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SYNTHESIS OF TWO 8-[(ANTHRAQUINONE-2-YL)-LINKED]-2'-DEOXYADENOSINE 3'-BENZYL HYDROGEN PHOSPHATES FOR STUDIES OF PHOTOINDUCED HOLE TRANSPORT IN DNA

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[•] The challenge in working with anthraquinone-2'-deoxyadenosine (AQ-dA) conjugates is that they are insoluble in water and only sparingly soluble in most organic solvents. However, water-soluble AQ-dA conjugates with short linkers are required for study of their electrochemical and intramolecular electron transfer properties in this solvent prior to their use in laser kinetics investigations of photoinduced hole (cation) transport in DNA. This article first describes the synthesis of a water-soluble, ethynyl-linked AQ-dA conjugate, &-[(anthraquinone-2-yl)ethynyl]-2'-deoxyadenosine 3'-benzyl hydrogen phosphate, based on initial formation of a 5'-O-(4,4'-dimethoxytrityl) (5'-O-DMTr) intermediate. Because intended H_2 over Pd/C reduction of the ethynyl linker in 5'-O-DMTr-protected 2'-deoxyadenosines cleaves the DMTr protecting group and precipitates multiple side products, this work also describes the synthesis of an ethylenyl-linked AQ-dA conjugate, &-[2-(anthraquinone-2-yl)ethyl]-2'-deoxyadenosine 3'-benzyl hydrogen phosphate, starting with a 5'-O-tert-butyldiphenylsilyl protecting group.

Keywords Photoinduced Electron Transfer, Modified DNA, Modified Nucleoside, Anthraquinone-modified 2'-Deoxyadenosine, 2-Ethynylanthraquinone, Anthraquinone-2'-Deoxyadenosine Phosphate

INTRODUCTION

The DNA double helix presents a unique medium for electron transfer (ET) due to the π -stacked array of its aromatic heterocyclic base pairs. Several approaches have been developed to study ET in DNA.^[1–23] In most of these approaches, either photoexcitation or ionizing irradiation is employed to inject a hole (cation radical) or an excess electron (anion radical) into the DNA base stack depending, respectively, upon whether a DNA base is initially oxidized or reduced.^[24,25] Long-range ET is then monitored, generally indirectly, by detecting effects due to the oxidation or reduction of a nucleobase remote from the injection site.^[26–33] In these experiments yields of the detected oxidized or reduced bases or

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FIGURE 1 Structures of four AQ-dA conjugates: the 3'-benzyl phosphate nucleotides 1 and 2 are soluble in both water and MeOH, while the nucleosides 1a and 2a are insoluble in water but sparingly soluble in MeOH.

their chemical products are low ($\leq 5 \times 10^{-3}$).^[34–38] Our approach is to develop modified nucleosides that will permit direct study of the short- and long-range dynamics of charge transport in modified DNA duplexes using real-time transient absorbance (TA) spectroscopy. Key to reaching this goal is the construction of DNA containing covalently modified nucleosides that can yield long-lived charge-separated (CS) products upon photoexcitation. CS products can be comprised of



SCHEME 1 Reagents and conditions: (a) DMTrCl, 4-DMAP, TEA, Py, rt, 4 h; (b) *i*. $(BnO)_2PN(iPr)_2$, Metetrazol, THF, rt, 1 h; *ii. m*-CPBA in CH₂Cl₂, -78°C, 15 min; (c) Pd(Ph₃P)₄, CuI, TEA, DMF, 65°C, 6 h; (d) 30% DCA in CH₂Cl₂, rt, 30 min; (e) DABCO, 1,4-dioxane, reflux, 2 h.

either holes or excess electrons on DNA bases depending on the nature of the conjugate group joined to a particular base.

From a hole transfer perspective, conjugates between electron-deficient derivatives of anthraquinone (AQ) and 2'-deoxyadenosine (dA) are interesting as sources of holes in DNA.^[12,13,15,16,39-47] In AQ-dA conjugates, photoexcited AQ is expected to be the electron acceptor, and adenine is expected to be the electron donor; thus photoexcitation of such conjugates is expected to form the AQ^{•-}/dA^{•+} CS product. Separating AQ^{•-} from its associated hole in the AQ^{•-}/dA⁺⁺ photoproduct by allowing the initial dA^{•+} hole to hop to a nearby G should prolong the lifetime of the resulting AQ^{•-}/dA/dG^{•+} secondary charge-separated (SCS) product. Key questions concern how efficiently can SCS products be produced and how long can they be made to live. Our goal here is to synthesize the water-soluble AQ-dA 3'-phosphates, **1** and **2** (see Figure 1) so that their electrochemistry and intramolecular ET photochemistry can be studied in water. If they can be shown to undergo reductive quenching of their π,π^* excited states to form AQ^{•-}/dA^{•+} photoproducts in water, it will then be desirable to transform them into the corresponding phosphoramidite reagents for incorporation into DNA oligomers for studies of hole transport in DNA.



SCHEME 2 Reagents and conditions: (a) TBDPSCI, Im, Py, rt, 3h; (b) $Pd(Ph_3P)_4$, CuI, TEA, DMF, 65°C, 6 h; (c) 10% Pd/C, H_2 , 40 psi, EtOAc/MeOH, rt, 24 h; (d) *i*. (BnO)₂PN(*i*Pr)₂, Me-tetrazol, THF, rt, 1 h; *ii*. *m*-CPBA in CH₂Cl₂, -78° C, 15 min; (e) NH₄F, MeOH/THF, 60°C, 6 h; (f) 10% Pd/C, H₂, 40–45 psi, EtOAc/MeOH, rt, 31 h.



SCHEME 3 Reagents and conditions: (a) *i*. HCl, NaNO₂, THF/H₂O, 0°C; *ii*. KI, 0°C, 75 min; (b) Pd(Ph₃P)₂Cl₂, CuI, Et₃N, THF, TMSA, rt, 10 min; (c) KF, THF/MeOH, rt, 1 h.

Synthesis of the 3'-phosphate AQ-dA conjugates 1 and 2 appears appealing for study of the chemistry of water-soluble AQ-dA conjugates because the phosphate group is attached to the sugar and, therefore, is not likely to affect the redox potentials of either the AQ or dA subunits. From the perspective of substitution of 1 and 2 into DNA duplexes, the rigid ethynyl linker in 1 appears advantageous over the more flexible ethylenyl linker in 2 because it will likely permit fewer nonbonded interactions between the anthraquinonyl group and neighboring DNA bases. However, at this point the electrochemistry and ET photochemistry of neither compound is known in water and both need to be made and studied. The challenge in working with AQ-dA conjugates is that in general they are insoluble in water and only sparingly soluble in most organic solvents. Thus the goal of producing moderate amounts of the 3'-phosphates 1 and 2 requires development of protecting group strategies to increase the solubility of synthetic intermediates. Since the 4,4'-dimethoxytrityl (DMTr) group is commonly used to make phosphoramidite reagents for use on automated solid-phase DNA synthesizers, we begin this work with a description of the synthesis of the ethynyl-linked AQ-dA 3'-phosphate conjugate **1** based on initial formation of a 5'-O-DMTr intermediate as shown in Scheme 1. Unfortunately, attempted reduction of the ethynyl linker in 5'-O-DMTr-protected 2'-deoxyadenosines with H_2 over Pd/C cleaves the DMTr protecting group and precipitates multiple side products. Thus this work also describes in Scheme 2 a synthetic strategy based on initial 5'-O-tert-butyldiphenylsilyl (5'-O-TBDPS) protection of 8-bromo-2'-deoxyadenosine to make the ethylenyl-linked AQ-dA conjugate 2. Finally, useful syntheses of two substituted anthraquinones are described in Scheme 3.

RESULTS AND DISCUSSION

Synthesis of an Ethynyl-Linked AQ-dA Conjugate, 1

The water-insoluble AQ-dA nucleosides **1a** and **2a** were made on a 100-mg scale without protecting groups, but with silica gel column purification difficulties.

However, their extremely poor solubility in organic solvents precluded phosphorylating them directly with POCl₃ in trimethyl phosphate^[48–50] or β -cyanoethyl phosphate.^[51] To allow chemical transformations of AQ-dA intermediates in organic solvents, 8-bromo-2'-deoxyadenosine must first be protected at the 5'-O position to ensure that its AQ-adducts remain soluble. With this in mind, we attempted to use (BnO)₂POCl and *tert*-BuMgCl to produce a 5'-O-protected 3'-phosphate. Unfortunately, this modified version of a reported reaction^[52] did not succeed. Either phosphite triester^[53,54] or phosphoramidite coupling^[55–58] followed by oxidation also appeared reasonable as alternate ways of producing our desired 5'-O-protected 3'-phosphates of AQ-dA. We chose the latter procedure since dibenzyl *N*,*N*-diisopropylphosphoramidite was commercially available, whereas tribenzyl phosphite was not.

The synthetic strategy to form **1** described in Scheme 1 was developed based on trial phosphorylation reactions of 2'-deoxyadenosine rather than the more expensive 8-bromo-2'-deoxy adenosine reagent. The goal of these trial reactions was threefold: 1) to test phosphoramidite chemistry without N^6 protection, 2) to determine the stability of phosphate protection toward DMTr deprotection, and 3) to establish the stability of both the N-glycosidic bond and the phosphate group itself toward the conditions needed to produce the 2'deoxyadenosine 3'-benzyl phosphate products in Scheme 1. While unprotected ethynyl and ethylenyl AQ-dA conjugates are only sparingly soluble in most solvents, all three 3'-dibenzyl phosphates in Scheme 1 were readily soluble in a variety of standard organic solvents. However, purification of **7** was sometimes a problem, as will be discussed.

Synthesis of 5'-O-Dimethoxytrityl-8-bromo-2'-deoxyadenosine 3'-Dibenzyl Phosphate (5) from 2'-Deoxyadenosine

Treatment of 2'-deoxyadenosine with Br_2 in a 1 M solution of acetate buffer at pH 4.0 produced **3** in 79% yield. Adjusting the pH to 4.0 rather than $5.0^{[59]}$ or $5.4^{[60]}$ and using a buffer concentration of 1 M was essential to dissolve the starting materials. Additionally, pure **3** was obtained by extracting it from the buffer with chloroform (CHCl₃);^[61] extraction was aided by CHCl₃ mixing with the large amount of acetic acid required to drop the pH of the buffer to 4.0. ¹H and ¹³C NMR data for **3** were identical to those previously published, and the product was used without further purification.^[61] Alternately, separation of **3** from the buffer was also done by precipitation following neutralization with sodium hydroxide.^[62] However, in this case recrystallization from boiling water was required to separate a trace amount of unreacted 2'-deoxyadenosine. The yield for this latter product collection method was only 50%.

5'-O-Dimethoxytrityl-8-bromo-2'-deoxyadenosine (**4**) was prepared in 72% yield by tritylation of **3** using DMTrCl, TEA, and 4-DMAP (as a catalyst) in pyridine.^[63] A solution of DMTrCl in pyridine was added drop-wise at 0°C. This procedure was intended to increase the selectivity of tritylation at 5'-OH. Phosphorylation of **4** by coupling with (BnO)₂PN(*i*Pr)₂ followed by oxidation produced **5** as shown in Scheme 1. Based on our trial phosphorylation of 2'-deoxyadenosine, we avoided using less than 1.5 equivalents of $(BnO)_2PN(iPr)_2$ in order to react **4** completely, and hoped that any N⁶-phosphorylated side product would be easily removed by silica gel chromatography as in the trial chemistry. However, the amount of this side product, as shown by TLC, was larger than the amount seen previously when phosphorylating 5'-O-DMTr-2'-deoxyadenosine. Worse, complete separation of the 3',N⁶-bis(dibenzyl phosphate) side product from the 3'-dibenzyl phosphate **5** required biotage chromatography. Therefore, to eliminate N⁶-phosphorylation, it was worth re-optimizing the number of equivalents of $(BnO)_2PN(iPr)_2$ used. Some published procedures used lower equivalents of similar phosphoramidite reagents but an excess of the required base.^[64,65] Based on this reasoning, 2.2 equivalents of Me-tetrazol were used with 1.2 equivalents of $(BnO)_2PN(iPr)_2$, keeping all other conditions unchanged. This modified procedure yielded a single spot of **5** on TLC with complete consumption of **4**.

Coupling Anthraquinone to 5 Followed by Two Deprotections to Yield 1

5'-O-Dimethoxytrityl-8-[(anthraquinone-2-yl)ethynyl]-2'-deoxyadenosine 3'dibenzyl phosphate (7) was synthesized by Pd(0) catalyzed cross-coupling of 5 and 6. Monitoring the progress of this reaction by TLC was not possible because both the starting material 5 and the product 7 had the same R_f in most commonly used eluting solvent mixtures. The time of the reaction was suggested by comparison with similar Pd(0)-catalyzed cross-coupling reactions in the literature (2.5–6 h).^[65–67] Complete consumption of 5 by reaction with 6 was essential to obtain 7 pure after silica gel chromatography; purity of 7 was checked by ¹H NMR. Frequently, however, 5 reacted incompletely even with 30% excess of 6. Unfortunately, increasing the reaction time still left a trace amount of unreacted 5. Because unreacted 5 and 7 underwent the same kinds of reactions in Scheme 1, proceeding to the next step also yielded products with the same R_f values as 5 and 7. Thus, obtaining 8 pure was also a problem unless all of 5 reacted when forming 7. However, obtaining 1 pure was not a problem as HPLC separated it cleanly from all other reaction products.

The DMTr group of **7** in Scheme 1 was cleaved by stirring with 40 equivalents of 30% DCA in dichloromethane (CH₂Cl₂) at room temperature for 30 min. (Lower concentrations or equivalents of the acid caused incomplete detritylation of trial compound 5'-O-DMTr-2'-deoxyadenosine 3'-dibenzyl phosphate.) After silica gel chromatographic purification, 8-[(anthraquinone-2-yl)ethynyl]-2'-deoxyadenosine 3'-dibenzyl phosphate (**8**) was obtained in 76% yield. No depurination of **8** was observed during the acidic cleavage of DMTr.

Mono-deprotection of the dibenzyl phosphate group in 8 to produce 1 was achieved by treatment with 2.7 equivalents of DABCO under anhydrous conditions in refluxing 1,4-dioxane. During purification of 1 by preparative HPLC eluting with MeCN/water, the Bn-quaternarized DABCO counter-cation was replaced by hydrogen as judged by ¹H NMR. Hydrogenolysis was not used for benzyl deprotection, as this would have also reduced the alkynyl linker. Additionally, benzyl deprotection of trial 2'-adenosine 3'-dibenzyl phosphate with 5 equivalents of TMSBr in anhydrous CH_2Cl_2 followed by quenching with 1 M aqueous ammonium bicarbonate^[68] produced a mixture of unidentified products as judged by ¹H NMR. Thus this benzyl deprotection method was not used either. Note also that 2.7 equivalents of DABCO produced only monobenzyl deprotected **1** without evidence of any dibenzyl deprotected product.

Synthesis of an Ethylenyl Linked AQ-dA Conjugate, 2

The initial strategy to synthesize 2 was based on using Pd/C catalyzed hydrogenation of 8 both to reduce the ethynyl linker and also to remove the benzyl groups on the 3'-phosphate.^[69] Unfortunately, this strategy was not successful due to precipitation of the reactant following benzyl cleavage prior to complete reduction of the triple bond. (In our experience, unprotected ethynyl-linked AQ-dA conjugates had poorer solubility in most organic solvents than the corresponding ethylenyl-linked conjugates.) Therefore, we decided to reduce the triple bond independently from 3'-dibenzyl phosphate deprotection. Additionally, since protected phosphates were more stable and easier to handle than unprotected ones, we also decided to form a 3'-dibenzyl-protected phosphate intermediate immediately after reduction of the ethynyl linker. The last step in our synthesis of the water-soluble AQ-dA nucleotide 2 (as shown in Scheme 2) was a second hydrogenation to monobenzyl-deprotect the 3'-dibenzyl phosphate intermediate 13.

To improve the solubility of AQ-dA intermediates prior to hydrogenation of the alkynyl linker, we tried to use DMTrCl to protect the 5'-OH of 3 before coupling it to 6 (2-ethynylanthraquinone). Accordingly, we reacted 5'-O-DMTrprotected 4 (see Scheme 1) with 6 using Pd(0) catalyzed cross-coupling chemistry. However, hydrogenation of the resulting product, 5'-O-DMTr-8-[anthraquinone-2-yl]ethynyl-2'-deoxyadenosine, using 10% Pd/C and H_2 (40 psi) at room temperature for 24 h, cleaved the DMTr group and precipitated multiple side products as determined by TLC. This was surprising, because DMTr protection of 5'-OH on 2'-deoxyuridine was stable to the same hydrogenation conditions.^[70,71] Perhaps the 5'-O DMTr group in 2'-deoxypurine nucleosides was more labile than in 2'-deoxypyrimidine nucleosides.^[72] However, it was also true that trityl groups on other compounds were cleaved by hydrogenation under similar conditions.^[73] Clearly, a different 5'-OH protecting group was needed to solubilize intermediates during our synthesis of 2. We selected the *tert*-butyldiphenylsilyl (TBDPS) group because it could selectively protect 5'-OH in 2'-deoxyribonucleosides [74-77] and it could be cleaved under mild conditions using NH_4F in MeOH.^[78] Finally, our second water-soluble AQ-dA target compound 2 was successfully prepared as described in Scheme 2 following initial 5'-OH protection of 3 with TBDPSCl.

Synthesis of 5'-O-tert-Butyldiphenylsilyl-8-[2-(anthraquinone-2-yl)ethyl]-2'-deoxyadenosine (11)

Compound 11 was synthesized in three steps starting with 3 as described in Scheme 2. Treatment of 3 with TBDPSCl and imidazol (1 equivalent each) in dry pyridine produced 9 in 91% yield. Because of disilylation of 3, this yield decreased significantly when excess equivalents of TBDPSCl were used. Importantly for future work, both the purity and yield of 5'-O-TBDPS-protected 9 were better than those of 5'-O-DMTr-protected 4 (see Scheme 1).

5'-0-tert-Butyldiphenylsilyl-8-[(anthraquinone-2-yl)ethynyl]-2'-deoxyadenosine (10) was synthesized in 90% yield via Pd(0)-catalyzed cross-coupling between 9 and 6 under the same conditions described in Scheme 1. Unfortunately, 10 was frequently still mixed with a trace amount of unreacted 9 after chromatographic purification. This was the case because nucleosides 9 and 10 had nearly the same R_f in most commonly used eluting solvent mixtures. A similar problem was encountered previously when synthesizing 1 also starting with 3; in fact, both 8-bromo-2'-deoxyadenosine nucleosides 9 and 4 protected, respectively, with TBDPS and DMTr groups had the same R_f values. Again using 30% excess of 6, and increased reaction time did not completely eliminate 9. The latter contaminant was easily eliminated, however, after ethynyl reduction during purification of 11.

5'-0-tert-Butyldiphenylsilyl-8-[2-(anthraquinone-2-yl)ethyl]-2'-deoxyadenosine (11) was produced in 86% yield by hydrogenation of 10 using Pd/C and H₂ in MeOH/ethyl acetate (EtOAc) (3:2). The yellow color of 11 was less intense than that of 10 and it was more soluble in organic solvents. Importantly, 11 had a more polar R_f value on TLC than 10. Since unreacted 9 from the Pd(0)-catalyzed cross-coupling step did not undergo hydrogenation, traces of 9 were easily separated from 11 using Biotage silica gel chromatography. Importantly for the synthesis of 2, the 5'-0-TBDPS group in 10 was stable with respect to hydrogenation, and thus the ethylenyl-linked product 11 remained soluble in MeOH/EtOAc solution.

Phosphorylation of 11 and Two Subsequent Deprotections to Form 2

5'-O-tert-Butyldiphenylsilyl-8-[2-(anthraquinone-2-yl)ethyl]-2'-deoxyadenosine 3'dibenzyl phosphate (12) was prepared by phosphorylation of 11 using 1.2 equivalents of (BnO)₂PN(iPr)₂ and 2.2 equivalents of Me-tetrazol in THF, followed by oxidation with *m*-CPBA. Phosphorylation of the ethylenyl-linked AQ-dA conjugate 11 showed five product spots in addition to a minor amount of unreacted 11 on TLC compared to a single spot found earlier when phosphorylating 4. The major TLC spot corresponded to 12, while the side products were not identified. Nevertheless, silica gel column chromatography easily purified 12 in 82% yield. The desilylated product 8-[2-(anthraquinone-2-yl)ethyl]-2'-deoxyadenosine 3'dibenzyl phosphate (13) was produced in 88% yield by treatment of 12 with excess NH₄F in THF/MeOH. The amount of added NH₄F was not fully soluble in the reaction solvent. Nevertheless, the product was purified via silica gel chromatography without prior separation of NH₄F by filtration or water workup. Finally, the monobenzyl-deprotected product 2 was formed from the 3'-dibenzyl phosphate intermediate 13 by catalytic hydrogenation using Pd/C and H₂ in MeOH/EtOAc (8:1). Although Pd/C hydrogenolysis has been reported many times to cleave both benzyls on a phosphate group,^[53–55,57,69,79] hydrogenolysis of 13 produced only monobenzyl deprotection. Analytical reverse-phase HPLC of the crude product mixture showed 71% yield of 2. Due to an error in sample handling, however, purification by preparative reverse-phase HPLC gave 2 in only 22% yield.

Syntheses of Two Substituted Anthraquinones: 2-lodoanthraquinone (15) and 2-Ethynylanthraquinone (6)

Early steps in the syntheses of both 1 and 2 involve Pd(0)-catalyzed crosscoupling between a 5'-O-protected 2'-deoxyadenosine (5 or 9) and 2-ethynylanthraquinone (6). Compound 6 in turn is prepared in two steps beginning with 15 as shown in Scheme 3. In the first step, Pd(Ph₃P)₂Cl₂ catalyzed cross-coupling of trimethylsilylacetylene (TMSA) with 15 gives 2-(trimethylsilylethynyl)anthraquinone (16); then the terminal alkyne of 16 is deprotected with KF to give 6. Although 2-chloroanthraquinone is commercially available, its Pd(0)-catalyzed cross-coupling reaction is likely to occur less readily than those for either 2-bromo or 2-iodoanthraquinone. Also, direct bromination of commercially available anthraquinone yields a mixture of polybromoanthraquinones that is difficult to separate.^[80] Other reported syntheses of 2-bromoanthraquinone either have low yields^[81] or require harsh conditions.^[82] For these reasons, as well as the fact that iodide is a better leaving group than bromide, 15 appears to be a good precursor for forming 6.

Synthesis of 2-lodoanthraquinone (15)

To form 15, 2-aminoanthraquinone (14) was diazotized with nitrous acid that was prepared in situ from HCl and NaNO₂ and then substituted with iodide in a manner similar to the Sandmeyer reaction. TLC of the product mixture, however, showed a less polar, minor product very close to 15. Thus, although 15 was difficult to purify by silica gel column chromatography, three separations using 30% CH_2Cl_2 in hexane as the mobile phase produced 3.4 g of 15 in 75% yield.

Synthesis of 2-Ethynylanthraquinone (6)

Following a general procedure for Pd-catalyzed cross-coupling between an aryl halide and trimethylsilylacetylene (TMSA),^[83] **15** was readily converted to **16** via cross-coupling with TMSA using dichlorobis(triphenylphosphine)palladium(II)

 $[Pd(Ph_3P)_2Cl_2]$ as the catalyst. This reaction was complete within 10 min in tetrahydrofuran (THF) at room temperature. However, the above difficulty in purifying 15 made using commercially available 2-chloroanthraquinone to produce 16 attractive. Unfortunately, both of our attempts to do so by substituting 2-chloroanthraquinone for 15 (a) under the same reaction conditions and (b) by heating the reaction mixture at 60°C for 24 h failed. Thus, at present, the best route for producing 6 appears to be via precursors 14 and 15.

All of the anthraquinones in Scheme 3 had low solubility in organic solvents. For example, 26 mL of THF/MeOH (1:1 v:v) along with 30 min of stirring were required to dissolve 200 mg of **16** for deprotection by potassium fluoride to produce **6**, and it was harder to dissolve **6** than **16** in CH₂Cl₂, CHCl₃, THF, MeOH, or EtOAc. Additionally, the low solubility of **6** made difficult purification of its crude reaction mixture by silica gel chromatography. Thus the crude product was purified initially by extraction and recrystallization. However, TLC analysis of the precipitated crystals showed very faint spots with higher polarity than **6**, and ¹H NMR of the crystals showed extra proton resonances. Complete purification of 100 mg of **6** required silica gel chromatography on a 20-cm long × 5-cm dia. column, an impractical procedure for large quantities of **6**. Late in our work, we found that light below 370 nm degraded **6**. In particular, **6** changed its color from pale yellow to brown soon after silica gel purification when exposed to fluorescent laboratory light.

EXPERIMENTAL

Materials and General Synthetic Methods

2'-Deoxyadenosine monohydrate was purchased from TCI America as white a powder. TMSA obtained from GFS Chemicals was used after vacuum transfer from CaH₂. DMTrCl and Br₂ were obtained from Alfa-Aesar. Ten percent Pd on activated carbon catalyst (Pd/C) and Pd(Ph₃P)₂Cl₂ was obtained from Strem Chemicals and used as received. 2-Amino-anthraquinone was purchased from Aldrich as a brown powder (93% pure) and was used as received. Other remaining reagents used were purchased from Aldrich or VWR. 2-Ethynylanthraquinone (6) was synthesized as described in Scheme 3. $Pd(Ph_3P)_4$ was prepared according to the literature^[84] and stored between uses in our glove box's freezer at -20° C. Anhydrous DMF was purchased from Aldrich and stored in our Vacuum Atmospheres M040-2 glove box that was pressurized with nitrogen boil-off gas from a liquid nitrogen tank. All starting materials for anhydrous reactions were dried prior to use on a vacuum line $(1-4 \times 10^{-4} \text{ torr})$ for at least 12 h. Two to three coevaporation cycles were also used for drying compounds as indicated below. Solvents for synthesis were dried and redistilled in continuous circulation distillation apparati: THF was dried with benzophenone /Na⁰ and stored over activated molecular sieves in our glove box. Pyridine was always freshly distilled over CaH₂ before use. Water was deionized by a Milli pore (Milli-Q Plus) ultrapure water system (18.0 M Ω). All manipulations of DMTrCl, TBDPSCl, Pd(Ph₃P)₄, $Pd(Ph_3P)_2Cl_2$, and $(BnO)_2PN(iPr)_2$ were performed in our glove box. Most of the reactions were monitored with glass-backed TLC Plates precoated with silica gel 60 F_{254} (EMD Chemicals). TLC was run using 5–7% MeOH in CH_2Cl_2 as the eluent. HPLC-grade solvents were used for chromatographic purifications. Flash column chromatography was carried out on either a Biotage Flash-40[™] system using prepackaged KP-Sil[™] cartridges or on Whatman[™] flash silica (60 Å pore, 230–400 mesh) that was packed in glass columns and pressurized with boil-off nitrogen. NMR Spectra were recorded at GSU on three spectrometers, a Varian Unity + 300, a Varian Unity Inova 500, and a Brucker Avance 400, using either $CDCl_3$ or DMSO-d₆ as solvents. Chemical shifts for ¹H NMR in these solvents were referenced, respectively, relative to tetramethylsilane (0.00 ppm) and DMSO (2.49 ppm). ³¹P NMR spectra were recorded using orthophosphoric acid (85%) as an external standard in a capillary tube inside of the NMR tube. Low-resolution (LR) MS were obtained at GSU: for substituted anthraquinones EI (electron impact) MS were recorded in positive ion mode on a Shimadzu 5050A MSD single quadrupole spectrometer with one amu resolution; for substituted 2'-deoxyadenosines ESI (electrospray ionization), MS were recorded in either positive or negative ion modes on a Waters Micromass Q-TOFTM with 50 ppm error.

8-Bromo-2'-deoxyadenosine, 3. 2'-Deoxyadenosine monohydrate (6 g, 22.28 mmol) was dissolved in 800 mL of 1 M acetate buffer at pH 4.0 (prepared by adding glacial acetic acid to 700 mL of 1 M sodium acetate and adjusting the pH). Br₂ (2.3 mL, 44.43 mmol, 2 equiv.) was added, and the reaction mixture was stirred at room temperature for 4 h in the dark. The reaction was quenched by gradual addition of a saturated aqueous solution of NaHSO₃ until the red color of Br₂ disappeared. The product was extracted by shaking with CHCl₃ (8 × 500 mL) in a separatory funnel; the combined extracts were dried over anhydrous MgSO₄ and evaporated to yield a solution of the product in acetic acid. Co-evaporation with toluene (2 × 200 mL) provided **3** as a pale yellow powder that was used without further purification (5.96 g, 79% yield). ¹H and ¹³C NMR spectra for **3** were identical to ones published in the literature.^[61]

5'-O-Dimethoxytrityl-8-bromo-2'-deoxyadenosine, 4. Compound **3** (640 mg, 1.94 mmol) was dried 3 times by co-evaporation with dry pyridine and suspended in dry pyridine (5 mL). To the suspension was added TEA (0.37 mL, 2.72 mmol, 1.4 equiv.) and 4-DMAP (13 mg, 0.1 mmol, 0.05 equiv.) in our glove box. The mixture was next removed from our glove box, and DMTrCl (789 mg, 2.33 mmol, 1.2 equiv.) was dissolved in dry pyridine and added drop-wise at 0°C to the reaction mixture with **3** under a nitrogen atmosphere using a cannula. The orange reaction mixture was stirred at room temperature under a nitrogen atmosphere for 4 h, after which time the mixture was homogeneous and

TLC showed complete consumption of **3**. The reaction was quenched with a saturated aqueous solution of NaHCO₃, and the solvent was evaporated. The residue was dissolved in CH₂Cl₂ (50 mL) and water (20 mL); the organic layer was separated, washed with water (2 × 20 mL), and dried over MgSO₄. The crude product was purified by silica gel chromatography on a column that had been pre-equilibrated with 1% TEA in CH₂Cl₂ and eluted with MeOH/CH₂Cl₂ (0:100–3:97). Evaporation of the eluting solvent afforded **4** as pale yellow foam (940 mg, 72% yield). The ¹H NMR spectrum given here is very similar to ones previously reported in CD₂Cl₂^[66] and CDCl₃.^[65] ¹H NMR (300 MHz, CDCl₃): δ (ppm) 2.31–2.4 (1H, m, H₂), 3.39 (2H, d, *J*=5.7 Hz, H₅', H₅''), 3.51–3.60 (1H, m, H₂'), 3.77 [6H, s, OCH₃ (DMTr)], 4.12 (1H, dd, *J*=5.7 and 10.2 Hz, H₄'), 4.95 (1H, dd, *J*=4.8 and 10.2 Hz, H₃'), 5.78 (2H, br s, NH₂), 6.4 (1H, t, *J*=6.7 Hz, H₁'), 7.66 [4H, dd, *J*=4.2 and 8.7 Hz, OPh-meta (DMTr)], 7.16–7.28 [7H, m, OPh-ortho (DMTr, 4H) and Ph-meta and para (DMTr, 3H)], 7.37 [2H, d, *J*=7.5 Hz, Ph-ortho (DMTr)], and 8.06 [1H, s, H₂ (dA)].

5'-0-Dimethoxytrityl-8-bromo-2'-deoxyadenosine 3'-dibenzyl **phosphate**, 5. To 4 (440 mg, 0.70 mmol), previously dried 2 times by coevaporation with anhydrous THF, was added Me-tetrazole (130 mg, 1.54 mmol, 2.2 equiv.) and anhydrous THF (5 mL) in our glove box. The mixture was removed from our glove box and cooled to 0° C using an ice-water bath, and $(BnO)_2PN(iPr)_2$ (0.28 mL, 0.84 mmol, 1.2 equiv.) was added drop-wise under nitrogen with a syringe. The reaction mixture was stirred under a nitrogen atmosphere for 10 minutes at 0° C; then it was warmed to room temperature, and the reaction progress was monitored by TLC. A white precipitate began to form after 20 min, and TLC showed complete consumption of 4 after a total reaction time of 1.5 h. The suspension obtained was cooled to -78° C using a dry ice-acetone bath, and a solution of *m*-CPBA (250 mg) in CH_2Cl_2 (5 mL) was added gradually to the chilled mixture. After 15 minutes of stirring at -78° C, the mixture became homogeneous, and TLC showed conversion of an intermediate spot to a more polar one. The mixture was next warmed to room temperature, and saturated aqueous NaHCO₃ was added. More CH_2Cl_2 (30 mL) and water (15 mL) were added; the organic layer was separated, washed with water, dried with anhydrous MgSO₄, and evaporated to dryness. The syrup obtained was purified using silica gel chromatography on a Biotage column that had been pre-equilibrated with 1% TEA and eluted with MeOH/CHCl₃ (0:100-3:97). Evaporation of the eluting solvent afforded 5 as white foam (469 mg, 75% yield). ¹H NMR (500 MHz, CDCl₃): δ (ppm) 2.39 (1H, ddd, J = 2, 6.5 and 13.5 Hz, H₂), 3.30 (1H, dd, J = 5.5 and 10 Hz, H₅), 3.39 (1H, dd, J = 6.5 and 10 Hz, H_{5"}), 3.75–3.81 [7H, m, H_{2"} and OCH₃ (DMTr)], 4.33–4.35 [1H, m, $H_{4'}$), 5.05 (4H, m, CH₂ (Bn)], 5.35–5.37 (1H, m, $H_{3'}$), 5.65 (2H, br s, NH₂), 6.4 $(1H, t, J = 7 Hz, H_1), 6.72 [4H, dd, J = 7 and 9 Hz, OPh-meta (DMTr)], 7.16-7.25$ [7H, m, OPh-ortho (DMTr, 4H) and Ph-meta and para (DMTr, 3H)], 7.31 [10 H, s, Ph (Bn)], 7.36 [2H, d, J = 6.5 Hz, Ph-ortho (DMTr)], and 7.94 [1H, s, H₂ (dA)]. ¹³C

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NMR (75 MHz, CDCl₃): δ (ppm) 43.26 (C₂'), 55.15 [OCH₃ (DMTr)], 62.93 (C₅'), 69.55 [d, $J_{C_{-P}} = 5.7$, CH₂ (Bn)], 84.68, 86.19, 88.75 [C₁', C₄', and CAr₃ (DMTr)], 112.94, 120.41 [OPh-*meta* (DMTr), and C₅ (dA)], 126.67 [C₈ (dA)], 127.66, 128, 128.11, 128.62, 130, 135.56, 135.81, 144.61 [Ar (DMTr and Bn)], 150.82 [C₄ (dA)], 152.49 [C₂ (dA)], 154.07 [C₆ (dA)], and 158.35 [OPh-C₄ (DMTr)]. ³¹P NMR (121 MHz, CDCl₃): δ (ppm) -1.19. Low-resolution ESI MS m/z (M + H)⁺: calc'd. 892.21, found 892.18.

5'-O-dimethoxytrityl-8-[(anthraquinone-2-yl)ethynyl]-2'-deoxyadenosine 3'-dibenzyl phosphate, 7. To 5 (410 mg, 0.46 mmol) was added in our glove box Pd(Ph₃P)₄ (24 mg, 0.02 mmol, 0.05 equiv.), CuI (9 mg, 0.05 mmol, 0.1 equiv.), TEA (0.13 mL, 0.92 mmol, 2 equiv.), compound **6** (130 mg, 0.56 mmol, 1.3 equiv.), and anhydrous DMF (5 mL). The mixture was removed from our glove box and stirred under a nitrogen atmosphere for 6 h at 65°C in an oil bath, after which time DMF was removed under reduced pressure. The residue was dissolved in CH₂Cl₂ and filtered over celite to remove insoluble materials. After evaporation of solvent, the crude product was applied to a silica gel column that had been pre-equilibrated with 1% TEA in CHCl₃ and eluted with MeOH/CHCl₃ (0:100-3:97). Evaporation of the eluting solvent afforded **6** as a yellow foam (469 mg, 57% yield). ¹H NMR (300 MHz, CDCl₃): δ (ppm) 2.53 (1H, ddd, J=2.7, 6.6 and 14.1 Hz, $H_{2'}$), 3.36–3.49 (2H, m, $H_{5'}$ and $H_{5''}$), 3.66–3.75 [7H, m, $H_{2''}$ and OCH₃ (DMTr)], 4.39–4.43 (1H, m, $H_{4'}$), 5.06 [4H, d, J_{H-P} =8.4 Hz, CH₂ (Bn)], 5.39–5.43 $(1H, m, H_{3'}), 5.73 (2H, br s, NH_2), 6.57 (1H, t, J=6.9 Hz, H_{1'}), 6.71 [4H, dd, J=4.2]$ and 8.7 Hz, OPh-meta (DMT)], 7.15-7.39 [19H, m, OPh-ortho (DMT, 4H), Ph (DMT, 5H), and Ph (Bn, 10H)], 7.82-7.85 [2H, m, H₆ (AQ) and H₇ (AQ)], 7.94 [1H, dd, J=1.5 and 8.1 Hz, H₃ (AQ)], 8.04 [1H, s, H₂ (dA)], 8.30-8.36 [3H, m, H₄ (AQ), H_5 (AQ) and H_8 (AQ)], and 8.53 [1H, d, J=1.5 Hz, H_1 (AQ)].

8-[(Anthraquinone-2-yl)ethynyl]-2'-deoxyadenosine 3'-dibenzyl phosphate, 8. Compound 7 (250 mg, 0.24 mmol) was dissolved in a 30% DCA in CH₂Cl₂ mixture (7.5 mL), and the resulting red solution was stirred at room temperature for 30 min. (Note that many times it was convenient to perform this detritylation step directly on the crude product 7 without silica gel purification.) The reaction was quenched by addition of saturated aqueous NaHCO₃ until the red color of the DMTr cation disappeared. More CH₂Cl₂ (25 mL) and water (10 mL) were added, and the organic layer was separated, washed with water, dried with anhydrous MgSO₄, and evaporated to dryness. The syrup obtained was purified using flash silica gel chromatography on a biotage column with MeOH/ CHCl₃ (0:100–3:97) as the eluting system to yield yellow foam after evaporating the eluting solvent. This foam was dissolved in a minimum amount of CH₂Cl₂ and precipitate afforded 8 as a bright yellow solid (135 mg, 76% yield). ¹H NMR (300 MHz, CDCl₃): δ (ppm) 2.46 (1H, dd, J=5.7 and 14.1 Hz, H₂), 3.08–3.15 (1H, m, $H_{5''}$), 3.37–3.65 (1H, m, 5) 3.86–3.91 (1H, m, $H_{5''}$), 4.33 (1H, s, $H_{4'}$), 5.04–5.18 [4H, m, CH₂ (Bn)], 5.20–5.24 (1H, m, H₃), 6.17 (2H, br s, NH₂), 6.56–6.62 (2H, m, H_{1'} and OH_{5'}), 7.29–7.37 [10H, m, Ph (Bn)], 7.72–7.83 [2H, m, H₆ (AQ) and H₇ (AQ)], 7.92 [1H, d, J=8.1 Hz, H₃ (AQ)], 8.23-8.26 [3H, m, H₂ (dA), H₅ (AQ) and H₈ (AQ)], 8.32 [1H, d, J=8.1 Hz, H₄ (AQ)], and 8.56 [1H, s, H₁ (AQ)]. ¹H NMR $(500 \text{ MHz}, \text{CDCl}_3 + \text{D}_2\text{O}): \delta$ (ppm) 2.45 (1H, dd, J=5 and 14 Hz, $\text{H}_{2'}$), 3–3.14 (1H, m, $H_{2''}$), 3.59 (1H, d, J = 12.5 Hz, $H_{5'}$) 3.87 (1H, d, J = 12.5 Hz, $H_{5''}$), 4.33 (1H, s, $H_{4'}$), 5.05-5.16 [4H, m, CH₂ (Bn)], 5.21-5.23 (1H, m, H_{3'}), 6.59 (1H, dd, J=5 and 9 Hz, H₁, 7.31–7.38 [10H, m, Ph (Bn)], 7.76–7.82 [2H, m, H₆ (AQ) and H₇ (AQ)], 7.93 $[1H, d, J=8 Hz, H_3 (AQ)], 8.23-8.25 [3H, m, H_2 (dA), H_5 (AQ) and H_8 (AQ)], 8.32$ [1H, d, J=8 Hz, H₄ (AQ)], and 8.56 [1H, s, H₁ (AQ)]. ³¹P NMR (121 MHz, CDCl₃): δ (ppm) -1.55. ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 38.67 (C_{2'}), 63.10 (C_{5'}), 69.79 $[d, J_{P-C}=6, CH_2 (Bn)], 80.05 (d, J_{P-C}=6, C_{3'}), 80.86 [dA-C (ethynyl)], 87.19, 88.04$ (C_{1'} and C_{4'}), 94.48 [AQ-C (ethynyl)], 120.85 [C₅ (dA)], 126.11 [C₈ (dA)], 127.40, 127.60, 128.19, 128.71, 128.87, 131.08 [AQ and Ph (Bn)], 132.05, 133.25, 133.40, 133.54, 133.63 (AQ), 134.44 [d, J_{P-C} =3.1, Ph-C₁ (Bn)], 135.50, 136.78 [AQ and Ph (Bn)], 148.40 (AQ), 152.20 [C₄ (dA)], 153.36 [C₂ (dA)], 155.67 [C₆ (dA)], 181.89 (CO), and 182.15 (CO). Low-resolution ESI MS m/z (M + H)⁺: calc'd 742.21, found 742.18.

8-[(Anthraquinone-2-yl)ethynyl]-2'-deoxyadenosine 3'-benzyl hydrogen phosphate, 1. Compound 8 (59 mg, 0.08 mmol) was dissolved in anhydrous 1,4-dioxane (8 mL) by heating to 60°C. DABCO (24 mg, 0.22 mmol, 2.7 equiv.) was added to this solution in our glove box, and the homogeneous mixture was refluxed on the bench top for 2 h under a nitrogen atmosphere. The solvent was evaporated, and the crude product was separated by analytical HPLC to give ca. 95% yield of 1. The crude product was then purified by preparative HPLC using a Varian Microsorb C-18 reverse-phase column (250 mm \times 41.4 mm dia.). The column was eluted with a flow rate of 40 mL/min, and the fractions were monitored by UV detection at 260 nm. The mobile phase consisted of a programmed gradient of solution A (70% MeCN in water) and solution B (water): from 0% A/100% B to 50% A/50% B over 15 min; then to 100% A/0% B over 5 min, and finally at 100% A/0% B for another 10 min. Evaporation of the eluent was facilitated by co-evaporation with MeOH to afford 1 as yellow plates (30 mg, 58%) yield). ¹H NMR (500 MHz, DMSO- d_6): δ (ppm) 2.52–2.56 (1H, m, H₂), 3.08–3.14 (1H, m, H_{2"}), 3.35 (1H, br s, OH_{5'}), 3.52–3.54 (1H, m, H_{5'}), 3.64–3.66 (1H, m, H_{5"}), 4.14 (1H, s, $H_{4'}$), 4.80 [2H, d, J_{H-P} = 5.5 Hz, CH₂ (Bn)], 5.03 (1H, s, $H_{3'}$), 6.55 (1H, t, J = 7 Hz, $H_{1'}$), 7.17 [1H, t, J = 7.5 Hz, Ph-para (Bn)], 7.24 [2H, t, J = 7.5, Ph-meta (Bn)], 7.33 [2H, d, J = 7.5 Hz, Ph-ortho (Bn)], 7.68 (2H, br s, NH₂), 7.94 [2H, dd, J = 5.5 and 3.5 Hz, H₆ (AQ) and H₇ (AQ)], 8.13 [1H, s, H₂ (dA)], 8.17 [1H, d, J = 8Hz, H₃ (AQ)], 8.20-8.22 [3H, m, H₄ (AQ), H₅ (AQ) and H₈ (AQ)], and 8.32 [1H, s, H₁ (AQ)]. ¹H NMR (500 MHz, DMSO- d_6 + D₂O): δ (ppm) 2.52–2.56 (1H, m, H₂), $3.11 (1H, s, H_{2'}), 3.50-3.53 (1H, m, H_{5'}), 3.65-3.67 (1H, m, H_{5'}), 4.15 (1H, s, H_{4'}),$

4.79 [2H, s, CH₂ (Bn)], 5.0 (1H, s, H₃'), 6.55 (1H, s, H₁'), 7.18 [1H, d, J = 6 Hz, Phpara (Bn)], 7.24 [2H, t, J = 6, Ph-meta (Bn)], 7.32 [2H, d, J = 6 Hz, Ph-ortho (Bn)], 7.94 [2H, d, J = 2.5 Hz, H₆ (AQ) and H₇ (AQ)], 8.11 [1H, s, H₂ (dA)], 8.14 [1H, d, J = 8.5 Hz, H₃ (dA)], 8.19–8.21 [3H, m, H₄ (AQ), H₅ (AQ) and H₈ (AQ)], and 8.30 [1H, s, H₁ (AQ)]. ¹³C NMR (125 MHz, DMSO- d_6): δ (ppm) 45.22(C₂'), 62.38 (C₅'), 66.07 [d, $J_{C-P} = 4.6$ Hz, CH₂ (Bn)], 75.31 (d, J = 20 Hz, C₃'), 82.22 [dA-C (ethynyl)], 84.92, 86.96 (C₁' and C₄'), 92.73 [AQ-C (ethynyl)], 119.85 [C₅ (dA)], 125.57 [C₈ (dA)], 126.87, 127.07, 127.30, 128.07, 129.65, 132.07 [AQ and Ph (Bn)], 132.83, 132.97, 133.05, 133.16, 136.96, 134.75 (AQ) 139.28 [d, $J_{C-P} = 8.3$, Ph-C₁ (Bn)], 148.48 [C₄ (dA)], 153.75 [C₂ (dA)], 156.16 [C₆ (dA)], 181.55 (CO), and 181.66 (CO). ³¹P NMR (202 MHz, DMSO- d_6): δ (ppm) -0.35. Low resolution ESI MS m/z(M-H)⁻: calc'd 650.14, found 650.11.

5'-0-tert-butyldiphenylsilyl-8-bromo-2'-deoxyadenosine, 9. Compound 3 (5 g, 15 mmol) was dried two times by co-evaporation with anhydrous pyridine and then suspended in anhydrous pyridine (40 mL); imidazol (1.02 g, 15 mmol, 1 equiv.) was added to this suspension in our glove box. The mixture was removed from the glove box and cooled to 0°C using an ice-water bath. TBDPSCl (4.09 mL, 15.7 mmol, 1.05 equiv.) was added drop-wise (over 27 min) under nitrogen with a syringe. The pale yellow reaction mixture was warmed to room temperature, at which time the mixture became homogeneous. Stirring continued at room temperature under a nitrogen atmosphere, and the reaction progress was monitored with TLC. The starting materials were completely consumed after a total reaction time of 3 h. The reaction was quenched with MeOH (5 mL), and the solvent was evaporated. The residue was dissolved in EtOAc (500 mL) and washed with water $(2 \times 200 \text{ mL})$; the organic phase was dried over MgSO₄. The crude product was purified on a silica gel column that was eluted with MeOH/CH₂Cl₂ (0:100–3:97). Evaporation of the eluting solvent afforded $\mathbf{9}$ as white foam (7.755 g, 91% yield). ¹H NMR (300 MHz, CDCl₃): δ (ppm) 1.02 [9H, s, t-Bu (TBDPS)] 2.3–2.41 (2H, m, $H_{2'}$ and $OH_{3'}$), 3.53–3.62 (1H, m, $H_{2''}$), 3.84 (1H, dd, J=8.1 and 10.2 Hz, H₅), 3.98 (1H, dd, J=7.5 and 10.2 Hz, H₅), 4.04-4.1 (1H, m, $H_{4'}$, 4.99–5.08 (1H, m, $H_{3'}$), 5.6 (2H, br s, NH₂), 6.38 (1H, dd, J=6.3 and 7.2 Hz, H₁'), 7.29–7.43 [6H, m, Ph-ortho and para (TBDPS)], 7.62 [4H, dt, J=1.5 and 8.1 Hz, Ph-meta (TBDPS)], and 8.09 [1H, s, H₂ (dA)]. ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 19 [CMe₃ (TBDPS)], 26.67 [CH₃ (TBDPS)], 36.37 (C_{2'}), 63.68 (C_{5'}), 72.09 (C_{3'}), 86.04, 87.05 (C_{4'} and C_{1'}), 120.15 [C₅ (dA)], 127.51 [Ph-meta (TBDPS)], 127.66 [C₈ (dA)], 129.63 [Ph-para (TBDPS)], 133 [Ph-C₁ (TBDPS)], 135.38 [Ph-ortho (TBDPS)], 150.55 [C₄ (dA)], 152.38 [C₂ (dA)], and 154.28 [C₆ (dA)]. Low-resolution ESI MS m/z (M + H)⁺: Calc'd 568.14, found 568.13.

5'-O-tert-Butyldiphenylsilyl-8-[(anthraquinone-2-yl)ethynyl]-2'-deoxyadenosine, 10. To 9 (1.914 g, 3.37 mmol) was added in our glove box Pd(Ph₃P)₄ (194 mg, 0.17 mmol, 0.05 equiv.), CuI (65 mg, 0.34 mmol, 0.1 equiv.), TEA (0.94 mL, 6.7 mmol, 2 equiv.), compound 6 (1.016 g, 4.38 mmol, 1.3 equiv.), and anhydrous DMF (29 mL). The mixture was removed from our glove box and stirred under a nitrogen atmosphere in the dark for 6 h at 65°C in an oil bath. DMF was removed under reduced pressure, and the residue was dissolved in 10% MeOH in CH₂Cl₂; insoluble materials were removed by filtration over celite. After evaporation the crude product was purified with two silica gel columns using MeOH/CH₂Cl₂ (0:100–3:97) as the eluting system to yield yellow foam after evaporation of the eluting solvent. This foam was dissolved in a minimum amount of CH₂Cl₂ and precipitated by adding hexane. Evaporation of CH₂Cl₂/hexane from the precipitate afforded **10** as a bright yellow solid (2.19 g, 90%). ¹H NMR (300 MHz, CDCl₃): δ (ppm) 1.03 [9H, s, t-Bu (TBDPS)] 2.45–2.53 (1H, m, H₂), 2.63 $(1H, d, J=3 Hz, OH_3), 3.5-3.59 (1H, m, H_{2''}), 3.89 (1H, dd, J=5.1 and 10.2 Hz,$ $H_{5'}$, 4.03 (1H, dd, J=7.8 and 10.2 Hz, $H_{5''}$), 4.13–4.19 (1H, m, $H_{4'}$), 5–5.08 (1H, m, $H_{3'}$), 5.96 (2H, br s, NH₂), 6.32 (1H, t, J = 6.9 Hz, $H_{1'}$), 7.29–7.42 [6H, m, Ph-ortho and para (TBDPS)], 7.63 [4H, t, J=6.6 Hz, Ph-meta (TBDPS)], 7.79 [2H, t, J=3.6, H_6 (AQ) and H_7 (AQ)], 7.88 [1H, d, J=8.1 Hz, H_3 (AQ)], 8.12 [1H, s, H_2 (dA)], 8.25 [1H, d, J=8.1 Hz, H₄ (AQ)], 8.27-8.32 [2H, m, H₅ (AQ) and H₈ (AQ)], and 8.48 [1H, s, H₁ (AQ)]. ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 19.17 [CMe₃ (TBDPS)], 26.80 [CH₃ (TBDPS)], 37.02 (C₂), 64.12 (C₅), 73.05 (C₃), 81.78 [dA-C (ethynyl)], 85.19, 87.02 ($C_{4'}$ and $C_{1'}$), 93.74 [AQ-C (ethynyl)], 120.01 [C_5 (dA)], 126.32 [C₈ (dA)], 127.30, 127.67 (Ph-meta (TBDPS), and AQ), 129.74 [Ph-para (TBDPS)], 130.80 (AQ), 133.10, 133.30, 134.02, 134.27, 134.32 (Ph-C₁ (TBDPS) and AQ), 135.48 [Ph-ortho (TBDPS)], 136.47(AQ), 149.12 [C_4 (dA)], 153.69 [C_2 (dA)], 155.24 [C₆ (dA)], 181.89 (CO), and 182.06 (CO). Low-resolution ESI MS m/z $(M + H)^+$: Calc'd 720.26, found 720.25.

5'-O-tert-Butyldiphenylsilyl-8-[2-(anthraquinone-2-yl)ethyl]-2'deoxyadenosine, 11. Compound 10 (940 mg, 1.3 mmol) was dissolved in EtOAc (60 mL) by slight heating while stirring; MeOH (90 mL) was then added to the solution. The resulting solution was transferred to a hydrogenation vessel containing 10% Pd/C (500 mg) that had been activated by stirring under H_2 (40 psi) in MeOH (20 mL) for 30 min at room temperature. The vessel was next charged with H_2 gas and then degassed using an aspirator in a cycle that was repeated 5–6 times. The vessel was finally charged with hydrogen gas at 40 psi and stirred at room temperature for 24 h, by which time TLC showed complete conversion of an initial spot to a more polar spot. The Pd/C catalyst was then removed by filtration over celite, and adsorbed nucleoside residue was extracted from the catalyst by washing with boiling 10% MeOH in $CHCl_3$. The crude product was applied to a silica gel column and eluted with $MeOH/CH_2Cl_2$ (0:100-3:97). Evaporation of the eluting solvent afforded **11** as a pale yellow foam (810 mg, 86% yield). ¹H NMR $(300 \text{ MHz}, \text{CDCl}_3)$: δ (ppm) 0.98 [9H, s, t-Bu (TBDPS)], 2.28 (1H, ddd, J = 3.9, 6.9and 13.2 Hz, H₂), 3.03 (1H, br s, OH₃), 3.19-3.4 (4H, m, ethylene), 3.58-3.68 (1H, m, $H_{2''}$), 3.8 (1H, dd, J = 4.8 and 10.5 Hz, $H_{5'}$), 3.96 (1H, dd, J = 6.9 and 10.5 Hz,

H_{5'}), 4.05–4.1 (1H, m, H_{4'}), 4.92–4.98 (1H, m, H_{3'}), 5.67 (2H, br s, NH₂), 6.25 (1H, t, J = 6.9 Hz, H_{1'}), 7.26–7.38 [6H, m, Ph-*ortho* and *para* (TBDPS)], 7.52–7.66 [5H, m, Ph-*meta* (TBDPS) and H₃ (AQ)], 7.79 [2H, t, J = 4.5 Hz, H₆ (AQ) and H₇ (AQ)], 8.09 [1H, s, H₂ (dA)], 8.16 [1H, d, J = 7.8 Hz, H₄ (AQ)], 8.2 [1H, d, J = 1.8 Hz, H₁ (AQ)], and 8.24–8.3 [2H, m, H₅ (AQ) and H₈ (AQ)]. ¹³C NMR (125 MHz, CDCl₃): δ (ppm) 19.17 [CMe₃ (TBDPS)], 26.79 [CH₃ (TBDPS)], 29.16 [dA-CH₂ (ethyl)], 33.35 [AQ-CH₂ (ethyl)], 36.86 (C_{2'}), 64.02 (C_{5'}), 72.69 (C_{3'}), 84.18, 86.76 (C_{4'} and C_{1'}), 118.96 [C₅ (dA)], 127.17 [C₈ (dA)], 127.65 [Ph-*meta* (TBDPS)], 129.73 [Ph-*para* (TBDPS)], 131 (AQ), 133.2, 133.52, 133.63 (Ph-C₁ (TBDPS) and AQ), 135.49 [Ph-*ortho* (TBDPS)], 147.52 (AQ), 150.84 [C₄ (dA)], 151.92 [C₂ (dA)], 154.62 [C₆ (dA)], 182.75 (CO), and 183.14 (CO). Low-resolution ESI MS *m/z* (M + H)⁺: Calc'd 724.30, found 724.25.

5'-O-tert-butyldiphenylsilyl-8-[2-(anthraquinone-2-yl)ethyl]-2'deoxyadenosine 3'-dibenzyl phosphate, 12. To 11 (750 mg, 1.036 mmol), previously dried two times by co-evaporation with anhydrous THF, was added Me-tetrazole (193 mg, 2.28 mmol, 2.2 equiv.) and anhydrous THF (7 mL) in our glove box. The mixture was removed from our glove box and cooled to $0^{\circ}C$ using an ice-water bath, and (BnO)₂PN(*i*Pr)₂ (0.41 mL, 1.24 mmol, 1.2 equiv.) was added drop-wise under nitrogen with a syringe. The reaction mixture was stirred under a nitrogen atmosphere for 10 minutes at $0^{\circ}C$ and then allowed to warm to room temperature with continued stirring for a total reaction time of 1 h. A white precipitate began to form after 20 min of stirring, and TLC showed formation of a spot that was less polar than the starting material. This new TLC spot did not increase with additional stirring. The suspension was cooled to -78° C using a dry ice-acetone bath, and a solution of *m*-CPBA (375 mg) in CH₂Cl₂ (7 mL) was added gradually to the chilled mixture. After 15 minutes of stirring at -78° C, the mixture became homogeneous, and TLC showed conversion of an initial spot to a more polar one. The mixture was next warmed to room temperature, and saturated aqueous NaHCO₃ (8 mL) was added. More CH_2Cl_2 (50 mL) and water (20 mL) were then added. Finally, the organic layer was separated, washed with water, dried with anhydrous MgSO₄, and evaporated to dryness. The syrup obtained was purified on silica gel column (16 cm \times 2.5 cm dia.) that was eluted with MeOH/ $CHCl_3$ (0:100–3:97). Evaporation of the eluting solvent afforded **12** as pale yellow foam (833 mg, 82% yield). ¹H NMR (300 MHz, CDCl₃): δ (ppm) 0.99 [9H, s, t-Bu (TBDPS)], 2.4 (1H, ddd, J = 2.1, 6 and 13.8 Hz, $H_{2'}$), 3.18–3.37 (4H, m, ethylene), 3.70 (1H, dd, J = 5.4 and 11.1 Hz, $H_{5'}$), 3.82–3.90 (1H, m, $H_{2''}$), 3.96 (1H, dd, J = 6.6 and 11.1 Hz, $H_{5''}$, 4.23–4.28 (1H, m, $H_{4'}$), 5–5.12 [4H, m, CH_2 (Bn)], 5.35– 5.39 (1H, m, $H_{3'}$), 5.54 (2H, br s, NH_2), 6.4 (1H, dd, J = 6 and 7.8 Hz, $H_{1'}$), 7.23–7.4 [16H, m, Ph-ortho and para (TBDPS, 6H) and Ph (Bn, 10H)], 7.54-7.59 [4H, m, Ph*meta* (TBDPS)], 7.62 [1H, dd, J = 1.8 and 8.1 Hz, H₃ (AQ)], 7.76–7.82 [2H, m, H₆ (AQ) and H_7 (AQ)], 7.98 [1H, s, H_2 (dA)], 8.21 [1H, d, J = 8.1 Hz, H_4 (AQ)], 8.2 $[1H, d, J = 1.8 \text{ Hz}, H_1 \text{ (AQ)}], \text{ and } 8.23-8.32 \text{ [2H, m, } H_5 \text{ (AQ)} \text{ and } H_8 \text{ (AQ)}].$

¹³C NMR (125 MHz, CDCl₃): δ (ppm) 19.13 [CMe₃ (TBDPS)], 26.69 [CH₃ (TBDPS)], 29.05 [dA-CH₂ (ethyl)], 33.07 [AQ-CH₂ (ethyl)], 34.68 (C₂), 63.04 (C₅), 69.31–69.68 [m, CH₂ (Bn)], 78.66 (C_{3'}), 84.18, 86.76 (C_{4'} and C_{1'}), 118.85 [C₅ (dA)], 127.13 [C₈ (dA)], 127.58 [Ph-*meta* (TBDPS)], 128.02, 128.6 [Ph (Bn)], 129.68 [Ph-*para* (TBDPS)], 131.88 (AQ), 132.95 [d, $J_{P-C} = 6.1$, Ph-C₁ (Bn)], 133.43, 133.44, 133.52 (Ph-C₁ (TBDPS) and AQ), 134.04, 134.3 [Ph (Bn)], 135.48 [Ph-*ortho* (TBDPS)], 147.42 (AQ), 150.86 [C₄ (dA)], 151.80 [C₂ (dA)], 154.48 [C₆ (dA)], 182.82 (CO), and 183.16 (CO). ³¹P NMR (121 MHz, CDCl₃): δ (ppm) –1.19. Low-resolution ESI MS m/z (M + H)⁺: Calc'd 984.36, found 984.31.

8-[2-(Anthraquinone-2-yl)ethyl]-2'-deoxyadenosine 3'-dibenzyl **phosphate**, 13. Compound 12 (375 mg, 0.38 mmol) was dissolved in THF (1.5 mL) by stirring at 60° C for 1 min, and then MeOH (10 mL) was added. To this solution was added NH₄F (162 mg, 4.38, 11.5 equiv.), and the reaction mixture was stirred at 60° C for 6 h, by which time TLC showed nearly complete consumption of the starting material. The solvent was reduced in volume, and the residue was adsorbed on silica gel. The adsorbed residue was applied to flash silica gel on a biotage column that was eluted with MeOH/CHCl₃ (0:100-5:95). Evaporation of the eluting solvent yielded pale yellow foam. This foam was dissolved in a minimum amount of CH_2Cl_2 and precipitated by adding hexane. Evaporation of CH_2Cl_2 /hexane from the precipitate afforded **13** as pale yellow powder (250 mg, 88% yield). ¹H NMR (300 MHz, CDCl₃): δ (ppm) 2.22 (1H, dd, J = 5.4 and 14.1 Hz, H_{2'}), 3.02-3.38 (5H, m, ethylene, and H_{2"}), 3.55 (1H, d, J = 12.9 Hz, H_{5'}), 3.8 (1H, d, J = 12.9 Hz, $H_{5''}$), 4.21 (1H, s, $H_{4'}$), 5.0–5.17 (5H, m, CH₂ (Bn), and $H_{3'}$), 5.77 $(2H, br s, NH_2), 6.13 (1H, dd, J = 5.1 and 9.9 Hz, H_{1'}), 6.73 (1H, br s, OH_{5'}), 7.31 -$ 7.38 [10H, m, Ph (Bn)], 7.65 [1H, dd, J = 1.5 and 7.8 Hz, H₃ (AQ)], 7.78–7.82 [2H, m, H₆ (AQ) and H₇ (AQ)], 8.22-8.33 [5H, m, H₂ (dA), H₄ (AQ), H₁ (AQ), H₅ (AQ), and H₈ (AQ)]. ¹³C NMR (125 MHz, CDCl₃): δ (ppm) 29.01 [dA-CH₂ (ethyl)], 33.01 [AQ-CH₂ (ethyl)], 38.16 (C₂), 63.01 (C₅), 69.71 [d, $J_{P-C} = 1$, CH₂ (Bn)], 80.21 ($C_{3'}$), 85.67, 87.60 ($C_{1'}$ and $C_{4'}$), 119.38 [C_5 (dA)], 127.22 [C_8 (dA)], 127.83, 128.20, 128.7, 128.83 [AQ and Ph (Bn)], 132.05 (AQ), 133.45 [d, $J_{P-C} = 3.1$, Ph-C₁ (Bn)], 133.63 (AQ), 134.09, 134.20, 134.32, 135.41, 135.46 [AQ and Ph (Bn)], 147.01, 149.78 (AQ), 150.62 [C₄ (dA)], 151.75 [C₂ (dA)], 155.08 [C₆ (dA)], 182.82 (CO), and 183.17 (CO). ³¹P NMR (162 MHz, CDCl₃): δ (ppm) -1.23. Lowresolution ESI MS m/z (M + H)⁺: Calc'd 746.24, found 746.24.

8-[2-(Anthraquinone-2-yl)ethyl]-2'-deoxyadenosine 3'-benzyl hydrogen phosphate, 2. Compound 13 (210 mg, 0.28 mmol) was dissolved in a mixture of EtOAc (10 mL) and MeOH (80 mL). The resulting solution was transferred to a hydrogenation vessel containing 10% Pd/C (30 mg) that had been activated by stirring under H₂ (40 psi) in MeOH (20 mL) for 30 min at room temperature. The vessel was next charged with H₂ gas and then degassed using an aspirator in a cycle that was repeated 5–6 times. The vessel was finally charged with hydrogen gas at 40 psi and stirred at room temperature for 24 h, at which time TLC showed that some 13 was still present. More 10%Pd/C (20 mg) was added, and the hydrogenation vessel was recharged with H_2 as described above. The mixture was stirred at room temperature for an additional 7 h under H_2 gas (45 psi), by which time TLC showed complete consumption of 13. The Pd/C catalyst was then removed by filtration over celite, and adsorbed nucleotide residue was extracted from the catalyst by washing with boiling MeOH. The crude product was then purified by preparative HPLC using a Varian Microsorb C-18 reverse-phase column (250 mm \times 41.4 mm dia.). The column was eluted with a flow rate of 40 mL/min, and the fractions were monitored with UV detection at 260 nm. The mobile phase consisted of a programmed gradient of solution A (70% MeCN in water) and solution B (water): from 0% A/100% B to 50% A/50% B over 15 min, then to 100% A/0% B over 5 min, and finally at 100%A/0% B for another 10 min. Evaporation of the eluent was facilitated by co-evaporation with MeOH and afforded **2** as yellow plates (30 mg, 22% yield). ¹H NMR (500 MHz, DMSO- d_6): δ (ppm) 2.33 (1H, ddd, $J = 3.5, 6.5, and 13 Hz, H_2$), 2.98–3.04 (1H, m, H_{2''}), 3.25–3.4 $(4H, m, ethylene), 3.45-3.49 (1H, m, H_{5'}), 3.5-3.58 (1H, m, H_{5''}), 4.01 (1H, d, J = 3)$ Hz, $H_{4'}$), 4.71 [2H, d, J_{H-P} = 5 Hz, CH₂ (Bn)], 4.87–4.96 (1H, m, H_{3'}), 6.12 (1H, br d, J = 7 Hz, OH₅), 6.28 (1H, t, J = 7 Hz, H₁), 7.15 (2H, br s, NH₂), 7.18 [1H, t, J = 7.5 Hz, Ph-para (Bn)], 7.25 [2H, t, J = 7.5, Ph-meta (Bn)], 7.33 [2H, d, J = 7.5 Hz, Ph-ortho (Bn)], 7.87 [1H, d, J = 8 Hz, H₃ (AQ)], 7.91–7.93 [2H, m, H₆ (AQ) and H₇ (AQ)], 8.05 [1H, s, H₂ (dA)], 8.12-8.14 [2H, m, H₁ (AQ) and H₄ (AQ)], and 8.18-8.22 [2H, m, H₅ (AQ) and H₈ (AQ)]. ¹H NMR (500 MHz, DMSO- d_6 + D₂O): δ (ppm) 2.3-2.38 (1H, m, H_{2'}), 2.98-3.04 (1H, m, H_{2"}), 3.25-3.4 (4H, m, ethylene), 3.52–3.6 (2H, m, H_{5'} and H_{5''}), 4.05 (1H, s, H_{4'}), 4.71 [2H, d, J_{H-P} = 5 Hz, CH₂ (Bn)], 4.86 (1H, s, $H_{3'}$), 6.27 (1H, t, J = 7 Hz, $H_{1'}$), 7.18 [1H, t, J = 7.5 Hz, Ph-para (Bn)], 7.25 [2H, t, J = 7.5, Ph-meta (Bn)], 7.32 [2H, d, J = 7.5 Hz, Ph-ortho (Bn)], 7.87 $[1H, d, J = 8 Hz, H_3 (AQ)], 7.91 [2H, s, H_6 (AQ) and H_7 (AQ)], 8.04 [1H, s, H_2$ (dA)], 8.1-8.13 [2H, m, H₁ (AQ) and H₄ (AQ)], and 8.19 [2H, m, H₅ (AQ) and H₈ (AQ)]. ¹³C NMR (125 MHz, DMSO-d₆): δ (ppm) 28.34 [dA-CH₂ (ethyl)], 32.72 $[AQ-CH_2 \text{ (ethyl)}]$, 37.15 (C_{2'}), 62.42 (C_{5'}), 65.96 [d, $J_{C-P} = 1$ Hz, CH₂ (Bn)], 75.4 (d, $J = 20.3 \text{ Hz}, C_{3'}, 84.16 (C_{4'}), 86.79 (C_{1'}), 118.18 [C_5 (dA)], 126.71 [C_8 (dA)], 127.03,$ 128.05, 131.28 [AQ and Ph (Bn)], 132.98, 133, 134.52, 134.92 (AQ), 139.5 [d, $J_{C-P} = 7.4$, Ph-C₁ (Bn)], 148.15, 149.79 (AQ), 150.82 [C₄ (dA)], 151.63 [C₂ (dA)], 155.49 [C₆ (dA)], 182.22 (CO), and 182.53 (CO). ³¹P NMR (202 MHz, DMSO- d_6): δ (ppm) 0.77. Low-resolution ESI MS *m/z* (M-H)⁻: Calc'd 654.18, found 654.20.

2-Iodoanthraquinone, 15. To a suspension of **14** (3.06 g, 0.137 mol) in THF (21 mL) was added HCl (28 mL) and water (7 mL). The mixture was stirred at 40°C for 24 h to give a thick, rosey beige suspension. This suspension was cooled to 0°C using an ice-water bath, and a solution of NaNO₂ (1.90 g, 0.027 mol, 2 equiv.) in H₂O (6.5 mL) was added drop-wise with a syringe. A solution of KI (5.69 g, 0.034 mol, 2.5 equiv.) in H₂O (12.5 mL) was added gradually to the reaction mixture

while stirring at 0°C. The reaction mixture was then stirred for an additional 15 min at 0°C, for 30 min at room temperature, and finally for 30 min at 60°C. THF was evaporated from the mixture, and the residue was filtered. The precipitate was collected and washed first with water and then with a saturated solution of aqueous Na₂CO₃. The residue was dissolved in CHCl₃ (54 mL), and the solution was shaken with an aqueous solution of Na₂S₂O₃. The CHCl₃ layer was separated, dried with anhydrous MgSO₄, and evaporated to dryness. Three consecutive silica gel columns eluted with CH₂Cl₂/hexane (10:90–30:70) afforded **15** as yellow powder (3.42 g, 75% yield). ¹H NMR (300 MHz, CDCl₃): δ (ppm) 7.83 (2H, m, H₇), 8.01 (1H, d, *J*=8.4, H₄), 8.16 (1H, dd, *J*=8.4, 1.5, H₃), 8.30–8.33, (2H, m, H₅, and H₈), and 8.66 (1H, s, H₁). ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 127.30, 128.6, 132.5, 133, 133.27, 134, 134.34, 136.23, 143.06, 181.87, and 182.58. Low-resolution EI MS *m/z* (M⁺): 334.

2-(Trimethylsilanylethynyl)anthraquinone, 16. $Pd(Ph_3P)_2Cl_2$ (24 mg, 0.03 mmol, 0.05 equiv.), CuI (13.1 mg, 0.07 mmol, 0.1 equiv.), TEA (0.19 mL, 1.38 mmol, 2 equiv.), and **15** (229.8 mg, 0.69 mmol) were combined and stirred in dry THF (4.6 mL) under a nitrogen atmosphere until dissolved; then TMSA (0.23 mL, 2.064 mmol, 3 equiv.) was added. After 10 minutes of stirring at room temperature, TLC (CH₂Cl₂/hexanes, 1:1 v:v) showed complete consumption of **15**. The solvent was evaporated in vacuo, and the crude material was purified by flash silica gel chromatography (CH₂Cl₂/hexanes, 0:100–20:80 v:v) to give **16** as pale yellow solid (210 mg, 96% yield). ¹H NMR (300 MHz, CDCl₃): δ (ppm) 0.3 (9H, s, 3 × CH₃), 7.84–7.77 (3H, m, H₄, H₆, and H₇), 8.234 (1H, dd, *J* = 8.1, 0.3, H₃), 8.319–8.268 (2H, m, H₅, and H₈), and 8.35 (1H, dd, *J* = 1.5, 0.3, H₁). ¹³C NMR (75 MHz, CDCl₃): δ (ppm) –0.27, 100.11, 103.14, 126.21, 127.26, 127.29, 129.30, 130.62, 132.44, 133.26, 133.33, 133.45, 134.17, 134.26, 136.80, 182.43, and 182.47. Low-resolution EI MS *m/z* (M⁺): 304.

2-Ethynylanthraquinone, 6. To a solution of **16** (200 mg, 0.657 mmol) in THF/MeOH (1:1 v:v, 26 mL) was added potassium fluoride (57.26 mg, 0.985 mmol, 1.5 equiv.) at room temperature. After 1 h the solvent was evaporated; the product was extracted with CHCl₃, shaken with charcoal, and recrystallized from CHCl₃ to afford **6** as brown solid (150 mg, 99% yield). NMR spectra were run on a pale yellow, silica gel purified portion of this product. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 3.37 (1H, s, \equiv C–H), 7.82 (2H, dd, $J = 5.7, 3.3, H_6, H_7$), 7.67 (1H, dd, $J = 8.1, 1.8, H_3$), 8.34–8.27 (3H, m, H₄, H₅, H₈), and 8.41 (1H, d, $J = 1.5, H_1$). ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 81.88, 127.33, 130.85, 134.3, 134.36, 137.1, and 182.42. EI MS m/z (M⁺): 232.

CONCLUSIONS

Working with **6** as described in Schemes 1 and 2 to make, respectively, the 3'benzyl phosphates **1** and **2** imposes synthetic constrains due to the photo-instability of **6** and the poor solubility of anthraquinonyl intermediates. Nevertheless, careful control of reaction conditions, including avoiding short wavelength light when using 6, allows synthesis of 1 and 2 and their precursors on a few-gram scale. Based on our experience with the chemistry in Schemes 1-3, a common modification to Schemes 1 and 2 appears worth investigating in the future as a means of possibly making the 3'-phosphate conjugates 1 and 2 and related AQ-dA nucleosides with less effort and in larger quantities. This alternate chemistry would switch the order of the alkynylation steps in each scheme. Schemes 1 and 2 alkynylate 2iodoanthraquinone (15) with TMSA first and then Pd cross-couple the resulting 6with the 5'-protected 8-bromo-2'-deoxyadenosines, respectively, $\mathbf{5}$ and $\mathbf{9}$. An interesting modification of these two schemes would alkynylate their 5'-protected 8bromo-2'-deoxyadenosines with TMSA first and then Pd cross-couple the resulting 5'-protected 8-ethynyl-2'-deoxyadenosines with **15**. One clear advantage of such a switched reaction order would be that use of photochemically unstable 6 would be avoided. A second and also important advantage would be that 5'-protected 8ethynyl-2'-deoxyadenosine intermediates would replace the 5'-protected 8-bromo-2'deoxyadenosines 5 and 9. Thus, in these two cases the vexing coincidence of R_f values for intermediates 5 and 7 and 9 and 10 would also be eliminated. In short, the work presented here provides a sound basis for synthesizing the 3'-benzyl phosphates 1 and 2 for investigation of their electrochemical reduction and photoinduced intramolecular ET properties in water. Lacking the solubilizing effect of the 3'-benzyl phosphate group, the nucleosides 1a and 2a are insoluble in water, and thus these physical chemical experiments cannot be done on them. Finally, future synthesis of AQ-dA-substituted DNA oligomers based on standard solidphase synthetic protocols appears achievable based either on the chemistry of Schemes 1-3 themselves or on variations of Schemes 1 and 2 that use a switched order of alkynylation.

LIST OF ABBREVIATIONS

$(BnO)_2PN(iPr)_2$	Dibenzyl N,N-diisopropylphosphoramidite
(BnO) ₂ POCl	Dibenzyl phosphorochloridate
(EtO) ₂ POCl	Diethyl phosphorochloridate
4-DMAP	4-(Dimethylamino)pyridine
AQ	Anthraquinone
AQ [●] [−]	Anthraquinone anion radical
AQ*	Lowest energy ${}^{3}(\pi,\pi^{*})$ state of anthraquinone
AQS^{-}	2-Anthraquinone sulfonic acid sodium salt
CS	Charge separated
dA	2'-Deoxyadenosine
<i>m</i> -CPBA	meta-Chloroperbenzoic acid
DABCO	1,4-Diazabicyclo[2,2,2]octane
DCA	Dichloroacetic acid

DMF	<i>N,N</i> -Dimethylformamide
DMTrCl	4,4'-Dimethoxytrityl chloride
ET	Electron transfer
EtOAc	Ethyl acetate
HPLC	High-performance liquid chromatography
Im	Imidazole
MeCN	Acetonitrile
MeOH	Methanol
Me-tetrazol	5-Methyl-1H-tetrazol
Pd	Palladium
Pd/C	Palladium on activated carbon catalyst
$Pd(Ph_3P)_4$	Tetrakis(triphenylphosphine) palladium(0)
$Pd(Ph_3P)_2Cl_2$	Dichlorobis(triphenylphoshine) palladium(II)
Ру	Pyridine
rt	Room temperature
SCS	Secondary charge-separated
TA	Transient absorbance
TBDPSCl	tert-Butyldiphenylsilyl chloride
TEA	Triethylamine
tert-BuMgCl	tert-Butylmagnesium chloride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMSA	Trimethylsilylacetylene
TMSBr	Trimethylsilyl bromide
TMSC1	Trimythylsilyl chloride

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