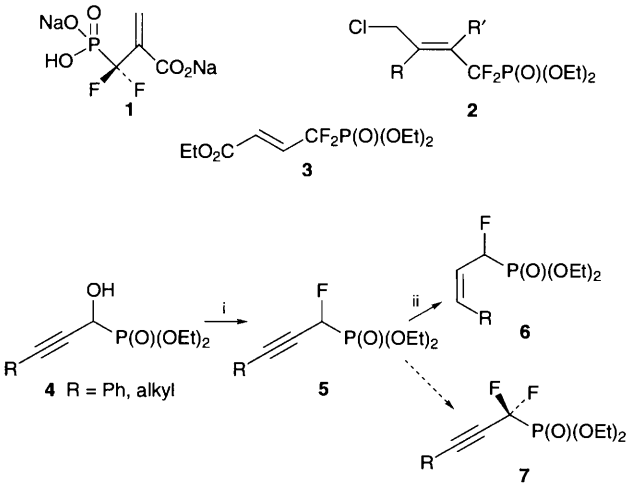
An expedient synthesis of (α,α-difluoroprop-2-ynyl)phosphonate esters

Farid Benayoud and Gerald B. Hammond*

Department of Chemistry, University of Massachusetts Dartmouth, North Dartmouth, MA 02747-2300, USA

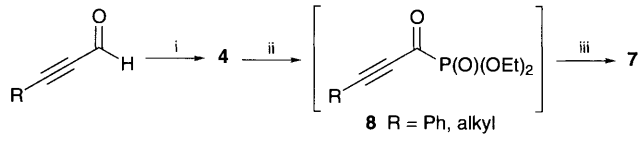
Pfitzner–Moffatt oxidation of diethyl α-hydroxyalkynephosphonate 4, prepared by nucleophilic attack of diethyl phosphite on the corresponding aldehyde, followed by DAST fluorination of the resulting α-ketophosphonate 8, results in the smooth formation of α,α-difluoroalkynephosphonate 7.

The contribution of α-fluoro- and α,α-difluoro-methylenephosphonates to the study of phosphate ester mimicry is unquestionable,[1] despite the controversy surrounding the issue of whether mono- or di-fluoro substitution yields a more effective phosphate mimic.[2] An additional benefit arising from fluorine substitution in phosphonates is the conformational information provided by the distinct NMR spin-coupling between phosphorus and fluorine nuclei. Recent findings in the field of phosphate mimicry such as the discovery of antiviral activity in certain cyclic and acyclic unsaturated phosphonate nucleosides,[3] will surely increase demand for new methods for the construction of elaborate fluorinated alkenephosphonates. One area of interest to us is the study of non-benzylic α,α-di-fluoro-β,γ-unsaturated phosphonates, the synthesis of which is not trivial. Not surprisingly, only a handful of syntheses have appeared in the literature, including difluorophosphoenolpyruvate[4] **1**, sought as potential inhibitor of EPSP synthase; δ-functionalized α,α-di-fluoroallylphosphonate[5] **2**; and more recently, phosphonobutenoate[2] **3**. This is in stark contrast to the numerous published preparations of α-mono- and α,α-difluoroalkanephosphonates.[6] All the above synthesis of difluorophosphonates **1–3** utilized the anion of ethyl difluoromethanephosphonate as a fluorine-containing molecular building block. We have recently discovered a regiospecific fluorination strategy that produced the first synthesis of α-fluoroprop-2-ynylphosphonate ester **5** starting from a prop-2-ynylic alcohol,[7] aldehyde or ketone[8] (Scheme 1). We argued that **5** could serve as a fluorinated scaffold for the synthesis of α-fluoro-β,γ-unsaturated alkenephosphonates and advanced this argument by preparing **6** from **5**. Moreover, we speculated that our approach to the synthesis of **5** could be extended to the hitherto unknown α,α-difluoroprop-2-ynylphosphonate **7**. We now report the first preparation of **7** from readily available α-hydroxyphosphonate **4** through a two-step sequence that includes oxidation followed by DAST fluorination.



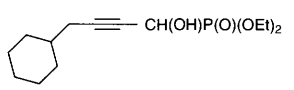
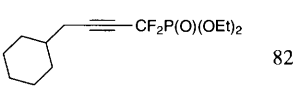
Scheme 1 *Reagents and conditions*: i, 1.2 equiv. DAST, CH_2Cl_2, −78 °C, 1 h; ii, H_2, $Pd/BaSO_4$, quinoline, MeOH, room temp.

In our quest for a viable route to the synthesis of **7** we considered two distinct approaches, both of which sought to introduce fluorine selectively on the carbon backbone. First, we attempted to introduce an additional fluorine atom on the α-carbon of **5** using an electrophilic fluorinating agent, *N*-fluorobenzenesulfonimide. This procedure led to an unidentified mixture of products, probably due to the low stability of the carbanion. The second approach involved oxidation of α-hydroxyphosphonate **4** followed by DAST fluorination of the expected α-oxophosphonate **8**. This strategy had been used successfully by Burke and coworkers[9] in the fluorination of α-oxobenzylphosphonates and in other non-hydrolysable phosphotyrosine analogues used for the preparation of phosphatase-resistant substrates. Burke found that a variety of reagents and conditions (MnO_2, pyridinium dichromate in CH_2Cl_2, Swern oxidation) oxidized the α-hydroxybenzylphosphonate precursor yielding a stable α-oxobenzylphosphonate. In our case, treatment of **4a**[8,10] with pyridinium dichromate either in DMF[11] or CH_2Cl_2, pyridinium chlorochromate, Ag_2O, and Swern oxidation conditions failed to yield the desired α-ketophosphonate **8**. Our first attempt using a modification of the Pfitzner–Moffatt oxidation[12] showed a singlet in ^{31}P NMR at δ −2.9 corresponding to the desired product, but this signal disappeared after stirring the reaction mixture overnight. Lowering the temperature, reducing the number of equivalents of carbodiimide and monitoring the reaction by ^{31}P NMR allowed us to isolate **8a** which was fluorinated without delay using a



Scheme 2 *Reagents and conditions*: i, $HP(O)(OEt)_2$, KF, room temp.; ii, 5 equiv. $(Me)_2N(CH_2)_3N{=}C{=}NEt{\cdot}HCl$, Cl_2CHCO_2H, Me_2SO–toluene, 0 °C, 5 h; iii, 20 equiv. DAST, CH_2Cl_2, 0 °C to room temp., overnight.

Table 1 Synthesis of **7**

	α-Hydroxyphosphonate **4**	α,α-Difluoroprop-2-ynylphosphonate[a] **7**	Yield (%)
a	Ph—≡—$CH(OH)P(O)(OEt)_2$	Ph—≡—$CF_2P(O)(OEt)_2$	74
b			82
c	C_5H_{11}—≡—$CH(OH)P(O)(OEt)_2$	C_5H_{11}—≡—$CF_2P(O)(OEt)_2$	72
d	$C_{10}H_{21}$—≡—$CH(OH)P(O)(OEt)_2$	$C_{10}H_{21}$—≡—$CF_2P(O)(OEt)_2$	74
e	$THPOC_{10}H_{20}$—≡—$CH(OH)P(O)(OEt)_2$	$THPOC_{10}H_{20}$—≡—$CF_2P(O)(OEt)_2$	55

[a] Satisfactory analytical and/or spectroscopic data have been obtained for all products.

large excess of DAST. This procedure furnished α,α-difluoroprop-2-ynylphosphonate **7a** in very good yield (Scheme 2).† Table 1 shows the usefulness of this methodology which has also been applied to acid sensitive substrates (*e.g.*, **7e**). Compounds **7a–e** are stable at room temperature but decompose partially on silica-gel chromatography.

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Footnote

† *Typical procedure* for the synthesis of diethyl (α,α-difluoroprop-2-ynyl)phosphonates. Diethyl 1,1-difluoro-3-phenyl-2-propynephosphonate **7a**: 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.48 g, 2.5 mmol, 5 equiv.) and dichloroacetic acid (0.096 g, 0.75 mmol, 1.5 equiv.) were added to a cold solution (0 °C) of **4a**[8,10] (0.134 g, 0.5 mmol) in Me_2SO–toluene (1 : 1, 10 ml). The reaction was stirred for 5 h, after which the mixture was quenched with water and extracted with $CHCl_3$ (3 × 25 ml). The organic layers were combined, washed with sat. $NaHCO_3$ (3 × 20 ml), dried over $MgSO_4$, filtered and concentrated. The resulting oil was dissolved in dry CH_2Cl_2 (10 ml) and treated with DAST (1.6 ml, 0.01 mol, 20 equiv.) at 0 °C after which the stirred mixture was allowed to warm to 25 °C. After stirring at 25 °C for 12 h, the mixture was diluted with CH_2Cl_2 and transferred dropwise into KOH solution at 0 °C. The aqueous layer was separated and the organic layer washed with sat. $NaHCO_3$ (3 × 20 ml). Organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to yield **7a** (0.107, 74%). An analytically pure sample was obtained by silica gel chromatography (hexane : EtOAc, 4 : 1), ^1H NMR ($CDCl_3$) δ 1.13–1.38 (m, 6 H), 4.31–4.43 (m, 4 H), 7.15–7.63 (m, 5 H); ^{31}P NMR ($CDCl_3$) δ 4.27 (t, *J* 108 Hz); ^{19}F NMR ($CDCl_3$) δ −96.6 (d, *J* 108 Hz); EIMS 232 (M^+ − 56, 17%), 180 (6), 151 (100), 132 (28), 109 (65), 91 (32), 81 (56). (Calc. for $C_{13}H_{15}F_2PO_3$: C, 54.16; H, 5.20. Found: C, 54.24; H, 5.19).

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