Chemical Synthesis of Cross-Link Lesions Found in Nitrous Acid Treated DNA: A General Method for the Preparation of N2-Substituted 2′-Deoxyguanosines

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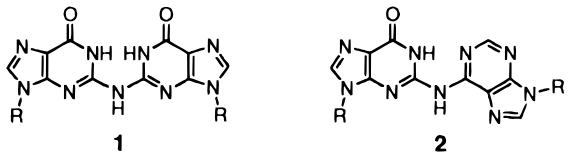
Treatment of DNA with nitrous acid results in the formation of DNA−DNA cross-links. Two cross-link lesions have previously been isolated and their structures assigned based on spectroscopic data. The major lesion has been proposed to consist of two deoxyguanosine (dG) nucleosides sharing a common N2 atom (**1**), while the structure of the minor lesion has been proposed to consist of a common nitrogen atom linking C2 of a dG nucleoside to C6 of deoxyadenosine (**2**). The chemical synthesis of **1** and **2**, utilizing a palladium-catalyzed coupling, is described herein. It is demonstrated that the spectroscopic properties of synthetic **1** are identical to that of lesion **1** obtained from nitrous acid cross-linked DNA, thus providing a proof of its structure. Comparison of the limited spectroscopic data available for lesion **2** originating from nitrous acid cross-linked DNA to synthetic **2** supports its structural assignment. The synthetic approach used for synthesis of **1** and **2** is shown to be a general method for the preparation of a variety of N2-substituted dG nucleosides in good yields.

Introduction

Nitrous acid is capable of chemically modifying DNA. The most abundant of these modifications is conversion of the exocyclic amino groups of the DNA bases to carbonyl groups by diazotization of the amine followed by hydrolysis of the diazonium ion. This deamination reaction has been widely used to alter genetic material[1] and is perhaps important in vivo due to the abundant dietary uptake of nitrite in cured meats and other foods.[2−4] In addition to deamination reactions, treatment of DNA with nitrous acid in vitro also results in formation of DNA−DNA cross-links. Two cross-link lesions have been isolated from enzymatic digests of nitrous acid treated calf thymus DNA.[5] The covalent structure of the major cross-link lesion has been proposed to consist of two deoxyguanosine (dG) nucleosides, each linked at C2 to a common nitrogen atom (**1**). This major cross-link lesion has subsequently been shown to form in DNA−DNA nitrous acid interstrand cross-linking reactions at the sequence [5′-d(CG)]$_2$.[6] Lesion **1** is presumably formed by diazotization of N2 of dG on one strand, followed by a nucleophilic attack by the N2 amino group of the dG nucleotide on the complementary strand.[6] The structure of the minor lesion was proposed by Shapiro and coworkers to consist of a common nitrogen atom linking C2 of a dG nucleoside to C6 of deoxyadenosine (dA) (**2**).[5] It has not been determined if lesion **2** is formed in interstrand or intrastrand reactions. It is also possible that lesion **2** does not form in duplex DNA, as it could have formed in denatured regions of calf thymus DNA.



1 **2**

R=2-deoxy-β-D-ribofuranosyl

We became interested in synthesizing homogeneous samples of nitrous acid interstrand cross-linked DNA for structural analyses and for studies of repair mechanisms of DNA containing cross-link lesions. However, homogeneous samples cannot be made by simple treatment of duplex DNA with nitrous acid due to concomitant deamination of the other nucleotide bases, yielding a heterogeneous mixture of cross-linked DNAs. We have pursued an alternate strategy, in which the cross-link lesion is chemically synthesized and incorporated into oligonucleotides via solid-phase synthesis.[7] Here we describe the chemical synthesis of **1** and **2** and their comparison to the cross-link lesions, obtained by digestion of nitrous acid cross-linked DNA. We also show that other biologically interesting N2-substituted dG nucleosides can be readily prepared by the approach described herein. A similar method for the preparation of N6 substituted dA nucleosides has recently been published.[8]

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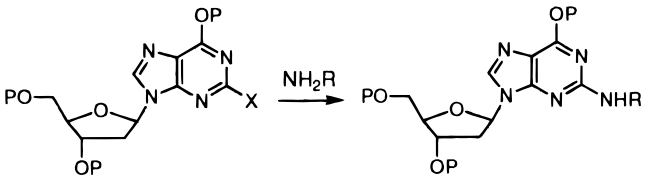
Scheme 1



P = H or protecting group
X = halogen

Results and Discussion

Synthesis and Analysis of Compounds 1 and 2. Our initial efforts focused on the synthesis of lesion **1**. The most common strategy for synthesizing N2-substituted deoxyguanosine nucleosides is by reaction of 2-haloinosine derivatives with the appropriate amine (Scheme 1).[9−13] Several attempts were made to prepare lesion **1** using this general strategy, in which the exocyclic amino group of dG (**3**), or its derivatives, served as the nucleophilic amine. However, these attempts were unsuccessful. A simple explanation is that the exocyclic amino group is a poor nucleophile, presumably due to the electron-withdrawing effects of the aromatic heterocycle.

During the course of this work, reports appeared by Buchwald and co-workers describing a homogeneous catalyst for the formation of aromatic carbon−nitrogen bonds.[14,15] Bromo pyridines and bromo benzenes were shown to react with a variety of aromatic and aliphatic amines, in the presence of a soluble palladium catalyst, to form the desired carbon−nitrogen bond. To test the feasibility of this new catalyst system for the synthesis of **1**, dG nucleoside derivatives containing either an aromatic amino group (**5**) or a bromide substituent (**6**) in the 2-position were prepared (Scheme 2). Silylation of the 5′- and 3′-hydroxyl functions of dG (**3**) by reaction with TBDMS chloride and imidazole gave **4** in excellent yield.[16] The O6 position of **4** was subsequently protected as a benzyl ether to give compound **5** in high yield.[7] Treatment of **5** with antimony(III) bromide and *tert*-butyl nitrite in methylene bromide yielded compound **6**.[7]

For the coupling reaction, **5** and **6** were heated at 80 °C in toluene with sodium *tert*-butoxide, (*R*)-(+)-2,2′-bis-(diphenylphosphino)-1,1′-binaphthyl (BINAP), and tris-(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) (Scheme 2).[14] This reaction gave compound **7** (a protected form of **1**) in 44% yield.[7] Similarly, reaction of protected dA (**10**)[17] with **6** under the same conditions produced compound **11** (a protected form of **2**) in 47% yield (Scheme 3).[7] Compounds **7** and **11** were treated sequentially with tetrabutylammonium fluoride (TBAF) and 1,4-cyclohexadiene/palladium black to remove the silyl and benzyl protecting groups, respectively, to yield compounds **1** and **2**. The ^{1}H NMR spectrum of an equimolar mixture of synthetic **1** and lesion **1**, isolated from nitrous acid cross-linked DNA, revealed a single set of resonances (Supporting Information). Moreover, UV spectra (at three different pHs) for **1** were identical to that previously reported for the compound isolated from nitrous acid treated DNA (Supporting Information).[5,18] Furthermore, HPLC analysis revealed that synthetic **1** coelutes with lesion **1** isolated from nitrous acid cross-linked DNA (data not shown). The aforementioned data provides a conclusive proof of structure for lesion **1**.

Shapiro and co-workers have previously assigned the structure of lesion **2** isolated from nitrous acid treated calf thymus DNA.[5] Due to the small amounts that were isolated, only the UV and MS data for lesion **2** were reported. Synthetic **2** and lesion **2** have an identical mass (the mass of 2′-deoxyguanosine plus 2′-deoxyadenosine minus ammonia). The UV spectra of synthetic **2** had absorption maxima (pH 6.0: 307 nm; pH 10.5: 257, 301, and 340 nm) nearly identical to that of lesion **2** from nitrous acid cross-linked DNA[5] (pH 6.0: 306 nm; pH 10.5: 258, 301, and 344 nm). Insofar as the rich UV spectra constitute a fingerprint, these data constitute substantial additional proof of the structure **2** proposed by Shapiro et al.

A General Method for the Preparation of N2-Substituted dG Nucleosides. Many toxins, mutagens, and drugs exert their biological action by alkylating DNA.[19,20] One common alkylation site on DNA is N2 of dG nucleotides. For example, it has been shown that metabolites of polycyclic aromatic hydrocarbons alkylate N2 of dG in DNA, which can cause mutations and/or lead to cancer.[21,22] The antibiotic and antitumor agent mitomycin C[23] and quinone methides[24] have also been shown to alkylate N2 of dG. Moreover, dG nucleosides containing aryl groups at N2 have shown interesting biological effects. For example, O6-allyl-N2-aryl dG compounds are inhibitors of DNA methyl transferase and thus have potential uses in cancer chemotherapy.[25] In addition, N2 aryl derivatives of dG have been shown to be inhibitors of herpes simplex virus type 1[26−28] and DNA polymerase α.[29] Thus, N2 aryl dG compounds are potentially a rich source of medicinally important molecules.

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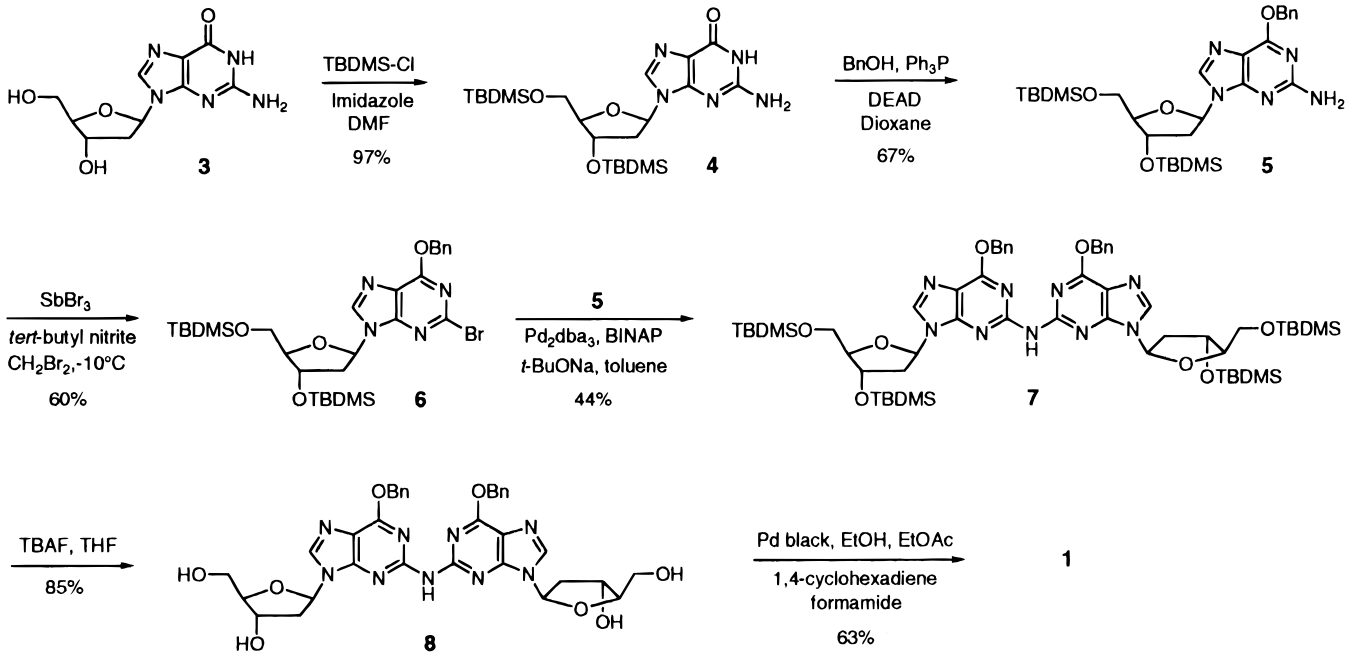
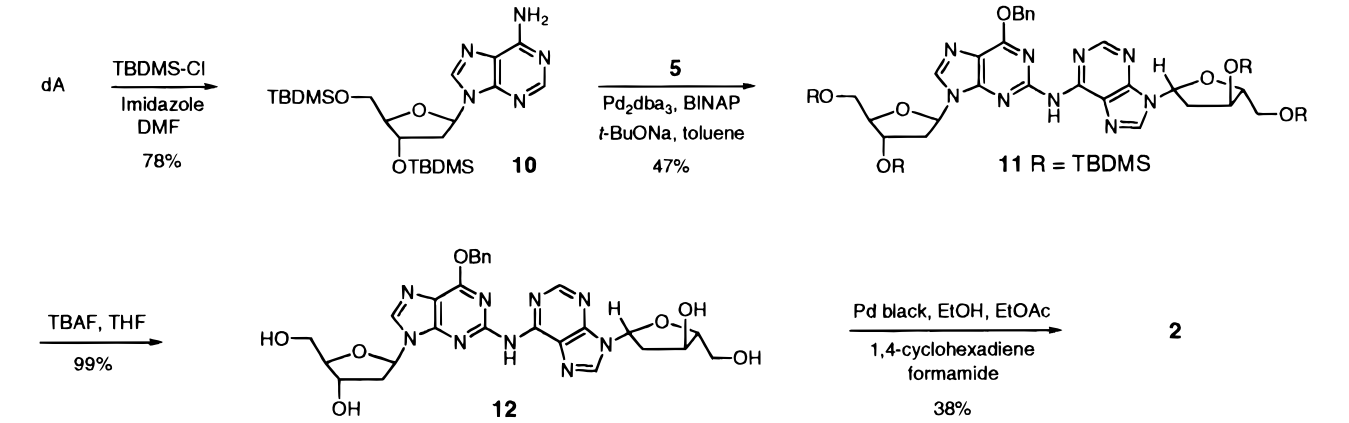
Scheme 2



Scheme 3



Only a few examples of synthetic approaches to N2 aryl-substituted dG derivatives have been reported.[13,25,30−33] One example is the reaction of 2-bromohypoxanthines with the appropriate aniline under reflux, followed by glycosylation.[30−32] The drawbacks of this method are that glycosylation yields a mixture of four isomers and the overall yields are very low. A more direct approach has been developed by Edwards et al. who introduced a trifluoromethanesulfonate moiety at the 2 position of a protected dG which was displaced with amines.[25] However, for aromatic amines, a large excess of the amine was required and only low to moderate yields of the N2-arylated dG product were obtained after prolonged heating. More recently, N2-(2-aminofluoren-3-yl) dG has been synthesized by reaction of a bromofluorene derivative with dG.[13] However, the reaction was only successful by first activating the fluorene ring with nitro and carbonyl groups that had to be reduced after the coupling reaction.

Because of the biological importance and relative inaccessibility of N2 aryl-substituted dG nucleosides, we set out to determine if this new palladium catalyst system could be applied as a general method for their synthesis. A wide variety of commercially available amines (Table 1) and bromides (Table 2) were selected based on their varied electronic and steric properties. These compounds were reacted with **5** or **6** under the same conditions as used in the synthesis of **1** and **2**, and the major products were isolated and subsequently characterized by NMR and mass spectrometry. The results show that this is indeed a generally applicable method for preparation of N2 alkyl- and aryl-substituted dG nucleosides in good to excellent yields.

We observed the same general trend for the reactivity of these compounds as noted by Buchwald and coworkers.[14,15] The best yields were obtained with electron-rich amines and electron-poor bromides. For example, reactions of **6** with *p*-methoxyaniline, aniline, and *p*-nitroaniline gave the desired products in 73%, 70%, and

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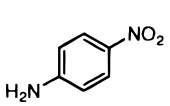
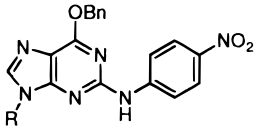
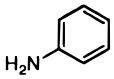
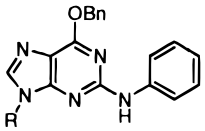
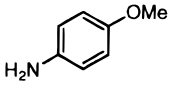
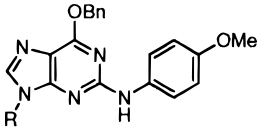
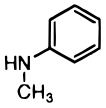
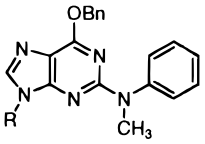
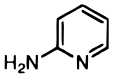
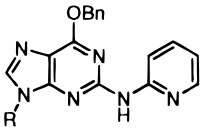
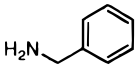
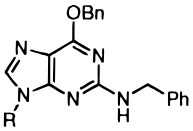
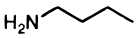
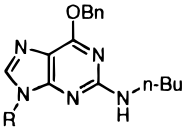
Table 1. Reactions of Bromide 6 with Various Amines

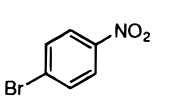
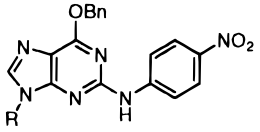
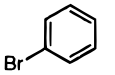
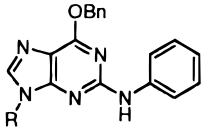
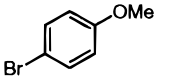
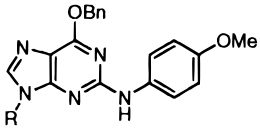
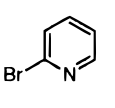
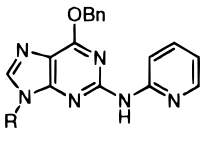
amine	product[a)]		isolated yield
		**13**	58%
		**14**	82%
		**15**	73%
		**16**	45%
		**17**	51%
		**18**	58%
		**19**	49%

[a] R = 5-*O*-3-Bis(*tert*-butyldimethylsilyl)-2-deoxy-*β*-D-ribofuranosyl.

58% yield, respectively (Table 1). Conversely, the reverse trend can be seen in Table 2, where reaction of **5** with *p*-nitrobromobenzene resulted in a 77% yield of the desired product while the yield for bromobenzene was only 57%. No reaction was observed between **5** and the electron-rich *p*-methoxybromobenzene to yield **15** (Table 2). However, as mentioned above, compound **15** can be readily obtained by reacting *p*-methoxyaniline with bromide **5** (Table 1). As would be expected, the sterically hindered *N*-methyl aniline gave a somewhat lower yield than aniline. In agreement with the results observed by Buchwald, reaction of aliphatic amines with **6** resulted in formation of N2-alkyl dG nucleosides in good yields (Table 1). Aliphatic amines have been used for direct (uncatalyzed) displacement of fluoride from the 2-position of O6-protected 2′-deoxyguanosine derivatives.[9,16] In contrast, the palladium catalyst was essential in the reactions of **5** with aliphatic amines: reaction of butylamine with **5**, in the absence of catalyst, resulted in decomposition of **5** without detectable formation of **19**.

In summary, we have designed an efficient synthesis of the cross-linked lesions **1** and **2**. Comparison of synthetic **1** to lesion **1**, obtained from nitrous acid cross-

Table 2. Reactions of Amine 5 with Various Bromides

bromide	product[a)]		isolated yield
		**13**	77%
		**14**	57%
		**15**	0%
		**17**	55%

[a] R = 5-*O*-3-*O*-bis(*tert*-butyldimethylsilyl)-2-deoxy-*β*-D-ribofuranosyl.

linked DNA, confirmed the structural assignment made by Shapiro and co-workers.[5] In addition, the comparison of the limited data available for lesion **2**, isolated from nitrous acid treated DNA, to synthetic **2** supports its structural assignment. Furthermore, we present a general method for preparing N2-substituted dG nucleosides, which will enable a variety of studies involving such modified nucleosides to be carried out.

While this paper was being reviewed and revised, two reports were published[34,35] describing the use of palladium catalyzed C−N bond formation for the preparation of N2- and N6-aryl-substituted purine nucleosides, including synthesis of compound **2**.[35]

Experimental Section

General Methods. All air or water sensitive reactions were performed in flame-dried glassware under a positive pressure of argon. All air or water sensitive materials were transferred in oven-dried syringes unless otherwise specified. Commercial solvents and reagents were used without further purification with the following exceptions: CH_2Cl_2 and CH_2Br_2 were distilled under nitrogen from calcium hydride; toluene and dioxane were distilled from sodium under nitrogen. Water was purified on a MILLI-Q Water System. UV spectra of **1** and **2** were recorded in water, and the pH was adjusted by addition of 2.5% aqueous phosphoric acid, concentrated ammonia, or aqueous NaOH. NMR spectra were reported relative to the NMR solvent peaks ($CHCl_3$ at 7.26 ppm and DMSO at 2.49 ppm), except for compounds **6**, **7**, **15**, **16** where TMS (at 0.0 ppm) was used as an internal reference.

Preparative TLC purifications were performed on 20 cm × 20 cm × 1 mm silica gel plates with a fluorescent indicator (Aldrich). UV monitoring for HPLC analyses was at 260 nm. The solvent gradient was run at 10 mL/min for preparative separations (Rainin, 300 Å, C_{18}, 250 mm × 21.4 mm column) and 1 mL/min for analytical separations (Alltech, 5-μm, C_{18}, 250 mm × 4.6 mm Econosphere column). The solvent gradient

(34) De Riccardis, F.; Bonala, R.; Johnson, F. *J. Am. Chem. Soc.* **1999**, *121*, 10453−10460.
(35) De Riccardis, F.; Johnson, F. *Org. Lett.* **2000**, *2*, 293−295.

was as follows: solvent A: 10 mM ammonium acetate (pH 7.0); solvent B: acetonitrile; isocratic 92% A for 7 min, 10 min linear gradient to 70% A, 5 min linear gradient to 40% A, 5 min linear gradient to 30% A, 5 min linear gradient to 92% A.

General Procedure for Amination of 5′-*O*-3′-*O*-bis-(*tert*-butyldimethylsilyl)-6-*O*-benzyl-2-bromo-2′-deoxyinosine (6) (procedure A). Bromide **6** (100 mg, 0.154 mmol), amine (0.170 mmol), sodium *tert*-butoxide (20.7 mg, 0.216 mmol), tris(dibenzylideneacetone)dipalladium(0) (Pd_2dba_3) (2.0 mg, 0.0022 mmol), and (R)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) (4.0 mg, 0.0064 mmol) were placed in a 5 mL conical flask and purged with argon. Freshly distilled toluene (1.0 mL) was added and the reaction vessel heated at 80 °C until the reaction was complete (TLC analysis). The reaction was cooled to 25 °C, diluted with ether (5 mL), and filtered through Celite. The filtrate was concentrated and purified by silica gel flash column chromatography.

General Procedure for Arylation of 5′-O-3′-*O*-bis(*tert*-butyldimethylsilyl)-6-*O*-benzyl-2′-deoxyguanosine (5) (procedure B). The procedure was identical to the one described above for the amination of **6** with the exception that the amine **5** was the limiting reagent and the bromide was present in 1.1 molar excess.

2-*N*-(2-(2′-Deoxyinosyl))-2′-deoxyguanosine (1). Tetraol **8** (108 mg, 0.155 mmol) was dissolved in a mixture of 1.6 mL of formamide, 1.6 mL of EtOH, 1.0 mL of MeOH, 0.4 mL of ethyl acetate, and 1.2 mL of 1,4-cyclohexadiene. A slow stream of argon was bubbled through the solution for 5 min, followed by addition of palladium black (25 mg, Aldrich). The mixture was sonicated for ca. 5 s to disperse the catalyst and stirred for 16 h. The reaction mixture was centrifuged, and the supernatant decanted and concentrated in vacuo to a volume of ca. 1 mL. The crude reaction mixture was purified by HPLC using gradient A to yield 50.1 mg (63%) of **1** as a white solid. ^{1}H NMR (ca. 5% D_2O/d_6−DMSO), 500 MHz): δ 8.08 (s, 1H), 6.21 (dd, J = 6.5, 7.5 Hz, 1H), 4.53 (bs, 1H), 3.84 (ddd, J = 5.0, 4.0, 3.5 Hz, 1H), 3.59 (dd, J = 11.5, 4.0 Hz, 1H), 3.50 (dd, 11.5, 5.0 Hz, 1H), 2.64 (ddd, J = 13.0, 7.5, 6.5 Hz, 1H), 2.32 (ddd, J = 13.0, 6.5, 3.5 Hz, 1H);^{13}C NMR (d_6-DMSO, 125 MHz): δ 158.5, 150.1, 148.6, 137.7, 119.3, 87.9, 83.5, 70.3, 61.8, 48.7; FAB-HRMS: *m*/*e* 518.1750 (M + H$^+$) (calcd. 518.1748); UV λ_{max} (nm) 267.0, 299.3 (pH 2.5); 293.2 (pH 7.0); 252.0, 260.0, 288.1 (pH 13.0).

6-*N*-(2-(2′-Deoxyinosyl))-2′-deoxyadenosine (2). Compound **12** (139.0 mg, 0.235 mmol) was dissolved in 2.0 mL of formamide which was subsequently diluted with 2.0 mL of EtOH, 1.5 mL of 1,4-cyclohexadiene, and 0.5 mL of ethyl acetate. Palladium black (25.0 mg) was added to the mixture, and the reaction was briefly sonicated and then allowed to stir at 25 °C. After 16 h, the catalyst was removed by filtration and the filtrate concentrated in vacuo to a final volume of ca. 1.0 mL. The crude reaction was purified by HPLC to obtain 45 mg (38%) of **2** as a white solid. ^{1}H NMR (d_6-DMSO, 500 MHz): δ 8.49 (s, 1H), 8.45 (s, 1H), 8.04 (s, 1H), 6.40 (dd, J = 7.5, 6.0 Hz, 1H), 6.28 (dd, J = 7.0, 7.0 Hz, 1H), 4.43 (ddd, J = 6.5, 3.0, 1.5 Hz, 1H), 4.40 (ddd, J = 6.0, 3.0, 2.0 Hz, 1H), 3.89 (J = 7.5, 2.0, 1.5 Hz, 1H), 3.84 (ddd, J = 7.5, 2.0, 1.5 Hz, 1H), 3.64−3.59 (m, 2H), 3.55−3.50 (m, 2H), 2.72 (ddd, J = 13.0, 7.0, 6.5 Hz, 1H), 2.64 (ddd, 13.0, 7.5, 6.0 Hz, 1H), 2.30 (ddd, J = 13.0, 6.0, 3.0 Hz, 1H), 2.23 (ddd, J = 13.0, 7.0, 3.0 Hz, 1H);^{13}C NMR (d_6-DMSO, 125 MHz): δ 162.9, 154.2, 152.4, 150.6, 150.1, 149.2, 140.5, 136.9, 123.0, 118.6, 88.1, 87.8, 83.9, 83.4, 70.8, 70.8, 61.8, 61.7, 55.0, 39.5; FAB-HRMS: *m*/*e* 502.1800 (M + H$^+$) (calcd 502.1799); UV λ_{max} (nm) 306.8 (pH 6.0); 257.0, 300.6, 339.8 (pH 10.5).

2-N-(2-(5′-*O*-3′-*O*-Bis(*tert*-butyldimethylsilyl)-6-*O*-benzyl-2′-deoxyinosyl))-5′-*O*-3′-*O*-bis(*tert*-butyldimethylsilyl)-6-*O*-benzyl-2′-deoxyguanosine (7). Amine **5** (100 mg, 0.170 mmol), bromide **6** (122 mg, 0.188 mmol), (Pd_2dba_3) (2 mg, 0.002 mmol), BINAP (4 mg, 0.006 mmol), and sodium *tert*-butoxide (23 mg, 0.24 mmol) were placed in a dry flask. Toluene (1.0 mL) was added, and the reaction was stirred at 80 °C for 4 h, after which the flask was cooled to 25 °C and diethyl ether (5 mL) added. The mixture was filtered through a plug of Celite, the filtrate was concentrated in vacuo, and the residue was purified by silica gel flash column chromatography (1% MeOH/CH_2Cl_2) to obtain 87 mg (40%) of pure **7** as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.10 (s, 2H), 7.83 (s, 1H), 7.53 (d, J = 6.9 Hz, 4H), 7.34−7.29 (m, 6H), 6.46 (dd, J = 6.2, 6.4 Hz, 2H), 5.74 (d, J = 12.0 Hz, 2H), 5.71 (d, J = 12.0 Hz, 2H), 4.59 (ddd, J = 6.0, 4.4, 3.2 Hz, 2H), 3.90 (ddd, J = 4.1, 3.2, 3.0 Hz, 2H), 3.82 (dd, J = 11.1, 4.1 Hz, 2H), 3.73 (dd, J = 11.1, 3.0 Hz, 2H), 2.62 (ddd, J = 13.2, 6.4, 6.0 Hz, 2H), 2.34 (ddd, J = 13.2, 6.2, 4.4 Hz, 2H), 0.903 (s, 18H), 0.892 (s, 18H), 0.0732 (s, 6H), 0.0673 (s, 6H), 0.0602 (s, 12H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 160.7, 153.6, 153.3, 139.2, 136.5, 128.8, 128.6, 128.2, 117.8, 95.6, 87.7, 83.9, 71.5, 68.3, 62.4, 41.3, 26.1, 26.0, 18.6, 18.2, −4.5, −4.4, −5.2, −5.3; FAB-HRMS: *m*/*e* 1153.6220 (M + H$^+$) (calcd 1153.6068).

2-*N*-(2-(6-*O*-Benzyl-2′-deoxyinosyl))-6-*O*-benzyl-2′-deoxyguanosine (8). A solution of compound **7** (42 mg, 0.036 mmol) in THF (1.0 mL) was treated with a 1.0 M solution of tetrabutylammonium fluoride in THF (180 μL) at 25 °C. The reaction was stirred for 30 min, concentrated in vacuo, and purified by preparative TLC (20% MeOH/CH_2Cl_2) to yield 21 mg (85%) of **8** as a white solid.^{1}H NMR (ca. 10% d_6-DMSO/$CDCl_3$, 500 MHz): δ 7.96 (s, 2H), 7.73 (s, 1H), 7.39 (d, J = 7.2 Hz, 4H), 7.26−7.19 (m, 6H), 6.37 (dd, J = 8.2, 5.9 Hz, 2H) 5.56 (s, 4H), 4.52 (bs, 6H), 3.99 (bd, J = 2.0 Hz, 2H), 3.71 (ddd, J = 12.1, 3.4, 3.4 Hz, 2H), 3.61 (ddd, J = 12.1, 7.7, 2.9 Hz, 2H), 2.83 (ddd, J = 13.6, 8.2, 5.4 Hz, 2H), 2.34 (ddd, J = 13.6, 5.9, 4.6 Hz, 2H); ^{13}C NMR (ca. 10% d_6-DMSO/$CDCl_3$, 125 MHz): δ 159.5, 153.3, 153.0, 140.1, 136.3, 128.5, 128.3, 128.0, 116.5, 87.6, 83.2, 70.6, 67.5, 61.4, 39.4; FAB-HRMS: *m*/*e* 697.2628 (M + H$^+$) (calcd. 697.2609).

6-*N*-(2-(5′-*O*-3′-*O*-Bis(*tert*-butyldimethylsilyl)-6-*O*-benzyl-2′-deoxyinosyl))-5′-O-3′-*O*-bis(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (11). Amine **10** (696 mg, 1.45 mmol), bromide **6** (1130 mg, 1.74 mmol), (Pd_2dba_3) (22 mg, 0.024 mmol), BINAP (44 mg, 0.071 mmol), and sodium *tert*-butoxide (220 mg, 2.29 mmol) were placed in a dry flask to which toluene (11.0 mL) was added. The reaction was stirred at 80 °C for 2 h. At this time, the flask was cooled to 25 °C and diethyl ether (40 mL) added. The solids were removed by filtration through a plug of Celite, the filtrate was concentrated in vacuo, and the residue purified by silica gel flash column chromatography (0.25% MeOH/CH_2Cl_2) to obtain 850 mg (47%) of **11** as a clear oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.75 (s, 1H), 8.63 (bs, 1H), 8.32 (s, 1H), 8.15 (s, 1H), 7.60 (d, J = 7.0 Hz, 2H), 7.39−7.32 (m, 3H), 6.57 (dd, J = 6.5, 6.5 Hz, 1H), 6.52 (dd, J = 6.5, 6.5 Hz, 1H), 5.73 (d, J = 11.5 Hz, 1H), 5.70 (d, J = 11.5 Hz, 1H), 4.68 (ddd, J = 6.2, 3.2, 3.2 Hz, 1H), 4.64 (ddd, J = 6.2, 3.5, 3.5 Hz, 1H), 4.09 (ddd, J = 3.2, 3.2, 3.2 Hz, 1H), 4.05 (ddd, J = 3.5, 3.5, 3.5 Hz, 1H), 3.95 (dd, J = 11.0, 4.5 Hz, 1H), 3.89 (dd, J = 11.0, 4.5 Hz, 1H), 3.83 (dd, J = 11.0, 3.0 Hz, 1H), 3.80 (dd, J = 11.0, 3.0 Hz, 1H), 2.80−2.72 (m, 2H), 2.54−2.49 (m, 2H), 0.969 (s, 9H), 0.964 (s, 18H), 0.930 (s, 9H), 0.158 (s, 9H), 0.148 (s, 3H), 0.140 (s, 6H), 0.0971 (s, 3H), 0.0903 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.4, 152.6, 152.5, 152.3, 150.4, 149.9, 140.0, 139.6, 136.0, 128.5, 128.3, 128.2, 122.0, 118.1, 87.9, 87.8, 84.4, 84.3, 72.1, 71.9, 68.5, 62.8, 62.7, 41.3, 41.1, 26.0, 25.8, 18.4, 18.4, 18.0, −4.6, −4.6, −4.7, −5.3, −5.4, −5.4; FAB-HRMS: *m*/*e* 1048.5726 (M + H$^+$) (calcd. 1048.5726).

***N*2-(6-(2′-Deoxy)adenosyl)-*O*6-benzyl-2′-deoxyguanosine (12).** To a solution of compound **11** (14 mg, 0.013 mmol) in THF (1.0 mL) was added 1.0 M tetrabutylammonium fluoride in THF (67 μL). After stirring the reaction for 30 min, it was concentrated in vacuo and the residiue purified by preparative TLC (15% methanol/methylene chloride) to yield 7.6 mg (99%) of **12** as a white solid. ^{1}H NMR (CD_3OD, 500 MHz): δ 9.19 (s, 1H), 9.08 (s, 1H), 8.87 (s, 1H), 7.92 (d, J = 9.0 Hz, 2H), 7.75−7.67 (m, 3H), 6.78 (dd, J = 8.5, 7.5 Hz, 1H), 6.68 (dd, J = 8.0, 7.5 Hz, 1H), 5.73 (s, 2H), 4.60 (ddd, J = 6.5, 5.5, 4.0 Hz, 1H), 4.54 (ddd, J = 7.5, 3.5, 2.5 Hz, 1H), 3.93 (ddd, J = 4.5, 3.5, 3.5 Hz, 1H) 3.81 (ddd, J = 6.0, 4.0, 4.0 Hz, 1H), 3.66 (dd, J = 14.0, 3.5 Hz, 1H), 3.56 (dd, J = 14.5, 4.5 Hz, 1H), 3.54 (dd, J = 13.5, 4.0 Hz, 1H) 3.48 (dd, J = 14.5, 6.0 Hz, 1H), 2.55 (ddd, J = 16.0, 8.0, 7.5 Hz, 1H), 2.51 (ddd, J = 15.5, 8.5, 6.5 Hz, 1H), 2.06 (ddd, J = 15.5, 7.5, 2.5 Hz, 1H), 2.01

(ddd, J = 16.0, 8.0, 5.5 Hz, 1H);^{13}C NMR (d_6-DMSO, 125 MHz): δ 159.6, 152.8, 152.7, 151.7, 151.2, 150.7, 141.3, 141.2, 136.3, 128.5, 128.3, 128.1, 122.7, 117.5, 88.0, 87.9, 83.9, 83.9, 70.9, 70.8, 67.7, 61.8, 61.7, 48.7, 39.6; FAB-HRMS: *m/e* 592.2266 (M + H$^+$) (calcd 592.2268).

5′-*O*-3′-*O*-Bis(*tert*-butyldimethylsilyl)-6-*O*-benzyl-2-*N*-(4-nitrophenyl)-2′-deoxyguanosine (13). Compound **13** was prepared by both procedure A (reaction time 5 h, 58%) and procedure B (reaction time 3 h, 77%) and purified by silica gel flash column chromatography (0.5% MeOH/CH_2Cl_2) to yield a bright-yellow foam. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.18 (d, J = 9.5 Hz, 2H), 7.92 (s, 1H), 7.81 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 6.6 Hz, 2H), 7.36−7.29 (m, 3H), 6.47 (dd, J = 6.2, 6.2 Hz, 1H), 5.60 (d, J = 12.5 Hz, 1H), 5.56 (d, J = 12.5 Hz, 1H), 4.63 (ddd, J = 5.9, 2.9, 2.9 Hz, 1H), 4.07 (ddd, J = 6.6, 2.9, 2.9 Hz, 1H), 3.87 (dd, J = 11.0, 2.9 Hz, 1H), 3.83 (dd, J = 11.0, 2.9 Hz, 1H), 2.52 (ddd, J = 13.0, 6.2, 2.9 Hz, 1H), 2.44 (ddd, J = 13.0, 6.2, 2.9 Hz, 1H), 0.947 (s, 9H), 0.914 (s, 9H), 0.125 (s, 6H), 0.0940 (s, 3H), 0.0917 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.2, 153.9, 152.4, 145.8, 141.1, 138.7, 135.7, 128.2, 127.9, 127.6, 125.0, 117.0, 87.7, 83.9, 71.9, 68.4, 62.8, 41.6, 25.9, 25.7, 18.4, 17.9, 9.3, −4.6, −4.7, −5.4, −5.5; FAB-HRMS: *m/e* 706.3353 (M + H$^+$) (calcd 706.3330).

5′-O-3′-*O*-Bis(*tert*-butyldimethylsilyl)-6-*O*-benzyl-2-*N*-phenyl-2′-deoxyguanosine (14). Compound **14** was prepared by both procedure A (reaction time 3 h, 82%) and B (reaction time 4 h, 57%) and purified by silica gel flash column chromatography (1% MeOH/CH_2Cl_2) to yield a light-yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.00 (s, 1H), 7.63 (d, J = 8.1 Hz, 2H), 7.50 (d, J = 7.3 Hz, 1H), 7.37−7.30 (m, 5H), 7.04−7.01 (m, 2H), 6.42 (dd, J = 7.3, 7.1 Hz, 1H), 5.63 (d, J = 12.5 Hz, 1H), 5.60 (d, J = 12.5 Hz, 1H), 4.59 (ddd, J = 5.9, 2.9, 2.9 Hz, 1H), 4.02 (dd, J = 4.8, 2.9 Hz, 1H), 3.82 (dd, J = 11.3, 4.4 Hz, 1H), 3.78 (dd, J = 11.5, 3.7 Hz, 1H), 2.56 (ddd, J = 13.2, 7.3, 5.9 Hz, 1H), 2.43 (ddd, J = 13.2, 7.1, 2.9 Hz, 1H), 0.945 (s, 9H), 0.922 (s, 9H), 0.127 (s, 6H), 0.0943 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.5, 155.5, 153.2, 139.9, 138.1, 136.4, 128.8, 128.4, 128.0, 127.9, 122.1, 118.8, 116.4, 87.8, 83.9, 72.1, 68.2, 62.9, 41.4, 25.9, 25.7, 18.4, 18.0, −4.7, −4.8, −5.4, −5.5; FAB-HRMS: *m/e* 661.3473 (M + H$^+$) (calcd 661.3480).

5′-*O*-3′-*O*-Bis(*tert*-butyldimethylsilyl)-6-*O*-benzyl-2-*N*-(4-methoxyphenyl)-2′-deoxyguanosine (15). Compound **15** was prepared by procedure A (reaction time 3.5 h, 73%) and purified by silica gel flash column chromatography (1% MeOH/CH_2Cl_2) to obtain a dark oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.98 (s, 1H), 7.51 (d, J = 8.5 Hz, 2H), 7.47 (d, J = 7.0 Hz, 2H), 7.36−7.28 (m, 3H), 6.99 (s, 1H), 6.87 (d, J = 8.5 Hz, 2H), 6.40 (dd, J = 6.5, 6.5 Hz, 1H), 5.59 (d, J = 12.5 Hz, 1H), 5.55 (d, J = 12.5 Hz, 1H), 4.58 (ddd, J = 5.5, 3.5, 3.0 Hz, 1H), 4.01 (ddd, J = 4.0, 3.0, 3.0 Hz, 1H), 3.81 (dd, J = 11.0, 4.0 Hz, 1H), 3.80 (s, 3H), 3.78 (dd, J = 11.0, 3.0 Hz, 1H), 2.54 (ddd, J = 13.5, 6.5, 5.5 Hz, 1H), 2.40 (ddd, J = 13.5, 6.5, 3.5 Hz, 1H), 0.938 (s, 9H), 0.920 (s, 9H), 0.119 (s, 6H), 0.0921 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.4, 155.9, 155.0, 153.2, 137.7, 136.4, 133.1, 128.3, 128.0, 127.8, 120.9, 114.7, 113.9, 87.6, 83.8, 72.0, 67.9, 62.8, 55.4, 41.2, 25.9, 25.7, 18.3, 17.9, −4.7, −4.8, −5.5, −5.6; FAB-HRMS: *m/e* 692.3665 (M + H$^+$) (calcd 692.3664).

5′-*O*-3′-*O*-Bis(*tert*-butyldimethylsilyl)-6-*O*-benzyl-2-*N*-methyl-2-*N*-phenyl-2′-deoxyguanosine (16). Compound **16** was prepared by procedure A (reaction time 2 h, 45%) and purified by silica gel flash column chromatography (1% MeOH/CH_2Cl_2) to obtain a light-yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.85 (s, 1H), 7.39−7.31 (m, 5H), 7.25−7.19 (m, 5H), 6.30 (dd, J = 7.0, 6.5 Hz, 1H), 5.35 (d, 11.5 Hz, 1H), 5.32 (d, J = 11.5 Hz, 1H), 4.54 (ddd, J = 7.0, 6.0, 3.5 Hz, 1H), 3.96 (dd, J = 7.0, 4.5 Hz, 1H), 3.75 (d, J = 4.5 Hz, 2H), 3.55 (s, 3H), 2.68 (ddd, J = 13.0, 7.0, 6.0 Hz, 1H), 2.30 (ddd, J = 13.0, 6.5, 3.5 Hz, 1H), 0.912 (s, 9H), 0.903 (s, 9H), 0.0991 (s, 3H), 0.0965 (s, 3H), 0.0703 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.5, 157.7, 153.3, 146.0, 137.8, 136.7, 128.4, 128.4, 128.0, 127.6, 126.5, 124.9, 115.4, 87.6, 84.1, 72.2, 67.5, 63.1, 40.5, 38.7, 26.0, 25.8, 18.5, 18.1, −4.5, −4.6, −5.2, −5.3; FAB-HRMS: *m/e* 675.3618 (M + H$^+$) (calcd 675.3636).

5′-*O*-3′-*O*-Bis(*tert*-butyldimethylsilyl)-6-*O*-benzyl-2-*N*-(2-pyridyl)-2′-deoxyguanosine (17). Compound **17** was prepared by both procedure A (reaction time 2 h, 51%) and procedure B (reaction time 4.5 h, 55%) and purified by silica gel flash column chromatography (1% MeOH/CH_2Cl_2) to obtain a light-yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.37 (d, J = 9.0 Hz, 1H), 8.34 (d, J = 4.8 Hz, 1H), 8.29 (bs, 1H), 8.07 (s, 1H), 7.64 (ddd, J = 9.0, 9.0, 2.0 Hz, 1H), 7.51 (d, J = 7.5 Hz, 2H), 7.37−7.26 (m, 3H), 6.91 (dd, J = 7.5, 5.0 Hz, 1H), 6.46 (dd, 7.0, 6.5 Hz, 1H), 5.64 (d, J = 12.5 Hz, 1H), 5.61 (d, J = 12.5 Hz, 1H), 4.59 (ddd, J = 6.0, 3.5, 2.0 Hz, 1H), 4.03 (ddd, J = 4.5, 3.5, 2.0 Hz, 1H), 3.83 (dd, J = 12.0, 4.5 Hz, 1H), 3.79 (dd, J = 12.0, 3.5 Hz, 1H), 2.51 (ddd, J = 13.0, 7.0, 6.0 Hz, 1H), 2.44 (ddd, J = 13.0, 6.5, 3.5 Hz, 1H), 0.944 (s, 9H), 0.919 (s, 9H), 0.126 (s, 6H), 0.0981 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.3, 154.2, 152.9, 152.7, 147.9, 138.2, 137.6, 136.2, 128.3, 128.0, 127.9, 117.1, 116.7, 112.0, 87.7, 83.9, 72.0, 68.3, 62.9, 41.7, 26.0, 25.8, 18.5, 18.0, −4.6, −4.7, −5.3, −5.4; FAB-HRMS: *m/e* 662.3438 (M + H$^+$) (calcd 662.3432).

5′-*O*-3′-*O*-Bis(*tert*-butyldimethylsilyl)-6-*O*-benzyl-2-*N*-benzyl-2′-deoxyguanosine (18). Compound **18** was prepared by procedure A (reaction time 0.5 h, 58%) and purified by silica gel preparative scale TLC (1.5% MeOH/CH_2Cl_2) to obtain a light-yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.93 (s,1H), 7.51 (d, J = 8.0 Hz, 2H), 7.42−7.32 (m, 8H), 6.38 (dd, J = 6.5, 6.5 Hz, 1H), 5.60 (d, J = 12.5 Hz, 1H), 5.57 (d, J = 12.5 Hz, 1H), 5.43 (t, J = 5.5 Hz, 1H), 4.70 (d, J = 5.5 Hz, 2H), 4.62 (ddd, J = 6.5, 4.0, 3.0 Hz, 1H), 4.03 (ddd, J = 4.5, 3.5, 3.0 Hz, 1H), 3.87 (dd, J = 11.0, 4.5 Hz, 1H), 3.82 (dd, J = 11.0, 3.5 Hz, 1H), 2.65 (ddd, J = 13.0, 6.5, 6.5 Hz, 1H), 2.36 (ddd, J = 13.0, 6.5, 4.0 Hz, 1H), 0.973 (s, 9H), 0.969 (s, 9H), 0.159 (s, 6H), 0.138 (s, 3H), 0.135 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.4, 158.5, 153.5, 139.4, 137.3, 136.5, 128.3, 128.2, 128.1, 127.7, 127.4, 127.0, 115.4, 87.5, 83.8, 72.0, 67.7, 62.9, 46.1, 40.6, 26.0, 25.8, 18.4, 18.0, −4.6, −4.7, −5.3, −5.4; FAB-HRMS: *m/e* 675.3622 (M + H$^+$) (calcd 675.3636).

5′-*O*-3′-*O*-Bis(*tert*-butyldimethylsilyl)-6-*O*-benzyl-2-*N*-(1-butyl)-2′-deoxyguanosine (19). Compound **19** was prepared by procedure A (reaction time 0.5 h, 49%) and purified by silica gel preparative scale TLC (1.5% MeOH/CH_2Cl_2) to obtain a light-yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.89 (s, 1H), 7.50 (d, J = 7.5 Hz, 2H), 7.40−7.32 (m, 3H), 6.37 (dd, J = 7.0, 6.0 Hz, 1H), 5.62 (d, J = 12.0 Hz, 1H), 5.59 (d, J = 12.0 Hz, 1H), 5.05 (bs, 1H), 4.63 (ddd, J = 6.0, 3.5, 3.0 Hz, 1H), 4.02 (ddd, J = 5.0, 3.0, 3.0 Hz, 1H), 3.86 (dd, J = 11.0, 5.0 Hz, 1H), 3.81 (dd, J = 11.0, 3.0 Hz, 1H), 3.47 (q, J = 6.5 Hz, 2H), 2.67 (ddd, J = 13.0, 7.0, 6.0 Hz, 1H), 2.38 (ddd, J = 13.0, 6.0, 3.5 Hz, 1H), 1.63 (m, 2H), 1.47 (m, 2H), 1.00 (t, J = 7.5 Hz, 3H), 0.967 (s, 9H), 0.961 (s, 9H), 0.155 (s, 6H), 0.130 (s, 3H), 0.128 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.4, 158.8, 153.5, 137.1, 136.6, 128.2, 128.0, 127.7, 115.1, 87.5, 83.7, 72.0, 67.6, 62.9, 41.7, 40.7, 31.8, 26.0, 25.8, 20.2, 18.4, 18.0, 13.9, −4.6, −4.7, −5.3, −5.4; FAB-HRMS: *m/e* 641.3775 (M + H$^+$) (calcd 641.3793).

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Supporting Information Available: UV spectra of synthetic **1** and **1** isolated from nitrous acid cross-linked DNA at pH 2.5, pH 7.0 and pH 13.0; UV spectra of compound **2** at pH 6.0 and pH 10.5; ^{1}H NMR spectra of compounds **1**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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