

SYNTHESIS OF 5-SUBSTITUTED PYRIMIDINE NUCLEOSIDES
THROUGH A PALLADIUM-CATALYZED CROSS-COUPLING OF
ALKENYLHALOSILANES

Hayao Matsubishi, Yasuo Hatanaka,[†] Manabu Kuroboshi,
and Tamejiro Hiyama*

Research Laboratory of Resources Utilization, Tokyo Institute of Technology
4259 Nagatsuta, Midori-ku, Yokohama 226, Japan

[†]Sagami Chemical Research Center

4-4-1 Nishiohnuma, Sagamihara, Kanagawa 229, Japan

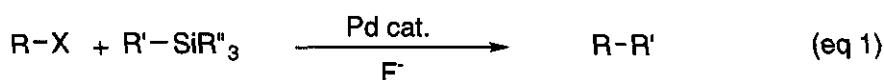
Dedicated to the memory of late professor Yoshio Ban.

Abstract- Palladium-catalyzed cross-coupling of alkenylhalosilanes with 5-iodouracil and 5-iodouridine derivatives was described. 5-Iodo-1,3-dimethyluracil coupled with alkenylfluorodimethylsilanes to give the corresponding cross-coupled products in good yield. Fully protected 5-iodo-2'-deoxyuridine derivative also underwent the cross-coupling reaction. Noteworthy is that unprotected 5-iodo-2'-deoxyuridine could be converted into the corresponding cross-coupled products in good yields using alkenyl(difluoro)methylsilanes.

INTRODUCTION

Derivation of purine and pyrimidine nucleosides has attracted much attention because of potent antitumor or antiviral activity.¹ Modification of the nucleosides is well studied regarding to sugar and pyrimidine moiety. In particular, introduction of organic functional group to C5 and/or C6 position has been shown to be fruitful. Straightforward method for the synthesis of such derivatives is transition metal catalyzed cross-coupling reaction² by means of an organometallic reagent of mercury,³ stannane,⁴ boron,^{4b} or aluminum.⁵

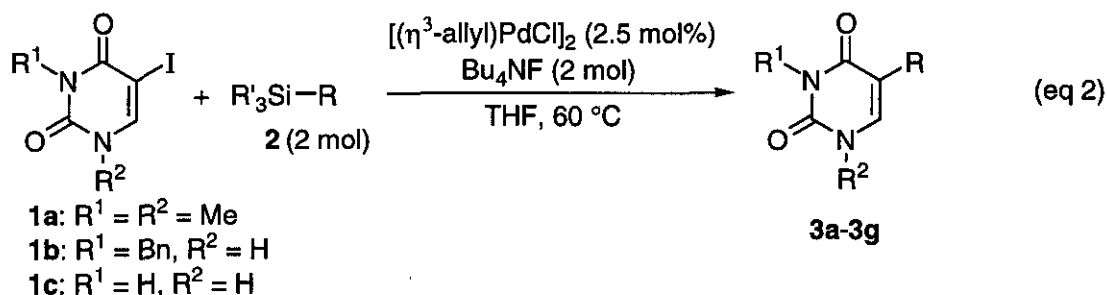
Palladium-catalyzed coupling of C5-mercuriouracil or -uridine with an organic halide or an alkene is well investigated by Bergstrom.³ More recently, organostannanes are reported to undergo palladium-catalyzed cross-coupling with 5-iodouracil or -uridine derivatives.⁴ However, these organometals are toxic to be used in large scale synthesis.



We have studied the palladium-catalyzed cross-coupling of organofluorosilanes with organic electrophiles mediated by fluoride ion (eq 1).⁶ Organosilicon compounds have some advantages over other metal reagents: Low toxicity, thermal and moisture stability, readily availability, and inexpensiveness. Thus we have applied this reaction to the synthesis of HMG-CoA reductase inhibitor.⁷ In this article, we describe a convenient synthesis of 5-substituted uracil derivatives and 5-substituted 2'-deoxyuridines through a palladium-catalyzed cross-coupling of organofluorosilanes with 5-iodouracil and uridine derivatives.

RESULTS and DISCUSSION

At first, we studied the reaction with 5-iodo-1,3-dimethyluracil (**1a**) to optimize the structure of organofluorosilanes and a catalyst, and found that the reaction successfully proceeded in tetrahydrofuran (THF) at 60 °C with $[(\eta^3\text{-allyl})\text{PdCl}]_2$ catalyst and tetrabutylammonium fluoride (TBAF) (eq 2). Another Pd catalyst like $\text{Pd}(\text{PPh}_3)_4$ or $\text{Pd}(\text{OAc})_2$ was less effective.



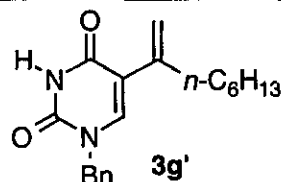
The results are summarized in Table 1. Alkenylfluorodimethylsilanes (**2a-2c**) smoothly reacted with **1a** to provide the cross-coupled products in moderate to good yields with retention of olefin geometry (runs 1, 2, and 3). It is worth to note that sterically congested alkenylsilane (**2c**) was reactive enough (run 3). We

found that alkenylchlorodimethylsilane (**2d**) and (**2e**) also exhibited enough reactivity in the presence of an excess amount of TBAF.⁷ Mono protected substrate (**1b**) successfully coupled with alkenyl-(difluoro)methylsilane (**2f**) and (**2g**) to give the expected products. The reaction of **1b** and **2g** gave the desired cross-coupled product (**3g**) with considerable amount of regioisomer (**3g'**) (run 7). The isomerization process is not clear at this stage. Unfortunately, non-protected 5-iodouracil (**1c**) did not react under these reaction conditions.

Table 1. Cross-coupling of organosilanes with uracil derivatives

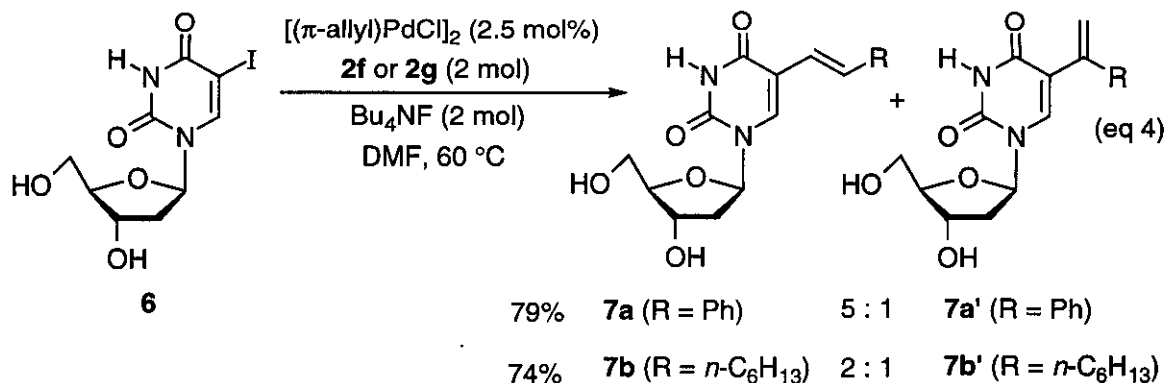
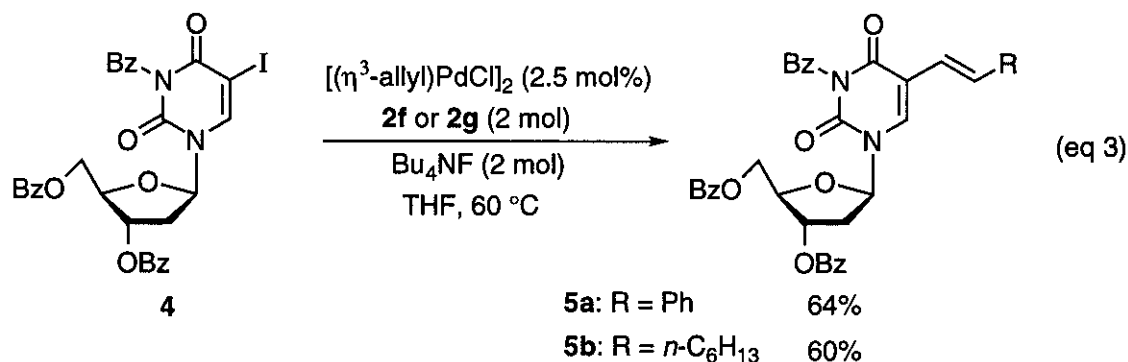
run	substrate	R ₃ Si-R	time(h)	yield(%)
1	1a	Me ₂ FSi-CH=CH-Ph (2a)	16	3a (69)
2		Me ₂ FSi-CH=CH- <i>n</i> -C ₆ H ₁₃ (2b)	14	3b (70)
3		Me ₂ FSi-C(Pr)=CH-Pr (2c)	11	3c (63)
4 ^{a)}		Me ₂ ClSi-CH=CH ₂ (2d)	14	3d (82)
5 ^{a)}		Me ₂ ClSi-CH=CH-Ph (2e)	14	3a (70)
6	1b	MeF ₂ Si-CH=CH-Ph (2f)	48	3f (58)
7		MeF ₂ Si-CH=CH- <i>n</i> -C ₆ H ₁₃ (2g)	44	3g (53) ^{b)}
8	1c	2a	72	no reaction

a) TBAF (4 eq.) was used. b) Regio isomer (**3g'**) was also obtained in 2 : 1 ratio of **3g** : **3g'**.



We next studied the reaction of 3,3',5'-tribenzoyl-5-iodo-2'-deoxyuridine (**4**) with alkenylfluorodimethylsilanes (**2a** or **2b**), but all attempts failed. However, alkenyl(difluoro)methylsilanes (**2f** or **2g**) was found to couple with **4** to give **5a** or **5b** (eq 3). Worthy to note is that non-protected 5-iodo-2'-deoxyuridine (**6**) also reacted with **2f** or **2g** in *N,N*-dimethylformamide (DMF) (eq 4). The reaction in

THF was very slow due to low solubility of the substrate. Both **2f** and **2g** reacted with **6**, giving undesirable regioisomers (**7a'**) and (**7b'**) in fair amounts.



CONCLUSION

We found that 5-iodouracil derivatives reacted with alkenylfluorosilanes and alkenylchlorosilanes in the presence of a Pd catalyst and TBAF. It should be noted that the cross-coupling reaction of non-protected 5-iodo-2'-deoxyuridine was achieved for the first time with alkenyl(difluoro)methylsilanes. The substituent at Si atom was found to be extremely important for the success of the cross-coupling: Alkenyl(difluoro)methylsilanes are potent agent for the cross-coupling of 5-iodouracil derivatives.

EXPERIMENTAL SECTION

THF and ether were distilled from benzophenone/Na prior to use. Dichloromethane, DMF, DMSO, and hexane were distilled from CaH₂ and stored over Molecular Sieves 4A. All the reactions were carried out under an Ar atmosphere in a flame dried glass ware unless otherwise noted. Flash column chromatography

was performed using Merck Kieselgel (230-400 mesh). All the temperatures were uncorrected. Melting points were measured with a Yanagimoto Micro Melting Point apparatus. Ir spectra were recorded on a Hitachi Ir 260-10 or JASCO FT-IR 3A spectrometers. ^1H Nmr spectra were measured with a Bruker AC-200 (200.1 MHz) or JEOL EX-400 (400.1 MHz) spectrometers; ^{13}C nmr spectra with a Bruker AC-200 (50.3 MHz) or JEOL EX-400 (100.4 MHz). Mass spectra were measured by electron ionization method with a Hitachi M-80 spectrometer. Substrates 1-benzyl-5-iodouracil (**1b**)⁹ and 3,3',5'-tribenzoyl-5-iodo-2'-deoxyuridine (**4**)^{4c} were prepared according to the literature.

5-Iodo-1,3-dimethyluracil (1a)

Sodium hydride (60% oil dispersion, 0.24 g, 6.0 mmol) was washed with dry hexane for 3 times and suspended in DMF (7 ml). A solution of 5-iodouracil (0.48 g, 2.0 mmol) in DMF (5 ml) was added dropwise to NaH suspension, and the resultant mixture was stirred for 1 h at room temperature. Methyl iodide (0.37 ml, 6.0 mmol) was added dropwise to the mixture and stirring was continued for additional 30 min. The reaction was quenched with H_2O (20 ml) and extracted with dichloromethane for 2 times. Combined organic layer was washed with H_2O and dried over Na_2SO_4 . After filtration, the filtrate was concentrated to give **1a** (0.47 g) as pale yellow powder. Pure **1a** (0.40 g) was obtained in 76% yield by recrystallization from ethyl acetate.

Cross-coupling reaction of 1a-c and 4: A General Procedure.

To a solution of a substrate (0.20 mmol) and $[(\eta^3\text{-allyl})\text{PdCl}]_2$ (1.8 mg, 5.0 μmol) in THF (1 ml) were added an alkenylsilane (0.40 mmol) and TBAF (1 M THF sol., 0.40 ml, 0.40 mmol) at room temperature in a glass tube. The reaction tube was sealed and heated at 60 $^\circ\text{C}$ until the substrate was consumed. THF was removed in vacuo, and the residue was purified by a short column chromatography on a silica gel (Wakogel C-200) to give a crude coupled product. Further purification was performed by flash column chromatography.

1,3-Dimethyl-5-[(E)-2-phenylethenyl]uracil (3a)

Purification by short column (hexane-ethyl acetate 1 : 1) followed by flash chromatography (hexane-ethyl acetate 2 : 1) provided **3a** as a colorless crystals. mp 149-152 $^\circ\text{C}$. ^1H Nmr (CDCl_3) δ 3.42 (s, 3 H), 3.47 (s, 3 H), 6.84 (dd, $J = 1.0, 16.0$ Hz, 1 H), 7.20-7.49 (m, 7 H). ^{13}C Nmr (CDCl_3) δ 28.12, 37.19, 111.47, 119.92, 126.36, 127.64, 127.80, 128.63, 129.32, 137.31, 139.20, 151.03, 162.24. Ir (KBr) 3058, 1694, 1657, 1643, 1622, 1597, 1574, 1484, 1454, 1089, 973, 962, 792, 745, 687 cm^{-1} . Ms (70

eV, rel intensity) m/z 242 (M^+ , 19), 157 (23), 115 (34), 108 (53), 77 (6.8), 42 (100). Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.39; H, 5.78; N, 11.54.

1,3-Dimethyl-5-[(E)-1-octenyl]uracil (3b)

Purification by short column (hexane-ethyl acetate 1 : 1) followed by flash chromatography (hexane-ethyl acetate 2 : 1) provided **3b** as a colorless viscous oil. R_f 0.29 (hexane-ethyl acetate 2 : 1) 1H Nmr ($CDCl_3$) δ 0.88 (m, 3 H), 1.26 (m, 6 H), 1.38 (m, 2 H), 2.13 (dt, $J = 7.0, 7.0$ Hz, 2 H), 3.35 (s, 3 H), 3.40 (s, 3 H), 6.10 (d, $J = 16.0$ Hz, 1 H), 6.33 (dt, $J = 16.0, 7.0$ Hz, 1 H), 7.12 (s, 1 H). ^{13}C Nmr ($CDCl_3$) δ 14.03, 22.54, 27.95, 28.83, 29.19, 31.66, 33.37, 111.82, 120.64, 132.43, 137.92, 151.19, 162.42. Ir (neat) 2920, 2850, 1705, 1655, 1460, 1350, 1090, 970, 915, 755, 730 cm^{-1} . Ms (70 eV, rel intensity) m/z 251 ($M^+ + 1$, 14), 222 (3.0), 180 (28), 166 (4.2), 154 (37), 123 (12), 81 (14), 42 (32), 32 (100).

1,3-Dimethyl-5-(1-propyl-1-pentenyl)uracil (3c)

Purification by short column (hexane-ethyl acetate 1 : 1) followed by flash chromatography (hexane-ethyl acetate 3 : 1) provided **3c** as a colorless viscous oil. R_f 0.30 (hexane-ethyl acetate 3 : 1) 1H Nmr ($CDCl_3$) δ 0.87 (t, $J = 7.5$ Hz, 3 H), 0.94 (t, $J = 7.0$ Hz, 3 H), 1.22-1.52 (m, 4 H), 2.11 (q, $J = 7.0$ Hz, 2 H), 2.41 (br t, $J = 7.5$ Hz, 2 H), 3.35 (s, 3 H), 3.40 (s, 3 H), 5.46 (t, $J = 7.0$ Hz, 1 H), 6.98 (s, 1 H). ^{13}C Nmr ($CDCl_3$) δ 30.04, 30.86, 36.79, 117.42, 131.59, 134.68, 139.14, 151.73, 162.64. Ir (neat) 3005, 2940, 2850, 1680, 1630, 1440, 1320, 1250, 1215, 1180, 1065, 765, 715, 680 cm^{-1} . Ms (70 eV, rel intensity) m/z 250 (M^+ , 47), 221 (54), 207 (95), 193 (45), 153 (56), 96 (22), 42 (100). Anal. Calcd for $C_{14}H_{22}N_2O_2$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.05; H, 9.01; N, 11.28.

1-Benzyl-5-[(E)-2-phenylethenyl]uracil (3f)

Purification by short column (CH_2Cl_2 -ethyl acetate 5 : 1) followed by flash chromatography (CH_2Cl_2 -ethyl acetate 8 : 1) provided **3f** as a colorless crystals. mp 189-192 $^{\circ}C$. 1H Nmr ($CDCl_3$) δ 4.97 (s, 2 H), 6.72 (d, $J = 16.5$ Hz, 1 H), 7.25-7.44 (m, 12 H), 8.85 (br s, 1 H). ^{13}C Nmr ($CDCl_3$) δ 51.40, 112.97, 119.21, 126.41, 127.77, 128.01, 128.61, 129.19, 130.31, 135.06, 137.13, 140.02, 150.08, 162.06. Ms (10 eV, rel intensity) m/z 304 (M^+ , 27), 213 (2.5), 128 (2.3), 115 (7.9), 91 (100), 65 (10). Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30. Found: C, 74.91; H 5.20.

1-Benzyl-5-[(E)-1-octenyl]uracil (3g)

Chromatography through a short column (CH_2Cl_2 -ethyl acetate 5 : 1) followed by flash column chromatography (CH_2Cl_2 -ethyl acetate 10 : 1) provided an inseparable mixture of **3g** and **3g'** as a pale yellow viscous oil. R_f 0.26 (CH_2Cl_2 -ethyl acetate 10 : 1) 1H Nmr ($CDCl_3$) δ 0.87 (m, 3 H), 1.27 (m, 6

H), 1.40 (m, 2 H), 2.11 (dt, $J = 6.5, 6.5$ Hz, 2 H), 4.93 (s, 2 H), 6.02 (dd, $J = 0.5, 16.0$ Hz, 1 H), 6.39 (td, $J = 6.5, 16.0$ Hz, 1 H), 7.10 (s, 1 H), 7.26-7.43 (m, 5 H), 8.73 (br s, 1 H). Ms (70 eV, rel intensity) m/z 312 (M^+ , 20), 255 (9.3), 243 (7.5), 229 (17), 221 (12), 151 (22), 91 (100), 65 (8.3).

3,3',5'-Tribenzoyl-5-[(E)-2-phenylethenyl]-2'-deoxyuridine (5a)

Purification by short column chromatography (hexane-ethyl acetate 1 : 1) followed by flash column chromatography (hexane-ethyl acetate 2 : 1) provided **5a** as a colorless amorphous solid. R_f 0.30 (hexane-ethyl acetate 3 : 1) 1H Nmr ($CDCl_3$) δ 2.44 (ddd, $J = 6.5, 9.0, 14.0$ Hz, 1 H), 2.85 (ddd, $J = 1.5, 5.5, 14.0$ Hz, 1 H), 4.62 (m, 1 H), 4.77 (dd, $J = 4.0, 12.5$ Hz, 1 H), 4.87 (dd, $J = 3.0, 12.5$ Hz, 1 H), 5.69 (brd, $J = 6.5$ Hz, 1 H), 6.48 (d, $J = 16.5$ Hz, 1 H), 6.49 (dd, $J = 5.5, 9.0$ Hz, 1 H), 7.14-7.71 (m, 15 H), 7.78 (s, 1 H), 7.92-8.12 (m, 6 H). ^{13}C Nmr ($CDCl_3$) δ 38.83, 64.69, 75.24, 83.51, 86.03, 113.40, 119.23, 126.76, 128.08, 128.61, 128.76, 128.90, 129.14, 129.34, 129.52, 129.78, 130.05, 130.75, 131.50, 131.66, 134.08, 134.17, 135.10, 135.49, 137.24, 148.58, 161.24, 166.26, 166.34, 168.77. Ir (neat) 3060, 1745, 1710, 1660, 1600, 1450, 1375, 1315, 1270, 1175, 1110, 1100, 1075, 1025, 735, 710, 690 cm^{-1} . Ms (10 eV, rel intensity) m/z 642 (M^+ , 0.9), 422 (1.0), 318 (18), 214 (17), 105 (90), 81 (100). Anal. Calcd for $C_{38}H_{30}N_2O_8$: C, 71.02; H, 4.71; N, 4.36. Found: C, 70.72; H, 4.61; N, 4.33.

3,3',5'-Tribenzoyl-5-[(E)-1-octenyl]-2'-deoxyuridine (5b)

Purification by short column chromatography (hexane-ethyl acetate 1 : 1) followed by flash column chromatography (hexane-ethyl acetate 3 : 1) provided **5b** as a pale yellow amorphous solid. R_f 0.30 (hexane-ethyl acetate 3 : 1) 1H Nmr ($CDCl_3$) δ 0.88 (m, 3 H), 1.25 (m, 8 H), 1.92 (m, 2 H), 2.41 (ddd, $J = 6.5, 9.0, 14.0$ Hz, 1 H), 2.79 (ddd, $J = 1.5, 5.5, 14.0$ Hz, 1 H), 4.58 (m, 1 H), 4.72 (dd, $J = 3.5, 12.5$ Hz, 1 H), 4.83 (dd, $J = 3.0, 12.5$ Hz, 1 H), 5.68 (br d, $J = 6.0$ Hz, 1 H), 5.74 (d, $J = 15.5$ Hz, 1 H), 6.35 (dt, $J = 15.5, 6.5$ Hz, 1 H), 6.47 (dd, $J = 5.5, 8.5$ Hz, 1 H), 7.41-7.69 (m, 10 H), 7.90-8.10 (m, 6 H). ^{13}C Nmr ($CDCl_3$) δ 14.05, 22.52, 28.87, 28.94, 31.63, 33.48, 38.25, 64.33, 74.90, 82.93, 85.39, 113.49, 119.67, 128.54, 128.66, 128.79, 128.87, 129.12, 129.18, 129.49, 129.71, 130.36, 131.44, 133.29, 133.69, 134.46, 135.03, 148.45, 161.03, 165.90, 165.94, 168.61. Ir (neat) 2930, 1750, 1720, 1665, 1600, 1450, 1315, 1270, 1105, 735, 710, 685 cm^{-1} . Ms (10 eV, rel intensity) m/z 326 ($M^+ - 324$, 12), 222 (1.5), 122 (2.3), 105 (50), 81 (100). Anal. Calcd for $C_{38}H_{38}N_2O_8$: C, 70.14; H, 5.89; N, 4.30. Found: C, 70.04; H, 6.01; N, 4.29.

Cross-coupling of 1a with alkenylchlorodimethylsilanes (2d) and (2e).

To a solution of **1a** (53.2 mg, 0.20 mmol) and $[(\eta^3\text{-allyl})\text{PdCl}]_2$ (1.8 mg, 5.0 μmol) in THF (1 ml) was added TBAF (1 M THF sol., 0.80 ml, 0.80 mmol) at room temperature in a glass tube. Then **2d** or **2e** (0.40 mmol) was added dropwise to this solution, the tube was sealed, and the reaction mixture was heated at 60 °C for 14 h. Workup and a short chromatography on a silica gel (Wakogel C-200, hexane-ethyl acetate 1:1) gave a pale yellow solid, which was further purified by flash column chromatography (hexane-ethyl acetate 1 : 1) to provide **3a** (33.9 mg, 70% yield) or **3d** (27.1 mg, 82% yield) respectively.

5-Ethenyl-1,3-dimethyluracil (3d)

Colorless crystal. mp 72-75 °C. ^1H Nmr (CDCl_3) δ 3.38 (s, 1 H), 3.44 (s, 3 H), 5.22 (dd, $J = 1.5, 11.5$ Hz, 1 H), 5.90 (dd, $J = 1.5, 17.5$ Hz, 1 H), 6.46 (ddd, $J = 0.5, 11.5, 17.5$ Hz, 1 H), 7.22 (s, 1 H). ^{13}C Nmr (CDCl_3) δ 27.96, 37.05, 111.53, 115.00, 128.12, 139.39, 151.17, 162.18. Ir (KBr) 1709, 1697, 1662, 1630, 1509, 1485, 1454, 1364, 1344, 902, 785, 756 cm^{-1} . Ms (70 eV, rel intensity) m/z 166 (M^+ , 100), 135 (42), 93 (7.1), 81 (64), 57 (22). Anal. Calcd for $\text{C}_8\text{H}_{10}\text{N}_2\text{O}_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.71; H, 6.18; N, 16.86.

Cross-coupling reaction of 6 with 2f or 2g.

2f or **2g** (0.40 mmol) and TBAF (1 M THF sol., 0.40 ml, 0.40 mmol) were added to a solution of **6** (70 mg, 0.20 mmol) and $[(\eta^3\text{-allyl})\text{PdCl}]_2$ (1.8 mg, 5.0 μmol) in DMF (1 ml) and the reaction mixture was heated at 60 °C until all of **6** was consumed. Removing all solvents in vacuo followed by a short column chromatography (Wakogel C-200, CH_2Cl_2 -MeOH 5 : 1) gave a crude brown oil, which was further purified by flash column chromatography (CH_2Cl_2 -MeOH 9 : 1) to give a desired and undesired isomer as inseparable mixture.

5-[(E)-2-Phenylethenyl]-2'-deoxyuridine (7a)

Pale yellow amorphous solid. R_f 0.16 (CH_2Cl_2 -MeOH 10 : 1). Following spectrum was assigned to **7a** and **7a'** respectively: **7a** ^1H Nmr (acetone- d_6) δ 2.35 (m, 2 H), 3.86 (dd, $J = 3.0, 3.0$ Hz, 2 H), 3.99 (dt, $J = 3.0, 3.0$ Hz, 1 H), 4.56 (m, 1 H), 6.34 (t, $J = 6.5$ Hz, 1 H), 6.89 (dd, $J = 0.5, 16.5$ Hz, 1 H), 7.15-7.48 (m, 5 H), 7.50 (d, $J = 16.5$ Hz, 1 H), 8.35 (s, 1 H). Protons of NH and OH could not be detected. **7a'** ^1H Nmr (acetone- d_6) δ 2.37 (m, 2 H), 3.62 (d, $J = 3.0$ Hz, 2 H), 3.93 (m, 1 H), 4.53 (m, 1 H), 5.45 (d, $J = 1.5$ Hz, 1 H), 5.66 (d, $J = 1.5$ Hz, 1 H), 6.32 (t, $J = 6.0$ Hz, 1 H), 7.15-7.48 (m, 5 H), 7.93 (s, 1 H). The ratio was determined by vinyl proton integration: **7a** (δ 6.89) : **7a'** (δ 5.45) = 5 : 1. Ms (10 eV, rel intensity) m/z 330 (M^+ , 1.2), 215 (14), 214 (100), 143 (65), 116 (10), 73 (12).

5-[(E)-1-Octenyl]-2'-deoxyuridine (7b)

Pale yellow viscous oil. R_f 0.33 (CH_2Cl_2 -MeOH 9 : 1). Following spectrum was assigned to **7b** and **7b'** respectively: **7b** ^1H Nmr (acetone- d_6) δ 0.88 (m, 3 H), 1.22-1.50 (m, 8 H), 2.11 (m, 2 H), 2.29 (m, 2 H), 2.81 (br s, 1 H), 3.31 (br s, 1 H), 3.82 (br d, $J = 3.0$ Hz, 2 H), 3.95 (dd, $J = 3.0, 6.0$ Hz, 1 H), 4.53 (m, 1 H), 6.09 (br d, $J = 16.0$ Hz, 1 H), 6.32 (dd, $J = 7.0, 7.0$ Hz, 1 H), 6.51 (dt, $J = 6.5, 16.0$ Hz, 1 H), 8.09 (s, 1 H), 9.94 (br s, 1 H). **7b'** ^1H Nmr (acetone- d_6) δ 0.88 (m, 3 H), 1.22-1.50 (m, 8 H), 2.29 (m, 2 H), 2.42 (t, $J = 7.0$ Hz, 2 H), 2.81 (br s, 1 H), 3.31 (br s, 1 H), 3.82 (m, 2 H), 3.97 (m, 1 H), 4.53 (m, 1 H), 5.01 (m, 1 H), 5.53 (d, $J = 2.0$ Hz, 1 H), 8.05 (s, 1 H), 9.94 (br s, 1 H). The ratio was determined by vinyl proton integration: **7b** (δ 6.51) : **7b'** (δ 5.53) = 2 : 1. Ms (10 eV, rel intensity) m/z 338 (M^+ , 1.4), 223 (13), 222 (67), 179 (6.2), 152 (51), 138 (42), 117 (100), 99 (41), 73 (29).

ACKNOWLEDGMENT

The present work was partially supported by Grant-in-Aid from Ciba-Geigy Foundation (Japan) for the Promotion of Science.

REFERENCES

1. a) E. De Clercq, C. Desgranges, P. Herdewijn, I. S. Sim, A. S. Jones, M. J. McLean, and R. T. Walker, *J. Med. Chem.*, **1986**, 29, 213. b) M. E. Perlman, K. A. Watanabe, R. F. Schinazi, and J. J. Fox, *J. Med. Chem.*, **1985**, 28, 741. c) L. A. Al-Razzak, D. S. Schwepler, C. J. Decedue, J. Balzarini, E. De Clercq, and M. P. Mertes, *J. Med. Chem.*, **1987**, 30, 409. d) T-S. Lin, J-Y. Guo, R. F. Schinazi, C. K. Chu, J. N. Xiang, and W. H. Prusoff, *J. Med. Chem.*, **1988**, 31, 336.
2. a) R. F. Heck, "Palladium Reagents in Organic Syntheses", Academic Press, New York, 1985. b) D. W. Knight, "Comprehensive Organic Synthesis," Ed by B. M. Trost, Pergamon Press, **1991**, Vol. 3, p. 481.
3. D. E. Bergstrom, *Nucleosides and Nucleotides*, **1982**, 1, 1 and references cited therein.
4. a) G. T. Crisp, *Synth. Commun.*, **1989**, 19, 2117. G. T. Crisp and V. Macolino, *Synth. Commun.*, **1990**, 20, 413. b) G. T. Crisp and B. L. Flynn, *Tetrahedron Lett.*, **1990**, 31, 1347. c) P. Herdewijn, L. Kerremans, W. F. Vandendriessche, and A. Van Aerschot, *Tetrahedron Lett.*, **1991**, 32, 4397. d) V. Farina and S. I. Hauck, *Synlett*, **1991**, 157.

5. a) K.Hirota, Y. Kitade, Y. Kanbe, and Y. Maki, *J. Org. Chem.*, **1992**, *57*, 5286. b) K. Hirota, Y. Kitade, Y. Kanbe, Y. Isobe, and Y. Maki, *Synthesis*, **1993**, 213.
6. a) Y. Hatanaka and T. Hiyama, *Synlett*, **1991**, 845. b) T. Hiyama and Y. Hatanaka, *Pure Appl. Chem.*, **1994**, *66*, 1471 and references cited therein.
7. K. Takahashi, T. Minami, Y. Ohara, and T. Hiyama, *Tetrahedron Lett.*, **1993**, *34*, 8263.
8. Y. Hatanaka and T. Hiyama, *J. Org. Chem.*, **1989**, *54*, 268.
9. I. Ishikawa, T. Itoh, R. G. Melik-Ohanjanian, H. Takayanagi, Y. Mizuno, and H. Ogura, *Heterocycles*, **1990**, *31*, 1641.

Received, 30th March, 1995