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Aust. J. Chem. **2007**, *60*, 291–295

Synthesis of a Novel Bicyclic Nucleoside with a 3,7-Anhydrooctofuranosyl Skeleton

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We have developed an efficient route for the synthesis of a novel bicyclic nucleoside using a key intermediate **13**, which was prepared from 1,2:5,6-di-*O*-isopropylidene-α-D-glucose. 1,2-Nucleophilic addition of aldehyde **8** with allyltrimethylsilane and intramolecular Williamson reaction were successfully achieved to synthesize an intermediate with a 3,7-anhydrooctofuranosyl skeleton.

Manuscript received: 3 January 2007.
Final version: 15 February 2007.

Introduction

Since 3′-azido-3′-deoxythymidine (AZT) was approved for the treatment of AIDS by the Food and Drug Administration (FDA),[1] several nucleoside analogues with a modified sugar moiety have been synthesized and evaluated as antiviral and/or anticancer agents.[2] In general, conventional nucleosides exist in fast equilibrium between S-type (2′-*endo*/3′-*exo*) and N-type (2′-*exo*/3′-*endo*) conformation in the solution state due to the low energy barrier between these two dominating conformers.[3] However, nucleosides adopt only one conformation at the active site when binding to the target enzyme. Therefore, several nucleoside analogues with a conformationally restricted sugar moiety have been synthesized in order to study the conformational preferences of enzymes and receptors with nucleoside or nucleotide substrates,[4,5] and for potential antiviral agents.[6–9] Among them, bicyclic nucleoside analogues fused with a methylene group **1**,[10] an oxirane **2**,[11] and an oxetane **3**[12] have been synthesized and reported to have anti-HIV activities through inhibition of HIV reverse transcriptase. Also, naturally occurring octosyl nucleosides such as octosyl acid A and nikkomycin, that have a rigid sugar skeleton, have exhibited a variety of antibiological activities[13] (Fig. 1).

In the course of our continued research on the synthesis of antiviral nucleoside analogues with a restricted sugar moiety, we present the synthesis of a novel bicyclic nucleoside **4** with a 3,7-anhydrooctofuranosyl skeleton, starting from 1,2:5,6-di-*O*-isopropylidene-α-D-glucose.

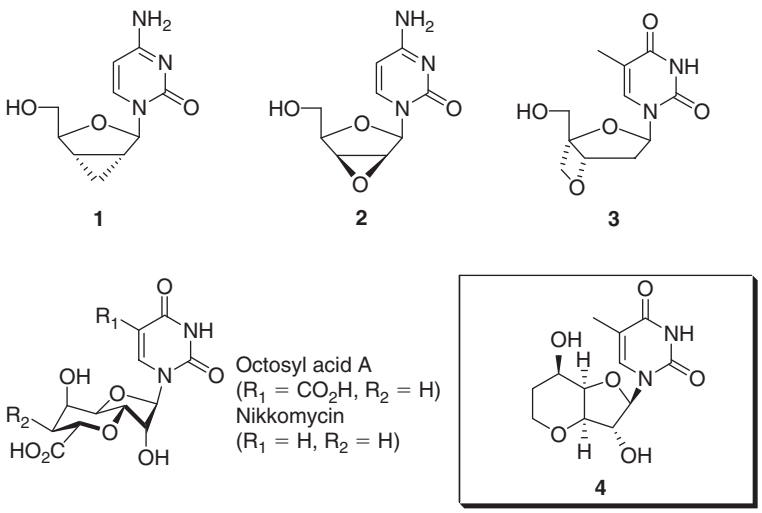


Fig. 1. The rationale for the design of the target molecules.

 10.1071/CH07002 0004-9425/07/040291

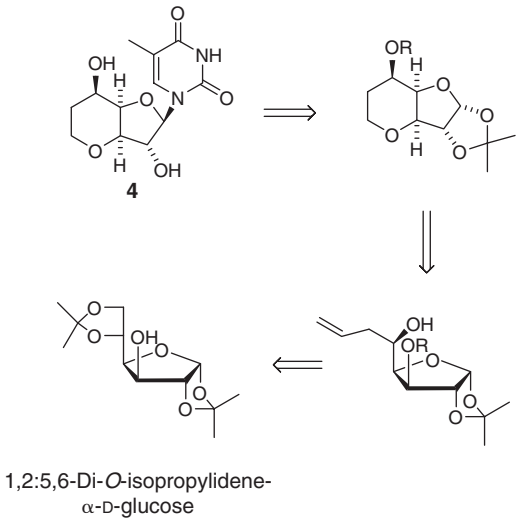
Results and Discussion

Our synthetic strategy to the target bicyclic nucleoside was to synthesize the 3,7-anhydrooctofuranosyl derivative **13** as the key intermediate, followed by a condensation reaction with nucleosidic base as illustrated in Scheme 1.

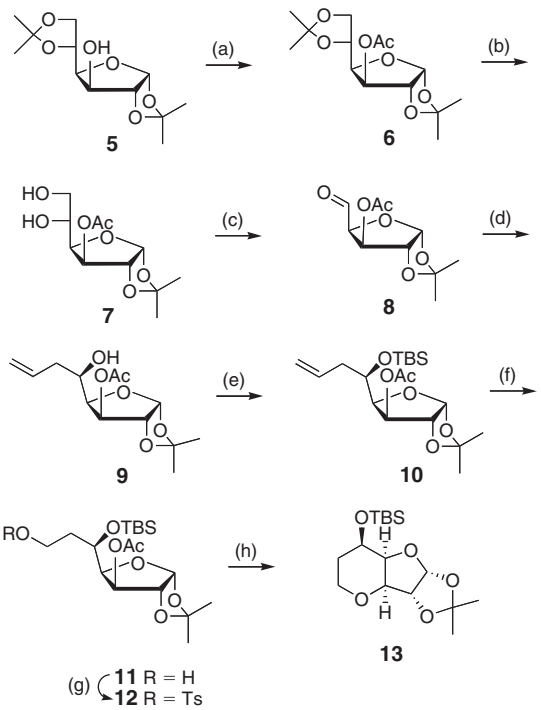
For the synthesis of the key intermediate, we tried to construct the bicyclic system using an S_N2 reaction (intramolecular Williamson reaction) as shown in Scheme 2.

1,2;5,6-Di-*O*-isopropylidene-α-D-glucose **5** was treated with acetic anhydride in pyridine to give the acetate **6**, in which the 5,6-*O*-isopropylidene group was selectively hydrolyzed with 75% acetic acid to afford the diol **7**. Oxidative cleavage of the diol **7** with sodium periodate gave the aldehyde **8**. In order to introduce an allyl group at C5, the Lewis acid-catalyzed carbonyl addition of allyltrimethylsilane was employed as a key step.

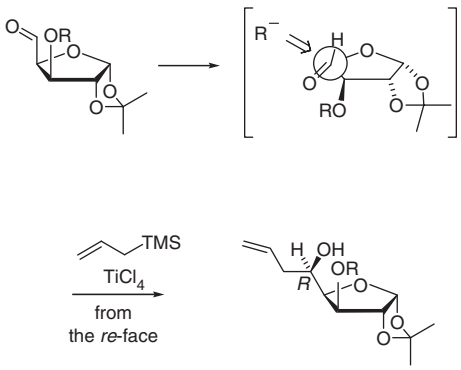
It has been reported that Lewis acids play an important role in the control of stereochemistry in that reaction.[14] When $TiCl_4$[14] or $Yb(OTf)_3$[15] was used as Lewis acid, high *anti*-diastereoselectivity was observed. On the other hand, the stereoselectivity was reversed with $SnCl_4$[14] and $BF_3{\cdot}Et_2O$[15] as catalyst. Therefore, we used allytrimethylsilane and $TiCl_4$ as Lewis acid in the allylation of aldehyde **8** in order to obtain the desired (5*R*)-configuration. 1,2-Addition of aldehyde **8** with allyltrimethylsilane in the presence of $TiCl_4$ afforded the allylated product **9** with (5*R*)-configuration, and this result can be explained in terms of non-chelated transition states as shown in Scheme 3. The hydroxyl group of **9** was protected with *tert*-butyldimethylsilyl chloride (TBDMSCl) to give the silyl ether **10**. Oxidative cleavage of the allyl group of **10** with $NaIO_4$–OsO_4 followed by reduction with $NaBH_4$ gave **11**. The primary hydroxyl group of **11** was treated with *p*-toluenesulfonyl chloride to give the tosylate **12**, which was cyclized by treatment with K_2CO_3 in MeOH via an S_N2 reaction to afford the 3,7-anhydrooctofuranoyl derivative **13** as a key intermediate. To determine the configuration at position 5, an NOE experiment



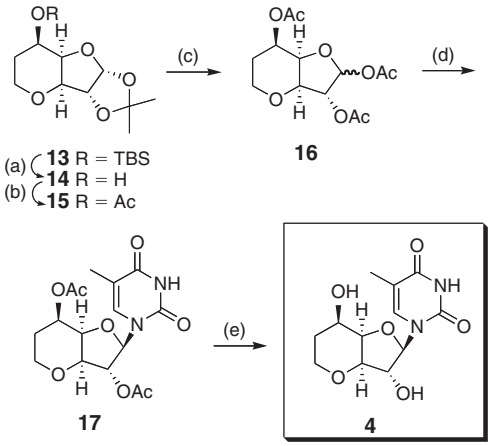
Scheme 1. Retrosynthetic analysis of the target nucleoside **4**.



Scheme 2. (a) Ac_2O, pyridine, room temp., 5 h, 90%; (b) 75% AcOH, 55°C, 1.5 h, 90%; (c) $NaIO_4/H_2O$, EtOH, 0°C, 20 min; (d) $TiCl_4$, allyltrimethylsilane, CH_2Cl_2, 0°C to room temp., 3 h, 80%; (e) TBDMSCl, imidazole, DMF, room temp., 18 h, 92%; (f) $NaIO_4$–OsO_4, THF/H_2O, room temp., 18 h; then $NaBH_4$, THF/H_2O, room temp., 1 h, 85%; (g) TsCl, DMAP, CH_2Cl_2, room temp., 18 h, 95%; (h) K_2CO_3, MeOH, room temp., 18 h, 85%.



Scheme 3. Non-chelated transition state leading to (5*R*)-configuration.



Scheme 4. (a) TBAF, THF, room temp., 3 h, 95%; (b) Ac_2O, pyridine, room temp., 18 h, 96%; (c) 85% HCO_2H, 55°C, 1.5 h; then Ac_2O, pyridine, room temp., 18 h, 90%; (d) HDMS, thymine, TMSOTf, $C_2H_4Cl_2$, room temp., 3 h, 70%; (e) NH_3 in MeOH, room temp., 16 h, 90%.

was performed with compound **13**. The configuration at C5 was confirmed as *R* by the lack of NOEs between H5 and H1/H2.

The silyl group of **13** was removed with tetrabutylammoniumfluoride (TBAF) to give the bicyclic sugar **14**, which was treated with Ac_2O to afford the acetate **15**. The 1,2-*O*-isopropylidene group of **15** was hydrolyzed with 85% formic acid, and the resulting diol was then treated with acetic anhydride in pyridine to give the glycosyl donor **16**. Vorbrüggen-type coupling of **16** with thymine gave exclusively the β-nucleoside **17** due to the anchimeric assistance of the 2′-*O*-acetyl group.[16] Treatment of **17** with methanolic ammonia afforded the desired 3,7-anhydrooctofuranosyl nucleoside **4** (Scheme 4). The antiviral activity of bicyclic nucleoside **4** was evaluated against HIV-1 in MT-4 cells. However, no significant anti-HIV activity was observed up to 100 μM, with no cytotoxicity.

Conclusions

In summary, we have efficiently synthesized the 3,7-anhydro nucleoside derivative **4** using nucleophilic 1,2-addition of allyltrimethylsilane to an aldehyde followed by intramolecular Williamson reaction. This methodology can be used for the synthesis of other bicyclic nucleosides.

Experimental

General

^{1}H NMR spectra were recorded in a 300 MHz apparatus using tetramethylsilane (TMS) as an internal standard, and the chemical shifts are reported in ppm (δ). Coupling constants are reported in Hertz. Infrared spectra were recorded with a Perkin–Elmer 1710 Fourier-transform IR spectrophotometer. FAB (fast atom bombardment) mass spectra were recorded on a VG Tro-2 GC-MS. TLC analysis was carried out on Merck silica gel 60 F_{254} precoated plates, while silica gel column chromatography was performed on Merck silica gel 60, 230–400 mesh. All anhydrous solvents were distilled over CaH_2 or Na/benzophenone before use.

3-O-Acetyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose ***6***

To a stirred solution of 1,2:5,6-di-*O*-isopropylidene-α-D-glucose (5 g, 19.21 mmol) in pyridine (50 mL) was added Ac_2O (3.62 mL, 38.42 mmol) at room temperature. After being stirred for 5 h at the same temperature, the solvent was evaporated, and the residue partitioned between EtOAc and water. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and the solvent evaporated. The residue was purified by silica gel column chromatography (3:1 hexanes/ethyl acetate) to give **6** (5.23 g, 90%). Found: C 55.4, H 7.3. $C_{14}H_{22}O_7$ requires C 55.6, H 7.3%. ν_{max}/cm^{-1} (KBr) 2927, 1735, 1464, 1373, 1240, 1154, 1070. δ_H (300 MHz, $CDCl_3$) 5.88 (d, 1H, *J* 3.6), 5.25 (d, 1H, *J* 2.2), 4.50 (d, 1H, *J* 3.7), 4.19–4.26 (m, 2H), 4.01–4.13 (m, 2H), 2.11 (s, 3H), 1.52, 1.42, 1.33, 1.31 (4s, 12H). *m/z* 325 $[M + Na]^+$.

3-O-Acetyl-1,2-O-isopropylidene-α-D-glucofuranose ***7***

Compound **6** (5.23 g, 17.31 mmol) was dissolved in 75% acetic acid (60 mL). After being stirred at 55°C for 1.5 h, the reaction mixture was cooled to room temperature, evaporated, and coevaporated with toluene. The residue was purified by silica gel column chromatography (1:4 hexanes/ethyl acetate) to give **7** (4.08 g, 90%). Found: C 50.0, H 6.9. $C_{11}H_{18}O_7$ requires C 50.4, H 6.9%. ν_{max}/cm^{-1} 3462, 2988, 1744, 1377, 1240, 1087, 1022. δ_H (300 MHz, $CDCl_3$) 5.90 (d, 1H, *J* 3.6), 5.27 (d, 1H, *J* 2.8), 4.56 (d, 1H, *J* 3.6), 4.16 (dd, 1H, *J* 2.6, 8.8), 3.91 (m, 1H), 3.63–3.75 (m, 2H), 2.15 (s, 3H), 1.52, 1.32 (2s, 6H). *m/z* 285 $[M + Na]^+$.

(5R)-3-O-Acetyl-1,2-O-isopropylidene-6,7,8-trideoxy-α-D-gluco-oct-7-enofuranose ***9***

To a stirred solution of **7** (2 g, 7.63 mmol) in EtOH (40 mL) was added a solution of $NaIO_4$ (2 g, 9.34 mmol) in H_2O (20 mL). After being stirred at 0°C, the reaction mixture was filtered through a Celite pad and the filtrate was evaporated. The residue was partitioned between EtOAc and water. The organic layer was dried over $MgSO_4$, filtered, and evaporated to give **8**.

To a stirred solution of **8** in CH_2Cl_2 (100 mL) was added 1 M $TiCl_4$ in toluene (11.4 mL) at 0°C. After 15 min, allyltrimethylsilane (1.46 mL, 9.16 mmol) was added to this solution at 0°C. The reaction mixture was stirred at room temperature for 3 h, then poured into saturated $NaHCO_3$ solution, and extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (1:2 hexanes/ethyl acetate) to give **9** (1.66 g, 80%). Found: C 57.4, H 7.4. $C_{13}H_{20}O_6$ requires C 57.3, H 7.4%. ν_{max}/cm^{-1} (KBr) 3465, 2986, 1740, 1375, 1240, 1075, 1018. δ_H (300 MHz, $CDCl_3$) 5.94 (d, 1H, *J* 3.9), 5.74 (m, 1H), 5.09–5.31 (m, 3H), 4.57 (m, 1H), 4.12–4.17 (m, 2H), 2.23–2.42 (m, 2H), 2.09 (s, 3H), 1.50, 1.31 (2s, 6H). *m/z* 295 $[M + Na]^+$.

(5R)-3-O-Acetyl-5-O-tert-butyldimethylsilyl-1,2-O-isopropylidene-6,7,8-trideoxy-α-D-gluco-oct-7-enofuranose ***10***

To a stirred solution of **9** (1.66 g, 6.1 mmol) and imidazole (1.25 g, 18.3 mmol) in DMF (20 mL) was added TBDMSCl (1.38 g, 9.15 mmol) at room temperature. The reaction mixture was stirred at the same temperature overnight and then partitioned between diethyl ether and water. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and the solvent evaporated. The residue was purified by silica gel column chromatography (3:1 hexanes/ethyl acetate) to give **10** (2.17 g, 5.62 mmol, 92%). Found: C 58.9, H 8.9. $C_{19}H_{34}O_7Si$ requires C 59.0, H 8.9%. ν_{max}/cm^{-1} (KBr) 2933, 2857, 1750, 1375, 1227, 1096, 1024, 835. δ_H (300 MHz, $CDCl_3$) 5.72–5.82 (m, 2H), 4.94–5.04 (m, 3H), 4.36 (d, 1H, *J* 3.6), 4.00 (dd, 1H, *J* 2.8, 8.0), 3.79 (m, 1H), 1.97–2.14 (m, 5H), 1.42, 1.21 (2s, 6H), 0.80 (s, 9H), 0.03, 0.00 (2s, 6H). *m/z* 409 $[M + Na]^+$.

(5R)-3-O-Acetyl-5-O-tert-butyldimethylsilyl-6-deoxy-1,2-O-isopropylidene-α-D-gluco-heptofuranose ***11***

To a stirred solution of **10** (2 g, 5.18 mmol) in THF (20 mL) and water (20 mL) were added sodium periodate (3.32 g, 15.34 mmol) and a 2.5% solution of osmium tetraoxide in *tert*-butyl alcohol (v/v, 5.27 mL). The reaction mixture was stirred at room temperature for 18 h, quenched with water (50 mL), and the mixture was extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was redissolved in a mixture of THF (20 mL) and water (20 mL), and then sodium borohydride (580 mg, 15.34 mmol) was added. The reaction mixture was stirred at room temperatue for 1 h, water (30 mL) was added, and the mixture was extracted twice with CH_2Cl_2. The

combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (2:1 hexanes/ethyl acetate) to give **11** (1.72 g, 85%). Found: C 55.1, H 8.9. $C_{18}H_{34}O_7Si$ requires C 55.4, H 8.8%. ν_{max}/cm^{-1} (KBr) 3500, 2933, 1747, 1375, 1247, 1164, 1097, 1023, 838. δ_H (300 MHz, $CDCl_3$) 5.75 (d, 1H, *J* 3.8), 4.98 (d, 1H, *J* 3.0), 4.29 (d, 1H, *J* 3.8), 4.02–4.11 (m, 2H), 3.62–3.68 (m, 2H), 1.94 (s, 3H), 1.40–1.61 (m, 2H), 1.33, 1.15 (2s, 6H), 0.75 (s, 9H), 0.03–0.03 (2s, 6H). *m/z* 391 $[M + H]^+$.

*(5*R*)-3-*O*-Acetyl-5-*O*-tert-butyldimethylsilyl-6-deoxy-1,2-*O*-isopropylidene-7-*O*-p-toluenesulfonyl-α-D-gluco-heptofuranose **12***

To a stirred solution of **11** (1.72 g, 4.41 mmol) in CH_2Cl_2 (30 mL) were added DMAP (1.08 g, 8.82 mmol) and TsCl (1.26 g, 6.62 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 h, and then partitioned between CH_2Cl_2 and water. The organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (3:1 hexanes/ethyl acetate) to give **12** (2.28 g, 95%). Found: C 55.0, H 7.5, S 5.8. $C_{25}H_{40}O_9SSi$ requires C 55.1, H 7.4, S 5.9%. ν_{max}/cm^{-1} (KBr) 2933, 1748, 1369, 1230, 1177, 1101, 1023, 837. δ_H (300 MHz, $CDCl_3$) 7.73 (d, 2H, *J* 8.1), 7.30 (d, 2H, *J* 7.8), 5.87 (d, 1H, *J* 3.8), 5.08 (d, 1H, *J* 2.8), 4.41 (d, 1H, *J* 3.9), 3.93–4.16 (m, 4H), 2.42 (s, 3H), 2.08 (s, 3H), 1.56–1.79 (m, 2H), 1.46, 1.27 (2s, 6H), 0.78 (s, 9H), 0.09, 0.00 (2s, 6H). *m/z* 545 $[M + H]^+$.

*(5*R*)-3,7-Anhydro-5-*O*-tert-butyldimethylsilyl-6-deoxy-1,2-*O*-isopropylidene-D-*glycero*-α-D-gluco-heptofuranose **13***

Compound **12** (1.5 g, 2.76 mmol) was dissolved in MeOH (30 mL), and K_2CO_3 (1.14 g, 8.27 mmol) was added. The reaction mixture was stirred at room temperature for 18 h and then evaporated. The residue was partitioned between CH_2Cl_2 and water. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (4:1 hexanes/ethyl acetate) to give **13** (775 mg, 85%). Found: C 58.1, H 9.2. $C_{16}H_{30}O_5Si$ for C 58.2, H 9.2%. ν_{max}/cm^{-1} (KBr) 2931, 1376, 1251, 1091, 1020, 838, 778. δ_H (300 MHz, $CDCl_3$) 5.83 (d, 1H, *J* 3.7), 4.35 (d, 1H, *J* 3.7), 4.07 (d, 1H, *J* 2.8), 4.00 (d, 1H, *J* 1.7), 3.68–3.81 (m, 2H), 3.51 (dd, 1H, *J* 3.3, 11.0), 1.86 (m, 1H), 1.43 (s, 3H), 1.28 (m, 1H), 1.25 (s, 3H), 0.83 (s, 9H), 0.01, 0.00 (2s, 6H). *m/z* 331 $[M + H]^+$.

*(5*R*)-3,7-Anhydro-6-deoxy-1,2-*O*-isopropylidene-D-*glycero*-α-D-gluco-heptofuranose **14***

To a stirred solution of **13** (775 mg, 2.35 mmol) in THF (15 mL) was added a 1 M solution of TBAF in THF (2.82 mL). The reaction mixture was stirred at room temperature for 3 h and the solvent then evaporated. The residue was purified by silica gel column chromatography (1:1 hexanes/ethyl acetate) to give **14** (483 mg, 95%). Found: C 55.8, H 7.5. $C_{10}H_{16}O_5$ requires C 55.6, H 7.5%. ν_{max}/cm^{-1} (KBr) 3466, 2928, 1378, 1215, 1164, 1088, 1016. δ_H (300 MHz, $CDCl_3$) 5.90 (d, 1H, *J* 3.7), 4.45 (d, 1H, *J* 3.6), 4.24 (m, 1H), 4.12 (d, 1H, *J* 1.7), 3.98 (m, 1H), 3.73 (m, 1H), 3.62 (m, 1H), 2.01 (m, 1H), 1.54 (m, 1H), 1.50, 1.32 (2s, 6H). *m/z* 217 $[M + H]^+$.

*(5*R*)-5-*O*-Acetyl-3,7-anhydro-6-deoxy-1,2-O-isopropylidene-D-*glycero*-α-D-gluco-heptofuranose **15***

To a stirred solution of **14** (480 mg, 2.22 mmol) in pyridine (15 mL) was added Ac_2O (0.25 mL, 2.66 mmol). The reaction mixture was stirred at room temperature for 18 h and the solvent then evaporated. The residue was partitioned between EtOAc and water. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (2:1 hexanes/ethyl acetate) to give **15** (550 mg, 96%). Found: C 56.1, H 7.0. $C_{12}H_{18}O_6$ requires C 55.8, H 7.0%. ν_{max}/cm^{-1} (KBr) 2981, 1744, 1375, 1240, 1091, 1019, 904. δ_H (300 MHz, $CDCl_3$) 5.90 (d, 1H, *J* 3.7), 5.22 (d, 1H, *J* 2.6), 4.46 (d, 1H, *J* 3.6), 4.06 (s, 1H), 3.97 (s, 1H), 3.59–3.73 (m, 2H), 2.11 (s, 3H), 2.00 (m, 1H), 1.63 (m, 1H), 1.50, 1.32 (2s, 6H). *m/z* 259 $[M + H]^+$.

*(5*R*)-1,2,5-Tri-*O*-acetyl-3,7-anhydro-6-deoxy-D-*glycero*-(α/β)-D-gluco-heptofuranose **16***

Compound **15** (530 mg, 2.05 mmol) was dissolved in 85% HCO_2H (15 mL), and the mixture was stirred at 55°C for 1.5 h. After being cooled to room temperature, the reaction mixture was evaporated and coevaporated with benzene. The residue was dissolved in pyridine (15 mL), and Ac_2O (2.52 mL, 26.7 mmol) was added. The reaction mixture was stirred at room temperature for 18 h and the solvent then evaporated. The residue was partitioned between EtOAc and water. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (2:1 hexanes/ethyl acetate) to give **16** (557 mg, 90%). ν_{max}/cm^{-1} (KBr) 2988, 1750, 1375, 1222, 1164, 1076, 1024, 847. δ_H (300 MHz, $CDCl_3$) 6.06 (d, 1H, *J* 9.7), 5.13–5.34 (m, 2H), 4.00–4.22 (m, 2H), 3.63–3.80 (m, 2H), 2.06–2.18 (m, 10H), 1.63 (m, 1H). *m/z* 243 $[M + H]^+$.

*(5′*R*)-1-(2′,5′-Di-*O*-acetyl-3′,7′-anhydro-6′-deoxy-D-*glycero*-β-D-gluco-heptofuranosyl)thymine **17***

A mixture of thymine (459 mg, 3.64 mmol) and ammonium sulfate (50 mg) in anhydrous HMDS (15 mL) was refluxed under a nitrogen atmosphere for 16 h and then concentrated under anhydrous conditions. The residue was dissolved in anhydrous dichloroethane (15 mL), and a solution of **16** (550 mg, 1.82 mmol) in anhydrous dichloroethane (10 mL) was added to this solution, followed by TMSOTf (0.66 mL, 3.64 mmol) at 0°C. After being stirred at room temperature for 3 h, the reaction mixture was quenched by the addition of saturated $NaHCO_3$ solution, and filtered through a Celite pad. The filtrate was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (1:2 hexanes/ethyl acetate) to give **17** (469 mg, 70%). Found: C 52.0, H 5.5, N 7.5. $C_{16}H_{20}N_2O_8$ requires C 52.2, H 5.5, N 7.6%. ν_{max}/cm^{-1} (KBr) 2935, 1741, 1372, 1236, 1157, 1083, 1024. δ_H (300 MHz, $CDCl_3$) 8.39 (s, 1H), 7.55 (d, 1H, *J* 1.3), 6.12 (d, 1H, *J* 2.0), 5.27 (m, 1H), 5.17 (m, 1H), 4.04–4.18 (m, 2H), 3.64–3.79 (m, 2H), 2.14 (s, 3H), 2.10 (s, 3H), 2.02 (m, 1H), 1.95 (d, 3H, *J* 1.1), 1.72 (m, 1H). *m/z* 391 $[M + Na]^+$, 369 $[M + H]^+$.

*(5′*R*)-1-(3′,7′-Anhydro-6′-deoxy-*D*-*glycero*-β-*D*-gluco-heptofuranosyl)thymine* ***4***

A solution of **17** (460 mg, 1.25 mmol) in saturated methanolic ammonia (30 mL) was stirred at room temperature for 16 h and then concentrated. The residue was purified by silica gel column chromatography (7:1 CH_2Cl_2/MeOH) to give **4** (320 mg, 90%). Found: C 50.5, H 5.7, N 9.7. $C_{12}H_{16}N_2O_6$ requires C 50.7, H 5.7, N 9.9%. ν_{max}/cm^{-1} (KBr) 3362, 2928, 1696, 1471, 1263, 1075. δ_H (300 MHz, $CDCl_3$) 11.36 (s, 1H), 7.59 (s, 1H), 5.84 (d, 1H, *J* 4.4), 5.75 (d, 1H, *J* 2.7), 5.22 (d, 1H, *J* 3.5), 3.96 (m, 1H), 3.89 (m, 1H), 3.83 (d, 1H, *J* 2.0), 3.78 (m, 1H), 3.66 (m, 2H), 1.84 (m, 1H), 1.76 (s, 3H), 1.43 (m, 1H). *m*/*z* 307 $[M + Na]^+$, 285 $[M + H]^+$.

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