[15-$^2H_2$]Progesterone (1c). Hydrogenolysis of **2g** (70 mg, 0.12 mmol) with lithium triethylborodeuteride, followed by acid hydrolysis as described above, gave **1c**. The **1c** was purified by preparative TLC and crystallized from acetone: 16 mg; mp 126-128 °C; ^1H NMR δ 0.68 (3 H, s, 18-H), 1.17 (3 H, s, 19-H), 2.1 (3 H, s, 21-H), 5.7 (1 H, s, 4-H); ^2H NMR δ 1.22 (1-^2H, s, 15β-^2H), 1.66 (1-^2H, s, 15α-^2H); mass spectrum m/e 316 (M^+, 95% d_1).

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Registry No. **1a**, 85098-39-1; **1b**, 85098-40-4; **1c**, 85115-79-3; **1d**, 600-73-7; **2a**, 24377-04-6; **2b**, 24377-10-4; **2e**, 85098-41-5; **2f**, 85098-42-6; **2g**, 85098-43-7; **2h**, 24377-05-7; **2j**, 85098-44-8; **2k**, 85098-45-9; **3b**, 85098-46-0; ethylene glycol, 107-21-1.

Studies on a Convergent Route to Side-Chain Analogues of Vitamin D: 25-Hydroxy-23-oxavitamin D_3[1]

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Permanganate oxidation of vitamin D_3 affords the 7,8-diol **4a**, which was successively silylated to **4b** and then oxidatively cleaved and reduced to afford **3c**. The latter was converted in several steps to phosphine oxide **3b**, a useful A-ring fragment for analogue synthesis. The readily available diol **2** was selectively alkylated to give **6a**, which was easily transformed to **6b** and **9c**. Horner-Wittig coupling of **3b** with **6b** followed by deprotection afforded **8a**, which upon oxymercuration-demercuration afforded the 23-oxavitamin **1b** in low yield. By contrast, coupling of **9c** and **3b** followed by deprotection afforded **1b** in satisfactory yield.

In the vitamin D field,[2] there is a continuing need for side-chain analogues that might serve as biochemical research tools for metabolism studies. For example, analogues of 25-hydroxyvitamin D_3 (**1a**) (Chart I) possessing side-chain carbons that cannot be hydroxylated or further oxidized are of considerable interest. Since C_{23} oxidation of **1a** appears at least in part to be involved in its catabolism,[3] blocking of this position was expected to make this metabolite more resistant to degradation. Accordingly, the 23-oxa analogue **1b** was targeted for synthesis since the 23-position is blocked and the replacement of a methylene unit by an ether oxygen was not expected to impart significant steric perturbation.[4]

Since **1b** represents only one example of a family of analogues that are of interest in this laboratory, we have devoted some of our recent efforts toward utilizing the readily available Inhoffen-Lythgoe diol **2**[5] as a basic building block in convergent syntheses of analogues. Once appropriate fragments are available, the convergent approach would appear to be more versatile and efficient than the classical photochemical approach to a family of analogues needed for systematic structure-activity studies. Since **1b** possesses the simple, unmodified A ring of readily available vitamin D_3, application of Lythgoe's method[6] for attaching the phosphine oxide **3a** to an appropriate C/D

Chart I

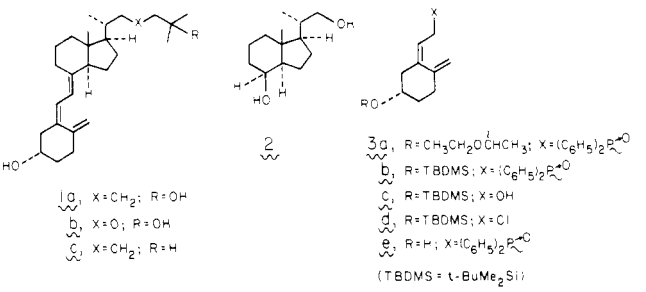
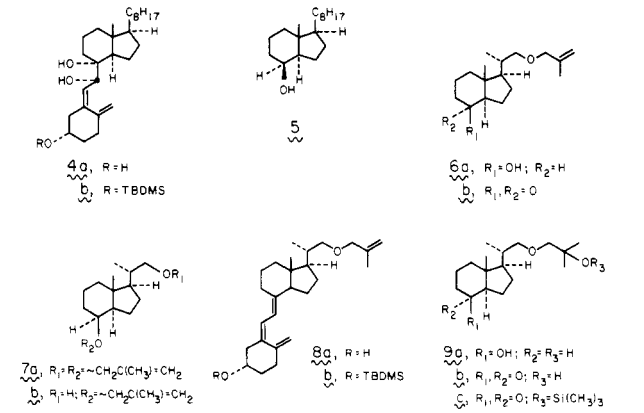


Chart II



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ketone seemed attractive. The reported synthesis of **3a** from degradation of vitamin D_2 is lengthy[6,7] however, and it is the purpose of this paper to also report a more efficient preparation of the equivalent fragment **3b** as well as its coupling to an appropriate C/D fragment derived from **2** to afford the oxavitamin **1b**.

Results and Discussion

Oxidation ($KMnO_4$, ethanol; 73% yield) of vitamin D_3 (**1c**) afforded in a remarkably clean reaction the previously unknown triol **4a**,[8] which was selectively converted (*t*-$BuMe_2Si$-Cl, imidazole, DMF; 86%)[9] to the monosilyl ether **4b** (Chart II). Oxidative cleavage of **4b** followed by direct reduction [$Pb(OAc)_4$, benzene; $(CH_3OCH_2CH_2O)_2AlH_2Na$, toluene; flash chromatography] afforded protected A-ring alcohol **3c** (56%)[7] and Grundmann's 8β-alcohol **5** (87%).[10] Alcohol **3c** was successively converted to the chloride **3d** and then to the desired phosphine oxide **3b** in 91% and 52% yields, respectively.[11] The oxide **3b** proved identical with the silyl ether prepared from **3e**, which in turn was prepared from vitamin D_2 by Lythgoe's method.[6]

The most efficacious route to the required C/D fragment proved to be the direct alkylation of the Inhoffen–Lythgoe diol **2**.[5] Thus, treatment of **2** with *n*-butyllithium (1 equiv, THF) and then, after diluting with DMF, 2-methyl-3-chloropropene (5 equiv) followed by heating produced (after separation) the desired **6a** (47%) as well as **7a** (26%), **7b** (5%), and starting material (17%). Oxidation (PDC, 91%) of **6a** afforded the ketone **6b**,[12] which was coupled with **3b** in a Horner–Wittig process[6] to give after deprotection[9] a 61% yield of **8a**. In the initial plan, it was anticipated that oxymercuration–demercuration of **8a**[13,14] would afford the target **1b**. This approach would be ideal for providing a means for radioisotopic labeling of **1b** at $C_{26,27}$ at the latest possible stage (at the demercuration step) in its synthesis. In the event, only a 29% yield of **1b** could be obtained.

In a more successful route, **6a** was subjected to oxymercuration–demercuration (88%) to afford diol **9a**, which was oxidized (PDC, 79%) to the keto alcohol **9b**. Protection[15] of **9b** as the silyl ether **9c** followed by direct coupling to **3b** and then deprotection afforded **1b** in 59% yield. In summary, this study provides an improved prototype for the preparation of a family of analogues possessing the vitamin D_3 A-ring with different side chains.

Experimental Section

General Methods. Spectroscopic (^1H NMR, IR, UV, and high- and low-resolution MS) data are given in the supplementary material section. Air-sensitive materials were generally stored under nitrogen in a −80 °C freezer, and reactions involving organometallic materials were performed under an atmosphere of dry nitrogen. References to aqueous $NaHCO_3$, NH_4Cl, and NaCl during experimental workup procedures refer to saturated aqueous solutions unless otherwise stated. Dry ether or THF (tetrahydrofuran) refers to reagent-grade material freshly distilled from benzophenone ketyl or $LiAlH_4$ under nitrogen. Skellysolve B, hexanes and lbpe (low-boiling petroleum ether, bp 30–60 °C) were distilled from CaH_2 prior to use. Pyridine was distilled from CaH_2 or KOH and stored over 4-Å molecular sieves. Kugelrohr distillation boiling points (bp) refer to the external-air bath temperature. Melting points (mp) (uncorrected) were obtained on a Thomas-Hoover capillary apparatus.

High-pressure liquid chromatography (high-pressure LC) was performed on a Waters 6000A solvent delivery system equipped with a U6K injector and dual detector system (M450 variable wavelength UV and R401 refractive index detectors). A Whatman M9 10/50 Partisil (10-μm particle size, 9.4 mm i.d. × 50 cm) column was used for normal-phase conditions unless otherwise noted. All chromatography solvents were distilled prior to use. Solvents and solvent mixtures were vacuum filtered through a 0.45-μm Millipore filter and vacuum degassed immediately prior to use. Silica gel 60 (230–300 mesh) obtained from MCB-Merck was used for flash chromatography.[16] Ordinary column chromatography was performed on J. T. Baker silica gel (60–200 mesh). Thin-layer chromatography (TLC) was performed on precoated plates with silica gel 60 F-254 from MCB-Merck.

7,8-Dihydroxy-7,8-dihydrovitamin D_3 (4a) and -vitamin D_2. A solution of vitamin D_3 (3.00 g, 7.80 mmol) in absolute ethanol (300 mL) was placed in a 500-mL three-necked round-bottom flask fitted with a thermometer, a stirrer, and a 100-mL dropping funnel. The solution was cooled to −20 °C, and potassium permanganate (2.50 g, 15.6 mmol) in water (75 mL) was added dropwise to the stirred solution at such a rate that the temperature did not rise above −10 °C (ca. 45 min). The brown suspension was stirred for another hour, after which it was warmed to ca. 40 °C in a water bath with occasional swirling for 10 min to facilitate coagulation of the fine manganese dioxide. The solid was allowed to settle at room temperature undisturbed (ca. 30 min). The upper layer was carefully decanted off, and the residual brown suspension was centrifuged to separate the solid from the ethanol solution. The combined ethanol solution was filtered through a 2-in. layer of silica gel. The clear yellow solution was evaporated ty dryness under reduced pressure. The solid residue was triturated with hot lbpe (100 mL) and filtered to remove the lbpe-soluble starting vitamin D_3. Crystallization of the solid from ethyl acetate yielded the triol **4a** [0.81 g (mp 175–177 °C, first crop) and 0.90 g (mp 171–173 °C, second crop)]. Flash chromatography (ethyl acetate) of the combined mother liquors from the crystallization and the lbpe extract from the trituration afforded an additional 0.67 g of product, to afford a total yield of 2.38 g (73%). Under similar conditions, vitamin D_2 was converted to its triol (mp 177–78 °C, lit.[7a] mp 177–78 °C).

3β-*O*-(*tert*-Butyldimethylsilyl)-7,8-dihydroxy-7,8-dihydrovitamin D_3 (4b). A mixture of the triol **4a** (1.2 g, 2.87 mmol), *tert*-butyldimethylsilyl chloride (0.45 g, 3 mmol), and imidazole (0.44 g, 6.5 mmol) in 10 mL of DMF was stirred at room temperature under nitrogen until TLC indicated completion of reaction (ca. 2 h). The mixture was poured into ice-cold water and was extracted twice with chloroform. The combined chloroform extracts were dried ($MgSO_4$) and evaporated to give an oil. Flash chromatography (5% EtOAc in Skellysolve B) followed by vacuum drying afforded the diol **4b** as an oil (1.32 g, 86%).

(*S*)-(*Z*)-2-(5-(*tert*-Butyldimethylsiloxy)-2-methylenecyclohexylidene)ethanol (3c). To a solution of the siloxy diol **4b** (525 mg, 0.99 mmol) in benzene (4 mL) containing 0.25 mL of pyridine at 25 °C was added lead tetraacetate (525 mg, 1.19 mmol) in portions. The mixture was stirred for 10 min after which the white solid was filtered off and washed with benzene (2 × 5 mL). To the combined filtrate and washings at 0 °C was added dropwise 1 mL of Red-Al (Aldrich) (70% solution of sodium

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bis(2-methoxyethoxy)aluminum hydride in toluene). The mixture was stirred for 1.5 h, and then water was added dropwise until a grayish precipitate formed. Complete precipitation was obtained after a further 15 min of stirring. The precipitate was removed by filtration and washed thoroughly with ether (6 × 10 mL). The combined filtrates were washed with brine and then dried ($MgSO_4$). Evaporation of the solvent followed by flash chromatography (15% EtOAc in Skellysolve B) yielded the A-ring dienol **3c** (149 mg, 56%) and the C/D-fragment alcohol **5** (238 mg, 87%) as viscous oils.

(*S*)-(*Z*)-2-(5-(*tert*-Butyldimethylsiloxy)-2-methylenecyclohexylidene)-1-chloroethane (3d). To a solution of *N*-chlorosuccinimide (134 mg, 1.0 mmol) in anhydrous CH_2Cl_2 (4 mL) at 0 °C was added dropwise dimethyl sulfide (0.08 mL, 1.1 mmol). A white precipitate was obtained after the introduction of the first few drops of dimethyl sulfide. To the cooled (−20 °C) solid suspension was slowly added (~3 min) **3c** (134 mg, 0.5 mmol) in CH_2Cl_2 (0.5 mL). The mixture was stirred at −20 °C for 30 min and then at 0 °C for an additional 30 min. The reaction mixture was diluted with ethyl acetate, washed with cold brine (2 × 5 mL), dried ($MgSO_4$), and then filtered. Evaporation of the solvent under reduced pressure afforded a mixture of a white solid and an oil. The oil was separated by decantation with Skellysolve B, and then the concentrated Skellysolve B fraction was flash chromatographed (1% EtOAc in Skellysolve B) to afford the allylic chloride **3d** as an oil (130 mg, 91%).

(*S*)-(*Z*)-(2-(5-(*tert*-Butyldimethylsiloxy)-2-methylenecyclohexylidene)ethyl)diphenylphosphine Oxide (3b). A solution of *n*-butyllithium (1.5 mmol, 1.3 M solution in hexane) was added dropwise to diphenylphosphine (280 mg, 1.5 mmol) in dry THF (4 mL) at 0 °C. A portion (1.4 mL) of the orange $(C_6H_5)_2PLi$ solution was added dropwise to a solution of allylic chloride **3d** (95 mg, 0.33 mmol) in dry THF (3 mL) at −50 °C. The initially yellow solution, upon standing for 15 min, turned orange, which was immediately discharged by the addition of 1 drop of water. The solvent was evaporated under reduced pressure, leaving a gummy residue. Chloroform (15 mL) and 5% H_2O_2 (11 mL) were added successively to the flask, and the mixture was shaken for 1 min. The chloroform layer was separated, washed with aqueous sodium sulfite and water, and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography (70:30 EtOAc–Skellysolve B) afforded the phosphine oxide **3b** (77 mg, 52%, mp 107–108 °C).

In a separate series of experiments, (*S*)-(*Z*)-(2-(5-hydroxy-2-methylenecyclohexylidene)ethyl)diphenylphosphine oxide (**3e**) was prepared from vitamin D_2 exactly as described by Lythgoe and co-workers.[6,7] A mixture of this alcohol (110 mg, 0.33 mmol), *tert*-butyldimethylsilyl chloride (105 mg, 0.7 mmol), and imidazole (60 mg, 1.0 mmol) in DMF (5 mL) was reacted and then worked up in the usual way to afford the same phosphine oxide **3b** (105 mg, 72%, mp 107–108 °C).

De-*A*,*B*-23-oxa-25,26-dehydrocholestan-8β-ol (6a). To an ice-cold, stirred solution of de-*A*,*B*-22,23-dinorcholane-8β,24-diol (**2**, the Inhoffen–Lythgoe diol; 212 mg, 1.00 mmol) in tetrahydrofuran (1 mL) under nitrogen was added *n*-butyllithium (0.88 mL, 1.05 mmol; 1.2 M solution in hexane) dropwise. After the addition, the ice bath was removed and then *N*,*N*-dimethylformamide (4 mL) and 2-methyl-3-chloropropene (0.4 mL, 5 mmol) were added successivley to the lithium salt. The mixture was heated in an oil bath at 75–80 °C for 1.5 h. After cooling to room temperature, the mixture was diluted with ether (20 mL) and then washed with ice-cold brine (6 × 5 mL), dried ($MgSO_4$), and evaporated to dryness under reduced pressure. Flash chromatography (20% EtOAc in Skellysolve B) afforded four components eluted in the following order: **7a** (83 mg, 26%), **6a** (126 mg, 47%), **7b** (13 mg, 5%), and **2** (27 mg, 17%) (95% mass balance).

De-*A*,*B*-23-oxacholestane-8β,25-diol (9a). Mercuric acetate (191 mg, 0.6 mmol) was dissolved in water (0.5 mL), and then THF (0.5 mL) was added to give a fine yellow suspension. Alcohol **6a** (133 mg, 0.5 mmol) in THF (1 mL) was added dropwise to the stirred yellow suspension (N_2, room temperature). The yellow suspension turned to a pale yellow clear solution in ca. 2 min. After 1 h, 3 M NaOH (0.5 mL) was added followed by sodium borohydride (0.5 mL of 0.5 M solution in 3 M NaOH), giving a gray suspension. Sodium chloride was added to saturate the aqueous layer. The mixture was then extracted with ether (4 × 5 mL), dried ($MgSO_4$), and evaporated to dryness to give an oil. Flash chromatography (30% EtOAc in Skellysolve B) afforded diol **9a** as an ^1H NMR pure oil (125 mg, 88%).

De-*A*,*B*-23-oxacholestan-25-ol-8-one (9b) and De-*A*,*B*-23-oxa-25,26-dehydrocholestan-8-one (6b). Pyridinium trifluoroacetate (20 mg, 0.01 mmol) and pyridinium dichromate (279 mg, 0.8 mmol) were added successively to a stirred solution of **9a** (76 mg, 0.27 mmol) in CH_2Cl_2 (4 mL) at room temperature under N_2. After 4 h, the brown mixture was filtered through a short silica gel column (5 in.) by eluting with 25 mL of 40% EtOAc in Skellysolve B. Evaporation of the solvent to dryness gave **9b**, sufficiently pure for the next step. Further purification by high-pressure LC (Partisil; 40% EtOAc in Skellysolve B) afforded hydroxy ketone **9b** as an oil (60 mg, 79%).

Oxidation of **6a** (90 mg) under the above condition yielded enone **6b** as an oil (82 mg, 91%).

23-Oxa-25,26-dehydrovitamin D_3 (8a). To a stirred solution of phosphine oxide **3b** (25 mg, 0.055 mmol) in dry THF (1 mL) under N_2 at −78 °C was added *n*-butyllithium (0.07 mmol, 1.3 M solution in hexane), giving a deep orange solution. To the latter was slowly added dropwise ketone **6b** (15 mg, 0.057 mmol) in THF (0.3 mL). The orange solution turned pale yellow after 1.25 h and became nearly colorless upon warming to room temperature. The solvent was evaporated, and then the residue was dissolved in ether and washed with aqueous $NaHCO_3$ and brine. After drying ($MgSO_4$) and concentrating the solution, flash chromatography (5% EtOAc in Skellysolve B) of the residue afforded silyl ether **8b** (20 mg, 73% from phosphine oxide **3b**). Treatment of **8b** with tetra-*n*-butylammonium fluoride (100 mg, 0.38 mmol) in THF (1 mL) at room temperature for 2 h, followed by the usual workup and then high-pressure LC purification (Partisil, 20% EtOAc/Skellysolve B), afforded the vitamin **8a** (13 mg, 61% from phosphine oxide **3b**).

23-Oxa-25-hydroxyvitamin D_3 (1b) by Oxymercuration-Demercuration. Mercuric acetate (7 mg, 22 μmol) was added in one lot to the 25,26-dehydrovitamin **8a** (2.4 mg, 6 μmol) in a mixture of THF (0.4 mL) and water (0.1 mL) under nitrogen at 0 °C. After 2.25 h, 3 M NaOH (0.1 mL) was added followed by 0.1 mL of 0.5 M sodium borohydride in 3 M NaOH. Solid $NaHCO_3$ was added to saturate the aqueous layer, and then the mixture was extracted with ether (4 × 5 mL). The combined ether extracts were washed with ice-cold brine (2 × 5 mL) and dried ($MgSO_4$). High-pressure LC (Partisil; 40% EtOAc in Skellysolve B) separated the 25-hydroxyvitamin **1b** (0.7 mg, 29% based on UV calculations assuming ϵ_{262nm} 18 300) from unreacted **8a** (0.55 mg) and other unidentified products. Attempts to increase the percent conversion failed since the amount of the unidentifiable components increased.

25-(Trimethylsiloxy)-de-*A*,*B*-23-oxacholestan-8-one (9c). *N*-(Trimethylsilyl)imidazole (40 mg, 0.29 mmol) was added to hydroxy ketone **9b** (26 mg, 0.09 mmol) in dry THF (1 mL) at room temperature under argon. After 2 h, the mixture was directly flash chromatographed (15% EtOAc in Skellysolve B). High-pressure LC purification (10% EtOAc in Skellysolve B) followed by vacuum drying afforded the siloxy ketone **9a** as an oil (32 mg, 98%). This material, which exhibited an ^1H NMR spectrum similar to the starting alcohol **9b** with the expected differences, was used directly in the next step without further characterization.

23-Oxa-25-hydroxyvitamin D_3 (1b) from 9c. The Horner coupling and deprotonation was carried out exactly as described for the 25,26-dehydrovitamin 8. The phosphine oxide **3b** (20 mg, 0.004 mmol) was reacted with *n*-butyllithium (0.046 mmol, 0.035 mL, 1.3 M in hexanes), and then siloxy ketone **9c** (16 mg, 0.045 mmol) was added. After workup, double deprotection (*n*-Bu_4NF, 74 mg, 0.28 mmol, THF) and high-pressure LC purification (40% EtOAc in Skellysolve B on Partisil), the pure 25-hydroxyvitamin **1b** was obtained in 59% yield (10.5 mg) based on phosphine oxide.

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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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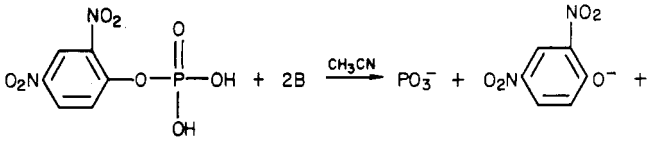
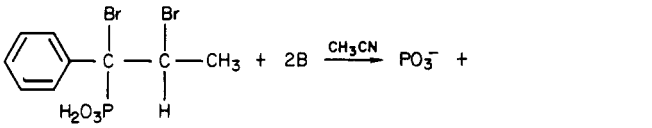
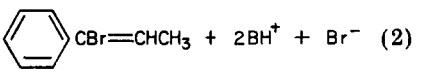
Dihydrogen phosphate esters derived from steroids having one, two, and three conjugated or nonconjugated double bonds have been conveniently prepared by a procedure that probably involves the monomeric metaphosphate anion as an intermediate. The source of metaphosphate is a 1:2 molar mixture of (1-phenyl-1,2-dibromoethyl)phosphonic 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).



(1)





(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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