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Practical synthesis of 6-aryluridines via palladium(II) acetate catalyzed Suzuki–Miyaura cross-coupling reaction

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ABSTRACT

Sugar-protected 6-halouridine derivatives underwent Suzuki–Miyaura cross-coupling reactions with arylboronic acids in the presence of palladium(II) acetate as a catalyst, triphenylphosphine as a ligand, and sodium carbonate as a base. This methodology is applicable to both the C5- and C6-position of uridine and provides a direct access for versatile uridine derivatives.

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1. Introduction

C-Aryl-substituted uridine derivatives are an important class of pyrimidine nucleoside analogs that have received considerable attention in recent years. 5-Aryluridines have been extensively utilized as fluorescent probes for the studies of electron-transfer in DNA,[1–10] or as biosensors for the detection of uridine-related protein targets.[11] In addition, 5-aryluridines represent a series of dimensional analogs of thymidine[12–19] or flexible ring-split analogs ('fleximers') of purine nucleosides,[20] which have been used as spatial probes to investigate related enzymes or receptors. The synthesis of 5-aryluridines from 5-halouridines was readily achieved by the palladium-catalyzed cross-coupling reactions in which both Suzuki–Miyaura[1–6,11–13,21,22] and Stille[7–10,14–20,22] reactions were applicable.

In contrast, very few examples of 6-aryluridines have been reported in the literature.[23–28] The introduction of aryl substituents at the *C*6-position of uridine was limited to the following two approaches with a restricted scope: (1) photochemical arylation of 6-iodouridines with arenes;[28] (2) Stille coupling reactions of 6-iodouridines with arylstannanes or 6-tributylstannyluridines with aryl halides.[24–27] The synthesis of 6-aryluridine derivatives via the widely-used Suzuki–Miyaura reaction was only very recently reported by Van Calenbergh et al.[23] In an effort to explore the chemical synthesis and biological significance of 6-substituted uridine derivatives, we embarked on an investigation of a general and practical synthesis of 6-aryluridines via the Suzuki–Miyaura reaction.

2. Results and discussion

In the initial trials, 6-halo-1,3-dimethyluracils (**1a**,**b**) were chosen as non-nucleoside models to investigate the C–C bond formation reaction. Using a conventional approach,[29] $Pd(PPh_3)_4$ was selected as the catalyst, and commercially available arylating reagents, including phenylboronic acid (**3a**), phenylboronic acid pinacol ester (**4a**), and tributylphenylstannane (**4b**), along with various bases and solvents, were examined. The survey of reaction conditions showed that both Suzuki–Miyaura and Stille coupling reactions could take place with excellent yields under various conditions (Table 1).

However, our attempts to apply the tested conditions (Table 1) to 5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylidene-6-iodouridine[30] (**6**) were unsuccessful. In contrast to the model reactions, we speculated that this failure could be attributed to the interaction of the unsubstituted N^3-position with the palladium catalyst or the arylating reagents. To test this hypothesis, a series of N^3-substituted 6-iodouridine derivatives (**10a**,**b** and **11**) were prepared by N^3-alkylation[31,32] of 5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylideneuridine (**5**) followed by lithiation-iodination.[27,30,33] The N^3-substituted 6-iodo-uridines **10a**,**b** and **11** were subjected to the optimized condition (entries 1 and 6 in Table 1) and the desired N^3-substituted 6-phenyluridines **12a**,**b** and **13a** were obtained in very good yields (Scheme 1). The results indicated that a protecting group for the reactive N^3-imide is necessary when $Pd(PPh_3)_4$ is used as the catalyst.

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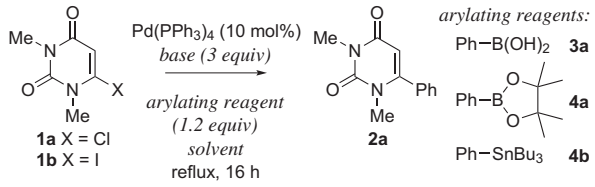
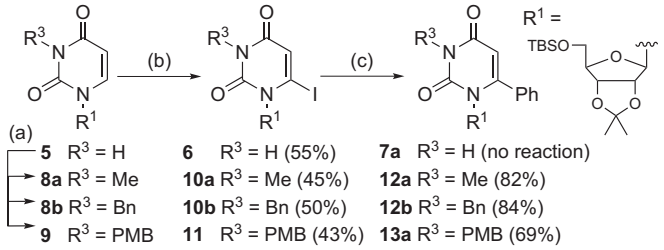
Table 1
Cross-coupling reaction of 6-halo-1,3-dimethyluracils (**1a**,**b**) with arylating reagents (**3a** and **4a**,**b**) using $Pd(PPh_3)_4$ as the catalyst



Entry	Substrate	Base (3 equiv)	Arylating reagent (1.2 equiv)	Solvent[a]	Yield[b] (%)
1	**1a**	2 M Na_2CO_3[c]	**3a**	DME[d]	73
2	**1a**	2 M Na_2CO_3[c]	**4a**	DME[d]	94
3	**1a**	2 M Na_2CO_3[c]	**4b**	DME[d]	86
4	**1a**	DBU	**3a**	DME	59
5	**1a**	DBU	**4a**	DME	59
6	**1b**	2 M Na_2CO_3[c]	**3a**	DME[d]	86
7	**1b**	DBU	**3a**	DME	62
8	**1b**	DBU	**4a**	DME	14

[a] Concentration=0.1 M.
[b] Isolated yield.
[c] 2 M in H_2O.
[d] Approximately DME/H_2O=1:0.15 (v/v).

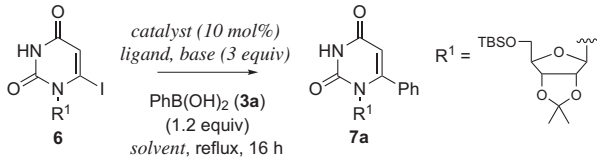


Scheme 1. Reagents and conditions: (a) R^3=Me: MeI, K_2CO_3, DMF, rt, 94%; R^3=Bn: BnBr, K_2CO_3, cat. $^nBu_4NI$, DMF, rt, 84%; R^3=PMB: PMBCl, DBU, CH_3CN, 70 °C, 69%; (b) (i) LDA, THF, −78 °C; (ii) I_2, THF, −78 °C; (c) $Pd(PPh_3)_4$ (10 mol %), $PhB(OH)_2$ (1.2 equiv), 2 M Na_2CO_3 in H_2O (3 equiv), DME, reflux, 16 h.

Meanwhile, our investigation also focused on the direct activation of 5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylidene-6-iodouridine[30] (**6**) for the C–C bond formation reaction. In a continuous screening of palladium catalysts ($Pd(OAc)_2$, $PdCl_2$, $Pd(PPh_3)_2Cl_2$, Pd_2dba_3), only $Pd(OAc)_2$ and $PdCl_2$ were found to give a minimal yield of the desired product, while $Pd(PPh_3)_4$ was unable to catalyze the coupling reaction. Optimization studies were then performed with various solvents, bases, temperature, boron reagents, and ligands/additives (part of the results was summarized in Table 2). Our investigation revealed that the maximal yield was obtained when the reaction was carried out in toluene with $Pd(OAc)_2$ as the catalyst, PPh_3 as the ligand, and Na_2CO_3 as the base (entry 11 in Table 2). Alternatively, using DME as the solvent, Cs_2CO_3 as the base, or dppf as the ligand, respectively (entries 3, 4, 12, and 14 in Table 2), could provide comparative yields.

The reaction of sugar-protected 6-iodouridine **6** with a variety of arylboronic acids (**3b**–**i**), as shown in Table 3, was examined to explore the scope and generality of the reaction. Under the optimized condition (entry 11 in Table 2), 6-iodouridine **6** could react with most of the arylboronic acids to give the target compounds **7** in good yields except for **3g** and **3i**, which did not give the desired products under all tested conditions (Table 3). It is notable that, although the reactions with 3-thiopheneboronic acid (**3f**) and 3-furanboronic acid (**3h**) proceeded flawlessly under the optimized condition (entries 9–11 in Table 3), their 2-position isomeric congeners (**3e** and **g**) were problematic. Upon changing the solvent from toluene to DME, the reaction with 2-thiopheneboronic acid (**3e**) was

Table 2
Cross-coupling reaction of 5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylidene-6-iodouridine (**6**) with phenylboronic acid (**3a**)



Entry	Catalyst (10 mol %)	Ligand (equiv)	Base (3 equiv)[a]	Solvent[b]	Yield[c] (%)
1	$Pd(PPh_3)_4$	—	Na_2CO_3	DME	0
2	$Pd(OAc)_2$	—	Na_2CO_3	DME	4
3[d]	$Pd(OAc)_2$	PPh_3 (0.2)	Na_2CO_3	DME	35
4	$Pd(OAc)_2$	PPh_3 (0.2)	Cs_2CO_3	DME	43
5	$Pd(OAc)_2$	PPh_3 (0.2)	K_3PO_4	DME	28
6	$Pd(OAc)_2$	PPh_3 (0.2)	Na_2CO_3	Dioxane	5
7	$Pd(OAc)_2$	PPh_3 (0.2)	Na_2CO_3	THF	8
8	$Pd(OAc)_2$	PPh_3 (0.2)	Na_2CO_3	CH_3CN	0
9	$Pd(OAc)_2$	PPh_3 (0.2)	Na_2CO_3	DMF	0
10	$Pd(OAc)_2$	PPh_3 (0.2)	Na_2CO_3	*t*-BuOH	37
11[e]	$Pd(OAc)_2$	PPh_3 (0.2)	Na_2CO_3	Toluene	82
12	$Pd(OAc)_2$	PPh_3 (0.2)	Cs_2CO_3	Toluene	49
13	$Pd(OAc)_2$	PPh_3 (0.2)	K_3PO_4	Toluene	58
14	$Pd(OAc)_2$	dppf (0.1)[f]	Na_2CO_3	Toluene	62
15	$PdCl_2$	—	Na_2CO_3	DME	5
16	$PdCl_2$	PPh_3 (0.2)	Na_2CO_3	Toluene	11

[a] 2 M in H_2O.
[b] Concentration=0.1 M.
[c] Isolated yield.
[d] Using **4a** (1.2 equiv) as the arylating reagent: 17%.
[e] Using **4a** (1.2 equiv) as the arylating reagent: 0%.
[f] dppf=1,1′-Bis(diphenylphosphino)ferrocene.

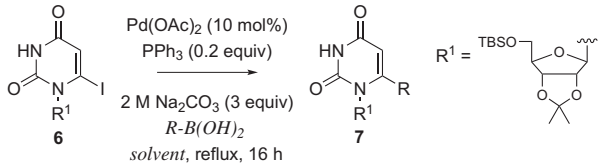
improved, while 2-furanboronic acid (**3g**), *p*-nitrophenylboronic acid (**3c**), and *n*-butylboronic acid (**3i**) remained ineffective.

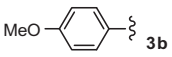
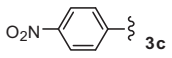
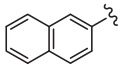
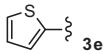
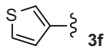
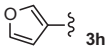
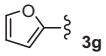
The results prompted us to re-examine the reactivity of these boronic acids (**3c**,**g**, and **i**) with the model reaction. It was found that **3c** and **3i** could react with 6-chloro-1,3-dimethyluracil (**1a**) to afford the desired products under the optimized condition (entries 1–7 in Table 4). This allowed us to apply our successful approach in Scheme 1 to use N^3-(*p*-methoxybenzyl)-5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylidene-6-iodouridine (**11**) for the coupling reaction with less reactive boronic acids. Thus, N^3-PMB-substituted 6-iodouridine **11** was treated with **3c** and **3i** under the optimized condition to give the corresponding sugar- and N^3-protected 6-substituted uridine derivatives (**13c** and **13i**) (entries 8–14 in Table 4). The results confirmed that the N^3-imide interferes with the coupling reaction and the N^3-protection is required for less reactive reactants.

A product analysis of the reaction mixtures was performed during the optimization studies. Besides the dehalogenated product, another common by-product was identified as *N*-(5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-β-D-ribofuranosyl)malonamide (**15**) on the basis of mass spectrometry and intensive NMR studies. Since 6-halouracil derivatives are very accessible to the nucleophilic aromatic substitution, we rationalized that the hydrolysis of 6-iodouridine **6** under the aqueous alkaline condition first took place to give the corresponding 6-hydroxyuridine derivative (**14**). Subsequently, tautomerization of the 6-hydroxyuridine **14** to the barbiturate nucleoside (**14′**) followed by the ring-opening hydrolysis resulted in the formation of the by-product **15** and further degradation products (Scheme 2).

The hydrolytic degradation appeared to be the competing reaction with the Suzuki–Miyaura cross-coupling reaction. The formation of **15** could only be suppressed when the cross-coupling reaction was effective enough to overcome the hydrolysis, which could account for the low yields of the less reactive boronic acids. In most of the coupling reactions with 6-iodouridine **6**, toluene is a better solvent than DME, due to the fact that water is less miscible with toluene, which decreased the water content in the reaction to

Table 3
Cross-coupling reaction of 5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylidene-6-iodouridine (**6**) with various boronic acids (**3b**–**i**) using $Pd(OAc)_2$ as the catalyst



Entry	Boronic acid, R–$B(OH)_2$ (equiv)		Solvent[a]	Product (yield %)[b]
1		**3b** (1.2)	Toluene	**7b** (41)[c]
2		**3b** (4)	Toluene	**7b** (93)[c,d]
3		**3c** (4)	Toluene	**7c** (13)[c]
4		**3c** (4)	DME	**7c** (0)[c]
5		**3d** (2)	Toluene	**7d** (81)
6		**3d** (4)	Toluene	**7d** (99)[d]
7		**3e** (4)	Toluene	**7e** (12)
8		**3e** (4)	DME	**7e** (60)[c]
9		**3f** (2)	Toluene	**7f** (43)
10		**3f** (4)	Toluene	**7f** (89)[d]
11		**3h** (4)	Toluene	**7h** (92)[d]
	No reactions: 			

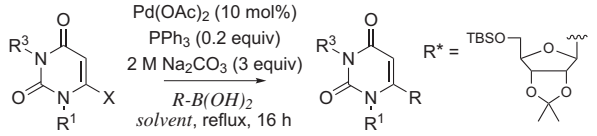
[a] Concentration=0.1 M.
[b] Isolated yield.
[c] Using dppf (0.1 equiv) as the ligand presumably gave the same yield.
[d] Using DME as the solvent tremendously reduced the yield.

minimize the hydrolytic degradation. Our effort to further reduce the amount of water used in the reaction was unsuccessful.

The acid-labile isopropylidene and TBS groups of **7** were deblocked with aqueous trifluoroacetic acid (TFA) to give the desired 6-aryluridines (**16**) in good yields. The oxidative removal of the N^3-PMB group from **13** with cerium ammonium nitrate[32] (CAN) resulted in a mixture of products, in which the isopropylidene and TBS groups were found to be removed prior to the PMB group. As a result, a global deprotection (including PMB, isopropylidene, and TBS groups) of **13** with an excess of CAN furnished the corresponding 6-substituted uridines (**16**) effectively. However, the deprotected products were contaminated with impurities, which were identified as diol–cerium complexes by mass spectrometry. In order to obtain metal-free samples, **13c** and **13i** were treated with an excess of CAN to remove all the protecting groups followed by acetylation of the sugar hydroxy groups to give **17c** and **17i**. Basic deacetylation with aqueous ammonia gave the metal-free 6-substituted uridines **16c** and **16i** (Scheme 3).

The reaction protocol could also be applied to the 5-halouridine derivatives (**18a**,**b**).[34,35] DME was found to be a better solvent than toluene for the coupling reaction of **18a**,**b**. Our studies have also shown that Na_2CO_3 is more suitable for 5-iodouridine **18b**, while Cs_2CO_3 for the reactions with 5-bromouridine **18a** gave better yields. Both 5-bromo- and 5-iodouridines **18a**,**b** were treated with boronic acids **3a**–**c** under the optimized conditions to give the corresponding sugar-protected 5-aryluridines **19a**–**c** in good yields (Table 5). Subsequent deprotection with aqueous TFA afforded the 5-aryluridines **20a**–**c** (Scheme 4).

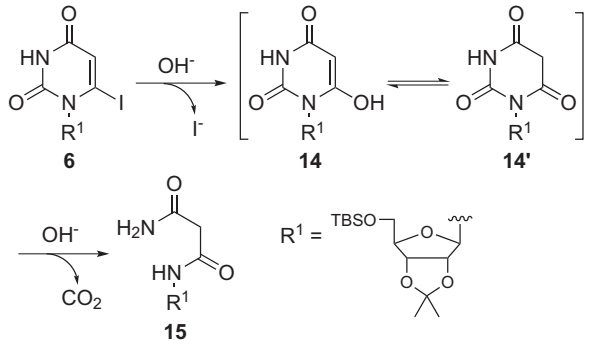
Table 4
Cross-coupling reactions of 1,3-dimethyl-6-chlorouracil (**1a**) and N^3-(*p*-methoxybenzyl)-5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylidene-6-iodouridine (**11**) with boronic acids **3a**,**c**,**g**, and **i**



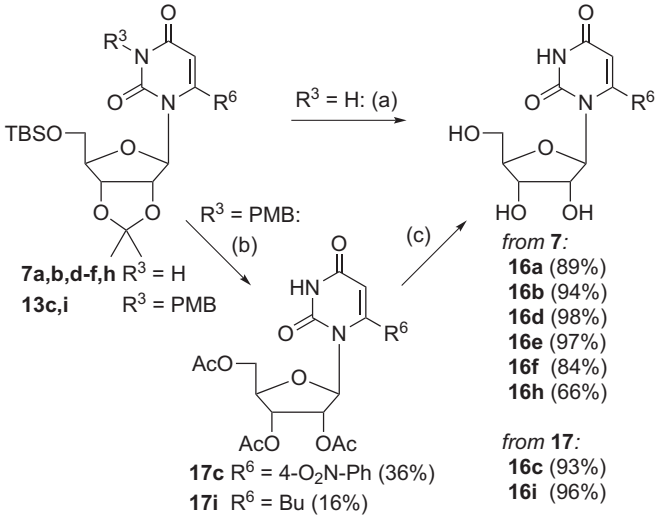
1a $R^1=R^3$ = Me, X = Cl
11 R^1 = R*, R^3 = PMB, X = I
2 $R^1=R^3$ = Me
13 R^1 = R*, R^3 = PMB

Entry	Substrate	R–$B(OH)_2$ (equiv)	Solvent[a]	Product (yield %)[b]
1[c]	**1a**	**3a** (1.2)	Toluene	**2a** (81)
2	**1a**	**3c** (1.2)	Toluene	**2c** (18)
3	**1a**	**3c** (1.2)	DME	**2c** (79)
4	**1a**	**3g** (1.2)	Toluene	**2g** (0)
5	**1a**	**3g** (1.2)	DME	**2g** (0)
6	**1a**	**3i** (2)	Toluene	**2i** (35)
7	**1a**	**3i** (2)	DME	**2i** (42)
8	**11**	**3c** (2)	Toluene	**13c** (85)
9	**11**	**3c** (2)	DME	**13c** (98)
10	**11**	**3g** (2)	Toluene	**13g** (0)
11	**11**	**3g** (2)	DME	**13g** (0)
12	**11**	**3i** (2)	Toluene	**13i** (0)
13	**11**	**3i** (2)	DME	**13i** (11)
14[d]	**11**	**3i** (4)	DME	**13i** (26)

[a] Concentration=0.1 M.
[b] Isolated yield.
[c] The reaction with **3a** was used as a benchmark to evaluate their reactivities under the optimized condition.
[d] Base=2 M Cs_2CO_3 in H_2O (3 equiv).

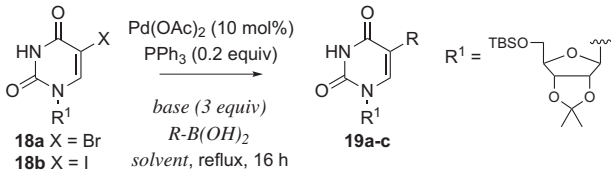


Scheme 2.



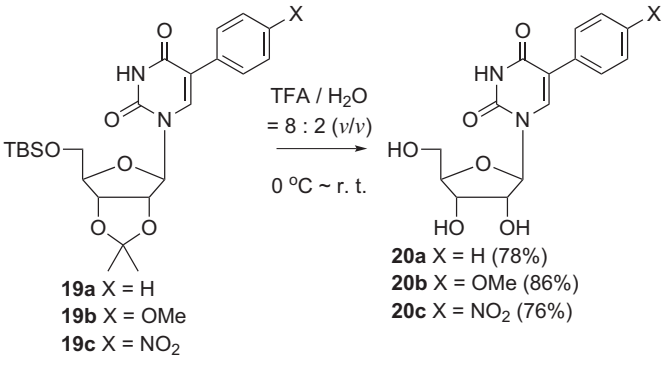
Scheme 3. Reagents and conditions: (a) TFA/H_2O=8:2 (v/v), 0 °C to rt; (b) (i) CAN (6 equiv), CH_3CN/H_2O=1:2 (v/v), 70 °C; (ii) Ac_2O, Et_3N, cat. DMAP, CH_2Cl_2, rt; (c) 28% NH_4OH/MeOH, rt.

Table 5
Cross-coupling reaction of 5-halogenated 5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylideneuridines (**18a**,**b**) with boronic acids (**3a**–**c**)



Entry	Substrate	Base (3 equiv)[a]	R–B(OH)$_2$ (equiv)	Solvent[b]	Product (yield %)[c]
1	**18a**	Na_2CO_3	**3a** (1.2)	Toluene	**19a** (37)
2	**18a**	Na_2CO_3	**3a** (1.2)	DME	**19a** (18)
3	**18a**	Cs_2CO_3	**3a** (1.2)	DME	**19a** (77)
4	**18b**	Na_2CO_3	**3a** (1.2)	Toluene	**19a** (18)
5	**18b**	Na_2CO_3	**3a** (1.2)	DME	**19a** (46)
6	**18a**	Cs_2CO_3	**3b** (1.2)	DME	**19b** (61)
7	**18b**	Na_2CO_3	**3b** (1.2)	DME	**19b** (55)
8	**18a**	Cs_2CO_3	**3c** (2)	DME	**19c** (35)
9	**18b**	Na_2CO_3	**3c** (2)	DME	**19c** (38)

[a] 2 M in H_2O.
[b] Concentration=0.1 M.
[c] Isolated yield.



Scheme 4.

3. Conclusion

In summary, our investigation has revealed that, although 6-iodouridine **6** is more reactive in the Suzuki–Miyaura coupling reaction than 5-halouridines **18a**,**b**, it is also susceptible to alkaline hydrolysis competitively, which leads to the consumption of the substrate during the coupling reaction. Herein, we have developed an effective synthesis of 6-alkyl and 6-aryl-substituted uridines from sugar-protected 6-iodouridine **6** via the $Pd(OAc)_2$-catalyzed Suzuki–Miyaura cross-coupling reaction. The methodology is amenable to the synthesis of a collective compound library of substituted uridine derivatives for biological applications.

4. Experimental section

4.1. General chemical procedures

The chemical shift values are reported in δ values (parts per million, ppm) relative to the standard chemical shift for the hydrogen residue peak in the deuterated solvent, $CDCl_3$, or DMSO-d_6 (*J. Org. Chem.* **1997**, *62*, 7512–7515). The coupling constant (*J*) values are expressed in hertz (Hz). Thin-layer chromatography (TLC) was performed on silica gel plates. Compounds on TLC were visualized by illumination under UV light (254 nm), or dipped into 10% ethanolic sulfuric acid followed by charring on a hot plate. Solvent systems are expressed as a percentage of the more polar component with respect to total volume (v/v %). Silica gel (230–400 mesh) was used for flash column chromatography as described by W.C. Still et al. (*J. Org. Chem.* **1978**, *43*, 2923–2925). Evaporations were carried out under reduced pressure (water aspirator) with the bath temperature below 50 °C unless specified otherwise. Materials obtained from commercial suppliers were used without further purification.

4.2. Preparation of 6-iodouridine derivatives

*4.2.1. 5′-O-tert-Butyldimethylsilyl-2′,3′-O-isopropylidene-6-iodo-N^3-methyluridine (**10a**).* To a solution of 5′-*O*-*tert*-butyldimethylsilyl-2′,3′-*O*-isopropylidene-*N*^{3}-methyluridine[31] (**8a**, 7.67 g, 14.25 mmol) in THF (50 mL) under argon at −78 °C was added LDA (2 M solution in THF/*n*-heptane/ethylbenzene, Acros, 14.3 mL, 28.5 mmol, 2.0 equiv). The reaction mixture was stirred at −78 °C for 1 h. Iodine (7.23 g, 28.50 mmol, 2.0 equiv) was added and the mixture was stirred at −78 °C for additional 3 h. The reaction was quenched by adding acetic acid at −78 °C, then was allowed to warm up to room temperature. The solvent was removed under reduced pressure, and the residue was dissolved in EtOAc. The solution was washed with saturated aqueous $NaHCO_3$ solution, 10% aqueous $Na_2S_2O_3$ solution, and saturated aqueous NaCl solution. The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (Hex/EtOAc=8:2, R_f=0.25) to give the product (**10a**, oil, 3.45 g, 6.41 mmol, 45%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.46 (s, 1H, 5-H), 6.06 (d, 1H, *J*=0.7 Hz, 1′-H), 5.15 (dd, 1H, *J*=1.0 and 6.4 Hz, 2′-H), 4.82 (dd, 1H, *J*=4.5 and 6.3 Hz, 3′-H), 4.19–4.13 (m, 1H, 4′-H), 3.80 (dd, 1H, *J*=5.6 and 10.8 Hz, 5′-H), 3.77 (dd, 1H, *J*=7.1 and 10.8 Hz, 5′-H), 3.22 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 0.86 (s, 9H, CH_3), 0.02 (s, 3H, CH_3), 0.01 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.7, 148.1, 116.2 (CH), 113.7, 110.9, 102.4 (CH), 89.6 (CH), 84.4 (CH), 81.9 (CH), 63.9 (CH_2), 27.8 (CH_3), 27.2 (CH_3), 25.9 (CH_3), 25.3 (CH_3), 18.4, −5.30 (CH_3), −5.32 (CH_3); MS (ESI) *m*/*z* 561 (100) (M+Na); HRMS calcd for $C_{19}H_{32}IN_2O_6Si$ (M+1): 539.1074. Found: 539.1106.

*4.2.2. 5′-O-tert-Butyldimethylsilyl-2′,3′-O-isopropylidene-N^3-benzyl-6-iodouridine (**10b**).* Compound **10b** was prepared from 5′-*O*-*tert*-butyldimethylsilyl-2′,3′-*O*-isopropylidene-*N*^{3}-benzyl-uridine (**8b**, prepared from 5′-*O*-*tert*-butyldimethylsilyl-2′,3′-*O*-isopropylideneuridine (**5**) by the same method for **8a**[31]) by the method described for **10a**. The reaction was purified by flash column chromatography (Hex/EtOAc=8:2, R_f=0.26) to give the product (**10b**, oil, 50%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (d, 2H, *J*=6.6 Hz, Ph), 7.31–7.25 (m, 3H, Ph), 6.49 (s, 1H, 5-H), 6.08 (s, 1H, 1′-H), 5.15 (d, 1H, *J*=6.4 Hz, 2′-H), 5.04 (d, 1H, *J*=13.1 Hz, CH_2), 4.98 (d, 1H, *J*=13.1 Hz, CH_2), 4.87 (dd, 1H, *J*=4.3 and 6.2 Hz, 3′-H), 4.17 (dd, 1H, *J*=6.1 and 10.8 Hz, 4′-H), 3.79 (dd, 1H, *J*=5.8 and 10.6 Hz, 5′-H), 3.72 (dd, 1H, *J*=7.1 and 10.6 Hz, 5′-H), 1.55 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 0.89 (s, 9H, CH_3), 0.03 (s, 3H, CH_3), 0.02 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.4, 148.0, 135.9, 128.9 (CH), 128.4 (CH), 127.8 (CH), 116.4 (CH), 113.6, 111.2, 102.7 (CH), 89.8 (CH), 84.4 (CH), 82.3 (CH), 63.8 (CH_2), 44.5 (CH_2), 27.2 (CH_3), 25.9 (CH_3), 25.4 (CH_3), 18.4, −5.2 (CH_3), −5.3 (CH_3); MS (ESI) *m*/*z* 637 (100) (M+Na); HRMS calcd for $C_{25}H_{35}IN_2O_6Si$ Na (M+Na): 637.1207. Found: 637.1208.

*4.2.3. 5′-O-tert-Butyldimethylsilyl-2′,3′-O-isopropylidene-6-iodo-N^3-(p-methoxybenzyl)uridine (**11**).* Compound **11** was prepared from 5′-*O*-*tert*-butyldimethylsilyl-2′,3′-*O*-isopropylidene-*N*^{3}-(*p*-methoxybenzyl)uridine[32] (**9**) by the method described for **10a**. The reaction was purified by flash column chromatography (Hex/EtOAc=8:2, R_f=0.21) to give the product (**11**, oil, 43%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 (d, 2H, *J*=8.7 Hz, Ph), 6.81 (d, 2H, *J*=8.6 Hz, Ph), 6.47 (s, 1H, 5-H), 6.06 (s, 1H, 1′-H), 5.15 (d, 1H, *J*=6.1 Hz, 2′-H), 4.97 (d, 1H, *J*=13.6 Hz, CH_2), 4.89–4.87 (m, 2H, 3′-H, and CH_2), 4.17 (dd, 1H, *J*=6.1 and 10.8 Hz, 4′-H), 3.81 (dd, 1H, *J*=5.8 and 10.6 Hz, 5′-H), 3.76

(s, 3H, OCH_3), 3.73 (dd, 1H, J=7.2 and 10.6 Hz, 5′-H), 1.55 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 0.89 (s, 9H, CH_3), 0.03 (s, 3H, CH_3), 0.02 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.4, 159.2, 148.0, 130.6 (CH), 128.1, 116.4 (CH), 113.7 (CH), 113.6, 111.0, 102.6 (CH), 89.9 (CH), 84.4 (CH), 82.3 (CH), 63.9 (CH_2), 55.1 (CH_3), 43.9 (CH_2), 27.2 (CH_3), 25.9 (CH_3), 25.4 (CH_3), 18.4, −5.3 (CH_3), −5.4 (CH_3); MS (ESI) m/z 667 (100) (M+Na); HRMS calcd for $C_{26}H_{37}IN_2O_7Si\cdot Na$ (M+Na): 667.1313. Found: 667.1312.

4.3. General procedure for the Suzuki–Miyaura cross-coupling reaction

To a mixture of 5′-*O*-*tert*-butyldimethylsilyl-2′,3′-*O*-isopropylidene-6-iodouridine[30] (**6**, 0.2620 g, 0.50 mmol), arylboronic acid (1.2–4.0 equiv), triphenylphosphine (0.0262 g, 0.10 mmol, 0.2 equiv), and palladium(II) acetate (0.0112 g, 0.05 mmol, 0.1 equiv) in toluene (5 mL) was added 2 M aqueous sodium carbonate solution (0.75 mL, 1.50 mmol, 3 equiv) at room temperature. The reaction system was filled with argon then the reaction mixture was heated at reflux temperature for 16 h. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was partitioned between EtOAc and H_2O. The organic layer was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography to give the product.

*4.3.1. 5′-O-tert-Butyldimethylsilyl-2′,3′-O-isopropylidene-6-phenyluridine[23,27] (**7a**).* The reaction was purified by flash column chromatography (Hex/ether=5:5, R_f=0.19) to give the product (**7a**, white solid, 82%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.13 (s, 1H, NH), 7.50–7.48 (m, 5H, Ph), 5.65 (s, 1H, 1′-H), 5.47 (s, 1H, 5-H), 5.21 (d, 1H, J=6.4 Hz, 2′-H), 4.80 (dd, 1H, J=4.6 and 6.0 Hz, 3′-H), 4.05 (dd, 1H, J=6.2 and 10.7 Hz, 4′-H), 3.85 (d, 2H, J=6.4 Hz, 5′-H), 1.35 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 0.89 (s, 9H, CH_3), 0.06 (s, 6H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.1, 156.8, 150.7, 132.5, 130.6 (CH), 129.0 (CH), 128.2 (CH), 113.5, 104.0 (CH), 93.1 (CH), 89.2 (CH), 84.0 (CH), 82.2 (CH), 64.2 (CH_2), 27.0 (CH_3), 25.9 (CH_3), 25.3 (CH_3), 18.4, −5.2 (CH_3); MS (ESI) m/z 497 (100) (M+Na); HRMS calcd for $C_{24}H_{34}N_2O_6Si\cdot Na$ (M+Na): 497.2084. Found: 497.2091.

*4.3.2. 5′-O-tert-Butyldimethylsilyl-2′,3′-O-isopropylidene-6-(p-methoxyphenyl)uridine (**7b**).* The reaction was purified by flash column chromatography (Hex/ether=4:6, R_f=0.27) to give the product (**7b**, foam, 93%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.30 (br s, 1H, NH), 7.41 (br d, 2H, J=6.7 Hz, Ph), 7.0 (d, 2H, J=8.8 Hz, Ph), 5.61 (s, 1H), 5.55 (s, 1H), 5.20 (d, 1H, J=6.2 Hz, 2′-H), 4.80 (dd, 1H, J=4.6 and 6.0 Hz, 3′-H), 4.05 (dd, 1H, J=6.2 and 10.6 Hz, 4′-H), 3.87 (s, 3H, CH_3), 3.85 (d, 2H, J=6.4 Hz, 5′-H), 1.39 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 0.90 (s, 9H, CH_3), 0.07 (s, 6H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.6, 161.4, 156.8, 150.6, 129.9 (CH), 124.6, 114.5 (CH), 113.5, 103.7 (CH), 93.0 (CH), 89.3 (CH), 84.2 (CH), 82.2 (CH), 64.2 (CH_2), 55.4 (CH_3), 27.1 (CH_3), 25.9 (CH_3), 25.3 (CH_3), 18.4, −5.19 (CH_3); MS (ESI) m/z 505 (37) (M+1), 527 (100) (M+Na); HRMS calcd for $C_{25}H_{37}N_2O_7Si$ (M+1): 505.2370. Found: 505.2407.

*4.3.3. 5′-O-tert-Butyldimethylsilyl-2′,3′-O-isopropylidene-6-(2-naphthyl)uridine[23] (**7d**).* The reaction was purified by flash column chromatography (Hex/EtOAc=6.5:3.5, R_f=0.24) to give the product (**7d**, foam, 99%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.37 (br s, 1H, NH), 7.98–7.91 (m, 4H, Np), 7.64–7.48 (m, 3H, Np), 5.75 (s, 1H), 5.55 (s, 1H), 5.24 (d, 1H, J=5.6 Hz, 2′-H), 4.81 (t, 1H, J=5.3 Hz, 3′-H), 4.08–3.98 (m, 1H, 4′-H), 3.87 (d, 2H, J=6.0 Hz, 5′-H), 1.31 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 0.92 (s, 9H, CH_3), 0.10 (s, 3H, CH_3), 0.09 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.8, 156.9, 150.6, 133.8, 132.8, 129.8, 128.9(CH), 128.6 (CH), 128.5 (CH), 127.9 (CH), 127.8 (CH), 127.2 (CH), 124.7 (CH), 113.6, 104.3 (CH), 93.2 (CH), 89.3 (CH), 84.1 (CH), 82.2 (CH), 64.2 (CH_2), 27.0 (CH_3), 25.9 (CH_3), 25.3 (CH_3), 18.4, −5.16 (CH_3), −5.19 (CH_3); MS (ESI) m/z 523 (100) (M−1); HRMS calcd for $C_{28}H_{37}N_2O_6Si$ (M+1): 525.2421. Found: 525.2422.

*4.3.4. 5′-O-tert-Butyldimethylsilyl-2′,3′-O-isopropylidene-6-(2-thiophenyl)uridine[23] (**7e**).* The reaction was purified by flash column chromatography (Hex/EtOAc=7:3, R_f=0.17; $CHCl_3$/Ether=9:1, R_f=0.20) to give the product (**7e**, foam, 60%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.95 (br s, 1H, NH), 7.53 (d, 1H, J=5.0 Hz, Tp), 7.48 (d, 1H, J=3.5 Hz, Tp), 7.17 (dd, 1H, J=3.9 and 4.8 Hz, Tp), 5.81 (s, 1H), 5.80 (s, 1H), 5.22 (d, 1H, J=6.4 Hz, 2′-H), 4.83 (t, 1H, J=5.2 Hz, 3′-H), 4.12 (dd, 1H, J=6.1 and 10.6 Hz, 4′-H), 3.85 (d, 2H, J=6.4 Hz, 5′-H), 1.43 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 0.90 (s, 9H, CH_3), 0.07 (s, 6H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.9, 150.4, 149.8, 132.4, 130.5 (CH), 129.3 (CH), 128.2 (CH), 113.5, 104.9 (CH), 93.0 (CH), 89.5 (CH), 84.2 (CH), 82.3 (CH), 64.2 (CH_2), 27.1 (CH_3), 25.9 (CH_3), 25.4 (CH_3), 18.4, −5.19 (CH_3), −5.22 (CH_3); MS (ESI) m/z 479 (100) (M−1); HRMS calcd for $C_{22}H_{31}N_2O_6SSi$ (M−1): 479.1672. Found: 479.1711.

*4.3.5. 5′-O-tert-Butyldimethylsilyl-2′,3′-O-isopropylidene-6-(3-thiophenyl)uridine (**7f**).* The resulting residue was purified by flash column chromatography (Hex/EtOAc=6.5:3.5, R_f=0.28) to give the product (**7f**, foam, 89%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.76 (br s, 1H, NH), 7.66 (d, 1H, J=1.7 Hz, Tp), 7.47 (dd, 1H, J=3.0 and 4.9 Hz, Tp), 7.27 (d, 1H, J=5.1 Hz, Tp), 5.71 (d, 1H, J=1.7 Hz), 5.62 (s, 1H), 5.21 (d, 1H, J=6.4 Hz, 2′-H), 4.81 (dd, 1H, J=4.4 and 6.2 Hz, 3′-H), 4.10 (dd, 1H, J=6.2 and 10.6 Hz, 4′-H), 3.84 (d, 2H, J=6.4 Hz, 5′-H), 1.42 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 0.90 (s, 9H, CH_3), 0.07 (s, 6H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.7, 151.9, 150.5, 132.7, 127.6 (CH), 127.5 (CH), 127.3 (CH), 113.5, 103.6 (CH), 93.1 (CH), 89.5 (CH), 84.1 (CH), 82.3 (CH), 64.2 (CH_2), 27.1 (CH_3), 25.9 (CH_3), 25.4 (CH_3), 18.4, −5.20 (CH_3), −5.22 (CH_3); MS (ESI) m/z 479 (100) (M−1); HRMS calcd for $C_{22}H_{32}N_2O_6SSi$ (M+1): 481.1829. Found: 481.1829.

*4.3.6. 5′-O-tert-Butyldimethylsilyl-2′,3′-O-isopropylidene-6-(3-furanyl)uridine (**7h**).* The reaction was purified by flash column chromatography (Hex/EtOAc=6.5:3.5, R_f=0.24) to give the product (**7h**, foam, 92%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.52 (br s, 1H, NH), 7.80 (s, 1H, Fr), 7.54 (s, 1H, Fr), 6.70 (d, 1H, J=0.8 Hz, Fr), 5.74 (s, 1H), 5.72 (d, 1H, J=1.6 Hz), 5.21 (d, 1H, J=6.4 Hz, 2′-H), 4.83 (dd, 1H, J=4.4 and 6.1 Hz, 3′-H), 4.14 (dd, 1H, J=6.2 and 10.6 Hz, 4′-H), 3.84 (d, 2H, J=6.4 Hz, 5′-H), 1.46 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 0.89 (s, 9H, CH_3), 0.06 (s, 6H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.7, 150.5, 149.0, 144.3 (CH), 142.8 (CH), 118.6, 113.5, 110.3 (CH), 103.2 (CH), 93.0 (CH), 89.7 (CH), 84.1 (CH), 82.3 (CH), 64.2 (CH_2), 27.1 (CH_3), 25.9 (CH_3), 25.3 (CH_3), 18.4, −5.22 (CH_3); MS (ESI) m/z 463 (100) (M−1); HRMS calcd for $C_{22}H_{33}N_2O_7Si$ (M+1): 465.2057. Found: 465.2063.

*4.3.7. 5′-O-tert-Butyldimethylsilyl-2′,3′-O-isopropylidene-N^3-methyl-6-phenyluridine (**12a**).* The reaction was purified by flash column chromatography (Hex/EtOAc=8:2, R_f=0.20) to give the product (**12a**, oil, 82%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50–7.47 (m, 5H, Ph), 5.71 (s, 1H, 5-H), 5.53 (d, 1H, J=1.3 Hz, 1′-H), 5.23 (dd, 1H, J=1.4 and 6.4 Hz, 2′-H), 4.85 (dd, 1H, J=4.4 and 6.4 Hz, 3′-H), 4.08–4.04 (m, 1H, 4′-H), 3.88 (d, 2H, J=6.2 Hz, 5′-H), 3.34 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 0.90 (s, 9H, CH_3), 0.07 (s, 3H, CH_3), 0.06 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.0, 154.2, 151.3, 132.7, 130.4 (CH), 129.0 (CH), 128.3 (CH), 113.5, 103.5 (CH), 93.6 (CH), 89.0 (CH), 84.1 (CH), 82.2 (CH), 64.2 (CH_2), 27.5, 27.0 (CH_3), 25.9 (CH_3), 25.4 (CH_3), 18.5, −5.2 (CH_3); MS (ESI) m/z 511 (100) (M+Na); HRMS calcd for $C_{25}H_{36}N_2O_6Si\cdot Na$ (M+Na): 511.2240. Found: 511.2247.

*4.3.8. 5′-O-tert-Butyldimethylsilyl-2′,3′-O-isopropylidene-N^3-benzyl-6-phenyluridine (**12b**).* The reaction was purified by flash column

chromatography (Hex/EtOAc=8:2, R_f=0.31) to give the product (**12b**, oil, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50–7.46 (m, 7H, Ph), 7.34–7.27 (m, 3H, Ph), 5.69 (s, 1H, 5-H), 5.49 (d, 1H, J=1.1 Hz, 1′-H), 5.18 (dd, 1H, J=1.3 and 6.5 Hz, 2′-H), 5.15 (d, 1H, J=13.8 Hz, CH_2), 5.09 (d, 1H, J=13.8 Hz, CH_2), 4.85 (dd, 1H, J=4.2 and 6.4 Hz, 3′-H), 4.06–4.02 (m, 1H, 4′-H), 3.85 (dd, 1H, J=5.7 and 10.6 Hz, 5′-H), 3.78 (dd, 1H, J=7.3 and 10.6 Hz, 5′-H), 1.35 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 0.90 (s, 9H, CH_3), 0.04 (s, 6H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.8, 154.4, 151.1, 136.6, 132.6, 130.4 (CH), 129.0 (CH), 128.9 (CH), 128.4 (CH), 128.3 (CH), 127.6 (CH), 113.4, 103.7 (CH), 93.8 (CH), 89.2 (CH), 84.1 (CH), 82.4 (CH), 64.1 (CH_2), 44.1 (CH_2), 27.0 (CH_3), 25.9 (CH_3), 25.4 (CH_3), 18.4, −5.2 (CH_3), −5.3 (CH_3); MS (ESI) m/z 587 (100) (M+Na); HRMS calcd for $C_{31}H_{40}N_2O_6Si\cdot Na$ (M+Na): 587.2553. Found: 587.2546.

*4.3.9. 5′-O-tert-Butyldimethylsilyl-2′,3′-O-isopropylidene-N^3-(p-methoxybenzyl)-6-phenyluridine (**13a**).* The reaction was purified by flash column chromatography (Hex/EtOAc=8.5:1.5, R_f=0.20) to give the product (**13a**, oil, 69%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48–7.46 (m, 7H, Ph), 6.85 (d, 2H, J=8.6 Hz, Ph), 5.69 (s, 1H, 5-H), 5.51 (d, 1H, J=1.1 Hz, 1′-H), 5.21 (dd, 1H, J=1.2 and 6.4 Hz, 2′-H), 5.11 (d, 1H, J=13.6 Hz, CH_2), 5.05 (d, 1H, J=13.6 Hz, CH_2), 4.89 (dd, 1H, J=4.2 and 6.4 Hz, 3′-H), 4.09–4.05 (m, 1H, 4′-H), 3.89 (dd, 1H, J=5.6 and 10.6 Hz, 5′-H), 3.84–3.78 (m, 1H, 5′-H), 3.81 (s, 3H, OCH_3), 1.35 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 0.91 (s, 9H, CH_3), 0.05 (s, 6H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.8, 159.1, 154.2, 151.1, 132.7, 130.8 (CH), 130.4 (CH), 128.9 (CH), 128.8, 128.2 (CH), 113.7 (CH), 113.3, 103.8 (CH), 93.8 (CH), 89.2 (CH), 84.1 (CH), 82.5 (CH), 64.1 (CH_2), 55.2 (CH_3), 43.5 (CH_2), 27.0 (CH_3), 25.9 (CH_3), 25.4 (CH_3), 18.4, −5.2 (CH_3), −5.3 (CH_3); MS (ESI) m/z 617 (100) (M+Na); HRMS calcd for $C_{32}H_{42}N_2O_7Si\cdot Na$ (M+Na): 617.2659. Found: 617.2662.

*4.3.10. 5′-O-tert-Butyldimethylsilyl-2′,3′-O-isopropylidene-N^3-(p-methoxybenzyl)-6-(p-nitrophenyl)uridine (**13c**).* The reaction was purified by flash column chromatography (Hex/ether=6:4, R_f=0.19; Hex/EtOAc=8:2, R_f=0.23) to give the product (**13c**, 98%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.34 (d, 2H, J=9.0 Hz, Ph), 7.67 (br d, 2H, J=4.8 Hz, Ph), 7.46 (d, 2H, J=8.6 Hz, Ph), 6.84 (d, 2H, J=8.6 Hz, Ph), 5.88 (s, 1H), 5.27 (s, 1H), 5.18 (d, 1H, J=6.5 Hz, 2′-H), 5.08 (d, 1H, J=13.6 Hz, CH_2), 5.02 (d, 1H, J=13.6 Hz, CH_2), 4.88 (dd, 1H, J=4.3 and 6.3 Hz, 3′-H), 4.08–4.04 (m, 1H, 4′-H), 3.86 (dd, 1H, J=5.6 and 10.6 Hz, 5′-H), 3.81–3.77 (m, 1H, 5′-H), 3.78 (s, 3H, OCH_3), 1.36 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 0.90 (s, 9H, CH_3), 0.06 (s, 6H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.2, 159.3, 151.8, 150.7, 148.9, 138.6, 130.8 (CH), 129.5 (CH), 128.5, 124.2 (CH), 113.7 (CH), 113.6, 104.5 (CH), 94.0 (CH), 89.6 (CH), 84.0 (CH), 82.3 (CH), 64.0 (CH_2), 55.2 (CH_3), 43.7 (CH_2), 27.0 (CH_3), 25.9 (CH_3), 25.3 (CH_3), 18.4, −5.26 (CH_3), −5.29 (CH_3); MS (ESI) m/z 662 (100) (M+Na); HRMS calcd for $C_{32}H_{41}N_3O_9Si\cdot Na$ (M+Na): 662.2510. Found: 662.2504.

*4.3.11. 5′-O-tert-Butyldimethylsilyl-2′,3′-O-isopropylidene-6-(n-butyl)-N^3-(p-methoxybenzyl)uridine (**13i**).* The reaction was purified by flash column chromatography (Hex/EtOAc=8:2, R_f=0.20) to give the product (**13i**, oil, 26%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (d, 2H, J=8.7 Hz, Ph), 6.81 (d, 2H, J=8.7 Hz, Ph), 5.68 (s, 1H, CH), 5.59 (s, 1H, CH), 5.17 (d, 1H, J=6.4 Hz, 2′-H), 5.0 (d, 1H, J=13.6 Hz, CH_2), 4.93 (d, 1H, J=13.7 Hz, CH_2), 4.88 (dd, 1H, J=4.3 and 6.4 Hz, 3′-H), 4.16–4.12 (m, 1H, 4′-H), 3.83 (dd, 1H, J=5.4 and 10.7 Hz, 5′-H), 3.78–3.72 (m, 1H, 5′-H), 3.76 (s, 3H, OCH_3), 2.51 (t, 2H, J=7.7 Hz, CH_2), 1.64–1.56 (m, 2H, CH_2), 1.53 (s, 3H, CH_3), 1.46–1.37 (m, 2H, CH_2), 1.34 (s, 3H, CH_3), 0.95 (t, 3H, J=7.3 Hz, CH_3), 0.87 (s, 9H, CH_3), 0.01 (s, 6H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.1, 159.0, 154.3, 151.2, 130.5 (CH), 128.9, 113.6 (CH), 113.5, 101.6 (CH), 92.1 (CH), 89.6 (CH), 84.4 (CH), 82.4 (CH), 64.2 (CH_2), 55.1 (CH_3), 43.3 (CH_2), 32.4 (CH_2), 29.5 (CH_2), 27.2 (CH_3), 25.9 (CH_3), 25.4 (CH_3), 22.1 (CH_2), 18.4, 13.6 (CH_3), −5.3 (CH_3), −5.4 (CH_3); MS (ESI) m/z 573 (100) (M−1); HRMS calcd for $C_{30}H_{45}N_2O_7Si$ (M−1): 573.2996. Found: 573.2994.

*4.3.12. 5′-O-tert-Butyldimethylsilyl-2′,3′-O-isopropylidene-5-phenyluridine (**19a**).* The reaction was purified by flash column chromatography (Hex/EtOAc=8:2, R_f=0.13) to give the product (**19a**, 77%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.17 (br s, 1H, NH), 7.61 (s, 1H, 6-H), 7.47–7.32 (m, 5H, Ph), 5.93 (d, 1H, J=3.2 Hz, 1′-H), 4.82–4.73 (m, 2H, 2′-H, and 3′-H), 4.34 (t, 1H, J=2.8 Hz, 4′-H), 3.91–3.77 (m, 2H, 5′-H), 1.60 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 0.77 (s, 9H, CH_3), −0.03 (s, 3H, CH_3), −0.10 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.9, 149.6, 137.8, 132.2, 128.4 (CH), 128.3 (CH), 128.0 (CH), 115.4 (CH), 114.2, 92.9 (CH), 86.7 (CH), 85.0 (CH), 80.6 (CH), 63.3 (CH_2), 27.2 (CH_3), 25.7 (CH_3), 25.3 (CH_3), 18.2, −5.5 (CH_3), −5.6 (CH_3); MS (ESI) m/z 475 (100) (M+1).

*4.3.13. 5′-O-tert-Butyldimethylsilyl-2′,3′-O-isopropylidene-5-(p-methoxyphenyl)uridine (**19b**).* The reaction was purified by flash column chromatography (Hex/EtOAc=6.5:3.5, R_f=0.25) to give the product (**19b**, 61%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.87 (br s, 1H, NH), 7.53 (s, 1H, 6-H), 7.39 (d, 1H, J=8.6 Hz, Ph), 6.90 (d, 1H, J=8.6 Hz, Ph), 5.91 (d, 1H, J=2.6 Hz, 1′-H), 4.83 (dd, 1H, J=2.8 and 6.1 Hz, 3′-H), 4.75 (dd, 1H, J=2.7 and 6.1 Hz, 2′-H), 4.32 (d, 1H, J=2.8 Hz, 4′-H), 3.89 (dd, 1H, J=2.5 and 11.4 Hz, 5′-H), 3.81–3.78 (m, 4H, CH_3, and 5′-H), 1.60 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 0.79 (s, 9H, CH_3), −0.01 (s, 3H, CH_3), −0.07 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.2, 159.5, 149.7, 137.1 (CH), 129.6 (CH), 124.6, 115.1, 114.2, 114.0 (CH), 93.0 (CH), 86.7 (CH), 84.9 (CH), 80.7 (CH), 63.4 (CH_2), 55.3 (CH_3), 27.2 (CH_3), 25.8 (CH_3), 25.3 (CH_3), 18.3, −5.5 (CH_3), −5.6 (CH_3); MS (ESI) m/z 505 (100) (M+1), 527 (46) (M+Na); HRMS calcd for $C_{25}H_{35}N_2O_7Si$ (M−1): 503.2214. Found: 503.2212.

*4.3.14. 5′-O-tert-Butyldimethylsilyl-2′,3′-O-isopropylidene-5-(p-nitrophenyl)uridine (**19c**).* The reaction was purified by flash column chromatography (Hex/EtOAc=7:3, R_f=0.28) to give the product (**19c**, 38%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.61 (s, 1H, NH), 8.20 (d, 1H, J=8.8 Hz, Ph), 7.83 (br s, 1H, 6-H), 7.70 (d, 1H, J=8.8 Hz, Ph), 5.91 (d, 1H, J=2.6 Hz, 1′-H), 4.82 (dd, 1H, J=2.7 and 6.1 Hz, 2′-H), 4.73 (dd, 1H, J=2.2 and 6.1 Hz, 3′-H), 4.40 (d, 1H, J=2.3 Hz, 4′-H), 3.90 (dd, 1H, J=2.1 and 11.6 Hz, 5′-H), 3.80 (dd, 1H, J=3.3 and 11.6 Hz, 5′-H), 1.59 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 0.75 (s, 9H, CH_3), −0.04 (s, 3H, CH_3), −0.11 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.7, 149.5, 147.1, 139.4 (CH), 139.1, 128.8 (CH), 123.6 (CH), 114.2, 112.5, 93.6 (CH), 87.1 (CH), 85.3 (CH), 80.7 (CH), 63.4 (CH_2), 27.1 (CH_3), 25.7 (CH_3), 25.2 (CH_3), 18.2, −5.5 (CH_3), −5.6 (CH_3); MS (ESI) m/z 518 (100) (M−1); HRMS calcd for $C_{24}H_{33}N_3O_8Si$ (M−1): 518.1959. Found: 518.1963.

*4.3.15. N-(5′-O-tert-Butyldimethylsilyl-2′,3′-O-isopropylidene-β-D-ribofuranosyl)malonamide (**15**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44 (s, 1H, NH), 7.28 (d, 1H, J=9.1 Hz, NH), 5.85 (d, 1H, J=9.1 Hz, 1′-H), 5.61 (s, 1H, NH), 4.72 (d, 1H, J=5.9 Hz, 2′-H), 4.51 (d, 1H, J=5.9 Hz, 3′-H), 4.31 (s, 1H, 4′-H), 3.82–3.74 (m, 2H, 5′-H), 3.15 (d, 1H, J=16.6 Hz, CH_2), 3.09 (d, 1H, J=16.6 Hz, CH_2), 1.53 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 0.96 (s, 9H, CH_3), 0.17 (s, 3H, CH_3), 0.16 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.1, 167.1, 112.9, 87.3 (CH), 86.7 (CH), 86.6 (CH), 82.2 (CH), 65.2 (CH_2), 42.8 (CH_2), 26.7 (CH_3), 26.0 (CH_3), 25.1 (CH_3), 18.5, −5.3 (CH_3). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.61 (d, 1H, J=8.5 Hz, NH), 7.44 (s, 1H, NH), 7.07 (s, 1H, NH), 5.34 (dd, 1H, J=2.1 and 8.5 Hz, 1′-H), 4.62 (dd, 1H, J=1.6 and 6.3 Hz, 3′-H), 4.55 (dd, 1H, J=2.2 and 6.2 Hz, 2′-H), 3.94–3.91 (m, 1H, 4′-H), 3.61 (d, 2H, J=6.0 Hz, 5′-H), 3.01 (s, 2H, CH_2), 1.43 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 0.87 (s, 9H, CH_3), 0.06 (s, 3H, CH_3), 0.05 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 168.8, 167.5, 113.0, 85.9 (CH), 85.2 (CH), 84.3 (CH), 82.0 (CH), 63.9 (CH_2), 43.8 (CH_2), 27.3(CH_3), 26.3 (CH_3), 25.6 (CH_3), 18.5, −4.8 (CH_3),

−4.9 (CH_3); MS (ESI) *m*/*z* 411 (100) (M+Na); HRMS calcd for $C_{17}H_{30}N_2O_6Si$ (M−1): 387.1950. Found: 387.1951.

4.4. Deprotection

*4.4.1. 2′,3′,5′-Tri-O-acetyl-6-(p-nitrophenyl)uridine (**17c**).* To a solution of 5′-*O*-*tert*-butyldimethylsilyl-2′,3′-*O*-isopropylidene-N^3-(*p*-methoxybenzyl)-6-(*p*-nitrophenyl)uridine (**13c**, 1.7999 g, 2.8156 mmol) in a mixture of CH_3CN/H_2O (54 mL, 2:1 (v/v)) was added cerium ammonium nitrate (9.2614 g, 16.8936 mmol, 6.0 equiv) and the reaction mixture was heated at 70 °C for 3 h. After cooling to room temperature, the solvents were removed under reduced pressure. The resulting residue was purified by flash column chromatography ($CHCl_3$/MeOH=9:1, R_f=0.16) to give the crude intermediate (**16′c**). To a mixture of the crude intermediate, triethylamine (3.9 mL, 2.849 g, 28.156 mmol, 10.0 equiv) and 4-dimethylaminopyridine (0.1576 g, 1.29 mmol, 0.30 equiv) in CH_2Cl_2 (28.2 mL) was added acetic anhydride (1.0 mL, 1.1210 g, 10.98 mmol, 3.9 equiv) dropwise. After the addition was completed, the reaction mixture was stirred at room temperature for 1.5 h. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc, washed with H_2O, saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, then the solvent was evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (Hex/EtOAc=4:6, R_f=0.24) to give the product (**17c**, oil, 0.5017 g, 1.021 mmol, 36%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.49 (s, 1H, NH), 8.34 (d, 2H, *J*=8.4 Hz, Ph), 7.66 (br s, 2H, Ph), 5.71 (dd, 1H, *J*=1.9 and 6.8 Hz, 2′-H), 5.65 (s, 1H, 5-H), 5.51 (t, 1H, *J*=7.6 Hz, 3′-H), 4.93 (d, 1H, *J*=1.9 Hz, 1′-H), 4.45 (dd, 1H, *J*=3.0 and 12.1 Hz, 5′-H), 4.23 (dd, 1H, *J*=6.2 and 12.1 Hz, 4′-H), 4.12−4.07 (m, 1H, 5′-H), 2.10 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 1.94 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.7, 170.1, 169.4, 161.8, 153.6, 149.8, 149.0, 138.4, 129.5 (CH), 124.1 (CH), 104.9 (CH), 92.9 (CH), 79.6 (CH), 73.8 (CH), 70.2 (CH), 63.0 (CH_2), 20.7 (CH_3), 20.4 (CH_3), 20.3 (CH_3); MS (ESI) *m*/*z* 490 (100) (M−1); HRMS calcd for $C_{21}H_{21}N_3O_{11}$ (M−1): 490.1098. Found: 490.1098.

*4.4.2. 2′,3′,5′-Tri-O-acetyl-6-(n-butyl)uridine (**17i**).* Compound **17i** was prepared from 5′-*O*-*tert*-butyldimethylsilyl-2′,3′-*O*-isopropylidene-N^3-(*p*-methoxybenzyl)-6-(*n*-butyl)uridine (**13i**) by the method described for **17c**. The reaction was purified by flash column chromatography (Hex/EtOAc=4.5:5.5, R_f=0.15) to give the product (**17i**, oil, 16%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.82 (s, 1H, NH), 5.78 (dd, 1H, *J*=2.3 and 6.6 Hz, 2′-H), 5.62−5.58 (m, 1H, 3′-H), 5.54 (s, 1H, 5-H), 5.47 (d, 1H, *J*=2.2 Hz, 1′-H), 4.46−4.41 (m, 1H, 4′-H), 4.22−4.16 (m, 2H, 5′-H), 2.43 (t, 2H, *J*=7.6 Hz, CH_2), 2.07 (s, 3H, CH_3), 2.04 (s, 6H, CH_3), 1.57−1.49 (m, 2H, CH_2), 1.43−1.34 (m, 2H, CH_2), 0.91 (t, 3H, *J*=7.3 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.6, 169.7, 169.1, 163.0, 156.2, 150.4, 102.0 (CH), 90.3 (CH), 79.4 (CH), 73.8 (CH), 70.2 (CH), 63.4 (CH_2), 32.1 (CH_2), 29.2 (CH_2), 22.0 (CH_2), 20.6 (CH_3), 20.4 (CH_3), 20.2 (CH_3), 13.5 (CH_3); MS (ESI) *m*/*z* 340 (30), 425 (100) (M−1); HRMS calcd for $C_{19}H_{27}N_2O_9$ (M+1): 427.1717. Found: 427.1737.

*4.4.3. 6-Phenyluridine[23,27] (**16a**).* To a solution of 5′-*O*-*tert*-butyldimethylsilyl-2′,3′-*O*-isopropylidene-6-phenyluridine (**7a**, 0.8824 g, 1.861 mmol) in a mixture of THF (2 mL) and H_2O (9 mL) was added TFA (9 mL) at 0 °C. After stirring at 0 °C for 10 min, the solution was allowed to warm to room temperature and was stirred for another 30 min. The solvents were removed under reduced pressure. The resulting residue was purified by flash column chromatography ($CHCl_3$/MeOH=9:1, R_f=0.20) to give the product (**16a**, solid, 0.5326 g, 1.664 mmol, 89%). The compound was recrystallized from MeOH/EtOAc to give an analytical product (white solid, 0.1751 g, 0.547 mmol, 29%). Mp 177−179 °C [lit[27] 181−183 °C (MeOH/EtOAc)]; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.48 (s, 1H, NH), 7.54−7.50 (m, 5H, Ph), 5.51 (s, 1H, 5-H), 5.06 (d, 1H, *J*=3.7 Hz, 1′-H), 5.04 (d, 1H, *J*=5.1 Hz, OH), 4.81 (d, 1H, *J*=6.1 Hz, OH), 4.62−4.56 (m, 2H, OH, and 2′-H), 4.01 (dd, 1H, *J*=5.9 and 11.7 Hz, 3′-H), 3.60−3.53 (m, 2H, 4′-H and 5′-H), 3.46−3.42 (m, 1H, 5′-H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.9, 156.8, 151.2, 133.7, 130.8 (CH), 129.5 (CH), 128.7 (CH), 104.2 (CH), 94.3 (CH), 85.5 (CH), 71.6 (CH), 70.5 (CH), 62.8 (CH_2); MS (ESI) *m*/*z* 319 (100) (M−1); HRMS calcd for $C_{15}H_{15}N_2O_6$ (M−1): 319.0930. Found: 319.0931. Anal. Calcd for $C_{15}H_{16}N_2O_6$: C, 56.25; H, 5.04; N, 8.75. Found: C, 56.02; H, 5.19; N, 8.60.

*4.4.4. 6-(p-Methoxyphenyl)uridine (**16b**).* Compound **16b** was prepared from 5′-*O*-*tert*-butyldimethylsilyl-2′,3′-*O*-isopropylidene-6-(*p*-methoxyphenyl)uridine (**7b**) by the method described for **16a**. The reaction was purified by flash column chromatography ($CHCl_3$/MeOH=9:1, R_f=0.16) to give the product (**16b**, solid, 94%). The compound was recrystallized from MeOH/EtOAc to give an analytical product (white solid, 47%). Mp 127−129 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.45 (s, 1H, NH), 7.44 (d, 2H, *J*=8.4 Hz, Ph), 7.07 (d, 2H, *J*=8.4 Hz, Ph), 5.48 (s, 1H, 5-H), 5.13 (d, 1H, *J*=3.6 Hz, 1′-H), 5.06 (d, 1H, *J*=5.1 Hz, OH), 4.85 (d, 1H, *J*=6.2 Hz, OH), 4.65 (t, 1H, *J*=5.4 Hz, OH), 4.58 (dd, 1H, *J*=5.1 and 9.5 Hz, 2′-H), 4.03 (dd, 1H, *J*=5.7 and 11.6 Hz, 3′-H), 3.82 (s, 1H, OCH_3), 3.61−3.54 (m, 2H, 4′-H, and 5′-H), 3.47−3.43 (m, 1H, 5′-H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.7, 161.1, 156.6, 151.3, 130.2 (CH), 125.7, 114.7 (CH), 103.8 (CH), 94.1 (CH), 85.4 (CH), 71.4 (CH), 70.5 (CH), 62.7 (CH_2), 55.9 (CH_3); MS (ESI) *m*/*z* 217 (36), 349 (100) (M−1); HRMS calcd for $C_{16}H_{17}N_2O_7$ (M−1): 349.1036. Found: 349.1049. Anal. Calcd for $C_{16}H_{18}N_2O_7\cdot H_2O$: C, 52.17; H, 5.47; N, 7.61. Found: C, 52.01; H, 5.54; N, 7.71.

*4.4.5. 6-(p-Nitrophenyl)uridine (**16c**).* To a solution of 2′,3′,5′-tri-*O*-acetyl-6-(*p*-nitrophenyl)uridine (**13c**, 0.4717 g, 0.960 mmol) in MeOH (10 mL) was added 28% ammonium hydroxide (10 mL) and the reaction mixture was stirred at room temperature for 90 min. The solvent was removed under reduced pressure. The resulting residue was purified by flash column chromatography ($CHCl_3$/MeOH=9:1, R_f=0.24) to give the product (**16c**, solid, 0.3271 g, 0.896 mmol, 93%). The compound was recrystallized from MeOH to give an analytical product (white solid, 0.0520 g, 0.1424 mmol, 15%). Mp 116−118 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.59 (s, 1H, NH), 8.36 (d, 2H, *J*=8.4 Hz, Ph), 7.78 (d, 2H, *J*=8.4 Hz, Ph), 5.64 (s, 1H, 5-H), 5.07 (d, 1H, *J*=5.2 Hz, OH), 4.91 (d, 1H, *J*=4.0 Hz, 1′-H), 4.85 (d, 1H, *J*=6.0 Hz, OH), 4.63−4.59 (m, 2H, 2′-H, and OH), 4.0 (dd, 1H, *J*=5.7 and 11.5 Hz, 3′-H), 3.59−3.55 (m, 2H, 4′-H, and 5′-H), 3.45−3.42 (m, 1H, 5′-H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.4, 154.4, 150.9, 148.8, 139.7, 130.2 (CH), 124.4 (CH), 104.9 (CH), 94.2 (CH), 85.6 (CH), 71.2 (CH), 70.4 (CH), 62.5 (CH_2); MS (ESI) *m*/*z* 232 (38), 364 (100) (M−1); HRMS calcd for $C_{15}H_{14}N_3O_8$ (M−1): 364.0781. Found: 364.0815. Anal. Calcd for $C_{15}H_{15}N_3O_8\cdot H_2O$: C, 47.0; H, 4.47; N, 10.96. Found: C, 47.08; H, 4.55; N, 10.95.

*4.4.6. 6-(2-Naphthyl)uridine[23] (**16d**).* Compound **16d** was prepared from 5′-*O*-*tert*-butyldimethylsilyl-2′,3′-*O*-isopropylidene-6-(2-paphthyl)uridine (**7d**) by the method described for **16a**. The reaction was purified by flash column chromatography ($CHCl_3$/MeOH=9:1, R_f=0.17) to give the product (**16d**, solid, 98%). The compound was recrystallized from MeOH/EtOAc to give an analytical product (white solid, 41%). Mp 268−270 °C (dec); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.53 (s, 1H, NH), 8.09−8.0 (m, 4H, Np), 7.66−7.57 (m, 3H, Np), 5.66 (s, 1H, 5-H), 5.12 (d, 1H, *J*=3.2 Hz, 1′-H), 5.05 (d, 1H, *J*=5.2 Hz, OH), 4.79 (d, 1H, *J*=6.0 Hz, OH), 4.63 (s, 2H, 2′-H, and OH), 4.02 (dd, 1H, *J*=5.6 and 11.3 Hz, 3′-H), 3.60−3.54 (m, 2H, 4′-H, and 5′-H), 3.48−3.43 (m, 1H, 5′-H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.7, 156.6, 151.2, 133.7, 132.8, 131.1, 129.0 (CH), 128.7 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 127.6 (CH), 104.5 (CH), 94.3 (CH), 85.4 (CH), 71.4 (CH), 70.4 (CH), 62.6 (CH_2); MS (ESI) *m*/*z* 237 (19), 369 (100) (M−1); HRMS calcd for $C_{19}H_{18}N_2O_6\cdot Na$ (M+Na):

393.1063. Found: 393.1095. Anal. Calcd for $C_{19}H_{18}N_2O_6$: C, 61.62; H, 4.90; N, 7.56. Found: C, 61.61; H, 4.92; N, 7.66.

4.4.7. 6-(2-Thiophenyl)uridine[28] *(**16e**).* Compound **16e** was prepared from 5′-*O*-*tert*-butyldimethylsilyl-2′,3′-*O*-isopropylidene-6-(2-thiophenyl)uridine (**7e**) by the method described for **16a**. The reaction was purified by flash column chromatography ($CHCl_3$/MeOH=9:1, R_f=0.19) to give the product (**16e**, solid, 97%). The compound was crystallized from MeOH/MeCN to give an analytical product (solid, 25%). Mp 142–144 °C [lit.[28] 111–114 °C (Hex/acetone)]; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.53 (s, 1H, NH), 7.86 (dd, 1H, J=0.6 and 5.0 Hz, Tp), 7.48 (d, 1H, J=2.7 Hz, Tp), 7.23 (dd, 1H, J=3.7 and 4.9 Hz, Tp), 5.68 (s, 1H, 5-H), 5.36 (d, 1H, J=3.8 Hz, 1′-H), 5.12 (d, 1H, J=5.1 Hz, OH), 4.88 (d, 1H, J=6.2 Hz, OH), 4.66 (t, 1H, J=5.6 Hz, OH), 4.60 (dd, 1H, J=5.2 and 9.5 Hz, 2′-H), 4.05 (dd, 1H, J=5.9 and 11.9 Hz, 3′-H), 3.64–3.57 (m, 2H, 4′-H, and 5′-H), 3.49–3.41 (m, 1H, 5′-H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.3, 151.0, 149.8, 133.3, 130.7 (CH), 130.4 (CH), 128.6 (CH), 105.0 (CH), 94.0 (CH), 85.4 (CH), 71.4 (CH), 70.5 (CH), 62.6 (CH_2); MS (ESI) m/z 193 (23), 325 (100) (M−1); HRMS calcd for $C_{13}H_{14}N_2O_6S\cdot$Na (M+Na): 349.0470. Found: 349.0483.

*4.4.8. 6-(3-Thiophenyl)uridine (**16f**).* Compound **16f** was prepared from 5′-*O*-*tert*-butyldimethylsilyl-2′,3′-*O*-isopropylidene-6-(3-thiophenyl)uridine (**7f**) by the method described for **16a**. The reaction was purified by flash column chromatography ($CHCl_3$/MeOH=9:1, R_f=0.16) to give the product (**16f**, solid, 84%). The compound was recrystallized from MeOH/EtOAc to give an analytical product (white solid, 31%). Mp 183–185 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.46 (s, 1H, NH), 7.95 (d, 1H, J=1.2 Hz, Tp), 7.76 (dd, 1H, J=3.2 and 4.4 Hz, Tp), 7.32 (d, 1H, J=5.2 Hz, Tp), 5.62 (s, 1H, 5-H), 5.21 (d, 1H, J=3.6 Hz, 1′-H), 5.13 (d, 1H, J=5.0 Hz, OH), 4.87 (d, 1H, J=6.1 Hz, OH), 4.66 (t, 1H, J=5.5 Hz, OH), 4.59 (dd, 1H, J=5.0 and 9.3 Hz, 2′-H), 4.03 (dd, 1H, J=5.8 and 11.7 Hz, 3′-H), 3.60–3.58 (m, 2H, 4′-H, and 5′-H), 3.48–3.42 (m, 1H, 5′-H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.3, 151.8, 151.1, 133.7, 128.3, 128.2, 127.7, 103.8 (CH), 94.0 (CH), 85.3 (CH), 71.4 (CH), 70.5 (CH), 62.7 (CH_2); MS (ESI) m/z 193 (23), 325 (100) (M−1); HRMS calcd for $C_{13}H_{13}N_2O_6S$ (M−1): 325.0494. Found: 325.0522. Anal. Calcd for $C_{13}H_{14}N_2O_6S$: C, 47.85; H, 4.32; N, 8.58. Found: C, 47.92; H, 3.93; N, 8.61.

*4.4.9. 6-(3-Furanyl)uridine (**16h**).* Compound **16h** was prepared from 5′-*O*-*tert*-butyldimethylsilyl-2′,3′-*O*-isopropylidene-6-(3-furanyl)uridine (**7h**) by the method described for **16a**. The reaction was purified by flash column chromatography ($CHCl_3$/MeOH=9:1, R_f=0.12) to give the product (**16h**, solid, 66%). The compound was crystallized from MeOH/EtOAc to give an analytical product (white solid, 48%). Mp 180–182 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.45 (s, 1H, NH), 8.17 (s, 1H, Fr), 7.88 (s, 1H, Fr), 6.80 (s, 1H, Fr), 5.68 (s, 1H, 5-H), 5.34 (d, 1H, J=3.8 Hz, 1′-H), 5.18 (d, 1H, J=5.2 Hz, OH), 4.90 (d, 1H, J=6.2 Hz, OH), 4.66 (t, 1H, J=5.7 Hz, OH), 4.62 (dd, 1H, J=5.2 and 9.7 Hz, 2′-H), 4.05 (dd, 1H, J=5.9 and 11.9 Hz, 3′-H), 3.67–3.58 (m, 2H, 4′-H, and 5′-H), 3.51–3.42 (m, 1H, 5′-H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.7, 151.1, 148.8, 145.1 (CH), 143.9 (CH), 119.3, 110.8 (CH), 103.4 (CH), 93.8 (CH), 85.3 (CH), 71.3 (CH), 70.5 (CH), 62.6 (CH_2); MS (ESI) m/z 177 (24), 309 (100) (M−1); HRMS calcd for $C_{13}H_{13}N_2O_7$ (M−1): 309.0723. Found: 309.0740. Anal. Calcd for $C_{13}H_{14}N_2O_7\cdot 0.5H_2O$: C, 48.91; H, 4.74; N, 8.77. Found: C, 48.55; H, 4.77; N, 8.78.

4.4.10. 6-(n-Butyl)uridine[36] *(**16i**).* Compound **16i** was prepared from 2′,3′,5′-tri-*O*-acetyl-6-(*n*-butyl)uridine (**17i**) by the method described for **16c**. The reaction was purified by flash column chromatography ($CHCl_3$/MeOH=9:1, R_f=0.15) to give the product (**16i**, oil, 0.1482 g, 0.4935 mmol, 96%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.24 (br s, 1H, NH), 5.52 (s, 1H, 5-H), 5.37 (d, 1H, J=3.8 Hz, 1′-H), 5.19 (d, 1H, J=5.3 Hz, OH), 4.93 (d, 1H, J=6.4 Hz, OH), 4.63 (t, 1H, J=5.7 Hz, OH), 4.54 (dd, 1H, J=5.3 and 9.6 Hz, 2′-H), 4.07 (dd, 1H, J=6.2 and 12.3 Hz, 3′-H), 3.73–3.69 (m, 1H, 4′-H), 3.63–3.58 (m, 1H, 5′-H), 3.47–3.41 (m, 1H, 5′-H), 2.55–2.50 (m, 2H, CH_2), 1.58–1.54 (m, 2H, CH_2), 1.38–1.32 (m, 2H, CH_2), 0.90 (t, 3H, J=7.3 Hz, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.9, 157.3, 151.2, 102.3 (CH), 92.3 (CH), 85.3 (CH), 71.5 (CH), 70.3 (CH), 62.6 (CH_2), 33.3 (CH_2), 29.9 (CH_2), 22.0 (CH_2), 14.0 (CH_3); MS (ESI) m/z 323 (100) (M+Na); HRMS calcd for $C_{13}H_{21}N_2O_6\cdot$Na (M+Na): 323.1219. Found: 323.1211.

4.4.11. 5-Phenyluridine[11,37] *(**20a**).* Compound **20a** was prepared from 5′-*O*-*tert*-butyldimethylsilyl-2′,3′-*O*-isopropylidene-5-phenyluridine (**19a**) by the method described for **16a**. The reaction was purified by flash column chromatography ($CHCl_3$/MeOH=9:1, R_f=0.13) to give the product (**20a**, 78%). The compound was recrystallized from MeOH/EtOAc to give an analytical product (white solid, 27%). Mp 181–182 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.51 (s, 1H, NH), 8.27 (s, 1H, 6-H), 7.56–7.55 (m, 2H, Ph), 7.54–7.35 (m, 2H, Ph),7.32–7.29 (m, 1H, Ph), 5.86 (d, 1H, J=4.8 Hz, 1′-H), 5.43 (d, 1H, J=5.5 Hz, OH), 5.22 (t, 1H, J=4.7 Hz, OH), 5.09 (d, 1H, J=5.2 Hz, OH), 4.15 (dd, 1H, J=5.0 and 10.2 Hz, 2′-H), 4.04 (dd, 1H, J=4.9 and 9.7 Hz, 3′-H), 3.90–3.88 (m, 1H, 4′-H), 3.68 (ddd, 1H, J=3.0, 4.6, and 12.0 Hz, 5′-H) 3.58 (ddd, 1H, J=2.6, 4.4, and 12.0 Hz, 5′-H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.6, 150.7, 138.6, 133.6, 128.6 (CH), 128.4 (CH), 127.7 (CH), 114.0 (CH), 88.8 (CH), 85.2 (CH), 74.5 (CH), 70.1 (CH), 60.9 (CH_2); MS (ESI) m/z 319 (100) (M−1); HRMS calcd for $C_{15}H_{15}N_2O_6$ (M−1): 319.0930. Found: 319.0926.

4.4.12. 5-(p-Methoxyphenyl)uridine[38] *(**20b**).* Compound **20b** was prepared from 5′-*O*-*tert*-butyldimethylsilyl-2′,3′-*O*-isopropylidene-5-(*p*-methoxyphenyl)uridine (**19b**) by the method described for **16a**. The reaction was purified by recrystallization from MeOH/EtOAc to give the product (**20b**, white crystal, 86%). Mp 194–195 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.45 (s, 1H, NH), 8.17 (s, 1H, 6-H), 7.48 (d, 2H, J=8.8 Hz, Ph), 6.93 (d, 2H, J=8.8 Hz, Ph), 5.85 (d, 1H, J=4.9 Hz, 1′-H), 5.39 (d, 1H, J=5.6 Hz, OH), 5.18 (t, 1H, J=4.7 Hz, OH), 5.06 (d, 1H, J=5.3 Hz, OH), 4.14 (dd, 1H, J=5.1 and 10.3 Hz, 2′-H), 4.03 (dd, 1H, J=4.9 and 9.7 Hz, 3′-H), 3.89–3.88 (m, 1H, 4′-H), 3.67 (ddd, 1H, J=3.1, 4.5, and 12.0 Hz, 5′-H) 3.58 (ddd, 1H, J=2.8, 4.3, and 12.0 Hz, 5′-H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.7, 159.0, 150.6, 137.5 (CH), 129.5 (CH), 125.8, 114.0 (CH), 113.7, 88.7 (CH), 85.2 (CH), 74.3 (CH), 70.1 (CH), 60.9 (CH_2), 55.6 (CH_3); MS (ESI) m/z 349 (100) (M−1); HRMS calcd for $C_{16}H_{17}N_2O_7$ (M−1): 349.1036. Found: 349.1039. Anal. Calcd for $C_{16}H_{18}N_2O_7\cdot H_2O$: C, 52.17; H, 5.47; N, 7.60. Found: C, 51.82; H, 5.43; N, 7.61.

*4.4.13. 5-(p-Nitrophenyl)uridine (**20c**).* Compound **20c** was prepared from 5′-*O*-*tert*-butyldimethylsilyl-2′,3′-*O*-isopropylidene-5-(*p*-nitrophenyl)uridine (**19c**) by the method described for **16a**. The reaction was purified by recrystallization from MeOH/EtOAc to give the product (**20c**, yellow solid, 76%). Mp 262–264 °C (dec); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.68 (s, 1H, NH), 8.63 (s, 1H, 6-H), 8.21 (d, 1H, J=8.8 Hz, Ph), 7.89 (d, 1H, J=8.8 Hz, Ph), 5.83 (d, 1H, J=3.8 Hz, 1′-H), 5.46 (d, 1H, J=5.3 Hz, OH), 5.33 (t, 1H, J=4.4 Hz, OH), 5.07 (d, 1H, J=5.8 Hz, OH), 4.15 (dd, 1H, J=4.8 and 9.1 Hz, 2′-H), 4.08 (dd, 1H, J=5.3 and 10.6 Hz, 3′-H), 3.92–3.91 (m, 1H, 4′-H), 3.77–3.73 (m, 1H, 5′-H), 3.64–3.61 (m, 1H, 5′-H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.1, 150.3, 146.4, 140.8, 140.7 (CH), 128.8 (CH), 123.7 (CH), 111.4 (CH), 89.4 (CH), 84.9 (CH), 74.7 (CH), 69.5 (CH), 60.3 (CH_2); MS (ESI) m/z 364 (100) (M−1); HRMS calcd for $C_{15}H_{14}N_3O_8$ (M−1): 364.0781. Found: 364.0779. Anal. Calcd for $C_{15}H_{15}N_3O_8$: C, 49.32; H, 4.14; N, 11.50. Found: C, 49.17; H, 3.84; N, 11.36.

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Supplementary data

^{1}H and ^{13}C NMR spectra for representative compounds. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.03.051.

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