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C–C BOND FORMATION ON 5-POSITION OF URIDINE RING BY MORITA–BAYLIS–HILLMAN TYPE REACTION

Yasunari Monguchi, Kanoko Yasunaga, Takashi Tsunoda, Takayuki Ando, Tomohiro Maegawa,[§] Kosaku Hirota,[¶] and Hironao Sajiki*

Laboratory of Organic Chemistry, Department of Organic and Medicinal Chemistry, Gifu Pharmaceutical University, 5-6-1 Mitahora-higashi, Gifu 502-8585, Japan. E-mail address: sajiki@gifu-pu.ac.jp

Abstract – A useful and efficient C–C bond formation reaction at the 5-position of uridine derivatives using a wide range of aldehydes was established on the basis of the Morita–Baylis–Hillman type reaction.

This paper is dedicated to the 80th birthday of Professor Emeritus Akira Suzuki, Hokkaido University.

INTRODUCTION

A significant possibility related to drug development is investigating the biological activity of uridine analogs possessing various functional groups at the 5-position of the pyrimidine ring.[1] For example, (*E*)-5-(2-bromovinyl)-2'-deoxyuridine[2] and (*E*)-5-(2-chlorovinyl)-2'-deoxyuridine[3,4] have been synthesized as antiherpes agents. In addition, their analogs possessing azide,[5] methoxy[6] and cinnamide[7] functional groups on the C_1 carbon at the 5-position indicated strong inhibitory activities against HSV-1.

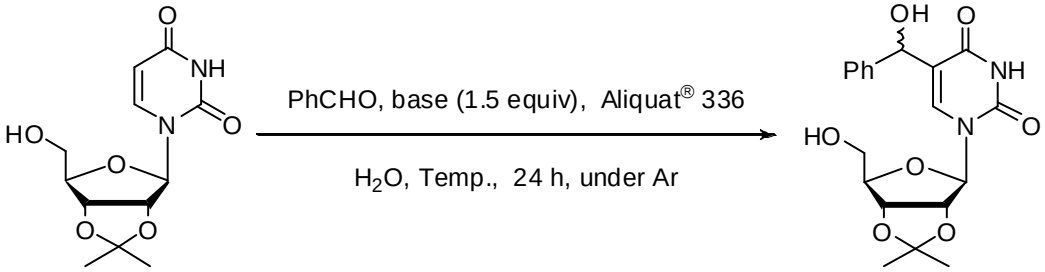
The Morita–Baylis–Hillman (MBH) reaction[8] is one of the most useful methods for C–C bond formation. Since the MBH reaction can transform the simple starting materials into highly functionalized products, it has been widely used for the total syntheses of natural products and functional materials.[9–12] Although a number of approaches toward 5-substituted pyrimidine nucleoside has been reported,[13–15] the application of the MBH reaction for introduction of substituents at the 5-position of uridine nuclei has not been reported until our communication.[16]

In this paper, we describe the practical C–C bond formation method at the 5-position of uridine derivatives using an MBH type reaction and the detail investigation, such as optimum conditions, scope, limitations and reaction mechanism.

RESULTS AND DISCUSSION

During our initial attempt of modification at the 5-position of uridine using the MBH-type reaction, trace quantities of 5-α-hydroxybenzyl-2',3'-*O*-isopropylideneuridine (**2a**, Entry 1 in Table 1) were obtained as a mixture of diastereomers by heating (50 °C) a mixture of 2',3'-*O*-isopropylideneuridine (**1**),[17] benzaldehyde (10 equiv), and KOH (1.0 equiv) in H_2O. When a small amount of Aliquat® 336 (methyloctylammonium chloride) was added to the aqueous reaction mixture containing lipophilic substrates (**1** and benzaldehyde) as a phase transfer catalyst, the coupling efficiency was significantly enhanced and the desired product (**2a**) was obtained in 29% yield (Entry 2). By the use of triethylamine (Et_3N) instead of KOH as the base, the yield of **2a** was also improved to 38% (Entry 3). Furthermore, the

Table 1. Base catalyzed 5-α-hydroxybenzylation of 2',3'-*O*-isopropyrideneuridine (**1**) under various conditions



1 **2a**

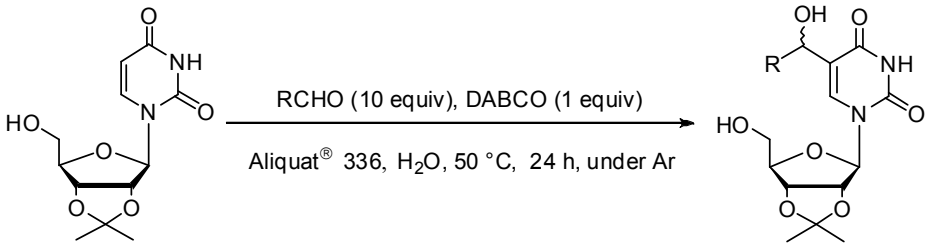
Entry	Base	PhCHO (equiv)	Temperature (°C)	Yield (%)[a]
1	KOH	10	50	trace[b]
2	KOH	10	50	29
3	Et_3N	10	50	38[b]
4	Et_3N	6.7	50	78
5	Et_3N	5	50	67
6	Et_3N	2	50	45
7	Et_3N	10	50	83
8	Et_3N	10	rt	trace
9	Et_3N	10	80	51
10	none	10	50	0[c]
11	NaOH	10	50	26[c]
12	K_2CO_3	10	50	70
13	DBU	10	50	59[c]
14	$^{i}Pr_2NEt$	10	50	69
15	pyridine	10	50	4[c]
16	DMAP	10	50	77
17	DABCO[d]	10	50	93
18	DABCO[e]	10	50	trace[h]
19	DABCO[f]	10	50	trace[h]
20	DABCO[g]	10	50	trace[h]

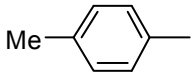
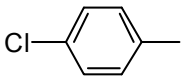
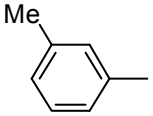
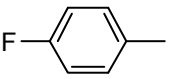
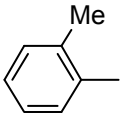
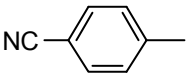
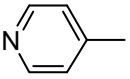
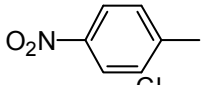
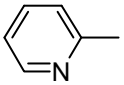
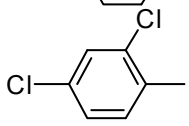
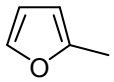
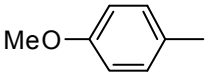
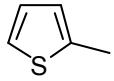
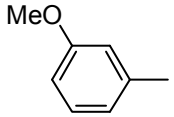
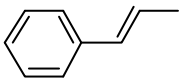
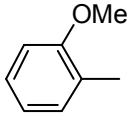
[a] Isolated yield. [b] Without Aliquat® 336. [c] Determined by ^1H NMR. [d] Only 1.0 equiv of DABCO was used. [e] CH_2Cl_2 was used instead of H_2O. [f] THF was used instead of H_2O. [g] 1,4-Dioxane was used instead of H_2O. [h] Recoverd **1** was isolated in >96% yield.

coupling reaction was significantly improved by the combined use of Et_3N and Aliquat® 336, and **2a** was obtained in 83% yield (Entry 7).

Further optimization of the reaction conditions was investigated. The yield of **2a** was reduced with the decreasing amount of benzaldehyde to 6.7, 5 and 2 equiv (Entries 4–6) from 10 equiv. A further rise in the temperature to 80 °C also gave an inefficient result (Entry 9, 51% yield), and instead decrease to room temperature led to little formation of **2a** (Entry 8). Next, various bases instead of Et_3N were used in the reaction. No reaction was observed without base (Entry 10). By the use of K_2CO_3, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), *N*,*N*-diisopropylethyamine (*i*Pr_2NEt) and

Table 2. 5-α-Hydroxyalkylation of **1** with various aromatic aldehydes



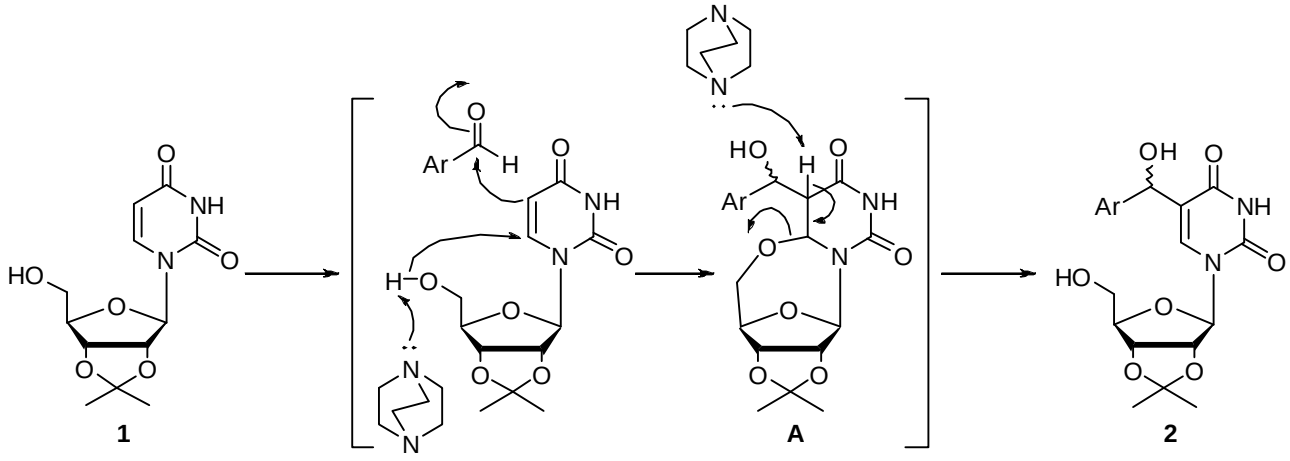
Entry	R	Product	Yield (%)[a]	Entry	R	Product	Yield (%)[a]
1	Ph	**2a**	93	10		**2j**	69
2		**2b**	100	11		**2k**	77
3		**2c**	84	12		**2l**	0
4[b]		**2d**	95	13		**2m**	72[d]
5[b]		**2e**	89	14		**2n**	75
6		**2f**	86	15[c]		**2o**	84
7		**2g**	50	16		**2p**	81
8		**2h**	71	17		**2q**	89
9		**2i**	65				

[a] Isolated yield. [b] 5 equiv of aldehydes were used. [c] The reaction required the use of 15 equiv of 2-furaldehyde and 48 h heating. [d] 1.5 equiv of Et_3N instead of DABCO (1 equiv) were used.

N,*N*-dimethyl-4-aminopyridine (DMAP), the desired product could be obtained in moderate yields (59–77%, Entries 12–14 and 16), while NaOH and pyridine (Entries 11 and 15) were not effective. When 1,4-diazabicyclo[2.2.2]octane (DABCO) was used as the base in aqueous media, the reaction was completed to afford **2a** in 93% yield (Entry 17), although the reaction in CH_2Cl_2, THF, or 1,4-dioxane, which are generally used for MBH reaction, hardly took place (Entries 18–20).

The scope and limitations of the substrates using a wide-range of aryl aldehydes possessing electron-donating or -withdrawing groups were examined. Electron-deficient aromatic aldehydes (Table 2, Entries 2–6) gave the desired coupling products in good yields (86–100%), whereas the reactions with electron-sufficient aromatic aldehydes (Entries 7–11) gave moderate yields (50–77%). It is interesting that no reaction was observed using *ortho*-substiuted 2-methylbenzaldehyde as the substrate (Entry 12), although reactions using *para*- and *meta*-methyl-substituted benzaldehydes and even *ortho*-methoxybenzaldehydes smoothly proceeded (Entries 9–11). Heterocyclic aldehydes (Entries 13–16) and an allylaldehyde (Entry 17) were also applicable to the reaction.

The proposed reaction mechanism of the MBH type 5-α-hydroxybenzylation at the 5-position of uracil nuclei is postulated in Scheme 1. The 5'-hydroxyl group of **1** is activated by the base to afford the cyclic adduct (**A**), followed by the C–O bond cleavage that gives the corresponding 5-substituted product (**2**). It may be regarded as a base-catalyzed MBH reaction. Since no product was observed using the 5'-*O*-*tert*-butyldimethylsilyl (TBS)-protected uridine (**3**)[18] and 5'-deoxyuridine (**4**)[19] as the substrates, the importance of the 5′-hydroxyl group-supported activation process of the enaminoketone moiety of the pyrimidine ring was strongly suggested (Figure 1). The coupling reactions using uridine (**5**) and 2',3'-*O*-TBS uridine (**6**)[20] as the substrate hardly proceeded because of the unsuitable spatial distance between the 5'-hydroxyl group and 6-position of the pyrimidine nucleus. There is no doubt that the spatially tuned 5-hydroxyl group due to the strain of the ring-fused structure based on the isopropylidene protective group plays a crucial role in the initial stage of the C–C bond formation.[21]



Scheme 1. Plausible reaction mechanism of 5-α-hydroxybenzylation

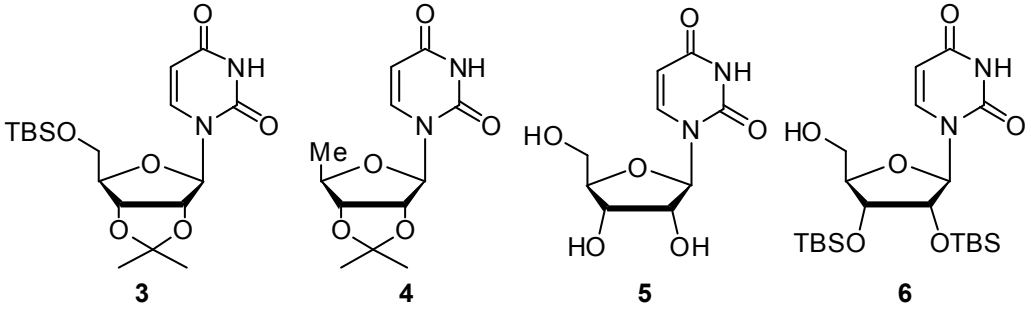
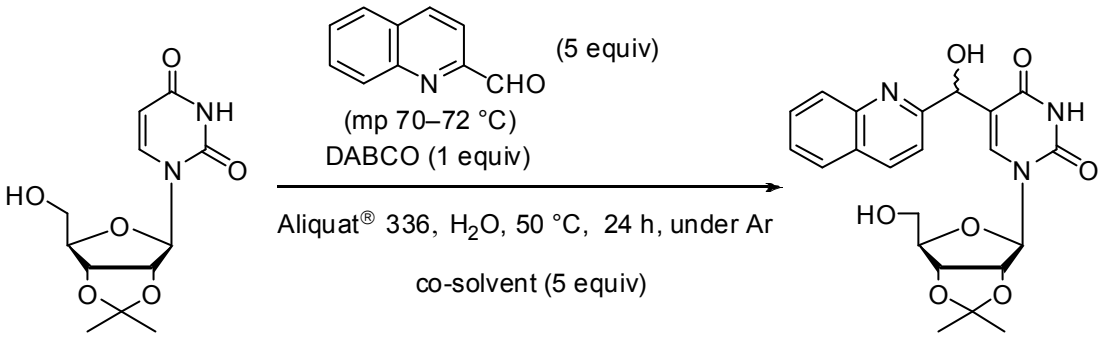
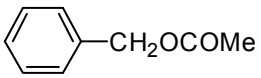
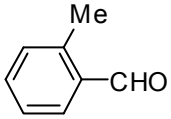
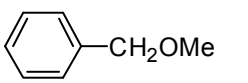
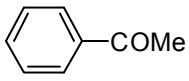
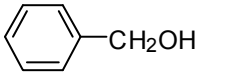
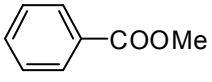


Figure 1.

The coupling reaction of several solid aldehydes such as 2-quinoline carboxyaldehyde, which are insoluble in H_2O gave disappointing results (Table 3, Entry 1 and Table 4, Entries 1, 3, 5, 7, 9 and 10). To overcome such a problem, the concomitant use of various co-solvents was carefully examined. As shown in Table 3, relatively lipophilic co-solvents as typified by benzyl alcohol were effective for the coupling reaction between **1** and 2-quinoline carboxyaldehyde, and the yields of **2r** were significantly enhanced (Entry 1 vs. Entry 7). Furthermore, the coupling reaction using other solid aromatic aldehydes, such as 4-nitrocinnamaldehyde, 4-phenylbenzaldehyde, 4-methoxycinnamaldehyde and 2-fluorenecarboxyaldehyde, were performed in the presence of 5 equiv of benzyl alcohol (Table 4), and significant improvements were observed when compared to the benzyl alcohol-free reactions.

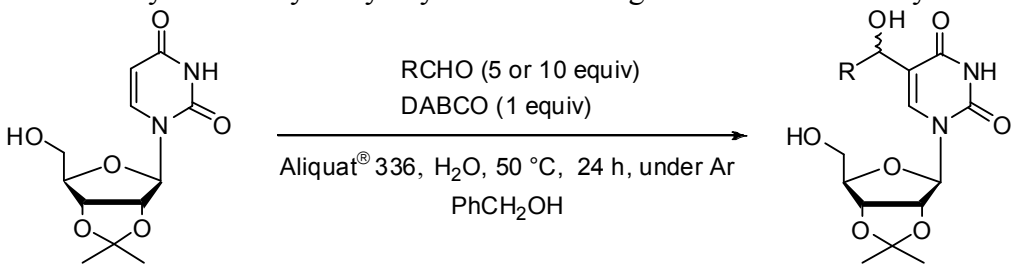
Table 3. 5-α-Hydroxyalkylation of **1** with 2-quinolinecarboxyaldehyde using various organic co-solvents

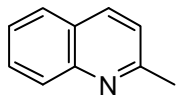
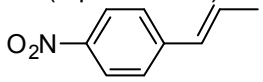
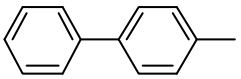
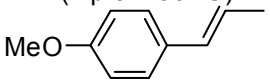
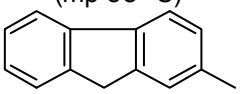


Entry	co-solvent	Yield (%)[a]	Entry	co-solvent	Yield (%)[a]
1	None	40	5		80
2		90	6		86
3		60	7		96
4		79			

[a] Products were contaminated with trace amounts of ketones oxidized by oxygen in the air.

Table 4. DABCO-Catalyzed 5-α-hydroxyalkylation of **1** using *solid* aromatic aldehydes with co-solvent

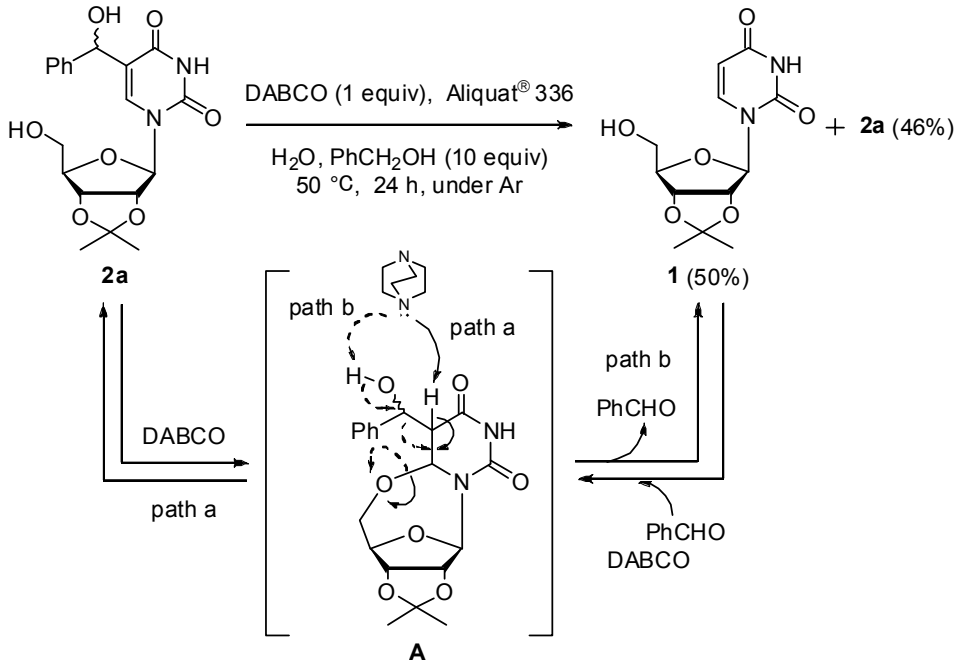


Entry	R	RCHO (equiv)	$PhCH_2OH$	Product	Yield[a] (%)
1	 (mp 70–72 °C)	10	none	**2r**	40[b]
2		5	5 equiv		96[c]
3	 (mp 140–142 °C)	10	none	**2s**	24
4		5	5 equiv		62
5	 (mp 57–59 °C)	10	none	**2t**	79
6		5	5 equiv		90
7	 (mp 58 °C)	10	none	**2u**	18
8		5	5 equiv		37
9	 (mp 85–86 °C)	10	none	**2v**	23
10		5	none		27
11		5	5 equiv		57

[a] Isolated yield. [b] Obtained as the corresponding ketone. [c] Product was contaminated with ca. 7 % of oxidized product (ketone form).

During the detailed investigation, we also found an interesting retro reaction. 5-Hydroxybenzyl-2',3'-*O*-isopropylideneuridine **2a** was converted into **1** in 50% yield under benzaldehyde-free conditions together with the unchanged **2a** (Scheme 2). This result suggested that the equilibrium between **2a** and **1** via a cyclic intermediate (**A**) should exist. When pathway a is superior to pathway b, the following ring opening process gave the desired product **2a**. In the reverse case, **1** could be obtained from the same intermediate (**A**) accompanied by the cleavage of the corresponding hydroxy benzyl group. On an equilibrium basis, the use of excess amounts of the aldehyde was expected to accelerate the reaction progress toward the desired MBH reaction product **2a**.

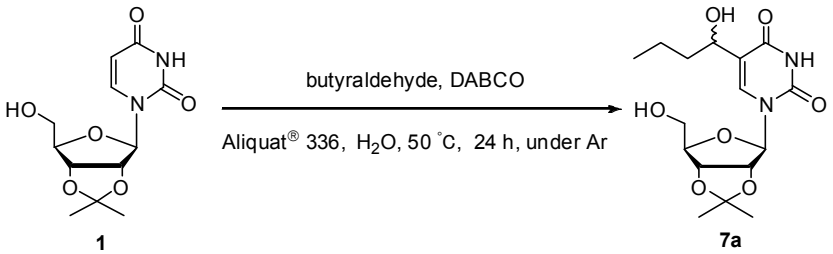
Although aliphatic aldehydes were quite difficult to apply to the present MBH type reaction, the 5-α-hydroxybutyluridine derivative was obtained in 23% yield by the use of 10 equiv of butylaldehyde (Table 5, Entry 1). Unfortunately, a significant improvement could not be achieved by the use of 50 or 100 equiv of butylaldehyde (25 and 32 %, Entries 2 and 3). It seemed likely that the formation of a self-condensation product of butylaldehyde prevents the path b in Scheme 2 during the reaction (24 h).



Scheme 2. DABCO-Catalyzed equilibrium between the MBH reaction product and 2',3'-*O*-isopropyrideneuridine

The remarkable improvement of the yield (54%) was observed when using an increased amount (6 equiv) of DABCO to accelerate the reaction rate of path b in Scheme 2 (Table 5, Entry 4). Finally, the efficiency of the coupling reaction could be improved up to 59% yield by the application of heat at 80 °C (Entry 5), although a further rise in the temperature to 100 °C led to a lower yield of **7a** (Entry 6, 22%). In addition, we investigated the time-course of the coupling reaction between **1** and butylaldehyde (100 equiv) in ^{1}H NMR tube. It was found that the maximum yield of the desired product (**7a**) was achieved around 24 h and the yield decreased after 30 h of the reaction (Figure 2).

Table 5. DABCO-Catalyzed 5-α-hydroxybutylation of **1** with butyraldehyde



Entry	Butyraldehyde (equiv)	DABCO (equiv)	Temperature (°C)	Yield (%) [a]
1	10	1	50	23
2	50	1	50	25
3	100	1	50	32
4	100	6	50	54
5	100	6	80	59
6	100	6	100	22

[a] Isolated yield.

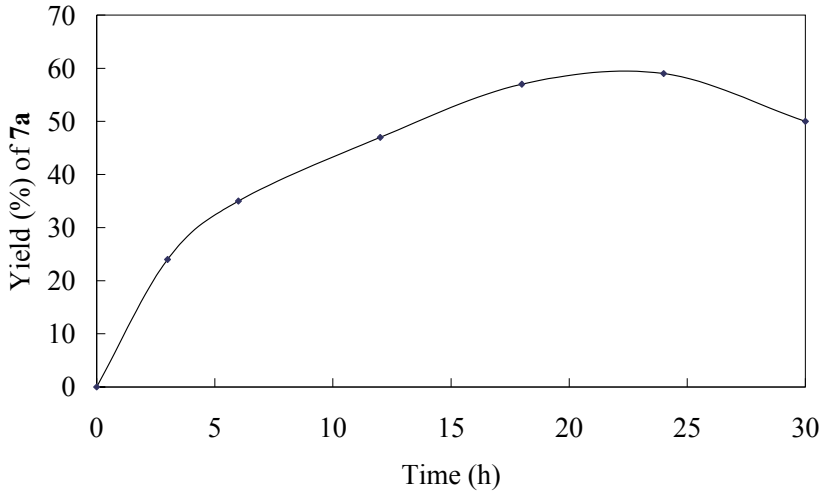
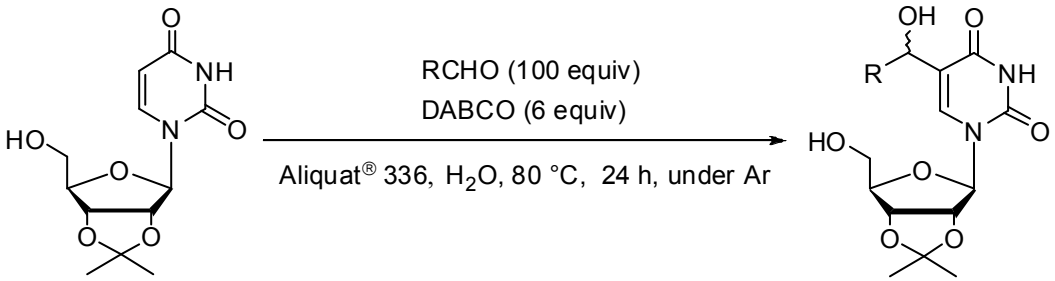


Figure 2. Time-course of the 5-α-hydroxybutylation of **1** under the reaction conditions indicated in Table 5, Entry 5

In order to confirm our novel establishment, other aliphatic aldehydes were used as substrates. Eventually, the corresponding coupling products (**7a**–**7f**) were obtained in moderate yields (30–59%, Entries 1–6, in Table 6).

Table 6. DABCO-Catalyzed 5-α-hydroxyalkylation of **1**



Entry	R	Product	Yield[a] (%)
1	$CH_3(CH_2)_2$	**7a**	59 (23)
2	$CH_3(CH_2)_3$	**7b**	65 (24)
3	$(CH_3)_2CHCH_2$	**7c**	62 (34)
4	$CH_3(CH_2)_4$	**7d**	50 (23)
5	$CH_3(CH_2)_5$	**7e**	30 (23)
6	$PhCH_2CH_2$	**7f**	41 (21)

[a] Isolated yield. Yields obtained by the reaction using 10 equiv of RCHO and 1 equiv of DABCO at 50 °C are shown in parentheses.

CONCLUSION

In conclusion, a general method for the chemical modification at the 5-position of uridine derivatives by the MBH reaction was established. The present reaction efficiently proceeded in H_2O in the presence of

DABCO as the base and Aliquat® 336 as the phase transfer catalyst. The broad substrate applicability will significantly contribute to the chemical synthesis of biologically active pyrimidine nucleoside analogs.

EXPERIMENTAL

General : The ^{1}H and ^{13}C NMR spectra were recorded by a JEOL EX 400 spectrometer (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR). Chemical shifts (δ) are expressed in ppm relative to a residual solvent or tetramethylsilane as the internal standard. Low and high resolution mass spectra were taken by a JEOL JMS-SX 102 machine. All reagents were commercially available and used without purification. All new compounds were further characterized by HRMS. Compounds known in the literature were characterized by comparison of their ^{1}H NMR data with previously reported data.

Optimization of 5-α-hydroxybenzylation of 2',3'-*O*-isopropyrideneuridine (1a) (Table 1): To a suspension of 2',3'-*O*-isopropylideneuridine (**1**, 100 mg, 0.35 mmol) in H_2O (1.1 cm^3) were added benzaldehyde (0.36 cm^3, 3.5 mmol), Aliquat® 336 (40 mm^3) and base (0.525 mmol), and the mixture was stirred at the given temperature for 24 h. The reaction mixture was diluted with water (5 cm^3) and extracted with EtOAc (20 cm^3). The organic solution was dried over $MgSO_4$ and the solvent was evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel ($CHCl_3$/MeOH, 100:1 to 50:1) to afford **2a**.

General procedure for the preparation of 2a–q (Table 2): To a suspension of **1** (100 mg, 0.35 mmol) in H_2O (1.1 cm^3) were added an aromatic aldehyde (10 equiv see Table 2), Aliquat® 336 (40 mm^3) and DABCO (39.5 mg, 0.35 mmol), and the mixture was stirred at 50 °C for 24 h. The reaction mixture was diluted with water (5 cm^3) and extracted with EtOAc (20 cm^3). The organic solution was dried over $MgSO_4$ and the solvent was evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel ($CHCl_3$/MeOH, 100:1 to 50:1) to afford **2a–q**.

5-(1-Hydroxy-1-phenylmethyl)-2',3'-*O*-isopropylideneuridine (2a): 127mg (93%); white powder; ^{1}H NMR ($CDCl_3$) δ 1.33 and 1.54 (each s, each 3H, isopropylidene), 2.33 (brs, 1H, 5'-OH or 5-CH(O<u>H</u>), deuterium exchangeable), 3.68 (m, 2H, 5'-H), 3.79 (brs, 1H, 5'-OH or 5-CH(O<u>H</u>), deuterium exchangeable), 4.24 (m, 1H, 4'-H), 4.80–4.88 (m, 2H, 2'-H and 3'-H), 5.61 (m, 1H, 1'-H or 5-CH), 5.78 (m, 1H, 1'-H or 5-CH), 7.18 (s, 1H, 6-H), 7.33–7.43 (m, 5H, benzene ring-H), 9.04 (brs, 1H, NH, deuterium exchangeable); ^{13}C NMR ($CDCl_3$) δ 163.3, 149.3, 140.4, 140.0, 128.6, 128.1, 126.7, 117.5, 114.2, 114.2, 95.2, 86.8, 84.2, 84.1, 80.5, 80.4, 69.2, 62.6, 27.2, 25.2, the spectrum as a mixture of two diastereomers was obtained; MS (EI) *m/z*: 390 (M^+); HRMS (EI) calcd for $C_{19}H_{22}N_2O_7$ (M^+) 390.1427, found 390.1418.

5-[1-(4-Chlorophenyl)-1-hydroxymethyl]-2',3'-*O*-isopropylideneuridine (2b): 149 mg (100%); white

powder; ^{1}H NMR ($CDCl_3$) δ 1.33 and 1.54 (each s, each 3H, isopropylidene), 2.90 (brs, 1H, 5'-OH or 5-CH(OH), deuterium exchangeable), 3.77 (m, 2H, 5'-H), 3.90 (br, 1H, 5'-OH or 5-CH(OH), deuterium exchangeable), 4.26 (m, 1H, 4′-H), 4.87–4.91 (m, 2H, 2'-H and 3'-H), 5.57 (m, 1H, 5-CH), 5.69 (d, *J* = 5.4 Hz, 1H, 1'-H), 7.23 (s, 1H, 6-H), 7.31–7.33 (m, 5H, benzene ring-H), 8.64 (br, 1H, NH, deuterium exchangeable); ^{13}C NMR ($CDCl_3$) δ 163.1, 150.0, 140.1, 139.0, 133.8, 128.7, 128.0, 117.1, 114.4, 95.6, 86.9, 83.9, 80.3, 68.7, 62.5, 27.2, 25.2; MS (EI) *m*/*z*: 424 (M^+); HRMS (EI) calcd for $C_{19}H_{21}N_2O_7Cl$ (M^+) 424.1037, found 424.1028.

5-[1-(4-Fluorophenyl)-1-hydroxymethyl]-2',3'-*O*-isopropylideneuridine (2c): 121 mg (84%); white powder; ^{1}H NMR ($CDCl_3$) δ 1.35 and 1.56 (each s, each 3H, isopropylidene), 2.32 (brs, 1H, 5'-OH or 5-CH(OH), deuterium exchangeable), 3.48 (brs, 1H, 5'-OH or 5-CH(OH), deuterium exchangeable), 3.75–3.78 (m, 2H, 5'-H), 4.26 (m, 1H, 4'-H), 4.88 (m, 1H, 3'-H), 4.93 (m, 1H, 2'-H), 5.55 (m, 1H, 1'-H), 5.73 (s, 1H, 1'-H or 5 -CH), 7.08 (d, *J* = 7.0 Hz, 2H, benzene-H), 7.30 (s, 1H, 6-H), 7.41 (d, *J* = 7.0 Hz, 2H, benzene ring-H), 8.50 (brs, 1H, NH, deuterium exchangeable); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 149.9, 140.0, 136.2, 128.4, 117.3, 115.6, 115.4, 114.4, 95.7, 86.9, 84.1, 83.9, 80.4, 80.3, 68.8, 62.6, 27.2, 25.2, the spectrum as a mixture of two diastereomers was obtained; MS (EI) *m*/*z*: 408 (M^+); HRMS (EI) calcd for $C_{19}H_{21}N_2O_7F$ (M^+) 408.1333, found 408.1324.

5-[1-(4-Cyanophenyl)-1-hydroxymethyl]-2',3'-*O*-isopropylideneuridine (2d): 5 Equiv of aldehyde was used. 139 mg (95%); white powder; ^{1}H NMR (DMSO-d_6) δ 1.28 and 1.47 (each s, each 3H, isopropylidene), 3.31–3.53 (m, 2H, 5'-H), 4.05 (m, 1H, 4'-H), 4.74 (m, 1H, 3'-H), 4.95 (m, 1H, 2'-H), 5.01 (m, 1H, 5'-OH, deuterium exchangeable), 5.54 (d, *J* = 4.9 Hz, 1H, 5-CH(OH), deuterium exchangeable), 5.83 (m, 1H, 1'-H or 5-CH), 5.94 (m, 1H, 1'-H or 5-CH), 7.55 (d, *J* = 8.3 Hz, 2H, benzene ring-H), 7.75 (d, *J* = 8.3 Hz, 2H, benzene ring-H), 7.83 (s, 1H, 6-H), 11.43 (brs, 1H, NH, deuterium exchangeable); ^{13}C NMR (DMSO-d_6) δ 185.3, 179.6, 177.7, 175.5, 172.2, 162.0, 156.1, 149.9, 149.2, 139.0, 138.5, 131.9, 127.5, 127.4, 118.9, 116.4, 112.8, 109.7, 92.1, 92.0, 86.7, 83.6, 80.8, 67.2, 62.1, 61.4, 26.9, 25.2, the spectrum as a mixture of two diastereomers was obtained; MS (FAB, Gly) m/z 416 (M^++H); HRMS (FAB) calcd for $C_{20}H_{22}N_3O_7$ 416.1458; found, 416.1467.

5-[1-(4-Nitrophenyl)-1-hydroxymethyl]-2',3'-*O*-isopropylideneuridine (2e): 5 Equiv of aldehyde was used. 136 mg (89%); yellow powder; ^{1}H NMR ($CDCl_3$) δ 1.35 and 1.56 (each s, each 3H, isopropylidene), 2.35 (brs, 1H, 5'-OH or 5-CH(OH), deuterium exchangeable), 3.57 (brs, 1H, 5'-OH or 5-CH(OH), deuterium exchangeable), 3.77–3.81 (m, 2H, 5'-H), 4.29 (m, 1H, 4'-H), 4.85–4.95 (m, 2H, 2'-H and 3'-H), 5.58 (m, 1H, 5-CH or 1'-H), 5.82 (m, 1H, 5-CH or 1'-H), 7.35 (s, 1H, 6-H), 7.62 (d, *J* = 8.8 Hz, 2H, benzene ring-H), 8.22 (d, *J* = 8.8 Hz, 2H, benzene ring-H), 8.75 (brs, 1H, NH, deuterium exchangeable); ^{13}C NMR ($CDCl_3$) δ 162.9, 149.8, 148.1, 147.6, 140.5, 127.3, 123.7, 116.3, 114.5, 114.4, 95.8, 95.5, 87.2, 86.9, 84.1, 83.9, 80.4, 80.3, 68.7, 68.6, 62.5, 27.1. 25.2, the spectrum as a mixture of two

diastereomers was obtained; MS (EI) m/z 435 (M^+); HRMS (EI) calcd for $C_{19}H_{21}N_3O_9$ 435.1278; found, 435.1286.

5-[1-(2,4-Dichlorophenyl)-1-hydroxymethyl]-2',3'-*O*-isopropylideneuridine (2f): 119 mg (74%); yellow powder; ^{1}H NMR ($CDCl_3$) δ 1.34 and 1.58 (each s, each 3H, isopropylidene), 2.42 (brs, 1H, 5'-OH or 5-CH(O<u>H</u>), deuterium exchangeable), 2.60 (brs, 1H, 5'-OH or 5-CH(O<u>H</u>), deuterium exchangeable), 3.72–3.75 (m, 2H, 5'-H), 4.26 (m, 1H, 4'-H), 4.85–4.95 (m, 2H, 2'-H and 3'-H), 5.54 (m, 1H, 5-CH), 6.00 (d, *J* = 4.4 Hz, 1H, 1'-H), 7.04 (s, 1H, 6-H), 7.33–7.66 (m, 3H, benzene ring-H), 9.30 (brs, 1H, NH, deuterium exchangeable); ^{13}C NMR ($CDCl_3$) δ 163.3, 150.0, 140.3, 140.1, 136.2, 134.4, 132.9, 129.4, 129.3, 127.1, 115.1, 115.0, 114.4, 114.3, 95.5, 87.1, 86.9, 84.2, 84.1, 80.3, 66.1, 65.8, 62.6, 27.2, 25.2, the spectrum as a mixture of two diastereomers was obtained; MS (FAB, Gly) m/z 459 (M^++H); HRMS (FAB) calcd for $C_{19}H_{21}N_2O_8Cl_2$ 459.0726; found: 459.0623.

5-[1-(4-Methoxyphenyl)-1-hydroxymethyl]-2',3'-*O*-isopropylideneuridine (2g): 74 mg (50%); white powder; ^{1}H NMR ($CDCl_3$) δ 1.32 and 1.54 (each s, each 3H, isopropylidene), 2.00 (brs, 1H, 5'-OH or 5-CH(O<u>H</u>), deuterium exchangeable), 2.90 (brs, 1H, 5'-OH or 5-CH(O<u>H</u>), deuterium exchangeable), 3.70–3.73 (m, 2H, 5'-H), 3.79 (s, 3H, -OCH_3), 4.20 (m, 1H, 4'-H), 4.84–4.94 (m, 2H, 2'-H and 3'-H), 5.56 (m, 1H, 5-CH), 5.63 (d, *J* = 4.7 Hz, 1H, 1'-H), 6.89 (d, *J* = 8.5 Hz, 2H, benzene ring-H), 7.23 (s, 1H, 6-H), 7.30 (d, *J* = 8.5 Hz, 2H, benzene ring-H), 9.60 (brs, 1H, NH, deuterium exchangeable); ^{13}C NMR ($CDCl_3$) δ 163.3, 159.3, 150.0, 139.9, 132.5, 127.9, 117.7, 117.6, 114.3, 114.1, 113.9, 113.6, 95.5, 95.4, 87.1, 86.9, 84.2, 84.0, 80.5, 80.4, 68.8, 62.5, 55.3, 27.2, 25.5, the spectrum as a mixture of two diastereomers was obtained; MS (FAB, Gly) m/z 421 (M^++H); HRMS (FAB) calcd for $C_{20}H_{25}N_2O_7$ 421.1611; found, 421.1533.

5-[1-(3-Methoxyphenyl)-1-hydroxymethyl]-2',3'-*O*-isopropylideneuridine (2h): 105 mg (71%); white powder; ^{1}H NMR ($CDCl_3$) δ 1.33 and 1.55 (each s, each 3H, isopropylidene), 2.42 (brs, 1H, 5'-OH or 5-CH(O<u>H</u>), deuterium exchangeable), 3.70–3.73 (m, 2H, 5'-H), 3.82 (s, 3H, -OCH_3), 4.26 (m, 1H, 4'-H), 4.85–4.88 (m, 2H, 2'-H and 3'-H), 5.59 (m, 1H, 5-CH or 1'-H), 5.74 (d, *J* = 3.5 Hz, 1H, 5-CH or 1'-H), 6.86 (d, *J* = 8.3 Hz, 2H, benzene ring-H), 6.96–6.99 (m, 2H, benzene ring-H), 7.28 (s, 1H, 6-H), 7.31 (d, *J* = 8.2 Hz, 2H, benzene ring-H), 9.05 (brs, 1H, NH, deuterium exchangeable); ^{13}C NMR ($CDCl_3$) δ 163.3, 160.0, 150.0, 142.0, 140.1, 129.6, 119.0, 117.3, 114.1, 113.4, 112.3, 95.4, 95.3, 87.0, 84.2, 84.1, 80.5, 80.4, 69.0, 62.6, 55.3, 27.2, 25.2, the spectrum as a mixture of two diastereomers was obtained; MS (FAB, Gly) m/z 421 (M^++H); HRMS (FAB) calcd for $C_{20}H_{25}N_2O_8$ 421.1611; found: 421.1602.

5-[1-(2-Methoxyphenyl)-1-hydroxymethyl]-2',3'-*O*-isopropylideneuridine (2i): 96 mg (65%); white powder; ^{1}H NMR ($CDCl_3$) δ 1.33 and 1.55 (each s, each 3H, isopropylidene), 2.18 (brs, 1H, 5'-OH or 5-CH(O<u>H</u>), deuterium exchangeable), 3.67–3.71 (m, 2H, 5'-H), 3.82 (s, 3H, -OCH_3), 4.24 (m, 1H, 4'-H), 4.83–4.89 (m, 2H, 2'-H and 3'-H), 5.57 (d, *J* = 2.9 Hz, 0.5H, 1'-H), 5.61 (d, *J* = 2.9 Hz, 0.5H, 1'-H), 6.01

(s, 1H, 5-CH), 6.90 (d, *J* = 7.8 Hz, 1H, benzene ring-H), 7.03–7.06 (m, 1H, benzene ring-H), 7.15 (s, 1H, 6-H), 7.32 (t, *J* = 7.8 Hz, 1H, benzene ring-H), 7.51 (d, *J* = 7.8 Hz, 1H, benzene ring-H), 9.08 (brs, 1H, NH, deuterium exchangeable), the spectrum as a mixture of two diastereomers was obtained; ^{13}C NMR ($CDCl_3$) δ 163.4, 156.3, 150.0, 139.5, 129.0, 128.4, 127.7, 127.6, 120.9, 116.3, 116.2, 114.1, 110.6, 110.5, 95.4, 95.1, 86.8, 84.3, 84.2, 80.5, 80.4, 64.7, 64.6, 62.7, 55.6, 55.5, 27.2, 25.2, the spectrum as a mixture of two diastereomers was obtained; MS (FAB, Gly) m/z 421 (M^++H); HRMS (FAB) calcd for $C_{20}H_{25}N_2O_8$ 421.1611; Found, 421.1602.

5-[1-(4-Methylphenyl)-1-hydroxymethyl]-2',3'-*O*-isopropylideneuridine (2j): 98 mg (69%); white powder; ^{1}H NMR ($CDCl_3$) δ 1.34 and 1.53 (each s, each 3H, isopropylidene), 2.38 (s, 3H, CH_3), 2.62 (brs, 1H, 5'-OH or 5-CH(O<u>H</u>), deuterium exchangeable), 3.64–3.72 (m, 2H, 5'-H), 3.82 (brs, 1H, 5'-OH or 5-CH(O<u>H</u>), deuterium exchangeable), 4.20 (m, 1H, 4'-H), 4.80–4.89 (m, 2H, 2'-H and 3'-H), 5.54 (m, 1H, 5-CH), 5.69 (d, *J* = 4.4 Hz, 1H, 1'-H), 7.14–7.34 (m, 5H, benzene ring-H and 6-H), 9.28 (brs, 1H, NH, deuterium exchangeable); ^{13}C NMR ($CDCl_3$) δ 163.1, 149.8, 140.0, 139.8, 138.0, 137.3, 130.2, 129.3, 129.2, 126.7, 126.5, 117.6, 114.2, 114.1, 95.7, 95.4, 86.9, 84.2, 84.0, 80.4, 69.4, 62.7, 27.2, 25.2, 21.7, the spectrum as a mixture of two diastereomers was obtained; MS (FAB, Gly) m/z 405 (M^++H); HRMS (FAB) calcd for $C_{20}H_{25}N_2O_7$ 405.1660; Found, 405.1662.

5-[1-(3-Methylphenyl)-1-hydroxymethyl]-2',3'-*O*-isopropylideneuridine (2k): 110 mg (77%); white powder; ^{1}H NMR ($CDCl_3$) δ 1.33 and 1.55 (each s, each 3H, isopropylidene), 2.37 (brs, 1H, 5′-OH or 5-CH(O<u>H</u>), deuterium exchangeable), 2.38 (s, 3H, CH_3), 3.64–3.71 (m, 2H, 5'-H), 4.24 (m, 1H, 4'-H), 4.80–4.88 (m, 2H, 2'-H and 3'-H), 5.57 (d, *J* = 2.9 Hz, 0.5H, 1'-H), 5.60 (d, *J* = 2.9 Hz, 0.5H, 1'-H), 5.73 (s, 1H, 5-CH), 7.14–7.30 (m, 5H, benzene ring-H and 6-H), 9.28 (brs, 1H, NH, deuterium exchangeable), the spectrum as a mixture of two diastereomers was obtained; ^{13}C NMR ($CDCl_3$) δ 163.3, 150.0, 140.3, 140.1, 138.4, 128.8, 128.5, 127.4, 123.8, 117.6, 114.2, 95.5, 95.4, 87.0, 84.2, 80.5, 69.4, 62.7, 27.2, 25.3, 21.5, the spectrum as a mixture of two diastereomers was obtained; MS (FAB, NBA) m/z 405 (M^++H); HRMS (FAB) calcd for $C_{20}H_{25}N_2O_7$ 405.1656; Found, 405.1662.

5-[1-(3-Methylphenyl)-1-hydroxymethyl]-2′,3′-*O*-isopropylideneuridine (2l): Not obtained.

5-[1-(4-Pyridyl)-1-hydroxymethyl]-2',3'-*O*-isopropylideneuridine (2m): 1.5 Equiv of Et_3N was used instead of DABCO. 99 mg (72%); yellow powder; ^{1}H NMR (DMSO-d_6) δ 1.28 and 1.46 (each s, each 3H, isopropylidene), 3.53 (m, 2H, 5'-H), 4.05 (m, 1H, 4'-H), 4.73 (m, 1H, 3'-H), 4.93 (m, 1H, 2'-H), 5.02 (t, *J* = 4.4 Hz, 1H, 5'-OH or 5-CH(O<u>H</u>), deuterium exchangeable), 5.48 (d, *J* = 4.4 Hz, 1H, 5-CH or 1'-H), 5.90 (d, *J* = 4.4 Hz, 1H, 5-CH or 1'-H), 7.35 (d, *J* = 5.9 Hz, 2H, pyridyl), 7.80 (s, 1H, 6-H), 8.45 (d, *J* = 5.9 Hz, 2H, pyridyl), 12.00 (brs, 1H, NH, deuterium exchangeable); ^{13}C NMR (DMSO-d_6) δ 162.2, 152.4, 150.1, 149.5, 139.4, 121.7, 116.4, 113.1, 92.2, 87.0, 83.9, 81.0, 66.7, 61.6, 56.2, 27.2, 25.3, the spectrum as a mixture of two diastereomers was obtained. MS (FAB, Gly) m/z 392 (M^++H); HRMS (FAB) calcd for

$C_{18}H_{22}N_3O_7$ 392.1458; Found, 392.1454.

5-[1-(2-Pyridyl)-1-hydroxymethyl]-2',3'-*O*-isopropylideneuridine (2n): 103 mg (75%); yellow powder; ^{1}H NMR ($CDCl_3$) δ 1.35 and 1.57 (each s, each 3H, isopropylidene), 3.75 (m, 1H, 5'-H), 3.91 (m, 1H, 5'-H), 4.33 (d, *J* = 2.4 Hz, 0.5H, 4'-H), 4.44 (d, *J* = 2.4 Hz, 0.5H, 4'-H), 4.88–4.99 (m, 2H, 2'-H and 3'-H), 5.21 (t, *J* = 4.4 Hz, 1H, 5'-OH or 5-CH(OH), deuterium exchangeable), 5.65–5.69 (m, 2H, 5-CH and 1′-H), 7.23 (d, *J* = 5.4 Hz, 1H, pyridyl), 7.60–7.78 (m, 3H, 6-H and pyridyl), 8.45 (d, *J* = 4.8 Hz, 0.5H, pyridyl), 8.50 (d, *J* = 4.8 Hz, 0.5H, pyridyl), 8.92 (brs, 1H, NH, deuterium exchangeable), the spectrum as a mixture of two diastereomers was obtained; ^{13}C NMR ($CDCl_3$) δ 163.3, 163.0, 159.9, 159.3, 150.0, 149.9, 148.2, 148.1, 140.0, 139.9, 137.6, 123.0, 121.6, 114.5, 113.7, 95.4, 95.2, 87.9, 87.5, 85.0, 84.4, 80.5, 68.7, 62.3, 27.1, 27.0, 25.1, the spectrum as a mixture of two diastereomers was obtained; MS (FAB, Gly) m/z 392 (M^++H); HRMS (FAB) calcd for $C_{18}H_{22}N_3O_7$ 392.1458; Found, 392.1463.

5-[1-(Furan-2-yl)-1-hydroxymethyl]-2',3'-*O*-isopropylideneuridine (2o): Further 5 equiv of 2-furaldehyde was additionally used after 12 h. 48 h heating. 112 mg (84% yield); white powder; ^{1}H NMR ($CDCl_3$) δ 1.35 and 1.57 (each s, each 3H, isopropylidene), 3.11 (brs, 1H, 5'-OH, deuterium exchangeable), 3.72–3.86 (m, 2H, 5'-H), 4.29 (m, 1H, 4'-H), 4.83–4.99 (m, 2H, 2'-H and 3'-H), 5.66 (dd, *J* = 2.9 and 7.8 Hz, 1H, 1′-H), 5.75 (s, 1H, 5-CH), 6.35 (m, 2H, furan ring-H), 7.42 (s, 0.5H, 6-H), 7.39 (s, 0.5H, 6-H), 7.50 (d, *J* = 3.9 Hz, 1H, furan ring-H), 9.35 (brs, 1H, NH, deuterium exchangeable), the spectrum as a mixture of two diastereomers was obtained; ^{13}C NMR ($CDCl_3$) δ 162.8, 153.1, 149.9, 142.6, 140.5, 114.3, 114.2, 110.6, 107.9, 95.6, 95.3, 87.1, 86.9, 84.0, 80.5, 80.3, 63.5, 62.5, 27.2, 25.2, the spectrum as a mixture of two diastereomers was obtained; MS (FAB, Gly) m/z 381 (M^++H); HRMS (FAB) calcd for $C_{17}H_{21}N_2O_8$ 381.1298; found, 381.1305.

5-[1-(Thiophen-2-yl)-1-hydroxymethyl]-2',3'-*O*-isopropylideneuridine (2p): 113 mg (81%); white powder; ^{1}H NMR ($CDCl_3$) δ 1.35 and 1.56 (each s, each 3H, isopropylidene), 2.67 (brs, 1H, 5'-OH, deuterium exchangeable), 3.68–3.82 (m, 2H, 5'-H), 4.28 (m, 1H, 4'-H), 4.85–4.94 (m, 2H, 2'-H and 3'-H), 5.66 (m, 1H, 1'-H), 5.99 (s, 1H, 5-CH), 6.99–7.03 (m, 2H, thiophene ring-H), 7.30 (d, *J* = 4.9 Hz, 1H, thiophen ring-H), 7.42 (s, 1H, 6-H), 9.19 (brs, 1H, NH, deuterium exchangeable); ^{13}C NMR ($CDCl_3$) δ 162.8, 150.0, 144.5, 140.0, 127.0, 125.5, 125.2, 116.9, 114.3, 95.4, 86.9, 86.8, 84.3, 84.1, 80.5, 80.4, 66.1, 62.7, 27.2, 25.2, the spectrum as a mixture of two diastereomers was obtained; MS (FAB, Gly) m/z 397 (M^++H); HRMS (FAB) calcd for $C_{17}H_{21}N_2O_7S$ 397.1069; found, 397.1076.

5-(1-Hydroxy-4-phenylbut-3-enyl)-2',3'-*O*-isopropylideneuridine (2q): 130 mg (89%); white powder; ^{1}H NMR ($CDCl_3$) δ 1.33 and 1.55 (each s, each 3H, isopropylidene), 3.03 (brs, 1H, 5'-OH or 5-CH(OH), deuterium exchangeable), 3.74–3.84 (m, 2H, 5'-H), 4.27–4.28 (m, 1H, 4'-H), 4.89–4.96 (m, 2H, 2'-H and 3'-H), 5.30 (m, 1H, 5-CH), 5.66 (m, 1H, 1'-H), 6.29 (dd, *J* = 6.5 and 16.1 Hz, 1H, -CH=CH-Ph), 6.73 (d, *J* = 16.1 Hz, 1H, -CH=CH-Ph), 7.24–7.39 (m, 5H, benzene ring-H), 7.56 (d, *J* = 12.7 Hz, 1H, 6-H), 9.34

(brs, 1H, NH, deuterium exchangeable); ^{13}C NMR ($CDCl_3$) δ 163.1, 150.0, 139.8, 131.8, 128.7, 128.1, 127.9, 126.6, 116.1, 114.3, 95.7, 87.1, 87.0, 84.1, 83.8, 80.4, 80.3, 68.1, 68.0, 62.6, 27.2, 25.2, the spectrum as a mixture of two diastereomers was obtained; MS (FAB, Gly) m/z 417 (M^++H); HRMS (FAB) calcd for $C_{21}H_{25}N_2O_7$ 417.1662; Found, 417.1653.

Effect of co-solvent on the 2r synthesis (Table 3): To a suspension of **1** (100 mg, 0.35 mmol) in H_2O (1.1 cm^3) were added 2-quinolinaldehyde (530 mg, 3.5 mmol), Aliquat® 336 (40 mm^3), DABCO (39.5 mg, 0.35 mmol) and co-solvent (5 equiv, see Table 3), and the mixture was stirred for 24 h at 50 °C. The reaction mixture was diluted with water (5 cm^3) and extracted with EtOAc (20 cm^3). The organic solution was dried over $MgSO_4$ and the solvent was evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel ($CHCl_3$/MeOH, 100:1 to 50:1) to afford **2r**.

General procedure for the preparation of 2r–v (Table 4): To a suspension of **1** (100 mg, 0.35 mmol) in H_2O (1.1 cm^3) were added an aldehyde (Entries 1, 3, 5, 7 and 9: 530 mg, 3.5 mmol, Entries 2, 4, 6, 8, 10 and 11 : 265 mg, 1.75 mmol, see Table 4), Aliquat® 336 (40 mm^3), DABCO (39.5 mg, 0.35 mmol) and benzyl alcohol (Entries 1, 3, 5, 7 and 9 : none, Entries 2, 4, 6, 8, 10 and 11: 0.18 cm^3, 1.75 mmol), and the mixture was stirred for 24 h at 50 °C. The reaction mixture was diluted with water (5 cm^3) and extracted with EtOAc (20 cm^3). The organic solution was dried over $MgSO_4$ and the solvent was evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel ($CHCl_3$/MeOH, 100:1 to 50:1) to afford **2r–v**.

5-[1-(Quinolin-2-yl)-1-hydroxymethyl]-2',3'-*O*-isopropylideneuridine (2r): 148 mg (96%); yellow powder; ^{1}H NMR ($CDCl_3$) δ 1.33 and 1.53 (each s, each 3H, isopropylidene), 3.44 (brs, 1H, 5'-OH or 5-CH(O<u>H</u>), deuterium exchangeable), 3.71–3.90 (m, 2H, 5'-H), 4.32 (m, 1H, 4'-H), 4.90 (m, 1H, 3'-H), 4.97 (m, 1H, 2'-H), 5.64 (m, 1H, 1'-H), 5.94 (s, 0.5H, 5-CH), 6.02 (s, 0.5H, 5-CH), 7.56–7.58 (m, 1H, quinoline ring-H), 7.71–7.85 (m, 4H, quinoline ring-H and 6-H), 8.08 (d, *J* = 8.8 Hz, 1H, quinoline ring-H), 8.20 (d, *J* = 8.8 Hz, 1H, quinoline ring-H), 9.03 (brs, 1H, NH, deuterium exchangeable), the spectrum as a mixture of two diastereomers was obtained; ^{13}C NMR ($CDCl_3$) δ 163.2, 160.2, 150.0, 146.2, 138.4, 130.6, 128.2, 128.1, 127.3, 127.2, 120.0, 119.5, 114.4, 114.3, 96.4, 88.0, 87.5, 85.0, 84.4, 80.9, 80.8, 68.9, 62.7, 27.4, 25.5, 25.4, the spectrum as a mixture of two diastereomers was obtained; MS (FAB, Gly) m/z 442 (M^++H); HRMS (FAB) calcd for $C_{22}H_{24}N_2O_7$ 442.1614; found, 442.1610.

5-[1-Hydroxy-4-(4-nitrophenyl)but-3-enyl]-2',3'-*O*-isopropylideneuridine (2s): 100 mg (62%); white powder; ^{1}H NMR ($CDCl_3$) δ 1.33 and 1.57 (each s, each 3H, isopropylidene), 2.78 (brs, 1H, 5'-OH or 5-CH(O<u>H</u>), deuterium exchangeable), 3.34 (brs, 1H, 5'-OH or 5-CH(O<u>H</u>), deuterium exchangeable), 3.79 (m, 1H, 5'-H), 3.90 (m, 1H, 5'-H), 4.30 (m, 1H, 4'-H), 4.94 (m, 1H, 3'-H), 5.03 (m, 1H, 2'-H), 5.33 (m, 1H, 1'-H), 5.62 (d, *J* = 2.5 Hz, 1H, 5-CH), 6.50 (m, 1H, -C<u>H</u>=CH-Ph), 6.82 (d, *J* = 6.1 Hz, 1H, -CH=C<u>H</u>-Ph), 7.52–7.57 (m, 3H, 6-H and benzene ring-H), 8.18 (d, *J* = 8.8 Hz, 2H, benzene ring-H), 8.83 (brs, 1H, NH,

deuterium exchangeable); ^{13}C NMR ($CDCl_3$) δ 162.7, 149.9, 147.2, 140.0, 133.0, 127.2, 124.1, 115.4, 114.5, 96.1, 87.1, 87.0, 83.9, 80.4, 68.0, 67.8, 62.7, 30.9, 27.2, 25.3, the spectrum as a mixture of two diastereomers was obtained; MS (FAB, Gly) m/z 462 (M^++H); HRMS (FAB) calcd for $C_{21}H_{24}N_3O_9$ 462.1513; Found, 462.1507.

5-{1-[4-(1,1'-Biphenyl)]-1-hydroxymethyl}-2',3'-*O*-isopropylideneuridine (2t): 147 mg (90%); white powder; ^{1}H NMR ($CDCl_3$) δ 1.32 and 1.54 (each s, each 3H, isopropylidene), 3.65–3.76 (m, 2H, 5'-H), 4.25 (m, 1H, 4'-H), 4.82–4.94 (m, 2H, 2'-H and 3'-H), 5.61 (m, 1H, 1'-H), 5.80 (s, 0.3H, 5-CH), 5.82 (s, 0.7H, 5-CH), 7.28 (s, 1H, 6-H), 7.36 (t, *J* = 7.3 Hz, 1H, benzene ring-H), 7.24–7.48 (m, 4H, benzene ring-H), 7.57–7.60 (m, 4H, benzene ring-H), 9.05 (brs, 1H, NH, deuterium exchangeable), the spectrum as a mixture of two diastereomers was obtained; ^{13}C NMR ($CDCl_3$) δ 163.3, 150.0, 148.9, 140.5, 140.1, 139.5, 128.9, 127.5, 127.2, 127.1, 117.4, 114.2, 95.4, 87.1, 84.2, 80.5, 68.9, 62.6, 27.2, 25.2, the spectrum as a mixture of two diastereomers was obtained; MS (FAB, Gly) m/z 467 (M^++H); HRMS (FAB) calcd for $C_{25}H_{27}N_2O_7$ 467.1818; found, 467.1812

5-[1-Hydroxy-4-(4-methoxyphenyl)but-3-enyl]-2',3'-*O*-isopropylideneuridine (2u): 57.8 mg (37%); yellow powder; ^{1}H NMR ($CDCl_3$) δ 1.33 and 1.55 (each s, each 3H, isopropylidene), 3.03 (brs, 1H, 5'-OH or 5-CH(O<u>H</u>), deuterium exchangeable), 3.74–3.84 (m, 5H, 5'-H and -OCH_3), 4.27 (m, 1H, 4'-H), 4.90–4.97 (m, 2H, 2'-H and 3'-H), 5.25 (m, 1H, 1'-H), 5.65 (s, 0.5H, 5-CH), 5.67 (s, 0.5H, 5-CH), 6.16 (d, *J* = 16.1 Hz, 1H, -C<u>H</u>=CH-Ph), 6.66 (d, *J* = 16.1 Hz, 1H, -CH=C<u>H</u>-Ph), 6.84 (d, *J* = 8.8 Hz, 2H, benzene ring-H), 7.32 (d, *J* = 8.8 Hz, 2H, benzene ring-H), 7.52 (d, *J* = 12.7 Hz, 1H, 6-H), 9.30 (brs, 1H, NH, deuterium exchangeable), the spectrum as a mixture of two diastereomers was obtained; ^{13}C NMR ($CDCl_3$) δ 163.1, 160.0, 150.0, 139.7, 131.4, 128.9, 127.8, 125.6, 116.2, 114.3, 114.1, 95.6, 87.1, 86.9, 84.1, 83.8, 80.4, 80.3, 68.1, 62.6, 55.3, 27.2, 25.2, the spectrum as a mixture of two diastereomers was obtained; MS (FAB, Gly) m/z 447 (M^++H); HRMS (FAB) calcd for $C_{22}H_{27}N_2O_8$ 447.1767; found, 447.1773.

5-[1-(Fluoren-2-yl)-1-hydroxymethyl]-2',3'-*O*-isopropylideneuridine (2v): 95.5 mg (57%); white powder; ^{1}H NMR ($CDCl_3$) δ 1.29 and 1.50 (each s, each 3H, isopropylidene), 2.97 (brs, 1H, 5'-OH or 5-CH(O<u>H</u>), deuterium exchangeable), 3.61–3.67 (m, 2H, 5'-H), 3.82 (s, 2H, fluorene ring-H), 4.18 (m, 1H, 4'-H), 4.79 (m, 1H, 3'-H), 4.91 (m, 1H, 2'-H), 5.52 (d, *J* = 2.4 Hz, 1H, 1'-H), 5.77 (s, 1H, 5-CH), 7.29–7.37 (m, 4H, fluorene ring-H), 7.50–7.53 (m, 3H, fluorene ring-H and 6-H), 7.71 (m, 2H, fluorene ring-H) 9.57 (brs, 1H, NH, deuterium exchangeable); ^{13}C NMR ($CDCl_3$) δ 163.5, 150.1, 143.6, 143.4, 141.5, 141.1, 140.2, 139.1, 126.7, 125.4, 125.1, 123.3, 119.9, 119.8, 117.4, 114.0, 95.6, 87.3, 84.3, 80.6, 69.1, 62.5, 36.8, 27.1, 25.2, the spectrum as a mixture of two diastereomers was obtained; MS (FAB, NBA) m/z 479 (M^++H); HRMS (FAB) calcd for $C_{26}H_{27}N_2O_7$ 479.1818; found, 479.1809.

General procedure for 7a–7f (Table 5): To a suspension of **1** (100 mg, 0.35 mmol) in H_2O (1.1 cm^3)

were added an aliphatic aldehyde (10 equiv, see Table 5), Aliquat® 336 (40 mm^3) and DABCO (39.5 mmol, 0.35 mmol), and the mixture was stirred for 24 h at 50 °C. The reaction mixture was diluted with water (5 cm^3) and extracted with EtOAc (20 cm^3). The organic solution was dried over $MgSO_4$ and the solvent was evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel ($CHCl_3$/MeOH, 100:1) to afford **7a**–**f**.

5-(1-Hydroxybut-1-yl)-2',3'-*O*-isopropylideneuridine (7a): 73.6 mg (59%); colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.93 (t, *J* = 7.3 Hz, 3H, *n*-butyl), 1.33 (s, 3H, isopropylidene), 1.50 (m, 2H, *n*-butyl), 1.58 (s, 3H, isopropylidene), 1.66 (m, 2H, *n*-butyl), 1.89 (brs, 1H, 5'-OH or 5-CH(OH), deuterium exchangeable), 3.51 (brs, 1H, 5'-OH or 5-CH(OH), deuterium exchangeable), 3.80–3.91 (m, 2H, 5'-H), 4.30 (m, 1H, 4'-H), 4.54 (m, 1H, 5-CH), 4.94–5.02 (m, 2H, 2'-H and 3'-H), 5.65 (m, 1H, 1'-H), 7.46 (d, *J* = 5.8 Hz, 1H, 6-H), 9.43 (brs, 1H, NH, exchangeable); ^{13}C NMR ($CDCl_3$) δ 163.2, 150.2, 139.2, 139.0, 117.3, 114.5, 114.3, 95.8, 95.1, 87.2, 86.9, 83.9, 83.8, 80.5, 80.3, 67.7, 67.4, 62.5, 62.4, 38.0, 27.2, 25.3, 19.0, 13.9, the spectrum as a mixture of two diastereomers was obtained; MS (FAB, Gly) m/z 357 (M^++H); HRMS (FAB) calcd for $C_{16}H_{25}N_2O_7$ 357.1662; found, 357.1667.

5-(1-Hydroxypent-1-yl)-2',3'-*O*-isopropylideneuridine (7b): 84.3 mg (65%); colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, *J* = 7.3 Hz, 3H, *n*-pentyl), 1.25–1.43 (m, 7H, *n*-pentyl and isopropylidene), 1.58 (s, 3H, isopropylidene), 1.63–1.74 (m, 2H, *n*-pentyl), 2.02 (brs, 1H, 5'-OH or 5-CH(OH), deuterium exchangeable), 3.77 (m, 1H, 5'-H), 3.89 (m, 1H, 5'-H), 4.31 (m, 1H, 4'-H), 4.54 (m, 1H, 5-CH), 4.90–5.04 (m, 2H, 2'-H and 3'-H), 5.65 (d, *J* = 2.9 Hz, 0.5H, 1'-H), 5.74 (d, *J* = 2.9 Hz, 0.5H, 1'-H), 7.50 (d, *J* = 5.8 Hz, 1H, 6-H), 9.60 (brs, 1H, NH, deuterium exchangeable), the spectrum as a mixture of two diastereomers was obtained; ^{13}C NMR ($CDCl_3$) δ 163.2, 150.2, 139.1, 139.0, 117.3, 114.4, 95.8, 95.0, 87.2, 86.9, 83.9, 80.5, 80.3, 67.8, 67.6, 62.5, 62.4, 35.7, 27.9, 27.2, 25.3, 22.5, 14.0, the spectrum as a mixture of two diastereomers was obtained; MS (FAB, Gly) m/z 371 (M^++H); HRMS (FAB) calcd for $C_{17}H_{27}N_2O_7$ 371.1818; found, 371.1809.

5-(1-Hydroxy-3-methylbut-1-yl)-2',3'-*O*-isopropylideneuridine (7c): 80.4 mg (62%); colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.93 (d, *J* = 7.3 Hz, 6H, isopentyl), 1.36 (s, 3H, isopropylidene), 1.49 (m, 1H, isopentyl), 1.57–1.74 (m, 5H, isopentyl and isopropylidene), 2.40 (brs, 1H, 5'-OH or 5-CH(OH), deuterium exchangeable), 3.75–3.87 (m, 2H, 5'-H), 4.30 (m, 1H, 4'-H), 4.62 (m, 1H, 5-CH), 4.89–5.04 (m, 2H, 2'-H and 3'-H), 5.66 (d, *J* = 2.4 Hz, 0.5H, 1'-H), 5.77 (d, *J* = 2.4 Hz, 0.5H, 1'-H), 7.53 (d, *J* = 5.8 Hz, 1H, 6-H), 9.89 (brs, 1H, NH, deuterium exchangeable), the spectrum as a mixture of two diastereomers was obtained; ^{13}C NMR ($CDCl_3$) δ 163.3, 150.2, 139.1, 138.9, 117.7, 117.6, 114.4, 114.3, 95.8, 94.8, 87.2, 86.9, 84.0, 83.9, 80.5, 80.3, 66.0, 65.7, 62.5, 62.3, 44.9, 27.2, 25.3, 24.8, 23.3, 21.8, the spectrum as a mixture of two diastereomers was obtained; MS (FAB, Gly) m/z 371 (M^++H); HRMS (FAB) calcd for $C_{17}H_{27}N_2O_7$ 371.1818; found, 371.1813.

5-(1-Hydroxyhex-1-yl)-2',3'-*O*-isopropylideneuridine (7d): 67.3 mg (50%); colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, *J* = 6.4 Hz, 3H, *n*-hexyl), 1.29–1.44 (m, 9H, isopropylidene and *n*-hexyl), 1.58 (s, 3H, isopropylidene), 1.65 (m, 2H, *n*-hexyl), 3.78 (m, 1H, 5'-H), 3.89 (m, 1H, 5'-H), 4.29 (m, 1H, 4'-H), 4.54 (m, 1H, 5-CH), 4.89–5.03 (m, 2H, 2'-H and 3'-H), 5.67 (d, *J* = 2.9 Hz, 0.5H, 1'-H), 5.77 (d, *J* = 2.9 Hz, 0.5H, 1'-H), 7.52 (d, *J* = 7.8 Hz, 1H, 6-H), 9.77 (brs, 1H, NH, deuterium exchangeable), the spectrum as a mixture of two diastereomers was obtained; ^{13}C NMR ($CDCl_3$) δ 163.3, 150.2, 139.2, 138.9, 117.3, 114.4, 114.3, 95.0, 87.2, 86.8, 83.8, 80.5, 80.3, 67.9, 67.6, 62.5, 62.3, 35.9, 31.6, 27.2, 25.4, 25.2, 22.6, 14.0, the spectrum as a mixture of two diastereomers was obtained; MS (FAB, Gly) m/z 385 (M^++H); HRMS (FAB) calcd for $C_{18}H_{29}N_2O_7$ 385.1975; found, 385.1978.

5-(1-Hydroxyhept-1-yl)-2',3'-*O*-isopropylideneuridine (7e): 41.8 mg (30%); colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, *J* = 6.8 Hz, 3H, *n*-heptyl), 1.28 (brs, 8H, *n*-heptyl), 1.36 and 1.58 (each s, each 3H, isopropylidene), 1.69 (m, 2H, *n*-heptyl), 3.52 (brs, 1H, 5'-OH or 5-CH(O<u>H</u>), deuterium exchangeable), 3.79 (m, 1H, 5'-H), 3.91 (m, 1H, 5'-H), 4.29 (m, 1H, 4'-H), 4.52 (m, 1H, 5-CH), 4.90–5.03 (m, 2H, 2'-H and 3'-H), 5.65 (d, *J* = 2.9 Hz, 0.3H, 1'-H), 5.72 (d, *J* = 2.9 Hz, 0.7H, 1'-H), 7.52 (d, *J* = 7.8 Hz, 1H, 6-H), 9.49 (brs, 1H, NH, deuterium exchangeable), the spectrum as a mixture of two diastereomers was obtained; ^{13}C NMR ($CDCl_3$) δ 163.1, 150.1, 139.2, 139.0, 117.3, 114.4, 114.3, 95.5, 87.2, 86.9, 83.7, 80.5, 80.3, 68.0, 67.8, 62.6, 62.5, 36.0, 31.8, 29.1, 27.2, 25.7, 25.3, 22.6, 14.1, the spectrum as a mixture of two diastereomers was obtained; MS (FAB, Gly) m/z 399 (M^++H); HRMS (FAB) calcd for $C_{19}H_{31}N_2O_7$ 399.2131; found, 399.2121.

5-(1-Hydroxy-3-phenylpropyl)-2',3'-*O*-isopropylideneuridine (7f): 60.0 mg (41%); colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.35 and 1.57 (each s, each 3H, isopropylidene), 1.98–2.04 (m, 2H, -C<u>H</u>$_2$CH$_2$Ph), 2.19 (brs, 1H, 5'-OH or 5-CH(O<u>H</u>), deuterium exchangeable), 2.66 (m, 1H, -CH$_2$C<u>H</u>$_2$Ph), 2.80 (m, 1H, -CH$_2$C<u>H</u>$_2$Ph), 3.59 (brs, 1H, 5'-OH or 5-CH(O<u>H</u>), deuterium exchangeable), 3.74 (m, 1H, 5'-H) 3.85 (m, 1H, 5′-H), 4.26 (m, 1H, 4'-H), 4.53 (m, 1H, 5-CH), 4.86–4.99 (m, 2H, 2'-H and 3'-H), 5.61 (d, *J* = 2.9 Hz, 0.3H, 1'-H), 5.71 (d, *J* = 2.9 Hz, 0.7H, 1'-H), 7.14–7.18 (m, 2H, Ph), 7.23–7.27 (m, 3H, Ph), 7.43 (d, *J* = 7.3 Hz, 1H, 6-H), 9.71 (brs, 1H, NH, deuterium exchangeable), the spectrum as a mixture of two diastereomers was obtained; ^{13}C NMR ($CDCl_3$) δ 163.1, 150.0, 141.3, 139.1, 128.4, 125.9, 116.9, 114.4, 95.9, 95.2, 86.8, 83.7, 80.3, 67.6, 67.2, 62.4, 37.1, 31.9, 27.2, 25.3, the spectrum as a mixture of two diastereomers was obtained; MS (FAB, Gly) m/z 419 (M^++H); HRMS (FAB) calcd for $C_{21}H_{27}N_2O_7$ 419.1818; found, 419.1828.

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§ Current address: Laboratory of Synthetic Organic Chemistry, Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita 565-0871, Japan

¶ Current address: School of Pharmacy, Aichi Gakuin University, 1-100 Kusumoto-cho, Chikusa-ku, Nagoya 464-8650, Japan

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21. Treatment of **1** with *N*-bromosuccinamide in $CHCl_3$–AcOH (10:1) at rt afforded 5-bromo-O^6,5'-cyclo-5,6-dihydro-2',3'-*O*-isopropyrideneuridine in 54% yield, suggesting existence of the cyclic adduct **A** as the intermediate in the present reaction. K. Hirota, T. Tomishi, M. Sako, and Y. Maki, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2227.