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A Diastereoselective Synthesis of 5′-Substituted-Uridine Derivatives

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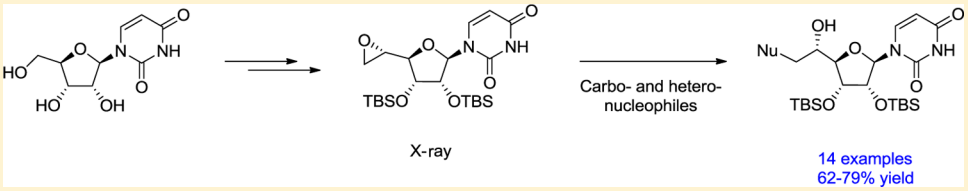
Supporting Information



ABSTRACT: A straightforward strategy for the synthesis of 5′-substituted-uridine derivatives is described. It relies on the introduction of various substituents at C-5′ at the last step of the synthesis by regioselective nucleophilic opening of a unique epoxide that provides access to a small library of compounds. This epoxide results from the diastereoselective epoxidation, performed at a multigram scale, of a uridine-derived alkene. The configuration of the newly created 5′ asymmetric center has been unambiguously assigned by X-ray diffraction analysis.

Nucleotides and nucleosides are key compounds involved in major biological processes, such as nucleic acids and proteins synthesis, cell signaling, enzyme regulation, and metabolism. Indeed, many nucleoside analogues are already clinically used as antiviral[1] and antitumoral agents.[2] However, their efficiency is sometimes reduced by the appearance of resistance mechanisms.[3] The availability of new nucleoside derivatives,[4] therefore, is still of prime importance. Among the numerous nucleoside analogues previously described, only a few display a stereogenic center at their C-5′ position. This particular structure is typical of complex nucleoside antibiotics, such as tunicamycins,[5] liposidomycins,[6] caprazamycins,[7] and muraymycins[8] (Figure 1). These natural compounds isolated from *Streptomyces* species are natural inhibitors[9] of the bacterial transferase MraY,[10,11] and their stereochemistry at C-5′ has been proven to be crucial for their biological activity.[9] Other examples of 5′-substituted nucleoside analogues are the synthetic nucleoside β-(5′*S*)-hydroxyphosphonate derivatives that have been developed as 5′-nucleotidase inhibitors containing a nonhydrolyzable P−C bond.[12] It is noteworthy that a 5′*R* configuration was shown to be detrimental to nucleotidase inhibition.[13]

A number of synthetic methods toward 5′-substituted nucleosides have already been described. In several of these approaches, the 5′ stereogenic center is intrinsically present within the starting material belonging to the chiral pool. Indeed, many syntheses of nucleosides analogues were achieved from D-allofuranose,[14] the nucleobase being later introduced under Vorbrüggen conditions.[15] However, despite its generality, this strategy usually requires long multistep synthesis. More frequently, this 5′ stereogenic center is newly created by a diastereoselective reaction on a trigonal carbon atom located at the C-5 or C-5′ position of a sugar or a nucleoside derivative. Thus, the diastereoselective reduction of the corresponding ketone has been described from a ribose[16] or a nucleoside[17] derivative. In a complementary manner, various nucleophiles, such as enolates,[18] allylborane,[19] dialkyl phosphites,[20] TMSCN,[21] or Grignard reagents,[22] have also been introduced on an aldehyde at the C-5′ position. However, with few exceptions,[17a,22b,c] the reactions usually proceed with modest diastereoselectivities (about 2/1). Additionally, an asymmetric center has been generated at C-5′ from a nucleoside-derived aldehyde by a sulfur ylide approach,[23] leading to a disubstituted epoxide as a single diastereoisomer, the configuration of which having recently been revised.[24] The 5′ stereogenic center has also been generated from an alkene at C-5′ by Sharpless asymmetric epoxidation,[25] aminohydroxylation,[26] and asymmetric dihydroxylation.[27] In the latter two cases, the use of a complex chiral reagent led to the corresponding epoxide with good to high diastereoselectivities (dr 86/14 for $(DHQD)_2AQN$[26] and dr 84/16 to 98/2 for AD-mix α[27]). When these reactions were carried out without a chiral ligand[26] or with AD-mix β,[27b] the diastereoselectivity drops to 2/1 or 1/1, showing that, in the latter case, the stereochemistry of the substrate has a stronger impact on the course of the oxidation than the one of the chiral reagent. In summary, even if several methods have been developed to control the 5′ carbon atom stereochemistry, the development of a strategy providing access

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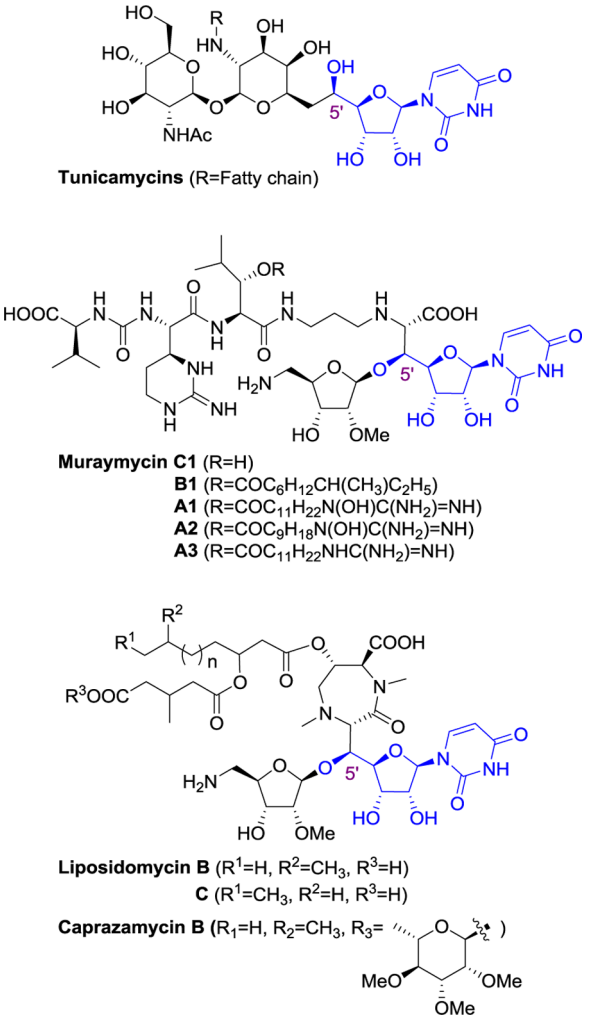


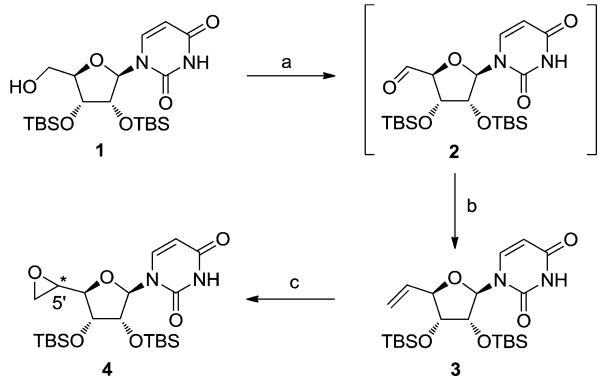
Figure 1. Examples of natural 5′-substituted-uridine derivatives.

to a large variety of 5′-substituted nucleoside derivatives is still particularly challenging. In the context of our ongoing program dedicated to new MraY inhibitors,[28] we have focused our study on 5′-substituted-uridine derivatives.

We report herein a straightforward, diastereoselective, and multigram scale synthesis of new 5′-substituted-uridine derivatives. Our strategy toward the targeted compounds is depicted in Figure 2. A wide variety of alcohol **A** would result from the regioselective nucleophilic ring opening of a unique epoxide **B** that would be obtained by oxidation of the terminal alkene **C** derived from commercially available uridine.

We first focused on the synthesis of alkene **3** (Scheme 1) from the aldehyde **2** that was synthesized according to known routes.[29] The latter was obtained on a 13 g scale after a three-step sequence involving the persilylation of uridine by an excess of *tert*-butyldimethylsilyl chloride in the presence of imidazole[28] and subsequent selective deprotection of the 5′ position with

Scheme 1. Synthesis of Epoxide 4[a]



[a]Reagents and conditions: (a) IBX, acetonitrile, 45 min ; (b) $CH_3PPh_3^+Br^-$, *t*-BuOK, 0 °C, 10 min, then rt, 1 h, then **2**, 0 °C, 10 min, then rt, 16 h, 61% over two steps; (c) see Table 1.

*p*TSA, furnishing the corresponding primary alcohol **1**,[18b] followed by oxidation of the 5′ position with 2-iodoxybenzoic acid (IBX)[30] to give **2** after simple filtration. Then, Wittig olefination in the presence of methyltriphenyl phosphonium bromide in excess and freshly sublimated potassium *tert*-butoxide as a base readily afforded the alkene **3** in 61% overall yield from **1**.

With this alkene **3** in hand, we next turned to the epoxidation reaction (Scheme 1). It was first attempted with commercially available and inexpensive *meta*-chloroperbenzoic acid (*m*-CPBA) in excess (3 equiv), in dichloromethane, in the presence of sodium bicarbonate as a base to neutralize the *meta*-chlorobenzoic acid formed in the reaction (Table 1, entry 1). After 3 days at 30 °C, the reaction remained uncompleted, leading to a 75/25 mixture of diastereoisomers at C5′. Isolation of the major diastereoisomer **4a** by flash chromatography was achieved in only 23% yield, due to its delicate separation from the starting alkene **3**. In the absence of a base, the conversion was slightly improved (entry 2). Attempts to carry out the reaction in refluxing chloroform did not improve the yield, probably due to *m*-CPBA decomposition (entry 3). Increasing the amount of *m*-CPBA to 4 equiv (entry 4) allowed total conversion of alkene **3**, but it required 3 days at 30 °C so that **4a** was isolated in a modest 36% yield due to the formation of numerous byproducts. However, we were delighted to observe that the use of 5 equiv of *m*-CPBA (entry 5) speeded up the reaction, leading to its completion in only 16 h and provided pure **4a** in a good 70% yield. Surprisingly, **4b** proved to decompose on silica gel so that only an analytical sample could be isolated to confirm its structure. Such an instability of **4b** could result from an intramolecular nucleophilic opening of the epoxide by uracil, leading to the corresponding anhydro derivative[14a] possibly followed by silyl protective group migration. It is noteworthy to mention that decreasing the temperature to 0 °C (entry 6) did not improve the

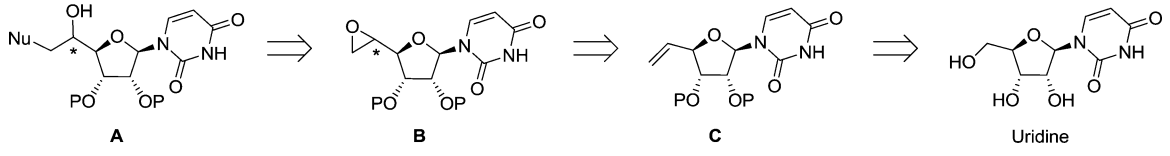


Figure 2. Retrosynthesis toward the targeted compounds.

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Table 1. Conditions for the Epoxidation of the Alkene 3

entry	t (h)	T (°C)	mCPBA (equiv)	solvent	additive	**4**/**3** ratio[a]	**4a**/**4b** ratio[a]	**4a** yield (%)
1	72	30	3	CH_2Cl_2	$NaHCO_3$	86/14	75/25	23
2	72	30	3	CH_2Cl_2		91/9	75/25	32
3	24	62	3	$CHCl_3$		100/0	75/25	28
4	72	30	4	CH_2Cl_2		>98/2	75/25	36
5	16	30	5	CH_2Cl_2		100/0	75/25	70
6	128	0	5	CH_2Cl_2		63/37	75/25	n.d.[b]

[a]Determined by ^{1}H NMR of the crude mixture. [b]Not determined.

diastereoisomeric ratio while the reaction remained uncompleted after 7 days.

With the pure major epoxide **4a** in hand, we turned to the determination of its absolute configuration at C-5′. Attempts of crystallization of the latter in ethanol gave successful results, and X-ray diffraction analysis of the resulting monocrystal (see the Supporting Information) allowed us to unambiguously attribute the *S* configuration to the C-5′ carbon atom of the major epoxide **4a**. It should be noted that the C-5′ configuration of **4a** matches that of liposidomycins, capraza-mycins, and muraymycins. The stereochemistry at the C-5′ carbon atom of the major epoxide **4a** is in agreement with an approach of the *m*-CPBA predominantly on the *Si* face of the double bond. Considering the conformation of the alkene **3** in which the 1,3-allylic strains are minimized (Figure 3), the *O*-3′-silyl group would hinder the alkene *Re* face, disfavoring an electrophilic addition onto this face and promoting *m*-CPBA attack on the *Si* face.

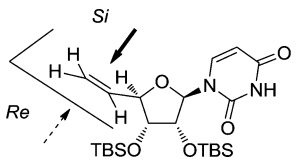

Figure 3. Conformation of the alkene **3** minimizing the 1,3-allylic strains.

To take advantage of the synthetic potential of epoxide **4a** as a chiral building block for the synthesis of 5′-substituted-uridine derivatives, we next studied its ring opening with various halogen-, carbon-, nitrogen-, oxygen-, or sulfur-containing nucleophiles (Scheme 2), which are key functional groups to introduce chemical diversity.

We first focused on the reaction of aliphatic or aromatic primary amines with epoxide 5′*S*-**4a**, which was carried out by a simple and mild heating at 40 °C in methanol,[31] giving the corresponding β-amino alcohols **5a**−**c** in 68−71% yield. Opening of the epoxide 5′*S*-**4a** by a secondary amine such as morpholine led to **5d** in 76% yield. Amino acid derivatives, for instance alanine or serine methyl esters, could also be introduced according to the same procedure, providing the corresponding *N*-alkyl amino acids **6a** and **6b** in 73% and 69% yield, respectively. However, in the case of serine, a slight epimerization was observed at the α carbon atom (85:15 dr). Opening of the epoxide 5′*S*-**4a** with azide ions in the presence of ammonium chloride[32] afforded the azido alcohol **7** in 72% yield. Benzyl alcoholate generated by the action of sodium hydride in benzylic alcohol required heating at 60 °C in DMF to achieve the epoxide 5′*S*-**4a** opening and gave **8a** in 66% yield. Softer nucleophiles such as potassium phenolate or 4-bromophenolate could also be introduced by heating the epoxide 5′*S*-**4a** and the corresponding phenol in DMF in the presence of potassium carbonate[33] to provide **8b** in 62% yield or **8c** in 66% yield. Sodium thiophenolate generated by treatment of thiophenol with sodium methoxide[34] efficiently achieved the epoxide 5′*S*-**4b** opening at 100 °C in DMF to furnish the thioether **9** in 73% yield. We next turned to the introduction of carbon nucleophiles. Toward this goal, the epoxide 5′*S*-**4a** was opened by potassium cyanide in the presence of ammonium chloride[35] to afford the β-cyano alcohol **10** in 68% yield. Then, the opening of epoxide 5′*S*-**4a** by acetylide ions was also envisaged. First attempts with Grignard reagents such as ((trimethylsilyl)ethynyl)magnesium bromide or ((triethylsilyl)ethynyl)magnesium bromide resulted in epoxide ring opening by bromide ions, leading to **11** in 67% or 74% yield, respectively. It should be noted that the compound **11** was also prepared in 79% yield by direct nucleophilic opening of epoxide 5′*S*-**4a** by lithium bromide in THF in the presence of boron trifluoride etherate[36] as a Lewis acid. Finally, the alkyne group was successfully introduced by using lithium trimethylsilylacetylide in the presence of BF_3·Et_2O, furnishing the targeted homopropargylic alcohol **12** in 77% yield. This reaction benefits from a large scope, and in all cases, a complete regioselectivity was observed in favor of the opening on the less sterically hindered pole of the epoxide. Moreover, a temporary uracile protection was unnecessary since no intramolecular nucleophilic opening by the uracile moiety was observed.[14a] The secondary alcohols **5**−**12** constitute advanced valuable intermediates for the synthesis of new 5′-substituted-uridine nucleoside derivatives.

We have developed a new route toward 5′-substituted-uridine derivatives, a challenging structure encountered in biologically active compounds such as complex nucleoside antibiotics for which only a few synthetic routes are described. It involves the multigram scale, diastereoselective, and direct epoxidation of a uridine-alkene derivative that is obtained from commercially available uridine in only four steps. The major diastereoisomer epoxide **4a** was isolated in a 70% yield, and the *S* configuration at its C-5′ carbon atom has been unambiguously assigned by X-ray diffraction analysis. The chemical diversity was then introduced at the ultimate step of the synthesis, by a totally regioselective ring opening of this key intermediate with various nucleophiles, affording the corresponding secondary alcohols in good yield.

■ EXPERIMENTAL SECTION

General Experimental Methods. When needed, reactions were carried out under an argon atmosphere. They were monitored by thin-layer chromatography with precoated silica on aluminum foil. Flash chromatography was performed with silica gel 60 (40−63 μm); the solvent systems were given v/v. Spectroscopic ^{1}H and ^{13}C NMR, MS, and/or analytical data were obtained using chromatographically homogeneous samples. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded in $CDCl_3$ unless indicated. Chemical

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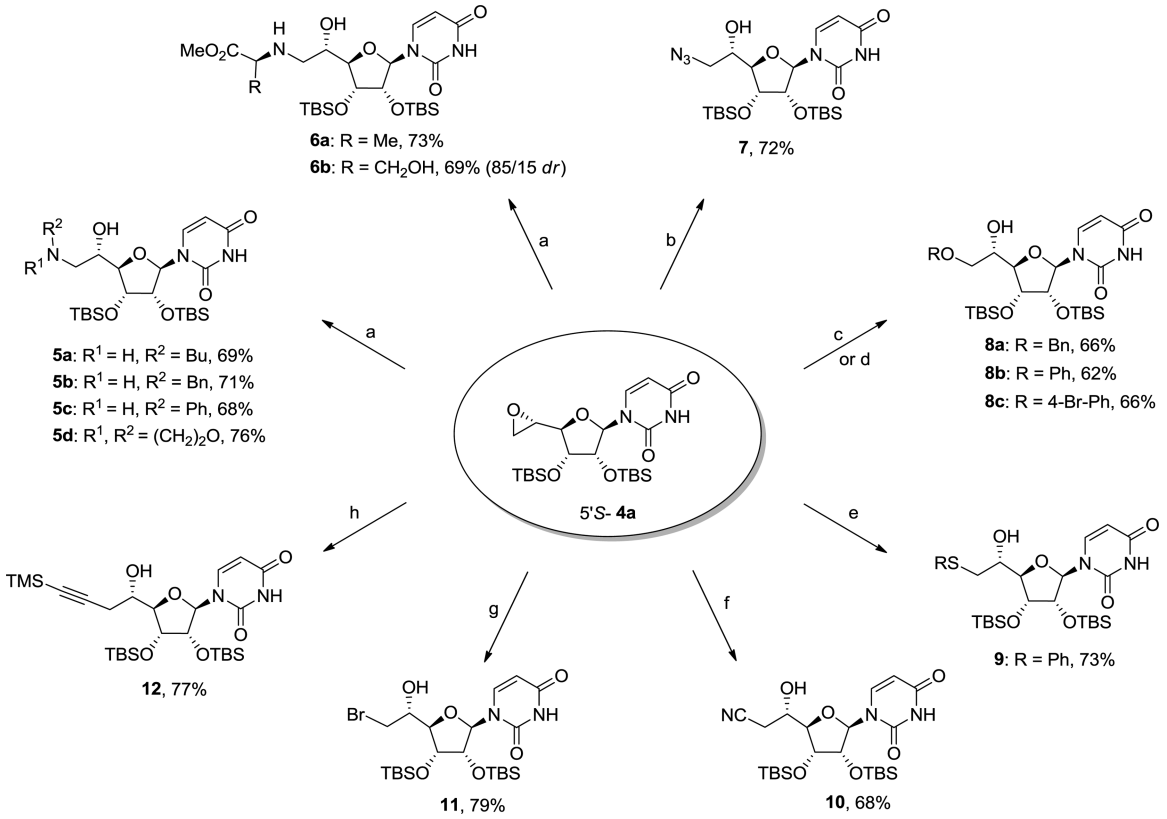
Scheme 2. Ring-Opening Reactions of the Epoxide 5′*S*-4a[a]



[a]Reagents and conditions: (a) Amine, MeOH, 40 °C, 16 h; (b) NaN_3, DMF, 70 °C, 16 h; (c) NaH, BnOH, 60 °C, 16 h; (d) PhOH or 4-Br-PhOH, K_2CO_3, DMF, 50 °C, 16 h; (e) PhSH, MeONa, DMF, 100 °C, 16 h; (f) KCN, NH_4CI, DMF, 100 °C, 16 h; (g) LiBr, BF_3.OEt_2, THF, −50 °C, 5 min then rt, 1 h; (h) Trimethylsilylacetylene, *n*-BuLi, $BF_3{\cdot}OEt_2$, −78 to −10 °C, 16 h.

shifts (δ) are reported in ppm and coupling constants are given in Hz. For each compound, detailed peak assignments have been made according to COSY, HSQC, and HMBC experiments. The numbering of molecules is indicated in the Supporting Information. Optical rotations were measured with a sodium (589 nm) lamp at 20 °C. Melting points were measured on a hot bench. IR spectra were recorded on an FT-IR spectrophotometer, and the wavelengths are reported in cm^{-1}. Low-resolution mass spectra (LRMS) were recorded with an ion trap mass analyzer under electrospray ionization (ESI) in positive ionization mode detection or atmospheric pressure chemical ionization (APCI). High-resolution mass spectra (HRMS) were recorded with a TOF mass analyzer under electrospray ionization (ESI) in positive ionization mode.

5′-Methylideneuridine 3. To a solution of alcohol **1** (13.19 g, 27.9 mmol, 1 equiv) in acetonitrile (450 mL) was added IBX (23.4 g, 83.7 mmol, 3 equiv). The mixture was refluxed for 45 min, cooled to rt, and filtrated on a Celite pad. The solid was washed with EtOAc, and the filtrate was concentrated in vacuo. The crude aldehyde **2** (13.13 g, quantitative yield) was dried by coevaporation with toluene and used without further purification (all spectral data were in agreement with the literature).[18b] At 0 °C, under Ar, to a well-stirred suspension of methyltriphenylphosphonium bromide (29.9 g, 83.7 mmol, 3 equiv) in THF (180 mL) was added freshly sublimated potassium *tert*-butoxide (9.4 g, 83.7 mmol, 3 equiv). The bright yellow suspension was stirred at 0 °C for 10 min and then at rt for 1 h. The crude aldehyde **2** was dissolved in THF (180 mL), transferred into a dropping funnel, and slowly added to the solution of ylide at 0 °C. The mixture was vigorously stirred at 0 °C for 10 min and then at rt for 16 h. The mixture was diluted in DCM (300 mL), and the reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (100 mL). The aqueous phase was extracted with DCM (4 × 200 mL), and the combined organic layers were dried over Na_2SO_4, filtrated, and concentrated in vacuo. The crude foam (45 g) was purified by flash chromatography (cyclohexane/EtOAc = 7/3 to 1/1), and the alkene **3** was obtained as a white foam (7.93 g, 61% yield); R_f = 0.43 (cyclohexane/EtOAc = 7/3); mp 210−212 °C; $[\alpha]_D$ + 79 (*c* 1.0, CH_2Cl_2); IR (film) 3628*w*, 2859*s*, 2356*m* 1695*s*, 1263*m*; ^{1}H NMR δ 9.92 (br s, 1H, NH), 7.42 (d, 1H, $J_{H6\text{-}H5}$ = 8.0 Hz, H_6), 5.92 (ddd, 1H, $J_{H5'\text{-}H6'a}$ = 17.0 Hz, $J_{H5'\text{-}H6'b}$ = 10.0 Hz, $J_{H5'\text{-}H4'}$ = 7.5 Hz, $H_{5'}$), 5.76 (d, 1H, $J_{H5\text{-}H6}$ = 8.0 Hz, $J_{H5\text{-}NH}$ = 1.5 Hz, H_5), 5.67 (d, 1H, $J_{H1'\text{-}H2'}$ = 2.5 Hz, $H_{1'}$), 5.45 (d, 1H, $J_{H6'a\text{-}H5'}$ = 17.0 Hz, $H_{6'a}$), 5.35 (d, 1H, $J_{H6'b\text{-}H5'}$ = 10.0 Hz, $H_{6'b}$), 4.48 (t, 1H, $J_{H4'\text{-}H3'}$ = 7.5 Hz, $J_{H4'\text{-}H5'}$ = 7.5 Hz, $H_{4'}$), 4.21 (dd, 1H, $J_{H2'\text{-}H3'}$ = 4.0 Hz, $J_{H2'\text{-}H1'}$ = 2.5 Hz, $H_{2'}$), 3.78 (dd, 1H, $J_{H3'\text{-}H2'}$ = 4.0 Hz, $J_{H3'\text{-}H4'}$ = 7.5 Hz, $H_{3'}$), 0.91 (s, 9H, -C($C\underline{H}_3$)$_3$), 0.89 (s, 9H, -C($C\underline{H}_3$)$_3$), 0.15, 0.09, 0.06, 0.05 (4s, 12H, -($C\underline{H}_3$)$_2$); ^{13}C NMR δ 163.9 (C_4), 150.3 (C_2), 139.8 (C_6), 134.9 ($C_{5'}$), 119.3 ($C_{6'}$), 102.2 (C_5), 91.8 ($C_{1'}$), 84.2 ($C_{4'}$), 75.5 ($C_{2'}$), 75.3 ($C_{3'}$), 25.9, 25.9 (-C($\underline{C}H_3$)$_3$), 18.2, 18.1 (-$\underline{C}$(CH$_3$)$_3$), −4.1, −4.4, −4.5, −4.7 (-($\underline{C}H_3$)$_2$); HRMS APCI$^+$ calcd for $C_{22}H_{41}N_2O_5Si_2^+$ (M + H)$^+$ 469.2549, found 469.2557.

5′(*S*)-*C*-(Butylaminomethyl)-2′,3′-di-*O*-(*tert*-butyldimethylsilyl)uridine 4a. To a solution of alkene **3** (6.73g, 14.36 mmol, 1 equiv) in DCM (260 mL) was added *m*-CPBA (77% stabilized, 16.09 g, 71.8 mmol, 5 equiv). The mixture was stirred at 30 °C for 16 h and then cooled to rt, and the reaction was quenched by addition of a 10% aqueous solution of $Na_2S_2O_3$ (150 mL). The aqueous phase was extracted with DCM (3 × 200 mL), and the combined organic layers were washed with a 10% aqueous solution of $NaHCO_3$ (100 mL), and water (100 mL), dried over Na_2SO_4, filtrated, and concentrated in vacuo. The crude white foam revealed to be a 75/25 mixture of epoxides **4a**/**4b** as determined by ^{1}H NMR of the crude and was purified by flash chromatography (cyclohexane/EtOAc = 8/2 to 7/3) to afford the major diastereoisomer **4a** as a white foam (4.90 g, 70% yield). An analytical sample of the minor **4b** could also be isolated.

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Data for major isomer **4a**: R_f = 0.31 (cyclohexane/EtOAc = 7/3); mp 186−190 °C; $[\alpha]_D$ + 39 (*c* 1.0, CH_2Cl_2); IR (film) 3216*w*, 2860*m*, 1696*s*, 1472*m*; ^{1}H NMR δ 8.99 (br s, 1H, NH), 7.78 (d, 1H, $J_{H6\text{-}H5}$ = 8.5 Hz, H_6), 5.85 (d, 1H, $J_{H1'\text{-}H2'}$ = 3.0 Hz, $H_{1'}$), 5.76 (dd, 1H, $J_{H5\text{-}H6}$ = 8.5 Hz, $J_{H5\text{-}NH}$ = 1.5 Hz, H_5), 4.28 (dd, 1H, $J_{H2'\text{-}H1'}$ = 3.0 Hz, $J_{H2'\text{-}H3'}$ = 1.0 Hz, $H_{2'}$), 4.11−4.08 (m, 2H, $H_{3'}$, $H_{4'}$), 3.20−3.19 (m, 1H, $H_{5'}$), 2.93 (dd, 1H, $J_{H6'a\text{-}H6'b}$ = 5.0 Hz, $J_{H6'a\text{-}H5'}$ = 2.5 Hz, $H_{6'a}$), 2.88 (t, 1H, $J_{H6'b\text{-}H6'a}$ = 5.0 Hz, $J_{H6'b\text{-}H5'}$ = 5.0 Hz, $H_{6'b}$), 0.94 (s, 9H, -C(C$\underline{H}_3$)$_3$), 0.90 (s, 9H, -C(C$\underline{H}_3$)$_3$), 0.14, 0.13, 0.10, 0.09, (4s, 12H, -(C$\underline{H}_3$)$_2$); ^{13}C NMR δ 163.4 (C_4), 150.5 (C_2), 139.9 (C_6), 102.7 (C_5), 88.9 ($C_{1'}$), 79.6 ($C_{4'}$), 75.6 ($C_{2'}$), 73.5 ($C_{3'}$), 51.5 ($C_{5'}$), 44.3 ($C_{6'}$), 25.9, 25.9 (-C(C$\underline{H}_3$)$_3$), 18.2, 18.1 (-C$\underline{(}$CH$_3$)$_3$), −4.2, −4.5, −4.6, −4.7 (-(C$\underline{H}_3$)$_2$); HRMS ESI$^+$ calcd for $C_{22}H_{41}N_2O_6Si_2^+$ (M + H)$^+$ 485.2498, found 485.2499. Data for **4b**: white powder, R_f = 0.27 (cyclohexane/EtOAc = 7/3); mp 177−180 °C; $[\alpha]_D$ − 46 (*c* 0.26, CH_2Cl_2); IR (film) 2857*br*, 1693*s*, 1462*m*, 1257*m*, 865*m*; ^{1}H NMR δ 8.42 (br s, 1H, NH), 7.43 (d, 1H, $J_{H6\text{-}H5}$ = 8.0 Hz, H_6), 5.82 (d, 1H, $J_{H1'\text{-}H2'}$ = 5.5 Hz, $H_{1'}$), 5.78 (dd, 1H, $J_{H5\text{-}H6}$ = 8.0 Hz, $J_{H5\text{-}NH}$ = 2.0 Hz, H_5), 4.34 (dd, 1H, $J_{H2'\text{-}H1'}$ = 5.5 Hz, $J_{H2'\text{-}H3'}$ = 4.0 Hz, $H_{2'}$), 4.13 (t, 1H, $J_{H4'\text{-}H3'}$ = $J_{H4'\text{-}H5'}$ = 3.0 Hz, $H_{4'}$), 3.87 (dd, 1H, $J_{H3'\text{-}H2'}$ = 4.0 Hz, $J_{H3'\text{-}H4'}$ = 3.0 Hz, $H_{3'}$), 3.27 (dt, 1H, $J_{H5'\text{-}H6'a}$ = 4.5 Hz, $J_{H5'\text{-}H6'b}$ = $J_{H5'\text{-}H4'}$ = 3.0 Hz, $H_{5'}$), 2.94 (t, 1H, $J_{H6'a\text{-}H6'b}$ = $J_{H6'a\text{-}H5'}$ = 4.5 Hz, $H_{6'a}$), 2.73 (dd, 1H, $J_{H6'b\text{-}H6'a}$ = 4.5 Hz, $J_{H6'b\text{-}H5'}$ = 3.0 Hz, $H_{6'b}$), 0.92 (s, 9H, -C(C$\underline{H}_3$)$_3$), 0.89 (s, 9H, -C(C$\underline{H}_3$)$_3$), 0.11, 0.09, 0.07, 0.05, (4s, 12H, -(C$\underline{H}_3$)$_2$); ^{13}C NMR δ 162.8 (C_4), 150.2 (C_2), 140.8 (C_6), 102.8 (C_5), 90.1 ($C_{1'}$), 84.7 ($C_{4'}$), 74.9 ($C_{2'}$), 71.7 ($C_{3'}$), 51.4 ($C_{5'}$), 45.7 ($C_{6'}$), 25.9, 25.9 (-C(C$\underline{H}_3$)$_3$), 18.2, 18.1 (-C$\underline{(}$CH$_3$)$_3$), −4.1, −4.5, −4.5, −4.8 (-(C$\underline{H}_3$)$_2$); HRMS ESI$^+$ calcd for $C_{22}H_{41}N_2O_6Si_2^+$ (M + H)$^+$ 485.2498, found 485.2492

General Procedure for Epoxide Ring Opening by Amine. To a solution of epoxide (80 mg, 0.165 mmol, 1 equiv) in methanol (1 mL) was added the appropriate amine (0.33 mmol, 2 equiv). The resulting solution was heated at 40 °C for 16 h, concentrated in vacuo, and purified by flash chromatography.

5′(S)-C-(N′-Butyl-N-methyl)-2′,3′-di-O-(tert-butyldimethylsilyl)-uridine ***5a***. Compound **5a** was synthesized according to the general procedure for epoxide ring opening by amine from epoxide **4a** (80 mg, 0.165 mmol, 1 equiv) and butylamine (32 μL, 0.33 mmol, 2 equiv). Flash chromatography (DCM/MeOH/Et_3N = 95/5/0.3%) of the crude afforded **5a** as a white foam (63 mg, 69% yield): R_f = 0.15 (DCM/MeOH/Et_3N = 95/5/0.3%); mp 100−104 °C; $[\alpha]_D$ + 9 (*c* 0.25, CH_2Cl_2); IR (film) 3055*br*, 2957*s*, 1686*s*, 1463*m*; ^{1}H NMR δ 8.05 (d, 1H, $J_{H6\text{-}H5}$ = 8.0 Hz, H_6), 6.09−5.80 (br s, 3H, NH, OH), 5.74 (d, 1H, $J_{H1'\text{-}H2'}$ = 4.5 Hz, $H_{1'}$), 5.70 (d, 1H, $J_{H5\text{-}H6}$ = 8.0 Hz, H_5), 4.26 (t, 1H, $J_{H2'\text{-}H1'}$ = 4.5 Hz, $J_{H2'\text{-}H3'}$ = 4.5 Hz, $H_{2'}$), 4.16 (t, 1H, $J_{H3'\text{-}H2'}$ = 4.5 Hz, $J_{H3'\text{-}H4'}$ = 4.5 Hz, $H_{3'}$), 3.90−3.87 (m, 2H, $H_{5'}$, $H_{4'}$), 2.85 (dd, 1H, $J_{H6'a\text{-}H6'b}$ = 13.0 Hz, $J_{H6'a\text{-}H5'}$ = 9.0 Hz, $H_{6'a}$), 2.80 (dd, 1H, $J_{H6'b\text{-}H6'a}$ = 13.0 Hz, $J_{H6'b\text{-}H5'}$ = 4.0 Hz, $H_{6'b}$), 2.79−2.70 (m, 2H, $H_{7'}$), 1.56 (qt, 2H, $J_{H8'\text{-}H7'}$ = $J_{H8'\text{-}H9'}$ = 8.0 Hz, $H_{8'}$), 1.34 (sext, 2H, $J_{H9'\text{-}H8'}$ = $J_{H9'\text{-}H10'}$ = 8.0 Hz, $H_{9'}$), 0.89 (t, 2H, $J_{H10'\text{-}H9'}$ = 8.0 Hz, $H_{10'}$), 0.87 (s, 9H, -C(C$\underline{H}_3$)$_3$), 0.85 (s, 9H, -C(C$\underline{H}_3$)$_3$), 0.06, 0.04, (2s, 12H, -(C$\underline{H}_3$)$_2$); ^{13}C NMR δ 164.2 (C_4), 150.9 (C_2), 141.6 (C_6), 102.3 (C_5), 90.2 ($C_{1'}$), 85.6 ($C_{4'}$), 75.1 ($C_{2'}$), 72.4 ($C_{3'}$), 66.9 ($C_{5'}$), 51.6 ($C_{6'}$), 48.9 ($C_{7'}$), 30.9 ($C_{8'}$), 26.0, 25.9 (-C(C$\underline{H}_3$)$_3$), 20.3 ($C_{9'}$), 18.2, 18.1 (-C$\underline{(}$CH$_3$)$_3$), 13.9 ($C_{10'}$), −4.2, −4.5, −4.6, −4.7 (-(C$\underline{H}_3$)$_2$); HRMS APCI$^+$ calcd for $C_{26}H_{52}N_3O_6Si_2^+$ (M + H)$^+$ 558.3389, found 558.3389.

5′(S)-C-(N′-Benzyl-N-methyl)-2′,3′-di-O-(tert-butyldimethylsilyl)-uridine ***5b***. Compound **5b** was synthesized according to the general procedure for epoxide ring opening by amine from epoxide **4a** (80 mg, 0.165 mmol, 1 equiv) and benzylamine (36 μL, 0.33 mmol, 2 equiv). Flash chromatography (cyclohexane/EtOAc = 1/1) of the crude afforded **5b** as a white foam (69 mg, 71% yield): R_f = 0.17 (cyclohexane/EtOAc = 1/1); mp 88−92 °C; $[\alpha]_D$ + 22 (*c* 0.25, CH_2Cl_2); IR (film) 3418*br*, 2929*w*, 1781*w*, 1686*s*, 1462*m*; ^{1}H NMR δ 8.03 (d, 1H, $J_{H6\text{-}H5}$ = 8.0 Hz, H_6), 7.32−5.21 (m, 5H, H_{ar}), 5.72 (d, 1H, $J_{H1'\text{-}H2'}$ = 4.0 Hz, $H_{1'}$), 5.66 (d, 1H, $J_{H5\text{-}H6}$ = 8.0 Hz, H_5), 4.94−4.60 (br s, 2H, NH), 4.23 (t, 1H, $J_{H2'\text{-}H1'}$ = 4.0 Hz, $J_{H2'\text{-}H3'}$ = 4.0 Hz, $H_{2'}$), 4.15 (t, 1H, $J_{H3'\text{-}H2'}$ = 4.0 Hz, $J_{H3'\text{-}H4'}$ = 4.0 Hz, $H_{3'}$), 3.88−3.87 (m, 1H, $H_{4'}$), 3.84 (d, 1H, $J_{H7'a\text{-}H7'b}$ = 13.0 Hz, $H_{7'a}$), 3.80 (d, 1H, $J_{H7'b\text{-}H7'a}$ = 13.0 Hz, $H_{7'b}$), 3.74−3.71 (m, 1H, $H_{5'}$), 2.85 (dd, 1H, $J_{H6'a\text{-}H6'b}$ = 13.0 Hz, $J_{H6'a\text{-}H5'}$ = 9.0 Hz, $H_{6'a}$), 2.80 (dd, 1H, $J_{H6'b\text{-}H6'a}$ = 13.0 Hz, $J_{H6'b\text{-}H5'}$ = 4.0 Hz, $H_{6'b}$), 0.87 (s, 9H, -C(C$\underline{H}_3$)$_3$), 0.86 (s, 9H, -C(C$\underline{H}_3$)$_3$), 0.07, 0.06, 0.06, 0.05 (4s, 12H, -(C$\underline{H}_3$)$_2$); ^{13}C NMR δ 163.4 (C_4), 150.7 (C_2), 141.4 (C_6), 139.6 ($C_{8'}$), 128.7 (C_{Har}), 128.3 (C_{Har}), 127.4 (C_{Har}), 102.1 (C_5), 90.2 ($C_{1'}$), 85.2 ($C_{4'}$), 75.3 ($C_{2'}$), 72.1 ($C_{3'}$), 67.6 ($C_{5'}$), 53.5 ($C_{7'}$), 51.6 ($C_{6'}$), 25.9, 25.8 (-C(C$\underline{H}_3$)$_3$), 18.2, 18.1 (-C$\underline{(}$CH$_3$)$_3$), −4.2, −4.5, −4.6, −4.7 (-(C$\underline{H}_3$)$_2$); HRMS APCI$^+$ calcd for $C_{29}H_{50}N_3O_6Si_2^+$ (M + H)$^+$ 592.3233, found 592.3242.

5′(S)-C-(N′-Phenyl-N-methyl)-2′,3′-di-O-(tert-butyldimethylsilyl)-uridine ***5c***. Compound **5c** was synthesized according to the general procedure for epoxide ring opening by amine from epoxide **4a** (80 mg, 0.165 mmol, 1 equiv) and aniline (30 μL, 0.33 mmol, 2 equiv). Flash chromatography (DCM/Et_2O = 9/1) of the crude afforded **5c** as a white foam (65 mg, 68% yield): R_f = 0.28 (cyclohexane/EtOAc = 1/1); mp 88−92 °C; $[\alpha]_D$ + 2 (*c* 0.4, CH_2Cl_2); IR (film) 3418*br*, 2929*w*, 1781*w*, 1686*s*, 1462*m*; ^{1}H NMR δ 9.24−9.08 (br s, 1H, NH), 7.72 (d, 1H, $J_{H6\text{-}H5}$ = 8.0 Hz, H_6), 7.17 (t, 2H, $J_{H9'\text{-}H8'}$ = $J_{H9'\text{-}H10'}$ = 8.0 Hz, $H_{9'}$), 6.77 (t, 1H, $J_{H10'\text{-}H9'}$ = 8.0 Hz, $H_{10'}$), 6.70 (d, 1H, $J_{H8'\text{-}H9'}$ = 8.0 Hz, $H_{8'}$), 5.72 (d, 1H, $J_{H5\text{-}H6}$ = 8.0 Hz, H_5), 5.52 (d, 1H, $J_{H1'\text{-}H2'}$ = 5.0 Hz, $H_{1'}$), 4.94−4.60 (br s, 2H, NH), 4.51 (t, 1H, $J_{H2'\text{-}H1'}$ = 5.0 Hz, $J_{H2'\text{-}H3'}$ = 5.0 Hz, $H_{2'}$), 4.17 (t, 1H, $J_{H3'\text{-}H2'}$ = 5.0 Hz, $J_{H3'\text{-}H4'}$ = 5.0 Hz, $H_{3'}$), 4.04−4.03 (m, 1H, $H_{4'}$), 3.97−3.94 (m, 1H, $H_{5'}$), 3.70−3.62 (br s, 1H, OH), 3.33 (dd, 1H, $J_{H6'a\text{-}H6'b}$ = 13.0 Hz, $J_{H6'a\text{-}H5'}$ = 8.0 Hz, $H_{6'a}$), 3.30 (dd, 1H, $J_{H6'b\text{-}H6'a}$ = 13.0 Hz, $J_{H6'b\text{-}H5'}$ = 5.0 Hz, $H_{6'b}$), 0.88 (s, 9H, -C(C$\underline{H}_3$)$_3$), 0.87 (s, 9H, -C(C$\underline{H}_3$)$_3$), 0.06, 0.05, 0.04, 0.02 (4s, 12H, -(C$\underline{H}_3$)$_2$); ^{13}C NMR δ 163.4 (C_4), 150.6 (C_2), 147.2 ($C_{7'}$), 142.9 (C_6), 129.7 ($C_{9'}$), 119.2 ($C_{10'}$), 127.4 ($C_{8'}$), 102.4 (C_5), 93.4 ($C_{1'}$), 86.3 ($C_{4'}$), 73.6 ($C_{2'}$), 72.8 ($C_{3'}$), 68.6 ($C_{5'}$), 48.3 ($C_{6'}$), 25.9, 25.8 (-C(C$\underline{H}_3$)$_3$), 18.2, 18.1 (-C$\underline{(}$CH$_3$)$_3$), −4.3, −4.5, −4.6, −4.7 (-(C$\underline{H}_3$)$_2$); HRMS APCI$^+$ calcd for $C_{28}H_{48}N_3O_6Si_2^+$ (M + H)$^+$ 578.3076, found 578.3076.

5′(S)-C-(Morpholino-N-methyl)-2′,3′-di-O-(tert-butyldimethylsilyl)uridine ***5d***. Compound **5d** was synthesized according to the general procedure for epoxide ring opening by amine from epoxide **4a** (80 mg, 0.165 mmol, 1 equiv) and morpholine (28 μL, 0.33 mmol, 2 equiv). Flash chromatography (cyclohexane/EtOAc = 1/1) of the crude afforded **5d** as a white foam (71 mg, 76% yield): R_f = 0.19 (cyclohexane/EtOAc = 1/1); mp 102−106 °C; $[\alpha]_D$ + 24 (*c* 0.4, CH_2Cl_2); IR (film) 3418*br*, 2930*m*, 1693*s*, 1462*m*; ^{1}H NMR δ 9.83−9.64 (br s, 1H, NH), 8.16 (d, 1H, $J_{H6\text{-}H5}$ = 8.0 Hz, H_6), 5.77 (d, 1H, $J_{H1'\text{-}H2'}$ = 3.0 Hz, $H_{1'}$), 5.71 (d, 1H, $J_{H5\text{-}H6}$ = 8.0 Hz, H_5), 4.22 (t, 1H, $J_{H2'\text{-}H1'}$ = 4.0 Hz, $J_{H2'\text{-}H3'}$ = 4.0 Hz, $H_{2'}$), 4.18 (t, 1H, $J_{H3'\text{-}H2'}$ = 4.0 Hz, $J_{H3'\text{-}H4'}$ = 4.0 Hz, $H_{3'}$), 3.88−3.84 (m, 2H, $H_{4'}$, $H_{5'}$), 3.77−3.70 (m, 4H, $H_{8'}$), 2.73 (t, 1H, $J_{H6'a\text{-}H6'b}$ = $J_{H6'a\text{-}H5'}$ = 12.0 Hz, $H_{6'a}$), 2.68−2.64 (m, 2H, $H_{7'a}$), 2.47−2.43 (m, 2H, $H_{7'b}$), 2.39 (dd, 1H, $J_{H6'b\text{-}H6'a}$ = 13.0 Hz, $J_{H6'b\text{-}H5'}$ = 3.0 Hz, $H_{6'b}$), 0.89 (s, 9H, -C(C$\underline{H}_3$)$_3$), 0.88 (s, 9H, -C(C$\underline{H}_3$)$_3$), 0.11, 0.09, 0.07 (3s, 12H, -(C$\underline{H}_3$)$_2$); ^{13}C NMR δ 163.9 (C_4), 150.6 (C_2), 141.2 (C_6), 101.2 (C_5), 89.9 ($C_{1'}$), 83.7 ($C_{4'}$), 75.5 ($C_{2'}$), 71.8 ($C_{3'}$), 67.0 ($C_{8'}$), 64.6 ($C_{5'}$), 61.0 ($C_{6'}$), 53.5 ($C_{7'}$), 25.9, 25.8 (-C(C$\underline{H}_3$)$_3$), 18.2, 18.1 (-C$\underline{(}$CH$_3$)$_3$), −4.2, −4.5, −4.7, −4.8 (-(C$\underline{H}_3$)$_2$); HRMS APCI$^+$ calcd for $C_{26}H_{50}N_3O_7Si_2^+$ (M + H)$^+$ 572.3182, found 572.3189.

5′(S)-C-(Methyl-L-alaninate-N-methyl)-2′,3′-di-O-(tert-butyldimethylsilyl)uridine ***6a***. Compound **6a** was synthesized according to the general procedure for epoxide ring opening by amine from epoxide **4a** (80 mg, 0.165 mmol, 1 equiv) and L-alanine methyl ester (30 μL, 0.33 mmol, 2 equiv). Flash chromatography (cyclohexane/EtOAc = 4/6) of the crude afforded **6a** as a white foam (70 mg, 73%): R_f = 0.22 (cyclohexane/EtOAc = 4/6); mp 82−88 °C; $[\alpha]_D$ + 15 (*c* 1.0, CH_2Cl_2); IR (film) 3418*br*, 2929*w*, 1781*w*, 1686*s*, 1462*m*; ^{1}H NMR δ 8.06 (d, 1H, $J_{H6\text{-}H5}$ = 8.0 Hz, H_6), 5.76 (d, 1H, $J_{H1'\text{-}H2'}$ = 4.0 Hz, $H_{1'}$), 5.73 (d, 1H, $J_{H5\text{-}H6}$ = 8.0 Hz, H_5), 4.28 (t, 1H, $J_{H2'\text{-}H1'}$ = 4.0 Hz, $J_{H2'\text{-}H3'}$ = 4.0 Hz, $H_{2'}$), 4.18 (t, 1H, $J_{H3'\text{-}H2'}$ = 4.0 Hz, $J_{H3'\text{-}H4'}$ = 4.0 Hz, $H_{3'}$), 3.90−3.87 (m, 1H, $H_{4'}$), 3.76−3.74 (br s, 1H, NH), 3.73 (s, 3H, -O-C$\underline{H}_3$), 3.44 (q, 1H, $J_{H7'\text{-}H8'}$ = 7.0 Hz, $H_{7'}$), 2.84 (dd, 1H, $J_{H6'a\text{-}H6'b}$ = 13.0 Hz $J_{H6'a\text{-}H5'}$ = 9.0 Hz, $H_{6'a}$), 2.74 (dd, 1H, $J_{H6'b\text{-}H6'a}$ = 13.0 Hz, $J_{H6'b\text{-}H5'}$ = 4.0 Hz, $H_{6'b}$), 1.35 (d, 3H, $J_{H8'\text{-}H7'}$ = 7.0 Hz, $H_{8'}$), 0.90 (s, 9H, -C(C$\underline{H}_3$)$_3$), 0.89 (s, 9H, -C(C$\underline{H}_3$)$_3$), 0.09, 0.08, 0.07 (3s, 12H, -(C$\underline{H}_3$)$_2$); ^{13}C NMR δ 175.5 (-$\underline{C}$O-OCHH$_3$), 163.6 (C_4), 150.6 (C_2), 141.5 (C_6), 102.2 (C_5), 90.2 ($C_{1'}$), 85.2 ($C_{4'}$), 75.2 ($C_{2'}$), 72.4 ($C_{3'}$),

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67.7 ($C_{5'}$), 56.1 ($C_{7'}$), 52.2 (-CO-O$\underline{C}H_3$), 50.1 ($C_{6'}$), 26.0, 25.9 (-C($\underline{C}H_3$)$_3$), 19.3 ($C_{8'}$), 18.2, 18.1 (-$\underline{C}$(CH$_3$)$_3$), −4.2, −4.5, −4.6, −4.7 (-($\underline{C}H_3$)$_2$); HRMS APCI$^+$ calcd for $C_{26}H_{50}N_3O_8Si_2^+$ (M + H)$^+$ 588.3131, found 588.3138.

5′(S)-C-(Methyl-serinate-N-methyl)-2′,3′-di-O-(tert-butyldimethylsilyl)uridine ***6b***. Compound **6b** was synthesized according to the general procedure for epoxide ring opening by amine from epoxide **4a** (80 mg, 0.165 mmol, 1 equiv) and L-serine methyl ester (39 mg, 0.33 mmol, 2 equiv). Flash chromatography (cyclohexane/EtOAc = 4/6) of the crude afforded **6b** as a white foam (68 mg, 69% yield) as an inseparable 85/15 mixture of diastereoisomers at the α carbon atom (the major diastereoisomer is labeled by"*" and the minor one by"°" in NMR description): R_f = 0.21 (cyclohexane/EtOAc = 4/6); IR (film) 3355*br*, 2953*m*, 2928*m*, 1686*s*, 1446*m*; ^{1}H NMR δ 8.11 (d, 0.15H, $J_{H6°\text{-}H5°}$ = 8.0 Hz, $H_{6°}$), 7.97 (d, 0.85H, $J_{H6*\text{-}H5*}$ = 8.0 Hz, H_{6*}), 5.74 (d, 1H, $J_{H5\text{-}H6}$ = 8.0 Hz, H_5), 5.71 (d, 0.15H, $J_{H1'°\text{-}H2'°}$ = 4.5 Hz, $H_{1'°}$),5.67 (d, 0.85H, $J_{H1'*\text{-}H2'*}$ = 4.5 Hz, $H_{1'*}$), 5.07−4.54 (br s, 2H, NH), 4.37 (t, 0.85H, $J_{H2'*\text{-}H1'*}$ = 4.5 Hz, $J_{H2'*\text{-}H3'*}$ = 4.5 Hz, $H_{2'*}$), 4.27 (t, 0.15H, $J_{H2'°\text{-}H1'°}$ = 4.5 Hz, $J_{H2'°\text{-}H3'°}$ = 4.5 Hz, $H_{2'°}$), 4.19 (t, 1H, $J_{H3'\text{-}H2'}$ = 4.5 Hz, $J_{H3'\text{-}H4'}$ = 4.5 Hz, $H_{3'}$), 3.95−3.89 (m, 2H, $H_{4'}$, $H_{8'a}$), 3.84−3.82 (m, 1H, $H_{5'}$), 3.80−3.78 (m, 1H, $H_{8'b}$), 3.77, 3,73 (2s, 3H, -O-C$\underline{H}_3$), 3.49 (t, 1H, $J_{H7'\text{-}H8'a}$ = $J_{H7'\text{-}H8'b}$ = 4.5 Hz, $H_{7'}$), 2.99 (dd, 1H, $J_{H6'a\text{-}H6'b}$ = 12.5 Hz $J_{H6'a\text{-}H5'}$ = 9.0 Hz, $H_{6'a}$), 2.80 (dd, 1H, $J_{H6'b\text{-}H6'a}$ = 12.5 Hz, $J_{H6'b\text{-}H5'}$ = 4.0 Hz, $H_{6'b}$), 0.90 (s, 9H, -C(C$\underline{H}_3$)$_3$), 0.88 (s, 9H, -C(C$\underline{H}_3$)$_3$), 0.08, 0.07, 0.06 (3s, 12H, -(C$\underline{H}_3$)$_2$); ^{13}C NMR δ 172.7 (-$\underline{C}$O-OCHH$_3$), 163.9 (C_4), 150.8 (C_2), 142.2 (C_6), 102.2 (C_5), 91.3 ($C_{1'}$), 86.0 ($C_{4'}$), 75.2 ($C_{2'°}$), 74.6 ($C_{2'*}$), 72.5 ($C_{3'}$), 68.6 ($C_{5'°}$), 68.2 ($C_{5'*}$), 63.2 ($C_{8'°}$), 62.7 ($C_{8'*}$), 62.7 ($C_{7'}$), 52.6 (-CO-O$\underline{C}$H$_3$), 50.9 ($C_{6'}$), 25.9, 25.9 (-C($\underline{C}$H$_3$)$_3$), 18.2, 18.1 (-C($\underline{C}$H$_3$)$_3$), −4.2, −4.6, −4.6, −4.7 (-($\underline{C}$H$_3$)$_2$)); HRMS APCI$^+$ calcd for $C_{26}H_{50}N_3O_9Si_2^+$ (M + H)$^+$ 604.3080, found 604.3075.

5′(S)-C-(Azidomethyl)-2′,3′-di-O-(tert-butyldimethylsilyl)uridine ***7***. To a solution of epoxide **4a** (1 g, 2.1 mmol, 1 equiv) in DMF (25 mL) were successively added NaN_3 (520 mg, 8.4 mmol, 4 equiv) and NH_4Cl (220 mg, 4.2 mmol, 2 equiv). The resulting suspension was heated at 70 °C for 16 h, cooled to rt, and diluted with Et_2O (30 mL) and brine (30 mL). The aqueous phase was extracted with Et_2O (3 × 40 mL), and the combined organic layers were washed with water (2 × 30 mL), dried over Na_2SO_4, filtrated, and concentrated in vacuo. Flash chromatography of the residue (cyclohexane/EtOAc = 6/4) afforded azido alcohol **7** as a white foam (820 mg, 72% yield): R_f = 0.60 (cyclohexane/EtOAc = 1/1); mp 80−84 °C; $[\alpha]_D$ − 11 (*c* 0.5, CH_2Cl_2); IR (film) 2955*m*, 2932*m*, 2096*s*, 1686*s*, 1472*w*; ^{1}H NMR δ 9.83 (br s, 1H, NH), 7.71 (d, 1H, $J_{H6\text{-}H5}$ = 8.0 Hz, H_6), 5.75 (d, 1H, $J_{H5\text{-}H6}$ = 8.0 Hz, H_5), 5.45 (d, 1H, $J_{H1'\text{-}H2'}$ = 5.0 Hz, $H_{1'}$), 4.53 (t, 1H, $J_{H2'\text{-}H1'}$ = $J_{H2'\text{-}H3'}$ = 5.0 Hz, $H_{2'}$), 4.18 (dd, 1H, $J_{H3'\text{-}H2'}$ = 5.0 Hz, $J_{H3'\text{-}H4'}$ = 4.0 Hz, $H_{3'}$), 4.04−4.01 (m, 1H, $H_{4'}$), 3.93−3.90 (m, 1H, OH), 3.85−3.80 (m, 1H, $H_{5'}$), 3.52 (dd, 1H, $J_{H6'a\text{-}H6'b}$ = 12.0 Hz, $J_{H6'a\text{-}H5'}$ = 8.0 Hz, $H_{6'a}$), 3.40 (dd, 1H, $J_{H6'b\text{-}H6'a}$ = 12.0 Hz, $J_{H6'b\text{-}H5'}$ = 5.0 Hz, $H_{6'b}$), 0.91 (s, 9H, -C(C$\underline{H}_3$)$_3$), 0.87 (s, 9H, -C(C$\underline{H}_3$)$_3$), 0.09, 0.08, 0.06, 0.04, (4s, 12H, -(C$\underline{H}_3$)$_2$); ^{13}C NMR δ 163.9 (C_4), 150.7 (C_2), 143.2 (C_6), 102.3 (C_5), 93.9 ($C_{1'}$), 85.5 ($C_{4'}$), 73.5 ($C_{2'}$), 72.6 ($C_{3'}$), 69.5 ($C_{5'}$), 54.1 ($C_{6'}$), 25.9, 25.9 (-C($\underline{C}$H$_3$)$_3$), 18.1, 18.0 (-$\underline{C}$(CH$_3$)$_3$), −4.3, −4.6, −4.6, −4.7 (-($\underline{C}$H$_3$)$_2$); HRMS APCI$^+$ calcd for $C_{22}H_{42}N_5O_6Si_2^+$ (M + H)$^+$ 528.2668, found 528.2669.

5′(S)-C-(Benzyloxymethyl)-2′,3′-di-O-(tert-butyldimethylsilyl)-uridine ***8a***. NaH (60% dispersion in mineral oil, 20 mg, 0.49 mmol, 3 equiv) was added to a solution of benzylic alcohol (54 mg, 0.49 mmol, 3 equiv) in THF (1 mL). At 0 °C, a solution of epoxide **4a** (80 mg, 0.165 mmol, 1 equiv) in THF (500 μL) was added dropwise. The suspension was heated at 60 °C for 16 h, cooled to rt, and diluted in DCM (10 mL) and saturated NH_4Cl aqueous solution (10 mL). The aqueous layer was extracted with DCM (3 × 10 mL), and the combined organic layers were dried over Na_2SO_4, filtrated, and concentrated in vacuo. Flash chromatography of the residue (cyclohexane/EtOAc = 8/2 to 7/3) afforded **8a** as a white film (64 mg, 66% yield): R_f = 0.44 (cyclohexane/EtOAc = 1/1); $[\alpha]_D$ + 23 (*c* 0.8, CH_2Cl_2); IR (film) 3384*br*, 2952*m*, 2929*m*, 1682*s*, 1471*m*; ^{1}H NMR δ 8.50 (br s, 1H, NH), 7.97 (d, 1H, $J_{H6\text{-}H5}$ = 8.0 Hz, H_6), 7.39−7.31 (m, 5H, H_{ar}), 5.70 (dd, 1H, $J_{H5\text{-}H6}$ = 8.0 Hz, $J_{H5\text{-}NH}$ = 2.5 Hz, H_5), 5.67 (d, 1H, $J_{H1'\text{-}H2'}$ = 4.5 Hz, $H_{1'}$), 4.62 (d, 1H, $J_{H7'a\text{-}H7'b}$ = 12.0 Hz, $H_{7'a}$), 4.58 (d, 1H, $J_{H7'b\text{-}H7'a}$ = 12.0 Hz, $H_{7'b}$), 4.30 (t, 1H, $J_{H2'\text{-}H1'}$ = 4.5 Hz, $J_{H2'\text{-}H3'}$ = 4.5 Hz, $H_{2'}$), 4.18 (t, 1H, $J_{H3'\text{-}H2'}$ = 4.5 Hz, $J_{H3'\text{-}H4'}$ = 4.5 Hz, $H_{3'}$), 4.01 (dd, 1H, $J_{H4'\text{-}H3'}$ = 4.5 Hz, $J_{H4'\text{-}H5'}$ = 1.0 Hz, $H_{4'}$), 3.99−3.96 (m, 1H, $H_{5'}$), 3.63 (t, 1H, $J_{H6'a\text{-}H6'b}$ = 9.5 Hz, $J_{H6'a\text{-}H5'}$ = 9.5 Hz, $H_{6'a}$), 3.60 (dd, 1H, $J_{H6'b\text{-}H6'a}$ = 9.5 Hz, $J_{H6'b\text{-}H5'}$ = 4.5 Hz, $H_{6'b}$), 3.10−3.07 (m, 1H, OH), 0.91 (s, 9H, -C(C$\underline{H}_3$)$_3$), 0.90 (s, 9H, -C(C$\underline{H}_3$)$_3$), 0.09, 0.08, 0.08, (3s, 12H, -(C$\underline{H}_3$)$_2$); ^{13}C NMR δ 163.1 (C_4), 150.4 (C_2), 141.7 (C_6), 137.8 ($C_{8'}$), 128.7 ($C_{9'}$), 128.1 ($C_{11'}$), 127.4 ($C_{10'}$), 102.1 (C_5), 91.3 ($C_{1'}$), 83.9 ($C_{4'}$), 74.9 ($C_{2'}$), 73.7 ($C_{7'}$), 71.9 ($C_{3'}$), 71.9 ($C_{6'}$), 69.1 ($C_{5'}$), 26.0, 25.9 (-C($\underline{C}$H$_3$)$_3$), 18.2, 18.1 (-$\underline{C}$(CH$_3$)$_3$), −4.2, −4.5, −4.6, −4.7 (-($\underline{C}$H$_3$)$_2$); HRMS APCI$^+$ calcd for $C_{29}H_{49}N_2O_7Si_2^+$ (M + H)$^+$ 593.3073, found 593.3076.

General Procedure for Epoxide Ring Opening by Phenol Derivatives. To a solution of epoxide **4a** (80 mg, 0.165 mmol, 1 equiv) and phenol derivative (2 equiv) in dry DMF (1 mL) was added potassium carbonate (0.25 equiv). The suspension was heated at 50 °C for 16 h, cooled to rt, and diluted in DCM (10 mL) and brine (10 mL). The aqueous layer was extracted with DCM (3 × 10 mL), and the combined organic layers were dried over Na_2SO_4, filtrated, and concentrated in vacuo. The residue was purified by flash chromatography.

5′(S)-C-(Phenyloxymethyl)-2′,3′-di-O-(tert-butyldimethylsilyl)-uridine ***8b***. Compound **8b** was synthesized according to the general procedure for epoxide ring opening with phenol derivatives from epoxide **4a** (80 mg, 0.165 mmol, 1 equiv) and phenol (31 mg, 0.33 mmol, 2 equiv). Flash chromatography of the residue (cyclohexane/EtOAc = 8/2 to 7/3) afforded **8b** as a white film (59 mg, 62%): R_f = 0.60 (cyclohexane/EtOAc = 1/1); $[\alpha]_D$ + 12 (*c* 0.5, CH_2Cl_2); IR (film) 2954*m*, 2927*m*, 1684*s*, 1462*m*; ^{1}H NMR δ 8.41 (br s, 1H, NH), 7.84 (d, 1H, $J_{H6\text{-}H5}$ = 8.5 Hz, H_6), 7.32−7.29 (m, 2H, $H_{9'}$), 7.00−6.97 (m, 1H, $H_{10'}$), 6.95−6.91 (m, 2H, $H_{8'}$), 5.72 (dd, 1H, $J_{H5\text{-}H6}$ = 8.5 Hz, $J_{H5\text{-}NH}$ = 2.5 Hz, H_5), 5.62 (d, 1H, $J_{H1'\text{-}H2'}$ = 5.0 Hz, $H_{1'}$), 4.46 (t, 1H, $J_{H2'\text{-}H1'}$ = 4.5 Hz, $J_{H2'\text{-}H3'}$ = 4.5 Hz, $H_{2'}$), 4.26 (t, 1H, $J_{H3'\text{-}H2'}$ = 4.5 Hz, $J_{H3'\text{-}H4'}$ = 4.5 Hz, $H_{3'}$), 4.18 (dd, 1H, $J_{H4'\text{-}H3'}$ = 4.5 Hz, $J_{H4'\text{-}H5'}$ = 1.0 Hz, $H_{4'}$), 4.17−4.12 (m, 1H, $H_{5'}$), 4.12 (t, 1H, $J_{H6'a\text{-}H6'b}$ = 9.0 Hz, $J_{H6'a\text{-}H5'}$ = 9.0 Hz, $H_{6'a}$), 4.06 (dd, 1H, $J_{H6'b\text{-}H6'a}$ = 9.0 Hz, $J_{H6'b\text{-}H5'}$ = 4.5 Hz, $H_{6'b}$), 3.39−3.29 (m, 1H, OH), 0.93 (s, 9H, -C(C$\underline{H}_3$)$_3$), 0.90 (s, 9H, -C(C$\underline{H}_3$)$_3$), 0.13, 0.12, 0.09, 0.08, (4s, 12H, -(C$\underline{H}_3$)$_2$); ^{13}C NMR δ 162.9 (C_4), 158.4 ($C_{7'}$), 150.4 (C_2), 142.3 (C_6), 129.7 ($C_{9'}$), 121.5 ($C_{10'}$), 114.7 ($C_{8'}$), 102.3 (C_5), 92.5 ($C_{1'}$), 84.5 ($C_{4'}$), 74.2 ($C_{2'}$), 72.3 ($C_{3'}$), 69.3 ($C_{6'}$), 69.1 ($C_{5'}$), 26.0, 25.9 (-C($\underline{C}$H$_3$)$_3$), 18.3, 18.1 (-$\underline{C}$(CH$_3$)$_3$), −4.2, −4.5, −4.6 (-($\underline{C}$H$_3$)$_2$); HRMS ESI$^-$ calcd for $C_{28}H_{45}N_2O_7Si_2^-$ (M − H)$^-$ 577.2771, found 577.2733.

5′(S)-C-(4-Bromo-phenyloxymethyl)-2′,3′-di-O-(tert-butyldimethylsilyl)uridine ***8c***. Compound **8c** was synthesized according to the general procedure for epoxide ring opening with phenol derivatives from epoxide **4a** (80 mg, 0.165 mmol, 1 equiv) and 4-bromo-phenol (57 mg, 0.33 mmol, 2 equiv). Flash chromatography of the residue (cyclohexane/EtOAc = 8/2 to 7/3) afforded **8c** as a white film (71 mg, 66% yield): R_f = 0.60 (cyclohexane/EtOAc = 1/1); $[\alpha]_D$ + 13 (*c* 0.5, CH_2Cl_2); IR (film) 3585*br*, 2952*m*, 2857*m*, 1682*s*, 1489*m*; ^{1}H NMR δ 8.49 (br s, 1H, NH), 7.76 (d, 1H, $J_{H6\text{-}H5}$ = 8.5 Hz, H_6), 7.40−7.37 (m, 2H, $H_{9'}$), 6.82−6.79 (m, 2H, $H_{8'}$), 5.72 (dd, 1H, $J_{H5\text{-}H6}$ = 8.0 Hz, $J_{H5\text{-}NH}$ = 2.5 Hz, H_5), 5.55 (d, 1H, $J_{H1'\text{-}H2'}$ = 5.0 Hz, $H_{1'}$), 4.50 (t, 1H, $J_{H2'\text{-}H1'}$ = 5.0 Hz, $J_{H2'\text{-}H3'}$ = 5.0 Hz, $H_{2'}$), 4.25 (t, 1H, $J_{H3'\text{-}H2'}$ = 5.0 Hz, $J_{H3'\text{-}H4'}$ = 5.0 Hz, $H_{3'}$), 4.01 (dd, 1H, $J_{H4'\text{-}H3'}$ = 5.0 Hz, $J_{H4'\text{-}H5'}$ = 1.0 Hz, $H_{4'}$), 4.15−4.11 (m, 1H, $H_{5'}$), 4.08 (t, 1H, $J_{H6'a\text{-}H6'b}$ = 9.0 Hz, $J_{H6'a\text{-}H5'}$ = 9.0 Hz, $H_{6'a}$), 3.60 (dd, 1H, $J_{H6'b\text{-}H6'a}$ = 9.0 Hz, $J_{H6'b\text{-}H5'}$ = 5.5 Hz, $H_{6'b}$), 3.48−3.42 (m, 1H, OH), 0.93 (s, 9H, -C(C$\underline{H}_3$)$_3$), 0.90 (s, 9H, -C(C$\underline{H}_3$)$_3$), 0.12, 0.09, 0.07, (3s, 12H, -(C$\underline{H}_3$)$_2$); ^{13}C NMR δ 162.9 (C_4), 157.5 ($C_{7'}$), 150.4 (C_2), 142.6 (C_6), 132.6 ($C_{9'}$), 116.5 ($C_{8'}$), 113.7 ($C_{10'}$), 102.3 (C_5), 93.2 ($C_{1'}$), 84.7 ($C_{4'}$), 73.9 ($C_{2'}$), 72.4 ($C_{3'}$), 69.5 ($C_{6'}$), 69.0 ($C_{5'}$), 26.0, 25.9 (-C($\underline{C}$H$_3$)$_3$), 18.2, 18.1 (-$\underline{C}$(CH$_3$)$_3$), −4.2, −4.5, −4.6, −4.6 (-($\underline{C}$H$_3$)$_2$); HRMS ESI$^+$ calcd for $C_{28}H_{46}$-$BrN_2O_7Si_2^+$ (M + H)$^+$ 657.2021, found 657.2024.

5′(S)-C-(Phenylthiomethyl)-2′,3′-di-O-(tert-butyldimethylsilyl)-uridine ***9***. To a solution of epoxide **4a** (80 mg, 0.165 mmol, 1 equiv) and thiophenol (84 μL, 0.83 mmol, 5 equiv) in dry DMF was added sodium methoxide (23 mg, 0.41 mmol, 2.5 equiv). The resulting

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suspension was heated at 100 °C for 16 h, cooled to rt, and diluted in Et_2O (10 mL) and a saturated aqueous solution of $NaHCO_3$ (10 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL), and the combined organic layers were washed with brine (10 mL) and water (10 mL), dried over Na_2SO_4, filtrated, and concentrated in vacuo. Flash chromatography of the residue (cyclohexane/EtOAc = 6/4) afforded **9** as a white powder (71 mg, 73% yield): R_f = 0.76 (cyclohexane/EtOAc = 1/1); mp 190−192 °C; $[\alpha]_D$ − 13 (*c* 1.0, CH_2Cl_2); IR (film) 3201*br*, 2950*m*, 2885*m*, 1697*s*, 1464*m*; ^{1}H NMR δ 9.24 (br s, 1H, NH), 7.84 (d, 1H, $J_{H6\text{-}H5}$ = 8.0 Hz, H_6), 7.41−7.31 (m, 2H, $H_{8'}$), 7.32−7.29 (m, 2H, $H_{9'}$), 7.25−7.22 (m, 1H, $H_{10'}$), 5.73 (dd, 1H, $J_{H5\text{-}H6}$ = 8.0 Hz, $J_{H5\text{-}NH}$ = 2.0 Hz, H_5), 5.57 (d, 1H, $J_{H1'\text{-}H2'}$ = 4.5 Hz, $H_{1'}$), 4.42 (t, 1H, $J_{H2'\text{-}H1'}$ = 4.5 Hz, $J_{H2'\text{-}H3'}$ = 4.5 Hz, $H_{2'}$), 4.14 (t, 1H, $J_{H3'\text{-}H2'}$ = 4.5 Hz, $J_{H3'\text{-}H4'}$ = 4.5 Hz, $H_{3'}$), 4.09 (dd, 1H, $J_{H4'\text{-}H3'}$ = 4.5 Hz, $J_{H4'\text{-}H5'}$ = 1.0 Hz, $H_{4'}$), 3.72−3.69 (m, 1H, $H_{5'}$), 3.59−3.53 (br s, 1H, OH), 3.16 (dd, 1H, $J_{H6'a\text{-}H6'b}$ = 14.0 Hz, $J_{H6'a\text{-}H5'}$ = 7.5 Hz, $H_{6'a}$), 3.13 (dd, 1H, $J_{H6'b\text{-}H6'a}$ = 14.0 Hz, $J_{H6'b\text{-}H5'}$ = 6.5 Hz, $H_{6'b}$), 0.88 (s, 9H, -C(C$\underline{H}_3$)$_3$), 0.84 (s, 9H, -C(C$\underline{H}_3$)$_3$), 0.06, 0.05, 0.04, 0.00 (4s, 12H, -(C$\underline{H}_3$)$_2$); ^{13}C NMR δ 163.5 (C_4), 150.5 (C_2), 142.5 (C_6), 134.2 ($C_{7'}$), 130.6 ($C_{8'}$), 129.3 ($C_{9'}$), 127.2 ($C_{10'}$), 102.2 (C_5), 92.7 ($C_{1'}$), 85.5 ($C_{4'}$), 74.2 ($C_{2'}$), 72.5 ($C_{3'}$), 67.9 ($C_{5'}$), 38.5 ($C_{6'}$), 25.9 (-C(C$\underline{H}_3$)$_3$), 18.2, 18.1 (-$\underline{C}$(CH$_3$)$_3$), −4.3, −4.6, −4.6, −4.8 (-($\underline{C}$H$_3$)$_2$) HRMS APCI$^+$ calcd for $C_{28}H_{47}N_2O_6SSi_2^+$ (M + H)$^+$ 595.2688, found 595.2696.

5′(S)-C-(Cyanomethyl)-2′,3′-di-O-(tert-butyldimethylsilyl)uridine ***10***. ***Warning!*** *HCN gas. The reaction should be performed in a fumehood.* To a solution of epoxide **4a** (80 mg, 0.165 mmol, 1 equiv) in DMF (1 mL) were successively added KCN (88 mg, 1.32 mmol, 8 equiv) and NH_4Cl (13.3 mg, 0.25 mmol, 1.5 equiv). The resulting suspension was heated at 100 °C for 16 h, cooled to rt, and diluted with Et_2O (10 mL) and water (10 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL), and the combined organic layers were washed with brine (1 × 10 mL), dried over Na_2SO_4, filtrated, and concentrated in vacuo. Flash chromatography of the residue (cyclohexane/EtOAc = 6/4) afforded **10** as a white foam (57 mg, 68% yield): R_f = 0.21 (cyclohexane/EtOAc = 6/4); mp 118−120 °C; $[\alpha]_D$ − 78 (*c* 0.8, CH_2Cl_2); IR (film) 2929*m*, 2857*m*, 1686*s*, 1431*w*; ^{1}H NMR δ 9.44 (br s, 1H, NH), 7.48 (d, 1H, $J_{H6\text{-}H5}$ = 8.0 Hz, H_6), 5.80 (dd, 1H, $J_{H5\text{-}H6}$ = 8.0 Hz, $J_{H5\text{-}NH}$ = 2.0 Hz, H_5), 5.36 (d, 1H, $J_{H1'\text{-}H2'}$ = 7.0 Hz, $H_{1'}$), 4.70 (dd, 1H, $J_{H2'\text{-}H1'}$ = 7.0 Hz, $J_{H2'\text{-}H3'}$ = 4.5 Hz, $H_{2'}$), 4.48−4.43 (m, 1H, OH), 4.20 (dd, 1H, $J_{H3'\text{-}H2'}$ = 4.5 Hz, $J_{H3'\text{-}H4'}$ = 2.5 Hz, $H_{3'}$), 4.09−4.03 (m, 2H, $H_{4'}$, $H_{5'}$), 2.71 (dd, 1H, $J_{H6'a\text{-}H6'b}$ = 17.0 Hz, $J_{H6'a\text{-}H5'}$ = 7.5 Hz, $H_{6'a}$), 2.80 (dd, 1H, $J_{H6'b\text{-}H6'a}$ = 17.0 Hz, $J_{H6'b\text{-}H5'}$ = 6.0 Hz, $H_{6'b}$), 0.92 (s, 9H, -C(C$\underline{H}_3$)$_3$), 0.87 (s, 9H, -C(C$\underline{H}_3$)$_3$), 0.11, 0.06, −0.01, (3s, 12H, -(C$\underline{H}_3$)$_2$); ^{13}C NMR δ 163.3 (C_4), 150.7 (C_2), 144.2 (C_6), 117.5 ($C_{7'}$), 102.7 (C_5), 95.8 ($C_{1'}$), 87.3 ($C_{4'}$), 72.9 ($C_{2'}$), 72.3 ($C_{3'}$), 67.6 ($C_{5'}$), 26.0, 25.9 (-C(C$\underline{H}_3$)$_3$), 23.1 ($C_{6'}$), 18.2, 18.1 (-$\underline{C}$(CH$_3$)$_3$), −4.3, −4.4, −4.5, −4.8 (-($\underline{C}$H$_3$)$_2$); HRMS APCI$^+$ calcd for $C_{23}H_{42}N_3O_6Si_2^+$ (M + H)$^+$ 512.2607, found 512.2609.

5′(S)-C-(Bromomethyl)-2′,3′-di-O-(tert-butyldimethylsilyl)uridine ***11***. At −50 °C, under argon, to a suspension of epoxide **4a** (40 mg, 0.08 mmol, 1 equiv) and lithium bromide (12.9 mg, 0.15 mmol, 1.8 equiv) in THF (1 mL) was added boron trifluoride etherate (12 μL, 0.09 mmol, 1.1 equiv). The reaction mixture was stirred at −50 °C for 5 min and then at rt for 1 h. After addition of $NaHCO_3$ 10%, the aqueous phase was extracted with DCM (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtrated, and concentrated in vacuo. Flash chromatography of the residue (cyclohexane/EtOAc = 6/4) afforded **11** as a white powder (37 mg, 79% yield): R_f = 0.53 (cyclohexane/EtOAc = 1/1); mp 202−204 °C; $[\alpha]_D$ − 16 (*c* 1.0, CH_2Cl_2); IR (film) 3385*br*, 2953*m*, 1683*s*, 1472*m*, 1259*m*; ^{1}H NMR δ 9.59 (br s, 1H, NH), 7.62 (d, 1H, $J_{H6\text{-}H5}$ = 8.0 Hz, H_6), 5.76 (d, 1H, $J_{H5\text{-}H6}$ = 8.0 Hz, H_5), 5.46 (d, 1H, $J_{H1'\text{-}H2'}$ = 5.0 Hz, $H_{1'}$), 4.58 (t, 1H, $J_{H2'\text{-}H1'}$ = $J_{H2'\text{-}H3'}$ = 5.0 Hz, $H_{2'}$), 4.28 (d, 1H, $J_{H4'\text{-}H3'}$ = 3.0 Hz, $H_{4'}$), 4.18 (dd, 1H, $J_{H3'\text{-}H2'}$ = 5.0 Hz, $J_{H3'\text{-}H4'}$ = 3.0 Hz, $H_{3'}$), 3.99−3.95 (m, 1H, OH), 3.94−3.90 (m, 1H, $H_{5'}$), 3.50 (dd, 1H, $J_{H6'a\text{-}H6'b}$ = 11.5 Hz, $J_{H6'a\text{-}H5'}$ = 1.0 Hz, $H_{6'a}$), 3.46 (dd, 1H, $J_{H6'b\text{-}H6'a}$ = 11.5 Hz, $J_{H6'b\text{-}H5'}$ = 2.0 Hz, $H_{6'b}$), 0.92 (s, 9H, -C(C$\underline{H}_3$)$_3$), 0.87 (s, 9H, -C(C$\underline{H}_3$)$_3$), 0.1, 0.06, 0.03 (3s, 12H, -(C$\underline{H}_3$)$_2$); ^{13}C NMR δ 163.6 (C_4), 150.6 (C_2), 143.4 (C_6), 102.4 (C_5), 94.2 ($C_{1'}$), 85.4 ($C_{4'}$), 73.1 ($C_{2'}$), 73.0 ($C_{3'}$), 71.1 ($C_{5'}$), 34.0 ($C_{6'}$), 26.0, 25.9 (-C(C$\underline{H}_3$)$_3$), 18.2, 18.1 (-$\underline{C}$(CH$_3$)$_3$), −4.3, −4.5, −4.5, −4.8, (-($\underline{C}$H$_3$)$_2$); HRMS APCI$^+$ calcd for $C_{22}H_{42}BrN_2O_6Si_2^+$ (M + H)$^+$ 565.1759, found 565.1761.

5′(S)-C-(Trimethylsilylacetylenylmethyl)-2′,3′-di-O-(tert-butyldimethylsilyl)uridine ***12***. At −78 °C, to a solution of alkyne (2.29 g, 23.35 mmol, 4 equiv) in dry THF (35 mL) was dropwise added *n*-BuLi (1.9 M in hexane, 12.3 mL, 23.35 mmol, 4 equiv). The resulting solution was stirred at −78 °C for 1 h. At −78 °C were successively added dropwise a solution of epoxide **4a** (2.83 g, 5.84 mmol, 1 equiv) in freshly distillated THF (35 mL) and $BF_3{\cdot}Et_2O$ (2.9 mL, 23.35 mmol, 4 equiv). The resulting solution was allowed to warm from −78 to −10 °C, and the mixture was diluted in DCM. A saturated aqueous solution of NH_4Cl was then added (20 mL), and the aqueous phase was extracted with DCM (3 × 40 mL). The combined organic phases were dried over Na_2SO_4, filtrated, and concentrated in vacuo. Flash chromatography of the residue (cyclohexane/EtOAc = 8/2 to 7/3) afforded **12** as a white powder (2.63 g, 77% yield): R_f = 0.60 (cyclohexane/EtOAc = 1/1); mp 192−196 °C; $[\alpha]_D$ − 5 (*c* 0.5, CH_2Cl_2); IR (film) 2954*m*, 2501*w*, 2857*m*, 1690*s*, 1472*m*; ^{1}H NMR δ 8.79 (br s, 1H, NH), 7.59 (d, 1H, $J_{H6\text{-}H5}$ = 8.0 Hz, H_6), 5.74 (dd, 1H, $J_{H5\text{-}H6}$ = 8.0 Hz, $J_{H5\text{-}NH}$ = 2.0 Hz, H_5), 5.48 (d, 1H, $J_{H1'\text{-}H2'}$ = 6.0 Hz, $H_{1'}$), 4.60 (dd, 1H, $J_{H2'\text{-}H1'}$ = 6.0 Hz, $J_{H2'\text{-}H3'}$ = 5.0 Hz, $H_{2'}$), 4.20−4.16 (m, 2H, $H_{3'}$, $H_{4'}$), 3.88−3.82 (m, 1H, $H_{5'}$), 3.57−3.50 (m, 1H, OH), 2.60 (dd, 1H, $J_{H6'a\text{-}H6'b}$ = 17.0 Hz, $J_{H6'a\text{-}H5'}$ = 7.0 Hz, $H_{6'a}$), 2.49 (dd, 1H, $J_{H6'b\text{-}H6'a}$ = 17.0 Hz, $J_{H6'b\text{-}H5'}$ = 8.0 Hz, $H_{6'b}$), 0.93 (s, 9H, -C(C$\underline{H}_3$)$_3$), 0.88 (s, 9H, -C(C$\underline{H}_3$)$_3$), 0.16 (s, 9H, -Si-(C$\underline{H}_3$)$_3$) 0.11, 0.06, 0.00, (3s, 12H, -(C$\underline{H}_3$)$_2$); ^{13}C NMR δ 163.1 (C_4), 150.4 (C_2), 143.5 (C_6), 102.7 ($C_{8'}$), 102.4 (C_5), 93.9 ($C_{1'}$), 87.6 ($C_{7'}$), 86.6 ($C_{4'}$), 73.3 ($C_{2'}$), 73.0 ($C_{3'}$), 69.9 ($C_{5'}$), 26.0, 25.9 (-C(C$\underline{H}_3$)$_3$), 25.8 ($C_{6'}$), 18.2, 18.0 (-$\underline{C}$(CH$_3$)$_3$), 0.19 (-($\underline{C}$H$_3$)$_3$), −4.3, −4.4, −4.5, −4.8 (-($\underline{C}$H$_3$)$_2$) HRMS APCI$^+$ calcd for $C_{27}H_{51}N_2O_6Si_3^+$ (M + H)$^+$ 583.3049, found 583.3055.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of all new compounds. X-ray crystallographic data of **4a** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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