Pergamon

Tetrahedron Vol. 50, No. 35, pp. 10397-10406, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00641-5

Nucleosides and Nucleotides. 134. Synthesis of 2'-*C*-Alkynyl-2'-Deoxy-1-β-D-Arabinofuranosylpyrimidines via Radical Deoxygenation of *Tert*-Propargyl Alcohols in the Sugar Moiety[1]

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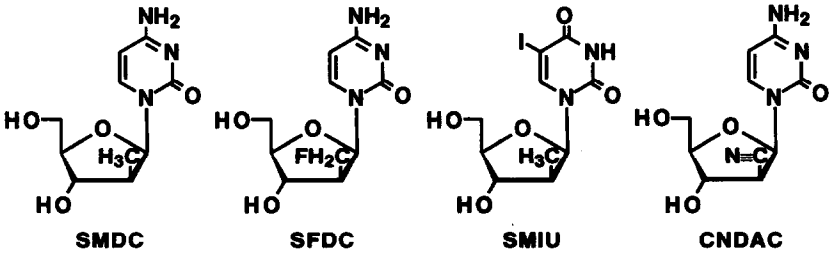
Key Words: nucleoside; radical deoxygenation; branched-chain sugar nucleoside; alkyne; radical reaction; cytotoxicity

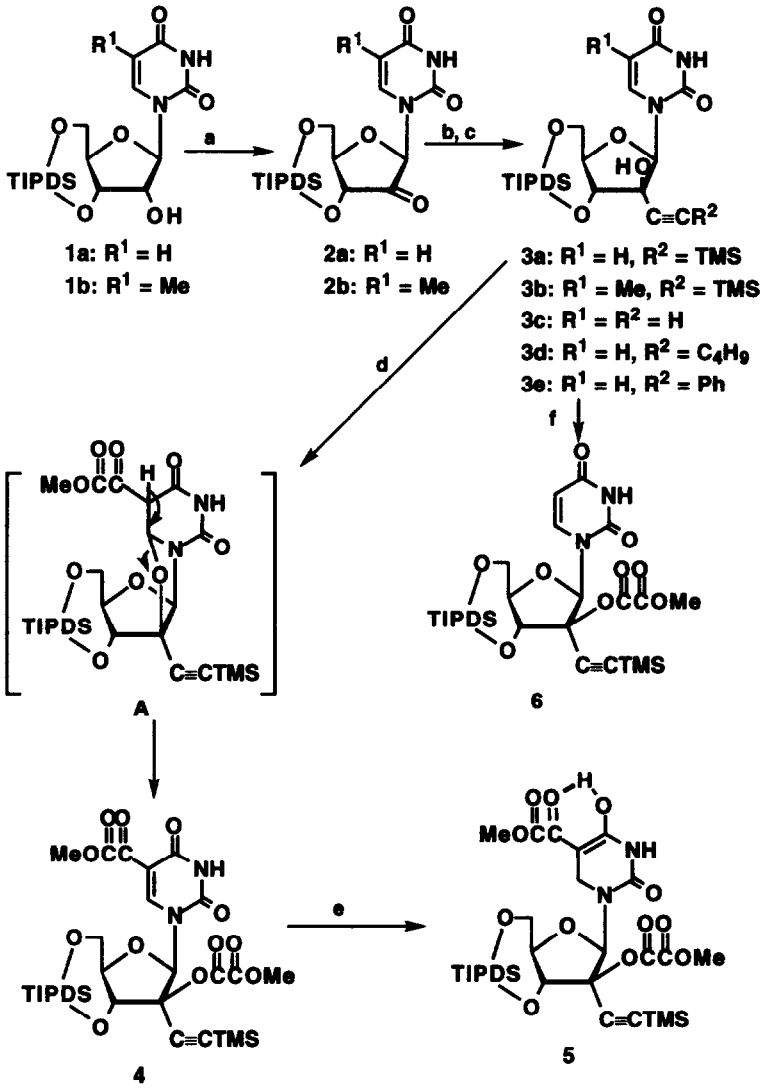
Abstract: Synthesis of 2'-deoxy-2'-*C*-ethynyl-1-β-D-arabinofuranosyluracil (**8c**), -thymine (**8f**), and -cytosine (**11**) has been done by stereospecific radical deoxygenation of the corresponding 2'-*tert*-TMSpropargyl methoxalyl esters with Bu_3SnH in the presence of AIBN. 2'-Deoxy-2'-*C*-hexynyl derivative **8d** was also prepared under similar conditions. On the other hand, the deoxygenation of the phenylpropargyl or propargyl esters gave complex mixtures due to hydrostannylation of the triple bonds.

The radical deoxygenation of nucleoside derivatives having tertiary hydroxyl groups, which are readily obtained by nucleophilic additions of carbanions to the corresponding ketones, has provided biologically interesting branched nucleosides.[2-5] We have designed (2'*S*)-2'-deoxy-2'-*C*-methyl-1-β-D-arabinofuranosylcytosine (SMDC)[2a,e,5] as well as (2'*S*)-2'-deoxy-2'-*C*-fluoromethyl-1-β-D-arabinofuranosylcytosine (SFDC)[2g] as antimetabolites, and they had cytotoxicity 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-1-β-D-arabinofuranosyl-5-iodouracil (SMIU) showed potent anti-HSV-1 activity *in vitro* while showing no toxicity.[2f] On the other hand, 2'-*C*-cyano-2'-deoxy-1-β-D-arabinofuranosylcytosine (CNDAC) has also been designed based upon the hypothesis that introduction of an electron-withdrawing group at the 2'β position of 2'-deoxycytidine would exert a potentially DNA-strand-breaking effect.[4,5] Eventually, CNDAC showed excellent antitumor activity against various human tumor cells including human solid tumors *in vitro* as well as *in vivo*.[4b,c,5] Although it is still unknown whether the activity of CNDAC is related to our hypothesis, these results prompted us to synthesize nucleosides bearing an alkynyl group as an electron-withdrawing functionality at the 2'β position to study the structure-activity relationship of the 2'β substituent.



Introduction of the alkynyl group at the 2'β position of pyrimidine nucleosides is rather straightforward. Addition of lithium alkylides to the 2'-keto nucleosides would afford stereospecifically *tert*-propargyl alcohols.

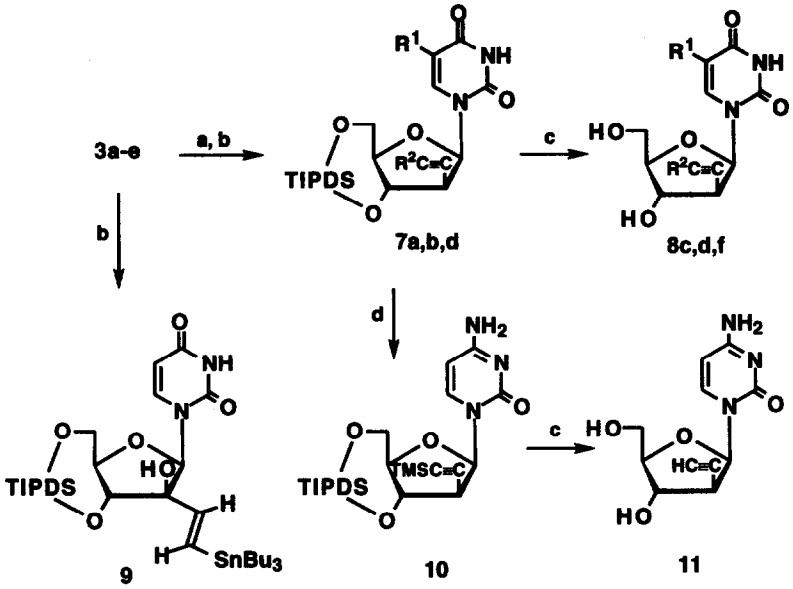
After esterification of the alcohol with a phenoxythiocarbonyl or a methoxalyl group, radical deoxygenations with Bu_3SnH would result in a 2'-*C*-alkynyl-2'-deoxy derivative with the β-configuration due to the steric hindrance of the β-face, if one could prevent hydrostannylation of the alkynyl groups.



Reagents and conditions: a) ref. 6, 7; b) RC≡CH, BuLi, THF, -78 °C; c) NH_3/MeOH; d) methoxalyl chloride, Et_3N, DMAP, CH_2Cl_2, 0 °C; e) Bu_3SnH, AIBN, toluene, 110 °C; f) methoxalyl chloride, DMAP, CH_2Cl_2

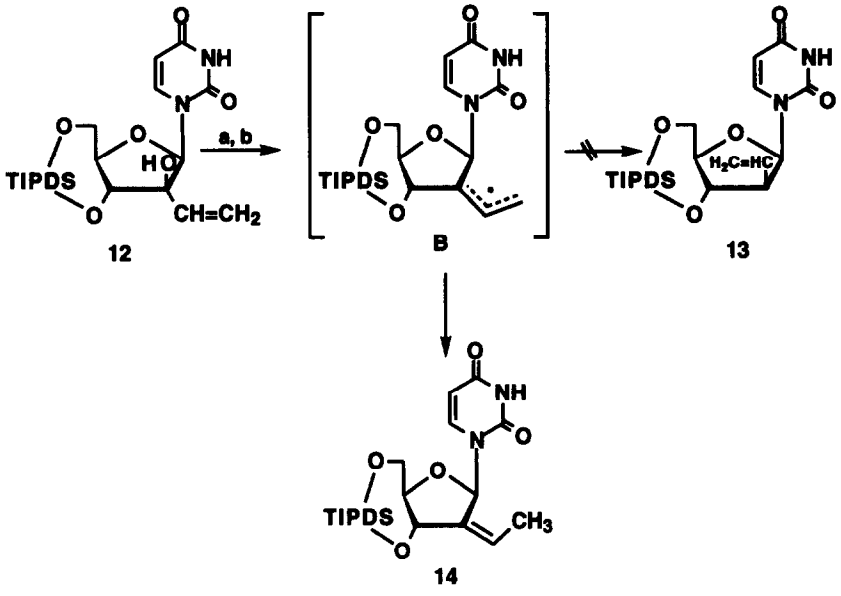
The starting *tert*-propargyl alcohols **3a,b,d**, and **e** were readily accessible from the corresponding 2'-keto-uridine and -5-methyluridine derivatives **2a,b**[6,7] by the nucleophilic addition of the corresponding LiC≡CR, in good yields.[5,8] The addition reactions furnished only one diastereomer, the configuration of

which could not be identified in this stage but was assumed to be **3** due to the steric hindrance of the β-face of the ketones. Compound **3c** was prepared by a selective desilylation of **3a** on treatment with NH_3/MeOH. Introduction of the phenoxythiocarbonyl group into the *tert*-propargyl alcohol in **3a** failed under several conditions using phenyl chlorothionoformate in the presence of DMAP and triethylamine. However, the reaction of **3a** with methoxalyl chloride in the presence of triethylamine and a catalytic amount of DMAP in CH_2Cl_2 proceeded smoothly, giving two nucleosidic products. The ^{1}H-NMR spectrum of the less polar one, obtained in 85% yield, showed two methyl protons due to the methoxalyl groups at 3.88 and 3.94 ppm, each as a singlet, along with the absence of the H-5 proton of the uracil base. UV spectrum of the compound showed an absorption maximum at 297 nm in MeOH that was largely red-shifted compared to the unmodified uracil nucleosides, indicating modification at the base moiety. These data together with its mass spectral data indicated this compound is a bis-methoxalylated product **4** at both the 2'- and 5 positions. The radical reaction of **4** with Bu_3SnH in the presence of AIBN gave the 5,6-dihydro derivative **5** in 45% yield, which is a further evidence of the structure **4**. The more polar product (14% yield) was assigned as the desired methoxalyl ester **6**. Therefore, the use of triethylamine for the methoxalylation of **3a** accelerated the addition of the *tert*-propargyl alcohol, which would be more acidic than the usual *tert*-alcohol, to the 6 position of the uracil ring followed by reaction with methoxalyl chloride, producing an intermediate **A**. Elimination of the fairly acidic H-5 by triethylamine and subsequent methoxalylation of the 2'-O$^-$ afforded **4**. Since a direct acylation of a carbanion at the 5-position of 5,6-dihydrouridine derivatives[9] was known, the formation of **4** is plausible as described above.



Reagents and conditions: a) methoxalyl chloride, DMAP, CH_2Cl_2, r.t.; b) Bu_3SnH, AIBN, toluene, 110 °C; c) TBAF, AcOH, THF, r.t.; d) (i) TPSCl, Et_3N, DMAP, CH_3CN, r.t, (ii) c. NH_4OH

Without addition of triethylamine, use of a stoichiometric amount of DMAP gave good yields in the formation of **6**. Without purification, **6** could be used in the next step. The crude methoxalyl ester **6** was subjected to radical deoxygenation with Bu_3SnH in the presence of AIBN in hot toluene. As expected, the radical deoxygenation proceeded smoothly to give the desired 2'-deoxynucleoside **7a** in 79% yield. The stereochemistry at the 2'-position was confirmed by its ^{1}H-NMR spectrum, which had a coupling constant between H-1' and H-2' in **7a** of 7.6 Hz, which is similar to those of CNDAC[4b] and 2'-azido-2'-deoxy-1-β-D-arabinofuranosylcytosine.[10] Careful analyses of the TLC and ^{1}H-NMR spectra of the reaction mixture showed that only a negligible amount of the ribo-isomer was produced. Similarly, **3b** and **3d** gave stereospecifically **7b** and **7d** in 44 and 53% yields, respectively. On the other hand, the radical deoxygenation of **3c** and **3e** afforded complex mixtures, in which several of these products isolated were found to have tributylstannyl groups from their ^{1}H-NMR and mass spectra (data not shown). Actually, when **3c** was treated with Bu_3SnH under conditions similar to those of the deoxygenation, the *E*-stannylethene derivative **9** was isolated in 41% yield. Thus, although further studies would be needed to preclude such undesired hydrostannylations to the alkynes, bulky substituents attached at the ethynyl group can be successfully incorporated into the 2'β position of the pyrimidine nucleosides. This method can be used in other systems to construct new types of alkynes.



Reagents and conditions: a) methoxalyl chloride, DMAP, CH_2Cl_2, r.t.; b) Bu_3SnH, AIBN, toluene, 110 °C;

We also investigated the synthesis of 2'-deoxy-2'β-*C*-ethenyl derivative **13** from the corresponding allyl alcohol **12**, since attempts to prepare **13** by partial reductions of **7a** or **8c** using H_2/Lindlar catalyst gave only 2'β-*C*-ethyl derivatives (data not shown). Reaction of **2a** with vinylmagnesium bromide in THF afforded the desired allyl alcohol **12**. Methoxalylation of **12** then radical deoxygenation afforded a nucleosidic product. The ^{1}H-NMR spectrum of the product showed a methyl proton at 1.69 ppm as a doublet and a vinylic proton

at 5.92 ppm as a multiplet. This is consistent with the structure of 2'-deoxy-2'-ethylidene derivative **14** but not the desired **13**. The stereochemistry of the ethylidene was identified as a *Z* form by NOE experiments, in which the NOE was observed at the terminal methyl group (4%) when H-1' was irradiated. Thus, the allylic radical intermediate **B** reacted with Bu_3SnH at the terminal position to produce **14**.[11]

Compounds **7a,b,d** were deblocked by tetrabutylammonium fluoride (TBAF) in the presence of AcOH[4b,12] in THF giving the corresponding 2'-deoxy-2'-*C*-ethynyl-1-β-D-arabinofuranosyluracil (**8c**), 2'-deoxy-2'-*C*-hexynyl-1-β-D-arabinofuranosyluracil (**8d**), and 2'-deoxy-2'-*C*-ethynyl-1-β-D-arabinofuranosylthymine (**8f**). Compound **7a** was also converted into the cytosine derivative **10** by triisopropylbenzenesulfonylation of the O^4-position of **7a**, followed by treatment with concentrated NH_4OH. Desilylation of **10** with TBAF furnished 2'-deoxy-2'-*C*-ethynyl-1-β-D-arabinofuranosylcytosine (**11**).

Cytotoxicity of **8c,d,f and 11** against mouse leukemic L1210 and human oral epidermoid carcinoma KB cells *in vitro* was examined. Unlike the activity of SMDC[2a,e] and CNDAC,[4a,b] these nucleosides did not show any significant cytotoxicity to both cell lines up to 100 μg/mL. None of these compounds showed any significant anti HSV-1 or HIV-1 activity.

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 FX-270FT 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-[3,5-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-2-*C*-(trimethylsilyl)ethynyl-β-D-arabinofurnosyl]uracil (3a). A hexane solution of BuLi (1.56 M, 9.6 mL, 15 mmol) was added dropwise over 40 min to a solution of (trimethylsilyl)acetylene (2.1 mL, 15 mmol) in THF (20 mL) at -78° C under an argon atmosphere. A solution of **2a** (2.4 g, 5 mmol) in THF (10 mL) was added dropwise over 10 min to the above solution at -78° C. The whole was stirred for 110 min at -78° C and was quenched by addition of aqueous 1 M NH_4Cl (25 mL). The mixture was extracted by EtOAc (3 x 25 mL). The separated organic phase was further washed with brine (80 mL), dried (Na_2SO_4), and concentrated to dryness. The residue was purified on a silica gel column (3 x 22 cm) with 20% EtOAc in hexane to give **3a** (2.2 g, 74%, as a foam); EI-MS *m/z* 582 (M^+); IR ($CHCl_3$) νC≡C 2400 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 0.19 (9 H, s, TMS), 1.00-1.07 (28 H, m, isoPr), 2.98 (1 H, s, 2'-OH), 3.94-4.01 (1 H, m, H-4'), 4.11 (1 H, d, H-3', $J_{3',4'}$ = 9.2 Hz), 4.03-4.16 (2 H, m, H-5'a,b), 5.69 (1 H, dd, H-5, $J_{5,6}$ = 8.4, $J_{5,NH}$ = 2.2 Hz), 6.64 (1 H, s, H-1'), 7.85 (1 H, d, H-6, $J_{5,6}$ = 8.4 Hz), 8.35 (1 H, br s, NH). *Anal.* Calcd for $C_{26}H_{46}N_2O_7Si_3$: C, 53.57; H, 7.95; N, 4.81. Found: C, 53.25; H, 7.94; N, 4.72.

1-[3,5-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-2-*C*-(trimethylsilyl)ethynyl-β-D-arabinofuranosyl]thymine (3b). From the reaction of **2b** (500 mg, 1 mmol) with LiC≡CTMS [prepared from BuLi (1.56 M, 1.85 mL, 3 mmol) and HC≡CTMS (0.42 mL, 3 mmol) as described in the synthesis of **3a**], **3b** (539 mg, 90%) was obtained as a white foam; EI-MS *m/z* 596 (M^+); IR ($CHCl_3$) νC≡C 2400 cm^{-1};

^{1}H-NMR ($CDCl_3$): 0.18 (9 H, s, TMS), 1.23 (28 H, m, isoPr), 1.91 (3 H, d, 5-Me, $J_{Me,6}$ = 1.0 Hz), 3.93 (1 H, m, H-4'), 4.01 (1 H, dd, H-5'a, $J_{5'a,4'}$ = 2.7, $J_{a,b}$ = 13.4 Hz), 4.14 (1 H, d, H-3', $J_{3',4'}$ = 9.3 Hz), 4.16 (1 H, dd, H-5'b, $J_{5'b,4'}$ = 1.2, $J_{a,b}$ = 13.4 Hz), 6.04 (1 H, s, H-1'), 7.53 (1 H, d, H-6, $J_{6,Me}$ = 1.0 Hz), 8.36 (1 H, br s, NH). *Anal.* Calcd for $C_{27}H_{48}N_2O_7Si_3$: C, 54.33; H, 8.10; N, 4.69. Found: C, 54.17; H, 8.11; N, 4.62.

1-[2-*C*-Hexynyl-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-arabinofuranosyl]uracil (3d). From the reaction of **2a** (1.5 g, 3.1 mmol) with $LiC{\equiv}CC_4H_9$ [prepared from BuLi (1.56 M, 7.7 mL, 12.4 mmol) and $HC{\equiv}CC_4H_9$ (1.4 mL, 12.4 mmol) as described in the synthesis of **3a**], **3d** (1.6 g, 92%) was obtained as a foam; EI-MS *m/z* 567 (M^++1), 523 (M^+-isoPr); IR ($CHCl_3$) νC≡C 2400 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 0.91 (3 H, t, $CH_2CH_2CH_2CH_3$), 1.02-1.10 (28 H, m, isoPr), 1.22-1.53 (4 H, m, $CH_2CH_2CH_2CH_3$), 2.29 (2 H, t, $CH_2CH_2CH_2CH_3$), 2.74 (1 H, br s, 2'-OH), 3.92-3.96 (1 H, m, H-4'), 4.00 (1 H, dd, H-5'a, $J_{5'a,4'}$ = 2.6, $J_{a,b}$ = 13.6 Hz), 4.09 (1 H, d, H-3', $J_{3',4'}$ = 9.2 Hz), 4.16 (1 H, d, H-5'b, $J_{a,b}$ = 13.6 Hz), 5.68 (1 H, dd, H-5, $J_{5,6}$ = 8.1, $J_{5,NH}$ = 2.2 Hz), 6.00 (1 H, s, H-1'), 7.87 (1 H, d, H-6, $J_{5,6}$ = 8.1 Hz), 8.18 (1 H, br s, NH). *Anal.* Calcd for $C_{27}H_{46}N_2O_7Si_2$: C, 57.21; H, 8.18; N, 4.94. Found: C, 57.20; H, 8.37; N, 4.84.

1-[2-*C*-(2-Phenylethynyl)-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-arabinofuranosyl]uracil (3e). From the reaction of **2a** (0.97 g, 2 mmol) with LiC≡CPh [prepared from BuLi (1.56 M, 4.9 mL, 8 mmol) and HC≡CPh (0.9 mL, 8 mmol) as described in the synthesis of **3a**], **3e** (1.1 g, 91%) was obtained as a foam; EI-MS *m/z* 586 (M^+), 543 (M^+-isoPr); IR ($CHCl_3$) νC≡C 2400 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.06-1.19 (28 H, m, isoPr), 3.35 (1 H, br s, 2'-OH), 4.22 (4 H, m, H-3', 4', 5'a,b), 5.71 (1 H, d, H-5, $J_{5,6}$ = 8.1 Hz), 6.61 (1 H, s, H-1'), 7.30-7.59 (5 H, m, Ph), 7.89 (1 H, d, H-6, $J_{5,6}$ = 8.1 Hz), 8.82 (1 H, br s, NH). *Anal.* Calcd for $C_{29}H_{42}N_2O_7Si_2$: C, 59.36; H, 7.21; N, 4.77. Found: C, 59.26; H, 7.31; N, 4.62.

1-[2-*C*-Ethynyl-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-arabinofuranosyl]uracil (3c). A solution of **3a** (2.0 g, 3.4 mmol) in NH_3/MeOH (saturated at 0 °C, 35 mL) was stirred for 13 h at room temperature. The solvent was removed and the residue was purified on a silica gel column (3.8 x 12 cm) with 30% EtOAc in hexane to give **3c** (1.5 g, 87% as a foam); EI-MS *m/z* 510 (M^+); IR ($CHCl_3$) νC≡C 2400 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.10-1.05 (28 H, m, isoPr), 2.73 (1 H, s, C≡CH), 3.47 (1 H, br s, 2'-OH), 3.96-4.00 (1 H, m, H-4'), 4.00 (1 H, dd, H-5'a, $J_{a,b}$ = 13.6 Hz), 4.09-4.14 (1 H, m, H-3'), 4.17 (1 H, dd, H-5'b, $J_{b,4'}$ = 1.8, $J_{b,a}$ = 13.6 Hz), 5.71 (1 H, dd, H-5, $J_{5,6}$ = 8.1, $J_{5,NH}$ = 2.2 Hz), 6.07 (1 H, s, H-1'), 7.87 (1 H, d, H-6, $J_{5,6}$ = 8.1 Hz), 8.82 (1 H, br s, NH). *Anal.* Calcd for $C_{23}H_{38}N_2O_7Si_2$: C, 54.09; H, 7.50; N, 5.48. Found: C, 53.95; H, 7.51; N, 5.47.

Reaction of 3a with Methoxalyl Chloride in the Presence of Triethylamine. Methoxalyl chloride (0.47 mL, 5.2 mmol) was added to a mixture of **3a** (1.0 g, 1.7 mmol), Et_3N (0.8 mL, 5.6 mmol), and DMAP (14 mg) in CH_2Cl_2 (60 mL) at 0 °C. The mixture was stirred for 6 h at room temperature and was washed with H_2O (3 x 50 mL) and brine (50 mL). The separated organic phase was dried (Na_2SO_4) and concentrated. The residue was purified on a silica gel column (2.2 x 18 cm) eluted with 10% EtOAc in hexane to afford **4** (1.1 g, 85%, as a foam), then eluted with 15% EtOAc in hexane to give **6** (168 mg, 14%, as a foam). Data for **4**: EI-MS *m/z* 738 (M^+-Me); UV λmax (MeOH) 297 nm; ^{1}H-NMR ($CDCl_3$): 0.15 (9 H, s, TMS), 1.06-1.10 (28 H, m, isoPr), 3.81 (1 H, dd, H-5'a, $J_{a,4'}$ = 9.0, $J_{a,b}$ = 11.7 Hz), 3.88 (3 H, s, 2'-COCOCH_3), 3.94 (3 H, s, 5-COCOCH_3), 4.03-4.07 (1 H, m, H-4'), 4.17 (1 H, dd, H-5'b, $J_{b,4'}$ = 3.9, $J_{a,b}$

= 11.7 Hz), 4.39 (1 H, d, H-3', $J_{3',4'}$ = 4.4 Hz), 6.43 (1 H, s, H-1'), 8.58 (1 H, s, H-6), 8.75 (1 H, br s, NH). Data for **6**: EI-MS *m/z* 669 (M^+); ^{1}H-NMR ($CDCl_3$): 0.17 (9 H, s, TMS), 1.06-1.25 (28 H, m, isoPr), 3.89 (3 H, s, 2'-COCOCH_3), 3.92-3.96 (1 H, m, H-4'), 4.14-4.18 (2 H, m, H-5'a,b), 4.56 (1 H, m, H-3'), 5.69 (1 H, dd, H-5, $J_{5,6}$ = 8.1, $J_{5,NH}$ = 2.4 Hz), 7.26 (1 H, s, H-1'), 7.53 (1 H, d, H-6, $J_{6,5}$ = 8.1 Hz), 8.05 (1 H, br s, NH).

5,6-Dihydro-5-*C*-methoxalyl-1-[2-*O*-methoxalyl-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-2-*C*-(trimethylsilyl)ethynyl-β-D-arabinofuranosyl]uracil (5). A solution of **4** (1.25 g, 1.7 mmol), AIBN (7 mg), and Bu_3SnH (0.69 mL, 2.6 mmol) in toluene (40 mL) was heated for 1 h at 110° C. The solvent was removed *in vacuo* and the residue was purified by a silica gel column (2.2 x 17 cm) eluted with 15% EtOAc in hexane to afford **5** (336 mg, 45%, as an orange foam); EI-MS *m/z* 756 (M^+); UV λmax (MeOH) 286 nm, λmax (H^+) 283 nm, λmax (HO^-) 297 nm; ^{1}H-NMR ($CDCl_3$): 0.16 (9 H, s, TMS), 1.10 (28 H, m, isoPr), 3.83 (3 H, s, 2'-methoxalyl), 3.86 (1 H, m, H-4'), 3.89 (3 H, s, 5-methoxalyl), 4.03 (1 H, dd, H-5'a, $J_{5'a,4'}$ = 4.2, $J_{a,b}$ = 12.9 Hz), 4.08 (1 H, dd, H-5'b, $J_{5'b,4'}$ = 3.4, $J_{a,b}$ = 12.9 Hz), 4.25 (1 H, d, H-6a, *J*a,b = 16.1 Hz), 4.67 (1 H, d, H-3', $J_{3',4'}$ = 8.3 Hz), 4.96 (1 H, d, H-6b, *J*a,b = 16.1 Hz), 6.44 (1 H, s, H-1'), 7.51 (1 H, s, NH), 13.14 (1 H, br s, 4-OH).

1-[2-Deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-2-*C*-(trimethylsilyl)-ethynyl-β-D-arabinofuranosyl]uracil (7a). Methoxalyl chloride (0.63 mL, 6.9 mmol) was added to a solution of **3a** (2.0 g, 3.4 mmol) and DMAP (0.84 g, 6.9 mmol) in CH_2Cl_2 (100 mL) at room temperature under an argon atmosphere. After being stirred for 2 h, the mixture was washed with H_2O (3 x 100 mL) and brine (2 x 100 mL). The separated organic phase was dried (Na_2SO_4), concentrated to dryness, and coevaporated with toluene. A solution of the residue, AIBN (7 mg), and Bu_3SnH (1.85 mL, 6.7 mmol) in toluene (50 mL) was heated for 90 min at 110° C. Further amounts of AIBN (7 mg) and Bu_3SnH (1.85 mL, 6.7 mmol) were added to the mixture, which was heated for 180 min more at 110° C. The solvent was removed *in vacuo* and the residue was purified by a silica gel (2.8 x 20 cm) eluted with 15% EtOAc in hexane to afford **7a** (1.52 g, 79%, crystallized from EtOAc/hexane); mp 196-198° C; EI-MS *m/z* 566 (M^+); IR ($CHCl_3$) νC≡C 2400 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 0.06 (9 H, s, TMS), 1.11 (28 H, m, isoPr), 3.44 (1 H, dd, H-2', $J_{2',1'}$ = 7.6, $J_{2',3'}$ = 9.8 Hz), 3.73 (1 H, ddd, H-4', $J_{4',5'a}$ = 2.7, $J_{4',5'b}$ = 1.5, $J_{4',3'}$ = 8.6 Hz), 4.00 (1 H, dd, H-5'a, $J_{5'a,4}$ = 2.7, $J_{a,b}$ = 13.4 Hz), 4.13 (1 H, dd, H-5'b, $J_{5'b,4'}$ = 1.5, $J_{a,b}$ = 13.4 Hz), 4.39 (1 H, t, H-3'), 5.55 (1 H, dd, H-5, $J_{5,6}$ = 8.1, $J_{5,NH}$ = 2.2 Hz), 6.29 (1 H, d, H-1', $J_{1',2'}$ = 7.6 Hz), 7.65 (1 H, d, H-6, $J_{5,6}$ = 8.1 Hz), 8.12 (1 H, br s, NH). *Anal.* Calcd for $C_{26}H_{46}N_2O_6Si_3$: C, 55.09; H, 8.18; N, 4.94. Found: C, 54.95; H, 8.22; N, 5.01.

1-[2-Deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-2-*C*-(trimethylsilyl)-ethynyl-β-D-arabinofuranosyl]thymine (7b). Reaction of **3b** (1.66 g, 2.8 mmol) with methoxalyl chloride (0.38 mL, 4.2 mmol) and DMAP (0.51 g, 4.2 mmol) in CH_2Cl_2 (80 mL), followed by treatment with AIBN (100 mg) and Bu_3SnH (1.87 mL, 7 mmol) in toluene (20 mL) for 70 min at 110 °C as described in the synthesis of **7a** afforded **7b** (712 mg, 44%, crystallized from hexane); mp 93-96° C; EI-MS *m/z* 581 (M^++1); IR ($CHCl_3$) νC≡C 2400 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 0.03 (9 H, s, TMS), 1.11 (28 H, m, isoPr), 1.92 (3 H, d, 5-Me, $J_{Me,6}$ = 1.0 Hz), 3.42 (1 H, dd, H-2', $J_{2',1'}$ = 8.3, $J_{2',3'}$ = 9.3 Hz), 3.68 (1 H, ddd, H-4', $J_{4',5'a}$ = 2.9, $J_{4',5'b}$ = 1.5, $J_{4',3'}$ = 8.8 Hz), 4.00 (1 H, dd, H-5'a, $J_{5'a,4}$ = 2.9, $J_{a,b}$ = 13.2 Hz), 4.13 (1 H, dd, H-5'b, $J_{5'b,4'}$ = 1.5, $J_{a,b}$ = 13.2 Hz), 4.42 (1 H, dd, H-3', $J_{3',2'}$ = 9.3, $J_{3',4'}$ = 8.8 Hz), 6.31 (1 H, d, H-1', $J_{1',2'}$ =

8.3 Hz), 7.33 (1 H, d, H-6, $J_{6,Me}$ = 1.0 Hz), 8.39 (1 H, br s, NH). *Anal.* Calcd for $C_{27}H_{48}N_2O_6Si_3$: C, 55.82; H, 8.33; N, 4.82. Found: C, 55.77; H, 8.31; N, 4.85.

1-[2-Deoxy-2-*C*-hexynyl-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-arabinofuranosyl]uracil (7d). Reaction of **3d** (1.2 g, 2.1 mmol) with methoxalyl chloride (0.58 mL, 6.4 mmol) and DMAP (776 mg, 6.4 mmol) in CH_2Cl_2 (15 mL), followed by treatment with AIBN (30 mg) and Bu_3SnH (1.29 mL, 4.8 mmol) in toluene (15 mL) for 4 h at 80 °C as described in the synthesis of **7a** afforded **7b** (900 mg, 54%, crystallized from hexane); EI-MS *m/z* 550 (M^+), 507 (M^+-isoPr); ^{1}H-NMR ($CDCl_3$) 0.85 (3 H, t, Me, J = 7.1 Hz), 1.02-1.11 (28 H, m, isoPr), 1.26-1.36 (4 H, m, $CH_2CH_2CH_2CH_3$), 2.05-2.10 (2 H, m, $CH_2CH_2CH_2CH_3$), 3.42 (1 H, ddd, H-2', $J_{2',3'}$ = 9.3, $J_{2',1'}$ = 7.7, $J_{2',\equiv CCH2}$ = 2.2 Hz), 3.74 (1 H, ddd, H-4', $J_{4',5'b}$ = 1.7, $J_{4',5'a}$ = 2.8, $J_{4',3'}$ = 8.8 Hz), 4.00 (1 H, dd, H-5'a, $J_{a,4'}$ = 2.8, $J_{a,b}$ = 13.2 Hz), 4.12 (1 H, d, H-5'b, $J_{b,4'}$ = 1.7, $J_{b,a}$ = 13.2 Hz), 4.32 (1 H, d, H-3', $J_{3',4'}$ = 8.8, $J_{3',2'}$ = 9.3 Hz), 5.69 (1 H, dd, H-5, $J_{5,6}$ = 8.2, $J_{5,NH}$ = 2.2 Hz), 6.27 (1 H, d, H-1', $J_{1',2'}$ = 7.7 Hz), 7.66 (1 H, d, H-6, $J_{6,5}$ = 8.2 Hz), 7.98 (1 H, br s, NH). *Anal.* Calcd for $C_{27}H_{46}N_2O_6Si_2$: C, 58.87; H, 8.42; N, 5.09. Found: C, 58.63; H, 8.43; N, 4.98.

1-[2-Deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-2-*C*-(trimethylsilyl)-ethynyl-β-D-arabinofuranosyl]cytosine (10). Et_3N (0.32 mL, 2.3 mmol) was added to a mixture of **7a** (660 mg, 1.2 mmol), TPSCl (706 mg, 2.3 mmol), and DMAP (285 mg, 2.3 mmol) in CH_3CN (50 mL). After the mixture was stirred for 22 h at room temperature under Ar, concentrated NH_4OH (28%, 30 mL) was added to the mixture and the whole was stirred for further 3 h at room temperature. The solvent was removed *in vacuo* and the residue was purified on a silica gel column (2.8 x 15 cm) with 5% EtOH in $CHCl_3$ to give **10** (621 mg, 95%, as a white foam); EI-MS *m/z* 565 (M^+); UV λmax (MeOH) 274 nm, λmax (H^+) 285 nm; ^{1}H-NMR ($CDCl_3$): 0.00 (9 H, s, TMS), 1.05-1.10 (28 H, m, isoPr), 3.44 (1 H, dd, H-2', $J_{2',1'}$ = 7.6, $J_{2',3'}$ = 8.3 Hz), 3.69-3.73 (1 H, m, H-4'), 4.00 (1 H, dd, H-5'a, $J_{5'a,4}$ = 2.9, $J_{a,b}$ = 12.3 Hz), 4.09 (1 H, dd, H-5'b, $J_{5'b,4'}$ = 2.0, $J_{a,b}$ = 12.3 Hz), 4.37 (1 H, dd, H-3', $J_{3',2'}$ = 8.3, $J_{3',4'}$ = 8.6 Hz), 5.73 (1 H, d, H-5, $J_{5,6}$ = 6.6 Hz), 6.39 (1 H, d, H-1', $J_{1',2'}$ = 7.6 Hz), 7.65 (1 H, d, H-6, $J_{6,5}$ = 6.6 Hz). *Anal.* Calcd for $C_{26}H_{47}N_3O_5Si_3$: C, 55.18; H, 8.37; N, 7.42. Found: C, 55.30; H, 8.38; N, 7.29.

2'-Deoxy-2'-*C*-ethynyl-1-β-D-arabinofuranosyluracil (8c). A solution of **7a** (500 mg, 0.88 mmol) in THF (20 mL) containing AcOH (0.1 mL, 1.8 mmol) was treated with TBAF (1M THF, 3.1 mL, 3.1 mmol) for 1 h at room temperature. Silica gel (about 5 g) was added to the solution and the whole was concentrated to dryness. The residue was placed on a top of a silica gel column (2.8 x 9 cm) eluted with 10% MeOH in $CHCl_3$ to give **8c** (173 mg, 78%, crystallized from EtOH/Et_2O); mp 146-147 °C; EI-MS *m/z* 252 (M^+); IR (nujol) νC≡C 2400 cm^{-1}; ^{1}H-NMR (DMSO-d_6): 3.15 (1 H, d, C≡C*H*, $J_{C\equiv CH,2'}$ = 2.4 Hz), 3.38 (1 H, dt, H-2', $J_{2',C\equiv CH}$ = 2.4, $J_{2',1'}$ = 7.3, $J_{2',3'}$ = 7.3 Hz), 3.61 (1 H, ddd, H-5'a, $J_{5'a,4}$ = 3.7, $J_{a,b}$ = 11.5 Hz), 3.67 (1 H, m, H-4'), 3.71 (1 H, ddd, H-5'b, $J_{5'b,4}$ = 2.7, $J_{a,b}$ = 11.5 Hz), 4.16 (1 H, ddd, H-3', $J_{3',4'}$ = 7.3, $J_{3',2'}$ = 7.3, $J_{3',OH}$ = 5.9 Hz), 5.13 (1 H, t, 5'-OH, J = 5.1 Hz), 5.62 (1 H, d, H-5, $J_{5,6}$ = 7.8 Hz), 6.17 (1 H, d, H-1', $J_{1',2'}$ = 7.3 Hz), 7.85 (1 H, d, H-6, $J_{5,6}$ = 7.8 Hz), 11.32 (1 H, br s, NH). *Anal.* Calcd for $C_{11}H_{12}N_2O_5 \cdot 1/2$ EtOH: C, 52.36; H, 5.49; N, 10.18. Found: C, 52.58; H, 5.44; N, 10.14.

2'-Deoxy-2'*C*-ethynyl-1-β-D-arabinofuranosylthymine (8f). Compound **7b** (500 mg, 0.86 mmol) was deblocked as described above to afford **8f** (119 mg, 52%, crystallized from EtOH/EtOAc); mp 169-170 °C; EI-MS *m/z* 266 (M^+); ^{1}H-NMR (DMSO-d_6): 1.77 (3 H, d, 5-Me, $J_{Me,6}$ = 1.0 Hz), 3.12 (1 H, d, C≡C*H*, $J_{C\equiv CH,2'}$ = 2.9 Hz), 3.37 (1 H, dt, H-2', $J_{2',C\equiv CH}$ = 2.9, $J_{2',1'}$ = 7.8, $J_{2',3'}$ = 7.8 Hz), 3.61 (1 H, m,

H-5'a, $J_{5'a,4}$ = 3.4, $J_{a,b}$ = 11.7 Hz), 3.66 (1 H, m, H-4'), 3.73 (1 H, ddd, H-5'b, $J_{5'b,4}$ = 2.4, $J_{b,OH}$ = 4.9, $J_{a,b}$ = 11.7 Hz), 4.21 (1 H, ddd, H-3', $J_{3',4'}$ = 7.3 = $J_{3',2'}$ = 7.8, $J_{3',OH}$ = 6.4 Hz), 5.18 (1 H, t, 5'-OH, J = 5.1 Hz), 5.81 (1 H, d, 3'-OH, J = 5.9 Hz), 6.16 (1 H, d, H-1', $J_{1',2'}$ = 7.8 Hz), 7.76 (1 H, d, H-6, $J_{6,Me}$ = 1.0 Hz), 11.30 (1 H, br s, NH). *Anal.* Calcd for $C_{12}H_{14}N_2O_5 \cdot 1/10$ EtOH: C, 53.77; H, 5.34; N, 10.45. Found: C, 53.77; H, 5.32; N, 10.40.

2'-Deoxy-2'-*C*-hexynyl-1-β-D-arabinofuranosyluracil (8d). Compound **7d** (580 mg, 1.1 mmol) was deblocked as described above to afford **8d** (246 mg, 76%, as a white foam); EI-MS *m/z* 308 (M^+); ^{1}H-NMR (DMSO-d_6): 0.78-1.28 (6 H, m, -Bu), 2.04-2.07 (2 H, m, C≡CC*H*$_2$), 3.31 (1 H, dt, H-2', $J_{2',1'}$ = $J_{2',3'}$ = 7.1, $J_{2',\equiv CCH_2}$ = 2.2 Hz), 3.60-3.66 (3 H, m, H-4',5'), 4.16 (1 H, dd, H-3',$J_{3',2'}$ = 7.1, $J_{3',OH}$ = 5.5 Hz), 5.07 (1 H, t, 5'-OH, J = 5.0 Hz), 5.61 (1 H, d, H-5, $J_{5,6}$ = 7.9 Hz), 5.72 (1 H, d, 3'-OH, J = 5.5 Hz), 6.15 (1 H, d, H-1', $J_{1',2'}$ = 7.1 Hz), 7.79 (1 H, d, H-6, $J_{5,6}$ = 7.9 Hz), 11.30 (1 H, br s, NH).

2'-Deoxy-2'-*C*-ethynyl-1-β-D-arabinofuranosylcytosine•Hydrochloride (11). Compound **10** (355 mg, 0.63 mmol) was deblocked as described as above and the residue was coevaporated with EtOH containing aqueous 1 N HCl to give **11** as an HCl salt (173 mg, 36%, crystallized from EtOH/Et_2O); mp 205-207° C; EI-MS *m/z* 251 (M^+); ^{1}H-NMR (DMSO-d_6): 3.03 (1 H, d, C≡C*H*, $J_{C\equiv CH,2'}$ = 2.4 Hz), 3.29 (1 H, dt, H-2', $J_{2',C\equiv CH}$ = 2.4, $J_{2',1'}$ = 7.3, $J_{2',3'}$ = 5.9 Hz), 3.59 (1 H, ddd, H-5'a, $J_{5'a,4}$ = 4.9, $J_{a,b}$ = 11.7 Hz), 3.65-3.68 (1 H, m, H-4'), 3.68-3.71 (1 H, m, H-5'b), 4.14 (1 H, t, H-3', $J_{3',4'}$ = $J_{3',2'}$ = 5.9 Hz), 5.05 (1 H, br s, 5'-OH), 5.68 (1 H, d, H-5, $J_{5,6}$ = 7.3 Hz), 5.78 (1 H, br s, 3'-OH), 6.15 (1 H, d, H-1', $J_{1',2'}$ = 7.3 Hz), 7.14 (2 H, br s, 4-NH_2), 7.71 (1 H, d, H-6, $J_{5,6}$ = 7.3 Hz). *Anal.* Calcd for $C_{11}H_{13}N_3O_4 \cdot$HCl: C, 45.92; H, 4.90; N, 14.61; Cl, 12.31. Found: C, 45.70; H, 4.96; N, 14.61; Cl, 12.13.

1-[2-Deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-2(*E*)-*C*-(tributylstannyl)ethenyl-β-D-arabinofuranosyl]cytosine (9). A mixture of AIBN (12 mg) and Bu_3SnH (0.17 mL, 0.64 mmol) in toluene (2 mL) was added dropwise to a solution of **3c** (250 mg, 0.49 mmol) in toluene (10 mL) at 100 °C and the whole was heated at 100 °C for 1.5 h. The solvent was removed *in vacuo* and the residue was purified on a silica gel column (2.8 x 12 cm) with 20% EtOAc in hexane to give **9** (162 mg, 41%, as a white foam); ^{1}H-NMR ($CDCl_3$) 0.81-1.54 (55 H, m, isoPr, Bu), 2.37 (1 H, br s, 2'-OH), 3.74-3.78 (1 H, m, H-4'), 3.98 (1 H, dd, H-5'a, $J_{5'a,4'}$ = 2.8, $J_{a,b}$ = 13.2 Hz), 4.14 (1 H, dd, H-5'b, $J_{5'b,4'}$ = 1.7, $J_{a,b}$ = 13.2 Hz), 4.19 (1 H, d, H-3', $J_{3',4'}$ = 8.8 Hz), 5.70 (1 H, dd, H-5, $J_{5,6}$ = 8.2, $J_{5,NH}$ = 2.2 Hz), 6.02 (1 H, s, H-1'), 6.36, 6.56 (each 1 H, d, vinylic, J = 19.8 Hz), 7.92 (1 H, d, H-6, $J_{6,5}$ = 8.2 Hz), 8.20 (1 H, br s, NH).

1-[2-Deoxy-2-*C*-ethenyl-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-arabinofuranosyl]uracil (12). A THF solution of vinylmagnesium bromide (1 M THF solution, 16.5 mL, 16.5 mmol) was added dropwise over 15 min to a solution of **2a** (2.0 g, 4.1 mmol) in THF (50 mL) at -40 °C under Ar and the whole was stirred for 4 h at -30 °C. Aqueous NH_4Cl (1 M, 40 mL) was added to the mixture, which was then stirred for 1 h at room temperature. The mixture was extracted with EtOAc (x 3) and the organic phase was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified on a silica gel column (3.6 x 10 cm) with 15% EtOAc in hexane to give **12** (1.7 g, 81%, as a white foam); EI-MS *m/z* 513 (M^++1), 469 (M^+-isoPr); ^{1}H-NMR ($CDCl_3$) 1.01-1.11 (28 H, m, isoPr), 2.44 (1 H, br s, 2'-OH), 3.77 (1 H, ddd, H-4', $J_{4',5'a}$ = 2.2, $J_{4',5'b}$ = 2.7, $J_{4',3'}$ = 9.2 Hz), 3.98 (1 H, dd, H-5'a, $J_{5'a,4'}$ = 2.2, $J_{a,b}$ = 13.2 Hz), 4.15 (1 H, dd, H-5'b, $J_{5'b,4'}$ = 2.7, $J_{b,a}$ = 13.2 Hz), 4.20 (1 H, m, H-3'), 5.50 (1 H, d, 2'-CH=CH_2, J_{vinyl} = 11.4 Hz), 5.60 (1 H, d, 2'-CH=CH_2, J_{vinyl} = 17.6 Hz), 5.71 (1 H, dd, H-5, $J_{5,6}$ =

8.4, $J_{5,NH}$ = 2.2 Hz), 6.00 (1 H, s, H-1'), 6.27 (1 H, dd, 2'-C*H*=CH_2, J_{vinyl} = 11.4 and 17.6 Hz), 7.92 (1 H, d, H-6, $J_{6,5}$ = 8.4 Hz), 8.43 (1 H, br s, NH).

1-[2-Deoxy-2(Z)-ethylene-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-*erythro*-pentofuranosyl]uracil (14). Methoxalyl chloride (100 μL, 1.1 mmol) was added to a solution of **12** (144 mg, 0.28 mmol) and DMAP (137 mg, 1.2 mmol) in CH_2Cl_2 (4 mL) at 0 °C under Ar, and the mixture was stirred for 1 h at 0 °C. The mixture was diluted with CH_2Cl_2 and washed with H_2O (x 3) and brine. The separated organic phase was dried (Na_2SO_4) and the solvent was removed. The residue was coevaporated twice with toluene. A mixture of AIBN (12 mg) and Bu_3SnH (0.23 mL, 0.84 mmol) in toluene (2.5 mL) was added dropwise to a solution of the residue in toluene (5 mL) at 80 °C under Ar and the mixture was heated for 2 h. The solvent was removed *in vacuo* and the residue was purified on a silica gel column (2.8 x 7 cm) with 20% EtOAc in hexane to give **14** (119 mg, 85%, as a white foam); EI-MS *m/z* 497 (M^++1), 481 (M^+-Me), 453 (M^+-isoPr); ^{1}H-NMR ($CDCl_3$) 1.06-1.11 (28 H, m, isoPr), 1.69 (3 H, dd, 2'=CHC*H*$_3$, $J_{Me,CH}$ = 7.3, $J_{Me,3'}$ = 1.8 Hz), 3.59 (1 H, dt, H-4', $J_{4',5'}$ = 2.6, $J_{4',3'}$ = 8.4 Hz), 4.05 (2 H, d, H-5'a,b, $J_{5',4'}$ = 2.6 Hz), 4.81 (1 H, dd, H-3', $J_{3',4'}$ = 8.4, $J_{3',CH}$ = 2.2 Hz), 5.72 (1 H, dd, H-5, $J_{5,6}$ = 8.1, $J_{5,NH}$ = 2.2 Hz), 5.90 (1 H, ddq, 2'=C*H*CH_3, $J_{CH,Me}$ = 7.3, $J_{CH,3'}$ = 2.2, $J_{CH,1'}$ = 2.2 Hz), 6.68 (1 H, br s, H-1'), 7.16 (1 H, d, H-6, $J_{6,5}$ = 8.1 Hz), 8.77 (1 H, br s, NH).

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12. Without addition of AcOH, the yield was greatly reduced due to decomposition.

(*Received in Japan* 10 *June* 1994; *accepted* 15 *July* 1994)