A Convenient Synthesis of Dibenzyl α,α-Difluoromethyl-β-ketophosphonates

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The first synthesis of dibenzyl α,α-difluoro-β-ketophosphonates has been accomplished by an original fluorination reaction, namely addition of the F^+ ion to the enolate form of the corresponding dibenzyl β-ketophosphonate. After an easy cleavage of the benzyloxy protecting groups on the phosphorus atom, α-fluoro-β-ketophosphonic acids were subsequently obtained as stable carboxyphosphate mimics. This approach enables α,α-difluoro-β-ketophosphonate moieties to be introduced into multiply functionalised molecules, thus making the previously described diethyl phosphonate route no longer relevant. Moreover, study of their stability under neutral and basic conditions showed the importance of the keto-enol equilibrium in the decomposition pathway of these molecules.
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Introduction

The constant need for new drugs displaying high and specific antiparasitic activity — particularly for new trypanocidal molecules — caused us to focus our attention on substrate analogues of glycolytic enzymes.[1] Carbohydrate metabolism in trypanomastidae is compartmentalised into specific organelles called glycosomes, and is the sole energy source of the bloodstream form of *Trypanosoma brucei*,[2] the parasite responsible for sleeping sickness. The inhibition of any step of the glycolytic pathway should result in the death of the parasite.[3−5]

Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) from trypanosomastidae[6] was chosen as a promising drug target[7] for two reasons: i) according to the kinetic model of trypanosome glycolysis,[8,9] the flux is mainly controlled by glucose transport and by four glycolytic enzymes, GAPDH among them, and ii) a cysteine at its active site plays a key role in the multi-step mechanism of this enzyme. GAPDH catalyses the oxidative phosphorylation of glyceraldehyde-3-phosphate (GAP) into 1,3-bisphospho-D-glyceric acid (1,3-diPG) in the presence of NADH and inorganic phosphate. This 1,3-diPG, also the common substrate of two other glycolytic enzymes, phosphoglycerate kinase (PGK) and phosphoglycerate mutase (PGM), is one of the few glycolytic metabolites able to cross the glycosomal membrane.[2] Consequently, analogues of such a substrate should offer the advantage of easy uptake into the parasite's microbody. Several diphosphonates and phosphono-phosphates[10] have already been synthesised and have proved to be valuable inhibitors of GAPDH from *Trypanosoma brucei*. From results accumulated from Blackburn's work[11−13] on the electronic and structural analogy between α,α-difluoromethylphosphonate and the phosphate group,[14] it has been shown that α,α-difluoromethyl-β-ketophosphonates have higher affinities than their corresponding non-fluorinated analogues for GAPDH from different organisms (parasite and mammals).[10] This improvement was ascribed to the effects of the two fluorine atoms on the pK_a of the phosphonate (the pK_{a_2} of an α,α-difluoromethylphosphonate is two units lower than the pK_a of the corresponding methylphosphonate), as well as to the narrowing of the P−C−C(O) angle. Thus, α-fluoromethyl-β-ketophosphonate appeared to be a more hydrolytically stable mimic of the mixed anhydride moiety P(O)OC(O) than the corresponding α-methyl-β-ketophosphonates. The high affinities of these fluorinated substrate analogues may also be explained by association of the fluorine atoms with residues of the targeted protein active site through H-bonding.[15]

To date, α-methyl-β-ketophosphonic acids have mainly been synthesised via their corresponding diethoxy- or diisopropyloxyphosphonate neutral analogues,[16−18] the dialkyloxy protecting groups of which were then cleaved by a fast hydrolysis of the bis-trimethylsilyl esterphosphonate intermediate.[19] This deprotection becomes very slow with α,α-difluorinated analogues[20,21] and such a long exposure to an acidic medium is incompatible with numerous chemically sensitive functions. To synthesise polyfunctionalised molecules bearing α-fluoro-β-ketophosphonate moieties, dibenzyl protection on the phosphoryl group appeared to be the only alternative, since this can easily and quickly be cleaved by reduction under mild and neutral conditions, even in the presence of fluorine atoms on the C_α−P.[22] However, the general route through condensation of the dibenzyl α,α-difluoromethanephosphonate carbanion with carboxylic esters or carboxylic acid chlorides would no

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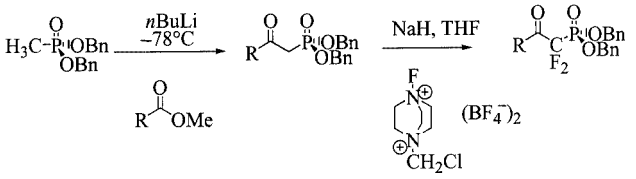
longer be applicable, since this carbanion is too unstable to react.[23] Reaction with a triflate group is the only previously reported successful example, by Berkowitz.[22] Consequently, no dibenzyl α-fluoromethyl-β-ketophosphonate has previously been isolated.

In this report we describe a novel and convenient method for the synthesis of dibenzyl α,α-difluoromethyl-β-ketophosphonates resulting from the phosphonylation of compounds bearing chemically sensitive groups such as alcohols, α-diols, ketones or other phosphoryl groups. Moreover, the stabilities of such compounds were studied with regard to the number of fluorine atoms introduced onto the methylene group, as well as the nature of the carbonyl substituents.

Results and Discussion

General Procedure for the Synthesis of Dibenzyl α,α-Difluoromethyl-β-ketophosphonates

All syntheses were carried out by a convenient two-step reaction sequence (Scheme 1).



Scheme 1

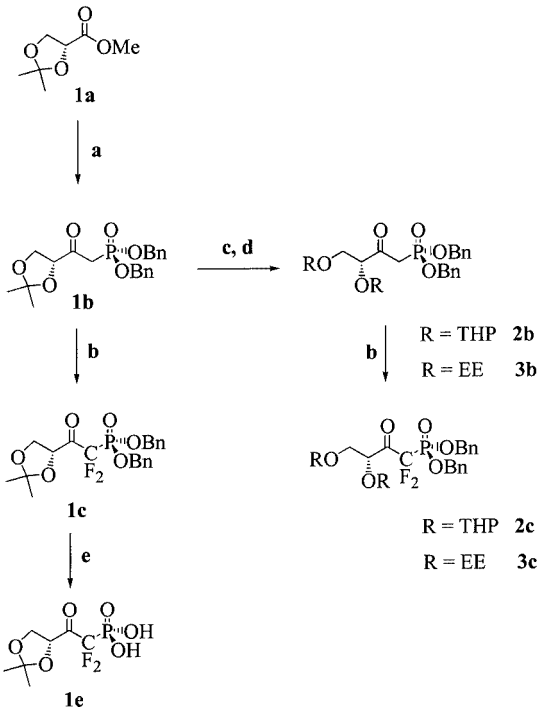
(i) The first step deals with the synthesis of the nonfluorinated β-ketophosphonate derivatives by condensation of the $(BnO)_2P(O)CH_2Li$ carbanion with the appropriate methyl ester. The stable intermediates were isolated and purified.

(ii) In the second step, the fluorination of the α-methylene group of the β-ketophosphonate framework was carried out with an F^+ donor, namely 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (F-TEDA), usually employed for fluorination of 1,3-dicarbonylated compounds.[24,25] The fluorination process consists of initial deprotonation of the α-methylene group of the β-ketophosphonate with sodium hydride (2 equiv.) at low temperature, followed by treatment with the F-TEDA reagent (2 equiv.). The resulting dibenzyl α,α-difluoromethyl-β-ketophosphonates were thus obtained in moderate to good yields (up to 60%). Whatever the concentration of NaH (from 0.5 to 3 equiv.), these syntheses always generated minor amounts of monofluorinated phosphonate (5 to 10%) as side-products, which were systematically characterised by spectral analysis. For a few examples, these were isolated during the purification of the difluorinated derivatives.

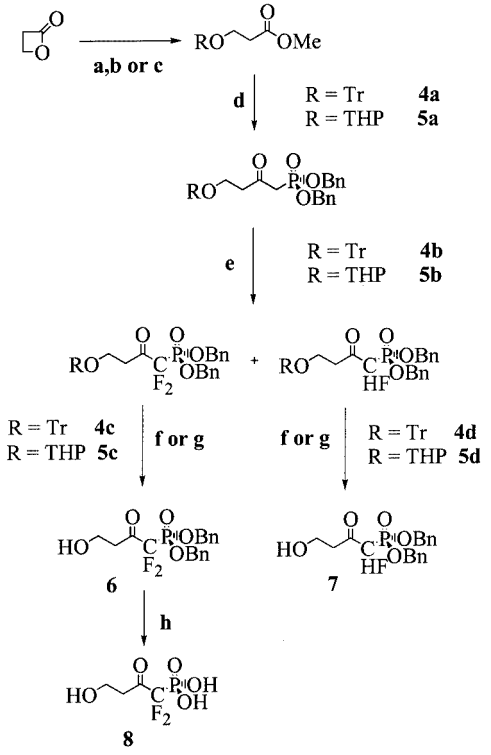
This general method was successfully used for the synthesis of several dibenzyl β-ketophosphonates bearing either α-diol or monoalcohol moieties as substituents. The precursors were synthesised from 1,2;5,6-di-*O*-isopropylidene-D-mannitol and β-propionolactone by a previously described procedure.[10] Protection of all hydroxyl groups before the fluorination step was necessary, since F-TEDA is known to oxidise hydroxy functions to carbonyl groups.[26] We chose tetrahydropyranyl (THP), ethoxyethyl (EE) and trityloxy (Tr) groups, owing to their stability under alkaline conditions and their easy cleavage by mild acidic hydrolysis. Tetrahydropyranyl and ethoxyethyl groups were introduced under anhydrous acidic conditions by use of catalytic amounts of pyridinium *para*-toluenesulfonic acid. The tritylation reaction was achieved under basic conditions by addition of the alcohol to trityl chloride in anhydrous pyridine (Scheme 2 and 3). Selected representative spectroscopic data (^{13}C, ^{31}P, $J_{P,C}$ and $J_{P,F}$) of all α-monofluoro- and α,α-difluoro-β-ketophosphonates obtained by this synthetic pathway are presented in Table 1 and compared to those of the nonfluorinated parent molecules. All the nonfluorinated phosphonates (**1b**−**5b**) exist only in their ketone forms, as attested to by the ^{13}C chemical shifts of their C_α−P moieties. For the di-*O*-THP- and di-*O*-EE-protected compounds, the diastereoisomers were not isolated and were only detected by ^{31}P NMR spectroscopy.

Of the α-monofluoro-β-ketophosphonates, compounds **1d**, **2d** and **3d** were identified only by ^{31}P NMR spectroscopy, while compounds **4d** and **5d** were isolated and purified.

All the α,α-difluoro-β-ketophosphonates **1**−**5c** and **6** were isolated and characterised by NMR spectroscopy and mass spectrometry. They exist in equilibria with their hy-



Scheme 2. a) $CH_3P(O)(OBn)_2$, *n*BuLi, THF, −78 °C, 99%; b) NaH, F-TEDA, THF/DMF (50:50), 60%; c) HCl, H_2O; d) PPTS, ethyl vinyl ether (or 3,4-dihydro-2*H*-pyran), CH_2Cl_2, 73% and 90%; e) H_2 Pd/C, CH_3OH, 98%



Scheme 3. a) NaOH, MeOH; b) TrCl, pyridine; c) 3,4-dihydro-2*H*-pyran, PPTS, CH_2Cl; d) $CH_3P(O)(OBn)_2$, *n*BuLi, THF, −78 °C; e) NaH, F-TEDA, THF/DMF (50:50), **4c** 48%, **4d** 5%, **5c** 55%, **5d** 5%; f) Et_2O/HCOOH; g) PPTS, MeOH, **6** 72%, **7** 83%; h) H_2 Pd/C, CH_3OH, 96%

drated forms, which account for about 10−20% by ^{13}C NMR spectroscopy [$C(OH)_2$ signal, td, δ = 95−96 ppm]. This equilibrium can be completely displaced towards the ketone form by azeotropic distillation with anhydrous benzene. The dibenzyloxy protecting groups of the α-monofluoro- and α,α-difluoro-β-ketophosphonates were easily and completely removed by catalytic hydrogenolysis. The dibenzyl α,α-difluoro-β-ketophosphonates were thus quickly converted into their corresponding phosphonic acids under neutral conditions. The efficiency of such mild deprotecting conditions was illustrated by the almost quantitative conversion of the dibenzyl esters **1c** and **6** into their corresponding phosphonic acids **1e** and **8**.

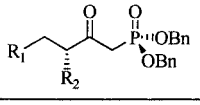
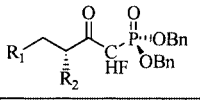
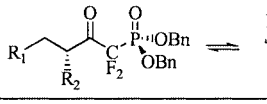
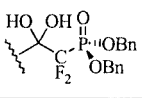
Fluorination Mechanism

A few electrophilic fluorinations have already been described in the literature, all of them involving a specific synthetic approach:

(i) The fluorination of nonfunctionalised diethyl phosphonates has been reported to involve the addition of the fluorine ion F^+ to a "stabilized" α-phosphoryl anion $(EtO)_2P(O)YRC^-$, in which the stabilizing groups Y were either aryl,[27] trialkylsilyl[28,29] or arenesulfonyl.[30,24]

(ii) For β-diketones, electrophilic fluorination occurs at an enolic intermediate.[24] Under neutral conditions, the β-diketones exist almost completely as enols,[31] and treatment with one equivalent of F-TEDA afforded the corresponding α-monofluoro derivative in excellent yield. Under the same conditions, the fluorination of keto-esters (8 to 10% of en-

Table 1. NMR spectral data of the fluorinated and non-fluorinated dibenzyl-β-ketophosphonates

														
R_1 R_2	**δ ^{31}P (ppm)**	**$^1J_{P-C}$ (Hz)**	**δ $^{13}C_α$-P (ppm)**		**δ ^{31}P (ppm)**	**$^2J_{P-F}$ (Hz)**	**δ $^{13}C_α$-P (ppm)**		**δ ^{31}P (ppm)**	**$^2J_{P-F}$ (Hz)**	**δ $^{13}C_α$-P (ppm)**	**δ ^{31}P (ppm)**	**$^2J_{P-F}$ (Hz)**	
	**1b**	20.8	132.2	37.7	**1d**	d, 10.1	71.7	—	**1c**	t, 3.3	96.0	116.8	t, 7.3	96.0
$R_1 = R_2$ = THP														
	**2b**	21.6 22.5	132.0 132.0	38.6 38.7	**2d**	d, 10.3 d, 10.5	71.5 71.5	—	**2c**	t, 3.3 t, 3.5	95.0 95.0	116.2 116.3	t, 7.1 t, 7.2	95.8 95.8
$R_1 = R_2$ = EE														
	**3b**	21.5 22.4	131.9 131.9	39.0 39.1	**3d**	d, 10.8 d, 11.0	71.3 71.3	—	**3c**	t, 3.2 t, 3.6	95.2 95.2	116.3 116.5	t, 7.2 t, 7.3	95.9 95.9
R_1 = O-Tr **R_2 = H**	**4b**	21.2	128.5	42.6	**4d**	d, 11.0	71.7	91.8	**4c**	t, 4.1	98.2	113.2	t, 8.4	99.6
R_1 = O-THP **R_2 = H**	**5b**	21.1	128.7	43.1	**5d**	d, 11.1	71.2	91.8	**5c**	t, 4.0	98.1	113.0	t, 8.4	99.2
R_1 = OH **R_2 = H**		21.2	128.3	42.9	**7**	d, 11.0	71.7	91.8	**6**	t, 3.8	97.0	113.0	t, 8.2	99.4

olic form) occurred much more slowly, but could rapidly be accomplished by complete displacement of the equilibrium towards the enolate species under basic conditions.

The fluorination method we report here was successfully achieved only in the presence of at least one equivalent of base (NaH), no fluorination of dibenzyl β-ketophosphonates being observed under neutral conditions. This caused us to postulate that the fluorination mechanism involved an enolate intermediate resulting from the deprotonation of the β-ketophosphonate moiety. This enolisation was detected for dibenzyl 2-oxopropyl-phosphonate, the enolate species being unambiguously identified by ^{13}C NMR spectroscopy [δ = 63.8 ppm (d, $^{1}J_{C\text{-}P}$ = 196 Hz, =*C*H-P)] and IR spectroscopy (disappearance of $\nu_{C=O}$ = 1714 cm^{-1}).

The experimental procedure was optimised to favour the synthesis of the α,α-difluoro-β-ketophosphonates (2 equivalents of base). Nevertheless, the fluorination reaction does not seem to depend on the amount of base, since the α,α-difluorophosphonate is always the main product whatever the quantity of sodium hydride added, varying from 0.5 to 3 equivalents relative to the β-ketophosphonate. This predominant difluorination reaction occurs through an initial addition of F-TEDA to the enolate tautomer, followed by a fast *gem* fluorination of the more stable enolate resulting from the monofluoro derivative. For the latter, as in the case of β-diketones, the enol form is able to exist in the absence of base, and can therefore give rise to the difluoro derivative despite the use of less than one equivalent of base.

Stability of Dibenzyl α-Fluoro-β-ketophosphonates

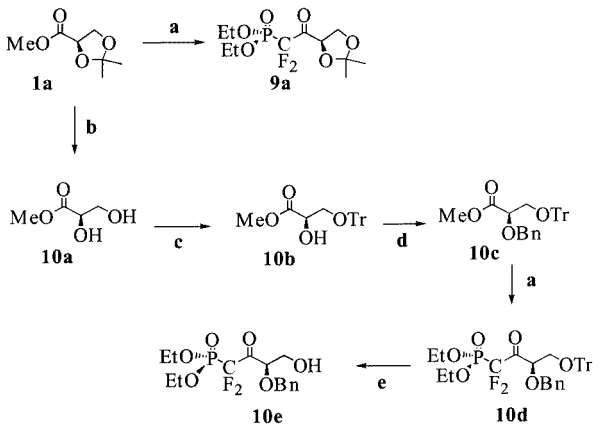
In order to achieve the synthesis of the 1,3-diPG analogues 4,4-difluoro-3-oxo-4-phosphonobutyl phosphates deprotection of the hydroxyl groups was required in order to phosphorylate the primary alcohol selectively. This could be effected by a recently reported procedure already successfully applied to nonfluorinated analogues.[10]

At first, the reaction was studied with the monohydroxylated derivatives **4c,d** and **5c,d** (Scheme 3). The tritylhydroxy (**4c** and **4d**) and tetrahydropyranyl (**5c** and **5d**) protecting groups were removed, affording the corresponding mono- and difluorinated alcohols **7** (from **4d** and **5d**) and **6** (from **4c** and **5c**) as stable compounds. Whereas the cleavage of the hydroxyl protecting groups by acidic hydrolysis was complete in nearly quantitative yields for the monofluorinated dibenzylphosphonates **4d** and **5d**, use of the same experimental conditions for the difluorinated compounds **4c** and **5c** resulted in the hydrolysis of a single benzyloxy group. Consequently, for the two difluorophosphonates **4c** and **5c**, cleavage of the THP or Tr groups must have occurred simultaneously with a partial benzyloxy cleavage, which could be taken to completion by hydrogenolysis to afford the completely deprotected phosphoric acid **8.** This increased sensitivity of the dibenzyl difluoro-β-keto-phosphonates towards acidic hydrolysis relative to their α-monofluorinated analogues can be explained by the electron-withdrawing effect of the two fluorine atoms, the introduction of a second fluorine atom on the C_α−P weakening the P−O phosphoric ester bond and thus facilitating hydrolysis.[32,33,34]

For the protected α-diols **1c, 2c** and **3c** (Scheme 2), the complete hydrolysis of both primary and secondary alcohol protecting groups (THP, EE, isopropylidene bridge) did not produce the expected dibenzyl (3*R*)-1,1-difluoro-3,4-dihydroxy-2-oxobutylphosphonate, regardless of whether the conditions of cleavage employed mild acidic conditions or specific catalysts such as $[PdCl_2(CH_3CN)_2]$[35] or $FeCl_3$ adsorbed on silica gel.[34] In parallel, partial hydrolysis of the benzyloxy groups around the phosphorus atom was observed. Replacement of the benzyloxy groups by ethoxy groups, which are less sensitive to acidic hydrolysis, gave a similar result.

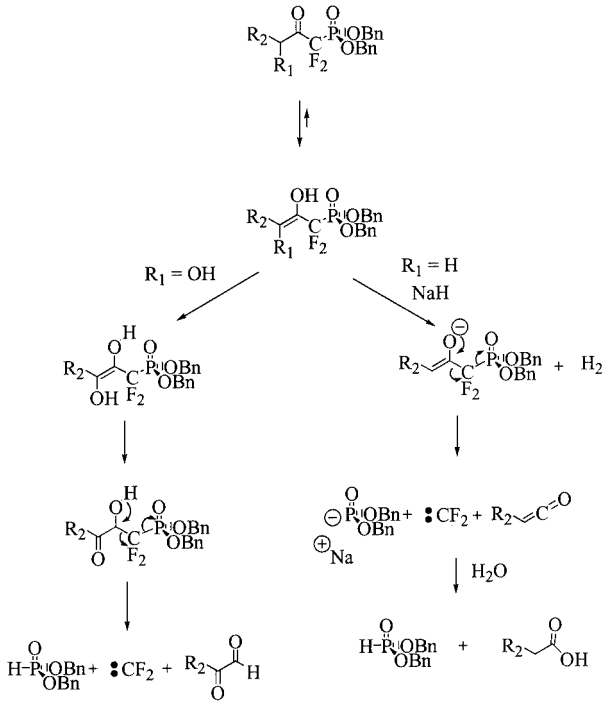
These diethoxy analogues were synthesised as previously described, by condensation of the diethylmethylphosphonate carbanion (Scheme 4). Unfortunately, the hydrolysis of the isopropylidene bridge was no more successful for diethyl α,α-difluoromethyl-β-ketophosphonate **9a** (Scheme 4) than it had been for its dibenzyl ester analogue **1b**. The orthogonal protection of both primary and secondary hydroxyl groups allowed the isolation of the stable monoalcohol **10e** (Scheme 4). However, the removal of the benzyl ether by hydrogenolysis under neutral conditions did not enable isolation of the corresponding α-diol. This seems to indicate that the overall instability of this series of molecules probably involves the α-hydroxy ketone moiety. In all the attempts described above, the degradation of the α,α-difluoromethylphosphonate moiety was clearly evident in the ^{31}P, ^{13}C and ^{19}F NMR spectra. Indeed, P−F coupling was no longer observed in the crude material, and the main phosphorylated product was the appropriate dialkyl phosphite $(RO)_2P(O)H$, as confirmed by ^{31}P NMR spectroscopy (δ = 7.2 ppm, $J_{P\text{-}H}$ = 690 Hz).

From these experimental results, it appears that the α,α-difluoromethyl-γ-hydroxy-β-ketodiesterphosphonates are intrinsically unstable whatever the pH conditions, whereas the decomposition of the α,α-difluoromethyl-δ-hydroxy-β-ketophosphonates (such as **6** in Scheme 3) is only observed under alkaline conditions. Both sensitivities can be ac-



Scheme 4. a) $(EtO)_2P(O)CF_2H$, LDA, THF, −78 °C; b) HCl, H_2O; c) TrCl, pyridine, CH_2Cl_2; d) BnBr, Ag_2O, benzene; e) Et_2O/HCOOH

counted for by the easy enolisation of the ketone moiety induced by the two fluorine atoms (Scheme 5). Indeed, these α,α-difluoro-β-ketophosphonates are only enolisable towards the C-3 atom, and are easily and irreversibly decomposed from this enolic form into stable compounds.



Scheme 5

For the γ-hydroxy derivatives, this enolisation results in the displacement of the carbonyl group from the β- to the γ-position, with the corresponding α,α-difluoro-β-hydroxy-γ-ketophosphonates then spontaneously decomposing into the appropriate aldehyde, dibenzylphosphite and CF_2 carbene.

For the non-hydroxylated β-ketophosphonates, which are stable under acidic or neutral conditions, the corresponding enolate, formed only under basic conditions, decomposes into an unstable ketene, which is probably hydrolysed instantaneously.

For both series of compounds, the decomposition reactions affording dibenzylphosphite imply the formation of a very reactive carbene, CF_2, which has also been detected previously in decomposition reactions of difluoromethanes.[37,38] In this present study, we were able to characterise the concomitantly formed dibenzylphosphite by phosphorus NMR spectroscopy, thus corroborating our mechanistic hypothesis.

Conclusion

The synthesis of stable α,α-difluorinated analogues of 1,3-diphosphoglycerate can be achieved by fluorination of dibenzyl β-ketophosphonate esters, through the corresponding enolate for the first fluorination, and eventually through the enolic form for the second. The synthetic process we describe here has been successfully applied to a set of protected β-hydroxy or α,β-dihydroxy esters. It appears to be the best alternative for the introduction of α,α-difluoro-β-keto-phosphonates into pH-sensitive molecules for which the previously described diethyl difluoromethylphosphonate route cannot be used.

While the use of the dibenzyl difluoromethanephosphonate carbanion is not applicable because of the low stability of this species (contrary to what has been observed with dialkyl difluoromethanephosphonate anion), stabilization by the carbonyl group allows the electrophilic fluorination of the β-ketophosphonate system. The removal of the benzyl groups under mild conditions offers access to the targeted compounds. We have demonstrated that the methodology we describe here is of general applicability and indicated why the α,α-difluorophosphono-phosphate 1,3-diPG isosteric analogue cannot exist, because of the intrinsic instability of the α,α-difluoro-γ-hydroxy-β-ketophosphonate scaffold.

Experimental Section

Before use, tetrahydrofuran and diethyl ether were distilled from over sodium and benzophenone, dichloromethane was distilled from over P_2O_5, and pyridine and triethylamine from over KOH. ^1H, ^{13}C, ^{19}F and ^{31}P NMR spectra were obtained on Bruker Instruments AC 250, AC 50, AC 188 and AC 81 machines, respectively. Chemical shifts (δ) reported for signal centres are expressed in ppm from the internal standard references: TMS (^1H and ^{13}C), CF_3COOH (^{19}F) and H_3PO_4 (^{31}P). Coupling constants (*J*) are given in Hz. IR spectra were recorded on a Perkin−Elmer 1600 series FTIR spectrophotometer. Mass spectra (chemical ionisation) were recorded on a Nermag R10−10 quadrupolar spectrometer and performed by the "service commun" of the Institute of Molecular Chemistry Paul Sabatier (ICMPC, IR-1744). Preparative column chromatography was performed on 70−230 mesh Merck silica gel.

General Procedure for Phosphorylation: A solution of *n*BuLi (1.6 M, 4.4 mL, 6.9 mmol) was slowly added at −78 °C to a solution of the dibenzyl methylphosphonate (1.76 g, 6.4 mmol) in THF (20 mL). After stirring for 30 min at −78 °C, this solution was slowly added at −78 °C, by cannula, to a solution of carboxylic ester (5.8 mmol) in THF (20 mL). After one hour at −78 °C, the mixture was allowed to warm to room temperature overnight. The organic layer was then neutralised with a saturated aqueous solution of NH_4Cl and, after evaporation of THF, the residue was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated, and the residue was purified by flash chromatography (CH_2Cl_2/MeOH), affording the expected β-ketophosphonate. This procedure was successfully applied for the synthesis of compounds **1b**, **4b** and **5b**.

General Procedure for Fluorination: NaH (50 mg, 2 mmol) was slowly added at 0 °C to a solution of the β-ketophosphonate (1.3 mmol) in THF (20 mL). After stirring the mixture for 15 min at 0 °C, F-TEDA (1 g, 2.8 mmol) and DMF (20 mL) were added successively. Stirring was continued for two hours at room temperature, and the reaction was quenched by addition of Et_2O and

NH_4Cl (aq). The organic layer was washed with NaCl (aq) and water, dried ($MgSO_4$) and filtered, and the solvents were evaporated. The residue was purified by flash chromatography (CH_2Cl_2/MeOH), affording dibenzyl (α,α-difluoro)-β-ketophosphonate (from 40 to 60%). Some starting material (20 to 30%) was also recovered. This method was successfully applied for the synthesis of compounds **1c**, **2c**, **3c**, **4c**, **5c**, **4d** and **5d**.

General Procedure for Dibenzyl Hydrogenolysis: Pd/C (10%, 60 mg) was added to a solution of the dibenzyl phosphonate (1 mmol) in MeOH (20 mL), and the heterogeneous solution was stirred under an H_2 atmosphere for half an hour at room temperature. The Pd/C was then filtered off and washed with MeOH, and the solvent was evaporated off, quantitatively affording the corresponding dihydroxyphosphonate as a colourless oil (yield around 98%). This method was successfully applied for the synthesis of compounds **1e** and **8**.

Dibenzyl {2-[(1*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-1,1-difluoro-2-oxoethyl}phosphonate (1c): This compound (yield 59%) was synthesised from dibenzyl {2-[(1*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-oxoethyl}phosphonate (564 mg, 1.4 mmol).[10] ^1H NMR (250 MHz, $CDCl_3$): δ = 1.42 (s, 3 H, CH_3), 1.50 (s, 3 H, CH_3), 4.13 (dd, 2 H, CH_2-O hydrated form), 4.28 (dd, 2 H, CH_2-O ketone form), 4.46 (t, 1 H, CH-O hydrated form), 4.60 (t, 1 H, CH-O ketone form), 5.2 (m, 4 H, CH_2 Bn), 7.35 (m, 10 H, Ph) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) ketone form: δ = 25.4 (s, CH_3), 25.7 (s, CH_3), 65.7 (CH_2-O), 70.8 (d, $J_{C\text{-}P}$ = 6.3 Hz, CH_2 Bn), 77.2 (d, $J_{C\text{-}P}$ = 7.2 Hz, CH-O), 116.8 (td, CF_2), 128−129 (m, Ph), 135.2 (d, $J_{C\text{-}P}$ = 6.6 Hz, C_q Bn), 207.1 (m, CO); hydrated form: δ = 25.4 (s, CH_3), 25.7 (s, CH_3), 65.3 (CH_2-O), 70.4 (d, $J_{C\text{-}P}$ = 6.2 Hz, CH_2 Bn), 74.7 (d, $J_{C\text{-}P}$ = 7.2 Hz, CH-O), 93.9 [td, $C(OH)_2$], 116.8 (td, CF_2), 128−129 (m, Ph), 135.2 (d, $J_{C\text{-}P}$ = 6.6 Hz, C_q Bn) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) ketone form: δ = −43.1 (d, $J_{P\text{-}F}$ = 96 Hz); hydrated form: δ = −39.5 (d, $J_{P\text{-}F}$ = 96 Hz) ppm. ^{31}P NMR (81 MHz, $CDCl_3$) ketone form: δ = 3.29 (t, $J_{P\text{-}F}$ = 96 Hz); hydrated form: δ = 7.30 (t, $J_{P\text{-}F}$ = 96 Hz) ppm.

Dibenzyl [(3*R*)-2-Oxo-3,4-bis(tetrahydro-2*H*-2-pyranyloxy)butyl]-phosphonate (2b): 3,4-Dihydro-2*H*-pyran (0.82 mL, 9.0 mmol) and pyridinium *p*-toluenesulfonate (75 mg, 0.3 mmol) were added to a solution of dibenzyl [(3*R*)-3,4-dihydroxybutyl]-2-oxophosphonate[10] (542 mg, 1.49 mmol) in anhydrous CH_2Cl_2 (15 mL). After stirring the mixture at room temperature for 5 days, diethyl ether (100 mL) was added, and the organic mixture was washed with semisaturated brine (30 mL), dried ($MgSO_4$) and filtered, and the solvents were evaporated. The residue was then purified by chromatography (CH_2Cl_2/MeOH, 99:1) to give **2b** as a colourless oil (yield: 73%). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.8−20.2 (m, CH_2 THP), 25.2 (m, CH_2 THP), 61.9 (m, CH_2-O), 67.9 (m, CH_2 Bn), 81.3 (m, CH-O), 99.0 (m, O-CH-O), 128−129 (m, Ph), 135.9 (d, $J_{C\text{-}P}$ = 6.5 Hz, C_q Bn), 204.0 (m, C=O) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ = 21.6, 22.5 ppm. MS (DCI, NH_3): *m*/*z* = 533 [MH^+], 550 [MNH_4^+]. $C_{28}H_{37}O_8P$ (532.2): calcd. C 63.15, H 7.00; found C 63.09, H 6.97.

Dibenzyl [(3*R*)-3,4-Bis(1-ethoxyethyl)-2-oxobutyl]phosphonate (3b): Ethyl vinyl ether (0.38 mL, 4.0 mmol) and pyridinium *p*-toluenesulfonate (63 mg, 0.25 mmol) were added to a solution of dibenzyl [(3*R*)-3,4-dihydroxy-2-oxobutyl]phosphonate[10] (410 mg, 1.1 mmol) in anhydrous CH_2Cl_2 (15 mL). After stirring the mixture at room temperature for 3 hours, diethyl ether (150 mL) was added, and the organic mixture was washed with brine (30 mL), dried ($MgSO_4$) and filtered, and the solvents were evaporated to afford compound **3b** as a colourless oil (516 mg, 90%). ^1H NMR (250 MHz, $CDCl_3$): δ = 1.0−1.4 (m, 12 H, CH_3 EE), 3.1−3.7 (m, 10 H, CH_2-CO, CH_2 et CH-O EE), 4.15 (m, 0.5 H, CH-O), 4.30 (m, 0.5 H, CH-O), 4.65 (m, 2 H, CH_2-O), 5.05 (m, CH_2 Bn), 7.29 (m, 10 H, Ph) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ = 21.5, 22.4 ppm. MS (DCI, NH_3): *m*/*z* = 509 [MH^+], 526 [MNH_4^+].

Dibenzyl [(3*R*)-1,1-Difluoro-2-oxo-3,4-bis(tetrahydro-2*H*-2-pyranyloxy)butyl]phosphonate (2c): This compound (yield 52%) was synthesised from **2b** (438 mg, 0.82 mmol). ^{31}P NMR (81 MHz, $CDCl_3$): δ = 3.3 (t, $J_{P\text{-}F}$ = 95 Hz), 3.5 (t, $J_{P\text{-}F}$ = 95 Hz) ppm. MS (DCI, NH_3): *m*/*z* = 569 [MH^+], 586 [MNH_4^+]. $C_{28}H_{35}F_2O_8P$ (568.2): calcd. C 59.15, H 6.20; found C 59.04, H 6.27.

Dibenzyl [(3*R*)-3,4-Bis(1-ethoxyethyl)-1,1-difluoro-2-oxobutyl]phosphonate (3c): This compound (yield 50%) was synthesised from **3b**. ^{31}P NMR (81 MHz, $CDCl_3$): δ = 3.2 (t, $J_{P\text{-}F}$ = 95.2 Hz), 3.6 (t, $J_{P\text{-}F}$ = 95.2 Hz) ppm. MS (DCI, NH_3): *m*/*z* = 545 [MH^+], 562 [MNH_4^+].

Methyl 3-Trityloxypropanoate (4a): Chlorotriphenylmethane (7.77 g, 27.9 mmol) was added at 0 °C to a solution of methyl 3-hydroxypropanoate[27] (2.9 g, 27.9 mmol) in anhydrous pyridine (60 mL). After stirring the mixture overnight at room temperature, the pyridine was evaporated off. The oily residue was chromatographed (CH_2Cl_2/petroleum ether 50:50), to afford compound **4a** (6.95 g, 72%) as a white powder. ^1H NMR (250 MHz, $CDCl_3$): δ = 2.62 (t, 2 H, CH_2-CO), 3.44 (t, 2 H, CH_2-O), 3.72 (s, 3 H, CH_3), 7.23−7.50 (m, 15 H, Ph) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 35.4 (CH_2-CO), 51.7 (CH_3), 59.6 (CH_2-O), 86.8 [$C(Ph)_3$], 127.2 (Ph), 128.0 (Ph), 128.8 (Ph), 144.1 (C_q Ph), 172.3 (C=O) ppm. MS (DCI, NH_3): *m*/*z* = 347 [MH^+], 364 [MNH_4^+].

Methyl 3-(Tetrahydro-2*H*-pyranyloxy)propanoate (5a): 3,4-Dihydro-2*H*-pyran (9.6 mL, 105 mmol) and pyridinium *p*-toluenesulfonate (1.75 g, 7 mmol) were added to a solution of methyl 3-hydroxypropanoate[39] (7.75 g, 47.5 mmol) in anhydrous CH_2Cl_2 (40 mL). After stirring the mixture overnight at room temperature, diethyl ether (150 mL) was added and the organic layer was washed with semisaturated brine (50 mL), dried ($MgSO_4$) and filtered. After distillation (b.p. = 115 °C, 16 Torr), compound **5a** was obtained pure as a colourless liquid (11.5 g, 82%). ^1H NMR (250 MHz, $CDCl_3$): δ = 1.4−1.8 (m, 6 H, 3 × CH_2 THP), 2.56 (t, 2 H, CH_2-CO), 3.4 (m, 1 H, CH_2-O THP), 3.6 (td, 1 H, CH_2-O), 3.64 (s, 3 H, CH_3), 3.78 (m, 1 H, CH_2-O THP), 3.93 (td, 1 H, CH_2-O), 4.57 (t, 1 H, O-CH-O) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.3 (CH_2 THP), 25.4 (CH_2 THP), 30.5 (CH_2 THP), 34.9 (CH_2-CO), 51.5 (CH_3), 62.0 (CH_2-OH), 62.8 (CH_2-O THP), 98.8 (O-CH-O), 172.0 (CO) ppm. MS (DCI, NH_3): *m*/*z* = 189 [MH^+], 206 [MNH_4^+].

Dibenzyl (2-Oxo-4-trityloxybutyl)phosphonate (4b): This compound (3.75 g, 55%) was synthesised from compound **4a** (4.0 g, 11.6 mmol). It was obtained as a colourless oil after flash chromatography ($CHCl_3$/MeOH 99:1). ^1H NMR (250 MHz, $CDCl_3$): δ = 2.82 (t, 2 H, CH_2-CO), 3.13 (d, $J_{P\text{-}C}$ = 22.6 Hz, 2 H, CH_2-P), 3.41 (t, 2 H, CH_2-O), 5.01−5.13 (m, 4 H, CH_2-Ph), 7.25−7.47 (m, 25 H, Ph) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 42.6 (d, $J_{P\text{-}C}$ = 128.5 Hz, CH_2-P), 44.4 (CH_2-CO), 58.9 (CH_2-O), 68.1 (d, $J_{P\text{-}C}$ = 6.3 Hz, CH_2-Ph), 86.9 [C_q-$(Ph)_3$], 127.1 (Ph), 127.9 (Ph), 128.2 (Ph), 128.7 (Ph), 135.8 (d, $J_{P\text{-}C}$ = 6.2 Hz, C_q-Ph Bn), 143.9 (C_q-Ph Tr), 200.4 (d, $J_{P\text{-}C}$ = 6.3 Hz, C=O) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ = 21.2 ppm. MS (DCI, NH_3): *m*/*z* = 591 [MH^+], 608 [MNH_4^+].

Dibenzyl [2-Oxo-4-(tetrahydro-2*H*-pyranyloxy)butyl]phosphonate (5b): This compound (7.1 g, 57%) was synthesised from compound **5a** (5.5 g, 29 mmol). It was obtained as a colourless oil after puri-

fication by flash chromatography (petroleum ether/diethyl ether 30:70). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.4−1.7 (m, 6 H, 3 × CH_2 THP), 2.80 (t, 2 H, CH_2-CO), 3.15 (d, 2 H, J_{H-P} = 22.6 Hz, CH_2-P), 3.45 (td, 1 H, CH_2-O THP), 3.62 (td, 1 H, CH_2-O), 3.76 (m, 1 H, CH_2-O THP), 3.93 (td, 1 H, CH_2-O), 4.55 (t, 1 H, O-CH-O), 5.05 (m, 4 H, CH_2-Ph), 7.33 (m, 10 H, Ph) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.4 (CH_2 THP), 25.4 (CH_2 THP), 30.5 (CH_2 THP), 43.1 (d, J_{C-P} = 128.7 Hz, CH_2-P), 44.1 (CH_2-CO), 62.0 (CH_2-O), 62.2 (CH_2-O THP), 68.0 (d, J_{C-P} = 6.2 Hz, CH_2-Ph), 99.0 (O-CH-O), 128.1 (Ph), 128.6 (Ph), 135.8 (d, J_{C-P} = 6.2 Hz, C_q Bn), 200.2 (d, J_{C-P} = 6.3 Hz, C=O) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ = 21.1 ppm. MS (DCI, NH_3): *m/z* = 433 [MH^+], 450 [MNH_4^+].

Dibenzyl (1,1-Difluoro-2-oxo-4-trityloxybutyl)phosphonate (4c): This compound (yield 48%) was synthesised from compound **4b** (3 g, 5.1 mmol). It was obtained as a colourless oil after purification by flash chromatography ($CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.11 (t, 2 H, CH_2-CO), 3.56 (t, 2 H, CH_2-O), 5.2−5.3 (m, 4 H, CH_2-Ph), 7.27−7.58 (m, 25 H, Ph) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 38.4 (CH_2-CO), 57.6 (CH_2-OTr), 70.5 (d, J_{C-P} = 6.5 Hz, CH_2-Ph), 87.1 [C_q-$(Ph)_3$], 113.2 (td, J_{C-P} = 197.9 Hz, J_{C-F} = 274.2 Hz, CF_2), 127.2−129.7 (Ph), 134.9 (d, J_{P-C} = 6.1 Hz, C_q-Ph Bn), 143.9 (C_q-Ph Tr), 197.0 (td, J_{P-C} = 16.3 Hz, J_{C-F} = 2.6 Hz, C=O) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = −42.0 (d, J_{P-F} = 98.2 Hz) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ = 4.07 (t, J_{P-F} = 98.2 Hz) ppm. MS (DCI, NH_3): *m/z* = 627 [MH^+], 644 [MNH_4^+]. $C_{37}H_{33}F_2O_5P$ (626.2): calcd. C 70.92, H 5.31; found C 71.04, H 5.23.

Dibenzyl [1,1-difluoro-2-oxo-4-(tetrahydro-*2H*-pyranyloxy)butyl]-phosphonate (5c): This compound (yield: 55%) was synthesised from compound **5b** (4.5 g, 10.4 mmol). It was obtained as a colourless oil after purification by flash chromatography (petroleum ether/diethyl ether 30:70). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.4−1.7 (m, 6 H, 3 × CH_2 THP), 2.91 (t, 2 H, CH_2-CO), 3.49 (m, 2 H, CH_2-O THP), 3.96 (m, 1 H, CH_2-O), 4.57 (t, 1 H, O-CH-O), 5.15 (m, 4 H, CH_2 Bn), 7.33 (m, 10 H, Ph) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.3 (CH_2 THP), 25.3 (CH_2 THP), 30.5 (CH_2 THP), 38.1 (CH_2-CO), 61.0 (d, J_{C-P} = 5.2 Hz, CH_2-O), 62.0 (CH_2-O THP), 70.4 (dd, J_{C-P} = 6.2 Hz, CH_2-Ph), 98.9 (O-CH-O), 113.0 (td, J_{C-P} = 197.4 Hz, J_{C-F} = 273.8 Hz, CF_2), 127.9 (Ph), 128.5 (Ph), 134.9 (d, J_{C-P} = 5.5 Hz, C_q Bn), 197.0 (td, J_{C-P} = 16.7 Hz, J_{C-F} = 2.6 Hz, C=O) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = −42.1 (d, J_{P-F} = 98.1 Hz) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ = 4.0 (t, J_{P-F} = 98.1 Hz) ppm. MS (DCI, NH_3): *m/z* = 469 [MH^+], 486 [MNH_4^+].

Dibenzyl (1-Fluoro-2-oxo-4-trityloxybutyl)phosphonate (4d): This compound (yield: 5%) was synthesised from compound **4b** (3 g, 5.1 mmol). It was obtained as a colourless oil after flash chromatography (CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.89 (t, 2 H, CH_2-CO), 3.37 (t, 2 H, CH_2-O), 5.05−5.13 (m, 4 H, CH_2-Ph), 5.15 (dd, J_{H-P} = 14.6 Hz, J_{H-F} = 47.6 Hz, 1 H, CHF), 7.22−7.42 (m, 25 H, Ph) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ = 11.0 (t, J_{P-F} = 71.7 Hz) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = −29.7 (d, J_{P-F} = 71.7 Hz) ppm. MS (DCI, NH_3): *m/z* = 609 [MH^+], 626 [MNH_4^+]. $C_{37}H_{34}FO_5P$ (608.2): calcd. C 73.02, H 5.63; found C 73.11, H 5.70.

Dibenzyl [1-Fluoro-2-oxo-4-(tetrahydro-2*H*-pyranyloxy)butyl]phosphonate (5d): This compound (235 mg, 5%) was synthesised from compound **5b** (4.5 g, 10.4 mmol). It was obtained pure as a colourless oil after flash chromatography (petroleum ether/diethyl ether 50:50). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.4−1.7 (m, 6 H, 3 × CH_2 THP), 2.91 (t, 2 H, CH_2-CO), 3.49 (m, 1 H, CH_2-O THP), 3.64 (m, 1 H, CH_2-O), 3.80 (m, 1 H, CH_2-O THP), 3.96 (m, 1 H, CH_2-O), 4.57 (t, 1 H, O-CH-O), 5.15 (m, 4 H, CH_2-Ph), 5.20 (dd, J_{H-P} = 14.2 Hz, J_{H-F} = 48.2 Hz, 1 H, CHF), 7.33 (m, 10 H, Ph) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.3 (CH_2 THP), 25.4 (CH_2 THP), 30.5 (CH_2 THP), 39.5 (d, J_{C-P} = 5.0 Hz, CH_2-CO), 61.5 (d, J_{C-P} = 5.1 Hz, CH_2-O), 62.1 (CH_2-O THP), 69.4 (dd, J_{C-P} = 6.2 Hz, CH_2 Bn), 91.8 (dd, J_{C-P} = 153.0 Hz, J_{C-F} = 198.4 Hz, CHF), 99.0 (O-CH-O), 127.9 (Ph), 128.5 (Ph), 135.2 (d, J_{C-P} = 5.6 Hz, C_q Bn), 200.7 (dd, J_{C-P} = 16.7 Hz, J_{C-F} = 2.6 Hz, C=O) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = −29.5 (dd, J_{P-F} = 71.2 Hz) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ = 11.1 (d, J_{P-F} = 71.2 Hz) ppm. MS (DCI, NH_3): *m/z* = 451 [MH^+], 468 [MNH_4^+].

Dibenzyl (1,1-Difluoro-4-hydroxy-2-oxobutyl)phosphonate (6): This compound was obtained from both compounds **4c** and **5c**.

(i) Formic acid (10 mL) was added to a solution of **4c** in diethyl ether (10 mL). After stirring the mixture for 4 hours, the solvent was evaporated off and the residue was purified by chromatography (CH_2Cl_2).

(ii) Pyridinium *p*-toluenesulfonate (63 mg, 0.19 mmol) was added to a solution of **5c** (870 mg, 1.86 mmol) in ethanol (15 mL). After stirring the mixture for 3 hours at 55 °C, the ethanol was evaporated off and the residue was purified by chromatography ($CHCl_3$ and then EtOAc). Compound **6** (740 mg, 72%) was obtained pure as a colourless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.56 (s, 1 H, OH), 2.99 (t, 2 H, CH_2-CO), 3.90 (t, 2 H, CH_2-O), 5.18 (m, 4 H, CH_2-Ph Bn), 7.35 (m, 10 H, Ph) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 40.6 (CH_2-CO), 57.0 (CH_2-O), 70.7 (d, J_{C-P} = 6.1 Hz, CH_2-Ph), 113.0 (td, J_{C-P} = 197.0 Hz, J_{C-F} = 265.8 Hz, CF_2), 128.1 (Ph), 128.7 (Ph), 129.1 (Ph), 134.7 (d, J_{C-P} = 5.5 Hz, C_q Bn), 199.0 (d, J_{C-P} = 11.3 Hz, C=O) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = −42.1 (d, J_{P-F} = 97.0 Hz) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ = 3.8 (t, J_{P-F} = 97.0 Hz) ppm. MS (DCI, NH_3): *m/z* = 385 [MH^+], 402 [MNH_4^+].

Dibenzyl (1-Fluoro-4-hydroxy-2-oxobutyl)phosphonate (7): Pyridinium *p*-toluenesulfonate (10 mg, 0.03 mmol) was added to a solution of **5d** (130 mg, 0.29 mmol) in ethanol (5 mL). After stirring the mixture for 3 hours at 55 °C, the ethanol was evaporated off and the residue was purified by chromatography ($CHCl_3$ and than EtOAc). Compound **7** (88 mg, 83%) was obtained pure as a colourless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.43 (s, 1 H, OH), 2.87 (m, 2 H, CH_2-CO), 3.88 (t, 2 H, CH_2-O), 5.10 (m, 4 H, CH_2-Ph), 5.15 (dd, 1 H, J_{H-P} = 14.6 Hz, J_{H-F} = 47.6 Hz, CHF), 7.35 (m, 10 H, Ph) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 41.9 (CH_2-CO), 57.0 (d, J_{C-P} = 1.6 Hz, CH_2-O), 69.6 (dd, J_{C-P} = 6.2 Hz, CH_2-Ph), 91.8 (dd, J_{C-P} = 153.1 Hz, J_{C-F} = 198.8 Hz, CHF), 127.9 (Ph), 128.5 (Ph), 135.1 (d, J_{C-P} = 5.5 Hz, C_q Bn), 203.0 (d, J_{C-P} = 19.5 Hz, C=O) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = −29.5 (dd, J_{P-F} = 71.7 Hz) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ = 11.0 (d, J_{P-F} = 71.7 Hz) ppm. MS (DCI, NH_3): *m/z* = 367 [MH^+], 384 [MNH_4^+]. $C_{18}H_{20}FO_5P$ (366.1): calcd. C 59.02, H 5.50; found C 58.90, H 5.44.

{2-[1(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-1,1-difluoro-2-oxoethyl} phosphonic Acid, Hydrated Form (1e): This compound (105 mg, 98%) was synthesised from dibenzyl {2-[(1*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1,1-difluoro-2-oxoethyl}phosphonate **1c** (180 mg, 0.4 mmol). ^{1}H NMR (250 MHz, D_2O): δ = 1.39 (s, 3 H, CH_3), 1.47 (s, 3 H, CH_3), 4.02 (dd, 2 H, CH_2-O), 4.30 (t, 1 H, CH-O) ppm. ^{13}C NMR (50 MHz, D_2O): δ = 25.0 (s, CH_3), 25.3 (s, CH_3), 64.2 (s, CH_2-O), 72.3 (d, J_{C-P} = 7.5 Hz, CH-O), 91.2 (td, $C(OH)_2$], 113.9 (td, CF_2) ppm. ^{19}F NMR (188 MHz, D_2O): δ = −38.4 (d,

J_{F-P} = 98 Hz) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ = 7.05 (t, J_{F-P} = 98 Hz) ppm.

(1,1-Difluoro-4-hydroxy-2-oxobutyl)phosphonic acid (8): This compound (210 mg, 96%) was synthesised from compound **6** (355 mg, 0.73 mmol). ^1H NMR (250 MHz, CD_3OD): δ = 4.12 (t, 2 H, CH_2-O), 4.62 (t, 1 H, O-CH-O) ppm. ^{13}C NMR (50 MHz, CD_3OD): δ = 36.8 (s, CH_2-CO), 58.9 (d, J_{C-P} = 5.5 Hz, CH_2-O), 108.8 (td, J_{C-P} = 196.6 Hz, J_{C-F} = 273.5 Hz, CF_2), 195.3 (td, J_{C-P} = 16.2 Hz, J_{C-F} = 2.7 Hz, C=O) ppm. ^{19}F NMR (188 MHz, D_2O): δ = −38.6 (d, J_{F-P} = 97 Hz) ppm. ^{31}P NMR (81 MHz, CD_3OD): δ = 3.44 (t, J_{F-P} = 97 Hz) ppm. $C_4H_7F_2O_5P$ (204.00): calcd. C 23.54, H 3.46; found C 23.66, H 3.60.

Diethyl {2-[1(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-1,1-difluoro-2-oxoethyl}phosphonate (9a): A solution of diethyl difluoromethylphosphonate (1.0 mL, 6.4 mmol) in anhydrous THF (8 mL) was slowly added at −80 °C to a 2 M solution of LDA (3.2 mL, 6.4 mmol) in anhydrous THF (5 mL). After stirring the mixture for 30 min at −80 °C, a solution of **1a** (1.0 g, 6.4 mmol) in anhydrous THF (10 mL) was added. After stirring for 2 h at −80 °C, the mixture was neutralised with glacial acetic acid (0.66 mL, 6.4 mmol), a saturated aqueous solution of NH_4Cl (30 mL) was added, and the mixture was extracted with EtOAc (2 × 50 mL). The organic layer was washed with water, dried ($MgSO_4$) and filtered, and the solvents were evaporated. After purification by flash chromatography (CH_2Cl_2/MeOH 98:2), compound **9a** was obtained pure as a colourless oil (85%).

Methyl (2*R*)-2,3-Dihydroxypropanoate (10a): A solution of HCl (1 M, 2 mL) was added to a solution of **1a** (4 g, 25 mmol) in a THF/H_2O mixture (1:1, 50 mL). After stirring the mixture at room temperature for 24 hours, the aqueous layer was washed with EtOAc (20 mL), neutralised with a 1 M solution of NaOH and then lyophilised. CH_2Cl_2 was added, and the resulting salts were filtered to afford, after evaporation, a colourless oil (1.74 g, 58%). ^1H NMR (250 MHz, $CDCl_3$): δ = 3.70 (s, 3 H, CH_3), 3.80 (m, 2 H, CH_2-O), 4.2 (t, 1 H, CH-O), 4.4 (OH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 52.5 (CH_3-O), 64.0 (CH_2-O), 71.9 (CH-O), 173.5 (C=O) ppm. MS (DCI, NH_3): *m*/*z* = 121 [MH^+], 138 [MNH_4^+].

Methyl (2*R*)-2-Hydroxy-3-trityloxypropanoate (10b): Anhydrous pyridine (1.05 mL, 16.6 mmol) and chlorotriphenylmethane (2.6 g, 9.3 mmol) were added successively to a solution of **10a** (1 g, 8.4 mmol) in anhydrous THF (30 mL). After stirring the mixture overnight at room temperature, the THF was evaporated off and the residue was purified by chromatography ($CHCl_3$). Compound **10b** (1.9 g, 62%) was obtained pure as a white powder. ^1H NMR (250 MHz, $CDCl_3$): δ = 3.6 (m, 2 H, CH_2), 3.80 (s, 3 H, CH_3), 4.4 (m, 1 H, CH-O), 7.2−7.7 (m, 15 H, Ph) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 52.5 (CH_3-O), 65.6 (CH_2-O), 70.9 (CH-O), 86.6 [$C(Ph)_3$], 127.3 (Ph), 128.1 (Ph), 128.8 (Ph), 143.8 (Cq Ph), 173.7 (C=O) ppm. MS (DCI, NH_3): *m*/*z* = 363 [MH^+], 380 [MNH_4^+].

Methyl (2*R*)-2-Benzyloxy-3-trityloxypropanoate (10c): Benzyl bromide (0.43 mL, 3.6 mmol) and silver oxide (1.7 g, 7.2 mmol) were added successively to a solution of **10b** (1.12 g, 3.1 mmol) in anhydrous benzene (10 mL). After stirring the mixture for 18 hours at room temperature, the salts were filtered off and washed with EtOAc (30 mL). After evaporation and flash chromatography (petroleum ether/Et_2O 4:1), compound **10c** (1.09 g, 78%) was obtained pure as a colourless oil. ^1H NMR (250 MHz, $CDCl_3$): δ = 3.50 (d, 2 H, CH_2-O), 3.77 (s, 3 H, CH_3), 4.21 (t, 1 H, CH-O), 4.71 (dd, 2 H, CH_2 Bn), 7.24−7.66 (m, 20 H, Ph) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 52.0 (CH_3-O), 64.6 (CH_2-OTr), 77.9 (CH-O), 86.8 [$C(Ph)_3$], 127.1 (Ph), 127.9 (Ph), 128.5 (Ph), 128.8 (Ph), 137.5 (Cq Bn) 143.8 (Cq Tr), 171.4 (C=O) ppm. IR (film): $\nu_{C=O}$ = 1750 cm^{-1} ppm. MS (DCI, NH_3): *m*/*z* = 453 [MH^+], 470 [MNH_4^+]. $C_{30}H_{28}O_4$ (452.2): calcd. C 79.62, H 6.24; found C 79.54, H 6.32.

Diethyl [(3*R*)-3-Benzyloxy-1,1-difluoro-2-oxo-4-trityloxybutyl]phosphonate (10d): A solution of diethyl difluoromethylphosphonate (0.85 mL, 5.3 mmol) in anhydrous THF (5 mL) was slowly added at −80 °C to a solution of LDA (2 M, 2.65 mL, 5.3 mmol) in anhydrous THF (10 mL). After stirring the mixture for 30 min at −80 °C, a solution of **10c** (2 g, 4.4 mmol) in anhydrous THF (10 mL) was added. After stirring for 2 h at −80 °C, the mixture was neutralised with glacial acetic acid (0.54 mL, 5.3 mmol), a saturated aqueous solution of NH_4Cl (30 mL) was added, and the mixture was extracted with EtOAc (2 × 50 mL). The organic layer was washed with water, dried ($MgSO_4$) and filtered, and the solvents were evaporated.

Diethyl [(3*R*)-3-Benzyloxy-1,1-difluoro-2-oxo-4-hydroxybutyl]phosphonate (10e): Formic acid (10 mL) was added to a solution of **10d** (2.7 g, 4.4 mmol) in diethyl ether (10 mL). After stirring the mixture for 3 hours at room temperature, the solvents were evaporated off and the remaining crude oil was purified by flash chromatography (CH_2Cl_2/MeOH 98:2). Compound **10e** (1.19 g, 74%) was obtained pure as a colourless oil. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.35 (td, 6 H, CH_3 Et), 3.94 (m, 2 H, CH_2OH), 4.27 (m, 4 H, CH_2 Et), 4.52 (dd, 2 H, CH_2 Bn), 4.63 (m, 1 H, CH-OBn), 7.32 (m, 5 H, Ph) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.3 (d, J_{C-P} = 5.5, CH_2 Et), 62.1 (CH_2-OH), 65.9 (d, J_{C-P} = 6.2 Hz, CH_2 Et), 72.5 (CH_2-Ph Bn), 82.1 (CH-O), 113.5 (td, J_{C-P} = 194.9 Hz, J_{C-F} = 274.9 Hz, CF_2), 127.8 (Ph), 128.5 (Ph), 136.9 (Cq Bn), 197.6 (td, J_{C-P} = 12.5 Hz, J_{C-F} = 23.4 Hz, C=O) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = −41.9 (d, J_{P-F} = 94 Hz) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ = −2.92 (t, J_{P-F} = 94.1 Hz) ppm. MS (DCI, NH_3): *m*/*z* = 367 [MH^+], 384 [MNH_4^+]. $C_{15}H_{21}F_2O_6P$ (366.1): calcd. C 49.18, H 5.78; found C 49.09, H 5.86.

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[1] C. L. M. J. Verlinde, V. Hannaert, C. Blonski, M. Willson, J. J. Périé, L. A. Fothergill-Gilmore, F. R. Opperdoes, M. H. Gelb, W. G. J. Hol, P. A. M. Michels, *Drug Resistance Updates* **2001**, *4*, 50−65.
[2] F. R. Opperdoes, *Ann. Rev. Microbiol.* **1987**, *41*, 127−151.
[3] A. H. Fairlamb, F. R. Opperdoes, P. Borst, *Nature* **1977**, *265*, 270−273.
[4] A. B. Clarkson, F. H. Brown, *Science* **1976**, *194*, 204−206.
[5] J. M. Sommer, C. C. Wang, *Ann. Rev. Microbiol.* **1994**, *48*, 105−138.
[6] A. M. Lambeir, A. M. Loiseau, D. A. Kuntz, F. M. Vellieux, P. A. M. Michels, F. R. Opperdoes, *Eur. J. Biochem.* **1991**, *198*, 429−435.
[7] M. Willson, N. Lauth, J. Périé, M. Callens, F. R. Opperdoes, *Biochemistry* **1994**, *33*, 214−220.
[8] B. M. Bakker, H. V. Westerhoff, P. A. M. Michels, *J. Bioenerg. Biomembranes* **1995**, *27*, 513−525.
[9] B. M. Bakker, P. A. M. Michels, F. R. Opperdoes, H. V. Westerhoff, *P. N. A. S.* **1999**, *21*, 14551−14559.
[10] S. Ladame, M. Bardet, J. Périé, M. Willson, *Bioorg. Med. Chem.* **2001**, *9*, 773−783.
[11] G. M. Blackburn, D. E. Kent, *J. Chem. Soc., Chem. Commun.* **1981**, 511−519.
[12] G. M. Blackburn, *Chem. Ind. (London)* **1981**, 134−136.

[13] G. M. Blackburn, D. E. Kent, *J. Chem. Soc., Perkin Trans. 1* **1984**, 1119−1121.
[14] J. Nieschalk, A. Batsanov, D. O'Hagan, J. A. K. Howard, *Tetrahedron* **1996**, *52*, 165−176.
[15] D. B. Berkowitz, M. Bose, *J. Fluorine Chem.* **2001**, *112*, 13−33.
[16] T. P. Lequeux, J. Percy, *J. Chem. Soc., Chem. Commun.* **1995**, 2111−2112.
[17] D. B. Berkowitz, M. Eggen, Q. Shen, R. K. Shoemaker, *J. Org. Chem.* **1996**, *61*, 4666−4670.
[18] K. Blades, T. P. Lequeux, J. M. Percy, *Tetrahedron* **1997**, *53*, 10623−10628.
[19] C. J. Salomon, E. Breuer, *Tetrahedron Lett.* **1995**, *36*, 6759−6760.
[20] G. M. Blackburn, D. L. Jakeman, A. J. Ivory, M. P. Williamson, *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2573−2578.
[21] D. L. Jakeman, A. J. Ivory, M. P. Williamson, G. M. Blackburn, *J. Med. Chem.* **1998**, *41*, 4439−4452.
[22] D. B. Berkowitz, D. Bhuniya, G. Peris, *Tetrahedron Lett.* **1999**, *40*, 1869−1872.
[23] S. R. Piettre, P. Raboisson, *Tetrahedron Lett.* **1996**, *37*, 2229−2232.
[24] R. E. Banks, N. J. Lawrence, A. L. Popplewell, *J. Chem. Soc., Chem. Commun.* **1994**, 343−344.
[25] G. S. Lal, *J. Org. Chem.* **1993**, *58*, 2791−2796.
[26] S. Stavber, M. Zupan, *J. Chem. Soc., Chem. Commun.* **1994**, 149−150.
[27] S. D. Taylor, A. N. Dinaut, A. N. Thadani, Z. Huang, *Tetrahedron Lett.* **1996**, *37*, 8089−8092.
[28] B. Ioga, F. Eymery, P. Savignac, *Synthesis* **2000**, 576−580.
[29] B. Ioga, F. Eymery, P. Savignac, *Tetrahedron* **1999**, *55*, 2671−2686.
[30] S. F. Wnuk, M. J. Robins, *J. Am. Chem. Soc.* **1996**, *118*, 2519−2520.
[31] E. M. Arnett, J. A. Harrelson, *Gazz. Chim. Ital.* **1987**, *117*, 237−241.
[32] R. D. Chambers, R. Jaouhari, D. O'Hagan, *Tetrahedron* **1989**, *45*, 5101−5105.
[33] G. R. J. Thatcher, A. S. Campbell, *J. Org. Chem.* **1993**, *58*, 2272−2275.
[34] J. Nieschalk, D. O'Hagan, *J. Chem. Soc., Chem. Commun.* **1995**, 719−720.
[35] C. Schmeck, L. S. Hegedus, *J. Am. Chem. Soc.* **1994**, *116*, 9927−9934.
[36] K. S. Kim, Y. H. Song, B. H. Lee, C. S. Hahn, *J. Org. Chem.* **1986**, *51*, 404−407.
[37] C. Wakselman, *L'Actualité Chimique* **1987**, 137−141.
[38] M. R. Cameron, G. B. Bacskay, *J. Phys. Chem. A.* **2000**, *104*, 11212−11219.
[39] T. L. Gresham, J. E. Jansen, F. W. Shaver, J. T. Gregory, W. L. Beears, *J. Am. Chem. Soc.* **1948**, *70*, 1004−1006.

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