ORGANIC LETTERS

2001
Vol. 3, No. 13
2009−2012

A Convergent Triflate Displacement Approach to (α-Monofluoroalkyl)phosphonates

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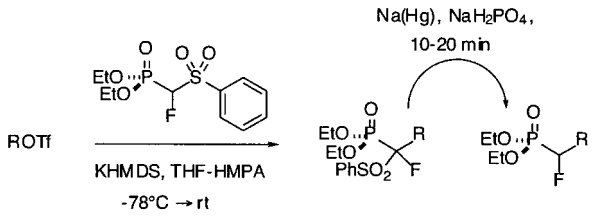
Received April 14, 2001

ABSTRACT



Treatment of primary alkyl triflates or iodides with the potassium salt of diethyl (α-fluoro-α-phenylsulfonylmethyl)phosphonate yields (α-fluoro-α-phenylsulfonylalkyl)phosphonates. These can be cleanly desulfonated, in a matter of minutes, with Na(Hg) in MeOH/THF/NaH_2PO_4. This two-step procedure complements previously reported triflate displacement approaches to α-nonfluorinated and α,α-difluorinated phosphonates.

Nature has selected the phosphate ester functional group as a handle for metabolic intermediates, as the backbone for the genetic information, and as a common regulatory switch (i.e., phospho-Tyr, -Ser, and -Thr) for proteins.[1] Yet, aside from pro-drug applications, phosphate esters are normally considered invalid functional groups for drug design, as they are subject to cleavage by ubiquitous digestive phosphatases. For these reasons, we and others have been interested in developing effective and hydrolytically stable mimics of biological phosphates.

While simple phosphonates have been under investigation for some time,[2] early work by Blackburn[3] and McKenna[4] raised the possibility that α-fluorination might render better phosphate mimics.[5] In particular, recent years have seen considerable development of the class of α,α-difluorinated phosphonates.[6]

However, though less well-studied, it is the α-monofluorinated phosphonates whose second pK_a's most closely match those of phosphates themselves. Several of the more interesting known "bioisosteres" in this family are illustrated in Figure 1.[7] Among these, the phosphoinositide (PI) analogue **2** of Thatcher[7b] and the 3-phosphoglycerol mimic **3** of O'Hagan[7c] are of particular interest. The former resembles the cyclic phosphodiester intermediate along the

(1) For a discussion on "Why Nature chose phosphates?" see: Westheimer, F. H. *Science* **1987**, *235*, 1173−1178.

(2) For reviews, see: (a) Wiemer, D. F. *Tetrahedron* **1997**, *53*, 16609−16644. (b) Engel, R. *Chem. Rev.* **1977**, *77*, 349−367.

(3) (a) Blackburn, G. M. *Chem. Ind. (London)* **1981**, 134−138. (b) Blackburn, G. M.; Kent, D. E.; Kolkmann, F. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1119−1125.

(4) McKenna, C. E.; Shen, P. *J. Org. Chem.* **1981**, *46*, 4573−457.

(5) For more recent discussions on the potential effects of fluorination α to phosphorus, see: (a) O'Hagan, D.; Rzepa, H. S. *J. Chem. Soc., Chem. Commun.* **1997**, 645−652. (b) Chen, Li.; Wu, Li.; Otaka, A.; Smyth, M. S.; Roller, P. P.; Burke, T. R., Jr.; den Hertog, J.; Zhang, Z.-Y. *Biochem. Biophys. Res. Commun.* **1995**, *216*, 976−984. (c) Thatcher, G. R. J.; Campbell, A. S. *J. Org. Chem.* **1993**, *58*, 2272−2281.

(6) Reviews: (a) Tozer, M. J.; Herpin, T. F. *Tetrahedron* **1996**, *52*, 8619−8683. (b) Burton, D. J.; Yang, Z.-Y.; Qiu, W. *Chem. Rev.* **1996**, *96*, 1641−1715. (c) Welch, J. T. *Fluorine in Bioorganic Chemistry*; Wiley: New York, 1991.

(7) (a) pTyr analogue/SH2 domain binding: Burke, T. R., Jr.; Smyth, M. S.; Otaka, A.; Nomizu, M.; Roller, P. P.; Wolf; G.; Case, R.; Shoelson, S. E. *Biochem.* **1994**, *33*, 6490−6494. (b) Cyclic phosphoinositide analogue/PI-PLC inhibitor: Campbell, A. S.; Thatcher, G. R. J. *Tetrahedron Lett.* **1991**, *32*, 2207−2210. (c) Glycerol 3-P analogue, G3PDH pseudosubstrate: Nieschalk, J.; Batsanov. A. S.; O'Hagan, D. J.; Howard, J. A. K. *Tetrahedron* **1996**, *52*, 165−176. (d) Uridine 5′-monophosphate analogue: Wnuk; S. F.; Robins, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2519−2520.

10.1021/ol015983z CCC: $20.00
Published on Web 06/01/2001

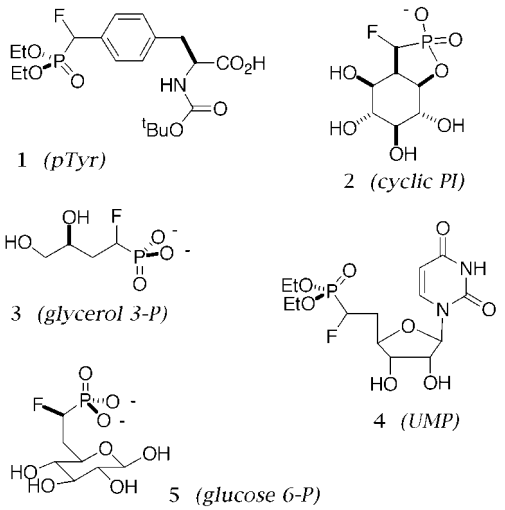


Figure 1. α-Monofluoroalkylphosphonate analogues of biological phosphates (the phosphate counterpart of these mimics is listed in parentheses).

reaction coordinate of PI-specific phospholipase C and inhibits this enzyme. The latter is a good pseudo-substrate for glycerol 3-phosphate dehydrogenase. Compound **4** represents one member of an intriguing class of α-monofluorinated nucleoside phosphonates[7d] and may be of interest from an anti-sense point of view.

We recently completed a "fluorinated phosphonate scan" of the well-defined phosphate binding pocket of G6PDH.[8] Interestingly, in terms of K_m, both the best phosphonate pseudo-substrate (**5**; 7*S* stereochemistry) and the phosphonate with the lowest affinity (7*R* diastereomer) are of the α-monofluorinated variety. Stereochemical dependencies such as these have also been observed by O'Hagan.[7c] Thus, at least in some active sites, the additional stereocenter present in this class of phosphate mimics may be used to fine-tune their binding.

With growing interest in this class of phosphate mimics, there has been significant interest in synthetic methods for accessing (α-monofluoroalkyl)phosphonates. Current approaches include electrophilic fluorination [Selectfluor, FN-$(SO_2Ph)_2$],[7d,9] nucleophilic fluorination (DAST),[8,10] HWE- or Peterson-olefination entries into α-fluorovinylphosphonates, followed by hydrogenation,[7b,11] transition metal-mediated $(RO)_2P(O)CHF-C(sp^2)$ bond formation,[12] and SET-induced addition of the $(RO)_2P(O)CHF$ radical to alkenes.[13]

Given our *convergent* triflate displacement approaches to both the CH_2- and CF_2-phosphonates,[8,14] we were particularly interested in developing a related route to the CHF-phosphonates. To be sure, displacement reactions with dialkyl lithiofluoromethylphosphonates [$(RO)_2P(O)CHFLi$] had been reported,[15] but both in our hands and elsewhere, these reagents have proved difficult to handle.[16] In one elegant solution to this problem, Savignac and co-workers report the transient in situ generation and subsequent displacement reactions of $(RO)_2P(O)CF(TMS)Li$. Careful, base-mediated desilylation is then required to release the targeted monofluorinated phosphonate product.[17]

We report a complementary approach here, wherein a phenylsulfonyl group is used to stabilize that α-fluoromethylphosphonate anion. McCarthy had reported the in situ generation of $(RO)_2P(O)CF(SO_2Ph)Li$ and its condensation reactions with carbonyl compounds to give α-fluorovinyl sulfones.[18,19] Whereas McCarthy normally generates this anion in situ from $PhSO_2CH_2Li$ and diethyl chlorophosphate, we have found it much more convenient to begin with $(RO)_2P(O)CHF(SO_2Ph)$ (**8**). Appell has described a convenient synthesis of this phosphonate that is amenable to scale-up.[20]

Pleasingly, deprotonation of **8** at low temperature, followed by addition of a primary alkyl iodide or triflate, leads to efficient displacement upon removal of the cold bath (Table 1). To evaluate the counterion dependence of this displacement, several bases were examined, with the isopropylidene-protected glyceryl triflate (**9c**) serving as the model electrophile. KHMDS provided the best results, with lower yields being obtained with LiHMDS, NaHMDS, LDA, and Schwesinger's P1-t-Bu phosphazene base ($^{MeCN}pK_{BH+}$ =

(8) Berkowitz, D. B.; Bose, M. B.; Pfannenstiel, T. J.; Doukov, T. *J. Org. Chem.* **2000**, *65*, 4498−4508.
(9) (a) Iorga, B.; Eymery, F.; Savignac, P. *Synthesis* **2000**, 576−580. (b) Taylor, S. D.; Dinaut, A. N.; Thadani, A. T.; Huang, Z. *Tetrahedron Lett.* **1996**, *37*, 8089−8092. (c) Lal, G. S. *J. Org. Chem.* **1993**, *58*, 2791−2796. (d) Differding, E.; Duthaler, R. O.; Krieger, A.; Rüegg, G. M.; Schmit, C. *Synlett* **1991**, 385−396.
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(13) Zhang, X.; Qiu, W.; Burton, D. J. *J. Fluorine Chem.* **1998**, *89*, 39−49.
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(15) Blackburn, G. M.; Parratt, M. J. *J. Chem. Soc., Perkin Trans. I* **1986**, 1425−1430.
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(17) Waschbüsch, R.; Carran, J.; Savignac, P. *J. Chem. Soc., Perkin Trans. I* **1997**, 1135−1138.
(18) (a) McCarthy, J. R.; Matthews, D. P.; Paolini, J. P. *Org. Synth.* **1993**, *72*, 216−224. (b) McCarthy, J. R.; Matthews, D. P.; Stemerick, D. M.; Huber, E. W.; Bey, P.; Lippert, B. J.; Snyder, R. D.; Sunkara, P. S. *J. Am. Chem. Soc.* **1991**, *113*, 7439−7440. (c) McCarthy, J. R.; Matthews, D. P.; Edwards, M. L.; Stemerick, D. M.; Jarvi, E. T. *Tetrahedron Lett.* **1990**, *31*, 5449−5452.
(19) We are aware of only an isolated report in which McCarthy's reagent was used for nucleophilic displacement reactions. Note that these authors used only simple alkyl halides and reported being unable to reductively cleave the sulfonyl group without P−C cleavage. Koizumi, T.; Hagi, T.; Horie, Y.; Takeuchi, Y. *Chem. Pharm. Bull.* **1987**, *35*, 3959−3962.
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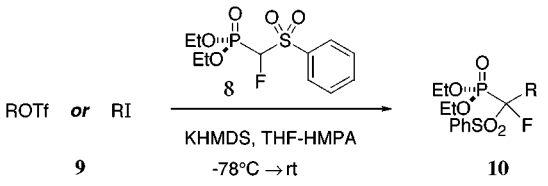
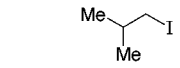
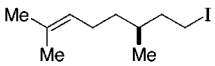
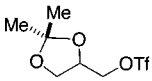
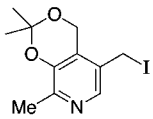
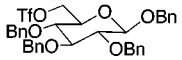
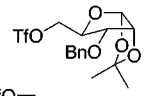
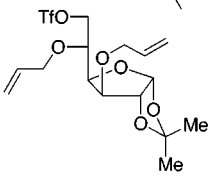
Table 1. Displacements with Diethyl (α-Fluoro-α-phenylsulfonylmethyl)phosphonate Anion



entry	triflate/halide		% yield[a]
a		*(isobutyl)*	71%
b		*(citronellyl)*	69%[b]
c		*(glyceryl)*	68%
d		*(pyridoxyl)*	50%[c]
e		*(glucopyranosyl)*	60%
f		*(ribofuranosyl)*	78%
g		*(glucofuranosyl)*	66%[d]

[a] All yields are for isolated, with chromatographically purified compounds giving satisfactory spectral data. For all reactions, phosphonate deprotonation was carried out at −78 °C with KHMDS (5 min), followed by addition of the alkyl triflate or halide. The cold bath was then removed and the reaction mixture was then allowed to warm. In all cases a mixture of diastereomeric products was obtained, in the ratios indicated in the Experimental Section (see Supporting Information). [b] In this case, 1.5 equiv of the alkyl halide was employed. The reported yield is based on the McCarthy reagent. [c] The pyridoxyl phosphonate yield is based on the starting chloride, although it appears that the displacement actually occurs on the in situ generated iodide (Bu_4NI). [d] This yield is calculated over two steps from the corresponding alcohol. This triflate is somewhat sensitive and, therefore, is not subjected to chromatography. Rather, after precipitation of 4-methyl-2,6-di-*tert*-butylpyridinium triflate with cold hexane, filtration provides the triflate in sufficient purity for use in the displacement.[14c]

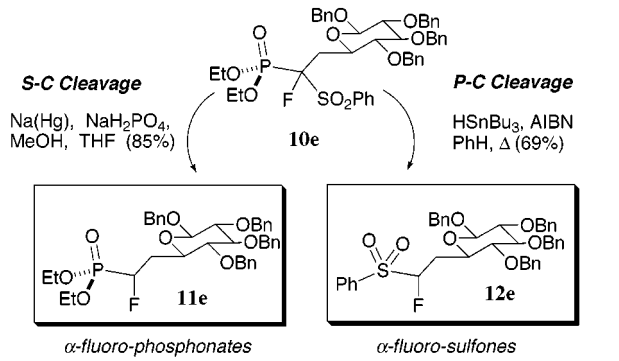
27),[21] approximately in that order. No product was observed with n-BuLi as base.

Primary triflates react within 10−20 min upon removal of the cold bath. For the alkyl iodides examined, longer reaction times are required. Typically these are complete within an hour. Care must be taken to use only 1 equiv of $(RO)_2P(O)CF(SO_2Ph)K$. In cases where two equivalents are used, a significant amount of an ethyl phosphonate byproduct, $(RO)_2P(O)CF(SO_2Ph)CH_2CH_3$, is isolated, presumably formed either via "self-condensation" of the excess reagent or via reaction of the reagent with the alkylation product. This byproduct has TLC mobility similar to that of most alkylation products and complicates purification. One sees essentially none of the byproduct when employing rigorously stoichiometric anionic reagent.

As can be seen, (α-fluoro-α-sulfonylalkyl)phosphonates bearing branched chain alkyl, terpenoid, glyceryl, furanose, and pyranose backbones could be efficiently constructed. The pyridoxol phosphate analogue (**d** series) was constructed in a slightly different manner. The 5′-iodide, **9d**, was found to be much more reactive than the corresponding chloride.[22] While the iodide could be generated and its NMR spectrum recorded immediately upon concentrating, it decomposed upon standing. For alkylation reactions, it was found to be more convenient to depart from the chloride, and generate the iodide, in situ, via exposure to one full equivalent of Bu_4NI in the presence of the potassium anion of **8**. The pyridoxyl 5′-chloride itself was synthesized from the corresponding pyridoxol acetonide in nearly quantitative yield using MsCl (NEt_3, CH_2Cl_2).

Two chemoselective reaction manifolds were uncovered for reductively processing the (α-fluoro-α-sulfonylalkyl)-phosphonates (Scheme 1). On one hand, $HSnBu_3$ under free

Scheme 1. (α-Fluoro-α-sulfonyl)phosphonates as Versatile Synthetic Intermediates: Dephosphonylation vs Desulfonation



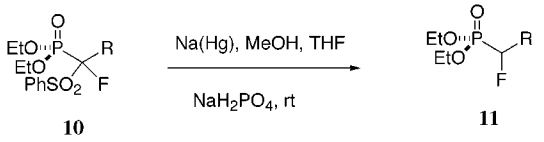
radical conditions produces dephosphonylation, thereby providing a novel route to α-fluoroalkyl sulfones. Alternatively, the targeted (α-fluoroalkyl)phosphonates may be accessed with ease via Na(Hg)-mediated desulfonation, provided that the mercury amalgam is made or purchased fresh. Other potential desulfonation methods [including (i) Al(Hg)/10% aqueous THF; (ii) Mg, $HgCl_2$/EtOH−THF; (iii) LiDTBB/THF−MeOH; (iv) SmI_2/HMPA−THF] proved far less successful.

The Na(Hg)-mediated reductive desulfonation is especially efficient as it proceeds in a matter of minutes and in high

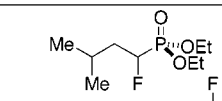
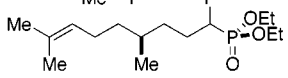
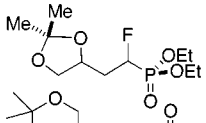
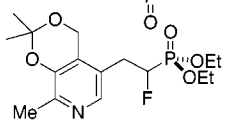
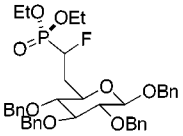
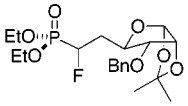
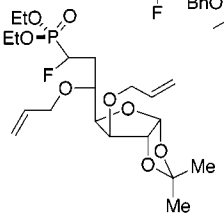
(22) Stirtan, W. G.; Withers, S. G. *Biochemistry* **1996**, *35*, 150157−15064.

(23) In the ribofuranose case (**10f**), whether starting from a 1:1 mixture of diastereomeric (α-fluoro-α-phenylsulfonylalkyl)phosphonates or from the first eluting diastereomer alone, we obtain essentially a 1:1 mixture of (α-fluoroalkyl)phosphonates (**11f**), as judged by crude ^{31}P NMR. So, it appears that the desulfonation proceeds with loss of stereochemical information at the α-center, at least under these conditions.

Table 2. Facile Desulfonylation to the α-Fluorinated Phosphonates



10 11

entry	product	% yield[a]
a		79%
b		80%
c		89%
d		71%
e		85%
f		80%
g		78%

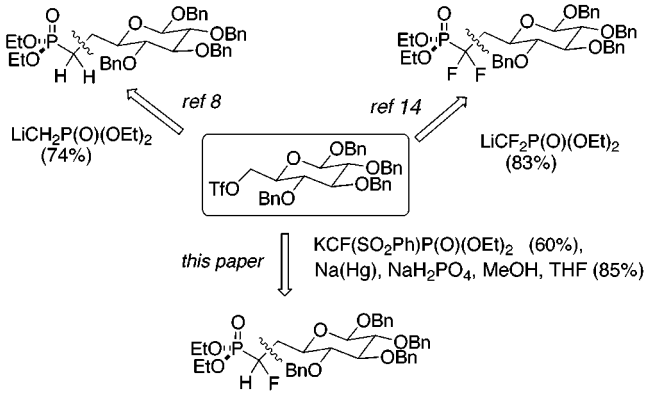
[a] All reactions were complete in 10−20 min. Yields are for isolated products, following workup and chromatography. For entries **b**, **c**, **e**, **f**, and **g** two diastereomers were obtained.

yields (Table 2). Mixtures of diastereomers are obtained in all cases in which a resident stereogenic center is present.[23] For the glucopyranose case **11e**, the (7*S*)- and (7*R*)-diastereomers could be separated by standard flash SiO_2 chromotography. Entries **11b**,**c**,**f**,**g** present greater challenges, appearing as essentially single spots on TLC. To demonstrate proof of principle here, the two ribofuranose diastereomers (**11f**) were separated by chiral HPLC, using a chiracel OD stationary phase.

Of particular note is entry **11d**, as this represents the first approach to the 5′-monofluorophosphonate analogue of pyridoxol phosphate, to the best of our knowledge. Phosphonate analogues of pyridoxal phosphate are useful biochemical tools as they may serve as surrogate cofactors for PLP-dependent enzymes.[24] However, hitherto only the nonfluorinated and difluorinated phosphonate analogues of the cofactor were available.[25]

This chemistry now firmly establishes the third α-monofluorinated phosphonate branch in our divergent triflate displacement approach to phosphate mimics (Scheme 2).

Scheme 2. A Divergent Triflate Displacement Approach to Phosphonate "Bioisosteres"



From a single primary triflate, one can now obtain all four phosphonates needed for a complete "fluorinated phosphonate scan" [8] in order to ascertain both the optimal degree and directionality of α-fluorination for binding to a targeted active site. Future studies along these lines will be reported in due course.

Acknowledgment. D.B.B. is an Alfred P. Sloan Fellow. We thank R. K. Shoemaker and R. L. Cerny for NMR and MS support, respectively. N.G.A. was a participant in the University of Nebraska NSF-REU program (NSF 9820528).

Supporting Information Available: Experimental procedures and spectral data (including ^{1}H, ^{19}F, and ^{31}P NMR's) for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL015983Z

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(25) The availability of a complete set of α-non-, mono-, and difluorinated phosphonate analogues of PLP will permit biochemists to examine PLP-enzyme kinetics as a function of cofactor pK_a. For a study along these lines with previously available phosphonates, see ref 22.