Synthesis of 5-(5-Deoxy-β-D-*erythro*-pent-4-enofuranosyl)-1,3-dimethyluracil. A Potentially Versatile Intermediate[1]

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A potentially versatile crystalline intermediate, 5-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)-1,3-dimethyluracil (**7**), was synthesized in seven steps from pseudouridine in 67% overall yield. Pseudouridine was sequentially methylated to 1,3-dimethylpseudouridine (**1**), acetonated to **2**, and iodinated to **3** with methyltriphenoxyphosphonium iodide. After O-deisopropylidenation to **4** followed by acetylation, the product **5** was treated with AgF in pyridine. Crystalline 4′,5′-olefin 2′,3′-diacetate **6** was obtained, which was saponified with NH_3/MeOH to give **7**. When 2′,3′-*O*-isopropylidene-5′-*O*-mesyl-1,3-dimethylpseudouridine (**8**) was treated with AgF the 5′-deoxy-5′-fluoro C-nucleoside **9** was obtained. Treatment of **8** with *t*-BuOK in Me_2SO afforded 5-[(3*R*,4*R*)-2,3-dihydroxy-4,5-epoxy-2,3-*O*-isopropylidene-1-penten-1-yl]-1,3-dimethyluracil (**10**), which was further converted into 1,3-dimethyl-5-[(3*R*,4*R*)-4,5-*O*-isopropylidene-1-nitrilo-3,4,5-trihydroxy-5-hexen-6-yl]uracil (**11**) by treatment with NaCN in Me_2SO. Reaction of **6** with $HgCl_2$ in acetone afforded racemic 5-(4-acetoxy-5-methylfuran-2-yl)-1,3-dimethyluracil (**12**). Deacetylation of **12** gave 1,3-dimethyl-5-(5-methyl-4-oxo-4,5-dihydrofuran-2-yl)uracil (**13**). Treatment of **6** with methanol in the presence of acetic acid afforded 5-(2,3-di-*O*-acetyl-5-deoxy-4-methoxy-β-D-ribofuranosyl)-1,3-dimethyluracil (**14**) and the isomeric α-L-lyxo nucleoside **15** in 76.5 and 13.5% yield, respectively. Acid-catalyzed addition of the 4′,5′-double bond with 1,2,4-triazole occurred smoothly, giving rise to crystalline 5-[2,3-di-*O*-acetyl-5-deoxy-4-(1*H*-1,2,4-triazol-1-yl)-β-D-ribofuranosyl]-1,3-dimethyluracil (**16**) and its α-L lyxo isomer **17**.

1,3-Dialkyluracil derivatives undergo various ring transformation reactions with 1,3-ambident nucleophiles.[4] Thus, treatment of 1,3-dimethyluracil derivatives with guanidine, thiourea, or urea in base afforded the corresponding isocytosine, 2-thiouracil, or 1,3-unsubstituted uracil derivatives (pyrimidine to pyrimidine ring transformation).[5] By use of ambident nucleophiles that contain a nitrogen and a carbon nucleophile, such as α-substituted acetamides, a number of 2,6-dihydroxypyridines have been prepared from 1,3-dimethyluracils.[6,7] Conversion of the pyrimidine ring into the benzene system was achieved by reaction of 1,3-dimethyl-5-nitrouracil with 1,3-ambident reagents bearing two carbon nucleophilic centers.[8] The uracil ring was also converted into pyrido[2,3-*d*]pyrimidine by treatment of 1,3-dimethyluracils with a cyclic 1,3-ambident nucleophile, such as 6-aminouracils,[7] or by reaction of 5-cyano-1,3-dimethyluracil with α-substituted acetamides.[9]

Reports on the synthesis of C-nucleosides with a modified ribosyl moiety are rather sparse. Several 2′-deoxy C-nucleosides have been prepared from preformed C-nucleosides[10-16] or by metal-mediated condensation of a heterocyclic base with a protected ribal.[17-21] We have also reported conversion of pseudouridine into 2′-substituted arabinosyl analogues by nucleophilic introduction of a 2′-"up" substituent.[22,23] Some arabinofuranosyl C-nucleosides have also been prepared.[16,24]

In this report, we describe the synthesis of 5-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)-1,3-dimethyluracil (**7**) (Scheme I) as a potentially useful intermediate in modification of the base or sugar or both moieties. We also report conversion of the 2′,3′-di-*O*-acetyl-4-enofuranosyl derivative **6** into several novel C-nucleosides, and an unusual reaction discovered during the course of our studies.

1,3-Dimethylpseudouridine[5] (**1**) was isopropylidenated with 2,2-dimethoxypropane in acetone in the presence of *p*-TsOH[25] to 2′,3′-*O*-isopropylidene-1,3-dimethylpseudouridine (**2**), which was converted into the 5′-deoxy-5′-iodo derivative **3** by treatment with methyltriphenoxyphosphonium iodide in DMF.[26] Methyl 5-deoxy-2,3-*O*-isopropylidene-β-D-*erythro*-pent-4-enofuranoside[27] and 1-(5-deoxy-2,3-*O*-isopropylidene-β-D-*erythro*-pent-4-eno-

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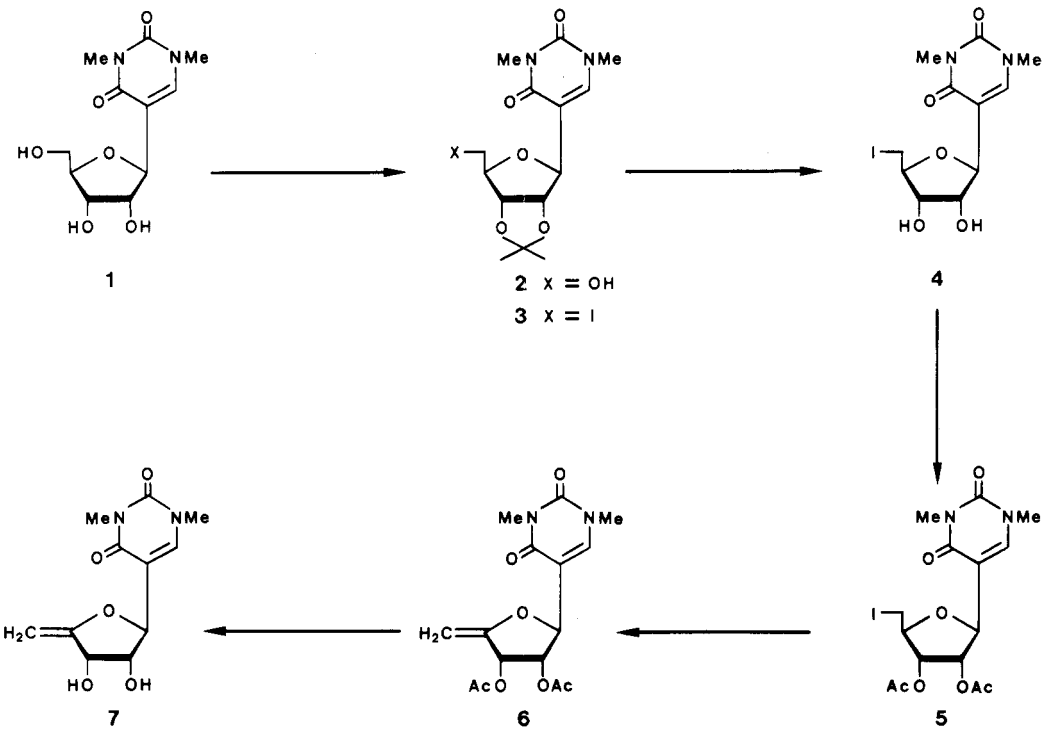
Scheme I[a]

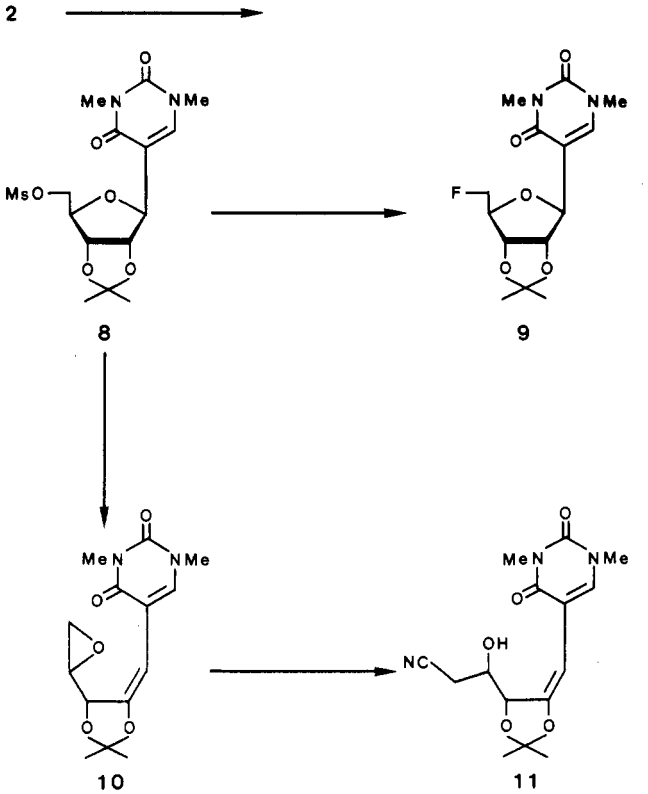


[a] (a) $TsOH/Me_2C(OMe)_2 + Me_2CO$; (b) $(PhO)_3PMeI/DMF$; (c) 50% AcOH; (d) Ac_2O/pyridine; (e) AgF/pyridine; (f) concentrated NH_4OH.

furanosyl)uracil[28] have been prepared from their corresponding 5-iodo-ribo precursors by treatment with AgF in pyridine and potassium *tert*-butoxide in DMSO, respectively. It was reported that the exocyclic vinyl ether system in the product is more sensitive to acid than is the isopropylidene group,[28,29] and 2′,3′-unprotected 5′-iodouridine did not afford the corresponding 4′,5′-olefin;[28] **3** was O-deisopropylidenated to **4** and then acetylated to the 2′,3′-di-*O*-acetyl derivative **5** prior to the olefin formation. 5-(2,3-Di-*O*-acetyl-5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)-1,3-dimethyluracil (**6**) was obtained in high yield as colorless crystals from the reaction of **5** with AgF at room temperature for 4 days in anhydrous pyridine under protection from light. This compound showed a pair of double double doublets at δ 4.22 and 4.52 ($J_{5',5''}$ = 2.1, $J_{3',5'}$ = 1.0, $J_{3',5''}$ = 2.1 Hz) in the ^1H NMR spectrum, the overall spectral pattern was very similar to that of 1-(2,3-di-*O*-acetyl-5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)uracil.[28] Saponification of **6** with NH_3/MeOH afforded the unprotected olefin **7** in high yield in crystalline form.

We prepared crystalline 2′,3′-*O*-isopropylidene-5′-*O*-mesyl-1,3-dimethylpseudouridine in quantitative yield (**8**, Scheme II) by mesylation of **2** with MsCl in pyridine. Treatment of **8** with AgF in pyridine afforded the 5′-fluoro derivative **9** as the only isolable product. It was reported[28] that 2′,3′-*O*-isopropylidene-5′-*O*-mesyluridine was converted into 1-(5-deoxy-2,3-*O*-isopropylidene-β-D-*erythro*-pent-4-enofuranosyl)uracil in 84% yield by treatment with potassium *tert*-butoxide in DMSO. The mesylate **8**, however, did not afford the 4′,5′-olefin **6**, upon butoxide treatment in Me_2SO, but, after column chromatography, gave 5-[(3*R*,4*R*)-2,3-dihydroxy-4,5-epoxy-2,3-*O*-isopropyliden-1-yl]-1,3-dimethyluracil **10**, albeit in low yield (5.6%), and 54% of unreacted **8** was recovered from the

Scheme II[a]



[a] (a) MsCl/pyridine; (b) AgF/pyridine; (c) *t*-BuOK/Me_2CO; (d) $NaCN/Me_2SO$.

reaction mixture. Treatment of **8** with sodium methylsulfinylmethide instead of potassium *tert*-butoxide afforded the with **10** in a similar yield. The ^1H NMR spectrum of **10** showed the signal for 5′ and 5″ protons as a doublet at δ 2.82 and the H-4′ signal as a multiplet

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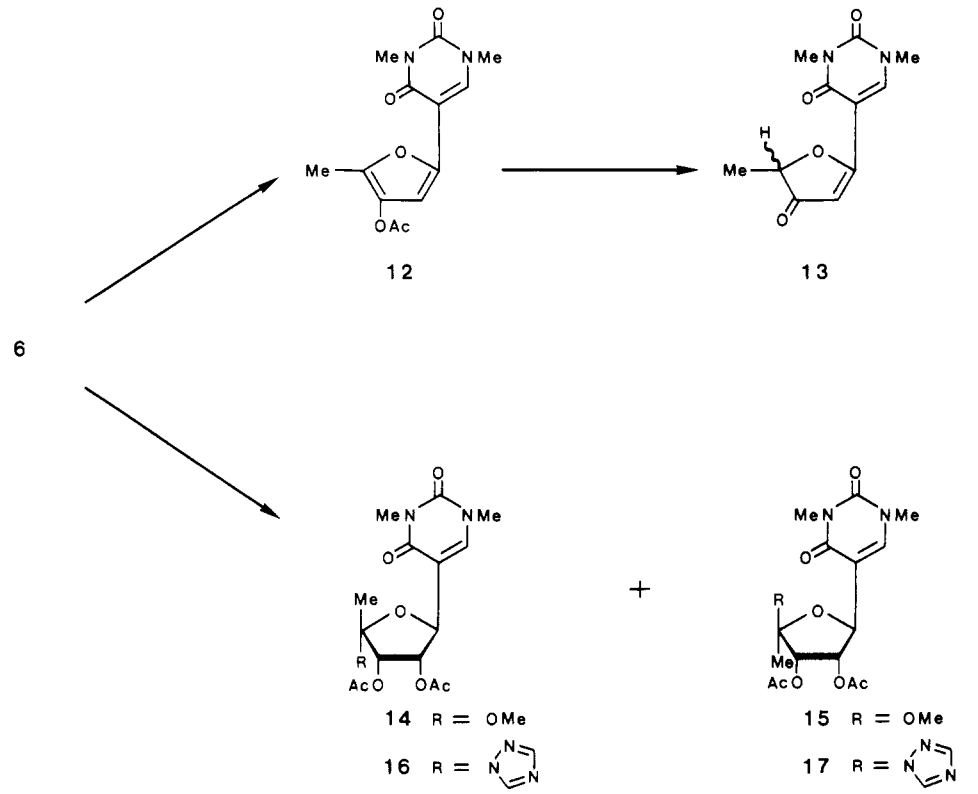
Scheme III[a]



[a] (a) $HgCl_2$ or concentrated H_2SO_4/Me_2CO; (b) concentrated NH_4OH/EtOH; (c) AcOH/MeOH; (d) triazole + H_3PO_4/MeCN.

centered at 3.15 ppm. The H-1′ signal appeared at δ 5.56 and showed a typical allylic coupling[30] with H-3′ ($J_{1',3'}$ = 1.7 Hz). The large red shift of this product in the UV spectrum (by 42 nm) also established the extension of conjugation. The elemental analyses are fully consistent with the vinyl–epoxy structure **10** for the product. It should be noted that the formation of **10** from **8** is very unusual, since the reaction mechanism apparently involved in the dissociation of the 2′-bridgehead proton.

Reaction of **10** with NaCN in DMF at room temperature for 2 days afforded 1,3-dimethyl-5-[(3*R*,4*R*)-4,5-*O*-isopropylidene-1-nitrilo-3,4,5-trihydroxy-5-hexen-6-yl]uracil (**11**) in 65% yield. The IR spectrum of **11** showed CN and OH group stretching frequencies at 2250 and 3420 cm^{-1}, respectively. The ^1H NMR spectrum exhibited H-2′ and H-3′ as a doublet and a quartet, respectively, centered at δ 2.67 and 4.06 ppm ($J_{2',3'}$ = 5.8, $J_{3',4'}$ = 5.0 Hz). The formation of **11** also supports the epoxy–vinyl structure of **10**.

Reaction of the 4′,5′-olefin **6** with $HgCl_2$ in acetone afforded 5-(4-acetoxy-5-methylfuran-2-yl)-1,3-dimethyluracil (**12**, Scheme III) in 55% yield in crystalline form after chromatographic purification. The ^1H NMR spectrum of this product showed only six sharp singlets, four for methyl signals for 5-Me, Ac, 1 and 3 NMe at δ 2.20, 2.25, 3.22, and 3.41 and two for H-3′ and H-6 at δ 6.52 and 8.06. The large bathochromic shift (nm) in the UV spectrum is also consistent with the elongated conjugation in **12**. Deacetylation of **12** with NH_3/MeOH afforded in quantitative yield a crystalline product. The two singlets for the Ac and 5-Me signals of **12** in the ^1H NMR spectrum disappeared completely, and a one proton quartet for H-5′ and a doublet for 5′-Me appeared at δ 4.96 and 1.36, respectively, establishing the enone structure **13** for this product.

Treatment of **6** with a catalytic amount of AcOH in MeOH afforded 5-(2,3-di-*O*-acetyl-5-deoxy-4-methoxy-β-D-ribofuranosyl)-1,3-dimethyluracil (**14**) and 5-(2,3-*O*-acetyl-5-deoxy-4-methoxy-α-L-lyxofuranosyl)-1,3-dimethyluracil (**15**) in 76.5 and 13.5% yield after chromatographic purification. The H-1′ signal of the β-ribo isomer **14** in the ^1H NMR spectrum appeared at considerably higher magnetic field (δ 4.65) than that the α-L isomer **15** (δ 5.08). The $J_{1',2'}$ value for **14** (3.0 Hz) is larger than that for **15** (7.0 Hz). These spectral characteristics are very similar to those reported by Verheyden and Moffatt[31] for 1-(2,3-di-*O*-acetyl-5-deoxy-4-methoxy-β-D-ribofuranosyl)-uracil and its α-L-lyxo isomer.

Reaction of **6** with 1,2,4-triazole in dry acetonitrile in the presence of a catalytic amount of phosphoric acid gave 5-[2,3-di-*O*-acetyl-5-deoxy-4-(1*H*-1,2,4-triazol-1-yl)-β-D-ribofuranosyl]-1,3-dimethyluracil (**16**) and its α-L-lyxo isomer **17** in 62 and 29% yield, respectively. The structural assignment was made on the basis of stereochemical consideration that the conformation of the intermediate is more favorable in the envelope form. Also, the ^1H NMR spectral patterns of **16** and **17** are very similar to those of the 4′-methoxy-β-D-ribo derivative **14** and 4′-methoxy-α-L C-nucleoside **15**.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Elemental analyses were carried out on a Perkin-Elmer Model 240C analyzer at KAIST or performed by M-H-W Laboratories, Phoenix, AZ. ^1H NMR spectra were recorded on a JEOL PMS-60 or a Varian T-60A or a JEOL FX90Q spectrometer with Me_4Si as the internal standard. Chemical shifts are reported in ppm (δ), and signals are described

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as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br s (broad singlet), dd (double doublet). Values given for coupling constants are first order. IR spectra were recorded on a Analect FX-6160 FT-IR and UV spectra on a Beckmann DU-7 spectrometer. TLC was performed on precoated glass plates with Kieselgel 60 F-254 (0.25 mm, Merck), and column chromatography on Kieselgel 60 (70–230 mesh, Merck).

1,3-Dimethyl-5-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)uracil (2). A mixture of 1[5] (45.7 g, 0.168 mol), 2,2-dimethoxypropane (52 mL, 0.42 mol), and *p*-TsOH (10 g) in Me_2CO (1 L) was stirred at room temperature for 2 h. $NaHCO_3$ (20 g) was added, and the mixture was stirred at room temperature for 3 h. Insoluble salts were removed by filtration, the filtrate was concentrated in vacuo, and the residue was crystallized from $CHCl_3$–Et_2O to give **2** (50.7 g, 97%): mp 80–85 °C; ^1H NMR (Me_2SO-d_6) δ 1.26 (3 H, s, *i*-Pr), 1.48 (3 H, s, *i*-Pr), 3.17 (3 H, s, NMe), 3.31 (3 H, s, NMe), 3.52 (2 H, m, H-5′, 5″), 3.89 (1 H, m, H-4′), 4.67 (3 H, m, H-1′,2′,3′), 4.83 (1 H, br s, OH), 7.80 (1 H, s, H-6). Anal. Calcd for $C_{14}H_{20}N_2O_6$: C, 53.85; H, 6.41; N, 8.97. Found: C, 53.79; H, 6.49; N, 8.69.

5-(5-Deoxy-5-iodo-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-1,3-dimethyluracil (3). A mixture of **2** (46.9 g, 0.15 mol) and $(PhO)_3PMeI$ (97 g) in DMF (400 mL) was stirred at room temperature for 2 h. The mixture was concentrated in vacuo, and the residue was chromatographed on a column of silica gel (C_6H_{14}–EtOAc, 4:1) to give **3** (62.4 g, 98%) as a foam: ^1H NMR ($CDCl_3$) δ 1.35 (3 H, s, *i*-Pr), 1.47 (3 H, s, *i*-Pr), 3.37 (3 H, s, NMe), 3.43 (3 H, s, NMe), 3.47 (2 H, m, H-5′,5″), 3.97 (1 H, m, H-4′), 4.49–4.85 (2 H, m, H-2′,3′), 4.92 (1 H, s, H-1′), 7.45 (1 H, s, H-6). Anal. Calcd for $C_{14}H_{19}IN_2O_5$: C, 39.82; H, 4.54; N, 6.64. Found: C, 39.90; H, 4.62; N, 6.43.

5-(5-Deoxy-5-iodo-β-D-ribofuranosyl)-1,3-dimethyluracil (4). A mixture of **3** (45.7 g, 0.11 mol), AcOH (210 mL), and H_2O (210 mL) was heated at reflux for 30 min. The solution was concentrated in vacuo, and the residue was crystallized from EtOH (200 mL) to give **4** (36.1 g, 87%): mp 149–150 °C dec; UV (MeOH) λ_{max} 270.0 nm (7500), 202.0 (ε 12800), λ_{min} 236.8 (ε 700); ^1H NMR ($CDCl_3$) δ 3.22 (3 H, s, NMe). Anal. Calcd for $C_{11}H_{15}IN_2O_5$: C, 34.57; H, 3.96; N, 7.33. Found: C, 34.64; H, 4.03; N, 7.37.

5-(2,3-Di-*O*-acetyl-5-deoxy-5-iodo-β-D-ribofuranosyl)-1,3-dimethyluracil (5). A suspension of **4** (30.0 g, 78.5 mmol) in Ac_2O (380 mL) was stirred at 120–125 °C for 5 h. The resulting solution was concentrated in vacuo, and the residue was crystallized from EtOH (300 mL) to give 35.2 g of **5**, mp 100.5–101.5 °C. From the mother liquor, an additional amount of **5** (0.9 g) was obtained to give a total yield of 96%. UV (MeOH) λ_{max} 256.5 nm (ε 13000), 201.2 (ε 35800), λ_{min} 234.4 (ε 8900); ^1H NMR ($CDCl_3$) δ 2.10 (6 H, s, 2 Ac), 3.32 (3 H, s, NMe), 3.40 (3 H, s, NMe), 3.47–3.55 (2 H, m, H-5′,5″), 3.97 (1 H, m, H-4′), 4.92 (1 H, d, H-1′, $J_{1',2'}$ = 4.5 Hz), 5.14 (1 H, t, H-3′, $J_{2',3'} = J_{3',4'}$ = 5.1 Hz), 5.40 (1 H, dd, H-2′, $J_{1',2'}$ = 4.5, $J_{2',3'}$ = 5.1 Hz), 7.52 (1 H, s, H-6). Anal. Calcd for $C_{15}H_{19}IN_2O_7$: C, 38.64; H, 4.11; N, 6.01. Found: C, 38.89; H, 4.36; N, 5.98.

5-(2,3-Di-*O*-acetyl-β-D-*erythro*-pent-4-enofuranosyl)-1,3-dimethyluracil (6). A mixture of **5** (30.58 g, 65.6 mmol) and AgF (24.6 g, 194 mmol) in anhydrous pyridine (300 mL) was stirred at room temperature under protection of light for 4 days. Insoluble salts were removed by filtration, and the filtrate was concentrated in vacuo. The residue was shaken well with a mixture of $CHCl_3$ (600 mL) and 1 M NH_4Cl (300 mL). After filtration from insoluble salts, the organic layer was washed with H_2O (150 mL), dried (Na_2SO_4), and concentrated in vacuo, and the residue was chromatographed on a silica gel column (C_6H_{14}–EtOAc, 1:1) to give **6** (22.7 g, 98%) as a foam, which was crystallized from Et_2O: mp 47–48 °C; UV (MeOH) λ_{max} 270.8 nm (ε 6900), 207.2 (ε 8700), λ_{min} 236.4 (ε 50); ^1H NMR ($CDCl_3$) δ 2.07 (6 H, s, 2 Ac), 3.30 (3 H, s, NMe), 3.37 (3 H, s, NMe), 4.22 (1 H, dd, H-5′, $J_{5',5''}$ = 2.1, $J_{3',5'}$ = 1.0 Hz), 4.52 (1 H, t, H-5″, $J_{5',5''} = J_{3',5''}$ = 2.1 Hz), 5.08 (1 H, d, H-1′, $J_{1',2'}$ = 3.8 Hz), 5.42 (1 H, dd, H-2′, $J_{1',2'}$ = 3.8, $J_{2',3'}$ = 5.0 Hz), 5.77 (1 H, m, H-3′), 7.12 (1 H, s, H-6). Anal. Calcd for $C_{15}H_{18}N_2O_7$: C, 51.53; H, 5.56; N, 8.59. Found: C, 51.49; H, 5.40; N, 8.40.

5-(5-Deoxy-β-D-*erythro*-pent-4-enofuranosyl)-1,3-dimethyluracil (7). To a solution of **6** (326 mg, 1 mmol) in MeOH (5 mL) was added a drop of concentrated NH_4OH, and the mixture was stirred at room temperature for 1 h. After concentration of the mixture in vacuo, the residue was crystallized from EtOH–Et_2O to give **7** (216 mg, 86%): mp 149–150 °C; UV (MeOH) λ_{max} 272.8 nm (ε 6300), 208.8 (ε 5600), λ_{min} 253.6 (ε 50); ^1H NMR (Me_2SO-d_6) δ 3.16 (3 H, s, NMe), 3.32 (3 H, s, NMe), 4.05 (2 H, m, H-5′, OH), 4.21 (2 H, m, H-2′,5″), 4.85 (1 H, m, H-3′), 5.06 (1 H, d, H-1′, $J_{1',2'}$ = 5.0 Hz), 7.57 (1 H, s, H-6). Anal. Calcd for $C_{11}H_{14}N_2O_5 \cdot 0.5H_2O$: C, 50.18; H, 5.74; N, 10.64. Found: C, 50.20; H, 5.63; N, 10.81. The presence of a small amount of H_2O was detected by ^1H NMR spectroscopy.

1,3-Dimethyl-5-(2,3-*O*-isopropylidene-5-*O*-mesyl-β-D-ribofuranosyl)uracil (8). To an ice-cooled solution of **2** (11 g, 35.2 mmol) in pyridine (50 mL) was added MsCl (3.27 mL, 42.3 mmol). The mixture was stirred at 0 °C for 2 h and then at room temperature for 1 h. The mixture was concentrated in vacuo, and the residue was dissolved in $CHCl_3$, washed (H_2O), dried (Na_2SO_4), and concentrated in vacuo. The residue was triturated with Et_2O to give crystalline **8** (12.8 g, 93%): mp 117–119 °C; UV λ_{max} (MeOH) 268 and 207.5 nm; ^1H NMR ($CDCl_3$) δ 1.35 (3 H, s, *i*-Pr), 1.58 (3 H, s, *i*-Pr), 3.04 (3 H, s, Ms), 3.33 (3 H, s, NMe), 3.40 (3 H, s, NMe), 4.07–4.80 (3 H, m, H-2′,3′,4′), 4.90 (3 H, m, H-1′,5′,5″), 7.37 (1 H, s, H-6). Anal. Calcd for $C_{15}H_{22}N_2O_8S$: C, 46.14; H, 5.68; N, 7.18. Found: C, 46.22; H, 5.86; N, 6.96.

5-(5-Deoxy-5-fluoro-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-1,3-dimethyluracil (9). A mixture of **8** (3.9 g, 0.01 mol) and AgF (2.5 g, 0.02 mol) in pyridine (50 mL) was heated at refluxed for 1.5 h. The mixture was concentrated in vacuo, and the residue was chromatographed on a silica gel column (C_6H_{14}–EtOAc, 1:1) to give **9** (2.24 g, 77%) as an oil: ^1H NMR ($CDCl_3$) δ 1.35 (3 H, s, *i*-Pr), 1.59 (3 H, s, *i*-Pr), 3.35 (3 H, s, NMe), 3.40 (3 H, s, NMe), 4.06–4.36 (1 H, dm, H-4′, $J_{4',F}$ = 26.1 Hz), 4.62 (2 H, dm, H-5′,5″, $J_{5',F} = J_{5'',F}$ = 47.2 Hz), 4.72–4.77 (2 H, m, H-2′,3′), 4.88 (1 H, s, H-1′), 7.27 (1 H, s, H-6). Anal. Calcd for $C_{14}H_{19}FN_2O_5$: C, 55.50; H, 6.09; N, 8.91. Found: C, 53.53; H, 6.24; N, 8.81.

5-[(3*R*,4*R*)-2,3-Dihydroxy-4,5-epoxy-2,3-*O*-isopropylidene-1-penten-1-yl]-1,3-dimethyluracil (10). To a solution of **8** (20.66 g, 53 mmol) in anhydrous DMSO (100 mL) was added finely pulverized *t*-BuOK (4.75 g, 42.4 mmol), and the mixture was stirred at room temperature for 1 h. The mixture was acidified with AcOH (3 mL) and then diluted with $CHCl_3$ (200 mL) and H_2O (100 mL). The organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo, and the residue was chromatographed on a silica gel column (C_6H_{14}–EtOAc, 1:1). Compound **10** (870 mg, 5.6%), mp 142–144 °C, was eluted first from the column, followed by 11.2 g (54%) of unreacted **8**: UV (MeOH) λ_{max} 311.2 nm (ε 7700), 247.2 (ε 12900), λ_{min} 278.0 (ε 3100), 224.4 (ε 7600); ^1H NMR (**10**) ($CDCl_3$) δ 1.48 (3 H, s, *i*-Pr), 1.63 (3 H, s, *i*-Pr), 2.82 (2 H, d, H-5′,5″), 3.10–3.21 (1 H, m, H-4′), 3.38 (3 H, s, NMe), 3.44 (3 H, s, NMe), 4.63 (1 H, dd, H-3′, $J_{1',3'}$ = 1.5, $J_{3',4'}$ = 3.4 Hz), 5.56 (1 H, d, H-1′), 7.76 (1 H, s, H-6); UV (MeOH) λ_{max} 310 and 249.5 nm. Anal. Calcd for $C_{14}H_{18}N_2O_5$: C, 57.13; H, 6.17; N, 9.52. Found: C, 56.99; H, 6.17; N, 9.71.

1,3-Dimethyl-5-[(3*R*,4*R*)-4,5-*O*-isopropylidene-1-nitrilo-3,4,5-trihydroxy-5-hexen-6-yl]uracil (11). A mixture of **10** (294 mg, 1 mmol) and NaCN (98 mg, 2 mmol) in DMSO (10 mL) was stirred at room temperature for 2 days. The mixture was partitioned between $CHCl_3$ (100 mL) and 1 M NH_4Cl (50 mL). The organic layer was separated, washed (H_2O, 20 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on a silica gel column (C_6H_{14}–EtOAc, 1:2) to give **11** (209 mg, 65.1%): mp 181–182 °C (from EtOH–Et_2O); UV λ_{max} (MeOH) 310.4 nm (ε 7500), 254.0 (12600), λ_{min} 281.2 (ε 4900), 227.6 (ε 9600); ^1H NMR ($CDCl_3$) δ 1.48 (3 H, s, *i*-Pr), 1.61 (3 H, s, *i*-Pr), 2.67 (2 H, d, H-2′, $J_{2',3'}$ = 5.8 Hz), 3.37 (3 H, s, NMe), 3.45 (3 H, s, NMe), 4.02 (1 H, br s, OH), 4.06 (1 H, m, H-3′), 4.77 (1 H, dd, H-4′, $J_{3',4'}$ = 5.0, $J_{4',6'}$ = 1.5 Hz), 5.54 (1 H, d, H-6′, $J_{4',6'}$ = 1.5 Hz), 7.74 (1 H, s, H-6); IR (KBr) ν 2250 cm^{-1} (CN). Anal. Calcd for $C_{15}H_{19}N_3O_5$: C, 56.06; H, 5.96; N, 13.08. Found: C, 55.87; H, 6.13; N, 13.00.

5-(4-Acetoxy-5-methylfuran-2-yl)-1,3-dimethyluracil (12). A mixture of **6** (652 mg, 2 mmol) and $HgCl_2$ (542 mg, 2 mmol) in Me_2CO (20 mL) was stirred at room temperature for 1 h. The mixture was concentrated in vacuo, and the residue was chromatographed on a silica gel column (C_6H_{14}–EtOAc, 5:4) to give **12** (360 mg, 55%, after crystallization from $CHCl_3$-C_6H_{14}): mp 162–163 °C; UV (MeOH) λ_{max} 323.5 and 255.0 nm; ^1H NMR

($CDCl_3$) δ 2.20 (3 H, s, Ac), 2.25 (3 H, s, 5-Me), 3.22 (3 H, s, NMe), 3.41 (3 H, s, NMe), 6.82 (1 H, s, H-3′), 8.08 (1 H, s, H-6). Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.10; H, 5.07; N, 10.07. Found: C, 56.01; H, 5.11; N, 9.98.

1,3-Dimethyl-5-(5-methyl-4-oxo-4,5-dihydrofuran-2-yl)-uracil (13). To a solution of **12** (163 mg, 0.5 mmol) in EtOH (5 mL) was added concentrated NH_4OH (5 mL). The mixture was stirred at room temperature for 1 h and then concentrated in vacuo. The residue was crystallized from EtOH to give **13** (160 mg, 98%): mp 204.5–206 °C; UV (MeOH) λ_{max} 325.0 and 255.5 nm; ^1H NMR ($CDCl_3$) δ 1.36 (3 H, d, spacing 7.14 Hz), 3.22 (3 H, s, NMe), 3.46 (3 H, s, NMe), 4.69 (1 H, q, H-5′), 6.24 (1 H, s, H-3′), 8.54 (1 H, s, H-6). Anal. Calcd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.86. Found: C, 56.23; H, 5.02; N, 11.92.

5-(2,3-Di-*O*-acetyl-5-deoxy-4-methoxy-β-D-ribofuranosyl)-1,3-dimethyluracil (14) and 5-(2,3-Di-*O*-acetyl-5-deoxy-4-methoxy-α-L-lyxofuranosyl)-1,3-dimethyluracil (15). To a solution of **6** (600 mg, 1.77 mmol) in anhydrous MeOH (5 mL) was added a drop of AcOH. The mixture was heated under reflux, excluding moisture, for 3 days. After removal of the solvent in vacuo, the residue was chromatographed on a column of silica gel (EtOAc).

Compound **15** was eluted from the column first (R_f 0.54 on TLC, AcOEt) (88.5 mg, 13.5%): mp 109–110 °C (after crystallization from Et_2O); UV (MeOH) λ_{max} 269.2 nm (ε 12000), 206.8 (ε 13600), λ_{min} 234.8 (ε 880); ^1H NMR ($CDCl_3$) δ 1.43 (3 H, s, 5′-Me), 2.03 (3 H, s, OAc), 2.13 (3 H, s, OAc), 3.30 (6 H, s, 2 NMe), 3.38 (3 H, s, OMe), 5.08 (1 H, d, H-1′, $J_{1',2'}$ = 7.0 Hz), 5.26 (1 H, d, H-3′, $J_{2',3'}$ = 5.0 Hz), 5.57 (1 H, dd, H-2′), 7.28 (1 H, s, H-6). Anal. Calcd for $C_{16}H_{22}N_2O_8$: C, 51.88; H, 5.99; N, 7.56. Found: 51.68; H, 5.99; N, 7.51.

Compound **14** was then eluted from the column (R_f 0.28 on TLC, EtOAc) (501.5 mg, 76.5%): mp 100–101 °C (crystallization from Et_2O); UV (MeOH) λ_{max} 270.8 nm (ε 8200), 210.0 (ε 8500), λ_{min} 234.8 (ε 220); ^1H NMR ($CDCl_3$) δ 1.50 (3 H, s, 5′-Me), 2.12 (6 H, s, 2 OAc), 3.32 (6 H, s, NMe and OMe), 3.40 (3 H, s, NMe), 4.65 (1 H, d, H-1′, $J_{1',2'}$ = 3.0 Hz), 5.12–5.43 (2 H, m, H-2′,3′), 7.17 (1 H, s, H-6). Anal. Calcd for $C_{16}H_{22}N_2O_8$: C, 51.88; H, 5.99; N, 7.56. Found: C, 51.62; H, 5.99; N, 7.40.

5-[2,3-Di-*O*-acetyl-5-deoxy-4-(1*H*-1,2,4-triazol-1-yl)-β-D-ribofuranosyl]-1,3-dimethyluracil (16) and 5-[2,3-Di-*O*-acetyl-5-deoxy-4-(1*H*-1,2,4-triazol-1-yl)-α-L-lyxofuranosyl]-1,3-dimethyluracil (17). To a mixture of **6** (200 mg, 0.6 mmol) and 1,2,4-triazole (100 mg, 1.45 mmol) in dry MeCN (3 mL) was added a drop of H_3PO_4. The mixture was heated under reflux overnight. After concentration in vacuo, the residue was chromatographed on a silica gel column (EtOAc).

Compound **17** eluted from the column (R_f 0.43 on TLC $CHCl_3$–MeOH, 15:1) (70.9 mg, 29%): mp 136–137 °C (after crystallization from CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.98 (3 H, s, 5′-Me), 2.13 (3 H, s, OAc), 2.17 (3 H, s, OAc), 3.38 (3 H, s, NMe), 3.43 (3 H, s, NMe), 5.18 (1 H, d, H-1′, $J_{1',2'}$ = 5.0 Hz), 5.78 (1 H, t, H-2′, $J_{1',2'} = J_{2',3'}$ = 5.0 Hz), 6.03 (1 H, d, H-3′), 7.47 (1 H, s, H-6), 8.05 (1 H, s, triazole), 8.47 (1 H, s, triazole). Anal. Calcd for $C_{17}H_{21}N_5O_7$: C, 50.12; H, 5.20; N, 17.19. Found: C, 50.13; H, 5.18; N, 17.33.

Compound **16** was then eluted from the column (R_f 0.32 on TLC $CHCl_3$–MeOH, 15:1 v/v) (151.5 mg, 62% after recrystallization from CH_2Cl_2): mp 150–151 °C; UV (MeOH) λ_{max} 266.8 nm (ε 11000), 204.4 (ε 15900), λ_{min} 231.6 (5300); ^1H NMR ($CDCl_3$) δ 1.93 (6 H, s, 2 OAc), 1.97 (3 H, s, 5′-Me), 3.33 (3 H, s, NMe), 3.42 (3 H, s, NMe), 5.06 (1 H, d, $J_{1',2'}$ = 4.0 Hz), 5.63 (1 H, dd, H-2′, $J_{1',2'}$ = 4.0, $J_{2',3'}$ = 6.0 Hz), 5.78 (1 H, d, H-3′), 7.27 (1 H, s, H-6), 7.87 (1 H, s, triazole), 8.30 (1 H, s, triazole). Anal. Calcd for $C_{17}H_{21}N_5O_7$: C, 50.12; H, 5.20; N, 17.19. Found: C, 49.87; H, 5.15; N, 17.04.

Anchimeric Assistance of a 5′-*O*-Carbonyl Function for Inversion of Configuration at the 3′-Carbon Atom of 2′-Deoxyadenosine. Synthesis of 3′-Azido-2′,3′-dideoxyadenosine and 3′-Azido-2′,3′-dideoxyinosine

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3′-Azido-2′,3′-dideoxyadenosine was synthesized in two steps from N^6,5′-*O*-dibenzoyl-2′-deoxyadenosine in 65% yield. The configuration at the 3′ position was inverted by reaction of N^6,5′-*O*-dibenzoyl-2′-deoxyadenosine with triflic anhydride–pyridine and water. The product distribution under different reaction conditions is described together with a benzoyl migration reaction. The azido group was introduced by a nucleophilic substitution reaction with lithium azide on the 3′-*O*-triflate of *N*-benzoyl-9-(5-*O*-benzoyl-2-deoxy-β-D-*threo*-pentofuranosyl)adenine. Enzymatic deamination of 3′-azido-2′,3′-dideoxyadenosine gave 3′-azido-2′,3′-dideoxyinosine.

Introduction

3′-Azido-2′,3′-dideoxyadenosine (**3**) is a nucleoside analogue with interesting antitumoral activity.[1] It has been tested against the multiplication of the human immunodeficiency virus (HIV)[2] in vitro, but its selectivity index is too low. With respect to the synthesis of larger amounts of **3** for further in vivo tests on its antitumoral characteristics, a new and more straightforward synthesis than those described[2-5] is needed. Apart from these considerations, the continual research on effective and less toxic nucleosides such as 3′-azido-2′,3′-dideoxythymidine against the replication of the AIDS virus prompted us to synthesize 3′-azido-2′,3′-dideoxyinosine (**4**). Because of the altered substrate specificity of the HIV reverse transcriptase, compared to DNA polymerases,[6] it was reasoned that compound **4**, as its triphosphate, could eventually block selectively the function of the first enzyme. On the other hand, inosine 5′-phosphate is a direct precursor of

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