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Stereoselective synthesis of 4-deoxy-4-nucleobase-2,5-anhydro-L-mannitol derivatives

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Abstract: 2,5:3,4-Dianhydro-L-talofuranose dimethylacetal **7** was synthesized from D-glucose in 7 steps. A series of 4-deoxy-4-nucleobase-2,5-anhydro-L-mannitols **13–16** were synthesized regioselectively from **7** in good yields. 6-O-p-Tolylsulfonyl-2,5:3,4-dianhydro-L-talofuranose dimethylacetal **8** reacted with uracil or thymine to give the corresponding isonucleosides **17** and **19**, but in the case of reaction of **8** with adenine, reformation of tetrahydrofuran ring took place, giving 4-(*S*)-adenyl-5-(*R*)-[1′-(*R*)-hydroxy-2′,2′-dimethoxy] ethyl-2,3-dihydrofuran **21** and 4-deoxy-4-adenyl-2,5:3,6-dianhydro-L-mannofuranose dimethylacetal **22**. © 1997 Elsevier Science Ltd

Introduction

A number of nucleoside analogues have been found to possess anticancer and antiviral activities.[1–4] In the search for effective, selective and nontoxic anticancer and antiviral agents, the discovery of a new class of nucleosides is of immense importance. Isonucleoside is a new class of nucleoside analogues in which the nucleobase is linked to a position of ribose other than C-1′. Therefore isonucleosides have attracted much attention owing to their chemical and enzymatic stability and potential antiviral activities.[5] A series of isomers of 2′,3′-dideoxynucleosides which contain a modified carbohydrate moiety have been synthesized and some of these compounds exhibited significant and selective anti-HIV activity.[6,7] New regioisomers of AZT, AZU, BVDU and IDU have also been synthesized.[8] Recently, a number of nucleosides with the unnatural L-configuration have been reported as potent chemotherapeutic agents against HIV, HBV and certain forms of cancer. It is interesting that these L-nucleosides have potent biological activities, while some of them show lower toxicity profiles than their D-counterparts.[9] We have reported the synthesis of 4′-(*R*)-hydroxy-5′-(*S*)-hydroxymethyl-tetrahydrofuranyl purines and pyrimidines from D-xylose.[10] In this paper, we describe the synthesis of some derivatives of 4-deoxy-4-nucleobase-2,5-anhydro-L-mannitols from D-glucose.

Many isonucleosides syntheses have been achieved by use of epoxide opening by an azide anion, with subsequent reduction furnishing an amino group which is used to build up a heterocyclic moiety. An alternative synthesis involves the substitution of a leaving group on the sugar ring by a heterocyclic nucleophile under basic conditions. In order to avoid lengthy synthetic routes, we synthesized isonucleosides by using an epoxide opening by a nucleobase itself in basic conditions. The desired epoxide can be obtained from a corresponding sugar. Our strategy for the synthesis of the epoxide required the leaving group and hydroxyl group in a trans relationship on the sugar moiety. The key intermediates **5** and **6** were synthesized from 1,2-O-isopropylidene-3,5-di-O-p-tolylsulfonyl-6-O-benzoyl-α-D-glucofuranose **2** or 1,2-O-isopropylidene-3,5,6-tri-O-p-tolylsulfonyl-α-D-glucofuranose **3**, respectively, which in turn was prepared from D-glucose.[11]

Results and discussion

When **2** was treated with 2% TFA in methanol under reflux for 72 h, a mixture of α- and β-methyl-3,5-di-O-p-tolylsulfonyl-6-O-benzoyl-D-glucofuranosides was obtained. We modified the procedure

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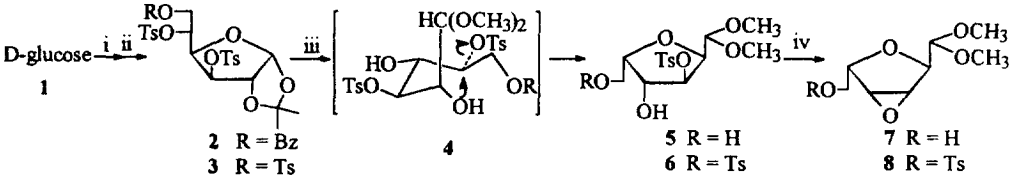
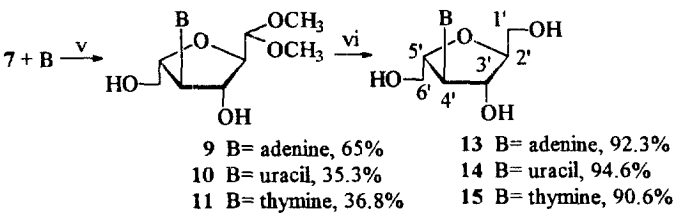
for the synthesis of **5** and **6** in reasonable yields. Thus, **2** or **3** was refluxed in methanol with 1% HCl for 70 h or 6 days to give **5** (94.4%) and **6** (87.2%) respectively. Treatment of **5** or **6** with potassium carbonate in methanol at room temperature for 2.5 h gave epoxide **7** (92.6%) or **8** (94.0%) (Scheme 1).

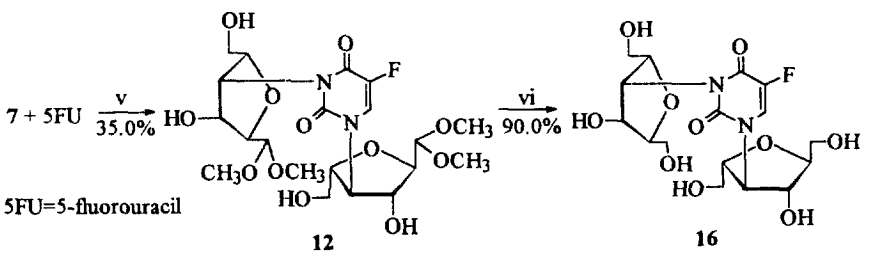


i.- ii. see reference[11]; iii. 1% HCl in methanol; iv. K_2CO_3/methanol.

Scheme 1.

Compound **7** reacted with nucleobases (adenine, uracil, thymine and 5-fluorouracil) in DMF, and a regioselective epoxide opening took place in the presence of potassium carbonate and a crown ether at 80–100°C to give **9–12**. Compound **12** was obtained in the form of a 5-fluorouracil combined with two tetrahydrofuran rings. The structures of **9–12** were identified by 2D NMR (for example in **10**, strong NOE effects were observed between H-6 and H-3′, H-4′ or H-5′). In the molecular mechanics minimized conformation of **10**, the distance between H-6 and H-3′, H-4′ or H-5′ is 0.233, 0.235 or 0.258 nm respectively. On the other hand, if the nucleobase is linked to C-3′, an NOE effect should be observed between H-6 and H-1′ (the distance is 0.259 nm). In the ^{1}H NMR of **12**, four single peaks of MeO and one proton of H-6 (d, J=7.2 Hz, $J_{H\text{-}6,\ F}$) showed the existance of two tetrahydrofuran rings and one pyrimidine ring. The ^{1}H–^{1}H COSY NMR also identified the structure of **12**. Compounds **9–12** were hydrolyzed by 0.5% of TFA to remove the dimethylacetal, followed by reduction with sodium borohydride to give the desired compounds **13–16** in >90% yield (Scheme 2).



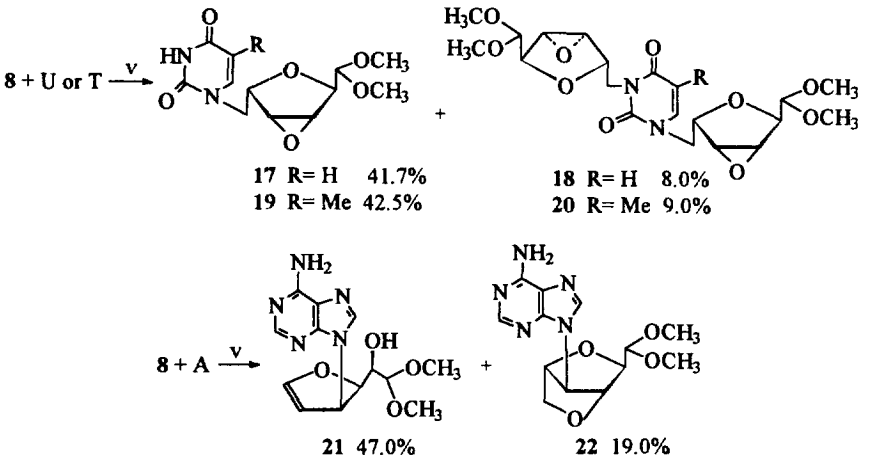


v K_2CO_3/18-crown/DMF; vi a. 0.5% TFA/H_2O; b. $NaBH_4$.

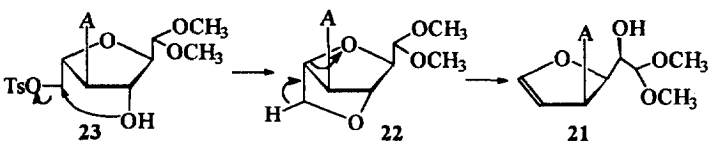
Scheme 2.

There are two active centers, the epoxide and tosyl group, in **8** which can be substituted by nucleophilic reagents. The pyrimidine bases prefer to attack the tosyl group under the same reaction conditions as **7**, **8** reacted with uracil or thymine in the presence of potassium carbonate and a crown ether to give **17–20**. Surprisingly, when adenine was used instead of pyrimidine under the same conditions, two new compounds **21** and **22** were obtained (Scheme 3). ^{1}H NMR of **22** is very similiar

to the spectrum of **9** except $\delta_{H\text{-}3',5'}$ is shifted slightly up field,[12] but there is no hydroxy group in **22** and the molecular weight of **22** (M^+ 307) showed that **22** is the anhydro derivative of **9** (M^+ 325). **22** is unstable even at room temperature and converts to **21**. Comparing the ^1H NMR of **22** with **21**, it was found that a double bond and a hydroxy group were formed in **21** (δ: 6.58 and 7.36, J=14.5 Hz; δ: 3.33, D_2O exchangeable). It seems that adenine attacks the epoxide to give an intermediate **23** in which the tosyl group was substituted by the neighbouring hydroxy group to give **22**. **22** was converted to **21** by ring opening under the basic conditions (Scheme 4).



Scheme 3.



Scheme 4. Mechanism of the formation of **21**.

Conclusion

New types of isonucleosides **13–16** were synthesized regioselectively by the reaction of nucleobases with epoxide **7** in good yield. When two functional groups, TsO^- and epoxide, exist in the same molecule, TsO^- is more active to the nucleophilic attack of pyrimidine base. Due to the feasible stereochemical reason, the preferential substitution of epoxide of **8** by the stronger nucleophile, adenine, and reformation of tetrahydrofuran ring took place.

Experimental section

General procedures

All solvents were dried and distilled prior to use. Thin layer chromatography was performed using silica gel GF-254 (Qing-Dao Chemical Company, China) plates with detection by UV, or charting with 5% phosphomolybdic acid hydrate in ethanol. Column chromatography was performed on silica gel (200–300 mesh, purchased from Qing-Dao Chemical Company, China). 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 were used for mass spectra. NMR spectra were recorded with Varian VXR-300 or Bruker DPX-400 with TMS as internal standard. Evaporations were carried out under reduced pressure with bath temperature below 45°C.

1,2-O-Isopropylidene-3,5-di-O-p-tolylsulfonyl-6-O-benzoyl-α-D-glucofuranose **2**

2 was obtained from 1,2-O-propylidene-3-O-p-tolylsulfonyl-6-O-benzoyl-α-D-glucofuranose in 84.7% yield. ^{1}H NMR ($CDCl_3$): δ=1.28 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 2.29 (s, 3H, Ts-CH_3), 2.42 (s, 3H, Ts-CH_3), 4.34 (dd, J=6.3 Hz, 12.6 Hz, 1H, H-4), 4.49 (m, 2H, H-6), 4.80 (dd, J=4.2 Hz, 6.3 Hz, 1H, H-3), 4.92 (m, 1H, H-5), 5.02 (dd, J=3.3 Hz, 4.2 Hz, 1H, H-2), 5.86 (d, J=3.3 Hz, 1H, H-1), 7.12 (d, J=8.4 Hz, 2H), 7.65 (d, J=8.1 Hz, 2H), 7.38 (dd, J=8.4, 8.1 Hz, 4H), 7.55 (t, J=6.6 Hz, 1H), 7.81 (d, J=8.1H, 2H), 7.91 (d, J=8.4 Hz, 2H) (arom H). ^{13}C NMR ($CDCl_3$): δ=21.6 (CH_3), 21.7 (CH_3), 26.2 (Ts-CH_3), 26.5 (Ts-CH_3), 62.5 (C-6), 75.7 (C-4), 78.2 (C-3), 81.0 (C-5), 82.3 (C-2), 104.4 (C-1), 112.7 (quat C of isopropylidene), 133.5, 132.2, 132.9, 129.2, 127.5, 128.1, 129.5, 129.6, 130.0, 144.8, 145.6 (Arom C), 165.2 (Bz-CO).

1,2-O-Isopropylidene-3,5,6-tri-O-p-tolylsulfonyl-α-D-glucofuranose **3**

3 (colorless syrup) was obtained from 1,2-O-isopropylidene-α-D-glucofuranose in 77.5% yield. ^{1}H NMR ($CDCl_3$): δ=1.24 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 2.40 (s, 3H, Ts-H_3), 2.43 (s, 3H, Ts-H_3), 2.46 (s, 3H, Ts-H_3), 3.99 (dd, 1H, H-4), 4.11 (m, 1H, H-6a), 4.36 (m, 1H, H-6b), 4.72 (m, 2H, H-3,5), 4.75 (d, 1H, H-2), 4.91 (d, 1H, H-1), 7.26–7.86 (m, 12H).

3-O-p-Tolylsulfonyl-2,5-anhydro-L-idofuranose dimethylacetal **5**

1,2-O-isopropylidene-3,5-di-O-p-tolylsulfonyl-6-O-benzoyl-α-D-glucofuranose **2** (12.3g, 19.45 mmol) was dissolved in methanol (180 ml). After hydrochloric acid (37%) (2.0 ml) was added, the solution was refluxed for 70 h. After cooling, neutralization with $NaHCO_3$ and evaporation, the residue was extracted with chloroform. The extract was purified by silica gel chromatography. **5** (6.65 g, colorless syrup) was obtained in 94.4% yield. $[\alpha]_D^{25}$ + 38.5 (c 0.172, MeOH). MS (FAB): m/z=385 (M+Na). ^{1}H NMR ($CDCl_3$): δ=2.45 (s, 3H, Ts-CH_3), 3.14 (s, 3H, 1-OCH_3), 3.39 (s, 3H, 1-OCH_3), 3.40 (br.s, 1H, 6-OH), 3.91 (m, 2H, H-6), 4.18 (dd, J=3.6 Hz, $J_{4,5}$, 7.5 Hz, $J_{4,3}$, 1H, H-4), 4.30 (m, 1H, H-5), 4.41 (d, J=7.5 Hz, $J_{3,4}$, 1H, H-3), 4.46 (d, J=2.4 Hz, $J_{2,1}$, 1H, H-2), 4.65 (br.s, 1H, 4-OH) 4.86 (d, J=2.4 Hz, $J_{1,2}$, 1H, H-1), 7.37 (d, J=8.4 Hz, 2H, Ts-2′,6′), 7.82 (d, J=8.4 Hz, 2H, Ts-3′,5′). ^{13}C NMR ($CDCl_3$): δ=21.6 (Ts-CH_3), 53.5 (1-OCH_3), 54.7 (1-OCH_3), 61.2 (C-6), 76.5 (C-4), 78.3 (C-3), 79.4 (C-5), 85.3 (C-2), 101.7 (C-1), 127.7, 127.9, 129.9, 130.0, 133.3, 145.2 (arom C). Analysis calcd for $C_{15}H_{22}O_8S_1$ (362.4): C, 49.72; H, 6.12. Found: C, 49.58; H, 5.89.

3,6-Di-O-p-tolylsulfonyl-2,5-anhydro-L-idofuranose dimethylacetal **6**

A solution of **3** (10.0g, 14.66 mmol) in methanol (100 ml) was treated with hydrochloric acid (37%) (1.1 ml) under reflux for 6 days. Compound **6** (6.6g, white crystal, mp:136–138°C dec.) was obtained from the $CHCl_3$ extracts in 87.2% yield. $[\alpha]_D^{25}$ + 43.4 (c 0.145, MeOH). MS (FAB): m/z=539 (M+Na). ^{1}H NMR ($CDCl_3$): δ=2.46 (s, 3H, Ts-CH_3), 2.47(s, 3H, Ts-CH_3), 3.10 (s, 3H, 1-OCH_3), 3.32 (s, 3H, 1-OCH_3), 4.08 (dd, J=9.9 Hz, $J_{6b,6a}$, 5.5 Hz, $J_{6b,5}$, H-6b), 4.19 (dd, J=7.8 Hz, $J_{2,1}$, 3.3 Hz, $J_{2,3}$, H-2), 4.25 (dd, J=9.9 Hz, $J_{6a,6b}$, 7.5 Hz, $J_{6a,5}$, H-6a), 4.32 (ddd, J=3.3 Hz, $J_{5,4}$, 5.5 Hz, $J_{5,6b}$, 7.5 Hz, $J_{5,6a}$, H-5), 4.35 (d, J=7.8 Hz, $J_{1,2}$, H-1), 4.48 (dd, J=1.5 Hz, $J_{4,3}$, 3.3 Hz, $J_{4,5}$, H-4), 4.85 (dd, J=1.5 Hz, $J_{3,4}$, 3.3 Hz, $J_{3,2}$, H-3), 6.37 (dd, 2H, J=8.1, 9.3 Hz, Ts-2′,6′), 7.79 (dd, 2H, J=8.1, 9.3 Hz, Ts-3′,5′). ^{13}C NMR ($CDCl_3$): δ=21.8 (2×Ts-CH_3), 55.1 (1-OCH_3), 55.9 (1-OCH_3), 66.2 (C-6), 74.3 (C-4), 77.9 (C-5), 78.2 (C-2), 84.0 (C-3), 101.2 (C-1), 127.9 (Ts-3′, 3″, 5′, 5″), 130.0 (Ts-2′, 2″, 6′, 6″), 133.1 (Ts-4′), 132.2 (Ts-4″), 145.2 (Ts-1″), 145.4 (Ts-1′). Analysis calcd for $C_{22}H_{28}O_{10}S_2$ (516.6): C, 51.15; H, 5.46. Found: C, 51.49; H, 5.70.

2,5:3,4-Dianhydro-L-talofuranose dimethylacetal **7**

Compound **5** (6.65 g, 18.92 mmol) was dissolved in methanol (90 ml), and potassium carbonate (7.5 g) was added. The mixture was stirred at room temperature for 2.5 h. After filtration, neutralization and evaporation, the residue was extracted with chloroform. The extract was purified with silica gel chromatography eluting with cyclohexane and ethyl acetate. Compound **7** (3.23 g, colorless syrup) was obtained in 92.6% yield. $[\alpha]_D^{25}$ + 38.5 (c 0.175, MeOH). MS (FAB): m/z=191 (M+1). ^{1}H NMR

(acetone-d_6): δ=3.26 (s, 1H, 6-OH), 3.42 (s, 3H, 1-OCH_3), 3.34 (s, 3H, 1-OCH_3), 3.59 (m, 2H, H-6), 3.75 (d, J=3.0 Hz, $J_{3,4}$, 1H, H-3), 3.82 (d, J=3.0 Hz, $J_{4,3}$, 1H, H-4), 3.96 (d, J=5.1 Hz, $J_{2,1}$, 1H, H-2), 4.05 (t, J=6.3 Hz, $J_{5,6}$, 1H, H-5), 4.34 (d, J=5.1 Hz, $J_{1,2}$, 1H, H-1). ^{13}C NMR (acetone-d_6): δ=54.0 (1-OCH_3), 54.9 (1-OCH_3), 55.8 (C-4), 59.8 (C-3), 65.9 (C-6), 77.7 (C-5), 77.8 (C-2), 104.1 (C-1). Analysis calcd for $C_8H_{14}O_5$ (190.1): C, 50.50; H, 7.42. Found: C, 50.23; H, 7.43.

6-O-p-Tolylsulfonyl-2,5:3,4-dianhydro-L-talofuranose dimethyl acetal ***8***

8 (colorless syrup) was obtained from **6** in 94.0% yield by the same procedure used for **7**. $[\alpha]_D^{25}$ +29.0 (c 0.170, MeOH). MS (FAB): m/z=345 (M+1). ^{1}H NMR ($CDCl_3$): δ=2.44 (s, 3H, Ts-CH_3), 3.42 (s, 3H, 1-OCH_3), 3.44 (s, 3H, 1-OCH_3), 3.77 (d, J=3.0 Hz, $J_{3,4}$, 1H, H-3), 3.81 (d, J=3.0 Hz, $J_{4,3}$, 1H, H-4), 4.04-4.12 (m, 3H, H-5, 6), 4.23 (d, J=4.8 Hz, $J_{2,1}$, 1H, H-2), 4.28 (d, J=4.8 Hz, $J_{1,2}$, 1H, H-1), 7.35 (d, J=8.1 Hz, 2H, Ts-3′, 5′), 7.79 (d, J=8.1 Hz, 2H, Ts-2′, 6′). ^{13}C NMR ($CDCl_3$): δ=21.85 (Ts-CH_3), 54.4 (1-OCH_3), 54.9 (1-OCH_3), 60.0 (C-4), 65.1 (C-3), 65.9 (C-6), 75.7 (C-5), 78.8 (C-2), 102.1 (C-1), 127.9 (Ts-3′, 5′), 132.2 (Ts-2′, 6′), 133.1 (Ts-4′), 145.4 (Ts-1′). Analysis calcd for $C_{14}H_{20}O_7S_1$ (344.1): C, 52.31; H, 5.86; Found: C, 52.54; H, 5.62.

4-Deoxy-4-(adenin-9-yl)-2,5-anhydro-L-mannofuranose dimethyl acetal ***9***

A mixture of adenine (0.351 g, 2.59 mmol), potassium carbonate (0.50 g, 3.62 mmol) and 18-crown-6 (0.35 g, 1.32 mmol) were dissolved in DMF (10 ml). The solution of **7** (0.40 g, 2.11 mmol) in DMF (5 ml) was added under nitrogen at room temperature. After stirring for 0.5 h, the mixture was heated at 80°C for 28 h. After filtration and evaporation, the residue was purified on silica gel chromatography eluting with chloroform, ethyl acetate and methanol, white powder was obtained with total gross 80.4% yield. After recrystallization from ethanol, pure **9** (white powder, mp: 149–151°C) was obtained in 65.0% yield. $[\alpha]_D^{25}$ +7.5 (c 0.076, MeOH). UV (MeOH): λ_{max}=208, 261 nm (ε=19620, 14304). MS (FAB): m/z=326 (M+1). ^{1}H NMR (DMSO-d_6): δ=3.38 (s, 6H, 1′- OCH_3), 3.48 (m, 2H, H-6′), 3.86 (t, J=5.8 Hz, 1H, H-2′), 4.39 (m, 1H, H-5′), 4.57 (d, J=5.8 Hz, $J_{1',2'}$, 1H, H-1′), 4.78 (ddd, J=5.8 Hz, $J_{3'2'}$, 5.8, 8.8 Hz, $J_{3',4'}$, 1H, H-3′), 4.72 (dd, J=8.8 Hz, $J_{3',4'}$, 7.4 Hz, $J_{4',5'}$, 1H, H-4′), 4.81 (br.s, 1H, 6′-OH), 5.56 (d, J=5.8 Hz, 1H, 3′-OH), 7.18 (br.s, 2H, 6-NH_2,), 8.15 (s, 1H, H-2), 8.16 (s, 1H, H-8). ^{13}C NMR (DMSO-d_6): δ=53.82 (1′-OCH_3), 54.5 (1′-OCH_3), 60.8 (C-6′), 63.3 (C-4′), 74.8 (C-3′), 79.5 (C-5′), 82.2 (C-2′), 104.0 (C-1′), 119.2 (C-5), 140.2 (C-8), 149.5 (C-4), 152.2 (C-2), 156.0 (C-6). Analysis calcd for $C_{13}H_{19}N_5O_5$ (325.1): C, 47.98; H, 5.89; N, 21.53. Found: C, 47.59; H, 5.58; N, 21.07.

4-Deoxy-4-(uracil-1-yl)-2,5-anhydro-L-mannofuranose dimethylacetal ***10***

10 (white foam) was obtained in 35.3% yield. $[\alpha]_D^{25}$ −12.7 (c 0.105, MeOH). UV (MeOH): λ_{max}=210, 266 nm (ε=6883, 9175). MS (FAB): m/z=303 (M+1). ^{1}H NMR (DMSO-d_6): δ=3.33 (s, 3H, 1′-OCH_3), 3.35 (s, 3H, 1′-OCH_3), 3.43 (m, 2H, H-6′), 3.76 (dd, J=5.5 Hz, $J_{2',1'}$, 5.8 Hz, $J_{2',3'}$, 1H, H-2′), 3.99 (ddd, J=8.6, 4.2, 4.7 Hz, 2H, H-5′), 4.39 (dd, J=5.8 Hz, $J_{3',2'}$, 7.0 Hz, $J_{3',4'}$, 1H, H-3′), 4.45 (d, J=5.5 Hz, $J_{1',2'}$, 1H, H-1′), 4.57 (dd, J=7.0 Hz, $J_{4',3'}$, 8.6 Hz, $J_{4',5'}$, 1H, H-4′), 4.80 (t, 1H, 6′-OH), 5.52 (d, 1H, 3′-OH), 5.63(d, J=8.0 Hz, 1H, H-5), 7.62 (d, J=8.0 Hz, 1H, H-6). 1D NOE, H-6 as standard, H-5, H-3′, H-4′ and H-5′ were observable. ^{13}C NMR (DMSO-d_6): δ=54.0 (1-OCH_3), 54.7 (1-OCH_3), 61.3 (C-6′), 65.4 (C-4′), 74.0 (C-3′), 79.1 (C-5′), 82.2 (C-2′), 101.6 (C-5), 104.2 (C-1′), 143.2 (C-6), 150.9 (C-2), 162.9 (C-4). Analysis calcd for $C_{12}H_{18}N_2O_7$ (302.1): C, 47.66; H, 6.00; N, 9.27. Found: C, 47.32; H, 5.89; N, 8.95.

4-Deoxy-4-(thymin-1-yl)-2,5-anhydro-L-mannofuranose dimethylcetal ***11***

11 (white foam) was obtained in 36.8% yield. $[\alpha]_D^{25}$ −10.2 (c 0.095, MeOH). UV (MeOH): λ_{max}=210, 266 nm (ε=6372, 7280). MS (FAB): m/z=317 (M+1). ^{1}H NMR (CD_3OD): δ=1.87 (s, 3H, 5-CH_3), 3.46 (s, 3H, 1′-OCH_3), 3.49 (s, 3H, 1′-OCH_3), 3.54−3.69 (m, 2H, H-6′), 3.92 (dd, J=4.8 Hz, $J_{2',1'}$, 5.4 Hz, $J_{2',3'}$, 1H, H-2′), 4.18 (m, 1H, H-5′), 4.53 (d, J=4.8 Hz, 1H, H-1′), 4.62 (dd, J=6.9 Hz, $J_{3',4'}$, 5.4 Hz, $J_{3',2'}$, 1H, H-3′), 4.72 (dd, J=8.1, $J_{4',5'}$, 6.9 Hz, $J_{4',3'}$, 1H, H-4′), 5.00 (br.s, 1H, 6′-OH),

5.63 (br.s, 1H, 3′-OH), 7.49 (d, J=1.5 Hz, 1H, H-6). ^{13}C NMR (CD_3OD): δ=12.4 (5-CH_3), 55.4 (1′-OCH_3), 56.3 (1′-OCH_3), 62.7 (C-6′), 67.0 (C-4′), 75.8 (C-3′), 81.2 (C-5′), 84.4 (C-2′), 106.4 (C-1′), 111.8 (C-5), 140.7 (C-6), 153.0 (C-2), 166.3 (C-4). Analysis calcd for $C_{13}H_{20}N_2O_7$ (316.3): C, 49.36; H, 6.37; N, 8.86. Found: C, 49.10; H, 6.26; N, 8.74.

*1,3-Di-(4-deoxy-2,5-anhydro-*L*-manofuranose dimethylacetal-4-yl)-5-fluorouracil* ***12***

12 (colorless syrup) was obtained in 35% yield. $[\alpha]_D^{25}$ +1.44 (c 0.090, MeOH). UV (MeOH): λ_{max}=201, 274 nm (ε=10348, 6628). MS (FAB): m/z=511 (M+1). ^{1}H NMR (acetone-d_6): δ=3.40 (s, 3H), 3.41 (s, 3H), 3.45 (s, 3H), 3.48 (s, 3H), (4×OCH_3), 3.58 (dd, 1H, H-6″b), 3.67 (dd, 1H, H-6″a), 3.69 (dd, 1H, H-6′b), 3.70 (dd, 1H, H-6′a), 3.88 (dd, J=3.3, 6.3 Hz, 1H, H-2″), 3.91 (m, 1H, H-5″), 3.97 (dd, J=4.5, 6.0 Hz, 1H, H-2′), 4.04 (t, J=3.3 Hz, 1H, H-4″), 4.11 (t, J=3.3 Hz, 1H, H-3″), 4.23 (m, 1H, H-5′), 4.45 (d, J=6.3 Hz, 1H, H-1″), 4.55 (d, J=4.5 Hz, 1H, H-1′), 4.67 (t, J=4.5 Hz, 1H, H-3′), 4.87 (t, J=7.5 Hz, 1H, H-4′), 5.12 (br.s, 2H, 6′,6″-OH), 5.65 (br.s, 2H, 3′, 3″-OH), 7.93 (d, J=7.2 Hz, 1H, H-6). ^{13}C NMR (acetone-d_6): δ=53.8, 54.5, 55.0, 55.4, (1′,1″-OMe), 62.1 (C-6′), 62.7 (C-6″), 66.0 (C-4′), 70.7 (C-4″), 75.5 (C-3′), 79.0 (C-3″), 80.8 (C-5′), 84.0 (C-5″), 85.5 (C-2′), 86.3 (C-2″), 104.9 (C-1′), 105.5 (C-1″), 127.5 (C-5, d, J=136.0 Hz), 142.1 (C-6), 150.4 (C-2), 162.0 (C-4). Analysis calcd for $C_{20}H_{31}FN_2O_{12}.H_2O$ (528.5): C, 45.45; H, 6.29; N, 5.30. Found: C, 45.16; H, 6.67; N, 5.64.

*4-Deoxy-4-(adenin-9-yl)-2,5-anhydro-*L*-mannitol* ***13***

After **9** (130 mg, 0.40 mmol) was dissolved in water (9.0 ml), TFA (45 μl) was added. The solution was heated at 80°C for 5 h. After cooling and neutralization, 25 mg of sodium borohydride was added. The solution was stirred at room temperature for 45 min then neutralized with 2 N HCl. The mixture was purified by silica gel chromatography. **13** (115 mg, white crystal, mp, 158–160°C) was obtained in 92.3% yield. $[\alpha]_D^{25}$ +0.55 (c 0.060, MeOH). UV (MeOH): λ_{max}=206, 260 nm (ε=20732, 15781). MS (FAB): m/z=282 (M+1). ^{1}H NMR (DMSO-d_6): δ=3.41 (m, 1H, H-6′b), 3.49 (m, 1H, H-6′a), 3.54 (m, 1H, H-1′a), 3.57 (m, 1H, H-1′b), 3.65 (m, 1H, H-2′), 3.82 (m, 1H, H-5′), 4.37 (m, J=3.5, 4.1, 8.4 Hz, 1H, H-3′), 4.64 (dd, J=7.0, 7.6 Hz, 1H, H-4′), 4.75 (m, 2H, 1′, 6′-OH), 5.53 (d, J=5.0 Hz, 1H, 3′-OH), 7.15 (s, 2H, N_6-H), 8.14 (s, 1H, H-2), 8.18 (s, 1H, H-8), ^{13}C NMR (DMSO-d_6): δ=61.3 (C-6′), 61.5 (C-1″), 62.7 (C-4′), 73.7 (C-3′), 79.2 (C-5′), 83.3 (C-2′), 119.3 (C-5), 140.3 (C-8), 149.6 (C-4), 152.3 (C-2), 156.0 (C-6). Analysis calcd for $C_{11}H_{15}N_5O_4$ (281.1): C, 46.96; H, 5.38; N, 24.91. Found: C, 46.78; H, 5.43; N, 24.73.

*4-Deoxy-4-(uracil-1-yl)-2,5-anhydro-*L*-mannitol* ***14***

14 (white foam) was obtained in 94.6% yield. $[\alpha]_D^{25}$ −6.67 (c 0.070, MeOH). UV (MeOH): λ_{max}=210, 267 nm (ε=4810, 6639). MS (FAB): m/z=259 (M+1). ^{1}H NMR (DMSO-d_6): δ=3.60–3.45 (m, 4H, H-1′, 6′), 3.61 (dd, 1H, H-2′), 3.72 (t, 1H, H-5′), 3.96 (dt, J=7.7, 4.8 Hz, 1H, H-3′), 4.26 (t, J=7.7 Hz, 1H, H-4′), 4.67 (m, J=7.7 Hz, 2H, 1′, 6′-OH), 5.46 (br.s, 1H, 3′-OH), 5.61 (d, J=7.9 Hz, 1H, H-5), 7.64 (d, J=7.9 Hz, 1H, H-6), 11.21 (s, 1H, N_3-H). ^{13}C NMR (DMSO-d_6): δ=60.0 (C-6′), 60.4 (C-1′), 63.0 (C-4′), 71.8 (C-3′), 77.7 (C-5′), 81.7 (C-2′), 100.3 (C-5), 141.6 (C-6), 149.6 (C-2), 161.6 (C-4). Analysis calcd for $C_{10}H_{14}N_2O_6$ (258.1): C, 46.50; H, 5.47; N, 10.85. Found: C, 46.22; H, 5.60; N, 10.46.

*4-Deoxy-4-(thymin-1-yl)-2,5-anhydro-*L*-mannitol* ***15***

15 (white foam) was obtained in 90.6% yield. $[\alpha]_D^{25}$ −2.67 (c 0.075, MeOH). UV (MeOH): λ_{max}=209, 270 nm (ε=6000, 6366). MS (FAB): m/z=273 (M+1). ^{1}H NMR (DMSO-d_6): δ=3.42 (m, 2H, H-6′), 3.51 (m, 2H, H-1′), 3.60 (m, 1H, H-2′), 3.72 (m, 1H, H-5′), 3.96 (dt, J=4.7 Hz, $J_{3',2'}$, 8.0 Hz, $J_{3',4'}$, 1H, H-3′), 4.24 (t, J=8.0 Hz, $J_{4',3'}$ and $J_{4'5'}$, 1H, H-4′), 4.67 (t, J=8.0 Hz, 1H, 1′-OH′), 4.77 (br.s, 1H, 6′-OH), 5.48 (br.s, 1H, 3′-OH), 7.53 (s, 1H, H-6), 11.20 (s, 1H, N_3-H). ^{13}C NMR (DMSO-d_6): δ=10.5 (5-CH_3), 60.0 (C-6′), 60.4 (C-1′), 62.5 (C-4′), 71.6 (C-3′), 77.7 (C-5′), 81.6 (C-2′), 107.9

(C-5), 137.0 (C-6), 149.6 (C-2), 162.2 (C-4). Analysis calcd for $C_{11}H_{16}N_2O_6$ (272.3): C, 48.53; H, 5.92; N, 10.29. Found: C, 48.60; H, 5.56; N, 10.01.

1,3-Di-(4-deoxy-2,5-anhydro-L-manitol-4-yl)-5-fluorouracil ***16***

16 (colorless syrup) was obtained in 90.0% yield. $[\alpha]_D^{25}$ −7.5 (c 0.04, MeOH). UV (MeOH): λ_{max}=207, 273 nm (ε=11900, 11846). MS (FAB): m/z=423 (M+1). ^{1}H NMR (DMSO-d_6): δ=3.41–3.54 (m, 4H, 6′, 6″-H), 3.62 (m, 4H, 1′, 1″-H), 3.74 (m, 4H, 2′, 2″, 5′, 5″-H), 3.96 (m, 2H, 3′, 3″-H), 4.23 (m, 2H, 4′, 4″-H), 4.68 (m, 4H, 1′, 1″, 6′, 6″-OH), 4.99 (s, 2H, 3′, 3″-OH), 8.08 (d, J=7.2 Hz, 1H, H-6). ^{13}C NMR (DMSO-d_6): δ=61.5 (6′, 6″), 61.7 (1′, 1″), 64.0 (C-4′, 4″), 73.1 (C-3′, 3″), 77.2 (2′, 2″), 78.7 (C-5′), 83.0 (C-5″), 127.6 (d, J=138 Hz, C-5), 138.8 (C-6), 149.7 (C-2), 158.0 (C-4). Analysis calcd for $C_{16}H_{23}FN_2O_{10}$ (422.4): C, 45.50; H, 5.49; N, 6.63. Found: C, 45.63; H, 5.36; N, 6.21.

6-Deoxy-6-(uracil-1-yl)-2,5:3,4-dianhydro-L-talofuranose dimethylacetal ***17*** *and 1,3-di-(6-deoxy-2,5:3,4-dianhydro-L-talofuranose dimethylacetal-6-yl)-uracil* ***18***

A mixture of uracil (0.355 g, 3.17 mmol), potassium carbonate (0.88 g, 6.38 mmol) and 18-crown-6 (0.84 g) were dissolved in DMF (12 ml). The solution of **8** (1.09 g, 3.17 mmol) in DMF (6 ml) was added under nitrogen. After being stirred for 0.5 h under nitrogen, the mixture was heated at 80°C for 48 h. After neutralization and evaporation, the residue was purified by silica gel chromatography eluting with chloroform and methanol to give **17** (0.375 g, white powder, m.p.: 163–165°C) in 41.7% yield and **18** (60 mg, syrup) in 8.0% yield. **17**: $[\alpha]_D^{25}$ +98.4 (c 0.105, MeOH). UV (MeOH): λ_{max}=207, 265 nm (ε=5356, 5981). MS (FAB): m/z=285 (M+1). ^{1}H NMR (DMSO-d_6): δ=3.33 (s, 6H, 1′-OCH_3), 3.73 (d, J=3.0 Hz, 1H, H-3′), 3.80 (m, J=4.5, 4.8 Hz, 2H, H-6′), 3.85 (d, J=3.0 Hz, 1H, H-4′), 3.97 (d, J=4.2 Hz, 1H, H-2′), 4.15 (dd, J=4.5, 4.8 Hz, 1H, H-5′), 4.33 (d, J=4.2 Hz, 1H, H-1′), 5.49 (d, J=7.8 Hz, 1H, H-5), 7.46 (d, J=7.8 Hz, 1H, H-6), 11.24 (s, 1H, N_3-H). ^{13}C NMR (DMSO-d_6): δ=47.6 (C-6′), 55.2 and 55.6 (1′-OCH_3), 55.9 (C-4′), 56.1 (C-3′), 74.8 (C-5′), 77.7 (C-2′), 103.8 (C-1′), 100.3 (C-5), 146.2 (C-6), 150.9 (C-2), 163.7 (C-4). Analysis calcd for $C_{12}H_{16}N_2O_6$ (284.1): C, 50.70; H, 5.67; N, 9.85. Found: C, 50.35; H, 6.01; N, 9.35. **18**: UV (MeOH): λ_{max}=211, 265 nm. MS (FAB): m/z=457 (M+1). ^{1}H NMR (DMSO-d_6): δ=3.31 (s, 3H), 3.32 (s, 3H), 3.33 (s, 6H), (1′, 1″-OCH_3), 3.70–3.74 (m, 3H, H-6′, 6″a), 3.84 (d, J=2.7 Hz, 1H, H-6″b), 3.90–3.98 (m, 7H, H-5′, 2′, 2″, 3′, 3″, 4′, 4″), 4.17 (t, 1H, H-5″), 4.29 (d, J=4.5 Hz, 1H, H-1′), 4.32 (d, J=4.5 Hz, 1H, H-1″), 5.63 (d, J=8.1 Hz, 1H, H-5), 7.51 (d, J=8.1 Hz, 1H, H-6). ^{13}C NMR (DMSO-d_6): δ=48.5 (C-6′), 55.0 (C-6″), 55.1 (C-3′), 55.5 (1′-OCH_3), 55.6 (1′-OCH_3), 55.8 (C-3″), 56.2 (1″-OCH_3), 56.3 (1″-OCH_3), 56.6 (C-4′), 56.6 (C-4″), 74.6 (C-2′), 74.7 (C-2″), 77.2 (C-5′), 77.7 (C-5″), 103.8 (C-1′), 103.9 (C-1″), 99.5 (C-5), 145.0 (C-6), 151.2 (C-2), 162.4 (C-4). Analysis calcd for $C_{20}H_{28}N_2O_{10}$ (456.2): C, 52.61; H, 6.19; N, 6.14. Found: C, 52.39; H, 6.24; N, 6.01.

6-Deoxy-6-(thymin-1-yl)-2,5:3,4-dianhydro-L-talofuranose dimethylacetal ***19***

19 was obtained as a white powder, m.p.: 172–174°C, yield 42.5%. $[\alpha]_D^{25}$ +106.1 (c 0.070, MeOH). UV (MeOH): λ_{max}=210, 269 nm (ε=6946, 7822). MS (EI): m/z=298 (M). ^{1}H NMR (DMSO-d_6): δ=1.72 (s, 5-CH_3), 3.33 (s, 6H, 1′-OCH_3), 3.74 (d, J=3.0 Hz, 1H, H-3′), 3.80 (m, J=4.8, 6.0 Hz, 2H, H-6′), 3.84 (d, J=3.0 Hz, 1H, H-4′), 3.98 (d, J=4.5 Hz, 1H, H-2′), 4.15 (dd, J=3.8, 4.0 Hz, 1H, H-5′), 4.32 (d, J=4.5 Hz, 1H, H-1′), 7.37 (s, H-6), 11.24 (s, N_3-H). ^{13}C NMR (DMSO-d_6): δ=12.0 (5-CH_3), 47.7 (C-6′), 55.2 and 55.6 (1′-OCH_3), 56.0 and 56.1 (C-3′, 4′), 74.9 (C-5′), 77.7 (C-2′), 103.9 (C-1′), 107.9 (C-6), 142.0 (C-5), 150.8 (C-2), 164.2 (C-4). Analysis calcd for $C_{13}H_{18}N_2O_6 \cdot C_2H_5OH$ (344.2): C, 52.30; H, 7.03; N, 8.14. Found: C, 52.80; H, 7.04; N, 8.04.

1,3-Di-(6-deoxy-2,5:3,4-dianhydro-L-talofuranose dimethylacetal-6-yl)-thymine ***20***

Yield 9.0% (syrup). UV (MeOH): λ_{max}=214, 269 nm. MS (FAB): m/z=471(M+1). ^{1}H NMR (DMSO-d_6): δ=3.32 (s, 3H), 3.32 (s, 3H), 3.33 (s, 6H, 1′, 1″-OCH_3), 3.70–3.74 (m, 3H, H-6″a, 6′), 3.84 (d, J=3.0 Hz, 1H, H-6″b), 3.90–3.98 (m, 7H, H-5″, 3′, 3″, 4′, 4″, 2′, 2″), 4.39 (d, J=4.5 Hz, 1H, H-1′),

4.24 (t, 1H, H-5″), 4.46 (d, J=4.5 Hz, 1H, H-1″), 7.53 (s, 1H, H-6). ^{13}C NMR (DMSO-d_6): δ=10.5 (5-CH_3), 48.5 (C-6′), 54.8 (C-6″), 55.1 (C-3′), 55.5 (1′-OCH_3), 55.6 (1′-OCH_3), 55.8 (C-3″), 56.2 (1″-OCH_3), 56.3 (1″-OCH_3), 56.6 (C-4′), 56.6 (C-4″), 74.6 (C-2′), 74.7 (C-2″), 77.2 (C-5′), 77.7 (C-5″), 102.9 (C-1′), 103.1 (C-1″), 107.5 (C-5), 140.3 (C-6), 150.2 (C-2), 162.2 (C-4). Analysis calcd for $C_{21}H_{30}N_2O_{10}$ (470.2): C, 53.60; H, 6.43; N, 5.96. Found: C, 53.89; H, 6.38; N, 6.08.

4-(S)-adenyl-5-(R)-[1′-(R)-hydroxy-2′,2′-dimethoxy]ethyl-2,3-dihydrofuran ***21*** *and 4-deoxy-4-adenyl-2,5:3,6-dianhydro-*L*-mannose dimethylacetal* ***22***

A mixture of adenine (1.66 g, 12.3 mmol), potassium carbonate (2.54 g, 18.40 mmol) and 18-crown-6 (1.62 g, 6.14 mmol) were dissolved in DMF (50 ml). The solution of **8** (3.53 g, 10.26 mmol) in DMF (30 ml) was added under nitrogen at room temperature. After being stirred for 0.5 h under nitrogen, the mixture was heated at 80°C for 32 h. The solid was filtered and the solution was neutralized and evaporated. Then the residue was purified by silica gel chromatography eluting with chloroform, ethyl acetate and methanol to give **21** (1.50 g, light yellow powder) in 47.0% yield and **22** (0.83 g, white foam) in 26.3% yield. **21** was recrystallized from ethanol to give white powder. **21**: m.p.: 188–190°C (dec.), $[\alpha]_D^{25}$ −22.57 (c 0.089, MeOH), UV (MeOH): λ_{max}=227, 257 nm (ε=19932, 10594). MS (EI): m/z=307 (M). ^{1}H NMR (DMSO-d_6): δ=3.33 (s, 1H, D_2O exchangeable), 3.35 (s, 6H, 1′-OCH_3), 3.88 (d, J=3.0 Hz, 1H, H-6′), 3.94 (d, J=3.0 Hz, 1H, H-5′), 4.77 (d, J=7.8 Hz, 1H, H-4′), 5.00 (s, 1H, H-7′), 6.58 (dd, J=7.8, 14.5 Hz, 1H, H-3′), 7.36 (d, J=14.5 Hz, 1H, H-2′), 7.39 (br.s, 2H, 6-NH_2), 8.22 (s, 1H, H-2), 8.44 (s, 1H, H-8). ^{13}C NMR (DMSO-d_6): δ=54.9 and 55.0 (7′-OCH_3), 55.9 (C-6′), 56.1 (C-4′), 78.7 (C-5′), 102.1 (C-7′), 116.3 (C-3′), 119.0 (C-5), 124.2 (C-2′), 139.0 (C-8), 148.6 (C-4), 153.1 (C-2), 155.9 (C-6). Analysis calcd for $C_{13}H_{17}N_5O_4$ (307.1): C, 50.79; H, 5.58; N, 22.80. Found: C, 50.42; H, 5.60; N, 22.41. **22**: UV (MeOH): λ_{max}=207, 261 nm. MS (FAB): m/z=308 (M+1). ^{1}H NMR (DMSO-d_6): δ=3.33 (s, 6H, 1′-OCH_3), 3.53 (m, 2H, H-6′), 3.78 (s, 1H, H-2′), 3.89 (s, 1H, H-5′), 4.04 (d, J=3.2 Hz, 1H, H-1′), 4.32 (dd, 1H, H-3′), 4.41 (dd, 1H, H-4′), 7.35 (br.s, 2H, 6-NH_2), 8.10 (s, 1H, H-2), 8.20 (s, 1H, H-8). Analysis calcd for $C_{13}H_{17}N_5O_4$ (307.1): C, 50.79; H, 5.58; N, 22.80. Found: C, 50.93; H, 5.69; N, 22.52.

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