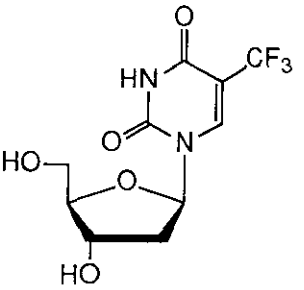
THE SYNTHESIS OF 2'-DEOXY-5-TRIFLUOROMETHYLURIDINE UTILIZING A COUPLING REACTION

Hiroshi Kawakami,* Takashi Ebata, Koshi Koseki, Hajime Matsushita, Yoshitake Naoi,† Kazuo Itoh†, and Nobuhiro Mizutani†
Life Science Research Laboratory, Japan Tobacco Inc.,
6-2 Umegaoka, Midori-ku, Yokohama, Kanagawa 227, Japan
†Tokyo Research Laboratory, Yuki Gosei Kogyo Co., Ltd.,
3-37-1 Sakashita, Itabashi-ku, Tokyo 174, Japan

Abstract The coupling reaction between 1-α-chloro-2-deoxyribose derivative and silylated 5-trifluoromethyluracil was examined. The best stereoselectivity was obtained when the reaction was carried out using a large amount of silylated base in the presence of anhydrous zinc chloride.

2'-Deoxy-5-trifluoromethyluridine (**1**) has attracted much attention because of its potent antitumor and/or antiviral activities.[1] This nucleoside **1** has been reported to be synthesized in a number of ways; biological nucleic base transfer,[2] trifluoromethylation of 2'-deoxyuridine[3] or 2'-deoxy-5-halouridine,[4] or a coupling reaction between 2-deoxyribose derivatives and silylated 5-trifluoromethyluracil.[5] In the last case, because of no stereoselectivity the synthesis of the nucleoside by this method is seriously hampered. In the course of our study of the coupling reactions[6] with 2-deoxy-α-D-erythro-pentofuranosyl chloride derivatives (**2**), which could be obtained as pure crystals, our interest was drawn to the coupling reaction with silylated 5-trifluoromethyluracil (**3**), and here we present a practical method for the preparation of **1** utilizing a stereoselective coupling reaction between **2** and **3**.



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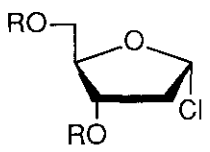
Hubbard et al. have reported that the coupling reactions between **2** and silylated uracil derivatives containing the substituents at base-5 position in chloroform mainly gave β-



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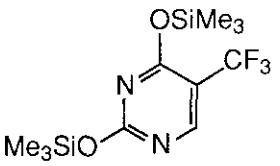

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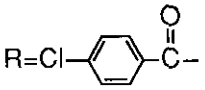

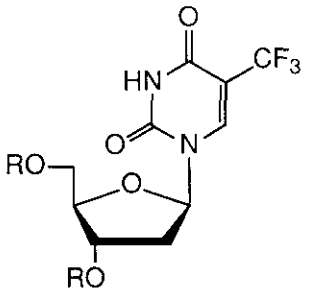

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anomers.[7] We first carried out the coupling reaction between **2** and **3** under these conditions (two equivalent of **3**, in chloroform, with no catalysts, room temperature, overnight). However, the reaction proceeded in a non-stereoselective manner to give the anomeric mixture in the ratio $\alpha:\beta = 44:56$. To raise the stereoselectivity, reaction conditions were examined, and the results are summarized in the Table.

Table. Stereoselectivities in the Coupling Reactions between 2-Deoxy-erythro-pentofuranosyl Chloride **2** and Silylated Base **3**[a]

Entry	**2** : **3**	Additive	Yield/%[b] (α+β)	Stereoselectivity[b] (α : β)
1	1 : 2	---	66	44:56
2	1 : 4	---	78	35:65
3	1 : 8	---	82	26:74
4	1 : 2	p-nitrophenol	77	47:53
5	1 : 2	$ZnCl_2$	78	25:75
6	1 : 4	$ZnCl_2$	58[c]	7:93

a. Coupling reactions were carried out under the following conditions; 0.25 mmol scale, in 2 ml of solvent at room temperature overnight.

b. Yields and stereoselectivities were determined by hplc after aqueous workup. (uv detection, 254 nm, compared to acetophenone as an internal standard)

c. Experimental loss might be assumed.

When the equivalent of silylated 5-trifluorouracil **3** to the sugar **2** was varied (entries 1 - 3), stereoselectivity toward β-anomer improved in the presence of an

increasing amount of **3**. (entry 3) It was reported that the addition of a catalytic amount of p-nitrophenol[8] and anhydrous zinc chloride[7] caused good stereoselectivities in the coupling reactions with silylated uracil derivatives. In our case, the addition of p-nitrophenol did not affect the stereoselectivity (entry 4). On the other hand, the addition of anhydrous zinc chloride was found to increase the selectivity (entry 5). As the combined result of these two factors, the best stereoselectivity was obtained when the coupling reaction was carried out using four equivalents of the silylated base **3** in the presence of a catalytic amount of anhydrous zinc chloride (entry 6; $\alpha:\beta = 7:93$).

These results can be explained as follows. The electron withdrawing effect of the trifluoromethyl substituent on the base decreases its reactivity. As reported by Hubbard et al.,[7] the rate of the coupling reaction becomes slower than that of the anomerization of 2-deoxy-erythro-pentofuranosyl chloride **2** which causes the low stereoselectivity. As the increase of the concentration of the silylated base **3** makes the rate of the coupling reaction faster, the stereoselectivity becomes better. Zinc chloride also seems to catalyze the coupling reaction. When the coupling reaction with no catalysts was traced with ^{1}H-nmr, it took 9 h for the signal of H-1 of **2** (δ=6.46 ppm) to disappear. On the other hand, in the presence of zinc chloride its signal had disappeared only after 15 min.

In conclusion, we have found that the coupling reaction between 2-deoxy-α-D-erythro-pentofuranosyl chloride derivative **2** and a large amount of silylated 5-trifluoromethyluracil **3** in chloroform in the presence of anhydrous zinc chloride proceeded in a stereoselective manner to give mainly the β-anomer **4**. Purification of **4** can be achieved simply by recrystallization from ethanol. After removal of the p-chlorobenzoyl group with sodium methoxide, 2'-deoxy-5-trifluoromethyluridine can easily be obtained.

EXPERIMENTAL

5-Trifluoromethyl-2,4-bis(trimethylsilyloxy)pyrimidine (3)

To a suspension of 2.16 g (12.0 mmol) of 5-trifluoromethyluracil in 12 ml of 1,2-dichloroethane were added 12 ml of hexamethyldisilazane and 0.2 ml of chlorotrimethylsilane, and the mixture was refluxed under an argon atmosphere for 45 min.

After the crystals were dissolved , the solvent was concentrated under reduced pressure (2 mmHg) at room temperature for 30 min. The residual oil was used in the next step without further purification.

1-[3,5-Bis-O-(p-chlorobenzoyl)-2-deoxy-β-D-erythro-pentofuranosyl]-5-trifluoromethyluracil (**4**)

Under an argon atmosphere, 1.25 g (2.91 mmol) of dry-powdered 3,5-bis-O-(p-chlorobenzoyl)-2-deoxy-α-D-erythro-pentofuranosyl chloride (**2**) were added to a solution of 3.89 g (12.0 mmol) of 5-trifluoromethyl-2,4-bis(trimethysilyloxy)-pyrimidine (**3**) and 60 mg (0.44 mmol) of anhydrous zinc chloride in 24 ml of dry chloroform, and the mixture was stirred at room temperature for 15 h. The reaction mixture was poured into a saturated aqueous solution of sodium bicarbonate[9] and extracted with chloroform three times. The organic layer was dried over anhydrous magnesium sulfate, and then the solvent was distilled away under reduced pressure. The residue obtained was purified by recrystallization from ethanol to give 1-[3,5-bis-O-(p-chlorobenzoyl)-2-deoxy-β-D-erythro-pentofuranosyl]-5-trifluoromethyluracil (**4**) (1.34 g, 80%); mp 173-176°C; $[\alpha]_D$ -17.1° (c 1.00, 26 °C, $CHCl_3$); ir(KBr) 1139 cm^{-1} (CF); uv($CHCl_3$) 249 nm (log ε 4.60); ^{1}H-nmr($CDCl_3$) δ 8.05 (1H, s, H-6), 7.99 (2H, d, J=8.7 Hz, aromatic-H), 7.92(2H, d, J=8.7 Hz, aromatic-H), 7.46 (2H, d, J=8.7 Hz, aromatic-H), 7.43 (2H, d, J=8.7 Hz, aromatic-H), 6.30 (1H, dd, J=8.3 and 5.5 Hz, H-1'), 5.61 (1H, d, J=6.6 Hz, H-3'), 4.74 (2H, d, J=3.7 Hz, H-5'), 4.61 (1H, dd, J=5.9 and 3.6 Hz, H-4'), 2.88 (1H, ddd, J=14.5, 5.6, and 1.6 Hz, H-2'), 2.31 (1H, ddd, J=14.7, 8.0, and 6.7 Hz, H-2'); ^{13}C-nmr($CDCl_3$) δ 165.19 (C=O), 165.10 (C=O), 157.98 (C-4), 149.04 (C-2), 140.46 (aromatic-C), 140.32 (aromatic-C), 139.88 (q, J=6Hz, C-6), 131.17 (aromatic-C), 130.83 (aromatic-C), 129.06 (aromatic-C), 129.02 (aromatic-C), 127.34 (aromatic-C), 127.16 (aromatic-C), 121.48 (q, J=270 Hz, CF_3), 105.78 (q, J=34 Hz, C-5), 86.51 (C-4'), 83.46 (C-1'), 74.89 (C-3'), 64.09 (C-5'), 38.74 (C-2'); ms m/z 572 (M^+), 393 (sugar), 180 (base unit + 1), and 139 (p-chlorobenzoyl unit); Anal. Calcd for $C_{24}H_{17}N_2O_7Cl_2F_3$:C, 50.28; H, 2.98; N, 4.88; Cl, 12.36; F, 9.94%. Found C, 50.22; H, 2.90; N, 4.91; Cl, 11.99; F, 9.90%.

2'-Deoxy-5-trifluoromethyluridine(**1**)

Sodium methoxide (0.16 g ; 3.0 mmol) was added to a solution of 1.32 g (2.30 mmol) of 1-[3,5-bis-O-(p-chlorobenzoyl)-2-deoxy-β-D-erythro-pentofuranosyl]-5-trifluoromethyl-uracil (**4**) in 80 ml of absolute methanol, and the mixture was stirred at room temperature for 1 h. The reaction solution was neutralized with an ion-exchange

resin (Amberlite IR-120B, pyridinium form), filtered off to remove the resin, and concentrated under reduced pressure. The residue was dissolved in water, washed twice with chloroform, and then the solvent was distilled away under reduced pressure. The residue obtained was purified by silica gel column chromatography (chloroform:methanol=85:15 v/v), and by recrystallization from ethanol to give 2'-deoxy-5-trifluoromethyluridine(**1**) (458 mg, 67%); mp 177-179 °C; $[\alpha]_D$ +47.3° (c 1.00, 25 °C, H_2O); ir(KBr) 1131 cm^{-1} (CF); uv(CH_3OH) 263 nm (log ε 3.94); ^{1}H-nmr(CD_3OD) δ 8.81 (1H, s, H-6), 6.24 (1H, t, J=6.2 Hz, H-1'), 4.41 (1H, dt, J=5.9 and 4.1 Hz, H-3'), 3.96 (1H, dd, J=6.4 and 2.9 Hz, H-4'), 3.84 (1H, dd, J=11.9 and 2.8 Hz, H-5'), 3.74 (1H, dd, J=11.9 and 2.8 Hz, H-5'), 2.37 (1H, ddd, J=13.7, 6.3, and 4.4 Hz, H-2'), 2.27 (1H, dq, J=13.1 and 6.2 Hz, H-2'); ^{13}C-nmr(CD_3OD) δ 161.23 (C-4), 151.32 (C-2), 143.79 (q, J=6 Hz, C-6), 123.93 (q, J=269 Hz, CF_3), 105.28 (q, J=33 Hz, C-5), 89.26 (C-4'), 87.51 (C-1'), 71.65 (C-3'), 62.09 (C-5'), 42.09 (C-2'); ms m/z 296 (M^+), 180 (base unit +1), and 117 (sugar); Anal. Calcd for $C_{10}H_{11}N_2O_5F_3$:C, 40.55; H, 3.74; N, 9.45; F, 19.24%. Found C, 40.65; H, 3.81; N, 9.37; F,18.93%.

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9. In this point, the unreacted 5-trifluoromethyluracil was crystallized. These were purified by recrystallization from ethanol to give the pure one (recovery in 74% yield based on the excess 5-trifluoromethyluracil).

Received, 11th January, 1990