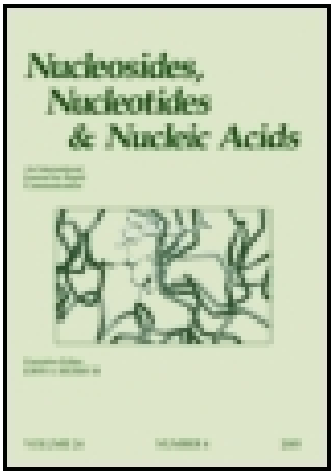

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Nucleosides and Nucleotides. 139. Stereoselective Synthesis of (2′S)-2′-C-Alkyl-2′-deoxyuridines

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NUCLEOSIDES AND NUCLEOTIDES. 139. STEREOSELECTIVE SYNTHESIS OF (2'*S*)-2'-*C*-ALKYL-2'-DEOXYURIDINES[#,1]

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Abstract: A synthetic method for (2'*S*)-2'-*C*-alkyl-2'-deoxyuridines (**9**) has been described. Catalytic hydrogenation of 1-[2-*C*-alkynyl-2-*O*-methoxalyl-3,5-*O*-TIPDS-β-D-*arabino*-pentofuranosyl]uracils (**5**) gave 1-[2-*C*-(2-alkyl)-2-*O*-methoxalyl-3,5-*O*-TIPDS-β-D-*arabino*-pentofuranosyl]uracils (**4**) as a major product, which were then subjected to the radical deoxygenation, affording (2'*S*)-2'-alkyl-2'-deoxy-3',5'-*O*-TIPDS-uridines (**7**) along with a small amount of their 2'*R* epimers.

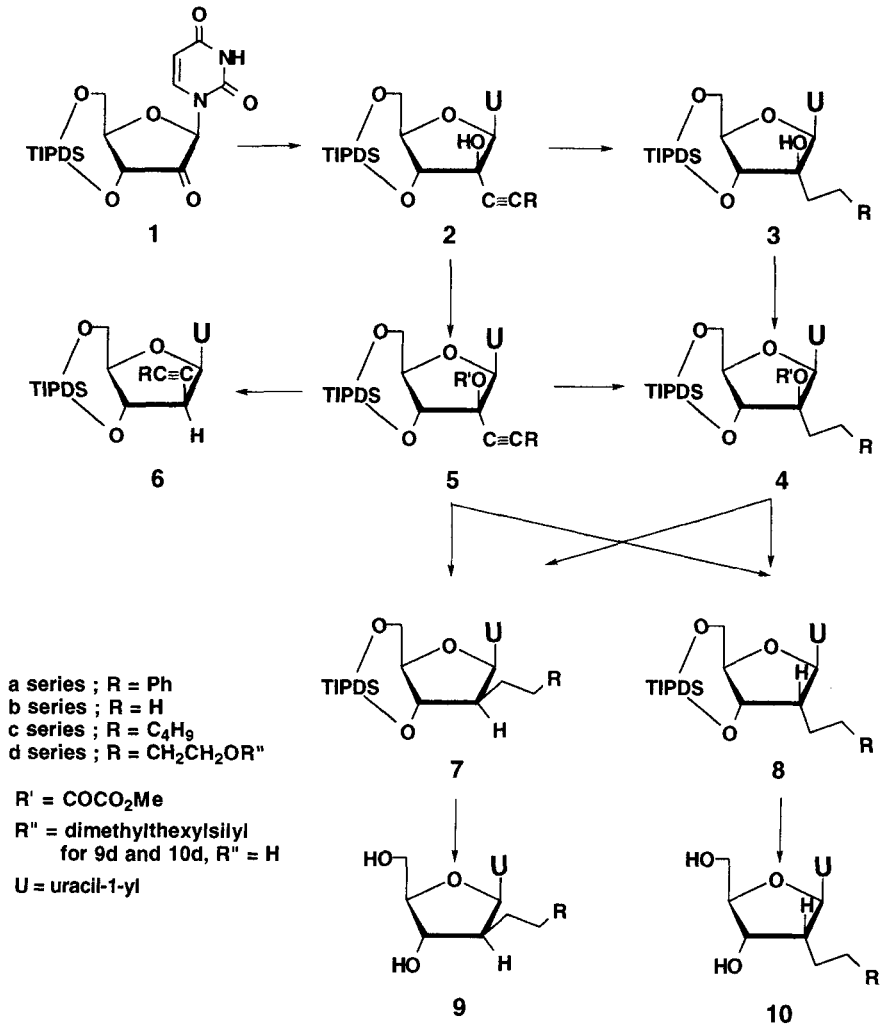
Radical deoxygenation of sugar hydroxyls of nucleosides is frequently used for preparation of biologically interesting nucleosides. Such reactions can also be used for the deoxygenation of tertiary hydroxyls in branched nucleosides, which are readily obtained by nucleophilic additions of carbanions to the corresponding ketones.[2] Alkyl addition reactions to 2'-keto nucleosides using MeMgBr, Me_3Al, or MeLi usually proceed from the α-face of the sugar moiety.[2,3] The resulting *tert*-alcohol is then converted into the corresponding methoxalyl ester, which is subjected to radical deoxygenation using Bu_3SnH in the presence of 2,2'-azobis(isobutyronitrile) (AIBN), giving highly stereoselectively (2'*S*)-2'-deoxy-2'-*C*-methyl derivatives.[2a,c,e,f] We have designed (2'*S*)-2'-deoxy-2'-*C*-methylcytidine (SMDC)[2a,e] as well as (2'*S*)-2'-deoxy-2'-*C*-fluoromethylcytidine (SFDC)[2g] as antimetabolites, and they showed tumor cell growth inhibitory activity spectra similar to that of 1-β-D-arabinofuranosylcytosine (araC), which is currently used as an antileukemic agent. We also reported that (2'*S*)-2'-deoxy-2'-*C*-methyl-5-iodouridine (SMIU)[2f] showed potent anti-HSV-1 activity *in vitro* without showing undesired host-cell toxicity. This

#This paper is dedicated to Dr. Yoshihisa Mizuno on the occasion of his 75th birthday.

stereoselective radical deoxygenation reaction is used for the deoxygenation of a cyanohydrin and a propargyl alcohol to synthesize 2'-*C*-cyano-2'-deoxy-1-β-D-arabinofuranosylcytosine (CNDAC),[4] a potent anti-solid-tumor nucleoside, and 2'-deoxy-2'-*C*-ethynyl nucleosides.[5] Thus, these sequential reactions are very useful for the synthesis of methyl, cyano, and ethynyl branched-sugar nucleosides. To examine structure-activity relationships of these branched-sugar nucleosides, we required other alkyl-branched sugar nucleosides. However, when the reagent of the alkyl addition reaction is expanded to other than a methyl carbanion, we have encountered some difficulties in introducing alkyls at the 2'-position. For example, the reaction of the 2'-ketone with EtMgBr or Et_3Al gave undesired secondary alcohols by nucleophilic additions of the β-hydride of the reagents.[2b] Since we found that lithium salts of alkynes readily added to the 2'-ketone from the α-face,[5b] these products can be used as synthons for the synthesis of (2'*S*)-2'-*C*-alkyl-2'-deoxyuridines. In this paper, we describe the stereoselective synthetic method for 2'-branched 2'-deoxyuridine derivatives.

We have reported that alkynyl groups were easily introduced at the 2'α-position when 1-[3,5-*O*-[tetraisopropyldisiloxan-1,3-diyl (TIPDS)]-β-D-*erythro*-2-pentulofuranosyl]]uracil (**1**) was treated with LiC≡CR.[5a,b] Although subsequent introduction of the methoxalyl group at the resulting 2'-*tert*-alcohol gave **5** in good yields, the radical deoxygenation of **5** with Bu_3SnH in the presence of AIBN gave a complex mixture,[5a,b] except that 2'-(trimethylsilyl)ethynyl derivative **5** afforded **6** (R = trimethylsilyl) in 68% yield. This would be due to addition of the Bu_3Sn group to the triple bond without regioselectivity. On the other hand, although catalytic reduction of **2** gave **3** without any problems, introduction of a methoxalyl group or phenoxythiocarbonyl group to the *tert*-alcohols in **3** was troublesome to give **4** even under forced conditions. We encountered such difficulties when the methoxalylation was tried to 4-ethoxy-1-[2-*C*-methyl-3,5-*O*-TIPDS-β-D-*arabino*-pentofuranosyl]-2(1*H*)pyrimidinone.[2e] However, 1-[2-*C*-methyl-3,5-*O*-TIPDS-β-D-*arabino*-pentofuranosyl]uracil derivatives were found to readily reacted with methoxalyl chloride in the presence of a stoichiometric amount of DMAP in CH_2Cl_2.[2f] These different reactivities would be interpreted by the Lewis basicity of the carbonyl oxygen at the 2-position. The 4-ethoxy group increases the Lewis basicity of the 2-carbonyl oxygen, and resulting strong intramolecular hydrogen bonding between the 2-carbonyl and the 2'β-hydroxyl group would prevent the acylation reaction. On the other hand, an increase in the bulkiness at the 2'α-substituent in **3** may also interfere with such reactions by steric hindrance. From these consideration, we next tried hydrogenation of **5** to obtain **4**, which then would afford the desired **7** by radical deoxygenation.

When **2a** was treated with methoxalyl chloride in the presence of DMAP and Et_3N in CH_2Cl_2, the desired ester **5a** was obtained quantitatively. Catalytic hydrogenation



Scheme 1.

of **5a** in the presence of 10% Pd/C in EtOAc under atmospheric H_2 pressure gave three products on TLC, which were separated on a silica gel column. A less polar product was assigned as the desired **4a** (65% yield). In its ^{1}H-NMR spectrum, one methyl proton due to the 2'-methoxalyl ester was observed at 3.86 ppm as a singlet, and phenethyl protons (at 7.14-7.29 ppm and 2.33-2.87 ppm) were also observed. More polar products, which were a mixture of **7a** and **8a** (15% yield), did not show methyl proton signals, and each

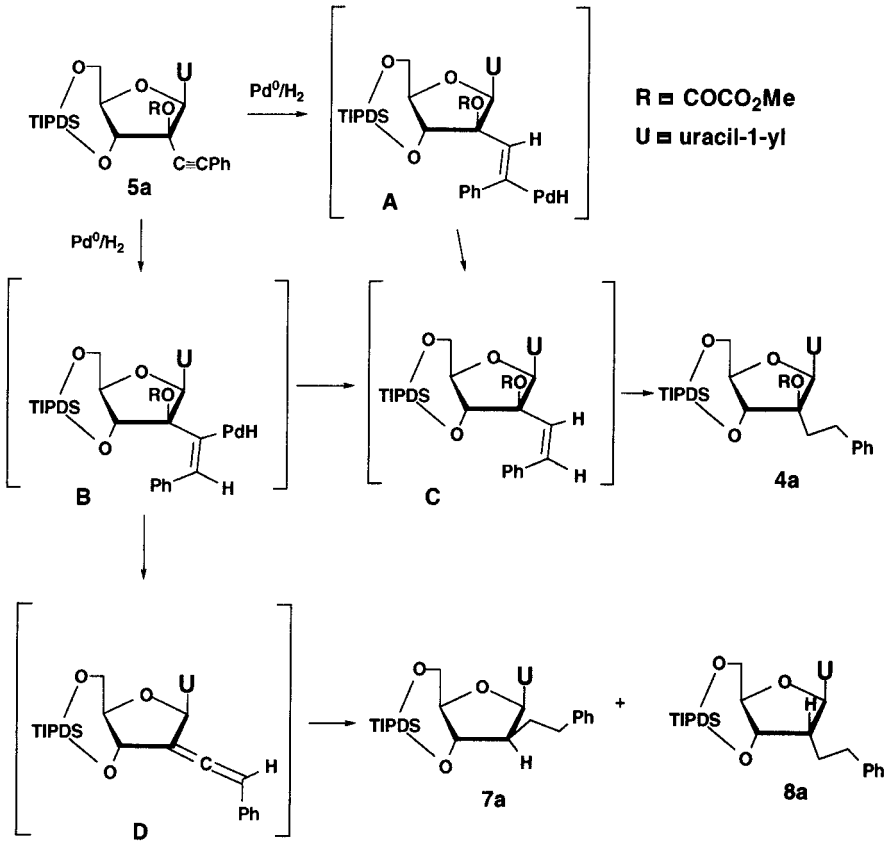
1'-proton was a doublet in its ^{1}H-NMR spectrum. The ratio of **7a** and **8a** was calculated as 1:1.6 from the peak area of each H-6 proton at 7.74 and 7.79 ppm, respectively.

A plausible mechanism of formation of **4a**, **7a**, and **8a** is shown in Scheme 2. Addition of $Pd^{II}H_2$ to the triple bond would give the intermediates **A** and **B**, and the palladium atom would be reductively eliminated to afford the intermediate **C**, which is then catalytically reduced to form the desired **4a**. On the other hand, β-elimination of HPd-$OCCO_2Me$ from **B** would give the intermediate **D**, which is then reduced to furnish **7a** and **8a**. Since we have found that catalytic reduction of 2'-deoxy-2'-methylidenecytidine gave both (2'*R* and *S*)-2'-deoxy-2'-*C*-methylcytidine (2'*R* > 2'*S*),[6] the ratio of **7a** and **8a** is consistent with this observation. Attempts to use other catalysts such as Rh and Pt derivatives did not improve the yield of **4a**.

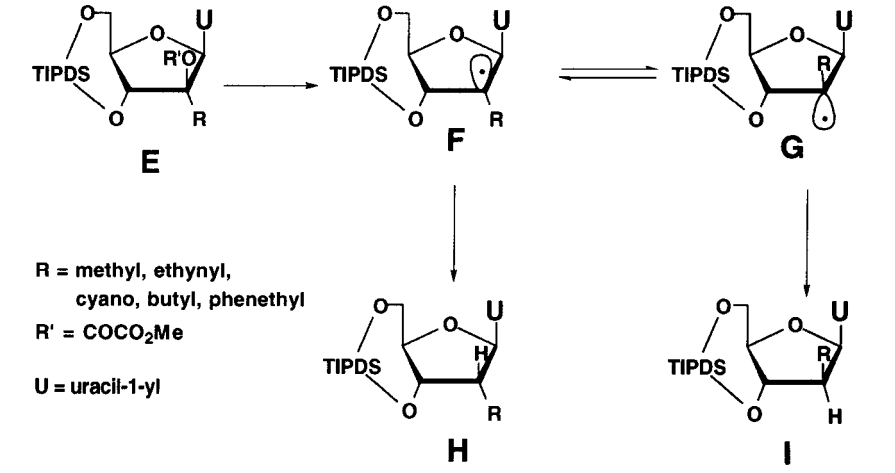
Radical deoxygenation of **4a** with Bu_3SnH in the presence of AIBN gave a mixture of **7a** and **8a** in a ratio of 7:1 in 80% yield. Since these products could not be separated at this stage, the mixture was then deprotected using tetrabutylammonium fluoride (TBAF) in THF, followed by separation using a semi-preparative HPLC column to afford **9a** and **10a**. The structure of these nucleosides were assigned using ^{1}H-NMR spectroscopy. In the spectra of **9a** and **10a**, the 1'-protons were detected at 6.23 and 5.91 ppm each as a doublet with $J_{1',2'}$ values of 7.7 and 9.3 Hz, respectively. Previously reported data of the $J_{1',2'}$ values for (2'*S*)-2'-deoxy-2'-*C*-methylcytidine hydrochloride and its 2'*R* epimer were 7.6 and 8.1 Hz, respectively. These values are consistent with each other. NOE experiments of **9a** and **10a** were also done for unambiguous structural identification. When we irradiated at the 1'-protons of **9a** and **10a**, increases were observed at the 2'-proton in 8.7 and 0.9%, respectively. Therefore, **9a** was assigned as (2'*S*)-2'-deoxy-2'-*C*-(2-phenethyl)uridine and **10a** as (2'*R*)-2'-deoxy-2'-*C*-(2-phenethyl)-uridine.

In a similar way, other nucleosides **5b-d** were catalytically reduced to give a mixture of **4**, **7**, and **8** in each series. Major products **4b-d** were subjected to the radical deoxygenation as described for **4a**, giving a mixture of **7** and **8** in each series, which were deprotected and separated by HPLC furnishing **9b-d** and **10b-d**.

As shown in Scheme 3, in the radical deoxygenation reaction of 2'-*tert*-hydroxyl in **E**, the 2'-radical intermediate would be in an equilibrium between **F** and **G**. The β-face of the sugar moiety of the intermediates would be more hindered than the α-face so that the intermediate **G** would react with Bu_3SnH more readily than **F** to give selectively the 2'*S*-product **I**. In our previous studies, the 2'*S*-product **I** was obtained as a sole product when the 2'-substituent is not bulky, such as methyl,[2a,c,e,f] cyano,[4] and 2'-(trimethylsilyl)ethynyl[5a] groups. In the present case, the 2'-substituents such as



Scheme 2.



Scheme 3.

phenethyl, butyl, and silyloxybutyl groups are thought to be bulkier than the above substituents. Since the steric repulsion between the 2'-substituent and the uracil moiety in **G** would be expected, the intermediate **F** would be predominant in the equilibrium. Consequently, the 2'*R*-products **H** from **F** are produced in some extent, although significant steric hindrance may exist when the intermediate **F** reacts with Bu_3SnH.

EXPERIMENTAL SECTION

General Methods. Melting points were measured on a Yanagimoto MP-3 micromelting point apparatus and are uncorrected. The ^{1}H-NMR spectra were recorded on a Jeol JNM-EX270 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (δ), and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad). All exchangeable protons were detected by addition of D_2O. UV absorption spectra were recorded with a Shimadzu UV-240 spectrophotometer. Mass spectra (MS) were measured on a Jeol JMX-DX303 spectrometer. TLC was done on Merck Kieselgel F254 precoated plates. Silica gel used for column chromatography was YMC gel 60A (70-230 mesh).

1-[2-*O*-Methoxalyl-2-*C*-(2-phenylethynyl)-3,5-*O*-TIPDS-β-D-*arabino*-pentofuranosyl]uracil (5a). Methoxalyl chloride (1.1 mL, 11.6 mmol) was added to a mixture of **2a**[5b] (2.0 g, 3.4 mmol) and DMAP (1.4 g, 11.6 mmol) in CH_2Cl_2 (20 mL) at 0 °C under Ar. After being stirred for 4 h at 0 °C, the mixture was washed with H_2O (15 mL x 3). The separated organic phase was dried (Na_2SO_4) and concentrated to dryness *in vacuo*. The residue was purified on a silica gel column (2.8 x 16 cm) with 40% EtOAc in hexane to give **5a** (2.3 g, 100% as a white foam): EI-MS *m/z* 673 (M^+); ^{1}H-NMR ($CDCl_3$) 8.05 (1 H, br s, 3-NH), 7.59 (1 H, d, H-6, $J_{6,5}$ = 8.1 Hz), 7.48-7.28 (5 H, m, 2'-Ph), 6.56 (1 H, s, H-1'), 5.72 (1 H, dd, H-5, $J_{5,6}$ = 8.1, $J_{5,NH}$ = 2.2 Hz), 4.69 (1 H, d, H-3', $J_{3',4'}$ = 5.9 Hz), 4.14 (1 H, dd, H-5'a, $J_{a,b}$ = 11.7, $J_{a,4'}$ = 3.3 Hz), 4.08-4.02 (1 H, ddd, H-4', $J_{4',3'}$ = 5.9, $J_{4',5'a}$ = 3.3, $J_{4',5'b}$ = 6.2 Hz), 3.84 (1 H, dd, H-5'b, $J_{b,4'}$ = 6.2, $J_{b,a}$ = 11.7 Hz), 3.89 (3 H, s, 2'-OCOCO$_2$Me), 1.15-1.04 (28 H, m, iPr). Anal. Calcd for $C_{32}H_{44}N_2O_{10}Si_2$: C, 57.12; H, 6.59; N, 4.16. Found: C, 56.98; H, 6.64; N, 4.11.

1-[2-*C*-Ethynyl-2-*O*-methoxalyl-3,5-*O*-TIPDS-β-D-*arabino*-pentofuranosyl]-uracil (5b). Compound **2b**[5b] (2.0 g, 3.9 mmol) was converted to **5b** (2.4 g, 100% as a white foam) as described for the synthesis of **5a**. Physical data for **5b**: EI-MS *m/z* 597 (M^++1); ^{1}H-NMR ($CDCl_3$) 8.44 (1 H, br s, 3-NH), 7.53 (1 H, d, H-6, $J_{6,5}$ = 8.1 Hz), 6.50 (1 H, s, H-1'), 5.72 (1 H, d, H-5, $J_{5,6}$ = 8.1 Hz), 4.62 (1 H, d, H-3', $J_{3',4'}$ = 6.2 Hz), 4.10 (1 H, dd, H-5'a, $J_{a,b}$ = 11.4, $J_{a,4'}$ = 2.6 Hz), 4.02-3.90 (1 H, m, H-4'), 3.94 (1 H, dd, H-5'b, $J_{b,4'}$ = 3.3, $J_{b,a}$ = 11.4 Hz), 3.89 (3 H, s, 2'-OCOCO$_2$Me), 2.89 (1 H, s, 2'-C≡CH),

1.10-1.05 (28 H, m, iPr). Anal. Calcd for $C_{26}H_{40}N_2O_{10}Si_2$: C, 52.33; H, 6.76; N, 4.69. Found: C, 52.22; H, 6.76; N, 4.57.

1-[2-*C*-Hexynyl-2-*O*-methoxalyl-3,5-*O*-TIPDS-β-D-*arabino*-pentofuranosyl]-uracil (5c). Compound **2c**[5b] (2.0 g, 3.5 mmol) was converted to **5c** (2.1 g, 92% as a white foam) as described for the synthesis of **5a**. Physical data for **5c**: EI-MS *m/z* 652 (M^+), 602 (M^+-iPr); ^{1}H-NMR ($CDCl_3$) 8.26 (1 H, br s, 3-NH), 7.55 (1 H, d, H-6, $J_{6,5}$ = 8.1 Hz), 6.44 (1 H, s, H-1'), 5.70 (1 H, dd, H-5, $J_{5,6}$ = 8.1, $J_{5,NH}$ = 1.5 Hz), 4.57 (1 H, d, H-3', $J_{3',4'}$ = 6.2 Hz), 4.21-3.90 (3 H, m, H-4', 5'a,b), 3.88 (3 H, s, 2'-OCOCO$_2$Me), 2.27 (2 H, t, 2'-C≡CC*H*$_2$CH$_2$CH$_2$CH$_3$), 1.54-1.29 (4 H, m, 2'-C≡CCH$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.10-1.03 (28 H, m, iPr), 0.89 (3 H, t, 2'-C≡CCH$_2$CH$_2$CH$_2$C*H*$_3$).

1-[2-*C*-(4-Dimethylthexylsilyloxy-1-butynyl)-2-*O*-methoxalyl-3,5-*O*-TIPDS-β-D-*arabino*-pentofuranosyl]uracil (5d). A hexane solution of BuLi (1.56 M, 6.2 mL, 10 mmol) was added dropwise over 50 min to a solution of 4-dimethylthexylsilyloxy-1-butyne (2.1 g, 10 mmol, prepared from 3-butyn-1-ol and dimethylthexyl chloride) in THF (10 mL) at -78 °C under Ar. A solution of **1** (0.97 g, 2 mmol) in THF (5 mL) was added dropwise over 15 min to the above solution at -78 ° C. The whole was stirred for 75 min at -78 °C and was quenched by addition of aqueous 1 M NH_4Cl (20 mL). The mixture was extracted with EtOAc (3 x 25 mL). The separated organic phase was further washed with brine (30 mL), dried (Na_2SO_4), and concentrated to dryness. The residue was purified on a silica gel column (2.8 x 6 cm) with 30% EtOAc in hexane to give **2d** (1.2 g, 88%, as a foam); EI-MS *m/z* 696 (M^+); ^{1}H-NMR ($CDCl_3$) 8.30 (1 H, br s, 3-NH), 7.87 (1 H, d, H-6, $J_{6,5}$ = 8.2 Hz), 6.00 (1 H, s, H-1'), 5.68 (1 H, dd, H-5, $J_{5,6}$ = 8.2, $J_{5,NH}$ = 2.2 Hz), 4.29-3.93 (4 H, m, H-3', 4', 5'a,b), 3.72 (2 H, t, 2'-C≡CC*H*$_2$CH$_2$OSi, *J* = 7.1 Hz), 2.87 (1 H, br s, 2'-OH), 2.49 (2 H, t, 2'-C≡CCH$_2$C*H*$_2$OSi, *J* = 7.1 Hz), 1.66-1.56 (1 H, m, 2'-SiCMe$_2$C*H*Me$_2$), 1.10-1.04 (28 H, m, iPr), 0.89-0.84 (12 H, m, Me x 4), 0.10-0.07 (6 H, m, Me x 2). Compound **2d** (2.5 g, 3.6 mmol) was converted to **5d** (2.7 g, 95% as a white foam) as described for the synthesis of **5a**. Physical data for **5d**: EI-MS *m/z* 739 (M^+-iPr), 693 (M^+-thexyl); ^{1}H-NMR ($CDCl_3$) 9.88 (1 H, br s, 3-NH), 7.54 (1 H, d, H-6, $J_{6,5}$ = 8.1 Hz), 6.42 (1 H, s, H-1'), 5.70 (1 H, dd, H-5, $J_{5,6}$ = 8.1, $J_{5,NH}$ = 1.5 Hz), 4.57 (1 H, d, H-3', $J_{3',4'}$ = 6.2 Hz), 4.10-3.90 (3 H, m, H-4', 5'a,b), 3.87 (3 H, s, 2'-OCOCO$_2$Me), 3.68 (2 H, t, 2'-C≡CC*H*$_2$CH$_2$OSi, *J* = 7.3 Hz), 2.47 (2 H, t, 2'-C≡CCH$_2$C*H*$_2$OSi, *J* = 7.3 Hz), 1.64-1.54 (1 H, m, 2'-SiCMe$_2$C*H*Me$_2$), 1.41-0.75 (40 H, m, iPr, Me x 4), 0.07 (6 H, s, Me x 2).

Catalytic Reduction of 5a. A suspension of **5a** (2 g, 3 mmol) and 10% Pd/C (202 mg) in EtOAc (40 mL) was stirred for 23 h at room temperature under atmospheric pressure of H_2. Insoluble materials were removed by filtration through a Celite pad,

which was washed well with EtOAc. Combined filtrate and washings were concentrated *in vacuo* and the residue was purified on a silica gel column (2.8 x 20 cm) with 16% EtOAc in hexane to give 1-[2-*O*-methoxalyl-2-*C*-(2-phenethyl)-3,5-*O*-TIPDS-β-D-*arabino*-pentofuranosyl]-uracil (**4a**, 1.2 g, 60% as a white foam). A further elution of the column with 18% EtOAc in hexane gave a mixture of (2'*R*)-2'-deoxy-2'-*C*-(2-phenethyl)-3',5'-*O*-TIPDS-uridine (**8a**) and (2'*S*)-2'-deoxy-2'-*C*-(2-phenethyl)-3',5'-*O*-TIPDS-uridine (**7a**) (257 mg, 15% as a foam; the ratio of **8a**:**7a** was 1.6:1). Physical data for **4a**: EI-MS *m/z* 633 (M^+-iPr); ^{1}H-NMR ($CDCl_3$) 8.83 (1 H, br s, 3-NH), 7.65 (1 H, d, H-6, $J_{6,5}$ = 8.1 Hz), 7.29-7.14 (5 H, m, 2'-Ph), 6.27 (1 H, s, H-1'), 5.74 (1 H, dd, H-5, $J_{5,6}$ = 8.1, $J_{5,NH}$ = 2.2 Hz), 4.71 (1 H, d, H-3', $J_{3',4'}$ = 6.2 Hz), 4.14 (1 H, dd, H-5'a, $J_{a,b}$ = 12.7, $J_{a,4'}$ = 3.3 Hz), 3.94 (1 H, dd, H-5'b, $J_{b,4'}$ = 5.5, $J_{b,a}$ = 12.7 Hz), 3.89-3.61 (1 H, m, H-4'), 3.86 (3 H, s, 2'-OCOCO$_2$Me), 2.87-2.33 (4 H, m, 2'-CH_2CH_2Ph), 1.08-1.05 (28 H, m, iPr). Anal. Calcd for $C_{32}H_{48}N_2O_{10}Si_2$: C, 56.78; H, 7.15; N, 4.14. Found: C, 56.48; H, 7.11; N, 4.16.

Catalytic Reduction of 5b. As described for the reduction of **5a**, **5b** (2.1 g, 3.6 mmol) was hydrogenated in the presence of 10% Pd/C (200 mg) in EtOAc (40 mL) for 18 h at room temperature to give 1-[2-*C*-ethyl-2-*O*-methoxalyl-3,5-*O*-TIPDS-β-D-*arabino*-pentofuranosyl]uracil (**4b**, 752 mg, 35% as a foam) and a mixture of (2'*R*)-2'-deoxy-2'-*C*-ethyl-3',5'-*O*-TIPDS-uridine (**8b**) and (2'*S*)-2'-deoxy-2'-*C*-ethyl-3',5'-*O*-TIPDS-uridine (**7b**) (701 mg, as a foam, 2:1). Physical data for **5b**: EI-MS *m/z* 601 (M^++1), 557 (M^+-iPr); ^{1}H-NMR ($CDCl_3$) 8.11 (1 H, br s, 3-NH), 7.64 (1 H, d, H-6, $J_{6,5}$ = 8.4 Hz), 6.15 (1 H, s, H-1'), 5.71 (1 H, dd, H-5, $J_{5,6}$ = 8.4, $J_{5,NH}$ = 2.2 Hz), 4.67 (1 H, d, H-3', $J_{3',4'}$ = 5.9 Hz), 4.16-3.81 (3 H, m, H-4', 5'a,b), 3.88 (3 H, s, 2'-OCOCO$_2$Me), 2.66-2.05 (2 H, m, 2'-CH_2CH$_3$), 1.08-0.99 (28 H, m, iPr), 0.92 (3 H, t, 2'-CH$_2$CH_3).

Catalytic Reduction of 5c. As described for the reduction of **5a**, **5c** (219 mg, 0.34 mmol) was hydrogenated in the presence of 10% Pd/C (26 mg) in EtOAc (10 mL) for 48 h at room temperature to give 1-[2-*C*-hexyl-2-*O*-methoxalyl-3,5-*O*-TIPDS-β-D-*arabino*-pentofuranosyl]uracil (**4c**, 118 mg, 54% as foam) and a mixture of (2'*R*)-2'-deoxy-2'-*C*-hexyl-3',5'-*O*-TIPDS-uridine (**8c**) and (2'*S*)-2'-deoxy-2'-*C*-hexyl-3',5'-*O*-TIPDS-uridine (**7c**) (68 mg, 37% as a foam, 1.8:1). Physical data for **5c**: EI-MS *m/z* 613 (M^+-iPr); ^{1}H-NMR ($CDCl_3$) 8.13 (1 H, br s, 3-NH), 7.62 (1 H, d, H-6, $J_{6,5}$ = 8.1 Hz), 6.15 (1 H, s, H-1'), 5.70 (1 H, dd, H-5, $J_{5,6}$ = 8.1, $J_{5,NH}$ = 2.2 Hz), 4.65 (1 H, d, H-3', $J_{3',4'}$ = 5.5 Hz), 4.16-4.08 (1 H, m, H-4'), 3.96-3.81 (2 H, m, H-5'a,b), 3.87 (3 H, s, 2'-OCOCO$_2$Me), 2.51-2.02 (2 H, m, 2'-CH_2C$_5$H$_{11}$), 1.76-0.84 (39 H, m, iPr, 2'-CH$_2$C$_5$H$_{11}$).

Catalytic Reduction of 5d. As described for the reduction of **5a**, **5d** (2.65 g, 3.4 mmol) was hydrogenated in the presence of 10% Pd/C (260 mg) in EtOAc (45 mL) for 18 h at room temperature to give 1-[2-*C*-(4-dimethylthexyloxybutyl)-2-*O*-methoxalyl-3,5-

O-TIPDS-β-D-*arabino*-pentofuranosyl]uracil (**4d**, 910 mg, 34% as a foam) and a mixture of (2'*R*)-2'-deoxy-2'-*C*-(4-dimethylthexyloxybutyl)-3',5'-*O*-TIPDS-uridine (**8d**) and (2'*S*)-2'-deoxy-2'-*C*-(4-dimethylthexyloxybutyl)-3',5'-*O*-TIPDS-uridine (**7d**) (908 mg, 39% as a foam, 1.8:1). Physical data for **5c**: EI-MS *m/z* 787 (M^++1), 771 (M^+-Me), 743 (M^+-iPr); ^{1}H-NMR ($CDCl_3$) 8.16 (1 H, br s, 3-NH), 7.63 (1 H, d, H-6, $J_{6,5}$ = 8.4 Hz), 6.14 (1 H, s, H-1'), 5.70 (1 H, dd, H-5, $J_{5,6}$ = 8.4, $J_{5,NH}$ = 2.2 Hz), 4.66 (1 H, d, H-3', $J_{3',4'}$ = 5.9 Hz), 4.14-3.89 (3 H, m, H-4', 5'a,b), 3.86 (3 H, s, 2'-$OCOCO_2Me$), 3.54 (2 H, t, 2'-C≡CCH_2-, J = 6.2 Hz), 2.63-2.01 (2 H, m, 2'-C≡CCH_2CH_2-), 1.88-0.81 (45 H, m, iPr, 2'-$CH_2CH_2C_2H_4OSiMe_2CMe_2CHMe_2$), 0.04 (6 H, m, Me x 2).

Radical Deoxygenation of 4a. A mixture of AIBN (21 mg), and Bu_3SnH (0.48 mL, 1.8 mmol) in toluene (20 mL) was added dropwise over 50 min to a solution of **4a** (600 mg, 0.88 mmol) in toluene (30 mL) at 75 °C under Ar. After being stirred for 2.5 h, further amounts of AIBN (12 mg) and Bu_3SnH (0.24 mL, 0.88 mmol) was added and the mixture was continued to heating for 2 h. The solvent was removed *in vacuo* and the residue was purified on a silica gel column (2.8 x 20 cm) with 20% EtOAc in hexane to give a 1:6.9 mixture of **8a** and **7a** (406 mg, 80% as a white foam). Physical data for the mixture of **7a** and **8a**: EI-MS *m/z* 574 (M^+); ^{1}H-NMR (assignment of the major isomer **7a** was described, $CDCl_3$) 8.58 (1 H, br s, 3-NH), 7.74 (1 H, d, H-6, $J_{6,5}$ = 8.1 Hz), 7.31-7.12 (5 H, m, 2'-Ph), 6.37 (1 H, d, H-1', $J_{1',2'}$ = 7.3 Hz), 5.69 (1 H, dd, H-5, $J_{5,6}$ = 8.1, $J_{5,NH}$ = 2.2 Hz), 4.18-4.11 (2 H, m, H-3', 5'a), 4.03 (1 H, dd, H-5'b, $J_{b,4'}$ = 2.9, $J_{b,a}$ = 13.6 Hz), 3.73 (1 H, ddd, H-4', $J_{4',3'}$ = 8.4, $J_{4',5'b}$ = 1.7 Hz), 2.87-2.66 (2 H, m, 2'-CH_2CH_2Ph), 2.64-2.52 (1 H, m, H-2'), 1.92-1.32 (2 H, m, 2'-CH_2CH_2Ph), 1.10-1.03 (28 H, m, iPr). Anal. Calcd for $C_{29}H_{46}N_2O_6Si_2$: C, 60.59; H, 8.07; N, 4.87. Found: C, 60.68; H, 8.22; N, 4.76.

Radical Deoxygenation of 4b. As described for the deoxygenation of **4a**, **4b** (638 mg, 1.1 mmol) was deoxygenated in the presence of AIBN (15 mg) and Bu_3SnH (0.63 mL, 2.3 mmol) in toluene (30 mL) for 8 h at 70 °C to give a mixture of **8b** and **7b** (372 mg, 70% as a foam, 1:6.4). Physical data for the mixture **7b** and **8b**: EI-MS *m/z* 499 (M^++1), 455 (M^+-iPr); ^{1}H-NMR (assignment of the major isomer **7b** was described, $CDCl_3$) 8.06 (1 H, br s, 3-NH), 7.70 (1 H, d, H-6, $J_{6,5}$ = 8.1 Hz), 6.33 (1 H, d, H-1', $J_{1',2'}$ = 7.3 Hz), 5.69 (1 H, dd, H-5, $J_{5,6}$ = 8.1, $J_{5,NH}$ = 2.2 Hz), 4.15-4.08 (2 H, m, H-3', 5'a), 4.02 (1 H, dd, H-5'b, $J_{b,4'}$ = 2.9, $J_{b,a}$ = 13.2 Hz), 3.75-3.71 (1 H, m, H-4'), 2.53-2.41 (1 H, m, H-2'), 1.67-0.83 (33 H, m, iPr, 2'-Et).

Radical Deoxygenation of 4c. As described for the deoxygenation of **4a**, **4c** (500 mg, 0.76 mmol) was deoxygenated in the presence of AIBN (15 mg) and Bu_3SnH (0.45 mL, 1.7 mmol) in toluene (20 mL) for 9 h at 70 °C to give a mixture of **8c** and **7c** (293 mg, 70% as a foam, 1:7.3). Physical data for the mixture of **7c** and **8c**: EI-MS *m/z*

511 (M^+-iPr); ^{1}H-NMR (assignment of the major isomer **7c** was described, $CDCl_3$) 8.18 (1 H, br s, 3-NH), 7.70 (1 H, d, H-6, $J_{6,5}$ = 8.1 Hz), 6.31 (1 H, d, H-1', $J_{1',2'}$ = 7.3 Hz), 5.69 (1 H, dd, H-5, $J_{5,6}$ = 8.1, $J_{5,NH}$ = 2.2 Hz), 4.14-4.07 (2 H, m, H-3', 5'a, $J_{3',4'}$ = 8.4, $J_{a,b}$ = 13.2 Hz), 4.02 (1 H, dd, H-5'b, $J_{b,4'}$ = 2.6, $J_{b,a}$ = 13.2 Hz), 3.78-3.61 (1 H, m, H-4'), 2.58-2.47 (1 H, m, H-2'), 1.68-0.84 (41 H, m, iPr, 2'-C_6H_{13}).

Radical Deoxygenation of 4d. As described for the deoxygenation of **4a**, **4d** (740 mg, 0.94 mmol) was deoxygenated in the presence of AIBN (15 mg) and Bu_3SnH (0.56 mL, 2.1 mmol) in toluene (35 mL) for 8 h at 70 °C to give a mixture of **8d** and **7d** (355 mg, 55% as a foam, 1:7.7). Physical data for the mixture of **7d** and **8d**: EI-MS *m/z* 641 (M^+-iPr); ^{1}H-NMR (assignment of the major isomer **7d** was described, $CDCl_3$) 8.18 (1 H, br s, 3-NH), 7.70 (1 H, d, H-6, $J_{6,5}$ = 8.4 Hz), 6.30 (1 H, d, H-1', $J_{1',2'}$ = 7.3 Hz), 5.68 (1 H, dd, H-5, $J_{5,6}$ = 8.4, $J_{5,NH}$ = 2.2 Hz), 4.14-4.07 (2 H, m, H-3', 5'a, $J_{3',4'}$ = 8.4, $J_{a,b}$ = 13.9 Hz), 4.02 (1 H, dd, H-5'b, $J_{b,4'}$ = 2.6, $J_{b,a}$ = 13.9 Hz), 3.72 (1 H, m, H-4'), 3.53-3.51 (2 H, m, 2'-CH_2-), 2.53-2.47 (1 H, m, H-2'), 1.65-0.82 (47 H, m, iPr, 2'-$CH_2C_3H_6OSiMe_2CMe_2CHMe_2$), 0.06 (6 H, m, Me x 2).

(2'*R*)-2'-Deoxy-2'-*C*-(2-phenethyl)uridine (10a) and (2'*S*)-2-deoxy-2-*C*-(2-phenethyl)uridine (9a). A solution of the above mixture (385 mg, 0.67 mmol) in THF (15 mL) was treated with TBAF (1 M THF solution, 1.4 mL, 1.4 mmol) for 10 min at room temperature. AcOH (80 mL, 1.4 mmol) was added to the mixture and the solvent was removed *in vacuo*. The residue was purified on a silica gel column (1.8 x 11 cm) with 4% EtOH in $CHCl_3$ to give a mixture of **9a** and **10a** (221 mg, 99% as a solid), which was separated by HPLC (YMC D-ODS-5, 2 x 25 cm, 30% MeOH in H_2O, 6.5 mL/min). From the peak corresponding to the retention time at 91 min, **10a** (24 mg, 11% as a white foam) was obtained and from the retention time at 99 min, **9a** (156 mg, 71% as a white foam) was obtained. Physical data for **10a**: EI-MS *m/z* 332 (M^+); ^{1}H-NMR (DMSO-d_6) 11.30 (1 H, br s, 3-NH), 7.79 (1 H, d, H-6, $J_{6,5}$ = 8.1 Hz), 7.35-7.13 (5 H, m, 2'-Ph), 5.91 (1 H, d, H-1', $J_{1',2'}$ = 9.3 Hz), 5.63 (1 H, d, H-5, $J_{5,6}$ = 8.1 Hz), 5.30 (1 H, d, 3'-OH, $J_{OH,3'}$ = 5.0 Hz), 5.03 (1 H, t, 5'-OH), 4.19 (1 H, dd, H-3', $J_{3',OH}$ = 5.0, $J_{3',2'}$ = 4.4 Hz), 3.86 (1 H, br s, H-4'), 3.55 (2 H, t, H-5'), 2.70-2.59 (2 H, m, 2'-CH_2CH_2Ph), 2.25-2.11 (1 H, m, H-2'), 1.92-1.42 (2 H, m, 2'-CH_2CH_2Ph). HREI-MS (M^+): Calcd for $C_{17}H_{20}N_2O_5$: 332.1372. Found: 332.1371. Physical data for **9a**: EI-MS *m/z* 332 (M^+); ^{1}H-NMR (DMSO-d_6) 11.37 (1 H, br s, 3-NH), 7.89 (1 H, d, H-6, $J_{6,5}$ = 8.2 Hz), 7.35-7.10 (5 H, m, 2'-Ph), 6.23 (1 H, d, H-1', $J_{1',2'}$ = 7.7 Hz), 5.61 (1 H, d, H-5, $J_{5,6}$ = 8.2 Hz), 5.40 (1 H, d, 3'-OH, $J_{OH,3'}$ = 5.0 Hz), 5.09 (1 H, t, 5'-OH), 3.93 (1 H, ddd, H-3', $J_{3',OH}$ = 6.0, $J_{3',4'}$ = $J_{3',2'}$ = 8.2 Hz), 3.77-3.57 (3 H, m, H-4', 5'), 2.64-2.58 (2 H, m, 2'-CH_2CH_2Ph), 2.44-2.32 (1 H, m, H-2', $J_{2',1'}$ = 7.7, $J_{2',3'}$ = 8.2 Hz), 1.71-1.35 (2 H, m, 2'-CH_2CH_2Ph).

Anal. Calcd for $C_{17}H_{20}N_2O_5$ 1/10 H_2O: C, 61.11; H, 6.09; N, 8.38. Found: C, 61.05; H, 6.16; N, 8.29.

(2'*R*)-2'-Deoxy-2'-*C*-ethyluridine (10b) and (2'*S*)-2'-deoxy-2'-*C*-ethyluridine (9b). A mixture of **7b** and **8b** (357 mg, 0.72 mmol) obtained by radical deoxygenation was deprotected as described for the synthesis of **9a** and **10a** to give a mixture of **9b** and **10b** (196 mg, 100% as a foam) after purification by short column chromatography. These nucleosides were then separated by HPLC (YMC D-ODS-5, 2 x 25 cm, 10% MeOH in H_2O, 9.9 mL/min). From the peak corresponding to the retention time at 26 min, **10b** (11 mg, 6% as a white foam) was obtained and from the retention time at 36 min, **9b** (124 mg, 63% as a white foam) was obtained. Physical data for **10b**: EI-MS *m/z* 256 (M^+); ^{1}H-NMR (DMSO-d_6) 11.29 (1 H, br s, 3-NH), 7.84 (1 H, d, H-6, $J_{6,5}$ = 8.1 Hz), 5.87 (1 H, d, H-1', $J_{1',2'}$ = 9.3 Hz), 5.66 (1 H, d, H-5, $J_{5,6}$ = 8.1 Hz), 5.19 (1 H, d, 3'-OH, $J_{OH,3'}$ = 4.9 Hz), 5.03 (1 H, t, 5'-OH), 4.12 (1 H, dd, H-3', $J_{3',OH}$ = 4.9, $J_{3',2'}$ = 5.0 Hz), 3.83 (1 H, dd, H-4', $J_{4',5'a}$ = 4.3, $J_{4',5'b}$ = 3.9 Hz), 3.53 (2 H, m, H-5'), 2.07-2.01 (1 H, m, H-2'), 1.60-1.17 (2 H, m, 2'-CH_2CH$_3$), 0.87-0.82 (3 H, m, 2'-CH$_2$CH_3). HREI-MS (M^+): Calcd for $C_{11}H_{16}N_2O_5$: 256.1059. Found: 256.1050. Physical data for **9b**: EI-MS *m/z* 256 (M^+); ^{1}H-NMR (DMSO-d_6) 11.31 (1 H, br s, 3-NH), 7.84 (1 H, d, H-6, $J_{6,5}$ = 8.2 Hz), 6.18 (1 H, d, H-1', $J_{1',2'}$ = 7.7 Hz), 5.60 (1 H, d, H-5, $J_{5,6}$ = 8.2 Hz), 5.30 (1 H, d, 3'-OH), 5.06 (1 H, t, 5'-OH), 3.86 (1 H, ddd, H-3', $J_{3',OH}$ = 6.1, $J_{3',4'}$ = 8.8, $J_{3',2'}$ = 7.7 Hz), 3.90-3.56 (3 H, m, H-4', 5'), 2.30-2.24 (1 H, m, H-2', $J_{2',1'}$ = 7.7, $J_{2',3'}$ = 8.8 Hz), 1.39-1.11 (2 H, m, 2'-CH_2CH$_3$), 0.92-0.86 (3 H, m, 2'-CH$_2$CH_3). Anal. Calcd for $C_{11}H_{16}N_2O_5$ 1/10 H_2O: C, 51.20; H, 6.33; N, 10.86. Found: C, 51.20; H, 6.34; N, 10.60.

(2'*R*)-2'-Deoxy-2'-*C*-hexyluridine (10c) and (2'*S*)-2'-deoxy-2'-*C*-hexyluridine (9c). A mixture of **7c** and **8c** (289 mg, 0.52 mmol) obtained by radical deoxygenation was deprotected as described for the synthesis of **9a** and **10a** to give a mixture of **9c** and **10c** (149 mg, 92% as a foam) after purification by short column chromatography. These nucleosides were then separated by HPLC (YMC D-ODS-5, 2 x 25 cm, 40% MeOH in H_2O, 9.9 mL/min). From the peak corresponding to the retention time at 56 min, **10c** (10 mg, 7% as a white foam) was obtained and from the retention time at 36 min, **9c** (95 mg, 64% as a white foam) was obtained. Physical data for **10c**: EI-MS *m/z* 312 (M^+); ^{1}H-NMR (DMSO-d_6) 11.32 (1 H, br s, 3-NH), 7.89 (1 H, d, H-6, $J_{6,5}$ = 8.2 Hz), 5.86 (1 H, d, H-1', $J_{1',2'}$ = 10.4 Hz), 5.63 (1 H, d, H-5, $J_{5,6}$ = 8.2 Hz), 5.25 (1 H, d, 3'-OH), 5.02 (1 H, t, 5'-OH), 4.12 (1 H, dd, H-3', $J_{3',OH}$ = 4.9, $J_{3',2'}$ = 5.0 Hz), 3.87-3.83 (1 H, m, H-4'), 3.53 (2 H, m, H-5'), 2.35-2.14 (1 H, m, H-2'), 1.37-1.10 (10 H, m, 2'-C$_5H_{10}$CH$_3$), 0.87-0.82 (3 H, m, 2'-C$_5$H$_{10}$CH_3). HREI-MS (M^+): Calcd for $C_{15}H_{24}N_2O_5$: 312.1685. Found: 312.1671. Physical data for **9c**: EI-MS *m/z* 312 (M^+); ^{1}H-NMR (DMSO-d_6) 11.30 (1 H, br s, 3-NH), 7.82 (1 H, d, H-6, $J_{6,5}$ = 8.2 Hz), 6.17 (1 H, d, H-1', $J_{1',2'}$ = 7.7

Hz), 5.60 (1 H, d, H-5, $J_{5,6}$ = 8.2 Hz), 5.28 (1 H, d, 3'-OH), 5.03 (1 H, t, 5'-OH), 3.88-3.80 (1 H, m, H-3'), 3.74-3.55 (3 H, m, H-4', 5'), 2.44-2.24 (1 H, m, H-2', $J_{2',1'}$ = 7.7 Hz), 1.43-1.18 (10 H, m, 2'-$C_5H_{10}CH_3$), 0.86-0.81 (3 H, m, 2'-$C_5H_{10}CH_3$). Anal. Calcd for $C_{15}H_{24}N_2O_5$ 2/5 H_2O: C, 56.38; H, 7.82; N, 8.77. Found: C, 56.37; H, 7.64; N, 8.66.

(2'*R*)-2'-Deoxy-2'-*C*-(4-hydroxybutyl)uridine (10d) and (2'*S*)-2'-deoxy-2'-*C*-(4-hydroxybutyl)uridine (9d). A mixture of **7d** and **8d** (352 mg, 0.51 mmol) obtained by radical deoxygenation was deprotected as described for the synthesis of **9a** and **10a** to give a mixture of **9d** and **10d** (129 mg, 84% as a foam) after purification by short column chromatography. However, we could not separate these compounds from each other even using a C-18 HPLC. Physical data for the mixture of **9d** and **10d**: EI-MS *m/z* 299 (M^+); ^{1}H-NMR (DMSO-d_6) 11.31 (1 H, br s, 3-NH, **10d**), 11.29 (1 H, br s, 3-NH, **9d**), 7.89 (1 H, d, H-6, $J_{6,5}$ = 8.2 Hz, **10d**), 7.83 (1 H, d, H-6, $J_{6,5}$ = 8.2 Hz, **9d**), 6.17 (1 H, d, H-1', $J_{1',2'}$ = 7.7 Hz, **9d**), 5.86 (1 H, d, H-1', $J_{1',2'}$ = 9.9 Hz, **10d**), 5.65 (1 H, d, H-5, $J_{5,6}$ = 8.2 Hz, **10d**), 5.60 (1 H, d, H-5, $J_{5,6}$ = 8.2 Hz, **9d**), 5.27 (1 H, d, 3'-OH, **9d**), 5.18 (1 H, d, 3'-OH, **10d**), 5.04 (1 H, t, 5'-OH, **9d**), 5.02 (1 H, t, 5'-OH, **10d**), 4.32 (1 H, t, 2'-C_4H_8OH, **10d**), 4.29 (1 H, t, 2'-C_4H_8OH, **9d**), 4.15 (1 H, dd, H-3', $J_{3',OH}$ = 4.9, $J_{3',2'}$ = 5.0 Hz, **10d**), 3.87-3.83 (1 H, m, H-4', **10d**), 3.85 (1 H, ddd, H-3', $J_{3',OH}$ = 6.6, $J_{3',2'}$ = 8.2, $J_{3',4'}$ = 8.2 Hz, **9d**), 3.72 (1 H, ddd, H-5'a, $J_{a,b}$ = 10.4, $J_{a,OH}$ = 4.9, $J_{a,4'}$ = 3.7 Hz, **9d**), 3.59 (1 H, ddd, H-5'b, $J_{b,a}$ = 10.4, $J_{b,OH}$ = 4.9, $J_{b,4'}$ = 6.6 Hz, **9d**), 3.53 (2 H, m, H-5', **10d**), 3.53-3.31 (1 H, m, H-4', **9d**), 3.34 (2 H, m, 2'-$C_3H_6CH_2OH$, **10d**), 3.31 (2 H, m, 2'-$C_3H_6CH_2OH$, **9d**), 2.35-2.14 (1 H, m, H-2', **10d**), 2.36-2.30 (1 H, m, H-2', **9d**), 1.41-1.23 (6 H, m, 2'-$C_3H_6CH_2OH$, **9d**), 1.37-1.10 (6 H, m, 2'-$C_3H_6CH_2OH$, **10d**).

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