A Mild Preparation of Protected Phosphate Esters from Alcohols[1]

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Treatment of a wide variety of alcohols with trimethyl phosphite and carbon tetrabromide in pyridine leads to the formation of the corresponding dimethyl phosphate esters in high yields. The reaction is presumed to proceed by formation of an intermediate alkoxy trimethoxyphosphonium salt which undergoes selective demethylation by bromide. Poor yields are generally obtained if solvents other than pyridine are employed or if carbon tetrabromide is replaced by carbon tetrachloride. The mildness of the procedure is illustrated by the conversion of the highly acid sensitive 2-(4,4'-dimethoxytrityloxy)-1-phenylethanol to its dimethyl phosphate ester (74%) and the base sensitive N-CBZ-tyrosine *p*-nitrophenyl ester to the corresponding *O*-(dimethyl phosphate ester) (82%). The availability of methods for the demethylation of methyl phosphate esters makes this oxidative phosphorylation reaction a mild and inexpensive method for the synthesis of protected phosphate esters.

Phosphate monoesters appear in a wide variety of natural products. The phosphorylation of the free hydroxyl groups of serine and tyrosine residues in peptides constitutes an important regulatory mechanism for intracellular enzymic activity.[2] The phosphorylation of nucleosides and nucleoside analogs results in compounds which are of biological interest in of themselves or which may be precursors to biologically important compounds.

Chemical synthesis of a biologically significant phosphate monoester $ROPO_3H_2$ may proceed from the alcohol to give the phosphate directly.[3] However, in most instances the phosphate is introduced in a protected form as a mixed triester $ROP(O)(OR')_2$, both to avoid unwanted side reactions in subsequent chemical transformations, as well as to provide a compound which is more easily handled and purified than the highly polar and often negatively charged monoester. A wide variety of protecting groups are available which combine varying degrees of stability to commonly encountered reaction conditions with susceptibilities to cleavage under specialized conditions.[4–6] Methyl and benzyl (or substituted benzyl) esters are of particular note due to their frequent utilization in the syntheses of a wide variety of target classes of phosphates and phosphonates. While the number of methods available for cleaving benzyl phosphate esters may be used to advantage for their selective deprotection, this versatility may also be disadvantageous; for example, benzyl ethers are susceptible to cleavage under conditions commonly employed in solid phase peptide synthesis.[7] Methyl esters of phosphoric acid are substantially more robust than benzyl esters; quite stable to mild acids and bases, and inert to hydrogenolysis. The harshly (Bronsted) acidic conditions originally utilized for their cleavage in the presence of nucleophiles have been largely supplanted by much milder methods involving Lewis acidic-nucleophilic reagents such as trimethylsilyl iodide[8] and trimethylsilyl bromide,[9] allowing deprotection in the presence of other functional groups, such as carboxylic acid methyl esters.[8,10]

Phosphorylation of alcohols is generally accomplished by reaction with an activated P(IV) species (e.g., $(RO)_2P(O)Cl$,[11] tetraalkyl pyrophosphate,[10a] or mixed ester[12]) or by coupling with a P(III) species followed by oxidation.[13] Both of these routes suffer from the disadvantage that the desired phosphorylating agent is generally either commercially unavailable by virtue of low stability, or if available, extraordinarily expensive. In the course of the synthesis of some nucleotide analogs we required multigram quantities of a protected monophosphate ester of a primary alcohol. We found the cost of the reagents required for established P(III) routes to be higher than desirable, while the P(IV) reagents examined led to decomposition of our acid sensitive substrate. The deficiencies in these methodologies led us to develop the extremely mild and inexpensive phosphorylation procedure described below.

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(1) Portions of this work were presented at the March, 1994 National Meeting of the American Chemical Society, March 1994, San Diego, CA.

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(5) Base labile: (a) Teng, C.-Y. P.; Yukimoto, Y.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 21. (b) Himmelsbach, R.; Pfleiderer, W. *Tetrahedron Lett.* **1982**, *23*, 4793. (c) Tener, G. M. *J. Am. Chem. Soc.* **1961**, *83*, 159.

(6) Specialized protecting groups: (a) Photochemical deprotection of substituted benzyl esters: Pirrung, M. C.; Shuey, S. W. *J. Org. Chem.* **1994**, *59*, 3890; and references therein. (b) Fluoride cleavage of (trimethylsilyl)ethanol esters: Sawabe, A.; Filla, S. A.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 7685. (c) Phosphine cleavage of Cl_3CCMe_2O esters: Letsinger, R. L.; Groody, E. P.; Lander, N.; Tanaka, T. *Tetrahedron* **1984**, *40*, 137.

(7) (a) Valerio, R. M.; Perich, J. W.; Kitas, E. A.; Alewood, P. F.; Johns, R. B. *Aust. J. Chem.* **1989**, *42*, 1519. (b) Perich, J. W.; Johns. R. B. *J. Org. Chem.* **1989**, *54*, 1750.

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(9) (a) Kitas, E. A.; Perich, J. W.; Johns, R. B.; Tregear, G. W. *Tetrahedron Lett.* **1988**, *29*, 3591–2. (b) McKenna, C. E.; Higa, M. T.; Cheung, N. H.; McKenna, M.-E. *Tetrahedron Lett.* **1977**, 155.

(10) (a) Chouinard, P. M.; Bartlett, P. A., *J. Org. Chem.* **1986**, *51*, 75–8. (b) Bartlett, P. A.; McQuaid, L. A. *J. Am. Chem. Soc.* **1984**, *106*, 785. (c) McKenna, C. E.; Schmidhauser, J. *J. Chem. Soc., Chem. Commun.* **1979**, 739.

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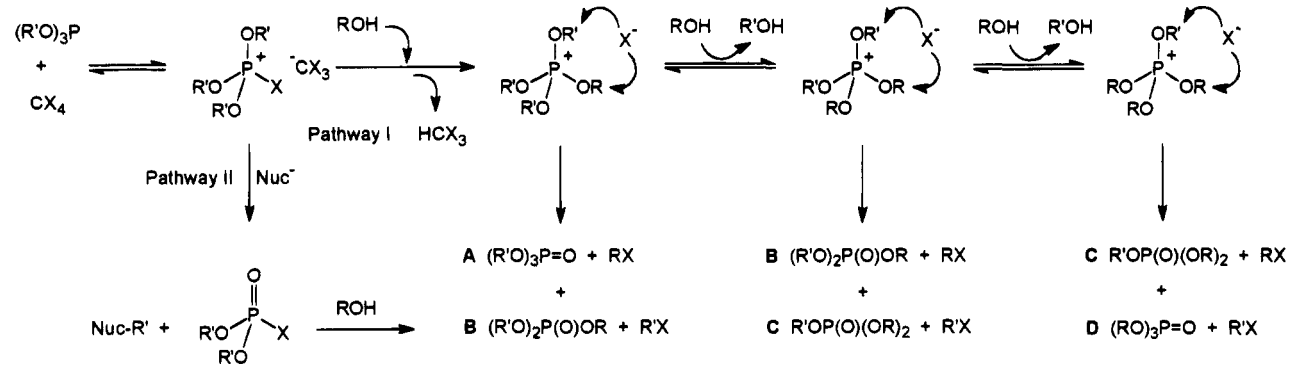
(13) For a review focussing on the uses of these reactions in the preparation of oligonucleotides, see Beaucage, S. L.; Iyer, R. P. *Tetrahedron* **1993**, *49*, 1925–63.

0022-3263/95/1960-3680$09.00/0

Scheme 1



Results

The basis of our phosphorylation procedure is the oxidation of phosphites by carbon tetrahalides in the presence of alcohols, first reported by Burn and Cadogan[14] more than thirty years ago (eq 1). The formation of mixtures of trialkyl phosphates when alcohols other than ethanol were employed led Burn and Cadogan to suggest that the reaction might be useful for the phosphorylation of alcohols, provided that a suitable choice of phosphite and alcohol were made.

$$(EtO)_3P + EtOH + CCl_4 \longrightarrow (EtO)_3P{=}O + HCCl_3 + EtCl \quad (1)$$

Subsequent mechanistic investigations[15] with a variety of $(R'O)_3P$ and ROH substrates ($R \neq R'$) were not encouraging from the standpoint of the potential utility of the reaction for the synthesis of mixed phosphate triesters. The reaction of the trialkyl phosphite with carbon tetrahalide proceeds by a nonradical pathway[16,17] to a mixed tetralkoxyphosphonium halide $[(R'O)_3POR]^+ X^-$ (Scheme 1, pathway I). In addition to nucleophilic cleavage reactions at R and R' which lead to the phosphate triesters $(R'O)_3P{=}O$ (**A**) and $(R'O)_2P(O)OR$ (**B**), respectively, this tetraalkoxyphosphonium salt may undergo an exchange reaction with additional ROH to give $(R'O)_2P(OR)_2^+$. This new tetraalkoxyphosphonium salt may be cleaved nucleophilically, or undergo yet another alcohol exchange reaction to give $(R'O)P(OR)_3^+$, which may then be cleaved. This multitude of reaction pathways leads, in many instances, to the formation of all four possible triesters **A**–**D**; the best yield reported by Cadogen and co-workers for formation of a mixed phosphate triester $(R'O)_2P(O)(OR)$ from $(R'O)_3P$ and ROH was 45% (R' = Et, R = Bu), but this was contaminated by 33% $(R'O)P(O)(OR)_2$, along with the two symmetrical phosphate triesters.[15] The low yields of this reaction, and especially the difficulty in separating the structurally very similar phosphate triester products, are likely responsible for the lack of reports of its use in the preparation of mixed trialkyl phosphate esters.[18]

We thought that this oxidative phosphorylation reaction warranted reexamination, since the operational simplicity of the procedure, as well as the lack of any reactive byproducts formed in the reaction, would make it a very useful method for the synthesis of mixed trialkyl phosphate esters. From examination of Scheme 1 it is evident that optimal yields of the simple mixed phosphate triester **B** would result from increasing the rate of the nucleophilic cleavage of R' relative to that of R, as well as with respect to the rate of alcohol exchange. The requirement of high susceptibility to nucleophilic cleavage (or unimolecular elimination) is met by most of the common alkyl groups used for the protection of phosphate esters (CH_3, CH_2Ar, allyl, and *tert*-butyl). However, the choice of R' = CH_3 is a particularly attractive one due to the somewhat greater stability of methyl esters as protecting groups (see above) and because of the very low cost and ready commercial availability of trimethyl phosphite.

Our initial investigations focussed on the reaction of 2-phenylethanol with trimethyl phosphite and carbon tetrabromide. The reaction is significantly solvent dependent, giving high yields of the desired 2-phenylethyl dimethyl phosphate uncontaminated by other esters when performed in pyridine. Reactions in diethyl ether or methylene chloride occurred more slowly and gave small but significant amounts of bis(2-phenylethyl) methyl phosphate as a byproduct. Use of tetrahydrofuran, *N*,*N*-dimethylformamide, or acetonitrile led to complex mixtures of phosphorous and non-phosphorus-containing products.

Replacement of carbon tetrabromide by the less expensive carbon tetrachloride led to complex mixtures of products; presumably the various possible mixed phosphate triesters, though no effort was made to establish this with certainty. It seems likely that the lower nucleophilicity of Cl^- relative to Br^- allows more of an opportunity for alcohol exchange. Carbon tetraiodide was not examined. While it seems likely that this reagent would be even more effective than carbon tetrabromide, its much higher cost did not seem to justify its use in a reaction which already proceeds in excellent yield.

Reaction of a wide range of alcohols under the conditions which had been established as optimal for 2-phenylethanol gives the corresponding dimethyl phosphate esters in uniformly high yields (Table 1). The reactions are conveniently performed by simply adding trimethyl phosphite to a mixture of the alcohol and carbon tetrabromide in pyridine at 0 °C and allowing the mixture to warm to room temperature. After the indicated time the reaction may be worked up by dilution with ether and washing successively with dilute aqueous acid, sodium bicarbonate, and brine.[19] Although the reaction may be applied with a great deal of generality, giving comparable yields in the phosphorylation of primary (entries 1–3), secondary (entries 4–6), and aromatic alcohols (entry 7),

(14) Burn, A. J.; Cadogan, J. I. G. *Chem. Ind. (London)* **1963**, 736.
(15) Burn, A. J.; Cadogan, J. I. G. *J. Chem. Soc.* **1963**, 5788.
(16) Cadogan, J. I. G.; Sharp, J. R. *Tetrahedron Lett.* **1966**, 2733.
(17) The corresponding reaction of thiols with $(RO)_3P/CX_4$ appears to proceed partially or predominantly by a radical mechanism: (a) Murdock, L. L.; Hopkins, T. L. *J. Org. Chem.* **1968**, *33*, 907. (b) Bunyan, P. J.; Cadogan, J. I. G. *J. Chem. Soc.* **1962**, 2953.
(18) There has been a single report of the reaction of trialkyl phosphites/carbon tetrahalide with hydroxy aromatics, in which competitive nucleophilic cleavage of R/R' groups is likely: Napier, R. P.; Gough, S. T. D. *Org. Prep. Proc. Int.* **1971**, *3*, 117–20.

Table 1. Conversion of Alcohols to Dimethylphosphate Esters

$$ROH + (MeO)_3P + CBr_4 \xrightarrow{\text{pyridine}} ROP(O)(OMe)_2$$

entry	substrate	reaction time (h)	yield,[a,b] %	product
1	$PhCH_2CH_2OH$	2.5	98	$PhCH_2CH_2OP(O)(OCH_3)_2$
2	$CH_3CH{=}CHCH_2OH$[c]	1.25	85	$CH_3CH{=}CHCH_2OP(O)(OCH_3)_2$
3	2′,3′-isopropylideneadensoine	20	78	2′,3′-isopropylideneadensoine, 5′-(dimethyl phosphate ester)
4	cyclohexanol	2.75	86	$c\text{-}C_6H_{11}OP(O)(OCH_3)_2$
5	cholesterol	4.75	86	cholesterol, dimethyl phosphate ester
6	$PhCH(OH)CH_2ODMT$[d]	2.75	74	$PhCH(OPO_3Me_2)CH_2ODMT$
7	N-CBZ-tyrosine *p*-nitrophenyl ester	2.5	82	N-CBZ-tyrosine *p*-nitrophenyl ester, *O*-(dimethyl phosphate ester)
8	1,2-dodecanediol	3.75	70	1-[(dimethylphosphoryl)oxy]-2-dodecanol
9	$PhCH(OH)CH_2OH$	10	72	$PhCH(OH)CH_2OP(O)(OCH_3)_2$

[a] Yield of isolated, pure product. [b] Reactions not optimized except for 2-phenylethanol, entry 1. [c] Mixture of *E*/*Z* isomers. [d] DMT = 4,4′-dimethoxytriphenylmethane.

there are many instances in which the procedure exhibits very useful selectivity when there are multiple reaction pathways possible. Two aspects of the selectivity of this phosphorylation procedure may be seen in the reactions of 1,2-decanediol and 1-phenyl-1,2-ethanediol (entries 8 and 9). Both of these compounds are selectively phosphorylated at the primary alcohol, rather than the secondary alcohol.[20] In addition, the phosphorylation reaction surprisingly gave only the open chain dimethyl phosphate esters for both of these substrates; none of the cyclic phosphate which might be expected to arise through intramolecular alcohol exchange was observed. An example of site selectivity which may have some utility in the synthesis of nucleotides and nucleotide analogs is seen in entry 3, in which apparent exclusive O-phosphorylation of 2′,3′-isopropylideneadenosine occurs; use of the P(IV) reagent $(EtO)_2P(O)Cl$ may at times give reaction at the NH_2 of adenosine derivatives if the 5′-hydroxyl is not activated by conversion to its anion, or the nitrogen protected in some fashion.[11] A final aspect of the selectivity of this reaction is exhibited in the phosphorylation of the allylic alcohol 2-buten-1-ol (entry 2). It might have been anticipated that cleavage of an intermediate 2-buten-1-oxy trimethoxy phosphonium salt at the allylic group would compete with the desired cleavage at one of the methyl groups. However, this does not apparently occur to a significant extent, as evidenced by the high yield of the target dimethyl phosphate ester.

A particularly attractive feature of the trimethyl phosphite/carbon tetrabromide oxidative phosphorylation is the mild nature of the reaction conditions. The suitability of the procedure for substrates highly sensitive to nucleophilic bases is well illustrated by the conversion of the commercially available *p*-nitrophenyl ester of *N*-(carbobenzyloxy)tyrosine to its dimethyl phosphate ester (entry 7), a compound which could be used without additional activating agents in the solid or solution phase synthesis of phosphotyrosine-containing polypeptides. The compatibility of the phosphorylation procedure with highly acid sensitive substrates is seen in the conversion of 2-(4,4′-dimethoxytrityloxy)-1-phenyl-1-ethanol into the corresponding dimethyl phosphate ester (entry 6).

To provide convincing evidence of the potential utility of this phosphorylation procedure we chose to examine the deprotection of 2-phenylethyl dimethyl phosphate by *in situ*-generated iodotrimethylsilane.[21] While the product phosphate is not of particular interest in of itself, the substrate constitutes a fairly challenging test case due to the requirement for nucleophilic discrimination between the methyl groups and a substituted ethyl group. In fact, treatment of 2-phenylethyl dimethyl phosphate with chlorotrimethylsilane/sodium iodide in acetonitrile at room temperature, followed by hydrolysis with water, led to the formation of the target 2-phenylethyl phosphate in 79% yield and >95%purity (eq 2).

$$PhCH_2CH_2OPO_3Me_2 \xrightarrow[\text{ii) } H_2O]{\text{i) } Me_3SiCl/NaI,\ CH_3CN} PhCH_2CH_2OPO_3H_2 \quad (2)$$

There are superficial similarities between the phosphorylation procedure described in this work and the Atherton–Todd reaction, in which an alcohol or amine is treated with a dialkyl phosphite, carbon tetrahalide, and a trialkylamine base.[22] Certain aspects of the mechanism of the latter reaction are still under debate;[23] however, it is clear that a P(IV) dialkyl halophosphate is formed which subsequently phosphorylates the alcohol. Though we cannot absolutely rule out the intermediacy of dimethyl bromophosphate in our phosphorylation reaction we favor the reaction mechanism outlined in Scheme 1, pathway I. Formation of dimethyl bromophosphate would require nucleophilic C–O bond cleavage of the initially formed trimethoxyphosphonium bromide (Scheme 1, pathway II, R′ = CH_3, X = Br). Potential nucleophiles include the tribromomethyl carbanion counterion, the alcohol, the solvent, or bromide derived from decomposition of the tribromomethyl carbanion. Cleavage by either of the first two of these potential nucleophiles may readily be excluded since the resultant products would be 1,1,1-tribromoethane and ROMe, neither of which is observed. Instead, the reaction cleanly produces the target phosphate triester, tribromomethane, and *N*-methylpyridinium bromide. Nucleophilic cleavage of the trimethoxyphosphonium bromide by tribromomethyl carbanion-derived bromide would necessitate the generation of dibromocarbene. This carbene would be expected to react with trimethyl phosphite to form an ylide, in analogy to the reaction of trialkyl- and triarylphosphines with tetrahalomethanes

(19) Modified workup procedures are necessary to obtain high yields of the more water soluble dimethyl phosphate esters of low molecular weight alcohols, as well as for acid- or base sensitive products; see the Experimental Section for representative examples.

(20) To confirm this selectivity in the case of 1,2-decanediol the phosphate ester was acetylated with acetyl chloride, resulting in a downfield shift of the methine proton.

(21) Machida, Y.; Nomoto, S.; Saito, I. *Synth. Commun.* **1979**, *9*, 97.

(22) (a) Atherton, F. R.; Openshaw, H. T.; Todd, A. R. *J. Chem. Soc.* **1945**, 660. (b) Atherton, F. R.; Todd, A. R. *J. Chem. Soc.* **1947**, 674.

(23) (a) Georgiev, E. M.; Kaneti, J.; Troev, K.; Roundhill, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 10964. (b) Steinberg, G. M. *J. Org. Chem.* **1950**, *15*, 637.

in the absence of alcohols.[24] This possibility may be excluded on the basis of the stoichiometry of the reaction (only 1 equiv of phosphite is necessary) and on the basis of our examination of the ^{31}P NMR spectrum of the phosphorylation reaction of 2-phenylethyl alcohol performed in d_5-pyridine; the only phosphorus species present in any significant amounts were the product and residual trimethyl phosphite. In the absence of the alcohol substrate the reaction of trimethyl phosphite with carbon tetrabromide in d_5-pyridine led to a complex mixture (>10 phosphorus-containing species). The most likely candidate for a nucleophile would, of course, be the pyridine solvent. However, if pyridine were to play this role its replacement by the sterically hindered 2,6-dimethylpyridine should drastically reduce the rate of dimethyl bromophosphate production,[25] and thus of phosphorylation. In fact, the rate of the phosphorylation reaction is slightly faster in 2,6-dimethylpyridine.[26]

A last feature of this reaction which lends support to the mechanism shown in pathway I, and which weighs against the intermediacy of dimethyl bromophosphate, is the formation of mixed esters of the type $(RO)_2P(O)$-OCH_3 (and others) in many solvent systems. The formation of these mixed esters is readily accommodated by the mechanism of pathway I. However, if dimethyl bromophosphate were the active phosphorylating agent, only alkyl dimethyl phosphate esters should be produced, since alcohol exchange in trialkyl phosphite[27] and trialkyl phosphate[28] esters is known to be quite slow in the absence of acidic or basic catalysts.[29] In fact, in all except pyridine-derived solvents which we and others have examined, formation of mixtures of esters is the rule rather than the exception (see above). While it is *possible* that the reaction follows an entirely different course in pyridine than in other solvents, in the absence of compelling evidence to the contrary we believe that it is reasonable to assume that the mechanism of our phosphorylation reaction is as outlined in pathway I, and that any involvement of dimethyl bromophosphate as a phosphorylating species constitutes at most a minor pathway. The *N*-methylpyridinium bromide formed in the reaction presumably arises from alkylation of pyridine by the methyl bromide generated in the cleavage reaction of the alkoxy trimethoxyphosphonium salt.

Conclusion

The reaction of alcohols with trimethyl phosphite and carbon tetrabromide in pyridine provides the corresponding dimethyl phosphate esters in high yields. The extremely mild reaction conditions employed and the low cost of the required reagents make this a useful method for the preparation of a wide variety of alkyl and aryl dimethyl phosphate esters. The demonstrated selectivity of iodotrimethylsilane in the cleavage of the methyl groups rather than the substituted ethyl group of 2-phenylethyl dimethylphosphate suggests that the phosphorylation/deprotection procedure need not be restricted to a structurally limited class of substrates.

Experimental Section

General. ^1H NMR spectra were obtained at 275 or 400 MHz. ^{13}C NMR spectra were obtained at 68.8 MHz. Chemical shifts were referenced to the residual solvent peak. ^{31}P NMR spectra were obtained at 162.1 MHz with the chemical shifts referenced to phosphoric acid as an external reference. All reactions were performed under nitrogen atmosphere, and standard precautions to avoid moisture were taken. THF and ether were distilled under nitrogen atmosphere from potassium/benzophenone. Acetonitrile, pyridine, 2,6-lutidine, and methylene chloride were distilled over calcium hydride. Dimethylformamide was distilled from calcium oxide. 2-Phenylethanol, cyclohexanol, and crotyl alcohol (obtained from Aldrich Chemical Co. as a mixture of isomers) were distilled over calcium hydride. Cholesterol was recrystallized from warm ethyl acetate and dried thoroughly under high vacuum before being used. Isopropylidineadenosine obtained from Aldrich Chemical Co. was used without any further purification. Flash chromatography refers to the method of Still and coworkers.[30] Purifications by radial chromatography were accomplished with a Harrison Research Model 7924T Chromatotron using silica gel plates of 1, 2, or 4 mm thickness. R_f values reported are for 0.25 mm EM Science silica gel 60 TLC plates.

General Phosphorylation Procedure: Phosphoric Acid, 2-Phenylethyl Dimethyl Ester. 2-Phenylethanol (0.122 g, 1 mmol) and carbon tetrabromide (0.365 g, 1.1 mmol) were added to a nitrogen purged vial equipped with a magnetic stirring bar and a rubber septum. After addition of pyridine (0.5 mL) the resulting solution was cooled to 0 °C and trimethyl phosphite (0.15 mL, 1.25 mmol) was added to it in a dropwise manner. Upon completion of the addition of trimethyl phosphite the ice bath was removed and the reaction mixture was allowed to stir at room temperature. After 2.5 h the reaction mixture was transferred into a separatory funnel, diluted with ether (5 mL), and then washed with 5% HCl (2 × 1.5 mL), saturated aqueous $NaHCO_3$ (1 × 1.5 mL), and brine (1 × 1.5 mL). Each of the aqueous layers was collected in a separate flask, and any remaining traces of product from aqueous layers were individually extracted back into the organic phase using ether (3 × 5 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to a yellow oil which was purified by flash chromatography to give 0.225 g (98%) of the desired product as an oil (R_f 0.3 with 50% ethyl acetate/petroleum ether). ^1H NMR indicated a purity of >99%. ^1H NMR ($CDCl_3$): δ 7.3–7.2 (m, 5H), 4.2–4.1 (dt, $J_{HH} = J_{PH} = 7.2$ Hz, 2H), 3.58 (d, $^3J_{PH} = 11.2$ Hz, 6H), 3.05 (t, $J_{HH} = 7.0$ Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 136.9, 128.8, 128.3, 126.5, 67.9 (d, $^2J_{PC} = 5.5$ Hz), 53.9 (d, $^2J_{PC} = 5.5$ Hz), 36.5 (d, $^3J_{PC} = 5.5$ Hz). ^{31}P NMR ($CDCl_3$): δ 1.70. HRMS(FAB): (M + 1) calculated for $C_{10}H_{16}O_4P$ 231.0786, found 231.07895.

With the exceptions noted, the remainder of the dimethyl phosphate esters were prepared by analogous procedures. Reaction times after removal of the cooling bath are given in Table 1.

Phosphoric Acid, Cyclohexyl Dimethyl Ester. From cyclohexanol (0.10 g, 1 mmol) was obtained cyclohexyl dimethyl phosphate (0.180 g, 86%, R_f 0.3 with 50% ethyl acetate/petroleum ether). ^1H NMR ($CDCl_3$): δ 4.45–4.35 (m, 1H), 3.75 (d, $^3J_{PH} = 11.2$ Hz, 6H), 2.0–1.1 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 77.3 (d, $^2J_{PC} = 5.5$ Hz), 53.8 (d, $^2J_{PC} = 5.5$ Hz), 33.1 (d, $^3J_{PC} = 4.4$ Hz), 24.9, 23.3. ^{31}P NMR ($CDCl_3$): δ 1.15. HRMS (FAB): (M + 1) calculated for $C_8H_{18}O_4P_1$ 209.0943, found 209.09405 (100%).

(24) For a discussion of reactions of this type, see Castro, B. R. *Org. Reac.* **1983**, *29* 1.

(25) (a) Brown, H. C.; Gintis, D.; Podall, H. *J. Am. Chem. Soc.* **1956**, *78*, 5375. (b) Brown, H. C.; Cahn, A. *J. Am. Chem. Soc.* **1954**, *77*, 1715.

(26) The increase in rate is a qualitative estimate based on monitoring the reaction of 2-phenylethyl alcohol by thin layer chromatography. The number and quantities of side products formed seem to be slightly greater than when pyridine is employed; as a result, the latter solvent is recommended.

(27) Hoffmann, R. W.; Ess, R. J.; Usinger, R. P. *J. Am. Chem. Soc.* **1956**, *78*, 5817.

(28) Rueggeberg, W. H. C.; Chernack, J. *J. Am. Chem. Soc.* **1948**, *70*, 1802.

(29) We have established that pyridine is insufficiently basic to catalyze this process; a mixture of trimethyl phosphite and 2-phenylethyl alcohol in d_5-pyridine showed no evidence of exchange after 36 h at room temperature. In contrast, exchange in $CDCl_3$ is fairly rapid unless the solvent is treated (filtration through K_2CO_3) to remove acidic impurities.

(30) Still W. C.; Kahn, M.; Mitra A. *J. Org. Chem.* **1978**, *43*, 2923.

(31) Due to extensive overlap between the spectra of the two isomers only data for the major isomer is reported.

Phosphoric Acid, 2-Butenyl Dimethyl Ester. From a roughly 6:1 *E*/*Z* isomeric mixture of crotyl alcohols (0.0724 g, 1 mmol) was obtained a roughly 6:1 ratio of the corresponding dimethylphosphate esters (0.153 g, 85%, R_f 0.3 with 50% ethyl acetate/petroleum ether).[31] ^{1}H NMR ($CDCl_3$): δ 5.8–5.6 (m, 2H), 4.44 (dd, J = 8.6, 7.3 Hz, 2H), 3.73 (d, $^3J_{PH}$ = 11.2 Hz, 6H), 1.70 (d, J_{HH} = 6.6 Hz, 3H). ^{13}C NMR($CDCl_3$): δ 131, 125.4 (d,$^3J_{PC}$ = 5.5 Hz), 68.2 (d, $^2J_{PC}$ = 5.5 Hz), 54.1 (d, $^2J_{PC}$ = 6.6 Hz), 17.6. ^{31}P NMR($CDCL_3$): δ 0.38. HRMS (EI): *m*/*e* calculated for $C_6H_{13}O_4P$ 180.0551, found *m*/*e* 180.0554.

Cholest-5-en-3α-ol, dimethylphosphate ester. The general procedure was applied to cholesterol (0.387 g, 1 mmol) in an increased volume of pyridine (1.0 mL) and the reaction mixture worked up with ethyl acetate to yield the dimethyl phosphate ester (0.426 g, 86%, mp 117–119 °C, R_f 0.4 with 50% ethyl acetate/petroleum ether). ^{1}H NMR ($CDCl_3$): δ 5.28 (d, J_{HH} = 6.8 Hz, 1H), 4.13 (m, 1H), 3.64 (d, $^3J_{PH}$ = 11.2 Hz, 6H) 2.32 (d, J_{HH} = 7.3 Hz, 2H), 2–0.9 (m, 38H), 0.56 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 139.1, 122.9, 78.3 (d, $^2J_{PC}$ = 6.6 Hz), 56.5, 56, 53.9 (d, $^2J_{PC}$ = 5.5 Hz), 49.8, 42.2, 39.8 (d, $^3J_{PC}$ = 4.4 Hz), 39.6, 39.4, 36.7, 36.2, 36, 35.6, 31.76, 31.72, 29.48, 29.41, 28.12, 27.89, 24.17, 23.72, 22.72, 22.46, 20.95, 19.16, 18.61, 11.75. ^{31}P NMR ($CDCl_3$): δ 0.98. HRMS (FAB): (M + Na) calculated for $C_{29}H_{51}O_4PNa$ 517.3423, found $(M + Na)^+$ = 517.3410.

2′,3′-Isopropylidineadenosine, 5′-(Dimethyl Phosphate Ester). Application of the general procedure to 2′,3′-isopropylidineadenosine (0.155 g, 0.5 mmol) in pyridine (1.5 mL) was followed by dilution with chloroform (10 mL) and extraction with 5% HCl (2 × 3 mL), saturated $NaHCO_3$ (1 × 3 mL) and brine (1 × 3 mL). After back extraction of the aqueous layers (3 × 10 mL each), the combined organics were dried, concentrated, and purified as usual to give the 5′-(dimethyl phosphate ester) as a white solid (0.157 g, 78%, mp 156–157 °C, R_f 0.5 with 30% absolute ethanol/ethyl acetate). ^{1}H NMR ($CDCl_3$): δ 8.4 (s, 1H), 7.95 (s, 1H), 6.15 (d, J = 2.64 Hz, 1H), 5.65 (bs, 2H), 5.43 (dd, 1H), 5.11 (dd, J = 3.3, 6.6 Hz, 1H), 4.48 (m, 1H), 4.29–4.20 (m, 2H), 3.73 (d, $^3J_{PH}$ = 4.61 Hz, 3H), 3.69 (d, $^3J_{PH}$ = 4.62 Hz, 3H), 1.63 (s, 3H), 1.4 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 155.9, 153.1, 149.0, 139.4, 119.9, 114.3, 90.7, 85.25 (d, $^3J_{PC}$ = 7.8 Hz), 84.1, 81.2, 66.75 (d, $^2J_{PC}$ = 5.5 Hz), 54.33 (d, $^2J_{PC}$ = 5.5 Hz), 26.9, 25.2. ^{31}P NMR($CDCl_3$): δ 1.75. HRMS (EI): *m*/*e* calculated for $C_{15}H_{22}N_5O_7P$ 415.1257, found 415.1243.

Phosphoric Acid, 2-(4, 4′-Dimethoxytrityloxy)-1-phenylethyl Dimethyl Ester. Application of the general procedure to 2-(4,4′-dimethoxytrityloxy)-1-phenylethanol (0.044 g, 0.1 mmol) in pyridine (0.1 mL) was followed by dilution with chloroform (10 mL). After washing the solution with phosphate buffer (3 × 2 mL of 0.2 M solution, pH = 8) the aqueous washes were back-extracted with chloroform (3 × 10 mL). The combined organics were dried over anhydrous sodium sulfate and filtered, and the solvent was removed by rotary evaporation. Purification by chromatography on a basic alumina column (Brockmann I, standard grade, ~150 mesh, 58 Å) afforded the product as a slightly yellowish white gelatinous solid (0.0406 g, 74%, R_f 0.45 with 50% ethyl acetate/petroleum ether). Note: To obtain pure product, it is essential to avoid any exposure to even mild acid.

^{1}H NMR ($CDCl_3$): δ 7.4–7.11 (m, 14H), 6.87–6.7 (m, 4H), 5.4 (ddd, J = 4.0, 7.8, 11.2 Hz, 1H), 3.7 (s, 6H), 3.58 (d, $^3J_{PH}$ = 11.1 Hz, 3H), 3.49 (d, $^3J_{PH}$ = 11.1 Hz, 3H), 3.41 (dd, J = 7.8, 10.3 Hz, 1H), 3.18 (dd, 1H). ^{13}C NMR ($CDCl_3$): δ 158.4, 144.6, 137.9, 135.8, 130.1, 128.5, 128.4, 128.2, 127.7, 126.7, 113.1, 86.4, 79.78 (d, J_{PC} = 5.5 Hz), 67.4 (d, J_{PC} = 6.7Hz), 55.2, 54.23 (d, $^2J_{PC}$ = 5.5 Hz), δ 53.99 (d, $^2J_{PH}$ = 5.5 Hz). ^{31}P NMR ($CDCl_3$): δ 1.51. HRMS (EI): *m*/*e* calculated for $C_{31}H_{33}O_7P_1$ 548.1964, found *m*/*e* 548.19686.

***N*-(Carbobenzyloxy)-L-tyrosine *p*-Nitrophenyl Ester, *O*-Dimethyl Phosphate Ester).** Application of the general procedure to *N*-Cbz-L-tyrosine *p*-nitrophenyl ester (0.044 g, 0.1 mmol) in pyridine (0.1 mL) was followed by dilution with chloroform (10 mL). After washing with citric acid–sodium citrate buffer (3 × 2 mL 0.1 M solution, pH = 4) the aqueous layers were combined and back-extracted with chloroform (3 × 10 mL). The combined organic layers were dried, filtered, and concentrated under reduced pressure, and the crude product was purified by flash chromatography to give the product as a white gelatinous solid (0.045 g, 82%, R_f 0.2 with 50% ethyl acetate/petroleum ether). ^{1}H NMR ($CDCl_3$): δ 8.17–8.14 (d, J = 9.2 Hz, 2H), 7.2–7 (m, 11H), 5.35 (bd, 1H), 5.05 (s, 2H), 4.75 (bdd, 1H), 3.78 (d, $^3J_{PH}$ = 11.2 Hz, 6H), 3.14 (bd, J = 5.9 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 169.4, 155.7, 154.7, 150.1 (d, $^2J_{PC}$ = 5.8 Hz), 145.6, 135.9, 132.0, 130.7, 128.6, 128.4, 128.2, 125.3, 122.2, 120.4, 67.4, 55.05 (d, $^2J_{PC}$ = 17.6 Hz), 37.4. ^{31} P NMR ($CDCl3$): δ –3.43. HRMS (FAB): $(M+H)^+$ calculated for $C_{25}H_{26}N_2O_{10}P$ 545.1325, found 545.1341.

Phosphoric Acid, 2-Hydroxydodecyl Dimethyl Ester. Dimethylphosphorylation of 1,2-dodecanediol (0.202 g, 1 mmol) as for 2-(4,4′-dimethoxytrityloxy)-1-phenylethanol and purification by radial chromatography gave the pure product as an oil (0.216 g, 70%, R_f 0.45 with 50% ethyl acetate/petroleum ether). ^{1}H NMR($CDCl_3$): δ 4.08 (ddd, J = 2.7, 6.0, 16.5 Hz) 1H), 3.9 (m, 2H), 3.80 (d, $^3J_{PH}$ = 11.2 Hz, 6H), 2.89 (m, 1H), 1.47–1.26 (2 bs, 18H), 0.87 (t, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 72.1 (d, $^3J_{PC}$ = 5.5 Hz), 70.4 (d, $^2J_{PC}$ = 5.5 Hz), 54.4 (d, $^2J_{PC}$ = 5.5 Hz), 32.6, 31.8, 29.5, 29.3, 25.3, 22.6, 14.0. ^{31}P NMR ($CDCl_3$): δ 2.75. HRMS (EI): $(M + H)^+$ calculated for $C_{14}H_{32}O_5P$ 311.1987, found 311.19953.

Phosphoric Acid, 2-Acetoxydodecyl Dimethyl Ester. Acetyl chloride (14 μL, 0.2 mmol) was added to an ice cold solution of phosphoric acid, 2-hydroxydodecyl dimethyl ester (0.031 g, 0.1 mmol) in pyridine (0.5 mL). After removal of the ice bath and stirring 40 min the mixture was diluted with chloroform (10 mL) and washed (3 × 4 mL 0.2 M pH 7 phosphate buffer). After back extraction of the aqueous (3 × 15 mL) the combined organics were dried (Na_2SO_4), filtered, and concentrated by rotary evaporation. Flash chromatography yielded the acetate ester (27.9 mg, 80%, R_f 0.3 with 50% ethyl acetate/petroleum ether). ^{1}H NMR ($CDCl_3$): δ 5.05 (m, 1H), 4.12 (m, 2H), 3.78 (d, $^3J_{PH}$ = 3 Hz, 3H), 3.76 (d, $^3J_{PH}$ = 3.0 Hz, 3H), 2.08 (s, 3H), 1.58 (m, 2H), 1.25 (m, 16H), 0.88 (t, J_{HH} = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 170.52, 72.1 (d, J_{PC} = 7.8 Hz), 68.18 (d, J_{PC} = 5.5 Hz), 54.35 (d, J_{PC} = 6.6 Hz), 31.86, 30.19, 29.54, 29.49, 29.40, 29.28, 25.03, 22.65, 21.06, 14.09. ^{31}P NMR ($CDCl_3$): δ 1.92. HRMS (EI): $(M+H)^+$ calculated for $C_{16}H_{33}O_6P$ 353.2093, found 353.20902.

Phosphoric Acid, 2-Hydroxy-2-Phenylethyl Dimethyl Ester. From 1,2-phenylethanediol (0.138 g, 1 mmol) was obtained the dimethyl phosphate ester (0.177 g, 72%, R_f 0.25 with 50% ethyl acetate/petroleum ether). ^{1}H NMR ($CDCl_3$): δ 7.39–7.27 (m, 5H), 4.94 (dd, J_{HH} = 3.6, 7.3 Hz, 1H), 4.14 (m, 2H), 3.72 (d, $^3J_{PH}$ = 11.2 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 139.4, 128.3, 127.9, 126.2, 72.58 (d, J_{PC} = 5.5 Hz), 72.39 (d, J_{PC} = 5.5 Hz), 54.35 (d, J_{PC} = 5.5 Hz). ^{31}P NMR ($CDCl_3$): δ 2.43. HRMS (EI): *m*/*e* calculated for $C_{10}H_{15}O_5P_1$ 246.0657, found *m*/*e* 246.06547.

2-Phenylethyl Phosphate. Chlorotrimethylsilane (6.04 mL, 47.6 mmol) was added dropwise to a mixture of 2-phenylethyl dimethyl phosphate (4.56 g, 19.8 mmol) and sodium iodide (7.13 g, 47.6 mmol) in acetonitrile (19 mL). After stirring 2 h protected from light the mixture was centrifuged and the precipitated sodium chloride washed with methylene chloride (3 × 10 mL). Evaporation of the combined supernatents was followed by redissolution in methylene chloride (10 mL) and extraction with water (3 × 30 mL). Evaporation of the aqueous extracts under reduced pressure afforded 2-phenylethyl phosphate (3.18 g, 79%). ^{31}P NMR indicated less than 2% phosphorus-containing impurities, while integration of the acidic OH and methylene resonances indicated >95% purity. ^{1}H NMR ($CDCl_3$): δ 11.03 (bs, 2H), 7.4–7.0 (m, 5H), 4.1 (bs, 2H), 2.85 (bs, 2H). ^{13}C NMR ($CDCl_3$): δ 136.5, 128.8, 128.3, 126.4, 68.3, 36.1. ^{31}P NMR ($CDCl_3$): δ 1.09.

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Supplementary Material Available: Copies of ^{1}H, ^{13}C, and ^{31}P NMR spectra of compounds listed in the Experimental Section (31 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.

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