Tetrahedron Letters, Vol.31, No.50, pp 7327-7328, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

Enzymatic Regioselective Acylation of the 3'-Hydroxyl Groups of 2'- Deoxy-5-fluorouridine (FUdR) and 2'-Deoxy-5-Trifluoromethyluridine (CF_3UdR).

Kenji Nozaki*, Atuhiko Uemura, Jun-ichi Yamashita, and Mitsugi Yasumoto

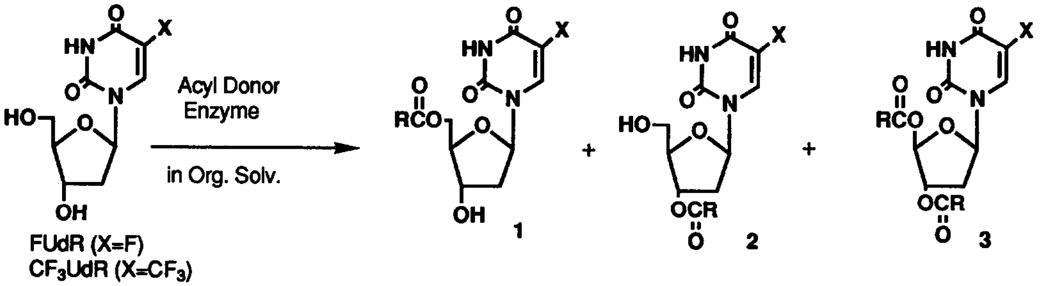
Chemical Synthesis Research Laboratory, Taiho Pharmaceutical Co.,Ltd.
Kodama-gun, Saitama, 367-02 JAPAN

Abstract: A lipase from *Pseudomonas sp.* (Amano PS) catalyzes regioselective acylation of the 3'-hydroxyl groups of FUdR and CF_3UdR.

FUdR and CF_3UdR are highly attractive compounds as anti-cancer and anti-viral drugs.[1,2] In order to synthesize these compounds, regioselective protection of the functional groups in these nucleosides is quite important. There is no report on direct regioselective acylation of a hydroxyl group of the nucleosides, both chemically and enzymatic method.

Lipase-catalyzed regioselective acylation of hydroxyl groups in the sugar moieties of pyrimidinenucleosides in aprotic polar solvents such as DMF, DMA, and DMSO has been reported previously.[3] However, the selective acylation between 3'- and 5'- hydroxyl groups was not satisfactory,decreasing polarity of the solvent tends to increase the regioselectivity. FUdR and CF_3UdR are found to be soluble in dioxane.

In this paper, we wish to report an enzymatic mono-acylation of these nucleosides in dioxane. The reaction of the above nucleosides with acetic anhydride,vinyl acetate or hexanoic anhydride in the presence of Amano PS (a lipase from *Pseudomonas sp.*) afforded preferentially the 3'-acyl derivatives as shown in Table 1. Other enzymes such as PPL (a lipase from *Porcine pancreas*) and subtilisin (an esterase from *Batilus subtilis*) were less reactive and less regioselective than Amano PS. Hexanoic anhydride seems to be better acylating agent than vinyl acetate, especially for CF_3UdR, and the reaction proceeds slightly less regio selective in THF than that in dioxane.



For example, Amano PS (200 mg) was added to a solution of FUdR(1 mmol) and acetic anhydride (3 mmol) in commercial dioxane (10 ml) at room temperature and the mixture was stirred for 24 hr under aerobic conditions.

Table 1. Acylation of FUdR and CF_3UdR in the Presence of Enzyme

							Yield (%) a			
Run	Enzyme	X	Org.Solv.	Acyl Donor	R	Conv. (%)	1	2	3	1/2
1	PS	F	Dioxane	Ac_2O	CH_3	88.4	17.3	45.3	25.7	0.38
2				Vinyl Acetate		98.6	8.1	82.0	8.5	0.09
3	PPL			Ac_2O		80.8	48.4	27.9	4.5	1.73
4				Vinyl Acetate		75.5	49.3	25.7	0.4	1.92
5	Subtilisin			Vinyl Acetate		trace				
6	PS	CF_3	Dioxane	Ac_2O		86.7	2.9	81.3	2.5	0.03
7				Vinyl Acetate		92.1	3.9	84.4	3.8	0.04
8				$(C_5H_{11}CO)_2O$	C_5H_{11}	95.0	0.2	94.1	0.7	>0.01
9			THF	Ac_2O	CH_3	59.4	5.2	51.4	2.7	0.10
10				Vinyl Acetate		92.3	9.3	80.3	2.8	0.12
11	PPL		Dioxane	Ac_2O		34.4	10.1	22.8	1.4	0.44
12				Vinyl Acetate		42.5	14.3	27.9	0.3	0.51
13	Subtilisin			Vinyl Acetate		trace				

a Yields were determined by UV absorption on HPLC (Reversed phase column ODS from Nacalai Tesque Mobil phase, CH_3CN:H_2O = 8:2 v/v).

The reaction was quenched by filtration the enzyme. The enzyme portion was washed with 20 ml of ethyl acetate. After usual workup, silica gel column chromatography was perfomed (CH_2Cl_2: AcOEt=1:1).

3'-O- Acetyl-2'-deoxy-5-fluorouridine[4] was isolated in 80 % yield. In a similar manner, 3'-O-hexanoyl-2'-deoxy-5-trifluoromethyluridine[5] was also isolated in 85 % yield.

Acknowledgment. We thank Amano Pharmaceutical Co.,Ltd. for kind gift of the enzymes.

References and Notes

*Current address: Original Compound R.& D. Operation Center, Taiho Pharmaceutical Co., Ltd.
Misugi-Dai, Hanno City, Saitama, 357 JAPAN

1) Ozaki, S.; Akiyama, T.; Ike, Y.; Mori, H.; Hoshi, A.: *Chem. Pharm. Bull.*, **1990**, *37*, 3405.

2) Kautman, H. E.; Heidelberger, C.: *Science*, **1964**, *145*, 585.

3) Uemura, A.; Nozaki, K.; Yamashita, J.; Yasumoto, M.: *Tetrahedron Lett.*, **1989**, *29*, 3817.

4) ^{1}HNMR (DMSO-d_6)δ 2.06(3H,s), 2.32(2H,q), 3.64(2H,d), 4.02(1H,m), 5.22(1H,m), 5.40(1H,br), 6.15(1H,m), 8.15(1H,d), 11.83(1H,br).

5) ^{1}HNMR (DMSO-d6) δ 0.86(3H,s), 1.00-1.85(6H,m), 2.05-2.60(4H,m), 3.55-3.70(2H,m) 3.80-4.03(1H,br), 5.10-5.30(2H,br), 6.08(1H,t), 8.70(1H,d), 11.80(1H,br).

(Received in Japan 20 September 1990)