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SYNTHESIS OF PROTECTED D-ALTRITOL NUCLEOSIDES AS BUILDING BLOCKS FOR OLIGONUCLEOTIDE SYNTHESIS

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Abstract: D-Altritol nucleosides with an adenine and uracil base moiety were obtained by nucleophilic opening of the epoxide ring of 1,5:2,3-dianhydro-4,6-*O*-benzylidene-D-allitol using the sodium salt of the above mentioned bases. The use of a 2-trimethylsilylethyl protecting group for the O^6-function of the guanine base offers a useful compromise between stability and acceptable alkylation yields of the N^9-position if the guanine base. The cytosine nucleoside was synthesized starting from the uracil congener. The 3'-hydroxyl function was protected with a benzoyl group.

INTRODUCTION

After 20 years of intensive research, the first antisense oligonucleotide has been approved for clinical use, [1] and is a phosphorothioate oligonucleotide from the first generation of modified oligonucleotides. An intensive research topic in the antisense field is the development of conformationally restricted oligomers, able to inhibit gene expression by blocking the function of messenger RNA [2]. During recent years, we have developed hexitol nucleic acids (HNA) for this purpose [3]. Such modified oligonucleotides are built up from a phosphorylated 1,5-anhydrohexitol backbone and natural nucleobases. HNA hybridize strongly and selectively with their RNA complements [3]. The synthesis of the nucleotide building blocks of HNA was carried out starting from D-glucose [4]. In an effort further to increase the hybridization properties, we also studied D-altritol nucleic acids (ANA) [5]. They differ from HNA by the presence of a supplementary hydroxyl group in the 3'-α-position. Melting point data demonstrate that ANA has indeed better hybridization properties than HNA [5]. The synthesis of the D-altritol building blocks is, however, more difficult than the synthesis of the 1,5-anhydrohexitol building blocks [4], due to the presence of the 3'-hydroxyl group which needs selective protection. Here we describe the synthesis of the protected D-altritol nucleosides with a uracil, adenine, cytosine and guanine base moiety. These building blocks are being used succesfully for oligonucleotide synthesis [5].

RESULTS

1,5:2,3-Dianhydro-4,6-*O*-benzylidene-D-allitol **1** was prepared from commercially available tetraacetyl-α-D-bromoglucose in 5 steps (54% overall yield), basically according to the procedure described by Kocienski [6]. The *altro*-hexitol nucleoside building blocks were prepared following a common strategy [7]. This is first exemplified by synthesis of the uracil phosphoramidite (Scheme 1). The uracil *altro*-hexitol derivative **2**

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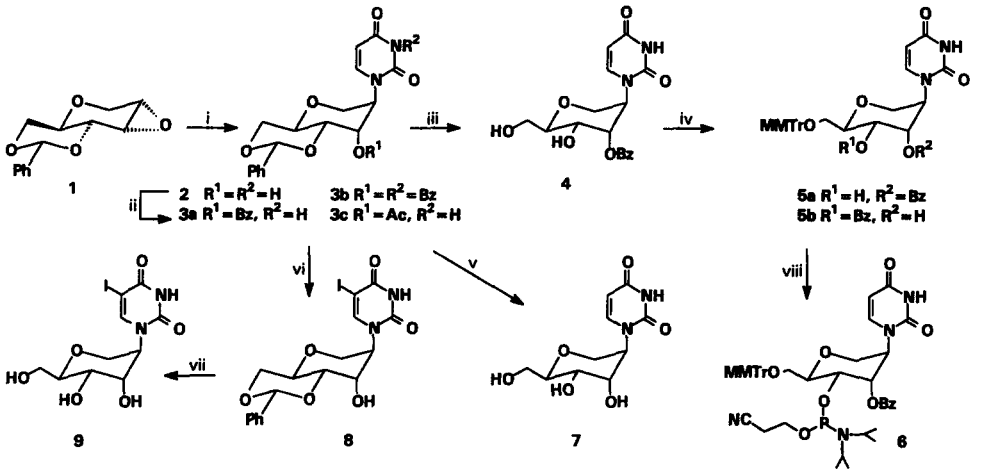
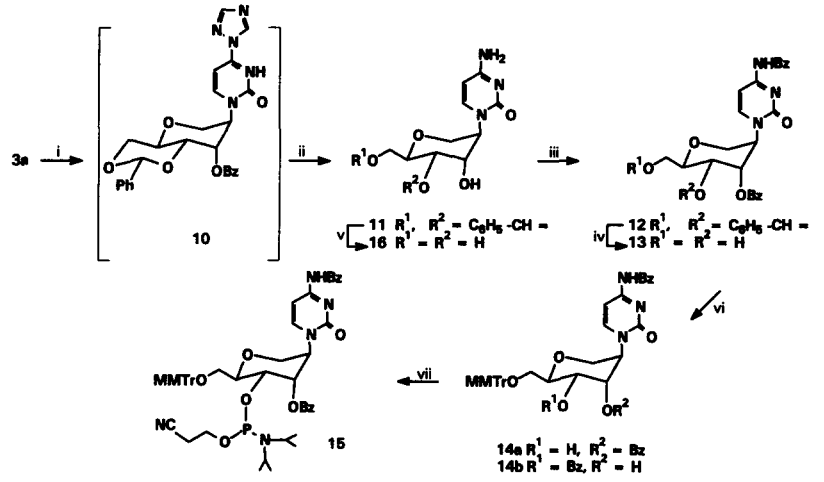


i: uracil, NaH, DMF (86%); ii: BzCl, DMAP, pyr. (70% of 3a and 10% of 3b); iii: 90% TFA; iv: MMTrCl, $AgNO_3$, coll., DMF (56% for iii and iv); v: 80% HOAc (82%); vi: I_2, CAN, CH_3CN (82%); vii: 80% HOAc (73%); viii: DIEA, CH_2Cl_2, $(iPr)_2N(CN)PCl$ (94%).

Scheme 1

was prepared by nucleophilic opening of the epoxide **1** by the sodium salt of uracil in DMF at 120 °C [8]. The use of a large excess (3 equiv) of base increased the yield to 86%, with not more than 5% of the less polar O^2-alkylation product formed. This side compound was easily separated from **2** by chromatography. Functionalization of the *altro*-hexitol derivative **2** into the required building block for (6' → 4') oligonucleotide synthesis mandates the choice of a suitable protecting group for the additional 3'-hydroxyl function. The choice thereof is governed by two opposite imperatives: the protecting group should be stable enough to allow for 4',6'-functionalization of the nucleosides and oligonucleotide assembly (without isomerisation reaction), but at the same time it should be labile enough to be removed quantitatively under mild conditions upon oligonucleotide deprotection. The *tert*-butyldimethylsilyl group is most commonly used to protect the 2'-OH function of ribonucleosides for RNA synthesis and can be introduced with good regioselectively on the primary hydroxyl-protected nucleoside [9]. Unfortunately, attempts to use a similar strategy for regioselective 3'-*O*-silylation of the 1,5-anhydro-D-*altro*-hexitol nucleoside derivative (involving benzylidene deprotection of **2**, 6'-*O*-monomethoxytritylation and followed by silylation with only a slight excess of *tert*-butyldimethylsilyl chloride) proved to be inefficient [10]. Treatment of the benzylidene protected *altro*-nucleoside **2** with TBDMSCl (3.5 equiv) in the presence of imidazole (4.5 equiv) in DMF [11] at 60 °C proceeded in very low yield (11%) due to steric hindrance. Therefore, and in view of the difficulties encountered during removal of the *tert*-butyldimethylsilyl group in the mannitol nucleic acids (MNA) series [12], we selected for the benzoyl group as a 3'-*O*-protecting group likely to fulfil the criteria of straightforward introduction as well as removal. Moreover, this group has been successfully used by Eshenmoser in the synthesis of pyranosyl-RNA [13]. Treatment of **2** with a large excess of benzoyl chloride at 60 °C in pyridine in

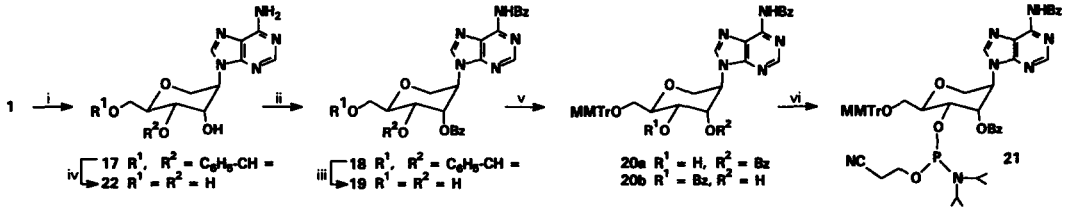
the presence of a catalytic amount of 4-dimethylaminopyridine afforded **3a** in satisfactory yield along with 10% of the base protected analogue **3b**. Nevertheless, a major drawback of the 3'-*O*-benzoyl group is its migration from the 3'-axial to the 4'-equatorial position during deprotection of the benzylidene group, mandating a change of the conditions for benzylidene cleavage and subsequent monomethoxytritylation. Whereas treatment of compound **3a** with 80% aqueous acetic acid at 80 °C provided a mixture of **4** and its 4'-*O*-benzoyl regioisomer, a short time treatment of **3a** with 90% aqueous trifluoroacetic acid at ambient temperature followed by evaporation below 40 °C and by precipitation in diethyl ether afforded the expected crude 3'-*O*-benzoylated derivative **4**. Benzoyl migration from the 3'- to the 4'-position, which occurred very rapidly upon monomethoxytritylation in pyridine in the presence of 4-dimethylaminopyridine, was avoided using silver nitrate as the catalyst [9,14] in DMF. Only a trace of by-product resulting from 4',6'-bis-*O*-monomethoxytritylation was detected. Flash chromatography using non-protic solvents allowed us to minimize benzoyl migration on silica gel and to isolate the expected **5a** (56% from **3a**). The more polar compound **5b** resulting from isomerization of **5a** was only detected when running the chromatographic separation over a longer time span (more than 2 hours). Compound **5a** was converted into the corresponding ß-cyanoethyl-*N,N*-diisopropyl-phosphoramidite **6** by a general procedure [15] in 80% yield. Synthesis of the cytosine altro-nucleoside building block **15** (Scheme 2) was performed according to the same general route as used for the synthesis of **6**, with the following modifications: since nucleophilic opening of 1,5:2,3-dianhydro-4,6-*O*-benzylidene-D-allitol **1** by the sodium salt of cytosine was unsuccessful (5% of O^2-alkylation product was isolated and no N^1-alkylation was observed), the cytosine *altro*-nucleoside **11** was prepared from the uracil derivative **3a** via ammonia treatment of the 1,2,4-triazolyl intermediate **10** [16]. Treatment of **11** with an excess of benzoyl chloride and catalytic DMAP at 70 °C in pyridine, followed by *in situ* mono-*N*-debenzoylation afforded **12** in 67% yield from **3a**. Benzylidene cleavage and subsequent monomethoxytritylation as for the synthesis of **5a**, gave **14a** (51% yield from **12**), and a small quantity of its regioisomer **14b**. Phosphitylation following standard procedures afforded 91% of the amidite **15**. In contrast to the pyrimidine series, the nucleophilic opening of epoxide **1** by the sodium salt (3 equiv) of adenine in DMF at 130 °C was highly regioselective, with no trace of the more polar by-product resulting from N^7-alkylation detected (Scheme 3). This is in contrast to displacement of a 2'-α-tosylate, which was used for the synthesis of the adenine nucleoside in the 1,5-anhydro-3-deoxy-D-arabino-hexitol series [17]. The desired product **17** was isolated in 73% yield. Similarly to the preparation of **12**, perbenzoylation of **17** followed by *in situ* mono-*N*-debenzoylation afforded **18** (77%). Benzylidene cleavage and monomethoxytritylation were performed in the same way as described for **5a**, affording **20a** (79% from **18**) with a minor quantity of the regioisomer **20b**. Phosphitylation of **20a** afforded the adenine phosphoramidite **21** (80% yield). Preparation of the *altro*-hexitol building block with a guanine base moiety proved to be more



i: $POCl_3$, triazole, Et_3N, pyr.; ii: NH_3, H_2O; iii: BzCl, DMAP, pyr and NH_3,H_2O (67% total yield for i to iii); iv: 90% TFA; v: 80% HOAc (66%); vi: MMTrCl, $AgNO_3$, coll., DMF, (51% for iv and vi); vii: DIEA, CH_2Cl_2, $(iPr)_2$ N(CN)PCl (91%)

Scheme 2

problematic (Scheme 4). Opening of the epoxide **1** by the sodium (or lithium) salt of 2-amino-6-chloropurine in DMF at 90 °C (method A) yielded 40% of **23** and 10% of **24**. The reaction of **1** with 2-amino-6-chloropurine in THF in the presence of triethylaluminium, according to a procedure reported recently by Griengl and co-workers [18] (method B) afforded **25** as the major product resulting from N^7-alkylation. The displacement of chlorine in compound **23** by sodium hydroxide assisted by 1,4-diazabicyclo[2.2.2]octane [19], afforded the guanine analogue **26** in 78% yield. This isobutyryl group whas then introduced on the 2-amino function of **26**, via transient protection using 5 equivalents of bis-trimethylsilylacetamide [15,16]. The removal of the stable 3'-*O*-trimethylsilyl group was carried out by treatment with 1M tetrabutylammonium fluoride in THF or with 1 M potassium fluoride dihydrate in ethanol, affording after standard workup compound **27**. Treatment of **27** with benzoyl chloride in pyridine in the presence of DMAP yielded **28** (40%) together with **29**. The transamidation could be avoided when the benzoylation reaction is carried out with benzoyl cyanide in acetonitrile [20] in the presence of tri-n-butylamine. Compound **28** is obtained in 72% yield as the only product. Benzylidene

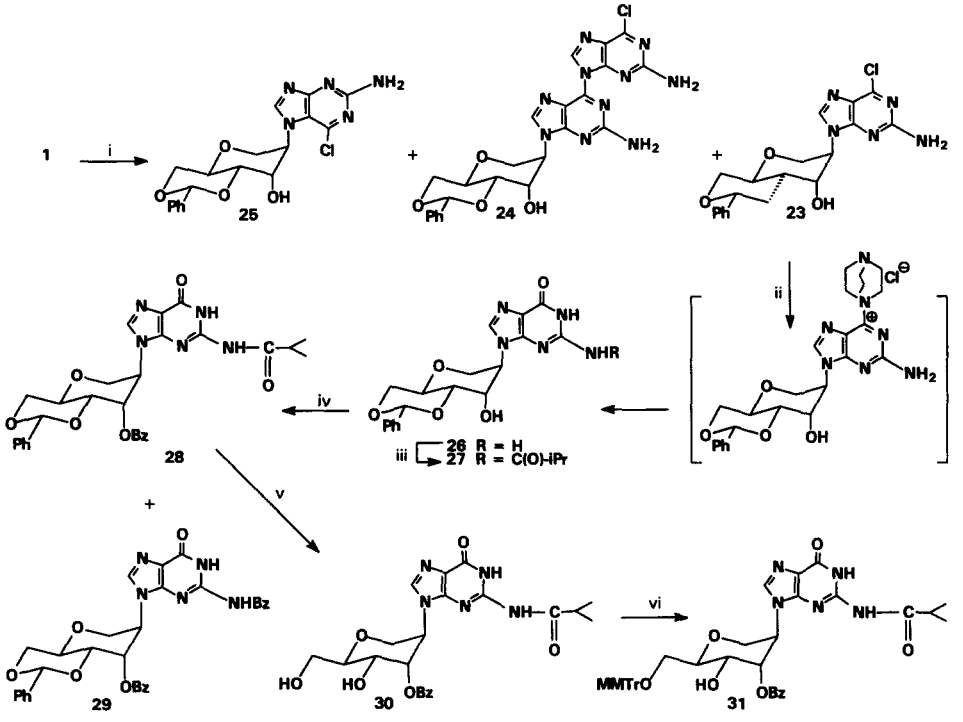


i: NaH, adenine, DMF (72%); ii: BzCl, DMAP, pyr. and NH_3, H_2O (77%); iii: 90% TFA; iv: 80% HOAc (61%); v: MMTrCl, $AgNO_3$, coll., DMF (79% for iii and v); vi: DIEA, CH_2Cl_2 $(iPr)_2N(CN)PCl$ (80%)

Scheme 3

cleavage with trifluoroacetic acid followed by monomethoxytritylation using silver nitrate as the catalyst in DMF gave **31** in 47% yield, which was used, in its phosphitylated form, as building block for oligonucleotide synthesis.

However, because of the problems with scaling up the first step of this synthetic scheme (poor reproducibility on scales larger than 2 mmol) we developed a second route, making use of the more base labile N^2-dimethylformamidine (dmf) [21-23] protecting group. Reaction of **1** with the lithium salt of N^2-acetyl-2-amino-6-[2-(trimethylsilyl)ethoxy]purine [24] (Scheme 5) in DMF at 130-140 °C afforded a mixture of **32** and its N^2-

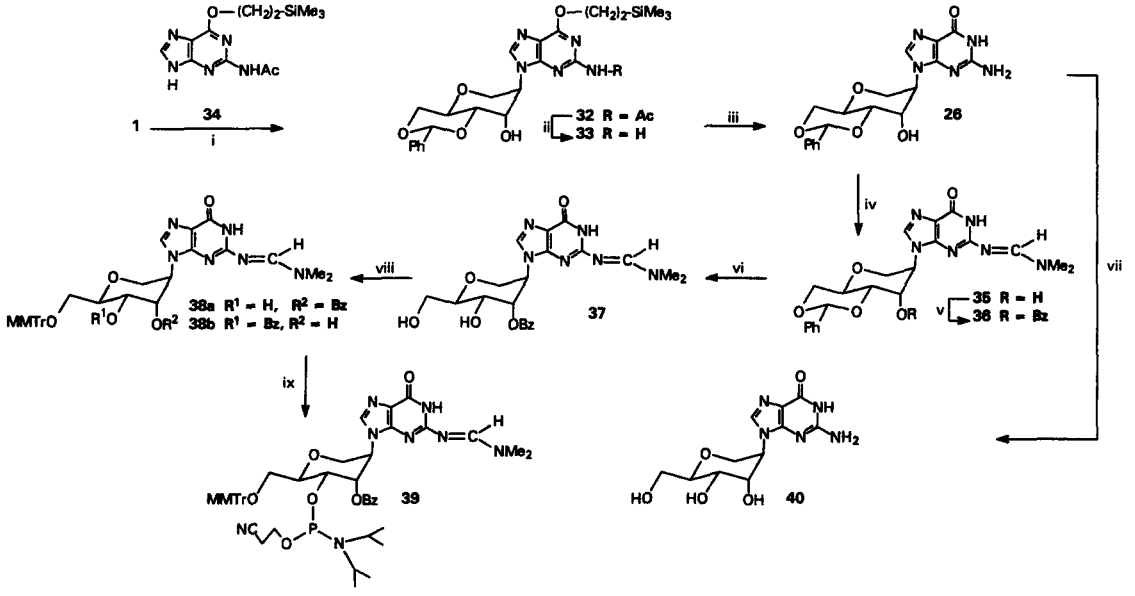


i: 2-amino-6-chloropurine, NaH, DMF (40% of 23); ii: DABCO, DMF and NaOH 1M, CH_2Cl_2 (78%); iii: BSA, pyr. and $(iPrCO)_2O$ and 1M KF, EtOH (72%); iv: BzCN,Bu_3N, CH_3CN (72%); v: 90% TFA; vi: MMTrCl, $AgNO_3$, Coll., DMF (47% for v and vi)

Scheme 4

deacetylated derivative **33**. Compound **32** was hydrolized using sodium hydroxide in dioxane to afford **33** in a total yield of 45% from **1**. This reaction sequence can be performed in large scale and is highly reproducable. The protected guanine base **34** was prepared from N^2,N^9-diacetylguanine [25] and 2-(trimethylsilyl)ethanol via Mitsunobu reaction as previously described for the preparation of the O^6-[2-(p-nitrophenyl)ethyl]guanine derivative [26]. N^9-deacetylation was carried out using silica gel. O^6-deprotection of **33** was achieved with 0.5 M tetrabutylammonium fluoride to afford **26** (78%) and the N^2-protecting group was introduced using *N,N*-dimethylformamide diethylacetal in DMF. Compound **35** was benzoylated with benzoyl cyanide and tri-n-butylamine in DMF [27] to yield **36** (78%) which was subjected to benzylidine cleavage. Benzylidene cleavage

with 90% trifluoroacetic acid at room temperature results in significant benzoyl migration from the 3'-axial to the 4'-equatorial position as well as partial cleavage of the dmf group. These side reactions could be suppressed adequately by performing the reaction at -15 °C and quick evaporation of TFA/CH_2Cl_2 in vacuo at 4 °C, followed by precipitation of crude **37** in diethyl ether. The obtained **37** was 6'-*O*-monomethoxytritylated to afford **38** in 60% yield from **36**. Minor isomerization of **38a** into **38b** occurred during flash chromatography. Phosphitylation of **38a** proceeded sluggishly, and afforded the expected 3'-*O*-benzoyl-4'-*O*-phosphoramidite **39** along with a small quantity of a more polar side compound corresponding to the regio-isomer of **39** as a result of benzoyl migration. Compound **6**, **15**, **21** and **39** were used succesfully for oligonucleotide synthesis [5].



Scheme 5

The *altro*-nucleoside analogues were fully deprotected to enable antiviral screening. Hereto, deprotection of **2**, **11**, **17** and **26** by treatment with 80% aqueous acetic acid afforded the free nucleosides **7**, **16**, **22** and **40**, respectively. Alternatively, compound **2** was used for synthesis of the 5-iodouracil congener **9**: treatment of **2** with acetic anhydride in pyridine in the presence of triethylamine gave **3c**, which was treated with iodine and ceric ammonium nitrate in acetonitrile (Scheme 1) to afford **8**, according to the procedure described by Asakura and Robins [28]. Benzylidene cleavage using 80% acetic acid afforded **9** in moderate yield. None of the synthesized *altro*-nucleoside analogues (**7**, **9**, **16**, **22**, **40**) displayed any significant antiviral activity.

EXPERIMENTAL SECTION

General methods :

Tetra-*O*-acetyl-α-D-bromoglucose was provided by Fluka; adenine, cytosine, guanine and uracil were from ACROS. All other chemicals were provided by Aldrich or ACROS and were of the highest quality. Ultraviolet spectra of nucleosides were recorded with a Philips PU 8740 UV/Vis spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were determined unless otherwise indicated with a 200 MHz Varian Gemini apparatus with tetramethylsilane as internal standard for the ^{1}H NMR spectra (s = singlet, d = doublet, dd = double doublet, t = triplet, br s = broad signal, br d = broad doublet, m = multiplet) and the solvent signal DMSO-*d6* (39.6 ppm) or $CDCl_3$ (76.9 ppm) for the ^{13}C NMR spectra. For some products a Varian Unity-500 spectrometer (500 MHz for ^{1}H) was used. When necessary assignments were confirmed by attached proton test (APT) spectra or by 2D-correlation experiments such as COSY or HETCOR spectra. Coupling constant values were derived by first-order spectral analysis. ^{31}P NMR chemical shifts quoted are downfield from 85% H_3PO_4 (external). Liquid secondary ion mass spectra (LSIMS) with Cs^+ as primary ion beam were recorded on a Kratos Concept IH mass spectrometer equipped with a MASPEC2 data system (Mass Spectrometry Services Ltd, Manchester), with thioglycerol (thgly) as matrix. Precoated Machery-Nagel Alugram SILG/UV_{254} plates were used for TLC, and the spots were examined with UV light and sulfuric acid/anisaldehyde spray. Column chromatography was performed on ACROS silica gel (0.060-0.200 mm or 0.035-0.060 mm). Before use, Dowex AG50WX4 resin was washed successively with 1M NaOH (1 L), distilled water (until pH = 7), 1M HCl (1 L), distilled water (until pH = 7), methanol and diethyl ether. Reversed phase HPLC purifications were performed on a Merck-Hitachi L-6200A system with the aid of a semi-preparative PLRPS column (250 x 9 mm) using the indicated solvents as the eluent. Anhydrous solvents were obtained as follows: diethyl ether and tetrahydrofuran were stored on sodium/benzophenone, refluxed and distilled. Dichloromethane and 1,2-dichloroethane were stored over calcium hydride, refluxed and distilled. Acetonitrile was stored over phosphorus pentoxide, refluxed and distilled. Pyridine and *N,N*-diisopropylethylamine were refluxed over potassium hydroxide pellets and distilled. Dimethylformamide was dried over 4 Å activated molecular sieves. n-Hexane and acetone, used for chromatography of the phosphoramidites, were freshly distilled. Absolute methanol was refluxed overnight over magnesium iodide and distilled. Methanolic ammonia was prepared by bubbling NH_3 gas through absolute methanol at 0 °C and was stored at -20 °C. Unless otherwise stated, all reactions requiring anhydrous conditions were conducted in flame-dried apparatus under a static atmosphere of nitrogen. Elemental analyses were determined at the University of Konstanz, Germany.

1,5-Anhydro-4,6-*O*-benzylidene-2-deoxy-2-(uracil-1-yl)-D-*altro*-hexitol (2)

A mixture of 3.09 g (27.57 mmol) of uracil and 769 mg (25.64 mmol) of sodium hydride (80% in mineral oil) in 320 mL of dry DMF was stirred under nitrogen at 110 °C for 2 h. After addition of a solution of 2.01 g (8.57 mmol) of epoxide **1** [29,30] in dry DMF (20 mL), stirring was continued for 18 h at 120-130 °C. The reaction mixture was then cooled and evaporated to dryness. The residue was dissolved in ethyl acetate (1000

mL) and the organic layer was washed with a satured $NaHCO_3$ solution (2 x 350 mL) and brine (2 x 350 mL). The combined aqueous layer was extracted with ethyl acetate. After drying on $MgSO_4$ and filtering, the organic layer was evaporated to dryness. Column chromatography on silica gel [CH_2Cl_2:MeOH (100:0) to (98:2)] followed by crystallization from CH_2Cl_2:hexane afforded 2.55 g (7.37 mmol; 86% yield) of **2**, together with 148 mg (0.43 mmol, 5% yield) of the less polar O^2-isomer. UV (MeOH) : λ_{max} = 266 nm. ^{1}H NMR ($CDCl_3$) δ 3.65 (dd, 1H, J = 9.6 and 2.5 Hz, 4'-H); 3.72 (t, 1H, J= 10.6 Hz, 6'-Ha); 3.85 (br s, 1H, 3'-OH); 3.89 (app d, J = 13.6 Hz, 1'-Ha); 4.10 (dt, 1H, J = 4.7 and 9.9 Hz; 5'-H); 4.26-4.44 (m, 3H, 6'-He, 1'-He, 3'-H); 4.43 (t, 1H, 2'-H); 5.60 (s, 1H, Ph-C<u>H</u>); 5.78 (dd, 1H, J = 8.1 and 2.0 Hz, 5-H); 7.33-7.47 (m, 5H, ar-H), 7.99 (d, 1H, J = 8.1 Hz, 6-H). ^{13}C NMR ($CDCl_3$) δ 56.60 (C-2'); 64.01 (C-1'); 65.83 (C-3'); 66.20 (C-5'); 68.80 (C-6'); 76.51 (C-4'); 102.13 (Ph-<u>C</u>H); 102.86 (C-5); 126.17 (ar-C_o); 128.26 (ar-C_m); 129.23 (ar-C_p); 137.00 (ar-C_i); 142.19 (C-6); 151.36 (C-2); 163.41 (C-4). HRMS (thgly) calcd. for $C_{17}H_{18}N_2O_6$ $(MH)^+$ 347.1243, found 347.1291.

1,5-Anhydro-3-*O*-benzoyl-4,6-*O*-benzylidene-2-deoxy-2-(uracil-1-yl)-D-*altro*-hexitol (3a)

A solution of compound **2** (517 mg, 1.50 mmol), 510 μL (4.50 mmol) of benzoyl chloride and 36 mg (0.3 mmol) of 4-dimethylaminopyridine in 6 mL of dry pyridine was heated for 3 h at 80 °C. The solution was cooled in an ice-bath and 2 mL of water was added. After 15 min, the volatiles were removed *in vacuo* and the residue was coevaporated three times with toluene. The resulting solid was dissolved in 200 mL of CH_2Cl_2 and the solution was washed with satured $NaHCO_3$ (80 mL) and brine (2 x 80 mL). The combined aqueous layer was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by column chromatography [(EtOAc:hexane (20:80) to (80:20)], affording 470 mg (1.04 mmol, 70% yield) of **3a** along with 68 mg (0.15 mmol, 10% yield) of the base protected product **3b**. ^{1}H NMR (DMSO-*d6*) δ 3.72-3.90 (m, 1H, 4'-H); 4.10 (m, 2H, 5'-H, 6'-Ha); 4.22-4.45 (m, 3H, 6'-He, 1'-Ha, 1'-He); 4.48 (t, 1H, 2'-H); 5.69 (s, 1H, Ph-C<u>H</u>); 5.71 (d, 1H, J = 8.1 Hz, 5-H); 5.73 (br s, 1H, 3'-H); 7.20-7.35 (m, 5H, Bn); 7.54-7.85 (m, 3H, Bz_{m+p}); 7.96 (d, 1H, J = 8.1 Hz, 6-H); 8.13 (d, 2H, J = 7.0 Hz, Bz_o); 11.42 (br s, 1H, N3-H). HRMS (thgly) calcd. for $C_{24}H_{23}N_2O_7$ $(MH)^+$ 451.1505, found 451.1510.

1,5-Anhydro-3-*O*-benzoyl-2-deoxy-2-(uracil-1-yl)-D-*altro*-hexitol (4)

A solution of 675 mg of compound **3a** (1.50 mmol) in 8 mL of 90% aq. TFA was kept at room temperature for 1 h. The reaction mixture was then rapidly concentrated *in vacuo* at a temperature below 40 °C. The crude residue was dissolved in a small volume of CH_2Cl_2:acetone (1:1) and triturated with cold diethyl ether, till precipitation of **4**. Repeated washing of the precipitate with cold diethyl ether removed the main part of residual TFA and benzaldehyde. The white residue was dried *in vacuo* and used without further purification for the next step. Compound **4** was stored not longer than one night at -20 °C before conversion into **5a**. ^{1}H NMR (DMSO-*d6*) δ 3.60-3.80 (m, 3H, 4'-H, 6'-Ha, 6'-He); 3.95 (m, 1H, 5'-H); 4.0-4.13 (m, 2H, 1'-Ha+e); 4.66 (dd, 1H, 2'-H); 4.77 (t, 1H, 6'-OH); 5.33 (d, 1H, J = 5.5 Hz, 4'-OH); 5.50 (dd, 1H, J = 6.0 and 2.9Hz, 3'-

H); 5.59 (dd, 1H, J = 8.1 and 2.1 Hz, 5-H); 7.50-7.75 (m, 3H, Bz_{m+p}); 7.98-8.10 (m, 3H, Bz_o, 6-H); 11.35 (br s, 1H, N3-H). LSIMS (thgly) 363 $(MH)^+$. HRMS (thgly) calcd. for $C_{17}H_{18}N_2O_7$ (MH^+) 363.1192, found 363.1185.

1,5-Anhydro-2-deoxy-2-(uracil-1-yl)-D-*altro*-hexitol (7)

An amount of 1.01 g (2.93 mmol) of 1,5-Anhydro-4,6-*O*-benzylidene-2-deoxy-2-(uracil-1-yl)-D-*altro*-hexitol (**2**) was treated with 80% aq. acetic acid (60 mL) at 80 °C for 2 h. After evaporation and coevaporation with toluene, the residue was suspended in water (200 mL). After neutralization by 4 M NaOH, evaporation and coevaporation with toluene, the resulting brown residue was purified by flash chromatography on silica gel [CH_2Cl_2:MeOH (80:20)], affording 625 mg (2.41 mmol, 82% yield) of **7** as a white foam. An analytical pure sample of **7** was obtained by purification on RP HPLC, using a methanol gradient [H_2O:MeOH (100 : 0) to (80 : 20), 4 mL/min]. The pure fractions were combined, concentrated under reduced pressure and lyophilized. UV (MeOH): λ_{max} = 266 nm. ^1H NMR (D_2O, 500 MHz) δ 3.71-3.80 (m, 4H, 4'-H, 5'-H, 6'-Ha, 6'-He); 4.03 (dd, 1H, J = 3.9 and 13.4 Hz, 1'-Ha); 4.09 (dd, 1H, J = 4.4 and 13.4 Hz, 1'-He); 4.11 (dd, 1H, 3'-H); 4.42 (dd, 1H, J = 3.9 and 8.8 Hz, 2'-H); 5.78 (d, 1H, J = 7.8 Hz, 5-H); 8.01 (d, 1H, J = 7.8 Hz, 6-H). ^{13}C NMR (D_2O, 125 MHz) δ 57.20 (C-2'); 60.95 (C-6'); 63.11 (C-1'); 65.92 (C-4'); 67.75 (C-3'); 77.28 (C-5'); 102.53 (C-5); 145.29 (C-6); 153.00 (C-2); 167.06 (C-4). HRMS (thgly) calcd. for $C_{10}H_{15}N_2O_6$ $(MH)^+$ 259.0930, found 259.0923. Elemental analysis calcd. for $C_{10}H_{14}N_2O_6.H_2O$: N: 10.14; C: 43.46; H: 5.84; Found : N: 10.13; C: 43.26; H: 5.75.

1,5-Anhydro-4,6-*O*-benzylidene-2-deoxy-2-(5-iodouracil-1-yl)-D-*altro*-hexitol (8)

Compound **2** (2.50 g, 7.23 mmol) was dissolved in dry pyridine (18 mL) and 440 mg of 4-dimethylaminopyridine (3.61 mmol), 1.2 mL of triethylamine (8.67 mmol) and 820 µl (8.67 mmol) of acetic anhydride were added. The mixture was stirred at room temperature for 3 h. The residue obtained after solvent evaporation was coevaporated 3 times with toluene and purified by chromatography on silica gel [EtOAc:hexane (50:50) then (80:20)] to yield **3c** as a white foam (2.55 g, 91%). ^1H NMR ($CDCl_3$) δ 3.68-3.81 (m, 2H, 4'-H, 6'-Ha); 3.99 (dt, J = 4.8 and 9.9 Hz, 1H, 5'-H); 4.14 (d, 1H, J = 13.8 Hz, 1'-Ha); 4.26-4.40 (m, 2H, 6'-He, 1'-He); 4.43 (t, 1H, J = 2.8 Hz, 2'-H); 5.57 (s, 1H, Ph-C<u>H</u>); 5.62 (br s, 3'-H); 5.78 (d, 1H, J = 8.1 Hz, 5-H); 7.33-7.45 (m, 5H, ar-H), 8.02 (d, 1H, J = 8.1 Hz, 6-H); 9.27 (br s, 1H, N3-H). ^{13}C NMR ($CDCl_3$) δ 20.76 (CH_3); 54.38 (C-2'); 64.93 (C-1'); 65.68 (C-3'); 67.31 (C-5'); 68.61 (C-6'); 74.83 (C-4'); 101.58 (Ph-<u>C</u>H); 102.83 (C-5); 125.72 (2C, ar-C_o); 128.11 (2C, ar-C_m); 128.92 (ar-C_p); 136.64 (ar-C_i); 141.45 (C-6); 150.38 (C-2); 162.78 (C-4); 168.42 (CH_3-<u>C</u>O). LSIMS (thgly) $(MH)^+$ 387. This compound was used directly in the next reaction step. A mixture of 291 mg (0.75 mmol) of **3c**, 248 mg (0.98 mmol) of iodine, and 905 mg (1.65 mmol) of ceric ammonium nitrate (CAN) in 9 mL of dry acetonitrile was stirred at room temperature for 5 h. Following evaporation of the solvent under reduced pressure, the resulting oil was treated with a cold mixture (ice-water bath) of ethyl acetate (30 mL), 5% aq. $NaHSO_3$ (10 mL) and brine (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layer was carefully washed with successively cold 5% aq. $NaHSO_3$, brine and water, dried over

Na_2SO_4 and evaporated. Deacetylation was performed by treatment of the crude product with methanolic ammonia (10 mL). The solution was evaporated to dryness and the residue was coevaporated with acetone and adsorbed on silica. Flash chromatography on silica gel [CH_2Cl_2:MeOH (98.5:1.5) to (97:3)] followed by precipitation from CH_2Cl_2:hexane afforded 290 mg (0.61 mmol, 82% yield) of **8** as a colorless oil. UV (MeOH) : λ_{max} = 286 nm. ^{1}H NMR ($CDCl_3$) δ 3.74 (dd, 1H, J = 9.4 and 3.1 Hz, 4'-H); 3.78 (t, 1H, J = 10.4 Hz, 6'-Ha); 4.04-4.44 (m, 6H, 1'-Ha, 1'-He, 3'-H, 5'-H, 6'-He, 3'-OH); 4.50 (m, 1H, 2'-H); 5.66 (s, 1H, Ph-C<u>H</u>); 7.27-7.50 (m, 5H, ar-H), 8.49 (s, 1H, 6-H). ^{13}C NMR ($CDCl_3$) δ 56.90 (C-2'); 64.04 (C-1'); 65.65 (C-3'); 66.41 (C-5'); 68.87 (C-6'); 69.08 (C-5); 76.36 (C-4'); 102.13 (Ph-<u>C</u>H); 126.23 (2C, ar-C_o); 128.35 (2C, ar-C_m); 129.29 (ar-C_p); 137.03 (ar-C_i); 146.78 (C-6); 151.02 (C-2); 160.13 (C-4). HRMS (thgly) calcd. for $C_{17}H_{18}N_2O_6I$ $(MH)^+$ 473.0210, found 473.0212.

1,5-Anhydro-2-deoxy-2-(5-iodouracil-1-yl)-D-*altro*-hexitol (9)

A small sample of **8** (82 mg, 0.17 mmol) was treated with 80% aq. acetic acid (3.5 mL) at 80 °C for 2 h. After workup as described for the synthesis of **7**, flash chromatography on silica gel [CH_2Cl_2:MeOH (98:2) to (90:10)] 49 mg (0.13 mmol, 73% yield) of **9** was obtained as a white foam. An analytical sample was obtained by RP HPLC [H_2O:MeOH (100 : 0) to (77 : 23), 4 mL/min]. The pure fractions were combined, concentrated under reduced pressure and lyophilized. UV (MeOH) : λ_{max} = 287 nm. ^{1}H NMR (D_2O) δ 3.70 (br, 4H, 4'-H, 5'-H, 6'-Ha, 6'-He); 4.00 (m, 3H, 3'-H, 1'-He, 1'-Ha); 4.40 (m, 1H, 2'-H); 8.31 (s, 1H, 6-H). HRMS (thgly) calcd. for $C_{10}H_{14}N_2O_6I$ $(MH)^+$ 384.9898, found 384.9853. Elemental analysis calcd. for $C_{10}H_{134}N_2O_6I$. 1.5HO : N: 6.81; C: 29.21; H: 3.92; Found : N: 6.85; C: 29.10; H: 3.85.

1,5-Anhydro-4,6-*O*-benzylidene-2-deoxy-2-(cytosin-1-yl)-D-*altro*-hexitol (11)

Triethylamine (9.9 mL, 71.33 mmol) was added dropwise to a stirred, cooled mixture of 1,2,4-triazole (5.15 g, 74.46 mmol) and phosphoryl chloride (1.48 mL, 15.83 mmol) in 40 mL of anhydrous pyridine. After stirring for 30 min at 0 °C a solution of **3a** (3.21 g, 8.27 mmol) in 40 mL of anhydrous pyridine was added and the reaction mixture was stirred at room temperature for 2 h. The red solution was evaporated to dryness. The residue was dissolved in 250 mL of chloroform and washed with brine (2 x 100 mL). The combined aqueous layer was washed with chloroform (50 mL). The organic layer was dried over $MgSO_4$. The residue obtained after filtration and evaporation was dissolved in dioxane (180 mL), cooled and 60 mL of concentrated aqueous ammonia was added. The solution was left for reaction overnight at room temperature. Subsequently, volatiles were removed, the residue was coevaporated with toluene and dissolved in 50 mL of CH_2Cl_2:MeOH (1:1). The dark red suspension was filtered on a small path of Celite and the product was eluted by CH_2Cl_2:MeOH (90:10). The crude product was further purified by two successive chromatographic separations on silica gel [CH_2Cl_2:MeOH (98:2) to (95:5)] to yield **11** (3.05 g) as a yellow-orange foam which was coevaporated 3 times with toluene and used without further purification for the next step. UV (MeOH) : λ_{max} = 276 nm. ^{1}H NMR (DMSO-*d6*) δ 3.60 (dd, 1H, J = 2.3 and 9.6 Hz, 4'-H); 3.64 (t, 1H, J = 10.2 Hz; 6'-Ha); 3.91 (dd, 1H, J = 4.9 and 9.6 Hz, 5'-H); 4.00 (m, 1H, 3'-H); 4.00-4.26 (m, 3H, 1'-Ha, 1'-He, 6'-He); 4.29

(m, 1H, 2'-H); 5.65 (s, 1H, Ph-CH); 5.72 (d, 1H, J = 4.2 Hz, 3'-OH); 5.77 (d, 1H, J = 7.5 Hz, 5-H); 7.05 and 7.19 (2 br s, 2H, 4-NH_2); 7.30-7.45 (m, 5H, ar-H); 7.94 (d, 1H, J = 7.5 Hz, 6-H). ^{13}C NMR (DMSO-*d6*) δ 57.46 (C-2'); 64.00 (C-1'); 64.87 (C-3'); 65.79 (C-5'); 68.28 (C-6'); 76.50 (C-4'); 94.09 (C-5); 101.20 (Ph-CH); 126.50 (2C, ar-C_o); 128.10 (2C, ar-C_m); 128.95 (ar-C_p); 137.93 (ar-C_i); 143.75 (C-6); 154.98 (C-2); 165.19 (C-4). HRMS (thgly) calcd. for $C_{17}H_{20}N_3O_5$ $(MH)^+$ 346.1403, found 346.1380.

1,5-Anhydro-3-*O*-benzoyl-4,6-*O*-benzylidene-2-deoxy-2-(N^4-benzoylcytosin-1-yl)-D-*altro*-hexitol (12)

Benzoyl chloride (7.7 mL, 65 mmol) was added dropwise at 0 °C to a solution of compound **11** (3.05 g) and 4-dimethylaminopyridine (120 mg, 0.98 mmol) in 100 mL of anhydrous pyridine. The mixture was left to react for 30 min at room temperature and stirred for 5 h at 70 °C. The suspension was cooled to 0 °C and the reaction was quenched by addition of 35 mL of water. After 15 min of stirring at 0 °C, 125 mL of concentrated ammonia were added and the mixture was stirred for 1 h at 0 °C. Volatiles were removed and the residue was coevaporated with toluene. The crude product was purified by flash chromatography on silica gel [EtOAc:hexane (80:20) then CH_2Cl_2:MeOH (998.5:0.5) to (97:3)]. Following concentration of the product containing fractions, the title product **12** (3.07 g, 5.55 mmol) precipitated and was isolated in 67% yield from **3a**. ^{1}H NMR (DMSO-*d6*) δ 3.85 (m, 1H, 4'-H); 4.00-4.60 (m, 5H, 5'-H, 1'-Ha, 1'-He, 6'-Ha, 6'-He); 4.63 (br s, 1H, 2'-H); 5.70 (s, 1H, Ph-CH); 5.81 (br s, 1H, 3'-H); 7.20-7.35 (m, 5H, ar-H); 7.45-7.80 (m, 7H, 2 x Bz, 5-H); 8.04 (d, 2H, J = 7 Hz, Bz_o); 8.15 (d, 2H, J = 7 Hz, Bz_o); 8.48 (d, 1H, J = 7.7 Hz, 6-H); 11.35 (br s, 1H, N4-H). ^{13}C NMR (DMSO-*d6*) δ 55.83 (C-2'); 64.84 (C-1'); 66.20 and 67.23 (C-3', C-5'); 68.08 (C-6'); 74.21 (C-4'); 97.14 (C-5); 100.81 (Ph-CH); 126.03, 128.18, 128.64, 128.97, 129.08, 129.44, 129.76, 132.95, 133.29, 133.88, 137.60 (ar-C); 147.71 (C-6); 155.20 (C-2); 163.24 (C-4). 164.11 (PhCONH and PhCOO). HRMS (thgly) calcd. for $C_{31}H_{28}N_3O_7$ $(MH)^+$ 554.1927, found 554.1892.

1,5-Anhydro-3-*O*-benzoyl-2-deoxy-2-(N^4-benzoylcytosin-1-yl)-D-*altro*-hexitol (13)

Compound **13** was obtained using the same procedure (2.5 mmol scale) as described for the synthesis of **4**. Compound **13** was stored not longer than one night at -20 °C before conversion into **14a**. ^{1}H NMR (DMSO-*d6*) δ 3.60-4.00 (m, 3H, 4'-H, 6'-Ha, 6'-He); 4.10-4.40 (m, 3H, 5'-H, 1'-Ha, 1'-He); 4.65-4.85 (m, 2H, 2'-H, 6'-OH); 5.25 (br s, 1H, 4'-OH); 5.65 (m, 1H, 3'-H); 7.35 (d, 1H, J = 7.8 Hz, 5-H); 7.45-7.80 (m, 6H, ar-H); 7.90-8.15 (m, 4H, ar-H); 8.48 (d, 1H, J = 7.8 Hz, 6-H); 11.35 (br s, 1H, N4-H). LSIMS (thgly, negative mode) 466.2 $(MH)^+$. HRMS (thgly) calcd. for $C_{24}H_{23}N_3O_7$ (MH^+) 466.1614, found 466.1603.

1,5-Anhydro-2-deoxy-2-(cytosin-1-yl)-D-*altro*-hexitol (16)

An aliquot of **11** (75 mg, 0.22 mmol) was treated with 80% aq. acetic acid (4.5 mL) at 80 °C for 2 h. After similar workup as described for the synthesis of **7**, filtration over 15 g of Amberlite XAD-4 [water:MeOH (100:0) to (90:10)] afforded 76 mg of crude **16** as a white foam. The product was purified further by RP HPLC. [H_2O:MeOH (100 : 0) to (80 : 20), 4 mL/min]. The pure fractions were combined, concentrated under reduced pressure and lyophilized, yielding 37 mg (0.14 mmol, 66% yield) of **16**. UV (MeOH) : λ_{max} = 276 nm.

^{1}H NMR (D_2O) δ 3.67 (s, 4H, 1'-Ha, 1'-He, 6'-Ha, 6'-He); 3.97 (m, 3H, 3'-H, 4'-H, 5'-H); 4.34 (m, 1H, 2'-H); 5.87 (d, 1H, J = 7.3 Hz, 5-H); 7.91 (d, 1H, J = 7.3 Hz, 6-H). HRMS (thgly) calcd. for $C_{10}H_{16}N_3O_5$ $(MH)^+$ 258.1090, found 258.1115. Elemental analysis calcd. for $C_{10}H_{15}N_3O_5$. $1.5H_2O$: N: 14.78; C: 42.25; H: 6.38; Found : N: 14.75; C: 42.45; H: 6.06.

1,5-Anhydro-4,6-*O*-benzylidene-2-deoxy-2-(adenin-9-yl)-D-*altro*-hexitol (17)

A mixture of 3.59 g (26.55 mmol) of adenine and 768 mg (25.64 mmol) of sodium hydride (80% in mineral oil) in 120 mL of dry DMF was stirred under nitrogen at 110 °C for 2 h. After addition of a solution of 2.00 g (8.55 mmol) of epoxide **1** in dry DMF (20 mL), stirring was continued for 18 h at 120-130 °C. After workup (using the same procedure as described for compound **2**) and column chromatography on silica gel [CH_2Cl_2:MeOH (98:2)], precipitation from CH_2Cl_2: hexane gave 2.27 g (6.15 mmol; 72% yield) of the title product **17**. UV (MeOH) : λ_{max} = 262 nm. ^{1}H NMR (DMSO-*d6*) δ 3.60 (dd, 1H, 4'-H); 3.80 (t, 1H, 6'-Ha); 4.0 (m, 1H, 5'-H); 4.20-4.40 (m, 4H, 1'-Ha, 1'-He, 3'-H, 6'-He); 4.60 (br s, 1H, 2'-H); 5.62 (s, 1H, Ph-C<u>H</u>); 5.99 (d, 1H, J = 4.4 Hz, 3'-OH); 7.25-7.40 (m, 5H, ar-H); 8.18 (s, 1H, 2-H); 8.26 (s, 1H, 8-H); 8.55 (br s, 6-NH_2). ^{13}C NMR (DMSO-*d6*) δ 56.17 (C-2'); 64.55 (C-1'); 65.28 (C-3'); 66.61 (C-5'); 68.34 (C-6'); 76.35 (C-4'); 101.30 (Ph-<u>C</u>H); 118.54 (C-5); 126.65 (2C, ar-C_o); 128.32 (2C, ar-C_m); 129.17 (ar-C_p); 138.03 (ar-C_i); 139.49 (C-8); 149.96 (C-4); 152.99 (C-2); 156.42 (C-6). HRMS (thgly) calcd. for $C_{18}H_{20}N_5O_4$ $(MH)^+$ 370.1515, found 370.1559.

1,5-Anhydro-3-*O*-benzoyl-4,6-O-benzylidene-2-deoxy-2-(N^6-benzoyladenin-9-yl)-D-*altro*-hexitol (18)

A solution of **17** (517 mg, 1.40 mmol), 1.27 mL (4.21 mmol) of benzoyl chloride and 20 mg (0.16 mmol) of 4-dimethylaminopyridine in 5 mL of dry pyridine was heated for 3 h at 55 °C. The solution was cooled in an ice bath and 3 mL of water was added. After 15 min, concentrated ammonia (21 mL) was added to afford selective N^6-monodebenzoylation. After stirring for 1 h at 0 °C, the volatiles were removed *in vacuo* and the residue was coevaporated three times with toluene. The main part of benzamide was removed from the crude residue by precipitation from CH_2Cl_2. Column chromatography on silica gel [EtOAc:hexane (40:60) to (80:20)] followed by crystallization from $CHCl_3$:diethyl ether afforded 624 mg (1.08 mmol; 77% yield) of **18**. ^{1}H NMR (DMSO-*d6*, 500 MHz) δ 3.82 (t, 1H, J = 10.25 Hz, 6'-Ha); 3.91 (dd, 1H, J = 9.7 and 2.6 Hz, 4'-H); 4.28 (dt, 1H, J = 5.1 and 9.7 Hz, 5'-H); 4.46 (m, 2H, 1'-Ha, 6'-He); 4.57 (dd, 1H, J = 2.6 and 13.3 Hz, 1'-He); 5.08 (t, 1H, J = 2.6 Hz, 2'-H); 5.52 (s, 1H, PhC<u>H</u>); 5.99 (t, 1H, J = 2.6 Hz, 3'-H); 7.22-7.27 and 7.30-7.34 (m, 5H, Bn); 7.48-7.54 (m, 4H, two Bz_o); 7.58-7.64 (m, 2H, two Bz_p); 8.05 (d, 2H, J = 7.3 Hz); 8.16 (d, 2H, J = 8.4 Hz, Bz_m); 8.63 (s, 1H, 2-H); 8.85 (s, 1H, 8-H); 9.19 (br s, 6-NH). ^{13}C NMR (DMSO-*d6*) δ 53.42 (C-2'); 65.74 (C-1'); 67.02 (C-5'); 68.41 (C-3'); 68.96 (C-6'); 74.79 (C-4'); 102.13 (Ph-<u>C</u>H); 122.83 (C-5); 125.99, 128.02, 128.20, 128.66, 128.87, 129.12, 129.35, 129.96, 132.88, 133.69 and 136.70 (ar-C); 141.77 (C-8); 149.78 (C-4); 152.51 (C-2); 153.21 (C-6); 164.89 (two Bz-C_o). HRMS (thgly) calcd. for $C_{32}H_{28}N5O_6$ $(MH)^+$ 578.2040, found 578.2073.

1,5-Anhydro-3-*O*-benzoyl-2-deoxy-2-(N^6-benzoyladenin-9-yl)-D-*altro*-hexitol (19)

Compound **19** was obtained using the same procedure (3.72 mmol scale) as described for synthesis of **4**. The title compound **19** was stored not longer than one night at -20 °C before conversion into **20a**. ^{1}H NMR (DMSO-*d6*) δ 3.70-4.00 (m, 4H, 4'-H, 5'-H, 6'-Ha, 6'-He); 4.28 (dd, 1H, J = 2.9 and 12.9 Hz, 1'-Ha); 4.39 (dd, 1H, J = 2.2 and 12.9 Hz, 1'-He); 4.87 (br s, 1H, 6'-OH); 5.06 (br d, 1H, 2'-H); 5.34 (br d, 1H, 4'-OH); 5.74 (dd, 1H, J = 2.5 Hz and 4.5 Hz, 3'-H); 7.50-7.75 (m, 6H, two Bz_{m+p}); 8.05 (d, 4H, two Bz_o); 8.76 (s, 1H, 2-H); 8.80 (s, 1H, 8-H); 11.21 (br s, 6-NH). ^{13}C NMR (DMSO-*d6*) δ 52.62 (C-2'); 59.85 (C-6'); 62.61 (C-4'); 63.82 (C-1'); 70.38 (C-3'); 78.34 (C-5'); 125.43 (C-5); 128.59, 128.85, 128.20, 129.65, 132.57, 133.47 and 133.68 (12C, ar-C); 143.56 (C-8); 150.42 (C-4); 151.85 (C-2); 152.66 (C-6); 164.78, 165.71 (two Bz-Co). HRMS (thgly) calcd. for $C_{25}H_{24}N_5O_6$ $(MH)^+$ 490.1727, found 490.1740.

1,5-Anhydro-2-deoxy-2-(adenin-9-yl)-D-*altro*-hexitol (22)

1,5-Anhydro-4,6-*O*-benzylidene-2-deoxy-2-(adenin-9-yl)-D-*altro*-hexitol (**17**) (120 mg, 0.32 mmol) was treated with 80% aq. acetic acid (6.5 mL) at 80 °C for 2 h. After workup as described for the synthesis of **7**, flash chromatography on silica gel [CH_2Cl_2:MeOH (80:20)] afforded 68 mg (0.24 mmol, 75% yield) of **22** as a white foam. The product was purified further by RP HPLC [H_2O:MeOH (100 : 0) to (77 : 23), 4 mL/min]. The pure fractions were combined, concentrated under reduced pressure and lyophilized, yielding 55 mg (0.22 mmol, 61% yield) of **22** [30]. UV (MeOH): λ_{max} = 261 nm. ^{1}H NMR (D_2O) δ 3.59 (m, 1H, 6'-Ha); 3.65-3.83 (m, 3H, 4'-H, 5'-H, 6'-He); 4.17 (br s, 3H, 1'-Ha, 1'-He, 3'-H); 4.56 (m, 1H, 2'-H); 8.06 (s, 1H, 2-H); 8.30 (s, 1H, 8-H). ^{13}C NMR (D_2O+ DMSO-*d6*) δ 57.03 (C-2'); 62.37 (C-6'); 65.23 (C-1'); 66.26 (C-4'); 69.38 (C-3'); 78.43 (C-5'); 119.40 (C-5); 142.93 (C-8); 151.03 (C-4); 154.49 (C-2), 157.75 (C-6). HRMS (thgly) calcd. for $C_{11}H_{16}N_5O_4$ $(MH)^+$ 282.1202, found 282.1228. Elemental analysis calcd. for $C_{11}H_{15}N_5O_4.0.7H_2O$: C: 23.84; H: 44.94; N: 5.63; Found : C: 23.74; H: 44.95; N: 5.44.

1,5-Anhydro-4,6-*O*-benzylidene-2-deoxy-2-[2-amino-6-(2-trimethylsilylethoxy]purin-9-yl]-D-*altro*-hexitol (33)

A mixture of 6.76 g (23 mmol) of **34** and 178 mg (22.39 mmol) of lithium hydride in 60 mL of dry DMF was stirred under nitrogen at 70 °C for 2 h. After addition of 1.50 g (6.41 mmol) of the epoxide **1** dissolved in 20 mL of dry DMF, stirring was continued for 3 h at 130 °C. The reaction mixture was cooled and evaporated to dryness. The residue was divided in 3 equal parts. Each part was suspended in 1.5 L of ethyl acetate and washed with brine (2 x 500 mL). A small part of the base precipitated during extraction and was filtered off and kept for recycling. Organic layers were combined and dried over Na_2SO_4, filtered and evaporated. The residue was suspended in CH_2Cl_2, affording efficient precipitation of remaining **34** (82% of the excess of base could be recovered this way). The filtrate was concentrated and adsorbed on silica gel. Since partial deacetylation of **32** occurred during the transformation, the mixture of **32** and **33** isolated after flash chromatography on silica gel [CH_2Cl_2:MeOH (100:0) to (98.4:1.6), then (80:20) for elution of the base] was

subjected to N^2-deacetylation. The excess of **34** (and possible traces of the N^2-deacetylated derivative) recovered from work-up and chromatography was dried in vacuo at 90 °C and was recrystallized from ethyl acetate:diethyl ether before reuse. The mixture was treated overnight at room temperature with 50 mL of 1 M NaOH:dioxane (45:55). After neutralization by 1 M HCl at 0 °C, the suspension was concentrated to half volume and the product was extracted by ethyl acetate. The organic layer was washed with water (3 x 10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated and from the residue compound **33** was crystallized from CH_2Cl_2:hexane (1.40 g, 2.88 mmol, 45% yield). ^{1}H NMR (DMSO-d6) δ 0.08 (9H, $Si(CH_3)_3$); 1.19 (t, J = 8.4 Hz, 2H, CH_2Si); 3.61 (dd, 1H, J' = 2.2 and 9.3 Hz, 4'-H); 3.75 (t, 1H, J = 9.9 Hz; 6'-Ha); 4.20-4.80 (m, 8H, 1'-Ha, 1'-He, 2'-H, 3'-H, 5'-H, 6'-He, OCH_2); 4.92 (br s, 1H, 3'-OH); 5.53 (s, 1H, Ph-C<u>H</u>); 7.34-7.55 (m, 5H, ar-H); 7.62 (br s, 2-NH_2); 8.18 (s, 1H, 8-H). ^{13}C NMR ($CDCl_3$) δ -1.52 (3C, $Si(CH_3)_3$); 17.45 (CH_2Si); 56.06 (C-2'); 64.65 (O-CH_2); 65.10 (C-1',C-3'); 66.53 (C-5'); 69.05 (C-6'); 76.36 (C-4'); 102.40 (Ph-<u>C</u>H); 115.21 (C-5); 126.50 (ar-C_o); 128.38 (ar-C_m); 129.66 (ar-C_p); 136.52 (ar-C_i); 138.13 (C-8); 152.94 (C-4); 159.37 (C-2); 161.92 (C-6). LSIMS (thgly/gly) 486 $(MH)^+$. HRMS (thgly/gly) calcd. for $C_{23}H_{31}N_5O_5Si$ (MH^+) 486.2173, found 486.2165.

1,5-Anhydro-4,6-*O*-benzylidene-2-deoxy-2-(guanin-9-yl)-D-*altro*-hexitol (26)

A 0.5 M solution of tetrabutylammonium fluoride in dry acetonitrile (22 mL, 4 eq) was added to **33** (1.40 g, 2.88 mmol) and the mixture was stirred at room temperature under N_2 for 2 h after which water (10 mL) was added. The pH was adjusted to 5 with acetic acid and the mixture was evaporated. The product was purified by flash chromatography [CH_2Cl_2:MeOH (98:2) to (90:10)] to yield **26** (866 mg, 2.25 mmol, 78% yield) as a white foam. ^{1}H NMR (DMSO-*d6*) δ 3.67 (dd, 1H, J = 1.8 and 9.5 Hz, 4'-H); 3.79 (t, 1H, J = 9.9 Hz; 6'-Ha); 3.98 (dt, 1H, J = 4.8 and 9.9 Hz, 5'-H); 4.07-4.31 (m, 4H, 1'-Ha, 1'-He, 6'-He, 3'-H); 4.34 (br s, 1H, 2'-H); 5.66 (s, 1H, Ph-C<u>H</u>); 5.81 (d, 1H, J = 4.3 Hz, 3'-OH); 6.55 (br s, 2H, 2-NH_2); 7.28-7.49 (m, 5H, ar-H); 7.88 (s, 1H, 8-H). ^{13}C NMR (DMSO-*d6*) δ 55.50 (C-2'); 64.68 (C-1'); 65.36 (C-3'); 66.45 (C-5'); 68.25 (C-6'); 76.37 (C-4'); 101.17 (Ph-<u>C</u>H); 116.29 (C-5); 126.55 (ar-C_o); 128.11 (ar-C_m); 128.98 (ar-C_p); 135.88 (C-8); 137.88 (ar-C_i); 151.49 (C-4); 153.88 (C-2); 157.04 (C-6). HRMS (thgly) calcd for $C_{18}H_{19}N_5O_5$ $(MH)^+$ 386.1464, found 386.1496.

1,5-Anhydro-4,6-*O*-benzylidene-2-deoxy-2-(N^2-(dimethylamino)methylene-guanin-9-yl)-D-*altro*-hexitol (35)

An amount of **26** (3.18 g, 8.27 mmol) was coevaporated 3 times with pyridine, dissolved in 30 mL of dry DMF and N,N-dimethylformamide diethylacetal (5.80 mL, 33.18 mmol) was added. The mixture was stirred at rt for 18 h. The solvent was evaporated *in vacuo* and the oily residue was coevaporated 3 times with xylene and adsorbed on silica. Column chromatography on silica gel [CH_2Cl_2:MeOH (98:2) to (90:10)] afforded 2.69 g of **35** (6.12 mmol, 74% yield). ^{1}H NMR ($CDCl_3$) δ 3.04 and 3.13 (two s, 6H), $(N(CH_3)_2)$; 3.60-4.60 (m, 7H, 1'-Ha, 1'-He, 3'-H, 4'-H, 5'-H, 6'-Ha, 6'-He); 4.68 (br s, 1H, 2'-H); 5.30 (s, 1H, 3'-OH); 5.52 (s, 1H, Ph-C<u>H</u>);

7.20-7.48 (m, 5H, ar-H); 8.10 (s, 1H, 8-H); 8.61 (s, 1H, N=CH-N); 10.06 (N1-H). ^{13}C NMR ($CDCl_3$) δ 35.09 and 41.34 ($N(CH_3)_2$); 54.72 (C-2'); 65.10 (C-1'); 66.38 and 66.80 (C-3',C-5'); 68.90 (C-6'); 76.36 (C-4'); 101.98 (Ph-CH); 119.61 (C-5); 126.05 (ar-C_o); 128.14 (ar-C_m); 129.08 (ar-C_p); 137.00 (ar-C_i), 137.25; 150.63 (C-4); 156.97 (C-2,C-6); 158.37 (N=CH-N). LSIMS (thgly) 441 $(MH)^+$. HRMS (thgly) calcd. for $C_{21}H_{24}N_6O_5$ (MH^+) 441.1886, found 441.1879.

1,5-Anhydro-3-*O*-benzoyl-4,6-*O*-benzylidene-2-deoxy-2-(N^2-(dimethylamino)methylene-guanin-9-yl)-D-*altro*-hexitol (36)

The compound **35** and benzoyl cyanide were separately coevaporated 3 times with xylene and stored under nitrogen before use. To a solution of **35** (2.19 g, 4.97 mmol) and tri-n-butylamine (1 mL, 4.13 mmol) in dry DMF (10 mL) was added benzoyl cyanide (1.33 g, 9.94 mmol). The solution was stirred under nitrogen at rt for 1 h. Precipitation of **36** in the orange-red reaction mixture was observed. After an additional 30 min, methanol (20 mL) was added to destroy the excess of reactant. After 30 min of stirring, the solvent was evaporated *in vacuo*. The residue was dissolved in dichloromethane (500 mL) and the solution was washed successively with 0.1M KH_2PO_4 buffer pH 5.5 (4 x 200 mL) and water (3 x 200 mL). The combined aqueous layer was washed with dichloromethane. Organic layers were combined, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was adsorbed on silica and purified by column chromatography [CH_2Cl_2:MeOH (100:0) to (96.5:3.5)] and subsequently precipitated from CH_2Cl_2:hexane, affording 2.12 g (3.90 mmol, 78% yield) of **36**. ^{1}H NMR ($CDCl_3$) δ 3.16 and 3.32 (two s, 6H, $N(CH_3)_2$); 3.80 (t, 1H, J = 10 Hz, 6'-Ha); 3.83 (dd, 1H, J = 10.6 and 2.6 Hz, 4'-H); 4.25 (dt, 1H, J = 4.8 and 9.9 Hz, 5'-H); 4.39-4.53 (m, 3H, J = 5 Hz, 1'-Ha, 1'-He, 6'-He); 4.65 (br d, 1H, 2'-H); 5.52 (s, 1H, Ph-CH); 6.20 (t, 1H, J = 2.9 Hz, 3'-H); 7.20-7.40 (m, 5H, Bn); 7.42-7.67 (m, 3H, BZ_{m+p}); 8.05 (s, 1H, 8-H); 8.13 (d, 2H, Bz_o); 9.15 (s, 1H, N=CH-N); 9.38 (N1-H). ^{13}C NMR ($CDCl_3$) δ 35.06 and 41.40 ($N(CH_3)_2$); 53.72 (C-2'); 65.01 (C-1'); 67.14 (C-5'); 68.30 (C-3'); 68.99 (C-6'); 74.42 (C-4'); 102.19 (Ph-CH); 119.89 (C-5); 126.08, 128.20, 128.72, 129.11 (ar-C); 129.75, 133.69, 136.85, 136.24 (C-8), 150.66 (C-4); 157.67 (C-2); 158.00 (C-6); 160.25 (N=CH-N); 165.14 (Bz-CO). LSIMS (thgly) 545 $(MH)^+$. HRMS (thgly) calcd. for $C_{28}H_{28}N_6O_6$ (MH^+) 545.2148, found 545.2145.

1,5-Anhydro-3-*O*-benzoyl-2-deoxy-2-(N^2-(dimethylamino)methylene-guanin-9-yl)-D-*altro*-hexitol (37)

Compound **36** (1.10 g, 2.02 mmol) was treated at -15 °C with 35 mL of 90% TFA in dichloromethane for 2 h. The reaction mixture was then diluted in dichloromethane (30 mL) and immediately evaporated *in vacuo* at 4. Remaining benzaldehyde was removed *in vacuo* at a temperature below 40 °C. The crude residue was triturated with cold diethyl ether (-20 °C to -5 °C), affording precipitation of **37**. Repeated washings of the precipitate with cold diethyl ether removed the main part of residual TFA and benzaldehyde. The white residue was dried *in vacuo* at 4 °C and used without further purification for the next step. (Compound **37** could not be stored longer than one night at -20 °C before conversion into **38a**) ^{1}H NMR (DMSO-*d6*) δ3.09 and 3.27 (two s, 6H, $N(CH_3)_2$); 3.57-3.84 (m, 4H, 4'-H, 5'-H, 6'-Ha, 6'-He); 4.21 (dd, 1H, 1'-Ha); 4.38 (br d, 1H, 1'-He); 4.74 (br d, 1H, 2'-H); 5.65 (br s, 1H, 6'-OH); 5.86 (br s, 1H, 3'-H); 6.20 (br s, 1H, 4'-OH); 7.50-

7.78 (m, 3H,Bz_{m+p}); 8.07 (s, 1H, 8-H); 8.08 (d, 2H, J = 7.0 Hz, Bz_o); 8.43 (N1-H); 8.93 (s, 1H, N=CH-N). ^{13}C NMR (DMSO-*d6*) δ 34.83 and 40.85 ($N(CH_3)_2$); 53.29 (C-2'); 60.18 (C-6'); 62.18 (C-4'); 63.46 (C-1'); 70.04 (C-3'); 78.21 (C-5'); 126.13 (C-5); 128.95 (ar-C_o); 129.75 (ar-C_m); 133.78 (ar-C_p); (ar-C_i not detected); 144.49 (C-8); (C-4 not detected); 157.82 (C-2); 158.12 (C-6); 159.34 (N=CH-N); 165.13 (Bz-CO). LSIMS (thgly) 457 $(MH)^+$. HRMS (thgly) calcd. for $C_{21}H_{24}N_6O_6$ (MH^+) 457.1835, found 457,1827.

1,5-Anhydro-2-deoxy-2-(guanin-9-yl)-D-*altro*-hexitol (40)

A sample of **26** (105 mg, 0.27 mmol) was treated with 80% aq. acetic acid (5.5 mL) at 80 °C for 2 h. Following evaporation and repeated coevaporation with toluene, the residue was dissolved in water, and filtrated on 20 g of Amberlite XAD-4 [water:MeOH (100:0) to (80:20)] afforded 76 mg of **40** as a white foam. Further purification was done on RP HPLC [MeOH:H_2O (0 : 100) to (15 : 85), 4 mL/min]. The pure fractions were combined, concentrated under reduced pressure and lyophilized, affording 60 mg (0.20 mmol, 74% yield) of **40**. UV (MeOH) : λ_{max} = 256 nm. ^1H NMR (D_2O) δ 3.63 (m, 1H, 6'-Ha); 3.68-3.82 (m, 3H, 4'-H, 5'-H, 6'-He); 4.08-4.22 (m, 3H, 1'-Ha, 1'-He, 3'-H); 4.42 (br s, 1H, 2'-H); 7.97 (s, 1H, 8-H). HRMS (thgly) calcd for $C_{11}H_{15}N_5O_5$ $(MH)^+$ 298.1151, found 298.1163.

General procedure for monomethoxytritylation of 3'-*O*-benzoylated *altro*-hexitol nucleosides:

About 1 g of the respective precursor was suspended in DMF at a total concentration of approximately 150 mM. Following addition of 0.5 eq of 2,4,6-collidine and 1 eq of silver nitrate, the mixture was treated with 1.1 eq of monomethoxytrityl chloride for 3 to 6 h. The progress of the reaction was monitored carefully by TLC. Whenever necessary, small amounts (0.1 to 0.2 eq) of reactants were added after a few hours in order to accelerate the monomethoxytritylation and limit the possibility of competitive benzoyl migration. Upon completion of the reaction the mixture was diluted into 1 L of EtOAc and the silver salts were removed by filtration. The filtrate was quickly mixed with a 5% $NaHCO_3$ solution (500 mL) and following separation, the organic layer was washed successively with a 5% $NaHCO_3$ solution (400 mL), water (2 x 400 mL), a 1 M KH_2PO_4 buffer pH 5.0 (2 x 400 mL) and brine (400 mL). After drying over Na_2SO_4 and filtration, solvent evaporation afforded a yellow oil which was purified by flash chromatography on a short column of silica gel followed by precipitation whenever possible.

1,5-Anhydro-3-*O*-benzoyl-6-*O*-monomethoxytrityl-2-deoxy-2-(uracil-1-yl)-D-*altro*-hexitol (5a)

TLC analysis : EtOAc:hexane (80:20): **5a**: Rf = 0.71; regioisomer **5b** : Rf = 0.56. Flash chromatography on silica gel [EtOAc:hexane (20:80) to (80:20)] afforded a 56% yield from **3a**. The regioisomer, detected only by TLC, was not isolated. ^1H NMR ($CDCl_3$) δ 3.42 (dd, J = 10.4 and 3.1 Hz, 6'-Ha); 3.54 (dd, 1H, J = 10.4 and 2.7 Hz, 6'-He); 3.77 (s, 3H, O-CH_3); 3.75-3.85 (m, 1H, 4'-H); 4.12 (dd, 1H, J = 14.0 Hz and 7.2 Hz, 1'-Ha); 4.31 (dd, 1H, J = 14.0 and 3.6 Hz, 1'-He); 4.17-4.38 (m, 1H, 5'-H); 4.73 (app t, 1H, 2'-H); 5.69-5.80 (m, 2H, 3'-H, 5-H); 6.82 (d, 2H, J = 8.9 Hz, ar-H); 7.18-7.60 (m, 15H, ar-H); 7.99 (d, 2H, J = 7.0 Hz, ar-H); 8.29 (d, 1H, J = 8.2 Hz, 6-H); 8.80 (br s, 1H, N3-H). ^{13}C NMR ($CDCl_3$) δ 53.70 (C-2'); 55.20 (O-CH_3); 62.12 (C-6');

64.50 (C-4'); 64.69 (C-1'); 69.92 (C-3'); 76.37 (C-5'); 86.65 (C^{Tr}-O); 102.89 (C-5); 113.21, 127.07, 127.91, 128.14, 128.32, 128.52, 129.17, 129.85, 130.39, 133.55, 135.08, 144.12, 158.55 (ar-C); 142.43 (C-6); 150.77 (C-2); 162.72 (C-4); 165.63 (Bz-CO). HRMS (thgly:NaOAc) calcd. for $C_{37}H_{34}N_2O_8Na$ $(M+Na)^+$ 657.2213 found 657.2219.

1,5-Anhydro-3-*O*-benzoyl-6-*O*-monomethoxytrityl-2-deoxy-2-(N^4-benzoylcytosin-1-yl)-D-*altro*-hexitol (14a)

TLC analysis: CH_2Cl_2:acetone (80:20) : **14a** : Rf = 0.58; regioisomer **14b** : Rf = 0.18; CH_2Cl_2:MeOH (96:4): **13** : Rf = 0.27; **14a** : Rf = 0.54; regioisomer **14b** : Rf = 0.37. The regioisomer was efficiently purified by flash chromatography on silica gel [EtOAc:hexane (60:40) to (80:20)]. Precipitation from EtOAc:hexane:diethyl ether afforded a 51% yield of **14a** from **12**. ^{1}H NMR (DMSO-d6) δ 3.43 (dd, 1H, J = 10.1 and 3.1 Hz, 6'-Ha); 3.53 (dd, 1H, 6'-He); 3.65 (m, 1H, 4'-H); 3.79 (s, 3H, OCH_3); 3.75-3.90 (m, 1H, 5'-H); 4.05-4.42 (m, 3H, 1'-Ha, 1'-He, 4'-OH); 4.93 (br s, 1H, 2'-H); 5.84 (app t, 1H, J = 3.1 Hz, 3'-H); 6.86 (d, 2H, J = 8.8 Hz, ar-H); 7.15-7.70 (m, 19H, ar-H, 5-H); 7.90-8.05 (m, 4H, ar-H); 8.78 (d, 1H, J = 7.7 Hz, 6-H). ^{13}C NMR ($CDCl_3$) δ 55.07 and 55.20 (C-2',OCH_3); 62.08 (C-6'); 64.24 (C-4'); 64.82 (C-1'); 69.66 (C-3'); 75.96 (C-5'); 86.59 (C^{Tr}-O); 97.28 (C-5); 113.21; 127.07, 127.65, 127.91, 128.46, 129.02, 129.32, 129.86, 130.16, 133.02, 133.17, 133.47, 135.57, 143.99, 144.13 and 158.62 (ar-C); 147.56 (C-6); 155.0 (C-2); 162.20 (C-4); 165.83 (CO-O and CO-N). HRMS (thgly) calcd. for $C_{44}H_{39}N_3O_8Na$ $(M+Na)^+$ 760.2635 found 760.2642.

1,5-Anhydro-3-*O*-benzoyl-6-*O*-monomethoxytrityl-2-deoxy-2-(N^6-benzoyladenin-9-yl)-D-*altro*-hexitol (20a)

TLC system for monitoring the reaction: EtOAc:hexane (80:20) : **20a** : Rf = 0.45; regioisomer **20b** : Rf = 0.19; CH_2Cl_2:MeOH (96:4) : **19** : Rf = 0.19; **20a** : Rf = 0.61. Flash chromatography on silica gel [EtOAc:hexane (40:60) to (100:0)] followed by crystallization from EtOAc:hexane:diethyl ether afforded a 79% yield of the title product starting from **18**. ^{1}H NMR (DMSO-*d*) δ 3.20-3.50 (m, 2H, 6'-Ha, 6'-He); 3.71 (s, 3H, OCH_3); 4.01 (br s, 2H, 4'-H, 5'-H); 4.34 (br d, J = 12.5 Hz, 1'-Ha); 4.52 (br d, 1H, J = 12.5 Hz, 1'-He); 5.06 (m, 2'-H); 5.27 (t, 1H, 4'-OH); 5.85 (d, 1H, J = 4.7 Hz, 3'-H); 6.91 (d, 2H, J = 9.2 Hz, ar-H); 7.17-7.75 (m, 18H, ar-H); 8.07 (d, J = 7.7 Hz, 4H, ar-H); 8.79 (s, 2H, 2-H, 8-H); 11.27 (br s, 1H, 6-NH). ^{13}C NMR (DMSO-*d6*) δ 52.94 (C-2'); 55.08 (OCH_3); 62.34 (C-6'); 62.87 (C-4'); 63.88 (C-1'); 70.03 (C-3'); 76.42 (C-5'); 85.65 (C^{Tr}-O); 125.24 (C-5); 113.29, 126.90, 127.97, 128.22, 128.58, 128.80, 129.58, 129.70, 130.08, 132.56, 133.48, 133.65, 135.46, 144.36 and 158.20 (ar-C); 143.39 (C-8); 150.57 (C-4); 151.85 (C-2); 152.62 (C-6); 164.77 (CO-O); 165.75 (CO-N). HRMS (thgly) calcd. for $C_{45}H_{39}N_5O_7Na$ $(M+Na)^+$ 784.2747, found 784.2743.

1,5-Anhydro-3-*O*-benzoyl-6-*O*-monomethoxytrityl-2-deoxy-2-(N^2-(dimethylamino)methylene-guanin-9-yl)-D-*altro*-hexitol (38a)

Compound **38a** was obtained using the general procedure (2.02 mmol scale) [16] with tritylation performed in DMF catalyzed by silver nitrate. Flash chromatography on silica gel [CH_2Cl_2:acetone (85:15) to (0:100)] afforded 60% of the title product **38a** from **36.** TLC analysis : CH_2Cl_2:Acetone (50:50) : **38a** : Rf = 0.33; (regioisomer **38b** : Rf = 0.16) ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.08 and 3.24 (two s, 3H, $N(CH_3)_2$); 3.36-3.65 (m, 2H, 6'-Ha, 6'-He); 3.77 (s, 3H, OCH_3); 3.85-4.10 (m, 2H, 4'-H, 5'-H); 4.23-4.48 (m, 2H, 1'-Ha, 1'-He); 4.60 (br d, 1H, J = 2.9 Hz, 2'-H); 6.02 (t, 1H, J = 3.0 Hz, 3'-H); 6.84 (d, 2H, ar-H); 7.10-7.70 (m, 15H, ar-H); 8.06 (d, 2H, J = 5.8 Hz, ar-H); 8.08 (s, 1H, 8-H); 8.97 (s, 1H, N=C<u>H</u>-N); 9.26 (1-NH). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 34.97 and 41.34 ($N(CH_3)_2$); 53.18 (C-2'); 55.15 (OCH_3); 63.77 (C-6'); 64.47 (C-4'); 64.80 (C-1'); 69.60 (C-3'); 76.03 (C-5'); 86.93 (C^{Tr}-O); 119.67 (C-5); 113.27, 127.08, 128.02, 128.35, 128.63, 129.75, 130.33, 133.57 and 135.18; 136.85 (C-8); 144.11 (MMTr); 150.69 (C-4); 157.31 (C-2); 158.10 (C-6); 158.73 (MMTr); 159.83 (N=<u>C</u>H-N); 165.44 (Ph<u>C</u>O/OBz). HRMS (thgly:NaOAc) calcd. for $C_{41}H_{40}N_6O_7Na$ $(MNa)^+$ 751.2856 found 751.2878.

General procedure for phosphoramidite synthesis:

The phosphitylation reaction was carried out on 0.6 to 1 mmol of the sugar and base-protected *altro*-hexitol nucleoside (**5a**, **14a**, **20a** or **38a,** respectively) in dichloromethane (5 to 10 mL), using 3 eq. of freshly distilled *N,N*-diisopropylethylamine and 2 eq. of 2-cyanoethyl-*N,N*-diisopropylchlorophosphoramidite. The reaction mixture was stirred at room temperature under argon and progress of the reaction was monitored by TLC (hexane:acetone:triethylamine). For all *altro*-nucleoside phosphoramidites prepared, both stereoisomers gave the same Rf value on TLC analysis. Due to steric hindrance by the 3'-*O*-benzoyl group, the reaction was quite slow, in particular for the adenine analogue **20a**. To avoid benzoyl migration, a larger excess (1 eq. more) of each reactant was added after 1 h of reaction. The mixture was stirred at rt under argon for 1 to 3 h and quenched by addition of 3 mL of distilled water. After 10 min, the mixture was partitioned between 50 mL of dichloromethane and 30 mL of 5% aqueous $NaHCO_3$. The organic layer was washed with brine (3 x 30 mL), dried over Na_2SO_4, and evaporated. The residue was coevaporated with dichloromethane, purged with nitrogen and lyophilized. The residual foam was flash purified on silica gel. The obtained product was dissolved in 1 mL of dichloromethane and was precipitated by dropwise addition to 80 mL of cold hexane (-60 °C). The precipitate was collected, dried *in vacuo* and stored under nitrogen at -20 °C until use for oligonucleotide synthesis.

	Yield	TLC-system	Rf	MS[b]	^{31}P NMR
6	94%	59:40:1	0.39	856[M + Na]$^+$	151.16/150.21
15	91%	64:35:1	0.27	960[M + Na]$^+$	151.45/150.07
21	80%	59:40:1	0.28	984[M + Na]$^+$	151.64/149.54
39	71%	19:80:1	0.33	929[M + Na]$^+$	151.49/149.97

a) the ratios given are those for the system n-hexane/acetone/triethylamine.

b) LSIMS (thgly: NaOAc)

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