[Chem. Pharm. Bull. 26(10)2990—2997(1978)]

UDC 547.963.32.04.09 : 615.277.4.011.5.076.7

# Synthetic Nucleosides and Nucleotides. XI.[1] Facile Synthesis and Antitumor Activities of Various 5-Fluoropyrimidine Nucleosides

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(Received March 13, 1978)

Condensation of 2,4-bis-trimethylsilyloxy-5-fluoropyrimidine (**2a**) with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (**3a**) by Friedel-Crafts catalysts has been studied. When the reaction was run in acetonitrile at room temperature for 3 hr with 1 : 1 : 1 molar ratio of the base, sugar and stannic chloride, 2′,3′,5′-tri-O-benzoyl-5-fluorouridine (**4a**) was obtained in an excellent yield (98%). As 1-O-acetyl sugars, 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose (**3b**), 1,2,3,4,6-penta-O-acetyl-α-D-glucopyranose (**3c**), and 1,2-di-O-acetyl-3-*p*-toluenesulfonyl-5-O-methoxycarbonyl-D-xylofuranose (**3d**) could also be used in place of **3a** to give the corresponding 1-β-D-glycosyl nucleosides highly stereoselectively. The same method of nucleoside synthesis was extended to the 5-fluorocytosine series to afford 5-fluorocytidine (**7a**) and 1-β-D-arabinofuranosyl-5-fluorocytosine (**7b**) in good yields starting from trimethylsilylated $N_4$-acetyl-5-fluorocytosine (**6**). Additionally, 2,4-dimethoxy-5-fluoropyrimidine (**2b**) could be coupled with **3a** in similar conditions to give 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-4-methoxy-5-fluoro-1,2-dihydropyrimidin-2-one (**4e**) in good yield.

The antitumor activities of the various products obtained against ascites Sarcoma 180 are also described.

**Keywords**——5-fluoropyrimidine nucleosides; synthesis; 1-O-acetyl sugars; 2,4-bis-trimethylsilyloxy-5-fluoropyrimidine; Friedel-Crafts catalysts; antitumor activity; Sarcoma 180

5-Fluorouracil (5FU, **1**) and its nucleosides such as 5-fluorouridine (FUR, **5a**) and 5-fluoro-2′-deoxyuridine (FUdR) have shown significant antitumor activities in experimental tumor systems and have successfully been put to clinical use.[3]

In contrast with 5FU, 5-fluorocytosine (5FC) shows little biological activities except against several fungi.[4] However, 5-fluoro-2′-deoxycytidine (FCdR),[5] 1-β-D-arabinofuranosyl-5-fluorocytosine (AraFC, **7b**),[6] and 2,2′-anhydro-1-β-D-arabinofuranosyl-5-fluorocytosine (Cyclo-AraFC)[7] have shown antitumor activities.

Number of papers from various laboratories have described preparations of 5-fluoropyrimidine nucleosides and several methods such as mercuri-process,[8] Hilbert-Johnson

1) Part X of this series: M. Saneyoshi, M. Inomata, T. Sekine, A. Hoshi, and F. Fukuoka, *J. Pharmacobio-Dynamics*, **1**, 168 (1978). Part of this study was presented at the 94th Annual Meeting of the Pharmaceutical Society of Japan, Sendai, April, 1974 and Nishinomiya, April, 1975.
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3) *a*) C. Heidelberger, *Cancer Res.*, **30**, 1549 (1970) and references cited therein.; *b*) J.H. Burchenal, V.E. Currie, M.D. Dowling, J.J. Fox and I.H. Krakoff, *Ann. N. Y. Acad. Sci.*, **255**, 202 (1975) and references cited therein.
4) C. Heidelberger, L. Griesbach, B.J. Montag, D. Mooren, O. Gut, R.J. Schnitzer, and E. Grunberg, *Cancer Res.*, **18**, 305 (1958).
5) J.H. Burchenal, E.A. Holmberg, J.J. Fox, S.C. Hemphill, and J.A. Reppert, *Cancer Res.*, **19**, 494 (1959).
6) J.H. Burchenal, H.H. Adams, N.S. Newll, and J.J. Fox, *Cancer Res.*, **26**, 370 (1966).
7) *a*) J.J. Fox, E.A. Falco, I. Wempen, D. Pomeroy, M.D. Dowling, and J.H. Burchenal, *Cancer Res.*, **32**, 2269 (1972); *b*) A. Hoshi, M. Yoshida, F. Kanzawa, K. Kuretani, T. Kanai, and M. Ichino, *Gann*, **64**, 519 (1973); *c*) M. Yoshida, A. Hoshi, K. Kuretani, T. Kanai, and M. Ichino, *Gann*, **66**, 561 (1975).
8) *a*) N.C. Yung, J.H. Burchenal, R. Fecher, R. Duschinsky, and J.J. Fox, *J. Am. Chem. Soc.*, **83**, 4060 (1961); *b*) E.J. Reist, J.H. Osieski, L. Goodman and B.R. Baker, *J. Am. Chem. Soc.*, **83**, 2208 (1961).

method[9] and silyl method,[10] are now available for the synthesis of 5-fluoropyrimidine nucleosides. However, it is still important to devise a simple and facile procedure which will afford 5-fluoropyrimidine nucleosides in high yields for further systematic study of their antitumor activities. Stannic chloride catalyzed glycosylation method for pyrimidine nucleoside synthesis was first introduced by Niedballa and Vorbrüggen[11] to improve the yield of 6-azauridine and extended to general method for the synthesis of pyrimidine nucleosides.[12–15]

In this paper, application and modification of this method to the facile synthesis of various 5-fluoropyrimidine nucleosides and their antitumor activities against ascites Sarcoma 180 in mice are described.

## Synthesis

First, the reaction of 2,4-bis-trimethylsilyloxy-5-fluoropyrimidine (**2a**) with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (**3a**) in 1,2-dichloroethane in the presence of $SnCl_4$ (0.78 equivalent mol) was attempted according to the procedure of Niedballa and Vorbrüggen.[11] However, the desired benzoylated nucleoside was obtained only in a low yield and also some α-isomer was detected in the reaction mixture. A similar observation was also reported by Ohrui *et al.* in the case of the synthesis of 1-(5-azido-5-deoxy-2,3,6-tri-O-benzoyl-β-D-allofuranosyl)thymine by the same procedure.[16] Thus, the reaction conditions were reinvestigated in detail as summarized in Tables I and II.

The yield of 2′,3′,5′-tri-O-benzoyl-5-fluorouridine (**4a**) was found to be highly dependent on the reaction medium employed. The first factor examined was the effect of the solvent on the yield of **4a**. When **3a** was coupled with **2a** in 1,2-dichloroethane and benzene, isolated

Table I. Effect of the Solvent on the Yield of 2′,3′,5′-Tri-O-benzoyl-5-fluorouridine (**4a**)

| Ex. no. | **2a** (mmol) | ABR (**3a**) mg (mmol) | $SnCl_4$ (mg) | Solvent | Yield[a] of **4a** (%) |
|---|---|---|---|---|---|
| 1 | 1 | 505 (1) | 260 | $ClCH_2CH_2Cl$ | 45 |
| 2 | 1 | 1010 (2) | 260 | $ClCH_2CH_2Cl$ | 48 |
| 3 | 1 | 505 (1) | 260 | Benzene | 34 |
| 4 | 1 | 505 (1) | 260 | $CH_3NO_2$ | 90 |
| 5 | 1 | 505 (1) | 260 | $CH_3CN$ | 98 |

A mixture of 2,4-bis-trimethylsilyloxy-5-fluoropyrimidine (**2a**) and 2,3,5-tri-O-benzoyl-1-O-acetyl-β-D-ribofuranose (ABR, **3a**) in 15 ml of a solvent was stirred under cooling in ice bath. To this solution, $SnCl_4$ (1 mmol) in 3 ml of anhydrous solvent was added dropwise and the mixture was stirred at room temperature for additional 3 hr. After work-up (see Experimental), crystalline **4a** was weighed and its yield calculated.

yield of **4a** was 45—48% and 34%, respectively, whereas the use of acetonitrile or nitromethane as solvent gave **4a** in a yield of more than 90%. The procedural superiority of the acetonitrile or nitromethane method over the 1,2-dichloroethane method was thus demonstrated in the 5-fluorouridine series.


9) *a*) M. Prystas and F. Sorm, *Coll. Czech. Chem. Commn.*, **29**, 2956 (1964); *b*) M. Prystas and F. Sorm, *Coll. Czech. Chem. Commn.*, **30**, 1900 (1965).
10) *a*) T. Kanai, M. Ichino, A. Hoshi, F. Kanazawa and K. Kuretani, *J. Med. Chem.*, **15**, 1218 (1972); *b*) M. Bobek, A. Bloch, R. Partharathy, and R.L. Whistler, *J. Med. Chem.*, **18**, 784 (1975).
11) U. Niedballa and H. Vorbrüggen, *Angew. Chem.*, **9**, 461 (1970).
12) H. Vorbrüggen and U. Niedballa, *Tetrahedron Lett.*, **1970**, 3571.
13) U. Niedballa and H. Vorbrüggen, *J. Org. Chem.*, **39**, 3625 (1974).
14) U. Niedballa and H. Vorbrüggen, *J. Org. Chem.*, **39**, 3660 (1974).
15) H. Vorbrüggen and U. Niedballa, *J. Org. Chem.*, **39**, 3672 (1974).
16) H. Ohrui, H. Kuzuhara, and S. Emoto, *Tetrahedron Lett.*, **1971**, 4267.

The use of other Friedel-Crafts catalysts such as titanium chloride, aluminum chloride, and zinc chloride in place of stannic chloride resulted in somewhat lower yields of **4a.** The maximum yield was obtained when equivalent amounts of **2a**, **3a**, and $SnCl_4$ were used as shown in Table II.

The study of the time-course of the reaction revealed that the yield became almost constant after 3 hr.

TABLE II. Effect of Catalyst on the Yield of 2′,3′,5′,-Tri-O-benzoyl-5-fluorouridine (**4a**)

| Ex. no. | Catalyst (mmol) | Solvent | Yield[a] of **4a** (%) |
|---|---|---|---|
| 6 | $SnCl_4$ (0.78) | $CH_3CN$ | 62[b] |
| 7 | $SnCl_4$ (0.78) | $ClCH_2CH_2Cl$ | 49[b] |
| 5 | $SnCl_4$ (1.0) | $CH_3CN$ | 98 |
| 8 | $SnCl_4$ (1.2) | $CH_3CN$ | 94 |
| 9 | $SnCl_4$ (2.0) | $CH_3CN$ | 78 |
| 10 | $TiCl_4$ (1.0) | $CH_3CN$ | 68 |
| 11 | $TiCl_4$ (1.0) | $ClCH_2CH_2Cl$ | 39 |
| 12 | $AlCl_3$ (1.0) | $CH_3CN$ | 38 |
| 13 | $ZnCl_2$ (1.0) | $CH_3CN$ | 42 |

*a*) To a solution of 1 mmol each of **2a** and **3a** in 15 ml of a solvent, a catalyst in 3 ml of the solvent was added dropwise under ice-cooling. After having been stirred for 3 hr at room temperature, the reaction mixture was worked up in the usual manner and crystalline **4a** was weighed and its yield calculated as described above.
*b*) In this reaction, the α-isomer was also detected on silica gel TLC of the reaction mixture.

Replacement of **3a** with other 1-O-acetylated sugars in this reaction was found to be useful for the synthesis of 5-fluorouracil nucleoside analogues which have unusual carbohydrate moieties. For example, the reaction of 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose (**3b**) and **2a** with $SnCl_4$ afforded 2′,3′,5′-tri-O-acetyl-5-fluorouridine (**4b**), mp 128—130°, in *ca.* 80% yield. Similarly, 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-5-fluorouracil (**4c**) was obtained from

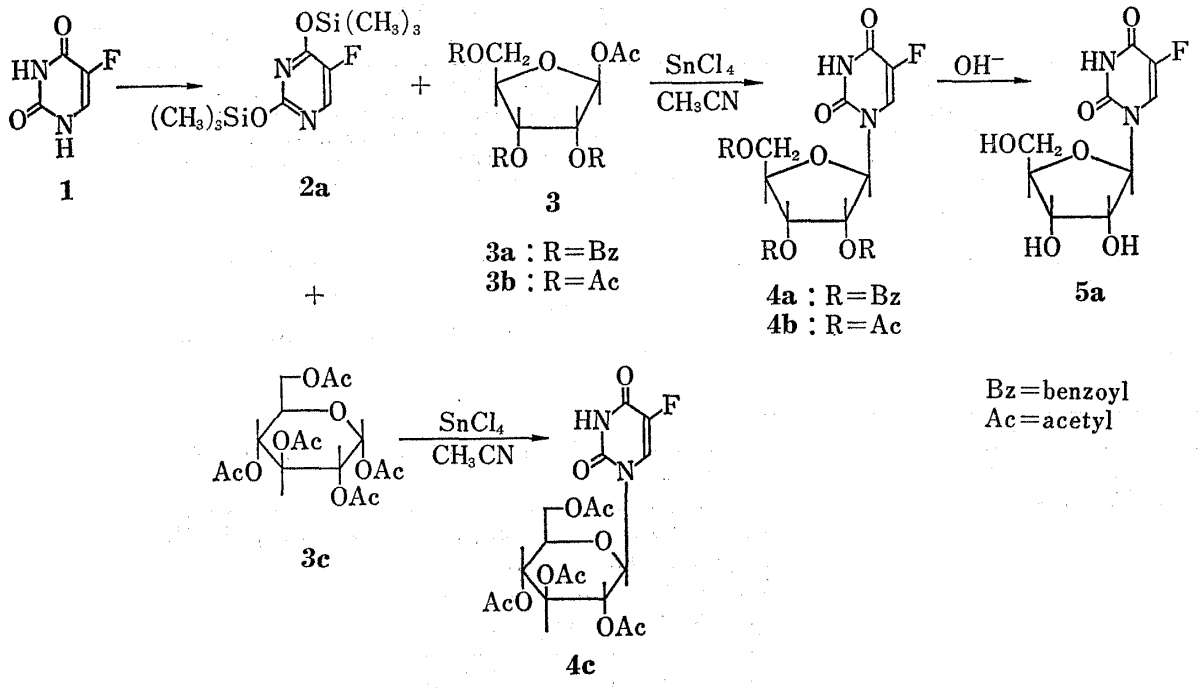


Chart 1

reaction of **2a** and 1,2,3,4,6-penta-O-acetyl-α-D-glucopyranose (**3c**) in 78% isolated yield as crystals. For the synthesis of 2,2′-anhydro-1-β-D-arabinofuranosyl-5-fluorouracil (**5b**), the coupling of **2a** with 1,2-di-O-acetyl-3-*p*-toluenesulfonyl-5-O-methoxycarbonyl-D-xylofuranose (**3d**)[17] in the presence of $SnCl_4$ was successfully applied. After usual work-up, the reaction mixture was passed through a column of silica gel to give 1-(2-O-acetyl-3-O-*p*-toluenesulfonyl-5-O-methoxycarbonyl-β-D-xylofuranosyl)-5-fluorouracil (**4d**) as thin-layer chromatographically homogeneous syrup. This was treated with cold 0.5 N methanolic sodium methoxide at 0° and the mixture was further stirred for several hours at room temperature.

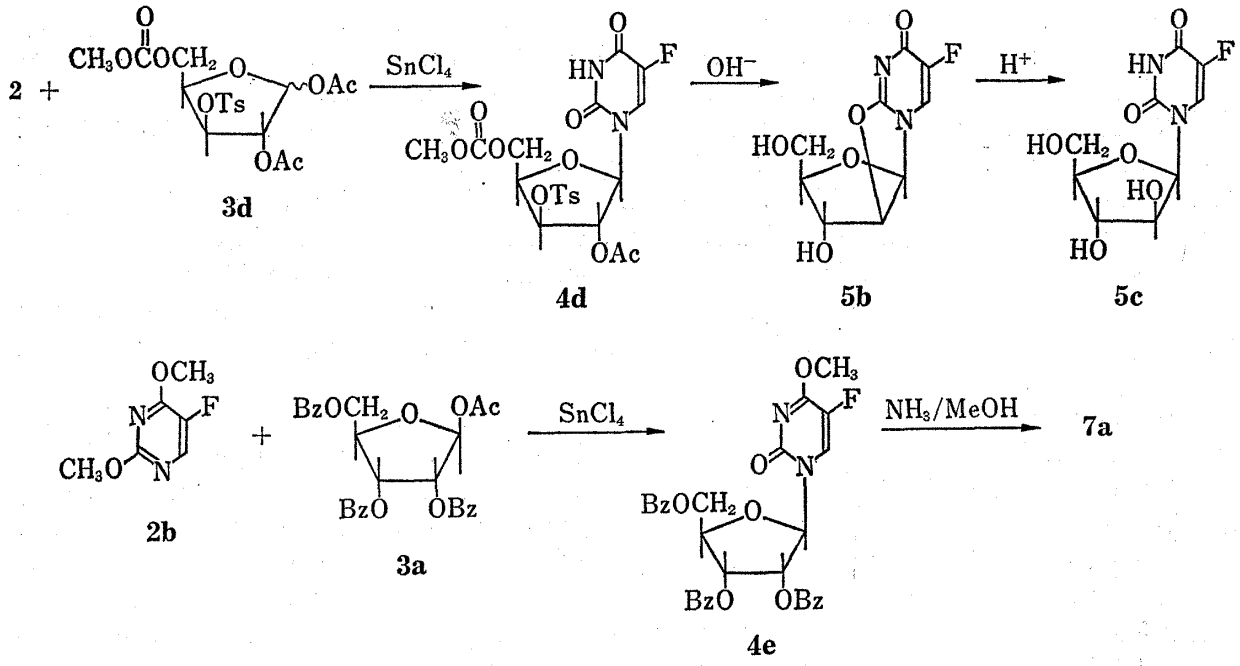


Chart 2

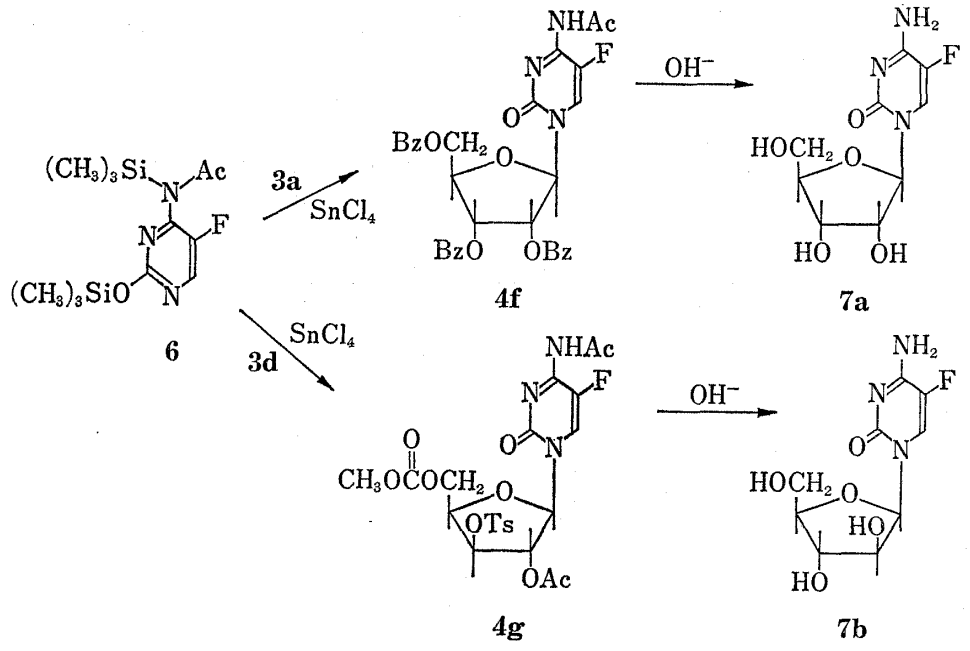


Chart 3

17) C.D. Anderson, L. Goodman, and B.R. Baker, *J. Am. Chem. Soc.*, **80**, 5247 (1958).

After neutralization with Dowex 50 ($H^+$-form), the product was crystallized from ethanol to give 2,2′-anhydro-1-β-D-arabinofuranosyl-5-fluorouracil (**5b**), mp 196—197°, UV, $\lambda_{max}$ 223 and 254 nm. The overall yield from 5-fluorouracil (**1**) was 70%. This compound (**5b**) was readily converted to 1-β-D-arabinofuranosyl-5-fluorouracil (**5c**)[8a] by treatment with refluxing 0.5 N sulfuric acid.

As expected from the above reactions, another base, 2,4-dimethoxy-5-fluoropyrimidine (**2b**),[9a] similarly reacted with **3a** to give 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-4-methoxy-5-fluoro-1,2-dihydropyrimidin-2-one (**4e**),[9b] which could easily be converted to **4a** and 5-fluorocytidine (**7a**).

On the other hand, this method has been extended to the synthesis of biologically important 5-fluorocytosine nucleosides.[3b,6-7] Known methods for the synthesis of these nucleosides involve long reaction steps and the overall yields are poor.

$N_4$-Acetyl-5-fluorocytosine was first converted to its trimethylsilyl derivative (**6**), followed by reaction with **3a** in the presence of $SnCl_4$ in dry acetonitrile to give fully acylated nucleoside (**4f**) which could not be crystallized. After purification of **4f** by column chromatography on silica gel, the residue was treated with 0.5 N sodium methoxide in methanol at room temperature for 10 hr. After neutralization of the reaction mixture with Dowex 50 ($H^+$-form), the product was purified by Dowex 1 ($OH^-$-form) column chromatography. On crystallization from aqueous ethanol, 5-fluorocytidine (**7a**) was obtained as crystals in 66.5% yield from 5-fluorocytosine.

In a similar manner, the 2,4-bis-trimethylsilylated $N_4$-acetyl-5-fluorocytosine (**6**) was condensed with **3d**, followed by treatment with sodium methoxide, to give 1-β-D-arabinofuranosyl-5-fluorocytosine (**7b**) in crude state. Purification of this material with Dowex 50 ($H^+$) and Dowex 1 column chromatography afforded pure **7b** in a crystalline form, mp 234—236°.

In conclusion, the coupling of trimethylsilylated 5-fluoropyrimidine with suitably protected 1-O-acetyl sugars, catalyzed by $SnCl_4$ in acetonitrile or nitromethane, has proved quite useful for the synthesis of biologically important 5-fluoropyrimidine nucleosides. The advantages of this method, compared with other coupling processes, are that 1) prior halogenation of 1-O-acyl sugar is not necessary, 2) the reaction mixture is homogeneous throughout the coupling reaction, 3) the reaction proceeds rapidly at room temperature and blocked β-nucleosides are obtained in excellent yields when the catalyst and reaction solvent are suitably chosen.

Table III. Antitumor Activity of the Compounds against Sarcoma 180

| Compound | Dose (mg/kg/day) T/C (%)[a] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 150 | 100 | 60 | 30 | 20 | 10 | 3 | 1 | 0.3 |
| 5FU (**1**) | | | | | 0 | 21 | 65 | 83 | |
| 5FUdR[b] | Toxic | 1.6 | 35 | 87 | | | | | |
| 5FUR (**5a**) | | | | Toxic | | 0 | 1 | 31 | 80 |
| **4a** | | 0 | 20.5 | 55 | | 78 | | | |
| **4b** | | 0 | 1.4 | 11 | | 68 | | | |
| **4d** | 91 | 96 | | | | | | | |
| **4e** | | 94 | | | | | | | |
| **5b** | 82 | | | | | | | | |
| **5c** | 92 | | | | | | | | |
| 5FC | 92 | | | | | | | | |
| 5FCR (**7a**) | | | Toxic | 0 | | 0 | 2.1 | 80 | 90 |

a) Expressed as percentage of total packed cell volume of the treated mice to that controls.
b) This compound was supplied from Mitsui Pharm. Co., Ltd.

## Antitumor Activities

Antitumor activities of 11 kinds of 5-fluoropyrimidines and related nucleosides, 5FU (**1**), FUdR, FUR (**5a**), **4a**, **4b**, **4d**, **4e**, **5b**, **5c**, 5-fluorocytosine, and FCR (**7a**), being assayed with ascites Sarcoma 180 (S180A) in mice,[18] are as follows.

Sarcoma 180 ($5\times10^6$ cells) was implanted intraperitoneally into ICR female mice. Compounds to be tested were injected *i.p.* once a day for a period of 5 days starting 24 hr after tumor implantation. In this system, the average total packed cell volume of the treated group was compared with that of the control group 7 days after transplantation. The results of this study are summarized in Table III. As can be seen from Table III, FUR (**5a**) and its acylated derivatives, **4a** and **4b** are highly active against this tumor system as expected. However, 2,2′-anhydro-1-β-D-arabinofuranosyl-5-fluorouracil (**5b**) is inactive and 1-β-D-arabinofuranosyl-5-fluorouracil (**5c**), which was reported as active against Leukemia B-82[8a] is also inactive against this system. Compound **4e** as methoxy analogue of **4a** and glucopyranosyl analogue of **4b** are both essentially inactive.

In the 5-fluorocytosine series, 5-fluorocytosine was inactive, however, 5-fluorocytidine (**7a**) was remarkably active against this system as shown in Table III. A more detailed study of the biological aspect of this material and **7b** will be reported elsewhere.

## Experimental

### Starting Materials

5-Fluorouracil and 5-fluorocytosine were kindly supplied from Mitsui Pharmaceutical Co., Ltd. 1-O-Acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose and 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose were purchased from Waldhof (Germany). Stannic chloride and other Friedel-Crafts catalysts were obtained from Wako Chemical Co., Ltd.

**Trimethylsilylation of 5-Fluorouracil**——Well ground 5-fluorouracil 2.6 g (20 mmol) was suspended in 15 ml of hexamethyldisilazane and the suspension heated under reflux for 2—3 hr until a clear solution resulted. The excess hexamethyldisilazane was removed under reduced pressure and the residual gum (4.2 g) dissolved in anhydrous benzene. A small amount of insoluble material was removed by filtration and the filtrate evaporated to dryness. The residue was used directly for the condensation step without purification.

**Trimethylsilylation of $N_4$-Acetyl-5-fluorocytosine**——$N_4$-Acetyl-5-fluorocytosine[19] (2 g) was suspended in 10 ml of hexamethyldisilazane and 2 ml of trimethylchlorosilane. When the mixture was refluxed for 3 hr under exclusion of atmospheric moisture, all the solid material was dissolved. The solution was evaporated under diminished pressure and the residue redissolved in anhydrous benzene (30 ml). The solution was filtered and evaporated to give a colorless gum, which could be used directly for the subsequent reaction.

**2′,3′,5′-Tri-O-benzoyl-5-fluorouridine** (**4a**)——2,4-Bis-trimethylsilyloxy-5-fluoropyrimidine (**2a**) derived from 2.6 g (20 mmol) of 5-fluorouracil (**1**) was mixed with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (**3a**) (10.08 g, 20 mmol) in 80 ml of anhydrous acetonitrile. To the solution, stannic chloride (4.2 g) in 20 ml of anhydrous acetonitrile was added dropwise under stirring and cooling in ice bath (the temperature of the reaction mixture should be kept below 10°). The resulting clear solution was stirred for another hour, whereupon the ice bath was removed and the reaction mixture stirred for additional 2 hr at room temperature. Thin-layer chromatography (TLC) (silica gel, $CHCl_3$–ethyl acetate=9: 1, v/v) of the reaction mixture showed main spot ($Rf$=0.56) corresponding to **4a** with two minor spots ($Rf$=0.76 and 0.12) corresponding to the benzoyl-sugar and the base, respectively. After concentration of the reaction mixture to 20 ml, well powdered sodium hydrogen carbonate (10 g) and 10 ml of distilled water added carefully under stirring. After checking the pH of the reaction mixture, which should be 8.5, the solvent was removed under reduced pressure. The gummy residue was co-evaporated with benzene (20 ml×3) for complete removal of trace of water. The resulting hard glass was extracted with boiling acetone (50 ml×3). The acetone extracts were filtered and evaporated. The residue was dissolved in 200 ml of boiling chloroform. A small amount of insoluble material was removed by filtration, and the filtrate was stored in a freezer. Fine needles which precipitated were collected on a glass filter to give 11.2 g (98%) of **4a**, mp 205—208°. Recrystallization from hot toluene gave an analytical sample which melted at 208—209° (lit.[8a] 207—209°); $[\alpha]_D^{20}$ −34.5° (*c*, 2.0, $CH_2Cl_2$), lit.[8a]

18) *a*) A. Hoshi, F. Kanazawa and K. Kuretani, *Cancer Chemother. Rep.*, Part 1, **55**, 229 (1971); *b*) M. Saneyoshi, M. Inomata, T. Sekine, A. Hoshi, and F. Fukuoka, *J. Pharmacobio-Dynamics*, **1**, 168 (1978).

19) R. Duschinsky, T. Gabriel, M. Hoffer, J. Berger, E. Titsworth, E. Grunberg, J.H. Burchenal, and J.J. Fox, *J. Med. Chem.*, **9**, 566 (1966).

$[\alpha]_D^{28}$ −33° (*c*, 2.0, $CHCl_3$); *Anal.* Calcd. for $C_{30}H_{23}FN_2O_9$: C, 62.72; H, 4.04; N, 4.88. Found: C, 62.66; H, 4.09; N, 4.72.

**2′,3′,5′-Tri-O-acetyl-5-fluorouridine (4b)**——To a solution of 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose (**3b**) (3.78 g, 10 mmol) and **2a** (derived from 1.3 g of **1**) in 40 ml of anhydrous acetonitrile, stannic chloride (2.1 g) in 10 ml of acetonitrile was added portionwise under cooling in ice bath. The clear solution thus obtained was stirred vigorously under exclusion from moisture at room temperature for 3 hr. After evaporation of the solvent, sodium hydrogen carbonate (5 g) and 10 ml of distilled water were added. After work up as described in the case of the synthesis of **4a**, the residue was extracted with boiling ethyl acetate (50 ml×3). The extracts were evaporated under reduced pressure and the residue was crystallized from absolute ethanol to give fine needles. 3.14 g (81%), mp 128—130°. UV, $\lambda_{max}$ (nm), in ethanol, 270 (ε, 8700), $[\alpha]_D^{23}$ +27° (*c*, 2.0, $CHCl_3$). *Anal.* Calcd. for $C_{15}H_{17}FN_2O_9$: C, 46.40; H, 4.41; N, 7.22; F, 4.89. Found: C, 46.28; H, 4.30; N, 6.98; F, 4.70. When 90% ethanol was used as crystallization solvent, cubic crystals were obtained. They melted at 96—98°, and from comparison of IR (KBr), NMR ($CDCl_3$) and elemental analytical data, it should be a monohydrate of **4b**. *Anal.* Calcd. for $C_{15}H_{17}FN_2O_9 \cdot H_2O$: C, 44.34; H, 4.71; N, 6.89; F, 4.67. Found: C, 44.21; H, 4.70; N, 6.78; F, 4.51.

**1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-5-fluorouracil (4c)**——To a solution of 1,2,3,4,6-penta-O-acetyl-α-D-glucopyranose (**3c**) (5 mmol) and **2a** (5 mmol) in 50 ml of dry acetonitrile, $SnCl_4$ (0.7 ml, 5 mmol) in the same solvent was added under stirring below 10° and the mixture was further stirred for 3 hr. After similar work-up as described before, **4c** was crystallized from ethanol to give fine crystals which melted at 153—155°. Yield, 80%.

This sample was identified with an authentic specimen, which was prepared according to literature,[20] by mixed melting point and IR spectra.

**2,2′-Anhydro-1-β-D-arabinofuranosyl-5-fluorouracil (5b)**——A solution of 10 mmol each of **2a** and 1,2-di-O-acetyl-3-O-*p*-toluenesulfonyl-5-O-methoxycarbonyl-D-xylofuranose[17] (**3d**) was treated with 10 mmol of stannic chloride. After stirring for 3 hr at room temperature, the solvent was removed under reduced pressure. The residual gum was extracted with boiling acetone (50 ml×3). The acetone extracts were filtered and evaporated. The residue was dissolved in 10 ml of chloroform and the solution was applied to a column of silica gel (2.5×35 cm). Elution was performed using chloroform–ethyl acetate (4: 1, v/v) and UV absorbing fraction was collected and evaporated. The resulting colorless gum (**4d**, 4.6 g) was treated with 0.5 N methanolic sodium methoxide (60 ml) and the mixture was stirred for 10 hr at room temperature. The solvent was removed under reduced pressure and the residue was re-dissolved in 100 ml of distilled water. After neutralization with Dowex 50 ($H^+$-form) resin, the solution was evaporated to dryness and the residue crystallized from ethanol to give **5b**, 1.7 g (70%). mp 195—198°. Further recrystallization from ethanol gave an analytical sample, mp 196—197° (lit.[8] 196—197°), $[\alpha]_D^{20}$ −58° (*c*, 0.2, MeOH) (lit[8a] $[\alpha]_D^{24}$ −61° *c*, 0.28, EtOH, UV, $\lambda_{max}$ (nm) in $H_2O$, 222.5 and 254.5 (ε, 7300 and 9100). *Anal.* Calcd. for $C_9H_9FN_2O_5$: C, 44.28; H, 3.73; N, 11.47. Found: C, 44.39; H, 3.85; N, 11.40.

This compound (100 mg) was refluxed with 0.5 N sulfuric acid for 2 hr. The reaction mixture was neutralized with Dowex 1 ($HCO_3^-$ form) and evaporated. The residue was crystallized from ethanol, giving 85 mg of 1-β-D-arabinofuranosyl-5-fluorouracil (**5c**), mp 190—191°, (lit.[8a] 187—188°). UV, $\lambda_{max}$ in ethanol (nm), 270. $[\alpha]_D^{20}$ +130° (*c*, 0.2, $H_2O$).

**1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-4-methoxy-5-fluoro-1,2-dihydropyrimidin-2-one**——To a mixed solution of **3a** and 2,4-dimethoxy-5-fluoropyrimidine[9b] (10 mmol each) in anhydrous acetonitrile (50 ml), stannic chloride (2.1 g) was added under similar conditions to those described above. The resulting clear solution was kept at 50—60° under stirring for 10 hr. TLC analysis of the reaction mixture using silica gel plate with $CHCl_3$–ethyl acetate (7: 1, v/v) as developing solvent showed main spot ($Rf$=0.76) and minor two spots ($Rf$=0.92, 0.82), which were corresponding to those of **4e**, the benzoylated sugar and the base, respectively. The solvent was evaporated and residue was extracted with chloroform (50 ml×3). The extracts were dried and evaporated to dryness. The residue was crystallized from ethanol to give fine crystals. 5.1 g of **4e**. (87%). mp 196—197° (lit.[9a] 197—198°) $[\alpha]_D^{25}$ +3.0 (*c*, 1.0, $CHCl_3$), lit.[9a] $[\alpha]_D^{25}$ +2.4 (*c*, 0.08, pyridine). *Anal.* Calcd. for $C_{31}H_{25}FN_2O_9$: C, 63.26; H, 4.28; N, 4.76. Found, C, 63.32; H, 4.36; N, 4.98.

**5-Fluorocytidine (7a)**——Method A. 2,4-Bis-trimethylsilyl-$N_4$-acetyl-5-fluorocytosine (**6**) derived from 10 mmol of $N_4$-acetyl-5-fluorocytosine[19] was mixed with **3a** (5.04 g, 10 mmol) in anhydrous acetonitrile (100 ml). To the solution, stannic chloride (4.2 g) in the same solvent (10 ml) was added under cooling below 10° for 15 min. The clear reaction mixture was allowed to room temperature and was stirred for additional 2 hr. TLC on silica gel, $CHCl_3$–ethyl acetate (7: 1, v/v) as developing solvent, of the reaction mixture gave three spots, corresponding to the benzoyl-sugar ($Rf$=0.86), benzoylated nucleoside ($Rf$=0.59), and base ($Rf$=0.14).

The solvent was removed under reduced pressure at room temperature and the residual gum treated with sodium hydrogen carbonate (5 g) and distilled water (20 ml). After vigorous evolution of carbon dioxide gas had ceased, the mixture was evaporated *in vacuo*. The residue was extracted with hot ethyl

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acetate (50 ml×3). The extracts were dried over magnesium sulfate and was evaporated to dryness. The resulting light yellow gum, which was still contaminated with the benzoyl-sugar, was dissolved in 30 ml of a 7:1 mixture of $CHCl_3$ and ethyl acetate, and the solution was applied to a column of silica gel (3 cm×35 cm), and the column eluted with the same solvent. The major fraction was 4.8 g of a syrup which was thin-layer chromatographically homogeneous but could not be crystallized from several solvents. This syrup (**4f**) was treated with 0.5 N methanolic sodium methoxide (60 ml) and the mixture stirred at room temperature for 10 hr. After evaporation of the solvent, distilled water (50 ml) was added and the pH of the solution adjusted to pH 8.0 by addition of Dowex 50 ($H^+$-form) ion-exchange resin. The resin was removed by filtration and washed well with water. The filtrates and washings were combined and extracted with chloroform (15 ml×5) to remove methyl benzoate. The aqueous phase was evaporated to dryness to give a thick syrup, which was dissolved in 30 ml of absolute ethanol by heating at reflux temperature. A small amount of active charcoal was added and the mixture filtered while hot. The clear filtrate was stored at 4° overnight to deposit granular **7a**. The precipitate was collected by filtration and re-dissolved in 30 ml of aqueous methanol and the solution was applied to a column of Dowex 1 ($OH^-$ form) (2.5 cm×30 cm). The column was eluted with the same solvent and the fractions showing UV absorbing peak at 280 nm were collected and evaporated. The resulting colorless glass was crystallized from ethanol to give fine needles. 1.7 g, (66.5%). mp 192—193° (lit.,[21] 193—193.5°, lit.,[9a] 193°). UV, $\lambda_{max}$ (nm) in 0.01 N HCl, 290; in 0.01 N NaOH, 237 and 280.5 *Anal.* Calcd. for $C_9H_{12}FN_3O_5$: C, 41.38; H, 4.63; N, 16.08; Found, C, 41.46; H, 4.55; N, 15.91. Method B: Reaction of **4e** with methanolic ammonia in a sealed tube at 100° for 10 hr and work-up as described above, gave **7a** in 63% yield.

**1-β-D-Arabinofuranosyl-5-fluorocytosine (7b)**——Compound **6** derived from 1 mmol of $N_4$-acetyl-5-fluorocytosine was mixed with **3d** (446 mg, 1 mmol) in anhydrous acetonitrile (10 ml). To the solution was added dropwise at 0° stannic chloride (1 mmol) in 2 ml of acetonitrile under stirring. The clear solution was stirred at room temperature for additional 2.5 hr. TLC analysis of the reaction mixture on silica gel plate using ethyl acetate as developing solvent showed a main spot ($Rf$=0.49) and two minor spots $Rf$=0.11 and 0.77, corresponding to the protected nucleoside (**4g**), the unreacted base and sugar, respectively. To this mixture was added 500 mg of sodium hydrogen carbonate and 2 ml of distilled water under stirring. After vigorous carbon dioxide evolution had ceased, the solvent was removed under reduced pressure at room temperature. The residue was treated with anhydrous benzene (2 ml×2) and evaporated to dryness. The resulting hard glass was treated with boiling ethyl acetate (10 ml×3) and the mixture filtered. The filter cake was re-suspended in 10 ml of the same solvent and the mixture heated at reflux temperature for 1 hr and filtered while hot. The combined filtrates were evaporated to give a yellow gum. This was dissolved in 2 ml of chloroform and the solution was subjected to a column of silica gel (1 cm×20 cm).

The elution of the column was performed successively with 100 ml of chloroform, 50 ml of ethyl acetate–chloroform (1:1, v/v), and with 50 ml of ethyl acetate. The chloroform fraction contained only small amount of the unchanged sugar component. Both the latter two fractions contained the acylated nucleoside and they were combined and evaporated. The residue obtained was homogeneous on silica gel thin-layer chromatogram (ethyl acetate as developing solvent), but it could not be crystallized from several solvents. The syrupy residue (300 mg) was dissolved in 5 ml of 0.5 N methanolic sodium methoxide and the solution was stirred at room temperature for 10 hr, whereupon all of the starting material disappeared. The solvent was evaporated at room temperature under reduced pressure and the residue dissolved in 5 ml of distilled water. The solution thus obtained was neutralized carefully with Dowex 50 ($H^+$-form) resin to pH 6.0. The solution was extracted with chloroform (3 ml×4) and the aqueous phase evaporated to dryness. The residue was re-dissolved in 3 ml of water and the solution was applied to a column of Dowex 50 ($H^+$-form) (1 cm×15 cm). The column was washed with water (50 ml) and then eluted with 0.1 N hydrochloric acid. The eluate was evaporated to give crude hydrochloride salt of **7b**. This sample was further purified by Dowex 1 ($HCO_3^-$ form) (1 cm×20 cm) using 30% methanol as eluting solution. The fractions showing UV absorbing peak at 280 nm were collected, combined and evaporated to dryness. The residue was crystallized from boiling ethanol to give 120 mg of pure crystals. (47%). mp 234—235° (lit.,[22] 237—238°) $[\alpha]_D^{20}$ +160° (*c*, 0.1, water) lit.[22] $[\alpha]_D^{23}$ +163±2° (*c*, 0.18, water), UV, $\lambda_{max}$ (nm) in 0.01 N HCl, 291; in 0.01 N NaOH, 237 and 280. *Anal.* Calcd. for $C_9H_{12}FN_3O_5$: C, 41.38; H, 4.63; N, 16.08. Found: C, 41.51; H, 4.66; N, 15.97.

**Acknowledgement** The authors are indebted to Drs. Hiroyoshi Kuzuhara and Sakae Emoto, Institute of Chemical and Physical Research, Wako-shi, for their helpful discussion. This work was supported in part by Princess Takamatsu Cancer Research Fund and also by a grant from Japan Society for Promotion of Cancer Research.

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