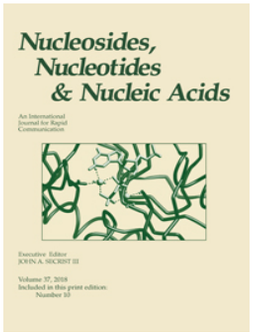


Nucleosides, Nucleotides and Nucleic Acids

ISSN: 1525-7770 (Print) 1532-2335 (Online) Journal homepage: https://www.tandfonline.com/loi/lncn20

An alternative method for the synthesis of 2'-halogeno-1',2'-unsaturated uridine derivatives through *syn*-elimination of pivalic acid of 2'-halogeno- 2'-deoxy-1'-pivaloyloxyuracil nucleoside: preparation of its 2'-*C*-branched nucleosides

Kazuhiro Haraguchi, Eisen Gen, Hiroki Kumamoto, Yoshiharu Itoh & Hiromichi Tanaka

To cite this article: Kazuhiro Haraguchi, Eisen Gen, Hiroki Kumamoto, Yoshiharu Itoh & Hiromichi Tanaka (2019): An alternative method for the synthesis of 2′-halogeno-1′,2′-unsaturated uridine derivatives through *syn*-elimination of pivalic acid of 2′-halogeno- 2′-deoxy-1′-pivaloyloxyuracil nucleoside: preparation of its 2′-*C*-branched nucleosides, Nucleosides, Nucleotides and Nucleic Acids, DOI: 10.1080/15257770.2019.1641724

To link to this article: https://doi.org/10.1080/15257770.2019.1641724

Published online: 20 Aug 2019.

NUCLEOSIDES, NUCLEOTIDES AND NUCLEIC ACIDS
https://doi.org/10.1080/15257770.2019.1641724

An alternative method for the synthesis of 2′-halogeno-1′,2′-unsaturated uridine derivatives through *syn*-elimination of pivalic acid of 2′-halogeno-2′-deoxy-1′-pivaloyloxyuracil nucleoside: preparation of its 2′-*C*-branched nucleosides

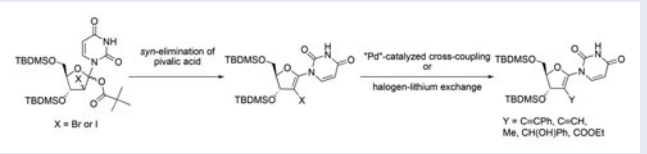
Kazuhiro Haraguchi[a], Eisen Gen[b], Hiroki Kumamoto[a], Yoshiharu Itoh[b], and Hiromichi Tanaka[b]

[a]Department of Pharmaceutical Sciences, Nihon Pharmaceutical University, Saitama, Japan; [b]School of Pharmacy, Showa University, Tokyo, Japan

ABSTRACT

An alternative method for the preparation of 2′-bromo- (**5b**) and 2′-iodo- (**5c**) 1′,2′-unsaturated uracil nucleosides has been developed. The protocol was on the basis of the *syn*-elimination of pivalic acid from 2′-bromo-(**7a,b**) and 2′-iodo-(**9a,b**) 1′-pivaloyloxy-2′-deoxyuridine derivatives, which were derived from the halo-pivaloyloxylation of 3′,5′-bis-*O*-TBDMS-1′, 2′-unsaturated uridine **1**. Compounds **5b** and **5c** were shown to serve as versatile synthons for the respective 2′-*C*-branched 1′,2′-unsaturated uracil nucleosides, through palladium-catalyzed cross-coupling or halogen-lithium exchange reactions.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 30 May 2019
Accepted 5 July 2019

KEYWORDS
Nucleoside; unsaturated sugar; electrophilic addition; syn-elimination; Pd-catalyst; cross-coupling; halogen–lithium exchange reaction

1. Introduction

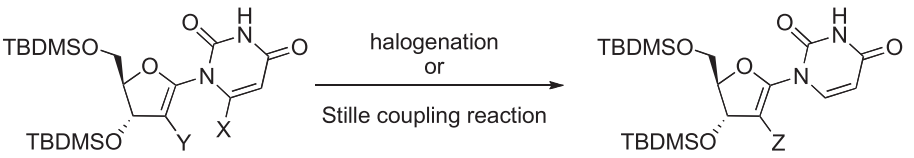
Nucleoside analogs are recognized as an important class of biologically active compounds, especially as antiviral and antitumor agents.[1–21] Among sugar-modified nucleosides, nucleosides having an unsaturated sugar moiety have been known for a long time. We have demonstrated through a series of publications that this class of compounds are useful substrates for constructing C–C bonds in the sugar portion.[22,23] Among the possible four types of unsaturated-sugar nucleosides, the 1′,2′-

CONTACT Kazuhiro Haraguchi harakazu@nichiyaku.ac.jp Department of Pharmaceutical Sciences, Nihon Pharmaceutical University, 10281 Komuro, Inamachi, Kita-adachi-gun, Saitama 362-0806, Japan.

unsaturated derivatives (**1**) have attracted scant attention presumably due to their reported instability, during deprotection to undergo further elimination which results in the formation of furan derovative **(2a)** (Figure 1).

In this context, we have reported a method for introducing substituents at the 2′-position of **1**, which furnished the first examples of nucleoside analogs (Scheme 1).[24,25] Thus, when 6-tributylstannylated **3**, which could be prepared through LDA-lithiation of **1** followed by quenching the 6-lithiated species with Bu_3SnCl, was treated with LTMP, anionic stannyl migration occurred to yield 2′-stannylated product **4**. Reaction of **4** with I_2, *N*-bromosuccinimide (NBS) or *N*-chlorosuccinimide (NIS) gave the respective 2′-halogenated **5a-c**. Compounds **4** and **5c** could be utilized for introducing carbon-substituents to the 2′-positon by means of Stille coupling to furnish **6a–d**. This study demonstrated that the bulkiness of the 2′-substituent led to conformational change around the N1–C1′ pivot bond avoiding sterically unfavorable coplanarity which render **5a–c** and **6a–d** more stable. This assumption has been supported by the UV absorption maximum of **5a–c** and **6a–d** in MeOH appearing at 251–255 nm while a longer wavelength of 276 nm was measured in **1**. In fact, desilylation of **5a–c** and **6a–d** caused no further elimination and furnished the hitherto unknown free nucleosides without the formation of the furan derivatives. These compounds would be useful precursors for novel nucleoside derivatives by manipulation of the 1′,2′-unsaturated bond.

The above chemistry stimulated us to develop another synthetic method, which would be applicable to the respective adenine nucleoside. However, the above strategy is not applicable to the adenine nucleoside. Therefore, we have intended to develop an alternative method, which provides the both of 2′-halogeno-1′,2′-unsaturated pyrimidine and purine nucleosides In this article, we will describe the novel synthetic method on the basis of *syn*-elimination of pivalic acid of 2′-halogeno-1′-pivaloyloxyuracil nucleosides, which would be applicable to the respective adenine nucleoside.[26]



3: X = $SnBu_3$, Y = H
4: X = H, Y = $SnBu_3$

5a: Z = Cl, **5b**: Z = Br, **5c**: Z = I
6a: Z = Ph, **6b**: Z = CH_2Ph,
6c: Z = Me, **6d**: $CH{=}CH_2$

Scheme 1. Previous protocol for the synthesis of **5a–c** and **6a-d** from **4** through anionic stannyl migration of **3.**

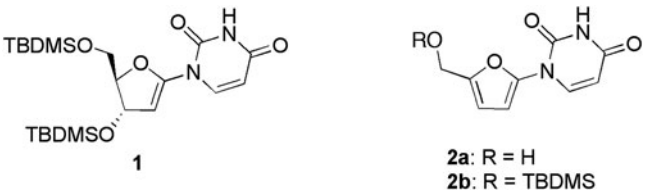
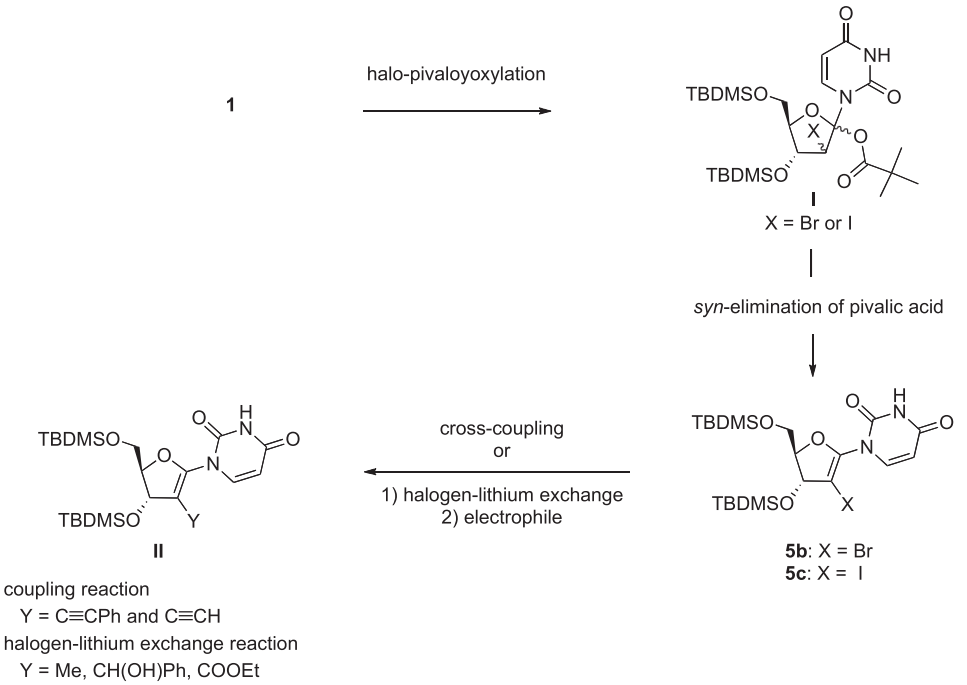


Figure 1. Structures of **1** and **2**.



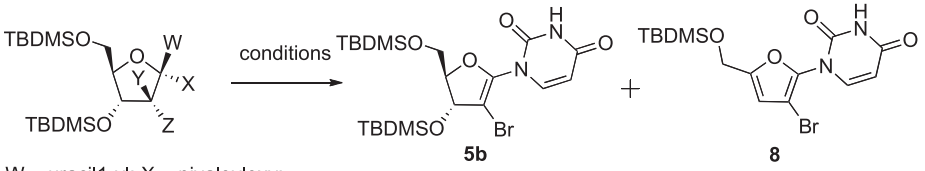
Scheme 2. Synthetic plan for synthesis of **5b,c** and **II**.

2. Results and discussion

2.1. Chemistry

Our synthetic plan is outlined in Scheme 2. The target molecule **III** was intended to be synthesized from **II** through coupling reaction and halogen-lithium exchange reaction.[27,28] 2′-Halogenated **II** would be obtained from **I** through *syn*-β-elimination of the pivalic acid derivative of **I**. This plan was motivated by the fact that **5b** was formed as a by-product in the reaction of **I** and $Al(CH_2CHMe_2)_3$.[29,30] The substrate **I** is accessible from electrophilic halo-pivaloyloxylation to **1**.[30]

Initially, synthesis of 2′-bromo-1′,2′-unsaturated uridine derivative **5b** was examined (Scheme 3 and Table 1). The substrates **7a** and **7b** were prepared in 91% yield in a ratio of 4.9:1, according to the published procedure ($Me_3COOH/Et_3N/NBS/Et_2O$).[29,30] To investigate whether or not the desired *syn*-elimination proceed, a solution of **7a**,**b** in toluene was heated



7a: W = uracil1-yl; X = pivaloyloxy; Y = Br, Z = H
7b: W = pivaloyloxy; X = uracil1-yl; Y = H, Z = Br

Scheme 3. Synthesis of **5b** from **7a,b** by *syn*-elimination of pivalic acid.

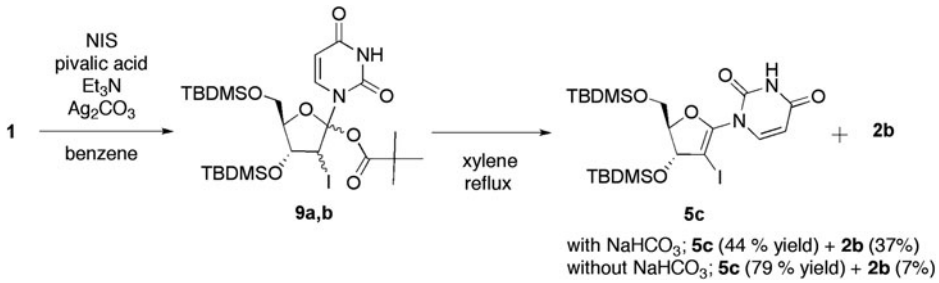
Table 1. Synthesis of 2′-bromo-1′,2′-unsaturated uracil nucleoside **5b**.

					Isolated yields (%)	
Entry	Solvent	Base	Temp (°C)	Time (h)	5b	8
1	toluene	–	110	7	32	27
2	xylene	–	140	2	78	5
3	xylene	$NaHCO_3$	140	4	98	–

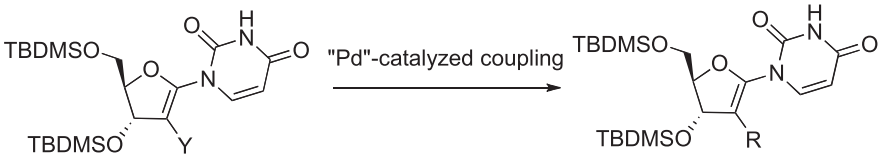
under reflux conditions for 3 h, in which **5b** was obtained in 32% isolated yield (entry 1, Table 1). In this case, the furan derivative **8** was formed in 27% yield. The reaction temperature was elevated to 140 °C by using xylene as a solvent, the *syn*-elimination was completed in 1 h and **5b** could be obtained in 78% yield along with 5% of **8** (entry 2). One would readily assume that the formation of **8** is promoted by concomitantly formed pivalic acid. To trap pivalic acid, the reaction was carried out in the presence of sodium bicarbonate, **5b** then being obtained in 98% yield without the formation of **5b** (entry 3).

We have previously demonstrated that 2′-iodo-1′,2′-unsaturated **5c** was stable and a highly reactive substrate for palladium-catalyzed cross-coupling reaction.[25] Therefore, the above-mentioned *syn*-elimination protocol was examined for the synthesis of **5c** (Scheme 4). Unexpectedly, iodo-pivaloyloxylation of **1** ($Me_3COOH/Et_3N/NIS/Et_2O$) resulted in the formation of complex mixture. When the above reaction was performed in benzene, the desired **9a,b** were obtained in 45% yield as a diasteromeric mixture along with the furan **2b** (22%). It was found that silver carbonate was effective for suppressing the formation of **2b**, resulting in the formation of **9a,b** (67% yield). Next, when a diastereomeric mixture of **9a,b** was heated in xylene in the presence of $NaHCO_3$, **5c** was obtained in 44% yield along with **2b** (37% yield). On the other hand, when the reaction was performed in the absence of $NaHCO_3$, the undesired formation of **2b** was diminished to 7% yield and **5c**[25] was could be obtained in 79% yield.

With **5b** and **5c** in hand, introduction of carbon-substituents to the 2′-position was examined (Scheme 5 and Table 2)[27,28] As shown in



Scheme 4. Synthesis of 2′-iodo-1′,2′-unsaturated uridine derivative **5c** by *syn*-elimination of pivalic acid of **9a,b.**



5b: Y = Br
5c: Y = I

10: R = C≡CPh
11: R = C≡CH

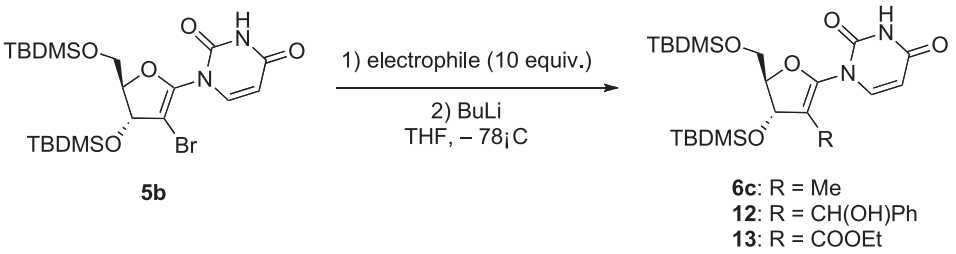
Scheme 5. Cross-coupling of **5b** or **5c** leading to **10** and **11**.

Table 2. Palladium-catalyzed coupling reaction of **5b** or **5c**.

			Isolated yields (%)	
Entry	Substrate	Reagents (equiv) and conditions	**10** or **11**	5b
1	**5b**	PhC≡CH (4), $(Ph_3P)_2PdCl_2$ (0.3), CuI (0.3), Et_3N, THF, 80 °C, 15 h	**10** (9)	85
2	**5b**	PhC≡C$SnBu_3$ (4), $(Ph_3P)_4Pd$ (0.3), DMF, 60 °C, 15 h	**10** (10)	48
3	**5c**	PhC≡C$SnBu_3$ (2), $(Ph_3P)_4Pd$ (0.1), MF, 100 °C, 10 min	**10** (58)	–
4	**5c**	HC≡C$SnBu_3$ (2), $(Ph_3P)_4Pd$ (0.1), DMF, 100 °C, 10 min	**11** (84)	–

entry 1, Sonogashira coupling of **5b** with ethynylbenzene was carried out in the presence of $(Ph_3P)_2PdCl_2$ and CuI in THF. This gave the target 2′-*C*-phenylethynyl derivative **10** in 9% yield with the recovery of **5b** (85% yield). The inertness of **5b** was observed in Stille coupling (**10**; 10%, **5b**; 48%) (entry 2, Table 2). The above results prompted us to utilize 2′-iodo derivative **5c** as a substrate in Stille coupling (entries 3–4, Table 2). The reaction of **5c** with PhC≡C$SnBu_3$ catalyzed by $(Ph_3P)_4Pd$ was completed within 10 min to give the target **10** in 58% yield (entry 3, Table 3). The respective 2′-*C*-ethynyl derivatives (**11**) was obtained in 84% yield (entry 4, Table 2).

Next, we carried out the halogen-lithium exchange reaction of the 2′-bromo derivative **5b** (Scheme 6 and Table 3). Reaction of **5b** with 3 equiv. of BuLi in THF below −70 °C followed by immediate addition of MeI gave 2′-*C*-methyl-1′,2′-unsaturated uridine derivative **6c** in 27% yield along with **1** (40% yield) (entry 1, Table 3). This observation suggests that the incipiently formed vinyl lithium species is highly basic and thus is protonated before reacting with the added electrophile. We finally found that an



Scheme 6. Halogen–lithium exchange reaction (*in situ* trapping) of **5b** to lead to **6C, 12** and **13**.

Table 3. Halogen–lithium exchange reaction (*in-situ* trapping) of **5b** to lead to **6c**, **12** and**13**.

			Isolated yields (%)	
Entry	Electrophile	BuLi (equiv)	**6c**, **12** or **13**	1
1*	MeI	3	**6c** (27)	40
2	MeI	2	**6c** (76)	11
3	PhCHO	9	**12** (82)	6
4	ClCOOEt	9	**13** (65)	18

*Methyl iodide was added immediately after halogen–lithium exchange reaction.

"in-situ" trapping protocol, wherein a mixture of **5b** and MeI (10 equiv.) is reacted with BuLi (3 equiv), furnished a good yield of the desired product **6c** (76% yield) (entry 2, Table 3).[27,28] This result suggests that the halogen-lithium exchange reaction is an earlier event than the anticipated deprotonation from N^3H. To examine the applicability of this approach, benzaldehyde was reacted (entry 3, Table 3). We found that 9 equiv. of BuLi was necessary to assure complete disappearance of the starting material and **12** was isolated in 82% yield. Diastereomeric ratio of **12** was determined to be ca 7:1 by inspecting the integrated ^1H NMR spectrum. In this reaction, 6% yield of **1** was inevitably formed (entry 3, Table 3). Finally, 2′-*C*-ethoxycarbonyl derivative **13** was synthesized in 65% yield (**1**; 18% yield) by reacting with $ClCO_2Et$ (entry 4, Table 3) under the same reaction conditions as for **12**.

3. Conclusions

In this study, an alternative method for the synthesis of 2′-bromo (**5b**)- and 2′-iodo-(**5c**) 1′,2′-unsaturated uracil nucleosides has been developed by way of *syn*-elimination of pivalic acid from 2′-halogeno-2′-deoxy-1′-pivaloyoxyuridine derivative (**7a**,**b** and **9a**,**b**). Stille coupling of **5c** and halogen-lithium exchange reaction of **5b** has disclosed the novel 2′-*C*-carbon-substituted (**10**–**11** and **12**–**13**) 1′,2′-unsaturated uridine derivatives. This method should be applicable to adenine nucleosides and this chemistry is under investigation in our laboratory.

4. Methods

4.1. General methods

Melting points are uncorrected. ^{1}H and 13C NMR spectra were recorded either at 400 MHz or at 500 MHz. Chemical shifts are reported relative to Me_4Si. Mass spectra (MS) were taken in FAB mode with *m*-nitrobenzyl alcohol as a matrix or ESI mode. Column chromatography was carried out on silica gel. Thin-layer chromatography (TLC) was performed on silica gel. When necessary, analytical samples were purified by high performance liquid chromatography (HPLC). THF was distilled from benzophenone ketyl.

4.1.1. 1-[2-Bromo-3,5-bis-O-(tert-butyldimethylsilyl)-2-deoxy-1-pivaloyloxy-β-D-arabinofuranosyl]uracil (7a) and 1-[2-Bromo-3,5-bis-O-(tert-butyldimethylsilyl)-2-deoxy-1-pivaloyloxy-α-D-ribofuranosyl]uracil (7b)

To a solution of pivalic acid (2.67 g, 26.20 mmol) in ether (40.0 mL) was added triethylamine (3.66 mL, 26.20 mmol) and the mixture was stirred for 0.5 h. To the resulting mixture was added **1** (2.38 g, 5.23 mmol) and NBS (1.13 g, 6.33 mmol) and the mixture was stirred for 0.5 h. The reaction mixture was partitioned between cold $CHCl_3$/saturated $NaHCO_3$ and silica gel column chromatography(hexane/ethyl acetate = 9/1)of the organic layer gave a mixture of **7a** (2.64 g, 79%, solid) and **7b** (0.39 g, 12%, foam).

Physical data for **7a**: mp, 157–159 °C; UV (MeOH) λ_{max} 254 nm (ε 10700) and λ_{min} 227 nm (ε 3500); ^{1}H NMR ($CDCl_3$) δ 0.09, 0.12 and 0.17 (12H, each as s, Si–Me), 0.91 and 0.92 (18H, each as S, Si-*tert*-Bu), 1.20 (9H, s, $C(CH_3)_3$), 3.87–3.89 (2H, m, CH_2-5′), 4.12–4.13 (1H, m, H-4′), 4.73 (1H, d, $J_{3',4'}$ = 3.3 Hz, H-3′), 4.89 (1H, s, H-2′), 5.68 (1H, dd, $J_{5,6}$ = 8.4 and $J_{5,NH}$ = 2.6 Hz, H-5), 7.82 (1H, d, $J_{5,6}$ = 8.4 Hz, H-6);; FAB-MS (*m*/*z*) 657 and 659 (M^+ + Na). *Anal.* Calcd for $C_{26}H_{47}BrN_2O_7Si_2$ (635.74): C, 49.12; H, 7.45; N, 4.41. Found: C, 49.13; H, 7.72; N, 4.42.

Physical data for **7b**: UV (MeOH) λ_{max} 255 nm (ε 10800) and λ_{min} 227 nm (ε 2900); ^{1}H NMR ($CDCl_3$) δ 0.07, 0.08, 0.14 and 0.16 (12H, each as s, Si–Me), 0.91 and 0.93 (18H, each as s, Si-*tert*-Bu), 1.17 (9H, s, $C(CH_3)_3$), 3.69 (1H, dd, $J_{4',5'a}$ = 1.8 and $J_{5'a,5'b}$ = 12.1 Hz, CH_{2a}-5′), 3.96 (1H, dd, $J_{4',5'a}$ = 4.8 and $J_{5'a,5'b}$ = 12.1 Hz,CH_{2b}-5'), 4.26–4.28 (1H, m, H-4'), 4.41 (1H, dd, $J_{2',3'}$ = 8.8 and $J_{3',4'}$ = 4.4 Hz, H-3'), 4.89 (1H, d, $J_{2',3'}$ = 8.8 Hz, H-2'), 5.70 (1H, dd, $J_{5,6}$ = 8.4 and $J_{5,NH}$ = 2.2 Hz, H-5), 7.91 (1H, d, $J_{5,6}$ = 8.4 Hz, H-6); FAB-MS (*m*/*z*) 657 and 659 (M^+ + Na). *Anal.* Calcd for $C_{26}H_{47}BrN_2O_7Si_2$ (635.74): C, 49.12; H, 7.45; N, 4.41. Found: C, 49.53; H, 7.62; N, 4.28.

4.1.2. Syn-elimination of pivalic acid in toluene under reflux conditions; formation of 1-[3,5-Bis-O-(tert-butyldimethylsilyl)-2-bromo-2-deoxy-erythro-pento-1-enofuranosyl]uracil (5b) and 1-[5-O-(tert-Butyldimethylsilyl)-2-bromofuryl]uracil (8) (entry 1, Table 1)

A solution of a mixture of **7a** and **7b** (99.8 mg, 0.16 mmol) in toluene (3.0 mL) was stirred under reflux conditions for 4.0 h. The reaction mixture was chromatographed on silica gel(hexane/ethyl acetate = 4/1)to give **5b** (27.3 mg, 32%, syrup) and **8** (17.3 mg, 27%, foam).

Physical data for **5b**; UV (MeOH) λ_{max} 254 nm (ε 9600) and λ_{min} 236 nm (ε 8100); ^{1}H NMR ($CDCl_3$) δ 0.09, 0.15 and 0.18 (12H, each as s, Si–Me), 0.90 and 0.92 (18H, each as S, Si-*tert*-Bu), 3.74 (1H, dd, $J_{4',5'a} = 5.9$ and $J_{5'a,5'b} = 11.0$ Hz, CH_{2a}-5'), 3.83 (1H, dd, $J_{4',5'a} = 5.0$ and $J_{5'a,5'b} = 11.0$ Hz, CH_{2b}-5'), 4.44–4.47 (1H, m, H-4'), 4.95 (1H, d, $J_{3',4'} = 3.3$ Hz, H-3'), 5.79 (1H, d, $J_{5,6} = 8.1$ Hz, H-5), 7.19 (1H, d, $J_{5,6} = 8.1$ Hz, H-6), 8.85 (1H, br, NH); FAB-MS (*m*/*z*) 555 and 557 (M^+ + Na) and 533 and 535 (M^+ + H). *Anal.* Calcd for $C_{21}H_{37}BrN_2O_5Si_2$ (533.63): C, 47.27; H, 5.25; N, 6.99. Found: C, 47.30; H, 5.18; N, 7.08.

Physical data for **8**; ^{1}H NMR ($CDCl_3$) δ 0.09, 0.11 (6H, s, Si–Me), 0.91 (9H, s, Si-*tert*-Bu), 4.61 (2H, s, CH_2-5'), 5.79 (1H, d, $J_{5,NH} = 1.8$ and $J_{5,6} = 8.1$ Hz, H-5), 6.41 (1H, s, H-3'), 7.17 (1H, d, $J_{5,6} = 8.1$ Hz, H-6), 9.53 (1H, br, NH); 13C NMR ($CDCl_3$) δ: −5.0, 18.7, 26.1, 58.5, 97.8, 104.0, 111.9139.9, 144.0, 149.3, 154.3, 163.5. ESI-MS(*m*/*z*): 423 and 425 (M^+ + Na); ESI-HRMS (*m*/*z*): calcd for $C_{15}H_{21}O_4N_2BrNaSi_2$: 423.03462, found: 423.03409 (M^+ + Na).

4.1.3. Syn-elimination of pivalic acid in xylene under reflux conditions in the presence of $NaHCO_3$; formation of 5b (entry 3, Table 1)

To a solution of a mixture of **7a** and **7b** (53.6 mg, 0.084 mmol) in xylene (3.0 mL) was added sodium hydrogen carbonate (7.1 mg, 0.084 mmol) and the mixture was stirred under reflux conditions for 4.0 h. The reaction mixture was partitioned between $CHCl_3$/saturated $NaHCO_3$ and silica gel column chromatography(hexane/ethyl acetate = 7/1)of the organic layer gave a mixture of **5b** (43.9 mg, 98%) as a syrup.

4.1.4. 1-[3,5-Bis-O-(tert-butyldimethylsilyl)-2-deoxy-2-iodo-erythro-pento-1-enofuranosyl]uracil (5c)

To a solution of a mixture of pivalic acid (362.6 mg, 3.55 mmol) and silver carbonate (117.5 mg, 0,43 mmol) in benzene (20.0 mL) was added triethylamine (0.49 mL, 3.55 mmol) and the mixture was stirred for 0.5 h. To the resulting mixture was added a solution of **1** (321.9 mg, 0.71 mmol) in benzene (5.0 mL) and a solution of NIS (287.5 mg, 1.28 mmol) in THF

(1.0 mL) at 0 °C under Ar atmosphere and the mixture was stirred for 5 min. The reaction mixture was partitioned between cold benzene/0.5 M $Na_2S_2O_3$-saturated $NaHCO_3$ and neutral silica gel column chromatography(hexane/ethyl acetate = 10/1)of the organic layer gave a mixture of **9a** and **9b** (325.3 mg, 67%) as a solid. The solution of the mixture of **9a**,**b** (136.2 mg, 0.2 mmol) in xylene (10.0 mL) was heated under reflux conditions for 50 min. Silica gel column chromatography (hexane/ethyl acetate = 9:1) gave **5c** (129.0 mg, 79%, syrup) and **2** (5.0 mg, 7%, syrup).

Physical data of **5c**; UV (MeOH) $\lambda_{sholder}$ 242 nm (ε 13400) 227 nm (ε 15800); ^{1}H NMR ($CDCl_3$) δ 0.08, 0.15 and 0.20 (12H, each as s, Si–Me), 0.90 and 0.92 (18H, each as S, Si-*tert*-Bu), 3.74 (1H, dd, $J_{4',5'a} = 5.9$ and $J_{5'a,5'b} = 11.4$ Hz, CH_{2a}-5′), 4.50 (1H, dd, $J_{4',5'a} = 4.8$ and $J_{5'a,5'b} = 11.4$ Hz,CH_{2b}-5′), 4.49–4.52 (1H, m, H-4'), 4.90 (1H, d, $J_{3',4'} = 2.9$ Hz, H-3'), 5.80 (1H, dd, $J_{5,6} = 8.1$ and $J_{5,NH} = 1.8$ Hz, H-5), 7.18 (1H, d, $J_{5,6} = 8.1$ Hz, H-6);; FAB-MS (*m*/*z*) 603 (M^+ + Na) and 581 (M + H). *Anal.* Calcd for $C_{21}H_{37}IN_2O_5Si_2$ (580.61): C, 43.44; H, 6.42; N, 4.82. Found: C, 43.44; H, 6.48; N, 4.78.

4.1.5. 1-[3,5-Bis-O-(tert-butyldimethylsilyl)-2-deoxy-2-C-phenylethynyl-erythro-pento-1-enofuranosyl]uracil (10)

To a solution of **5c** (93.1 mg, 0.16 mmol) in DMF (1.0 mL) was added $Bu_3SnC{\equiv}CPh$ (0.11 mL, 0.32 mmol) and $Pd(PPh_3)_4$ (18.5 mg, 0.03 mol) at rt under Ar atmosphere. The mixture was stirred at 100 °C for 10 min. The reaction mixture was partitioned between ethyl acetate/H_2O and silica gel column chromatography (hexane/ethyl acetate = 4/1) of the organic layer gave **10** (51.5 mg, 58%) as a syrup; ^{1}H NMR ($CDCl_3$) δ 0.09, 0.10, 0.19 and 0.21 (12H, each as s, Si–Me), 0.91 and 0.94 (18H, each as s, Si-*tert*-Bu), 3.74 (1H, dd, $J_{4',5'a} = 6.2$ and $J_{5'a,5'b} = 10.8$ Hz, CH_{2a}-5'), 3.85 (1H, dd, $J_{4',5'a} = 5.2$ and $J_{5'a,5'b} = 10.8$ Hz, CH_{2b}-5'), 4.51–4.53 (1H, m, H-4'), 5.08 (1H, d, $J_{3',4'} = 2.9$ Hz, H-3'), 5.81 (1H, dd, $J_{5,6} = 7.9$ and $J_{5,NH} = 2.2$ Hz, H-5), 7.27–7.38 (5H, m, Ph), 7.41 (1H, d, $J_{5,6} = 7.9$ Hz, H-6), 8.64 (1H, br, NH); 13C NMR ($CDCl_3$) δ: –5.42, –5.37, –4.6, –4.0, 18.1, 18.4, 25.8, 25.9, 61.9, 79.9, 89.8, 95.4, 96.9, 102.8, 122.8, 126.3, 128.4, 131.1, 131.5, 142.8, 147.5, 152.4, 162.6. ESI-MS(*m*/*z*): 577 (M^++Na); ESI-HRMS (*m*/*z*): calcd for $C_{29}H_{42}O_5N_2NaSi_2$: 577.25245, found: 577.25201 (M^++Na).

4.1.6. 1-[3,5-Bis-O-(tert-butyldimethylsilyl)-2-deoxy-2-C-ethynyl-erythro-pento-1-enofuranosyl]uracil (11)

To a solution of **5c** (94.9 mg, 0.16 mmol) in DMF (1.0 mL) was added $Bu_3SnC{\equiv}CH$ (93 µL, 0.32 mmol) and $Pd(PPh_3)_4$ (18.5 mg, 0.02 mol) at rt under Ar atmosphere. The mixture was stirred at 100 °C for 10 min. The

reaction mixture was partitioned between ethyl acetate/H_2O and silica gel column chromatography (hexane/ethyl acetate = 7/1) of the organic layer gave **11** (64.7 mg, 84%) as a foam; UV (MeOH) λ_{max} 248 nm (ε 15500), λ_{min} 222 nm (ε 8700); ^{1}H NMR ($CDCl_3$) δ 0.08, 0.14 and 0.16 (12H, each as s, Si–Me), 0.89 and 0.91 (18H, each as s, Si-*tert*-Bu), 3.23 (1H, s, C≡CH), 3.70 (1H, dd, $J_{4',5'a}$ = 6.2 and $J_{5'a,5'b}$ = 11.2 Hz, CH_{2a}-5'), 3.81 (1H, dd, $J_{4',5'a}$ = 4.8 and $J_{5'a,5'b}$ = 11.0 Hz,CH_{2b}-5'), 4.47–4.59 (1H, m, H-4'), 5.00 (1H, d, $J_{3',4'}$ = 2.9 Hz, H-3'), 5.79 (1H, dd, $J_{5,6}$ = 8.1 and $J_{5,NH}$ = 1.2 Hz, H-5), 7.32 (1H, d, $J_{5,6}$ = 8.1 Hz, H-6), 8.73 (1H, br, NH); FAB-MS (*m*/*z*) 501 (M^+ + Na) and 479 (M + H). *Anal.* Calcd for $C_{23}H_{38}N_2O_3Si_2 \cdot 1/2\,H_2O$: C, 57.17; H, 8.03; N, 5.80. Found: C, 57.28; H, 8.06; N, 5.66.

4.1.7. 1-[3,5-Bis-O-(tert-butyldimethylsilyl)-2-deoxy-2-C-methyl-erythro-pento-1-enofuranosyl]uracil (6c)

To a solution of **5b** (111.2 mg, 0.21 mmol) and MeI (0.13 mL, 2.10 mmol) in THF (10.0 mL) was added BuLi (1.34 M hexane solution) (0.47 mL, 0.63 mmol) and at −78 °C under Ar atmosphere. After being stirred for 15 min, the mixture was quenched with AcOH (36.0 μL) and partitioned between chloroform/saturated $NaHCO_3$. Silica gel column chromatography(hexane/ethyl acetate = 3/1)of the organic layer gave **6c** (74.9 mg, 76%, syrup) and **1** (10.5 mg, 11%, solid).

Physical data for **6c**; UV (MeOH) λ_{max} 257 nm (ε 8400), λ_{min} 235 nm (ε 6100); ^{1}H NMR ($CDCl_3$) δ 0.07 and 0.11 (12H, each as s, Si–Me), 0.89 and 0.90 (18H, each as s, Si-*tert*-Bu), 3.68 (1H, dd, $J_{4',5'a}$ = 5.9 and $J_{5'a,5'b}$ = 11.0 Hz, CH_{2a}-5'), 3.77 (1H, dd, $J_{4',5'a}$ = 5.3 and $J_{5'a,5'b}$ = 11.0 Hz, CH_{2b}-5'), 4.29–4.31 (1H, m, H-4'), 4.81 (1H, d, $J_{3',4'}$ = 3.3 Hz, H-3'), 5.75 (1H, d, $J_{5,6}$ = 8.1 Hz, H-5), 7.22 (1H, d, $J_{5,6}$ = 8.1 Hz, H-6), 8.93 (1H, br, NH); FAB-MS (*m*/*z*) 491 (M^+ + Na) and 469 (M^+ + H). *Anal.* Calcd for $C_{22}H_{40}N_2O_5Si_2$: C, 56.37; H, 5.98; N, 8.60. Found: C, 56.28; H, 5.98; N, 8.84.

4.1.8. 1-[3,5-Bis-O-(tert-butyldimethylsilyl)-2-deoxy-2-C-(1-phenylhydroxymethyl)-erythro-pento-1-enofuranosyl]uracil (12)

To a solution of **5b** (334.1 mg, 0.60 mmol) and PhCHO (0.61 mL, 6.0 mmol) in THF (30.0 mL) was added BuLi (1.34 M hexane solution) (3.60 mL, 5.40 mmol) dropwise at −78 °C under Ar atmosphere. After being stirred for 15 min, the reaction mixture was quenched with AcOH (0.31 mL) and partitioned between chloroform/saturated $NaHCO_3$. Silica gel column chromatography(hexane/ethyl acetate = 2/1)of the organic layer gave a mixture of diastereomer of **12** (0.0 mg, 82%, major:minor = 7:1) and **1** (16.4 mg, 6%, solid). The major **12** and minor **12** were separated by HPLC (hexane/ethyl

acetate = 2/1) to give major **12** (248.5 mg, 71%, syrup) and minor **12** (38.5 mg, 11%, syrup).

Physical data for major **12**; UV (MeOH) λ_{max} 257 nm (ε 9000), λ_{min} 238 nm (ε 6200); ^{1}H NMR ($CDCl_3$) δ 0.04, 0.05, 0.06 and 0.10 (12H, each as s, Si–Me), 0.88 and 0.92 (18H, each as s, Si-*tert*-Bu), 3.42 (1H, d, $J_{CH,OH}$ = 8.8 Hz, CH(OH)Ph), 3.64 (1H, dd, $J_{4',5'a}$ = 6.2 and $J_{5'a,5'b}$ = 11.0 Hz, CH_{2a}-5'), 3.78 (1H, dd, $J_{4',5'a}$ = 5.5 and $J_{5'a,5'b}$ = 11.0 Hz, CH_{2b}-5'), 4.36–4.40 (1H, m, H-4'), 5.05 (1H, d, $J_{3',4'}$ = 2.9 Hz, H-3'), 5.37 (1H, d, $J_{CH,OH}$ = 8.8 Hz, CH(OH)Ph), 5.56 (1H, dd, $J_{5,NH}$ = 1.8 and $J_{5,6}$ = 7.9 Hz, H-5), 7.06 (1H, d, $J_{5,6}$ = 7.9 Hz, H-6), 7.17–7.36 (5H, m, Ph), 8.41 (1H, br, NH); FAB-MS (*m*/*z*) 583 (M^+ + Na) and 561 (M^+ + H). *Anal.* Calcd for $C_{28}H_{44}N_2O_6Si_2$: C, 59.97; H, 5.00; N, 7.91. Found: C,60.30; H, 4.75; N, 8.03.

Physical data for minor **12**; ^{1}H NMR ($CDCl_3$) δ 0.04, 0.06, 0.07 and 0.09 (12H, each as s, Si–Me), 0.89 and 0.91 (18H, each as s, Si-*tert*-Bu), 3.15 (1H, br, CH(OH)Ph), 3.68 (1H, dd, $J_{4',5'a}$ = 6.2 and $J_{5'a,5'b}$ = 10.6 Hz, CH_{2a}-5'), 3.80 (1H, dd, $J_{4',5'a}$ = 4.8 and $J_{5'a,5'b}$ = 10.6 Hz, CH_{2b}-5'), 4.92–4.96 (1H, m, H-4'), 4.97 (1H, d, $J_{3',4'}$ = 2.6 Hz, H-3'), 5.43 (1H, br, CH(OH)Ph), 5.49 (1H, d, $J_{5,6}$ = 8.1 Hz, H-5), 6.96 (1H, d, $J_{5,6}$ = 8.1 Hz, H-6), 7.17–7.47 (5H, m, Ph), 8.78 (1H, br, NH); ^{13}C NMR ($CDCl_3$) δ: –5.44, –5.42, –4.7, –4.1, 17.9, 18.5, 25.8, 25.9, 62.2, 69.2, 78.2, 87.0, 102.1, 112.6, 126.3, 127.9, 128.5, 140.7, 142.9, 144.8, 148.8, 162.4. ESI-MS (*m*/*z*) 583 (M^+ + Na); ESI-HRMS (*m*/*z*): calcd for $C_{28}H_{44}O_6N_2NaSi_2$: 583.26301, found: 583.26301 (M^++Na).

4.1.9. 1-[3,5-Bis-O-(tert-butyldimethylsilyl)-2-deoxy-2-C-ethoxycarbonyl-erythro-pento-1-enofuranosyl]uracil (13)

To a solution of **5b** (59.1 mg, 0.11 mmol) and ethyl chloroformate (0.11 mL, 1.10 mmol) in THF (10.0 mL) was added BuLi (1.34 M hexane solution) (0.75 mL, 1.10 mmol) and at –78 °C under Ar atmosphere. After being stirred for 15 min, the mixture was quenched with AcOH (63.0 µL) and partitioned between chloroform/saturated $NaHCO_3$. Silica gel column chromatography (hexane/ethyl acetate = 2/1) of the organic layer gave **13** (37.7 mg, 65%, foam) and **1** (9.0 mg, 18%, solid).

Physical data of **13**; ^{1}H NMR ($CDCl_3$) δ 0.08, 0.13 and 0.16 (12H, each as s, Si–Me), 0.89 and 0.90 (18H, each as s, Si-*tert*-Bu), 1.25 (3H, t, $J_{CH2,CH3}$ = 7.0 Hz, $COOCH_2CH_3$), 3.68 (1H, dd, $J_{4',5'a}$ = 6.6 and $J_{5'a,5'b}$ = 11.0 Hz, CH_{2a}-5'), 3.83 (1H, dd, $J_{4',5'a}$ = 5.1 and $J_{5'a,5'b}$ = 11.0 Hz, CH_{2b}-5'), 4.13 and 4.21 (2H, each as m, $COOCH_2CH_3$), 4.47–4.51 (1H, m, H-4'), 5.17 (1H, d, $J_{3',4'}$ = 1.8 Hz, H-3'), 5.79 (1H, d, $J_{5,NH}$ = 1.8 and $J_{5,6}$ = 8.1 Hz, H-5), 7.23 (1H, d, $J_{5,6}$ = 8.1 Hz, H-6), 8.59 (1H, br, NH); ^{13}C NMR ($CDCl_3$) δ: –5.49, –5.46, –4.7, 14.3, 18.0, 18.3, 25.7, 25.8, 60.5, 61.7, 74.4, 90.2, 102.4, 104.7, 131.0, 142.7, 147.7, 156.4, 162.6, 162.7; ESI-MS (*m*/

z) 549 (M^+ + Na); ESI-HRMS (*m*/*z*): calcd for $C_{24}H_{42}O_7N_2NaSi_2$: 549.24228, found: 549.24115 (M^++Na).

Funding

Financial supports from Japan Society for the Promotion of Science (KAKENHI No. 24590144 to K. H.) are gratefully acknowledged.

References

[1] Huryn, D. M.; Okabe, M. AIDS-Driven Nucleoside Chemistry. *Chem. Rev.* **1992**, *92*, 1745–1768. DOI: 10.1021/cr00016a004.

[2] Chu, C. K.; Baker, D. C.; Eds. *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*. New York: Plenum Press, **1993**.

[3] Franchetti, P.; Grifantini, M. Nucleoside and Non-Nucleoside IMP Dehydrogenase Inhibitors as Antitumor and Antiviral Agents. *Curr. Med. Chem.* **1999**, *6*, 599–614. DOI: 10.1002/chin.199940260.

[4] Ichikawa, E.; Kato, K. Sugar-Modified Nucleosides in Past 10 Year, A Review. *CMC.* **2001**, *8*, 385–423. DOI: 10.2174/0929867013373471.

[5] Simons C., Ed. *Nucleoside Mimetics: Their Chemistry and Biological Properties*. Amsterdam: Gordon and Breach Science Publishers, **2001**.

[6] Ichikawa, E.; Kato, K. Synthesis of Oxcetanocin a and Related Unusual Nucleosides with Bis(Hydroxymethyl)-Branched Sugars. *Synthesis* **2002**, *2002*, 1–28. DOI: 10.1055/s-2002-19289.

[7] Chu, C. K., Ed. *Recent Advances in Nucleosides: Chemistry and Chemotherapy*. Amsterdam: Elsevier B. V., **2002**.

[8] Chu, C. K., Ed. *Antiviral Nucleosides: Chemical Synthesis and Chemotherapy*. Amsterdam: Elsevier B. V., **2003**.

[9] Vaghefi, M. Ed. *Nucleoside Triphosphates and Their Analogs: Chemistry, Biotechnology, and Biological Applications*. Boca Raton, London, New York, Singapore: Tayler & Francis, **2005**.

[10] Lawton, P. Purine Analogues as Antiparasitic Agents. *Expert. Opin. Ther. Patents.* **2005**, *15*, 987–994. DOI: 10.1517/13543776.15.8.987.

[11] Richardson, S.; K.; Howell, A. R.; Taboada, R. Synthesis and Properties of Psico-Nucleosides. *Org. Prep. Proc. Int.* **2006**, *38*, 101–176. DOI: 10.1080/00304940609355987.

[12] Peters, G. J., Ed. *Deoxynucleoside Analogs in Cancer Therapy*. New Jersey: Humana Press, **2006**.

[13] Herdewijn, P., Ed. *Modified Nucleosides in Biochemistry, Biotechnology and Medicine*. Weinheim: Wiley-VCH Verlag GmbH & Co. KGaA, **2008**.

[14] Romeo, G.; Chiacchio, U.; Corsaro, A.; Merino, P. Chemical Synthesis of Heterocyclic-Sugar Nucleoside Analogues. *Chem. Rev.* **2010**, *110*, 3337–3370. DOI: 10.1021/cr800464r.

[15] DeClercq, E., Ed. *Antiviral Drug Design*. Weinheim: Wiley-VCH Verlag GmbH & Co. KGaA, **2011**.

[16] Calenbergh, S. V.; Pochet, S.; Munier-Lehman, H. Frug Design and Identification of Potent Leads against *Mycobacterium tuberculosis* Thymidine Monophosphate Kinase. *CTMC.* **2012**, *12*, 694–705. DOI: 10.2174/156802612799984580.

[17] Merino, P., Ed. *Chemical Synthesis of Nucleoside Analogues*. Hoboken, New Jersey: John Wiley & Sons, **2013**.

[18] De Clercq, E. Highlights in Antiviral Drug Research: antivirals at the Horizon. *Med. Res. Rev.* **2013**, *33*, 1215–1248. DOI: 10.1002/med.21256.

[19] Jordheim, L. P.; Durantel, D.; Zoulim, F.; Dumontet, C. Advances in the Development of Nucleoside and Nucleotide Analogues for Cancer and Viral Diseases. *Nat. Rev. Drug Discov.* **2013**, *12*, 447–464. DOI: 10.1038/nrd4010.

[20] De Clercq, E.; Li, G. Approved Antiviral Drugs Over the Past 50 Years. *Clin. Microbiol. Rev.* **2016**, *29*, 695–747. DOI: 10.1128/CMR.00102-15.

[21] Shelton, J.; Lu, X.; Hollenbaugh, J. A.; Cho, J. H.; Amblard, F.; Schinazi, R. F. Metabolism, Biochemical Actions, and Chemical Synthesis of Anticancer Nucleosides, Nucleotides, and Base Analogs. *Chem. Rev.* **2016**, *116*, 14379–14455. DOI: 10.1021/acs.chemrev.6b00209.

[22] Haraguchi, K.; Itoh, Y.; Tanaka, H. Carbon-Carbon Bond Formation at the Sugar Portion of Nucleosides: synthetic Potential of Unsaturated-Sugar Nucleosides. *J. Syn. Org. Chem Jpn.* **2003**, *61*, 974. DOI: 10.5059/yukigoseikyokaishi.61.974.

[23] Haraguchi, K.; Takeda, S.; Kubota, Y.; Kumamoto, H.; Tanaka, H.; Hamasaki, T.; E.; Baba, M.; Paintsil, E.; Cheng, Y.-C.; Urata, Y. Next Generation Anti-HIV Agent 4'-Ethynylstavudine: From The Bench To The Clinic. In *Frontiers in Clinical Drug Research: HIV*, Atta-ur-Rahman, J., ed.; Bentham Science Publishing: Sharjah, U.A.E., **2015**; Vol. 1, pp. 123–184.

[24] Kumamoto, H.; Shindoh, S.; Tanaka, H.; Gen, E.; Haraguchi, K.; Kittaka, A.; Miyasaka, T. Stannyl Migration from the Base to the Sugar Portion of 1',2'-Unsaturated Uridine: The First Example of Substitution at the 2'-Position. *Tetrahedron Lett.* **1998**, *39*, 3761–3764. DOI: 10.1016/S0040-4039(98)00579-6.

[25] Kumamoto, H.; Shindoh, S.; Tanaka, H.; Itoh, Y.; Haraguchi, K.; Gen, E.; Kittaka, A.; Miyasaka, T.; Kondo, M.; Nakamura, K. T. An Intramolecular Anionic Migration of a Stannyl Group from the 6-Position of 1-(2-deoxy-D-*Erythro*-Pent-1-Enofuranosyl)Uracil to the 2'-Position: Synthesis of 2'-Substituted 1',2'-Unsaturated Uridines. *Tetrahedron* **2000**, *56*, 5363–5371. DOI: 10.1016/S0040-4020(00)00441-5.

[26] A part of the results of this study has been appeared inTetrahedron, **2000**, *56*, 5363–5371.

[27] Haraguchi, K.; Itoh, Y.; Tanaka, H.; Miyasaka, T. Preparation and Reactions of 2'- and 3'-Vinyl Bromides of Uracilnucleosides: Versatile Synthons for anti-HIV Agents. *Tetrahedron Lett.* **1991**, *32*, 3391–3394. DOI: 10.1016/S0040-4039(00)92715-1.

[28] Haraguchi, K.; Itoh, Y.; Tanaka, H.; Akita, T.; Miyasaka, T. Uracil and Adenine Nucleosides Having a 2'- or 3'-Bromovinyl Structure: highly Versatile Synthons for the Synthesis of 2'-*C*- and 3'-*C*-Branched 2',3'-Unsaturated Derivatives. *Tetrahedron* **1993**, *49*, 1371–1390. DOI: 10.1016/S0040-4020(01)90190-5.

[29] Haraguchi, K.; Itoh, Y.; Tanaka, H.; Yamaguchi, K.; Miyasaka, T. Anomeric Manipulation of Nucleosides: Stereospecific Entry to 1'-*C*-Branched Uracil Nucleosides. *Tetrahedron Lett.* **1993**, *34*, 6913–6916. DOI: 10.1016/S0040-4039(00)91829-X.

[30] Itoh, Y.; Haraguchi, K.; Tanaka, H.; Gen, E.; Miyasaka, T. Divergent and Stereo-Controlled Approach to the Synthesis of Uracil Nucleosides Branched at the Anomeric Position. *J. Org. Chem.* **1995**, *60*, 656–662. DOI: 10.1021/jo00108a031.