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Asymmetric Synthesis of 2′-*C*-Methyl-4′-selenonucleosides as Anti-Hepatitis C Virus (HCV) Agents

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Abstract

In search of a new template for anti-hepatitis C virus (HCV) agents, we designed and synthesized the 2′-*C*-methyl-4′-selenopyrimidine and -purine nucleosides and their phosphoramidate prodrugs to replace a furanose oxygen of anti-HCV nucleos(t)ides with a selenium atom, on the basis that selenium is a chemical isostere of oxygen. These nucleosides are expected to show different physicochemical properties such as better lipophilicity which might enhance the penetration across cell membranes, and the conformational constraint induced by bulky selenium atom in the sugar ring. The 2′-*C*-methyl-4′-selenopyrimidine and -purine nucleosides were synthesized from 2-*C*-methyl-D-ribono-*γ*-lactone via construction of 2-*C*-methyl-D-selenosugar through *C*-4 epimerization and S_N2 cyclization with Se^{2-} as key steps. The key 4′-selenosugar was converted to the 2′-*C*-methyl-4′-selenopyrimidine and -purine nucleosides using Pummerer-type rearrangement and Vorbrüggen glycosylation, respectively. In addition, the ProTide strategy has been applied to synthesize the adenine and uracil phosphoramidate derivatives to overcome the limitations associated with parent nucleosides such as inefficient conversion to their corresponding 5′-monophosphate form and poor cellular uptake. The regio- and stereochemistry of 4′-selenonucleosides were confirmed by 2D NOESY NMR spectroscopy and X-ray crystallography. None of the final pyrimidine and purine nucleosides and their prodrugs exhibited significant anti-HCV activity up to 100 μM.

Keywords: Hepatitis C virus, 2′-*C*-methyl-4′-selenonucleosides, phosphoramidate prodrug, Pummerer-type base condensation, Vorbrüggen condensation

Introduction

Hepatitis C is caused by the hepatitis C virus (HCV), which has a 50 nm enveloped virion containing a single strand of linear RNA.[1,2] HCV is a member of the Flaviviridae family and is classified into multiple genotypes.[1,2] Hepatitis C has reached epidemic proportions worldwide, with more than 1 million new cases reported annually.[3] In most cases, an acute HCV infection leads to a chronic disease state.[4]

The treatment of chronic hepatitis C infection was revolutionized with the approval of direct-acting antiviral agents (DAAs).[5-7] DAAs are a relatively new class of medication that acts to target-specific steps in the life cycle of HCV. There are four current classes of DAAs, which are defined by their mechanism of action and therapeutic targets: nonstructural protein (NS) 3/4A protease inhibitors, NS5B nucleoside polymerase inhibitors, NS5B non-nucleoside polymerase inhibitors, and NS5A inhibitors.[7] The main targets of the DAAs are the HCV-encoded proteins that are vital to the replication of the virus.[5-7]

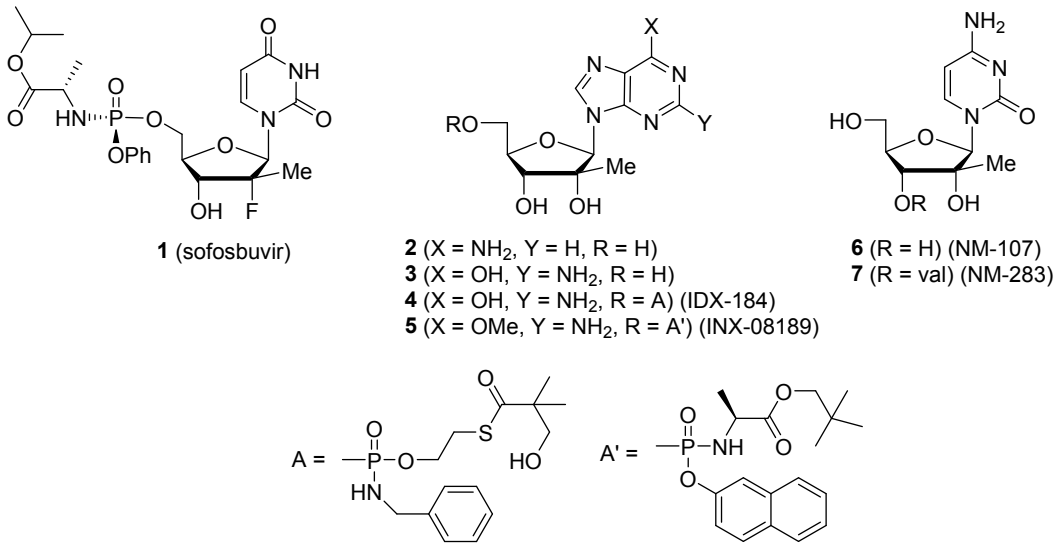


Figure 1. Chemical structures of anti-HCV nucleos(t)ides **1-7**

The past few years have witnessed an expanding interest in the prodrug approach in the antiviral drug development.[8] Among these, recently approved nucleos(t)ide analogue, sofosbuvir (**1**)[9] (Figure 1), a phosphoramidate prodrug, has been proven to be most effective orally available antiviral drug for chronic HCV treatment as a highly potent NS5B inhibitor. Ribavirin was being used for the treatment of HCV infection in combination with pegylated interferon (peg-IFN) α before the approval of sofosbuvir.[10] Compound **1** is available in a fixed-dose combination with ledipasvir for the treatment of HCV genotypes 1, 4, 5, and 6.[11] In addition, 2′-*C*-methylribofuranosylpurine derivatives **2** and **3** were also identified as potent HCV polymerase inhibitors.[12] However, the therapeutic potency of adenosine derivative **2** and guanosine derivative **3** was limited due to metabolic deamination and poor

conversion to the corresponding active triphosphate, respectively.[12] To solve these drawbacks, the phosphoramidate prodrugs, IDX-184 (**4**)[13] and INX-08189 (**5**)[14] were developed as potent and selective inhibitors of HCV replication. Unfortunately, both compounds have been removed from clinical trials due to their cardiotoxicity complications.[8,15] 2′-*C*-Methylcytidine (**6**) and its 3′-*O*-valine ester prodrug, NM-283 (**7**)[16] have also been reported as potent and selective inhibitors of HCV replication in cell culture. These prodrugs have been developed to improve pharmacokinetic properties such as low oral bioavailability of parent nucleosides.[17,18] These nucleos(t)ide analogues target the catalytic site of NS5B and are activated within a hepatocyte through phosphorylation by cellular kinases to nucleoside 5′-triphosphates, which then mimic the natural nucleoside 5′-triphosphates, and are incorporated into the growing HCV RNA chain by the NS5B polymerase, resulting in the viral RNA chain termination.[17,18] Introduction of 2′-*C*-methyl group to the ribofuranosyl nucleosides has been reported to shift the sugar puckering toward the 3′-endo (North) conformation in solution.[12,19] It has been also suggested that the presence of 2′-*C*-methyl group induce non-obligate viral RNA chain termination by restricting the subsequent elongation step through steric hindrance exerted between the 2′-*C*-methyl group and the ribose moiety of the next incoming natural nucleoside 5′-triphosphate.[8,20] Based on the mechanism of action, it has been identified that 2′-*C*-methylribofuranosyl nucleosides inhibit the

replication of other RNA viruses such as yellow fever, bovine diarrhea virus, and West African Nile viruses which are genetically homologous with HCV.[20]

On the other hand, it has been reported that the sugar conformation of nucleosides is closely related to the antiviral activity, which might be decided by the binding affinity to cellular kinases and/or DNA/RNA polymerases.[21-24] Van Roey et. al.[22] have reported the correlation between the sugar conformation of nucleosides and anti-HIV activity, suggesting that anti-HIV nucleosides adopt the C3'-exo (South) conformation. Marquez et al.[21] have reported that herpes 1 kinase and cellular DNA polymerase can discriminate between two isomers of methanocarba thymidine (MCT), on the basis of specific sugar conformation, wherein the kinases preferred the substrate that adopt the South sugar puckering (*S*-MCT), while the DNA polymerase preferred the substrate that adopt North sugar puckering (*N*-MCT). Marquez et al.[23] have also demonstrated that HIV-1 reverse transcriptase (RT) prefers specific sugar conformation of nucleotides using two conformationally restricted carbocyclic 3′-azidothymidine (AZT)-5′-triphosphate analogues. In this study, the (*N*)-methanocarba-AZT-5′-triphosphate (North conformer) exhibited potent inhibition against RT, while (*S*)-methanocarba-AZT 5′-triphosphate (South conformer) was found to be inactive against RT, demonstrating that RT prefers the northern sugar puckering. Kirby et al.[24] have also suggested that North (2′-exo/3′-endo) sugar puckering of 4′-ethynyl-2-fluoro-2′-deoxyadenosine is essential for recognition by RT at both dNTP incorporation step and primer (elongation step)

binding sites. Thus, the sugar conformation of the nucleos(t)ides is very crucial to meet the specific conformational demands of the catalytic enzymes.

Recently, we have reported the 4′-selenonucleosides as next generation nucleosides, which belong to nonclassical nucleosides in that the furanose ring oxygen is replaced by selenium.[25,26] The bulky selenium atom is expected to change the profiles of the nucleoside such as the sugar conformation and lipophilicity. For example, it was identified that the X-ray crystal structure of 4′-selenouridine showed unusual 2′-endo/3′-exo (South) conformation, which is opposite to uridine, adopting a 2′-exo/3′-endo (North) conformation.[26] This conformational difference might affect the phosphorylation by the cellular kinases or the binding affinity to cellular or viral DNA/RNA polymerases. The cellular phosphorylation study of 4′-selenonucleosides and 5′-homo-4′-selenonucleosides demonstrated that 4′-selenonucleosides were not phosphorylated by cellular kinases probably due to the steric repulsion between cellular kinase and bulky selenium, possibly explaining their poor antiviral activity or anticancer activity.[25] In contrast, the corresponding 5′-homo-4′-selenonucleosides were phosphorylated by cellular kinases most likely due to no steric repulsion between cellular kinase and bulky selenium, resulting in potent antiviral or antitumor activity.[25]

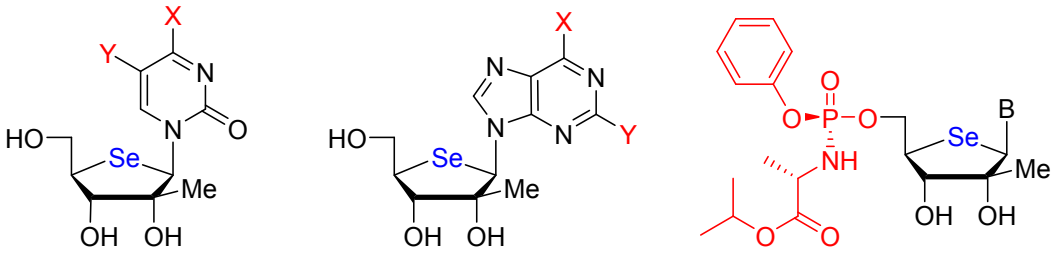
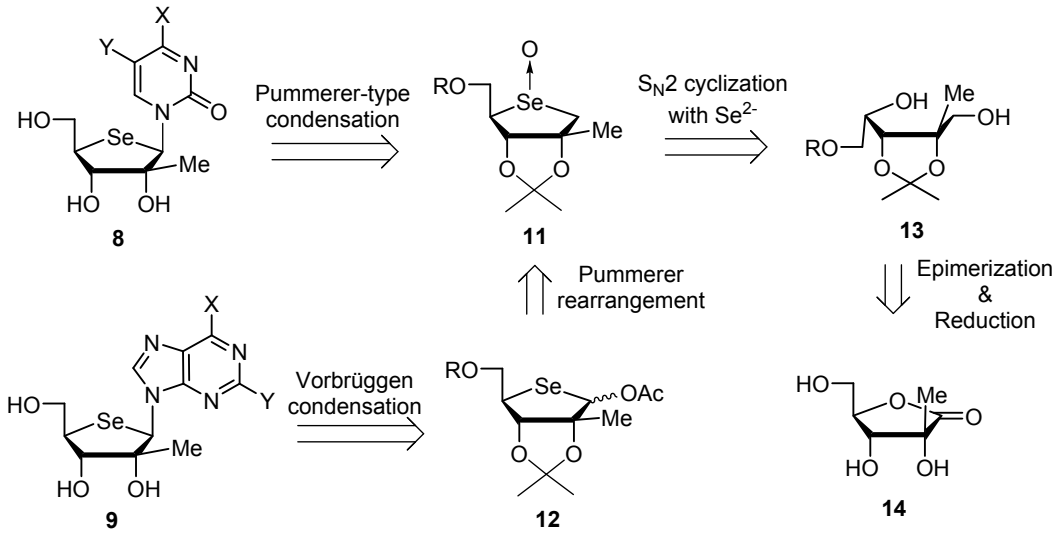


Figure 2. The structures of target nucleos(t)ides **8-10**

Thus, based on the bioisosteric relationships between oxygen and selenium, we designed and synthesized the 4′-seleno derivatives **8** and **9** of 2′-*C*-methylribofuranosyl-pyrimidines and purines shown in Figure 2 to discover new anti-HCV agents. We also synthesized the pyrimidine and purine phosphoramidate prodrugs **10**, which are designed to avoid the rate-determining monophosphorylation by the cellular kinases as well as the poor cellular uptake. Herein, we report the synthesis and anti-HCV activity of 2′-*C*-methyl-4′-selenonucleosides **8** and **9** and their phosphoramidate prodrugs **10**.

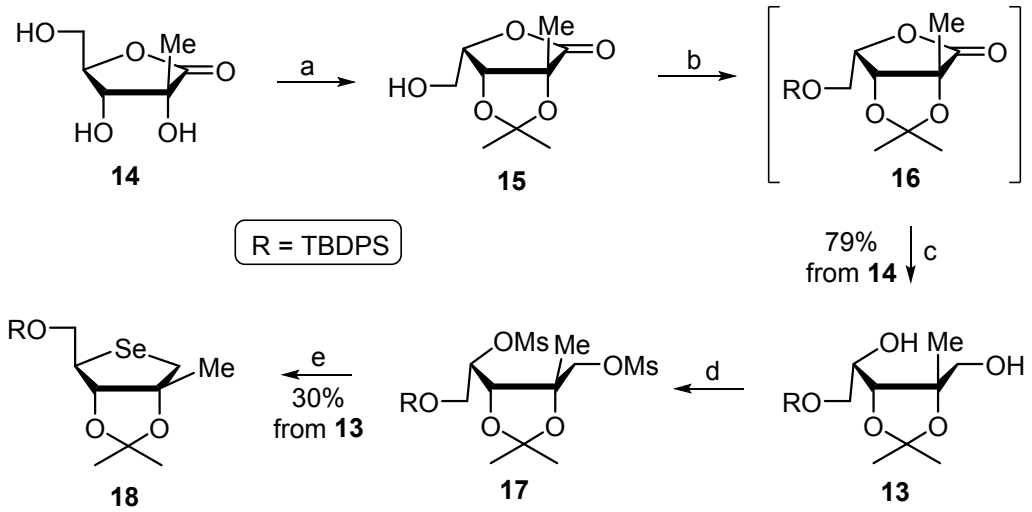
Results and Discussion

The retrosynthetic plan towards designed nucleosides **8** and **9** is illustrated in Scheme 1.



Scheme 1. Retrosynthetic plan towards the target nucleosides **8** and **9**.

The synthetic strategy to the desired pyrimidine nucleosides **8** was to synthesize the glycosyl donor **11** and then to condense with pyrimidine bases under Pummerer-type conditions. The targeted purine nucleosides **9** could be derived from the condensation of another glycosyl donor **12**, obtained from Pummerer rearrangement of **11**, with purine bases under Vorbrüggen conditions. The key compound **11** could be easily obtained from diol **13** via mesylation followed by S_N2 ring cyclization with Se^{2-}. Diol **13** could be derived from commercially available 2-*C*-methyl-D-ribono-*γ*-lactone (**14**) via *C*4-epimerization and subsequent reduction of lactone.

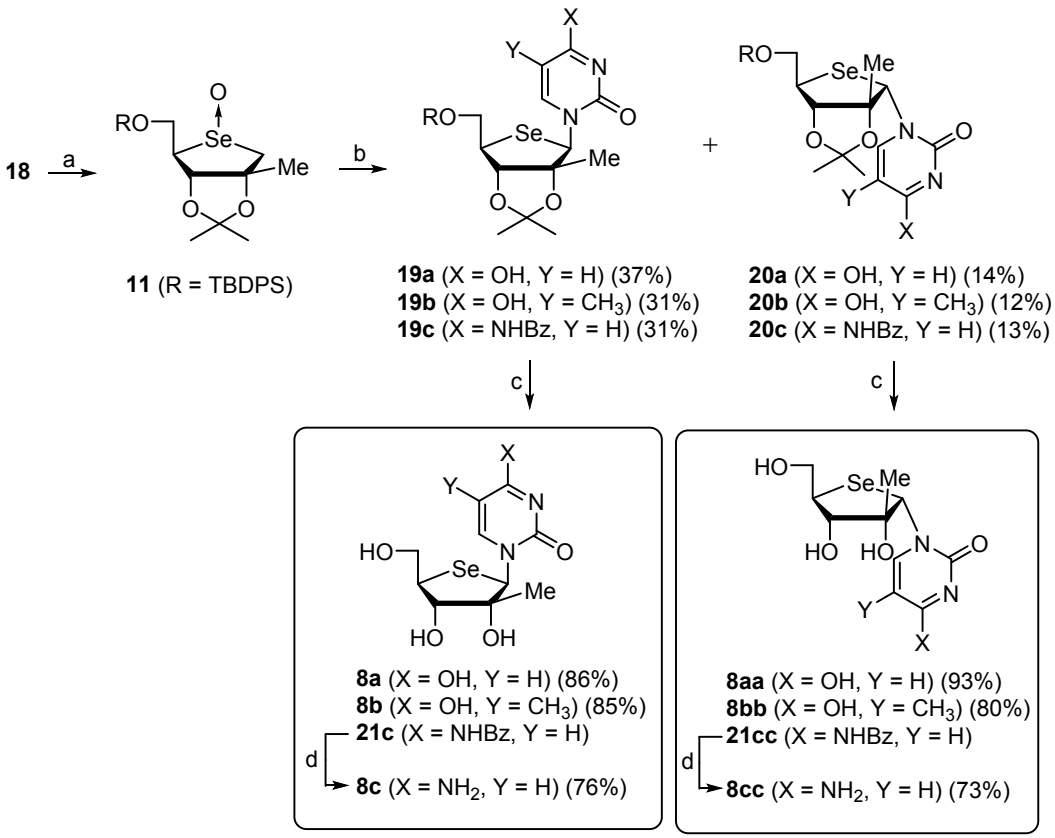


Reagent and conditions: (a) i. acetone, H_2SO_4 (*cat.*), $CuSO_4$, rt, 5 h; ii. MsCl, DMAP, pyridine, 0 °C-rt, 15 h; iii. KOH,dioxane/H_2O, 0 °C-rt, 4 h; (b) TBDPSCl, imidazole, CH_2Cl_2, rt, 12 h; (c) $LiBH_4$, ether,THF/H_2O, 0 °C to rt, 1.5 h; (d) MsCl, Et_3N, CH_2Cl_2, 0 °C- rt, 2 h; (e) Se, $NaBH_4$, DMF, EtOH, 140 °C, 5.5 h.

Scheme 2. Synthesis of 2-*C*-methyl-4-selenosugar **18**.

Synthesis of the final nucleosides **8** and **9** began with the synthesis of the key intermediate, 2-*C*-methyl-4-selenosugar **18**, starting from commercially available 2-*C*-methyl-D-ribono-γ-lactone (**14**), as shown in Scheme 2. The starting material **14** was converted to **15** in three steps, according to similar procedure used in the preparation of L-lyxono-γ-lactone from D-ribono-γ-lactone.[27] Briefly, treatment of **14** with acetone in the presence of a catalytic amount of sulfuric acid followed by the treatment with mesyl chloride afforded 5-mesyl-2-*C*-methyl-D-ribono-γ-lactone-2,3-*O*-isopropylidene. Without purification, the crude mesylate was treated with aqueous potassium hydroxide, upon which the inversion of the configuration at the C4 chiral center in **14** occurred to yield 2-*C*-methyl-L-lyxono-γ-lactone-2,3-

O-isopropylidene (**15**) via intramolecular S_N2 ring opening of the epoxide intermediate by the carboxylate nucleophile. The primary hydroxyl group of **15** was protected with TBDPS group to give **16**, which was directly subjected to reduction with $LiBH_4$ to give diol **13**. Mesylation of **13** followed by treatment of resulting dimesylate **17** with selenium powder in the presence of $NaBH_4$ in DMF-EtOH afforded the desired 2-*C*-methyl-4-selenosugar **18**.



Reagent and conditions: (a) *m*-CPBA, CH_2Cl_2, -78 °C, 45 min; (b) pyrimidine bases, TMSOTf, Et_3N, toluene/CH_2Cl_2, rt, 15 h; (c) TFA/H_2O (1/1), MeOH, rt, 4-14 h; (d) NH_3, MeOH, rt, 15 h.

Scheme 3. Synthesis of pyrimidine nucleosides **8a-c** and **8aa-cc**.

With the key precursor selenosugar **18** in hand, we first synthesized the desired pyrimidine nucleosides **8**, as illustrated in Scheme 3. The selenosugar **18** was oxidized to selenoxide **11**, which was directly condensed with various pyrimidine bases such as uracil, thymine, and N^4-benzoylcytosine using Pummerer rearrangement in the presence of TMSOTf and Et_3N to afford the β anomers **19a-c** and the α anomers **20a-c**, respectively. The anomeric configurations of **19a** and **20a** were confirmed on the basis of their 2D NOESY NMR spectral data, and also confirmed by further transformation of **19a** into **8a** whose structure was finally decided based on 2D NOESY, NOE, and the X-ray crystallography (vide infra). The 2D NOESY NMR spectrum of **19a** displayed a correlation between the 5′-H and H-6, indicating the β-anomeric configuration. Anomeric configurations of other pyrimidine nucleosides **19b-c** and **20b-c** were assigned based on their spectral characteristics and the comparison with the spectral features of **19a** and **20a**. For example, the chemical shifts of the β anomeric protons of **19a-c** in the NMR spectra appeared downfield relative to those of the α anomeric protons of **20a-c**. Treatment of **19a-c** with 50% aqueous trifluoroacetic acid afforded the **8a**, **8b**, and **21c**, respectively. Compound **21c** was further treated with methanolic ammonia to produce **8c.** Similarly, the α anomers **20a-c** were converted to the final nucleosides **8aa-cc**. The stereochemistry of the desired final nucleosides **8a-c** and **8aa-8cc** were confirmed by 2D NOESY NMR spectroscopy and comparison with the NMR spectral features of **8a** whose structure was established by X-ray crystallography

(see the Supporting Information, Figure S1). 2D NOESY spectrum of the β-anomer **8a** showed correlations between H-6 and protons 5′-H, 2′-*C*-methyl and 3′-H, confirming the β-anomeric configuration, while 2D NOESY NMR spectrum of α-anomer **8aa** indicated the correlation between 1′-H and 3′-H and also a correlation between 1′-H and 2′-*C*-methyl protons, demonstrating the α-anomeric configuration. Furthermore, due to the deshielding effects by heteroaromatic pyrimidine bases,[28] the chemical shifts of the 4′-H's in the β anomers **8a-c** appeared more upfield than those of the α anomers **8aa-cc**, while the 3′-H's of the β anomers **8a-c** appeared more downfield than those observed for the α anomers **8aa-cc**. The X-ray crystal structure of **8a** illustrated that it adopts a 2′-exo/3′-endo (North) conformation, which is opposite to that of 4′-selenouridine,[26] taking a 2′-endo/3′-exo (South) conformation. This conformational difference might be attributed to the steric effects between 2′-*C*-Me group and bulky selenium atom. We have also investigated the sugar conformation of **8a** in the solution state using 2D NOESY NMR spectroscopy because we could not determine the North or South conformation from the comparison of $^{3}J_{\text{H-H}}$ coupling constants in ^{1}H NMR due to the absence of 2′-H in the structure of **8a** (Figure 3).

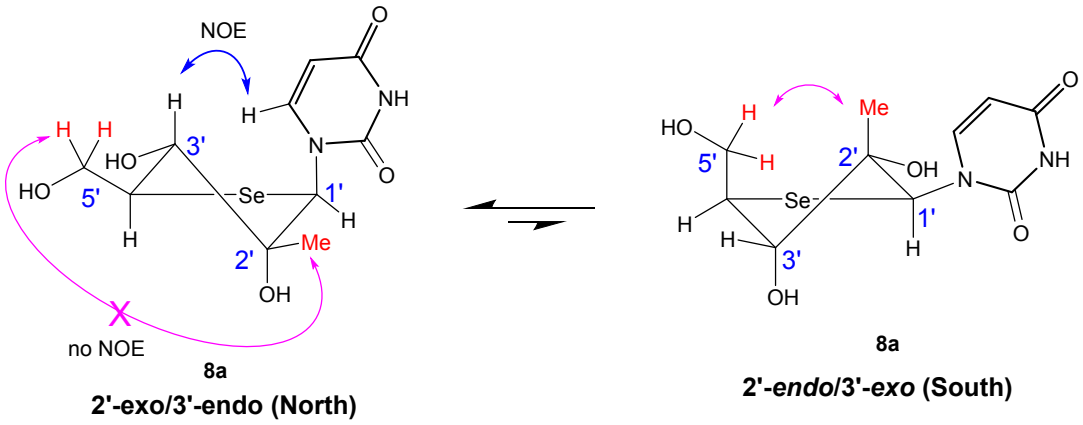
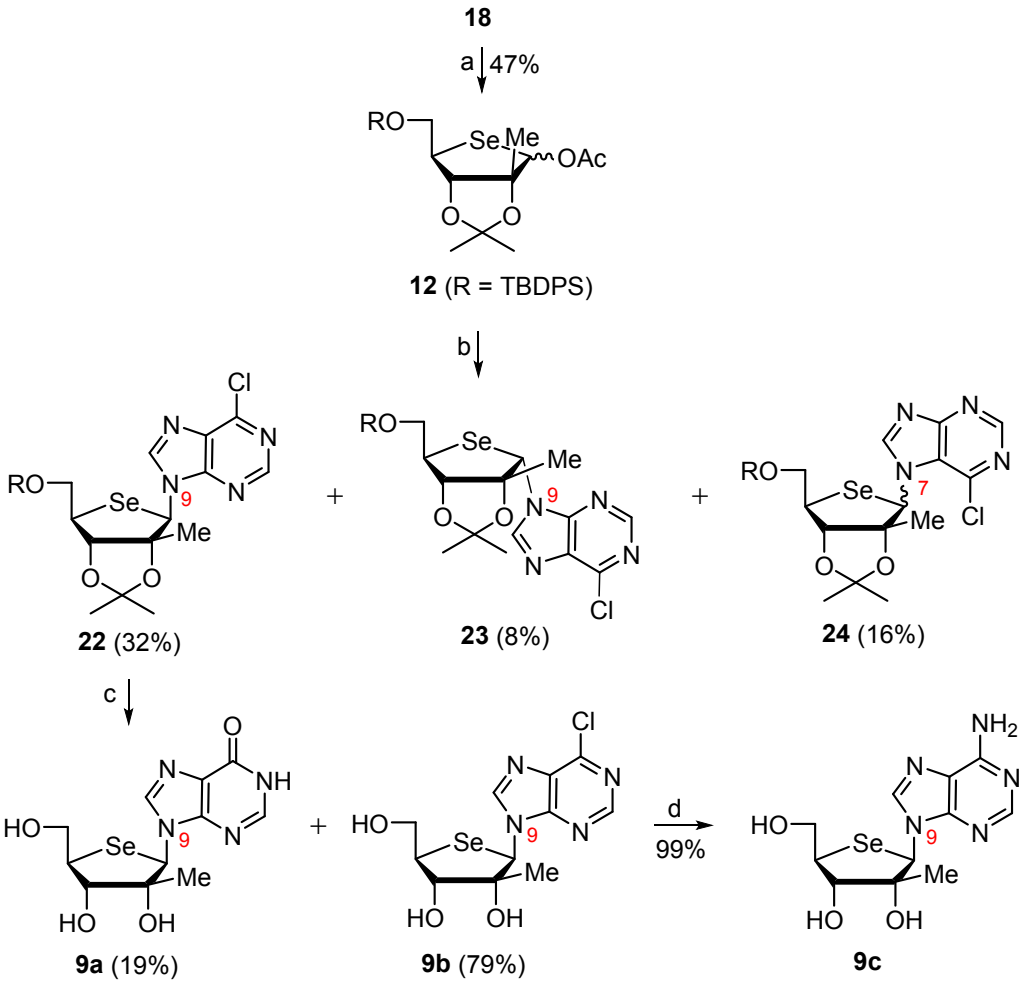


Figure 3. Confirmation of a North conformation in sugar puckering of **8a** in the solution state using 2D NOESY NMR spectroscopy.

2D NOESY spectrum of **8a** in D_2O displayed a strong NOE between H-6 and the 3'-H, whereas no correlation between 5'-H and 2'-Me, confirming that the North sugar conformation of **8a** is predominant in the solution state.



Reagent and conditions: (a) i, *m*-CPBA, CH_2Cl_2, -78 °C, 45 min, ii, Ac_2O, 50 °C, 15 h; (b) μW, 6-chloropurine, BSA, TMSOTf, toluene, 100 °C, 17 h; (c) TFA/H_2O (1/1), THF, rt, 12 h; (d) NH_3, *t*-BuOH, 88 °C, 20 h.

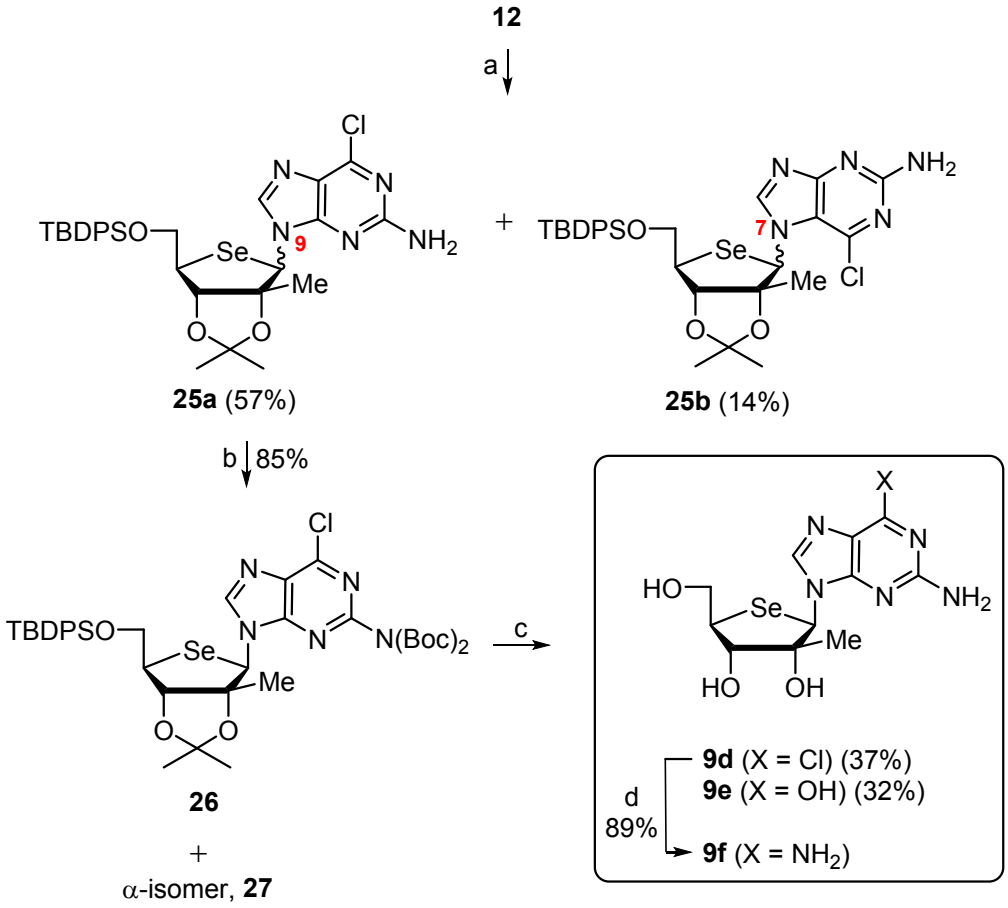
Scheme 4. Synthesis of N^6-substituted purine nucleosides **9a-c**

For the synthesis of 2′-*C*-Me-4′-seleno-N^6-substituted-purine nucleosides **9a-c**, the key intermediate **18** was converted to the glycosyl donor **12**, which is suitable for the Lewis acid-catalyzed Vorbrüggen condensation (Scheme 4). Thus, oxidation of **18** with *m*CPBA followed by heating with acetic anhydride at 50 °C gave **12**.

Condensation of **12** with silylated 6-chloropurine in the presence of TMSOTf under microwave conditions afforded N^9-β-anomer **22** (32%), N^9-α-anomer **23** (8%), and inseparable anomeric mixture (α:β = 1:3.4, based on ^{1}H NMR) of N^7-regioisomer **24** (16%). It is interesting to note that Vorbrüggen condensation without microwave irradiation gave the desired products in low yield. In order to improve the formation of desired β-anomer **22**, the direct condensation of selenoxide **11** with 6-chloropurine under Pummerer-type base condensation conditions, previously successful for the synthesis of pyrimidine analogues was also attempted, but no significant improvement was observed on anomeric ratio, regioisomeric ratio and condensation yield. It was extremely difficult to distinguish the N^9/N^7-regioisomers, along with α/β-stereoisomers, based on ^{1}H NMR spectra. First, the structural assignment of the N^9/N^7-regioisomers was accomplished by the comparison of UV and ^{1}H NMR spectra in the literature[25d] and finally by the X-ray crystallography. The UV spectra of **22** and **24** showed λ_{max}'s at 264.9 and 259.9 nm, indicating the N^9- and N^7-isomers, respectively. Secondly, anomeric configurations of **22** and **23** were confirmed by 2D NOESY NMR spectroscopy after the transformation of **22** into **9b**, which was further confirmed by the X-ray crystallography. Treatment of **22** with 50% TFA afforded **9b** along with the concomitant formation of the hydrolyzed product **9a**. Treatment of **9b** with *tert*-butanolic ammonia yielded **9c**. The 2D NOESY experiment of **9b** demonstrated the correlations between 3′-H, 5′-H, or 2′-*C*-methyl protons and H-8, confirming the β-anomeric configuration,

which was also determined by the X-ray crystallography, as shown in Figure S2 (see the Supporting Information). The 2D NOESY NMR analysis of **9b** revealed that it preferred the North sugar conformation in the solution state because of no NOE between 5'-H and 2'-Me (see the Supporting Information), which is the same as that obtained from the X-ray crystal structure of **9b**.

Using a similar strategy, 2′-*C*-Me-4′-seleno-2,6-disubstituted-purine nucleosides **9d-f** were synthesized according to the procedure shown in Scheme 5. Condensation of **12** with silylated 2-amino-6-chloropurine afforded an inseparable anomeric mixture of N^9-isomer **25a** (57%) with concomitant minor formation of an inseparable anomeric mixture of N_7-isomer **25b** (14%). The anomeric α and β ratios of N^9- and N^7-isomers were 1:3 and 1:2, respectively. In order to separate the anomers from mixture **25a**, it was protected with *tert*-butyloxycarbonyl (Boc) group to yield β-anomer **26** and its α-anomer **27** after separation by silica gel column chromatography.



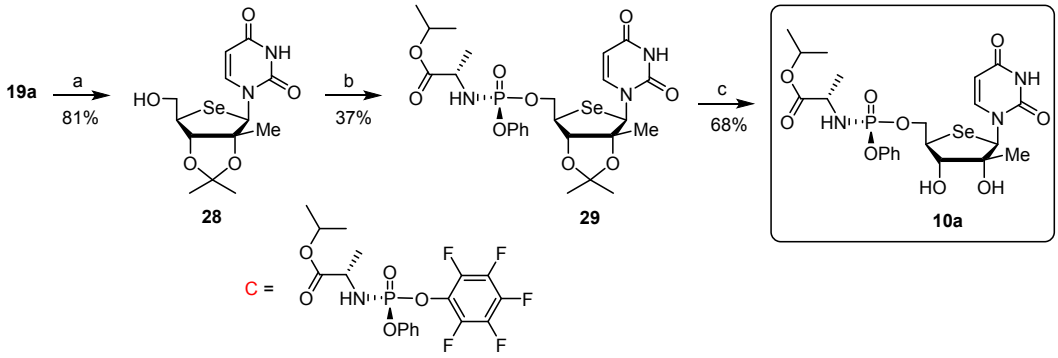
Reagent and conditions: (a) μW, 2-amino-6-chloropurine, BSA, TMSOTf, toluene, 100 °C, 15 h; (b) Boc_2O, DMAP, THF, rt, 15 h; (c) TFA/H_2O (1/1), THF, 28 °C, 12 h; (d) NH_3, *t*-BuOH, 95 °C, 68 h.

Scheme 5. Synthesis of 2,6-disubstituted purine nucleosides **9d-f**

Treatment of **26** with 50% TFA afforded 2-amino-6-chloropurine derivative **9d** along with its hydrolyzed guanine derivative **9e**. The anomeric configuration of **9d** was confirmed by 2D NOESY NMR experiment showing the correlation between 3′-H and H-8, and further by X-ray crystallography, illustrated in Figure S3 (see the

Supporting Information). Amination of **9d** with *tert*-butanolic ammonia yielded 2,6-diamino derivative **9f**.

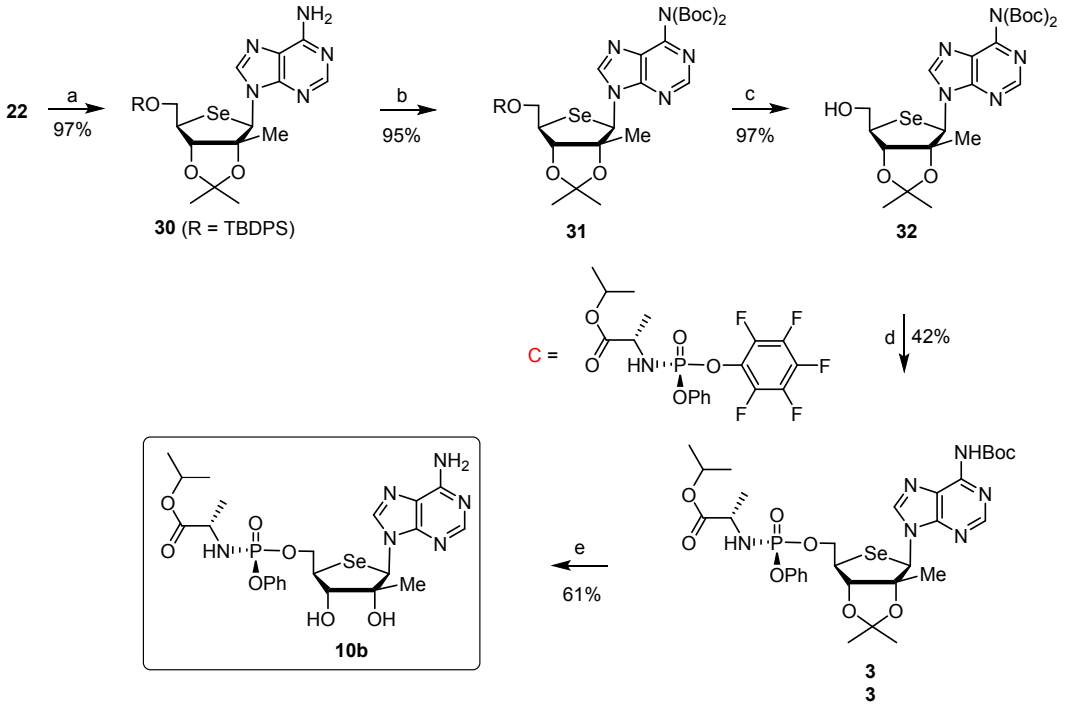
Phosphoramidate prodrugs have stimulated interest in the development of antiviral drug discovery due to their pharmacokinetics profiles.[14,16-18] They were especially synthesized to overcome the possibility of low cellular uptake and poor conversion to their corresponding 5′-monophosphate form by cellular kinases. Thus, we decided to synthesize the phosphoramidate prodrugs **10a-b** of 2′-*C*-methyl-4′-selenonucleosides **8a** and **9c**, as shown in Schemes **6** and **7**.



Reagent and conditions: (a) TBAF, THF, rt, 1.5 h; (b) C, *t*-BuMgCl, molecular sieves, THF, 0 °C-rt, 48 h; c) 50% HCO_2H, rt, 12 h.

Scheme 6. Synthesis of uracil phosphoramidate prodrug **10a**

The removal of the TBDPS group of **19a** with TBAF afforded the 5′-hydroxyl derivative **28**, which was treated with the phosphoramidate reagent (C)[29] in the presence of *tert*-butylmagnesium chloride to afford the phosphoramidate derivative **29** (Scheme 6). Treatment of **29** with 50% HCOOH yielded the final uracil phosphoramidate derivative **10a**.



Reagent and conditions: (a) NH_3, *t*-BuOH, 88 °C, 25 h; (b) Boc_2O, DMAP, THF, rt, 12 h; (c) TBAF, THF, rt, 30 min; (d) C, *t*-BuMgCl, Molecular sieves, THF, 0 °C-rt, 24 h; (e) 50% HCO_2H, rt, 12 h.

Scheme 7. Synthesis of adenine phosphoramidate prodrug **10b**

In order to synthesize the adenine phosphoramidate derivative **10b**, the key intermediate **22** was converted into **32** in three steps as shown in Scheme 7. N^6-Amination of **22** with *tert*-butanolic ammonia gave **30**, which was protected with Boc group to yield *N*,*N*-di-Boc derivative **31**. The removal of the TBDPS group of **31** produced **32,** which was treated with phosphoramidate reagent (C)[29] in the presence of *tert*-butylmagnesium chloride to afford **33** in 42% yield. Final removal of acetonide and Boc groups of **33** with 50% formic acid yielded the desired adenine phosphoramidate derivative **10b** in 61% yield.

Conclusion

In summary, the key intermediate, 2-*C*-methyl-D-4-selenosugar **18** was synthesized from 2-*C*-methyl-D-ribono-*γ*-lactone (**14**) via *C*4-epimerization and S_N2 cyclization with Se^{2-} as key steps. 2′-*C*-Methyl-4′-selenopyrimidine nucleosides **8a-c** were synthesized from condensation of selenoxide **11** with pyrimidine bases under a Pummerer-type rearrangement conditions, while 2′-*C*-methyl-4′-selenopurine nucleosides **9a-f** were synthesized from condensation of 4-selenoacetate **12** with silylated purine bases under Vorbrüggen conditions. In addition, 2′-*C*-Methyl-4′-selenouridine **19a** and 2′-*C*-methyl-4′-selenoadenosine **30** were converted to their corresponding phosphoramidate prodrugs **10a** and **10b** in order to circumvent the rate-determining 5′-monophosphorylation step of parent compounds by the cellular kinases. The structures of pyrimidine and purine nucleosides were confirmed by UV, NOE correlation, the NOESY NMR spectroscopy and X-ray crystallography. The X-ray crystallographic analyses of final nucleosides **8a**, **9b**, and **9d** indicated that they adopted the C2′-exo/C3′-endo (North) conformations, which are same as the corresponding 4′-oxonucleosides, which is opposite to that of 4′-selenoribofuranosyl nucleosides,[25d,26] taking a 2′-endo/3′-exo (South) conformation. This result might indicate that the effect of the 2′-methylation on the sugar puckering of 4′- selenoribofuranosyl nucleosides cancels the one induced by the 4′-selenium replacement. All the final nucleosides including prodrugs were assayed for anti-HCV activity, but they did not show significant anti-HCV activity up to 100 μM probably due to no phosphorylation by cellular kinases or slow hydrolysis

of phosphoramidate by steric effects induced by bulky selenium atom. We believe that the results described here may find applications in nucleic acid structural biology or enzyme mechanistic studies in determining the conformational preferences of kinases and nucleases, and will also contribute to the conformational studies of oligonucleotide containing 4′-selenonucleoside.

Experimental Section

General Methods

Proton (^{1}H) and carbon ^{13}C{^{1}H} NMR spectra were obtained on a Bruker AV 400 (400/100 MHz), AMX 500 (500/125 MHz), Jeol JNM-ECA 600 (600/150 MHz) or Bruker AVANCE III 800 (800/200 MHz) spectrometer. The ^{1}H NMR data were reported as peak multiplicities: s for singlet; d for doublet; dd for doublet of doublets; t for triplet; td for triplet of doublet; q for quartet; quin for quintet; bs for broad singlet and m for multiplet. Coupling constants were reported in Hertz. The chemical shifts were reported as ppm (δ) relative to the solvent peak. All reactions were routinely carried out under an inert atmosphere of dry nitrogen. IKA RCT basic type heating mantle was used to provide a constant heat source. Microwave-assisted reactions were carried out in sealed vessels using a Biotage Initiator+ US/JPN (part no. 356007) microwave reactor and the reaction

temperatures were monitored by an external surface IR sensor. High resolution mass spectra were measured with electrospray-ionization quadrupole time-of-flight (ESI-Q-TOF) techniques. Melting points were recorded on Barnstead electrothermal 9100 instrument and are uncorrected. Reactions were checked by thin layer chromatography (Kieselgel 60 F254, Merck). Spots were detected by viewing under a UV light, and by colorizing with charring after dipping in a *p*-anisaldehyde solution. The crude compounds were purified by column chromatography on a silica gel (Kieselgel 60, 70-230 mesh, Merck). All the anhydrous solvents were redistilled over CaH_2, or P_2O_5, or sodium/benzophenone prior to the reaction.

(*S*)-2-((*tert*-Butyldiphenylsilyl)oxy)-1-((4*R*,5*S*)-5-(hydroxymethyl)-2,2,5-trimethyl-1,3-dioxolan-4-yl)ethan-1-ol (13).

To a suspension of 2-*C*-Methyl-D-ribono-1,4-lactone (**14**) (25 g, 0.15 mol) in acetone (500 mL) were added anhydrous copper(II) sulfate (10 g) and catalytic concentrated sulfuric acid (2.5 mL) at room temperature under nitrogen atmosphere. After stirring for 5 h, the reaction mixture was neutralized with anhydrous sodium carbonate (63 g), filtered through a Celite bed, and washed with ethyl acetate. The filtrate was concentrated *in vacuo* to afford the acetonide, which was used directly for next step without any further purification,

To a solution of above obtained crude acetonide in pyridine (230 mL) were added

methanesulfonyl chloride (24 mL, 0.31 mol) and *N,N*-dimethylaminopyridine (1.9 g, 0.016 mol) under nitrogen atmosphere at 0 °C. After which the reaction mixture was stirred for 15 h at room temperature, concentrated *in vacuo*, and co-evaporated with toluene (70 mL x 2). The residue was dissolved in CH_2Cl_2 (250 mL) and washed with water (100 mL) and brine (100 mL). The aqueous layer was extracted with CH_2Cl_2 (150 mL x 3). The combined organic layers were dried over anhydrous magnesium sulfate and filtered. The filtrate was evaporated to give crude mesylate. To a solution of crude mesylate in dioxane (560 mL) was added a solution of potassium hydroxide (26.2 g, 0.467 mol) in water (440 mL) at 0 °C and the reaction mixture was stirred vigorously for 4 h at room temperature. After which it was acidified to pH 2 with 2 M hydrochloric acid. The reaction mixture was extracted with CH_2Cl_2 (150 mL x 3) and the combined organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was evaporated to give crude **15**[20](19 g), which was directly subjected to TBDPS protection reaction as follows. To a stirred solution of **15** (19 g) in CH_2Cl_2 (300 mL) were added imidazole (12.8 g, 0.188 mol) and *tert*-butyldiphenylsilyl chloride (25.8 g, 24.4 mL, 0.094 mol) at room temperature and the reaction mixture was stirred for 12 h at the same temperature. After which it was partitioned between dichloromethane (150 mL) and water (100 mL) and the organic layer was washed with brine (125 mL), dried over anhydrous $MgSO_4$, and evaporated to give crude **16** (35 g), which was directly used for next reduction step without any further purification as follows.

To a suspension of lithium borohydride (4.07 g, 0.187 mol) in ether (125 mL) was added a solution of **16** (35 g) in THF/H_2O (125 mL/2.5 mL) at 0 °C and the reaction mixture was stirred at room temperature for 1.5 h. After which it was neutralized with glacial acetic acid and brine (100 mL) was added to the mixture. The reaction mixture was extracted with ethyl acetate (200 mL x 3), dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 4/1) to give **13** (54 g, 79% from **14**) as a colorless syrup: $[\alpha]_D^{25}$ = -3.55 (*c* 0.45, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.66-7.70 (m, 4 H), 7.34-7.48 (m, 6 H), 3.97 (s, 1 H), 3.89-3.92 (m, 1 H), 3.82 (dd, *J* = 9.9, 6.2 Hz, 1 H), 3.72 (dd, *J* = 9.7, 6.9 Hz, 1 H), 3.62 (d, *J* = 11.9 Hz, 1 H), 3.42 (d, *J* = 11.9 Hz, 1 H), 3.15 (bs, 2 H), 1.48 (s, 3 H), 1.38 (s, 3 H), 1.29 (s, 3 H), 1.07 (s, 9 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 135.7, 133.2, 130.1, 130.0, 128.0, 127.9, 107.8, 81.8, 80.9, 68.23, 68.17, 65.7, 65.4, 28.1, 27.0, 26.8, 22.1, 19.3; HRMS (ESI-Q-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{25}H_{36}NaO_5Si^+$ 467.2224; Found 467.2235.

(*S*)-2-((*tert*-Butyldiphenylsilyl)oxy)-1-((4*R*,5*S*)-2,2,5-trimethyl-5-(((methylsulfonyl)oxy)methyl)-1,3-dioxolan-4-yl)ethyl methanesulfonate (17)

To a solution of **13** (25 g, 0.056 mmol) in CH_2Cl_2 (500 mL) were added triethylamine (47 mL, 0.337 mol) and methanesulfonyl chloride (17.4 mL, 0.225 mol) at 0 °C and the reaction mixture was stirred at room temperature for 2 h. After which it was diluted with saturated aqueous NH_4Cl solution (100 mL) and extracted

with dichloromethane (170 mL x 3). The combine organic layer was washed with brine (150 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was dissolved in ethyl acetate (300 mL), filtered through a pad of silica gel, and washed with ethyl acetate (100 mL x 2). After the combined filtrate was evaporated to give crude mesylate **17**, which was used for next reaction without further purification.

***tert*-Butyldiphenyl(((3a*S*,6a*R*)-2,2,6a-trimethyltetrahydroselenopheno[3,4-*d*][1,3]dioxol-4-yl)methoxy)silane (18)**

To a cooled (0 °C) suspension of selenium powder (11.2 g, 0.141 mol) in anhydrous ethanol (150 mL) was slowly added sodium borohydride (10 g, 0.264 mol) until the color of the reaction mixture changed from black to colorless. To this mixture was added a solution of crude mesylate **17** (33.95 g) in anhydrous DMF (500 mL) and the mixture was heated at 140 °C for 5.5 h and evaporated. The residue was diluted with water and extracted with *n*-hexane (300 mL x 3). The organic layer was washed with water (50 mL), brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 133/1) to give **18** (8.31 g, 30% in 2 steps) as pale yellow syrup: $[\alpha]_D^{25}$ = 68.49 (*c* 0.63, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.66-7.72 (m, 4 H), 7.37-7.45 (m, 6 H), 4.44 (s, 1 H), 3.74-3.80 (m, 3 H), 3.12 (d, *J* = 11.2 Hz, 1 H), 2.82 (d, *J* = 10.4 Hz, 1 H), 1.53 (s, 3 H), 1.42 (s, 3 H), 1.35 (s, 3 H), 1.08 (s, 9 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 135.65, 135.63, 133.21, 133.17,

129.83, 129.80, 127.8, 127.7, 110.6, 93.7, 90.7, 65.9, 46.9, 34.6, 28.3, 26.82, 26.75, 24.9, 19.3; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{35}O_3SeSi^+$ 491.1517; Found 491.1545.

General procedure for the synthesis of 19a-c and 20a-c (Pummerer-type pyrimidine base condensation)

[Oxidation] To a stirred solution of **18** (0.66 g, 1.348 mmol) in anhydrous CH_2Cl_2 (20 mL) was dropwise added a solution of 3-chloroperbenzoic acid (1.1 equiv, 70%) in CH_2Cl_2 (5 mL) at –78 °C under nitrogen atmosphere and the reaction mixture was stirred at the same temperature for 45 min. After which it was quenched with saturated aqueous $NaHCO_3$ solution, and diluted with CH_2Cl_2. The organic layer was washed with water (20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated below 10 °C to give **11** as colorless syrup. The residue **11** was used immediately for next step without further purification.

[Pummerer-type condensation] To a suspension of uracil or thymine or N^4-benzoylcytosine (2 equiv) in anhydrous toluene (7.0 mL) were dropwise added triethylamine (4 equiv) and trimethylsilyl trifluoromethanesulfonate (6 equiv) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 45 min and diluted with anhydrous CH_2Cl_2 (6.0 mL). To this mixture were dropwise added a solution of **11** (1 equiv) in CH_2Cl_2 (6.0 mL) and additional triethylamine (2 equiv) in toluene (0.5 mL) at 0 °C and the mixture was stirred at the room temperature for 15 h. The reaction mixture was quenched

with saturated aqueous $NaHCO_3$ solution, and diluted with CH_2Cl_2. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by repeated silica gel column chromatography (hexanes/ethyl acetate = 100/0 to 4/1) to give the β-anomers **19a-c** and the α-anomers **20a-c**, respectively.

1-((3a*R*,4*R*,6*R*,6a*S*)-6-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2,2,3a-trimethyltetrahydroselenopheno[3,4-*d*][1,3]dioxol-4-yl)pyrimidine-2,4(1*H*,3*H*)-dione (19a) and 1-((3a*R*,4*S*,6*R*,6a*S*)-6-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2,2,3a-trimethyltetrahydroselenopheno[3,4-*d*][1,3]dioxol-4-yl)pyrimidine-2,4(1*H*,3*H*)-dione (20a)

19a: Yield (299 mg, 37%, 2 steps), pale yellow foam; $[\alpha]_D^{25}$ = 38.20 (*c* 0.26, CH_3OH); UV (CH_3OH) λ_{max} 266.7 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.86 (bs, 1 H, N-*H*), 7.64-7.67 (m, 4 H, phenyl), 7.54 (d, *J* = 8.1 Hz, 1 H, C6-*H*), 7.38-7.46 (m, 6 H, phenyl), 6.57 (s, 1 H, C1′-*H*), 5.59 (d, *J* = 8.2 Hz, 1 H, C5-*H*), 4.28 (s, 1 H, C3′-*H*), 3.95-4.00 (m, 2 H, C4′-*H*, C5′-*H*a), 3.83 (dd, *J* = 13.4, 10.8 Hz, 1 H, C5′-*H*b), 1.62 (s, 3 H, O-C(CH_3)$_2$-O), 1.31 (s, 3 H, O-C(CH_3)$_2$-O), 1.18 (s, 3 H, C2′-CH_3), 1.06 (s, 9 H, C(CH_3)$_3$); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 162.6 (*C*4), 150.3 (*C*2), 143.3 (*C*6), 135.7 (phenyl), 135.6 (phenyl), 132.9 (phenyl), 132.8 (phenyl), 130.1 (phenyl), 130.0 (phenyl), 127.9 (phenyl), 127.8 (phenyl), 111.7 (O-*C*(CH$_3$)$_2$-

O), 102.1 (*C*5), 94.4 (*C*2′), 88.6 (*C*3′), 65.7 (*C*5′), 60.5 (*C*1′), 45.8 (*C*4′), 28.2(O-C(CH_3)$_2$-O), 26.83 (C(CH_3)$_3$), 26.79 (O-C(CH_3)$_2$-O), 20.0 (C2′-CH_3), 19.3 (C(CH$_3$)$_3$); HRMS (ESI-Q-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{29}H_{37}N_2O_5SeSi^+$ 601.1634; Found 601.1651.

20a: Yield (113 mg, 14%, 2 steps). pale yellow foam; $[\alpha]_D^{25}$ = 19.76 (*c* 0.23, CH_3OH); UV (CH_3OH) λ_{max} 265.4 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 (bs, 1 H), 7.87 (d, *J* = 8.2 Hz, 1 H), 7.65-7.68 (m, 4 H), 7.38-7.46 (m, 6 H), 6.22 (s, 1 H), 5.74 (d, *J* = 8.2 Hz, 1 H), 4.50 (s, 1 H), 3.82-3.88 (m, 3 H), 1.49 (s, 3 H), 1.43 (s, 3 H), 1.33 (s, 3 H), 1.07 (s, 9 H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 163.0, 150.8, 144.8, 135.21, 135.16, 132.4, 132.3, 130.1, 130.0, 128.0, 111.4, 100.7, 93.7, 90.8, 66.5, 61.2, 47.6, 26.6, 26.4, 26.0, 24.8, 18.8; HRMS (ESI-Q-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{29}H_{37}N_2O_5SeSi^+$ 601.1634; Found 601.1654.

1-((3a*R*,4*R*,6*R*,6a*S*)-6-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2,2,3a-trimethyltetrahydroselenopheno[3,4-*d*][1,3]dioxol-4-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (19b) and 1-((3a*R*,4*S*,6*R*,6a*S*)-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2,3a-trimethyltetrahydroselenopheno[3,4-*d*][1,3]dioxol-4-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (20b)

19b: Yield (256 mg, 31%, 2 steps), pale yellow foam; $[\alpha]_D^{25}$ = 29.29 (*c* 0.41, CH_3OH); UV (CH_3OH) λ_{max} 271.3 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (bs, 1 H),7.65-7.67 (m, 4 H), 7.37-7.46 (m, 6 H), 7.32 (s, 1 H), 6.55 (s, 1 H), 4.24 (s, 1

H), 3.95-4.00 (m, 2 H), 3.83 (dd, *J* = 12.8, 11.1 Hz, 1 H), 1.86 (s, 3 H), 1.62 (s, 3 H), 1.30 (s, 3 H), 1.21 (s, 3 H), 1.06 (s, 9 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 163.3, 150.5, 138.9, 135.62, 135.59, 132.89, 132.86, 130.01, 129.95, 127.9, 127.8, 111.6, 110.5, 94.0, 88.3, 65.8, 60.2, 45.3, 28.1, 26.8, 26.7, 19.8, 19.2, 12.6; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{30}H_{39}N_2O_5SeSi^+$ 615.1790; Found 615.1817.

20b: Yield (99 mg, 12%, 2 steps), pale yellow foam; $[\alpha]_D^{25} = 23.47$ (*c* 0.52, CH_3OH); UV (CH_3OH) λ_{max} 271.4 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (bs, 1 H) 7.65-7.69 (m, 5 H), 7.37-7.46 (m, 6 H), 6.27 (s, 1 H), 4.54 (s, 1 H), 3.85 (s, 3 H), 1.93 (s, 3 H), 1.48 (s, 3 H), 1.45 (s, 3 H), 1.35 (s, 3 H), 1.09 (s, 9 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 163.7, 151.0, 140.8, 135.63, 135.59, 132.73, 132.68, 129.98, 129.96, 127.8, 111.9, 109.4, 94.0, 91.5, 66.3, 61.2, 48.2, 26.8, 26.7, 26.3, 25.5, 19.2, 12.5; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{30}H_{39}N_2O_5SeSi^+$ 615.1790; Found 615.1807.

4-Amino-1-((3a*R*,4*R*,6*R*,6a*S*)-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2,3a-trimethyltetrahydroselenopheno[3,4-*d*][1,3]dioxol-4-yl)pyrimidin-2(1*H*)-one (19c) and 4-Amino-1-((3a*R*,4*S*,6*R*,6a*S*)-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2,3a-trimethyltetrahydroselenopheno[3,4-*d*][1,3]dioxol-4-yl)pyrimidin-2(1*H*)-one (20c)

19c: Yield (294 mg, 31% in 2 steps); pale yellow foam; $[\alpha]_D^{25} = -10.23$ (*c* 0.3, CH_3OH); UV (CH_3OH) λ_{max} 311.2 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* =

7.5 Hz, 1 H), 7.89 (d, J = 7.5 Hz, 2 H), 7.67 (merged dd, $J_1 = J_2$ = 6.8 Hz), 7.57 (merged dd, $J_1 = J_2$ = 7.3 Hz, 1 H), 7.38-7.50 (m, 9 H), 6.71 (s, 1 H), 4.39 (d, J = 1.3 Hz, 1 H), 3.96-4.05 (m, 2 H), 3.89 (dd, J = 8.5, 6.4 Hz, 1 H), 1.63 (s, 3 H), 1.33 (s, 3 H), 1.17 (s, 3 H), 1.08 (s, 9 H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 161.8, 147.9, 135.6, 135.5, 133.1, 132.9, 132.7, 129.97, 129.95, 128.9, 127.81, 127.78, 127.7, 127.6, 111.4, 96.9, 95.1, 89.9, 65.8, 63.0, 47.0, 28.2, 27.0, 26.8, 26.7, 20.6, 19.2; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{36}H_{42}N_3O_5SeSi^+$ 704.2057; Found 704.2072.

20c: Yield (123 mg, 13% in 2 steps); pale yellow foam; $[\alpha]_D^{25}$ = 21.46 (*c* 0.19, CH_3OH); UV (CH_3OH) λ_{max} 310.0 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 7.5 Hz, 1 H), 7.90 (d, J = 6.4 Hz, 2 H), 7.65-7.71 (m, 4 H), 7.59 (merged dd, $J_1 = J_2$ = 7.4 Hz, 1 H),, 7.38-7.52 (m, 9 H), 6.49 (s, 1 H), 4.58 (s, 1 H), 3.81-3.91 (m, 3 H), 1.54 (s, 3 H), 1.39 (s, 3 H), 1.33 (s, 3 H), 1.08 (s, 9 H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 161.8, 149.8, 135.5, 133.1, 133.0, 132.71, 132.70, 129.93, 129.90, 128.9, 127.81, 127.78, 127.7, 127.6, 111.9, 96.2, 96.1, 93.9, 91.6, 66.1, 62.3, 48.1, 26.8, 26.7, 26.2, 25.7, 19.2; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{36}H_{42}N_3O_5SeSi^+$ 704.2057; Found 704.2077.

General procedure for the synthesis of 8a-b and 8aa-bb

To a solution of **19a** or **20a** or **19b** or **20b** (100 mg, 0.1668 mmol) in methanol (1 mL) was dropwise added 50% aqueous trifluoroacetic acid solution (10 mL) at room temperature and the mixture was stirred at the same temperature for 4 to 14

h, concentrated *in vacuo*, and further coevaporated with toluene. The residue was purified by silica gel column chromatography (dichloromethane/methanol = 23/2) to give **8a** or **8aa** or **8b** or **8bb**, respectively.

8a: Yield (46 mg, 86%), as a white solid, mp 240-244 °C; $[\alpha]_D^{25}$ = 56.13 (*c* 0.17, CH_3OH); UV (CH_3OH) λ_{max} 267.1 nm; ^{1}H NMR (600 MHz, CD_3OD) δ 8.27 (d, *J* = 7.8 Hz, 1 H, C6-*H*), 6.15 (s, 1 H, C1′-*H*), 5.74 (d, *J* = 8.2 Hz, 1 H, C5-*H*)), 4.10 (dd, *J* = 11.2, 2.3 Hz, 1 H, C5′-*H*a), 3.92-3.95 (m, 1 H, C5′-*H*b), 3.71-3.72 (m, 2 H, C3′-*H*, C4′-*H*), 1.15 (s, 3 H, C2′-CH_3); ^{13}C{^{1}H} NMR (150 MHz, CD_3OD) δ 166.7 (*C*4), 153.6 (*C*2), 146.2 (*C*6), 103.4 (*C*5), 85.1 (*C*2′), 80.3 (*C*3′), 64.1 (*C*5′), 62.5 (*C*1′), 50.8 (*C*4′), 22.0 (C2′-*C*H_3); HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{15}N_2O_5Se^+$ 323.014; Found 323.0151.

8b: Yield (46 mg, 85%), as a white solid; mp 268-270 °C; $[\alpha]_D^{25}$ = 88.04 (*c* 0.04, CH_3OH); UV (CH_3OH) λ_{max} 271.7 nm; ^{1}H NMR (400 MHz, CD_3OD) δ 8.17 (d, *J* = 1.2 Hz, 1 H, C6-*H*), 6.12 (s, 1 H, C1′-*H*), 4.05 (dd, *J* = 11.7, 3.0 Hz, 1 H, C5′-*H*a), 3.96 (dd, *J* = 11.7, 5.2 Hz, 1 H, C5′-*H*b), 3.78 (d, *J* = 9.7 Hz, 1 H, C3′-*H*), 3.66-3.70 (m, 1 H, C4′-*H*), 1.88 (d, *J* = 1.1 Hz, 3 H, C5-CH_3), 1.14 (s, 3 H, C2′-CH_3); ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 167.0 (*C*4), 153.7 (*C*2), 141.8 (*C*6), 112.2

(*C*5), 85.1 (*C*2′), 80.0 (*C*3′), 63.3 (*C*5′), 62.7 (*C*1′), 50.7 (*C*4′), 22.1 (C2′-*C*H_3), 13.3 (C5-*C*H_3); HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{17}N_2O_5Se^+$ 337.0298; Found 337.0305.

8aa: Yield (50 mg, 93%), as a white solid; mp 112-116 °C; $[\alpha]_D^{25}$ = 24.80 (*c* 0.21, CH_3OH); UV (CH_3OH) λ_{max} 267.0 nm; ^{1}H NMR (400 MHz, CD_3OD) δ 8.22 (d, *J* = 8.4 Hz, 1 H, C6-*H*), 6.33 (s, 1 H, C1′-*H*), 5.66 (d, *J* = 8.4 Hz, 1 H, C5-*H*), 4.20 (dd, *J* = 11.0, 3.7 Hz, 1 H, C5′-*H*a), 4.00-4.06 (m, 1 H, C4′-*H*), 3.69 (dd, *J* = 11.0, 8.7 Hz, 1 H, C5′-*H*b), 3.53 (d, *J* = 10.0 Hz, 1 H, C3′-*H*), 1.19 (s, 3 H, C2′-C*H*$_3$); ^{13}C{^{1}H} NMR (125 MHz, CD_3OD) δ 167.1 (*C*4), 153.8 (*C*2), 148.6 (*C*6), 101.8 (*C*5), 82.4 (*C*2′), 81.8 (*C*3′), 66.4 (*C*5′), 56.7 (*C*1′), 51.8 (*C*4′), 24.5 (C2′-*C*H_3); HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{15}N_2O_5Se^+$ 323.0141; Found 323.0143.

8bb: Yield (43 mg, 80%), as a white solid; mp 74-78 °C; $[\alpha]_D^{25}$ = 21.54 (*c* 0.04, CH_3OH); UV (CH_3OH) λ_{max} 271.0 nm; ^{1}H NMR (400 MHz, CD_3OD) δ 8.06 (d, *J* = 1.2 Hz, 1 H, C6-*H*), 6.34 (s, 1 H, C1′-*H*), 4.22 (dd, *J* = 11.1, 3.7 Hz, 1 H, C5′-*H*a), 4.02-4.07 (m, 1 H, C4′-*H*), 3.71 (dd, *J* = 11.1, 8.8 Hz, 1 H, C5′-*H*b), 3.55 (d, *J* = 10.2 Hz, 1 H, C3′-*H*), 1.87 (d, *J* = 1.1 Hz, 3 H, C5-C*H*$_3$), 1.21 (s, 3 H, C2′-C*H*$_3$);

$^{13}C\{^{1}H\}$ NMR (100 MHz, CD_3OD) δ 167.2 (*C*4), 154.0 (*C*2), 144.2 (*C*6), 110.3 (*C*5), 82.5 (*C*2′), 81.7 (*C*3′), 66.4 (*C*5′), 56.6 (*C*1′), 51.7 (*C*4′), 24.4 (C2′-*C*H_3), 13.4 (C5-*C*H_3); HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{17}N_2O_5Se^+$ 337.0298; Found 337.0298.

4-Amino-1-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)-3-methyltetrahydroselenophen-2-yl)pyrimidin-2(1*H*)-one (8c) and 4-Amino-1-((2*S*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)-3-methyltetrahydroselenophen-2-yl)pyrimidin-2(1*H*)-one (8cc)

To a solution of **19c** or **20c** (28 mg, 0.0398 mmol) in methanol (0.5 mL) was dropwise added 50% aqueous trifluoroacetic acid solution (3.0 mL) at room temperature and the reaction mixture was stirred at the same temperature for 10 h, concentrated *in vacuo*, and further co-evaporated with toluene (10 mL) to give crude residue **21c** and **21cc**, respectively, which were directly subjected for deprotection of benzoyl group as follows.

The solution of **21c** or **21cc** in methanolic ammonia (5 mL) was stirred in glass-sealed tube at room temperature for 15 h. Solvent was evaporated and the residue was purified by reversed phase column chromatography, using distilled water as the eluent to give **8c** or **8cc,** respectively.

8c: Yield (9.65 mg, 76%, 2 steps), as a white solid, mp 256-259 °C; $[\alpha]_D^{25}$ = 80.18 (*c* 0.13, CH_3OH); UV (CH_3OH) λ_{max} 278.0 nm; ^{1}H NMR (500 MHz, CD_3OD) δ

8.27 (d, J = 7.6 Hz, 1 H), 6.32 (s, 1 H), 5.93 (d, J = 7.5 Hz, 1 H), 4.09 (dd, J = 11.6, 2.5 Hz, 1 H), 3.92-3.95 (m, 1 H), 3.69-3.71 (m, 2 H), 1.10 (s, 3 H); $^{13}C\{^{1}H\}$ NMR (125 MHz, CD_3OD) δ 167.3, 158.9, 147.1, 97.0, 85.2, 80.2, 64.1, 63.4, 50.7, 22.0; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{16}N_3O_4Se^+$ 322.0301; Found 322.0302.

8cc: Yield (9.27 mg, 73%, 2 steps), as a white solid, mp 141-145 °C; $[\alpha]_D^{25}$ = 50.38 (*c* 0.04, CH_3OH); UV (CH_3OH) λ_{max} 277.1 nm; ^{1}H NMR (400 MHz, CD_3OD) δ 8.25 (d, J = 7.6 Hz, 1 H), 6.51 (s, 1 H), 5.85 (d, J = 7.6 Hz, 1 H), 4.21 (dd, J = 11.0, 3.7 Hz, 1 H), 4.01-4.07 (m, 1 H), 3.71 (dd, J = 11.0, 8.9 Hz, 1 H), 3.56 (d, J = 10.1 Hz, 1 H), 1.19 (s, 3 H); $^{13}C\{^{1}H\}$ NMR (150 MHz, CD_3OD) δ 168.1, 159.9, 149.0, 95.7, 82.4, 81.9, 66.5, 57.2, 51.6, 24.4; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{16}N_3O_4Se^+$ 322.0301; Found 322.0305.

(3a*R*,6*R*,6a*S*)-6-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2,2,3a-trimethyltetrahydroselenopheno[3,4-*d*][1,3]dioxol-4-yl acetate (12)

[Oxidation] To a solution of **18** (1.03 g, 2.0997 mmol) in CH_2Cl_2 (30 mL) was dropwise added a solution of 70% 3-chloroperbenzoic acid (560 mg, 2.3097 mmol) in CH_2Cl_2 (10 mL) at –78 °C under nitrogen atmosphere and the reaction mixture was stirred at same temperature for 45 min. After which the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution, and diluted with CH_2Cl_2 (30 mL). The organic layer was washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated below 10 °C (water bath temperature) to give

selenoxifde **11**, which was immediately used for the next step without further purification.

[Acetylation] A solution of above-generated crude selenoxide **11** in acetic anhydride (10 mL) was stirred at 50 °C for 15 h under nitrogen atmosphere. The reaction mixture was evaporated and dissolved in ethyl acetate (80 mL). To this solution was carefully added aqueous $NaHCO_3$ solution (20 mL), and the organic layer was separated. After which organic layer was washed with water (20 mL), brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 97/3) to give **12** (0.54 g, 47%, 2 steps) as a pale yellow syrup: Major diastereomer: $[\alpha]_D^{25}$ = -82.72 (*c* 0.27, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.65-7.69 (m, 4 H), 7.37-7.46 (m, 6 H), 6.05 (s, 1 H), 4.79 (s, 1 H), 3.83 (dd, *J* = 9.6, 5.6 Hz, 1 H), 3.70-3.78 (m, 2 H), 1.90 (s, 3 H), 1.52 (s, 3 H), 1.40 (s, 3 H), 1.35 (s, 3 H), 1.08 (s, 9 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 169.1, 135.6, 135.5, 133.2, 133.0, 129.8, 127.7, 110.7, 95.6, 91.4, 83.0, 66.2, 49.7, 27.9, 27.1, 26.8, 22.2, 21.0, 19.2; HRMS (ESI-Q-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{27}H_{36}NaO_5SeSi^+$ 571.1391; Found 571.1389.

9-((3a*R*,4*R*,6*R*,6a*S*)-6-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2,2,3a-trimethyltetrahydroselenopheno[3,4-*d*][1,3]dioxol-4-yl)-6-chloro-9*H*-purine (22), 9-((3a*R*,4*S*,6*R*,6a*S*)-6-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2,2,3a-trimethyltetrahydroselenopheno[3,4-*d*][1,3]dioxol-4-yl)-6-chloro-9*H*-purine (23) and 7-((3a*R*,6*R*,6a*S*)-6-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2,2,3a-

trimethyltetrahydroselenopheno[3,4-*d*][1,3]dioxol-4-yl)-6-chloro-7*H*-purine (24)

To a suspension of 6-chloropurine (171 mg, 1.1044 mmol) in dry toluene (12 mL) in a microwave vial was added *N,O*-bis(trimethylsily)acetamide (BSA, 0.338 mL, 1.3805 mmol) under nitrogen atmosphere and the reaction mixture was stirred at 40 °C for 1 h to obtain the silylated 6-chloropurine, during the course a suspension becomes clear solution. To this clear solution were added a solution of **12** (504 mg, 0.9203 mmol) in dry toluene (8 mL) and trimethylsilyl trifluoromethanesulfonate (327 mg, 0.267 mL, 1.4725 mmol) at 40 °C and the reaction mixture was stirred at 100 °C in microwave for 17 h. After which it was quenched with saturated aqueous $NaHCO_3$ solution. The organic layer was separated and aqueous layer was extracted with ethyl acetate (200 mL x 3). The combine organic layer was washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by repeated silica gel column chromatography (hexane/ethyl acetate = 100/0 to 6/1 to 4/1) to give **22** (186.4 mg, 32%), **23** (46.6 mg, 8%), and N^7- anomeric mixture of **24** (97 mg, 16%) (β: α = 3.4:1, determined by ^{1}H NMR).

Compound **22**: as a yellow foam; $[\alpha]_D^{25}$ = 51.22 (*c* 0.22, CH_3OH); UV (CH_3OH) λ_{max} 264.9 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1 H), 8.34 (s, 1 H), 7.66-7.70 (m, 4 H), 7.40-7.51 (m, 6 H), 6.65 (s, 1 H), 4.37 (d, *J* =0.9 Hz, 1 H), 4.06-4.14 (m, 2 H), 3.87 (dd, *J* = 9.2, 6.9 Hz, 1 H), 1.75 (s, 3 H), 1.31 (s, 3 H), 1.13 (s, 3 H), 1.08 (s, 9 H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 152.3, 152.1, 151.1, 145.5, 135.6,

135.5, 132.7, 132.6, 131.5, 130.0, 127.85, 127.80, 111.8, 93.4, 87.9, 77.3, 77.2, 77.0, 76.8, 65.5, 57.5, 44.7, 28.2, 26.7, 26.1, 19.2, 19.1; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{30}H_{36}ClN_4O_3SeSi^+$ 643.1405; Found 643.1430.

Compound **23**: as a yellow foam; $[\alpha]_D^{25} = 43.72$ (*c* 0.22, CH_3OH); UV (CH_3OH) λ_{max} 265.0 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1 H), 8.59 (s, 1 H), 7.70-7.73 (m, 4 H), 7.33-7.49 (m, 6 H), 6.37 (s, 1 H), 4.66 (s, 1 H), 3.95 (s, 3 H), 1.53 (s, 3 H), 1.31 (s, 3 H), 1.25 (s, 3 H), 1.13 (s, 9 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.4, 152.2, 151.1, 147.5, 135.9, 135.94, 135.86, 132.9, 132.7, 131.5, 130.29, 130.27, 130.3, 128.8, 128.1, 127.8, 127.2, 112.6, 93.9, 92.3, 66.9, 59.2, 49.4, 27.1, 26.9, 26.6, 25.1, 19.5; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{30}H_{36}ClN_4O_3SeSi^+$ 643.1405; Found 643.1427.

Compound **24**: as a yellow foam; λ_{max} 259.9 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 8.89 and 8.88 (s, 2 H, β and α), 8.84 and 8.73 (s, 2 H, β and α), 7.65-7.70 (m, 8 H), 7.38-7.51 (m, 12 H), 6.94 and 6.31 (s, 2 H, α and β), 4.50 and 4.49 (d, *J* = 1.8 Hz, 2 H, β and α), 3.81-4.31 (m, 6 H), 1.64 and 1.59 (s, 6 H, α and β), 1.31 and 1.20 (s, 6 H, α and β), 1.09 (s, 18 H), 0.97 and 0.67 (s, 6 H, α and β); HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{30}H_{36}ClN_4O_3SeSi^+$ 643.1405; Found 643.1410.

9-((2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(hydroxymethyl)-3-methyltetrahydroselenophen-2-yl)-1,9-dihydro-6*H*-purin-6-one (9a) and (2*R*,3*R*,4*S*,5*R*)-2-(6-Chloro-9*H*-purin-9-yl)-5-(hydroxymethyl)-3-methyltetrahydroselenophene-3,4-diol (9b)

A solution of **22** (148 mg, 0.2305 mmol) in THF (0.9 mL) and 50% aqueous trifluoroacetic acid solution (3.2 mL) was stirred at room temperature for 12 h. The reaction mixture was evaporated and the residue was purified by flash silica gel column chromatography (dichloromethane/methanol = 16/1 to 6/1) to give **9a** (15 mg, 19%) and **9b** (66 mg, 79%).

Compound **9a**: as a white solid; mp 182-186 °C; $[\alpha]_D^{25}$ = 37.64 (*c* 0.04, CH_3OH); UV (CH_3OH) λ_{max} 250.2 nm; ^1H NMR (400 MHz, D_2O) δ 8.38 (s, 1 H), 8.03 (s, 1 H), 5.77 (s, 1 H), 4.06 (dd, *J* = 11.8, 3.8 Hz, 1 H), 3.88-3.94 (m, 2 H), 3.64-3.69 (m, 1 H), 0.77 (s, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, D_2O) (100 MHz, D_2O) δ 158.7, 149.2, 146.0, 142.5, 123.6, 83.4, 77.5, 62.0, 57.8, 57.4, 57.0, 47.9, 47.6, 47.3, 20.1; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{15}N_4O_4Se^+$ 347.0254; Found 347.0259.

Compound **9b**: as a white solid; mp 192-196 °C (decomposed); $[\alpha]_D^{25}$ = 68.22 (*c* 0.05, CH_3OH); UV (CH_3OH) λ_{max} 264.8 nm; ^1H NMR (500 MHz, CD_3OD), δ 9.07 (s, 1 H), 8.76 (s, 1 H), 6.10 (s, 1 H), 4.18 (dd, *J* = 11.4, 3.1 Hz, 1 H), 4.12 (d, *J* = 9.7 Hz, 1 H), 4.07 (dd, *J* = 11.4 Hz, 6.4 Hz, 1 H), 3.86-3.89 (m, 1 H), 0.91 (s, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, CD_3OD) δ 154.2, 153.9, 152.4, 149.8, 133.4, 85.0, 79.8, 64.1, 59.7, 51.0, 22.4; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{14}ClN_4O_3Se^+$ 364.9912; Found 364.9926.

(2*R*,3*R*,4*S*,5*R*)-2-(6-Amino-9*H*-purin-9-yl)-5-(hydroxymethyl)-3-methyltetrahydroselenophene-3,4-diol (9c)

A solution of **9b** (15 mg, 0.0412 mmol) in NH_3/*t*-BuOH (15 mL) was stirred at 88 °C in a steel bomb for 20 h. The reaction mixture was evaporated and the residue was purified by reversed phase column chromatography (distilled water/methanol = 17/3) to give **9c** (14 mg, 99%) as a white solid: mp 245-248 °C; $[\alpha]_D^{25}$ = 31.58 (*c* 0.03, CH_3OH); UV (CH_3OH) λ_{max} 260.9 nm; ^1H NMR (400 MHz, CD_3OD) (400 MHz, CD_3OD) δ 8.58 (s, 1 H), 8.19 (s, 1 H), 5.95 (s, 1 H), 4.16 (dd, *J* = 11.4, 3.2 Hz, 1 H), 4.00-4.08 (m, 2 H), 3.81-3.86 (m, 1 H), 0.88 (s, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD) δ 157.7, 154.0, 151.3, 143.5, 120.2, 84.4, 79.3, 63.7, 58.4, 50.2, 21.7; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{16}N_5O_3Se^+$ 346.0413; Found 346.0421.

9-((3a*R*,6*R*,6a*S*)-6-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2,2,3a-trimethyltetrahydroselenopheno[3,4-*d*][1,3]dioxol-4-yl)-6-chloro-9*H*-purin-2-amine (25a) and 7-((3a*R*,6*R*,6a*S*)-6-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2,2,3a-trimethyltetrahydroselenopheno[3,4-*d*][1,3]dioxol-4-yl)-6-chloro-7*H*-purin-2-amine (25b)

To a suspension of 2-amino-6-chloropurine (130 mg, 0.6391 mmol) in dry toluene (12 mL) in a microwave vial was added *N,O*-bis(trimethylsily)acetamide (0.547 mL, 2.2369 mmol) and the reaction mixture was stirred at 110 °C for 30 min under nitrogen to obtain the silylated 2-amono-6-chloropurine, during the course suspension becomes clear solution. To this clear solution were added a solution of **12** (350 mg, 0.6391 mmol) in dry toluene (6 mL) and trimethylsilyl

trifluoromethanesulfonate (0.185 mL, 1.0226 mmol) at room temperature and the reaction mixture was stirred at 100 °C in microwave for 15 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (50 mL) and extracted with ethyl acetate (200 mL). The organic layer was washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 7/3 to 2/3) to give N^9- anomeric mixture of **25a** (240 mg, 57%, α:β = 1:3, determined by ^{1}H NMR) as pale yellow foam and N^7- anomeric mixture of **25b** (59 mg, 14%, α:β = 1:2, determined by ^{1}H NMR) as yellow foam.

Compound **25a**: UV (CH_3OH) λ_{max} 311.0 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 and 7.96 (s, 2 H, α and β), 7.63-7.74 (m, 8 H), 7.39-7.48 (m, 12 H), 6.44 and 6.23 (s, 2 H, β and α), 5.10 and 5.06 (bs, 2 H, β and α), 4.66 and 4.34 (d, J = 1.4 Hz, 2 H, α and β), 3.81-4.08 (m, 6 H), 1.08-1.72 (m, 36 H); HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{30}H_{37}ClN_5O_3SeSi^+$ 658.1514; Found 658.1525.

Compound **25b**: UV (CH_3OH) λ_{max} 325.5 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 and 8.47 (s, 2 H, β and α), 7.65-7.69 (m, 8 H), 7.38-7.51 (m, 12 H), 6.77 and 6.18 (s, 2 H, α and β), 5.12 (bs, 4 H), 4.50 and 4.46 (d, J = 2.2 Hz, 2 H, β and α), 3.84-4.16 (m, 6 H), 1.62 and 1.54 (s, 6 H, α and β), 1.30 and 1.23 (s, 6 H, α and β), 1.09 and 1.08 (s, 18 H, β and α), 0.98 and 0.86 (2s, 6 H, α and β); HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{30}H_{37}ClN_5O_3SeSi^+$ 658.1514; Found 658.1519.

9-((3a*R*,6*R*,6a*S*)-6-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2,2,3a-trimethyltetrahydroselenopheno[3,4-*d*][1,3]dioxol-4-yl)-6-chloro-9*H*-purin-2-*N*,*N*-di-*t*-butyloxycarbonylamine (26) and its α-isomer (27)

To a solution of **25a** (200 mg, 0.3043 mmol) in THF (13 mL) were added DMAP (4 mg, 0.0304 mmol) and di-*tert*-butyl dicarbonate (266 mg, 1.2174 mmol) at room temperature and the reaction mixture was stirred at same temperature for 15 h. The solvent was evaporated and the residue was purified by repeated silica gel column chromatography (hexanes/ethyl acetate = 100/0 to 9/1) to give **26** (165.8 mg, 64%) and **27** (55.3 mg, 21%).

Compound **26**: white foam; $[\alpha]_D^{25}$ = 48.18 (*c* 0.57, CH_3OH); UV (CH_3OH) λ_{max} 271.3 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1 H), 7.66-7.69 (m, 4 H), 7.39-7.49 (m, 6 H), 6.56 (s, 1 H), 4.32 (s, 1 H), 4.02-4.10 (m, 2 H), 3.80-3.89 (m, 1 H), 1.67 (s, 3 H), 1.41 (s, 18 H), 1.26 (s, 3 H), 1.08 (s, 12 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) 153.0, 152.1, 151.3, 150.4, 146.3, 135.7, 135.6, 132.8, 132.7, 130.1, 129.8, 127.91, 127.89, 111.8, 93.4, 88.0, 83.5, 65.6, 57.7, 44.8, 28.4, 27.8, 26.8, 26.3, 19.2; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{40}H_{53}ClN_5O_7SeSi^+$ 858.2564; Found 858.2589.

Compound **27**: white foam; $[\alpha]_D^{25}$ = 2.84 (*c* 0.44, CH_3OH); UV (CH_3OH) λ_{max} 271.2 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1 H), 7.68-7.73 (m, 4 H), 7.38-7.48 (m, 6 H), 6.34 (s, 1 H), 4.65 (s, 1 H), 3.90-3.96 (m, 3 H), 1.49 (s, 3 H), 1.38 (s, 18 H), 1.29 (s, 3 H), 1.28 (s, 3 H), 1.12 (s, 9 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$)

δ 153.3, 152.0, 151.2, 150.5, 148.4, 136.0, 135.8, 132.9, 132.6, 130.3, 130.0, 128.1, 112.5, 93.8, 92.4, 83.7, 66.9, 59.3, 49.6, 28.1, 27.1, 27.0, 26.7, 25.0, 19.5; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{40}H_{53}ClN_5O_7SeSi^+$ 858.2564; Found 858.2583.

(2*R*,3*R*,4*S*,5*R*)-2-(2-Amino-6-chloro-9*H*-purin-9-yl)-5-(hydroxymethyl)-3-methyltetrahydroselenophene-3,4-diol (9d) and 2-Amino-9-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)-3-methyltetrahydroselenophen-2-yl)-1,9-dihydro-6*H*-purin-6-one (9e)

A solution of **26** (142 mg, 1.61 mmol) in THF (0.9 mL) and 50% aqueous trifluoroacetic acid solution (3 mL) was stirred at 28 ˚C for 12 h. The reaction mixture was evaporated and the residue was purified by silica gel column chromatography (dichloromethane/methanol = 93/7 to 4/1) to give **9d** (23 mg, 37%) and **9e** (19 mg, 32%).

Compound **9d**: as a white solid; mp 221-223 °C; $[\alpha]_D^{25}$ = 101.93 (*c* 0.04, CH_3OH); UV (CH_3OH) λ_{max} 311.1 nm; ^1H NMR (400 MHz, CD_3OD) δ 8.53 (s, 1 H), 5.86 (s, 1 H), 4.14 (dd, *J* = 11.5, 3.2 Hz, 1 H), 3.98-4.05 (m, 2 H), 3.78-3.83 (m, 1 H), 0.93 (s, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, CD_3OD) δ 162.5, 156.3, 152.6, 145.7, 125.7, 85.0, 80.0, 64.3, 58.8, 50.8, 22.4; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{15}ClN_5O_3Se^+$ 380.0021; Found 380.0035.

Compound **9e**: as a white solid; mp 249-253 °C (decomposed); $[\alpha]_D^{25}$ = 129.00 (*c* 0.03, CH_3OH); UV (CH_3OH) λ_{max} 259.2 nm; ^1H NMR (400 MHz, CD_3OD) δ 8.16

(s, 1 H), 5.78 (s, 1 H), 4.14 (dd, J = 11.3, 3.0 Hz, 1 H), 3.94-3.99 (m, 2 H), 3.76-3.81 (m, 1 H), 0.93 (s, 3 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, CD_3OD) δ 159.7, 155.5, 153.7, 140.1, 117.5, 84.5, 79.4, 63.8, 57.7, 50.0, 21.7; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{16}N_5O_4Se^+$ 362.0363; Found 362.0376.

(2*R*,3*R*,4*S*,5*R*)-2-(2,6-Diamino-9*H*-purin-9-yl)-5-(hydroxymethyl)-3-methyltetrahydroselenophene-3,4-diol (9f)

The solution of **9d** (13 mg, 0.0343 mmol) in NH_3/*t*-BuOH (15 mL) was stirred at 95 °C in a steel bomb for 68 h. The reaction mixture was evaporated and the residue was purified by flash silica gel column chromatography (dichloromethane/methanol = 22/3) to give **9f** (12 mg, 89%) as a white solid: mp 181-185 °C; $[\alpha]_D^{25}$ = 52.89 (*c* 0.023, CH_3OH); UV (CH_3OH) λ_{max} 283.1 nm; ^{1}H NMR (400 MHz, CD_3OD) δ 8.19 (s, 1 H), 5.79 (s, 1 H), 4.14 (dd, J = 11.5, 3.2 Hz, 1 H), 3.96-4.03 (m, 2 H), 3.78-3.82 (m, 1 H), 0.92 (s, 3 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, CD_3OD) δ 162.1, 157.9, 153.5, 140.3, 114.2, 84.5, 79.5, 63.8, 57.9, 50.0, 21.7; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{17}N_6O_3Se^+$ 361.0522; Found 361.0534.

1-((3a*R*,4*R*,6*R*,6a*S*)-6-(Hydroxymethyl)-2,2,3a-trimethyltetrahydroselenopheno[3,4-*d*][1,3]dioxol-4-yl)pyrimidine-2,4(1*H*,3*H*)-dione (28)

To a stirred solution of **19a** (275 mg, 0.4586 mmol) in THF (20 mL) was added TBAF (1 M solution in THF, 0.688 mL, 0.688 mmol) and the reaction mixture was

stirred at room temperature for 1.5 h. After which it was quenched with saturated aqueous NH_4Cl solution and diluted with ethyl acetate (40 mL) and brine (25 mL). The organic layer was separated and aqueous layer was extracted with ethyl acetate (60 mL x 3). The combined organic extract was dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (dichloromethane/methanol = 39/1) to give **28** (134 mg, 81%) as white foam: $[\alpha]_D^{25}$ = 32.04 (*c* 0.3, CH_3OH); UV (CH_3OH) λ_{max} 267.3 nm; ^1H NMR (500 MHz, CD_3OD) δ 8.16 (d, *J* = 8.1 H, 1 H, C6-*H*), 6.50 (s, 1 H, C1′-*H*), 5.71 (d, *J* = 8.1 Hz, 1 H, C5-*H*), 4.55 (d, *J* = 1.2 Hz, 1 H, C3′-*H*), 3.93 (dd, *J* = 13.7, 9.2 Hz, 1 H, C5′-*H*a), 3.82-3.86 (m, 2 H, C4′-*H*, C5′-*H*b), 1.58 (s, 3 H, O-C(CH_3)$_2$-O), 1.35 (s, 6 H, O-C(CH_3)$_2$-O, C2′-CH_3); $^{13}C\{^1H\}$ NMR (125 MHz, CD_3OD) δ 166.7 (*C*4), 153.2 (*C*2), 147.0 (*C*6), 113.0 (O-*C*(CH_3)$_2$-O), 103.2 (*C*5), 98.1 (*C*2′), 93.3 (*C*3′), 66.2 (*C*5′), 64.5 (*C*1′), 49.5 (merged with solvent peak, *C*4′), 29.5 (O-C(*C*H_3)$_2$-O), 28.2 (O-C(*C*H_3)$_2$-O), 21.9 (C2′-*C*H_3); HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{19}N_2O_5Se^+$ 363.0454; Found 363.0466.

iso-Propyl ((_S_)-(((3a_S_,4_R_,6_R_,6a_R_)-6-(2,4-dioxo-3,4-dihydropyrimidin-1(2_H_)-yl)-2,2,6a-trimethyltetrahydroselenopheno[3,4-_d_][1,3]dioxol-4-yl)methoxy)(phenoxy)phosphoryl)-_L_-alaninate (29)

To a cooled (0 °C) suspension of **28** (20 mg, 0.055 mmol) and powdered molecular sieves (4 Å, 30 mg) in anhydrous THF (15 mL) was added a *tert*-butylmagnesium chloride solution (1.0 M solution in THF, 0.27 mL, 0.27 mmol) under nitrogen atmosphere and the reaction mixture was stirred at the same temperature for 5 min. To this reaction mixture was added a solution of pentafluro-phosphoramidate reagent (C)[29] (27 mg, 0.060 mmol) in anhydrous THF (7 mL) and the reaction mixture was stirred at room temperature for 48 h. After which it was cooled in an ice bath, and quenched by dropwise addition of methanol (40 mL). The reaction mixture was filtered through a Celite bed, washed with methanol (20 mL), and filtrate was evaporated. The residue was purified by silica gel column chromatography (dichloromethane/methanol = 19/1) to give **29** (12.5 mg, 37%) as colorless liquid: $[\alpha]_D^{25}$ = 16.26 (*c* 0.4, CH_3OH); UV (CH_3OH) λ_{max} 267.1 nm; ^1H NMR (400 MHz, CD_3OD) δ 7.81 (d, *J* = 8.1 Hz, 1 H), 7.36 (merged dd, $J_1 = J_2$ = 7.9 Hz, 2 H), 7.25 (d, *J* = 7.7 Hz, 2 H), 7.19 (merged dd, $J_1 = J_2$ = 7.4 Hz, 1 H), 6.28 (s, 1 H), 5.68 (d, *J* = 8.0 Hz, 1 H), 4.93-5.02 (m, 1 H), 4.61 (d, *J* = 2.1 Hz, 1 H), 4.51-4.57 (m, 1 H), 4.34-4.40 (m, 1 H), 3.87-3.95 (m, 2 H), 1.57 (s, 3 H), 1.32-1.36 (m, 9 H), 1.24 (d, *J* = 6.3 Hz, 3 H), 1.23 (d, *J* = 6.3 Hz, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD) δ 174.5 (d, *J* = 4.8 Hz), 166.1, 152.3 (d, *J* = 6.7 Hz), 152.1,

146.4, 130.9, 126.4, 121.6 (d, J = 4.8 Hz), 112.5, 102.8, 97.8, 92.8, 70.3, 69.8 (d, J = 4.8 Hz), 65.8, 51.8, 46.8 (d, J = 7.7 Hz), 28.9, 28.2, 22.19, 22.08, 21.5, 20.6 (d, J = 6.7 Hz); HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{35}N_3O_9PSe^+$ 632.1273; Found 632.1292.

iso-Propyl ((*S*)-(((2*R*,3*S*,4*R*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-3,4-dihydroxy-4-methyltetrahydroselenophen-2-yl)methoxy)(phenoxy)-phosphoryl)-*L*-alaninate (10a)

A solution of **29** (11 mg, 0.017 mmol) in 50% aqueous formic acid (5 mL) was stirred at room temperature for 12 h and evaporated at 25 °C. The residue was purified by silica gel column chromatography (dichloromethane/methanol = 9/1), followed by lyophilization (H_2O/acetonitrile = 3:1, 2 mL) to give **10a** (7 mg, 68%) as a white solid: mp 68-72 °C; $[\alpha]_D^{25}$ = 9.75 (*c* 0.017, CH_3OH); UV (CH_3OH) λ_{max} 267.1 nm; ^{1}H NMR (500 MHz, CD_3OD) δ 8.09 (d, J = 8.2 Hz, 1 H), 7.36 (merged dd, $J_1 = J_2$ = 7.9 Hz, 2 H), 7.26 (d, J = 8.5 Hz, 2 H), 7.19 (merged dd, $J_1 = J_2$ = 7.3 Hz, 1 H), 6.17 (s, 1H), 5.69 (d, J = 8.1 Hz, 1 H), 4.94-5.01 (m, 1 H), 4.64-4.67 (m, 1 H), 4.47-4.52 (m, 1 H), 3.88-3.94 (m, 1 H), 3.82-3.86 (m, 1 H), 3.70 (d, J = 9.9 Hz, 1 H), 1.35 (d, J = 7.1 Hz, 3 H), 1.23 (d, J = 6.3 Hz, 3 H), 1.22 (d, J = 6.3 Hz, 3 H), 1.15 (s, 3 H); ^{13}C{^{1}H} NMR (200 MHz, CD_3OD) δ 175.2 (d, J = 5.3 Hz), 166.6, 153.5, 153.0 (d, J = 6.6 Hz), 145.9, 131.6, 126.9, 122.1 (d, J = 4.8 Hz), 103.6, 84.5, 80.2, 70.9, 69.7 (d, J = 10.3 Hz), 62.8, 52.5, 47.4 (d, J = 8.3 Hz), 22.8, 22.7, 21.9,

21.4 (d, J = 6.5 Hz); HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{31}N_3O_9PSe^+$ 592.0959; Found 592.0999.

9-((3a*R*,4*R*,6*R*,6a*S*)-6-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2,2,3a-trimethyltetrahydroselenopheno[3,4-*d*][1,3]dioxol-4-yl)-9*H*-purin-6-amine (30)

A solution of **22** (110 mg, 0.1713 mmol) in NH_3/*t*-BuOH (15 mL) was stirred at 88 °C in a steel bomb for 25 h and evaporated. The residue was purified by silica gel column chromatography (dichloromethane/methanol = 49/1) to give **30** (104 mg, 97%) as a white solid: mp 157-161 °C; $[\alpha]_D^{25}$ = 37.90 (*c* 0.057, CH_3OH); UV (CH_3OH) λ_{max} 260.9 nm; ^1H NMR (400 MHz, CD_3OD) δ 8.17 (s, 1 H), 8.10 (s, 1 H), 7.63-7.69 (m, 4 H), 7.36-7.45 (m, 6 H), 6.46-6.54 (m, 1 H), 4.51 (s, 1 H), 4.12-4.19 (m, 1 H), 3.95-4.02 (m, 2 H), 1.64 (s, 3 H), 1.28 (s, 3 H), 1.07 (s, 3 H), 1.04 (s, 9 H); $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD) δ 157.4, 154.1, 151.4, 142.9, 137.01, 136.96, 134.4, 134.3, 131.4, 131.3, 129.2, 129.1, 120.2, 112.9, 95.9, 90.6, 67.3, 59.3, 47.3, 28.9, 27.5, 27.3, 20.6, 20.2; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{30}H_{38}N_5O_3SeSi^+$ 624.1906; Found 624.1926.

***iso*-Propyl ((*S*)-(((3aS,4*R*,6R,6aR)-6-(6-((*tert*-butoxycarbonyl)amino)-9*H*-purin-9-yl)-2,2,6a-trimethyltetrahydroselenopheno[3,4-*d*][1,3]dioxol-4-yl)methoxy)(phenoxy)phosphoryl)-*L*-alaninate (33)**

[Boc protection]

A solution of **30** (75 mg, 0.1204 mmol), DMAP (44 mg, 0.3613 mmol), and di-*tert*-butyl dicarbonate (158 mg, 0.7227 mmol) in THF (15 mL) was stirred at room

temperature for 12 h. The reaction mixture was evaporated and the residue was purified by silica gel column chromatography (hexanes/ethyl acetate = 4/1) to give **31** (94 mg, 95%) as colorless liquid: $[\alpha]_D^{25}$ = 20.91 (*c* 0.18, CH_3OH); UV (CH_3OH) λ_{max} 267.1 nm; ^1H NMR (500 MHz, $CDCl_3$) δ 8.82 (s, 1 H), 8.29 (s, 1 H), 7.67-7.68 (m, 4 H), 7.38-7.47 (m, 6 H), 6.64 (s, 1 H), 4.39 (s, 1 H), 4.04-4.08 (m, 2 H), 3.87-3.91 (m, 1 H), 1.74 (s, 3 H), 1.43 (s, 18 H), 1.31 (s, 3 H), 1.10 (s, 3 H), 1.08 (s, 9 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 153.6, 152.4, 150.41, 150.36, 145.0, 135.63, 135.58, 132.8, 132.7, 130.0, 128.6, 127.89,127.85, 111.7, 93.7, 88.4, 83.7, 65.7, 57.7, 44.8, 28.3, 27.8, 26.8, 26.3, 19.4, 19.2; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{40}H_{54}N_5O_7SeSi^+$ 824.2956; Found 824.2931.

[Removal of TBDPS group]

Compound **31** (95 mg, 0.1154 mmol) was converted to **32** (65 mg, 97%), according to the same procedure described in the preparation of **28,** as a pale yellow foam after silica gel column chromatography (hexanes/ethyl acetate = 6/4),: $[\alpha]_D^{25}$ = 6.36 (*c* 0.04, CH_3OH); UV (CH_3OH) λ_{max} 268.5 nm; ^1H NMR (500 MHz, CD_3OD) δ 9.02 (s, 1 H), 8.87 (s, 1 H), 6.70 (s, 1 H), 4.71 (s, 1 H), 3.99-4.06 (m, 2 H), 3.94 (dd, *J* = 5.5, 10.2 Hz, 1 H), 1.71 (s, 3 H), 1.37 (s, 21 H), 1.23 (s, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD) δ 155.3, 153.4, 151.5, 151.2, 148.9, 130.3, 112.6, 96.9, 92.6, 85.5, 65.5, 61.2, 28.8, 28.1, 27.0, 20.7; HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{36}N_5O_7Se^+$ 586.1776; Found 586.1793.

[Synthesis of phosphoramidate]

Compound **32** (16 mg, 0.027 mmol) was converted to adenine phosphoramidate **33** (8.7 mg, 42%) by using the same procedure described in the preparation of uracil phosphoramidate **29**, as colorless liquid after silica gel column chromatography (dichloromethane/methanol = 9:1), $[\alpha]_D^{25}$ = 17.07 (*c* 0.16, CH_3OH); UV (CH_3OH) λ_{max} 261.4 nm; ^{1}H NMR (500 MHz, CD_3OD) δ 8.59 (s, 1 H), 8.51 (s, 1 H), 7.37 (merged dd, $J_1 = J_2$ = 7.8 Hz, 2 H), 7.27 (d, J = 8.2 Hz, 2 H), 7.20 (merged dd, $J_1 = J_2$ = 7.4 Hz, 1 H), 6.63 (s, 1 H), 4.94-4.99 (m, 1 H), 4.76 (s, 1 H), 4.66-4.71 (m, 1 H), 4.42-4.46 (m, 1 H), 4.05-4.08 (m, 1 H), 3.91-3.95 (m, 1 H), 1.68 (s, 3 H), 1.57 (s, 9 H), 1.35-1.36 (m, 6 H), 1.22-1.23 (m, 9 H); ^{13}C{^{1}H} NMR (150 MHz, CD_3OD) δ 175.2 (d, J = 5.0 Hz), 154.1, 153.4 (d, J = 53.1 Hz), 153.0 (d, J = 6.4 Hz), 152.2, 146.2, 131.6, 130.9 (d, J = 10.0 Hz), 127.0, 123.9, 122.3 (d, J = 4.3 Hz), 113.5, 97.5, 92.6, 83.6, 70.79, 70.12 (d, J = 5.0 Hz), 61.7 (d, J = 2.9 Hz), 52.5, 45.9 (d, J = 7.9 Hz), 29.5, 29.2, 28.1, 22.83, 22.72, 21.71 (d, J = 6.4 Hz); HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{31}H_{44}N_6O_9PSe^+$ 755.2070; Found 755.2108.

***iso*-Propyl ((*S*)-(((2*R*,3*S*,4*R*,5*R*)-5-(6-amino-9*H*-purin-9-yl)-3,4-dihydroxy-4-methyltetrahydroselenophen-2-yl)methoxy)(phenoxy)phosphoryl)-*L*-alaninate (10b)**

Compound **33** (12 mg, 0.015 mmol) was converted to adenine phosphoramidate prodrug **10b** (5.96 mg, 61%) by following the same procedure described for the preparation of uracil prodrug **10a**, as a white solid after silica gel column chromatography (dichloromethane/methanol = 9:1), followed by lyophilization

(H_2O/acetonitrile = 3:1, 2 mL): mp 100-104 °C; $[\alpha]_D^{25}$ = 15.96 (*c* 0.02, CH_3OH); UV (CH_3OH) λ_{max} 261.4 nm; ^1H NMR (500 MHz, CD_3OD) δ 8.44 (s, 1 H), 8.22 (s, 1 H), 7.36 (merged dd, $J_1 = J_2 = 8$ Hz, 2 H), 7.32 (d, $J = 8.2$ Hz, 2 H), 7.19 (merged dd, $J_1 = J_2 = 7.4$ Hz, 1 H), 6.01 (s, 1 H), 4.93-4.98 (m, 1 H), 4.74-4.78 (m, 1 H), 4.57-4.62 (m, 1 H), 4.12 (d, $J = 9.8$ Hz, 1 H), 3.91-4.00 (m, 2 H), 1.36 (d, $J = 7.2$ Hz, 3 H), 1.21 (d, $J = 6.3$ Hz, 3 H), 1.17 (d. $J = 6.3$ Hz, 3 H), 0.91 (s, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD) δ174.6 (d, $J = 5.8$ Hz), 157.6, 154.1, 152.4 (d, $J = 6.7$ Hz) 151.3, 143.2, 131.0, 126.3, 121.6 (d, $J = 4.8$ Hz), 120.3, 84.0, 79.5, 70.3, 69.7 (d, $J = 4.8$ Hz), 58.7, 51.8, 46.8 (d, $J = 8.6$ Hz), 22.15, 22.06, 21.6, 20.8 (d, $J = 6.7$ Hz); HRMS (ESI-Q-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{32}N_6O_7PSe^+$ 615.1231; Found 615.1270.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website http://pubs.acs.org. at DOI:

^1H, $^{13}C\{^1H\}$ NMR, and 2D NMR copies of all new compounds (PDF).

X-ray crystallography data of compounds **8a, 9b**, and **9d** (ZIP)

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Notes

The authors declare no competing financial interest.

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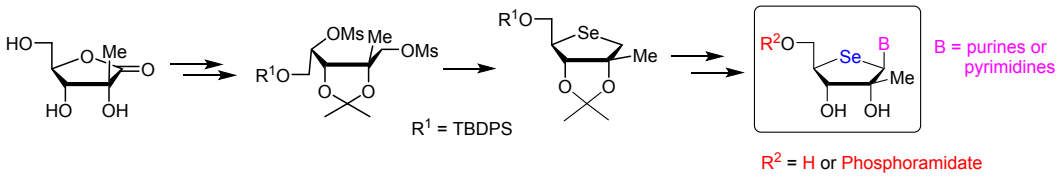
TOC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B = purines or pyrimidines
R2 = H or Phosphoramidate