Photoremovable Protecting Groups for Phosphorylation of Chiral Alcohols. Asymmetric Synthesis of Phosphotriesters of (−)-3′,5′-Dimethoxybenzoin

Michael C. Pirrung* and Steven W. Shuey

Department of Chemistry, P. M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27708-0346

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Procedures have been developed for the preparation of dimethoxybenzoinyl (DMB) phosphate triesters that can be deprotected photochemically. These compounds can be useful in light-directed synthesis and caging. The photochemistry of a wide variety of fluorine-, oxygen-, and nitrogen-substituted benzoin acetates was examined to determine the substitution pattern in the nonacylated aromatic ring producing optimum chemical yields. Two groups, 2′,3′-dimethoxybenzoin and 3′,5′-dimethoxybenzoin, were found to give the highest yields of the benzofuran product and were further developed for the photochemical deprotection of phosphate esters. These reactions could not be quenched, suggesting a singlet photosolvolysis mechanism. An asymmetric synthesis of 3′,5′-dimethoxybenzoin via the benzaldehyde cyanohydrin was developed that minimizes the number of diastereomers formed in the phosphorylation of chiral alcohols. A phosphoramidite reagent for the derivatization of alcohols was prepared and used to produce scalemic dimethoxybenzoinyl phosphate esters from pantolactone and glycerol, serine, and tyrosine derivatives. These compounds were deprotected photochemically to produce the phosphodiesters in high yield.

Introduction

Photochemically-removable groups have several applications in bioorganic chemistry. Besides providing deprotection that can be accomplished under conditions that leave most other protecting groups untouched,[1] they can be used in the technique of caging,[2] wherein a biological molecule is rendered both inactive and membrane-permeable by the protecting group. Once located inside a cell or an enzyme active site,[3] the protecting group can be released on a time scale much faster than that of the biological or enzymatic process, permitting the study of the time evolution of the phenomena. Photoremovable groups are also key to the novel technique of light-directed synthesis, whereby the preparation of large arrays consisting of thousands of biopolymer sequences can be accomplished.[4]

The experiments described here were aimed at the development of groups giving the highest efficiency in the derivatization of alcohols with phosphate triesters and their photochemical deprotection. Previous reports of such groups have included the well-known *o*-nitrobenzyl derivatives that have been used to protect 5′-mononucleotides[5] and 5′-trinucleotides.[6] Based on analogy to the earlier work of Sheehan concerning benzoin and 3′,5′-dimethoxybenzoin (DMB) esters as photoremovable carboxylate protecting groups,[7] Givens provided an initial report of photoremovable benzoinyl phosphotriester protecting groups and subsequently reviewed the field.[8] More recently, Givens has investigated the mechanism of the photochemical cleavage of benzoin phosphate derivatives and has "caged" cyclic AMP with a benzoin ester.[9] Baldwin has used benzoin and 3′,5′-DMB for the photolabile protection of inorganic phosphate,[10] and Iwamura has used pyrenemethanol for photolabile protection of diethyl phosphate.[11] Corrie and Trentham studied the release of phosphate from 3′,5′-DMB monophosphate and other benzoin monophosphates by flash photolysis and reported in an abstract the caging of nucleotides with benzoins.[12] They had significant difficulty in preparing their derivatives. It is reasonable that the observations of Sheehan are beginning to be more extensively exploited, since he reported that deprotection of 3′,5′-DMB carboxylate esters occurs at 365 nm with a high quantum yield (0.64), and the only byproduct of the deprotection is the relatively inert 2-phenyl-5,7-dimethoxybenzofuran. This is in contrast to the *o*-nitrobenzyl groups, which have widely varying quantum yields depending on the identity of the substituent at the benzylic position and produce a nitrosoaldehyde byproduct that can be toxic in biological systems and is reactive with many functional groups. Below are listed examples of phosphate mono- or triesters of these groups, the quantum yields of deprotection, and references.

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(1) Pillai, V. N. R. In *Organic Photochemistry*; Padwa, A., Ed.; Marcel Dekker, Inc.: New York, 1987; Vol. 9, pp 225–323; *Synthesis* **1980**, 1.

(2) Adams, S. R.; Kao, J. P. Y.; Tsien, R. Y. *J. Am. Chem. Soc.* **1989**, *111*, 7957–7968.

(3) Schlichting, I.; Rapp, G.; John, J.; Wittinghoffer, A.; Pai, E. F.; Goody, R. S. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 7687–7690.

(4) Fodor, S. P. A.; Read, J. L.; Pirrung, M. C.; Stryer, L.; Liu, A. T.; Solas, D. *Science* **1991**, *251*, 767.

(5) Rubinstein, M.; Amit, B.; Patchornik, A. *Tetrahedron Lett.* **1975**, 1445–48.

(6) Walker, J. W.; Reid, G. P.; McCray, J. A.; Trentham, D. R. *J. Am. Chem. Soc.* **1988**, *110*, 7170–7177. Wootton, J. F.; Trentham, D. R. *Photochemical Probes in Biochemistry*; Nielsen, P. E., Ed.; Kluwer: Dordrecht, 1989; pp 277–296.

(7) Sheehan, J. L.; Wilson, R. M.; Oxford, A. W. *J. Am. Chem. Soc.* **1971**, *93*, 7222–7227.

(8) Givens, R. S.; Matuszewski, B. *J. Am. Chem. Soc.* **1984**, *106*, 6860–6861. Givens, R. S.; Kueper, L. W., III. *Chem. Rev.* **1993**, *93*, 55–66.

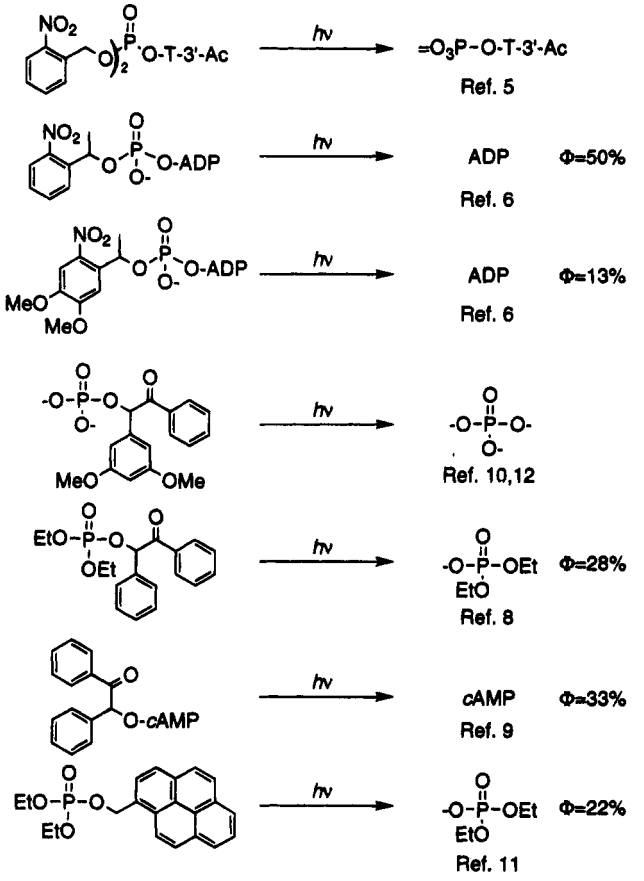
(9) Givens, R. S.; Athey, P. S.; Kueper, L. W., III; Matuszewski, B.; Xue, J.-y. *J. Am. Chem. Soc.* **1992**, *114*, 8708–8710. Givens, R. S.; Athey, P. S.; Kueper, L. W., III; Matuszewski, B.; Xue, J.-y.; Fister, T. *J. Am. Chem. Soc.* **1993**, *115*, 6001–6012.

(10) Baldwin, J. E.; McConnaughie, A. W.; Maloney, M. G.; Pratt, A. J.; Shim, S. B. *Tetrahedron* **1990**, *46*, 6879–6884.

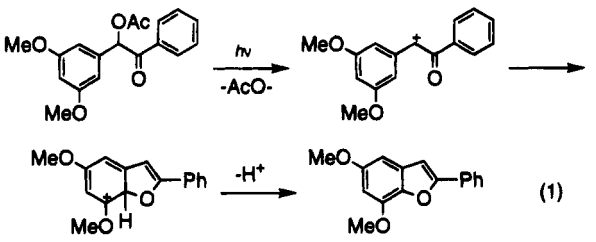
(11) Furuta, T.; Torigai, H.; Osawa, T.; Iwamura, M. *Chem. Lett.* **1993**, 1179–1182.

(12) Corrie, J. E. T.; Trentham, D. R. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2409–2417. Corrie, J. E. T.; Trentham, D. R. *Biophys. J.* **1992**, *61*, A295.

0022-3263/94/1959-3890$04.50/0



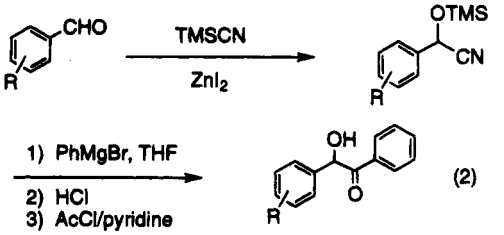
The mechanism of the photochemical lysis of benzoin esters has been the subject of proposals from a number of laboratories. Sheehan had postulated a rather unlikely mechanism for deprotection of benzoin carboxylates involving Paterno–Buchi addition of the n,π^* excited state of the benzoyl carbonyl to the substituted aromatic ring and subsequent fragmentation. Our work was initiated based on a hypothesis[13] that the reaction proceeds by photosolvolysis (eq 1). Support for this idea



came from Sheehan's report that 3′,5′-dimethoxy substitution on the benzoin results in a superior reaction, similar to the results of Zimmerman on the electronic influence of *meta* donor substituents on benzene excited states.[14] Solvolysis of benzylic derivatives is promoted by *m*-methoxy groups, opposite to the situation in the ground state where *ortho* and *para* donors are most effective. However, Wan,[15] in a reinvestigation of the work of Zimmerman, concluded that while *meta* groups are indeed superior to *para* groups in promoting excited-state solvolysis, *ortho* groups are even more powerful than *meta*. This report provided the impetus for a study of substituent effects in benzoin ester photochemistry as well as efforts to develop a new class of superior photoremovable groups. This mechanism requires a relatively good leaving group, so the fact that the benzoins themselves do not form benzofurans but rather undergo α-cleavage processes also supports photosolvolysis. It would be reasonable that the benzylic α-ketocation formed by photosolvolysis of a benzoin ester undergoes ring closure and proton loss, which can be viewed as an intramolecular electrophilic aromatic substitution, to give the observed products. The electrophilic addition step would also be favored by *meta* donor groups in the reactants, since they are *ortho/para* to the site of electrophilic attack in the cationic intermediate. Alternatively, this intermediate can be viewed as a benzo-fused oxapentadienyl cation which undergoes electrocyclization to the benzofuranyl cation. Precedent for the ring closure step comes from a study in which *p*-anisoyl(bis(anisyl)-carbenium) cyclizes to the corresponding benzofuran.[16] While this work was underway, Givens studied the photochemical deprotection of benzoin esters in detail and proposed a similar but somewhat different mechanism that will be discussed below.[9]

Results

A first goal of our study was to examine a variety of substituted benzoin esters to evaluate the influence of substitution on their photodeprotection, with the highest priority being placed on isolated yields since this is crucial for synthetic purposes. Our mechanistic hypothesis suggested that substituents should influence the deprotection of carboxylic and phosphate esters in a similar way, so benzoinyl acetates were prepared. The route shown in eq 2 is specifically suited to the generation



of unsymmetrical benzoins,[17] which were desired targets because Sheehan had shown that electron-donating substituents in the "benzoyl" ring were deleterious for the deprotection of benzoin esters. (Trimethylsilyl)cyanohydrins were prepared from commercially-available substituted benzaldehydes via the procedure of Evans[18] and converted by the addition of phenyl Grignard into the benzoins. Acetylation with acetyl chloride/pyridine provided test substrates for the influence of aromatic substituents. Reactions were conducted in benzene with irradiation by 350-nm lamps in a Rayonet reactor, and conversions (listed in Table 1) were evaluated by isolation after 3 h of the highly fluorescent phenylbenzofuran products using chromatography. The products are stable under the irradiation/workup conditions, and the starting

(13) Pirrung, M. C; Shuey, S. W. 4th DOE Genome Meeting, Santa Fe, Feb 12, 1993.
(14) Zimmerman, H. E.; Sandel, V. R. *J. Am. Chem. Soc.* **1963**, *85*, 915. Zimmerman, H. E.; Somasekhara, S. *Ibid.* **1963**, *85*, 922.
(15) Wan, P.; Chak, B; Carrier, L. *Tetrahedron Lett.* **1986**, *27*, 2937–40. Wan, P.; Chak, B. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1751–56.
(16) Takeuchi, K.; Kitigawa, T.; Okamoto, K. *J. Chem. Soc., Chem. Commun* **1983**, 7.
(17) Jackson, W. R.; Jacobs, H. A.; Jayatilake, G. S.; Matthews, B. R.; Watson, K. G. *Aust. J. Chem.* **1990**, *43*, 2045.
(18) Evans, D. A.; Truesdale, L. K.; Carroll, G. L. *J. Chem. Soc., Chem. Commun.* **1973**, 55.

Table 1. Conversion (As Reflected in Isolated Yield) to Substituted Benzofurans in the Irradiation of Substituted Benzoinyl Acetates[a]

benzoin acetate	% conversion
3′,5′-dimethoxy	93[b]
3′-methoxy	82[b]
2′-methoxy	2
2′,3′-dimethoxy	87
2′,3′-(methylenedioxy)	36
2′,5′-dimethoxy	0
3′,5′-difluoro	31
3′-fluoro	41
2′-fluoro	3
2′,3′-difluoro	21
3′-(dimethylamino)	32

[a] At the concentrations used in this experiment (4 mM), the products are stable under the irradiation conditions. [b] Sheehan reports 93.5 and 88% for these, respectively, and 20% for benzoinyl acetate itself.

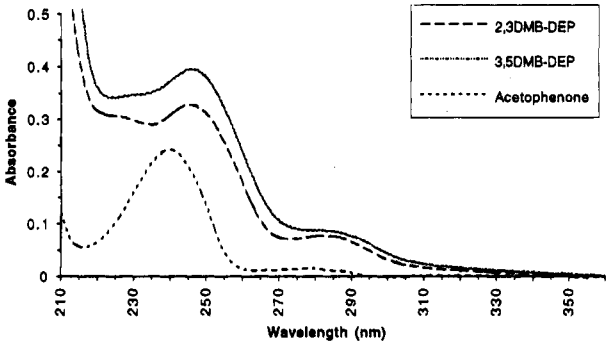


Figure 1. Absorption spectra of dimethoxybenzoinyl diethyl phosphates and acetophenone: [**2**] = 2.94 × 10^{-5} M; [**4**] = 2.94 × 10^{-5} M; [PhAc] = 1.03 × 10^{-5} M.

benzoin esters could be recovered from reactions where high conversions were not achieved.

With these results in hand, the 3′,5′-dimethoxy- and 2′,3′-dimethoxybenzoins were chosen for further evaluation. Each was converted to its diethyl phosphate (**2** and **4**) using chloro phosphite chemistry.[19] The absorption spectra of these compounds are shown in Figure 1, and for comparison the absorption spectrum of acetophenone is included. These 2′,3′- and 3′,5′-DMB diethyl phosphates were irradiated in a Rayonet reactor at 350 nm for 30 min (eqs 3 and 4). Proton NMR analysis showed only the benzofurans and diethyl phosphate. Kinetic study of the two phosphate esters in comparison to 3′,5′-dimethoxybenzoinyl acetate showed the following half-lives: 3′,5′-DMBO-P (**2**), 3.78 min; 2′,3′-DMBO-P (**4**), 4.18 min; 3′,5′-DMBO-Ac, 4.18 min. Analysis of the phosphorus-containing reaction products in ^{31}P NMR by integration against a trimethyl phosphite reference shows both protecting groups release diethyl phosphate quantitatively. The decision to develop the 3′,5′-dimethoxybenzoin group for photolabile phosphate protection was made based on its crystallinity and slightly greater rate. However, the optically-pure benzoin is an oil (*vide infra*). One of the virtues of the benzoin protecting groups generally is the highly fluorescent 2-phenylbenzofuran byproduct, making it possible to measure the yield of a photochemical deprotection of a DMB group by sensitive optical methods, analogous to the use of the dimethoxytrityl cation absorbance in DNA synthesis. The

(19) Letsinger, R. L.; Finnan, J. L.; Heavner, G. A.; Lunsford, W. B. *J. Am. Chem. Soc.* **1975**, *97*, 3278.

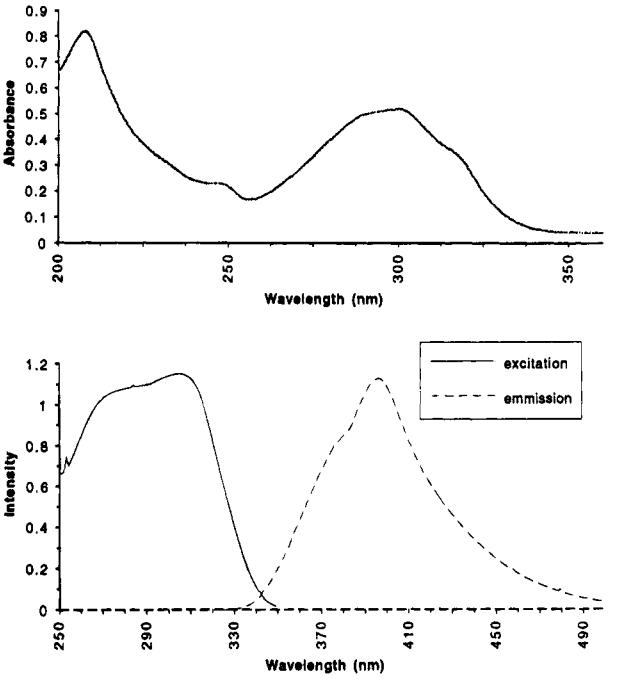
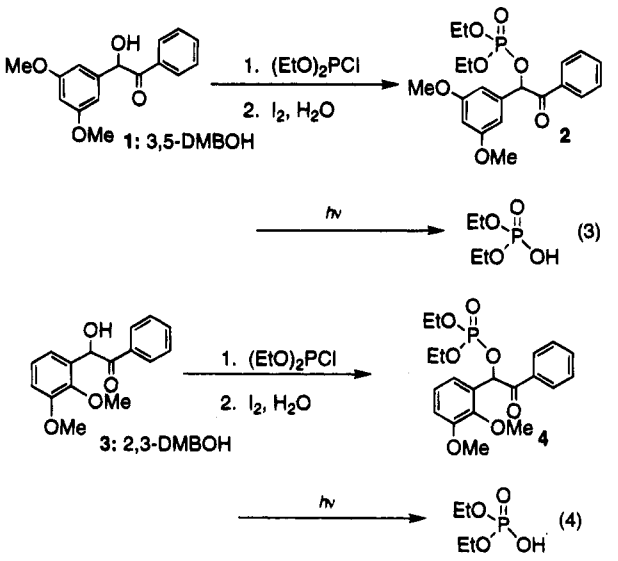


Figure 2. Absorption and fluorescence (emission and excitation) spectra of 2-phenyl-5,7-dimethoxybenzofuran at 1.82 × 10^{-5} M and 3.65 × 10^{-5} M concentration, respectively. Excitation maximum (396-nm emisson) = 310 nm. Emission maximum (310-nm excitation) = 396.

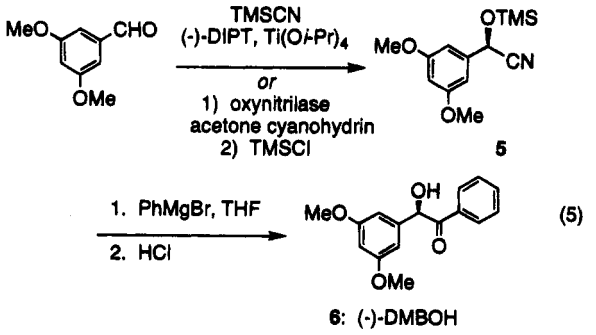


absorbance and fluorescence spectra of 2-phenyl-5,7-dimethoxybenzofuran are shown in Figure 2.

The lack of meaningful mechanistic comparisons between different benzoin esters prompted a study of 3′,5′-DMBO-Ac and 3′,5′-DMBO-P (**2**). The photodeprotection of neither is quenched by 30 mM methylnaphthalene, a concentration that should (at the diffusion-controlled rate) quench a 3-ns lifetime triplet state (the τ reported by Givens for benzoinyl phosphate[9]) by 50%. Even at concentrations of naphthalene as high as 0.15 M, no quenching is observed. These data suggest that the photodeprotections of *both* DMB esters are singlet reactions.

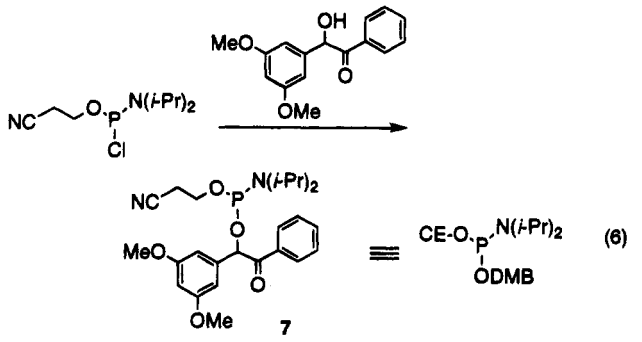
One matter that has heretofore been unaddressed in the preparation of phosphate protecting groups derived from benzoins is chirality. Since their phosphotriesters are stereogenic at phosphorus and in the benzoin, they

can exist as mixtures of diastereomers. While for some applications this may have no great consequence, for others it causes difficulties in the chemical characterization of the materials. When these esters are derived from alcohols that themselves bear stereogenic centers, a complicated mixture results. Therefore, for the widest possible application of these groups, the benzoin should be a single enantiomer. An asymmetric synthesis of the desired benzoin has been accomplished by two routes via the cyanohydrin. Using the asymmetric synthesis method of Oguni,[20] the (trimethylsilyl)cyanohydrin **5** can be prepared directly (eq 5). Alternatively, the enzymatic



method of Kyler[21] can be used to produce the cyanohydrin (10 mmol scale, 58% yield after chromatography) in 95% ee. This factor was assessed by ^{1}H NMR in the presence of the Eu(hfc)$_3$ chiral shift reagent, wherein the carbinol protons show a $\Delta\delta$ of 0.21 ppm. On a 44 mmol scale, the cyanohydrin is obtained in > 99% ee (44% yield) after crystallization. It is silylated in a subsequent step to give **5**, which is converted to the benzoin as previously described. The enantiomeric excess of **6** obtained via the one-step synthesis of **5** can be raised to >97% by removal of the racemate by crystallization.

With the desired optically-active benzoin in hand, it was used to form DMB-phosphates using standard phosphoramidite protocols.[22] For the synthesis of the DMB-phosphate of the 3′-OH of thymidine, two approaches have been taken. The commercially-available (diisopropylamino)(cyanoethoxy)chlorophosphine was treated with DMB-OH in methylene chloride in the presence of diisopropylethylamine to form the DMB-phosphoramidite **7** in 69% yield after chromatography (eq 6). Because it



is hygroscopic, it is important to carefully dry by azeotropic distillation the dimethoxybenzoin used in this

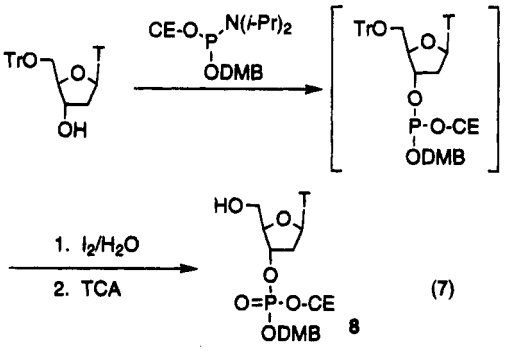
(20) Hayashi, M.; Matsuda, T.; Oguni, N. *J. Chem. Soc., Chem. Commun.* **1990**, 1364.
(21) Ognyanov, V. I.; Datcheva, V. K.; Kyler, K. S. *J. Am. Chem. Soc.* **1991**, *113*, 6992.
(22) McBride, L. S.; Caruthers, M. H. *Tetrahedron Lett.* **1983**, *24*, 245. Beaucage, S. L.; Caruthers, M. H. *Tetrahedron Lett.* **1981**, *22*, 1859.

Table 2. Protection of Alcohols by 7 and Photochemical Deprotection of DMB-Phosphotriesters[a]

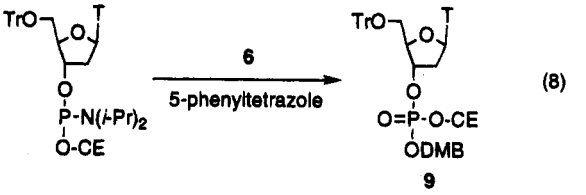
entry	compd	protection (% yield)	deprotection (% yield)	half-life (s)
1	BOC-Ser-OMe (**10**)	45	85	182
2	BOC-Tyr-OMe (**12**)	82	86	202
3	(*R*)-pantolactone	58	85	216
4	5′-DMTr-thymidine	60	83	128
5	(*S*)-glycerol acetonide	55	87	209

[a] Long wavelength, phosphor-coated lamps (350 nm) were used in a Rayonet reactor. Half-lives were determined by ^{31}P NMR at <4 mM concentration of the CE-benzoin phosphate.

coupling (J.-C. Bradley, unpublished results). The phosphoramidite **7** was treated with 5′-O-DMTr-thymidine and 1*H*-tetrazole, followed by iodine/water oxidation (eq 7). The protected DMB-phosphate was isolated in 64%



yield, and the dimethoxytrityl group was removed with dichloroacetic acid to give **8**. Treatment of the commercially-available DMTr-thymidine CE-phosphoramidite with dimethoxybenzoin followed by oxidation produces phosphate **9** in 61% yield (eq 8). When this



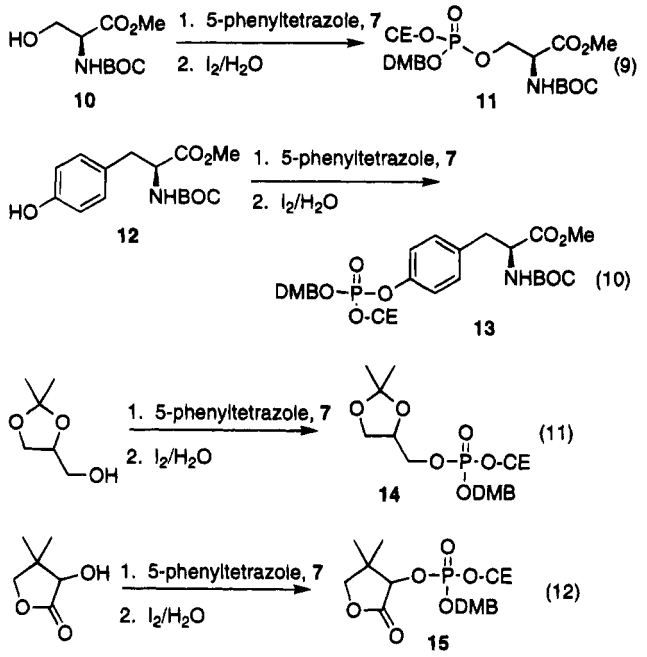
material was purified by flash chromatography, a sample of a single phosphorus diastereomer was obtained along with a mixture of both diastereomers, something that could not have been accomplished if four diastereomers had been present because of a racemic DMB group.

Phosphoramidite **7** was also used in the derivatization of optically-active primary and secondary alcohols and a phenol (45–82% yield, Table 2) of significance in biological systems (eqs 9–12). Because these materials are homogeneous at the alcohol stereocenters but no stereocontrol is exerted at phosphorus, they are produced as a mixture of (only two) diastereomers, readily discerned by ^{31}P NMR.

The photochemical deprotection of these substances was conducted as described earlier. The half-life for photochemical deprotection for each compound was determined by ^{31}P NMR. The product diesters were all isolated in excellent yields as the triethylammonium salts after chromatography; the crude reaction mixtures are very clean, and the deprotection yields are essentially quantitative.

Discussion

The phosphoramidite method reported herein for the preparation of dimethoxybenzoinyl phosphate triesters



is an improvement on and expansion of synthetic approaches previously developed toward benzoinyl phosphates. Alkylation of phosphate diesters by deoxybenzoinyl bromides reported by Givens[9] gives low yields because they are such poor nucleophiles. Use of P(V) phosphorylating reagents followed by hydrolysis as reported by Baldwin is useful only for the preparation of caged phosphate. The approach of Corrie and Trentham[11] to the synthesis of caged phosphate, phosphitylation of the DMB ketal to prevent neighboring group participation under aqueous hydrolysis conditions, adds steps to the synthetic sequence and reduces the overall yields.

The pathway of the deprotection reaction is not particularly germane to the synthetic focus of this work, but is of some interest for extending this approach to functional groups other than phosphates and for comparison to previous work in the field. The absorption spectra of the dimethoxybenzoins raises questions concerning the basis of the excitation of these groups. Their major absorption is not at the 350-nm wavelength used for deprotection. In fact, the substituted aromatic ring that we postulated promotes photosolvolysis does not absorb at all this far to the red, so there must be a special influence of the benzoyl group on the reactivity of the benzylic ester. One possibility is initial absorption by the benzoyl group, followed by energy transfer. The multiplicity of the excited state is also a significant issue. There seems to be divergence in the behavior of different benzoin carboxylates and phosphates, as Givens has shown that naphthalene and naphthalenesulfonate quench the benzoin phosphate deprotections, but Sheehan reported that benzoin carboxylate deprotections could not be quenched. Our results with both 3′,5′-DMB carboxylate and phosphate esters show no quenching, suggesting that these are singlet reactions. Givens has proposed a triplet mechanism for the conversion of benzoinyl phosphates to 2-phenylbenzofuran involving homolytic cleavage of the ketone α-C—O bond to form a radical pair which undergoes electron transfer to generate an α-keto cation–phosphate ion pair. At this stage, his mechanism converges with that hypothesized in eq 1. Both homolytic/electron transfer and heterolytic mechanisms for generation of the α-keto cation are therefore in principle available to benzoin esters. This is a subtle point that has heretofore gone unaddressed in mechanistic studies of benzoin ester photochemistry. Both the identity of the acid group, which affects the relative stabilities of the oxy radical and anion, and the aromatic substitution pattern, which affects the stabilities of the benzylic radical and cation, can influence the pathway. The radical mechanism has been shown only for unsubstituted benzoin phosphates. When electron-donating *meta* substituents are present, the stabilization afforded to the cationic intermediate seems sufficient to promote the photosolvolysis mechanism with either leaving group. The substituent effects shown in Table 1 suggest areas for fruitful future investigation of this issue.

Our data support and extend the original report of Sheehan in that 3′,5′-dimethoxy substitution gave excellent results, while the results of Wan were borne out only in part. This may be related to imperfections in our model of photosolvolysis as the rate-determining step. That 2′,3′-dimethoxy substitution is competitive with 3′,5′-suggests that *ortho* groups can be as effective in promoting this reaction as *meta*, but it is clear that an *o*-methoxy alone is not sufficient to afford the benzofuran product from carboxylate esters in high yield. The data in Table 1 also suggest that a donor group *meta* to the carbon substituent (*ortho* or *para* to the site of electrophilic addition onto the aromatic ring) that can stabilize the ring-closed intermediate is also required. It is difficult to rationalize our data without an electrophilic component to the rate-determining step of this photoreaction. The trends *are* somewhat consistent with the Zimmerman photosolvolysis, which is generally thought of as a singlet process, and the reactive excited state of these 3′,5′-DMB reactions could not be quenched. If the triplet state is involved by analogy to the proposal of Givens, it must be nonquenchable. To account for substituent effects consistent with photosolvolysis within a triplet mechanism, electron transfer to form the ion pair must be rate-determining.

Dimethoxybenzoinyl phosphates, prepared by reliable methods in this work, should be useful reagents to control the release of biomolecules using light.

Experimental Section

General. All starting materials were purchased from Aldrich (except 5′-*O*-tritylthymidine and its (cyanoethyl)-phosphoramidite, from Cruachem) and were used without further purification. Dichloromethane, acetonitrile, benzene, and pyridine were freshly distilled from calcium hydride. THF and diethyl ether were distilled from sodium/benzophenone ketyl. Triethylamine and diisopropylamine were distilled from sodium and stored under argon. All reactions were carried out under an atmosphere of argon in glassware which was oven dried and/or flame dried. Chromatography was performed using EM Reagents 0.042–0.063-mm-grade silica gel (Kieselgel 60).

All NMR spectra were recorded on a Varian XL-300 spectrometer operating at 121 MHz for phosphorus, 75 MHz for carbon, and 300 MHz for proton. Phosphorus shifts are reported referenced to 85% phosphoric acid. Melting points were measured on a Haake–Buchler melting point apparatus and are uncorrected. Optical rotations were determined on a Perkin-Elmer Model 241 polarimeter. HPLC was performed on a Hewlett-Packard 1090L with a 5-μm silica column. Elemental analyses were performed by Atlantic Microlabs. High-resolution mass spectrometry was performed at the University of North Carolina and the University of South Carolina. Silica gel used for chromatography of phosphoramidites was slurried with a 20% solution of triethylamine in CH_2Cl_2, filtered, and dried *in vacuo*.

General Procedures for the Preparation and Study of Benzoinyl Acetates. Benzaldehyde Cyanohydrins. To the aldehyde and a catalytic amount of ZnI_2 in methylene chloride was slowly added TMSCN at 0 °C. The reaction mixture was stirred for 4 h at rt and quenched by the addition of water. The phases were separated, and the organic layer was washed with water. Drying over $MgSO_4$ and filtration through a pad of silica provided a crude silylcyanohydrin after evaporation. Yields ranged from 88 to 97% on a 3−5-g scale. **Benzoins.** The substituted benzaldehyde TMS-cyanohydrin was slowly added to phenylmagnesium bromide (2 equiv) at 0 °C in THF. After being stirred for 1 h, the reaction mixture was carefully quenched by the addition of 2 N HCl. After the mixture was stirred for 6 h at rt to hydrolyze the imine and the silyl ether, the phases were separated and the organic layer was washed with 2 N HCl and water. After drying, the solvent was removed and the benzoin was recrystallized from ethanol or methylene chloride/methanol to give the pure unsymmetrical benzoin. Yields ranged from 68 to 87% on a 2-g scale. **Benzoinyl Acetates.** To the substituted benzoin and 1.1 equiv of dry pyridine in methylene chloride was added 1.1 equiv of acetyl chloride. The reaction mixture was stirred for 2 h, and water was added. The phases were separated, and the organic layer was washed with 5% $NaHCO_3$, 0.1 N HCl, and water. The solvent was dried, and the acetate was purified by silica gel chromatography (4:1 hexanes:EtOAc). Yields ranged from 93 to 99% on a 1−2-g scale. **Photolysis.** A benzoinyl acetate (100 mg) in 10 mL of purified benzene was purged of oxygen by argon bubbling and irradiated in a Rayonet photochemical reactor with 350-nm lamps for 3 h. The solvent was removed by rotary evaporation, and the acetic acid was taken off under high vacuum. The benzofuran was isolated by flash chromatography, eluting with a gradient of CCl_4−$CHCl_3$ (4:1 → 3:1). Yields are as shown in Table 1.

Diethyl 3′,5′-Dimethoxybenzoinyl Phosphate (2). To a solution of diisopropylethylamine (0.476 g, 3.68 mmol) and 3′,5′-dimethoxybenzoin (0.50 g, 1.84 mmol) in 20 mL of methylene chloride cooled in an ice bath was added 0.43 g (2.76 mmol) of diethyl chlorophosphite via syringe. The mixture was stirred for 15 min and quenched by the addition of 5% sodium bicarbonate. The layers were separated, and the organic layer was washed with brine and dried over $MgSO_4$. Removal of the solvent followed by silica gel chromatography (1:1 hexanes: ethyl acetate, R_f 0.34) gave 0.624 g (83%) of the title compound as a clear syrup. ^1H NMR ($CDCl_3$): δ 1.19 (t, J = 7.2 Hz, 3H), 1.35 (t, J = 7.2 Hz, 3H), 3.86 (s, 3H), 3.97 (m, 2H), 3.99 (s, 3H), 4.26 (dq, J = 7.1, 7.2 Hz, 2H), 6.41 (m, 2H), 6.52 (d, J = 5.8 Hz, 1H), 6.63 (m, 2H), 7.41 (m, 2H), 7.52 (m, 1H), 7.93 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 15.90, 16.05, 55.43, 64.00 (d, J = 6.3 Hz), 64.31 (d, J = 6.3 Hz), 80.75 (d, J = 4.73 Hz), 101.17, 105.84, 128.60, 128.96, 133.53, 136.85, 161.15, 189.53. ^{31}P NMR ($CDCl_3$): δ −1.30. Anal. Calcd for $C_{20}H_{25}O_7P$: C, 58.82; H, 6.17. Found: C, 58.61; H, 6.27.

Diethyl 2′,3′-Dimethoxybenzoinyl Phosphate (4). The procedure for **2** was followed exactly giving 0.689 g (90%) as a clear syrup, R_f 0.37, 1:1 hexanes:ethyl acetate. ^1H NMR ($CDCl_3$): δ 1.18 (t, J = 7.3 Hz, 3H), 1.36 (t, J = 7.3 Hz, 3H), 3.85 (s, 3H), 3.97 (m, 2H), 3.99 (s, 3H), 4.24 (dq, J = 7.1, 7.3 Hz, 2H), 6.88 (m, 1H), 7.03 (m, 2H), 7.08 (d, J = 6.12 Hz, 1H), 7.48 (m, 2H), 7.97 (m, 1H), 7.99 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 15.80, 16.09, 55.72, 61.94, 63.84 (d, J = 6.0 Hz), 64.25 (d, J = 6.0 Hz), 74.26, 113.31, 120.64, 124.56, 128.52, 128.66, 129.09, 133.37, 134.19, 146.40, 152.78, 193.40. ^{31}P NMR ($CDCl_3$): δ −1.35 Anal. Calcd for $C_{20}H_{25}O_7P$: C, 58.82; H, 6.17. Found: C, 58.63; H, 6.22.

(*R*)-(−)-3′,5′-Dimethoxybenzoin (6). To a solution of Oguni's catalyst[14] (diisopropyl L-tartrate (50.0 mmol) and titanium tetraisopropoxide (50.0 mmol)) and trimethylsilyl cyanide (25.0 g, 252 mmol) in 500 mL of CH_2Cl_2 at 0 °C was added 3′,5′-dimethoxybenzaldehyde (30.0 g, 180 mmol) in 100 mL of CH_2Cl_2 over 1 h. The solution was maintained at 0 °C for 6 h, allowed to warm to 25 °C, and stirred for an additional 12 h. Filtration through a pad of silica gel followed by Kugelrohr distillation at 0.2 Torr gave 45.34 g (95%) of the optically-active (trimethylsilyl)cyanohydrin **5**. ^1H NMR ($CDCl_3$): δ 6.60 (m, 2H), 6.45 (m, 1H), 5.42 (s, 1H), 3.81 (s, 6H), 0.24 (s, 9H). ^{13}C NMR ($CDCl_3$): δ −0.26, 55.45, 63.55, 101.08, 104.28, 119.05, 138.40, 161.16. $[\alpha]_D$: +19.6 (c = 1.5, $CHCl_3$). This material was suitable for use in the next step.

To a 3.0 M solution of phenylmagnesium bromide in ether (10.4 mL, 31.1 mmol) was added a solution of 4.13 g (15.6 mmol) of **5** (82% ee, from the Ti-catalyzed route) in 120 mL of ether. The rate of addition was maintained to result in a gentle reflux. Addition was complete in 15 min, and the resulting suspension was heated to reflux for 3 h. THF (75 mL) was added, the mixture was brought to 0 °C, and 2 N HCl was carefully added until the aqueous layer remained acidic. Vigorous stirring was maintained for 12 h. The reaction mixture was extracted 3 × 50 mLwith EtOAc, and the combined organic layers were washed with 5% $NaHCO_3$ and brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation to leave a yellow, viscous residue. This residue was chromatographed on silica gel using a gradient elution of 4:1 to 1:1 hexane:EtOAc in four steps. The product-containing fractions were pooled, and the solvent was removed to give a slightly yellow viscous residue. Repeated recrystallization of this residue from ethanol removed the racemate and left the desired optically-active benzoin as a pale yellow syrup (2.69 g, 64%), $[\alpha]_D$: −118.4 (c = 2.18, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.93 (d, J = 7.1 Hz, 2H), 7.53 (t, J = 7.1 Hz, 1H), 7.41 (t, J = 7.1 Hz, 2H), 6.47 (d, J = 2.2 Hz, 2H), 6.35 (t, J = 2.2 Hz, 1H), 5.86 (d, J = 5.9 Hz, 1H), 4.53 (d, J = 5.9 Hz, 1H), 3.74 (s, 6H). Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.56; H, 5.93. Found: C, 70.33; H, 5.90.

An alternate enzymatic route to **6** is as follows. To a solution of 3′,5′-dimethoxybenzaldehyde (7.32 g, 44.0 mmol) and acetone cyanohydrin (4.88 g, 57.3 mmol) in 480 mL of ether was added 1000 units of oxynitrilase (mandelonitrile lyase) in 22 mL of pH 5.0 acetate buffer. The mixture was stirred under an argon atmosphere and the reaction progress monitored by TLC (3:1 hexane:EtOAc) or by NMR. After 2 days the reaction had stopped at 50−60% conversion. The layers were separated and the aqueous layer washed with 50 mL of ether. The combined ether layers were dried over $MgSO_4$, filtered, and evaporated to give a white solid. Recrystallization from CH_2Cl_2/petroleum ether gave in two crops 3.82 g of the cyanohydrin as a white solid, mp 58.7−60.7 °C. $[\alpha]_D$: +32.1 (c = 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.82 (d, J = 6.4 Hz, 1H), 3.81 (d, s, 6H), 5.46 (d, J = 6.4 Hz, 1H), 6.49 (t, J = 2.2 Hz, 1H), 6.66 (d, J = 2.2 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 55.52, 63.69, 101.69, 104.48, 137.31, 161.32. The cyanohydrin (0.776 g, 4.02 mmol) in 2 mL of DMF was added dropwise to a solution of imidazole (0.547 g, 8.04 mmol) and TMSCl (0.665 g, 0.765 mL, 6.03 mmol) in 10 mL of DMF at 0 °C and stirred for 1 h at 25 °C. The resulting solution was poured into 200 mL of water and extracted 3× with 50 mL of ether. The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed to give a yellow liquid which was purified by Kugelrohr distillation (0.5 Torr, 110 °C) to give **5** (1.11 g, 92%) which was identical to the material prepared as above except $[\alpha]_D$ +24.3 (c = 1.0, $CHCl_3$). A solution of **5** in 5 mL of ether was added dropwise to a freshly prepared solution of phenylmagnesium bromide (8.4 mmol) in 15 mL of ether. The resulting mixture was heated to reflux for 3 h. The reaction mixture was cooled in an ice bath, 2 N HCl was added until the aqueous layer remained acidic, and then the mixture was stirred for 8 h at 25 °C. Workup and chromatography as above gave 0.848 g of 3′,5′-dimethoxybenzoin.

Recrystallization from ethanol to remove the racemate provided **6** (0.771g, 68%) which was identical to the material above.

((*R*)-(−)-3′,5′-Dimethoxybenzoinyl)(2′-cyanoethoxy)(*N*,*N*-diisopropylamino)phosphine (7). To a solution of **6** (3.0 g, 11 mmol) and diisopropylethylamine (4.2 g, 33 mmol) in 50 mL of acetonitrile at 0 °C was added (2′-cyanoethoxy)(*N*,*N*-diisopropylamino)chlorophosphine (3.13 g, 13.2 mmol). The reaction mixture was stirred for 1 h and checked for the disappearance of starting material by TLC (3:1 hexanes:EtOAc). The mixture was transferred with 75 mL of EtOAc to a separatory funnel and extracted 3 × 20 mL with 5% $NaHCO_3$ and with 20 mL of brine. The organic layer was

dried over Na_2SO_4 and the solvent removed by rotary evaporation. The resulting yellow oily residue was eluted from silica gel (2:1 hexanes:EtOAc) which had been pretreated with triethylamine to give 3.41 g (66%) of a pale yellow syrup which was >97% pure by ^{31}P and ^1H NMR and was used as such. With 1.5 equiv of chlorophosphine, the yield increases to 93%, $[\alpha]_D$ +14.5 (c = 1.1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.97 (m, 2H), 7.48 (m, 1H), 7.38 (m, 2H), 6.64 (m, 2H), 6.36 (m, 1H), 5.84 (dd, J = 14.6, 7.2 Hz, 1H), 3.81 (m, 2H), 3.78 (s, 6H), 3.59 (m, 2H), 2.60 (m, 2H), 1.19–1.05 (m, 12H). ^{31}P NMR ($CDCl_3$): δ 150.4, 151.4

***N*-(*tert*-Butyloxycarbonyl)-*O*-[((*R*)-3′,5′-dimethoxybenzoinyl)(2′-cyanoethyl)phosphoryl]-(*S*)-serine Methyl Ester (11).** To a solution of (*S*)-serine methyl ester hydrochloride (5.0 g, 32 mmol) and triethylamine (6.5 g, 64 mmol) in 40 mL of CH_2Cl_2 at 0 °C was added dropwise a solution of di-*tert*-butyl dicarbonate (8.38 g, 38.4 mmol) in 20 mL of CH_2Cl_2. The mixture was stirred for 12 h at 25 °C. Water (20 mL) was added and the mixture stirred an additional 30 min. The layers were separated and the organic layer washed 3× with 0.05 M HCl (15 mL), water, and brine. The organic phase was dried with $MgSO_4$ and the solvent removed by rotary evaporation. The resulting residue was distilled in a Kugelrohr apparatus at 0.2 Torr to give **10** (6.72 g, 94%) as a clear viscous material.[18] ^1H NMR ($CDCl_3$): δ 5.46 (broad, 1H), 4.40 (m, 1H), 3.92 (m, 2H), 3.79 (s, 3H), 2.23 (br, 1H), 1.46 (s, 9H). This material was used in the next step without purification. To a solution of **7** (0.928 g, 1.97 mmol) and **10** (0.287 g, 1.31 mmol) in 25 mL of acetonitrile was added 5-(*p*-nitrophenyl)tetrazole (0.753 g, 3.94 mmol) in 5 mL of acetonitrile. A tan precipitate formed, and the reaction mixture was stirred at 25 °C for 30 min. The intermediate phosphite was oxidized *in situ* by addition of a standard oxidizing solution of iodine/THF/2,6-lutidine/water until the brown iodine color persisted. The mixture was transferred with 50 mL of EtOAc to a separatory funnel and washed with 20-mL portions of water, 10% sodium bisulfite, 5% sodium bicarbonate, saturated aqueous copper sulfate, water, and brine. The organic layer was dried over Na_2SO_4 and the solvent removed by rotary evaporation to leave a brown residue. This material was applied to a silica gel column and eluted with 2:1 EtOAc:hexanes to give **11** (0.353 g, 45%) as a clear oil. ^1H NMR ($CDCl_3$): δ 1.47 (s, 9H), 2.60 (m, 1H), 2.85 (m, 1H), 3.71 (s, 3H), 3.77 (s, 6H), 4.09 (m, 1H), 4.39 (m, 2H), 4.50 (m, 2H), 5.52 (br, 1H), 6.42 (m, 1H), 6.57 (m, 3H), 7.41 (m, 2H), 7.52 (m, 1H), 7.90 (m, 2H). ^{31}P NMR ($CDCl_3$): δ −1.9, −2.4. $[\alpha]_D$: −39.6° (c = 1.2, $CHCl_3$). Anal. Calcd for $C_{28}H_{35}N_2O_{11}P$: C, 55.44; H, 5.82; N, 4.62. Found: C, 55.84; H, 6.22; N, 4.96.

***N*-(*tert*-butyloxycarbonyl)-*O*-[((*R*)-3′,5′-dimethoxybenzoinyl)(2′-cyanoethyl)phosphoryl]-(*S*)-tyrosine Methyl Ester (13).** To a solution of (*S*)-tyrosine methyl ester (5.0 g, 26 mmol) and 5.2 g (51 mmol) triethylamine in 25 mL of CH_2Cl_2 at 0 °C was added 6.7 g (31 mmol) of di-*tert*-butyl dicarbonate in 15 mL of CH_2Cl_2. The reaction mixture was stirred for 12 h at 25 °C, 50 mL of water was added, and the mixture was stirred for 30 min. The layers were separated, and the organic layer was washed with 20-mL portions of water, 0.05 M HCl, water, and brine. The solution was dried over $MgSO_4$ and the solvent removed to give a white solid which was chromatographed on silica gel with 4:1 hexanes:EtOAc as the eluent to give 6.01 g (88%) of a white solid (**12**), R_f 0.33 (4:1 hexanes:EtOAc). ^1H NMR ($CDCl_3$): δ 6.97 (d, 7.2 Hz, 2H), 6.72 (d, 7.2 Hz, 2H), 4.99 (broad, 1H), 4.53 (m, 1H), 3.72 (s, 3H), 3.01 (m, 2H), 1.42 (s, 9H). To a solution of **12** (0.388 g, 1.31 mmol) and **7** (0.928 g, 1.97 mmol) in 15 mL of acetonitrile was added 5-(*p*-nitrophenyl)tetrazole (0.753 g, 3.94 mmol) in 10 mL of acetonitrile. The resulting solution was stirred for 30 min at 25 °C and oxidized *in situ* with iodine/THF/lutidine/water solution. The reaction was worked up exactly as for **11** and purified by elution from silica gel using 3:2 hexanes:EtOAc to give **13** (0.537 g, 82%) as a clear syrup. ^1H NMR ($CDCl_3$): δ 1.43 (s, 9H), 2.55 (m, 2H), 3.04 (m, 2H), 3.69 (m, 3H), 3.77 (m, 6H), 4.12 (m, 2H), 4.38 (m, 1H), 5.02 (m, 1H), 6.45 (m, 1H), 6.70 (m, 3H), 7.06 (d, J = 7.4 Hz, 2H), 7.17 (d, J = 7.4 Hz, 2H), 7.41 (m, 2H), 7.52 (m, 1H), 7.90 (m, 2H). ^{31}P NMR ($CDCl_3$): δ −7.1, −7.9. $[\alpha]_D$: −29.0 (c = 3.8, $CHCl_3$) Anal. Calcd for $C_{33}H_{39}N_2O_{10}P$: C, 59.82; H, 5.76; N, 4.10. Found: C, 59.41; H, 6.06; N, 4.09.

3′-Thymidyl (*R*)-3′,5′-Dimethoxybenzoinyl 2-Cyanoethyl Phosphate (8). To a solution of 5′-*O*-(4″,4″-dimethoxytrityl)thymidyl 2-(cyanoethyl)*N*,*N*-diisopropylphosphoramidite (0.80 g, 1.07 mmol) and (*R*)-(−)-3′,5′-dimethoxybenzoin (0.146 g, 0.54 mmol) in 15 mL of acetonitrile was added 0.075 g (1.07 mmol) of 1*H*-tetrazole in 3 mL of acetonitrile. The reaction mixture was stirred for 30 min and oxidized *in situ* by addition of iodine/THF/lutidine/water solution until brown color persisted in the solution. The solution was worked up exactly as for **11** to give 0.302 g (60%) of the DMTr-DMB phosphate **9** as a white foam which was taken on to the next step without purification.

Alternatively, to a solution of 5′-*O*-(4″,4″-dimethoxytrityl)thymidine (0.174 g, 0.32 mmol) and **7** (0.305 g, 0.65 mmol) in 8 mL of acetonitrile was added 1*H*-tetrazole (0.20 g, 3.2 mmol) in 3 mL of acetonitrile. The resulting solution was stirred for 30 min at 25 °C and oxidized *in situ* with iodine/THF/lutidine/water solution. The reaction was worked up exactly as for **11** to give **9** (0.181 g, 61%) as a colorless foam. The trityl group was removed as described below, and column chromatography (98:2 CH_2Cl_2:EtOH; R_f 0.19) on silica gel provided a sample of a single diastereomer at phosphorus. ^1H NMR ($CDCl_3$): δ 1.89 (s, 3H), 2.38 (m, 2H), 2.89 (m, 2H), 3.71 (m, 2H), 3.76 (s, 6H), 4.08 (m, 1H), 4.46 (q, J = 7.4 Hz, 2H), 5.04 (m, 1H), 6.03 (t, J = 6.7 Hz, 1H), 6.44 (m, 1H), 6.60 (m, 2H), 6.62 (d, J = 5.9 Hz, 1H), 7.37 (s, 1H), 7.41 (m, 2H), 7.53 (m, 1H), 7.90 (m, 2H), 8.18 (br, 1H). ^{31}P NMR ($CDCl_3$): δ −2.90 along with the mixture of diastereomers as below.

To a solution of **9** (0.300 g, 0.322 mmol) in 5 mL of CH_2Cl_2 was added 5 mL of 3% dichloroacetic acid in CH_2Cl_2. After being stirred for 3 min, the mixture was poured into 10 mL of 10% Na_2CO_3. The layers were separated, and the organic layer was washed with 10% Na_2CO_3 and brine. The organic layer was dried over sodium sulfate and the solvent removed to give a white foam which was chromatographed on silica gel, eluting with 98:2 EtOAc:ethanol to give **8** (0.193 g, 96%) as a white foam which was crushed to a white powder. ^1H NMR ($CDCl_3$): δ 1.89 (m, 3H), 2.39 (m, 1H), 2.56 (m, 1H), 2.63 (m, 1H), 2.89 (m, 1H), 3.66 (m, 1H), 3.75 (m, 6H), 4.00 (m, 1H), 4.12 (m, 2H), 4.44 (m, 2H), 5.06 (m, 1H), 5.35 (m, 1H), 6.04 (m, 1H), 6.19 (m, 1H), 6.42 (m, 1H), 6.59 (m, 2H), 6.74 (m, 1H), 7.41 (m, 2H), 7.53 (m, 1H), 7.89 (m, 2H). ^{31}P NMR ($CDCl_3$): δ −2.60, −2.89. $[\alpha]_D$: −24.8 (c = 4.6, $CHCl_3$). Anal. Calcd for $C_{29}H_{32}N_3O_{11}P$: C, 55.32; H, 5.12; N, 6.67. Found: C, 55.60; H, 5.28; N, 6.44.

(*R*)-4′,4′-Dimethyl-2-oxo-2(3*H*)-dihydrofur-3-yl (*R*)-3′,5′-Dimethoxybenzoinyl 2′-Cyanoethyl Phosphate (15). To a solution of (*R*)-(−)-pantolactone (0.200 g, 1.54 mmol) and **2** (1.45 g, 3.07 mmol) in 15 mL of acetonitrile was added 1*H*-tetrazole (0.587 g, 3.07 mmol) in 10 mL of acetonitrile. The resulting solution was stirred for 30 min, oxidized by the addition of iodine/THF/lutidine/water, and worked up as for **11**. Purification by elution from silica gel with 2:1 EtOAc:hexanes gave 0.463 g (58%) of **15** as a white foam, R_f 0.32 (2:1 EtOAc:hexanes). ^1H NMR ($CDCl_3$): δ 7.92 (m, 2H), 7.53 (m, 1H), 7.39 (m, 2H), 6.64 (m, 2H), 6.41 (m, 1H), 4.94 (d, J = 13.1 Hz, 1H), 4.85 (d, J = 13.1 Hz, 1H), 4.52 (m, 1H), 4.32 (m, 2H), 3.99 (m, 2H), 3.74 (s, 6H), 2.87 (m, 1H), 2.71 (m, 1H), 1.24 (d, J = 6.1 Hz, 3H), 1.10 (d, J = 6.1, 3H). ^{13}C NMR ($CDCl_3$): δ 193.00, 192.23, 172.16, 160.98, 135.54, 133.56, 128.53, 116.47, 106.20, 105.84, 80.54, 80.05, 79.61, 75.58, 62.54 (d, J = 12 Hz), 55.17, 40.32, 21.86, 19.01. ^{31}P NMR ($CDCl_3$): δ −1.76. $[\alpha]_D$: −33.2 (c = 2.3, $CHCl_3$). Anal. Calcd for $C_{25}H_{28}NO_9P$: C, 58.02; H, 5.45; N, 2.71. Found: C, 58.22; H, 5.36; N, 2.63.

(*S*)-2,3-*O*-Isopropylideneglyceryl (*R*)-3′,5′-Dimethoxybenzoinyl 2″-Cyanoethyl Phosphate (14). To a solution of (*S*)-(+)-2,2-dimethyl-1,3-dioxolane-4-methanol (0.254 g, 1.92 mmol) and **2** (1.362 g, 2.88 mmol) in 20 mL of acetonitrile was added 5-(*p*-nitrophenyl)tetrazole (0.55 g, 2.88 mmol) in 10 mL of acetonitrile. The reaction mixture was stirred for 1 h at 25 °C and oxidized by addition of a 0.5 M solution of iodine in THF/lutidine/water until the brown color persisted. The

mixture was stirred for an additional 15 min and extractively worked up as for **11**. A silica gel column developed with 2:1 EtOAc:hexanes gave **14** (0.548 g, 55%), R_f (0.28) 2:1 EtOAc: hexanes. ^{1}H NMR ($CDCl_3$): δ 1.43 (m, 6H), 2.59 (m, 1H), 2.84 (m, 1H), 3.66 (m, 1H), 3.74 (s, 6H), 3.82 (m, 1H), 3.95 (m, 1H), 4.16 (m, 2H), 4.37 (m, 2H), 6.42 (m, 1H), 6.58 (m, 3H), 7.39 (m, 2H), 7.52 (m, 1H), 7.91 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 19.33, 25.17, 26.61, 53.40, 55.41, 62.26 (d, J = 5.2 Hz), 65.87, 68.15 (d, J = 6.2 Hz), 73.71, 80.66, 101.35, 106.15, 109.86, 116.22, 128.77, 133.88, 136.04, 161.28, 193.01. ^{31}P NMR ($CDCl_3$): δ −1.95, −2.05. $[\alpha]_D$: −69.3 (c = 1.13, $CHCl_3$). Anal. Calcd for $C_{25}H_{30}NO_9P$: C, 57.80; H, 5.82; N, 2.70. Found: C, 58.01; H, 6.01; N, 2.61.

Triethylammonium N-(*tert*-Butyloxycarbonyl)-*O*-[(2-cyanoethyl)phosphoryl]-(*S*)-serine. A 16- × 150-mm Pyrex test tube was charged with a solution of **11** (0.345 g, 0.56 mmol) in 10 mL of benzene and sealed with a septum. The solution was degassed by bubbling with argon for 20 min and irradiated with 350-nm bulbs in a Rayonet reactor for 45 min. Triethylamine (0.5 mL) was added, and the solvent was removed. The residue was dissolved in 1 mL of 90:9:1 methylene chloride:ethanol:triethylamine and loaded onto a silica gel column that was eluted with the same solvent to give the title compound (0.217 g, 85%) as an amorphous solid, R_f 0.14 (90:9:1 methylene chloride:ethanol:triethylamine). ^{1}H NMR ($CDCl_3$): δ 1.25 (t, J = 8.7 Hz, 9H), 1.31 (s, 9H), 2.61, (t, J = 7.7 Hz, 2H), 2.99 (m, 6H), 3.46, (q, J = 7.7 Hz, 2H), 3.63 (s, 3H), 3.97 (m, 1H), 4.15−4.3 (m, 2H), 6.40 (br, 1H). ^{13}C NMR ($CDCl_3$): δ 8.37, 19.50, 28.11, 29.37, 45.53, 52.21 (d, J = 5.4 Hz), 54.57, 62.53, 65.20, 79.30, 117,60, 155,43, 170.52. ^{31}P NMR ($CDCl_3$): δ 0.84. $[\alpha]_D$: −61.1 (c = 2.2, MeOH). MS (FAB) m/z: calcd for $C_{18}H_{36}N_3O_8P$, 454.2320, found 454.2308.

Triethylammonium *N*-(*tert*-Butyloxycarbonyl)-*O*-[(2-cyanoethyl)phosphoryl]-(*S*)-tyrosine. A solution of **13** (0.352 g, 0.526 mmol) in 10 mL of benzene was degassed by 20 min of argon bubbling and irradiated at 350 nm in a Rayonet reactor for 45 min. Triethylamine (0.5 mL) was added, and the solvent was removed by rotary evaporation. The residue was purified by silica gel chromatography using 90:9:1 methylene chloride:ethanol:triethylamine as eluent (R_f 0.21) to give the title compound (0.241 g, 86%). ^{1}H NMR ($CDCl_3$): δ 1.18 (t, J = 8.8 Hz, 9H), 1.32 (s, 9H), 2.59, (t, J = 5.9 Hz, 2H), 2.83 (q, J = 8.7 Hz, 6H), 3.44 (q, J = 5.9 Hz, 2H), 3.62 (s, 3H), 4.07 (m, 2H), 4.43 (m, 1H), 4.92 (m, 1H), 6.93 (d, J = 9.1 Hz, 2H), 7.10 (d, J = 9.1 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 8.57, 19.60, 28.09, 37.10, 45.41, 51.99, 52.52, 54.30, 60.43, 79.66, 117.67, 119.94 (d, J = 5.1 Hz), 129.84, 130.19, 152.01, 154.91, 172.05. ^{31}P NMR ($CDCl_3$): δ −4.77. $[\alpha]_D$:+1.7 (c = 1.76, MeOH). MS (FAB) m/z: calcd for $C_{24}H_{40}N_3O_8P$ 530.2633, found 530.2636.

3′-Thymidyl 2-Cyanoethyl Triethylammonium Phosphate. A solution of **8** (0.57 g, 0.091 mmol) in 15 mL of THF in a 16- × 150-mm Pyrex test tube was degassed by 20 min of argon bubbling. The solution was irradiated for 45 min at 350 nm in a Rayonet reactor. Triethylamine (0.5 mL) was added, and the solvent was evaporated. The resulting residue was eluted from a silica gel column with 90:9:1 methylene chloride: ethanol:triethylamine (R_f 0.10) to give the title compound as a white solid (0.36 g, 83%). ^{1}H NMR ($CDCl_3$): δ 1.19 (t, J = 8.9 Hz, 9H), 1.85 (s, 3H), 2.33 (m, 1H), 2.49 (m, 1H), 2.71 (m, 2H), 2.87 (q, J = 8.9 Hz, 6H), 3.00 (m, 2H), 3.80 (m, 3H), 4.09 (m, 2H), 4.94 (broad, 1H), 6.21 (m, 1H), 8.62 (s, 1H). ^{31}P NMR ($CDCl_3$): δ −1.99. $[\alpha]_D$: −24.8 (c = 2.2, MeOH). MS (neg FAB) m/z: calcd for $C_{13}H_{17}N_3O_8P$ 374.0754, found 374.0757.

(*R*)-4′,4′-Dimethyl-2-oxo-2(3*H*)-dihydrofur-3-yl 2′-Cyanoethyl Triethylammonium Phosphate. A solution of **15** (0.120 g, 0.232 mmol) in 8 mL of benzene in a Pyrex test tube was degassed for 20 min and irradiated at 350 nm in a Rayonet reactor for 45 min. Triethylamine (0.5 mL) was added and the solvent removed by rotary evaporation. The resulting residue was chromatographed on silica gel with 90:9:1 (methylene chloride:ethanol:triethylamine) as eluent (R_f 0.19) to give the title compound (0.072 g, 85%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 1.06 (s, 3H), 1.21 (s, 3H), 1.38 (m, 9H), 2.72 (m, 1H), 3.09 (m, 6H), 3.56 (m, 3H), 3.91 (m, 1H), 4.18 (m, 1H), 4.69 (d, J = 6.5 Hz, 1H). ^{31}P NMR ($CDCl_3$): −0.26. $[\alpha]_D$: −8.7 (c = 1.7, methanol). MS (neg FAB) m/z: calcd for $C_9H_{13}NO_8P$ 262.0481, found 262.0482.

(*S*)-2′,3′-*O*-Isopropylideneglyceryl 2″-Cyanoethyl Triethylammonium Phosphate. A solution of **14** (0.240 g, 0.460 mmol) in 10 mL of benzene in a Pyrex test tube was degassed for 20 min and irradiated at 350 nm in a Rayonet reactor for 45 min. Triethylamine (0.5 mL) was added and the solvent removed by rotary evaporation. The residue was chromatographed on silica gel with 90:9:1 methylene chloride: ethanol:triethylamine as eluent (R_f 0.16) to give the title compound (0.147 g, 87%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 1.17 (s, 3H), 1.20 (s, 3H), 1.23 (m, 9H), 2.58 (t, J = 6.3 Hz, 2H), 2.95 (m, 6H), 3.42 (q, J = 7.4 Hz, 2H), 3.78 (m, 2H), 3.95 (m, 2H), 4.14 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 8.27, 19.40, 24.97, 26.43, 29.22, 45.41, 52.35, 59.91 (d, J = 5.4 Hz), 65.84 (d, J = 5.7 Hz), 66.19, 74.32 (d, J = 8.5 Hz), 108.93, 117.54. ^{31}P NMR ($CDCl_3$): δ 1.12. δ −0.81. $[\alpha]$: +2.5 (c = 2.4, MeOH). MS (FAB) m/z: calcd for $C_{15}H_{31}N_2O_6P$ 367.1999, found 367.2035.

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