DOI: 10.1002/ejoc.200901428

Chemoenzymatic Synthesis of 3′-*O*-Acetal-Protected 2′-Deoxynucleosides as Building Blocks for Nucleic Acid Chemistry

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Dedicated to Professor Benito Alcaide on the occasion of his 60th birthday

Keywords: Nucleosides / Enzymes / Acylation / Protecting groups / Green chemistry

We have developed a simple and convenient synthetic strategy for the preparation of tetrahydropyranyl, 4-methoxytetrahydropyranyl, and tetrahydrofuranyl ethers of 2′-deoxynucleosides, which are useful building blocks for nucleic acid chemistry. Enzymatic benzoylation provides an efficient alternative for protecting the 5′-hydroxy group of the parent nucleosides in a regioselective manner. Subsequently, tetrahydropyranylation and tetrahydrofuranylation of the 2′-deoxynucleosides at the 3′-hydroxy group were accomplished with *p*-toluensulfonic acid, $MgBr_2$, or camphorsulfonic acid as catalysts. Deprotection of the 5′-*O*-benzoyl group furnished 3′-*O*-acetal-protected 2′-deoxynucleosides. The three-step process is expected to enable the large-scale synthesis of protected nucleosides.

Introduction

The demand for DNA sequencing has never been greater than it is today due to its wide-spread application in genomics research, forensics, medical diagnostics, and therapeutic discovery. 2′-Deoxyribonucleoside-5′-triphosphates (dNTPs) modified at the 3′-hydroxy position have been extensively utilized in DNA sequencing as chain terminators.[1] The synthesis of 3′-modified nucleotides requires the selective introduction and removal of protecting groups in multifunctional molecules, which is an essential part of organic synthesis.[2] The presence of various hydroxy, amino, and phosphate linkages in nucleic acids demands the use of appropriate blocking functions to simplify the synthetic sequences. For example, orthogonal protecting groups are core to the success of therapeutic oligonucleotides assembled by solid-phase synthesis.[3]

The protection of hydroxy groups as esters is one of the oldest and most frequently used strategies in the synthesis of nucleosides. Acetyl and benzoyl protecting groups are prized because they can be removed by alkaline hydrolysis without cleaving the glycosidic bond in nucleosides.[4] Protecting groups that can be removed under milder acid conditions or even under neutral conditions are of considerable value. A recent report on the thermolabile deprotection of tetrahydropyranyl (THP) and tetrahydrofuranyl (THF) ethers during the polymerase chain reaction (PCR) has attracted our attention.[5] The merits of acetal groups like THP and THF lie in their stability in the presence of various reagents such as basic media, alkyllithiums, metal hydrides, Grignard reagents, oxidative reagents, and alkylating or acylating reagents and under mild acidic conditions or heating, which promote cleavage.[6]

Numerous methods have been reported for the tetrahydropyranylation of alcohols.[2] Generally, protic and Lewis acids are used as catalysts for this reaction.[7] The reaction proceeds by the protonation of the enol ether carbon atom to generate a highly electrophilic oxonium ion, which is then attacked by the hydroxy group of the alcohol. Some reagents recently used for acetal protection are SO_3H-functionalized silica,[8] polystyrene-supported $AlCl_3$,[9] bromodimethylsulfonium bromide,[10] magnesium halides,[11] bismuth triflate,[12] or ruthenium trichloride.[13]

The use of the THF group is less prolific due to the limited protocols available in the literature. The reaction of tetrahydrofuran with an alcohol in the presence of ceric triethylammonium nitrate also provides a general procedure for protecting the hydroxy group.[14] Recently, an efficient method that involves the use of Mn^0 powder and CCl_4 in tetrahydrofuran has also been reported.[15]

The THP group has found considerable use in oligonucleotide synthesis.[16] The synthesis of 2′-*O*-THP and 2′,5′-

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200901428.

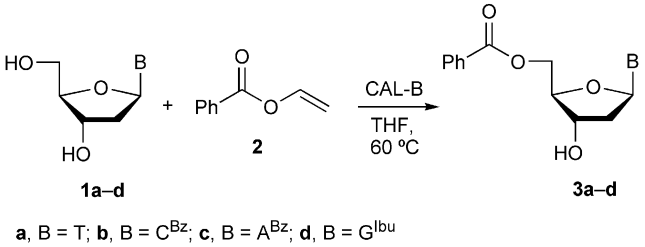
di-*O*-THP derivatives of nucleosides starting from appropriately protected precursors has been described. One of the practical problems of THP or THF protection is the complexity of the NMR spectroscopic data, which is a result of the introduction of a new chiral center into the molecule. As an alternative, the 4-methoxytetrahydropyran-4-yl group (MTHP) has been used for oligonucleotide synthesis as a symmetrical protecting group devoid of chirality.[17,18] The use of THF is preferred over THP as a protecting group because the hydrolysis of THF ethers is much faster than that of THP ethers. The synthesis of 2′-*O*-THF nucleosides has been reported from 2,3-dihydrofuran via 3′,5′-di-*O*-*tert*-butyldimethylsilyl nucleosides.[19]

However, protocols for the synthesis of 3′-*O*-THP and 3′-*O*-THF ethers of 2′-deoxynucleosides are not efficient. Often, dimethoxytrityl and silyl protecting groups are employed as blocking groups for the 5′-hydroxy group during the synthesis of the 3′-*O*-acetal. The use of these reagents has limitations for scale-up due to the higher cost and corrosive nature of the silyl chloride. Furthermore, *tert*-butyldimethylsilyl-protected nucleosides require chromatographic purification.[20] Similarly, 5′-*O*-acyl protection by a chemical route is nonselective, resulting in a mixture of products. We have already addressed the selectivity problems arising during the acylation of nucleosides by enzymatic processes.[21] For example, 5′-*O*-benzoyl-2′-deoxynucleoside derivatives have been synthesized by selective acylation of the parent nucleosides with vinyl benzoate catalyzed by *Candida antarctica* lipase B (CAL-B).[21a] This procedure is very attractive for a variety of reasons. First, the reagents are available at a reasonable cost. Secondly, enzyme-catalyzed reactions are nonhazardous, avoid pollution, and use less energy than conventional chemistry-based methods using trityl or silyl reagents.

Herein, we report a practical and efficient synthetic protocol for the large-scale synthesis of 3′-*O*-THP-, 3′-*O*-MTHP-, and 3′-*O*-THF-2′-deoxynucleosides starting from readily available 5′-*O*-benzoyl-protected derivatives.

Results and Discussion

The regioselective synthesis of 5′-*O*-benzoyl-2′-deoxynucleosides was accomplished by the reaction of 2′-deoxynucleosides **1** with vinyl benzoate in the presence of *Candida antarctica* lipase B (Scheme 1). Different ratios of acylating agent and conditions were tested.[21a] The results are summarized in Table 1. The enzymatic benzoylation of thymidine (**1a**) with 5 equiv. of vinyl benzoate afforded exclusively 5′-*O*-benzoylthymidine in 93% yield (entry 1, Table 1). For the acylation of N^4-benzoyl-2′-deoxycytidine (**1b**), 10 equiv. of the vinyl ester was required for optimum conversion. The lower solubility of the starting material required the use of a dilute solution (0.1 M instead 0.2 M) for completion of the reaction (entry 2, Table 1). N^6-Benzoyl-2′-deoxyadenosine (**1c**) was more reactive and only 3 equiv. of vinyl benzoate were necessary to drive the reaction to completion (entry 3, Table 1). The poor solubility of N^2-isobutyryl-2′-deoxyguanosine (**1d**) hampered the reaction rate. In this case, the use of 10 equiv. of vinyl benzoate, a substrate/enzyme ratio of 1:2 (w/w), and a 0.1 M concentration furnished the best results. Note that exclusive selectivity towards the 5′-position was maintained, resulting in the easy isolation of the products in high yields by simple precipitation from the crude reaction mixtures. No further purification of **3a**–**d** was needed. Moreover, the excess acylating agent was recovered by solvent evaporation from the filtrate and successfully recycled.



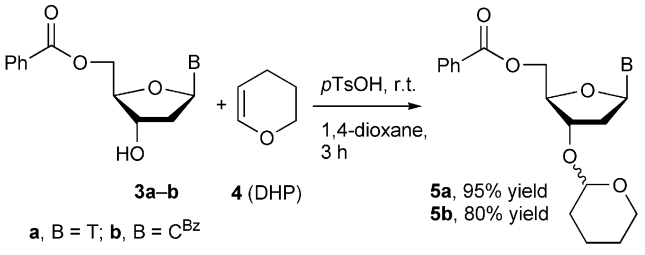
Scheme 1. Enzymatic benzoylation of 2′-deoxynucleosides.

Table 1. Reaction conditions for the benzoylation of **1a**–**d**.

Entry	**1**	**2** [equiv.]	**1**/CAL-B[a]	Conc. [M]	*t* [h]	Yield of **3** [%][b]
1	**1a**	5	1:1	0.2	116	93
2	**1b**	10	1:1	0.1	68	92
3	**1c**	3	1:1	0.2	23	95
4	**1d**	10	1:2	0.1	95	89

[a] Ratio substrate/enzyme, w/w. [b] Isolated yield.

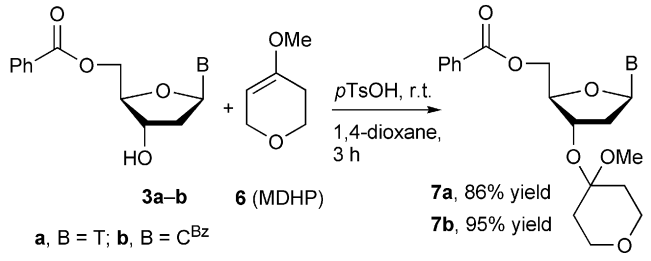
The tetrahydropyranylation of pyrimidine nucleoside derivatives **3a**,**b** was accomplished by conventional treatment with 3,4-dihydro-2*H*-pyran (DHP, **4**) in the presence of catalytic *p*-toluenesulfonic acid (Scheme 2). The reactions were carried out at room temperature in 1,4-dioxane, which proved to be the solvent of choice among the other organic solvents tested. After 3 h, the starting nucleosides had been completely transformed into the tetrahydropyranyl ethers **5a**,**b**, which were isolated in 95 and 80% yields, respectively. The ^{1}H NMR spectra show the presence of two diastereoisomers (1:1).



Scheme 2. Reaction of 5′-*O*-Bz-T and 5′-*O*-Bz-dC^{Bz} with DHP.

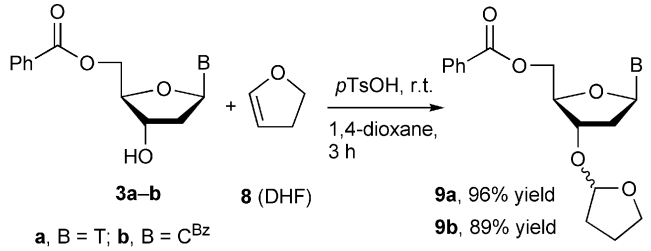
This procedure was also shown to be effective for the tetrahydropyranylation of **3a**,**b** with 4-methoxy-5,6-dihydro-2*H*-pyran (MDHP, **6**) with high yields of MTHP ethers **7a**,**b** being obtained (Scheme 3). 4-Methoxytetrahydropyran-4-yl ethers have the advantage that they generate no new

stereogenic centers. Recently, an efficient preparation of MDHP was reported which allows the wider use of MTHP protection.[17]



Scheme 3. Reaction of 5′-*O*-Bz-T and 5′-*O*-Bz-dC^{Bz} with MDHP.

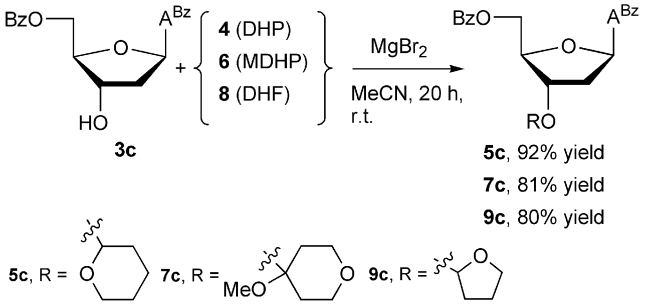
To develop a general and convenient procedure for the protection of the 3′-hydroxy group in nucleosides with an acetal, the reaction was explored with 2,3-dihydrofuran (DHF, **8**). Tetrahydrofuranylation proceeded well and THF ethers **9a**,**b** were isolated in excellent yields (Scheme 4).



Scheme 4. Reaction of 5′-*O*-Bz-T and 5′-*O*-Bz-dC^{Bz} with DHF.

Next we attempted the THP and THF protection of the purine nucleosides **3c**,**d**. The reaction of *N*-protected 5′-*O*-benzoyl-2′-deoxyadenosine and 5′-*O*-benzoyl-2′-deoxyguanosine derivatives with DHP in 1,4-dioxane with *p*-toluenesulfonic acid as catalyst did not yield the desired THP ethers. In the case of the adenosine derivative **3c**, cleavage of the glycosidic bond was observed, probably due to the acidic reaction media. For the guanosine derivative **3d**, a mixture of complex products was observed.

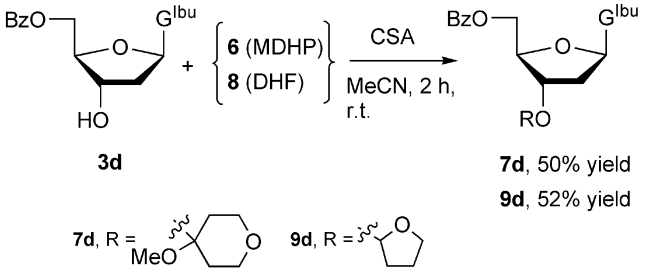
It has been shown that the tetrahydropyranylation of alcohols can be accomplished under neutral conditions using a catalytic amount of $MgBr_2$ with CH_2Cl_2 as solvent.[11] The reaction with **3c** in CH_2Cl_2 failed to proceed due to its poor solubility. Thus, the reaction was carried out with DHP in the presence of $MgBr_2$ and MeCN as solvent (Scheme 5). After 20 h at room temperature, 3′-*O*-THP derivative **5c** was isolated in 92% yield. Similarly, we successfully converted **3c** into the corresponding 3′-*O*-MTHP and 3′-*O*-THF ethers **7c** and **9c** under identical reaction conditions using the same catalyst. However, the reaction of a solution of 5′-*O*-benzoyl-N^2-isobutyryl-2′-deoxyguanosine (**3d**) in MeCN with 5 equiv. of DHP and $MgBr_2$ afforded undesired products.



Scheme 5. Reaction of 5′-*O*-Bz-dA^{Bz} with DHP, MDHP, and DHF.

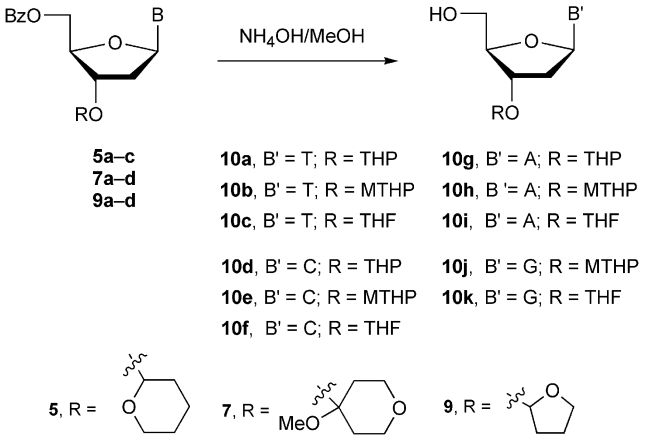
In the search for a suitable procedure for the installation of a 3′-*O*-acetal into guanosine derivative **3d**, we used DHF instead of DHP and *p*-toluenesulfonic acid as the catalyst. MeCN proved to be a more convenient solvent than 1,4-dioxane. These conditions provided the THF ether **9d** in 40% yield.

The use of camphorsulfonic acid (CSA) as the catalyst led to improved yields (Scheme 6). When **3d** was treated with MDHP or DHF in the presence of a catalytic amount of CSA at room temperature for 2 h, ethers **7d** and **9d** were isolated in 50–52% yields. However, treatment of **3d** with DHP led to the formation of several byproducts.



Scheme 6. Reaction of 5′-*O*-Bz-dG^{Ibu} with DHF and MDHP.

The 5′-*O*-benzoyl group was deprotected with ammonia in MeOH to afford the corresponding THP and THF ethers **10** as the exclusive products in high yields (Scheme 7). In addition to the 5′-*O*-benzoyl group, concomitant cleavage



Scheme 7. Synthesis of 3′-*O*-THP-, MTHP-, and THF-2′-deoxynucleosides.

of the base protecting group in cytidine, adenosine, and guanosine derivatives occurred. In the case of guanosine derivatives **7d** and **9d**, the reaction temperature was increased to 60 °C to drive the hydrolysis reaction to completion.

In view of the potential industrial applications, it should be noted that purification by flash chromatography of the 3′,5′-protected intermediates was not necessary, with the exception of the guanosine derivatives **7d** and **9d**, for which chromatographic purification was required. Compounds **5a**–**c**, **7a**–**c**, and **9a**–**c** were sufficiently pure to carry forward to the deprotection step without purification.

Large-Scale Studies

The industrial utility of this protocol was proven by the synthesis of 3′-*O*-tetrahydropyranylthymidine on a large scale. Thus, treatment of thymidine (10 g) with 5 equiv. of vinyl benzoate in the presence of CAL-B at 60 °C provided 5′-*O*-benzoylthymidine (**3a**) in the pure form and in 96% yield by precipitation from hexane. Nucleoside **3a** was subjected to tetrahydropyranylation with 3,4-dihydro-2*H*-pyran and *p*-toluenesulfonic acid as the catalyst, which cleanly allowed the conversion to the 5′-*O*-benzoyl-3′-*O*-THP derivative **5a**. Treatment of crude **5a** with NH_4OH/MeOH furnished 3′-*O*-(tetrahydropyranyl)thymidine (**10a**) in high purity and 80% overall yield.

Conclusions

An efficient and high yielding preparation of 3′-*O*-(tetrahydropyranyl)-, 3′-*O*-(4-methoxytetrahydropyranyl)-, and 3′-*O*-(tetrahydrofuranyl)-2′-deoxynucleosides has been described. The easy access to 3′-*O*-acetal-protected nucleosides will lead to the expeditious synthesis of 5′-triphosphates (dNTPs) required for PCR related applications.[5,22] The chemoenzymatic methodology detailed herein is a significant improvement over reported methods. A key step in the synthesis is the regioselective 5′-hydroxy protection of the 2′-deoxynucleosides catalyzed by *Candida antarctica* lipase B. Enzyme-catalyzed reactions are environmentally attractive due to their safe and cost-effective features relative to conventional chemistry-based methods using silyl or dimethoxytrityl reagents. The immobilized CAL-B used herein offers considerable advantages due to its high selectivity, stability, reusability, and ease of handling during large-scale operations.[21] Also, we found that tetrahydropyranylation and tetrahydrofuranylation can be achieved efficiently under mild reaction conditions and shorter reaction times. In addition, this strategy does not require solvents traditionally used in nucleoside chemistry such as pyridine or DMF thereby avoiding tedious reaction work-up. We believe this strategy will find use in the large-scale synthesis of 3′-protected nucleosides, which are needed for diagnostic[23] and therapeutic applications.

Experimental Section

General: *Candida antarctica* lipase B (CAL-B, Novozym 435, 7300 PLU/mg solid) was a gift from Novo Nordisk Co. All the enzymatic reactions were carried out in a temperature-controlled incubator shaker (Heidolph Unimax 2010) at 250 rpm and 60 °C. Melting points were taken on samples in open capillary tubes and are uncorrected. IR spectra were recorded with an Infrared FT spectrophotometer by using NaCl pellets. TLC was performed on silica gel 60 F_{254} plates (Merck), and column chromatography was carried out by using silica gel Merck 60 (230–240 mesh). NMR spectra were recorded with Bruker DPX-300 or NAV300 spectrometers in $CDCl_3$, [D_6]DMSO or [D_4]MeOH. APCI+ and ESI+ were used to record mass spectra (MS).

General Procedure for the Synthesis of 3a–d: A suspension of **1** (0.4 mmol), vinyl benzoate, and CAL-B in anhydrous THF under nitrogen was stirred at 60 °C and 250 rpm (orbital shaker) under the conditions and reaction times indicated in Table 1. The enzyme was filtered off and washed with CH_2Cl_2 and THF, and the solvents were then evaporated under vacuum. The residue was precipitated in hexane to afford, after filtration and washing with hexane, the 5′-*O*-benzoyl nucleosides **3** as solids. Excess vinyl benzoate was recovered by solvent evaporation under vacuum from the hexane mother liquors.

5′-*O*-Benzoylthymidine (3a): White solid, yield 128.8 mg, 93%. R_f (10% MeOH/CH_2Cl_2) = 0.7; m.p. 167–169 °C. $[\alpha]_D^{20}$ = –9.6 (*c* = 1.1, MeOH). IR (NaCl): $\tilde{\nu}$ = 3371, 3188, 1723, 1657 cm^{-1}. ^1H NMR ([D_6]DMSO, 300 MHz): δ = 1.57 (s, 3 H, Me), 2.20 (m, 2 H, 2′-H), 4.03 (m, 1 H, 4′-H), 4.37–4.55 (m, 3 H, 5′-H, 3′-H), 5.47 (d, $^3J_{HH}$ = 3.7 Hz, 1 H, OH), 6.19 (apparent t, $^3J_{HH}$ = 6.8 Hz, 1 H, 1′-H), 7.37 (s, 1 H, 6-H), 7.53 (m, 2 H, *m*-H), 7.67 (m, 1 H, *p*-H), 7.97 (apparent d, $^3J_{HH}$ = 8.3 Hz, 2 H, *o*-H), 11.3 (s, 1 H, NH) ppm. ^{13}C NMR ([D_6]DMSO, 75.5 MHz): δ = 11.8 (Me), 38.7 (C-2′), 64.3 (C-5′), 70.2 (C-3′), 83.6, 83.7 (C-1′, C-4′), 109.7 (C-5), 128.8, 129.1 (C_o, C_m), 129.3 (C_i), 133.5 (C_p), 135.6 (C-6), 150.3 (C-2), 163.6 (C-4), 165.5 (Ph-C=O) ppm. MS (ES^+): *m*/*z* (%) = 347 (10) [M + H]$^+$, 369 (45) [M + Na]$^+$.

***N*^{4},5′-*O*-Dibenzoyl-2′-deoxycytidine (3b):** White solid; yield 160.1 mg, 92%. R_f (10% MeOH/CH_2Cl_2) = 0.45; m.p. 190–192 °C. $[\alpha]_D^{20}$ = +68.1 (*c* = 1.1, DMSO). IR (NaCl): $\tilde{\nu}$ = 3393, 2936, 1705, 1698 cm^{-1}. ^1H NMR ([D_6]DMSO, 300 MHz): δ = 2.23 (m, 1 H, 2′-H), 2.40 (m, 1 H, 2′-H), 4.20 (m, 1 H, 4′-H), 4.37 (m, 1 H, 3′-H), 4.54 (m, 2 H, 5′-H), 5.52 (d, $^3J_{HH}$ = 4.3 Hz, 1 H, OH), 6.18 (apparent t, $^3J_{HH}$ = 6.1 Hz, 1 H, 1′-H), 7.29 (d, $^3J_{HH}$ = 6.8 Hz, 1 H, 5-H), 7.28–7.64 (m, 6 H, *m*-H, *p*-H), 7.97 (m, 4 H, *o*-H), 8.18 (d, $^3J_{HH}$ = 7.4 Hz, 1 H, 6-H), 11.24 (br. s, 1 H, NH) ppm. ^{13}C NMR ([D_6]DMSO, 75.5 MHz): δ = 40.1 (C-2′), 64.3 (C-5′), 69.9 (C-3′), 84.4, 86.4 (C-1′, C-4′), 96.2 (C-5), 128.4, 128.7, 129.1 (C_o, C_m), 129.3 (C_i), 132.7 (C_p), 133.1 (C_i), 133.5 (C_p), 144.7 (C-6), 154.2 (C-2), 162.9 (C-4), 165.5 (Ph-C=O), 167.3 (Ph-C=O) ppm. MS (ES^+): *m*/*z* (%) = 436 (35) [M + H]$^+$, 458 (15) [M + Na]$^+$.

***N*^{6},5′-*O*-Dibenzoyl-2′-deoxyadenosine (3c):** White solid; yield 174.5 mg, 95%. R_f (10% MeOH/CH_2Cl_2) = 0.5; m.p. 165–167 °C. $[\alpha]_D^{20}$ = –7.7 (*c* = 1.1, DMSO). IR (NaCl): $\tilde{\nu}$ = 3279, 3092, 1705, 1674 cm^{-1}. ^1H NMR ([D_6]DMSO, 300 MHz): δ = 2.47 (m, 1 H, 2′-H), 3.00 (m, 1 H, 2′-H), 4.18 (m, 1 H, 4′-H), 4.45–4.54 (m, 2 H, 5′-H), 4.68 (m, 1 H, 3′-H), 5.60 (d, $^3J_{HH}$ = 4.4 Hz, 1 H, OH), 6.50 (apparent t, $^3J_{HH}$ = 6.7 Hz, 1 H, 1′-H), 7.49 (m, 4 H, *m*-H), 7.63 (m, 2 H, *p*-H), 7.90 (apparent, $^3J_{HH}$ = 7.4 Hz, 2 H, *o*-H), 8.63 (s, 1 H, 8-H), 8.69 (s, 1 H, 2-H), 11.19 (s, 1 H, NH) ppm. ^{13}C NMR

([D$_6$]DMSO, 75.5 MHz): δ = 38.2 (C-2′), 64.3 (C-5′), 70.4 (C-3′), 83.6, 83.1 (C-1′, C-4′), 125.9 (C-5), 128.4, 128.7, 129.1 (C$_o$, C$_m$), 129.3 (C$_i$), 132.4 (C$_p$), 133.2 (C$_i$), 133.4 (C$_p$), 143.3 (C-8), 150.3 (C-6), 151.5 (C-2), 151.8 (C-4), 165.5 (Ph-C=O), 165.6 (Ph-C=O) ppm. MS (ES$^+$): *m*/*z* (%) = 460 (95) [M + H]$^+$, 482 (60) [M + Na]$^+$.

5′-*O*-Benzoyl-*N*^{2}-isobutyryl-2′-deoxyguanosine (3d): White solid; yield 157.1 mg, 89%. R_f (15% MeOH/CH$_2$Cl$_2$) = 0.6; m.p. 117–119 °C. $[a]_D^{20}$ = –18.3 (*c* = 1.0, DMSO). IR (NaCl): $\tilde{\nu}$ = 3351, 1721, 1684 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 1.07 (d, $^3J_{HH}$ = 6.9 Hz, 6 H, Me-Ibu), 2.36 (m, 1 H, 2′-H), 2.67 (m, 2 H, CH-Ibu + 2′-H), 4.12 (m, 1 H, 4′-H), 4.35–4.55 (m, 3 H, 2′-H, 5′-H), 6.25 (apparent t, $^3J_{HH}$ = 6.6 Hz, 1 H, 1′-H), 7.50 (m, 2 H, *m*-H), 7.66 (m, 1 H, *p*-H), 7.92 (d, $^3J_{HH}$ = 7.2 Hz, 2 H, *o*-H), 8.03 (s, 1 H, 8-H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75.5 MHz): δ = 18.9 (Me), 34.8 (CH-Ibu), 38.8 (C-2′), 64.5 (C-5′), 70.4 (C-3′), 82.9 (C-1′), 84.1 (C-4′), 120.4 (C-5), 128.4, 129.2 (C$_o$, C$_m$), 129.4 (C$_i$), 133.5 (C$_p$), 137.5 (C-8), 148.1 (C-2), 148.4 (C-4), 154.8 (C-6), 165.6 (Ph-C=O), 180.1 (Ibu-C=O) ppm. MS (ES$^+$): *m*/*z* (%) = 442 (20) [M + H]$^+$, 464 (100) [M + Na]$^+$.

General Procedure for the Synthesis of 5a,b, 7a,b, and 9a,b: *p*-Toluenesulfonic acid monohydrate (0.1 mmol) was added to a solution of 5′-*O*-benzoyl-protected thymidine or *N*^{4}-benzoyl-2′-deoxycytidine (0.2 mmol) in anhydrous 1,4-dioxane (1.3 mL) followed by 3,4-dihydro-2*H*-pyran, 4-methoxy-5,6-dihydro-2*H*-pyran or 2,3-dihydrofuran (1 mmol). After 3 h, the reaction mixture was poured into a saturated NaHCO$_3$ solution and extracted with CH$_2$Cl$_2$. The combined organic fractions were dried (Na$_2$SO$_4$) and concentrated under vacuum. The resulting crude was purified by flash chromatography using 50% hexane/EtOAc for **5a**, **7a**, and **9a** and 33% hexane/EtOAc for **5b**, **7b**, and **9b**.

5′-*O*-Benzoyl-3′-*O*-(tetrahydropyranyl)thymidine (5a): White hygroscopic solid (two diastereoisomers); yield 81.8 mg, 95%. R_f (5% MeOH/CH$_2$Cl$_2$) = 0.50. IR (NaCl): $\tilde{\nu}$ = 3431, 3055, 2944, 1703, 1623, 1260 cm^{-1}. ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 1.43–1.59 (m, 4 H, 4′′-H), 1.63 (d, $|^4J_{HH}|$ = 1.3 Hz, 3 H, Me), 1.65 (d, $|^4J_{HH}|$ = 1.1 Hz, 3 H, Me), 1.66–1.86 (m, 8 H, 3′′-H, 5′′-H), 2.08 (m, 1 H, 2′-H), 2.20 (m, 1 H, 2′-H), 2.45 (m, 1 H, 2′-H), 2.59 (m, 1 H, 2′-H), 3.52 (m, 2 H, 6′′-H), 3.82 (m, 2 H, 6′′-H), 4.30–4.74 (m, 10 H, 2′′-H, 3′-H, 4′-H, 5′-H), 6.30 (apparent q, $^3J_{HH}$ = 6.8 Hz, 2 H, 1′-H), 7.21 (d, $|^4J_{HH}|$ = 1.1 Hz, 1 H, 6-H), 7.24 (d, $|^4J_{HH}|$ = 1.3 Hz, 1 H, 6-H), 7.45 (t, $^3J_{HH}$ = 7.2 Hz, 4 H, *m*-H), 7.59 (t, $^3J_{HH}$ = 7.2 Hz, 2 H, *p*-H), 8.02 (dd, $^3J_{HH}$ = 7.2, 1.2 Hz, 4 H, *o*-H), 9.37 (s, 2 H, NH) ppm. ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ = 12.1 (Me), 19.1, 19.2, 25.1, 30.5 (C-3′′, C-4′′, C-5′′), 37.9 (C-2′), 39.0 (C-2′), 62.6 (C-6′′), 64.2 (C-5′), 75.4 (C-3′), 76.2 (C-3′), 82.1 (C-4′), 82.9 (C-4′), 84.8 (C-1′), 85.1 (C-1′), 97.8 (C-2′′), 98.5 (C-2′′), 111.2 (C-5), 128.6, 129.4 (C$_o$, C$_m$), 129.4 (C$_i$), 133.4 (C$_p$), 134.6 (C-6), 134.8 (C-6), 150.3 (C-2), 163.7 (C-4), 166.0 (Ph-C=O) ppm. MS (ES$^+$): *m*/*z* (%) = 431 (20) [M + H]$^+$, 453 (90) [M + Na]$^+$.

***N*^{4},5′-*O*-Dibenzoyl-3′-*O*-(tetrahydropyranyl)-2′-deoxycytidine (5b):** White hygroscopic solid. (two diastereoisomers); yield 83.1 mg, 80%. R_f (5% MeOH/CH$_2$Cl$_2$) = 0.48. IR (NaCl): $\tilde{\nu}$ = 3411, 3072, 2956, 1718, 1698, 1623, 1481, 1264 cm^{-1}. ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 1.47–1.80 (m, 12 H, 3′′-H, 4′′-H, 5′′-H), 2.13 (m, 1 H, 2′-H), 2.30 (m, 1 H, 2′-H), 2.79 (m, 2 H, 2′-H), 3.49 (m, 2 H, 6′′-H), 3.73 (m, 2 H, 6′′-H), 4.33–4.69 (m, 10 H, 3′-H, 4′-H, 5′-H, 2′′-H), 6.22 (apparent q, $^3J_{HH}$ = 6.2 Hz, 2 H, 1′-H), 7.39–7.68 (m, 14 H, 5-H, *m*-H, *p*-H), 7.83–7.89 (m, 8 H, *o*-H), 8.11 (d, $^3J_{HH}$ = 7.5 Hz, 1 H, 6-H), 8.12 (d, $^3J_{HH}$ = 7.4 Hz, 1 H, 6-H), 9.01 (br. s, 2 H, NH) ppm. ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ = 18.8, 19.2, 25.0, 30.2, 30.3 (C-3′′, C-4′′, C-5′′), 38.8 (C-2′), 40.1 (C-2′), 62.2, 62.5, 63.6, 63.8 (C-5′, C-6′′), 74.6 (C-3′), 75.3 (C-3′), 82.6 (C-4′), 83.5 (C-4′), 87.3 (C-1′), 96.9, 97.5, 98.5 (C-5, C-2′′), 127.4, 128.4, 128.5, 128.7, 129.0, 129.1, 129.2, 129.3 (C$_o$, C$_m$, C$_i$), 132.8 (C$_i$), 132.4 (C$_p$), 143.5 (C-6), 154.5 (C-2), 162.1 (C-4), 165.9 (Ph-C=O) ppm. MS (ES$^+$): *m*/*z* (%) = 520 (10) [M + H]$^+$, 542 (75) [M + Na]$^+$.

5′-*O*-Benzoyl-3′-*O*-(4-methoxytetrahydropyranyl)thymidine (7a): White solid; yield 79.2 mg, 86%. R_f (5% MeOH/CH$_2$Cl$_2$) = 0.47; m.p. 84–86 °C. IR (NaCl): $\tilde{\nu}$ = 3413, 3059, 2954, 1698, 1606, 1461, 1265 cm^{-1}. ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 1.63 (s, 3 H, Me), 1.77 (m, 4 H, 3′′-H), 2.19 (m, 1 H, 2′-H), 2.43 (m, 1 H, 2′-H), 3.20 (s, 3 H, OMe), 3.55–3.81 (m, 4 H, 2′′-H), 4.29 (apparent q, $^3J_{HH}$ = 3.5 Hz, 1 H, 4′-H), 4.43–4.7 (m, 3 H, 3′-H, 5′-H), 6.28 (apparent t, $^3J_{HH}$ = 6.5 Hz, 1 H, 1′-H), 7.21 (d, $|^4J_{HH}|$ = 1.1 Hz, 1 H, 6-H), 7.39–7.47 (m, 2 H, *m*-H), 7.55–7.61 (m, 1 H, *p*-H), 8.01 (apparent d, $^3J_{HH}$ = 7.2 Hz, 2 H, *o*-H), 9.6 (s, 1 H, NH) ppm. ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ = 12.1 (Me), 34.2 (C-3′′), 34.7 (C-3′′), 39.6 (C-2′), 48.1 (OMe), 63.7, 64.6 (C-2′′, C-5′), 69.1 (C-3′), 83.0 (C-4′), 84.9 (C-1′), 99.1 (C-4′′), 111.1 (C-5), 128.5, 129.2 (C$_o$, C$_m$), 129.3 (C$_i$), 133.4, 134.6 (C$_p$, C-6), 150.3 (C-2), 163.7 (C-4), 165.9 (Ph-C=O) ppm. MS (ES$^+$): *m*/*z* (%) = 483 (90) [M + Na]$^+$.

***N*^{4},5′-*O*-Dibenzoyl-3′-*O*-(4-methoxytetrahydropyranyl)-2′-deoxycytidine (7b):** White solid; yield 104.4 mg, 95%. R_f (5% MeOH/CH$_2$Cl$_2$) = 0.39; m.p. 79–81 °C. IR (NaCl): $\tilde{\nu}$ = 3415, 3060, 2948, 1723, 1697, 1621, 1484, 1271 cm^{-1}. ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 1.74–1.89 (m, 4 H, 3′′-H), 2.22 (m, 1 H, 2′-H), 2.72 (m, 1 H, 2′-H), 3.17 (s, 3 H, OMe), 3.58–3.75 (m, 4 H, 2′′-H), 4.40 (apparent q, $^3J_{HH}$ = 3.7 Hz, 1 H, 4′-H), 4.51–4.67 (m, 3 H, 3′-H, 5′-H), 6.22 (apparent t, $^3J_{HH}$ = 5.9 Hz, 1 H, 1′-H), 7.39–7.61 (m, 7 H, *m*-H, *p*-H, 5-H), 7.87 (apparent d, $^3J_{HH}$ = 7.2 Hz, 2 H, *o*-H), 7.96 (apparent d, $^3J_{HH}$ = 7.0 Hz, 2 H, *o*-H), 8.12 (d, $^3J_{HH}$ = 7.4 Hz, 1 H, 6-H), 8.97 (br. s, 1 H, NH) ppm. ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ = 34.2 (C-3′′), 34.7 (C-3′′), 40.7 (C-2′), 48.1 (OMe), 63.3 (C-5′), 64.6 (C-2′′), 68.3 (C-3′), 83.6 (C-4′), 87.3 (C-1′), 96.4 (C-5), 99.6 (C-4′′), 127.5, 128.6, 128.7, 129.1, 129.3 (C$_o$, C$_m$, C$_i$), 132.8 (C$_i$), 132.9 (C$_p$), 133.5 (C$_p$), 143.1 (C-6), 154.5 (C-2), 162.1 (C-4), 165.6 (Ph-C=O) ppm. MS (ES$^+$): *m*/*z* (%) = 550 (50) [M + H]$^+$, 572 (100) [M + Na]$^+$.

5′-*O*-Benzoyl-3′-*O*-(tetrahydrofuranyl)thymidine (9a): White hygroscopic solid (two diastereoisomers); yield 79.9 mg, 96%. R_f (5% MeOH/CH$_2$Cl$_2$) = 0.46. IR (NaCl): $\tilde{\nu}$ = 3316, 2938, 1718, 1664, 1509, 1263 cm^{-1}. ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 1.60 (d, $|^4J_{HH}|$ = 1.1 Hz, 3 H, Me), 1.62 (d, $|^4J_{HH}|$ = 1.1 Hz, 3 H, Me), 1.78–2.23 (m, 10 H, 2′-H, 3′′-H, 4′′-H), 2.45 (m, 2 H, 2′-H), 3.83 (m, 4 H, 5′′-H), 4.21–4.67 (m, 8 H, 3′-H, 4′-H, 5′-H), 5.20 (m, 2 H, 2′′-H), 6.26 (m, 2 H, 1′-H), 7.17 (d, $|^4J_{HH}|$ = 1.1 Hz, 1 H, 6-H), 7.20 (d, $|^4J_{HH}|$ = 1.1 Hz, 1 H, 6-H), 7.42 (m, 4 H, *m*-H), 7.56 (m, 2 H, *p*-H), 7.98 (d, $^3J_{HH}$ = 7.3 Hz, 2 H, *o*-H), 7.99 (d, $^3J_{HH}$ = 7.3 Hz, 2 H, *o*-H), 9.45 (s, 2 H, NH) ppm. ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ = 12.0 (Me), 23.2, 23.3, 32.2, 32.3 (C-3′′, C-4′′), 37.9 (C-2′), 39.3 (C-2′), 63.9, 64.0, 67.1 (C-5′, C-5′′), 75.5 (C-3′), 76.1 (C-3′), 81.9, 83.1, 84.6, 84.7 (C-1′, C-4′), 103.2 (C-2′′), 103.9 (C-2′′), 111.0 (C-5), 111.1 (C-5), 128.5, 129.3 (C$_o$, C$_m$), 129.4 (C$_i$), 133.3, 133.4, 134.6, 134.7 (C$_p$, C-6), 150.3 (C-2), 163.6 (C-4), 165.9 (Ph-C=O) ppm. MS (ES$^+$): *m*/*z* (%) = 417 (10) [M + H]$^+$, 439 (85) [M + Na]$^+$.

***N*^{4},5′-*O*-Dibenzoyl-3′-*O*-(tetrahydrofuranyl)-2′-deoxycytidine (9b):** White hygroscopic solid (two diastereoisomers); yield 89.9 mg, 89%. R_f (5% MeOH/CH$_2$Cl$_2$) = 0.38. IR (NaCl): $\tilde{\nu}$ = 3413, 3065, 2955, 1720, 1698, 1661, 1487, 1268 cm^{-1}. ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 1.81–2.17 (m, 9 H, 2′-H, 3′′-H, 4′′-H), 2.33 (m, 1 H, 2′-H), 2.77 (m, 2 H, 2′-H), 3.89 (m, 4 H, 5′′-H), 4.28–4.46 (m,

4 H, 3′-H, 4′-H), 4.66 (m, 4 H, 5′-H), 5.19 (m, 2 H, 2′′-H), 6.24 (apparent t, $^3J_{HH}$ = 5.5 Hz, 2 H, 1′-H), 7.45–7.62 (m, 14 H, *m*-H, *p*-H, 5-H), 7.92–8.04 (m, 8 H, *o*-H), 8.15 (d, $^3J_{HH}$ = 7.5 Hz, 2 H, 6-H), 9.02 (br. s, 2 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 23.2, 23.3, 32.2 (C-3′′, C-4′′), 39.1 (C-2′), 40.6 (C-2′), 63.5 (C-5′), 63.8 (C-5′), 67.3 (C-5′′), 74.8 (C-3′), 75.1 (C-3′), 82.7 (C-4′), 83.9 (C-4′), 87.3 (C-1′), 87.4 (C-1′), 96.4 (C-5), 103.1 (C-2′′), 104.2 (C-2′′), 127.6, 128.6, 128.7, 128.9 (C_o, C_m), 129.4 (C_i), 129.5 (C_i), 132.8, 133.6 (C_p), 144.1 (C-6), 154.5 (C-2), 161.9 (C-4), 166.1 (Ph-C=O) ppm. MS (ES$^+$): *m*/*z* (%) = 506 (10) [M + H]$^+$, 528 (100) [M + Na]$^+$.

General Procedure for the Synthesis of 5c, 7c, and 9c: 3,4-Dihydro-2*H*-pyran, 4-methoxy-5,6-dihydro-2*H*-pyran, or 2,3-dihydrofuran (1.1 mmol) and catalytic amounts (8–10 mol-%) of $MgBr_2$ were added to a solution of N^6,5′-*O*-dibenzoyl-2′-deoxyadenosine (**3c**; 0.22 mmol) in anhydrous acetonitrile (4.4 mL). The solution was stirred for 20 h at room temperature. After completion of the reaction, the solvent was evaporated and the crude was purified by flash chromatography using 2% MeOH/CH_2Cl_2.

***N*^{6},5′-*O*-Dibenzoyl-3′-*O*-(tetrahydropyranyl)-2′-deoxyadenosine (5c):** White hygroscopic solid (two diastereoisomers); yield 110.1 mg, 92%. R_f (2% MeOH/CH_2Cl_2) = 0.41. IR (NaCl): $\tilde{\nu}$ = 3409, 3058, 2947, 1717, 1611 cm^{-1}. ^{1}H NMR ([D$_4$]MeOH, 300 MHz): δ = 1.62–2.11 (m, 12 H, 3′′-H, 4′′-H, 5′′-H), 2.84 (m, 2 H, 2′-H), 3.25 (m, 2 H, 2′-H), 3.66 (m, 2 H, 6′′-H), 4.09 (m, 2 H, 6′′-H), 4.55–4.86 (m, 6 H, 4′-H, 5′-H), 4.95 (m, 4 H, 2′′-H, 3′-H), 6.45 (apparent q, $^3J_{HH}$ = 6.6 Hz, 2 H, 1′-H), 7.56 (t, $^3J_{HH}$ = 7.9 Hz, 4 H, *m*-H), 7.73 (m, 8 H, *m*-H, *p*-H), 8.07 (d, $^3J_{HH}$ = 8.6 Hz, 4 H, *o*-H), 8.22 (d, $^3J_{HH}$ = 8.6 Hz, 4 H, *o*-H), 8.63 (s, 2-H or 8-H), 8.77 (s, 2-H or 8-H) ppm. ^{13}C NMR ([D$_4$]MeOH, 75.5 MHz): δ = 20.7, 22.1, 26.7, 32.1, 33.7 (C-3′′, C-4′′, C-5′′), 38.0 (C-2′), 39.3 (C-2′), 64.2, 65.4, 65.6 (C-5′, C-6′′), 78.0 (C-3′), 78.6 (C-3′), 84.3 (C-4′), 85.0 (C-4′), 86.7 (C-1′), 86.9 (C-1′), 100.0 (C-2′′), 100.3 (C-2′′), 125.4 (C-5), 129.6, 129.8, 129.9, 130.7 (C_o, C_m), 131.1 (C_i), 131.2 (C_i), 134.1 (C_i), 134.6 (C_p), 135.2 (C_p), 144.6 (C-8), 151.3 (C-6), 153.1 (C-2), 153.3 (C-4), 167.7 (Ph-C=O), 168.0 (Ph-C=O) ppm. MS (ES$^+$): *m*/*z* (%) = 544 (90) [M + H]$^+$. HRMS (EI): calcd. for $C_{29}H_{30}N_5O_6$ [M]$^+$ 544.2188; found 544.2191.

***N*^{6},5′-*O*-Dibenzoyl-3′-*O*-(4-methoxytetrahydropyranyl)-2′-deoxyadenosine (7c):** White solid; yield 102.2 mg, 81%. R_f (2% MeOH/CH_2Cl_2) = 0.37; m.p. 107–110 °C. IR (NaCl): $\tilde{\nu}$ = 3439, 3056, 2963, 1708, 1634 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.85 (m, 4 H, 3′′-H), 2.61 (m, 1 H, 2′-H), 3.02 (m, 1 H, 2′-H), 3.23 (s, 3 H, OMe), 3.59 (m, 2 H, 2′′-H), 3.72 (m, 2 H, 2′′-H), 4.44 (m, 2 H, 4′-H, 5′-H), 4.66 (dd, $|^2J_{HH}|$ = 11.8, $^3J_{HH}$ = 3.7 Hz, 1 H, 5′-H), 4.87 (m, 1 H, 3′-H), 6.44 (apparent t, $^3J_{HH}$ = 6.4 Hz, 1 H, 1′-H), 7.36–7.58 (m, 6 H, *m*-H, *p*-H), 7.94 (m, 4 H, *o*-H), 8.17 (s, 1 H, 2-H or 8-H), 8.71 (s, 1 H, 2-H or 8-H) ppm. ^{13}C NMR ([D$_4$]MeOH, 75.5 MHz): δ = 35.8 (C-3′′), 36.4 (C-3′′), 39.5 (C-2′), 48.9 (OMe), 65.0 (C-5′), 66.2 (C-2′′), 71.4 (C-3′), 85.1 (C-4′), 86.9 (C-1′), 99.6 (C-4′′), 125.5 (C-5), 129.6, 129.8, 130.7 (C_o, C_m), 131.1 (C_i), 134.1 (C_p), 134.7 (C_p), 135.2 (C_i), 145.1 (C-8), 151.3 (C-6), 153.3 (C-2), 153.4 (C-4), 167.7 (Ph-C=O), 168.1 (Ph-C=O) ppm. MS (ES$^+$): *m*/*z* (%) = 574 (100) [M + H]$^+$. HRMS (EI): calcd. for $C_{30}H_{32}N_5O_7$ [M]$^+$ 574.2305; found 574.2296.

***N*^{6},5′-*O*-Dibenzoyl-3′-*O*-(tetrahydrofuranyl)-2′-deoxyadenosine (9c):** White hygroscopic solid (two diastereoisomers); yield 93.1 mg, 80%. R_f (2% MeOH/CH_2Cl_2) = 0.34. IR (NaCl): $\tilde{\nu}$ = 3299, 3056, 1710, 1674 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.81–2.06 (m, 8 H, 3′′-H, 4′′-H), 2.65 (m, 2 H, 2′-H), 2.93 (m, 2 H, 2′-H), 3.88 (m, 4 H, 5′′-H), 4.36–4.70 (m, 8 H, 3′-H, 4′-H, 5′-H), 5.26 (m, 2 H, 2′′-H), 6.42 (m, 2 H, 1′-H), 7.36–7.58 (m, 12 H, *m*-H, *p*-H), 7.96 (m, 8 H, *o*-H), 8.15 (s, 1 H, 2-H or 8-H), 8.16 (s, 1 H, 2-H or 8-H), 8.70 (s, 1 H, 2-H or 8-H), 8.71 (s, 1 H, 2-H or 8-H) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 23.2, 23.3, 32.5 (C-3′′, C-4′′), 37.9 (C-2′), 39.0 (C-2′), 64.0, 64.1. 67.3 (C-5′′, C-5′), 76.1 (C-3′), 76.4 (C-3′), 82.6, 83.8, 84.8, 84.9 (C-1′, C-4′), 103.5 (C-2′′), 104.1 (C-2′′), 123.4 (C-5), 123.5 (C-5), 127.8, 128.8, 128.7, 129.1, 129.3 (C_o, C_m), 129.5 (C_i), 133.1 (C_p), 133.2 (C_p), 133.4 (C_i), 141.3 (C-8), 141.4 (C-8), 149.5 (C-6), 151.3 (C-2), 151.4 (C-4), 165.1 (Ph-C=O), 166.0 (Ph-C=O) ppm. MS (ES$^+$): *m*/*z* (%) = 530 (100) [M + H]$^+$. HRMS (EI): calcd. for $C_{28}H_{28}N_5O_6$ [M]$^+$ 530.2041; found 530.2034.

General Procedure for the Synthesis of 7d and 9d: 5,6-Dihydro-4-methoxy-2*H*-pyran or 2,3-dihydrofuran (1.15 mmol) and camphorsulfonic acid (0.12 mmol) were added to a solution of 5′-*O*-benzoyl-N^2-isobutyryl-2′-deoxyguanosine (**3d**; 0.23 mmol) in anhydrous 1,4-dioxane (2.3 mL). After 2 h, the solvent was evaporated and the crude was purified by flash chromatography using 2% MeOH/CH_2Cl_2.

5′-*O*-Benzoyl-*N*^{2}-isobutyryl-3′-*O*-(4-methoxytetrahydropyranyl)-2′-deoxyguanosine (7d): White solid; yield 63.9 mg, 50%. R_f (2% MeOH/CH_2Cl_2) = 0.35; m.p. 111–112 °C. IR (NaCl): $\tilde{\nu}$ = 3427, 2930, 1721, 1683 cm^{-1}. ^{1}H NMR ([D$_4$]MeOH, 300 MHz): δ = 1.39 (dd, $^3J_{HH}$ = 6.8, 1.8 Hz, 6 H, Me-Ibu), 1.99 (m, 4 H, 3′′-H), 2.72 (m, 1 H, CH-Ibu), 2.90 (m, 1 H, 2′-H), 3.06 (m, 1 H, 2′-H), 3.41 (s, 3 H, OMe), 3.74–3.93 (m, 4 H, 2′′-H), 4.55 (m, 1 H, 4′-H), 4.74 (m, 2 H, 5′-H), 4.94 (m, 1 H, 3′-H), 6.49 (apparent t, $^3J_{HH}$ = 6.4 Hz, 1 H, 1′-H), 7.61 (t, $^3J_{HH}$ = 7.8 Hz, 2 H, *m*-H), 7.75 (t, $^3J_{HH}$ = 7.4 Hz, 1 H, *p*-H), 8.09 (d, $^3J_{HH}$ = 7.2 Hz, 2 H, *o*-H), 8.25 (s, 1 H, 8-H) ppm. ^{13}C NMR ([D$_4$]MeOH, 75.5 MHz): δ = 19.6 (Me), 35.8 (C-3′′), 36.3 (C-3′′), 37.2 (CH-Ibu), 40.1 (C-2′), 48.8 (OMe), 65.5 (C-5′), 66.1 (C-2′′), 66.2 (C-2′′), 71.8 (C-3′), 85.3, 86.4 (C-4′, C-1′), 122.1 (C-5), 129.9, 130.8 (C_o, C_m), 131.1 (C_i), 134.8 (C_p), 139.5 (C-8), 148.5 (C-2), 149.8 (C-4), 157.6 (C-6), 167.8 (Ph-C=O), 181.9 (Ibu-C=O) ppm. MS (ES$^+$): *m*/*z* (%) = 556 (100) [M + H]$^+$. HRMS (EI): calcd. for $C_{27}H_{34}N_5O_8$ [M]$^+$ 556.2386; found 556.2402.

5′-*O*-Benzoyl-*N*^{2}-isobutyryl-3′-*O*-(tetrahydrofuranyl)-2′-deoxyguanosine (9d): White hygroscopic solid (two diastereoisomers); yield 61.2 mg, 52%. R_f (2% MeOH/CH_2Cl_2) = 0.33. IR (NaCl): $\tilde{\nu}$ = 3429, 1715, 1683 cm^{-1}. ^{1}H NMR ([D$_4$]MeOH, 300 MHz): δ = 1.40 (d, $^3J_{HH}$ = 6.8 Hz, 6 H, Me-Ibu), 1.42 (d, $^3J_{HH}$ = 6.8 Hz, 6 H, Me-Ibu), 2.16 (m, 8 H, 3′′-H, 4′′-H), 2.79 (m, 2 H, CH-Ibu), 2.91 (m, 2 H, 2′-H), 3.11 (m, 2 H, 2′-H), 4.08 (m, 4 H, 5′′-H), 4.54 (m, 2 H, 4′-H), 4.79 (m, 6 H, 3′-H, 5′-H), 5.53 (m, 2 H, 2′′-H), 6.49 (apparent t, $^3J_{HH}$ = 7.5 Hz, 2 H, 1′-H), 7.63 (m, 4 H, *m*-H), 7.78 (m, 2 H, *p*-H), 8.11 (m, 4 H, *o*-H), 8.25 (s, 2 H, 8-H) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 18.8 (Me), 18.9 (Me), 23.2, 23.3, 32.2, 33.3 (C-3′′, C-4′′), 35.9 (CH-Ibu), 36.8 (C-2′), 38.3 (C-2′), 63.8, 67.1 (C-5′′, C-5′), 75.6 (C-3′), 76.7 (C-3′), 82.1, 83.2, 85.0, 85.1 (C-1′, C-4′), 103.1 (C-2′′), 103.7 (C-2′′), 121.7 (C-5), 128.3, 128.4, 129.2 (C_o, C_m), 129.3 (C_i), 133.2 (C_p), 133.3 (C_p), 137.9 (C-8), 147.5 (C-2), 147.7 (C-4), 155.8 (C-6), 166.5 (Ph-C=O), 166.6 (Ph-C=O), 179.1 (Ibu-C=O) ppm. MS (ES$^+$): *m*/*z* (%) = 512 (50) [M + H]$^+$. HRMS (EI): calcd. for $C_{25}H_{30}N_5O_7$ [M]$^+$ 512.2155; found 512.2140.

General Procedure for the Synthesis of 10: Compounds **5a**–**c**, **7a**–**d**, and **9a**–**d** (0.27 mmol) were each treated with NH_4OH/MeOH (5.4 mL, 1:1, v/v) and the solutions were stirred overnight at room temperature (at 60 °C for **7d** and **9d**). The solvents were evaporated and the crude products were purified by flash chromatography using 4% MeOH/CH_2Cl_2 (10% MeOH/CH_2Cl_2 for **10d**–**f**).

Large-Scale Preparation of 3′-*O*-(Tetrahydropyranyl)thymidine (10a): A suspension of thymidine (10 g, 0.04 mol), vinyl benzoate (29 mL, 0.21 mol), and CAL-B (10 g) in anhydrous THF (200 mL) was stirred under nitrogen at 250 rpm and 60 °C for 116 h. The enzyme was filtered off and washed with CH_2Cl_2 and THF. The solvents were then evaporated under vacuum. The residue was precipitated in hexane to afford after filtration 5′-*O*-benzoylthymidine (**3a**) as a white solid. 3,4-Dihydro-2*H*-pyran (18 mL, 0.19 mol) and *p*TsOH (3.8 g, 0.02 mol) were added to a solution of **3a** in anhydrous 1,4-dioxane (266 mL) and the reaction was stirred at room temperature for 3 h. Next the mixture was poured into a saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic fractions were dried (Na_2SO_4) and concentrated under vacuum. The crude material was dissolved in NH_4OH/MeOH (800 mL, 1:1, v/v) and the mixture was stirred overnight at room temperature. The solvents were evaporated and the residue purified by flash chromatography using 2% MeOH/CH_2Cl_2 to afford 10.5 g of **10a** as a white hygroscopic solid (80% yield).

3′-*O*-(Tetrahydropyranyl)thymidine (10a): White hygroscopic solid (two diastereoisomers); yield 74.1 mg, 84%. R_f (5% MeOH/CH_2Cl_2) = 0.37. IR (NaCl): $\tilde{\nu}$ = 3433, 3057, 2948, 1691, 1260 cm^{-1}. ^1H NMR ([D$_4$]MeOH, 300 MHz): δ = 1.71–1.85 (m, 8 H, 4′′-H, 5′′-H), 1.89–2.04 (m, 4 H, 3′′-H), 2.06 (s, 6 H, Me), 2.31–2.67 (m, 4 H, 2′-H), 3.73 (m, 2 H, 6′′-H), 3.87–4.09 (m, 6 H, 5′′-H, 6′′-H), 4.02 (apparent q, $^3J_{HH}$ = 3.4 Hz, 1 H, 4′-H), 4.28 (apparent q, $^3J_{HH}$ = 3.2 Hz, 1 H, 4′-H), 4.61 (m, 1 H, 3′-H), 4.67 (m, 1 H, 3′-H), 4.94 (m, 2 H, 2′′-H), 6.42 (apparent q, $^3J_{HH}$ = 7.4 Hz, 2 H, 1′-H), 7.97 (d, $|^4J_{HH}|$ = 1.2 Hz, 1 H, 6-H), 7.98 (d, $|^4J_{HH}|$ = 1.1 Hz, 1 H, 6-H) ppm. ^{13}C NMR ([D$_4$]MeOH, 75.5 MHz): δ = 12.9 (Me), 21.0, 21.1, 26.9, 32.4 (C-4′′, C-5′′, C-3′′), 38.9 (C-2′), 40.1 (C-2′), 63.3 (C-5′), 63.5 (C-5′), 64.2 (C-6′′), 77.8 (C-3′), 78.6 (C-3′), 86.6, 86.8, 87.1, 87.7 (C-1′, C-4′), 99.6 (C-2′), 100.3 (C-2′), 112.0 (C-5), 112.1 (C-5), 138. 5 (C-6), 152.8 (C-2), 166.8 (C-4) ppm. MS (ES$^+$): *m*/*z* (%) = 349 (100) [M + Na]$^+$. HRMS (EI): calcd. for $C_{15}H_{22}N_2NaO_6$ [M + Na]$^+$ 349.1368; found 349.1370.

3′-*O*-(4-Methoxytetrahydropyranyl)thymidine (10b): White solid; yield 82.7 mg, 86%. R_f (5% MeOH/CH_2Cl_2) = 0.35; m.p. 128–130 °C. IR (NaCl): $\tilde{\nu}$ = 3434, 3057, 2967, 1691, 1471, 1260 cm^{-1}. ^1H NMR ([D$_4$]MeOH, 300 MHz): δ = 1.91–2.06 (m, 4 H, 3′′-H), 2.07 (d, $|^4J_{HH}|$ = 1.1 Hz, 3 H, Me), 2.36–2.55 (m, 2 H, 2′-H), 3.43 (s, 3 H, OMe), 3.76–4.02 (m, 6 H, 5′-H, 2′′-H), 4.21 (apparent q, $^3J_{HH}$ = 3.4 Hz, 1 H, 4′-H), 4.77 (m, 1 H, 3′-H), 6.43 (apparent t, $^3J_{HH}$ = 6.2 Hz, 1 H, 1′-H), 7.97 (d, $|^4J_{HH}|$ = 1.1 Hz, 1 H, 6-H) ppm. ^{13}C NMR ([D$_4$]MeOH, 75.5 MHz): δ = 12.4 (Me), 35.6 (C-3′′), 36.1 (C-3′′), 40.3 (C-2′), 48.4 (OMe), 62.6, 65.9 (C-2′′, C-5′), 70.8 (C-3′), 86.3, 87.6 (C-1′, C-4′), 100.1 (C-4′′), 111.6 (C-5), 138.1 (C-6), 152.3 (C-2), 166.3 (C-4) ppm. MS (ES$^+$): *m*/*z* (%) = 379 (100) [M + Na]$^+$. HRMS (EI): calcd. for $C_{16}H_{24}N_2NaO_7$ [M + Na]$^+$ 379.1488; found 379.1476.

3′-*O*-(Tetrahydrofuranyl)thymidine (10c): White hygroscopic solid (two diastereoisomers); yield 90.2 mg, 81%. R_f (5% MeOH/CH_2Cl_2) = 0.32. IR (NaCl): $\tilde{\nu}$ = 3369, 3059, 2949, 1711, 1664, 1270 cm^{-1}. ^1H NMR ([D$_4$]MeOH, 300 MHz): δ = 2.05 (d, $|^4J_{HH}|$ = 1.0 Hz, 6 H, Me) 2.06–2.94 (m, 8 H, 3′′-H, 4′′-H), 2.31–2.55 (m, 4 H, 2′-H), 3.87–4.21 (m, 10 H, 4′-H, 5′-H, 5′′-H), 4.55 (m, 2 H, 3′-H), 5.45 (m, 2 H, 2′′-H), 6.39 (apparent t, $^3J_{HH}$ = 6.6 Hz, 2 H, 1′-H), 7.98 (d, $|^4J_{HH}|$ = 1.0 Hz, 1 H, 6-H), 8.01 (d, $|^4J_{HH}|$ = 1.0 Hz, 1 H, 6-H) ppm. ^{13}C NMR ([D$_4$]MeOH, 75.5 MHz): δ = 12.4 (Me), 24.3, 33.5 (C-3′′, C-4′′), 38.7 (C-2′), 39.9 (C-2′), 62.6, 62.8, 68.0 (C-5′, C-5′′), 77.4 (C-3′), 77.8 (C-3′), 86.1, 86.3, 86.6, 87.6 (C-1′, C-4′), 104.5 (C-2′′), 105.1 (C-2′′), 111.6 (C-5), 138.1 (C-6), 152.4 (C-2), 166.4 (C-4) ppm. MS (ES$^+$): *m*/*z* (%) = 335 (70) [M + Na]$^+$. HRMS (EI): calcd. for $C_{14}H_{20}N_2NaO_6$ [M + Na]$^+$ 335.1216; found 335.1214.

3′-*O*-(Tetrahydropyranyl)-2′-deoxycytidine (10d): White hygroscopic solid (two diastereoisomers); yield 73.1 mg, 87%. R_f (5% MeOH/CH_2Cl_2) = 0.22. IR (NaCl): $\tilde{\nu}$ = 3362, 3060, 2947, 1653, 1612, 1493, 1268 cm^{-1}. ^1H NMR ([D$_4$]MeOH, 300 MHz): δ = 1.72–2.03 (m, 12 H, 3′′-H, 4′′-H, 5′′-H), 2.32 (m, 2 H, 2′-H), 2.66 (m, 2 H, 2′-H), 3.67 (m, 2 H, 6′′-H), 3.86–4.10 (m, 6 H, 5′-H, 6′′-H), 4.22 (apparent q, $^3J_{HH}$ = 3.4 Hz, 1 H, 4′-H), 4.31 (apparent q, $^3J_{HH}$ = 3.1 Hz, 1 H, 4′-H), 4.62 (m, 2 H, 3′-H), 4.91–4.98 (m, 2 H, 2′′-H), 6.11 (d, $^3J_{HH}$ = 7.2 Hz, 2 H, 5-H), 6.42 (apparent q, $^3J_{HH}$ 6.6 Hz, 2 H, 1′-H), 8.17 (d, $^3J_{HH}$ 7.2 Hz, 2 H, 6-H) ppm. ^{13}C NMR ([D$_4$]MeOH, 75.5 MHz): δ = 20.5 (C-3′′), 20.6 (C-3′′), 26.4, 31.9 (C-4′′, C-5′′), 39.1 (C-2′), 40.4 (C-2′), 62.7 (C-5′), 62.8 (C-5′), 63.7 (C-5′′), 63.8 (C-5′′), 77.3 (C-3′), 77.9 (C-3′), 86.8, 87.4, 87.5, 87.6 (C-1′, C-4′), 96.1 (C-5), 99.1 (C-2′′), 99.9 (C-2′′), 142.7 (C-6), 158.1 (C-2), 167.4 (C-4) ppm. MS (ES$^+$): *m*/*z* (%) = 312 (20) [M + H]$^+$, 334 (95) [M + Na]$^+$. HRMS (EI): calcd. for $C_{14}H_{22}N_3O_5$ [M]$^+$ 312.1553; found 312.1554.

3′-*O*-(4-Methoxytetrahydropyranyl)-2′-deoxycytidine (10e): White solid; yield 82.9 mg, 90%. R_f (5% MeOH/CH_2Cl_2) = 0.2; m.p. 145–147 °C. $[\alpha]_D^{20}$ = +67 (*c* = 0.7, MeOH). IR (NaCl): $\tilde{\nu}$ = 3357, 3061, 2966, 2873, 1651, 1612, 1492 cm^{-1}. ^1H NMR ([D$_4$]MeOH, 300 MHz): δ = 1.91–2.07 (m, 4 H, 3′′-H), 2.35 (m, 1 H, 2′-H), 2.57 (m, 1 H, 2′-H), 3.42 (s, 3 H, OMe), 3.75–4.01 (m, 6 H, 5′-H, 2′′-H), 4.24 (apparent q, $^3J_{HH}$ = 3.4 Hz, 1 H, 4′-H), 4.74 (m, 1 H, 3′-H), 6.10 (d, $^3J_{HH}$ = 7.5 Hz, 1 H, 5-H), 6.42 (apparent t, $^3J_{HH}$ = 6.9 Hz, 1 H, 1′-H), 8.17 (d, $^3J_{HH}$ = 7.5 Hz, 1 H, 6-H) ppm. ^{13}C NMR ([D$_4$]MeOH, 75.5 MHz): δ = 35.6 (C-3′′), 36.0 (C-3′′), 41.1 (C-2′), 47.2 (OMe), 62.5 (C-5′), 65.9 (C-2′′), 70.8 (C-3′), 87.6, 87.7 (C-1′, C-4′), 96.1 (C-5), 100.1 (C-4′′), 142.6 (C-6), 158.1 (C-2), 167.4 (C-4) ppm. MS (ES$^+$): *m*/*z* (%) = 342 (18) [M + H]$^+$, 364 (100) [M + Na]$^+$. HRMS (EI): calcd. for $C_{15}H_{24}N_3O_6$ [M]$^+$ 342.1657; found 342.1660.

3′-*O*-(Tetrahydrofuranyl)-2′-deoxycytidine (10f): White hygroscopic solid (two diastereoisomers); yield 71.4 mg, 89%. R_f (5% MeOH/CH_2Cl_2) = 0.17. IR (NaCl): $\tilde{\nu}$ = 3346, 3085, 2985, 2948, 1651, 1610, 1268 cm^{-1}. ^1H NMR ([D$_4$]MeOH, 300 MHz): δ = 1.98–2.39 (m, 10 H, 2′-H, 3′′-H, 4′′-H), 2.62 (m, 2 H, 2′-H), 3.88–4.11 (m, 8 H, 5′-H, 5′′-H), 4.17 (apparent q, $^3J_{HH}$ = 3.8 Hz, 1 H, 4′-H), 4.22 (apparent q, $^3J_{HH}$ = 3.4 Hz, 1 H, 4′-H), 4.50 (m, 1 H, 3′-H), 4.55 (m, 1 H, 3′-H), 5.45 (m, 2 H, 2′′-H), 6.11 (d, $^3J_{HH}$ = 7.4 Hz, 2 H, 5-H), 6.38 (m, 2 H, 1′-H), 8.18 (d, $^3J_{HH}$ = 7.5 Hz, 1 H, 6-H), 8.19 (d, $^3J_{HH}$ = 7.5 Hz, 1 H, 6-H) ppm. ^{13}C NMR ([D$_4$]MeOH, 75.5 MHz): δ = 24.8 (C-3′′), 24.8 (C-3′′), 33.9 (C-4′′), 39.9 (C-2′), 41.3 (C-2′), 63.2 (C-5′), 68.5 (C-5′′), 77.9 (C-3′), 78.1 (C-3′), 87.2, 88.1, 88.2 (C-1′, C-4′), 96.6 (C-5), 105.1 (C-2′′), 105.6 (C-2′′), 143.2 (C-6), 158.6 (C-2), 167.9 (C-4) ppm. MS (ES$^+$): *m*/*z* (%) = 298 (50) [M + H]$^+$, 320 (35) [M + Na]$^+$. HRMS (EI): calcd. for $C_{13}H_{19}N_3NaO_5$ [M + Na]$^+$ 320.1211; found 320.1217.

3′-*O*-(Tetrahydropyranyl)-2′-deoxyadenosine (10g): White hygroscopic solid (two diastereoisomers); yield 72.4 mg, 80%. R_f (5% MeOH/CH_2Cl_2) = 0.23. IR (NaCl): $\tilde{\nu}$ = 3402, 3056, 2948, 1642, 1266 cm^{-1}. ^1H NMR ([D$_6$]DMSO, 300 MHz): δ = 1.49–1.78 (m, 12 H, 3′′-H, 4′′-H, 5′′-H), 2.53 (m, 2 H, 2′-H), 2.81 (m, 2 H, 2′-H), 3.55–3.82 (m, 8 H, 5′-H, 6′′-H), 4.11 (m, 2 H, 4′-H), 4.51 (m, 2 H, 3′-H), 4.77 (s, 2 H, OH), 5.43 (m, 2 H, 2′′-H), 6.35 (m, 2 H, 1′-H), 7.36 (s, 4 H, NH), 8.18 (s, 2 H, 2-H or 8-H), 8.38 (s, 1 H, 2-H or 8-H), 8.39 (s, 1 H, 2-H or 8-H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75.5 MHz): δ = 23.2, 23.3, 29.0, 34.5, 34.6 (C-3′′, C-4′′, C-5′′), 40.3 (C-2′), 41.3 (C-2′), 65.7, 66.1 (C-6′′, C-5′), 80.1 (C-3′), 81.1 (C-3′), 81.2, 81.3, 89.7, 90.2 (C-1′, C-4′), 100.6 (C-2′′), 101.6 (C-

2′′), 123.4 (C-5), 143.7 (C-8), 152.9 (C-6), 156.5 (C-2), 160.2 (C-4) ppm. MS (ES^+): *m/z* (%) = 336 (100) $[M + H]^+$. HRMS (EI): calcd. for $C_{15}H_{22}N_5O_4$ $[M]^+$ 336.1657; found 336.1666.

3′-*O*-(4-Methoxytetrahydropyranyl)-2′-deoxyadenosine (10h): White solid; yield 87.7 mg, 89%. R_f (5% MeOH/CH_2Cl_2) = 0.21; m.p. 161–163 °C. IR (NaCl): $\tilde{\nu}$ = 3405, 3056, 2983, 1638, 1288 cm^{-1}. ^1H NMR ([D$_4$]MeOH, 300 MHz): δ = 1.96–2.11 (m, 4 H, 3′′-H), 2.68 (m, 1 H, 2′-H), 3.01 (m, 1 H, 2′-H), 3.46 (s, 3 H, OMe), 3.83 (m, 2 H, 2′′-H), 3.94 (m, 3 H, 2′′-H, 5′-H),4.03 (dd, $|^2J_{HH}|$ = 12.2, $^3J_{HH}$ = 3.2 Hz, 1 H, 5′-H), 4.37 (m, 1 H, 4′-H), 4.96 (m, 1 H, 3′-H), 6.60 (dd, $^3J_{HH}$ = 7.8, 6.1 Hz, 1 H, 1′-H), 8.37 (s, 1 H, 8-H), 8.51 (s, 1 H, 2-H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75.5 MHz): δ = 38.4 (C-3′′), 38.6 (C-3′′), 42.4 (C-2′), 51.7 (OMe), 65.8, 68.4 (C-2′′, C-5′), 74.3 (C-3′), 88.4, 90.7 (C-1′, C-4′), 102.9 (C-4′′), 123.4 (C-5), 143.8 (C-8), 153.0 (C-6), 156.6 (C-2), 160.2 (C-4) ppm. MS (ES^+): *m/z* (%) = 366 (100) $[M + H]^+$. HRMS (EI): calcd. for $C_{16}H_{24}N_5O_5$ $[M]^+$ 366.1778; found 366.1772.

3′-*O*-(Tetrahydrofuranyl)-2′-deoxyadenosine (10i): White hygroscopic solid (two diastereoisomers); yield 70.3 mg, 81%. R_f (5% MeOH/CH_2Cl_2) = 0.19. IR (NaCl): $\tilde{\nu}$ = 3337, 3058, 1642, 1266 cm^{-1}. ^1H NMR ([D$_4$]MeOH, 300 MHz): δ = 2.16 (m, 8 H, 3′′-H, 4′′-H), 2.74 (m, 2 H, 2′-H), 2.99 (m, 2 H, 2′-H), 3.89–4.17 (m, 8 H, 5′-H, 5′′-H), 4.35 (m, 2 H, 4′-H), 4.74 (m, 2 H, 3′-H), 5.50 (m, 2 H, 2′′-H), 6.55 (apparent t, $^3J_{HH}$ = 6.0 Hz, 2 H, 1′-H), 8.37 (s, 2 H, 8-H), 8.49 (s, 1 H, 2-H), 8.51 (s, 1 H, H^2) ppm. ^{13}C NMR ([D$_4$]MeOH, 75.5 MHz): δ = 24.6, 33.7, 33.8 (C-3′′, C-4′′), 39.4 (C-2′), 40.6 (C-2′), 63.8, 63.9, 68.3 (C-5′′, C-5′), 78.6 (C-3′), 78.9 (C-3′), 87.3, 87.4, 87.8, 88.9 (C-1′, C-4′), 104.9 (C-2′′), 105.4 (C-2′′), 121.1 (C-5), 141.7 (C-8), 150.2 (C-6), 153.8 (C-2), 157.8 (C-4) ppm. MS (ES^+): *m/z* (%) = 322 (100) $[M + H]^+$. HRMS (EI): calcd. for $C_{14}H_{20}N_5O_4$ $[M]^+$ 322.1509; found 322.1510.

3′-*O*-(4-Methoxytetrahydropyranyl)-2′-deoxyguanosine (10j): White solid; yield 101.8 mg, 99%. R_f (5% MeOH/CH_2Cl_2) = 0.26; m.p. 106–109 °C. IR (NaCl): $\tilde{\nu}$ = 3422, 3056, 2962, 1694, 1266 cm^{-1}. ^1H NMR ([D$_4$]MeOH, 300 MHz): δ = 2.06 (m, 4 H, 3′′-H), 2.66 (m, 1 H, 2′-H), 2.88 (m, 1 H, 2′-H), 3.45 (s, 3 H, OMe), 3.89 (m, 6 H, 2′′-H, 5′-H), 4.32 (m, 1 H, 4′-H), 4.91 (m, 1 H, 3′-H), 6.45 (apparent t, $^3J_{HH}$ = 6.2 Hz, 1 H, 1′-H), 8.16 (s, 1 H, 8-H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75.5 MHz): δ = 38.5, 38.7 (C-3′′), 42.1 (C-2′), 65.7, 68.5 (C-2′′, C-5′), 74.2 (C-3′), 87.1, 90.4 (C-4′, C-1′), 102.9 (C-4′′), 120.8 (C-5), 139.7 (C-8), 151.1 (C-2), 153.9 (C-4), 157.2 (C-6) ppm. MS (ES^+): *m/z* (%) = 382 (50) $[M + H]^+$. HRMS (EI): calcd. for $C_{16}H_{24}N_5O_6$ $[M]^+$ 382.1708; found 382.1721.

3′-*O*-(Tetrahydrofuranyl)-2′-deoxyguanosine (10k): White hygroscopic solid (two diastereoisomers); yield 78.3 mg, 86%. R_f (5% MeOH/CH_2Cl_2) = 0.24. IR (NaCl): $\tilde{\nu}$ = 3427, 2930, 1694, 1266 cm^{-1}. ^1H NMR ([D$_4$]MeOH, 300 MHz): δ = 2.02–2.25 (m, 8 H, 3′′-H, 4′′-H), 2.67 (m, 2 H, 2′-H), 2.89 (m, 2 H, 2′-H), 3.87–4.15 (m, 8 H, 5′′-H, 5′-H), 4.29 (m, 2 H, 4′-H), 4.69 (m, 2 H, 3′-H), 5.48 (m, 2 H, 2′-H), 6.38 (apparent t, $^3J_{HH}$ = 6.4 Hz, 2 H, 1′-H), 8.14 (s, 2 H, 8-H) ppm. ^{13}C NMR ([D$_6$]DMSO, 75.5 MHz): δ = 27.1, 36.2 (C-3′′, C-4′′), 40.7 (C-2′), 41.9 (C-2′), 65.6, 70.4 (C-5′′, C-5′), 80.2 (C-3′), 80.7 (C-3′), 86.7, 86.8, 89.2, 90.0 (C-4′, C-1′), 106.3 (C-2′′), 106.9 (C-2′′), 120.7 (C-5), 139.4 (C-8), 154.9 (C-2), 157.7 (C-4), 160.8 (C-6) ppm. MS (ES^+): *m/z* (%) = 338 (90) $[M + H]^+$. HRMS (EI): calcd. for $C_{14}H_{20}N_5O_5$ $[M]^+$ 338.1458; found 338.1459.

Supporting Information (see also the footnote on the first page of this article): ^1H, ^{13}C, and DEPT NMR spectra in addition to some 2D NMR experiments (HSQC, HMBC, COSY, NOESY), which were used for peak assignment.

Acknowledgments

Financial support of this work by the Spanish Ministerio de Educación y Ciencia (MEC) (Project MEC-07-CTQ-61126) is gratefully acknowledged. S.M.-M. thanks MEC for a predoctoral FPU fellowship.

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Received: December 7, 2009
Published Online: February 3, 2010

