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Synthesis of Radioiodinated Carbocyclic Cytosine Analogues

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The synthesis of carbocyclic analogues of normal nucleosides has grown exclusively since they have shown potential antiviral and antitumor activities. Radiolabeled *cis*-1-[4-(hydroxy-methyl)-cyclopent-2-enyl]-5-[^{124}I]-iodocytosine (carbocyclic d4IC) and *cis*-1-[4-(hydroxy-methyl)-cyclopent-2-enyl]-5-(2-[^{124}I]iodovinyl)cytosine (carbocyclic d4IVC) were synthesized. The synthetic route employed Pd(0)-catalyzed coupling reaction together with organotin and exchange reaction for radioiodination as key reactions. Carbocyclic [^{124}I]d4IC gave more than 75% radiochemical yield with greater than 95% radiochemical purity. Carbocyclic [^{124}I]d4IVC gave more than 80% radiochemical yield with greater than 95% radiochemical purity.

Key Words : Carbocyclic nucleoside, Radioiodine, PET, Radiopharmaceutical, Labeling

Introduction

Herpes Simplex Virus type-1 thymidine kinase (HSV1-tk) is widely studied for the imaging of gene expression.[1] Various radiolabeled nucleoside analogues, both pyrimidine and acycloguanosine derivatives, have been synthesized and evaluated for HSV1-tk imaging.[2] Normal nucleoside analogues have lesser metabolic stability. The glycosidic linkage in normal nucleosides is cleaved by thymidine phosphorylase enzymes.[3] The replacement of furanose oxygen by carbon gives the nucleoside greater stability *in vivo*. Because of this metabolic stability, carbocyclic nucleosides and their analogues have been investigated by many research groups.[4,5] Recently, our group reported synthesis and biological evaluation of uracil based radioiodinated carbocyclic nucleosides, *cis*-1-[4-(hydroxymethyl)-cyclopent-2-enyl]-5-[^{124}I]iodouracil (carbocyclic d4IU, **1**) and *cis*-1-[4-(hydroxymethyl)-cyclopent-2-enyl]-5-(2-[^{124}I]iodovinyl)uracil (carbocyclic d4IVU, **2**) (Figure 1).[6] Since the previous result showed the radioiodine labeled carbocyclic d4IU (**1**) and d4IVU (**2**) are potent imaging materials for HSV1-tk, we decided to extend our research to synthesize cytosine-based carbocyclic nucleosides. Here, we report the synthesis of cytosine-based radiolabeled carbocylic nucleosides, *cis*-1-[4-(hydroxymethyl)-cyclopent-2-enyl]-5-[^{124}I]iodocytosine (carbocyclic d4IC, **3**) and *cis*-1-[4-(hydroxymethyl)-cyclopent-2-enyl]-5-(2-[^{124}I]iodovinyl)cytosine (carbocyclic d4IVC, **4**) as potential HSV1-tk imaging reporter probes (Figure 1).

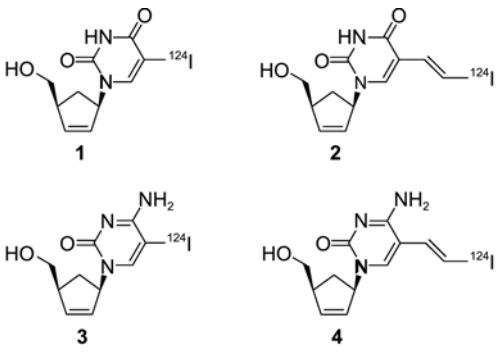
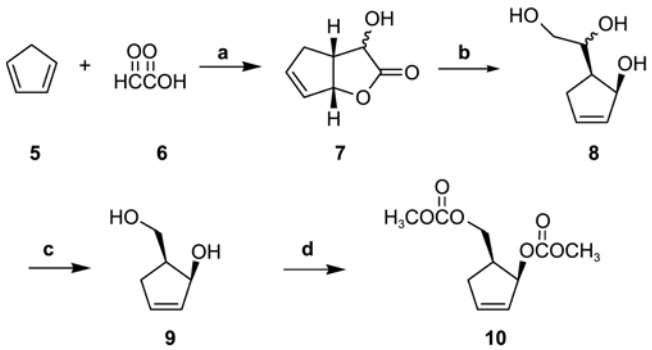


Figure 1. Carbocyclic [^{124}I]d4IU (**1**), [^{124}I]d4IVU (**2**), [^{124}I]d4IC (**3**) and [^{124}I]d4IVC (**4**).

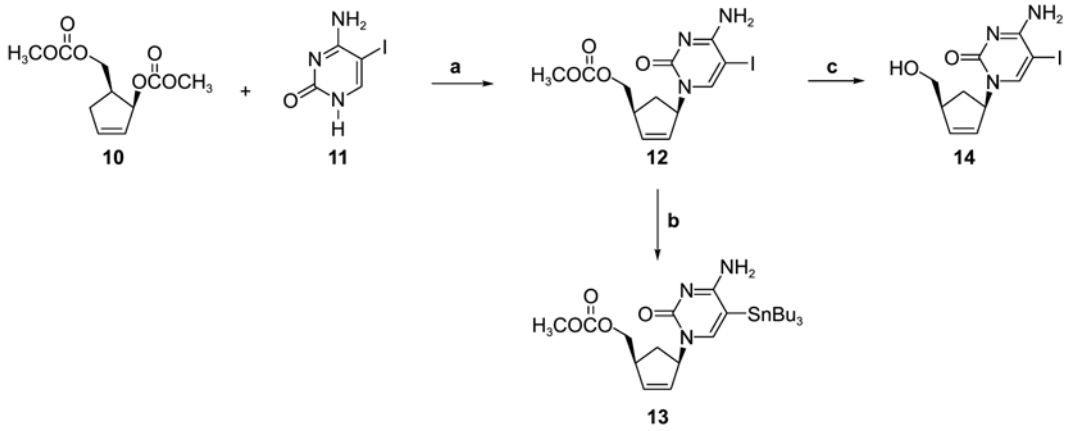
Results and Discussion

In recent years, our group has synthesized carbocylic nucleosides and their analogues.[5-7] We have prepared dicarbonate **10** (Scheme 1) as a key intermediate. In this paper, we used this dicarbonate **10** again to synthesize new carbocyclic nucleosides. Synthesis of the dicarbonate **10** was carried out using known procedures with a minor modification. For the ring-opening step of hydroxylactone **7** to triol **8**, sodium borohydride was used.[8] This method has an advantage in having a simpler and faster work-up than when using lithium aluminumhydride.[5]

Compounds **10** and 5-iodocytosine (**11**) were coupled by a



Scheme 1. (a) Toluene, H_2O, rt, 12 h, 40% (b) $NaBH_4$, CH_3OH, rt, 1 h, 90%. (c) (i) $NaIO_4$, diethyl ether, H_2O, rt, 2 h (ii) ethylene glycol, rt, 1 h (iii) $NaBH_4$, rt, 2 h, 70%. (d) methyl chloroformate, DMAP, $CHCl_3$, pyridine, 0 °C, 1 h, 93%.



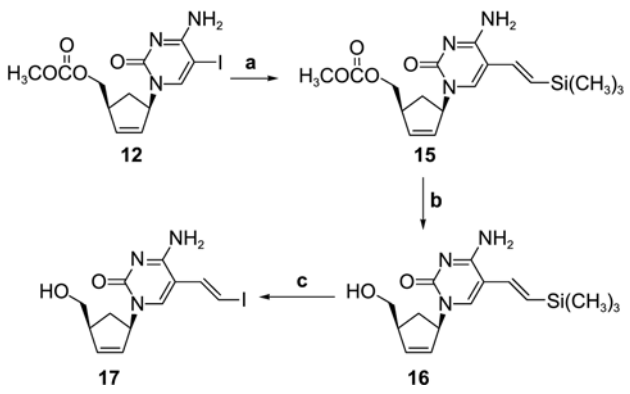
Scheme 2. (a) (i) $Pd(OAc)_2$, $(i\text{-PrO})_3P$, THF, under argon, rt (ii) *n*-BuLi, hexane, rt. (iii) **11** and NaH in DMSO (iv) **10** in anhydrous THF, 12 h, 70%. (b) (i) $Pd_2(dba)_3$, DMF (ii) bis(tributyltin), 100 °C, 7 h, 47%. (c) (i) 0.5 *N* aqueous K_2CO_3, rt, 12 h (ii) 1.0 *N* HCl to pH 7.0, 71%.

Pd(0)-catalyzed Tsuji-Trost cross-coupling reaction.[9] The Pd(0) catalyst was prepared *in situ* using $Pd(OAc)_2$ in THF with triisopropyl phosphite and *n*-BuLi. The produced π-allylpalladium complex of compound **10** undergoes nucleophilic attack by the anion on the pyrimidine base **11**.[5-7] Radiolabeling reactions with organotin compounds have been reported as a facile strategy.[6,10] Thus, we applied this method for our synthesis. Compound **12** was converted to the desired stannylated precursor **13** by the Pd(0)-catalyzed condensation of bis(tributyltin).[6] In addition, compound **12** was hydrolyzed to produce *cis*-1-[4-(hydroxylmethyl)-2-cyclopenten-1-yl]-5-iodocytosine (**14**) as a cold form of the reference compound.

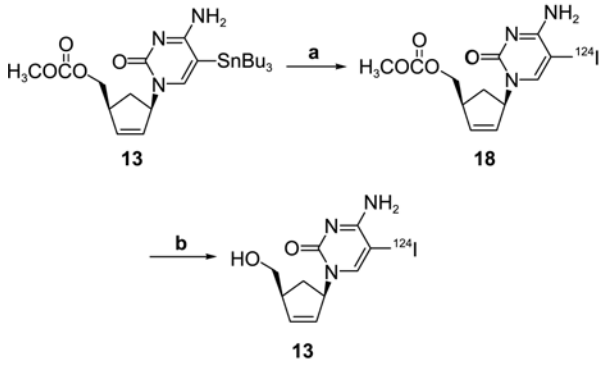
For synthesis of the iodovinyl compound, a trialkylsilylvinyl precursor was selected.[7,11] Compound **12** was converted to a trimethylsilylvinyl compound **15** by using a Pd(0)-catalyzed Stille coupling reaction.[7,12] After the hydrolysis of compound **15** and the following exchange reaction of compound **16** with ICl, compound **17** was obtained as a cold form of reference material.[7]

As shown in Scheme 4, the radioiodination of **13** was performed using a no-carrier-added iodine-124 produced by the Korea Institute of Radiological and Medical Sciences (KIRAMS). Labeled compound **18** was hydrolyzed by 0.5 *N* potassium carbonate. Then the desired carbocyclic d4IC (**3**) was separated, collected, and analyzed using reverse phase HPLC with UV and radioactivity detectors. The HPLC chromatographic retention time of carbocyclic d4IC (**3**) was 19.65 min with a radiochemical yield > 75% and radiochemical purity > 95%. We confirmed that no side products were produced except for the unreacted radioiodide based on radio-TLC monitoring. Moreover, radiolabeled and reference compounds have the same retention time in HPLC.

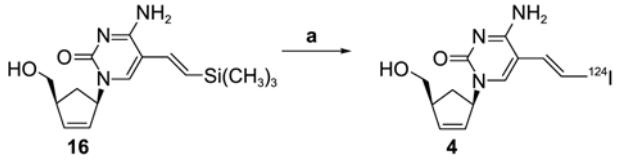
With the same method, compound **16** was radioiodinated, separated, collected, and analyzed using reverse phase HPLC with UV and radioactivity detectors. The HPLC chromatographic retention time of carbocyclic d4IVC (**4**) was 17.0 min with a radiochemical yield > 80% and radiochemical purity > 95%.



Scheme 3. (a) (*E*)-$Bu_3SnCH{=}CHSiMe_3$, $Pd_2(dba)_3$, DMF, 12 h, 60 °C, 60%. (b) (i) 0.5 *N* aqueous K_2CO_3, rt, 12 h (ii) 1.0 *N* HCl, 93%. (c) ICl, CH_3CN, 30 min, 70%.



Scheme 4. (a) (i) $Na^{124}I$, 0.01 *N* NaOH, MeOH (ii) 1.0 *N* HCl to pH 4.0, 30% H_2O_2, 10 min (iii) $NaHSO_3$. (b) (i) 1.0 *N* K_2CO_3, rt, 1 h (ii) 1.0 *N* HCl to pH 7.



Scheme 5. (a) (i) $Na^{124}I$, 0.01 *N* NaOH, MeOH (ii) 1.0 *N* HCl to pH 4.0, 30% H_2O_2, 10 min (iii) $NaHSO_3$.

Conclusions

We successfully synthesized radioiodinated *cis*-1-[4-(hydroxymethyl)-cyclopent-2-enyl]-5-[^{124}I]iodocytosine (carbocyclic d4IC, **3**) and *cis*-1-[4-(hydroxymethyl)-cyclopent-2-enyl]-5-(2-[^{124}I]iodovinyl)cytosine (carbocyclic d4IVC, **4**). The biological evaluation of these compounds will be reported in due course.

Experimental

General. ^{1}H and ^{13}C NMR spectra were obtained using a Bruker 300 spectrometer (300 MHz) and a Varian 500 spectrometer (500 MHz). Infrared spectra were recorded on a Bruker Alpha FT-IR spectrometer. Uncorrected melting points were determined with a Sanyo Gallenkamp melting point apparatus. HRMS were obtained with a JMS 700 spectrometer. Analytical thin layer chromatography (TLC) was conducted on E. Merck 60 F254 aluminum-backed silica-gel plates (0.2 mm) with a fluorescent indicator. Radio-TLC was measured with a Bioscan AC-3000 scanner (Washington D.C.). High performance liquid chromatography (HPLC) was carried out on a μBondapak C18 column (7.8 × 300 mm, Waters). Developed plates were visualized with UV light or a 2.0% phosphomolybdic acid staining solution. Flash column chromatography was performed using Merck silica-gel 60 (230-400 mesh) under positive pressure. All reagents and solvents were reagent grade and purified by known procedures before use. For radioiodine labeling, no-carrier-added iodine-124 was produced *via* the ^{125}Te(p, 2n) ^{124}I nuclear reaction in an enriched $^{125}TeO_2$ at the KIRAMS MC-50 cyclotron.

5-(1,2-Dihydroxyethyl)-2-cyclopentenol (8).[5] Sodium borohydride (17.0 g, 450 mmol) was slowly added to a solution of **7** (21.0 g, 150 mmol) in anhydrous methanol (1.0 L) in an ice bath. After stirring the resulting solution for 1 h at ambient temperature, the solvent was removed by rotary-evaporation. The residue was diluted with water and neutralized with 1.0 *N* aqueous HCl to reach a pH of 7. The aqueous solution was concentrated by rotary-evaporation. The residue was diluted with ethyl acetate, dried with anhydrous $MgSO_4$, and concentrated by rotary-evaporation. The crude mixture was purified by silica-gel column chromatography (CH_2Cl_2:MeOH = 7:1, v/v) to give coloress oil **8** (R_f = 0.25; 15.1 g, 70%). ^{1}H NMR ($CDCl_3$) δ 6.05 (dd, J = 6.0, 3.3 Hz, 1H), 5.84 (dd, J = 5.4, 1.8 Hz, 1H), 4.75 (m, 1H), 4.25 (m, 1H), 4.11 (m, 1H), 3.98 (m, 1H), 3.78 (br s, 3H), 2.58 (m, 1H), 2.30 (m, 2H).

***cis*-1-[4-(Methoxycarbonyloxymethyl)-2-cyclopenten-1-yl]-5-iodocytosine (12).** Tri-isopropyl phosphite (0.42 mL, 1.74 mmol) was added to a solution of $Pd(OAc)_2$ (0.098 g, 0.434 mmol) at ambient temperature in anhydrous THF (8.0 mL) under argon. After stirring this solution for 5 min, *n*-BuLi (1.6 *N* in hexane, 0.54 mL, 0.868 mmol) was added at ambient temperature. The resulting mixture was stirred for 5 min to obtain the tetrakis(triisopropylphosphite) palladium-(0) catalyst. The *in situ* prepared Pd(0) catalyst was added to a solution of 5-iodocytosine (**11**) (1.24 g, 5.2 mmol) and sodium hydride (0.208 g, 5.2 mmol) in anhydrous DMSO (16.0 mL) *via* cannula at ambient temperature. Next, a solution of dicarbonate **10** (1.0 g, 4.34 mmol) in anhydrous THF (8.0 mL) was added to the reaction mixture. After stirring for 2 h, the reaction mixture was diluted with $CHCl_3$ (20 mL) and washed with a brine solution (20 mL × 3). The aqueous phase was extracted with $CHCl_3$ (20 mL × 2). The organic phase was collected, dried with anhydrous $MgSO_4$, and concentrated by rotary-evaporation. The residue was purified by silica-gel column chromatography ($CHCl_3$: MeOH = 20:1, v/v) to give a white solid **12** (R_f = 0.15; 1.19 g, 70%). mp 180 °C; IR (thin film): 3456, 3062, 2995, 2950, 1748, 1714, 1649, 1622, 1478, 1281, 957 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.69 (br s, 1H), 7.61 (s, 1H), 6.51 (br s, 1H), 6.05 (m, 1H), 5.79 (m, 1H), 5.50 (m, 1H), 4.21 - 4.07 (m, 2H), 3.70 (s, 3H), 3.03 (m, 1H), 2.60 (m, 1H), 1.30 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 164.10, 155.66, 154.97, 148.44, 137.65, 131.72, 69.90, 62.02, 56.70, 55.09, 44.30, 34.23; HRMS: calculated for $C_{12}H_{14}IN_3O_4$ [M$^+$, FAB] 392.0107, found 392.0108.

***cis*-1-[4-(Methoxycarbonyloxymethyl)-2-cyclopenten-1-yl]-5-tributylstannylcytosine (13).** Bis(tributyltin) (0.4 mL, 0.75 mmol) and $Pd_2(dba)_3$ (0.023 g, 0.025 mmol) were added to a solution of compound **12** (0.20 g, 0.5 mmol) in anhydrous DMF (10 mL) at ambient temperature. The reaction mixture was stirred at 60 °C for 12 h. After removal of the solvent by rotary-evaporation, the residue was diluted with methanol (10 mL). Silica-gel (2.0 g) was added to the solution, and the resulting suspension was dried under reduced pressure. A pale yellow gummy solid **13** (R_f = 0.27; 0.155 g, 47%) was obtained from preloaded silica-gel column chromatography (CH_2Cl_2:MeOH = 20:1, v/v). IR (thin film): 3454, 3005, 2970, 2956, 2872, 1739, 1366, 1228, 1217, 528 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.11 (s, 1H), 6.08 (m, 1H), 5.83 (s, 1H), 5.74 (m, 1H), 4.18-4.06 (m. 2H), 3.77 (s, 3H), 3.10 (m, 1H), 2.82 (m, 1H), 1.54-1.46 (m, 6H), 1.36-1.29 (m, 7H), 1.13-1.02 (m, 6H), 0.93-0.88 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 169.76, 156.87, 155.74, 147.33, 136.78, 131.85, 100.90, 70.12, 61.46, 54.82, 44.02, 34.67, 28.93, 27.21, 13.66, 9.68; HRMS: calculated for $C_{24}H_{43}N_3O_4Sn$ [M$^+$, FAB] 556.2202, found 556.2200.

***cis*-1-[4-(Hydroxymethyl)-2-cyclopenten-1-yl]-5-iodocytosine (14)** Compound **12** (0.20 g, 0.511 mmol) was added to 0.5 *N* aqueous potassium carbonate (10.0 mL) and stirred at room temperature for 12 h. The reaction mixture was neutralized to pH 7-8 with 1.0 *N* HCl. After removal of the solvent by rotary-evaporation, the residue was diluted with methanol (10 mL). Silica-gel (2.0 g) was added to the solution, and the resulting suspension was dried under reduced pressure. A white solid **14** (R_f = 0.14; 0.155 g, 91%) was obtained from preloaded silica-gel column chromatography (CH_2Cl_2:MeOH = 20:1 to 15:1, v/v). mp 192 °C; IR (thin film): 3423, 2940, 2872, 1632, 1596, 1484 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.79 (s, 1H), 7.68 (br s, 1H), 6.48 (br s, 1H), 6.80 (m, 1H), 5.69 (m, 1H), 5.50 (m, 1H), 4.75 (m, 1H), 3.52-3.35 (m, 2H), 2.79 (m, 1H), 2.49 (m, 1H), 1.32 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 163.99, 155.00, 148.95, 139.97, 130.60, 63.69, 61.82, 56.31, 47.71, 34.03; HRMS: calculated

for $C_{10}H_{13}N_3O_2I$ [M^+, FAB] 334.0053, found 334.0051.

***cis*-1-[4-(Hydroxymethyl)-2-cyclopenten-1-yl]-5-[^{124}I]iodocytosine (3).** Approximately 4.0 mg of the tributylstannylated compound **13** was dissolved in 5.0 mL of MeOH. The amount of radioiodide (0.3 mCi (11.1 MBq) $Na^{124}I$) in 0.01 *N* aqueous NaOH was added to the precursor **13** solution (100 μL). The reaction mixture was acidified to a pH of 4.0 with 1.0 *N* aqueous HCl, and 30% H_2O_2 (50 μL) was added. After stirring for 10 min at ambient temperature, the reaction mixture was quenched with saturated $NaHSO_3$. 1.0 *N* aqueous K_2CO_3 (100 μL) was added. After stirring for 1 h at ambient temperature, the reaction mixture was neutralized with 1.0 *N* aqueous HCl to pH 7. Purification of the radioiodinated product **3** was performed by HPLC separation on a μBondapak C18 column (7.8 mm × 300 mm). The product was eluted at a flow rate of 2.0 mL/min with 0.1% trifluoroacetic acid in water/ethanol (9:1, v/v). The retention time of the product was 19.65 min. The radiochemical purity of the product was determined by the HPLC system used for purification and radio-thin layer chromatography (radio-TLC). Radio-TLC was performed on a silica-gel plate (Merck 60 F254 aluminum backed silica-gel plates), which was developed with acetonitrile/water (19:1, v/v) solvent (R_f = 0.23 for the product). The total elapsed time was about 110 minutes, including radioiodination and HPLC purification. The overall radiochemical yield and purity were more than 75% (8.33 MBq) and 95%, respectively.

***cis*-1-[4-(Methoxycarbonyloxymethyl)-2-cyclopenten-1-yl]-5-(2-trimethylsilylvinyl) cytosine (15).** (*E*)-Bu_3SnCH = $CHSiMe_3$ (2.0 g, 5.11 mmol) and $Pd_2(dba)_3$ (0.234 g, 0.256 mmol) were added to a solution of compound **12** (1.0 g, 2.56 mmol) in anhydrous DMF (30 mL) at ambient temperature. The reaction mixture was stirred at 60 °C for 12 h. After removal of the solvent by rotary-evaporation, the residue was diluted with methanol (10 mL). Silica-gel (~2.0 g) was added to the solution, and the resulting suspension was dried under reduced pressure. A yellow solid **15** (R_f = 0.23; 0.56 g, 60%) was obtained from preloaded silica-gel column chromatography (CH_2Cl_2:MeOH = 20:1, v/v). mp 123 °C; IR (thin film): 3428, 2956, 1750, 1646, 1474, 1444, 1273, 866, 841, 791 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.38 (s, 1H), 6.48 (d, *J* = 19.2 Hz, 1H), 6.13 (d, *J* = 19.2 Hz, 1H), 6.11 (m, 1H), 5.84 (m, 1H), 5.78 (m, 1H), 4.29-4.10 (m, 2H), 3.77 (s, 3H), 3.12 (m, 1H), 2.85 (m, 1H), 1.41 (m, 1H), 0.14 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 163.45, 155.81, 155.80, 139.78, 137.45, 134.33, 131.91, 131.43, 107.24, 69.73. 61.85, 54.90, 44.23, 34.41, −1.26; HRMS: calculated for $C_{17}H_{25}N_3O_4Si$ [M^+, FAB] 364.1693, found 364.1695.

***cis*-1-[4-(Hydroxymethyl)-2-cyclopenten-1-yl]-5-(2-trimethylsilylvinyl)cytosine (16).** Compound **15** (0.16 g, 0.44 mmol) was added to 0.5 *N* aqueous potassium carbonate (1.0 mL) and stirred at room temperature for 12 h. The reaction mixture was neutralized to pH 7-8 with 1.0 *N* HCl. After removal of the solvent by rotary-evaporation, the residue was diluted with methanol (10 mL). Silica-gel (~2.0 g) was added to the solution, and the resulting suspension was dried under reduced pressure. A yellow solid **16** (R_f = 0.25; 0.125 g, 93%) was obtained from preloaded silica-gel column chromatography ($CHCl_3$:MeOH = 15:1 to 10:1, v/v). mp 166 °C; IR (thin film): 3341, 3202, 2953, 2895, 1644, 1592, 1507, 1475, 1248, 866, 840 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.55 (s, 1H), 6.44 (d, *J* = 19.2 Hz, 1H), 6.14 (m, 1H), 6.08 (d, *J* = 19.2 Hz, 1H), 5.74 (m, 1H), 5.73 (m, 1H), 4.77 (m, 1H), 3.77-3.66 (m, 2H), 2.79 (m, 1H), 2.75 (m, 1H), 1.50 (m, 1H), 0.13 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 163.17, 155.88, 140.59, 138.67, 134.21, 131.95, 130.98, 106.89, 65.04, 62.48, 47.38, 34.07, −1.27; HRMS: calculated for $C_{15}H_{23}N_3O_2Si$ [M^+, FAB] 306.1638, found 306.1642.

***cis*-1-[4-(Hydroxymethyl)-2-cyclopenten-1-yl]-5-(2-iodovinyl)cytosine (17).** ICl (0.053 g, 0.33 mmol) was added into solution of compound **16** (0.10 g, 0.33 mmol) in acetonitrile (8.0 mL). The reaction mixture was stirred at ambient temperature for 30 min. After removal of the solvent by rotary-evaporation, a yellow solid **17** (R_f = 0.24; 0.082 g, 70%) was obtained from silica-gel column chromatography (CH_2Cl_2:MeOH = 10:1, v/v). mp 145 °C; IR (thin film): 3362, 3255, 3050, 2929, 2873, 1635, 1501, 1488, 1401, 1290, 1223 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.68 (s, 1H), 7.19 (br s, 1H), 7.28 (d, *J* = 14.6 Hz, 1H), 6.63 (d, *J* = 14.6 Hz, 1H), 6.08 (m, 1H), 5.71 (m, 1H), 5.56 (m, 1H), 4.80 (m, 1H), 3.54-3.38 (m, 2H), 2.80 (m, 1H), 2.51 (m, 1H), 1.35 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 162.44, 155.23, 140.36, 139.70, 136.22, 130.72, 105.48, 77.29. 63.81, 61.76, 47.75, 34.12; HRMS: calculated for $C_{12}H_{15}N_3O_2I$ [M^+, FAB] 360.0209, found 360.0205.

***cis*-1-[4-(Hydroxymethyl)-2-cyclopenten-1-yl]-5-(2-[^{124}I]-iodovinyl)cytosine (4).** Approximately 4.0 mg of trimethylsilyl compound **16** was dissolved in 5.0 mL of MeOH. The amount of radioiodide (0.3 mCi (11.1 MBq) $Na^{124}I$) in 0.01 *N* aqueous NaOH was added to the precursor **16** solution (100 μL). The reaction mixture was acidified to a pH of 4.0 with 1.0 *N* aqueous HCl, and 30% H_2O_2 (50 μL) was added. After stirring for 10 min at ambient temperature, the reaction mixture was quenched with saturated $NaHSO_3$. Purification of the radioiodinated product **4** was performed by HPLC separation on a μBondapak C18 column (7.8 mm × 300 mm). The product was eluted at a flow rate of 2.0 mL/min with 0.1% trifluoroacetic acid in water/acetonitrile (4:1, v/v). The retention time of the product was 17.0 min. The radiochemical purity of the product was determined by the HPLC system used for purification and radio-thin layer chromatography (radio-TLC). Radio-TLC was performed on a silica-gel plate (Merck 60 F254 aluminum backed silica-gel plates), which was developed with acetonitrile/water (19:1, v/v) solvent (R_f = 0.53 for the product). The total elapsed time was about 60 minutes, including radioiodination and HPLC purification. The overall radiochemical yield and purity were more than 80% (8.88 MBq) and 95%, respectively.

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