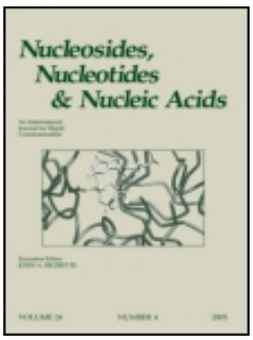

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SYNTHESIS AND CONFORMATIONAL ANALYSIS OF 1,5-ANHYDRO-2,4-DIDEOXY-D-MANNITOL NUCLEOSIDES

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ABSTRACT: 1,5-Anhydro-4,6-*O*-benzylidene-D-glucitol was used as starting material for the synthesis of 1,5-anhydro-2,4-dideoxy-D-mannitol nucleosides with an adenine and uracil base moiety. The compound with a purine base was obtained by direct nucleophilic substitution of a triflate. The pyrimidine nucleoside could be obtained by epoxide opening followed by inversion of configuration at the 3'-position. Both nucleosides adopt a C1 conformation with an axial base moiety.

INTRODUCTION

Nucleosides with a six membered carbohydrate moiety have several interesting characteristics: a) when compared with natural furanose nucleosides, the presence of an additional carbon atom increases the number of substitution sites from 5 to 6; b) the molecule is mostly frozen in a C_1 or ^1C conformation (limiting the possible conformations) so that conformational analysis is easier than with furanose nucleosides and, consequently, the modified nucleoside may be used as a model to investigate structure-function relationship; c) new nucleoside analogues may be obtained without anomeric centre but still having a ring oxygen atom and a 1,4-relationship between the nucleobase and the hydroxymethyl group. This latter arrangement of functional groups is found in anhydrohexitol nucleosides and, therefore these molecules can be considered as analogues of carbocyclic nucleosides. This means that they are chemically and

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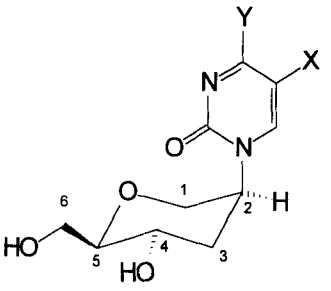
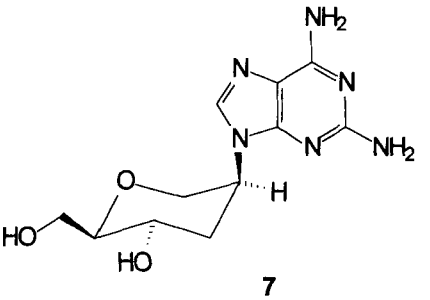
enzymatically more stable than natural nucleosides. Several of these 1,5-anhydrohexitol nucleosides have been found to possess antiviral activity. Some of them (1,5-anhydro-[1] 2,3-dideoxy-D-arabino-hexitol nucleosides with a 5-iodouracil[1] **1**, 5-ethyluracil[2] **2**, 5-trifluoromethyluracil[3] **3**, 5-vinyluracil[3] **4**, 5-propynyluracil[3] **5**, 5-fluorocytosin[2] **6** and 2,6-diaminopurine[2] **7** base moiety in the 2-position) show potent antiherpes activity. Other congeners demonstrate either weak antiherpes acitivity [1,5-anhydro-2-(5-iodouracil-1-yl)-2-deoxy-D-mannitol[4] **8**, 1,5-anhydro-2-(cytosin-1-yl)-2,3-dideoxy-D-ribohexitol[5] **9**, (1*RS*,3*SR*,4*RS*)-9-[4-(hydroxymethyl)-3-hydroxycyclohexyl]guanine[6] **10**, 1,5-anhydro-2-(thymin-1-yl)-2,3-dideoxy-3-*C*-hydroxymethyl-D-mannitol[7] **11**] or weak anti-HIV activity (1,5-anhydro-3-ene-2,3,4-trideoxy-D-threo-hexitol with an adenine[8] **12** and thymine **13** base moiety[8]). When considering the antiherpes (HSV-1) activity, it is of interest to mention that some of these nucleoside analogues (**1-5, 11**) show clearly different biological activity when evaluated against TK^+ and TK^- strains of HSV-1, which indicates that their anti-HSV activity must rely on the virus encoded thymidine kinase (TK). This difference in biological activity is less pronounced with compounds **6**, **7**, **9** and **10**, indicating that also other cellular/viral mechanisms may play a role in their mode of action. Structure-activity relationship studies, however, only make sense when a series of compounds are envisaged with similar mode of action. The most striking observation is that, till now, all active antiherpes agents have an axially oriented base moiety and an equatorially oriented hydroxymethyl group in a 1,4-relationship[8]. In this conformation the 1,5-anhydrohexitol nucleosides can be considered as mimics of furanose nucleosides in the 2'-exo/3'-endo conformation. This suggests that this conformation might be important for interaction of the nucleoside (or one of its metabolites) with one of the enzymes involved in its mode of action (i.e. kinases and/or polymerases). In order to further explore this structure-activity relationship we synthesized 1,5-anhydro-2,4-dideoxy-D-mannitol nucleosides **14a-b**. These molecules lack the equatorial 4-hydroxylgroup, which is replaced by an equatorial 3-hydroxylgroup. The gauche effect (O-C3-C2-N) should likewise be favourable for stabilizing the C_1 conformation and this may lead to biological activity. The synthesis of these compounds, additionally, allows us to evaluate the importance of the presence of the 4-hydroxyl group for biological activity.



1 X = I; Y = OH
2 X = C_2H_5; Y = OH
3 X = CF_3; Y = OH
4 X = CH=CH_2; Y = OH
5 X = C≡C–CH_3 ; Y = OH
6 X = F; Y = NH_2



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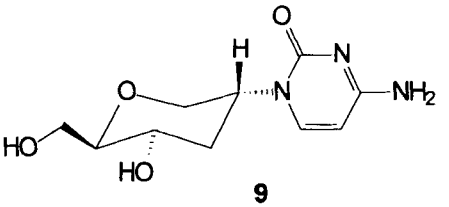

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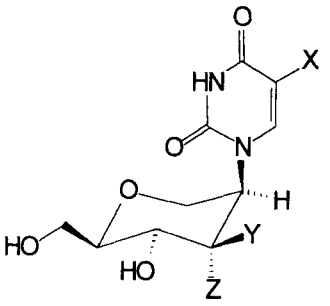
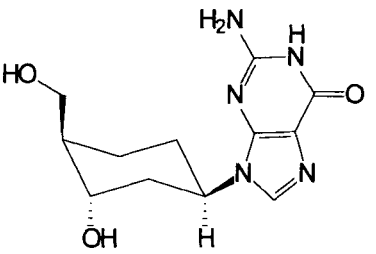


8 X = I; Y = OH; Z = H
11 X = CH_3; Y = CH_2OH; Z = H



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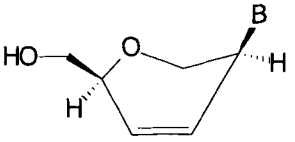
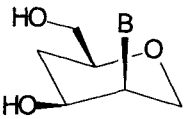


12 B = adenin-9-yl
13 B = thymin-1-yl



14a B = adenin-9-yl
14b B = uracil-1-yl

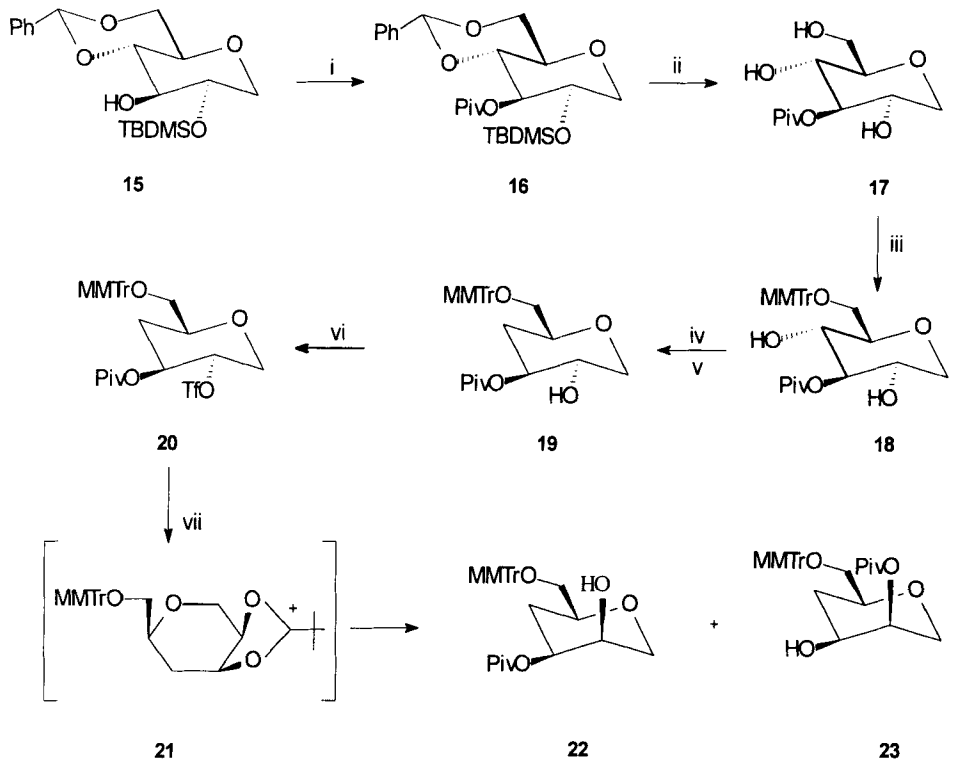
FIG. 1

RESULTS AND DISCUSSIONS

(A) Synthesis

Recently, we have reported[9] the synthesis of 1,5-anhydro-6-*O*-MMTr-3-*O*-TBDMS-2-(adenin-9-yl)-2-deoxy-D-mannitol. This compound is similar to **14a**, but has an additional hydroxyl group at the 4'-position. For the synthesis of 1,5-anhydro-2,4-dideoxy-D-mannitol type nucleosides it seems logical to consider the deoxygenation of the 4-position of the above mentioned 2-deoxy-D-mannitol compound. Thus, 1,5-anhydro-6-*O*-MMTr-3-*O*-TBDMS-N^6-benzoyl-2-(adenin-9-yl)-2-deoxy-D-mannitol was treated with phenoxythiocarbonyl chloride in the presence of *N,N*-dimethylaminopyridine (DMAP) in acetonitrile and, after usual work up, the crude reaction mixture was treated with n-tributyltin hydride in the presence of azobisisobutyronitrile (AIBN). The same reaction was repeated using pyridine both as base and solvent instead of DMAP and acetonitrile. Both deoxygenation reactions, however, led to an intractable mixture of compounds for which the reason is not totally clear. Therefore, we decided to use an alternate reaction scheme starting with another intermediate obtained during the synthesis of 1,5-anhydro-2-deoxy-D-mannitol nucleosides, i.e. 1,5-anhydro-4,6-*O*-benzylidene-2-*O*-TBDMS-D-glucitol **15**[9].

Treatment of **15** with pivaloyl chloride in pyridine at room temperature gave **16** in 94% yield. The 4,6-*O*-benzylidene group of **16** was removed by treatment of **16** with trifluoroacetic acid in dichloromethane. This acid treatment, however, also removed the 2-*O*-TBDMS protecting group, giving **17** in 73% yield. Under identical reaction conditions, the *O*-TBDMS group situated in β-position is stable as described previously[9]. The instability of the equatorially oriented 2-*O*-TBDMS group in α-configuration clearly demonstrates the difference in stability of a protecting group by its stereochemical environment. The primary hydroxyl group of **17** was protected with a monomethoxytrityl (MMTr) group upon treatment with MMTrCl in pyridine, yielding **18** in 76%. Treatment of **18** with phenoxythiocarbonyl chloride (1.2 equiv.) and DMAP in acetonitrile, followed by n-tributyltin hydride and AIBN in toluene at 110 °C, gave **19** in 41% yield. This two step reaction sequence was preferred over a multistep approach using complicated protection and deprotection strategies. At this stage of the reaction scheme, we tried to introduce the nucleobase in the 2-position of **19**. Therefore, compound **19** was treated with trifluoromethanesulphonic anhydride in the

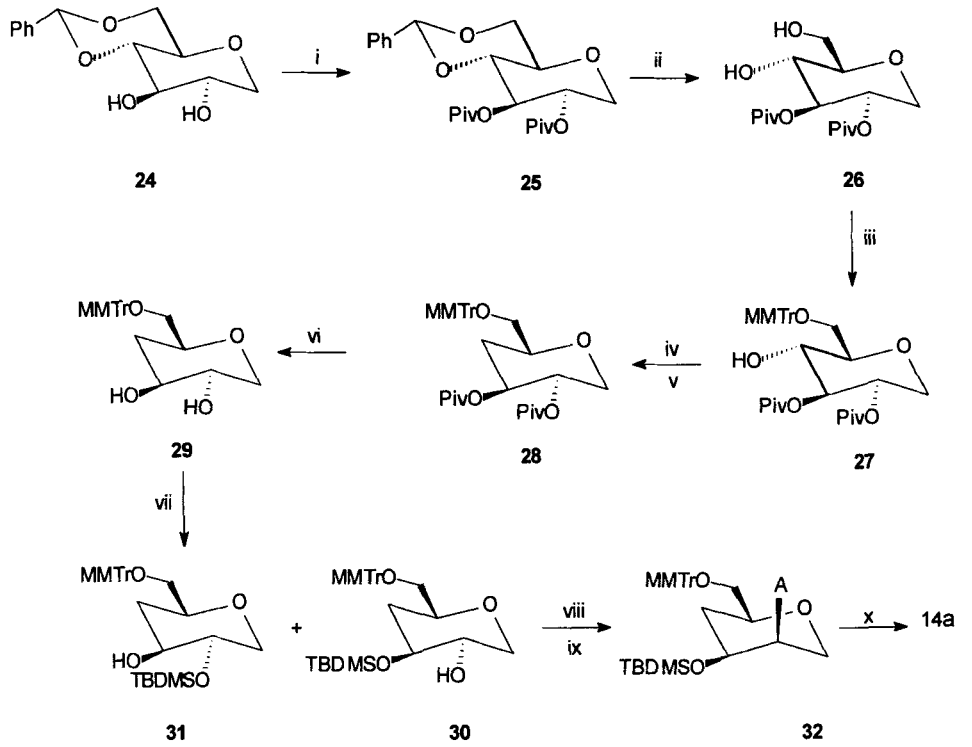


i: Pivaloyl chloride, pyridine, 94%; ii: CF_3COOH, CH_2Cl_2, 73%; iii: MMTr chloride, pyridine, 76%; iv: PhOC(S)Cl, DMAP, CH_3CN; v: nBu_3SnH, AIBN, toluene, Δ, 41% (iv and v); vi: $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, vii: tetrabutylammonium salt of adenine, CH_2Cl_2, 28% of **22** and 48% of **23**, Ph=phenyl.

Scheme 1

presence of pyridine in dichloromethane at –5 °C, and, after usual work-up procedure[9], crude **20** was reacted with tetrabutylammonium salt of adenine[10,11] in dichloromethane. However, this reaction procedure resulted in the isolation of **22** and **23** in a combined yield of 76% for the two steps. The intermediate **21** may give rise to the formation of both compounds. No trace of the desired adenine derivative could be detected.

Apparently, the neighbouring group participation reaction leading to inversion of stereochemistry at position-2 is much faster than the intermolecular nucleophilic substitution reaction. Another protecting group strategy is necessary in order to obtain the 2,4-dideoxy-D-mannitol nucleosides. As shown in Scheme 2, we selected the



i: Pivaloyl chloride, pyridine, 98%; ii: 80% CF_3COOH, CH_2Cl_2, 95%; iii: MMTr chloride, pyridine, 90%; iv: PhOC(S)Cl, DMAP, CH_3CN; v: nBu_3SnH, AIBN, toluene, Δ, 64%; vi: aq. 1N NaOH, dioxane, 92%; vii: TBDMSCl, Imidazole, DMF, 60% of **30** and 18% of **31**; viii: $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2; ix: tetrabutylammonium salt of adenine, CH_2Cl_2, 18%; x = aq. CF_3COOH, 49%. A = adenin-9-yl.

Scheme 2

TBDMS group for protection of the 3-hydroxylgroup. This protecting group is less prone to migration and neighbouring participation reactions.

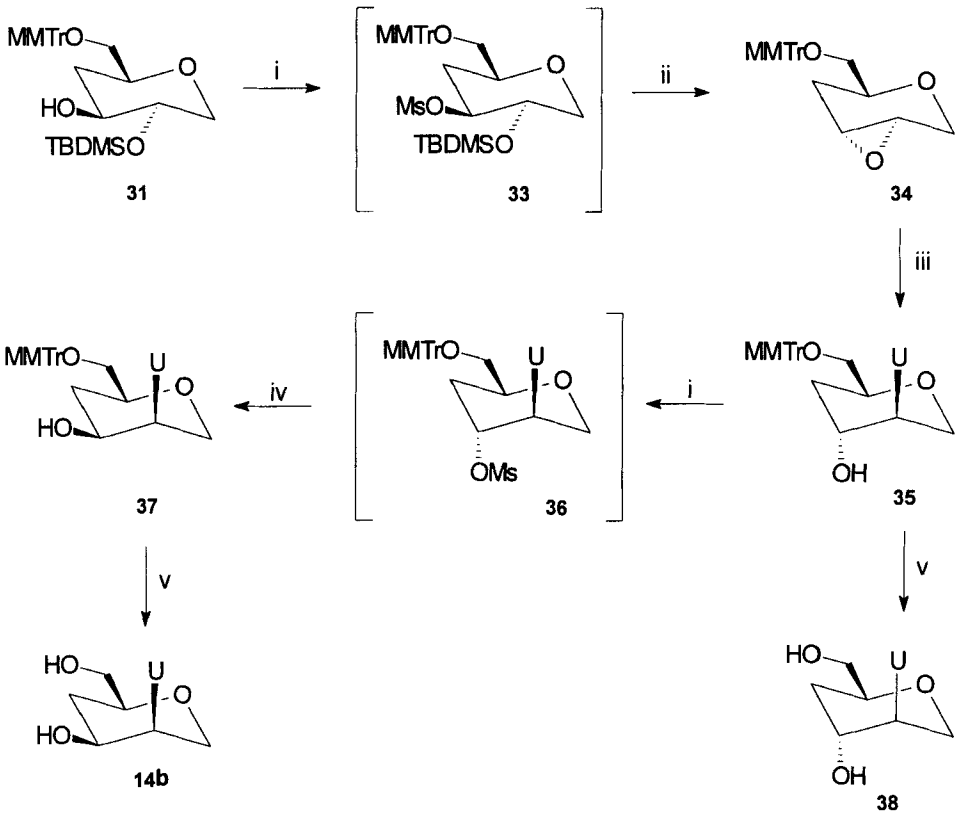
Treatment of compound **24**[9] with pivaloyl chloride in pyridine gave **25** in 98% yield. The 4,6-*O*-benzylidene protecting group of **25** was removed upon treatment with trifluoroacetic acid in dichloromethane to afford **26** (95%). Treatment of **26** with MMTrCl in pyridine gave **27** in 90% yield. Deoxygenation of the 4-hydroxyl group of **27**, via phenoxythiocarbonylation under Barton conditions as described above, yielded

28 in 64% yield (for two steps). Both pivaloyl groups of **28** were removed upon treatment with 1N NaOH in dioxane to give **29** in 92% yield. The 3-hydroxyl group of **29** can now be protected in a rather selective way. When **29** is treated with *t*-butyldimethylsilyl chloride in the presence of imidazole in DMF[12], **30** was obtained as major compound (60%) together with **31** (18%). The compounds **30** and **31** were differentiated by the use of NMR spectroscopy. For compound **30**, the signal of the OH-proton, proved by exchange with D_2O, shows a crosspeak with the C1' signal in a long-range ^1H-^{13}C heteronuclear correlation experiment (long-range Hetcor) which clearly indicates that the OH-group is positioned in the 2'-position. Activation of the 2-hydroxyl group of **30** as 2-*O*-triflate, followed by reaction with the tetrabutylammonium salt of adenine[10,11] in dichloromethane afforded **32** in 18% yield. TLC (CH_2Cl_2-MeOH 95 :5) shows the presence of four other compounds in the reaction mixture, which were not identified. Finally, the 6-*O*-MMTr and 3-*O*-TBDMS protecting groups of **32** were simultaneously removed using aqueous trifluoroacetic acid, giving 1,5-anhydro-2-(adenin-9-yl)-2,4-dideoxy-D-mannitol **14a** in 49% yield. For the preparation of uracil derivatives **14b** and **38** (Scheme 3) we started with **31**. Thus, **31** was treated with methanesulfonyl chloride (MsCl) in the presence of Et_3N in CH_2Cl_2 to afford **33** which after usual work up and treatment with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) gave the epoxide **34** in 64% yield (for two steps). The epoxide **34** was treated with uracil in the presence of NaH in DMF to give **35** in 76% yield. The configuration at C3' was inverted using O^2 neighbouring group participation reaction[4].

Treatment of **35** with MsCl in the presence of Et_3N in dichloromethane gave the corresponding mesylate **36** which was treated with aqueous 1 N NaOH in ethanol at 60 °C to afford **37** in 83% yield. The 6-*O*-MMTr group in **37** was removed upon treatment with aqueous 80% acetic acid to give **14b** (77%). Finally, **35** was treated with aqueous 80% acetic acid to afford **38** in 85% isolated yield. The determination of the antiviral activity of **14a**, **14b** and **38** is in progress.

(B) Determination of configuration and conformation of 14a, 14b and 38 by high resolution NMR spectroscopy.

The assignment of the resonances of the protons of **14a**, **14b** and **38** was made by using a combination of a DQF-COSY spectrum of **14a** and 1D ^1H NMR spectra of **14a**,



i: MsCl, Et_3N, CH_2Cl_2; ii: TBAF.$3H_2O$, THF, 64% for two steps; iii: sodium salt of uracil, DMF, 76%; iv: 1N NaOH, H_2O, EtOH, 83% for two steps; v: 80% CH_3COOH, H_2O, 85% for 38 and 77% for **14b**.

Scheme 3

14b and **38** at 27 °C at 500 MHz. The ^1H chemical shifts are given in the experimental section.

The configuration and conformation of **14a**, **14b** was determined on the basis of their $^3J_{HH}$ values. For **14a** and **14b** following $^3J_{HH}$ values are obtained: (**14a**): $^3J_{1',2'}$ = 1.4, $^3J_{1'',2'}$ = 2.3, $^3J_{2',3'}$ = 5.0, $^3J_{3',4''}$ = 12.0, $^3J_{3',4'}$ = 5.0, $^3J_{4'',5'}$ = 11.5, $^3J_{4',5'}$ = 2.1; (**14b**): $^3J_{1',2'}$ = 1.3, $^3J_{1'',2'}$ = 3.3, $^3J_{2',3'}$ = 5.0, $^3J_{3',4''}$ = 12.3, $^3J_{3',4'}$ = 5.0, $^3J_{4'',5'}$ = 11.5, $^3J_{4',5'}$ = 2.1. Inspection of these coupling constants reveals the following conclusions: i) the high values found for the vicinal coupling constants $^3J_{4'',5'} \approx 11$, $^3J_{3',4''} \approx 12$ implies that H3',

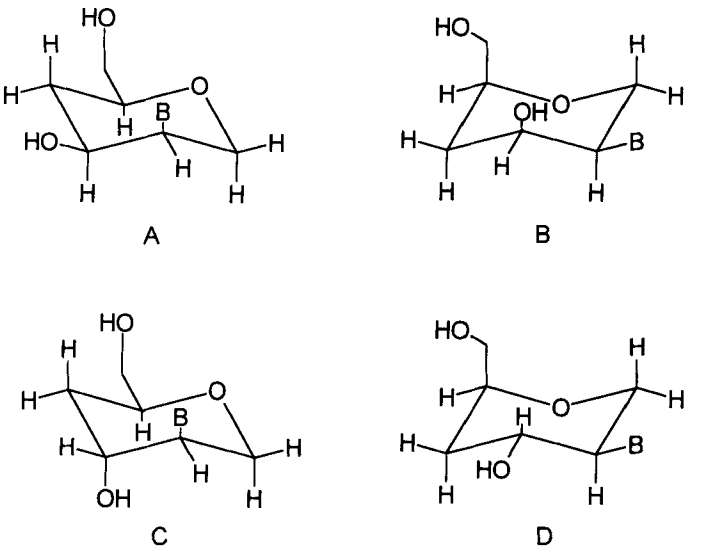


FIG. 2

H4" and H5' are axially oriented which is only possible when the OH group is β positioned and the conformation is C_1 as in A in FIG. 2; ii) the small coupling $^3J_{H2'-H3'} \approx$ 5 excludes that H2' and H3' are diaxially disposed which implies that the base is axial or in the β-position.

For compound **38**, there was severe overlap of the signals of H1', H1", H2', H3' and the signals of H6' and H6" resonate at the same chemical shift. The signals of H4' and H4" are separated and give a doublet of double doublet as pattern ($^3J \cong$ 3 Hz, 10 Hz, 13 Hz) and a double triplet ($^3J \cong$ 2 à 3 Hz (2 x), 13 Hz), respectively. Decoupling of H6' and H6" gives a double doublet for H5' with coupling constants of $^3J_{4',5'} \approx$ 10 and $^3J_{4",5'} \approx$ 2 à 3 which implies that H5' and H4' are diaxially disposed as in C_1 (FIG. 2, C).

The compounds **14a,b** and **38** adopt the C_1 conformation as is evident from their NMR spectra. In the light of our previous results this is not unexpected, especially because the base is in 1,3 position with respect to the ring oxygen and they experience then much less steric hindrance when in a axial position. Under these conditions the CH_2OH group will orient itself equatorially and thus determines the conformation as C_1

EXPERIMENTAL SECTION

The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Gemini-200 spectrometer using tetramethylsilane as an internal standard. When DMSO-d_6 was used as solvent, the resonance peak at 2.50 ppm was used as internal standard (for ^{1}H-NMR) and 39.6 ppm (for ^{13}C-NMR). (*s*: singlet, *d*: doublet, *dd*: double doublet, *ddd*: doublet of double doublet, *t*: triplet, *dt*: double triplet, *m*: multiplet and *br. s*: broad singlet). All chemical shifts are given in δ values. The ^{1}H and ^{13}C NMR spectra of **14a**, **14b** and **38** in D_2O solution have been recorded on a Varian Unity 500 MHz spectrometer at 27 °C. The carbon assignments were based on ATP experiments or 2D ^{1}H-^{13}C heteronuclear correlation experiments (HMQC and long-range Hetcor). The DQF-COSY of **14a** was recorded at 27 °C using 256 experiments of 2K complex data points and a relaxation delay of 1.5 s. The HMQC of **14a** and the long-range Hetcor of **30** were recorded with 128 increments in t_1, 2K data points in t_2. High resolution mass spectra (HRMS) were recorded on a Kratos Concept 1H mass spectrometer. The solvent was concentrated in vacuo. All other technical data were identical to those previously described[5,9].

1,5-Anhydro-4,6-*O*-benzylidene-3-*O*-pivaloyl-2-*O*-TBDMS-D-glucitol (16). To a cold solution (ice-water) of **15**[9] (2.0 g, 5.46 mmol) in pyridine (30 mL), pivaloyl chloride (1.34 mL, 10.92 mmol) was added and the reaction mixture was kept at room temperature for seven days. A cold solution of saturated aqueous sodium bicarbonate (100 mL) was added slowly to the reaction mixture. The reaction mixture was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with water (10 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (0-6% EtOAc in hexane) to give **16** (2.3 g, 94%). ^{1}H-NMR (DMSO-d_6): 7.38 (s, 5H) arom; 5.60 (s, 1H) benzylidene; 5.05 (t, $J_{2,3} \cong J_{3,4} \cong$ 9.2 Hz, 1H) H3; 4.23 (dd, J = 4.6, 9.8 Hz, 1H); 3.88 (m, 2H); 3.73-3.36 (m, 5H); 1.14 (s, 9H) piv; 0.81 (s, 9H) TBDMS; 0.07 (s, 3H) TBDMS; 0.04 (s, 3H) TBDMS. ^{13}C-NMR (DMSO-d_6): 176.9, 137.5, 128.8, 128.1, 125.8, 100.0, 78.8, 75.3, 70.5, 70.0, 69.3, 67.9, 27.1, 25.6, 17.7, -4.3, -5.0 (the quaternary carbon of the piv. group was hidden under the solvent peak). HRMS calcd. for $C_{24}H_{39}O_6Si$ $(M+H)^+$ 451.2515, found 451.2535.

1,5-Anhydro-3-*O*-pivaloyl-D-glucitol (17). Compound **16** (1.9 g, 4.22 mmol) was treated with CF_3COOH (40 mL) in CH_2Cl_2 (40 mL) at room temperature for 24 h.

The solvent was removed, the residue was dissolved in MeOH (20 mL) and treated with NH_4OH (4 mL). After concentration the residue was purified by silica gel column chromatography (0-6% MeOH in CH_2Cl_2) to give **17** (760 mg, 73%). ^{1}H-NMR (DMSO-d_6): 5.15 (d, J = 1.9 Hz, 1H); 4.95 (d, J = 0.7 Hz, 1H); 4.68 (t, J = 9.0 Hz, 1H); 4.65 (t, J = 5.9 Hz, 1H); 3.73 (dd, J = 5.3, 10.8 Hz, 1H); 3.62 (ddd, J = 1.8, 5.8, 11.8 Hz, 1H); 3.40 (m, 2H); 3.28-3.0 (m, 3H); 1.16 (s, 9H). ^{13}C-NMR (DMSO-d_6): 177.1, 81.6, 79.4, 69.6, 68.1 (two C), 61.1, 38.8, 27.2. HRMS calcd. for $C_{11}H_{21}O_6$ $(M+H)^+$ 249.1338, found 249.1334.

1,5-Anhydro-6-*O*-MMTr-3-*O*-pivaloyl-D-glucitol (18). Compound **17** (750 mg, 3.02 mmol) was treated with MMTrCl (1.11 g, 3.62 mmol) in pyridine (10 mL) at room temperature overnight. A cold solution of saturated aqueous sodium bicarbonate (10 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layer was washed with H_2O (10 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (0-1.5% MeOH in CH_2Cl_2) to give **18** (1.2 g, 76%). ^{1}H-NMR ($CDCl_3$): 7.50-6.78 (m, 14H) arom; 4.71 (t, J ≅ 9.1 Hz, 1H) H3; 4.05 (dd, J = 5.6, 11.3 Hz, 1H) H5; 3.79 (s, 3H) OCH_3; 3.78-3.51 (m, 2H) H2, H1'; 3.41-3.18 (m, 2H) H1", H4; 2.78 (d, 1H) H6'; 2.67 (d, 1H) H6"; 1.21 (s, 9H). ^{13}C-NMR ($CDCl_3$): 180.9, 158.6, 144.0, 135.1, 130.3, 128.3, 127.9, 127.0, 113.2, 86.9, 81.0, 78.8, 70.5, 69.9, 69.2, 64.3, 55.2, 39.0, 27.1. HRMS calcd. for $C_{31}H_{36}O_7Na$ $(M+Na)^+$ 543.2358, found 543.2354.

1,5-Anhydro-6-*O*-MMTr-3-*O*-pivaloyl-4-deoxy-D-glucitol (19). To a cold (ice-water) solution of **18** (3.0 g, 5.76 mmol) in acetonitrile was added DMAP (1.4 g, 11.52 mmol) followed by slow addition of phenoxythionocarbonyl chloride (955 μL, 6.91 mmol). The reaction mixture was kept at room temperature for 24 h, and after being concentrated the residue was dissolved in CH_2Cl_2 (100 mL), and washed successively with saturated aqueous NH_4Cl solution (4 x 15 mL) and H_2O (10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The crude residue was dissolved in toluene (50 mL) and treated with tributyltin hydride (3.09 mL, 11.52 mmol) and AIBN (236 mg, 1.44 mmol) at 110 °C overnight. The reaction mixture was concentrated and the residue was purified by silica gel column chromatography (0-6% EtOAc in hexane) to give **19** (1.20 g, 41% in two steps). ^{1}H-NMR ($CDCl_3$): 7.50-6.78 (m, 14H) arom; 4.28 (m, $J_{2,3}$ = 14.2, $J_{3,4'}$ = 9.0, $J_{3,4"}$ = 5.3 Hz, 1H) H3; 3.97 (ddd, J =

1.5, 4.9, 11.8 Hz, 1H) H5; 3.79 (s, 3H) OCH_3; 3.65-3.43 (m, 2H) H2, H1'; 3.38 (m, 3H) H1", H6' and H6"; 2.68 (d, $J_{2,OH}$ = 3.1 Hz, 1H) 2OH; 1.98 (m, $J_{3,4'}$ = 9.0, $J_{4',5}$ = 11.8 Hz, 1H) H4'; 1.65 (m, $J_{3,4"}$ = 5.3 Hz, $J_{4',5'}$ = 4.9, $J_{4',4"}$ = 12.7 Hz, 1H) H4"; 1.20 (s, 9H) piv. ^{13}C-NMR ($CDCl_3$): 177.7, 158.5, 144.2, 135.3, 130.3, 128.3, 127.8, 126.9, 113.1, 86.6, 77.7, 72.0, 67.2, 65.8, 63.5, 55.1, 38.8, 27.1, 25.7. HRMS calcd. for $C_{31}H_{36}O_6Na$ $(M+Na)^+$ 527.2409, found 527.2385.

1,5-Anhydro-6-*O*-MMTr-3-*O*-pivaloyl-4-deoxy-D-mannitol (22) and 1,5-Anhydro-6-*O*-MMTr-2-*O*-pivaloyl-4-deoxy-D-mannitol (23). To a cold (-5 °C) solution of **19** (504 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) was added pyridine (171 µL) followed by slow addition of trifluoromethanesulfonic anhydride (252 µL in CH_2Cl_2, 10 µL) under nitrogen atmosphere. The reaction mixture was kept at -5 °C for 2 h, quenched with ice-water and diluted by addition of CH_2Cl_2 (30 mL). The two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers was washed successively with pre-cooled (-5 °C) saturated Na_2HPO_4 (3 x 10 mL) and H_2O (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated at 16 °C. This crude material was dissolved in CH_2Cl_2 (2 mL) and added to a solution of tetrabutylammonium salt of adenine in CH_2Cl_2 (40 mL). The reaction mixture was kept at room temperature for 24 h. The precipitate was filtered off and washed with CH_2Cl_2. The combined filtrate was concentrated and the residue purified by silica gel column chromatography (0-30% EtOAc in hexane) to give **22** (140 mg, 28%) and **23** (240 mg, 48%) in a total yield of 76% for two steps. **Compound 22**, ^{1}H-NMR ($CDCl_3$): 7.50-6.78 (m, 14H) arom; 4.80 (ddd, $J_{2,3}$ = 2.6, $J_{3,4'}$ = 4.9, $J_{3,4"}$ = 11.7 Hz, 1H) H3; 4.11-3.94 (m, 2H) H2, H5; 3.79 (s, 3H) OCH_3; 3.58-3.28 (m, 4H) H6', H6", H1' and H1"; 2.19 (d, $J_{2,OH}$ = 4.8 Hz, 1H) 2OH; 2.05 (m, 1H) H4', 1.68 (m, 1H) H4''; 1.21 (s, 9H) piv. ^{13}C-NMR ($CDCl_3$): 177.7, 158.5, 144.2, 135.3, 130.3, 128.3, 127.8, 126.8, 113.1, 86.6, 77.7, 72.0, 67.2, 65.8, 63.5, 55.1, 38.8, 27.1, 25.7. HRMS calcd. for $C_{31}H_{36}O_6Na$ $(M+Na)^+$ 527.2409, found 527.2395. **Compound 23**, ^{1}H-NMR ($CDCl_3$): 7.48-6.76 (m, 14H) arom; 5.30 (m, 1H); 4.96 (m, 2H); 3.79 (s, 3H); 3.65-3.40 (m, 2H), 3.28 (dd, J = 5.9, 9.1 Hz, 1H); 3.05 (dd, J = 9.0, 7.2 Hz, 1H); 2.25 (d, J = 2.8 Hz, 1H); 1.93-1.63 (m, 2H); 1.10 (s, 9H). ^{13}C-NMR ($CDCl_3$): 179.7, 158.6, 144.0, 135.4, 130.3, 128.4, 127.8, 126.9, 113.0, 86.5, 76.4, 70.0, 69.7, 66.0, 62.4, 55.2, 38.4, 29.3, 27.0. HRMS calcd. for $C_{31}H_{36}O_6Na$ $(M+Na)^+$ 527.2409, found 527.2391.

1,5-Anhydro-4,6-*O*-benzylidene-2,3-*O*-bis-pivaloyl-D-glucitol (25). To a cold solution (ice-water) of **24** (10.31 g, 40.91 mmol) in pyridine (200 mL) was added pivaloyl chloride (15.12 mL, 122.76 mmol) and the reaction mixture was kept at room temperature for 7 days. A cold solution of saturated aqueous $NaHCO_3$ (200 mL) was added slowly to the reaction mixture and the mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with H_2O (25 mL), dried over Na_2SO_4, filtered, concentrated to give pure **25** (17.18 g, 98%). ^{1}H-NMR ($CDCl_3$): 7.49-7.32 (m, 5H) arom; 5.51 (s, 1H) benzylidene; 5.37 (t, J = 9.4 Hz, 1H); 5.05 (m, 1H); 4.35 (dd, J = 4.9, 10.4 Hz, 1H); 4.11 (dd, J = 5.8, 11.0 Hz, 1H); 3.78-3.59 (m, 2H); 3.53-3.31 (m, 2H); 1.17 (s, 9H); 1.16 (s, 9H). ^{13}C-NMR ($CDCl_3$): 177.5, 177.2, 137.0, 128.9, 128.2, 125.9, 101.2, 79.2, 72.0, 71.5, 69.3, 68.2, 67.6, 38.8 (two C), 27.1 (two C). HRMS calcd. for $C_{23}H_{33}O_7$ $(M+H)^+$ 421.2226, found 421.2225.

1,5-Anhydro-2,3-*O*-bis-pivaloyl-D-glucitol (26). Compound **25** (12.0 g, 28.6 mmol) was treated with CF_3COOH (100 mL) in CH_2Cl_2 (100 mL) at room temperature for 48 h. The reaction mixture was concentrated, the residue dissolved in MeOH (60 mL) and treated with concentrated NH_4OH (6 mL). The residue, after concentration, was purified by silica gel column chromatography (0-50% EtOAc in hexane) to give **26** (9.0 g, 95%). ^{1}H-NMR ($CDCl_3$): 5.15 – 4.80 (m, 2H) H2 H3; 4.07 (dd, $J_{1',2}$ = 5.3, $J_{1',1''}$ = 11.3, 1H)H1'; 3.92 (dd, $J_{5,6'}$ = 3.3, $J_{6',6''}$ = 11.9 Hz, 1H) H6'; 3.78 (dd, $J_{5,6''}$ = 4.6, $J_{6',6''}$ = 11.9, 1H) H6"; 3.67 (t, $J_{4',5} \cong J_{3,4'} \cong$ 9.5, 1H) H4'; 3.45 – 3.20 (m, 2H) H5, H1", 2.62 (br. s, 2H) 4OH and 6OH; 1.20 (s, 9H) piv; 1.15 (s, 9H) piv. ^{13}C-NMR ($CDCl_3$): 179.5, 177.4, 80.4, 76.7, 70.0, 68.7, 66.7, 62.4, 39.0, 38.8, 27.1 (two C). HRMS calcd. for $C_{16}H_{29}O_7$ $(M+H)^+$ 333.1913, found 333.1922.

1,5-Anhydro-6-*O*-MMTr-2,3-*O*-bis-pivaloyl-D-glucitol (27). To a solution of **26** (10.24 g, 30.96 mmol) in pyridine (150 mL) was added MMTrCl (11.46 g, 37.14 mmol) and the reaction mixture was kept at room temperature overnight. A cold solution of saturated aqueous $NaHCO_3$ (200 mL) was added slowly to the reaction mixture and the mixture was extracted with CH_2Cl_2 (3 x 200 mL). The combined organic layer was washed with H_2O (30 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (0-15% EtOAc in hexane) to give **27** (16.8 g, 90%). ^{1}H-NMR ($CDCl_3$): 7.50-6.78 (m, 14H) arom; 5.15 – 4.80 (m, 2H) H2 H3; 4.95 (m, 1H); 4.08 (dd, $J_{1',2}$ = 5.4, $J_{1',1''}$ = 11.2 Hz, 1H) H1'; 3.78 (s, 3H) OCH_3;

3.62 (m, 1H) H4; 3.38 (m, 3H) H5, H6', H6"; 3.23 (t, $J_{1",2} = J_{1',1"} = 11.2$, 1H) H1" ; 2.53 (d, $J_{4,OH} = 4.0$, 1H) 4OH; 1.21 (s, 9H) Piv; 1.16 (s, 9H) piv. ^{13}C-NMR ($CDCl_3$): 178.8, 177.4, 158.7, 144.1, 135.3, 130.4, 128.4, 127.9, 127.0, 113.3, 87.0, 79.2, 76.1, 71.2, 68.8, 66.8, 64.1, 55.2, 38.9, 38.8, 27.1 (two C). HRMS calcd. for $C_{36}H_{44}O_8Na$ $(M+Na)^+$ 627.2934, found 627.2943.

1,5-Anhydro-6-*O*-MMTr-2,3-*O*-bis-pivaloyl-4-deoxy-D-glucitol (28). To a cold (ice-water) solution of **27** (7.0 g, 11.58 mmol) in acetonitrile (100 mL) was added DMAP (3.39 g, 27.79 mmol) followed by slow addition of phenoxythiocarbonyl chloride (1.92 mL, 13.89 mmol) and the reaction mixture was kept at room temperature for 48 h. The reaction mixture was concentrated and the residue dissolved in CH_2Cl_2 (200 mL), washed successively with saturated aqueous solution of NH_4Cl (5 x 20 mL) and H_2O (20 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The crude residue was dissolved in dry toluene (60 mL) and treated with n-tributyltin hydride (6.22 mL, 23.16 mmol) in the presence of AIBN (480 mg, 2.89 mmol) at 110 °C for 60 min. The reaction mixture was concentrated and the residue was purified by silica gel column chromatography (0-2.5% EtOAc in hexane) to give **28** (4.34 g, 64% in two steps). ^{1}H-NMR ($CDCl_3$): 7.50-6.78 (m, 14H) arom; 5.01 (m, 1H) H3; 4.90 (m, 1H) H2; 4.08 (dd, $J_{1',2} = 5.2$, $J_{1',1"} = 11.1$ Hz, 1H) H1'; 3.79 (s, 3H) OCH_3; 3.62 (m, 1H) H5; 3.23 (m, 2H) H6', H1"; 3.04 (dd, $J_{5,6"} = 4.7$, $J_{6',6"} = 9.7$ Hz, 1H) H6"; 2.08 (ddd, $J_{4',5} = 1.8$, $J_{3,4'} = 4.7$, $J_{4',4"} = 12.5$, 1H) H4'; 1.48 (m, 1H) H4". 1.18 (s, 18H) 2 x piv. ^{13}C-NMR ($CDCl_3$): 177.7, 177.5, 158.6, 144.3, 135.5, 130.3, 128.4, 127.8, 126.9, 113.1, 86.3, 75.5, 71.4, 69.7, 67.0, 66.0, 55.2, 38.7 (two C), 33.4, 27.1 (two C). HRMS calcd. for $C_{36}H_{44}O_7Na$ $(M+Na)^+$ 611.2984, found 611.2975.

1,5-Anhydro-6-*O*-MMTr-4-deoxy-D-glucitol (29). Compound **28** (3.3 g, 5.6 mmol) was treated with aqueous (1N) NaOH (50 mL) in dioxane (50 mL) at 55 °C for 24 h. The pH of the reaction mixture was adjusted to 7.0 by slow addition (in ice-water) of aqueous HCl. The volume of the reaction mixture was reduced to 1/3 of it's original volume and extracted with EtOAc (3 x 100 mL). The combined organic layers were concentrated and the residue was purified by silica gel column chromatography (0-3% MeOH in CH_2Cl_2) to give **29** (2.15 g, 92%). ^{1}H-NMR ($CDCl_3$): 7.49-6.78 (m, 14H); 3.98 (dd, $J_{1',2} = 4.7$, $J_{1',1"} = 11.0$ Hz, 1H) H1'; 3.79 (s, 3H) OCH_3; 3.65-3.40 (m, 3H) H2, H3, H5; 3.26-2.97 (m, 3H) H1", H6', H6"; 2.07 (ddd, J = 2.0, 4.2, 12.5 Hz, 1H) H4';

1.43 (m, 1H) H4". ^{13}C-NMR ($CDCl_3$): 158.5, 144.4, 135.5, 130.4, 128.4, 127.8, 126.9, 113.0, 86.3, 75.8, 73.4, 72.3, 69.7, 66.0, 55.2, 36.0. HRMS calcd. for $C_{26}H_{28}O_5Na$ $(M+Na)^+$ 443.1834, found 443.1827.

1,5-Anhydro-6-*O*-MMTr-2-*O*-TBDMS-4-deoxy-D-glucitol (31) and 1,5-Anhydro-6-*O*-MMTr-3-*O*-TBDMS-4-deoxy-D-glucitol (30). To a solution of **29** (2.15 g, 5.1 mmol) in DMF (30 mL), imidazole (416 mg, 6.12 mmol) and TBDMSCl (845 mg, 5.61 mmol) were added in two portions at an interval of 10 h. The reaction mixture was kept at room temperature for 20 h. The reaction mixture was concentrated, the residue was dissolved in CH_2Cl_2 (100 mL), washed successively with saturated aqueous solution of NH_4Cl (3 x 15 mL) and H_2O (10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (0-15% EtOAc in hexane) to give **31** (500 mg, 18%) and **30** (1.65 g, 60%). This reaction was also performed using pyridine both as a base and solvent. Thus, to a solution of **29** (2.96 g, 7.03 mmol) in pyridine (35 mL) was added TBDMSCl (1.16 g, 7.73 mmol) in two portions at an interval of 10 h and kept at room temperature for 40 h. The reaction mixture was quenched with cold aqueous saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 50 mL). The organic layer was concentrated, coevaporated with toluene and the residue was purified by silica gel column chromatography (0-15% ethyl acetate in hexane) to give **30** (2.0 g, 53%) and **31** (1.0 g, 27%). **Compound 31**, ^{1}H-NMR ($CDCl_3$) 7.50-6.80 (m, 14H) arom; 3.88 (dd, $J_{1',2}$ = 4.6, $J_{1',1"}$ = 11.2, 1H) H1'; 3.78 (s, 3H) OCH_3; 3.70-3.40 (m, 3H) H2, H3, H5; 3.24-2.99 (m, 3H) H1", H6', H6"; 2.28 (br. s, 1H) 3OH; 2.08 (dd, J = 4.0, 12.0 Hz, 1H) H4'; 1.45 (apparent dt, J ≅ 12, 1H) H4". ^{13}C-NMR ($CDCl_3$) 158.6, 144.5, 135.6, 130.4, 128.5, 127.8, 126.9, 113.0, 86.2 (MMTr); 76.4 (C5); 73.6 (C2, C3); 70.1 (C1); 66.0 (C6); 55.1 (OCH_3); 35.1 (C4); 25.7, 17.9, -4.5, -4.8 (TBDMS). HRMS calcd. for $C_{32}H_{42}O_5SiNa$ $(M+Na)^+$ 557.2699, found 557.2679. **Compound 30**, ^{1}H-NMR ($CDCl_3$) 7.50-6.80 (m, 14H) arom; 4.05 (dd, $J_{1',2}$ = 4.8, $J_{1',1"}$ = 12.0 Hz, 1H) H1'; 3.78 (s, 3H) OCH_3; 3.62-3.40 (m, 3H) H2, H3, H5; 3.30-3.10 (m, 2H) H1", H6'; 3.00 (dd, J = 4.0, J = 13.7 Hz, 1H) H6", 2.20 (d, 1H) OH (exchanges with D_2O and shows long-range coupling with C1' in a long-range Hetcor experiment), 1.90 (dd, J = 4.0, 12.0 Hz, 1H) H4'; 1.26 (apparent dt, J ≅ 12 Hz, 1H) H4". ^{13}C-NMR ($CDCl_3$) 158.6, 144.6, 135.7, 130.4, 128.5, 127.8, 126.9, 113.0, 86.2 (MMTr); 75.8 (C5); 74.8 (C3); 72.3 (C2); 69.3 (C1); 66.2 (C6); 55.1 (OCH_3); 36.9

(C4); 25.7, 18.0, -4.2, -4.6 (TBDMS). HRMS calcd. for $C_{32}H_{42}O_5SiNa$ $(M+Na)^+$ 557.2699, found 557.2681.

1,5-Anhydro-6-*O*-MMTr-3-*O*-TBDMS-2-(adenin-9-yl)-2,4-dideoxy-D-mannitol (32). The *O*-triflate of **30** was prepared following identical reaction conditions as described for **20** using **30** (535 mg, 1.0 mmol), trifluoromethanesulfonic anhydride (252 μL in 10 μL CH_2Cl_2) in the presence of pyridine (171 μL) in CH_2Cl_2 (10 mL). The crude triflate was dissolved in CH_2Cl_2 (5 mL) and added to a solution of tetrabutylammonium salt of adenine in CH_2Cl_2 (40 mL). The reaction mixture was kept at room temperature for 48 h. The precipitate was filtered, and washed with CH_2Cl_2. The combined filtrate was concentrated and the residue purified by silica gel column chromatography (0-4% MeOH in CH_2Cl_2) to give **32** (120 mg, 18% overall yield). ^{1}H-NMR ($CDCl_3$) 8.30 (s, 1H) H8/H2; 8.25 (s, 1H) H2/H8; 7.50-6.80 (m, 14H) arom; 5.70 (br. s, 2H) NH2; 4.90 (m, 1H) H2; 4.40-3.20 (m, 9H) H1',H1", H3, H5, H6', H6" and OCH_3; 1.70 (m, 2H) H4', H4". ^{13}C-NMR ($CDCl_3$) 158.7, 155.4 (C6), 152.8 (C2), 152.0 (C4), 144.4, 141.2 (C8), 135.5,130.4, 128.5, 127.9, 127.0, 119.5 (C5), 113.2, 86.5, 76.0, 68.8, 68.1, 66.2, 55.2, 53.3, 33.2, 25.3, -5.0. HRMS calcd. for $C_{37}H_{45}N_5O_4SiNa$ $(M+Na)^+$ 674.3138, found 674.3099.

1,5-Anhydro-2'-(adenin-9-yl)-2,4-dideoxy-D-mannitol (14a). Compound **32** (100 mg, 0.15 mmol) was treated with aqueous 80% CF_3COOH (10 mL) at room temperature overnight. The reaction mixture was concentrated. The residue was dissolved in MeOH (10 mL) and treated with NH_4OH (2 mL), concentrated and crystallized from MeOH to give **14a** (20 mg, 49%). ^{1}H-NMR (D_2O) 8.51 (s, 1H) H2/H8; 8.15 (s, 1H) H2/H8; 4.84 (m, 1H) H2'; 4.31 (dt, $J_{2',3'} = J_{3',4'} = 5.0$, $J_{3',4"} = 12.0$, 1H) H3'; 4.22 (dd, $J_{1',2'} = 1.4$, $J_{1',1"} = 13.2$, 1H) H1'; 3.99 (dd, $J_{1",2'} = 2.3$, $J_{1',1"} = 13.2$, 1H) H1"; 3.75-3.68 (m, 2H) H5', H6'; 3.63 (dd, $J_{5',6"} = 6.5$, $J_{6',6"} = 12.4$, 1H) H6"; 1.83-1.70 (m, after decoupling of H2', multiplet becomes ddd, $J_{4',5'} \cong 2.1$, $J_{3',4'} = 5.0$, $J_{4',4"} \cong 13.2$ Hz, 1H) H4'; 1.49 (apparent dt, $J_{3'4"} = 12.1$, $J_{4",5'} = 11.5$, $J_{4',4"} \cong 13.2$, 1H) H4". ^{13}C-NMR (D_2O) 156.4 (C6), 153.2 (C2), 151.2 (C4), 142.6 (C8), 119.0 (C5), 77.8 (C5'), 68.8 (C1'), 67.5 (C3'), 64.7 (C6'), 54.2 (C2'), 30.7 (C4'). HRMS calcd. for $C_{11}H_{16}N_5O_3$ $(M+H)^+$ 266.1253, found 266.1297. Elem. anal. calcd. for $C_{11}H_{15}N_5O_3.2H_2O$: C: 43.83, H: 6.36 , N: 23.25. Found C: 43.75, H : 6.27, N: 23.17.

1,5;2,3-Di-anhydro-6-*O*-MMTr-D-allitol (34). To a cold (ice-water) solution of **31** (950 mg, 1.77 mmol) in CH_2Cl_2 (15 mL), Et_3N (368 μL, 2.65 mmol) was added,

followed by MsCl (164 μL, 2.13 mmol) and the reaction mixture was kept at 5 °C for 2 h. The reaction mixture was quenched with cold aqueous saturated $NaHCO_3$ and after addition of CH_2Cl_2 (30 mL), the two layers were separated. The aqueous layer was reextracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed with water (1 x 10 mL), dried over Na_2SO_4, filtered and concentrated to give crude **33**. The crude residue was dissolved in THF (20 mL), TBAF.$3H_2O$ (1.24 g, 3.54 mmol) was added and kept at 50 °C for 48 h. The solvent was removed and the residue was purified by silica gel column chromatography (0-10% ethyl acetate in hexane) to give **34** (460 mg, 64%). ^{1}H-NMR ($CDCl_3$) 7.50-6.80 (m, 14H) arom; 4.22 (dd, $J_{1',2}$ = 4.0 Hz, $J_{1',1''}$ = 13.5 Hz, 1H) H1'; 3.93 (d, $J_{1',1''}$ = 13.5, 1H) H1"; 3.65-3.52 (m, 1H) H5; 3.40-3.30 (m, 1H) H3; 3.23 (t, $J_{1',2} \cong J_{2,3}$ = 4.0, Hz, 1H) H2; 3.08 (dd, $J_{5,6'}$ = 5.9, $J_{6',6''}$ = 9.7, 1H) H6'; 2.94 (dd, $J_{5,6''}$ = 4.7, $J_{6',6''}$ = 9.7, 1H) H6"; 2.05 (m, 1H) H4'; 1.76 (ddd, J = 2.9, 11.1, 14.5, 1H) H4". ^{13}C-NMR ($CDCl_3$) 158.6, 144.5, 135.7, 130.4, 128.5, 127.8, 126.9, 113.0, 86.1, 69.6, 66.2, 65.7, 55.1, 51.2, 50.7, 28.2. HRMS calcd. for $C_{26}H_{26}O_4Na$ $(M+Na)^+$ 425.1729, found 425.1771.

1,5-Anhydro-6-*O*-MMTr-2-(uracil-1-yl)-2,4-dideoxy-D-altritol (35). A mixture of uracil (233 mg, 2.08 mmol) and NaH 80% in oil (125 mg, 4.16 mmol) in DMF (10 mL) was heated at 100 °C for 60 min. To that mixture **34** (420 mg, 1.04 mmol) in DMF (5 mL) was added and kept at 120 °C for 48 h. The reaction mixture was cooled to room temperature and concentrated. A mixture of ethyl acetate (50 mL) and H_2O (10 mL) was added and the two layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 30 mL). The combined organic layer was dried over Na_2SO_4, filtered, concentrated and purified by silica gel column chromatography (0-2.5% MeOH in CH_2Cl_2) to give **35** (410 mg, 76%). ^{1}H-NMR ($CDCl_3$) 10.25 (s, 1H) NH; 8.44 (d, $J_{5,6}$ = 8.4Hz, 1H) H6; 7.50-6.80 (m, 14H) arom; 5.78 (d, $J_{5,6}$ = 8.4 Hz, 1H) H5; 4.42 (m, 1H) H1'; 4.16 (m, 4H) H1", H2', H3', H5'; 3.78 (s, 3H) OCH_3; 3.24 (dd, 1H) H6'; 3.03 (dd, 1H) H6"; 1.90 (t, 1H) H4'; 1.62 (m, 2H) H4", 3'OH. ^{13}C-NMR ($CDCl_3$) 163.6, 158.7, 151.8, 144.5, 143.8, 135.5, 130.5, 128.4, 127.9, 127.0, 113.1, 102.6, 86.2, 70.9, 65.9, 64.6, 64.0, 55.2, 54.7, 29.5. HRMS calcd. for $C_{30}H_{29}N_2O_6Na_2$ $(M+2Na-H)^+$ 559.1821, found 559.1844.

1,5-Anhydro-6-*O*-MMTr-2-(uracil-1-yl)-2,4-dideoxy-D-mannitol (37). To a cold (ice-water) solution of **35** (230 mg, 0.45 mmol) in CH_2Cl_2 (10 mL) was added Et_3N

(93 μL, 0.67 mmol) followed by addition of MsCl (42 μL, 0.54 mmol) and the mixture was kept at 5 °C for 2 h. The reaction mixture was quenched with cold aqueous saturated $NaHCO_3$. After addition of CH_2Cl_2 (20 mL), the two layers were separated. The aqueous layer was reextracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with H_2O (10 mL), dried over Na_2SO_4, filtered and concentrated to give crude **36**. Crude **36** in EtOH (20 mL) was heated until it became a clear solution and treated with aqueous (1N) NaOH (3 mL) at 60 °C for 5 h. The reaction mixture was cooled to 5 °C and the pH was adjusted to 7.0 by addition of dil. HCl. The reaction mixture was concentrated, the residue dissolved in CH_2Cl_2 (50 mL), washed with aqueous saturated $NaHCO_3$ (10 mL), H_2O (10 mL), dried, filtered and concentrated. The residue was purified by silica gel column chromatography (0-2.5% MeOH in CH_2Cl_2) to give **37** (190 mg, 83%). ^{1}H-NMR ($CDCl_3$) 9.46 (br. s, 1H) NH; 8.43 (d, $J_{5,6}$ = 8.4 Hz, 1H); 7.50-6.80 (m, 14H) arom; 5.71 (d, $J_{5,6}$ = 8.4 Hz, 1H) H5; 4.78 (m, 1H) H2'; 4.26 (d, $J_{1',1"}$ = 13.7 Hz, 1H) H1'; 4.25-4.18 (m, 1H) H3'; 3.90 (dd, $J_{1",2'}$ = 3.0, $J_{1',1"}$ = 13.7 Hz, 1H) H1"; 3.78 (s, 3H) OCH_3; 3.65-3.60 (m, 1H) H5'; 3.50 (s, 1H) 3'OH; 3.33 (dd, $J_{5',6'}$ = 3.7, $J_{6',6"}$ = 9.9 Hz, 1H) H6'; 3.17 (dd, $J_{5',6"}$ = 3.8, $J_{6',6"}$ = 9.9 Hz, 1H) H6"; 1.85-1.80 (m, 2H) H4', H4". ^{13}C-NMR ($CDCl_3$) 163.2 (C4); 158.7 (MMTr); 153.0 (C2); 144.3 (MMTr); 144.1 (C6); 135.3, 130.4, 128.4, 127.8, 127.0, 113.1 (MMTr); 102.4 (C5); 86.4 (MMTr); 76.0 (C5'); 68.5 (C1'); 67.4 (C3'); 65.7 (C6'); 55.2 (OCH3); 53.3 (C2'); 30.4 (C4'). HRMS calcd. for $C_{30}H_{29}N_2O_6Na_2$ $(M+2Na-H)^+$ 559.1821, found 559.1802.

1,5-Anhydro-2-(uracil-1-yl)-2,4-dideoxy-D-altritol (38). Compound **35** (100 mg, 0.19 mmol) was treated with aqueous 80% acetic acid (10 mL) at room temperature overnight. The solvent was removed, coevaporated with methanol and toluene. The residue was purified by silica gel column chromatography (0-7% MeOH in CH_2Cl_2) to give **38** (40 mg, 85%). ^{1}H-NMR (D_2O) 8.24 (d, $J_{5,6}$ = 8.0 Hz, 1H) H6; 5.88 (d, $J_{5,6}$ = 8.0 Hz, 1H) H5; 4.28-4.16 (m, 4H) H1', H1", H2' and H3'; 3.95-4.05 (m, 1H) H5'; 3.70 (d, 2H) H6', H6"; 1.88-1.80 (ddd, $J_{3',4'}$ = 3.2, $J_{4',5'}$ = 10.1, $J_{4'4"}$ = 13.0 Hz, 1H) H4'; 1.73 (dt, $^3J \cong 2$ à 3 Hz, $J_{4'4"}$ = 13 Hz, 1H) H4". ^{13}C-NMR (D_2O) 167.1 (C4); 153.0 (C2), 145.6 (C6), 102.3 (C5), 73.0 (C5'), 64.7 (C1'), 64.1 (C3'), 63.5 (C6'), 55.7 (C2'), 30.1 (C4'). HRMS calcd. for $C_{10}H_{15}N_2O_5$ $(M+H)^+$ 243.0980, found 243.1008. Elem. anal. calcd. for $C_{10}H_{14}N_2O_5$: C: 49.58, H: 5.83, N: 11.56. Found C: 49.51, H: 5.97, N: 11.62.

1,5-Anhydro-2'-(uracil-1-yl)-2,4-dideoxy-D-mannitol (14b). Compound **37** (165 mg, 0.32 mmol) was treated with aqueous 80% CH_3COOH (10 mL) at room temperature overnight. The reaction mixture was concentrated, coevaporated with methanol and toluene. The residue was purified by silica gel column chromatography (0-7% MeOH in CH_2Cl_2) to give **14b** (60 mg, 77%). ^{1}H-NMR (D_2O) 8.42 (d, $J_{5,6}$ = 8.2 Hz, 1H) H6; 5.88 (d, $J_{5,6}$ = 8.2 Hz, 1H) H5; 4.88 (m, 1H) H2'; 4.36 (dt, $J_{2',3'} = J_{3',4'}$ = 5.0, $J_{3',4''}$ = 12.3 Hz, 1H) H3'; 4.33 (dd, $J_{1',2'}$ = 1.3, $J_{1',1''}$ = 13.6 Hz, 1H)H1'; 4.05 (dd, $J_{1'',2'}$ = 3.3, $J_{1',1''}$ = 13.6 Hz, 1H) H1"; 3.80-3.75 (m, 2H) H5', H6'; 3.70 (dd, $J_{5',6''}$ = 6.8, $J_{6',6''}$ = 12.7 Hz, 1H) H6"; 1.86 (m, after decoupling of H2', multiplet becomes ddd, $J_{4',5'} \cong$ 2.1, $J_{3',4'}$ = 5.0, $J_{4',4''} \cong$ 13.3 Hz, 1H) H4'; 1.59 (apparent dt, $J_{3'4''}$ = 12.3, $J_{4'',5'}$ = 11.5 Hz, $J_{4',4''} \cong$ 13.3 Hz, 1H) H4". ^{13}C-NMR (D_2O) 166.9 (C4), 154.0 (C2), 146.6 (C6), 102.0 (C5), 77.6 (C5'), 68.0 (C1'), 67.5 (C3'), 64.6 (C6'), 53.1 (C2'), 30.3 (C4'). HRMS calcd. for $C_{10}H_{15}N_2O_5$ $(M + H)^+$ 243.0980, found 243.1041.

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