Note

Synthesis of 5-Radioiodoarabinosyl Uridine Analog for Probing the HSV-1 Thymidine Kinase Gene

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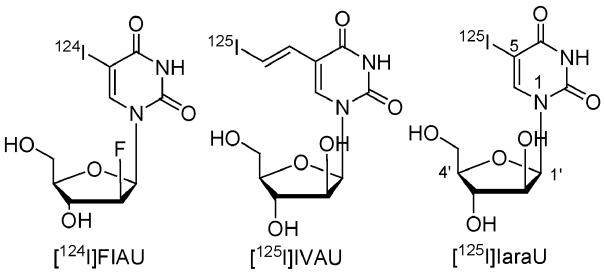
Tumor cells transduced with herpes simplex virus thymidine kinase gene have been intensively applied to the field of positron emission tomography via imaging of its substrate. As a pilot synthesis approach, a facile preparation of 5-[^{125}I]iodoarabinosyl uridine starting from commercially available uridine is reported herein.

Keywords: HSV-1 TK; Cancer; Arabinosyl uridine; Stannane; Radioiodine.

There is an increasing demand for radioiodo labeled nucleosides for the imaging of herpes simplex virus thymidine kinase (HSV-1 TK) transfected cancerous cells in cancer gene therapy research.[1-4] Briefly, the cancer lesion is first marked by the HSV-1 TK encoded gene, followed by the introduction of a non-toxic prodrug which is commonly a nucleoside analog. On entering the intracellular milieu, the prodrug can be phosphorylated by the cellular enzyme and forms a toxic metabolite which can lead to the premature termination of DNA replications, referred to as the suicide mechanism.[5-8] To achieve an optimized therapeutic effect, understanding of the localization where this event occurs using a tagged nucleoside analog is necessary. Furthermore, the assessment of gene expression levels of HSV-1 TK in animal models has been successfully quantified by using positron emission tomography (PET).[9,10] Among the positron emitters used, ^{124}I is a typical choice for PET applications with an adequate half-life of 4.0 days and its adequate positron content: 25% β^+ for one decay. So far, several compounds, including [^{124}I]FIAU, have been developed as powerful tools in PET studies (Scheme I).[11-13]

As part of our systematic syntheses of radiolabeled thymidine analogs,[14-20] we have accomplished the facile preparation of [^{125}I]IaraU and [^{125}I]IVAU via iododestannylation with iodine under oxidation.[21-27] Whereas the instability that arose from the unexpected chelating effect of

Scheme I Potential probes for HSV-1 TK



5-trimethylstannyl group was addressed, excellent radiochemical yield was still available.[15] Herein we wish to report the preparation of the tin compound (Scheme II). The whole synthesis starts either from the commercial uridine **1** or 2,2′-cyclouridine **2**. The epoxide ring can be mildly opened to generate a product **3** with a hydroxyl group with 'up' configuration. Although similar reactions were mostly reported by using alkaline conditions,[28-29] we could accomplish this step under acidic conditions with dilute TFA. ^{1}H- and ^{13}C-NMR data as well as the melting point of this product matched those of commercial araU **3**. To avoid complication while introducing the stannan in the following step, the hydroxyl groups were protected by acetyl groups even though the later iodination could be done either with or without protection. The stannylation was accomplished with a modest yield. The subsequent deprotection step to

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obtain the stannan precursor **7** was performed in the presence of NaOMe and further purified by chromatography. According to TLC estimation, approximately 60% of compound **7** was successfully recovered. To prevent the deteriorative fate of the tin compound, the whole deprotection process was performed at 0 °C. Unfortunately, satisfactory spectra from ESI-MS spectra were not available for compound **7** due to its extremely vulnerable half-life. However, we were able to identify a major peak corresponding to the clustering of the desired product and a minor peak for destannan byproduct, araU **8**.

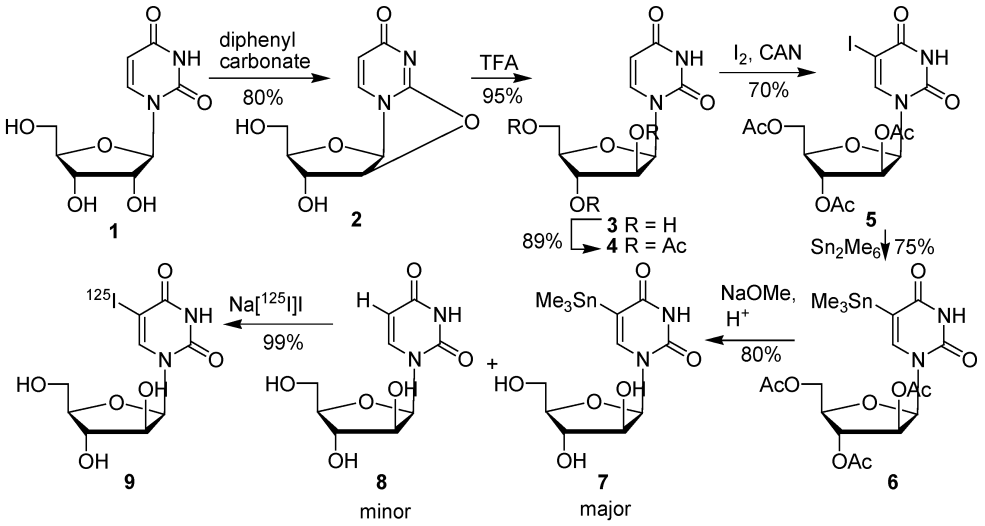
The radioiodination of the tin compound **7** was efficient and mild. Approximately 99% of radioactive Na[^{125}I]I was successfully converted into [^{125}I]IaraU **9**, as shown in the HPLC chromatogram (Fig. 1). Briefly, we have described the procedure for preparation of 5-trimethyl stannyl araU and its radiolabeling with [^{125}I]NaI. A preliminary result of radiolabeling with [^{124}I]NaI for imaging HSV-1 TK-transduced tumor cells using PET-CT indicated a significant accumulation of [^{124}I]IaraU. The result will be published elsewhere.

EXPERIMENTAL

General Methods

^{1}H- and ^{13}C-NMR spectra were recorded using 500 MHz instruments. Mass spectra were obtained by ESI (elec-

Scheme II Synthesis of 5-[^{125}I]IaraU



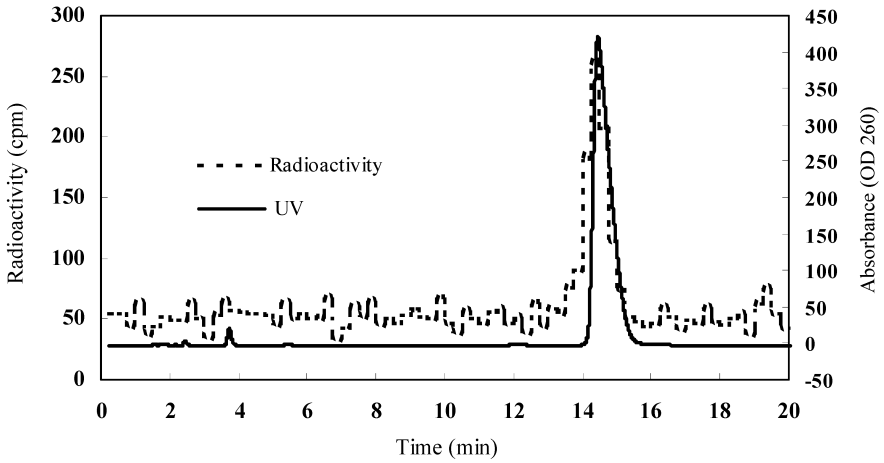


Fig. 1. HPLC chromatogram of 5-[^{125}I]IaraU **9**.

tron spray ionization) technique. Analytical thin layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates. Detection was examined by UV (254 nm) or heating with stain (5% *p*-Anisaldehyde, sulfuric acid, acetic acid, EtOH). Flash chromatography was performed using silica gel 60 (230-400 mesh).

^{2}*O*-2′-cyclouridine 2

A mixture of uridine **1** (500 mg, 2.05 mmol), diphenyl carbonate (570 mg, 2.65 mmol, 1.3 eq), and $NaHCO_3$ (10 mg, 0.12 mmol, 0.059 eq) in DMF (1 mL) was stirred at 140 °C for 100 min. Product **2** (R_f = 0.41) was observed in TLC (MeOH/$CHCl_3$ 1:4). The starting material **1** (R_f = 0.30) was consumed. After completion of the reaction, the solution was cooled to rt while precipitation occurred. The precipitate after washing with cold methanol was collected as a white solid. After concentration under reduced pressure, an offwhite powder (370 mg, 80%) was obtained. Mp: 250-253 °C. [lit.[30], 244-246 °C, lit.[31], 238-244 °C; commercial authentic sample: 248-251 °C]. anal. $C_9H_{10}N_2O_5$, calcd: C 47.79, H 4.46, N 12.39; found: C 47.41, H 4.44, N 12.41; MW: 226.2, ESI+Q-TOF MS, M = 226.1 (*m/z*), $[M+H]^+$ = 227.1, $[M+Na]^+$ = 249.0, $[2M+H]^+$ = 453.2, $[2M+Na]^+$ = 475.2; ^{1}H-NMR (500 MHz, CD_3OD): δ 3.45 (dd, $J_{5'a,4'}$ = 4.0, $J_{5'a,5'b}$ =12.0 Hz, 1H, $H_{5'a}$), 3.49 (dd, $J_{5'b,4'}$ = 4.0, $J_{5'b,5'a}$ =12.0 Hz, 1H, $H_{5'b}$), 4.23 (dd, $J_{4',5'a}$ = 4.0, $J_{4',5'b}$ = 4.0 Hz, 1H, $H_{4'}$), 4.54 (s, 1H, $H_{3'}$), 5.28 (d, $J_{2',1'}$ = 6.0 Hz, 1H, $H_{2'}$), 6.05 (d, $J_{5,6}$ = 7.5 Hz, 1H, H_5), 6.37 (d, $J_{1',2'}$ = 6.0 Hz, 1H, $H_{1'}$), 7.82 (d, $J_{6,5}$ = 7.5 Hz, 1H, H_6).

1-(β-D-arabinofuranosyl)-pyrimidin-2,4(3H)-dione 3

Cyclouridine **2** (500 mg, 2.23 mmol) was suspended with DMF (5 mL) followed by addition of TFA (70 mL, 0.05 N). Upon stirring, the mixture became clear. The solution was stirred at 80 °C for 10 h. Product **3** (R_f = 0.46) was observed in TLC (MeOH/$CHCl_3$ 1:3). The starting material (R_f = 0.26) was consumed. After completion of the reaction, the solvent was reduced at 45 °C under reduced pressure. The residue was purified by column chromatography with MeOH/$CHCl_3$ 1:3 to provide **3** as a white powder (95%, 510 mg). Mp: 209-216 °C [lit.[32], 209-211 °C, lit.[33], 210-215 °C]. anal. $C_9H_{12}N_2O_6$, calcd: C 44.27, H 4.95, N 11.47; found: C 43.13, H 5.01, N 11.08. anal. $C_9H_{12}N_2O_6$ MW: 244.2, ESI+Q-TOF MS, M = 244.1 (*m/z*), $[M+H]^+$ = 245.0, $[M+Na]^+$ = 267.1, $[2M+H]^+$ = 489.2, $[2M+Na]^+$ = 511.2, $[3M+Na]^+$ = 755.2; ^{1}H-NMR (500 MHz, CD_3OD): 3.77 (dd, $J_{5'a,4'}$ = 4.5, $J_{5'a,5'b}$ =12.0 Hz, 1H, $H_{5'a}$), 3.81 (dd, $J_{5'b,4'}$ = 4.0, $J_{5'b,5'a}$ =12.0 Hz, 1H, $H_{5'b}$), 3.91 (ddd, $J_{4',3'}$ = 3.5, $J_{4',5'b}$ = 4.0, $J_{4',5'a}$ = 4.5 Hz, 1H, $H_{4'}$), 4.06 (dd, $J_{3',2'}$ = 3.0, $J_{3',4'}$ = 3.5 Hz, 1H, $H_{3'}$), 4.14 (dd, $J_{2',3'}$ = 3.0, $J_{2',1'}$ = 4.5 Hz, 1H, $H_{2'}$), 5.64 (d, $J_{5,6}$ = 8.1 Hz, 1H, H_5), 6.12 (d, $J_{1',2'}$ = 4.5 Hz, 1H, $H_{1'}$), 7.84 (d, $J_{5,6}$ = 8.1 Hz, 1H, H_6).

1-(2′,3′,5′-Tri-*O*-acetyl-β-D-arabinofuranosyl)-pyrimidin-2,4(3H)-dione 4

3 (500 mg, 2.05 mmol) was dissolved in pyridine (35 mL) with stirring for 1 h. Acetic anhydride (11 mL) was added. The stirring was continued at rt for 30 min. Product **4** (R_f = 0.46) was observed in TLC (acetone/n-hexane 1:1). The starting material (R_f = 0.08) was consumed. After completion of the reaction, the distilling solvent was removed under reduced pressure. The residue was purified by column chromatography with acetone/n-hexane 4:5 to provide **4** (89%, 675 mg) as a white powder, Mp: 128-130 °C [lit.10[32], 128-130 °C, lit.[34], 129-130 °C]. anal. $C_{15}H_{18}N_2O_9$, calcd: C 48.65, H 4.90, N 7.56; found: C 48.41, H 5.01, N 7.54; MW: 370.3, ESI+ Q-TOF MS, M = 370 (*m/z*), $[M+H]^+$ = 371.1, $[M+Na]^+$ = 393.0, $[2M+H]^+$ = 741.1, $[2M+Na]^+$ = 763.1.

1-(2′,3′,5′-Tri-*O*-acetyl-β-D-arabinofuranosyl)-5-iodo-pyrimidin-2,4(3H)-dione 5

A mixture of **4** (454 mg, 1.23 mmol), I_2 (420 mg, 1.66 mmol, 1.3 eq), and ceric(IV) ammonium nitrate (700 mg, 1.27 mmol, 1 eq) in acetonitrile (15 mL) was stirred at 80 °C for 1 h. Product **5** (R_f = 0.54) was observed in TLC (acetone/n-hexane 1:1). The starting material **4** (R_f = 0.46) was consumed. Upon completion of the iodination, cold EtOAc (100 mL), $NaHSO_3$ (5%, 30 mL), and satd aq NaCl (30 mL) were added sequentially. The organic layer was collected and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with cold $NaHSO_3$ (5%) followed by satd NaCl (aq) and H_2O. After treatment with Na_2SO_4, the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography with acetone/n-hexane 2:3 to provide the product **5** in a yield of 70% (425 mg). White powder, Mp: 184-186 °C [lit.[35], 185-187 °C, lit.[36], 184-186 °C]. anal. $C_{15}H_{17}IN_2O_9$, calcd: C 36.31, H 3.45, N 5.65; found: C 36.09, H 3.52, N 5.85. anal. $C_{15}H_{17}IN_2O_9$, MW: 496.2, ESI+Q-TOF, M = 496.0 (*m/z*), $[M+H]^+$ = 497.0, $[M+Na]^+$ = 519.0, $[2M+H]^+$ = 993.0; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.04 (s, 3H, H_{Ac}), 2.13 (s, 3H, H_{Ac}), 2.17 (s, 3H, H_{Ac}), 4.19 (ddd, $J_{4',3'}$ = 3.5, $J_{4',5'a}$ = 4.5, $J_{4',5'b}$ = 5.5 Hz, 1H, $H_{4'}$), 4.38 (dd, $J_{5'a,4'}$ = 4.5,

$J_{5'a,5'b}$ =12.0 Hz, 1H, $H_{5'a}$), 4.44 (dd, $J_{5'b,4'}$ = 5.5, $J_{5'b,5'a}$ = 12.0 Hz, 1H, $H_{5'b}$), 5.10 (dd, $J_{3',2'}$ = 1.5, $J_{3',4'}$ = 3.5 Hz, 1H, $H_{3'}$), 5.38 (dd, $J_{2',3'}$ = 1.5, $J_{2',1'}$ = 4.0 Hz, 1H, $H_{2'}$), 6.27 (d, $J_{1',2'}$ = 4.0 Hz, 1H, $H_{1'}$), 7.89 (s, 1H, H_6), 8.87 (s, 1H, H_{NH}).

1-(2′,3′,5′-Tri-*O*-acetyl-β-D-arabinofuranosyl)-5-trimethylstannyl pyrimidin-2,4(3H)-dione 6

A mixture of **5** (600 mg, 1.21 mmol), hexamethylditin (1.42 g, 4.32 mmol, 3.6 eq), bis(triphenylphosphine)palladium dichloride (22 mg, 0.03 eq), and 1,4-dioxane (36 mL) was stirred at 100 °C for 2 h. Product **6** (R_f = 0.65) was observed in TLC (acetone/n-hexane 1:1). **5** (R_f = 0.54) was consumed. Upon completion, the distilling solvent was removed at 45 °C under reduced pressure. The residue was purified by column chromatography with EtOAc/n-hexane 1:1 to provide **6** in a yield of 75% (500 mg). White waxy solid, Mp: 63-73 °C. anal. $C_{18}H_{26}N_2O_9Sn$, calcd: C 40.55, H 4.92, N 5.25; found: C 42.36, H 5.79, N 5.01. MW: 533.1, ESI+Q-TOF MS, M = 532.1 (*m/z*), $[M+H]^+$ = 533.1, $[M+Na]^+$ = 555.1. Clustering of the peaks corresponding to isotope distribution of Sn was observed; ^{1}H-NMR (500 MHz, C_6D_6): δ 0.22-0.35 (m, 9H, $SnMe_3$), 1.47 (s, 3H, H_{Ac}), 1.48 (s, 3H, H_{Ac}), 1.69 (s, 3H, H_{Ac}), 3.81 (ddd, $J_{4',3'}$ = 3.5, $J_{4',5'a}$ = 4.0, $J_{4',5'b}$ = 6.5 Hz, 1H, $H_{4'}$), 4.24 (dd, $J_{5'a,4'}$ = 4.0, $J_{5'a,5'b}$ = 12.0 Hz, 1H, $H_{5'a}$), 4.32 (dd, $J_{5'b,4'}$ = 6.5, $J_{5'b,5'a}$ = 12.0 Hz, 1H, $H_{5'b}$), 5.06 (dd, $J_{3',2'}$ = 1.0, $J_{3',4'}$ = 3.5 Hz, 1H, $H_{3'}$), 5.48 (dd, $J_{2',3'}$ = 1.0, $J_{2',1'}$ = 5.5 Hz, 1H, $H_{2'}$), 6.35 (d, $J_{1',2'}$ = 5.5 Hz, 1H, $H_{1'}$), 7.28-7.38 (m, 1H, H_6), 9.76 (s, 1H, H_{NH}). ^{13}C-NMR (125.70 MHz, C_6D_6): -9.44 ($\underline{C}H_3Sn$), 19.84 ($\underline{C}H_3CO$), 19.92 ($\underline{C}H_3CO$), 20.32 ($\underline{C}H_3CO$), 62.54 (CH_2, C-5′), 75.08 (CH), 76.59 (CH), 80.76 (CH), 84.78 (CH), 111.43 (C-5), 144.09 (C-6), 150.91 (C=O, C-2), 166.38 (C=O, C-4), 168.19 ($CH_3\underline{C}O$), 169.35 ($CH_3\underline{C}O$), 169.84 ($CH_3\underline{C}O$).

1-(β-D-arabinofuranosyl)-5-trimethylstannylpyrimidin-2,4(3H)-dione 7 + 1-(β-D-arabinofuranosyl)-pyrimidin-2,4(3H)-dione 8

Starting material **6** (250 mg, 0.45 mmol) was dissolved in MeOH (15 mL) at 0 °C. NaOMe/MeOH (5 mL, 0.01 N) was added and stirring continued for 7 h. The formation of product **7** (R_f = 0.55) and decomposed byproduct, 1-(β-D-arabinofuranosyl)-pyrimidin-2,4(3H)-dione **8** (R_f = 0.24), was detected by TLC (MeOH/$CHCl_3$ 1:4). After the starting materials **6** (R_f = 0.93) have been completely consumed, the reaction was neutralized by cation exchange resin (Dowex 500 WX8-400, H^+ form) and filtered. The eluent was concentrated under reduced pressure at 30 °C yielding ~ 80% (140 mg) of product **7** with minor byproduct **8**. $C_{12}H_{20}N_2O_6Sn$ calcd mass: 406.0 amu, ESI+Q-TOF MS, M(**7**) = 406.0 (*m/z*), $[M+H]^+$ = 407.1; M(**8**) = 244.1 (*m/z*), $[M+H]^+$ = 245.1, $[M+Na]^+$ = 267.1, $[2M+H]^+$ = 489.2; Clustering of the peaks corresponding to isotope distribution of Sn was observed. ^{1}H-NMR (500 MHz, CD_3OD): δ 0.24 (t, $SnMe_3$, **7**), 3.74-3.84 (m, $H_{5'}$, **7**+**8**), 3.88-3.93 (m, $H_{4'}$, **7**+**8**), 4.06 (pt, *J* = 3.5 Hz, $H_{3'}$, **8**), 4.10 (pt, *J* = 3.5 Hz, $H_{3'}$, **7**), 4.14-4.17 (m, $H_{3'}$, **7**+**8**), 5.64 (d, $J_{5,6}$ = 8.0 Hz, H_5, **8**), 6.12 (d, $J_{1',2'}$ = 4.5 Hz, $H_{1'}$, **8**), 6.17 (d, $J_{1',2'}$ = 4.5 Hz, $H_{1'}$, **7**), 7.64 (s, H_6, **7**), 7.84 (d, $J_{6,5}$ = 8.0 Hz, H_6, **8**).

1-(β-D-arabinofuranosyl)-5-[^{125}I]iodopyrimidin-2,4(3H)-dione 9

Tin compound **7** (500 μg) was added to a microcentrifuge tube (1.5 mL) containing $CHCl_3$ (400 μL). Na[^{125}I]I (5×10^4 cpm/10 μL) in NaOH (800 μL, 0.1 N) was added to the above mixture followed by a solution mixture of acetic acid (200 μL) and hydrogen peroxide (30%) with a ratio of 1:3 (v/v). The whole reaction mixture was sonicated for 1 min and applied onto HPLC for analysis. Agilent HPLC was equipped with a sample loop (20 μL), an analytical column [4.6 × 150 mm ZORBAR Eclipse XDB-C8 (5 μm material)], and UV detector setting at 260 nm. The fractions collected from the UV detector were counted for liquid scintillation on a 96 well microtiter plate reader (Plate CHAMELEON^{TM}). Time delay between UV signal and radioactivity was calibrated in the chromatogram. The eluent used was 0.5 mM Na_3PO_4/H_3PO_4 (pH = 5.7), with a flow rate of 1 mL/min. More than 99% of the radioactivity in the radiochromatogram was obtained as a single peak, corresponding to that of IaraU **9** (t_R = 14.47 min). No further radioactivity was detected between 20 and 40 min when MeOH was set as isocratic auxiliary component from 0 to 30%.

Nonradioactive 1-(β-D-arabinofuranosyl)-5-iodopyrimidin-2,4(3H)-dione 9

5 (500 mg, 1.0 mmol) was dissolved in MeOH (8 mL) with stirring at rt and NaOMe/MeOH (5 mL, 0.5 N, 2.5 eq) was added. The stirring was continued for 30 min. **9** (R_f = 0.17) was observed in TLC (MeOH/$CHCl_3$ 1:9). **6** (R_f = 0.85) was consumed. After completion of the reaction, the solution was neutralized by cation exchange (Dowex 500 WX8-400, H^+ form). The volatiles were evaporated under reduced pressure at 40 °C. Yield of **9** was 80% (300 mg).

Mp: 224-226 °C , [lit.[37], 224-227 °C], $C_9H_{11}IN_2O_6$, calcd: C 29.21, H 3.00, N 7.57; found: C 29.09, H 3.40, N 7.32. anal. $C_9H_{11}IN_2O_6$, MW: 370.1, ESI+Q-TOF MS, M = 370.0 (*m/z*); $[M+H]^+$ = 371.1, $[M+NH_4]^+$ = 388.0, $[M+Na]^+$ = 393.0, $[2M+H]^+$ = 741.0, $[2M+NH_4]^+$ = 758.1, $[2M+Na]^+$ = 763.0, $[3M+NH_4]^+$ = 1128.1, $[3M+Na]^+$ = 1133.0; ^{1}H-NMR (500 MHz, CD_3OD): 3.77 (dd, $J_{5'a,4'}$ = 4.5, $J_{5'a,5'b}$ = 12.0 Hz, 1H, $H_{5'a}$), 3.83 (dd, $J_{5'b,4'}$ = 4.0, $J_{5'b,5'a}$ = 12.0 Hz, 1H, $H_{5'b}$), 3.90 (ddd, $J_{4',3'}$ = 3.5, $J_{4',5'b}$ = 4.0, $J_{4',5'a}$ = 4.5 Hz, 1H, $H_{4'}$), 4.06 (dd, $J_{3',2'}$ = 3.0, $J_{3',4'}$ = 3.5 Hz, 1H, $H_{3'}$), 4.14 (dd, $J_{2',3'}$ = 3.0, $J_{2',1'}$ = 4.5 Hz, 1H, $H_{2'}$), 6.10 (d, $J_{1',2'}$ = 4.5 Hz, 1H, $H_{1'}$), 8.27 (s, 1H, H_6).

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