Building Blocks for Ribozyme Mimics: Conjugates of Terpyridine and Bipyridine with Nucleosides

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The incorporation of the 2,2′:6′,2″-terpyridyl (terpy) complex of Cu(II) into a deoxyoligonucleotide has led to a functional mimic of ribozymes. The resulting mimic can cleave target RNA in a sequence-directed manner by a hydrolytic mechanism. Here we describe the synthesis and characterization of four modified nucleoside phosphoramidite reagents (**7**, **10**, **14**, and **18**) that contain pendant 2,2′-bipyridine or terpy ligands. The ligands are attached either to the nucleobase (**7**, **10**) or to the sugar (**14**, **18**). Nucleobase modification was carried out at the C-5 position of 2′-deoxyuridine (dU). One route to sugar modification was performed by synthesis of **18**, a 1′-functionalized analog of dU based on 1-[3-deoxy-β-D-psicofuranosyl]uracil. Another route to sugar functionaliztion resulted in **14**, a 2′-O-alkyl derivative of adenosine. These modified nucleosides are building blocks for ribozyme mimics. They are designed to deliver hydrolytically active metal complexes across either the major groove (**7**, **10**) or the minor groove (**14**, **18**) of an RNA/DNA duplex.

Introduction

We report a series of four DNA building blocks (**7**, **10**, **14**, and **18**) for the synthesis of ribozyme mimics, sequence-specific reagents for the hydrolytic cleavage of RNA. These ribozyme mimics contain a deoxyoligonucleotide, designed to form a sequence-specific RNA/DNA duplex by Watson−Crick base-pairing, and a pendant metal complex designed to cleave the target RNA. Our nucleoside phosphoramidites incorporate 2,2′-bipyridine (bipy) or 2,2′:6′,2″-terpyridine (terpy) ligands, allowing the synthesis of deoxyoligonucleotides that can deliver hydrolytically-active metal complexes to a complementary RNA strand. The bipy and terpy ligands are attached either to nucleobases or sugar moieties, to allow attack across either the major groove (**7**, **10**) or the minor groove (**14**, **18**) of an RNA/DNA duplex. A preliminary account of the synthesis of **7** has been reported, along with the successful cleavage of RNA by an oligodeoxynucleotide incorporating **7**.[1]

Metal bipy and terpy complexes have been used for a variety of applications in nucleic acid research. Fluorescent, redox-active, ruthenium-bipyridine complexes have been used to label DNA.[2,3] Platinum terpy complexes have been used to intercalate into DNA and to modify DNA in a covalent manner.[4,5] Bipyridine and terpyridine complexes of metal ions have also played an important role in the development of RNA hydrolysis agents.[6−8] The Cu(II) complexes of these ligands were among the first well-defined metal complexes found to cleave RNA hydrolytically.[9] Our mechanistic studies have shown that aqueous Cu(II) terpyridine promotes *both* the transesterification and hydrolysis of RNA substrates.[10] By linking bipyridine and terpyridine moieties to molecular recognition elements, we hoped to prepare sequence-specific RNA cleavage agents that operate *via* biocompatible hydrolytic pathways.[11] On the basis of this design, we recently reported[1] the first example of a wholly-synthetic ribozyme mimic. This mimic comprises a 17-mer DNA oligonucleotide with a covalently attached terpy ligand that is incorporated as a side chain on an internal nucleotide residue. Our design combines the binding specificity of the oligonucleotide with the hydrolytic activity of aqueous terpyridyl Cu(II). This approach allowed us to achieve sequence-specific cleavage of a 159-mer RNA fragment of the HIV *gag* gene mRNA. Recently, other examples of sequence-specific hydrolytic cleavage of RNA by synthetic reagents have been reported.[12−16]

One of our main goals since 1986 has been the preparation of catalytically active ribozyme mimics that may serve as catalytic antisense reagents for the control of viral gene expression. The desired catalytic cycle involves (1) binding of the ribozyme mimic to the RNA target, (2) cleavage of the RNA, and (3) release of the cleaved RNA fragments to regenerate the catalyst.

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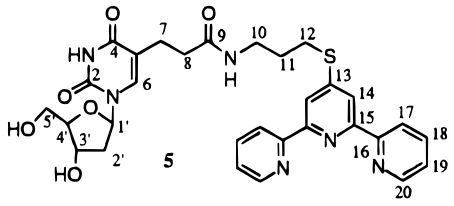
Failure to release the RNA fragments would result in product inhibition. The DNA building blocks reported here form part of our strategy for avoiding product inhibition and achieving turnover. As depicted in Scheme 1a, cleavage at an *internal* residue in the RNA/DNA duplex decreases the stability of the duplex and allows the product fragments to be displaced by a new substrate molecule. This occurs because RNA−DNA binding constants depend on the length (and sequence) of the duplex. As shown in Scheme 1b, cleavage *outside* the duplex region has no significant effect on RNA−DNA binding, and the product cannot be released efficiently from the "catalyst". The reagents described here allow incorporation of hydrolytic agents at internal sites in the ribozyme mimic. As we have shown, this strategy can achieve the desired cleavage *in the duplex region*, which is an important feature of our plans to achieve catalytic turnover.[1]

Results and Discussion

Our general route to deliver bipy and terpy complexes across the major groove of an RNA/DNA duplex is shown in Schemes 2 and 3. The reagents 4-(4-aminobutyl)-4′-methyl-2,2′-bipyridine **3**[17] and terpy derivative **2**[18] are each linked to nucleotides *via* reaction with active ester derivatives. Alkylamino terpyridine and bipyridine were coupled to 2′-deoxyuridine C-5 carboxyethyl nucleoside **1**.[19] The resulting nucleosides **5** and **8** were protected



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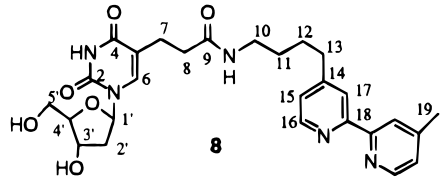

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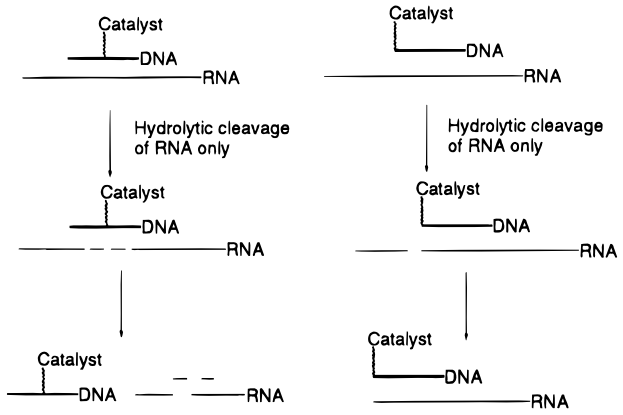
and phosphitylated to yield phosphoramidite reagents **7** and **10**, which are suitable for automated DNA synthesis.[20] Compound **7** has been used to prepare a 17-mer oligonucleotide that has shown ribozyme-like activity.[1] The bipyridine reagent **10** complements the series of nucleoside−bipyridine conjugates reported previously.[21,22] FABMS and HRMS were obtained for compounds **5**−**7** and **8**−**10**. NMR assignments of these compounds are provided in the Experimental Section.

Two complementary approaches were explored for the delivery of catalytic reagents across the minor groove. Both the 1′- and 2′-position of nucleosides point into the minor groove of an A-form double helix. Scheme 4 shows

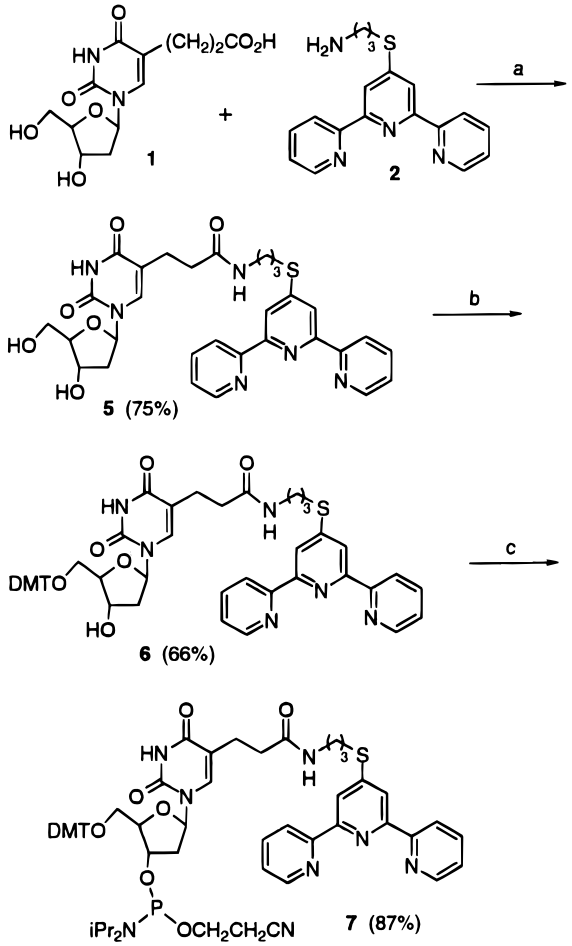
Scheme 1



a) The ribozyme mimic cleaves only its RNA target. The mimic releases the RNA fragments and is ready to bind another substrate molecule.

b) The hydrolytic cleavage occurs, but the ribozyme mimic remains bound to one of the product fragments (product inhibition occurs).

Scheme 2[a]



[a] EDC·HCl, DMSO, rt, 24 h; (b) pyridine, DMT-Cl, 26 h; (c) iPr_2NEt, THF, β-cyanoethyl *N*,*N*-diisopropylchlorophosphonamidite, 9 h.

the preparation of the 2′-functionalized adenosine phosphoramidite **14**. By analogy with a reported procedure,[23] we deprotonated adenosine with NaH/DMF at −5 °C and alkylated the resulting mixture of anions with alkyl

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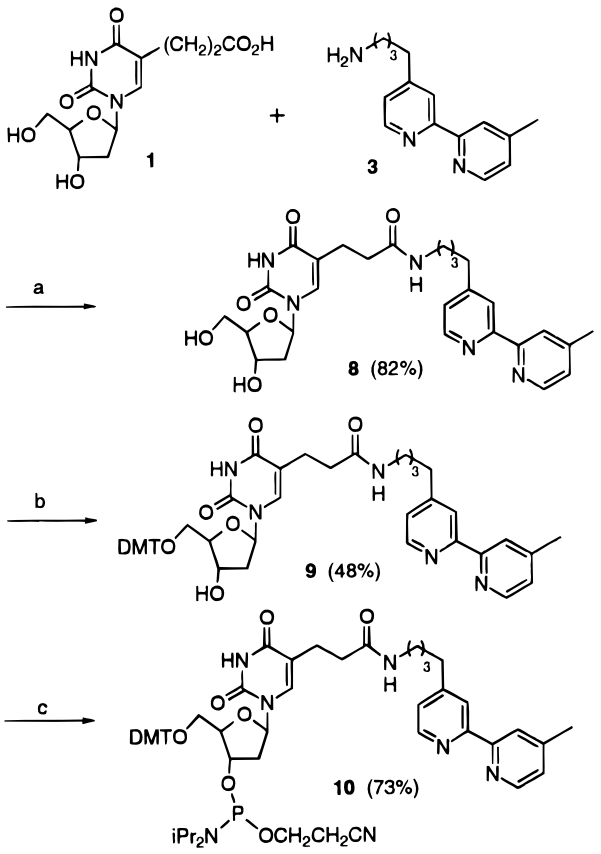
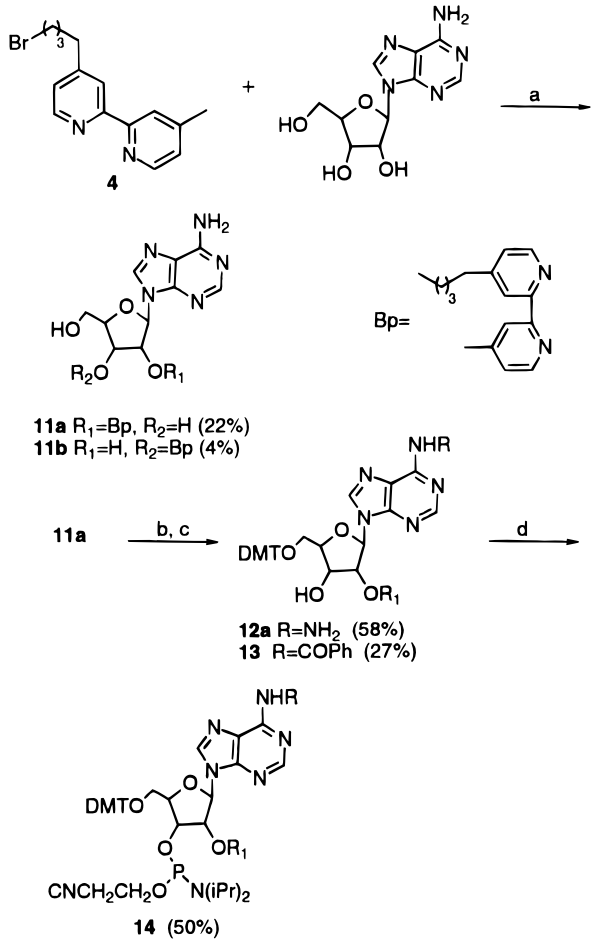
Scheme 3[a]



[a] (a) EDC·HCl, DMF, rt, 30 h; (b) pyridine, DMT-Cl, 6 h; (c) iPr_2NEt, THF, β-cyanoethyl *N,N*-diisopropylchlorophosphonamidite, 5 h.

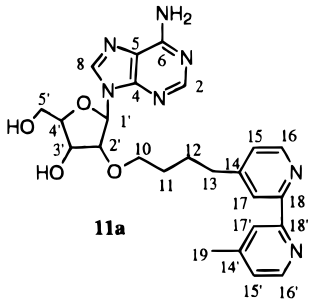
Scheme 4[a]



[a] (a) NaH, DMF, 24 h, −5 °C; (b) DMT-Cl, pyridine, overnight; (c) i. TMS-Cl; ii. benzoyl chloride; iii. 2 M NH_4OH; (d) iPr_2NEt, THF, β-cyanoethyl *N,N*-diisopropylchlorophosphonamidite

halide **4**. Nucleoside **11a**, the desired 2′-alkylated product, was isolated in 18% yield along with unreacted **4**. The mixture of the analogous 3′ isomer **11b** and additional **11a** was isolated in 8% yield. The 5′-sugar hydroxyls of this mixture were protected by treatment with dimethoxytrityl chloride (DMT-Cl) and the resultant mixture was conveniently separated into the 2′-O-isomer (**12a**) and 3′-O-isomer (**12b**) on a basic alumina column (<5% 3′-O-alkylated product was isolated).

For compounds **11a**, **12a,** and **12b**, the sites of alkylation were unambiguously identified *via* COSY, HMQC, and HMBC NMR studies. ^1H chemical shifts of **11a** were assigned by analysis of COSY (Figure 1) and HOHAHA spectra. Spin propagation and the $^1H-^1H$ connectivities of sugar (H1′ to H5′, H5"), and of the bipyridine-linker arm (H10 to H13, H15 to H16, and H15′ to H16′) were identified through vicinal $^3J_{H-H}$ coupling. Long-range coupling *via* the sugar H1′ enabled assignment of the nonexchangeable H8 proton of the adenine subunit. The presence of four-bond $^1H-^1H$ coupling of methyl-H19 to H15′ and H17′, and coupling of H13 to H15 and H17, facilitated an unambiguous assignment of the two pyridine residues. To complete the assignment of the ^{13}C spectrum and confirm the adenosine−bipyridine connection, HMQC and HMBC spectra (Figure 2, parts a and b) were obtained. The one-bond carbon correlations to the attached protons were determined by HMQC, which included all of the sugar carbons, the CH_2 and CH carbons of the bipyridine-linker arm, and two aromatic carbons, C2 and C8, bearing nonexchangeable protons of the adenine subunit. Quaternary carbons C14 and C14′ of the bipyridine were determined by HMBC through long-range carbon−proton coupling to H13 and H19, respectively. The C4, C5, and C6 carbons of the adenine base were unambiguously assigned based on their multiple-bond correlation to ribose H1′, or to adenine H2 and NH_2 (Figure 2b). Of particular importance, multiple bond $^{13}C-^1H$ couplings were observed between C10 and H2′, as well as between C2′ and H10, indicating that **11a** has a C2′−O−C10 connection. The result is consistent with the observed C2′ chemical shift, which is 11.9 ppm downfield from C3′, indicating that substitution has occurred at the C2′ site of **11a**. Moreover, the presence



of the strong cross peak between a hydroxyl proton and H3′, and the lack of such coupling to H2′ in the COSY spectrum, further confirm the structure of **11a**. Compounds **12a** and **12b** were confirmed by the same strategy, and complete ^{13}C and ^1H chemical shift assignments are listed in the Experimental Section.

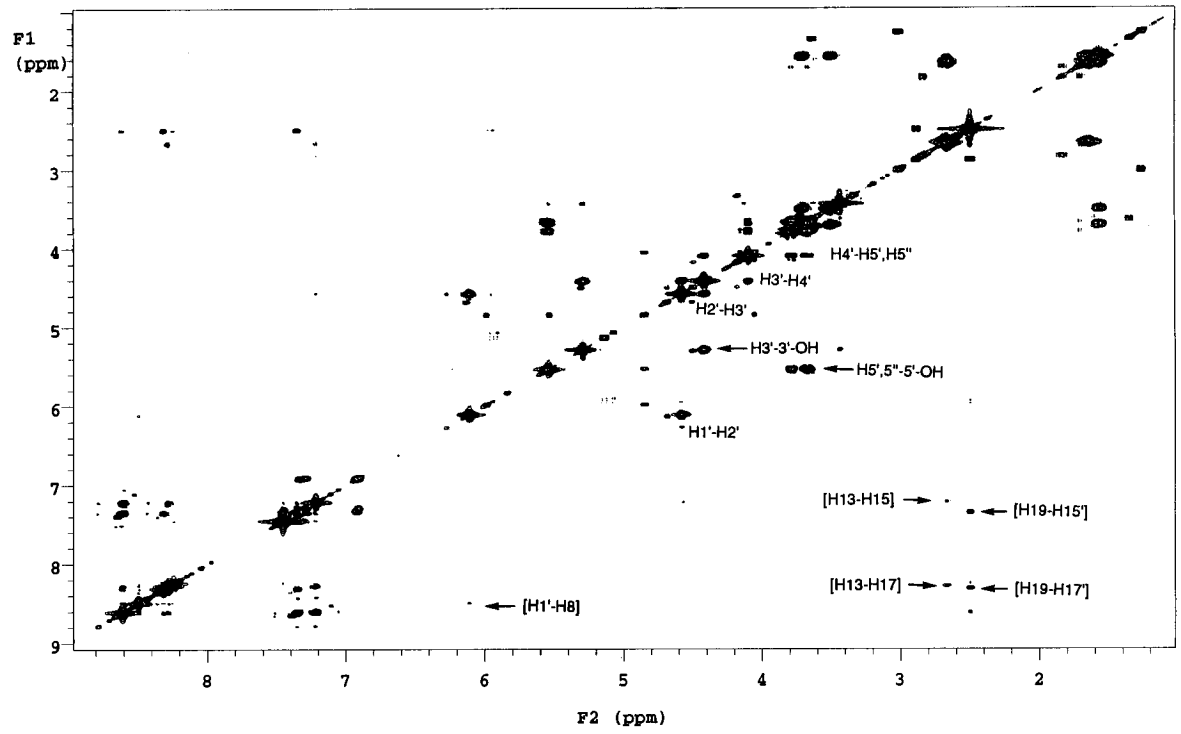


Figure 1. The 500 MHz COSY spectrum of **11a** in DMSO-d_6. A 500 × 2048 data matrix with 16 scans per t_1 value was acquired. The long-range $^1H-^1H$ couplings are drawn in brackets.

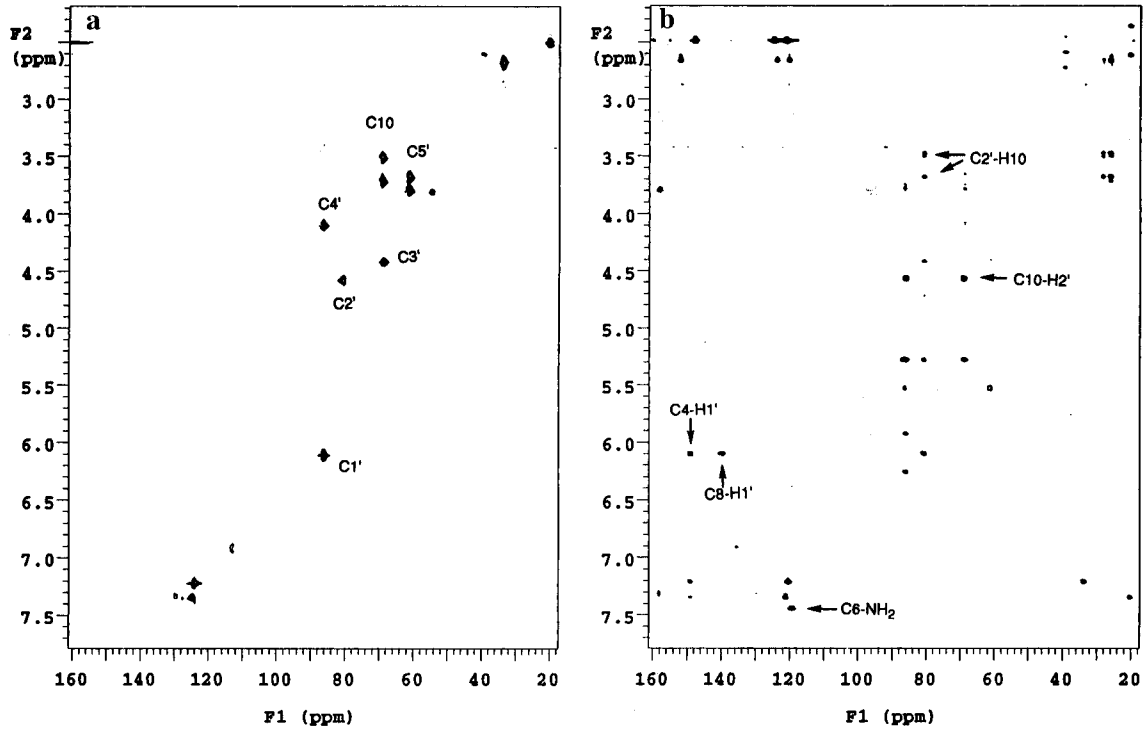


Figure 2. Expansion of (a) HMQC, and (b) HMBC spectra of **11a**. Multiple bond $^{13}C-^1H$ correlations allow unambiguous assignment of the quaternary carbons and establish the ribose and bipyridine-linker arm connection.

The 5′-OH of the pure 2′-O-isomer **11a** was protected with DMT-Cl to give **12a** in 58% yield. The modified nucleoside **12a** was then *N*-6-benzoyl-protected using the "Jones" transient protection[20] to give **13** in 27% yield. Phosphitylation gave phosphoramidite **14** in 50% yield.

The synthesis of the C1′-functionalized terpy nucleoside phosphoramidite **18** is given in Scheme 5. The starting nucleoside **15** was synthesized in six steps starting from D-fructose.[24,25] Protection of the 5′-OH with DMT-Cl gave nucleoside **16**. **16** was coupled to the terpyridine amine **2** using carbonyl diimidazole,[25] resulting in the two products **17a** and **17b**. Nucleoside **17a** was then converted to phosphoramidite **18**.[20] Initially,

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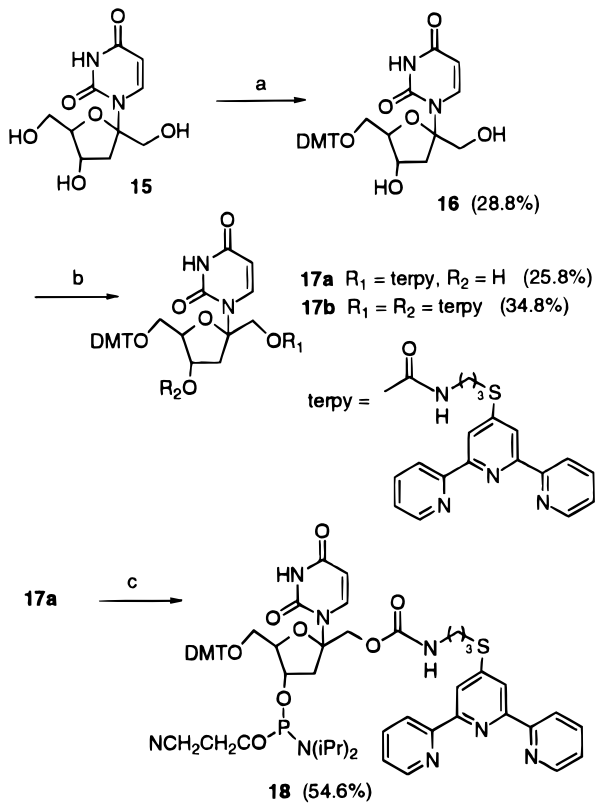
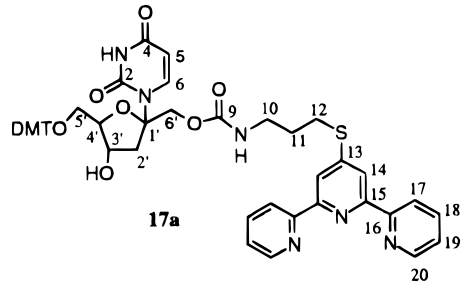
(25) Ono, A.; Dan, A.; Matsuda, A. *Bioconjugate Chem.* **1993**, *4*, 499−508.

Scheme 5[a]



[a] (a) Pyridine, DMT-Cl, 24 h; (b) carbonyldiimidazole, **2**, CH_2Cl_2; (c) β-cyanoethyl *N*,*N*-diisopropylchlorophosphonamidite, Et_3N, CH_2Cl_2, 30 min.



in order to achieve exclusive coupling at C1′, we attempted a published procedure[25] to protect the 3′ and 5′ hydroxyl groups of **15** with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane ($TIPDSCl_2$). However, in our hands, the diprotected analog of **15**, 3′,5′-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanediyl)-3′-deoxypsicouridine, was isolated as a very minor product. Recently, Hovinen reported similar results with this protection reaction.[26] Therefore, we performed the synthesis of **17a** as shown in Scheme 5, without protecting the 3′ and 5′ positions. The desired product **17a** (25.8%) and the disubstituted product **17b** (34.8%) were separated by basic alumina chromatography.

Conclusions

According to one of our working hypotheses, a ribozyme mimic's "active site" should reside adjacent to a phosphodiester and/or 2′-hydroxyl of the target RNA without seriously disrupting Watson−Crick base pairing. Substituents located at the C-5 position of 2′-deoxyuridine mimic the methyl group of thymidine: they point away from the A−T hydrogen bonds and across the major groove, toward the opposite strand. Appropriate DNA derivatives functionalized at the C-5 position can be prepared *via* the Heck reaction. Here we reported the preparation of 2′-deoxyuridine phosphoramidite reagents with pendant bi- and terpyridine ligands. We also investigated alternative sites of chemical modifications of nucleotides that involve the delivery of catalytic reagents across the minor groove.[25,27] We were particularly interested in placing hydrolysis agents on the nucleosides so that when the modified oligonucleotides hybridize with target RNA, the functionalities would reside in the minor groove of the heteroduplex, proximal to the 2′-hydroxyl group of the RNA strand. We presented two methods to tether bipyridine and terpyridine ligands in the minor groove. One approach led to an analog of 2′-deoxyuridine that was functionalized at the C1′ sugar position. In a second approach, a butyl linker was attached to the 2′-O-position of adenosine.[23] Generally, alkoxy modifications in the 2′-position of the ribose ring significantly increase the binding affinity of the oligomer to the RNA target and provide resistance to nucleases.[28] The effectiveness of **7** in forming active ribozyme mimics has already been demonstrated.[1] Work is ongoing to prepare ribozyme mimics with **10**, **14**, and **18**, and to assess the relative hydrolytic capabilities of major and minor groove attack.

Experimental Section

General. FAB mass spectra were recorded by the Washington University Resource for Biomedical and Bio-organic Mass Spectrometry, Department of Chemistry, Washington University. Thin-layer chromatography (TLC) was performed on Baker-Flex aluminum oxide IB-F plates, Baker-Flex silica gel IB2-F plates, and Merck DC-Fertigplattern RP-18 F_{254} S plates. Column (flash) chromatography was performed on basic alumina (Selecto Scientific, 23−75) or silica gel (Selecto Scientific, 40 μ). Reverse phase (RP) column chromatography was performed using Fisher Prep Sep-C18 extraction columns. DMT-Cl, 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (EDC), carbonyl diimidazole, $EtN(iPr)_2$, β-cyanoethyl *N*,*N*-diisopropylchlorophosphonamidite, adenosine, NaH, Et_3N, Me_3SiCl, benzoyl chloride, and all anhydrous solvents were purchased from Aldrich. All starting materials were dissolved in dry pyridine and evaporated under reduced pressure. This process was repeated twice to remove traces of moisture. During workup, all compounds were dried over anhydrous Na_2SO_4 or $MgSO_4$. All reactions were done under N_2 or Ar.

Deoxyuridine-C3-S-terpyridine 5. A pear-shaped two-neck flask was charged with 5-(2-carboxyethyl)-2′-deoxyuridine (**1**)[19] (601.0 mg, 2.0 mmol), EDC (306 mg, 2.0 mmol), and dry DMSO (2.0 mL) and stirred for 0.5 h. To this was added the amine **2**[18] (324 mg, 1.0 mmol), and the reaction was stirred at room temperature for 24 h. The reaction mixture was then evaporated and redissolved in $CHCl_3$, and the product **5** (455.2 mg, 74.9%) precipitated by adding hexanes. Analytically pure material was obtained by RP chromatography with 50% CH_3CN/H_2O: R_f 0.245 (50% CH_3CN/H_2O on RP plates); ^1H NMR (300 MHz, $CD_3OD/CDCl_3$) δ 1.83 (m, 2H, H11); 2.09 (m, 2H, H2′); 2.31−2.47 (m, 4H, H7 and H8); 3.08 (t, 2H, H10, J = 7.41 Hz); 3.22 (t, 2H, H12); 3.59 (dd, 1H, J = 12.09, 3.78 Hz, H5′); 3.67 (dd, 1H, J = 12.09, 3.24 Hz, H5′); 3.76 (q, 1H, H4′, J = 3.36 Hz); 4.26 (ddd, 1H, J = 5.12, 3.27, 3.27 Hz, H3″); 6.12 (t, 1H, H1′, J = 6.74 Hz); 7.35 (ddd, 2H, H19, J = 6.24,

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4.89, 1.17 Hz); 7.68 (s, 1H, H6); 7.86 (ddd, 2H, H18, J = 7.59, 7.59, 1.77 Hz); 8.11 (s, 2H, H14); 8.47 (m, 2H, H17, J = 8.1 Hz); 8.54 (ddd, 2H, H20, J = 5.01 Hz); ^{13}C NMR (75.1 MHz, $CD_3OD/CDCl_3$) ppm 24.21 C7, 28.81 C11, 29.39 C10, 35.49 C8, 39.15 C12, 41.27 C2′, 62.67 C5′, 71.94 C3′, 86.15 C1′, 88.62 C4′, 113.77 C5, 118.56 C14, 122.93 C17, 125.36 C19, 138.60 C18, 138.82 C6, 149.84 C20, 151.96 2CO, 152.77 C13, 156.05 C16, 156.71 C15, 165.51 4CO, 174.77 9CO; UV-vis (concn = 2.25 × 10^{-4} M, MeOH/0.02 M NH_4OAc) λ_{max} 277 nm (ϵ = 32680); FAB HRMS m/z $C_{30}H_{33}O_6N_6S$ $(M)^+$: calcd 605.2182, found 605.2175; MS (FAB) m/z 627 (18 $[M + Na]^+$), 605 (40 $[M + H]^+$), 550 (7), 511 (9), 489 (11), 478 (25), 456 (40), 388 (13), 340 (13), 323 (39), 307 (30), 303 (32), 292 (39), 289 (24), 279 (25), 266 (100), 233 (19), 224 (17). Anal. Calcd for $C_{30}H_{32}O_6N_6S$: C, 59.58; H, 5.33; N, 13.89; S, 5.30. Found: C, 56.92; H, 5.17; N, 13.82; S, 5.39.

DMT-deoxyuridine-C3-S-terpyridine 6. Deoxyuridine-C3-S-terpyridine **5** (557 mg, 0.921 mmol) was dissolved in anhydrous pyridine (3.0 mL). DMT-Cl (474.5 mg, 1.406 mmol) in dry pyridine (1.0 mL) was added, and the reaction mixture was stirred for 26 h at rt. The mixture was then quenched with CH_3OH and concentrated. The residue was dissolved in CH_2Cl_2 and extracted with H_2O, and the organic layer was dried and concentrated. Chromatography on a basic alumina column (12−30% MeOH/CH_2Cl_2) gave **6** (549 mg, 65.7%) as a white foam after evaporation: R_f 0.438 (15% MeOH/CH_2Cl_2 on basic alumina); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.8 (m, 2H, H11); 2.1−2.4 (m, 6H, H2′, H7 and H8); 3.05 (t, 2H, H10); 3.2−3.5 (ddd, 2H, H5′ and m, 2H, H12); 3.75 (s, 6H, H26-DMT-OCH_3); 4.05 (q, 1H, H4′); 4.50 (ddd, 1H, H3′); 6.35 (t, 1H, H1′ and t, 1H(exch), C9-amide NH); 6.7 (d, 4H, H23); 7.15−7.35 (m, 5H, H27−30 and d, 4H, H24) 7.4 (m, 2H, H19); 7.49 (s, 1H, H6); 7.82 (ddd, 2H, H18); 8.25 (s, 2H, H14); 8.55 (m, 2H, H17); 8.62 (ddd, 2H, H20); ^{13}C NMR (75.1 MHz, $CDCl_3$) ppm 23.33 C7, 27.80 C11, 28.10 C10, 35.07 C8, 38.03 C12, 40.45 C2′, 50.44 (MeOH), 55.14 C26 (DMT-OCH_3), 63.57 C5′, 71.81 C3′, 84.64 C1′, 85.89 C21, 86.49 C4′, 113.15, 113.36 C5, 117.67 C14, 121.52, 123.95 C17, 126.95, 127.88, 128.01, 129.99, 135.39, 135.45, 136.97, 144.41, 148.80 C20, 150.39 C2, 151.10 C13, 154.72 C15, 155.56 C16, 158.48, 163.94 C4, 172.03 C9; FAB HRMS m/z $C_{51}H_{51}O_8N_6S$ $(M)^+$: calcd 907.3489, found 907.3488; MS (FAB) m/z 907.4 (19 $(M + H)^+$), 758.4 (8), 550.6 (9), 303.2 (50), 154.1 (100).

DMT-deoxyuridine-C3-S-terpyridine Phosphoramidite 7. Nucleoside **6** (549.0 mg, 0.605 mmol) was dissolved in dry THF (4.5 mL) under N_2. Then $EtN(iPr)_2$ (0.156 g, 1.21 mmol, 0.21 mL) was added to the reaction vessel at −4 °C in an ice bath. To this cold reaction mixture was added β-cyanoethyl *N,N*-diisopropylchlorophosphonamidite (151.2 mg, 0.635 mmol, 0.143 mL). The reaction mixture was stirred for 2 h from −4 to 0 °C. TLC of the reaction mixture showed presence of the starting nucleoside. A second equivalent of $EtN(iPr)_2$ and β-cyanoethyl *N,N*-diisopropylchlorophosphonamidite was added and stirred for 9.0 h at 5−15 °C. After the reaction was complete, the solvent was evaporated by flushing with a steady stream of N_2. The residue was dissolved in CH_2Cl_2, loaded on to a basic alumina column, and eluted with 0−5% MeOH in CH_2Cl_2 to give pure product **7** (581 mg, 86.7%): R_f 0.345 (5% MeOH/CH_2Cl_2 on basic alumina); ^{31}P NMR (CD_3CN, referenced to 85% H_3PO_4) ppm 149.62, 149.59. FAB HRMS m/z $C_{60}H_{68}O_9N_8SP$ $(M)^+$: calcd 1107.4567, found 1107.4532; MS (FAB) m/z 1107.5 (2 $(M + H)^+$), 958.5 (2), 890.4 (2), 803.3 (1), 585.2 (2), 489.2 (2), 303.1 (100), 201.1 (5).

Deoxyuridine-C4-bipyridine 8. Nucleoside **1** (1.000 mg, 3.330 mmol), compound **3**[17] (535.0 mg, 2.215 mmol), and the coupling agent EDC (635.0 mg, 3.330 mmol) were dissolved in dry DMF (1.8 mL). After stirring at rt for 30 h, the reaction mixture was concentrated to dryness. The residue was applied to a C-18 RP column. Elution with 20% CH_3CN/H_2O gave the desired compound **8** (950 mg, 82%): R_f 0.30 (40% CH_3CN/H_2O on RP plates); ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.20 (t, 1H, H1′), 2.28 (m, 2H, H2′), 4.27 (m, 1H, H3′), 3.79 (m, 1H, H4′), 3.00 (m, 2H, H5′), 7.85 (s, 1H, H6), 2.09 and 2.54 (m, 4H, H7 and H8), 2.70 (t, 2H, H13), 1.40−1.70 (b, 4H, H12 and H11), 3.60 (m, 2H, H10), 7.30 (d, 2H, H15 and H15′), 8.59 (m, 2H, H16 and H16′), 8.27 (s, 2H, H17 and H17′), 2.45 (s, 3H, H19); ^{13}C NMR (125 MHz, DMSO-d_6) ppm 83.6 C1′, 40.5 C2′, 70.5 C3′, 87.3 C4′, 61.4 C5′, 150.3 2CO, 163.3 4CO, 112.6 C5, 136.5 C6, 22.8 C7, 34.1 C8, 38.1 C10, 28.7 C11, 27.2 C12, 34.1 C13, 152.4 and 148.2 C14 and C14′, 124.3 and 125.0 C15 and C15′, 148.9 and 148.7 C16 and C16′, 121.4 and 120.6 C17 and C17′, 154.7 C18 and C18′, 171.1 19CO; FAB HRMS m/z $C_{27}H_{34}N_5O_6$ $(M + H)^+$: calcd 524.2431, found 524.2501.

DMT-deoxyruidine-C4-bipyridine 9. Nucleoside **8** (600 mg, 1.146 mmol) and DMT-Cl (465.0 mg, 1.375 mmol) were dissolved in pyridine (10 mL) and allowed to stand at rt for 5−6 h. After the reaction was quenched with MeOH, the reaction mixture was concentrated to dryness. The residue was dissolved in CH_2Cl_2 (100 mL) and washed with H_2O (2 × 25 mL), and the organic layer was dried and concentrated. Purification was accomplished by chromatography on basic alumina (10% MeOH/CH_2Cl_2). Final product **9** was obtained as a white foam (450.0 mg, 48%): R_f 0.44 (10% MeOH /CH_2Cl_2 on basic alumina); ^{1}H NMR (500 MHz, CD_3OD) δ 6.24 (t, 1H, H1′), 2.27 (m, 2H, H2′), 4.42 (m, 1H, H3′), 3.98 (m, 1H, H4′), 3.10 (m, 2H, H5′), 7.54 (s, 1H, H6), 2.15 (m, 4H, H7 and H8), 3.38 (t, 2H, H10), 1.40-1.63 (b, 4H, H12 and H11), 2.70 (t, 2H, H13), 7.37 (dd, 2H, H15 and H15′), 8.47 (dd, 2H, H16 and H16′), 8.07 (dd, 2H, H17 and H17′), 2.45 (s, 3H, H19), 3.73 (s, 6H, OCH_3); ^{13}C NMR (125 MHz, CD_3OD) ppm 87.1 C1′, 41.9 C2′, 73.4 C3′, 88.64 C4′, 65.6 C5′, 155.3 2CO, 166.3 4CO, 115.0 C5, 139.1 C6, 25.1 C7, 36.5 C8, 175.0 9CO, 40.6 C10, 30.7 C11, 29.3 C12, 36.5 C13, 152.8 and 151.1 C14 and C14′, 126.8 and 126.2 C15 and C15′, 150.6 and 150.7 C16 and C16′, 123.7 and 124.2 C17 and C17′, 157.7 and 157.8 C18 and C18′, 21.9 C19, 56.4 OCH_3(DMT), 89.0 C(Ph)$(PhOMe)_2$; FAB HRMS m/z $C_{48}H_{51}N_5O_8$ $(M + H)^+$: calcd 826.3737, found 826.3802.

DMT-deoxyuridine-C4-bipyridine phosphoramidite 10. To a solution of **9** (400.0 mg, 0.504 mmol) and $EtN(iPr)_2$ (0.195 mL, 0.804 mmol) in dry THF (2.0 mL) was added β-cyanoethyl *N,N*-diisopropylchlorophosphonamidite (143.1 mg, 0.605 mmol). The reaction was complete in 4 h at rt. The reaction mixture was evaporated to dryness. The residue was purified by chromatography on basic alumina (3% MeOH/CH_2Cl_2). Final product **10** was obtained as a white foam (376.0 mg, 73%): R_f 0.41 (5% MeOH/CH_2Cl_2 on basic alumina); ^{31}P NMR (75.1 MHz, CD_3CN, referenced to 85% H_3PO_4) ppm 141.959, 141.656; FAB HRMS m/z $C_{57}H_{68}N_7O_9P$ $(M + H)^+$: calcd 1026.4894, found 1026.4897.

Adenosine-C4-bipyridine 11a. To a suspension of adenosine (5.34 g, 20 mmol) in dry DMF (180 mL) was added NaH (50% mineral oil dispersion, 1.24 g, 26 mmol, washed with benzene) at −5 °C. After stirring for 1 h, (4-bromobutyl)-bipyridine **4** (7.00 g, 24 mmol) in dry DMF (10 mL) was added dropwise to the reaction mixture over 50 min. The reaction was allowed to stand for 24 h at −5 °C. After quenching with ice−water (10 mL), the reaction mixture was concentrated to an oil. The oil was dissolved in H_2O (140 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The organic layer was dried and concentrated to give the crude mixture. The residue was purified by chromatography on basic alumina (5% MeOH/CH_2Cl_2). Final product **11a** was obtained as a white solid (1.678 g, 18.0%): R_f 0.47 (5% MeOH /CH_2Cl_2 on basic alumina); ^{1}H NMR (600 MHz, DMSO-d_6) δ 6.09 (d, 1H, H1′), 4.57 (t, 1H, H2′), 4.41 (t, 1H, H3′), 4.09 (t, 1H, H4′), 3.78 and 3.63 (m, 2H, H5′), 8.23 (s, 1H, H2), 8.48 (s, 1H, H8), 3.68 and 3.48 (m, 2H, H10), 1.56 (m, 2H, H11), 1.64 (m, 2H, H12), 2.65 (t, 2H, H13), 2.49 (s, 3H, H19), 7.21 (dd, 1H, H15), 7.34 (dd, 1H, H15′), 8.60 (dd, 1H, H16), 8.61 (dd, 1H, H16′), 8.27 (d, 1H, H17), 8.30 (d, 1H, H17′); ^{13}C NMR (150 MHz, DMSO-d_6) ppm 86.1 C1′, 80.9 C2′, 69.0 C3′, 86.4 C4′, 61.5 C5′, 152.4 C2, 149.0 C4, 156.1 C5, 119.3 C6, 139.7 C8, 69.3 C10, 28.5 C11, 26.3 C12, 34.1 C13, 152.0 C14, 147.7 C14′, 123.9 C15, 124.7 C15′, 148.9 C16, 148.8 C16′, 120.4 C17, 121.2 C17′, 155.2 C18 and C18′, 20.6 C19; FAB HRMS m/z $C_{25}H_{30}N_7O_4$ $(M + H)^+$: calcd 492.2359, found 492.2369.

DMT-adenosine-C4-bipyridine 12a. Nucleoside **11a** (2.825 g, 5.75 mmol), Et_3N (1.13 mL), and DMT-Cl (2.337 g, 6.89 mmol) were dissolved in pyridine (50 mL) and allowed to stand at rt for 5−6 h. After quenching with CH_3OH, the reaction mixture was concentrated to dryness. The residue was dissolved in CH_2Cl_2 (200 mL) and washed with H_2O (3 × 25 mL).

The organic layer was dried, concentrated, and chromatographed on basic alumina (4% MeOH/CH_2Cl_2). Final product **12a** was obtained as a yellow solid (2.65 g, 58%): R_f 0.34 (2% MeOH/CH_2Cl_2 on basic alumina); ^{1}H NMR (600 MHz, CD_2Cl_2) δ 6.14 (d, 1H, H1′), 4.50 (m, 2H, H2′ and H3′), 4.23 (t, 1H, H4′), 3.48 and 3.43 (m, 2H, H5′), 8.24 (s, 1H, H2), 8.05 (s, 1H, H8), 3.67 (m, 2H, H10), 1.64 (m, 2H, H11), 1.75 (m, 2H, H12), 2.68 (t, 2H, H13), 2.43 (s, 3H, H19), 7.09 (dd, 1H, H15), 7.13 (dd, 1H, H15′), 8.50 (dd, 1H, H16), 8.47 (dd, 1H, H16′), 8.25 (d, 1H, H17), 8.26 (d, 1H, H17′), 3.50 (s, 6H, OMe_3); ^{13}C NMR (150 MHz, CD_2Cl_2) ppm 87.4 C1′, 81.9 C2′, 70.2 C3′, 84.2 C4′, 63.6 C5′, 153.3 C2, 149.9 C4, 156.1 C5, 120.4 C6, 139.5 C8, 71.2 C10, 29.3 C11, 26.9 C12, 35.2 C13, 152.3 C14, 148.5 C14′, 124.2 C15, 124.9 C15′, 149.3 C16, 149.1 C16′, 121.3 C17, 122.2 C17′, 156.3 C18 and C18′, 21.2 C19, 55.7 OCH_3(DMT), 86.8 C(Ph)$(PhOMe)_2$; FAB HRMS m/z $C_{46}H_{48}N_7O_6$ $(M + H)^+$: calcd 794.3666, found 794.3657.

DMT-adenosine-C4-bipyridine 12b: ^{1}H NMR (600 MHz, CD_2Cl_2) δ 5.95 (d, 1H, H1′), 4.81 (t, 1H, H2′), 4.18 (t, 1H, H3′), 4.23 (t, 1H, H4′), 3.28 and 3.42 (m, 2H, H5′), 8.22 (s, 1H, H2), 7.98 (s, 1H, H8), 3.59 (m, 2H, H10), 1.65 (m, 2H, H11), 1.73 (m, 2H, H12), 2.70 (t, 2H, H13), 2.42 (s, 3H, H19), 7.11 (dd, 2H, H15 and H15′), 8.49 and 8.45 (dd, 2H, H16 and H16′), 8.26 (d, 2H, H17 and H17′), 3.76 (s, 6H, OMe_3); ^{13}C NMR (150 MHz, CD_2Cl_2) ppm 89.8 C1′, 74.0 C2′, 78.8 C3′, 82.5 C4′, 63.6 C5′, 153.3 C2, 140.0 C4, 155.9 C5, 120.5 C6, 139.7 C8, 70.9 C10, 29.5 C11, 27.1 C12, 35.3 C13, 152.4 C14, 148.5 C14′, 124.9 and 124.3 C15 and C15′, 149.3 and 149.1 C16 and C16′, 122.1 and 121.3 C17 and C17′, 156.3 C18 and C18′, 21.3 C19, 55.6 OCH_3(DMT), 86.9 C(Ph)$(PhOMe)_2$; FAB HRMS m/z $C_{46}H_{48}N_7O_6$ $(M + H)^+$: calcd 794.3666, found 794.3657.

DMT-adenosine(NH-Bz)-C4-bipyridine 13. Nucleoside **12a** (158.7 mg, 0.2 mmol) in dry pyridine (5 mL) was cooled in an ice bath. Me_3SiCl (0.127 mL, 1.0 mmol) was added, followed (after 30 min) by 5 equivalents of benzoyl chloride (0.116 mL, 1.0 mmol). The reaction mixture was stirred at rt for about 3 h. Cold water (4 mL) was added, followed by 4 mL of concentrated aqueous NH_3 (after 5 min), to give approximately 2 M ammonia solution. The mixture was stirred for another 30 min and concentrated to dryness. The residue was dissolved in CH_2Cl_2 (100 mL) and washed with H_2O (2 × 25 mL). The organic layer was dried, concentrated, and chromatographed on basic alumina (75% hexane/CH_2Cl_2). Final product **13** was obtained as a pale yellowish solid (80 mg, 27%): R_f 0.50 (CH_2Cl_2 on basic alumina); ^{1}H NMR (300 MHz, CD_3OD) δ 6.00 (d, 1H, H1′), 4.50 (t, 1H, H2′), 4.38 (t, 1H, H3′), 4.05 (t, 1H, H4′), 3.20 (m, 2H, H5′), 8.30 (s, 1H, H2), 8.40 (s, 1H, H8), 3.50 (m, 2H, H10), 1.60−1.50 (m, 4H, H11 and H12), 2.50 (t, 2H, H13), 2.30 (s, 3H, H19), 7.00 (dd, 2H, H15 and H15′), 8.22 (m, 2H, H16 and H16′), 7.85 (d, 2H, H17 and H17′), 3.50 (s, 6H, OMe_3); 7.65 (d, 1H, from Bz), 7.30−7.40 (m, 4H, from Bz); ^{13}C NMR (75 MHz, CD_3OD) ppm 90.5 C1′, 84.1 C2′, 72.4 C3′, 87.3 C4′, 65.9 C5′, 154.8 C2, 152.1 C4, 156.3 C5, 130.0 C6, 146.1 C8, 73.2 C10, 31.6 C11, 29.3 C12, 37.4 C13, 147.7 C14 and C14′, 127.7 and 126.9 C15 and C15′, 151.6 and 151.5 C16 and C16′, 124.5 and 125.2 C17 and C17′, 158.0 C18 and C18′, 22.8 C19, 57.2 OCH_3(DMT), 89.3 C(Ph)-$(PhOMe)_2$, 188.3 COPh; FAB HRMS m/z $C_{53}H_{51}N_7O_7$ $(M + H)^+$: calcd 898.3928, found 898.3913.

DMT-phosphoramidite-adenosine-bipyridine 14. To a solution of **13** (200.0 mg, 0.223 mmol) and $EtN(iPr)_2$ (0.195 mL, 0.804 mmol) in dry THF (2.0 mL) was added β-cyanoethyl *N,N*-diisopropylchlorophosphonamidite (143.1 mg, 0.605 mmol). The reaction was complete in 4 h at rt and was evaporated to dryness. The residue was chromatographed on basic alumina (3% MeOH/CH_2Cl_2). Final product **14** was obtained as a white foam (120 mg, 50%): R_f 0.30 (3% MeOH/CH_2Cl_2 on basic alumina); ^{31}P NMR (75.1 MHz, CD_3CN, referenced to TMP) ppm 148.2, 147.6; FAB HRMS m/z $C_{62}H_{68}N_9O_8P$ $(M + H)^+$: calcd 1098.5007, found 1098.4979.

DMT-nucleoside-C1′ 16. Triol nucleoside **15** (4.0 g, 15.5 mmol) and DMT-Cl (5.248 g, 15.49 mmol) were dissolved in 45 mL of dry pyridine. The reaction was cooled to −20 °C and allowed to warm to rt while stirring for 22 h. TLC showed that some starting material remained. More DMT-Cl (1.05 g, 3.10 mmol) was added to the solution and stirred for 4 h. CH_3OH was added to quench the reaction and the mixture was concentrated to give an orange-yellow residue. The residue was dissolved in CH_2Cl_2 and washed with H_2O. The CH_2Cl_2 layer was dried; chromatography on silica (2−5% CH_3CH_2OH/CH_2Cl_2) gave pure product (2.5 g, 28.8%) which was evaporated to a white foam: R_f 0.154 (5% MeOH/CH_2Cl_2 on silica); ^{1}H NMR (300 MHz, CD_3OD) δ 2.3 (dd, 1H, H2a′, J = 0.835, 4.95 Hz), 2.7 (dd, 1H, H2b′, J = 2.00, 4.97 Hz), 3.12 (dq, 2H, H5′, J = 1.48, 3.55, 5.62 Hz), 3.65 (s, 6H, OCH_3), 3.75 (q, 2H, H6′, J = 3.91, 6.98 Hz), 4.09 (m, 1H, H4′), 4.15 (m, 1H, H3′), 5.32 (d, 1H, H5, J = 2.74 Hz), 7.84 (d, 1H, H6, J = 2.75 Hz); ^{13}C NMR (75.1 MHz, $CDCl_3$) ppm 44.05 C2′, 55.12 OCH_3, 63.27 and 64.91 C5′ and C6′, 72.85 C3′, 100.83 C1′, 89.12 C4′, 100.14 C5, 141.38 C6, 150.55 C2, 164.43 C4; FAB HRMS m/z $C_{31}H_{32}N_2O_8$ $(M)^+$: calcd 560.2158 found 560.2181.

DMT-nucleoside-C1′-C3-S-terpyridine 17a. Nucleoside **16** (0.420 g, 0.75 mmol) and carbonyl diimidazole (0.195 g, 1.2 mmol) were dissolved in dry CH_2Cl_2 (6.25 mL) and stirred for 50 min. H_2O (22 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined, dried, and filtered. Terpyridine amine **2** (0.680 g, 2.10 mmol) was then added to the filtrate (100 mL) and stirred for 13 h at rt. The solution was concentrated to 50 mL by blowing Ar into the flask. The reaction was stirred for another 2 days and concentrated to dryness. The residue was dissolved in CH_2Cl_2 and washed with H_2O. The organic layer was chromatographed on basic alumina (10% CH_3OH/CH_2Cl_2). After evaporation, product **17a** was obtained as a white foam (0.176 g, 25.8%). The disubstituted product **17b** (0.328 g, 34.8%) also was obtained. Data for **17a**: R_f 0.209 (MeOH/CH_2Cl_2 on basic alumina); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.94 (m, 2H, H11), 2.78 (m, 2H, H2′), 3.15 (m, 4H, H10 and H12), 3.30 (m, 2H, H5′), 3.72 (s, 6H, OCH_3), 4.35 (m, 2H, H4′ and H3′), 4.49 (d, 1H, H6a′, J = 3.85 Hz), 4.65 (d, 1H, H6b′, J = 3.85 Hz), 5.42 (d, 1H, H5, J = 2.8 Hz), 5.91 (t, 1H, C9-NH, J = 1.9 Hz), 7.75 (d, 1H, H6, J = 2.8 Hz), 7.83 (m, 2H, H18 and H18′), 8.25 (m, 2H, H14 and H14′), 8.56 (m, 2H, H17 and H17′, J = 2.5 Hz), 8.65 (d, 2H, H20 and H20′, J = 1.5 Hz); ^{13}C-NMR (75.1 MHz, $CDCl_3$) ppm 27.52 C11, 28.51 C10, 39.83 C12, 44.29 C2′, 55.13 OMe, 63.08 and 66.21 C5′ and C6′, 72.45 C3′, 98.16 C1′, 86.60 C4′, 100.61 C5, 123.98 C17 and C17′, 117.62 C14 and C14′, 126.92 C19 and C19′, 137.01 C18 and C18′, 141.17 C6, 148.91 C20 and C20′, 150.11 C2, 151.09 C13, 155.65 C16 and C16′, 154.80 C15 and C15′, 156.08 C9, 163.79 C4; FAB HRMS m/z $C_{50}H_{48}N_6O_9S$ $(M + H)^+$: calcd 909.3203, found 909.3298. **17b**: R_f 0.389 (MeOH/CH_2Cl_2 on basic alumina); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86−1.98 (m, 4H, H11 H11′), 2.86 (m, 2H, H2′), 3.05−3.30 (m, 10H, H10 and H10′ and H12 and H12′ and H5′), 3.70 (s, 6H, OCH_3), 4.48 (m, 2H, H4′ and H3′), 4.64 (d, 1H, H6a′), 5.20 (m, 1H, H6b′), 5.39 (d, 1H, H5, J = 2.8 Hz), 6.20 (t, 1H, NH, J = 1.7 Hz), 6.34 (t, 1H, NH, J = 1.7 Hz), 7.68 (d, 1H, H6, J = 2.8 Hz), 7.78 (m, 4H, H18 and H18′ and H18″ and H18‴), 8.20 and 8.26 (s and s, 4H, H14 and H14′ and H14″ and H14‴), 8.50−8.54 (m, 4H, H17 and H17′ and H17″ and H17‴), 8.63 (m, 4H, H20 and H20′ and H20″ and H20‴); ^{13}C NMR (75.1 MHz, $CDCl_3$) ppm 27.45 and 27.77 C11 and C11′, 28.51 C10 and C10′, 39.77 and 39.85 C12 and C12′, 42.16 C2′, 55.02 OMe, 63.08 and 66.21 C5′ and C6′, 75.72 C3′, 86.52 C4′, 98.02 C1′, 100.27 C5, 117.36 and 117.43 C14 and C14′ and C14″ and C14‴, 123.81 C17 and C17′ and C17″ and C17‴, 126.83 C19 and C19′ and C19″ and C19‴, 136.79 C18 and C18′ and C18″ and C18‴, 141.49 C6, 148.78 C20 and C20′ and C20″ and C20‴, 150.01 C2, 150.81 and 150.89 C13 and C13′, 154.63 C15 and C15′ and C15″ and C15‴, 155.44 and 155.48 C16 and C16′ and C16″ and 16‴, 156.03 C9, 163.90 C4; FAB HRMS m/z $C_{69}H_{65}N_{10}O_{10}S_2$ $(M)^+$: calcd 1257.4326, found 1257.4327.

DMT-phosphoramidite-C1′-C3-S-terpyridine 18. Nucleoside **17** (45 mg, 0.0495 mmol) was dissolved in dry CH_2Cl_2 (0.768 mL). To this solution was added Et_3N (0.247 mmol, 0.035 mL) and β-cyanoethyl *N,N*-diisopropylchlorophosphonamidite (0.099 mmol, 0.022 mL). The reaction was stirred for 20 min at rt and quenched with saturated Na_2CO_3 solution (ca. 2 mL). The aqueous layer was extracted 3× with ethyl acetate. The organic layers were combined, dried, filtered, and concentrated to give a residue. The residue was chromatographed on basic alumina (0-3% MeOH/CH_2Cl_2) to give pure

product **18** (0.030 g, 55%) as a white foam after evaporation: R_f 0.488 (5% MeOH/CH_2Cl_2, on basic alumina); ^{31}P NMR (75.1 MHz, CD_3COCD_3, referenced to TMP) ppm 146.195, 146.121; FAB HRMS *m/z* $C_{59}H_{67}N_8O_{10}SP$ $(M)^+$: calcd 1110.4438, found 1110.4477.

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Supporting Information Available: Details of 2D NMR experiments (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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