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Nucleosides and Nucleotides. 120. Stereoselective Radical Deoxygenation of *tert*-Alcohols in the Sugar Moiety of Nucleosides: Synthesis of 2',3'-Dideoxy-2'-*C*-methyl- and -2'-*C*-ethynyl-β-D-*threo*-pentofuranosyl Pyrimidines and Adenine as Potential Antiviral and Antitumor Agents[1,#]

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Abstract: Radical deoxygenation of 2'-*O*-methoxalyl ester of the corresponding 3'-deoxy-2'-*C*-methyl-β-D-*threo*-pentofuranosyl-pyrimidines and -adenine, which were readily obtained from the reaction of 1-(3-deoxy-β-D-*erythro*-pentofuran-2-ulosyl)pyrimidines and adenine derivatives with MeMgBr, gave stereospecifically 2',3'-dideoxy-2'-*C*-methyl-β-D-*threo*-pentofuranosyl-uracil (**9a**), -thymine (**9b**), -cytosine (**9c**), and -adenine (**18**), respectively, after deprotection. Similarly, synthesis of 2',3'-dideoxy-2'-*C*-ethynyl-β-D-*threo*-pentofuranosyl-thymine (**25**) and -adenine (**31**) was achieved by the reaction of the corresponding ketones with LiC≡CTMS, followed by radical deoxygenation of the *tert*-methoxaly ester. Cytotoxicity and anti-HIV activities of these nucleosides in vitro were described.

A number of 2',3'-dideoxy and 2',3'-dideoxy-3'-substituted nucleosides have been synthesized as potential antiviral agents.[2] Among them, 3'-azide-3'-deoxythymidine (AZT), 2',3'-dideoxyinosine (DDI), and 2',3'-dideoxycytidine (DDC) have been introduced in clinical use for the treatment of HIV infection diseases. These are inhibitors of HIV reverse transcriptase (RT) after conversion into their corresponding 5'-triphosphates, which compete with natural substrates.[3] They are phosphorylated by certain cellular kinases, because HIV does not have any kinase activities, unlike herpes viruses that encoded a less substrate-specific nucleoside kinase called thymidine kinase. It is believed that cellular deoxycytidine kinase and thymidine kinase, which are plentiful in B- and T-cells, are the most important enzymes for their activation, because the substrate specificity of these enzyme are more strict than that of the other nucleotide kinases and nucleoside diphosphokinases. Once certain nucleoside analogues are phosphorylated to their 5'-monophosphates, they are readily phosphorylated to the corresponding 5'-polyphosphates to some extent. However, the substrate specificity of these kinases have not been sufficiently elucidated. Therefore, we synthesized several 2',3'-dideoxy-2'-*C*-methyl-β-D-*threo*-pentofuranosyl-pyrimidines and -adenine, and 2',3'-dideoxy-2'-*C*-ethynyl-β-D-*threo*-pentofuranosyl-thymine and -adenine as potential antiviral and antitu-

#This paper is dedicated to Professor Yoshifumi Maki on the occasion of his retirement from Gifu Pharmaceutical University in March 1994.

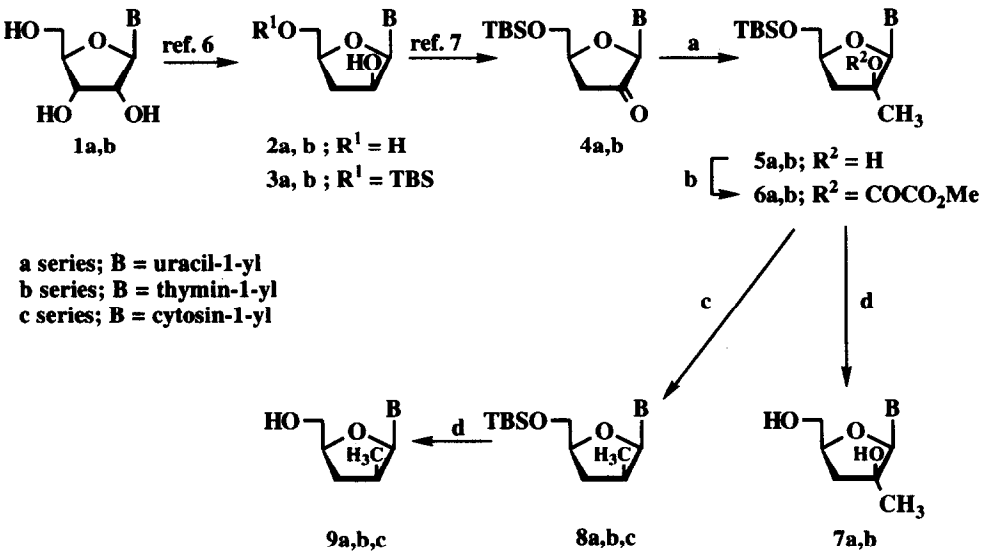
mor agents. Although a number of 2',3'-dideoxy analogues with a 3'-substituents have been synthesized and their biological activities evaluated, few are known to have a substituent at the 2'-β position in the 2',3'-dideoxy nucleosides.[4]

Radical deoxygenation is a useful method, especially in nucleoside chemistry. We have found that *tert*-alcohols having a substituent such as an alkyl, acetylene, or cyano group in the sugar moiety of certain pyrimidine nucleosides were effectively deoxygenated *via* their thiocarbonates or methoxalyl esters by Bu_3SnH.[5] These reactions generally proceed in a rather stereoselective manner to yield desired 2'-carbon substituted 2'-deoxy-β-D-arabinofuranosyl derivatives when the 2'-*tert*-alcohols were treated by radical deoxygenation. It has been generally recognized that introduction of a substituent into the 2'-β position starting from naturally occurring pyrimidine ribonucleosides having a leaving group at the 2'-α position by nucleophilic substitution is difficult because that intramolecular nucleophilic attack of the 2-carbonyl of the pyrimidine base is always predominant. Thus, the radical deoxygenation of the *tert*-alcohols, which are readily accessible from nucleophilic addition to the corresponding 2'-keto nucleosides, is a powerful method to synthesize a new type of biologically active nucleosides. Among them, we have found that (2'*S*)-2'-deoxy-2'-*C*-methylcytidine (SMDC)[5d] and 2'-*C*-cyano-2'-deoxy-1-β-D-arabinofuranosylcytosine (CNDAC)[5e] are potent inhibitors of tumor cell growth.

We, therefore, used 1-(3-deoxy-β-D-*erythro*-pentofuran-2-ulosyl)uracil derivative **4a** as a starting material (Scheme 1). Kawana *et al.* reported synthesis of 3'-deoxy-β-D-*threo*-pentofuranosyluracil (**2a**) from uridine (**1a**) by two-one pot reactions including the deoxygenative [1,2] hydride shift of the 3'-*O* methanesulfonates.[6] The 5'-hydroxyl group in **2a** was protected by a TBS group to give **3a**, and then the 2'-hydroxyl group was oxidized with the CrO_3-pyridine-acetic anhydride system in CH_2Cl_2 to give the desired ketone **4a**.[7] Treatment of **4a** with five equivalents of MeMgBr in THF furnished a single isomer, **5a**, in 74% yield. In this reaction, a small amount of the starting material was always detected by tlc. It is rather interesting that such an enolizable ketone reacted with the Grignard reagent in high yield. The stereochemistry at the 2'-position of **5a** was identified by nOe experiments. When 2'-Me protons at 1.37 ppm (singlet) were irradiated, an nOe was observed only at H-1' (δ 5.87, singlet) at about 7%. Therefore, the Grignard reagent attacked from the α-side of the sugar stereospecifically and this result is consistent to our previous accumulated results.[5] Reaction of **5a** with methoxalyl chloride in CH_3CN in the presence of 4-(dimethylamino)pyridine (DMAP) smoothly afforded **6a**, on which, without purification, radical deoxygenation was done with Bu_3SnH in the presence of AIBN in toluene. Only one nucleosidic product **8a** was obtained in 88% yield. The structure of **8a** was confirmed by its ^{1}H-NMR spectrum, in which one proton corresponding to H-1' at 6.22 ppm became a doublet with $J_{1',2'}$ = 7.3 Hz and 2'-*C*-methyl protons at 0.99 ppm were observed as a doublet with $J_{2',Me}$ = 6.8 Hz. We have reported the synthesis of (2'*S*)-2'-deoxy-2'-*C*-methylcytidine (SMDC) and its 2'*R* isomer, RMDC, in which $J_{1',2'}$ values were 7.6 and 8.1 Hz, respectively.[5d] Therefore, the value of $J_{1',2'}$ did not give useful information to identify the configuration at the 2'-position. However, when H-6 (δ 8.21, d) in **8a** was irradiated, nOes were observed at the 2'-Me of 13% along with H-6 and H-3'. From this experiment, the configuration at the 2'-position was assigned to be 2'-β and the 3'-"up"-proton (depicted as H-3'b in the Experimental section) could be assigned. Thus, the *tert*-radical initially generated from **6a** was stereospecifically hydrogenated from the α-side by Bu_3SnH to furnish **8a** due to the steric hindrance by the nucleobase moiety at the 1'-β position. Treatment of **5a** and **8a**

with tetrabutylammonium fluoride (TBAF) in THF furnished the corresponding uracil derivatives **7a** and **9a** in good yields.

Scheme 1[a]



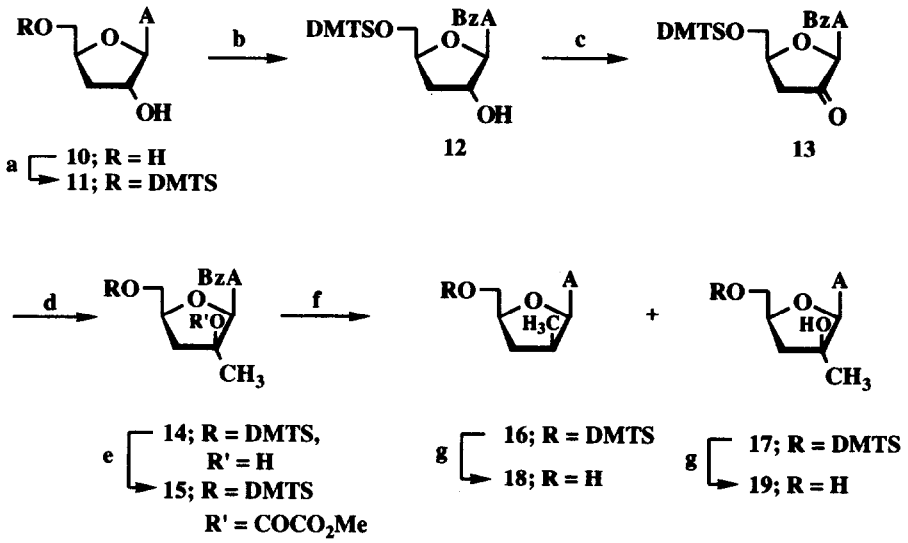
[a]a) MeMgBr in THF, -78 °C; b) MeO_2CCOCl, DMAP in CH_3CN, room temperature; c) Bu_3SnH, AIBN in toluene, 110 °C; d) 1 M TBAF in THF, room temperature.

Thymine derivatives **7b** and **9b** was also obtained similarly (Scheme 1). Conversion of **8a** to the cytosine derivative by a conventional method *via* the O^4-triisopropylbenzenesulfonate of **8a** with NH_4OH gave the desired **8c**, of which the 5'-*O*-TBS group was removed by TBAF, furnishing 1-(2,3-dideoxy-2-*C*-methyl-β-D-*threo*-pentofuranosyl)cytosine (**9c**) as a hydrochloride, which is a 3'-deoxy analogue of SMDC.

1-(2,3-Dideoxy-2-*C*-methyl-β-D-*threo*-pentofuranosyl)adenine (**18**) was prepared from cordycepin (**10**). Initially, the 5'-hydroxyl group of **10** was protected by a dimethylthexylsilyl (DMTS) group to give **11**, which was further treated with benzoyl chloride in pyridine, followed by 2 N NaOH in aqueous EtOH furnishing **12**. Oxidation of the 2'-hydroxyl group in **12** was done in a conventional manner using *N,N'*-dicyclohexylcarbodiimide in dry dimethylsulfoxide (DMSO) with dichloroacetic acid giving **13**.[8,9] The methyl addition reaction of **13** using MeMgBr in THF at -78 °C afforded 3-deoxy-2-*C*-methyl-β-D-*threo*-pentofuranosyl derivative **14** as a single isomer in 62% yield. Methoxalylation of the 2'-*tert*-alcohol in **14** proceeded smoothly, however the following radical deoxygenation reaction required six equivalents of Bu_3SnH for completion of the reaction. In the reaction mixture, there were two inseparable nucleosidic products on tlc. Therefore, the mixture was further treated with NH_3/MeOH to remove the N^6-benzoyl

group for two days at room temperature and then the products were separated by a silica gel column. A less polar nucleoside was isolated in 64% yield and assigned as the 2,3-dideoxy-2-*C*-methyl-β-D-*threo*-pentofuranosyl derivative **16** from its MS and ^{1}H-NMR spectroscopies. A more polar nucleoside (29% yield) was assigned as 3-deoxy-2-*C*-methyl-β-D-*threo*-pentofuranosyl derivative **17**, the pattern of which in the sugar moiety in its ^{1}H-NMR spectrum was quite akin to **14**. Since Rf values of **14** and **15** are different, during the deoxygenation, the methoxalyl group in **15** might be removed. Both derivatives **16** and **17** were deblocked with TBAF to afford **18** and **19**, respectively.

Scheme 2[a]

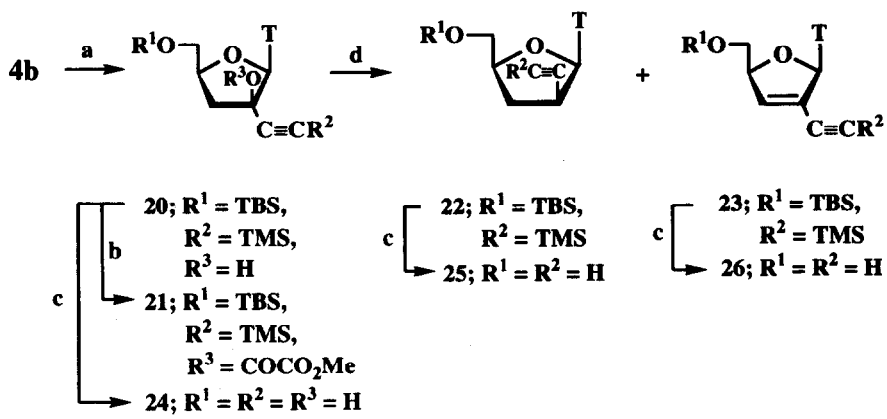


[a]a) DMTSCl in pyridine, room temperature; b) BzCl in pyridine, then NaOH; c) DCC, Cl_2CHCO_2H in DMSO, 0 °C; d) MeMgBr in THF, -78 °C; e) MeO_2CCOCl, DMAP in CH_3CN, room temperature; f) Bu_3SnH, AIBN in toluene, 110 °C; g) 1 M TBAF in THF, room temperature.

Next, we prepared 1-[2,3-dideoxy-2'-*C*-(2-ethynyl)-β-D-*threo*-pentofuranosyl]thymine (**25**) shown in Scheme 3. Reaction of **4b** with lithium (TMS)acetylide in THF at -78 °C gave 1-[3-deoxy-2-*C*-[2-(TMS)ethynyl]-β-D-*threo*-pentofuranosyl]thymine derivative **20**.[10] Compound **20** was similarly methoxalylated at the 2'-*tert*-propargyl alcohol giving **21**, which, without purification, was treated under the radical deoxygenation conditions described before to afford mainly two nucleosidic products. A less polar nucleoside was the desired deoxygenated 1-[2,3-dideoxy-2-*C*-[2-(TMS)ethynyl]-β-D-*threo*-

pentofuranosyl]thymine derivative **22**, which was assigned by its MS and ^{1}H-NMR spectra, and its elemental analysis. ^{1}H-NMR spectra of **22** showed that a proton due to H-1' was observed at 6.19 ppm with $J_{1',2'}$ = 6.8 Hz and the H-3' protons were detected at 2.12 and 2.29 ppm each as a double double doublet. However, ^{1}H-NMR spectra of a more polar nucleoside showed a proton due to the H-1' at 6.47 ppm as a double doublet having coupling constants of 1.5 and 2.0 Hz corresponding to H-4' and H-3', respectively. This type of long-range coupling was similarly observed in 2'-substituted 2',3'-didehydro-2',3'-dideoxy nucleosides.[7] Thus, **23** was assigned as 5'-*O*-TBS-3'-deoxy-2',3'-didehydro-2'-*C*-[2-(TMS)ethynyl]thymidine. This type of the elimination reaction during the radical reaction may be unusual and we assumed the reaction proceeded via *syn*-elimination from the 2'-β-methoxaly group. The crude **21** was then heated in toluene without addition of Bu_3SnH and AIBN. However, **21** did not give **23** at all. The formation of **23** from **21** would occur during the radical reactions and tributyltin radicals or intramolecular radicals formed in the reaction would abstract the 3'-proton to afford **23**. (TMS)ethynyl derivatives **20**, **22**, and **23** were deprotected by TBAF in THF to furnish the desired free nucleosides **24**, **25**, and **26**, respectively.

Scheme 3[a]

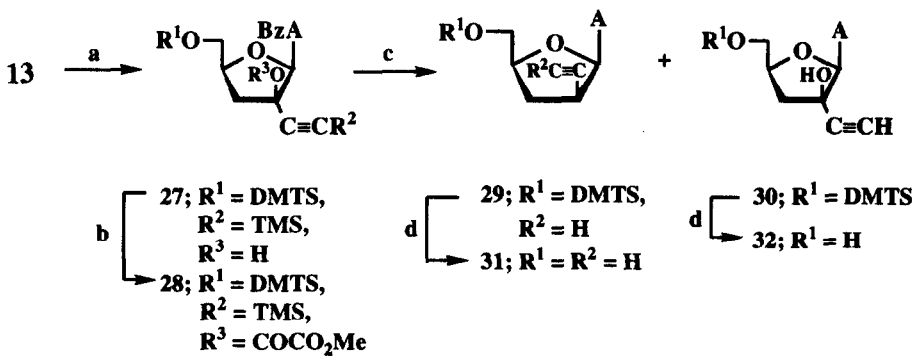


[a]a) TMSC≡CH, BuLi in THF, -78 °C; b) MeO_2CCOCl, DMAP in CH_3CN, room temperature; c) 1 M TBAF, AcOH in THF, room temperature; d) Bu_3SnH, AIBN in toluene, 110 °C.

Under the same conditions, lithium (TMS)acetylide was added to the 3'-deoxy-2'-ketoadenosine derivative **13** to afford **27**, which was then treated with methoxalyl chloride, followed by the radical deoxygenation furnishing the desired 9-(5-*O*-DMTS-2,3-dideoxy-2-*C*-ethynyl-β-D-*threo*-pentofuranosyl)-adenine (**29**) in 29% yield along with 9-(5-*O*-DMTS-3-deoxy-2-*C*-ethynyl-β-D-*threo*-pentofuranosyl)-

adenine (**30**) in 31% yield (Scheme 4). The formation of **30** was similarly observed in the deoxygenation reaction of **15**. However, elimination products such as **23** were not detected in this reaction. These ethynylated adenosine derivatives **29** and **30** were converted to the corresponding free nucleosides **31** and **32**, respectively, by treatment with TBAF.

Scheme 4[a]



A = adenin-9-yl
BzA = N^6-benzoyladenin-9-yl

[a]a) TMSC≡CH, BuLi in THF, -78 °C; b) MeO_2CCOCl, DMAP in CH_3CN, room temperature; c) Bu_3SnH, AIBN in toluene, 110 °C, then NH_3/MeOH, room temperature; d) 1 M TBAF in THF, room temperature.

Tumor cell growth inhibitory activity of **7a**, **7b**, **9a**, **9b**, **9c**, **18**, **19**, **24**, **25**, **26**, **31**, and **32** against mouse leukemic L1210 and human oral epidermoid carcinoma KB cells *in vitro* was first examined as described previously.[5d] These nucleosides except **9a** did not show any significant tumor cell growth inhibitory activity to both cells up to 100 μg/mL, while **9a** had IC_{50} values of 16.5 μg/mL and 33 μg/mL, for the above cell lines, respectively. Unlike the activity of SMDC[5d] (IC_{50} = 0.26 μg/mL for L1210 cells), **9c** is a 3'-deoxy analogue of SMDC, showed only 27% and 16% inhibitions at 100 μg/mL against both cell lines. Therefore, tumor cell growth inhibition of SMDC required a hydroxyl group at the 3'-position in the molecule. Inhibition of the cytopathogenicity of HIV-1 (MT-4 cells) by these nucleosides was also tested.[11] However, none of them had any significant inhibitory activity up to 100 μg/mL concentrations. For showing these activities, these nucleoside derivatives should be phosphorylated at the 5'-hydroxyl group. The ineffectivity of these nucleosides might be related to insusceptibility to nucleoside kinases due to the bulky substituents at the 2'-β position.

EXPERIMENTAL SECTION

General Methods. Melting points were measured on a Yanagimoto MP-3 micromelting point apparatus and are uncorrected. The ^{1}H-NMR spectra were recorded on a JEOL JNM-FX 100 (100 MHz) or JEOL JNM-GX 270 (270 MHz) spectrometer with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (δ), and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad). All exchangeable protons were detected by addition of D_2O. UV absorption spectra were recorded with a Shimadzu UV-240 spectrophotometer. Mass spectra (MS) were measured on a JEOL JMX-DX303 spectrometer. TLC was done on Merck Kieselgel F254 precoated plates. The silica gel used for column chromatography was YMC gel 60A (70-230 mesh).

1-(5-*O*-TBS-3-deoxy-2-*C*-methyl-β-D-*threo*-pentofuranosyl)uracil (5a). A solution of MeMgBr in THF (1 M, 25 ml, 25 mmol) was added dropwise over 20 min to a solution of **4a**[7] (1.7 g, 5 mmol) in THF (50 ml) at -78 °C under argon. The mixture was stirred for 2.5 h at -78 °C, and then aqueous 1N NH_4Cl solution (25 ml) was added. After warming to room temperature, the mixture was extracted with EtOAc (30 ml x 4), and the separated organic phase was washed with brine (40 ml), dried (Na_2SO_4), and concentrated to dryness. The residue was purified on a silica gel column (4 x 12 cm) with benzene/EtOAc (1:1-1:2) to afford **5a** (1.31 g, 74% crystallized from hexane/EtOAc): mp 166.5-167.5 °C; EI-MS *m/z* 357 (M^++1), 341 (M^+-Me), 299 (M^+-*t*-Bu); ^{1}H-NMR ($CDCl_3$, 270 MHz) 8.52 (1H, br s, NH), 7.75 (1H, d, H-6, $J_{6,5}$ = 7.8 Hz), 5.87 (1H, s, H-1'), 5.64 (1H, dd, H-5, $J_{5,6}$ = 7.8, $J_{5,NH}$ = 2.0 Hz), 4.60 (1H, s, 2'-OH), 4.33 (1H, dddd, H-4', $J_{4',3'a}$ = 9.8, $J_{4',3'b}$ = 3.4, $J_{4',5'a}$ = 2.0, $J_{4',5'b}$ = 1.5 Hz), 4.03 (1H, dd, H-5'a, $J_{5'a,4'}$ = 2.0, $J_{5'a,b}$ = 11.2 Hz), 3.63 (1H, dd, H-5'b, $J_{5'b,4'}$ = 1.5, $J_{5'a,b}$ = 11.2 Hz), 2.36 (1H, dd, H-3'a, $J_{3'a,b}$ = 14.2, $J_{3'a,4'}$ = 9.8 Hz), 2.14 (1H, dd, H-3'b, $J_{3'b,a}$ = 14.2, $J_{3'b,4'}$ = 3.4 Hz), 1.37 (3H, s, 2'-Me), 0.96 (9H, s, *t*-Bu), 0.17 (6H, s, Me_2Si). Anal Calcd for $C_{16}H_{28}N_2O_5Si$; C, 53.91; H, 7.92; N, 7.86. Found: C, 53.91; H, 7.94; N, 7.78.

1-(5-*O*-TBS-3-deoxy-2-*C*-methyl-β-D-*threo*-pentofuranosyl)thymine (5b). A solution of MeMgBr in THF (1 M, 10 ml, 10 mmol) was added dropwise over 20 min to a solution of **4b**[7] (709 mg, 2 mmol) in THF (20 ml) at -78 °C under argon. The mixture was stirred for 2.5 h at -78 °C, and then aqueous 1 N NH_4Cl solution (25 ml) was added. After warming to room temperature, the mixture was extracted with EtOAc (20 ml x 4), and the separated organic phase was washed with brine (40 ml), dried (Na_2SO_4), and concentrated to dryness. The residue was purified on a silica gel column (3 x 16 cm) with hexane/EtOAc (1:1-1:2) to afford **5b** (615 mg, 83%, crystallized from hexane/EtOAc): mp 110-111 °C; EI-MS *m/z* 371 (M^++1), 355 (M^+-Me), 313 (M^+-*t*-Bu); ^{1}H-NMR ($CDCl_3$, 270 MHz) 8.40 (1H, br s, NH), 7.50 (1H, d, H-6, $J_{6,Me}$ = 1.5 Hz), 5.87 (1H, s, H-1'), 4.79 (1H, s, 2'-OH), 4.34 (1H, dddd, H-4', $J_{4',3'a}$ = 10.0, $J_{4',3'b}$ = 2.7, $J_{4',5'a}$ = 2.0, $J_{4',5'b}$ = 1.5 Hz), 4.03 (1H, dd, H-5'a, $J_{5'a,4'}$ = 2.0, $J_{5'a,b}$ = 11.2 Hz), 3.63 (1H, dd, H-5'b, $J_{5'b,4'}$ = 1.5, $J_{5'a,b}$ = 11.2 Hz), 2.40 (1H, dd, H-3'a, $J_{3'a,b}$ = 13.9, $J_{3'a,4'}$ = 10.0 Hz), 2.12 (1H, dd, H-3'b, $J_{3'b,a}$ = 13.9, $J_{3'b,4'}$ = 2.7 Hz), 1.90 (3H, d, 5-Me, $J_{Me,6}$ = 1.5 Hz), 1.33 (3H, s, 2'-Me), 0.98 (9H, s, *t*-Bu), 0.21 (3H, s, MeSi), 0.20 (3H, s, MeSi). Anal Calcd for $C_{17}H_{30}N_2O_5Si$; C, 55.11; H, 8.16; N, 7.56. Found: C, 54.82; H, 8.22; N, 7.52.

1-(3-Deoxy-2-*C*-methyl-β-D-*threo*-pentofuranosyl)uracil (7a). A THF solution of TBAF (1 M, 1.2 ml, 1.2 mmol) was added to a mixture of **5a** (291 mg, 0.82 mmol) in THF (7 ml). The mixture

was stirred for 1 h at room temperature, and was concentrated to dryness. The residue was purified on a silica gel column (2.3 x 10 cm) with 4% MeOH in $CHCl_3$ to give **7a** (197 mg, 95%) as a foam: EI-MS *m/z* 243 (M^++1); ^{1}H-NMR (DMSO-d_6, 400 MHz) 11.21 (1H, br s, NH), 7.76 (1H, d, H-6, $J_{6,5}$ = 8.3 Hz), 5.71 (1H, s, H-1'), 5.56 (1H, dd, H-5, $J_{5,6}$ = 8.3, $J_{5,NH}$ = 2.4 Hz), 5.21 (1H, s, 2'-OH), 5.17 (1H, t, 5'-OH), 4.04 (1H, dddd, H-4', $J_{4',5'a}$ = 3.9, $J_{4',5'b}$ = 4.9, $J_{4',3'a}$ = 7.6, $J_{4',3'b}$ = 7.1 Hz), 3.62 (1H, dd, H-5'a, $J_{5'a,b}$ = 11.7, $J_{5'a,\ OH}$ = 4.9, $J_{5'a,4'}$ = 3.9 Hz), 3.53 (1H, ddd, H-5'b, $J_{5'b,a}$ = 11.7, $J_{5'b,\ OH}$ = 5.4,$J_{5'b,4'}$ = 4.9 Hz), 2.05 (1H, dd, H-3'a, $J_{3'a,4'}$ = 7.6, $J_{3'a,b}$ = 12.9 Hz), 1.92 (1H, dd, H-3'b, $J_{3'b,4'}$ = 7.1, $J_{3'b,a}$ = 12.9 Hz), 1.28 (3H, s, 2'-Me). Anal Calcd for $C_{10}H_{14}N_2O_5$: C, 49.59; H, 5.83; N, 11.56. Found: C, 49.45; H, 5.88; N, 11.43.

1-(3-Deoxy-2-*C*-methyl-β-D-*threo*-pentofuranosyl)thymine (7b). Compound **5b** (200 mg, 0.54 mmol) was desilylated as above to give **7b** (126 mg, 91%, crystallized from EtOH/Et_2O): mp 172.5-173 °C; EI-MS *m/z* 256 (M^+); ^{1}H-NMR (DMSO-d_6, 270 MHz) 11.20 (1H, br s, NH), 7.66 (1H, s, H-6), 5.69 (1H, s, H-1'), 5.22 (1H, br s, 5'-OH), 5.16 (1H, s, 2'-OH), 4.06-4.00 (1H, m, H-4'), 3.64 (1H, dd, H-5'a, $J_{5'a,b}$ = 11.7, $J_{5'a,4'}$ = 2.3 Hz), 3.54 (1H, dd, H-5'b, $J_{5'b,a}$ = 11.7, $J_{5'b,4'}$ = 3.7 Hz), 2.03 (1H, dd, H-3'a, $J_{3'a,4'}$ = 7.3, $J_{3'a,b}$ = 13.2 Hz), 1.94 (1H, dd, H-3'b, $J_{3'b,4'}$ = 7.3, $J_{3'b,a}$ = 13.2 Hz), 1.76 (3H, s, 5-Me), 1.28 (3H, s, 2'-Me). Anal Calcd for $C_{11}H_{16}N_2O_5$•1/2 H_2O: C, 51.20; H, 6.33; N, 10.86. Found: C, 51.23; H, 6.35; N, 10.82.

1-(5-*O*-TBS-2,3-dideoxy-2-*C*-methyl-β-D-*threo*-pentofuranosyl)uracil (8a). Methoxalyl chloride (0.39 ml, 4.22 mmol) was added to a solution of **5a** (1.0 g, 2.81 mmol) and DMAP (684 mg, 5.62 mmol) in dry CH_3CN (20 ml). The mixture was stirred for 1.5 h at room temperature under argon, and then diluted with EtOAc (50 ml). The mixture was washed successively with saturated $NaHCO_3$ solution (30 ml), H_2O (30 ml), and brine (30 ml). The separated organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure to give a crude **6a**. The residue containing **6a** was coevaporated several times with toluene. Without further purification, this crude **6a** was used for the next step. A mixture of **6a**, AIBN (40 mg), and Bu_3SnH (1.14 ml, 4.22 mmol) in toluene (25 ml) was heated at 110 °C for 1 h under argon, and the solvent was removed under reduced pressure. The residue was purified on a silica gel column (3.7 x 10 cm) with 20-40% EtOAc in hexane to afford **8a** (842 mg, 88%) as a syrup: EI-MS *m/z* 341 (M^++1), 325 (M^+-Me), 283 (M^+-*t*-Bu); ^{1}H-NMR ($CDCl_3$, 400 MHz) 8.52 (1H, br s, NH), 8.21 (1H, d, H-6, $J_{6,5}$ = 7.8 Hz), 6.22 (1H, d, H-1', $J_{1',2'}$ = 7.3 Hz), 5.66 (1H, dd, H-5, $J_{5,6}$ = 7.8, $J_{5,NH}$ = 2.0 Hz), 4.15-4.10 (2H, m, H-4'), 4.12 (1H, dd, H-5'a, $J_{5'a,4'}$ = 2.0, $J_{5'a,b}$ = 12.2 Hz), 3.72 (1H, dd, H-5'b, $J_{5'b,a}$ = 12.2, $J_{5'b,4'}$ = 2.5 Hz), 2.79-2.71 (1H, m, H-2'), 1.88 (1H, ddd, H-3'a, $J_{3'a,4'}$ = 5.4, $J_{3'a,b}$ = 12.2, $J_{3'a,2'}$ = 6.8 Hz), 1.81-1.72 (1H, m, H-3'b), 0.99 (3H, d, 2'-Me, $J_{Me,2'}$ = 6.8 Hz), 0.94 (9H, s, *t*-Bu), 0.11 (6H, s, Me_2Si). EI-HR-MS *m/z* calcd for $C_{15}H_{25}N_2O_4Si$ (M^+-Me): 325.1583. Found: 325.1569.

1-(5-*O*-TBS-2,3-dideoxy-2-*C*-methyl-β-D-*threo*-pentofuranosyl)thymine (8b). Compound **5b** (509 mg, 1.38 mmol) was converted as above to afford **8b** (388 mg, 79.5%, crystallized from hexane): mp 128-129 °C; EI-MS *m/z* 355 (M^++1), 339 (M^+-Me), 297 (M^+-*t*-Bu); ^{1}H-NMR ($CDCl_3$, 270 MHz) 8.38 (1H, br s, 3-NH), 7.60 (1H, d, H-6, $J_{6,Me}$ = 1.0 Hz), 6.20 (1H, d, H-1', $J_{1',2'}$ = 7.3 Hz), 4.10-4.04 (2H, m, H-5'a,b), 3.78 (1H, dddd, H-4', $J_{4',3'ab}$ = 12.0, $J_{4',5'ab}$ = 3.7 Hz), 2.79-2.72 (1H, m, H-2'), 1.98-1.92 (1H, m, H-3'a), 1.93 (3H, d, 5-Me, $J_{Me,6}$ = 1.0 Hz), 1.71-1.61 (1H, m, H-3'b), 0.95 (3H, d, 2'-Me, $J_{Me,2'}$ = 6.8 Hz), 0.95 (9H, s, *t*-Bu), 0.14 (3H, s, MeSi), 0.13 (3H, s, MeSi). Anal Calcd for $C_{17}H_{30}N_2O_4Si$: C, 57.60; H, 8.53; N, 7.90. Found: C, 57.62; H, 8.40; N, 7.97.

1-(2,3-Dideoxy-2-*C*-methyl-β-D-*threo*-pentofuranosyl)uracil (9a). Compound **8a** (160 mg, 0.47 mmol) was desilylated as above to give **9a** (55 mg, 51%, crystallized from hexane/EtOAc): mp 154.5-155 °C; EI-MS *m/z* 226 (M^+); ^{1}H-NMR (DMSO-d_6, 400 MHz) 11.28 (1H, br s, NH), 8.11 (1H, d, H-6, $J_{6,5}$ = 8.3 Hz), 6.04 (1H, d, H-1', $J_{1',2'}$ = 7.3 Hz), 5.58 (1H, dd, H-5, $J_{5,6}$ = 8.3, $J_{5,NH}$ = 2.4 Hz), 5.14 (1H, dd, 5'-OH, $J_{OH,5'a}$ = 5.4, $J_{OH,5'b}$ = 4.9 Hz), 4.05-3.99 (1H, m, H-4'), 3.76 (1H, ddd, H-5'a, $J_{5'a,b}$ = 12.2, $J_{5'a,\ OH}$ = 5.4, $J_{5'a,4'}$ = 2.9 Hz), 3.57 (1H, ddd, H-5'b, $J_{5'b,a}$ = 12.2, $J_{5'b,\ OH}$ = 4.9,$J_{5'b,4'}$ = 2.9 Hz), 2.74-2.66 (1H, m, H-2'), 1.91 (1H, ddd, H-3'a, $J_{3'a,4'}$ = 5.4, $J_{3'a,b}$ = 12.2, $J_{3'a,2'}$ = 7.3 Hz), 1.60-1.51 (1H, m, H-3'b), 0.83 (3H, d, 2'-Me, $J_{Me,\ 2'}$ = 6.8 Hz). Anal Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 52.85; H, 6.27; N, 12.27.

1-(2,3-Dideoxy-2-*C*-methyl-β-D-*threo*-pentofuranosyl)thymine (9b). Compound **8b** (200 mg, 0.56 mmol) in THF (8 ml) was desilylated as above to give **9b** (95 mg, 70%, crystallized from EtOAc): mp 147-148 °C; EI-MS *m/z* 240 (M^+); ^{1}H-NMR (DMSO-d_6, 400 MHz) 11.24 (1H, br s, NH), 8.04 (1H, d, H-6, $J_{6,Me}$ = 1.0 Hz), 6.03 (1H, d, H-1', $J_{1',2'}$ = 6.8 Hz), 5.20 (1H, dd, 5'-OH, $J_{OH,5'a}$ = 5.4, $J_{OH,\ 5'b}$ = 4.4 Hz), 4.04-3.99 (1H, m, H-4'), 3.79 (1H, dd, H-5'a, $J_{5'a,b}$ = 12.2, $J_{5'a,OH}$ = 5.4, $J_{5'a,4'}$ = 2.9 Hz), 3.57 (1H, ddd, H-5'b, $J_{5'b,a}$ = 12.2, $J_{5'b,OH}$ = 4.4, $J_{5'b,4'}$ = 2.9 Hz), 2.72-2.64 (1H, m, H-2'), 1.89 (1H, ddd, H-3'a, $J_{3'a,4'}$ = 5.4, $J_{3'b,a}$ = 12.2, $J_{3'a,2'}$ = 7.3 Hz), 1.76 (3H, d, 5-Me, $J_{5,6}$ = 1.0 Hz), 1.66-1.57 (1H, m, H-3'b), 0.82 (3H, d, 2'-Me, $J_{Me,\ 2'}$ = 6.8 Hz). Anal Calcd for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 55.09; H, 6.72; N, 11.80.

1-(5-*O*-TBS-2,3-dideoxy-2-*C*-methyl-β-D-*threo*-pentofuranosyl)cytosine (8c). Triethylamine (0.47 ml, 3.36 mmol) was added to a mixture of **8a** (572 mg, 1.68 mmol), 2,4,6-triisopropylbenzenesulfonyl chloride (1.02 g, 3.36 mmol), and DMAP (410 mg, 3.36 mmol) in CH_3CN (20 ml) under argon atmosphere. The mixture was stirred for 4.5 h at room temperature, and then concentrated NH_4OH (28%, 10 ml) was added to the mixture, which was further stirred for 1.5 h at room temperature. The solvent was removed under reduced pressure and the residue was purified on a silica gel column (2.8 x 9 cm) with 2-4% EtOH in $CHCl_3$ to afford **8c** (560 mg, 98%) as a foam: EI-MS *m/z* 339 (M^+), 324 (M^+-Me), 282 (M^+-*t*-Bu); ^{1}H-NMR ($CDCl_3$, 400 MHz) 8.19 (1H, d, H-6, $J_{6,5}$ = 7.8 Hz), 6.28 (1H, d, H-1', $J_{1',2'}$ = 7.3 Hz), 5.86 (1H, d, H-5, $J_{5,6}$ = 7.8 Hz), 4.11-4.07 (2H, m, H-4'), 4.07 (1H, dd, H-5'a, $J_{5'a,4'}$ = 2.4, $J_{5'a,b}$ = 11.7 Hz), 3.73 (1H, dd, H-5'b, $J_{5'b,a}$ = 11.7, $J_{5'b,4'}$ = 2.4 Hz), 2.86-2.71 (1H, m, H-2'), 1.88 (1H, ddd, H-3'a, $J_{3'a,4'}$ = 4.9, $J_{3'a,b}$ = 12.7, $J_{3'a,2'}$ = 7.3 Hz), 1.72-1.63 (1H, m, H-3'b), 0.93 (9H, s, *t*-Bu), 0.92 (3H, d, 2'-Me, $J_{Me,2'}$ = 2.4 Hz), 0.11 (6H, s, Me_2Si). EI-HR-MS *m/z* calcd for $C_{16}H_{29}N_3O_3Si$ (M^+): 339.1978. Found: 339.1977.

1-(2,3-Dideoxy-2-*C*-methyl-β-D-*threo*-pentofuranosyl)cytosine Hydrochloride (9c). A THF solution of TBAF (1 M, 2.2 ml, 2.2 mmol) was added to a solution of **8c** (499 mg, 1.47 mmol) in THF (10 ml). The mixture was stirred for 1 h at room temperature and concentrated to dryness. The residue was purified on a silica gel column (2.8 x 12 cm) with 8% MeOH in $CHCl_3$ to give **9c**, which was dissolved in EtOH (10 ml) and 1 N HCl (1.77 ml). The solution was coevaporated several times with EtOH to give a hydrochloride of **9c** (200 mg, 52%, crystallized from EtOH): mp 240-242 °C; ^{1}H-NMR (DMSO-d_6, 400 MHz) 9.79 (1H, br s, 4-NH), 8.72 (1H, br s, 4-NH), 8.50 (1H, d, H-6, $J_{6,5}$ = 7.8 Hz), 6.15 (1H, d, H-5, $J_{5,6}$ = 7.8 Hz), 6.06 (1H, d, H-1', $J_{1',2'}$ = 6.8 Hz), 4.10-4.07 (1H, m, H-4'), 3.79 (1H, dd, H-5'a, $J_{5'a,b}$ = 12.2, $J_{5'a,4'}$ = 2.4 Hz), 3.60 (1H, dd, H-5'b, $J_{5'b,a}$ = 12.2, $J_{5'b,4'}$ = 2.7 Hz), 2.81-2.72 (1H, m, H-2'), 1.96-1.90 (1H, m, H-3'a), 1.60-1.51 (1H, m, H-3'b), 0.86 (3H, d, 2'-Me, $J_{Me,\ 2'}$ = 6.8 Hz).

Anal Calcd for $C_{10}H_{15}N_3O_3$•HCl: C, 45.89; H, 6.16; N, 16.06. Found: C, 45.86; H, 6.16; N, 13.57.

9-(5-*O*-DMTS-3-deoxy-β-D-*erythro*-pentofuranosyl)adenine (11). Dimethylthexylsilyl chloride (18.8 ml, 95.5 mmol) was added dropwise to a solution of cordycepin **10** (20.0 g, 80 mmol) in dry pyridine (300 ml) at 0 °C. The mixture was stirred for 20 h at room temperature under argon, and then H_2O (about 10 ml) was added to the mixture. The solvent was removed under reduced pressure and the residue was purified on a silica gel column (6 x 18 cm) with 8% EtOH in $CHCl_3$ to give **11** (21.3 g, 68%, crystallized from EtOH): mp 163-164 °C; EI-MS *m/z* 394 (M^++1), 378 (M^+-Me), 308 (M^+-thexyl); ^{1}H-NMR (DMSO-d_6, 400 MHz) 8.27 (1H, s, H-8), 8.16 (1H, s, H-2), 7.26 (2H, br s, 6-NH_2), 5.90 (1H, d, H-1', $J_{1',2'}$ = 1.5 Hz), 5.69 (1H, d, 2'-OH, $J_{OH,2'}$ = 3.9 Hz), 4.57 (1H, m, H-2'), 4.38 (1H, dddd, H-4', $J_{4'5'a}$ = $J_{4',5'b}$ = 3.4, $J_{4',3'a}$ = 9.3, $J_{4',3'b}$ = 5.9 Hz), 3.87 (1H, dd, H-5'a, $J_{5'a,b}$ = 11.2, $J_{5'a,4'}$ = 3.4 Hz), 3.72 (1H, dd, H-5'b, $J_{5'b,a}$ = 11.2, $J_{5'b,4'}$ = 3.4 Hz), 2.25 (1H, ddd, H-3'a, $J_{3'a,4'}$ = 9.3, $J_{3'a,b}$ = 13.2, $J_{3'a,2'}$ = 5.4 Hz), 1.91 (1H, ddd, H-3'b, $J_{3'b,4'}$ = 5.9, $J_{3'b,a}$ = 13.2, $J_{3'b,2'}$ = 2.4 Hz), 1.58 and 0.82 (13H, m, thexyl), 0.07 (6H, m, Me_2Si). Anal Calcd for $C_{18}H_{31}N_5O_3Si$: C, 54.93; H, 7.94; N, 17.79. Found: C, 54.84; H, 7.95; N, 17.73.

9-(5-*O*-DMTS-3-deoxy-β-D-*erythro*-pentofuranosyl)-N^6-benzoyladenine (12). Benzoyl chloride (23.6 ml, 203 mmol) was added dropwise to a solution of **11** (20.0 g, 50.8 mmol) in dry pyridine (200 ml) at 0 °C. The mixture was stirred for 5 h at room temperature under argon, and then H_2O (about 10 ml) was added to the mixture. The solvent was removed under reduced pressure and the residue was diluted with EtOAc (500 ml), which was washed with saturated $NaHCO_3$ (200 ml x 5) and brine (500 ml). The separated organic phase was dried (Na_2SO_4) and concentrated to dryness. 2 N NaOH (250 ml, 50% aqueous EtOH solution) was added to the above residue in pyridine (250 ml) at 0 °C and the mixture was stirred for 20 min at 0 °C. The mixture was neutralized with AcOH and concentrated to dryness to give an oil, which was partitioned between $CHCl_3$ (300 ml) and H_2O (300 ml). The separated water phase was back-extracted with $CHCl_3$ (100 ml x 4). The combined organic phase was washed with brine (300 ml) and dried (Na_2SO_4). The solvent was concentrated to dryness and the residue was purified on a silica gel column (6 x 17 cm) with EtOAc to give **12** (22.4 g, 89%) as a colorless foam: EI-MS *m/z* 498 (M^++1), 482 (M^+-Me), 412 (M^+-thexyl); ^{1}H-NMR (DMSO-d_6, 270 MHz) 11.17 (1H, br s, NH), 8.75 (1H, s, H-8), 8.57 (1H, s, H-2), 8.06-8.03 (2H, m, Ph), 7.68-7.52 (3H, m, Ph), 6.05 (1H, s, H-1'), 5.77 (1H, d, 2'-OH, $J_{OH,2'}$ = 3.8 Hz), 4.68 (1H, m, H-2'), 4.43-4.42 (1H, m, H-4'), 3.88 (1H, dd, H-5'a, $J_{5'a,b}$ = 11.0, $J_{5'a,4'}$ = 3.3 Hz), 3.75 (1H, dd, H-5'b, $J_{5'b,a}$ = 11.0, $J_{5'b,4'}$ = 4.4 Hz), 2.35-2.24 (1H, m, H-3'a), 1.99-1.96 (1H, m, H-3'b), 1.62-1.52 and 0.85-0.81 (13H, m, thexyl), 0.07 (6H, m, Me_2Si). Anal Calcd for $C_{25}H_{35}N_5O_4Si$: C, 60.34; H, 7.09; N, 14.07. Found: C, 60.42; H, 7.06; N, 14.02.

9-(5-*O*-DMTS-3-deoxy-β-D-*erythro*-pentofuran-2-ulosyl)-N^6-benzoyladenine (13). Dichloroacetic acid (0.33 ml, 4 mmol) was added to a mixture of **12** (4.98 g, 10 mmol) and *N,N'*-dicyclohexylcarbodiimide (6.19 g, 30 mmol) in dry DMSO (30 ml) at 0 °C. After being stirred for 30 min at room temperature under argon, more dichloroacetic acid (0.33 ml, 4 mmol) was added to the mixture at 0 °C, which was further stirred for 30 min at room temperature. A MeOH solution of oxalic acid dihydrate (2 M, 10 ml) was added to the mixture at 0 °C and the mixture was stirred for further 30 min at room temperature. Insoluble materials were removed on filtration and the filtrate was concentrated *in vacuo*. The residue was purified by a silica gel column (5.2 x 13 cm) with hexane/EtOAc (1:2-1:4) to give **13** (3.65 g, 74%) as a yellowish foam: EI-MS *m/z* 496 (M^++1), 480 (M^+-Me), 410 (M^+-thexyl); ^{1}H-NMR ($CDCl_3$, 100 MHz)

8.99 (1H, br s, NH), 8.78 (1H, s, H-2), 8.06 (1H, s, H-8), 8.00-7.98 (2H, m, Ph), 7.58-7.51 (3H, m, Ph), 6.02 (1H, s, H-1'), 4.70-4.51 (1H, m, H-4'), 4.00 (1H, dd, H-5'a, $J_{5'a,b}$ = 11.2, $J_{5'a,4'}$ = 3.9 Hz), 3.85 (1H, dd, H-5'b, $J_{5'b,a}$ = 11.2, $J_{5'b,4'}$ = 4.2 Hz), 3.18 (1H, dd, H-3'a, $J_{3'a,4'}$ = 8.1, $J_{3'a,b}$ = 18.6 Hz), 2.82 (1H, dd, H-3'b, $J_{3'b,4'}$ = 6.8, $J_{3'b,a}$ = 18.6 Hz), 1.70-1.48 and 0.90-0.84 (13H, m, thexyl), 0.09 (6H, m, Me_2Si). Anal Calcd for $C_{25}H_{33}N_5O_4Si$: C, 60.58; H, 6,71; N, 14.13. Found: C, 60.49; H, 6.81; N, 13.83.

9-(5-*O*-DMTS-3-deoxy-2-*C*-methyl-β-D-*threo*-pentofuranosyl)-N^6-benzoyladenine (14). Compound **13** (1.49 g, 3 mmol) was converted as described for the synthesis of **5a** to give **14** (0.95 g, 62%) as a colorless foam after silica gel column chromatographic purification (3.4 x 15 cm) with benzene/EtOAc (1:2-1:4): EI-MS *m/z* 511 (M^+); ^{1}H-NMR ($CDCl_3$, 270 MHz) 9.06 (1H, br s, NH), 8.79 (1H, s, H-2), 8.49 (1H, s, H-8), 8.04-8.01 (2H, m, Ph), 7.63-7.48 (3H, m, Ph), 6.09 (1H, s, H-1'), 5.12 (1H, s, 2'-OH), 4.43 (1H, dddd, H-4', $J_{4',5'a}$ = 1.8, $J_{4',5'b}$ = 1.5, $J_{4',3'a}$ = 9.9, $J_{4',3'b}$ = 2.9 Hz), 4.03 (1H, dd, H-5'a, $J_{5'a,b}$ = 11.4, $J_{5'a,4'}$ = 1.8 Hz), 3.66 (1H, dd, H-5'b, $J_{5'b,a}$ = 11.4, $J_{5'b,4'}$ = 1.5 Hz), 2.49 (1H, dd, H-3'a, $J_{3'a,4'}$ = 9.9, $J_{3'a,b}$ = 13.9 Hz), 2.26 (1H, dd, H-3'b, $J_{3'b,4'}$ = 2.9, $J_{3'b,a}$ = 13.9 Hz), 1.31 (3H, s, 2'-Me), 1.71-1.62 and 0.94-0.91 (13H, m, thexyl), 0.24 and 0.23 (each 3H, s, MeSi). EI-HR-MS *m/z*: calcd for $C_{26}H_{37}N_5O_4Si$ (M^+) 511.2615. Found: 511.2612.

9-(5-*O*-DMTS-2,3-dideoxy-2-*C*-methyl-β-D-*threo*-pentofuranosyl)adenine (16) and **9-(5-*O*-DMTS-3-deoxy-2-*C*-methyl-β-D-*threo*-pentofuranosyl)adenine (17)**. Methoxalyl chloride (0.41 ml, 4.5 mmol) was added to a mixture of **14** (768 mg, 1.5 mmol) and DMAP (641 mg, 5.25 mmol) in dry CH_3CN (20 ml). The mixture was stirred for 4 h at room temperature under argon, and then diluted with EtOAc (30 ml), which was washed successively with H_2O (30 ml) and brine (30 ml). The separated organic phase was dried (Na_2SO_4) and concentrated to dryness *in vacuo* to give **15**. The residue was coevaporated two times with toluene. A mixture of **15**, AIBN (30 mg), and Bu_3SnH (2.43 ml, 9 mmol) in toluene (15 ml) was heated at 110 °C for 3 h under argon, and then the solvent was removed *in vacuo*. The residue was further treated with NH_3/MeOH (saturated at 0 °C, 30 ml) for 2 days at room temperature. The mixture was concentrated *in vacuo* and the residue was purified on a silica gel column (3.4 x 15 cm) with 1-4% EtOH in $CHCl_3$ to give **16** (374 mg, 64%) as a yellow syrup, and with 4% EtOH in $CHCl_3$ to give **17** (177 mg, 29%) as a colorless glass. Physical data for **16**: EI-MS *m/z* 391 (M^+), 376 (M^+-Me), 306 (M^+-thexyl); ^{1}H-NMR ($CDCl_3$, 270 MHz) 8.45 (1H, s, H-2), 8.32 (1H, s, H-8), 6.40 (1H, d, H-1', $J_{1',2'}$ = 6.6 Hz), 5.74 (2H, br s, 6-NH_2), 4.25-4.16 (1H, m, H-4'), 4.08 (1H, dd, H-5'a, $J_{5'a,b}$ = 11.4, $J_{5'a,4'}$ = 2.9 Hz), 3.82 (1H, dd, H-5'b, $J_{5'b,a}$ = 11.4, $J_{5'b,4'}$ = 2.6 Hz), 2.89-2.77 (1H, m, H-2'), 2.05-1.91 (2H, m, H-3'a,b), 1.73-1.63 and 0.93 (13H, m, thexyl), 0.71 (3H, d, 2'-Me, $J_{Me,2'}$ = 7.0 Hz), 0.20 (6H, s, Me_2Si). EI-HR-MS *m/z*: calcd for $C_{19}H_{33}N_5O_2Si$ (M^+) 391.2403. Found: 391.2426. Physical data for **17**: EI-MS *m/z* 408 (M^++1), 392 (M^+-Me), 322 (M^+-thexyl); ^{1}H-NMR ($CDCl_3$, 270 MHz) 8.33 (1H, s, H-2), 8.31 (1H, s, H-8), 5.99 (1H, s, H-1'), 5.66 (2H, br s, 6-NH_2), 5.09 (1H, br s, 2'-OH), 4.39 (1H, dddd, H-4', $J_{4',5'a} = J_{4',5'b}$ = 1.8, $J_{4',3'a}$ = 9.9, $J_{4',3'b}$ = 3.3 Hz), 4.01 (1H, dd, H-5'a, $J_{5'a,b}$ = 11.4, $J_{5'a,4'}$ = 1.8 Hz), 3.65 (1H, dd, H-5'b, $J_{5'b,a}$ = 11.4, $J_{5'b,4'}$ = 1.8 Hz), 2.45 (1H, dd, H-3'a, $J_{3'a,4'}$ = 9.9, $J_{3'a,b}$ = 13.9 Hz), 2.24 (1H, dd, H-3'b, $J_{3'b,4'}$ = 3.3, $J_{3'b,a}$ = 13.9 Hz), 1.30 (3H, s, 2'-Me), 1.73-1.63 and 0.93-0.91 (13H, m, thexyl), 0.23-0.22 (each 3H, s, MeSi). EI-HR-MS *m/z*: calcd for $C_{19}H_{33}N_5O_3Si$ (M^+) 407.2352. Found: 407.2351.

9-(2,3-Dideoxy-2-*C*-methyl-β-D-*threo*-pentofuranosyl)adenine (18). A THF solution of

TBAF (1 M, 1.37 mmol, 1.37 mmol) was added to a solution of **16** (358 mg, 0.92 mmol) in THF (10 ml). The mixture was stirred for 3 h at room temperature, and concentrated to dryness. The residue was purified on a silica gel column (2.8 x 14 cm) with 4-8% MeOH in $CHCl_3$ to give **18** (138 mg, 60.5%, crystallized from EtOH): mp 232-233 °C; EI-MS *m/z* 249 (M^+); ^{1}H-NMR (DMSO-d_6, 270 MHz) 8.49 (1H, s, H-8), 8.12 (1H, s, H-2), 7.23 (2H, br s, 6-NH_2), 6.26 (1H, d, H-1', $J_{1',2'}$ = 7.1 Hz), 5.16 (1H, dd, 5'-OH, $J_{OH,5'a}$ = 5.5, $J_{OH,5'b}$ = 5.0 Hz), 4.16-4.10 (1H, m, H-4'), 3.79 (1H, ddd, H-5'a, $J_{5'a,b}$ = 12.1, $J_{5'a,4'}$ = 2.8, $J_{5',OH}$ = 5.5 Hz), 3.63 (1H, ddd, H-5'b, $J_{5'b,a}$ = 12.1, $J_{5'b,4'}$ = 3.8, $J_{5',OH}$ = 5.0 Hz), 2.87-2.75 (1H, m, H-2'), 2.05-1.81 (2H, m, H-3'a,b), 0.58 (3H, d, 2'-Me, $J_{Me,2'}$ = 6.6 Hz). Anal Calcd for $C_{11}H_{15}N_5O_2$: C, 53.00; H, 6.07; N, 28.09. Found: C, 53.17; H, 6.09; N, 28.11.

9-(3-Deoxy-2-*C*-methyl-β-D-*threo*-pentofuranosyl)adenine (19). Compound **17** (166 mg, 0.41 mmol) was desilylated as above to give **19** (71 mg, 66%, crystallized from EtOH) after silica gel column chromatographic purification with 8% MeOH in $CHCl_3$: mp 218-221 °C; EI-MS *m/z* 265 (M^+); ^{1}H-NMR (DMSO-d_6, 270 MHz) 8.27 (1H, s, H-8), 8.12 (1H, s, H-2), 7.20 (2H, br s, 6-NH_2), 5.88 (1H, s, H-1'), 5.34-5.30 (2H, m, 2', 5'-OH), 4.20-4.12 (1H, m, H-4'), 3.67 (1H, ddd, H-5'a, $J_{5'a,b}$ = 11.7, $J_{5'a,4'}$ = 3.7, $J_{5',OH}$ = 5.1 Hz), 3.58 (1H, ddd, H-5'b, $J_{5'b,a}$ = 11.7, $J_{5'b,4'}$ = 4.4, $J_{5',OH}$ = 5.1 Hz), 2.19-2.15 (2H, m, H-3'a,b), 1.30 (3H, s, 2'-Me). Anal Calcd for $C_{11}H_{15}N_5O_3$: C, 49.81; H, 5.70; N, 26.40. Found: C, 49.77; H, 5.70; N, 26.11.

1-[5-*O*-TBS-3-deoxy-2-*C*-[2-(TMS)ethynyl]-β-D-*threo*-pentofuranosyl]thymine (20). n-BuLi (1.55 M hexane solution, 9.68 ml, 15 mmol) was added dropwise to a mixture of (TMS)acetylene (2.21 ml, 15 mmol) in THF (30 ml) with stirring for 30 min at -78 °C under argon atmosphere. A solution of **4b** (1.77 g, 5 mmol) in THF (10 ml) was added dropwise to the above acetylide solution at -78 °C and the mixture was further stirred for 2.5 h at -78 °C. Aqueous NH_4Cl solution (1 M, 20 ml) was added to the mixture and after warming to room temperature, the whole was extracted with EtOAc (30 ml x 4). The separated organic phase was washed with brine (50 ml), dried (Na_2SO_4), and concentrated dryness. The residue was purified by a silica gel column (3.7 x 13 cm) with 10 % EtOAc in hexane to afford **20** (1.9 g, 84%, crystallized from hexane/EtOAc): mp 70-72 °C; EI-MS *m/z* 453 (M^++1), 437 (M^+-Me), 395 (M^+-*t*-Bu); IR ($CHCl_3$) ν 2170 cm-1 (C≡C); ^{1}H-NMR ($CDCl_3$, 400 MHz) 8.26 (1H, br s, 3-NH), 7.51 (1H, d, H-6, $J_{6,5}$ = 1.2 Hz), 6.15 (1H, s, H-1'), 4.82 (1H, br s, 2'-OH), 4.39 (1H, dddd, H-4', $J_{4',5'a}$ = $J_{4',5'b}$ = 1.8, $J_{4',3'a}$ = 8.9, $J_{4',3'b}$ = 4.4 Hz), 4.02 (1H, dd, H-5'a, $J_{5'a,b}$ = 11.4, $J_{5'a,4'}$ = 1.8 Hz), 3.64 (1H, dd, H-5'b, $J_{5'a,b}$ = 11.4, $J_{5'b,4'}$ = 1.8 Hz), 2.68 (1H, dd, H-3'a, $J_{3'a,4'}$ = 8.9, $J_{3'a,b}$ = 13.9 Hz), 2.32 (1H, dd, H-3'b, $J_{3'b,4'}$ = 4.4, $J_{3'a,b}$ = 13.9 Hz), 1.89 (3H, d, 5-Me, $J_{Me,5}$ = 1.2 Hz), 0.97 (9H, s, *t*-Bu), 0.18-0.15 (15H, m, Me_2Si, Me_3Si). Anal Calcd for $C_{21}H_{36}N_2O_5Si_2$: C, 55.73; H, 8.02; N, 6.19. Found: C, 55.65; H, 8.01; N, 6.12.

1-[5-*O*-TBS-2,3-dideoxy-2-*C*-[2-(TMS)ethynyl]-β-D-*threo*-pentofuranosyl]thymine (22) and 5'-*O*-TBS-3'-deoxy-2',3'-didehydro-2'-*C*-[2-(TMS)ethynyl]thymidine (23). Methoxalyl chloride (0.2 ml, 2.2 mmol) was added to a solution of **20** (500 mg, 1.1 mmol) and DMAP (338 mg, 2.75 mmol) in dry CH_3CN (15 ml). The mixture was stirred for 3.5 h at room temperature under argon atmosphere, and then diluted with EtOAc (40 ml). The mixture was washed successively with saturated $NaHCO_3$ solution (40 ml), H_2O (40 ml), and brine (40 ml). The separated organic phase was dried (Na_2SO_4) and concentrated to dryness. The residue was coevaporated several times with toluene. A mixture of **21**, AIBN (50 mg), and Bu_3SnH (0.45 ml, 1.65 mmol) in dry benzene (30 ml) was heated for 1

h at 80 °C under argon. The solvent was removed under reduced pressure and the residue was purified on a silica gel column (2.8 x 12 cm) with 15% EtOAc in hexane to give **22** (200 mg, 41.5%, crystallized from hexane) and with 15-30% EtOAc in hexane to afford **23** (72 mg, 15%, crystallized from hexane). Physical data for **22**: mp 126-127 °C; EI-MS *m/z* 437 (M^++1), 421 (M^+-Me), 379 (M^+-*t*-Bu); ^{1}H-NMR ($CDCl_3$, 400 MHz) 8.29 (1H, br s, 3-NH), 7.49 (1H, d, H-6, $J_{6,5}$ = 1.0 Hz), 6.19 (1H, d, H-1', $J_{1',2'}$ = 6.8 Hz), 4.07 (1H, dddd, H-4', $J_{4',5'a}$ = 3.4, $J_{4',5'b}$ = 3.9, $J_{4',3'a}$ = 5.9, $J_{4',3'b}$ = 9.3 Hz), 3.97 (1H, dd, H-5'a, $J_{5'a,b}$ = 11.2, $J_{5'a,4'}$ = 3.4 Hz), 3.80 (1H, dd, H-5'b, $J_{5'b,a}$ = 11.2, $J_{5'b,4'}$ = 3.9 Hz), 3.52 (1H, ddd, H-2', $J_{2',3'a}$ = 8.3, $J_{2',3'b}$ = 9.3, $J_{2',1'}$ = 6.8 Hz), 2.29 (1H, ddd, H-3'a, $J_{3'a,4'}$ = 9.3, $J_{3'a,b}$ = 12.7, $J_{3'a,2'}$ = 8.3 Hz), 2.12 (1H, ddd, H-3'b, $J_{3'b,4'}$ = $J_{3'b,2'}$ = 9.3, $J_{3'b,a}$ = 12.7 Hz), 1.94 (3H, d, 5-Me, $J_{5,6}$ = 1.0 Hz), 0.95 (9H, s, *t*-Bu), 0.13 (6H, s, Me_2Si), 0.05 (9H, s, Me_3Si). Anal Calcd for $C_{21}H_{36}N_2O_4Si_2$: C, 57.76; H, 8.31; N, 6.41. Found: C, 57.76; H, 8.35; N, 6.43. Physical data for **23**: mp 126-128 °C; EI-MS *m/z* 434 (M^+), 419 (M^+-Me), 377 (M^+-*t*-Bu); IR ($CHCl_3$) ν 2160 cm-1 (C≡C); ^{1}H-NMR ($CDCl_3$, 400 MHz) 8.75 (1H, br s, NH), 7.21 (1H, d, H-6, $J_{6,5}$ = 1.5 Hz), 6.90 (1H, dd, H-3', $J_{3',4'}$ = 3.9, $J_{3',1'}$ = 2.0 Hz), 6.47 (1H, dd, H-1', $J_{1',4'}$ = 1.5, $J_{1',3'}$ = 2.0 Hz), 4.91-4.89 (1H, m, H-4'), 3.85-3.77 (2H, m, H-5'a,b), 1.93 (3H, d, 5-Me, $J_{5,6}$ = 1.5 Hz), 0.91 (9H, s, *t*-Bu), 0.16 (9H, s, Me_3Si), 0.09 and 0.08 (each 3H, s, Me_2Si). Anal Calcd for $C_{21}H_{34}N_2O_4Si_2$: C, 58.03; H, 7.88; N, 6.44. Found: C, 57.90; H, 7.91; N, 6.47.

1-(3-Deoxy-2-*C*-ethynyl-β-D-*threo*-pentofuranosyl)thymine (24). Acetic acid (0.12 ml, 2.16 mmol) and a THF solution of TBAF (1 M, 2.16 ml, 2.16 mmol) were added to a solution of **20** (326 mg, 0.72 mmol) in THF (7 ml). The mixture was stirred for 1.5 h at room temperature and concentrated to dryness. The residue was purified on a silica gel column (2.8 x 7 cm) with 1-4% MeOH in $CHCl_3$ to give **24** (151 mg, 79%) as colorless glass: EI-MS *m/z* 266 (M^+); ^{1}H-NMR (DMSO-d_6, 400 MHz) 11.22 (1H, br s, NH), 7.69 (1H, d, H-6, $J_{6,Me}$ = 1.2 Hz), 6.28 (1H, s, 2'-OH), 6.02 (1H, s, H-1'), 5.17 (1H, br s, 5'-OH), 4.09 (1H, dddd, H-4', $J_{4',5'a}$ = 3.4, $J_{4',5'b}$ = 3.9, $J_{4',3'a}$ = 6.0, $J_{4',3'b}$ = 9.0 Hz), 3.69 (1H, d, H-5'a, $J_{5'a,b}$ = 12.2 Hz), 3.60 (1H, s, C≡CH), 3.57 (1H, d, H-5'b, $J_{5'b,a}$ = 12.2 Hz), 2.31 (1H, dd, H-3'a, $J_{3'a,4'}$ = 6.3, $J_{3'a,b}$ = 12.9 Hz), 2.13 (1H, dd, H-3'b, $J_{3'b,4'}$ = 9.0, $J_{3'b,a}$ = 12.9 Hz), 1.75 (3H, d, 5-Me, $J_{Me,6}$ = 1.2 Hz). Anal Calcd for $C_{12}H_{14}N_2O_5$•1/10 H_2O: C, 53.77; H, 5.34; N, 10.45. Found: C, 53.73; H, 5.50; N, 10.31.

1-(2,3-Dideoxy-2-*C*-ethynyl-β-D-*threo*-pentofuranosyl)thymine (25). Compound **22** (403 mg, 0.92 mmol) was desilylated as above to give **25** (194 mg, 84%, crystallized from hexane/EtOAc) after silica gel chromatographic purification with hexane/EtOAc (1:2-0:1): mp 181-182 °C; ^{1}H-NMR (DMSO-d_6, 400 MHz) 11.26 (1H, br s, NH), 7.91 (1H, d, H-6, $J_{6,Me}$ = 1.0 Hz), 6.13 (1H, d, H-1', $J_{1',2'}$ = 7.3 Hz), 5.21 (1H, t, 5'-OH, $J_{OH,5'}$ = 5.4 Hz), 4.05-3.99 (1H, m, H-4'), 3.79-3.73 (1H, m, H-2'), 3.64-3.55 (1H, m, H-5'a,b), 3.06 (1H, d, C≡CH, $J_{C≡CH,2'}$ = 2.5 Hz), 2.19 (1H, ddd, H-3'a, $J_{3'a,4'}$ = 4.9, $J_{3'a,b}$ = 12.7, $J_{3'a,2'}$ = 7.8 Hz), 2.03-1.95 (1H, m, H-3'b), 1.77 (3H, d, 5-Me, $J_{Me,6}$ = 1.0 Hz). Anal Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.56; H, 5.66; N, 11.12.

3'-Deoxy-2',3'-didehydro-2'-*C*-ethynylthymidine (26). Compound **23** (177 mg, 0.41 mmol) was desilylated as above to give **26** (77 mg, 76%, crystallized from hexane/EtOAc) after purification with a silica gel column with hexane/EtOAc (1:2-0:1): mp 187-188 °C; ^{1}H-NMR (DMSO-d_6, 400 MHz) 11.40 (1H, br s, NH), 7.73 (1H, d, H-6, $J_{6,Me}$ = 1.0 Hz), 6.78 (1H, dd, H-3', $J_{3',4'}$ = 3.4, $J_{3',1'}$ = 1.0 Hz), 6.76 (1H, m, H-1'), 5.15 (1H, br s, 5'-OH), 4.90 (1H, m, H-4'), 4.28 (1H, s, C≡CH), 3.64 (2H, m, H-5'a,b), 1.74 (3H, d, 5-Me, $J_{Me,6}$ = 1.0 Hz). Anal Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N,

11.28. Found: C, 58.22; H, 5.05; N, 11.30.

9-[5-*O*-DMTS-3-deoxy-2-*C*-[2-(TMS)ethynyl]-β-D-*threo*-pentofuranosyl]-N^6-benzoyladenine (27). Compound **13** (1.49 g, 3 mmol) was converted as described the synthesis of **20** to give **27** (1.21 g, 68%) as a yellowish foam: EI-MS *m/z* 593 (M^+); IR ($CHCl_3$) ν 2170 cm^{-1} (C≡C); ^{1}H-NMR ($CDCl_3$, 270 MHz) 9.04 (1H, br s, NH), 8.80 (1H, s, H-2), 8.48 (1H, s, H-8), 8.04-8.01 (2H, m, Ph), 7.63-7.49 (3H, m, Ph), 6.35 (1H, s, H-1'), 5.26 (1H, br s, 2'-OH), 4.53-4.49 (1H, m, H-4'), 4.02 (1H, dd, H-5'a, $J_{5'a,b}$ = 11.4, $J_{5'a,4'}$ = 1.8 Hz), 3.68 (1H, dd, H-5'b, $J_{5'b,a}$ = 11.4, $J_{5'b,4'}$ = 1.5 Hz), 2.83 (1H, dd, H-3'a, $J_{3'a,4'}$ = 9.9, $J_{3'a,b}$ = 13.9 Hz), 2.50 (1H, dd, H-3'b, $J_{3'b,4'}$ = 3.3, $J_{3'a,b}$ = 13.9 Hz), 1.72-1.65 and 0.92 (13H, m, thexyl), 0.23 (6H, s, Me_2Si), 0.07 (3H, s, Me_3Si). Anal Calcd for $C_{30}H_{43}N_5O_4Si_2$: C, 60.67; H, 7.30; N, 11.79. Found: C, 60.55; H, 7.32; N, 11.65.

9-(5-*O*-DMTS-2,3-dideoxy-2-*C*-ethynyl-β-D-*threo*-pentofuranosyl)adenine (29) and 9-(5-*O*-DMTS-3-deoxy-2-*C*-ethynyl-β-D-*threo*-pentofuranosyl)adenine (30). Methoxalyl chloride (0.14 ml, 1.5 mmol) was added to a mixture of **27** (297 mg, 0.5 mmol) and DMAP (214 mg, 1.75 mmol) in dry CH_3CN (8 ml). The mixture was stirred for 3.5 h at room temperature under argon, and then diluted with EtOAc (20 ml). The mixture was washed successively with H_2O (20 ml) and brine (20 ml), and the separated organic phase was dried (Na_2SO_4), and concentrated and coevaporated two times with toluene *in vacuo* to give **28**. A mixture of **28**, AIBN (20 mg), and Bu_3SnH (0.60 ml, 2.25 mmol) in benzene (10 ml) was heated at 90 °C for 3 h under argon, and the solvent was removed *in vacuo*. The residue was treated with NH_3/MeOH (saturated at 0 °C, 20 ml) for 1 day at room temperature. The solvent was removed *in vacuo* and the residue was purified on a silica gel column (2.3 x 8 cm) with 1% EtOH in $CHCl_3$ to give **29** (56 mg, 28%) as a colorless glass, and with 2% EtOH in $CHCl_3$ to give **30** (65 mg, 31%) as a colorless syrup. Physical data for **29**: EI-MS *m/z* 402 (M^++1), 386 (M^+-Me), 316 (M^+-thexyl); ^{1}H-NMR ($CDCl_3$, 270 MHz) 8.37 (1H, s, H-2), 8.35 (1H, s, H-8), 6.49 (1H, d, H-1', $J_{1',2'}$ = 7.0 Hz), 5.69 (2H, br s, 6-NH_2), 4.22 (1H, dddd, H-4', $J_{4',5'a}$ = 3.7, $J_{4',5'b}$ = 3.3, $J_{4',3'a}$ = 12.8, $J_{4',3'b}$ = 6.2 Hz), 4.03 (1H, dd, H-5'a, $J_{5'a,b}$ = 11.4, $J_{5'a,4'}$ = 3.7 Hz), 3.84 (1H, dd, H-5'b, $J_{5'b,a}$ = 11.4, $J_{5'b,4'}$ = 3.3 Hz), 3.65-3.54 (1H, m, H-2'), 2.49-2.33 (2H, m, H-3'a,b), 1.83 (1H, d, C≡CH, $J_{C≡CH,\ 2'}$ = 2.6 Hz), 1.72-1.62 and 0.94-0.93 (13H, m, thexyl), 0.18 (6H, s, Me_2Si). EI-HR-MS *m/z*: calcd for $C_{20}H_{31}N_5O_2Si$ (M^+) 401.2247. Found: 401.2268. Physical data for **30**: EI-MS *m/z* 418 (M^++1), 402 (M^+-Me), 332 (M^+-thexyl); ^{1}H-NMR ($CDCl_3$, 270 MHz) 8.34 (2H, s, H-2, 8), 6.25 (1H, s, H-1'), 5.69 (2H, br s, 6-NH_2), 5.55 (1H, br s, 2'-OH), 4.48 (1H, dddd, H-4', $J_{4',\ 5'a}$ = 2.2, $J_{4',5'b}$ = 1.8, $J_{4',3'a}$ = 9.5, $J_{4',3'b}$ = 4.0 Hz), 4.00 (1H, dd, H-5'a, $J_{5'a,b}$ = 11.4, $J_{5'a,4'}$ = 2.2 Hz), 3.67 (1H, dd, H-5'b, $J_{5'b,a}$ = 11.4, $J_{5'b,4'}$ = 1.8 Hz), 2.78 (1H, dd, H-3'a, $J_{3'a,4'}$ = 9.5, $J_{3'a,b}$ = 13.9 Hz), 2.50 (1H, dd, H-3'b, $J_{3'b,4'}$ = 4.0, $J_{3'b,a}$ = 13.9 Hz), 2.49 (1H, s, C≡CH), 1.72-1.62 and 0.93-0.90 (13H, m, thexyl), 0.22 (6H, s, Me_2Si). EI-HR-MS *m/z*: calcd for $C_{20}H_{31}N_5O_3Si$ (M^+) 417.2196. Found: 417.2188.

9-(2,3-Dideoxy-2-*C*-ethynyl-β-D-*threo*-pentofuranosyl)adenine (31). Compound **29** (55 mg, 0.14 mmol) was desilylated as described above to afford **31** (24 mg, 67%, crystallized from EtOH): mp 226-227 °C; EI-MS m/z 259 (M^+); ^{1}H-NMR (DMSO-d_6, 270 MHz) 8.41 (1H, s, H-8), 8.13 (1H, s, H-2), 7.21 (2H, br s, 6-NH_2), 6.38 (1H, d, H-1', $J_{1',2'}$ = 7.1 Hz), 5.16 (1H, t, 5'-OH, $J_{OH,5'}$ = 5.5 Hz), 4.16-4.11 (1H, m, H-4'), 3.81-3.71 (1H, m, H-2'), 3.74 (1H, ddd, H-5'a, $J_{5'a,OH}$ = 5.5, $J_{5'a,b}$ = 12.1, $J_{5'a,4'}$ = 2.9 Hz), 3.62 (1H, d, ddd, H-5'b, $J_{5'b,OH}$ = 5.5, $J_{5'b,a}$ = 12.1, $J_{5'a,4'}$ = 2.9 Hz), 2.74 (1H, d, C≡CH, $J_{C≡CH,2'}$ = 2.2 Hz), 2.34-2.27 (2H, m, H-3'a,b). EI-HR-MS *m/z* calcd for $C_{12}H_{13}N_5O_2$: 259.1069.

Found: 259.1053.

9-(3-Deoxy-2-*C*-ethynyl-β-D-*threo*-pentofuranosyl)adenine (32). Compound **30** (65 mg, 0.16 mmol) was desilylated as described above to afford **32** (28 mg, 66%, crystallized from EtOH): mp 196-197.5 °C; EI-MS m/z 275 (M^+); ^{1}H-NMR (DMSO-d_6, 270 MHz) 8.30 (1H, s, H-8), 8.14 (1H, s, H-2), 7.24 (2H, br s, 6-NH_2), 6.37 (1H, s, 2'-OH), 6.17 (1H, s, H-1'), 5.23 (1H, dd, 5'-OH, $J_{OH,5'a}$ = 5.5, $J_{OH,5'b}$ = 5.0 Hz), 4.23 (1H, dddd, H-4', $J_{4',5'a}$ = 3.7, $J_{4',5'b}$ = 4.0, $J_{4',3'a}$ = 7.1, $J_{4',3'b}$ = 8.2 Hz), 3.68 (1H, ddd, H-5'a, $J_{5'a,OH}$ = 5.5, $J_{5'a,b}$ = 12.1, $J_{5'a,4'}$ = 3.7 Hz), 3.61 (1H, s, C≡CH), 3.59 (1H, d, ddd, H-5'b, $J_{5'b,OH}$ = 5.0, $J_{5'b,a}$ = 12.1, $J_{5'a,4'}$ = 3.7 Hz), 2.46 (1H, dd, H-3'a, $J_{3'a,4'}$ = 7.1, $J_{3'a,b}$ = 13.2 Hz), 2.37 (1H, dd, H-3'b, $J_{3'b,4'}$ = 8.2, $J_{3'b,a}$ = 13.2 Hz). EI-HR-MS *m/z* calcd for $C_{12}H_{13}N_5O_3$: 275.1018. Found: 275.0993.

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