Nucleosides. 132. Synthesis of 5-(2′-Substituted-2′-deoxy-β-D-arabinofuranosyl)-1-methyluracils from 1-Methyl-ψ-uridine. The First Direct Introduction of the 2′-Substituent to C-2′ in the "Up" Configuration by Nucleophilic Reactions. Studies Directed toward the Synthesis of 2′-Deoxy 2′-Substituted *arabino* Nucleosides 3[1]

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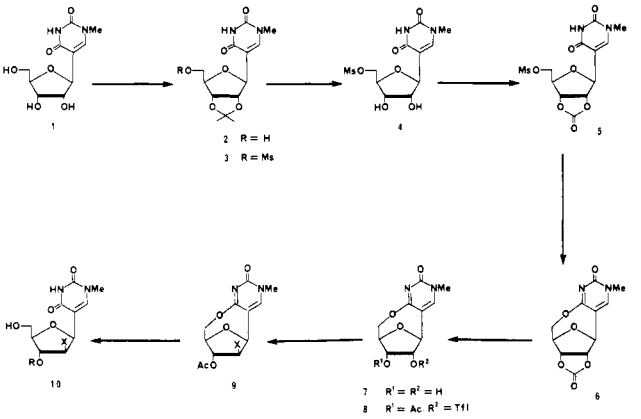
A general method is developed for the synthesis of pyrimidine C-nucleosides containing the 2′-substituted-2′-deoxyarabinofuranosyl moiety from a preformed *ribo* C-nucleoside by direct nucleophilic displacement reactions. 1-Methyl-ψ-uridine (**1**) was converted to the 2′,3′-*O*-acetonate **2** which was mesylated to **3**. Treatment of **3** in aqueous acetic acid gave 5′-*O*-mesyl-1-methyl-ψ-uridine (**4**) which was converted in three steps to 4,5′-anhydro-1-methyl-ψ-uridine (**7**) via the 2′,3′-*O*-carbonate **5** and the anhydro C-nucleoside **6**. 3′-*O*-Acetyl-2′-*O*-triflyl-4,5′-anhydro-ψ-uridine (**8**) was prepared in two steps from **7**. The 2′-triflate function was directly displaced by various nucleophiles by treatment with LiCl, LiBr, NaN_3, and NaOAc to afford the corresponding 4,5′-anhydro C-nucleosides (**9**) with the 2′-substituent in the "up" *arabino* configuration. The anhydro linkage of **9** was readily hydrolyzed by treatment with Dowex 50 (H^+) in aqueous solution to give the respective 5-(2′-deoxy-2′-substituted-β-D-arabinofuranosyl)-1-methyluracils (**10**).

Several 1-(2-substituted-2-deoxy-β-D-arabinofuranosyl)pyrimidine nucleosides have shown antitumor[2-4] and/or antiviral[5-7] activities. All of these nucleosides have been synthesized by condensation of an appropriate sugar halide and pyrimidine base. All attempts so far to introduce a substituent at the C-2′ position in the "up" *arabino* configuration from a preformed pyrimidine nucleosides by nucleophilic reaction have failed due to close proximity of the carbonyl function of the aglycon to C-2′[8] even in pyrimidine C-nucleosides.[9]

Syntheses of pyrimidine C-nucleosides containing the 2′-substituted arabinosyl moiety from an appropriate sugar either by condensation[10] or by multistep chain elongation and cyclization procedure[11] would be extremely inefficient due to formation of isomers, troublesome separations, and very low yield of the desired products. We have searched for a method of direct introduction of a 2′-up substituent into preformed pyrimidine C-nucleosides,[9,12] and found that preferential participation of the carbonyl group of the aglycon in intramolecular reaction of C-2′ is decreased in C-nucleosides vs. N-nucleosides. Consequently, substantial amounts of the 2′-up chloro derivative are formed during the reaction of ψ-uridine with α-acetoxyisobutyryl chloride. This report describes the first C-nucleoside interconversion

Scheme I



which should have general applicability for the synthesis of 2′-substituted arabinosylpyrimidine C-nucleosides.

Our strategy is to prevent participation of the carbonyl oxygen of the aglycon in an intramolecular nucleophilic reaction. In a 4,5′-anhydro C-nucleoside such as **7** (Scheme I), O-4 is tied up with the C-5′ position and thereby precludes its participation in the nucleophilic reaction which occurred on C-2′. Though the 2,5′-anhydrouridine is very susceptible to nucleophilic attack,[13] the anhydro linkage of 4,5′-anhydro-ψ-uridine is rather stable.[14] Nucleophilic displacement at C-2′ should occur much more readily in C-nucleosides than in N-nucleosides or glycosides due to the reduced inductive effect of the aglycon in the former. Therefore, a good leaving group such as [(trifluoromethyl)sulfonyl]oxy at C-2′ may be displaced directly by the SN_2 mechanism with various nucleophiles without rupturing the 4,5′-anhydro linkage.[15]

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We therefore prepared 3′-*O*-acetyl-2′-*O*-[(trifluoromethyl)sulfonyl]-4,5′-anhydro-1-methyl-ψ-uridine (**8**) as shown in Scheme I for studies on direct nucleophilic displacement of the 2′-function. 4,5′-Anhydro-1-methyl-ψ-uridine (**7**) was prepared from 1-methyl-ψ-uridine[16,17] by adaptation of the procedure developed in our laboratory for the synthesis of 4,5′-anhydro-ψ-uridine.[14] Acetonation of **1** to **2** followed by mesylation afforded **3** in high yield. Deactonation of **3** in aqueous HOAc gave **4** which was converted into the cyclic 2′,3′-*O*-carbonate **5** by treatment with 1,1′-carbonyldiimidazole. This multistep procedure described herein to prepare **5** appeared to be more practical to use than the alternate route by direct 2′,3′-*O*-cyclic carbonylation of **1** according to the procedure of Letsinger and Ogilvie[18] followed by mesylation in terms of reaction time and isolation of the product. Treatment of **5** with DBU in DMF afforded the anhydro C-nucleoside **6** in quantitative yield. Removal of the cyclic 2′,3′-*O*-carbonate of **6** with aqueous pyridine[18] afforded **7**. All the intermediates (**2**–**7**) were obtained as crystals in good to excellent yields. Compound **7** analyzed correctly and the ^{1}H NMR spectrum in Me_2SO-d_6 showed the presence of two secondary OH doublets at δ 5.8 and 5.10 and the absence of an NH signal. These data are consistent with the 4,5′-anhydro nucleoside structure.

Monoacetylation of **7**, via 2′,3′-*O*-stannylation[19] afforded a mixture containing the 3′-acetate as the major component[20] which, without separation, was directly treated with (trifluoromethyl)sulfonyl chloride (triflyl chloride) and 4-(dimethylamino)pyridine in a mixture of CH_2Cl_2 and Et_3N. The major product **8** (the less polar component) was obtained in pure crystalline form in 66% yield. Displacement of the triflate function occurred very smoothly by treatment of **8** with LiCl, LiBr, NaOAc, or NaN_3 in DMF or HMPA at room temperature, and the corresponding 2′-substituted arabinosyl 4,5′-anhydro C-nucleosides (**9**) were obtained in about 20–70% yield in crystalline form after purification. The 4,5′-anhydro linkage of **9** was found to be hydrolyzed under very mild conditions by treatment with Dowex 50 (H^+) in aqueous solution at room temperature, and the desired 5-(2-substituted-2-deoxy-β-D-arabinofuranosyl)-1-methyluracils (**10**) were obtained. The 2′-chloro derivative (**10b**) was converted into the known 2′-deoxy-1-methyl-ψ-uridine[17,21] upon reduction with *n*-Bu_3SnH under the Barton's conditions.[22] This conversion unambiguously established the location of substituent at C-2′ and the structure of the triflate **8**. The ^{1}H NMR spectrum of **10b** was identical with that of the known 5-(2′-chloro-2′-deoxy-β-D-arabinosyl)-1,3-dimethyluracil[9] except that the latter shows an extra methyl signal and lacks the NH signal. The 2′,3′-di-*O*-acetyl derivative (**9d**), upon treatment with Dowex 50 (H^+) gave a product (**10d**, X = OH, R = H), which was different from the isomeric 1-methyl-ψ-uridine.[16,17] The ^{1}H NMR spectrum of **10d** was very similar to that of 5-arabinosyluracil.[21] The above data established the arabinosyl structure of **10**.

We have thus developed a general method of converting pyrimidine C-ribonucleosides into 2′-substituted arabinosyl C-nucleosides by direct introduction of a substituent by nucleophilic reactions. Application of this method to the synthesis of arabinosyl regular pyrimidine nucleosides is currently being studied in our laboratory.

Experimental Section

General Methods. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL-PFT-100 spectrometer, and Me_4Si was the internal standard for organic solvents and DSS for D_2O; chemical shifts are reported in parts per million (δ). Apparent shapes of signals are described as s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), m (multiplet), and brs (broad singlet). Values given for coupling constants are first order. TLC was performed on Uniplates (Analtech Co., Newark, DE) and column chromatography on Woelm silica gel (70–230 mesh). Microanalyses were performed by Galbraith Laboratories, Inc., M.H.W. Laboratories, or Spang Microanalytical Laboratory.

1-Methyl-5-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-uracil (2, 1-Methyl-2′,3′-*O*-isopropylidene-ψ-uridine). A mixture of **1** (13 g, 0.05 mol), 2,2-dimethoxypropane (15 mL, 0.12 mol), and *p*-TsOH (2 g) in acetone (500 mL) was stirred at room temperature for 1 h. To the clear solution was added solid $NaHCO_3$ (5 g), and the mixture was stirred for 3 h. Insoluble salts were removed by filtration and the filtrate was concentrated in vacuo. The residue was covered with Et_2O and stored overnight at 4 °C. Colorless crystals were collected by filtration to give 12 g (80%) of **2**: mp 139–140 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.27 (3 H, s, CMe), 1.48 (3 H, s, CMe), 3.24 (3 H, s, NMe), 3.52 (2 H, m, H-5′,5″), 3.90 (1 H, q, H-4′), 4.65 (3 H, m, H-1′,2′,3′), 4.83 (1 H, t, 5′-OH), 7.76 (1 H, s, H-6), 11.38 (1 H, s, NH).

Anal. Calcd for $C_{13}H_{18}N_2O_6$: C, 52.34; H, 6.08; N, 9.39. Found: C, 52.15; H, 5.91; N, 9.29.

1-Methyl-5-(2′,3′-*O*-isopropylidene-5′-*O*-mesyl-β-D-ribofuranosyl)uracil (3, 1-Methyl-2′,3′-*O*-isopropylidene-5′-*O*-mesyl-ψ-uridine). A solution of **2** (12 g, 0.04 mol) in pyridine (100 mL) was cooled in an ice bath, and MsCl (3.42 mL, 0.044 mol) was added dropwise with stirring. The mixture was stirred at 0 °C for 3 h and then at room temperature for 1 h. The mixture was concentrated in vacuo, and the residue dissolved in $CHCl_3$ (200 mL), washed (H_2O), dried (Na_2SO_4), and then concentrated in vacuo. The residue was triturated with Et_2O to give 14.6 g (97%) of crystalline **3**: mp 146–148 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.28 (3 H, s, CMe), 1.48 (3 H, s, CMe), 3.23 (3 H, s, NMe), 3.32 (3 H, s, Ms), 4.13–4.38 (3 H, m, H-4′,5′,5″), 4.62–4.87 (3 H, m, H-1′,2′,3′), 7.73 (1 H, s, H-6), 11.41 (1 H, s, NH). An analytical sample was prepared by recrystallization of the above material from EtOH, mp 151–152 °C.

Anal. Calcd for $C_{14}H_{20}N_2O_8S$: C, 44.67; H, 5.36; N, 7.44. Found: C, 44.65; H, 5.44; N, 7.37.

1-Methyl-5-(5′-*O*-mesyl-β-D-ribofuranosyl)uracil (4, 1-Methyl-5′-*O*-mesyl-ψ-uridine). Compound **3** (5.73 g, 0.015 mol) in 50% aqueous HOAc (150 mL) was heated under reflux for 25 min and then concentrated to dryness in vacuo. The residue was triturated with $CHCl_3$ (50 mL), and crystals were collected and recrystallized from EtOH to give 4.57 g (89%) of **5**: mp 131–133 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.21 (3 H, s, NMe), 3.23 (3 H, s, Ms), 3.91–3.98 (3 H, m, H-4′,5′,5″), 4.38–4.55 (3 H, m, H-1′,2′,3′), 7.58 (1 H, s, H-6), 11.33 (1 H, s, NH).

Anal. Calcd for $C_{11}H_{16}N_2O_8S \cdot {}^1/_2H_2O$: C, 38.26; H, 4.96; N, 8.11. Found: C, 38.62; H, 4.96; N, 8.10.

1-Methyl-5-(2′,3′-*O*-carbonyl-5′-*O*-mesyl-β-D-ribofuranosyl)uracil (5). To an ice-cooled solution of **4** (10.1 g, 0.03 mol) in dry DMF (100 mL) was added 1,1′-carbonyldiimidazole (10.2 g, 0.06 mol). The mixture was stirred for 24 h at room temperature and then concentrated to dryness in vacuo. The oily residue was dissolved in EtOAc (300 mL), washed (H_2O, 3 × 20 mL), dried (Na_2SO_4), and concentrated in vacuo, and the residue was crystallized from MeOH. The yield of **5** was 7.52 g (69%): mp 163–164 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.20 (3 H, s, NMe), 3.24 (3 H, s, Ms), 4.31–4.53 (3 H, m, H-4′,5′,5″), 4.87 (1 H, d, H-1′, $J_{1',2'}$ = 3.0 Hz), 5.19 (1 H, m, H-3′), 5.35 (1 H, dd, H-2′, $J_{1',2'}$ = 3.0, $J_{2',3'}$

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= 7.8 Hz), 7.82 (1 H, s, H-6), 11.52 (1 H, s, NH).

Anal. Calcd for $C_{12}H_{14}N_2O_9S$: C, 39.70; H, 3.90; N, 7.73. Found: C, 39.67; H, 3.92; N, 7.83.

4,5′-Anhydro-1-methyl-(2′,3′-*O*-carbonyl-β-D-ribofuranosyl)uracil (6). A mixture of **5** (7.0 g, 0.019 mol) and DBU (3.18 mL, 0.021 mol) in DMF (100 mL) was heated at 100 °C for 1 h. After concentration of the mixture in vacuo, the residue was crystallized from EtOH to give **6** (4.9 g, 95%): mp >300 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.36 (3 H, s, NMe), 4.02 (1 H, d, H-5′, $J_{5',5''}$ = 13.4 Hz), 4.54–4.70 (2 H, m, H-4′,5″), 5.08 (1 H, s, H-1′), 5.40 (1 H, d, H-3′, $J_{2',3'}$ = 6.4 Hz), 5.57 (1 H, d, H-2′, $J_{2',3'}$ = 6.4 Hz), 8.38 (1 H, s, H-6).

Anal. Calcd for $C_{11}H_{10}N_2O_6$: C, 49.63; H, 3.79; N, 10.52. Found: C, 49.57; H, 3.83; N, 10.50.

4,5′-Anhydro-1-methyl-5-(β-D-ribofuranosyl)uracil (7, 4,5-Anhydro-1-methyl-ψ-uridine). A mixture of **6** (4.9 g, 0.018 mol), pyridine (100 mL), and water (100 mL) was heated at reflux for 3.5 h and then concentrated to dryness in vacuo. The residue was triturated with MeOH (20 mL) and crystalline **7** (3.62 g, 82%) was collected by filtration: mp 250–251 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 3.37 (3 H, s, NMe), 3.87–4.00 (2 H, m, H-4′,5′), 4.27–4.35 (2 H, m, H-2′,3′), 4.46 (1 H, dd, H-5″, $J_{5',5''}$ = 11.0, $J_{4',5''}$ = 2.5 Hz), 4.60 (1 H, s, H-1′), 8.24 (1 H, s, H-6).

Anal. Calcd for $C_{10}H_{12}N_2O_5$: C, 50.00; H, 5.04; N, 11.66. Found: C, 49.89; H, 5.27; N, 11.42.

Monoacetylation of 7. A mixture of **7** (720 mg, 3 mmol) and n-Bu_2SnO (150 mg, 3 mmol) in MeOH (75 mL) was heated at reflux until a clear solution was obtained. The solvent was removed in vacuo, the solid residue was dissolved in DMF (30 mL) and treated with Ac_2O (0.3 mL) overnight at room temperature. The mixture was concentrated in vacuo, and the residue was triturated with Et_2O (3 × 100 mL) to give 800 mg (91%) of a crude mixture. The ^{1}H NMR spectrum of this mixture showed two signals for H-6 at δ 8.31 and 8.28 in a ratio of 3:1. The crude product was, without purification, used directly in the next step.

An analytical sample of 3′-*O*-acetyl-4,5′-anhydro-1-methyl-ψ-uridine was obtained by trituration of the crude product with n-C_6H_{12} (3 × 100 mL) followed by three recrystallizations of the residue from MeOH: mp 250–253 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 2.07 (3 H, s, Ac), 3.35 (3 H, s, NMe), 3.89–4.18 (3 H, m, H-4′,5′,5″), 4.16–4.59 (2 H, m, H-1′,2′), 5.26 (1 H, d, H-3′, $J_{2',3'}$ = 6.3 Hz), 5.56 (1 H, d, OH), 8.30 (1 H, s, H-6).

Anal. Calcd for $C_{12}H_{14}N_2O_6$: C, 51.06; H, 5.00; N, 9.92. Found: C, 50.87; H, 5.12; N, 9.58.

3′-*O*-Acetyl-2′-*O*-triflyl-4,5′-anhydro-1-methyl-ψ-uridine (8). To a mixture of the above crude monoacetate (1.5 g, 5.3 mmol), 4-(dimethylamino)pyridine (648 mg, 5.3 mmol), and Et_3N (1.5 mL, 106 mmol) in CH_2Cl_2 (200 mL) was added CF_3SO_2Cl (1.2 mL) in CH_2Cl_2 (20 mL), and the mixture was stirred at room temperature for 1 h. The mixture was concentrated in vacuo, and the residue was thoroughly triturated with freshly distilled EtOAc (50 mL) to give crystalline **8** (1.45 g, 66%): mp 130–135 °C dec, ^{1}H NMR (Me_2SO-d_6) δ 2.12 (3 H, s, Ac), 3.39 (3 H, s, NMe), 4.12 (1 H, d, H-5′, $J_{5',5''}$ = 12.5 Hz), 4.56 (1 H, d, H-5″, $J_{5',5''}$ = 12.5 Hz), 4.63 (1 H, s, H-4′), 5.29 (1 H, s, H-1′) 5.65 (2 H, s, H-2′,3′), 8.35 (1 H, s, H-6).

Anal. Calcd for $C_{13}H_{13}F_3N_2O_8 \cdot H_2O$: C, 36.11; H, 3.50; N, 6.47; S, 7.41. Found: C, 35.80; H, 3.58; N, 6.35; S, 7.33. One molecule of water was detected by ^{1}H NMR.

4,5′-Anhydro-5-(3′-*O*-acetyl-2′-azido-2′-deoxy-β-D-arabinofuranosyl)-1-methyluracil (9a, X = N_3). A mixture of **8** (414 mg, 1 mmol) and LiN_3 (490 mg, 10 mmol) in DMF (25 mL) was stirred at room temperature for 6 h and then partitioned between EtOAc (200 mL) and water (100 mL). The aqueous layer was extracted with EtOAc (3 × 70 mL). The organic extracts were combined with the original EtOAc layer, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on a silica gel column with EtOAc–EtOH (9:1 v/v) as the eluent to give **9** (X = N_3, 205 mg, 67%): mp 225–227 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 2.12 (3 H, s, Ac), 3.40 (3 H, s, NMe), 4.01 (1 H, d, H-5″, $J_{5',5''}$ = 12.7 Hz), 4.45 (1 H, s, H-4′), 4.51 (1 H, d, H-5′, $J_{5',5''}$ = 12.7 Hz), 4.67 (1 H, dd, H-2′, $J_{1',2'}$ = 2.7, $J_{2',3'}$ = 8.0 Hz), 5.14 (1 H, s, H-1′), 5.20 (1 H, d, H-3′, $J_{2',3'}$ = 8.0 Hz), 8.26 (1 H, s, H-6); mass spectrum (IBu/DCI$^+$), m/e 308 (MH$^+$), 280 (MH$^+$ – N_2).

Anal. Calcd for $C_{12}H_{13}N_5O_5$: C, 46.91; H, 4.26; N, 22.79. Found: C, 46.73; H, 4.29; N, 22.65.

In a similar manner except using LiCl or LiBr and a longer reation time (36 h), **9b** (X = Cl), mp 257–260 °C, and **9c** (X = Br), mp 218–220 °C, were prepared in 48 and 20% yields, respectively. ^{1}H NMR (Me_2SO-d_6) for **9b** (X = Cl): δ 2.11 (3 H, s, Ac), 3.39 (3 H, s, NMe), 4.06 (1 H, dd, H-5′, $J_{4',5'}$ = 1.5 Hz, $J_{5',5''}$ = 12.2 Hz), 4.77 (1 H, brs, H-4′), 4.53 (1 H, dd, H-5″, $J_{4',5''}$ = 1.5, $J_{5',5''}$ = 12.2 Hz), 4.83 (1 H, dd, H-2′, $J_{1',2'}$ = 3.3, $J_{2',3'}$ = 8.0 Hz), 5.26 (1 H, d, H-3′, $J_{2',3'}$ = 8.0, $J_{3',4'}$ = 0 Hz), 5.28 (1 H, d, H-1′, $J_{1',2'}$ = 3.3 Hz), 8.29 (1 H, s, H-6); mass spectrum (IBu/DCI$^+$), m/e 301 (MH$^+$), 267 (MH$^+$ – Cl), 207 (MH$^+$ – Cl – OAc).

Anal. Calcd for $C_{12}H_{13}ClN_2O_5 \cdot {}^1/_{10}CHCl_3$: C, 46.48; H, 4.23; Cl, 14.73; N, 8.96. Found: C, 46.73; H, 4.29; Cl, 14.36; N, 9.04. Contamination of 0.1 mol of $CHCl_3$ was detected in ^{1}H NMR spectrum of this analytical sample.

For **9c** (X = Br): ^{1}H NMR (Me_2SO-d_6) δ 2.11 (3 H, s, Ac), 3.39 (3 H, s, NMe), 3.99 (1 H, dd, H-5′, $J_{4',5'}$ = 1.5, $J_{5',5''}$ = 12.0 Hz), 4.46 (1 H, brs, H-4′), 4.50 (1 H, dd, H-5″, $J_{4',5''}$ = 1.5, $J_{5',5''}$ = 12.0 Hz), 4.78 (1 H, dd, H-2′, $J_{1',2'}$ = 3.6, $J_{2',3'}$ = 8.0 Hz), 5.25 (1 H, d, H-3′, $J_{2',3'}$ = 8.0, $J_{3',4'}$ = 0 Hz), 5.35 (1 H, d, H-1′, $J_{1',2'}$ = 3.6 Hz), 8.25 (1 H, s, H-6); mass spectrum (IBu/DCI$^+$), m/e 347 (MH$^+$ + 2 H), 345 (MH$^+$), 301 (MH$^+$ – Ac), 207 (MH$^+$ – Br – OAc).

Anal. Calcd for $C_{12}H_{13}BrN_2O_5$: C, 41.76; H, 3.79; Br, 23.15; N, 8.11. Found: C, 41.82; H, 3.83; Br, 23.08; N, 8.16.

4,5′-Anhydro-1-methyl-5-(2′,3′-di-*O*-acetyl-β-D-arabinofuranosyl)uracil (9d, X = OAc). A mixture of **8** (414 mg, 1 mmol) and NaOAc (850 mg, 10 mmol) in HMPA (20 mL) was stirred overnight at room temperature. The mixture was poured into water (100 mL) and extracted with $CHCl_3$ (3 × 100 mL). The organic extracts were dried (Na_2SO_4) and evaporated, and the residue was triturated with Et_2O (300 mL). The semisolid precipitates were crystallized from EtOH to give **9d** (X = OAc): 85 mg (26%); mp 220–225 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.79 (3 H, s, Ac), 2.01 (3 H, s, Ac), 3.37 (3 H, s, NMe), 4.07 (1 H, d, H-5′, $J_{5',5''}$ = 13.4 Hz), 4.41 (1 H, brs, H-4′), 4.53 (1 H, d, H-5″, $J_{5',5''}$ = 13.4 Hz), 5.23–5.29 (3 H, m, H-1′,2′,3′), 8.12 (1 H, s, H-6).

Anal. Calcd for $C_{14}H_{16}N_2O_7 \cdot {}^1/_2H_2O$: C, 50.45; H, 5.14; N, 8.40. Found: C, 50.36; H, 4.84; N, 8.66.

5-(2′-Chloro-2′-deoxy-β-D-arabinofuranosyl)-1-methyluracil (10b, X = Cl, R = H). To a solution of **9b** (X = Cl) (200 mg, 0.67 mmol) in water (50 mL) was added Dowex-50 (H$^+$) (10 mL), and the mixture was stirred at room temperature until all the starting material was consumed (about 24 h). [TLC (EtOAc–EtOH 5:1) showed two product spots at this time.] The resin was filtered and washed with water. The combined filtrate and washings were concentrated in vacuo, and the residue was chromatographed on a silica gel column with $CHCl_3$–acetone (1:1 v/v) as the eluent. The first nucleoside product eluted from the column was **10b** (X = Cl, R = Ac) (35 mg, 16.5%) which was obtained as a foam: ^{1}H NMR (Me_2SO-d_6) δ 2.10 (3 H, s, Ac), 3.29 (3 H, s, NMe), 3.63 (2 H, m, H-5′,5″), 3.86–3.95 (1 H, m, H-4′), 4.59 (1 H, d, H-2′, $J_{1',2'}$ = 3.5, $J_{2',3'}$ = 0 Hz), 4.93 (1 H, dd, H-1′, $J_{1',2'}$ = 3.5, $J_{1',6}$ = 1.0 Hz), 5.14 (1 H, d, H-3′, $J_{2',3'}$ = 0, $J_{3',4'}$ = 2.7 Hz), 7.59 (1 H, d, H-6, $J_{1',6}$ = 1.0 Hz), 11.48 (1 H, s, NH).

Anal. Calcd for $C_{12}H_{15}ClN_2O_6 \cdot {}^1/_5CHCl_3$: C, 42.85; H, 4.48; Cl, 16.40; N, 8.19. Found: C, 42.92; H, 4.61; Cl, 16.27; N, 8.09. A small amount of $CHCl_3$ was detected in the ^{1}H NMR spectrum of this sample at δ 8.31.

From the second fraction, the deacetylated product **10b** (X = Cl, R = H) was obtained as a foam (110 mg, 60%): ^{1}H NMR (Me_2SO-d_6) δ 3.29 (3 H, s, NMe), 3.41–3.75 (2 H, m, H-5′,5″, collapsed to a doublet upon addition of D_2O), 3.73 (1 H, dd, H-4′, $J_{3',4'}$ = 2.1, $J_{4',5'}$ = 7.3, $J_{4',5''}$ = 0 Hz), 4.18 (1 H, m, H-3′, changed into a double upon D_2O exchange, $J_{2',3'}$ = 0, $J_{3',4'}$ = 2.1 Hz), 4.42 (1 H, d, H-2′, $J_{1',2'}$ = 3.7, $J_{2',3'}$ = 0 Hz), 4.86 (1 H, t, 5′-OH), 4.97 (1 H, dd, H-1′, $J_{1',2'}$ = 3.7, $J_{1',6}$ = 1.2 Hz), 5.90 (1 H, d, 3′-OH), 7.53 (1 H, d, H-6, $J_{1',6}$ = 1.2 Hz), 11.43 (1 H, s, NH); mass spectrum (IBu/DCI$^+$), m/e 277 (MH$^+$), 241 (MH$^+$ – Cl).

Anal. Calcd for $C_{10}H_{13}ClN_2O_5 \cdot {}^1/_2H_2O$: C, 42.14; H, 4.94; N, 9.79. Found: C, 42.56; H, 5.11; N, 9.37.

This product was very hygroscopic. A small amount of water was detected in the ^{1}H NMR spectra of the dried samples.

In a similar manner, **9c** (X = Br) was converted into **10c** (X = Br, R = H) which was obtained as a foam: ^{1}H NMR (Me_2SO-d_6) δ 3.29 (3 H, s, NMe), 3.50–3.74 (3 H, m, H-4′,5′,5″), 4.35 (1 H, m, H-3′), 4.52 (1 H, d, H-2′, $J_{1',2'}$ = 3.4, $J_{2',3'}$ = 0 Hz), 4.84 (1 H, dd, H-1′, $J_{1',2'}$ = 3.4, $J_{1',6}$ = 1.2 Hz), 4.88 (1 H, t, 5′-OH), 5.95 (1 H,

d, 3′-OH), 7.52 (1 H, d, H-6, $J_{1',6}$ = 1.2 Hz), 11.43 (1 H, s, NH).

Anal. Calcd for $C_{10}H_{13}BrN_2O_5 \cdot {}^1/_2C_2H_5OH$: C, 38.38; H, 4.67; Br, 23.32; N, 8.14. Found: C, 38.25; H, 4.50; Br, 23.22; N, 8.48. Contamination of $^1/_2$ molecule of C_2H_5OH was determined by ^1H NMR of this sample.

5-(β-D-Arabinofuranosyl)-1-methyluracil (10d, X = OH, R = H) was obtained in crystalline form by treatment of **9d** (X = OAc) (70 mg, 0.22 mmol) in water (25 mL) with Dowex-50 (H^+) (~5 mL) at 70 °C for 5 h, followed by filtration of the resin, condensation of the filtrate, and crystallization of the residue from EtOH: 35 mg (63%); mp 226–228 °C; ^1H NMR (Me_2SO-d_6) δ 3.25 (3 H, s, NMe), 3.40–3.53 (2 H, m, H-5′,5″), 3.62–3.67 (1 H, m, H-4′), 3.85 (2 H, s, H-2′,3′), 4.76 (1 H, d, H-1′), 7.39 (1 H, s, H-6), 11.24 (1 H, s, NH). This spectrum pattern is quite similar to that of 5-(β-D-arabinofuranosyl)uracil.[2]

Anal. Calcd for $C_{10}H_{14}N_2O_6 \cdot {}^1/_4H_2O$: C, 45.73; H, 5.52; N, 10.66. Found: C, 45.86; H, 5.73; N, 10.21.

Treatment of **9a** (X = N_3) (100 mg, 0.33 mmol) in aqueous solution with Dowex 50 (H^+) at room temperature for 24 h and regular workup yielded 50 mg (54%) of crystalline **5-(2′-azido-2′-deoxy-β-D-arabinofuranosyl)-1-methyluracil (10a, X = N_3, R = H)**, mp 186–188 °C, and 27 mg (25%) of the 3′-*O*-acetyl derivative **10a** (X = N_3, R = Ac) as a foam.

^1H NMR data for **10a** (X = N_3, R = Ac) in Me_2SO-d_6: δ 2.10 (3 H, s, Ac), 3.29 (3 H, s, NMe), 3.63 (2 H, m, H-5′,5″), 3.82–3.99 (1 H, m, H-4′), 4.35 (1 H, dd, H-2′, $J_{1',2'}$ = 4.5, $J_{2',3'}$ = 0.5 Hz), 4.82 (1 H, dd, H-1′, $J_{1',2'}$ = 4.5, $J_{1',6}$ = 0.5 Hz), 4.91 (1 H, t, 5′-OH), 5.00 (1 H, dd, H-3′, $J_{2',3'}$ = 0.5, $J_{3',4'}$ = 3.6 Hz), 7.59 (1 H, d, H-6, $J_{1',6}$ = 0.5 Hz).

Anal. Calcd for $C_{12}H_{15}N_5O_6 \cdot {}^1/_2H_2O$: C, 43.11; H, 4.82; N, 20.95. Found: C, 43.35; H, 4.88; N, 20.75.

^1H NMR (Me_2SO-d_6) for **10a** (X = N_3, R = H): δ 3.28 (3 H, s, NMe), 3.51–3.68 (3 H, m, H-4′,5′,5″), 3.99 (1 H, m, H-3′, became dd on addition of D_2O, $J_{2',3'}$ = 2.1, $J_{3',4'}$ = 4.6 Hz), 4.12 (1 H, dd, H-2′, $J_{1',2'}$ = 3.4, $J_{2',3'}$ = 2.1 Hz), 4.80 (1 H, t, 5′-OH), 4.88 (1 H, dd, H-1′, $J_{1',2'}$ = 3.4, $J_{1',6}$ = 1.2 Hz), 5.67 (1 H, d, 3′-OH), 7.56 (1 H, d, H-6, $J_{1',6}$ = 1.2 Hz), 11.44 (1 H, s, NH).

Anal. Calcd for $C_{10}H_{13}N_5O_5$: C, 42.40; H, 4.62; N, 24.73. Found: C, 42.93; H, 4.90; N, 24.96.

2′-Deoxy-1-methyl-ψ-uridine (10, X = R = H) from 10 (X = Cl, R = H). A mixture of **10** (X = Cl, R = H) (50 mg), *n*-Bu_3SnH (100 mg), and 2,2′-azobis(2-methylpropionitrile) (15 mg) in toluene (11 mL) was heated under reflux for 1 h. The mixture was concentrated in vacuo, and the residue was purified by chromatography on a silica gel column with $CHCl_3$–EtOH (9:1 v/v) as the eluent. The major nucleoside fraction was concentrated and the residue was directly examined by ^1H NMR spectroscopy. The spectrum of the product was identical with that of 2′-deoxy-1-methyl-ψ-uridine.[21]

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Registry No. 1, 13860-38-3; 2, 97416-14-3; 3, 97416-15-4; 4, 97416-16-5; 5, 97416-17-6; 6, 97416-18-7; 7, 97416-19-8; 7 (2′,3′-*O*-dibutylstannyl deriv), 97416-30-3; 8, 97430-85-8; 9a, 97416-20-1; 9b, 97416-21-2; 9c, 97416-22-3; 9d, 97416-23-4; 10 (X = R = H), 65358-15-8; 10a (X = N_3, R = H), 97416-24-5; 10a (X = N_3, R = Ac), 97416-25-6; 10b (X = Cl, R = H), 97416-26-7; 10b (X = Cl, R = Ac), 97416-27-8; 10c (X = Br, R = H), 97416-28-9; 10d (X = OH, R = H), 97416-29-0; 3′-*O*-acetyl-4,5′-anhydro-1-methyl-ψ-uridine, 97416-31-4; 2′-*O*-acetyl-4,5′-anhydro-1-methyl-ψ-uridine, 97416-32-5.

Bis(indole) Alkaloids. A Nonbiomimetic Approach to the Blue Pigment Trichotomine Dimethyl Ester

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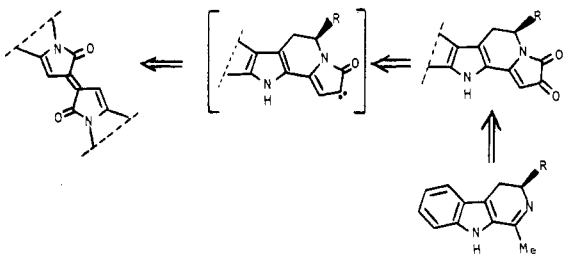
Two alternative routes have been developed for the synthesis of trichotomine dimethyl ester **2**. Both routes involve the synthesis of keto lactam **3** by reaction of the chiral imine **4** [obtained starting from (*S*)-(−)-tryptophan] with oxalyl chloride. The elaboration of **3** into **2** is achieved through the intermediacy of diazo lactam **5** and subsequent copper-assisted thermolysis furnishes **2**. A more efficient route involves a carbene-mediated olefination of keto lactam **3** to give trichotomine dimethyl ester **2** in good yield. The preparation of decarboxytrichotomine **6** is also described.

The bis(indole) alkaloid trichotomine **1**, is an unusual naturally occurring blue pigment, first isolated in 1974 by Iwadare et al.[1] from the fruits of *Clerodendron trichotomum* and *Premna microphylla*. In connection with the proof of structure and stereochemistry of **1**, its dimethyl ester **2** was synthesized through a five-step sequence of reactions in 5% overall yield.[2] A biomimetic variant of the first synthesis of **2** started from its presumptive natural precursors—tryptophan and α-ketoglutaric acid—and attempted to reproduce in vitro, albeit in poor yield (3%!), the regio- and stereoselectivity of the biogenetic process.[3]

Scheme I



(1) Iwadare, S.; Shizuri, Y.; Sasaki, K.; Hirata, Y. Japanese Patent 7 641 415; *Chem. Abstr.* **1976**, *85*, 25376v.

(2) Iwadare, S.; Shizuri, Y.; Yamada, K.; Hirata, Y. *Tetrahedron* **1978**, *34*, 1457 and references cited therein.

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