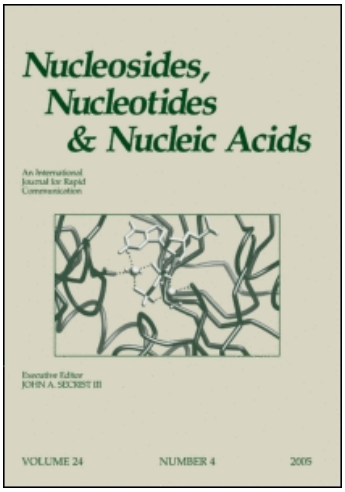

Nucleosides, Nucleotides and Nucleic Acids

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SYNTHESIS OF 1,5-ANHYDROHEXITOL NUCLEOSIDES AS MIMICS OF AZT, D4T AND DDC+

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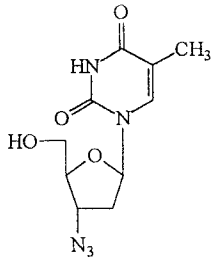
Laboratory of Medicinal Chemistry[1] and Laboratory of Experimental Chemotherapy[2], Rega Institute for Medical Research, K.U.Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium.

Abstract : 1,5-Anhydrohexitol congeners of AZT, D4T and DDC were synthesized. These compounds did not show anti-HIV activity.

Introduction

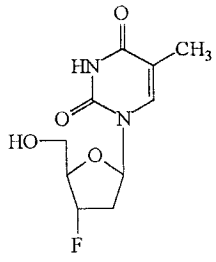
Numerous targets in the replicative cycle of HIV (human immunodeficiency virus) could be exploited in the development of chemotherapeutic agents for the treatment of AIDS[1]. In view of its unique role in the replicative cycle of retroviruses, the reverse transcriptase (RNA-directed DNA polymerase) has been envisaged as the most attractive target for anti-HIV agents[2]. The first nucleoside that was identified as an effective reverse transcriptase inhibitor is 3'-azido-2',3'-dideoxythymidine (**1**, AZT, AzddThd, Retrovir®, Zidovudine, Fig. 1). Since the discovery of AZT, various other 2',3'-dideoxynucleoside analogues containing a pyrimidine base moiety (FddThd **2**, D4T, **3**; D4C, **4**; ddCyd, **5**; 3TC, **6** Fig. 1) have been synthesized and it became clear that the dideoxynucleoside analogues represent one of the most promising leads in the pursuit of an effective chemotherapy for AIDS[3]. These compounds are inhibitory to HIV-1 at a concentration of 0.1 - 1 μM and are not toxic to the host cell up to a ≥ 100 -fold higher concentration, thus achieving a therapeutic index of ≥ 100. The difference in the antiviral activity of different 2',3'-dideoxynucleosides may be due to either differences in the inhibitory effect of their 5'-triphosphates on the reverse transcriptase or differences in the efficiency by which the 2',3'-dideoxynucleosides are converted intracellularly to their 5'-

+ Dedicated to Professor Yoshihisa Mizuno on the occasion of his 75th birthday.



1

3'-azido-2',3'-deoxythymidine
(AZT,AzddThd)



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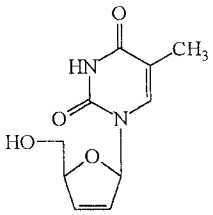
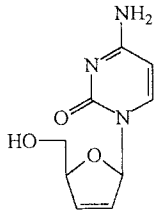
3'-fluoro-2',3'-dideoxythymidine
(FddThd)



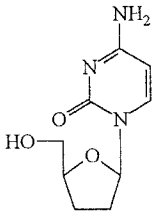
3

2',3'-dideoxy-2',3'-didehydrothymidine
(D4T, ddeThd)



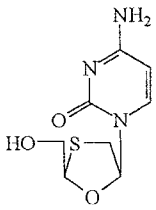
4

2',3'-dideoxy-2',3'-didehydrocytidine
(D4C, ddeCyd)



5

2',3'-dideoxycytidine
(ddCyd)



6

β-L-oxathiolanyl-cytosine
(3TC)

FIG. 1 Examples of 2',3'-dideoxynucleoside analogues with anti-HIV activity.

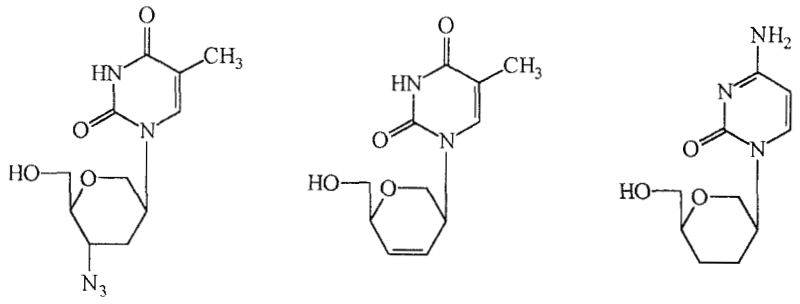
triphosphates. Since HIV does not encode for any nucleoside kinase, the phosphorylation to the 5'-triphosphates is dependent on the action of mammalian enzymes. The efficiency of this phosphorylation is a crucial determinant in the antiviral activity of the dideoxynucleosides.

Because of the resemblance of the 2'-deoxyfuranose ring and the 1,5-anhydrohexitol moiety[4], we considered the synthesis of AZT, D4T and DDC analogues **7-9**. These compounds can be considered as analogues of the well known 2',3'-dideoxynucleosides and, thus, as potential anti-HIV agents.

Chemistry

Our synthetic strategy for the synthesis of the 2',3'-dideoxynucleoside mimics started from the previously described 1,5-anhydrohexitol nucleosides[4]. 1,5-Anhydro-2,3-dideoxy-2-(thymin-1-yl)-D-*arabino*hexitol **10**[4] was used as starting material for the synthesis of **7** and **8** (Fig. 3). After protection of the 6'-hydroxymethyl function with a monomethoxytrityl group (MMTr), the configuration in the 4'-position was inverted. A first attempt to invert the 4-OH under Mitsunobu reaction conditions[5] *via* formation of an inverted ester, using 2 equivalents of triphenylphosphine, DEAD and 1.5 equivalents of p-NO_2-benzoic acid in THF was not successful. Even after 5 days at room temperature the starting material **11** was intact. Therefore we decided to invert the configuration of the secondary hydroxyl function by the method described by Hansske *et al.*[6]. Oxidation of **11** with a freshly prepared complex of CrO_3/pyridine/Ac_2O (1:2:1)[7] gave the 4-keto-derivative **12**. The 4-keto-nucleoside was used for further reaction without purification. Reduction using $NaBH_4$ in EtOH (0°C) resulted in formation of the 4-epimeric compound **13** in 51% yield starting from **11**. Methanesulphonylation of **13** gave the methanesulfonate **14**, which was treated with 5 equivalents of lithium azide in *N,N*-dimethylformamide at 80°C to give a mixture of **15** and **16**. These two compounds which could not be separated by column chromatography, were first detritylated with 80% acetic acid and the resulting mixture of **7** and **8** was separated by reverse phase Rogel HPLC to afford **7** and **8** in 24% and 33% yield, respectively, starting from **14**.

The D4T analogue **8** could also be obtained by another route. When **13** was treated with 2 equivalents of diethylaminosulfur trifluoride (DAST) in a mixture of CH_2Cl_2/THF (9:1)[8] in an effort to synthesize a fluorinated analogue, only elimination occurred. The two reaction products **8** and **17** were identified by NMR after detritylation (Fig. 3). Compound **17** can be considered as the degradation compound resulting from the 4,5-unsaturated derivative. The ddCyd analogue **9** could be prepared by deoxygenation of 1,5-anhydro-2,3-dideoxy-2-(N^4-benzoylcytosin-1-yl)-D-*arabino*hexitol **18** (obtained by deprotection of 1,5-anhydro-4,6-O-benzylidene-2,3-dideoxy-2-(N^4-benzoylcytosin-1-yl)-



7 8 9

FIG. 2 2,3,4-Trideoxynucleoside analogues with a 1,5-anhydrohexitol carbohydrate moiety.

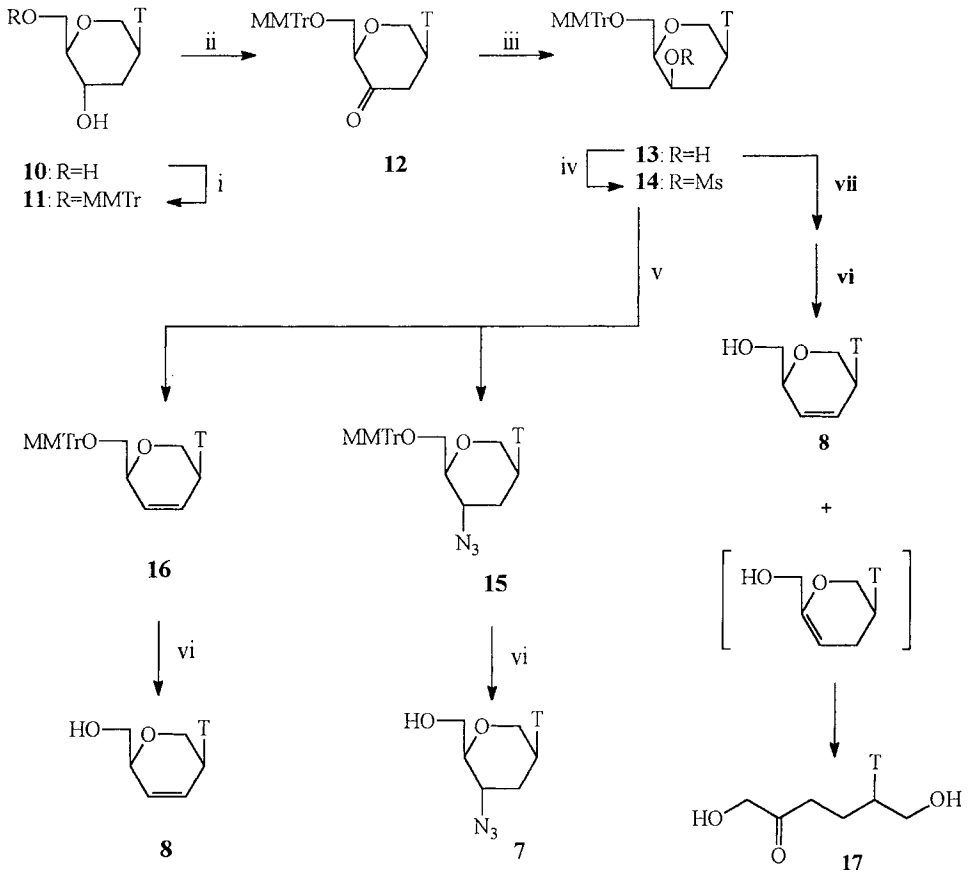
D-*arabino*hexitol[4]), in which the primary OH function was first protected with a monomethoxytrityl group (Fig. 4). This deoxygenation method[9] involved the conversion of **19** into the thiocarbonyl derivative **20** by reaction with DMAP, thiophosgene and 2,4-dichlorophenol. Radical reduction of **20** with tributyltin hydride in the presence of a free radical initiator, such as AIBN, afforded **21** in 21% yield starting from **19**. The final product **9**, obtained by ammonolysis of **21** followed by detritylation, was purified by reverse phase Rogel HPLC to give, after lyophilisation, an hygroscopic amorphous product.

Biological activity

Compounds **7**, **8** and **9** were evaluated for their inhibitory effect on human immunodeficiency virus type 1 (HIV-1)- and type 2 (HIV-2)-induced cytopathogenicity in human T-lymphocyte (MT-4) and CEM cells[10]. None of the compounds proved inhibitory to the cytopathogenicity of HIV-1 or HIV-2 at a concentation of 100μg/mL. None of the compounds showed cytotoxicity at this concentration.

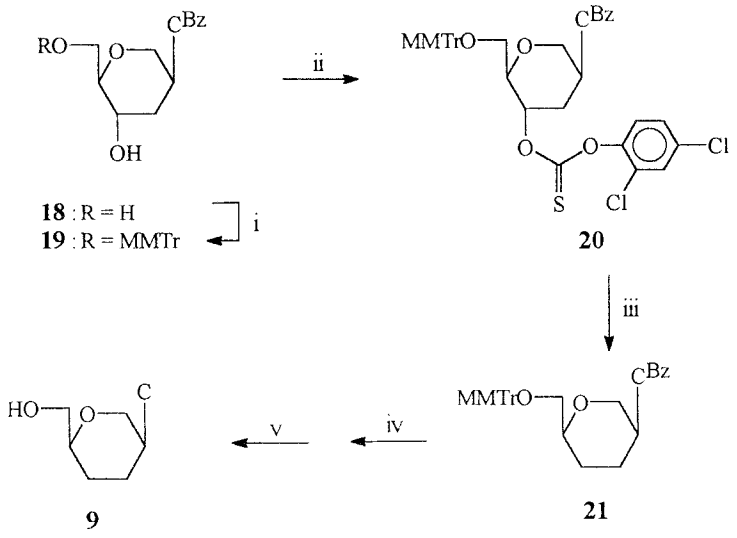
Conclusion

Although there is a close resemblance between the 1,5-anhydrohexitol moiety and the 2'-deoxyfuranose ring, no activity against HIV could be observed for the compounds presented here. Most probably, the 2,3,4-dideoxy-1,5-anhydrohexitol nucleosides are not recognized by the mammalian enzymes necessary for phosphorylation.



(i) MMTrCl, pyridine; (ii) CrO_3/pyridine/Ac_2O (1:2:1); (iii) $NaBH_4$; (iv) CH_3SO_2Cl, pyridine; (v) LiN_3, DMF; (vi) 80% HOAc; (vii) DAST, CH_2Cl_2 /THF (9:1).

FIG. 3 Synthesis of 1,5-anhydro-4-azido-2,3,4,-trideoxy-2-(thymin-1-yl)-D-arabino-hexitol (**7**) and 1,5-anhydro-2,3,4-trideoxy-2-(thymin-1-yl)-D-threohex-3-enose (**8**) and elimination reaction by treatment of **13** with DAST.



(i) MMTrCl, pyridine; (ii) DMAP, $CSCl_2$, 2,4-dichlorophenol, $ClCH_2CH_2Cl$; (iii) Bu_3SnH, AIBN, toluene; (iv) NH_3/MeOH; (v) 80% HOAc.

FIG. 4 Synthesis of the ddCyd analogue **9**.

Experimental section

Melting points were determined in capillary tubes with a Büchi-Tottoli apparatus and are uncorrected . Ultraviolet spectra were recorded with a Philips PU 8740 UV/VIS spectrophotometer. The ^{1}H-NMR and ^{13}C-NMR spectra were determined with a JEOL FX 90Q spectrometer and a Varian Gemini 200 MHz with tetramethylsilane as internal standard for the ^{1}H-NMR spectra and DMSO-d_6 (39.6 ppm) or $CDCl_3$ (76.9 ppm) for the ^{13}C-NMR spectra (s = singlet, d = doublet, dd = double doublet, t = triplet, br s = broad signal, m = multiplet). Electr. ionisation (EI) and liquid secondary ion (LSIMS) [with thioglycerol (Thgly) as matrix] mass spectra were obtained using a KRATOS Concept 1H mass spectrometer. Precoated Machery-Nagel Alugram® Sil G/UV_{254} plates were used for TLC and the spots were examined with UV light and sulfuric acid-anisaldehyde spray. Column chromatography was performed on Janssen Chimica silica gel (0.060-0.200 nm). Preparative TLC was done on glass plates coated with Macherey-Nagel silica gel P/UV_{254}. Purification by HPLC on a Rogel RP column (25 x 2.5 cm) was performed with a Gilson model 303 pump and model 802c manometric module, a Pharmacia LKB-Uvicord SII UV detector with a fixed wavelength (254 nm) and a

recorder. Anhydrous solvents were obtained as follows : methanol and ethanol were refluxed with magnesium-iodine overnight and then distilled; water was removed from DMF by standing over powdered BaO, followed by filtration and distillation *in vacuo*; pyridine was dried by distillation after storage on potassium hydroxide; dichloromethane and 1,2-dichloroethane were refluxed on phosphorus pentoxide followed by distillation; tetrahydrofuran was refluxed on lithium aluminum hydride and distilled; toluene was refluxed overnight on sodium and distilled. Elemental analyses were obtained from Dr. W. Rozdzinski, Institut für Organische Chemie, Biochemie und Isotopenforschung, D-7000 Stuttgart 80, Germany.

1,5-Anhydro-2,3-dideoxy-6-*O*-monomethoxytrityl-2-(thymin-1-yl)-D-*arabino*hexitol (11). A mixture of 1.49 g (5.8 mmol) of 1,5-anhydro-2,3-dideoxy-2-(thymin-1-yl)-D-*arabino*hexitol **10** and 2.15 g (6.9 mmol) of 4-anisyl-chlorodiphenylmethane in 50 mL of anhydrous pyridine was stirred overnight at room temperature. The reaction mixture was diluted with CH_2Cl_2 and washed twice with a saturated $NaHCO_3$ solution. The organic layer was dried over Na_2SO_4, evaporated and coevaporated with toluene. The title compound was purified by column chromatography (CH_2Cl_2 to CH_2Cl_2-MeOH, 95:5) affording 2.8 g (5.3 mmol, 92% yield) as a foam. UV(MeOH): λ_{max} 273 nm (ε = 10900); LSIMS (Thgly doped with NaOAc) m/e: 551 $[M+Na]^+$, 127 $[B+2H]^+$; ^1H NMR ($CDCl_3$): δ 1.87 (s, 1H, CH_3), 1.60-2.50 (m, 2H, H-3', H-3"), 3.12-3.62 (m, 2H, H-5', H-4'), 3.78 (s, 1H, OCH_3), 3.65-4.17 (m, 4H, H-6', H-6", H-1', H-1"), 4.53 (s, 1H, H-2'), 4.88 (d, 1H, J = 5.1, Hz 4'-OH), 6.83 (d, J = 8.6 Hz, 2H, aromatic H), 7.09-7.53 (m, 12H, aromatic H), 8.14 (s, 1H, H-6), 8.75 (br s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$): δ 12.6 (CH_3), 35.9 (C-3'), 50.6 (C-2'), 55.0 (OCH_3), 60.9, 62.8 (C-4', C-6'), 67.5 (C-1'), 80.8 (C-5'), 86.4 (Ph_3C), 108.1 (C-5), 138.6 (C-6), 151.3 (C-2), 163.8 (C-4), 113.1, 127.1, 127.8, 128.0, 130.0, 134.9, 144.1, 158.8 (aromatic C) ppm.

1,5-Anhydro-2,3-dideoxy-6-*O*-monomethoxytrityl-2-(thymin-1-yl)-D-*lyxo*hexitol (13). A solution of 2.64 g (5 mmol) of **11** in 50 mL of dry CH_2Cl_2 was added dropwise to a freshly prepared complex of CrO_3/pyridine/Ac_2O 1:2:1 (1.5 g/2.5 mL/1.5 mL) in 10 mL of CH_2Cl_2. The mixture was stirred at room temperature for 30 min. The resulting dark brown solution was poured into 100 mL of EtOAc and filtered over silicagel. After washing the silicagel with EtOAc, the combined filtrate was evaporated to give 1.66 g (3.15 mmol, 63% yield) of **12** as a foam. This foam was used for further reaction without purification. To a solution of 1.66 g of crude **12** in 30 mL absolute ethanol was added 376 mg (10 mmol) of $NaBH_4$ at 0°C. The mixture was stirred at 0°C for 2.5 h. After adding 10 mL of methanol and stirring for 10 min. at room temperature, the solution was

adsorbed on silicagel. Purification by column chromatography (CH_2Cl_2 to CH_2Cl_2-MeOH, 98:2) yielded 1.35 g (2.55 mmol, 51% yield) of the title compound **13**. UV(MeOH): λ_{max} 271 nm (ε = 11300); LSIMS (Thgly doped with NaOAc) m/e: 551 $[M+Na]^+$, 127 $[B+2H]^+$; ^1H NMR ($CDCl_3$): δ 1.93 (s, 3H, CH_3), 1.55-2.45 (m, 2H, H-3', H-3"), 3.25-3.54 (m, 2H, H-5', H-4'), 3.79 (s, 3H, OCH_3), 3.55-4.12 (m, 4H, H-6', H-6", H-1', H-1"), 4.22 (s, 1H, H-2'), 4.42 (d, 1H, J = 4.1, Hz 4'-OH), 6.84 (d, J = 8.8 Hz, 2H, aromatic H), 7.12-7.50 (m, 12H, aromatic H), 8.27 (s, 1H, H-6), 8.67 (br s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$): δ 12.5 (CH_3), 33.1 (C-3'), 47.3 (C-2'), 55.1, (OCH_3), 64.2, 65.4 (C-4', C-6'), 69.6 (C-1'), 77.5 (C-5'), 87.2 (Ph_3C), 108.7 (C-5), 140.5 (C-6), 151.5 (C-2), 163.8 (C-4), 113.2, 127.1, 127.9, 128.1, 130.1, 134.7, 143.8, 158.7 (aromatic C) ppm.

1,5-Anhydro-4-azido-2,3,4-trideoxy-6-*O*-monomethoxytrityl-2-(thymin-1-yl)-D-*arabino*hexitol (15) and **1,5-Anhydro-2,3,4-trideoxy-6-*O*-monomethoxytrityl-2-(thymin-1-yl)-D-*threo*hex-3-enose (16).** A solution of 1.06 g (2.01 mmol) of **13** and 1 mL of methanesulphonyl chloride in 30 mL of anhydrous pyridine was kept at room temperature for 2.5 h. Methanol (10 mL) was added, the solvent was evaporated, the resulting residue was dissolved in CH_2Cl_2 and washed with a saturated $NaHCO_3$ solution. The organic layer was dried, evaporated and coevaporated with toluene. The resulting oil (1.10 g, 1.81 mmol) was used for further reaction without purification. The mesylation of the 4'-OH group was verified by NMR spectroscopy. ^1H NMR ($CDCl_3$) showed the appearance of a singlet at δ 3.02 ppm (CH_3SO_2), and a downfield shift for H-4' (δ 3.68-4.20 ppm). The ^{13}C NMR spectrum showed a strong downfield shift for C-4' (68.5 ppm) and the appearance of the methylsulfonyl group at 37.9 ppm. A mixture of 880 mg (1.45 mmol) of crude mesylate **14** and 3.55 g (7.25 mmol) of lithium azide in 40 mL of dimethylformamide dry was heated for 16 h at 80°C. The mixture was concentrated to about 10 mL, diluted with EtOAc (100 mL) and washed with a saturated $NaHCO_3$ solution (100 mL). The organic layer was dried, evaporated and purified by column chromatography (CH_2Cl_2 to CH_2Cl_2-MeOH, 98:2) to yield 590 mg of a mixture of **15** and **16**. These two compounds could not be separated by normal column chromatography. Separation and identification was carried out after deprotection.

1,5-Anhydro-4-azido-2,3,4-trideoxy-2-(thymin-1-yl)-D-*arabino*hexitol (7) and **1,5-anhydro-2,3,4-trideoxy-2-(thymin-1-yl)-D-*threo*hex-3-enose (8).** Deprotection of the mixture containing **15** and **16** with 80% acetic acid at 60°C afforded 7 and **8** (Rf values in CH_2Cl_2-MeOH, 85:15 are 0.57 and 0.51 respectively). The mixture was concentrated

and coevaporated with toluene. The residue was taken up in water and washed with diethyl ether. The water layer was concentrated and the two title compounds were separated by HPLC on a Rogel (polystyrene-divinylbenzene) column (MeOH-H_2O, 25:75) affording 122 mg of **7** (0.43 mmol, 24% yield starting from **14**) and 168 mg of **7** (0.60 mmol, 33% yield starting from **14**).

identification of **7** : UV(MeOH): λ_{max} 271 nm (ε = 9700); EIMS m/e: 281 $[M]^+$, 239 $[M-N_3]^+$, 127 $[B+2H]^+$; ^1H NMR (DMSO-d_6): 1.79 (s, 3H, CH_3), 1.93-2.24 (m, 2H, H-3', H-3"), 3.10-3.29 (m, 1H, H-5'), 3.35-4.48 (m, 5H, H-1', H-1", H-4', H-6', H-6") 4.51 (m, 1H, H-2'), 4.70 (t, J = 5.4 Hz, 6'-OH), 7.95 (s, 1H, H-6), 10.24 (br s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ 12.4 (CH_3), 31.3 (C-3'), 49.0 (C-2'), 52.6 (C-4'), 60.3 (C-6'), 66.8 (C-1'), 79.4 (C-5'), 108.5 (C-5), 138.8 (C-6), 151.1 (C-2), 163.9 (C-4) ppm. Anal. ($C_{11}H_{15}O_4N_5$ x 0.5 H_2O) calcd. C : 45.52, H : 5.56, N : 24.13; found C : 45.46, H : 5.46, N : 23.94.

identification of **8** : UV(MeOH): λ_{max} 272 nm (ε = 9700); EIMS m/e: 238 $[M]^+$, 127 $[B+2H]^+$; ^1H NMR (DMSO-d_6): δ 1.68 (s, 3H, CH_3), 3.26 (m, 1H, H-1ax), 3.54 (m, 2H, H-6', H-6"), 3.72 (m, 1H, H-1eq), 4.06 (m, 1H, H-5'), 4.82 (m, 1H, H-2'), 4.96 (t, J = 5.5 Hz, 1H, 6'-OH), 5.82 (m, 1H, H-3'), 6.18 (d, 1H, J = 10 Hz, H-4'), 7.67 (s, 1H, H-6), 11.23 (br s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ 12.3 (CH3), 46.8 (C-2'), 62.9 (C-6'), 67.8 (C-1'), 75.2 (C-5'), 109.0 (C-5), 122.9 (C-3'), 135.7 (C-4'), 139.1 (C-6), 150.1 (C-2), 164.0 (C-4) ppm. Anal. ($C_{11}H_{14}O_4N_2$) calcd. C : 55.46, H : 5.92, N : 11.76; found C : 55.07, H : 5.83, N : 11.31.

1,5-Anhydro-3,4-didehydro-2,3,4-trideoxy-(2-cytosin-1-yl)-D-*threo*-hexitol (9)

The protected cytosine derivative **19** (500 mg, 0.81 mmol) and 695 mg (5.67 mmol) of DMAP were dissolved in 50 mL of dry 1,2-dichloroethane. The reaction mixture was cooled to -40 °C and 75 µL (0.97 mmol) of thiophosgene was added slowly under stirring. After 1 h, 185 mg (1.14 mmol) of 2,4-dichlorophenol was added and stirring was continued for 2 more hours. The mixture was poured into 100 mL 1M KH_2PO_4 and extracted twice with CH_2Cl_2. The combined organic layers were dried and the volatiles were removed. The resulting crude thiocarbonyl compound **20** was dissolved in 50 mL of anhydrous toluene. After bubbling N_2 through the solution for a few minutes, 270 µL of Bu_3SnH (1 mmol) and 30 mg (0.2 mmol) of AIBN were added. The reaction mixture was refluxed for 1 h. After concentration, the resulting residue was purified by preparative thin layer chromatography (CH_2Cl_2-MeOH, 98:2) to yield 100 mg (0.17 mmol, 21 % yield) of **21** as an oil. The benzoyl group was removed by treating **21** with 20 mL of methanol saturated with ammonia. The reaction mixture was concentrated and the obtained oil was heated in 35 mL of 80 % aqueous acetic acid until complete

hydrolysis of the trityl group. After concentration, the residue was taken up in 20 mL of water and washed with ether. Final purification of the concentrated water layer was carried out by HPLC on a Rogel column (MeOH-H_2O, 20:80) to give 15 mg of **9** as a hygroscopic amorphous mass (0.07 mmol, 8% yield starting from **21**). UV(MeOH): λ_{max} 275 nm (ε = 10500); LSIMS (Thgly) m/e : 226 $[M]^+$, 112 $[B+H]^+$; ^1H NMR (DMSO-d_6): δ 1.33-2.05 (m, 4H, H-3', H-3", H-4', H-4"), 3.50-4.21 (m, 6H), 4.32 (1H, 6'-OH), 5.73 (d, 1H, J = 8 Hz, H-5), 7.07 (br s, 2H, NH_2), 8.15 (d, 1H, J = 8 Hz, H-6) ppm; ^{13}C NMR (DMSO-d_6): δ 22.0, 26.0 (C-3', C-4'), 48.6 (C-2'), 63.9 (C-6'), 68.1 (C-1'), 77.5 (C-5'), 92.8 (C-5), 144.2 (C-6), 155.7 (C-2), 165.5 (C-4) ppm. Anal. ($C_{10}H_{15}N_3O_3$ x $1H_2O$) calcd. C : 49.37, H : 7.04, N : 17.27; found C : 48.81, H : 6.97, N : 17.13.

Antiviral activity assay procedure

Assays for activity against human immunodeficiency virus type 1 (HIV-1) (strain III_B) and type 2 (HIV-2) (strain ROD), were performed as described previously[10]

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