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Syntheses of ω-Hydroxy-α,α-difluoromethylphosphonates by Oxacycle Ring-Opening Reactions†

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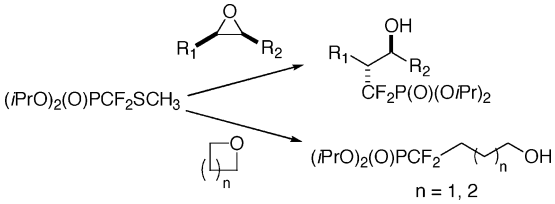
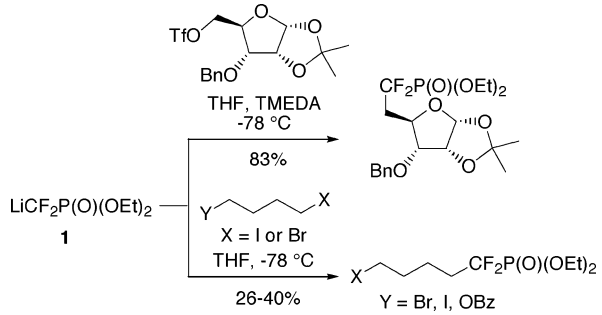
ABSTRACT



Oxacycle ring-opening reactions from a non-HCFC-based source of phosphonodifluoromethyl carbanion 1 are reported. This straightforward strategy opens access to a variety of primary and secondary ω-hydroxy-α,α-difluoromethylphosphonates via one step. The syntheses of a glycerol monophosphate analogue and precursors to nucleoside phosphorylase inhibitors are described using this method.

Hydroxylated difluoromethylphosphonates are important pivotal structures to design stable analogues of biologically important phosphate esters. Numerous examples are described in the field of nucleotide analogues and enzyme inhibitors.[1] Direct approaches to prepare primary ω-hydroxy-α,α-difluoromethylphosphonates are based on the displacement of a leaving group with phosphonodifluoromethyl carbanion (i.e., triflates or halides).[2] From primary triflates, phosphonates were produced in high yields, and no displacement was observed from secondary ones. From primary halides, substitution reactions suffer the major drawback that products were isolated in low and unreproducible yields (Scheme 1).[3]

Scheme 1. Preparation of Primary ω-Alkoxy-α,α-difluoromethylphosphonates by Alkylation of **1**



The synthesis of secondary ω-hydroxy-α,α-difluoromethylphosphonates as nucleotide precursors can be realized in a multistep pathway going through a radical deoxygenation of intermediate tertiary alcohols prepared from functionalized aldehydes and *O*,*O*-diethyl phosphonodifluoromethyllithium[4] or directly through conjugate additions of the carbanion onto

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(1) (a) Xu, Y.; Prestwich, G. D. *Org. Lett.* **2002**, *4*, 4021. (b) Chambers, R. D.; Jaouhari, R.; O'Hagan, D. *Tetrahedron* **1989**, *45*, 5101. (c) Vinot, T. K.; Griffith, O. H.; Keana, J. F. W. *Tetrahedron Lett.* **1994**, *35*, 7193. (d) Matulic-Adamic J.; Haeberli, P.; Usman, N. *J. Org. Chem.* **1995**, *60*, 2563. (e) Berkowitz, D. B.; Shen, Q.; Maeng, J. *Tetrahedron Lett.* **1994**, *35*, 6445. (f) Ladame, S.; Willson, M.; Périé, J. *Eur. J. Org. Chem.* **2002**, 2640. (g) Butt, A. H.; Percy, J. M.; Spencer, N. S. *Chem. Commun.* **2000**, 1691. (h) Lopin, C.; Gautier, A.; Gouhier, G.; Piettre, S. R. *J. Am. Chem. Soc.* **2002**, *124*, 14668.

(2) (a) Halazy, S.; Ehrhard, A.; Danzin, C. *J. Am. Chem. Soc.* **1991**, *113*, 315. (b) Bigge, C. F.; Drummond, J. T.; Johnson, G. *Tetrahedron Lett.* **1989**, *30*, 7013. (c) Jakeman, D. L.; Ivory, A. J.; Williamson, M. P.; Blackburn, G. M. *J. Med. Chem.* **1998**, *41*, 4439. (d) 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.

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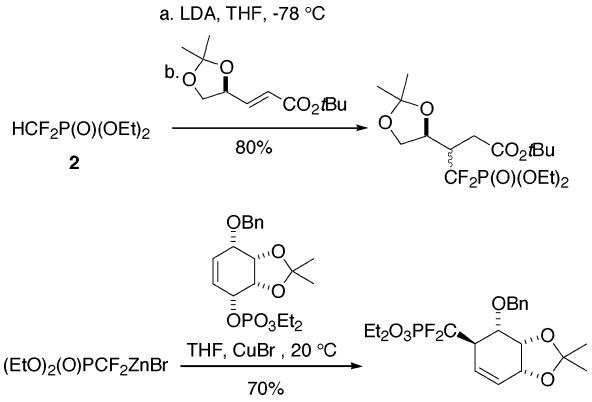
hindered α,β-unsaturated esters, nitroalkenes, vinylsulfoxides, or vinyl sulfones (Scheme 2).[5]

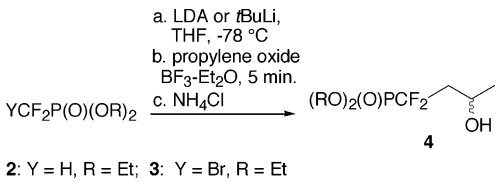
Scheme 2. Preparation of Secondary ω-Alkoxy-α,α-difluoromethylphosphonates



Recently, preparation of secondary difluoromethylphosphonates was reported by the displacement of allylic phosphate and applied to the preparation of cyclitol precursors (Scheme 2).[6] In this paper, we report our recent progress in the synthesis of ω-hydroxy-α,α-difluoromethylphosphonates through oxacycle ring-opening reactions as a new method that allows the one-step preparation of precursors of enzyme inhibitors.

The synthesis of ω-hydroxy-methylphosphonates has been largely studied by ring-opening reaction involving oxirane or oxetane and phosphonomethyl organometallic reagents.[7,8] This efficient strategy was never applied to the corresponding phosphonodifluoromethyl carbanion **1**. We decided to explore the ring-opening reaction from various sources of carbanion **1** and propylene oxide following this scheme. First, the carbanion obtained by deprotonation of **2** with LDA at −78 °C[9] was reacted in THF with propylene oxide (Scheme 3). After the usual workup, the starting materials were recovered. This result was not surprising in light of a previous report showing that epoxides were not reactive toward the carbanion **1**.[10] Epoxide ring-opening reactions usually needed the presence of Lewis acids as catalyst, and boron trifluoride diethyl etherate was largely used to activate this reaction.[11]

Scheme 3. Epoxide Ring-Opening Reaction from Various Sources of Carbanion



When the same reaction was attempted even in the presence of BF_3-Et_2O (even with 3 equiv), only traces of alcohol **4** were detected by ^{19}F NMR analysis of the crude (Scheme 3).[12]

We decided to explore other methods to prepare *O,O*-dialkyl phosphonodifluoromethyllithium **1**. The first method is the halogen−metal exchange reaction from the diethyl bromodifluoromethylphosphonate **3** and alkyllithium,[13] and the second is the thiaphilic attack of the diisopropyl methylsulfanyldifluoromethylphosphonate **5** and *tert*-butyllithium.[14] Surprisingly, addition of **3** to a cooled solution of *tert*-butyllithium in THF (−78 °C, 2 equiv), followed by a sequential addition of epoxide and BF_3-Et_2O, afforded after 30 min only traces of the resulting alcohol **4** (<5% by ^{19}F NMR). Difluoromethylphosphonate **2** was the major product present in the medium after hydrolysis (Scheme 3).

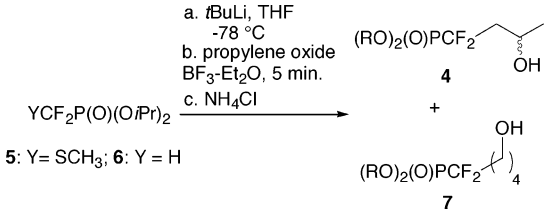
Recently, we described an alternative non-HCFC-based route to the phosphonodifluoromethyl carbanion equivalent through a thiaphilic addition of *tert*-butyllithium to sulfide **5**.[14] During this work, we also noticed that the carbanion formed in this new medium presented contrasting reactivity to that reported previously, allowing addition with a wide range of electrophiles without need for transmetalation. This observation prompted us to investigate the epoxide ring-opening reactions in this medium.

The carbanion formed by addition of diisopropyl methylsulfanyldifluoromethylphosphonate **5** to a cooled solution of *tert*-butyllithium in THF (−78 °C, 1.1 equiv) was trapped by sequential addition of epoxide (1.1 equiv) and BF_3-Et_2O (2 equiv). After 5 min of stirring, two products identified as alcohols **4** and **7**, accompanied by the phosphonate **6**, were obtained (Scheme 4) and detected in about a 1:1:1 ratio. The unexpected alcohol **7** issued from a competitive THF ring-opening reaction, a reaction occasionally observed when carbanions were reacted in THF in the presence of BF_3-Et_2O.[15]

Using dried diethyl ether instead of THF, a mixture of alcohol **4** and phosphonate **6** was obtained in a 1:2 ratio and δ-hydroxy-α,α-difluoromethylphosphonate **4** was isolated in

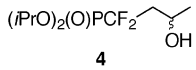
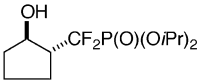
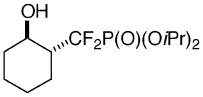
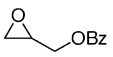
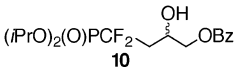
(3) Burton, D. J.; Yang, Z.; Qiu, W. *Chem. Rev.* **1996**, *96*, 1.
(4) Berkowitz, D. B.; Eggen, M.; Shen, Q.; Shoemarker, R. K. *J. Org. Chem.* **1996**, *61*, 4666.
(5) (a) Murano, T.; Muroyama, S.; Yokomatsu, T.; Shibuya, S. *Synlett* **2002**, 1657. (b) Murano, T.; Yuasa, Y.; Muroyama, S.; Yokomatsu, T.; Shibuya, S. *Tetrahedron* **2003**, *59*, 9059. (c) Blades, K.; Lapôtre, D.; Percy, J. M. *Tetrahedron Lett.* **1997**, *38*, 5895. (d) Blades, K.; Percy, J. M. *Tetrahedron Lett.* **1998**, *39*, 9085.
(6) Yokomatsu, T.; Kato, J.; Sakuma, C.; Shibuya, S. *Synlett* **2003**, 1407.
(7) (a) Tanaka, H.; Fukui, M.; Haraguchi, K.; Masaki, M.; Miyasaka, T. *Tetrahedron Lett.* **1989**, *30*, 2567. (b) Montchamp, J. L.; Frost, J. W. *J. Am. Chem. Soc.* **1991**, *113*, 6296. (c) Racha, S.; Li, Z.; El-Subbagh, H.; Abushanab, E. *Tetrahedron Lett.* **1992**, *33*, 5491. (d) Montchamp, J. L.; Piehler, L. T.; Frost, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 4453. (e) Li, Z.; Racha, S.; Dan, L.; El-Subbagh, H.; Abushanab, E. *J. Org. Chem.* **1993**, *58*, 5779. (e) Montchamp, J. L.; Migaud, M. E.; Frost, J. W. *J. Org. Chem.* **1993**, *58*, 7679.
(8) Smith, J. G. *Synthesis* **1984**, 629.
(9) Obayashi, M.; Ito, E.; Kondo, K. *Tetrahedron Lett.* **1982**, *23*, 2323.
(10) Blades, K.; Percy, J. M. *Tetrahedron Lett.* **1998**, *39*, 9085.
(11) Eis, M. J.; Wrobel, J. E.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3693.
(12) It has been reported that epoxide ring-opening reactions could be performed from **2** in the presence of $TiCl_4$ (Röschenthaler, G. V. et al. abstract of poster presentation (P59), 14th European Symposium on Fluorine Chemistry, Poznan, Poland, 11−16 July, 2004).
(13) (a) Wachbüsch, R.; Samadi, M.; Savignac, P. *J. Organomet. Chem.* **1997**, *529*, 267. (b) See also ref 1h.
(14) Henry-dit-Quesnel, A.; Toupet, L.; Pommelet, J. C.; Lequeux, T. *Org. Biomol. Chem.* **2003**, *1*, 2486.

Scheme 4. Epoxide Ring-Opening Reaction from **5**



low yield (15%). When the reaction was run in the presence of an excess of epoxide (3 equiv), alcohol **4** was formed as the major product accompanied with less than 5% of phosphonate **6** (monitored by ^{19}F NMR), and pure **4** was isolated in moderate yield (61%). When the addition was performed in the presence of excess of carbanion (2 equiv), the same results were obtained. The need for an excess of one or the other reagents indicated that a probable *retro*-reaction should occur. This first evidence of the synthesis of δ-hydroxy-α,α-difluoromethylphosphonate in one step by epoxide ring-opening reaction was extended to 1,2-disubstituted epoxides and functionalized epoxides (Table 1).

Table 1. Epoxide Ring-Opening Reaction from Sulfide **5**

Epoxide	Product	Yield (%)
	 **4**	61[a]
	 **8**	54[b]
	 **9**	60[b]
	 **10**	69[b]

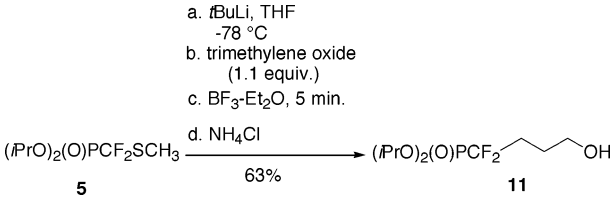
[a] Epoxide/sulfide/BF_3-Et_2O ratio = 3:1:2. [b] Epoxide/sulfide/BF_3-Et_2O ratio = 1:2:2.

From cyclopentene oxide, the reaction proceeded smoothly, but the corresponding alcohol **8** was isolated in only 30% yield, even when an excess of epoxide (3 equiv) was used. With cyclohexene oxide, comparable results were observed. When excess of carbanion was involved (2 equiv), the corresponding δ-hydroxy-α,α-difluorophosphonates **8** and **9** were isolated in 54% and 60% yields, respectively.

In all cases, the stereochemical outcome of this reaction is undoubtedly due to the need for the nucleophile to attack the least hindered site of the oxirane ring. From the rigid cyclohexene oxide, ring-opening reaction occurs to give *trans* product **9** as a single diastereomer. This was deduced from

(15) (a) Eis, M. J.; Wrobel, J. E.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3693. (b) Millon, J.; Linstrumelle, G. *Tetrahedron Lett.* **1976**, 1095.

Scheme 5. Oxetane Ring-Opening Reaction



proton-NMR data revealing the presence of two *trans* diaxial coupling constant (J = 9.9 Hz) in the pattern of the proton H_1.

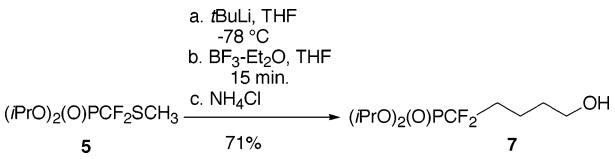
The potential of this strategy was illustrated by a straightforward synthesis of a glycerol-1-phosphate analogue. From a racemic mixture of *O*-benzyl glycidyl ether, addition of excess of carbanion proceeded in the presence of BF_3-Et_2O at −78 °C to afford the corresponding alcohol **10** in 69% yield (Table 1).

The study was extended to larger oxacycles, in particular oxetane, tetrahydrofuran, and tetrahydropyran derivatives, to prepare a variety of ω-hydroxy-α,α-difluoromethylphosphonates. Such structures, containing a spacer between the phosphonate and hydroxyl functions, have been reported as useful intermediates for the synthesis of purine nucleoside phosphorylase inhibitors by Halazy[2a] and more recently by Yokomatsu.[16]

Oxetanes are reactive species, and ring opening proceeded spontaneously upon reacting equimolar amount of oxetane with the carbanion in the presence of Lewis acid in diethyl ether (Scheme 5). The exothermic reaction needed scrupulous temperature control,[17] and slow addition of trimethylene oxide followed by BF_3-Et_2O afforded γ-hydroxy-α,α-difluoromethylphosphonate **11**[2d] in satisfactory yield (63%).

Tetrahydrofuran used as both reagent and solvent was readily opened only when previously complexed to BF_3 (Scheme 6). Slow addition of a THF solution of BF_3-Et_2O

Scheme 6. Preparation of Diisopropyl 1,1-Difluoro-5-hydroxypentylphosphonate **7** from Sulfide **5**



to a THF solution of carbanion afforded exclusively ϵ-hydroxy-α,α-difluoromethylphosphonate **7**, whereas addition of neat BF_3-Et_2O afforded **7** and **6** in a 3:7 ratio. Alcohol **7** could be isolated in good yield (71%) on a gram scale.

(16) (a) Yokomatsu, T.; Abe, H.; Sato, M.; Suemune, K.; Kihara, T.; Soeda, S.; Shimeno, H.; Shibuya, S. *Bioorg. Med. Chem.* **1998**, *6*, 2495. (b) Yokomatsu, T.; Abe, H.; Sato, M.; Suemune, K.; Masumoto, K.; Kihara, T.; Soeda, S.; Shimeno, H.; Shibuya, S. *Tetrahedron* **1997**, *53*, 11297.

(17) Rapid addition of reagents induced a decomposition of the carbanion and formation of unidentified byproducts.

The reaction with tetrahydropyran was explored in order to insert a larger spacer between the phosphonate and the hydroxyl functions. However, no ring-opening reaction occurred, and phosphonate **6** was the exclusive product.

In summary, the first one-step synthesis of a variety of δ-, γ-, and ϵ-hydroxy-α,α-difluoromethylphosphonates has been developed from a non-HCFC-based source of phosphonodifluoromethyl carbanion, through oxacycle ring-opening reactions. In this medium the use of BF_3-Et_2O as Lewis acid was essential, and ring-opening reactions were easily performed from epoxides, oxetane, and also THF to prepare important pivotal structures for the design of enzyme inhibitors in one step. The syntheses of cyclitol derivatives and inhibitors of nucleoside phosphorylases are currently under investigation using this new methodology.

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Supporting Information Available: Experimental procedures, analytical data, and ^1H and ^{13}C NMR spectra of compounds **4** and **9**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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