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Stereoselective Synthesis and Conformational Study of Novel 2′,3′-Didehydro-2′,3′-dideoxy-4′-selenonucleosides

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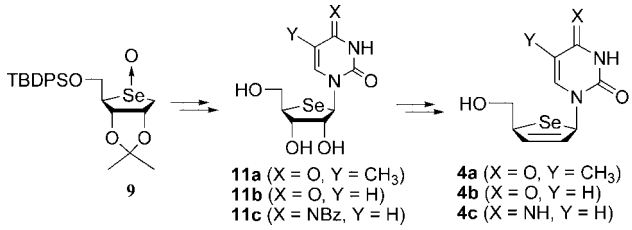

Stereoselective synthesis of novel 2′,3′-didehydro-2′,3′-dideoxy-4′-selenonucleosides (4′-seleno-d4Ns) **4a**−**c** was accomplished via 4′-selenoribofuranosyl pyrimidines **11a**−**c**, as key intermediates. 4′-Selenoribofuranosyl pyrimidines **11a**−**c** were efficiently synthesized from D-ribose or D-gulonic γ-lactone using a Pummerer-type condensation as a key step. Introduction of 2′,3′-double bond was achieved by treating cyclic 2′,3′-thiocarbonate with 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine.

2′,3′-Didehydro-2′,3′-dideoxynucleosides (**1**, d4Ns) have played an important role in developing nucleoside human immunodeficiency virus (HIV) reverse transcriptase (RT) inhibitors[1] along with 2′,3′-dideoxynucleosides (d2Ns) (Figure 1). Among these, the thymine analogue (d4T, stavudine)[2] is being clinically used for the treatment of AIDS patients. Since the discovery of d4Ns, 4′-carbonucleosides (**2**, 4′-carbo-d4Ns), whose furanose oxygen of d4Ns was replaced with the bioisosteric methylene (CH_2) have been synthesized and evaluated for their anti-HIV activity. Among them, 2-amino-6-cyclopropylaminopurine analogue

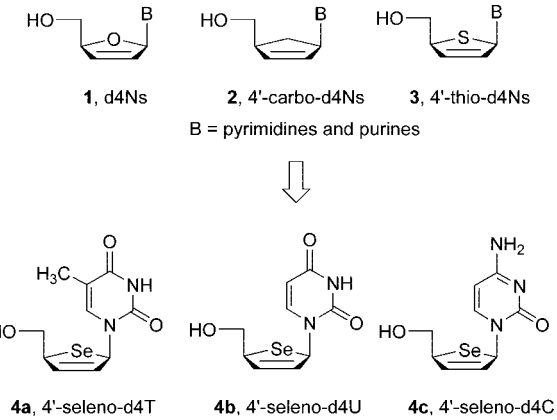

FIGURE 1. The rationale for the design of the target 4′-seleno-d4Ns.

(abacavir)[3,4] was discovered as a potent HIV RT inhibitor and approved for the clinical use. Also, 4′-thionucleoside analogues (**3**, 4′-thio-d4Ns)[5] whose furanose oxygen of d4Ns was replaced with the bioisosteric sulfur exhibited potent anti-HIV activity. All these compounds exert their anti-HIV activity by competitively inhibiting HIV RT and/or by terminating viral DNA chain.[6] However, because they cause some unwanted effects[7] such as peripheral neuropathy and drug resistance, it is highly desirable to discover a new template for the development of novel anti-HIV agents.

Selenium is in the bioisosteric relationship with oxygen and sulfur and also acts as a chemical isostere of methylene (CH_2). In the previous communication,[8] we reported the stereoselective synthesis of 4′-selenocytidine and 4′-selenouridine and their unusual "South" conformations and it was of great interest to synthesize the selenium analogues of d4Ns, 4′-seleno-d4Ns and compare their anti-HIV activity. It was also interesting to compare the conformations of d4Ns with those of 4′-seleno-d4Ns because selenium is bulkier than oxygen. In this note, we

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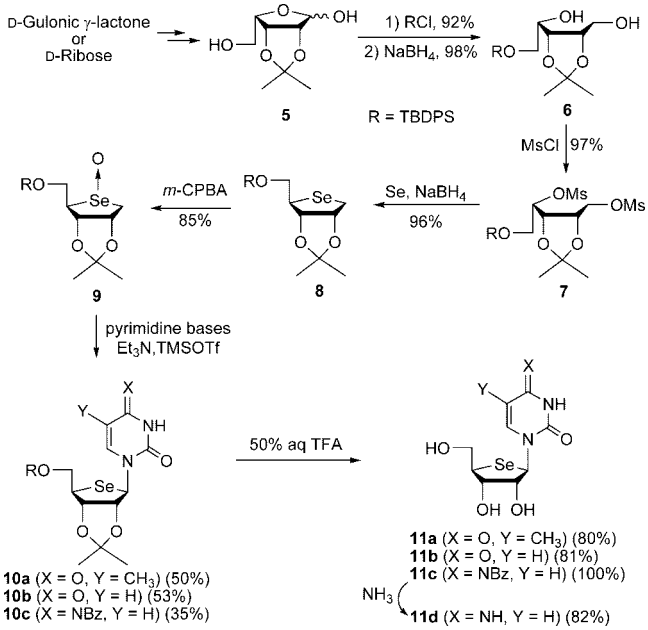
SCHEME 1. Synthesis of 4′-Selenoribofuranosyl Pyrimidines



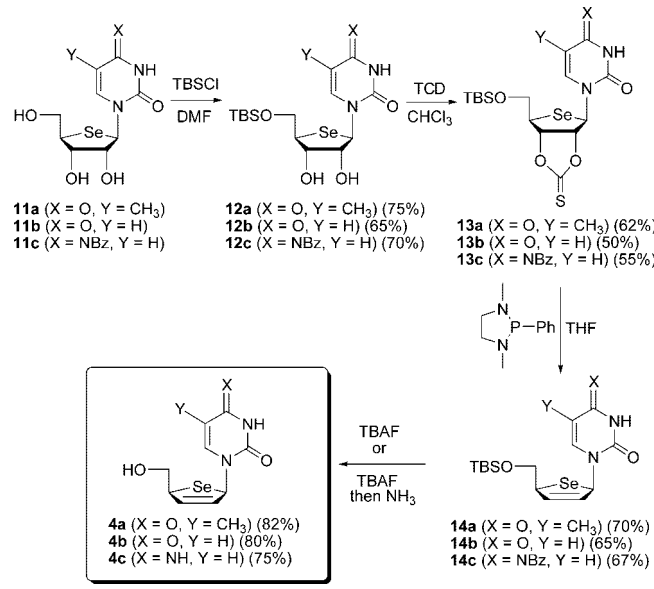
report the stereoselective synthesis of 4′-seleno-d4Ns **4a**−**c** and their conformational analysis based on X-ray crystal structures.

Synthesis of the target nucleosides **4a**−**c** was completed via 4′-selenoribofuranosyl pyrimidines **11a–c**, which were synthesized, starting from D-gulonic acid γ-lactone or D-ribose, as shown in Scheme 1.[8]

D-Gulonic acid γ-lactone or D-ribose was converted to the known intermediate, L-lyxose derivative **5**.[8,9] TBDPS protection of **5** followed by reduction with $NaBH_4$ afforded the diol **6** in excellent yield. Mesylation of **6** gave the dimesylate **7**. Ring closure reaction of **7** with Se^{2-} formed *in situ* by reacting Se with $NaBH_4$ yielded the 4-selenosugar **8**. Oxidation of **8** with *m*CPBA gave the 4-selenoxide **9** as a diastereomeric mixture. The Pummerer-type condensation of **9** with uracil, thymine, and N^4-benzoylcytosine in the presence of TMSOTf and Et_3N afforded the thymine derivative **10a**, the uracil derivative **10b**, and the cytosine derivative **10c**, respectively without the formation of the corresponding α-isomers. The condensation reaction mechanistically proceeded via the formation of α-selenocarbocation formed by an E2 elimination reaction followed by the attack of the nucleobase from less hindered β-side. Removals of the protecting groups in **10a**, **10b**, and **10c** afforded the 5-methyl-4′-selenouridine (**11a**), 4′-selenouridine (**11b**),[8] and 4′-selenocytidine (**11d**),[8] respectively.

The stereochemical assignments of β-anomers, **11a**, **11b**, and **11d** were based on the X-ray crystal structure[8] of **11b**. It was illustrated that 4′-selenouridine **11b** adopted an unusual C2′-*endo*/C3′-*exo* twist (South) conformation, whereas uridine[10] showed the C2′-*exo*/C3′-endo twist (North) conformation (see Supporting Information). These results indicated that the *anti* orientation by the steric effects of selenium was the dominant factor in determining the conformation of the 4′-selenonucleoside. The orientation of the O5′-hydroxyl group in **11b** was also

SCHEME 2. Synthesis of 4′-Seleno-d4Ns



in the unusual *antiperiplanr* (*ap*) orientation, while uridine adopted the +*synclinical* (+*sc*) orientation. The uracil base in **11b** adopted *anti* orientation same as uridine, in which the six-membered uracil ring is pointing away from the sugar. In addition to X-ray crystallographic data, conformations of 4′-selenouridine and uridine were easily distinguished by ^1H NMR data. The $^3J_{1'\text{-H},2'\text{-H}}$ value of 4′-selenouridine was large (8.70 Hz), usually appeared in the C2′-*endo* ribose ring puckering, whereas the corresponding coupling constant of uridine was small (4.62 Hz), shown in the C3′-*endo* ribose ring puckering. A strong ^1H NOE effect between H-6 and 2′-H was observed in 4′-selenouridine, indicating the C2′-*endo* conformation, but no NOE effect was detected in uridine, indicating the C3′-*endo* conformation.

Conversion of 4′-selenopyrimidine nucleosides **11a**−**c** into 4′-seleno-d4Ns **4a**−**c** is illustrated in Scheme 2. The primary hydroxyl groups of **11a**−**c** were protected with TBS group to give **12a**−**c**. To convert the 2′,3′-dihydroxyl groups into the 2′,3′-dideoxy-2′,3′-didehydro groups, compounds **12a**−**c** were treated with 1,1′-thiocarbonyl diimidazole (TCD) to give the cyclic 2′,3′-thiocarbonates **13a**−**c**, which were reacted with 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine[11] to give the protected 4′-seleno-d4Ns **14a**−**c**. Removal of the protecting groups in **14a**−**c** afforded the final 4′-seleno-d4Ns **4a**−**c**.

Structures of the final 4′-seleno-d4Ns **4a**-**c** were confirmed by spectral and analytical data. The structure of 4′-seleno-d4T (**4a**) was further confirmed by its X-ray crystal structure (see Supporting Information).

All synthesized compounds were evaluated for their anti-HIV activity in MT-4 cells, but they showed neither anti-HIV activity nor cytotoxicity up to 100 μM. In order to elucidate the unexpected anti-HIV activity of the 4′-seleno-d4Ns **4a**-**c**, compared with that of d4T, molecular modeling study was performed based on the X-ray crystal structures of d4T and 4′-seleno-d4T (**4a**).

For the comparison of the conformations of d4T and 4′-seleno-d4T, three essential parameters were considered: 1)

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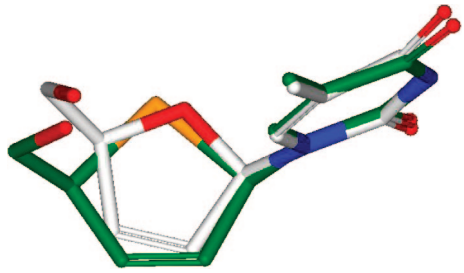

FIGURE 2. Superimposition of X-ray crystal structures between 4′-seleno-d4T (**4a**) and d4T. Selenium, oxygen, and nitrogen are shown in orange, red, and blue, respectively. Carbon atoms for 4′-seleno-d4T and d4T are shown in green and white, respectively.

the pseudorotation phase angle *P* (C1′−C2′−C3′−C4′) showing the puckering of the sugar ring; 2) the torsional angle χ (C2−N1−C1′−O4′ or Se4′) describing the geometry of the glycosyl link; 3) the torsional angle γ (C3′−C4′−C5′−O5′) indicating the orientation of the 5′-hydroxyl group relative to the sugar ring. The sugar ring in the d4T crystal structure showed an absolute Northern conformation ($P = 358.9°$), and 4′-seleno-d4T also showed almost same Northern conformation ($P = 356.9°$). However, it should be considered that preference of specific sugar ring conformations in solution is determined by the interplay of important interactions resulting from anomeric and *gauche* effects.[12] The torsional angles (χ) of 4′-seleno-d4T and d4T (255.3 and 258.0°, respectively) appeared to be very similar as −*anticlinal* (−*ac*). The last parameter γ values were 56.6° in 4′-seleno-d4T and 50.4° in d4T, showing the orientation of 5′-hydroxyl group as +*synclinal* (+*sc*), but these values appeared to be relatively different, compared with other parameters in the two crystal structures, possibly explaining no anti-HIV activity of 4′-seleno-d4T. Furthermore, in the solid state, it should be considered that their conformations might have been influenced by crystal-packing forces.[13,14] In addition, when these nucleosides bind to its target enzyme, their conformations would be influenced by their binding interactions at the active site.

X-ray crystal structures of d4T[15] and 4′-seleno-d4T were superimposed using FitAtoms module implemented in SYBYL 7.3.5 (Figure 2).

Atom pairs of N1, C1′, and C2′ along with O4′ and Se4′ of the two crystal structures were fitted on each other. As shown in Figure 2, the crystal structures were not completely superimposed, and that might be due to several differences between Se and O. Selenium is bulkier (with the Van der Waals radius of 1.90 Å) than oxygen (whose Van der Waals radius is 1.52 Å). The angles of C1′−Se−C4′ and C1′−O−C4′ are quite different (91.02° and 111.72°, respectively), and the bond lengths of Se−C and O−C are different (1.99 and 1.42 Å, respectively) in the two crystal structures. Also, the 5-membered selenosugar was completely flat in contrast with the furanose ring whose ring oxygen was slightly puckered up toward the base part. It appears that due to the combination of these reasons, the orientation of the 5′-hydroxyl group in 4′-seleno-d4T was significantly different from that of d4T, as shown in Figure 2. This result might explain the loss of anti-HIV activity of 4′-seleno-d4T, compared with that of d4T.

In summary, we have accomplished the synthesis of novel 2′,3′-didehydro-2′,3′-dideoxy-4′-selenonucleosides (4′-seleno-d4Ns) **4a**−**c** via 4′-selenoribofuranosyl pyrimidines **11a**−**c** and their conformational study using molecular modeling based on X-ray crystal structures. 4′-Selenoribofuranosyl pyrimidines **11a**−**c** were synthesized from D-ribose or D-gulonic γ-lactone using a Pummerer-type condensation as a key step. Conversion of 4′-selenoribofuranosyl moiety into 4′-seleno-2′,3′-didehydro-2′,3′-dideoxyribofuranosyl moiety was achieved using 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine without the N^3-methylation of the pyrimidine bases. A molecular modeling study based on the superimposed X-ray crystal structures of 4′-seleno-d4T (**4a**) and d4T 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. Those differences may affect the cellular phosphorylation by kinases, resulting in no anti-HIV activity of 4′-seleno-d4T. However, the reason(s) for their loss of anti-HIV activity is not clear yet whether it is because they are not easily converted to the triphosphates and/or because their triphosphates are not inhibiting HIV RT, and it is under investigation in our laboratory.

Experimental Section

1,4-Anhydro-5-*O*-tert-butyldiphenylsilyl-2,3-*O*-isopropylidene-4-seleno-D-ribitol (8). To a suspension of selenium powder (1.08 g, 13.67 mmol) in ethanol (90 mL) was added sodium borohydride at room temperature until the color of the reaction mixture changed from black to colorless. Compound **7** (3.93 g, 6.69 mmol) in THF (50 mL) was then added to the mixture and heated at 60 °C overnight. The solvent was evaporated, the residue was dissolved in ethyl acetate (50 mL), and the mixture was washed with water (3 × 30 mL) and brine, dried ($MgSO_4$), filtered, and evaporated. The residue was purified on flash silica gel column chromatography (hexane/ethyl acetate = 10:1) to give **8** (3.0 g, 96%) as pale-yellow syrup: MS (FAB) *m*/*z* 475 ($M-H^+$); $[\alpha]^{20}_D$ 54.30 (*c* 0.15, CH_3OH); ^1H NMR ($CDCl_3$) δ 1.07 (s, 9 H), 1.31 (s, 3 H), 1.52 (s, 3 H), 2.96 (dd, 1 H, J = 2.0, 11.4 Hz), 3.14 (dd, 1 H, J = 5.2, 11.4 Hz), 3.63−3.67 (m, 1 H), 3.70−3.74 (m, 1 H), 3.84−3.88 (m, 1 H), 4.78 (dd, 1 H, J = 1.8, 5.2 Hz), 4.82−4.85 (m, 1 H), 7.26−7.46 (m, 6 H), 7.65−7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 19.4, 24.8, 27.0, 27.1, 30.0, 50.4, 66.6, 85.3, 87.5, 110.5, 127.9, 130.0, 130.1, 133.3, 133.4, 135.8; Anal. Calcd for $C_{24}H_{32}O_3SeSi$: C, 60.61; H, 6.78. Found C, 60.98; H, 7.13.

General Procedure for Pummerer-Type Nucleobase Condensation. To a stirred solution of seleno sugar **8** (3.50 g, 7.36 mmol) in CH_2Cl_2 (60 mL was added a solution of *m*CPBA (1.81 g, 7.35 mmol, 70%) in CH_2Cl_2 (25 mL) at −78 °C and the mixture was stirred at the same temperature for 45 min. The reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and evaporated. The residue was purified on flash silica gel column chromatography (methylene chloride/methanol = 30:1) to give the selenoxide **9** (3.0 g, 85%) as a colorless syrup. Due to the unstable nature of the selenoxide **9**, it was immediately used for the next step.

A suspension of nucleobase (12.05 mmol) in toluene (48 mL) was treated with triethylamine (24.39 mmol) and TMSOTf (50.06 mmol), and the resulting mixture was stirred at room temperature for 1 h. After adding additional methylene chloride (24 mL), the silylated base was added to a solution of **9** (6.10 mmol) in methylene

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chloride (24 mL) slowly over a period of 30 min at 0 °C. An additional amount of triethylamine (24.39 mmol) in toluene was added dropwise to the reaction mixture to initiate the Pummerer reaction at 0 °C. After overnight stirring at room temperature, water (40 mL) was added and the aqueous layer was extracted with methylene chloride (3 × 40 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered, and evaporated. The residue was purified on flash silica gel column chromatography (hexane/ethyl acetate = 2:1) to give the condensed products **10a**−**c**.

1-(5-*O*-tert-Butyldiphenylsilyl-2,3-*O*-isopropylidene-4-seleno-β-D-ribofuranosyl)thymine (10a). Yield 50%; mp 88−90 °C; UV (MeOH) λ_{max} 263 nm; MS (FAB) *m*/*z* 601 (M+H$^+$); $[\alpha]^{20}_D$ −48.62 (*c* 0.02, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 1.05 (s, 9 H), 1.27 (s, 3 H), 1.50 (s, 3 H), 1.79 (d, 3 H, *J* = 1.2 Hz,), 3.94−3.95 (m, 2 H), 4.12 (d, 1 H, *J* = 4.0 Hz), 4.91−4.93 (m, 2 H), 6.21 (d, 1 H, *J* = 3.6 Hz), 7.37−7.50 (m, 6 H), 7.49 (t, 1 H, *J* = 1.2 Hz), 7.67−7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 12.5, 20.2, 25.6, 27.4, 28.2, 52.4, 61.2, 67.7, 79.7, 87.0, 90.9, 112.6, 112.9, 129.0, 129.1, 131.2, 131.2, 134.3, 134.6, 136.8, 136.9, 140.1; Anal. Calcd for $C_{29}H_{36}N_2O_5SeSi$: C, 58.09; H, 6.05; N, 4.67. Found C, 58.30; H, 6.48; N, 4.37.

1-(4-Seleno-β-D-ribofuranosyl)thymine (11a). A solution of **10a** (0.65 g, 1.00 mmol) in 50% aqueous trifluoroacetic acid (25 mL) was stirred at room temperature for 1 h. The solvent was evaporated and further coevaporated with toluene to give a white solid, which was recrystallized from methanol/water (1:1) to **11a** (0.26 g, 80%) as a colorless solid: mp 128−130 °C; UV (MeOH) λ_{max} 265 nm; MS (FAB) *m*/*z* 323 (M+H$^+$); $[\alpha]^{20}_D$ −111.62 (*c* 0.86, CH_3OH); ^{1}H NMR (CD_3OD) δ 1.91 (s, 3 H); 3.53−3.56 (m, 1 H); 3.82 (dd, 1 H, *J* = 5.4, 11.8 Hz); 3.87 (dd, 1 H, *J* = 6.4, 11.8 Hz); 4.26 (t, 1 H, *J* = 3.0 Hz); 4.38 (dd, 1 H, *J* = 3.4, 8.2 Hz); 6.29 (d, 1 H, *J* = 8.4 Hz); 7.91 (d, 1 H, *J* = 1.2 Hz); ^{13}C NMR (CD_3OD) δ 12.6, 30.8, 57.6, 65.2, 76.4, 80.1, 112.2, 139.6, 153.1, 166.3; Anal. Calcd for $C_{10}H_{14}N_2O_5Se$: C, 37.39; H, 4.39; N, 8.72. Found C, 37.53; H, 4.02; N, 8.47.

1-(5-*O*-tert-Butyldimethylsilyl-4-seleno-β-D-ribofuranosyl)thymine (12a). To a solution of **11a** (0.120 g, 0.373 mmol) in DMF (5 mL) was added a mixture of TBDMSCl (0.078 g, 0.517 mmol) and imidazole (0.063 g, 0.925 mmol) in DMF (5 mL) dropwise at 0 °C and the mixture was stirred at the same condition for 3 h. Solvent was evaporated under reduced pressure and the residue was purified on flash silica gel column chromatography (CH_2Cl_2/MeOH = 15:1) to give **12a** (0.121 g, 75%) as a colorless syrup: UV (MeOH) λ_{max} 265 nm; MS (FAB) *m*/*z* 459 (M+Na$^+$); $[\alpha]^{20}_D$ −73.98 (*c* 0.12, CH_3OH); ^{1}H NMR (CD_3OD) δ 0.14 (s, 6 H), 0.95 (s, 9 H), 1.90 (s, 3 H), 3.55−3.59 (m, 1 H), 3.88 (dd, 1 H, *J* = 6.0, 10.6 Hz); 3.99 (dd, 1 H, *J* = 6.8, 10.6 Hz), 4.24 (m, 1 H), 4.35 (dd, 1 H, *J* = 3.6, 7.8 Hz), 6.28 (d, 1 H, *J* = 8.0 Hz); 7.74 (d, 1 H, *J* = 1.6 Hz); ^{13}C NMR (CD_3OD) δ −4.9, 12.6, 26.5, 57.4, 66.8, 76.0, 79.8, 112.2, 139.2, 153.1, 166.2; Anal. Calcd for $C_{16}H_{28}N_2O_5SeSi$: C, 44.13; H, 6.48; N, 6.43. Found: C, 44.25; H, 6.15; N, 6.48.

1-(5-*O*-tert-Butyldimethylsilyl-2,3-*O*-thiocarbonate-4-seleno-β-D-ribofuranosyl)thymine (13a). To a solution of **12a** (0.081 g, 0.186 mmol) in dry $CHCl_3$ (4 mL), was added a solution of 1,1-thiocarbonyldiimidazole (0.036 g, 0.202 mmol) in dry $CHCl_3$ (4 mL) dropwise and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with $CHCl_3$ and washed with water, dried ($MgSO_4$), filtered, and evaporated. The residue was purified on flash silica gel column chromatography (hexane/ethyl acetate = 1:1) to give **13a** (0.054 g, 62%) with recovered starting material (0.018 g): UV (MeOH) λ_{max} 264 nm; MS (FAB) *m*/*z* 479 (M+H$^+$); $[\alpha]^{20}_D$ −46.2 (*c* 0.13, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 6 H); 0.90 (s, 9 H); 1.94 (s, 3 H); 3.83−3.89 (m, 1 H); 4.11−4.17 (m, 2 H); 5.72−5.74 (m, 1 H); 5.80−5.83 (m, 2 H); 6.98 (d, 1 H, *J* = 1.2 Hz); 8.11 (br s, 1 H).

1-(5-*O*-tert-Butyldimethylsilyl-2,3-dideoxy-2,3-didehydro-4-seleno-β-D-ribofuranosyl)thymine (14a). To a solution of **13a** (0.15 g, 0.31 mmol) in dry THF (10 mL) was added 1,1-dimethyl-2-phenyl-1,3,2-diazaphospholidine (0.28 mL, 1.55 mmol) dropwise and the mixture was stirred at room temperature overnight. Solvent was evaporated and the residue was purified on flash silica gel column chromatography (hexane/ethyl acetate = 1:1) to give **14a** (0.085 g, 70%) as a syrup: UV (MeOH) λ_{max} 265 nm; MS (FAB) *m*/*z* 402 (M+H$^+$); $[\alpha]^{20}_D$ −20.0 (*c* 0.06, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 6 H); 0.92 (s, 9 H); 1.91 (s, 3 H), 3.83 (dd, 1 H, *J* = 7.0, 10.2 Hz); 3.95 (dd, 1 H, *J* = 7.2, 10.4 Hz); 5.74−4.62 (m, 1 H); 5.73−5.76 (m, 1 H); 6.27−6.30 (m, 1 H); 7.15 (m, 1 H); 7.18−7.21 (m, 1 H); 7.97 (br s, 1 H); ^{13}C NMR (CD_3OD) δ −5.0, 4.99, 12.9, 18.6, 26.0, 53.1, 60.6, 68.0, 112.0, 130.6, 136.7, 138.0, 150.4, 163.5; Anal. Calcd for $C_{16}H_{26}N_2O_3SeSi$: C, 47.87; H, 6.53; N, 6.98. Found: C, 47.58; H, 6.34; N, 6.59.

1-(2,3-Dideoxy-2,3-didehydro-4-seleno-β-D-ribofuranosyl)thymine (4a). To a solution of **14a** (0.030 g, 0.074 mmol) in dry THF (4 mL) was added TBAF (0.1 mL of 1 M solution in THF, 0.10 mmol) and the mixture was stirred at room temperature for 45 min. The reaction mixture was evaporated and the residue was purified on flash silica gel column chromatography (CH_2Cl_2/MeOH = 15:1) to give **4a** (0.017 g, 82%) as colorless solid: mp 173−175 °C; UV (MeOH) λ_{max} 267 nm; MS (FAB) *m*/*z* 289 (M+H$^+$); $[\alpha]^{20}_D$ −188.8 (*c* 0.12, CH_3OH); ^{1}H NMR (CD_3OD) δ 1.84 (d, 3 H, *J* = 1.6 Hz); 3.82−3.90 (m, 2 H); 4.62−4.65 (m, 1 H); 5.82−5.85 (m, 1 H); 6.26−6.29 (m, 1 H); 7.08−7.10 (m, 1 H); 7.67 (m, 1 H); ^{13}C NMR (CD_3OD) δ 12.6, 54.9, 61.8, 66.3, 112.3, 131.5, 139.4, 139.8, 152.4, 166.4; Anal. Calcd for $C_{10}H_{12}N_2O_3Se$: C, 41.82; H, 4.21; N, 9.75. Found: C, 42.08; H, 4.53; N, 9.43.

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Supporting Information Available: Complete experimental details and full characterization data of novel compounds and X-ray crystallographic data, as well as copies of ^{1}H and ^{13}C NMR spectra for all synthetic compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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