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Synthesis of 3-deoxy-3-nucleobase-2,5-anhydro-D-mannitol: a novel class of hydroxymethyl-branched isonucleosides

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Abstract

A concise synthesis of 3-deoxy-3-nucleobase-2,5-anhydro-D-mannitol **6**(**a**–**d**) has been achieved, using the deamination of 2-amino-2-deoxy-D-glucose to construct in one step the sugar skeleton with the desired sense of chirality at each asymmetric center. The selective dibenzoylation of 2,5-anhydro-D-mannitol **9** was investigated, and the key epoxide intermediate **13** was obtained in good yield via an intramolecular Mitsunobu reaction. The process of opening of epoxide **13** by nucleobases appeared to be regioselective.

1. Introduction

Nucleoside analogues play an important role in antiviral and anticancer chemotherapy. Among numerous nucleoside analogues,[1] hydroxymethyl-branched nucleosides such as naturally occurring Oxetanocin-A **1a**[2] and its analogues **1b** and **2**,[3] have received much attention owing to their profound biological activities. It was reported that the two primary hydroxyl groups in these hydroxymethyl-branched nucleosides could improve their interaction with corresponding kinase and polymerase.[4] Isonucleosides represent another class of nucleoside analogues in which the nucleobase is linked at various positions of ribose other than C-1′, and have attracted great interest because of their enhanced chemical and enzymatic stability.[5–7] Both D- and L-stereomeric isonucleosides, such as (*S*,*S*)-*iso*-ddA **3**[6] and its enantiomer **4**,[7] have exhibited some activities against a broad spectrum of virus and some tumor cell lines (Scheme 1).

In our search for antiviral and anticancer agents, we have synthesized hydroxymethyl-branched L-isonucleosides **5** starting from D-glucose.[8] In further studies on the structure–activity relationship of these types of nucleoside analogues, we aimed to synthesize their enantiomers, 3-deoxy-3-nucleobase-2,5-anhydro-D-mannitol **6** (Scheme 2).

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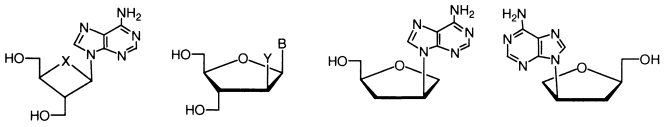
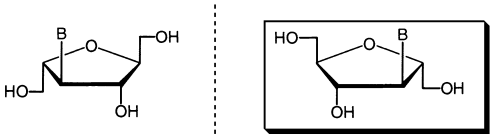


1 **2** **3** **4**

1a: X=O, **1b**: X=S **2a**: Y=H, **2b**: Y=OH (S,S)-iso-ddA

Scheme 1.

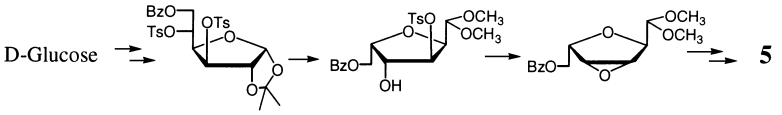


5 **6**

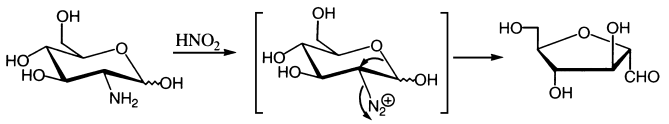
Scheme 2.

2. Results and discussion

In our previous work[8] compounds **5** were obtained from D-glucose via nine steps with a ring reformation process leading to construction of the sugar skeleton with the configuration related to L-mannitol (Scheme 3). Similarly, the title compounds **6** might be prepared from L-glucose. Due to the high expense of L-glucose, however, it was desirable to seek a practical and convenient synthetic method for the preparation of **6**. It was reported that the deamination of 2-amino-2-deoxy-D-glucose **7** with nitrous acid led to 2,5-anhydro-D-mannose **8** (Scheme 4).[9] Compound **8** could be used to construct the whole desired sugar skeleton and all of four stereogenic centers in **6**.



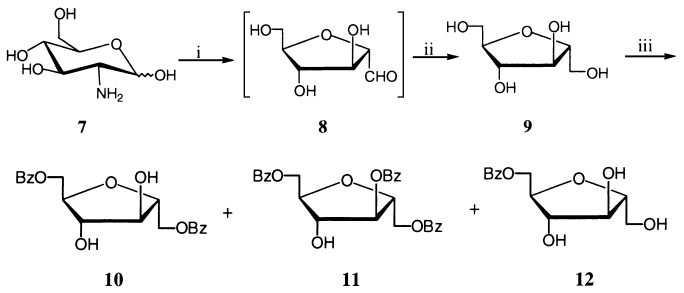
Scheme 3.



7 **8**

Scheme 4.

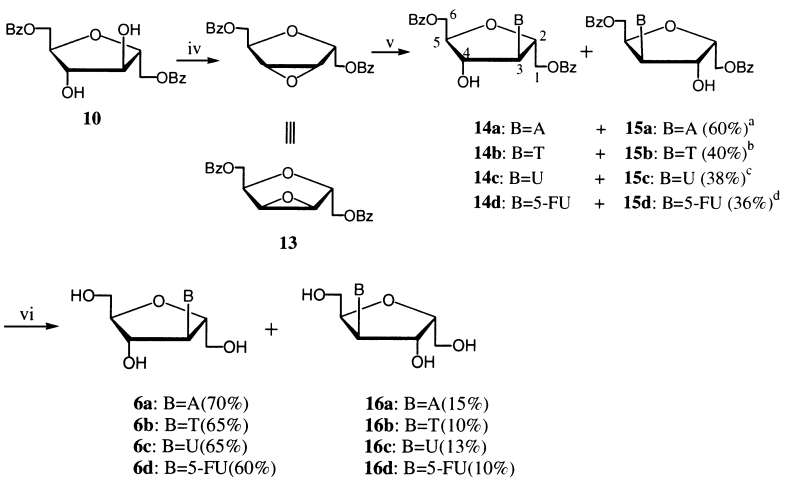
The nitrous acid deamination of **7** was carried out in aqueous solution at 0°C, followed by reduction with sodium borohydride to give 2,5-anhydro-D-mannitol **9** (Scheme 5). Compound **9** is highly water-soluble and extremely difficult to extract from water and isolate from salts. Its synthesis reported in literature involved time-consuming work-ups in both steps.[10] In our case, a simplified one-pot procedure was developed to afford crude **9**, which was directly applied to the next step.



Scheme 5. Reagents and conditions: (i) $NaNO_2$, concentrated HCl, H_2O, 0°C; (ii) $NaBH_4$, H_2O; (iii) BzCl, pyridine, CH_2Cl_2 (1:2 v/v)

The selective protection of the two primary hydroxyls in **9** was accomplished by the treatment of crude **9** with benzoyl chloride under an optimized reaction condition. The desired dibenzoate **10** was obtained in an overall yield of 37% of three steps starting from **7**. Two other side-products, tribenzoate **11** and monobenzoate **12**, were also isolated from the reaction mixture in 5% and 1% yields, respectively (Scheme 5).

Compound **10** is a C_2-symmetric molecule in which the two secondary hydroxyl groups are identical. Therefore, under the intramolecular Mitsunobu reaction condition[11] compound **10** was converted to epoxide **13** in 90% yield, irrespective of which of the hydroxyl groups attacked the phosphonium cation (Scheme 6).

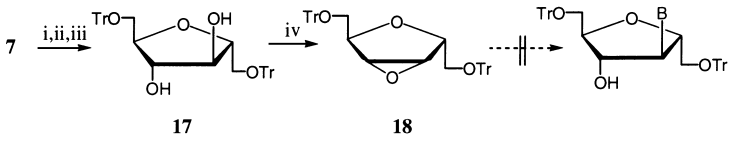


Scheme 6. Reagents and conditions: (iv) PPh_3, diethyl azodicarboxylate, 1,4-dioxane, 70°C, 90%; (v) nucleobases, DBU, DMF, 90–100°C; (vi) $NaOCH_3$, CH_3OH. [a]Total yield of **14a** and **15a** (4.0:1 estimated from ^1H NMR spectrum); [b]total yield of **14b** and **15b** (4.5:1 estimated); [c]total yield of **14c** and **15c** (4.6:1 estimated); [d]total yield of **14d** and **15d** (4.2:1 estimated)

The regioselective opening of epoxide **13** by nucleobases was achieved in reasonable yields in the presence of DBU. ^1H NMR spectra of the partially purified products showed that the desired and predominant compounds **14** (**a**–**d**) were accompanied by a mixture with their C-4 regio-

isomers **15** (**a**–**d**). Further separation of the two isomers failed because of their similar chromatographic mobility. However, after the treatment of the mixture with sodium methoxide in methanol (deprotection), the title molecules **6** (**a**–**d**) and their C-4 regioisomers **16** (**a**–**d**) were obtained after column chromatography (Scheme 6). The structures of **6** (**a**–**d**) and **16** (**a**–**d**) were identified by ^{1}H NMR and NOESY spectra.

It is worthy to mention that triphenylmethyl chloride was also evaluated as a reagent for selective protection of the primary hydroxyls in **9**. Bis-tritylated derivative **17** was obtained in a higher overall yield of 45% in three steps from **7**, and compound **17** was easily converted to epoxide **18**. However, the nucleophilic epoxide ring opening in **18** by nucleobases failed, most probably owing to the steric hindrance of trityl groups (Scheme 7). This observation suggested that benzoyl group was a desirable choice in presented strategy due to its reasonable selectivity and low steric hindrance.



17 **18**

Scheme 7. Reagents and conditions: (i) $NaNO_2$, concentrated HCl, H_2O, 0°C; (ii) $NaBH_4$, H_2O; (iii) TrCl, pyridine; (iv) PPh_3, diethyl azodicarboxylate, 1,4-dioxane, 70°C, 80%

3. Conclusion

In this work we reported on a six-step facile synthesis of a novel class of hydroxymethyl-branched D-isonucleosides **6**. The C_2-symmetric molecule **10** was constructed from 2-amino-2-deoxy-D-glucose **7** via deamination. This synthetic strategy offers a simple way for the preparation of branched-chain sugar isonucleosides of desired sense of chirality at each asymmetric centre.

4. Experimental

4.1. General procedures

Melting points were determined on a XT-4A melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 243B polarimeter and UV spectra were recorded on a Varian DMS200 UV–visible spectrophotometer. Mass spectra were obtained on either ZAB-HS or KYKY-ZHP-5 mass spectrometer. HRMS were recorded on APEX II (Bruker, Inc.) FTICR mass spectrometer. NMR spectra were recorded on a Varian-300 or JEOL AL300 spectrometer with TMS as internal standard. Exchangable protons were detected by addition of D_2O. Elemental analyses were performed using PE-240C analyzer. Column chromatography was performed on silica gel (200–300 mesh) purchased from the Qingdao Chemical Company, China. Thin layer chromatography was performed using DC-Alufolien 60 F254 (Alltech Associate, Inc.) plate with detection by UV, or charting with 5% ethanolic solution of phosphomolybdic acid hydrate.

4.2. 1,6-Di-O-benzoyl-2,5-anhydro-D-mannitol **10**, 1,3,6-tri-O-benzoyl-2,5-anhydro-D-mannitol **11** and 1-O-benzoyl-2,5-anhydro-D-mannitol **12**

A solution of 2-amino-2-deoxy-D-glucose hydrochloride (technical grade, 32.4 g, 0.15 mol) in water (300 ml) was cooled to 0°C. Sodium nitrite (30.75 g, 0.45 mol) was added in several portions at 0°C. Concentrated hydrochloric acid (25.5 ml, 0.3 mol) was then added dropwise at a rate that the temperature did not exceed 2°C. The solution was stirred for an additional 5 h at 0°C, and then was brought to 25°C. Nitrogen was bubbled through the reaction mixture for 30 min to remove an excess of nitrous acid, and then it was neutralized to PH 7 with 10N NaOH.

The solution was cooled to 0°C, sodium borohydride (5.70 g, 0.15 mol) was added in small portions, and stirring was continued at ambient temperature for 24 h. The solution was neutralized with 6N HCl and the aqueous solution was concentrated under reduced pressure. The remaining semisolid material was twice treated with methanol which was then removed by evaporation. The residue was then extracted with methanol. The extracts were stirred with ion-exchange resins (Cation 732# and Anion 717#). After removal of methanol, the residue was dried under high vaccum to give crude **9** (15 g) as a yellow syrup.

A suspension of crude **9** (15 g) in dry pyridine (150 ml) and dry dichloromethane (250 ml) was cooled to –10°C, and benzoyl chloride (9.8 ml, 0.92 equiv.) was added dropwise with rigorous stirring. The solution was kept below 0°C for 2 h, then cooled again to –10°C, and another portion of benzoyl chloride (9.8 ml, 0.92 equiv.) was added dropwise. The reaction mixture was kept at 0°C for 4 h and at ambient temperature for an additional 24 h. After removal of the solvents, the residue was stirred with ice-cooled saturated $NaHCO_3$ solution (240 ml) for 30 min, and extracted with ethyl acetate (3×90 ml). The combined organic layer was washed with brine, 2N HCl, brine, and dried over Na_2SO_4. After the solution was concentrated, the residue was applied to silica gel chromatography (ethyl acetate–petroleum ether) to afford **10** (20.7 g, 37% from **7**, white solid), **11** (3.57 g, 5% from **7**, white solid), and **12** (0.4 g, 1% from **7**, colorless syrup), respectively.

Compound **10**: m.p. 88–92°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 4.03 (m, 4H, H-1, H-6), 4.38–4.45 (m, 4H), 5.53 (br s, 2H, 3-OH, 4-OH), 7.53 (m, 4H), 7.67 (m, 2H), 7.98 (m, 4H). FAB-MS m/z: 373 [M+H]$^+$. Anal. calcd. for $C_{20}H_{20}O_7$: C, 64.52; H, 5.38. Found: C, 64.09; H, 5.48.

Compound **11**: m.p. 80–84°C. $[\alpha]_D^{15}$ +54.0 (c 0.100, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 4.30–4.58 (m, 7H), 5.36 (m, 1H, H-3), 5.95 (d, J = 3.6 Hz, D_2O exchangeable, 1H, 4-OH), 7.51 (m, 6H), 7.66 (m, 3H), 7.98 (m, 6H). FAB-MS m/z: 477 [M+H]$^+$. Anal. calcd. for $C_{27}H_{24}O_8$: C, 68.07; H, 5.04. Found: C, 67.99; H, 5.20.

Compound **12**: $[\alpha]_D^{15}$ +42.7 (c 0.075, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.36–3.97 (m, 6H), 4.30–4.41 (m, 2H, H-1), 4.73(t, J = 5.7 Hz, 1H, D_2O exchangeable, 6-OH), 5.23 (d, J = 5.1 Hz, 1H, D_2O exchangeable, 4-OH), 5.34 (d, J = 4.8 Hz, 1H, D_2O exchangeable, 3-OH), 7.54 (t, J = 7.2 Hz, 2H), 7.67 (t, J = 6.9 Hz, 1H), 7.97 (d, J = 8.4 Hz, 2H). FAB-MS m/z: 269 [M+H]$^+$. HRMS (FAB) calcd. for $C_{13}H_{16}O_6$: [M+H]$^+$269.1020. Found: 269.1025.

4.3. 1,6-Di-O-benzoyl-2,5:3,4-dianhydro-D-talitol **13**

Compound **10** (10.5 g, 28.2 mmol) and triphenylphosphine (11.1 g, 42.3 mmol) were dissolved in dry 1,4-dioxane (250 ml). A solution of diethyl azodicarboxylate (6.66 ml, 42.3 mmol) in dry 1,4-dioxane (50 ml) was added dropwise to the solution. The reaction mixture was stirred at 70°C for 2 h. The solvent was removed in vacuo and the residue was applied to silica gel chromatography (ethyl acetate–petroleum ether) to afford **13** (8.98 g, 90%) as a white solid.

Compound **13**: m.p. 67–70°C. $[\alpha]_D^{15}$ –76.8 (*c* 0.125, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ: 3.87, 3.94 (d, d, J = 2.7 Hz, 2H, H-3, H-4), 4.23 (m, 2H, H-2, H-5), 4.54 (m, 4H, H-1, H-6), 7.46 (m, 4H), 7.57 (m, 2H), 8.04 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 56.68, 57.32, 63.21, 64.41, 75.57, 128.37, 128.55, 129.59, 129.74, 133.13, 133.37, 166.24. FAB-MS *m*/*z*: 355 $[M+H]^+$. Anal. calcd. for $C_{20}H_{18}O_6$: C, 67.80; H, 5.08. Found: C, 68.00; H, 5.14.

4.4. Procedure for **6** (**a**–**d**) and **16** (**a**–**d**)

To a stirred suspension of **13** (4 g, 11.3 mmol) and dry nucleobases (1.5 equiv.) in dry DMF (80 ml), DBU (5.1 ml, 34 mmol) was added dropwise. The clear solution was stirred at 90°C for 24 h. After removal of DMF in vacuo, the resulting brown residue was diluted with dry dichloromethane. Silica gel (40 g) was added and the mixture evaporated to dryness. The dry powder was applied to silica gel chromatography eluting with ethyl acetate–petroleum ether to recover unreacted **13**, then with dichloromethane–methanol to afford a mixture of **14** and **15**.

The mixture obtained was dissolved in 15 ml of dry methanol and sodium methoxide (1 equiv.) was added. The solution was stirred for 3 h and then neutralized to PH 7 with cation ion-exchange resin 732#. After removal of methanol, the residue was applied to silica gel chromatography (dichloromethane–methanol), to afford **6** and **16,** respectively.

4.5. 3-Deoxy-3-(adenin-9′-yl)-2,5-anhydro-D-mannitol **6a** and 4-deoxy-4-(adenin-9′-yl)-2,5-anhydro-D-iditol **16a**

The procedure was carried out as described above. A mixture of **14a** and **15a** was obtained (60%) as a foam. After debenzoylation, **6a** (70%) and **16a** (15%) were afforded, each as a white hygroscopic solid.

Compound **6a**: m.p. 140°C. $[\alpha]_D^{15}$ –9.0 (*c* 0.067, MeOH). UV λ_{max}^{MeOH} (lg ε): 260.4 (4.16). ^1H NMR (300 MHz, DMSO-d_6) δ: 3.40 (m, 1H), 3.51 (m, 1H), 3.57 (m, 1H), 3.63 (m, 1H), 3.78 (m, 1H), 4.35 (m, 1H), 4.60 (m, t after D_2O exchange, 1H, H-4), 4.73 (dd, 1H, H-3), 4.83 (m, 2H, D_2O exchangeable, 1-OH, 6-OH), 5.57 (d, J = 5.4 Hz, 1H, D_2O exchangeable, 4-OH), 7.22 (s, 2H, D_2O exchangeable, NH_2), 8.13 (s, 1H, H-2′), 8.18 (s, 1H, H-8′). CI-MS *m*/*z*: 282 $[M+H]^+$. Anal. calcd. for $C_{11}H_{15}N_5O_4$: C, 46.96; H, 5.38; N, 24.91. Found: C, 47.03; H, 5.54; N, 24.69.

Compound **16a**: m.p. 136–140°C. $[\alpha]_D^{15}$ –16.0 (*c* 0.100, MeOH). UV λ_{max}^{MeOH} (lg ε): 266.7 (4.08). ^1H NMR (300 MHz, DMSO-d_6) δ: 3.11 (m, 2H), 3.60 (m, 2H), 4.32 (m, 2H, H-2, H-5), 4.57 (m, 1H, D_2O exchangeable), 4.67 (m, 1H, D_2O exchangeable), 4.70 (m, 1H, H-3), 5.01 (m, 1H, H-4), 5.65 (d, J = 4.8 Hz, 1H, D_2O exchangeable, 3-OH), 7.25 (s, 2H, D_2O exchangeable, NH_2), 8.01 (s, 1H, H-2′), 8.13 (s, 1H, H-8′). CI-MS *m*/*z*: 282 $[M+H]^+$. HRMS (FAB) calcd. for $C_{11}H_{15}N_5O_4$: $[M+H]^{\cdot}$ 282.1197. Found: 282.1194.

4.6. 3-Deoxy-3-(thymin-1′-yl)-2,5-anhydro-D-mannitol **6b** and 4-deoxy-4-(thymin-1′-yl)-2,5-anhydro-D-iditol **16b**

The procedure was carried out as described above. A mixture of **14b** and **15b** was obtained (40%) as a foam. After debenzoylation, **6b** (65%) and **16b** (10%) were afforded, each as a white hygroscopic solid.

Compound **6b**: m.p. 100–106°C. $[\alpha]_D^{15}$ +12.2 (*c* 0.900, MeOH). UV λ_{max}^{MeOH} (lg ε): 271.7(4.08). ^1H NMR (300 MHz, DMSO-d_6) δ: 3.40 (m, 2H), 3.48 (m, 1H), 3.58 (m, 1H), 3.70 (m, 1H), 3.94 (m,

1H), 4.20 (m, dd after D_2O exchange, J = 7.8 Hz, 1H, H-4), 4.65 (t, J = 7.8 Hz, 1H, H-3), 4.77 (m, 2H, D_2O exchangeable, 1-OH, 6-OH), 5.46 (d, J = 5.1 Hz, 1H, D_2O exchangeable, 4-OH), 7.55 (s, 1H, H-6′), 11.26 (s, 1H, D_2O exchangeable, NH). FABMS *m/z*: 273 $[M+H]^+$, 295 $[M+Na]^+$. Anal. calcd. for $C_{11}H_{16}N_2O_6$: C, 48.53; H, 5.88; N, 10.29. Found: C, 48.27; H, 6.01; N, 9.93.

Compound **16b**: m.p. 134–136°C. $[\alpha]_D^{15}$ +144.8 (*c* 0.105, MeOH). UV λ_{max}^{MeOH} (lg ε): 271.0(4.03). ^1H NMR (300 MHz, DMSO-d_6) δ: 3.28 (m, 2H), 3.54 (m, 2H), 4.15 (m, 2H, H-2, 5), 4.52 (t, J = 5.7 Hz, 1H, D_2O exchangeable, 1-OH), 4.59 (m, t after D_2O exchange, J = 6 Hz, 1H, H-3), 4.75 (t, J = 5.1 Hz, 1H, D_2O exchangeable, 6-OH), 4.84 (t, J = 6 Hz, 1H, H-4), 5.47 (dd, J = 5.4 Hz, 1H, D_2O exchangeable, 3-OH), 7.34 (s, 1H, H-6′), 11.30 (s, 1H, D_2O exchangeable, NH). FAB-MS *m/z*: 273 $[M+H]^+$, 295 $[M+Na]^+$. Anal. calcd. for $C_{11}H_{16}N_2O_6$: C, 48.53; H, 5.88; N, 10.29. Found: C, 49.00; H, 6.05; N, 9.82.

4.7. 3-Deoxy-3-(uracil-1′-yl)-2,5-anhydro-D-mannitol **6c** *and 4-deoxy-4-(uracil-1′-yl)-2,5-anhydro-D-iditol* **16c**

The procedure was carried out as described above. A mixture of **14c** and **15c** was obtained (38%) as a foam. After debenzoylation, **6c** (65%) and **16c** (13%) were afforded, each as a white hygroscopic solid.

Compound **6c**: m.p. 100–104°C. $[\alpha]_D^{15}$ +14.4 (*c* 0.090, MeOH). UV λ_{max}^{MeOH} (lg ε): 267.0 (4.06). ^1H NMR (300 MHz, DMSO-d_6) δ: 3.45–3.60 (m, 4H, H-1, H-6), 3.70 (m, 1H), 3.93 (m, 1H), 4.23 (m, t after D_2O exchange, J = 7.6 Hz, 1H, H-4), 4.67 (t, J = 7.6 Hz, 1H, H-3), 4.76–4.80 (broad, 2H, D_2O exchangeable, 1-OH, 6-OH), 5.50 (d, J = 4.8 Hz, 1H, D_2O exchangeable, 4-OH), 5.62 (d, J = 7.6 Hz, 1H, H-5′), 7.66 (d, J = 7.6 Hz, 1H, H-6′), 11.27 (s, 1H, D_2O exchangeable, NH). CI-MS *m/z*: 259 $[M+H]^+$. Anal. calcd. for $C_{10}H_{14}N_2O_6$: C, 46.51; H, 5.43; N, 10.85. Found: C, 46.11; H, 5.56; N, 10.50.

Compound **16c**: m.p. 80–83°C. $[\alpha]_D^{15}$ +180.0 (*c* 0.075, MeOH). UV λ_{max}^{MeOH} (lg ε): 266.4 (4.11). ^1H NMR (300 MHz, DMSO-d_6) δ: 3.30–3.53 (m, 4H), 4.10 (m, 1H), 4.17 (m, 1H), 4.53 (broad s, 1H, D_2O exchangeable), 4.57 (m, t after D_2O exchange, 1H, H-3), 4.75 (broad s, 1H, D_2O exchangeable), 4.85 (t, J = 6 Hz, 1H, H-4), 5.50 (d, J = 5.1 Hz, 1H, D_2O exchangeable, 3-OH), 5.56 (d, J = 8.1 Hz, 1H, H-5′), 7.52 (d, J = 8.1 Hz, 1H, H-6′), 11.30 (s, 1H, D_2O exchangeable, NH). CI-MS *m/z*: 259 $[M+H]^+$. Anal. calcd. For $C_{10}H_{14}N_2O_6$: C, 46.51; H, 5.43; N, 10.85. Found: C, 46.59; H, 5.72; N, 10.52.

4.8. 3-Deoxy-3-(5′-fluorouracil-1′-yl)-2,5-anhydro-D-mannitol **6d** *and 4-deoxy-4-(5′-fluorouracil-1′-yl)-2,5-anhydro-D-iditol* **16d**

The procedure was carried out as described above. A mixture of **14d** and **15d** was obtained (36%) as a foam. After debenzoylation, **6d** (60%) and **16d** (10%) were afforded, each as a white hygroscopic solid.

Compound **6d**: m.p. 95–97°C. $[\alpha]_D^{15}$ +163.0 (*c* 0.100, MeOH). UV λ_{max}^{MeOH} (lg ε): 274.0 (4.04). ^1H NMR (300 MHz, DMSO-d_6) δ: 3.33–3.70 (m, 4H), 3.73 (m, 1H), 3.94 (m, 1H), 4.19 (m, t after D_2O exchange, 1H, H-4), 4.65 (m, t after D_2O exchange, 1H, H-3), 4.71–5.05 (m, 2H, D_2O exchangeable, 1-OH, 6-OH), 5.50 (d, J = 5.1 Hz, 1H, D_2O exchangeable, 4-OH), 8.12 (d, J = 7.2 Hz, 1H, H-6′), 11.81 (d, J = 4.8 Hz, 1H, D_2O exchangeable, NH). CI-MS *m/z*: 277 $[M+H]^+$. HRMS (FAB) calcd. for $C_{10}H_{13}N_2O_6F$: $[M+H]^+$ 277.0830. Found: 277.0824.

Compound **16d**: m.p. 104–106°C. $[\alpha]_D^{15}$ +124.0 (*c* 0.075, MeOH). UV λ_{max}^{MeOH} (lg ε): 272.7 (4.03). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.36 (m, 2H), 3.53 (m, 2H), 4.13 (m, 2H), 4.53 (m, D_2O exchangeable, 1H), 4.65 (m, t after D_2O exchange, 1H, H-3), 4.85 (overlapped, 2H, H-4, OH), 5.48 (d, J = 5.1 Hz, 1H, D_2O exchangeable, 3-OH), 7.88 (d, J = 7.8 Hz, 1H, H-6′), 11.85 (d, J = 5.1 Hz, 1H, D_2O exchangeable, NH). CI-MS *m*/*z*: 277 $[M+H]^+$. HRMS (FAB) calcd. for $C_{10}H_{13}N_2O_6F$: $[M+H]^+$ 277.0830. Found: 277.0821.

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