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Toward a New Genetic System with Expanded Dimensions: Size-Expanded Analogues of Deoxyadenosine and Thymidine

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Abstract: We describe the design, preparation, and properties of two key building blocks of a size-expanded genetic system. Nucleoside analogues of the natural nucleosides dA and dT are reported in which the fusion of a benzo ring increases their size by ca. 2.4 Å. The expanded dA analogue (dxA), having a tricyclic base, was first reported by Leonard nearly three decades ago. We describe a shortened and more efficient approach to this compound. The expanded dT analogue (dxT), a methylquinazolinedione C-glycoside, was previously unknown; we describe its preparation in eight steps from 5-methylanthranilic acid. The key glycoside bond formation employed Pd-mediated coupling of an aryl iodide precursor with a dihydrofuran derivative of deoxyribose. Both nucleosides are shown to be efficient fluorophores, emitting light in the blue-violet range. The base-protected phosphoramidite derivatives were prepared, and short oligonucleotides containing them were characterized. The two size-expanded nucleosides are key components of a new four-base genetic system designed to form helical paired structures having a diameter greater than that of natural DNA. Elements of the design of this expanded genetic molecule, termed xDNA, are discussed, including the possibility of up to eight base pairs of information storage capability.

Introduction

The design and synthesis of modified versions of the DNA double helix has received much attention in the past two decades, primarily boosted by the development of automated solid-phase chemistry for the assembly of oligonucleotides.[1] The motivation behind such work has been multifold: first is the basic scientific exploration of how the natural helix assembles and functions biochemically; second is the possibility that modified oligonucleotide analogues could have biomedical applications in the detection and treatment of disease; third is the possibility that chemists might expand the natural genetic alphabet by providing new base pairs; and finally, there is the exploration of possible primordial precursors of life on earth.

This work has involved chemical approaches to modification both of the phosphodiester backbone of the DNA or of the bases themselves. Modification of the backbone can lead to enhanced properties in hybridization and biochemical stability. A few prominent recent examples include the peptide nucleic acids,[2] locked nucleic acids,[3] phosphoramidate nucleic acids,[4] and threose nucleic acids.[5,6] Those analogues have generally retained natural nucleobases so that the molecules can recognize DNA or RNA of the natural genetic system.

In addition to work with modified backbones, the nucleobases themselves have recently been the targets of modification, often with the goal of designing new base pairs. Early work by Benner proposed a number of new hydrogen bonded pairs that might provide a larger genetic alphabet for hybridization and for encoding genetic information.[7] Work in other laboratories has explored not only hydrogen-bonded pairs,[8] but also nonpolar pairs[9−11] and metal-mediated pairs as well.[12,13] A main focus of those approaches has been to match the geometry of the natural double helical DNA framework, since that is believed to be a chief factor in biochemical function of replication.[14,15]

Because much of the preceding work has focused on maintaining the geometry of pairing within the natural DNA framework, little attention has been devoted to preparation of

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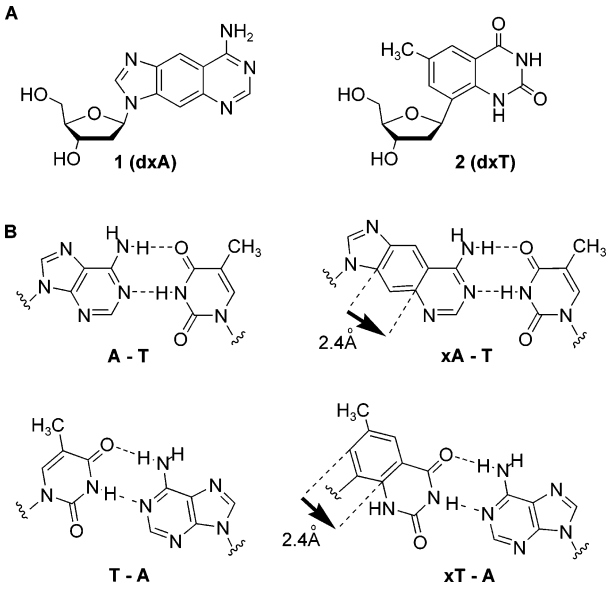

Figure 1. Structures of benzo-fused deoxynucleosides dxA and dxT. (A) The free nucleosides. (B) Proposed structures of hydrogen-bonded base pairs involving extended bases (right), with comparison to the natural analogous pairs (left). The arrows illustrate the vectors of extension of the heterocyclic bases upon insertion of the benzene ring into the framework. The C1′−C1′ glycosidic distances are expected to be ca. 13.0 Å for the extended pairs; by comparison, the distance for B-form DNA is ca. 10.7 Å.

nucleotide analogues of larger size. However, in pioneering work by Leonard nearly three decades ago, a "stretched-out" analogue of adenosine was described in which a benzene ring was inserted between the two rings of adenine.[16] This ribonucleoside and its triphosphate derivative were used to probe the active sites of ATP-dependent enzymes.[17,18] Later work described conversion of the ribonucleoside to the deoxyribonucleoside derivative (here termed dxA) as well.[18] That work was far ahead of its time, and the analogue was never incorporated into oligodeoxynucleotides (automated synthesizers were not yet invented). More recently, a thienyl group has been used as a spacer in tricyclic purine analogues screened for antiviral activity.[19] Leonard recognized that a "stretched out" adenine base would likely not pair well within the natural DNA framework, unless it were paired with a shortened version of thymine to compensate for the size differential.[20]

We have undertaken a program to develop a new artificial genetic system that is not constrained by the dimensions and geometries of the natural DNA helix.[21] By combining size-expanded nucleobase analogues with the natural ones, we envision size-expanded pairs (Figure 1). Assembly of strands containing only size-expanded pairs might result in a fully expanded helix (termed xDNA) with diameter larger than the natural one, and this might avoid the geometric problem of including an isolated larger pair within the natural framework. Ultimately, such a nonnatural genetic system might one day be combined with modified enzymes that could replicate it, yielding a new information-storing and amplifiable molecular system.

Here, we describe the preparation of the two new key components of xDNA, namely, the size-expanded forms of deoxyadenosine, dxA, and thymidine, dxT (Figure 1). When paired with the natural pairing partners thymidine and deoxyadenosine, these compounds create the possibility of a large-diameter four-base paired system, with information encoding potential the same as the natural genetic system. Aspects of the base pair designs are also described.

Results and Discussion

Design Aspects. In considering the structure of the expanded adenine base, Leonard pointed out that, if paired with T, the xA base would be too large for the natural DNA helix. Indeed, he designed a possible new size-compressed pairing partner to compensate for this extended base, although it was apparently never successfully tested.[20] We envisioned, by contrast, that rather than adjust for the added size of xA, one might take advantage of its geometric extension. A fully analogous geometric extension of pyrimidines and purines (Figure 1), paired with natural DNA bases, could potentially yield a regular helix with expanded diameter. Modeling studies in our laboratory (data not shown) suggested that the natural DNA backbone could accept this stretching of all four pairs, requiring only small adjustments of bond angles and requiring no large change to sugar conformations. Subsequent experimental studies have borne this out.[21] There is one significant adjustment that is likely needed to adapt to the large cylindrical diameter of such a helix, however. Because the outer circumference that the backbone must traverse is larger, it is expected that there will be a greater number of base pairs per turn. Our modeling suggested that roughly 14 base pairs per turn might be optimum for xDNA; this contrasts with natural B-DNA (at ca. 10.5 pairs per turn).

Our molecular design for benzo fusion of xT involves a C-nucleoside framework (Figure 1). This design moves the point of attachment to C-1 of deoxyribose by ca. 2.4 Å, virtually the same length increase that occurs with insertion of benzene into the xA base. Thus, the lengths of the two are fully analogous, and the extensions push the hydrogen-bonding surfaces outward toward the backbone of the opposite strand. As a result, the major and minor groove widths in an xDNA duplex are likely to be increased as well. The vector orientations of the two extensions are expected to be slightly different, with the xT base extension oriented about 12° toward the minor groove relative to the xA extension (Figure 1B). This difference arises from the fact that xA has a five-membered-ring glycosidic attachment, whereas xT is attached via a six-membered ring. This difference is relatively small, and (we expect) might be accommodated with modest changes in bond torsional angles in the sugars and backbones.

The two nucleosides dxA and dxT enable the possibility of a full four-base genetic pairing system. The four pairs of this system are xA−T, T−xA, xT−A, and A−xT (Figure 1). This is the same information-encoding potential as the natural genetic system. If the natural bases A and T do not pair together well within this expanded framework, and if xDNA bases do not pair well within the natural framework, then the xDNA system is orthogonal to the natural DNA system. Note also that analogous extended cytosine and guanine base analogues are

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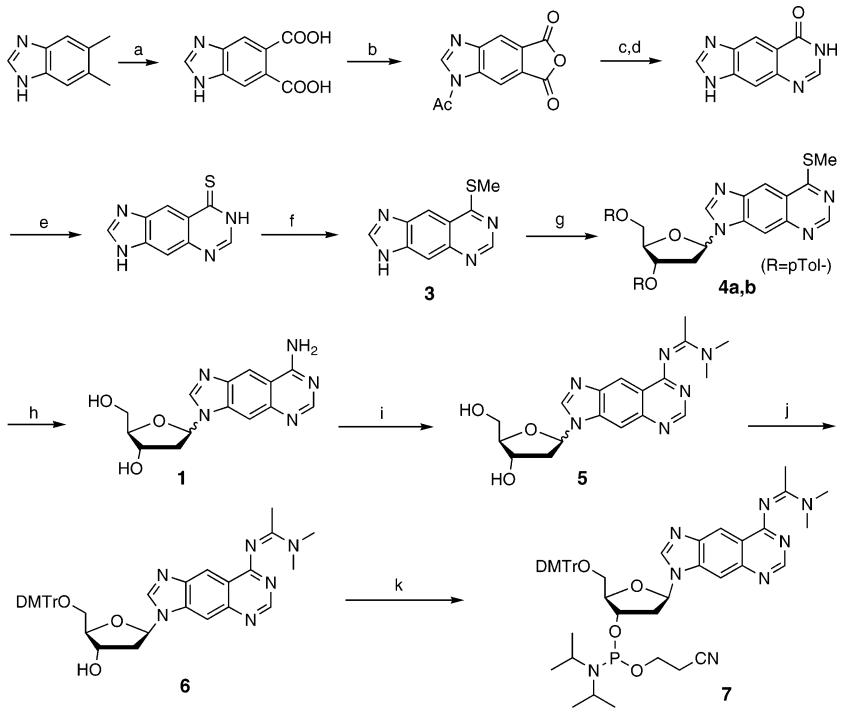
Scheme 1 [a]



[a] Reagents and conditions: (a) $KMnO_4$, *t*BuOH, water, 75 °C, 1.5 h, 60%. (b) Ac_2O, 155 °C, 3 h, 90%. (c) $TMSN_3$, 90−95 °C, 3 h. (d) Formamidine acetate, DMF, 155 °C, 3 h, 55% (two steps). (e) P_2S_5, pyridine, 140 °C, 36 h, 100%. (f) CH_3I, KOH, 1 h, 64%. (g) NaH, CH_3CN, chlorosugar, 6 h, 37%. (h) NH_3, EtOH, 150 °C, 4 × 12 h, 61%. (i) *N*,*N*-Dimethyl acetamide dimethylacetal, MeOH, 60 °C, 72 h, 73%. (j) 4,4′-Dimethoxytrityl chloride, DIPEA, pyridine, 6 h, 72%. (k) *N*,*N*-Diisopropyl cyanoethyl chlorophosphoramidite, CH_2Cl_2, DIPEA, 5 h, 100%.

envisioned; combination of those with natural G and C (along with the above four pairs) leads to a possible eight-base paired genetic system.

Interestingly, these expanded bases are expected to be either orthogonal to or compatible with natural DNA (RNA) strands, depending on the sequence design. If the extended bases are placed in both strands of an expanded duplex, the pairing is expected to be orthogonal by selective size requirements (three rings paired with one or two paired with two but selective against two paired with one, as occurs in DNA). However, if all expanded bases are segregated into one strand, then this xDNA strand can pair with natural DNA or RNA strands to form an expanded helix.[21]

The reasons for our study of xDNA are multifold. First, we expect that the new helix may be more stable thermodynamically than that of natural DNA because the bases are larger and thus might stack more efficiently.[22] This could enable useful applications in hybridization with natural DNA and RNA. Second, the greater electronic conjugation xDNA bases could yield useful properties such as fluorescence. Third, we hope to use such size-expanded nucleobases to probe steric effects in the active sites of polymerase enzymes.[14,15,23] Fourth, if xDNA can indeed undergo stable and selective self-recognition, then it is a candidate for the genetic component of possible extraterrestrial forms of life. Finally, there is our aforementioned goal of developing a new genetic system that is orthogonal to the natural one.

Expanded Deoxyadenosine Analogue. The expanded deoxyadenosine nucleoside **1** was prepared by a route different from that reported by Leonard.[18] That previous approach involved deoxygenation of a ribonucleoside derivative; we envisioned instead a more direct approach to the deoxyribonucleoside. The previously known extended base precursor 8-methythioimidazo-[4,5-g]quinazoline (**3**, Scheme 1) was prepared repeating a six-step procedure in 19% overall yield, starting from 5,6-dimethylbenzimidazole. In a new approach to the deoxyriboside, compound **3** was then subjected to coupling with Hoffer's α-chlorosugar[24] in anhydrous acetonitrile, using NaH (95%, dry) as a strong base. Due to a lack of stereocontrolling factors, this coupling reaction afforded four products as two approximately 1:1 mixtures of deoxyribosides (Scheme 2), with methylthio group oriented down (toward the sugar) (**4b**) or up (**4a**). Each mixture was composed of two C1′-anomers, with the β-isomers dominant. Regioisomers **4a** and **4b** were easily separated by silica chromatography. However, no separation of C1′-isomers was accomplished until at a later stage. The structure of each regioisomer was assigned by 2D-ROESY NMR experiments. Different ROE signal patterns were observed, as shown in Scheme 2. In compound **4b**, there was an aromatic proton that had correlations with both H1′ and SMe, while there was no such proton in **4a**.

The desired regioisomers **4a** were then treated with ammonia in ethanol at 150 °C in a sealed tube. This step simultaneously converted the methylthio group to an amino group and removed 3′ and 5′ hydroxyl protections, thus furnishing the free dxA nucleoside **1**. The overall preparation from **3** was accomplished in eight steps in 4.3% overall yield (assuming a single major β-epimer); this compares favorably to Leonard's approach[20] (12 steps, <2.9% yield).

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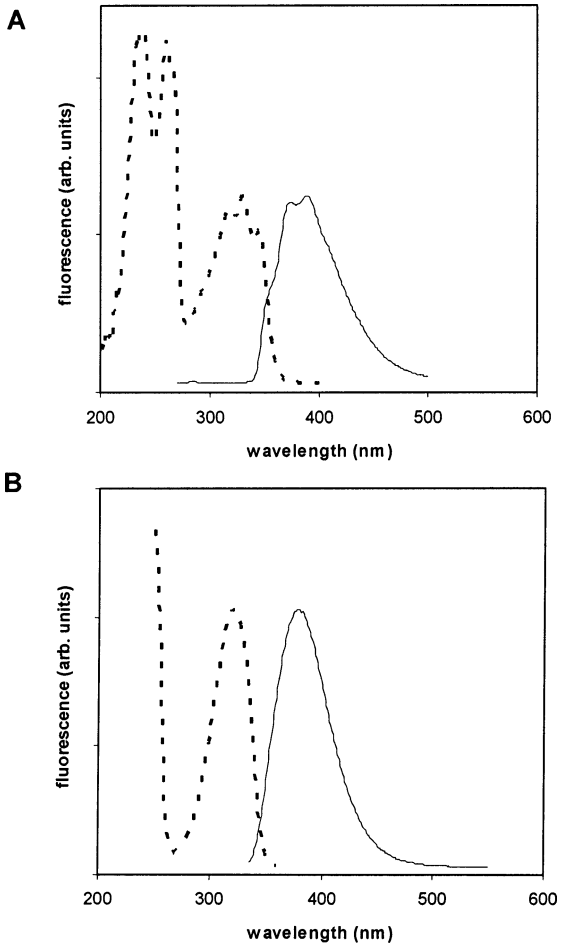
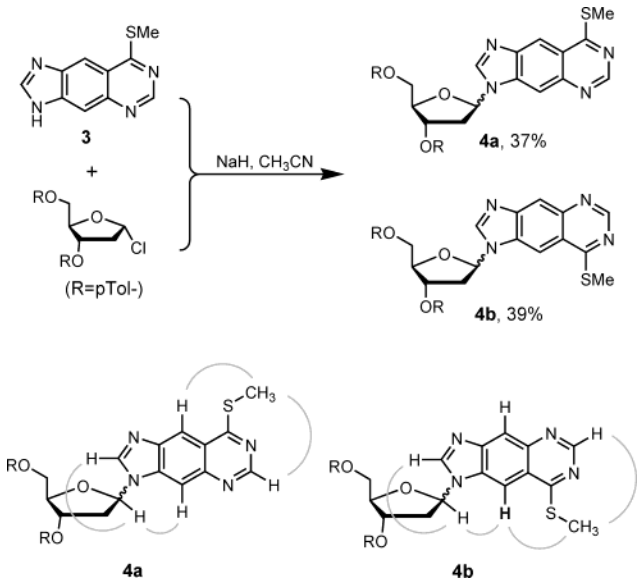


Figure 2. Fluorescence properties of extended nucleosides dxA and dxT. (A) Excitation (dashed line, $\lambda_{em} = 393$ nm) and emission (solid, $\lambda_{ex} = 333$ nm) spectra of dxA nucleoside **1** in methanol. (B) Excitation ($\lambda_{em} = 377$ nm) and emission ($\lambda_{ex} = 320$ nm) spectra for quinazolinedione dxT nucleoside **2** in methanol.

Scheme 2



As was reported previously for the ribonucleoside derivative of the xA base,[16] our data showed that the deoxynucleoside dxA was fluorescent (Figure 2). In methanol solution it absorbed light with maxima at 231, 260, 319, 333, and 348 nm; the 333 nm maximum had a molar absorptivity of 11 080 L/mol·cm. The compound fluoresced in the blue-violet ($\lambda_{max,em} = 393$ nm) with a quantum yield of 0.44. This compares to other fluorescent adenine analogues such as 2-aminopurine, which has a low molar absorptivity and emits in the UV ($\lambda_{max,em} = 365$ nm),[25] and ethenoadenine, which has a similar quantum yield of 0.56 ($\lambda_{max,em} = 410$ nm).[26]

Simple AM1 calculations were carried out for the free base of dxA to explore tautomeric preferences. The results suggested, as expected by analogy to adenine, that the benzo-fused adenine base of dxA preferred the amino tautomer over imino variants (Figure 3).

For eventual incorporation into oligonucleotides, this nucleoside required base protection and sugar functionalization steps. The amino functional group in nucleoside **1** was protected with *N*,*N*-dimethylacetamide dimethylacetal in 73% yield (compound **5**). In the next step, the 5′-OH was selectively protected with dimethoxytrityl. Interestingly, this tritylation reaction furnished the 1′-β anomer (**6**) as the only isolated product in 72% yield. The C1′-β configuration was assigned by means of COSY and 2D-ROESY NMR spectroscopy. ROEs between H1′ and H4′, H2 and H3′, H5′ were observed (data not shown), which were used as proof for the C1′-β configurational assignment. Finally, the dxA phosphoramidite derivative (**7**) was prepared in quantitative yield by treating the DMT-dxA ether with 2-cyanoethyl-diisopropyl-chlorophosphoramidite. To demonstrate intact incorporation into DNA, we prepared the oligonucleotide dT−xA−T following the reported procedure[21] and characterized its proton NMR spectrum without purification. The spectrum (see Supporting Information) confirmed the removal of the protecting group as well as high yield of coupling.

Expanded Thymidine Analogue. We designed the methylquinazolinedione analogue dxT (**2**) as a benzo-fused variant of thymidine having analogous geometric changes as was found in the benzoadenine moiety of dxA (Figure 1). The methyl group of dxT was retained in analogy to that of thymidine. A previously reported quinazolinedione nucleoside[27] did not have expanded pairing dimensions due to a different position of glycosidic attachment.

This second building block, with 6-methyl-quinazoline-2,4-(*1H,3H*)-dione as the nucleobase, was prepared by a route somewhat shorter and more efficient than the dxA analogue (Scheme 3). The 8-iodo derivative of 6-methyl-quinazoline-2,4-(*1H,3H*)-dione **10** was made through two-step synthesis with 5-methyl-2-aminobenzoic acid **8** as starting material. First, iodination with iodine monochloride of **8** gave 2-amino-3-iodo-5-methylbenzoic acid **9** in high yield; subsequent cyclization of **9** in urea melt afforded compound **10** in excellent yield. Attempts were made to use compound **10** directly in a Heck coupling reaction with 1,2-dehydro-3-*O*-(*tert*-butyl-diphenylsilyl)-5-hydroxymethyl-furan **11**, a ribofuranoid glycal designed for stereospecific formation of β C-glycosyl bonds.[28] However, none of the expected product was obtained under several reaction conditions, presumably due to nitrogen complexation with palladium. To circumvent this problem, compound **12**, a

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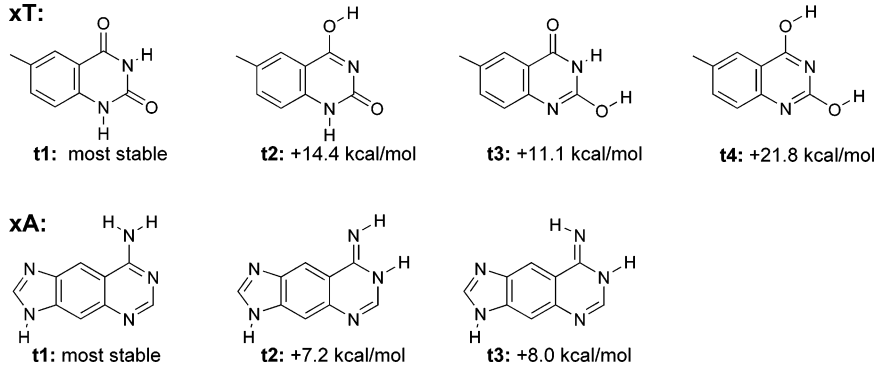
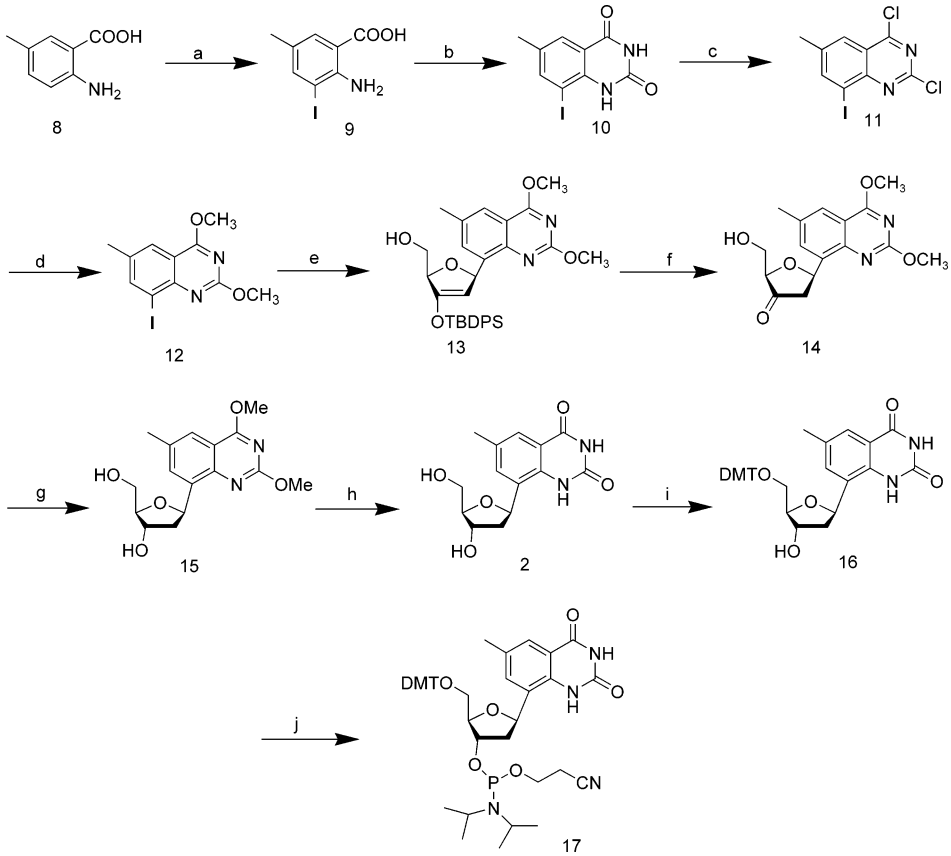


Figure 3. Preliminary calculations of relative tautomeric preferences for the xT and xA bases in the gas phase. Spartan software (Wavefunction, Inc.) was used to perform AM1 geometry optimizations and heats of formation calculations.

Scheme 3 [a]



[a] Reagents and conditions: (a) ICl, HCl (aq), 96%. b) Urea, 150 °C, 92%. (c) $POCl_3$, *N*,*N*-Diethylaniline, reflux, 90%. (d) $NaOCH_3/CH_3OH$, reflux, 87%. (e) 1,2-Dehydro-3-*O*-(*tert*-butyl-diphenylsilyl)-5-hydroxymethyl-furan, $Pd(OAc)_2$, $AsPh_3$, $N(Bu)_3$, 70 °C, 64%. (f) TBAF, THF, 0 °C, 84%. (g) $NaB(OAc)_3H$, THF, AcOH, 15 °C, 93%. (h) NaI, AcOH, 60 °C, 100%. (i) 4,4′-Dimethoxytrityl chloride, DIPEA, pyridine, 84%. (j) *N*,*N*-Diisopropylammonium tetrazolide, 2-cyanoethyl tetraisopropylphosphoramidite, CH_2Cl_2, 82%.

dimethyl-protected derivative of **10**, was made through a two-step synthesis in very good yield.

Heck coupling between **11** and **12** was relatively efficient with $Pd(OAc)_2/AsPh_3$ combination as catalyst. The coupled product **13** was obtained in 64% yield. The *tert*-butyl-diphenylsilyl protecting group was easily removed with TBAF, and the resulting compound **14** was then stereoselectively reduced with sodium triacetoxyborohydride to form the β-nucleoside of dimethoxy-protected quinazoline **15** as the only product. The stereochemistry was confirmed by 1-D NOE experiments: irradiation of 2′*H*-β gave an NOE signal on 3′*H* (6.2%), whereas irradiation at 2′*H*-α yielded significant enhancement on the 1′*H* (4.8%).[29]

The free expanded T nucleoside dxT **2** was obtained by removing the methyl-protecting groups on compound **15**. The overall approach afforded this new nucleoside in eight steps and 34% yield.

Because of the added benzo fusion, the extended conjugation of the xT base rendered it fluorescent, in contrast to the parent thymine base. The absorption and emission properties of the nucleoside **2** were measured in methanol. As with the xA base, xT (as the deoxynucleoside) showed multiple absorption maxima, and the long-wavelength maximum of xT (at 320 nm) had a molar absorptivity of 3400 L/mol·cm (Figure 2). The

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fluorescence emission maximum appeared at 377 nm, in the blue-violet range, and had a quantum yield of 0.30. These properties were similar to that of a previously reported quinazolinedione derivative.[27]

For this new nucleobase analogue there were several possible variations of keto−enol tautomers (Figure 3). Preliminary semiempirical calculations of heats of formation suggested, however, that the bis-keto tautomer was preferred (at least in the gas phase) by a wide margin of >11 kcal/mol.

DMT protection of the 5′-OH of the dxT deoxynucleoside was done following standard procedures (Scheme 3). In the subsequent reaction between DMT-protected nucleoside **16** and 2-cyanoethyl *N*,*N*-diisopropylchlorophosphoramidite, a commonly used reagent to introduce phosphoramidite groups at the 3′-OH group of nucleosides, a double phosphorylation occurred. Presumably, nucleophilicity of O4 on the quinazolinedione is quite significant; thus, it can be phosphorylated as well. In response to this, the milder reagent 2-cyanoethyl bis(diisopropylamino)phosphoramidite[30] was used instead, which gave the desired xT-phosphoramidite **17** in good yield. This reactivity at O4 foreshadowed the possibility of undesired reactions with phosphoramidites during oligonucleotide synthesis; such reactions could lead to branched side products. Thus, we also retained the *O*-methyl-protected nucleoside and prepared the 5′-dimethoxytrityl-3′-phosphoramidite derivatives of it as well, for possible future application to oligonucleotide synthesis. Preliminary studies have suggested, however, that this protection is not necessary and leads to complications in the subsequent deprotection.[21] To demonstrate intact incorporation, we prepared the oligonucleotide dT−xT−T following the reported procedure[21] and characterized its proton NMR spectrum without purification. The spectrum is given in the Supporting Information and confirms removal of the protecting groups as well as high yield of coupling.

Studies of DNAs that contain dxA and dxT are underway and will be reported in due course. Further work will be aimed at synthesis and study of analogous size-expanded variants of cytosine and guanine as well.

Experimental Section

General Methods. Reagents were purchased from Aldrich and used without further purification. All water-sensitive reactions were carried out in oven-dried glassware with a stirring bar under a nitrogen or argon atmosphere. Anhydrous solvents pyridine, CH_3CN, CH_2Cl_2, and THF, were distilled under a nitrogen atmosphere. THF was dried over Na^0, and the other three solvents were dried over CaH_2. All other anhydrous solvents were purchased from Aldrich and used directly. Thin-layer chromatography was carried out using EM Science Silica Gel 60 F_{254} plates. Column chromatography was performed using Selecto Scientific Silica Gel, sizes 32−63. All ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on Varian Mercury-400 or Inova-500 instruments as noted. ^{31}P NMR spectra were referenced to 85% H_3PO_4 in water as external standard (0.0 ppm). 2D-COSY and 2D-ROESY spectra were acquired on an Inova-500 instrument. High-resolution mass spectrometry was performed at UC Riverside Mass Spectrometry Facilities.

8-Methylthio-3-(2′-deoxy-3′,5′-di-*O*-toluoyl-D-ribofuranosyl)-imidazo[4,5-g]quinazoline (4). 8-Methythioimidazo[4,5-g]quinazoline[31] (1.90 g) was suspended in 300 mL anhydrous acetonitrile, to which was added 95% dry NaH (583 mg). After being stirred at room temperature for 1 h, Hoffer's chlorosugar[24] (4.90 g) was added in one portion. The reaction mixture was stirred for 6 h at r.t. under nitrogen atmosphere and then was filtered, concentrated, and redissolved in ethyl acetate (250 mL), which was washed with 2% HCl (aq), 5% $NaHCO_3$ (aq), and brine (125 mL each). After drying over Na_2SO_4, the crude product was purified by silica column chromatography (33−100% EtOAc in hexanes). An ∼1:4 mixture of 1′-α,β epimers was obtained as a yellow solid foam (1.86 g, 37%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.90 (s, 1H), 8.54 (s, 0.20H), 8.51 (s, 0.80H), 8.46 (s, 0.20H), 8.36 (s, 0.80H), 8.10 (s, 0.24H), 8.08 (s, 0.76H), 7.92−7.89 (m, 2H), 7.79−7.77 (m, 1.50H), 7.64−7.63 (d, 0.5H), 7.24−7.19 (m, 2H), 7.14−7.12 (m, 2H), 6.53−6.52 (m, 0.23H), 6.47−6.44 (m, 0.80H), 5.70−5.68 (m, 1H), 4.82−4.81 (m, 0.21H), 4.67−4.59 (m, 2.90H), 3.10−3.07 (m, 0.22H), 2.84−2.79 (m, 1.96H), 2.71 (s, 3H), 2.38−0.230 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.14, 173.04, 171.36, 166.37, 166.16, 152.19, 146.27, 145.70, 144.91, 144.52, 144.47, 144.17, 143.79, 138.16, 138.03, 130.05, 129.92, 129. 87, 129.82, 129.60, 129.56, 126.90, 126.71, 126.50, 126.13, 120.62, 120.57, 115.05, 114.88, 107.83, 107.49, 86.89, 85.81, 84.74, 83.13, 75.06, 74.96, 64.30, 64.07, 60.61, 38.74, 38.41, 22.00, 21.91, 21.28, 14.43, 12.97. HRMS: (M + H) calcd for $C_{31}H_{29}N_4O_5S$, 569.1859; found, 569.1877. A second product was eluted with 100% ethyl acetate and was identified as the next regioisomer.

8-Methylthio-1-(2′-deoxy-3′,5′-di-*O*-toluoyl-D-ribofuranosyl)-imidazo[4,5-g]quinazoline. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.94 (s, 0.2H), 8.93 (s, 0.8H), 8.54 (s, 0.2H), 8.45 (s, 0.8H), 8.39 (s, 1H), 8.20 (s, 0.2H), 8.17 (s, 0.8H), 7.95−7.91 (m, 2H), 7.73−7.71 (m, 2H), 7.26−7.22 (m, 2H), 7.15−7.10 (m, 2H), 6.49−6.47 (dd, 1H), 5.72−5.70 (m, 1H), 4.69−4.66 (m, 2H), 4.64−4.60 (m, 1H), 2.94−2.86 (m, 2H), 2.77 (s, 0.6H), 2.71 (s, 2.4H), 2.39−2.31 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.10, 165.93, 151.23, 145.62, 144.70, 144.26, 144.09, 129.81, 129.66, 129.58, 129.54, 129.35, 129.32, 126.39, 126.14, 120.20, 114.98, 114.79, 106.48, 86.66, 85.52, 84.59, 82.95, 74.77, 74.65, 64.00, 63.79, 38.59, 38.24, 21.76, 21.66, 12.89.

3-[2′-Deoxy-D-ribofuranosyl]-8-aminoimidazo[4,5-g]quinazoline (1). 4a (790 mg) was dissolved in EtOH (12 mL), ammonia gas was bubbled through at 0 °C for 35 s, and then the solution was heated at 150 °C for 12 h in an Ace pressure tube. To complete the reaction, the same operation was repeated 4 times. The product was purified by silica column chromatography (33−50% MeOH in CH_2Cl_2). The product was obtained as a light yellow solid (252 mg, 61%), which was a mixture of ∼2:5 1′-α and β epimers. ^{1}H NMR (CD_3OD, 500 MHz): δ 8.83 (s, 0.28H), 8.79 (s, 0.71H), 8.57 (s, 1H), 8.38 (s, 1H), 8.00, 7.98 (s, 1H), 6.56−6.52 (m, 1H), 4.61−4.59 (m, 0.30H), 4.56−4.55 (m, 0.70H), 4.28−4.27 (m, 0.32H), 4.10−4.08 (m, 0.72H), 3.86−3.78 (m, 1.49H), 3.73−3.70 (m, 0.64H), 2.93−2.90 (m, 0.30H), 2.80−2.74 (m, 0.66H), 2.59−2.53 (m, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 163.07, 154.74, 154.64, 147.19, 147.09, 146.22, 143.45, 137.97, 114.14, 114.01, 107.66, 107.59, 88.19, 85.41, 85.28, 71.15, 71.00, 62.11. HRMS: (M + H) calcd for $C_{14}H_{16}N_5O_3$, 302.1253; found, 302.1243.

3-[2′-Deoxy-D-ribofuranosyl]-8-[*N*-[1-(dimethyl-amino)ethylidine]-amino]-imidazo[4,5-g]quinazoline (5). 1 (700 mg) was dissolved in 12 mL of dry MeOH, to which was added 90% *N*,*N*-dimethylacetamide dimethyl acetal in MeOH (8 mL). After being heated at 60 °C for 72 h, the reaction mixture was concentrated and purified by silica column chromatography (5−20% MeOH in CH_2Cl_2). A light yellow foamy solid was obtained (626 mg, 73%), which was a mixture of ∼1:3 1′-α and β epimers. ^{1}H NMR (D_2O, 500 MHz): δ 8.20 (s, 0.24H), 8.07 (s, 0.71H), 7.95 (s, 0.22H), 7.88 (0.61H), 7.55 (0.24H), 7.44 (s, 0.68H), 6.96 (s, 0.25H), 6.86 (s, 0.70H), 5.95−5.94 (m, 1H), 4.45−4.42 (m, 0.76H), 4.39−4.37 (m, 0.31H), 4.09−4.08 (m, 0.29H), 3.95−3.93 (m, 0.78H), 3.65−3.53 (m, 2H), 2.99 (s, 6H), 2.51−2.41 (m, 1H), 2.37−2.27 (m, 1H), 1.93 (s, 2.3H), 1.96 (s, 0.82H). ^{13}C NMR (D_2O 125 MHz): δ 166.39, 166.16, 163.85, 152.24, 145.63, 143.83, 141.27, 141.07, 136.55, 116.88, 114.9, 104.68, 87.68, 86.99, 85.45, 84.61, 70.86,

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61.58, 61.31, 39.09, 38.68, 16.86. HRMS: (M + H) calcd for $C_{18}H_{23}N_6O_3$, 371.1832; found, 371.1840.

3-[2′-Deoxy-5′-*O*-(4,4′-dimethoxytrityl)-β-D-ribofuranosyl]-8-[*N*-[1-(dimethyl-amino)ethylidine]amino]-imidazo[4,5-g]quinazoline (6). **5** (544 mg, 1.47 mmol) was coevaporated with anhydrous pyridine (3 × 8.0 mL) and then dissolved in 20 mL of anhydrous pyridine, to which was added DIPEA (1.65 mL), DMAP (50 mg), and 4,4′-dimethoxytrityl chloride (944 mg, 2.65 mmol). After being stirred at r.t. under nitrogen atmosphere for 8 h, the reaction was quenched with addition of MeOH. The reaction mixture was concentrated, redissolved in EtOAc (120 mL), and washed with 5% NaOH (aq) (2 × 50 mL), followed by washing with brine (50 mL). The organic phase was then dried over Na_2SO_4, filtered, concentrated, and purified by silica column chromatography (0−5% MeOH in CH_2Cl_2, with 1% TEA). The title compound was obtained as a yellow foam solid (710 mg, 72%). The 1′-β configuration was assigned based on 2D ROESY spectra. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.68 (s, 1H), 8.58 (s, 1H), 8.23 (s, 1H), 7.88 (s, 1H), 7.30−7.07 (m, 9H), 6.67−6.64 (m, 4H), 6.50 (t, 7 Hz), 4.63−4.62 (m, 1H), 4.29−4.28 (m, 1H), 3.64 (s, 6H), 3.30−3.29 (m, 2H), 3.18 (s, 3H), 3.09 (s, 3H), 2.60−2.57 (m, 2H), 2.15 (s, 3H). ^{13}C NMR ($CDCl_3$,125 MHz): δ 168.05, 161.68, 158.70, 154.46, 146.48, 145.09, 144.78, 143.71, 138.24, 135.93, 135.83, 130.25, 130.21, 128.35, 128.11, 127.11, 118.55, 117.19, 113.41, 105.59, 86.72, 86.64, 85.57, 72.12, 64.22, 55.42, 53.19, 46.15, 41.40, 38.76, 17.07, 9.48, 8.25. HRMS: (M + H) calcd for $C_{39}H_{41}N_6O_5$, 673.3138; found, 673.3168.

3-[2′-Deoxy-3′-*O*-(2-cyanoethyl-*N*,*N*-diisopropylphosphino)-5′-*O*-(4-4′-dimethoxy-trityl)-β-D-ribofuranosyl]-8-[*N*-[1-(dimethyl-amino)-ethylidine]amino]-imidazo-[4,5-g]quinazoline (7). **6** (215 mg, 0.30 mmol) was dissolved in 12 mL of anhydrous methylene chloride, to which was added 0.80 mL of DIPEA and 143 μL (0.60 mmol) of 2-cyanoethyl diisopropylchlorophosphoramidite. After being stirred at room temperature under nitrogen atmosphere for 7 h, the reaction was quenched with a few drops of methanol, then purified by silica column chromatography (0−3% MeOH in CH_2Cl_2). A light yellow foamy solid was obtained (100%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.78 (s, 0.5H), 8.77 (s, 0.5H), 8.69 (s, 0.5H), 8.68 (s, 0.5H), 8.37 (s, 0.5H), 8.34 (s, 0.5H), 7.98 (s, 0.5H), 7.95 (s, 0.5H), 7.40−7.17 (9H), 6.89−6.74 (4H), 6.44−6.41 (m, 1H), 4.72−4.69 (m, 1H), 4.36−4.33 (m, 1H), 3.88−3.87 (m, 1H), 3.81−3.80 (d, 1H), 3.76−3.74 (m, 6H), 3.67−3.55 (m, 2H), 3.44−3.41 (m, 1H), 3.37−3.34 (m, 1H), 3.30 (s, 3H), 3.22 (s, 3H), 2.79−2.78 (m, 1H), 2.71−2.69 (m, 1H), 2.67−2.65 (t, 1H), 2.49−2.47 (t, 1H), 2.30 (s, 3H), 1.28−1.12 (m, 12H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.32, 144.65, 144.39, 143.47, 143.35, 137.83, 137.74, 135.37, 135.31, 135.28, 135.00, 129.89, 129.84, 127.96, 127.89, 127.78, 127.72, 126.76, 126.71, 117.73, 117.49, 117.31, 117.00, 116.81, 112.99, 105.48, 86.78, 86.34, 86.31, 85.58, 85.35, 85.14, 73.94, 73.80, 73.41, 73.28, 63.26, 63.11, 58.20, 58.14, 58.05, 57.99, 57.95, 57.50, 55.04, 53.47, 52.74, 46.92, 46.75, 46.20, 45.63, 45.46, 45.14, 45.09, 34.20, 43.14, 43.10, 43.04, 39.85, 38.66, 24.45, 24.42, 23.21, 22.81, 22.73, 22.71, 22.47, 22.32, 22.17, 20.33, 20.28, 20.10, 20.04, 19.97, 19.91, 18.91, 17.20, 8.49, 8.00. ^{31}P NMR ($CDCl_3$, 202 MHz): δ 146.57, 146.52. HRMS: (M + H) calcd for $C_{53}H_{65}N_{10}O_8P$, 873.4217; found, 873.4198.

2-Amino-3-iodo-5-methylbenzoic Acid (9). In a round-bottom flask, 5-methyl-2-aminobenzoic acid **8** (4.4 g, 29.1 mmol) was dissolved in 80 mL of a 6% HCl (aq) solution. The mixture was warmed to 50 °C. To this was added ICl (14.17 g, 87.3 mmol) dissolved in 20 mL of a 6% HCl (aq) solution in a single portion. The mixture was stirred briskly for 30 min and then was allowed to cool to room temperature. Sodium metabisulfate (16.6 g, 87.3 mmol) was added in a single portion. The solution was subsequently neutralized with potassium hydroxide pellets. The precipitate was filtered, washed with ice-cold water, and dried to give a brown powder (7.8 g, 96%). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.70 (s, 1H), 7.61 (s, 1H), 2.51 (s, 2H), 2.15 (s, 3H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 169.67, 148.76, 145.18, 132.50, 126.42, 111.30, 86.97, 19.89. HRMS *m*/*z*: $[M]^+$ (EI+) calcd for $C_8H_8NO_2I$, 276.9600; found, 276.9606.

8-Iodo-6-methylquinazoline-2,4-dione (10). 2-Amino-3-iodo-5-methylbenzoic acid **9** (7.8 g, 28.1 mmol) and urea (16.9 g, 281 mmol) were heated to 150 °C in a round-bottom flask, and the melt was stirred for 12 h. The mixture was then allowed to cool to 100 °C, and a volume equivalent of water was added. The resulting mixture was then stirred for a few minutes to allow urea to dissolve. The solid was filtered, resuspended in 200 mL of 0.5 M NaOH (aq), and then heated to 100 °C to allow formation of the sodium salt of the product. The mixture was retriturated with glacial acetic acid. The mixture was filtered, and the precipitate was collected and allowed to dry to a fine brown powder (7.8 g, 92%). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 11.51 (s, 1H), 9.48 (s, 1H), 8.00 (s, 1H), 7.74 (s, 1H), 2.30 (s, 3H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 126.85, 150.48, 146.48, 139.81, 134.53, 128.05, 116.06, 84.21, 20.20. HRMS *m*/*z*: $[M]^+$ (EI+) calcd for $C_9H_7N_2O_2I$, 301.9552; found, 301.9540.

8-Iodo-2,4-dichloro-6-methylquinazoline (11). To a flame-dried round-bottom flask outfitted with a condenser, 8-iodo-6-methylquinazoline-2,4-dione **10** (1.20 g, 4 mmol) was dissolved in phosphorus oxychloride (8.00 mL, 87 mmol). To this solution was added *N*,*N*-diethylaniline (1.2 mL, 7.6 mmol). The mixture was stirred under reflux for 3 h. Then the reaction mixture was allowed to cool to room temperature, and volatiles were removed under vacuum. The remaining residue was dissolved in 60 mL of chloroform and washed twice with ice-cold water. The organic layer was collected, dried, and concentrated. Silica column chromatography (hexanes/ethyl acetate 4:1) gave the product **11** as yellowish powder (1.23 g, 90%). ^{1}H NMR ($CDCl_5$, 400 MHz): δ 8.42 (s, 1H), 8.02 (s, 1H), 2.59 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.88, 155.48, 150.86, 148.65, 141.43, 125.64, 122.91, 99.82, 21.67. HRMS *m*/*z*: $[M]^+$ (EI+) calcd for $C_9H_5N_2Cl_2I$, 337.8874; found, 337.8866.

8-Iodo-2,4-dimethoxy-6-methylquinazoline (12). 8-Iodo-2,4-dichloro-6-methylquinazoline **11** (1.20 g, 3.5 mmol) was suspended in 0.5 M sodium methoxide solution in methanol. The reaction mixture was heated to reflux and stirred under reflux for 14 h. Then the reaction was allowed to cool to room temperature and was neutralized with 1 M HCl (aq). A precipitate was formed upon neutralization. After cooling in ice water for 30 min, the precipitate was filtered to give the crude product, which was further purified by silica column chromatography to give **12** as a yellowish powder (1.02 g, 87%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.13 (s, 1H), 7.81 (s, 1H), 4.16 (s, 3H), 4.14 (s, 3H), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.70, 162.31, 150.17, 145.73, 135.76, 123.71, 113.97, 98.35, 55.34, 55.19, 20.08. HRMS *m*/*z*: $[M]^+$ calcd for $C_{11}H_{11}N_2O_2I$, 329.9865; found, 329.9855.

2,4-Dimethoxy-6-methyl-8-{(2′*R*)-*cis*-3-[2′,3′-dehydro-3′-(*tert*-butyl-diphenylsilyloxy)]-5′-hydroxymethyl-2′-furanyl}quinazoline (13). 1,2-Dehydro-3-*O*-(*tert*-butyl-diphenylsilyl)-5-hydroxymethyl-furan[28] (1.20 g, 3.38 mmol) and the dimethoxy-protected quinazoline **12** (1.12 g, 3.38 mmol) were charged into a 250 mL round-bottom flask. Anhydrous DMF (40 mL) was added to form a suspension. $Pd(OAc)_2$ (152 mg, 0.68 mmol) and $AsPh_3$ (416 mg, 1.36 mmol) were charged into a 100 mL conical flask, and 60 mL of dry DMF was added. The catalyst−ligand mixture was stirred at room temperature for 30 min before being transferred to the glycal-quinazoline suspension via syringe. Tri(*n*-butyl) amine (1.29 mL, 5.41 mmol) was added to the reaction mixture in one portion. Then the reaction mixture was heated to 75 °C and was stirred for 36 h. Volatiles were removed under vacuum, and the residue was purified with silica column chromatography (hexanes/ethyl acetate 4:1). Product **13** was obtained as yellow foam (1.22 g, 64%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83−7.60 (m, 4H), 7.71 (m, 1H), 7.46−7.37 (m, 7H), 6.58 (dd, 1H, J = 4 Hz, 1.6 Hz), 4.86 (m, 1H), 4.54 (m, 1H), 4.11 (s, 3H), 3.91 (s, 1H), 3.90 (m, 2H), 2.38 (s, 3H), 1.08 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.14, 137.26, 135.95, 135.67, 133.82, 133.44, 131.82, 131.58, 130.42, 128.12, 128.05, 122.86, 113.55, 103.46, 83.46, 79.63, 62.96, 54.81, 54.67, 26.62,

21.77, 19.48. HRMS *m/z*: $[M + H]^+$ (FAB+) calcd for $C_{32}H_{37}N_2O_5Si$, 557.2471; found, 557.2453.

2,4-Dimethoxy-8-(*β*-D-*glycero*-pentofuran-3′-ulos-1′yl)-6-methylquinazoline (14). Compound **13** (540 mg, 0.97 mmol) was dissolved in 20 mL of THF, and the solution was cooled to 0 °C by an ice−water bath. Glacial acetic acid (0.24 mL) and TBAF solution (1 M solution in THF, 1.46 mL, 1.46 mmol) were added sequentially via syringe. The reaction mixture was allowed to stir 10 min at 0 °C. Volatiles were removed under vacuum, and silica column chromatography (hexanes/ethyl acetate 1:1) gave product **14** as white solid (260 mg, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82 (s, 1H), 7.78 (s, 1H), 5.84 (dd, 1H, J = 10.8 Hz, 6.0 Hz), 4.15 (s, 3H), 4.03 (s, 5H), 3.18 (m, 1H), 2.68 (m, 1H), 2.49 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 215.06, 169.44, 161.40, 147.99, 134.93, 134.02, 132.85, 123.05, 113.70, 82.37, 75.49, 62.11, 55.04, 54.82, 45.00, 21.70. HRMS *m/z*: $[M]^+$ (EI+) calcd for $C_{16}H_{18}N_2O_5$, 318.1216; found, 318.1203.

1′-*β*-[8-(2,4-dimethoxy-6-methylquinazoline)]-2′-deoxyribofuranose (15). Compound **14** (123 mg, 0.39 mmol) was dissolved in a mixture of 10 mL of CH_3CN and 10 mL of glacial acetic acid. The solution was chilled to −15 °C by an ice−salt bath. Sodium triacetoxyborohydride (110 mg, 0.52 mmol) was added in one portion. Then the mixture was stirred at −15 °C for 30 min. Solvents were removed under vacuum, and the residue was purified by silica column chromatography (ethyl acetate to ethyl acetate/methanol 95:5) to give product **15** as a yellowish solid (116 mg, 93%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.77 (s, 1H), 7.67 (s, 1H), 5.79 (dd, 1H, J = 11.2 Hz, 6 Hz), 4.53 (m, 1H), 4.16 (s, 3H), 4.06 (s, 3H), 3.93 (m, 1H), 3.84 (m, 1H), 2.53 (m, 1H), 2.46 (s, 3H), 2.26 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.19, 160.94, 147.90, 136.01, 133.61, 132.88, 122.17, 113.34, 87.46, 78.12, 74.36, 63.66, 54.77, 54.49, 43.07, 21.45. HRMS *m/z*: $[M]^+$ (EI+) calcd for $C_{16}H_{20}N_2O_5$, 320.1372; found, 320.1385.

1′-*β*-[8-(6-Methylquinazoline-2,4-dione)]-2′-deoxyribofuranose (2). Compound **15** (123 g, 0.39 mmol) was dissolved in 8 mL of glacial acetic acid, to which was added sodium iodide (288 mg, 1.92 mmol). The reaction mixture was heated to 60 °C and then was stirred for 45 min. Volatiles were removed under vacuum. The residue was suspended in 10 mL of saturated sodium bicarbonate solution, which was extracted with 5 × 30 mL ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated. Silica column chromatography (ethyl acetate/methanol 10:1) gave the product **2** as white solid (113 mg, 100%). ^{1}H NMR (CD_3OD, 500 MHz): δ 7.83 (s, 1H), 7.47 (s, 1H), 5.31 (dd, 1H, J = 11.5 Hz, 5 Hz), 4.49 (m, 1H), 4.07 (m, 1H), 3.85 (m, 2H), 2.40 (s, 3H), 2.23 (m, 1H), 2.14 (m, 1H). ^{13}C NMR (CD_3OD, 125 MHz): δ 163.96, 150.91, 136.52, 135.57, 132.63, 126.76, 126.15, 115.65, 88.73, 80.83, 73.45, 61.75, 42.16, 19.37. HRMS $[M]^+$ *m/z*: (EI+) calcd for $C_{14}H_{16}N_2O_5$, 292.1059; found, 292.1066.

1′-*β*-[8-(6-Methylquinazoline-2,4-dione)]-5′-*O*-(4,4′-dimethoxytrityl)-2′-deoxyribofuranose (16). The nucleoside **2** (150 mg, 0.51 mmol) was coevaporated with dry pyridine (3 × 10 mL), and the residue was dissolved in 4 mL of pyridine. *N*,*N*-diisopropylethylamine (266 μL, 1.53 mmol) was added via syringe in one portion. 4,4′-Dimethoxytrityl chloride (227 mg, 0.67 mmol), dissolved in 6 mL of dry pyridine, was transferred to the nucleoside solution via syringe. The mixture was stirred at room temperature for 6 h. Volatiles were removed under vacuum, and the crude product was purified by silica column chromatography (ethyl acetate to ethyl acetate/methanol 10:1) to give 155 mg of product **16** as yellowish foam. Free nucleoside (62 mg) was recovered from the reaction, which was allowed to react with DMT chloride again following the procedure above, and 78 mg of additional product was obtained. Total yield was 84%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.88 (s, 1H), 7.41 (s, 1H), 7.37 (m, 2H), 7.28−7.17 (m, 7H), 6.78−6.75 (m, 4H), 5.44 (dd, 1H, J = 11.2 Hz, 4.8 Hz), 4.46 (d, 1H, J = 5.2 Hz), 4.18 (m, 1H), 3.75 (s, 6H), 3.29 (m, 2H), 2.44 (m, 1H), 2.34 (s, 3H), 2.23 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 163.50, 158.70, 151.21, 145.00, 136.14, 136.05, 133.63, 133.31, 130.30, 128.36, 128.06, 127.43, 127.25, 127.06, 115.23, 113.34, 87.45, 86.52, 76.35, 74.50, 64.37, 55.43, 34.78, 21.04. HRMS *m/z*: $[M + Na]^+$ (FAB+) calcd for $C_{35}H_{34}N_2O_7Na$, 617.2264; found, 617.2278.

1′-*β*-[8-(6-Methylquinazoline-2,4-dione)]-5′-*O*-(4,4′-dimethoxytrityl)-2′-deoxyribofuranose-3′-(2-cyanoethyl phosphoramidite) (17). 5′-DMT-protected nucleoside **16** (233 mg, 0.39 mmol) and *N*,*N*-diisopropylammonium tetrazolide (40 mg, 0.23 mmol) were dissolved in 10 mL of dry dichloromethane. 2-Cyanoethyl tetraisopropylphosphoramidite (137 μL, 0.43 mmol) was added via syringe in one portion. The reaction mixture was stirred at room temperature for 3 h. Volatiles were then removed under vacuum, and the crude product was purified by silica column chromatography to give product **17** as white foam (254 mg, 82%, as a mixture of two diastereomers). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91 (s, 2H), 7.37−7.16 (m, 20H), 6.77−6.73 (m, 8H), 5.38 (m, 2H), 4.56 (m, 2H), 4.30 (m, 2H), 3.76 (s, 6H), 3.75 (s, 6H), 3.60 (m, 4H), 3.23 (m, 4H), 2.64 (t, 4H, J = 6 Hz), 2.53 (m, 2H), 2.36 (s, 6H), 2.32 (m, 2H), 1.31−1.13 (m, 28H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 162.13, 157.40, 149.16, 143.64, 135.58, 134.71, 134.62, 132.61, 132.40, 131.61, 131.57, 129.01, 127.03, 126.74, 126.22, 125.74, 125.23, 116.66, 114.15, 112.02, 85.22, 76.64, 62.68, 57.24, 57.08, 54.13, 44.56, 42.24, 42.14, 39.12, 23.61, 23.56, 22.45, 22.10, 21.80, 21.19. HRMS *m/z*: $[M + Na]^+$ (FAB+) calcd for $C_{44}H_{51}N_4O_8NaP$, 817.3342; found, 817.3338.

Fluorescence Measurements. Samples were measured in methanol. UV−vis absorption spectra were recorded on a Varian Cary 1 UV−vis spectrometer. Fluorescence excitation and emission spectra were measured on a Spex Fluorolog 3 spectrometer. To prevent aggregation and reabsorption of light, samples were diluted to an absorption at λ_{max} of less than 0.05. Quantum yields were calculated with fluorescein in 0.1 N NaOH solution as a reference.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of all dxA and dxT synthetic intermediates, 2D ROESY data for intermediates **4a**, **4b**, and **6**, and COSY data for **6** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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