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Synthesis of 5-Fluoroalkylated Pyrimidine Nucleosides via Negishi Cross-Coupling

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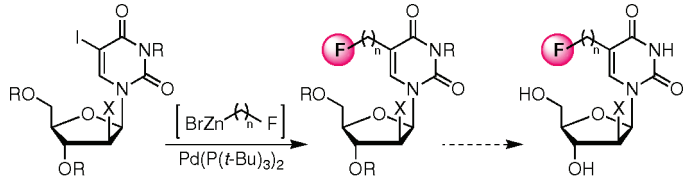
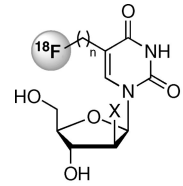


R = Bz; X = H or F; n = 3, 4, 5

5-Fluoroalkylated pyrimidine nucleosides (**1**) have potential as therapeutic agents and molecular imaging agents targeting HSV1-*tk* suicide gene therapy. Thus, straightforward preparation of 5-fluoroalkylated nucleoside derivatives has been developed. Reported herein are the first examples of Pd-catalyzed Negishi cross-coupling of 3-*N*-benzoyl-3′,5′-di-*O*-benzoyl-5-iodo-2′-deoxyuridine (**2a**) and 3-*N*-benzoyl-3′,5′-di-*O*-benzoyl-5-iodo-2′-deoxy-2′-fluoroarabinouridine (**2b**) with unactivated Csp^3 fluoroalkylzinc bromides. This paper demonstrates the first synthesis of six 5-fluoroalkyl-2′-deoxypyrimidine nucleoside derivatives with three to five methylene chain lengths (**5**). Furthermore, this methodology has been extended to create a series of 13 5-alkyl-substituted nucleosides, including the target nucleosides **5** and 5-silyloxypropyl and 5-cyanobutyl derivatives.

Introduction

The convenient access to functionalized nucleosides has been driven by the demonstrated pharmacological activity of nucleoside analogues against a broad spectrum of biological targets.[1] In particular, several 5-substituted pyrimidine nucleosides show potent and selective antiherpes activity.[2] The selectivity of pyrimidine nucleosides for herpes-infected cells is due to the specific phosphorylation of nucleoside substrates by the virus-encoded thymidine kinase, HSV1-TK. Parallel to this paradigm, the HSV1-*tk* gene expressing the HSV1-TK protein[3] has been exploited as an important strategy for the suicide gene therapy of cancer where transduced cancer cells expressing the viral protein are made more sensitive to nucleoside therapy.[4] Our research interest is in the development of ^{18}F-radiolabeled[5] 5-fluoroalkylated pyrimidine nucleosides ([^{18}F]**1a**−**f**) (Figure 1) that can be used as probes for the noninvasive in vivo molecular imaging of HSV1-TK in genetically transduced cells to correlate with the effectiveness of gene therapy and to monitor chemo-



[^{18}F]1a-f
[^{18}F]**1a** (n = 3, X = H)
[^{18}F]**1b** (n = 3, X = F)
[^{18}F]**1c** (n = 4, X = H)
[^{18}F]**1d** (n = 4, X = F)
[^{18}F]**1e** (n = 5, X = H)
[^{18}F]**1f** (n = 5, X = F)

FIGURE 1. Structure of 5-[^{18}**F**]fluoroalkyl nucleosides as molecular imaging agents for HSV1-*tk* gene therapy.

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(1) For examples, see: (a) Galmarini, C.; Mackey, J.; Dumontet, C. *Lancet Oncol.* **2002**, *3*, 415–24. (b) Balzarini, J.; McGuigan, C. *J. Antimicrob. Chemother.* **2002**, *50*, 5–9. (c) Gumina, G.; Song, G.; Chu, C. *FEMS Microbiol. Lett.* **2001**, *202*, 9–15. (d) Jordheim, L. P.; Galmarini, C. M.; Dumontet, C. *Recent Patents Anticancer Drug Discov.* **2006**, *1*, 163–70.

(2) Kumar, R. *Curr. Med. Chem.* **2004**, *11*, 2749–66, and all references therein.

(3) Note that HSV1-*tk* denotes the gene and HSV1-TK denotes the protein (i.e., the gene product).

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(5) **CAUTION**: ^{18}F is a radioactive material (radioactive half-life ($t_{1/2}$) = 110 min, β^+ emission = 511 keV) and should only be used by trained research personnel with the appropriate safety precautions.

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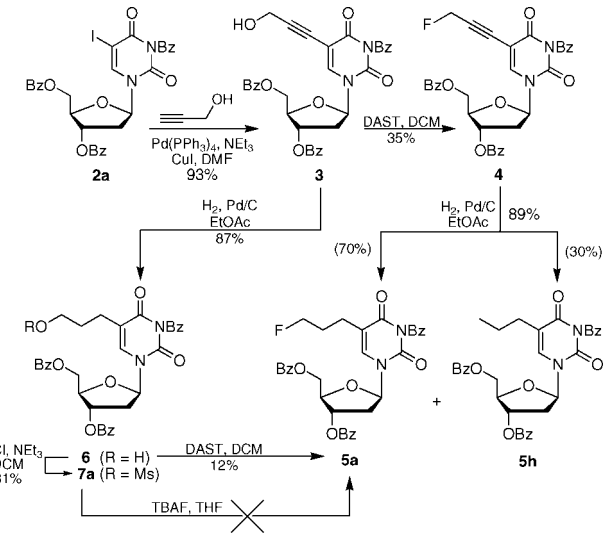
therapy.[6] These radioactive probes have been designed to allow for: (i) rapid and efficient preparation of **[^{18}F]1a−f** by convenient radiochemistry, (ii) assessment of the stability effect of the 2′-hydrogen vs 2′-fluorine on the glycosidic bond in vivo, and (iii) selective phosphorylation by HSV1-TK and thus accumulation in HSV1-TK expressing cells. However, in order to validate the preparation of the ^{18}F-labeled nucleosides, a practical synthesis of the nonradioactive molecules **1a−f** first needs to be developed. This research effort is also motivated by the potential antiviral and antitumor activity of these novel nucleosides.

Several synthetic approaches allow access to 5-fluoroalkylpyrimidine nucleosides. The classical approach calls for the preparation of 5-substituted uracils from corresponding 5-alkylbarbituric acids[7] followed by glycosylation of the uracils with reactive pentose derivatives.[8] This methodology suffers from typically low yields due to multiple steps, and extensive purification due to insufficient anomeric selectivity during the coupling step. A straightforward method to C-5-modified pyrimidine nucleosides is the palladium-catalyzed cross-coupling reactions of 5-iodouridine derivatives with terminal alkynes[9] or by means of an organometallic reagent of mercury,[10] stannane,[11] boron,[11c] or zinc,[12] for example. During our studies on the synthesis of HSV1-TK molecular imaging probes with a pyrimidine core, 3-*N*-benzoyl-3′,5′-di-*O*-benzoyl-5-iodo-2′-deoxyuridine (**2a**) and 3-*N*-benzoyl-3′,5′-di-*O*-benzoyl-5-iodo-2′-deoxy-2′-fluoroarabinouridine (**2b**), were found to be the key synthetic intermediates in metal-catalyzed cross-coupling reactions. These intermediates were readily accessible from 5-iodo-2′-deoxyuridine,[13,14] which is commercially available, or from 5-iodo-2′-deoxy-2′-fluoroarabinouridine[15] obtained following a modified literature procedure.[16]

Our initial approach to 5-fluoroalkyl nucleosides was to follow the palladium-catalyzed Sonogashira coupling route that has been reported by several groups.[9,17] One example is shown in Scheme 1 for the preparation of the tribenzoyl-protected 5-fluoropropyl-2′-deoxyuridine **5a**. The propargylated derivative **3** was obtained in very good yield, and the critical fluorination step, using DAST, afforded the fluoroalkyne **4** in moderate yields.[18] However, this synthetic route was plagued by the significant defluorination observed during hydrogenation of **4** using Pd/C as the catalyst, resulting in an inseparable mixture of products **5a** and **5h** (70:30 ratio, 89%). Our observation mirrored that of a report that monofluoro-substituted olefins, such as fluoroethene and 3-fluoropropene, tend to eliminate fluorine during the course of coupling reactions with palladium.[19] First hydrogenating **3**, then fluorinating the saturated alcohol **6** with DAST, avoided the fluorine-elimination route, although the limitation to this approach was the very low yield of **5a** (12%). TBAF was employed as an alternative fluorination method. However, reaction of mesylate **7a** with TBAF did not afford the fluorinated nucleoside **5a**. The disappointing results of this strategy, in particular, that of the hydrogenation step to **5a** and the fluorination step to **5a**, obviated the need to look at other strategies that allowed for direct coupling of the intact fluoroalkyl moiety.[20]

SCHEME 1. Synthesis of 5-(3-Fluoropropyl)pyrimidine Nucleoside 5a via Sonogashira Coupling Approach



The palladium-catalyzed Negishi cross-coupling reactions of organohalides with organozinc reagents are another well-established and powerful method to forming carbon−carbon bonds.[21] The ease in preparation,[22] the high functional group

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(20) For detailed syntheses of materials depicted in Scheme 1, see the Supporting Information.

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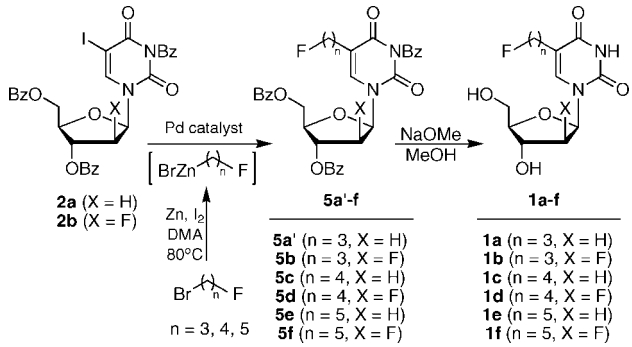
SCHEME 2. Synthesis of 5-Fluoroalkylated Pyrimidine Nucleosides 5a−f Using Saturated Fluoroalkylzincates



tolerance, and reactivity of organozinc reagents[21d] increases their synthetic utility. Contingent upon the preparation of the unactivated and saturated fluoroalkylzinc bromides from commercially available fluoroalkyl bromides, we chose the Negishi method to prepare our target nonradioactive nucleosides **1a**−**f**.

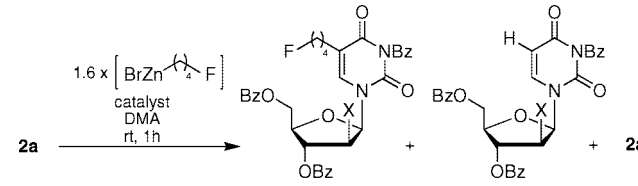
The first examples of Negishi coupling reactions employing 5-iodo-2′-deoxyuridine nucleosides described the Pd- or Ni-catalyzed Csp^2-Csp^2 coupling of alkynyl-, indolyl- and thienylzinc reagents to 5-iodo-3′,5′-di-*O*-bis-trimethylsilyl-protected 2′-deoxyuridine in 7−50% yields.[12] A trifluoroisopropenylzincate with a Csp^2 center was also successfully coupled to 5-iodo-3′,5′-di-*O*-benzoyl-protected 2′-deoxyuridine using $Pd(PPh_3)_4$ in 70% yield.[23] Most recent reports indicate zincated nucleosides as an entry into 5-aryl-substituted uridines (Csp^2-Csp^2 coupling).[24] However, to our knowledge, there exist no examples of Csp^2-Csp^3 cross-coupling reactions between 5-iodo-2′-deoxyuridine derivatives and unactivated and fully saturated alkylzincates. Reported herein are our efforts toward a convenient and efficient procedure for the preparation of 5-fluoroalkylated pyrimidine nucleosides **1a**−**f** by Negishi cross-coupling.

Results and Discussion

Our latest efforts to realize **1a**−**f** by the Negishi cross-coupling approach focused on a rapid one-step preparation of tribenzoyl-protected 5-fluoroalkyl nucleosides **5a′**−**f** from the strategic intermediates **2a**,**b** (Scheme 2) and commercially available saturated fluoroalkyl bromides. Again, although compounds **5a′**−**f** themselves would be inactive against HSV1-TK, they represent the key precursors toward the final target nucleosides **1a**−**f**.

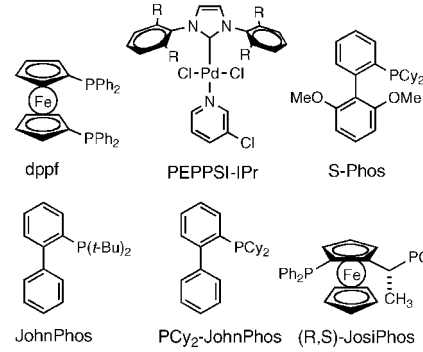
At the onset of our investigation, efforts were made to prepare the critical zinc reagent for subsequent coupling. Following an important report by Huo on the mild and facile preparation of alkylzinc bromides from alkyl bromides and 325-mesh zinc powder with catalytic amounts of iodine,[22a,25] we observed high conversion of 4-fluorobutyl bromide to (4-fluorobutyl)zinc bromide in our model reaction.[26] With the zinc reagent in hand, experimentation began by monitoring the effect of catalyst on

TABLE 1. Effect of Catalyst on the Negishi Coupling of (4-Fluorobutyl)zinc Bromide with 2a



entry	catalytic system	yield[a] (%) 5c	8	2a
1	$Pd(PPh_3)_4$ (5 mol %)	2	3	95
2	$Cl_2Ni(PPh_3)_2$ (5 mol %)	0	23	77
3	$Pd(dppf)Cl_2$ (5 mol %); CuI (6 mol %)	1	30	69
4	PEPPSI-IPr (5 mol %); LiBr (2 equiv)	1	9	90
5	$Pd(P(t\text{-}Bu_3)_2$ (5 mol %)	47[b]	31	12
6	$Pd(dba)_2$ (0.1 mol %); S-Phos (0.2 mol %)	5	10	85
7	Pd_2dba_3 (0.1 mol %); JohnPhos (0.2 mol %)	4	10	86
8	Pd_2dba_3 (0.1 mol %); PCy_2-JohnPhos (0.2 mol %)	0	2	98
9	Pd_2dba_3 (0.1 mol %); (*R*,*S*)-JosiPhos (0.2 mol %)	0	4	96

[a] HPLC yield. [b] Isolated yield: 43%.



the Negishi cross-coupling reaction of **2a** with (4-fluorobutyl)-zinc bromide, using the coupling conditions as described by Huo.[22a] Nine catalysts were selected for this analysis and the results of these experiments are summarized in Table 1. The $Pd(PPh_3)_4$ catalyst, which successfully coupled the activated isopropenylzinc reagent with the dibenzoyl-protected 5-iodo-2′-deoxyuridine,[23] as described previously, afforded trace amounts of the coupling product **5c** (entry 1, Table 1).[27] Employing a variety of catalytic systems shown to be effective in Negishi coupling reactions, including $Cl_2Ni(PPh_3)_2$[22a] and $Pd(dppf)Cl_2$,[28] afforded the product in negligible yields (entries 2 and 3, Table 1). In addition, the Pd−N-heterocyclic carbene (NHC) catalyst, PEPPSI-IPr,[29] did not yield any appreciable product (entry 4, Table 1).

Unlike the previous catalysts, experiments with $Pd(P(t\text{-}Bu)_3)_2$[30] gave very encouraging results (entry 5, Table 1). We observed the coupling product **5c** in 47% yield. The major byproduct isolated is the deiodinated nucleoside **8**, in which the iodide is replaced by hydrogen. The reason for this exchange has not been investigated.

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(25) Efforts were made to prepare the fluoroalkylzinc bromides using commercial Rieke zinc. Even in large excess, the active zinc suspension in THF (Aldrich) was not able to convert the fluoroalkyl bromide to the corresponding zinc reagent.

(26) Concentration of fluoroalkylzinc bromide was determined by titration of an aliquot with iodine. For further detail, see: Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, 890–891.

(27) Reactions were monitored by RP-HPLC at 268 nm and products isolated where indicated. Details are outlined in the Supporting Information.

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However, the major side product **8** would most likely arise from competitive β-hydride elimination of the nucleoside-Pd(II)-alkyl intermediate as opposed to the desired reductive elimination of the same intermediate Pd(II) species to yield the coupled product. Subsequent reductive elimination of the nucleoside−Pd-H intermediate would form the deiodinated product **8**. It may be suggested that acceleration of the reductive elimination step of the second intermediate Pd(II) species is critical to maximizing the yield of these reactions.

Bulky biphenylphosphine ligands are reported as improving Pd-catalyzed coupling yields by suppressing the tendency for destructive β-hydride elimination, thus favoring reductive elimination.[31] Contrary to expectations, bulky Buchwald ligands such as S-Phos,[24b,32] cyclohexylJohnPhos (PCy_2-JohnPhos),[32] JohnPhos,[33] and the Solvias ligand (*R*,*S*)-JosiPhos[34] did not improve the coupling yields (entries 6−9, Table 1). Apparently, for most of the catalytic systems employed, oxidative addition was the rate-limiting step in the Negishi cross-coupling reactions as evidenced by the substantial recovery of starting material **2a**.

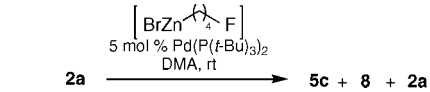
These initial experiments established that in our system, $Pd(P(t\text{-}Bu)_3)_2$ is the most effective catalyst in achieving cross-coupling between **2a** and (4-fluorobutyl)zinc bromide. Having obtained the coupling product we focused on further optimizing the reaction by increasing the consumption of the starting material **2a** and by increasing the ratio between product **5c** and deiodinated nucleoside **8** (i.e., reductive elimination vs β-hydride elimination).

Upon a more detailed investigation into the optimization of the coupling conditions several interesting observations were made (Table 2). A 1.6:1 ratio of Zn reagent/nucleoside resulted in a reasonably good yield within 1 h (entries 1−4, Table 2). Even more impressively, an increase in the stoichiometry increased the rate of reaction to afford the same product ratios in half the time (entries 5−12, Table 2) and lead to maximal consumption of the starting material. The reaction time is a critical factor due to the HPLC detection of degradation products within 30 min of initiation of the reaction, which typically increased in relative intensity with longer reaction times. The data also suggested that the stability of the nucleoside in the reaction mixture was dependent on the Zn reagent/nucleoside ratio since degradation products were observed to a greater degree and isolated yields are lower with larger excesses of Zn reagent (entries 8, 12, and 13, Table 2). Regardless of the stoichiometry of reagents used, no more than 53% of **5c** could be obtained in any of the coupling conditions investigated. Furthermore, the ratio of **5c** to **8** remained more or less constant, and there typically remained trace amounts of starting material **2a**. As such, based on isolated yields, entry 6 of Table 2 was chosen as the optimized Negishi cross-coupling condition.

Preparation of a Series of 5-Alkylated Nucleoside Derivatives. To demonstrate the utility and versatility of the optimized Negishi cross-coupling methodology, a series of 5-alkylated nucleosides derivatives, including our desired 5-fluoroalkyl nucleosides **5a′**−**f**, were prepared using a variety of alkylzinc reagents (Table 3). The zinc reagents could be successfully coupled to the nucleosides **2a** or **2b** in appreciable yields. As expected, (4-fluorobutyl)zinc and (5-fluoropentyl)zinc bromides were prepared in high yields (>0.74 M) following the Huo method,[22a] and subsequent coupling to **2a, 2b** afforded the coupling products **5c**−**f** in moderate yields (entries 4−7, Table 3). Interestingly, attempts at preparing the short-chained (3-fluoropropyl)zinc and (2-fluoroethyl)zinc bromides were unsuccessful (entries 1 and 8, Table 3). Using the more reactive 3-iodo-1-fluoropropane, we obtained the corresponding alkylzinc iodide reagent, albeit in lower yields as compared to the longer chain fluoroalkylzinc bromides.[35] Cross-coupling of the zinc reagent with **2a**,**b** afforded the coupled products **5a′**,**b** after 24 h in very low yield (≤8%) (entry 2 and 3, Table 3). In an analogous fashion, short chain alkanes were coupled to **2a** through an alkylzinc iodide intermediate (entries 9−11, Table 3). The nucleosides **5g**−**i** were generated in low yields (15−23%) but it is important to note that they were obtained in yields higher than those observed with the short chain fluoroalkyl zincates. This result suggests that the fluorine moiety confers instability to the desired zinc intermediate, thus leading to low (or no) yields of the zinc reagent and very low isolated yields of the coupling product.

The efficiency of Negishi cross-coupling reactions employing dialkylzinc derivatives[36] led us to explore the effect of using the dialkylzinc in place of the alkylzinc halides for cross-coupling reactions with **2a**. When using the commercially available $(n\text{-}Bu)_2Zn$, the nucleoside derivative **5g′** was easily prepared, and in much greater yield (44%) as compared to utilizing the monoalkylzinc reagent (15%) (entry 12, Table 3). There was no difference in the isolated yield of **5i′** (23%) when Et_2Zn vs EtZnI was used (entry 13, Table 3). Of note, however, is that either zinc reagent successfully generated nucleoside **5i/**

TABLE 2. Optimization of Negishi Cross-coupling Reaction Using $Pd(P(t\text{-}Bu)_3)_2$ under Various Conditions



			yield[a] (%)		
entry	Zn reagent (equiv)	time	**5c**[b]	**8**	**2a**
1	1.6	15 min	40	25	35
2	1.6	30 min	48	31	30
3	1.6	45 min	47	32	13
4	1.6	1 h	47 (43)	31	12
5	3	15 min	43	21	36
6	3	30 min	56 (53)	40	4
7	3	45 min	55	32	7
8	3	1 h	57 (43)	36	6
9	5	15 min	34	23	38
10	5	30 min	52 (48)	33	5
11	5	45 min	56	36	7
12	5	1 h	50 (44)	32	5
13	8	1 h	65 (26)	28	4

[a] HPLC yield. [b] Values in parentheses represent isolated yield.

(31) (a) Vittorio, F. *Adv. Synth. Catal.* **2004**, *346*, 1553–1582. (b) Hartwig, J. F.; Richards, S.; Baranano, D.; Paul, F. *J. Am. Chem. Soc.* **1996**, *118*, 3626–3633.

(32) (a) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028–13032. (b) Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem.* **2005**, *117*, 1395–1399.

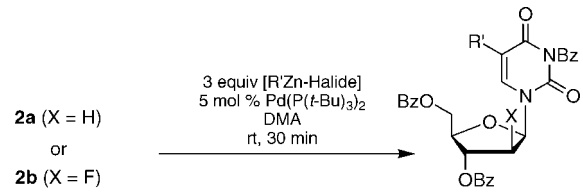
(33) (a) Tomori, H.; Fox, J. M.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5334–5341. (b) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413–2416. (c) Rieth, R. D.; Mankad, N. P.; Calimano, E.; Sadighi, J. P. *Org. Lett.* **2004**, *6*, 3981–3983.

(34) (a) Hansen, A. L.; Ebran, J. P.; Gogsig, T. M.; Skrydstrup, T. *J. Org. Chem.* **2007**, *72*, 6464–6472. (b) Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem.* **2005**, *117*, 1395–1399. (c) Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062–4066.

(35) Maximal yields of (3-fluoropropyl)zinc iodide were only modest as compared to our previous examples and were obtained when the reactions were performed at 60°C for 45 min. Heating for longer led to loss of activity of zinc reagent (as determined by iodine titration).

(36) (a) Casares, J. A.; Espinet, P.; Fuentes, B.; Salas, G. *J. Am. Chem. Soc.* **2007**, *129*, 3508–3509. (b) Gong, L.-Z.; Knochel, P. *Synlett* **2005**, 267–270.

TABLE 3. Preparation of Library of 5-Alkylated Nucleosides by Pd(P(*t*-Bu)$_3$)$_2$-Catalyzed Negishi Cross-Coupling of Nucleoside 2a or 2b with Zincated Alkyl Halides (R′Zn−Halide)[a]



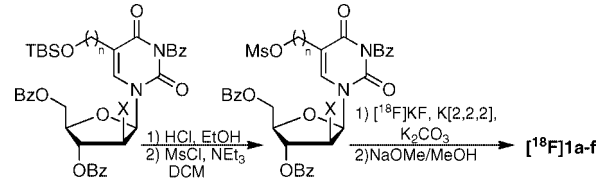
Entry	Nucleoside Substrate	Zincate[a] (R′Zn-Halide)	Nucleoside Product	Product Yield[b] (%)
1	**2a**		**5a′** (X = H; R′ = $(CH_2)_3F$)	Not obtained[c]
2	**2a**		**5a′** (X = H; R′ = $(CH_2)_3F$)	8
3	**2b**		**5b** (X = F; R′ = $(CH_2)_3F$)	5
4	**2a**		**5c** (X = H; R′ = $(CH_2)_4F$)	53
5	**2b**		**5d** (X = F; R′ = $(CH_2)_4F$)	43
6	**2a**		**5e** (X = H; R′ = $(CH_2)_5F$)	50
7	**2b**		**5f** (X = F; R′ = $(CH_2)_5F$)	53
8	**2a**		(X = H; R′ = $(CH_2)_2F$)	Not obtained[c]
9	**2a**		**5g** (X = H; R′ = Bu)	15
10	**2a**		**5h′** (X = H; R′ = Pr)	17
11	**2a**		**5i** (X = H; R′ = Et)	23
12	**2a**		**5g′** (X = H; R′ = Bu)	44
13	**2a**		**5i′** (X = H; R′ = Et)	23
14	**2a**		**5j** (X = H; R′ = $(CH_2)_5OCOCH_3$)	33
15	**2a**		**5k** (X = H; R′ = $(CH_2)_3COOEt$)	39
16	**2a**		**5l** (X = H; R′ = $(CH_2)_3CN$)	29
17	**2a**		**5m** (X = H; R′ = $(CH_2)_3OTBS$)	30

[a] Zinc reagents were prepared following the Huo method.[22a] Iodoalkylzinc reagents employed for entries 2, 3, 9−11. Commercial dialkylzinc reagents (3 equiv) employed for entries 12 and 13. [b] Isolated yields based on nucleoside substrate **2a/2b**. [c] Bromoalkylzinc reagents could not be prepared following the Huo method;[22a] thus, coupling to **2a** or **2b** was not performed.

5i′, which upon deprotection of the benzoyl groups would afford the potent antiherpes agent 5-ethyl-2′-deoxyuridine (EDU, Edoxuridine, Aedurid).[2,37] Employment of the Negishi cross-coupling approach using dialkylzinc reagents[38] thus represents an alternative for synthesizing 5-alkylated nucleosides.

We extended our methodology to include other readily accessible functionalized alkylzinc reagents (entries 14−17, Table 3). Of particular interest was the successful coupling reaction employing (3-*tert*-butyldimethylsiloxypropyl)zinc bromide to afford **5m** (entry 15, Table 3). As elaborated in Scheme 3, silylated coupling products, via the OTBS moiety, offer an alternative route to rapidly obtaining mesylate precursors for subsequent ^{18}F-radiolabeling to achieve our target HSV1-TK molecular imaging probes **[^{18}F]1a−f**.[39] We have since prepared the series of six mesylate precursors **7a−f** that upon labeling with [^{18}F]KF and Kryptofix (K[2,2,2]), followed by deprotection, have successfully afforded no-carrier added **[^{18}F]1a−f** in good yields and in short preparation times. Details of the radiolabeling studies and biological characterizations of **[^{18}F]1a−f** will be published elsewhere.

SCHEME 3. Synthesis of 5-[^{18}F]Fluoroalkylated Pyrimidine Nucleosides [^{18}F]1a−f



Deprotection. Access to the bioactive nucleosides targeting HSV1-TK was exemplified using the above-prepared nucleoside derivatives **5c** and **5d**. The 3-*N*-benzoyl and 3′,5′-di-*O*-benzoyl protecting groups were hydrolyzed by treatment of **5c**,**d** with a standard solution of sodium methoxide in

(37) Prusoff, W. H. *Biochim. Biophys. Acta* **1959**, *32*, 295–6.
(38) For preparation of dialkylzinc reagents, see: Cote, A.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 52–54, and references therein.

anhydrous methanol for 15 min under reflux. The corresponding unprotected nucleosides 5-fluorobutyl-2′-deoxyuridine (**1c**) and 5-fluorobutyl-2′-deoxy-2′-fluoroarabinouridine (**1d**) were obtained in very high yields (>95%) demonstrating that benzoyl removal was compatible with the presence of the 5-fluoroalkyl moieties. This procedure allowed for the rapid and efficient two-step preparation of the bioactive compounds **1c** from **2a** and **1d** from **2b** in 52% and 41% overall yields.

Conclusions

Our studies demonstrate the first Pd(P(*t*-Bu)$_3$)$_2$-catalyzed cross-coupling reactions between fully protected 5-iodo-2′-deoxyuridine nucleosides and unactivated alkylzinc reagents. Furthermore, this methodology represents a significant improvement over conventional syntheses to 5-alkyl-substituted pyrimidine nucleosides that typically involve multiple steps affording products in lower overall chemical yields.[7,8] As such, our approach provides easier access to biologically important 5-alkyl substituted pyrimidine nucleosides, including our new series of 5-fluoroalkylated pyrimidine nucleosides. We are currently expanding the scope of this reaction to include more elaborate zinc reagents.

Experimental Section

Typical Procedure for Cross-Coupling of 2a or 2b with Organozinc Species. To a flame-dried 5-mL two-neck flask equipped with a stir bar were added **2a** (0.08 mmol) or **2b** (0.08 mmol), Pd(P(*t*-Bu)$_3$)$_2$ (1.9 mg, 0.004 mmol), and anhyd DMA (1 mL) under argon. To the reaction mixture was added alkylzinc reagent[22a] (0.6−0.9 M solution in DMA, 0.23 mmol) or dialkylzinc reagent (230 μL of 1 M in heptane, 0.23 mmol) dropwise and the reaction stirred at room temperature for 30 min. The reaction was monitored by HPLC (method A, CH_3CN/NH_4HCO_3 (10 mM) (70/30)) and judged to be complete. The reaction mixture was quenched with saturated NH_4Cl (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product mixture was purified by silica gel preparative thin-layer chromatography (PTLC) using 20%−30% EtOAc in hexanes.

3-*N*-Benzoyl-3′,5′-di-*O*-benzoyl-5-(3-fluoropropyl)-2′-deoxyuridine (5a′). Compound **2a** (50 mg, 0.08 mmol) and Pd(P(*t*-Bu)$_3$)$_2$ (1.9 mg, 0.004 mmol) with (3-fluoropropyl)zinc iodide (375 μL of 0.6 M solution in DMA, 0.23 mmol) afforded 4 mg of **5a′**, 8% yield: ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.10−7.90 (m, 6H), 7.70−7.42 (m, 9H + 1H), 6.45 (dd, 1H, J_1 = 5.5 Hz, J_2 = 8.4 Hz), 5.70−5.66 (m, 1H), 4.79 (dd, 1H, J_1 = 12.3 Hz, J_2 = 25.1 Hz), 4.77 (dd, 1H, J_1 = 12.2 Hz, J_2 = 26.0 Hz), 4.58 (m, 1H), 4.33 (dt, 2H, J_1 = 5.7 Hz, J_2 = 47.3 Hz), 2.78 (dd, 1H, J_1 = 5.2 Hz, J_2 = 14.1 Hz), 2.47−2.32 (m, 1H,), 2.18−2.09 (m, 2H), 1.69−1.39 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.8, 166.2, 162.3, 149.4, 135.3, 135.0, 135.96, 131.7, 130.6, 130.0, 129.7, 129.5, 129.4, 129.2, 129.1, 128.8, 114.9, 85.6, 83.3 (d, J = 164.7 Hz), 83.2, 75.1, 64.5, 38.4, 29.2 (d, J = 19.9 Hz), 23.8 (d, J = 5.6 Hz); HRMS calcd for $C_{33}H_{29}FN_2O_8Na$ ([M + Na]$^+$) 623.1806, found 623.1830; HPLC A t_R = 10.5 min.

3-*N*-Benzoyl-3′,5′-di-*O*-benzoyl-5-(3-fluoropropyl)-2′-deoxy-2′-fluoroarabinouridine (5b). Compound **2b** (51 mg, 0.08 mmol) and Pd(P(*t*-Bu)$_3$)$_2$ (1.9 mg, 0.004 mmol) with (3-fluoropropyl)zinc iodide (375 μL of 0.6 M solution in DMA, 0.23 mmol) afforded 3 mg of **5b**, 5% yield: ^{1}H NMR (200 MHz, CD_3CN) δ 8.12−7.94 (m, 6H), 7.79−7.43 (m, 9H + 1H), 6.31 (dd, 1H, J_1 = 3.2 Hz, J_2 = 20.7 Hz), 5.69 (ddd, 1H, J_1 = 1.0 Hz, J_2 = 3.6 Hz, J_3 = 19.0 Hz), 5.44 (ddd, 1H, J_1 = 1.0 Hz, J_2 = 3.3 Hz, J_3 = 50.2 Hz), 4.79 (dd, 1H, J_1 = 12.1 Hz, J_2 = 24.6 Hz), 4.77 (dd, 1H, J_1 = 12.1 Hz, J_2 = 25.8 Hz), 4.65−4.59 (m, 1H), 4.37 (dt, 2H, J_1 = 5.9 Hz, J_2 = 47.4 Hz), 2.34−2.27 (m, 2H), 1.76−1.70 (m, 2H); ^{13}C NMR (50 MHz, CD_3CN) δ 170.4, 167.1, 166.4, 163.5, 150.1, 138.4, 138.3, 136.6, 135.0, 134.6, 132.6, 131.4, 130.9, 130.5, 130.1, 129.8, 114.2, 94.4 (d, J = 189.8 Hz), 85.7 (d, J = 16.5 Hz), 84.4 (d, J = 161.6 Hz), 81.5, 77.9 (d, J = 30.3 Hz), 64.3, 30.1 (d, J = 19.5 Hz), 23.8 (d, J = 5.7 Hz); HRMS calcd for $C_{33}H_{29}F_2N_2O_8$ ([M + H]$^+$) 619.1892, found 619.1896; HRMS calcd for $C_{33}H_{28}F_2N_2O_8$ Na ([M + Na]$^+$) 641.1711, found 641.1710; HPLC A t_R = 12.1 min.

3-*N*-Benzoyl-3′,5′-di-*O*-benzoyl-5-(4-fluorobutyl)-2′-deoxyuridine (5c). Compound **2a** (50 mg, 0.08 mmol) and Pd(P(*t*-Bu)$_3$)$_2$ (1.9 mg, 0.004 mmol) with (4-fluorobutyl)zinc bromide (250 μL of 0.9 M solution in DMA 0.23 mmol) afforded cross-coupling product **5c** as a white solid (24 mg, 53% yield): ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.10−7.89 (m, 6H), 7.70−7.39 (m, 9H + 1H), 6.46 (dd, 1H, J_1 = 5.4 Hz, J_2 = 8.8 Hz), 5.68 (dt, 1H, J_1 = 1.5 Hz, J_2 = 6.5 Hz), 4.78 (dd, 1H, J_1 = 12.2 Hz, J_2 = 28.8 Hz), 4.77 (dd, 1H, J_1 = 12.2 Hz, J_2 = 29.5 Hz), 4.59−4.55 (m, 1H), 4.35 (dt, 2H, J_1 = 5.7 Hz, J_2 = 47.3 Hz), 2.78 (ddd, 1H, J_1 = 1.3 Hz, J_2 = 5.4 Hz, J_3 = 14.2 Hz), 2.47−2.32 (m, 1H), 2.22−2.12 (m, 2H), 1.69−1.39 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.9, 166.2, 162.4, 149.4, 135.3, 134.6, 134.0, 131.8, 130.6, 130.0, 129.7, 129.5, 129.4, 129.2, 129.1, 128.8, 128.3, 115.7, 85.6, 83.8 (d, J = 163.9 Hz), 83.1, 75.2, 64.5, 38.3, 30.1 (d, J = 19.7 Hz), 26.9, 24.6 (d, J = 5.1 Hz); HRMS calcd for $C_{34}H_{32}FN_2O_8$ ([M + H]$^+$) 615.2143, found 615.2148; HPLC A t_R = 11.6 min.

3-*N*-Benzoyl-3′,5′-di-*O*-benzoyl-5-(4-fluorobutyl)-2′-deoxy-2′-fluoroarabinouridine (5d). Compound **2b** (51 mg, 0.08 mmol) and Pd(P(*t*-Bu)$_3$)$_2$ (1.9 mg, 0.004 mmol) with (4-fluorobutyl)zinc bromide (281 μL of 0.8 M solution in DMA, 0.23 mmol) afforded 20 mg of **5d**, 43% yield: ^{1}H NMR (200 MHz, CD_3CN) δ 8.13−7.94 (m, 6H), 7.79−7.49 (m, 9H + 1H), 6.32 (dd, 1H, J_1 = 3.1 Hz, J_2 = 20.8 Hz), 5.70 (dd, 1H, J_1 = 3.2 Hz, J_2 = 18.8 Hz), 5.45 (dd, 1H, J_1 = 2.4 Hz, J_2 = 50.2 Hz), 4.80 (dd, 1H, J_1 = 12.1 Hz, J_2 = 29.2 Hz), 4.78 (dd, 1H, J_1 = 12.1 Hz, J_2 = 30.6 Hz), 4.65−4.62 (m, 1H), 4.36 (dt, 2H, J_1 = 6.0 Hz, J_2 = 47.4 Hz), 2.25−2.18 (m, 2H), 1.64−1.46 (m, 4H); ^{13}C NMR (50 MHz, CD_3CN) δ 170.4, 166.4, 163.5, 150.1, 138.2, 138.1, 136.5, 134.9, 134.6, 134.2, 132.6, 131.4, 130.8, 130.5, 130.1, 129.8, 129.6, 114.7, 94.4 (d, J = 189.7 Hz), 85.6 (d, J = 16.5 Hz), 84.9 (d, J = 160.9 Hz), 81.4, 77.8 (d, J = 30.3 Hz), 64.2, 30.5 (d, J = 19.5 Hz), 27.2, 25.1 (d, J = 5.4 Hz); HRMS calcd for $C_{34}H_{31}F_2N_2O_8$ ([M + H]$^+$) 633.2048, found 633.2062; HPLC A t_R = 13.2 min.

3-*N*-Benzoyl-3′,5′-di-*O*-benzoyl-5-(5-fluoropentyl)-2′-deoxyuridine (5e). Compound **2a** (50 mg, 0.08 mmol) and Pd(P(*t*-Bu)$_3$)$_2$ (1.9 mg, 0.004 mmol) with (5-fluoropentyl)zinc bromide (250 μL of 0.9 M solution in DMA, 0.23 mmol) afforded 24 mg of **5e**, 50% yield: ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.10−7.90 (m, 6H), 7.66−7.43 (m, 9H), 7.36 (s, 1H), 6.47 (dd, 1H, J_1 = 5.4 Hz, J_2 = 8.8 Hz), 5.70−5.67 (m, 1H), 4.78 (dd, 1H, J_1 = 12.2 Hz, J_2 = 28.7 Hz), 4.76 (dd, 1H, J_1 = 12.2 Hz, J_2 = 29.5 Hz), 4.5 (m, 1H), 4.34 (dt, 2H, J_1 = 5.7 Hz, J_2 = 47.2 Hz), 2.78 (dd, 1H, J_1 = 5.3 Hz, J_2 = 14.2 Hz), 2.40 (ddd, 1H, J_1 = 6.3 Hz, J_2 = 8.5 Hz, J_3 = 14.5 Hz), 2.18−1.97 (m, 2H), 1.72−1.27 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.9, 166.2, 162.4, 149.4, 135.3, 134.4, 134.0, 131.8, 130.6, 130.0, 129.7, 129.5, 129.4, 129.2, 129.1, 128.8, 116.0, 85.5, 84.0 (d, J = 163.5 Hz), 83.1, 75.2, 64.6, 38.3, 30.2 (d, J = 19.5 Hz), 28.3, 27.2, 25.0 (d, J = 5.1 Hz); HRMS calcd for $C_{35}H_{34}FN_2O_8$ ([M + H]$^+$) 629.2299, found 629.2298; HPLC A t_R = 13.7 min.

3-*N*-Benzoyl-3′,5′-di-*O*-benzoyl-5-(5-fluoropentyl)-2′-deoxy-2′-fluoroarabinouridine (5f). Compound **2b** (51 mg, 0.08 mmol) and

(39) (a) Balatoni, J.; Doubrovin, M.; Ageyeva, L.; Pillarsetty, N.; Finn, R.; Gelovani, J.; Blasberg, R. *Nucl. Med. Biol.* **2005**, *32*, 811–9. (b) Toyohara, J.; Hayashi, A.; Gogami, A.; Hamada, M.; Hamashima, Y.; Katoh, T.; Node, M.; Fujibayashi, Y. *Nucl. Med. Biol.* **2006**, *33*, 751–64. (c) Toyohara, J.; Hayashi, A.; Gogami, A.; Fujibayashi, Y. *Nucl. Med. Biol.* **2006**, *33*, 765–772.

$Pd(P(t\text{-}Bu)_3)_2$ (1.9 mg, 0.004 mmol) with (5-fluoropentyl)zinc bromide (268 μL of 0.84 M solution in DMA, 0.23 mmol) afforded 26 mg of **5f**, 53% yield: ^{1}H NMR (200 MHz, CD_3CN) δ 8.13−7.95 (m, 6H), 7.75−7.50 (m, 9H + 1H,), 6.33 (dd, 1H, J_1 = 3.0 Hz, J_2 = 20.8 Hz), 5.70 (dd, 1H, J_1 = 3.0 Hz, J_2 = 18.9 Hz), 5.46 (dd, 1H, J_1 = 2.6 Hz, J_2 = 50.2 Hz), 4.80 (dd, 1H, J_1 = 12.1 Hz, J_2 = 31.0 Hz), 4.78 (dd, 1H, J_1 = 12.1 Hz, J_2 = 32.5 Hz), 4.65−4.61 (m, 1H), 4.38 (dt, 2H, J_1 = 6.0 Hz, J_2 = 47.5 Hz), 2.21−2.14 (m, 2H), 1.71−1.28 (m, 6H); ^{13}C NMR (50 MHz, CD_3CN) δ 170.4, 166.4, 163.5, 150.1, 138.0, 137.9, 136.5, 134.9, 134.6, 134.2, 132.6, 131.3, 130.8, 130.6, 130.5, 130.1, 129.83, 129.81, 129.6, 115.0, 94.4 (d, J = 189.8 Hz), 85.6 (d, J = 16.3 Hz), 85.0 (d, J = 160.8 Hz), 81.5, 77.8 (d, J = 30.3 Hz), 64.2, 30.8 (d, J = 19.3 Hz), 28.9, 27.4, 25.4 (d, J = 5.6 Hz); HRMS calcd for $C_{35}H_{33}F_2N_2O_8$ ([M + H]$^+$) 647.2205, found 647.2202; HPLC A: t_R = 15.2 min.

3-*N*-Benzoyl-3′,5′-di-*O*-benzoyl-5-butyl-2′-deoxyuridine (5g/5g′). Compound **2a** (50 mg, 0.08 mmol) and $Pd(P(t\text{-}Bu)_3)_2$ (1.9 mg, 0.004 mmol) with butylzinc iodide (281 μL of 0.8 M solution in DMA, 0.23 mmol) afforded 7 mg of **5g**, 15% yield. Employing $(n\text{-}Bu)_2Zn$ (230 μL of 1 M in heptane, 0.23 mmol) afforded 20 mg of **5i′**, 44% yield: ^{1}H NMR of **5g** (200 MHz, $CDCl_3$) δ 8.10−7.90 (m, 6H), 7.69−7.43 (m, 9H) 7.34 (s, 1H), 6.47 (dd, 1H, J_1 = 5.5 Hz, J_2 = 8.7 Hz), 5.70−5.67 (m, 1H), 4.78 (dd, 1H, J_1 = 12.2 Hz, J_2 = 28.5 Hz), 4.76 (dd, 1H, J_1 = 12.2 Hz, J_2 = 29.3 Hz), 4.57−4.56 (m, 1H), 2.77 (dd, 1H, J_1 = 5.0 Hz, J_2 = 13.9 Hz), 2.47−2.33 (m, 1H), 2.10−2.05 (m, 2H), 1.29−1.12 (m, 4H), 0.81 (t, 3H, J = 7.0 Hz); ^{13}C NMR of **5g** (50 MHz, $CDCl_3$) δ 169.0, 166.2, 162.4, 149.5, 135.2, 134.1, 134.0, 131.9, 130.6, 130.0, 129.8, 129.5, 129.4, 129.2, 129.0, 128.8, 116.5, 85.5, 83.1, 75.2, 64.6, 38.3, 30.8, 27.0, 22.5, 13.8; HRMS calcd for $C_{34}H_{32}N_2O_8Na$ ([M + Na]$^+$) 619.2056, found 619.2048; HPLC A t_R = 16.1 min.

3-*N*-Benzoyl-3′,5′-di-*O*-benzoyl-5-propyl-2′-deoxyuridine (5h′). Compound **2a** (50 mg, 0.08 mmol) and $Pd(P(t\text{-}Bu)_3)_2$ (1.9 mg, 0.004 mmol) with propylzinc iodide (281 μL of 0.8 M solution in DMA, 0.23 mmol) afforded 8 mg of **5h′**, 17% yield: ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.10−7.90 (m, 6H), 7.69−7.43 (m, 9H) 7.32 (s, 1H), 6.47 (dd, 1H, J_1 = 5.5 Hz, J_2 = 8.7 Hz), 5.71−5.68 (m, 1H), 4.78 (dd, 1H, J_1 = 12.3 Hz, J_2 = 32.6 Hz), 4.76 (dd, 1H, J_1 = 12.3 Hz, J_2 = 33.4 Hz), 4.57 (m, 1H), 2.77 (dd, 1H, J_1 = 4.7 Hz, J_2 = 14.1 Hz), 2.47−2.32 (m, 1H), 2.11−2.01 (m, 2H), 1.42−1.31 (m, 2H), 0.77 (t, 3H, J = 7.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.0, 166.2, 162.4, 149.5, 135.2, 134.2, 134.0, 131.9, 130.6, 130.0, 129.7, 129.5, 129.4, 129.2, 129.0, 128.8, 116.2, 85.4, 83.0, 75.2, 64.5, 38.3, 29.2, 21.8, 13.8; HRMS calcd for $C_{33}H_{30}N_2O_8Na$ ([M + Na]$^+$) 605.1900, found 605.1944; HPLC A t_R = 13.5 min.

3-*N*-Benzoyl-3′,5′-di-*O*-benzoyl-5-ethyl-2′-deoxyuridine (5i/5i′). Compound **2a** (50 mg, 0.08 mmol) and $Pd(P(t\text{-}Bu)_3)_2$ (1.9 mg, 0.004 mmol) with ethylzinc iodide (312 μL of 0.72 M solution in DMA, 0.23 mmol) afforded 10 mg of **5i**, 23% yield. Employing Et_2Zn (230 μL of 1 M in heptane, 0.23 mmol) afforded 10 mg of **5i′**, 23% yield: ^{1}H NMR of **5i** (200 MHz, $CDCl_3$) δ 8.09−7.91 (m, 6H), 7.69−7.43 (m, 9H), 7.33 (s, 1H), 6.47 (dd, 1H, J_1 = 5.4 Hz, J_2 = 8.6 Hz), 5.70−5.67 (m, 1H), 4.79 (dd, 1H, J_1 = 12.2 Hz, J_2 = 29.2 Hz), 4.77 (dd, 1H, J_1 = 12.2 Hz, J_2 = 29.9 Hz), 4.57−4.56 (m, 1H), 2.77 (dd, 1H, J_1 = 5.1 Hz, J_2 = 13.9 Hz), 2.40 (ddd, 1H, J_1 = 6.7 Hz, J_2 = 8.3 Hz, J_3 = 14.5 Hz), 2.15 (q, 2H, J = 7.3 Hz), 0.93 (t, 3H, J = 7.4 Hz); ^{13}C NMR of **5i** (50 MHz, $CDCl_3$) δ 169.0, 166.21, 166.16, 162.4, 149.5, 135.2, 134.0, 133.7, 131.9, 130.7, 130.4, 130.0, 129.8, 129.6, 129.4, 129.2, 129.0, 128.8, 128.7, 117.7, 85.5, 83.1, 75.2, 64.5, 38.3, 20.6, 13.0; HRMS calcd for $C_{32}H_{28}N_2O_8Na$ ([M + Na]$^+$) 591.1743, found 591.1739; HPLC A t_R = 10.7 min.

3-*N*-Benzoyl-3′,5′-di-*O*-benzoyl-5-(5-acetoxypentyl)-2′-deoxyuridine (5j). Compound **2a** (50 mg, 0.08 mmol) and $Pd(P(t\text{-}Bu)_3)_2$ (1.9 mg, 0.004 mmol) with (5-acetoxypentyl)zinc bromide (281 μL of 0.8 M solution in DMA, 0.23 mmol) afforded 17 mg of **5j**, 33% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.41−7.90 (m, 6H), 7.69−7.43 (m, 9H), 7.36 (s, 1H), 6.46 (dd, 1H, J_1 = 5.4 Hz, J_2 = 8.6 Hz), 5.70−5.67 (m, 1H), 4.78 (dd, 1H, J_1 = 12.2 Hz, J_2 = 30.5 Hz), 4.76 (dd, 1H, J_1 = 12.2 Hz, J_2 = 31.4 Hz), 4.58−4.57 (m, 1H), 4.00 (t, 2H, J = 6.6 Hz), 2.78 (dd, 1H, J_1 = 5.2 Hz, J_2 = 14.1 Hz), 2.48−2.33 (m, 1H), 2.18−2.05 (m, 2H), 2.05 (s, 3H), 1.59−1.21 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.3, 169.0, 166.2, 162.4, 149.4, 135.3, 134.4, 134.0, 131.8, 130.6, 130.0, 129.8, 129.6, 129.4, 129.2, 129.1, 128.8, 116.1, 85.6, 83.1, 75.2, 64.5, 38.3, 28.5, 27.2, 25.8, 21.2; HRMS calcd for $C_{37}H_{36}N_2O_{10}Na$ ([M + Na]$^+$) 691.2248, found 691.2268; HPLC A t_R = 11.8 min.

3-*N*-Benzoyl-3′,5′-di-*O*-benzoyl-5-(4-ethoxy-4-oxobutyl)-2′-deoxyuridine (5k). Compound **2a** (50 mg, 0.08 mmol) and $Pd(P(t\text{-}Bu)_3)_2$ (1.9 mg, 0.004 mmol) with (4-ethoxy-4-oxobutyl)zinc bromide (300 μL of 0.75 M solution in DMA, 0.23 mmol) afforded 19 mg of **5k**, 39% yield: ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.09−7.91 (m, 6H), 7.65−7.41 (m, 9H + 1H), 6.44 (dd, 1H, J_1 = 5.4 Hz, J_2 = 8.6 Hz), 5.69−5.66 (m, 1H), 4.78 (dd, 1H, J_1 = 12.2 Hz, J_2 = 22.4 Hz), 4.76 (dd, 1H, J_1 = 12.2 Hz, J_2 = 23.2 Hz), 4.57−4.56 (m, 1H), 4.1 (q, 2H, J = 7.1 Hz), 2.77 (dd, 1H, J_1 = 5.1 Hz, J_2 = 13.8 Hz), 2.42 (ddd, 1H, J_1 = 6.5 Hz, J_2 = 8.3 Hz, J_3 = 14.5 Hz), 2.21−2.14 (m, 2H), 2.17 (t, 2H, J = 7.2 Hz), 1.77−1.67 (m, 2H), 1.25 (t, 3H, J = 7.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.2, 168.9, 166.2, 162.3, 149.4, 135.2, 135.0, 133.9, 131.8, 130.7, 130.0, 129.8, 129.6, 129.4, 129.2, 129.0, 128.8, 128.3, 115.2, 85.7, 83.1, 75.2, 64.5, 38.3, 33.9, 26.8, 23.9, 14.5; HRMS calcd for $C_{36}H_{34}N_2O_{10}Na$ ([M + Na]$^+$) 677.2111, found 677.2093; HRMS calcd for $C_{36}H_{35}N_2O_{10}$ ([M + H]$^+$) 655.2292, found 655.2272; HPLC A t_R = 11.4 min.

3-*N*-Benzoyl-3′,5′-di-*O*-benzoyl-5-(3-cyanopropyl)-2′-deoxyuridine (5l). Compound **2a** (50 mg, 0.08 mmol) and $Pd(P(t\text{-}Bu)_3)_2$ (1.9 mg, 0.004 mmol) with (3-cyanopropyl)zinc bromide (256 μL of 0.88 M solution in DMA, 0.23 mmol) afforded 13 mg of **5l**, 29% yield: ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.11−7.91 (m, 6H), 7.67−7.43 (m, 9H + 1H), 6.43 (dd, 1H, J_1 = 5.4 Hz, J_2 = 8.5 Hz), 5.69−5.66 (m, 1H), 4.80 (dd, 1H, J_1 = 12.2 Hz, J_2 = 27.3 Hz), 4.79 (dd, 1H, J_1 = 12.2 Hz, J_2 = 28.6 Hz), 4.59 (m, 1H), 2.81 (dd, 1H, J_1 = 5.3 Hz, J_2 = 14.2 Hz), 2.47−2.36 (m, 1H), 2.33−2.08 (m, 4H), 1.79−1.69 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.7, 166.2, 162.3, 149.3, 135.8, 135.4, 134.1, 134.0, 131.7, 130.7, 130.0, 129.8, 129.6, 129.5, 129.2, 128.9, 119.4, 113.6, 85.9, 83.4, 75.2, 53.6, 38.5, 26.9, 24.2, 16.9; HRMS calcd for $C_{34}H_{29}N_3O_8Na$ ([M + Na]$^+$) 630.1852, found 630.1874; HPLC A t_R = 8.5 min.

3-*N*-Benzoyl-3′,5′-di-*O*-benzoyl-5-(3-*tert*-butyldimethylsilyloxypropyl)-2′-deoxyuridine (5m). Compound **2a** (50 mg, 0.08 mmol) and $Pd(P(t\text{-}Bu)_3)_2$ (1.9 mg, 0.004 mmol) with (3-*tert*-butyldimethylsilyloxypropyl)zinc bromide (321 μL of 0.7 M solution in DMA, 0.23 mmol) afforded 25 mg of **5m**, 47% yield: ^{1}H NMR (200 MHz, CD_3CN) δ 8.09−7.90 (m, 6H), 7.69−7.42 (m, 9H), 7.40 (s, 1H), 6.43 (dd, 1H, J_1 = 5.4 Hz, J_2 = 8.7 Hz), 5.67−5.64 (m, 1H), 4.77 (dd, 1H, J_1 = 12.2 Hz, J_2 = 14.4 Hz), 4.75 (dd, 1H, J_1 = 12.2 Hz, J_2 = 14.6 Hz), 4.59−4.55 (m, 1H), 3.51 (t, 2H, J = 6.2 Hz), 2.77 (ddd, 1H, J_1 = 1.4 Hz, J_2 = 5.4 Hz, J_3 = 14.2 Hz), 2.40 (ddd, 1H, J_1 = 6.6 Hz, J_2 = 8.6 Hz, J_3 = 14.4 Hz), 2.30−2.19 (m, 2H), 1.66−1.52 (m, 2H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.0, 166.2, 162.4, 149.4, 135.2, 134.4, 134.0, 133.9, 131.9, 130.7, 130.0, 129.8, 129.6, 129.4, 129.2, 129.0, 128.8, 115.9, 85.8, 83.1, 75.2, 64.5, 62.6, 38.3, 31.5, 26.2, 24.1, 18.5, −5.1; HRMS calcd for $C_{39}H_{44}N_2O_9SiNa$ ([M + Na]$^+$) 735.2714, found 735.2688; HRMS calcd for $C_{39}H_{45}N_2O_9Si$ ([M + H]$^+$) 713.2894, found 713.2881; HPLC A t_R = 15.1 min.

Typical Procedure for Deprotection of Tribenzoyl-Protected Nucleosides. In a vial equipped with a stir bar was added tribenzoylprotected nucleosides. Dry sodium methoxide solution (0.5 M in MeOH, 3 mL) was added dropwise. Reaction vial was sealed and then stirred at 80 °C for 15 min. Reaction judged to be complete by HPLC (method B, MeOH/H_2O (30/70)). After the mixture was cooled to room temperature, the reaction was quenched with 1 N HCl (1.5 mL) and the solvent removed in vacuo. The

crude product residue was purified by silica gel PTLC using 10% MeOH in dichloromethane.

5-(4-Fluorobutyl)-2′-deoxyuridine (1c). The deprotection procedure described above, using **5c** (23.4 mg, 0.04 mmol) afforded 11.5 mg of **1c**, 99% yield: ^{1}H NMR (200 MHz, CD_3OD) δ 8.06 (s, 1H), 6.49 (t, 1H, $J_1 = 6.7$ Hz), 4.64 (dt, 2H, $J_1 = 5.6$ Hz, $J_2 = 47.6$ Hz), 4.64−4.57 (m, 1H), 4.12 (t, 1H, $J_1 = 3.1$ Hz), 3.98 (dd, 1H, $J_1 = 12.1$ Hz, $J_2 = 16.8$ Hz), 3.96 (dd, 1H, $J_1 = 12.1$ Hz, $J_2 = 17.3$ Hz), 2.59−2.37 (m, 2H + 2H), 2.00−1.81 (m, 4H); ^{13}C NMR (50 MHz, CD_3OD) δ 166.1, 152.4, 138.6, 115.6, 89.1, 86.6, 84.8 (d, $J = 162.8$ Hz), 72.4, 62.9, 41.5, 31.2 (d, $J = 19.6$ Hz), 27.5, 25.6 (d, $J = 5.1$ Hz); HRMS calcd for $C_{13}H_{20}FN_2O_5$ ($[M + H]^+$) 303.1356, found 303.1349; HPLC B $t_R = 7.6$ min.

5-(4-Fluorobutyl)-2′-deoxy-2′-fluoroarabinouridine (1d). The deprotection procedure above, using **5d** (12.7 mg, 0.021 mmol), afforded 6.1 mg of **1d**, 95% yield: ^{1}H NMR (200 MHz, CD_3CN with D_2O) δ 7.53 (s, 1H), 6.13 (dd, 1H, $J_1 = 4.1$ Hz, $J_2 = 16.4$ Hz), 5.02 (dt, 2H, $J_1 = 3.9$ Hz, $J_2 = 52.2$ Hz), 4.43 (dt, 2H, $J_1 = 5.9$ Hz, $J_2 = 47.3$ Hz), 4.24−4.20 (m, 1H), 3.90−3.70 (m, 1H + 2H), 2.32−2.25 (m, 2H), 1.78−1.45 (m, 4H). ^{13}C NMR (50 MHz, CD_3CN with D_2O) δ 164.2, 151.2, 138.0 (d, $J = 3.0$ Hz), 114.2, 96.8 (d, $J = 190.4$ Hz), 85.0 (d, $J = 160.7$ Hz), 84.5 (d, $J = 4.6$ Hz), 84.0 (d, $J = 16.6$ Hz), 74.4 (d, $J = 24.5$ Hz), 61.5, 30.6 (d, $J = 19.4$ Hz), 27.1, 25.0 (d, $J = 5.4$ Hz); HRMS calcd for $C_{13}H_{19}F_2N_2O_5$ $[(M + H)^+]$ 321.1262, found 321.1253; HPLC B $t_R = 10.9$ min.

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Supporting Information Available: General experimental procedures and characterization data for compounds **2a**,**b**, **3**, **4**, **5a** (with **5 h**), **6**, and **7a**, HPLC chromatogram of typical coupling reaction, and NMR spectra (^{1}H and ^{13}C) for compounds **2a**,**b**, **3**, **4**, **6**, **7a**, **5a′**−**m**, and **1c**,**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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