

# Syntheses of 5-Fluoro and (*E*)-5-(2-Fluorovinyl) Arabinosyl Uridine Analogues as Potential Probes for the HSV-1 Thymidine Kinase Gene

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**Abstract:** The syntheses of 5-fluoro (FaraU) and (*E*)-5-(2-fluorovinyl) arabinosyl uridine (FVAU) via 5-trimethylstannyl and (*E*)-5-(2-tributylstannylvinyl) arabinosyl uridine analogues with selectfluor is described. Boc protection of the uridine moiety improved the yield of synthesis and differences between *N*-Boc and *O*-Boc isomers were established by  $^1\text{H}$ - and  $^{13}\text{C}$  NMR. The Boc-protected stannyl intermediates may be fluorinated with  $^{18}\text{F}$  to produce [ $^{18}\text{F}$ ]FaraU and [ $^{18}\text{F}$ ]FVAU.

**Key words:** stannane, fluoro, arabinosyl, cancer, gene therapy

There is an increasing demand for radiofluoro-labeled nucleosides that can be used for imaging herpes simplex virus thymidine kinase (HSV-1 TK) transfected cancerous cells in cancer gene therapy research.<sup>1</sup> In these approaches, 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 analogue. After entering the intracellular milieu, the prodrug can be phosphorylated by cellular enzymes to form a toxic metabolite capable of causing premature termination of DNA replication, through a suicide mechanism.<sup>2</sup> To achieve an optimal therapeutic effect, however, localizing where this event occurs using a tagged nucleoside analogue is necessary. Such an assessment of gene expression levels of HSV-1 TK in animal studies has been successfully quantified using positron emission tomography (PET).<sup>3,4</sup> Among the positron emitters used,  $^{18}\text{F}$  is a typical choice for PET applications since it has an adequate half-life of 110 minutes and a high positron content: 99%  $\beta^+$  for one decay. So far, several compounds, including [ $^{18}\text{F}$ ]FHBG and [ $^{124}\text{I}$ ]FIAU, have been developed and used as powerful tools in PET studies (Figure 1).<sup>5,6</sup>

Fluoro and fluorovinyl groups represent one class of substituents with which to modify nucleoside bioactivities against various diseases such as HSV infection and cancers.<sup>7</sup> While the syntheses of 5-fluoro (FaraU) and 5-fluorovinyl arabinosyl uridines (FVAU) were first reported a decade ago, there have been relatively few subsequent studies undertaken.<sup>8</sup> This may be due to a number of factors such as the tedious manipulation and extensive purification procedures involved. A survey of the literature shows that there are two predominant methods that have been used for the synthesis of 5-fluorovinyl uridine. Both meth-

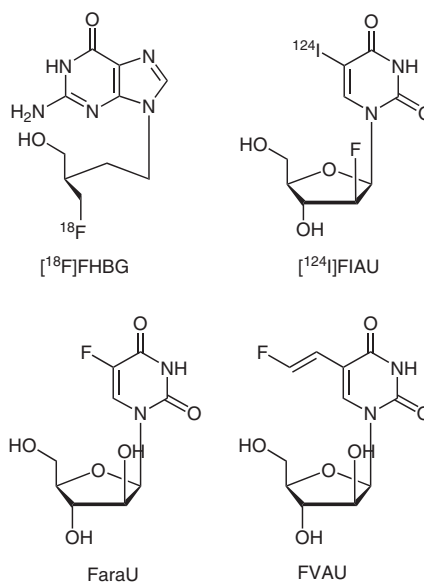
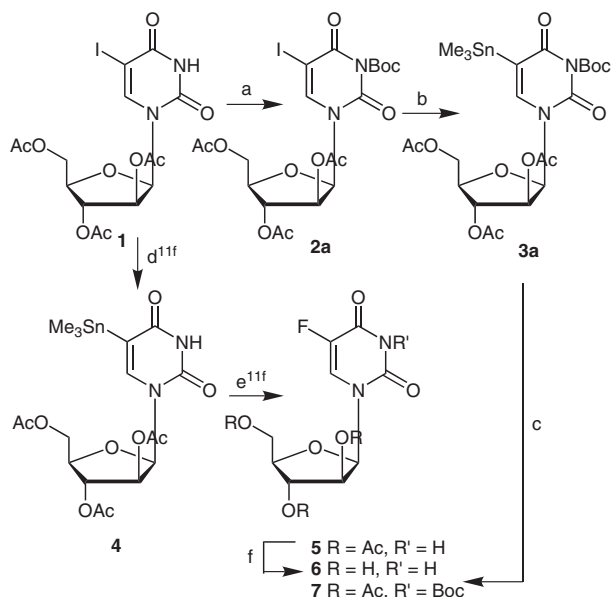


Figure 1 Potential genetic probes for HSV TK

ods involve multiple steps. One approach includes the introduction of alpha-fluoro ethyl acetate onto the 5-methylene of 5-bromomethyl uridine, a UV-induced incorporation of bromine onto 5-methylene, base-induced elimination of HBr and final treatment with a cation exchange resin at high temperature to eliminate carbon dioxide. The second approach employs a similar strategy using sodium hydride, purification using ethyl acetate and sodium hydroxide on silica gel and final acid-induced decarboxylation.

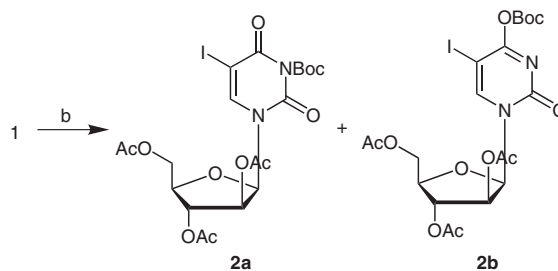
Compared with 5-(2-bromovinyl)-2'-deoxyuridine (BVDU), which is one of the most potent inhibitors of HSV-1 TK, its fluoro counterpart, FVDU, is ten-fold less effective.<sup>9</sup> This characteristic does, however, make 5-(2-fluorovinyl)arabinosyl uridine (FVAU) suitable for *in vivo* studies. It should be noted that the 2'-hydroxy group with 'up' configuration is crucial in maintaining both stability and bioactivity *in vivo*.<sup>10</sup> In order to prepare  $^{18}\text{F}$ -labeled arabinosyl uridine, a practical syntheses of the nonradioactive FaraU and FVAU first needed to be developed. As part of our systematic syntheses of radiolabeled thymidine analogues,<sup>11</sup> we wish to report here the preparation of FaraU and FVAU via fluorodestannylation with Selectfluor, a common fluorinating reagent.<sup>12,13</sup>

Preparation of 5-trimethylstannyl arabinosyl uridine **4** could be readily achieved through a published procedure<sup>11f</sup> (Scheme 1) and subsequent fluorination afforded the protected fluorinated product **5** in 30% yield. After deprotection, a satisfactory yield of FaraU **6** was obtained, which could be used as an authentic sample. However, as our previous report on the radiofluorination of stannylvinyl uridine analogue with [<sup>18</sup>F]F<sub>2</sub> indicated, the proton at N-3 was prone to substitution by fluorine, leading to a labile N–F bond, which was eventually reprotonated.<sup>11d</sup> This process led to the formation of [<sup>18</sup>F]HF which was no longer capable of serving as an electrophilic fluorine with which to replace stannane, resulting in poor radiochemical yield. In order to overcome this drawback, the nitrogen at N-3 was protected as its butoxycarbonylamide (Boc). This modified tin precursor **3a**, when fluorinated under the conditions described above, improved the yield of fluorinated product **7** to 50%. Subsequent removal of the Boc group, unlike that of the relatively stable tolyl group,<sup>14</sup> was trivial.



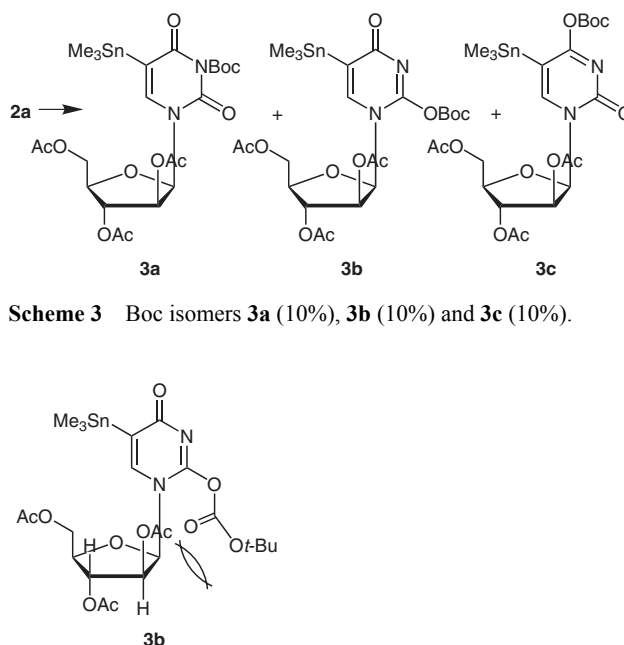
**Scheme 1** Reagents and conditions: (a) (Boc)<sub>2</sub>O, DMAP, THF, 50%; (b) Sn<sub>2</sub>Me<sub>6</sub>, (PPh<sub>3</sub>)<sub>2</sub>PdCl<sub>2</sub>, dioxane, 80 °C, 30%; (c) Selectfluor, MeCN, 50 °C, 50%; (d) 75%; (e) 30%; (f) NaOMe, MeOH, 95%.

Interestingly, the Boc group tended to migrate during its introduction and the subsequent stannylation (Schemes 2 and 3). The distinction between O-substituted (**2b**, **3b** and **3c**) and N-substituted isomers (**2a** and **3a**) could be made through <sup>13</sup>C NMR: a down-field shift of about 85 ppm was observed for the O-substituted tertiary carbon of Boc, compared to that of the N-substituted isomer. Furthermore, in contrast to the clear carbonyl carbon signal arising from the Boc group of **3b** at 163 ppm, only very weak or even no corresponding signals for **2a**, **3a** or **3c** were detected.



**Scheme 2** Boc isomers **2a** (10%) and **2b** (40%).

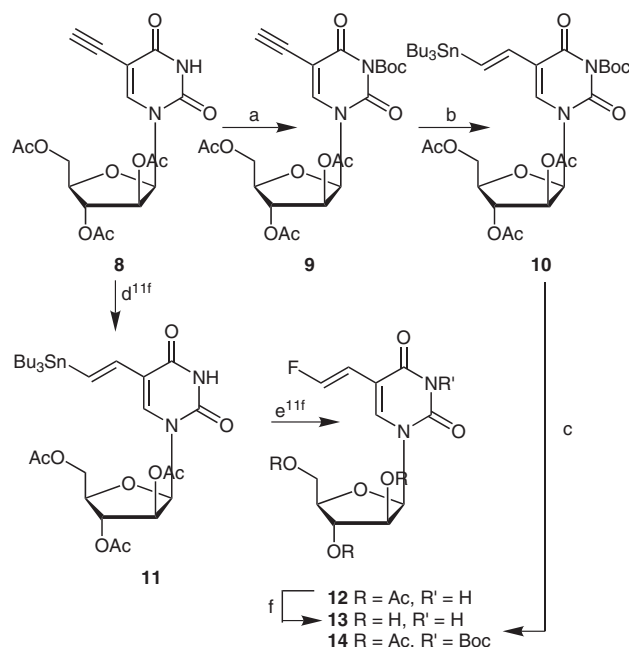
A further differentiation between 2-*O*-Boc **3b** and 4-*O*-Boc **3c** isomers was made by <sup>1</sup>H NMR. Compared to **3a** and **3c**, an unusual up-field shift of the 2'- and 3'-protons of 0.6 and 1 ppm, respectively, was seen for the 2-*O*-Boc isomer **3b**. The shielding effect depicted in Figure 2, caused by a steric interaction of the Boc group, may account for this observation.



**Figure 2** Shielding of the 2'- and 3'-protons by Boc.

By adopting a similar synthetic approach to that described above, tin compounds **10** and **11** were obtained in excellent yields (Scheme 4). Both the fluoro nucleosides **12** and **14** could be obtained in limited yields after fluorination, with the *E*-isomer of both compounds being unambiguously assigned by <sup>1</sup>H, <sup>13</sup>C and <sup>19</sup>F NMR. Interestingly, in contrast to products obtained using F<sub>2</sub>, where a ratio of *E*- and *Z*-isomers of 2:1 was observed,<sup>11d</sup> in this approach, none of the *Z*-isomer was detected. Furthermore, the proposed Pd-mediated migration of Boc during stannylation discussed above, apparently did not take place in this case since no isomers of 5-(2-stannanyl)vinyl counterparts **10** were detected either by TLC or after column chromatography. This might be due to the relative inertness of the Boc group towards radical-catalyzed stannylation.

In conclusion, practical syntheses of FaraU **6** and FVAU **13** have been developed. Though the limited yield of FVAU **13** seems far below that required for mass production, our yields of the final products are still sufficient for both bioscreening studies and radiofluorination experiments. Furthermore, we have found that the use of Boc-protected tin precursors **3a**, **3b**, **3c** and **10** is crucial for the efficient production of  $^{18}\text{F}$ -labeled **6** and **13** with  $[^{18}\text{F}]\text{F}_2$ .<sup>11a,d</sup>



**Scheme 4** Reagents and conditions: (a)  $(\text{Boc})_2\text{O}$ , DMAP, THF, 80 °C, 37%; (b)  $\text{HSnBu}_3$ , AIBN, toluene, 80 °C, 86%; (c) Selectfluor, MeCN, r.t., 10%; (d) 80%; (e) 8%; (f) NaOMe, MeOH, 95%.

Electrospray mass spectra were measured on a quadrupole mass spectrometer equipped with an electrospray source (MICROMASS Waters 600S). NMR spectra were recorded with a Varian Unity Inova spectrometer operating at 500 MHz ( $^1\text{H}$  NMR) or 125.7 MHz ( $^{13}\text{C}$  NMR). Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F254. TLC monitoring was performed by staining with *p*-anisaldehyde and by UV at 254 nm. Flash column chromatography was performed with Merck Geduran Si 60 (230–400 mesh). Eluents EtOAc, acetone and *n*-hexane were freshly distilled for column chromatography. Normal-phase HPLC (Agilent 1100) was equipped with a sample loop (500  $\mu\text{L}$ ) and a semipreparative column (9.4  $\times$  250 mm ZORBAX SIL, 5  $\mu\text{m}$  material). Constant conditions were used: flow rate of 3 mL/min; detection, UV (260 nm). RP-HPLC (Agilent 1100) was equipped with a semipreparative column (Astec, 10  $\times$  250 mm, C18, 5  $\mu\text{m}$  material). Isocratic conditions were used: mobile phase MeOH– $\text{H}_2\text{O}$  3:7; flow rate of 3 mL/min; detection, UV (260 nm). All retention times are quoted in minutes. Acetonitrile and toluene were dried by refluxing over calcium hydride. THF was dried by refluxing over sodium. MeOH was dried by refluxing over magnesium. Chemicals were obtained commercially and used in all experiments without purification.

### 3-*N*-Boc-5-iodo-2',3',5'-tri-*O*-acetyl Arabinosyl Uridine (**2a** and **2b**)

Compound **1** (500 mg, 1.00 mmol) and  $(\text{Boc})_2\text{O}$  (327 mg, 1.50 mmol) were stirred in THF (7 mL) at r.t. for 80 min. DMAP (1.3 mmol, 160 mg) was added to the reaction mixture and the reaction was allowed to proceed for a further 4 h until product **2** was formed and the starting material **1** ( $R_f = 0.19$ ; EtOAc–*n*-hexane, 1:1) was consumed. After removal of the volatile solvents, EtOAc (30 mL) was added and sequentially washed with  $\text{H}_2\text{O}$  (10 mL), HCl (1 N, 5 mL), and aq  $\text{NaHCO}_3$  (sat., 10 mL). The organic layer was then dried ( $\text{Na}_2\text{SO}_4$ ), evaporated and purified by column chromatography on silica gel (EtOAc–*n*-hexane, 1:3) to give **2a** and **2b**.

#### **2a**

Yield: 60 mg (10%); white foam;  $R_f = 0.55$  (*n*-hexane–EtOAc, 1:1).

$^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta = 1.39$  (s, 3 H,  $\text{H}_{\text{Ac}}$ ), 1.46 (s, 3 H,  $\text{H}_{\text{Ac}}$ ), 1.66 (s, 9 H,  $\text{H}_{\text{Boc}}$ ), 1.74 (s, 3 H,  $\text{H}_{\text{Ac}}$ ), 3.71 (ddd,  $J_{4'-3'} = 4.0$ ,  $J_{4'-5'a} = 4.0$ ,  $J_{4'-5'b} = 5.5$  Hz, 1 H,  $\text{H}_{4'}$ ), 4.09 (dd,  $J_{5'a-4'} = 4.0$ ,  $J_{5'a-5'b} = 12.0$  Hz, 1 H,  $\text{H}_{5'a}$ ), 4.22 (dd,  $J_{5'b-4'} = 5.5$ ,  $J_{5'b-5'a} = 12.0$  Hz, 1 H,  $\text{H}_{5'b}$ ), 4.94 (br s, 1 H,  $\text{H}_{3'}$ ), 5.42 (dd,  $J_{2'-1'} = 3.5$ ,  $J_{2'-3'} = 2.0$  Hz, 1 H,  $\text{H}_{2'}$ ), 6.18 (d,  $J_{1'-2'} = 3.5$  Hz, 1 H,  $\text{H}_{1'}$ ), 7.84 (s, 1 H,  $\text{H}_6$ ).

$^{13}\text{C}$  NMR (125 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta = 19.74$  ( $\text{CH}_3$ , Ac), 19.84 ( $\text{CH}_3$ , Ac), 20.45 ( $\text{CH}_3$ , Ac), 29.45 ( $\text{CH}_3$ , Boc), 62.22 ( $\text{CH}_2$ , C-5'), 63.43 (CCH<sub>3</sub>, Boc), 69.25 (C-5), 74.66 (CH), 76.35 (CH), 80.82 (CH), 85.45 (CH), 141.92 (CH), 150.89 (C=O, C-2), 160.70 (C=O, C-4), 168.35 ( $\text{CH}_3\text{CO}$ ), 169.11 ( $\text{CH}_3\text{CO}$ ), 169.77 ( $\text{CH}_3\text{CO}$ ). No signal corresponding to carbonyl of Boc was found.

ESI-QTOF:  $m/z = 596.1$  [ $\text{M}^+$ ], 497.0 [ $\text{M} - \text{Boc} + 2\text{H}^+$ ], 597.1 [ $\text{M} + \text{H}^+$ ], 614.0 [ $\text{M} + \text{NH}_4^+$ ], 619.0 [ $\text{M} + \text{Na}^+$ ], 635.0 [ $\text{M} + \text{K}^+$ ].

#### **2b**

Yield: 240 mg (40%); white foam;  $R_f = 0.44$  (*n*-hexane–EtOAc, 1:1).

$^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta = 1.41$  (s, 3 H,  $\text{H}_{\text{Ac}}$ ), 1.46 (s, 3 H,  $\text{H}_{\text{Ac}}$ ), 1.77 (s, 3 H,  $\text{H}_{\text{Ac}}$ ), 3.61 (ddd,  $J_{4'-3'} = 4.0$ ,  $J_{4'-5'a} = 4.0$ ,  $J_{4'-5'b} = 5.0$  Hz, 1 H,  $\text{H}_{4'}$ ), 4.00 (dd,  $J_{5'a-4'} = 4.0$ ,  $J_{5'a-5'b} = 12.5$  Hz, 1 H,  $\text{H}_{5'a}$ ), 4.16 (dd,  $J_{5'b-4'} = 5.5$ ,  $J_{5'b-5'a} = 12.5$  Hz, 1 H,  $\text{H}_{5'b}$ ), 4.99 (dd,  $J_{3'-2'} = 3.0$ ,  $J_{3'-4'} = 4.0$  Hz, 1 H,  $\text{H}_{3'}$ ), 5.40 (dd,  $J_{2'-1'} = 4.5$ ,  $J_{2'-3'} = 3.0$  Hz, 1 H,  $\text{H}_{2'}$ ), 6.01 (d,  $J_{1'-2'} = 4.5$  Hz, 1 H,  $\text{H}_{1'}$ ), 7.74 (s, 1 H,  $\text{H}_6$ ).

$^{13}\text{C}$  NMR (125 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta = 19.24$  ( $\text{CH}_3$ , Ac), 19.44 ( $\text{CH}_3$ , Ac), 20.71 ( $\text{CH}_3$ , Ac), 26.93 ( $\text{CH}_3$ , Boc), 61.42 ( $\text{CH}_2$ , C-5'), 66.88 (C-5), 74.15 (CH), 74.91 (CH), 80.18 (CH), 84.40 (CCH<sub>3</sub>, Boc), 86.56 (CH), 143.57 (CH), 146.91 (C=O, C-2), 147.85 (C=O, C-4), 156.77 (C=O, Boc), 167.89 ( $\text{CH}_3\text{CO}$ ), 168.76 ( $\text{CH}_3\text{CO}$ ), 169.31 ( $\text{CH}_3\text{CO}$ ).

ESI-QTOF:  $m/z = 596.0$  [ $\text{M}^+$ ], 497.0 [ $\text{M} - \text{Boc} + 2\text{H}^+$ ], 597.0 [ $\text{M} + \text{H}^+$ ], 614.0 [ $\text{M} + \text{NH}_4^+$ ], 619.0 [ $\text{M} + \text{Na}^+$ ], 635.0 [ $\text{M} + \text{K}^+$ ].

### 3-*N*-Boc-5-trimethylstannyl-2',3',5'-tri-*O*-acetyl Arabinosyl Uridine **3a–c**

Compound **2a** (170 mg, 0.285 mmol), hexamethylditin (165 mg, 0.5 mmol), bis(triphenylphosphine)palladium dichloride (5 mg, 8  $\mu\text{mol}$ ), and 1,4-dioxane (10 mL) were stirred at 80 °C for 2 h to give a mixture of compounds **3a–c** (monitored by TLC). Upon completion, the solvent was removed at 45 °C under reduced pressure and the residue was purified by column chromatography (*n*-hexane–EtOAc, 1:4) to provide a mixture of **3** in 30% overall yield (60 mg). Further purification with normal-phase HPLC separated the three isomers in a ratio of 1:1:1. The HPLC (Agilent 1100) was equipped with a sample loop (500  $\mu\text{L}$ ), a semipreparative column (ZORBAX SIL, 9.4  $\times$  250 mm, 5  $\mu\text{m}$ ) and was eluted with *n*-hexane–EtOAc (3:1), flow rate: 3 mL/min and UV detector setting at 254 nm.

**3a**

$R_f = 0.70$  (*n*-hexane–EtOAc, 1:1); colorless oil.

$^1\text{H NMR}$  (500 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta = 0.27\text{--}0.40$  (m, 9 H,  $\text{SnMe}_3$ ), 1.41 (s, 3 H,  $\text{H}_{\text{Ac}}$ ), 1.49 (s, 3 H,  $\text{H}_{\text{Ac}}$ ), 1.71 (s, 3 H,  $\text{H}_{\text{Ac}}$ ), 1.77 (s, 9 H,  $\text{H}_{\text{Boc}}$ ), 3.82 (ddd,  $J_{4'-3'} = 3.0$ ,  $J_{4'-5'a} = 4.0$ ,  $J_{4'-5'b} = 7.5$  Hz, 1 H,  $\text{H}_{4'}$ ), 4.24 (dd,  $J_{5'a-4'} = 4.0$ ,  $J_{5'a-5'b} = 12.0$  Hz, 1 H,  $\text{H}_{5'a}$ ), 4.35 (dd,  $J_{5'b-4'} = 7.5$ ,  $J_{5'b-5'a} = 12.0$  Hz, 1 H,  $\text{H}_{5'b}$ ), 5.02 (br s, 1 H,  $\text{H}_{3'}$ ), 5.53 (dd,  $J_{2'-1'} = 3.5$ ,  $J_{2'-3'} = 1.5$  Hz, 1 H,  $\text{H}_{2'}$ ), 6.35 (br s, 1 H,  $\text{H}_{1'}$ ), 7.26–7.36 (m, 1 H,  $\text{H}_6$ ).  $^{13}\text{C NMR}$  (125 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta = -9.22$  ( $\text{CH}_3$ ,  $\text{SnMe}_3$ ), 19.83 ( $\text{CH}_3$ , Ac), 19.87 ( $\text{CH}_3$ , Ac), 20.32 ( $\text{CH}_3$ , Ac), 29.62 ( $\text{CH}_3$ , Boc), 61.69 ( $\text{CCH}_3$ , Boc), 62.52 ( $\text{CH}_2$ , C-5'), 75.04 (CH), 76.73 (CH), 80.86 (CH), 85.67 (CH), 112.93 (C-5), 140.63 (CH, C-6), 151.99 (C=O, C-2), 164.80 (C=O, Boc), 167.92 (C=O, C-4), 168.06 ( $\text{CH}_3\text{CO}$ ), 169.19 ( $\text{CH}_3\text{CO}$ ), 169.75 ( $\text{CH}_3\text{CO}$ ).

ESI-QTOF:  $m/z = 634.1$  [ $\text{M}^+$ ], 534.9 [ $\text{M} - \text{Boc} + 2\text{H}$ ] $^+$ . Clustering of the peaks corresponding to isotope distribution of Sn was observed.

**3b**

$R_f = 0.59$  (*n*-hexane–EtOAc, 1:1); colorless oil.

$^1\text{H NMR}$  (500 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta = 0.23\text{--}0.37$  (m, 9 H,  $\text{SnMe}_3$ ), 1.43 (s, 3 H,  $\text{H}_{\text{Ac}}$ ), 1.48 (s, 9 H,  $\text{H}_{\text{Boc}}$ ), 1.50 (br d, 3 H,  $\text{H}_{\text{Ac}}$ ), 1.70 (s, 3 H,  $\text{H}_{\text{Ac}}$ ), 3.90–3.95 (m, 2 H), 4.15 (dd,  $J_{5'a-4'} = 4.0$ ,  $J_{5'a-5'b} = 12.0$  Hz, 1 H,  $\text{H}_{5'a}$ ), 4.36 (dd,  $J_{5'b-4'} = 6.5$ ,  $J_{5'b-5'a} = 12.0$  Hz, 1 H,  $\text{H}_{5'b}$ ), 4.73 (br s, 1 H,  $\text{H}_3$ ), 6.09 (d,  $J_{1'-2'} = 3.5$  Hz, 1 H,  $\text{H}_{1'}$ ), 7.35–7.44 (m, 1 H,  $\text{H}_6$ ).

$^{13}\text{C NMR}$  (125 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta = -9.34$  ( $\text{CH}_3$ ,  $\text{SnMe}_3$ ), 19.95 ( $\text{CH}_3$ , Ac), 20.30 ( $\text{CH}_3$ , Ac), 27.42 ( $\text{CH}_3$ , Boc), 62.87 ( $\text{CH}_2$ , C-5'), 73.93 (CH), 79.05 (CH), 81.82 (CH), 86.02 ( $\text{CCH}_3$ , Boc), 87.05 (CH), 110.30 (C-5), 144.60 (CH, C-6), 149.09 (C=O, C-2), 149.55 (C=O, C-4), 163.66 (C=O, Boc), 169.37 ( $\text{CH}_3\text{CO}$ ), 169.77 ( $\text{CH}_3\text{CO}$ ). The corresponding signals for one set of  $\text{CH}_3\text{CO}$  were not found.

ESI-QTOF:  $m/z = 634.1$  [ $\text{M}^+$ ], 535.0 [ $\text{M} - \text{Boc} + 2\text{H}$ ] $^+$ , 635.0 [ $\text{M} + \text{H}$ ] $^+$ . Clustering of the peaks corresponding to isotope distribution of Sn was observed.

**3c**

$R_f = 0.55$  (*n*-hexane–EtOAc, 1:1); colorless oil.

$^1\text{H NMR}$  (500 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta = 0.20\text{--}0.33$  (m, 9 H,  $\text{SnMe}_3$ ), 1.40 (s, 3 H,  $\text{H}_{\text{Ac}}$ ), 1.43 (s, 9 H,  $\text{H}_{\text{Boc}}$ ), 1.44 (s, 3 H,  $\text{H}_{\text{Ac}}$ ), 1.69 (s, 3 H,  $\text{H}_{\text{Ac}}$ ), 3.73 (ddd,  $J_{4'-3'} = 4.0$ ,  $J_{4'-5'a} = 3.0$ ,  $J_{4'-5'b} = 6.0$  Hz, 1 H,  $\text{H}_{4'}$ ), 4.19 (dd,  $J_{5'a-4'} = 3.0$ ,  $J_{5'a-5'b} = 12.0$  Hz, 1 H,  $\text{H}_{5'a}$ ), 4.35 (dd,  $J_{5'b-4'} = 6.0$ ,  $J_{5'b-5'a} = 12.0$  Hz, 1 H,  $\text{H}_{5'b}$ ), 5.02 (br s, 1 H,  $\text{H}_{3'}$ ), 5.43 (dd,  $J_{2'-1'} = 4.0$ ,  $J_{2'-3'} = 1.5$  Hz, 1 H,  $\text{H}_{2'}$ ), 6.26 (d,  $J_{2'-1'} = 4.0$  Hz, 1 H,  $\text{H}_{1'}$ ), 7.24–7.33 (m, 1 H,  $\text{H}_6$ ).

$^{13}\text{C NMR}$  (125 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta = -9.35$  ( $\text{CH}_3$ ,  $\text{SnMe}_3$ ), 19.75 ( $\text{CH}_3$ , Ac), 19.78 ( $\text{CH}_3$ , Ac), 20.28 ( $\text{CH}_3$ , Ac), 27.35 ( $\text{CH}_3$ , Boc), 62.33 ( $\text{CH}_2$ , C-5'), 75.01 (CH), 76.29 (CH), 80.87 (CH), 84.94 ( $\text{CCH}_3$ , Boc), 86.06 (CH), 111.06 (C-5), 143.41 (C-H, C-6), 148.58 (C=O, C-2), 149.21 (C=O, C-4), 162.80\* (C=O, Boc), 168.03 ( $\text{CH}_3\text{CO}$ ), 169.17 ( $\text{CH}_3\text{CO}$ ), 169.72 ( $\text{CH}_3\text{CO}$ ). \* = very weak signal.

ESI-QTOF:  $m/z = 634.1$  [ $\text{M}^+$ ], 535.0 [ $\text{M} - \text{Boc} + 2\text{H}$ ] $^+$ , 635.0 [ $\text{M} + \text{H}$ ] $^+$ , 652.1 [ $\text{M} + \text{NH}_4$ ] $^+$ , 673.0 [ $\text{M} + \text{K}$ ] $^+$ . Clustering of the peaks corresponding to isotope distribution of Sn was observed.

**5-Fluoro-2',3',5'-tri-O-acetyl Arabinosyl Uridine (5)**

To a dried round-bottomed flask (25 mL), compound **4** (100 mg, 0.19 mmol), MeCN (15 mL) and Selectfluor (69 mg, 0.20 mmol) were added. The mixture was stirred at 55 °C for 10 h, during which the progress of the reaction was followed by TLC, until the starting material **4** [ $R_f = 0.78$  (*n*-hexane–acetone, 1:1)] had been consumed (~10 h). The solvent was removed and the crude mixture was purified by column chromatography (*n*-hexane–EtOAc, 3:2).

Yield: 25 mg (30%); white foam;  $R_f = 0.50$  (*n*-hexane–acetone, 1:1).

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta = 2.05$  (s, 3 H,  $\text{H}_{\text{Ac}}$ ), 2.13 (s, 3 H,  $\text{H}_{\text{Ac}}$ ), 2.13 (s, 3 H,  $\text{H}_{\text{Ac}}$ ), 4.19 (ddd,  $J_{4'-5'a} = 4.0$ ,  $J_{4'-3'} = 4.0$ ,  $J_{4'-5'b} = 6.0$  Hz, 1 H,  $\text{H}_{4'}$ ), 4.36 (dd,  $J_{5'a-4'} = 4.0$ ,  $J_{5'a-5'b} = 12.0$  Hz, 1 H,  $\text{H}_{5'a}$ ), 4.43 (dd,  $J_{5'b-4'} = 6.0$ ,  $J_{5'b-5'a} = 12.0$  Hz, 1 H,  $\text{H}_{5'b}$ ), 5.09 (dd,  $J_{3'-4'} = 4.0$ ,  $J_{3'-2'} = 2.0$  Hz, 1 H,  $\text{H}_{3'}$ ), 5.42 (dd,  $J_{2'-3'} = 2.0$ ,  $J_{2'-1'} = 4.0$  Hz, 1 H,  $\text{H}_{2'}$ ), 6.23 (dd,  $J_{1'-2'} = 4.0$ ,  $J_{1'-F} = 1.0$  Hz, 1 H,  $\text{H}_{1'}$ ), 7.63 (d,  $J_{6-F} = 7.0$  Hz, 1 H,  $\text{H}_6$ ), 8.26 (d,  $J_{\text{NH-F}} = 7.0$  Hz, 1 H, NH).

$^{19}\text{F NMR}$  (470.7 MHz,  $\text{CDCl}_3$ ):  $\delta = -165.21$  (dd,  $J_{F-6} = 7.0$ ,  $J_{F-\text{NH}} = 7.0$  Hz, 1 F).

ESI-QTOF:  $m/z = 388.1$  [ $\text{M}^+$ ], 389.0 [ $\text{M} + \text{H}$ ] $^+$ , 411.0 [ $\text{M} + \text{Na}$ ] $^+$ , 799.2 [ $2 \times \text{M} + \text{Na}$ ] $^+$ .

**5-Fluoro Arabinosyl Uridine (6)**

To a solution of **5** (25 mg) in MeOH (1 mL), NaOMe in MeOH (0.2 M, 1 mL) was added and the reaction was stirred for 30 min [monitored by TLC (MeOH– $\text{CHCl}_3$ , 1:3)]. The resulting solution was treated with Dowex 500 (500 mg, WX8-400,  $\text{H}^+$  form) and filtered. After evaporation under reduced pressure at 40 °C, the crude product **6** was obtained as a colorless solid (16 mg, 95%). Further purification was performed by RP-HPLC (Agilent 1100), sample loop (500  $\mu\text{L}$ ), semipreparative column (C-18, 10  $\times$  250 mm, 5  $\mu\text{m}$ ; MeOH– $\text{H}_2\text{O}$ , 3:7; 3 mL/min) with UV detection at 260 nm.

$^1\text{H NMR}$  (500 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta = 3.78$  (dd,  $J_{5'a-4'} = 5.0$ ,  $J_{5'a-5'b} = 12.0$  Hz, 1 H,  $\text{H}_{5'a}$ ), 3.82 (dd,  $J_{5'b-4'} = 3.5$ ,  $J_{5'b-5'a} = 12.0$  Hz, 1 H,  $\text{H}_{5'b}$ ), 3.90 (ddd,  $J_{4'-3'} = 3.5$ ,  $J_{4'-5'a} = 5.0$ ,  $J_{4'-5'b} = 3.5$  Hz, 1 H,  $\text{H}_{4'}$ ), 4.06 (dd,  $J_{3'-2'} = 3.0$ ,  $J_{3'-4'} = 3.5$  Hz, 1 H,  $\text{H}_{3'}$ ), 4.16 (dd,  $J_{2'-1'} = 3.0$ ,  $J_{2'-3'} = 3.0$  Hz, 1 H,  $\text{H}_{2'}$ ), 6.09 (dd,  $J_{1'-2'} = 3.0$ ,  $J_{1'-F} = 4.0$  Hz, 1 H,  $\text{H}_{1'}$ ), 8.03 (d,  $J_{6-F} = 7.0$  Hz, 1 H,  $\text{H}_6$ ).

$^{19}\text{F NMR}$  (470.7 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta = -171.10$  (br d,  $J_{F-6} = 7.0$  Hz, 1 F).

ESI-QTOF:  $m/z = 262.1$  [ $\text{M}^+$ ], 263.0 [ $\text{M} + \text{H}$ ] $^+$ , 285.0 [ $\text{M} + \text{Na}$ ] $^+$ , 547.1 [ $2 \times \text{M} + \text{Na}$ ] $^+$ .

**3-N-Boc-5-fluoro-2',3',5'-tri-O-acetyl Arabinosyl Uridine (7)**

Following the procedure for the preparation of **5** above, **3a** (10 mg, 0.02 mmol), MeCN (1.5 mL) and Selectfluor (8 mg, 0.02 mmol) were stirred at 50 °C for 5 h to give the crude product **7**, which was purified by column chromatography (*n*-hexane–EtOAc, 3:1) and normal-phase HPLC (EtOAc–*n*-hexane, 1:3).

Yield: 4 mg (50%); colorless oil.

$^1\text{H NMR}$  (600 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta = 1.38$  (s, 3 H,  $\text{H}_{\text{Ac}}$ ), 1.40 (s, 3 H,  $\text{H}_{\text{Ac}}$ ), 1.65 (s, 3 H,  $\text{H}_{\text{Ac}}$ ), 1.71 (s, 9 H,  $\text{H}_{\text{Boc}}$ ), 3.74 (ddd,  $J_{4'-5'a} = 4.2$ ,  $J_{4'-3'} = 7.8$ ,  $J_{4'-5'b} = 6.0$  Hz, 1 H,  $\text{H}_{4'}$ ), 4.08 (dd,  $J_{5'a-4'} = 4.2$ ,  $J_{5'a-5'b} = 12.0$  Hz, 1 H,  $\text{H}_{5'a}$ ), 4.23 (dd,  $J_{5'b-4'} = 6.0$ ,  $J_{5'b-5'a} = 12.0$  Hz, 1 H,  $\text{H}_{5'b}$ ), 4.95 (br s, 1 H,  $\text{H}_{3'}$ ), 5.46 (dd,  $J_{2'-3'} = 4.2$ ,  $J_{2'-1'} = 3.0$ , 1 H,  $\text{H}_{2'}$ ), 6.18 (d,  $J_{1'-2'} = 3.0$  Hz, 1 H,  $\text{H}_{1'}$ ), 7.44 (s,  $J_{6-F} = 5.4$  Hz, 1 H,  $\text{H}_6$ ).

$^{13}\text{C NMR}$  (150.77 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta = 19.62$  ( $\text{CH}_3$ , Ac), 19.80 ( $\text{CH}_3$ , Ac), 20.14 ( $\text{CH}_3$ , Ac), 29.61 ( $\text{CH}_3$ , Boc), 62.27 ( $\text{CH}_2$ , C-5'), 63.64 ( $\text{CCH}_3$ , Boc), 74.64 (CH), 76.07 (CH), 80.56 (CH), 85.19 (CH), 120.68 (d,  $J_{\text{C6-F}} = 35.1$  Hz, C-6, CH), 140.12 (d,  $J_{\text{C6-F}} = 231.6$  Hz, C-5), 149.98 (C=O, C-2), 158.26 (C=O, C-4), 158.42 (C=O, Boc), 168.31 ( $\text{CH}_3\text{CO}$ ), 169.10 ( $\text{CH}_3\text{CO}$ ), 169.82 ( $\text{CH}_3\text{CO}$ ).

$^{19}\text{F NMR}$  (564.2 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta = -163.60$  (br s, 1 F).

ESI-Q-TOF:  $m/z = 488.1$  [ $\text{M}^+$ ], 371.0 [ $\text{M} - \text{Boc} + 2\text{H}$ ] $^+$ , 511.1 [ $\text{M} + \text{Na}$ ] $^+$ .

**3-N-Boc-5-ethynyl-2',3',5'-tri-O-acetyl Arabinosyl Uridine (9)**

Compound **8** (569 mg, 1.4 mmol),  $(\text{Boc})_2\text{O}$  (1.1 mL, 4.9 mmol) and THF (30 mL) were stirred at 80 °C for 5 min. The solution was allowed to come to r.t. then DMAP (176 mg, 1.44 mmol) was added and the mixture was stirred for 4 h [reaction monitored by TLC (*n*-

hexane–acetone, 1:1)]. The reaction mixture was isolated as described for compound **2**, then the crude product was purified by column chromatography (*n*-hexane–acetone, 8:2→7:3).

Yield: 37% (264 mg); white solid; mp 143–144 °C.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 1.57 (s, 9 H, 3 × CH<sub>3</sub>, Boc), 2.05 (s, 3 H, H<sub>Ac</sub>), 2.10 (s, 3 H, H<sub>Ac</sub>), 2.15 (s, 3 H, H<sub>Ac</sub>), 3.18 (s, 1 H, H<sub>8</sub>), 4.19 (ddd, *J*<sub>4'-3'</sub> = 4.0, *J*<sub>4'-5'a</sub> = 4.5, *J*<sub>4'-5'b</sub> = 4.5 Hz, 1 H, H<sub>4'</sub>), 4.38 (d, *J*<sub>5'-4'</sub> = 4.5 Hz, 2 H, H<sub>5'</sub>), 5.12 (dd, *J*<sub>3'-2'</sub> = 3.0, *J*<sub>3'-4'</sub> = 4.0 Hz, 1 H, H<sub>3'</sub>), 5.46 (dd, *J*<sub>2'-3'</sub> = 2.5, *J*<sub>2'-1'</sub> = 4.5 Hz, 1 H, H<sub>2'</sub>), 6.23 (d, *J*<sub>1'-2'</sub> = 4.0 Hz, 1 H, H<sub>1'</sub>), 7.84 (s, 1 H, H<sub>6</sub>).

<sup>13</sup>C NMR (125.70 MHz, CDCl<sub>3</sub>): δ = 20.41 (CH<sub>3</sub>, Ac), 20.59 (CH<sub>3</sub>, Ac), 20.78 (CH<sub>3</sub>, Ac), 27.34 (CH<sub>3</sub>, Boc), 62.20 (CH<sub>2</sub>, C-5'), 74.14 (CH), 75.19 (CH), 80.36 (CH), 82.34 (CH), 82.34 (C-7), 84.38 (CH), 87.61 (CCH<sub>3</sub>, Boc), 98.57 (C-5), 142.83 (CH), 146.43 (C=O, C-2), 147.09 (C=O, C-4), 158.53 (C=O, Boc), 168.50 (CH<sub>3</sub>CO), 169.53 (CH<sub>3</sub>CO), 170.36 (CH<sub>3</sub>CO).

ESI-QTOF: *m/z* = 494.2 [M<sup>+</sup>], 495.0 [M + H]<sup>+</sup>, 517.0 [M + Na]<sup>+</sup>, 533.0 [M + K]<sup>+</sup>, 395.0 [M – Boc + 2H]<sup>+</sup>, 417.0 [M – Boc + H + Na]<sup>+</sup>, 433.0 [M – Boc + H + K]<sup>+</sup>.

### 3-Boc-(*E*)-5-(2-tributylstannylvinyl)-2',3',5'-tri-*O*-acetyl Arabinosyl Uridine (**10**)

The preparation was based on the literature procedure<sup>11d</sup> using **9** (200 mg, 0.4 mmol), HSnBu<sub>3</sub> (688 mg, 2.36 mmol) and AIBN (40 mg, 0.238 mmol). The crude mixture was purified by column chromatography (*n*-hexane–EtOAc, 4:1).

Yield: 272 mg, (86%); white waxy solid.

<sup>1</sup>H NMR (500 MHz, C<sub>6</sub>D<sub>6</sub>): δ = 0.93 (t, *J* = 7.5 Hz, 9 H, 3 × CH<sub>3</sub>, *n*-Bu), 1.01 (t, *J* = 8.5 Hz, 6 H, 3 × CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, *n*-Bu), 1.37 (sextet, *J* = 7.5 Hz, 6 H, 3 × CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, *n*-Bu), 1.42 (s, 3 H, H<sub>Ac</sub>), 1.44 (s, 9 H, H<sub>Boc</sub>), 1.48 (s, 3 H, H<sub>Ac</sub>), 1.61 (quintet, *J* = 7.5 Hz, 6 H, 3 × CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, *n*-Bu), 1.77 (s, 3 H, H<sub>Ac</sub>), 3.73 (ddd, *J*<sub>4'-5'a</sub> = 3.0, *J*<sub>4'-3'</sub> = 4.0, *J*<sub>4'-5'b</sub> = 6.0 Hz, 1 H, H<sub>4'</sub>), 4.07 (dd, *J*<sub>5'-4'</sub> = 3.5, *J*<sub>5'a-5'b</sub> = 12.0 Hz, 1 H, H<sub>5'a</sub>), 4.34 (dd, *J*<sub>5'b-4'</sub> = 6.0, *J*<sub>5'b-5'a</sub> = 12.0 Hz, 1 H, H<sub>5'b</sub>), 4.97 (s, 1 H, H<sub>3'</sub>), 5.47 (dd, *J*<sub>2'-3'</sub> = 2.0, *J*<sub>2'-1'</sub> = 4.0, 1 H, H<sub>2'</sub>), 6.16 (d, *J*<sub>1'-2'</sub> = 4.0 Hz, 1 H, H<sub>1'</sub>), 7.00 (d, *J*<sub>8-7</sub> = 19.5 Hz, 1 H, H<sub>8</sub>), 7.35 (d, *J*<sub>7-8</sub> = 19.5 Hz, 1 H, H<sub>7</sub>), 7.62 (s, 1 H, H<sub>6</sub>).

<sup>13</sup>C NMR (125.70 MHz, C<sub>6</sub>D<sub>6</sub>): δ = 9.80 [CH<sub>2</sub>, (*n*-Bu)<sub>3</sub>], 13.90 [CH<sub>3</sub>, (*n*-Bu)<sub>3</sub>], 19.63 (CH<sub>3</sub>, Ac), 19.80 (CH<sub>3</sub>, Ac), 20.40 (CH<sub>3</sub>, Ac), 27.35 (CH<sub>3</sub>, Boc), 27.65 [CH<sub>2</sub>, (*n*-Bu)<sub>3</sub>], 29.49 [CH<sub>2</sub>, (*n*-Bu)<sub>3</sub>], 62.06 (CH<sub>2</sub>, C-5'), 74.63 (CH), 75.94 (CH), 81.07 (CH), 85.16 (CH), 86.30 (CCH<sub>3</sub>), 113.10 (C-5), 131.50 (CH), 135.57 (CH), 136.88 (CH), 147.87 (C=O, C-2), 148.07 (C=O, C-4), 159.67 (C=O, Boc), 168.17 (CH<sub>3</sub>CO), 169.19 (CH<sub>3</sub>CO), 169.72 (CH<sub>3</sub>CO).

ESI-QTOF: *m/z* = 784.2 [M<sup>+</sup>], 807.5 [M + Na]<sup>+</sup>, 685.3 [M – Boc + H]<sup>+</sup>, 707.4 [M – Boc + Na]<sup>+</sup>. Clustering of the peaks corresponding to isotope distribution of Sn was observed.

### 1-(2',3',5'-Tri-*O*-acetyl-β-*D*-arabinofuranosyl)-(*E*)-5-(2-fluorovinyl)pyrimidin-2,4-(3*H*)-dione (**12**)

A mixture of **11**<sup>11e</sup> (240 mg, 0.348 mmol), MeCN (30 mL) and Selectfluor (120 mg, 0.35 mmol) were stirred at r.t. for 6 h, until the starting material (*R*<sub>f</sub> = 0.73; *n*-hexane–acetone, 1:1) had been consumed. Column chromatography (EtOAc–*n*-hexane, 1:1) and normal-phase HPLC (EtOAc–*n*-hexane, 1:1) gave the pure product **12**.

Yield: 9 mg (8%); *R*<sub>f</sub> = 0.50 (*n*-hexane–acetone, 1:1).

<sup>1</sup>H NMR (500 MHz, C<sub>6</sub>D<sub>6</sub>): δ = 1.45 (s, 3 H, H<sub>Ac</sub>), 1.49 (s, 3 H, H<sub>Ac</sub>), 1.72 (s, 3 H, H<sub>Ac</sub>), 3.88 (ddd, *J*<sub>4'-5'a</sub> = 4.0, *J*<sub>4'-3'</sub> = 4.0, *J*<sub>4'-5'b</sub> = 7.0 Hz, 1 H, H<sub>4'</sub>), 4.09 (dd, *J*<sub>5'-4'</sub> = 4.0, *J*<sub>5'a-5'b</sub> = 12.0 Hz, 1 H, H<sub>5'a</sub>), 4.51 (dd, *J*<sub>5'b-4'</sub> = 7.0, *J*<sub>5'b-5'a</sub> = 12.0 Hz, 1 H, H<sub>5'b</sub>), 4.97 (br s, 1 H, H<sub>3'</sub>), 5.42 (dd, *J*<sub>2'-3'</sub> = 1.5, *J*<sub>2'-1'</sub> = 4.0 Hz, 1 H, H<sub>2'</sub>), 6.06 (dd, *J*<sub>7-8</sub> = 11.0,

*J*<sub>7-F</sub> = 22.0 Hz, 1 H, H<sub>7</sub>), 6.31 (dd, *J*<sub>1'-2'</sub> = 4.0 Hz, 1 H, H<sub>1'</sub>), 7.36 (s, 1 H, H<sub>6</sub>), 7.53 (s, 1 H, NH), 8.33 (dd, *J*<sub>8-7</sub> = 11.0, *J*<sub>8-F</sub> = 86.5 Hz).

<sup>19</sup>F NMR (470.7 MHz, C<sub>6</sub>D<sub>6</sub>): δ = –122.56 (dd, *J*<sub>F-7</sub> = 22.0, *J*<sub>F-8</sub> = 86.5 Hz, 1 F).

ESI+Q–TOF: *m/z* = 414.1 [M<sup>+</sup>], 415.1 [M + H]<sup>+</sup>, 437.1 [M + Na]<sup>+</sup>.

### 1-(β-*D*-Arabinofuranosyl)-(*E*)-5-(2-fluorovinyl)pyrimidin-2,4-(3*H*)-dione (**13**)

Compound **12** (3 mg, 8 μmol), MeOH (1 mL) and a solution of NaOMe in MeOH (25 mM, 1 mL) were used as described for the preparation of **6**. Treatment with Dowex 500 (50 mg, WX8-400, H<sup>+</sup> form) and concentration gave **13** as a colorless oil (2 mg, 95%). An analytical sample was obtained by purification with RP HPLC as described above for compound **6**.

<sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>OD): δ = 3.78 (dd, *J*<sub>5'a-4'</sub> = 5.0, *J*<sub>5'a-5'b</sub> = 12.0 Hz, 1 H, H<sub>5'a</sub>), 3.82 (dd, *J*<sub>5'b-4'</sub> = 3.5, *J*<sub>5'b-5'a</sub> = 12.0 Hz, 1 H, H<sub>5'b</sub>), 3.90 (ddd, *J*<sub>4'-3'</sub> = 3.8, *J*<sub>4'-5'a</sub> = 5.2, *J*<sub>4'-5'b</sub> = 3.5 Hz, 1 H, H<sub>4'</sub>), 4.05 (dd, *J*<sub>3'-2'</sub> = 3.8, *J*<sub>3'-4'</sub> = 3.8 Hz, 1 H, H<sub>3'</sub>), 4.15 (dd, *J*<sub>2'-1'</sub> = 4.8, *J*<sub>2'-3'</sub> = 3.8 Hz, 1 H, H<sub>2'</sub>), 6.06 (dd, *J*<sub>7-8</sub> = 11.2, *J*<sub>7&ndash;8;F</sub> = 22.6 Hz, 1 H, H<sub>7</sub>), 6.11 (dd, *J*<sub>1'-2'</sub> = 4.8 Hz, 1 H, H<sub>1'</sub>), 7.58 (s, 1 H, H<sub>6</sub>), 7.66 (dd, *J*<sub>8-7</sub> = 11.2, *J*<sub>8-F</sub> = 87.5 Hz).

<sup>19</sup>F NMR (564.8 MHz, CD<sub>3</sub>OD, CFCl<sub>3</sub>): δ = –126.88 (dd, *J*<sub>F-7</sub> = 22.6, *J*<sub>F-8</sub> = 87.5 Hz, 1 F).

ESI-QTOF: *m/z* = 288.1 [M<sup>+</sup>], 289.1 [M + H]<sup>+</sup>, 311.0 [M + Na]<sup>+</sup>, 577.1 [2 × M + H]<sup>+</sup>, 599.1 [2 × M + Na]<sup>+</sup>.

### 3-Boc-(*E*)-5-(2-fluorovinyl)-2',3',5'-tri-*O*-acetyl Arabinosyl Uridine (**14**)

Following the procedure for the preparation of **5** above, compound **10** (50 mg, 0.06 mmol), MeCN (4 mL) and Selectfluor (44 mg, 0.12 mmol) were stirred at r.t. for 4 h to give the crude product **14**, which was purified by column chromatography (*n*-hexane–EtOAc, 7:3→5:4). An analytical sample was obtained by purification with normal-phase HPLC.

Yield: 3 mg (10%).

<sup>1</sup>H NMR (600 MHz, C<sub>6</sub>D<sub>6</sub>): δ = 1.34 (s, 3 H, H<sub>Ac</sub>), 1.36 (s, 3 H, H<sub>Ac</sub>), 1.40 (s, 9 H, H<sub>Boc</sub>), 1.57 (s, 3 H, H<sub>Ac</sub>), 3.68 (dddd, *J*<sub>4'-2'</sub> = 0.84, *J*<sub>4'-5'b</sub> = 3.3, *J*<sub>4'-3'</sub> = 3.6, *J*<sub>4'-5'a</sub> = 6.6 Hz, 1 H, H<sub>4'</sub>), 3.93 (dd, *J*<sub>5'a-4'</sub> = 3.3, *J*<sub>5'a-5'b</sub> = 12.0 Hz, 1 H, H<sub>5'a</sub>), 4.30 (dd, *J*<sub>5'b-4'</sub> = 6.6, *J*<sub>5'b-5'a</sub> = 12.0 Hz, 1 H, H<sub>5'b</sub>), 4.87 (br s, 1 H, H<sub>3'</sub>), 5.37 (ddd, *J*<sub>2'-4'</sub> = 0.84, *J*<sub>2'-3'</sub> = 2.5, *J*<sub>2'-1'</sub> = 4.3, 1 H, H<sub>2'</sub>), 5.84 (dd, *J*<sub>8-7</sub> = 10.9, *J*<sub>8-F</sub> = 21.6 Hz, 1 H, H<sub>7</sub>), 6.06 (d, *J*<sub>1'-2'</sub> = 4.2 Hz, 1 H, H<sub>1'</sub>), 7.14 (s, 1 H, H<sub>6</sub>), 8.09 (dd, *J*<sub>8-7</sub> = 10.9, *J*<sub>7-F</sub> = 86.3 Hz, 1 H, H<sub>8</sub>).

<sup>13</sup>C NMR (150.77 MHz, C<sub>6</sub>D<sub>6</sub>): δ = 19.27 (CH<sub>3</sub>, Ac), 19.48 (CH<sub>3</sub>, Ac), 19.92 (CH<sub>3</sub>, Ac), 27.06 (CH<sub>3</sub>, Boc), 61.73 (CH<sub>2</sub>, C-5'), 74.13 (CH), 75.32 (CH), 80.70 (CH), 84.83 (CH), 86.36 (CCH<sub>3</sub>, Boc), 106.40 (d, *J*<sub>C7-F</sub> = 21.7 Hz, C-7), 107.50 (C-5), 135.70 (C-6, CH), 147.22 (C=O, C-2), 147.40 (C=O, C-4), 152.86 (d, *J*<sub>C8-F</sub> = 259.6 Hz, C-8), 158.53 (C=O, Boc), 167.84 (CH<sub>3</sub>CO), 168.84 (CH<sub>3</sub>CO), 169.67 (CH<sub>3</sub>CO).

<sup>19</sup>F NMR (564.2 MHz, C<sub>6</sub>D<sub>6</sub>, CFCl<sub>3</sub>): δ = –63.6 (dd, *J*<sub>F-7</sub> = 21.6, *J*<sub>F-8</sub> = 86.3 Hz).

ESI-QTOF: *m/z* = 514.2 [M<sup>+</sup>], 515.2 [M + H]<sup>+</sup>, 532.2 [M + NH<sub>4</sub>]<sup>+</sup>, 537.2 [M + Na]<sup>+</sup>, 415.1 [M – Boc + H]<sup>+</sup>, 437.1 [M – Boc + H + Na]<sup>+</sup>, 453.1 [M – Boc + H + K]<sup>+</sup>.

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