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Preparation of C-5-substituted 6,5′-*O*-anhydrouridine by Sn–Pd transmetallation-coupling process and their use

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ABSTRACT

The palladium-catalyzed reaction of 5-tributylstannyluridine derivative (**9**) with a variety of aryl, vinyl halides provides an efficient method for the synthesis of the corresponding 5-substituted 6,5′-*O*-anhydrouridines. Additionally the 5-fluoro 6,5′-*O*-anhydrouridine (**16**) via fluoro-destannylation with Selectfluor is described. A dialkylphosphonate moiety was then introduced at C5 from the allyl derivative **10a** under cross-metathesis conditions.

1. Introduction

Modified pyrimidine and purine nucleoside derivatives play a prominent role as bioactive compounds.[1] Recently, some cyclonucleosides,[2] bearing additional linkage between the heterocyclic ring and the sugar moiety, have been shown to possess a wide range of antiviral[3] or antitumor[4] activities. Among them, the 2,5′-*O*-anhydrouridine (**1**) analog of BVDU exhibited an anti-HSV-1 activity[5] while 2,5′-*O*-bridged analogs of AZT (**2**) and AZU (**3**) were tested against HIV and R-MuLV.[6] The anhydroadenosine (**4**) inhibited *uridine phosphorylase*,[8] while the 2,5′-*O*-anhydrouridine (**5**) inhibited *uridine phosphorylase*,[7] (Fig. 1).

To achieve heterocycle modifications, the Pd(0) cross-coupling reactions and especially under Stille conditions, allowed us and others to synthesize broad range of modified nucleosides.[9] The classic method for the synthesis of C5-substituted pyrimidines by the Stille protocol involves the Pd-mediated cross-coupling of a haloaromatic or aryltriflate with an organostannane.

Thus, following our research on the synthesis and modification of 6,5′-*O*-anhydrouridines,[10] we decided to report herein the synthesis of *hitherto unknown* C5-substituted-6,5′-*O*-anhydronucleoside derivatives through the Stille palladium-catalyzed reaction starting from 5-iodo-6,5′-*O*-anhydrouridine. Although the palladium-mediated reactions are very useful tool for the synthesis of modified nucleosides, the Pd(0) cross-coupling for anhydronucleoside modification has not been explored to date. As a result of our interest in studying Pd-mediated C–C bond formation and cyclonucleosides, we became involved in addressing this problem.

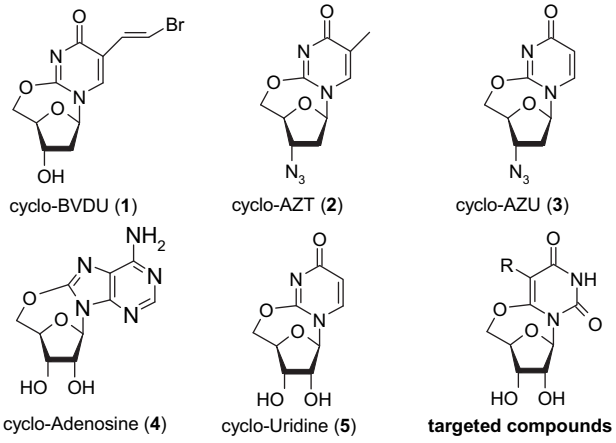

Figure 1. Some bioactive anhydrornucleosides.

2. Results and discussion

In first attempt, we tried to react the 5-iodo-2′,3′-*iso*-propylidene-6,5′-*O*-anhydrouridine (**7**)[10,11] with related reagents including organostannane (Stille), organoboron reagents (Suzuki) or alkene (Heck), under various Pd catalytic systems (such as Pd_2dba_3, $Pd(PPh)_3$, $Pd(PPh_3)Cl_2/As_3P$, $(2\text{-furyl})_3P$, PPh_3/CuI), $(IPr)Pd(Allyl)Cl$ (Scheme 1), with or without the addition of an inorganic salt as co-catalyst. Unfortunately in all cases, no reaction occurred and after work-up, the iodo derivative **7** was fully recovered (Scheme 1).

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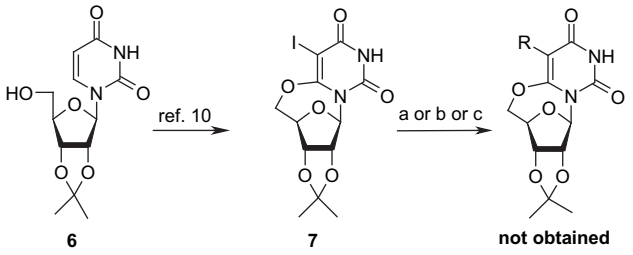
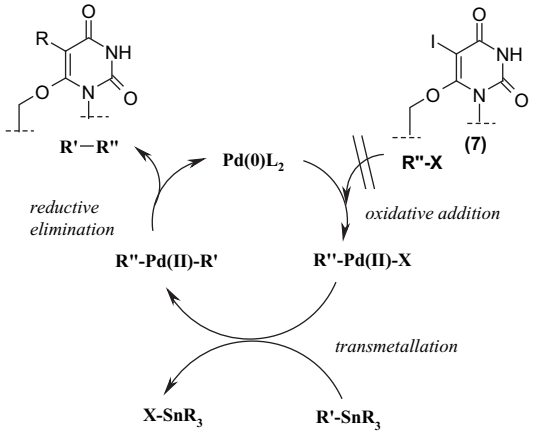


Scheme 1. Reagents and conditions: (a) Bu_3SnAll, Pd(0), dioxane or DMF, heating; (b) $PhB(OH)_2$, Pd(0), $AsPh_3$, dioxane, 70 °C, overnight; (c) acrylonitrile or vinylmethylketone, NBu_3, Pd(0), $AsPh_3$, DMF, 70 °C, 2 days.

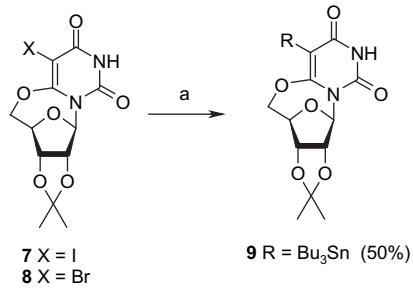
Based on the well admitted mechanism for Pd(0) cross-coupling (Scheme 2) and to explain the lack of reactivity of cyclonucleoside **7** for Pd(0) chemistry, we hypothesized that the Ar-X (**7**) oxidative addition to the active $Pd(0)L_2$ species does not proceed. In fact, in the catalytic cycle of a series of important palladium-catalyzed reactions (Heck, Suzuki, Stille, Negishi), an electrophilic aryl halide is oxidatively added to a nucleophilic palladium(0) d^{10} complex before being transferred onto the other coupling partner. The 6,5′-*O*-linkage leading to the 6-alkoxy-5-iodo-pyrimidine moiety increases the nucleophilic character at C5, the vinyl ether group having a strong electron-donating character.



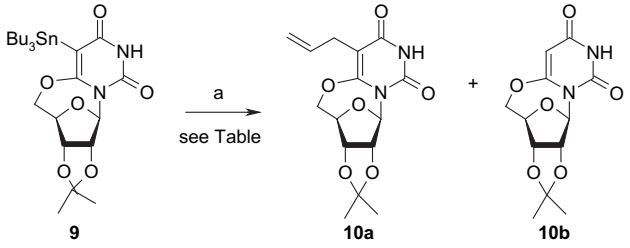
Scheme 2.

Thus, to circumvent this problem, we decided to introduce a tributylstannyl substituent at C5 position and to use the obtained 5-trialkylstannyl nucleoside for the transmetallation step. Similar approaches have been used for the synthesis of C5 labeling[12] and C4-substituted nucleosides.[13] The C5-trialkylstannyl nucleosides were obtained from the 5-halo nucleoside parent and hexa-*n*-butyldistannane in the presence of $Pd_2(PPh_3)_2Cl_2$[14] or by a direct lithiation method.[15] Thus, either the 5-iodo- (**7**) or the 5-bromo-2′,3′-*iso*propylidene-6,5′-*O*-anhydrouridine (**8**),[10] obtained by bromidation of **6** with an excess of *N*-bromosuccinimide,[11a] were lithiated at −78 °C with *n*-butyllithium and treated with a large excess of tributyltin chloride (Scheme 3). After reaction, 5-(tri-*n*-butylstannyl)-2′,3′-*iso*propylidene-6,5′-*O*-anhydrouridine (**9**) was isolated with 50%.

Having the 5-(tri-*n*-butylstannyl)-2′,3′-*iso*propylidene-6,5′-*O*-anhydrouridine (**9**) in hand, we decided to optimize the Stille reaction with allyl bromide in a presence of various catalytic systems (Scheme 4). Obtained results are presented in Table 1. The addition of CuI as co-catalyst was necessary to form the desired product **10a** (entries 2–5). In all cases, the byproduct of destannylation **10b** was isolated. Optimized conditions were obtained with the $Pd(PPh_3)Cl_2$/CuI catalytic system (entry 5), leading the desired product **10a** in 62% with 22% of **10b**.



Scheme 3. *Reagents and conditions*: (a) *i.* 1 equiv NaH, 10 min., rt, THF then 2 equiv BuLi, −78 °C; *ii.* Bu_3SnCl.

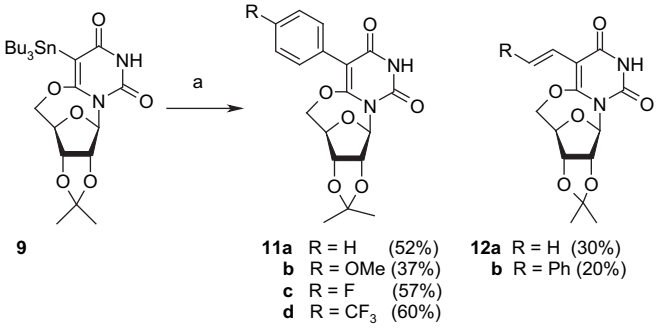


Scheme 4. Reagents and conditions: (a) AllBr, Pd(0) catalytic system (see Table 1), dioxane or DMF, heating.

Table 1

Entry	Catalyst (0.1 equiv)	Ligand	Co-catalyst (0.2 equiv)	Solvent	Temp. (°C)	Yield of **10a** [%]	Yield of **10b** [%]
1	Pd_2dba_3	As_3P	—	dioxane	70	No reaction	
2	Pd_2dba_3	$(2\text{-furyl})_3P$	CuI	dioxane	70	45	37
3	Pd_2dba_3	As_3P	CuI	dioxane	70	46	37
4	$Pd(PPh_3)_4$	—	CuI	DMF	60	52	28
5	**$Pd(PPh_3)_2Cl_2$**	—	**CuI**	**DMF**	**60**	**62**	**22**

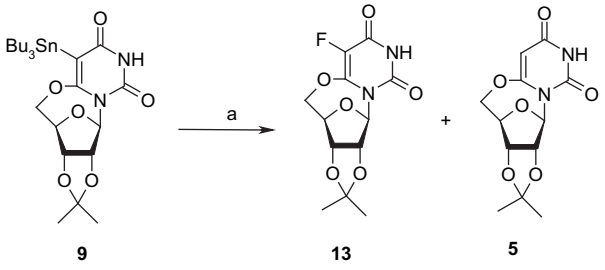
Under those Pd(0) optimized conditions, the 5-tri-(*n*-butylstannyl)-2′,3′-*iso*propylidene-6,5′-*O*-anhydrouridine (**9**) was reacted with several aryl or vinyl iodide, which led to various C5-substituted cyclouridine **11a**–**d** with yields ranging from 37 to 60%, Scheme 5. As expected, best yields were obtained with aryl iodide bearing an EWG favoring the oxidative insertion with Pd(0). The vinyl analog **12a** was isolated with 30% yield while the styryl derivative (**12b**) was isolated as the only *E* isomer (J=16.5 Hz) with 20% yield.



Scheme 5. Reagents and conditions: (a) Aryl or vinyl iodide, $Pd(PPh_3)Cl_2$/CuI, DMF, 70 °C.

We then turned our attention to the introduction at C5 of a fluorine. The access to C5-florinated nucleosides is rather limited to few

methods including enzymatic synthesis using phosphorylases,[16] direct fluorination using F_2 in AcOH[17] or cesium fluoroxy phosphate—$CsSO_4F$.[18] Following a recent procedure from Yu et al.[19] tri-(*n*-butylstannyl)-2′,3′-*iso*propylidene-6,5′-*O*-anhydrouridine (**9**) was treated with Selectfluor in THF to give the 5-fluoro-2′,3′-*iso*-propylidene-6,5′-*O*-anhydrouridine (**13**) with 51% together with 49% of destanyllated product **5** (Scheme 6).

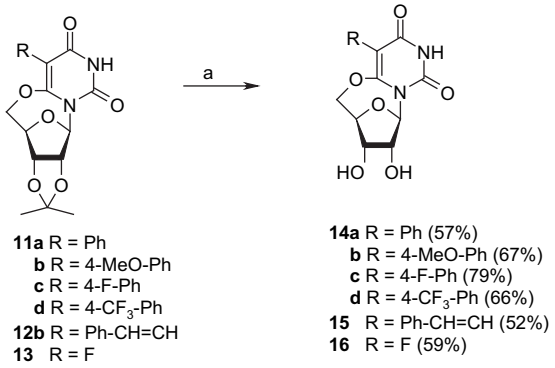


Scheme 6. Reagents and conditions: (a) Selectfluor, MeCN, 4 h, rt, 51%.

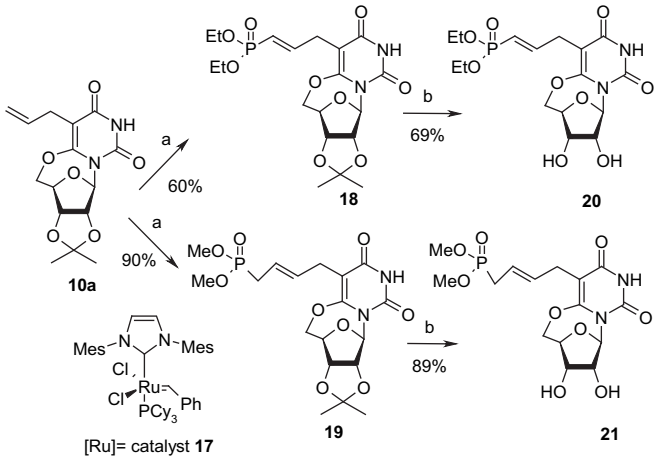
Finally, all obtained allyl, aryl or vinyl derivatives **11a–d**, **13** were successfully deprotected with 10% TFA solution to final products **14a–d**, **16**, respectively, with moderate to good yields (Scheme 7). Compound **12b** was deprotected with scandium triflate to **15**, however all efforts leading to deprotection of vinyl derivative **12a** resulted in the decomposition of the substrate.

Finally, it is known that organophosphorus compounds are remarkable for their diverse and potent biological activities,[20] often enhanced by their association with various heterocycles and especially azaheterocycle.[21] For instance, Qu et al.[22] synthesized novel C6-phosphonated purine nucleosides by SNAr-Arbuzov reaction of trialkyl phosphite with 6-chloropurine nucleosides. Previously, Honjo et al. have described the sysnthesis and biological properties of several di-Et and mono-Et esters of phosphonopyrimidine and purine ribonucleosides and shown that the di-Et-6-chloro-9-(β-D-ribofuranosyl)purine-8-phosphonates exhibited some antiviral and cytostotic activities, which were comparable to those of the unphosphornylated compounds.

Thus, we turn our attention to the introduction on a dialkylphosphonate moiety at C5 from the allyl derivative **10a** under cross-metathesis conditions.[23] Compound **10a** was reacted with the commercially available vinyl phosphonic acid diethyl ester with catalyst **17**,[24] to afford the desired heterodimer **18** as the *E*-isomer. Under the same conditions, reaction between allyl derivative **10a** and dimethylallyl phosphonate afforded **19** in 90% yield as the major and thermodynamically stable *E*-isomer, (Scheme 8).



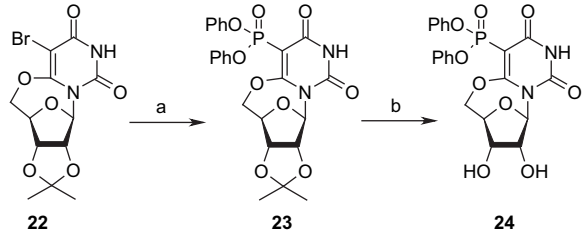
Scheme 7. Reagents and conditions: (a) 10% TFA in H_2O, 70 °C, 1 h or 10 mol % of $Sc(OTf)_3$, 1% AcCN in water, 1 h, 120 °C, microwaves.



Scheme 8. Reagents and conditions (a) [Ru] catalyst **17** (6 mol %), dry CH_2Cl_2, rfx, 7 h, diethyl vinylphosphonate (for **18**) or dimethylallyl phosphonate (for **19**); b) 10% TFA in H_2O, 70 °C, 1 h.

After treatment of **18** and **19** with 10% TFA solution, the deprotected products **20** and **21** were isolated with 69% and 89%, respectively.

The C5-diphenylphosphonate **24** was directly obtained from 5-bromo-6,5′-*O*-anhydrouridine **22**,[10] by a lithiation/alkylation step, (Scheme 9). Thus, the 5′-bromoderivative **22** was treated with 1 equiv NaH and 2 equiv of BuLi followed by the addition of 5 equiv of diphenyl chlorophosphate to afford **23** with moderate yield. Deprotection of **23** with 10% TFA solution led the desired product **24** in a low yield.



Scheme 9. Reagents and conditions: (a) 1 equiv NaH, 10 min., rt, THF then 2 equiv BuLi, −78 °C then $(PhO)_2POCl$; b) 10% TFA:H_2O 1:2, rt, 3 days.

For all 6,5′-*O*-anhydronucleosides, characteristic AB systems were observed by ^1H NMR data. For protected compounds, two AB systems appeared, e.g., for C5′ protons and for C2′/C3′ protons. For deprotected compounds, only AB system for C5′ protons still existed, while C2′/C3′ protons usually had identical shifts giving one multiplet.

3. Conclusion and perspectives

6,5′-*O*-Anhydrouridine derivatives bearing aryl or vinyl substituents at C5 position were synthesized by Sn–Pd transmetallation cross-coupling protocol starting from the easily available 5-tri-(*n*-butylstannyl)-2′,3′-*iso*propylidene-6,5′-*O*-anhydrouridine (**9**). The 5-fluoro derivative was also obtained from tributystannyl intermediate. This procedure allows the synthesis of broad range of C5-substituted 6,5′-*O*-anhydronucleosides not accessible by other methods (e.g.. lithiation at C5 position). A dialkylphosphonate moiety was then introduced at C5 position using cross-metathesis or lithiation. No significant activity against HCV was found.

4. Experimental

4.1. General

Commercially available chemicals were used as-received. Microwave reactions were carried out in a Biotage Initiator with a maximum power of 300 W and temperatures were measured by IR-sensor. Reactions were monitored by thin-layer chromatography (TLC) analysis using silica gel plates (Kieselgel 60 F_{254}). Compounds were visualized by UV irradiation and/or spraying with ethanol solution 2.5% in phosphomolybdic acid, followed by charring at 150 °C. Column chromatography was performed on Silica Gel 60 M (0.040–0.063 mm).

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE DPX 250 (^{1}H 249.88 MHz, ^{13}C: 62.84 MHz) and Varian Inova$_{Unity}$ 400 spectrometer (^{1}H 399.91 MHz, ^{13}C: 100.54 MHz) in DMSO-d_6 or mixture of $CDCl_3$/DMSO-d_6. The NMR spectra were recorded at room temperature. The chemical shifts are given in ppm relative to the residual signal of the solvent, TMS being used as calibration standard with different deuteriated solvents. Signals are reported as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), q_i (quintuplet) and m (multiplet) with the relevant coupling constants *J* in Hertz. For protected compounds to differentiate signals from aliphatic chain and *iso*propylidene group: *i*—signals derived from *iso*propylidene group, *c*—signals from aliphatic chain in C5 position. Polarity index was measured on: Perkin Elmer Model 341 Polarimeter. Evidence of purity has been done from a proton-decoupled ^{13}C NMR spectrum with a signal-to-noise ratio sufficient to permit seeing peak with 5% of the intensity of the strongest peak.

4.2. 5-(Tri-*n*-butylstannyl)-2′,3′-isopropylidene-6,5′-*O*-anhydrouridine (9)

1 equiv of 5-halo-2′,3′-*iso*propylidene-6,5′-*O*-anhydrouridine (**7** for X=I or **8** for X=Br)[10] was dissolved in dry THF (20 mL) and 1 equiv of sodium hydride was added. The reaction mixture was cooled at −78 then 2 equiv of *n*-Buli was added. After stirring 30 min, 5 equiv tributyltin chloride were added. The reaction mixture was stirred at −78 °C overnight, then warm up to room temperature. NH_4Cl satd was added, organic phase was separated and aqueous phase was extracted three times with CH_2Cl_2. Organic phases were evaporated and the residue was purified by liquid chromatography on silica gel using petroleum ether/EtOAc, 7:3. Recrystallization of **9** from hexane gave white crystals. $[\alpha]_D$ +50 (*c* 1.0, MeOH). ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.89 (9H, t, *J*=7.3 Hz), 1.00–1.11 (6H, m), 1.23–1.41 (9H, m), 1.42–1.57 (19H, m), 4.12 (1H, dd, *J*=0.7, *1*2.3 Hz), 4.33 (1H, dd, *J*=1.3, 12.3 Hz), 4.56 (1H, s), 4.80 (1H, d, *J*=5.6 Hz), 4.89 (1H, d, *J*=5.6 Hz), 6.60 (1H, s), 8.28 (1H, s); ^{13}C NMR (62 MHz, $CDCl_3$) δ 11.3, 14.1, 24.7, 26.2, 27.7, 29.4, 76.8, 82.4, 83.7, 85.6, 89.6, 98.6, 113.1, 140.4, 163.0, 166.3; HRMS (ESI): *m*/*z* calcd for $C_{24}H_{40}N_2O_6Sn$ $(M+Na)^+$: 594.2902, found: 594.2897.

4.3. Procedure for Stille reaction

1 equiv of tri-*n*-butylstannyl derivative **9** was dissolved in dry DMF (20 mL), 0.1 equiv of $Pd(PPh_3)Cl_2$, 0.2 equiv of CuI and 3 equiv of RX were added under argon. Reaction mixture was heated on oil bath in 70 °C for an 8 h, then solvent was evaporated, and residue was chromatographed using petroleum ether/EtOAc, 7:3 then 6:4.

*4.3.1. 5-Allyl-2′,3′-isopropylidene-6,5′-O-anhydrouridine (**10a**).* $[\alpha]_D$ +96 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.36 (3H, s), 1.54 (3H, s), 2.97–3.21 (2H, m), 3.93 (1H, dd, *J*=0.7,12.4 Hz), 4.47 (1H, dd, *J*=1.2, 12.5 Hz), 4.59 (1H, s), 4.84 (1H, d, *J*=5.6 Hz), 4.94 (1H, d, *J*=5.6 Hz), 4.96–5.11 (2H, m), 5.72–9.94 (1H, m), 6.60 (1H, s), 9.44 (s, 1H); ^{13}C NMR (62 MHz, $CDCl_3$) δ 24.6, 26.2, 28.6, 77.1, 82.4, 84.0, 85.5, 89.9, 101.3, 113.0, 115.3, 135.3, 149.0, 157.8, 163.4, HRMS (ESI): *m*/*z* calcd for $C_{15}H_{18}N_2O_6$ $(M+Na)^+$: 345.3067, found: 345.3065.

*4.3.2. 5-Phenyl-2′,3′-isopropylidene-6,5′-O-anhydrouridine (**11a**).* $[\alpha]_D$ +49 (*c* 1.0, MeOH). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.34 (3H, s), 1.54 (3H, s), 3.93 (1H, dd, *J*=0.6, 12.4 Hz), 4.27 (1H, dd, *J*=1.0, 12.4 Hz), 4.58 (1H, s), 4.88 (2H, s), 6.66 (1H, s), 7.32 (5H, m), 9.06 (1H, s); ^{13}C NMR (62 MHz, $CDCl_3$) δ 24.6, 26.2, 77.6, 82.3, 84.0, 85.5, 90.9, 104.8, 113.1, 127.9, 128.1, 129.2, 130.3, 148.7, 157.5, 162.5; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{18}N_2O_6$ $(M+Na)^+$: 381.3397, found: 381.3395.

*4.3.3. 5-(4-Methoxyphenyl)-2′,3′-isopropylidene6,5′-O-anhydrouridine (**11b**).* $[\alpha]_D$ +37 (*c* 0.6, MeOH). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.34 (3H, s), 1.54 (3H, s), 3.82 (3H, s), 3.96 (1H, dd, *J*=0.5, 12.4 Hz), 4.36 (1H, dd, *J*=1.0, 12.4 Hz), 4.58 (1H, s), 4.89 (2H, s), 6.66 (1H, s), 6.92 (2H, d, *J*=8.8 Hz), 7.21 (2H, d, *J*=8.8 Hz), 8.78 (1H, s); ^{13}C NMR (62 MHz, $CDCl_3$) δ 24.6, 26.2, 55.3, 77.6, 82.3, 84.0, 85.6, 90.2, 104.5, 113.1, 113.7, 31.4, 121.3, 148.6, 157.2, 159.2, 162.6; HRMS (ESI): *m*/*z* calcd for $C_{19}H_{20}N_2O_7$ $(M+Na)^+$: 411.3659, found: 411.3658.

*4.3.4. 5-(4-Fluorophenyl)-2′,3′-isopropylidene-6,5′-O-anhydrouridine (**11c**).* $[\alpha]_D$ +52 (*c* 1.0, MeOH). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.35 (3H, s), 1.54 (3H, s), 3.95 (1H, dd, *J*=0.6, 12.4 Hz), 4.35 (1H, dd, *J*=1.0, 12.4 Hz), 4.58 (1H, s), 4.89 (2H, s), 6.66 (1H, s), 7.06 (2H, t, *J*=8.6 Hz), 7.26 (2H, t, *J*=8.6 Hz), 9.07 (1H, s); ^{13}C NMR (62 MHz, $CDCl_3$) δ 24.6, 26.2, 77.6, 82.3, 83.9, 85.5, 90.2, 103.8, 113.1, 115.2, 125.3, 132.1, 148.6, 157.6, 162.2, 162.5; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{17}FN_2O_6$ $(M+Na)^+$: 399.3302, found: 399.3298.

*4.3.5. 5-[4-(Trifluoromethyl)phenyl]-2′,3′-isopropylidene-6,5′-O-anhydrouridine (**11d**).* $[\alpha]_D$ +49 (*c* 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (3H, s), 1.54 (3H, s), 3.98 (1H, dd, *J*=0.8, 12.4 Hz), 4.37 (1H, dd, *J*=1.2, 12.4 Hz), 4.60 (1H, d), 4.90 (2H, m), 6.67 (1H, s), 7.43 (2H, d, *J*=8.1 Hz), 7.63 (2H, d, *J*=8.1 Hz), 9.05 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6, 26.2, 77.8, 82.3, 83.9, 85.5, 90.3, 103.5, 113.3, 124.0, 125.0, 129.9, 130.8, 133.1, 148.5, 158.0, 162.1; HRMS (ESI): *m*/*z* calcd for $C_{19}H_{17}F_3N_2O_6$ $(M+Na)^+$: 449.3380, found: 449.3379.

*4.3.6. 5-Vinyl-2′,3′-isopropylidene-6,5′-O-anhydrouridine (**12a**).* $[\alpha]_D$ +93 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (3H, s), 1.54 (3H, s), 4.00 (1H, dd, *J*=0.7, 12.4 Hz), 4.56 (1H, dd, *J*=1.1, 12.4 Hz), 4.62 (1H, s), 4.86 (1H, d, *J*=5.6 Hz), 4.96 (1H, d, *J*=5.6 Hz), 5.33 (1H, dd, *J*=2.1, 11.9 Hz), 6.20 (1H, dd, *J*=2.1, 17.8 Hz, CH_2=), 6.45 (1H, dd, *J*=11.9, 17.8 Hz), 6.62 (1H, s, H1′), 8.92 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6, 26.2, 77.1, 82.4, 84.0, 85.6, 90.2, 101.1, 113.2, 118.4, 123.5, 148.2, 157.4, 162.0; HRMS (ESI): *m*/*z* calcd for $C_{14}H_{16}N_2O_6$ $(M+Na)^+$: 331.2799, found: 331.2796.

*4.3.7. 5-(E)-Styryl-2′,3′-isopropylidene-6,5′-O-anhydrouridine (**12b**).* $[\alpha]_D$ +76 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.37 (3H, s), 1.55 (3H, s), 4.04 (1H, dd, *J*=0.7, 12.4 Hz), 4.59–4.66 (2H, m), 4.89 (1H, d, *J*=5.6 Hz), 4.99 (1H, d, *J*=5.6 Hz), 6.65 (1H, s), 6.85 (1H, d, *J*=16.5 Hz), 7.18–7.56 (5H, m), 7.72 (1H, d, *J*=16.5 Hz), 8.89 (1H, s); ^{13}C NMR (62 MHz, $CDCl_3$) δ 24.7, 26.2, 77.3, 82.4, 84.0, 85.6, 90.3, 101.3, 113.2, 115.7, 126.4, 127.6, 128.6, 132.1, 137.9, 148.0, 157.1, 161.9; HRMS (ESI): *m*/*z* calcd for $C_{20}H_{20}N_2O_6$ $(M+Na)^+$: 407.3775, found: 407.3772.

4.4. General deprotection with TFA solution

The *iso*propylidene derivatives were treated with 10% TFA in H_2O for 1 h in 70 °C, respectively. Solvent was evaporated and co-evaporated with toluene. The residue was dissolved and purified by

liquid chromatography on silica gel (petroleum ether/EtOAc, from 5/5 to 7/3).

*4.4.1. 5-Phenyl-6,5′-O-anhydrouridine (**14a**).* $\alpha]_D$ +47 (*c* 1.0, DMF). ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.08 (1H, d, *J*=12.3 Hz), 4.19–4.26 (1H, m), 4.30–4.45 (3H, m), 5.19 (1H, d, *J*=4.6 Hz), 5.47 (1H, d, *J*=7.2 Hz), 6.27 (1H, s), 7.20–7.40 (5H, m), 11.55 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 72.0, 76.5, 77.5, 86.3, 91.6, 103.3, 126.9, 127.5 130.5, 130.7, 149.2, 157.5, 162.7; HRMS (ESI): *m*/*z* calcd for $C_{15}H_{14}N_2O_6$ (M+Na)$^+$: 341.2751, found: 341.2748.

*4.4.2. 5-(4-Methoxyphenyl)-6,5′-O-anhydrouridine (**14b**).* $[\alpha]_D$ +36 (*c* 0.6, DMF). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.74 (1H, s), 4.02 (1H, d, *J*=11.8 Hz), 4.18–4.27 (1H, m), 4.30–4.43 (3H, m), 5.20 (1H, d, *J*=3.3 Hz), 5.50 (1H, d, *J*=6.6 Hz), 6.25 (1H, s), 6.85–9.94 (2H, m), 7.12–7.21 (2H, m), 11.50 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 55.2, 72.3, 76.7, 77.7, 86.6, 91.8, 103.3, 113.3, 122.8, 131.8, 158.5, 149.4, 157.6, 163.2; HRMS (ESI): *m*/*z* calcd for $C_{16}H_{16}N_2O_7$ (M+Na)$^+$: 371.3013, found: 371.3011.

*4.4.3. 5-(4-Fluorophenyl)-6,5′-O-anhydrouridine (**14c**).* $[\alpha]_D$ +58 (*c* 1.0, DMF). ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.10 (1H, d, *J*=12.3 Hz), 4.20–4.27 (1H, m), 4.32–4.45 (3H, m), 5.18 (1H, br s), 5.45 (1H, d, *J*=6.9 Hz), 6.27 (1H, s), 7.13–7.21 (2H, m), 7.25–7.35 (2H, m), 11.57 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 72.0, 76.4, 77.5, 86.3, 91.6, 102.3, 114.5, 126.9, 132.5, 149.1, 157.6, 161.1, 162.7; HRMS (ESI): *m*/*z* calcd for $C_{15}H_{13}FN_2O_6$ (M+Na)$^+$: 359.2656, found: 359.2654.

*4.4.4. 5-[4-(Trifluoromethyl)phenyl]-6,5′-O-anhydrouridine (**14d**).* $[\alpha]_D$ +61 (*c* 1.0, DMF). ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.15 (1H, d, *J*=12.1 Hz), 4.20–4.27 (1H, m), 4.33–4.41 (2H, m), 4.45 (1H, d, *J*=12.1 Hz), 5.20 (1H, br s), 5.44 (1H, d), 6.28 (1H, s), 7.52 (2H, d, *J*=8.3 Hz), 7.70 (2H, d, *J*=8.3 Hz), 11.66 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 71.9, 76.6, 77.7, 86.3, 91.7, 101.9, 124.2, 124.3, 127.4, 131.3, 135.3, 149.2, 158.1, 162.4; HRMS (ESI): *m*/*z* calcd for $C_{16}H_{13}F_3N_2O_6$ (M+Na)$^+$: 409.2734, found: 409.2731.

4.5. 5-(*E*)-Styryl-6,5′-*O*-anhydrouridine (15)

54 mg of styrene derivative **12b** were dissolved in 3 mL of 1% AcCN in H_2O, then 7 mg (0.1 equiv) of scandium triflate were added. The reaction mixture was heated in 120 °C for a 1 h under the microwaves conditions in a sealed tube. Then solvent was evaporated and residue was purified by liquid chromatography on silica gel column using petroleum ether/EtOAc 3:7. 25 mg (52%) of product were obtained. $[\alpha]_D$ +108 (*c* 1.0, DMSO). ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.05 (1H, d, *J*=12.5 Hz), 4.34–4.44 (2H, m), 4.46 (1H, s), 4.80 (1H, d, *J*=12.5 Hz), 5.28 (1H, br s), 5.50 (1H, d, *J*=6.3 Hz), 6.27 (1H, s), 6.91 (1H, d, *J*=16.5 Hz), 7.27 (1H, d, *J*=7.3 Hz), 7.35 (2H, t, *J*=7.5 Hz), 7.46 (2H, d, *J*=7.5 Hz), 7.60 (1H, d, *J*=16.5 Hz), 11.66 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 72.2, 76.6, 77.6, 86.5, 91.9, 117.7, 125.9, 127.2, 128.7, 129.0, 138.9, 148.6, 158.2, 162.5; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{16}N_2O_6$ (M+Na)$^+$: 367.3129, found: 367.3125.

4.6. 5-Fluoro-6,5′-*O*-anhydrouridine (16)

The fluorinated compound **13** was deprotected with 10% TFA following the general procedure reported above. $[\alpha]_D$ +84 (*c* 1.0, DMSO). ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.11 (1H, dd, *J*=0.7, 12.4 Hz), 4.27–4.33 (1H, m), 4.33–4.39 (1H, m), 4.41 (1H, m), 4.69 (1H, dd, *J*=1.2, 12.4 Hz), 5.25 (1H, s), 5.45 (1H, s), 6.15 (1H, s), 11.89 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 71.9, 76.4, 78.4, 86.6, 92.2, 129.9, 147.6, 149.0, 157.2; HRMS (ESI): *m*/*z* calcd for $C_9H_9FN_2O_6$ (M+Na)$^+$: 283.1680, found: 283.1677.

4.7. 5-[(*E*)-3-Diethoxyphosphinyl-2-propenyl]-2′,3′-*iso*propylidene-6,5′-*O*-anhydrouridine (18)

To a dry CH_2Cl_2 (10 mL) solution of N^1-allyl-5-substituted anhydrouridine **10** (100 mg, 0.0.31 mmol) and diethyl vinylphosphonate (254 mg, 0.26 mL, 1.55 mmol), catalyst **17** (15 mg, 0.02 mmol) was added. This solution was refluxed for 7 h under positive pressure of dry Ar. After evaporation of all volatiles, the residue was purified by chromatography on silica gel (EtOAc/MeOH=15:1) to afford 18 (66 mg, 60%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.31 (6H, t, *J*=7.3 Hz), 1.36 (3H, s), 1.54 (3H, s), 3.12 (2H, m), 3.93 (1H, d, *J*=0.7, 12.4 Hz), 4.07 (2H, q, *J*=7.3 Hz), 4.12 (2H, q, *J*=7.3 Hz), 4.47 (1H, dd, *J*=1.2, 12.5 Hz), 4.59 (1H, s), 4.84 (1H, d, *J*=5.6 Hz), 4.94 (1H, d, *J*=5.6 Hz), 5.85 (1H, t, *J*=16.9 Hz), 6.78 (1H, ddt, *J*=5.0, 16.9, 21.9 Hz), 6.59 (1H, s), 9.82 (1H, s); ^{13}C NMR (62 MHz, $CDCl_3$) δ 16.2, 16.3, 24.6, 26.2, 28.6, 61.2, 61.4, 77.1, 82.4, 84.0, 85.5, 89.9, 101.3, 113.0, 117.4 (J_{CP}), 149.0, 149.2 (J_{CP}), 149.0, 157.8, 163.4; HRMS (ESI): *m*/*z* calcd for $C_{19}H_{27}N_2O_9P$ (M+Na)$^+$: 481.3937, found: 481.3935.

4.8. 5-[(*E*)-4-Dimethoxyphosphinyl-2-butenyl]-2′,3′-*iso*propylidene-6,5′-*O*-anhydrouridine (19)

A mixture of protected N^1-allyl-5-substituted anhydrouridine **10** (100 mg, 0.0.31 mmol), dimethylallyl phosphonate (223 mg, 0.2 mL, 1.5 mmol), and catalyst **17** (15 mg, 0.02 mmol) in CH_2Cl_2 (10 mL) was refluxed for 4 h under positive pressure of dry Ar. After evaporation of all volatiles, the residue was purified by chromatography on silica gel (EtOAc/MeOH=20:1) to yield the desired compound **19** (112 mg, 90%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.36 (3H, s), 1.54 (3H, s), 2.51 (1H, d, *J*=7.5 Hz), 2.60 (1H, d, *J*=7.5 Hz), 3.09 (2H, m), 3.7 (6H, m), 3.92 (1H, d, *J*=12.5 Hz), 4.53 (1H, d, *J*=12.5 Hz), 4.59 (1H, s), 4.82 (1H, d, *J*=5.6 Hz), 4.93 (1H, d, *J*=5.6 Hz), 5.44 (1H, m), 5.62 (1H, m) 6.57 (1H, s), 9.33 (1H, s); ^{13}C NMR (62 MHz, $CDCl_3$) δ 24.6, 25.5, 26.2, 28.6 (J_{CP}), 56.2, 77.0, 82.3, 84.1, 85.5, 89.9, 101.3, 113.0, 119.4 (J_{CP}), 132.5 (J_{CP}), 149.0, 157.8, 163.4; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{25}N_2O_9P$ (M+Na)$^+$: 467.3669, found: 467.3666.

4.9. 5-[(*E*)-3-Diethoxyphosphinyl-2-propenyl]-6,5′-*O*-anhydrouridine (20)

Compound **20** was deprotected with 10% TFA following the general procedure reported above. ^{1}H NMR (250 MHz, MeOH-d_4) δ 1.31 (6H, t, *J*=7.3 Hz), 3.3 (2H, m), 4.04 (5H, m), 4.45 (3H, m), 4.57 (1H, d, *J*=12.6 Hz), 5.76 (1H, m), 6.4 (1H), 6.74 (1H, m), 5.44 (1H, d, *J*=6.4 Hz), 5.66–5.87 (1H, m), 6.19 (1H, s); ^{13}C NMR (67 MHz, MeOH-d_4) δ 16.2, 16.3, 26.2, 61.2, 72.1 (C3′), 76.6 (C2′), 77.0 (C5′), 86.3 (C4′), 91.4 (C1′), 100.9 (C5), 117.4 (J_{CP}), 149.2 (J_{CP}), 149.2 (C2), 157.9 (C6), 163.5 (C4); HRMS (ESI): *m*/*z* calcd for $C_{16}H_{23}N_2O_9P$ (M+H)$^+$:418.3394, found: 418.3391.

4.10. 5-[(*E*)-4-Dimethoxyphosphinyl-2-butenyl]-6,5′-*O*-anhydrouridine (21)

Compound **21** was deprotected with 10% TFA following the general procedure reported above. ^{1}H NMR (250 MHz, MeOH-d_4) δ 2.60 (1H, d, *J*=7.5 Hz), 2.68 (1H, d, *J*=7.5 Hz), 3.09 (2H, m), 3.73 (6H, m), 3.95 (1H, d, *J*=12.5 Hz), 4.47 (3H, m), 4.53 (1H, d, *J*=12.5 Hz), 5.44 (1H, m), 5.62 (1H, m) 6.38 (1H, s); ^{13}C NMR (62 MHz, MeOH-d_4) δ 25.5, 28.6 (J_{CP}), 56.2, 77.0, 82.3, 84.1, 85.5, 89.9, 101.3, 113.0, 119.4 (J_{CP}), 132.5 (J_{CP}), 149.0, 157.8, 163.4; HRMS (ESI): *m*/*z* calcd for $C_{15}H_{21}N_2O_9P$ (M+H)$^+$: 405.3205, found: 405.3204.

4.11. 5-[Diphenylphosphinyl]-2′,3′-*iso*propylidene-6,5′-*O*-anhydrouridine (23)

1 equiv of 5-bromo-2′,3′-isopropylidene-6,5′-*O*-anhydrouridine **22**[10] (1.5 g, 4.15 mmol) was dissolved in dry THF (50 mL) and 1 equiv of sodium hydride (0.17 g) was added followed by 3 equiv of HMPA (2.16 mL, 12.45 mmol). The reaction mixture was cooled down under nitrogen to −78 °C, then 2 equiv of 2.5 M *n*-BuLi (3.34 mL, 8.30 mmol) was added. After stirring for a 30 min, 5 equiv of diphenyl chlorophosphate (4.29 mL, 20.75 mmol) was added. The reaction mixture was stirred at −78 °C overnight, then warmed up to rt. Satd NH_4Cl was added, organic phase was separated, and aqueous phase was extracted three times with CH_2Cl_2. Organic phases were evaporated and the residue was purified by liquid chromatography on silica gel (petroleum ether/EtOAc, 7:3 then 6:4) to led the desired product **23** (400 mg, 20%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.32 (3H, s), 1.52 (3H, s), 3.89 (1H, dd, J_1=0.9, 12.4 Hz), 4.58 (1H, s), 4.60 (1H, dd, J_1=1.3, 12.4 Hz), 4.76 (1H, d, J=5.6 Hz), 4.89 (1H, d, J=5.6 Hz), 6.55 (1H, s), 6.55–7.38 (m, 10H), 9.36 (1H, br s); ^{13}C NMR (62 MHz, $CDCl_3$) δ 24.6, 26.2, 76.7, 82.2, 84.2, 85.4, 90.4, 91.2 (J_{CP}), 113.2, 120.7, 125.3, 129.6, 148.1, 150.1 160.2, 167.2; HRMS (ESI): *m*/*z* calcd for $C_{24}H_{23}N_2O_9P$ (M^++Na): 537.4171, found: 537.4169.

4.12. 5-[Diphenylphosphinyl]-6,5′-*O*-anhydrouridine (24)

Compound 24 was deprotected with 10% TFA following the general procedure reported except the reaction occurred at rt. ^{1}H NMR (250 MHz, MeOH-d_4) δ 3.83 (1H, dd, J_1=0.9, 12.4 Hz), 4.2 (3H, m), 4.51 (1H, dd, J_1=1.3, 12.4 Hz), 6.27 (1H, s), 6.55–7.38 (m, 10H); ^{13}C NMR (62 MHz, MeOH-d_4) δ 73.8, 78.3, 80.01, 88.3, 94.3, 121.6, 126.6, 130.9, 150.3, 151.6, 162.9, 169.9; HRMS (ESI): *m*/*z* calcd for $C_9H_{11}N_2O_9P$ (M^++Na): 345.1573, found: 345.1571.

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