Synthesis of (-)-Neplanocin A Analogues as Potential Antiviral Agents

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Based on (-)-neplanocin A with the 5'-hydroxyl substituted with fluoro, azido, or amino group, the corresponding xylo- and arabino derivatives were synthesized from D-ribose using the Mitsunobu reaction as a key step. None of the final nucleosides did show either significant antiviral activities or cytotoxicities.

Key words: Neplanocin A, Nucleosides, Antiviral activity, Cytotoxicity, *S*-adenosylhomocysteine hydrolase

INTRODUCTION

S-Adenosylhomocysteine (AdoHcy) hydrolase catalyzes the interconversion of AdoHcy into adenosine and homocysteine and plays an important role in regulating *S*-adenosylmethionine (AdoMet)-dependent methyl transferase (Ueland *et al.*, 1982). Since 5'-Capped methylated structure of mRNA catalyzed by AdoMet methyl transferase is essential for the transcription and replication of the virus, inhibition of AdoHcy hydrolase results in the accumulation of AdoHcy, subsequently inhibiting the transmethylation (Keller *et al.*, 1986). Thus, AdoHcy hydrolase has become an attractive target for the development of new antiviral agents (Liu *et al.*, 1992). A number of compounds have been synthesized and evaluated for AdoHcy hydrolase inhibitor to search for broad spectrum antiviral agents. These compounds are classified into two categories. First, type I mechanism based inhibitor which inactivates the AdoHcy hydrolase by depleting cofactor NAD^+, converting it into its inactive form, NADH. Second, type II mechanism based inhibitor which not only deplete the cofactor as does type I inhibitor, but also bind covalently to the active site of an enzyme (Wolfe *et al.*, 1991).

Although (-)-neplanocin A (**1**) has been known to be one of the most potent inhibitor of AdoHcy hydrolase, its high cytotoxicity hampered it to be developed as clinically useful agent (Borchardt *et al.*, 1984 and Fabianowska-Majewska *et al.*, 1994). The high cytotoxicity of neplanocin A is attributed to the formation of the triphosphate by cellular kinases, resulting in the inhibition of cellular polymerase (Saunders *et al.*, 1985). Since it is possible to reduce cytotoxicity by substituting the 5'-hydroxyl group with bioisosteric fluorine or azide to prevent 5'-phosphorylation, 5'-fluoro- or azido-substituted neplanocin A, **2** was synthesized and evaluated as an AdoHcy hydrolase inhibitor. Besides the ribo derivative, since it was interesting to design and synthesize arabino or xylo derivatives **3** and **4** of neplanocin A with fluoro or azido substituent, we synthesized the target compounds and evaluated for antiviral activities (Fig. 1).

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MATERIALS AND METHODS

^1H NMR spectra were recorded on a Bruker DPX (300 MHz) spectrometer using $CDCl_3$ or DMSO-d_6 with TMS

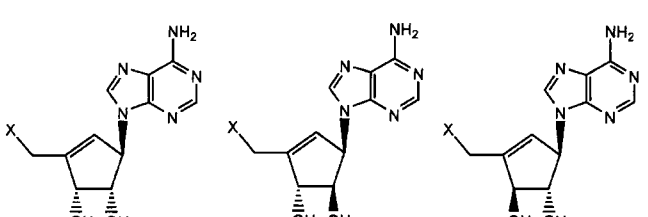


Fig. 1. Structures of (-)-Neplanocin A and Target Compounds.

as internal standard. Ultra Violet (UV) spectra were recorded on a DU-68 spectrometer. TLC was performed on Merck precoated $60F_{254}$ plates. Flash column chromatography was performed using silica gel 60 (230-400 mesh, Merck). All reagents were purchased from Aldrich Co. All anhydrous solvents were distilled over CaH_2 or P_2O_5 or Na/benzophenone prior to reaction.

2,3-*O*-Isopropylidene-D-ribofuranose (7)

To a solution of D-ribose (**6**) (5 g, 0.033 mol) in anhydrous acetone (250 ml) was added a catalytic amount of sulfuric acid and the mixture was stirred at room temperature for 1.5 h. After neutralization with triethyl amine, the mixture was evaporated and the residue was used for next reaction.

1-(5-Hydroxymethyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-ethane-1,2-diol (8)

To a solution of **7** (14.07 g, 0.074 mol) in ethanol (100 ml) was added sodium borohydride (4.17 g, 011 mol) at 0°C and the mixture was stirred at the same temperature for 1 h. The mixture was diluted with ethyl acetate and water and the organic layer was separated, dried and evaporated. The residue was purified by silica gel column chromatography (methylene chloride:methanol=8:1) to give **8** (13.8 g, 98%) as a colorless syrup.

2-(*tert*-butyldimethylsilanyloxy)-1-[5-(*tert*-butyldimethylsilanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl)-ethanone (9)

To a solution of **8** (9.04 g, 0.047 mol) and imidazole (7.95 g, 0.117 mol) in DMF (20 ml) was added t-butyldimethysilyl chloride (17.5 g, 0.117 mol) at 0°C and the mixture was stirred at the same temperature for 2 h. The mixture was diluted with ethyl acetate and water and the organic layer was separated, dried and evaporated. The residue was purified by silica gel column chromatography (hexanes:ethyl acetate=10:1) to give **9** (13.2 g, 73%) as a colorless syrup: ^{1}H NMR ($CDCl_3$) δ 0.21 (s, 12 H), 1.15 (s, 9 H), 1.18 (s, 18 H), 3.62-3.75 (m, 3 H), 4.01 (m, 1 H), 4.24 (m, 2 H), 4.49 (d, *J*=10.1 Hz, 1 H), 4.72 (d, *J* =10.1 Hz, 1 H).

2-(*tert*-butyldimethylsilanyloxy)-1-[5-(*tert*-butyldimethylsilanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl)-ethanol (10)

To a solution of oxalyl chloride (0.15 ml, 0.0034 mol) in anhydrous methylene chloride (2 ml) was added a solution of DMSO (0.36 ml, 0.005 mol) at -78°C and the solution was stirred at the same temperature for 10 min. To this solution was added a solution of **9** (0.725 g, 1.73 mmol) in methylene chloride (2 ml) dropwise and the mixture was stirred at -78°C for 1 h. After adding triethylamine at -78°C, the mixture was stirred at 0°C for 30 min. The mixture was diluted with methylene chloride and water and the organic layer was separated, dried and evaporated. The residue was purified by silica gel column chromatography (hexanes:ethyl acetate=10:1) to give **10** (0.63 g, 98%) as a colorless syrup: ^{1}H NMR ($CDCl_3$) δ 0.21 (s, 12 H), 1.15 (s, 9 H), 1.18 (s, 9 H), 1.21 (s, 6 H), 3.60-3.73 (m, 2 H), 4.24 (m, 2 H), 4.49 (d, J=10.5 Hz, 1 H), 4.70 (d, *J*=10.5 Hz, 1 H).

(2R,3S)-4-(*tert*-butyldimethylsilanyloxy)-6-[5-(*tert*-butyldimethylsilanyloxymethyl)-2,2-dimethyl-4,6a-dihydro-3a*H*-cyclopenta[1,3]dioxole (11)

To a solution of trimethylsilyl diazomethane (0.36 ml, 0.0028 mol) in anhydrous methylene chloride (2 ml) was added *n*-BuLi (0.92 ml, 0.0028 mol) at -78°C and the solution was stirred at the same temperature for 1 h. To this solution was added a solution of **10** (0.4 g, 0.96 mmol) in methylene chloride (2 ml) dropwise and the mixture was stirred at -78°C for 1 h. The mixture was diluted with methylene chloride and saturated ammonium chloride solution and the organic layer was separated, dried and evaporated. The residue was purified by silica gel column chromatography (hexanes:ethyl acetate=20 : 1) to give **11** (0.29 g, 64%) as a colorless syrup: ^{1}H NMR ($CDCl_3$) δ 0.20 (s, 12 H), 1.15 (s, 9 H), 1.19 (s, 9 H), 1.21 (s, 6 H), 4.24 (m, 2 H), 4.49 (dd, *J*=5.6 Hz, 1 H), 4.92 (d, *J*=3.0 Hz, 1 H), 5.81 (s, 1 H).

(2R,3S)-6-Hydroxymethyl)-2,2-dimethyl-4,6a-dihydro-3a*H*-cyclopenta[1,3]dioxol-4-ol (12)

To a solution of **11** (0.8 g, 1.93 mmol) in anhydrous THF (10 ml) was added tetra-*n*-butylammonium fluoride (1 M solution in THF, 4.11 ml) and the solution was stirred at room temperature for 1 h. The mixture was evaporated and the residue was purified by silica gel column chromatography (hexanes:ethyl acetate=1:1) to give **12** (0.38 g, 98%) as a colorless syrup: ^{1}H NMR ($CDCl_3$) δ 1.21 (s, 6 H), 2.59 (br s, 2 H), 4.24 (m, 2 H), 4.50 (dd, *J*=5.5 Hz, 1 H), 4.91 (d, *J*=5.5 Hz, 1 H), 5.84 (s, 1 H).

(2R,3S)-6-[5-(*tert*-Butyldimethylsilanyloxymethyl)-2,2-dimethyl-4,6a-dihydro-3a*H*-cyclopenta[1,3]dioxol-4-ol (13)

A solution of **12** (0.7 g, 3.76 mmol), imidazole (0.511 g, 7.4 mmol), and *tert*-butyldiphenylsilyl chloride (1.17 ml) in anhydrous DMF (10 ml) was stirred at room temperature for 2 h. The mixture was diluted with ethyl acetate and water and the organic layer was separated, dried and evaporated. The residue was purified by silica gel column chromatography (hexanes:ethyl acetate=10:1) to give **13** (0.9 g, 82%) as a colorless syrup: ^{1}H NMR ($CDCl_3$) δ 1.12 (s, 9 H), 1.30 (s, 6 H), 2.59 (br s, 1 H), 4.24 (m, 2 H), 4.49 (dd, *J*=5.5 Hz, 1 H), 4.90 (d, *J*=5.5

Hz, 1 H), 5.62 (s, 1 H), 7.32-7.73 (m, 10 H).

(2R,3S)-6-[5-(*tert*-Butyldimethylsilanyloxymethyl)-2,2-dimethyl-4,6a-dihydro-3a*H*-cyclopenta[1,3]dioxol-4-one (14)

To a solution of **13** (5.4 g, 0.013 mol) in anhydrous methylene chloride (20 ml) was added pyridinium dichromate (9.5 g, 0.0254 mol) and the solution was stirred at room temperature for 16 h. The mixture was filtered through a florisil and the solvent was evaporated. The residue was purified by silica gel column chromatography (hexanes: ethyl acetate=10:1) to give **12** (4.8 g, 81%) as a colorless syrup: ^{1}H NMR ($CDCl_3$) δ 1.12 (d, 9 H), 1.33 (s, 6 H), 4.32 (m, 2 H), 4.46 (dd, *J*=5.5 Hz, 1 H), 5.64 (s, 1 H), 7.33-7.78 (m, 10 H).

(2R,3S,4S)-6-[5-(*tert*-Butyldimethylsilanyloxymethyl)-2,2-dimethyl-4,6a-dihydro-3a*H*-cyclopenta[1,3]dioxol-4-ol (15)

To a solution of **14** (3.01 g, 7.13 mmol) in ethanol (10 ml) was added sodium borohydride (0.418 g, 10.6 mmol) at 0°C and the solution was stirred at the same temperature for 1 h. The mixture was diluted with water and the solvent was evaporated. The residue was purified by silica gel column chromatography (hexanes:ethyl acetate=10 :1) to give **15** (2.7 g, 85%) as a colorless syrup: ^{1}H NMR ($CDCl_3$) δ 1.12 (d, 9 H), 1.30 (s, 6 H), 2.58 (br s, 1 H), 4.24 (m, 2 H), 4.49 (dd, *J*=5.8 Hz, 1 H), 4.55 (d, *J*=5.7 Hz, 1 H), 5.84 (s, 1 H), 7.33-7.78 (m, 10 H).

(2S,3R,4R)-5-(*tert*-Butyldimethylsilanyloxymethyl)-2,2-dimethyl-4,6a-dihydro-3a*H*-cyclopenta[1,3]dioxol-4-ol (16)

To a solution of **15** (0.19 g, 0.45 mmol) in anhydrous acetone (5 ml) was added a catalytic amount of p-toluenesulfonic acid and the solution was stirred at 40°C for 2 h. After neutralization with triethylamine, the mixture was diluted with water and ethyl acetate. The organic layer was separated, dried, and evaporated. The residue was purified by silica gel column chromatography (hexanes: ethyl acetate=8:1) to give **16** (0.07 g, 48%) as a colorless syrup: ^{1}H NMR ($CDCl_3$) δ 1.12 (d, 9 H), 1.38 (s, 6 H), 2.41 (br s, 1 H), 4.18 (m, 2 H), 4.53 (dd, *J*=5.8 Hz, 1 H), 4.77 (d, *J*=5.5 Hz, 1 H), 5.82 (s, 1 H), 7.35-7.78 (m, 10 H).

(2S,3R,4S)-Benzoic acid 5-(*tert*-Butyldimethylsilanyloxymethyl)-2,2-dimethyl-4,6a-dihydro-3a*H*-cyclopenta[1,3]dioxol-4-yl ester (17)

To a solution of **16** (1.0 g, 2.35 mmol), triphenylphosphine (1.85 g, 7.05 mol, and benzoic acid (0.86 g, 7.05 mol) in anhydrous THF (10 ml) was added DEAD (1 ml) and the solution was stirred at room temperature for 18 h. After evaporation, the residue was diluted with water and ethyl acetate. The organic layer was separated, dried, and evaporated. The residue was purified by silica gel column chromatography (hexanes:ethyl acetate=10:1) to give **17** (1.8 g, 75%) as a colorless syrup: ^{1}H NMR ($CDCl_3$) δ 1.12 (d, 9 H), 1.37 (s, 6 H), 4.18 (m, 2 H), 4.50 (dd, *J*=5.8 Hz, 1 H), 4.72 (d, *J*=5.5 Hz, 1 H), 5.80 (s, 1 H), 7.34-7.78 (m, 10 H).

(3S,4R,5S)-Benzoic acid 2-(*tert*-Butyldimethylsilanyloxymethyl)-4,5-dihydroxy-cyclopent-2-enyl ester (18)

To a solution of **17** (0.5 g, 0.95 mmol) in THF (2 ml) was added 1 N HCl (2 ml) and the solution was stirred at 40°C for 2 h. After neutralization with triethyl amine, the mixture was diluted with water and ethyl acetate. The organic layer was separated, dried, and evaporated. The residue was purified by silica gel column chromatography (hexanes:ethyl acetate=5:1) to give **18** (0.38 g, 92%) as a colorless syrup: ^{1}H NMR ($CDCl_3$) δ 1.12 (d, 9 H), 2.46-2.60 (m, 2 H), 4.16 (m, 2 H), 4.49 (dd, *J* = 5.5 Hz, 1 H), 4.61 (d, *J*=5.3 Hz, 1 H), 5.83 (s, 1 H), 7.33-7.79 (m, 15 H).

(1S,4R,5S)-1-Benzoyl-2-(*tert*-butyldimethylsilanyloxymethyl)-4-(6-chloropurine-9-yl)-5-hydroxy-cyclopent-2-ene (19)

To a solution of **18** (0.34 g, 0.70 mmol), 6-chloropurine (0.53 g, 3.54 mmol) and triphenylphosphine (1.2 g, 3.54 mmol) in benzene/acetonitrile (6 ml, 5/1) was added DEAD (1 ml, 3.54 mmol) at 0°C and the mixture was stirred at room temperature for 4 h. Solvents was evaporated and the residue was purified by silica gel column chromatography (methylene:methanol 15:1) to give **19** (0.18 g, 38%) as a white foam: ^{1}H NMR ($CDCl_3$) δ 1.12 (d, 9 H), 2.46-2.60 (m, 2 H), 4.24 (m, 2 H), 4.48 (dd, *J*=5.6 Hz, 1 H), 4.60 (d, *J*=5.5 Hz, 1 H), 6.01 (s, 1 H), 6.05 (s, 1 H), 7.33-7.79 (m, 15 H), 7.72 (s, 1 H), 8.45 (s, 1 H).

(1S,4R,5S)-1-Benzoyl-2-(*tert*-butyldimethylsilanyloxymethyl)-4-(6-aminopurine-9-yl)-5-hydroxy-cyclopent-2-ene (20)

A solution of **19** (0.11 g, 0.18 mmol) and methanolic ammonia (6 ml) was heated at 65°C for 48 h in autoclave. Solvents was evaporated and the residue was purified by silica gel column chromatography (methylene : methanol 12:1) to give **20** (0.04 g, 32%) as a white foam: ^{1}H NMR ($CDCl_3$) δ 1.12 (d, 9 H), 2.45-2.60 (m, 2 H), 4.25 (m, 2 H), 4.48 (dd, *J*=5.5 Hz, 1 H), 4.60 (d, *J*=5.5 Hz, 1 H), 6.01 (s, 1 H), 6.05 (s, 1 H), 7.33-7.79 (m, 15 H), 7.72 (s, 1 H), 8.45 (s, 1 H).

(1S,4R,5S)-1,5-Dibenzoyl-2-(*tert*-Butyldimethylsilanyloxymethyl)- 4-(6-aminopurine-9-yl)-cyclopent-2-ene (21)

To a solution of **20** (0.5 g, 0.83 mmol) in anhydrous pyridine (10 ml) was added benzoyl chloride (1 ml, 2.3 mmol) and the solution was stirred at room temperature for 5 h. After evaporation, the residue was diluted with water and ethyl acetate. The organic layer was separated, dried, and evaporated. The residue was purified by silica gel column chromatography (hexanes:ethyl acetate=1:

2) to give **21** (0.67 g, 72%): ^{1}H NMR ($CDCl_3$) δ 1.12 (d, 9 H), 4.24 (m, 2 H), 4.49 (d, *J*=5.3 Hz, 1 H), 4.61 (d, *J*=5.4 Hz, 1 H), 6.02 (s, 1 H), 6.05 (s, 1 H), 6.06 (s, 1 H), 7.33-7.79 (m, 20 H), 7.72 (s, 1 H), 8.45 (s, 1 H).

(1S,4R,5S)-1-Benoyl-2-hydroxymethyl-4-(6-aminopurine-9-yl)-5-benzoyl-cyclopent-2-ene (22)

To a solution of **21** (0.1 g, 0.14 mmol) in anhydrous THF (10 ml) was added tetra-n-butylammonium fluoride (1 M solution in THF, 0.15 ml) and the solution was stirred at room temperature for 1 h. The mixture was evaporated and the residue was purified by silica gel column chromatography (hexanes:ethyl acetate=1:4) to give **22** (0.05 g, 78%): ^{1}H NMR ($CDCl_3$) δ 3.66 (m, 1 H), 4.24 (m, 2 H), 4.49 (d, *J*=5.4 Hz, 1 H), 4.63 (d, *J*=5.4 Hz, 1 H), 6.05 (s, 1 H), 6.07 (s, 1 H), 6.61 (s, 1 H), 7.34-7.79 (m, 10 H), 7.72 (s, 1 H), 8.45 (s, 1 H).

(1S,4R,5S)-1-Benzoyl-2-fluoromethyl-4-(6-aminopurine-9-yl)-5-benzoyl-cyclopent-2-ene (23)

To a solution of **22** (0.05 g, 0.11 mmol) in anhydrous methylene chloride (5 ml) was added DAST (0.1 ml, 0.28 mmol) at -78°C and the solution was stirred at room temperature for 18 h. The mixture was evaporated and the residue was purified by silica gel column chromatography (hexanes:ethyl acetate=1:1) to give **22** (0.04 g, 72%): ^{1}H NMR ($CDCl_3$) δ 4.24 (m, 2 H), 4.49 (d, *J*=5.5 Hz, 1 H), 4.61 (d, *J*=5.4 Hz, 1 H), 6.02 (s, 1 H), 6.05 (s, 1 H), 6.61 (s, 1 H), 7.34-7.73 (m, 10 H), 7.72 (s, 1 H), 8.45 (s, 1 H).

(1S,2R,5R)-5-(6-aminopurine-9-yl)-3-fluoromethyl-cyclopent-3-ene-1,2-diol (24)

A solution of **23** (0.03 g, 0.063 mmol) and methanolic ammonia (1 ml) was stirred at room temperature for 2 h. Solvents was evaporated and the residue was purified by silica gel column chromatography (methylene:methanol 12:1) to give **24** (0.01 g, 85%) as a white foam: ^{1}H NMR ($CDCl_3$) δ 2.46-2.61 (m, 2 H), 4.24 (m, 2 H), 4.49 (d, *J*= 5.6 Hz, 1 H), 4.61 (d, *J*=5.5 Hz, 1 H), 6.61 (s, 1 H), 7.73 (s, 1 H), 8.44 (s, 1 H).

(1S,4R,5S)-1-Benzoyl-2-azidomethyl-4-(6-aminopurine-9-yl)-5-benzoyl-cyclopent-2-ene (25)

To a solution of **24** (0.02 g, 0.075 mmol) in anhydrous pyridine (2 ml) was added mesyl chloride (0.1 ml, 0.075 mmol) and the solution was stirred at room temperature for 4 h. The mixture was diluted with water and ethyl acetate. The organic layer was separated, dried, and evaporated. To a solution of this residue in DMF (5 ml) was added sodium azide (0.1 g) and the mixture was heated on reflux for 18 h. The mixture was diluted with water and ethyl acetate. The organic layer was separated, dried, and evaporated. The residue was purified by silica gel column chromatography (hexanes:ethy; acetate=1:4) to give **25** (0.05 g, 75%): ^{1}H NMR ($CDCl_3$) δ 4.31 (m, 2 H), 4.49 (d, *J*=5.5 Hz, 1 H), 4.61 (d, *J*=5.5 Hz, 1 H), 5.41 (m, 1 H), 6.02 (s, 1 H), 6.05 (s, 1 H), 6.61 (s, 1 H), 7.72 (s, 1 H), 8.45 (s, 1 H).

(1S,2R,5R)-5-(6-aminopurine-9-yl)-3-azidomethyl-cyclopent-3-ene-1,2-diol (26)

A solution of **25** (0.05 g, 0.11 mmol) and methanolic ammonia (1 ml) was stirred at room temperature for 2 h. Solvents was evaporated and the residue was purified by silica gel column chromatography (methylene:methanol 12:1) to give **26** (0.03 g, 86%) as a white foam: ^{1}H NMR ($CDCl_3$) δ 2.46-2.60 (m, 2 H), 4.33 (m, 2 H), 4.49 (d, *J*= 5.4 Hz, 1 H), 4.61 (d, *J*=5.4 Hz, 1 H), 5.40 (m, 1 H), 6.02 (s, 1 H), 6.05 (s, 1 H), 6.61 (s, 1 H), 7.72 (s, 1 H), 8.45 (s, 1 H).

(1S,2R,5R)-5-(6-aminopurine-9-yl)-3-aminomethyl-cyclopent-3-ene-1,2-diol (27)

To a solution of **26** (0.03 g, 0.10 mmol) in methanol (3 ml) was added Lindlar's catalyst (0.01 g) and the mixture was stirred at room temperature for 3 h under hydrogen. The mixture was filtered through a Celite pad and solvent was evaporated and the residue was purified by silica gel column chromatography (methylene:methanol 10:1) to give **27** (0.02 g, 95%) as a white foam: ^{1}H NMR ($CDCl_3$) δ 1.75 (br s, 2 H), 2.46-2.65 (m, 2 H), 4.30 (m, 2 H), 4.49 (d, *J* = 5.5 Hz, 1 H), 4.61 (d, *J*=5.5 Hz, 1 H), 5.41 (m, 1 H), 6.02 (s, 1 H), 6.05 (s, 1 H), 6.61 (s, 1 H), 7.72 (s, 1 H), 8.45 (s, 1 H).

(2S,3S,4S)-Benzoic acid 5-(*tert*-Butyldimethylsilanyloxymethyl)-2,2-dimethyl-4,6a-dihydro-3a*H*-cyclopenta[1,3]dioxol-4-yl ester (28)

To a solution of **16** (0.54 g, 1.27 mmol) in anhydrous pyridine (10 ml) was added benzoyl chloride (1 ml, 3.81 mmol) and the solution was stirred at room temperature for 18 h. After evaporation, the residue was diluted with water and ethyl acetate. The organic layer was separated, dried, and evaporated. The residue was purified by silica gel column chromatography (hexanes:ethyl acetate=1:1) to give **28** (0.67 g, 78%): ^{1}H NMR ($CDCl_3$) δ 1.12 (d, 9 H), 1.30 (s, 6 H), 4.24 (m, 2 H), 4.33 (d, *J*=5.4 Hz, 1 H), 4.49 (d, *J*=5.5 Hz, 1 H), 4.62 (d, *J*=5.4 Hz, 1 H), 5.82 (s, 1 H), 7.33-7.78 (m, 15 H).

(3R,4R,5S)-Benzoic acid 2-(*tert*-Butyldimethylsilanyloxymethyl)- 4,5-dihydroxy-cyclopent-2-enyl ester (29)

To a solution of **28** (0.3 g, 0.57 mmol) in THF (2 ml) was added 1 N HCl (2 ml) and the solution was stirred

at 40°C for 2 h. After neutralization with triethyl amine, the mixture was diluted with water and ethyl acetate. The organic layer was separated, dried, and evaporated. The residue was purified by silica gel column chromatography (hexanes:ethyl acetate=1:1) to give **29** (0.21 g, 94%) as a colorless syrup: ^{1}H NMR ($CDCl_3$) δ 1.12 (d, 9 H), 2.46-2.60 (m, 2 H), 4.24 (m, 2 H), 4.32 (m, 1 H), 4.49 (d, *J*=5.5 Hz, 1 H), 4.61 (d, *J*=5.4 Hz, 1 H), 5.83 (s, 1 H), 7.33-7.75 (m, 15 H).

(1R,4S,5R)-Benzoic acid 4-(*tert*-Butyldimethylsilanyloxy)-2-*tert*-Butyldimethylsilanyloxymethyl)-5-hydroxy-cyclopent-2-enyl ester (30)

A solution of **29** (0.5 g, 1.02 mmol), imidazole (0.41 g, 1.7 mmol), and tert-butyldiphenylsilyl chloride (1.1 ml, 1.2 mmol) in anhydrous DMF (10 ml) was stirred at room temperature for 2 h. The mixture was diluted with ethyl acetate and water and the organic layer was separated, dried and evaporated. The residue was purified by silica gel column chromatography (hexanes:ethyl acetate=5:1) to give **30** (0.82 g, 85%) as a colorless syrup: ^{1}H NMR ($CDCl_3$) δ 1.12 (d, 18 H), 2.46-2.65 (m, 1 H), 4.24 (m, 2 H), 4.30 (d, *J*=5.6 Hz, 1 H), 4.46 (d, *J*=5.6 Hz, 1 H), 4.61 (d, *J*=5.5 Hz, 1 H), 5.80 (s, 1 H), 7.32-7.73 (m, 25 H).

(1R,4S,5S)-Benzoic acid 4-(*tert*-Butyldimethylsilanyloxy)-2-*tert*-Butyldimethylsilanyloxymethyl)-5-benzoyl-cyclopent-2-enyl ester (31)

To a solution of **30** (0.5 g, 0.69 mmol), benzoic acid (0.6 g, 3.7 mmol) and triphenylphosphine (1.8 g, 3.7 mmol) in benzene/acetonitrile (6 ml, 5/1) was added DEAD (1 ml, 3.7 mmol) at 0°C and the mixture was stirred at room temperature for 4 h. Solvents was evaporated and the residue was purified by silica gel column chromatography (hexanes:ethyl acetate=10:1) to give **19** (0.28 g, 31%): ^{1}H NMR ($CDCl_3$) δ 1.12 (d, 18 H), 4.24 (m, 2 H), 4.34 (m, 1 H), 4.49 (d, *J*=5.3 Hz, 1 H), 4.61 (d, *J*=5.3 Hz, 1 H), 5.80 (s, 1 H), 7.32-7.73 (m, 30 H).

(1R,4S,5S)-4-Hydroxy-2-hydroxymethyl-1,5-dibenzoyl-cyclopent-2-ene (32)

To a solution of **31** (0.3 g, 0.36 mmol) in anhydrous THF (5 ml) was added tetra-n-butylammonium fluoride (1 M solution in THF, 1.0 ml) and the solution was stirred at room temperature for 1 h. The mixture was evaporated and the residue was purified by silica gel column chromatography (hexanes:ethyl acetate=1:1) to give **32** (0.19 g, 90%): ^{1}H NMR ($CDCl_3$) δ 2.44-2.50 (m, 2 H), 4.24 (m, 2 H), 4.30 (m, 1 H), 4.49 (d, *J*=5.5 Hz, 1 H), 4.61 (d, *J*=5.5 Hz, 1 H), 5.82 (s, 1 H), 7.34-7.79 (m, 10 H).

(1R,4S,5S)-4-Methanesulfonyl-2-*tert*-Butyldimethylsilanyl oxymethyl-1,5-dibenzoyl-cyclopent-2-ene (33)

A solution of **32** (0.1 g, 0.28 mmol), imidazole (0.2 g, 0.45 mmol), and tert-butyldiphenylsilyl chloride (1.0 ml, 0.28 mmol) in anhydrous DMF (10 ml) was stirred at room temperature for 2 h. The mixture was diluted with ethyl acetate and water and the organic layer was separated, dried and evaporated. The residue was dissolved in pyridine (5 ml) followed by the addition of mesyl chloride (0.5 ml, 0.22 mmol) and the mixture was stirred at room temperature for 4 h. After usual work-up as mentioned above, the residue was purified by silica gel column chromatography (hexanes:ethyl acetate=5:1) to give **33** (0.19 g, 95%): ^{1}H NMR ($CDCl_3$) δ 1.12 (s, 9 H), 3.09 (s, 3 H), 4.24 (m, 2 H), 4.36 (m, 1 H), 4.49 (d, *J*=5.3 Hz, 1 H), 4.61 (d, *J*=5.3 Hz, 1 H), 5.83 (s, 1 H), 7.34-7.79 (m, 20 H).

(1R,4R,5R)-1,5-Dibenzoyl-2-(*tert*-Butyldimethylsilanyloxy-methyl)-4-(6-aminopurine-9-yl)-cyclopent-2-ene (34)

To a solution of adenine (0.128 g, 0.84 mmol), 18-crown-6-ether (0.375 g, 0.84 mmol) and NaH (0.056 g, 67% in oil, 0.84 mmol) in anhydrous DMF (10 ml) was stirred at room temperature for 0.5 h. To this mixture was added a solution of **33** (0.32 g, 0.48 mmol) in methylene chloride (3 ml) and the mixture was heated to reflux for 18 h. The mixture was diluted with water and ethyl acetate. The organic layer was separated, dried, and evaporated. The residue was purified by silica gel column chromatography (hexanes : ethyl acetate=1:3) to give **34** (0.26 g, 48%): ^{1}H NMR ($CDCl_3$) δ 1.12 (s, 9 H), 4.24 (m, 2 H), 4.32 (m, 1 H), 4.49 (d, *J*=5.5 Hz, 1 H), 4.61 (d, *J*=5.5 Hz, 1 H), 6.02 (s, 1 H), 6.61 (s, 1 H), 7.33-7.79 (m, 10 H), 7.72 (s, 1 H), 8.45 (s, 1 H).

(1R,4R,5R)-1-Benoyl-2-hydroxymethyl-4-(6-aminopurine-9-yl)-5-benzoyl-cyclopent-2-ene (35)

To a solution of **34** (0.1 g, 0.14 mmol) in anhydrous THF (10 ml) was added tetra-n-butylammonium fluoride (1 M solution in THF, 0.16 ml) and the solution was stirred at room temperature for 1 h. The mixture was evaporated and the residue was purified by silica gel column chromatography (hexanes:ethyl acetate=1:4) to give **35** (0.06 g, 98%): ^{1}H NMR ($CDCl_3$) δ 2.64 (m, 1 H), 4.24 (m, 2 H), 4.32 (m, 1 H), 4.49 (d, *J*=5.5 Hz, 1 H), 4.61 (d, *J*=5.4 Hz, 1 H), 6.02 (s, 1 H), 6.05 (s, 1 H), 6.61 (s, 1 H), 7.34-7.79 (m, 10 H), 7.72 (s, 1 H), 8.45 (s, 1 H).

(1R,2S,5R)-5-(6-aminopurine-9-yl)-3-fluoromethyl-cyclopent-3-ene-1,2-diol (36)

To a solution of **35** (0.02 g, 0.04 mmol) in anhydrous methylene chloride (1 ml) was added DAST (0.01 ml, 0.096 mmol) at -78°C and the solution was stirred at room temperature for 18 h. The mixture was evaporated and the residue was purified by silica gel column chromato-

graphy (hexanes:ethyl acetate=1:1) to give fluoro derivative (0.014 g, 71%): ^{1}H NMR ($CDCl_3$) δ 4.24 (m, 2 H), 4.49 (d, J=5.6 Hz, 1 H), 4.61 (d, J=5.6 Hz, 1 H), 6.02 (s, 1 H), 6.05 (s, 1 H), 6.61 (s, 1 H), 7.34-7.73 (m, 10 H), 7.72 (s, 1 H), 8.45 (s, 1 H).

A solution of fluoro derivative (0.01 g, 0.019 mmol) and methanolic ammonia (1 ml) was stirred at room temperature for 2 h. Solvents was evaporated and the residue was purified by silica gel column chromatography (methylene chloride:methanol 12:1) to give **36** (0.01 g, 85%) as a white solid: mp 229°C; ^{1}H NMR ($CDCl_3$) 2.30-2.43 (m, 2 H), δ 4.24 (m, 2 H), 4.33 (m, 1 H), 4.45 (d, J =5.6 Hz, 1 H), 4.58 (d, J = 5.6 Hz, 1 H), 6.02 (s, 1 H), 6.05 (s, 1 H), 6.61 (s, 1 H), 7.72 (s, 1 H), 8.45 (s, 1 H).

(1R,4R,5R)-1-Benzoyl-2-azidomethyl-4-(6-aminopurine-9-yl)-5-benzoyl-cyclopent-2-ene (37)

Compound **35** (0.01 g, 0.021 mmol) was mesylated according to the similar procedure described in the preparation of **25** to give mesylate (0.019 g, 95%): ^{1}H NMR ($CDCl_3$) δ 3.09 (s, 3 H), 4.24 (m, 2 H), 4.35 (m, 1 H), 4.45 (d, J=5.6 Hz, 1 H), 4.58 (d, J=5.6 Hz, 1 H), 6.02 (s, 1 H), 6.05 (s, 1 H), 6.61 (s, 1 H), 7.30-7.74 (m, 10 H), 7.72 (s, 1 H), 8.45 (s, 1 H).

Mesylate (0.01 g, 0.016 mmol) was reacted with sodium azide to give **37** (0.014 g, 67%) as a white foam: ^{1}H NMR ($CDCl_3$) δ 4.24 (m, 2 H), 4.33 (m, 1 H), 4.45 (dd, J =5.6 Hz, 1 H), 4.58 (d, J=5.6 Hz, 1 H), 6.02 (s, 1 H), 6.05 (s, 1 H), 6.61 (s, 1 H), 7.30-7.71 (m, 10 H), 7.72 (s, 1 H), 8.45 (s, 1 H).

(1R,2S,5R)-5-(6-aminopurine-9-yl)-3-azidomethyl-cyclopent-3-ene-1,2-diol (38)

Compound **37** (0.014 g, 0.028 mmol) was debenzoylated according to the similar procedure described in the preparation of **26** to give **38** (0.008 g, 98%) as a white solid: mp 203-207°C; ^{1}H NMR ($CDCl_3$) δ 2.33-2.41 (m, 2 H), 4.20 (m, 2 H), 4.32 (m, 1 H), 4.49 (d, J=5.6 Hz, 1 H), 4.61 (d, J=5.6 Hz, 1 H), 6.02 (s, 1 H), 6.05 (s, 1 H), 6.61 (s, 1 H), 7.72 (s, 1 H), 8.45 (s, 1 H).

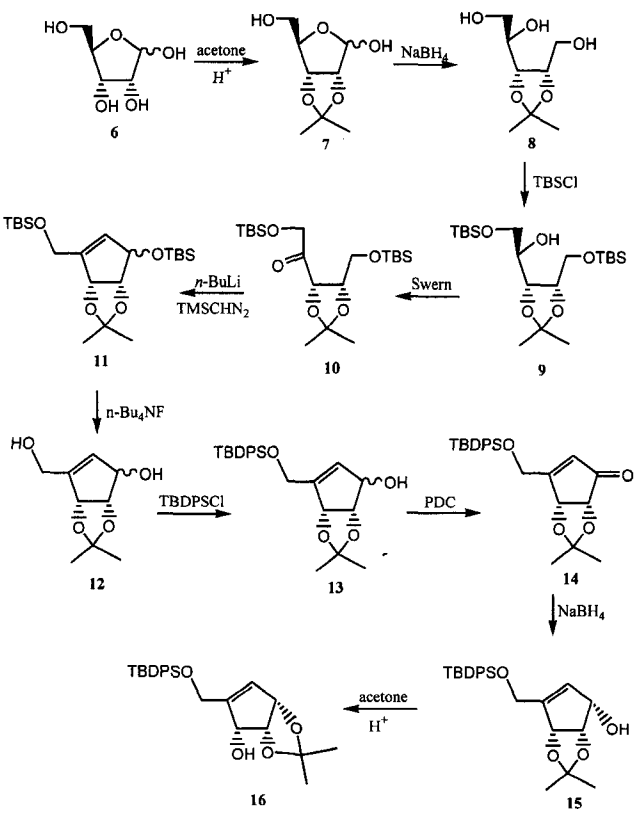
(1R,2S,5R)-5-(6-aminopurine-9-yl)-3-aminomethyl-cyclopent-3-ene-1,2-diol (39)

Compound **38** (0.01 g, 0.035 mmol) was reduced according to the similar procedure described in the preparation of **27** to give **39** (0.008 g, 92%): ^{1}H NMR ($CDCl_3$) 1.67 (br s, 2 H), 2.30-2.42 (m, 2 H), 4.24 (m, 2 H), 4.31 (m, 1 H), 4.45 (d, J=5.5 Hz, 1 H), 4.58 (d, J=5.5 Hz, 1 H), 6.02 (s, 1 H), 6.05 (s, 1 H), 6.61 (s, 1 H), 7.72 (s, 1 H), 8.45 (s, 1 H).

RESULTS AND DISCUSSION

In order to synthesize the desired arabino- and xylo-nucleoside derivatives with 5'-hydroxyl groups substituted with fluoro or azido or amino groups, we first prepared the ribo sugar derivative as shown in Scheme 1, and then convereted it to the arabino- or xylosugar derivatives. D-Ribose (**6**) was protected as 2,3-acetonide under the standard conditions to give **7** which was reduced to the triol **8** with sodium borohydride in 98% yield. Primary hydroxyl groups of **8** was reacted with t-butyldimethyllsilyl chloride to give the disilylate **9** (73%) which was oxidized to the ketone **10** under the Swern oxidation conditions in 98% yield. Treatment of **10** with trimethylsilyl diazomathane in the presence of n-BuLi at -78°C afforded the cyclopentene derivative **11** in 64% yield. Disilyl groups were deprotected with n-tetrabutylammonium fluoride to give the diol **12** whose primary hydroxyl group was selectively protected as t-butyldiphenylsilyl group to give **13** (82%). Oxidation of **13** with PDC produced the allylic ketone **14** with ribosyl moiety. Stereoselective reduction of the allylic ketone **14** with sodium borohydride in the presence of cerium (III) chloride yielded the allylic alcohol **15** (85%). Acid-catalyzed isomerization of the 2,3-acetonide **15** in refluxing acetone gave 1,2-acetonide **16** in 48% yield with the recovered starting material.

Synthesis of xylo derivatives from the acetonide **16** is illustrated in Scheme 2. Since stereochemistry of the hydroxyl group in **16** was inverted for the synthesis of the

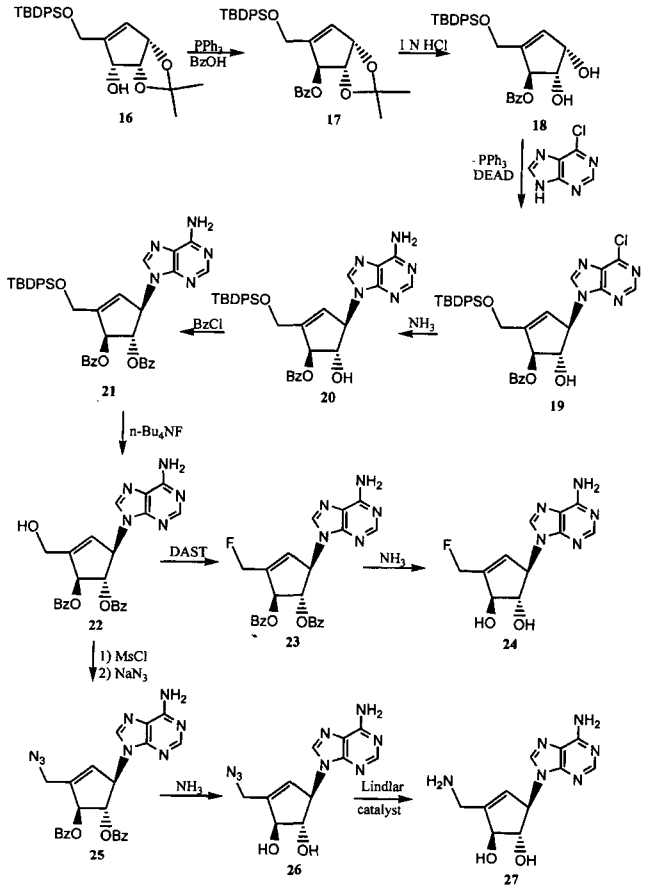


Scheme 1. Synthesis of the Key Intermediate **16** .

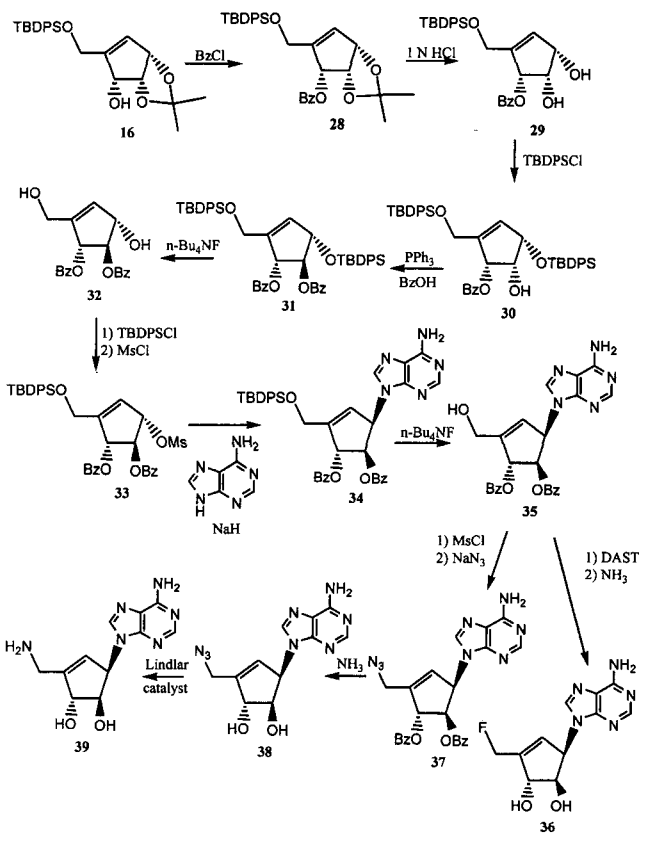
xylosugar moiety, the standard Mitsunobu conditions were employed to synthesize the xylo derivative **17**. 1,2-Acetonide of **17** was removed using 1 N HCl to give diol **18** in 92% yield. Condensation of **19** with 6-chloropurine under the Mitsunobu conditions gave the regioselective nucleoside **19** without the formation of N-7 adduct. Treatment of 6-chloropurine derivative **19** with methanolic ammonia at 65°C gave the amino analogue **20**. Benzoylation of the secondary hydroxyl group with benzoyl chloride in pyridine afforded the benzoate **21** which was desilylated using n-tetrabutylammonium fluoride to give **22**. Treatment of **22** with DAST produced the allyic fluoride **23** (72%) which was debenzoylated with methanolic ammonia to give the final fluoro nucleoside **24** (85%). For the preparation of azido and amino derivatives **26** and **27**, compound **22** was mesylated and successively treated with sodium azide to yield azido derivative **25** which was deblocked with methanolic ammonia to give the final azido derivative **26**. Reduction of the azido group in **26** with Lindlar's catalyst afforded the final amino derivative **27** (95%).

Synthesis of arabino derivatives from the same intermediate **16** is shown in Scheme 3. Benzoylation of **16** followed by acid-catalyzed hydroysis of the resulting acetonide **28** produced diol **29** in 94% yield. Selective silyl protection of the allylic alcohol over homoallyilc alcohol in **29** gave the disilylate **30** (85%). In order to obtain the arabinosugar derivative, the stereochemsitry of the hydroxyl in **30** was inverted using the Mitsunobu conditions to give arabino derivative **31** (31%). Desilylation (90%) of **31** followed by the primary hydroxyl silyl protection (93%) and successive mesylation (95%) of the resulting diol **32** afforded the mesylate **33**. Condensation of **33** with adenine anion in the presence of 18-crown-6 in DMF yielded the adenine derivative **34** in 48% yield. Desilylation of **34** using *n*-tetrabutylammonium fluoride gave the alcohol **35** which was converted to the fluoro **36**, azido **38**, and amino derivative **39**, according to the same procedure used in the preparation of the corresponding the xylo derivatives, respectively.

The synthesized final nucleosides were tested against several viruses such as herpes simplex virus (HSV) type 1 and 2, and human immunodeficiency virus (HIV)-1. None of the final nucleosides did show any significant antiviral activities or cytotoxicities. The enzyme assay against *S*-adenosylhomocysteine hydrolase is in progress in our laboratory and its result will be published in due course.



Scheme 2. Synthesis of the Xylo Nucleosides **24**, **26**, and **27**



Scheme 3. Synthesis of the Arabino Nucleosides **36**, **38**, and **39**

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