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Novel isonucleoside analogues: synthesis of 2′-deoxy-2′-nucleobase-5′-deoxy-1′,4′-anhydro-D-altritol

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Abstract

A new class of isonucleoside analogues with branched-sugar 2′-deoxy-2′-nucleobase-5′-deoxy-1′,4′-anhydro-D-altritol (**21**, **23a**–**c**) has been synthesized from D-glucose in 11 steps. The construction of branched-chain sugars has been carried out by hydroboration–oxidation of a double bond in the corresponding hexose. The key intermediate **12** was synthesized from the branched-chain sugar **11** by the reductive cleavage reaction in the presence of TMSOTf and triethylsilane. A strong solvent effect was observed in the intramolecular nucleophilic substitution of **12**. The protic solvent is favorable to form the bicyclic compound **18** by double S_N2 substitution. The opening reaction of epoxide **17** by nucleobases was achieved regioselectively to give the desired isonucleosides in reasonable yield.

1. Introduction

It is well known that compounds such as AZT and carbovir are potent and selective inhibitors of HIV reverse transcriptase and have been applied to anti-HIV chemotherapy.[1] Second generation antiviral nucleoside analogues has been announced including enantiomeric forms of L-3TC and L-5F-ddC. These compounds have shown remarkable activity against HIV and HBV with relatively lower toxicity.[2] In such a context, isonucleosides, another class of nucleoside analogues have attracted much attention owing to their chemical and enzymatic stability and potential antiviral and anticancer activities. It has been reported that both D- and L-isonucleosides exhibit some activity against a broad spectrum of viruses and some tumor cell lines.[3] It should be pointed out that branched-chain sugar isonucleosides also possess interesting biological activities.[4,5] In this paper we present the synthesis of novel isonucleoside analogues, namely 2′-deoxy-2′-nucleobase-5′-deoxy-1′,4′-anhydro-D-altritols, in which a branched-chain sugar was introduced in the isonucleoside molecule.

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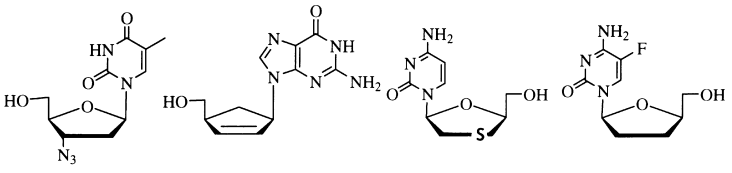
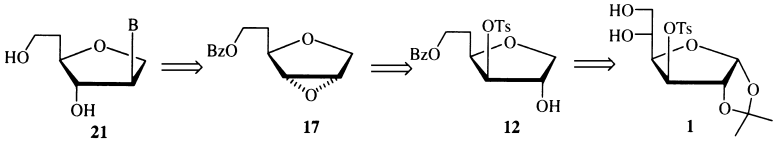


2. Results and discussion

The synthesis of 5-*C*-hydroxymethyl branched sugars has been achieved by several methods.[6,7] We intended to design a general method to prepare 5-*C*-(hydroxymethyl)isonucleosides. The novel isonucleoside with a branched-chain sugar such as **21** was selected as a target molecule. A versatile approach to the preparation of such compounds would involve the stereo- and regioselective ring opening of epoxide **17** which could be obtained from the intermediate **12**. Retrosynthetic analysis suggested that the key intermediate **12** should become available from the corresponding hexose (Scheme 1).

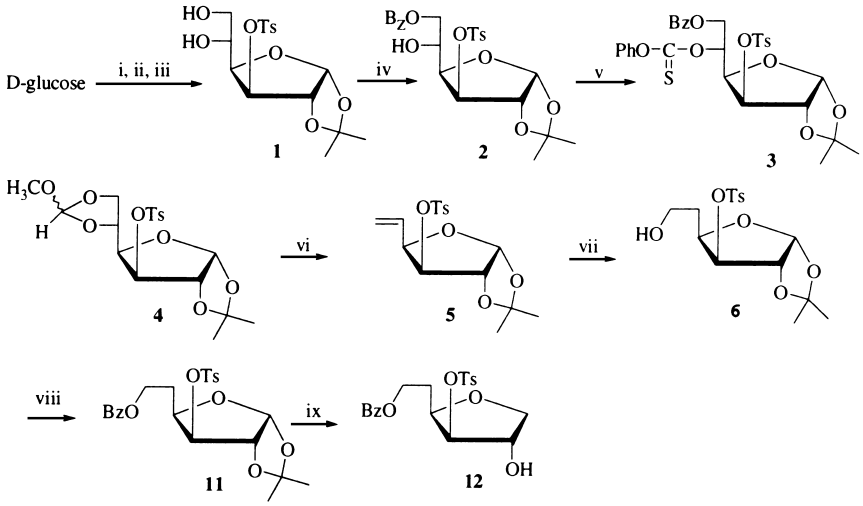


Scheme 1. Retrosynthetic analysis of target molecule **21**

To check the feasibility of this retrosynthetic scheme, compound **3** was prepared from D-glucose in high yield.[6a–c] Unfortunately, attempts to obtain compound **12** directly from **3** by means of reductive deoxygenation[6b] failed. An alternative route to **12** would involve the hydroboration–oxidation of alkene **5** (Scheme 2).

Several methods for the synthesis of this compound have also been reported.[8] In our hands, compound **1** was treated with trimethyl orthoformate in the presence of *p*-toluenesulphonic acid providing orthoformate **4**, which was further converted under treatment with acetic anhydride at 140–150°C for 4 h into **5** in 98% yield. Compound **5** was hydroborated with the borane–dimethyl sulphide complex; treatment of the resulting complex with hydrogen peroxide gave the desired compound **6** in 54% yield. However, the formation of **6** was accompanied with the appearance of three other compounds, namely **7**, **8** and **9**, which were isolated in 10, 5 and 10% yields, respectively (vide infra). Reaction of **6** with benzoyl chloride in the presence of pyridine (6-*C*-hydroxy group protection) followed by triethylsilane/trimethylsilyl trifluoromethanesulphonate (TMSOTf) provided the desired key intermediate **12** in 53% yield. From the reaction mixture, besides the desired **12**, two other compounds were separated and identified as **13** and **14**.

Compound **12** was used for the preparation of epoxide **17**, which was obtained if a DMF or THF solution of **12** was treated at –10°C with *t*-BuOK for 30 min. The yields were in the range 85–100%. However, we found that the conversion of **12** to **17** is solvent-dependent. If the same



Scheme 2. Reagents and conditions: (i) H_2SO_4, acetone, $CuSO_4$, 60%; (ii) TsCl, pyridine, 91%; (iii) 98% H_2SO_4, H_2O, CH_3OH, $CHCl_3$, 30–35°C, 98%; (iv) BzCl, pyridine, 81%; (v) PhOCSCl, DMAP, CH_2Cl_2 85%; (vi) acetic anhydride, reflux, 88%; (vii) BH_3–SMe_2, THF; 2N NaOH, 30% H_2O_2, 54%; (viii) BzCl, pyridine, rt, 98%; (ix) Et_3SiH, TMSOTf, CH_2Cl_2, 0°C to rt, 53%

reaction was carried out in *n*-butanol or methanol instead of DMF or THF, the formation of bicyclic compound **18** in the yield 95–100% occurred.

The structure of **18** was established by X-ray analysis of its crystalline derivative **19** (**18** is an oil at room temperature) after its tosylation (Fig. 1).

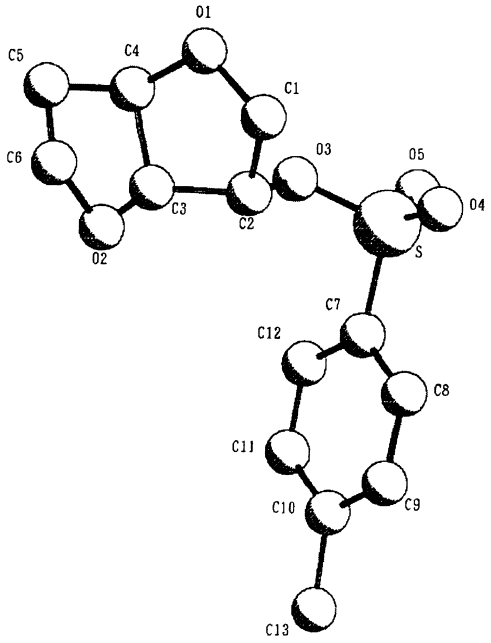
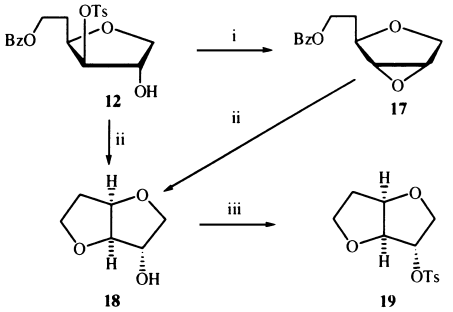
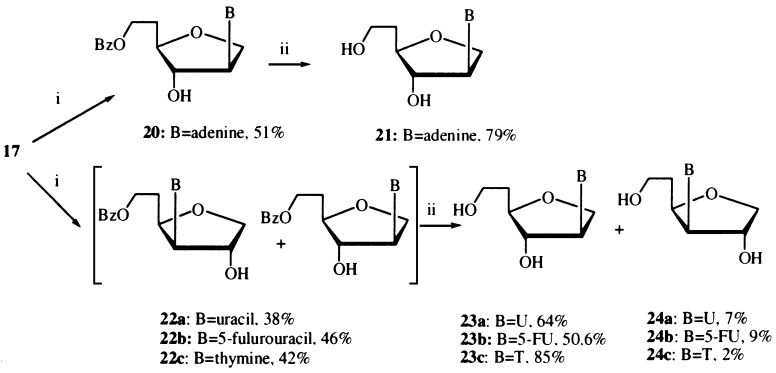


Figure 1. X-Ray crystal structure of compound **19**

The X-ray analysis of **19** clearly indicated the *cis*-fusion of two tetrahydrofuran rings both in an envelope conformation. The configuration of the new stereogenic center at C-3 is *S*. Therefore, stereoselective formation of **18** directly from **12** must involve double intramolecular S_N2 nucleophilic substitutions, and protic solvents are favorable for the second substitution. As depicted in Scheme 3, compound **17** under the conditions as used for the **12** to **19** conversion, also gave compound **19**. Therefore, we report here a convenient approach to stereoselective preparation of 5-deoxy-1,4:3,6-dianhydroglucitol in high yield. Preparation of similar bicyclic compounds such as 3,6-anhydroglucofuranose, 1,4:3,6-dianhydroglucitol, and 3,6-dideoxy-3,6-epithioglucofuranose derivatives from D-glucose, D-glucitol and D-allose, respectively, have been reported.[9] The final reaction, ring opening of epoxide **17** with nucleobases, was achieved in DMF solution. This process required the assistance of a strong base such as DBU, temperature 85–110°C, and reaction time 48–72 h. Although this process was regioselective and ring opening occurred exclusively via attack at the C-2 position with adenine as the nucleophile, in the case of pyrimidines the yields were moderate, and the desired products were contaminated with small amounts of C-3-regioisomers, as shown in Scheme 4.



Scheme 3. Solvent-dependent formation of **17** and **18** from **12**. Reagents and conditions: (i) *t*-BuOK, THF or DMF, ice–salt bath, 30 min, 85–100%; (ii) *t*-BuOK, *t*-BuOH or MeOH, ice–salt bath, 30 min, 95–100%; (iii) TsCl, pyridine, 24 h, 86%



Scheme 4. Reactions and conditions: (i) nucleobase, DBU, DMF, 85–110°C, 48–72 h; (ii) K_2CO_3/CH_3OH or CH_3ONa/CH_3OH, rt

The structure of the novel isonucleosides **21** and **23a–c** was established by ^1H–^1H COSY or NOESY NMR spectroscopy.

As mentioned earlier, compounds **8** and **9** were separated from the reaction mixture as side products of the hydroboration-oxidation of alkene **5**. The 5-*C*-hydroxyl group in compound **9**

was protected by the benzoyl group to give derivative **10**. A single crystal of **10** suitable for X-ray analysis was obtained via crystallization from petroleum ether:ethyl acetate (8:1, v/v). The *R* configuration of the new stereogenic center at C-5 of **9** was confirmed by X-ray analysis of **10** (Fig. 2).

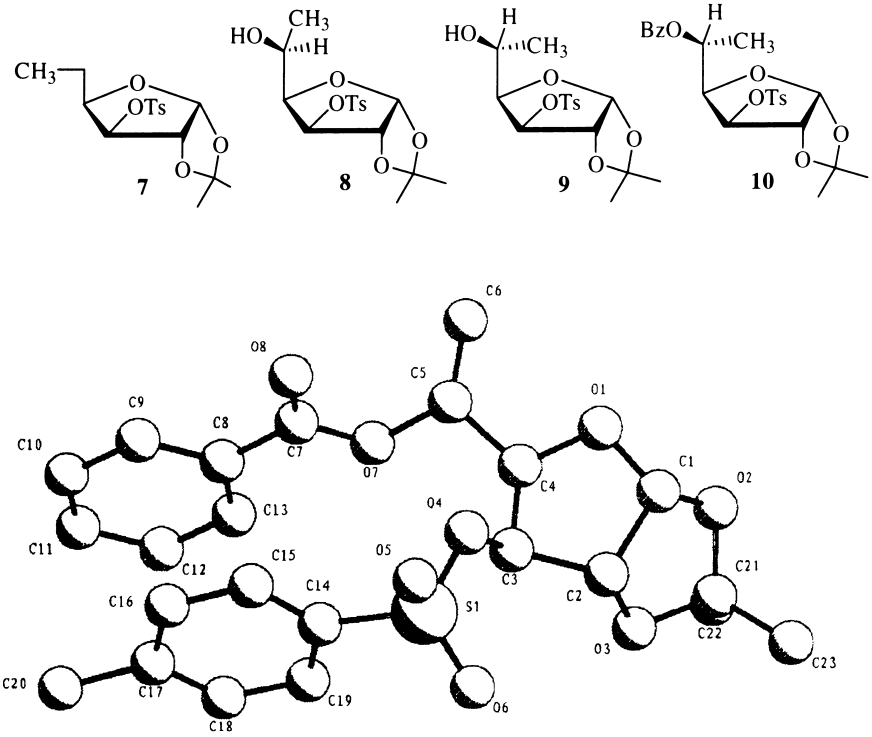
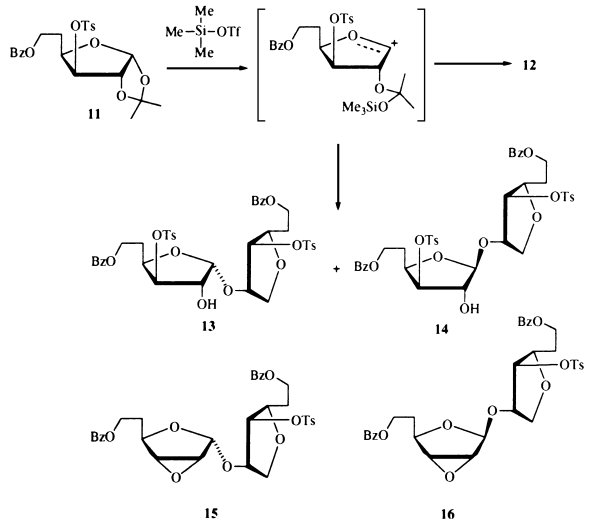


Figure 2. Compounds **7**–**9** and X-ray crystal structure of compound **10**



Scheme 5. Potential mechanism for the formation of **13** and **14** from **11**

The two disaccharides **13** and **14** were the side products isolated from the reaction mixture after treatment of compound **11** with triethylsilane/TMSOTf. They could not be separated by any simple means. The mixture of **13**/**14** was treated with *t*-BuOK in THF at –10°C to give epoxides **15** and **16**, which could be separated by column chromatography. The stereochemistry of **13** was assigned by X-ray analysis of its crystalline derivative **15** (Scheme 5 and Fig. 3).

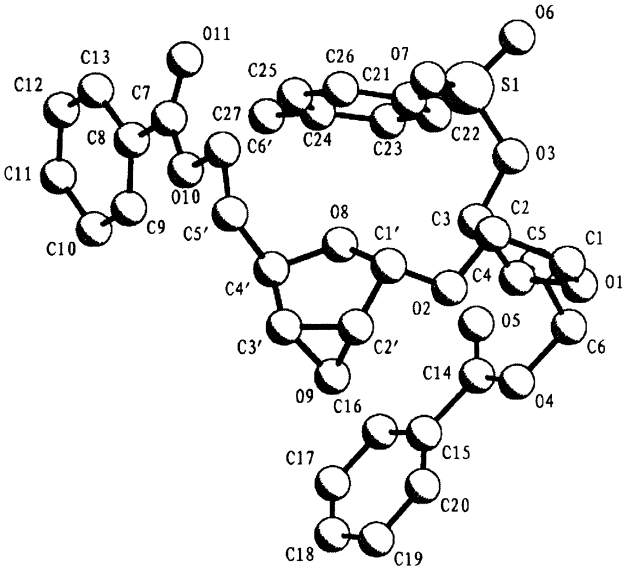


Figure 3. X-Ray crystal structure of compound **15**

3. Experimental

3.1. General procedures

All solvents were dried and distilled prior to use. Thin layer chromatography was performed using DC-Alufolien Kieselgel 60 F_{254} (Alltech Assoclates, Inc.) plates with detection by UV, or staining with 5% phosphomolybdic acid hydrate in ethanol. Column chromatography was performed on silica gel (200–300 mesh, purchased from Qing-Dao Chemical Company, China). Melting points were determined on an XT-4A melting point apparatus and are uncorrected. UV spectra were recorded with a Pharmacia LKB Biochrom 4060 spectrophotometer. Optical rotations were recorded on a Perkin–Elmer 243B polarimeter. ZAB-HS and KYKY-ZHP-5 and BIFLEX III (Bruker, Inc.) were used for mass spectra. HRMS were recorded on APEX II (Bruker, Inc.) FTICR MS. NMR spectra were recorded with a Varian VXR-300 or Bruker APE-400 spectrometer with TMS as internal standard. Elemental analyses were performed by using a PE-240C instrument. Evaporations were carried out under reduced pressure with a bath temperature below 45°C.

3.2. 1,2-O-*Isopropylidene*-3-O-*tosyl*-5,6-*dideoxy*-α-D-xylo-*hex*-5-*enofuranose* **5**

To a solution of **1** (4.7 g, 12.6 mmol) and trimethyl orthoformate (11.8 mL) was added a catalytic amount of *p*-toluenesulfonic acid monohydrate (91 mg, 0.48 mmol). The reaction mixture was

stirred for 24 h at room temperature until TLC indicated that the reaction was complete. The reaction mixture was neutralized with 2N NaOH. Water (20 mL) was poured into the solution, then the aqueous layer was extracted with CH_2Cl_2 and dried over Na_2SO_4. The solution was concentrated and diastereoisomeric mixture **4** was obtained as a pale yellow syrup. A solution of **4** (0.6 g, 1.47 mmol) in acetic anhydride (5 mL) was refluxed for 4 h. The solvent was removed under reduced pressure, the residue was dissolved in ethyl acetate (50 mL), washed with saturated $NaHCO_3$ (50 mL), water (2×30 mL) and dried over Na_2SO_4. After removal of ethyl acetate, the residue was purified by silica gel chromatography, eluting with cyclohexane:AcOEt (5:1) to give **5** (0.49 g, 88%) as a colorless syrup.

Compound **5**, $[\alpha]_D^{22}$ –34.6 ($c=0.14$, CH_3OH). ^1H NMR ($CDCl_3$): δ 1.30 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 2.46 (s, 3H, CH_3-Ts), 4.46 (m, 1H, H-2), 4.71–4.75 (dd, 2H, H-6), 5.18 (m, 1H, H-4), 5.32 (m, 1H, H-3), 5.64 (m, 1H, H-5), 5.95 (d, J = 2.4, 1H, H-1), 7.34–7.79 (m, 4H, arom H). ^{13}C NMR ($CDCl_3$): δ 21.7, 26.2, 26.5, 79.8, 83.4, 104.5, 112.3, 120.1, 130.0, 128.0, 129.8, 132.9, 145.3. FAB-MS: m/z 341 $(M+H)^+$, 363 $(M+Na)^+$. Anal. calcd for $C_{16}H_{20}O_6S$: C, 56.45; H, 5.92. Found: C, 56.78; H, 6.09.

*3.3. 1,2-*O*-Isopropylidene-3-*O*-tosyl-5-deoxy-α-D-glucofuranose **6**, 1,2-*O*-isopropylidene-3-*O*-tosyl-5,6-dideoxy-α-D-glucofuranose **7**, 1,2-*O*-isopropylidene-3-*O*-tosyl-6-deoxy-α-D-idofuranose **8**, and 1,2-*O*-isopropylidene-3-*O*-tosyl-6-deoxy-α-D-glucofuranose **9***

To an ice-cold solution of **5** (13.04 g, 38.35 mmol) in THF (65 mL) was added dropwise a solution of $BH_3{\cdot}SMe_2$ (4.6 mL, 46 mmol) over 20 min and then the mixture was warmed to room temperature. After 2 h, the reaction was quenched with methanol at 0°C. To the resulting mixture at 0°C was added dropwise 2 M NaOH (15.34 mL, 30.68 mmol) and then 30% H_2O_2 (5.22 mL, 46.02 mmol) sequentially. After stirring at room temperature for an additional 2 h, the solvent was removed and the residue was extracted with ether (2×100 mL), the combined organic phase was washed with water, saturated $NaHCO_3$ and water, and dried over Na_2SO_4. The solvent was evaporated in vacuo and the products were isolated by means of silica gel chromatography, eluting system cyclohexane:AcOEt (4:1), to give **6** (7.34 g, 53.5%) as a colorless syrup, **7** (1.39 g, 10%) as a pale yellow syrup, **8** (0.7 g, 5%) as a light yellow foam and **9** (1.0 g, 9.7%) as a colorless syrup.

Compound **6**, $[\alpha]_D^{22}$ –4.3 ($c=0.175$, CH_3OH). ^1H NMR ($CDCl_3$): δ 1.28 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.63 (m, 1H, H-5), 1.81 (br s, 1H, -OH), 1.86 (m, 1H, H-5), 2.47 (s, 3H, CH_3-Ts), 3.70 (m, 2H, H-6), 4.38 (m, 1H, H-4), 4.46 (d, $J_{1,2}=3.6$, 1H, H-2), 4.77 (d, $J_{3,4}=2.4$, 1H, H-3), 5.89 (d, J = 3.6, 1H, H-1), 7.36–7.83 (dd, 4H, arom H). FAB-MS: m/z 343 $(M-CH_3)^+$, 359 $(M+H)^+$, 381 $(M+Na)^+$. Anal. calcd for $C_{16}H_{22}O_7S$: C, 53.62; H, 6.19. Found: C, 53.78; H, 6.57.

Compound **7**, $[\alpha]_D^{22}$ –13.0 ($c=0.15$, CH_3OH). ^1H NMR ($CDCl_3$): δ 0.80 (t, 3H, H-6), 1.28 (s, 3H, CH_3), 1.45 (m, 1H, H-5), 1.48 (s, 3H, CH_3), 1.68 (m, 1H, H-5), 2.47 (s, 3H, CH_3-Ts), 4.07 (m, 1H, H-4), 4.65 (d, $J_{1,2}=2.4$, 1H, H-2), 4.73 (d, $J_{3,4}=1.8$, 1H, H-3), 5.88 (d, $J_{1,2}=2.4$, 1H, H-1), 7.36–7.82 (dd, 4H, arom H). FAB-MS: m/z 343 $(M+H)^+$, 365 $(M+Na)^+$, 327 $(M-CH_3)^+$. Anal. calcd for $C_{16}H_{22}O_6S$: C, 56.13; H, 6.48. Found: C, 56.13; H, 6.49.

Compound **8**, $[\alpha]_D^{22}$ –22.4 ($c=0.197$, CH_3OH). ^1H NMR ($CDCl_3$): δ 0.39 (d, J = 3.6, 3H, H-6), 1.29 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.86 (br s, 1H, -OH), 2.47 (s, 3H, CH_3-T_S), 3.90 (m, 1H, H-5), 3.98 (m, 1H, H-4), 4.70 (d, $J_{1,2}=3.6$, 1H, H-2), 4.70 (d, $J_{3,4}=2.4$, 1H, H-2), 4.82 (d, $J_{3,4}=1.8$, 1H, H-3), 5.92 (d, J = 3.3, 1H, H-1), 7.37–7.83 (dd, 4H, arom H). FAB-MS: m/z 359 $(M+H)^+$, 381 $(M+Na)^+$. Anal. calcd for $C_{16}H_{22}O_7S$: C, 53.62; H, 6.19. Found: C, 53.72; H, 6.31.

Compound **9**, $[\alpha]_D^{22}$ –28.8 ($c=0.285$, CH_3OH). ^1H NMR ($CDCl_3$): δ 1.26 (s, 3H, CH_3), 1.31 (d, $J_{5,6}=3.6$, 3H, H-6), 1.48 (s, 3H, CH_3), 2.48 (s, 3H, CH_3-T_S), 3.96 (m, 2H, H-4,5), 4.51 (d, $J_{1,2}=1.8$, 1H, H-2), 4.99 (s, 1H, H-3), 5.87 (d, $J_{1,2}=1.8$, 1H, H-1), 7.39–7.85 (dd, 4H, arom H). FAB-MS: m/z 359 $(M+H)^+$, 381 $(M+Na)^+$. Anal. calcd for $C_{16}H_{22}O_7S$: C, 53.62; H, 6.19. Found: C, 53.94; H, 6.37.

3.4. 5-O-*Benzoyl-1,2*-O-*isopropylidene-3*-O-*tosyl-6-deoxy-α-D-glucofuranose* **10**

To an ice-cold solution of **9** (8.52 g, 23.8 mmol) in dry pyridine (50 mL) was added dropwise benzoyl chloride (5.34 mL, 46.0 mmol) and then the mixture was stirred at room temperature for 20 h. The mixture was concentrated under reduced pressure, the residue was dissolved in CH_2Cl_2 (100 mL), washed with 1.4 M H_2SO_4 (50 mL), saturated $NaHCO_3$ (100 mL) and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by silica gel chromatography, eluting system petroleum ether:AcOEt (8:1), to give **10** (8.07 g, 81% yield) as crystalline needles. A single crystal was prepared by recrystallization from petroleum ether:ethyl acetate (8:1, v/v). Compound **10**, m.p. 123–124°C, $[\alpha]_D^{22}$ –41.5 ($c=0.205$, CH_3OH). ^1H NMR ($CDCl_3$): δ 1.28 (s, 3H, CH_3), 1.30 (d, $J_{5,6}=6.4$, 3H, H-6), 1.47 (s, 3H, CH_3), 2.14 (s, 3H, CH_3-Ts), 4.32 (dd, $J_{3,4}=2.8$, $J_{4,5}=8.6$, 1H, H-4), 4.77 (d, $J_{1,2}=3.6$, 1H, H-2), 4.90 (s, $J_{3,4}=2.8$, 1H, H-3), 4.97 (m, 1H, H-5), 6.04 (d, $J_{1,2}=3.6$, 1H, H-1), 7.18–7.83 (m, 9H, arom H). FAB-MS: m/z 463 $(M+H)^+$. Anal. calcd for $C_{23}H_{26}O_8S$: C, 59.73; H, 5.67. Found: C, 59.94; H, 5.60. Crystal data: empirical formula, $C_{23}H_{26}O_8S$; formula weight, 62.52; crystal system, orthorhombic, space group, $P2_12_12_1$, $a=8.012$ (1), $b=10.692(1)$, $c=27.606(1)$ Å, $V=2364.8(4)$ Å^3, $Z=4$, $Dc=1.304$ g/cm^3; $R=0.054$, $Rw=0.049$.

3.5. 6-*Benzoyl-1,2*-O-*isopropylidene-3*-O-*tosyl-5-deoxy-α-D-glucofuranose* **11**

To an ice-cold solution of **6** (7.34 g, 20.5 mmol) in dry pyridine (30 mL) was dropped benzoyl chloride (4.76 mL, 41.0 mmol) and then the mixture was stirred at room temperature for 18 h. The mixture was concentrated under reduced pressure, the residue was dissolved in ethyl acetate (50 mL), washed with 1.4 M H_2SO_4 (50 mL), saturated $NaHCO_3$ (100 mL) and water (100 mL), and dried over Na_2SO_4. After removal of ethyl acetate, the residue was purified by silica gel chromatography, eluting system cyclohexane:AcOEt (5:1), providing **11** (9.27 g, 98%) as a colorless syrup.

Compound **11**, $[\alpha]_D^{22}$ –3.2 ($c=0.14$, CH_3OH). ^1H NMR ($CDCl_3$): δ 1.29 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.85 (m, 1H, H-5), 2.10 (m, 1H, H-5), 2.44 (s, 3H, CH_3-Ts), 4.28 (m, 2H, H-6), 4.38 (m, 1H, H-4), 4.67 (d, $J_{1,2}=3.6$, 1H, H-2), 4.77 (d, $J=2.7$, 1H, H-3), 5.91 (d, $J=3.9$, 1H, H-1), 7.35–7.57 (dd, 4H, arom H). FAB-MS: m/z 447 $(M-CH_3)^+$, 485 $(M+Na)^+$. Anal. calcd for $C_{23}H_{26}O_8S$: C, 59.73; H, 5.67. Found: C, 59.75; H, 5.92.

3.6. 6-O-*Benzoyl-3*-O-*tosyl-5-deoxy-1,4-anhydro-D-glucitols* **12**, **13** *and* **14**

To a solution of **11** (28.7 g, 62 mmol) in dichloromethane (450 mL) at 0°C was added dropwise TMSOTf (24.24 mL, 124 mmol) and then the solution was stirred under nitrogen at room temperature for 0.5 h. Et_3SiH (50 mL, 310 mmol) was added to the stirred mixture at 0°C and stirring was continued for an additional 48 h. The reaction was quenched with saturated $NaHCO_3$ (240 mL). The aqueous layer was extracted with CH_2Cl_2 (2×100 mL), the combined organic phase was washed with brine (2×200 mL) and dried over Na_2SO_4. The solvent was removed and

the residue was purified on a silica gel column with petroleum ether/ethyl acetate as an eluent, to give **12** (12.53 g, 53%) as a pale yellow syrup and a mixture of **13** and **14** (3.47 g, 7%).

Compound **12**, $[\alpha]_D^{22}$ –12.4 ($c=0.227$, CH_3OH). ^1H NMR ($CDCl_3$): δ 1.82 (m, 1H, H-5), 2.00 (m, 1H, H-5), 3.67 (m, 1H, H-1), 4.15 (m, 1H, H-1), 2.38 (s, 3H, CH_3-T_S), 4.27 (m, 3H, H-4,6), 4.47 (m, 1H, H-2), 4.78 (d, J = 3.6, 1H, H-3), 7.30–8.00 (m, 9H, arom H). FAB-MS: *m/z* 407 $(M+H)^+$, 429 $(M+Na)^+$. Anal. calcd for $C_{20}H_{22}O_7S$: C, 59.10; H, 5.46. Found: C, 58.56; H, 5.76.

3.7. 2-O-(6′-O-Benzoyl-5′-deoxy-α-D-2′,3′-anhydroallofuranosyl)-6-O-benzoyl-3-O-tosyl-5-deoxy-1,4-anhydro-D-glucitol **15** *and 2-O-(6′-O-benzoyl-5′-deoxy-β-D-2′,3′-anhydroallofuranosyl)-6-O-benzoyl-3-O-tosyl-5-deoxy-1,4-anhydro-D-glucitol* **16**

To a solution of the mixture of **13** and **14** (1.946 g, 2.40 mmol) in THF (20 mL) at –10°C was added *t*-BuOK (0.296 g, 2.64 mmol). The reaction mixture was stirred for 30 min at –10°C, then the reaction neutralized with AcOH. The solvent was removed in vacuo and the residue was purified on silica gel column with cyclohexane:AcOEt (4:1) as an eluent to give **15** (1.042 g, 67.9%) as a crystalline powder and **16** (0.407 g, 26.5%) as a colorless syrup (**15**:**16** = 2.5:1).

Compound **15**, m.p. 67–68°C, $[\alpha]_D^{22}$ –7.8 ($c=0.18$, CH_3OH). ^1H NMR (DMSO-d_6): δ 1.66 (m, 1H, H-5′), 1.85 (m, 2H, H-5, H-5′), 1.97 (m, 1H, H-5′), 2.33 (s, 3H, CH_3-Ts), 3.63 (dd, 1H, H-1), 3.83 (d, J = 6.96, 1H, H-2′), 3.86 (d, J = 2.90, 1H, H-3′), 4.00 (m, 1H, H-4), 4.08 (m, 1H, H-1), 4.15 (m, 2H, H-6), 4.33 (m, 2H, H-2, H-4′), 4.42 (m, 2H, H-6′), 4.97 (d, J = 28, 1H, H-3), 5.19 (s, 1H, H-1′), 7.41–7.99 (m, 14H, arom H). ^{13}C NMR (DMSO-d_6): δ 21.00, 26.3, 27.5, 55.4, 57.0, 61.0, 61.6, 71.1, 75.1, 75.6, 82.5, 83.9, 101.4, 127.58, 128.67, 128.72, 129.04, 129.13, 129.59, 130.16, 132.4, 133.25, 133.32, 145.3, 165.44, 165.62. MALDI-TOF MS *m/z*: 661.27 $(M+Na)^+$, 677.25 $(M+K)^+$. Anal. calcd for $C_{33}H_{34}O_{11}S{\cdot}0.5C_6H_{12}$: C, 63.53, H; 5.93. Found: C, 64.01; H, 6.32. Crystal data: empirical formula, $C_{33}H_{34}O_{11}S$; formula weight, 638.68; crystal system, triclinic; space group, *P*1, $a=9.825(1)$, $b=12.891(1)$, $c=16.621(1)$ Å, $V=1859.2(3)$ Å^3, $Z=2$, $Dc=1.141$ g/cm^3; $R=0.057$, $Rw=0.070$.

Compound **16**, $[\alpha]_D^{22}$ –16.1 ($c=0.25$, CH_3OH). ^{1} H NMR (DMSO-d_6): δ 1.73 (m, 2H, H-5,5′), 1.91 (m, 2H, H-5,5′), 2.34 (s, 3H, CH_3-Ts), 3.51 (dd, $J_{1a,1b}=2.8$, $J_{1a,2}=10.2$, 1H, H-1), 3.71 (d, J = 2.8, 1H, H-2′), 3.92 (d, J = 2.8, 1H, H-3′), 4.06 (m, 2H, H-1, H-4), 4.19 (m, 2H, H-6), 4.27 (m, 3H, H-2, H-4′, H-6′), 4.37 (m, 1H, H-6′), 4.91 (s, 1H, H-1′), 5.04 (d, J = 3.4, 1H, H-3), 7.46 –7.99 (m, 14H, arom H). ^{13} C NMR (DMSO-d_6): δ 21.00, 27.6, 31.5, 55.8, 56.00, 61.3, 61.6, 70.7, 75.5, 75.8, 79.9, 83.4, 99.9, 127.70, 128.67, 128.69, 129.07, 129.62, 130.22, 132.46, 133.26, 145.36, 165.51, 165.57. MALDI-TOF MS *m/z*: 661.23 $(M+Na)^+$, 677.18 $(M+K)^+$. Anal. calcd for $C_{33}H_{34}O_{11}S$: C, 62.06; H, 5.37. Found: C, 62.63; H, 5.46.

3.8. 6-O-Benzoyl-5-deoxy-1,4:2,3-dianhydro-D-allitol **17**

To a solution of **12** (2.34 g, 5.76 mmol) in THF (15 mL) at –10°C was added *t*-BuOK (0.774 g, 6.91 mmol) and then the mixture was stirred for 30 min at –10°C. The solvent was removed under vacuum. The residue was dissolved in ethyl acetate, washed with brine (50×2 mL) and dried over Na_2SO_4. After removing ethyl acetate, the syrupy **17** was obtained (1.28 g, 95%), its cyclohexane–acetone solution providing colorless needles.

Compound **17**, m.p. 53–54°C, $[\alpha]_D^{22}$ +48.0 ($c=0.2$, CH_3OH). ^1H NMR ($CDCl_3$): δ 1.84 (m, 1H, H-5), 1.96 (m, 1H, H-5), 3.69 (d, $J_{1a,2}=2.8$, 1H, H-1a), 3.76 (d, $J_{1b,2}=10.7$, 1H, H-1b), 3.80 (dd,

J = 2.8, 1H, H-2), 4.02 (d, J = 10.7, 1H, H-3), 4.33 (q, 1H, H-4), 4.41 (m, 1H, H-6), 4.52 (m, 1H, H-6), 7.44–8.03 (m, 5H, arom H). ^{13}C NMR ($CDCl_3$): δ 30.2, 55.9, 58.9, 61.2, 66.2, 74.7, 128.4, 129.5, 130.0, 233.1, 166.4. FAB-MS *m*/*z*: 235(M+H)$^+$. Anal calcd for $C_{13}H_{14}O_4$: C, 66.66; H: 6.02. Found: C, 66.33; H: 6.01.

3.9. 5-Deoxy-1,4:3,6-dianhydro-D-glucitol **18**

A mixture of **12** (16.59 g, 48.86 mmol), K_2CO_3 (14.1 g, 102.15 mmol) and methanol (200 mL) was stirred at room temperature for 2.5 h. Undissolved material was filtered off. Removal of the solvent in vacuo and column chromatography (SiO_2, petroleum ether:acetone, 6:1) yielded **18** (4.82 g, 91%) as a colorless oil. $[\alpha]_D^{22}$ +6.7 (c = 0.06, CH_3OH). ^{1}H NMR (DMSO-d_6): δ 1.88 (m, 2H, H-5), 3.58 (m, 2H, H-1, H-6), 3.73 (m, 2H, H-1, H-6), 4.02 (m, 1H, H-2), 4.17 (d, J = 4.1, 1H, H-3), 4.65 (q, 1H, H-4), 5.06 (d, J = 3.96, 1H, -OH). ^{13}C NMR (DMSO-d_6): δ 35.1, 68.3, 75.4, 76.5, 83.0, 89.7.

3.10. 2-O-Tosyl-5-deoxy-1,4:3,6-dianhydro-D-glucitol **19**

To a stirred solution of **18** (3.505 g, 27 mmol) in dry pyridine (30 mL) at 0°C was added TsCl (8.29 g, 43.5 mmol). The mixture was stirred for 29 h at room temperature and then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (40 mL), washed with water (50 mL), 1.4 M H_2SO_4 (50 mL), saturated $NaHCO_3$ (2×50 mL) and brine (50 mL), and dried over Na_2SO_4. After removal of the solvent, the residue was purified by silica gel chromatography, eluting system petroleum ether:acetone (7.5:1), providing **19** (6.6 g, 86%) as a crystalline solid. Recrystallization from ethanol provided a single crystal for X-ray analysis.

Compound **19**, m.p. 60–61°C, $[\alpha]_D^{22}$ +35.7 (c = 0.205, CH_3OH). ^{1}H NMR ($CDCl_3$): δ 1.96 (m, 1H, H-5), 1.99 (m, H, 1H, H-5), 2.46 (s, 3H, CH_3-Ts), 3.72 (m, 1H, H-6), 3.89 (m, 3H, H-1, H-6), 4.43 (t, 1H, H-3), 4.79 (q, 1H, H-2), 4.85 (d, 1H, H-4), 7.27–7.82 (m, 4H, arom H). FAB-MS *m*/*z*: 285 [M+H]$^+$, 113 [M–TsO]$^+$. Anal calcd for $C_{13}H_{16}O_5S$: C, 54.91; H, 5.67. Found: C, 54.84; H, 5.66. Crystal data: empirical formula, $C_{13}H_{16}O_5S$; formula weight, 284.33; crystal system, orthorhombic; space group, $P2_12_12_1$; a = 6.313(1), b = 7.534(1), c = 28.579(1) Å, V = 1359.3(3) Å^3, Z = 4, Dc = 1.389 g/cm^3, R = 0.053, Rw = 0.060.

3.11. 6′-O-Benzoyl-2′-deoxy-2′-(adenine-9-yl)-5′-deoxy-1′,4′-anhydro-D-altritol **20**

To a solution of epoxide **17** (1 g, 4.27 mmol) and adenine (1.15 g, 8.54 mmol) in DMF (30 mL) was added DBU (1.9 mL, 12.81 mmol), and the solution was heated to 85°C for 48 h. After the mixture cooled to room temperature, the solvent was removed at reduced pressure and the residue purified by silica gel column chromatography, eluting system CH_2Cl_2:MeOH (9:1), providing **20** (0.357g, 51%) as a white powder, as well as unreacted epoxide **17** (0.552 g). $[\alpha]_D^{22}$ –35.0 (c = 0.145, MeOH). UV (MeOH): λ_{max} = 261 nm (ε 15 663). ^{1}H NMR (DMSO-d_6): δ 2.04 (m, 1H, H-5′), 2.14 (m, 1H, H-5′), 3.85 (m, 1H, H-4′), 4.18 (m, 2H, H-1′), 4.43 (m, 3H, H-3′, H-6′), 4.90 (q, 1H, H-2′), 5.82 (d, J = 5.48, 1H, 3′-OH), 7.25 (br s, 2H, -NH_2), 7.35–7.57 (m, 5H,Ph), 8.14 (s, 1H, H-2), 8.19 (s, 1H, H-8). ^{13}C NMR (DMSO-d_6): δ 31.8, 61.7, 68.7, 78.6, 80.6, 118.9, 128.7, 129.2, 129.7, 133.2, 139.2, 149.4, 152.3, 156.0, 165.6. FAB-MS *m*/*z*: 370 [M+H]$^+$, 136 [adenine+H]$^+$ (base peak). Anal calcd for $C_{18}H_{19}N_5O_4$: C, 58.53; H, 5.81; N, 18.96. Found: C, 58.80; H, 5.49; N, 18.45.

3.12. 2′-Deoxy-2′-(adenine-9-yl)-5′-deoxy-1′,4′-anhydro-D-altritol **21**

To a vigorously stirred solution of **20** (0.35 g, 0.948 mmol) in methanol (10 mL) was added potassium carbonate (0.327 g, 2.37 mmol) and then the mixture was stirred for 2 h. After filtration and concentration, the residue was purified by silica gel column chromatography, eluting with CH_2Cl_2:MeOH (10:1) to give **21** (0.199 g, 79%) as a white powder. $[\alpha]_D^{22}$ –28.5 ($c = 0.197$, MeOH). UV (MeOH): $\lambda_{max} = 261$ nm (ε 13 519). ^{1}H NMR (DMSO-d_6): δ 1.70 (m, 1H, H-5′), 1.80 (m, 1H, H-5′), 2.08 (m, 2H, H-1′), 3.54 (m, 2H, H-6′), 3.74 (m, 1H, H-4′), 4.27 (q, 1H, H-3), 4.49 (t, $J_{H6',OH} = 5.1$, 1H, 6′-OH), 4.85 (q, 1H, H-2′), 5.71 (d, $J_{H3',OH} = 5.5$, 1H, 3′-OH), 7.23 (br s, 2H, -NH_2), 8.15 (s, 1H, H-2), 8.16 (s, 1H, H-8). ^{13}C NMR (DMSO-d_6): δ 36.1, 57.7, 61.8, 68.6, 78.9, 80.9, 118.9, 139.2, 149.4, 152.3, 155.9. HRMS (FAB) calcd for $C_{11}H_{15}N_5O_3$ [M+H]$^+$: 266.1248. Found: 266.1251.

3.13. 2′-Deoxy-2′-(uracil-1-yl)-5′-deoxy-1′,4′-anhydro-D-altritol **23a** and 3′-deoxy-3′-(uracil-1-yl)-5′-deoxy-1′,4′-anhydro-D-altritol **24a**

Reaction was performed as above. A mixture **22a** was obtained (0.215 g, 38%) as a foam. A mixture of **22a** (150 mg, 0.434 mmol) and sodium methoxide (23.44 mg, 0.434 mmol) in methanol (1.5 mmL) was stirred for 12 h at room temperature. The reaction mixture was neutralized with anion ion-exchange resin 717#. After filtration and concentration, the residue was purified by column chromatography (CH_2Cl_2:MeOH, 10:1) to give a mixture of **23a** and **24a** (98 mg, 93.3%) as a pale yellow foam. The mixture was separated by reversed phase HPLC (7% CH_3OH in water) to give **23a** (t_R 22.9 min, 67 mg, 64%) and **24a** (t_R 22.9 min, 7 mg, 7%), both as a white hygroscopic powder.

Compound **23a**, $[\alpha]_D^{22}$ +4.4 ($c = 0.09$, CH_3OH). ^{1}H NMR (DMSO-d_6): δ 1.69 (m, 1H, H-5′), 1.80 (m, 1H, H-5′), 3.51 (m, 2H, H-6′), 3.60 (m, 1H, H-4′), 3.80 (m, 1H, H-1′), 3.89 (m, 1H, H-1′), 3.97 (m, 1H, H-3′), 4.48 (t, J = 5.2, 1H, 6′-OH, exchangeable in D_2O), 4.75 (m, 1H, H-2′), 5.60 (m, 1H, H-5), 5.63 (m, 1H, 3′-OH, exchangeable in D_2O), 7.57 (d, J = 8.0, 1H, H-6), 11.29 (s, 1H, -NH-, exchangeable in D_2O). HRMS (FAB) calcd for $C_{10}H_{14}N_2O_5$ [M+H]$^+$: 243.0975. Found: 243.0973.

Compound **24a**, ^{1}H NMR (DMSO-d_6): δ 1.40 (m, 2H, H-5′), 3.40 (m, 3H, H-1′, H-6′), 4.10 (m, 1H, H-4′), 4.29 (m, 1H, H-1′), 4.36 (m, 1H, H-2′), 4.51 (t, J = 5.2, 1H, 6′-OH), 4.75 (m, 1H, H-3′), 5.58 (d, J = 8.0, 1H, H-5), 5.67 (d, J = 4.4, 2′-OH), 7.23 (d, J = 8.0, 1H, H-6), 11.38 (s, 1H, -NH-). HRMS (FAB) calcd for $C_{10}H_{14}N_2O_5$ [M+H]$^+$: 243.0975. Found: 243.0974.

3.14. 2′-Deoxy-2′-(5-fluorouracil-1-yl)-5′-deoxy-1′,4′-anhydro-D-altritol **23b** and 3′-deoxy-3′-(5-fluorouracil-1-yl)-5′-deoxy-1′,4′-anhydro-D-altritol **24b**

The reaction was performed as above. A mixture of **22b** was obtained (0.159 g, 46%) as a pale yellow foam. Debenzoylation was performed as above to yield a mixture of **23b** and **24b** (88 mg, 80%) as a white foam. The mixture was separated by reversed phase HPLC (8% CH_3OH in water) to give **23b** (t_R 25.7 min, 56 mg, 50.6%) and **24b** (t_R 25.7 min, 10 mg, 9%), both as a white hygroscopic powder.

Compound **23b**, $[\alpha]_D^{22}$ +6.4 ($c = 0.14$, CH_3OH). ^{1}H NMR (DMSO-d_6): δ 1.71 (m, 1H, H-5′), 1.79 (m, 1H, H-5′), 3.52 (m, 2H, H-6′), 3.59 (m, 1H, H-4), 3.81 (m, 1H, H-1′), 3.96 (m, 2H, H-1′, H-3′), 4.48 (t, J = 5.2, 1H, 6′-OH, exchangeable in D_2O), 4.73 (m, 1H, H-2′), 5.58 (d, J = 5.6, 1H, 3′-OH, exchangeable in D_2O), 7.92 (d, J = 7.2, 1H, H-6), 11.83 (d, J = 5.2, 1H, -NH-, exchangeable in D_2O). HRMS (FAB) calcd for $C_{10}H_{13}FN_2O_5$ [M+H]$^+$: 261.0881. Found: 261.0880.

Compound **24b**, $[\alpha]_D^{22}$ +129.2 ($c = 0.065$, CH_3OH). ^1H NMR (DMSO-d_6): δ 1.43 (m, 2H, H-5′), 3.35 (m, 1H, H-1′), 3.41 (m, 2H, H-6′), 4.08 (m, 1H, H-4′), 4.34 (m, 2H, H-1′, H-2′), 4.50 (t, J = 5.2, 1H, 6′-OH), 4.74 (d, J = 4.9, 1H, H-3′), 5.64 (d, 1H, 2′-OH), 7.44 (d, J = 6.8, 1H, H-6), 11.93 (s, 1H, -NH-). HRMS (FAB) calcd for $C_{10}H_{13}FN_2O_5$ $[M+H]^+$: 261.0881. Found: 261.0881.

3.15. 2′-Deoxy-2′-(thymin-1-yl)-5′-deoxy-1′,4′-anhydro-D-altritol ***23c*** *and 3′-deoxy-3′-(thymin-1-yl)-5′-deoxy-1′,4′-anhydro-D-glucitol* ***24c***

The reaction was performed as above. A mixture of **22c** was obtained (3.178 g, 42%) as a light yellow foam. Deprotection was performed as above to give **23c** as a pale yellow foam (1.656 g, 85%). The crude product **24c** was purified by preparative layer chromatography to give **24c** (25 mg, 2%) as a white powder.

Compound **23c**, $[\alpha]_D^{22}$ –17.1 ($c = 0.07$, MeOH). UV (MeOH): $\lambda_{max} = 271$ nm (ε 9961). ^1H NMR (DMSO-d_6): δ 1.66 (m, 1H, -5′), 1.78 (d, 3H, 5-CH_3), 1.79 (m, 1H, H-5′), 3.51 (m, 2H, H-6′), 3.59 (m, 1H, H-4′), 3.77 (m, 1H, H-1′), 3.95 (m, 2H, H-1′, H-3′), 4.49 (t, 1H, 6′-OH, exchangeable in D_2O), 4.78 (m, 1H, H-2′), 5.56 (d, J = 5.6, 1H, 3′-OH, exchangeable in D_2O), 7.45 (d, J = 0.88, 1H, H-6), 11.28 (s, 1H, -NH-, exchangeable in D_2O). ^{13}C NMR (DMSO-d_6): δ 12.1, 35.9, 57.8, 62.5, 68.2, 78.8, 80.5, 109.5, 137.7, 151.1, 163.8. HRMS (FAB) calcd for $C_{11}H_{16}N_2O_5$ $[M+H]^+$: 257.1132. Found: 257.1129.

Compound **24c**, $[\alpha]_D^{22}$ +170.8 ($c = 0.065$, MeOH). UV (MeOH): $\lambda_{max} = 271$ nm (ε 11722). ^1H NMR (DMSO-d_6): δ 1.40 (m, 2H, H-5′), 1.78 (d, J = 8.0, 3H, 5-CH_3), 3.36 (m, 2H, H-6′), 3.44 (m, 1H, H-1′a), 4.07 (m, 1H, H-4′), 4.34 (m, 2H, H-1′b, H-2′), 4.49 (br s, 1H, 6′-OH, exchangeable in D_2O), 4.75 (d, J = 5.0, 1H, H-3′), 5.64 (br s, 1H, 3′-OH, exchangeable in D_2O), 7.06 (d, J = 1.2, 1H, H-6), 11.37 (s, 1H, -NH-, exchangeable in D_2O). ^{13}C NMR (DMSO-d_6): δ 12.0, 32.0, 57.5, 64.0, 73.5, 75.4, 76.5, 109.1, 138.3, 151.1, 163.5. HRMS (FAB) calcd for $C_{11}H_{16}N_2O_5$ $[M+H]^+$: 257.1132. Found: 257.1130.

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