Synthesis and Antiviral Activity of Oxaselenolane Nucleosides

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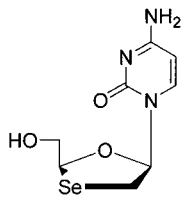
As dioxolane and oxathiolane nucleosides have exhibited promising antiviral and anticancer activities, it was of interest to synthesize isoelectronically substituted oxaselenolane nucleosides, in which the 3′-CH_2 is replaced by a selenium atom. To study structure−activity relationships, various pyrimidine and purine oxaselenolane nucleosides were synthesized from the key intermediate, (±)-2-benzoyloxymethyl-1,2-oxaselenolane 5-acetate **(6)**. Among the synthesized racemic nucleosides, cytosine and 5-fluorocytosine analogues exhibited potent anti-HIV and anti-HBV activities. It was of interest to obtain the enantiomerically pure isomers to determine if they have differential antiviral activities. However, due to the difficult and time-consuming nature of enantiomeric synthesis, a chiral HPLC separation was performed to obtain optical isomers from the corresponding racemic mixtures. Each pair of enantiomers of Se-ddC and Se-FddC was separated by an amylose chiral column using a mobile phase of 100% 2-propanol. The results indicate that most of the anti-HIV activity of both cytosine and fluorocytosine nucleosides resides with the (−)-isomers.

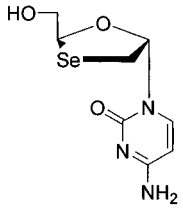
Introduction

During the past 10 years, 2′,3′-dideoxynucleoside analogues have been intensively studied as potential antiviral agents. Among 14 antiviral agents, which have been approved by the Food and Drug Administration for the treatment of HIV infection (6 reverse transcriptase inhibitors, 3 nonnucleoside reverse transcriptase inhibitors, and 5 protease inhibitors), 6 are 2′,3′-dideoxynucleoside analogues (AZT,[1] ddC,[2] ddI,[2] d4T,[3] 3TC,[4−8] and Abacavir[9]). The use of these agents in combination with protease inhibitors has been responsible for the marked reduction of opportunistic infections and mortality in HIV patients in the past decade.[10] However, the side effects of certain antiviral agents and the emergence of drug-resistant viral strains have prompted the development of additional anti-HIV agents to circumvent these drawbacks.[11−13] Particularly, 3′-heteroatom-substituted dideoxynucleosides have proven valuable, including oxathiolane and dioxolane nucleosides, in which the 3′-CH_2 group is replaced by a sulfur or oxygen atom. Among these modified nucleosides, 3TC,[4−8] FTC,[14,15] L-OddC,[16] DAPD,[17] and OTC[18] are the most promising compounds. This fact prompted us to consider an isosteric substitution of 3′-CH_2 by selenium (Se), for which preliminary results were reported as a communication.[19]

Enantiomeric compounds often have different activities in biological systems since they interact with receptors or enzymes that are chiral. The antiviral activity of 3TC[4−8] and FTC[14,15] was primarily associated with the β-enantiomers, with the (−)-enantiomers being more potent and less toxic (in the case of 3TC). FTC and 3TC analogues containing a selenium, such as 5-fluoro-1-[2-(hydroxymethyl)-1,3-oxaselenolan-5-yl]cytosine (Se-FddC) and 1-[2-(hydroxymethyl)-1,3-oxaselenolan-5-yl]cytosine (Se-ddC), could have similar activity as FTC or SddC since selenium is isoelectronic with sulfur or oxygen.



(±)-β-Se-ddC



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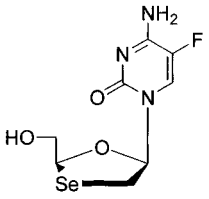

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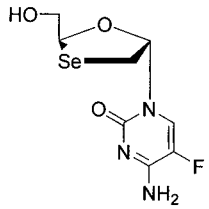

(±)-α-Se-FddC

In general, it takes significant efforts to develop enantiomeric synthesis. Therefore, we decided to perform a chiral separation of the racemic mixture of the cytosine and 5-fluorocytosine derivatives to obtain the enatiomeric compounds for biological evaluation.

Results and Discussion

The synthesis of β-oxaselenolane nucleosides reported in this paper was accomplished by the condensation of

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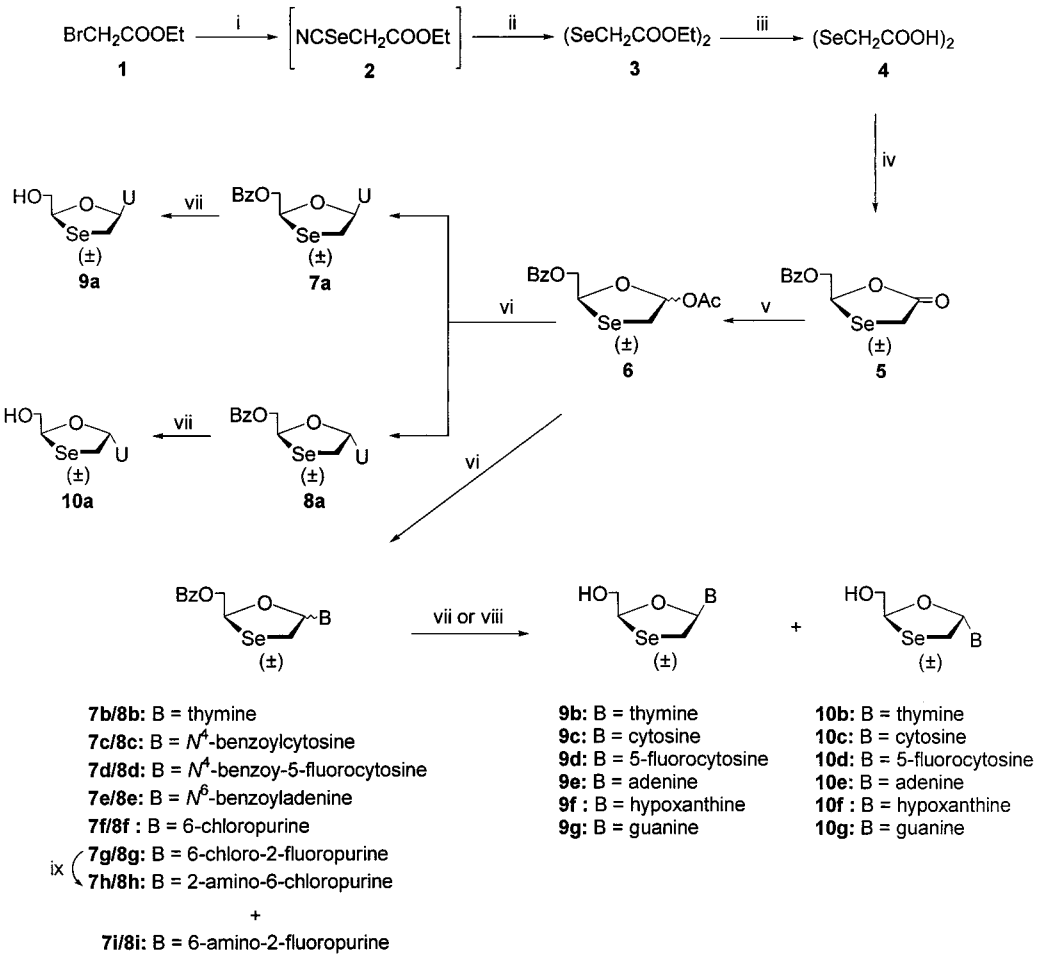
Scheme 1. Synthesis of Oxaselenolane Nucleosides[a]



[a] Reagents: (i) KSeCN, EtOH, reflux; (ii) $NaBH_4$, EtOAc, EtOH, 0 °C; (iii) aq AcOH (50%), reflux; (iv) $BzOCH_2CHO$, H_3PO_2, toluene, reflux; (v) (1) DIBAL-H (1 M in hexanes), THF, −78 °C, (2) Ac_2O, rt; (vi) silylated bases, TMSOTf, 1,2-dichloroethane, rt; (vii) $MeNH_2$, MeOH, rt; (viii) MeONa, MeOH, $HS(CH_2)OH$, reflux; (ix) NH_3, dimethyleneglycol dimethyl ether.

silylated bases with acetylated derivative **6**, prepared from the oxaselenolane intermediate **5** (Scheme 1). Refluxing ethyl bromoacetate **(1)** with potassium selenocyanate in ethanol for 1 h,[20] followed by reduction of the intermediate selenocyanate **2** with sodium borohydride[21] at 0 °C for 20−30 min, gave diselaneoliylbis(acetic acid) diethyl ester **(3)** in 81% yield. Hydrolysis of **3** with refluxing aqueous acetic acid (50%) afforded the corresponding acid **4**, which was condensed with 2-(benzoyloxy)acetaldehyde without purification, to give lactone **5** in 33% yield. Reduction of **5** with DIBAL-H followed by in situ acetylation gave the acetylated oxaselenolane derivative **6**, which was condensed with the desired silylated bases without purification. Pyrimidine oxaselenolane nucleosides were prepared under Vorbrüggen conditions using TMSOTf as the catalyst. Condensation of the intermediate **6** with uracil gave a mixture of α- and *β*-anomers (**7a** and **8a**), which were separated by preparative TLC and individually deprotected with methylamine in methanol to give uracil nucleosides **9a** and **10a**. In the case of thymine, N^4-benzoylcytosine, and N^4-benzoyl-5-fluorocytosine, the condensation reaction gave inseparable α/*β*-mixtures. However, after deprotection with methylamine in methanol, the anomers could be separated to give the final compounds **9b**, **10b**, **9c**, **10c**, **9d**, and **10d**. The same condensation method was applied for the synthesis of purine oxaselenolane nucleosides. Thus, condensation of the intermediate **6** with N^6-benzoyladenine gave an inseparable α/*β*-mixture. Both anomers **9e** and **10e** were separated after deprotection with methylamine in methanol. To obtain the hypoxanthine derivatives, silylated 6-chloropurine was condensed with **6** to give an α/*β*-mixture **7f/8f**, which was refluxed with sodium methoxide and mercaptoethanol in methanol to give the hypoxanthine derivatives **9f** and **10f**. Condensation of the intermediate **6** with silylated 6-chloro-2-fluoropurine followed by ammonolysis gave 2-amino-6-chloropurine and 6-amino-2-fluoropurine derivatives **7h/8h** and **7i/8i**. The guanine derivatives **9g/10g** were obtained by refluxing **7h/8h** with sodium methoxide and mercaptoethanol in methanol.

To obtain the enantiomeric compounds, we used an inclusion chromatography chiral column, ChiralPak AS, using 100% 2-propanol as the mobile phase in most cases (vide infra). The nature of the chiral stationary phase (CSP) can explain the better separation factor and resolution achieved for the *β*-isomers as compared to the α-isomers. In fact, the chiral separation on an inclusion CSP is based on the interaction between the molecules of the racemate and chiral cavities in the CSP. From comparison of the retention times in our chromatograms, it is evident that *β*-isomers, which are structurally more "compact", intrude more easily into these

Table 1. Characteristics and Purity of Resolved Enantiomers of Oxaselenolane and Oxathiolane Nucleosides

compd	t_R (min)	absorption wavelength (nm)	optical rotation (deg)	purity (%)
(−)-β-Se-FddC	4.8	247.3, 285.1	−103.2 (*c* 0.5, MeOH)	100
(+)-β-Se-FddC	7.7	247.3, 285.1	+96.8 (*c* 0.5, MeOH)	100
(−)-α-Se-FddC	4.8	247.3, 285.1	ND[a]	100
(+)-α-Se-FddC	6.6	247.3, 285.1	ND	90
(−)-β-FTC	4.7	242.6, 285.1	−120.5 (*c* 0.88, EtOH)	100
(+)-β-FTC	6.9	242.6, 285.1	+113.4 (*c* 0.88, EtOH)	100
(−)-β-Se-ddC	9.5	242.6, 270.9	−72.4 (*c* 1.0, DMSO)	100
(+)-β-Se-ddC	11.9	242.6, 270.9	+56.4 (*c* 1.0, DMSO)	96
(−)-α-Se-ddC	ND	242.6, 270.9	−46.7 (*c* 1.0, DMSO)	100
(+)-α-Se-ddC	ND	242.6, 270.9	ND	94

[a] ND = not determined.

Table 2. Anti-HIV-1 and Anti-HBV Activities of Various Racemic Oxaselenolane Nucleosides

	EC_{50} (μM)		cytotoxicity IC_{50} (μM)		
base	HIV-1 PBM cells	HBV 2.2.15 cells	PBM cells	CEM cells	Vero cells
β-uracil (**9a**)	>100	>10	>100	>100	>100
α-uracil (**10a**)	101	>10	>100	>100	>100
β-thymine (**9b**)	>10	>10	>100	>100	>100
α-thymine (**10b**)	>100	>10	>100	>100	>100
β-cytosine (**9c**)	2.7	1.2	>100	>100	>100
α-cytosine (**10c**)	>100	ND[a]	>100	>100	>100
β-5-fluorocytosine (**9d**)	0.73	1.2	>100	>100	>100
α-5-fluorocytosine (**10d**)	57.1	>10	>100	>100	>100
β-adenine (**9e**)	>50	>10	>100	>100	>100
α-adenine (**10e**)	>100	>10	>100	>100	>100
β-hypoxanthine (**9f**)	>100	>10	>100	>100	>100
α-hypoxanthine (**10f**)	>100	>10	>100	>100	>100
β-guanine (**9g**)	28.9	>10	>100	>100	>100
α-guanine (**10g**)	>100	>10	>100	>100	>100
3TC[4−8]	0.07	0.008	>100	>100	>100

[a] ND = not determined.

cavities. This results in a more efficient interaction between molecules and CSP and, consequently, in higher separation and resolution factors for the β-isomers. Comparison between α- and β-Se-FddC as well as FTC showed that also electrostatic factors play a role in the chiral recognition and resolution, although not as important as the steric factors discussed above. In any case, optimized conditions let us achieve a baseline separation for each pair of enantiomers. The UV spectra and the optical rotations of the two eluted products of each chromatography indicated that these were the enantiomers constituting the mixture injected on the chiral column. The optical purity was confirmed by chiral HPLC (Table 1).

Experimental results indicated that β-Se-ddC could not be resolved on our CSP using 2-propanol as the mobile phase. However, when the mobile phase was changed to 60:40 hexane:ethanol, the resolution factor was increased from 1.04 to 1.25, and although the resolution was not complete, the enantiomer could be separated close to baseline level. Analogously, to achieve a good resolution of α-Se-ddC, we had to use 100% ethanol as the mobile phase.

The synthesized racemic nucleosides were evaluated for antiviral activity against immunodeficiency virus type-1 (HIV-1) and hepatitis B virus (HBV) in peripheral blood mononuclear cells and 2.2.15 cells, respectively. Results are shown in Table 2. The cytosine and 5-fluorocytosine analogues **9c** and **9d** were found to exhibit the most potent anti-HIV activity (EC_{50} 2.69 and 5.55 μM, respectively) and anti-HBV activity (EC_{50} 1.2 μM for both compounds) with no in vitro toxicities up to 100 μM in various cell lines (PBM, CEM, and Vero). It is worth mentioning that the α-5-fluorocytosine derivative **10d** also exhibited very weak activity against HIV (57.1 μM). We confirmed by HPLC that this activity was not due to the contamination of the β-isomer **9d**. Other than the cytosine derivatives, the only other nucleoside that showed antiviral activity against HIV-1 and HBV was the β-guanine derivative **9g** (EC_{50} 28.9 μM against HIV-1), whereas the adenine and hypoxanthine analogues were inactive. These data indicate that the isosteric substitution with selenium in place of oxygen or sulfur still maintains some antiviral activity.

Table 3. Anti-HIV-1 Activity and Cytotoxicity of Enantiomerically Resolved Oxaselenolane Nucleosides in Human PBM Cells

			EC_{50} (μM)	cytotoxicity IC_{50} (μM)		
compd	enant	purity (%)	anti-HIV-1 activity	CEM cells	PBM cells	Vero cells
β-Se-ddC (**9c**)	±	50	2.7	>100	>100	>100
β-Se-ddC	−	≈100	0.9	>100	>100	>100
β-Se-ddC	+	≈96	3.4	>100	>100	>100
α-Se-ddC (**10c**)	±	50	>100	>100	>100	>100
α-Se-ddC	−	≈100	>100	>100	>100	>100
α-Se-ddC	+	≈94	>100	>100	>100	>100
β-Se-FddC (**9d**)	±	50	0.73	>100	>100	>100
β-Se-FddC	−	≈100	0.2	>100	>100	>100
β-Se-FddC	+	≈100	41.9	>100	>100	>100
α-Se-FddC (**10d**)	±	50	57.1	NA[a]	>100	>100
α-Se-FddC	−	≈100	6.4	>100	>100	>100
α-Se-FddC	+	≈90	95.3	>100	>100	>100

[a] NA = not available.

Table 4. Effect of Oxaselenolane Cytosine Nucleosides Against Cloned xxBRU[a] and M184V[b] HIV-1

				anti-HIV activity		FI[c]	
compd	enant	virus	purity (%)	EC_{50} (μM)	EC_{90} (μM)	EC_{50}	EC_{90}
β-Se-ddC (**9c**)	±	xxBRU	50	1.84	6.90		
β-Se-ddC	−	xxBRU	≈100	0.11	0.95		
β-Se-ddC	+	xxBRU	≈96	8.62	35.1		
β-Se-ddC (**9c**)	±	M184V	50	108	337	59	49
β-Se-ddC	−	M184V	≈100	>50	>50	>455	>53
β-Se-ddC	+	M184V	≈96	>50	>50	>6	>1

[a] FTC-sensitive mutant. [b] FTC/3TC-resistant mutant. [c] FI (fold increase) EC_x = EC_x data from M184V virus/EC_x data from xxBRU virus.

The anti-HIV-1 activity of resolved α- and β-enantiomers of Se-ddC and Se-FddC was evaluated (Table 3). It was found that, like the sulfur analogues, (−)-enantiomers are more active than their (+)-counterparts. The most potent compounds were (−)-β-Se-FddC (EC_{50} 0.2 μM) and (−)-β-Se-ddC (EC_{50} 0.9 μM), about 3 and 12 times less potent than 3TC, respectively. Since the viral resistance is the most important limit of current anti-HIV therapy, we studied the effect of (−)-β-Se-ddC against cloned xxBRU (3TC/FTC-sensitive) and M184V (3TC/FTC-resistant) mutants. The results indicate that (−)-β-Se-ddC was cross-resistant with its sulfur analogues (Table 4).

Experimental Section

Melting points were determined on a Mel-temp II apparatus and are uncorrected. NMR spectra were recorded on a Bruker 400 AMX spectrometer at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR with TMS as internal standard. Chemical shifts (δ) are reported in parts per million (ppm), and signals are reported as s (singlet), d (doublet), t (triplet), q (quartet), m

(multiplet), or bs (broad singlet). IR spectra were measured on a Nicolet 510P FT-IR spectrometer. Mass spectra were recorded on a Micromass Autospec high-resolution mass spectrometer. TLC were performed on Uniplates (silica gel) purchased from Analtech Co. Column chromatography was performed using either silica gel 60 (220−440 mesh) for flash chromatography or silica gel G (TLC grade, >440 mesh) for vacuum flash column chromatography. UV spectra were obtained on a Beckman DU 650 spectrophotometer. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA, or Galbraith Laboratories, Inc., Knoxville, TN. HPLC was performed with a Waters HPLC system (Millipore Corp., Milford, MA) equipped with a model 600 controller, a model 996 photodiode array detector and a model 717 plus autosampler. Millennium 2010 software was used for system control, data acquisition and processing. A chiralyser polarimetric detector, Perkin-Elmer model 241MC polarimeter (Wilton, CT), was used for the determination of optical rotations.

Diselanediyl-bis(acetic acid) Diethyl Ester (3). Ethyl bromoacetate **(1)** (25.0 g, 0.15 mol) was added to a solution of potassium selenocyanate (14.4 g, 0.10 mol) in ethanol (250 mL) and the mixture was refluxed for 1 h, filtered, and washed with EtOAc (250 mL). To the combined filtrate was added $NaBH_4$ (0.95 g, 25.0 mmol) portionwise at 0 °C in 20 min and the reaction mixture was stirred at 0 °C for an additional 10 min. After the starting material had disappeared (TLC), the reaction solvent was evaporated and the residue was partitioned between water and EtOAc. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvents were evaporated under reduced pressure and the residue was coevaporated with toluene to remove excess bromoacetate, giving an oily residue that was purified by silica gel chromatography (0−30% EtOAc in hexane) to give **3** as an oil (13.5 g, 81.3%): IR (film) 1728, 1260 cm^{-1}.

(±)-2-Benzoyloxymethyl-1,3-oxaselenolan-5-one (5). A solution of compound **3** (7.30 g, 22.0 mmol) and aqueous acetic acid (50%, 300 mL) was refluxed for 24 h. The reaction solvent was concentrated to dryness under reduced pressure and then coevaporated with toluene twice to give crude diselanediyl-bis(acetic acid) **(4)**. 2-Benzoyloxyacetaldehyde (14.6 g, 69.5 mmol) was added slowly to the solution of the acid **4** in toluene (250 mL) and the mixture was gently refluxed under N_2. H_3PO_2 (50%, 16.5 mL) was added slowly to the above reaction mixture and the reaction mixture was refluxed using a Dean−Stark apparatus to remove water until all the aldehyde had reacted (20−30 min). The reaction mixture was diluted with EtOAc (100 mL) and partitioned between water and EtOAc. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure and the syrupy residue was purified by silica gel column chromatography (10−30% EtOAc in hexanes) to give **5** (4.2 g, 33%) as a yellow oil: IR (film) 1767, 1720, 1273 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 174.3, 166.3, 134.0, 130.2, 129.6, 129.0, 70.5, 67.7, 24.1; MS (FAB) 286.6 (MH^+). Anal. ($C_{11}H_{10}O_4Se$) C, H.

(±)-β-1-(2-Benzoyloxymethyl-1,3-oxaselenolan-5-yl)uracil (7a) and (±)-α-1-(2-Benzoyloxymethyl-1,3-oxaselenolan-5-yl)uracil (8a). A 1 M solution of DIBAL-H in hexanes (3.5 mL, 3.5 mmol) was slowly added to a solution of **5** (500 mg, 1.75 mmol) in THF (10 mL) at −78 °C and the reaction mixture was stirred at −78 °C for 1 h. Then, acetic anhydride (0.5 mL, 5.25 mmol) was added dropwise and the resulting mixture was allowed to warm to room temperature and stirred for 3 more h. The mixture was diluted with EtOAc (10 mL) and washed successively with brine (10 mL), water (10 mL), and then extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, and then the solvent was evaporated under reduced pressure to give crude acetate **6** as a syrup. The solution of crude **6** in CH_2Cl_2 (18 mL) was added to persilylated uracil [prepared by refluxing uracil (588 mg, 5.25 mmol) with $(NH_4)_2SO_4$ (35 mg) in HMDS (17 mL) for 3 h and removal of the solvent under reduced pressure]. TMSOTf (17 mL, 10.5 mmol) was then added and the resulting mixture was stirred for 3 h at room temperature under anhydrous conditions. After all the starting material had reacted, the reaction mixture was quenched with aqueous $NaHCO_3$ solution. The resulting solid was filtered off and the filtrate was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated to a residue, which was purified by silica gel column chromatography (0−3% MeOH in CH_2Cl_2) to give **7a** and **8a** as a mixture (220 mg, 33% from **5**, β/α = 1.1). The individual enantiomers were obtained by preparative TLC after multiple developments (5% MeOH in $CHCl_3$): UV (MeOH) λ_{max} 261.0 nm; HRMS calcd for $C_{15}H_{14}N_2O_5Se$, 383.0150; found, 383.0356.

(±)-β-1-(2-Hydroxymethyl-1,3-oxaselenolan-5-yl)uracil (9a) and (±)-α-1-(2-Hydroxymethyl-1,3-oxaselenolan-5-yl)uracil (10a). A solution of compound **7a** (70 mg, 0.18 mmol) or **8a** (61 mg, 0.16 mmol) in MeOH (4.7 mL and 4.2 mL, respectively) was treated with a solution of methylamine in water (40%, 2.3 mL and 2.0 mL, respectively) and the resulting mixture was stirred at room temperature for 24 h. The reaction solvents were concentrated to dryness under reduced pressure and the residues were purified by silica gel column chromatography (5% MeOH in CH_2Cl_2) to give pure β-isomer **9a** (29 mg, 58%) or α-isomer **10a** (27 mg, 61%), which were crystallized from MeOH/Et_2O. **9a:** mp 159−161 °C; UV (H_2O) λ_{max} 260.5 nm (ϵ 25100) (pH 2), 260.5 nm (ϵ 24400) (pH 7), 260.5 nm (ϵ 19800) (pH 11); ^{13}C NMR (DMSO-d_6) δ 161.09, 148.22, 138.56, 130.78, 100.34, 85.08, 75.92, 62.15, 25.96; HRMS calcd for $C_8H_{10}N_2O_4Se$, 278.9884; found, 278.9889. Anal. ($C_8H_{10}N_2O_4Se$) C, H, N. **10a:** mp 129−131 °C; UV (H_2O) λ_{max} 261.0 nm (ϵ 34300) (pH 2), 261.0 nm (ϵ 31000) (pH 7), 261.5 (ϵ 25300) (pH 11); ^{13}C NMR (DMSO-d_6) δ 163.51, 150.55, 140.93, 132.96, 101.85, 87.73, 81.09, 65.22, 29.01; HRMS calcd for $C_8H_{10}N_2O_4Se$, 278.9884; found, 278.9874. Anal. ($C_8H_{10}N_2O_4Se$) C, H, N.

β-(±)-1-(2-Benzoyloxymethyl-1,3-oxaselenolan-5-yl)thymine (7b) and α-(±)-1-(2-Benzoyloxymethyl-1,3-oxaselenolan-5-yl)thymine (8b). A solution of crude acetate **6** [prepared from 1.45 g (5.0 mmol) of **5**] in CH_2Cl_2 (60 mL) was added to persilylated thymine [prepared by refluxing thymine (1.89 g, 15 mmol) with $(NH_4)_2SO_4$ in HMDS (50 mL) for 4 h and removal of the solvent under reduced pressure]. A 1 M solution of $SnCl_4$ in CH_2Cl_2 (10 mL, 10 mmol) was then added and the reaction was continued at room temperature for 30 min. The resulting mixture was diluted with EtOAc (50 mL) and quenched with aqueous $NaHCO_3$. The salts were filtered off and the filtrate was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was purified by silica gel column chromatography (0−10% MeOH in CH_2Cl_2) to give **7b** and **8b** as a mixture (150 mg, 7.6% from **5**, β/α = 2/1): UV (MeOH) λ_{max} 265.0 nm; HRMS calcd for $C_{16}H_{16}N_2O_5Se$, 397.0340; found, 397.0303.

(±)-β-1-(2-Hydroxymethyl-1,3-oxaselenolan-5-yl)thymine (9b) and (±)-α-1-(2-Hydroxymethyl-1,3-oxaselenolan-5-yl)thymine (10b). A solution of methylamine in water (40%, 5 mL) was added to a solution of the mixture **7b**/**8b** (150 mg, 0.38 mmol) in MeOH (10 mL), and the resulting mixture was stirred at room temperature for 24 h. The reaction mixture was then concentrated to dryness under reduced pressure, and the residue was purified by preparative TLC (5%, then 7% MeOH in CH_2Cl_2 repeatedly developed) to give β-isomer **9b** (16 mg, 14.5%) and α-isomer **10b** (13 mg, 11.8%). **9b**: mp 200−202 °C; UV (H_2O) λ_{max} 266.0 (ϵ 10014) (pH 2), 266.0 (ϵ 10968) (pH 7), 265.5 nm (ϵ 8546) (pH 11); ^{13}C NMR (DMSO-d_6) δ 163.5, 150.2, 136.0, 109.8, 86.5, 76.8, 63.8, 27.1, 11.7; MS (FAB) 292.8 (M^+). Anal. ($C_9H_{12}N_2O_4Se$) C, H, N. **10b**: mp 144−145.5 °C; UV (H_2O) λ_{max} 266.5 nm (ϵ 10133) (pH 2), 266.5 nm (ϵ 11524) (pH 7), 266.5 nm (ϵ 8918) (pH 11); ^{13}C NMR (DMSO-d_6) 163.5, 149.8, 135.6, 109.0, 86.6, 79.7, 64.6, 28.0, 11.8; MS (FAB) 293.0 (MH^+). Anal. ($C_9H_{12}N_2O_4Se$) C, H, N.

(±)-β-1-(2-Benzoyloxymethyl-1,3-oxaselenolan-5-yl)-N^4-benzoylcytosine (7c) and (±)-α-1-(2-Benzoyloxymethyl-1,3-oxaselenolan-5-yl)-N^4-benzoylcytosine (8c). A solution of crude acetate **6** [prepared from 1.4 g (5.0 mmol) of **5**] in CH_2Cl_2 (50 mL) was added to persilylated N^4-benzoylcytosine

[prepared by refluxing N^4-benzoylcytosine (2.2 g, 10 mmol) with $(NH_4)_2SO_4$ (100 mg) in HMDS (50 mL) for 4 h and removal of the solvent under reduced pressure]. TMSOTf (2.2 g, 10 mmol) was then added, and the mixture was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. The resulting solid was filtered off and the filtrate was extracted with EtOAc. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give a residue, which was purified by silica gel column chromatography (0−5% MeOH in $CHCl_3$) to give a syrup. This was dissolved in a small amount of MeOH and was allowed to stay overnight at room temperature to afford a white solid that was filtered to give **7c** and **8c** as a mixture (250 mg, 10.3% from **5**, $\beta/\alpha = 2/1$): UV (MeOH) λ_{max} 304.5 nm; HRMS calcd for $C_{22}H_{19}N_3O_5Se$, 486.0568; found, 486.0573.

(±)-β-1-(2-Hydroxymethyl-1,3-oxaselenolan-5-yl)cytosine (9c) and (±)-α-1-(2-Hydroxymethyl-1,3-oxaselenolan-5-yl)cytosine (10c). A solution of methylamine in water (40 wt %, 10 mL) was added to a solution of the mixture **7c**/**8c** (200 mg, 0.413 mmol) in MeOH (20 mL), and the resulting mixture was stirred at room temperature for 8 h. After checking for completeness by TLC, the reaction mixture was concentrated to dryness at 30 °C, and the residue purified by a silica gel column (10−20% MeOH in $CHCl_3$) to give **9c** and **10c** as a mixture (65 mg, 57%, $\beta/\alpha = 2/1$). Fractional recrystallization from MeOH/Et_2O gave the pure α-isomer **10c** (25 mg): mp 237−238 °C; UV (H_2O) λ_{max} 278.5 (ϵ 8367) (pH 2), 270.0 (ϵ 6041) (pH 7), 270.0 nm (ϵ 6308) (pH 11); ^{13}C NMR (DMSO-d_6) δ 165.2, 154.5, 140.7, 93.7, 87.8, 80.2, 64.7, 29.0; MS (FAB) 277.8 (M^+). Anal. ($C_8H_{11}N_3O_3Se$) C, H, N. The mother liquor, enriched with β-isomer, was repeatedly purified by preparative HPLC (C-18 column, 20% MeOH in H_2O, flow rate: 50 mL/min), to give β-isomer **9c** (15 mg): mp 173−175 °C; UV (H_2O) λ_{max} 278.0 (ϵ 8787) (pH 2), 269.5 (ϵ 6344) (pH 7), 269.5 nm (ϵ 6364) (pH 11); MS (FAB) 278.0 (MH^+). Anal. ($C_8H_{11}N_3O_3Se \cdot {}^1/_3H_2O$) C, H, N.

β-(±)-1-(2-Benzoyloxymethyl-1,3-oxaselenolan-5-yl)-N^4-benzoyl-5-fluorocytosine (7d) and α-(±)-1-(2-Benzoyloxymethyl-1,3-oxaselenolan-5-yl)-N^4-benzoyl-5-fluorocytosine (8d). A solution of crude acetate **6** [prepared from 4.28 g of **5** (15.0 mmol)] in CH_2Cl_2 (30 mL) was added to persilylated N^4-benzoyl-5-fluorocytosine [prepared by refluxing N^4-benzoyl-5-fluorocytosine (3.5 g, 15.0 mmol) in $CHCl_3$ (60 mL) with HMDS (10 mL) for 5 h with $(NH_4)_2SO_4$ (100 mg) and removal of the solvent under reduced pressure]. TMSOTf (4.3 mL, 22.0 mmol) was then added, and the mixture was stirred at room temperature for 3 h. The reaction was quenched with $NaHCO_3$, the resulting solid was filtered off and the filtrate was extracted with $CHCl_3$. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (5−50% EtOAc in hexanes) to give **7d** and **8d** as a mixture (2.0 g, 26% from **5**, $\beta/\alpha = 1.6$): UV (MeOH) λ_{max} 323.0 nm, 259.0 nm, 228.5 nm; HRMS calcd for $C_{22}H_{18}FN_3O_5Se$, 504.0474; found, 504.0473.

(±)-β-1-(2-Hydroxymethyl-1,3-oxaselenolan-5-yl)-5-fluorocytosine (9d) and (±)-α-1-(2-Hydroxymethyl-1,3-oxaselenolan-5-yl)-5-fluorocytosine (10d). A solution of compound **7d** and **8d** (2 g, 3.85 mmol) in saturated methanolic ammonia (50 mL) was stirred at room temperature for 20 h. Then, the reaction mixture was evaporated to dryness under reduced pressure and the residue was purified by silica gel chromatographic column chromatography (0−15% MeOH in $CHCl_3$) to give β-isomer **9d** and α-isomer **10d** as a mixture (0.82 g, 73%, $\alpha/\beta = 1.2$). The individual isomers were obtained by another silica gel column chromatography (EtOAc:hexanes:EtOH:$CHCl_3$ = 5:5:1:2). **9d**: mp 192−194 °C; UV (H_2O) λ_{max} 280.0 (ϵ 8573) (pH 7), 289.0 (ϵ 10636) (pH 2), 280.0 nm (ϵ 7511) (pH 11); ^{13}C NMR (DMSO-d_6) δ 157.7, 153.3, 137.6, 135.2, 88.3, 78.2, 64.0, 28.9; MS (FAB) 295 (M^+). Anal. ($C_8H_{10}FN_3O_3Se$) C, H, N. **10d**: mp 220−223 °C; UV (H_2O) λ_{max} 279.5 (ϵ 7654) (pH 7), 287.5 (ϵ 9095) (pH 2), 281.0 nm (ϵ 6949) (pH 11); ^{13}C NMR (DMSO-d_6) δ 157.8, 153.2, 137.3, 134.9, 88.6, 80.9, 65.5, 29.4; MS (FAB) 295.0 (MH^+). Anal. ($C_8H_{10}FN_3O_3Se$) C, H, N.

(±)-β-9-(2-Benzoyloxymethyl-1,3-oxaselenolan-5-yl)-N^6-benzoyladenine (7e) and (±)-α-9-(2-Benzoyloxymethyl-1,3-oxaselenolan-5-yl)-N^6-benzoyladenine (8e). A solution of acetate **6** [prepared from 630 mg of **5** (1.9 mmol)] in 1,2-dichloroethane (5 mL) was added to persilylated N^6-benzoyladenine [prepared by refluxing N^6-benzoyladenine (530 mg, 2.6 mmol) with $(NH_4)_2SO_4$ (30 mg) in HMDS (10 mL)]. TMSOTf (0.5 mL, 2.6 mmol) was then added, and the reaction mixture was stirred at room temperature for 22 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and the resulting solid was filtered off. The filtrate was extracted with EtOAc and the organic layer was washed with brine and dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was purified by flash chromatography (0−3% MeOH in $CHCl_3$) to give **7e** and **8e** as a mixture (260 mg, 27% from **5**, $\beta/\alpha = 1$): UV (MeOH) λ_{max} 228.5, 279.0 nm; HRMS calcd for $C_{23}H_{19}N_5O_4Se$, 510.0703; found, 510.0680.

(±)-β-9-(2-Hydroxymethyl-1,3-oxaselenolan-5-yl)adenine (9e) and (±)-α-9-(2-Hydroxymethyl-1,3-oxaselenolan-5-yl)adenine (10e). A solution of methylamine in water (40 wt %, 2 mL) was added to a solution of the mixture **7e**/**8e** (260 mg, 0.51 mmol) in MeOH (10 mL), and the mixture was stirred at room temperature for 24 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ solution and the resulting solid was filtered off. The filtrate was extracted with EtOAc and the organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was purified by preparative TLC (5% and 8% MeOH in $CHCl_3$, developed twice) and extracted with 10% MeOH in EtOAc to give two yellow solids, which were triturated with Et_2O and filtered to give pure β-isomer **9e** (10 mg, 6.5%) and α-isomer **10e** (10 mg, 6.5%). **9e**: mp 230−232 °C; UV (H_2O) λ_{max} 258.5 nm (ϵ 10881) (pH 2), 259.5 nm (ϵ 12760) (pH 7), 260.0 nm (ϵ 10964) (pH 11); MS (FAB) 302.0 (MH^+). Anal. ($C_9H_{11}N_5O_2Se$) C, H, N. **10e:** mp 175−177 °C; UV (H_2O) λ_{max} 257.5 nm (ϵ 10128) (pH 2), 259.0 nm (ϵ 11992) (pH 7), 259.5 nm (ϵ 10836) (pH 11); MS (FAB) 302.0 (MH^+). Anal. ($C_9H_{11}N_5O_2Se$) C, H, N.

(±)-β-9-(2-Benzoyloxymethyl-1,3-oxaselenolan-5-yl)-6-chloropurine (7f), and (±)-α-9-(2-Benzoyloxymethyl-1,3-oxaselenolan-5-yl)-6-chloropurine (8f). A solution of crude acetate **6** [prepared from 1.0 g of **5** (3.5 mmol)] in CH_2Cl_2 (40 mL) was added to silylated 6-chloropurine [prepared by refluxing 6-chloropurine (650 mg, 4.2 mmol) with $(NH_4)_2SO_4$ (70 mg) in HMDS (10.8 mL) for 3 h and removal of the solvent under reduced pressure]. TMSOTf (0.8 mL, 4.2 mmol) was then added, and the reaction mixture was stirred at room temperature under argon for 22 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution, and the resulting solid was filtered off. The filtrate was extracted with CH_2Cl_2 and the organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated to dryness. The residue was purified by silica gel column chromatography (0−10% MeOH in CH_2Cl_2) to give **7f** and **8f** as a mixture (310 mg, 21% from **5**, $\beta/\alpha = 0.9$): UV (CH_2Cl_2) λ_{max} 264.0 nm; HRMS calcd for $C_{16}H_{13}ClN_4O_3Se$, 424.9920; found, 424.9928.

(±)-β-9-(2-Hydroxymethyl-1,3-oxaselenolan-5-yl)hypoxanthine (9f) and (±)-α-9-(2-Hydroxymethyl-1,3-oxaselenolan-5-yl)hypoxanthine (10f). A solution of **7f** and **8f** (300 mg, 0.7 mmol), 2-mercaptoethanol (0.2 mL, 2.8 mmol) and NaOMe (152 mg, 2.8 mmol) in MeOH (35 mL) was refluxed for 5 h under argon atmosphere. The resulting mixture was cooled to room temperature, neutralized with Dowex H^+ resin and filtered. The filtrate was evaporated to dryness under reduced pressure to give a residue that was purified by silica gel column chromatography (0−8% of MeOH in CH_2Cl_2) to give β-isomer **9f** and α-isomer **10f** as a mixture (99 mg, 87%, $\beta/\alpha = 3/2$). The individual enantiomers were separated by preparative TLC (10% MeOH in CH_2Cl_2 repeatedly developed) and crystallized from MeOH. **9f**: mp 192−194 °C; UV (H_2O) λ_{max} 248.5 nm (ϵ 17100) (pH 2), 251.0 nm (ϵ 21900) (pH 7), 254.0 (ϵ 31800) (pH 11); ^{13}C NMR (DMSO-d_6) δ 155.8, 147.2, 145.3,

137.8, 123.3, 86.3, 77.7, 63.5, 27.1; HRMS calcd for $C_9H_{10}O_3N_4Se$, 303.0037; found, 303.0028. Anal. ($C_9H_{10}N_4O_3Se$) C, H, N. **10f**: mp 178−180 °C; UV (H_2O) λ_{max} 249.0 nm (ϵ 14100) (pH 2), 250.0 nm (ϵ 18500) (pH 7), 253.5 (ϵ 18500) (pH 11); ^{13}C NMR (DMSO-d_6) δ 156.9, 148.2, 146.4, 138.3, 124.4, 86.9, 81.4, 64.7, 29.4; HRMS calcd for $C_9H_{10}N_4O_3Se$, 303.0037; found, 303.0060. Anal. ($C_9H_{10}N_4O_3Se$) C, H, N.

(±)-β-9-(2-Benzoyloxymethyl-1,3-oxaselenolan-5-yl)-6-chloro-2-fluoropurine (7g) and (±)-α-9-(2-Benzoyloxymethyl-1,3-oxaselenolan-5-yl)-6-chloro-2-fluoropurine (8g). A solution of crude acetate **6** [prepared from 1.38 g of **5** (4.86 mmol)] in 1,2-dichloroethane (50 mL) was added to silylated 6-chloro-2-fluoropurine [prepared by refluxing 6-chloro-2-fluoropurine (1.0 g, 5.83 mmol) with $(NH_4)_2SO_4$ (120 mg) in HMDS (23 mL) for 4 h and removal of the solvent under reduced pressure]. TMSOTf (1.06 mL, 6.80 mmol) was then added, and the resulting mixture was stirred at room temperature under argon for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and the resulting solid was filtered off. The filtrate was extracted with EtOAc and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to dryness. The residue was purified by silica gel column chromatography ($CHCl_3$) to give **7g/8g** (1.64 g, 76.3% from **5**, $\beta/\alpha = 1$) as a mixture: UV (CH_2Cl_2) λ_{max} 269.5 nm; HRMS calcd for $C_{16}H_{12}ClFN_4O_2Se$, 424.9826; found, 424.9825.

(±)-β-9-(2-Benzoyloxymethyl-1,3-oxaselenolan-5-yl)-2-amino-6-chloropurine (7h), (±)-α-9-(2-Benzoyloxymethyl-1,3-oxaselenolan-5-yl)-2-amino-6-chloropurine (8h), (±)-β-9-(2-Benzoyloxymethyl-1,3-oxaselenolan-5-yl)-6-amino-2-fluoropurine (7i) and (±)-α-9-(2-Benzoyloxymethyl-1,3-oxaselenolan-5-yl)-6-amino-2-fluoropurine (8i). A mixture of **7g** and **8g** (1.64 g, 3.7 mmol) was dissolved in dimethyleneglycol dimethyl ether (59 mL) and dry ammonia gas was bubbled into the mixture at room temperature for 15 h. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography ($CHCl_3$) to give **7h**/**8h** (0.5 g, 32%, $\beta/\alpha = 3/2$) and **7i/8i** (134 mg, 46%, $\beta/\alpha = 1/2$) as a mixture. **7h**/**8h**: UV (CH_2Cl_2) λ_{max} 309.5 nm; HRMS calcd for $C_{16}H_{14}ClN_5O_2Se$, 440.0038; found, 440.0029. **7i/8i**: UV (CH_2Cl_2) λ_{max} 259.5 nm; HRMS calcd for $C_{16}H_{14}FN_5O_2Se$, 424.0403; found, 424.0324.

(±)-β-9-(2-Hydroxymethyl-1,3-oxaselenolan-5-yl) guanine (9g) and (±)-α-9-(2-Hydroxymethyl-1,3-oxaselenolan-5-yl)guanine (10g). A solution of **7h** and **8h** (500 mg, 0.11 mmol), 2-mercaptoethanol (0.28 mL, 0.4 mmol), and NaOMe (216 mg, 0.4 mmol) in MeOH (50 mL) was refluxed for 22 h under argon atmosphere. The resulting mixture was cooled to room temperature, neutralized with Dowex H^+ resin, filtered, and evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (0−5% of MeOH in CH_2Cl_2) to give β-isomer **9g** and α-isomer **10g** as a mixture (200 mg, 55%, $\beta/\alpha = 1$). The individual enantiomers were obtained by preparative TLC (5% MeOH in CH_2Cl_2 repeatedly developed) and crystallized from MeOH. **9g**: mp 236−238 °C; UV (H_2O) λ_{max} 255.0 nm (ϵ 10400) (pH 2), 254.0 nm (ϵ 10900) (pH 7), 262.0 (ϵ 9300) (pH 11); MS (FAB) 317.0 (MH^+). Anal. ($C_9H_{11}N_5O_3Se \cdot {}^2/_5H_2O$) C, H, N. **10g**: mp 214−217 °C; UV (H_2O) λ_{max} 254.0 nm (ϵ 33700) (pH 2), 254.0 nm (ϵ 22600) (pH 7), 265.0 (ϵ 19700) (pH 11); MS (FAB) 317.0 (MH^+) Anal. ($C_9H_{11}N_5O_3Se \cdot {}^1/_5H_2O$) C, H, N.

Chiral HPLC Separation. α-D/L-Se-ddC was acetylated before starting the HPLC separation on a chiral column (ChiralPak AS). Thus, acetic anhydride (0.1 mL) was added to an ice-cooled solution of α-D/L-Se-ddC (8 mg), 4-(dimethylamino)pyridine (2 mg), and Et_3N (0.2 mL) in dry DMF (1 mL). The resulting solution was stirred at 0 °C to room temperature overnight under argon. After removal of the solvent by evaporation under reduced pressure, the residue was treated with $CHCl_3$ (20 mL) and water (10 mL). The organic layers were combined, washed with water and brine, and concentrated. The resulting white solid was subjected to chiral HPLC separation without further purification. After the chiral separation, α-D- and α-L-Se-ddC acetates were deprotected by treatment with 2 M methanolic ammonia solution (1 mL) at room temperature for 1 h. After removal of the solvent and drying under vacuum, α-D- and α-L-Se-ddC were obtained as white solids.

Samples (10 mg) were dissolved in 1 mL of methanol. The flow rates were 1.2 mL/min and 1.0 mL/min for α- and β-Se-FddC, respectively. For β-Se-ddC, the mobile phase was 60:40 hexane:ethanol, and the flow rate was 0.6 mL/min. For α-Se-ddC acetate, the mobile phase was 100% ethanol and the flow rate was 0.6 mL/min. The identity of each pair of enantiomers was confirmed by their UV spectra prior to collection from several runs. The mobile phase solutions were evaporated under vacuum and the residues dissolved in methanol for further tests. The total amount of each enantiomers collected was about 3 mg. The optical purity of the separated enantiomers was determined by chiral HPLC and optical rotation.

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Supporting Information Available: Tables of ^1H NMR data and elemental analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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