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Stereoselective synthesis of 4′-selenonucleosides using the Pummerer glycosylation reaction

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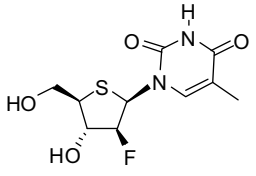
Abstract—The syntheses of four selenonucleosides, namely 4′-β-selenoadenosine, -cytidine, -thymidine, and -uridine are described. Commercially available D-ribonolactone was converted to the key intermediate 1,4-anhydro-4-seleno-D-ribitol in seven steps in overall excellent yield. Oxidation of the seleno-D-ribitol with MCPBA gave a single diastereomeric selenoxide in excellent yield, which upon Pummerer reaction in the presence of silylated purine or pyrimidine bases gave stereoselectively the corresponding 4′-β-selenonucleosides. The stereochemistry at the anomeric center was determined by means of 1D-NOE experiments.

Keywords: Selenonucleosides; Purine base; Pyrimidine bases; Pummerer reactions; Selenoxides

1. Introduction

The substitution of one or more oxygen atoms in nucleosides by other heteroatoms, most notably by sulfur, has been the subject of numerous synthetic studies.[1] The potent antiviral activity of some of the modified nucleosides has given impetus to these studies and many thio-substituted derivatives have been prepared and tested.[2] More recently, 4′-thionucleotides were incorporated into short RNA oligonucleotides to stabilize some small interfering RNA (siRNA) duplex constructs that are being developed for therapeutic gene-silencing purposes.[3] Encouragingly, the incorporation of only a few 4′-thionucleotides at either the 3′ or the 5′ end of the sense and/or the antisense stands gave significant resistance to nucleosidase degradation without adversely affecting the gene-silencing activity.[4] We have reported similar studies using 2′-F-substituted-4′-thioarabinonucleoside **1**.[5] Studies of selenium-modified nucleosides have been much less numerous. The utility of heavy atoms in X-ray structural studies of oligonucleotides with synchrotron radiation using multi wavelength anomalous dispersion (MAD) has led to the development of solid-phase synthetic methods for the production of oligonucleotides containing 2′-$SeCH_3$ nucleosides such as **2**. The preparation of oligonucleotides in which one or more 2′-OH groups were replaced by 2′-$SeCH_3$ groups gave compounds having similar crystallization behavior and stereochemistry to the native RNA structures; however, X-ray structural studies were simplified through more convenient phasing of the data using the heavy-atom anomalous diffraction effect.[6–8]



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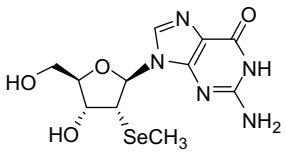

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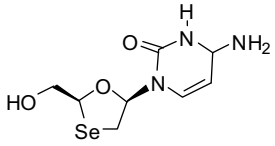

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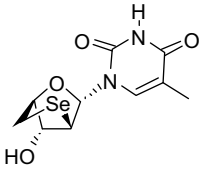

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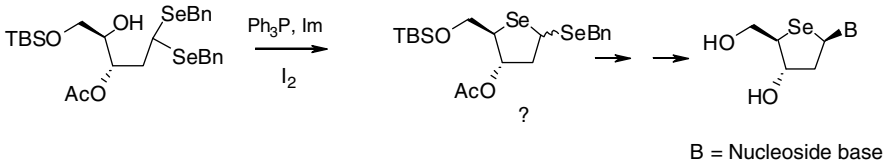


Scheme 1.

Selenium has been incorporated in various other positions of synthetic nucleoside derivatives to give, for example, a 3′-Se analogue (**3**) of the anti-AIDS drug 3TC[9] and bicyclic nucleoside analogues such as compound **4** having a 2′-Se-anhydro bridge.[10] Huang[11] has applied for a patent covering the preparations of several nucleosides and nucleotide derivatives having $SeCH_3$ groups at the 2′ or 5′ positions as well as compounds with selenium atoms substituting for various oxygen atoms in the phosphate or nitrogenous base portions of the molecules. Included in the patent disclosure was a single example of a proposed strategy for the incorporation of selenium as the ring atom in 2-deoxyribose nucleosides and nucleosides (Scheme 1).

However, it is our contention that the application of the illustrated reagents to effect ring-closure of dibenzylseleno acetal intermediates is likely, at least in some cases, to involve inversion rather than retention at the 4′-position, and could thus lead to the corresponding 2-deoxy-L-lyxose derivatives rather than the claimed 2-deoxy-D-ribose compounds. A similar reaction for a related dithioacetal was initially reported[12] to proceed with retention; however, this was later corrected by subsequent investigators[13] who proved that the true course of such reactions yields products from inversion at C-4. The very recently reported[14] syntheses of 4′-selenouridine and 4′-selenocytidine prompts us to report our own findings on the synthesis of this class of molecules, containing purine and pyrimidine bases.

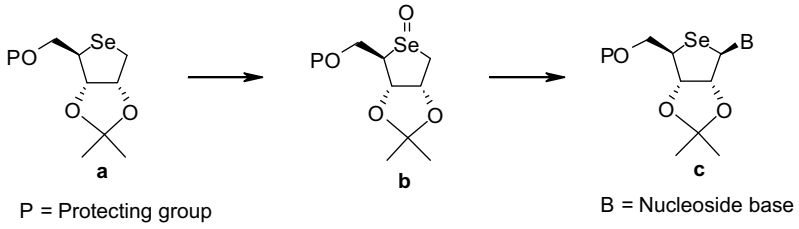
We describe herein the synthesis of 4′-selenonucleosides, based on the Pummerer rearrangement of a selenoxide, with trapping of reaction intermediates by the silylated pyrimidine or purine bases. The selenonucleosides could be incorporated into oligonucleotides for gene-silencing applications. The recently reported preference for the southern conformation of 4′-selenouridine,[14] and the reported northern conformation in our previous work with 2′-F-substituted-4′-thioarabinonucleoside **1**,[5] certainly augurs well for interesting biological applications of the corresponding 4′-selenooligonucleotides.[5b]

2. Results and discussion

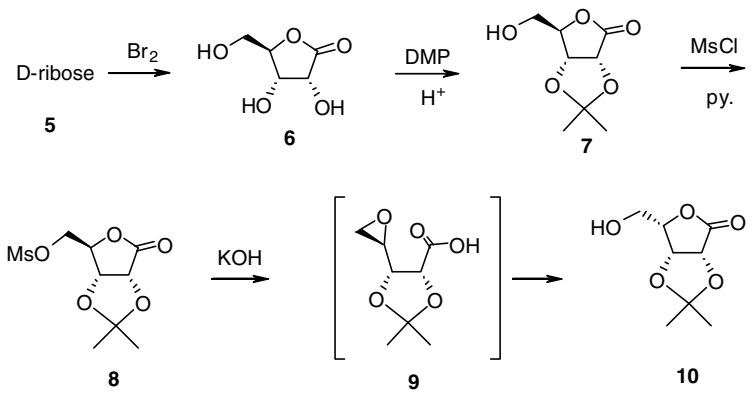
Our approach to 4′-Se-ribonucleosides is based on procedures reported for the practical synthesis of 4′-S-ribonucleosides.[15] By analogy with these methods, we propose the use of a 2,3-*O*-isopropylidene-protected 1,4-anhydro-4-seleno-D-ribitol derivative (compound **a**, Scheme 2). Oxidation to selenoxide (**b**) and Pummerer glycosylation with silylated pyrimidine or purine bases, as developed by Matsuda's group[16] for the synthesis of 4′-thio nucleosides should lead to the desired nucleoside derivatives (**c**) with good selectivity for the desired β-isomers.

The choice of a benzyl group for the protection of the 5′-hydroxyl functional group, which has been developed for the synthesis of thionucleosides,[2c] was considered. However, this option would have required removal either by hydrogenolysis using a Pd catalyst or by treatment with BCl_3; neither possibility was attractive based on preliminary studies with other compounds containing selenium. The use of a protecting group that could be removed under the mildly acidic conditions necessary for simultaneous isopropylidene removal was therefore given priority, and the 5-*t*-butyldimethylsilyl (TBS) group was chosen as the candidate. The initial target compound, 1,4-anhydro-5-*t*-butyldimethylsilyl-2,3-*O*-isopropylidene-4-seleno-D-ribitol **14**, was readily prepared in quantity by the procedures outlined in Schemes 3 and 4.

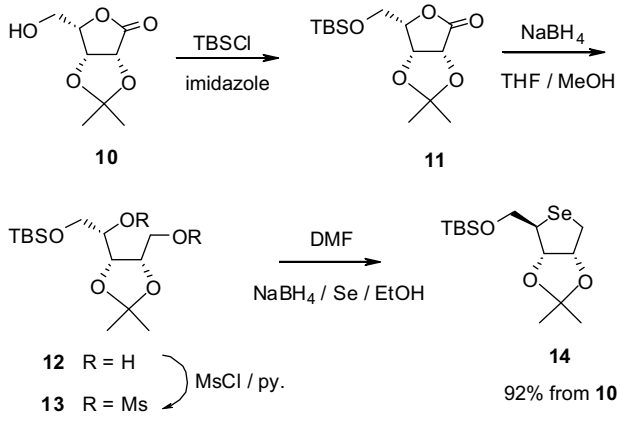
The starting compound, D-ribonolactone (**6**), is available commercially or can be advantageously prepared in high yield by bromine oxidation of ribose **5**.[17] Protection as the 2,3-*O*-isopropylidene acetal (**7**) and activation of



Scheme 2.



Scheme 3.[17]



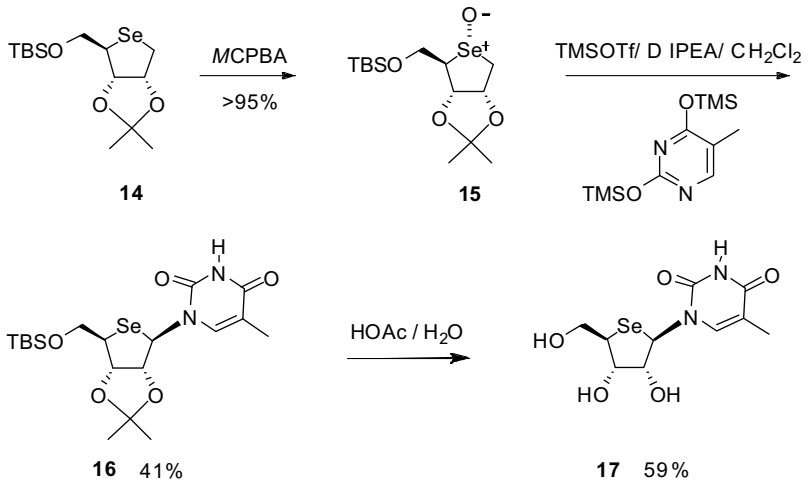
Scheme 4.

the 5-position by mesylation gave the intermediate compound **8**.[18] Treatment with base resulted in lactone hydrolysis and the formation of an intermediate open-chain epoxide (**9**), which immediately recyclized when acidified to produce a γ-lactone (**10**) with inversion at the 4-position.[19] This route to compound **10** from D-ribose was recently optimized[17] for use on a large scale and gives the L-lyxonolactone derivative **10** as an easily-purified, crystalline compound in good yield. Protection of the 5-hydroxyl group as the *t*-butyldimethylsilyl ether gave the fully-protected compound **11**.[15] This was reduced with sodium borohydride to 1,4-diol **12**, which was treated with excess methanesulfonyl chloride and pyridine to give the dimesylate **13**, that was treated immediately with sodium selenide in EtOH/DMF to afford the key intermediate **14** in excellent overall yield (Scheme 4).

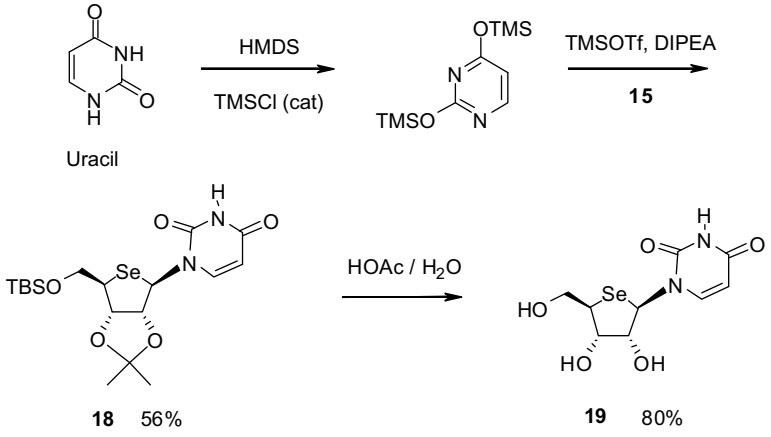
Oxidation of the selenium center with *m*-chloroperoxybenzoic acid (MCPBA) yielded selenoxide **15** as a single diastereomer. The configuration of the selenoxide was tentatively assigned as the *R*-Se isomer based on steric arguments. The compound was reacted immediately after its formation. Pummerer rearrangement of selenoxide **15** in the presence of trimethylsilylated thymine, trimethylsilyl triflate (TMSOTf, 2 equiv), and diisopropylethylamine (DIPEA, 2 equiv) gave selenonucleoside **16** in very poor yield. We attempted to optimize the yield by changing solvent, (acetonitrile or dichloromethane), temperature (between −30 °C and rt), and the quantity of reagents (between 2 equiv and 9 equiv of TMSOTf and DIPEA). Under optimized conditions, the use of 6 equiv of each of TMSOTf and DIPEA at 0 °C, in dichloromethane resulted in an improvement of the yield to 41%. Stereoselectivity for the formation of the β-isomer at the anomeric center **16** was excellent, with less than 1% contamination by the corresponding α-isomer (according to ^{1}H NMR). Simultaneous removal of the silyl and isopropylidene protecting groups by treatment of compound **16** with aqueous acetic acid gave the target nucleoside **17** as a crystalline solid (Scheme 5). The configuration at C-1′ was confirmed as β by analysis of the 1D-NOE spectrum of **17**. Clear, positive NOE correlations were observed between the thymine H-6 resonance and the ribose H-2′ and H-3′ resonances. The H-6/H-2′ NOE was larger than the H-6/H-1′ NOE, as expected if the thymine moiety preferentially populates the *anti*-conformation around the C-1′–N1 bond, as shown to be the case for the related 2′-deoxy-4′-thio system.[20]

Under the optimized conditions, the treatment of selenoxide **15** with trimethylsilylated uracil gave the selenouridine derivative **18** in 56% yield, with complete β-stereoselectivity (Scheme 6). The TBS and acetonide protecting groups were removed in good yield by heating at reflux with 60% aqueous acetic acid for 30 min. Once again, the stereochemistry at C-1′ was confirmed by means of 1D-NOE experiments.

Under similar conditions to those reported above, selenoxide **15** reacted with trimethylsilylated cytosine to give the selenocytidine derivative in very low yield (~10%). Thus, we examined the use of the *N*-acetylcytosine derivative in the Pummerer reaction. Accordingly, a solution of selenoxide **15** and silylated *N*-acetylcytosine



Scheme 5.

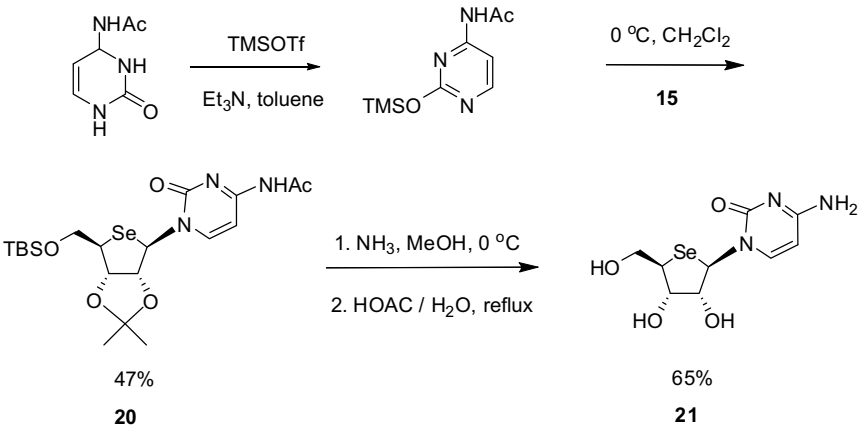


Scheme 6.

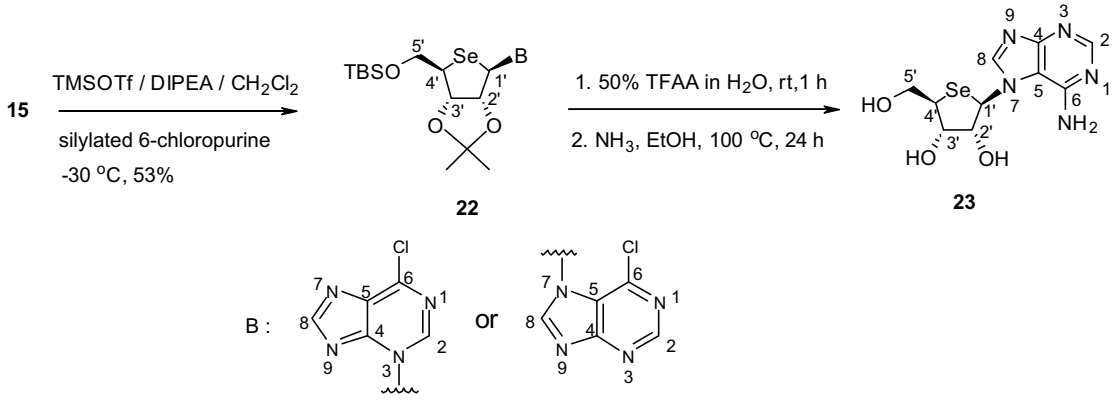
in CH_2Cl_2 were added to an excess of DIPEA and TMSOTf at 0 °C. The reaction proceeded immediately, but the desired protected selenocytidine **20** was produced in low yield (35%). Although the stereoselectivity of the resulting nucleoside was β as expected, the isolated yield was not satisfactory. Thus, the reaction conditions were modified: silylation of *N*-acetylcytosine using Et_3N and TMSOTf in toluene,[16] followed by the addition of selenoxide **15** in CH_2Cl_2 improved the yield to 47%. Hydrolysis of *N*-acetate in **20** using methanolic ammonia at 0 °C, followed by removal of the TBS and acetonide groups in acetic acid gave the desired nucleoside **21** in 65% yield over two steps (Scheme 7).

We next turned our attention to purine-containing nucleosides, and report here the synthesis of the first candidate. Thus, the reaction of selenoxide **15** with adenine gave a complex mixture, while the reaction with 6-chloropurine at 0 °C gave the coupled product in 41% yield as a mixture of two regioisomers (Scheme 8) as indicated by ^{1}H NMR of the mixture. No attempt was made to identify these isomers as the mixture was found to be unstable. However, when the reaction was carried out at −30 °C, it yielded exclusively one regioisomer in 53% yield (Scheme 8). This regioisomer could be either the N-3 or N-7-linked isomer. The configuration of **22** at the anomeric center was assigned as β on the basis of 1D-NOE experiments. Thus, irradiation of the H-8 resonance gave enhancements of the H-5′ and TBS resonances. Moreover, the H-8/H-2′ NOE was larger than the H-8/H-1′ NOE, as observed for the pyrimidine nucleosides. Further, no enhancements were observed between protons H-8 and H-4′.

Compound **22** was treated with 50% trifluoroacetic acid at room temperature to remove the TBS and acetonide protecting groups, followed by heating with ethanolic ammonia at 100 °C to give the adenine nucleoside **23** in 72% yield over two steps (Scheme 8). The ^{1}H NMR signals for compound **23** were observed at δ 8.62 and 8.11 (H-2 and H-8), and 6.04 ppm (H-1′). The absorption maximum appeared at 270 nm



Scheme 7.

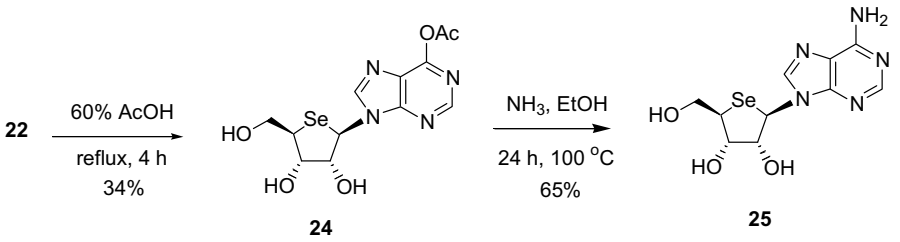


Scheme 8.

in H_2O. The regioisomer **23** was finally identified as being the N-7 isomer, as discussed below.

Formation of the N-3 isomer of adenosine was observed in the alkylation reaction of adenine with glycosyl halides[22a] or by blocking the N-7 and N-9 positions by substituting a bulky group at the N-8 position.[22b] Otherwise, only the N-7 isomers were generally preferred to form as intermediates during glycosylation reactions of silylated adenine with anomeric acetates and sulfoxides.[16,23] These N-7 linked intermediates were converted into the thermodynamically more stable N-9 isomers by heating them in the presence of acids. Recently, an interesting N-1 isomer was also identified by Boryski and co-workers[23a] under silylation and glycosylation of an N-6 protected adenine. These various regioisomers were generally differentiated by UV spectroscopy. Thus, λ_{max} of N-3, N-7, and N-9 isomers were observed at 274–280, ~270 and ~259 nm, respectively, at neutral pH. Because λ_{max} of **23** appears at 270 nm, we conclude that this compound is an N-7-linked regioisomer, and by inference, that **22** is also the N-7-linked regioisomer. It is noteworthy that a similar result was observed in the formation of a 4′-thio-adenosine derivative by Pummerer reaction under similar conditions.[16]

In view of the fact that the kinetic N-7 isomer was expected to rearrange[16,23] into the N-9 isomer, the N-7 isomer **22** was heated at reflux in 60% aqueous acetic acid for 15 min; however, the only isolated product was the deprotected N-7 isomer. Therefore, heating at reflux was continued for 4 h; interestingly, rearrangement and deprotection of **22** to the desired **24** in 34% yield was observed (Scheme 9). The product **24** has an acetate group, resulting from the displacement of the chlorine atom by acetic acid. The presence of the acetate group was confirmed by the observed carbonyl ^{13}C resonance at δ 171.2, and a ^{1}H methyl resonance at δ 2.12. Treatment of **24** with ethanolic ammonia at 100 °C gave the desired selenoadenosine **25** in 65% yield (Scheme 9). The UV spectrum of the N-9 isomer **25** in H_2O showed an absorption maximum at 259 nm, characteristic of the N-9-glycosyl adenosine. The ^{1}H NMR signals for the N-9 isomer (**25**) were observed at δ 8.56 and 8.01 (H-2 and H-8), and 6.22 ppm (H-1′), while those of the N-7 isomer **23** were observed further downfield at δ 8.62 and 8.11 (H-2 and H-8), and 6.04 ppm (H-1′), consistent



Scheme 9.

with the literature precedent for the sulfur congeners.[16,23d]

3. Conclusions

In summary, we have developed a stereoselective route to the synthesis of 4′-β-selenonucleosides. The starting precursor, 1,4-anhydro-4-seleno-D-ribitol **14** was readily prepared in a few steps, in multigram quantities from the commercially available D-ribonolactone. Oxidation of the 1,4-anhydro-4-seleno-D-ribitol using MCPBA gave a single selenoxide diastereomer in excellent yield, which upon treatment under Pummerer glycosylation conditions, gave the 4′-seleno-thymidine, -cytidine, -adenosine, and -uridine derivatives with high β-stereoselectivity. Deprotection then offered the target 4′-selenonucleosides.

4. Experimental

4.1. General experimental methods

Optical rotations were measured at 20 °C. ^{1}H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively. All assignments were confirmed with the aid of two-dimensional ^{1}H, ^{1}H (COSYDFTP) or ^{1}H, ^{13}C (INVBTP) experiments using standard pulse programs. Column chromatography was performed with Silica Gel 60 (230–400 mesh). High resolution mass spectra were obtained by the Fast Atom Bombardment (FAB) technique, using a JEOL AX505HA high resolution magnetic sector mass spectrometer.

4.2. 5-*O*-*t*-Butyldimethylsilyl-2,3-di-*O*-isopropylidene-L-lyxono-γ-lactone (11)

A solution of 2,3-di-*O*-isopropylidene-L-lyxono-γ-lactone **10** (4.79 g, 25.5 mmol) in CH_2Cl_2 (80 mL) containing imidazole (2.05 g, 30.1 mmol) was stirred at ambient temperature while *t*-butyldimethylsilyl chloride (4.30 g, 28.5 mmol) was added in small portions over 10 min. The mixture was stirred under an inert atmosphere for 50 min and then diluted with CH_2Cl_2 (150 mL) and washed with satd aq $NaHCO_3$ solution (80 mL). The organic phase was dried over anhyd $MgSO_4$, filtered, and concentrated to give a waxy solid which changed into a dry, crystalline solid when placed under high vacuum. The yield of crude product, which was pure by ^{1}H NMR except for a trace of imidazole, was 7.71 g (~100%). This material could be purified if necessary by flash chromatography (hexanes/ethyl acetate, 3:1), but was generally suitable for use without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.82–4.79 (2H, m, H-2 and H-3), 4.52 (1H, m, H-4), 3.98 (1H, dd, $J_{4,5a} = 6.1$, $J_{5a,5b} = 10.8$ Hz, H-5a), 3.93 (1H, dd, $J_{4,5b} = 6.6$ Hz, H-5b), 1.46 (3H, s, CH_3), 1.39 (3H, s, CH_3), 0.90 (9H, s, $SiC(CH_3)_3$), 0.10 (6H, s, $2 \times SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$); δ 173.8 (C=O), 114.0 ($C(CH_3)_2$), 79.4 (C-2), 76.0 and 75.7 (C-3 and C-4), 60.9 (C-5), 26.8 and 25.9 ($2 \times CH_3$) 25.8 ($SiC(CH_3)_3$), 18.3 ($SiC(CH_3)_3$), −5.4 and −5.5 ($2 \times SiCH_3$).

4.3. 5-*O*-*t*-Butyldimethylsilyl-2,3-di-*O*-isopropylidene-L-lyxitol (12)

The previous crude silyl derivative **11** (7.71 g) was dissolved in a mixture of THF/MeOH (5:1, 80 mL) and the solution was stirred at ambient temperature while $NaBH_4$ (1.1 g, 29 mmol) was added in portions over 20 min. The mixture was stirred for 1 h and then concentrated on a rotary evaporator. The residue was partitioned between EtOAc (150 mL) and 20% aq tartaric acid solution (50 mL). The organic phase was washed with saturated 20% aq tartaric acid solution (20 mL), saturated aq $NaHCO_3$ solution (20 mL), saturated aq NaCl solution (20 mL), and then dried over anhyd $MgSO_4$, filtered, and concentrated to give diol **12** as a colorless crystalline solid (7.49 g, 96% for two steps from lactone **10**). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.26–4.21 (2H, m, H-2 and H-3), 3.84–3.74 (3H, m, H-4, H-1a, and H-1b), 3.72 (1H, dd, $J_{4,5a} = 6.3$, $J_{5a,5b} = 9.8$ Hz, H-5a), 3.62 (1H, dd, $J_{4,5b} = 6.8$ Hz, H-5b), 1.50 (3H, s, CH_3), 1.37 (3H, s, CH_3), 0.89 (9H, s, $SiC(CH_3)_3$), 0.07 (6H, s, $2 \times SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 108.2 ($C(CH_3)_2$), 77.3 and 75.7 (C-2 and C-3), 69.2 (C-4), 64.5 (C-5), 62.7 (C-1), 27.1 and 25.0 ($2 \times CH_3$), 25.8 ($SiC(CH_3)_3$), 18.3 ($SiC(CH_3)_3$), −5.4 and −5.5

($2 \times SiCH_3$); Anal. Calcd for $C_{14}H_{30}SiO_5$: C, 54.87; H, 9.87. Found: C, 54.99; H, 10.03.

4.4. 5-*O*-*t*-Butyldimethylsilyl-2,3-di-*O*-isopropylidene-1,4-di-*O*-methanesulfonyl-L-lyxitol (13)

The previous diol **12** (7.49 g, 24.5 mmol) was dissolved in CH_2Cl_2 (20 mL) and the solution was added dropwise to a stirred mixture of MsCl (18.6 mL, 0.24 mol) and pyridine (19.3 mL, 0.24 mol) with ice-bath cooling. The cooling bath was removed and the mixture stirred at ambient temperature for 2 h. The cooling bath was replaced and the excess MsCl was hydrolyzed by the addition of ice (~10 g). After 10 min, the reaction mixture was poured into cold water (350 mL) and extracted with Et_2O (3×100 mL). The combined extracts were washed with satd 20% aq tartaric acid solution (3×50 mL), satd aq $NaHCO_3$ solution (50 mL), satd aq NaCl solution (50 mL), and then dried over anhyd $MgSO_4$, filtered, and concentrated to give the dimesylate **13** as a pale yellow oil (12.4 g) that was used immediately in the next reaction. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.74 (1H, ddd, H-4), 4.49–4.34 (4H, m, H-1a, H-1b, H-2, and H-3), 3.96 (1H, dd, $J_{4,5a} = 5.4$, $J_{5a,5b} = 10.9$ Hz, H-5a), 3.82 (1H, dd, $J_{4,5b} = 6.2$ Hz, H-5b), 3.12 (3H, s, OSO_2CH_3), 3.08 (3H, s, OSO_2CH_3), 1.51 (3H, s, CH_3), 1.38 (3H, s, CH_3), 0.90 (9H, s, $SiC(CH_3)_3$), 0.10 (3H, s, $SiCH_3$), 0.097 (3H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 109.6 ($C(CH_3)_2$), 78.9 (C-4), 75.4 and 74.5 (C-2 and C-3), 67.9 (C-1), 63.1 (C-5), 38.9 and 37.6 ($2 \times OSO_2\ CH_3$), 27.2 and 25.4 ($2 \times CH_3$), 25.8 ($SiC(CH_3)_3$), 18.3 ($SiC(CH_3)_3$), −5.5 (2C, $2 \times SiCH_3$).

4.5. 5-*O*-*t*-Butyldimethylsilyl-2,3-di-*O*-isopropylidene-1,4-anhydro-4 seleno-D-ribitol (14)

A solution of Na_2Se was first prepared by the method of Krief et al.[21] Thus, dry gray selenium (2.20 g, 27.9 mmol) and $NaBH_4$ (2.11 g, 55.8 mmol) were mixed and stirred in an ice-bath while anhyd EtOH (10 mL) was slowly added. The cooling bath was removed and the mixture was allowed to reach ambient temperature over 15 min, giving a brown suspension of partially reduced selenium. The cooling bath was replaced and anhydrous DMF (35 mL) was added. This gave a vigorous reaction, accompanied by H_2 evolution, to eventually produce a colorless solution of Na_2Se upon warming to room temperature. This Na_2Se solution was then rapidly added to a pre-prepared solution of the previous crude dimesylate **13** (12.4 g) in DMF (40 mL). The resulting mixture was placed under an N_2 atmosphere and slowly warmed to 60 °C over 2 h, and maintained at 60 °C for a further 1 h. The mixture was cooled to ambient temperature, and poured into water (800 mL), and extracted with 1:1 Et_2O/hexanes (3×100 mL) and with ethyl acetate (3×100 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated to give the crude product as an oily residue containing small amounts of pyridine and DMF. This was purified by flash chromatography to give the product **14** as a pale yellow oil (8.32 g, 92% for 4 steps from isopropylidene lyxonolactone (**10**)). $[\alpha]_D^{20}$ +104.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.94 (1H, ddd, H-2), 4.78 (1H, dd, $J_{2,3} = 1.7$ Hz, H-3), 3.86 (1H, dd, $J_{4,5a} = 5.2$, $J_{5a,5b} = 10.6$ Hz, H-5a), 3.69 (1H, dd, $J_{4,5b} = 6.9$ Hz, H-5b), 3.59 (1H, ddd, H-4), 3.24 (1H, dd, $J_{1a,2} = 5.2$, $J_{1a,1b} = 11.1$ Hz, H-1a), 2.95 (1H, dd, $J_{1b,2} = 2.3$ Hz, H-1b), 1.53 (3H, s, CH_3), 1.32 (3H, s, CH_3), 0.90 (9H, s, $SiC(CH_3)_3$), 0.07 (6H, s, $2 \times SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 110.2 ($C(CH_3)_2$), 87.6 and 85.3 (C-2 and C-3), 66.2 (C-5), 66.1 (C-1), 50.5 (C-4), 26.8 and 24.6 ($2 \times CH_3$), 25.9 ($SiC(CH_3)_3$), 18.3 ($SiC(CH_3)_3$), −5.4 (2C, $2 \times SiCH_3$); MALDI MS *m/e* 375.46 $[M+Na]^+$, 353.51 $[M+H]^+$; Anal. Calcd for $C_{14}H_{28}SiO_3Se$: C, 47.85; H, 8.03. Found: C, 47.58; H, 8.21.

4.6. 5-*O*-*t*-Butyldimethylsilyl-2,3-di-*O*-isopropylidene-1,4-anhydro-4-seleno-D-ribitol selenoxide (15)

A solution of selenoether **14** (427 mg, 1.21 mmol) in CH_2Cl_2 (10 mL) was cooled in an ice-bath and stirred while 68% MCPBA (344 mg, 1.35 mmol) was added in small portions over 15 min. After a further 10 min at 0 °C, the mixture was warmed to rt and diluted with CH_2Cl_2 (100 mL). The solution was washed with satd aq $NaHCO_3$ (30 mL), dried over $MgSO_4$, and concentrated to give selenoxide **15** in quantitative yield as a colorless unstable crystalline solid. This material was used immediately in subsequent reactions. Analysis by ^{1}H NMR indicated that the product was composed of a single selenoxide diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.19 (1H, ddd, H-2), 5.02 (1H, dd, $J_{2,3} = 3.9$ Hz, H-3), 4.14 (1H, dd, $J_{4,5a} = 3.8$, $J_{5a,5b} = 11.5$ Hz, H-5a), 4.04 (1H, dd, $J_{4,5b} = 7.2$ Hz, H-5b), 3.59 (1H, ddd, H-4), 3.43 (1H, dd, $J_{1a,2} = 2.5$, $J_{1a,1b} = 12.8$ Hz, H-1a), 3.12 (1H, dd, $J_{1b,2} = 6.1$ Hz, H-1b), 1.46 (3H, s, CH_3), 1.31 (3H, s, CH_3), 0.90 (9H, s, $SiC(CH_3)_3$), 0.12 (6H, s, $2 \times SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 111.0 ($C(CH_3)_2$), 83.6 and 81.5 (C-2 and C-3), 63.4 (C-5), 56.6 (C-4), 52.7 (C-1), 27.3 and 24.4 ($2 \times CH_3$), 25.8 ($SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), −5.4 and −5.6 ($2 \times SiCH_3$).

4.7. *N*-1-(5′-*O*-*t*-Butyldimethylsilyl-2′,3′-di-*O*-isopropylidene-4′-seleno-β-D-ribofuranosyl)-thymine (16)

Thymine (1.24 g, 9.88 mmol) in acetonitrile (30 mL) was heated at reflux with hexamethyldisilazane (8.0 mL) and trimethylsilyl chloride (0.5 mL) for 40 min under N_2. The mixture was cooled to room temperature and

concentrated to give di-O-silylated thymine as a cloudy syrup. Meanwhile, selenoether **14** (1.76 g, 5.02 mmol) was oxidized to the selenoxide as described above. The crude selenoxide **15** (1.81 g) was combined with silylated thymine in CH_2Cl_2 (80 mL) and the mixture was cooled in an ice-bath. Diisopropylethylamine (5.2 mL, 30 mmol) was added, followed by dropwise addition of TMSOTf (5.4 mL, 30 mmol). The mixture was stirred in the ice-bath for 30 min and then allowed to warm to room temperature, and quenched by the addition of a satd aq $NaHCO_3$ (50 mL) and, after a further 10 min of rapid stirring, the two-phase mixture was filtered through Celite with the aid of additional CH_2Cl_2. The filtrate was separated and the organic phase was washed with water (80 mL) and dried over $MgSO_4$. Filtration and solvent removal yielded the crude product as an orange semi-solid mixture that was purified by column chromatography on silica gel (hexanes/ethyl acetate, 1:1) to give selenonucleoside **16** as a pale yellow foam (1.11 g, 46%); $[\alpha]_D^{20}$ −52.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.56 (1H, br s, NH), 7.37 (1H, q, $J = 1.2$ Hz, H-6), 6.34 (1H, d, $J_{1',2'} = 4.6$ Hz, H-1′), 4.77 (1H, dd, $J_{2',3'} = 5.6$ Hz, H-2′), 4.71(1H, dd, $J_{3',4'} = 3.4$ Hz, H-3′), 4.03 (1H, dd, $J_{4',5'a} = 5.0$, $J_{5'a,5'b} = 9.7$ Hz, H-5′a), 3.97 (1H, ddd, H-4′), 3.89 (1H, dd, $J_{4',5'b} = 6.1$ Hz, H-5′b), 1.94 (3H, d, $J = 1.2$ Hz, 5-CH_3), 1.59 (3H, s, CH_3), 1.30 (3H, s, CH_3), 0.92 (9H, s, SiC(CH_3)$_3$), 0.10 (3H, s, SiCH_3), 0.096 (3H, s, SiCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.2 (C═O), 150.0 (C═O), 137.5 (C-6), 112.7 and 111.9 (C-5 and $C(CH_3)_2$), 89.5 (C-2′), 84.7 (C-3′), 65.2 (C-5′), 59.0 (C-1′), 49.9 (C-4′), 27.9 and 25.4 (2 × CH_3), 25.8 (SiC(CH_3)$_3$), 18.4 (SiC(CH$_3$)$_3$), 12.6 (5-*C*H3), −5.2 and −5.3 (2 × SiCH_3); MALDI MS *m*/*e* 499.34 $[M+Na]^+$, 477.21 $[M+H]^+$; Anal. Calcd for $C_{19}H_{32}N_2SiO_5Se$: C, 47.99; H, 6.78; N, 5.89. Found: C, 48.08; H, 6.84; N, 6.08.

4.8. *N*-1-(4′-Seleno-β-D-ribofuranosyl)-thymine (17)

The protected selenonucleoside **16** (1.02 g, 2.15 mmol) was heated at reflux in 60% aqueous HOAc (50 mL) for 0.5 h. The mixture was cooled and concentrated by rotary evaporation under high vacuum. Water (30 mL) was added and removed under reduced pressure to remove the last of the HOAc. This crude product was purified by a silica gel column, eluted with CH_2Cl_2/MeOH (10:1) to give **17** as a pale tan-colored solid (0.604 g, 59%). Mp 150–153 °C; $[\alpha]_D^{20}$ −21.5 (*c* 0.7, H_2O); ^{1}H NMR (400 MHz, D_2O); δ 7.85 (1H, q, $J = 1.2$ Hz, H-6), 6.13 (1H, d, $J_{1',2'} = 7.9$ Hz, H-1′), 4.40 (1H, dd, $J_{2',3'} = 3.5$ Hz, H-2′), 4.28 (1H, dd, $J_{3',4'} = 2.8$ Hz, H-3′), 3.90 (1H, dd, $J_{4',5'a} = 6.7$, $J_{5'a,5'b} = 12.0$ Hz, H-5′a), 3.80 (1H, dd, $J_{4',5'b} = 5.8$ Hz, H-5′b), 3.54 (1H, ddd, H-4′), 1.84 (3H, d, $J = 1.2$ Hz, 5-CH_3); ^{13}C NMR (125 MHz, D_2O): δ 169.1 (C═O), 152.5 (C═O), 139.3 (C-6), 112.0 (C-5), 78.3 (C-2′), 74.5 (C-3′), 63.3 (C-5′), 59.3 (C-1′), 47.8 (C-4′), 11.7 (5-*C*H3); MALDI MS *m*/*e* 345.46 $[M+Na]^+$, 323. 14 $[M+H]^+$; Anal. Calcd for $C_{10}H_{14}N_2O_5Se$: C, 37.40; H, 4.39; N, 8.72. Found: C, 37.67; H, 4.51; N, 8.95.

4.9. *N*-1-(5′-*O*-*t*-Butyldimethylsilyl-2′,3′-di-*O*-isopropylidene-4′-seleno-β-D-ribofuranosyl)-uracil (18)

In the same manner as described for **16**, selenoxide **15** (1.04 g, 2.84 mmol), when reacted with trimethylsilylated uracil (1.45 g, 5.68 mmol), gave **18** as a pale yellow syrup (0.733 g, 56%); $[\alpha]_D^{20}$ −42.5 (*c* 1.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.36 (1H, br s, NH), 7.72 (1H, d, $J = 8.0$ Hz, H-6), 6.30 (1H, d, $J_{1',2'} = 3.0$ Hz, H-1′), 5.70 (1H, d, $J = 8.0$ Hz, H-5), 4.64 (2H, m, H-2′, H-3′), 3.88 (3H, m, H-4′, H-5′a, H-5′b), 1.49 (3H, s, CH_3), 1.20 (3H, s, CH_3), 0.81 (9H, s, SiC(CH_3)$_3$), 0.01 (3H, s, SiCH_3), 0.00 (3H, s, SiCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.0 (C═O), 150.0 (C═O), 142.3 (C-6), 111.9 ($C(CH_3)_2$), 103.2 (C-5), 90.6 and 85.6 (C-2′ and C-3′), 65.5 (C-5′), 59.9 (C-1′), 50.2 (C-4′), 27.9 and 25.4 (2 × CH_3), 25.8 (SiC(CH_3)$_3$), 18.4 (SiC(CH$_3$)$_3$), −5.2 and −5.3 (2 × SiCH_3); FAB HRMS (*m*-nitrobenzoic acid (MNBA)) calcd for $C_{18}H_{30}N_2O_5SeSi$, 463.1167 $[M+H]^+$; found, 463.1170.

4.10. *N*-1-(4′-Seleno-β-D-ribofuranosyl)-uracil (19)

Selenouridine **18** (0.50 g, 1.08 mmol) was deprotected, using the procedure that was used to obtain **17** as a colorless solid (0.265 g, 80%). Mp 190–193 °C; $[\alpha]_D^{20}$ −90.0 (*c* 0.4, H_2O); ^{1}H NMR (500 MHz, D_2O): δ 7.98 (1H, d, $J = 8.0$ Hz, H-6), 6.03 (1H, d, $J_{1',2'} = 7.5$ Hz, H-1′), 5.79 (1H, d, $J = 8.0$ Hz, H-5), 4.31 (1H, dd, $J_{2',3'} = 3.5$ Hz, H-2′), 4.17 (1H, dd, $J_{3',4'} = 3.0$ Hz, H-3′), 3.80 (1H, dd, $J_{4',5'a} = 6.5$, $J_{5'a,5'b} = 12.0$ Hz, H-5′a), 3.70 (1H, dd, $J_{4',5'b} = 6.0$ Hz, H-5′b), 3.46 (1H, ddd, H-4′); ^{13}C NMR (125 MHz, D_2O): δ 166.2 (C═O), 152.3 (C═O), 143.9 (C-6), 102.7 (C-5), 78.4 (C-2′), 74.6 (C-3′), 63.4 (C-5′), 59.6 (C-1′), 47.8 (C-4′); FAB HRMS (MNBA) calcd for $C_9H_{12}N_2O_5$ Se, 308.9990 $[M+H]^+$; found, 308.9994.

4.11. N^4-Acetyl-1-(5′-*O*-*t*-butyldimethylsilyl-2′,3′-di-*O*-isopropylidene-4′-seleno-β-D-ribofuranosyl)-cytosine (20)

N-Acetylcytosine (0.869 g, 5.68 mmol) was silylated using TMSOTf (3.1 mL, 17.04 mmol) and Et_3N (1.2 mL, 8.52 mmol) in toluene (10 mL) according to the procedure of Matsuda[15] for the silylation of uracil. A solution of selenoxide **15** (1.04 g, 2.84 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise to the solution of the trimethylsilylated cytosine in toluene/CH_2Cl_2 (2:1, 12 mL) at 0 °C. An additional amount of Et_3N (1.2 mL, 8.52 mmol) in CH_2Cl_2 (2 mL) was added

dropwise to the reaction mixture at the same temperature. After stirring for 15 min at 0 °C, the reaction was quenched by the addition of satd aq $NaHCO_3$ (25 mL), and the reaction mixture was partitioned between CH_2Cl_2 (20 mL) and H_2O (10 mL). The organic layer was dried over Na_2SO_4, and the resulting residue was purified by silica gel column (hexanes/ethyl acetate, 4:1) to give selenonucleoside **16** as a pale yellow oil (0.67 g, 47%). $[\alpha]_D^{20}$ −36.5 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.82 (1H, br s, NH), 8.12 (1H, d, $J = 7.5$ Hz, H-6), 7.36 (1H, d, $J = 7.5$ Hz, H-5), 6.28 (1H, d, $J_{1',2'} = 1.5$ Hz, H-1′), 4.75 (2H, m, H-2′, H-3′), 3.90 (3H, m, H-4′, H-5′a, H-5′b), 2.20 (3H, s, NAc), 1.49 (3H, s, CH_3), 1.21 (3H, s, CH_3), 0.82 (9H, s, SiC(CH_3)$_3$), 0.01 (3H, s, SiCH_3), 0.00 (3H, s, SiCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0 (C=O), 162.6 (C=NH), 154.8 (C=O), 147.3 (C-6), 111.6 ($C(CH_3)_2$), 97.5 (C-5), 91.2 and 86.3 (C-2′ and C-3′), 65.5 (C-5′), 62.8 (C-1′), 51.8 (C-4′), 27.7 and 25.9 (2 × CH_3), 25.8 (SiC(CH_3)$_3$), 24.9 (C(O)CH_3), 18.4 (SiC(CH$_3$)$_3$), −5.2 and −5.3 (2 × SiCH_3); FAB HRMS (MNBA) calcd for $C_{20}H_{33}N_3O_5SeSi$, 504.1433 $[M+H]^+$; found, 504.1437.

4.12. *N*-1-(4′-Seleno-β-D-ribofuranosyl)-cytosine (21)

The protected selenocytidine **20** (100 mg, 0.20 mmol) was dissolved in methanolic ammonia (saturated at 0 °C, 7 mL) and the reaction mixture was kept overnight at room temperature. The solvent was removed under vacuum, the residue was dissolved in 60% AcOH (10 mL), and the reaction mixture was heated under reflux for 1 h. The mixture was cooled and concentrated by rotary evaporation under high vacuum. Water (3 mL) was added and removed under reduced pressure to remove the remaining HOAc. The crude product was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 10:1) to give **21** as a colorless solid (40 mg, 65%, over 2 steps). Mp 151–154 °C; $[\alpha]_D^{20}$ −155.5 (*c* 0.5, H_2O); ^{1}H NMR (500 MHz, D_2O): δ 8.14 (1H, d, $J = 8.0$ Hz, H-6), 6.28 (1H, d, $J_{1',2'} = 7.0$ Hz, H-1′), 5.79 (1H, d, $J = 8.0$ Hz, H-5), 4.33 (1H, dd, $J_{2',3'} = 3.5$ Hz, H-2′), 4.22 (1H, dd, $J_{3',4'} = 3.0$ Hz, H-3′), 3.90 (1H, dd, $J_{4',5'a} = 6.5$, $J_{5'a,5'b} = 12.0$ Hz, H-5′a), 3.80 (1H, dd, $J_{4',5'b} = 6.0$ Hz, H-5′b), 3.59 (1H, ddd, H-4′); ^{13}C NMR (125 MHz, D_2O): δ 166.1 (C=O), 157.7 (C=O), 143.3 (C-6), 95.4 (C-5), 79.1 (C-2′), 75.1 (C-3′), 63.9 (C-5′), 57.7 (C-1′), 47.8 (C-4′); FAB HRMS (*M*NBA) calcd for $C_9H_{13}N_3O_4Se$, 308.0150 $[M+H]^+$; found, 308.0159.

4.13. 6-Chloro-7-(5′-*O*-*t*-Butyldimethylsilyl-2′,3′-di-*O*-isopropylidene-4′-seleno-β-D-ribofuranosyl)-9*H*-purine (22)

6-Chloropurine (0.88 g, 5.67 mmol) in acetonitrile (10 mL) was heated at reflux with hexamethyldisilazane (4.0 mL) and trimethylsilyl chloride (0.25 mL) for 60 min under N_2. The mixture was cooled to room temperature and concentrated to give the silylated 6-chloropurine as a syrup. The crude selenoxide **15** (1.05 g, 2.84 mmol) was combined with the silylated 6-chloropurine in CH_2Cl_2 (20 mL) and the mixture was cooled to −30 °C. Diisopropylethylamine (3.5 mL, 20 mmol) was added followed by dropwise addition of TMSOTf (3.6 mL, 20 mmol). The mixture was stirred at the same temperature for 30 min and then quenched by the addition of satd $NaHCO_3$ (25 mL) and, after a further 10 min of rapid stirring, the two-phase mixture was filtered through Celite with the aid of additional CH_2Cl_2. The filtrate was separated and the organic phase was washed with water (50 mL) and dried over $MgSO_4$. Filtration and solvent removal yielded the crude product as a brown syrup that was purified by column chromatography on silica gel (hexanes/ethyl acetate, 1:1) to give selenonucleoside **22** as a yellow syrup (0.758 g, 53%). $[\alpha]_D^{20}$ +20.0 (*c* 1.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.95 (1H, s, H-8), 8.77 (1H, s, H-2), 6.70 (1H, d, $J_{1',2'} = 3.0$ Hz, H-1′), 4.83 (1H, dd, $J_{2',3'} = 5.5$ Hz, H-2′), 4.77 (1H, dd, $J_{3',4'} = 3.0$ Hz, H-3′), 3.97 (1H, m, H-4′), 3.90 (2H, m, H-5′a, H-5′b) 1.52 (3H, s, CH_3), 1.22 (3H, s, CH_3), 0.81 (9H, s, SiC(CH_3)$_3$), 0.03 (3H, s, SiCH_3), 0.00 (3H, s, SiCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.3, 143.0, and 122.2 (C-4, C-5, and C-6), 152.6 (C-2), 148.9 (C-8), 112.2 ($C(CH_3)_2$), 92.3 (C-2′) 86.2 (C-3′), 65.5 (C-5′), 60.0 (C-1′), 51.2 (C-4′), 27.6 and 25.9 (2 × CH_3), 25.2 (SiC(CH_3)$_3$), 18.5 (SiC(CH$_3$)$_3$), −5.2 and −5.3 (2 × SiCH_3); FAB HRMS (MNBA) calcd for $C_{19}H_{29}ClN_4O_3SeSi$, 505.0939 $[M+H]^+$; found, 505.0940.

4.14. 7-(4′-Seleno-β-D-ribofuranosyl) adenine (23)

The protected selenonucleoside **22** (0.10 g, 0.2 mmol) was dissolved in 50% aq trifluoroacetic acid and the reaction mixture was stirred at room temperature for 1 h. The mixture was concentrated by rotary evaporation under vacuum, water (1 mL) was added, and the last traces of TFAA were removed. The crude product was dissolved in ethanolic ammonia (5 mL) and heated for 24 h at 100 °C in a steel container. The solvent was removed in vacuo, and the residue was purified by silica gel chromatography to give **23** as a colorless solid (48 mg, 72% over two steps). Mp 185 °C (dec) $[\alpha]_D^{20}$ +42.2 (*c* 0.9, H_2O); ^{1}H NMR (500 MHz, D_2O): δ 8.62 (1H, s, H-8), 8.11 (1H, s, H-2), 6.04 (1H, d, $J_{1',2'} = 7.5$ Hz, H-1′), 4.53 (1H, dd, $J_{2',3'} = 3.0$ Hz, H-2′), 4.32 (1H, dd, $J_{3',4'} = 2.3$ Hz, H-3′), 3.98 (1H, dd, $J_{4',5'a} = 7.0$, $J_{5'a,5'b} = 12.0$ Hz, H-5′a), 3.79 (1H, dd, $J_{4',5'b} = 7.0$ Hz, H-5′b), 3.61 (1H, ddd, H-4′); ^{13}C NMR (125 MHz, D_2O): δ 158.2, 154.6, and 148.2 (C-4, C-5, and C-6), 154.4 (C-2), 152.1 (C-8), 80.3

(C-2′), 74.8 (C-3′), 63.2 (C-5′), 57.4 (C-1′), 48.8 (C-4′); FAB HRMS (MNBA) calcd for $C_{10}H_{13}N_5O_3Se$, 332.0262 $[M+H]^+$; found, 332.0263.

4.15. 6-Acetyl-9-(4′-seleno-β-D-ribofuranosyl)-9*H*-purine (24)

The protected selenonucleoside **22** (0.50 g, 1.0 mmol) was heated at reflux in 60% aqueous HOAc (15 mL) for 4 h. The mixture was cooled and concentrated by rotary evaporation under high vacuum. Water (5 mL) was added and removed under reduced pressure to remove the last of the HOAc. The crude product was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 10:1) to give the nucleoside **23** as a pale brown solid (127 mg, 34%). Mp 210 °C (dec); $[\alpha]_D^{20}$ +16.0 (*c* 0.5, H_2O); ^1H NMR (500 MHz, D_2O): δ 8.64 (1H, s, H-8), 8.05 (1H, s, H-2), 6.48 (1H, d, $J_{1',2'} = 6.5$ Hz, H-1′), 4.84 (1H, dd, $J_{2',3'} = 3.5$ Hz, H-2′), 4.68 (1H, dd, $J_{4',5'a} = 7.5, J_{5'a,5'b} = 11.5$ Hz, H-5′a), 4.41 (1H, dd, $J_{4',5'b} = 6.5$ Hz, H-5′b), 4.30 (1H, dd, $J_{3',4'} = 3.0$ Hz, H-3′), 3.81 (1H, ddd, H-4′); ^{13}C NMR (125 MHz, D_2O): δ 171.1 (C=O), 157.7, 154.9, and 145.9 (C-4, C-5, and C-6), 145.3 (C-2), 144.0 (C-8), 79.8 (C-2′), 75.1 (C-3′), 75.0 (C-3′), 65.6 (C-5′), 57.5 (C-1′), 44.0 (C-4′), 19.5 (C(O)*C*H3); FAB HRMS (MNBA) calcd for $C_{12}H_{14}N_4O_5Se$, 375.0228 $[M+H]^+$; found, 375.0224.

4.16. 9-(4′-Seleno-β-D-ribofuranosyl) adenine (25)

A solution of **24** (100 mg, 0.268 mmol) in ethanolic ammonia (saturated at 0 °C, 10 mL) was heated for 24 h at 100 °C in a steel container. The solvent was removed in vacuo, and the residue was purified by silica gel chromatography (CH_2Cl_2/MeOH, 10:1), to give **25** as a yellow solid (57 mg, 65%). Mp 194 °C (dec); $[\alpha]_D^{20}$ +83.1 (*c* 0.7, H_2O); ^1H NMR (500 MHz, D_2O): δ 8.56 (1H, s, H-8), 8.01 (1H, s, H-2), 6.22 (1H, d, $J_{1',2'} = 5.5$ Hz, H-1′), 4.64 (1H, dd, $J_{2',3'} = 3.5$ Hz, H-2′), 4.20 (1H, dd, $J_{3',4'} = 3.0$ Hz, H-3′), 3.98 (1H, dd, $J_{4',5'a} = 6.0$, $J_{5'a,5'b} = 12.0$ Hz, H-5′a), 3.79 (1H, dd, $J_{4',5'b} = 6.5$ Hz, H-5′b), 3.61 (1H, ddd, H-4′); ^{13}C NMR (125 MHz, D_2O): δ 158.2, 157.4, and 156.0 (C-4, C-5, and C-6), 146.0 (C-2), 145.0 (C-8), 80.0 (C-2′), 74.5 (C-3′), 63.0 (C-5′), 57.1 (C-1′), 47.7 (C-4′); FAB HRMS (MNBA) calcd for $C_{10}H_{13}N_5O_3Se$, 332.0262 $[M+H]^+$; found, 332.0268.

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Supplementary data

^1H and ^{13}C NMR spectra of compounds **14** and **16**–**25**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2008.02.014.

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