Synthesis and Antiviral Activity of Novel 4'-Branched Carbocyclic *C*-Nucleoside

Ying Lan Jin and Joon Hee Hong*

*College of Pharmacy, Chosun University, Gwangju 501-759, Korea. *E-mail: hongjh@chosun.ac.kr*
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The first synthesis of a 4'-branched carbocyclic *C*-nucleoside **11** was achieved via the key intermediate **6**, which was prepared using Knovenagel type condensation from ketone derivative **4**.

Key Words : Nucleoside, Antiviral agents, Knovenagel reaction

Introduction

Extensive efforts in the search of chemotherapeutic agents against cancer and viral infectious disease have led to the discovery of a variety of biologically active nucleoside analogs, including carbocyclic nucleosides[1] (*i.e.*, abacavir[2]) and *C*-nucleosides[3] (*i.e.*, 9-deazaadenosine[4]). Carbocyclic *C*-nucleoside is a unique class of nucleosides in which the heterocycle is connected to a sugar moiety by a *C*-*C* bond instead of the *C*-*N* bond of the natural nucleosides (Figure 1). *C*-Nucleosides have received considerable attention due not only to the chemical stability but also to the interesting biological activities of naturally occurring compounds such as showdomycin, formycins, oxazinomycin, etc.[5] Also, several biologically active synthetic *C*-nucleosides such as pseudoisocytidine,[6] thiazofurin,[7] and 9-deazaadenosine have been reported.

Carbocyclic nucleosides are another class of metabolically stable nucleosides in which a methylene group replaces the oxygen in the furan ring of the natural nucleosides. Another interesting feature of carbocyclic nucleosides is that a number of carbocyclic adenosine analogues are assumed to exert their antiviral action *via* the inhibition of *S*-adenosyl-homocysteine hydrolase.[8] Moreover, this mechanism might be exploited in a combination therapy in association with the nucleosides with a different mechanism of action.

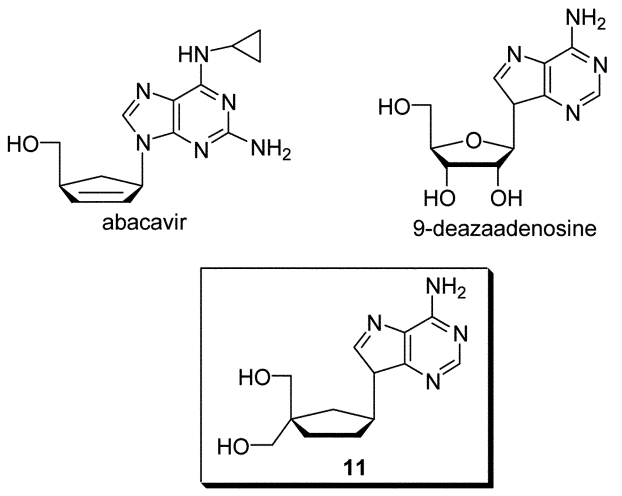
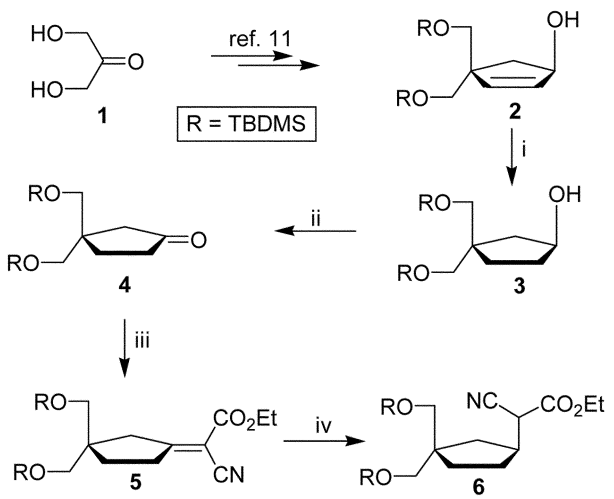


Figure 1. Synthesis rationale of target compound.

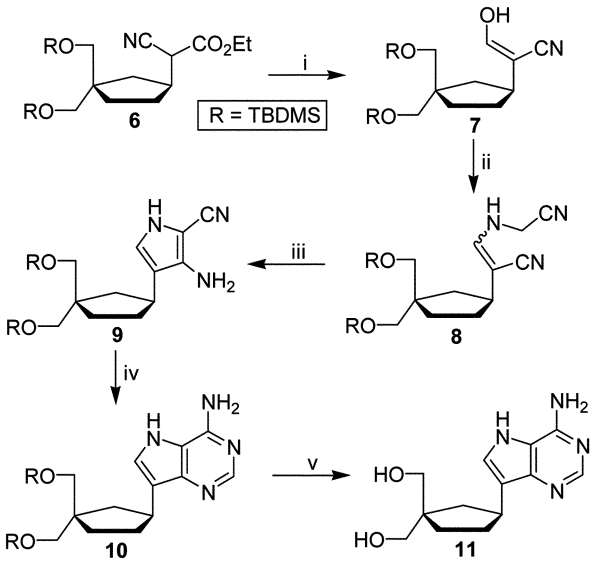
On the basis of these interesting chemical and biological properties of *C*-nucleosides and carbocyclic nucleosides, it was of interest to synthesize hybrid nucleosides, carbocyclic *C*-nucleosides. Although some carbocyclic and *C*-nucleosides are naturally occurring, so far no natural carbocyclic *C*-nucleosides have been reported. The history of synthesis of carbocyclic *C*-nucleosides dates back to the 1960s.[9] Despite the long history of carbocyclic *C*-nucleosides, only a few carbocyclic *C*-nucleosides have been synthesized,[10] probably due to the synthetic difficulties of these nucleosides. Herein, we would like to report the synthesis procedure of a novel 4'-branched carbocyclic *C*-nucleoside **11**.

Results and Discussion

For the synthesis of target carbocyclic *C*-nucleosides, we utilized the key intermediate **2** as a starting material, which was readily prepared by previously reported procedure.[11] Cyclopentenol **2** was reduced under the catalytic hydrogenation conditions to give alcohol **3** (Scheme 1). The hydroxyl group of **3** was oxidized using pyridium chlorochromate (PCC) in CH_2Cl_2 to provide cyclopentanone **4**, which was subjected to Knovenagel type condensation with ethy cyanoacetate and potassium *tert*-butoxide in EtOH to



Scheme 1. Synthesis of key intermediate **6**. Reagents: i) H_2, 10% Pd/C, MeOH; ii) PCC, 4A-MS, CH_2Cl_2; iii) $NCCH_2CO_2Et$, Kot-Bu, EtOH; iv) H_2, 10% Pd/C, MeOH.



Scheme 2. Synthesis of target nucleoside. Reagents: i) Dibal-H, ether, ii) NH_2CH_2CN, NaOAc, MeOH; iii) (a) ethyl chloroformate, DBU, CH_2Cl_2; (b) DBU; (c) Na_2CO_3, MeOH; iv) formidine acetate, EtOH; v) TBAF, THF.

give intermediate **5** in 70% yield. The reduction of **5** using H_2-Pd/C method produced compound **6**.

The intermediate **6** was reduced to the enol **7** by DIBALH, which was converted to enamine **8** by treatment of $H_2NCH_2CN{\cdot}H_2SO_4$ in MeOH (Scheme 2). *N*-protection of **8** with ethyl chloroformate and DBU in CH_2Cl_2 followed by cyclization with Na_2CO_3 gave the pyrrole derivative **9**.[12] Treatment of **9** with $H_2NC{=}NH{\cdot}HOAc$ gave the protected 9-deazaadenosine **10**, which was desilylated with tetrabutylammonium fluoride (TBAF) to give the target nucleoside **11**.

Also, it should be noted the synthesized nucleosides **11** is novel compound based on extensive literature search. The antiviral assays against the human immunodeficiency virus 1 (HIV-1), herpes simplex virus-1,2 (HSV-1,2) and human cytomegalovirus (HCMV) were performed. Compound **11** exhibited moderate anti-HIV activity in the MT-4 cell (EC_{50} = 25.1 μmol) without any cytotoxicity up to 100 μmol. This observation strongly suggests that this novel nucleoside structure might be a candidate as a new lead compound for the development of new antiviral agents.

Experimental Section

Melting points were determined on a Mel-temp II laboratory device and are uncorrected. NMR spectra were recorded on a Bruker 300 Fourier transform spectrometer; chemical shifts are reported in parts per million (δ) and signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and dd (doublet of doublets). UV spectra were obtained on a Beckman DU-7 spectrophotometer. The elemental analyses were performed using an Elemental Analyzer System (EA1112). TLC was performed on Uniplates (silica gel) purchased from Analtech Co. All reactions were carried out under an atmosphere of nitrogen unless specified. Dry dichloromethane, benzene and pyridine were obtained by distillation from CaH_2. Dry THF was obtained by distillation from Na and benzophenone immediately prior to use.

(±)-3,3-Bis-(*tert*-butyldimethylsilanyloxymethyl)cyclopentanol (3). To a solution of **2** (2.0 g, 5.36 mmol) in methanol (20 mL), Pd/C (10%, 200 mg) was added. The mixture was thoroughly deoxygenated, then saturated with hydrogen and stirred for 24 h. The charcoal was, then, removed by filtration through a short Celite pad, which was thoroughly washed with methanol. Evaporation of the solvent gave a crude product which was purified by column chromatography (EtOAc/hexane, 1 : 10) to yield 1.92 g (96%) of **3** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.58 (m, 1H), 3.40 (dd, J = 11.4, 9.9 Hz, 4H), 1.48 (dd, J = 12.4, 3.8, 2H), 1.27 (d, J = 7.5 Hz, 2H), 0.89 (s, 18H), 0.73 (t, J = 7.5 Hz, 2H), 0.03 (s, 12H); Anal. Calc. for $C_{19}H_{42}O_3Si_2$: C, 60.90; H, 11.30. Found: C, 60.74; H, 11.41.

3,3-Bis-(*tert*-butyldimethylsilanyloxymethyl)cyclopentanone (4). To a solution of compound **3** (1.19 g, 3.2 mmol) in CH_2Cl_2 (20 mL), 4 Å molecular sieves (1.8 g) and PCC (1.72 g, 8.02 mmol) were added slowly at 0 °C, and stirred overnight at room temperature. To the mixture, excess diethyl ether (100 mL) was then added. The mixture was stirred vigorously for 2 h at the same temperature, and the resulting solid was filtered through a short silica gel column. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1 : 30) to give compound **4** (1.0 g, 84%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.46 (s, 4H), 3.25 (t, J = 8.1 Hz, 2H), 2.11 (s, 2H), 1.83 (t, J = 8.1 Hz, 2H), 0.89 (s, 18H), 0.02 (s, 12H); Anal. Calc. for $C_{19}H_{40}O_3Si_2$: C, 61.23; H, 10.82. Found: C, 60.97; H, 10.67.

[3,3-Bis-(*tert*-butyldimethyl-silanyloxymethyl)cyclopentylidene]cyanoacetic acid ethyl ester (5). Potassium *tert*-butoxide (1.12 g, 10.0 mmol) was added to a solution of **4** (745 mg, 2.0 mmol) and ethyl cyanoacetate (1.12 mmol) in ethanol (15 mL) at 0 °C. The mixture was stirred for 2 h and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1 : 20) to give ester derivative **5** (654 mg, 70%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.24 (q, J = 6.9 Hz, 2H), 3.46 (s, 4H), 2.71 (s, 2H), 2.23 (t, J = 6.8 Hz, 2H), 1.84 (t, J = 6.8 Hz, 2H), 1.27 (t, J = 6.9 Hz, 3H), 0.90 (s, 12H), 0.03 (s, 12H); Anal. Calc. for $C_{24}H_{45}NO_4Si_2$: C, 61.62; H, 9.70; N, 2.99. Found: C, 61.42; H, 9.85; N, 3.13.

(±)-[3,3-Bis-(*tert*-butyldimethylsilanyloxymethyl)cyclopentyl]isocyanoacetic acid ethyl ester (6). Compound **6** was synthesized from **5** using the similar method as described for **3**: yield 80%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.23 (q, J = 7.0 Hz, 2H), 3.41-38 (m, 5H), 2.52 (m, 1H), 1.44 (m, 2H), 2.38 (t, J = 6.6 Hz, 2H), 1.30 (d, J = 5.6 Hz, 2H), 1.25 (t, J = 7.0 Hz, 3H), 0.89 (s, 12H), 0.04 (s, 12H); Anal. Calc. for $C_{24}H_{47}NO_4Si_2$: C, 61.36; H, 10.08; N, 2.98. Found: C, 61.17; H, 9.87; N, 3.09.

(±)-2-[3,3-Bis-(*tert*-butyldimethylsilanyloxymethyl)cyclopentyl]3-hydroxyacrylonitrile (7). DIBALH (2.43 mL, 1

M in hexane) was added to a solution of **6** (1.14 g, 2.43 mmol) in anhydrous ether at –78 °C over 10 min. The resulting mixture was stirred for 10 min and quenched with MeOH (10 mL). The resulting white solid was filtered, and filtrate was concentrated in reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1 : 10) to give enol **7** (7.3 mg, 68%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.01 (s, 1H), 3.50-3.41 (m, 4H), 2.91 (m, 1H), 1.69-1.47 (m, 6H), 0.89 (s, 18H), 0.05 (s, 12H); Anal. Calc. for $C_{22}H_{43}NO_3Si_2$: C, 62.06; H, 10.18; N, 3.29. Found: C, 62.32; H, 9.97, N, 3.30.

(±)-2-[3,3-Bis-(*tert*-butyldimethylsilanyloxymethyl)cyclopentyl]3-(cyanomethyl-amino)-acrylonitrile (8). Compound **7** (1.84 g, 4.32 mmol) was dissolved in MeOH (60 mL) followed by addition of aminoacetonitrile (1.68 g, 18.1 mmol) and sodium acetate (3.1 g, 31.58 mmol). The mixture was stirred at room temperature 24 h, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (EtOAc/Hexane, 1 : 10) to give **8** (2.0 g, 72%) as a mixture *E/Z* diastereomers. The mixture was subjected directly to the next step.

(±)-3-Amino-4-[3,3-bis-(*tert*-butyldimethylsilanyloxymethyl)cyclopentyl]1H-pyrrole-2-carbonitrile (9). To a solution of **8** (973 mg, 2.1 mmol) in anhydrous CH_2Cl_2 (15 mL) was added 1,8-diazabicyclo[5,4,0] undec-7-ene (DBU, 0.5 mL, 4.19 mmol) and ethyl chloroformate (0.3 mL, 3.14 mmol). The mixture was stirred at 0 °C for 2 h and reation temperature was elevated to room temperature. To the mixture was added DBU (0.5 mL, 4.19 mmol) and stirred at the same temperature for 24 h. After the reaction solvent was concentrated under reduced pressure and replaced with MeOH (10 mL). To the mixture was added solid Na_2CO_3 (22 mg, 0.21 mmol) and stirred for 2 h. The reaction mixture was extracted with CH_2Cl_2/H_2O, and the organic layer was dried over anhydrous $MgSO_4$, filtered, concentrated. The residue was purified by flash column chromatography (EtOAc/Hexane, 3 : 1) to give **9** (486 mg, 50%, 3 steps); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.99 (br s, 1H), 6.48 (s, 1H), 3.55 (m, 4H), 3.01 (s, 1H), 2.02 (m, 2H), 1.75-1.64 (m, 4H), 0.87 (s, 18H), 0.04 (s, 12H); Anal calc for $C_{24}H_{45}N_3O_3Si_2$: C, 62.15; H, 9.78; N, 9.06. Found: C, 62.35; H, 9.63; N, 9.16.

(±)-7-[3,3-Bis-(*tert*-butyldimethylsilanyloxymethyl)cyclopentyl]5H-pyrrolo[3,2-d]pyrimidin-4-yl-amine (10). To a solution of **9** (579 mg, 1.25 mmol) in EtOH (10 mL), formamidine acetate (650 mg, 6.26 mmol) was added and the reaction mixture was refluxed for 24 h. The solvent was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/Hexane, 4 : 1) to give **10** (478 mg, 78%) as a white solid: mp 162-163 °C; UV (MeOH) λ_{max} 274.0 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.72 (s, 1H), 7.58 (br s, 2H), 7.17 (s, 1H), 3.33-3.21 (m, 4H), 2.87 (t, J = 5.7 Hz, 1H), 2.23 (m, 2H), 1.94 (m, 2H), 1.79 (m, 2H), 0.89 (s, 18H), 0.02 (s, 12H); Anal. Calc. for $C_{25}H_{46}N_4O_2Si_2$: C, 61.18; H, 9.45, N, 11.41. Found: C, 61.26; H, 9.54; N, 11.54.

(±)-[3-(4-Amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-1-hydroxymethylcyclopentyl]methanol (11). To a solution of compound **10** (196 mg, 0.40 mmol) in THF (7 mL), tetrabutylammonium fluoride (TBAF, 1.5 mL, 1.0 M solution in THF) at 0 °C was added. The mixture was stirred at room temperature for 24 h, and concentrated. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1 : 5) to give compound **11** (62.95 mg, 60%) as a white solid: mp 180-182 °C; UV (H_2O) λ_{max} 274.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.75 (s, 1H, D_2O exchangeable), 8.05 (s, 1H), 7.29 (s, 1H), 6.79 (s, 2H, D_2O exchangeable), 5.07 (s, 1H, D_2O exchangeable), 4.99 (s, 1H, D_2O exchangeable), 3.40-3.29 (m, 4H), 2.89 (m, 1H), 2.28 (t, J = 6.2 Hz, 2H), 1.97 (m, 2H), 1.81 (m, 2H); Anal calc for $C_{13}H_{18}N_4O_2$: C, 59.53; H, 6.92; N, 21.36. Found: C, 59.74; H, 7.11; N, 21.49.

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