Pergamon

Tetrahedron Letters, Vol. 38, No. 39, pp. 6841-6844, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01613-4

Synthesis of a Novel Dioxane Nucleoside Having Two Bases, 2(*R*)-(5-Fluorouracil-1-yl)-5(*R*)-hydroxymethyl-3(*R*)-(uracil-1-yl)-1,4-dioxane and its 2(*S*)-Isomer, from Uridine

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Abstract: A novel dioxane nucleoside for chemotherapy, 2(*R*)-(5-fluorouracil-1-yl)-5(*R*)-hydroxymethyl-3(*R*)-(uracil-1-yl)-1,4-dioxane and its 2(*S*)-isomer, were conveniently synthesized from uridine with several steps including periodate oxidation, partial reduction to form hemiacetals, and glycosidation of the second base, 5-fluorouracil, using stannic chloride as the catalyst. © 1997 Elsevier Science Ltd.

Recently, many reports have been published regarding anti-viral nucleosides consisting of an acyclic chain (acyclonucleosides), oxolane or its positional isomers, thiolane, dioxolane or oxathiolane, oxathiane or dithiane, and dioxane as the sugar moiety[1-8]. In an attempt to develop a novel type of nucleoside for therapeutic use, we have synthesized a form in which the sugar moiety is altered from *D*-ribose to dioxane having another aglycone in the ring (**7a** and **7b**), as shown in Figure 1.

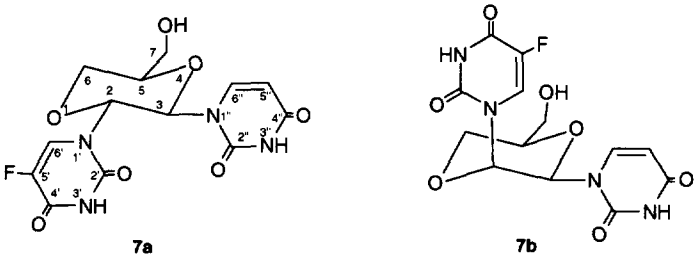

Figure 1

The seco-nucleoside monoaldehyde, [seco-uridine-2'-aldehyde, or 2-*O*-{2(*R*)-(uracil-1-yl)acetaldehyde-2-yl}glycerol (**3**)], was selected as the starting material, as shown in Figure 2. It was synthesized from uridine (**1**) in a more than 80% yield with a small amount of fully reduced seco-uridine using sodium periodate oxidation[9], followed by treatment with sodium borohydride in a saturated boric acid aqueous solution in the presence of acetic acid (0.3 M)[10]. The monoaldehyde **3** was dissolved in dry pyridine and acetic anhydride

was added to the solution and the mixture was allowed to stand overnight to give an epimeric mixture of 2-acetoxy-5(*R*)-acetoxymethyl-3(*R*)-(uracil-1-yl)-1,4-dioxane (**5**). The intramolecular cyclization of **3** is at equilibrium to provide two sets of hemiacetals (**4**), one with an equatorial configuration of the hydroxymethyl group at the 5 position, and the other with an axial configuration of the hydroxymethyl group, the absolute

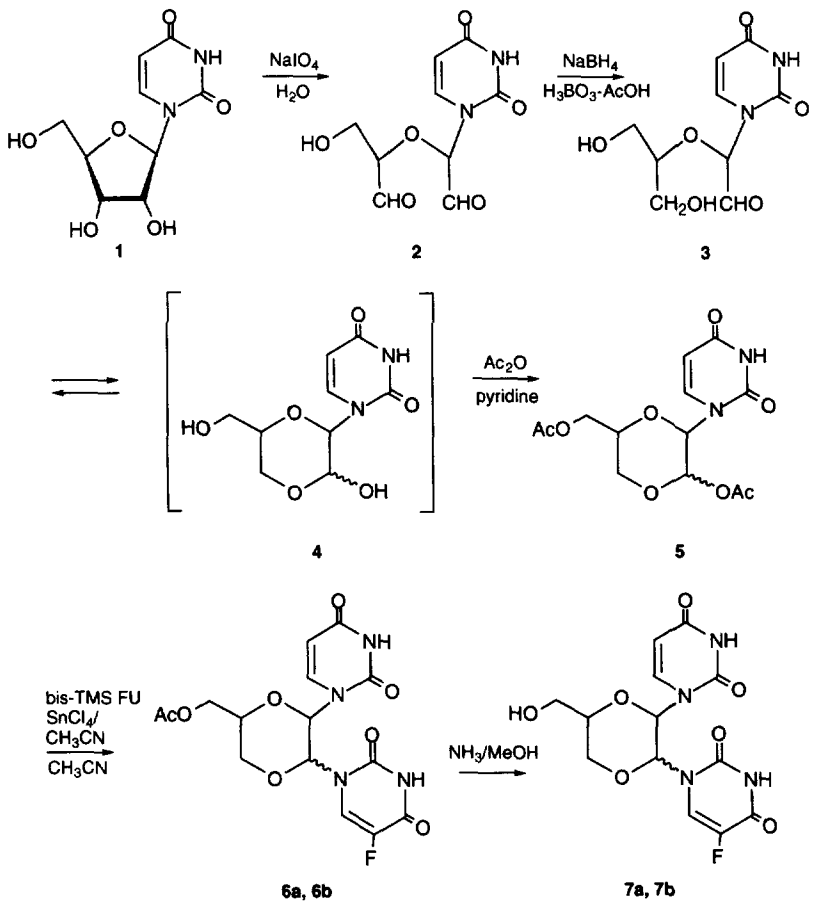

Figure 2.

configurations of which at position 5 are *R* and *S*, respectively. The hemiacetal formation mainly occurred between the 2'-aldehyde and 3'-hydroxy group with a small amount of 5'-hydroxy group cyclized product in **3**, which was estimated from products analysis after the glycosidation. Thus, the hydroxymethyl group originating from the 3'-carbon of uridine participated in the hemiacetals formation is more stable than the other hydroxymethyl group participating in ring formation, that is, formation of an equatrial hydroxymethyl having dioxane ring is more favorable for the reaction than an axial hydroxymethyl group. A solution of stannic

chloride in acetonitrile and bis-trimethylsilyl-5-fluorouracil[11] was then added to a solution of the mixture **5** in acetonitrile at room temperature to give a new type of nucleoside as a mixture of 5(*R*)-acetoxymethyl-2(*R*)-(5-fluorouracil-1-yl)-3(*R*)-(uracil-1-yl)-1,4-dioxane (**6a**) and 5(*R*)-acetoxyoxymethyl-2(*S*)-(5-fluorouracil-1-yl)-3(*R*)-(uracil-1-yl)-1,4-dioxane (**6b**) (the ratio, *R/S*=10/1) with other form(s) (less than 1%). After separation of each isomer by silica gel column chromatography, compound **6a**[12] was recrystallized from ethanol-ether to afford white needles, m.p., 232~236 °C (dec.) in a 30% yield from the monoaldehyde (**3**) (Figure 2). Deprotection of the acetyl group was carried out with ammonia-methanol to afford the desired nucleosides, 2(*R*)-(5-fluorouracil-1-yl)-5(*R*)-hydroxymethyl-3(*R*)-(uracil-1-yl),-1,4-dioxane (**7a**), m.p. 253~256 °C (dec.) and 2(*S*)-(5-fluorouracil-1-yl)-5(*R*)-hydroxymethyl-3(*R*)-(uracil-1-yl)-1,4-dioxane (**7b**). The structure of **7a** could be determined on the basis of the data of X-ray crystallographic analysis[13], as well as spectral and elemental analysis[14]. Nuclear Overhauser effects observed between H3 and H5 in ^{1}H-nmr indicate that the two substituents, hydroxymethyl and uracil, are equatorial. The circular dichroism spectrum of **7a** in water had a very large [θ] value at 270 nm suggesting that both bases have an *anti* conformation. However, the amount of **7b** was too small to allow its elucidation. Acid hydrolysis of **7a** was carried out in hydrochloric acid (6 mol/dm^3) at 110 °C for 14 h. The result showed that the two glycosidic bonds were both degraded to produce 5-fluorouracil and uracil, in an approximately 1:1 molar ratio. Thus, the stability of both N-glycosidic bonds is similar regarding resistance to acid hydrolysis. Dissociation constants of the NH protons of FU and U in **7a** were estimated to be 7.2 and 9.5, respectively, by pH titration with uv spectroscopy in a buffer solution[15].

It has been shown that simple dioxane nucleosides (with adenine, 5-fluorouracil, or guanine as the base) do not exert any anti-viral activity[6a, 8a]. The reason might be that the distance and/or their configuration between the primary hydroxymethyl group and the base in the nucleoside are not suitable, since they are in a *cis* configuration. Therefore, an axial position for one of substituents could be favorable in the activity of dioxane nucleoside.

It is noteworthy that when naturally occurring ribonucleosides such as adenosine, cytidine, guanosine, and uridine are used as the starting material in our synthetic method, a total 16 combinations of pairs of bases in **7** can be generated. Moreover, when 5-fluorouridine, inosine and ribothymidine are included in the starting material, the possibilities increased to 49. Synthesis of some of these is now in progress in our laboratory along with assessment of the anti-viral and anti-tumor activity.

ACKNOWLEDGMENTS: The authors thank Dr. Hiroyuki Tsuda, Chief of the Chemotherapy Division, National Cancer Center Research Institute, for his encouragement during this work, Dr. Kazuho Harada of Kitasato University for his X-ray crystallographic analysis, and Dr. Koichi Hashimoto of Morinaga Milk Industry Co., Ltd. for his nmr measurements.

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12. All data from elemental analysis, mass spectra, ^{1}H-nmr, and ^{13}C-nmr supported conclusion of the structure shown as **6a**.
13. The uracil ring was found to be in anti conformation at state with the C2 carbonyl oriented to the 1 proton while 5-fluorouracil was in the opposite direction. Two pyrimidine rings were in nearly reverse parallel tc each other.
14. Elemental analysis (C, H, and N) was satisfactory achieved for the compound: Calcd for $C_{13}H_{13}N_4O_7$, C, 43.83%, H, 3.68%, N, 15.73%, Found, C, 43.87%, H, 3.75%, N, 15.61% for (**7a**). Mass spectrometry, m/z 572 (TMS x 3), 557 (M^+-Me), 388 (M^+-TMS-U), 370 (M^+-TMS-FU). Uv spectra in water, λmax 260 nm (ε=16,700), λmin 230 nm (pH 1), and λmax260 nm (ε=12,000), λmin 247 nm (pH 13). ^{1}H-nmr spectra in DMSO-*d6* were as follows; δ (ppm), 3.45 (1H, m, $J_{7A\text{-}5}$ = 5.3 Hz and Jgem = 11.8 Hz, H7A), 3.47 (1H, m, $J_{7B\text{-}5}$ = 5.3 Hz, H7B), 3.82 (1H, t, $J_{6a\text{-}5}$ = 11.1 Hz and Jgem = 11.8 Hz, H6a), 4.02 (1H, dd, $J_{6e\text{-}5}$ = 2.6 Hz, H6e), 4.16 (1H, m, H5), 4.91 (1H, t, J = 5.7 Hz, OH), 5.70 (1H, d, $J_{5''\text{-}6''}$ = 8.1 Hz, H5"), 5.72 (1H, dd, $J_{2\text{-}3}$ = 8.6 Hz, and $J_{2\text{-}F}$ = 1.4 Hz, H2), 5.92 (1H, d, H3), 7.86 (1H, d, H6"), 8.32 (1H, d, $J_{6'\text{-}F}$ = 7.0 Hz, H6'), 11.37 (1H, bs, NH, H3'), 11.93 (1H, bs, NH, H3"). ^{13}C-nmr in DMSO-*d6* spectra were as follows; δ (ppm), 59.87 (C7), 67.66 (C6), 75.93 (C5), 78.25 (C3), 78.75 (C2), 102.13 (C5"), 125.60 (d, J = 35 Hz, C6'), 139.88 (d, J = 231 Hz, C5'), 140.91 (C6"), 148.84 (C2'), 150.13 (C2"), 156.71 (d, J = 25 Hz, C4'), 162.55 (C4").
15. Two isosbestic points which correspond to each pKa were at least observed in uv titration curves.

(*Received in Japan* 18 *June* 1997; *revised* 29 *July* 1997; *accepted* 4 *August* 1997)