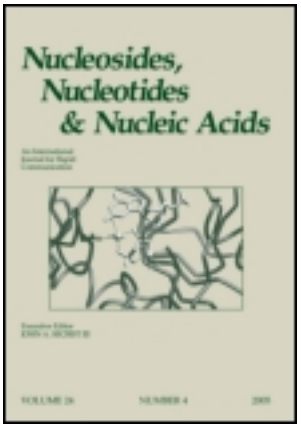

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Trimethylsilyl Trifluoromethanesulfonate-promoted Reductive 2′-O-arylmethylation of Ribonucleoside Derivatives

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TRIMETHYLSILYL TRIFLUOROMETHANESULFONATE-PROMOTED REDUCTIVE 2′-*O*-ARYLMETHYLATION OF RIBONUCLEOSIDE DERIVATIVES

Naoki Uchiyama, Toshihiko Ogata, Natsuhisa Oka, and Takeshi Wada
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□ *Arylmethyl groups such as benzyl, p-methoxybenzyl, and 1-pyrenylmethyl groups were introduced to the 2′-O-position of nucleosides by reductive etherification. Combining corresponding aromatic aldehydes with 2′-O-trimethylsilylnucleoside derivatives in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) resulted in moderate to good yields of the 2′-O-arylmethyluridine derivatives, whereas the corresponding cytidine and adenosine derivatives were obtained in low yields. The reaction of ribonucleosides with aliphatic aldehydes did not proceed smoothly. Anomerization of the uridine derivatives by TMSOTf was observed in CH_2Cl_2, toluene, and CH_3CN, but was completely suppressed when the reactions were conducted in 1,4-dioxane.*

Keywords 2′-*O*-modified ribonucleoside; reductive etherification; arylmethylation

INTRODUCTION

Chemically modified oligonucleotides have a wide range of applications such as target gene therapy[1,2] and diagnosis.[3,4] 2′-*O*-Alkyloligoribonucleotide analogues are especially attractive for these applications because of their resistance to nuclease degradation and high hybridization affinity for complementary mRNA.[5,6] For these reasons, 2′-*O*-alkylribonucleosides are attractive synthetic targets. Various methods for 2′-*O*-modification of ribonucleosides have been developed,[7] including the reaction of partially protected ribonucleosides with alkylating agents,[8,9] ring-opening reaction of 2,2′-anhydrouridine derivatives,[10] and glycosylation.[11] Although some of these reactions generate high yields of the desired

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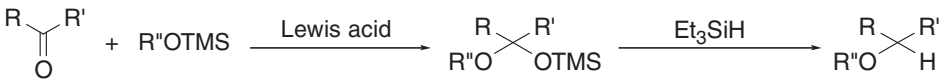
compounds, further optimization of the process is needed because of persistent difficulties such as undesired base alkylation, low regioselectivity, dependence of hazardous reagents, and limited product ranges. Thus, we sought to develop a new method for the synthesis of 2′-*O*-alkylribonucleosides.

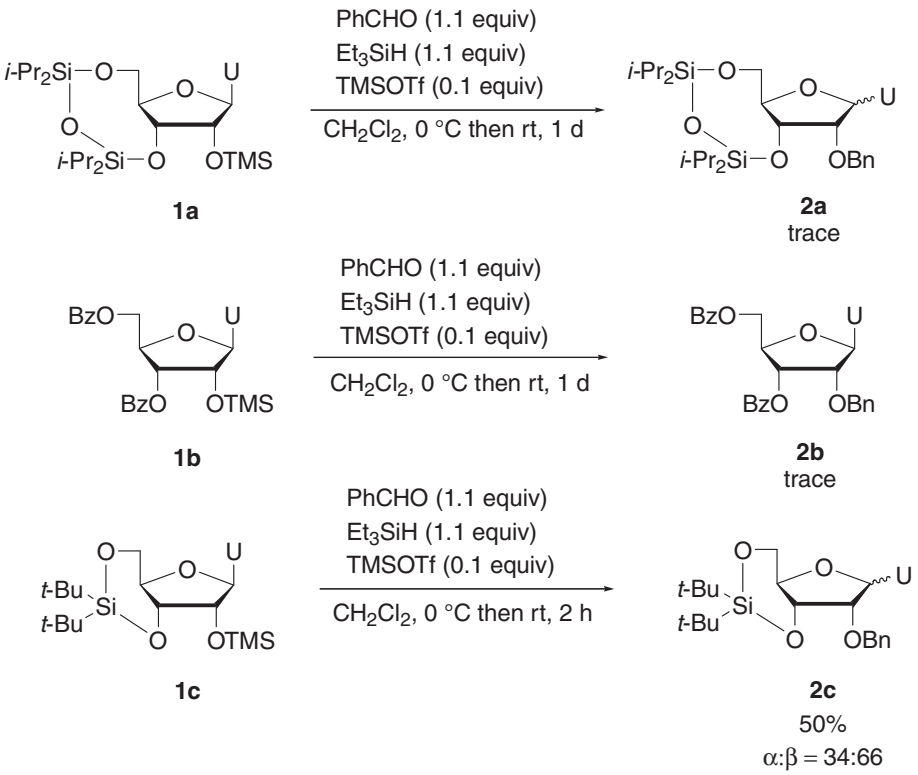
Reductive etherification of aldehydes and ketones with hydrosilanes, silylated alcohols, and Lewis acids is useful for the synthesis of a wide range of asymmetric ethers (Scheme 1).[12] This reaction is promoted by a catalytic amount of a Lewis acid and is compatible with a variety of functional groups, including esters, amides, nitriles, and acetals. Therefore, we expected that this methodology could be employed in the synthesis of 2′-*O*-alkylribonucleosides. To the best of our knowledge, this reaction has not been previously applied to the synthesis of *O*-alkylnucleoside derivatives. In this paper, we describe the results of our study on the 2′-*O*-alkylation of 3′,5′-*O*-protected ribonucleoside derivatives by reductive etherification.



SCHEME 1 Synthesis of asymmetric ethers from aldehydes and ketones by reductive etherification.

RESULTS AND DISCUSSION

To examine the applicability of reductive etherification for the synthesis of 2′-*O*-modified nucleosides, we carried out 2′-*O*-benzylation of three types of 3′,5′-*O*-protected 2′-*O*-TMS-uridine derivatives: 1,1,3,3-tetraisopropyldisiloxane-1,3-diyl (TIPDS) (**1a**), benzoyl (**1b**), and di-*tert*-butylsilanediyl (DTBS) (**1c**) substituted uridine compounds. The derivatives were allowed to react with benzaldehyde and triethylsilane in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf) at 0°C (Scheme 2). However, **1a** and **1b** produced only trace amounts of the desired 2′-*O*-benzyluridine derivatives **2a**,**b**. The major side reaction was 2′-desilylation, and the results were not improved even when the reactions were carried out under strictly anhydrous conditions. In contrast, 2′-*O*-benzylation proceeded smoothly when **1c** was used as the starting materials, resulting in moderate to high yield of the desired product **2c**, in a mixture of α- and β-isomers.[16] The significant difference in reactivity remains unexplained, although low reactivity of **1b** may be related to the Lewis basicity of the benzoyl groups, which can coordinate with TMSOTf. The difference in reactivity between **1a** and **1c** can be attributed to the difference in the steric hindrance around their 2′-OH; however, there is no conclusive evidence for this because it has been reported that the 2′-OH of a DTBS-protected guanosine derivative is less reactive to sulfonylation than to the TIPDS-protected counterpart,

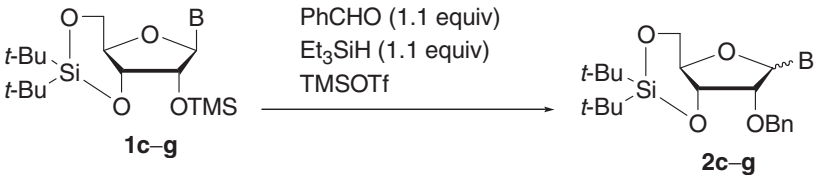


SCHEME 2 2′-*O*-Benzylation of 3′,5′-*O*-protected uridine derivatives **1a–c** by reductive etherification.

and the difference in reactivity was attributed to the steric hindrance on the basis of a conformational search.[8a] Although the difference in reactivity of **1a–c** remains unexplained, our results showed that the DTBS was the most effective choice for the reductive 2′-*O*-benzylation of ribonucleoside derivatives.

Next, we attempted to optimize the reaction conditions, aiming to minimize anomerization and increase the yield of the desired product. The 2′-*O*-benzylation of **1c** was carried out in various solvents listed in Table 1 (entries 1–8). CH_2Cl_2, toluene, and CH_3CN did not suppress anomerization (Table 1, entries 1–3). In contrast, ether-type solvents such as 1,2-dimethoxyethane (DME) and 1,4-dioxane successfully suppressed the anomerization (Table 1, entries 4 and 5). The reaction in dioxane was particularly effective, giving moderate yield of the desired 2′-*O*-benzyl-β-uridine derivative **2c** (β) without any observable anomerization (Table 1, entry 5). Anomerization was also suppressed in other ether-type solvents, such as THF, Et_2O and *t*-BuOMe, although the reaction was slowed down probably because of the deactivation of TMSOTf by the stronger Lewis basic solvents (entries 6–8).[15] These results indicate that the moderate

TABLE 1 Optimization of reaction conditions for 2′-*O*-benzylation of uridine derivative **1c** and reactions of N^3-benzoyluridine, cytidine and adenosine derivatives **1d–g** in 1,4-dioxane



1c–g **2c–g**

Entry	B[a]	Solvent	Equiv of TMSOTf	Temp (°C)	Reaction time	Product	Yield of **2c–g** (β) (%)	Yield of **2c–g** (α) (%)
1	U (**1c**)	CH_2Cl_2	0.1	0	2 h	**2c**	33	17
2	U (**1c**)	toluene	0.1	0	4 h	**2c**	19	ca. 20[b]
3	U (**1c**)	CH_3CN	0.1	0	4 h	**2c**	29	11
4	U (**1c**)	DME	0.2	0	8 h	**2c**	40	trace
5	U (**1c**)	1,4-dioxane	0.1	rt	6 h	**2c**	54	0
6	U (**1c**)	THF	0.1	0	20 h	**2c**	8	trace
7	U (**1c**)	ether	0.1	0	24 h	**2c**	7	trace
8	U (**1c**)	*t*-BuOMe	0.1	0	10 h	**2c**	trace	trace
9	U^{bz} (**1d**)	1,4-dioxane	0.1	rt	2 h	**2d**	61	0
10	U^{bz} (**1d**)	1,4-dioxane	0.5	rt	1 h	**2d**	70	0
11	U^{bz} (**1d**)	1,4-dioxane	1.0	rt	20 min	**2d**	75	0
12	C (**1e**)	1,4-dioxane	10	rt	4 h	**2e**	11	0
13	C^{bz} (**1f**)	1,4-dioxane	2	rt	19 h	**2f**	16	0
14	A^{bz2} (**1g**)	1,4-dioxane	1	rt	27 h	**2g**	21	0

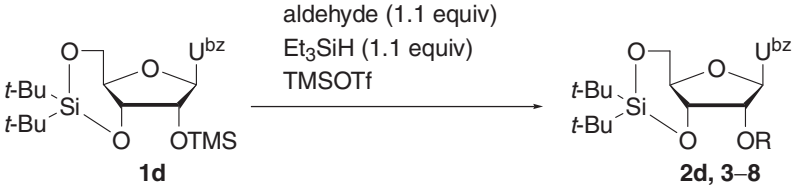
[a] U^{bz} = N^3-benzoyluracil-1-yl, C^{bz} = N^4-benzoylcytosin-1-yl, A^{bz2} = N^6,N^6-dibenzoyladenin-9-yl.
[b] Not isolated.

Lewis basicity of dioxane may be appropriate for the suppression of anomerization without deactivating TMSOTf.

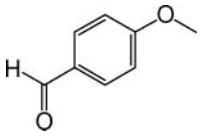
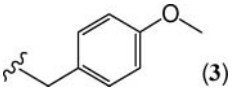
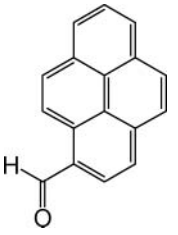
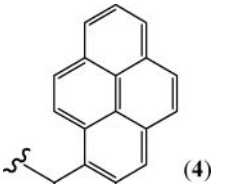
The reaction was further improved by protecting of the N^3-position of uracil (entry 9), and increasing the amount of TMSOTf. The addition of TMSOTf accelerated the reaction and improved the yield of **2d** (entries 10 and 11). Remarkably, epimerization of the product was not observed following the additional stoichiometric amounts of TMSOTf in dioxane (entry 11). Although the synthesis of substituted uridine was successful, attempts to synthesize 2′-*O*-benzylcytidine and adenosine derivatives **1e–g** gave low yields of the products despite complete suppression of epimerization (entries 12–14). 2′-Desilylation was the major side reaction, although there were other unidentified byproducts. The low yields might also be due to the Lewis basicity of cytosine and adenine base.

Finally, 2′-*O*-alkylation of the uridine derivative **1d** was attempted using various aldehydes listed in Table 2. As in the case of 2′-*O*-benzylation, 2′-*O*-arylmethyl groups, such as *p*-methoxybenzyl and 1-pyrenylmethyl groups were introduced into the 2′-*O*-position of **1d** to give the desired 2′-*O*-arylmethyluridine derivatives **3** and **4** with moderate yields (entries 2 and 3). In contrast, aliphatic aldehydes did not produce the desired 2′-*O*-alkyluridine derivatives efficiently, probably because of the low reactivity of the

TABLE 2 2′-*O*-Alkylation of uridine derivative **1d** with various aldehydes



1d **2d, 3–8**

Entry	Aldehyde	Equiv of TMSOTf	R	Reaction time	Yield (%)
1	PhCHO	1.0	Bn (**2d**)	20 min	75
2		0.5	 (**3**)	10 min	48
3		0.5	 (**4**)	5 min	53
4[a]	$CH_2 = CHCHO$	1.0	Allyl (**5**)	70 min	14[c]
5[b]	CH_3CHO	1.0	Et (**6**)	2 h	0[c]
6	CH_3CH_2CHO	1.0	Pr (**7**)	12 h	0[c]
7[b]	HCHO	1.0	Me (**8**)	15 min	0

[a] Additional 1.1 equiv of acrolein and Et_3SiH were added after 60 minutes.
[b] Excess aldehydes were used.
[c] Decomposition of starting material **1d** was observed.

corresponding aldehydes (entries 4–7); only α,β-unsaturated aldehyde gave the product **5** in low yield (entry 4).

CONCLUSION

We demonstrated successful use of reductive etherification in the synthesis of 2′-*O*-arylmethyluridine derivatives. Using moderate Lewis basic dioxane as a solvent, anomerization of uridine derivatives was suppressed, despite the presence of stoichiometric amounts of TMSOTf. Anomerization of cytidine and adenosine derivatives was also completely suppressed by dioxane, although the desired 2′-*O*-arylmethylnucleoside derivatives were obtained in low yields.

EXPERIMENTAL

General

^{1}H NMR (300 MHz) spectra were recorded on a Varian MERCURY 300 spectrometer. ^{1}H NMR spectra were obtained with tetramethylsilane

(TMS) as an internal standard in $CDCl_3$. Analytical thin-layer chromatography (TLC) was performed on Merck TLC plates (No. 5715) precoated with silica gel 60 F_{254}. Silica gel column chromatography was carried out using Kanto silica gel 60N (spherical, neutral). Dry organic solvents were purified and dried by appropriate procedures. Other organic solvents were reagent grade and used as received. TMSOTf was purified by distillation prior to use.

Synthesis of 2′-O-trimethylsilyl-3′,5′-O-(di-tert-butylsilanediyl)uridine (1c)

Typical procedure for 2′-O-trimethylsilylation of 3′,5′-O-protected uridine derivatives. 3′,5′-*O*-(Di-*tert*-butylsilanediyl)uridine was synthesized according to the procedure described in the literature.[13] The obtained 3′,5′-*O*-(di-*tert*-butylsilanediyl)uridine (1.15 g, 3.00 mmol) was dried by repeated coevaporations with dry pyridine and dissolved in dry pyridine (10 mL). Chlorotrimethylsilane (0.53 mL, 4.2 mmol) was added dropwise to the solution at 0°C under argon. The reaction mixture was stirred until completion and evaporated under reduced pressure. The residue was then dissolved in CH_2Cl_2 (50 mL). The solution was washed with saturated $NaHCO_3$ aqueous solution (3 × 40 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography [hexane-ethyl acetate (2/1, v/v)] to afford **1c** (1.36 g, 2.98 mmol, 99%) as a colorless foam. ^{1}H NMR ($CDCl_3$) δ 8.91 (1H, br, NH), 7.31 (1H, d, $J = 8.4$ Hz, 6-H), 5.74 (1H, d, $J = 8.4$ Hz, 5-H), 5.62 (1H, s, 1′-H), 4.52-4.48 (1H, m, 4′-H), 4.24-4.18 (2H, m, 3′-H, 5′-H), 3.98 (1H, t, $J = 9.9$ Hz, 5′-H), 3.77 (1H, dd, $J = 9.6, 4.2$ Hz, 2′-H), 1.04 (9H, s, *t*-Bu-H), 1.02 (9H, s, *t*-Bu-H), 0.20 (9H, s, TMS-H).

2′-O-Trimethylsilyl-3′,5′-O-(1,1,3,3-tetraisopropyldisiloxanediyl)uridine (1a). Compound **1a** was obtained from 3′,5′-*O*-(tetraisopropyldisiloxanediyl) uridine (4.88 g, 10.0 mmol) as a colorless solid (5.61 g, 10.0 mmol, quant). ^{1}H NMR ($CDCl_3$) δ 8.27 (1H, br, NH), 7.95 (1H, d, $J = 7.8$ Hz, 6-H), 5.64 (1H, dd, $J = 8.4, 2.4$ Hz, 5-H), 5.57 (1H, s, 1′-H), 4.27-3.98 (5H, m, 2′-H, 3′-H, 4′-H, 5′-H, 5″-H), 1.09-0.94 (27H, m, $CH(CH_3)_2$), 0.19 (9H, s, TMS-H).

2′-O-Trimethylsilyl-3′,5′-O-dibenzolyluridine (1b). 3′,5′-*O*-Dibenzoyluridine was synthesized according to the procedure described in the literature.[14] Compound **1b** was obtained from 3′,5′-*O*-dibenzoyluridine (0.65 g, 1.4 mmol) as a colorless foam (0.75 g, 1.4 mmol, quant). ^{1}H NMR ($CDCl_3$) δ 8.88 (1H, br, NH), 8.09-7.45 (11H, m, Ar-H, 6-H), 5.91 (1H, d, $J = 3.0$ Hz, 1′-H), 5.52 (1H, d, $J = 7.8$ Hz, 5-H), 5.31 (1H, t, $J = 5.7$ Hz, 3′-H), 4.85-4.57 (4H, m, 2′-H, 4′-H, 5′-H, 5″-H), 0.05 (9H, s, TMS-H).

N^3-Benzoyl-2′-O-trimethylsilyl-3′,5′-O-(di-tert-butylsilanediyl)uridine (1d). Uridine (1.22 g, 5.0 mmol) was dried by repeated coevaporations with dry pyridine and dissolved in dry DMF (25 mL). Di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (2.0 mL, 5.5 mmol) was added dropwise to the solution at 0°C under argon. After being stirred for 10 minutes, imidazole (1.70 g, 25 mmol) and chlorotrimethylsilane (0.89 mL, 7.0 mmol)

were added to the mixture and stirring was continued for another 10 minutes. Then the mixture was diluted with ethyl acetate (100 mL), washed with water (7 × 100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved dry pyridine (20 mL) and cooled to 0°C under argon. Diisopropylethylamine (4.3 mL, 25 mmol) and benzoyl chloride (0.85 mL, 7.5 mmol) were added to the solution and the mixture was stirred for 12 hours. After completion, the reaction was quenched with EtOH (3 mL), and the mixture evaporated under reduced pressure and then diluted with CH_2Cl_2 (50 mL). The solution was washed with saturated $NaHCO_3$ aqueous solution (3 × 30 mL), dried over Na_2SO_4, filtered, evaporated under reduced pressure and coevaporated with toluene (3 × 5 mL). The residue was purified by silica gel column chromatography [hexane-ethyl acetate (4/1, v/v)] to afford **1d** (2.68 g, 4.78 mmol, 96% from uridine). Colorless foam. ^{1}H NMR ($CDCl_3$) δ 8.64 (1H, s, 8-H), 8.12 (1H, s, 2-H), 7.87-7.34 (10H, m, Ar-H), 5.99 (1H, s, 1′-H), 4.58-4.50 (2H, m, 3′-H, 4′-H), 4.34-4.26 (2H, m, 2′-H, 5′-H), 4.02 (1H, t, J = 9.4 Hz, 5″-H), 1.04 (9H, s, *t*-Bu-H), 1.04 (9H, s, *t*-Bu-H), 0.23 (9H, s, TMS-H).

2′-O-Trimethylsilyl-3′,5′-O-(di-tert-butylsilanediyl)cytidine (1e). Cytidine (0.972 g, 4.0 mmol) was dried by repeated coevaporations with dry pyridine and dissolved in dry DMF (20 mL). Di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (1.6 mL, 4.4 mmol) was added dropwise to the solution at 0°C under argon. After being stirred for 10 minutes, imidazole (1.36 g, 20 mmol) and chlorotrimethylsilane (0.56 mL, 4.4 mmol) were added to the mixture and stirring was continued for another 10 minutes. Then the mixture was diluted with ethyl acetate (100 mL), washed with water (7 × 100 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography [ethyl acetate-acetone-triethylamine (9/1/0.2, v/v/v)] to afford **1e** (1.08 g, 2.37 mmol, 60% from cytidine). Colorless foam. ^{1}H NMR ($CDCl_3$) δ 7.35 (1H, d, J = 7.8 Hz, 6-H), 5.81 (1H, d, J = 7.8 Hz, 5-H), 5.66 (1H, s, 1′-H), 4.51 (1H, dd, J = 8.6, 4.8 Hz, 4′-H), 4.27-4.22 (2H, m, 3′-H, 5′-H), 3.98 (1H, t, J = 9.9 Hz, 5″-H), 3.75 (1H, dd, J = 9.6, 4.2 Hz, 2′-H), 1.07 (9H, s, *t*-Bu-H), 1.02 (9H, s, *t*-Bu-H), 0.19 (9H, m, TMS-H).

N^4-Benzoyl-2′-O-trimethylsilyl-3′,5′-O-(di-tert-butylsilanediyl)cytidine (1f). 2′-*O*-Trimethylsilyl-3′,5′-*O*-(di-*tert*-butylsilanediyl)cytidine **1e** (456 mg, 1.0 mmol) was dried by repeated coevaporations with dry pyridine and dissolved in dry pyridine (5 ml). Benzoyl chloride (0.13 mL, 1.1 mmol) was added to the solution at 0°C under argon. The mixture was then stirred for 10 minutes. The reaction was then quenched with EtOH (1 mL), and the mixture was evaporated under reduced pressure and diluted with CH_2Cl_2 (25 mL). The solution was washed with saturated $NaHCO_3$ aqueous solution (3 × 20 mL), dried over Na_2SO_4, filtered, evaporated under reduced pressure and coevaporated with toluene (4 × 5 mL). The residue was purified by silica gel column chromatography [hexane–ethyl acetate (1/1, v/v)] to afford

1f (363 mg, 0.65 mmol, 65%). Colorless foam. ^{1}H NMR ($CDCl_3$) δ 8.65 (1H, br, NH), 7.90-7.27 (7H, m, Ar-H, 6-H, 5-H), 5.74 (1H, s, 1′-H), 4.57 (1H, m, 3′-H), 4.37-3.70 (4H, m, 2′-H, 4′-H, 5′-H, 5″-H), 1.04 (9H, s, *t*-Bu-H), 1.04 (9H, s, *t*-Bu-H), 0.25 (9H, s, TMS-H).

***N*^{6},*N*^{6}-Dibenzoyl-2′-*O*-trimethylsilyl-3′,5′-*O*-(di-tert-butylsilanediyl)adenosine (1g).** Adenosine (1.07 g, 4.0 mmol) was dried by repeated coevaporations with dry pyridine and dissolved in dry DMF (20 mL). Di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (1.6 mL, 4.4 mmol) was added dropwise to the solution at 0°C under argon. After being stirred for 10 minutes, imidazole (1.36 g, 20 mmol) and chlorotrimethylsilane (0.56 mL, 4.4 mmol) were added to the mixture and stirring was continued for another 10 minutes. Then the mixture was diluted with ethyl acetate (100 mL), washed with water (7 × 100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was coevaporated with dry pyridine (3 × 7 mL), dissolved dry pyridine (20 mL) and cooled to 0°C under argon. Benzoyl chloride (1.21 mL, 10.5 mmol) was added to the solution and the mixture was stirred for 7 hours. After completion, the reaction was quenched with EtOH (3 mL), and the mixture was evaporated under reduced pressure and diluted with CH_2Cl_2 (50 mL). The organic solution was washed with saturated $NaHCO_3$ aqueous solution (3 × 30 mL), dried over Na_2SO_4, filtered, evaporated under reduced pressure and coevaporated with toluene (3 × 5 mL). The residue was purified by silica gel column chromatography [hexane–ethyl acetate (5/1 to 4/1, v/v)] to afford **1g** (2.00 g, 2.91 mmol, 73% from adenosine). Colorless foam. ^{1}H NMR ($CDCl_3$) δ 8.64 (1H, s, 8-H), 8.12 (1H, s, 2-H), 7.87-7.34 (10H, m, Ar-H), 5.99 (1H, s, 1′-H), 4.58-4.50 (2H, m, 3′-H, 4′-H), 4.34-4.26 (2H, m, 2′-H, 5′-H), 4.02 (1H, t, J = 9.4 Hz, 5″-H), 1.04 (9H, s, *t*-Bu-H), 1.04 (9H, s, *t*-Bu-H), 0.23 (9H, s, TMS-H).

***N*^{3}-Benzoyl-2′-*O*-benzyl-3′,5′-*O*-(di-tert-butylsilanediyl)uridine (2d)**

General procedure for synthesis of 2′-O-alkylribonucleoside derivatives 2a-g, 3-8. *N*^{3}-Benzoyl-2′-*O*-trimethylsilyl-3′,5′-*O*-(di-*tert*-butylsilyanediyl)uridine **1d** (56 mg, 0.10 mmol) was dried by coevaporations with dry pyridine (3 × 1 mL) and dry toluene (3 × 1 mL), and dissolved in dry 1,4-dioxane (0.40 mL) under argon. A 0.28 M solution of benzaldehyde and triethylsilane in dry 1,4-dioxane (0.40 mL) was added to the solution. The 0.5 M solution of TMSOTf in dry 1,4-dioxane (0.20 mL) was added dropwise and the mixture was stirred at room temperature. After completion, the reaction was quenched with saturated $NaHCO_3$ aqueous solution (1.0 mL) and the mixture was diluted with $CHCl_3$ (20 mL). The organic layer was separated and washed with saturated $NaHCO_3$ aqueous solution (3 × 20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography [hexane-ethyl acetate (4/1, v/v)] to afford **2d** (43.6 mg, 0.075 mmol, 75%). Colorless foam. ^{1}H NMR

($CDCl_3$) δ 7.96-7.26 (11H, m, ArH, 6-H), 5.86 (1H, d, $J = 8.4$ Hz, 5-H), 5.81 (1H, s, 1′-H), 4.87 (2H, dd, $J = 36.2$, 12.0 Hz, 2′-*O*-CH_2Ph), 4.53 (1H, dd, $J = 37.9$, 4.8 Hz, 4′-H), 4.27-4.20 (1H, m, 3′-H), 4.15 (1H, d, $J = 4.8$ Hz, 5′-H), 4.05-3.96 (2H, m, 2′-H, 5″-H), 1.08 (9H, s, *t*-Bu-H), 1.05 (9H, s, *t*-Bu-H).

2′-O-Benzyl-3′,5′-O-dibenzoyluridine (2b). Colorless oil. ^{1}H NMR ($CDCl_3$) δ 8.11-7.19 (17H, m, Ar-H, 6-H), 6.08 (1H, d, $J = 3.9$ Hz, 1′-H), 5.45 (1H, t, $J = 5.1$ Hz, 3′-H), 5.36 (1H, d, $J = 8.1$ Hz, 5-H), 4.78-4.59 (6H, m, 4′-H, 5′-H, 5″-H, 2′-*O*-CH_2Ph), 4.28 (1H, t, $J = 5.1$ Hz, 2′-H).

2′-O-Benzyl-3′,5′-O-(di-tert-butylsilanediyl)uridine (2c(α)). Colorless oil. ^{1}H NMR ($CDCl_3$) δ 8.92 (1H, br, NH), 8.05 (1H, d, $J = 8.1$ Hz, 6-H), 7.38-7.28 (5H, m, Ar-H), 5.89 (1H, s, 1′-H), 5.24 (1H, d, $J = 8.1$ Hz, 5-H), 4.69-3.80 (7H, m, 2′-H, 3′-H, 4′-H, 5′-H, 5″-H, 2′-*O*-CH_2Ph), 1.05 (18H, s, *t*-Bu-H).

2′-O-Benzyl-3′,5′-O-(di-tert-butylsilanediyl)uridine (2c(β)). Colorless oil. ^{1}H NMR ($CDCl_3$) δ 9.20 (1H, br, NH), 7.43-7.25 (6H, m, Ar-H, 6-H), 5.78 (1H, s, 1′-H), 5.75 (1H, d, $J = 8.9$ Hz, 5-H), 4.91 (2H, dd, $J = 41.3$, 12.0 Hz, 2′-*O*-CH_2Ph), 4.51 (1H, dd, $J = 9.0$, 4.8 Hz, 4′-H), 4.27-4.18 (1H, m, 3′-H), 4.13 (1H, d, $J = 4.8$ Hz, 5′-H), 4.03-3.96 (2H, m, 2′-H, 5″-H), 1.07 (9H, s, *t*-Bu-H), 1.05 (9H, s, *t*-Bu-H).

2′-O-Benzyl-3′,5′-O-(di-tert-butylsilanediyl)cytidine (2e). Colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.48-7.26 (6H, m, Ar-H, 6-H), 5.88 (1H, s, 1′-H), 5.68 (1H, d, $J = 7.5$ Hz, 5-H), 4.99 (2H, s, 2′-*O*-CH_2Ph), 4.52 (1H, dd, $J = 8.5$, 5.1 Hz, 4′-H), 4.30-4.25 (1H, m, 3′-H), 4.12 (1H, d, $J = 4.2$ Hz, 5′-H), 4.00 (1H, t, $J = 9.9$ Hz, 5″-H), 3.92-3.86 (1H, m, 2′-H), 1.05 (18H, s, *t*-Bu-H).

N^4-Benzoyl-2′-O-benzyl-3′,5′-O-(di-tert-butylsilanediyl)cytidine (2f). Colorless oil. ^{1}H NMR ($CDCl_3$) δ 8.70 (1H, br, NH), 7.91-7.24 (12H, m, Ar-H, 6-H, 5-H), 5.94 (1H, s, 1′-H), 5.02 (2H, s, 2′-*O*-CH_2Ph), 4.48 (1H, dd, $J = 9.2$, 4.8 Hz, 4′-H), 4.38-4.33 (1H, m, 3′-H), 4.15 (1H, d, $J = 4.2$ Hz, 5′-H), 4.05 (1H, t, $J = 10.5$ Hz, 5″-H), 3.88 (1H, dd, $J = 9.6$, 4.2 Hz, 2′-H), 1.06 (18H, s, *t*-Bu-H).

N^6,N^6-Dibenzoyl-2′-O-benzyl-3′,5′-O-(di-tert-butylsilanediyl)adenosine (2g). Colorless oil. ^{1}H NMR ($CDCl_3$) δ 8.63 (1H, s, 8-H), 8.06 (1H, s, 2-H), 7.86-7.25 (15H, m, Ar-H), 6.07 (1H, s, 1′-H), 4.95 (2H, dd, $J = 97.5$, 12.0 Hz), 4.67 (1H, dd, $J = 9.6$, 4.8 Hz, 4′-H), 4.52-4.48 (2H, m, 3′-H, 5′-H), 4.33-4.25 (1H, m, 2′-H), 4.04 (1H, t, $J = 9.9$ Hz, 5″-H), 1.10 (9H, s, *t*-Bu-H), 1.07 (9H, s, *t*-Bu-H).

N^3-Benzoyl-2′-O-(p-methoxybenzyl)-3′,5′-O-(di-tert-butylsilanediyl)urdine (3). Colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.96-6.79 (10H, m, Ar-H, 6-H), 5.84 (1H, d, $J = 8.4$ Hz, 5-H), 5.77 (1H, s, 1′-H), 4.70 (2H, dd, $J = 45.0$, 11.4 Hz, 2′-*O*-CH_2Ar), 4.54-4.49 (1H, dd, $J = 11.6$, 4.6 Hz, 4′-H), 4.26-4.18 (1H, m, 3′-H), 4.13 (1H, d, $J = 4.5$ Hz, 5′-H), 4.04-3.95 (2H, m, 2′-H, 5″-H), 3.79 (3H, s, Ar-OCH_3), 1.07 (9H, s, *t*-Bu-H), 1.06 (9H, s, *t*-Bu-H).

N^3-Benzoyl-2′-O-(1-pyrenylmethyl)-3′,5′-O-(di-tert-butylsilanediyl)uridine (4). Colorless form. ^{1}H NMR ($CDCl_3$) δ 8.41-7.25 (15H, m, Ar-H, 6-H), 5.87 (1H, s, 1′-H), 5.74 (1H, d, $J = 8.4$ Hz, 5-H), 5.58 (2H, dd, $J = 12.3$, 5.4 Hz,

2′-*O*-CH_2Ar), 4.52 (1H, dd, $J = 9.3$, 4.8 Hz, 4′-H), 4.31-4.25 (2H, m, 3′-H, 5′-H), 4.05-3.99 (2H, m, 27-H, 5′′-H), 1.07 (18H, s, *t*-Bu-H).

***N*³-Benzoyl-2′-O-allyl-3′,5′-O-(di-tert-butylsilanediyl)uridine (5).** Colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.96-7.37 (6H, m, Ar-H, 6-H), 5.91-5.82 (2H, m, 5-H, 2′-*O*-$CH_2CH = CH_2$), 5.72 (1H, s, 1′-H), 5.23 (2H, dd, $J = 45.0$, 13.2 Hz, 2′-*O*-$CH_2CH = CH_2$), 4.54-4.51 (1H, m, 4′-H), 4.38-3.98 (6H, m, 2′-H, 3′-H, 5′-H, 5′′-H, 2′-*O*-$CH_2CH = CH_2$), 1.05 (18H, m, *t*-Bu-H).

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