edges a sabbatical leave provided by the University of Malaya, Department of Chemistry, Kuala Lumpur, Malaysia.

Registry No. **1b**, 84927-61-7; **1c**, 67-97-0; **2**, 64190-52-9; **3b**, 84927-62-8; **3c**, 84927-63-9; **3d**, 84927-64-0; **3e**, 84927-65-1; **4a**, 84927-66-2; **4b**, 84927-67-3; **5**, 33813-99-9; **6a**, 84927-68-4; **6b**, 84927-69-5; **7a**, 84927-70-8; **7b**, 84927-71-9; **8a**, 84927-72-0; **8b**, 84927-73-1; **9a**, 84927-74-2; **9b**, 84927-75-3; **9c**, 84927-76-4; vitamin D_2, 50-14-6; trihydroxyvitamin D_2, 84985-78-4; *tert*-butylchlorodimethylsilane, 18162-48-6; diphenylphosphine, 829-85-6; 3-chloro-2-methyl-1-propene, 563-47-3; 1-(trimethylsilyl)imidazole, 18156-74-6.

Supplementary Material Available: Spectral data (6 pages). Ordering information is given on any current masthead page.

Synthesis of Steroid Phosphates via Monomeric Metaphosphate

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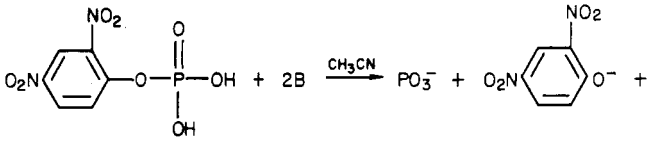
Dihydrogen phosphate esters derived from steroids having one, two, and three conjugated or nonconjugated double bonds have been conveniently prepared by a procedure that probably involves the monomeric metaphosphate anion as an intermediate. The source of metaphosphate is a 1:2 molar mixture of (1-phenyl-1,2-dibromoethyl)phosphonic acid and diisopropylethylamine (B) in a 0.05 M dichloromethane solution at 20 °C: (1) $C_6H_5C(Br)(PO_3H_2)CH_2Br + 2B + ROH \rightarrow ROPO_3H^-BH^+ + C_6H_5CBr{=}CH_2 + Br^-BH^+$; (2) $ROPO_3H^-BH^+ + HCl \rightarrow ROPO_3H_2 + BH^+Cl^-$. Yields of steroid dihydrogen phosphates with one or two double bonds range from 65% to 75%. The labile $\Delta^{5,7,9}$-cholestatriene 3β-*O*-phosphate can be isolated in a pure state, although in lower yield (46%), by this procedure.

Recent investigations[1-6] have led to the conclusion that acetonitrile solutions of 2,4-dinitrophenyl dihydrogen phosphate or (*erythro*-1-phenyl-1,2-dibromopropyl)-phosphonic acid containing 2 molar equiv of the hindered tertiary amine diisopropylethylamine behave as sources of the monomeric metaphosphate anion at ambient temperatures (eq 1 and 2).



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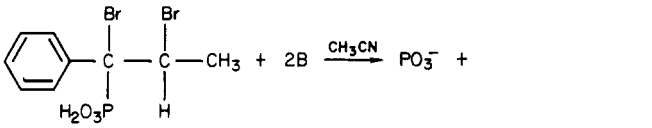

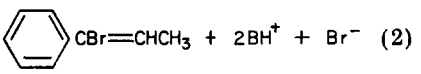

(2)

The monomeric metaphosphate postulated in these reactions has not been detected by physical methods.[7] However, the transient formation of this intermediate[1-11] would account for the observation[1-6] that the reactions of eq 1 and 2 generate methyl phosphate or *tert*-butyl phosphate at approximately the same rates when 1 molar equiv of the corresponding alcohol is present in the solution (eq 3 or 4).

$$PO_3^- + CH_3OH \xrightarrow{CH_3CN} CH_3OPO_3H^- \quad (3)$$

$$PO_3^- + (CH_3)_3COH \xrightarrow{CH_3CN} (CH_3)_3COPO_3H^- \quad (4)$$

Analogous studies have been carried out in other aprotic solvents such as dichloromethane,[1-6] and in all cases it has been found that the decomposition of the dibromophosphonate dianion is much faster than that of the aryl phosphate. For example, the half-life for the disappearance of the phosphonate is too fast to measure by techniques that give the value $t_{1/2} = 2.5 \pm 0.5$ h for the disappearance of the phosphate in the presence of 1 molar equiv of *tert*-butyl alcohol (0.2 M acetonitrile solution at 25 °C). This same $t_{1/2}$ value is observed when 2 or 3 molar equiv of *tert*-butyl alcohol are present in the solution of the phosphate dianion.[5] It appears, therefore, that the decompositions of the phosphate and phosphonate dianions are rate limiting in the formation of the alkyl phosphates according to eq 1–4. Earlier studies on the behavior of 2,4-dinitrophenyl phosphate had been carried out in aqueous solution.[12,13]

This paper shows that with suitable modifications in reaction conditions and in the structure of the metaphosphate source, sensitive and valuable alcohols can be converted into their crystalline alkyl dihydrogen phosphates via the monomeric metaphosphate anion. The present work builds on earlier research from three groups of investigators. Conant and Coyne[14] described a convenient preparation of (1-phenyl-1,2-dibromoethyl)-phosphonic acid from acetophenone and phosphorus trichloride. The same group[14] showed that this phosphonate undergoes facile decomposition in aqueous alkaline solutions. Kenyon and Westheimer[15] and Satterthwait and Westheimer[16] expanded those studies along mechanistic

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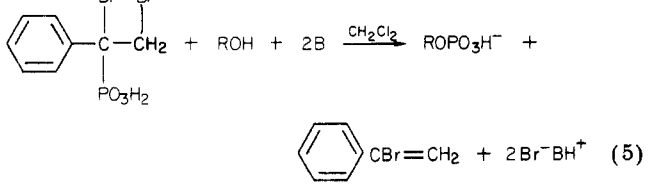
lines based on the metaphosphate-intermediate hypothesis. These authors worked with 1-phenyl-1,2-dibromopropyl phosphonic acid, which is made from propiophenone and phosphorus trichloride in lower yields and with greater difficulty than the ethylphosphonic homologue. Maynard and Swan[17,18] entertained the possibility of preparing phosphomonoesters from the reaction of alcohols with potential monomeric metaphosphate sources. However, these authors worked in a large excess of the alcohol as solvent, which imposes a severe limitation to the use of this procedure for synthetic purposes. The β-chloro phosphonic acids, e.g., (2-chlorodecyl)phosphonic acid, utilized by Maynard and Swan[17,18] as metaphosphate sources are not sufficiently reactive to generate monomeric metaphosphate under optimum synthetic conditions.

In this paper, we have explored the synthetic capabilities of monomeric metaphosphate in the particular field of steroid alcohols for the following reasons. Cholesterol and other steroids play an important and still poorly understood role in biological membranes.[19] Cholesterol phosphate and other steroid phosphates have an enhanced amphipathic character,[20] i.e., the hydrophilicity of the polar head group relative to the hydrophobicity of the nonpolar hydrocarbon region is greater than that in the parent steroid. This property of the steroid phosphates has led to important pharmacological applications.[21] However, no systematic studies on the effect of steroid phosphates on phase-transition properties of phospholipids[20] have been reported. For such studies, a mild and general procedure for the conversion of highly sensitive steroids into their phosphates is required. This synthetic problem is not altogether trivial, as a review of the literature[21-26] immediately reveals. The steroid phosphates have been prepared by reactions of the sterols with phosphorus oxychloride, followed by hydrolysis of the intermediate phosphorodichloridates.[22-26] Molecular rearrangements as well as side reactions may occur in such a synthetic procedure. A new approach to the problem, therefore, seemed warranted, as the need for substantial amounts of high-purity steroid phosphates arose during our investigations of steroid derivatives with modified amphipathic character, e.g., phosphatidylcholesterol.[27]

Results and Discussion

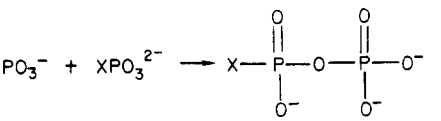
The source of metaphosphate chosen for synthetic purposes is (1-phenyl-1,2-dibromoethyl)phosphonic acid (eq 5). This compound is readily available[14] and undergoes decompositions in aprotic solvents at convenient



(5)

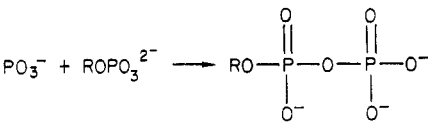
rates. For example, in the presence of 2 and 1 molar equiv of diisopropylethylamine and methanol, respectively, a 0.2 M dichloromethane solution of this phosphonic acid decomposes with a half-life of about 30 min at 25 °C and yields mainly methyl phosphate (eq 5, R = CH_3). Since the reagents have only moderate solubility in dichloromethane, the steroid phosphates are conveniently synthesized in 0.05 M solutions, following the general procedure given in the Experimental Section. The results are summarized in Table I.

We conclude that some of the reactions that are capable of generating monomeric metaphosphate in aprotic solvents can be adapted to yield phosphomonoesters in satisfactory yields. The main consideration appears to be the relative rate of generation of PO_3^- vs. the rates at which PO_3^- reacts with its source (eq 6), itself (eq 7), the steroid



(6)

$$n\text{-}PO_3^- \rightarrow (PO_3^-)_n \quad (7)$$



(8)

phosphate (eq 8), and the desired alcohol (eq 5). Previous research[1-7] has shown that certain sources of metaphosphate, e.g., the 2,4-dinitrophenyl phosphate dianion can generate pyrophosphates according to eq 6, in the absence of alcohols. Other metaphosphate sources such as (1-phenyl-1,2-dibromopropyl)phosphonic acid tend to form acyclic linear and branched polyphosphates, as in eq 7. Finally, in the present work we have noticed the results of eq 8, i.e., the formation of the alkyl pyrophosphates. However, this and the other side reactions (eq 6–8) can be minimized to the point at which the desired phosphomonoester synthesis is satisfactory. Evidently, the synthesis of phosphomonoesters via monomeric metaphosphate is competitive with or superior to the alternative involving phosphorus oxychloride only in those cases in which the alcohol is sensitive to either the reagent during the reaction or the hydrolytic step involving the phosphorodichloridate intermediate.

Experimental Section

$\Delta^{5,7,9}$-Cholestatrien-3β-ol was prepared as described below; other steroids were obtained from Sigma Chemical Co. Steroids with conjugated diene and triene functions were rendered anhydrous by storing their dichloromethane solutions over 4-Å molecular sieves at 5 °C for 15 h. Other sterols were dried under vacuum at 20 °C for 3 h before the reaction. Thin-layer chromatography was performed on plates coated with Merck silica gel H; visualization was made by sulfuric acid charring. ^{31}P NMR spectra were obtained on a Nicolet NTC-300 Fourier Transform spectrometer (121.5 MHz). Ultraviolet absorption spectra were measured in a Varian Techtron 635. Optical rotations were measured with a Perkin-Elmer Model 241 polarimeter. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. The properties of the compounds are give in Table I.

(1-Phenyl-1,2-dibromoethyl)phosphonic acid was prepared by the procedure of Conant and Coyne.[14]

$\Delta^{5,7,9}$-Cholestatrien-3β-ol Acetate.[28,29] A solution of mercuric acetate (13.4 g, 0.042 mol) in glacial acetic acid (235 mL) was added at once to a solution of 7-dehydrocholesterol (9.0 g, 0.021 mol) in chloroform (125 mL). The mixture was stirred for 15 h at 20

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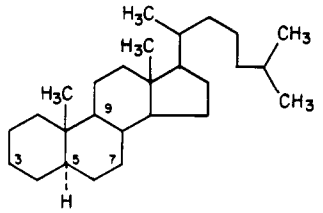
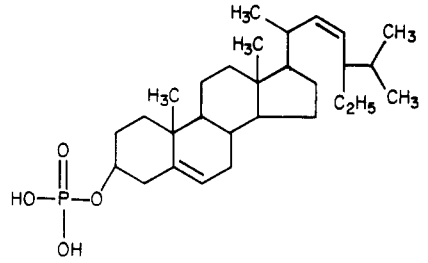
°C in the dark. The precipitated mercurous acetate was removed by filtration and washed with ether. The combined filtrate and washings were evaporated under vacuum (30 torr, then 1 torr at 20 °C). The residue was triturated with methanol (20 mL), filtered, and washed with methanol (2 × 10 mL). The solid was dissolved in warm ether (25 mL), and the solution was filtered and diluted with methanol (20 mL). The solvent was removed (30 torr at 20 °C) until crystals appeared, and the mixture was kept a few hours at −10 °C. Colorless, crystalline $\Delta^{5,7,9}$-cholestatrien-3β-ol acetate (3.69 g) was obtained after filtration, washing with cold methanol (40 mL), and drying (0.5 torr, 20 °C). A second crop (1.23 g) was obtained for an overall yield of 55%: mp 91–94 °C; R_f 0.67 (silica gel H, hexane/ether, 1:1).

$\Delta^{5,7,9}$-Cholestatrien-3β-ol. Lithium aluminum hydride (0.23 g, 6.0 mmol) was added to a solution of $\Delta^{5,7,9}$-cholestatrien-3β-ol acetate (2.00 g, 4.5 mmol) in anhydrous ether (40 mL) under N_2. The mixture was stirred for 30 min at reflux temperature. The excess hydride was destroyed by addition of a few drops of acetone. Aqueous hydrochloric acid (0.2 M) was cautiously added until the aqueous phase remained acidic. The mixture was diluted with more ether (40 mL). The washed (2 × 25 mL of water) and dried (Na_2SO_4) ether phase was filtered and evaporated to yield the colorless crystalline $\Delta^{5,7,9}$-cholestatrien-3β-ol (1.55 g, 82% yield): mp 106–108 °C; R_f 0.20 (silica gel H, hexane/ether, 1:1).

General Procedure for the Synthesis of Steroid Dihydrogen Phosphates 1–7. Solid (1-phenyl-1,2-dibromo-



1; Δ^5-ene 3β-*O*-PO_3H_2
2; Δ^5-ene 3α-*O*-PO_3H_2
3; $\Delta^{5,7}$-diene 3β-*O*-PO_3H_2
4; $\Delta^{5,7,9}$-triene 3β-*O*-PO_3H_2



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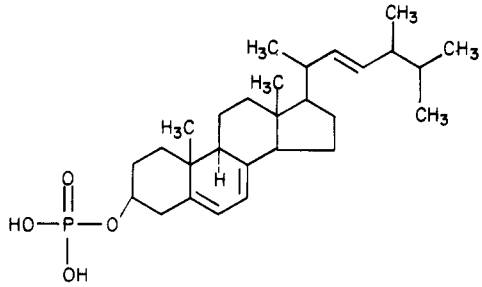

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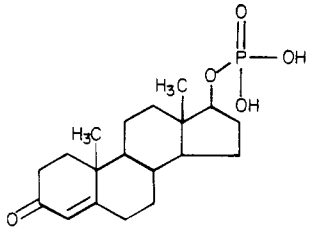

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Table I. Steroid Phosphates from the Reaction of Steroids with (1-Phenyl-1,2-dibromoethyl)phosphonic Acid and Diisopropylethylamine in Dichloromethane Solution

compd	parent steroid	yield, %	mp,[a] deg	$[\alpha]^{20}_D$,[b] deg: parent steroid	$[\alpha]^{20}_D$,[b] deg: steroid phosphate	$\delta^{31}P$,[c] ppm	R_f (solvent)[d]	molecular formula, (M_r)	calcd C	calcd H	found C	found H
1	cholesterol	74	186–188[e,f]	−35	−29[g]	0.3	0.48 (A)					
2	epicholesterol	66	164–167[e]	−44	−22	0.5	0.74 (A)	$C_{27}H_{47}O_4P$ (466.63)[h]	69.49	10.15	69.66	10.39
3	$\Delta^{5,7}$-cholestadien-3β-ol	65	144–148[e]	−109	−49	0.3	0.46 (B)	$C_{27}H_{45}O_4P{\cdot}2H_2O$ (500.64)[i]	64.77	9.87	64.08	9.48
4	$\Delta^{5,7,9}$-cholestatrien-3β-ol	46	126–129	+98	+43	0.1	0.53 (A)	*j,k*				
5	stigmasterol	72	179–182[e]	−49	−38	0.2	0.60 (B)	$C_{29}H_{49}O_4P{\cdot}H_2O$ (510.67)[l]	68.20	10.07	67.77	10.25
6	ergosterol	65	164–167[m]	−109	−72	0.3	0.48 (B)	*n*				
7	testosterone	65	139–142[o,p]	+121	+75[q]	0.7	0.64 (B)					

[a] Melt with decomposition, preceded by color changes. [b] All in chloroform/methanol (2:1, v/v); c = 1. [c] In parts per million from 85% H_3PO_4 in deuterochloroform/methanol (2:1, v/v). Positive values are to low field from reference. [d] Solvents are chloroform/methanol/acetic acid/water: (A) (25:15:4:2); (B) 35:10:4:2 (v/v). [e] Can be recrystallized from dioxane. [f] Lit. mp 186–188 °C ref 24–26. [g] Lit. −40.8 (chloroform), ref 22. [h] P: calcd, 6.64; found, 6.77. [i] λ_{max} (ε): 267 (shoulder, 5890), 277 (7960), 287 (8250), 279 (5010). [j] λ_{max} (ε): 267 (shoulder, 4480), 277 (5700), 288 (6520), 300 (6110), 317 (6520), 332 (7330), 346 (4890). [k] Too unstable for elemental analysis. [l] P: calcd, 6.07; found, 5.83. [m] Lit. mp 160 °C, ref 24–26; 165–168 °C, ref 22. [n] λ_{max} (ε): 267 (shoulder, 5720), 277 (8270), 287 (8690), 298 (5090). [o] Recrystallized from methanol/water (1/1). [p] Lit. mp 140–141 °C, ref 23. [q] Lit. +73 (methanol), ref 23.

ethyl)phosphonic acid (1.05 mmol) was added to a solution of the *dried* steroid (1.0 mmol) in anhydrous dichloromethane (20 mL). Diisopropylethylamine (2.1 mmol) was added (via syringe) to the well-stirred mixture. The homogeneous solution was kept for 15 h at 20 °C (in the dark, in the case of a conjugated di- or triunsaturated steroid). The solvent was evaporated, and the residue was triturated with ether (3 × 15 mL) to remove the α-bromostyrene byproduct and any unreacted steroid. The residual fine powder was dried for a few minutes at 20 °C (0.5 torr). This trialkylammonium phosphate salt was dissolved in a 2:1 v/v chloroform/methanol mixture (45 mL). The solution was treated with 3:48:47 v/v chloroform/methanol/1 N aqueous HCl reagent (15 mL) in order to liberate the free phosphoric acid under the mildest conditions. The two-phase system was stirred for a few min. The lower organic phase was separated and resubmitted to the same acidification procedure. Finally the lower organic phase was washed (twice) with a 3:48:47 v/v chloroform/methanol/water mixture (10 mL). The organic phase was evaporated at 20 °C (1 torr), and the residue was triturated with ether (10 mL) to remove any unreacted steroid that may have remained as contaminant. The steroid phosphate was dried at 20 °C for 6 h (0.5 mm). TLC and ^{31}P NMR spectroscopy disclosed that the steroid phosphates thus obtained were of at least 97% purity. The nonconjugated unsaturated compounds were recrystallized (cf. Table I) without significant changes in physical properties. The conjugated unsaturated compounds were submitted to ultraviolet absorption spectrometry and elemental analysis without crystallization. The presence of two very weak ^{31}P NMR signals at about −11 ppm (to high field from 85% H_3PO_4) that are observable in some of the steroid phosphate samples are attributable to trace amounts of sterol pyrophosphates formed in a secondary reaction.

The reaction time was reduced to 8 h in the synthesis of the labile $\Delta^{5,7,9}$-cholestatriene 3β-*O*-phosphate (**4**). Testosterone phosphate (**7**) is relatively hydrophilic; therefore, minimum volumes of the acidification reagent and the washing mixture were employed in its isolation.

Acknowledgment. This research was supported by the National Institutes of Health (Grant GM 20672).

Registry No. 1, 4358-16-1; **2**, 85135-01-9; **3**, 84284-80-0; **4**, 85135-02-0; **5**, 85135-03-1; **6**, 24352-60-1; **7**, 1242-14-4; cholesterol, 57-88-5; epicholesterol, 474-77-1; $\Delta^{5,7}$-cholestadien-3β-ol, 434-16-2; $\Delta^{5,7,9}$-cholestatrien-3β-ol, 51982-45-7; stigmasterol, 83-48-7; ergosterol, 57-87-4; testosterone, 58-22-0; $\Delta^{5,7,9}$-cholestatrien-3β-ol acetate, 1255-91-0; (1-phenyl-1,2-dibromoethyl)phosphonic acid, 85135-04-2.

Reactions of Oxaphospholenes. 2.[1] Hydrolysis of Neopentyl Esters, Phenyl Esters, and Amides

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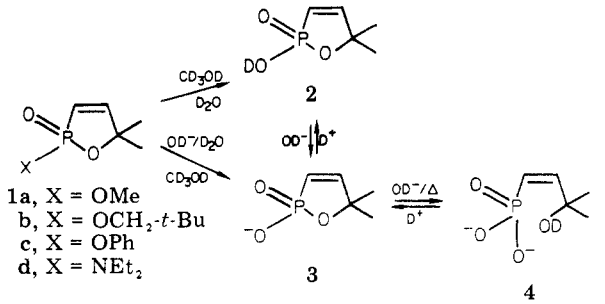
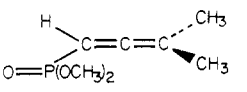
The neopentyl (**1b**) and phenyl (**1c**) esters of 2-hydroxy-5,5-dimethyl-1,2-oxaphosphol-3-ene 2-oxide (**2**) as well as the corresponding diethyl amide (**1d**) were synthesized, and their hydrolytic behavior was examined. Comparisons were made with the hydrolytic behavior of the methyl ester **1a** and allenic phosphonate **5**. The hydrolyses of **1a–c** in initially neutral aqueous methanol exhibited autocatalytic kinetics owing to acid catalysis by hydrolysis product **2**. Amide **1d** hydrolyzed only in the presence of added acid catalyst; allene phosphonate **5** was inert to both neutral and acidic conditions. The hydrolyses of **1b–d** in basic aqueous methanol proceeded via ring-opened intermediates **8b–d**, which then reclosed to the conjugate base of **2**. Phosphonate **5** lost only one methyl group during basic hydrolysis, but it simultaneously underwent isotope exchange of the olefinic hydrogen.

We recently described[1] the hydrolytic behavior of oxaphospholene ester **1a**. In 50% aqueous methanol **1a** hydrolyzed to free acid **2** (which served to autocatalyze the reaction). Complete hydrolysis required 5.5 h at 68 °C, with <10% hydrolysis occurring after 18 h at 25 °C. By



contrast, **1a** was converted instantaneously to salt **3** in aqueous methanolic KOH. In both these reactions the oxaphospholene ring remained intact; i.e., hydrolysis occurred with exocyclic cleavage. Only when **3** was heated to 70 °C in the presence of excess hydroxide was endocyclic cleavage observed to give **4**. Because the reaction of **1a** with *methoxide* led to salt **3** in addition to degenerate transesterification, we surmised that the exocyclic hydrolyses (**1a** → **2** and **1a** → **3**) occurred at least in part by alkyl–oxygen cleavage; only with elevated temperatures or potent nucleophiles did products arise from attack at phosphorus (e.g., ring-opening via phosphoryl–oxygen cleavage). If our conclusions were correct, it should be possible by altering the alkoxy group in **1a** to suppress exocyclic alkyl–oxygen cleavage and activate exocyclic phosphoryl–oxygen cleavage. Exocyclic alkyl–oxygen cleavage should be eliminated sterically in the neopentyl ester **1b** and structurally (because of hybridization) in phenyl ester **1c**. Furthermore, the phenoxy group in **1c** should be a considerably better nucleofuge than either methoxy (**1a**) or neopentoxy (**1b**). We have now prepared these two phosphonate esters and examined their hydrolytic behavior. We have also examined phosphonamide **1d** and, for comparison's sake, dimethyl allenic phosphonate ester **5**.[3]



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(1) Part 1: Macomber, R. S.; Krudy, G. A. *J. Org. Chem.* **1981**, *46*, 4038.

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