds are designed to act as potential inhibitors in the shikimic acid pathway.

The unique physiological and physical properties of organofluorine compounds make them attractive for use as medicinal products, herbicides and polymers.

Although the replacement of a phosphate functional group with a phosphonate moiety in biologically important molecules constitutes an attractive strategy for the design of non-hydrolysable substrate analogues as inhibitors or alternate substrate analogues, and for enzymes that process naturally occurring phosphates, it has been proposed that the corresponding 1,1-difluoroalkylphosphonate should be a superior replacement since this surrogate should more accurately mimic the steric and polar character of the phosphate function.[1]

Nieschalk *et al.*[2] described the synthesis of monofluoro- and difluoro-methylenephosphonate analogues of *sn*-glycerol-3-phosphate as substrates for glycerol-3-phosphate dehydrogenase. The synthesis of fluorophosphonate derivatives of N^9-benzylguanine as potent, slow-binding multisubstrate analogue inhibitors of purine nucleoside phosphorylase has been described by Halazy *et al.*[3]

Small peptides containing the non-hydrolysable phosphotyrosyl mimetic difluorophosphonomethylphenylalanine (F_2Pmp) have been shown to be extremely potent protein-tyrosine phosphatase inhibitors, with the fluorines increasing inhibitory potency 1000-fold relative to the unfluorinated species. Bien Ye *et al.*[4] reported the synthesis of one such inhibitor [difluoro(4-hydroxy-2-naphthyl)methyl]phosphonic acid, which is prepared in 12 steps from commercially available 1,3-dihydroxynaphthalene.

Phosphoenol pyruvate (PEP) plays an important role in the shikimic acid pathway for the formation of 5-enolpyruvylshikimic-3-phosphate (5-EPS-3-P) **5**, which is enzymatically synthesized by the nucleophilic attack of the 5-OH of the shikimate 3-phosphate (S3P) on the C-2 position of PEP with the elimination of phosphate[5] (Fig. 1). The reaction proceeds through a tetrahedral intermediate **3**, which has previously been isolated and characterized by Anderson *et al.*[6] Structural mimics of this intermediate are indeed potent EPSPS inhibitors.[7]

The tetrahedral intermediate **3**, although stable under alkaline conditions, is hydrolysed readily at neutral pH, although the configuration of the ketal carbon has not been elucidated.[5] It also decomposes under acidic conditions to form pyruvate and S3P.[6]

Replacement of the C–O–P group in the phosphoenol pyruvate by C–CF_2–P is one strategy used to stabilize the ketal phosphate structure of the tetrahedral intermediate **3**, and gives some stable analogues that could be potential inhibitors of EPSP synthase.

There are a variety of PEP analogues that have been examined as alternate substrates and/or inhibitors of 5-EPS-3-P synthase. Walker and Jones[8] reported the first evidence that (*Z*)-3-fluoro-PEP **6** functions as a pseudo substrate for 5-EPS-3-P synthase, producing in one step the unexpected monofluoro analogue **7**, which remains tightly bound at the enzyme site.

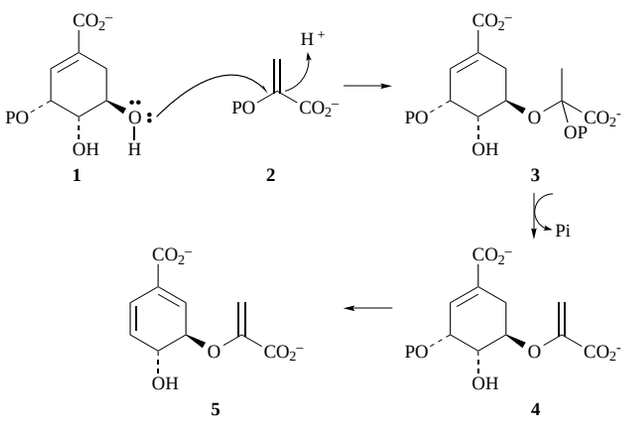
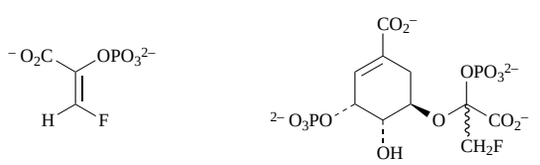
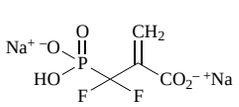


Fig. 1 Proposed mechanism of 5-EPS-3-P synthase

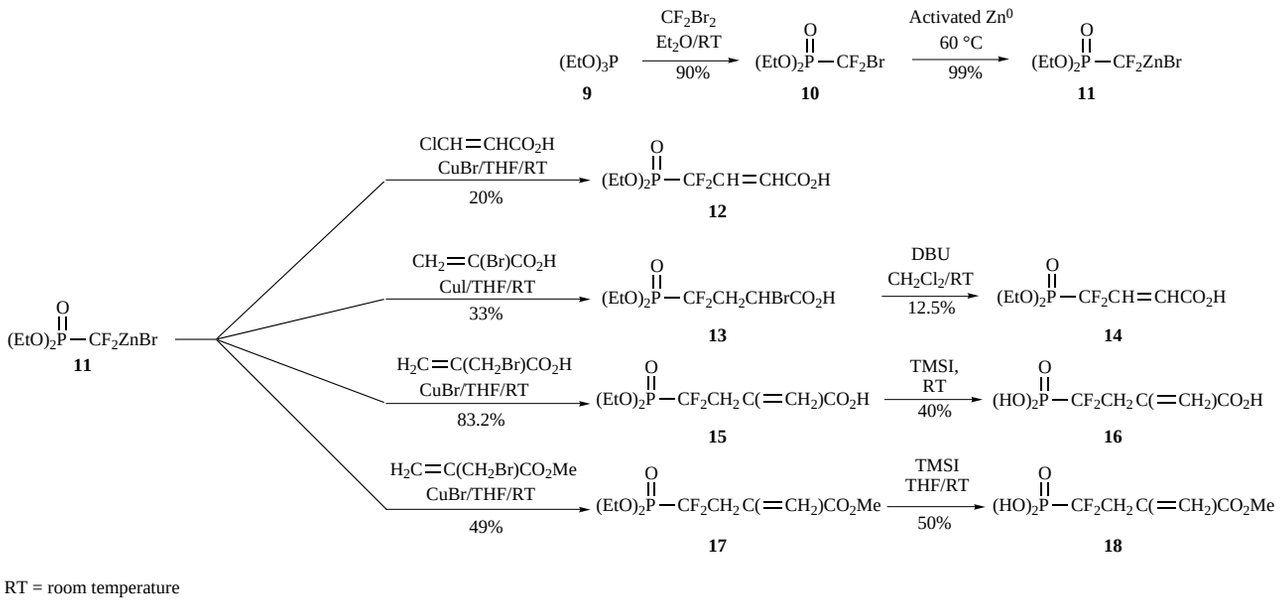
Philion *et al.*[9] described the synthesis of disodium salt **8**,





which is an isopolar and isosteric analogue of PEP. According to the authors this analogue was envisioned to be a potential Michael acceptor which could bind irreversibly to an enzyme active site for which PEP is a substrate.

PEP has also been tested as an inhibitor of prolidase by Radzicka and Wolfenden.[10] They described the action of derivatives of phosphoenol pyruvic acid—fluorinated, chlorinated or brominated—as strong competitive inhibitors of prolidase, which is an enzyme present in microorganism and mammalian tissues, where it is believed to catalyse terminal degradation of exogenous proteins. In humans, a deficiency of prolidase results in a complex clinical syndrome involving mental retardation.



RT = room temperature

Scheme 1

This work describes the synthesis of a new class of difluorovinylphosphonate analogues of PEP: 4,4-difluoro-4-(diethoxyphosphinoyl)-2-methylenebutanoic acid **15**, methyl 4,4-difluoro-4-(diethoxyphosphinoyl)butanoate **17**, (*E*)-4,4-difluoro-4-(diethoxyphosphinoyl)but-2-enoic acid **14** and (*Z*)-4,4-difluoro-4-(diethoxyphosphinoyl)but-2-enoic acid **12** and 4,4-difluoro-4-(diethoxyphosphinoyl)-2-methylenebutanoic acid **16**. Compounds **14**, **16** and **17** are expected to act as effective inhibitors of EPSP synthase, and compound **15** is expected to act as a potential inhibitor of prolidase.

Results and discussion

The proposed routes to the targets compounds **12**–**18** are outlined in Scheme 1.

Reaction with zinc dust of diethyl bromodifluoromethylphosphonate **10**, prepared from triethyl phosphite **9** and dibromodifluoromethane,[11] gave the stable [(diethoxyphosphinoyl)difluoromethyl]zinc bromide **11**[12] which by four different routes afforded compounds **12**–**18** respectively.

Reaction of **11** with 2-bromoacrylic acid gave the novel intermediate, 2-bromo-4,4-difluoro-4-(diethoxyphosphinoyl)-butanoic acid **13**, which was treated with DBU in dichloromethane to yield compound **14**. The *E* isomer was formed, and this might be the result of elimination from Newman conformation **A**, rather than **B** (Fig. 2), although there are mechanisms for the conversion of the *Z* isomer into the *E* isomer.

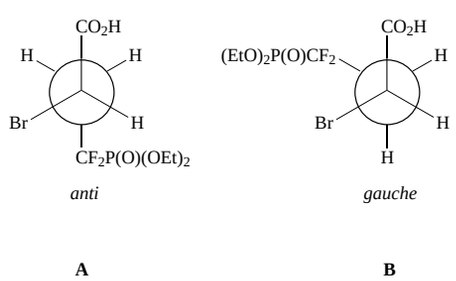


Fig. 2

In the *gauche* conformation the three groups [Br, CO_2H and $(EtO)_2P(O)CF_2$] are near each other, resulting in a steric strain and less stable conformation.

The NOE experiments confirmed the *E* configuration of compound **14**. Thus, irradiation of 2α-H (δ 6.40) had no effect on the 3β-H resonance. Furthermore, irradiation at the 3β-H resonance had no effect on the 2α-H resonance. Since the NOE effect is only noticeable over short distances, generally 2–4 Å, it is clear that the two protons (2α and 3β) are in the *trans*-position.

Table 1

	2α Vinylic proton		3β Vinylic proton	
Compound	Chemical shift	Coupling constant (Hz)	Chemical shift	Coupling constant (Hz)
E-**14**	6.40	15.8	6.92	15.9
Z-**12**	6.37	12.9	6.01	12.8

Reaction of **11** with *cis*-3-chloroacrylic acid afforded compound **12** in the same *Z* configuration as the starting material. This configuration was established by a comparative NMR analysis of compounds **12** and **14**. The chemical shifts and coupling constants for both compounds are given in Table 1.

The β vinylic hydrogen signal for compound **12** was shifted downfield to δ 6.9; a smaller coupling constant for compound **12** indicated a *Z* configuration.

The NOE experiments were used to confirm the *Z* configuration of the compound **12**. Irradiation of 2-H (δ 6.37) increased the integration for 3-H (42%) whilst irradiation of 3-H (δ 6.01) increased the integration for 2-H (42%). The NOE effect observed in compound **12** indicated a short distance, 2–4 Å, between 2-H and 3-H which confirmed their *cis* disposition.

A proposed mechanism for the formation of this product is illustrated in Fig. 3.[13]

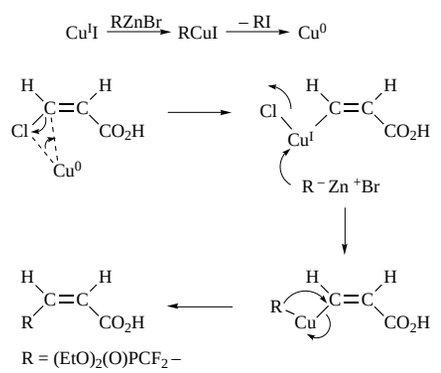
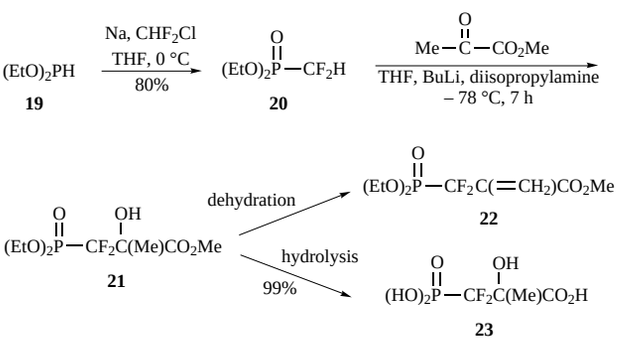


Fig. 3 Proposed mechanism for the preparation of compound **12**

Compounds **15** and **17** were prepared by the reaction of compound **11** with methyl 2-(bromomethyl)acrylate and methyl 2-(bromomethyl)acrylic acid, respectively. It was thought that the complete hydrolysis of compounds **15** and **17** with TMSI would yield the corresponding difluorodihydroxybutanoic acid **16**, *via* the tris(trimethylsilyl) phosphonate ester as intermediate. However the methyl ester **17** was not hydrolysed in this fashion and yielded compound **18** instead. The presence of the OMe group was evident from the NMR spectra, where it gave rise to a singlet at δ 3.63 in the ^{1}H NMR spectrum and a singlet at δ 53.55 in the ^{13}C NMR spectrum.

The organic zinc compound **11** is relatively stable (days to months) at room temperature and reacts with a wide variety of electrophiles in the presence of a catalytic amount of cuprous bromide to give the corresponding difluoroalkylphosphonates in good yields as reported earlier.[12,14] However, the unexpected low yields in some of the target compounds may be a result of a hydrolysis side reaction of **11** with the starting acid compounds leading to the diethyl difluoromethylphosphonate **20** as a by-product. When methyl acrylate was treated with compound **11** in order to verify the reactivity of the ester with the organic zinc reagent, there was no reaction even when the mixture was heated overnight in refluxing THF.

Compound **21**, another target compound because of its potential use in the shikimate pathway, is outlined in Scheme 2.



Scheme 2

Diethyl (difluoromethyl)phosphonate **20**, prepared from diethyl phosphite **19** and chlorodifluoromethane,[15] reacted with methyl pyruvate to yield compound **21**, which was hydrolysed to compound **23** at 60 °C in the presence of solvent (THF, ether, DCM), over a period of 7 days. It was shown that the hydrolysis of the methyl ester was incomplete even after 3 weeks under reflux. The presence of the OMe group was confirmed by ^{1}H NMR analysis in D_2O which showed one singlet at approximately δ 3.87.

Another important reaction, the dehydration of compound **21** to give the corresponding olefin **22**, which is an analogue of PEP, were unsuccessful. Thus, the method of Hofmann *et al.*[16] for dehydration of a secondary alcohol led only to decomposition of alcohol **21**. Conversion of the hydroxy group of **21** into a triflate or acetate, followed by elimination was investigated. Treatment of the alcohol with trifluoromethanesulfonic anhydride gave the triflate but it failed to undergo elimination.

Although Posner *et al.*[17] used Woelm alumina at room temperature to effect high-yield dehydrosulfonation of both secondary cyclic and acyclic alcohols and primary sulfonate esters, attempted use of basic alumina (Brockman I) for the desired elimination resulted only in recovery of starting material after several days.

Other unsuccessful attempts to dehydrate the compound **21** to give the corresponding olefin **22** were as follows: dehydration by using DAST, following the method described by Blackburn and Kent;[18] reaction of the OH group of compound **21** with acetyl chloride or mesyl choride, and then elimination with a strong base (LDA, NaH or DBU); dehydration of compound **21** using Martin Sulfurane dehydrating agent, bis[α,α-bis(trifluoromethyl) benzenemethanolato]diphenylsulfur.

Experimental

Melting points were determined on a commercially available apparatus (Electrothermal melting point apparatus), or Büchi 510, and are uncorrected. Elemental microanalysis was carried out using a Carlo Erba 1106 Elemental Analyser. Infrared spectra were recorded in the range of 4000–600 cm^{-1}, using a Perkin-Elmer 1600 FT-IR spectrophotometer and peaks are reported (ν_{max}) in wavenumbers (cm^{-1}). Spectra of liquid samples were taken as Nujol mulls, or in chloroform solution, as indicated.

^{1}H NMR Spectra were recorded on a JEOL GX FT-270 (270 MHz) spectrometer although, where indicated, a JEOL GX FT-400 (400 MHz) spectrometer was used. ^{13}C NMR Spectra were recorded on a JEOL GX FT-270 spectrometer operating at 67.8 MHz and using 90 and 135 DEPT pulse sequences to aid multiplicity determination. Chemical shifts (δ) are expressed in ppm downfield from internal tetramethylsilane ($SiMe_4$). Mass spectra were recorded using a VG Analytical 7070 E instrument with a VG 2000 data system. Electron ionisation (EI) was produced using an ionising potential of 70 eV. Chemical ionisation (CI) was employed using isobutane as the reagent gas although, where indicated, ammonia was also used.

All general reagents and solvents were purified and dried when required, using the methods described in D. D. Perrin, W. L. F. Armarego and D. R. Perrin, *Purification of Laboratory Chemicals*, Pergamon Press, Oxford, 1980.

Diethyl bromodifluoromethylphosphonate 10

This compound [δ_H($CDCl_3$) 1.4 (6 H, t) and 4.3–4.4 (4 H, m)] was prepared by the reaction in diethyl ether of triethyl phosphite and dibromodifluoromethane at room temperature.[11]

[(Diethoxyphosphinoyl)difluoromethyl]zinc bromide 11

This compound [δ_H($CDCl_3$) 1.4 (6 H, t) and 4.2–4.3 (4 H, m)] was prepared by the reaction in dry THF of **10** with acid-washed zinc powder at 60 °C.

Diethyl (difluoromethyl)phosphonate 20

This compound [δ_H($CDCl_3$) 1.4 (6 H, t), 4.2–4.3 (4 H, m) and 5.9 (1 H, td)] was prepared by the reaction in THF of diethyl phosphite with chlorodifluoromethane at 0 °C.[15]

Methyl 4,4-difluoro-4-(diethoxyphosphinoyl)-2-methylenebutanoate 17

To the solution of [(diethoxyphosphinoyl)difluoromethyl]zinc bromide (1800 mg, 5.41 mmol) in dry THF (6 cm^3) was added a catalytic amount of cuprous bromide followed by methyl 2-(bromomethyl)acrylate (1000 mg, 5.6 mmol), added dropwise at room temperature. The mixture was stirred overnight after which it was filtered, poured into water (10 cm^3) and extracted with diethyl ether (3 × 10 cm^3). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The product was purified using column chromatography on silica gel with ethyl acetate–light petroleum (bp 60–80 °C) (3:7) as the eluent to give the title compound (757 mg, 49%); R_F 0.48 (light petroleum–ethyl acetate, 1:1) (Found: C, 42.1; H, 6.10. $C_{10}H_{17}F_2O_5P$ requires C, 42.0; H, 6.0%); ν_{max}(liquid film)/cm^{-1} 3502, 2988, 1725 (C=O), 1634 (C=CH_2), 1274 (P=O) and 1042 (OCH_3); δ_H($CDCl_3$) 1.39 (t, C$H_3$$CH_2$OP, J 7.05), 3.09–3.25 (td, CF_2CH_2, $J_{H,F}$ 19.64, $J_{H,P}$ 4.76), 3.79 (s, OCH_3), 4.29 (m, CH_3CH_2OP), 5.89 (s, vinylic H) and 6.47 (s, vinylic H); δ_C($CDCl_3$) 1.62 (d, CH_3CH_2OP, $J_{C,P}$ 5.5), 34.89 (td, CF_2CH_2, $J_{C,F}$ 21.15, $J_{C,P}$ 16.53), 52.02 (s, OCH_3), 64.42 (d, CH_3CH_2OP, $J_{C,P}$ 7.3), 118.79 (td, CF_2, $J_{C,F}$ 261.5, $J_{C,P}$ 216.7), 131.15 (s, C=CH_2) and 166.45 (s, C=O); *m*/*z* (EI) 286 (M$^+$, 34%), 255

($M^+ - OMe$, 25), 199 (58) and 109 (100); *m/z* (CI) 287 (MH^+, 100%).

4,4-Difluoro-4-(diethoxyphosphinoyl)-2-methylenebutanoic acid 15

To a solution of [(diethoxyphosphinoyl)difluoromethyl]zinc bromide (1200 mg, 3.4 mmol) in dry THF (6 cm^3) was added a catalytic amount of cuprous bromide followed by 2-bromomethylacrylic acid (600 mg, 3.64 mmol). The mixture was stirred overnight at room temperature after which it was filtered, poured into water (10 cm^3) and extracted with diethyl ether (3 × 10 cm^3). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The product was purified using column chromatography on silica gel with chloroform–methanol (98.5:1.5) as eluent, to give the title compound (769 mg, 83.2%); R_F 0.40 ($CHCl_3$–MeOH, 9:1) (Found: C, 39.5; H, 5.6. $C_9H_{15}F_2O_5P$ requires C, 39.7; H, 5.6%); ν_{max}(liquid film)/cm^{-1} 3498 (CO_2H), 1725 (C=O), 1634 (C=CH_2) and 1269 (P=O); δ_H($CDCl_3$) 1.39 (t, C$H_3$$CH_2$OP, *J* 7.08), 3.17 (td, CF_2CH_2, $J_{H,F}$ 19.5, $J_{H,P}$ 4.88), 4.25–4.23 (m, CH_3CH_2OP), 5.98 (s, vinylic H) and 6.6 (s, vinylic H); δ_C($CDCl_3$) 16.2 (d, CH_3CH_2OP, $J_{C,P}$ 5.5), 34.6 (td, CF_2CH_2, $J_{C,F}$ 29.2, $J_{C,P}$ 16.5), 64.8 (d, CH_3CH_2OP, $J_{C,P}$ 7.7), 118.1 (td, CF_2, $J_{C,F}$ 261.1, $J_{C,P}$ 217.1), 133.0 (s, C=CH_2) and 170.3 (s, C=O); *m/z* (CI) 273 (MH^+, 100%); *m/z* (EI) 272 (M^+, 2%), 227 ($M^+ - CO_2H$, 12), 201 [$M^+ - C(CH_2)CO_2H$, 13], 199 (50) and 109 (100).

4,4-Difluoro-4-(phosphono)-2-methylenebutanoic acid 16

Compound **15** (1200 mg, 4.4 mmol) in dry THF (100 cm^3) was stirred with TMSI (2100 mg, 10.5 mmol), under N_2 at room temperature for 6 h. The excess of silylating reagent and ethyl iodide were removed *in vacuo* to give the bis(trimethylsilyl)-phosphonate esters, which were dissolved in diethyl ether (30 cm^3) and then treated with water (20 cm^3) to give the title compound **16** (475 mg, 50%); this was purified by column chromatography ($CHCl_3$–MeOH, 90:10); R_F 0.33 (chloroform–methanol, 1:1), mp 72 °C; ν_{max}(D_2O)/cm^{-1} 3424, 2527, 1700 (C=O), 1630 (C=C) and 1209 (P=O); δ_H(D_2O) 3.14 (dt, CF_2CH_2, $J_{H,F}$ 20.4, $J_{H,P}$ 2.47), 5.89 (s, vinylic H) and 6.34 (s, vinylic H); δ_C(D_2O) 35.65 [q, CF_2CH_2C(=CH_2), $J_{C,P}$ 21.5, $J_{C,F}$ 36.9], 122.7 (td, CF_2, $J_{C,P}$ 204.9, $J_{C,F}$ 271.8), 132.9 (s, C=CH_2) and 171.8 (C=O); *m/z* (−ve FAB) 215 (MH^-, 35%), 197 (20), 177 (12) and 159 (10).

4,4-Difluoro-4-(diethoxyphosphinoyl)-2-bromobutanoic acid 13

To a solution of [(diethoxyphosphinoyl)difluoromethyl]zinc bromide (1304 mg, 4.03 mmol) in dry THF (3 cm^3), was added a catalytic amount of cuprous iodide followed by 2-bromoacrylic acid (700 mg, 4.64 mmol) dissolved in dry THF (3 cm^3), added dropwise at room temperature. The mixture was stirred for 4 days after which it was filtered, poured into brine (10 cm^3) and extracted with diethyl ether (3 × 10 cm^3). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The product was purified using column chromatography on silica gel with chloroform–methanol–acetic acid (95:4:1) as eluent to give the title compound (450 mg, 33%); R_F 0.46 ($CHCl_3$–MeOH–AcOH, 90:8:2) (Found: C, 28.6; H, 4.3. $C_8H_{14}BrF_2O_5P$ requires C, 28.3; H, 4.2%); ν_{max}(liquid film)/cm^{-1} 3459 (CO_2H), 3057, 2981, 1739 (C=O), 1596, 1243 (P=O) and 1174; δ_H($CDCl_3$) 1.39 (t, C$H_3$$CH_2$OP, *J* 7.05), 2.59–2.83 (m, CF_2CHH), 3.09–3.34 (m, CF_2CH*H*), 4.25–4.36 (m, CH_3CH_2OP) and 4.55 (dd, CH_2CH*H*Br, $J_{2,3b}$ 4.39, $J_{2,3a}$ 9.28); δ_C($CDCl_3$) 16.2 (d, CH_3CH_2OP, $J_{C,P}$ 5.5), 34.9 (s, CF_2CH_2-*C*HBr), 39.3 (dd, CF_2CH_2CHBr, $J_{C,F}$ 36.35, $J_{C,P}$ 19.85), 65.5 (d, CH_3CH_2OP, $J_{C,P}$ 8.9), 118.7 (td, CF_2, $J_{C,P}$ 219.2) and 171.6 (s, C=O); δ_F($CDCl_3$) −112.1 (dddd, $J_{F,F}$ 301.7, $J_{F,P}$ 105.2, $J_{3b,F}$ 25.4, $J_{3a,F}$ 12.7, 1 F) and −113.2 (dddd, $J_{F,F}$ 301.7, $J_{F,P}$ 105.7, $J_{3b,F}$ 25.5, $J_{3a,F}$ 11.6, 1 F); δ_P($CDCl_3$) 5.08 (t, ^{1}H decoupled, $J_{P,F}$ 104; m, ^{1}H coupled, $J_{P,3a} = J_{P,3b}$ 4.03); *m/z* (CI) 339, 341 (MH^+, 98%) 321, 323 ($M^+ - OH$, 20) and 293, 295 ($M^+ - CO_2H$, 7).

(*E*)-4,4-Difluoro-4-(diethoxyphosphinoyl)but-2-enoic acid 14

To a solution of the butanoic acid **13** (490 mg, 1.44 mmol) in dry CH_2Cl_2 (6 cm^3) was added dropwise DBU (439 mg, 2.88 mmol) at 0 °C. The solution was allowed to warm to room temperature after which it was stirred overnight. The solution was then acidified to pH 2.0 with $KHSO_4$ (0.5 M), washed with brine and extracted with CH_2Cl_2. After work-up the product was purified using column chromatography on silica gel with chloroform–methanol–acetic acid (95:4:1) as eluent to give the product as an amber liquid (43.6 mg, 12.5%); R_F 0.55 ($CHCl_3$–MeOH–AcOH, 90:8:2); ν_{max}(liquid film)/cm^{-1} 3423, 2917 (CO_2H), 1722 (C=O), 1641 (C=C) and 1443, 1260 (P=O); δ_H($CDCl_3$) 1.38 (t, C$H_3$$CH_2$OP, *J* 7.15), 4.23–4.36 (m, CH_3CH_2OP), 6.40 (dq, CF_2CH=C*H*, $J_{2\alpha,3\beta}$ 15.8, $J_{2\alpha,F}$ 5.31, $J_{2\alpha,P}$ 2.57), 6.92 (dtd, CF_2CH=CH, $J_{3\beta,2\alpha}$ 15.8, $J_{3\beta,F}$ 12.7, $J_{3\beta,P}$ 1.95) and 9.99 (br s, CO_2H); δ_C($CDCl_3$) 16.3 (d, CH_3CH_2OP, $J_{C,P}$ 5.5), 65.4 (d, CH_3CH_2OP, $J_{C,P}$ 6.6), 117.9 (td, CF_2, $J_{C,F}$ 260.0, $J_{C,P}$ 218.2), 127.9 (q, CF_2CH=C*H*, $J_{C,P} = J_{C,F}$ 7.0), 136.3 (td, CF_2CH=CH, $J_{C,P}$ 13.2, $J_{C,F}$ 22.05) and 167.6 (s, C=O); *m/z* (CI) 259 (MH^+, 259.0547. $C_8H_{13}O_5F_2P$ requires *M*, 259.0547, 100%) and 213 ($M^+ - CO_2H$, 3).

(*Z*)-4,4-Difluoro-4-(diethoxyphosphinoyl)but-2-enoic acid 12

To a solution of [(diethoxyphosphinoyl)difluoromethyl]zinc bromide (1191 mg, 3.58 mmol) in dry THF (6 cm^3) was added, under N_2, a catalytic amount of cuprous bromide followed by *cis*-3-chloroacrylic acid (382 mg, 3.59 mmol). The mixture was stirred for 24 h at room temperature after which it was filtered, poured into brine (10 cm^3) and extracted with diethyl ether (3 × 10 cm^3). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The product was purified using column chromatography on silica gel with chloroform–methanol–acetic acid (95:4:1) as eluent to give the title compound (924 mg, 20%); R_F 0.35 ($CHCl_3$–MeOH–AcOH, 90:8:2) (Found: C, 37.2; H, 5.4. $C_8H_{13}F_2O_5P$ requires C, 37.2; H, 5.1%); ν_{max}(liquid film)/cm^{-1} 3417, 2989 (CO_2H), 2571, 1731 (C=O), 1657 (C=C), 1620, 1479, 1396 and 1254 (P=O); δ_H($CDCl_3$) 1.41 (t, C$H_3$$CH_2$OP, *J* 7.05), 4.29–4.40 (m, CH_3CH_2OP), 6.01 (dtd, CF_2CH=CH, $J_{3\beta,2\alpha}$ 12.8, $J_{3\beta,F}$ 12.7, $J_{3\beta,P}$ 1.94) and 6.37 (dq, CF_2CH=C*H*, $J_{2\alpha,3\beta}$ 12.9, $J_{2\alpha,F}$ 2.47, $J_{2\alpha,P}$ 2.47); δ_C($CDCl_3$) 16.2 (d, CH_3CH_2OP, $J_{C,P}$ 5.5), 66.2 (d, CH_3CH_2OP, $J_{C,P}$ 6.6), 116.1 (td, CF_2, $J_{C,F}$ 261.7, $J_{C,P}$ 214.9), 126.9 (td, CF_2CH=CH, $J_{C,P}$ 13.6, $J_{C,F}$ 23.9), 129.9 (q, CF_2CH=C*H*, $J_{C,P} = J_{C,F}$ 7.2) and 166.1 (s, C=O); *m/z* (CI) 259 (MH^+, 259.0547. $C_8H_{13}O_5F_2P$ requires *M*, 259.0547, 100%), 241 ($M^+ - OH$, 35) and 213 ($M^+ - CO_2H$, 20).

Methyl [3,3-difluoro-3-(diethoxyphosphinoyl)-2-hydroxy-2-methyl]propionate 21

A solution of butyllithium (2.91 cm^3, 4.66 mmol) in hexane was added at 0 °C to a stirred solution of diisopropylamine (472 mg, 4.66 mmol) in dry THF (10 cm^3), and the mixture was stirred for 30 min. It was then cooled to −78 °C and treated with a solution of diethyl difluoromethylphosphonate (761 mg, 4.05 mmol) in dry THF (10 cm^3), pre-cooled to −78 °C, added slowly. The mixture was then stirred for 1 h at −78 °C. Methyl pyruvate (623 mg, 6.1 mmol) in dry THF (10 cm^3), pre-cooled to −78 °C, was added dropwise to the mixture which was then stirred at −78 °C for 6 h, slowly warmed to room temperature, and then stirred for an additional 2 h. The reaction mixture was then poured into dry diethyl ether (50 cm^3) and washed with saturated aqueous NH_4Cl (3 × 10 cm^3). The organic layer was then dried (Na_2SO_4) and concentrated *in vacuo*. The product was purified using column chromatography on silica gel with ethyl acetate–light petroleum (bp 60–80 °C) (1:1) as eluent, to give a colourless oil; R_F 0.26 (light petroleum–ethyl acetate, 1:1) (Found: C, 37.2; H, 6.1. $C_9H_{17}F_2O_6$ requires C, 37.2;

H, 5.9%); ν_{max}(liquid film)/cm^{-1} 3474, 2990, 1747 (C=O), 1657, 1265 (P=O), 1168, 1022 (OCH_3); δ_H($CDCl_3$) 1.38 (t, CH_3CH_2OP, $J_{H,H}$ 7.1), 1.62 [t, $CF_2C(OH)CH_3$, $J_{H,F}$ 1.47], 3.87 (s, OCH_3), 4.01 (s, OH) and 4.29 (m, CH_3CH_2OP); δ_C($CDCl_3$) 16.2 (d, CH_3CH_2OP, $J_{C,P}$ 4.4), 19.1 (s, CCH_3), 53.5 (s, OCH_3), 64.8 (d, CH_3CH_2OP, $J_{C,P}$ 6.6), 117.7 (td, CF_2, $J_{C,F}$ 274.3, $J_{C,P}$ 207.1) and 171.9 (s, C=O); δ_F($CDCl_3$) −115.1 (dd, $J_{F,F}$ 306.9, $J_{F,P}$ 98.9, 1 F) and −118.4 (dd, $J_{F,F}$ 306.9, $J_{F,P}$ 102.3, 1 F); δ_P($CDCl_3$) 5.1 (t, ^{1}H decoupled, $J_{P,F}$ 101.1; m, ^{1}H coupled, $J_{P,H}$ 7.74); *m*/*z* (EI) 290 (M^+, 2%), 231 ($M^+ - CO_2Me$, 68), 187 (95) and 175 (100); *m*/*z* (CI) 291 (MH^+, 100%).

3,3-Difluoro-3-phosphono-2-hydroxy-2-methylpropionic acid 23

The ester **21** (1006 mg, 0.3466 mmol) was stirred with TMSI in excess (30 cm^3) without solvent at room temperature for 2 days and then heated to 60 °C for 5 days. The excess of silylating reagent and ethyl iodide were removed under reduced pressure to give the trisilylated ester. This was dissolved in diethyl ether (50 cm^3) and hydrolysed with water (3 × 20 cm^3), to give a viscous brown product (76 mg, 100%); ν_{max}(D_2O)/cm^{-1} 3416, 2518, 1724 (C=O), 1451, 1209 (P=O) and 1084; δ_H(D_2O) 1.44 (s, CH_3); δ_C(D_2O) 19.0 (s, CH_3), 118.4 (td, CF_2, $J_{C,F}$ 269.9, $J_{C,P}$ 191.4) and 173.8 (s, C=O); *m*/*z* (+ve FAB) 221 (MH^+, 100%), 175 ($M^+ - CO_2H$, 65), 149 (20) and 91 (60); *m*/*z* (−ve FAB) 219 (MH^-, 218.9861. $C_4H_7F_2O_6P$ requires MH^-, 218.9870, 100%).

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