# Synthesis of (α,α-Difluoroalkyl)phosphonates by Displacement of Primary Triflates

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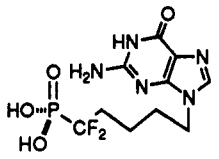
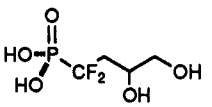
*Summary:* Simple primary alkyl triflates and those derived from several monosaccharides are cleanly displaced by diethyl (lithiodifluoromethyl)phosphonate to provide the corresponding (α,α-difluoroalkyl)phosphonates in minutes at −78 °C.

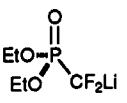
There is currently considerable interest in (α,α-difluoroalkyl)phosphonates as hydrolytically stable analogues of phosphate esters.[1-7] It has been argued that (α,α-difluoroalkyl)phosphonates are approximately isopolar and isosteric with the corresponding phosphates.[1] Indeed, the difluoromethylene analog of glycerol 3-phosphate, **2**, is a substrate for glycerol 3-phosphate dehydrogenase,[2] and 9-(5′,5′-difluoro-5′-phosphonopentyl)guanine, **1**, is a potent bisubstrate analog inhibitor for purine nucleoside phosphorylase.[3]



**1**



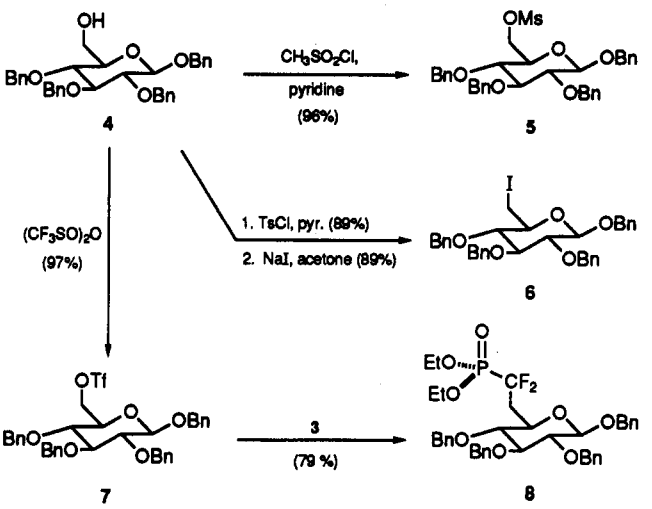
**2**



**3**

Most synthetic approaches to these difluoroalkylphosphonates rely upon the disclosure by Soborovskii and Baina that the P–$CF_2$ bond may be constructed via a Michaelis–Becker reaction of sodium diethyl phosphite upon chlorodifluoromethane to generate diethyl (difluoromethyl)phosphonate.[8] However, construction of the $PCF_2$–C bond has been much more challenging. Kondo reported that diethyl (difluoromethyl)phosphonate could be deprotonated with LDA and that the corresponding lithium salt **3** underwent displacement reactions with ethyl bromide and *n*-hexyl bromide.[9] However, subsequent workers have found that **3** *does not* generally readily undergo displacement reactions with primary alkyl halides.[10] Reported yields range from 0%[11b] to 23%[12] to 40%.[3] The problem apparently lies in the relatively weak nucleophilicity and thermal instability of **3**.[13] Hence, elegant, alternative methods of fashioning the $PCF_2$–C bond have recently been developed.[11,14] However, the most efficient of these methods are less direct than simple displacement, as they require dehalogenation[14] or deoxygenation[11] following construction of the $PCF_2$–C bond.

**Scheme I**



We wish to report that **3** does undergo rapid, efficient direct displacement reactions with primary alkyl triflates (Scheme I). In our initial synthetic approaches to a glucose 6-phosphate analogue, we examined mesylate **5** and iodide **6** and found that neither underwent displacement with **3**. Triflate **7**, on the other hand, was stable to an aqueous bicarbonate workup and silica gel chromatography, yet reactive enough to be displaced by **3** at −78 °C in 5–10 min.

Tetrahydrofuran was far superior to diethyl ether or 1,2-dimethoxyethane as solvent. Attempts to carry out displacements on triflate **7** with (difluoromethylene)phosphonate anions related to **3** but bearing counterions other than lithium, such as potassium (KHMDS as base), sodium (NaHMDS as base), or phosphazonium (Schwesinger's P4 phosphazene base),[15] failed. Three methods were found to give efficient displacement. In method A, the anion **3** is generated *in situ*. LDA (5 equiv) is added via cannula to a solution containing triflate and diethyl (difluoromethyl)phosphonate(5 equiv) in THF at −78 °C. Remarkably, one sees efficient displacement and no competing E2 elimination under these conditions. In Method B, the anion **3** (3.5 equiv) is *preformed* with LDA (3.5 equiv) in the presence of HMPA (3.5 equiv) at −78 °C.

• Abstract published in *Advance ACS Abstracts*, October 1, 1993.

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(9) Obayashi, M.; Eiji, I.; Matsui, K.; Kondo, K. *Tetrahedron Lett.* **1982**, *23*, 2323–2326.

(10) Allylic halides may constitute an exception to this rule as they couple with organozinc and organocadmium reagents related to **3**: (a) Burton, D. J.; Sprague, *J. Org. Chem.* **1989**, *54*, 613–617. (b) Chambers, R. D.; Jaouhari, R.; O'Hagan, D. *Tetrahedron* **1989**, *45*, 5101–5108.

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(12) Kim, C.-U.; Luh, B. Y.; Misco, P. F.; Bronson, J. J.; Hitchcock, M. J. M.; Ghazzouli, I.; Martin, J. C. *J. Med. Chem.* **1990**, *33*, 1207–1213.

(13) For a discussion of this point see ref 10a and references cited therein.

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(15) Pietzonka, T.; Seebach, D. *Chem. Ber.* **1991**, *124*, 1837–1843.

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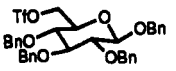
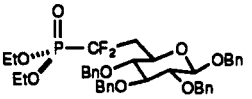
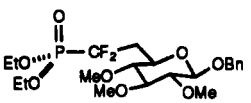
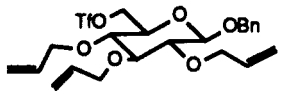
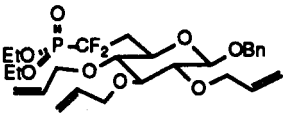
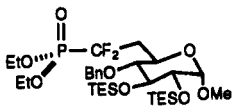
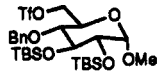
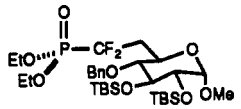
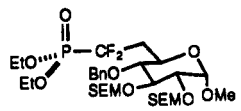
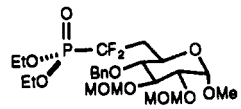
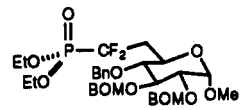
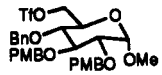
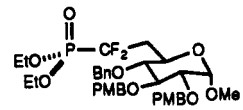
**Table I. Displacements with D-Glucopyranose Triflates**

| | triflate | yield[a,b] (%) | | (α,α-difluoroalkyl)-phosphonate | yield[b] (%) | method |
|---|---|---|---|---|---|---|
| 7 |  | 97 | 8 |  | 79 | A |
| 9 |  | 88 | 10 |  | 78 | A |
| 11 |  | 78 | 12 |  | 82 | A |
| 13 |  | 94 | 14 |  | 59 | B |
| 15 |  | 100 | 16 |  | 70 | C |
| 17 |  | 78 | 18 |  | 69 | B |
| 19 |  | 96 | 20 |  | 81 | B |
| 21 |  | 97 | 22 |  | 80 | B |
| 23 |  | 89 | 24 |  | 71 | C |

[a] Triflates chromatographically purified. [b] All yields are isolated yields.

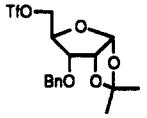
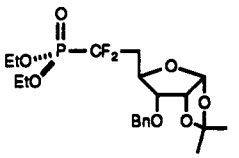
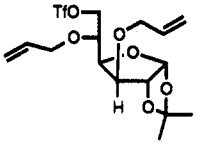
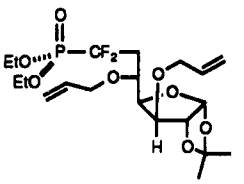
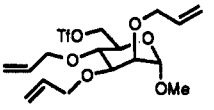
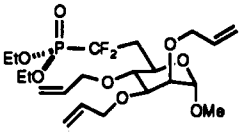
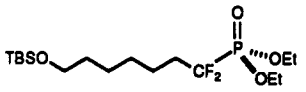
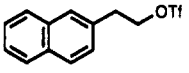
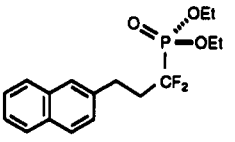
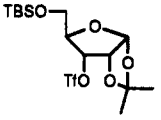
A solution of triflate in THF is added to the anion so formed. Method C is directly analogous to method B except that TMEDA replaces HMPA. Results using these three methods are collected in Table I. Regardless of the method chosen, the displacement reaction is complete in 5–10 min and proceeds in good to very good yield.[15]

The compatibility of this chemistry with a variety of ether and acetal protecting groups commonly employed in carbohydrate chemistry was examined. A series of protected D-glucopyranoside derivatives possessing both the β- and the α-anomeric stereochemistry were constructed. Indeed, the desired primary triflates could be obtained in high isolated yield after purification on silica gel. Moreover, these primary glucopyranose triflates underwent efficient direct displacement in a matter of minutes with 3.5–5 equiv of **3** (Table I).[16]

The remarkable stability of the primary triflates derived from glucopyranose may be attributed to their nearly neopentyl nature and is well precedented.[17] We have also found that this approach may be extended to primary triflates derived from other sugars such as α-D-ribofuranose, α-D-glucofuranose, and α-D-mannopyranose (Table II). Less stable primary triflates (i.e., **31** and **33**) were purified by extraction with pentane. This procedure yields triflates containing about 5 mol % of 2,6-di-*tert*-butyl-

(16) **Typical Experimental Procedure.** To a solution of diisopropylamine (91 μL, 0.65 mmol) and HMPA (113 μL, 0.65 mmol) at −78 °C in THF (1 mL) under Ar was added *n*-butyllithium (407 μL of a 1.6 M solution in hexane, 0.65 mmol). The resulting solution was allowed to stir for 25 min at 0 °C and then cooled to −78 °C. To this solution of LDA at −78 °C were added, via cannula, a (−78 °C) solution of diethyl (α,α-difluoromethyl)phosphonate (102 μL, 0.65 mmol) in THF (0.5 mL), and, 2 min later, a (−78 °C) solution of triflate **21** (122 mg, 0.186 mmol) in THF (1 mL), dropwise, via cannula. After 10 min at −78 °C, the reaction was quenched by adding aqueous $NH_4Cl$ (3 mL) and $Et_2O$ (3 mL). The aqueous layer was further extracted with EtOAc (2 × 10 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and evaporated. Silica gel flash chromatography (50% EtOAc/n-hexane) gave **22** (103 mg, 80%): $^1H$ NMR (500 MHz, $CDCl_3$) δ 1.32 (app t, $J$ = 7 Hz, 6 H), 2.05–2.22 (m, 1 H), 2.48–2.64 (m, 1 H), 3.20–3.24 (app t, $J$ = 9.5 Hz, 1 H), 3.40 (s, 3 H), 3.62–3.65 (dd, $J$ = 3.6, 9.5 Hz, 1 H), 4.09–4.12 (app t, $J$ = 9.5 Hz, 1 H), 4.13–4.17 (app t, $J$ = 10 Hz, 1 H), 4.19–4.24 (m, 4 H), 4.56 (d, $J$ = 12 Hz, 1 H), 4.61–4.64 (d, $J$ = 12 Hz, 1 H), 4.62–4.65 (d, $J$ = 11 Hz, 1 H), 4.68 (d, $J$ = 12 Hz, 1 H), 4.73 (d, $J$ = 12 Hz, 1 H), 4.82 (d, $J$ = 3.6 Hz, 1 H), 4.88 (d, $J$ = 7 Hz, 1 H), 4.89 (d, $J$ = 7 Hz, 1 H), 4.95 (d, $J$ = 11 Hz, 1 H), 4.99 (d, $J$ = 6 Hz, 1 H), 5.01 (d, $J$ = 6 Hz, 1 H), 7.24–7.35 (m, 15 H); $^{31}P$ NMR (81 MHz, $CDCl_3$): δ 5.10–7.76 (app t, $J_{F,P}$ = 108 Hz). Anal. Calcd for $C_{35}H_{45}O_{10}F_2P$: C, 60.51; H, 6.53. Found: C, 60.43; H, 6.42.

**Table II. Displacements with Primary Triflates**

| | triflate | yield[a] (%) | | (α,α-difluoroalkyl)-phosphonate | yield[a] (%) | method |
|---|---|---|---|---|---|---|
| 25 |  | 79 | 26 |  | 83 | B |
| 27 |  | 87 | 28 |  | 65 | B |
| 29 |  | 62 | 30 |  | 74 | B |
| 31 |  | 91 | 32 |  | 60 | A |
| 33 |  | 92 | 34 |  | 59 | A |
| 35 |  | 80 | | e | | B |

[a] All yields are isolated yields. [b] Triflate chromatographically purified. [c] Triflate purified by filtration and aqueous ($NaHCO_3$) workup. [d] Triflate purified by pentane extraction. [e] No displacement product observed.

4-methylpyridine[18] that, nonetheless, are efficiently displaced by **3**. However, an attempt to extend this direct displacement methodology to secondary sugar triflates failed, with the ribofuranose triflate **35** yielding only products resulting from cleavage of the triflate sulfur–oxygen bond.[19]

In summary, the first efficient direct displacement approach to (α,α-difluoroalkyl)phosphonates is reported. Thus, the displacement of primary triflates with **3** proceeds in very good yield in 5–10 min at −78 °C. This approach is compatible with a considerable range of protecting groups (Table I) and a variety of carbon skeletons but appears to be limited to primary triflates. This methodology provides an expedient entry into a variety of (difluoroalkyl)phosphonate analogues of naturally occurring phosphates, such as glucose 6-phosphate, ribose 5-phosphate, and mannose 6-phosphate.

**Acknowledgment.** We gratefully acknowledge support from the Elsa U. Pardee Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society. High-resolution mass spectra were obtained from the Midwest Center for Mass Spectrometry, supported by NSF DIR9017262. M.E. and D.G.S. are recipients of GAANN Fellowships from the U.S. Department of Education (P200A100067).

**Supplementary Material Available:** Experimental procedures for the preparation of and spectral data for all compounds and $^1H$ NMR spectra for compounds **7-35** (56 pages). This material is contained in libraries on microfiche, immediately follows this article on the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(17) For the use of related sugar triflates, see: (a) Vlahov, I. R.; Vlahova, P. I.; Schmidt, R. R. *Tetrahedron Lett.* **1992**, *33*, 7503–7506. (b) Paulsen, H.; von Deyn, W. *Liebigs Ann. Chem.* **1987**, 141–152 and references cited therein.

(18) All triflates were synthesized from the corresponding alcohols with triflic anhydride and 2,6-di-*tert*-butyl-4-methylpyridine in methylene chloride. Pyridine is known to displace primary triflates: (a) Binkley, R. W.; Ambrose, M. G.; *J. Org. Chem.* **1983**, *48*, 674–677. (b) Hall, L.; Miller, D. C. *Carbohydr. Res.* **1976**, *47*, 299–305.

(19) Triflate **35** was consumed to give only starting alcohol, 5-*O*-(*tert*-butyldimethylsilyl)-1,2-*O*-isopropylidene-α-D-ribofuranoside, and the corresponding 3-(diethylphosphate) ester, presumably derived therefrom.