Bioorganic & Medicinal Chemistry 16 (2008) 9891–9897

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

# Design and synthesis of novel 2′,3′-dideoxy-4′-selenonucleosides as potential antiviral agents

Lak Shin Jeong [a,*], Yoo Na Choi [a], Dilip K. Tosh [a], Won Jun Choi [a], Hea Ok Kim [a], Jungwon Choi [b]

[a] Laboratory of Medicinal Chemistry, College of Pharmacy, Ewha Womans University, Seoul 120-750, Republic of Korea
[b] Department of Chemistry, The University of Suwon, Kyunggi 445-743, Republic of Korea

ARTICLE INFO

*Article history:*
Received 26 August 2008
Revised 13 October 2008
Accepted 14 October 2008
Available online 17 October 2008

*Keywords:*
Anti-HIV agents
2′,3′-Dideoxy-4′-selenonucleosides
2′,3′-Dideoxycytidine
Pummerer type condensation
South conformation

ABSTRACT

On the basis of potent anti-HIV activity of 2',3'-dideoxynucleosides (ddNs), their bioisosteric analogues, 2',3'-dideoxy-4'-selenonucleosides (4'-seleno-ddNs) were first synthesized from a chiral template, D-glutamic acid using stereoselective ring-closure reaction of the dimesylate with $Se^{2-}$ and Pummerer type condensation of the selenoxide with nucleobases as key steps. X-ray crystallographic analysis indicated that 4'-seleno-ddNs adopted the same C2'-endo/C3'-exo (South) conformation as anti-HIV active ddNs, but did not show anti-HIV activity, indicating that RT seems to prefer the C2'-exo/C3'-endo (North) conformation on binding with their triphosphates.



## 1. Introduction

Since the discovery of AZT as an anti-AIDS drug, 2',3'-dideoxynucleosides (ddNs) have been the representative in developing nucleoside reverse transcriptase (RT) inhibitors.[1] Among these, 2',3'-dideoxycytidine (**1**, ddC)[2] and 2',3'-dideoxyinosine (ddI)[3] were approved by FDA for the treatment of AIDS and AIDS-related complex (ARC). 2',3'-Dideoxynucleosides, adopting C2'-endo/C3'-exo (South) conformation (Fig. 1)[4] exert their anti-HIV activity by the competitive reversible inhibition of RT and/or viral DNA chain termination.[5] However, these nucleoside analogues suffer from adverse effects[6] such as pancreatitis, peripheral neuropathy, and appearance of resistant strains. Thus, it has been highly demanded to discover new templates to overcome these unwanted effects. On the basis of bioisosteric rationale, new templates of 2',3'-dideoxynucleosides, 4'-thio[7] and 4'-carbo[8] analogues were synthesized, but did not exhibit significant anti-HIV activity, probably due to conformational difference. Thus, it has been urgent to discover another template showing anti-HIV activity, in which 4'-selenonucleosides have been considered as possible substitutes because of bioisosteric relationship between 4'-oxonucleosides and 4'-selenonucleosides.

Recently, we reported the stereoselective synthesis of 4'-selenouridine and its unusual South conformation (Fig. 1), in which *gauche* effects found in uridine were overwhelmed by the steric effects of the bulky selenium in 4'-selenouridine.[9] Very recently, we have also reported the stereoselective synthesis of the selenium analogues, 4′-seleno-d4Ns of 2',3'-didehydro-2',3'-dideoxynucleosides (d4Ns) and their conformational analysis as potential anti-HIV agents.[10] Molecular modeling study indicated that the orientation and position of 5′-hydroxyl group in 4′-seleno-d4T were significantly different from those of the potent anti-HIV drug, d4T, possibly affecting the cellular phosphorylation by kinases.[10]

Because ddC (**1**) is another representative anti-HIV drug, it is of great interest to synthesize the selenium analogues, 4′-seleno-ddNs (**2**–**4**) of ddC and to compare their anti-HIV activity (Fig. 2). It is also interesting to compare the conformations of ddC and 4′-seleno-ddC for their anti-HIV activity. Herein, we report the asymmetric synthesis of 4′-seleno-ddNs (**2**–**4**) from a chiral template, D-glutamic acid and their conformational study based on the X-ray crystal structure.

## 2. Results and discussion

First, the glycosyl donor **11** was synthesized from a chiral template, D-glutamic acid, using similar procedure in the preparation of 4'-seleno-ribofuranosyl pyrimidines[9] (Scheme 1).

Diazothization of D-glutamic acid followed by spontaneous cyclization produced L-γ-butyrolactone **5**, of which acid moiety was reduced with borane–dimethylsulfide complex to give the primary alcohol derivative **6**.[11] Treatment of **6** with TBDPSCl gave 5-*O*-TBDPS ether **7**[12] which was reduced with $LiBH_4$ to yield the diol **8**. Mesylation of **8** followed by $S_N2$ cyclization of the resulting

* Corresponding author. Tel.: +82 2 3277 3466; fax: +82 2 3277 2851.
*E-mail address:* lakjeong@ewha.ac.kr (L.S. Jeong).

0968-0896/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2008.10.034

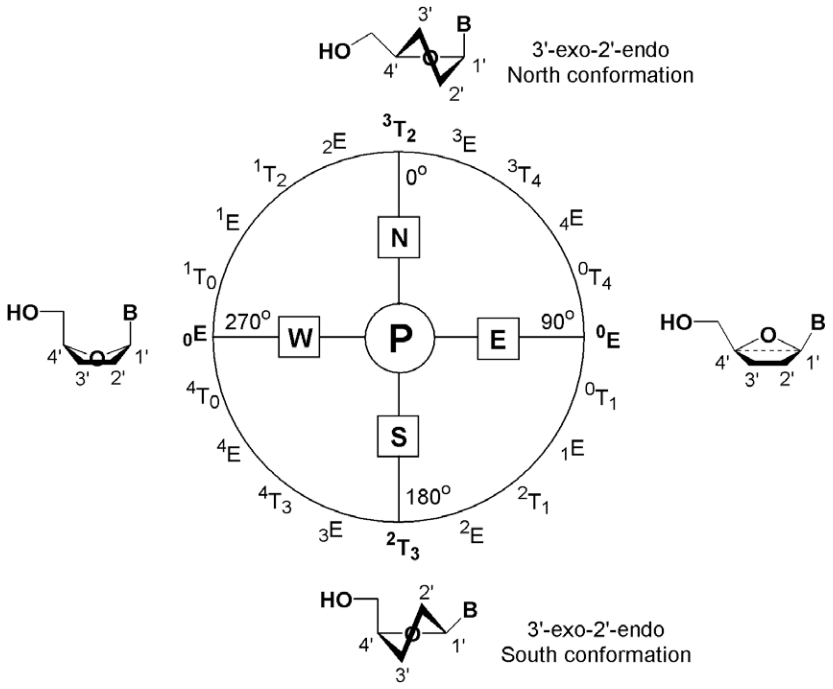



**Figure 1.** The pseudorotation cycle.

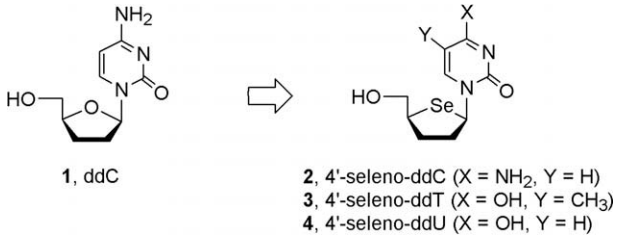
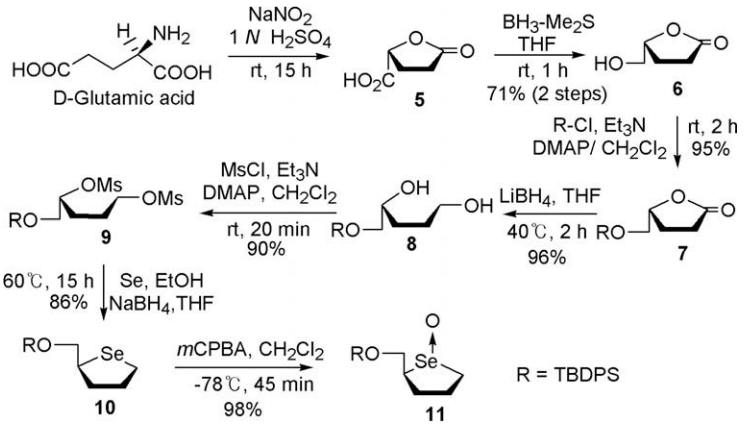



**Figure 2.** The rationale for the design of 4′-seleno-ddNs (**2**–**4**).

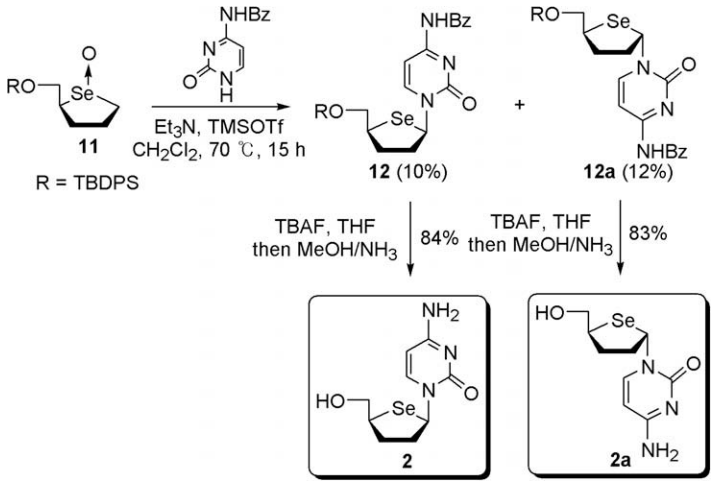
dimesylate **9** with $Se^{-2}$ formed *in situ* by reacting Se with $NaBH_4$ afforded the D-4-selenosugar **10**. Treatment of **10** with *m*CPBA gave the D-4-selenoxide **11** as a diastereomeric mixture, which was ready for the condensation with nucleobases.

With the glycosyl donor **11** in hand, it was next condensed with $N^4$-benzoylcytosine in the presence of TMSOTf and $Et_3N$ to give the β-isomer **12** and the α-isomer **12a** (Scheme 2).

Disappointingly, this condensation resulted in major formation of unidentified nonpolar and heavy UV absorbing material on TLC. The formation of condensed products **12** and **12a** occurred via 1-selenoxonium ion intermediate formed from the abstraction of less hindered 1-H than 4-H. Anomeric configurations of **12** and **12a** were easily assigned by $^1H$ NMR experiments. NOE between 1'-H and 4'-H of compound **12** was observed, indicating that it is β-isomer, while no NOE in compound **12a** was observed on the same experiment, showing it is α-isomer. Furthermore, $^1H$ NMR patterns of **12** and **12a** were similar to those of the corresponding 4'-oxonucleosides. Chemical shift of 5'-H of β-isomer **12** moved to more downfield than that of α-isomer **12a** because of the deshielding effect by heteroaromatic $N^4$-benzoylcytosine, whereas chemical shift of 4'-H of α-isomer **12a** shifted to more downfield than that of β-isomer **12** because of the same effect. The anomeric assignment of **12** was finally confirmed by X-ray crystal structure of the final nucleoside **2**. Removals of the TBDPS and benzoyl groups of **12** and **12a** under the standard conditions afforded 2',3'-dideoxy-4'-selenocytidine (**2**) and its α-isomer **2a**, respectively.




**Scheme 1.**




**Scheme 2.**

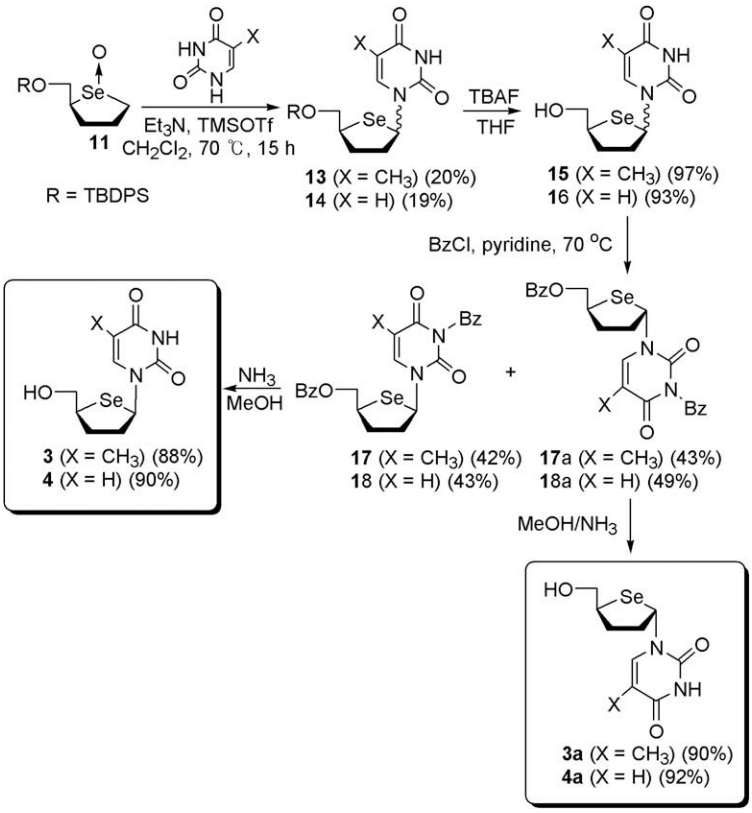
In addition to the cytosine derivative **2**, the thymine derivative **3** and the uracil derivative **4** were synthesized using the similar approach described in Scheme 2, as illustrated in Scheme 3. Pummerer-type condensation of **11** with thymine and uracil gave **13** and **14** as the inseparable α/β-mixtures, respectively. Treatment of the inseparable α/β-mixtures **13** and **14** with tetra-*n*-butylammonium fluoride still afforded the inseparable α/β-mixtures, **15** and **16**, respectively. Perbenzoylation of compound **15** yielded a separable mixture of β-isomer **17** and α-isomer **17a**. Treatment of **17** and **17a** with methanolic ammonia gave 4'-seleno-ddT (**3**) and its α-isomer **3a**, respectively. Similarly, the inseparable α/β-mixture of compound **16** was converted to 4'-seleno-ddU (**4**) and its α-isomer **4a**.

Structures of the final 4′-seleno-ddNs **2**–**4** were confirmed by spectral and analytical data as well as the X-ray crystal structure[13] of 4′-seleno-ddC (**2**), as shown in Figure 3.

X-ray crystallographic analysis of **2** showed that 2',3'-dideoxy-4'-selenouridine (**2**) adopted the same South-type puckered (C2'-*endo*/C3'-*exo*) conformation with pseudorotation phase angle $P = 183.3^{\circ}$ as 2',3'-dideoxycytidine (ddC)[14] ($P = 207.9^{\circ}$), indicating that 4'-seleno-ddC might give similar anti-HIV activity to that of ddC, but it did not give significant anti-HIV activity. Thus, the crystal structure of 4′-seleno-ddC has been superimposed with that of ddC.[14]

As shown in Figure 4, the marked conformational change was observed in the sugar ring. Elucidating the conformational differences, only five atoms in the sugar ring are used for the superimposition.

The large differences in the bond lengths and angles were observed in C1′–Se4′ and C4′–Se4′, and C4′–Se4′–C1′. The bond lengths C1′–Se4′ and C4′–Se4′ of 4′-seleno-ddC (**2**) were 1.977(2)




**Scheme 3.**

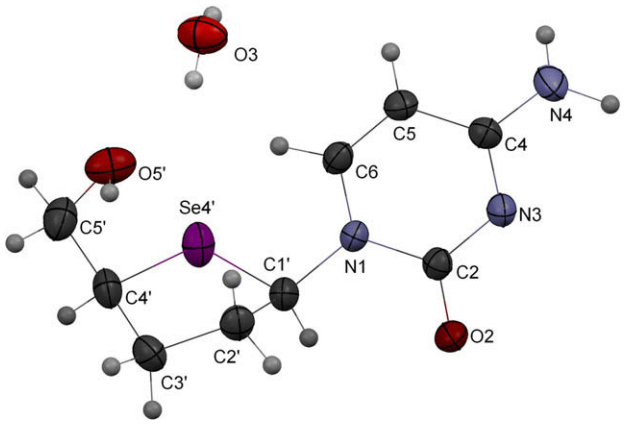



**Figure 3.** X-ray crystal structure of 4′-seleno-ddC (**2**).

and 1.973(2) Å, respectively, while the corresponding bond lengths of ddC were 1.401(3) and 1.461(3) Å, respectively. These longer bond lengths lead to the shrink of the bond angle C4′–Se4′–C1′ to the 90.2(1)°, which is 20.2° less than that of ddC. Although 4′-seleno-ddC (**2**) and ddC showed almost same South conformation, another major structural difference between two molecules can be described in terms of the geometry of glycosyl linkage and the orientation of the 5′-hydroxyl group relative to the sugar ring. The torsional angle $\chi$ (C2–N1–C1′–Se4′) of 4′-seleno-ddC is −129.6°, while that of ddC is −156.8°, which shows the same anti conformation but quite distorted conformation. The torsional angle (C3′–C4′–C5′–O5′) is 62.3° in 4′-seleno-ddC and 165.6° in ddC, showing the orientation of 5′-hydroxyl group is in the almost other direction. This result might explain the loss of anti-HIV activity of 4′-seleno-ddC, compared with that of ddC.

However, no anti-HIV activity of 4'-seleno-ddNs might be also explained in two ways, based on the report by Marquez et al.[15] First, can 4'-seleno-ddNs be phosphorylated by cellular kinase? They reported that thymidine kinase converts anti-HIV drug, AZT adopting South conformation to the AZT-triphosphate (TP), because it prefers South conformation. Therefore, 4'-seleno-ddNs seem to be phosphorylated to their 4'-seleno-ddNTPs by the cellular kinases because of the conformational similarity between anti-HIV active ddNs and 4'-seleno-ddNs. Secondly, can 4'-seleno-ddN triphosphates (TPs) bind to reverse transcriptase (RT)? It was reported that RT prefers the North conformation on binding with the AZT-TP, showing that AZT-TP is in dynamic equilibrium between a C2'-*endo*/C3'-*exo* twist (South) conformation and a C2'-*exo*/C3'-*endo* twist (North) conformation in the solution state, thus binding RT in the North conformation.[15] However, 4'-seleno-ddNTPs are not in dynamic N/S equilibrium, but fixed in South conformation because of the bulky selenium atom unlike interchangeable ddNTPs, showing these compounds cannot bind RT preferring the North conformation, resulting in no anti-HIV activity.

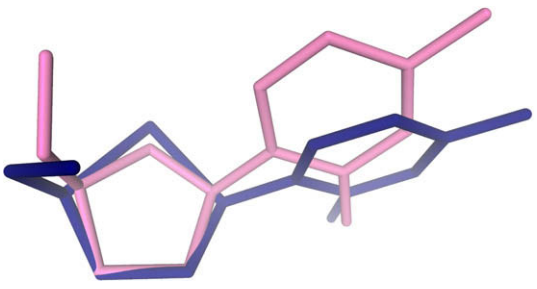


**Figure 4.** Superimposition of X-ray crystal structures between 4′-seleno-ddc (**2**, blue) and ddC (pink). Five atoms in the sugar ring are used for the alignment (RMSD = 0.270 Å).

## 3. Conclusion

We have accomplished the stereoselective synthesis of novel 2′,3′-dideoxy-4′-selenopyrimidine nucleosides (4′-seleno-ddNs) **2**–**4**, starting from a chiral template, D-glutamic acid and their conformational analysis based on X-ray crystal structure. Although we could not discover good anti-HIV agents, conformational analysis indirectly proved that RT prefers the North conformation on binding with NTPs. However, it should be further studied whether anti-HIV nucleosides prefer the South conformation for the phosphorylation and/or their triphosphates prefer the North conformation for binding with RT.

## 4. Experimental

### 4.1. General methods

$^1$H and $^{13}$C NMR Spectra ($CDCl_3$ or $CD_3OD$) were recorded on 400 and 100 MHz NMR, respectively. The $^1$H NMR data are reported as peak multiplicities: s for singlet, d for doublet, dd for doublet of doublets, t for triplet, q for quartet, br s for broad singlet and m for multiplet. Coupling constants are reported in hertz. The chemical shifts are reported as parts per million ($\delta$) relative to the solvent peak. Column chromatography was performed on silica gel 60 (230–400 mesh). All the anhydrous solvents were distilled over $CaH_2$, $P_2O_5$ or sodium/benzophenone prior to the reaction.

#### 4.1.1. (*R*)-5-(*tert*-Butyldiphenylsilanyloxy)pentane-1,4-diol (8)

To a stirred solution of compound **7** (35.88 g, 101.21 mmol) in THF (360 mL) was added lithium borohydride (4.64 g, 202.42 mmol, 95%) at 0 °C and the mixture was stirred at 40 °C for 2 h. The mixture was treated with $H_2O$ (100 mL) and the aqueous layer was extracted with EtOAc. The organic layer was dried with anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 2:1) to give **8** (34.84 g, 96%) as a white solid: mp 62.7–67.9 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.68–7.71 (m, 4H), 7.38–7.47 (m, 6H), 3.74–3.80 (m, 1H), 3.52–3.68 (m, 4H), 3.02 (s, 2H), 1.62–1.70 (m, 2H), 1.53–1.61 (m, 1H), 1.42–1.51 (m, 1H), 1.10 (s, 9H); $^{13}$C NMR ($CDCl_3$) $\delta$ 136.0, 135.8, 135.7, 133.29, 133.28, 130.0, 127.9, 127.9, 127.8, 72.1, 68.1, 62.8, 29.9, 29.2, 27.0, 19.4; *m/z* (FAB) 359 (M + $H^+$); $[\alpha]^{23}_D$ 2.37 (*c* 13.55 in $CH_2Cl_2$); Calcd for $C_{21}H_{30}O_3Si$: C, 70.35; H, 8.43. Found: C, 70.54; H, 8.25.

#### 4.1.2. (*R*)-1,4-di-*O*-Methanesulfonyl-5-*tert*-butyldiphenylsilanyloxypentane (9)

To a stirred solution of diol **8** (4.09 g, 11.41 mmol) and 4-DMAP (0.279 g, 2.282 mmol) in a mixture of $CH_2Cl_2$ (40 mL) and $Et_3N$ (12.72 mL, 91.28 mmol) was added dropwise methanesulfonyl chloride (3.53 mL, 45.64 mmol) at 0 °C. After being stirred for 0.5 h at room temperature, the mixture was extracted with $CH_2Cl_2$ and washed with saturated $NaHCO_3$ solution. The organic layer was dried with anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 3:1) to give **9** (5.29 g, 90%) as a colorless syrup: $^1$H NMR ($CDCl_3$) $\delta$ 7.64–7.67 (m, 4H), 7.41–7.46 (m, 6H), 4.75–4.77 (m, 1H), 4.21–4.26 (m, 2H), 3.83 (dd, 1H, *J* 6.0 and 11.6), 3.74 (dd, 1H, *J* 3.6 and 11.6), 2.99 (d, 6H, *J* 4.8), 1.79–1.89 (m, 4H), 1.07 (s, 9H); $^{13}$C NMR ($CDCl_3$) $\delta$ 135.8, 135.7, 132.9, 132.7, 130.32, 130.27, 128.2, 82.7, 69.3, 65.5, 38.9, 37.6, 27.7, 27.1, 24.9, 19.4; *m/z* (FAB) 515 (M + $H^+$); $[\alpha]^{23}_D$ 13.27 (*c* 1.78 in $CH_2Cl_2$); Calcd for $C_{23}H_{34}O_7S_2Si$: C, 53.67; H, 6.66. Found: C, 53.88; H, 6.26.

#### 4.1.3. (*S*)-2-(*tert*-Butyldiphenylsilyloxymethyl)-dihydroselenofuran (10)

To a stirred suspension of selenium (2.31 g, 29.21 mmol) in EtOH (250 mL) was added sodium borohydride pinch wise at room temperature until the color of the reaction mixture changed from black to colorless. To this mixture, **9** (10.02 g, 19.47 mmol) in THF (150 mL) was added and the mixture was stirred at 60 °C overnight. After the solvent was removed under reduced pressure, the residue was dissolved in EtOAc (50 mL) and washed with $H_2O$ (3× 30 mL), brine, dried with anhydrous $MgSO_4$, filtered, and evaporated. The resulting residue was purified by silica gel column chromatography (hexane/EtOAc = 20:1) to give **10** (6.76 g, 86%) as a pale yellow syrup: $^1$H NMR ($CDCl_3$) $\delta$ 7.67–7.71 (m, 4H), 7.37–7.44 (m, 6H), 3.69–3.78 (m, 3H), 2.85–2.89 (m, 2H), 1.93–2.04 (m, 4H), 1.08 (s, 9H); $^{13}$C NMR ($CDCl_3$) $\delta$ 135.73, 135.69, 133.8, 133.7, 129.8, 127.8, 68.0, 46.0, 35.1, 31.6, 27.0, 24.9, 19.4; *m/z* (FAB) 403 ($M^+$); $[\alpha]^{23}_D$ 37.75 (*c* 12.95 in $CH_2Cl_2$); Calcd for $C_{21}H_{28}OSeSi$: C, 62.51; H, 6.99. Found: C, 62.51; H, 6.68.

#### 4.1.4. (*S*)-2-(*tert*-Butyldiphenylsilyloxymethyl)-dihydroselenofuran-1-oxide (11)

To a stirred solution of **10** (3.11 g, 7.72 mmol) in $CH_2Cl_2$ (60 mL) was added a solution of *m*CPBA (1.90 g, 8.49 mmol, 77%) in $CH_2Cl_2$ (30 mL) dropwise at −78 °C and the reaction mixture was stirred at −78 °C for 45 min. The mixture was treated with saturated $NaHCO_3$ solution and extracted with $CH_2Cl_2$. The organic layer was washed with brine, dried with anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by short flash silica gel column chromatography ($CH_2Cl_2$/MeOH = 15:1) to give **11** (3.17 g, 98%) as a colorless syrup, which was immediately used for the condensation reaction because of unstable nature.

#### 4.1.5. β-D-5'-*tert*-Butyldiphenylsilyl-2',3'-dideoxy-4'-seleno-*N*$^4$-benzoylcytidine (12) and its α-isomer (12a)

To a stirred suspension of $N^4$-benzoylcytosine (2.72 g, 6.48 mmol) in toluene (28 mL) were added $Et_3N$ (3.62 mL, 25.94 mmol) and TMSOTf (9.54 mL, 51.87 mmol) at room temperature and the mixture was stirred at room temperature for 1 h and $CH_2Cl_2$ (11 mL) was added. This mixture was added to a solution of **11** (2.72 g, 6.48 mmol) in $CH_2Cl_2$ (11 mL) at 0 °C followed by addition of $Et_3N$ (3.62 mL, 25.94 mmol) in toluene (11 mL) at 0 °C. The reaction mixture was stirred at 70 °C overnight and then cooled, diluted with $CH_2Cl_2$, and washed with saturated $NaHCO_3$ solution and brine. The mixture was filtered through a Celite and the organic layer was separated, dried with anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 1:1) to give β-isomer **12** (0.40 g, 10%) as a pale brownish syrup and α-isomer **12a** (0.48 g, 12%) as a pale brownish syrup.

β-Isomer (**12**): UV $\lambda_{max}$ (MeOH) 277.0 nm; $^1$H NMR ($CDCl_3$) $\delta$ 8.31 (d, 1H, *J* 7.6), 7.92–7.94 (m, 2H), 7.69–7.73 (m, 4H), 7.54–7.58 (m, 1H), 7.40–7.49 (m, 9H), 6.55 (pseudo t, 1H, *J* 4.8), 3.84–4.12 (m, 3H), 2.33–2.36 (m, 1H), 2.15–2.22 (m, 2H), 1.86–1.92 (m, 1H), 1.10 (s, 9H); $^{13}$C NMR ($CDCl_3$) $\delta$ 162.0, 147.4, 135.9, 135.8, 133.3, 130., 130.2, 129.2, 128.0, 127.8, 96.8, 67.2, 60.8, 49.9, 39.2, 31.8, 29.9, 27.4, 19.4; *m/z* (FAB) 618 ($M^+$); $[\alpha]^{24}_D$ −43.10 (*c* 2.44 in $CH_2Cl_2$); Calcd for $C_{32}H_{35}N_3O_3SeSi$: C, 62.32; H, 5.72; N, 6.81. Found: C, 62.72; H, 5.98; N, 6.41.

α-Isomer (**12a**): UV $\lambda_{max}$ (MeOH) 277.0 nm; $^1$H NMR ($CDCl_3$) $\delta$ 8.37 (d, 1H, *J* 7.6), 7.90–7.92 (m, 2H), 7.38–7.69 (m, 14H), 6.60 (t, 1H, *J* 6.0), 4.09–4.17 (m, 1H), 3.85 (dd, 1H, *J* 7.2 and 10.4), 3.73 (dd, 1H, *J* 7.6, 10.4), 2.46–2.47 (m, 1H), 2.03–2.15 (m, 2H), 1.07 (s, 9H); $^{13}$C NMR ($CDCl_3$) $\delta$ 161.9, 147.3, 135.83, 135.8, 133.5, 133.3, 130.1, 129.2, 128.0, 97.0, 67.4, 60.0, 49.2, 39.1, 32.2, 29.9, 27.0, 19.5; *m/z* (FAB) 618 ($M^+$); $[\alpha]^{24}_D$ 110.02 (*c* 1.43 in $CH_2Cl_2$); Calcd for $C_{32}H_{35}N_3O_3SeSi$: C, 62.32; H, 5.72; N, 6.81. Found: C, 62.43; H, 5.77; N, 6.65.

#### 4.1.6. α,β-D-5'-*tert*-Butyldiphenylsilyl-2',3'-dideoxy-4'-selenothymidine (13)

Compound **11** (3.20 g, 7.63 mmol) was converted to **13** (0.60 g, 15%) as a pale brownish syrup according to the similar procedure used in the preparation of **12**: UV $\lambda_{max}$ ($CH_2Cl_2$) 271.0 nm; $^1$H NMR ($CDCl_3$) $\delta$ 7.64–7.71 (m, 8H), 7.58 (d, 2H, *J* 1.2) 7.38–7.47 (m, 2H), 6.49–6.53 (m, 2H), 4.11–4.17 (m, 1H), 3.84–3.91 (m, 4H), 3.70–3.74 (m, 1H), 2.09–2.46 (m, 8H), 1.83–2.05 (m, 6H), 1.08 (s, 9H), 1.06 (s, 9H); *m/z* (FAB) 529 ($M^+$); Calcd for $C_{26}H_{32}N_2O_3SeSi$: C, 59.19; H, 6.11; N, 5.31. Found: C, 59.48; H, 5.96; N, 5.13.

#### 4.1.7. α,β-D-5'-*tert*-Butyldiphenylsilyl-2',3'-dideoxy-4'-selenouridine (14)

Compound **11** (2.89 g, 6.88 mmol) was converted to **14** (0.46 g, 13%) as a pale brownish syrup according to the similar procedure used in the preparation of **12**: UV $\lambda_{max}$ (MeOH) 265.5 nm; $^1$H NMR ($CDCl_3$) $\delta$ 10.35 (s, 2H), 7.38–7.84 (m, 20H), 6.50–6.56 (m, 2H), 5.83 (d, 1H, *J* 8.0), 5.65 (d, 1H, *J* 8.0), 3.70–4.16 (m, 6H), 1.89–2.45 (m, 10H), 1.10 (s, 9H), 1.08 (s, 9H); *m/z* (FAB) 529 ($M+H^+$); Calcd for $C_{25}H_{30}N_2O_3SeSi$: C, 58.47; H, 5.89; N, 5.45. Found: C, 58.18; H, 5.49; N, 5.85.

#### 4.1.8. α,β-D-2',3'-Dideoxy-4'-selenothymidine (15)

To a stirred solution of compound **14** (0.27 g, 0.49 mmol) in THF (20 mL), TBAF (0.74 mL, 1 M solution in THF, 0.74 mmol) was added and the mixture was stirred at room temperature for 0.5 h. The reaction mixture was evaporated and the residue was purified by flash silica gel column chromatography ($CH_2Cl_2$/MeOH = 20:1) to give **15** (0.14 g, 97%) as a white foam: $^1$H NMR ($CDCl_3$) $\delta$ 7.94 (s, 1H), 7.81 (s, 1H), 6.48 (t, 1H, *J* 7.6), 6.43 (t, 1H, *J* 6.0), 4.10–4.17 (m, 1H), 3.75–3.93 (m, 4H), 3.58–3.63 (m, 1H), 2.13–2.49 (m, 8H), 1.85–1.94 (m, 6H). Calcd for $C_{10}H_{14}N_2O_3Se$: C, 41.53; H, 4.88; N, 9.69. Found: C, 41.87; H, 4.44; N, 9.98.

#### 4.1.9. α,β-D-2',3'-Dideoxy-4'-selenouridine (16)

Compound **14** (0.48 g, 0.93 mmol) was converted to **16** (0.24 g, 93%) as a white foam according to the similar procedure used in the preparation of **15**: $^1$H NMR ($CDCl_3$) $\delta$ 8.12 (d, 1H, *J* 8.0), 8.02 (d, 1H, *J* 8.4), 6.45 (t, 1H, *J* 6.8), 6.42 (t, 1H, *J* 6.0), 5.76 (d, 1H, *J* 6.4), 5.74 (d, 1H, *J* 6.4), 4.07–4.14 (m, 1H), 3.74–3.93 (m, 4H), 3.57–3.62 (m, 1H), 2.43–2.51 (m, 1H), 2.17–2.39 (m, 5H), 2.04–2.13 (m, 1H), 1.91–2.00 (m, 1H). Calcd for $C_9H_{12}N_2O_3Se$: C, 39.28; H, 4.40; N, 10.18. Found: C, 39.35; H, 4.30; N, 10.58.

#### 4.1.10. β-D-5'-Benzoyl-2',3'-dideoxy-4'-seleno-*N*$^3$-benzoylthymidine (17) and its α-isomer (17a)

To a stirred solution of compound **15** (0.12 g, 0.40 mmol) in pyridine (12 mL), BzCl (0.23 mL, 2.01 mmol) was added and the mixture was stirred at 70 °C overnight. The reaction mixture was evaporated and the residue was purified by silica gel column chromatography (hexane/EtOAc = 3:1) to give β-isomer **17** (83.6 mg, 42%) as a white foam and α-isomer **17a** (85.6 mg, 43%) as a white foam.

β-Isomer (**17**): UV $\lambda_{max}$ (MeOH) 254.0 nm; $^1$H NMR ($CDCl_3$) $\delta$ 8.06–8.08 (m, 2H), 7.90–7.93 (m, 2H), 7.73 (s, 1H), 7.59–7.67 (m, 2H), 7.46–7.51 (m, 4H), 6.58 (t, 1H, *J* 6.4), 4.72 (dd, 1H, *J* 7.6 and 11.2), 4.60 (dd, 1H, *J* 6.8 and 11.6), 2.47–2.52 (m, 1H), 2.22–2.30 (m, 3H), 1.93 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 171.8, 169.0, 166.5, 162.8, 149.7, 137.1, 135.3, 133.9, 133.6, 131.7, 130.7, 130.4, 129.9, 129.8, 129.3, 128.8, 128.7, 111.7, 67.3, 58.6, 44.8, 37.5, 33.0, 12.9; *m/z* (FAB) 497 ($M^+$); $[\alpha]^{23}_D$ -14.15 (*c* 6.34 in $CH_2Cl_2$); Calcd for $C_{24}H_{22}N_2O_5Se$: C, 57.95; H, 4.46; N, 5.63. Found: C, 58.15; H, 4.67; N, 5.26.

α-Isomer (**17a**): UV $\lambda_{max}$ (MeOH) 254.0 nm; $^1$H NMR ($CDCl_3$) $\delta$ 8.03–8.06 (m, 2H), 7.90–7.93 (m, 2H), 7.57–7.67 (m, 3H), 7.44–7.51 (m, 4H), 6.63 (t, 1H, *J* 6.8), 4.57–4.63 (m, 1H), 4.32–4.42 (m, 2H), 2.58–2.66 (m, 1H), 2.39–2.46 (m, 1H), 2.05–2.19 (m, 1H), 1.99 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 169.0, 166.3, 162.8, 149.7, 137.2, 135.3, 133.5, 131.7, 130.7, 129.9, 129.4, 128.7, 111.8, 67.9, 58.2, 45.0, 38.7, 33.8, 13.0; *m/z* (FAB) 497 ($M^+$); $[\alpha]^{23}_D$ 75.77 (*c* 10.51 in $CH_2Cl_2$); Calcd for $C_{24}H_{22}N_2O_5Se$: C, 57.95; H, 4.46; N, 5.63. Found: C, 57.76; H, 4.06; N, 5.44.

#### 4.1.11. β-D-5'-Benzoyl-2',3'-dideoxy-4'-seleno-*N*$^3$-benzoyluridine (18) and its α-isomer (18a)

Compound **16** (0.23 g, 0.84 mmol) was converted to β-isomer **18** (174.6 mg, 43%) as a white foam and α-isomer **18a** (199.0 mg, 49%) as a white foam according to the similar procedure used in the preparation of **17** and **17a**.

β-Isomer (**18**): UV $\lambda_{max}$ (MeOH) 253.5 nm; $^1$H NMR ($CDCl_3$) $\delta$ 8.04–8.07 (m, 2H), 8.00 (d, 1H, *J* 8.4), 7.91–7.93 (m, 2H), 7.58–7.66 (m, 2H), 7.45–7.51 (m, 4H), 6.53 (t, 1H, *J* 6.4), 5.80 (d, 1H, *J* 8.0), 4.73 (dd, 1H, *J* 7.2 and 11.6), 4.57 (dd, 1H, *J* 6.4 and 11.6), 4.08–4.13 (m, 1H), 2.43–2.50 (m, 1H), 2.26–2.33 (m, 2H), 2.12–2.19 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 171.6, 168.8, 166.4, 162.1, 149.7, 141.7, 135.4, 133.8, 133.7, 131.5, 130.7, 130.3, 129.8, 129.7, 129.4, 128.8, 128.6, 102.7, 67.0, 59.3, 45.2, 38.2, 32.9; *m/z* (FAB) 483 ($M^+$); $[\alpha]^{24}_D$ −3.71 (*c* 5.42 in $CH_2Cl_2$); Calcd for $C_{23}H_{20}N_2O_5Se$: C, 57.15; H, 4.17; N, 5.80. Found: C, 57.43; H, 4.56; N, 5.40.

α-Isomer (**18a**): UV $\lambda_{max}$ (MeOH) 253.5 nm; $^1$H NMR ($CDCl_3$) $\delta$ 8.02–8.05 (m, 2H), 7.91–7.94 (m, 2H), 7.63–7.67 (m, 1H), 7.56–7.61 (m, 1H), 7.44–7.52 (m, 4H), 6.59 (t, 1H, *J* 6.4), 5.92 (d, 1H, *J* 8.4), 4.58 (dd, 1H, *J* 6.8 and 10.8), 4.32–4.39 (m, 2H), 2.58–2.64 (m, 1H), 2.35–2.39 (m, 1H), 2.05–2.19 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 168.8, 166.2, 162.1, 149.6, 141.6, 135.4, 133.5, 131.5, 130.7, 129.9, 129.8, 129.4, 128.7, 102.9, 67.7, 58.6, 44.9, 38.7, 33.6; *m/z* (FAB) 483 ($M^+$); $[\alpha]^{24}_D$ 89.14 (*c* 3.61 in $CH_2Cl_2$); Calcd for $C_{23}H_{20}N_2O_5Se$: C, 57.15; H, 4.17; N, 5.80. Found: C, 56.96; H, 4.54; N, 5.54.

#### 4.1.12. β-D-2',3'-Dideoxy-4'-selenocytidine (2)

To a stirred solution of β-isomer **12** (0.46 g, 0.74 mmol) in THF (46 mL), TBAF (1.11 mL, 1 M solution in THF, 1.11 mmol) was added and the mixture was stirred at room temperature for 0.5 h and evaporated. To this residue, methanolic ammonia (5 mL) was added and the reaction mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was purified by silica gel column chromatography ($CH_2Cl_2$:MeOH = 30:1) to give **2** (0.17 g, 84%) as a white solid: mp 139.3–147.4 °C (from MeOH/ether); UV $\lambda_{max}$ (MeOH) 277.0 nm; $^1$H NMR ($CD_3OD$) $\delta$ 8.14 (d, 1H, *J* 7.6), 6.45 (t, 1H, *J* 5.6), 5.93 (d, 1H, *J* 7.6), 3.82–3.92 (m, 2H), 3.75 (dd, 1H, *J* 6.0 and 10.4), 2.29–2.38 (m, 2H), 2.18–2.27 (m, 1H), 2.00–2.09 (m, 1H); $^{13}$C NMR ($CD_3OD$) $\delta$ 167.4, 158.6, 144.6, 96.4, 66.8, 60.4, 50.3, 38.7, 33.7; *m/z* (FAB) 276 ($M^+$); $[\alpha]^{25}_D$ -141.18 (*c* 0.12 in MeOH); Calcd for $C_9H_{13}N_3O_2Se$: C, 39.43; H, 4.78; N, 15.33. Found: C, 39.43; H, 4.67; N, 15.12.

#### 4.1.13. α-D-2',3'-Dideoxy-4'-selenocytidine (2a)

Compound **12a** (0.48 g, 0.78 mmol) was converted to **2a** (0.18 g, 83%) as a white solid according to the similar procedure used in the preparation of **2**: mp 188.0–197.4 °C (from MeOH/ether); UV $\lambda_{max}$ (MeOH) 277.0 nm; $^1$H NMR ($CD_3OD$) $\delta$ 8.04 (d, 1H, *J* 7.6), 6.49 (t, 1H, *J* 6.8), 5.94 (d, 1H, *J* 7.6), 4.04–4.10 (m, 1H), 3.78 (dd, 1H, *J* 7.2 and 11.2), 3.60 (dd, 1H, *J* 7.2 and 10.8), 2.42–2.50 (m, 1H), 2.15–2.32 (m, 2H), 1.94–2.02 (m, 1H); $^{13}$C NMR ($CD_3OD$) $\delta$ 167.5, 158.7, 144.5, 96.6, 67.3, 59.7, 50.0, 38.8, 34.1; *m/z* (FAB) 276 ($M^+$); $[\alpha]^{25}_D$ 342.27 (*c* 0.10 in MeOH); Calcd for $C_9H_{13}N_3O_2Se$: C, 39.43; H, 4.78; N, 15.33. Found: C, 39.65; H, 5.18; N, 14.98.

#### 4.1.14. β-D-2',3'-Dideoxy-4'-selenothymidine (3)

The mixture of **17** (0.43 g, 0.86 mmol) in methanolic ammonia (5 mL) was stirred at room temperature overnight. The solvent was evaporated and the residue was purified by silica gel column chromatography ($CH_2Cl_2$/MeOH = 30:1) to give **3** (0.22 g, 88%) as a white solid: mp 144.7–147.9 °C (from MeOH/ether); UV $\lambda_{max}$ (MeOH) 271.5 nm; $^1$H NMR ($CD_3OD$) $\delta$ 7.94 (s, 1H), 6.43 (t, 1H, *J* 6.8), 3.84–3.93 (m, 2H), 3.77 (dd, 1H, *J* 5.2 and 10.4), 2.31–2.36 (m, 2H), 2.13–2.20 (m, 2H), 1.90 (s, 3H); $^{13}$C NMR ($CD_3OD$) $\delta$ 166.4, 152.7, 139.8, 111.7, 66.6, 59.2, 50.5, 38.4, 33.7, 12.6; *m/z* (FAB) 289 ($M^+$); $[\alpha]^{25}_D$ −120.16 (*c* 0.13 in MeOH); Calcd for $C_{10}H_{14}N_2O_3Se$: C, 41.53; H, 4.88; N, 9.69. Found: C, 41.87; H, 4.98; N, 10.08.

#### 4.1.15. α-D-2',3'-Dideoxy-4'-selenothymidine (3a)

Compound **17a** (0.58 g, 1.17 mmol) was converted to **3a** (0.30 g, 90%) as a white solid according to the similar procedure used in the preparation of **3**: mp 208.7–210.3 °C (from MeOH/ether); UV $\lambda_{max}$ (MeOH) 271.0 nm; $^1$H NMR ($CD_3OD$) $\delta$ 7.81 (s, 1H), 6.48 (t, 1H, *J* 6.8), 4.10–4.17 (m, 1H), 3.80 (dd, 1H, *J* 6.8 and 11.2), 3.61 (dd, 1H, *J* 7.6 and 11.6), 2.42–2.50 (m, 1H), 2.31–2.39 (m, 1H), 2.17–2.26 (m, 1H), 1.85–1.94 (m, 4H); $^{13}$C NMR ($CD_3OD$) $\delta$ 139.6, 112.1, 67.4, 58.2, 50.6, 38.7, 34.4, 12.6; *m/z* (FAB) 289 ($M^+$); $[\alpha]^{25}_D$ 230.43 (*c* 0.09 in MeOH); Calcd for $C_{10}H_{14}N_2O_3Se$: C, 41.53; H, 4.88; N, 9.69. Found: C, 41.93; H, 4.49; N, 9.99.

#### 4.1.16. β-D-2',3'-Dideoxy-4'-selenouridine (4)

Compound **18** (0.38 g, 0.79 mmol) was converted to **4** (0.19 g, 90%) as a white solid according to the similar procedure used in the preparation of **3**: mp 163.5–166.4 °C (from MeOH/ether); UV $\lambda_{max}$ (MeOH) 267.0 nm; $^1$H NMR ($CD_3OD$) $\delta$ 8.13 (d, 1H, *J* 8.0), 6.42 (t, 1H, *J* 6.0), 5.74 (d, 1H, *J* 8.0), 3.84–3.93 (m, 2H), 3.76 (dd, 1H, *J* 6.0 and 10.4), 2.31–2.37 (m, 2H), 2.19–2.24 (m, 1H), 2.08–2.11 (m, 1H); $^{13}$C NMR ($CD_3OD$) $\delta$ 166.3, 152.6, 144.3, 102.8, 66.7, 59.4, 50.6, 38.5, 33.7; *m/z* (FAB) 276 ($M+H^+$); $[\alpha]^{25}_D$ −176.04 (*c* 0.10 in MeOH); Calcd for $C_9H_{12}N_2O_3Se$: C, 39.28; H, 4.40; N, 10.18. Found: C, 39.54; H, 4.67; N, 9.98.

#### 4.1.17. α-D-2',3'-Dideoxy-4'-selenouridine (4a)

Compound **18a** (0.45 g, 0.93 mmol) was converted to **4a** (0.24 g, 92%) as a white solid according to the similar procedure used in the preparation of **3**: mp 187.1–188.1 °C (from MeOH/ether); UV $\lambda_{max}$ (MeOH) 267.0 nm; $^1$H NMR ($CD_3OD$) $\delta$ 8.03 (d, 1H, *J* 8.0), 6.46 (t, 1H, *J* 6.8), 5.75 (d, 1H, *J* 8.0), 4.07–4.14 (m, 1H), 3.79 (dd, 1H, *J* 6.8 and 11.2), 3.60 (dd, 1H, *J* 7.6 and 11.2), 2.43–2.51 (m, 1H), 2.27–2.35 (m, 1H), 2.17–2.25 (m, 1H), 1.91–2.00 (m, 1H); $^{13}$C NMR ($CD_3OD$) $\delta$ 166.2, 152.5, 144.3, 103.1, 67.3, 58.6, 50.5, 38.8, 34.2; *m/z* (FAB) 276 ($M+H^+$); $[\alpha]^{25}_D$ 268.37 (*c* 0.10 in MeOH); Calcd for $C_9H_{12}N_2O_3Se$: C, 39.28; H, 4.40; N, 10.18. Found: C, 39.08; H, 4.43; N, 10.09.

## Acknowledgments

This work was supported by Grant No. R15–2006-020 from the National Core Research Center (NCRC) program of the Ministry of Education, Science and Technology (MEST) and the Korea Science and Engineering Foundation (KOSEF) through the Center for Cell Signalling & Drug Discovery Research at Ewha Womans University.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2008.10.034.

## References and notes


1. (a) Jeong, L. S.; Kim, H. O.; Beach, J. W.; Chung, W. K.; Chun, M. W.; Chu, C. K. In *Nucleosides and Derivatives*; Mohan, P., Baba, M., Eds.; Harwood Academic Publishers, 1995; pp 39–63. ch. 2; (b) Nasr, M.; Litterst, C.; McGowan, J. *Antiviral Res.* **1990**, *14*, 125–148; (c) De Clercq, E. *AIDS Res. Hum. Retroviruses* **1992**, *8*, 119–134; (d) Nasr, M.; Cradock, J.; Johnston, M. I. *AIDS Res. Hum. Retroviruses* **1992**, *8*, 135–144.
2. Mitsuya, H.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 1911–1915.
3. Yarchoan, R.; Mitsuya, H.; Thomas, R. V.; Pluda, J. M.; Hartman, N. R.; Perno, C. F.; Narczyk, K. S.; Allain, J. P.; Johns, D. G.; Broder, S. *Science* **1989**, *245*, 412–415.
4. Marquez, V. E.; Siddiqui, M. A.; Ezzitouni, A.; Russ, P.; Wang, J.; Wagner, R.; Matteucci, M. D. *J. Med. Chem.* **1996**, *39*, 3739–3747.
5. De Clercq, E. *Trends Pharmacol. Sci.* **1987**, *8*, 339–345.
6. (a) Lambert, J. S.; Seidlin, M.; Reichman, R. C.; Plank, C. S.; Laverty, M.; Morse, G. D.; Knupp, C.; McLaren, C.; Pettinelli, C.; Valentine, F. T.; Dolin, R. *N. Engl. J. Med.* **1990**, *322*, 1333–1340; (b) Parker, W. B.; Cheng, Y. C. *J. NIH Res.* **1994**, *6*, 57–61.
7. (a) Secrist, J. A., III; Riggs, R. M.; Tiwari, K. N.; Montgomery, J. A. *J. Med. Chem.* **1992**, *35*, 533–538; (b) Gunaga, P.; Moon, H. R.; Choi, W. J.; Shin, D. H.; Park, J. G.; Jeong, L. S. *Curr. Med. Chem.* **2004**, *11*, 2585–2637.
8. (a) Piperno, A.; Chiacchio, M. A.; Iannazzo, D.; Romeo, R. *Curr. Med. Chem.* **2006**, *13*, 3675–3695; (b) Ferrero, M.; Gotor, V. *Chem. Rev.* **2000**, *100*, 4319–4347; (c) Lee, J. A.; Jeong, L. S. *Antiviral Chem. Chemother.* **2004**, *15*, 235–250; (d) Marquez, V. E.; Lim, M.-I. *Med. Res. Rev.* **1986**, *6*, 1–40.
9. Jeong, L. S.; Tosh, D. K.; Kim, H. O.; Wang, T.; Hou, X.; Yun, H. S.; Kwon, Y.; Lee, S. K.; Choi, J.; Zhao, L. X. *Org. Lett.* **2008**, *10*, 209–212.
10. Tosh, D. K.; Choi, W. J.; Kim, H. O.; Lee, Y.; Pal, S.; Hou, X.; Choi, J.; Choi, S.; Jeong, L. S. *J. Org. Chem.* **2008**, *73*, 4259–4262.
11. Cervinka, O.; Hub, L. *Collect. Czech. Chem. Commun.* **1968**, *33*, 2927–2932.
12. Hanessian, S.; Murray, P. J. *Tetrahedron* **1987**, *43*, 5055–5072.
13. $C_9H_{13}N_3O_2Se{\cdot}H_2O$, $M_r = 292.20$, orthorhombic, space group $P2_12_12_1$ (no. 19), $a = 9.2933(3)$ Å, $b = 10.9991(3)$ Å, $c = 11.3111(4)$ Å, $V = 1156.19(7)$ Å$^3$, $T = 293(2)$ K, $Z = 4$, $\rho_{calc} = 1.679$ gcm$^{-3}$, $F(000) = 592$, crystal dimension $0.50 \times 0.30 \times 0.20$ mm$^3$, μ(Mo Kα) = 3.25 mm$^{-1}$, Mo Kα radiation ($\lambda = 0.7107$ Å). Of 11317 reflections collected in the $2\theta$ range from 3.4 to 27.5° using an $\omega$ scans on a Rigaku Rapid *R*-axis diffractometer, 2638 were unique reflections ($R_{int} = 0.040$). The structure was solved and refined against $F^2$ using SHELXS97 and SHELXL97, 206 variables, $wR_2 = 0.055$, $R_1 = 0.023$ (the 2433 reflections having $Fo^2 > 2\sigma(Fo^2)$), GOF = 1.09, and max/min residual electron density 0.39/−0.41 eÅ$^{-3}$. Flack *x* parameter = -0.008(9). Further details of the crystal structure investigation(s) may be obtained from the Cambridge Crystallographic Data Centre (CCDC, 12 Union Road, Cambridge, CB2 1EZ (UK); Tel.: (+44)1223-336-408, fax: (+44)1223-336-033, e-mail: deposit@ccdc.cam.ac.uk) on quoting the Depository No. CSD-694409.
14. (a) Van Roey, P.; Taylor, E. W.; Chu, C. K.; Schinazi, R. F. *Ann. N.Y. Acad. Sci. U.S.A.* **1990**, *616*, 29–40; (b) Bimbaum, G. I.; Lin, T.; Prusoff, W. H. *Biochem. Biophys. Res. Comm.* **1988**, *151*, 608–614.
15. Marquez, V. E.; Ezzitouni, A.; Russ, P.; Siddiqui, M. A.; Ford, H., Jr; Feldman, R. J.; Mitsuya, H.; George, C.; Barchi, J. J., Jr *J. Am. Chem. Soc.* **1998**, *120*, 2780–2789.