[Chem. Pharm. Bull. 36(4)1298—1304(1988)]

Nucleosides. IV.[1] Synthesis and Reactions of 2′,3′,5′-Trichloro-2′,3′,5′-trideoxy-2′,3′-secouridines

KOSAKU HIROTA,* TETSUO TOMISHI, and YOSHIFUMI MAKI

Gifu Pharmaceutical University, Mitahora-higashi, Gifu 502, Japan

(Received September 3, 1987)

2′,3′,5′-Trichloro-2′,3′,5′-trideoxy-2′,3′-secouridines (**2a**, **b**) were synthesized from uridine or 5-fluorouridine by a combination of sodium metaperiodate oxidation, sodium borohydride reduction, and chlorination with Vilsmeier–Haack reagent. Reaction of **2a**, **b** with base gave some new pyrimidine acyclonucleosides (**3**—**5**) and (uracil-1-yl)-1,4-dioxanes (**8**, **9**). The preparation of 5′-chloro-5′-deoxy-2′,3′-secouridine (**11**) from 5′-chloro-5′-deoxyuridine (**10**) and its conversion into (uracil-1-yl)-1,4-dioxane **12** and 5′-deoxy-2′,3′-secouridine (**13**) are also described.

Keywords——acyclonucleoside; secouridine; uridine; sodium metaperiodate; sodium borohydride; Vilsmeier–Haack reagent; 5-fluorouridine

Recently, certain nucleoside analogues in which the ribosyl moiety is replaced by an acyclic side chain, *e.g.* 9-(2-hydroxyethoxymethyl)guanine (acyclovir)[2] and 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine (DHPG),[3] have received much attention due to their antiviral activity. Therefore, a number of purine and pyrimidine acyclonucleosides have been synthesized by means of condensation of the base moiety and the acyclic side chain.[4] On the other hand, recent reports[5,6] have shown that 2′,3′-seconucleosides,[7] a kind of acyclonucleoside, can be directly derived from pyrimidine and purine nucleosides. This background prompted us to report our own results concerning the chemical modification of the ribosyl moiety in nucleosides. The present paper describes the synthesis of 2′,3′,5′-trichloro-2′,3′,5′-trideoxy-2′,3′-secouridines **2** by the reaction of 2′,3′-secouridines **1** with the Vilsmeier–Haack reagent and some reactions involving conversion into novel acyclic uridine derivatives.

Treatment of 2′,3′-secouridine (**1a**)[8] with the Vilsmeier–Haack reagent [phosphorus oxychloride ($POCl_3$)/dimethylformamide (DMF)] in DMF at 60 °C for 3 h afforded the corresponding trichloro derivative **2a**[9] in 44% yield (based on uridine). Similarly, the 5-fluoro derivative **2b** was obtained in 38% yield (based on 5-fluorouridine) upon chlorination of 5-fluoro-2′,3′-secouridine (**1b**), which was prepared with ease from 5-fluorouridine. Although **2a** was obtainable by chlorination of **1a** with an excess of thionyl chloride in the presence of a catalytic amount of DMF at room temperature, the yield was not improved.

Treatment of the trichloro derivative **2a** with equimolar sodium methoxide in methanol under reflux for 70 min resulted in the formation of 2,2′-anhydro-3′,5′-dichloro-3′,5′-dideoxy-2′,3′-secouridine (**3a**) and 3′,5′-dichloro-3′,5′-dideoxy-2-*O*-methyl-2′,3′-secouridine (**4a**) in 72% and 13% yields, respectively. Analogous treatment of the 5-fluoro derivative **2b** gave the corresponding products **3b** and **4b** in 36% and 46% yields, respectively. The structure of **3a** was fully supported by spectral data; in particular, the proton nuclear magnetic resonance (^{1}H-NMR) spectrum shows a characteristic double doublet signal at 6.23 ppm (J= 2.0 and 5.3 Hz) assignable to the H-1′ proton, suggesting that free rotation of the $C_{1'}$–$C_{2'}$ bond is restricted due to the formation of the 2,2′-anhydro bond, and the ultraviolet (UV) spectrum (226 and 247 nm) of **3a** is superimposable on that of 2,2′-anhydrouridine.[10] The structure of **4a** was confirmed on the basis of microanalytical results, spectral data, and the

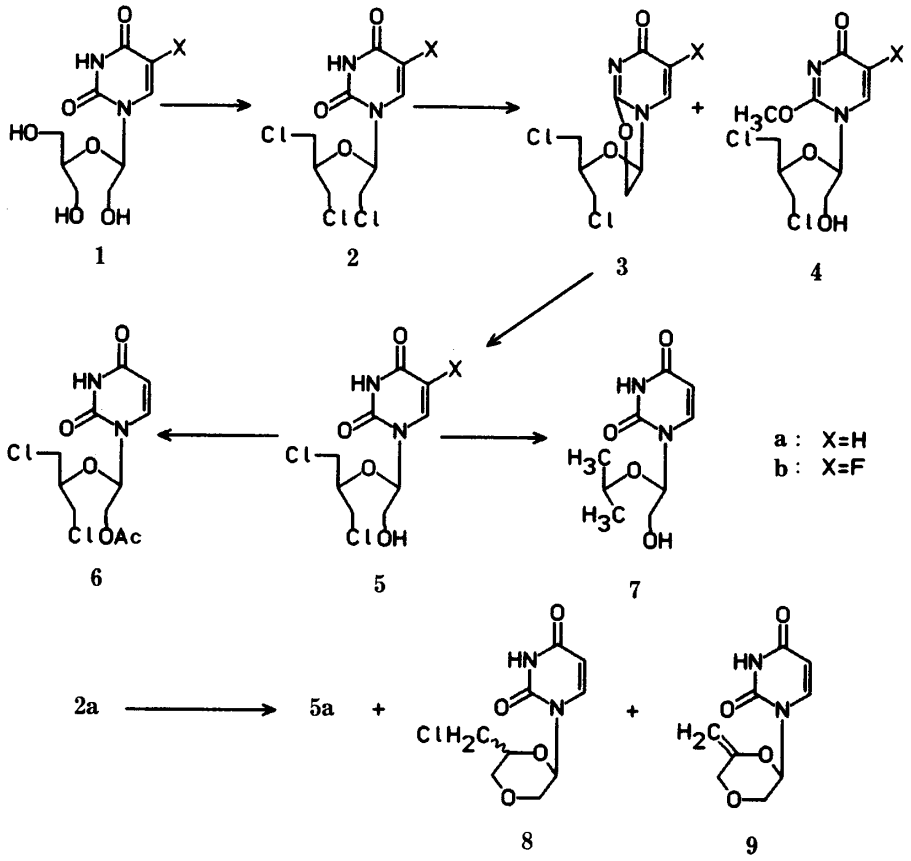

Chart 1

following chemical reactions. The products, **3a** and **4a**, underwent interconversion to each other on reaction with methanolic sodium methoxide, *i.e.*, independent treatment of **3a** and **4a** with sodium methoxide gave a mixture of **3a** and **4a**, respectively.

When 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used instead of sodium methoxide, the 2,2′-anhydro compounds **3a**, **b** were obtained as the sole product from **2a**, **b** in high yields. Hydrolysis of **3a**, **b** in aqueous sodium hydroxide (1 eq) gave 3′,5′-dichlorosecouridines (**5a**, **b**) quantitatively. Acetylation of **5a** with acetic anhydride in pyridine afforded the corresponding mono-*O*-acetyl derivative **6**. Furthermore, 3′,5′-dideoxy-2′,3′-secouridine (**7**) was obtained by reduction of **5a** with tributyltin hydride.

When the trichlorosecouridine **2a** was treated with excess aqueous sodium hydroxide, (2*R*)-6-methylene-2-(uracil-1-yl)-1,4-dioxane (**9**) was obtained as a major product together with two minor products **5a** and (2*R*)-6-chloromethyl-2-(uracil-1-yl)-1,4-dioxane (**8**). The structural proof of **9** rests upon microanalytical results and ^{1}H-NMR, mass, and UV spectral data. The UV spectrum of **9** shows an absorption band at 259 nm which is characteristic of a 1-substituted uracil.[11] The ^{1}H-NMR spectrum of **9** exhibited the exomethylene proton signals at 4.54 and 4.47 ppm with a geminal coupling constant (J=0.2 Hz). The configuration of the minor product **8**, which is one of two expected diastereoisomers, could not be determined.

The above reactions can be rationalized as outlined in Chart 2.

Jones *et al.* have synthesized 2′-chloro and 3′-chloro derivatives of 2′,3′-secouridine[6] with the exception of the 5′-chloro derivatives **11**. Our attempt to prepare **11** was carried out with the 5′-chloro-5′-deoxyuridines **10a**, **b** as starting materials. After the oxidation of **10a**, **b** with sodium metaperiodate in water, reduction was achieved by using sodium borohydride in acetic acid in order to avoid side reactions by alkaline hydrolysis, to give the expected products **11a**, **b** in moderate yields, respectively. Treatment of **11a** with potassium *tert*-

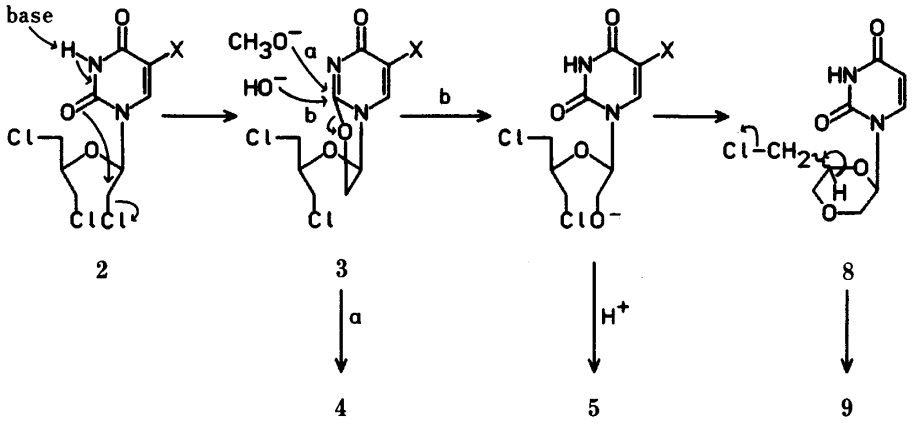

Chart 2

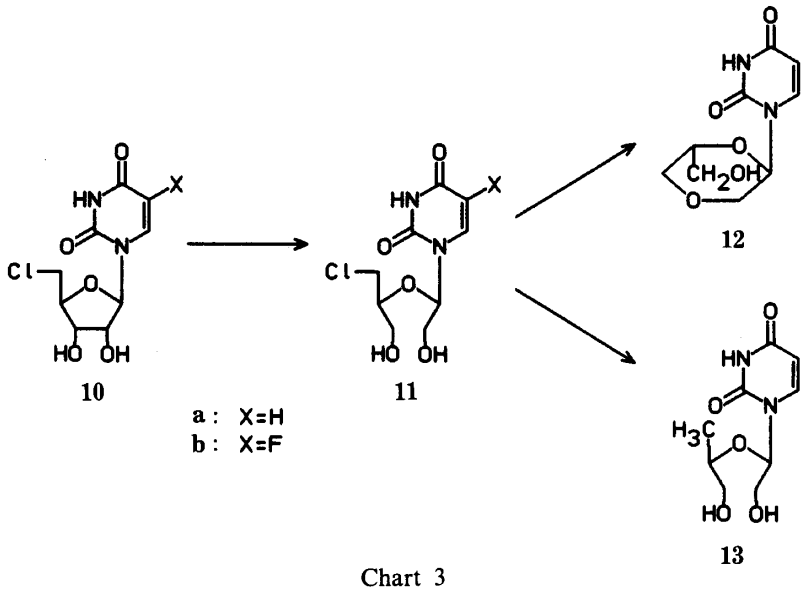

Chart 3

butoxide in dimethyl sulfoxide afforded (2*R*,6*S*)-6-hydroxymethyl-2-(uracil-1-yl)-1,4-dioxane (**12**) quantitatively. On the other hand, reduction of **11a** with tributyltin hydride afforded 5′-deoxy-2′,3′-secouridine (**13**) in 40% yield.

These pyrimidine acyclonucleosides, in particular the 5-fluoro derivatives, are expected to have antitumor activity, because Ozaki *et al.* have shown that 1-(2-alkoxyalkyl)-5-fluorouracil derivatives have moderate antitumor activity.[12]

Experimental

All melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. Elemental analyses were carried out at the Microanalytical Laboratory of our university. ^{1}H-NMR spectra (60 MHz) were recorded on a Hitachi Perkin-Elmer R-20B nuclear magnetic resonance spectrometer with tetramethylsilane for $CDCl_3$ solutions and sodium 2,2-dimethyl-2-silapentane-5-sulfonate for dimethylsulfoxide-d_6 (DMSO-d_6) solutions as internal standards. Chemical shifts are recorded in parts per million (δ), the J values are given in hertz, and signals are described as s (singlet), d (doublet), t (triplet), m (multiplet), or br (broad). Optical rotations were obtained with a JASCO DIP-4 automatic polarimeter. Mass spectra (MS) were taken on a JEOL JMS-D300 machine operating at 70 eV. UV spectra were obtained from ethanol on a Shimadzu 323 spectrophotometer. Column chromatography was carried out on silica gel (Wakogel C-300).

2′,3′,5′-Trichloro-2′,3′,5′-trideoxy-2′,3′-secouridine (2a)——Method A: Uridine (6 g, 25 mmol) and $NaIO_4$ (5.4 g, 25 mmol) were dissolved in water (100 ml) and the solution was stirred for 3 h at room temperature, protected from

light. The solution was poured into EtOH (600 ml), the mixture was stirred for 30 min and the resulting precipitate was removed by filtration. The filtrate was evaporated under reduced pressure and the residue was dissolved in water (100 ml). To this solution, $NaBH_4$ (7.2 g, 190 mmol) was added slowly. The mixture was stirred for 24 h at room temperature, protected from light, and then neutralized with Amberlite CG-50 (H^+). The solvent was removed under reduced pressure, giving a white solid containing boric acid. The acid was removed as methyl borate by several additions and evaporations of absolute MeOH. The residue was dissolved in DMF (150 ml). To this solution, Vilsmeier–Haack reagent [$POCl_3$ (11.4 g, 80 mmol) in DMF (150 ml)] was added and the mixture was heated at 60 °C for 3 h. The solvent was removed under reduced pressure and the residue was dissolved in $CHCl_3$. The solution was washed with water, the solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column eluting with benzene : ethyl acetate = 2 : 1. Evaporation of the appropriate fractions gave **2a** (3.27 g, 44%). Compound **2a** was hygroscopic and was obtained as a freeze-dried solid for analysis. $[\alpha]_D^{23}$ +37.0° (c = 1.0, CH_3OH). ^{1}H-NMR ($CDCl_3$) δ: 10.53 (1H, br, NH), 7.58 (1H, d, J = 8.3 Hz, H-6), 6.21 (1H, t, J = 6.0 Hz, H-1′), 5.93 (1H, d, J = 8.3 Hz, H-5), 4.30—3.90 (1H, m, H-4′), 3.90—3.58 (6H, m, H-2′, H-3′ and H-5′). UV λ_{max}^{EtOH} (ε): 257 nm (9000). MS m/z: 300 (M^+). *Anal.* Calcd for $C_9H_{11}Cl_3N_2O_5$: C, 35.85; H, 3.68; N, 9.29. Found: C, 36.06; H, 3.67; N, 9.29.

Method B: Uridine (6 g, 25 mmol) was oxidized with $NaIO_4$ (5.4 g, 25 mmol) and then reduced with $NaBH_4$ (3.5 g, 93 mmol) by the method mentioned above. The trihydroxy derivative was treated with $SOCl_2$ (50 ml) and DMF (2 ml), and the mixture was stirred for 4 d at room temperature. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column eluting with benzene : ethyl acetate = 2 : 1. Evaporation of the appropriate fractions gave **2a** (2.38 g, 32%).

2′,3′,5′-Trichloro-2′,3′,5′-trideoxy-5-fluoro-2′,3′-secouridine (2b)——This compound was obtained as a foam from 5-fluorouridine in 38% yield by method A as described for compound **2a**. $[\alpha]_D^{23}$ +36.0° (c = 1.0, CH_3OH). ^{1}H-NMR ($CDCl_3$) δ: 9.39 (1H, br, NH), 7.49 (1H, d, J = 5.6 Hz, H-6), 6.11 (1H, dt, J = 6.0 and 1.3 Hz, H-1′), 4.07—3.99 (1H, m, H-4′), 3.84—3.57 (6H, m, H-2′, H-3′ and H-5′). UV λ_{max}^{EtOH} (ε): 261 nm (9100). MS m/z: 318 (M^+). High-resolution MS m/z: 317.9750 (M^+). Calcd for $C_9H_{10}Cl_3FN_2O_5$: 317.9741.

Reaction of 2a with NaOMe——A solution of **2a** (2.15 g, 7.2 mmol) in methanolic sodium methoxide [prepared from Na (165 mg, 7.2 mmol) in absolute MeOH (50 ml)] was refluxed for 70 min. The mixture was neutralized with Amberlite CG-50 (H^+) and the ion exchanger was washed with MeOH. The combined solutions were concentrated under reduced pressure and the residue was chromatographed on a silica gel column eluting with $CHCl_3$: MeOH = 10 : 1. The faster-eluting fraction contained 3′,5′-dichloro-3′,5′-dideoxy-2-*O*-methyl-2′,3′-secouridine (**4a**) (278 mg, 13%), which was recrystallized from EtOH, mp 140—141 °C. $[\alpha]_D^{23}$ +89.0° (c = 1.0, CH_3OH). ^{1}H-NMR (DMSO-d_6) δ: 7.79 (1H, d, J = 7.5 Hz, H-6), 5.95 (1H, d, J = 7.5 Hz, H-5), 5.87 (1H, t, J = 6.0 Hz, H-1′), 5.36 (1H, t, J = 6.0 Hz, OH), 4.30—4.00 (1H, m, H-4′), 3.95 (3H, s, CH_3), 3.90—3.50 (6H, m, H-2′, H-3′ and H-5′). UV λ_{max}^{EtOH} (ε): 228 (10900) and 247 nm (10300). MS m/z: 296 (M^+). *Anal.* Calcd for $C_{10}H_{14}Cl_2N_2O_4$: C, 40.42; H, 4.75; N, 9.43. Found: C, 40.50; H, 4.75; N, 9.50.

The slower-eluting fraction contained 2,2′-anhydro-3′,5′-dichloro-3′,5′-dideoxy-2′,3′-secouridine (**3a**) (1.357 g, 72%), which was recrystallized from EtOH, mp 140—141 °C. $[\alpha]_D^{23}$ +32.3° (c = 1.0, CH_3OH). ^{1}H-NMR (DMSO-d_6) δ: 8.04 (1H, d, J = 7.5 Hz, H-6), 6.23 (1H, dd, J = 5.3 and 2.0 Hz, H-1′), 6.00 (1H, d, J = 7.5 Hz, H-5), 4.92 (1H, dd, J = 10.5 and 5.3 Hz, H-2′), 4.63 (1H, dd, J = 10.5 and 2.0 Hz, H-2′), 4.68—4.37 (1H, m, H-4′), 3.90 (4H, m, H-3′ and H-5′). UV λ_{max}^{EtOH} (ε): 226 (8200) and 247 nm (7000). MS m/z: 264 (M^+). *Anal.* Calcd for $C_9H_{10}Cl_2N_2O_3$: C, 40.78; H, 3.80; N, 10.57. Found: C, 41.03; H, 3.88; N, 10.66.

Reaction of 2b with NaOMe——A solution of **2b** (439 mg, 1.37 mmol) in methanolic sodium methoxide [prepared from Na (32 mg, 1.37 mmol) in absolute MeOH (30 ml)] was refluxed for 1 h. The reaction mixture was worked up in a manner similar to that described above. The fraster-eluting fraction contained 3′,5′-dichloro-3′,5′-dideoxy-5-fluoro-2-*O*-methyl-2′,3′-secouridine (**4b**) (199 mg, 46%), which was recrystallized from EtOH, mp 179 °C. $[\alpha]_D^{23}$ +75.0° (c = 1.0, CH_3OH). ^{1}H-NMR (DMSO-d_6) δ: 8.07 (1H, d, J = 6.2 Hz, H-6), 5.81 (1H, br t, J = 4.4 Hz, H-1′), 5.28 (1H, t, J = 5.9 Hz, OH), 4.14—4.07 (1H, m, H-4′), 3.93 (3H, s, CH_3), 3.91—3.62 (6H, m, H-2′, H-3′ and H-5′). UV λ_{max}^{EtOH} (ε): 227 (7800) and 253 nm (10600). MS m/z: 314 (M^+). *Anal.* Calcd for $C_{10}H_{13}Cl_2FN_2O_4$: C, 38.11; H, 4.16; N, 8.89. Found: C, 37.96; H, 4.11; N, 8.96.

The slower-eluting fraction contained 2,2′-anhydro-3′,5′-dichloro-3′,5′-dideoxy-5-fluoro-2′,3′-secouridine (**3b**) (140 mg, 36%), which was recrystallized from EtOH, mp 148—150 °C. $[\alpha]_D^{23}$ +27.3° (c = 1.0, CH_3OH). ^{1}H-NMR (DMSO-d_6) δ: 8.41 (1H, d, J = 5.0 Hz, H-6), 6.21 (1H, dd, J = 5.3 and 2.1 Hz, H-1′), 4.99 (1H, dd, J = 10.8 and 5.3 Hz, H-2′), 4.68 (1H, dd, J = 10.8 and 2.1 Hz, H-2′), 4.55 (1H, m, H-4′), 3.89 (4H, m, H-3′ and H-5′). UV λ_{max}^{EtOH} (ε): 227 (7600) and 249 nm (8600). MS m/z: 282 (M^+). *Anal.* Calcd for $C_9H_9Cl_2FN_2O_3$: C, 38.19; H, 3.20; N, 9.90. Found: C, 38.33; H, 3.18; N, 9.99.

Reaction of 2a with DBU——DBU (526 mg, 3.46 mmol) was added to a solution of **2a** (865 mg, 2.88 mmol) in DMF (30 ml), and the mixture was heated at 100 °C for 20 min. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column eluting with $CHCl_3$: MeOH = 10 : 1. Evaporation of the appropriate fractions gave **3a** (754 mg, 99%), which showed spectra identical with those of an authentic sample prepared as described above.

Reaction of 2b with DBU——DBU (200 mg, 1.31 mmol) was added to a solution of **2b** (350 mg, 1.09 mmol) in

DMF (30 ml), and the mixture was heated at 100 °C for 20 min then worked up in a manner similar to that described above to afford **3b** (258 mg, 83%), which showed spectra identical with those of an authentic sample prepared as described above.

3′,5′-Dichloro-3′,5′-dideoxy-2′,3′-secouridine (5a)——Compound **3a** (265 mg, 1 mmol) was added to a solution of NaOH (40 mg, 1 mmol) in H_2O (10 ml), and the mixture was stirred for 80 min at room temperature. The mixture was neutralized with Amberlite CG-50 (H^+) and the ion exchanger was washed with water. The combined solutions were concentrated under reduced pressure and the residue was chromatographed on a silica gel column eluting with $CHCl_3$: MeOH = 30 : 1. Evaporation of the appropriate fractions gave **5a** (270 mg, 96%), which was hygroscopic and was obtained as a freeze-dried solid for analysis. $[\alpha]_D^{23}$ +42.4° (c = 1.0, CH_3OH). ^{1}H-NMR (DMSO-d_6) δ: 11.28 (1H, br, NH), 7.67 (1H, d, J = 7.7 Hz, H-6), 5.88 (1H, t, J = 6.0 Hz, H-1′), 5.68 (1H, dd, J = 7.7 and 2.0 Hz, H-5), 5.19 (1H, t, J = 6.0 Hz, OH), 4.24—3.32 (7H, m, H-2′, H-3′, H-4′ and H-5′). UV λ_{max}^{EtOH} (ε): 259 nm (9500). MS m/z: 282 (M^+). *Anal.* Calcd for $C_9H_{12}Cl_2N_2O_4$: C, 38.18; H, 4.27; N, 9.90. Found: C, 38.16; H, 4.27; N, 9.88.

3′,5′-Dichloro-3′,5′-dideoxy-5-fluoro-2′,3′-secouridine (5b)——Compound **3b** (258 mg, 0.91 mmol) was added to a solution of NaOH (36 mg, 0.91 mmol) in H_2O (10 ml). The mixture was stirred for 1.5 h at room temperature and then worked up in a manner similar to that described above to afford **5b** (249 mg, 91%), which was hygroscopic and was obtained as a freeze-dried solid for analysis. $[\alpha]_D^{23}$ +48.0° (c = 1.0, CH_3OH). ^{1}H-NMR (DMSO-d_6) δ: 11.89 (1H, br, NH), 8.04 (1H, d, J = 7.0 Hz, H-6), 5.86 (1H, dt, J = 5.9 and 1.5 Hz, H-1′), 5.19 (1H, t, J = 6.2 Hz, OH), 4.15—3.33 (7H, m, H-2′, H-3′, H-4′ and H-5′). UV λ_{max}^{EtOH} (ε): 264 nm (8500). MS m/z: 300 (M^+). High-resolution MS m/z: 300.0049 (M^+). Calcd for $C_9H_{11}Cl_2FN_2O_4$: 300.0021.

2′-*O*-Acetyl-3′,5′-dichloro-3′,5′-dideoxy-2′,3′-secouridine (6)——A solution of **5a** (282 mg, 1 mmol) in acetic anhydride (1 ml) and pyridine (1 ml) was stirred for 12 h at room temperature. The solvent was removed under reduced pressure and the residue was crystallized from MeOH. Recrystallization from MeOH gave analytically pure **6** (270 mg, 83%), mp 92—94 °C. $[\alpha]_D^{23}$ +51.3° (c = 1.0, CH_3OH). ^{1}H-NMR ($CDCl_3$) δ: 9.83 (1H, br, NH), 7.55 (1H, d, J = 8.3 Hz, H-6), 6.25 (1H, dd, J = 6.0 and 5.6 Hz, H-1′), 5.93 (1H, br d, J = 8.3 Hz, H-5), 4.44 (1H, d, J = 5.6 Hz, H-2′), 4.32 (1H, d, J = 6.0 Hz, H-2′), 4.15—4.00 (1H, m, H-4′), 3.89—3.60 (4H, m, H-3′ and H-5′), 2.12 (3H, s, CH_3). UV λ_{max}^{EtOH} (ε): 257 nm (9500). MS m/z: 325 (M^+). *Anal.* Calcd for $C_{11}H_{14}Cl_2N_2O_5$: C, 40.63; H, 4.34; N, 8.62. Found: C, 40.60; H, 4.27; N, 8.69.

3′,5′-Dideoxy-2′,3′-secouridine (7)——A solution of **5a** (283 mg, 1 mmol), n-Bu_3SnH (5.8 g, 20 mmol) and azobisisobutyronitrile (AIBN) (40 mg, 0.24 mmol) in absolute EtOH (10 ml) was refluxed for 48 h under an N_2 stream. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column eluting with benzene : ethyl acetate = 3 : 7 to affrod **7** (193 mg, 89%), which was recrystallized from EtOH, mp 139—140 °C. $[\alpha]_D^{23}$ +61.0° (c = 1.0, CH_3OH). ^{1}H-NMR (DMSO-d_6) δ: 11.29 (1H, br, NH), 7.60 (1H, d, J = 8.1 Hz, H-6), 5.68 (1H, t, J = 5.4 Hz, H-1′), 5.64 (1H, d, J = 8.1 Hz, H-5), 5.10 (1H, t, J = 6.2 Hz, OH), 3.71—3.50 (3H, m, H-2′ and H-4′), 1.16 (3H, d, J = 6.2 Hz, CH_3), 1.07 (3H, d, J = 6.2 Hz, CH_3). UV λ_{max}^{EtOH} (ε): 261 nm (9700). MS m/z: 183 ($M^+ - CH_2OH$). *Anal.* Calcd for $C_9H_{14}N_2O_4 \cdot 1/5H_2O$: C, 49.63; H, 6.66; N, 12.86. Found: C, 49.53; H, 6.46; N, 12.85.

Reaction of 2a with 10 eq of NaOH——Aqueous NaOH solution (1.0 g, 25 mmol in 2 ml H_2O) was added to a solution of **2a** (760 mg, 2.5 mmol) in MeOH (30 ml), and the mixture was refluxed for 30 min. The mixture was neutralized with Amberlite CG-50 (H^+) and the ion exchanger was washed with MeOH. The combined solutions were concentrated under reduced pressure and the residue was chromatographed on a silica gel column eluting with benzene : ethyl acetate = 2 : 1. The first fraction contained (2*R*)-6-methylene-2-(uracil-1-yl)-1,4-dioxane (**9**) (220 mg, 41%), which was recrystallized from EtOH, mp 174—175 °C. $[\alpha]_D^{23}$ −43.8° (c = 1.0, CH_3OH). ^{1}H-NMR (DMSO-d_6) δ: 11.48 (1H, br, NH), 7.93 (1H, d, J = 8.3 Hz, H-6 of uracil ring), 5.97 (1H, br t, H-2 of dioxane ring), 5.71 (1H, d, J = 8.3 Hz, H-5 of uracil ring), 4.54 and 4.47 (1H, each d, J = 0.2 Hz, exomethylene of dioxane ring), 4.24 (2H, s, H-5 of dioxane ring), 4.03 (2H, br d, J = 5.3 Hz, H-3 of dioxane ring). UV λ_{max}^{EtOH} (ε): 259 nm (10000). MS m/z: 210 (M^+). *Anal.* Calcd for $C_9H_{10}N_2O_4$: C, 51.42; H, 4.80; N, 13.33. Found: C, 51.14; H, 4.78; N, 13.25.

The second fraction contained (2*R*)-6-chloromethyl-2-(uracil-1-yl)-1,4-dioxane (**8**) (45 mg, 7%), which was recrystallized from EtOH, mp 120 °C. $[\alpha]_D^{23}$ −115.2° (c = 1.0, CH_3OH). ^{1}H-NMR ($CDCl_3$) δ: 8.79 (1H, br, NH), 7.94 (1H, d, J = 8.1 Hz, H-6 of uracil ring), 5.91 (1H, t, J = 3.9 Hz, H-2 of dioxane ring), 5.76 (1H, d, J = 8.1 Hz, H-5 of uracil ring), 4.10—3.56 (7H, m, H-3, H-5 and H-6 of dioxane ring and CH_2Cl). UV λ_{max}^{EtOH} (ε): 258 nm (10100). MS m/z: 246 (M^+). *Anal.* Calcd for $C_9H_{11}ClN_2O_4 \cdot 1/10C_6H_6$: C, 45.31; H, 4.60; N, 11.01. Found: C, 45.54; H, 4.86; N, 10.99.

The last fraction contained **5a** (28 mg, 4%), which showed spectra identical with those of an authentic sample prepared above.

5′-Chloro-5′-deoxy-2′,3′-secouridine (11a)——A suspension of 5′-chloro-5′-deoxyuridine (**10a**)[13] (524 mg, 2 mmol) in H_2O (15 ml) was treated with $NaIO_4$ (514 mg, 2.4 mmol), and the mixture was stirred for 3 h at room temperature, protected from light. The solution was poured into EtOH (50 ml), the mixture was stirred for 30 min and the resulting precipitate was removed by filtration. The filtrate was evaporated under reduced pressure and the residue was dissolved in AcOH (15 ml). To this solution, $NaBH_4$ (151 mg, 4.0 mmol) was added slowly and the mixture was stirred for 8 h at room temperature, protected from light. The solvent was removed under reduced

pressure and the residue was chromatographed on a silica gel column eluting with $CHCl_3$: MeOH = 20 : 1 to afford **11a** (378 mg, 71%). Compound **11a** was hygroscopic and was obtained as a freeze-dried solid for analysis. $[\alpha]_D^{23}$ +48.5° (c = 1.0, CH_3OH). ^{1}H-NMR (DMSO-d_6) δ: 11.50 (1H, br, NH), 7.66 (1H, d, J = 7.8 Hz, H-6), 5.85 (1H, t, J = 6.0 Hz, H-1′), 5.68 (1H, d, J = 7.8 Hz, H-5), 5.50—4.80 (2H, br, OH), 4.10—3.10 (7H, m, H-2′, H-3′, H-4′, and H-5′). UV λ_{max}^{EtOH} (ε): 260 (9000). MS m/z: 264 (M^+). *Anal.* Calcd for $C_9H_{13}ClN_2O_5 \cdot 1/3H_2O$: C, 39.94; H, 5.09; N, 10.35. Found: C, 39.68; H, 4.86; N, 10.05.

5′-Chloro-5′-deoxy-5-fluoro-2′,3′-secouridine (11b)——A solution of 5′-chloro-5′-deoxy-5-fluorouridine (**10b**)[13] (700 mg, 2.5 mmol) in H_2O (15 ml) was treated with $NaIO_4$ (640 mg, 2.99 mmol), and the mixture was stirred for 1.5 h at room temperature, protected from light. The solution was poured into EtOH (100 ml), the mixture was stirred for 30 min and the resulting precipitate was removed by filtration. The filtrate was evaporated under reduced pressure and the residue was dissolved in AcOH (15 ml). To this solution, $NaBH_4$ (260 mg, 6.96 mmol) was added slowly and the mixture was stirred for 2 d at room temperature, protected from light, then was worked up in a manner similar to that described above to afford **11b** (471 mg, 67%). Compound **11b** was hygroscopic and was obtained as a freeze-dried solid for analysis. $[\alpha]_D^{23}$ +35.0° (c = 1.0, CH_3OH). ^{1}H-NMR (DMSO-d_6) δ: 11.03 (1H, br, NH), 7.59 (1H, d, J = 7.2 Hz, H-6), 5.88 (1H, t, J = 4.8 Hz, H-1′), 4.82 and 4.42 (1H, each m, OH), 3.86—3.50 (7H, m, H-2′, H-3′, H-4′ and H-5′). UV λ_{max}^{EtOH} (ε): 264 nm (7300). MS m/z: 282 (M^+). *Anal.* Calcd for $C_9H_{12}ClFN_2O_5 \cdot 1/3H_2O$: C, 37.45; H, 4.42; N, 9.70. Found: C, 37.52; H, 4.30; N, 9.53.

(2*R*,6*S*)-6-Hydroxymethyl-2-(uracil-1-yl)-1,4-dioxane (12)——A solution of **11a** (445 mg, 1.68 mmol) and *tert*-BuOK (452 mg, 4.0 mmol) in DMSO (10 ml) was stirred for 24 h at room temperature. Then water (2 ml) was added, and the mixture was neutralized with saturated aqueous $NaHSO_4$ solution. The resulting precipitate was removed by filtration and the solvent was removed under reduced pressure. The residue was chromatographed on a silica gel column eluting with $CHCl_3$: MeOH = 20 : 1 to afford **12** (381 mg, 99%) as a foam. $[\alpha]_D^{23}$ −123.5° (c = 1.0, CH_3OH). ^{1}H-NMR (DMSO-d_6) δ: 11.23 (1H, br, NH), 7.95 (1H, d, J = 8.3 Hz, H-6 of uracil ring), 5.66 (1H, t, J = 3.3 Hz, H-2 of dioxane ring), 5.58 (1H, d, J = 8.3 Hz, H-5 of uracil ring), 4.74 (1H, br, OH), 4.00—3.26 (7H, m, H-3, H-5, H-6 of dioxane ring and CH_2OH). UV λ_{max}^{EtOH} (ε): 257 nm (12300). MS m/z: 228 (M^+). High-resolution MS m/z: 228.0785 (M^+). Calcd for $C_9H_{12}N_2O_5$: 228.0746.

5′-Deoxy-2′,3′-secouridine (13)——A solution of **11a** (120 mg, 0.45 mmol), *n*-Bu_3SnH (1.45 g, 5.0 mmol), and AIBN (20 mg, 0.12 mmol) in absolute EtOH (10 ml) was refluxed for 48 h under an N_2 stream. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column eluting with ethyl acetate to afford **13** (42 mg, 40%), which was recrystallized from ethyl acetate, mp 102 °C. $[\alpha]_D^{23}$ +62.1° (c = 1.0, CH_3OH). ^{1}H-NMR (DMSO-d_6) δ: 11.27 (1H, br, NH), 7.61 (1H, d, J = 8.1 Hz, H-6), 5.79 (1H, t, J = 6.2 Hz, H-1′), 5.65 (1H, d, J = 8.1 Hz, H-5), 5.08 (1H, t, J = 6.2 Hz, OH), 4.74 (1H, t, J = 5.7 Hz, OH), 3.65—3.30 (5H, m, H-2′, H-3′ and H-4′), 1.00 (3H, d, J = 6.2 Hz, CH_3). UV λ_{max}^{EtOH} (ε): 262 nm (9800). MS m/z: 230 (M^+). *Anal.* Calcd for $C_9H_{14}N_2O_5$: C, 46.95; H, 6.13; N, 12.17. Found: C, 46.70; H, 6.14; N, 12.10.

References and Notes

1) Part III: K. Hirota, Y. Kitade, T. Tomishi, and Y. Maki, *Nucleosides & Nucleotides*, **4**, 681 (1985). This paper is part LVIII of a series entitled "Pyrimidines."
2) *a*) H. J. Schaeffer, L. Beauchamp, P. De Miranda, G. Elion, D. J. Bauer, and P. Collins, *Nature* (London), **272**, 583, (1978); *b*) G. B. Elion, P. A. Furman, J. A. Fyfe, P. De Miranda, L. Beauchamp, and H. J. Schaeffer, *Proc. Natl. Acad. Sci. U.S.A.*, **74**, 5716 (1977).
3) *a*) K. O. Smith, K. S. Galloway, W. L. Kennell, K. K. Ogilvie, and B. K. Radatus, *Antimicrob. Agents Chemother.*, **22**, 55, (1982); *b*) J. C. Martin, G. A. Jeffrey, D. P. C. McGee, M. A. Tippie, D. F. Smee, T. R. Matthews, and J. P. Verheyden, *J. Med. Chem.*, **28**, 358 (1985).
4) *a*) R. J. Remy and J. A. Secrist III, *Nucleosides & Nucleotides*, **4**, 411 (1985); *b*) C. K. Chu and S. J. Cutler, *J. Heterocycl. Chem.*, **23**, 289 (1986).
5) *a*) M. Bessodes and K. Antonakis, *Tetrahedron Lett.*, **26**, 1305 (1985); *b*) L. M. Lerner, *Carbohydr. Res.*, **13**, 465 (1970); *c*) J. X. Khym and W. E. Cohn, *J. Am. Chem. Soc.*, **82**, 6380 (1960).
6) *a*) A. S. Jones, R. T. Walker, P. G. Wyatt, J. Balzarini, and E. De Clercq, *J. Chem. Research* (*S*), **1985**, 336; *b*) A. S. Jones, M. J. McClean, H. Tanaka, R. T. Walker, J. Balzarini, and E. De Clercq, *Tetrahedron*, **41**, 5965 (1985).
7) Compound of this type can be considered to be ribonucleosides which lack a $C_{2'}$–$C_{3'}$ bond. It is convenient to call them 2′,3′-seconucleosides, as has already been proposed by McCormick and McElhinney: J. E. McCormick and R. S. McElhinney, *J. Chem. Research* (*S*), **1981**, 12.
8) 2′,3′-Secouridines (**1a**, **b**) were prepared by essentially the same procedure reported in the literature[5b] and employed without purification as a starting material.
9) It has been reported that the conversion of nucleoside derivatives into the corresponding 2′,3′-seconucleosides by oxidation with sodium metaperiodate and the subsequent reduction with sodium borohydride proceed with retention of configuration: *a*) A. M. Kritsyn, S. N. Mikhailov, A. Yu Misharin, N. S. Padyukova, and V. L. Florentev, *Bioorg. Khim.*, **2**, 1338 (1976) [*Chem. Abstr.*, **86**, 73048*g* (1977)]; *b*) G. I. Birnbaum, R. Stolarski, Z.

Kazimierczuk, and D. Shugar, *Can. J. Chem.*, **63**, 1215 (1985). The 2′,3′-secouridines **2**, **11** were also presumed to retain their configuration on the basis of the analogy of their optimal rotations to that of the known 2′,3′-secouridine (**1a**).[5b]
10) K. Kikugawa, M. Ichino, and T. Ukita, *Chem. Pharm. Bull.*, **17**, 785 (1969).
11) G. H. Beaven, E. R. Holiday, and E. A. Johnson, "The Nucleic Acids," Vol. 1, ed. by E. Chargaff and J. N. Davidson, Academic Press, New York, 1955, p. 493.
12) S. Ozaki, Y. Watanabe, T. Hoshiko, T. Nagase, T. Ogasawara, H. Furukawa, A. Uemura, K. Ishikawa, H. Mori, A. Hoshi, M. Iigo, and R. Tokuzen, *Chem. Pharm. Bull.*, **34**, 150 (1986).
13) H. Hrebabecky and J. Beranek, *Nucleic Acids Res.*, **5**, 1029 (1981).