A Regiospecific Fluorination Strategy: Synthesis of (α-Fluoropropargyl)- and (α-Fluoroallyl)phosphonate Esters

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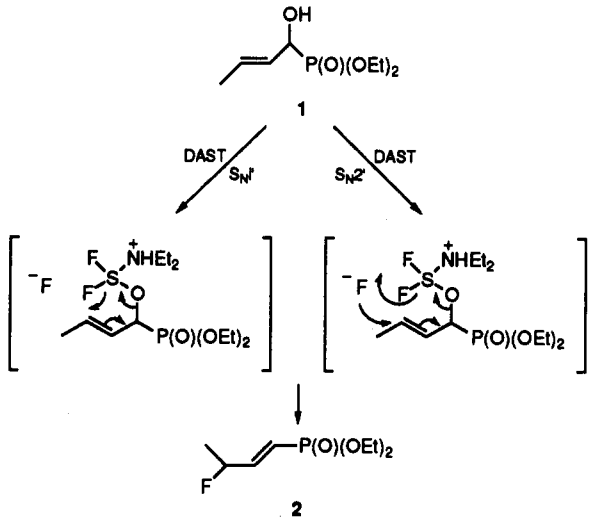
Received May 27, 1993 (Revised Manuscript Received August 13, 1993•)

Summary: A common approach to the synthesis of **6** and **7** involving regiospecific fluorination of the hydroxy group in β,γ-unsaturated α-hydroxy phosphonates is described.

The use of fluorine in biologically active molecules is widespread.[1] One such application is the substitution of the labile ester oxygen of phosphate biomolecules by monofluoro- or difluoromethylene groups. It has been proposed that the isosteric and isopolar relationship of phosphates and fluoro phosphonates allows the latter to mimic the biological activity of the parent phosphate. Following Blackburn's leading work on ^{31}P NMR shifts and pK_a correlation between phosphates and various α-halogeno phosphonates,[2] research on fluoro phosphonates has focused primarily on difluoromethylene phosphonate analogues of biological phosphates.[3,4] However, more recent theoretical calculations[5] have suggested that the presence of only one fluorine atom in phosphonates may be sufficient for molecular mimicry.

Our aim is to develop the syntheses of β,γ-unsaturated α-fluoro phosphonates (e.g., **6** and **7**). These hitherto unknown compounds could provide phosphate analogues with distinct geometrical attributes. They are also equipped with versatile synthetic handles (i.e. allylic and propargylic moieties) capable of further chemical manipulation. The reported syntheses of α-fluoro phosphonates and α,α-difluoro phosphonates include coupling reactions of (mono- or (difluoromethyl)phosphonate anions[4,6] with electrophiles, the palladium-catalyzed addition of (iododifluoromethyl)phosphonate to alkenes,[7] or the electrophilic fluorination of alkylphosphonates[8] using *N*-fluorobenzenesulfonamide. The above methodologies are not suitable for the synthesis of compounds such as **6** and **7**. One plausible route to the synthesis of β,γ-unsaturated α-fluoro phosphonates is the replacement of the hydroxy group in β,γ-unsaturated α-hydroxy phosphonates by fluorine. This has been attempted in the past[9] with mixed results: (α-hydroxybenzyl)phosphonate esters yielded the corresponding (α-fluorobenzyl)phosphonates by treatment with (diethylamino)sulfur trifluoride (DAST). However, in allylic systems (e.g., (α-hydroxyallyl)phosphonate **1**), the replacement of the hydroxy group by fluorine proceeds via an S_N2' or a cyclic S_Ni' mechanism producing exclusively the γ-fluoro isomer **2**. To avoid the unwanted



γ-isomer we substituted the alkene in **1** with an alkyne. We hypothesized that DAST fluorination of **5** should favor the formation of the α-fluoro isomer **6**, because the linearity of the alkyne system is expected to hinder intramolecular fluorine transfer via a cyclic S_Ni' mechanism. In addition, triple bond migration through a S_N2' mechanism would be more difficult on **5** because it involved a more energetically unfavorable allene intermediate. In this paper we describe a common approach to the synthesis of **6** and **7** beginning with a 1,2 O to C phosphorus migration of but-2-ynyl phosphate **4** that yields α-hydroxy phosphonate **5**. Regiospecific fluorination of the hydroxy group in **5** produces (α-fluoropropargyl)phosphonate **6**. Finally, catalytic hydrogenation of the triple bond in **6** furnishes diethyl 2-butenylphosphonate **7**.

Selective introduction of phosphorus was carried out via a two-step sequence starting from the commercially available alkynol **3**. Displacement of chloride in diethyl chlorophosphate under basic conditions and phase-transfer catalysis yielded but-2-ynyl phosphate **4** in 84% yield. Treatment of **4** with LDA in toluene at −50 °C promoted

• Abstract published in *Advance ACS Abstracts*, September 15, 1993.

(1) For reviews see: Filler, R; Kobayashi, Y. *Biomedicinal Aspects of Fluorine Chemistry;* Elsevier: Amsterdam, 1982. Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; Wiley Interscience: New York, 1991. *Selective Fluorination in Organic and Bioorganic Chemistry*; Welch, J. T., Ed.; ACS Symposium Series 456; American Chemical Society: Washington, DC, 1991; pp 136–204.

(2) Blackburn, M. J.; Kent, D. E.; Kolkmann, F. *J. Chem. Soc. Perkin Trans.1* **1984**,1119.

(3) For selected examples see: Blackburn, M. J.; Brown, D.; Martin, S. J.; Parratt, M. J. *J. Chem. Soc. Perkin Trans. 1* **1987**, 181. Chambers, R. D.; O'Hagan, D.; Lamont, R. B.; Jain, S. C. *J. Chem. Soc. Chem. Commun.* **1990**, 1053. Chambers, R. D.; Jaouhari, R.; O'Hagan D. *J. Chem. Soc. Chem. Commun.* **1988**, 1169.

(4) Halazy, S.; Gross-Berges, V. *J. Chem. Soc. Chem. Commun.* **1992**, 743, and refs therein.

(5) Thatcher, G. R.; Campbell, A. S. *J. Org. Chem.* **1993**, 58, 2272.

(6) Obayashi, M.; Ito, E.; Matsui, K.; Kondo, K. *Tetrahedron Lett.* **1982**, *23*, 2323. Blackburn, M. J.; Parratt, M. J. *J. Chem. Soc. Perkin Trans. 1* **1986**, 1417. Blackburn, M. J.; Parratt, M. J. *J. Chem. Soc. Perkin Trans. 1* **1986**, 1425. Burton, D. J.; Sprague, L. G. *J. Org. Chem.* **1989**, *54*, 613. Burton, D. J.; Ishihara, T.; Maruta, M. *Chem. Lett.* **1982**, 755. Burton, D. J.; Sprague, L. G. *J. Org. Chem.* **1988**, *53*, 1523. Martin, S. F.; Dean, D. W.; Wagman, A. S. *Tetrahedron Lett.* **1992**, *33*, 1839.

(7) Yang, Z.; Burton, D. J. *J. Org. Chem.* **1992**, *57*, 4676. Yang, Z.; Burton, D. J. *Tetrahedron Lett.* **1991**, *32*, 1019.

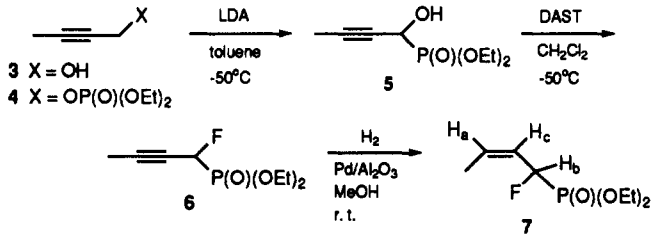
(8) Differding, E.; Duthaler, R. O.; Krieger, A.; Ruegg, G. M.; Schmit, C. *Synlett* **1991**, 395.

(9) Blackburn, M. J.; Kent, D. E. *J. Chem. Soc. Perkin Trans. 1* **1986**, 913. DAST action on alcohols of secondary alkylphosphonates promoted dehydration rather than fluorine substitution.

(10) Sturtz, G; Corbel, B. *C.R. Acad. Sc. Paris* **1973**, *276*, 1807. For examples of phosphorus migration in vinylic systems see: Calogeropoulou, T; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1987**, *52*, 4185. Jackson, J. J.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1989**, *54*, 4750.

0022-3263/93/1958-5598$04.00/0

migration of phosphorus[10] from oxygen to the α-allylic carbon with concomitant alcohol formation after mild acid workup. The above sequence could be done more conveniently in one pot starting with the phosphorylation of alkynol **3** using diethyl chlorophosphate (LDA, toluene, −50 °C). The resulting phosphate **4** was treated with an excess LDA (2.2 equiv, dropwise addition) and the mixture quenched with acetic acid (1 M) in ether after having stirred for 1 h.[11] DAST fluorination of **5** proceeded smoothly, yielding exclusively the desired α-fluoro isomer **6**. ^{31}P NMR of **6** showed the large coupling ($^2J_{PF}$ ca. 78 Hz) characteristic of α-fluoro phosphonates.



It is well known that fluorine in allylic and benzylic positions can undergo hydrogenolysis of the C–F bond[12] upon catalytic hydrogenation. There are no similar reports on the C–F stability of fluoropropargyl systems. To our satisfaction, we achieved partial hydrogenation of the triple bond in **6** without any apparent loss of fluorine. This was effected by bubbling hydrogen at room temperature through a methanolic solution of **6** stirred in the presence of catalytic amounts of Lindlar's catalyst mixed with alumina (1% Pd). This method yielded almost exclusively the *Z* stereoisomer of **7**. The stereochemistry of alkene **7** was deduced from homonuclear decoupling experiments (irradiation of the vinyl methyl protons simplified the olefinic region showing $J_{H_aH_c}$ = 10.5 Hz).[13]

Our efforts in this area continue. We are currently preparing more elaborate analogs of **6** capable of achieving fluorine-containing functional group transformations and undergoing chain-extension reactions. In an effort to expand the utility of this protocol we are exploring the transmission of chirality at the fluoromethylene carbon as well as the synthesis of (α,α-difluoroalkyl)phosphonates from **5**.

Acknowledgment. We gratefully acknowledge the financial support of the National Science Foundation (CHE-9122304). We also want to express our gratitude to Dr. Jim Van Epp of the Department of Chemistry of Brown University for his help with NMR measurements.

Supplementary Material Available: Experimental procedures and spectral data for compounds **4**–**7** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(11) Hydroxy phosphonate **5** decomposed partially on silica gel; it was thermally unstable and could not be vacuum distilled. Large-scale purification was achieved using dry-column chromatography (Florisil; ethyl acetate–hexane). The structure of **5** was confirmed by an X-ray crystallographic study. We are grateful to Dr. James Golen, Department of Chemistry, Univ. of Massachusetts Dartmouth, for carrying out the structure determination. Details will be reported elsewhere.

(12) Hudlicky, M. *J. Fluorine Chem.* **1989**, *44*, 345.

(13) The stereochemistry around the double bond as well as the chemical shift assignments for the vinylic protons were confirmed by nuclear Overhauser enhancement difference experiments. Thus, irradiation of the vinyl methyl protons (δ 1.77) caused enhancement of the signals due to H_a (δ 5.97) and H_b (δ 5.48).