Studies on Antitumor Agents. IX.[1] Synthesis of 3′-*O*-Benzyl-2′-deoxy-5-trifluoromethyluridine

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A practical synthesis of 3′-*O*-benzyl-2′-deoxy-5-trifluoromethyluridine (1), a candidate antitumor agent for clinical testing, was developed from 2′-deoxy-5-iodouridine (3). Benzylation of 2′-deoxy-5-iodo-5′-*O*-trityluridine (14) with benzyl bromide and sodium hydride in tetrahydrofuran gave the 3′-*O*-derivative (16). Benzoylation of 16 afforded the N^3-benzoyl derivative (17). Coupling of 17 with trifluoromethylcopper, prepared from bromotrifluoromethane and copper powder in the presence of 4-dimethylaminopyridine, gave the 5-trifluoromethyl derivative (19) minimally contaminated with the 5-pentafluoroethyl compound. Deprotection of 19 furnished 1.

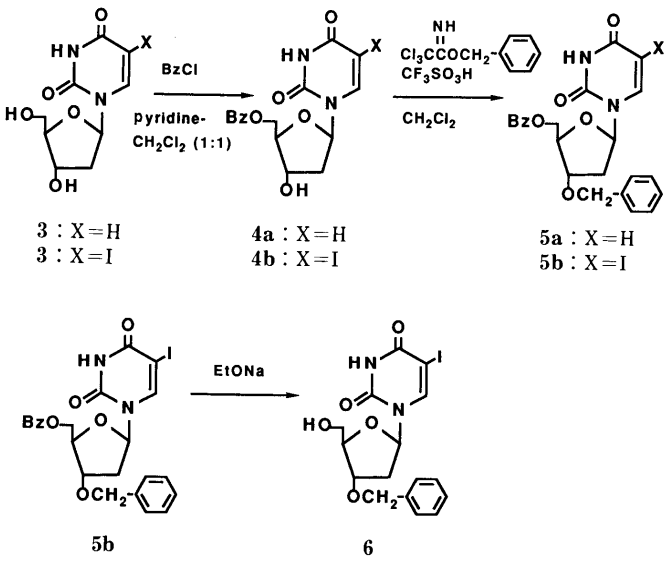
Keywords 3′-*O*-benzyl-2′-deoxy-5-trifluoromethyluridine; antitumor activity; 2′-deoxy-5-iodouridine; O-benzylation; trifluoromethylation; bromotrifluoromethane; trifluoromethylcopper

Recently we have reported the synthesis and antitumor activities of 3′- and 5′-*O*-alkyl derivatives of 2′-deoxy-5-trifluoromethyluridine (F_3Thd) and 2′-deoxy-5-fluorouridine (FUdR).[1] Although F_3Thd and FUdR inhibit the proliferation of some tumor cells strongly *in vitro*,[2] these unprotected nucleosides gave unsatisfactory results *in vivo* due to their short half-lives in plasma.[3,4] It is well known that thymidine phosphorylase cleaves these unprotected nucleosides rapidly.[3,5] However, the *O*′-alkylated derivatives of F_3Thd and FUdR are resistant to this enzymatic degradation and are slowly activated by microsomal drug-metabolizing enzymes after absorption, thus maintaining higher concentrations of F_3Thd or FUdR in plasma and showing improved antitumor activities. In fact, *O*′-alkyl derivatives of F_3Thd or FUdR were 4—10 fold more active than the parent nucleosides.[1] It should be noted that F_3Thd is active only in the form of the nucleoside, and the free base (5-trifluoromethyluracil) formed by thymidine phosphorylase action on F_3Thd is inactive, which is in contrast to the case of FUdR. Thus, suitable derivatives of F_3Thd might exclusively inhibit deoxyribonucleic acid (DNA) synthesis and would be expected to exhibit better chemotherapeutic indexes than FUdR. Among various *O*′-alkylated F_3Thds, 3′-*O*-benzyl-2′-deoxy-5-trifluoromethyluridine (**1**) showed the lowest acute toxicity, and this compound was selected as a candidate for further clinical tests.

This paper deals with a survey of synthetic methods suitable for large-scale preparation of **1**.

Compound **1** has been synthesized by benzylation of N^3-benzoyl-2′-deoxy-5-trifluoromethyluridine (**2**)[6] with benzyl halide in the presence of silver oxide, followed by debenzoylation with ammonia.[1] Besides the 3′-*O*-benzyl derivatives, 5′-*O*-benzyl and 3′,5′-di-*O*-benzyl compounds were also formed under these reaction conditions as would be expected. In addition, F_3Thd is generally unstable under alkaline conditions and is not readily accessible as a starting material.[7a,8] Therefore, we selected commercially available 2′-deoxy-5-iodouridine (**3**) as the starting material and developed a cross-coupling reaction of a 3′-*O*-benzyl derivative of **3** with a trifluoromethylcopper complex to introduce the 5-trifluoromethyl function in an appropriate step.

3′-*O*-Benzylation of 2′-Deoxy-5-iodouridine Numerous methods have been reported for the benzylation of the sugar hydroxyls of nucleosides. However, the selective 2′(3′)-*O*-benzylation of ribonucleosides by dibutyltin oxide-benzyl halide[9] or stannous chloride-phenyldiazomethane[10] cannot be applied to the 2′-deoxyribosides. Usually, alkylation of thymidine by alkyl halides occurs at the N^3-position of the base moiety under neutral or mild basic conditions. Under strong alkaline conditions where the sugar hydroxyls dissociate, alkylation with alkyl halides occurs at the sugar hydroxyls.[11–13] However, similar treatment of F_3Thd or **3**, or their 5′-*O*-trityl derivatives did not give the 3′-*O*-benzyl derivatives in satisfactory yield, and the N^3-benzyl or N^3,*O*′-dibenzyl derivatives were the main products (data not shown). Alkylation under acidic conditions has also been reported[14] and treatment of 5′-*O*-benzoyl-2′-deoxyuridine (**4a**) and the 5-iodo derivative (**4b**) with benzyl trichloroacetimidate[15] in the presence of trifluoromethanesulfonic acid as a catalyst gave the respective 3′-*O*-benzyl derivatives (**5**). The 5-iodination of **5a** to **5b** was also possible by treatment with iodine chloride in dichloromethane. The debenzoylation of **5b** afforded 3′-*O*-

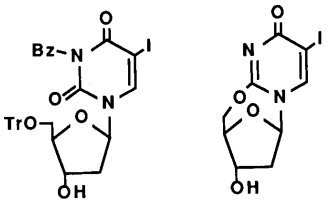


3 : X=H
3 : X=I
4a : X=H
4b : X=I
5a : X=H
5b : X=I
5b
6

Chart 1

benzyl-2′-deoxy-5-iodouridine (**6**). However, the separation of the benzylated products was somewhat laborious and the cross-coupling of **6** with trifluoromethylcopper to provide the target compound (**1**) did not proceed well, as will, be described later, probably due to non-protection of the N^3-H function of **6**.

Therefore, the efficacy of protection and de-protection of the base moiety as well as the 5′-hydroxyl group of 2′-deoxy-5-iodouridine by different functionalities for the 3′-*O*-benzylation was compared (Chart 2). N^3-Benzoyl-2′-deoxy-5-iodo-5′-*O*-trityluridine (**7**) showed a rapid migration of the N^3-benzoyl group to sugar hydroxyl under the conditions of the basic benzylation. O^2,5′-Cyclo-2′-deoxy-5-iodouridine (**8**), in which both the sugar and the base moieties are suitably protected, was hardly soluble in solvents suitable for 3′-*O*-benzylation. 2′-Deoxy-5-iodo-N^3-(*p*-methoxybenzyl)-5′-*O*-trityluridine (**9**) did not give the *N*-debenzylated compound on treatment with 2,3-dichloro-5,6-dicyanobenzoquinone or ceric ammonium nitrate, or trityl tetrafluoroborate. Although 2′-deoxy-5-iodo-N^3-(tetrahydro-2-furyl)-5′-*O*-trityluridine (**10**) gave the 3′-*O*-benzyl derivative in good yield by treatment with benzyl bromide and sodium hydride in dimethylformamide (DMF), the deprotection by acid treatment did not proceed well. 2′-Deoxy-O^4-ethyl-5-iodo-5′-*O*-trityluridine (**12**) was prepared and its utility was tested. Compound **12** gave the 3′-benzyl derivative (**13**) in high yield on treatment with benzyl bromide and sodium hydride in DMF or tetrahydrofuran (THF). Since the high yield suggested that this reaction would be the best for *O*-benzylation of 2′-deoxy-5-iodo-5′-*O*-trityluridine (**14**), the direct 3′-*O*-benzylation of **14** was re-investigated. Although treatment of **14** with an equimolar amount of sodium hydride and benzyl bromide in DMF gave the expected N^3-benzyl derivative (**15**), the treatment in THF did not give any product. This result suggested that the reactivity of the dissociated N^3-position of **14** toward alkylation is low in THF, and direct 3′-*O*-alkylation might occur in the presence of an excess of strong base. In practice, the reaction of **14** with benzyl bromide (or benzyl chloride with a catalytic amount of sodium iodide) using a 2-fold molar excess of sodium hydride in THF proceeded to give exclusively the 3′-*O*-benzyl derivative (**16**) in high yield. The de-tritylation of **16** by methanolic hydrogen chloride gave compound **6** which was identical with that previously prepared by acidic benzylation (Chart 3). Treatment of **16** with benzoyl chloride and triethylamine in dichloromethane afforded the N^3-benzoyl derivative (**17**).



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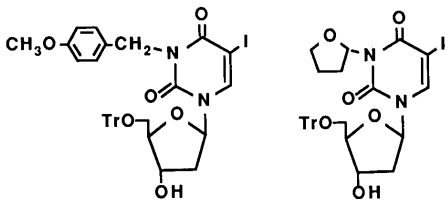

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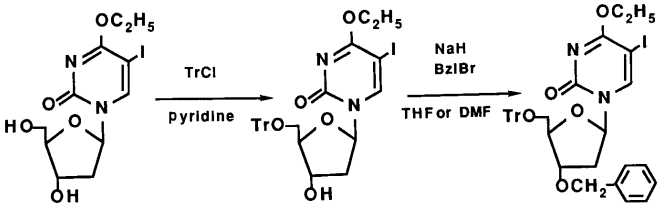
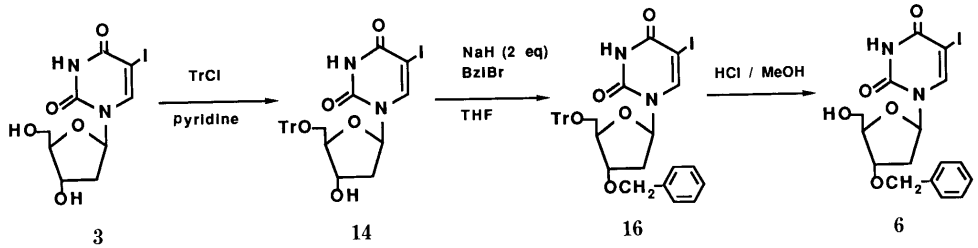


11 12 13

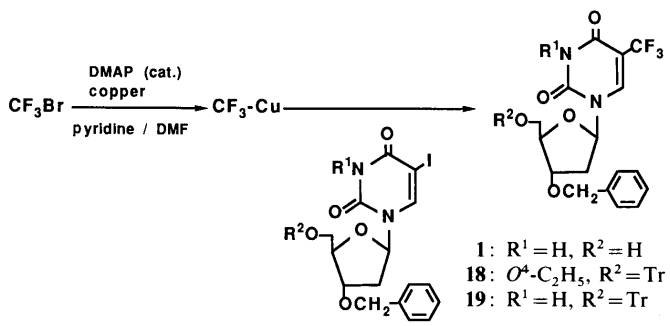
Chart 2

Coupling of 5-Iodouridine Derivatives with Trifluoromethylcopper The introduction of a trifluoromethyl group at the 5-position of pyrimidine nucleosides has been extensively studied by Kobayashi and his coworkers.[7] Their method involves the coupling of 5-iodopyrimidine nucleosides with trifluoromethylcopper complexes generated from iodotrifluoromethane and copper in hexamethylphosphoric triamide at elevated temperature. The use of bis(trifluoromethyl)mercury[16] may not be suitable for compounds for medicinal use. *N*-Nitroso-*N*-trifluoromethyltrifluoromethanesulfonamide[17] has been reported to give the 5-trifluoromethyl compound from 2′,3′,5′-tri-*O*-acetyluridine but the yield was rather low (*ca.* 30%). The addition of trifluoromethyl radical, generated by the electrolysis of trifluoroacetic acid,[18] to the 5-position of uracil was not successful in the nucleosides (data not shown). Of these reported methods, the use of trifluoromethylcopper seems attractive if the use of a carcinogenic solvent can be avoided and the expensive iodotrifluoromethane can be replaced with some other more readily available halide. A new method of preparation of trifluoromethylcopper has recently been reported which involved the use of difluorodihalomethanes, cadmium powder and cuprous iodide.[19] However, this method did not give satisfactory results in the present reaction in our hands.



3 14 16 6

Chart 3



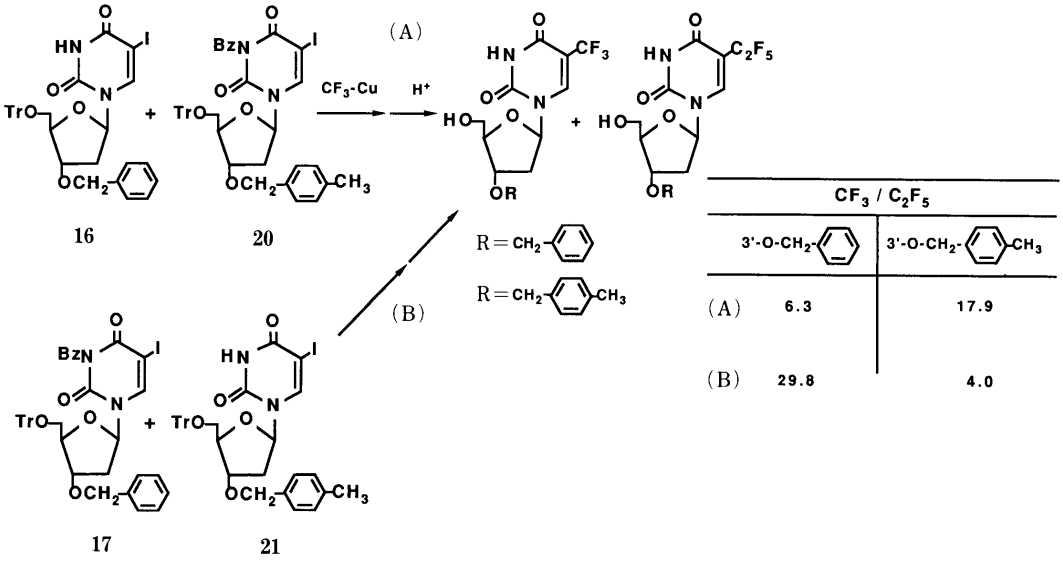
1: $R^1=H$, $R^2=H$
18: O^4-C_2H_5, $R^2=Tr$
19: $R^1=H$, $R^2=Tr$

6: $R^1=H$, $R^2=H$
13: O^4-C_2H_5, $R^2=Tr$
16: $R^1=H$, $R^2=Tr$
17: $R^1=Bz$, $R^2=Tr$

Chart 4

the protection of the N^3-H function of the base moiety (as in the case of **13**) may favor the selective coupling with the trifluoromethylcopper.

Therefore, the N^3-benzoyl derivative (**17**) was used in this reaction. In fact, the formation of the 5-pentafluoroethyl derivative was decreased to *ca.* 1%, despite the fact that the *N*-benzoyl group was lost during the reaction. Detritylation of **19** with methanolic hydrogen chloride furnished crystalline **1**. The importance of the N^3-benzoyl protection in the selectivity of the coupling reaction was further confirmed by the following examination. Thus, in the coupling reaction of a mixture of the N^3-unprotected and N^3-benzoylated derivatives of the 3′-*O*-benzyl and 3′-*O*-(*p*-methylbenzyl)-5-iodo compounds (**16** and **20**, and **17** and **21**) with the fluoroalkylcopper complex, higher ratios of formation of the 5-trifluoromethyl derivatives over the 5-



	CF_3 / C_2F_5	
	3′-O-CH_2-	3′-O-CH_2-(p-CH_3)
(A)	6.3	17.9
(B)	29.8	4.0

Chart 5

We then found that trifluoromethylcopper can be prepared from bromotrifluoromethane and copper powder in pyridine–DMF,[20] and this method may be a useful alternative to the method of Kobayashi *et al.*[7]

Heating a mixture of bromotrifluoromethane and copper powder in pyridine–DMF at 120 °C in a sealed tube gave a trifluoromethylcopper complex. Moreover, we found that the addition of 4-dimethylaminopyridine to the above mixture at 115 °C accelerated the rate of the reaction; the rate may be monitored by following the decrease of the initial pressure or precipitation of the product in the sealed reaction tube.

Treatment of this complex with 2′-deoxy-5-iodouridine derivatives (**6**, **13**, **16**) at 60 °C for 8 h gave the respective 5-trifluoromethyl derivatives (**1**, **18**, **19**) in satisfactory yields (Chart 4). However, we observed the formation of the 5-pentafluoroethyl derivatives as by-products (*ca.* 10%) in the reaction with **6** or **16**, which made the separation and purification of the desired product more laborious. By contrast, in the case of **13**, the formation of the by-product was almost negligible. Treatment of **18** with chlorotrimethylsilane and sodium iodide resulted in complete deprotection to furnish the title compound (**1**). Since the formation of the 5-perfluoroethyl derivative is due to the presence of perfluoroethylcopper in the copper complex,

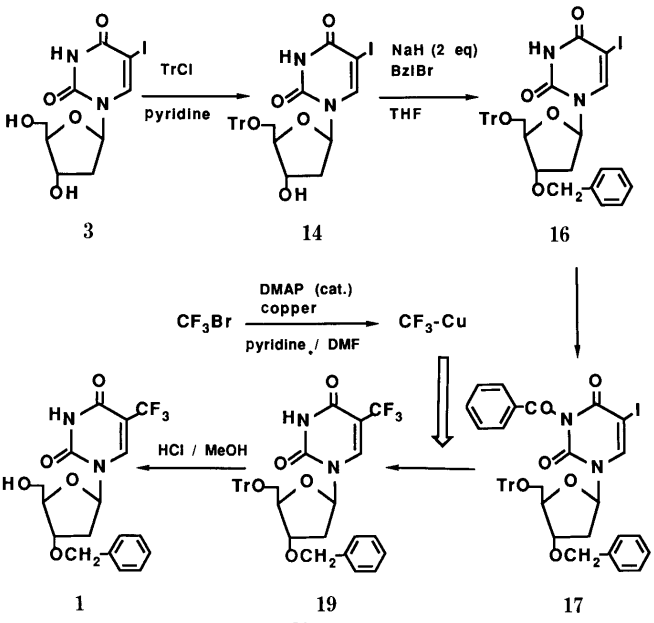


Chart 6

pentafluoroethyl derivatives were obtained in the N^3-benzoyl conterparts (Chart 5).

In conclusion, the following sequence of reactions was

finally established for the practical synthesis of **1** (Chart 6).

1) Tritylation of 2′-deoxy-5-iodouridine (**3**), 2) 3′-*O*-benzylation, 3) N^3-benzoylation, 4) cross-coupling reaction with trifluoromethylcopper, and 5) acidic deprotection to give **1**.

The overall yield of **1** from **3** was about 35% by this route, which is tolerable for a large-scale synthesis of **1** for clinical testing.

Experimental

Melting points were determined with a Yanagimoto MP-3 micro melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were obtained with a JEOL LMN-FX 100 spectrometer using tetramethylsilane as an internal standard. ^{19}F-NMR spectra were obtained with a JEOL JNM-FX 90Q spectrometer using trichlorofluoromethane as an internal standard. A Shimazu LC-4A liquid chromatograph equipped with a Waters μ-BONDAPAC C-18 chromatographic column was used for the separation of perfluoroalkyl derivatives. The structures of the compounds were confirmed by the elemental analyses as well as by ^{1}H-NMR measurements.

5′-*O*-Benzoyl-2′-deoxyuridine (4a) A solution of benzoyl chloride (8.4 g, 0.06 mol) in CH_2Cl_2 (16 ml) was added dropwise to a mixture of 2′-deoxyuridine (13.8 g, 0.06 mol), pyridine (48 ml) and CH_2Cl_2 (48 ml) below −10 °C and the mixture was stirred for 2 h. Water (40 ml) and CH_2Cl_2 (100 ml) were added and the mixture was stirred vigorously. The organic layer was separated and the solvent was evaporated off. The residue was recrystallized from $CHCl_3$–EtOH, giving 12.7 g of **4a** in 64% yield; mp 170 °C. NMR (dimethyl sulfoxide-d_6 (DMSO-d_6)): 11.62 (1H, s, N^3-H), 7.38—8.04 (5H, m, benzoyl group), 7.94 (1H, s, H-6), 6.10 (1H, s, H-1′), 5.44 (1H, d, HO-3′), 4.0—4.54 (4H, m, H-3′, 4′, 5′), 2.24 (2H, m, H-2′). *Anal.* Calcd for $C_{16}H_{16}N_2O_6$: C, 57.83; H, 4.85; N, 8.43. Found: C, 57.38; H, 4.81; N, 8.18.

5′-*O*-Benzoyl-2′-deoxy-5-iodouridine (4b) Benzoyl chloride (2.8 g, 0.02 mol) was added to a mixture of **3** (7 g, 0.02 mol), pyridine (32 ml) and CH_2Cl_2 (32 ml), and the mixture was stirred for 8 h at room temperature. Water and CH_2Cl_2 were added and stirred vigorously. Then the organic layer was separated, washed with water and concentrated. The residue was recrystallized from $CHCl_3$–EtOH, giving 6.4 g of **4b** in 70% yield; mp 169—170.5 °C. NMR (DMSO-d_6): 11.60 (1H, s, N^3-H), 7.3—8.0 (6H, m, benzoyl group and H-6), 6.16 (1H, t, H-1′), 5.40—5.56 (3H, m, H-5 and HO-3′), 3.94—4.54 (4H, m, H-3′, 4′, 5′), 2.24 (2H, t, H-2′). *Anal.* Calcd for $C_{16}H_{15}IN_2O_6$: C, 41.94; H, 3.30; N, 6.11. Found: C, 41.49; H, 3.30; N, 5.77.

5′-*O*-Benzoyl-3′-*O*-benzyl-2′-deoxyuridine (5a) Triflic acid (2.3 g, 0.015 mol) was added to a solution of benzyl trichloroacetimidate (5 g, 0.02 mol) in a mixture of CH_2Cl_2 (50 ml) and THF (25 ml) and the mixture was stirred for 15 min at room temperature. Then **4a** (3.3 g, 0.01 mol) was added and the reaction mixture was stirred overnight at room temperature. Triethylamine (3 ml) was added with stirring, and then water and CH_2Cl_2 were added and the mixture was stirred vigorously. The organic layer was separated and the solvent was evaporated off. The residue was purified by silica gel column chromatography ($CHCl_3$) and the appropriate eluate was concentrated to leave 1.65 g (39%) of oily **5a**.

5′-*O*-Benzoyl-3′-*O*-benzyl-2′-deoxy-5-iodouridine (5b) (a) Triflic acid (3.4 g, 0.03 mol) was added to a solution of benzyl trichloroacetimidate (7.6 g, 0.03 mol) in a mixture of CH_2Cl_2 (75 ml) and THF (37.5 ml), and the mixture was stirred for 10 min at room temperature. Then **4b** (6.9 g, 0.015 mol) was added and the reaction mixture was stirred for 50 min at room temperature. The solution was neutralized with 1 N $NaHCO_3$ (80 ml), and the organic layer was separated and concentrated. The residue was dissolved in benzene and the solution was allowed to stand overnight. The precipitate was filtered off and the filtrate was concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$) and the appropriate eluate was concentrated to leave 3 g (37%) of **5b** as an amorphous solid. NMR (DMSO-d_6): 11.73 (1H, s, N^3-H), 8.02 (1H, s, H-6), 7.4—8.0 (5H, m, benzoyl group), 7.34 (5H, s, benzyl group), 6.12 (1H, t, H-1′), 4.58 (2H, s, benzylic methylene), 4.2—4.6 (4H, m, H-3′, 4′,5′), 2.3—2.5 (2H, m, H-2′). *Anal.* Calcd for $C_{23}H_{21}IN_2O_6$: C, 50.38; H, 3.86; N, 5.11. Found: C, 50.57; H, 3.87; N, 5.00.

(b) Iodine monochloride (0.95 g, 0.0059 mol) was added to a solution of **5a** (1.65 g, 0.0039 mol) in CH_2Cl_2 (22 ml) and the mixture was stirred at room temperature,[21] then decolorized by careful addition of aqueous $NaHSO_3$ (2%). The organic layer was separated and washed with water, and then concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$) to yield 730 mg of **5b** (34%) as an amorphous solid. *Anal.* Calcd for $C_{23}H_{21}IN_2O_6$: C, 50.38; H, 3.86; N, 5.11. Found: C, 50.46; H, 3.78; N, 5.06. The structure was also confirmed by ^{1}H-NMR measurement.

3′-*O*-Benzyl-2′-deoxy-5-iodouridine (6) (a) A mixture of **5b** (1.27 g, 0.0023 mol) and 0.1 N EtONa (25 ml) was stirred for 2 h at room temperature. The mixture was neutralized with Dowex 50 W and filtered. The filtrate was evaporated and the residue was purified by silica gel column chromatography ($CHCl_3$: EtOH = 25 : 1). The appropriate eluate was concentrated and the residue was recrystallized from ethyl acetate, giving 740 mg of **6** in 72% yield; mp 137—138 °C. NMR (DMSO-d_6): 11.62 (1H, s, N^3-H), 8.36 (1H, s, H-6), 7.32 (5H, s, benzyl group), 6.08 (1H, t, H-1′), 5.22 (1H, t, HO-5′), 4.52 (2H, s, benzylic methylene), 3.92—4.3 (2H, m, H-3′, 4′), 3.62 (2H, s, H-5′), 2.0—2.48 (2H, m, H-2′). *Anal.* Calcd for $C_{16}H_{17}IN_2O_5$: C, 43.26; H, 3.86; N, 6.31. Found: C, 43.35; H, 3.84; N, 6.16.

(b) A mixture of **16** (5 g, 0.0073 mol) and 0.5 N methanolic hydrogen chloride (30 ml) and CH_2Cl_2 (6 ml) was stirred for 1.5 h at room temperature. The mixture was neutralized with $NaHCO_3$ (1.3 g, 0.0015 mol) and filtered. The filtrate was concentrated and the residue was purified by silica gel column chromatography ($CHCl_3$: EtOH = 25 : 1). The appropriate eluate was concentrated and the residue was crystallized from ethyl acetate, giving 2.47 g, of **6** in 76% yield. The structure was confirmed by ^{1}H-NMR.

N^3-Benzoyl-2′-deoxy-5-iodo-5′-*O*-trityluridine (7) 2′-Deoxy-5-iodo-5′-*O*-trityluridine (**14**) (3 g, 0.005 mol) was dissolved in DMF (7.5 ml). NaH (60%, 200 mg, 0.014 mol) was added to the solution, then benzoyl chloride (0.7 g, 0.005 mol) was added. The mixture was stirred for 1.5 h at room temperature, neutralized with Dowex 50 W and filtered. The filtrate was concentrated and the residue was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water and concentrated, and the residue was purified by silica gel column chromatography ($CHCl_3$). The later-eluting fractions were combined and concentrated to leave 1.3 g (37%) of **7** as an amorphous solid. NMR (DMSO-d_6): 8.22 (1H, s, H-6), 7.40—8.18 (5H, m, benzoyl group), 7.20—7.60 (15H, br, benzyl group), 6.12 (1H, t, H-1′), 5.36 (1H, br, HO-3′), 4.30 (1H, m, H-3′), 3.96 (1H, m, H-4′), 3.28 (2H, m, H-5′), 2.2—2.5 (2H, m, H-2′). *Anal.* Calcd for $C_{35}H_{29}IN_2O_6$: C, 60.01; H, 4.17; N, 4.00. Found: C, 60.48; H, 4.50; N, 4.46.

From the faster-moving fractions, a small amount of 3′-*O*-benzoyl-2′-deoxy-5-iodo-5′-*O*-trityluridine was obtained and crystallized from acetone–EtOH.

2,5′-*O*-Cyclo-2′-deoxy-5-iodouridine (8) A mixture of 2′-deoxy-5-iodo-5′-*O*-(*p*-toluenesulfonyl)uridine (5.1 g, 0.01 mol) and 1,8-diazabicyclo-[5.4.0]undecene (DBU, 1.67 g, 0.011 mol) in acetonitrile (134 ml) was stirred for 1.5 h at 60 °C.[22] The mixture was allowed to stand overnight at room temperature and the precipitate was filtered off. The filtrate was concentrated and the residue was crystallized from CH_3CN–EtOH, giving 1.5 g of **8** in 45% yield; mp 173—174 °C. NMR (DMSO-d_6): 8.44 (1H, s, H-6), 6.06 (1H, dd, H-1′), 5.26 (1H, d, HO-3′), 4.0—4.6 (4H, m, H-3′, 4′, 5′), 2.04—2.66 (2H, m, H-2′). *Anal.* Calcd for $C_9H_9IN_2O_4$: C, 32.17; H, 2.70; N, 8.34. Found: C, 31.97; H, 2.96; N, 8.54.

2′-Deoxy-N^3-(*p*-methoxybenzyl)-5-iodo-5′-*O*-trityluridine (9) A mixture of 2′-deoxy-5-iodo-5′-*O*-trityluridine (**14**) (4 g, 0.0067 mol), K_2CO_3 (930 mg, 0.0067 mol) and *p*-methoxybenzyl chloride (1 g, 0.0067 mol) was stirred for 2 h at 80 °C. The mixture was filtered and filtrate was concentrated. The residue was extracted with $CHCl_3$, and then the $CHCl_3$ layer was washed with water and concentrated. The residue was crystallized from $CHCl_3$–ether–pet. ether, giving 2.4 g of **9** in 60% yield; mp 166.5—167.5 °C. NMR (DMSO-d_6): 8.08 (1H, s, H-6), 7.10—7.58 (17H, m, trityl group and benzyl group), 6.16 (1H, t, H-1′), 5.34 (1H, d, HO-3′), 4.96 (2H, s, benzylic methylene), 4.26 (1H, m, H-3′), 3.94 (1H, m, H-4′), 3.20 (2H, br, H-5′), 2.24 (2H, t, H-2′). *Anal.* Calcd for $C_{36}H_{33}IN_2O_6$: C, 60.34; H, 4.64; N, 3.91. Found: C, 60.06; H, 4.66; N, 3.68.

2′-Deoxy-5-iodo-N^3-(tetrahydro-2-furyl)-5′-*O*-trityluridine (10) Freshly distilled 2-chlorotetrahydrofuran (0.64 g, 0.006 mol) was added to a solution of **14** (3 g, 0.005 mol) and triethylamine (0.84 ml, 0.006 mol) in dimethylacetamide (15 ml), and the mixture was stirred for 6 h at room temperature. The mixture was concentrated and the residue was extracted with $CHCl_3$. The $CHCl_3$ layer was concentrated, and the residue was purified by silica gel column chromatography ($CHCl_3$). The appropriate eluate was concentrated to leave 2.1 g (64%) of oily **10**.

Next, **10** (2.1 g, 0.0032 mol) was dissolved in DMF (10 ml). NaH (60%, 130 mg, 0.0032 mol) was added to the solution and the mixture was stirred for 10 min at room temperature. Benzyl bromide (0.65 g, 0.0038 mol) was

added and the reaction mixture was stirred for 1.5 h at room temperature. After being neutralized with Dowex 50 W, the mixture was concentrated and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water and concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$). The appropriate eluate was concentrated to leave 1.74 g (72%) of 3′-*O*-benzyl-2′-deoxy-5-iodo-N^3-(tetrahydro-2-furyl)-5′-*O*-trityluridine as an amorphous solid. NMR (DMSO-d_6): 8.04 (1H, s, H-6), 7.10—7.54 (20H, m, trityl group and benzyl group), 6.44 (1H, m, H-2 of tetrahydrofuryl group), 6.05 (1H, t, H-1′), 4.46 (2H, s, benzylic methylene), 3.92—4.60 (3H, m, H-3′, 4′ and H-5 of tetrahydrofuryl group), 3.80 (1H, br, H-5 of tetrahydrofuryl group), 3.20 (2H, m, H-5′), 1.70—2.56 (6H, m, H-2′ and H-3, 4 of tetrahydrofuryl group). *Anal.* Calcd for $C_{39}H_{37}IN_2O_6$: C, 61.91; H, 4.93; N, 3.70. Found: C, 61.95; H, 4.93; N, 3.63.

2′-Deoxy-*O*^{4}-ethyl-5-iodouridine (11)[23] Phosphorus oxychloride (23 g, 0.15 mol) was added dropwise to a solution of 2′-deoxy-3′,5′-di-*O*-acetyl-5-iodouridine (21.9 g, 0.05 mol) and 1-methylimidazole (40 g, 0.5 mol) in acetonitrile (250 ml), under cooling in ice bath, and the mixture was stirred for 0.5 h at room temperature. Triethylamine (25 ml, 0.15 mol) and then EtOH (25 ml) were added and the mixture was stirred for 2 d at room temperature. The mixture was filtered and the filtrate was concentrated. The residue was extracted with ethyl acetate, and the extract was washed with water and concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$). The faster-eluting fractions were combined and concentrated, giving the 3′,5′-di-*O*-acetyl derivative of **11**. The compound was dissolved in a solution of triethylamine (3.15 ml) in MeOH (65 ml) and the mixture was stirred overnight at room temperature. The solvent was evaporated off, and the residue was crystallized from EtOH–ethyl acetate, giving 8.5 g of **11** in 45% yield; mp 169—171 °C. NMR (DMSO-d_6): 8.61 (1H, s, H-6), 5.23 (1H, d, HO-3′), 5.17 (1H, t, HO-5′), 4.30 (2H, q, O-C$\underline{H}_2$CH$_3$), 4.20 (1H, m, H-3′), 3.84 (1H, m, H-4′), 3.62 (2H, m, H-5′), 1.88—2.38 (2H, m, H-2′), 1.30 (3H, t, O-CH$_2$C$\underline{H}_3$). *Anal.* Calcd for $C_{11}H_{15}IN_2O_5 \cdot 1/2H_2O$: C, 33.78; H, 4.12; N, 7.16. Found: C, 33.48; H, 4.08; N, 7.03.

2′-Deoxy-*O*^{4}-ethyl-5-iodo-5′-*O*-trityluridine (12) A mixture of **11** (1.15 g, 0.003 mol) and trityl chloride (836 mg, 0.03 mol) in pyridine (2 ml) was stirred for 1 h at 100 °C. The mixture was concentrated and the residue was extracted with $CHCl_3$. The extract was concentrated and the residue was purified by silica gel column chromatography ($CHCl_3$: EtOH = 10 : 1). The appropriate eluate was concentrated to leave 1.24 g (66%) of **12** as an amorphous solid. NMR (DMSO-d_6): 8.16 (1H, s, H-6), 7.08—7.54 (15H, m, trityl group),6.06 (1H, t, H-1′), 5.32 (1H, br, HO-3′), 4.32 (2H, q, O-C$\underline{H}_2$CH$_3$), 4.20 (1H, br, H-3′), 3.96 (1H, br, H-4′), 3.22 (2H, br, H-5′), 2.0—2.44 (2H, m, H-2′), 1.30 (3H, t, O-CH$_2$C$\underline{H}_3$). *Anal.* Calcd for $C_{30}H_{29}IN_2O_5$: C, 57.70; H, 4.68; N, 4.49. Found: C, 57.94; H, 4.76; N, 4.24.

3′-*O*-Benzyl-2′-deoxy-*O*^{4}-ethyl-5-iodo-5′-*O*-trityluridine (13) A solution of **12** (2.1 g, 0.0034 mol) in THF (7 ml) was treated with NaH (60%, 136 mg, 0.0034 mol), and the mixture was stirred for 15 min at room temperature. Then benzyl bromide (1.7 g, 0.0102 mol) was added and the reaction mixture was stirred for 1.5 h at room temperature, filtered and concentrated. The residue was extracted with $CHCl_3$, and the $CHCl_3$ layer was washed with water and concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$). The appropriate eluate was concentrated to leave 1.5 g (62%) of **13** as an amorphous solid. NMR (DMSO-d_6): 8.22 (1H, s, H-6), 7.1—7.5 (20H, br, benzyl group and trityl group), 6.04 (1H, t, H-1′), 4.46 (2H, s, benzyl group), 4.32 (2H, q, O-C$\underline{H}_2$CH$_3$), 4.04—4.3 (2H, m, H-3′, 4′), 3.26 (2H, br, H-5′), 2.06—2.3 (2H, m, H-2′), 1.32 (3H, t, O-CH$_2$C$\underline{H}_3$). *Anal.* Calcd for $C_{37}H_{35}IN_2O_5$: C, 62.19; H, 4.94; N, 3.92. Found: C, 62.03; H, 4.83; N, 3.77.

2′-Deoxy-5-iodo-5′-*O*-trityluridine (14) A mixture of **3** (7 g, 0.02 mol) and trityl chloride (5.6 g, 0.02 mol) in pyridine (14 ml) was stirred for 20 min at 100 °C. The mixture was extracted with $CHCl_3$, and the $CHCl_3$ layer was washed with water and concentrated. The residue was crystallized from EtOH, giving 8 g (67%) of **14**. mp 204—206.5 °C. *Anal.* Calcd for $C_{28}H_{25}IN_2O_5$: C, 56.39; H, 4.23; N, 4.70. Found: C, 56.29; H, 4.38; N, 4.56.

3′-*O*-Benzyl-2′-deoxy-5-iodo-5′-*O*-trityluridine (16) A solution of **14** (16.1 g, 0.027 mol) in THF (54 ml) was treated with NaH (60%, 2.16 g, 0.054 mol), and the mixture was stirred for 15 min at room temperature. Then benzyl bromide (5.54 g, 0.0324 mol) was added and the reaction mixture was stirred for 1.5 h at room temperature. After being neutralized with Dowex 50 W the mixture was filtered and concentrated. The residue was extracted with ethyl acetate and the extract was washed with water and concentrated. The residue was crystallized from CH_2Cl_2–MeOH, giving 13.5 g (73%) of **16**; mp 188—189 °C, NMR (DMSO-d_6): 11.76 (1H, s, N^3-H), 8.00 (1H, s, H-6), 7.1—7.52 (20H, br, benzyl group and trityl group), 6.06 (1H, t, H-1′), 4.47 (2H, s, benzylic methylene), 3.98—4.30 (2H, m, H-3′, 4′), 3.24 (2H, m, H-5′), 2.34 (2H, m, H-2′). *Anal.* Calcd for $C_{35}H_{31}IN_2O_5$: C, 61.23; H, 4.55; N, 4.08. Found: C, 60.99; H, 4.49; N, 3.96.

N^3-Benzoyl-3′-*O*-benzyl-2′-deoxy-5-iodo-5′-*O*-trityluridine (17) A mixture of **16** (3.43 g, 0.005 mol), triethylamine (0.84 ml, 0.006 mol) and benzoyl chloride (703 mg, 0.005 mol) in CH_2Cl_2 (50 ml) was stirred for 5 h at room temperature. The mixture was washed with water and the CH_2Cl_2 layer was concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$). The appropriate eluate was concentrated to leave 2.9 g (73%) of **17** as an amorphous solid. NMR (DMSO-d_6): 8.22 (1H, s, H-6), 7.12—8.16 (25H, m, benzoyl, benzyl and trityl groups), 6.08 (1H, t, H-1′), 4.48 (2H, s, benzylic methylene), 4.0—4.4 (2H, m, H-3′, 4′), 3.30 (2H, m, H-5′), 2.32—2.66 (2H, m, H-2′). *Anal.* Calcd for $C_{42}H_{35}IN_2O_6$: C, 63.80; H, 4.46; N, 3.54. Found: C, 63.86; H, 4.52; N, 3.36.

General Procedure of the Trifluoromethylation (a) Experimentaly, CF_3Br (6.85 g, 0.046 mol) was introduced into a mixture of pyridine (6 ml), DMF (6 ml) and copper powder (2.9 g, 0.046 mol) in a sealed glass tube (30 ml, Taiatsu Scientific Glass Co., Ltd.) below −70 °C. (Caution: it is dangerous to scale-up the reaction in a glass tube of 30 ml or to use a glass tube of more than 30 ml.) 4-Dimethylaminopyridine (220 mg, 0.0018 mol) was added to the mixture below −70 °C. The mixture was slowly brought to room temperature and then stirred at 115 °C until precipitation of the trifluoromethylcopper complexes occurred (for about 2.5 h). The reaction mixture was cooled to room temperature, and the sealed tube was opened carefully and allowed to stand to remove excess CF_3Br. Compound **16** (2.1 g, 0.0031 mol) was added to the complex mixture and the whole was stirred for 8 h at 60 °C.

Trifluoromethylations of **6**, **13** and **17** were carried out similarly.

(b) Practically, CF_3Br (33 g, 0.221 mol) was introduced into a mixture of pyridine (50 ml), copper powder (5 g, 0.079 mol), 4-dimethylaminopyridine (3 g, 0.025 mol) and DMF (100 ml) in a sealed stainless steel tube (250 ml) at room temperature. Then the mixture was heated at 115 °C with stirring until the pressure at 115 °C (initially *ca.* 16 kg/cm^2) fell to *ca.* 14.5 kg/cm^2 (for about 3.5 h). The mixture was cooled to room temperature and degassed. A toluene solution of **17** (23.7 g, 0.03 mol) was added to the complex mixture and the whole was stirred for 8 h at 60 °C.

3′-*O*-Benzyl-2′-deoxy-5-trifluoromethyluridine (1) The reaction mixture of **6** in the above method (a) was concentrated. To the residue, CH_2Cl_2 (100 ml) and dilute HCl (10%, 50 ml) were added, and the mixture was stirred vigorously at room temperature. The mixture was filtered, and the organic layer was separated and concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$: EtOH = 10 : 1). The appropriate eluate was concentrated and the residue was crystallized from benzene, giving 430 mg of **1** in 36% yield; mp 159—160 °C. NMR (DMSO-d_6): 11.88 (1H, s, N^3-H), 8.69 (1H, d, H-6), 6.10 (1H, t, H-1′), 5.30 (1H, t, HO-5′), 4.54 (2H, s, benzylic methylene), 4.0—4.3 (2H, m, H-3′, 4′), 3.60 (2H, br, H-5′), 2.32 (2H, t, H-2′). ^{19}F-NMR (DMSO-d_6): −61.3 (relative to $CFCl_3$). *Anal.* Calcd for $C_{17}H_{17}F_3N_2O_5$: C, 52.85; H, 4.44; N, 7.25. Found: C, 52.79; H, 4.47; N, 7.22.

3′-*O*-Benzyl-2′-deoxy-*O*^{4}-ethyl-5-trifluoromethyl-5′-*O*-trityluridine (18) The reaction mixture of **13** in the above method (a) was filtered through Celite and the filtrate was concentrated. To the residue, $CHCl_3$ (100 ml) and water (50 ml) were added, and the mixture was stirred at room temperature. Then the mixture was filtered, and the organic layer was separated and concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$: EtOH = 25 : 1). The appropriate eluate was concentrated to leave 1.1 g (63%) of oily **18**.

Next, NaI (1.24 g, 0.0083 mol) and trimethylsilyl chloride (815 mg, 0.0075 mol) were added to a solution of **18** (1.1 g, 0.0015 mol) in acetonitrile (15 ml), and the mixture was stirred for 2 h at room temperature. The mixture was concentrated. The residue was extracted with ethyl acetate, and the organic layer was washed with water and concentrated. The residue was purified by silica gel column chromatography (benzene : acetone = 5 : 4). The appropriate eluate was concentrated and the residue was crystallized from benzene, giving 575 mg of **1** in 48% yield from **13**.

3′-*O*-Benzyl-2′-deoxy-5-trifluoromethyl-5′-*O*-trityluridine (19) The reaction mixture of **16** in the above method (a) was filtered through celite and the filtrate was concentrated. To the residue, $CHCl_3$ (100 ml) and dilute HCl (10%, 50 ml) were added and the mixture was stirred at room temperature. The mixture was filtered, and the organic layer was separated and concentrated. The residue was purified by silica gel column chroma-

tography ($CHCl_3$). The appropriate eluate was concentrated and the residue was crystallized from CH_2Cl_2–MeOH, giving 1.2 g (63%) of **19**; mp 152 °C. NMR (DMSO-d_6): 11.96 (1H, s, N^3-H), 8.31 (1H, s, H-6), 7.12—7.48 (20H, m, benzyl group and trityl group), 6.04 (1H, t, H-1′), 4.46 (2H, s, benzylic methylene), 4.44 (2H, br, H-3′, 4′), 3.25 (2H, br, H-5′), 2.30—2.56 (2H, m, H-2′). *Anal.* Calcd for $C_{35}H_{31}F_3N_2O_5$: C, 68.17; H, 5.07; N, 4.54. Found: C, 68.67; H, 5.09; N, 4.32.

Compound **19** (1.2 g, 0.0019 mol) was dissolved in 0.5 N methanolic HCl (5 ml) and the solution was stirred for 2 h at room temperature. The solution was neutralized with $NaHCO_3$ and the precipitates were filtered off. Then the filtrate was concentrated and the residue was purified by silica gel column chromatography ($CHCl_3$: EtOH = 10 : 1). The appropriate eluate was concentrated and the residue was crystallized from benzene, giving 540 mg of **1** in 45% yield from **16**.

In the above treatment to obtain **19**, faster-eluting fractions were combined and evaporated to dryness. The residue was detritylated by the above mentioned method without purifying **19**. After filtration to remove **1** the filtrates were combined and concentrated. The residue was purified by silica gel column chromatography (benzene: acetone = 7 : 1). The faster-moving fractions were combined and evaporated to dryness, giving 3′-*O*-benzyl-2′-deoxy-5-pentafluoroethyluridine as an amorphous solid. NMR (DMSO-d_6): 11.86 (1H, s, N^3-H), 8.69 (1H, s, H-6), 7.35 (5H, s, benzyl group), 6.11 (1H, t, H-1′), 5.28 (1H, t, HO-5′), 4.54 (2H, s, benzylic methylene), 4.0—4.3 (2H, m, H-3′, 4′), 3.64 (2H, br, H-5′), 2.2—2.5 (2H, m, H-2′). ^{19}F-NMR (DMSO-d_6): −82.7, −111.7 (relative to $CFCl_3$).

Preparation of 1 from 17 The reaction mixture of **17** in the above method (b) was concentrated. To the residue, CH_2Cl_2 (1 l) and dilute HCl (10%, 0.5 l) were added and the mixture was stirred at room temperature. The mixture was filtered and the organic layer was separated and concentrated. The residue was dissolved in methanolic HCl (2%, 120 ml) and the solution was stirred for 2 h at room temperature. Then water was added to afford precipitates of tritanol. The precipitate was filtered off and the filtrate was neutralized with pyridine and concentrated. The residue was extracted with ethyl acetate and the extract was treated with silica gel, and then concentrated. The residue was crystallized from $CHCl_3$–toluene (1 : 1), giving 7.4 g of **1** in 64% yield from **17**.

***N*^{3}-Benzoyl-2′-deoxy-5-iodo-3′-*O*-(*p*-methylbenzyl)-5′-*O*-trityluridine (20)** Compound **20** was synthesized from **21** by the same method as **17**. NMR (DMSO-d_6): 8.21 (1H, s, H-6), 7.18—8.18 (20H, m, benzoyl group and trityl group), 7.12 (4H, s, benzyl group), 6.06 (1H, t, H-1′), 4.41 (2H, s, benzylic methylene), 3.90—4.24 (2H, m, H-3′, 4′), 3.22 (2H, m, H-5′), 2.2—2.4 (2H, m, H-2′), 2.28 (3H, s, *p*-CH_3). *Anal.* Calcd for $C_{43}H_{37}IN_2O_6$: C, 64.18; H, 4.63; N, 3.48. Found: C, 64.23; H, 4.69; N, 3.33.

2′-Deoxy-5-iodo-3′-*O*-(*p*-methylbenzyl)-5′-*O*-trityluridine (21) Compound **21** was synthesized from **14** by the same method as **16**. Crystallization from CH_2Cl_2–MeOH gave **21**; mp 179—180.5 °C. NMR (DMSO-d_6): 11.76 (1H, s, N^3-H), 8.03 (1H, s, H-6), 7.35 (15H, br, trityl group), 7.14 (4H, s, benzyl group), 6.07 (1H, t, H-1′), 4.42 (2H, s, benzylic methylene), 3.90—4.26 (2H, m, H-3′, 4′), 3.22 (2H, br, H-5′), 2.29 (3H, s, *p*-CH_3), 2.12—2.24 (2H, m, H-2′). *Anal.* Calcd for $C_{36}H_{33}IN_2O_5$: C, 61.72; H, 4.75; N, 4.00. Found: C, 61.48; H, 4.67; N, 3.91.

Trifluoromethylation of the Mixture of 16 and 20 A mixture of **16** (1.05 g, 0.0016 mol) and **20** (1.09 g, 0.0016 mol) was added to the complex mixture prepared by the above method (a), and the mixture was stirred for 8 h at 60 °C, then filtered using celite. The filtrate was concentrated. To the residue, $CHCl_3$ (100 ml) and dilute HCl (10%, 50 ml) were added and the mixture was stirred at room temperature. The mixture was filtered and the organic layer was separated and concentrated. Then the residue was applied to a silica gel column ($CHCl_3$). The faster-eluting fractions containing trifluoromethyl and pentafluoroethyl compounds were combined and concentrated. The residue was dissolved in 0.5 N methanolic HCl (6 ml) and the solution was stirred for 2 h at room temperature. The solution was neutralized with $NaHCO_3$ and the precipitates were filtered off. The filtrate was concentrated and the residue was dissolved in acetonitrile. This solution was injected into the liquid chromatograph, the mobile phase being CH_3CN–H_2O (1 : 1) and the flow rate being 2 ml/min. The CF_3/C_2F_5 ratios of the respective benzyl derivatives were calculated from the peak areas detected at UV 260 nm. (Retention times of **1**, 3′-*O*-benzyl-2′-deoxy-5-pentafluoroethyluridine, 2′-deoxy-3′-*O*-(*p*-methylbenzyl)-5-trifluoromethyluridine and 2′-deoxy-3′-*O*-(*p*-methylbenzyl)-5-pentafluoroethyluridine were 3.40, 4.66, 4.20 5.35, respectively.)

The mixture of **17** and **21** was treated similarly.

These results are shown in Chart 5.

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