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Nucleosides and Nucleotides. 183. Synthesis of 4'α-Branched Thymidines as a New Type of Antiviral Agent[1]

Isamu Sugimoto,[a] Satoshi Shuto,[a] Shuichi Mori, [b] Shiro Shigeta,[b] and Akira Matsuda[a, *]

[a]*Laboratory of Medicinal Chemistry, Graduate School of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060-0812, Japan, and* [b]*Department of Bacteriology, Fukushima Medical College, Fukushima 960-1247, Japan.*

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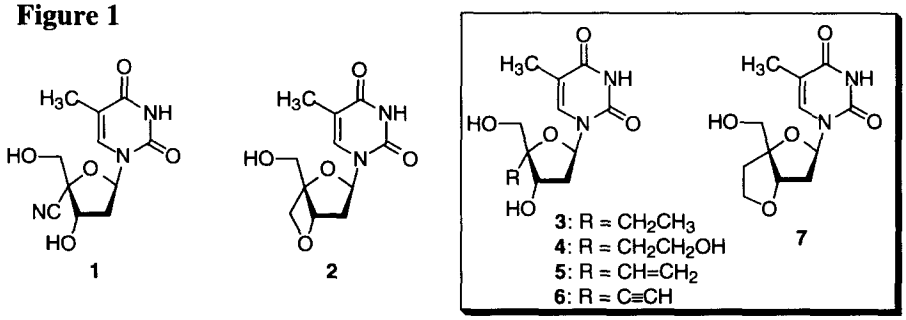
Abstract: A series of 4'α-branched thymidines was synthesized and evaluated as potential antiviral agents. 4'-Ethylthymidine (**3**), 4'-ethenylthymidine (**5**), and 4'-ethynylthymidine (**6**) exhibited potent anti-HSV-1 and anti-HIV-1 activities with no significant cytotoxicity.

The development of new effective antiviral agents is essential for overcoming diseases caused by viruses, such as acquired immunodeficiency syndrome (AIDS). Considerable effort has been made to synthesize branched nucleosides as potential antiviral agents. Although 4'α-branched thymidine derivatives, namely 4'α-*C*-cyanothymidine (**1**)[2] and the 4',3'-oxetane derivative of thymidine (**2**),[3] have been shown to have potent anti-human immunodeficiency virus 1 activities, few 4'α-branched nucleosides have been prepared or have had their antiviral activities tested.[2-6] This may be because there has been no efficient method for stereoselectively introducing a carbon substituent, except for a hydroxymethyl group, at the 4'α-position of nucleosides.

Figure 1



Recently, we developed a regio- and stereoselective method for introducing a hydroxyethyl group at the 4'α-position of nucleosides.[7-9] Thus, the intramolecular radical cyclization reaction with 4'-phenylseleno derivative **8** gave an endo-cyclization product **9**

*To whom correspondence should be addressed. Tel.: +81-11-706-3228. Fax: +81-11-706-4980.
E-mail: matuda@pharm.hokudai.ac.jp

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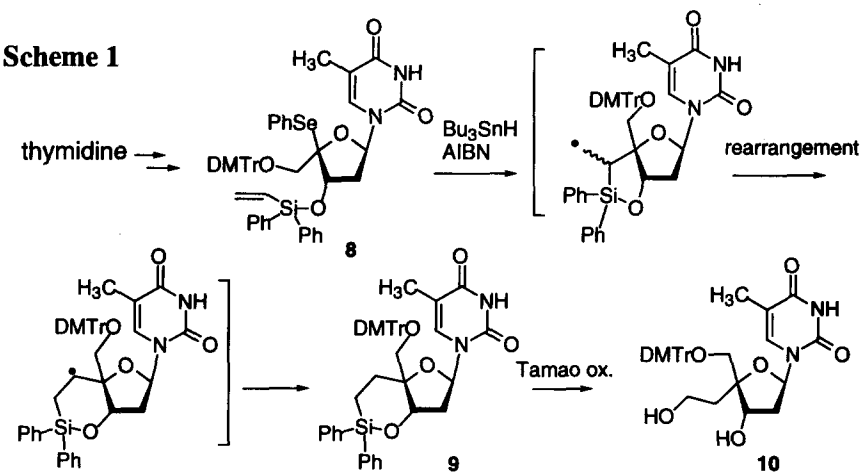
via a novel radical rearrangement reaction, which when followed by treatment with Tamao oxidation conditions, gave the corresponding 4'α-*C*-hydroxyethyl derivative **10** in high yield (Scheme 1). Therefore, we designed a series of novel 4'α-C_2-substituted analogues of thymidine, **3-6**, which can be derived from **10**, as novel potential antiviral agents. A 3',4'-cyclized analogue of thymidine, **7**, which corresponds to a homologue of the antiviral 4',3'-oxetane derivative **2**, was also designed. In this communication, we describe the synthesis of these 4'α-branched thymidines and their antiviral activities against herpes simplex virus type 1 (HSV-1) and human immunodeficiency virus type 1 (HIV-1).

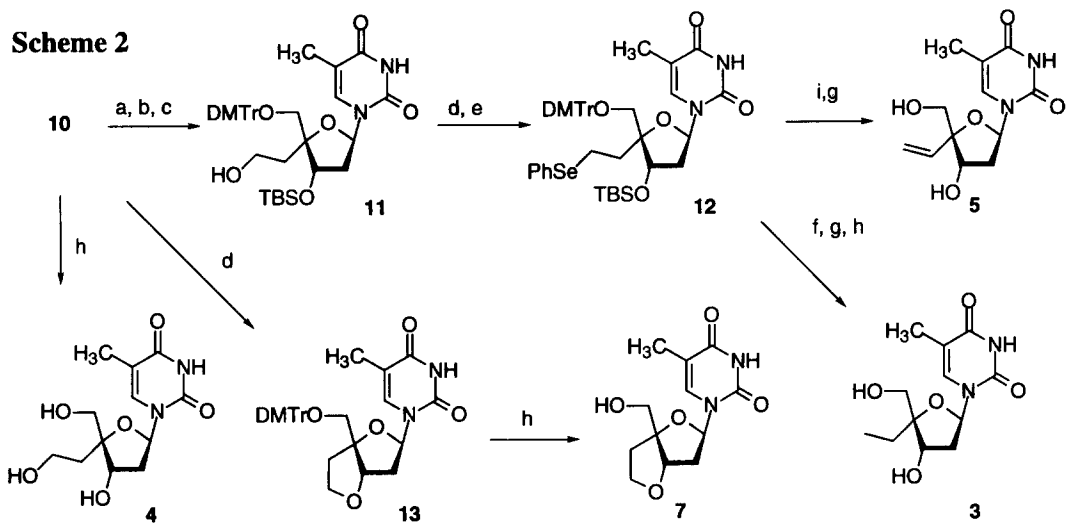
Scheme 1



The synthesis of 4'α-branched thymidines, **3**, **4**, **5**, and **7**, is shown in Scheme 2. Selective benzoylation of the primary hydroxyl group of **10** by treatment with BzCl and Et_3N in the presence of DMAP in CH_2Cl_2 at -78 °C gave the corresponding monobenzoate. After silylation of the 3'-hydroxyl group of the product by treatment with TBSOTf and *i*-Pr_2NEt in CH_2Cl_2, the benzoyl group was removed with K_2CO_3 in MeOH to give the 3'-*O*-TBS derivative **11** in 51% yield from **10**. Methanesulfonation of the primary hydroxyl of **11**, followed by treatment with NaSePh in THF/EtOH, gave the phenylseleno derivative **12** in 78% yield. Radical reduction of **12** with Bu_3SnH and AIBN under reflux in benzene, followed by deprotection of the silyl and dimethoxytrityl groups by usual methods gave 4'α-*C*-ethylthymidine **3**[10] in 54% yield. Successive treatment of **12** with H_2O_2 under reflux in THF and TBAF in THF at room temperature followed by deprotection of the protecting groups gave 4'α-*C*-ethenylthymidine **5**[11] in 75% yield from **12**. When **10** was treated with MsCl and Et_3N in the presence of DMAP, a cyclization product **13** was obtained in 48% yield. The DMTr group of **13** was removed with TFA to give the desired tetrahydrofuran derivative **7** in 78% yield. Compound **10** was also deprotected with TFA to give 4'α-*C*-hydoxyethylthymidine **4** in 72% yield.

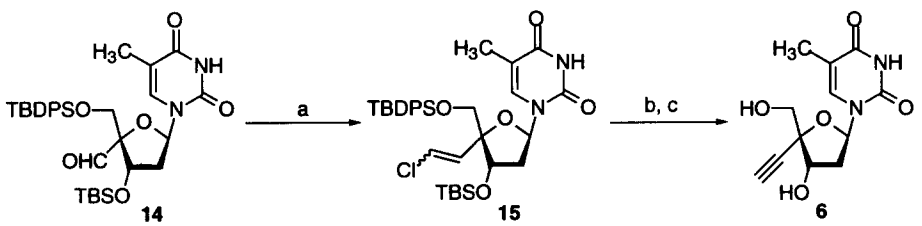
4'α-*C*-Ethynylthymidine (**6**) was prepared starting from 4'-formly derivative **14**, which was derived from a 4'α-*C*-hydroxymethylthymidine derivative.[12] The aldehyde **14** was treated with chloromethylenetriphenylphosphorane[13] in THF to give chlorovinyl derivative **15** as a mixture of *E*- and *Z* -isomers in a 59% yield. Subsequently, **15** was treated with BuLi in THF at -78 °C to form an ethynyl moiety at the 4'α-position. Deprotection with NH_4F in MeOH gave 4'α-*C*-ethynylthymidine **6**[14] in 39% from **15** (Scheme 3).

Scheme 2



a) BzCl, Et_3N, DMAP, CH_2Cl_2, -78 °C; b) TBSOTf, *i*-Pr_2NEt, CH_2Cl_2; c) K_2CO_3, MeOH; d) MsCl, Et_3N, DMAP, CH_2Cl_2; e) NaSePh, THF, EtOH; f) Bu_3SnH, AIBN, benzene, reflux; g) TBAF, THF; h) TFA, CH_2Cl_2; i) H_2O_2, THF, reflux.

Scheme 3



a) Ph_3P=CHCl, THF, -78 °C; b) BuLi, THF, -78 °C; c) NH_4F, MeOH, reflux

Table Antiviral activities of 4'α-branched thymidines (μM)[a]

Compound	HSV-1 EC_{50}[b]	HSV-1 CC_{50}	HIV-1 EC_{50}[b]	HIV-1 CC_{50}
3	7.4 ± 5.2	>100	16.1 ± 9.1	>100
4	>100	>100	>4.7	4.7
5	1.9 ± 0.56	>100	6.1 ± 3.0	>100
6	6.8 ± 1.1	>100	0.83 ± 0.83	>100
7	>100	>100	>100	>100
ACV	0.16 ± 0.09	>100		
AZT			0.0017 ± 0.0002	16.5

[a]To evaluate anti-HSV-1 and anti-HIV-1 activities, HSV-1 Kos strain vs. RPMI8226 cells (a B-cell line) and HIV-1 IIIb strain vs. MT-4 cells (a T-cell line) were used, respectively. Briefly, cells were infected with viruses at a multiplicity of infection (m.o.i.) of 0.02. Immediately after the virus infection, a cell suspension (100 μL) was placed into each well containing various concentrations of the compounds (100 μL). After 4 days of incubation at 36 °C, the number of viable cells was determined by the MTT method.[15,16] [b]Mean ± S.D. of 3 determinations.

Antiviral assays against HIV-1 and HSV-1 were performed using compounds **3-7**, and the results are summarized in the Table. The 4'α-*C*-hydroxyethyl derivative **4** and the 3',4'-cyclic derivative **7** were inactive in these evaluation systems. The ethyl derivative **3** and the ethynyl derivative **6** exhibited antiviral activity against HSV-1 with EC_{50} values of 7.4 μM and 6.8 μM, respectively. The ethenyl derivative **5** showed the strongest anti-HSV-1 activity of the synthesized compounds,with an EC_{50} value of 1.9 μM, which was about 12-fold weaker than that of acyclovir (ACV) (EC_{50} = 0.16 μM), a clinically useful anti-HSV agent. On the other hand, the ethynyl derivative **6** significantly inhibited HIV-1 replication in cells with an EC_{50} value of 0.83 μM. Although compounds **3** and **5** also showed anti-HIV-1 activity, their effects were moderate. However, it should be noted that **3**, **5**, and **6** were not cytotoxic to the host cells used for viral infection at up to 100 μM.

In summary, we prepared a series of 4'α-branched thymidines which have potent antiviral activities against HSV-1 and HIV-1. Although their activities were not greater than those of standard antiviral agents such as ACV or AZT, these may be important lead compounds for useful antiviral drugs since they showed no cytotoxicity to the host cells. The biological activities of other 4'α-branched nucleosides with different nucleobases or substituents are interesting, and further investigations are in progress.

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10. ^{1}H-NMR (270MHz, DMSO-d_6); δ : 11.23 (br.s, 1 H, NH), 7.75 (s, 1 H, H-6), 6.11 (t, 1 H, H-1'; *J* = 6.7 Hz), 5.08 (d, 1 H, 3'-OH), 5.02 (t, 1 H, 5'-OH), 4.28,(m, 1 H, H-3'), 3.47 (dd, 1 H, H-5'a; *J* = 11.6 Hz), 3.42 (dd, 1 H, H-5'b; *J* = 11.6 Hz), 2.23 (dt, 1 H, H-2'a; *J* = 13.2, 6.7 Hz), 2.09 (ddd, 1 H, H-2'b; *J* = 13.2, 6.7 Hz), 1.77 (s, 3 H, Me), 1.59 (dq, 1 H, H-6'a; *J* = 14.2, 7.(Hz), 1.50 (dq, 1 H, H-6'b; *J* = 14.2, 7.3 Hz), 0.86 (t, 3 H, H-7'; *J* = 7.6, 7.3 Hz). FAB-HRMS; calcd. for $C_{12}H_{18}N_2O_5$; 271.1293, found; 271.1299.
11. ^{1}H-NMR (270 MHz, DMSO-d_6); δ : 11.25 (s, 1 H, NH), 7.87 (d, 1H, H-6), 6.09 (dd, 1 H, H-1'; *J* = 6.6, 5.0 Hz), 5.91,(dd, 1 H, H-6'; *J* = 17.2 Hz), 5.32 (dd, 1 H, H-7'a; *J* = 17.2, 2.0 Hz), 5.22 (m, 1 H, OH), 5.18 (dd, 1 H, H7'b; *J* = 2.0 Hz), 4.45 (dd, 1 H, H-3'; *J* = 6.9 Hz), 2.16 (ddd, 1 H, H-2'a; *J* = 13.2, 6.9, 5.0 Hz), 2.07 (dt, 1 H, H-2'b; *J* = 13.2, 6.9, 6.6 Hz), 1.77 (s, 3 H, Me). Anal. calcd. for $C_{12}H_{16}N_2O_5$; C:53.73, H:6.01, N:10.44. Found; C:53.74, H:5.99, N:10.36.
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14. ^{1}H-NMR (270 MHz, DMSO-d_6); δ : 11.29 (s, 1 H, NH), 7.63 (s, 1 H, H-6), 6.15 (dd, 1 H, H-1'; *J* = 6.4, 6.1 Hz), 5.48 (d, 1 H, 3'-OH), 5.41 (dd, 1 H, 5'-OH), 4.36 (m, 1 H, H-3'), 3.64 (dd, 1 H, H-5'a; *J* = 12.0, 5.7 Hz), 3.59 (dd, 1 H, H-5'b; *J* = 12.0, 6.2 Hz), 3.48 (s, 1 H, ethynyl), 2.22 (m, 2 H, H-2'a, 2'b), 1.77 (s, 3 H, Me). Anal. calcd. for $C_{12}H_{14}N_2O_5$; C:54.13, H:5.30, N:10.5; Found; C:53.42, H:5.46, N:9.96.
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