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2′-Deoxy-2′-α-*C*-(hydroxymethyl)adenosine as Potential anti-HCV Agent

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Because of the importance of *C*-branched nucleosides in the discovery of new antiviral molecules, we decided to synthesize 2′-deoxy-2′-α-*C*-(hydroxymethyl)adenosine as a potential anti-HCV agent. The synthesis of a new adenosine analogue following two different synthetic routes is described. The new *C*-branched nucleoside was tested for its antiviral activity and found to be inactive.

Introduction

The naturally occurring *C*-branched nucleoside oxetanocin A (**1**, Figure 1) is known to exhibit potent anti-HIV-1 activity.[1–2] It was shown that 2′,3′-dideoxy-3′-*C*-(hydroxymethyl) nucleosides (**2** and **3**, Figure 1) display an anti-HIV-1 activity profile similar to oxetanocin A.[3–4] These observations have increased the interest in 3′-*C*-branched 2′,3′-dideoxynucleosides. For example, 1-[2′,3′-dideoxy-3′-*C*-(hydroxymethyl)-5′-*O*-trityl-β-D-*threo*-pentofuranosyl]thymine demonstrated selective antiviral activity against HIV-1 (**4**, Figure 1).[5]

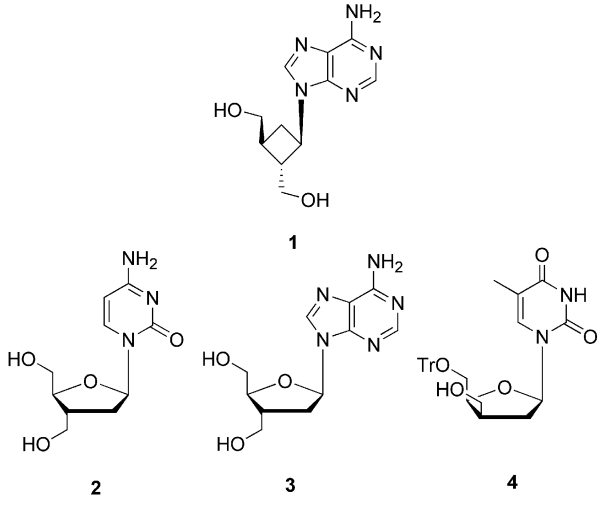

Figure 1. Potent anti-HIV-1 nucleosides.

Several other branched-chain sugar nucleosides were synthesized and tested for their antiviral activities. 4′-α-*C*-Branched-chain pyrimidine nucleosides were shown to possess antiviral activities against HSV-1, HSV-2 and HIV-1 in vitro.[6] A series of 2′-*C*-α-hydroxyalkyl- and 2′-*C*-α-alkylcytidines has been synthesised for incorporation into oligonucleosides for studies of group II intron RNA.[7] In another study, 2′-β-*C*-(hydroxymethyl)adenosine was found to exhibit potent anti-HCV activity (**6**, Figure 2), indicating that the hydroxy group of the 2′-*C*-(hydroxymethyl) substituent does not abolish the anti-HCV activity of 2′-*C*-methyladenosine (**7**, Figure 2).[8] In line with this result, 3′-*C*-(hydroxymethyl)-substituted nucleosides were recently explored as potential anti-HCV agents (biological tests under progress).[9]

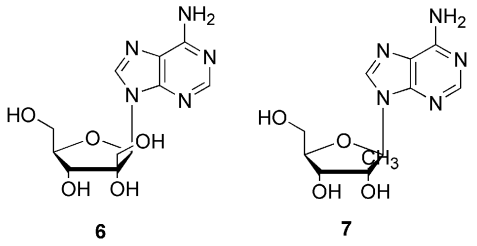

Figure 2. 2′-*C*-Branched nucleoside analogues showing anti-HCV activity.

It is clear that the introduction of a *C*-(hydroxymethyl) substituent has allowed the discovery of several new nucleoside analogues with antiviral activity. Here we describe the synthesis of 2′-*C*-(hydroxymethyl)adenosine and tested this adenosine derivative for its antiviral activity. The new modified adenosine was tested for its HCV, HIV and RSV activity.

A variety of procedures for preparing synthetic branched-chain sugar nucleosides have been described. However, the number of 2′-deoxy-2′-α-*C*-branched ribonucleosides reported are limited,[10–15] and their biological activities have not yet been investigated in a systematic manner, perhaps because of a lack of the availability of efficient synthetic methods leading to 2′-deoxy-2′-α-*C*-branched ribonucleosides.

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Only few publications report the synthesis of 2′-deoxy-2′-α-*C*-hydroxymethylpyrimidine nucleosides.[10–15] As far as we know, the synthesis of 2′-deoxy-2′-α-*C*-(hydroxymethyl)purine nucleosides has not been reported yet. Two schemes are used to synthesize such pyrimidine nucleosides. First, the preparation of 2′-deoxy-2′-α-*C*-(hydroxymethyl)-thymidine,[10] uridine,[11] or cytidine,[12] from the D-ribose sugar was described using a synthetic strategy as previously reported by Schmidt et al.[13] The second way to synthesize these modified nucleosides involves a radical reaction starting from the corresponding nucleoside. Two radical methods were investigated. The first one consists of a direct introduction of the vinyl or styryl group at the 2′ position.[14] The second one involves a double bond migration on the readily available allyl nucleoside through an ene reaction.[15] Another possibility, using an intramolecular radical C–C bond formation reaction, as described for the synthesis of branched aldopentopyranosyl nucleosides,[16] has not been considered yet.

Herein, we report the synthesis of 2′-deoxy-2′-α-*C*-(hydroxymethyl)adenosine as a potential anti-HCV agent using the two different synthetic routes: the common route starting from D-ribose and a second, more elegant method, starting from adenosine. Both synthetic routes are discussed.

Results

Synthesis of 2′-Deoxy-2′-α-*C*-(hydroxymethyl)-D-ribofuranosyladenosine Starting from D-Ribose

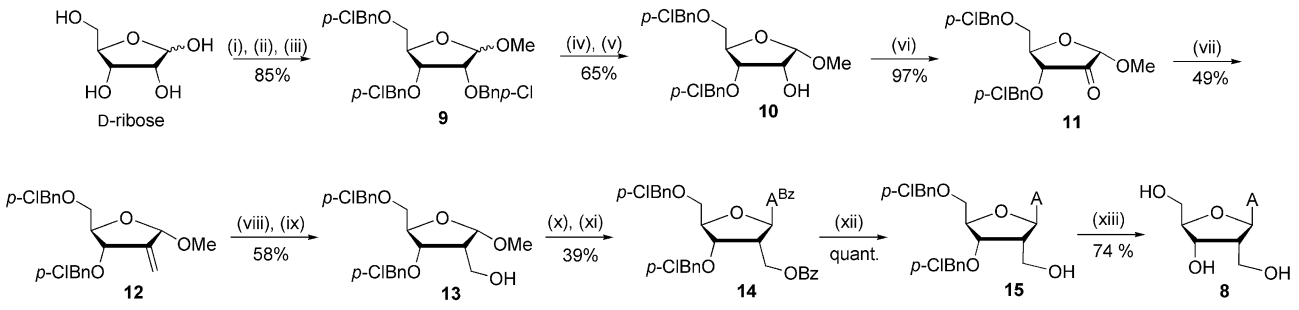
As described by Li et al.,[12] protected 2-deoxy-2-(hydromethyl)-D-ribofuranose **13** was synthesized starting from D-ribose (Scheme 1). Methyl 3,5-di-*O*-(4-chlorobenzyl)-α-D-ribofuranoside (**10**) was prepared according to the method of Martin et al.[17] D-Ribose was first fixed in its 1-OMe furanose form. Selective protection of positions 3 and 5 with a *p*-chlorobenzyl group was realized by selective deprotection of position 2 of compound **9** by reaction with tin(IV) chloride. Compound **10** was converted to methyl 3,5-di-*O*-(4-chlorobenzyl)-2-deoxy-2-α-(hydroxymethyl)-α-D-ribofuranoside (**13**) essentially via the same sequence of reactions as described by Li et al.[12] The major difference was the use of IBX (2-iodoxybenzoic acid) as oxidizing reagent for oxidation of the free alcohol at position 2 into the corresponding ketone **11**. This reagent, in fact a precursor of the Dess–Martin periodinane reagent that was initially used, is easier to obtain. It is inexpensive to prepare and easy to handle, can tolerate moisture and water, and gives very good yields. Moreover, IBX can easily be recycled by oxidation of IBA (2-iodobenzoic acid) released during the reaction. Ketone **11** was converted to alkene **12** by a Wittig reaction and then, to the desired hydroxymethyl compound **13** by hydroboration followed by oxidation.

The hydroxymethyl function at position 2 was then benzoylated before condensation of the sugar with N^6-benzoyladenine following the Vorbrüggen glycosylation procedure.[18] Two anomers were obtained, which were easily separated by silica gel column chromatography. The stereochemistry of compound **14** was established by a ^{1}H NOE experiment. Irradiation of the anomeric proton (δ = 6.50 ppm) gave a NOE (2.05%) on the 4′-H, indicating that the obtained compound is a β-anomer. Another indication for the β anomeric configuration is the determination of $^1J_{C1,H1}$.[19–20] In our case, we measured on the non ^{1}H-decoupled ^{13}C spectrum a value of 165.9 Hz for $^1J_{C1,H1}$, characteristic for adenosine (β-anomer) (literature value for adenosine is 165.6 Hz).[21]

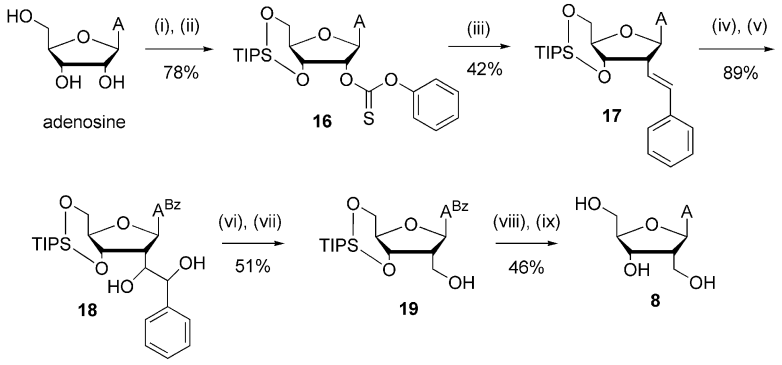
Finally, the nucleoside **14** was deprotected to afford the desired modified adenosine **8**. The order in which the functions are deprotected is important. Indeed, Li and Piccirilli described that attempts to debenzylate the alcohol functions of 2′-α-(acetoxymethyl)-N^6-benzoyl-3′,5′-di-*O*-(4-chlorobenzyl)-2′-deoxycytidine using hydrogen in the presence of Pd/C resulted in deamination of the nucleobase when the amine is benzoylated.[12] To render the nucleobase less susceptible to reductive deamination, we removed the benzoyl protecting groups before the benzyl protections. Following this procedure, 2′-deoxy-2′-α-*C*-(hydroxymethyl)adenosine was obtained in 13 steps in a total yield of 9%.

Synthesis of 2′-Deoxy-2′-α-*C*-(hydroxymethyl)-D-ribofuranosyladenosine Starting from Adenosine

2′-(Phenoxythiocarbonyl)-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)adenosine (**16**), obtained by reaction of



Scheme 1. Synthesis of the 2′-deoxy-2′-α-*C*-(hydroxymethyl)adenosine starting from D-ribose. (i) methanolic HCl (1%), MeOH; (ii) NaH, DMSO; (iii) 4-chlorobenzyl chloride (isomer mixture, β/α 2:1); (iv) $SnCl_4$, CH_2Cl_2, 0 °C; v) H_2O; (vi) IBX, acetonitrile, 80 °C; (vii) $Ph_3P^+CH_3Br^-$, *s*BuLi, THF, –78 °C; (viii) 9-BBN, THF, 40 °C; (ix) NaOH, H_2O_2, 80 °C; (x) BzCl, pyridine; (xi) N^6-benzoyl bis(trimethylsilyl)adenine, TMSOTf, DCE, reflux; (xii) NH_4OH, MeOH, 50 °C; (xiii) Pd/C, H_2, MeOH.



Scheme 2. Synthesis of the 2′-deoxy-2′-α-*C*-(hydroxymethyl)adenosine starting from adenosine. (i) TIPSCl, pyridine; (ii) phenyl chlorothionoformate, DMAP, acetonitrile; (iii) tributylstyryltin, AIBN, benzene, 80 °C; (iv) BzCl, pyridine; (v) $K_3Fe(CN)_6$, K_2CO_3, OsO_4, H_2O/*t*BuOH (1:1); (vi) $NaIO_4$, dioxane/H_2O (3:1); (vii) $NaBH_4$, MeOH; (viii) $3HF{\cdot}NEt_3$, NEt_3, THF; (ix) NH_4OH, MeOH, 50 °C.

3′,5′-protected adenosine with phenyl chlorothionocarbonate, was treated with β-(tributylstannyl)styrene. The solvent plays an important role in the radical reaction. Indeed, the desired 2′-deoxy-2′-α-*C*-styryl-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)adenosine (**17**) was obtained in dry benzene but not in dry toluene. As reported by De Mesmaeker et al.,[22] the radical reaction (modified Barton–McCombie reaction) led to a stereoselective introduction of a 2-phenylethenyl group at the α-side of the sugar ring because of the steric hindrance due to the presence of the base at the anomeric position on the β face.

The second main step of this route is the oxidative cleavage of the double bond. For the synthesis of 2′-deoxy-2′-α-*C*-(hydroxymethyl)pyrimidine nucleosides,[14–15] the authors performed the oxidative cleavage by ozonolysis. Because ozonolysis is not practical when larger amounts of material are needed, we tried to cleave the double bond by Lemieux-Johnson oxidation using OsO_4, *N*-methylmorpholine *N*-oxide (NMMO) and $NaIO_4$ followed by in situ reduction using $NaBH_4$.[23–25] In our case, the conversion of the phenylethenyl group of compound **17** into the hydroxymethyl group was not very efficient following this procedure (10%). To increase the yield of the reaction, the co-oxidant NMMO was replaced by $K_3Fe(CN)_6/K_2CO_3$, which was identified to be a better co-oxidant system by Minato et al.[26] and the two oxidation steps were carried out separately by isolating the dihydroxy compound **18**. Using this method we obtained the desired product **19** with an increased yield of 45%. It is to notice that the free amine of the adenine base has to be protected before the oxidative cleavage in order to avoid side reactions (Scheme 2).

Finally, the protected nucleoside **19** was deprotected to afford the desired modified adenosine **8**. Following this procedure, 2′-deoxy-2′-α-*C*-(hydroxymethyl)adenosine was obtained in 9 steps in a total yield of 7%.

Biological Tests

The synthesized 2′-deoxy-2′-α-*C*-(hydroxymethyl)adenosine was tested for its capacity to inhibit the replication of HCV 1a and 1b (huh-7 cells), HIV (MT4 cells) and RSV (hep2 cells) replicons. Unfortunately, this new adenosine derivative shows no antiviral activity (data not shown) up to 88 μM against HCV replicons, 53 μM against HIV replicons and 10 μM against RSV replicons.

Discussion

In this paper, we describe the synthesis of 2′-deoxy-2′-α-*C*-(hydroxymethyl)adenosine. Indeed, a limited number of successful selective substitutions at C-2′ are reported[7,8,10–15] and only few publications report the synthesis of 2′-deoxy-2′-α-*C*-(hydroxymethyl)pyrimidine nucleosides.[10–15] This can be explained by the inherent lower reactivity at C-2′. It has been reported that the electronegative anomeric carbon C-1′ effectively prevents ionization of a 2′-leaving group to produce a cationic S_N1 intermediate for 2′ modification.[27] Moreover, it is known that the reactivity of the 2′OH group can be potentially influenced by its preferred orientation,[28] dynamics[29] and pK_a.[30] Velikyan et al. reported that the pK_a is dictated by various factors such as the nature and orientation of the aglycon, the sugar conformation and the nature of the vicinal substituent.[30] A comparison of pK_a values for 2′OH in different nucleosides shows that the 2′-OH in adenosine is the most acidic (pK_a = 12.17 vs. 12.62 for uridine for example) because adenine-9-yl is a better stabilizer for the 2′-oxy anion compared to any other aglycons in the studied nucleoside series. This higher acidity might be less favourable to nucleophilic substitution and can partly explain why modification at the 2′ position of adenosine is more difficult. Another explanation for the decrease of reactivity at the 2′ position of adenosine compared to pyrimidine nucleosides could be the positioning of the heterocyclic base. Indeed, the heterocyclic base at C-1′ exerts a major steric and electronic barrier for nucleophiles to attack on C-2′. It has been demonstrated that the *N*-glycosyl bond in adenosine (1.467 Å) is shorter than those of thymidine (1.480 Å) and cytidine (1.497 Å).[31] The shorter *N*-glycosyl bond might contribute to a higher steric barrier.

Two different synthetic routes were explored to synthesize the targeted modified adenosine. The first starts from

D-ribose and allows us to obtain the modified nucleoside in 13 steps in a total yield of 9%. The second way involves a radical reaction starting from adenosine. Following this route, the desired nucleoside was obtained in 9 steps in a global yield of 7%.

Initially, a preference could be given to the second route since it involves few steps. But according to the results, the first route seems to be the best one for the synthesis of 2′-deoxy-2′-α-*C*-(hydroxymethyl)adenosine (better total yield). Indeed, the radical reaction and the oxidative cleavage are not very efficient steps. Moreover, to obtain larger quantities, we repeated these 2 steps several times. This route is only interesting when small amounts of material are required. When larger amounts of material are needed, the first route seems to be appropriate.

Because of its resemblance with compounds **1**–**7**,[1–5,8,32] we tested our new adenosine derivative for its anti-HIV, anti-HCV and anti-RSV activity. Unfortunately, 2′-deoxy-2′-α-*C*-(hydroxymethyl)adenosine did not inhibit the replication of HCV, HIV and RSV replicons.

Conclusions

In conclusion, we synthesized for the first time 2′-deoxy-2′-α-*C*-(hydroxymethyl)adenosine following two different strategies. The first strategy starting from D-ribose is more interesting than the second route involving a radical reaction directly from adenosine. Despite the number of additional steps, the first way gives a better total yield and in this way, is more interesting when larger amounts of the nucleoside are required.

Experimental Section

Synthesis: Nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded at room temperature on a Bruker AC 300 spectrometer. TMS was used as an internal standard and $CDCl_3$ as the solvent. ^{1}H NMR analyses were obtained at 300 MHz (s: singlet, d: doublet, t: triplet, dd: double doublet, dt: double triplet, q: quadruplet, quint: quintuplet, m: multiplet, AB: diastereotopic protons); whereas ^{13}C NMR analyses were obtained at 75.4 MHz, at 125.7 MHz (for **15**) or at 150.9 MHz (for **17**) (C^{IV}: quaternary carbon). The chemical shifts (δ) are given in parts per million relative to TMS (δ = 0.00 ppm). Exact mass spectra were obtained with a Q-Tof 2TM (Micromass Ltd.) coupled to a CapLC™ system (Waters). Silica gel chromatography was performed on Davisil® silica gel 60, 0.630–0.200 mm (Grace Davison). Reactions were monitored by thin-layer chromatography (TLC) on Alugram® silica gel UV254 mesh 60, 0.20 mm (Macherey–Nagel), detection by UV lamp or revelation by phosphomolybdenum cerium sulfate or *p*-anisaldehyde. All dry solvents were obtained after appropriate distillation except for DMSO (dimethyl sulfoxide, 99.7%, "Extra Dry", dried with molecular sieves, AcroSeal® was purchased from Acros Organics).

Methyl 2,3,5-Tri-*O*-(4-chlorobenzyl)-α/β-D-ribofuranoside (9): To a solution of D-ribose (10.0 g, 67 mmol) in dry methanol (120 mL) was added a solution of methanolic HCl (1%, 20 mL). The reaction mixture was stirred at room temperature for 3 d. The solution was neutralized with Na_2CO_3 and the formed solid was filtered. The filtrate was evaporated under reduced pressure and coevaporates with dry pyridine. The residue was dissolved in dry DMSO (200 mL) and added at 0 °C to a solution of dimsylsodium prepared by adding pentane-washed sodium hydride (16 g, 400 mmol) to dry DMSO (150 mL) and by heating the magnetically stirred suspension to 60 °C for 45 min. The reaction mixture was stirred at room temperature for 5 h. Then, 4-chlorobenzyl chloride (100 mL, 1.11 mol) was added slowly at 0 °C and the reaction mixture was stirred overnight at room temperature. The reaction was quenched with methanol (20 mL) and then water (100 mL). The mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried with Na_2SO_4 and evaporated under reduced pressure. The residue was purified on silica gel chromatography eluting with 10% ethyl acetate in hexane to give **β-9** as an orange oil (24.2 g, 45 mmol, 67% yield) and then, with 20% ethyl acetate in hexane to give **α-9** as an orange oil (9.6 g, 18 mmol, 18% yield).

β-9: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.25 (m, 12 H, Ar), 4.91 (s, 1 H, 1-H), 4.64 (d, J = 12.2 Hz, 1 H, AB-spin system, C^2-O-CH_2), 4.55 (d, J = 12.2 Hz, 1 H, AB-spin system, C^2-O-CH_2), 4.54 (d, J = 12.6 Hz, 1 H, AB-spin system, C^5-O-CH_2), 4.51 (d, J = 12.6 Hz, 1 H, AB-spin system, C^5-O-CH_2), 4.50 (d, J = 12.0 Hz, 1 H, AB-spin system, C^3-O-CH_2), 4.43 (d, J = 12.0 Hz, 1 H, AB-spin system, C^3-O-CH_2), 4.30 (q, J = 5.3 Hz, 1 H, 4-H), 4.00 (dd, J = 4.8, 6.7 Hz, 1 H, 3-H), 3.81 (d, J = 4.4 Hz, 1 H, 2-H), 3.59 (dd, J = 4.7, 10.5 Hz, 1 H, AB-spin system, 5-H), 3.50 (dd, J = 4.7, 10.5 Hz, 1 H, AB-spin system, 5-H), 3.35 (s, 3 H, CH_3) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 137.1 (Ar, C^{IV}), 136.6 (Ar, C^{IV}), 134.0 (Ar, 2 C^{IV}), 133.6 (Ar, C^{IV}), 132.5 (Ar, C^{IV}), 129.4 (Ar, 4 CH), 129.2 (Ar, 2 CH), 128.9 (Ar, 4 CH), 128.8 (Ar, 2 CH), 106.5 (C^1, CH), 80.7 (C^4, CH), 80.3 (C^2, CH), 78.8 (C^3, CH), 72.8 (C^5-O-CH_2, CH_2), 72.0 (C^2-O-CH_2, CH_2), 71.9 (C^3-O-CH_2, CH_2), 71.6 (C^5, CH_2), 55.5 (CH_3) ppm. HRMS (ESI) m/z $[M + Na]^+$ calcd. for $C_{27}H_{27}Cl_3NaO_5$ 559.0822; found 559.0813.

α-9: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.24 (m, 12 H, Ar), 4.89 (d, 1 H, 1-H), 4.64 (d, J = 17.1 Hz, 1 H, AB-spin system, C^2-O-CH_2), 4.61 (d, J = 22.0 Hz, 1 H, AB-spin system, C^5-O-CH_2), 4.55 (d, J = 17.1 Hz, 1 H, AB-spin system, C^2-O-CH_2), 4.53 (d, J = 22.0 Hz, 1 H, AB-spin system, C^5-O-CH_2), 4.46 (d, J = 12.2 Hz, 1 H, AB-spin system, C^3-O-CH_2), 4.43 (d, J = 12.2 Hz, 1 H, AB-spin system, C^3-O-CH_2), 4.23 (q, J = 3.8 Hz, 1 H, 4-H), 3.78 (s, 1 H, 2-H), 3.77 (d, J = 6.6 Hz, 1 H, 3-H), 3.45 (s, 3 H, CH_3), 3.41 (t, J = 3.2 Hz, 2 H, 5-H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 137.1 (Ar, C^{IV}), 136.6 (Ar, C^{IV}), 134.0 (Ar, 2 C^{IV}), 131.1 (Ar, C^{IV}), 130.7 (Ar, C^{IV}), 129.7 (Ar, 2 CH), 129.5 (Ar, 2 CH), 129.3 (Ar, 2 CH), 128.9 (Ar, 4 CH), 128.8 (Ar, 2 CH), 102.6 (C^1, CH), 82.1 (C^4, CH), 78.4 (C^2, CH), 75.7 (C^3, CH), 73.1 (C^5-O-CH_2, CH_2), 72.1 (C^3-O-CH_2, CH_2), 71.9 (C^2-O-CH_2, CH_2), 70.5 (C^5, CH_2), 55.9 (CH_3) ppm. HRMS (ESI) m/z $[M + Na]^+$ calcd. for $C_{27}H_{27}Cl_3NaO_5$ 559.0822; found 559.0812.

Methyl 3,5-Di-*O*-(4-chlorobenzyl)-α-D-ribofuranoside (10): To a cold (0 °C) solution of **9** (930 mg, 1.7 mmol) in dry CH_2Cl_2 (9 mL) was added a 10% (v/v) solution of tin(IV) chloride in dry CH_2Cl_2 (1.9 mL, 1.7 mmol). The reaction mixture was stirred at 0 °C for 6 h. Saturated aqueous $NaHCO_3$ (10 mL) was then added and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried with Na_2SO_4 and evaporated under reduced pressure. The residue was purified on silica gel chromatography eluting with 20% EtOAc in hexane to give **10** as an orange oil (460 mg, 1.1 mmol, 65% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.21 (m, 8 H, Ar), 4.88 (d, J = 4.6 Hz, 1 H, 1-H), 4.69 (d, J = 12.6 Hz, 1 H, AB-spin system, C^3-O-CH_2), 4.54 (d, J = 12.6 Hz, 1 H, AB-spin system, C^3-O-CH_2), 4.48 (d, J = 12.2 Hz, 1 H, AB-

spin system, C^5-O-CH_2), 4.42 (d, J = 12.2 Hz, 1 H, AB-spin system, C^5-O-CH_2), 4.16 (m, 1 H, 4-H), 4.12 (m, 1 H, 2-H), 3.74 (dd, J = 3.2, 7.0 Hz, 1 H, 3-H), 3.48 (s, 3 H, CH_3), 3.46 (dd, J = 4.4, 10.5 Hz, 1 H, AB-spin system, 5-H), 3.41 (dd, J = 4.4, 10.5 Hz, 1 H, AB-spin system, 5-H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 136.7 (Ar, C^{IV}), 136.6 (Ar, C^{IV}), 133.9 (Ar, 2 C^{IV}), 129.5 (Ar, 2 CH), 129.3 (Ar, 2 CH), 128.9 (Ar, 4 CH), 103.2 (C^1, CH), 82.1 (C^4, CH), 76.8 (C^3, CH), 73.1 (C^5-O-CH_2, CH_2), 72.5 (C^3-O-CH_2, CH_2), 72.1 (C^2, CH), 70.4 (C^5, CH_2), 56.0 (CH_3) ppm. HRMS (ESI) m/z [M + Na]$^+$ calcd. for $C_{20}H_{22}Cl_2NaO_5$ 435.0742; found 435.0743.

Methyl 3,5-Di-*O*-(4-chlorobenzyl)-2-oxo-α-D-ribofuranoside (11): Previously synthesized IBX (5.0 g, 17.9 mmol) was added to a solution of **10** (3.43 g, 8.3 mmol) in acetonitrile (80 mL). The reaction mixture was stirred at 80 °C for 3 h. The solid was filtered and washed with EtOAc (3 × 50 mL). The filtrate was washed with saturated aqueous $Na_2S_2O_3$ (50 mL), saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried with Na_2SO_4 and the solvents were evaporated under reduced pressure to give **11** as an orange oil (3.3 g, 8.0 mmol, 97% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.22 (m, 8 H, Ar), 4.91 (d, J = 11.9 Hz, 1 H, AB-spin system, C^3-O-CH_2), 4.83 (s, 1 H, 1-H), 4.64 (d, J = 11.9 Hz, 1 H, AB-spin system, C^3-O-CH_2), 4.55 (d, J = 12.1 Hz, 1 H, AB-spin system, C^5-O-CH_2), 4.45 (d, J = 12.1 Hz, 1 H, AB-spin system, C^5-O-CH_2), 4.31 (dt, J = 2.9, 8.1 Hz, 1 H, 4-H), 4.09 (d, J = 8.3 Hz, 1 H, 3-H), 3.66 (dd, J = 3.5, 11.2 Hz, 1 H, AB-spin system, 5-H), 3.62 (dd, J = 3.5, 11.2 Hz, 1 H, AB-spin system, 5-H), 3.48 (s, 3 H, CH_3) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 207.9 (C^2, C^{IV}), 136.3 (Ar, C^{IV}), 135.8 (Ar, C^{IV}), 134.3 (Ar, C^{IV}), 134.0 (Ar, C^{IV}), 129.8 (Ar, 2 CH), 129.3 (Ar, 2 CH), 129.0 (Ar, 2 CH), 99.0 (C^1, CH), 78.1 (C^4, CH), 75.8 (C^3, CH), 73.1 (C^5-O-CH_2, CH_2), 72.1 (C^3-O-CH_2, CH_2), 68.6 (C^5, CH_2), 56.2 (CH_3) ppm. HRMS (ESI) m/z [M + Na]$^+$ calcd. for $C_{20}H_{20}Cl_2NaO_5$ 433.0585; found 433.0608.

Methyl 3,5-Di-*O*-(4-chlorobenzyl)-2-methylene-α-D-ribofuranoside (12): *s*BuLi (1.4 M *in* cyclohexane, 13.2 mL, 18.5 mmol) was added to a suspension of triphenylmethylphosphonium bromide (6.3 g, 17.6 mmol) in dry THF (32 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 1 h and then, a solution of **11** (3.3 g, 8.0 mmol) in dry THF (16 mL) was added dropwise at –78 °C. The reaction mixture was stirred at room temperature overnight. The solid was filtered and washed with diethyl ether (3 × 50 mL). The filtrate was washed with saturated aqueous NH_4Cl (50 mL) and brine (50 mL). The organic layer was dried with Na_2SO_4 and evaporated under reduced pressure. The residue was purified on silica gel chromatography eluting with 20% ethyl acetate in hexane to give **12** as an orange oil (1.6 g, 3.9 mmol, 49% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.27 (m, 8 H, Ar), 5.46 (s, 1 H, C^2-CH_2), 5.39 (s, 1 H, C^2-CH_2), 5.24 (s, 1 H, 1-H), 4.61 (d, J = 11.9 Hz, 1 H, AB-spin system, C^3-O-CH_2), 4.53 (d, J = 15.1 Hz, 1 H, AB-spin system, C^5-O-CH_2), 4.51 (d, J = 11.9 Hz, 1 H, AB-spin system, C^3-O-CH_2), 4.48 (d, J = 15.1 Hz, 1 H, AB-spin system, C^5-O-CH_2), 4.27 (s, 2 H, H3, 4-H), 3.56 (s, 2 H, 5-H), 3.44 (s, 3 H, CH_3) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 205.9 (C^2, C^{IV}), 136.9 (Ar, C^{IV}), 136.8 (Ar, C^{IV}), 133.8 (Ar, 2 C^{IV}), 129.8 (Ar, 2 CH), 129.3 (Ar, 2 CH), 129.0 (Ar, 4 CH), 114.7 (C_2=CH_2, CH_2), 104.5 (C^1, CH), 81.3 (C^3, CH), 79.0 (C^4, CH), 73.0 (C^5-O-CH_2, CH_2), 70.3 (C^3-O-CH_2, CH_2), 70.2 (C^5, CH_2), 55.2 (CH_3) ppm. HRMS (ESI) m/z [M + Na]$^+$ calcd. for $C_{21}H_{22}Cl_2NaO_4$ 431.0793; found 431.00814.

Methyl 3,5-Di-*O*-(4-chlorobenzyl)-2-deoxy-2-α-(hydroxymethyl)-α-D-ribofuranoside (13): 12 (1 g, 2.4 mmol) was dissolved in 9-BBN solution (0.5 M in THF, 12 mL, 6.0 mmol). The reaction mixture was stirred at room temperature for 3 h, at 40 °C for 16 h and finally at room temperature for 1 h. While cooling the reaction at 0 °C, 6 M aqueous NaOH (4 mL, 30.0 mmol) was added dropwise to the solution followed by H_2O_2 solution (35%, 6 mL, 68.6 mmol). The resulting mixture was warmed to room temperature during 1 h and then, stirred at 80 °C for 2 h. The solution was concentrated under reduced pressure. The residue was diluted in CH_2Cl_2 (50 mL) and washed with brine (3 × 50 mL). The organic layer was dried with Na_2SO_4 and evaporated under reduced pressure. The residue was purified on silica gel chromatography eluting with 50% EtOAc in hexane to give **13** as an orange oil (590 mg, 1.4 mmol, 58% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.28 (m, 8 H, Ar), 5.02 (d, J = 5.1 Hz, 1 H, 1-H), 4.56 (d, J = 12.6 Hz, 1 H, AB-spin system, C^3-O-CH_2), 4.50 (d, J = 12.4 Hz, 1 H, C^5-O-CH_2), 4.45 (d, J = 12.4 Hz, 1 H, C^5-O-CH_2), 4.44 (d, J = 12.5 Hz, 1 H, AB-spin system, C^3-O-CH_2), 4.26 (dd, J = 4.9, 8.2 Hz, 1 H, 4-H), 3.94 (dd, J = 3.2, 7.6 Hz, 1 H, 3-H), 3.91 (d, J = 7.6 Hz, 2 H, CH_2OH), 3.46 (dd, J = 4.7, 10.4 Hz, 1 H, AB-spin system, 5-H), 3.40 (s, 3 H, CH_3), 3.39 (dd, J = 4.7, 10.4 Hz, 1 H, AB-spin system, 5-H), 2.29 (quint, J = 6.6 Hz, 1 H, 2-H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 136.7 (Ar, 2 C^{IV}), 133.9 (Ar, 2 C^{IV}), 129.5 (Ar, 2 CH), 129.4 (Ar, 2 CH), 128.9 (Ar, 4 CH), 105.7 (C^1, CH), 83.2 (C^4, CH), 79.2 (C^3, CH), 73.1 (C^5-O-CH_2, CH_2), 71.6 (C^3-O-CH_2, CH_2), 70.8 (C^5, CH_2), 58.2 (CH_2OH), 55.9 (CH_3), 49.3 (C^2, CH) ppm. HRMS (ESI) m/z [M + Na]$^+$ calcd. for $C_{21}H_{24}Cl_2NaO_5$ 449.0898; found 449.0899.

Methyl *N*^{6}-Benzoyl-2′-α-(benzoyloxymethyl)-3′,5′-di-*O*-(4-chlorobenzyl)-2′-deoxyadenosine (14): To a solution containing **13** (1.4 g, 3.3 mmol) in dry pyridine (45 mL) was added benzoyl chloride (710 μL, 6.2 mmol). The reaction mixture was stirred at room temperature for 5 h. The solution was evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2 (50 mL). The organic layer was washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL), dried with Na_2SO_4 and evaporated under reduced pressure. The residue was purified on silica gel chromatography eluting with 10% ethyl acetate in hexane followed by 30% ethyl acetate in hexane to give methyl 2-α-(benzoyloxymethyl)-3,5-di-*O*-(4-chlorobenzyl)-2-deoxy-α-D-ribofuranoside as a colourless oil. A mixture of previously synthesized *N*^{6}-benzoyladenine (3.4 g, 14.3 mmol), 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (27 mL) and $(NH_4)_2SO_4$ (catalytic amount) was heated under argon at 140 °C overnight. HMDS was evaporated under reduced pressure and carefully putted under argon in order to avoid the degradation of the persilylated base. A methyl 2-α-(benzoyloxymethyl)-3,5-di-*O*-(4-chlorobenzyl)-2-deoxy-α-D-ribofuranoside (1.7 g, 3.2 mmol) solution in dry 1,2-dichloroethane (40 mL) was added to the obtained *N*^{6}-benzoyl-bis(trimethylsilyl)adenine. To this solution was added TMSOTf (680 μL, 3.8 mmol). The reaction mixture was heated at 80 °C for 5 h. Saturated aqueous $NaHCO_3$ (50 mL) was added to the solution, which was then extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was washed with water (50 mL), dried with Na_2SO_4 and evaporated under reduced pressure. The residue was purified on silica gel chromatography eluting with 3% methanol in CH_2Cl_2 to give **14** as a white solid (930 mg, 1.3 mmol, 39% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.66 (s, 1 H, H8), 8.35 (s, 1 H, 2-H), 8.07 (d, J = 4.2 Hz, 4 H, Ar), 7.59 (quint, J = 4.5 Hz, 2 H, Ar), 7.52 (t, J = 4.5 Hz, 2 H, Ar), 7.45 (m, 2 H, Ar), 7.28 (m, 8 H, Ar), 6.50 (d, J = 8.1 Hz, 1 H, 1′-H), 4.76 (q, J = 5.8 Hz, 1 H, AB-spin system, CH_2-OBz), 4.62 (d, J = 7.1 Hz, 1 H, AB-spin system, $C^{3'}$-O-CH_2), 4.60 (d, J = 7.1 Hz, 1 H, AB-spin system, $C^{5'}$-O-CH_2), 4.58 (t, J = 6.2 Hz, 1 H, AB-spin system, CH_2-OBz), 4.51 (d, J = 7.1 Hz, 1 H, AB-spin system, $C^{5'}$-O-CH_2), 4.49

(d, J = 7.1 Hz, 1 H, AB-spin system, $C^{3'}$-O-CH_2), 4.43 (m, 1 H, 4′-H), 4.36 (dd, J = 1.8, 5.7 Hz, 1 H, 3′-H), 3.78 (dd, J = 4.5, 10.4 Hz, 1 H, AB-spin system, 5′-H), 3.62 (dd, J = 3.3, 10.2 Hz, 1 H, AB-spin system, 5′-H), 3.61 (m, 1 H, 2′-H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 170.7 (C=O, C^{IV}), 166.0 (C=O, C^{IV}), 152.2 (C8, CH), 151.7 (C^4, C^{IV}), 149.7 (C^6, C^{IV}), 141.6 (C^2, CH), 135.7 (Ar, C^{IV}), 135.4 (Ar, C^{IV}), 134.0 (Ar, C^{IV}), 133.9 (Ar, C^{IV}), 133.4 (Ar, CH), 133.2 (Ar, C^{IV}), 132.8 (Ar, C^{IV}), 130.0 (Ar, CH), 129.8 (Ar, CH), 129.6 (Ar, CH), 129.5 (Ar, CH), 129.2 (Ar, 2 CH), 129.1 (Ar, CH), 128.9 (Ar, CH), 128.8 (Ar, 2 CH), 128.7 (Ar, 2 CH), 128.6 (Ar, CH), 128.4 (Ar, CH), 128.3 (Ar, 3 CH), 123.1 (C^5, C^{IV}), 87.4 ($C^{1'}$, CH), 82.9 ($C^{4'}$, CH), 79.5 ($C^{3'}$, CH), 72.9 ($C^{5'}$-O-CH_2, CH_2), 71.0 ($C^{3'}$-O-CH_2, CH_2), 70.1 ($C^{5'}$, CH_2), 60.9 (CH_2-OBz, CH_2), 47.1 ($C^{2'}$, CH) ppm. HRMS (ESI) m/z $[M + H]^+$ calcd. for $C_{39}H_{33}Cl_2N_5O_6$ 738.1886; found 738.1888.

Methyl 3′,5′-Di-*O*-(4-chlorobenzyl)-2′-deoxy-2′-α-(hydroxymethyl)-adenosine (15): A solution containing **14** (22 mg, 0.03 mmol) in ammoniac solution in MeOH (7 M, 2 mL) was stirred at 50 °C in a sealed flask overnight. The solvent was evaporated under reduced pressure. The residue was purified on silica gel chromatography eluting with 5% methanol in dichloromethane to give **15** as a yellow oil (16 mg, 0.03 mmol, quantitative). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.28 (s, 1 H, H8), 8.02 (s, 1 H, 2-H), 7.32 (dd, J = 2.1, 8.6 Hz, 4 H, Ar), 7.26 (d, J = 4.2 Hz, 2 H, Ar), 7.20 (d, J = 8.5 Hz, 2 H, Ar), 6.37 (d, J = 7.6 Hz, 1 H, 1′-H), 5.78 (s, 2 H, NH_2), 4.62 (d, J = 10.1 Hz, 1 H, AB-spin system, $C^{3'}$-O-CH_2), 4.50 (s, 1 H, AB-spin system, $C^{5'}$-O-CH_2), 4.48 (d, J = 10.1 Hz, 1 H, AB-spin system, $C^{3'}$-O-CH_2), 4.37 (m, 2 H, 3′-H, 4′-H), 3.99 (dd, J = 5.4, 11.9 Hz, 1 H, AB-spin system, CH_2OH), 3.89 (dd, J = 5.4, 11.9 Hz, 1 H, AB-spin system, CH_2OH), 3.72 (dd, J = 4.8, 10.1 Hz, 1 H, AB-spin system, 5′-H), 3.60 (dd, J = 3.9, 10.1 Hz, 1 H, AB-spin system, 5′-H), 3.24 (quint, J = 13.4 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$, 25 °C): δ = 155.4 (C^4, C^{IV}), 152.8 (C8, CH), 149.4 (C^6, C^{IV}), 139.3 (C^2, CH), 135.9 (Ar, C^{IV}), 135.5 (Ar, C^{IV}), 134.0 (Ar, C^{IV}), 133.8 (Ar, C^{IV}), 129.2 (Ar, 2 CH), 129.1 (Ar, 2 CH), 128.8 (Ar, 2 CH), 128.7 (Ar, 2 CH), 120.1 (C^5, C^{IV}), 87.5 ($C^{1'}$, CH), 83.1 ($C^{3'}$, CH), 81.4 ($C^{4'}$, CH), 72.9 ($C^{5'}$-O-CH_2, CH_2), 71.2 ($C^{3'}$-O-CH_2, CH_2), 70.2 ($C^{5'}$, CH_2), 58.8 (CH_2OH, CH_2), 49.5 ($C^{2'}$, CH) ppm. HRMS (ESI) m/z $[M + H]^+$ calcd. for $C_{25}H_{26}Cl_2N_5O_4$ 530.1362; found 530.1354.

2′-Deoxy-2′-*C*-α-(hydroxymethyl)adenosine (8) from 15: Compound **15** (13 mg, 0.024 mmol) was dissolved in MeOH (2 mL). To this solution was added Pd/C 10% (catalytic amount). The reaction mixture was stirred under hydrogen atmosphere at room temperature for 24 h. The catalyst was filtered off and washed with MeOH. The solvent was removed under reduced pressure. The residue was purified on silica gel chromatography eluting with 10% methanol in dichloromethane to give **8** as a white solid (5 mg, 0.018 mmol, 74% yield). ^{1}H NMR (300 MHz, [D$_4$]MeOD, 25 °C): δ = 8.29 (s, 1 H, H8), 8.17 (s, 1 H, 2-H), 6.18 (d, J = 8.8 Hz, 1 H, 1′-H), 4.56 (d, J = 4.2 Hz, 1 H, 3′-H), 4.12 (d, J = 1.6 Hz, 1 H, 4′-H), 3.96 (dd, J = 6.5, 11.3 Hz, 1 H, AB-spin system, CH_2OH), 3.86 (dd, J = 2.9, 12.4 Hz, 1 H, 5′-H), 3.75 (dd, J = 2.9, 12.4 Hz, 1 H, 5′-H), 3.74 (dd, J = 6.5, 11.3 Hz, 1 H, AB-spin system, CH_2OH), 3.18 (quint, J = 7.4 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (75.4 MHz, [D$_4$]MeOD, 25 °C): δ = 157.5 (C^4, C^{IV}), 153.3 (C8, CH), 150.1 (C^6, C^{IV}), 142.1 (C^2, CH), 121.0 (C^5, C^{IV}), 90.3 ($C^{4'}$, CH), 90.2 ($C^{1'}$, CH), 74.1 ($C^{3'}$, CH), 64.0 ($C^{5'}$, CH_2), 59.1 (CH_2OH, CH_2), 51.8 ($C^{2'}$, CH) ppm. HRMS (ESI) m/z $[M + H]^+$ calcd. for $C_{11}H_{16}N_5O_4$ 282.1202; found 282.1218.

2′-(Phenoxythiocarbonyl)-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)adenosine (16): To a solution containing adenosine (2 g, 7.5 mmol) in dry pyridine (60 mL) was added 1,1,3,3-tetraisopropyldisiloxane (2.4 mL, 7.7 mmol). The reaction mixture was stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc (50 mL) and water (50 mL). The organic layer was washed with cold aqueous HCl (1 M, 25 mL) and saturated aqueous $NaHCO_3$ (50 mL). The organic layer was dried with Na_2SO_4 and evaporated under reduced pressure. The residue was dried under vacuum and dissolved in dry acetonitrile (90 mL). DMAP (2.1 g, 17.2 mmol) and phenyl chlorothionoformate (1.6 mL, 11.9 mmol) were added to the solution and the reaction mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2 (50 mL), washed with water (50 mL), dried with Na_2SO_4 and evaporated under reduced pressure. The residue was purified on silica gel chromatography eluting with 5% methanol in dichloromethane to give **16** as a white solid (3.8 g, 5.9 mmol, 78% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.30 (s, 1 H, H8), 7.97 (s, 1 H, 2-H), 7.43 (t, J = 7.5 Hz, 1 H, Ar), 7.30 (t, J = 7.4 Hz, 1 H, Ar), 7.13 (d, J = 8.0 Hz, 1 H, Ar), 6.38 (d, J = 3.5 Hz, 1 H, 2′-H), 6.16 (s, 1 H, 1′-H), 5.77 (s, 2 H, NH_2), 5.37 (dd, J = 5.3, 8.6 Hz, 1 H, 3′-H), 4.19 (dd, J = 2.5, 12.6 Hz, 1 H, AB-spin system, 5′-H), 4.12 (dt, J = 2.6, 9.1 Hz, 1 H, 4′-H), 4.05 (dd, J = 2.5, 12.6 Hz, 1 H, AB-spin system, 5′-H), 1.12 (s, 4 H, *i*Pr), 1.09 (s, 24 H, *i*Pr) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 194.1 (C=S, C^{IV}), 155.7 (Ar, C^{IV}), 153.5 (C^4, C^{IV}), 153.4 (C8, CH), 149.4 (C^6, C^{IV}), 139.7 (C^2, CH), 129.7 (Ar, 2 CH), 126.8 (Ar, CH), 121.8 (Ar, 2 CH), 120.4 (C^5, C^{IV}), 87.4 ($C^{1'}$, CH), 84.2 ($C^{2'}$, CH), 82.2 ($C^{4'}$, CH), 69.6 ($C^{3'}$, CH), 60.6 ($C^{5'}$, CH_2), 17.5 (*i*Pr, 2 CH_3), 17.4 (*i*Pr, 2 CH_3), 17.3 (*i*Pr, CH_3), 17.2 (*i*Pr, 2 CH_3), 17.1 (*i*Pr, CH_3), 13.4 (*i*Pr, CH), 13.1 (*i*Pr, CH), 13.0 (*i*Pr, 2 CH) ppm. HRMS (ESI) m/z $[M + Na]^+$ calcd. for $C_{29}H_{43}N_5NaO_6SSi_2$ 668.2370; found 668.2274.

2′-Deoxy-2′-α-*C*-styryl-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)adenosine (17): AIBN (250 mg, 1.5 mmol) and **16** (1 g, 1.5 mmol) were dried in dry benzene (10 mL). Styryl tributyltin (2.5 mL, 20 mmol) was added dropwise to the solution at 40 °C. The reaction mixture was heated at 80 °C. After 50 h, the reaction was cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was purified on silica gel chromatography eluting with 5% methanol in CH_2Cl_2 to give **17** as a white solid (371 mg, 0.62 mmol, 42% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.34 (s, 1 H, H8), 8.05 (s, 1 H, 2-H), 7.28 (m, 5 H, Ar), 6.51 (d, J = 16.1 Hz, 1 H, H7′), 6.42 (dd, J = 4.2, 8.1 Hz, 1 H, 6′-H), 6.40 (s, 2 H, NH_2), 6.17 (d, J = 2.7 Hz, 1 H, 1′-H), 4.87 (dd, J = 3.0, 3.6 Hz, 1 H, 3′-H), 4.17 (m, 1 H, 4′-H), 4.11 (m, 2 H, 5′-H), 3.68 (dd, J = 3.9, 6.9 Hz, 1 H, 2′-H), 1.10 (s, 6 H, 2 CH_3), 1.08 (s, 6 H, 2 CH_3), 1.07 (s, 6 H, 2 CH_3), 1.06 (s, 6 H, 2 CH_3), 1.01 (s, 2 H, 2 CH), 1.00 (s, 2 H, 2 CH) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 25 °C): δ = 155.6 (C^4, C^{IV}), 153.1 (C8, CH), 149.7 (C^6, C^{IV}), 139.1 (C^2, CH), 136.6 (C8′, C^{IV}), 134.5 (C7′, CH), 129.5 (Ar, CH), 128.5 (Ar, 2 CH), 126.3 (Ar, 2 CH), 122.7 ($C^{6'}$, CH), 120.2 (C^5, C^{IV}), 87.5 ($C^{1'}$, CH), 85.2 ($C^{4'}$, CH), 73.0 ($C^{3'}$, CH), 62.8 ($C^{5'}$, CH_2), 51.5 ($C^{2'}$, CH), 17.5 (CH_3), 17.4 (CH_3), 17.3 (CH_3), 17.2 (CH_3), 17.1 (CH_3), 17.0 (CH_3), 16.9 (CH_3), 16.8 (CH_3), 13.3 (CH), 13.2 (CH), 12.9 (CH), 12.7 (CH) ppm. HRMS (ESI) m/z $[M + Na]^+$ calcd. for $C_{30}H_{45}N_5NaO_4Si_2$ 618.2908; found 618.2962.

***N*^{6}-Benzoyl-2′-deoxy-2′-α-*C*-(1-phenylethane-1,2-diol)-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)adenosine (18):** To a solution containing **17** (1.4 g, 2.3 mmol) in dry pyridine (30 mL) was added benzoyl chloride (280 μL, 2.4 mmol). The reaction was stirred at room temperature for 5 h. The solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL) and washed with saturated aqueous $NaHCO_3$ (3 × 50 mL).

The organic layer was dried with Na_2SO_4 and evaporate under reduced pressure. The residue was purified on silica gel chromatography eluting with 1% methanol in CH_2Cl_2 to give N^6-benzoyl-2′-deoxy-2′-α-*C*-styryl-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)adenosine as an orange oil. The purified product (800 mg, 1.1 mmol) was dissolved in *t*BuOH (10 mL) and added dropwise at 0 °C to a solution of $K_3Fe(CN)_6$ (1.1 g, 3.3 mmol), K_2CO_3 (470 mg, 3.3 mmol) and OsO_4 (2.5% in *t*BuOH, 320 μL, 0.025 mmol). The reaction mixture was stirred at 0 °C to 4 °C during 24 h. Na_2SO_3 (in large excess) was added to the reaction mixture. After 10 min, the solution was extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was dried with Na_2SO_4 and evaporated under reduced pressure. The residue was purified on silica gel chromatography eluting with 2% methanol in CH_2Cl_2 to give **18** as a brown oil (678 mg, 0.9 mmol, 84% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 9.07 (s, 1 H, NH), 8.76 (s, 1 H, H8), 8.20 (s, 1 H, 2-H), 8.02 (d, *J* = 7.1 Hz, 2 H, Ar), 7.85 (d, *J* = 7.1 Hz, 1 H, Ar), 7.61 (t, *J* = 7.3 Hz, 1 H, Ar), 7.52 (t, *J* = 7.4 Hz, 2 H, Ar), 7.38 (m, 4 H, Ar), 7.20 (m, 3 H, Ar), 6.22 (s, 1 H, H7′), 5.81 (d, *J* = 5.1 Hz, 1 H, 1′-H), 5.22 (dd, *J* = 5.2, 8.8 Hz, 1 H, 3′-H), 4.12 (m, 5 H, 2′-H, 4′-H, 5′-H), 1.10 (s, 12 H, 4 CH_3), 1.09 (s, 12 H, 4 CH_3), 1.08 (s, 4 H, 4 CH) ppm. HRMS (ESI) *m/z* $[M + Na]^+$ calcd. for $C_{37}H_{51}N_5NaO_7Si_2$ 756.3225; found 756.3133.

N^6-Benzoyl-2′-deoxy-2′-*C*-α-(hydroxymethyl)-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)adenosine (19): Compound **18** (180 mg, 0.25 mmol) was dissolved in dioxane (3 mL). At 0 °C, a solution of $NaIO_4$ (550 mg, 0.73 mmol) in water (1 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 2 h and then, at room temperature for 6 h. The reaction was quenched with water (10 mL) and extracted with EtOAc (3 × 10 mL). The organic layer was dried with Na_2SO_4 and evaporated under reduced pressure. The residue was dissolved in dry MeOH (3 mL). $NaBH_4$ (10 mg, 0.27 mmol) was added and the reaction was stirred at room temperature for 30 min. The reaction was quenched with brine (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried with Na_2SO_4 and evaporated under reduced pressure. The residue was purified on silica gel chromatography eluting with 2% methanol in dichloromethane to give **19** as a white solid (80 mg, 0.13 mmol, 51% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 9.35 (s, 1 H, NH), 8.74 (s, 1 H, H8), 8.17 (s, 1 H, 2-H), 8.04 (d, *J* = 7.5 Hz, 2 H, Ar), 7.59 (d, *J* = 7.1 Hz, 1 H, Ar), 7.52 (t, *J* = 7.3 Hz, 2 H, Ar), 6.27 (d, *J* = 3.9 Hz, 1 H, 1′-H), 5.11 (t, *J* = 6.5 Hz, 1 H, 3′-H), 4.08 (m, 3 H, 4′-H, 5′-H), 4.07 (s, 2 H, CH_2OH), 3.12 (q, *J* = 4.2 Hz, 1 H, 2′-H), 1.09 (s, 12 H, 4 CH_3), 1.07 (s, 12 H, 4 CH_3), 1.02 (s, 4 H, 4 CH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 165.0 (C=O, C^{IV}), 152.6 (C^4, C^{IV}), 151.2 (C8, CH), 149.8 (C^6, C^{IV}), 141.9 (C^2, CH), 133.8 (Ar, C^{IV}), 132.9 (Ar, CH), 128.9 (Ar, 2 CH), 128.1 (Ar, 2 CH), 123.8 (C^5, C^{IV}), 86.8 ($C^{1'}$, CH), 84.9 ($C^{4'}$, CH), 72.8 ($C^{3'}$, CH), 62.6 ($C^{5'}$, CH_2), 60.3 (CH_2OH, CH_2), 49.3 ($C^{2'}$, CH), 17.6 (CH_3), 17.4 (2 CH_3), 17.3 (CH_3), 17.2 (2 CH_3), 17.1 (CH_3), 17.0 (CH_3), 13.5 (CH), 13.3 (CH), 12.9 (CH), 12.8 (CH) ppm. HRMS (ESI) *m/z* $[M + Na]^+$ calcd. for $C_{30}H_{45}N_5NaO_6Si_2$ 650.2806; found 650.2497.

2′-Deoxy-2′-*C*-α-(hydroxymethyl)adenosine (8) from 19: Compound **19** (80 mg, 0.13 mmol) was dissolved in dry THF (4 mL). To this solution were added $3HF{\cdot}NEt_3$ (100 μL, 0.61 mmol) and NEt_3 (270 μL, 1.94 mmol). The reaction mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure. The residue was dissolved in 7 M NH_3 in MeOH (2 mL, 14 mmol). The reaction was stirred at 50 °C overnight in a screw-cap-sealed reactor. The solvent was removed under reduced pressure. The residue was purified on silica gel chromatography eluting with 20% methanol in dichloromethane to give **8** as a white solid (18 mg, 0.06 mmol, 46% yield). ^{1}H NMR (300 MHz, [D$_4$]MeOD, 25 °C): δ = 8.29 (s, 1 H, H8), 8.17 (s, 1 H, 2-H), 6.18 (d, *J* = 8.7 Hz, 1 H, 1′-H), 4.57 (t, *J* = 5.6 Hz, 1 H, 3′-H), 4.13 (d, *J* = 1.6 Hz, 1 H, 4′-H), 3.97 (dd, *J* = 6.5, 11.3 Hz, 1 H, AB-spin system, CH_2OH), 3.87 (dd, *J* = 2.9, 12.4 Hz, 1 H, 5′-H), 3.75 (dd, *J* = 2.9, 12.4 Hz, 1 H, 5′-H), 3.74 (dd, *J* = 6.5, 11.3 Hz, 1 H, AB-spin system, CH_2OH), 3.16 (quint, *J* = 6.9 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (75.4 MHz, [D$_4$]MeOD, 25 °C): δ = 157.5 (C^4, C^{IV}), 153.3 (C8, CH), 150.1 (C^6, C^{IV}), 142.1 (C^2, CH), 121.0 (C^5, C^{IV}), 90.3 ($C^{4'}$, CH), 90.2 ($C^{1'}$, CH), 74.1 ($C^{3'}$, CH), 64.0 ($C^{5'}$, CH_2), 59.1 (CH_2OH, CH_2), 51.8 ($C^{2'}$, CH) ppm. HRMS (ESI) *m/z* $[M + Na]^+$ calcd. for $C_{11}H_{15}N_5NaO_4$ 304.1022; found 304.1001.

Biological Tests: The methods used for the evaluation of the antiviral activity have been described previously.[33–35]

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