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Graphical Abstract

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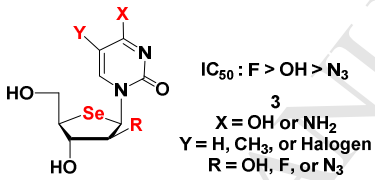

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Structure-Activity Relationships of 2'-Modified-4'-selenoarabinofuranosyl-pyrimidines as Anticancer Agents[‡]

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Key Words: 4'-selenonucleosides; antimetabolite; Mitsunobu reaction; structure-activity relationship; stereoselective fluorination

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Abstract

Based on the potent anticancer activity of the D-arabino-configured cytosine nucleoside ara-C, novel 2'-substituted-4'-selenoarabinofuranosyl pyrimidines **3a**-**3u**, comprising azido, fluoro, and hydroxyl substituents at C-2' were designed, synthesized, and evaluated for anticancer activity. The 2'-azido group was stereoselectively introduced by the Mitsunobu reaction using diphenylphosphoryl azide (DPPA), and the 2'-fluoro group was stereoselectively introduced through the double inversions of stereochemistry via the episelenium intermediate, which was formed by the participation of the selenium atom. Among the compounds tested, the 2'-fluoro derivative **3t** (X = NH_2, Y = H, R = F) was found to be the most potent anticancer agent and showed more potent anticancer activity than the control, ara-C in all tested human cancer cell lines (HCT116, A549, SNU638, T47D, and PC-3) except the leukemia cell lines (K562). The anticancer activity of the 2'-substituted-4'-selenonucleosides is in the following order: 2'-F > 2'-OH > 2'-N_3.

Introduction

DNA and RNA building blocks have long been regarded as valuable resources towards the development of therapeutically useful modified nucleosides. The major mechanism of action of these modified nucleosides for a variety of biological activities is to act as antimetabolites interfering with cellular or viral metabolism. Based on this mechanism, many anticancer or antiviral nucleosides have clinically been developed as antimetabolites.[1]

Uridine (**1a**, X = OH) and cytidine (**1b**, X = NH_2) are essential RNA pyrimidine building blocks and have also been served as important templates for the development of new antiviral and anticancer agents. On the basis of the structure of these templates, modifications have largely been done on the 2' or 3' position and 2'-modified nucleosides generally showed better biological activities.[2] For example, 1-β-D-arabinofuranosyl cytosine (ara-C, **2**, X = NH_2, Y = O, R = OH) with an *arabino* configuration is one of the representative nucleosides and is being used clinically as an anticancer agent.[3] Its bioisosteric 2'-fluoro (Y = O, R = F)[4] and 2'-azido (Y = O, R = N_3)[5] analogues **2** also showed good antiviral or anticancer activities (Figure 1).

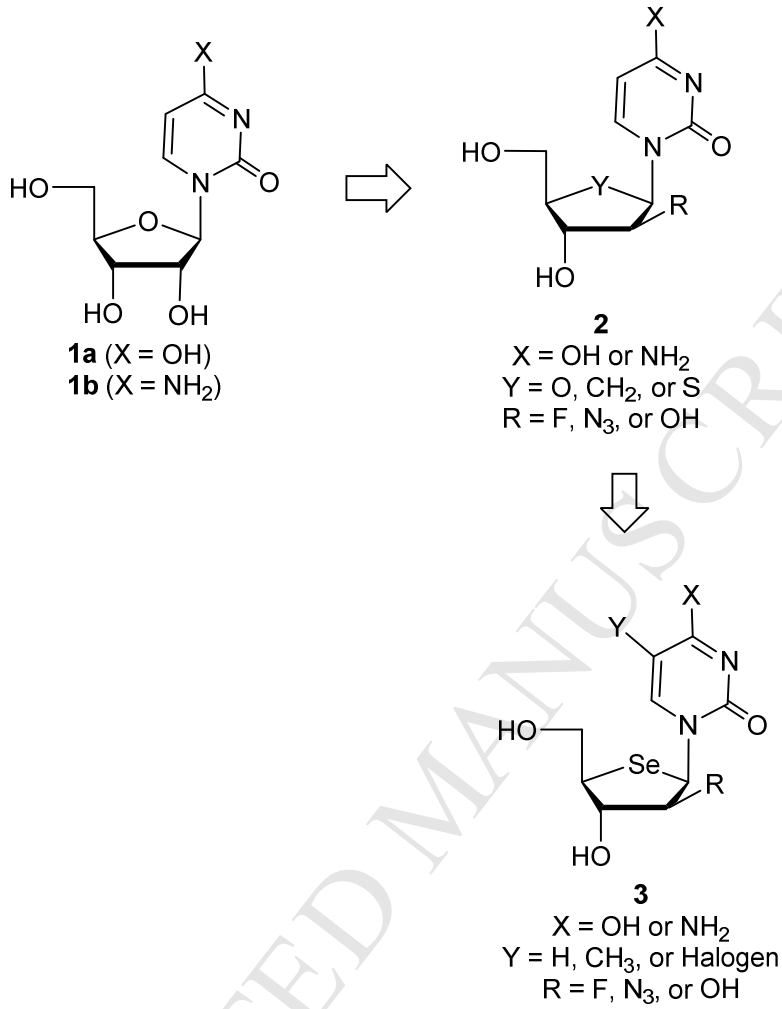


Figure 1. The rationale for the design of the target nucleoside **3**

On the basis of bioisosteric rationale, the corresponding 4'-methylene (carbocyclic)[6] and 4'-thionucleosides[7] **2** were also synthesized and reported to show various biological activities. Although they possessed better enzymatic and chemical stability than the corresponding 4'-oxonucleosides, only a few nucleosides showed attractive biological activity. Thus, the discovery of a new template to replace known modified nucleosides has highly been desirable.

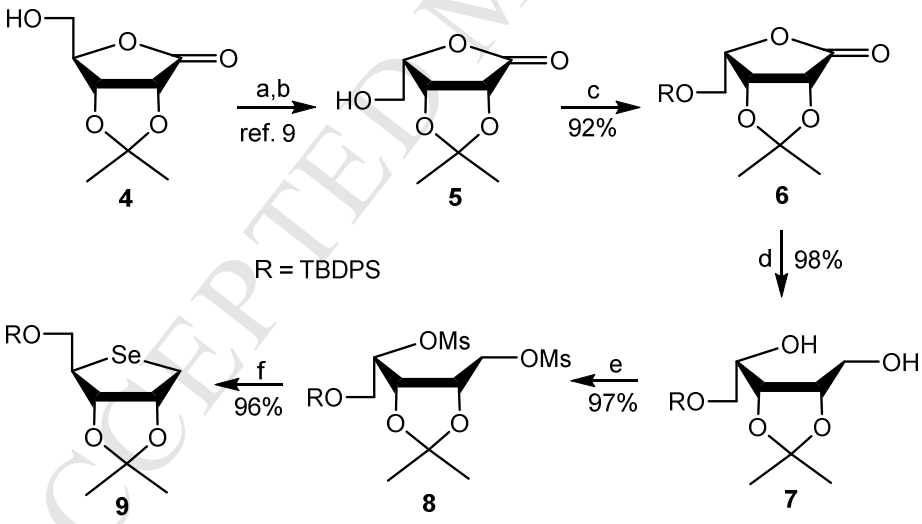
Recently, the 4'-selenonucleoside has been reported as the next generation nucleoside for the development of new therapeutic agents as well as new biological tools.[8] Among these, the 4'-seleno analogue **3** (X = NH_2, Y = H, R = F) of 2'-fluoro-ara C showed potent anticancer activity in a panel of human tumor cell lines.[8c] Thus, based on these findings, it was of great interest to study the structure-activity relationship of the 4'-selenoarabinofuranosyl-pyrimidines **3** substituted with bioisosteric azido, fluoro, or hydroxyl group at the 2' position as anticancer agents. The 2'-azido group was stereoselectively introduced by the Mitsunobu reaction using diphenylphosphoryl azide (DPPA) with inversion of configuration and the 2'-fluoro group was stereoselectively introduced by *N*,*N*-diethylaminosufur trifluoride (DAST) reaction via an episelenium ion intermediate through double inversions of configuration. In this article, we report the full accounts of the structure-activity relationships of 2'-modified-4'-selenoarabibofuranosyl pyrimidines **3** as anticancer agents.

Results and discussion

Chemistry

For the synthesis of the target nucleosides, the key intermediate 4-selenosugar **9** was first synthesized from D-ribose according to our previously reported procedure (Scheme 1).[8e] Commercially available 2,3-*O*-isopropylidene-D-ribonolactone (**4**) was converted to known 2,3-*O*-isopropylidene-L-lyxonolactone (**5**) in two steps.[9] Protection of the hydroxyl group of **5** with TBDPS group gave **6** which was treated with $NaBH_4$ to give diol **7**. Treatment of **7** with MsCl followed by the treatment with the resulting dimesylate **8** with Na_2Se (prepared *in situ* with Se and $NaBH_4$), afforded the 4-selenosugar **9**[8e] in excellent yield.

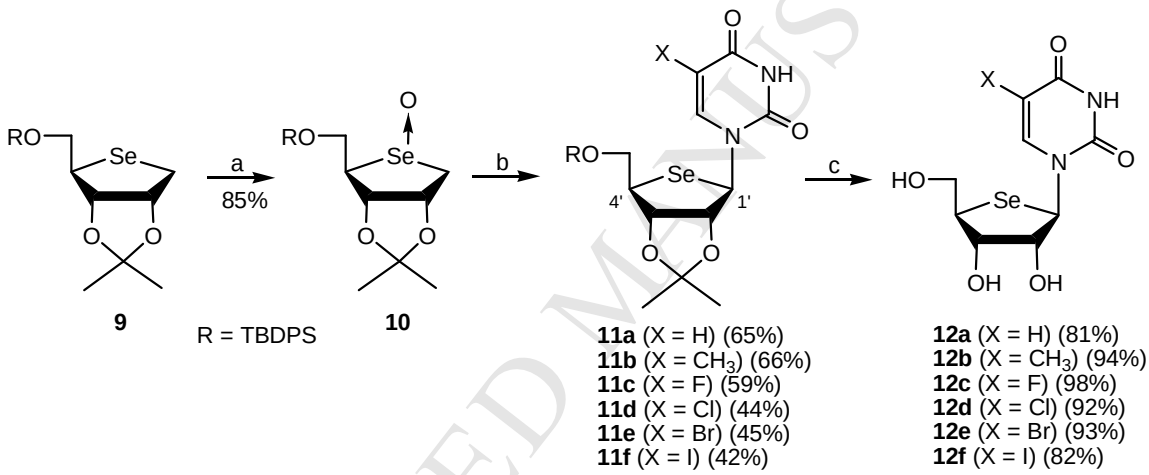
Scheme 1



Reagent and conditions: a) MsCl, TEA, MC, -20 °C to rt, 2 h; b) KOH, H_2O, rt, 15 h; c) TBDPSCl, Et_3N, DMAP, MC, rt, 3 h; d) $NaBH_4$, MeOH, 0 °C to rt, 3 h; e) MsCl, Et_3N, DMAP, MC, 0 °C, 30 min; f) Se, $NaBH_4$, MeOH, THF, 70 °C, 15 h.

The key intermediate **9** was first converted to the key precursors, 4'-selenoribofuranosyl pyrimidines **12a-12f** for the modification of the 2'-position, using a Pummerer type condensation reaction as a key step, as shown in Scheme 2.[8]

Scheme 2



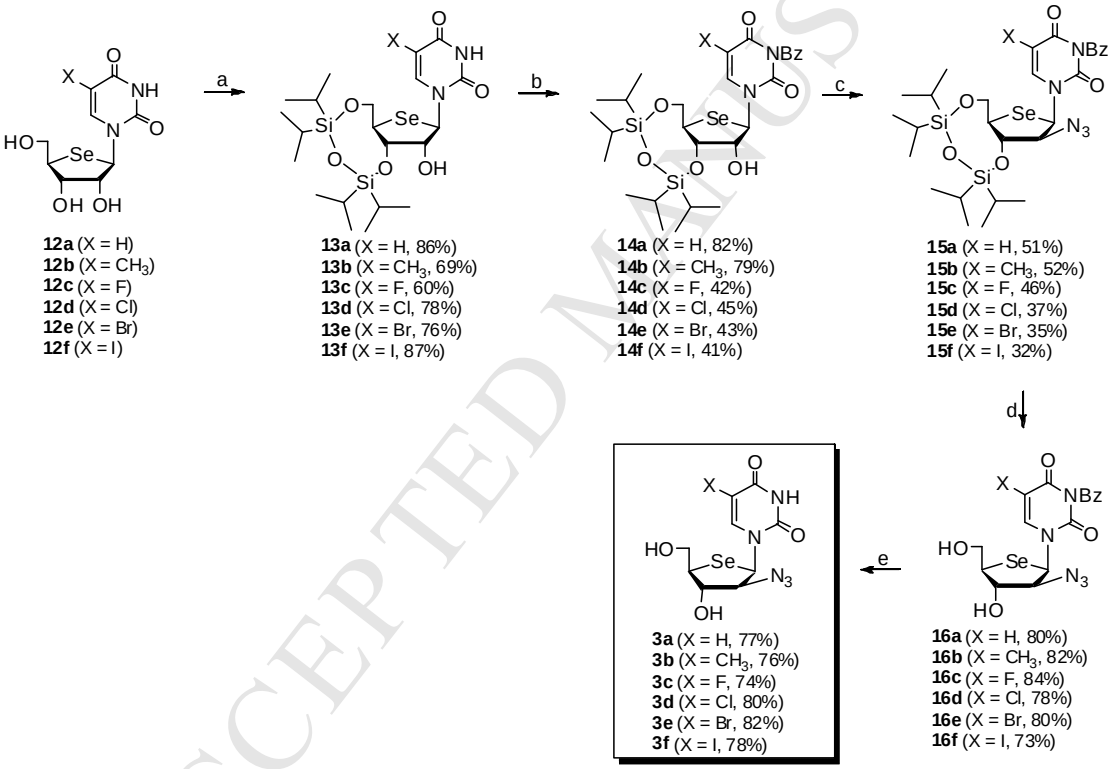
***Reagent and conditions**:* a) *m*CPBA, CH_2Cl_2, -78 ^oC, 45 min; b) Base, Et_3N, TMSOTf, CH_2Cl_2, toluene, 0 ^oC to rt; c) 50% TFA, THF, rt.

Oxidation of **9** with *m*-CPBA gave the glycosyl donor, 4-selenoxide **10**[8a,8e]. The Pummerer-type condensation of **10** with various pyrimidine bases such as uracil, thymine, and 5-halouracils in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) and Et_3N yielded the β-anomers **11a-11f**, exclusively. The anomeric configurations of **11a-11f** were easily confirmed by the NOE experiment between 1'-H

and 4'-H. Removal of the protecting groups of **11a-11f** with 50% TFA yielded the 4'-selenoribofuranosyl pyrimidines **12a-12f**.

For the synthesis of the 2'-azido-4'-selenoarabinofuranosyl pyrimidines **3a-3f**, the ribo analogues **12a-12f** were treated with $TIPDSCl_2$ to give the 3',5'-*O*-TIPDS protected nucleosides **13a-13f**, respectively (Scheme 3).

Scheme 3



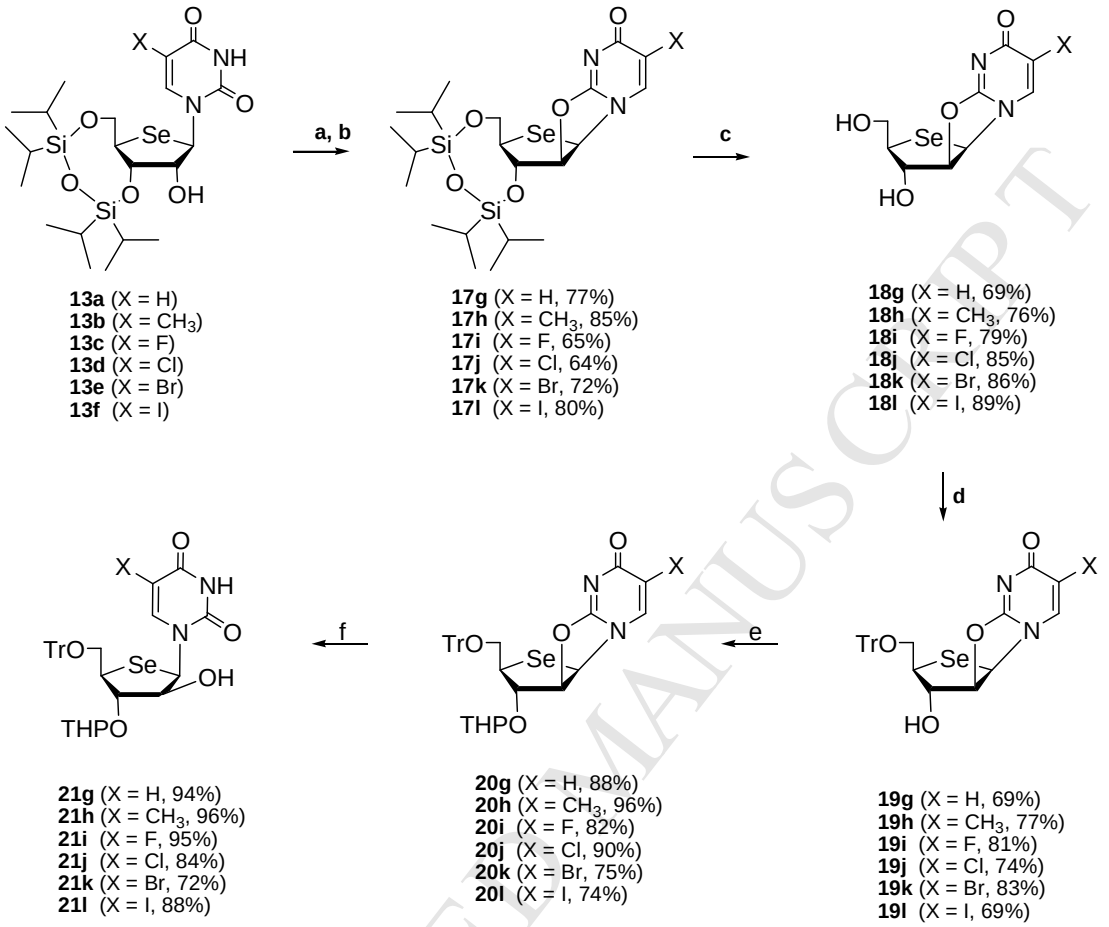
***Reagents and conditions*:** a)$TIPDSCl_2$, pyridine, rt; b) BzCl, $Et_4N^+Br^-$, in aqueous Na_2CO_3/CH_2Cl_2, rt for **13a**, **13c-13f** and BzCl, Et_3N, CH_2Cl_2, rt for **13b**; c) DEAD, DPPA, PPh_3, THF, rt; d) $3HF.Et_3N$, Et_3N, THF, 0 ^oC; e) NH_3/MeOH, rt.

To prevent the formation of *O*2,2'-anhydro nucleosides during the Mitsunobu reaction with diphenylphosphoryl azide (DPPA), the N-3 position of **13a-13f** was selectively protected with electron-withdrawing benzoyl group in the presence of the 2'-hydroxyl group to give **14a-14f**. Treatment of **14a-14f** with DPPA under the Mitsunobu

conditions afforded the desired 2'-azidoarabinofuranosyl derivatives **15a-15f** with inversion of stereochemistry, respectively. The removal of TIPDS groups of **15a-15f** with $3HF{\cdot}Et_3N$ yielded **16a-16f**, which were treated with methanolic ammonia to afford the final 2'-azido-4'-selenoarabinofuranosyl pyrimidines **3a-3f**, respectively. The configuration of the 2'-azido group of **3a-3f** was unambiguously confirmed by the comparison of ^1H NOE experiments of **3b**. Irradiation on 2'-H in **3b** gave the peak enhancement by 6.0% on 4'-H, while no NOE between 2'-H and H-6 was observed, indicating that the sugar moiety possesses an arabino configuration.

For the synthesis of 2'-fluoro-4'-selenoarabinofuranosyl pyrimidines **3g-3l**, the same intermediates **13a-13f** were converted to **21g-21l**, respectively which serve as the substrates for DAST fluorination, as shown in Scheme 4. Treatment of **13a-13f** with MsCl/DBU gave the *O*2,2'-anhydro nucleosides **17g-17l**. After the removal of the TIPDS groups of **17g-17l** with $3HF{\cdot}Et_3N$, the resulting diols **18g-18l** were protected with trityl (Tr) and THP groups to give **20g-20l**, respectively. Opening of the *O*2,2'-anhydro ring in **20g-20l** with 1 M NaOH afforded **21g-21l** with an *arabino* configuration at the 2'-position, respectively, which serve as the substrates for DAST fluorination.

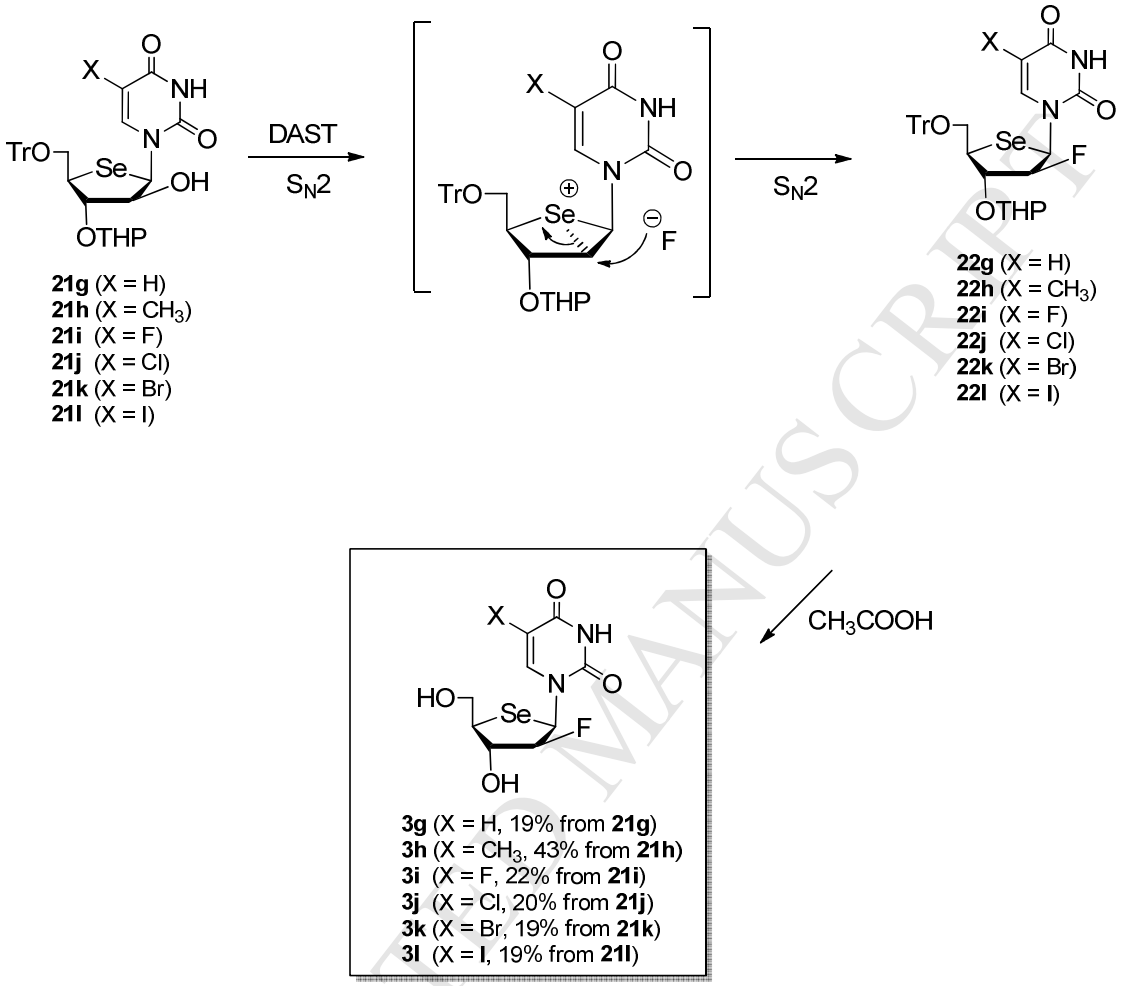
Scheme 4



Reagents and conditions: a) MsCl, DMAP, Et_3N, MC, 0 ^oC; b) DBU, acetone, rt; c) $3HF{\cdot}Et_3N$, Et_3N, THF, 0 ^oC; d) TrCl, DMAP, pyridine, 60 ^oC; e) DHP, MC, rt; f) 1*N* NaOH, CH_3CN, rt

Treatment of **21g-21l** with DAST gave the desired 2'-fluoro derivatives **22g-22l** with *arabino* configurations, which were formed by double S_N2 reactions via episelenium ion intermediates resulting from the participation of the selenium atom,[8c] as shown in Scheme 5. The stereochemistry of the fluoro group of **22g-22l** was confirmed by the comparison of the X-ray crystal structure of **3g** formed after the removal of all the protecting groups in **22g** (Figure 2). Treatment of **22g-22l** with 80% acetic acid afforded the final 2'-fluoro-4'-selenoarabinofuranosyl pyrimidines **3g-3l**, respectively.

Scheme 5

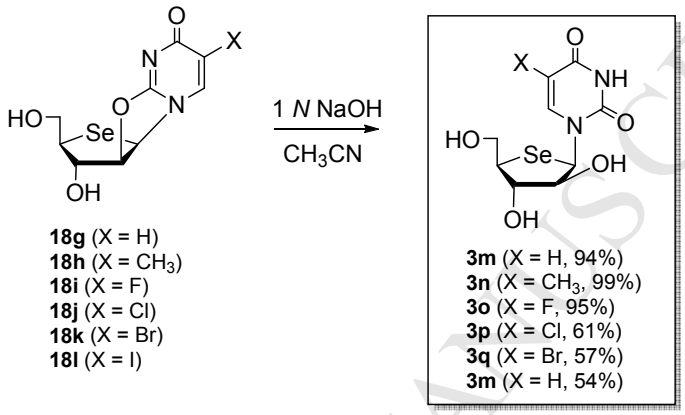


***Reagents and conditions*:** a) DAST, MC, -78 °C (30 min), 0 °C (2 h); b) aq. 80% CH_3COOH.

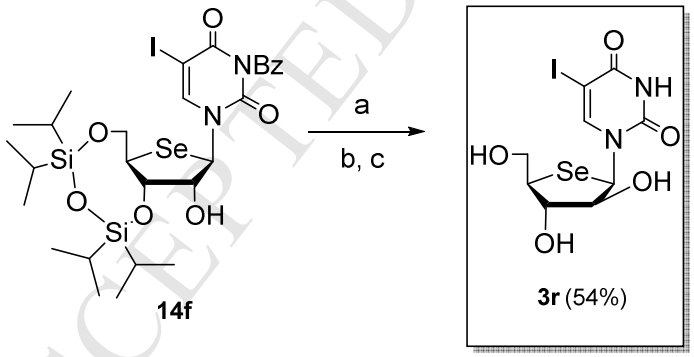
For the synthesis of the 4'-selenarabinofuranosyl derivatives, **18g-18k** were treated with 1 M NaOH to yield the final 4'-selenarabinofuranosyl pyrimidines **3m-3q**, respectively (Scheme 6). Surprisingly, the reaction of 5-iodo derivative **18l** under these set of conditions resulted in the formation of the dehalogenated uracil compound (**3m**, 54%) instead of giving **3r**. Thus, the synthesis of the 5-iodo derivative **3r** was

completed by the Mitsunobu reaction on **14f** followed by the removals of all protecting groups, as shown in Scheme 7.

Scheme 6

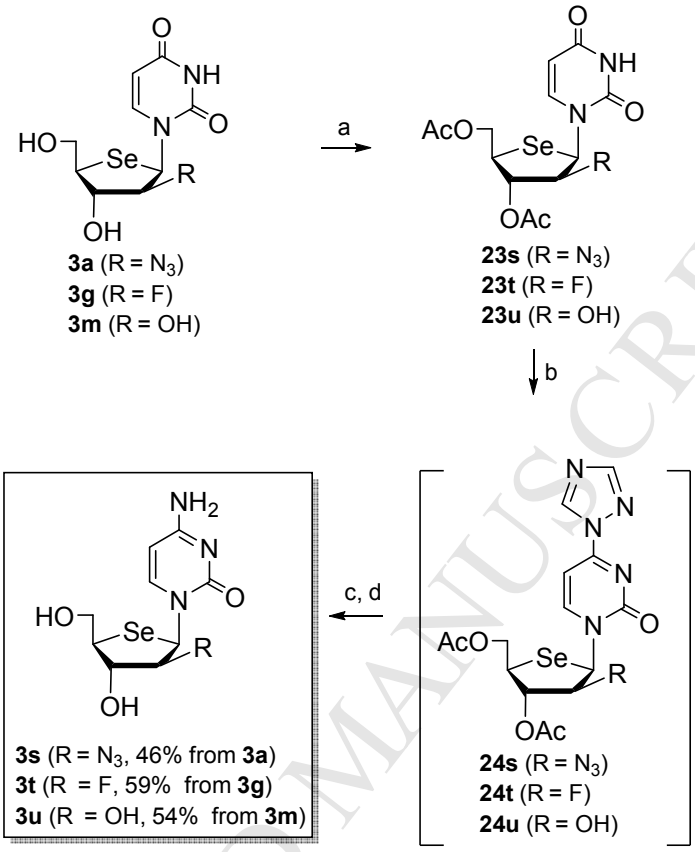


Scheme 7



***Reagents and conditions*:** a) DIAD, PPh_3, BzOH, THF, 0 °C to rt; b) 3HF.Et_3N, THF, 0 °C; c) NH_3/MeOH, rt.

Scheme 8



Reagents and conditions: a) Ac_2O, rt; b) 1,2,4-triazole, Et_3N, $POCl_3$, CH_3CN, rt; c) NH_4OH, 1,4-dioxane, rt; d) NH_3/MeOH, rt.

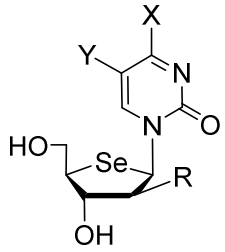
The uracil derivatives **3a**, **3g**, and **3m** were converted to the corresponding cytosine derivatives **3s**, **3t**, and **3u**, respectively, as illustrated in Scheme 8.[8c] The uracil derivatives **3a**, **3g**, and **3m** were peracetylated to give **23s**, **23t**, and **23u**, respectively. Treatment of **23s**, **23t**, and **23u** with $POCl_3$, 1,2,4-triazole, and Et_3N gave the corresponding triazole derivatives **24s**, **24t**, and **24u**, which were immediately used in the next step just after work-up because they are generally unstable during the

purification by silica gel column chromatography. Compounds **24s**, **24t**, and **24u** were successively treated with NH_4OH in 1,4-dioxane and methanolic ammonia to afford the cytosine derivatives **3s**, **3t**, and **3u**, respectively.[8c]

Antitumor activity evaluation

All the final 2'-modified-4'-selenoarabinofuranosyl pyrimidines **3a-3u** were assayed for cytotoxic effects in several human cancer cell lines such as colon cancer (HCT116), lung cancer (A549), stomach cancer (SNU638), breast cancer (T47D), prostate cancer (PC-3), and leukemia (K562) cells, using sulforhodamine B (SRB) protein staining method (Table 1).[10]

Table 1. Anticancer activity of all the final 2'-modified-4'-selenonucleosides, **3a-3u** in several human cancer cell lines.



Compound No.	IC_{50} (μM)[a]					
	HCT116[b]	A549[c]	SNU638[d]	T47D[e]	PC-3[f]	K562[g]
3a (X = OH, Y = H, R = N_3)	> 100	> 100	> 100	> 100	> 100	> 100
3b (X = OH, Y = Me, R = N_3)	> 100	> 100	> 100	> 100	> 100	> 100
3c (X = OH, Y = F, R = N_3)	> 100	> 100	> 100	> 100	> 100	> 100
3d (X = OH, Y = Cl, R = N_3)	> 100	> 100	> 100	> 100	> 100	> 100
3e (X = OH, Y = Br, R = N_3)	> 100	> 100	> 100	> 100	> 100	> 100
3f (X = OH, Y = I, R = N_3)	> 100	> 100	> 100	> 100	> 100	> 100
3g (X = OH, Y = H, R = F)[h]	> 100	> 100	> 100	> 100	> 100	> 100
3h (X = OH, Y = Me, R = F)	85.2	76.4	77.2	65.3	88.0	76.3

3i (X = OH, Y = F, R = F)	40.1	54.2	50.1	51.1	43.1	78.5
3j (X = OH, Y = Cl, R = F)	80.2	82.1	76.3	77.1	> 100	> 100
3k (X = OH, Y = Br, R = F)	> 100	> 100	> 100	> 100	> 100	> 100
3l (X = OH, Y = I, R = F)	> 100	> 100	> 100	> 100	> 100	> 100
3m (X = OH, Y = H, R = OH)[h]	> 100	> 100	> 100	> 100	> 100	> 100
3n (X = OH, Y = Me, R = OH)	> 100	> 100	> 100	> 100	> 100	> 100
3o (X = OH, Y = F, R = OH)	56.8	55.2	60.1	67.4	66.3	> 100
3p (X = OH, Y = Cl, R = OH)	> 100	> 100	> 100	> 100	> 100	> 100
3q (X = OH, Y = Br, R = OH)	> 100	> 100	> 100	> 100	> 100	> 100
3r (X = OH, Y = I, R = OH)	> 100	> 100	> 100	> 100	> 100	> 100
3s (X = NH_2, Y = H, R = N_3)	78.3	80.1	85.2	78.4	75.1	62.3
3t (X = NH_2, Y = H, R = F)[h]	1.1	0.47	0.14	0.79	0.58	0.63
3u (X = NH_2, Y = H, R = OH)[h]	7.13	8.83	4.72	8.91	4.54	86.6
Ara-C (2)[h]	5.3	1.90	0.15	2.72	55.9	0.05

[a]measured using SRB method; [b]human colon cancer cell lines; [c]human lung cancer cell lines; [d]human stomach cancer cell lines; [e]human breast cancer cell lines; [f]human prostate cancer cell lines; [g]human leukemia cell lines; [h]ref. 8c; ND.

As shown in Table 1, all the cytosine derivatives **3s**-**3u** showed significant anticancer activity in human tumor cell lines tested, among which the 2'-fluoro derivative **3t** was the most potent and was more potent than the control, Ara-C (**2**) except human leukemia cell lines (K562).[8c] The anticancer activity of the 2'-modified-4'-selenoarabinofuranosyl cytosines decreased in the following order: 2'-F derivative **3t** (R = F) > 2'-OH derivative **3u** (R = OH) > 2'-N_3 derivative **3s** (R = N_3). In case of all the uracil, thymine, and 5-halouracil derivatives, the same trend was also observed as the cytosine derivatives: 2'-F derivative **3i** (R = F) > 2'-OH derivative **3o** (R = OH), although they showed very weak activity. Interestingly, the 5-fluorouracil derivatives **3i** and **3o** with 2'-F and 2'-OH substitution exhibited more potent anticancer activity than other uracil, thymine, and 5-halouracil derivatives. All the 2'-azido derivatives did not

show significant anticancer activity up to 100 μM, except the cytosine derivative **3s** showing weak anticancer activity.

In order to determine if the anticancer activity of **3t** depends on the conversion to the corresponding triphosphate by cellular kinases, which are essential for the inhibition of DNA and/or RNA cellular polymerase, **3t** was incubated in the cell and the metabolites were analyzed by LC-MS. Surprisingly, none of any mono-, di-, or triphosphate was detected as the major metabolites unlike ara-C (**2**), which was converted to the corresponding triphosphate,[11] indicating that the anticancer activity of **3t** might come from different mechanism of action from that of ara-C (**2**) 16, lines used in the treatment of leukemia. This cellular metabolism study might explain why **3t** is less potent against human leukemia cell lines (K562) and more potent against solid tumor cell lines (HCT116, A549, SNU638, T47D, and PC-3) than ara-C (**2**). This result also demonstrates that all synthesized compounds might not act as cellular DNA and/or RNA polymerase inhibitors because of no phosphorylation by cellular kinases. No phosphorylation of **3t** by cellular kinases might be attributed to the different sugar puckering[12] of 4-selenosugar[8]. As shown by the X-ray crystal structure[13] of **3g** (Figure 2), bulky selenium atom pushes **3g** to adopt the 2'-endo/3'-exo (South) conformation with pseudorotation parameters of $P = 0.033^{\circ}$ and $\tau_m = 46.2^{\circ}$. When compared with the

corresponding 4'-oxo derivative (2'-deoxy-2'-fluorouridine), which takes the unusual 4'-exo/1'-endo sugar puckering with P = 70.84° and τ_m =38.2°, the conformation of 3**g** appears to be affected by selenium atom. Most of the 2'-fluoro derivatives including 2'-deoxy-2'-fluorocytidine and 2'-deoxy-2'-fluoro-4'-thiocytidine shows typical 2'-exo/3'-endo (North) conformation due to the gauche effect and this conformational difference will affect the orientation of the 5'-OH which is essential for the phosphorylation.

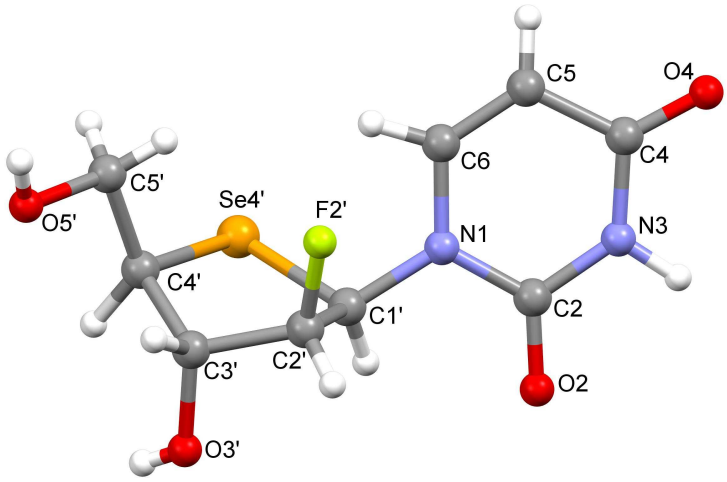


Figure 2. The X-ray crystal structure of 2'-deoxy-2'-fluoro-4'-selenouridine (**3g)**

Conclusions

On the basis of potent anticancer activity of ara-C (**2**) with the 2'-arabino configuration, the 2'-deoxy-4'-selenoarabinofuranosyl pyrimidines **3a**-**3u** with the 2'-azido, 2'-fluoro, or 2'-hydroxyl substitution were synthesized from D-ribose and evaluated for cytotoxic effects in a panel of human tumor cell lines. The highlight of our

synthetic endeavor is the Pummerer-type base condensation, Mitsunobu reaction with DPPA for the introduction of the 2'-azido group, and stereoselective fluorination via the episelenium intermediate. Among compounds tested**,** the 2'-fluoro derivative **3t** was found to exhibit the most potent anticancer activity and showed better anticancer activity than the reference, ara-C. Synthesis, conformational study, and cellular study executed in this study will provide the medicinal chemist with great insight into the design of novel modified nucleosides.

Experimental Section

General methods.

^{1}H-NMR Spectra ($CDCl_3$, CD_3OD or DMSO-d_6) were recorded on Varian Unity Invoa 400 MHz. 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. ^{13}C-NMR spectra ($CDCl_3$, CD_3OD or DMSO-d_6) were recorded on Varian Unity Inova 100 MHz. ^{19}F-NMR spectra ($CDCl_3$, CD_3OD) were recorded on Varian Unity Inova 376 MHz. The chemical shifts were reported as parts per million (δ) relative to the solvent peak. Optical rotations were determined on Jasco III in appropriate solvent. UV spectra were recorded on U-3000 made by Hitachi in methanol or water. Infrared spectra were

recorded on FT-IR (FTS-135) made by Bio-Rad. Melting points were measured on B-540 made by Buchi. Elemental analyses (C, H, and N) were used to determine purity of all synthesized compounds, and the results were within ± 0.4% of the calculated values, confirming > 95% purity. The progress of reactions was monitored via thin layer chromatography (TLC, Merck precoated 60 F_{254} plates) and ethyl acetate:hexane or dichloromethane/methanol. The TLC plates were visualized using UV lamp (254 nM) and/or staining in anisaldehyde solution with acetic acid, sulfuric acid and methanol. Flash column chromatography was performed using silica gel 60 (230-400 mesh, Merck) and ethyl acetate:hexane or dichloromethane/methanol mixtures as the mobile phase. Reagents were purchased from Aldrich Chemical Company. Solvents were obtained from local suppliers. All the anhydrous solvents were distilled over CaH_2, P_2O_5 or sodium/benzophenone prior to the reaction. All reactions sensitive to air or moisture were conducted under nitrogen atmosphere, unless otherwise stated. The yields given refer to purified products after column chromatography or recrystallization with appropriate solvents. 2.3-O-isopropyledene-L-lyxono-1,4-lactone (**5**) was synthesized from D-ribose using a known procedure.[9] Compounds **6-9** were synthesized according to our previously reported procedure.[8e]

General procedure for the synthesis of β-anomers **11a-11f.**

To a stirred solution of 4-selenosugar **9** in dichloromethane was added a solution of *m*-CPBA (1.1 equiv.) in dichloromethane 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 then extracted with dichloromethane. The organic layer was washed with saturated $NaHCO_3$, brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified on flash silica gel column chromatography (dichloromethane:methanol = 30:1) to give selenoxide **10** (85%) as a colorless syrup. Due to the unstable nature of selenoxide **10**, it was immediately used for the next step.

To a suspension of appropriate pyrimidine base (2 equiv.) in toluene were added triethylamine (4.1 equiv.) and trimethylsilyl trifluoromethanesulfonate (6.1 equiv.) and the mixture were stirred at room temperature for 1 h. The silylated base solution was diluted with additional dichloromethane and this solution was then added to a solution of **10** in dichloromethane dropwise over a period of 20 min at 0 °C. An additional amount of triethylamine (2.1 equiv.) was added dropwise to the reaction mixture to initiate the Pummerer reaction at 0 °C. After the reaction mixture was stirred at room temperature for 15 h, the reaction mixture was quenched with saturated $NaHCO_3$ and extracted with dichloromethane. The organic layers were washed with saturated $NaHCO_3$ solution, water and brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified on flash silica gel

column chromatography (hexane:ethyl acetate = 2:1) to give the β-anomers **11a-11f**.

(-)-1-[5-*O*-(*tert*-Butyldiphenylsilyl)-2,3-*O*-isopropylidene-4-seleno-D-ribofuranosyl]uracil (**11a**). Light yellow foam; Yield: 65%; $[\alpha]_D^{20}$ -47.74 (*c* 0.22, CH_3OH); UV (CH_3OH) λ_{max} 265 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (brs, 1H), 7.69-7.63 (m, 4H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.45-7.37 (m, 6H), 6.35 (d, *J* = 4.0 Hz, 1H), 5.56 (dd, *J* = 2.0, 8.0 Hz, 1H), 4.73 (dd, *J* = 4.2, 5.2 Hz, 1H), 4.67 (dd, *J* = 4.2, 5.2 Hz, 1H), 4.02-3.95 (m, 3H), 1.56 (s, 3H), 1.28 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 142.0, 135.8, 135.7, 133.2, 132.8, 130.3, 128.2, 128.1, 112.4, 103.5, 90.1, 85.3, 76.6, 66.1, 59.7, 50.3, 28.0, 27.1, 27.0, 26.8, 25.5 19.5; MS (FAB) m/z 587 $[M+H]^+$; Found: C, 57.04; H, 5.86; N, 4.66. Calc. for $C_{28}H_{34}N_2O_5SeSi$: C, 57.43; H, 5.85; N, 4.78%.

(-)-1-[5-*O*-(*tert*-Butyldiphenylsilyl)-2,3-*O*-isopropylidene-4-seleno-D-ribofuranosyl]thymine (**11b**).

Light yellow foam; Yield: 66%; $[\alpha]_D^{20}$ -29.79 (*c* 5.83, CH_2Cl_2); UV (CH_3OH) λ_{max} 278 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.69-7.67 (m, 4H), 7.43-7.37 (m, 6H), 6.33 (s, 1H), 4.71 (m, 2H), 4.04 (m, 2H), 3.92 (m, 1H), 1.83 (s, 3H), 1.56 (s, 3H), 1.08 (s, 9 H); ^{13}C NMR (100 MHz, CD_3OD) δ 140.1, 136.9, 136.8, 134.6, 134.3, 131.3, 131.2, 129.1, 129.0, 112.9, 112.6, 90.9, 87.0, 79.7, 67.7, 61.2, 52.4, 28.2, 27.4, 25.6, 20.2, 12.5; MS (FAB) m/z 601 $[M+H]^+$; Found: C, 58.30; H, 6.48; N, 4.37. Calc. for $C_{29}H_{36}N_2O_5SeSi$: C, 58.09; H, 6.05; N, 4.67%.

(-)-5-Fluoro-1-[5-*O*-(*tert*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-4-seleno-D-ribofuranosyl]uracil (**11c**).

Light yellow foam; Yield: 59%; $[\alpha]_D^{20}$ -21.52 (*c* 7.15, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 284 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69-7.66 (m, 4H), 7.61 (d, *J* = 2.0 Hz, 1H), 7.48-7.38 (m, 6H), 6.34

(dd, *J* = 1.2, 4.4 Hz, 1H), 4.68 (dd, *J* = 3.2, 5.6 Hz, 1H), 4.62 (t, *J* = 4.4 Hz, 1H), 4.05-4.00 (m, 2H), 3.92 (dd, *J* = 9.2, 12.4 Hz, 1H), 1.57 (s, 3H), 1.28 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.67 (d, *J* = 27.3 Hz), 148.9, 140.6 (d, *J* = 239.3 Hz), 135.8 (d, *J* = 8.8 Hz), 133.0 (d, *J* = 11.0 Hz), 130.2, 128.1 (d, *J* = 1.5 Hz), 126.0 (d, *J* = 33.8 Hz), 112.7, 89.7, 84.7, 66.0, 59.8, 50.1, 28.0, 27.1, 25.5, 19.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -161.88 (d, *J* = 5.2 Hz); MS (ESI) m/z 643.0957 $[M+K]^+$; Found: C, 55.78; H, 5.14; N, 4.62. Calc. for $C_{28}H_{33}FN_2O_5SeSi$: C, 55.71; H, 5.51; N, 4.64%.

(-)-5-Chloro-1-[5-*O*-(*tert*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-4-seleno-D-ribofuranosyl]uracil (**11d**).

Light yellow foam; Yield: 44%; $[\alpha]_D^{20}$ -29.31 (*c* 1.01, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 283 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (brs, 1H), 7.81 (s, 1H), 7.67 (m, 4H), 7.42 (m, 6H), 6.30 (d, *J* = 4.8 Hz, 1H), 4.69 (dd, *J* = 3.2, 5.6 Hz, 1H), 4.63 (dd, *J* = 4.4, 6.0 Hz, 1H), 4.03 (m, 2H), 3.91 (dd, *J* = 9.2, 12.4 Hz, 1H), 1.56 (s, 3H), 1.27 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 149.5, 138.8, 135.9, 133.1, 130.2, 128.1, 112.7, 110.1, 89.7, 84.6, 65.9, 59.7, 50.4, 27.9, 27.1, 25.5, 19.5; Found: C, 54.12; H, 5.67; N, 4.23. Calcd for $C_{28}H_{33}ClN_2O_5SeSi$: C, 54.24; H, 5.36; N, 4.52%.

(-)-5-Bromo-1-[5-*O*-(*tert*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-4-seleno-D-ribofuranosyl]uracil (**11e**).

Light yellow foam; Yield: 45%; $[\alpha]_D^{20}$ -25.41 (*c* 6.49, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 285 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 7.82 (s, 1H), 7.69-7.66 (m, 4H), 7.47-7.38 (m, 6H), 6.29 (d, *J* = 4.4 Hz, 1H), 4.72-4.65 (m, 2H), 4.07-3.90 (m, 3H), 1.56 (s, 3H), 1.28 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 149.7, 141.4, 135.8, 133.0, 130.2, 128.1, 112.7, 97.9. 89.7, 84.6, 66.0, 59.7, 50.5, 28.0, 27.1, 25.5, 19.5; Found: C, 50.66; H, 5.00; N, 4.21. Calc. for $C_{28}H_{33}BrN_2O_5SeSi$: C, 50.61; H, 5.01; N, 4.22%.

(-)-5-Iodo-1-[5-*O*-(*tert*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-4-seleno-D-ribofuranosyl]uracil (**11f**).

Light yellow foam; Yield: 42%; $[\alpha]_D^{20}$ -52.4 (*c* 0.11, CH_3OH); UV λ_{max} (CH_3OH) 284 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 7.89 (s, 1H), 7.69-7.66 (m, 4H), 7.48-7.38 (m, 6H), 6.24 (d, *J* = 4.4 Hz, 1H), 4.71-4.63 (m, 2H), 4.06-4.01 (m, 2H), 3.95-3.89 (m, 1H), 1.55 (s, 3H), 1.27 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 149.8, 146.5, 135.9, 135.8, 133.1, 133.0, 130.24, 130.21, 128.1, 128.0, 112.8, 89.7, 84.6, 69.4, 66.0, 59.6, 50.6, 28.0, 27.1, 25.5, 19.5; Found C, 46.99; H, 4.97; N, 3.99. Calc. for $C_{28}H_{33}IN_2O_5SeSi$: C, 47.26; H, 4.67; N, 3.94%.

General procedure for the synthesis of ribofuranosyl analogues **12a-12f**.

To a solution of compound **11a-11f** in tetrahydrofuran was added 50% aqueous trifluoroacetic acid at 0 °C and the mixture was allowed to stir at room temperature for 15 h. The solvent was evaporated under reduced pressure and then co-evaporated under reduced pressure three times with dry toluene to give **12a-12f**.

(-)-1-(4-Seleno-D-ribofuranosyl)uracil (**12a**).

White solid; Yield: 81%; mp 198-200 °C; $[\alpha]_D^{20}$ -113.93 (*c* 0.33, CH_3OH); UV (CH_3OH) λ_{max} 267 nm; ^1H NMR (400 MHz, CD_3OD) δ 8.00 (d, *J* = 8.0 Hz, 1H), 6.11 (d, *J* = 8.8 Hz, 1H), 5.77 (d, *J* = 8.0 Hz, 1H), 4.26 (dd, *J* = 3.6, 8.4 Hz, 1H), 4.19 (t, *J* = 2.5 Hz, 1H), 3.75 (dd, *J* = 7.8, 11.4 Hz, 1H), 3.63 (dd, *J* = 7.8, 11.4 Hz, 1H), 3.44-3.40 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 163.0, 150.9, 142.1, 102.1, 77.0, 73.5, 63.6, 55.3, 48.8; MS (FAB) m/z 307 (M^+); Found: C, 34.93; H, 3.82; N, 9.07. Calc. for $C_9H_{12}N_2O_5Se$: C, 35.19; H, 3.94; N, 9.12%.

(-)-1-(4-Seleno-D-ribofuranosyl)thymine (**12b**).

White solid, Yield: 94%; mp 128-130 ^{o}C; $[\alpha]_D^{20}$ -111.62; (*c* 0.86, CH_3OH); UV (CH_3OH) λ_{max} 275 nm; ^{1}H NMR (400 MHz, CD_3OD) δ 7.91 (s, 1H), 6.29 (d, *J* = 8.4 Hz, 1H), 4.38 (dd, *J* = 3.6, 8.0 Hz, 1H), 4.26 (t, *J* = 2.8 Hz, 1H), 3.88 (dd, *J* = 6.4, 11.6 Hz, 1H), 3.82 (dd, *J* = 5.6, 11.6 Hz, 1H), 3.56-3.53 (m, 1H), 1.91 (s, 3H); ^{13}C NMR (CD_3OD) δ 166.3, 153.1, 139.6, 112.2, 80.1, 76.4, 65.2, 57.6, 30.8, 12.6; MS (ESI) m/z 344.9961 $[M+Na]^+$; Found: C, 37.53; H, 4.02; N, 8.47. Calc. for $C_{10}H_{14}N_2O_5Se$: C, 37.39; H, 4.39; N, 8.72%.

(-)-1-(4-Seleno-D-ribofuranosyl)-5-fluorouracil (**12c**).

White solid; Yield: 98%; mp 199-200 ^{o}C; $[\alpha]_D^{20}$ -26.84 (*c* 0.79, CH_3OH); UV (CH_3OH) λ_{max} 275 nm; ^{1}H NMR (400 MHz, CD_3OD) δ 8.31 (t, *J* = 3.4 Hz, 1H), 6.27 (dd, *J* = 1.6, 7.6 Hz, 1H), 4.37 (dd, *J* = 3.4, 7.8 Hz, 1H), 4.26 (t, *J* = 3.0 Hz, 1H), 3.90-3.81 (m, 2H), 3.58-3.54 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 159.2 (d, *J* = 101.6 Hz), 151.3, 142.5, 140.2, 127.7 (d, *J* = 139.6 Hz), 80.2, 76.3, 64.6, 58.3; ^{19}F NMR (CD_3OD) δ -166.65 (t, *J* = 5.65 Hz); MS (ESI) m/z 364.9437 $[M+K]^+$; Found: C, 33.64; H, 3.79; N, 8.43. Calc. for $C_9H_{11}FN_2O_5Se$: C, 33.24; H, 3.41; N, 8.62%.

(-)-1-(4-Seleno-D-ribofuranosyl)-5-chlorouracil (**12d**).

White solid; Yield: 92%; mp 220-223 $^{\circ}$C; $[\alpha]_D^{25}$ -27.87 (*c* 0.24, CH_3OH); UV (CH_3OH) λ_{max} 280 nm; ^{1}H NMR (400 MHz, CD_3OD) δ 8.42 (s, 1H), 6.25 (d, *J* = 8.0 Hz, 1H), 4.39 (dd, *J* = 3.2, 7.6 Hz, 1H), 4.24 (t, *J* = 3.2 Hz, 1H), 3.90-3.81 (m, 2H), 3.59-3.55 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 161.4, 152.0, 141.1, 109.7, 80.4, 76.5, 64.8, 58.4, 50.1; MS (ESI) m/z 364.9613 $[M+Na]^+$; Found: C, 31.89; H, 3.33; N, 8.23. Calc. for $C_9H_{11}ClN_2O_5Se$: C, 31.64; H, 3.25; N, 8.20%.

(-)-1-(4-Seleno-D-ribofuranosyl)-5-chlorouracil (**12e**).

White solid; Yield: 93%; mp 169-173°C; $[\alpha]_D^{20}$ -61.81 (*c* 1.11, CH_3OH+H_2O); UV (CH_3OH) λ_{max} 282 nm; ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (s, 1H), 6.25 (d, *J* = 7.6 Hz, 1H), 4.39 (dd, *J*

= 3.6, 7.6 Hz, 1H), 4.24 (t, *J* = 3.0 Hz, 1H), 3.90-3.81 (m, 2H), 3.59-3.55 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 161.5, 152.2, 143.7, 97.4, 80.5, 76.5, 64.7, 58.4, 50.1; MS (ESI) m/z 408.8908 $[M+Na]^+$; Found: C, 27.89; H, 3.03; N, 7.44. Calc. for $C_9H_{11}BrN_2O_5Se$: C, 28.00; H, 2.87; N, 7.26%.

(-)-1-(4-Seleno-D-ribofuranosyl)-5-iodouracil (**12f**).

White solid; Yield: 82%; mp 242-244 °C; $[\alpha]_D^{20}$ -83.50 (*c* 0.61, CH_3OH+H_2O); UV λ_{max} (CH_3OH) 292 nm; ^{1}H NMR (400 MHz, CD_3OD) δ 8.55 (s, 1H), 6.22 (d, *J* = 7.6 Hz, 1H), 4.38 (dd, *J* = 3.6, 7.6 Hz, 1H), 4.23 (t, *J* = 3.2 Hz, 1H), 3.90-3.81 (m, 2H), 3.59-3.56 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 160.4, 150.8, 146.4, 77.5, 73.8, 69.9, 63.4, 55.9, 49.3; MS (ESI) m/z 456.8775 $[M+Na]^+$; Found: C, 25.04; H, 2.54; N, 6.07. Calc. for $C_9H_{11}IN_2O_5Se$: C, 24.96; H, 2.56; N, 6.47%.

General procedure for the synthesis of **13a-13f.**

To a solution of compound **12a-12f** in pyridine was added 1,3-dichloro-1,1,3,3-tetraisopropyl disiloxane (1.5 equiv.) at 0 °C and the mixture was allowed to stir at room temperature for 3 h. The reaction mixture was concentrated, and the residue co-evaporated under reduced pressure three times with toluene. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 2:1) to give **13a-13f**.

(-)-1-[3,5-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-4-seleno-D-ribofuranosyl]uracil (**13a**).

White foam; Yield: 86%; $[\alpha]_D^{20}$ -1.31; (*c* 0.84, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 265 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (brs, 1H), 8.20 (d, *J* = 8.0 Hz, 1H), 6.06 (s, 1H), 5.72 (d, *J* = 8.0 Hz, 1H), 4.34 (dd, *J* = 3.2, 9.2 Hz, 1H), 4.21 (t, *J* = 1.2 Hz, 1H), 4.14 (dd, *J* = 3.2, 13.2 Hz, 1H),

4.02 (d, *J* = 1.6, 12.8 Hz, 1H), 3.88 (dt, *J* = 2.4, 9.6 Hz, 1H), 3.19 (d, *J* = 1.6 Hz, 1H), 1.14-0.97 (m, 28H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 150.7, 143.0, 102.4, 80.3, 74.3, 59.0, 57.7, 46.4, 17.8, 17.7, 17.55, 17.53, 17.35, 17.27, 17.22, 17.1, 13.6, 13.5, 13.3, 12.7; MS (ESI) m/z 573.1326 $[M+Na]^+$; Found: C, 45.89; H, 6.99; N, 5.45. Calc. for $C_{21}H_{38}N_2O_6SeSi_2$: C, 45.89; H, 6.97; N, 5.10%.

(+)-1-[3,5-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-4-seleno-D-ribofuranosyl]thymine (**13b**).

White foam; Yield: 69%; $[\alpha]_D^{20}$ +12.70 (*c* 7.78, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 271 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (brs, 1H), 7.71 (d, *J* = 1.2 Hz, 1H), 6.11 (d, *J* = 1.6 Hz, 1H), 4.28 (dd, *J* = 3.6, 9.2 Hz, 1H), 4.22-4.11 (m, 2H), 4.04-4.00 (m, 1H), 3.92-3.89 (m, 1H), 2.91 (brs, 1H), 1.90 (d, *J* =1.2 Hz, 3H), 1.15-0.99 (m, 28H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 150.6, 138.1, 111.4, 80.2, 74.8, 59.1, 56.9, 46.9, 17.7, 17.69, 17.6, 17.5, 17.4, 17.3, 17.2, 17.1, 13.6, 13.5, 13.1, 12.7, 12.6; MS (ESI) m/z 587.1504 $[M+Na]^+$; Found: C, 46.76; H, 7.32; N, 5.01. Calc. for $C_{22}H_{40}N_2O_6SeSi_2$: C, 46.88; H, 7.15; N, 4.97%.

(+)-5-Fluoro-1-[3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-seleno-D-ribofuranosyl]uracil (**13c**).

White foam; Yield: 60%; $[\alpha]_D^{20}$ +21.48 (*c* 2.91, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 272 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 6.4 Hz, 1H), 6.04 (s, 1H), 4.32 (dd, *J* = 3.2, 9.2 Hz, 1H), 4.22 (d, *J* = 3.2 Hz, 1H), 4.14 (dd, *J* = 3.2, 12.8 Hz, 1H), 4.02 (dd, *J* = 1.6, 12.8 Hz, 1H), 3.89 (m, 1H), 1.14-0.98 (m, 28H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9 (d, *J* = 27.3 Hz), 149.2, 140.0 (d, *J* = 237.9 Hz), 127.2 (d, *J* = 35.3 Hz), 80.3, 74.3, 58.8, 58.1, 46.8, 17.7, 17.6, 17.5, 17.4, 17.3, 17.2, 17.1, 13.6, 13.5, 13.3, 12.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -163.0 (d, *J* = 6.02 Hz); MS (ESI) m/z 569.1416 $[M+H]^+$; Found: C, 44.13; H, 6.34; N, 4.76. Calc. for $C_{21}H_{37}FN_2O_6SeSi_2$: C, 44.43; H, 6.57; N, 4.93%.

(-)-5-Chloro-1-[3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-seleno-D-ribofuranosyl]uracil (**13d**).

White foam; Yield: 78%; $[\alpha]_D^{20}$ -4.61 (*c* 6.77, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 281 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (brs, 1H), 8.34 (s, 1H), 6.05 (d, *J* = 1.6 Hz, 1H), 4.33 (dd, *J* = 3.6, 9.6 Hz, 1H), 4.23 (d, *J* = 2.4 Hz, 1H), 4.14 (dd, *J* = 3.2, 13.2 Hz, 1H), 4.02 (dd, *J* = 2.0, 13.2 Hz, 1H), 3.93 (dt, *J* = 3.2, 9.6 Hz, 1H), 3.35 (brs, 1H), 1.14-0.98 (m, 28H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 149.9, 139.5, 109.5, 80.1, 74.4, 58.7, 57.9, 47.1, 17.8, 17.7, 17.6, 17.5, 17.4, 17.3, 17.2, 17.1, 13.6, 13.5, 13.2, 12.7; Found: C, 43.58; H, 6.08; N, 4.43. Calc. for $C_{21}H_{37}ClN_2O_6SeSi_2$: C, 43.18; H, 6.38; N, 4.80%.

(-)-5-Bromo-1-[3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-seleno-D-ribofuranosyl]uracil (**13e**).

White foam; Yield: 76%; $[\alpha]_D^{20}$ -20.36 (*c* 4.70, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 283 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.7 (brs, 1H), 8.41 (s, 1H), 6.04 (s, 1H), 4.32 (dd, *J* = 3.4, 9.4 Hz, 1H), 4.23 (d, *J* = 2.4 Hz, 1H), 4.14 (dd, *J* = 3.0, 13.0 Hz, 1H), 4.02 (dd, *J* = 2.0, 13.2 Hz, 1H), 3.96-3.92 (m, 1H), 3.42 (brs, 1H), 1.15-0.99 (m, 28H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 150.2, 142.1, 97.3, 80.0, 74.5, 58.7, 57.9, 47.1, 17.9, 17.8, 17.7, 17.5, 17.4, 17.3, 17.2, 17.1, 13.6, 13.5, 13.3, 12.7; Found: C, 40.01; H, 5.65; N, 4.77. Calc. for $C_{21}H_{37}BrN_2O_6SeSi_2$: C, 40.13; H, 5.93; N, 4.46%.

(-)-5-Iodo-1-[3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-seleno-D-ribofuranosyl]uracil (**13f**).

White foam; Yield: 87%; $[\alpha]_D^{20}$ -46.9, (*c* 0.60, CH_2Cl_2); UV λ_{max} (CH_3OH) 292 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.37 (s, 1H), 6.06 (d, *J* = 1.6 Hz, 1H), 4.39 (dd, *J* = 3.6, 9.2 Hz, 1H), 4.21 (t, *J* = 1.6 Hz, 1H), 4.15-4.00 (m, 2H), 3.94-3.91 (m, 1H), 2.94 (d, *J* = 2.0 Hz, 1H), 1.17-1.01 (m, 28H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 150.2, 146.9, 80.2, 74.9, 68.8,

59.0, 57.1, 47.4, 18.03, 18.00, 17.7, 17.5, 17.4, 17.3, 17.2, 17.1, 13.6, 13.5, 13.3, 12.7; Found: C, 37.73; H, 5.12; N, 3.87. Calc. for $C_{21}H_{37}IN_2O_6SeSi_2$: C, 37.34; H, 5.52; N, 4.15%.

General procedure for the synthesis of **14a** and **14c-14f**.

To a solution of compound **13a, 13c-13f** in dichloromethane were added benzoyl chloride (1.05 equiv.) and tetrabutylammonium bromide (0.3 equiv.) at room temperature and the mixture was stirred at the same temperature for 15 h. The mixture was diluted with dichloromethane and the organic layer was washed with water, brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 3:1) to give **14a** and **14c-14f**.

(+)-N^3-Benzoyl-1-[3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-seleno-D-ribofuranosyl]uracil (**14a**).

White foam; Yield: 82%; $[\alpha]_D^{20}$ +22.64 (*c* 2.08, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 255 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 1.6 Hz, 2H), 7.66 (t, *J* = 1.2 Hz, 1H), 7.50 (t, *J* = 1.6 Hz, 2H), 6.06 (s, 1H), 5.83 (d, *J* = 8.4 Hz, 1H), 4.41 (d, *J* = 3.6 Hz, 1H), 4.24 (t, *J* = 2.0 Hz, 1H), 4.16-4.02 (m, 2H), 3.87 (d, *J* = 2.4 Hz, 1H), 2.68 (s, 1H), 0.96-1.15 (m, 28H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 162.1, 149.5, 142.5, 135.4, 131.5, 130.7, 129.4, 102.3, 80.4, 74.4, 59.1, 57.6, 46.6, 17.6, 17.5, 17.4, 17.3, 17.2, 17.1, 13.6, 13.5, 13.3, 12.7; MS (ESI) m/z 759.2037 $[M+H]^+$ Found: C, 51.23; H, 6.56; N, 4.33. Calc. for $C_{28}H_{42}N_2O_7SeSi_2$: C, 51.44; H, 6.48; N, 4.28%.

(+)-N^3-Benzoyl-5-fluoro-1-[3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-seleno-D-ribofuranosyl]uracil (**14c**).

White foam; Yield: 42%; $[\alpha]_D^{20}$ +47.17 (*c* 1.13, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 272 nm; ^{1}H NMR

(400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 6.4 Hz, 1H), 8.07-8.04 (m, 2H), 7.61-7.56 (m, 1H), 7.48-7.44 (m, 2H), 6.16 (t, *J* = 1.2 Hz, 1H), 5.70 (d, *J* = 1.6 Hz, 1H), 4.51 (dd, *J* = 3.6, 10.0 Hz, 1H), 4.18 (dd, *J* = 2.0, 3.2 Hz, 1H), 4.06 (d, *J* = 12.8 Hz, 1H), 3.97 (d, *J* = 1.6 Hz, 1H), 1.16-0.89 (m, 28H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 156.7 (d, *J* = 26.9 Hz), 148.7, 140.2 (d, *J* = 238.4 Hz), 133.6, 130.1, 129.7, 128.7, 126.6 (d, *J* = 35.0 Hz), 79.5, 73.4, 58.2, 55.8, 47.7, 17.7, 17.6, 17.5, 17.4, 17.2, 17.1, 17.0, 13.6, 13.4, 13.3, 12.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -162.7 (d, *J* = 6.02 Hz); MS (ESI) m/z 695.1492 $[M+Na]^+$ Found: C, 49.90; H, 6.55; N, 3.87. Calc. for $C_{28}H_{41}FN_2O_7SeSi_2$: C, 50.06; H, 6.15; N, 4.17%.

(+)-*N*^{3}-Benzoyl-5-chloro-1-[3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-seleno-D-ribofuranosyl]uracil (**14d**).

White foam; Yield: 45%; $[\alpha]_D^{20}$ +5.15 (*c* 5.24, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 283 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.90-7.88 (m, 2H), 7.69-7.65 (m, 1H), 7.52-7.48 (m, 2H), 6.05 (d, *J* = 1.6 Hz, 1H), 4.41 (dd, *J* = 3.6, 9.2 Hz, 1H), 4.25-4.23 (m, 1H), 4.13 (dd, *J* = 3.2, 13.2 Hz, 1H), 4.03 (dd, *J* = 2.4, 12.8 Hz, 1H), 3.89 (dt, *J* = 2.4, 9.2 Hz, 1H), 2.72 (d, *J* = 2.4 Hz, 1H), 1.15-0.99 (m, 28H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 157.9, 148.7, 139.1, 135.6, 131.1, 130.8, 129.5, 109.2, 80.2, 74.6, 58.8, 57.6, 47.2, 17.7, 17.6, 17.5, 17.4, 17.3, 17.2, 17.1, 13.6, 13.5, 13.2, 12.7; Found: C, 48.88; H, 6.40; N, 3.98. Calc. for $C_{28}H_{41}ClN_2O_7SeSi_2$: C, 48.87; H, 6.00; N, 4.07%.

(-)-*N*^{3}-Benzoyl-5-bromo-1-[3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-seleno-D-ribofuranosyl]uracil (**14e**).

White foam; Yield: 43%; $[\alpha]_D^{20}$ -6.65 (*c* 3.91, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 286 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.90-7.88 (m, 2H), 7.69-7.64 (m, 1H), 7.52-7.48 (m, 2H), 6.06 (d, *J* = 1.6 Hz, 1H), 4.42 (dd, *J* = 3.6, 8.8 Hz, 1H), 4.25-4.23 (m, 1H), 4.13 (dd, *J* = 3.2, 12.8 Hz, 1H), 4.03 (dd, *J* = 2.8, 13.2, 1H), 3.89 (dt, *J* = 2.8, 9.2 Hz, 1H), 2.67 (d, *J* = 2.4 Hz,

1H), 1.16-1.02 (m, 28H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 157.9, 148.9, 141.6, 135.6, 131.1, 130.7, 129.4, 96.9, 80.2, 74.7, 58.9, 57.4, 47.3, 17.8, 17.6, 17.5, 17.4, 17.3, 17.2, 17.1, 13.6, 13.5, 13.2, 12.7; Found: C, 45.99; H, 5.54; N, 3.56. Calc. for $C_{28}H_{41}BrN_2O_7SeSi_2$: C, 45.90; H, 5.64; N, 3.82%.

(-)-*N*^{3}-Benzoyl-5-iodo-1-[3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-seleno-D-ribofuranosyl]uracil (**14f**).

White foam; Yield: 41%; $[\alpha]_D^{20}$ -27.16 (*c* 0.67, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 288 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.90-7.88 (m, 2H), 7.68-7.64 (m, 1H), 7.52-7.48 (m, 2H), 6.07 (d, *J* = 2.0 Hz, 1H), 4.44 (dd, *J* = 9.2, 4.0 Hz, 1H), 4.24 (dd, *J* = 2.0, 3.6 Hz, 1H), 4.16-4.09 (m, 1H), 4.03 (dd, *J* = 2.8,12.8 Hz, 1H), 3.91 (dt, *J* = 2.8, 8.8 Hz, 1H), 1.16-1.04 (m, 28H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 158.9, 149.3, 146.5, 135.6, 131.1, 130.8, 129.5, 80.3, 74.9, 68.5, 59.1, 57.0, 47.5, 18.0, 17.7, 17.5, 17.5, 17.3, 17.2, 17.1, 13.7, 13.6, 13.3, 12.8; Found: C, 43.33; H, 5.34; N, 3.34. Calc. for $C_{28}H_{41}IN_2O_7SeSi_2$: C, 43.13; H, 5.30; N, 3.59%.

(+)-*N*^{3}-Benzoyl-1-[3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-seleno-D-ribofuranosyl]thymine (**14b**).

To a solution of compound **13b** (1.0 g, 1.8 mmol) in dichloromethane were added benzoyl chloride (0.23 mL, 1.6 mmol) and triethylamine (0.33 mL, 2.4 mmol) at 0 ^{o}C and the mixture was allowed to stir at room temperature for 15 h. The mixture was diluted with dichloromethane and the organic layer was washed with 0.1 *N* HCl, saturated aqueous $NaHCO_3$, water and brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 5:1) to give **14b** as a white foam (969 mg, 79%; $[\alpha]_D^{20}$ +0.78 (*c* 4.73, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 271 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.85 (m, 2H), 7.66-7.62 (m, 1H), 7.50-7.47 (m, 2H), 6.11 (d, *J* = 1.6 Hz, 1H),

4.48 (dd, *J* = 3.6, 8.8 Hz, 1H), 4.254-4.245 (m, 1H), 4.13 (dd, *J* = 3.6, 13.2 Hz, 1H), 4.03 (dd, *J* = 2.4, 12.8 Hz, 1H), 3.88 (dt, *J* = 2.8, 8.8 Hz, 1H), 2.66 (d, *J* = 2.4 Hz, 1H), 1.95 (d, *J* = 0.8 Hz, 3H), 1.15-1.01 (m, 28H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 162.8, 149.6, 137.7, 135.2, 131.7, 130.6, 129.3, 111.5, 80.2, 74.9, 59.3, 56.7, 47.0, 17.7, 17.6, 17.61, 17.5, 17.4, 17.3, 17.2, 17.1, 13.6, 13.5, 13.1, 12.8, 12.7; MS (ESI) m/z 691.1743 $[M+Na]^+$; Found: C, 51.98; H, 6.34; N, 3.99. Calc. for $C_{29}H_{44}N_2O_7SeSi_2$: C, 52.16; H, 6.64; N, 4.19%.

General procedure for the synthesis of **15a-15f**.

To a solution of compound **14a-14f** (1 equiv.) and triphenylphosphine (3 equiv.) in tetrahydrofuran were added diethyl azodicarboxylate (3 equiv.) and diphenylphosphoryl azide (3 equiv.) at 0 ^{o}C and the mixture was allowed to stir at room temperature for 4 h. After adding EtOH, the mixture was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 5:1) to give **15a-15f**.

(-)-*N*^{3}-Benzoyl-1-[2-azido-2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-seleno-D-arabinofuranosyl]uracil (**15a**).

White foam; Yield: 51%; $[\alpha]_D^{20}$ -36.85 (*c* 0.89, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 265 nm; IR (KBr) 2116 cm^{-1}(N_3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.0 Hz, 1H), 7.99-7.96 (m, 2H), 7.67-7.63 (m, 1H), 7.52-7.48 (m, 2H), 6.41 (d, *J* = 6.8 Hz, 1H), 5.82 (d, *J* = 8.4 Hz, 1H), 4.23 (dd, *J* = 3.2, 13.2 Hz, 1H), 4.14 (d, *J* = 5.2 Hz, 1H), 4.06 (dd, *J* = 6.4, 10.8 Hz, 1H), 3.95 (dd, *J* = 1.2, 13.2 Hz, 1H), 3.47-3.44 (m, 1H), 1.18-1.04 (m, 28H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 162.1, 150.4, 142.5, 135.3, 131.5, 130.7, 129.4, 102.2, 74.4, 70.8, 58.9, 49.8, 43.8, 17.7, 17.6, 17.5, 17.4, 17.20, 17.2, 17.0, 13.9, 13.5, 13.4, 12.8; MS (ESI) m/z 674.1871 $[M+Na]^+$; Found: C, 49.99; H, 6.21; N, 10.00. Calc. for $C_{28}H_{41}N_5O_6SeSi_2$: C, 49.54; H, 6.09; N, 10.32%.

(+)-N^3-Benzoyl-1-[2-azido-2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-seleno-D-arabinofuranosyl]thymine (**15b**).

White foam; Yield: 52%; $[\alpha]_D^{20}$ +10.50 (*c* 2.02, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 255 nm; IR (KBr) 2114 cm^{-1} (N_3); ^1H NMR (400 MHz, $CDCl_3$) δ 7.97-7.95 (m, 1H), 7.81 (d, *J* = 1.2 Hz, 1H), 7.66-7.62 (m, 1H), 7.52-7.47 (m, 2H), 6.48 (d, *J* = 7.6 Hz, 1H), 4.24-4.19 (m, 2H), 4.12 (d, *J* = 1.6 Hz, 1H), 4.03 (dd, *J* = 7.2, 10.4 Hz, 1H), 3.95 (dd, *J* = 2.0, 13.2 Hz, 1H), 3.48-3.45 (m, 1H), 1.96 (s, 3H), 1.30-1.03 (m, 28H); MS (ESI) m/z 651.1842 $[M-H]^-$; Found: C, 50.45; H, 6.21; N, 9.99. Calc. for $C_{29}H_{43}N_5O_6SeSi_2$: C, 50.27; H, 6.26; N, 10.11%.

(+)-N^3-Benzoyl-5-fluoro-1-[2-azido-2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-seleno-D-arabinofuranosyl]uracil (**15c**).

White foam; Yield: 46%; $[\alpha]_D^{20}$ +12.39 (*c* 2.26, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 256 nm; IR (KBr) 2117 cm^{-1} (N_3); ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 6.4 Hz, 1H), 7.98-7.96 (m, 2H), 7.70-7.66 (m, 1H), 7.53-7.49 (m, 2H), 6.39 (d, *J* = 6.8 Hz, 1H), 4.23 (dd, *J* = 3.2, 13.2 Hz, 1H), 4.14 (d, *J* = 9.6 Hz, 1H), 4.06 (dd, *J* = 6.8, 10.8 Hz, 1H), 3.95 (d, *J* = 13.2 Hz, 1H), 3.47-3.43 (m, 1H), 1.19-1.01 (m, 28H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 150.6, 135.6, 131.1, 130.8, 130.1, 129.5, 126.5, 125.8, 120.4, 120.3, 74.5, 70.7, 58.6, 50.1, 44.2, 17.7, 17.6, 17.5, 17.2, 17.1, 13.9, 13.5, 13.4, 12.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -157.6 (d, *J* = 4.89 Hz); MS (ESI) m/z 698.1743 $[M+H]^+$; Found: C, 48.43; H, 5.99; N, 10.08. Calc. for $C_{28}H_{40}FN_5O_6SeSi_2$: C, 48.27; H, 5.79; N, 10.05%.

(+)-N^3-Benzoyl-5-chloro-1-[2-azido-2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-seleno-D-arabinofuranosyl]uracil (**15d**).

White foam; Yield: 37%; $[\alpha]_D^{20}$ +9.19 (*c* 1.85, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 284 nm; IR (KBr) 2114 cm^{-1} (N_3); ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.97-7.94 (m, 2H), 7.69-7.65 (m, 1H), 7.53-7.49 (m, 2H), 6.43 (d, *J* = 7.2 Hz, 1H), 4.22 (dd, *J* = 3.2, 13.2 Hz, 1H), 4.16 (t, *J* =

10.4 Hz, 1H), 4.04 (dd, *J* = 7.2, 10.8 Hz, 1H), 3.95 (dd, *J* = 1.6, 13.2 Hz, 1H), 3.48-3.45 (m, 1H), 1.17-1.05 (m, 28H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 157.9, 149.6, 138.9, 135.6, 131.1, 130.8, 129.5, 109.2, 75.2, 70.6, 58.6, 49.6, 44.6, 17.9, 17.7, 17.6, 17.4, 17.2, 17.1, 17.07, 13.9, 13.5, 13.4, 12.8; Found: C, 47.17; H, 5.89; N, 9.98. Calc. for $C_{28}H_{40}ClN_5O_6SeSi_2$: C, 47.15; H, 5.65; N, 9.82%.

(-)-*N*^{3}-Benzoyl-5-bromo-1-[2-azido-2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-seleno-D-arabinofuranosyl]uracil (**15e**).

White foam; Yield: 35%: $[\alpha]_D^{20}$ -10.00 (*c* 0.30, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 285 nm; IR (KBr) 2115 cm^{-1} (N_3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.96-7.94 (m, 2H), 7.69-7.65 (m, 1H), 7.53-7.49 (m, 2H), 6.44 (d, *J* = 7.2 Hz, 1H), 4.22 (dd, *J* = 3.2, 13.2 Hz, 1H), 4.16 (t, *J* = 10.4 Hz, 1H), 4.03 (dd, *J* = 7.2, 10.4 Hz, 1H), 3.95 (dd, *J* = 1.6, 13.2 Hz, 1H), 3.49-3.45 (m, 1H), 1.25-1.05 (m, 28H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 157.9, 149.8, 141.5, 135.6, 131.1, 130.8, 129.5, 96.9, 75.5, 70.6, 58.8, 49.4, 44.8, 18.0, 17.8, 17.7, 17.6, 17.2, 17.1, 17.1, 13.9, 13.5, 13.4, 12.8; Found: C, 44.44; H, 5,56; N, 8.98. Calc. for $C_{28}H_{40}BrN_5O_6SeSi_2$: C, 44.39; H, 5.32; N, 9.24%.

(-)-*N*^{3}-Benzoyl-5-iodo-1-[2-azido-2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-seleno-D-arabinofuranosyl]uracil (**15f**).

White foam; Yield: 32%: $[\alpha]_D^{20}$ -31.74 (*c* 0.92, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 289 nm; IR (KBr) 2116 cm^{-1} (N_3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.95-7.93 (m, 2H), 7.68-7.64 (m, 1H), 7.52-7.48 (m, 2H), 6.43 (d, *J* = 7.2 Hz, 1H), 4.21 (dd, *J* = 2.8, 13.2 Hz, 1H), 4.18 (t, *J* = 10.0 Hz, 1H), 4.03 (dd, *J* = 7.2, 10.4 Hz, 1H), 3.96 (dd, *J* = 2.8, 13.2 Hz, 1H), 3.47 (dt, *J* = 2.8, 9.2 Hz, 1H), 1.16-1.02 (m, 28H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 158.8, 150.1, 146.5, 135.5, 131.1, 130.7, 129.5, 75.9, 70.6, 68.3, 59.1, 49.1, 44.9, 18.2, 17.9, 17.7, 17.6, 17.2, 17.2, 17.1, 13.9, 13.6, 13.4, 12.8; Found: C, 41.65; H, 5.41; N, 8.30. Calc. for $C_{28}H_{40}IN_5O_6SeSi_2$: C,

41.79; H, 5.01; N, 8.70%.

General procedure for the synthesis of **16a-16f**.

To a solution of compound **15a-15f** (1 equiv.) in tetrahydrofuran were added $3HF{\cdot}Et_3N$ (3 equiv.) and triethylamine (3 equiv.) at 0 ^oC. After being stirred at the same temperature for 30 minutes, the reaction mixture was allowed to warm to room temperature and stirred for additional 30 minutes. The reaction mixture was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (dichloromethane:ethyl acetate:methanol = 10:10:1) to give **16a-16f**.

(+)-N^3-Benzoyl-1-(2-azido-2-deoxy-4-seleno-D-arabinofuranosyl)uracil (**16a**).

White foam; Yield: 80%: $[\alpha]_D^{20}$ +33.58 (*c* 0.67, CH_3OH); UV (CH_2Cl_2) λ_{max} 255 nm; IR (KBr) 2116 cm^{-1} (N_3); ^1H NMR (400 MHz, CD_3OD) δ 8.50 (d, *J* = 8.4 Hz, 1H), 7.98-7.96 (m, 2H), 7.74-7.70. (m, 1H), 7.57-7.53 (m, 2H), 6.40 (d, *J* = 6.4 Hz, 1H), 5.90 (d, *J* = 8.4 Hz, 1H), 4.19 (dd, *J* = 6.8, 10.4 Hz, 1H), 4.08-4.01 (m, 2H), 3.93 (dd, *J* = 5.6, 11.6 Hz, 1H), 3.56-3.51 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 169.8, 164.1, 151.6, 145.8, 136.4, 132.8, 131.4, 130.5, 102.1, 76.7, 73.2, 62.5, 52.4, 47.6; MS (ESI) m/z 460.0140 $[M+Na]^+$; Found: C, 43.98; H, 3.87; N, 16.00. Calc. for $C_{16}H_{15}N_5O_5Se$: C, 44.05; H, 3.47; N, 16.05%.

(-)-N^3-Benzoyl-1-(2-azido-2-deoxy-4-seleno-D-arabinofuranosyl)thymine (**16b**).

White foam, Yield: 82%; $[\alpha]_D^{20}$ -11.49 (*c* 1.14, CH_3OH); UV (CH_2Cl_2) λ_{max} 255 nm; IR (KBr) 2113 cm^{-1} (N_3); ^1H NMR (400 MHz, CD_3OD) δ 8.47 (s, 1H), 7.97-7.95 (m, 2H), 7.75-7.70 (m, 1H), 7.58-7.53 (m, 2H), 6.37 (d, *J* = 6.4 Hz, 1H), 4.20 (dd, *J* = 6.4, 10.4 Hz, 1H), 4.12 (dd, *J* = 8.4, 10.0 Hz, 1H), 3.97 (d, *J* = 4.0 Hz, 2H), 3.54-3.50 (m, 1H), 1.95 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 170.0, 164.7, 151.6, 141.6, 136.4, 132.9, 131.5, 130.4, 111.0, 76.3, 73.4, 61.7,

52.4, 47.4, 12.5; MS (ESI) m/z 452.0470 $[M+H]^+$; Found: C, 45.43; H, 3.87; N, 15.56. Calc. for $C_{17}H_{17}N_5O_5Se$: C, 45.34; H, 3.81; N, 15.55%.

(+)-5-Benzoyl-5-fluoro-1-(2-azido-2-deoxy-4-seleno-D-arabinofuranosyl)uracil (**16c**).

White foam; Yield: 84%; $[\alpha]_D^{20}$ +8.85 (*c* 2.18, CH_3OH); UV (CH_2Cl_2) λ_{max} 254 nm; IR (KBr) 2116 cm^{-1} (N_3); ^1H NMR (400 MHz, CD_3OD) δ 8.87 (d, *J* = 7.2 Hz, 1H), 8.01-7.99 (m, 2H), 7.77-7.73 (m, 1H), 7.60-7.55 (m, 2H), 6.37 (d, *J* = 6.4 Hz, 1H), 4.21 (dd, *J* = 6.4, 10.4 Hz, 1H), 4.13-4.07 (m, 1H), 4.00-3.92 (m, 2H), 3.54-3.50 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 168.5, 157.8 (d, *J* = 28.2), 150.2, 140.5 (d, *J* = 233.6 Hz), 136.7, 132.5, 131.6, 130.5, 130.0 (d, *J* = 35.9 Hz), 76.2, 73.3, 61.5, 53.2, 47.5; MS (ESI) m/z 478.0037 $[M+Na]^+$; Found: C, 42.32; H, 3.51; N, 15.82. Calc. for $C_{16}H_{14}FN_5O_5Se$: C, 42.30; H, 3.11; N, 15.42%.

(-)-N^3-Benzoyl-5-chloro-1-(2-azido-2-deoxy-4-seleno-D-arabinofuranosyl)uracil (**16d**).

White foam; Yield: 78%; $[\alpha]_D^{20}$ -32.44 (*c* 0.41, CH_3OH); UV (CH_3OH) λ_{max} 282 nm; IR (KBr) 2110 cm^{-1}(N_3); ^1H NMR (400 MHz, CD_3OD) δ 9.03 (s, 1H), 8.01-8.98 (m, 2H), 7.77-7.73 (m, 1H), 7.60-7.56 (m, 2H), 6.37 (d, *J* = 6.4 Hz, 1H), 4.23 (dd, *J* = 6.4, 10.4 Hz, 1H), 4.08 (dd, *J* = 1.2, 8.8 Hz, 1H), 3.98 (dd, *J* = 4.0, 12.0 Hz, 1H), 3.92 (dd, *J* = 2.8, 11.6 Hz, 1H), 3.55-3.51 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 168.7, 159.9, 150.7, 142.9, 136.7, 132.5, 131.6, 130.5, 108.5, 76.0, 73.3, 61.1, 53.4, 47.5; Found: C, 40.42; H, 3.40; N, 14.80. Calc. for $C_{16}H_{14}ClN_5O_5Se$: C, 40.82; H, 3.00, N, 14.88%.

(-)-N^3-Benzoyl-5-bromo-1-(2-azido-2-deoxy-4-seleno-D-arabinofuranosyl)uracil (**16e**).

White foam; Yield: 80%; $[\alpha]_D^{20}$ -20.00 (*c* 0.18, CH_3OH); UV (CH_3OH) λ_{max} 285 nm; IR (KBr) 2113 cm^{-1} (N_3); ^1H NMR (400 MHz, CD_3OD) δ 9.12 (s, 1H), 8.00-7.97 (m, 2H), 7.76-7.72 (m, 1H), 7.59-7.55 (m, 2H), 6.36 (d, *J* = 6.4 Hz, 1H), 4.22 (dd, *J* = 6.4, 10.4 Hz, 1H), 4.09 (dd, *J* = 9.2, 10.4 Hz, 1H), 3.97 (dd, *J* = 3.6, 11.6 Hz, 1H), 3.91 (dd, *J* = 2.8, 11.6 Hz, 1H), 3.55-3.51 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 168.9, 159.9, 150.9, 145.4, 136.6, 132.5, 131.6, 130.5,

95.9, 75.9, 73.4, 60.9, 53.4, 47.4; Found: C, 37.43; H, 2.74; N, 13.19. Calc. for $C_{16}H_{14}BrN_5O_5Se$: C, 37.30; H, 2.74; N, 13.59%.

(-)-N^3-Benzoyl-5-iodo-1-(2-azido-2-deoxy-4-seleno-D-arabinofuranosyl)uracil (**16f**).

White foam; Yield: 73%: $[\alpha]_D^{20}$ -57.33 (*c* 0.15, CH_3OH); UV (CH_3OH) λ_{max} 289 nm; IR (KBr) 2114 cm^{-1} (N_3); ^1H NMR (400 MHz, CD_3OD) δ 9.15 (s, 1H), 7.99-7.96 (m, 2H), 7.76-7.72 (m, 1H), 7.59-7.55 (m, 2H), 6.34 (d, *J* = 6.4 Hz, 1H), 4.22 (dd, *J* = 10.4, 6.0 Hz, 1H), 4.08 (dd, *J* = 10.4, 8.8 Hz, 1H), 3.97 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.91 (dd, *J* = 11.6, 2.8 Hz, 1H), 3.55-3.51 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 169.7, 161.1, 151.3, 150.4, 136.6, 132.5, 131.5, 130.5, 75.9, 73.5, 66.7, 60.9, 53.2, 47.4; Found: C, 34.18; H, 2.50; N, 12.48. Calc. for $C_{16}H_{14}IN_5O_5Se$: C, 34.18; H, 2.51; N, 12.46%.

General procedure for the synthesis of 2'-azido-2'-deoxy-4'-selenoarabinofuranosyl pyrimidines **3a-3f**.

A solution of **16a-16f** in saturated methanolic ammonia was stirred in a glass bomb at room temperature for 15 h. Then all volatiles were evaporated under reduced pressure and the residue was purified by silica gel column chromatography (dichloromethane: methanol = 10:1) to give the corresponding deprotected compound as a solid. This was finally recrystallized from diethyl ether/methanol to give **3a-3f**.

(+)-1-(2-Azido-2-deoxy-4-seleno-D-arabinofuranosyl)uracil (**3a**).

White solid; Yield: 77%; mp 164-170 °C; $[\alpha]_D^{20}$ +35.16 (*c* 2.23, CH_3OH); UV (CH_2Cl_2) λ_{max} 264 nm; IR (KBr) 2119 cm^{-1} (N_3); ^1H NMR (400 MHz, CD_3OD) δ 8.28 (d, *J* = 8.0 Hz, 1H), 6.44 (d, *J* = 6.8 Hz, 1H), 5.72 (d, *J* = 8.4 Hz, 1H), 4.17 (dd, *J* = 6.8, 10.4 Hz, 1H), 4.07-4.00 (m, 2H), 3.90 (dd, *J* = 6.0, 11.6 Hz, 1H), 3.55-3.51 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 166.1,

152.8, 145.6, 102.3, 76.8, 73.1, 62.8, 51.7, 47.7; MS (ESI) m/z 334.0049 $[M+H]^+$; Found: C, 32.43; H, 3.12; N, 19.98. Calc. for $C_9H_{11}N_5O_4Se$: C, 32.54; H, 3.34; N, 21.08%.

(+)-1-(2-Azido-2-deoxy-4-seleno-D-arabinofuranosyl)thymine (**3b**).

White solid; Yield: 76%; mp 166-168 °C; $[\alpha]_D^{20}$ +9.90 (*c* 1.05, CH_3OH); UV (CH_2Cl_2) λ_{max} 269 nm; IR (KBr) 2113 cm^{-1} (N_3); ^1H NMR (400 MHz, CD_3OD) δ 8.22 (s, 1H), 6.40 (d, *J* = 6.4 Hz, 1H), 4.18-4.09 (m, 2H), 3.96-3.94 (m, 2H), 3.54-3.49 (m, 1H), 1.88 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 166.4, 153.0, 141.3, 111.1, 76.5, 73.3, 62.0, 51.6, 47.5, 12.5; MS (ESI) m/z 348.0206 $[M+H]^+$; Found: C, 34.89; H, 3.99; N, 19.98. Calc. for $C_{10}H_{13}N_5O_4Se$: C, 34.69; H, 3.78; N, 20.23%.

(+)-1-(2-Azido-2-deoxy-4-seleno-D-arabinofuranosyl)-5-fluorouracil (**3c**).

White solid; Yield: 74%; mp 189-191 °C; $[\alpha]_D^{20}$ +49.87 (*c* 0.78, CH_3OH); UV (CH_2Cl_2) λ_{max} 271 nm; IR (KBr) 2119 cm^{-1} (N_3); ^1H NMR (400 MHz, CD_3OD) δ 8.61 (d, *J* = 7.2 Hz, 1H), 6.39 (dd, *J* = 1.6, 6.4 Hz, 1H), 4.18 (dd, *J* = 6.4, 10.4 Hz, 1H), 4.08 (dd, *J* = 8.8, 10.0 Hz, 1H), 3.94 (d, *J* = 4.0 Hz, 2H), 3.53-3.48 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 151.6, 140.9 (d, *J* = 231.6 Hz), 129.4 (d, *J* = 34.9 Hz), 109.1 (d, *J* = 3.2 Hz), 76.3, 73.2, 61.8, 52.4, 47.6; ^{19}F NMR (376 MHz, CD_3OD) δ -168.4 (d, *J* = 1.51 Hz); MS (ESI) m/z 373.9776 $[M+Na]^+$; Found: C, 30.47; H, 3.12; N, 20.40. Calc. for $C_9H_{10}FN_5O_4Se$: C, 30.87; H, 2.88; N, 20.00%.

(-)-1-(2-Azido-2-deoxy-4-seleno-D-arabinofuranosyl)-5-chlorouracil (**3d**).

White solid; Yield: 80%; mp 115-117 °C; $[\alpha]_D^{20}$ -24.00 (*c* 0.10, CH_3OH); UV (CH_3OH) λ_{max} 278 nm; IR (KBr) 2113 cm^{-1} (N_3); ^1H NMR (400 MHz, CD_3OD) δ 8.76 (s, 1H), 6.39 (d, *J* = 6.4 Hz, 1H), 4.19 (dd, *J* = 6.4, 10.4 Hz, 1H), 4.07 (dd, *J* = 8.4, 10.0 Hz, 1H), 3.97-3.89 (m, 2H), 3.54-3.50 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 161.5, 152.0, 142.5, 108.8, 76.2, 73.3, 61.4, 52.6, 47.6; MS (ESI) m/z 389.9483 $[M+Na]^+$; Found: C, 29.56; H, 2.77; N, 19.11. Calc. for $C_9H_{10}ClN_5O_4Se$: C, 29.48; H, 2.75; N, 19.10%.

(-)-1-(2-Azido-2-deoxy-4-seleno-D-arabinofuranosyl)-5-bromouracil (**3e**).

White solid; Yield: 82%; mp 108-113 °C; $[\alpha]_D^{20}$ -45.70 (*c* 0.42, CH_3OH); UV (CH_3OH) λ_{max} 282 nm; IR (KBr) 2113 cm^{-1} (N_3); ^1H NMR (400 MHz, CD_3OD) δ 8.86 (s, 1H), 6.38 (d, *J* = 6.4 Hz, 1H), 4.18 (dd, *J* = 6.4, 10.0 Hz, 1H), 4.07 (dd, *J* = 8.4, 10.0 Hz, 1H), 3.95-3.89 (m, 2H), 3.54-3.50 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 161.6, 152.2, 145.1, 96.4, 76.1, 73.3, 61.3, 52.6, 47.6; MS (ESI) m/z 449.8709 $[M+K]^+$; Found: C, 26.34; H, 2.45; N, 16.89. Calc. for $C_9H_{10}BrN_5O_4Se$: C, 26.30; H, 2.45; N, 17.04%.

(-)-1-(2-Azido-2-deoxy-4-seleno-D-arabinofuranosyl)-5-iodouracil (**3f**).

White solid, 78%: mp 147-153 °C; $[\alpha]_D^{20}$ -84.88 (*c* 0.25, CH_3OH); UV (CH_3OH) λ_{max} 291 nm; IR (KBr) 2113 cm^{-1} (N_3); ^1H NMR (400 MHz, CD_3OD) δ 8.90 (s, 1H), 6.36 (d, *J* = 6.4 Hz, 1H), 4.18 (dd, *J* = 6.4, 10.4 Hz, 1H), 4.05 (dd, *J* = 8.8, 10.4 Hz, 1H), 3.92 (d, *J* = 3.6 Hz, 2H), 3.52 (dt, *J* = 3.6, 8.4 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 162.8, 152.7, 150.1, 76.1, 73.4, 67.7, 61.3, 52.4, 47.6; MS (ESI) m/z 481.8835 $[M+Na]^+$; Found: C, 23.98; H, 2.21; N, 15.21. Calc. for $C_9H_{10}IN_5O_4Se$: C, 23.60; H, 2.20; N, 15.29%.

General procedure for the synthesis of *O*2,2'-anhydro nucleosides **17g-17l**.

To a solution of compound **13a-f** (1 equiv.) and 4-dimethylaminopyridine (0.1 equiv.) in dichloromethane were added triethylamine (4 equiv.) and methansufonyl chloride (2 equiv.) at 0 °C and the reaction mixture was stirred at same temperature for 30 min. The reaction was quenched with saturated $NaHCO_3$ and extracted with dichloromethane. The organic layer was washed with saturated $NaHCO_3$ solution, brine, dried over $MgSO_4$, filtered and evaporated. under reduced pressure. The residue was immediately used for next step without further purification. To a solution of the residue in acetone was added 1,8-diazabicyclo[5.4.0]undec-7-ene (2 equiv.) at room temperature and the mixture was allowed to stir at room temperature for

45 min. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash silica gel column chromatography (dichloromethane:methanol = 30:1) to give **17g-17l**.

(-)-2,2'-Anhydro-1-[3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-seleno-D-arabinofuranosyl]uracil (**17g**).

Pale yellow foam; Yield: 77%; $[\alpha]_D^{20}$ -120.57; (*c* 3.52, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 256 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 7.6 Hz, 1H), 6.07 (d, *J* = 7.6 Hz, 1H), 5.84 (d, *J* = 8.0 Hz, 1H), 5.20 (t, *J* = 8.0 Hz, 1H), 4.45 (dd, *J* = 8.0, 10.4 Hz, 1H), 4.13 (dd, *J* = 2.4, 13.2 Hz, 1H), 3.87 (dd, *J* = 1.6, 13.2 Hz, 1H), 3.71-3.68 (m, 1H), 1.13-0.92 (m, 28H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 158.7, 135.0, 110.8, 87.5, 78.0, 57.4, 51.7, 46.2, 17.4, 17.4, 17.3, 17.2, 17.2, 17.04, 17.02, 14.0, 13.5, 12.7; MS (ESI) m/z 533.1302 $[M+H]^+$;.Found: C, 47.41; H, 6.43; N, 5.07. Calc. for $C_{21}H_{36}N_2O_5SeSi_2$: C, 47.44; H, 6.83; N, 5.27%.

(-)-2,2'-Anhydro-1-[3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-seleno-D-arabinofuranosyl]thymine (**17h**).

Pale yellow foam; Yield: 85%; $[\alpha]_D^{20}$ -155.86 (*c* 0.29, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 260 nm; ^{1}H NMR (400 MHz, CD_3OD) δ 7.03 (d, *J* = 1.2 Hz, 1H), 5.94 (d, *J* = 7.6 Hz, 1H), 5.16 (t, *J* = 8.0 Hz, 1H), 4.39 (q, *J* = 7.8, 10.6 Hz, 1H), 4.07 (dd, *J* = 2.6, 12.6 Hz, 1H), 3.82 (dd, *J* = 1.6, 13.2 Hz, 1H), 3.65 (d, *J* = 10.0 Hz, 1H), 1.87 (d, *J* = 1.2 Hz, 3H), 1.17-0.91(m, 28H); ^{13}C NMR ($CDCl_3$) δ 172.7, 158.5, 131.3, 119.3, 93.5, 78.2, 57.5, 52.2, 46.0, 17.3, 17.2, 17.1, 16.99, 16.96, 14.2, 13.8, 13.4, 12.61, 12.58; MS (ESI) m/z 547.1580 $[M+H]^+$;. Found: C, 48.43; H, 7.42; N, 5.03. Calc. for $C_{22}H_{38}N_2O_5SeSi_2$: C, 48.42; H, 7.02; N, 5.13%.

(-)-2,2'-Anhydro-5-fluoro-1-[3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-seleno-D-arabinofuranosyl]uracil (**17i**).

Pale yellow foam; Yield: 65%; $[\alpha]_D^{20}$ -147.76 (*c* 8.33, CH_2Cl_2) UV (CH_2Cl_2) λ_{max} 235 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 3.6 Hz, 1H), 6.02 (d, *J* = 8.0 Hz, 1H), 5.25 (t, *J* = 8.0 Hz, 1H), 4.45 (dd, *J* = 8.4, 10.0 Hz, 1H), 4.11 (d, *J* = 13.0 Hz, 1H), 3.85 (d, *J* = 12.8 Hz, 1H), 3.69 (d, *J* = 10.4 Hz, 1H), 1.10-0.92 (m, 28H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4 (d, *J* = 16.8 Hz), 156.2, 147.5 (d, *J* = 254.6 Hz), 120.3 (d, *J* = 36.5 Hz), 88.2, 77.8, 57.1, 52.3, 45.7, 17.1, 16.8, 13.7, 13.2, 12.4; MS (ESI) m/z 589.0881 $[M+K]^+$;.Found: C, 45.89; H, 6.03; N, 4.98. Calc. for $C_{21}H_{35}FN_2O_5SeSi_2$: C, 45.89; H, 6.42; N, 5.10%;

(-)-2,2'-Anhydro-5-chloro-1-[3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-seleno-D-arabinofuranosyl]uracil (**17j**).

Pale yellow foam; Yield: 64%; $[\alpha]_D^{20}$ -200.68 (*c* 2.80, CH_2Cl_2); UV λ_{max} (CH_2Cl_2) 271 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 5.95 (d, *J* = 8.0 Hz, 1H), 5.26 (t, *J* = 8.0 Hz, 1H), 4.45 (q, *J* = 8.0, 10.4 Hz, 1H), 4.12 (dd, *J* = 2.8, 13.2 Hz, 1H), 3.87 (dd, *J* = 1.6, 13.2 Hz, 1H), 3.72 (d, *J* = 10.4 Hz, 1H), 1.12-0.91 (m, 28H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 157.8, 132.4, 118.9, 88.3, 78.1, 57.4, 52.2, 46.3, 17.4, 17.2, 17.1, 17.0, 16.9, 13.9, 13.5, 12.6; Found: C, 44.56; H, 6.32; N, 4.88. Calc. for $C_{21}H_{35}ClN_2O_5SeSi_2$: C, 44.56; H, 6.23; N 4.95%.

(-)-2,2'-Anhydro-5-bromo-1-[3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-seleno-D-arabinofuranosyl]uracil (**17k**).

Pale yellow foam; Yield: 72%; $[\alpha]_D^{20}$ -180.28 (*c* 3.98, CH_2Cl_2); UV λ_{max} (CH_2Cl_2) 274 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 5.97 (d, *J* = 8.0 Hz, 1H), 5.26 (q, *J* = 7.2, 14.4 Hz, 1H), 4.45 (q, *J* =8.0, 10.4 Hz, 1H), 4.12 (dd, *J* = 2.8, 13.2 Hz, 1H), 3.86 (dd, *J* = 1.6, 13.2 Hz, 1H), 3.73-3.69 (m, 1H), 1.11-0.91 (m, 28H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 158.2, 135.0, 108.3, 88.3, 78.1, 57.4, 52.1, 46.3, 17.4, 17.2, 17.1, 17.03, 17.0, 14.0, 13.5, 12.7; Found: C, 41.21; H, 5.88; N, 4.19. Calc. for $C_{21}H_{35}BrN_2O_5SeSi_2$: C, 41.31; H, 5.78; N 4.59%.

(-)-2,2'-Anhydro-5-iodo-1-[3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-seleno-D-

arabinofuranosyl]uracil (**17l**).

Yellowish foam; Yield: 80%; $[\alpha]_D^{20}$ -237.33 (*c* 1.20, CH_2Cl_2); UV λ_{max} (CH_2Cl_2) 281 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 5.88 (d, *J* = 12.0 Hz, 1H), 5.23 (t, *J* = 7.8 Hz, 1H), 4.46 (q, *J* = 8.0, 10.4 Hz, 1H), 4.13 (dd, *J* = 2.8, 13.2 Hz, 1H), 3.93 (dd, *J* = 1.6, 13.2 Hz, 1H), 3.74-3.70 (m, 1H), 1.12-0.92 (m, 28H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 158.9, 140.0, 88.2, 82.9, 78.0, 57.4, 51.8, 46.4, 17.4, 17.3, 17.1, 17.04, 17.01, 14.0, 13.5, 12.7; Found: C, 38.67; H, 5.77; N, 4.06. Calc. for $C_{21}H_{35}IN_2O_5SeSi_2$: C, 38.36; H, 5.37; N 4.26%.

General procedure for the synthesis of 2,2'-anhydro nucleosides **18g-18l.**

To a solution of **17g-17l** (1 equiv.) in tetrahydrofuran were added 3HF·Et_3N (3 equiv.) and triethylamine (3 equiv.) at 0 °C. After being stirred at the same temperature for 30 min, the reaction mixture was allowed to warm to room temperature and stirred for additional 1 h. The reaction mixture was concentrated and the residue was purified by silica gel column chromatography (dichloromethane:methanol = 7:1) to give **18g-18l**.

(-)-2,2'-Anhydro-1-(4-seleno-D-arabinofuranosyl)uracil (**18g**).

White solid; Yield: 69%: mp 262-265 °C; $[\alpha]_D^{20}$ -154.08 (*c* 1.30, CH_3OH+H_2O); UV (MeOH) λ_{max} 259 nm; ^{1}H NMR (400 MHz, CD_3OD) δ 7.74 (d, *J* = 0.4 Hz, 1H), 6.35 (d, *J* = 7.2 Hz, 1H), 6.09 (d, *J* = 7.6 Hz, 1H), 5.44 (dd, *J* = 2.4, 7.2 Hz, 1H), 4.86 (t, *J* = 2.6 Hz, 1H), 3.88-3.84 (m, 1H), 3.70-3.59 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 210.0, 139.2, 110.3, 94.2, 81.1, 64.9, 62.1, 56.2, 30.8; MS (ESI) m/z 290.9888 $[M+H]^+$;.Found: C, 37.34; H, 3.76; N, 9.99. Calc. for $C_9H_{10}N_2O_4Se$: C, 37.38; H, 3.49; N 9.69%.

(-)-2,2'-Anhydro-1-(4-seleno-D-arabinofuranosyl)thymine (**18h**).

White solid; Yield: 76%; mp 125-131 °C; $[\alpha]_D^{20}$ -219.68 (*c* 0.16, CH_3OH); UV (CH_3OH) λ_{max}

262 nm; ^{1}H NMR (400 MHz, CD_3OD) δ 7.66 (d, *J* = 1.2 Hz, 1H), 6.38 (d, *J* = 7.2 Hz, 1H), 5.47-5.44 (m, 1H), 4.85-4.84 (m, 1H), 3.88-3.83 (m, 1H), 3.70-3.57 (m, 2H), 1.94 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 174.8, 159.9, 134.9, 119.9, 94.0, 81.0, 64.9, 62.3, 56.2, 14.0; MS (ESI) m/z 305.0045 $[M+H]^+$;.Found: C, 39.65; H, 4.23; N, 9.43. Calc. for $C_{10}H_{12}N_2O_4Se$: C, 39.62; H, 3.99; N 9.24%.

(-)-2,2'-Anhydro-5-fluoro-1-(4-seleno-D-arabinofuranosyl)uracil (**18i**).

White solid; Yield: 79%; mp 164-170 °C; $[\alpha]_D^{20}$ -152.22 (*c* 0.18, MeOH); UV (MeOH) λ_{max} 262 nm; ^{1}H NMR (400 MHz, CD_3OD) δ 7.96 (d, *J* = 4.0 Hz, 1H), 6.36 (d, *J* = 8.0 Hz, 1H), 5.49 (dd, *J* = 2.4, 7.6 Hz, 1H), 4.86 (t, *J* = 2.4 Hz, 1H), 3.88-3.84 (m, 1H), 3.70-3.61 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 157.8, 148.5, 146.0, 123.6 (d, *J* = 37.2 Hz), 94.9, 81.5, 64.7, 62.9, 56.3; MS (ESI) m/z 308.9793 $[M+H]^+$; Found: C, 35.08; H, 2.87; N, 8.98. Calc. for $C_9H_9FN_2O_4Se$: C, 35.19; H, 2.95; N 9.12%.

(-)-2,2'-Anhydro-5-chloro-1-(4-seleno-D-arabinofuranosyl)uracil (**18j**).

White solid; Yield: 85%; mp 206-211 °C (decomposed); $[\alpha]_D^{20}$ -228.59 (*c* 1.56, CH_3OH); UV λ_{max} (CH_3OH) 272 nm; ^{1}H NMR (400 MHz, CD_3OD) δ 8.19 (s, 1H), 6.40 (d, *J* = 6.8 Hz, 1H), 5.51-5.49 (m, 1H), 4.85-4.84 (m, 1H), 3.89-3.84 (m, 1H), 3.71-3.61 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 169.3, 159.8, 136.7, 118.4, 95.1, 81.8, 64.9, 62.9, 56.6; Found: C, 33.03; H, 2.76; N, 9.04. Calc. for $C_9H_9ClN_2O_4Se$: C, 33.41; H, 2.80; N 8.66%.

(-)-2,2'-Anhydro-5-bromo-1-(4-seleno-D-arabinofuranosyl)uracil (**18k**).

White solid; Yield: 86%; mp 218-223 °C; $[\alpha]_D^{20}$ -235.47 (*c* 0.64, CH_3OH); UV λ_{max} (CH_3OH) 275 nm; ^{1}H NMR (400 MHz, CD_3OD) δ 8.29 (s, 1H), 6.38 (d, *J* = 7.6 Hz, 1H), 5.50-5.48 (m, 1H), 4.85-4.84 (m, 1H), 3.88-3.84 (m, 1H), 3.71-3.61 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 169.5, 160.3, 139.4, 107.5, 95.1, 81.7, 65.0, 62.7, 56.6; Found: C, 29.65; H, 2.76; N, 7.77. Calc. for $C_9H_9BrN_2O_4Se$: C, 29.37; H, 2.46; N 7.61%.

(-)-2,2'-Anhydro-5-iodo-1-(4-seleno-D-arabinofuranosyl)uracil (**18l**).

White solid; Yield: 89%; mp 101-106 °C; $[\alpha]_D^{20}$ -246.97 (*c* 1.85, CH_3OH); UV λ_{max} (CH_3OH) 282 nm; ^1H NMR (400 MHz, CD_3OD) δ 8.35 (s, 1H), 6.38 (dd, *J* = 0.6, 7.2 Hz, 1H), 5.49-5.46 (m, 1H), 4.85-4.84 (m, 1H), 3.87-3.83 (m, 1H), 3.70-3.60 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 170.9, 161.0, 144.5, 95.0, 81.6, 81.1, 65.0, 62.4, 56.6; Found: C, 26.05; H, 2.09; N, 6.34. Calc. for $C_9H_9IN_2O_4Se$: C, 26.04; H, 2.19; N 6.75%.

General procedure for the synthesis of **19g-19l.**

To a solution of compound **18g-18l** (1 equiv.) in pyridine were added trityl chloride (1.5 equiv.) and 4-dimethylaminopyridine (0.1 equiv.) at room temperature and the mixture was heated to stir at 55 °C for 15 h. The reaction mixture was concentrated. The residue was diluted with ethyl acetate and the organic layer was washed with water, brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by flash silica gel column chromatography (dichloromethane:methanol = 30:1) to give **19g-19l**.

(-)-2,2'-Anhydro-1-(5-*O*-trityl-4-seleno-D-arabinofuranosyl)uracil (**19g**).

White foam; Yield: 69%; $[\alpha]_D^{20}$ -4.93 (*c* 0.32, CH_3OH); UV (CH_3OH) λ_{max} 266 nm; ^1H NMR (CD_3OD) δ 7.80 (d, *J* = 8.4 Hz, 1H), 7.48-7.25 (m, 15H), 6.21 (d, *J* = 7.2 Hz, 1H), 5.61 (d, *J* = 8.4 Hz, 1H), 4.22 (t, *J* = 3.6 Hz, 1H), 4.14 (dd, *J* = 3.6, 6.8 Hz, 1H), 3.67-3.62 (m, 1H), 3.55 (dd, *J* = 6.4, 10.0 Hz, 1H), 3.47 (dd, *J* = 6.4, 10.0 Hz, 1H); ^{13}C NMR (CD_3OD) δ 166.0, 152.8, 145.2, 143.9, 130.1, 129.1, 128.5, 103.3, 88.8, 80.3, 76.5, 67.0, 58.2, 47.2; Found: C, 63.47; H, 4.78; N 5.00,. Calc. for $C_{28}H_{24}N_2O_4Se$: C, 63.28; H, 4.55; N, 5.27%.

(-)-2,2'-Anhydro-1-(5-*O*-trityl-4-seleno-D-arabinofuranosyl)thymine (**19h**).

White foam; Yield: 77%; $[\alpha]_D^{20}$ -58.42 (*c* 0.38, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 233 nm; ^1H NMR

($CDCl_3$) δ 7.27-7.11 (m, 15H), 7.07 (d, *J* = 1.2 Hz, 1H), 5.96 (d, *J* = 7.2 Hz, 1H), 5.15 (dd, *J* = 3.8, 7.4 Hz, 1H), 4.49 (t, *J* = 4.4 Hz, 1H), 3.77-3.87 (m, 1H), 3.41 (q, *J* = 6.4, 9.6 Hz, 1H), 3.03 (t, *J* = 9.6 Hz, 1H), 1.84 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 158.3, 143.4, 131.9, 128.5, 127.9, 127.3, 119.7, 91.6, 87.3, 79.9, 77.4, 65.5, 58.2, 51.0, 13.9; MS (ESI) m/z 569.0967 $[M+Na]^+$; Found: C, 63.90; H, 4.40; N 4.98,. Calc. for $C_{29}H_{26}N_2O_4Se$: C, 63.85; H, 4.80; N, 5.14%.

(-)-2,2'-Anhydro-5-fluoro-1-(5-*O*-trityl-4-seleno-D-arabinofuranosyl)uracil (**19i**).

White foam; Yield: 81%; $[\alpha]_D^{20}$ -42.91 (*c* 1.51, CH_2Cl_2 + CH_3OH); UV (CH_2Cl_2 + CH_3OH) λ_{max} 261 nm; ^{1}H NMR ($CDCl_3$) δ 7.35- 7.17 (m, 15H), 6.10 (d, *J* = 7.2 Hz, 1H), 5.41 (dd, *J* = 3.2, 7.2 Hz, 1H), 5.23 (d, *J* = 4.8 Hz, 1H), 4.61 (d, *J* = 3.6 Hz, 1H), 4.01-3.96 (m, 1H), 3.49 (q, *J* = 5.8, 9.2 Hz, 1H), 3.07 (t, *J* = 9.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 156.1, 143.5, 128.7, 128.1, 127.9, 127.4, 121.8, 121.4, 93.0, 87.3, 80.1, 65.3, 60.0, 51.9; MS (ESI) m/z 551.0901 $[M+H]^+$; Found: C, 61.23; H, 4.43; N, 5.09. Calc. for $C_{28}H_{23}FN_2O_4Se$: C, 61.21; H, 4.22; N, 5.10%.

(-)-2,2'-Anhydro-5-chloro-1-(5-*O*-trityl-4-seleno-D-arabinofuranosyl)uracil (**19j**).

White foam; Yield: 74%; $[\alpha]_D^{20}$ -49.49 (*c* 1.95, CH_2Cl_2 + CH_3OH); UV (CH_3OH) λ_{max} 271 nm; ^{1}H NMR (CD_3OD) δ 8.11 (s, 1H), 7.39-7.22 (m, 15H), 6.34 (d, *J* = 7.6 Hz, 1H), 5.45-5.42 (m, 1H), 4.79 (t, *J* = 2.6 Hz, 1H), 4.00-3.96 (m, 1H), 3.38-3.36 (m, 1H), 3.10 (t, *J* = 9.6 Hz, 1H); ^{13}C NMR (CD_3OD) δ 168.7, 158.9, 144.6, 135.9, 129.5, 128.7, 128.2, 118.7, 94.2, 88.2, 80.9, 66.6, 62.1, 53.8; Found: C, 59.02; H, 3.98; N, 4.89. Calc. for $C_{28}H_{23}ClN_2O_4Se$: C, 59.43; H, 4.10; N, 4.95%.

(-)-2,2'-Anhydro-5-bromo-1-(5-*O*-trityl-4-seleno-D-arabinofuranosyl)uracil (**19k**).

White foam; Yield: 83%; $[\alpha]_D^{20}$ -127.49 (*c* 0.86, CH_2Cl_2 + CH_3OH); UV (CH_3OH) λ_{max} 275 nm; ^{1}H NMR (CD_3OD) δ 8.22 (s, 1H), 7.39-7.20 (m, 15H), 6.34 (d, *J* = 7.2 Hz, 1H), 5.44-5.42 (m, 1H), 4.79 (t, *J* = 2.4 Hz, 1H), 4.00-3.95 (m, 1H), 3.38-3.33 (m, 1H), 3.11 (t, *J* = 9.6 Hz, 1H);

^{13}C NMR (CD_3OD) δ 168.2, 158.8, 144.1, 137.6, 129.1, 128.5, 127.8, 108.0, 93.6, 87.8, 80.5, 66.1, 61.1, 53.3; Found: C, 55.43; H, 4.12; N, 4.13. Calc. for $C_{28}H_{23}BrN_2O_4Se$: C, 55.10; H, 3.80; N, 4.59%.

(-)-2,2'-Anhydro-5-iodo-1-(5-*O*-trityl-4-seleno-D-arabinofuranosyl)uracil (**19l**).

White foam; Yield: 69%; $[\alpha]_D^{20}$ -171.03 (*c* 0.97, CH_2Cl_2 + CH_3OH); UV (CH_3OH) λ_{max} 282 nm; ^{1}H NMR (CD_3OD) δ 8.29 (s, 1H), 7.39-7.20 (m, 15H), 6.33 (d, *J* = 7.2 Hz, 1H), 5.42-5.40 (m, 1H), 4.78 (t, *J* = 2.6 Hz, 1H), 3.99-3.95 (m, 1H), 3.37-3.33 (m, 1H), 3.11 (t, *J* = 9.6 Hz, 1H); ^{13}C NMR (CD_3OD) δ 169.2, 159.3, 143.9, 142.3, 129.0, 128.3, 127.7, 93.3, 87.7, 82.1, 80.2, 65.9, 60.4, 53.0; Found: C, 51.08; H, 3.93; N, 3.98. Calc. for $C_{28}H_{23}IN_2O_4Se$: C, 51.16; H, 3.53; N, 4.26%.

General procedure for the synthesis of **20g-20l.**

To a solution of **19g-19l** (1 equiv.) in dichloromethane were added 3,4-dihydro-2*H*-pyran (50 equiv.) and pyridinium p-toluenesufonate (1 equiv.) at 0 °C, and the mixture was allowed to stir at room temperature for 20 h. The mixture was quenched with saturated $NaHCO_3$. The mixture was diluted with dichloromethane and the organic layer was washed with saturated $NaHCO_3$ solution, brine, dried over $MgSO_4$, filtered and evaporated. under reduced pressure. The residue was purified by flash silica gel column chromatography (dichloromethane:methanol= 30:1) to give **20g-20l**.

2,2'-Anhydro-1-(3-*O*-tetrahydropyranyl-5-*O*-trityl-4-seleno-D-arabinofuranosyl)uracil (**20g**).

White foam as an inseparable diastereomeric mixture; Yield: 88%; UV (CH_3OH) λ_{max} 259 nm; ^{1}H NMR (CD_3OD) (**major**) δ 7.72 (d, *J* = 7.6 Hz, 1H), 7.40-7.20 (m, 15H), 6.36 (d, *J* = 7.6 Hz, 1H), 6.04 (d, *J* = 7.6 Hz, 1H), 5.58 (dd, *J* = 1.6, 7.6 Hz, 1H), 5.08 (t, *J* = 2.4 Hz, 1H), 4.92 (t, *J*

= 3.6 Hz, 1H), 4.15 (td, *J* = 2.4, 8.0 Hz, 1H), 3.94-7-3.91 (m, 1H), 3.58-3.54 (m, 1H), 3.23-3.19 (m, 2H), 1.84-1.44 (m, 6H); (**minor**) δ 7.73 (d, *J* = 7.6 Hz, 1H), 7.40-7.20 (m, 15 H), 6.40 (d, *J* = 7.6 Hz, 1H), 6.05 (d, *J* = 7.6 Hz, 1H), 5.68 (dd, *J* = 1.6, 7.6 Hz, 1H), 5.06 (t, *J* = 2.0 Hz, 1H), 4.82 (t, *J* = 2.8 Hz, 1H), 3.96 (td, *J* = 2.0, 8.0 Hz, 1H), 3.90-3.87 (m, 1H), 3.61-3.59 (m, 1H), 3.23-3.19 (m, 2H), 1.84-1.44 (m, 6H).

2,2'-Anhydro-1-(3-*O*-tetrahydropyranyl-5-*O*-trityl-4-seleno-D-arabinofuranosyl)thymine (**20h**).

White foam as an inseparable diastereomeric mixture; Yield: 96%; UV (CH_2Cl_2) λ_{max} 254 nm; ^{1}H NMR ($CDCl_3$) (**major**) δ 7.30-7.21 (m, 15H), 6.96 (d, *J* = 1.2 Hz, 1H), 6.04 (d, *J* = 7.2 Hz, 1H), 5.34-5.32 (m, 1H), 4.95 (t, *J* = 2.8 Hz, 1H), 4.81 (t, *J* = 2.4 Hz, 1H), 4.15-4.10 (m, 1H), 3.82-3.75 (m, 1H), 3.53-3.47 (m, 1H), 3.42-3.36 (m, 1H), 3.19 (q, *J* = 8.4, 10.0 Hz, 1H), 1.93 (d, *J* = 1.2 Hz, 3H), 1.60-1.52 (m, 6H); (**minor**) δ 7.39-7.36 (m, 15 H), 6.98 (d, *J* = 1.6 Hz, 1H), 6.09 (d, *J* = 7.2 Hz, 1H), 5.56-5.53 (m, 1H), 4.97 (t, *J* = 1.8 Hz, 1H), 4.67 (t, *J* = 2.6 Hz, 1H), 3.90-3.84 (m, 1H), 3.82-3.75 (m, 1H), 3.58-3.56 (m, 1H), 3.42-3.36 (m, 1H), 3.25 (q, *J* = 8.0, 10.0 Hz, 1H), 1.96 (d, *J* = 1.2 Hz, 3H), 1.78-1.73 (m, 6H); ^{13}C NMR δ 171.9, 158.0, 143.6, 130.8, 130.7, 128.7, 128.2, 128.1, 127.50, 127.46, 120.3, 120.2, 99.5, 99.4, 91.4, 90.9, 87.5, 85.0, 84.6, 65.7, 65.5, 63.9, 63.6, 61.6, 60.0, 51.9, 51.3, 30.9, 30.8, 25.3, 20.1, 19.7, 14.4; MS (ESI) m/z 631.1728 $[M+H]^+$.

2,2'-Anhydro-5-fluoro-1-(3-*O*-tetrahydropyranyl-5-*O*-trityl-4-seleno-D-arabinofuranosyl)uracil (**20i**).

White foam as an inseparable diastereomeric mixture; Yield: 82%; UV (CH_2Cl_2) λ_{max} 232 nm; ^{1}H NMR ($CDCl_3$) (major) δ 7.28-7.19 (m, 15H), 6.16 (d, *J* = 7.6 Hz, 1H), 5.40 (dd, *J* = 7.6 Hz, 1H), 4.97 (d, *J* = 2.4 Hz, 1H), 4.80 (s, 1H), 4.16-4.09 (m, 1H), 3.84-3.79 (m, 2H), 3.55-3.50 (m, 1H), 3.20-3.11 (m, 2H), 1.55-1.49 (m, 6H); (minor) δ 7.37-7.35 (m, 15H), 6.18 (d, 1H), 5.62 (d, *J* = 6.6 Hz, 1H), 4.96 (d, *J* = 2.4 Hz, 1H), 4.68 (s, 1H), 3.84-3.79 (m, 2H), 3.55-3.50 (m, 2H),

3.32-3.27 (m, 2H), 1.80-1.68 (m, 6H); ^{13}C NMR δ 164.1, 164.0, 155.7, 147.8, 147.7, 145.3, 145.2, 143.5, 143.4, 128.6, 128.1, 128.0, 127.44, 127.40, 120.5, 120.1, 99.1, 92.6, 92.0, 87.32, 87.27, 84.8, 84.6, 65.5, 65.2, 63.7, 63.4, 62.4, 61.2, 51.5, 51.4, 31.1, 30.8, 30.6, 25.20, 25.16, 19.8, 19.5; MS (ESI) m/z 657.1304 $[M+Na]^+$.

2,2'-Anhydro-5-chloro-1-(3-*O*-tetrahydropyranyl-5-*O*-trityl-4-seleno-D-arabinofuranosyl)uracil (**20j**).

White foam as an inseparable diastereomeric mixture; Yield: 90%; UV (CH_2Cl_2) λ_{max} 267 nm; ^{1}H NMR ($CDCl_3$) (**major**) δ 7.39-7.23 (m, 16H), 6.14 (d, *J* = 7.6 Hz, 1H), 5.64 (d, *J* = 6.0 Hz, 1H), 4.98-4.97 (m, 1H), 4.70 (d, *J* = 5.2 Hz, 1H), 3.89-3.84 (m, 2H), 3.58-3.56 (m, 1H), 3.37 (q, *J* = 7.6, 10 Hz, 1H), 3.21 (q, *J* = 8.6, 10.2 Hz, 1H), 1.60-1.51 (m, 6H); ^{13}C NMR δ 168.4, 158.8, 144.5, 135.1, 129.2, 128.6, 128.3, 128.2, 127.5, 118.5, 100.7, 94.1, 80.9, 64.2, 62.8, 62.0, 56.0, 54.0, 31.0, 25.9, 19.9.

2,2'-Anhydro-5-bromo-1-(3-*O*-tetrahydropyranyl-5-*O*-trityl-4-seleno-D-arabinofuranosyl)uracil (**20k**).

White foam; Yield: 75%; UV (CH_2Cl_2) λ_{max} 272 nm; ^{1}H NMR ($CDCl_3$) δ (**major**) 7.49 (s, 1H), 7.31-7.23 (m, 15H), 6.15 (d, *J* = 7.2 Hz, 1H), 5.63 (dd,, *J* = 1.2, 7.2 Hz, 1H), 4.97-4.96 (m, 1H), 4.70 (t, *J* = 2.6 Hz, 1H), 3.88-3.84 (m, 2H), 3.59-3.52 (m, 1H), 3.39-3.32 (m, 1H), 3.23-3.18 (m, 1H), 1.54-1.52 (m, 6H); (**minor**) 7.47 (s, 1H), 7.39-7.36 (m, 15H), 6.11 (d, *J* = 7.6 Hz, 1H), 5.41 (dd, *J* = 2.2, 7.0 Hz, 1H), 4.97-4.96 (m, 1H), 4.82-4.81 (m, 1H), 4.20-4.11 (m, 1H), 3.81-3.79 (m, 1H), 3.59-3.52 (m, 1H), 3.39-3.32 (m, 1H), 3.17-3.13 (m, 1H), 1.79-1.72 (m, 6H); ^{13}C NMR δ 166.1, 157.7, 143.5, 143.5, 134.9, 128.7, 128.2, 128.1, 127.6, 127.5, 108.9, 108.7, 99.4, 99.3, 92.4, 91.9, 87.5, 84.9, 84.6, 65.6, 65.3, 63.9, 63.6, 61.7, 60.5, 52.2, 51.9, 30.9, 30.8, 25.3, 25.2, 20.0, 19.7.

2,2'-Anhydro-5-iodo-1-(3-*O*-tetrahydropyranyl-5-*O*-trityl-4-seleno-D-arabinofuranosyl)uracil

(**20l**).

White foam as an inseparable diastereomeric mixture; Yield: 74%; UV (CH_2Cl_2) λ_{max} 276 nm; ^{1}H NMR ($CDCl_3$) δ (**major**) 7.63-7.60 (m, 1H), 7.30-7.21 (m, 15H), 6.21-6.16 (m, 1H), 5.63 (dd, *J* = 1.0, 7.0 Hz, 1H), 5.00-4.94 (m, 1H), 4.70-4.69 (m, 1H), 3.86-3.80 (m, 2H), 3.57-3.53 (m, 1H), 3.37-3.30 (m, 1H), 3.22-3.17 (m, 1H), 1.58-1.51 (m, 6H); (**minor**) 7.600-7.597 (m, 1H), 7.38-7.36 (m, 15H), 6.21-6.16 (m, 1H), 5.43 (dd, *J* = 2.2, 7.4 Hz, 1H), 5.00-4.94 (m, 1H), 4.82-4.81 (m, 1H), 4.14-4.11 (m, 1H), 3.86-3.80 (m, 1H) 3.57-3.53 (m, 1H), 3.37-3.30 (m, 1H), 3.16-3.12 (m, 1H), 1.80-1.71 (m, 6H); ^{13}C NMR δ 167.5, 158.4, 143.5, 143.4, 140.3, 128.6, 128.14, 128.10, 127.5, 127.4, 99.2, 99.0, 92.4, 91.9, 87.40, 87.36, 84.8, 84.4, 83.4, 83.2, 65.6, 65.3, 61.6, 60.5, 51.8, 51.7, 30.8, 30.7, 25.3, 25.2, 19.8, 19.6.

General procedure for the synthesis of **21g-21l.**

To a solution of compound **20g-20l** (1 equiv.) in acetonitrile was added 1 M NaOH (acetonitrile:1 M NaOH = 3:1) and the mixture was stirred at room temperature for 2 h. The reaction mixture was neutralized with glacial acetic acid and concentrated. The residue was purified by flash silica gel column chromatography (dichloromethane:methanol = 30:1) to give **21g-21l**.

1-(3-*O*-Tetrahydropyranyl-5-*O*-trityl-4-seleno-D-arabinofuranosyl)uracil (**21g**).

White foam as diastereomeric mixture; Yield: 94%; UV (MeOH) λ_{max} 266nm; ^{1}H NMR (CD_3OD) (**major**) δ 8.11 (d, *J* = 8.0 Hz, 1H), 7.48-7.24 (m, 15H), 6.57 (d, *J* = 4.8 Hz, 1H), 5.55 (d, *J* = 8.4 Hz, 1H), 4.61-4.59 (m, 1H), 4.32-4.25 (m, 2H), 3.94-3.89. (m, 1H), 3.74 (dd, *J* = 6.2, 8.8 Hz, 1H), 3.63 (td, *J* = 6.4, 3.6 Hz, 1H), 3.54 (dd, *J* = 7.2, 9.2 Hz, 1H), 3.50-3.48 (m, 1H), 1.45-1.82 (m, 6H).

1-(3-*O*-Tetrahydropyranyl-5-*O*-trityl-4-seleno-D-arabinofuranosyl)thymine (**21h**).

White foam as diastereomeric mixture; Yield: 96%; UV (CH_2Cl_2) λ_{max} 281 nm; ^{1}H NMR (CD_3OD) (**major**) δ 8.28 (s, 1H), 7.71 (d, *J* = 1.2 Hz, 1H), 7.25-7.49 (m, 15H), 6.51 (d, *J* = 6.8 Hz, 1H), 4.72 (d, *J* = 1.2 Hz, 1H), 4.27 (q, *J* = 2.4, 6.4 Hz, 1H), 4.18-4.22 (m, 1H), 3.90-3.96 (m, 2H), 3.58-3.63 (m, 2H), 3.46-3.52 (m, 1H), 3.36-3.40 (m, 1H), 1.70 (d, *J* = 0.8 Hz, 3H), 1.34-1.52, (m, 6H); ^{13}C NMR δ 163.6, 151.2, 143.6, 139.5, 128.9, 128.2, 127.6, 110.4, 101.6, 87.5, 77.8, 65.0, 62.7, 52.3, 41.5, 31.2, 25.0, 20.6, 12.9; MS (ESI) m/z 671.1650 $[M+Na]^+$.

5-Fluoro-1-(3-*O*-tetrahydropyranyl-5-*O*-trityl-4-seleno-D-arabinofuranosyl)uracil (**21i**).

White foam as diastereomeric mixture; Yield: 95%; UV (CH_2Cl_2) λ_{max} 279 nm; ^{1}H NMR ($CDCl_3$) δ 8.16 (d, *J* = 6.4 Hz, 1H). 8.10 (d, *J* = 6.4 Hz, 1H), 7.23-7.50 (m, 30H), 6.51 (dd, *J* = 1.2, 6.6 Hz, 1H), 6.47 (dd, *J* = 1.2, 5.2 Hz, 1H), 4.79 (t, *J* = 3.4 Hz, 1H), 4.43 (t, *J* = 5.0 Hz, 1H), 4.21-4.26 (m, 3H), 3.89-3.98 (m, 2H), 3.78-3.87 (m, 2H), 3.68-3.73 (m, 1H), 3.62-3.66 (m, 1H), 3.60-3.56, (m, 1H), 3.47-3.54 (m, 2H), 3.38-3.46 (m, 2H), 1.33-1.77 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 158.3, 158.0, 157.8, 157.6, 150.15, 150.07, 143.8, 143.6, 140.4, 139.5, 138.0, 137.2, 130.6, 130.2, 128.9, 128.8, 128.1, 128.0, 127.4, 127.3, 100.9, 98.6, 87.5, 87.4, 85.9, 82.7, 65.1, 64.7, 62.8, 62.3, 57.7, 54.5, 48.7, 43.7, 31.1, 30.7, 25.4, 25.0, 20.5, 19.4; MS (ESI) m/z 675.1403 $(M+Na)^+$.

5-Chloro-1-(3-*O*-tetrahydropyranyl-5-*O*-trityl-4-seleno-D-arabinofuranosyl)uracil (**21j**).

White foam as an diastereomeric mixture; Yield: 84%; UV (CH_2Cl_2) λ_{max} 281 nm; ^{1}H NMR ($CDCl_3$) δ 10.4 (brs, 1H), 9.65 (brs, 1H), 8.23 (s, 1H), 8.20 (s, 1H), 7.52-7.24 (m, 30H), 6.56-6.54 (m, 2H), 4.85-4.51 (m, 2H), 4.51 (d, *J* = 4.4 Hz, 1H), 4.36-4.31 (m, 4H), 4.03-4.00 (m, 1H), 3.97-3.90 (m, 2H), 3.80-3.77 (m, 2H), 3.67-3.65 (m, 2H), 3.54-3.45 (m, 4H), 1.81-1.41 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 160.4, 159.7, 150.7, 150.4, 143.9, 143.7, 143.1, 141.6, 129.0, 128.9, 128.2, 128.0, 127.5, 127.3, 107.8, 106.9, 100.6, 98.6, 87.5, 87.4, 86.1, 83.2, 77.9, 77.7, 65.4,

64.6, 63.2, 62.8, 58.5, 55.0, 49.8, 44.7, 31.1, 30.8, 25.5, 25.1, 20.4, 19.5.

5-Bromo-1-(3-*O*-tetrahydropyranyl-5-*O*-trityl-4-seleno-D-arabinofuranosyl)uracil (**21k**).

White foam as diastereomeric mixture; Yield: 72%; UV (CH_2Cl_2) λ_{max} 284 nm; ^{1}H NMR ($CDCl_3$) δ 10.3 (brs, 1H), 9.54 (brs, 1H), 8.32 (s, 1H), 8.28 (s, 1H), 7.51-7.24 (m, 30H), 6.55 (t, *J* = 5.6 Hz, 2H) , 4.83-4.80 (m, 2H), 4.50-4.48 (m, 1H), 4.39-4.38 (m, 1H), 4.33-4.29 (m, 3H), 4.03-3.90 (m, 3H), 3.79-3.76 (m, 2H), 3.70-3.66 (m, 2H), 3.54-3.44 (m, 4H), 1.86-1.43 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 160.5, 159.8, 150.9, 150.7, 145.6, 144.2, 144.0, 143.8, 129.0, 128.9, 128.2, 128.0, 127.4, 127.3, 100.4, 98.6, 95.6, 95.0, 87.42, 87.35, 85.9, 83.2, 77.9, 77.7, 65.5, 64.5, 63.6, 62.8, 58.5, 55.2, 49.6, 45.1, 31.1, 30.8, 25.5, 25.1, 20.3, 19.4.

5-Iodo-1-(3-*O*-tetrahydropyranyl-5-*O*-trityl-4-seleno-D-arabinofuranosyl)uracil (**21l**).

White foam as diastereomeric mixture; Yield: 88%; UV (CH_2Cl_2) λ_{max} 289 nm; ^{1}H NMR ($CDCl_3$) δ 10.0 (brs, 1H), 9.26 (brs, 1H), 8.38 (s, 1H), 8.31 (s, 1H), 7.50-7.24 (m, 30H), 6.50 (t, *J* = 5.8 Hz, 2H) , 4.80 (s, 1H), 4.74 (d, *J* = 2.8 Hz, 1H), 4.43-4.38 (m, 2H), 4.30-4.22 (m, 3H), 3.96-3.89 (m, 3H), 3.81-3.77 (m, 1H), 3.74-3.64 (m, 3H), 3.53-3.46 (m, 2H), 3.45-3.41 (m, 2H), 1.79-1.41 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 161.2, 160.6, 151.3, 150.9, 150.3, 149.1, 143.9, 143.7, 129.0, 128.9, 128.2, 128.1, 127.5, 127.4, 100.7, 98.6, 87.5, 86.3, 83.1, 78.1, 77.8, 77.4, 67.4, 67.1, 65.7, 64.6, 63.9, 62.8, 57.9, 54.6, 48.8, 44.5, 31.1, 30.8, 25.5, 25.1, 20.4, 19.4.

General procedure for the synthesis of 2'-deoxy-2'-fluoro-4'-selenoarabinofuranosyl pyrimidines **3g-3l**.

To a solution of compound **21g-21l** (1 equiv.) in dichloromethane was added diethylaminosulfur trifluoride (1.5 eqiv.) at -78 °C, and the reaction mixture was stirred at the same temperature for 30 minutes. Then the reaction mixture was allowed to stir at 0 °C for 2 h. After saturated $NaHCO_3$ solution was carefully added at 0 °C, the mixture was diluted with

dichloromethane and the organic layer was washed with saturated $NaHCO_3$ solution, brine, dried over $MgSO_4$, filtered and evaporated. under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane:ethyl acetate = 2:1) to give the fluoride **22g-22l**. Since the fluoride **22g-22l** were mixed with the inseparable impurities, it was immediately used for next step without further purification.

A solution of compound **22g-22l** in 80% aqueous acetic acid was stirred at room temperature for 15 h. The reaction mixture was evaporated under reduced pressure and the residue was purified by flash silica gel column chromatography (dichloromethane:methanol= 5:1) to give the corresponding deprotected compound as a solid. This was finally recrystallized from diethyl ether/methanol to give **3g-3l**.

(-)-1-(2-Deoxy-2-fluoro-4-seleno-D-arabinofuranosyl)uracil (**3g**).

White solid; Yield: 19%; mp 211-215 °C; $[\alpha]_D^{20}$ -0.22 (*c* 0.20, CH_3OH); UV (CH_3OH) λ_{max} 260 nm; ^1H NMR (CD_3OD) δ 8.25 (dd, *J* = 1.2, 8.0 Hz, 1H), 6.65 (dd, *J* = 5.0, 15.0 Hz, 1H), 5.73 (d, *J* = 8.0 Hz, 1H), 5.02 (t, *J* = 5.6 Hz, 0.5H), 4.89 (t, *J* = 5.6 Hz, 0.5H), 4.39-4.34 (m, 1H), 4.01-3.96 (m, 1H), 3.86-3.81 (m, 1H); ^{13}C NMR (CD_3OD) δ 166.2, 152.7, 146.1, 102.4, 100.0, 98.1, 75.8 (*J* = 23.2 Hz), 63.9, 53.8 (*J* = 16.7 Hz); ^{19}F NMR (CD_3OD) δ -192.99 (dt, *J* = 11.7, 50.0 Hz); MS (ESI): m/z 310.9941 $[M+H]^+$; Found: C, 35.04; H, 3.56; N, 9.66. Calcd for $C_9H_{11}FN_2O_4Se$: C, 34.97; H, 3.59; N, 9.06%.

(+)-1-(2-Deoxy-2-fluoro-4-seleno-D-arabinofuranosyl)thymine (**3h**).

White solid; Yield: 43%; mp 107-114 °C; $[\alpha]_D^{20}$ +11.96 (*c* 1.00, CH_3OH); UV (CH_3OH) λ_{max} 269 nm; ^1H NMR (CD_3OD) δ 6.61 (dd, *J* = 5.2, 13.6 Hz, 1H) 5.49 (s, 1H), 5.00 (t, *J* = 5.6 Hz, 0.5H), 4.88 (t, *J* = 5.6 Hz, 0.5H), 4.35-4.41 (m, 1H), 3.84-4.00 (m, 2H), 3.55 (dd, *J* = 5.8, 11.2 Hz, 1H), 1.89 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (CD_3OD) δ 166.3, 152.8, 141.5, 111.0, 99.9, 98.0,

75.4 (*J* = 92 Hz), 63.2, 53.4 (*J* = 67 Hz), 12.5; ^{19}F NMR (CD_3OD) δ -188.4; MS (ESI) m/z 346.9913 $[M+Na]^+$; Found: C, 37.34; H, 3.99; N, 8.46. Calc. for $C_{10}H_{13}FN_2O_4Se$: C, 37.16; H, 4.05; N, 8.67%..

(-)-5-Fluoro-1-(2-deoxy-2-fluoro-4-seleno-D-arabinofuranosyl)uracil (**3i**).

White solid; Yield: 22%; mp 193-195 °C; UV (CH_3OH) λ_{max} 270 nm; $[\alpha]_D^{20}$ +5.59 (*c* 0.34, CH_3OH); ^{1}H NMR (CD_3OD) δ 8.48 (dd, *J* = 1.0, 7.0 Hz, 1H), 6.62-6.57 (m, 1H), 5.02 (dd, *J* = 5.2, 6.0 Hz, 0.5H), 4.90 (dd, *J* = 5.0, 6.2 Hz, 0.5H), 4.40-4.35 (m, 1H), 3.96-3.92 (m, 1H), 3.89-3.84 (m, 1H), 3.56 (dd, *J* = 5.8, 11.4 Hz, 1H); ^{13}C NMR (CD_3OD) δ 210.0, 129.7 (d, *J* = 133.2 Hz), 151.4, 100.0, 98.0, 75.2 (d, *J* = 92.0 Hz), 63.1, 54.1 (d, *J* = 63.2 Hz), 30.7; ^{19}F NMR (CD_3OD) δ -160.7, -187.4; MS (ESI) m/z 326.9712 $[M-H]^-$; Found: C, 33.04; H, 3.07; N, 8.45. Calc. for $C_9H_{10}F_2N_2O_4Se$: C, 33.04; H, 3.08; N, 8.56%..

(+)-5-Chloro-1-(2-deoxy-2-fluoro-4-seleno-D-arabinofuranosyl)uracil (**3j**).

White solid; Yield: 20%; mp 212-218 °C; UV (CH_3OH) λ_{max} 277 nm; $[\alpha]_D^{20}$ +12.05 (*c* 2.20, CH_3OH); ^{1}H NMR (CD_3OD) δ 8.61 (s, 1H), 6.59 (dd, *J* = 5.0, 13.4 Hz, 1H), 5.09 (t, *J* = 5.8 Hz, 0.5H), 4.90 (t, *J* = 5.6 Hz, 0.5H), 4.40-4.35 (m, 1H), 3.95-3.85 (m, 2H), 3.56 (dd, *J* = 5.4, 11.0 Hz, 1H); ^{13}C NMR (CD_3OD) δ 161.4, 151.8, 142.6, 108.8, 99.7, 97.8, 75.1 (d, *J* = 22.7 Hz), 62.9, 54.2 (d, *J* = 16.0 Hz); ^{19}F NMR (CD_3OD) δ -192.1 (dt, *J* = 12.0, 50.4 Hz); MS (ESI) m/z 344.9550 $[M+H]^+$; Found: C, 31.09; H, 2.75; N, 8.01. Calc. for $C_9H_{10}FClN_2O_4Se$: C, 31.46; H, 2.93; N, 8.15%..

(+)-5-Bromo-1-(2-deoxy-2-fluoro-4-seleno-D-arabinofuranosyl)uracil (**3k**).

White solid; Yield: 19%; mp 119-122 °C; $[\alpha]_D^{20}$ +20.58 (*c* 1.38, CH_3OH+H_2O); UV (CH_3OH) λ_{max} 279 nm; ^{1}H NMR (CD_3OD) δ 8.71 (d, *J* = 1.2 Hz, 1H), 6.58 (dd, *J* = 5.2, 13.2 Hz, 0.5H), 5.03 (dd, *J* = 5.2, 6.2 Hz , 0.5 H), 4.90 (dd, *J* = 5.2, 6.4 Hz, 0.5H), 4.40-4.34 (m, 1H), 3.95-3.85 (m, 2H), 3.56 (dd, *J* = 5.6, 10.8 Hz, 1H); ^{13}C NMR (CD_3OD) δ 161.5, 152.0, 145.2 (d, *J* = 2.2

Hz), 99.7, 97.8, 96.5, 75.1 (d, *J* = 22.7 Hz), 62.8 (d, *J* = 2.2 Hz), 54.1 (d, *J* = 16.2 Hz); ^{19}F NMR (CD_3OD) δ -192.0 (dt, *J* = 12.0, 50.4 Hz); MS (ESI) m/z 410.8857 $[M+Na]^+$; Found: C, 20.99; H, 2.90; N, 6.98. Calc. for $C_9H_{10}FBrN_2O_4Se$: C, 20.59; H, 2.60; N, 7.22%.

(-)-5-Iodo-1-(2-deoxy-2-fluoro-4-seleno-D-arabinofuranosyl)uracil (**3l**).

White solid; Yield: 19%; mp 245-246 °C (decomposed); $[\alpha]_D^{20}$ -21.63 (*c* 0.43, CH_3OH+H_2O); UV (CH_3OH) λ_{max} 289 nm; ^{1}H NMR (CD_3OD) δ 8.74 (s, 1H) 6.57 (dd, *J* = 5.2, 13.6 Hz, 1H), 5.00 (q, *J* = 5.2, 6.0 Hz, 0.5H), 4.88 (dd, *J* = 5.0, 6.2 Hz, 0.5H), 4.39-4.33 (m, 1H), 3.95-3.84 (m, 2H), 3.57 (dd, *J* = 5.6, 11.2 Hz, 1H); ^{13}C NMR (CD_3OD) δ 162.5, 152.2, 150.1, 99.5, 97.6, 74.9 (d, *J* = 23.3 Hz), 67.9, 62.7, 53.8 (d, *J* = 16.2 Hz); ^{19}F NMR (CD_3OD) δ -191.8 (dt, *J* = 11.7, 50.3 Hz); MS (ESI) m/z 436.8901 $[M+H]^+$; Found: C, 24.45; H, 2.01; N, 6.84. Calc. for $C_9H_{10}FIN_2O_4Se$: C, 24.85; H, 2.32; N, 6.44%.

General procedure for the synthesis of 4'-selenoarabinofuranosyl pyrimidines **3m-3q.**

To a solution of compound **18g-18l** in in acetonitrile was added 1 M NaOH (acetonitrile:1 M NaOH = 3:1) and the mixture was stirred at room temperature for 2 h. The reaction mixture was neutralized with glacial acetic acid and concentrated. The residue was purified by flash silica gel column chromatography (dichloromethane:methanol = 10:1) to give the corresponding compound as a solid. This was finally recrystallized from diethyl ether/methanol to give **3m-3q**.

(-)-1-(4-Seleno-D-arabinofuranosyl)uracil (**3m**).

White solid; Yield: 94%; mp 141-145 °C (decomposed); $[\alpha]_D^{20}$ -0.021 (*c* 0.093, CH_3OH); UV (CH_3OH) λ_{max} 266 nm; ^{1}H NMR (CD_3OD) δ 8.27 (d, *J* = 8 Hz, 1H), 6.52 (d, *J* = 5.6 Hz, 1H), 5.69 (d, *J* = 8.0 Hz, 1H), 4.16-4.13 (m, 1H), 4.11-4.04 (m, 2H), 3.60-3.54 (m, 1H); ^{13}C NMR (CD_3OD) δ 179.6, 166.4, 153.0, 147.1, 101.5, 80.5, 78.8, 64.4, 56.2; MS (ESI) m/z 308.9980

$[M+H]^+$; Found: C, 35.45; H, 4.34, N 8.88. Calcd for $C_9H_{12}N_2O_5Se$: C, 35.19; H, 3.94, N 9.12%.

(-)-1-(4-Seleno-D-arabinofuranosyl)thymine (**3n**).

White solid; Yield: 99%; mp 191-196 °C; $[\alpha]_D^{20}$ -12.42 (*c* 1.00, CH_3OH + H_2O); UV (CH_3OH) λ_{max} 271 nm; ^1H NMR (CD_3OD) δ 8.15 (d, *J* = 1.2 Hz, 1H), 6.48 (d, *J* = 5.2 Hz, 1H), 4.15-4.09 (m, 2H), 4.04-4.00 (m, 1H), 3.96-3.90 (m, 1H), 3.54 (dd, *J* = 5.6, 10.8 Hz, 1H), 1.88 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (CD_3OD) δ 166.6, 153.2, 142.7, 110.3, 80.5, 78.2, 63.6, 55.6, 50.0, 12.6; MS (ESI) m/z: 323.0139 $[M+H]^+$; Found: C, 37.77; H, 4.09; N, 9.12. Calc. for $C_{10}H_{14}N_2O_5Se$: C, 37.39; H, 4.39; N, 8.72%.

(+)-5-Fluoro-1-(4-seleno-D-arabinofuranosyl)uracil (**3o**).

White solid; Yield: 95%; mp 204-208 °C; $[\alpha]_D^{20}$ +45.49 (*c* 0.24, CH_3OH + H_2O); UV (CH_3OH) λ_{max} 274 nm; ^1H NMR (CD_3OD) δ 8.48 (d, *J* = 7.2 Hz, 1H), 6.48 (dd, *J* = 1.6, 5.2 Hz, 1H), 4.65-4.09 (m, 2H), 4.03-3.99 (m, 1H), 3.94-3.90 (m, 1H), 3.55 (dd, *J* = 5.4, 11.0 Hz, 1H); ^{13}C NMR (CD_3OD) δ 151.7, 141.6, 139.3, 130.8 (d, *J* = 35.9 Hz), 80.5, 78.3, 63.7, 56.7, 51.1; ^{19}F NMR (CD_3OD) δ -169.7 (d, *J* = 5.3 Hz); MS (ESI) m/z: 327.9896 $[M+H]^+$; Found: C, 33.20; H, 3.41; N, 8.54. Calc. for $C_9H_{11}FN_2O_5Se$: C, 33.24; H, 3.41; N, 8.62%.

(+)-5-Chloro-1-(4-seleno-D-arabinofuranosyl)uracil (**3p**).

White solid; Yield: 61%; mp 271-273 °C; $[\alpha]_D^{20}$ +1.82 (*c* 0.11, CH_3OH); UV (CH_3OH) λ_{max} 281 nm; ^1H NMR (CD_3OD) δ 8.59 (s, 1H), 6.50 (d, *J* = 4.8 Hz, 1H), 4.16-4.10 (m, 2H), 4.03-3.90 (m, 2H), 3.57 (q, *J* = 5.4, 10.6 Hz, 1H); ^{13}C NMR (CD_3OD) δ 161.7, 152.1, 143.8, 107.8, 80.5, 78.4, 63.7, 57.0, 51.6; MS (ESI) m/z: 364.9413 $[M+Na]^+$; Found: C, 31.45; H, 3.05; N, 8.02. Calc. for $C_9H_{11}ClN_2O_5Se$: C, 31.64; H, 3.25; N, 8.20%.

(+)-5-Bromo-1-(4-seleno-D-arabinofuranosyl)uracil (**3q**).

White solid; Yield: 57%; mp 243-244 °C (decomposed); $[\alpha]_D^{20}$ +3.33 (*c* 0.03, CH_3OH); UV (CH_3OH) λ_{max} 283 nm; ^1H NMR (CD_3OD) δ 8.70 (s, 1H), 6.49 (d, *J* = 4.8 Hz, 1H), 4.16-4.10

(m, 2H), 4.02-3.90 (m, 2H), 3.58 (t, *J* = 2.8 Hz, 1H); ^{13}C NMR (CD_3OD) δ 161.8, 152.3, 146.4, 96.0, 80.5, 78.4, 63.6, 57.0, 51.7; MS (ESI) m/z: 408.8906 $[M+Na]^+$; Found: C, 20.45; H, 2.47; N, 7.04. Calc. for $C_9H_{11}BrN_2O_5Se$: C, 20.70; H, 2.87; N, 7.26%.

(-)-5-Iodo-1-(4-seleno-D-arabinofuranosyl)uracil (**3r**).

To a solution of compound **14f** (1 equiv.) and triphenylphosphine (3 equiv.) in tetrahydrofuran were added benzoic acid (3 equiv.) and DIAD (3 equiv.) at 0 ^{o}C and the mixture was allowed to stir at room temperature for 3 h. After adding EtOH, the mixture was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 5:1) to give the desired compound mixed with DIAD impurities. To this solution in tetrahydrofuran was added 3HF·Et_3N (3 equiv.) and triethylamine (3 equiv.) at 0 ^{o}C. After being stirred at the same temperature for 30 min, the reaction mixture was allowed to warm to room temperature and stirred for additional 1 h. The reaction mixture was concentrated and the residue was purified by silica gel column chromatography (dichloromethane:methanol = 7:1) to give the TIPS deprotected derivative. This compound in saturated methanolic ammonia was stirred in a glass bomb at room temperature for 15 h. Then all volatiles were evaporated under reduced pressure and the residue was purified by silica gel column chromatography (dichloromethane: methanol = 10:1) to give the corresponding deprotected compound as a solid. This was finally recrystallized from diethyl ether/methanol to give **3r.**

White solid: mp 252-257 $^{\circ}$C; $[\alpha]_D^{20}$ -90.00 (*c* 0.02, CH_3OH); UV (CH_3OH) λ_{max} 289 nm; ^{1}H NMR (CD_3OD) δ 8.75 (s, 1 H), 6.47 (d, *J* = 4.8 Hz, 1H), 4.15-4.09 (m, 2H), 4.01 (dd, *J* = 5.2, 11.6 Hz, 1H), 3.92 (dd, *J* = 6.0, 11.6 Hz, 1H), 3.57 (dd, *J* = 5.0, 10.6 Hz, 1H); ^{13}C NMR (CD_3OD) δ 163.0, 152.7, 151.5, 80.5, 78.4, 66.7, 63.6, 56.8, 51.5; MS (ESI) m/z 456.8774 $[M+Na]^+$; Found: C,; H,; N,. Calc. for $C_9H_{11}IN_2O_5Se$: C, 24.96; H, 2.56; N, 6.47%.

General procedure for the synthesis of cytosine derivatives **3s**, **3t** and **3u**.

A solution of compound **3a**, **3g** or **3m** (1 equiv.) in anhydrous pyridine was treated with acetic anhydride (10 equiv.), and the mixture was stirred at room temperature for 15 h. The mixture was evaporated under reduced pressure and the residue was diluted with dichloromethane. This solution was washed consecutively with dilute HCl, saturated $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 1:1) to give peracetylated compound **23s**, **23t** or **23u** as a white foam.

To a solution of compound **23s**, **23t** or **23u** in acetonitrile were added 1,2,4-triazole (1 equiv.), phosphorus oxychloride (1.1 equiv.), and triethylamine (1.1 equiv.) and the mixture was stirred at room temperature for 15 h. The mixture was diluted with dichloromethane and the organic layer was washed with saturated $NaHCO_3$ solution, brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue obtained was used in the next step without further purification (**24s**, **24t** and **24u)**. To a solution of this residue in 1,4-dioxane was added ammonium hydroxide (28%), and the mixture was stirred at room temperature for 15 h. After removal of all volatiles, the residue was dissolved in methanolic ammonia and stirred again for 20 h. The reaction mixture was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (dichloromethane:methanol = 6:1) to give the corresponding deprotected compound as a solid. This was finally recrystallized from diethyl ether/methanol to give **3s**, **3t** and **3u**.

(+)-1-(2-Azido-2-deoxy-4-seleno-D-arabinofuranosyl)cytosine (**3s**).

White solid; Yield: 46%; mp 81-86 °C; $[\alpha]_D^{20}$ +8.89 (*c* 0.36, CH_3OH); UV (CH_3OH) λ_{max} 277 nm; IR (KBr) 2115 cm^{-1} (N_3); ^1H NMR (400 MHz, CD_3OD) δ 8.26 (d, *J* = 7.2 Hz, 1H), 6.58 (d,

J = 6.4 Hz, 1H), 5.91 (d, *J* = 7.2 Hz, 1H), 4.17-4.13 (m, 1H), 4.08-4.00 (m, 2H), 3.88 (dd, *J* = 6.0, 11.6 Hz, 1H), 3.55-3.51 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 159.0, 146.0, 96.0, 76.8, 73.3, 63.0, 52.6, 47.9; MS (ESI) m/z 355.0045 $[M+Na]^+$; Found: C, 32.54; H, 3.32; N, 25.54. Calc. for $C_9H_{12}N_6O_3Se$: C, 32.64; H, 3.65; N, 25.38%.

(+)-1-(2-Deoxy-2-fluoro-4-seleno-D-arabinofuranosyl)cytosine (**3t**).

White solid; Yield: 59%; mp 231-235 °C (decomposed); $[\alpha]_D^{20}$ +0.16 (*c* 0.05, CH_3OH); UV (CH_3OH) λ_{max} 274 nm; ^{1}H NMR (CD_3OD) δ 8.22 (dd, *J* = 1.8, 7.4 Hz, 1H), 6.80 (dd, *J* = 4.8, 17.2 Hz, 1H), 5.91 (d, *J* = 7.6 Hz, 1H), 5.01 (t, *J* = 5.0 Hz, 0.5H), 4.88 (t, *J* = 5.2 Hz, 0.5H), 4.42-4.38 (m, 1H), 4.00-3.96 (m, 1H), 3.84-3.79 (m, 1H), 3.62-3.60 (m, 1H); ^{13}C NMR (CD_3OD) δ 167.7, 158.8, 146.6 (*J* = 3.2 Hz), 100.1, 98.2, 96.0, 76.1 (*J* = 23.5 Hz), 64.2 (*J* = 3.3 Hz), 55.3 (*J* = 16.2 Hz), 50.9; ^{19}F NMR (CD_3OD) δ -193.69 (*J* = 9.4, 17.3 and 50.4 Hz) ; MS (ESI) m/z 331.9918 $[M+Na]^+$; Found: C, 35.07; H, 3.59; N, 13.68. Calcd for $C_9H_{12}FN_3O_3Se$: C, 35.08; H, 3.92; N, 13.64%.

(-)-1-(4-Seleno-D-arabinofuranosyl)cytosine (**3u**).

White solid; Yield: 54%; mp 220 °C (decomposed); $[\alpha]_D^{20}$ -1.73 (*c* 0.17, CH_3OH); UV (CH_3OH) λ_{max} 276 nm; ^{1}H NMR (CD_3OD) δ 8.27 (d, *J* = 7.6 Hz, 1H), 6.67 (d, *J* = 5.2 Hz, 1H), 5.88 (d, *J* = 7.6 Hz, 1H), 4.18-4.11 (m, 2H), 4.08-4.04 (m, 1H), 3.88 (dd, *J* = 6.8, 11.2 Hz, 1H), 3.60-3.56 (m, 1H); ^{13}C NMR (CD_3OD) δ 167.5, 159.2, 147.6, 95.2, 80.4, 79.3, 64.7, 57.4, 51.7; MS (ESI) m/z 308.0142 $[M+H]^+$; Found: C, 35.71; H, 4.67, N 13.89. Calc. for $C_9H_{13}N_3O_4Se$: C, 35.31; H, 4.28, N, 13.72%.

Cellular metabolism study

Sample preparation

PC-3, human prostate cancer cells were seeded into 100 mm dishes at a density of 5×10^5 cells/dish and incubated for 24 h. The cells were treated with 50 μM of compound **3t** for 24 h. After harvesting, cells were washed twice with DPBS. Cell pellets were suspended with 400 μL methanol and 200 μL chloroform. Samples were then vortex-mixed for 30 sec and submerged for 1 min in liquid N_2. After thawing at room temperature for 3 min, the samples were sonicated for 5 min. This liquid N_2-sonication process was repeated for three times. Then, 200 μL chloroform and 200 μL deionized water were added and the samples were centrifuged at 22,000 g for 20 min at 4 ℃. The 350 μL of supernatant (or upper-layer) was transferred to a centrifuge tube and dried by vacuum centrifugation. Before injection to HPLC-MS, the dried sample was dissolved with 10 μL buffer (deionized water:acetonitrile=1:1).

HPLC-MS experiments

The HILIC separation was performed using Agilent 1100 series HPLC system (Agilent Technologies, Palo Alto, Ca, USA). The analytes were detected using 150 x 2.1 mm SeQuant ZIC-pHILIC (Merck, Darmstadt, Germany) HPLC column coupled with mass spectrometry. The mobile phase contained (A) water with 10 mM ammonium carbonate and (B) acetonitrile. The gradient was linearly increased from 20% A to 80% in 30 min and kept for 15 min. It was then reduced to 20% in 0.1 min and kept for 15 min. The gradient was at a flow rate of 0.1 mL/min, and the column temperature was kept at 35 ℃. The injection volume was 3 μL. For mass spectrometry, the HPLC system was coupled to an LTQ-XL MS (Thermo Fisher, San Jose, CA) equipped with an electrospray source. The sheath gas flow was set to 35 (arbitrary unit), aux gas flow to 10 (arbitrary unit), sweep gas flow to 2 (arbitrary unit), Spray voltage to 4 kV, capillary temperature to 300 ℃, capillary voltage to 19 V, tube lens to 65 V, and normalized

collision energy to 35% for MS/MS experiment. The scan range was *m/z* 300 – 560 and total analysis time was 35 min.

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13. Crystal structure data for $C_9H_{11}N_2O_4FSe$: *M*r = 309.16, monoclinic, space group $P2_1$ (no. 4), a = 6.9286(5) Å, b = 6.7300(5) Å, c= 11.5320(8) Å, V = 533.67(7) Å^3, T = 173(2) K, Z = 2, ρ_{calc} = 1.924gcm^{-3}, F(000) = 308, crystal dimension 0.75×0.40×0.30 mm^3, μ(Mo Kα)= 3.54mm^{-1}, Mo Kα radiation(λ =0.71073 Å). Of 9378 reflections collected in the 2θ range 3.0–28.3° using an ϕ and ω scans on a Bruker SMART CCD Detector single crystal X-ray diffractometer, 2597 were unique reflections (R_{int} = 0.057). The structure was solved and refined against F^2 using SHELXS97 and SHELXL97, 198 variables, wR2 = 0.122, R1 = 0.049 (the 2569 reflections having $Fo^2 > 2\sigma(Fo^2)$), GOF = 1.06, and max/min residual electron density 0.71/-2.08 eÅ^{-3}. Flack x parameter = 0.017(17). 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. CCDC 742570

Highlights

- Novel 2'-substituted-4'-selenoarabinofuranosyl pyrimidines were synthesized.
- Pummerer-type base condensation was utilized.
- Mitsunobu reaction with DPPA was used for the introduction of the 2'-azido group.
- DAST fluorination proceeded via the episelenium intermediate.
- The 2'-F-4'-Se-AraC exhibited better anticancer activity than Ara-C.