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Palladium-Catalyzed Synthesis of Uridines on Polystyrene-Based Solid Supports

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In this paper, the solid-phase synthesis of various substituted pyrimidine nucleosides is described starting from 2′-deoxyuridine (**1**), which has been attached through a base labile linker **2** to polystyrene resins. The utility of the Pd(0) cross-coupling to functionalized pyrimidine nucleosides is expanded herein to include reactions of resin-supported 5-iodo-2′-deoxyuridine (**8**) under Sonogashira, Stille, Heck, and Suzuki conditions. Upon cleavage with MeONa, a library of 5-substituted pyrimidine nucleosides (**10a**−**e**, **11a**−**c**, **12a**−**e**) was obtained in good (under Sonogashira and Stille conditions) to moderate (under Heck or Suzuki conditions) yields and high purity. Except the Suzuki-type reactions, the presented methods exhibit a significant improvement and facilitate the synthetic procedure with respect to purification and yields (determined after filtration over silica gel).

Introduction

Studies into the biological activities of nucleosides and their phosphorylated derivatives have been a fundamental and fruitful field of research since the 1940s and 1950s.[1] Synthetic antibiotic, antitumor, and antiviral agents have convincingly demonstrated the huge potential of this class of compounds, with around 50 current drugs based on these compounds for a variety of diseases and over 80 in (pre)-clinical studies. The intense search for clinically useful nucleoside derivatives has resulted in a wealth of new approaches for their synthesis from hundreds of academic and pharmaceutical laboratories. One useful approach, recently reviewed by our group,[2] has involved the use of palladium-catalyzed insertion and cross-coupling reactions (Heck, Stille, Sonogashira, Tsuji-Trost, etc.), which have gained recognition due to their broad scope. Another approach that has developed rapidly in recent years involves the synthesis of small organic molecule libraries by a parallel solid-phase strategy.[3] Except for the very well-known solid-phase oligonucleotide synthesis, this powerful technology has tardy been applied to mononucleoside chemistry.[4] To the best of our knowledge, a combination of these two important reaction types has not yet been employed in the synthesis and modification of nucleosides, except by Crimmins et al.,[5] who reported the chemical synthesis of carbocyclic nucleosides using a palladium-catalyzed solid-phase allylation. Thus, as part of our drug discovery program, we describe here the successful application and optimization of palladium-assisted routes to pyrimidine nucleosides bound to polystyrene resins.

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Results and Discussion

Many pyrimidine nucleoside analogues substituted at the 5-position of the heterocycle, and especially in the 2′-deoxyuridine series, are known to have potent biological properties and have been developed as antiviral and anticancer agents. The 5-(2-substituted vinyl)-2′-deoxyuridines, in particular, have emerged as potent and selective inhibitors of herpes viruses (HSV-1 and HSV-2).[6] In general, 5-alkynyl-2′-deoxyuridines have been also evaluated as potential antiviral agents,[7] and SAR studies have indicated that the C-5 substituents, likely to confer activity, are those which are electron withdrawing and conjugated to the heterocycle.[8] Thus, starting from 2′-deoxyuridine (**1**), the nucleoside was attached via the 5′-OH moiety to a base labile linker **2**[9] (easily obtained in seven steps from commercially available *p*-bromomethyl benzoic acid)[10] (Scheme 1). Following acetylation of the 3′-hydroxyl group and removal of the *tert*-butyl ester group of **3**, the carboxylic acid **4** was coupled to commercially available resin **5** using the *N*-hydroxybenzotriazole activated ester and subsequent capping of residual amine groups borne by the resin. Analysis of the substitution level of the resin was performed by cleaving **6** via a basic transesterification with excess MeONa in a mixture of MeOH/dioxane, leading to a highly pure form of 2′-deoxy-D-uridine (**1**). An iodo group was selectively introduced at the C-5 position of the heterocyclic moiety using I_2/CAN, and cleavage of resulting **8** afforded the well-known antiviral **9**, 5-iodo-2′-deoxyuridine (IDU), reported by Prusoff et al.[11] in the early 1960s.

Different substituents were then introduced by reaction of the resin-bound 2′-deoxy-5-iodo-D-uridine **8** under various Pd(0)-catalyzed reactions, using our optimized conditions for palladium-mediated reactions. In almost all cases, conversion rates of these reactions were very high (>90%); nevertheless,

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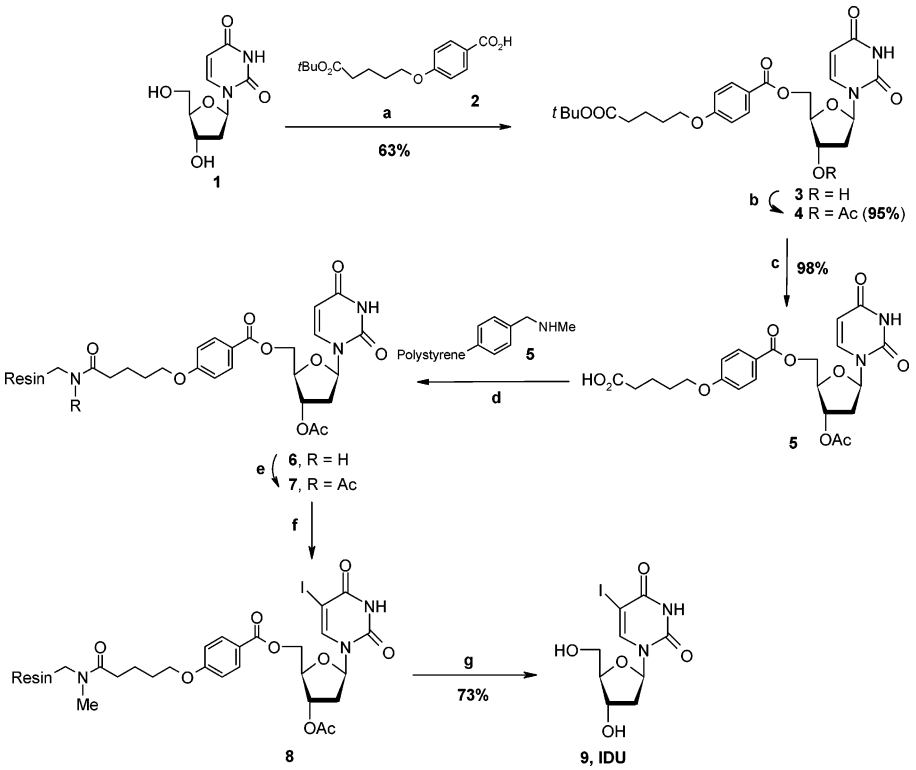
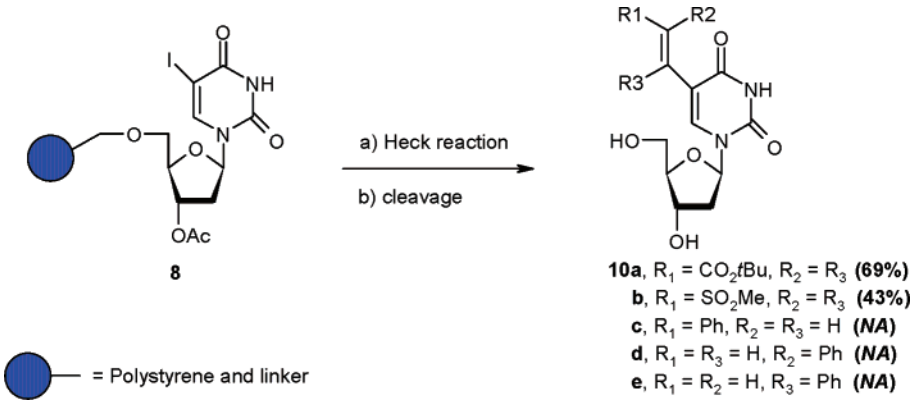
Scheme 1[a]



[a] Reagents and conditions: (a) **2** (1 equiv), $Me_2C{=}C(NMe_2)Cl$ (1.1 equiv), CH_2Cl_2, 3 h; then **1** (1 equiv), NEt_3 (1.5 equiv), pyridine (10 equiv), DMAP (0.2 equiv), CH_2Cl_2, 21 h; (b) Ac_2O, pyridine, 4 h; (c) CF_3CO_2H/CH_2Cl_2 (5/95), 15 h; (d) **4** (4 equiv), NEt_3 (4.4 equiv), *O*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyl uronium tetrafluoroborate (4.4 equiv), *N*-hydroxybenzotriazole (2 equiv), dioxane, 5 h, then resin **5** (1 equiv), NEt_3 (10 equiv), DMAP (1 equiv), dioxane, 60 h; (e) Ac_2O, pyridine, 18 h; (f) I_2/CAN; (g) MeONa (6 equiv), MeOH/dioxane (v/v 1:4), 24 h.

Scheme 2[a]



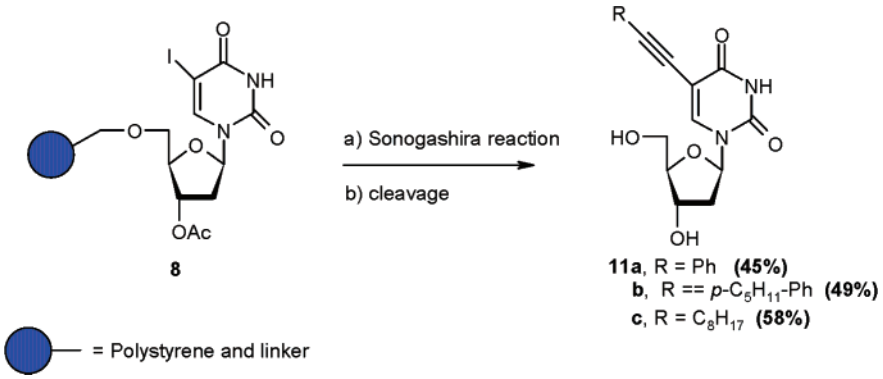
[a] Reagents and conditions: (a) resin **8** (0.08 mmol, 0.25 equiv), alkene (8 equiv), AcONa (3 equiv), $^nBu_4NCl$ (2 equiv), $Pd(OAc)_2$ (0.25 equiv), DMA (2 mL), 100 °C, 24 h; (b) MeONa (6 equiv), MeOH/dioxane (v/v 1:4), 24 h.

the solvent and palladium(0) residues make necessary a filtration over silica gel. The reported yields are thus those obtained after this filtration step.

We were first interested in the solid-phase application of the Heck reaction on nucleosides, pioneered in the liquid phase by Bergstrom et al.[12] and largely used for the preparation of biotin-labeled DNA probes,[13a] to link iron−EDTA to oligonucleotides,[13b] to construct oligomers attached to tris-(2,2′-bipyridine)ruthenium(II),[13c] to prepare nucleoside−peptide conjugates,[13d] or to synthesize oligodeoxyribonucleotide methyl thioether probes.[13e] In a typical example, **8** was treated with various alkenes and $Pd(OAc)_2$ in DMA, in the presence of AcONa and catalytic *n*-Bu_4NCl,[10] followed by cleavage of the nucleotide from the resin to produce the 5-alkylenyl-2′-deoxyuridines **10a**−**e** (Scheme 2). When using 2-phenylvinyl alkene in this reaction, the isomers **10c**, **10d**, and **10e** were not separable by classical chromatography.

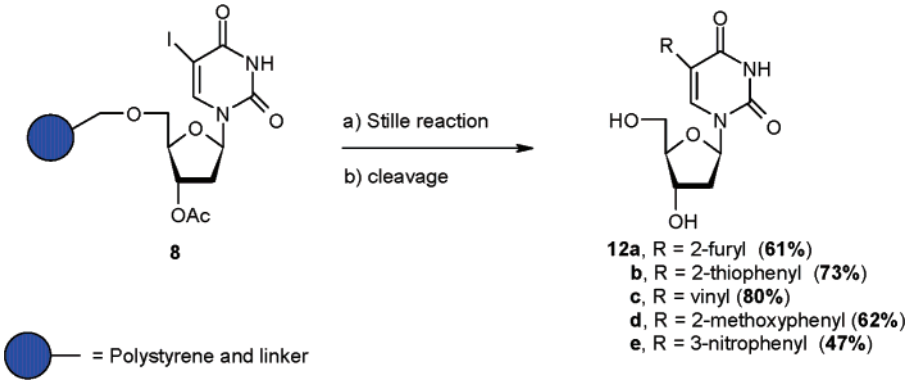
Attention was then turned to establish the scope and limitations of the Pd(0)-catalyzed synthesis of C-5-alkynyl derivatives under Sonogashira conditions.[14,15] The chemistry involved Pd-catalyzed coupling of arylacetylenes or terminal alkynes with 5-iodonucleosides. Thus, starting with the supported protected IDU (**8**), several C-5-alkynylnucleosides **11a**−**c** were obtained in moderate yields. It is important to note that this reaction must be run at room temperature to avoid the formation of unidentifiable coproducts produced when heating, while repeating the reaction gave 90−95% yields. The solid-supported ring closure of resin-bounded 5′-

Scheme 3[a]



[a] Reagents and conditions: (a) resin **8** (0.08 mmol, 0.25 equiv), alkyne (4 equiv), CuI (0.2 equiv), Et_3N (4 equiv), $Pd(PPh_3)_2Cl_2$ (0.2 equiv), DMF (2 mL), 20 h; (b) MeONa (6 equiv), MeOH/dioxane (v/v 1:4), 24 h.

Scheme 4[a]



[a] Reagents and conditions: (a) resin **8** (0.08 mmol, 0.25 equiv), R_3SnR' (9 equiv), CuI (0.4 equiv), Ph_3As (0.4 equiv), $Pd_2(dba)_3$ (0.2 equiv), dioxane (2 mL), 80 °C, 20 h; (b) MeONa (6 equiv), MeOH/dioxane (v/v 1:4), 24 h.

alkynyl nucleosides into furopyrimidone-type nucleosides was also investigated. Unfortunately, the standard treatment of **11a**−**c** with CuI in refluxing Et_3N followed by cleavage of the resin led only to a complex mixture of products. This is mainly due to the harsher conditions used for resin cleavage (excess MeONa).

The scope and limitation of the Stille reaction for the parallel solid-phase synthesis of mononucleosides (Scheme 4) were evaluated. Nucleoside modifications under Stille conditions have been reported by Farina et al.[16] with various unsaturated stannanes in the synthesis of 5-substituted uracil and uridine derivatives, and by Herdewijn et al.[17] using symmetric tetraorganotin compounds[18] R_4Sn, in which R = Me, vinyl, phenyl. Other applications of this procedure for the vinylation of the heterocyclic moiety have been described by Rahim et al. in the synthesis of anti-herpes agents (2′-deoxy-4′-thiopyrimidine nucleosides).[19] The reaction of supported protected 5-IDU (**8**) with a variety of aryl and vinylstannanes produced various nucleosides **12a**−**e** in good to moderate yields. As in the case of the Sonogashira reaction, simple coupling only afforded moderate conversions (65−80%), while double coupling allowed reactions to be driven more nearly to completion (85−95%).

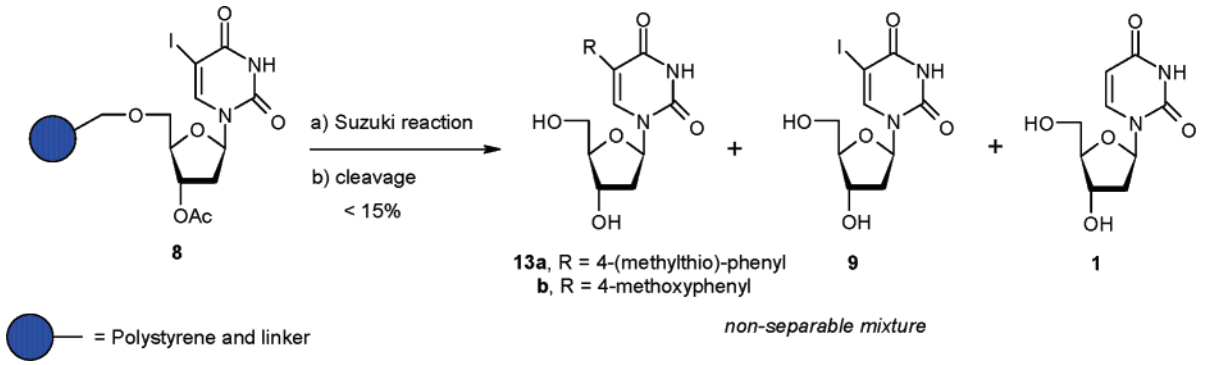
The Suzuki−Miyaura cross-coupling reaction of **8** (Scheme 5), unfortunately, led to a nonseparable mixture of the desired compound in very low yields (10−15%), with a large amount of starting IDU (**8**). All of our attempts to apply different reaction conditions (by increasing the temperature or adding an excess of the Pd(0) catalyst) led to a decrease of the yield due to a partial cleavage of the resin under basic conditions and/or formation of the deiodinated product **1**.

In summary, we have shown that the readily available 5-iodo-2′-deoxyuridine bound to polystyrene resin can be used as a versatile building block toward the preparation of different C-5-substituted nucleosides of types **10**, **11**, and **12** in good overall yield through palladium-catalyzed reaction with appropriate alkylating agents. Under different palladium-assisted routes to nucleosides, it appears that Sonogashira and Stille reactions are well-suited for a solid-phase synthesis, while Heck and Suzuki−Miyaura reactions led to either low yields of the desired compounds or a mixture of nonseparable isomers. This methodology can now be enlarged to other nucleoside analogues and coupled with parallel modification or substitution of the nucleoside core to give highly diverse structures.

Experimental Section

Melting points were determined on a Köfler hot-stage apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX250 spectrometer at 250 and 62.89 MHz, respectively. The chemical shifts (δ) are reported in ppm downfield from TMS as the internal standard. Coupling constants (J) are reported in hertz. Specific rotations were measured at 20 °C using a Perkin-Elmer polarimeter 141. HR-ESI-TOF-mass spectra were recorded on a Micromass LC TOF spectrometer. Evaporation

Scheme 5[a]



[a] Reagents and conditions: (a) resin **8** (0.08 mmol, 0.25 equiv), $RB(OH)_2$ (4 equiv), K_2CO_3 (9 equiv), $Pd(OAc)_2$ (0.1 equiv), dioxane (2 mL), H_2O (330 μL), 100 °C, 20 h; (b) MeONa (6 equiv), MeOH/dioxane (v/v 1:4), 24 h.

was conducted in vacuo with a Büchi rotary evaporator. Analytical TLC was carried out on precoated silica gel 60F-254 plates (E. Merck), and spots were detected by UV light (254 nm) and by heat treatment with a 10/85/5 mixture of sulfuric acid, ethanol, and water. Flash column chromatography was performed on Kieselgel 60 (230−400 mesh) silica gel (E. Merck).

General Procedure for Cleavage of the Resin. Resin (0.08 mmol) was suspended in a mixture of 2 mL of dioxane and 480 μL of a freshly prepared 1 M solution of MeONa/MeOH. The resulting suspension was stirred overnight and then filtered through a fritted glass funnel. The resin was washed with MeOH (5 mL) and dioxane (5 mL), and this process was repeated four times. The resulting clear solution was neutralized with DOWEX 50X2-200 and then filtered and concentrated under reduced pressure to give the crude nucleoside analogue.

5′-*O*-(4-(4-*tert*-Butoxycarbonyl-butoxy)benzoyl)-2′-deoxy-D-uridine (3). 4-(4-*tert*-Butoxycarbonyl-butoxy)-benzoic acid **2** (3.32 g, 10.95 mmol) was suspended in dry CH_3CN (50 mL). 1-Chloro-*N*,*N*,2-trimethyl-1-propenylamine (1.45 mL, 1.1 equiv) was added, and the reaction mixture was stirred at room temperature for 3 h. In another flask, 2′-deoxy-D-uridine **1** (2.5 g, 1.0 equiv) in dry CH_3CN (50 mL) was mixed with DMAP (270 mg, 0.2 equiv), pyridine (17.8 mL, 20 equiv), and Et_3N (1.19 mL, 1.5 equiv). The activated acid was then added dropwise to the above-mentioned solution which was stirred at room temperature for 18 h. Solvents were evaporated under reduced pressure, and the brown residue was subjected to flash column chromatography on silica gel (CH_2Cl_2/MeOH 40/1 then 20/1 then 10/ 1) to afford the desired ester (3.47 g, 63%) as a white solid. mp (EtOH) 130−132 °C. $[\alpha_D] = -3$ ($c = 1.0$, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.45 (s, 9H, Me_3C), 1.67−1.89 (m, 4H, CH_2-CH_2), 2.18 (dt, 1H, H-2′b, $J_{1'-2'b} = J_{2'b-3'} = 6.4$ Hz, $J_{2'a-2'b} = 13.9$ Hz), 2.30 (t, 2H, CH_2CO, $J_{CH2-CH2} = 6.7$ Hz), 2.18 (ddd, 1H, H-2′a, $J_{1'-2'b} = 5.9$ Hz, $J_{2'b-3'} = 4.9$ Hz), 4.04 (t, 2H, CH_2O, $J_{CH2-CH2} = 5.3$ Hz), 4.22−4.29 (m, 1H, H-4′), 4.43−4.51 (m, 1H, H-3′), 4.54 (dd, 1H, H-5′b, $J_{4-5'b} = 3.2$ Hz, $J_{5'a-5'b} = 12.5$ Hz), 4.64 (dd, 1H, H-5′a, $J_{4-5'a} = 3.7$ Hz), 5.60 (dd, 1H, H-5, $J_{5-6} = 8.0$ Hz, $J_{5-NH} = 1.5$ Hz), 6.26 (dd, 1H, H-1′), 6.91 (d, 2H, HAr, $J_{gem} = 8.8$ Hz), 7.54 (d, 1H, H-6), 7.94 (d, 2H, HAr), 9.03−9.13 (m, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 21.7 (CH_2), 28.2 (Me_3C), 28.6 (CH_2), 35.2 (CH_2CO), 40.8 (C-2′), 63.8 (C-5′), 67.9 (CH_2O), 71.2 (C-3′), 80.5 (CMe_3), 84.9 (C-4′), 85.7 (C-1′), 102.6 (C-5), 114.5, 121.4, and 131.7 (CAr), 139.7 (C-6), 150.6 (C-2), 163.4, 163.8, 166.3, and 173.0 (C-4, 2 × CO and CAr). HRMS: *m*/*z* $C_{25}H_{32}N_2O_9Na$ calcd 527.2005, found 527.2006.

3′-*O*-Acetyl-5′-*O*-(4-(4-*tert*-butoxycarbonyl-butoxy)benzoyl)-2′-deoxy-D-uridine (4). Alcohol **3** (3.47 g, 6.9 mmol) was dissolved in CH_2Cl_2 (25 mL) and pyridine (25 mL). Ac_2O (18 mL, 10 equiv) was added, and the reaction mixture was stirred at room temperature for 4 h. Solvents were evaporated under reduced pressure and then coevaporated with toluene (3 × 20 mL). The clear oily residue was dissolved in AcOEt (100 mL) and washed with water (2 × 50 mL) and brine (50 mL). The organic phases were concentrated under reduced to afford the acetylated compound **4** (3.59 g, 95%) as a white solid. mp (EtOH) 63−65 °C. $[\alpha_D] = -18$ ($c = 0.5$, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.45 (s, 9H, Me_3C), 1.72−1.92 (m, 4H, CH_2CH_2), 2.13 (s, 3H, CH_3CO), 2.13−2.25 (m, 1H, H-2′b), 2.30 (t, 2H, CH_2-CO, $J_{CH2-CH2} = 6.9$ Hz), 2.58 (ddd, 1H, H-2′a, $J_{1'-2'b} = 5.4$ Hz, $J_{2'b-3'} = 1.7$ Hz, $J_{2'a-2'b} = 14.2$ Hz), 4.04 (t, 2H, CH_2O, $J_{CH2-CH2} = 5.6$ Hz), 4.34−4. 43 (m, 1H, H-4′), 4.55 (dd, 1H, H-5′b, $J_{4-5'b} = 3.4$ Hz, $J_{5'a-5'b} = 12.5$ Hz), 5.64 (dd, 1H, H-5′a, $J_{4-5'a} = 3.2$ Hz), 5.32−5.40 (m, 1H, H-3′), 5.60 (dd, 1H, H-5, $J_{5-6} = 8.3$ Hz, $J_{5-NH} = 2.2$ Hz), 6.30 (dd, 1H, H-1′, $J_{1'-2'a} = 8.3$ Hz), 6.91 (d, 2H, HAr, $J_{gem} = 8.8$ Hz), 7.49 (d, 1H, H-6), 7.92 (d, 2H, HAr), 8.60−9.20 (m, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 20.8 (CH_3CO), 21.5 (CH_2), 28.0 (Me_3C), 28.3 (CH_2), 34.9 (CH_2CO), 37.8 (C-2′), 63.7 (C-5′), 67.7 (CH_2O), 74.2 (C-3′), 80.0 (CMe_3), 82.6 (C-4′), 85.2 (C-1′), 102.8 (C-5), 114.3, 121.2, and 131.4 (CAr), 138.9 (C-6), 150.4 (C-2), 163.2, 163.4, 165.6, 170.3, and 172.6 (C-4, 3 × CO and CAr). HRMS: *m*/*z* $C_{27}H_{34}N_2O_{10}Na$ calcd 569.2111, found 569.2110.

3′-*O*-Acetyl-5′-*O*-(4-(4-carboxybutoxy)-benzoyl)-2′-deoxy-D-uridine (5). Ester **4** (3.59 g, 6.55 mmol) was dissolved in CH_2Cl_2 (90 mL). TFA (10 mL) was added, and the resulting solution was stirred at room temperature for 18 h. After evaporation of the solvents under reduced pressure and coevaporation with toluene (3 × 20 mL), the resulting oily residue was triturated with pentane (50 mL). The white precipitate was filtered to afford acid **5** (3.15 g, 98%) as a white solid. mp (CH_2Cl_2) 161−163 °C. $[\alpha_D] = -3$ ($c = 1.0$, MeOH). ^{1}H NMR (DMSO-d_6): δ 1.58−1.83 (m, 4H, CH_2-

CH_2), 2.08 (s, 3H, CH_3CO), 2.28 (t, 2H, CH_2CO, $J_{CH2-CH2}$ = 6.9 Hz), 2.34−2.45 (m, 2H, H-2′a and H-2′b), 4.06 (t, 2H, CH_2O, $J_{CH2-CH2}$ = 5.7 Hz), 4.26−4.34 (m, 1H, H-4′), 4.39−4.53 (m, 2H, H-5′a and H-5′b), 5.27−5.37 (m, 1H, H-3′), 5.59 (dd, 1H, H-5, J_{5-6} = 8.2 Hz, J_{5-NH} = 1.6 Hz), 6.16 (t, 1H, H-1′, $J_{1'-2'a}$ = $J_{1'-2'b}$ = 6.8 Hz), 7.04 (d, 2H, HAr, J_{gem} = 8.8 Hz), 7.65 (d, 1H, H-6), 7.96 (d, 2H, HAr). ^{13}C NMR (DMSO-d_6): δ 20.8 (CH_3CO), 21.1 and 28.0 (CH_2), 28.3 (CH_2), 33.2 (CH_2CO), 35.8 (C-2′), 63.9 (C-5′), 67.6 (CH_2O), 73.8 (C-3′), 81.3 (C-4′), 84.7 (C-1′), 102.2 (C-5), 114.5, 121.3, and 131.4 (CAr), 140.4 (C-6), 150.4 (C-2), 162.8, 163.0, 165.2, 170.0, and 174.4 (C-4, 3 × CO and CAr). HRMS: *m*/*z* $C_{23}H_{26}N_2O_{10}Na$ calcd 513.1485, found 513.1494.

Resin-Bounded 3′-*O*-Acetyl-2′-deoxy-D-uridine (7). Acid **5** (3.15 g, 6.18 mmol) was dissolved in dry dioxane (30 mL), and Et_3N (1 mL, 1.2 equiv), TBTU (2.38 g, 1.2 equiv), and HOBT (418 mg, 0.5 equiv) were successively added, and the resulting mixture was stirred at room temperature for 3 h. In a second flask, the resin **6** (4.48 g, 1.0 equiv) was suspended in dioxane (15 mL) containing Et_3N (7.8 mL, 10 equiv). DMAP (684 mg, 1.0 equiv) was then added, followed by the activated acid contained in the first flask. The resulting suspension was moderately stirred with a conventional organic magnetic stirring apparatus at room temperature during 3 days and then filtered through a fritted glass funnel. The resin was successively washed with CH_2Cl_2 (3 × 50 mL), MeOH (1 × 50 mL), a MeOH/water mixture (v/v = 1:1, 3 × 50 mL), water (3 × 50 mL), MeOH (3 × 50 mL), and CH_2Cl_2 (3 × 50 mL) and then dried overnight at 50 °C under vacuum to afford 6.0 g of resin-bounded uridine. Residual amine functionalities were then end-capped by suspending the resin in CH_2Cl_2 (25 mL), then adding a mixture of pyridine (25 mL) and Ac_2O (25 mL). The suspension was gently stirred at room temperature for 3 h and then filtered off through a fritted glass funnel. The resin was washed with the same workup as mentioned above and then dried overnight at 50 °C under vacuum to afford 6.13 g of resin-bounded 3′-*O*-acetyl-2′-deoxy-D-uridine. Standard cleavage of 200 mg of resin afforded 24.6 mg of pure 2′-deoxy-D-uridine **1** with no need of further purification (51% over two steps, substitution rate 0.514 mmol/g).

Resin-Bounded 3′-*O*-Acetyl-2′-deoxy-5-iodo-D-uridine (8). First, 5.93 g of resin **7** (3.05 mmol) was suspended in a mixture of CH_3CN (30 mL) and dioxane (30 mL). CAN (9.14 g, 4 equiv) and I_2 (4.23 g) were added, and the resulting solution was stirred at 90 °C for 20 h and then filtered through a fritted glass funnel. The resin was worked-up as mentioned above and then dried overnight at 50 °C under vacuum to afford 6.46 g of resin-bounded 3′-*O*-acetyl-2′-deoxy-5-iodo-D-uridine. Standard cleavage of 200 mg of resin afforded 24.6 mg of pure 2′-deoxy-5-iodo-D-uridine **9** with no need of further purification (quantitative yield over two steps, substitution rate 0.472 mmol/g).

General Procedure for Solid-Phase Heck Reaction. The resin-bounded **8** (170 mg, 0.08 mmol) was suspended in dry DMA (2 mL), and then AcONa (20 mg, 3 equiv), *n*-Bu_4NCl (35 mg, 2 equiv), and $Pd(OAc)_2$ (4.5 mg, 0.25 equiv) were added prior to the addition of the alkene (8 equiv). The suspension was stirred at 100 °C during 24 h and then cooled to room temperature and filtered through a fritted glass funnel. The resin was worked-up as mentioned above and then dried overnight at 50 °C under vacuum to afford the resin-bounded 2′-deoxy-5-alkenyl-D-uridine. Standard cleavage of the resin followed by filtration over silica gel of the crude residue afforded the corresponding 2′-deoxy-5-alkenyl-D-uridines **10a**−**c**, respectively. **10c** is contaminated with **10d** and **10e**, as a nonseparable mixture.

5-((*E*)-2-*tert*-Butoxycarbonylvinyl)-2′-deoxy-D-uridine (10a). The application of the general procedure for solid-phase Heck reaction using *tert*-butyl acrylate led to the formation of **10a** which was purified using flash column chromatography on silica gel (CH_2Cl_2:MeOH 9:1 then 8:2) as an oil. [α_D] = +4 (*c* = 1.0, MeOH). ^{1}H NMR (CD_3OD): δ 1.50 (s, 9H, *t*Bu), 2.20−2.45 (m, 2H, H-2′a and H-2′b), 3.76 (dd, 1H, H-5′b, $J_{5'a-5'b}$ = 12.7 Hz, $J_{5'b-6}$ = 3.6 Hz), 3.81 (dd, 1H, H-5′a, $J_{5'a-6}$ = 3.0 Hz), 3.91−3.98 (m, 1H, H-4′), 4.38−4.47 (m, 1H, H-3′), 6.27 (t, 1H, H-1′, $J_{1'-2'a}$ = $J_{1'-2'b}$ = 6.9 Hz), 6.79 (d, 1H, H-2″, $J_{1''-2''}$ = 15.8 Hz), 7.28 (d, 1H, H-1″), 8.47 (s, 1H, H-6). ^{13}C NMR (DMSO-d_6): δ 28.4 (Me_3C), 41.9 (C-2′), 62.4 (C-5′), 71.7 (C-3′), 81.5 (CMe_3), 87.0 (C-1′), 89.2 (C-4′), 110.5 (C-5), 120.8 (C-2″), 137.5 (C-6), 144.4 (C-1″), 151.1 (C-2), 163.7 (C-4), 168.7 (COO*t*Bu). HRMS: *m*/*z* $C_{16}H_{22}N_2O_7Na$ calcd 377.1325, found 377.1324.

2′-Deoxy-5-((*E*)-2-methylsulfonylvinyl)-D-uridine (10b). The application of the general procedure for solid-phase Heck reaction using phenylvinyl sulfone led to the formation of **10b** which was purified using flash column chromatography on silica gel (eluent: CH_2Cl_2/MeOH 9:1 then 8:2) as an oil. [α_D] = +6 (*c* = 1.0, MeOH). ^{1}H NMR (CD_3OD): δ 2.20−2.43 (m, 2H, H-2′a and H-2′b), 2.99 (s, 3H, $MeSO_2$), 3.75 (dd, 1H, H-5′b, $J_{5'a-5'b}$ = 12.1 Hz, $J_{5'b-6}$ = 3.6 Hz), 3.81 (dd, 1H, H-5′a, $J_{5'a-6}$ = 3.0 Hz), 3.92−3.99 (m, 1H, H-4′), 4.38−4.46 (m, 1H, H-3′), 6.24 (t, 1H, H-1′, $J_{1'-2'a}$ = $J_{1'-2'b}$ = 6.9 Hz), 7.27 (d, 1H, H-2″, $J_{1''-2''}$ = 15.1 Hz), 7.59 (d, 1H, H-1″), 8.55 (s, 1H, H-6). ^{13}C NMR (DMSO-d_6): δ 42.0 (C-2′), 43.3 ($MeSO_2$), 62.3 (C-5′), 71.6 (C-3′), 87.3 (C-1′), 89.2 (C-4′), 108.5 (C-5), 127.2 (C-2″), 137.4 (C-6), 146.7 (C-1″), 151.0 (C-2), 163.4 (C-4). HRMS: *m*/*z* $C_{12}H_{16}N_2O_7$-SNa calcd 377.1325, found 377.1324.

2′-Deoxy-5-((*E*)-2-phenylvinyl-uridine (10c). The application of the general procedure for solid-phase Heck reaction using styrene led to the formation of **10c** which was purified using flash column chromatography on silica gel (CH_2Cl_2/MeOH 9:1 then 8:2) but was still contaminated with **10d** and **10e**. ^{1}H NMR (CD_3OD): δ 2.26−2.37 (m, 2H, H-2′a and H-2′b), 3.79 (dd, 1H, H-5′b, $J_{5'a-5'b}$ = 11.9 Hz, $J_{5'b-6}$ = 3.2 Hz), 3.88 (dd, 1H, H-5′a, $J_{5'a-6}$ = 2.2 Hz), 3.93−3.99 (m, 1H, H-4′), 4.42−4.50 (m, 1H, H-3′), 6.22 (t, 1H, H-1′, $J_{1'-2'a}$ = $J_{1'-2'b}$ = 6.4 Hz), 6.90 (d, 1H, H-1″, $J_{1''-3''}$ = 16.3 Hz), 7.16−7.50 (m, 6H, H-2″ and HAr), 8.33 (s, 1H, H-6). Other spectroscopic data are in agreement with those previously reported.[20]

General Procedure for Solid-Phase Sonogashira Cross-Coupling. The resin-bounded **8** (4.5 mg, 0.08 mmol) was suspended in dry DMF (2 mL), and then CuI (3 mg, 0.2 equiv), Et_3N (45 μL, 4 equiv), and $Pd(PPh_3)_2Cl_2$ (5.6 mg,

0.2 equiv) were successively added prior to the addition of the selected alkynes (4 equiv). The suspension was stirred at room temperature for 20 h and filtered through a fritted glass funnel. The resin was worked up as mentioned above and then dried overnight at 50 °C under vacuum. This procedure was applied a second time to the resulting resin to afford the resin-bounded 2′-deoxy-5-alkynyl-D-uridine. Standard cleavage of the resin followed by flash column chromatography of the crude residue afforded the corresponding 2′-deoxy-5-alkynyl-D-uridines **11a**−**c**, respectively.

2′-Deoxy-5-phenylethynyl-uridine (11a). The application of the general procedure for solid-phase Sonogashira cross-coupling using phenylacetylene led to the formation of **11a** which was purified using flash column chromatography on silica gel (CH_2Cl_2/MeOH 9:1 then 8:2). ^{1}H NMR (CD_3OD): δ 2.20−2.40 (m, 2H, H-2′a and H-2′b), 3.76 (dd, 1H, H-5′b, $J_{5'a-5'b}$ = 11.9 Hz, $J_{5'b-6}$ = 3.5 Hz), 3.86 (dd, 1H, H-5′a, $J_{5'a-6}$ = 3.1 Hz), 3.92−3.98 (m, 1H, H-4′), 4.38−4.47 (m, 1H, H-3′), 6.27 (t, 1H, H-1′, $J_{1'-2'a} = J_{1'-2'b}$ = 6.4 Hz), 7.30−7.39 (m, 3H, HAr), 7.45−7.54 (m, 2H, HAr), 8.43 (s, 1H, H-6). Other spectroscopic data are in agreement with those previously reported.[15a]

2′-Deoxy-5-(4-*n*-pentylphenyl)ethynyl-uridine (11b). The application of the general procedure for solid-phase Sonogashira cross-coupling using (4-*n*-pentylphenyl)acetylene led to the formation of **11b** which was purified using flash column chromatography on silica gel (eluent: CH_2Cl_2/MeOH 9:1 then 8:2). ^{1}H NMR (CD_3OD): δ 0.82−0.94 (m, 3H, CH_3), 1.24−1.48 (m, 6H, CH_2), 2.15−2.48 (m, 4H, H-2′a, H-2′b and CH_2), 3.74 (dd, 1H, H-5′b, $J_{5'a-5'b}$ = 11.5 Hz, $J_{5'b-6}$ = 3.8 Hz), 3.89 (dd, 1H, H-5′a, $J_{5'a-6}$ = 3.1 Hz), 3.91−3.99 (m, 1H, H-4′), 4.37−4.46 (m, 1H, H-3′), 6.29 (t, 1H, H-1′, $J_{1'-2'a} = J_{1'-2'b}$ = 6.4 Hz), 8.43 (s, 1H, H-6), 7.25 (d, 2H, HAr, J_{AB} = 7.9 Hz), 7.44 (d, 2H, HAr). Other spectroscopic data are in agreement with those previously reported.[15a]

2′-Deoxy-5-(*n*-dec-1-ynyl)-uridine (11c). The application of the general procedure for solid-phase Sonogashira cross-coupling using decyne led to the formation of **11c** which was purified using flash column chromatography on silica gel (CH_2Cl_2/MeOH 9:1 then 8:2). ^{1}H NMR (CD_3OD): δ 0.85−0.97 (m, 3H, CH_3), 1.26−1.64 (m, 12H, CH_2), 2.15−2.43 (m, 4H, H-2′a, H-2′b and CH_2), 3.73 (dd, 1H, H-5′b, $J_{5'a-5'b}$ = 11.4 Hz, $J_{5'b-6}$ = 3.5 Hz), 3.81 (dd, 1H, H-5′a, $J_{5'a-6}$ = 3.0 Hz), 3.89−3.97 (m, 1H, H-4′), 4.36−4.44 (m, 1H, H-3′), 6.24 (t, 1H, H-1′, $J_{1'-2'a} = J_{1'-2'b}$ = 6.6 Hz), 8.19 (s, 1H, H-6). Other spectroscopic data are in agreement with those previously reported.[15b]

General Procedure for Solid-Phase Stille Cross-Coupling. The resin-bounded **8** (170 mg, 0.08 mmol) was suspended in dry dioxane (2 mL), and then CuI (6 mg, 0.4 equiv), Ph_3As (20 mg, 0.4 equiv), and $Pd_2(dba)_3$ (14 mg, 0.2 equiv) were successively added prior to the addition of the stannylated reagent (9 equiv). The suspension was stirred at 80 °C during 20 h and then cooled to room temperature and filtered through a fritted glass funnel. The resin was worked-up as mentioned above and then dried overnight at 50 °C under vacuum to afford the resin-bounded 5-substituted 2′-deoxy-D-uridine. Standard cleavage of the resin followed by flash column chromatography of the crude residue afforded the corresponding 5-substituted 2′-deoxy-D-uridines **12a**−**e**, respectively.

2′-Deoxy-5-furyl-uridine (12a). The application of the general procedure for solid-phase Stille cross-coupling using 2-(tri-*n*-butylstannyl)-furan led to the formation of **12a**, which was purified using flash column chromatography on silica gel (CH_2Cl_2/MeOH 9:1 then 8:2). ^{1}H NMR (DMSO-d_6): δ 2.14−2.21 (m, 2H, H-2′a and H-2′b), 3.54−3.69 (m, 2H, H-5′a and H-5′b), 3.81−3.93 (m, 1H, H-4′), 4.27−4.44 (m, 1H, H-3′), 5.05−5.12 (m, 1H, OH), 5.24−5.31 (m, 1H, OH), 6.22 (t, 1H, H-1′, $J_{1'-2'a} = J_{1'-2'b}$ = 6.6 Hz), 6.52 (dd, 1H, H-3″, $J_{2''-3''}$ = 3.3 Hz, $J_{3''-4''}$ = 1.8 Hz), 6.85 (d, 1H, H-2″ Hz), 7.61 (dd, 1H, H-4″), 8.33 (s, 1H, H-6), 11.5−11.7 (m, 1H, NH). Other spectroscopic data are in agreement with those previously reported.[21]

2′-Deoxy-5-thienyl-uridine (12b). The application of the general procedure for solid-phase Stille cross-coupling using 2-(tri-*n*-butylstannyl)-thiophene led to the formation of **12b**, which was purified using flash column chromatography on silica gel (CH_2Cl_2/MeOH 9:1 then 8:2). ^{1}H NMR (CD_3OD): δ 2.30−2.38 (m, 2H, H-2′a and H-2′b), 3.79 (dd, 1H, H-5′b, $J_{5'a-5'b}$ = 11.9 Hz, $J_{5'b-6}$ = 3.0 Hz), 3.88 (dd, 1H, H-5′a, $J_{5'a-6}$ = 2.8 Hz), 3.95−4.01 (m, 1H, H-4′), 4.42−4.51 (m, 1H, H-3′), 6.35 (t, 1H, H-1′, $J_{1'-2'a} = J_{1'-2'b}$ = 6.5 Hz), 7.02 (dd, 1H, H-3″, $J_{2''-3''}$ = 5.2 Hz, $J_{3''-4''}$ = 3.6 Hz), 7.34 (dd, 1H, H-2″, $J_{1''-2''}$ = 1.2 Hz), 7.43 (dd, 1H, H-4″), 8.62 (s, 1H, H-6). Other spectroscopic data are in agreement with those previously reported.[21]

2′-Deoxy-5-vinyl-uridine (12c). The application of the general procedure for solid-phase Stille cross-coupling using tri-*n*-butyl-vinyltin led to the formation of **12c** which was purified using flash column chromatography on silica gel (CH_2Cl_2/MeOH 9:1 then 8:2). ^{1}H NMR (CD_3OD): δ 2.18−2.38 (m, 2H, H-2′a and H-2′b), 3.75 (dd, 1H, H-5′b, $J_{5'a-5'b}$ = 12.1 Hz, $J_{5'b-6}$ = 3.4 Hz), 3.84 (dd, 1H, H-5′a, $J_{5'a-6}$ = 3.0 Hz), 3.90−3.97 (m, 1H, H-4′), 4.39−4.46 (m, 1H, H-3′), 5.16 (dd, 1H, H-2″b, $J_{1''-2''b}$ = 11.5 Hz, $J_{2''a-2''b}$ = 1.8 Hz), 5.93 (dd, 1H, H-2″a, $J_{1''-2''a}$ = 17.7 Hz), 6.29 (t, 1H, H-1′, $J_{1'-2'a} = J_{1'-2'b}$ = 6.8 Hz), 6.45 (dd, 1H, H-1″), 8.22 (s, 1H, H-6). Other spectroscopic data are in agreement with those previously reported.[22]

2′-Deoxy-5-(2-methoxyphenyl)uridine (12d). The application of the general procedure for solid-phase Stille cross-coupling using tri-*n*-butyl-(2-methoxyphenyl)tin led to the formation of **12d** which was purified using flash column chromatography on silica gel (CH_2Cl_2/MeOH 9:1 then 8:2). ^{1}H NMR (CD_3OD): δ 2.24−2.37 (m, 2H, H-2′a and H-2′b), 3.70 (s, 3H, CH_3O), 3.74 (dd, 1H, H-5′b, $J_{5'a-5'b}$ = 12.0 Hz, $J_{5'b-6}$ = 3.4 Hz), 3.84 (dd, 1H, H-5′a, $J_{5'a-6}$ = 2.9 Hz), 3.92−3.98 (m, 1H, H-4′), 4.39−4.48 (m, 1H, H-3′), 6.29 (t, 1H, H-1′, $J_{1'-2'a} = J_{1'-2'b}$ = 6.6 Hz), 6.45 (dd, 1H, H-1″), 6.92 (d, 2H, HAr, J_{AB} = 8.7 Hz), 7.49 (d, 2H, HAr), 8.09 (s, 1H, H-6). Other spectroscopic data are in agreement with those previously reported.[23]

2′-Deoxy-5-(3-nitrophenyl)-uridine (12e). The application of the general procedure for solid-phase Stille cross-coupling using tri-*n*-butyl-(3-nitrophenyl)tin led to the formation of **12e** which was purified using flash column chromatography on silica gel (CH_2Cl_2/MeOH 9:1 then 8:2).

^{1}H NMR (CD_3OD): δ 2.28−2.36 (m, 2H, H-2′a and H-2′b), 3.75 (dd, 1H, H-5′b, $J_{5'a-5'b}$ = 11.7 Hz, $J_{5'b-6}$ = 3.4 Hz), 3.85 (dd, 1H, H-5′a, $J_{5'a-6}$ = 2.8 Hz), 3.90−3.98 (m, 1H, H-4′), 4.38−4.48 (m, 1H, H-3′), 6.20 (t, 1H, H-1′, $J_{1'-2'a}$ = $J_{1'-2'b}$ = 6.3 Hz), 6.45 (dd, 1H, H-1″), 7.65−8.72 (m, 5H, HAr and H-6). Other spectroscopic data are in agreement with those previously reported.[24]

General Procedure for Solid-Phase Suzuki Cross-Coupling. The resin-bounded **8** (170 mg, 0.08 mmol) was suspended in clean dioxane (2 mL) containing 330 μL of H_2O. K_2CO_3 (91 mg, 9 equiv) and $Pd(OAc)_2$ (2 mg, 0.1 equiv) were successively added prior to the addition of 4 equiv of the boronic acid derivatives. The suspension was stirred at 100 °C during 20 h and then cooled to room temperature and filtered through a fritted glass funnel. The resin was worked-up as mentioned above and then dried overnight at 50 °C under vacuum to obtain the corresponding resin-bounded 5-substituted 2′-deoxy-D-uridine. Standard cleavage of the resin followed by flash column chromatography of the crude resin afforded corresponding 5-substituted 2′-deoxy-D-uridines **13a**,**b** in a not separable mixture with starting IDU (**9**) and 2′-deoxyuridine (**1**).

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