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A concise synthesis of 4,6-dideoxy-4-base-6-amino-2,5-anhydro-L-mannitols

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Abstract—3,6-Di-*O*-methanesulfonyl-2,5-anhydro-L-idofuranose dimethyl acetal **9** was reacted with NaN_3 in DMF to give 6-azido substituted carbohydrate **10** selectively. A series of 6-amino-isonucleosides **4a–d** were synthesized by the reaction of nucleobases with epoxide **13**, followed by hydrolysis, reduction, and deprotection, in good yield.

1. Introduction

Nucleoside and nucleotide analogues play an important role in antiviral and anticancer chemotherapy.[1] Isonucleosides, which are a kind of nucleoside analogues where the nucleobase is linked at C-2′ or C-3′ of ribose, have attracted much attention owing not only to their chemical and enzymatic stability but also to their biological activities.[2] Among these isonucleosides, D- and L-isonucleosides have exhibited some activity against a broad spectrum of viruses and tumor cell lines[3] and some isonucleoside monophosphates showed very good activities against HIV-1.[4]

Antisense oligonucleotides (ASODNs) and small interfering RNAs (siRNAs) are both widely anticipated to become the next generation of mRNA-targeting drugs.[5] However, ASODN and siRNA-based therapy are obstructed by their intrinsic qualities, such as poor intracellular uptake, limited blood stability, and non-specific immune stimulation. Many efforts have been made to solve such problems.[6] We have reported a series of isonucleoside incorporated oligonucleotides, which showed better stability against degradation by nucleases.[7] The isonucleoside modification is also superior to other chemical modifications, since such modified oligonucleotides are good substrates for RNase H,[8] and isonucleoside triphosphates can be recognized by many different DNA polymerases.[9] We have reported the synthesis of amino-isonucleosides **4** (B = adenine, thymine; Fig. 1), and incorporated them into different positions of siRNA duplexes in the sense or antisense strands. Structural and functional analyses of such kinds of siRNAs indicated that sense strand modifications with amino-isonucleoside had less effect on the RNA duplex thermal and serum stabilities, and their functional activities were also comparable to their native siRNAs. In contrast, antisense strand modifications at the corresponding positions brought a striking negative effect on RNA duplex stability.[10]

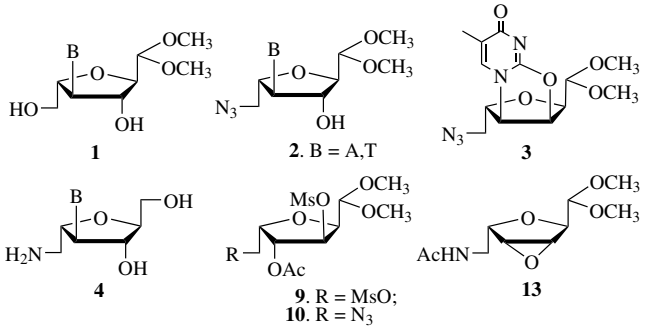

Figure 1.

In the previous reports, amino-isonucleosides **4** (B = adenine, thymine) were synthesized from azide-isonucleosides **2**, which could be obtained by a Misunobu reaction from

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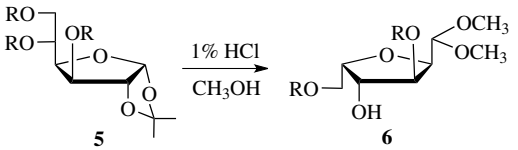
isonucleoside **1** with NaN_3. However, tricyclic isonucleosides, for example **3**, were unavoidable byproducts during the Misunobu reaction (Fig. 1) and isonucleoside **1** was obtained by the reaction of a nucleobase with an epoxide intermediate.[10,11] In this paper, we report a new method, in which the amino group was induced into the molecule first by selective 6-azido substitution of 3,6-di-*O*-methanesulfonyl-4-*O*-acetyl-2,5-anhydro-L-idofuranose dimethyl acetal **9**, and then the key intermediate compound **13** was reacted with nucleobases to afford the desired compounds **4** (Fig. 1).

2. Results and discussion

It is known that toluenesulfonyl protected D-glucose **5a** was treated with 1% HCl in methanol for 7 days to give 2,5-anhydro-L-idofuranose **6a** in 87.2% yield.[12] After optimization of the reaction condition, it was found that the reaction could be accelerated by using methanesulfonyl D-glucose **5b** instead of **5a**.[13] We found that compound **5b** was refluxed in 1% HCl/MeOH for 40 h to afford **6b** in 91.4% yield (Scheme 1). This indicated clearly that the smaller methanesulfonyl protected D-glucose is a better substance for this structural transformation.

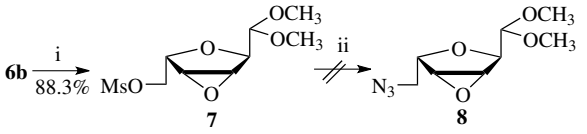


a. R = Ts, 87.2%; b. R = Ms, 91.4%

Scheme 1.

Starting from compound **6b**, several approaches were investigated for the synthesis of the key intermediate **13**. Compound **6b** could be converted into **7** by treatment with K_2CO_3 in methanol, but the substitution of the 6-methanesulfonyloxy group in **7** by NaN_3 in DMF to form **8** failed (Scheme 2).

It was reported that 1,2-*O*-isopropylidene-α-D-xylofuranose-3,5-di-*O*-tosylate reacted with 1.5 equiv of sodium azide in DMF at 120 °C for 2 h to give 5-azido sugar derivatives selectively in good yield (98%), while reaction with

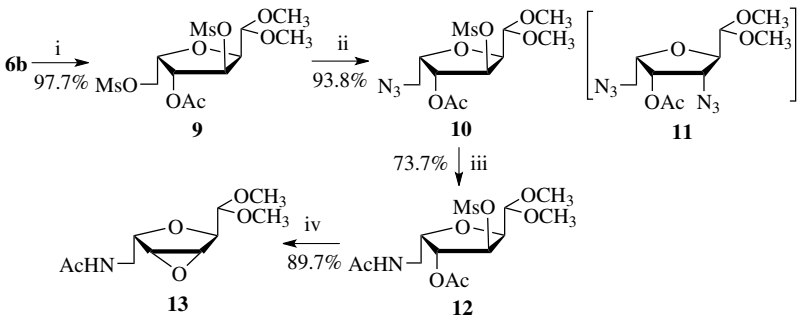


Scheme 2. Reagents and conditions: (i) K_2CO_3/MeOH, rt; (ii) NaN_3/DMF.

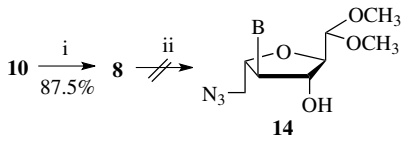
lithium azide in HMPT at 140 °C for 1 h afforded the 3,5-di-azido sugar derivative.[14] Compound **6b** was acetylated to give compound **9**. Compound **9** was treated with sodium azide in anhydrous DMF at 70 °C to yield 3-*O*-methanesulfonyl-4-*O*-acetyl-6-deoxy-6-azido-2,5-anhydro-L-idofuranose dimethyl-acetal **10** selectively in 93.8% yield (Scheme 3). The diazido substituted derivative, 3,6-dideoxy-3,6-di-azido-4-*O*-acetyl-2,5-anhydro-L-idofuranose dimethylacetal **11**, was not found in this reaction, even at 100 °C or by increasing the ratio of sodium azide. Computer simulation of the structures of **9**, **10**, and **11** was investigated with the semi-empirical quantum chemical method; it seemed that the reaction was endothermic and the 4-*O*-acetyl group might hinder the attack of N_3 to C-3 and could not result in the leaving of 3-methanesulfonyloxy group. Therefore, compound **10** was reduced by catalytic hydrogenation (H_2/Pd/C) in anhydrous ethanol followed by acetylation (Ac_2O/pridine) to give compound **12**. Compound **13** was obtained by treating **12** with K_2CO_3/MeOH (Scheme 3).

Epoxide **8** can be obtained from **10** by the general procedure, but the azido group at the 6-position made the epoxide ring opening reaction more difficult. Compound **14** cannot be obtained by the reaction of **8** with a nucleobase in the presence of K_2CO_3 and 18-crown-6 in DMF at 100 °C (Scheme 4).

The isonucleoside formation by the epoxide ring opening reaction by the nucleobase itself could be carried out with a different epoxide compound, that is, compound **13** reacted with adenine in anhydrous DMF in the presence of potassium carbonate and 18-crown-6 at 100 °C to give **15a** in 61.7% yield. HMBC NMR of **15a** gave a strong coupling effect of H-4 of the sugar ring with H-8 on the adenine, which indicated the formation of the linkage between N-9 of adenine and C-4 of the sugar ring. NOESY



Scheme 3. Synthesis of key intermediate **13**. Reagents and conditions: (i) Ac_2O, Py; (ii) NaN_3, DMF, 70 °C; (iii) (a) H_2, Pd/C, EtOH; (b) Ac_2O, Py; (iv) K_2CO_3, CH_3OH.



Scheme 4. Reagents and conditions: (i) K_2CO_3, CH_3OH; (ii) Nucleobase, K_2CO_3, 18-crown-6, DMF, 100 °C.

NMR of **15a** gave a strong coupling effect of H-8 on adenine with H-3 and H-5 of the sugar ring to confirm the structure of **15a**. Compound **13** reacted with a pyrimidine base under the same conditions but affording the products in lower yields. In the case of cytosine, a mixture of **15b-N** (43.3%) and **15b-O** (37.7%) was obtained. After separation, isomers **15b-N** and **15b-O** were characterized by HMBC NMR and **15b-N** also showed different UV absorptions ($\lambda_{max} = 272$ nm) from **15b-O** ($\lambda_{max} = 275$ nm). However, 5-fluorocytosine made the epoxide ring opening reaction more regioselective, **15c** was obtained in 59.1% yield. Thymine opened the epoxide ring of compound **13** under the conditions as described for **15a** and **15b**, but in very low yields. Isonucleoside **15d** (B = thymine) was obtained by the reaction of thymine and compound **13** by heating in a microwave reactor (180 °C) for 30 min. Compounds **15a–d** were reacted with 1% HCl, followed by reduction with sodium borohydride to give **16a–d**. After deacetylation, the desired compounds **4a–d** were provided in good yields (Scheme 5).

3. Conclusion

Compared to toluenesulfonyl protected D-glucose **5a**, methanesulfonyl D-glucofuranose **5b** was much easier to convert into 2,5-anhydro-L-idofuranose **6b**, and 3,6-dimethanesulfonyl compound **9** can be substituted selectively by NaN_3 to obtain the 6-azido compound **10** in high yield. The key intermediate epoxide **13** was reacted with a series of nucleobases (A, C, 5-FC, and T) at different conditions to give isonucleosides **15a–d**. In the cases of **15a**, **15c**, and **15d**, the epoxide ring opening reaction is regioselective. After reduction and deprotection, 6-amino-isonucleosides **4(a–d)** were afforded in good yields.

4. Experimental

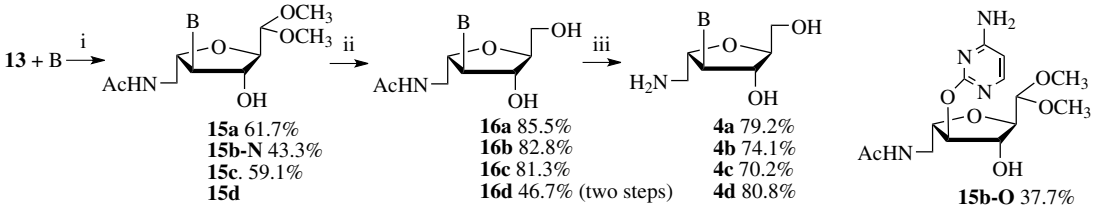
Unless specified otherwise, all starting materials and reagents were obtained from commercial suppliers without further purification. All anhydrous reactions were conducted in oven-dried glassware, under an argon atmosphere with anhydrous DMF, which was dried by CaH_2 and distilled before use. Thin layer 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). Optical rotations were recorded on a Perkin–Elmer 243B polarimeter. ^{1}H NMR (300 or 500 MHz) and ^{13}C NMR (75 or 125.7 MHz) spectra were recorded on Varian VXR-300, Varian Inova VXR-500, or Avance 500 Bruker spectrometer. When necessary, 2D NMR experiments were performed to assist in structure elucidation. Infrared spectra were recorded on a NEXUS-470 FTIR (Nicolet) spectrometer and only the more representative frequencies were reported (cm^{-1}). Mass spectra (ESI-TOF$^+$ MS) and high-resolution mass spectra (ESI-TOF$^+$ HRMS) were obtained on a MDS SCLEX QSTAR instrument and only the most representative peaks were reported (m/z).

4.1. 1,2-*O*-Isopropylidene-3,5,6-tri-*O*-methanesulfonyl-α-D-glucofuranose 5b

Compound **5b** (white powder) was obtained from 1,2-*O*-isopropylidene-α-D-glucofuranose in 97.4% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33 (s, 3H, $-CH_3$), 1.51 (s, 3H, $-CH_3$), 3.09 (s, 3H, $-SO_2CH_3$), 3.20 (s, 6H, $-SO_2CH_3$), 4.45 (dd, $J = 4.5$, 12.0 Hz, 1H, H-6a), 4.50 (dd, $J = 2.5$, 9.0 Hz, 1H, H-4), 4.70 (dd, $J = 2.5$, 12.0 Hz, 1H, H-6b), 4.99 (d, $J = 3.5$ Hz, 1H, H-2), 5.08 (m, 1H, H-5), 5.12 (d, $J = 3$ Hz, 1H, H-3), 5.97 (d, $J = 3.5$ Hz, 1H, H-1).

4.2. 3,6-Di-*O*-methanesulfonyl-2,5-anhydro-L-idofuranose dimethylacetal 6b

Compound **5b** (1.0 g, 2.20 mmol) was dissolved in methanol (100 ml). After hydrochloric acid (37%) (1.2 ml) was added, the solution was refluxed for 48 h. After cooling, neutralization with $NaHCO_3$ and evaporation, the residue was extracted with CH_2Cl_2. The extract was purified by silica gel chromatography; **6b** (0.76 g, colorless syrup) was obtained in 91.4% yield. $[\alpha]_D^{25} = +10.1$ (c 0.156, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.08 (s, 6H, $-SO_2CH_3$), 3.40 (s, 3H, $-OCH_3$), 3.45 (s, 3H, $-OCH_3$), 4.38 (m, 2H, H-2, H-5), 4.50 (m, 3H, H-4, H-6), 4.64 (m, 1H, H-3), 4.95 (dd, $J = 1.5$, 3.5 Hz, 1H, H-1). ^{13}C NMR



a. B = Adenine; b. B = Cytosine; c. B = 5-Fluorocytosine; d. B = Thymine

Scheme 5. Synthesis of amino-isonucleosides **4a–d**. Reagents and conditions: (i) B (A, C, 5-FC)/K_2CO_3/18-crown-6/DMF/100 °C or 180 °C in microwave reactor for B = T; (ii) (a) H^+/H_2O; (b) $NaBH_4$; (iii) 1.2 N HCl, reflux.

(125 MHz, $CDCl_3$): δ 37.6 (–SO_2CH_3), 38.1 (–SO_2CH_3), 53.6 (–OCH_3), 54.1 (–OCH_3), 66.2 (C-6), 74.9 (C-4), 77.9 (C-5), 78.2 (C-2), 84.5 (C-3), 101.2 (C-1). MS (ESI-TOF$^+$): calcd for $C_{10}H_{20}O_{10}S_2$ 373, found $m/z = 382$ (M^++NH_4), 387 (M^++Na). Elemental Anal. Calcd for $C_{10}H_{20}O_{10}S_2 \cdot 0.5H_2O$: C, 32.07; H, 5.6. Found: C, 31.54; H, 5.16.

4.3. 6-*O*-Methylsulfonyl-2,5:3,4-dianhydro-L-talose dimethyl acetal 7

Compound **6b** (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 by silica gel chromatography eluting with cyclohexane and ethyl acetate to give **7** (light yellow syrup in 88.3% yield). $[\alpha]_D^{25} = +14.4$ (*c* 0.190, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.06 (s, 3H, –SO_2CH_3), 3.46 (s, 3H, –OCH_3), 3.48 (s, 3H, –OCH_3), 3.81 (d, $J = 3.0$ Hz, 1H, H-4), 3.87 (d, $J = 3.0$ Hz, 1H, H-3), 4.14 (d, $J = 4.0$ Hz, 1H, H-2), 4.32 (m, 4H, H-1, H-5, H-6a, H-6b). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 37.4$ (–SO_2CH_3), 55.9 (–OCH_3), 56.2 (C-4), 56.8 (–OCH_3), 57.0 (C-3), 67.8 (C-6), 75.5 (C-5), 78.6 (C-2), 105.0 (C-1). MS (ESI-TOF$^+$): calcd for $C_9H_{16}O_7S$ 268, found $m/z = 286$ (M^++NH_4), 291 (M^++Na). Elemental Anal. Calcd for $C_9H_{16}O_7S$ (268.3): C, 40.29; H, 6.02. Found: C, 40.29; H, 5.74.

4.4. 6-Deoxy-6-azido-2,5:3,4-dianhydro-L-talose dimethylacetal 8

3-*O*-Methanesulfonyl-4-*O*-acetyl-6-deoxy-6-azido-2,5-anhydro-L-idofuranose dimethylacetal **10** (0.30 g, 0.85 mmol) was dissolved in methanol (8 ml), and potassium carbonate (0.31 g, 2.2 mmol) was added. The mixture was stirred at room temperature for 2.5 h. After filtration, neutralization, and evaporation, the residue was extracted with CH_2Cl_2. The extract was purified on silica gel chromatography. Compound **8** (colorless syrup) was obtained (0.16 g, 87.5%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.41–3.50 (m, 8 H, –OCH_3, H-6), 3.76 (dd, $J = 1.0$, 3.0 Hz, 1H, H-2), 3.85 (d, $J = 3.0$ Hz, 1H, H-5), 4.15–4.18 (m, 2H, H-1, H-3), 4.33 (d, $J = 4.0$ Hz, 1H, H-4). MS (ESI-TOF$^+$) calcd for $C_8H_{13}N_3O_4$, 215, found: $m/z = 233$ (M^++NH_4), 238 (M^++Na). IR: 2103 (–N_3).

4.5. 3,6-Di-*O*-methanesulfonyl-4-*O*-acetyl-2,5-anhydro-L-idofuranose dimethylacetal 9

Compound **6b** (4.0 g, 10.6 mmol) was dissolved in anhydrous pyridine (120 ml), under an ice bath and Ac_2O (3.0 ml, 31.7 mmol) was added dropwise. The solution was stirred for 17 h at room temperature. Volatile materials were evaporated, EtOAc/H_2O was added, the layers were separated, and the organic phase was washed (saturated $NaHCO_3$ and brine) and dried (Na_2SO_4). After evaporation, the residue was chromatographed to give **9** in 97.7% yield. $[\alpha]_D^{25} = +0.7$ (*c* 0.003, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.14 (s, 3H, –$COCH_3$), 3.06 (s, 3H, –SO_2CH_3), 3.16 (s, 3H, –SO_2CH_3), 3.44 (s, 3H, –OCH_3), 3.46 (s, 3H, –OCH_3), 4.26 (dd, $J = 3.5$, 7.5 Hz, 1H, H-2), 4.35 (s, 1H, H-6a), 4.37 (s, 1H, H-6b), 4.54 (d, $J = 7.5$ Hz, 1H, H-1), 4.61–4.64 (m, 1H, H-5), 5.04 (dd, $J = 1.5$, 3.5 Hz, 1H, H-3), 5.47 (dd, $J = 1.5$, 4.5 Hz, 1H, H-4). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.6 (–$COCH_3$), 37.8 (–SO_2CH_3), 38.5 (–SO_2CH_3), 53.8 (–OCH_3), 55.2 (–OCH_3), 65.7 (C-6), 75.6 (C-4), 77.3 (C-5), 78.8 (C-2), 82.2 (C-3), 101.5 (C-1), 169.4 (–$COCH_3$). MS (ESI-TOF$^+$): calcd for $C_{12}H_{22}O_{11}S_2$ 406, found $m/z = 424$ (M^++NH_4), 429 (M^++Na). Elemental Anal. Calcd for $C_{12}H_{22}O_{11}S_2$ (406.1): C, 35.46; H, 5.46. Found: C, 35.50; H, 5.56.

4.6. 3-*O*-Methanesulfonyl-4-*O*-acetyl-6-deoxy-6-azido-2,5-anhydro-L-idofuranose dimethylacetal 10

A mixture of **9** (2.7 g, 6.42 mmol) and sodium azide (3.3 g, 51.4 mmol) was suspended in anhydrous DMF (80 ml). The reaction was heated at 70 °C for 64 h. The mixture was filtered, and evaporated under reduced pressure. The residue was purified by silica gel chromatography, **10** (2.12 g, colorless syrup) was obtained in 93.8% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.14 (s, 3H, –$COCH_3$), 3.16 (s, 3H, –SO_2CH_3), 3.44 (m, 4H, –OCH_3, H-6a), 3.48 (m, 4H, –OCH_3, H-6b), 4.26 (dd, $J = 4.0$, 7.5 Hz, 1H, H-2), 4.46–4.48 (m, 1H, H-5), 4.53 (d, $J = 7.5$ Hz, 1H, H-1), 5.05 (dd, $J = 1.5$, 4.0 Hz, 1H, H-3), 5.40 (dd, $J = 1.5$, 4.0 Hz, 1H, H-4). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.6 (–$COCH_3$), 38.4 (–SO_2CH_3), 49.4 (C-6), 53.8 (–OCH_3), 55.1 (–OCH_3), 76.1 (C-4), 78.1 (C-5), 78.7 (C-2), 82.4 (C-3), 101.5 (C-1), 169.4 (–$COCH_3$). MS (ESI-TOF$^+$): calcd for $C_{11}H_{19}N_3O_8S$ 353, found $m/z = 371$ (M^++NH_4), 376 (M^++Na). Elemental Anal. Calcd for $C_{11}H_{19}N_3O_8S$(353.1): C, 37.39; H, 5.42; N, 11.89. Found: C, 37.74; H, 5.47; N, 12.01. IR: 2104 (–N_3).

4.7. 3-*O*-Methanesulfonyl-4-*O*-acetyl-6-deoxy-6-acetylamino-2,5-anhydro-L-idofuranose dimethylacetal 12

Azide **10** (0.73 g, 2.06 mmol) was dissolved in anhydrous ethanol (30 ml), Pd/C (73 mg, 10% w/w) was added and the mixture was evacuated with H_2 (4 kg/cm^2) several times. The suspension was stirred under an atmosphere of hydrogen for 7 h. After filtration, the volatile materials were evaporated. The residue was dissolved in anhydrous pyridine (20 ml), and Ac_2O (0.3 ml, 3.1 mmol) was added dropwise under an ice bath. The mixture was stirred for 18 h at room temperature. After evaporation, the residue was purified on silica gel chromatography, **12** (0.56 g, colorless syrup) was obtained in 73.7% yield. $[\alpha]_D^{25} = -5.5$ (*c* 0.004, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.99 (s, 3H, –NHAc), 2.14 (s, 3H, 4-$COCH_3$), 3.15 (s, 3H, –SO_2CH_3), 3.35–3.41 (m, 1H, H-6a), 3.44 (s, 3H, –OCH_3), 3.48 (s, 3H, –OCH_3), 3.50–3.55 (m, 1H, H-6b), 4.24 (dd, $J = 4.0$, 7.5 Hz, 1H, H-2), 4.39 (m, 1H, H-5), 4.52 (d, $J = 7.5$ Hz, 1H, H-1), 5.02 (dd, $J = 1.0$, 4.0 Hz, 1H, H-3), 5.37 (dd, $J = 1.0$, 3.5 Hz, 1H, H-4), 5.94 (t, $J = 5.0$ Hz, 1H, 6-NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.6 (–NHAc), 23.2 (4-$COCH_3$), 38.1 (C-6), 38.5 (–SO_2CH_3), 53.7 (–OCH_3), 55.1 (–OCH_3), 76.2 (C-4), 78.3 (C-5), 78.5 (C-2), 82.5 (C-3), 101.5 (C-1), 169.7 (6-NHAc), 170.1 (4-$COCH_3$). MS (ESI-TOF$^+$): calcd for $C_{13}H_{23}NO_9S$ 369, found $m/z = 370$ (M^++H), 392 (M^++Na). Elemental Anal. Calcd

for $C_{13}H_{23}NO_9S$ (369.1): C, 42.27; H, 6.28; N, 3.79. Found: C, 42.20; H, 6.16; N, 3.71.

4.8. 6-Deoxy-6-acetylamino-2,5:3,4-dianhydro-L-talose dimethylacetal 13

Compound **12** (0.56 g, 1.71 mmol) was dissolved in methanol (30 ml), and potassium carbonate (0.24 g, 1.71 mmol) was added. The mixture was stirred at room temperature for 2.5 h. After filtration, neutralization, and evaporation, the residue was extracted with CH_2Cl_2. The extract was purified by silica gel chromatography eluting with CH_2Cl_2 and methanol. Compound **13** (0.35 g, white crystal) was obtained in 89.7% yield. $[\alpha]_D^{25} = +34.6$ (c 0.005, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.99 (s, 3H, –$COCH_3$), 3.46 (m, 8H, 2-OCH_3, H-6a, H-6b), 3.70 (m, 1H, H-2), 3.73 (m, 1H, H-5), 4.13 (d, $J = 4.0$ Hz, 1H, H-1), 4.18 (dd, $J = 4.0$, 6.0 Hz, 1H, H-3), 4.30 (d, $J = 4.5$ Hz, 1H, H-4). ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.1 (–$COCH_3$), 35.2 (C-6), 50.5 (–OCH_3), 50.9 (–OCH_3), 51.3 (C-4), 51.8 (C-3), 70.6 (C-5), 73.1 (C-2), 99.6 (C-1). MS (ESI-TOF$^+$) calcd for $C_{10}H_{17}NO_5$ 231, found $m/z = 232$ (M^++H), 254 (M^++Na), 270 (M^++K). Elemental Anal. Calcd for $C_{10}H_{17}NO_5$ (231.1): C, 51.94; H, 7.41; N, 6.06. Found: C, 52.02; H, 7.40; N, 5.98.

4.9. 4,6-Dideoxy-4-(adenin-9-yl)-6-acetylamino-2,5-anhydro-L-mannofuranose dimethyl acetal 15a

A mixture of adenine (1.91 g, 14.2 mmol), potassium carbonate (2.60 g, 18.9 mmol), and 18-crown-6 (1.50 g, 5.53 mmol) was suspended in anhydrous DMF (50 ml). The solution of **13** (2.18 g, 9.43 mmol) in anhydrous DMF (20 ml) was added under argon at room temperature. After stirring for 0.5 h, the mixture was heated at 100 °C for 72 h. After filtration and evaporation, the residue was purified by silica gel chromatography eluting with CH_2Cl_2 and methanol. Compound **15a** (2.13 g, white foam) was obtained in 61.7% yield. UV (MeOH): $\lambda_{max} = 260$ ($\varepsilon = 11{,}345$). $[\alpha]_D^{25} = +4.0$ (c 0.001, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.75 (s, 3H, 6-CH_3CO), 3.20–3.40 (m, 8H, 1-OCH_3, H-6), 3.86 (t, $J = 6.0$ Hz, 1H, H-2), 4.43–4.50 (m, 2H, H-5, H-4), 4.60 (d, $J = 6.0$ Hz, 1H, H-1), 4.84 (dd, $J = 6.0$, 12.0 Hz, 1H, H-3), 5.67 (d, $J = 5.5$ Hz, 1H, 3-OH), 8.02 (t, $J = 5.5$ Hz, 1H, 6-*NH*Ac). For adenin-9-yl: 7.26 (s, 2H, 6-NH_2), 8.08 (s, 1H, H-8), 8.15 (s, 1H, H-2). ^{13}C NMR (125 MHz, DMSO-d_6): δ 22.4 (6-*CH*$_3$CO), 40.2 (C-6), 53.8 (1-CH_3O), 54.5 (1-CH_3O), 65.0 (C-4), 74.4 (C-3), 77.2 (C-5), 82.2 (C-2), 103.7 (C-1), 169.6 (6-*CO*CH_3). For adenin-9-yl: 119.3 (C-5), 140.6 (C-8), 149.3 (C-4), 152.3 (C-2), 156.1 (C-6). HRMS (ESI-TOF$^+$): calcd for $C_{15}H_{22}N_6O_5$ (M^++Na) 389.15439; found: 389.15462.

4.10. 4,6-Dideoxy-4-(cytosin-1-yl)-6-acetylamino-2,5-anhydro-L-mannofuranose dimethyl acetal 15b-N and 4,6-Dideoxy-4-(cytosin-2-*O*-yl)-6-acetylamino-2,5-anhydro-L-mannofuranose dimethyl acetal 15b-O

A mixture of cytosine (1.49 g, 13.37 mmol), potassium carbonate (2.46 g, 17.8 mmol), and 18-crown-6 (1.21 g, 4.46 mmol) was suspended in anhydrous DMF (45 ml). The solution of **13** (2.06 g, 8.91 mmol) in anhydrous DMF (15 ml) was added under argon at room temperature. After stirring for 0.5 h, the mixture was heated at 100 °C for 64 h. After filtration and evaporation, the residue was purified by silica gel chromatography eluting with CH_2Cl_2 and methanol. Compound **15b-N** (1.32 g, white foam) was obtained in 43.3% yield and **15b-O** (1.15 g, white foam) was obtained in 37.7% yield.

Compound **15b-N**, UV (MeOH): $\lambda_{max} = 272$ ($\varepsilon = 7300$). $[\alpha]_D^{25} = -11.0$ (c 0.002, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.78 (s, 3H, 6-CH_3CO), 3.07–3.12 (m, 1H, H-6a), 3.17–3.24 (m, 1H, H-6b), 3.33 (s, 6H, 1-OCH_3), 3.75 (t, $J = 5.5$ Hz, 1H, H-2), 4.10–4.14 (m, 1H, H-5), 4.24 (t, $J = 6.5$ Hz, 1H, H-4), 4.47 (d, $J = 6.5$ Hz, 1H, H-1), 4.50 (d, $J = 5.5$ Hz, 1H, H-3), 5.49 (s, 1H, 3-OH), 7.97 (t, $J = 6.0$ Hz, 1H, 6-*NH*Ac). For cytosin-1-yl: 5.71 (d, $J = 7.5$ Hz, 1H, H-5), 7.12 (br s, 2H, 4-NH_2), 7.48 (d, $J = 7.5$ Hz, 1H, H-6). ^{13}C NMR (125 MHz, DMSO-d_6): δ 22.5 (6-*CH*$_3$CO), 40.7 (C-6), 53.8 (1-OCH_3), 54.6 (1-OCH_3), 69.0 (C-4), 73.9 (C-3), 77.3 (C-5), 82.7 (C-2), 103.9 (C-1), 169.4 (6-*CO*CH_3). For cytosin-1-yl: 93.9 (C-5), 144.6 (C-6), 155.6 (C-2), 165.4 (C-4). HRMS (ESI-TOF$^+$): calcd for $C_{14}H_{22}N_4O_6$ (M^++Na) 365.14316; found: 365.14357.

Compound **15b-O**, UV (MeOH): $\lambda_{max} = 275$ ($\varepsilon = 7349$). $[\alpha]_D^{25} = -13.5$ (c 0.002, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.78 (s, 3H, N^6-*CH*$_3$CO), 3.30 (m, 8H, 1-OCH_3, H-6), 3.85 (dd, $J = 3.0$, 7.0 Hz, 1H, H-2), 3.95–3.98 (m, 1H, H-3), 4.12 (br s, 1H, H-4), 4.30 (d, $J = 7.5$ Hz, 1H, H-1), 4.87 (t, $J = 2.0$ Hz, 1H, H-5), 5.50 (d, $J = 3.5$ Hz, 1H, 3-OH), 7.94 (t, $J = 6.0$ Hz, 1H, 6-*NH*Ac). For cytosin-2-*O*-yl: 6.10 (d, $J = 6.0$ Hz, 1H, H-5), 6.92 (s, 2H, 4-NH_2), 7.85 (d, $J = 6.$ Hz, 1H, H-6). ^{13}C NMR (125 MHz, DMSO-d_6): δ 22.6 (N^6-*CH*$_3$CO), 40.8 (C-6), 53.2 (1-OCH_3), 54.2 (1-OCH_3), 76.5 (C-4), 82.0 (C-3), 83.7 (C-5), 84.5 (C-2), 103.2 (C-1), 169.3 (6-*CO*CH_3). For cytosin-2-*O*-yl: 99.8 (C-5), 156.2 (C-6), 164.0 (C-2), 165.4 (C-4). HRMS (ESI-TOF$^+$): calcd for $C_{14}H_{22}N_4O_6$ (M^++Na) 365.14316; found: 365.14350.

4.11. 4,6-Dideoxy-4-(5-fluorocytosin-1-yl)-6-acetylamino-2,5-anhydro-L-mannofuranose dimethyl acetal 15c

A mixture of 5-fluorocytosine (1.24 g, 9.60 mmol), potassium carbonate (1.77 g, 12.8 mmol), and 18-crown-6 (0.87 g, 3.20 mmol) was suspended in anhydrous DMF (40 ml). The solution of **13** (1.48 g, 6.40 mmol) in anhydrous DMF (10 ml) was added under argon at room temperature. After stirring for 0.5 h, the mixture was heated at 100 °C for 72 h. After filtration and evaporation, the residue was purified on silica gel chromatography eluting with CH_2Cl_2 and methanol. Compound **15c** (1.36 g, white foam) was obtained in 59.1% yield. UV (MeOH): $\lambda_{max} = 278$ ($\varepsilon = 7524$). $[\alpha]_D^{25} = -6.0$ (c 0.002, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.80 (s, 3H, 6-CH_3CO), 3.26–3.32 (m, 8H, H-6, 1-OCH_3), 3.87 (dd, $J = 3.0$, 7.5 Hz, 1H, H-2), 3.96–3.99 (m, 1H, H-5), 4.12 (t, $J = 3.5$ Hz, 1H, H-4), 4.30 (d, $J = 7.0$ Hz, 1H, H-1), 4.84 (t, $J = 2.0$ Hz, 1H, H-3), 5.49 (d, $J = 4.0$ Hz, 1H, 3-OH), 7.95 (s, 1H, 6-*NH*Ac). For 5-fluorocytosin-1-yl:

7.35 (s, 2H, 4-NH_2), 7.95 (s, 1H, H-6). ^{13}C NMR (125 MHz, DMSO-d_6): δ 22.5 (6-CH_3CO), 40.7 (C-6), 53.1 (1-OCH_3), 54.2 (1-OCH_3), 76.4 (C-4), 82.0 (C-3), 84.3 (C-5), 84.5 (C-2), 103.1 (C-1), 169.3 (6-$COCH_3$). For 5-fluorocytosin-1-yl: 139.7, 139.9 (C-6), 141.2, 143.2 (C-5), 155.0, 155.1 (C-2), 159.3 (C-4). HRMS (ESI-TOF$^+$): calcd for $C_{14}H_{21}FN_4O_6$ (M^++K, Na) 399.10767, 383.13374; found: 399.10669, 383.13347.

4.12. 4,6-Dideoxy-4-(thymin-1-yl)-6-acetylamino-2,5-anhydro-L-mannofuranose dimethyl acetal 15d and 4,6-dideoxy-4-(thymin-1-yl)-6-acetylamino-2,5-anhydro-L-mannitol 16d

A mixture of compound **13** (2.50 g, 10.8 mmol), thymine (2.20 g, 16.2 mmol), potassium carbonate (3.00 g, 21.6 mmol), and 18-crown-6 (1.50 g, 5.40 mmol) was suspended in anhydrous DMF (40 ml). The solution was stirred at 180 °C under microwave heating conditions for 30 min employing a focused microwave oven. After filtration and evaporation, the residue was purified by silica gel chromatography eluting with CH_2Cl_2 and methanol. The mixture of thymine and **15d** (yellow solid) was obtained. The mixture (3.86 g) was dissolved in 1% hydrochloric acid (200 ml) and heated at 70 °C for 9 h. After cooling and neutralization, sodium borohydride (900 mg) was added. The solution was stirred at room temperature for 2 h then neutralized with 2 N HCl. The mixture was purified by silica gel chromatography. Compound **16d** (1.58 g, white foam) was obtained in 46.7% yield (two steps).

Compound **16d**, UV (MeOH): $\lambda_{max} = 271.5$ ($\varepsilon = 7986$). $[\alpha]_D^{25} = -16.0$ (*c* 0.001, MeOH). ^1H NMR (500 MHz, DMSO-d_6): δ 1.78 (s, 3H, 6-CH_3CO), 3.08–3.12 (m, 1H, H-6a), 3.23–3.33 (m, 1H, H-6b), 3.50–3.54 (m, 1H, H-1a), 3.60–3.66 (m, 1H, H-1b), 3.72–3.75 (m, 1H, H-2), 4.01–4.10 (m, 1H, H-5), 4.25–4.29 (m, 1H, H-3), 4.46 (t, $J = 7.5$ Hz, 1H, H-4), 4.80 (t, $J = 6.5$ Hz, 1H, 1-OH), 5.53 (d, $J = 5.5$ Hz, 1H, 3-OH), 7.97 (t, $J = 5.5$ Hz, 1H, 6-*NH*Ac). For thymin-1-yl: 1.78 (s, 3H, 5-CH_3), 7.51 (d, $J = 1.0$ Hz, 1H, H-6), 11.30 (s, 1H, N_3-H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 22.5 (6-CH_3CO), 41.3 (C-6), 61.3 (C-1), 65.4 (C-4), 72.9 (C-3), 76.9 (C-5), 82.9 (C-2), 169.4 (6-$COCH_3$). For thymin-1-yl: 12.1 (5-CH_3), 109.3 (C-5), 138.6 (C-6), 151.0 (C-2), 163.7 (C-4). HRMS (ESI-TOF$^+$): calcd for $C_{13}H_{19}N_3O_6$ (M^++H) 314.13466; found: 314.13510.

4.13. 4,6-Dideoxy-4-(adenin-9-yl)-6-acetylamino-2,5-anhydro-L-mannitol 16a

Compound **15a** (1.49 g, 4.07 mmol) was dissolved in 1% hydrochloric acid (50 ml) and heated at 60 °C for 3 h. After cooling and neutralization, sodium borohydride (450 mg) was added. The solution was stirred at room temperature for 2 h then neutralized with 2 N HCl. The mixture was purified by silica gel chromatography. Compound **16a** (1.12 g, white foam) was obtained in 85.5% yield. UV (MeOH): $\lambda_{max} = 259.5$ ($\varepsilon = 11746$). $[\alpha]_D^{25} = +12.0$ (*c* 0.002, MeOH). ^1H NMR (500 MHz, DMSO-d_6): δ 1.73 (s, 3H, 6-CH_3CO), 3.18 (m, 2H, H-6), 3.56 (m, 1H, H-1a), 3.66 (m, 1H, H-1b), 3.81 (m, 1H, H-2), 4.40–4.43 (m, 1H, H-5), 4.52 (d, $J = 7.5$ Hz, 1H, H-3), 4.70 (dd, $J = 7.5$, 13.5 Hz, 1H, H-4), 4.84 (t, $J = 5.0$ Hz, 1H, 1-OH), 5.61 (d, $J = 5.5$ Hz, 1H, 3-OH), 8.00 (t, $J = 5.5$ Hz, 1H, 6-*NH*Ac). For adenin-9-yl: 7.24 (s, 2H, 6-NH_2), 8.09 (s, 1H, H-8), 8.13 (s, 1H, H-2). ^{13}C NMR (125 MHz, DMSO-d_6): δ 22.4 (6-CH_3CO), 40.0 (C-6), 61.5 (C-1), 64.5 (C-4), 73.3 (C-3), 76.9 (C-5), 83.3 (C-2), 169.6 (6-$COCH_3$). For adenin-9-yl: 119.3 (C-5), 140.5 (C-8), 149.4 (C-4), 152.3 (C-2), 156.1 (C-6). HRMS (ESI-TOF$^+$): calcd for $C_{13}H_{18}N_6O_4$ (M^++K) 361.10211; found: 361.10311.

4.14. 4,6-Dideoxy-4-(cytosin-1-yl)-6-acetylamino-2,5-anhydro-L-mannitol 16b

Compound **15b-N** (1.00 g, 2.92 mmol) was dissolved in 1% hydrochloric acid (25 ml) and heated at 60 °C for 5 h. After cooling and neutralization, sodium borohydride (250 mg) was added. The solution was stirred at room temperature for 1.5 h then neutralized with 2 N HCl. The mixture was purified by silica gel chromatography. Compound **16b** (0.72 g, white foam) was obtained in 82.8% yield. UV (MeOH): $\lambda_{max} = 276$ ($\varepsilon = 7186$). $[\alpha]_D^{25} = +7.0$ (*c* 0.001, MeOH). ^1H NMR (500 MHz, DMSO-d_6): δ 1.77 (s, 3H, 6-CH_3CO), 3.10 (m, 1H, H-6a), 3.24 (m, 1H, H-6b), 3.52 (m, 1H, H-1a), 3.60 (m, 1H, H-1b), 3.72 (m, 1H, H-2), 4.05 (m, 1H, H-5), 4.34 (dd, $J = 7.0$, 13.0 Hz, 1H, H-3), 4.42 (t, $J = 7.5$ Hz, 1H, H-4), 4.77 (t, $J = 5.5$ Hz,1H, 1-OH), 5.46 (d, $J = 6.0$ Hz, 1H, 3-OH), 7.95 (t, $J = 6.0$ Hz, 1H, 6-*NH*Ac). For cytosin-1-yl: 5.72 (d, $J = 7.5$ Hz, 1H, H-5), 7.10 (br s, 2H, 4-NH_2), 7.53 (d, 1H, $J = 7.5$ Hz, H-6). ^{13}C NMR (125 MHz, DMSO-d_6): δ 22.5 (6-CH_3CO), 41.3 (C-6), 61.5 (C-1), 67.5 (C-4), 73.2 (C-3), 77.5 (C-5), 83.5 (C-2), 169.4 (6-$COCH_3$). For cytosin-1-yl: 94.1 (C-5), 144.0 (C-6), 155.8 (C-2), 165.4 (C-4). MS (ESI-TOF$^+$): calcd for $C_{12}H_{18}N_4O_5$ 298, found $m/z = 299$ (M^++H), 321 (M^++Na). Elemental Anal. Calcd for $C_{12}H_{18}N_4O_5$ (298.1): C, 48.32; H, 6.08; N, 18.78. Found: C, 48.28; H, 6.27; N, 18.74.

4.15. 4,6-Dideoxy-4-(5-fluorocytosin-1-yl)-6-acetylamino-2,5-anhydro-L-mannitol 16c

Compound **15c** (37 mg, 0.10 mmol) was dissolved in 1% hydrochloric acid (3.5 ml) and heated at 60 °C for 6 h. After cooling and neutralization, sodium borohydride (8 mg) was added. The solution was stirred at room temperature for 1.5 h then neutralized with 2 N HCl. The mixture was purified by silica gel chromatography. Compound **16c** (26 mg, white foam) was obtained in 81.3% yield. UV (MeOH): $\lambda_{max} = 279$ ($\varepsilon = 6086$). $[\alpha]_D^{25} = -6.5$ (*c* 0.002, MeOH). ^1H NMR (500 MHz, DMSO-d_6): δ 1.78 (s, 3H, 6-CH_3CO), 3.27 (m, 1H, H-6a), 3.45 (m, 3H, H-6b, H-1a, H-1b), 3.80 (dd, $J = 5.5$, 10.0 Hz, 1H, H-2), 3.91 (m, 1H, H-5), 4.05 (dd, $J = 5.5$, 8.5 Hz, 1H, H-3), 4.73 (t, $J = 5.5$ Hz, 1H, H-4), 4.84 (t, $J = 3.0$ Hz, 1H, 1-OH), 5.39 (d, $J = 4.0$ Hz, 1H, 3-OH), 7.90 (t, $J = 5.5$ Hz,1H, 6-*NH*Ac). For 5-fluorocytosin-1-yl: 7.31 (s, 2H, 4-NH_2), 7.93 (d, $J = 3.0$ Hz, 1H, H-6). ^{13}C NMR (125 MHz, DMSO-d_6): δ 22.6 (6-CH_3CO), 40.9 (C-6), 61.2 (C-1), 75.9 (C-4), 81.2 (C-3), 84.7 (C-5), 84.9 (C-2), 169.2 (6-$COCH_3$); For 5-fluorocytosin-1-yl: 139.8, 139.9 (C-6), 141.2, 143.2 (C-5), 154.9, 155.0 (C-2), 159.6

(C-4). MS (ESI-TOF$^+$): calcd for $C_{12}H_{17}FN_4O_5$ 316, found $m/z = 317$ (M^++H), 339 (M^++Na). Anal. Calcd for $C_{12}H_{17}FN_4O_5$ (316.1): C, 45.57; H, 5.42; N, 17.71. Found: C, 45.39; H, 5.57; N, 17.49.

4.16. 4,6-Dideoxy-4-(adenin-9-yl)-6-amino-2,5-anhydro-L-mannitol 4a

Compound **16a** (28 mg, 0.087 mmol) was dissolved in 1.2 N hydrochloric acid (350 ml of H_2O and 40 ml of concentrated HCl, 7 ml) and heated at reflux for 10 h. After cooling and neutralization, the mixture was evaporated and dissolved in anhydrous ethanol. After filtration and evaporation, the residue was purified by silica gel chromatography. Compound **4a** (19 mg, white foam) was obtained in 79.2% yield.

UV (MeOH): $\lambda_{max} = 260$ ($\varepsilon = 13{,}125$). $[\alpha]_D^{25} = -11.0$ (c 0.001, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.53–2.57 (m, 1H, H-6a), 2.66–2.70 (m, 1H, H-6b), 3.42 (br s, 1H, 1-OH), 3.54–3.58 (m, 1H, H-1a), 3.64–3.67 (m, 1H, H-1b), 3.78–3.81 (m, 1H, H-2), 4.21–4.25 (m, 1H, H-5), 4.67 (t, $J = 8.0$ Hz, 1H, H-3), 4.73 (t, $J = 8.0$ Hz, 1H, H-4), 4.72 (br s, 2H, 6-NH_2), 5.46 (br s, 1H, 3-OH). For adenin-9-yl: 7.23 (s, 2H, 6-NH_2), 8.13 (s, 1H, H-8), 8.24 (s, 1H, H-2). ^{13}C NMR (125 MHz, DMSO-d_6): δ 43.5 (C-6), 61.7 (C-1), 63.1 (C-4), 73.7 (C-3), 80.0 (C-5), 83.4 (C-2); For adenin-9-yl: 119.2 (C-5), 140.1 (C-8), 149.6 (C-4), 152.4 (C-2), 156.1 (C-6). HRMS (ESI-TOF$^+$): calcd for $C_{11}H_{16}N_6O_3$ (M^++H) 281.13567; found: 281.13555.

4.17. 4,6-Dideoxy-4-(cytosin-1-yl)-6-amino-2,5-anhydro-L-mannitol 4b

Compound **16b** (32 mg, 0.107 mmol) was dissolved in 1.2 N hydrochloric acid (350 ml of H_2O and 40 ml of concentrated HCl, 8 ml) and heated at reflux overnight. After cooling and neutralization, the mixture was evaporated and dissolved in anhydrous ethanol. After filtration and evaporation, the residue was purified by silica gel chromatography. Compound **4b** (20 mg, white foam) was obtained in 74.1% yield. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.50–2.55 (m, 1H, H-6a), 2.56–2.65 (m, 1H, H-6b), 3.43 (br s, 1H, 1-OH), 3.48–3.52 (m, 1H, H-1a), 3.58–3.61 (m, 1H, H-1b), 3.69–3.72 (m, 1H, H-2), 3.77–3.81 (m, 1H, H-5), 4.27 (t, $J = 7.5$ Hz, 1H, H-3), 4.71 (t, $J = 7.5$ Hz, 1H, H-4), 4.76 (br s, 2H, 6-NH_2), 5.45 (br s, 1H, 3-OH). For cytosin-1-yl: 5.72 (d, $J = 7.5$ Hz, 1H, H-5), 7.04 and 7.10 (s, 2H, 4-NH_2), 7.63 (d, $J = 7.5$ Hz, 1H, H-6). ^{13}C NMR (125 MHz, DMSO-d_6): δ 43.8 (C-6), 61.6 (C-1), 64.7 (C-4), 73.4 (C-3), 80.9 (C-5), 83.4 (C-2); For cytosin-1-yl: 94.2 (C-5), 143.1 (C-6), 156.1 (C-2), 165.2 (C-4). HRMS (ESI-TOF$^+$): calcd for $C_{10}H_{16}N_4O_4$ (M^++H) 257.12443; found: 257.12455.

4.18. 4,6-Dideoxy-4-(5-fluorocytosin-1-yl)-6-amino-2,5-anhydro-L-mannitol 4c

Compound **16c** (120 mg, 0.380 mmol) was dissolved in 1.2 M hydrochloric acid (350 ml of H_2O and 40 ml of concentrated HCl, 25 ml) and heated at reflux for 24 h. After cooling and neutralization, the mixture was evaporated and dissolved in anhydrous ethanol. After filtration and evaporation, the residue was purified by silica gel chromatography. Compound **4c** (73 mg, white foam) was obtained in 70.2% yield. UV (MeOH): $\lambda_{max} = 278$ ($\varepsilon = 6990$). $[\alpha]_D^{25} = -15.0$ (c 0.001, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.71–2.75 (m, 1H, H-6a), 2.79–2.83 (m, 1H, H-6b), 3.37 (br s, 1H, 1-OH), 3.41–3.44 (m, 1H, H-1a), 3.46–3.50 (m, 1H, H-1b), 3.79–3.82 (m, 1H, H-2), 3.82–3.85 (m, 1H, H-5), 4.02 (t, $J = 2.5$ Hz, 1H, H-3), 4.71 (br s, 2H, 6-NH_2), 4.93 (t, $J = 2.5$ Hz, 1H, H-4), 5.42 (br s, <1H, 3-OH). For 5-fluorocytosin-1-yl: 7.32 (s, 2H, 4-NH_2), 7.93 (d, $J = 3.5$ Hz, 1H, H-6). ^{13}C NMR (125 MHz, DMSO-d_6): δ 43.1 (C-6), 61.4 (C-1), 75.6 (C-4), 84.2 (C-3), 84.5 (C-5), 85.8 (C-2). For 5-fluorocytosin-1-yl: 139.7, 139.8 (C-6), 141.2, 143.2 (C-5), 154.9, 155.0 (C-2), 159.6 (C-4). HRMS (ESI-TOF$^+$): calcd for $C_{10}H_{15}FN_4O_4$ (M^++H), 275.11501; found: 275.11552.

4.19. 4,6-Dideoxy-4-(thymin-1-yl)-6-amino-2,5-anhydro-L-mannitol 4d

Compound **16d** (31 mg, 0.099 mmol) was dissolved in 1.2 N hydrochloric acid (350 ml of H_2O and 40 ml of concentrated HCl, 6 ml) and heated under reflux for 12 h. After cooling and neutralization, the mixture was evaporated and dissolved in anhydrous ethanol. After filtration and evaporation, the residue was purified by silica gel chromatography. Compound **4d** (21 mg, white foam) was obtained in 80.8% yield. UV (MeOH): $\lambda_{max} = 270.5$ ($\varepsilon = 7950$). $[\alpha]_D^{25} = -10.0$ (c 0.001, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.58–2.61 (m, 1H, H-6a), 2.64–2.68 (m, 1H, H-6b), 3.36 (br s, 1H, 1-OH), 3.50–3.53 (m, 1H, H-1a), 3.60–3.63 (m, 1H, H-1b), 3.70–3.73 (m, 1H, H-2), 3.83–3.86 (m, 1H, H-5), 4.25 (t, $J = 8.0$ Hz, 1H, H-3), 4.65 (t, $J = 8.0$ Hz, 1H, H-4), 4.78 (br s, 2H, 6-NH_2), 5.42 (br s, <1H, 3-OH). For thymin-1-yl: 1.79 (s, 3H, 5-CH_3), 7.59 (s, 1H, H-6). ^{13}C NMR (125 MHz, DMSO-d_6): δ 43.8 (C-6), 61.6 (C-1), 63.7 (C-4), 72.9 (C-3), 79.7 (C-5), 82.9 (C-2). For thymin-1-yl: 12.0 (5-CH_3), 109.5 (C-5), 138.1 (C-6), 151.3 (C-2), 163.7 (C-4). HRMS (ESI-TOF$^+$): calcd for $C_{11}H_{17}N_3O_5$ (M^++H) 272.12410; found: 272.12408.

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