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A FACILE SYNTHESIS OF β- AND γ- HYDROXYPHOSPHONATE ESTERS FROM EPOXIDES

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Summary: A $BF_3.OEt_2$ catalyzed, regiospecific nucleophilic ring opening reaction of epoxides by dialkyl phosphite and methanephosphonate esters is described. The reaction proceeds in good to excellent yields to give the title compounds and is compatible with a variety of other functional groups.

In recent years phosphonate isosteres of biologically important phosphates have attracted considerable attention due to their stability towards the action of phosphatases, as they lack a scissile P-O bond.[1] In connection with studies for the synthesis of phosphonate isosteres of 1',2'-*seco*-nucleotides, an efficient method for the preparation of β- and γ- hydroxy-phosphonates was needed. These compounds could then serve as intermediates to prepare the target isosteres.

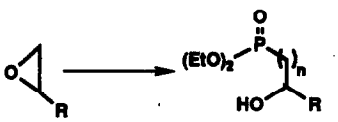
While alkylphosphonates are easily accessible by the Arbuzov reaction of alkyl halides with phosphite esters,[2] similar methodology fails to provide the title compounds since they tend to undergo elimination reactions leading to the formation of olefins and cyclopropanes respectively.[3] We report herein a general route to these compounds based on a $BF_3.Et_2O$ catalyzed, regiospecific nucleophilic ring opening reaction of epoxides by readily available and inexpensive phosphites and phosphonates.

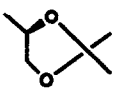
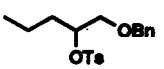
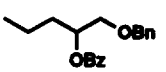
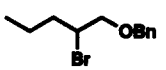
The easy access to epoxides from polyhydroxylic and unsaturated compounds, and the stereochemical predictability of their reactions make them among the most attractive starting materials in organic synthesis. Although a number of reports have appeared on ring opening reactions of epoxides involving carbon, nitrogen, oxygen, and sulfur nucleophiles,[4] surprisingly, very few examples are known in the literature, where phosphorus or phosphorus containing nucleophiles have been described.[5] The success of these reactions depended upon the use of excess epoxide, a procedure that was of little use in our hands when only one equivalent was used.

The report on the synthesis of the phosphonate isostere of AZT 5'-phosphate by the nucleophilic addition of diethyl methanephosphonate to an oxetane, catalyzed by $BF_3.Et_2O$,[1i] prompted us to apply the same reaction conditions to the opening of epoxides. Indeed, when the anion of the same phosphonate was generated with *n*-butyl lithium in THF, followed by the sequential addition of epoxide **1**[6] and $BF_3.Et_2O$, the corresponding γ-hydroxyphosphonate was obtained in quantitative yield. The reaction was complete in one hour at -78°. However, when the temperature was allowed to rise to -30°, the nucleophile reacted, instead, with THF generating a phosphonylated butylate anion, which in turn opened the epoxide.

Other ethereal solvents were found to participate in the reaction in a similar fashion. The reaction has been equally successful with other methane phosphonates.

Extension of this reaction to a phosphorus nucleophile proved to be equally effective. Thus, when diethyl phosphite was condensed with epoxide 1 under the same reaction conditions, the corresponding β–hydroxyphosphonate ester was obtained in comparable yield. A variety of epoxides were subjected to ring opening reactions as shown in the table.[7]



Epoxide	Nucleophile*	n	Yields%	Compound No.
R = 	a	2	100	1
	b	1	100	2
	a	2	100	3
	b	1	77	4
	a	2	65	5
	b	1	64	6
CH_2Ph	a	2	76	7
	b	1	77	8
CH_2OTs	a	2	79	9
	b	1	65	10
	a*	2	90	11
	b	1	72	12
	a	2	84	13
	b	1	65	14

*a = CH_3-P(=O)-$(EtO)_2$; b = H-P(=O)-$(EtO)_2$

* Ester cleavage took place

A typical procedure follows: A 2.5 M solution of n-butyllithium in hexanes (12 mL, 30 mmol was added dropwise to a stirred solution of diethyl phosphite or diethyl methanephosphonate (4.15 g, 30 mmol) in dry THF (30 mL) at -78 °C under nitrogen atmosphere. After the mixture was stirred for 15 min, a solution of epoxide (10 mmol) in THF (5 mL) was added dropwise. The reaction mixture was left with stirring for aditional 15 min, after which time $BF_3.OEt_2$ (5.68 g, 40 mmol) was slowly introduced, while maintaining the temperature at below -70 °C. This was stirred for 2 hr and quenched with saturated aqueous NH_4Cl. After warming to room temperature, the solvents were removed under reduced pressure and the residue was dissolved in ether. The etheral layer, after washing with brine, was dried, concentrated and chromatographed over silica gel column with ethyl acetate-hexane (1:3) as eluant to yield the pure hydroxy phosphonates.

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7. All new compounds had correct elemental analyses. Examples of 90 MHz ^{1}H NMR data in ($CDCl_3$) follow:

Diethyl (3R,4S)-4-benzyloxy-3-hydroxypentanephosphonate (1): $[\alpha]_D^{25}$: +27.55° (c = 0.53, EtOH); δ 1.02-2.20 (m, 13H), 3.22-3.78 (m, 3H), 3.82-4.32 (m, 4H), 4.32-4.76 (m, 2H), 7.23 (s, 5H).

Diethyl (2S,3S)-3-benzyloxy-2-hydroxybutanephosphonate (2): $[\alpha]_D^{25}$: +30.95° (c = 1.26, EtOH); δ 1.24 (t, J = 6 Hz, 6H), 1.34 (d, J = 6 Hz, 3H), 1.76-2.12 (m, 2H),3.29 (br d, 1H, D_2O exchangeable), 3.36-3.70 (m, 1H), 3.82-4.28 (m, 5H), 4.52 (AB_q, J = 9 Hz, 2H), 7.3 (s, 5H).

Diethyl (3S,4S)-4,5-O-isopropylidene-3,4,5-trihydroxypentane phosphonate (5): $[\alpha]_D^{25}$: -15.67° (c = 1.085 EtOH); δ 1.38 (t, J = 6Hz, 6H), 1.44 (s, 6H), 1.68-2.32 (m, 4H), 2.96 (br s, 1H, D_2O exchangeable), 3.62-4.42 (m, 8H).

Diethyl (2S,3S)-3,4-O-isopropylidine-2,3,4-trihydroxybutanephosphonate (6): $[\alpha]_D^{25}$: -10.16° (c = 0.61, EtOH), δ 1.32 (t, J = 6 HZ, 6H), 1.34 (2, 3H), 1.46 (s, 3H),1.96 (dd, J = 16 Hz and 6 Hz, 2H), 2.80-3.40 (m, 1H, OH, D_2O exchangeable), 3.68-4.26 (m, 8H).

Diethyl 3-hydroxy-4-tosyloxybutanephosphonate (9): δ 1.20 (t, J = 6Hz, 6H), 1.46-2.25 (m, 4H), 2.44 (s, 3H), 3.52-4.2 (m, 8H), 7.52 (A_2B_{2q}, J = 6Hz, 4H).

Diethyl 6-benzyloxy-2-hydroxy-5-tosyloxyhexanephosphonate (10): δ 1.12-2.02 (m, 12H), 2.40 (s, 3H), 3.45 (d, J = 6Hz, 2H), 3.76-4.27 (m, 6H), 4.30 (s, 2H), 4.48-4.76 (br s, 1H), 7.06-7.31 (m, 7H), 7.68 (d, J = 7 Hz, 2H).

Diethyl 6-benzyloxy-5-bromo-2-hydroxyhexanephosponate (13): δ 1.12-2.36 (m, 12H), 3.54-4.44 (m, 9H), 4.52 (s, 2H), 7.28 (s, 5H).

Diethyl 7-benzyloxy-6-bromo-3-hydroxyheptanephosphonate (14): δ 1.27 (t, J = 6Hz, 6H), 1.45-2.22 (m, 8H) 2.89 (br s, H, D_2O exchangeable), 3.68 (d, J = 6Hz, 2H), 3.82-4.27 (m, 6H), 4.53 (s, 2H), 7.32 (s, 5H).

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