Trapping Phosphodiester−Quinone Methide Adducts through in Situ Lactonization

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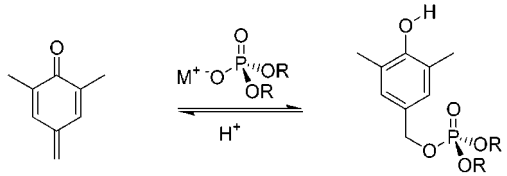
The goal of in situ modification of DNA via phosphodiester alkylation has led to our design of quinone methide derivatives capable of alkylating dialkyl phosphates. A series of catechol derivatives were investigated to trap the phosphodiester−quinone methide alkylation adduct through in situ lactonization. The catechol derivatives were uniquely capable of characterizable *p*-quinone methide formation for mechanistic clarity. These investigations revealed that with a highly reactive lactonization group (phenyl ester), lactonization competed with quinone methide formation. Lactone-forming groups of lower reactivity (methyl ester, *n*-propyl ester, and dimethyl amide) allowed quinone methide formation followed by phosphodiester alkylation; however, they were ineffective at in situ lactonization to drain the phosphodiester alkylation equilibrium to the desired phosphotriester product. The derivatives tethered with lactone-forming functionality of intermediate reactivity (chloro-, trichloro-, and trifluoroethyl esters), allowed quinone methide formation, phosphodiester alkylation, and in situ lactonization to efficiently afford the trapped phosphotriester adduct.

Introduction

Quinone methides have been studied in an array of alkylation and biomolecular alkylation processes.[1,2] Investigations of nucleic acid alkylation have focused on the reaction of nucleobases with various quinone methides including: (i) simple quinone methides with minimal functionalization,[3,4] (ii) quinone methides as active intermediates related to natural products,[5,6] and (iii) quinone methides generated in situ from de novo designed precursors.[7] Most of these alkylation studies required that the initial unstable nucleobase−quinone methide adducts undergo oxidation to a quinone derivative[5a−c;6a−c;7a−c] or be trapped as an acetate[5e−g] to facilitate full characterization.

Scheme 1



1 **2**

Previous investigations in our laboratories revealed that the facile alkylation of phosphodiesters with *p*-quinone methide **1** was promoted by a Brønsted acid (Scheme 1).[8] In situ modification of DNA might be readily achieved through trialkyl phosphate formation,[9] although this has proven quite challenging by reported approaches.[10] Further development of a reagent for the selective alkylation of phosphodiesters has led us to study derivatives designed to stabilize the phosphotriester

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product in the quinone methide−phosphodiester alkylation equilibrium. For mechanistic clarity, the present investigations have been limited to precursors that allow the formation of characterizable *p*-quinone methide intermediates. The reaction conditions for these investigations were intentionally conceived to allow analysis of a single aspect of a multifunctional phosphodiester alkylating reagent under systematic development.

Previous investigators have demonstrated approaches to stabilize quinone methide alkylation products. Angle and co-worker showed *o*-quinone methide−nucleic acid base alkylation products of anthracycline analogues could be isolated without decomposition if the phenol was acetylated.[5e−g] Other investigators have examined approaches to stabilize benzylic trialkyl phosphates. Meier and co-workers examined the stability of a series of di-AZT-benzyl phosphotriesters as potential prodrugs.[11] They investigated a series of para substituents on the phenyl ring of the benzyl group ranging from a methyl to a nitro group and found the half-life of the corresponding phosphotriesters in a phosphate buffer (pH 7.4) ranged from 0.37 to 744 h, respectively. Thomson and co-workers showed that no hydrolysis of bis(4-acyloxybenzyl)-AZT phosphotriester was found in a phosphate buffer−acetonitrile mixture (95:5 v/v, pH 7.4) at 37 °C over 3 h.[12] Givens and co-workers studied the solvolysis of two diethylbenzyl phosphates in methanol over 5.5 h, observing 88% solvolysis with a *p*-methoxy substituent on the phenyl ring of the benzyl group, while no solvolysis was observed with a *m*-methoxy substituent.[13]

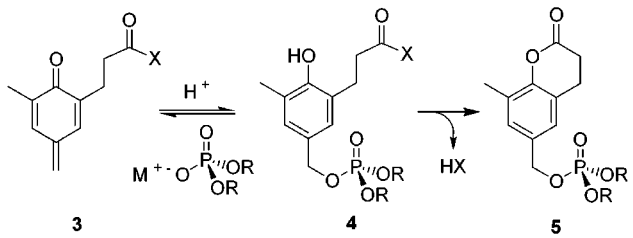
These studies suggest that the stability of phosphodiester−quinone methide adducts, such as **2** (Scheme 1), can be increased by lowering the resonance electron-donating capacity of the *p*-hydroxy substituent. We report the development of a catechol derivative designed to alkylate a phosphodiester via a characterizable *p*-quinone methide followed by in situ lactonization. This simple application of Le Chatelier's principle has allowed the alkylation equilibrium to be drained to the desired phosphotriester as the favored product.

Results and Discussions

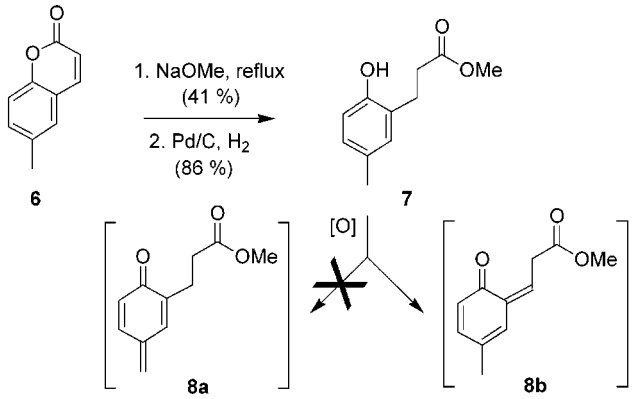
After our study of phosphodiester alkylation with *p*-quinone methide **1** (Scheme 1),[8] we sought a modification to trap out an isolable phosphotriester for complete characterization. We initially investigated the intermolecular acetylation of the trialkyl phosphate **2** with various activated acetylating reagents. However, due to the direct acetylation of phosphodiesters and competitive alkylation reaction with the quinone methide, no acetylated trialkyl phosphate from phosphodiester addition to the quinone methide was observed by ^{1}H NMR analysis.

An alternative intramolecular approach was designed to trap the resulting trialkyl phosphate. The designed *p*-quinone methide **3** (Scheme 2) contained a side chain carrying an activated acetylating group[14] for in situ

Scheme 2



Scheme 3



lactonization. The intent was to produce a lactone precursor of appropriate reactivity to allow quinone methide formation and phosphodiester addition to the quinone methide to produce trialkyl phosphate **4**, followed by a slower lactonization to afford trapped trialkyl phosphate **5**. This would allow the equilibrium addition of the phosphodiester to the quinone methide to be converted to the desired lactonized trialkyl phosphate product.

We initially examined the feasibility of this design with a simple methyl ester **7** (Scheme 3). Commercially available methyl coumarin **6** was converted into the methyl cinnamate in 41% yield by refluxing with sodium methoxide.[15] Hydrogenation of the intermediate cinnamate produced phenol **7** in 86% yield. Conversion to the desired *p*-quinone methide **8a** was attempted by oxidation of phenol **7** with Ag_2O or PbO_2. Unfortunately, only complex products were observed by ^{1}H NMR analysis through the presumed *o*-quinone methide intermediate **8b**. *o*-Quinone methides have been reported to dimerize rapidly even at very low concentrations,[16] as used advantageously in the synthesis of several natural products.[17]

Geminal dimethyl groups were added to the ortho position in an attempt to block *o*-quinone methide formation. In addition, such geminal dimethyl substituents have been reported to increase lactonization rates of related derivatives by 10^3-fold[18a] according to the Thorpe−Ingold effect.[18b,c] Condensation of 2,4-dimethylphenol

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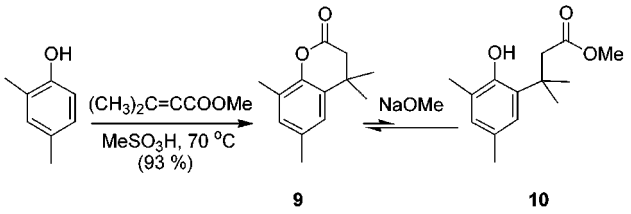
Scheme 4



Scheme 5

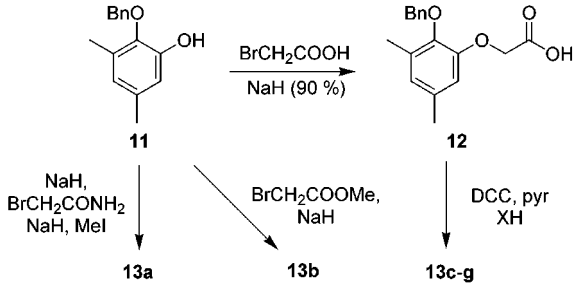
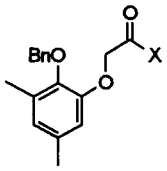


Table 1. Structures and Yields of Catechol Derivative 13

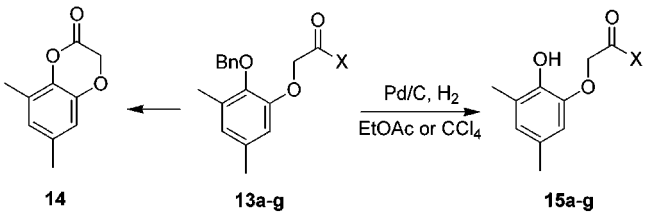
13	compound	X	yield (%)
	a	$N(CH_3)_2$	80
	b	OCH_3	82
	c	$O(CH_2)_2CH_3$	49
	d	OCH_2CH_2Cl	48
	e	OCH_2CCl_3	79
	f	OCH_2CF_3	71
	g	OPh	81

with methyl dimethyl acrylate afforded tetramethyl coumarin **9** in 93% yield (Scheme 4).[19] However, ester **10**, obtained upon refluxing **9** in NaOMe/MeOH, lactonized back at such a rate to preclude *p*-quinone methide formation.

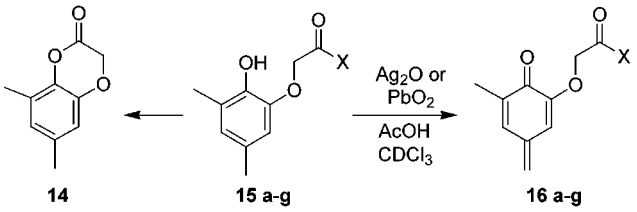
Our attention turned to the development of catechol derivatives in order to prevent competitive *o*-quinone methide formation and slow the rate of lactonization in these model studies (Scheme 5). Key intermediate **11** was synthesized through benzyl protection of 2-hydroxy-3,5-dimethylacetophenone[20] followed by Baeyer−Villiger oxidation[21] and hydrolysis. Alkylation of **11** with bromoacetic acid afforded **12** in 90% yield. From intermediates **11** and **12**, an amide and a variety of esters were synthesized (Table 1). Dimethyl amide **13a** was synthesized by alkylating **11** with bromoacetamide followed by exhaustive methylation in 80% overall yield.[22] Methyl ester **13b** was synthesized by alkylating **11** with methyl bromoacetate in 82% yield. Esters **13c**−**g** were synthesized by carbodiimide-assisted condensation of **12** with the corresponding alcohols in 48−81% yield (Table 1).[23]

Debenzylation via palladium-catalyzed hydrogenation of esters **13a**−**c** in EtOAc proceeded smoothly to afford **15a**−**c** (Scheme 6). However, lactone **14** was observed in the debenzylation of esters **13d**−**g**. Therefore, in addition to EtOAc as a debenzylation solvent, EtOH and CCl_4 were also examined (Scheme 6). It was found that when the polar protic solvent EtOH was used, a large amount of undesired lactone **14** was produced. Use of the nonpolar solvent CCl_4 and excess catalyst (1.5 equiv of Pd/C by weight) afforded pure catechol derivatives **15d**−**f**. In the debenzylation of **13g**, about 10% of lactone **14** was produced based on ^{1}H NMR area integration analysis.

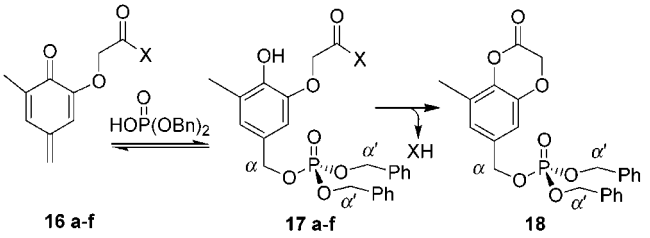
Scheme 6



Scheme 7



Scheme 8



Clean oxidation of phenols **15b**−**f** to the corresponding *p*-quinone methides **16b**−**f** (Scheme 7) was accomplished with lead(IV) oxide using low phenol concentrations (2.50 mM) in the presence of acetic acid (1 equiv). Silver(I) oxide was used to oxidize amide **15a** to quinone methide **16a**. Quinone methide **16g** (X = OPh) was formed from the oxidation of phenyl ester **15g** with PbO_2 along with 40% of lactone **14** based on the relevant resonance area integration from ^{1}H NMR analysis (Scheme 7). The competitive lactonization of **15g** precluded its further investigation.

The addition of dibenzyl phosphoric acid to *p*-quinone methides **16a**−**f** was monitored by ^{1}H NMR analysis in $CDCl_3$ (Scheme 8). A solution of dibenzyl phosphoric acid (1.5 equiv) in $CDCl_3$ was added to the solutions of quinone methide **16a**−**f** (2.50 mM in $CDCl_3$). The final concentrations of quinone methide **16a**−**f** and dibenzyl phosphoric acid were 2.1 and 3.2 mM, respectively. All of the quinone methide derivatives investigated successfully alkylated the phosphodiester to afford trialkyl phosphates **17a**−**f** at 24 °C (Scheme 8, Table 2). Conversion to trialkyl phosphate **17a** from quinone methide **16a** was complete in less than 5 min. Quinone methides **16b**−**f** required up to 2 h to reach alkylation equilibrium forming the corresponding trialkyl phosphate **17b**−**f**. Greater than 95% conversion to trialkyl phosphates **17a**−**f** from quinone methides **16a**−**f** was observed by ^{1}H NMR analysis. Relative to our previous studies of phosphodiester alkylation with 2,6-dimethylquinone methide,[8] these results revealed that catechol quinone methides were more

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Table 2. Alkylation of Dibenzyl Phosphoric Acid with Quinone Methides 16 Followed by in Situ Lactonization[a]

entry	quinone methide	X	trialkyl phosphate[b]	% convn to **18**
1	**16a**	$N(CH_3)_2$	**17a**[c]	*e*
2	**16b**	OCH_3	**17b**[d]	*f*
3	**16c**	$O(CH_2)_2CH_3$	**17c**[d]	*e*
4	**16d**	OCH_2CH_2Cl	**17d**[d]	51[g]
5	**16e**	OCH_2CCl_3	**17e**[d]	75[g]
6	**16f**	OCH_2CF_3	**17f**[d]	85[g]

[a] All experiments were carried out in $CDCl_3$ with dibenzylphosphoric acid (1.5 equiv). [b] The percent conversion to trialkyl phosphates **17** at 24 °C was >95% by ^{1}H NMR analysis relative to an internal standard (mesitylene). [c] The alkylation was complete within 5 min. [d] The alkylation was complete within 2 h. [e] No lactonized product was evident by ^{1}H NMR analysis at 24 °C after 48 h. [f] Less than 5% lactonized product was observed at 24 °C after 48 h. [g] The in situ lactonization was monitored at 35 °C over 92 h and the percent conversion was calculated relative to an internal standard (mesitylene).

reactive than 2,6-dimethylquinone methide as the alkylation equilibrium was shifted to fully favor phosphodiester alkylation.[24] Minor impurities detected in the alkylation reaction (<5% by ^{1}H NMR analysis relative to an internal standard) were consistent with hydrolysis byproducts of **17** and **18**.

The conversion of quinone methide **16a**−**f** to trialkyl phosphate **17a**−**f** was clearly observed by ^{1}H NMR analysis. The disappearance of the characteristic *p*-quinone methide alkylidene resonance of **16a**−**f** (∼5.75 ppm)[8,25] coincided with the appearance of two new doublets at ∼4.86 ppm ($^3J_{H-P}$ = 8.6−8.9 Hz, **17** α, Scheme 8) and ∼4.97 ppm ($^3J_{H-P}$ = 7.2−8.2 Hz, **17** α′, Scheme 8) in a 1:2 ratio. This is characteristic of the phosphorus coupled benzylic hydrogen resonances of the trialkyl phosphate and clearly revealed that phosphodiester addition occurred.[8]

The in situ lactonization of intermediates **17a**−**f** was initially monitored by ^{1}H NMR analysis at 24 °C over 48 h. Lactonized trialkyl phosphate **18** was evident by ^{1}H NMR analysis with intermediate phosphotriesters **17d**−**f** (Table 2). However, intermediate **17a** and **17c** showed no sign of lactonization to **18** and methyl ester **17b** afforded less than 5% lactonized trialkyl phosphate **18** during this time frame. This suggested that in situ lactonization of intermediates **17a**−**c** was inefficient for conversion of the trialkyl phosphate to the trapped product. The efficiencies of the in situ lactonization of intermediates **17d**−**f** to product **18** were then examined by ^{1}H NMR analysis at 35 °C over 92 h (Table 2). Among esters **17d**−**f** (entries 4−5, Table 2), trifluoroethyl ester **17f** afforded the highest percent conversion (85%) to the lactonized trialkyl phosphate **18** while intermediate **17d** and **17e** resulted in 51% and 75% conversion, respectively. The percent conversions given in Table 2 were determined relative to mesitylene as an internal standard.

A more detailed study of the in situ lactonization of intermediate **17f** was carried out by ^{1}H NMR analysis

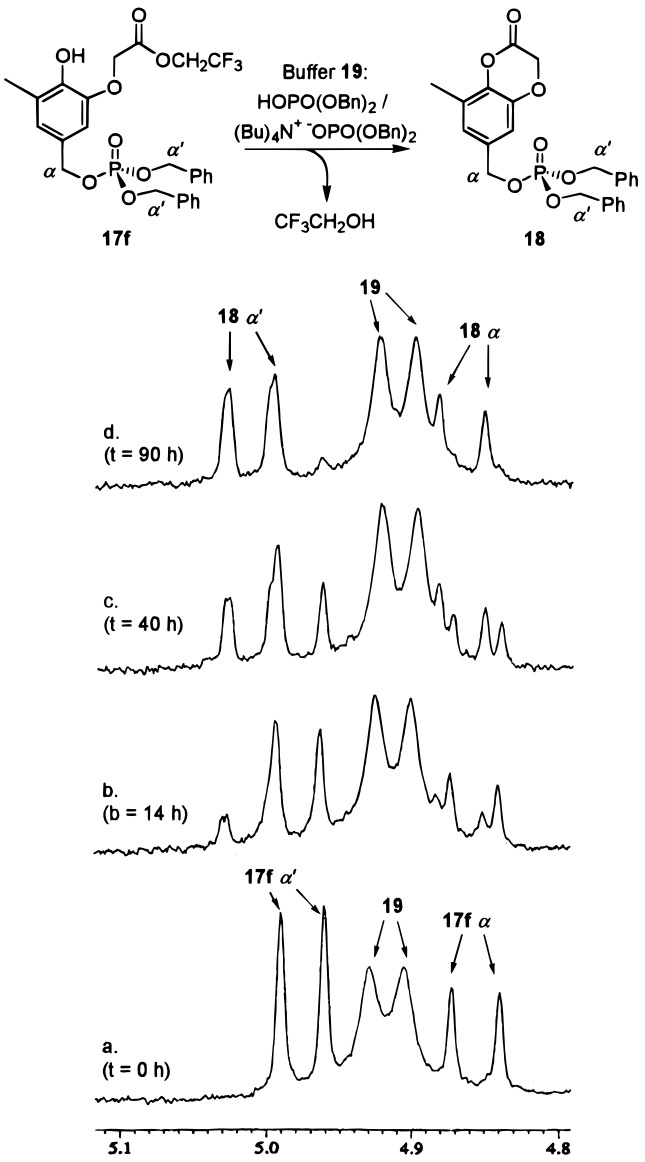

Figure 1. Progression of the in situ lactonization of **17f** to form **18** as monitored by ^{1}H NMR. (a) ^{1}H NMR spectrum of intermediate trialkyl phosphate **17f** at room temperature. (b) ^{1}H NMR spectrum after 14 h, 35 °C. (c) ^{1}H NMR spectrum after 40 h, 35 °C. (d) ^{1}H NMR spectrum after 90 h, 35 °C.

to confirm the formation of **18**. Progression of the lactonization of **17f** as monitored by ^{1}H NMR analysis is shown in Figure 1. Clean ^{1}H NMR analysis of this lactonization required that the benzylic resonances of the residual dibenzyl phosphoric acid be shifted. This was accomplished by adding 1 equiv of tetrabutylammonium dibenzyl phosphate to the reaction mixture of **17f** containing residual dibenzyl phosphoric acid. Addition of the salt appeared to have little effect on the reaction as the observed rates of lactonization were nearly identical to reactions without the added tetrabutylammonium dibenzyl phosphate. The resulting buffered dibenzyl phosphate **19** [$HOPO(OBn)_2/(Bu)_4N^+\ ^-OPO(OBn)_2$] appeared as a broad doublet at 4.92 ppm in the ^{1}H NMR spectra throughout the reaction (Figure 1a-d). The benzylic hydrogen resonances of the intermediate trialkyl phosphate **17f** appeared as doublets at 4.86 ppm ($^3J_{H-P}$ = 8.9 Hz, **17f** α) and at 4.97 ppm ($^3J_{H-P}$ = 8.2 Hz, **17f** α′) (Figure 1a). Over 90 h at 35 °C, the benzylic resonances

(24) The increased reactivity of a methoxy-substituted *p*-quinone methide relative to 2,6-dimethyl quinone methide has been reported in hydrolysis studies. The half-life of *p*-quinone methides in a phosphate buffer (pH 7.4, 25 °C) revealed that 2,6-dimethylquinone methide was about 20 times less reactive than the 2-methoxy derivative (26 vs 1.3 s) (a) Bolton, J. L.; Comeau, E.; Vukomanovic, V. *Chem.-Biol. Interact.* **1995**, *95*, 279−290. (b) Bolton, J. L.; Valerio, L. G., Jr.; Thompson, J. A. *Chem. Res. Toxicol.* **1992**, 5, 816−822.

(25) Dyall, L. K.; Winstein, S. *J. Am. Chem. Soc.* **1972**, *94*, 2196−2200.

of trialkyl phosphate **17f** gradually disappeared while the corresponding benzylic resonances of lactonized trialkyl phosphate **18** grew in at 4.87 ppm ($^3J_{H-P}$ = 8.4 Hz, **18** α) and at 5.01 ppm ($^3J_{H-P}$ = 8.1 Hz, **18** α′) (Figure 1b-d). After 90 h at 35 °C, near complete conversion to lactonized trialkyl phosphate **18** was evident by ^{1}H NMR analysis (Figure 1d). The lactonization also coincided with the release of trifluoroethanol (methylene resonance at 3.92 ppm) as the byproduct from the lactonization of trifluoroester **17f** (methylene resonance at 4.53 ppm). This clearly indicated that in situ lactonization effectively converted the intermediate trialkyl phosphate **17f** to the desired phosphotriester product **18**.

Based on the above results, the synthesis of the lactonized trialkyl phosphate **18** was carried out using **15f** as the starting ester (20.0 mg). The quinone methide solution **16f** (2.5 mM in $CHCl_3$) was formed with PbO_2 oxidation in the presence of acetic acid (3.0 equiv). Dibenzyl phosphoric acid (2.0 equiv) was added to the reaction solution and the resulting reaction was allowed to react at 35 °C for 6 days. Tetrabutylammonium acetate (1.5 equiv) was then added to buffer the reaction solution and the desired trialkyl phosphate **18** was purified through a flash column as a faint yellow oil in 58% isolated yield.

Conclusion

The development of a DNA phosphodiester alkylating reagent has driven our investigation of dialkyl phosphate alkylation by *p*-quinone methides. These investigations have shown that in situ lactonization can effectively convert the quinone methide−dialkyl phosphate alkylation intermediate to a trapped phosphotriester. A catechol system has been developed to examine this in situ lactonization process. Fast lactonization, which competed with the formation of *p*-quinone methide, precluded the study of derivative **15g** tethered with a highly reactive phenyl ester as the lactone precursor. Derivatives **15a**−**c**, tethered with less reactive lactone forming functional groups, allowed the formation of *p*-quinone methides and phosphodiester alkylation, yet were ineffective at lactonization. Derivatives **15d**−**f**, tethered with intermediate reactive lactone-forming esters, allowed the formation of *p*-quinone methides, alkylation of the phosphodiester, and in situ lactonization to convert the alkylation equilibrium to the desired lactonized phosphotriester **18**. These investigations have allowed a further understanding of mechanistic details regarding reactivity and stability of the alkylation process. This is allowing direct applications under anhydrous conditions and guiding the design of more advanced derivatives for projected in situ modification of nucleic acid polymers under biologically relevant conditions.

Experimental Section

All commercially available compounds were purchased from Aldrich Chemical Co. (Milwaukee, WI), Acros Organics (Fisher Scientific), or Lancaster Synthesis, Inc. (Windham, NH) and used without purification, unless noted otherwise. ^{31}P chemical shifts are reported relative to 85% phosphoric acid.

Methyl 2-Hydroxy-5-methylcinnamate. To a mixture of 6-methylcoumarin (2.00 g, 125 mmol) and sodium methoxide (3.20 g, 59.3 mmol) was slowly added dry MeOH (25.0 mL). The resulting yellow solution was refluxed under N_2 for 18 h. The reaction was neutralized with an aqueous HCl solution (2 N, 20 mL) and extracted with EtOAc (3 × 100 mL). The organic layers were washed with brine (2 × 150 mL), dried over $MgSO_4$, and concentrated. Flash chromatography (EtOAc in hexanes, 20%) afforded cinnamate (974 mg) in 41% yield as a white solid: mp 135−137 °C; IR (film, cm^{-1}) 3195 (br), 1677, 1583, 1298, 1213; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.99 (d, *J* = 16.2 Hz, 1H), 7.25 (s, 1H), 7.02 (d, *J* = 8.2 Hz, 1H), 6.74 (d, *J* = 8.2 Hz, 1H), 6.60 (d, *J* = 16.2 Hz, 1H), 6.24 (s, 1H), 3.81 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (68 MHz) δ 168.8, 153.2, 140.9, 132.2, 130.0, 129.5, 121.3, 117.9, 116.4, 51.8, 20.5; MS (EI) *m*/*z* (relative intensity) 192 (M^+, 29), 160 (88), 132 (100).

Methyl (2′-Hydroxy-5′-methylphenyl)propionate (7). To a solution of cinnamate (200 mg, 1.04 mmol) in MeOH (15.0 mL) was added palladium on activated carbon (10%, 200 mg). The suspension was shaken under H_2 (55 psi) on a Parr hydrogenator for 18 h. The catalyst was removed by filtration through a pad of Celite, and the filtrate was concentrated to afford **7** in 86% yield as a faint yellow oil (174 mg): IR (film, cm^{-1}) 3405 (br), 2951, 1713, 1508, 1441, 1264; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.00 (s, 1H), 6.90 (d, *J* = 8.3 Hz, 1H), 6.77 (d, *J* = 8.3 Hz, 1H), 6.89 (s, 1H), 3.68 (s, 3H), 2.87 (t, *J* = 6.7 Hz, 2H), 2.70 (t, *J* = 6.7 Hz, 2H), 2.25 (s, 3H); ^{13}C NMR (68 MHz) δ 176.0, 152.0, 131.1, 130.0, 128.5, 127.1, 116.9, 52.3, 35.1, 24.8, 20.5; MS (EI) *m*/*z* (relative intensity) 194 (M^+, 25), 162 (69), 134 (100), 121 (38).

Tetramethyldihydrocoumarin (9). To a mixture of 2,4-dimethylphenol (2.00 g, 16.4 mmol) and methyl 3,3-dimethylacrylate (2.00 g, 17.5 mmol) was added methanesulfonic acid (5.0 mL). The resulting brown solution was stirred under N_2 at 70 °C. After 24 h, the reaction solution was diluted with Et_2O (150 mL) and washed with H_2O (150 mL), saturated $NaHCO_3$ (100 mL), and brine (100 mL). The organic layer was dried over $MgSO_4$ and concentrated. Crystallization (EtOH/H_2O) afforded **9** (3.11 g) in 93% yield as a white solid: mp 96−97 °C; IR (KBr, cm^{-1}) 2960, 1762, 1474, 1266, 1206, 1116; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 6.92 (s, 1H), 6.91 (s, 1H), 2.57 (s, 2H), 2.29 (s, 3H), 2.26 (s, 3H), 1.31 (s, 6H); ^{13}C NMR (68 MHz) δ 168.7, 146.9, 133.7, 131.3, 130.4, 126.1, 122.3, 43.8, 33.3, 27.8, 21.0, 15.9; MS (EI) *m*/*z* (relative intensity) 204 (M^+, 85), 189 (87), 162 (100), 147 (68).

2-Benzyloxy-3,5-dimethylphenol (11). To a solution of 3,5-dimethyl-2-hydroxyacetophenone[26] (2.16 g, 13.2 mmol) and benzyl bromide (2.0 mL, 16.8 mmol) in DMF (15.0 mL) in an ice−salt bath was slowly added potassium hydride solid (710 mg, 17.7 mmol). After 12 h, the suspension was diluted with a saturated $NaHCO_3$ aqueous solution (100 mL) and extracted with Et_2O (3 × 100 mL). The organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography (EtOAc in hexanes, 2.5−4.5%) afforded the benzyl-protected phenol (2.85 g) in 85% yield as an oil: IR (film, cm^{-1}) 2923, 1683, 1465, 1255, 1211; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.43−7.28 (m, 5H), 7.21 (s, 1H), 7.13 (s, 1H), 4.79 (s, 2H), 2.56 (s, 3H), 2.30 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (68 MHz) δ 205.2, 154.1, 137.0, 135.8, 134.1, 133.9, 132.3, 128.8, 128.5, 128.3, 127.8, 76.7, 30.4, 20.3, 15.8; MS (EI) *m*/*z* (relative intensity) 254 (M^+, 3), 236 (1), 211 (5), 149 (3), 91 (100).

To a solution of the benzyl-protected phenol (2.84 g, 11.2 mmol) in CH_2Cl_2 (25.0 mL) was added *m*-CPBA (65%, 6.10 g, 23.0 mmol). The resulting solution was cooled in an ice bath, and trifluoroacetic acid (0.86 mL, 11.2 mmol) was slowly added. The resulting suspension was stirred in the dark for 5 h. The reaction solution was diluted in an aqueous Na_2SO_3 solution (10%, 100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The organic layers were washed with sat. $NaHCO_3$ (150 mL), H_2O (150 mL) and brine (150 mL), dried over $MgSO_4$, and concentrated. The resulting residue was dissolved in methanol (20.0 mL) and KOH solution (5 N, 20.0 mL) was added. The mixture was stirred for 12 h, neutralized with 2 N HCl, and extracted with CH_2Cl_2 (3 × 100 mL). The organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography (EtOAc in hexanes, 3−5%) afforded **11** (2.07 g) in 81% yield as a faint yellow oil: IR (film, cm^{-1}) 3512 (br), 2921, 1498, 1219, 1174;

(26) Cullinane, N. M.; Edward, B. F. R. *J Appl. Chem*. **1959**, 133−136.

^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.47−7.33 (m, 5H), 6.59 (s, 1H), 6.53 (s, 1H), 5.36 (s, 1H), 4.85 (s, 2H), 2.29 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (68 MHz) δ 148.9, 142.2, 137.4, 134.8, 130.9, 129.1, 128.8, 128.4, 123.3, 113.9, 75.4, 20.7, 15.8; MS (EI) *m*/*z* (relative intensity) 228 (M^+, 7), 137 (5), 91 (100).

(2-Benzyloxy-3,5-dimethyl)phenoxyacetic Acid (12). To a suspension of **11** (1.50 g, 6.58 mmol) and sodium hydride (200 mg, 8.3 mmol) in DMF (10.0 mL) was cannulated a suspension of bromoacetic acid (1.10 g, 7.89 mmol) and sodium hydride (316 mg, 13.2 mmol) in DMF (10.0 mL). The resulting suspension was stirred for 12 h. The reaction solution was diluted in an aqueous acetic acid solution (2%, 100 mL) and extracted with Et_2O (3 × 100 mL). The organic layers were washed with H_2O (2 × 200 mL), brine (200 mL), dried over $MgSO_4$, and concentrated. Flash chromatography (MeOH in CH_2Cl_2, 1−7%) afforded **12** (1.70 g) in 90% yield as a white solid: mp 104−106 °C; IR (KBr, cm^{-1}) 2918 (br), 1726, 1494, 1248, 1111; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.46−7.34 (m, 5H), 6.68 (s, 1H), 6.59 (s, 1H), 4.97 (s, 2H), 4.68 (s, 2H), 2.26 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (68 MHz) δ 173.2, 150.9, 144.9, 137.5, 134.4, 132.9, 128.7, 128.6, 128.4, 126.0, 114.3, 75.2, 67.0, 20.8, 15.7. Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.47; H, 6.14.

***N*,*N*-Dimethyl(2-benzyloxy-3,5-dimethyl)phenoxyacetamide (13a).** To a solution of bromoacetamide (191 mg, 1.39 mmol) and **11** (300 mg, 1.32 mmol) in DMF (5.0 mL) in an ice bath was added potassium hydride (79.0 mg, 2.00 mmol) under N_2. The resulting suspension was stirred for 3 h. Potassium hydride (270 mg, 6.75 mmol) and methyl iodide (1.0 mL, 12 equiv) were then slowly added to the reaction solution in an ice bath. After 5 h, the reaction solution was diluted in a saturated $NaHCO_3$ aqueous solution (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography (MeOH in CH_2Cl_2, 4%) afforded **13a** as an oil (334 mg) in 80% yield: IR (film, cm^{-1}) 2924, 1662, 1495, 1103; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.45−7.32 (m, 5H), 6.64 (s, 2H), 4.98 (s, 2H), 4.72 (s, 2H), 3.05 (s, 3H), 2.99 (s, 3H), 2.27 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (68 MHz) δ 167.9, 150.9, 144.3, 138.0, 133.6, 132.2, 128.3, 128.2, 127.8, 124.5, 112.9, 74.6, 68.3, 36.6, 35.6, 21.2, 16.1; MS (EI) *m*/*z* (relative intensity) 313 (M^+, 2), 268 (3), 222 (23), 149 (8), 135 (5), 91 (61).

Methyl (2-Benzyloxy-3,5-dimethyl)phenoxyacetate (13b). To a solution of methyl bromoacetate (55 μL, 0.60 mmol) in DMF (5.0 mL) was cannulated a suspension of **11** (110 mg, 0.48 mmol) and sodium hydride (40 mg, 1.00 mmol) in DMF (10.0 mL). The resulting suspension was stirred for 12 h. The reaction solution was diluted in a saturated $NaHCO_3$ aqueous solution (100 mL) and extracted with Et_2O (3 × 100 mL). The organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography (EtOAc in hexanes, 7−10%) afforded **13b** (118 mg) in 82% yield as an oil: IR (film, cm^{-1}) 2951, 1762, 1494, 1216; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.47−7.27 (m, 5H), 6.62 (s, 1H), 6.52 (s, 1H), 4.99 (s, 2H), 4.66 (s, 2H), 3.78 (s, 3H), 2.24 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (75 MHz) δ 169.5, 150.7, 144.5, 138.0, 133.4, 132.4, 128.4, 128.3, 127.8, 124.9, 113.0, 74.5, 66.3, 52.1, 21.1, 16.1; MS (EI) *m*/*z* (relative intensity) 300 (M^+, 9), 209 (23), 149 (28), 91 (100).

1-Propyl (2-Benzyloxy-3,5-dimethyl)phenoxyacetate (13c). To a suspension of **12** (200 mg, 0.70 mmol) and 1,3-dicyclohexylcarbodiimide (152 mg, 0.73 mmol) in CH_2Cl_2 (10.0 mL) were added pyridine (56 μL, 0.70 mmol) and 1-propanol (57 μL, 0.76 mmol). The suspension was stirred at room temperature for 12 h. The precipitate was filtered and the filtrate was concentrated. Flash chromatography (EtOAc in hexanes, 3−5%) afforded **13c** (112 mg) in 49% yield as an oil: IR (film, cm^{-1}) 2966, 1758, 1495, 1208, 1153, 1118; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.52−7.25 (m, 5H), 6.62 (s, 1H), 6.53 (s, 1H), 5.01 (s, 2H), 4.66 (s, 2H), 4.16 (t, J = 6.7 Hz, 2H), 2.24 (s, 3H), 2.16 (s, 3H), 1.67 (m, 2H), 0.91 (t, J = 7.7 Hz, 3H); ^{13}C NMR (68 MHz) δ 169.2, 150.7, 144.4, 138.0, 133.3, 132.3, 128.4, 128.3, 127.8, 124.7, 112.9, 74.5, 66.7, 66.2, 21.9, 21.1, 16.1, 10.3; MS (EI) *m*/*z* (relative intensity) 328 (M^+, 10), 237 (18), 195 (15), 149 (19), 137 (55), 91 (100).

2-Chloroethyl (2′-Benzyloxy-3′,5′-dimethyl)phenoxyacetate (13d). To a suspension of **12** (150 mg, 0.52 mmol) and 1,3-dicyclohexylcarbodiimide (152 mg, 0.74 mmol) in CH_2Cl_2 (10.0 mL) were added pyridine (42 μL, 0.52 mmol) and 2-chloroethanol (45 μL, 0.67 mmol). The suspension was stirred at room temperature for 12 h. The precipitate was filtered, and the filtrate was concentrated. Flash chromatography (EtOAc in hexanes 10%) afforded **13d** (89 mg) in 48% yield as a white solid: mp 40−42 °C; IR (film, cm^{-1}) 2915, 1769, 1496, 1210, 1154, 1118; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.51−7.27 (m, 5H), 6.64 (s, 1H), 6.55 (s, 1H), 5.01 (s, 2H), 4.72 (s, 2H), 4.44 (t, J = 5.5 Hz, 2H), 3.67 (t, J = 5.5 Hz, 2H), 2.25 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (68 MHz) δ 168.7, 150.5, 144.4, 137.9, 133.4, 132.4, 128.3 (2C), 127.8, 125.0, 113.0, 74.5, 66.0, 64.5, 41.3, 21.1, 16.1; MS (EI) *m*/*z* (relative intensity) 350 (M + 2, 3), 348 (M^+, 7), 257 (15), 149 (18), 137 (12).

2,2,2-Trichloroethyl (2′-Benzyloxy-3′,5′-dimethyl)phenoxyacetate (13e). To a suspension of **12** (270 mg, 0.94 mmol) and 1,3-dicyclohexylcarbodiimide (292 mg, 1.41 mmol) in CH_2Cl_2 (10.0 mL) were added pyridine (76 μL, 0.94 mmol) and 2,2,2-trichloroethanol (117 μL, 1.22 mmol). The suspension was stirred at room temperature for 12 h. The precipitate was filtered, and the filtrate was concentrated. Flash chromatography (EtOAc in hexanes, 5−10%) afforded **13e** (311 mg) in 79% yield as a white solid: mp 68−69 °C; IR (film, cm^{-1}) 2965, 1783, 1496, 1219, 1155, 1124; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.52−7.28 (m, 5H), 6.67 (s, 1H), 6.60 (s, 1H), 5.04 (s, 2H), 4.85 (s, 2H), 4.84 (s, 2H), 2.26 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (68 MHz) δ 167.6, 150.3, 144.4, 137.8, 133.4, 132.5, 128.3 (2C), 127.8, 125.1, 113.1, 94.4, 74.6, 74.0, 65.8, 21.1, 16.1; MS (EI) *m*/*z* (relative intensity), 420 (M + 4, 0.8), 418 (M + 2, 3), 416 (M^+, 3), 327 (4), 325 (3), 149 (12), 137 (9).

2,2,2-Trifluoroethyl (2′-Benzyloxy-3′,5′-dimethyl)phenoxyacetate (13f). To a suspension of **12** (150 mg, 0.52 mmol) and 1,3-dicyclohexylcarbodiimide (151 mg, 0.738 mmol) in CH_2Cl_2 (10.0 mL) were added pyridine (43 μL, 52 mmol) and 2,2,2-trifluoroethanol (46 μL, 0.64 mmol). The suspension was stirred at room temperature for 12 h. The precipitate was filtered, and the filtrate was concentrated. Flash chromatography (EtOAc in hexanes, 10−15%) afforded **13f** (138 mg) in 71% yield as a white solid: mp 48−50 °C; IR (film, cm^{-1}) 2924, 1782, 1495, 1218, 1169; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.52−7.25 (m, 5H), 6.66 (s, 1H), 6.54 (s, 1H), 4.99 (s, 2H), 4.60 (s, 2H), 4.56 (q, $^2J_{H-F}$ = 8.4 Hz, 2H), 2.25 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (75 MHz) δ 167.7, 150.4, 144.6, 137.9, 133.5, 132.6, 128.3 (2C), 127.9, 125.4, 122.7 (q, $^1J_{C-F}$ = 277.3 Hz), 113.5, 74.7, 65.9, 60.6 (q, $^2J_{C-F}$ = 36.7 Hz), 21.0, 16.1; MS (EI) *m*/*z* (relative intensity) 368 (M^+, 12), 277 (9), 219 (5), 149 (12), 91 (100).

Phenyl (2-Benzyloxy-3,5-dimethyl)phenoxyacetate (13g). To a suspension of **12** (100 mg, 0.35 mmol) and 1,3-dicyclohexylcarbodiimide (76 mg, 0.37 mmol) in CH_2Cl_2 (10.0 mL) were added pyridine (30 μL, 0.37 mmol) and phenol (33 mg, 0.35 mmol). The suspension was stirred at room temperature for 12 h. The precipitate was filtered, and the filtrate was concentrated. Flash chromatography (EtOAc in hexanes 5%) afforded **13g** (102 mg) in 81% yield as a white solid: mp 58−60 °C; IR (film, cm^{-1}) 2919, 1775, 1493, 1204, 1150, 1112; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.51−7.09 (m, 10H), 6.67 (s, 1H), 6.65 (s, 1H), 5.03 (s, 2H), 4.91 (s, 2H), 2.28 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (68 MHz) δ 167.7, 150.7, 150.2, 144.6, 138.0, 133.6, 132.6, 129.6, 128.5, 128.4, 128.0, 126.3, 125.2, 121.4, 113.4, 74.7, 66.5, 21.2, 16.2; MS (EI) *m*/*z* (relative intensity) 362 (M^+, 0.5), 269 (7), 213 (5), 184 (8), 178 (25), 150 (17), 91 (100).

Lactone (14). A suspension of **13g** (52 mg, 0.29 mmol) and potassium carbonate (425 mg) in CH_2Cl_2 (10 mL) was stirred for 3 h. The reaction solution was diluted in CH_2Cl_2 (50 mL) and washed with water (60 mL). The organic layer was dried over $MgSO_4$ and concentrated. Flash chromatography (EtOAc in hexanes, 2%) afforded **14** (26 mg) in 76% yield as a faint yellow oil: IR (film, cm^{-1}) 2920, 1773, 1495, 1330, 1201; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 6.68 (s, 1H), 6.67 (s, 1H), 4.60 (s, 2H), 2.25 (s, 6H); ^{13}C NMR (75 MHz) δ 163.6, 142.0, 137.4,

134.6, 126.7, 125.5, 115.0, 64.7, 20.8, 15.0; MS (EI) *m/z* (relative intensity) 178 (M^+, 49), 150 (68), 149 (100).

***N,N*-Dimethyl (2-hydroxy-3,5-dimethyl)phenoxyacetamide (15a).** To a solution of **13a** (110 mg, 0.49 mmol) in EtOAc (10.0 mL) was added palladium on activated carbon (10%, 100 mg). The resulting suspension was shaken under H_2 (55 psi) on a Parr hydrogenator for 3 h. The catalyst was removed by filtration through a pad of Celite, and the filtrate was concentrated to afford **15a** (74 mg) in 95% yield as a white solid: mp 89−91 °C; IR (film, cm^{-1}) 3144 (br), 2925, 1648, 1500, 1310; ^1H NMR ($CDCl_3$, 270 MHz) δ 9.16 (s, 1H), 6.67 (s, 1H), 6.64 (s, 1H), 4.70 (s, 2H), 2.98 (s, 3H), 2.90 (s, 3H), 2.22 (s, 3H), 2.20 (s, 3H); ^{13}C NMR δ (68 MHz) 170.2, 146.9, 145.3, 128.1, 126.8, 126.0, 117.7, 71.5, 35.7, 35.3, 20.5, 15.8; MS (EI) *m/z* (relative intensity) 223 (M^+, 12), 178 (14), 150 (14), 87 (54).

Methyl (2-Hydroxy-3,5-dimethyl)phenoxyacetate (15b). To a solution of **13b** (98 mg. 0.47 mmol) in EtOAc (10.0 mL) was added palladium on activated carbon (10%, 100 mg). The resulting suspension was shaken under H_2 (55 psi) on a Parr hydrogenator for 3 h. The catalyst was removed by filtration through a pad of Celite and the filtrate was concentrated to afford **15b** as a colorless oil (63 mg) in 91% yield: IR (film, cm^{-1}) 3481 (br), 2840, 1748, 1234; ^1H NMR ($CDCl_3$, 270 MHz) δ 6.65 (s, 1H), 6.53 (s, 1H), 4.63 (s, 2H), 3.79 (s, 3H), 2.22 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (68 MHz) δ 171.0, 145.4, 143.2, 128.6, 126.0, 125.2, 114.2, 68.6, 52.5, 20.7, 15.6; MS (EI) *m/z* (relative intensity) 210 (M^+, 69), 178 (23), 150 (100), 137 (32).

1-Propyl (2-Hydroxy-3,5-dimethyl)phenoxyacetate (15c). To a solution of **13c** (109 mg, 0.46 mmol) in EtOAc (10.0 mL) was added palladium on activated carbon (10%, 50 mg). The resulting suspension was shaken under H_2 (55 psi) on a Parr hydrogenator for 3 h. The catalyst was removed by filtration through a pad of Celite and the filtrate was concentrated to afford **15c** (78 mg) in 99% yield as a colorless oil: IR (film, cm^{-1}) 3383 (br), 2967, 1740, 1501, 1307, 1214; ^1H NMR ($CDCl_3$, 270 MHz) δ 6.64 (s, 1H), 6.55 (s, 1H), 4.62 (s, 2H), 4.15 (t, J = 6.7 Hz, 2H), 2.21 (s, 3H), 2.20 (s, 3H), 1.66 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR (68 MHz) δ 171.1, 145.7, 143.4, 128.7, 126.1, 125.2, 114.5, 68.9, 67.3, 22.0, 20.7, 15.6, 10.2; MS (EI) *m/z* (relative intensity) 238 (M^+, 23), 178 (32), 150 (100), 137 (31).

2-Chloroethyl (2′-Hydroxy-3′,5′-dimethyl)phenoxyacetate (15d). To a solution of **13d** (74 mg) in CCl_4 (10.0 mL) was added palladium on activated carbon (10%, 72 mg). The resulting suspension was shaken under H_2 (55 psi) on a Parr hydrogenator for 3 h. The catalyst was removed by filtration through Celite and the filtrate was concentrated to afford **15d** (53 mg) in 97% yield as a colorless oil: IR (film, cm^{-1}) 3420 (br), 2923, 1754, 1500, 1208; ^1H NMR ($CDCl_3$, 270 MHz) δ 6.65 (s, 1H), 6.55 (s, 1H), 4.86 (s, 2H), 4.44 (t, J = 5.4 Hz, 2H), 3.69 (t, J = 5.4 Hz, 2H), 2.22 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (68 MHz) δ 170.2, 145.2, 143.1, 128.7, 126.0, 125.1, 113.9, 68.3, 64.9, 41.2, 20.7, 15.6; MS (EI) *m/z* (relative intensity) 260 (M + 2, 0.4), 258 (M^+, 1), 178 (1), 150 (4), 137 (2), 91 (0.4).

2,2,2-Trichloroethyl (2′-Hydroxy-3′,5′-dimethyl)phenoxyacetate (15e). To a solution of **13e** (47 mg) in CCl_4 (10.0 mL) was added palladium on activated carbon (10%, 150 mg). The resulting suspension was shaken under H_2 (55 psi) on a Parr hydrogenator for 1 h. The catalyst was removed by filtration through Celite, and the filtrate was concentrated to afford **15e** (36 mg) in 99% yield as a faint yellow solid: mp 52−54 °C; IR (film, cm^{-1}) 3441 (br), 2924, 1772, 1501, 130, 1151; ^1H NMR ($CDCl_3$, 270 MHz) δ 6.65 (s, 1H), 6.54 (s, 1H), 6.28 (br, 1H); 4.83 (s, 2H), 4.80 (s, 2H), 2.21 (s, 6H); ^{13}C NMR (68 MHz) δ 168.8, 144.9, 142.8, 128.8, 126.1, 125.2, 113.2, 94.3, 74.4, 67.8, 20.9, 15.7; MS (EI) *m/z* (relative intensity) 332 (M + 6, 0.5), 330 (M + 4, 3), 328 (M + 2, 9), 326 (M^+, 9), 178 (13), 149 (100), 137 (25).

2,2,2-Trifluoroethyl (2′-Hydroxy-3′,5′-dimethyl)phenoxyacetate (15f). To a solution of **13f** (45 mg, 0.16 mmol) in CCl_4 (10.0 mL) was added palladium on activated carbon (10%, 150 mg). The resulting suspension was shaken under H_2 (55 psi) on a Parr hydrogenator for 1 h. The catalyst was removed by filtration through Celite, and the filtrate was concentrated to afford **15f** (30 mg) in 88% yield as a white solid: mp 52−54 °C; IR (film, cm^{-1}) 3463 (br), 2923, 1777, 1501, 1301, 1161; ^1H NMR ($CDCl_3$, 270 MHz) δ 6.65 (s, 1H), 6.52 (s, 1H), 6.27 (br, 1H); 4.74 (s, 2H), 4.56 (q, $^2J_{H-F}$ = 8.2 Hz, 2H), 2.21 (s, 6H); ^{13}C NMR (68 MHz) δ 168.9, 144.9, 142.9, 128.9, 126.2, 125.3, 122.6 (q, $^1J_{C-F}$ = 277.2 Hz), 113.3, 67.7, 61.0 (q, $^2J_{C-F}$ = 36.9 Hz), 20.8, 15.6; MS (EI) *m/z* (relative intensity) 278 (M^+, 3), 178 (13), 149 (13).

Phenyl (2′-Hydroxy-3′,5′-dimethyl)phenoxyacetate (15g). To a solution of **13g** (48 mg) in CCl_4 (10.0 mL) was added palladium on activated carbon (10%, 50 mg). The resulting suspension was shaken under H_2 (55 psi) on a Parr hydrogenator for 1 h. The catalyst was removed by filtration through Celite, and the filtrate was concentrated to afford **15g** (32 mg) in 80% yield as a mixture containing lactone **14** (10% based on the area integration in ^1H NMR analysis): ^1H NMR ($CDCl_3$, 270 MHz) δ 7.42−7.08 (m, 5H), 6.68 (s, 1H), 6.62 (s, 1H), 6.48 (br, 1H); 4.88 (s, 2H), 2.24 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (68 MHz) δ 169.2, 150.0, 145.3, 143.2, 129.7, 128.8, 126.5, 126.2, 125.4, 121.3, 114.0, 68.7, 20.9, 15.7.

General Procedure for the Formation of Quinone Methides (16a−g). Stock solutions (25.0 mM) of **15a−g** in $CDCl_3$ containing acetic acid (d_4, 1 equiv) were prepared and diluted to 2.5 mM with $CDCl_3$. The resulting solutions were oxidized with PbO_2 at room temperature for 5 min. The suspensions were filtered with Acrodisc filter (13 CR, 0.45 μm) to give the desired 2.5 mM solutions of quinone methides **16a−g**.

Quinone Methide (16a). Silver(I) oxide was used as the oxidizing reagent for 20 min: ^1H NMR ($CDCl_3$, 270 MHz) δ 6.97 (d, J = 2.2 Hz, 1H), 6.45 (d, J = 2.2 Hz, 1H), 5.81 (s, 1H), 5.73 (s, 1H), 4.67 (s, 2H), 3.10 (s, 3H), 2.94 (s, 3H), 2.03 (s, 3H).

Quinone methide (16b): ^1H NMR ($CDCl_3$, 270 MHz) δ 6.98 (d, J = 2.2 Hz, 1H), 6.24 (d, J = 2.2 Hz, 1H), 5.77 (s, 1H), 5.74 (s, 1H), 4.62 (s, 2H), 3.79 (s, 3H), 2.03 (s, 3H).

Quinone methide (16c): ^1H NMR ($CDCl_3$, 270 MHz) δ 6.98 (d, J = 1.8 Hz, 1H), 6.24 (d, J = 1.8 Hz, 1H), 5.75 (s, 1H), 5.73 (s, 1H), 4.62 (s, 2H), 4.15 (t, J = 6.9 Hz, 2H), 2.03 (s, 3H), 1.66 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H).

Quinone methide (16d): ^1H NMR ($CDCl_3$, 270 MHz) δ 6.98 (d, J = 2.0 Hz, 1H), 6.29 (d, J = 2.0 Hz, 1H), 5.78 (s, 1H), 5.75 (s, 1H), 4.68 (s, 2H), 4.45 (t, J = 5.7 Hz, 2H), 3.69 (t, J = 5.7 Hz, 2H), 2.03 (s, 3H).

Quinone methide (16e): ^1H NMR ($CDCl_3$, 270 MHz) δ 6.98 (d, J = 2.2 Hz, 1H), 6.33 (d, J = 2.2 Hz, 1H), 5.75 (s, 2H), 4.84 (s, 2H), 4.80 (s, 2H), 2.03 (s, 3H).

Quinone methide (16f): ^1H NMR ($CDCl_3$, 270 MHz) δ 6.99 (d, J = 2.5 Hz, 1H), 6.29 (d, J = 2.5 Hz, 1H), 5.78 (s, 1H), 5.77 (s, 1H), 4.75 (s, 2H), 4.58 (q, $^2J_{H-F}$ = 8.4 Hz, 2H), 2.03 (s, 3H).

Quinone Methide (16 g). The resulting quinone methide **16g** solution contained lactone **14** (40%) based on the area integration in ^1H NMR analysis: ^1H NMR ($CDCl_3$, 270 MHz) δ 7.42−7.08 (m, 5H), 7.00 (d, J = 2.2 Hz, 1H), 6.41 (d, J = 2.2 Hz, 1H), 5.81 (s, 1H), 5.78 (s, 1H), 4.87 (s, 2H), 2.05 (s, 3H).

Study of the Dibenzyl Phosphoric Acid Alkylation by Quinone Methides 16. To the $CDCl_3$ solutions of quinone methides **16a−f** (2.5 mM, 600 μL each) containing mesitylene as an internal standard was added a solution of dibenzyl phosphoric acid in $CDCl_3$ (100 μL each). The final concentrations of dibenzyl phosphoric acid and quinone methides **16** were 3.2 and 2.1 mM, respectively. The reaction was monitored by ^1H NMR analysis. Greater than 95% conversion to trialkyl phosphate **17** was observed by ^1H NMR analysis. Minor impurities detected in the alkylation reaction (<5% by ^1H NMR analysis relative to an internal standard) were consistent with hydrolysis byproducts **17** and **18**. Although the trialkyl phosphate **17** was not sufficiently stable to allow isolation, the following solution characterizations were consistent with the structural assignments.

Trialkyl phosphate **17a**: ^1H NMR ($CDCl_3$, 270 MHz) δ 7.33−7.28 (m, 10H), 6.85 (s, 1H), 6.81 (s, 1H), 4.97 (d, $^3J_{P-H}$ = 7.7 Hz, 4H), 4.87 (d, $^3J_{P-H}$ = 8.7 Hz, 2H), 4.61 (s, 2H), 2.97 (s, 3H), 2.84 (s, 3H), 2.21 (s, 3H).

Trialkyl phosphate **17b**: ^1H NMR ($CDCl_3$, 270 MHz) δ 7.35−7.27 (m, 10H), 6.77 (s, 1H), 6.70 (s, 1H), 4.97 (d, $^3J_{P-H}$ = 7.9

Hz, 4H), 4.85 (d, $^3J_{P-H}$ = 8.9 Hz, 2H), 4.54 (s, 2H), 3.77 (s, 3H), 2.22 (s, 3H).

Trialkyl phosphate **17c**: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.33−7.26 (m, 10H), 6.77 (s, 1H), 6.21 (s, 1H), 4.97 (d, $^3J_{P-H}$ = 7.9 Hz, 4H), 4.85 (d, $^3J_{P-H}$ = 8.6 Hz, 2H), 4.53 (s, 2H), 4.13 (t, J = 6.7 Hz, 2H), 2.20 (s, 3H), 1.65 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H).

Trialkyl phosphate **17d**: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.33−7.24 (m, 10H), 6.76 (s, 1H), 6.70 (s, 1H), 4.98 (d, $^3J_{P-H}$ = 8.2 Hz, 4H), 4.86 (d, $^3J_{P-H}$ = 8.9 Hz, 2H), 4.59 (s, 2H), 4.42 (t, J = 5.7 Hz, 2H), 3.67 (t, J = 5.7 Hz, 2H), 2.20 (s, 3H).

Trialkyl phosphate **17e**: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.33−7.28 (m, 10H), 6.76 (s, 1H), 6.69 (s, 1H), 4.98 (d, $^3J_{P-H}$ = 7.2 Hz, 4H), 4.85 (d, $^3J_{P-H}$ = 8.7 Hz, 2H), 4.80 (s, 2H), 4.69 (s, 2H), 2.16 (s, 3H).

Trialkyl phosphate **17f**: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.33−7.24 (m, 10H), 6.77 (s, 1H), 6.68 (s, 1H), 4.97 (d, $^3J_{P-H}$ = 8.2 Hz, 4H), 4.86 (d, $^3J_{P-H}$ = 8.9 Hz, 2H), 4.63 (s, 2H), 4.53 (q, J_{H-F} = 8.4 Hz, 2H), 2.20 (s, 3H).

Investigation of in Situ Lactonization of Trialkyl Phosphate 17a−f. Upon completion of the phosphate addition to quinone methides **16a−f**, the study of in situ lactonization was initially carried out at room temperature over 48 h. Intermediates **17d−f** produced the desired lactonized trialkyl phosphate product **18** as indicated by ^{1}H NMR analysis. However, no lactonized product **18** was produced with **17a** and **17c**. Less than 5% conversion was observed with **17b** by ^{1}H NMR analysis. The efficiency of in situ lactonization of intermediates **17d−f** was further examined at 35 °C in the presence of 4 Å molecular sieves (10 mg) over 92 h. The reaction was monitored by ^{1}H NMR analysis. The percent conversion was calculated relative to mesitylene, the internal standard.

A detailed analysis of the in situ lactonization of intermediate **17f** (prepared as described above) was studied by ^{1}H NMR analysis at 35 °C over 90 h to confirm the formation of **18**. Tetrabutylammonium dibenzyl phosphate (1.0 equiv to the residual dibenzyl phosphoric acid) was added to the reaction so that the benzylic resonances of trialkyl phosphates **17f** and **18** could be clearly resolved for observation. Progress of the in situ lactonization was monitored by ^{1}H NMR analysis in the presence of 4 Å molecular sieves (10 mg).

Lactonized Trialkyl Phosphate (18). To a solution of **15f** (20.0 mg, 0.07 mmol) in $CHCl_3$ (35.0 mL) containing acetic acid (14 μL, 0.21 mmol) was added lead(IV) oxide (2.50 g). The suspension was stirred for 3 min, and the solid was filtered through a fritted glass filter. Dibenzyl phosphoric acid (40.0 mg, 0.14 mmol) and 4 Å molecular sieves (50 mg) were added to the resulting yellow solution. The reaction solution was stirred at 25 °C for 4 h, and then dry acetonitrile (2.0 mL) was added. In situ lactonization was carried out at 35 °C for 6 days. Tetrabutylammonium acetate (32.6 mg, 1.5 equiv) was added, and the resulting solution was passed through a pad of Florisil (200 mesh). Flash chromatography (Florisil, 200 mesh; EtOAc in $CHCl_3$, 0−10%) gave **18** (18.3 mg) in 58% yield as a yellow oil: IR (film, cm^{-1}) 1783, 1328, 1265, 1204, 1017; ^{1}H NMR ($CDCl_3$) δ 7.37−7.25 (m, 10H), 6.80 (s, 2H), 5.01 (d, $^3J_{P-H}$ = 8.1 Hz, 4H), 4.87 (d, $^3J_{P-H}$ = 8.4 Hz, 2H), 4.59 (s, 2H), 2.25 (s, 3H); ^{13}C NMR (75 MHz) δ 163.2, 142.2, 139.5, 135.8 (d, $^3J_{P-C}$ = 7.5 Hz), 132.6 (d, $^3J_{P-C}$ = 7.5 Hz), 128.7(2C), 128.0, 127.5, 124.5, 114.4, 69.4 (d, $^2J_{P-C}$ = 5.7 Hz), 68.5 (d, $^2J_{P-C}$ = 6.4 Hz), 64.6, 15.2; ^{31}P NMR δ 8.75; MS (DCI, NH_3) *m*/*z* (relative intensity) 472 (MNH_4^+, 34), 455 (MH^+, 40), 296 (100), 279 (33), 240 (62), 223 (52), 194 (51), 177 (16), 149 (21), 108 (39), 106 (29), 91 (17); HRMS (DCI, NH_3), *m*/*z* [MH^+] calcd for $C_{24}H_{24}O_7P$ 455.1260, found 455.1240.

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Supporting Information Available: NMR spectra for compounds **7**, **9**, **11**, **13a−g**, **14**, **15a−f**, **15g**/**14**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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