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Synthesis of 2'-*C*-cyano-2'-deoxy- And 2'-*C*-cyano-2',3'-dideoxy-β-D-arabinofuranosyl Nucleosides

Sonsoles Velázquez and María-José Camarasa*

Instituto de Química Médica, Juan de la Cierva, 3. 28006 Madrid, Spain

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Abstract.—*A series of 2'-C-cyano-2'-deoxy- and 2'-C-cyano-2',3'-dideoxy arabinofuranosyl nucleosides have been prepared by reaction of the corresponding 2'-ulosyl- and 3'-deoxy-2'-ulosyl nucleosides with sodium cyanide followed by 2'-deoxygenation of the cyanohydrins formed and removal of the protecting groups of the sugar moiety.*

INTRODUCTION

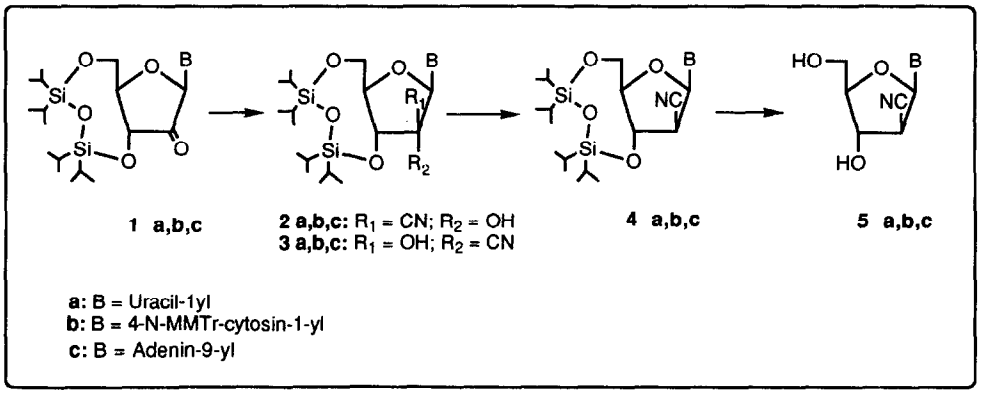
2',3'-Dideoxynucleosides, including AZT and ddI are potent and selective anti-HIV agents, which seem to act through inhibition of Reverse Transcriptase.[1,2,3] However, despite its benefits,[4] severe side effects with AZT treatment are described, mainly associated with bone marrow toxicity.[5,6] In an attempt to increase the antiviral activity and to decrease cytotoxicity of AZT, several analogs of AZT and 2'3'-dideoxynucleosides have been synthesized.[7,8] One approach in this field consisted of the synthesis of 2',3'-ddN derivatives in which the 3'-OH has been replaced by a 3'-substituent, which mimicks the stereoelectronic properties of the 3'-OH or the azido group of AZT.[7] 3'-*C*-Branched-chain sugar nucleosides bearing at the branching point groups that mimick the azido or the OH groups [CN, ethynyl, allyl, propargyl, cyanomethyl and other three atom fragments (C-C=X, C-C≡X)] were considered good candidates to inhibit the Reverse Transcriptase of HIV.[7]

As a part of our program on the synthesis of branched-chain sugar nucleosides as inhibitors of HIV replication, we reported on the synthesis and the anti HIV-1 activity [9] of 3'-*C*-cyano branched chain nucleosides. Our approach[10,11] involved the reaction of pentofuranos-3'-ulosyl nucleosides with sodium cyanide followed by deoxygenation of the cyanohydrin thus formed. We have used this procedure for the synthesis of a variety of 3'-*C*-cyano-3'-deoxynucleoside analogues.[9,11] In the present paper we extend this procedure to the pentofuranos-2'-ulosyl nucleosides and prepare 2'-*C*-cyano-2'-deoxy- and 2'-*C*-cyano-2',3'-dideoxypentofuranosyl derivatives of uracil, cytosine and adenine.

RESULTS AND DISCUSSION

Oxidation of 4-*N*-monomethoxytrityl-1[3',5'-*O*-(tetraisopropyldisiloxan-1,3-diyl)-β-D-ribofuranosyl]cytosine[12] with CrO_3/pyridine/Ac_2O[13] gave 4-*N*-monomethoxytrityl-1[3',5'-*O*-(tetraisopropyldisiloxan-1,3-diyl)-β-D-*erythro*-pentofuranos-2'-ulosyl] cytosine (**1b**) in 72% yield. Treatment of the 2'-ketonucleosides of uracil **1a**[13],

4-*N*-monomethoxytrityl (MMTr) cytosine **1b**, and adenine **1c**[13] with sodium cyanide in a two-phase ethyl ether / water system, in the presence of sodium bicarbonate, gave in each case a mixture of the two epimeric 2'-cyanohydrins **2** and **3**. These cyanohydrins, on standing in solution, reversed to the corresponding ketonucleosides **1**, used as starting materials. Thus, they were not isolated, and were used as such, without further purification for the next step. Deoxygenation[14,15] at the 2'-position of the mixtures of cyanohydrins **2** and **3** by treatment with (phenyloxy) thiocarbonyl chloride in the presence of 4-(dimethylamino)pyridine followed by reaction with tributyltin hydride in the presence of AIBN, afforded, stereoselectively, the 2'-*C*-cyano-2'-deoxy-arabinofuranosyl derivatives of uracil **4a**, 4-*N*-MMTr cytosine **4b** and adenine **4c**, in 40%, 42% and 45% yield, respectively.

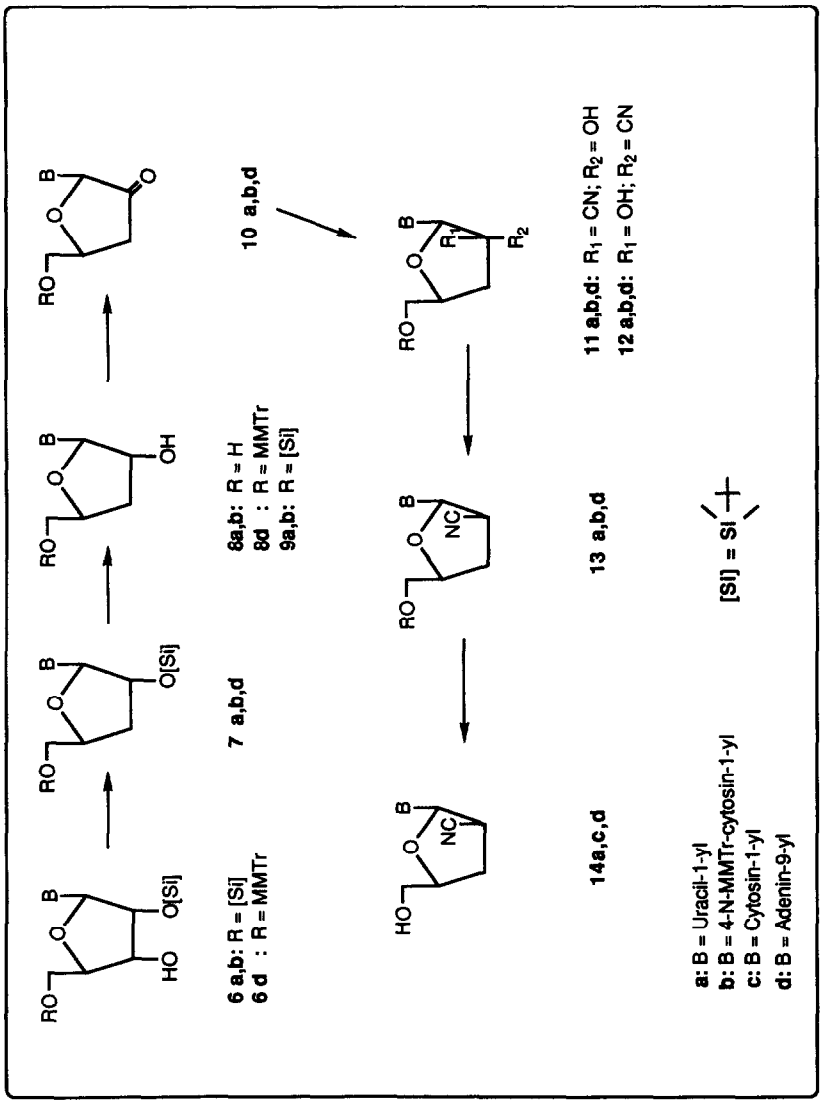


Deprotection of **4a-c** with tetrabutylammonium fluoride afforded the corresponding 2'-*C*-cyano-β-D-arabino deprotected nucleosides of uracil **5a** in low yield (30%) and adenine **5c** (60% yield), unfortunately the corresponding deprotected derivative of cytosine (**5b**) was not obtained and only cytosine was isolated from the reaction mixture. The low yield obtained of the uracil derivative and the no isolation of the corresponding cytosine derivative, would be explained by the higher acidity of the H-2' proton, with respect to other 2'-deoxynucleosides, due to the presence, in the same carbon atom, of the cyano group, which would lead to β-elimination of the nucleobase.

This made us to try a different strategy for the synthesis of the 2'-*C*-cyano-2',3'-ddN which consisted of deoxygenation of the 3' position of the conveniently 2',5'-protected nucleosides and then introduction of the cyano group at 2'-position followed by 2'-deoxygenation, and removal of the 5'-protecting group of the nucleoside under acidic conditions in order to avoid the β-elimination of the nucleobase.

The 2',3'-dideoxy-2'-*C*-cyano analogues were prepared from the corresponding 3'-deoxy-2'-ketonucleosides. Thus, the 2',5'-bis-*O*-silylated derivatives of uracil **6a**[16], 4-*N*-MMTr-cytosine **6b** and 5'-MMTr-2'-*O*-silylated derivative of adenine **6d**[16] were deoxygenated[14] at 3'-position by treatment with *N,N*-thiocarbonyldiimidazol followed by reaction with tributyltinhydride in the presence of α,α'-AIBN to give the 3'-deoxyderivatives **7a**, **7b** and **7d** in 73%, 52% and 75% yield, respectively.

Treatment of **7a-d** with tetrabutylammonium fluoride afforded the corresponding 2',5'-*O*-deprotected-3'-deoxyuridine **8a**[17], cytidine **8b** and the 5'-MMTr-2'-deprotected derivative of adenine **8d**.[18] Reaction of **8a** and


6 a,b: R = [Si]
6 d : R = MMTr
7 a,b,d
8a,b: R = H
8d : R = MMTr
9a,b: R = [Si]
10 a,b,d
14a,c,d
13 a,b,d
11 a,b,d: R1 = CN; R2 = OH
12 a,b,d: R1 = OH; R2 = CN
[Si] = Si
a: B = Uracil-1-yl
b: B = 4-N-MMTr-cytosin-1-yl
c: B = Cytosin-1-yl
d: B = Adenin-9-yl

8b with 1 eq. of *t*-butyldimethylsilyl chloride in dry pyridine gave the 5'-*O*-silylated nucleosides **9a** and **9b** in 72% and 81% yield, respectively. Oxidation of the 5'-*O*-protected nucleosides **9a**, **9b** and **8d** with CrO_3/pyridine/Ac_2O[13] afforded the 2'-ketonucleosides **10a**, **10b** and **10d** in 65%, 89% and 53% yield, respectively. **10a**, **10b** And **10d** were treated with sodium cyanide in ethyl ether/water, in the presence of sodium bicarbonate, to give a mixture of the epimeric nucleoside 2'-cyanohydrins **11** and **12**, further treatment of the mixture (**11+12**) with (phenyloxy)thiocarbonyl chloride and 4-(dimethylamino)pyridine followed by reaction with Bu_3SnH and AIBN, gave the 2'-*C*-cyano-2',3'-dideoxyderivatives **13a**, **13b** and **13d** in 50%, 36% and 25% yield, respectively.

Finally, deprotection of **13a** and **13b** with methanolic 0.1 M HCl gave the deprotected nucleosides of uracil **14a** and cytosine **14c** in 86% and 80% yield, respectively. Similarly, deprotection of the 5'-*O*-MMTr, group of **13d** with 80% aqueous acetic acid afforded **14d** in 70% yield.

The presence of the 2'-*C*-cyano-2'-deoxy grouping in nucleosides **4** and **5**, and the 2'-*C*-cyano-2',3'-dideoxy grouping in nucleosides **13** and **14** was established from their analytical and spectroscopic data. The IR spectra of **4a-c**, **5a-c**, **13a-d** and **14a-d** showed a band at 2220-2230 cm^{-1} characteristic of CN group. The ^{1}HNMR spectra of **4a-c** and **5a-c** showed the presence of H-2' at δ 3.60-4.07, as a doublet of doublets for **4a**, **4c** and **5c** or as a triplet for **4b** and **5a**, by coupling with H-1' and H-3'. The ^{13}CNMR of **4a-c** and **5a-c** showed a signal at δ 115.29-117.14 assigned to the CN carbon atom, and a signal at δ 42.15-45.12 corresponding to the C-2'. On the other hand, the ^{1}HNMR spectra of **13a-d** and **14a-d** showed the presence of a multiplet corresponding to H-2' at δ 3.59-4.30 and two multiplets, overlapped in some cases, corresponding to the 2H-3' at δ 2.1-2.30. The ^{13}CNMR of **13a-d** and **14a-d** showed the signal corresponding to the CN carbon atom at δ 116.25-118.27 and the signals corresponding to the C-2' at δ 34.21-35.30 and to the C-3' at δ 29.25-31.39.

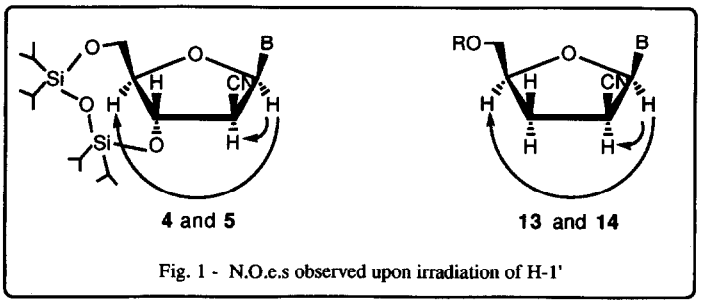


Fig. 1 - N.O.e.s observed upon irradiation of H-1'

The stereochemistry at C-2' of the *arabino* 2'-*C*-cyanonucleosides **4**, **5**, **13** and **14** was unequivocally determined by n.O.e. experiments,[19,20] the signal of H-1' was irradiated and the magnitude of n.O.e. at the protons of the sugar were observed (Fig 1). Thus, in compounds **4a-c** and **5a-c** irradiation of H-1' induced n.O.e. to H-2' [**4a** (21%), **4b** (19%), **4c** (14%), **5a** (20%), **5c** (19%)] and to H-4' [**4a** (1%), **4b** (3%), **4c** (4%), **5a** (1%), **5c** (2%)]. Similarly, irradiation of H-1' in **13a-d** and **14a-d** induced n.O.e. to H-2' [**13a** (10%), **13b** (15%), **13d** (10%), **14a** (17%), **14c** (16%), **14d** (15%)] and to H-4' [**13a** (3%), **13b** (4%), **13d** (2%), **14a** (4%), **14c** (1%), **14d** (1%)]. This demonstrates that protons H-1', H-2' and H-4' are all in the α-

face of the furanose ring and that no epimerization at C-2' had occurr during removal of the protecting groups of the final products **4** → **5** and **13** →**14.**

The *arabino* configuration of compounds **4, 5, 13** and **14** resulted from 2'-deoxygenation of cyanohydrins (**2** and **3**) and (**11** and **12**), and can be explained by steric hindrance of the β-face of the furanose ring, which facilitates the approach of the tributyltin hydride from the less hindered α face of the molecule,[14] opposite to the heterocyclic base at the anomeric position. The stereochemistry of the above reactions is in agreement with those observed in most 2'-radical deoxygenations.[21,22,23]

The compounds described above have been tested for antiviral activity against HIV-1, but none of them showed any significant activity, nor toxicity. Further tests of these compounds in other viruses are in progress.

EXPERIMENTAL

Microanalyses were obtained with a Heareus CHN-O-RAPID instrument. IR spectra were recorded with a Shimadzu IR-435 spectrometer. The ^{1}H- and ^{13}C-NMR spectra (internal Me_4Si) were obtained variously with Varian EM-390 and XL-300, and Brucker AM-200 and WP-80-SY spectrometers. Proximities were established conventionally on the basis of n.O.e. effects. Analytical TLC was preformed on Silica Gel 60 F_{254} (Merck). Silica Gel 60 (230-400 mesh) (Merck) was used for flash-column chromatography.

4-*N*-Monomethoxytrityl-1-[3',5'-*O*-(tetraisopropyldisiloxan-1,3-diyl)-β-D-*erythro*-pentofuranos-2'-ulosyl]cytosine (1b)

To a solution of CrO_3 (1.2 g, 12 mmol), pyridine (2 mL, 24 mmol), acetic anhydride (1.2 mL, 12 mmol) and methylene chloride (28 mL), 4-*N*-monomethoxytrityl-1-[3',5'-*O*-(tetraisopropyldisiloxan-1,3-diyl)-β-D-ribofuranosyl]cytosine[12] (3.0 g, 4 mmol) was added. The resulting mixture was stirred at room temperature for 45 min, evaporated to dryness, and the residue, suspended in ethyl acetate (10 mL), was filtered through a silica gel column (20 g) using ethyl acetate as eluent. The filtered solution was evaporated to dryness and the residue coevaporated with ethanol (3 x 5 mL) to give **1b** (2.17 g, 72%) as a white foam. IR (KBr) 1770 cm^{-1} (C=O furanosulose); ^{1}HNMR ($CDCl_3$, 90 MHz): δ 0.8-1.1 (m, 28H, isopropyl), 3.7 (s, 3H, OCH_3), 3.8-4.2 (m, 4H, H-3', H-4', 2H-5'), 4.7 (s, 1H, H-1'), 5.0 (d, 1H, H-5), 5.2 (d. 1H, H-6), 6.7-7.3 (m, 14H, Ar-H). Anal. Calcd. for $C_{41}H_{54}N_3O_7Si_2$: C, 65.04; H, 7.19; N, 5.55. Found: C, 65.33; H, 7.03; N, 5.34.

General procedure for the synthesis of 2'-*C*-Cyano-2'-deoxy-3',5'-*O*-(tetraisopyl-disiloxan-1,3-diyl)-β-D-arabinofuranosyl Nucleosides (4)

A mixture of the 2'-ketonucleoside **1** (1 mmol), water (4 mL), ethyl ether (8 mL), sodium bicarbonate (0.16 g, 2 mmol) and sodium cyanide (0.05 g, 1 mmol) was stirred vigorously at room temperature overnight. The organic phase was separated, and the aqueous phase was washed with ethyl ether (2 x 8 mL). The combined ethereal phases were dried over Na_2SO_4, filtered, and evaporated to dryness. The residue, a mixture of two epimeric cyanohydrins (**2** and **3**), was dissolved in dry acetonitrile (10 mL) to this solution were added 4-(dimethylamino)pyridine (0.25 g, 2 mmol) and (phenyloxy) thiocarbonyl chloride (0.2 mL, 1.1 mmol). The mixture was stirred at room temperature for 2 h, and the solvent was evaporated to dryness. The residue, suspended in toluene (20 mL), was transferred to a three-necked flask. Argon was bubbled through the suspension for 15 min. and then AIBN (0.03 g, 0.2 mmol) and tributyltinhydride (0.4 mL, 1.5 mmol) were added. The flask was heated in an oil bath at 80°C for 1-5 h, while the Argon bubbling was maintained. The reaction mixture was allowed to reach room temperature then, it was washed with water (20 mL), dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by column chromatography.

1-[2'-*C*-Cyano-2'-deoxy-3',5'-*O*-(tetraisopropyldisiloxan-1,3-diyl)-β-D-arabinofuranosyl] uracil (4a)

The residue was chromatographed with ethyl acetate/hexane (1:2) as the eluent to give 0.29 g (40%) of **4a** as a white foam. IR (KBr) 2230 cm^{-1} (CN); ^{1}HNMR ($CDCl_3$, 200 MHz): δ 1.02-1.11 (m, 28H, isopropyl), 3.60 (dd, 1H, $J_{1',2'}$=7.1, $J_{2',3'}$=9.5 Hz, H-2'), 3.82 (dt, 1H, H-4'), 4.03 (dd, 1H, $J_{4',5'a}$=2.8, $J_{5'a,5'b}$=13.4 Hz, H-5a), 4.17 (dd, 1H, $J_{4',5'b}$=2.4 Hz, H-5'b), 4.65 (dd, 1H, $J_{3',4'}$=8.4 Hz, H-3'), 5.78 (dd, 1H, $J_{5,6}$=8.3, $J_{5,NH}$=1.6 Hz, H-5), 6.29 (d, 1H, H-1'), 7.66 (d, 1H, H-6); ^{13}CNMR ($CDCl_3$, 50 MHz): d 42.15 (C-2'), 59.55 (C-5'), 71.84 (C-3'), 82.04, 84.17 (C-1', C-4'), 103.14 (C-5), 115.51 (CN), 138.28 (C-6), 149.89 (C-2), 162.44 (C-4). Anal. Calcd. for $C_{22}H_{37}N_3O_6Si_2$: C, 53.30; H, 7.52; N, 8.48. Found: C, 53.15; H, 7.46; N, 8.35.

4-N-Monomethoxytrityl-1-[2'-*C*-Cyano-2'-deoxy-3',5'-*O*-(tetraisopropyldisiloxan-1,3-diyl)-β-D-arabinofuranosyl]cytosine (4b)

The residue was chromatographed with ethyl acetate/hexane (1:1) as the eluent to give **4b** (0.32 g, 42%) as a white foam. IR (Nujol) 2225 cm^{-1} (CN); ^{1}HNMR ($CDCl_3$, 300 MHz): δ 0.9-1.1 (m, 28H, isopropyl), 3.66 (t, 1H, $J_{1',2'}$=$J_{2',3'}$=7.5 Hz, H-2'), 3.80 (m, 4H, OCH_3, H-4'), 4.03 (m, 2H, 2H-5'), 4.55 (t, 1H, $J_{3',4'}$=7.5 Hz, H-3'), 5.12 (d, 1H, H-5), 6.29 (d, 1H, H-1'), 6.85 (d, 2H, m-H of MMTr), 7.14-7.37 (m, 12H, Ar-H), 7.40 (d, 1H, H-6); ^{13}CNMR ($CDCl_3$, 50 MHz): δ 42.56 (C-2'), 55.23 (OCH_3), 60.60 (C-5'), 73.37 (C-3'), 82.89, 84.05 (C-1', C-4'), 95.12 (C-5), 115.80 (CN), 139.40 (C-6). Anal. Calcd. for $C_{42}H_{57}N_4O_6Si_2$: C, 65.76; H, 7.10; N, 7.30. Found: C, 65.84; H, 7.31; N, 7.42.

9-[2'-*C*-Cyano-2'-deoxy-3',5'-*O*-(tetraisopropyldisiloxan-1,3-diyl)-β-D-arabinofuranosyl] adenine (4c)

The residue was chromatographed with ethyl acetate/hexane (1:1) to yield **4c** (0.23 g, 45%) as a white foam. IR (KBr) 2220 cm^{-1} (CN); ^{1}HNMR ($CDCl_3$, 300 MHz): δ 1.10-1.30 (m, 28H, isopropyl), 3.86 (dd, 1H, $J_{1',2'}$=7.5, $J_{2',3'}$=8.5 Hz, H-2'), 4.01 (m, 1H, H-4'), 4.15 (dd, 1H, $J_{4',5'a}$=2.9, $J_{5'a,5'b}$=12.7 Hz, H-5'a), 4.32 (dd, 1H, $J_{4',5'b}$=4.2 Hz, H-5'b), 5.38 (t, 1H, $J_{3',4'}$=8.5 Hz, H-3'), 6.06 (bs, 2H, NH_2), 6.56 (d, 1H, H-1'), 8.16 (s, 1H, H-2), 8.43 (s, 1H, H-8); ^{13}CNMR ($CDCl_3$, 50 MHz): δ 45.12 (C-2'), 60.99 (C-5'), 73.46 (C-3'), 81.42, 84.43 (C-1', C-4'), 115.29 (CN), 119.93 (C-5), 138.29 (C-8), 149.25 (C-4), 153.15 (C-2), 155.72 (C-6). Anal. Calcd. for $C_{23}H_{38}N_6O_4Si_2$: C, 53.25; H, 7.38; N, 16.20. Found: C, 53.01; H, 7.30; N, 16.41.

Deprotection of Tetraisopropyldisiloxane Group. General Procedure:

To a solution of the silyl-protected nucleosides **4a-c** (1 mmol) in THF (15 mL) were added (20 mL, 2 mmol) of a 1M Bu_4NF in THF and the mixture was stirred at room temperature from 15 min. to 3 h. The mixture was evaporated to dryness and the residue was purified by flash column chromatography using ethyl acetate/methanol (10:1) as the eluent to afford the free nucleoside.

1-(2'-*C*-Cyano-2'-deoxy-β-D-arabinofuranosyl)uracil (5a)

Following the general procedure, **4a** (0.25 g, 0.5 mmol) reacted with Bu_4NF for 15 min, to give, after purification, **5a** (0.04 g, 30%) as a white foam. IR (KBr) 2220 cm^{-1} (CN); ^{1}HNMR [$(CD_3)_2$ SO, 300 MHz]: δ 3.56-3.74 (m, 3H, H-4', 2H-5'), 3.87 (t, 1H, $J_{1',2'}$=$J_{2',3'}$=7.8 Hz, H-2'), 4.40 (m, 1H, $J_{3',4'}$=7.8 Hz, H-3'), 5.20 (t, 1H, OH), 5.69 (d, 1H, $J_{5,6}$=8.1 Hz, H-5), 6.19 (m, 2H, H-1', OH), 7.93 (d, 1H, H-6). Anal. Calcd. for $C_{10}H_{11}N_3O_5$: C, 47.43; H, 4.38; N, 16.59. Found: C, 47.28; H, 4.11; N, 16.68.

9-(2'-*C*-Cyano-2'-deoxy-β-D-arabinofuranosyl)adenine (5c)

According to the general procedure **4c** (0.21 g, 0.4 mmol) reacted with Bu_4NF for 1.5 h, to afford, after purification 0.066 g (60%) of **5c** as a white foam. IR (KBr) 2220 cm^{-1} (CN); ^{1}HNMR [$(CD_3)_2$ SO, 50 MHz]: δ 3.45-3.85 (m, 3H, H-4', 2H-5'), 4.07 (dd, 1H, $J_{1',2'}$=7.1, $J_{2',3'}$=8.4 Hz, H-2'), 4.86 (m, 1H, $J_{3',4'}$=8.4 Hz, H-3'), 5.16 (t, 1H, OH), 6.26 (d, 1H, OH), 6.52 (d, 1H, H-1'), 7,34 (bs, 2H, NH_2), 8.16 (s, 1H, H-2), 8.39 (s, 1H, H-8); ^{13}CNMR [$(CD_3)_2SO$, 50 MHz] δ 42.61 (C-2'), 59.64 (C-5'), 71.53 (C-3'), 81.33, 85.29 (C-1', C-4'), 117.14 (CN), 118.76 (C-5), 139.00 (C-8), 148.89 (C-4), 152.86 (C-2), 156.05 (C-6). Anal. Calcd. for $C_{11}H_{12}N_6O_3$: C, 47.82; H, 4.38; N, 30.42. Found: C, 47.65; H, 4.45; N, 30.53.

2',5'-Bis-*O*-(*tert*-butyldimethylsilyl)-4-*N*-monomethoxytrityl-cytidine (6b)

2',5'-Bis-O-(*tert*-butyldimethylsilyl)cytidine[24] (8.00 g, 16.9 mmol) was dissolved in dry CH_2Cl_2 (80 mL) and treated with MMTrCl (10.48 g, 33.9 mmol) and DMAP (83 mg, 0.68 mmol). The mixture was stirred until it had become homogeneous and then Et_3N (4.69 mL, 33.8 mmol) was added. After the mixture being stirred for 1 h, the reaction was quenched by addition of (1:1) pyridine-water (50 mL). Then, the mixture was extracted with CH_2Cl_2 (2 x 50 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was chromatographed with ethylacetate/hexane (1:2) as the eluent to yield 12 g of **6b** (96%) as a yellow foam. ^{1}HNMR ($CDCl_3$, 90 MHz): δ 0.8 (s, 18H, *t*-Bu), 2.4 (bs, 1H, OH), 3.6-4.1 (m, 5H, H-2', H-3', H-4', 2H-5'), 3.7 (s, 3H, OCH_3), 4.9 (d, 1H, H-5), 5.9 (d, 1H, $J_{1',2'}$=2 Hz, H-1'), 6.7 (d, 2H, m-H of MMTr), 7.0-7.3 (m, 12H, Ar-H), 7.7 (d, 1H, H-6). Anal. Calcd. for $C_{41}H_{58}N_3O_6Si_2$: C, 66.09; H, 7.85; N, 5.64. Found: C, 66.12; H, 7.80; N, 5.90.

2',5'-Bis-*O*-(*tert*-butyldimethylsilyl)-3'-deoxyuridine (7a)

To a solution of **6a**[16] (3.31 g, 7 mmol) in toluene (80 mL), N,N'-thiocarbonyldiimidazol (1.87 g, 10.5 mmol) was added. The mixture was heated at 80°C for 3 h, and then, ethyl acetate (150 mL) and water (75 mL) were added. The organic layer was separated, washed with water (3 x 75 mL), dried over anhydrous sodium sulphate, filtered and evaporated to dryness. The residue, suspended in toluene (100 mL), was transferred to a three-necked flask, AIBN (0.23 g, 1.4 mmol) was added, Argon was bubbled through the suspension for 15 min, and then, tributyltin hydride (7.4 mL, 28 mmol) was added. The flask was heated in an oil bath at 80°C for 5 h, while Argon bubbling was maintained. The reaction mixture was allowed to reach room temperature, and the solvent, evaporated to dryness. The residue was purified by column chromatography with ethyl acetate/hexane (1:3) as the eluent to give 2.33 g (73%) of **7a** as white foam. ^{1}HNMR ($CDCl_3$, 90 MHz): δ 1.7-2.0 (m, 2H, 2H-3'), 3.7 (dd, 1H, $J_{4',5'a}$=2, $J_{5'a,5'b}$=12 Hz, H-5'a), 4.1 (dd, 1H, $J_{4',5'b}$=2 Hz, H-5'b), 4.1-4.5 (m, 2H, H-2', H-4'), 5.5 (d, 1H, H-5), 5.6 (s, 1H, H-1'), 8.0 (d, 1H, H-6), 9.2 (bs, 1H, NH). Anal. Calcd. for $C_{21}H_{40}N_2O_5Si_2$: C, 55.20; H, 8.83; N, 6.13. Found: C, 54.93: H, 8.75; N, 6.33.

2',5'-Bis-*O*-(*tert*-butyldimethylsilyl)-3'-deoxy-4-*N*-monomethoxytrityl-cytidine (7b)

The nucleoside **6b** (5.21 g, 7 mmol) dissolved in toluene (80 mL) was treated with N,N'-thiocarbonyldiimidazol and AIBN as described for the synthesis of **7a**. The residue obtained, after the work-up, was purified by column chromatography with ethyl acetate/hexane (1:3) to afford 2.65 g (52%) of **7b** as a white foam. ^{1}HNMR ($CDCl_3$, 90 MHz): δ 0.8 (s, 18H, t-Bu), 1.5-1.7 (m, 1H, H-3'a), 1.8-1.9 (m, 1H, H-3'b), 3.6 (d, 1H, $J_{5'a,5'b}$=12 Hz, H-5'a), 4.1 (d, 1H, H-5'b), 4.4 (d, 1H, $J_{2',3'}$=3 Hz, H-2'), 4.5 (m, 1H, H-4'), 4.9 (d, 1H, H-5), 5.8 (s, 1H, H-1'), 6.8 (d, 2H, m-H of MMTr), 7.1-7.3 (m, 12H, Ar-H), 8.0 (d, 1H, H-6). Anal. Calcd. for $C_{41}H_{58}N_3O_5Si_2$: C, 67.54; H, 8.02; N, 5.76. Found: C, 67.87; H, 8.12; N, 5.60.

2'-*O*-(*tert*-Butyldimethylsilyl)-3'-deoxy-5'-*O*-monomethoxytrityl-adenine (7d)

To a solution of the protected nucleoside **6d**[16] (4.58 g, 7 mmol) in DMF (70 mL), N,N'-thiocarbonyldiimidazol (3.74 g, 21 mmol) was added. After stirring at room temperature for 5 h. The reaction was treated with AIBN as described for the synthesis of **7a**. The residue obtained, after the work-up, was purified by column chromatography with ethyl acetate/hexane (1:2) as the eluent to give **7d** (3.34 g, 75%) as a white foam. ^{1}HNMR ($CDCl_3$, 90 MHz): δ 1.8-2.2 (m, 2H, 2H-3'), 3.4-3.5 (m, 2H, 2H-5'), 3.7 (s, 3H, OCH_3), 4.5-4.8 (m, 2H, H-2', H-4'), 5.8 (bs, 2H, NH_2), 5.9 (s, 1H, H-1'), 6.6 (d, 2H, m-H of MMTr), 7.2-7.5 (m, 12H, Ar-H), 8.0 (s, 1H, H-2), 8.3 (s, 1H, H-8). Anal Calcd. for $C_{36}H_{43}N_5O_4Si$: C, 67.79; H, 6.79; N, 10.98. Found: C, 67.59; H, 6.66; N, 10.75.

General Procedure for Removal of the Protecting Groups of the 2',5'-Bis-*O*-Silyl-Protected 3'-deoxynucleosides 7

To a solution of the silyl-protected nucleoside **7** (1 mmol) in THF (15 mL) a 1M solution Bu_4NF (20 mL, 2 mmol) was added, and the mixture was stirred at room temperature for 1-3 h. The reaction mixture was filtered to through a wet (THF) column of silica gel using THF as the eluent. The filtrate was evaporated to dryness, and the residue was purified by column chromatography with ethyl acetate/methanol (10:1) as the eluent to afford the free nucleoside.

3'-Deoxyuridine (8a)[17]

Following the general procedure **7a** (1.37 g, 3 mmol) reacted with Bu_4NF for 3 h, to yield, after purification, 0.66 g (96%) of **8a** as a white foam. ^{1}HNMR [$(CD_3)_2SO$, 90 MHz]: δ 1.6-1.9 (m, 2H, 2H-3'), 3.4-3.6 (m, 2H, 2H-5'), 3.9-4.3 (m, 2H, H-2', H-4'), 4.9 (t, 1H, OH), 5.3-5.6 (m, 3H, H-1', H-5, OH), 7.8 (d, 1H, H-6). Anal. Calcd. for $C_9H_{12}N_2O_5$: C, 47.36; H, 5.30; N, 12.28. Found: C, 47.68; H, 5.39; N, 12.03.

3'-Deoxy-4-*N*-monomethoxytrityl-cytidine (8b)

According to the general procedure **7b** (2.62 g, 3.6 mmol) reacted with Bu_4NF for 2 h, to give 1.25 (70%) of **8b** as a white foam. ^{1}HNMR [$(CD_3)_2SO$, 90 MHz]: δ 1.6-1.9 (m, 2H, 2H-3'), 3.5-3.7 (m, 2H, 2H-5'), 3.7 (s, 3H, OCH_3), 3.9-4.3 (m, 3H, H-2', H-4', H-5), 5.0 (t, 1H, OH), 5.4 (d, 1H, OH), 5.6 (d, 1H, $J_{1',2'}$=2 Hz, H-1'), 6.9 (d, 2H, m-H of MMTr), 7.1-7.4 (m, 12H, Ar-H), 7.9 (d, 1H, H-6), 8.3 (bs, 1H, NH). Anal. Calcd. for $C_{29}H_{29}N_3O_5$: C, 69.72; H, 5.85; N, 8.41. Found: C, 69.98; H, 5.96; N, 8.60.

3'-Deoxy-5'-*O*-monomethoxytrityl-adenosine (8d)[18]

Following the general procedure **7d** (3.19 g, 5 mmol) reacted with 1 eq of Bu_4NF (50 mL, 5 mmol) for 1 h. To give, after purification, 2.4 g (93%) of **8d** as a white foam. ^{1}HNMR ($CDCl_3$, 90 MHz): δ 2.0-2.2 (m, 2H, 2H-3'), 3.2-3.4 (m, 2H, 2H-5'), 3.7 (s, 3H, OCH_3), 4.6-4.8 (m, 2H, H-2', H-4'), 5.9 (d, 1H, $J_{1',2'}$=2 Hz, H-1'), 6.3 (bs, 2H, NH_2), 6.7 (d, 2H, m-H of MMTr), 7.1-7.4 (m, 12H, Ar-H), 8.0 (s, 1H, H-2), 8.2 (s, 1H, H-8). Anal. Calcd. for $C_{30}H_{29}N_5O_4$: C, 68.22; H, 5.58; N, 13.38. Found: C, 68.40; H, 5.64; N, 13.23.

5'-*O*-(*tert*-Butyldimethylsilyl)-3'-deoxyuridine (9a)

To an ice cooled solution of **8a** (0.66 g, 2.9 mmol) in dry pyridine (30 mL) *tert*-butyldimethylsilyl chloride (0.44 g, 2.9 mmol) was added, in portions, during 2 h. The resulting mixture was stirred at room temperature overnight, and then, evaporated to dryness. The residue, dissolved in chloroform, was washed with water (2 x 15 ml) dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by column chromatography with ethyl acetate/methanol (30:1) as the eluent to yield 0.71 g (72%) of **9a** as a white foam. ^{1}HNMR ($CDCl_3$, 90 MHz): δ 0.9 (s, 9H, *t*-Bu), 1.8-2.1 (m, 2H, 2H-3'), 3.7 (dd, 1H, $J_{4',5'a}$=1, $J_{5'a,5'b}$=12

Hz, H-5'a), 4.2 (dd, 1H, $J_{4',5'b}$=1 Hz, H-5'b), 4.4-4.7 (m, 3H, H-2', H-4', O-H), 5.6 (d, 1H, H-5), 5.7 (s, 1H, H-1'), 8.2 (d, 1H, H-6). Anal. Calcd. for $C_{15}H_{26}N_2O_5Si$: C, 52.60; H, 7.65; N, 8.18. Found: C, 52.30; H, 7.48; N, 8.03.

5'-*O*-(*tert*-Butyldimethylsilyl)-3'-deoxy-4-*N*-monomethoxytrityl-cytidine (9b)

Compound **8b** (1.25 g, 2.5 mmol) reacted with *tert*-butyldimethylsilylchloride (0.38 g, 2.5 mmol) as described for the synthesis of **9a**. After the work-up, the residue was purified by column chromatography with ethyl acetate/methanol (20:1) to give 1.24 g (81%) of **9b** as a white foam. ^{1}HNMR [$(CD_3)_2SO$, 90 MHz]: δ 0.9 (s, 9H, t-Bu), 1.7-1.9 (m, 2H, 2H-3'), 3.7 (s, 3H, OCH_3), 3.6-4.4 (m, 5H, H-2', H-4' 2H-5', H-5), 5.5 (bs, 1H, OH), 5.6 (s, 1H, H-1'), 6.9 (d, 2H, m-H of MMTr), 7.1-7.4 (m, 12H, Ar-H), 7.8 (d, 1H, H-6), 8.4 (bs, 1H, NH). Anal. Calcd. for $C_{35}H_{44}N_3O_5Si$: C, 68.37; H, 7.21; N, 6.83. Found: C, 68.00; H, 7.03; N, 6.97.

1-[5'-*O*-(*tert*-butyldimethylsilyl)-3'-deoxy-β-D-*glycero*-pentofuranos-2'-ulosyl]uracil (10a)

Compound **9a** (0.68 g, 2 mmol) was added to a solution of CrO_3/pyridine/acetic anhydride as described for the synthesis of **1b**. After the work-up 0.44 g (65%) of **10a** was obtained, as a yellow syrup. IR (Nujol) 1770 cm^{-1} (C=O furanosulose); ^{1}HNMR ($CDCl_3$, 200 MHz): δ 0.90 (s, 9H, t-Bu), 2.65 (dd, 1H, $J_{3'a,4'}$=7.5, $J_{3'a,3'b}$=18.6 Hz, H-3'a), 2.85 (dd, 1H, $J_{3'b,4'}$=7.6 Hz, H-3'b), 3.86 (dd, 1H, $J_{4',5'a}$=4.4, $J_{5'a,5'b}$=11.1 Hz, H-5'a), 3.93 (dd, 1H, $J_{4',5'b}$=3.9 Hz, H-5'b), 4.51 (m, 1H, H-4'), 5.50 (s, 1H, H-1'), 5.72 (d, 1H, H-5), 7.26 (d, 1H, H-6), 9.47 (bs, 1H, NH). Anal. Calcd. for $C_{15}H_{24}N_2O_5Si$: C, 52.91; H, 7.10; N, 8.23. Found: C, 52.59; H, 7.31; N, 8.03.

4-*N*-Monomethoxytrityl-1-[5'-*O*-(*tert*-butyldimethylsilyl)-3'-deoxy-β-D-*glycero*-pentofuranos-2'-ulosyl]cytosine (10b)

Following the oxidation procedure described for the synthesis of **1b**, compound **9b** (1.23 g, 2 mmol) reacted with CrO_3/pyridine/acetic anhydride for 1 h, to afford, after the work-up 1.08 g (89%) of **10b** as a whitte foam. IR (Nujol) 1775 cm^{-1} (C=O furanosulose); ^{1}HNMR ($CDCl_3$, 90 MHz): δ 0.9 (s, 9H, t-Bu), 2.4 (dd, 1H, $J_{3'a,4'}$=6.0, $J_{3'a,3'b}$=18.0 Hz, H-3'a), 2.9 (dd, 1H, $J_{3'b,4'}$=8.0 Hz, H-3'b), 3.7 (s, 3H, OCH_3), 3.8 (d, 2H, 2H-5'), 4.4 (m, 1H, H-4'), 5.0 (m, 2H, H-1', H-5), 6.7-7.3 (m, 15H, ArH, H-6). Anal. Calcd for $C_{35}H_{42}N_3O_5Si$: C, 68.59; H, 6.91; N, 6.86. Found: C, 68.29; H, 6.71; N, 6.79.

9-(3'-Deoxy-5'-*O*-monomethoxytrityl-β-D-*glycero*-pentofuranos-2'-ulosyl)adenine (10d)

According to the procedure described for the synthesis of **1b**, compound **8d** (1.05 g, 2 mmol) reacted with CrO3/pyridine/acetic anhydride for 45 min, to give 0.55 g (53%) of **10d** as a brown foam. IR (Nujol) 1770 cm^{-1} (C=O furanosulose); ^{1}HNMR ($CDCl_3$, 90 MHz): d 2.7 (dd, 1H, $J_{3'a,4'}$=7.0, $J_{3'a,3'b}$=18.0 Hz, H-3'a), 3.2 (dd, 1H, $J_{3'b,4'}$=7.0 Hz, H-3'b), 3.4 (d, 2H, 2H-5'), 3.7 (s, 3H, OCH_3), 4.5-4.7 (m, 1H, H-4') 5.7 (s, 1H, H-1'), 6.0 (bs, 2H, NH_2), 6.7 (d, 2H, m-H of MMTr) 7.1-7.4 (m, 12H, Ar-H), 7.8 (s, 1H, H-2), 8.2 (s, 1H, H-8). Anal. Calcd. for $C_{30}H_{27}N_5O_4$: C, 69.08; H, 5.22; N, 13.43. Found: C, 69.40; H, 5.13; N, 13.59.

1-[5'-*O*-(*tert*-Butyldimethylsilyl)-2'-*C*-cyano-2',3'-dideoxy-β-D-*threo*-pentofuranosyl] uracil (13a)

According to the general procedure described for the synthesis of 2'-*C*-cyano-2'-deoxynucleosides (**4**), the 2'-ketonucleoside **10a** (0.41 g, 1.2 mmol), reacted with NaCN overnight, then with (phenyloxy)thiocarbonyl chloride and finally with Bu_3SnH for 3 h, to give, after the work-up a residue which was chromatographed with ethyl acetate/hexane (1:2) to afford 0.21 g (50%) of **13a** as a white foam. IR (KBr) 2225 cm^{-1} (CN); ^{1}HNMR ($CDCl_3$, 200 MHz): δ 0.87 (s, 9H, t-Bu), 2.30 (m, 2H, 2H-3'), 3.59 (m, 1H, H-2'), 3.69 (dd, 1H, $J_{4',5'a}$=2.6,

$J_{5'a,5'b}$=11.7 Hz, H-5'a), 3.99 (dd, 1H, $J_{4',5'b}$=2.8 Hz, H-5'b), 4.1 (m, 1H, H-4'), 5.68 (d, 1H, H-5), 6.20 (d, 1H, $J_{1',2'}$=8.7 Hz, H-1'), 7.92 (d, 1H, H-6); ^{13}CNMR ($CDCl_3$, 50 MHz): δ 25.94 (CH_3), 29.45 (C-3'), 35.30 (C-2'), 62.19 (C-5'), 84.06, 81.04 (C-1', C-4'), 102.76 (C-5), 116.47 (CN), 139.18 (C-6), 150.31 (C-2), 162.89 (C-4). Anal. Calcd. for $C_{16}H_{25}N_3O_4Si$: C, 54.67; H, 7.17; N, 11.95. Found: C, 54.39; H, 7.06; N, 12.05.

1-[5'-*O*-(*tert*-butyldimethylsilyl)-2'-*C*-cyano-2',3'-dideoxy-b-D-*threo*-pentofuranosyl]-4-*N*-monomethoxytrityl-cytosine (13b)

The 2'-ketonucleoside **10b** (0.67 g, 1,1 mmol) reacted with NaCN/(phenyloxy) thiocarbonyl chloride/Bu_3SnH, following the general procedure described for the synthesis of 2'-*C*-cyano-2'-deoxynucleosides (**4**). After the work-up, the residue was purified by column chromatography with ethylacetate, as the eluent, to give **13b** (0.24 g, 36%) as a white foam. IR (KBr) 2220 cm^{-1} (CN); ^{1}HNMR ($CDCl_3$, 300 MHz): δ 0.78 (s, 9H, t-Bu), 2.27-2.34 (m, 2H, 2H-3'), 3.65-3.73 (m, 2H, H-2', H-5'a), 3.78 (s, 3H, OCH_3), 3.80 (dd, 1H, $J_{4',5'b}$=3.6, $J_{5'a,5'b}$=11.4 Hz, H-5'b), 4.13 (m, 1H, H-4'), 5.05 (d, 1H, H-5), 6.19 (d, 1H, $J_{1',2'}$=6.2 Hz, H-1'), 6.80-6.84 (d, 2H, m-H of MMTr), 7.10-7.32 (m, 12H, Ar-H), 7.63 (d, 1H, H-6); ^{13}CNMR ($CDCl_3$, 50 MHz): δ 29.94 (C-3'), 34.76 (C-2'), 55.20 (OCH_3) 62.77 (C-5'), 79.85-84.87 (C-1', C-4'), 116.91 (CN). Anal. Calcd. for $C_{36}H_{42}N_4O_4Si$: C, 69.42; H, 6.80; N, 9.00. Found: C, 69,10; H, 6.70; N, 8.88.

9-(2'-*C*-Cyano-2',3'-dideoxy-5'-*O*-monomethoxytrityl-β-D-*threo*-pentofuranosyl)adenine (13d)

The 2'-ketonucleoside **10d** (0.52 g, 1.0 mmol) reacted with NaCN/(phenyloxy) thiocarbonyl chloride/Bu_3SnH, according to the general procedure described for the synthesis of **4**. The residue was purified by column chromatography with ethyl acetate/hexane (2:1) to give **13d** (0.13 g, 25%) as a white foam. IR (KBr) 2220 cm^{-1} (CN); ^{1}HNMR ($CDCl_3$, 300 MHz): δ 2.51 (m, 1H, H-3'a), 2.64 (m, 1H, H-3'b), 3.48 (d, 2H, 2H-5'), 3.70 (m, 1H, H-2'), 3.78 (s, 3H, OCH_3), 4.30 (m, 1H, H-4'), 5.89 (bs, 2H, NH_2), 6.48 (d, 1H, $J_{1',2'}$=6.7 Hz, H-1'), 6.84 (d, 2H, m-H of MMTr), 7.2-7.4 (m, 12H, Ar-H), 8.17 (s, 1H, H-2), 8.30 (s, 1H, H-8); ^{13}CNMR ($CDCl_3$, 50 MHz): δ 31.39 (C-3'), 35.45 (C-2'), 55.23 (OCH_3) 63.89 (C-5'), 79.57-83.60 (C-1', C-4'), 116.25 (CN). Anal. Calcd. for $C_{31}H_{28}N_6O_3$: C, 69.91; H, 5.30; N, 15.78. Found: C, 70.24; H, 5.21; N, 15.97.

1-(2'-*C*-Cyano-2',3'-dideoxy-β-D-*threo*-pentofuranosyl)uracil (14a)

The protected nucleoside **13a** (0.2 g, 0.6 mmol) was stirred with methanolic 0.1 M HCl (4 mL) at room temperature for 45 min. The solution was neutralized with 1M NaOH-MeOH and the solvent was evaporated to dryness. The residue was purified by column chromatography using dichloromethane/methanol (20:1) as the eluent to afford 0.12 g (86%) of **14a** as white foam. IR (KBr) 2220 cm^{-1} (CN); ^{1}HNMR [$(CD_3)_2SO$, 200 MHz]: δ 2.13 (dd, 1H, H-3'a), 2.39 (m, 1H, H-3'b), 3.56 (m, 1H, $J_{4',5'a}$=$J_{5'a,5'b}$=10 Hz, H-5'a), 3.75 (m, 1H, $J_{4',5'b}$=2 Hz, H-5'b), 4.02 (m, 2H, H-2', H-4'), 5.20 (bs, 1H, OH), 5.67 (d, 1H, H-5), 6.15 (d, 1H, $J_{1',2'}$=7.1 Hz, H-1'), 8.03 (d, 1H, H-6), 10.6 (bs, 1H, NH). ^{13}CNMR [$(CD_3)_2SO$, 50 MHz): δ 29.25 (C-3'), 34.21 (C-2'), 60.26 (C-5'), 81.42-83.51 (C-1', C-4'), 101.62 (C-5), 117.81 (CN), 139.80 (C-6), 150.19 (C-2), 162.94 (C-4). Anal. Calcd. for $C_{10}H_{11}N_3O_4$: C, 50.63; H, 4.67; N, 17.71. Found: C, 50.55; H, 4.63; N, 17.60.

1-(2'-*C*-Cyano-2',3'-dideoxy-β-D-*threo*-pentofuranosyl)cytosine (14c)

The protected nucleoside **13b** (0.37 g, 0.6 mmol) was stirred with methanolic 0.1M HCl (8 mL) at room temperature for 48 h. The reaction was neutralized with 1M NaOH-MeOH and the solvent was evaporated to

dryness. The residue was purified by column chromatography with dichloromethane/methanol (5:1), as the eluent, to yield 0.11 g (80%) of **14c** as white foam. IR (KBr) 2220 cm^{-1} (CN); ^{1}HNMR [$(CD_3)_2SO$ 300 MHz]: δ 2.03-2.14 (m, 1H, H-3'a), 2.32-2.41 (m, 1H, H-3'b), 3.34 (s, 3H, OCH_3), 3.50-3.60 (m, 1H, $J_{5'a,5'b}$=12.3 Hz, H-5'a), 3.65-3.76 (m, 1H, $J_{4',5'b}$=3.2 Hz, H-5'b), 3.93-4.02 (q, 1H, $J_{1',2'}=J_{2',3'a}=J_{2',3'b}$=7.1 Hz, H-2'), 4.03-4.11 (m, 1H, H-4'), 5.15 (t, 1H, OH), 5.78 (d, 1H, H-5), 6.12 (d, 1H, H-1'), 7.20 (d, 2H, NH_2), 7.92 (d, 1H, H-6). ^{13}CNMR [$(CD_3)_2SO$, 50 MHz): δ 29.84 (C-3'), 34.23 (C-2'), 60.72 (C-5'), 80.68 (C-4'), 84.10 (C-1'), 94.10 (C-5), 118.27 (CN), 140.53 (C-6), 155.07 (C-2), 165.66 (C-4). Anal. Calcd. for $C_{10}H_{12}N_4O_3$: C, 50.84; H, 5.12; N, 23.72. Found: C, 50.70; H, 4.95; N, 27.98.

9-(2'-*C*-Cyano-2',3'-dideoxy-β-D-*threo*-pentofuranosyl)adenine (14d)

The protected nucleoside **13d** (0.13 g, 0.2 mmol) was dissolved in 80% acetic acid solution (2.4 mL) and the reaction mixture was heated at 90°C for 30 min. The solvent was evaporated to dryness. The residue was coevaporated with ethanol (2 x 2 mL) and purified by column chromatography with dichloromethane/methanol (10:1) to afford **14d** (0.40 g, 70%) as a white foam. IR (KBr) 2220 cm^{-1} (CN); ^{1}HNMR [$(CD_3)_2SO$, 300 MHz]: δ 2.45-2.55 (m, 2H, 2H-3'), 3.60-3.80 (m, 2H, 2H-5'), 4.25-4.30 (m, 2H, H-2', H-4'), 5.25 (t, 1H, OH), 6.52 (d, 1H, $J_{1',2'}$=7.0 Hz, H-1'), 7.25 (bs, 2H, NH_2), 8.19 (s, 1H, H-2), 8.50 (s, 1H, H-8). Anal. Calcd. for $C_{11}H_{12}N_6O_2$: C, 50.76; H, 4.65; N, 32.29. Found: C, 50.64; H, 4.59; N, 32.00.

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