Synthesis of Pyranoid Analogues of the Anti-HIV Active 3'-Deoxy-2',3'-didehydrothymidine (D4T)

H. Bue Hansen and Erik B. Pedersen*

Department of Chemistry, Odense University, DK-5230 Odense M, Denmark

Bent Faber Vestergaard

Retrovirus Laboratory, Enterovirus Department, Statens Seruminstitut, Amager Boulevard 80, DK-2300 Copenhagen, Denmark

Received June 13, 1991

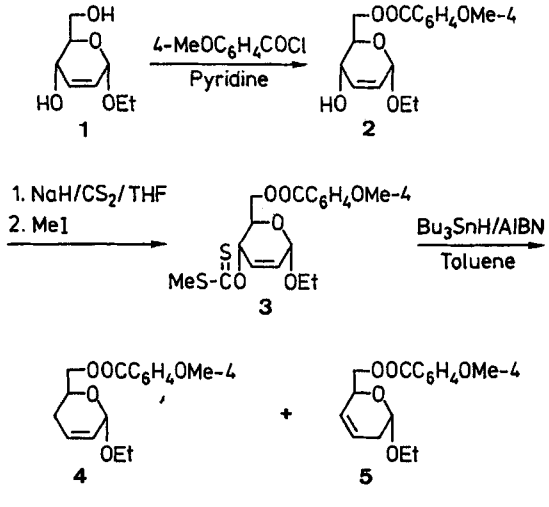
The primary hydroxy group of ethyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (**1**) was selectively protected and the secondary hydroxy group was deoxygenated *via* the dithiocarbonate **3** from which ethyl 6-*O*-(4-methoxybenzoyl)-2,3,4-trideoxy-α-D-*glycero*-hex-2-enopyranoside (**4**) and its regioisomer (**5**) were produced. These were converted into didehydro nucleosides by glycosylation of silylated heterocyclic bases in the presence of trimethylsilyl trifluoromethanesulfonate as catalyst. The configurations of the anomeric products were assigned by ^{1}H-NMR analysis of the corresponding saturated compounds which were obtained by hydrogenation of the double bond in the carbohydrate moiety. The compounds **9a,b,d**, **10a,b**, **14a,b,e,f**, and **15a,b,e,f** did not show any significant activity against HIV or HSV-1.

Synthese pyranoider Analoga des anti-HIV-aktiven 3'-Desoxy-2',3'-didehydrothymidins (D4T)

Die prim. OH-Gruppe des Ethyl-2,3-didesoxy-α-D-*erythro*-hex-2-enopyranosids (**1**) wurde selektiv zu **2** geschützt und die sek. OH-Gruppe über das Dithiocarbonat **3** desoxygeniert. So entstanden 6-*O*-(4-methoxybenzoyl)-2,3,4-tridesoxy-α-D-*glycero*-hex-2-enopyranosid (**4**) und sein Regioisomer **5**. Durch Glykosilierung silylierter Nukleobasen mit Trimethylsilyl-trifluormethansulfonat als Katalysator entstanden die entspr. Didehydronukleoside. - Die Konfigurationen der Anomeren wurden durch ^{1}H-NMR-Analyse der zugehörigen gesättigten Verbindungen bestimmt, die durch Hydrieren der Doppelbindung im Kohlenhydratanteil entstanden waren. - Die Verbindungen **9a,b,d**, **10a,b**, **14a,b,e,f** und **15a,b,e,f** zeigen keine signifikante Aktivität gegen HIV oder HSV-1.

Unfortunately, there is still a need of compounds with efficient and selective inhibition of the human retrovirus[1-3] (HIV). Among the nucleosides, the lead compound for the synthesis of new anti-HIV compounds is 3'-azido-3'-deoxythymidine (AZT)[4] which in absence of a free 3'-hydroxy group results in termination of DNA synthesis. Other sugar modified nucleosides such as 2',3'-didehydro-2',3'-dideoxycytosine (D4C)[5-8] and 2',3'-didehydro-3'-deoxythymidine (D4T)[6,8-10] have also shown antiviral activity. The latter compounds have stimulated our interest to synthesize unsaturated pyranosyl nucleosides.

Ethyl 4,6-*O*-diacetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside was obtained from 3,4,6-tri-*O*-acetyl-D-glucal as described by *Ferrier* and *Prasad*[11] and subsequently deacetylated with a catalytic amount of sodium in methanol at room temp. to give **1**. Ethyl 6-O-(4-methoxybenzoyl)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside **2** was readily prepared by selective protection of the prim. hydroxy group of **1** by reaction with 4-methoxybenzoyl chloride in dry pryridine and benzene at 0°C.- ^{1}H-NMR-spectrum of **2** shows 4-H as a doublet at $\delta = 4.18$ ppm in agreement with reports on similar compounds[12] showing that the protection had occurred at the prim. hydroxy group. The free hydroxy group at C-4 was transformed into an *S*-methyl dithiocarbonate **3** by reaction with NaH, CS_2, and a catalytic amount of imidazole in dry tetrahydrofuran at 0°C and then with H_3CI at room temp. This compound was reduced with tri-n-butyltin hydride using a catalytic amount of α,α'-azoisobutyronitrile in dry toluene. TLC analysis showed formation of two products **4** and **5**. Separation on silica column was rather difficult because of their similar polarity due to their only difference being the position of the double bound which was assigned by comparison of their ^{1}H-NMR- and ^{13}C-NMR-spectra with those of 2-hexenopyranoses and 3-hexenopyranoses[13,14]. Ethyl 6-*O*-(4-methoxybenzoyl)-2,3,4-trideoxy-α-D-*glycero*-hex-2-enopyranoside **4** and its regioisomer **5** were formed in almost equal amounts, most likely *via* a resonance stabilized allylic radical formed by reduction of compound **3**.



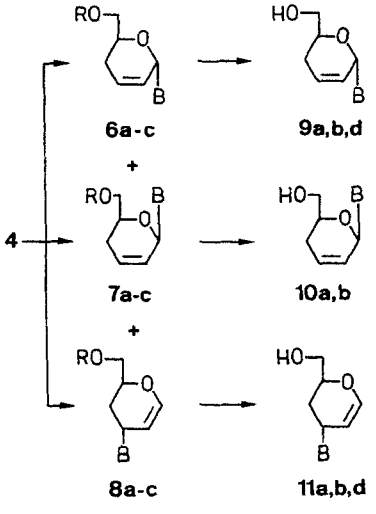
Scheme 1

The isomers **4** and **5** were used for glycosylation of silylated nucleobases with trimethyl trifluoromethanesulfonate as catalyst according to *Vorbrüggen* and co-workers[15,16].

  0365-6233/92/0808-0491 $ 3.50 + .25/0

The condensation between compound **4** and silylated uracil or thymine in dry acetonitrile gave a mixture of products which was separated by prep. reverse phase HPLC to give the pure α-anomers **6a,b** and β-anomers **7a,b** as well as the pure 1,2-unsaturated pyranos-3-yl-uracils **8a,b**. Glycosylation of the silylated N^4-isobutyrylcytosine[17] under the same condition at 0°C resulted in coupling of the 3-position of the sugar to give compound **8c** with only traces of the normal nucleosides **6c** and **7c**. Formation of compound **8c** was more favourable at higher temp. or longer reaction times. When the reaction temp. was lowered to -20°C, the proportion between **6c**, **7c**, and **8c** was changed into 16:1:2. The β-anomer **7c** and its regioisomer **8c** were isolated as a mixture. The condensation of 3,4-unsaturated pyranoside **5** with silylated pyrimidine bases or N^6-isobutyryladenine using trimethylsilyl trifluoromethanesulfonate afforded an anomeric mixture which was separated by reverse phase HPLC to give the nucleosides **12a-d** and **13a-d**.

Finally, treatment of the compounds **6-8**, **12**, and **13** with methanolic ammonia at room temp. followed by chromatographic purification afforded the unprotected nucleosides **9-11**, **14**, and **15**, respectively.

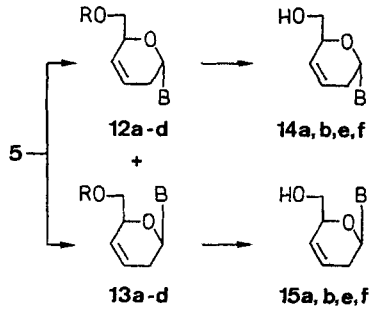


R= 4-MeOC$_6$H$_4$CO

6-11	B
a	Uracil-1-yl
b	Thymin-1-yl
c	N^4-isobutyrylcytosin-1-yl
d	Cytosin-1-yl

Scheme 2

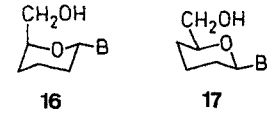
Because of complex ^{1}H-NMR-spectra of compounds **6**, **7**, **9**, **10**, and **12**, **15** it was not easy to assign which is α or β configuration. Reduction of the double bond in the carbohydrate moiety of the pure anomers of compounds **9a**, **10d**, **14e**, or **15a** with H_2/Pd/C gave the corresponding compounds **16** or **17** in ~ 80% yield of which the anomeric configuration of the starting material is readily deduced from ^{1}H-NMR coupling constants. Comparison was also done with the NMR data reported for compounds **14a,b,e**, **15a,b,e**, **16**, and **17** which were synthesized by an independent route from 2-deoxy-D-*arabino*-hexopyranosyl nucleosides[18].



R= 4-MeOC$_6$H$_4$CO

12-15	B
a	Uracil-1-yl
b	Thymin-1-yl
c	N^4-isobutyrylcytosin-1-yl
d	N^6-isobutyryladenin-9-yl
e	Cytosin-1-yl
f	Adenin-9-yl

Scheme 3



16,17	B
a	Uracil-1-yl
b	Cytosin-1-yl

Scheme 4

2D H-H-NMR-spectra were used to assign the protons in the unsaturated sugars and nucleosides. The ^{1}H-NMR-spectra of compound **11** showed large axial-axial and geminal coupling constants of ~ 13 Hz and a small axial-equatorial coupling constant of ~ 5 Hz which with the assumption of a half chair conformation assign the *erythro* configuration. For the cytosine nucleoside **11d** it was also possible to deduce the equatorial coupling constant $J_{3e,4a}$ = 5.0 Hz which shows that the nucleobase is in the axial position. This is opposite to full chair conformation which, according to our experience[19,20], has the large nucleobase in the equatorial position determining which chair conformation is possible for the sugar ring.

Compounds **9a,b,d**, **10a,b**, **14a,b,e,f**, and **15a,b,e,f** were selected for *in vitro* studies of biological effects. The compounds did not show any cytotoxicity or significant activity against Herpes Simplex Virus type 1 (HSV-1), strain *McIntyre*, when propagated in a continuous cell line from rabbit cornea (SIRL) which was maintained in *Eagle's* MEM containing 1% fetal calf serum and test compounds (100 μM). The same compounds were also devoid of cytotoxicity and activity against HIV-1 (strain HTLV-IIIB) in MT-4 cells, when MT-4 cells were incubated with virus, washed and added in a proportion of 1:10 to uninfected MT-4 cells which had been preincubated in test compound (100 μM)

containing growth medium for 2 h. The MT-4 cells were maintained with the culture medium likewise containing the test compound (100 μM) and expression of HIV in culture medium was quantitated by HIV antigen detection ELISA.

Experimental Part

NMR-spectra: Bruker AC 250 FT NMR, TMS as internal standard.- EI mass-spectra: Varian MAT 311A.- Silica gel TLC: Merck silica gel (0.040-0.063 mm).- Reverse-phase HPLC: C18 column (15 μm, 300 A).- Elemental analysis: NOVO-NORDISK Microanalytical Laboratory, Novo Allé, DK-2880 Bagsvaerd.

Ethyl 2,3-Dideoxy-6-O-(4-methoxybenzoyl)-α-D-erythro-hex-2-enopyranoside (**2**)

Compound **1**[11] (21.7 g, 124.6 mmol) was dissolved in dry pyridine (275 ml) and dry benzene (275 ml) at 0°C. 4-Methoxybenzoyl chloride (18.6 ml, 137.0 mmol) in dry pyridine (100 ml) and dry benzene (100 ml) was slowly added with stirring during 90 min. After 2 h at 0°C the solution was poured into 500 ml ice-water and extracted twice with benzene (300 ml). The combined org. layers were washed several times with water, dried with $MgSO_4$ and evaporated *in vacuo*. Pyridine was removed by co-evaporation with 100 ml dry toluene. The residual oil was purified by silica column chromatography (30 x 7.5 cm) with ethyl acetate/petroleum ether (60-80°C) (1:1). Yield 24.2 g (63%).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.22 (t, 7.1 Hz, 3H, CH_3), 3.55 (dq, 9.5 Hz, 7.1 Hz, OCH_a-CH_3), 3.84 (m, 4H, OCH_b-CH_3 and CH_3), 4.01 (ddd, 9.4 Hz, 5.2 Hz, 2.5 Hz 1H, 5-H), 4.18 (d, 9.4 Hz, 1H, 4-H), 4.56 (dd, J = 12.1 Hz, 2.5 Hz, 1H, 6-H_a), 4.63 (dd, 12.1 Hz, 5.2 Hz, 1H, 6H_b), 5.02 (br s, 1H, 1-H), 5.75 (m, 1H, 2-H), 6.01 (d, 10.1 Hz, 1H, 3-H), 6.89 (d, 8.9 Hz, 2H, Ar-H), 8.00 (d, 8.9 Hz, 2H, Ar-H).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 15.0 (CH_3), 55.1 (OCH_3), 63.6 (C-4), 63.7 (OCH_3), 64.0 (C-6), 70.2 (C-5), 93.9 (C-1), 113.9 and 121.9 (Ar), 126.1 (C-2), 131.5 (Ar), 131.1 (C-3), 163.3 (Ar), 166.7 (C=O).

Ethyl 2,3-Dideoxy-6-O-(4-methoxybenzoyl)-4-O-(S-methyl-dithiocarboxy)-α-D-erythro-hex-2-enopyranoside (**3**)

CS_2 (11.7 ml, 194.7 mmol) and a catalytic amount of imidazole were added to a suspension of NaH (4.87 g 50% in oil, 97.3 mmol) in dry tetrahydrofuran (250 ml). Compound **2** (20.0 g, 64.9 mmol) in 150 ml dry tetrahydrofuran was added dropwise with stirring during 30 min. The mixture was kept at 0°C for 60 min and CH_3I (8.0 ml, 129.8 mmol) was added. The solution was stirred for 60 min at room temp. Pyridinium acetat (pyridine/acetic acid 1:1) (25 ml) and a few drops of water were added. The mixture was concentrated, diluted with water (500 ml), and extracted with diethyl ether (2 x 400 ml). The org. layer was dried over $MgSO_4$ and evaporated. The residual oil was purified by silica cc (20 x 7.5 cm) with ethyl acetate/petroleum ether (60-80°C) (12:88). Yield 20.6 g (80%).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.24 (t, 7.1 Hz, 3H, CH_3), 2.55 (s, 3H, SCH_3), 3.58 (dq, 9.3 Hz, 7.1 Hz, 1H, OCH_a-CH_3), 3.86 (m, 4H, OCH_3 and OCH_b-CH_3), 4.44 (m, 3H, 5-H and 6-H), 5.08 (br s, 1H, 1-H), 5.91 (m, 1H, 2-H), 6.04 (d, 10.3 Hz, 1H, 3-H), 6.34 (d, 9.2 Hz, 1H, 4-H), 6.91 (d, 8.9 Hz, 2H, Ar-H), 8.01 (d, 8.9 Hz, 2H, Ar-H).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 15.1 (CH_3), 19.0 (SCH_3), 55.2 (OCH_3), 63.2 (OCH_2), 64.1 (C-6), 66.6 (C-4), 73.7 (C-5), 94.0 (C-1), 113.4 and 122.1 (Ar), 127.9 (C-2), 128.6 (C-3), 131.7 and 163.3 (Ar), 165.7 (C=O), 215.1 (C=S).

Ethyl 6-O-(4-Methoxybenzoyl)-2,3,4-trideoxy-α-D-glycero-hex-2-enopyranoside (**4**) *and ethyl 6-O-(4-Methoxybenzoyl)-2,3,4-trideoxy-α-D-glycero-hex-3-enopyranoside* (**5**)

97% tri-n-butyltin hydride (13.5 ml, 49.1 mmol) and α,α'-azoisobutyronitrile (50 mg) were added to dry toluene (600 ml). At gentle reflux a solution of compound **3** (12.0 g, 30.1 mmol) and α,α'-azoisobutyronitrile (300 mg) in dry toluene (150 ml) was added dropwise during 60 min with stirring under N_2. The mixture was refluxed for 2-5 h until TLC analysis (ethyl acetate/benzene 7:93) indicated the disappearance of starting material. The mixture was evaporated and the residual oil was chromatographed on silica gel column (70 x 5 cm) with ethyl acetate/benzene (7:93) to give compound **4** (3.21 g, 36%) and compound **5** (3.47 g, 39%).

4: ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.22 (t, 7.1 Hz, 3H, CH_3), 2.02 (dt, 17.8 Hz, 4.2 Hz, 1H, 4-H_e), 2.17 (dd, 17.8 Hz, 10.4 Hz, 1H, 4-H_a), 3.54 (dq, 9.5 Hz, 7.1 Hz, 1H, OCH_a-CH_3), 3.85 (m, 4H, OCH_3 and OCH_b-CH_3), 4.33 (m, 3H, 5-H and 6-H), 5.03 (d, 2.3 Hz, 1H, 1-H), 5.79 (dd, 9.7 Hz, 2.3 Hz, 1H, 2-H), 6.03 (dd, 9.7 Hz, 4.2 Hz, 1H, 3-H), 6.91 (d, 8.8 Hz, 2H, Ar-H), 8.01 (d, 8.8 Hz, 2H, Ar-H).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 15.4 (CH_3), 26.7 (C-4), 55.4 (OCH_3), 63.2 (OCH_2), 64.8 (C-6), 66.5 (C-5), 94.4 (C-1), 113.6 and 122.5 (Ar), 125.9 (C-2), 128.2 (C-3), 131.7 and 163.6 (Ar), 166.1 (C=O).- MS (70 eV): m/z (%) = 292 (9, M^+).

5: ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.24 (t, 7.1 Hz, 3H, CH_3), 2.09 (m, 1H, 2-H_e), 2.46 (m, 1H, 2-H_a), 3.56 (dq, 9.6 Hz, 7.1 Hz, 1H, OCH_a-CH_3), 3.84 (m, 4H, OCH_3 and OCH_b-CH_3), 4.39 (m, 2H, 6-H), 4.54 (m, 1H, 5-H), 5.05 (d, 4.0 Hz, 1H, 1-H), 5.75 (d, 10.3 Hz, 1H, 4-H), 5.85 (dd, 10.3 Hz, 4.3 Hz, 1H, 3-H), 6.91 (d, 8.6 Hz, 2H, Ar-H), 8.01 (d, 8.6 Hz, 2H, Ar-H).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 15.2 (CH_3), 30.1 (C-2), 55.4 (OCH_3), 63.2 (OCH_2), 66.0 (C-6), 66.7 (C-5), 95.6 (C-1), 113.6 and 122.5 (Ar), 123.9 (C-4), 124.9 (C-3), 131.7 and 163.5 (Ar), 166.0 (C=O).- MS (70 eV): m/z (%) = 292 (7, M^+).

Preparation of Nucleosides **6**, **7** *and* **8**. *General Procedure*

A solution of the appropriate pyrimidine or purine bases (1.5 equiv.) in hexamethyldisilazane (HMDS) (20 ml) and a catalytic amount of ammonium sulphate was refluxed for 4-6 h. The excess HMDS was removed by co-evaporation with 2 x 50 ml portions of dry toluene under reduced pressure. A mixture of the appropriate silyted nucleobase (1.5 equiv.) and compound **4** (1 equiv.) in 50 ml dry acetonitrile was stirred under N_2 and the mixture was cooled to 0°C. Trimethylsilyl trifluoromethanesulfonate (1.1 equiv.) was added and the resulting solution was kept at 0°C until analytical silica TLC (ethyl acetate/petroleum ether (60-80°C) (7:3)) showed disappearance of carbohydrate (15-120 min). The mixture was diluted with methylene chloride (100 ml) and shaken with saturated aqueous $NaHCO_3$ and washed with water (2 x 150 ml). The org. phase was dried over magnesium sulphate and concentrated under reduced pressure to give a crude product which was purified by preparative reverse phase HPLC or by column chromatography.

1-(6-O-(4-Methoxybenzoyl)-2,3,4-trideoxy-α-D-glycero-hex-2-enopyranosyl)uracil (**6a**), *its β-Isomer* **7a**, *and Regioisomer* **8a**

Prepared from silylated uracil (4.4 mmol) and compound **4** (0.85 g, 2.9 mmol) at 0°C for 15 min and separated by HPLC with 26% ethanol in water.

6a: Yield 373 mg (36%).- ^{1}H-NMR ([D_6]DMSO): δ (ppm) = 2.27 (m, 2H, 4'-H), 3.85 (s, 3H, OCH_3), 4.05 (m, 1H, 5'-H), 4.30 (m, 2H, 6'-H), 5.58 (d, 7.9 Hz, 1H, 5-H), 5.81 (dd, 10.2 Hz, 2.4 Hz, 1H, 2'-H), 6.25 (br s, 1H, 1'-H), 6.42 (m, 1H, 3'-H), 7.05 (d, 8.8 Hz, 2H, Ar-H), 7.70 (d, 7.9 Hz, 1H, 6-H), 7.87 (d, 8.8 Hz, 2H, Ar-H), 11.40 (s, 1H, N-H).- ^{13}C-NMR ([D_6]DMSO): δ (ppm) = 26.0 (C-4'), 55.4 (OCH_3), 65.4 (C-6'), 66.1 (C-5'), 76.7 (C-1'), 100.4 (C-5), 113.9 and 121.6 (Ar), 122.0 (C-2'), 131.1 (Ar), 132.0 (C-3'), 142.1 (C-6), 150.7 (C-2), 163.1 (C-4), 163.3 (Ar), 165.1 (C=O).

7a: Yield 80 mg (8%).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.24 (m, 2H, 4'-H), 3.85 (s, 3H, OCH_3), 4.30 (m, 3H, 5'-H and 6'-H), 5.62 (d, 9.9 Hz, 1H, 2'-H), 5.76 (d, 8.0 Hz, 1H, 5-H), 6.27 (m, 1H, 3'-H), 6.55 (br s, 1H, 1'-H), 6.92 (d, 8.7 Hz, 2H, Ar-H), 7.29 (d, 8.0 Hz, 1H, 6-H), 7.99 (d, 8.7 Hz, 2H, Ar-H).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 26.3 (C-4'), 55.2 (OCH_3), 65.7 (C-6'), 72.1 (C-5'), 78.6 (C-1'), 102.9 (C-5), 113.5 and 121.9 (Ar),

125.0 (C-2'), 131.1 (C-3'), 131.6 (Ar), 140.3 (C-6), 150.5 (C-2), 163.4 (C-4 and Ar), 165.8 (C=O).

8a: Yield 272 mg (24%).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.23 (m, 2H, 4'-H), 3.86 (s, 3H, OCH_3), 4.10 (m, 1H, 5'-H), 4.39 (dd, 12.0 Hz, 5.6 Hz, 1H, 6'-H_a), 4.48 (dd, 12.0 Hz, 3.0 Hz, 1H, 6'-H_b), 4.74 (t, 5.7 Hz, 1H, 2'-H), 5.07 (m, 1H, 3'-H), 5.72 (d, 8.0 Hz, 1H, 5-H), 6.87 (d, 5.7 Hz, 1H, 1'-H), 6.92 (d, 8.6 Hz, 2H, Ar-H), 7.68 (d, 8.0 Hz, 1H, 6-H), 8.00 (d, 8.6 Hz, 2H, Ar-H), 10.04 (br s, 1H, N-H).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 30.3 (C-4'), 46.8 (C-3'), 55.3 (OCH_3), 65.2 (C-6'), 69.3 (C-5'), 95.5 (C-2'), 101.2 (C-5), 113.5, 121.7, and 131.6 (Ar), 141.8 (C-6), 150.4 (C-1'), 150.8 (C-2), 163.4 (Ar), 163.7 (C-4), 165.7 (C=O).

1-(6-O-(4-Methoxybenzoyl)-2,3,4-trideoxy-α-D-glycero-hex-2-enopyranosyl)thymine (**6b**), *its β-Isomer* **7b**, *and Regioisomer* **8b**

Prepared from silylated thymine (5.1 mmol) and compound **4** (1.0 g, 3.4 mmol) at 0°C for 30 min and separated by HPLC with 29% ethanol in water.

6b: Yield 275 mg (23%).- ^{1}H-NMR ([D_6]DMSO): δ (ppm) = 1.77 (s, 3H, CH_3), 2.26 (m, 2H, 4'-H), 3.84 (s, 3H, OCH_3), 4.02 (m, 1H, 5'-H), 4.28 (d, 4.6 Hz, 2H, 6'-H), 5.79 (d, 9.2 Hz, 1H, 2'-H), 6.32 (br s, 1H, 1'-H), 6.42 (m, 1H, 3'-H), 7.04 (d, 8.8 Hz, 2H, Ar-H), 7.53 (s, 1H, 6-H), 7.86 (d, 8.8 Hz, 2H, Ar-H), 11.39 (s, 1H, N-H).- ^{13}C-NMR ([D_6]DMSO): δ (ppm) = 12.0 (CH_3), 25.7 (C-4'), 55.4 (OCH_3), 65.4 (C-6'), 66.1 (C-5'), 76.4 (C-1'), 108.1 (C-5), 114.0 and 121.6 (Ar), 122.3 (C-2'), 131.1 (Ar), 131.7 (C-3'), 137.7 (C-6), 150.7 (C-2), 163.1 (Ar), 163.8 (C-4), 165.1 (C=O).

7b: Yield 160 mg (13%).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.92 (s, 3H, CH_3), 2.22 (m, 2H, 4'-H), 3.86 (s, 3H, OCH_3), 4.28 (m, 1H, 5'-H), 4.39 (m, 2H, 6'-H), 5.62 (d, 10.0 Hz, 1H, 2'-H), 6.28 (dd, 10.0 Hz, 5.3 Hz, 1H, 3'-H), 6.56 (br s, 1H, 1'-H), 6.92 (d, 8.7 Hz, 2H, Ar-H), 7.08 (s, 1H, 6-H), 7.86 (d, 8.7 Hz, 2H, Ar-H).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 12.3 (CH_3), 26.4 (C-4'), 55.3 (OCH_3), 65.8 (C-6'), 72.1 (C-5'), 78.5 (C-1'), 111.3 (C-5), 113.5 and 121.9 (Ar), 125.4 (C-2'), 130.9 (C-3'), 131.6 (Ar), 135.9 (C-6), 150.6 (C-2), 163.4 (Ar), 163.9 (C-4), 165.9 (C=O).

8b: Yield 136 mg (11%).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.93 (s, 3H, CH_3), 2.15 (m, 2H, 4'-H), 3.86 (s, 3H, OCH_3), 4.11 (m, 1H, 5'-H), 4.39 (dd, 12.0 Hz, 5.7 Hz, 1H, 6'-H_a), 4.48 (dd, 12.0 Hz, 3.3 Hz, 1H, 6'-H_b), 4.74 (t, 5.6 Hz, 1H, 2'-H), 5.07 (m, 1H, 3'-H), 6.87 (d, 5.6 Hz, 1H, 1'-H), 6.90 (d, 8.7 Hz, 2H, Ar-H), 7.47 (s, 1H, 6-H), 8.00 (d, 8.7 Hz, 2H, Ar-H), 9.75 (br s, 1H, N-H).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 12.5 (CH_3), 30.5 (C-4'), 46.5 (C-3'), 55.3 (OCH_3), 65.2 (C-6'), 69.3 (C-5'), 95.5 (C-2'), 109.6 (C-5), 113.5, 121.8, and 131.6 (Ar), 137.8 (C-6), 150.1 (C-1'), 150.9 (C-2), 163.4 (Ar), 164.1 (C-4), 165.7 (C=O).

1-(6-O-(4-Methoxybenzoyl)-2,3,4-trideoxy-α-D-glycero-hex-2-enopyranosyl)-N^4-isobutyrylcytosine (**6c**) *and its Regioisomer* **8c**

8c was prepared from silylated N^4-isobutyrylcytosine[17] and compound **4** (0.925 g, 3.2 mmol) at 0°C for 2 h and purified by silica column chromatography (30 x 1.55 cm) with CH_2Cl_2 and methanol (95:5). When the reaction was carried out at -20°C for 5 h, **6c** was the main product, **7c** and **8c** were isolated as a mixture in low yield.

6c: Yield 751 mg (41%).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.19 (two overlapping doublets, 6.8 Hz, 6H, 2 CH_3), 2.32 (m, 2H, 4'-H), 2.84 (septet, 6.8 Hz, 1H, CH), 3.84 (s, 3H, OCH_3), 4.06 (m, 1H, 5'-H), 4.38 (m, 2H, 6'-H), 5.90 (d, 10.0 Hz, 1H, 2'-H), 6.43 (m, 1H, 3'-H), 6.58 (br s, 1H, 1'-H), 6.90 (d, 8.5 Hz, 2H, Ar-H), 7.42 (d, 7.1 Hz, 1H, 5-H), 7.91 (d, 7.1 Hz, 1H, 6-H), 7.98 (d, 8.5 Hz, 2H, Ar-H), 9.58 (br s, 1H, N^4-H).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 19.1 (2 CH_3), 26.6 (C-4'), 29.7 (CH), 55.4 (OCH_3), 65.7 (C-6'), 66.8 (C-5'), 78.9 (C-1'), 96.2 (C-5), 113.7 and 122.0 (Ar), 122.5 (C-2'), 131.7 (Ar), 131.8 (C-3'), 145.3 (C-6), 155.7 (C-2), 163.2 (Ar), 163.6 (C-4), 166.0 (C=O), 177.9 (C=O).

7c: Selected data for β-isomer.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 6.70 (br s, 1H, 1'-H).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 80.1 (C-1').

8c: Yield 798 mg (59%).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.21 (d, 6.8 Hz, 6H, 2 CH_3), 2.17 (m, 2H, 4'-H), 2.77 (septet, 6.8 Hz, 1H, CH), 3.85 (s, 3H, OCH_3), 4.02 (m, 1H, 5'-H), 4.41 (m, 2H, 6'-H), 4.79 (t, 5.6 Hz, 1H, 2'-H), 5.07 (m, 1H, 3'-H), 6.90 (m, 3H, 1'-H and Ar-H), 7.46 (d, 7.3 Hz, 1H, 5-H), 7.98 (d, 8.7 Hz, 2H, Ar-H), 8.07 (d, 7.3 Hz, 1H, 6-H), 9.40 (s, 1H, N^4-H).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 18.8 (CH_3), 18.9 (CH_3), 29.6 (C-4'), 36.1 (CH), 48.2 (C-3'), 55.2 (OCH_3), 65.2 (C-6'), 68.9 (C-5'), 95.6 (C-2'), 95.9 (C-5), 113.4, 121.7, and 131.5 (Ar), 146.5 (C-6), 150.4 (C-1'), 155.4 (C-2), 162.3 (C-4), 163.3 (Ar), 165.6 (C=O), 177.3 (C=O).

Preparation of Nucleosides **12** *and* **13**

Compound **5** (1.0 equiv.) in dry acetonitrile (10 ml) was added dropwise during 20 min to a solution of the appropriate silylated nucleobase (1.5 equiv.) and trimethylsilyl trifluoromethanesulfonate (1.5 equiv.) in dry acetonitrile (50 ml) under N_2 with stirring at room temp. The mixture was kept at this temp. until silica TLC analysis (ethyl acetate/petroleum ether (60-80°C) (7:3) showed disappearance of the starting carbohydrate (2-6 h). The mixture was diluted with CH_2Cl_2 (100 ml) and the crude product was worked up as mentioned for compound **6-8** followed by purification with preparative reverse phase HPLC.

1-(6-O-(4-Methoxybenzoyl)-2,3,4-trideoxy-α-D-glycero-hex-3-enopyranosyl)uracil (**12a**) *and its β-Isomer* **13a**

Prepared from silylated uracil (4.2 mmol) and compound **5** (0.86 g, 2.9 mmol) at room temp. for 5 h and separated by HPLC with 29% ethanol in water.

12a: Yield 372 mg (37%).- ^{1}H-NMR ([D_6]DMSO): δ (ppm) = 2.30 (dt, 13.9 Hz, 2.3 Hz, 1H, 2'-H_e), 2.50 (m, 1H, 2'-H_a), 3.83 (s, 3H, OCH_3), 4.29 (dd, 12.0 Hz, 3.1 Hz, 1H, 6'-H_b), 4.55 (dd, 12.0 Hz, 6.0 Hz, 1H, 6'-H_a), 4.70 (m, 1H, 5'-H), 5.62 (d, 8.1 Hz, 1H, 5-H), 5.86 (d, 9.6 Hz, 1H, 4'-H), 6.06 (m, 2H, 1'-H and 3'-H), 7.04 (d, 8.8 Hz, 2H, Ar-H), 7.72 (d, 8.1 Hz, 1H, 6-H), 7.95 (d, 8.8 Hz, 2H, Ar-H), 11.38 (s, 1H, N^4-H).- ^{13}C-NMR ([D_6]DMSO): δ (ppm) = 29.2 (C-2'), 55.2 (OCH_3), 65.3 (C-6'), 73.8 (C-5'), 75.6 (C-1'), 102.5 (C-5), 113.5 and 121.9 (Ar), 124.7 (C-4'), 124.8 (C-3'), 131.5 (Ar), 139.7 (C-6), 150.1 (C-2), 163.4 (C-4 and Ar), 165.8 (C=O).

13a: Yield 359 mg (36%).- ^{1}H-NMR ([D_6]DMSO): δ (ppm) = 2.24 (m, 1H, 2'-H_e), 2.49 (m, 1H, 2'-H_a), 3.84 (s, 3H, OCH_3), 4.35 (m, 2H, 6'-H), 4.81 (m, 1H, 5'-H), 5.64 (d, 8.1 Hz, 1H, 5-H), 5.81 (m, 2H, 1'-H and 4'-H), 6.00 (m, 1H, 3'-H), 7.05 (d, 8.8 Hz, 2H, Ar-H), 7.67 (d, 8.1 Hz, 1H, 6-H), 7.92 (d, 8.8 Hz, 2H, Ar-H).- ^{13}C-NMR ([D_6]DMSO): δ (ppm) = 28.6 (C-2'), 55.4 (OCH_3), 65.3 (C-6'), 74.6 (C-5'), 78.0 (C-1'), 102.1 (C-5), 114.0 and 121.6 (Ar), 125.2 (C-4'), 125.7 (C-3'), 131.3 (Ar), 140.4 (C-6), 150.2 (C-2), 163.1 (C-4), 163.2 (Ar), 165.2 (C=O).

1-(6-O-(4-Methoxybenzoyl)-2,3,4-trideoxy-α-D-glycero-hex-3-enopyranosyl)thymine (**12b**) *and its β-Anomer* **13b**

Prepared from silylated thymine (6.4 mmol) and compound **5** (1.26 g, 4.3 mmol) at room temp. for 2 h and separated by HPLC with 32% ethanol in water.

12b: Yield 334 mg (22%).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.94 (s, 3H, CH_3), 2.32 (m, 2H, 2'-H), 3.84 (s, 3H, OCH_3), 4.35 (dd, 12.0 Hz, 3.2 Hz, 1H, 6'-H_b), 4.54 (dd, 12.0 Hz, 6.0 Hz, 1H, 6'-H_a), 4.76 (m, 1H, 5'-H), 5.82 (d, 10.3 Hz, 1H, 4'-H), 6.00 (ddd, 10.3 Hz, 5.9 Hz, 2.9 Hz, 1H, 3'-H), 6.22 (dd, 7.1 Hz, 3.6 Hz, 1H, 1'-H), 6.94 (d, 8.7 Hz, 2H, Ar-H), 7.29 (s, 1H, 6-H), 8.03 (d, 8.7 Hz, 2H, Ar-H), 9.78 (s, 1H, N-H).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 12.4 (CH_3), 29.2 (C-2'), 55.2 (OCH_3), 65.0 (C-6'), 73.9 (C-5'), 75.3 (C-1'), 111.0 (C-5), 113.5 and 121.8 (Ar), 124.8 (C-4'), 124.9 (C-3'), 131.7 (Ar), 135.4 (C-6), 150.3 (C-2), 163.4 (Ar), 163.8 (C-4), 165.8 (C=O).

13b: Yield 225 mg (15%).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.93 (s, 3H, CH_3), 2.35 (m, 2H, 2'-H), 3.86 (s, 3H, OCH_3), 4.60 (m, 2H, 6'-H), 4.82 (m, 1H, 5'-H), 5.79 (d, 9.3 Hz, 1H, 4'-H), 5.94 (m, 2H, 1'-H and 3'-H), 6.93

(d, 8.8 Hz, 2H, Ar-H), 7.23 (s, 1H, 6-H), 8.01 (d, 8.8 Hz, 2H, Ar-H).- ^{13}CNMR ($CDCl_3$): δ (ppm) = 12.4 (CH_3), 30.0 (C-2'), 55.3 (OCH_3), 65.4 (C-6'), 75.1 (C-5'), 78.4 (C-1'), 111.3 (C-5), 113.6 and 122.1 (Ar), 125.0 (C-4'), 125.8 (C-3'), 131.6 (Ar), 135.1 (C-6), 150.1 (C-2), 163.5 (Ar), 163.7 (C-4), 165.9 (C=O).

1-(6-O-(4-Methoxybenzoyl)-2,3,4-trideoxy-α-D-glycero-hex-3-enopyranosyl)-N^4-isobutyrylcytosine (**12c**) *and its β-Anomer* **13c**

Prepared from silylated N^4-isobutyrylcytosine[17] and compound **5** (1.25 g, 4.3 mmol) at room temp. for 3 h and separated by HPLC with 32% ethanol in water.

12c: Yield 412 mg (23%).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.21 (d, 6.8 Hz, 6H, 2 CH_3), 2.14 (m, 1H, 2'-H_e), 2.73 (m, 2H, 2'-H_a and CH), 3.85 (s, 3H, OCH_3), 4.36 (dd, 12.1 Hz, 3.4 Hz, 1H, 6'-H_b), 4.58 (dd, 12.1 Hz, 6.2 Hz, 1H, 6'-H_a), 4.83 (m, 1H, 5'-H), 5.83 (d, 10.1 Hz, 1H, 4'-H), 6.02 (m, 1H, 3'-H), 6.23 (dd, 8.8 Hz, 3.2 Hz, 1H, 1'-H), 6.92 (d, 8.8 Hz, 2H, Ar-H), 7.48 (d, 7.5 Hz, 1H, 5-H), 7.92 (d, 7.5 Hz, 1H, 6-H), 8.01 (d, 8.8 Hz, 2H, Ar-H), 9.06 (br s, 1H, N^4-H).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 18.9 (2 CH_3), 30.2 (C-2'), 36.4 (CH), 55.3 (OCH_3), 64.7 (C-6'), 74.1 (C-5'), 77.1 (C-1'), 96.7 (C-5), 113.6 and 121.9 (Ar), 124.7 (C-4'), 125.1 (C-3'), 132.0 (Ar), 144.2 (C-6), 154.7 (C-2), 162.4 (C-4), 163.4 (Ar), 165.9 (C=O), 177.3 (C=O).

13c: Yield 347 mg (19%).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.21 (d, 6.9 Hz, 6H, 2 CH_3), 2.17 (m, 1H, 2'-H_e), 2.69 (m, 2H, 2'-H_a and CH), 3.86 (s, 3H, OCH_3), 4.46 (m, 2H, 6'-H), 4.84 (m, 1H, 5'-H), 5.79 (d, 10.2 Hz, 1H, 4'-H), 6.00 (m, 2H, 1'-H and 3'-H), 6.93 (d, 8.8 Hz, 2H, Ar-H), 7.48 (d, 7.5 Hz, 1H, 5-H), 7.91 (d, 7.5 Hz, 1H, 6-H), 8.00 (d, 8.8 Hz, 2H, Ar-H), 9.01 (s, 1H, N^4-H).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 18.8 (CH_3), 19.0 (CH_3), 30.7 (C-2'), 36.4 (CH), 55.3 (OCH_3), 65.3 (C-6'), 75.2 (C-5'), 80.2 (C-1'), 96.9 (C-5), 113.6 and 122.0 (Ar), 125.2 (C-4'), 125.3 (C-3'), 131.6 (Ar), 144.1 (C-6), 154.5 (C-2), 162.4 (C-4), 163.4 (Ar), 165.9 (C=O), 177.1 (C=O).

9-(6-O-(4-Methoxybenzoyl)-2,3,4-trideoxy-α-D-glycero-hex-3-enopyranosyl)-N^6-isobutyryladenine (**12d**) *and its β-Anomer* **13d**

Prepared from silylated N^6-isobutyryladenine (2.8 mmol) and compound **5** (0.56 g, 1.9 mmol) at 0°C for 4 h and separated by HPLC with 32% ethanol in water.

12d: Yield 103 mg (13%).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.30 (d, 6.8 Hz, 6H, 2 CH_3), 2.86 (m, 2H, 2'-H), 3.21 (septet, 6.8 Hz, 1H, CH), 3.84 (s, 3H, OCH_3), 4.31 (dd, 11.6 Hz, 3.2 Hz, 1H, 6'-H_b), 4.56 (m, 1H, 5'-H), 4.69 (dd, 11.6 Hz, 6.7 Hz, 1H, 6'-H_a), 5.93 (dd, 10.1 Hz, 1.8 Hz, 1H, 4'-H), 6.15 (dd, 10.1 Hz, 5.5 Hz, 1H, 3'-H), 6.42 (dd, 7.9 Hz, 3.9 Hz, 1H, 1'-H), 6.89 (d, 8.9 Hz, 2H, Ar-H), 7.98 (d, 8.9 Hz, 2H, Ar-H), 8.27 (s, 1H, 8-H), 8.73 (s, 1H, 2-H), 9.23 (br. 1H, N^6-H).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 19.0 (2 CH_3), 28.9 (C-2'), 35.8 (CH), 55.2 (OCH_3), 64.4 (C-6'), 71.6 (C-5'), 75.9 (C-1'), 113.5 and 121.8 (Ar), 122.0 (C-5), 124.5 (C-4'), 125.4 (C-3'), 131.6 (Ar), 141.1 (C-8), 149.3 (C-4), 151.2 (C-6), 152.5 (C-2), 163.4 (Ar), 165.9 (C=O), 176.2 (C=O).

13d: Yield 60 mg (8%).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.32 (d, 6.7 Hz, 6H, 2 CH_3), 2.63 (ddd, 15.3 Hz, 5.5 Hz, 2.6 Hz, 1H, 2'-H_e), 2.84 (dd, 15.3 Hz, 7.8 Hz, 1H, 2'-H_a), 3.24 (septet, 6.7 Hz, 1H, CH), 3.84 (s, 3H, OCH_3), 4.66 (m, 2H, 6'-H), 4.94 (m, 1H, 5'-H), 5.89 (d, 10.2 Hz, 1H, 4'-H), 6.11 (m, 2H, 1'-H and 3'-H), 6.89 (d, 8.8 Hz, 2H, Ar-H), 7.97 (d, 8.8 Hz, 2H, Ar-H), 8.30 (s, 1H, 8-H), 8.73 (s, 1H, 2-H), 9.32 (s, 1H, N^6-H).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 19.0 (2 CH_3), 30.8 (C-2'), 35.8 (CH), 55.2 (OCH_3), 65.2 (C-6'), 75.0 (C-5'), 78.5 (C-1'), 113.4 (Ar), 121.9 (Ar and C-5), 124.6 (C-4'), 125.9 (C-3'), 140.4 (C-8), 149.3 (C-4), 150.7 (C-6), 152.4 (C-2), 163.3 (Ar), 165.8 (C=O), 176.3 (C=O).

Deprotection to give **9-11**, **14**, *and* **15**

Compound **6**, **7**, **8**, **12**, or **13** was added to a saturated solution of methanolic ammonia (50 ml) and stirred at room temp. for 4 days. After evaporation *in vacuo*, the product was purified by flash chromatography with methanol/CH_2Cl_2 (5:95) to remove the impurities, followed by methanol to afford the product **9**, **10**, **11**, **14**, or **15**.

1-(2,3,4-Trideoxy-α-D-glycero-hex-2-enopyranosyl)uracil (**9a**)

Yield 119 mg (51%).- M.p. 112-124°C, hygroscopic.- ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 2.06 (m, 2H, 4'-H), 3.36 (m, 1H, 2H, 6'-H), 3.62 (dd, 9.6 Hz, 4.1 Hz, 5'-H), 4.77 (t, 5.3 Hz, 1H, 6'-OH), 5.54 (d, 8.0 Hz, 1H, 5-H), 5.73 (d, 10.3 Hz, 1H, 2'-H), 6.19 (s, 1H, 1'-H), 6.39 (ddd, 10.3 Hz, 5.0 Hz, 2.5 Hz, 1H, 3'-H), 7.67 (d, 8.0 Hz, 1H, 6-H), 11.36 (s, 1H, N-H).- ^{13}C-NMR ([D$_6$]DMSO): δ (ppm) = 26.0 (C-4'), 63.4 (C-6'), 68.7 (C-5'), 76.4 (C-1'), 100.4 (C-5), 122.0 (C-2'), 132.2 (C-3'), 142.2 (C-6), 150.7 (C-2), 163.3 (C-4).- MS (70 eV): m/z (%) = 224 (5.3, M$^+$).- $C_{10}H_{12}N_2O_4$ x 0.7 H_2O (236.8) Calcd. C 50.7 H 5.62 N 11.8 Found C 50.7 H 5.55 N 11.5.

1-(2,3,4-Trideoxy-β-D-glycero-hex-2-enopyranosyl)uracil (**10a**)

Yield 21 mg (42%).- M.p. 155-156°C.- ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 2.18 (m, 2H, 4'-H), 3.41 (m, 2H, 6'-H), 3.85 (dd, 9.6 Hz, 4.6 Hz, 1H, 5'-H), 4.79 (t, 5.1 Hz, 1H, 6'-OH), 5.63 (m, 2H, 2'-H and 5-H), 6.26 (m, 2H, 1'-H and 3'-H), 7.36 (d, 8.1 Hz, 1H, 6-H), 11.36 (s, 1H, N-H).- ^{13}C-NMR ([D$_6$]DMSO): δ (ppm) = 21.9 (C-4'), 63.5 (C-6'), 74.7 (C-5'), 78.1 (C-1'), 102.1 (C-5), 124.8 (C-2'), 131.5 (C-3'), 141.0 (C-6), 150.3 (C-2), 163.3 (C-4).- MS (70 eV): m/z (%) = 224 (0.3, M$^+$).

1-(2,3,4-Trideoxy-α-D-glycero-hex-2-enopyranosyl)thymine (**9b**)

Yield 106 mg (57%).- M.p. 174-176°C.- ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 1.77 (s, 3H, CH_3), 2.07 (m, 2H, 4'-H), 3.36 (m, 2H, 6'-H), 3.97 (dd, 9.8 Hz, 4.3 Hz, 1H, 5'-H), 4.76 (br s, 1H, 6'-OH), 5.72 (d, 10.1 Hz, 1H, 2'-H), 6.18 (br s, 1H, 1'-H), 6.38 (m, 1H, 3'-H), 7.5 (s, 1H, 6-H), 11.36 (br s, 1H, N-H).- ^{13}C-NMR ([D$_6$]DMSO): δ (ppm) = 11.9 (CH_3), 26.0 (C-4'), 63.4 (C-6'), 68.7 (C-5'), 76.1 (C-1'), 108.0 (C-5), 122.2 (C-2'), 132.0 (C-3'), 137.6 (C-6), 150.7 (C-2), 163.9 (C-4).- MS (70 eV): m/z (%) = 238 (2.0, M$^+$).- $C_{11}H_{14}N_2O_4$ (238.2) Calcd. C 55.5 H 5.92 N 11.8 Found C 55.2 H 6.04 N 11.7.

1-(2,3-4-Trideoxy-β-D-glycero-hex-2-enopyranosyl)thymine (**10b**)

Yield 48 mg (44%).- M.p. 121-122°C.- ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 1.78 (s, 3H, CH_3), 2.07 (m, 2H, 4'-H), 3.42 (m, 2H, 6'-H), 3.85 (dd, 9.7 Hz, 4.5 Hz, 1H, 5'-H), 4.81 (t, 5.7 Hz, 1H, 6'-OH), 5.63 (d, 10.1 Hz, 1H, 2'-H), 6.26 (m, 2H, 1'-H and 3'-H), 7.21 (s, 1H, 6-H), 11.36 (br s, 1H, N-H).- ^{13}C-NMR ([D$_6$]DMSO): δ (ppm) = 11.9 (CH_3), 26.0 (C-4'), 63.5 (C-6'), 74.8 (C-5'), 78.0 (C-1'), 109.7 (C-5), 125.1 (C-2'), 131.5 (C-3'), 136.4 (C-6), 150.4 (C-2), 163.7 (C-4).- MS (70 eV): m/z (%) = 238 (1.3, M$^+$).- $C_{11}H_{14}N_2O_4$ (238.2) Calcd. C 55.5 H 5.92 N 11.8 Found C 55.4 H 6.14 N 11.5.

1-(2,3,4-Trideoxy-α-D-glycero-hex-2-enopyranosyl)cytosine (**9d**)

Yield 251 mg (64%), hygroscopic foam.- ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 2.05 (m, 2H, 4'-H), 3.38 (m, 2H, 6'-H), 3.60 (dd, 9.5 Hz, 4.5 Hz, 1H, 5'-H), 4.78 (t, 5.5 Hz, 1H, 6'-OH), 5.71 (m, 2H, 2'-H and 5-H), 6.33 (m, 2H, 1'-H and 3'-H), 7.17 (br s, 1H, N^4-H), 7.29 (br s, 1H, N^4-H), 7.61 (d, 7.4 Hz, 1H, 6-H).- ^{13}C-NMR ([D$_6$]DMSO): δ (ppm) = 26.2 (C-4'), 63.5 (C-6'), 68.2 (C-5'), 76.5 (C-1'), 93.1 (C-5), 123.1 (C-2'), 131.2 (C-3'), 142.5 (C-6), 155.3 (C-2), 165.7 (C-4).- MS (70 eV): m/z (%) = 223 (3.3, M$^+$).- $C_{10}H_{13}N_3O_3$ x 1.4 H_2O (248.45) Calcd. C 48.3 H 6.41 N 16.9 Found C 48.2 H 6.24 N 16.8.

1-(1,5-Anhydro-2,3,4-trideoxy-D-erythro-hex-1-enitol-3-yl)uracil (**11a**)

Yield 80 mg (47%).- M.p. 155-156°C.- ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 1.85 (td, 12.4 Hz, 5.1 Hz, 1H, 4'-H_a), 1.96 (d, 12.4 Hz, 1H, 4'-H_e), 3.48

(d, 4.2 Hz, 2H, 6'-H), 3.68 (m, 1H, 5'-H), 4.72 (t, 5.4 Hz, 1H, 2'-H), 4.84 (m, 2H, 6'-OH and 3'-H), 5.54 (d, 8.0 Hz, 1H, 5-H), 6.89 (d, 5.4 Hz, 1H, 1'-H), 7.73 (d, 8.0 Hz, 1H, 6-H), 11.30 (br s, 1H, N-H).- ^{13}C-NMR ([D$_6$]DMSO): δ (ppm) = 30.1 (C-4'), 46.1 (C-3'), 62.7 (C-6'), 71.6 (C-5'), 96.1 (C-2'), 101.1 (C-5), 142.6 (C-6), 149.9 (C-1'), 150.7 (C-2), 163.4 (C-4).- MS (70 eV): m/z (%) = 224 (24.0, M$^+$).- $C_{10}H_{12}N_2O_4$ x 1.2 H_2O (245.8) Calcd. C 48.9 H 5.90 N 11.4 Found C 48.6 H 5.49 N 11.3.

1-(1,5-Anhydro-2,3,4-trideoxy-D-erythro-hex-1-enitol-3-yl)thymine (**11b**)

Yield 57 mg (62%).- M.p. 222-255°C (dec.).- ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 1.78 (s, 3H, CH_3), 1.90 (m, 2H, 4'-H), 3.48 (d, 4.8 Hz, 2H, 6'-H), 3.74 (m, 1H, 5'-H), 4.72 (t, 5.6 Hz, 1H, 2'-H), 4.84 (m, 2H, 6'-OH and 3'-H), 6.88 (d, 5.6 Hz, 1H, 1'-H), 7.57 (s, 1H, 6-H), 11.27 (br, 1H, N-H).- ^{13}C-NMR ([D$_6$]DMSO): δ (ppm) = 12.0 (CH_3), 30.3 (C-4'), 45.7 (C-3'), 62.7 (C-6'), 71.6 (C-5'), 96.4 (C-2'), 107.7 (C-5), 138.1 (C-6), 149.7 (C-1'), 150.6 (C-2), 150.6 (C-2), 164.0 (C-4).- MS (70 eV): m/z (%) = 238 (15.0, M$^+$).- $C_{11}H_{14}N_2O_4$ x 0.9 H_2O (254.5) Calcd. C 51.9 H 6.26 N 11.0 Found C 52.1 H 5.91 N 11.0.

1-(1,5-Anhydro-2,3,4-trideoxy-D-erythro-hex-1-enitol-3-yl)cytosine (**11d**)

Yield 251 mg (59%).- M.p. 215-216°C.- ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 1.77 (td, 13.5 Hz, 5.0 Hz, 1H, 4'-H$_a$), 1.92 (d, 13.5 Hz, 1H, 4'-H$_e$), 3.48 (m, 2H, 6'-H), 3.63 (m, 1H, 5'-H), 4.70 (t, 5.7 Hz, 1H, 2'-H), 4.81 (t, 5.4 Hz, 1H, 6'-OH), 4.88 (dd, 5.7 Hz, 5.0 Hz, 1H, 3'-H), 5.71 (d, 7.4 Hz, 1H, 5-H), 6.87 (d, 5.7 Hz, 1H, 1'-H), 7.03 (br, 1H, N^4-H), 7.10 (br, 1H, N^4-H), 7.69 (d, 7.4 Hz, 1H, 6-H).- ^{13}C-NMR ([D$_6$]DMSO): δ (ppm) = 30.4 (C-4'), 46.1 (C-3'), 62.9 (C-6'), 71.4 (C-5'), 92.7 (C-5), 97.0 (C-2'), 143.1 (C-6), 149.2 (C-1'), 155.4 (C-2), 165.5 (C-4).- MS (70 eV): m/z (%) = 223 (11.0, M$^+$).- $C_{10}H_{13}N_3O_3$ x 0.6 H_2O (234.0) Calcd. C 51.3 H 6.12 N 17.9 Found C 51.2 H 5.96 N 17.6.

1-(2,3,4-Trideoxy-α-D-glycero-hex-3-enopyranosyl)uracil (**14a**)

Yield 143 mg (61%), hygroscopic.- ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 2.34 (m, 2H, 2'-H), 3.85 (m, 2H, 6'-H), 4.28 (br s, 1H, 5'-H), 4.86 (br s, 1H, 6'-OH), 5.62 (d, 8.1 Hz, 1H, 5-H), 5.93 (m, 3H, 4'-H, 1'-H, and 3'-H), 7.66 (d, 8.1 Hz, 1H, 6-H), 11.36 (br s, 1H, N-H).- ^{13}C-NMR ([D$_6$]DMSO): δ (ppm) = 28.2 (C-2'), 62.5 (C-6'), 74.8 (C-5'), 75.5 (C-1'), 101.5 (C-5), 123.8 (C-4'), 126.6 (C-3'), 141.0 (C-6), 150.2 (C-2), 162.9 (C-4).- MS (70 eV): m/z (%) = 224 (0.1, M$^+$).

1-(2,3,4-Trideoxy-β-D-glycero-hex-3-enopyranosyl)uracil (**15a**)

Yield 126 mg (56%).- M.p. 176-178°C.- ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 2.18 (dt, 17.5 Hz, 2.8 Hz, 1H, 2'-H$_e$), 2.45 (m, 1H, 2'-H$_a$), 3.45 (d, 5.2 Hz, 2H, 6'-H), 4.39 (br s, 1H, 5'-H), 4.81 (br s, 1H, 6'-OH), 5.65 (d, 8.0 Hz, 1H, 5-H), 5.74 (m, 2H, 1'-H and 4'-H), 5.89 (ddd, 10.4 Hz, 5.4 Hz, 2.8 Hz, 1H, 3'-H), 7.77 (d, 8.0 Hz, 1H, 6-H), 11.39 (br s, 1H, N-H).- ^{13}C-NMR ([D$_6$]DMSO): δ (ppm) = 28.8 (C-2'), 63.3 (C-6'), 77.6 (C-5'), 78.1 (C-1'), 101.8 (C-5), 123.9 (C-4'), 127.2 (C-3'), 140.9 (C-6), 150.1 (C-2), 162.9 (C-4).- MS (70 eV): m/z (%) = 224 (0.3, M$^+$).

1-(2,3,4-Trideoxy-α-D-glycero-hex-3-enopyranosyl)thymine (**14b**)

Yield 120 mg (53%).- M.p. 146-148°C.- ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 1.79 (s, 3H, CH_3), 2.23 (dt, 17.2 Hz, 4.5 Hz, 1H, 2'-H$_e$), 2.43 (ddd, 17.2 Hz, 8.6 Hz, 2.4 Hz, 1H, 2'-H$_a$), 3.50 (m, 2H, 6'-H), 4.30 (m, 1H, 5'-H), 4.86 (t, 5.5 Hz, 1H, 6'-OH), 5.84 (m, 3H, 4'-H, 1'-H, and 3'-H), 7.55 (s, 1H, 6-H), 11.35 (s, 1H, N-H).- ^{13}C-NMR ([D$_6$]DMSO): δ (ppm) = 11.7 (CH_3), 28.2 (C-2'), 62.5 (C-6'), 74.5 (C-5'), 75.8 (C-1'), 109.1 (C-5), 123.8 (C-4'), 126.5 (C-3'), 136.4 (C-6), 150.1 (C-2), 163.5 (C-4).- MS (70 eV): m/z (%) = 238 (2.2, M$^+$).

1-(2,3,4-Trideoxy-β-D-glycero-hex-3-enopyranosyl)thymine (**15b**)

Yield 90 mg (49%).- M.p. 148-150°C.- ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 1.80 (s, 3H, CH_3), 2.15 (ddd, 17.3 Hz, 5.5 Hz, 2.4 Hz, 1H, 2'-H$_e$), 2.39 (dd, 17.3 Hz, 7.5 Hz, 1H, 2'-H$_a$), 3.46 (t, 5.7 Hz, 2H, 6'-H), 4.38 (m, 1H, 5'-H), 4.81 (t, 5.7 Hz, 1H, 6'-OH), 5.75 (m, 2H, 4'-H and 1'-H), 5.89 (dd, 10.1 Hz, 5.5 Hz, 3'-H), 7.64 (s, 1H, 6-H), 11.36 (s, 1H, N-H).- ^{13}C-NMR ([D$_6$]DMSO): δ (ppm) = 11.9 (CH_3), 28.7 (C-2'), 63.4 (C-6'), 77.6 (C-5'), 77.8 (C-1'), 109.5 (C-5), 124.1 (C-4'), 127.2 (C-3'), 136.4 (C-6), 150.1 (C-2), 163.6 (C-4).- MS (70 eV): m/z (%) = 238 (0.5, M$^+$).

1-(2,3,4-Trideoxy-α-D-glycero-hex-3-enopyranosyl)cytosine (**14e**)

Yield 157 mg (73%), hygroscopic foam.- ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 2.26 (m, 2H, 2'-H), 3.50 (m, 2H, 6'-H), 4.28 (m, 1H, 5'-H), 4.87 (t, 5.5 Hz, 1H, 6'-OH), 5.75 (d, 7.4 Hz, 1H, 5-H), 5.81 (dd, 10.3 Hz, 2.3 Hz, 1H, 4'-H), 5.88 (m, 2H, 1'-H and 3'-H), 7.18 (br s, 1H, N^4-H), 7.26 (br s, 1H, N^4-H), 7.60 (d, 7.4 Hz, 1H, 6-H).- ^{13}C-NMR ([D$_6$]DMSO): δ (ppm) = 28.9 (C-2'), 62.4 (C-6'), 75.0 (C-5'), 75.7 (C-1'), 93.9 (C-5), 124.1 (C-4'), 126.6 (C-3'), 141.2 (C-6), 154.8 (C-2), 165.5 (C-4).- MS (70 eV): m/z (%) = 223 (5.0, M$^+$).

1-(2,3,4-Trideoxy-β-D-glycero-hex-3-enopyranosyl)cytosine (**15e**)

Yield 127 mg (70%), hygroscopic foam.- ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 2.3 (m, 2H, 2'-H), 3.44 (m, 2H, 6'-H), 4.36 (m, 1H, 5'-H), 4.83 (t, 5.4 Hz, 1H, 6'-OH), 5.85 (m, 4H, 5-H, 4'-H, 1'-H, and 3'-H), 7.18 (br s, 1H, N^4-H), 7.29 (br s, 1H, N^4-H), 7.67 (d, 7.5 Hz, 1H, 6-H).- ^{13}C-NMR ([D$_6$]DMSO): δ (ppm) = 29.6 (C-2'), 63.4 (C-6'), 77.5 (C-5'), 78.6 (C-1'), 94.1 (C-5), 124.2 (C-4'), 127.3 (C-3'), 141.2 (C-6), 154.5 (C-2), 165.4 (C-4).- MS (70 eV): m/z (%) = 223 (2.6, M$^+$).

9-(2,3,4-Trideoxy-α-D-glycero-hex-3-enopyranosyl)adenine (**14f**)

Yield 26 mg (63%).- M.p. 194-196°C (dec.).- ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 2.53 (dt, 14.1 Hz, 5.4 Hz, 1H, 2'-H$_e$), 2.89 (ddd, 14.1 Hz, 5.4 Hz, 2.7 Hz, 1H, 2'-H$_a$), 3.55 (m, 2H, 6'-H), 4.07 (m, 1H, 5'-H) , 4.86 (t, 5.6 Hz, 1H, 6'-OH), 5.90 (d, 10.6 Hz, 1H, 4'-H), 6.04 (m, 1H, 3'-H), 6.18 (t, 5.4 Hz, 1H, 1'-H), 7.30 (s, 2H, N^6-H), 8.18 (s, 1H, 8-H), 8.24 (s, 1H, 2-H).- ^{13}C-NMR ([D$_6$]DMSO): δ (ppm) = 28.2 (C-2'), 62.7 (C-6'), 73.5 (C-5'), 74.6 (C-1'), 118.6 (C-5), 123.6 (C-4'), 126.8 (C-3'), 139.9 (C-8), 149.2 (C-4), 152.6 (C-2), 155.9 (C-6).- MS (70 eV): m/z (%) = 247 (1.3, M$^+$)

9-(2,3,4-Trideoxy-β-D-glycero-hex-3-enopyranosyl)adenine (**15f**)

Yield 20 mg (61%).- M.p. 198-196°C (dec.).- ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 2.41 (ddd, 15.7 Hz, 6.2 Hz, 3.9 Hz, 1H, 2'-H$_e$), 2.89 (dd, 15.7 Hz, 11.7 Hz, 1H, 2'-H$_a$), 3.42 (m, 2H, 6'-H), 4.46 (m, 1H, 5'-H), 4.84 (t, 5.8 Hz, 1H, 6'-OH), 5.89 (m, 3H, 4'-H, 1'-H, and 3'-H), 7.28 (s, 2H, N^6-H), 8.16 (s, 1H, 8-H), 8.41 (s, 1H, 2-H).- MS (70 eV): m/z (%) = 247 (1.3, M$^+$).

Hydrogenation to give **16** *and* **17**

Compound **9a**, **9c**, **15a**, or **15c** (0.11 mmol) was hydrogenated in methanolic solution/10% Pd/C at 1.4 bar room temp. for 2 h. The catalyst was removed, the filtrate was evaporated *in vacuo* to give compound **16** or **17**. ^{1}H-NMR and ^{13}C-NMR spectra of **16a,b** and **17a,b** were similarly to those reported[18].

References

1 F. Barré-Sinoussi, J.C. Chermann, F. Rey, M.T. Nugeyre, S. Chamaret, J. Gruest, C. Dauget, C. Axler-Blin, F. Vezinet-Brun, C. Rouzioux, W. Rosenbaum, and L. Montagnier, Science *220*, 868 (1983).

2 R.C. Gallo, S.Z. Salahuddin, M. Popovic, G.M. Shearer, M. Kaplan, B.F. Haynes, T.J. Palker, R. Redfield, J. Oleske, B. Safai, G. White, P. Foster, and P.D. Markham, Science *224*, 500 (1984).

3 M. Popovic, M.G. Sarngadharan, E. Read, and R.C. Gallo, Science *224*, 497 (1984).
4 H. Mitsuya, K.J. Weinhold, P.A. Furman, M.H. St. Clair, S.N. Lehrman, R.C. Gallo, D. Bolognesi, D.W. Barry, and S. Broder, Proc. Natl. Acad. Sci. U.S.A. *82*, 7096 (1985).
5 T.-S. Lin, R.F. Schinazi, M.S. Chen, E. Kinney-Thomas, and W.H. Prusoff, Biochem. Pharmacol. *36*, 311 (1987).
6 Y. Hamamoto, H. Nakashima, T. Matsui, A. Matsuda, T. Ueda, and N. Yamamoto, Antimicrob. Agents Chemother. *31*, 907 (1987).
7 J. Balzarina, R. Pauwels, P. Herdewijn, E. De Clercq, D.A. Cooney, G.-J. Kang, M. Dalal, D.G. Johns, and S. Broder, Biochem. Biophys. Res. Commun. *140*, 735 (1986).
8 J. Balzarina, G.-J. Kang, M. Dalal, P. Herdewijn, E. De Clercq, S. Broder, and D.G. Johns, Mol. Pharmacol. *32*, 162 (1987).
9 T.-S. Lin, R.F. Schinazi, and W.H. Prusoff, Biochem. Pharmacol. *36*, 2713 (1987).
10 M. Baba, R. Pauwels, P. Herdewijn, E. De Clercq, J. Desmyter, and M. Vandeputte, Biochem. Biophys. Res. Commun. *142*, 128 (1987).
11 R.J. Ferrier and N. Prasad, J. Chem. Soc. *1969*, 570.
12 B. Fraser-Reid and B. Boctor, Can. J. Chem. *47*, 393 (1969).
13 M. Chmielewski, J. Jurczak, and A. Zamojski, Org. Magn. Reson. *20*, 249 (1982).
14 M.B. Yunker and B. Fraser-Reid, Can. J. Chem. *54*, 3986 (1976).
15 H. Vorbrüggen, K. Krolikiewicz, and B. Bennua, Chem. Ber. *114*, 1234 (1981).
16 H. Vorbrüggen and G. Höfle, Chem. Ber. *114*, 1256 (1981).
17 Y. Sugiura, S. Furuya, and Y. Furukawa, Chem. Pharm. Bull. *36*, 3253 (1988).
18 P. Herdewijn and A. Van Aerschot, Bull. Soc. Chim. Belg. *99*, 895 (1990).
19 Z. Kaluza, E.B. Pedersen, C.M. Nielsen, and M. Chmielewski, Acta Chem. Scand. *44*, 294 (1990).
20 M.S. Motawia, E.S. Andreassen, E.B. Pedersen, and J.P. Jacobsen, Liebigs Ann. Chem. *1987*, 787.

[Ph953]