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Improved Alkylation and Product Stability in Phosphotriester Formation through Quinone Methide Reactions with Dialkyl Phosphates

Brian A. Bakke, Matthias C. McIntosh, and Kenneth D. Turnbull*

Department of Chemistry and Biochemistry, University of Arkansas, Fayetteville, Arkansas 72701

kturnbul@uark.edu

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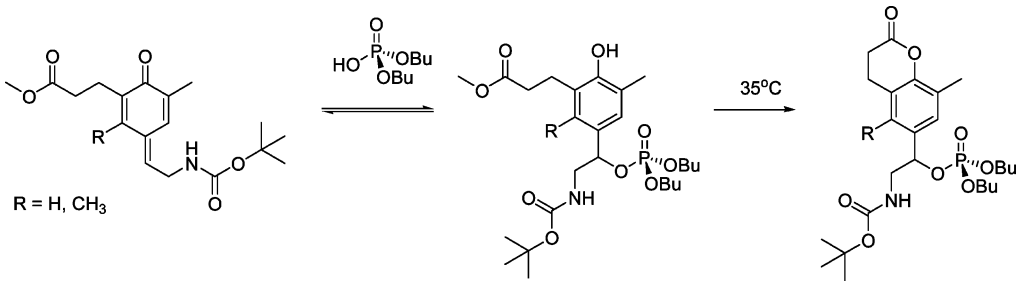

Investigating reactions of functionalized *p*-quinone methides continues to advance our design of a reagent being developed for controlled, in situ modification of DNA via phosphodiester alkylation. Previously reported investigations of *p*-quinone methides derived from catechols allowed for trapping of isolable trialkyl phosphates for characterization and mechanistic information. However, lactone formation with these derivatives required long reaction times, resulting in an unfavorable mixture of trialkyl phosphate and hydrolysis products. To enhance the rate and efficacy of trialkyl phosphate formation and trapping, a phenol derived *p*-quinone methide has been designed to enforce a conformation favoring lactonization of the dialkyl phosphate alkylated intermediate. The relative rates of phosphodiester alkylation and subsequent trapping of the phosphotriester adduct have been examined by UV and ^{1}H NMR analysis for *p*-quinone methide precursor **1** and the corresponding control, **1′**. The incorporation of a methyl group at the *meta*-position of **1** (relative to **1′**) significantly improves the rate of lactionization to provide a much higher yield of the desired product, lactonized phosphotriester **5**. The control reaction with **1′** afforded only a minor amount of the corresponding lactonized trialkyl phosphate **5′**.

Introduction

The role of quinone methide intermediates in bioreductive processes is well-established.[1−5] Investigations with DNA and nucleic acids have predominantly been carried out with *o*-quinone methides[6−12] and less with *p*-quinone methides[13−15] focusing on base alkylation. In developing a research program around the application of quinone methides to drug design, drug delivery, and biomolecular labeling, we have investigated the reactivity and formation of a variety of *p*-quinone methides to optimize alkylation of mildly nucleophilic phosphodiesters as models for nucleic acid polymers.

We have shown that phosphodiester alkylation with a *p*-quinone methide is a second-order, reversible process

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leading to the rapid, kinetic-favored formation of a phosphotriester followed by a very slow hydrolysis of that product to a benzyl alcohol. The quinone methide alkylation of the phosphodiester is in competition with the significantly slower, thermodynamic-favored, direct hydrolysis of the quinone methide to produce a benzyl alcohol.[16] To maximize phosphotriester product formation, the incorporation of a trapping moiety to stabilize the product and prevent reversibility became necessary. We previously reported an approach to accomplish this with a catechol-derived quinone methide designed to alkylate a phosphodiester via a characterizable *p*-quinone methide followed by in situ lactonization.[17] Although the approach proved effective, affording the desired trialkyl phosphate product in good yield, the intramolecular trapping via lactonization proved to be a slow, temperature-dependent process requiring rigorously anhydrous conditions, and product isolation was challenging.

Conformationally enforced acceleration of lactonization reaction rates through steric effects is well-precedented.[18−23] Lactonization studies of a variety of hydrocoumarinic acids demonstrated that the relative rates increased substantially with increasing substituent bulk. The Borchardt laboratory has extensively examined[24−35] and reviewed[36−38] the use of coumarin-based, esterase-sensitive cyclic prodrugs incorporating the "trimethyl lock" concept elegantly utilized within a linker for the facile release of drugs in vivo.

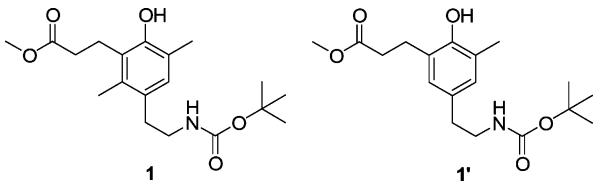

FIGURE 1. Quinone methide precursors **1** and **1′**.

Based on such steric effects for enhancing lactonization rates in related systems, we have redesigned the *p*-quinone methide derivative in an attempt to increase the rate of the lactonization reaction and afford a more stable phosphotriester product. However, as observed in our previous work,[17] lactoniozation rates that are too rapid can preclude the ability to form the quinone methide. Scheme 1 demonstrates the envisioned reaction of designed *p*-quinone methide **2**. Although the methyl propionate arm of **1** was designed for facile lactonization, it required sufficient stability to allow formation of *p*-quinone methide **2** without concomitant lactonization. It was necessary that *p*-quinone methide **2** maintain sufficient reactivity with the presence of the methyl substituent (R_1) adjacent to the alkylidene reaction center in order to rapidly alkylate a dialkyl phosphate to afford **3**. Alkylation to **3** was to be followed by lactonization through population of a reactive conformation enforced by steric interaction with the adjacent methyl group, leading to the desired stabilized trialkyl phosphate **5**. It was hoped that the lactonization of **3** might prove facile enough to allow the kinetic-favored product to be drained off through lactonization to afford **5** and preclude reversibility back to quinone methide **2**, where hydrolysis to the thermodynamic-favored **4** can undergo lactonization to afford **6**. It was further hoped that trialkyl phosphate **5** might prove more stable than the corresponding trialkyl phosphates afforded in our previous work.[17]

To determine the effect of the methyl group on quinone methide formation from **1**, alkylation of quinone methide **2**, and stereopopulation control in **3**, two functionalized quinone methide derivatives were desired for investigation. The syntheses of **1** and the corresponding control without the methyl group, **1′**, were accomplished for this purpose (Figure 1).

We report the results of our investigations, which demonstrate the effectiveness of incorporating a methyl substituent *ortho* to the propionic ester lactonizing functionality for enhanced lactonization and thereby stabilization of the kinetic-favored, phosphotriester product[16] derived from quinone methide alkylation of a phosphodiester. Notably, the incorporation of this propionic ester and *o*-methyl substituent still allowed for quantitative formation of the desired *p*-quinone methide from the phenol and offered no impedance to the quinone methide alkylation reaction with the phosphodiester. Further, the methyl substituent afforded considerable improvements in the rate and temperature dependence of lactone formation. The overall design also contributed to a highly stable trialkyl phosphate product.

Results and Discussion

Synthesis of Quinone Methide Precursors. Our investigations required the synthesis of phenols **1** and

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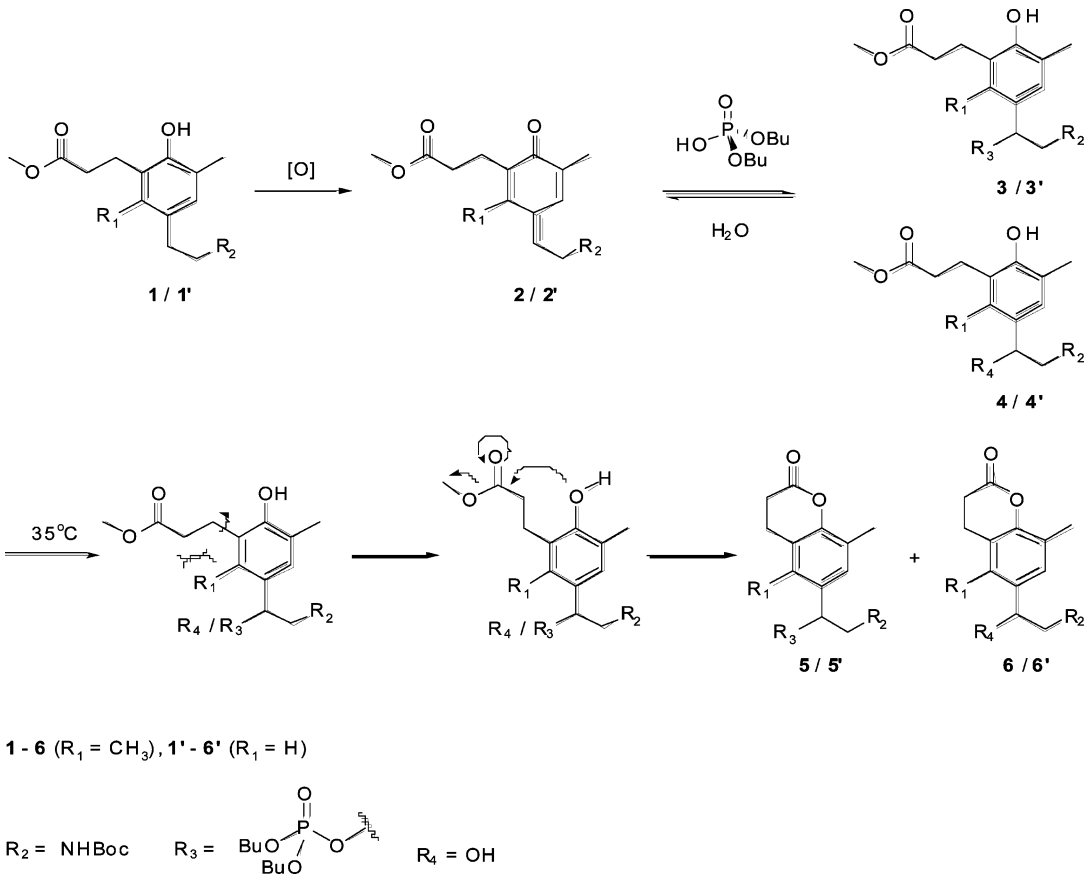
SCHEME 1



1′ as precursors for the corresponding quinone methides **2** and **2′**. Phenols **1** and **1′** also incorporated a carbamate protected amine in the *para*-postion for improved phosphodiester alkylation.[39] The 10-step synthesis was accomplished as shown in Scheme 2. Acetophenone **9** was obtained in two steps via the O-acylation[40] of commercially available 2,5-dimethyl phenol **7** followed by Fries rearrangement.[41] Bromo-ketone **10** was obtained via α-keto halogenation[42] of **9** followed by reductive deoxygenation[43] to yield **11**. Amine hydrochloride **13** was easily made in two steps from azide addition[44] to **11** followed by hydrogentation[45] of **12**. Functionalization of amine hydrochloride **13** with di-*tert*-butyl dicarbonate[46] provided the cinnimate precursor **14**. Treatment of **14** with bis(pyridine)iodonium tetrafluoroborate[47] followed by Heck reaction using methyl acrylate[48] gave **16** in two additional steps. Quinone methide precursor **1** was then obtained from magnesium reduction[49] of α,β-unsaturated ester **16**. This synthetic pathway was similarly applied to prepare **1′**.

Regiospecific Oxidation of 1 and 1′ to Quinone Methides 2 and 2′. The regiospecific generation of *p*-quinone methides using lead(II) oxide and silver(I) oxide from phenol precursors has been demonstrated.[50−52] It has been shown in our laboratory that phenolic derivatives functionalized equally at the *ortho*- and *para*-positions will oxidize specifically to the *p*-quinone methide.[39] This oxidative specificity has allowed derivation of the quinone methide starting from phenolic precursors rather than the catechol precursors used in our previous work,[17] which proved to be a key factor in greatly enhancing the product stability in this work (vida infra). The conversion of **1** and **1′** to *p*-quinone methides **2** and **2′** was monitored by ^{1}H NMR in $CDCl_3$ at 20 °C. The reaction with lead(II) oxide was quantitative and regiospecific for *p*-quinone methides **2** and **2′** as determined by relative integration of the *p*-quinone methide alkylidene resonance at 6.42 ppm (1H) relative to an internal standard of mesitylene (Ar-H, 6.79 ppm, 3H) (see Experimental Section). There was no sign of lactonization observed in either the preparation of **1** or the conversion

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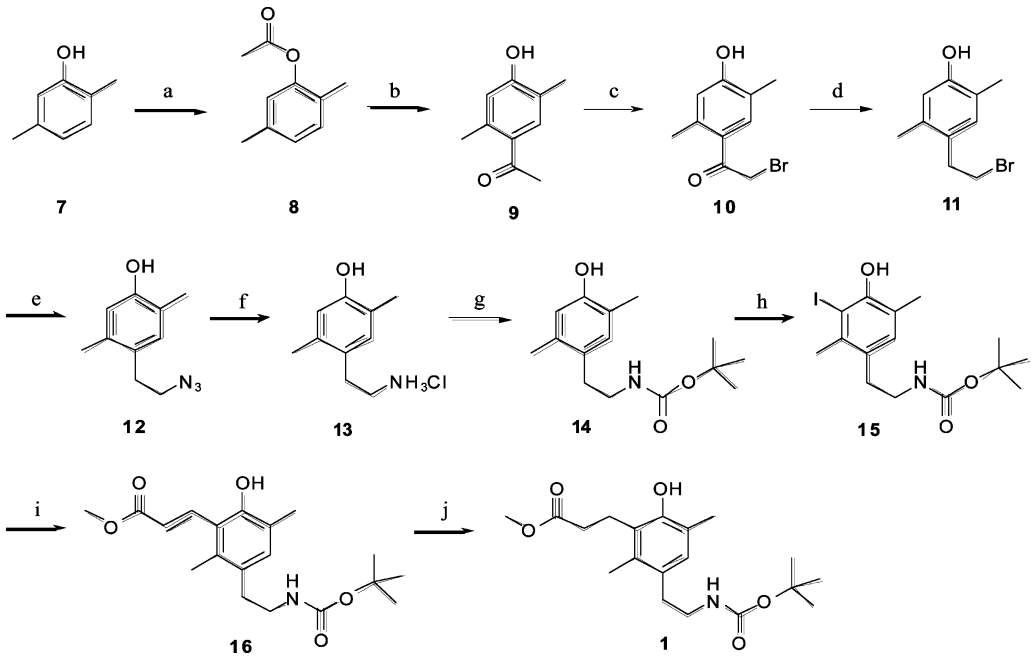
SCHEME 2[a]



[a] Reaction conditions, % isolated yields: (a) Ac_2O, TEA, CH_2Cl_2, 98%; (b) $AlCl_3$, $MeNO_2$, 75%; (c) $CuBr_2$, EtOAc, $CHCl_3$, 79%; (d) $NaBH_3CN$, TFA, 70%; (e) NaN_3, EtOH, 78%; (f) Pd−C, H_2, HCl, EtOH, 72%; (g) di-*tert*-butyl dicarbonate, TEA, MeOH, 83%; (h) Ipy_2BF_4, CH_2Cl_2, DMSO, 74%; (i) methyl acrylate, $Pd(OAc)_2$, NMP, TEA, NaOAc, 66%; (j) Mg, MeOH, 81%.

of **1** to quinone methide **2**, verifying that the methyl propionate with the accompanying *o*-methyl would not undergo lactonization in competition with quinone methide formation under the oxidative conditions used.

Alkylation of Dibutyl Phosphate by Quinone Methides 2 and 2′ (UV Analysis). The effect of the methyl substituent on the rate of quinone methide alkylation of a phosphodiester was initially investigated. It was unclear whether the methyl substituent would effect a slower rate for quinone methide alkylation due to a 1,3-allylic steric inhibition or increase the rate by increasing the reactivity of the quinone methide through the same interaction. Previous efforts in our laboratory have utilized both UV and ^{1}H NMR spectroscopy for the determination of *p*-quinone methide alkylation rates of simple phosphodiesters.[16,53] Our more recent work has focused on maximizing the rate of quinone methide phosphodiester alkylation. It was determined that incorporation of an NHBOC functional group in close proximity to the *p*-benzylic position of the desired *p*-quinone methide allowed for maximum alkylation rates of simple phosphodiesters.[39] The enhanced reactivity of the *p*-quinone methide toward phosphodiester alkylation precluded the ability to monitor the rate of phosphodiester alkylation by ^{1}H NMR. To quantify the alkylation rates of quinone methides **2** and **2′** the reactions were monitored in triplicate by UV spectroscopy, following the loss of quinone methide ($\lambda_{max} = 304$ nm) as a measure of the rate of phosphotriester formation during the initial 60% loss of quinone methide. These reactions were conducted in CH_3CN at 20 °C by micropipet addition of 800, 600, 400, and 200 μM solutions (1 mL) of serial diluted dibutyl phosphate (2 equiv) to 400, 300, 200 and 100 μM (1 mL) solutions of quinone methide/sodium perchlorate (0.1 M) in a temperature-controlled UV cuvette (200, 150, 100 and 50 μM final concentrations of quinone methide). A large excess of sodium perchlorate is required to buffer the change in ionic strength due to formation of the dibutyl phosphate salt in the equilibrium of quinone methide and trialkyl phosphate. The loss of absorbance of the quinone methide was found to be linear with respect to time for the first 60% loss. The linear nature of quinone methide loss indicates no product equilibrium over the monitored course of the reaction (120 s) under the conditions of these UV experiments.

A control reaction under acid-catalyzed conditions was used to determine if quinone methide hydrolysis was contributing to the observed rate of loss of quinone methide. Based on earlier work, the control reaction used methane sulfonic acid (2 equiv) and water (2 equiv) to activate the quinone methide toward acid-catalyzed hydrolysis[53] but resulted in no quinone methide loss after 2 min, suggesting hydrolysis is not a competitive reaction during the monitored analysis. However, upon addition of 2 equiv of dibutyl phosphate (containing 2 equiv of water) complete loss of the quinone methide absorption signal is observed within 120 s at all concentration levels.

Based on this UV analysis, the rate of quinone methide disappearance is 1.95×10^{-2} μM^{-1} s^{-1} for **2** and 2.03×10^{-2} μM^{-1} s^{-1} for **2′** (Figure 2). The negligible difference in the rates of reaction for quinone methides **2** and **2′** suggests there is not a significant allylic inhibitory effect on quinone methide alkylation for **2**.

Lactonization of Phosphotriesters 3 and 3′ (^{1}H NMR Analysis). Generation of quinone methides **2** and **2′** was carried out as described in Experimental Section. The conversion of quinone methide **2′** to trialkyl phosphate **3′** was clearly observed by ^{1}H NMR analysis upon addition of dibutyl phosphate (2 equiv). The disap-

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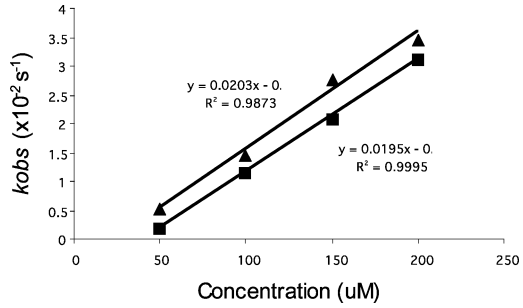

FIGURE 2. Plot of the relative rates of the loss of quinone methide **2** and **2′**. This demonstrates that the effect of the *m*-methyl substituent affords a negligible decrease in the rate of quinone methide alkylation. (▲) Quinone methide **2′**, slope: 2.03×10^{-2} μM^{-1} s^{-1} ($R^2 = 0.987$). (■) Quinone methide **2**, slope: 1.95×10^{-2} μM^{-1} s^{-1} ($R^2 = 0.999$). The percent error was determined to be less than 12% for each of the triplicated measurement points.

pearance of the characteristic *p*-quinone methide alkylidene resonance of **2′** at 6.21 ppm (t, $J = 7.18$ Hz, 1H) coincided with the appearance of a triplet of doublets at 5.20 ppm (td, $J_{H-P} = 3.72$ Hz, 1H). This resonance coupling and chemical shift is characteristic of the phosphorus-coupled benzylic proton resonance of the trialkyl phosphate and clearly revealed that phosphodiester alkylation had occurred.[17,39]

The rates of lactonization for alkylation products **3** and **3′** were obtained from ^{1}H NMR monitored analysis of the reaction in $CDCl_3$. This was most accurately accomplished by monitoring the loss of the methyl ester at 3.68 ppm (s, 3H) in **3** and **3′**. No other side reaction was seen to occur with the methyl ester other than lactonization, as evident by the 1:1 ratio of loss in methyl ester resonance with corresponding formation of lactone product. The rate of lactonization was measured by comparing the methyl ester resonance disappearance relative to an internal standard of mesitylene at 35 °C.

The ^{1}H NMR analysis for the non-*meta*-methylated derivative **3′** revealed no sign of lactonization in 1 h at 35 °C as evidenced by the fact that there was no loss of the methyl ester resonance for trialkyl phosphate **3′**. After 2 h of heating, 10% of the characteristic methyl ester resonance had been lost. Complete loss of methyl ester for trialkyl phosphate **3′** was observed after 12 h at 35 °C. As a result of the extended reaction times required for lactonization of **3′**, an unidentified reaction, thought to be a polymerization of the quinone methide, resulted in the signal loss of identifiable product to an as yet unidentified material. However, as this side reaction was not detectable in the initial 2 h reaction period, it was considered irrelevant for the purpose of relative comparison of **3′** as a control for **3** (vida infra).

The conversion of quinone methide **2** to trialkyl phosphate **3** was clearly observed by ^{1}H NMR analysis upon addition of dibutyl phosphate (2 equiv). The disappearance of the characteristic *p*-quinone methide alkylidene resonance of **2** at 6.42 ppm (t, $J = 7.18$ Hz, 1H) coincided with the appearance of a triplet of doublets at 5.52 ppm (td, $J_{H-P} = 3.24$ Hz, 1H). The in situ lactonization of trialkyl phosphate **3** was carefully monitored by ^{1}H NMR analysis during the 2 h required for the lactonization reaction to reach completion.

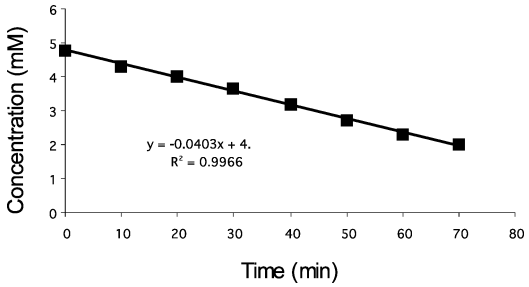

FIGURE 3. Loss of methyl ester concomitant with formation of lactonized trialkyl phosphate **5** and benzyl alcohol **6**. Each data point was based on relative resonance integration against an internal standard (mesitylene) of at least three independent analyses, as described in the experimental, affording a 5% error, with a slope = 6.72×10^{-4} mM s^{-1} ($R^2 = 0.997$).

In contrast to nonmethylated trialkyl phosphate **3′**, after 1 h at 35 °C, 50% of methylated trialkyl phosphate **3** had been converted to lactonized trialkyl phosphate **5**, as measured by the loss of methyl ester resonance, relative to the mesitylene internal standard, and as characterized by the appearance of the triplet of doublets at 5.57 ppm (td, $J_{P-H} = 3.24$, 1H), consistent with the resonance signal of the phosphorus-coupled benzylic hydrogen. There was also a small amount of benzyl alcohol **6** produced within the initial hour at 35 °C, as evident by the slight appearance of a resonance signal at 5.04 ppm, consistent with the benzylic hydrogen. After 2 h complete conversion of trialkyl phosphate **3** to lactonized trialkyl phosphate **5** and benzyl alcohol **6** was observed.

The relative rate of lactonization (as measured by the loss of methyl ester) was determined for the conversion of phosphotriester **3** and benzyl alcohol **4** at 35 °C in $CDCl_3$ to form **5** and **6**. The relative rate of lactonization for the first 60% loss of methyl ester is 6.72×10^{-4} mM s^{-1}.

The final ratio of lactonized trialkyl phosphate **5** to benzyl alcohol **6** was determined by ^{1}H NMR analysis against a mesitylene internal standard to be 3.0:1.0 in favor of the desired trialkyl phosphate based on an average of triplicated runs. This ratio was observed after lactonization was complete in 2 h at 35 °C. The reaction was allowed to continue for an additional 10 h at 35 °C to duplicate the conditions used in the control reaction with **3′**, and the ratio remained unchanged within that time, as did the quantity of **5** and **6** relative to the internal standard. This clearly concurs with earlier work[16] showing that hydrolysis occurs directly on the quinone methide leading to benzyl alcohol **4**, which lactonizes to **6**. While **3** may revert back to quinone methide **2** to undergo hydrolysis prior to lactonization, once lactonization to **5** occurs, the trialkyl phosphate product is stable under the reaction conditions. Further, **5** was found to be stable in $CDCl_3$ (with 2 equiv of water) for up to 20 days at 20 °C, and no change was observed in the ratio of lactonized trialkyl phosphate **5** to benzyl alcohol **6**.

Whereas our previous catechol-derived system verified the concept of trapping the trialkyl phosphate from quinone methide alkylation of a phosphodiester through lactonization,[17] this work offers significant improvement in both the rate of lactonization and the stability of the

resulting product. Final demonstration of product stability was shown by isolation of desired lactonized trialkyl phosphate **5** using standard silica gel preparative TLC to afford a 61% yield of the product.

Conclusion

We have synthesized and compared the rates of quinone methide alkylation of a phosphodiester followed by lactonization of the resulting trialkyl phosphate for two functionalized quinone methides. Our UV and ^{1}H NMR studies demonstrate that incorporation of a methyl group *ortho* to the propionic ester lactionization functionality still allows for the quantitative, oxidative formation of the *p*-quinone methide and has a negligible effect on the rate of phosphodiester alkylation with quinone methide **2** but significantly improves the ensuing lactonization rate of resulting trialkyl phosphate **3** to afford the stable, lactonized trialkyl phosphate **5**. Stability of trialkyl phosphate **5** has also been improved relative to our previous work with catechol-derived quinone methide alkylators.[17] Consequently, the overall yield of isolable trialklyphosphate relative to hydrolyzed product increases in favor of the desired trialkyl phosphate. However, to more effectively compete with reversibility of the phosphodiester alkylation with a *p*-quinone methide, a yet more facile lactonization process would be desired if *p*-quinone methide formation were not hindered. These results offer further improvements toward the development of a fully functional DNA phosphodiester alkylating reagent.

Experimental Section

^{1}H NMR analysis was carried out in $CDCl_3$ on a 270 NMR spectrometer. UV data were recorded at 304 nm in CH_3CN using a UV−vis spectrometer.

Acetic Acid 2,5-Dimethyl-phenyl Ester 8. Triethylamine (24.4 mL, 164 mmol) and acetic anhydride (6.18 mL, 65.5 mmol) were added to a stirring solution of **7** (6.67 g, 54.6 mmol) in CH_2Cl_2 (50 mL) at room temperature and stirred for 12 h. The reaction was diluted with EtOAc, washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo to yield a clear oil. The oil was purified by flash chromatography on silica gel (1:1 EtOAc/hexanes) to afford a clear oil (8.78 g, 98% yield): ^{1}H NMR δ 7.14 (d, J = 7.7 Hz, 1H), 6.99 (d, J = 7.7 Hz, 1H), 6.85 (s, 1H), 2.34 (s, 3H), 2.32 (s, 3H), 2.16 (s, 3H); ^{13}C NMR δ 169.4, 149.3, 137.0, 130.9, 126.9, 125.6, 122.5, 21.0, 20.9, 15.8; IR (NaCl) 2925, 1767, 1217 cm^{-1}. Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.20; H, 7.31. Found: C, 72.98; H, 7.12.

1-(4-Hydroxy-2,5-dimethyl-phenyl)-ethanone 9. Aluminum chloride (10.3 g, 76.8 mmol) was added to a stirring solution of **8** (5.04 g, 30.7 mmol) in nitromethane (100 mL) at 0 °C and subsequently stirred at 50 °C in an oil bath for 12 h. The reaction was quenched by pouring over ice (50 mL). The yellow solution was then extracted with EtOAc, washed with 6 N HCl, saturated $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated in vacuo to yield a yellow solid. The solid was purified by flash chromatography on silica gel (1:3 EtOAc/hexanes) to afford an off-white solid. The off-white solid was then recrystallized from EtOAc/hexanes to yield a white solid (3.78 g, 75% yield): mp 130−132 °C; ^{1}H NMR δ 7.59 (s, 1H), 6.67 (s, 1H), 2.56 (s, 3H), 2.49 (s, 3H), 2.25 (s, 3H); ^{13}C NMR δ 200.7, 157.6, 140.1, 134.3, 129.4, 121.2, 118.6, 29.1, 22.2, 15.5; IR (NaCl) 3431, 1640, 1280 cm^{-1}. Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.20; H, 7.31. Found: C, 73.40; H, 7.42.

2-Bromo-1-(4-hydroxy-2,5-dimethyl-phenyl)-ethanone 10. A solution of **9** (1.86 g, 11.4 mmol) in $CHCl_3$ (60 mL) was added to a refluxing solution of copper (II) bromide (5.07 g, 22.7 mmol) in EtOAc (50 mL). The mixture was refluxed for 10 h. The solution was filtered through charcoal/Celite and concentrated in vacuo to a green solid. The solid was purified by flash chromatography on silica gel (1:2 EtOAc/hexanes) to afford a light yellow solid. The solid was recrystallized from EtOAc/hexanes to yield clear plate crystals (2.19 g, 79%): mp 141−144 °C; ^{1}H NMR δ 7.55 (s, 1H), 6.66 (s, 1H), 5.28 (s, 1H), 4.39 (s, 2H), 2.49 (s, 3H), 2.25 (s, 3H); ^{13}C NMR δ 192.3, 157.5, 141.6, 133.7, 126.6, 121.1, 118.9, 33.5, 21.9, 15.4; IR (NaCl) 3408, 1648, 1269 cm^{-1}. Anal. Calcd for $C_{10}H_{11}BrO_2$: C, 49.43; H, 4.53; Br, 32.88. Found: C, 49.62; H, 4.64; Br, 33.04.

4-(2-Bromo-ethyl)-2,5-dimethyl-phenol 11. Sodium cyano-borohydride (2.06 g, 39.0 mmol) was added over 10 min to a stirring solution of **10** (2.37 g, 9.74 mmol) in trifluoroacetic acid (30 mL) at 0 °C and stirred for 3 h. The solution was concentrated in vacuo to yield a yellow oil. The oil was diluted in EtOAc, washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated in vacuo to a slight yellow oil. The oil was purified by flash chromatography on silica gel (1:3 EtOAc/hexanes) to afford a clear oil (1.56 g, 70%): ^{1}H NMR δ 6.91 (s, 1H), 6.59 (s, 1H), 5.03 (s, 1H), 3.48 (t, J = 7.92 Hz, 2H), 3.05 (t, J = 7.92 Hz, 2H), 2.24 (s, 3H), 2.20 (s, 3H); ^{13}C NMR δ 152.6, 135.0, 132.2, 129.5, 121.5, 117.1, 36.3, 32.4, 19.0, 15.4; IR (NaCl) 3418, 1283 cm^{-1}. Anal. Calcd for $C_{10}H_{13}$-BrO: C, 52.45; H, 5.68; Br, 34.89. Found: C, 52.52; H, 5.55; Br, 34.67.

4-(2-Azido-ethyl)-2,5-dimethyl-phenol 12. Sodium azide (0.858 g, 13.2 mmol) was added to a stirring solution of **11** (2.52 g, 11.0 mmol) in ethanol (60 mL) and refluxed for 10 h. The mixture was passed through Celite and concentrated in vacuo to yield a clear oil. The oil was diluted in EtOAc, washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo to a clear oil. The oil was purified by flash chromatography on silica gel (1:3 EtOAc/hexanes) to afford a clear oil (1.64 g, 78%): ^{1}H NMR δ 6.93 (s, 1H), 6.60 (s, 1H), 5.42 (s, 1H), 3.40 (t, J = 7.67 Hz, 2H), 2.79 (t, J = 7.67, 2H), 2.26 (s, 3H), 2.23 (s, 3H); ^{13}C NMR δ 152.6, 135.0, 132.2, 128.2, 121.7, 117.1, 51.9, 31.9, 19.0, 15.5; IR (NaCl) 3408, 2100, 1282 cm^{-1}. Anal. Calcd for $C_{10}H_{13}N_3O$: C, 62.85; H, 6.80. Found: C, 62.79; H, 7.00.

2-(4-Hydroxy-2,5-dimethyl-phenyl)-ethylammonium Chloride 13. Palladium/carbon (10%, 0.325 g, 20% w/w) and concentrated hydrochloric acid (1 mL) were added to a solution of **12** (1.63 g, 8.51 mmol) in ethanol (20 mL) in a high-pressure flask. The solution was hydrogenated under H_2 pressure (60 psi) with shaking for 8 h. The solution was passed through Celite and concentrated in vacuo to an off-white solid. The solid was recrystallized from EtOH/Et_2O to yield white crystals (1.23 g, 72%): mp 218−222 °C; ^{1}H NMR δ 6.86 (s, 1H), 6.59 (s, 1H), 3.03 (t, J = 5.69, 2H), 2.83 (t, J = 5.69, 2H), 2.23 (s, 3H), 2.12 (s, 3H); ^{13}C NMR δ 154.2, 134.3, 131.5, 125.1, 122.1, 116.5, 40.0, 30.1, 17.6, 14.4.

[2-(4-Hydroxy-2,5-dimethyl-phenyl)-ethyl]-carbamic Acid *tert*-Butyl Ester 14. Di-*tert*-butyl dicarbamate (0.734 g, 3.37 mmol) was added to a stirring solution of **13** (0.566 g, 2.80 mmol) in TEA/MeOH (1:3, 10 mL) at room temperature and stirred for 7 h. The solution was diluted with EtOAc, washed with saturated ammonium chloride and brine, dried ($MgSO_4$), and concentrated in vacuo to a light brown solid. The solid was recrystallized from EtOAc/hexanes to yield clear crystals (0.620 g, 83%): mp 160−162 °C; ^{1}H NMR δ 6.85 (s, 1H), 6.58 (s, 1H), 4.56 (bs, 1H), 3.28 (bq, J = 6.68, 2H), 2.68 (t, J = 6.68, 2H), 2.22 (s, 3H), 2.18 (s, 3H), 1.43 (s, 9H); ^{13}C NMR δ 156.0, 152.3, 135.2, 132.3, 129.1, 121.0, 116.9, 79.4, 41.1, 32.8, 28.5, 19.0, 15.3; IR (NaCl) 3328, 1684, 1516, 1282, 1166 cm^{-1}. Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.95; H, 8.68. Found: C, 68.12; H, 8.54.

[2-(4-Hydroxy-3-iodo-2,5-dimethyl-phenyl)-ethyl]-carbamic Acid *tert*-Butyl Ester 15. Bis(pyridine)iodonium tetrafluoroborate (0.844 g, 2.23 mmol) was added to a stirring

solution of **14** (0.547 g, 2.06 mmol) in DMSO/CH_2Cl_2 (1:10, 25 mL) at room temperature and stirred for 9 h. The solution was diluted with EtOAc, washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo to a yellow oil. The oil was purified by flash chromatography on silica gel (1:3 EtOAc/hexanes) to afford a pale yellow oil (0.598 g, 74%): ^{1}H NMR δ 6.84 (s, 1H), 5.45 (s, 1H), 4.59 (bs, 1H), 3.25 (q, J = 6.68, 2H), 2.80 (t, J = 6.68, 2H), 2.42 (s, 3H), 2.26 (s, 3H), 1.43 (s, 9H); ^{13}C NMR δ 156.0, 151.5, 137.0, 132.5, 129.6, 121.8, 95.9, 79.3, 41.3, 34.8, 28.5, 25.3, 16.9; IR (NaCl) 3402, 2248, 1693 cm^{-1}. Anal. Calcd for $C_{15}H_{22}INO_3$: C, 46.05; H, 5.67. Found: C, 46.26; H, 5.59.

3-[3-(2-*tert*-Butoxy carbonylamino-ethyl)-6-hydroxy-2,5-dimethyl-phenyl]-acrylic Acid Methyl Ester 16. Palladium acetate (0.017 g, 0.076 mmol), TEA (0.580 mL, 3.80 mmol), and NMP (10 mL) were combined in a test tube and heated to dissolve the palladium. The black solution was then added to a stirring mixture of **15** (0.598 g, 1.52 mmol), sodium acetate (0.125 g, 1.52 mmol), and NMP (10 mL) in a high-pressure reaction tube. The solution was stirred while heating at 75 °C in an oil bath for 14 h. The mixture was diluted with EtOAc, washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo to a dark brown solid. The solid was purified by flash chromatography on silica gel (1:3 EtOAc/hexanes) to afford a light brown solid. The solid was recrystallized from EtOAc/hexanes to yield clear crystals (0.352 g, 66%): mp 168−170 °C; ^{1}H NMR δ 7.83 (d, J = 16.33 Hz, 1H), 6.90 (s, 1H), 6.41 (d, J = 16.33 Hz, 1H), 5.21 (s, 1H), 4.56 (bs, 1H), 3.81 (s, 3H), 3.23 (bq, J = 6.68, 2H), 2.73 (t, J = 6.68, 2H), 2.25 (s, 3H), 2.21 (s, 3H), 1.43 (s, 9H); ^{13}C NMR δ 167.4, 156, 150.8, 141.0 134.1, 133.2, 129.2 123.3, 121.5, 121.2, 79.2, 51.9, 41.2, 33.6, 28.5, 16.2, 15.8; IR (NaCl) 3404, 1644 cm^{-1}. Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.36; H, 7.73. Found: C, 65.15; H, 7.59.

3-[3-(2-*tert*-Butoxycarbonyl)amino-ethyl)-6-hydroxy-2,5-dimethyl-phenyl]-propionic Acid Methyl Ester 1. Magnesium turnings dried at 80 °C (0.010 g, 0.421 mmol) were added to a stirring solution of **16** (0.015 g, 0.042 mmol) in dry MeOH (1 mL) at room temperature and stirred for 8 h. Acetic acid (0.200 mL) was added to the solution and then diluted with EtOAc, washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo to a light yellow solid. The solid was recrystallized from EtOAc/hexanes to yield clear crystals (0.008 g, 81%): mp 136−139 °C; ^{1}H NMR δ 7.37 (s, 1H), 6.80 (s, 1H), 4.57 (bs, 1H), 3.68 (s, 3H), 3.23 (q, J = 6.68, 2H), 2.95 (t, J = 5.69, 2H), 2.68 (m, 4H), 2.20 (s, 3H), 2.18 (s, 3H), 1.43 (s, 9H); ^{13}C NMR δ 176.6, 156.0, 151.5, 132.9, 130.6, 129.0, 126.0, 123.4, 79.3, 52.4, 41.2, 34.0, 33.6, 28.5, 21.4, 16.3, 15.0; IR (NaCl) 3376, 2977, 1695 cm^{-1}. Anal. Calcd for $C_{19}H_{29}NO_5$: C, 64.93; H, 8.32; N, 3.99. Found: C, 64.63; H, 8.27; N, 3.87.

Quinone Methide 2 and 2′ Solutions For UV Studies. In separate vials, solutions of phenol **1** (2.0 mg, 5.6 μmol) and **1′** (1.9 mg, 5.6 μmol) in CH_3CN (10 mL) were oxidized with lead(II) oxide (14 mg) by stirring at 20 °C for 20 min. The suspension of each was filtered through a 13 mm syringe filter with 0.45 μm PTFE membrane to give quinone methides **2** and **2′** as separate solutions.

Study of Quinone Methide 2 and 2′ Reaction in Dibutyl Phosphate/Acetonitrile Solution (2 equiv, 20 °C). The 560 μM stock solutions of quinone methide **2** and **2′** were serial diluted to concentrations of 400, 300, 200, and 100 μM. The 400 μM solution was prepared by adding 7.14 mL of stock quinone methide to a 10 mL volumetric flask with a 1000 micropipet. To this solution was then added 2.45 mL of $NaClO_4$ solution (0.1 M, 1.0 g $NaClO_4$/10 mL CH_3CN). The solution was then diluted with CH_3CN to give a final volume of 10 mL. To prepare the 300, 200, and 100 μM quinone methide solutions 0.620, 0.820, and 1.23 mL aliquots of $NaClO_4$ solution were added to each volumetric flask prior to dilution. The final concentration of $NaClO_4$ in each solution was 0.1 M. A stock solution (26.9 mM, 10 mL) of dibutyl phosphate was prepared by diluting the phosphate (50 μL, 269 μmol) in 10 mL of CH_3CN. The stock solution was then diluted to concentrations of 800, 600, 400, and 200 μM (2 equiv relative to the quinone methide solution) in 10 mL volumetric flasks with CH_3CN. The volumetric flasks were allowed to equilibrate in a 20 °C water bath prior to UV analysis. A 1 mL aliquot of quinone methide solution was combined with 1 mL of the corresponding dibutyl phosphate solution (2 equiv) to give four reactions with final concentrations of quinone methide of 200, 150, 100, and 50 μM. The disappearance of the quinone methide was measured at λ_{max} of 304 nm, where there was no other interfering absorbance signal. All experiments were performed in triplicate. The rates (k_{obs}) of loss of quinone methide **2** and **2′** were based upon their decaying absorbance signal recorded every 500 ms. The rates were determined in the first 60% loss of absorbance signal as the slope of ln A/t.

A control reaction containing an equimolar mixture of methane sulfonic acid (2 equiv) and water (2 equiv), similarly prepared as the dibutyl phosphate solutions, was added to the quinine methide at all concentration levels. The quinone methide absorbance signal (λ_{max} of 304 nm) revealed no decay after 2 min, suggesting that acid-catalyzed hydrolysis is not competitive with phosphate alkylation under the reaction conditions.

Quinone Methide 2 and 2′ for NMR Studies. A 22 mM solution of phenol **1** (5.0 mg phenol/0.65 mL $CDCl_3$) or **1′** (4.8 mg phenol/0.65 mL $CDCl_3$) and 1 equiv mesitylene (2 μL, 14.3 μmol) were combined with lead(II) oxide (34 mg) with stirring at 20 °C for 20 min. The suspensions were filtered as described above to afford a yellow solution of quinone methide. The reaction with lead(II) oxide was quantitative for *p*-quinone methides **2** and **2′** as determined by relative integration of the *p*-quinone methide alkylidene resonance at 6.42 ppm (1H) relative to an internal standard of mesitylene (Ar-H, 6.79 ppm, 3H). Quinone methide **2**: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.22 (s, 1H), 6.42 (t, J = 7.18, 1H), 4.21 (t, J = 6.18, 2H), 3.65 (s, 3H), 2.84 (t, J = 8.15, 2H), 2.41 (t, J = 8.15, 2H), 2.18 (s, 3H), 1.99 (s, 3H), 1.45 (s, 9H). Quinone methide **2′**: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.29 (s, 1H), 6.88 (s, 1H), 6.21 (t, J = 7.18, 1H), 4.16 (t, J = 6.43, 2H), 3.65 (s, 3H), 2.71 (t, J = 8.15, 2H), 2.57 (t, J = 8.15, 2H), 2.02 (s, 3H), 1.45 (s, 9H).

To the quinone methide solution was added 2 equiv of dibutyl phosphate (5.3 μL, 28.6 μmol). The conversion of quinone methide **2** or **2′** to trialkyl phosphate **3** or **3′** was monitored by ^{1}H NMR analysis upon addition of dibutyl phosphate. Trialkyl phosphate **3**: ^{1}H NMR δ 7.07 (s, 1H), 5.52 (td, J_{P-H} = 3.24, 1H), 4.04−3.88 (m, 4H), 3.86 (t, 2H), 3.68 (s, 3H), 2.94 (t, J = 6.91, 2H), 2.67 (t, J = 6.67, 2H), 2.25 (s, 3H), 2.21 (s, 3H), 1.62 (m, 4H), 1.45 (s, 9H), 1.31 (m, 4H), 0.89 (m, 6H). Trialkyl phosphate **3′**: δ 6.99 (s, 1H), 6.92 (s, 1H), 5.20 (td, J_{P-H} = 3.72, 1H), 4.04−3.88 (m, 4H), 3.89 (t, 2H), 3.68 (s, 3H), 2.84 (t, J = 6.45, 2H), 2.69 (t, J = 6.67, 2H), 2.23 (s, 3H), 1.62 (m, 4H), 1.45 (s, 9H), 1.31 (m, 4H), 0.89 (m, 6H).

Trialkyl phosphate **3′** was cleanly observed in the initial ^{1}H NMR spectra. The conversion of trialkyl phosphate **3′** to lactonized trialkyl phosphate **5′** was monitored by comparison of the relative integration of methyl ester at 3.68 ppm (s, 3H) to an internal standard of mesitilyene (Ar−H, 6.79 ppm, 3H) at 35 °C in $CDCl_3$ in five min. intervals for 120 min. During the first hour of lactonization monitoring the emergence of presumed benzyl alcohol **4′** is observed at 4.9 ppm with no measurable loss of methyl ester at 3.68 (s, 3H). After 2 h 10% of the methyl ester resonance signal had been lost and the ratio of trialkyl phosphate **3′** to presumed benzyl alcohol **4′** (based on its close ^{1}H NMR correspondence to **4** and **6**) is approximately 3:1. After 2 h of monitoring, a slight decrease in signal intensity was observed for presumed trialkyl phosphate **3′** and benzyl alcohol **4′** resonances relative to the integration of the internal standard. The reaction conditions ($CDCl_3$, 35 °C) were maintained for an additional 10 h. ^{1}H NMR analysis of the reaction mixture revealed the complete

loss of the methyl ester resonace signal and less than 30% of the combined characteristic signal intensity remained for presumed lactonized trialkyl phosphate **5′** and benzyl alcohol **6′** (based on their close ^{1}H NMR correspondence to **5** and **6**). The scale of the reaction and limited observable material prevented isolation and definitive characterization of lactonized trialkyl phosphate **5′** and benzyl alcohol **6′**. Additional, unidentified resonance signals were observed in the final ^{1}H NMR spectrum.

The conversion of trialkyl phosphate **3** to lactonized trialkyl phosphate **5** was monitored by comparison of the relative integration of the resonance signal consistent with the methyl ester at 3.68 ppm (s, 3H) to a resonance signal for the internal standard of mesitilyene (Ar−H, 6.79 ppm, 3H) at 35 °C in $CDCl_3$ in five min. intervals for 120 min. During the first hour of lactonization monitoring, the triplet of doublets at 5.52 ppm (J_{H-P} = 3.24 Hz, 1H) from **3** began to overlap with the emerging triplet of doublets at 5.57 ppm (td, J_{P-H} = 3.24, 1H), characteristic of lactonized trialkyl phosphate **5**. Concurrent with the formation of the triplet of doublets at 5.57 ppm for **5** was the disappearance of the resonance signal for the aromatic proton at 7.07 (s, 1H) of **3** and subsequent emergence of a resonance signal of an aromatic proton at 7.18 (s, 1H) consistent with the formation of **5**. Additionally, during the first hour of lactonization monitoring, the slight appearance of a resonance signal at 5.04 ppm and a singlet at 7.28 ppm was observed consistent with the formation of benzyl alcohol **6**. After 2 h, based on analysis of the already described resonance signals, complete conversion of quinone methide **2** to lactonized trialkyl phosphate **5** and lactonized benzyl alcohol **6** was observed in a 3.0:1.0 ratio favoring trialkyl phosphate **5**. The reaction conditions ($CDCl_3$, 35 °C) were maintained for an additional 10 h. No measurable change was detected in the ratio of lactonized trialkyl phosphate **5** and benzyl alcohol **6** following the completion of the lactonization reaction in the initial 2 h. This was determined by comparison of the relative integration of the aromatic proton of trialkyl phosphate **5** at 7.18 with the aromatic proton of benzyl alcohol **6** at 7.28 ppm and the triplet of doublets of trialkyl phosphate **5** at 5.57 ppm with the multiplet of benzyl alcohol **6** at 5.04 to an internal standard of mesitilyene (Ar−H, 6.79 ppm, 3H). The rate of lactonization was calculated as the slope of concentration of methyl ester (mM) vs time (min.) for the first 60% of methyl ester resonance signal loss. All experiments were performed in triplicate.

Lactonized Trialkyl Phosphate 5. A 22 mM solution of phenol **1** (5.0 mg phenol/0.65 mL $CHCl_3$) was stirred with lead-(II) oxide for 20 min. The suspension was filtered as described above to yield a yellow solution of quinone methide. To the resulting quinone methide solution was added 2 equiv of dibutyl phosphate (5.3 μL, 28.6 μmol), and the resulting solution was stirred at 35°C for 2 h. The mixture was concentrated in vacuo to yield a crude oil. The desired product was isolated via preparative TLC (3:1 EtOAc/hexanes) to yield a semi-white solid (4.8 mg, 61%): ^{1}H NMR δ 7.18 (s, 1H), 5.57 (td, J_{P-H} = 3.24, 1H), 3.96 (m, 4H), 3.53−3.44 (bm, 1H), 3.31−3.19 (bm, 1H), 2.94 (t, J = 6.91, 2H), 2.73 (t, J = 6.91, 2H), 2.27 (s, 3H), 2.26 (s, 3H), 1.62 (m, 4H), 1.44 (s, 9H), 1.31 (m, 4H), 0.89 (m, 6H); ^{13}C NMR δ 171.3, 156.0, 148.2, 135.7, 134.0, 132.6, 129.2, 126.4, 79.3, 74.2, 63.8, 47.3, 32.1, 29.7, 28.5, 21.4, 18.7, 16.3, 15.0, 13.1. Anal. Calcd for $C_{26}H_{42}NO_8P$: C, 59.19; H, 8.02; N, 2.65. Found: C, 59.41; H, 8.22; N, 2.83.

Lactonized Benzyl Alcohol 6. ^{1}H NMR δ 7.28 (s, 1H), 5.04 (bm, 1H), 3.40 (ddd, J = 2.97, 1H), 3.12 (m, 1H), 2.93 (t, J = 6.91, 2H), 2.73 (t, J = 6.91, 2H), 2.27 (s, 3H), 2.23 (s, 3H), 1.45 (s, 9H).

Acetic Acid *o*-Tolyl Ester 8′. 14.3 g, 99%; ^{1}H NMR δ 7.18 (m, 3H), 7.03 (d, 1H), 2.32 (s, 3H), 2.20 (s, 3H); ^{13}C NMR δ 169.3, 149.5, 131.2, 130.2, 127.0, 126.1, 122.0, 20.9, 16.2; IR (NaCl) 1761, 1213 cm^{-1}. Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.66. Found: C, 71.82; H, 6.80.

1-(4-Hydroxy-3-methyl-phenyl)-ethanone 9′. 11.3 g, 76%; mp 106−109 °C; ^{1}H NMR δ 7.79 (s, 1H), 7.74 (d, J = 8.41 Hz, 1H), 7.39 (s, 1H), 6.88 (d, J = 8.41 Hz, 1H), 2.57 (s, 3H), 2.29 (s, 3H); ^{13}C NMR δ 198.7, 159.6, 132.1, 129.6, 128.8, 124.6, 114.9, 26.4, 16.0; IR (NaCl) 3252, 1652, 1591, 1281 cm^{-1}. Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.66. Found: C, 72.14; H, 6.80.

2-Bromo-1-(4-hydroxy-3-methyl-phenyl)-ethanone 10′. 3.44 g, 72%; mp 118−20 °C; ^{1}H NMR δ 7.80 (s, 1H), 7.76 (d, J = 8.41 Hz, 1H), 6.85 (d, J = 8.41 Hz, 1H), 5.95 (s, 1H), 4.39 (s, 2H), 2.29 (s, 3H); ^{13}C NMR δ 190.7, 159.4, 132.6, 129.4, 126.9, 124.7, 115.2, 30.8, 15.9; IR (NaCl) 3386, 1670, 1587. Anal. Calcd for $C_9H_9BrO_2$: C, 47.19; H, 3.93; Br, 34.88. Found: C, 47.30; H, 4.03; Br, 34.64.

4-(2-Bromo-ethyl)-2-methyl-phenol 11′. 2.27 g, 79%; ^{1}H NMR δ 6.95 (s, 1H), 6.90 (d, J = 8.41 Hz, 1H), 6.69 (d, J = 8.41 Hz, 1H), 4.39 (b, 1H), 3.51 (t, J = 7.67 Hz, 2H), 3.05 (t, J = 7.67 Hz, 2H), 2.23 (s, 3H); ^{13}C NMR δ 152.8, 131.4, 131.2, 127.3, 124.2, 115.1, 38.7, 33.6, 15.9; IR (NaCl) 3415, 1510, 1261 cm^{-1}. Anal. Calcd for $C_9H_{11}BrO$: C, 50.25; H, 5.11; Br, 37.15. Found: C, 50.10; H, 5.18; Br, 36.94.

4-(2-Azido-ethyl)-2-methyl-phenol 12′. 1.57 g, 89%; ^{1}H NMR δ 6.96 (s, 1H), 6.90 (d, J = 8.16 Hz, 1H), 6.70 (d, J = 8.16 Hz, 1H), 4.85 (s, 1H), 3.45 (t, J = 7.18 Hz, 2H), 2.79 (t, J = 7.18 Hz, 2H), 2.23 (s, 3H); ^{13}C NMR δ 152.7, 131.5, 130.2, 127.3, 124.1, 115.2, 52.8, 34.6, 15.9; IR (NaCl) 3407, 2102, 1509 cm^{-1}. Anal. Calcd for $C_9H_{11}N_3O$: C, 61.00; H, 6.21; N, 23.71. Found: C, 61.20; H, 6.33; N, 23.58.

2-(4-Hydroxy-3-methyl-phenyl)-ethylammonium Chloride 13′. 1.19 g, 72%; mp 178−181 °C; ^{1}H NMR δ 6.97 (s, 1H), 6.89 (d, J = 8.16, 1H), 6.71 (d, J = 8.16 Hz, 1H), 3.10 (t, J = 15.09 Hz, 2H), 2.82 (t, J = 15.09 Hz, 2H), 2.17 (s, 3H); ^{13}C NMR δ 154.2, 130.8, 126.9, 126.7, 124.8, 114.7, 41.0, 32.5, 14.9. Anal. Calcd for $C_9H_{14}ClNO$: C, 57.60; H, 7.46; Cl, 18.89. Found: C, 57.45; H, 7.27; Cl, 19.03.

[2-(4-Hydroxy-3-methyl-phenyl)-ethyl]-carbamic Acid *tert*-Butyl Ester 14′. 1.69 g, 70%; mp 126−129 °C; ^{1}H NMR δ 6.91 (s, 1H), 6.87 (d, J = 8.16 Hz, 1H), 6.69 (d, J = 8.16 Hz, 1H), 3.30 (q, J = 6.93 Hz, 2H), 2.67 (t, J = 6.93 Hz, 2H), 2.21 (s, 3H), 1.43 (s, 9H); ^{13}C NMR δ 156.2, 152.8, 131.4, 130.6, 127.2, 124.1, 115.1, 79.5, 42.1, 35.3, 28.5, 15.9; IR (NaCl) 3347, 1685, 1611, 1512 cm^{-1}. Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.90; H, 8.36. Found: C, 67.00; H, 8.19.

[2-(4-Hydroxy-3-iodo-5-methyl-phenyl)-ethyl]-carbamic Acid *tert*-Butyl Ester 15′. 2.060 g, 81%; ^{1}H NMR δ 7.30 (s, 1H), 6.90 (s, 1H), 5.27 (s, 1H), 4.54 (bs, 1H), 3.27 (q, J = 6.93 Hz, 2H), 2.64 (t, J = 6.93 Hz, 2H), 2.26 (s, 3H), 1.43 (s, 9H); ^{13}C NMR δ 155.9, 151.6, 135.6, 132.8, 132.0, 124.9, 86.0, 79.4, 41.9, 34.9, 28.5, 17.3; IR (NaCl) 3356, 1693 cm^{-1}.

3-[5-(2-*tert*-Butoxycarbonylamino-ethyl)-2-hydroxy-3-methyl-phenyl]-acrylic Acid Methyl Ester 16′. 1.37 g, 75%; mp 138−140 °C; ^{1}H NMR δ 8.04 (d, J = 16.08 Hz, 1H), 7.14 (s, 1H), 6.97 (s, 1H), 6.50 (d, J = 16.08 Hz, 1H), 5.85 (s, 1H), 4.54 (bs, 1H), 3.79 (s, 3H), 3.30 (q, J = 6.93, 2H), 2.68 (t, J = 6.93 Hz, 2H), 2.25(s, 3H), 1.42 (s, 9H); ^{13}C NMR δ 168.3, 156.0, 152.2, 140.5, 133.3, 130.9, 126.5, 124.4, 121.6, 118.1, 79.5, 51.8, 41.9, 35.3, 28.5, 16.0; IR (NaCl) 3391, 1630 cm^{-1}. Anal. Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.45. Found: C, 64.58; H, 7.31.

3-[5-(2-*tert*-Butoxycarbonylamino-ethyl)-2-hydroxy-3-methyl-phenyl]-propionic Acid Methyl Ester 1′. 0.052 g, 77%; mp 76−79 °C; ^{1}H NMR δ 7.13 (s, 1H), 6.81 (s, 1H), 6.74 (s, 1H), 4.51 (bs, 1H), 3.68 (s, 3H), 3.27 (q, J = 6.43, 2H), 2.84 (t, 2H), 2.71 (t, J = 6.43, 2H), 2.63 (t, 2H), 2.22 (s, 3H), 1.42 (s, 9H); ^{13}C NMR δ 176.2, 156.0, 151.2, 130.6, 129.7, 128.4, 127.0, 125.8, 79.2, 52.3, 42.1, 35.2, 34.9, 28.5, 24.7, 16.4; IR (NaCl) 3372, 1693, 1169 cm^{-1}. Anal. Calcd for $C_{18}H_{27}NO5$: C, 64.07; H, 8.00. Found: C, 64.26; H, 8.02.

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