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A GENERAL METHOD FOR THE SYNTHESIS OF 1,1-DIFLUOROALKYLPHOSPHONATES

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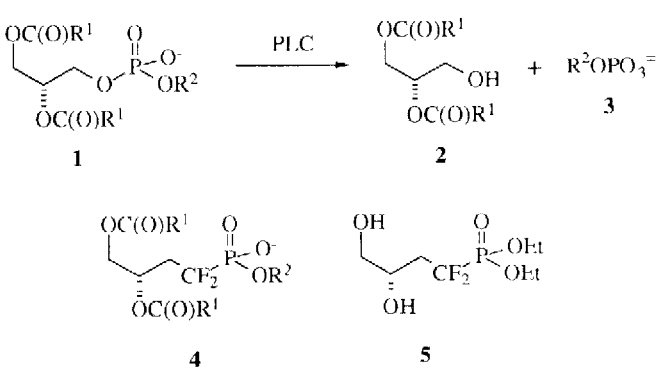
Abstract. A facile method for preparing 1,1-difluoroalkylphosphonates has been developed that features radical deoxygenation of thionocarbonates derived from the adducts formed upon addition of **9** to aldehydes.

Replacement of a phosphate functional group with a phosphonate moiety in biologically important molecules constitutes an attractive strategic device for the design of non-hydrolyzable substrate analogues as inhibitors or alternative substrates for enzymes that process naturally-occurring phosphates [1] Although a phosphonate moiety has been frequently employed as an isosteric replacement for a phosphate group, it has been proposed that the corresponding 1,1-difluoroalkylphosphonate should be a superior replacement since this surrogate should more accurately mimic the steric and polar character of the phosphate function.[2] To evaluate this hypothesis, a number of studies have been conducted to examine the efficacy of 1,1-difluoroalkylphosphonates as analogues of natural phosphates,[3,4] and in some cases these difluorophosphonates offered significant advantage over their nonfluorinated counterparts as enzyme inhibitors or as alternate substrates [4]

Members of the phospholipase C (PLC) family of enzymes cleave the phosphodiester bond of phospholipids **1** to afford a diacyl glycerol **2** and an organic phosphate **3** (Scheme 1), and selected isoenzymes of this class play pivotal roles in trans-membrane signalling processes and intracellular signal transduction [5] During the course of current investigations to probe the mechanistic features and mode of action of representative PLC isoenzymes, we had occasion to prepare a series of 1,1-difluoroalkylphosphonates related to **4** as potential inhibitors of phosphatidyl choline and phosphatidyl inositol specific PLC's We envisioned that difluorophosphonates **4** would be accessible from optically pure diol **5** by straightforward *O*-acylation and coupling with the requisite head group R^2OH.

Scheme 1



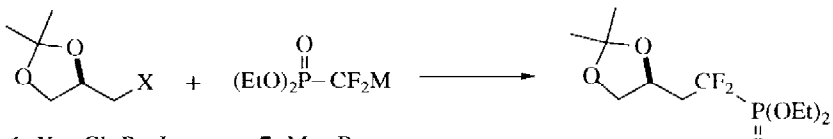
1 **2** **3**

4 **5**

R^1 = alkyl or unsaturated alkyl
R^2 = choline or inositol

The synthesis of the racemic diol **5** has been reported,[4a] but the route was somewhat inefficient. Although we developed an alternative and improved approach to racemic **5** from epichlorohydrin,[6] implementation of either of these procedures to the facile synthesis of quantities of optically pure **5** that were required for our enzymatic studies appeared problematic. Consequently, we set to the task of developing a general entry to functionalized 1,1-difluoroalkylphosphonates and have discovered a novel and efficient protocol for their synthesis that we disclose herein.

A number of approaches to 1,1-difluoroalkylphosphonates have been devised.[3c,4a,7] One common tactic for their preparation features the displacement of a leaving group from a suitably reactive substrate by various organometallic species derived from **7** and **8**. Indeed, **9**, which is thermally unstable, undergoes reaction with a number of primary and secondary alkyl bromides. Based upon these previous accounts, it occurred to us that the reaction of a glycidyl halide **6** with **9** might provide a useful route to **10** and thence to enantiomerically pure **5**. However, attempts to effect such a transformation were uniformly unsuccessful, and we turned to the exploration of other avenues.[6a]



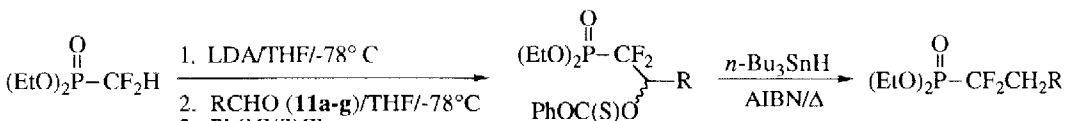
6: X = Cl, Br, I

7: M = Br
8: M = H
9: M = Li

10

The reaction of **9** with carbonyl compounds had been reported to give 1,1-difluoroalkenes or 1,1-difluoro-2-hydroxy alkylphosphonates depending upon the conditions.[7b] This observation stimulated us to examine an alternative route to 1,1-difluoroalkylphosphonates that involved radical deoxygenation of a suitable derivative of 1,1-difluoro-2-hydroxy alkylphosphonates (Scheme 2). Thus, metallation of **8** with lithium diisopropylamide at -78 °C followed by reaction of the **9** thus produced with a series of aldehydes **11a-g** afforded intermediate alkoxide adducts that were trapped *in situ* with phenyl chlorothionoformate to give the thionocarbonates **12a-g** in 71-90% yields.[8] Subsequent Barton deoxygenation[9] of **12a-g** proceeded smoothly upon treatment with tri-*n*-butyltin hydride in the presence of AIBN in refluxing toluene to deliver the desired 1,1-difluoroalkylphosphonates **13a-g** in 81-89% yields (Table 1).[8]

Scheme 2

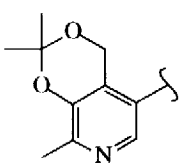
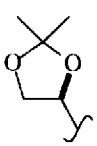
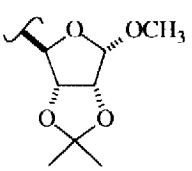


8 **12a-g** **13a-g**

General Experimental Procedure for the Conversion of 11a-g into 13a-g. To a solution of lithium diisopropylamide (7.14 mmol) in THF/hexane (15 mL, 2:1) at -78 °C was added *via* cannula over 5 min a solution of diethyl difluoromethylphosphonate (**8**)[7b] (1.27 g, 6.75 mmol) in THF (5.0 mL) that had also been pre-cooled to -78 °C. The lemon yellow solution was stirred at -78 °C for an additional 45 min, whereupon a solution of

the carbonyl compound **11a-g** (7.27 mmol) in THF (5 mL) that had also been pre-cooled to -78 °C was added *via* cannula over 10 min. The resulting lemon yellow solution was then stirred at -78 °C for 6 h, at which time phenyl chlorothionoformate (2.0 mL, 14.5 mmol) was added in one portion. Stirring was continued at -78 °C for an additional 45 min, and the mixture was allowed to warm to room temperature. The mixture was poured into ether (100 mL), and the mixture was washed with 50% saturated aq. NH_4Cl (3 x 30 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure, and the crude **12a-g** thus obtained was purified by flash chromatography. A solution of the purified thionocarbonate **12a-g** (5.0 mmol) in dry toluene (25 mL) containing freshly distilled tri-*n*-butyltin hydride (1.35 mL, 5.0 mmol) and AIBN (0.082 g, 0.5 mmol) was heated at reflux for 2 h. After cooling to room temperature, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography to furnish pure **13a-g**.

TABLE 1. Synthesis of 1,1-Difluoroalkylphosphonates 13a-g.

Entry	R	Yield of **12**	Yield of **13**
a	$CH_3(CH_2)_5$-	90	81
b	$Ph_2(CH_3)CSiOCH_2CH_2$-	71	86
c	*cyclo*-C_6H_{11}-	87	84
d	C_6H_5-	85	89
e		85	89
f		83	80
g		87	89

This method for preparing the 1,1-difluroalkylphosphonates **13a-g** constitutes an excellent complement to existing procedures.[7] Significantly, it allows for the facile preparation of 1,1-difluoroalkylphosphonates bearing a stereogenic center at the carbon beta to the difluoromethene moiety, this is a critical structural feature common to the phosphodiesters found in phospholipids and nucleic acids. Application of this general procedure to the preparation

of novel difluorophosphonates as isosteric and isopolar mimics of biologically important phosphates and the use of these substances as inhibitors of PLC and other phosphate processing enzymes will be reported in due course

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8. The structure assigned to each compound was in full accord with its spectral (^{1}H and ^{13}C NMR, IR and mass) characteristics Yields cited are for compounds judged to be >95% pure by ^{1}H NMR Analytical samples of all new compounds were obtained by flash chromatography and gave satisfactory combustion analysis (C, H) and/or identification by high resolution mass spectrometry

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