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Synthesis and antiviral activity of acyclic analogues of 1,5-anhydrohexitol nucleosides using Mitsunobu reaction.

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Abstract : Starting from protected hexenetriol, acyclic analogues of the 1,5-anhydrohexitol nucleosides were synthesized. The reaction sequence involved a stereoselective Sharpless dihydroxylation and a Mitsunobu-type alkylation of the nucleoside bases. The compounds did not show antiviral activity.

INTRODUCTION

The discovery of acyclovir[1] as a antiherpes agent ignited the search for new antiviral nucleosides with an acyclic carbohydrate-mimicking chain. During the last fifteen years, many new synthetic schemes for various acyclic nucleoside[2] analogues have been discovered and many of these molecules have shown promising antiviral activities.[3] Recently, we discovered the potent antiherpes activity of anhydrohexitol nucleosides[4] and reported on a first series of acyclic analogues[5] mimicking the upper part of the hexitols. These compounds, however, were not active against herpes viruses.

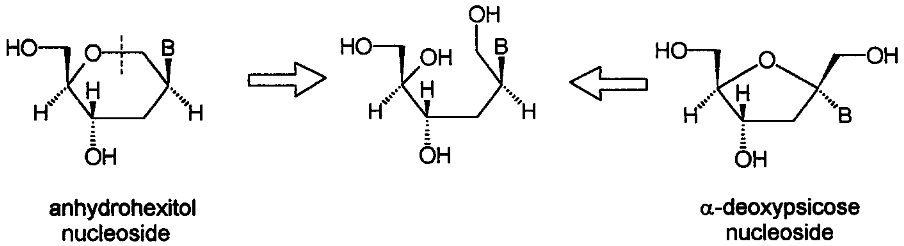


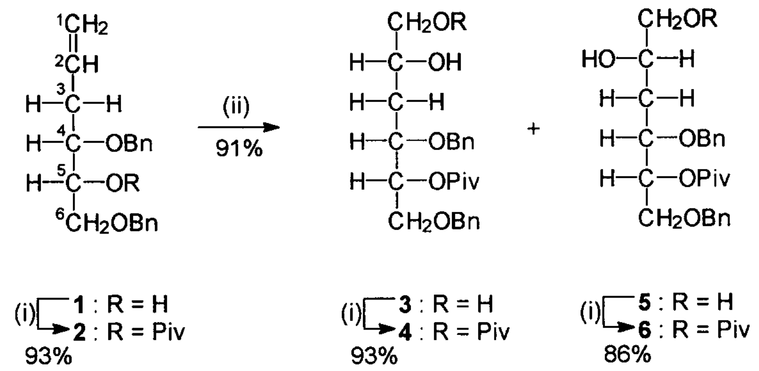
Figure 1

The present publication describes another series of acyclic nucleosides, resembling the front part of the anhydrohexitol structure (Figure 1). These molecules can be considered as reduced acyclic analogues of α-deoxypsicose nucleosides (Figure 1), also a series of hitherto unknown compounds with potential antiviral activity. We have derived a synthetic scheme starting from the easily available 2-deoxy-D-ribose and investigated the antiviral activity of these compounds (compounds **11**, **14**, **17**, **21**). During the last years α-nucleosides received much attention[6]. Therefore, we also undertook the synthesis of two acyclic analogues with the inversed configuration at position 2 (compound **24** and **28**).

RESULTS AND DISCUSSIONS

The starting material, 4,6-di-O-benzyl-hex-1-ene-4(*S*),5(*R*),6-triol **1**, is easily available following a literature procedure[7]. It may be noted that previously we have reported[7] the synthesis of **1** in 70% yield by slow addition of aldehyde to a suspension of methyl triphenylphosponium bromide and butyl lithium in dry toluene. Now we have found that this yield could be reproducibly increased to 85% using a dilute solution of aldehyde (12.0 g aldehyde in 100 mL dry toluene). This solution should be added dropwise to a suspension of methyl triphenylphosphonium bromide and butyl lithium in dry toluene, as mentioned earlier[7], over a period of 1.5-2 h. Protection of the secondary hydroxyl group in position 5 of compound **1** was performed with pivaloyl chloride in pyridine yielding **2** in 93%. The dihydroxylation of **2** was first carried out with $KMnO_4$ in ethanol.[8] The treatment of **2** with $KMnO_4$ in ethanol gave an epimeric mixture of **3** and **5** in only 50% yield. Both of the epimers **3** and **5** were formed in almost equal amounts. This low yield and the low stereoselectivity of the reaction stimulated us to test out the Sharpless reagent AD mix-α[9], which gives hydroxylation predominantly from α-face. Compound **2** was treated with AD mix-α in a *tert*-butanol/water mixture to afford **3** and **5** in an yield of 91%. Also the stereoselectivity of the reaction increased. Both **3** and **5** were isolated by silica gel column chromatography in 63% and 28% yield respectively. The primary hydroxy function in **3** and **5** was selectively protected with a pivaloyl group in order to introduce a nucleobase moiety at the site of the secondary hydroxy function (C-2 position). After introduction of the base moiety both pivaloyl groups (at C-1' and C-4') could be easily removed in one reaction step for further functionalization. Thus **3** and **5** was separately treated with pivaloyl chloride in pyridine to afford **4** (93%) and **6** (86%) respectively. Mitsunobu conditions[10,11] were used to introduce the heterocyclic bases. When **4** was treated with Ph_3P, diethyl azodicarboxylate (DEAD) and uracil, thymine or cytosine in dioxane, the corresponding O^2-isomer was obtained as a major product which is consistent with our earlier observations.[11] Thus protection of the N^3-position of uracil or thymine was necessary. However, the problem could not be solved in the same way for cytosine nucleosides. Indeed, treatment of **4** with N^4-benzoylcytosine under Mitsunobu reaction conditions gave predominantly the O^2-isomer. Thus for the preparation of the cytosine analogue we started from the uracil congener which was converted to the corresponding cytosine analogue at the level of the protected acyclic psicose nucleoside.

Scheme 1

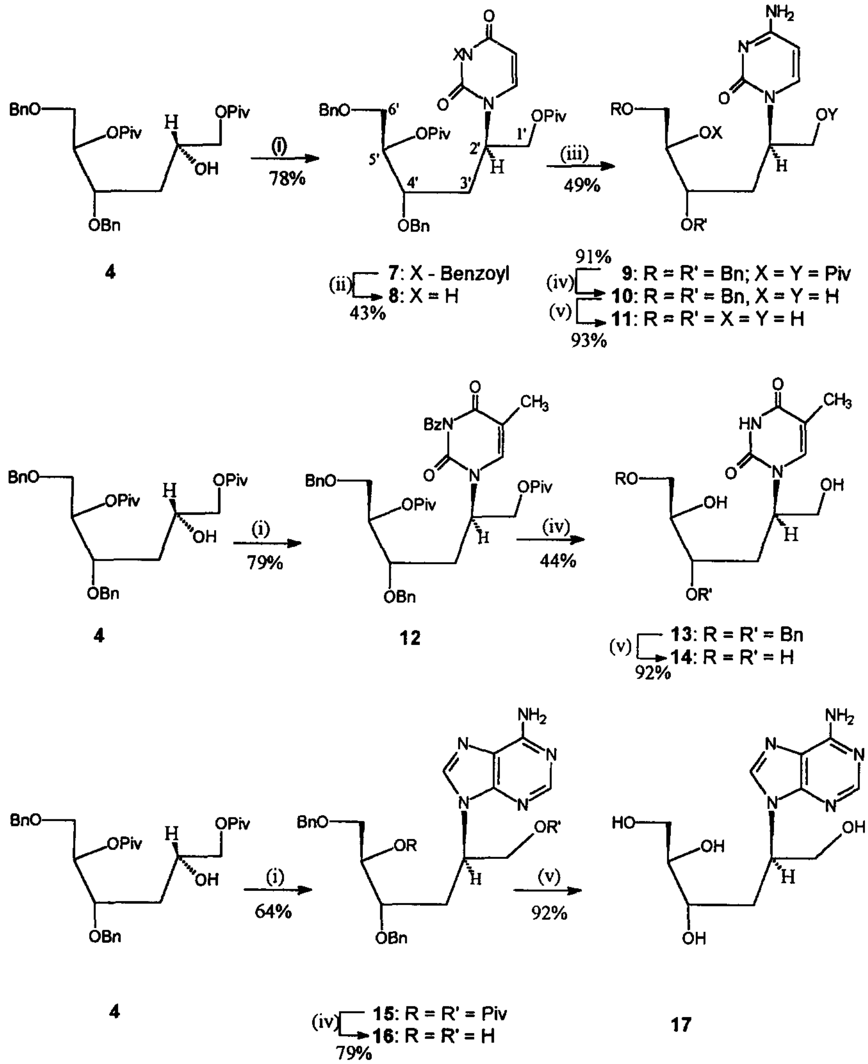


Reagents : (i) Pivaloyl chloride, pyridine, room temperature; (ii) AD-mix-α, t-BuOH, H_2O.

Treatment of **4** with N^3-benzoyluracil,[12] Ph_3P and diethyl azodicarboxylate in dioxane yielded 7 in 78% yield. This compound was contaminated with some impurity which could be easily removed in the next step. It may be noted that DEAD should be added slowly. For the transformation of uracil to cytosine the N^3-benzoyl group of 7 was removed. Treatment of 7 with aqueous ammonia in methanol gave **8** in 43% yield. This yield was calculated from alcohol **4** as 7 was contaminated with some impurity. The uracil moiety in **8** was transformed to the cytosine analogue using the $POCl_3$ method.[13] Thus **8** was treated with $POCl_3$ and 1,2,4-triazole in acetonitrile. After standard work up the residue was treated with NH_4OH to displace triazole moiety by ammonia to afford **9** in 49% yield. The pivaloyl groups of **9** were removed upon treatment with aqueous NaOH in dioxane to give **10** in 91% yield. Finally, **10** was treated with $Pd(OH)_2$ on C (20%)[14] in methanol/cyclohexene to yield **11** (93%).

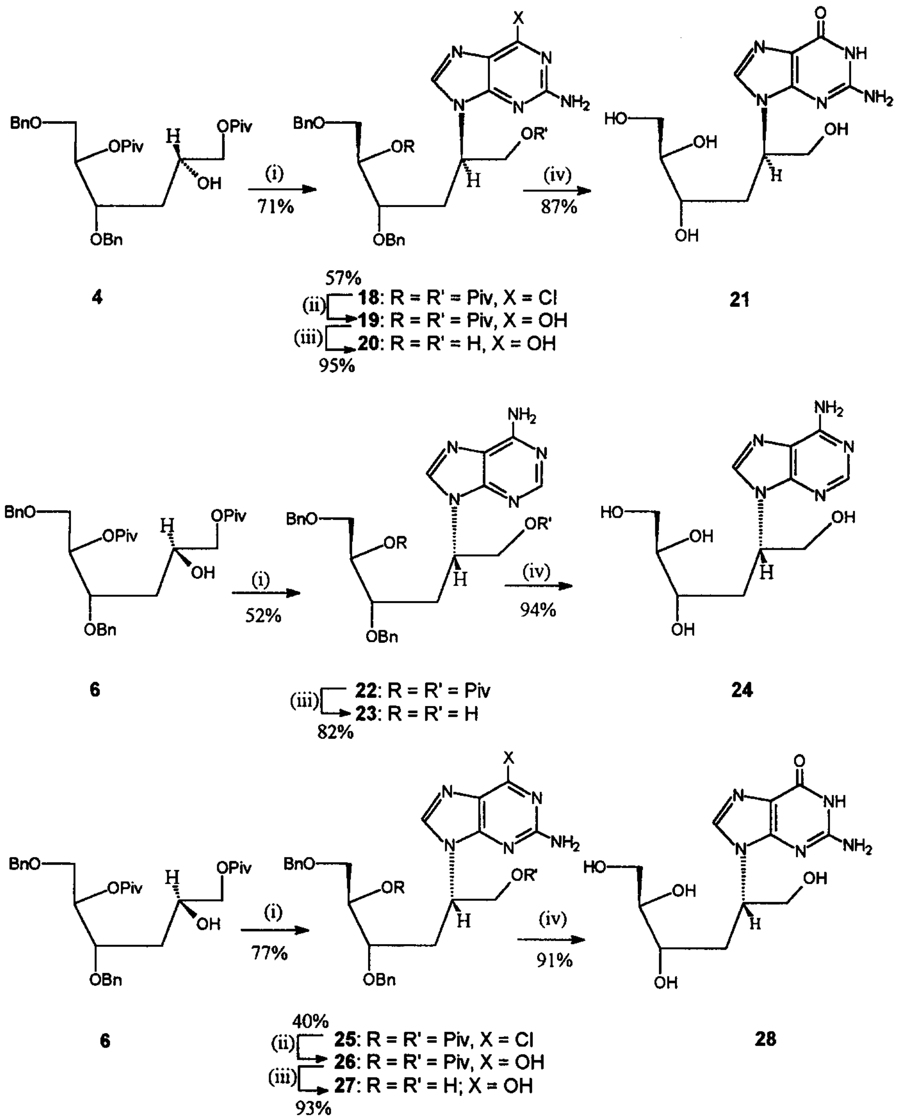
Treatment of **4** with N^3-benzoylthymine[12], Ph_3P and DEAD in dioxane afforded **12** in 79% yield. Again this **12** was contaminated with impurity which was easily removed in the next step. The N^3-benzoyl and two pivaloyl groups in **12** were removed upon treatment with aqueous NaOH in dioxane to give **13** in 44% yield. This yield was calculated for two steps. Compound **13** was treated with $Pd(OH)_2$ on C (20%) in methanol/cyclohexene to give **14** in 92% yield. Previously, it has been reported[11] that treatment of appropriately protected alcohol with adenine under Mitsunobu conditions gave very poor yield. The yield of the reaction with N^6-benzoyladenine even does not exceed 20%.[11] However, when alcohol **4** was treated with adenine, Ph_3P and DEAD in dioxane pure **15** was isolated in 64% yield. Treatment of **15** with aqueous NaOH in dioxane yielded **16** in 79% yield. This compound was easily crystallized from methanol. Benzyl groups in **16** were removed upon treatment with $Pd(OH)_2$ on C (20%) in methanol/cyclohexene to give **17** in 92% yield. For the synthesis of the guanine analogue, 6-chloro-2-aminopurine moiety was used as precursor. This base was introduced in **4** also using Mitsunobu reaction conditions. Thus **4** was treated with 6-chloro-2-aminopurine, Ph_3P and DEAD in dioxane to give **18** in 71% yield. The impurity in **18** could be easily removed in the next step.

Scheme 2



Reagents : (i) Ph_3P, N^3-benzoyluracil or N^3-benzoylthymine or adenine, DEAD, dioxane; (ii) NH_4OH, CH_3OH; (iii) $POCl_3$, 1,2,4-triazole, Et_3N, CH_3CN, NH_4OH; (iv) Aq NaOH (N), dioxane; (v) $Pd(OH)_2$ on C, CH_3OH.

Scheme 3



Reagents : (i) Ph_3P, 6-Chloro-2-aminopurine or adenine, DEAD, dioxane; (ii) CF_3COOH, H_2O; (iii) Aq NaOH (N), dioxane; (iv) $Pd(OH)_2$ on C, CH_3OH.

Compound **18** was treated with aqueos CF_3COOH[15] at room temperature to give corresponding guanine analouge **19** in 57% yield. Aqueous NaOH treatment of **19** afforded **20** in 95% yield. Deprotection of benzyl groups in **20** was achieved upon treatment of **20** with $Pd(OH)_2$ on C (20%) to give **21** (87%).

The acyclic nucleosides with inversed configuration at position 2 were obtained from the 3-deoxy-D-mannitol precursor **6**. The alcohol **6** was treated with adenine, Ph_3P and DEAD in dioxane to give pure **22** in 52% yield. The pivaloyl groups in **22** were removed upon treatment with aqueous NaOH in dioxane to yield **23** (82%). Removal of benzyl groups in **23** was done upon treatment with $Pd(OH)_2$ on C (20%) to give **24** (94%). When alcohol **6** was treated with 6-chloro-2-aminopurine, Ph_3P and DEAD in dioxane acyclic nucleoside analouge **25** was obtained in 77% yield. Contaminated impurities were removed in the next step. Treatment of **25** with aqueous CF_3COOH at room temperature afforded pure **26** in 40% yield (yield was calculated for two steps). The pivaloyl groups in **26** were removed upon treatment with aqueous NaOH in dioxane to give **27** in 93% yield. Finally, **27** was treated with $Pd(OH)_2$ on C (20%) in methanol and cyclohexene to give pure **28** in 91% yield. The direct transformation of **18** to **20** or **25** to **27** could be achieved by treatment of **18** or **20** with aqueous NaOH in dioxane at room temperature overnight, albeit at a very low yield (~20%).

All compounds (**11, 14, 17, 21, 24, 28**) were inactive when tested against vaccinia virus, vesicular stomatitis virus, Coxsackie virus B4, respiratory syncytical virus, parainfluenza-3 virus, reovirus-1, Sindbis virus, Punta Toro virus, herpes simplex virus-1, and herpes simplex virus-2 in either human embryonic skin-muscle (ESM) fibroblasts, Hela or Vero cell cultures.

STRUCTURE DETERMINATION OF 3-28 AT C2 /C2'-POSITION

The configuration of **3-28** at C-2 / C-2'-position was primarily based on the assumption that the Sharpless reagent AD-mix-α gives preponderant α-face hydroxylation. Thus treatment of **2** with Sharpless reagent AD-mix-α gave **3** (C-2 S) and **5** (C-2 R) in a ratio of 7:3. This assumption was confirmed by ring closure reaction of **13** (C-2' R) giving the corresponding 1,5-anhydrohexitol[4] (details of the ring closure reactions will be published elsewhere). The configuration at C-2' of this anhydrohexitol is R. Compound **3** (C-2 S) gave **4** (C-2 S). The Mitsunobu reaction of **4** (C-2 S) and consequent deblocking yielded **13** (C-2' R). The C-2' configuration of **13** (C-2' R) should be reverse to **3** (C-2 S) as Mitsunobu reaction mostly gives inverted configuration. During ring closure reaction of **13** (C-2' R) the configuration at C-2' did not change and gave anhydrohexitol with C-2' R configuration. This proves that during Sharpless hydroxylation of **2** indeed preponderant α-face hydroxylation occurred and the above ring closure reaction subsequently confirmed the configuration of **3-28** at the C-2/C-2' position.

EXPERIMENTALS

Melting points were determined in capillary tubes with a Buchi-Tottoli apparatus and are uncorrected. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded (in δ scale) on a Varian Gemini-200 spectrometer using tetramethylsilane (0.00 ppm) as internal standard. When DMSO-d_6 was used as solvent, the resonance peak at 2.50 ppm was used as internal standard. (s: singlet, d: doublet, dd: double doublet, ddd: double of double doublet, t: triplet, m: multiplet and br. s: broad singlet). Liquid secondary ion mass spectra (LSIMS) and high resolution mass spectra (HR) were recorded on a Kratos Concept 1H mass spectometer. Dioxane dried by molecular sieves was used for the Mitsunobu reaction. Analytical grade methanol was used for deprotection of benzyl group without further drying.

4(S),6-Di-O-benzyl-5(R)-O-pivaloyl-hex-1-ene-4,5,6-triol (2). Pivaloyl chloride (10.62 mL, 86.4 mmol) was added to an ice cold solution of **1** (18.0 g, 57.6 mmol) in pyridine (230 mL) and the reaction mixture was kept at room temparature overnight. The solvent was removed in vacuo, 50 mL of water was added and the reaction mixture was extracted twice with CH_2Cl_2 (2 x 500 mL). The combined organic layer was washed successively with saturated aqueous $NaHCO_3$ solution (3 x 50 mL) and water (1 x 50 mL). The solvent was removed in vacuo, co-evaporated with toluene and the residue was purified by column chromatography to give **2** (21.2 g, 93%). ^{1}H-NMR ($CDCl_3$): 7.39-7.18 (m, 10 H) arom; 6.00-5.78 (m, 1H) H2; 5.21-5.06 (m, 3H) H5, H1 and H1'; 4.65-4.42 (m, 4H) 2 x $ArCH_2$; 3.81-3.66 (m, 3H) H4, H6 and H6'; 2.35 (t, 2H) H3 and H3'. ^{13}C-NMR ($CDCl_3$): 177.2, 138.1, 134.3; 128.4, 127.8, 127.6, 126.9, 117.5, 77.8, 73.0, 72.7, 72.5, 68.4, 35.4, 27.2. HR LSIMS calcd. for $C_{25}H_{33}O_4$ $(M + H)^+$ 397.2378, found 397.2388.

4,6-Di-O-benzyl-5-O-pivaloyl-3-deoxy-D-glucitol (3) and **4,6-Di-O-benzyl-5-O-pivaloyl-3-deoxy-D-mannitol (5).** To a solution of tert-butanol (230 mL) and water (230 mL) 65.0 g AD mix-α was added and stirred at room temperature until two distinct clear phases appeared. The mixture was cooled to 0 °C, 18.2 g (46.0 mmol) of **2** was added and the reaction mixture was stirred at 0 °C for 6 h followed by room temperature overnight. The reaction mixture was cooled to 0 °C and, after addition of 68.0 g of sodium sulfite, was kept at room temperature for 60 min and extracted with dichloromethane (2 x 500 mL). The combined organic layer was concentrated in vacuo and purified by column chromatography to give pure **3** (12.5 g, 63%) and **5** (5.5 g, 28%) in combined yield of 91%. Compound **3**, ^{1}H-NMR ($CDCl_3$): 7.39-7.18 (m, 10 H) arom; 5.61 (m, $J_{4,5}$ = 4.0 Hz, 1H) H5; 4.67-4.43 (m, 4H) 2 x $ArCH_2$; 3.96 (m, 1H) H4; 3.85 (m, 1H) H2; 3.66 (m, 2H) H6 and H6'; 3.55 (m, $J_{1,2}$ = 3.0 Hz, $J_{1,1'}$ = 11.1 Hz, 1H) H1; 3.44 (m, $J_{1',2}$ = 6.8 Hz, 1H) H1'; 2.90 (br. s, 1H) 2-OH; 2.60 (br. s, 1H) 1-OH; 1.62 (t, 2H) H3 and H3'; 1.21 (s, 9H) Piv. ^{13}C-NMR ($CDCl_3$): 177.9, 137.9, 128.5, 128.1, 127.9, 127.6, 75.5, 73.2, 72.7, 72. 6, 68.8, 68.4, 66.9, 38.9 33.6 and 27.2. HR LSIMS calcd. for $C_{25}H_{35}O_6$ $(M + H)^+$ 431.2433, found 431.2408. Compound **5**. ^{1}H-NMR ($CDCl_3$): 7.41-7.20 (m, 10 H) arom; 5.38 (m, 1H) H5; 4.78-4.40 (m, 4H) 2 x $ArCH_2$; 3.91 (m, $J_{3,4}$ = 9.5 Hz, $J_{3',4}$ = 3.9 Hz, 1H) H4; 3.85 (m, 1H) H2; 3.62 (m, 2H) H6 and H6'; 3.51 (br. s, 1H) 2-OH; 3.42 (m, $J_{1,2}$ = 3.8 Hz, $J_{1',2}$ = 6.2 Hz, $J_{1,1'}$ = 11.0 Hz, 2H) H1 and H1'; 2.25 (t, 1H) 1-OH; 1.89-1.55 (m, 2H) H3 and H3'; 1.21 (s, 9H) Piv. ^{13}C-NMR ($CDCl_3$): 178.0, 137.8, 137.3, 128.6, 128.5, 128.3, 128.1, 127.8, 127.7, 78.5, 73.3, 72.2, 71.7, 71.0, 68.1, 66.6, 38.9, 33.2 and 27.2. HR LSIMS calcd. for $C_{25}H_{35}O_6$ $(M + H)^+$ 431.2433, found 431.2457.

4,6-Di-O-benzyl-1,5-di-O-pivaloyl-3-deoxy-D-glucitol (4). To a cold solution of **3** (8.5 g, 19.7 mmol) in pyridine (70 mL), pivaloyl chloride (2.66 mL, 21.6 mmol) was added and the reaction mixture was stirred at 0 °C for 2 h. The solvent was removed in vacuo, the residue was dissolved in dichloromethane (500 mL), washed successively with water (50 mL), saturated aquous $NaHCO_3$ (3 x 50 mL) and water (50 mL). The organic layer was concentrated in vacuo and purified by column chromatography to afford **4** (9.5 g, 93%). ^{1}H-NMR ($CDCl_3$): 7.41-7.20 (m, 10 H) arom; 5.35 (m, 1H) H5; 4.78-4.45 (m, 4H) 2 x $ArCH_2$; 4.10-3.90 (m, 4H) H1, H1', H2 and H4; 3.63 (m, 2H) H6 and H6'; 1.66 (m, 2H) H3 and H3'; 1.18 (s, 18 H) Piv. ^{13}C-NMR ($CDCl_3$): 178.6, 177.8, 138.0, 137.9, 128.5, 128.3, 127.9, 127.7, 75.1, 73.2, 72.6, 71.9, 68.5, 66.8, 36.9, 34.0, 27.2. HR LSIMS calcd. for $C_{30}H_{43}O_7$ $(M + H)^+$ 515.3008, found 515.3006.

4,6-Di-O-benzyl-1,5-di-O-pivaloyl-3-deoxy-D-mannitol (6) The reaction was performed as described for **4** using **5** (3.3 g, 7.7 mmol) and pivaloyl chloride (1.13 mL) in pyridine (70 mL) to give **6** (3.4 g, 86%). ^{1}H-NMR ($CDCl_3$): 7.41-7.22 (m, 10 H) arom; 5.38 (m, $J_{4,5}$ = 2.6 Hz, 1H) H5; 4.78-4.41 (m, 4H) 2 x $ArCH_2$; 4.07-3.85 (m, 4H) H2, H4, H1 and H1'; 3.64 (dd, $J_{5,6}$ = 6.4 Hz, $J_{6,6'}$ = 10.6 Hz, 1H) H6; 3.60 (dd, $J_{5,6'}$ = 5.3 Hz, 1H) H6'; 3.30 (br. s, 1H) 2OH; 1.98-1.62 (m, 2H) H3 and H3'. ^{13}C-NMR ($CDCl_3$): 178.6, 177.9 (Piv); 138.8, 137.4, 128.5, 128.3, 128.1, 127.9, 127.7, 126.9 (arom); 78.2 (C5); 73.4, 72.2 (2 x $ArCH_2$); 71.8 (C4); 68.9 (C2); 68.2, 67.9 (C6 and C1); 38.9 (piv); 33.6 (C3) and 27.3 (Piv). HR LSIMS calcd. for $C_{30}H_{43}O_7$ $(M + H)^+$ 515.3008, found 515.3029.

1-[4,6-Di-O-benzyl-1,5-di-O-pivaloyl-2,3-dideoxy-2-D-mannityl]N^3-benzoyluracil (7). General procedure for Mitsunobu reaction: to a mixture of alcohol **4** (772 mg, 1.5 mmol), N^3-benzoyluracil (645 mg, 3.0 mmol) and Ph_3P (789 mg, 3.0 mmol) in 15 mL dioxane was added DEAD (0.46 mL) in 17 mL dioxane over a period of 2 h. The reaction mixture was stirred at room temperature overnight. The solvent was removed in vacuo and directly purified by column chromatography to give **7** (840 mg, 78%) which was contaminated with some impurities that were removed after deprotection of N^3-benzoyl group. ^{1}H-NMR ($CDCl_3$): 7.90 (d, 1H) H6; 7.53-7.21 (m, 15 H) arom; 5.64 (d, 1H) H5; 5.28 (m, 1H) H5'; 4.72-4.05 (m, 7H) 2 x $ArCH_2$, H2', H1' and H1"; 3.77 (m, 1H) H4'; 3.62 (d, 2H) H6' and H6"; 2.08 (t, 2H) H3' and H3"; 1.21 (s, 9H) Piv; 1;11 (s, 9H) Piv. ^{13}C-NMR ($CDCl_3$): 177.8, 177.7, 162.0, 149.9, 142.6, 137.7, 137.3, 135.0, 131.4, 130.6, 129.4, 129.2, 128.7, 128.6, 128.3, 128.2, 128.0, 127.8, 101.7, 75.4, 73.5, 72.3, 71.7, 68.1, 63.5, 62.4, 39.0; 38.9, 30.7, 27.2. HR LSIMS calcd. for $C_{41}H_{49}N_2O_9$ $(M + H)^+$ 713.3437, found 713.3436.

1-[4,6-Di-O-benzyl-1,5-di-O-pivaloyl-2,3-dideoxy-2-D-mannityl]uracil (8). Compound 7 (800 mg, 1.1 mmol) was treated with ammonium hydroxide (6 mL) in methanol (20 mL) at room temperature for 8 h. The solvent was removed in vacuo and the residue was purified by column chromatography to give pure **8** (400 mg, 43% in two steps, Mitsunobu reaction and removal of benzoyl group). ^{1}H-NMR ($CDCl_3$): 8.48 (br. s, 1H) NH; 7.39-7.18 (m, 10 H) arom; 6.98 (d, $J_{5,6}$ = 7.8 Hz, 1H) H6; 5.03 (d, 1H) H5; 5.28 (m, $J_{4',5'}$ = 2.9 Hz, 1H) H5'; 4.77 (m, 1H) H2'; 4.70-4.15 (m, 5H) 2 x $ArCH_2$ and H1'; 4.04 (dd, $J_{1'',2'}$ = 4.0 Hz, $J_{1',1''}$ = 12.0 Hz, 1H) H1"; 3.73 (m, $J_{3',4'}$ = $J_{3'',4'}$ = 6.1 Hz, 1H) H4'; 3.62 (d, 2H) H6' and H6"; 2.01 (t, $J_{2',3'}$ = $J_{2',3''}$ = 6.6 Hz, 2H) H3' and H3"; 1.20 (s, 9H) Piv; 1.11 (s, 9H) Piv. ^{13}C-NMR ($CDCl_3$): 177.9, 177.7, 162.8, 150.8, 142.5, 137.8, 137.5, 129.0, 128.7, 128.3, 128.0, 127.9, 101.8, 76.2, 73.6, 72.4, 71.8, 68.2, 63.9, 62.4, 38.9, 30.7 and 27.2. HR LSIMS calcd. for $C_{34}H_{45}N_2O_8$ $(M + H)^+$ 609.3175, found 609.3195.

1-[4,6-Di-O-benzyl-1,5-di-O-pivaloyl-2,3-dideoxy-2-D-mannityl]cytosine (9). A mixture of $POCl_3$ (0.29 mL, 2.0 mmol) and 1,2,4-triazole (660 mg, 9.5 mol) in dry acetonitrile (5 mL) was stirred at 0 °C for 5 min followed by a slow addition of Et_3N (1.5 mL). The resulting mixture was left at 0 °C for 1 h and then **8** (309 mg, 0.5 mmol) in dry acetonitrile (3 mL) was added. The reaction mixture was stirred at room temperature for 5 h, filtered and the filtrate was diluted with ethyl acetate (50 mL) and washed successively with saturated $NaHCO_3$ (2 x 20 mL) and water (20 mL). The filtrate was concentrated in vacuo, co-evaporated with dioxane. The residue was dissolved in dioxane (5 mL) and treated with NH_4OH (4 mL) at room temperature overnight. The solvent was removed in vacuo and the residue was subjected to column chromatography to give **9** (150 mg, 49%). ^{1}H-NMR ($CDCl_3$): 8.18 (s, 2H) NH_2; 7.41-7.18 (m, 10 H) arom; 7.10 (d, $J_{5,6}$ = 7.3 Hz, 1H) H6; 5.58 (d, 1H) H5; 5.28 (m, $J_{4',5'}$ = 3.0 Hz, 1H) H5'; 4.90 (m, 1H) H2'; 4.68-4.28 (m, 5H) 2 x $ArCH_2$ and H1'; 4.12 (dd, $J_{1'',2'}$ = 4.0 Hz, $J_{1',1''}$ = 11.8 Hz, 1H) H1"; 3.77 (m, 1H) H4'; 3.62 (d, $J_{5',6'}$ = $J_{5',6''}$ = 5.2 Hz, 2H) H6' and H6"; 2.08 (m, 2H) H3' and H3"; 1.21 (s, 9H) Piv; 1.10 (s, 9H) Piv. ^{13}C-NMR ($CDCl_3$): 177.9, 177.8 (2 x Piv); 165.3 (C4); 156.8 (C2); 146.9 (C6); 144.2, 137.8, 137.6, 128.5, 128.3, 127.9, 127.8 (arom); 94.3 (C5); 76.1, 72.2 (C4' and C5'); 73.4, 72.3 (2 x $ArCH_2$); 68.3, 64.2 (C6' and C1'); 55.4 (C2', resonates as a broad); 38.9 (Piv); 31.0 (C3') and 27.2 (Piv). HR LSIMS calcd. for $C_{34}H_{46}N_3O_7$ $(M + H)^+$ 608.3335, found 608.3352.

1-[4,6-Di-O-benzyl-2,3-dideoxy-2-D-mannityl]cytosine (10). Compound **9** (140 mg, 0.22 mmol) was dissolved in dioxane (5 mL) and was treated with NaOH (N) (5 mL) at room temperature overnight. The reaction mixture was adjusted to pH 7 by addition of aqueous HCl (N). The solvent was removed in vacuo. The residue was dissolved in ethyl acetate (25 mL), washed successively with saturated aqueous $NaHCO_3$ (3 x 10 mL) and water (1 x 10 mL). The organic layer was concentrated in vacuo and the residue was purified by column chromatography to afford **10** (90 mg, 91%). ^{1}H-NMR ($CDCl_3$): 7.38-7.10 (m, 11 H) arom and H6; 5.58 (d, $J_{5,6}$ = 7.0 Hz, 1H) H5; 4.68 (m, 1H) H2'; 4.43 (m, 4H) 2 x $ArCH_2$; 3.88-3.38 (m, 6H) H6', H6", H5', H4', H1' and H1"; 1.91 (m, 2H) H3' and H3". HR LSIMS calcd. for $C_{24}H_{30}N_3O_5$ $(M + H)^+$ 440.2185, found 440.2160.

1-[2,3-dideoxy-2-D-mannityl]cytosine (11). A mixture of **10** (70 mg, 0.16 mmol) and $Pd(OH)_2$ on C (20%) in methanol (10 mL) and cyclohexene (3 mL) was kept at reflux overnight. The reaction mixture was filtered. The filtrate was concentrated in vacuo and washed successively with hexane and dichloromethane to afford **11** (38 mg, 93%). ^{1}H-NMR (DMSO-d_6): 7.50 (d, $J_{5,6}$ = 7.0 Hz, 1H) H6; 7.01 (br. s, 2H) NH_2; 5.65 (d, 1H) H5; 3.70-3.18 (m, 6H) H6', H6", H4', H5', H1' and H1"; 2.05 (m, 1H) H3'; 1.40 (m, 1H) H3". ^{13}C-NMR (DMSO-d_6): 165.1 (C4); 156.3 (C2); 144.8 (C6); 93.1 (C5); 75.2 (C5'); 69.0 (C4'); 63.3, 61.2 (C6' and C1'); 55.4 (C2') and 33.6 (C3'). HR LSIMS calcd. for $C_{10}H_{18}N_3O_5$ $(M + H)^+$ 260.1246, found 260.1253. Anal. ($C_{10}H_{17}N_3O_5$ 1.4 H_2O) calculated for C: 42.22, H: 7.02 and N: 14.77 found C: 42.44, H: 6.55 and N: 14.29.

1-[4,6-Di-O-benzyl-1,5-di-O-pivaloyl-2,3-dideoxy-2-D-mannityl]N^3-benzoylthymine (12). The reaction was performed as described for the general Mitsunobu reaction conditions for **7** using **4** (900 mg, 1.74 mmol), N^3-benzoyl thymine (796 mg, 3.48 mmol), Ph_3P (915 mg, 3.48 mmol), 17 mL of dioxane and DEAD (0.54 mL) in 8 mL dioxane to give **12** 1.0 g, 79%). This product was contaminated with some impurity which was easily removed after deprotection of benzoyl and pivaloyl groups. ^{1}H-NMR ($CDCl_3$): 7.95-6.93 (m, 16 H) arom and H6; 5.29 (m, 1H) H5'; 4.77-4.05 (m, 7H) 2 x $ArCH_2$, H2', H1' and H1"; 3.75 (m, 1H) H4'; 3.63 (d, 2H) H6' and H6"; 2.08 (t, 2H) H3' and H3"; 1.20 (s, 9H) Piv; 1.12 (s, 9H) Piv. ^{13}C-NMR ($CDCl_3$): 177.7, 177.6, 168.9, 162.6, 149.9, 138.6, 137.6, 137.3, 134.8, 131.6, 130.4, 129.0, 128.5, 128.0, 127.8, 127.6, 110.0, 75.6, 73.3, 72.1, 71.7, 68.0, 63.6, 55.2 (br.), 38.8, 38.7, 30.6, 27.1 and 12.3. HR LSIMS calcd. for $C_{42}H_{51}N_2O_9$ $(M + H)^+$ 727.3594, found 727.3582.

1-[4,6-Di-O-benzyl-2,3-dideoxy-2-D-mannityl]thymine (13). The reaction was performed as described for **10** using **12** (900 mg, 1.23 mmol), NaOH (N) (15 mL) and dioxane (15 mL) to give **13** (350 mg, 44%, calculated for two steps). ^{1}H-NMR ($CDCl_3$): 7.41-7.05 (m, 11 H) arom and H6; 4.65 (m, 1H) H2'; 4.58-4.38 (m, 4H) 2 x $ArCH_2$; 3.78 (m, 1H) H5'; 3.72-3.47 (m, 5H) H1', H1", H6', H6" and H4'; 2.06 (m, $J_{2',3'}$ = 7.0 Hz, $J_{3',4'}$ = 3.5 Hz, 1H) H3'; 1.90 (m, $J_{2',3''}$ = 7.0 Hz, $J_{3'',4'}$ = 6.5 Hz, $J_{3',3''}$ = 14.5 Hz, 1H) H3"; 1.78 (s, 3H) $5CH_3$. ^{13}C-NMR ($CDCl_3$): 164.0, 151.8, 139.0, 137.6, 128.5, 128.0, 110.3, 76.7, 73.5, 72.1, 71.5, 70.9, 63.2, 56.3, 30.4 and 12.4. HR LSIMS calcd. for $C_{25}H_{31}N_2O_6$ $(M + H)^+$ 455.2181, found 455.2171.

1-[2,3-Dideoxy-2-D-mannityl]thymine (14). The benzyl groups in **14** were removed under identical reaction conditions as described for **11** using **13** (100 mg, 0.22 mmol), $Pd(OH)_2$, methanol (10 mL) and cyclohexene (5 mL) to give **14** (55 mg, 92%). ^{1}H-NMR (DMSO-d_6): 4.98-4.26 (m, 4H) H2' and 3 x OH; 3.10-3.82 (m, 7H) H6', H6", H5', H4', H1', H1" and 1 x OH; 2.01 (m, 1H) H3'; 1.78 (s, 3H) 5CH$_3$; 1.44 (m, 1H) H3". ^{13}C-NMR (DMSO-d_6): 164.0 (C4); 151.4 (C2); 139.5 (C6); 107.8 (C5); 75.1 (C5'); 69.2 (C4'); 63.2, 61.2 (C6' and C1'); 54.8 (C2'); 33.2 (C3') and 12.3 (5CH$_3$). HR LSIMS calcd. for $C_{11}H_{19}N_2O_6$ (M + H)$^+$ 275.1243, found 275.1250. Anal. ($C_{11}H_{18}N_2O_6$. H_2O.) calculated for C: 45.20, H: 6.90 and N: 9.58 found C: 45.14, H: 6.71 and N: 9.15.

9-[4,6-Di-O-benzyl-1,5-di-O-pivaloyl-2,3-dideoxy-2-D-mannityl]adenine (15). The reaction was performed as described for the general Mitsunobu reaction conditions for 7 using **4** (900 mg, 1.74 mmol), Ph$_3$P (910 mg, 3.49 mmol), adenine (471 mg, 3.49 mmol), dioxane (20 mL) and DEAD (0.54 mL, 3.49 mmol) in 15 mL dioxane to give **15** (700 mg, 64%). Diethyl azodicarboxylate was added over a period of 4 h. ^{1}H-NMR (CDCl$_3$): 8.30 (s, 1H) H2; 7.70 (s, 1H) H8; 7.39-7.05 (m, 10 H) arom; 5.73 (br. s, 2H) NH$_2$; 5.28 (m, $J_{4',5'}$ = 2.9 Hz, 1H) H5'; 4.91 (m, $J_{1',2'}$ = 3.8 Hz, $J_{1'',2'}$ = 7.5 Hz, 1H) H2'; 4.60-4.20 (m, 6H) 2 x ArCH$_2$, H1' and H1"; 3.77 (m, $J_{3',4'}$ = 6.1 Hz, $J_{3'',4'}$ = 6.1 Hz, 1H) H4'; 3.64 (d, $J_{5',6'}$ = $J_{5',6''}$ = 4.4 Hz, 2H) H6' and H6"; 2.37 (t, $J_{2',3'}$ = 6.7 Hz, $J_{2',3''}$ = 6.7 Hz, 2H) H3' and H3"; 1.19 (s, 9H) Piv; 1.08 (s, 9H) Piv. ^{13}C-NMR (CDCl$_3$): 177.8, 177.7 (Piv); 155.4 (C6); 152.7 (C2); 150.0 (C4); 140.1 (C8); 137.4, 137.3, 128.5, 128.4, 128.0, 127.9, 127.7 (arom); 119.9 (C5); 75.5 (C5'); 73.4, 72.0, 71.9 (2 x ArCH$_2$ and C1'); 64.3 (C6'); 52.7 (C2'); 38.9, 38.7 (Piv); 31.7 (C3'); 27.2, 27.0 (Piv). HR LSIMS calcd. for $C_{35}H_{46}N_5O_6$ (M + H)$^+$ 632.3447, found 632.3458.

9-[4,6-Di-O-benzyl-2,3-dideoxy-2-D-mannityl]adenine (16). The pivaloyl groups were removed as described for **10** using **15** (550 mg, 0.87 mmol), NaOH (N) (20 mL) and dioxane (20 mL) to give **16** (320 mg, 79%). This compound was easily crystallized from methanol. ^{1}H-NMR (DMSO-d_6): 8.10 (s, 2H) H2 and H8; 7.39-7.05 (m, 12 H) arom and NH$_2$; 5.03 (t, $J_{1',OH}$ = $J_{1'',OH}$ = 5.2 Hz, 1H) 1'OH; 4.98 (d, $J_{5',OH}$ = 5.2 Hz, 1H) 5'OH; 4.68 (m, 1H) H2'; 4.48-4.20 (m, 4H) 2 x ArCH$_2$; 3.87-3.60 (m, 3H) H1', H1" and H5'; 3.53-3.38 (m, 3H) H6', H6" and H4'; 2.18 (m, 2H) H3' and H3". ^{13}C-NMR (DMSO-d_6): 156.1 (C6); 152.1 (C2); 149.7 (C4); 140.5 (C8); 138.6, 138.5, 128.3, 128.2, 127.8, 127.7, 127.5, 127.4 (arom); 119.2 (C5); 77.5 (C5'); 72.4, 71.6, 70.8 (C4', C6' and 2 x ArCH$_2$); 62.4 (C1'); 55.0 (C2'); 31.6 (C3'). HR LSIMS calcd. for $C_{25}H_{30}N_5O_4$ (M + H)$^+$ 464.2297, found 464.2268.

9-[2,3-Dideoxy-2-D-mannityl]adenine (17). Compound **16** (100 mg, 0.21 mmol) was treated with Pd(OH)$_2$ on C (20%) (100 m), methanol (15 mL) and cyclohexene (5 mL) at reflux overnight. The reaction mixture was filtered. The filtrate was concentrated in vacuo, washed with dichloromethane to give pure **17** (56 mg, 92%). ^{1}H-NMR (DMSO-d_6): 8.09, 8.03 (2 x s, 2H) H2 and H8; 7.10 (br. s, 2H) NH$_2$; 4.95 (t, $J_{1',OH}$ = $J_{1'',OH}$ = 5.2 Hz, 1H) 1'OH; 4.68 (m, 1H) H2'; 4.58 (d, $J_{4',OH}$ = 6.2 Hz, 1H) 4'OH; 4.52 (d, $J_{5',OH}$ = 5.1 Hz, 1H) 5'OH; 4.37 (t, $J_{6',OH}$ = $J_{6'',OH}$ = 5.5 Hz, 1H) 6'OH; 3.83 (m, $J_{1',2'}$ = 6.7 Hz, $J_{1',1''}$ = 11.6 Hz, 1H) H1'; 3.68 (m, $J_{1'',2'}$ = 3.3

Hz, 1H) H1"; 3.52-3.18 (m, 4H) H6', H6", H4' and H5'; 2.34 (m, $J_{2',3'}$ = 8.8 Hz, $J_{3',3''}$ = 13.5 Hz, 1H) H3'; 1.71 (m, $J_{2',3''}$ = 9.9 Hz, 1H) H3". ^{13}C-NMR (DMSO-d_6): 156.0 (C6); 152.0 (C2); 149.6 (C4); 140.6 (C8); 119.0 (C5); 75.2 (C5'); 68.8 (C4'); 63.2, 61.6 (C6' and C1'); 54.8 (C2') and 34.4 (C3'). HR LSIMS calcd. for $C_{11}H_{18}N_5O_4$ $(M + H)^+$ 284.1358, found 284.1367. Anal. ($C_{11}H_{17}N_5O_4$ 0.5 H_2O) calculated for C: 45.20, H: 6.21 and N: 23.96 found C: 45.05, H: 6.45 and N: 23.76.

9-[4,6-Di-O-benzyl-1,5-di-O-pivaloyl-2,3-dideoxy-2-D-mannityl]2-amino-6-chloro purine (18). The reaction was performed as described for the general reaction condition of Mitsunobu reaction for **7** using **4** (800 mg, 1.55 mmol), Ph_3P (815 mg, 3.1 mmol), 6-chloro-2-aminopurine (524 mg, 3.1 mmol), dioxane 20 mL and DEAD (0.479 mL, 3.1 mmol) in 15 mL of dioxane (addition of DEAD wad performed over a period of 4 h) to afford **18** (730 mg, 71%). This product was contaminated with some impurity which was easily removed in the next step). ^{1}H-NMR ($CDCl_3$): 7.68 (s, 1H) H8; 7.41-7.05 (m, 10 H) arom; 5.28 (m, $J_{5',6'}$ = 3.6 Hz, $J_{5',6''}$ = 3.7 Hz, 1H) H5'; 5.12 (br. s, 2H) NH_2; 4.78 (m, $J_{2',3'}$ = 7.0 Hz, $J_{2',3''}$ = 7.0 Hz, 1H) H2'; 4.60 (d, 2H) $ArCH_2$, 4.51 (s, 2H) $ArCH_2$; 4.39 (dd, $J_{1',2'}$ = 7.6 Hz, $J_{1',1''}$ = 11.8 Hz, 1H) H1'; 4.18 (dd, $J_{1'',2'}$ = 3.7 Hz, 1H) H1"; 3.72 (m, $J_{4',5'}$ = 2.6 Hz, 1H) H4'; 3.62 (d, 2H) H6' and H6"; 2.27 (t, $J_{3',4'}$ = 6.6 Hz, $J_{3'',4'}$ = 6.6 Hz, 2H) H3' and H3"; 1.22 (s, 9H) Piv; 1.08 (s, 9H) Piv. ^{13}C-NMR ($CDCl_3$): 177.7, 177.6 (Piv); 158.7 (C2); 153.6 (C4); 151.2 (C6); 141.6 (C8); 137.7, 137.2, 130.9, 128.8, 128.4, 127.9, 127.7 (arom); 125.4 (C5); 75.5 (C5'); 71.9 (C4'); 73.4, 72.2 (2 x $ArCH_2$); 68.0, 64.0 (C6' and C1'); 52.4 (C2'); 38.9, 38.7 (Piv); 31.6 (C3'); 27.1 and 27.0 (Piv). HR LSIMS calcd. for $C_{35}H_{45}N_5O_6Cl$ $(M + H)^+$ 666.3058, found 666.3047.

9-[4,6-Di-O-benzyl-1,5-di-O-pivaloyl-2,3-dideoxy-2-D-mannityl]guanine (19). Compound **18** (470 mg, 0.7 mmol) was treated with CF_3COOH and H_2O (8 : 2, 10 mL) at room temperature for 48 h. The solvent was removed in vacuo, co-evaporated with toluene. The residue was treated with NH_4OH (2 mL) in methanol (5 mL), concentrated in vacuo. The residue was subjected to column chromatography to give **19** (260 mg, 57%). ^{1}H-NMR ($CDCl_3$): 11.98 (br. s, 1H) NH; 7.44-7.18 (m, 11 H) arom and H8; 6.10 (br. s, 2H) NH_2; 5.30 (m, 1H) H5'; 4.75 (m, 1H) H2'; 4.63-4.28 (m, 5H) 2 x $ArCH_2$ and H1'; 4.18 (dd, $J_{1'',2'}$ = 3.7 Hz, $J_{1',1''}$ = 11.8 Hz, 1H) H1"; 3.72 (m, 1H) H4'; 3.63 (d, $J_{5',6'}$ = $J_{5',6''}$ = 5.2 Hz, 2H) H6' and H6"; 2.21 (m, 2H) H3' and H3"; 1.21 (s, 9H) Piv; 1.09 (s, 9H) Piv. ^{13}C-NMR ($CDCl_3$): 177.9, 177.7 (Piv); 159.2 (C6); 153.2 (C2); 151.9 (C4); 138.0 (C8); 137.8, 137.5, 128.5, 128.0, 127.8 (arom); 117.3 (C5); 75.5, 73.5, 72.3, 72.2, 68.2, 64.3 (C5', C4', C6', C1' and 2 x $ArCH_2$); 52.0 (C2'); 39.0, 38.8 (Piv); 32.1 (C3'); 27.2 and 27.1 (Piv). HR LSIMS calcd. for $C_{35}H_{46}N_5O_7$ $(M + H)^+$ 648.3397, found 648.3373.

9-[4,6-Di-O-benzyl-2,3-dideoxy-2-D-mannityl]guanine (20). The pivaloyl groups were removed as described for **10** using **19** (200 mg, 0.3 mmol), NaOH (N) (10 mL) and dioxane (10 mL) to give **20** (140 mg, 95%). ^{1}H-NMR (DMSO-d_6): 10.53 (br. s; 1H) NH; 7.69 (s, 1H) H8; 7.38-7.18 (m, 10 H) arom; 6.41 (br. s, 2H) NH_2;

5.05 (t, $J_{1',OH} = J_{1'',OH}$ = 4.8 Hz, 1H) 1'OH; 4.85 (d, $J_{5',OH}$ = 5.1 Hz, 1H) 5'OH; 4.53-4.12 (m, 5H) H2' and 2 x $ArCH_2$; 3.83-3.34 (m, 6H) H1', H1", H6', H6", H5' and H4'; 2.11 (m, 2H) H3' and H3". ^{13}C-NMR (DMSO-d_6): 157.0, 153.3, 151.1, 138.5, 136.9; 128.3, 128.2, 127.8, 127.6, 127.4, 116.8, 77.4, 72.4, 71.6, 70.9, 70.7, 62.3, 54.2 and 31.4. HR LSIMS calcd. for $C_{25}H_{30}N_5O_5$ $(M + H)^+$ 480.2246, found 480.2260.

9-[2,3-Dideoxy-2-D-mannityl]guanine (21). A mixture of **20** (65 mg, 0.13 mmol), $Pd(OH)_2$ on C (20%) (65 mg), methanol (9 mL) and cyclohexene (3 mL) was kept at reflux temperature overnight. The reaction mixture was filtered. The filtrate was concentrated in vacuo, washed succesively with hexane and dichloromethane to give **21** (35 mg, 87%). ^{1}H-NMR (DMSO-d_6): 10.59 (br. s, 1H) NH; 7.66 (s, 1H) H8; 6.44 (br. s, 2H) NH_2; 4.97 (t, $J_{1',OH} = J_{1'',OH}$ = 5.5 Hz, 1H) 1'OH; 4.58 (d, J = 6.2 Hz, 1H), 4.55 (d, J = 5.0 Hz, 1H) 4'OH and 5'OH; 4.51 (m, 1H) H2'; 4.42 (t, $J_{6',OH} = J_{6'',OH}$ = 4.8 Hz, 1H) 6'OH; 3.73-3.18 (m, 6H) H1', H1", H6', H6", H5' and H4'; 2.25 (m, 1H) H3'; 1.61 (m, 1H) H3". ^{13}C-NMR (DMSO-d_6): 157.0 (C6); 153.3 (C2); 151.1 (C4); 137.0 (C8); 116.9 (C5); 75.3 (C5'); 68.6 (C4'); 63.2, 61.5 (C6' and C1'); 53.8 (C2') and 34.4 (C3'). HR LSIMS calcd. for $C_{11}H_{18}N_5O_5$ $(M + H)^+$ 300.1307, found 300.1316. Anal. ($C_{11}H_{17}N_5O_5$. 2 H_2O) calculated for C: 39.39, H: 6.31 and N: 20.89 found C: 39.14, H: 5.98 and N: 20.45. m.p 200-205 °C (crystallize from MeOH and CH_2Cl_2).

9-[4,6-Di-O-benzyl-1,5-di-O-pivaloyl-2,3-dideoxy-2-D-glucityl]adenine (22). The reaction was performed as described for the general reaction conditions of Mitsunobu reaction for **7** using **6** (1.03 g, 2.0 mmol), Ph_3P (1.05 g, 4.0 mmol), adenine (540 g, 4.0 mmol), dioxane (20 mL) and DEAD (0.619 mL, 4.0 mmol) in 20 mL dioxane (addition of DEAD was performed over a period of 4 h) to give **22** (660 mg, 52%). ^{1}H-NMR ($CDCl_3$): 8.29 (s, 1H) H2; 7.41-7.09 (m, 11 H) arom and H8; 5.66 (br. s, 2H) NH_2; 5.33 (m, 1H) H5'; 4.80 (m, 1H) H2'; 4.62-4.08 (m, 6H) 2 x $ArCH_2$, H1' and H1"; 3.53 (dd, $J_{5',6'}$ = 5.6 Hz, $J_{6',6''}$ = 10.2 Hz, 1H) H6'; 3.42 (dd, $J_{5',6''}$ = 5.7 Hz, 1H) H6"; 3.30 (m, $J_{4',5'}$ = 3.1 Hz, 1H) H4'; 2.70 (m, $J_{2',3'}$ = 11.3 Hz, $J_{3',3''}$ = 14.6 Hz, 1H) H3'; 2.01 (m, $J_{2',3''}$ = 6.0 Hz, $J_{3'',4'}$ = 10.1 Hz, 1H) H3"; 1.23 (s, 9H) Piv and 1.02 (s, 9H) Piv. ^{13}C-NMR ($CDCl_3$): 177.4 (Piv); 155.4 (C6); 152.7 (C2); 150.0 (C4); 140.7 (C8); 137.7, 137.6, 128.7, 128.6, 128.4, 128.1, 127.8, 127.6 (arom); 120.2 (C5); 73.9 (C5'); 73.3, 71.8 (2 x $ArCH_2$); 70.9 (C4'); 68.2, 65.0 (C6' and C1'); 52.8 (C2'); 39.0, 38.7 (Piv); 30.6 (C3'); 27.3 and 27.0 (Piv). HR LSIMS calcd. for $C_{35}H_{46}N_5O_6$ $(M + H)^+$ 632.3447, found 632.3459.

9-[4,6-Di-O-benzyl-2,3-dideoxy-2-D-glucityl]adenine (23). The removal of pivaloyl groups was performed as described for **10** using **22** (450 mg, 0.71 mmol), NaOH (N) (10 mL) and dioxane (10 mL) to give **23** (270 mg, 82%). ^{1}H-NMR ($CDCl_3$): 8.10 (s, 1H) H2; 7.40-7.17 (m, 11 H) arom and H8; 6.11 (br. s, 2H) NH_2; 4.71 (m, 1H) H2'; 4.53-4.20 (m, 4H) 2 x $ArCH_2$; 3.98 (dd, $J_{1',2'}$ = 5.8 Hz, $J_{1',1''}$ = 12.6 Hz, 1H) H1'; 3.92 (m, 1H) H5'; 3.89 (dd, $J_{1'',2'}$ = 2.6 Hz, 1H) H1"; 3.54 (dd, $J_{5',6'}$ = 4.5 Hz, $J_{6',6''}$ = 9.5 Hz, 1H) H6'; 3.49 (dd, $J_{5',6''}$ = 4.4 Hz, 1H) H6"; 3.21 (m, $J_{4',5'}$ = 4.3 Hz, 1H) H4'; 2.48 (m, $J_{2',3'}$ = 10.9 Hz, $J_{3',3''}$ = 14.7 Hz, 1H) H3'; 2.08 (m, $J_{2',3''}$ = 2.3 Hz, $J_{3'',4'}$ = 9.6 Hz, 1H) H3". ^{13}C-NMR ($CDCl_3$): 155.3 (C6); 152.3 (C2); 149.3 (C4); 140.7 (C8); 137.7, 137.5, 128.5, 128.4, 128.2, 127.8 (arom); 119.4 (C5); 75.8 (C5'); 71.4 (C4'); 73.5, 72.1 (2 x $ArCH_2$); 70.8, 64.5 (C1' and C6'); 55.9 (C2') and 31.0 (C3'). HR LSIMS calcd. for $C_{25}H_{30}N_5O_4$ $(M + H)^+$ 464.2297, found 464.2289.

9-[2,3-Dideoxy-2-D-glucityl]adenine (24). A mixture of **23** (235 mg, 0.5 mmol), $Pd(OH)_2$ on C(20%) (235 mg), methanol (15 mL) and cyclohexene (5 mL) was kept at reflux overnight. The reaction mixture was filtered. The filtrate was concentrated in vacuo, washed successively with hexane and dichloromethane to give **24** (135 mg, 94%). ^{1}H-NMR (DMSO-d_6): 8.10, 8.00 (2 x s, 2H) H2 and H8; 7.18 (br. s, 2H) NH_2; 4.98 (t, $J_{1',OH}$ = $J_{1'',OH}$ = 5.4 Hz, 1H) 1'OH; 4.69 (m, 1H) H2'; 4.63 (d, $J_{5',OH}$ = 6.0 Hz, 1H) 5'OH; 4.49 (d, $J_{4',OH}$ = 4.8 Hz, 1H) 4'OH; 4.29 (t, $J_{6',OH}$ = $J_{6'',OH}$ = 5.1 Hz, 1H) 6'OH; 3.88 (m, $J_{1',2'}$ = 7.0 Hz, $J_{1',1''}$ = 11.3 Hz, 1H) H1'; 3.68 (m, $J_{1'',2'}$ = 4.5 Hz, 1H) H1"; 3.48-3.15 (m, 3H) H6', H6" and H5'; 2.92 (m, 1H) H4'; 2.39 (m, 1H) H3' and 1.66 (m, 1H) H3". ^{13}C-NMR (DMSO-d_6): 156.0 (C6); 152.0 (C2); 149.8 (C4); 140.8 (C8); 119.3 (C5); 75.2 (C5'); 67.8 (C4'); 63.2 (both C6' and C1'); 55.0 (C2') and 33.7 (C3'). HR LSIMS calcd. for $C_{11}H_{18}N_5O_4$ $(M + H)^+$ 284.1358, found 284.1359. Anal. ($C_{11}H_{17}N_5O_4$. 0.5 H_2O.) calculated for C: 45.20, H: 6.21 and N: 23.96 found C: 45.70, H: 6.26 and N: 23.46.

9-[4,6-Di-O-benzyl-1,5-di-O-pivaloyl-2,3-dideoxy-2-D-glucityl]2-amino-6-chloropurine (25). The reaction was performed as described for the general reaction conditions of Mitsunobu reaction for 7 using **6** (1.2 g, 2.33 mmol), Ph_3P (1.22 g, 4.66 mmol), 6-chloro-2-aminopurine (790 mg, 4.66 mmol), dioxane 30 mL and DEAD (0.72 mL, 4.66 mmol) in 30 mL dioxane (the addition of DEAD was performed over a period of 4 h) to give **25** (1.2 g, 77%). This compound was contaminated with some impurity which was easily removed in the next step. ^{1}H-NMR ($CDCl_3$): 7.30-6.98 (m, 11 H) arom and H8; 5.18 (m, 1H) H5'; 5.12 (br. s, 2H) NH_2; 4.60 (m, 1H) H2'; 4.50-3.90 (m, 6H) 2 x $ArCH_2$, H1' and H1"; 3.42 (dd, $J_{5',6'}$ = 5.4 Hz, $J_{6',6''}$ = 10.2 Hz, 1H) H6'; 3.36 (dd, $J_{5',6''}$ = 5.6 Hz, 1H) H6"; 3.20 (m, 1H) H4'; 2.45 (m, 1H) H3', 1.89 (m, 1H) H3"; 1.20 (s, 9H) Piv and 1.11 (s, 9H) Piv. HR LSIMS calcd. for $C_{35}H_{45}N_5O_6Cl$ $(M + H)^+$ 666.3058, found 666.3056.

9-[4,6-Di-O-benzyl-1,5-di-O-pivaloyl-2,3-dideoxy-2-D-glucityl]guanine (26). Compound **25** 1.1 g, 1.65 mmol) was treated with 80% aqueous CF_3COOH (25 mL) for 48 h. The solvent was removed in vacuo, co-evaporated with toluene. The residue was treated with NH_4OH (2 mL) in methanol (6 mL). The solvent was removed in vacuo. The residue was subjected to column chromatography to give **26** (600 mg, 40%, yield was calculated for two steps). ^{1}H-NMR ($CDCl_3$): 11.95 (br. s, 1H) NH; 7.41-7.18 (m, 11 H) arom and H8; 6.18 (br. s, 2H) NH_2; 5.35 (m, $J_{4',5'}$ = 2.9 Hz, 1H) H5'; 4.80 (m, 1H) H2'; 4.68-4.38 (m, 4H) $ArCH_2$ and H1'; 4.25 (dd, $J_{1'',2'}$ = 4.3 Hz, $J_{1',1''}$ = 11.4 Hz, 1H) H1"; 4.18 (d, 1H) $ArCH_2$; 3.56 (dd, $J_{5',6'}$ = 5.6 Hz, $J_{6',6''}$ = 10.5 Hz, 1H) H6'; 3.53 (dd, $J_{5',6''}$ = 5.4 Hz, 1H) H6"; 3.38 (m, 1H) H4'; 2.49 (m, $J_{2',3'}$ = 11.7 Hz, $J_{3',3''}$ = 14.3 Hz, 1H) H3'; 2.00 (m, $J_{3'',4'}$ = 10.3 Hz, 1H) H3"; 1.21 (s, 9H) Piv and 1.11 (s, 9H) Piv. ^{13}C-NMR ($CDCl_3$): 178.0, 177.8 (Piv); 159.3 (C6); 153.3 (C2); 152.1 (C4); 137.2 (C8); 137.9, 137.7, 128.6, 128.4, 128.0, 127.7 (arom); 117.6 (C5); 74.6 (C5'); 73.4, 72.3 (2 x $ArCH_2$); 71.4 (C4'); 68.5, 65.4 (C1' and C6'); 51.7 (C2'); 39.0, 38.9 (Piv); 31.4 (C3'); 27.3 and 27.2 (Piv). HR LSIMS calcd. for $C_{35}H_{46}N_5O_7$ $(M + H)^+$ 648.3397, found 648.3400.

9-[4,6-Di-O-benzyl-2,3-dideoxy-2-D-glucityl]guanine (27). The reaction was performed as described for **10** using **26** (550 mg, 0.84 mmol), NaOH (N) (20 mL) and dioxane (20 mL, during work up it was extracted with hot ethyl acetate) to give **27** (380 mg, 93%). ^{1}H-NMR (DMSO-d_6): 10.62 (br. s, 1H) NH; 7.60 (s, 1H) H8; 7.39-7.20 (m, 10 H) arom; 6.41 (br. s, 2H) NH_2; 5.02 (t, $J_{1',OH} = J_{1'',OH}$ = 5.1 Hz, 1H) 1'OH; 4.96 (d, $J_{5',OH}$ = 4.8 Hz, 1H) 5'OH; 4.52 (m, 1H) H2'; 4.49-4.10 (m, 4H) 2 x $ArCH_2$; 3.80 (m, 1H) H5'; 3.78-3.30 (m, 4H) H1', H1", H6' and H6"; 3.08 (m, $J_{4',5'}$ = 3.3 Hz, 1H) H4'; 2.28 (m, $J_{3',3''}$ = 14.0 Hz, 1H) H3'; 1.92 (m, $J_{3'',4'}$ = 10.3 Hz, 1H) H3". ^{13}C-NMR (DMSO-d6): 157.0 (C6); 153.3 (C2); 151.4 (C4); 138.7, 138.4 (arom); 136.9 (C8); 128.2, 127.7, 127.5 (arom); 116.9 (C5); 76.7 (C5'); 72.4, 71.5 (2 x $ArCH_2$ and C6'); 70.2 (C4'); 63.5 (C1'); 53.7 (C2') and 30.8 (C3'). HR LSIMS calcd. for $C_{25}H_{30}N_5O_5$ $(M + H)^+$ 480.2246, found 480.2232.

9-[2,3-Dideoxy-2-D-glucityl]guanine (28). A mixture of 27 (170 mg, 0.35 mmol), $Pd(OH)_2$ on C (20%) (170 mg), methanol (10 mL) and cyclohexene (3 mL) was kept at reflux temperature overnight. The reaction mixture was filtered. The filtrate was concentrated in vacuo, washed successively with hexene and dichloromethane to give **28** (96 mg, 91%). ^{1}H-NMR (DMSO-d_6): 10.40 (br. s, 1H) NH; 7.81 (s, 1H) H8; 6.23 (br. s, 2H) NH_2; 4.96 (t, $J_{1',OH} = J_{1'',OH}$ = 5.0 Hz, 1H) 1'OH; 4.57 (d, $J_{4',OH}$ = 6.0 Hz, 1H) 4'OH; 4.52 (d, $J_{5',OH}$ = 5.0 Hz, 1H) 5'OH; 4.49 (m, 1H) H2'; 4.35 (t, $J_{6',OH} = J_{6'',OH}$ = 5.3 Hz, 1H) 6'OH; 3.75 (m, $J_{1',2'}$ = 6.6 Hz, $J_{1',1''}$ = 11.0 Hz, 1H) H1'; 3.63 (m, $J_{1'',2'}$ = 4.7 Hz, 1H) H1"; 3.49-3.17 (m, 3H) H6', H6" and H5'; 2.98 (m, 1H) H4'; 2.28 (m, $J_{2',3'}$ = 11.7 Hz, $J_{3',3''}$ = 14.3 Hz, 1H) H3'; 1.63 (m, $J_{3'',4'}$ = 11.0 Hz, 1H) H3". ^{13}C-NMR (DMSO-d_6): 157.0 (C6); 153.2 (C2); 151.4 (C4); 137.0 (C8); 116.8 (C5); 75.2 (C5'); 67.7 (C4'); 63.4, 63.2 (C1' and C6'); 53.9 (C2') and 33.8 (C3'). HR LSIMS calcd. for $C_{11}H_{18}N_5O_5$ $(M + H)^+$ 300.1307, found 300.1290. Anal. ($C_{11}H_{17}N_5O_5$. 1 H_2O) calculated for C: 41.64, H: 6.04 and N: 22.07 found C: 41.58, H: 5.92 and N: 22.03. m.p 205-207 °C (crystallize from MeOH).

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