Design and Synthesis of 5''-Iodoneplanocin A and Its Analogues as Potential *S*-Adenosylhomocysteine Hydrolase Inhibitor†

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5''-Iodoneplanocin A (**1**) and its analogues **2** and **3** were designed and synthesized as potential SAHH inhibitor via iodocyclopentenol **6**, which was prepared using a Michael addition-iodination-elimination process. All final compounds did not show antiviral activity, maybe due to a steric hindrance induced by 5''-iodo substituent.

Key Words : 5''-Iodoneplanocin A, *S*-Adenosylhomocysteine hydrolase, Steric hindrance, Michael addition-iodination-elimination, Michael addition-elimination reaction

Introduction

Neplanocin A[1] (Figure 1), a naturally occurring carbocyclic nucleoside has been found to exhibit potent antitumor and antiviral activities by inhibiting polymerases and/or *S*-adenosylhomocysteine hydrolase (SAHH), which catalyzes hydrolysis of *S*-adenosylhomocysteine (SAH) to adenosine and homocysteine.[2] It is well known that the hydrolysis is the only catabolic pathway of SAH in eukaryotes.[3] Inhibition of SAHH causes an accumulation of SAH in cells, which in turn induces an inhibition of methyltransferases by a negative feedback inhibition mechanism.[2] Methyltransferases are related to formation of 5'-cap structure, which is responsible for the stability of *m*-RNA against phosphatases and ribonucleases, and a normal splicing. Therefore, the inhibition of SAHH might show potent antiviral and antitumor activities by interfering with formation of 5'-cap structure of viral and cellular *m*-RNA.[4]

Recently, fluoroneplanocin A,[5] synthesized by Jeong and coworkers has been reported to exhibit better and irreversible SAHH inhibition and more potent antitumor activity than neplanocin A. According to their results, after conversion of 3'-hydroxy group to a keto group by NAD^+ the fluorine atom acts as a leaving group during a Michael addition-elimination reaction induced by a nucleophile present in SAHH, as shown in Scheme 1. Generally, an iodide is much better leaving group than a fluoride. Therefore, it was of great interest to synthesize 5''-iodoneplanocin A (**1**), an isostere of fluoroneplanocin A, and its analogs, **2** and **3** having different purine nucleobases and to evaluate their antiviral activity and cytotoxicity.

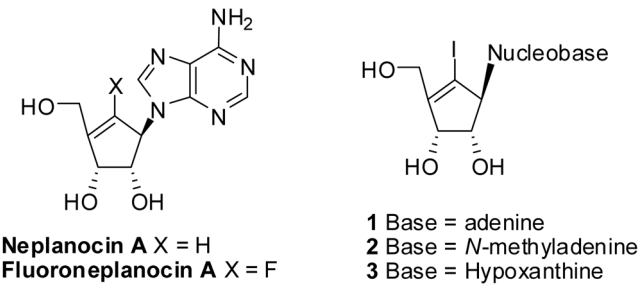
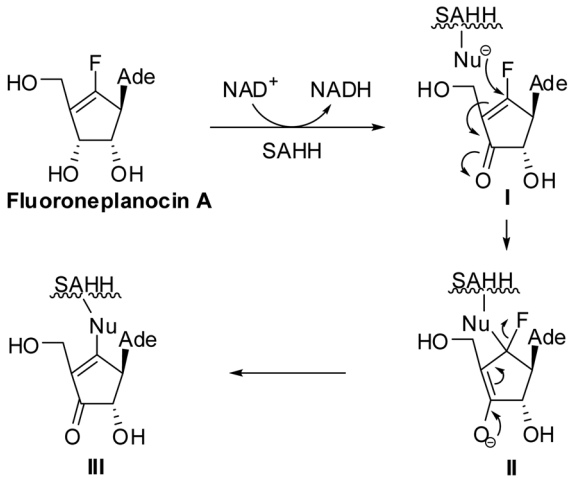


Figure 1. Neplanocin A, fluoroneplanocin A and targeted compounds, **1-3**.

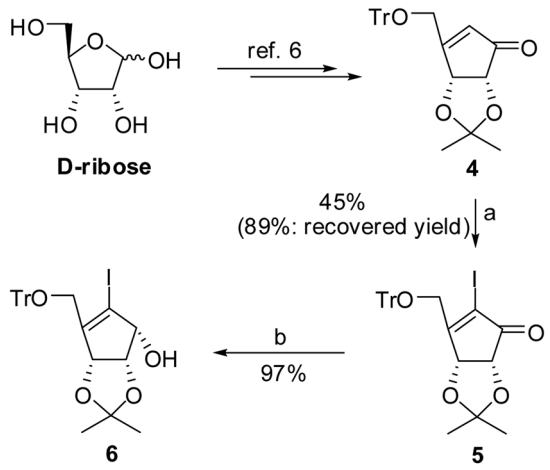
†Dedicated to Prof. Moon Woo Chun on the occasion of his 65th birthday and for his many contributions to the field of nucleoside chemistry

Results and Discussion

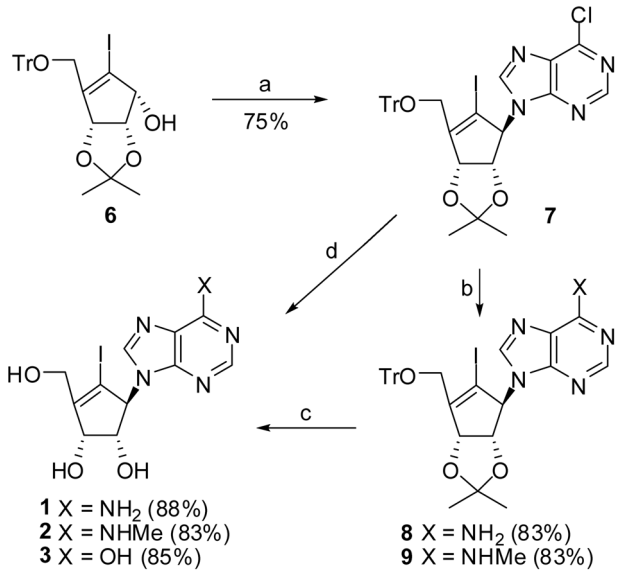
As shown in Scheme 2, D-ribose was used as starting material for the synthesis of glycosyl donor **6**. It was envisioned that cyclopentenone **4**[6] would be an appropriate intermediate for the synthesis of the glycosyl donor **6**. Compound **4** was prepared in the same manner as our previous report,[6] including a stereoselective Grignard reaction, ring closing metathesis (RCM)[7] and an oxidative rearrangement[8] of *tert*-allylic alcohol by PDC. Iodination[9] at α-position of



Scheme 1. A plausible inhibitory mechanism of SAHH by fluoroneplanocin A *via* a Michael addition-elimination process (SAHH: *S*-adenosylhomocysteine hydrolase, Ade: adenine).



Scheme 2. (a) I_2, pyridine, CCl_4, rt, 12 h; (b) $NaBH_4$, $CeCl_3$-$7H_2O$, MeOH, 0 °C, 30 min.



Scheme 3. (a) 6-chloropurine, PPh_3, DEAD, THF, rt, 12 h; (b) NH_3/MeOH, 80 °C, 7 h for **8**; 40% CH_3NH_2, MeOH, 80 °C, 5 h for **9**; (c) 2 *N* HCl, 1,4-dioxane, rt, 16 h for **1** and **2**; (d) 1 *N* HCl, 1,4-dioxane, reflux, 15 h.

α,β-unsaturated ketone **4** was achieved using I_2 and pyridine, probably *via* an addition of pyridine to β-position, iodination of the enolate generated temporarily and elimination of β-pyridinium ion by abstracting α-hydrogen. Conversion of cyclopentenone **5** to glycosyl donor, α-cyclopentenol **6** was accomplished by $NaBH_4$ in the presence of $CeCl_3$.[10] The reduction gave α-stereoisomer **6** as a sole product. The Ce(III) metal ion might assist stereo- and regioselectivity in the reduction of enone **5** by chelating the oxygen of carbonyl and the proximal oxygen of the acetonide at the more encumbered concave face.

Synthesis of purine nucleosides **1-3** is described in Scheme 3. 6-Chloropurine was coupled with glycosyl donor **6** under Mitsunobu conditions[11] using DEAD and triphenyl phosphine to give nucleoside **7**. Chloro substituent at 6-position was converted to amino and *N*-methylamino groups by treatment with methanolic ammonia and methylamine to afford adenine and *N*-methyladenine nucleosides, **8** and **9**, respectively. Finally, removal of the protecting groups, trityl and acetonide was achieved under acidic conditions (2 *N* HCl, 1,4-dioxane, rt) to give 5''-iodoneplanocin A (**1**) and its *N*-methyl analogue **2**, respectively. Hypoxanthine analog **3** was directly synthesized from 6-chloropurine nucleoside **7** by treating with 1 *N* HCl at reflux.

Antiviral activities of the synthesized purine compounds **1-3** were evaluated against HIV-1 and 2, influenza viruses (Seoul, Taiwan and Panama), EMCV, Cox. B3,[12] VSV, and HSV-1 and 2. All of them showed neither antiviral activity nor cytotoxicity up to 100 μg/mL. Considering that there have been many reports on the very close relationship between the inhibition of SAHH and antiviral activities, SAHH can not accommodate the final compounds properly at its active site, probably resulting from steric hindrance of the bulky iodo group upon the interaction with them. And also, considering no cytotoxicity, they might not be phosphorylated by kinases or their triphosphates might not be perceived by cellular polymerases, probably due to the same reason as the above. These facts provide very useful information for designing and developing SAHH inhibitors for medicinal chemists.

In conclusion, in order to find more potent antiviral and antitumor agents we have synthesized 5''-iodoneplanocin A (**1**) and its analogs **2** and **3** as potential SAHH inhibitor, on the basis that the fluorine atom in fluoroneplanocin A plays a role as a leaving group and that an iodide is much better leaving group than a fluoride. Introduction of an iodine substituent into the vinyl position was accomplished by a Michael addition-iodination-elimination process. All of the synthesized compounds did not exhibit antiviral activity and cytotoxicity. Maybe they might undergo a difficulty of phosphorylation upon the interaction with kinases, due to a steric hindrance induced by the introduction of the bulky iodo group into the 5''-vinyl position. And also they might not be a competitive inhibitor for SAHH due to the same steric hindrance derived from the iodine substituent. Synthesis of 5-chloroneplanocin A and 5-bromoneplanocin A are in progress in our laboratory and a series of halogen-containing structure-activity relationship will be reported in due course in close future.

Experiments

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Varian Unity INOVA 400 and Varian Unity AS 500 instruments. Chemical shifts are reported with reference to the respective residual solvent or deuteriated peaks (δ_H 3.30 and δ_C 49.0 for CD_3OD, δ_H 7.27 and δ_C 77.0 for $CDCl_3$). Coupling constants are reported in hertz. The abbreviations used are as follows: s (singlet), d (doublet), m (multiplet), t (triplet), dd (doublet of doublet), br s (broad singlet). All the reactions described below were performed under argon or nitrogen atmosphere and monitored by TLC. All anhydrous solvents were distilled over CaH_2 or Na/

benzophenone prior to use.

(3a*R*,6a*R*)-2,2-Dimethyl-6-(trityloxymethyl)-3a*H*-cyclopenta[*d*][1,3]dioxol-4(6a*H*)-one (4): Compound **4** was synthesized in the same manner as our previous report:[6] mp 161.2-163.2 °C; $[\alpha]_D^{25}$ +10.6° (*c* 1.80, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.74 (m, 15H, 3*Ar), 6.43 (brs, 1H, 5-H), 4.97 (dd, 1H, *J* = 2.4, 5.2 Hz, 6a-H), 4.46 (dd, 1H, *J* = 2.8, 5.6 Hz, 3a-H), 4.24 (brd, 1H, *J* = 18.0 Hz, TrOC*H*H), 3.94 (brd, 1H, *J* = 18.0 Hz, TrOCH*H*), 1.35 (s, 3H, CH_3), 1.34 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) *d* 202.0, 174.8, 143.5, 128.7, 128.5, 128.3, 127.6, 115.6, 87.7, 78.4, 77.9, 62.7, 27.7, 26.6.

(3a*S*,4*R*,6a*R*)-5-Iodo-2,2-dimethyl-6-(trityloxymethyl)-4,6a-dihydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-ol (6): To a solution of **4** (652 mg, 1.53 mmol) in CCl_4 (7 mL) was added iodine (582 mg, 2.29 mmol) and then pyridine (0.15 mL, 1.83 mmol) was added dropwise to the reaction mixture at 0 °C. After stirring for 12 h at room temperature, the reaction mixture was partitioned between CH_2Cl_2 and sodium thiosulfate aqueous solution and the organic layer was washed with water, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography using hexane and ethyl acetate (7:1 to 3:1) as the eluent to give iodo compound **5** (382 mg, 45%) as a colorless foam and recovered starting material (317 mg). **5** was used instantly for the next reduction. To a stirred solution of **5** (2.782 g, 5.04 mmol) and $CeCl_3$ heptahydrous (2.064 g, 5.54 mmol) in methanol (70 mL) was added portionwise $NaBH_4$ (210 mg, 5.54 mmol) at 0 °C and the reaction mixture was stirred for 30 min at the same temperature and then partitioned between ethyl acetate and water. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography using hexane and ethyl acetate (5:1) as the eluent to give allylic alcohol **6** (2.711 g, 97%) as a colorless foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.25 (m, 15H, 3*Ar), 5.25 (d, 1H, *J* = 6.0 Hz, 6a-H), 4.81 (t, 1H, *J* = 5.5 Hz, 3a-H), 4.42 (dd, 1H, *J* = 6.0, 11.0 Hz, 4-H), 3.93 (dd, 1H, *J* = 1.0, 12.5 Hz, TrOC*H*H), 3.83 (d, 1H, *J* = 12.0 Hz, TrOCH*H*), 2.83 (d, 1H, *J* = 10.0 Hz, OH), 1.46 (s, 3H, CH_3), 1.35 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 143.9, 129.0, 128.1, 127.3, 112.8, 106.4, 87.3, 83.1, 78.3, 76.7, 62.8, 27.7, 27.3; LRMS (FAB+) m/z 577 $(M+Na)^+$; HRMS (FAB+) m/z $C_{28}H_{27}IO_4Na$ $(M+Na)^+$ calcd 577.0852, obsd 577.0852.

9-((3a*S*,4*S*,6a*R*)-5-Iodo-2,2-dimethyl-6-(trityloxymethyl)-4,6a-dihydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)-9*H*-purin-6-amine (8) and 9-((3a*S*,4*S*,6a*R*)-5-iodo-2,2-dimethyl-6-(trityloxymethyl)-4,6a-dihydro-3a*H*-cyclopenta-[*d*][1,3]dioxol-4-yl)-6-methoxy-9*H*-purine (methoxy analog): To a solution of **6** (571 mg, 1.03 mmol), PPh_3 (541 mg, 2.06 mmol) and 6-chloropurine (319 mg, 2.06 mmol) in THF (15 mL) was added dropwise DEAD (0.32 mL, 2.06 mmol) at 0 °C and the reaction mixture was stirred for 12 h at room temperature. The mixture was concentrated under reduced pressure to give the resulting residue, which was purified by silica gel column chromatography using CH_2Cl_2 and MeOH (32:1) as the eluent to give 6-chloropurine nucleoside **7** (536 mg, 75%) as a colorless foam. A solution of **7** (159 mg, 0.23 mmol) in methanolic ammonia (6 mL) was heated to 80 °C in a glass bomb for 7 h. After cooling to room temperature, the volatiles were removed under reduced pressure. The resulting residue was purified by silica gel column chromatography using CH_2Cl_2 and MeOH (25:1) to give adenine nucleoside **8** (129 mg, 83%) as a white solid along with 6-methoxypurine nucleoside (19 mg, 12%) as a white solid: mp 113.7-115.3 °C; $[\alpha]_D^{25}$ −32.1° (*c* 0.92, $CHCl_3$); UV (CH_2Cl_2) λ_{max} 260.0 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H, H-8), 7.69 (s, 1H, H-2), 7.56-7.25 (m, 15H, 3*Ar), 6.48 (brs, 2H, NH_2), 5.80 (d, 1H, *J* = 5.5 Hz, 6a-H), 5.48 (s, 1H, 4-H), 4.98 (d, 1 H, *J* = 6.0 Hz, 3a-H), 3.97 (dd, 1H, *J* = 1.5, 13.0 Hz, TrOC*H*H), 3.93 (d, 1H, *J* = 12.5 Hz, TrOCH*H*), 1.47 (s, 3H, CH_3), 1.45 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0, 153.4, 152.4, 150.0, 144.0, 139.7, 129.1, 128.2, 127.4, 120.4, 113.0, 94.7, 87.6, 84.4, 82.4, 73.0, 63.3, 27.7, 26.7; LRMS (FAB+) m/z 672 $(M+H)^+$; HRMS (FAB+) m/z $C_{33}H_{31}IN_5O_3$ $(M+H)^+$ calcd 672.1472, obsd 672.1485; **methoxy analog:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (s, 1H, H-8), 7.78 (brs, 1H, H-2), 7.55-7.26 (m, 15H, 3*Ar), 5.78 (d, 1H, *J* = 5.5 Hz, 6a-H), 5.51 (s, 1H, 4-H), 4.95 (d, 1H, *J* = 6.0 Hz, 3a-H), 4.23 (s, 3H, OCH_3), 3.98 (dd, 1H, *J* = 2.0, 12.0 Hz, TrOC*H*H), 3.93 (d, 1H, *J* = 12.0 Hz, TrOCH*H*), 1.47 (s, 3H, CH_3), 1.44 (s, 3H, CH_3); LRMS (FAB+) m/z 687 $(M+H)^+$; HRMS (FAB+) m/z $C_{34}H_{32}IN_4O_4$ $(M+H)^+$ calcd 687.1468, obsd 687.1461.

9-((3a*S*,4*S*,6a*R*)-5-Iodo-2,2-dimethyl-6-(trityloxymethyl)-4,6a-dihydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)-*N*-methyl-9*H*-purin-6-amine (9): To a stirred solution of **7** (153 mg, 0.22 mmol) in methanol (3 mL) was added 40% methylamine aqueous solution (3 mL) and the reaction mixture was heated to 80 °C for 5 h. After cooling to room temperature, the volatiles were removed under reduced pressure. The resulting residue was purified by silica gel column chromatography using hexane and ethyl acetate (1:1.5) to give *N*-methyladenine nucleoside **9** (127 mg, 83%) as a colorless foam: $[\alpha]_D^{25}$ −31.8° (*c* 0.60, $CHCl_3$); UV (CH_2Cl_2) λ_{max} 267.0 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (brs, 1H, H-8), 7.63 (s, 1H, H-2), 7.55-7.25 (m, 15H, 3*Ar), 6.25 (brs, 1H, NH), 5.78 (d, 1H, *J* = 6.0 Hz, 6a-H), 5.46 (s, 1H, 4-H), 4.97 (d, 1 H, *J* = 5.5 Hz, 3a-H), 3.95 (dd, 1H, *J* = 2.0, 12.5 Hz, TrOC*H*H), 3.91 (d, 1H, *J* = 12.5 Hz, TrOCH*H*), 3.21 (brs, 3H, NCH_3), 1.46 (s, 3H, CH_3), 1.44 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.7, 153.7, 152.3, 148.9, 144.0, 138.9, 129.0, 128.2, 127.4, 120.7, 112.9, 94.9, 87.6, 84.4, 82.4, 72.9, 63.2, 27.8, 27.6, 26.7; LRMS (FAB+) m/z 686 $(M+H)^+$; HRMS (FAB+) m/z $C_{34}H_{33}IN_5O_3$ $(M+H)^+$ calcd 686.1628, obsd 686.1621.

(1*S*,2*R*,5*S*)-5-(6-Amino-9*H*-purin-9-yl)-3-(hydroxymethyl)-4-iodocyclopent-3-ene-1,2-diol (1): To a stirred solution of **8** (167 mg, 0.25 mmol) in 1,4-dioxane (1.5 mL) was added 2 N HCl (1.5 mL) at room temperature and the

reaction mixture was stirred at the same temperature overnight. After evaporation, the residue was purified by silica gel column chromatography using CH_2Cl_2 and MeOH (7:1) as the eluent to give the final adenine nucleoside **1** (86 mg, 88%) as a white solid: mp 168.2-172.5 °C; $[\alpha]_D^{25}$ −100.6° (*c* 0.83, MeOH); UV (MeOH) λ_{max} 260.0 nm; ^{1}H NMR (500 MHz, CD_3OD) δ 8.42 (s, 1H, H-8), 8.41 (s, 1H, H-2), 5.67 (d, 1H, *J* = 5.0 Hz, 2-H), 4.85 (d, 1H, *J* = 6.0 Hz, 5-H), 4.69 (t, 1H, *J* = 6.0 Hz, 1-H), 4.34 (brd, 1H, *J* = 13.0 Hz, HOC*H*H), 4.29 (d, 1H, *J* = 13.0 Hz, HOCH*H*); ^{13}C NMR (125 MHz, CD_3OD) δ 154.5, 151.9, 150.8, 145.4, 145.1, 120.5, 98.2, 77.1, 73.6, 73.2, 62.3; LRMS (FAB+) m/z 390 $(M+H)^+$; HRMS (FAB+) m/z $C_{11}H_{13}IN_5O_3$ $(M+H)^+$ calcd 390.0063, obsd 390.0048.

(1*S*,2*R*,5*S*)-3-(Hydroxymethyl)-4-iodo-5-(6-(methylamino)-9*H*-purin-9-yl)cyclopent-3-ene-1,2-diol (2): To a stirred solution of **8** (124 mg, 0.18 mmol) in 1,4-dioxane (1.5 mL) was added 2 N HCl (1.5 mL) at room temperature and the reaction mixture was stirred at the same temperature overnight. After evaporation, the residue was purified by silica gel column chromatography using CH_2Cl_2 and MeOH (10:1) as the eluent to give the final *N*-methyladenine nucleoside **2** (60 mg, 88%) as a white solid: mp 140.4-143.6 °C; $[\alpha]_D^{25}$ −98.8° (*c* 0.85, MeOH); UV (MeOH) λ_{max} 266.0 nm; ^{1}H NMR (500 MHz, CD_3OD) δ 8.41 (s, 1 H, H-8), 8.37 (s, 1H, H-2), 5.66 (brd, 1H, *J* = 4.5 Hz, 2-H), 4.86 (d, 1H, *J* = 6.0 Hz, 5-H), 4.71 (t, 1H, *J* = 5.5 Hz, 1-H), 4.34 (dd, 1H, *J* = 2.0, 13.0 Hz, HOC*H*H), 4.29 (d, 1H, *J* = 13.0 Hz, HOCH*H*), 3.26 (brs, 3H, NCH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 152.9, 150.2, 147.9, 144.5, 143.0, 119.6, 97.2, 75.7, 72.2, 71.7, 61.0, 27.8; LRMS (FAB+) m/z 404 $(M+H)^+$; HRMS (FAB+) m/z $C_{12}H_{15}IN_5O_3$ $(M+H)^+$ calcd 404.0220, obsd 404.0233.

(1*S*,2*R*,5*S*)-5-(6-Hydroxy-9*H*-purin-9-yl)-3-(hydroxymethyl)-4-iodocyclopent-3-ene-1,2-diol (3): To a stirred solution of **7** (50 mg, 0.07 mmol) in 1,4-dioxane (2 mL) was added 1 N HCl (2 mL) at room temperature and the reaction mixture was refluxed overnight. After cooling to room temperature, the volatiles were evaporated and the residue was purified by silica gel column chromatography using CH_2Cl_2 and MeOH (7:1) as the eluent to give the final hypoxanthine nucleoside **3** (24 mg, 85%) as a white solid: mp 169.5-171.4 °C; $[\alpha]_D^{25}$ −70.5° (*c* 0.48, MeOH); UV (MeOH) λ_{max} 250.0 nm; ^{1}H NMR (500 MHz, CD_3OD) δ 8.57 (brs, 1H, H-8), 8.13 (s, 1H, H-2), 5.64 (brd, 1H, *J* = 5.0 Hz, H-2), 4.85 (d, 1H, *J* = 6.0 Hz, 5-H), 4.71 (t, 1H, *J* = 5.5 Hz, 1-H), 4.33 (dd, 1H, *J* = 2.5, 13.5 Hz, HOC*H*H), 4.29 (d, 1H, *J* = 13.5 Hz, HOCH*H*); ^{13}C NMR (125 MHz, CD_3OD) δ 157.8, 154.4, 150.9, 147.9, 141.4, 123.7, 98.2, 76.9, 73.7, 73.6, 62.3; LRMS (FAB+) m/z 390 $(M+H)^+$, 413 $(M+Na)^+$.

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