Stereoselective Synthesis of 2′,3′-Dideoxy-3′-fluoro-2′-phenylselenenyl-*β*-nucleosides from Phenyl 1-Seleno-α-*arabino*-furanosides through Consecutive 1,2-Migration and Glycosylation under Mitsunobu Conditions. A New Entry to 2′,3′-Dideoxy-3′-fluoronucleosides

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2′,3′-Dideoxy-3′-fluoronucleosides are among the most potent antiviral drugs[1] avalaible, and 3′-deoxy-3′-fluorothymidine (FLT) in particular is an efficient agent against HIV viruses.[2] Consequently, much attention has been devoted to the preparation of different 3′-deoxy-3′-fluoronucleosides with additional modifications in the sugar ring or in the base. Two general methods are used to prepare these compounds: (a) fluorinating appropriately protected nucleosides[3] and (b) glycosylating a base with a fluorocarbohydrate.[4] This latter method, however, has no control over the stereoselectivity of the glycosidic bond formation.[5] In fact, this is a general problem in the synthesis of 2′-deoxy- and 2′,3′-dideoxynucleosides. To overcome this lack of stereoselectivity, the glycosylation has been performed using sugars having easily removable electron donor groups at position 2 of the sugar ring as glycosyl donors, (e.g., phenylsulfenyl[6] and phenylselenenyl[7] to give the corresponding 2-phenylsulfenyl and 2-phenylselenenyl nucleosides) (Scheme 1, via route 1). Phenylsulfenyl and phenylselenenyl groups were introduced into the sugar ring by reacting PhSCl or PhSeCl with the corresponding lactone enolate (Scheme 1, via route 1). An alternative procedure starts from glycals and successive NIS, I_2, PhSCl, or PhSeCl addition, and glycosylation (Scheme 1, via route 2, X = I, SPh, SePh, respectively) leads to the corresponding 2′,3′-dideoxy-2′-iodo-,[8] 2′,3′-dideoxy-2′-phenyl-sulfenyl-,[9] and 2′,3′-dideoxy-2′-phenylselenenyl nucleosides[10] with good to excellent stereoselectivities. A bicyclic cationic intermediate (A) has been proposed in these cases although some reports doubt this proposal.[11] These nucleoside derivatives can be transformed into 2′,3′-dideoxynucleosides by treatment with tributyltin hydride.

In this report, we describe a new procedure for the stereoselective synthesis of 2′,3′-dideoxy-3′-fluoro-*β*-nucleosides by converting phenyl 3-deoxy-3-fluoro-1-seleno-α-*arabino*-furanosides to 2′,3′-dideoxy-3′-fluoro-2′-phenylselenenyl-*β*-*ribo*-nucleosides through consecutive 2-OH activation, 1,2-migration, and glycosylation in Mitsunobu conditions (Scheme 2) and subsequent deselenization.

Initially we considered the possibility of obtaining 3′-deoxy-3′-fluoro-*β*-nucleosides by starting from the corresponding glycal with a fluorine at position 3 and using PhSeCl as electrophilic reagent.

To synthesize the 3-fluoroglycal we chose methyl 5-*O*-benzyl-3-deoxy-3-fluoro-α-D-*arabino*-furanoside **1** as the key compound which was prepared from D-xylose using the modification[12] of the method described by Wright and Taylor.[13] The formation of xanthate **2** followed by Barton's deoxygenation allowed deoxysugar **3** to be obtained in 62% yield, together with the starting material **1** (recovery 32%) (Scheme 3). The fluorosugar **3** was treated with phenylselenol in the presence of $BF_3{\cdot}Et_2O$ in dichloromethane, and after column chromatography, phenyl 1-selenoglycosides **4***β* (33.5% yield) and **4**α (62% yield) were isolated. The oxidation of **4***β* by *tert*-butyl hydroperoxide in the presence of triethylamine and tetraiso-

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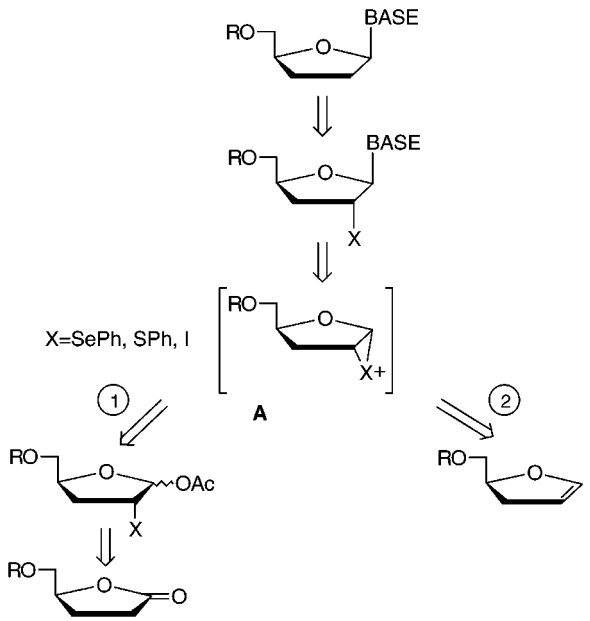
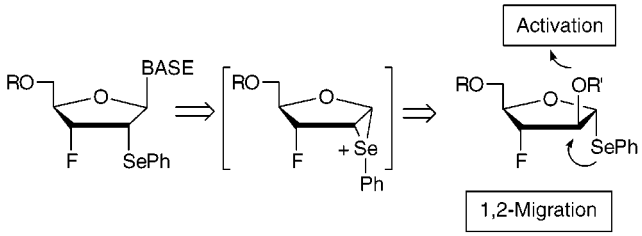
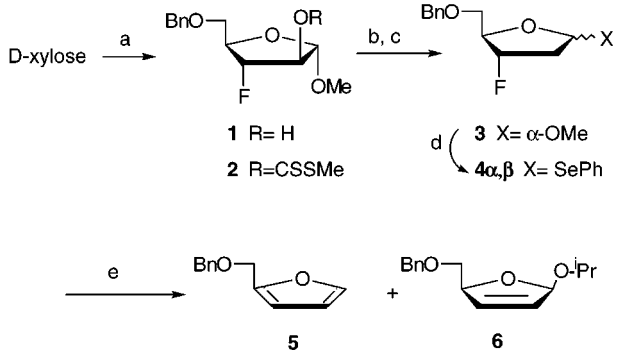
Scheme 1



Scheme 2



Scheme 3



a) Ref. 10. b) i) NaH, toluene, ii) CS_2, iii) MeI.
c) Bu_3SnH, AIBN. d) PhSeH, $BF_3.OEt_2$, CH_2Cl_2, r.t., 1h.
e) *t*-BuOOH, $Ti(O\text{-}iPr)_4$, NEt_3, CH_2Cl_2.

propyl orthotitanate[14] gave 2(5)-benzyloxymethylfuran **5** and compound **6** with yields of 84% and 6.4%, respectively.

When **4**α was oxidized using the same conditions, compounds **5** and **6** were isolated with yields of 62% and 10%, respectively. Both compounds may have been obtained due to the previous formation of the fluoroglycal which led to two competitive reactions: (a) the formation of the complex between glycal and tetraisopropyl orthotitanate where orthotitanate acts as the activator[15] of the carbon−fluorine bond leading to furan **5** by elimination or (b) the attack of the isopropoxy anion, generated in the reaction, on C-1 of the above-mentioned complex to give compound **6** through an S_N2' nucleophilic substitution reaction. Our attempts to generate the glycal from **1** or from the xanthate derivative **2** also failed.[16] This behavior is in good agreement with recently published results.[17] This method was used because it allowed rather unstable glycals to be obtained; the glycals with the electronegative substituent at position 3 in the sugar moiety are probably unstable and decompose quickly in the reaction conditions.

Then we speculated that a selenonium intermediate (Scheme 2) could be obtained through a 1,2-migration of the 1-α-phenylselenenyl group, for which the presence of a leaving group in the 2β position is necessary. Such 1,2-migration reactions have been used to modify sugars[18,19] starting from phenyl 1-thioglycosides with trans 1,2 substituents, but to the best of our knowledge, they have not been applied to the synthesis of nucleosides. Moreover, it is well-known that the hydroxyl group can be activated by the Mitsunobu reaction.[20] These conditions are compatible with the glycosidic bond formation in nucleoside synthesis.

In this context, compound **9** was considered appropriate to perform glycosylation under Mitsunobu conditions. Initially, we tried to obtain **9** by treating **1** with phenylselenol in the presence of $BF_3{\cdot}OEt_2$. However, the result was a very complex reaction mixture from which we failed to isolate the desired sugar in pure form. The following reaction sequence was found to be more effective. Compound **1** was acetylated by the action of acetic anhydride in pyridine and treated without purification with phenylselenol in the presence of $BF_3{\cdot}OEt_2$ in dichloromethane to afford **8**, the standard deprotection of which gave **9** (Scheme 4). The total yield of **9** from **1** was greater than 75%. In this way, only the α anomer is obtained.

To test glycosylation using the Mitsunobu reaction, we initially chose 6-chloropurine as the base because it can easily be transformed into other bases. The treatment of **9** with triphenylphosphine and DEAD in the presence of 6-chloropurine in DMF (Table 1, entry 1) led to a mixture of products from which the individual nucleosides **11**α,β and **12**α,β were isolated in 81% total yield with a N^9/N^7 ratio of 4.5:1. The α/β ratio was poor and did not exceed 1:1.8 in the case of N^7-nucleosides or 1:1.7 in the case of

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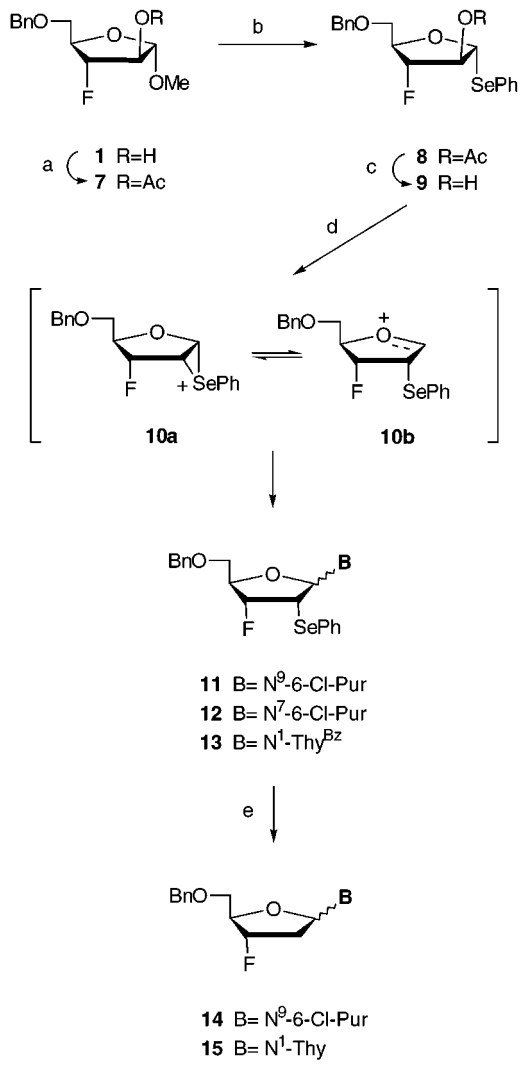
Scheme 4



a) Ac_2O, Py, rt, 4h. b) PhSeH, $BF_3.OEt_2$, CH_2Cl_2, r.t.
c) NH_3, MeOH. d) Ph_3P, DEAD, 6-Cl-Purine or Thy^{Bz}.
e) Bu_3SnH, AIBN, toluene, reflux.

N^9-nucleosides. All attempts to improve the α/β stereoselectivity by changing the solvents (entries 2, 3, 4, and 7) and the temperature (entry 5) or by using a silylated base (entry 4) or polymer-bounded triphenylphosphine[21] (entry 8) failed. The best results as far as α/β stereoselectivity was concerned (**11**α/**11**β = 1:2.7 and **12**α/**12**β = 1:3.5) were obtained when the ratio **9**/base increased from 1:2 to 1:4 (entry 6). It should be noted that using EtOAc (entry 7) or silylated base (entry 4) led to the formation of **11**α as the main product (ratio **11**β/**11**α = 1:4.6 and 1:3.7, respectively). The α anomer was formed because the selenonium cation **10a** generated under the Mitsunobu conditions was in equilibrium with the oxonium cation **10b**. This equilibrium is shifted to **10b**, which agrees with what was observed in the case of phenylsulfenyl derivatives obtained from glycals.[11]

The same glycosylation procedure can be used to obtain pyrimidine derivatives. Thus, when N^3-benzoylthymidine[22] was used as the base in the best glycosylation conditions described above (see Table 1), compounds **13**α,β were obtained in moderate yield and low stereoselectivity (58% yield, ratio α/β = 3:2) as an inseparable mixture.

When treated with tributyltin hydride, compounds **11**β and **13**α,β were easily converted with excellent yields into the corresponding 2′,3′-dideoxy-3′-fluoronucleosides **14** and **15**α,β, respectively. It should be pointed out that prolonged heating of compound **11**β led to the dechlorination of the purine base.

Compounds **11**α and **11**β were obtained in the crystalline form, and the X-ray diffraction of a monocrystal confirmed the proposed structures. The conformation of the sugar rings belongs in both cases to the *S*-hemisphere[23] and is $_3E$ for compound **11**α and ^2E for **11**β. In both compounds, the fluorine and the substituent at position 4 adopt pseudoaxial positions, while the PhSe group and 6-Cl-purine are also in pseudoequatorial position in both cases; the molecular geometry about the glycosidic bond is anti, and conformation about the C4′−C5′ bond is gauche−gauche in both structures.

In ^{1}H NMR spectroscopy, coupling constants $J_{1',2'}$ usually give information about the anomeric configuration, but in this case, both $J_{1',2'}$ constants have very similar values ($J_{1',2'}$ = 9.1−9.5 Hz for β anomer and 7.5 for α anomer). More informative are the ^{13}C NMR spectrum (the C-1′ resonance signal for the β anomers appears 2−3 ppm downfield of the signal for the α anomers, and the C-8 resonance signal in α anomers appears as a doublet due to a long-distance coupling constant, $^5J_{F3',C8}$ = ∼11.4−13.7 Hz) and the ^{19}F spectrum (F-3′ is shifted 4.4−4.8 ppm downfield in the α anomers).

In conclusion, 2′,3′-dideoxy-3′-fluoronucleosides were obtained from phenyl 3-deoxy-3-fluoro-1-seleno-α-*arabino*-furanosides. The synthesis of purinic nucleosides was more efficient than the synthesis of pyrimidinic nucleosides. A novel glycosylation procedure was established, which involved activating the 2-OH in Mitsunobu conditions, 1,2-migration of the phenylselenenyl group, and glycosylation at C-1. Since **10b** is the main intermediate in the reaction, modification in the phenylselenenyl group is expected to improve the stereoslectivity of the reaction. Deselenization by treatment with tributyltin hydride leads to the 2′-deoxynucleosides.

Experimental Section

General Procedures. Melting points were measured in an open capillary and are uncorrected. ^{1}H, ^{13}C, and ^{19}F spectra (300, 75, and 288 MHz, respectively) were recorded in $CDCl_3$ using Me_4Si, the central peak of $CDCl_3$ at 77 ppm, and $CFCl_3$, respectively, as internal reference. Chemical shifts are reported in parts per million and coupling constants in hertz. Elemental analyses were performed at the Servei de Recursos Cientifics (Universitat Rovira i Virgili). TLC was performed on silica gel G/UV254 plates: hexanes−Et_2O 4:1 v/v (A), CH_2Cl_2 (B), and hexanes−EtOAc 7:5 v/v (C) solvent systems were used. Flash column chromatography was performed on silica gel 60 A (35−70 μm) and MPLC on silica gel 60 A (6−35 μm). Solvents for chromatography were distilled at atmospheric pressure before use. All the reactions were carried out under an atmosphere of dry argon in oven-dried glassware.

Methyl 5-*O*-Benzyl-2,3-dideoxy-3-fluoro-α-D-*erythro*-pentofuranoside (3). NaH (1.0 g of a 60% suspension in oil, 25 mmol) was added to a cooled solution (0 °C) of **1** (5.4 g, 21.1 mmol) in

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Table 1. Synthesis of Nucleosides 11 and 12 from 9 via the Mitsunobu Reaction[a]

entry	molar ratio **9**:base:Ph_3P:DEAD	time (min)	solvent	ratio **11**β/**11**α	ratio **12**β/**12**α	ratio $\sum$ **11**α,β/$\sum$ **12**α,β	$\sum$ yield, %[b]
1	1:2.1:1.5:1.5	5	DMF	1.7:1	1.8:1	4.5:1	81
2	1:2.3:1.5:1.5	5	THF	2.2:1	1.2:1	1.4:1	40
3	1:2.0:1.5:1.5	10	MeCN	1:1.6	2.8:1	3.1:1	32
4[c]	1:2.0:1.5:1.5	*d*	toluene	1:3.7	1:1.2	4.6:1	78
5[e]	1:2.0:1.5:1.5	60[f]	DMF	1.5:1	1:1.2	4.7:1	59
6	1:4.0:1.9:1.5	5	DMF	2.7:1	3.5:1	3.8:1	77
7	1:4.0:1.5:1.5	5	EtOAc	1:4.6	1:1.8	2.5:1	68
8[g,h]	1:4.2:1.8:1.5	180	DMF	1.4:1	2.1:1	2.8:1	59

[a] Reactions were performed at 0.2 mmol scale of **9**. [b] Summary yields of pure nucleosides are given. [c] Silylated base was used. [d] Reaction time ~7 days. [e] Recovery of **9**, 36.5%. [f] The reaction was carried out at −15, −10 °C. [g] Recovery of **9**, 3.5%. [h] Polymer-bound triphenylphosphine was used.

dry toluene (150 mL), stirred for 1 h, and treated with CS_2 (1.4 mL, 1.76 g, 23.2 mmol). After stirring for 1 h, methyl iodide (1.44 mL, 3.28 g, 23.1 mmol) was added. The reaction mixture was heated to room temperature and left for 2 h. It was then evaporated, and the residue was dissolved in dry Et_2O (250 mL). The inorganic salts were filtered and washed with Et_2O (2 × 50 mL), and the combined filtrates were evaporated. The residue was dissolved in dry toluene (150 mL), and tri-*n*-butyltin hydride (6.8 mL, 7.466 g, 25.65 mmol) and AIBN (0.15 g, 0.91 mmol) were added to this solution. After boiling for 5 h, the reaction mixture was evaporated to dryness. The residue was partitioned between acetonitrile (250 mL) and hexane (200 mL) to remove tributyltin derivatives. The acetonitrile layer was separated and evaporated. The residue was chromatographed with a linear gradient of Et_2O in hexane (0−50% v/v, 2 L) to yield 3.15 g (62%) of **3** as an oil and 1.71 g (recovery 31.7%) of **1**. **3**: R_f 0.26 (A); $[\alpha]^{25}_D$ 96.8° (c = 1.31, $CHCl_3$); ^{1}H NMR δ 7.37−7.28 (m, 5H), 5.20−5.00 (m, 2H), 4.62−4.39 (m, 3H), 3.64−3.53 (m, 2H), 3.40 (s, 3H), 2.31−2.17 (m, 2H); ^{13}C δ 137.5, 128.4, 127.8, 127.6, 105.4, 94.0 (d, J = 177.7), 83.1 (d, J = 25.67), 73.53, 69.7 (d, J = 9.35), 55.2, 39.7 (d, J = 20.11); ^{19}F NMR δ −176.34 (m). Anal. Calcd for $C_{13}H_{17}O_3F$: C, 65.0; H, 7.13. Found: C, 65.06; H, 7.23.

Phenyl 5-*O*-Benzyl-1,2,3-trideoxy-3-fluoro-1-seleno-α,*β*-D-*erythro*-pentofuranoside (4α,*β*). Phenylselenol (60 μLl, 0.089 g, 0.57 mmol) and boron trifluoride ethyl etherate (50 μL, 0.056 g, 0.40 mmol) were added to a solution of 0.121 g (0.51 mmol) of **3** in dry CH_2Cl_2 (2.0 mL) protected from light. After stirring for 1 h, Et_3N (0.1 mL) was added and evaporated to dryness. The residue was chromatographed with hexane (300 mL) to remove an excess of phenylselenol and with Et_2O in hexane (2% v/v, 300 mL) to yield 0.062 g (33.5%) of **4***β* as an oil, and finally **4**α was eluted with Et_2O in hexane (5% v/v, 250 mL) to yield 0.114 g (62%) as white crystals. **4***β*: R_f 0.61 (A); $[\alpha]^{25}_D$ −120.8° (c = 1.53, $CHCl_3$); ^{1}H NMR δ 7.64−7.23 (m, 10H), 5.79 (dd, 1H, J = 8.85, 5.49), 5.12 (dd, 1H, J = 54.1, 4.95), 4.55 (d, 1H, J = 12.1), 4.50 (d, 1H, J = 12.1), 4.37 (ddt, 1H, J = 25.30, 6.20, 4.34), 3.57 (dd, 1H, J = 10.40, 4.34), 3.36 (ddd, 1H, J = 10.4, 6.19, 1.0), 2.61 (ddd, 1H, J = 20.94, 14.68, 5.49), 2.26 (m, 1H, J = 37.84, 14.68, 5.49, 4.95); ^{13}C NMR δ 137.68, 134.30, 129.00, 128.4, 127.7, 94.85 (d, C-3, J = 177.4), 84.94 (d, J = 23.4), 81.27, 73.45, 69.47 (d, J = 10.6), 40.07 (d, J = 21.1); ^{19}F NMR δ −178.56 (m, F-3). Anal. Calcd for $C_{18}H_{19}O_2FSe$: C, 59.18; H, 5.24. Found: C, 59.38; H, 5.33. **4**α: mp 63−65 °C (hexanes−Et_2O); R_f 0.51 (A); $[\alpha]^{25}_D$ 239.45° (c = 1.55, $CHCl_3$); ^{1}H NMR δ 7.67−7.25 (m, 10H), 6.09 (d, 1H, H-1, J = 6.87), 5.19 (dd, 1H, J = 56.07, 5.90), 4.63 dm, 1H, J = 26.4), 4.57 (d, 1H, J = 11.9), 4.49 (d, 1H, J = 11.9), 4.47 (m, 3H), 3.67 (ddd, 1H, J = 10.72, 3.51, 1.25), 3.60 (dd, 1H, J = 10.72, 3.81), 2.72 (m, 1H, J = 37.08, 14.96, 6.87, 5.89), 2.50 (dd, 1H, J = 23.7, 15.0); ^{13}C NMR δ 137.67, 133.5, 129.00, 128.4, 127.8, 127.6, 127.30, 93.98 (d, J = 177.56), 84.3, 83.64 (d, J = 24.91), 73.54, 69.01 (d, J = 9.11), 41.36 (d, J = 20.74); ^{19}F NMR δ −174.04 (m). Anal. Calcd for $C_{18}H_{19}O_2FSe$: C, 59.18; H, 5.24. Found: C, 59.29; H, 5.33.

Oxidation of Phenyl 1-Selenoglycosides 4α and 4*β*. (a) A total of 0.34 mL of *t*-BuOOH (3 M solution in toluene, 1.02 mmol), 0.14 mL (0.102 g, 1.02 mmol) of Et_3N, and 0.3 mL (0.289 g, 1.02 mmol) of tetraisopropyl orthotitanate were added to a solution of 0.369 g (1.02 mmol) of **4**α in dry CH_2Cl_2 (6.0 mL) at −15 °C with vigorous stirring. The reaction mixture was left to warm to room temperature for 2 h, and the stirring was maintained for 20 h. As the reaction was incomplete, an extra amount of 0.34 mL of *t*-BuOOH and 0.14 mL of Et_3N was added and the reaction mixture was stirred for 5 h. After adding 0.17 mL of *t*-BuOOH and 0.14 mL of Et_3N and stirring for 1 h, the TLC data showed the reaction to be complete and the solution was evaporated to dryness. The residue was chromatographed with a linear gradient of Et_2O in hexane (0−30% v/v, 1.5L) to give 0.118 g (62%) of **5** which was identical in all respects to the reference sample[24] and 0.025 g (10%) of **6**. **6**: R_f 0.34 (A); ^{1}H NMR δ 7.37−7.28 (m, 5H), 6.16 (dt, 1H, J = 6.3, 1.5, 1.5), 5.96 (ddd, 1H, J = 4.2, 1.5, 0.9), 5.86 (ddd, 1H, J = 6.3, 2.6, 0.9), 5.08 (m, 1H), 4.62 (d, 1H, J = 12.3), 4.56 (d, 1H, J = 12.3), 3.99 (m, 1H, J = 6.0), 3.54 (m, 2H), 1.18−1.24 (m, 6H); ^{13}C NMR δ 132.7, 132.5, 128.4, 128.2, 127.6, 107.1, 84.0, 73.4, 72.2, 70.0, 23.7; 22.3. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.58; H, 8.06. Found: C, 72.33, H, 8.22.

(b) Starting from 0.092 g (0.25 mmol) of **4***β* in analogous conditions, 0.04 g (84%) of **5** and 0.004 g (6.4%) of **6** were obtained which were identical in all the respects with reference samples.

Phenyl 2-*O*-Acetyl-5-*O*-benzyl-1,3-dideoxy-3-fluoro-1-seleno-α-D-*arabino*-furanoside (8). Ac_2O (3.0 mL) was added to a solution of 0.720 g (2.81 mmol) of **2** in pyridine (10 mL), and the solution was stirred for 3 h and evaporated to dryness. The residue was coevaporated with the mixture of toluene:EtOH (1:1 v/v, 5 × 30 mL) and dried in high vacuum for 5 h to give 0.827 g (98.5%) of **7**, which was used in the next step without purification: R_f 0.34 (B). Phenylselenol (0.44 mL, 0.653 g, 4.15 mmol) and boron trifluoride ethyl etherate (0.7 mL, 0.786 g, 5.54 mmol) were added to a solution of 0.827 g (2.77 mmol) of **7** in dry CH_2Cl_2 (15 mL), and the solution was stirred for 3 h. After standard workup the residue was chromatographed with hexane (400 mL) to remove the excess of phenylselenol. The compound **8** was eluted with CH_2Cl_2 to yield 1.073 g (92%) as an oil: R_f 0.72 (B); $[\alpha]^{25}_D$ +140.82° (c = 1.71, $CHCl_3$); ^{1}H NMR δ 7.68−7.25 (m, 10H), 5.83 (br s, 1H), 5.45 (dt, 1H, J = 15.7, 1.3, 1.3), 5.03 (dddd, 1H, J = 52.3, 4.0, 1.3, 1.1), 4.68−4.54 (m, 3H), 3.75 (dd, 1H, J = 10.8, 4.7), 3.69 (dd, 1H, J = 10.8, 4.73), 2.01 (s, 3H); ^{13}C NMR δ 137.8, 134.2, 129.1, 128.4, 127.9 127.8, 127.6, 95.4 (d, J = 184.26), 86.2, 82.1 (d, J = 5.2), 77.01, 81.7 (d, J = 3.8), 73.5, 67.9 (d, J = 5.95), 20.6; ^{19}F NMR δ 187.62 (m). Anal. Calcd for $C_{20}H_{21}O_4FSe$: C, 56.74; H, 5.00. Found: C, 56.94, H, 5.10.

Phenyl 5-*O*-Benzyl-3-deoxy-3-fluoro-1-seleno-α-D-*arabino*-furanoside (9). A total of 1.073 g (2.53 mmol) of **8** was treated at 0 °C for 4 h with a saturated solution of ammonia in MeOH (15 mL). After the evaporation, the residue was chromatographed with CH_2Cl_2 to yield 0.81 g (84%) of **9** as an oil: R_f 0.61(B), 0.71 (C); $[\alpha]^{21}_D$ +196.9° (c = 1.0, $CHCl_3$); ^{1}H NMR δ 7.68−7.25 (m, 10H), 5.84 (br s, 1H), 4.97 (br d, 1H, J = 52.2), 4.63 (dm, 1H, J = 28.9), 4.65 (d, 1H, J = 11.7), 4.51 (d, 1H, J = 11.7), 4.53 (br d, 1H,J = 12.4), 3.74 (d, 2H, J = 2.2), 3.70 (s, 1H); ^{13}C NMR δ 136.2, 133.8, 129.1, 128.7, 128.4, 128.0, 127.5, 97.4 (d, J = 183.9), 90.9, 83.5 (d, J = 26.1), 79.7 (d, J = 24.5), 74.0, 68.7 (d, J = 10.4); ^{19}F NMR δ 178.05 (m). Anal. Calcd for $C_{18}H_{19}O_3FSe$: C, 56.70, H, 5.02. Found: C, 56.93, H, 5.17.

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General Glycosylation Procedure. **Synthesis of 9-(5-*O*-Benzyl-2,3-dideoxy-3-fluoro-2-phenylselenenyl-α,*β*-D-ribofuranosyl)-6-chloropurine (11α, 11*β*) and 7-(5-*O*-Benzyl-2,3-dideoxy-3-fluoro-2-phenylselenenyl-α,*β*-D-ribofuranosyl)-6-chloropurine (12α and 12*β*).** 6-Chloropurine (59 mg, 0.38 mmol), Ph_3P (79 mg, 0.3 mmol), DMF (2.5 mL), and DEAD (52 mg, 0.3 mmol) were added under vigorous stirring to a mixture of **9** (76 mg, 0.2 mmol) which had been predried at 40 °C in an oil pump vacuum. After the reaction was complete (5 min), the reaction mixture was diluted with EtOAc (25 mL) and washed with H_2O (3 × 10 mL).The combined H_2O extracts were washed with EtOAc (10 mL), and the organic extracts were combined, dried, and evaporated to dryness. The residue was chromatographed using MPLC with a linear EtOAc gradient in hexane (0−75% v/v) to obtain 82 mg (81%) of **11**α,*β* and **12**α,*β* (see Table 1). The nucleosides were eluted in the following order: **11***β*, **11**α, **12***β*, and **12**α.

11*β*: R_f 0.59 (C); mp 110−111 °C (EtOH); $[\alpha]^{25}_D$ −11.03° (*c* = 0.29, $CHCl_3$); ^{1}H NMR *δ* 8.57 (s, 1H), 8.09 (s, 1H), 7.40−6.82 (m, 10H), 6.52 (d, 1H, *J* = 9.5), 5.41 (dd, 1H, *J* = 53.2, 4.1), 4.67−4.41 (m, 4H), 3.82 (ddd, 1H, *J* = 10.6, 3.5, 1.3), 3.76 (dd, 1H, *J* = 10.6, 3.1); ^{13}C NMR *δ* 151.7, 143.5, 136.9, 134.3, 128.7, 128.6, 128.2, 127.7, 95.5 (d, *J* = 179.7), 90.4, 83.4 (d, *J* = 24.9), 73.8, 69.4 (d, *J* = 11.3), 47.6 (d, *J* = 20.0); ^{19}F NMR *δ* −179.5 (ddd*J* = 54.1, 37.3, 26.3). Anal. Calcd for $C_{23}H_{20}N_4O_2SeFCl$: C, 53.35; H, 3.89; N, 10.82. Found: C, 53.55; H, 4.02; N, 10.81.

11α: R_f 0.5 (C); mp 97−98 °C (EtOH); $[\alpha]^{25}_D$ +141.02° (*c* = 1.17, $CHCl_3$); ^{1}H NMR *δ* 8.68 (s, 1H), 8.4 (s, 1H), 7.35−7.25 (m, 10H), 6.89 (d, 1H, *J* = 7.5), 5.38 (dd, 1H, *J* = 54.1, 4.5), 4.87 (dt, 1H, *J* = 23.6, 2.8, 2.8), 4.59 (d, 1H, *J* = 11.8), 4.51 (d, 1H, *J* = 11.8), 4.51 (ddd, 1H, *J* = 37.0, 7.5, 4.5), 3.74−3.65 (m, 2H); ^{13}C NMR *δ* 152.0, 144.3 (d, *J* = 13.7), 133.8, 129.4, 128.6, 128.3, 128.1, 127.5, 95.4 (d, *J* = 178.1), 86.4, 84.9 (d, *J* = 23.4), 73.8, 69.7 (d, *J* = 11.3), 49.3 (d, *J* = 19.9); ^{19}F NMR *δ* −174.7 (ddd *J* = 54.1, 37.0, 23.6). Anal. Calcd for $C_{23}H_{20}N_4O_2SeFCl$: C, 53.35; H, 3.89; N, 10.82. Found: C, 53.22; H, 4.05; N, 10.80.

12*β*: R_f 0.31 (C); mp 96−97 °C (EtOH); ^{1}H NMR *δ* 8.8 (s, 1H), 8.5 (s, 1H), 7.44−6.81 (m, 10H), 7.00 (d, 1H, *J* = 9.1), 5.37 (dd, 1H, *J* = 52.8, 3.9), 4.70 (d, 1H, *J* = 11.3), 4.61 (ddd, 1H, *J* = 26.1, 2.0, 1.8), 4.59 (d, 1H, *J* = 11.3), 4.13 (ddd, 1H, *J* = 36.4, 9.1, 3.9), 3.86 (dt, 1H, *J* = 10.9, 2.0, 2.0), 3.78 (dd, 1H, 10.9, 1.8); ^{13}C NMR *δ* 152.0, 146.6, 133.5, 129.0, 128.9, 128.5, 128.1, 95.8 (d, *J* = 179.7), 91.2, 83.6 (d, *J* = 25.0), 74.0, 69.5 (d, *J* = 11.8), 50.9 (d, *J* = 20.2); ^{19}F NMR *δ* −178.1 (ddd, *J* = 52.8, 36.4, 26.1). Anal. Calcd for $C_{23}H_{20}N_4O_2SeFCl$: C, 53.35; H, 3.89; N, 10.82. Found: C, 53.52; H, 4.00; N, 10.71.

12α: R_f 0.2 (C); mp 130−131 °C (EtOH); $[\alpha]^{21}_D$ +2.22° (*c* = 0.335, $CHCl_3$); ^{1}H NMR *δ* 8.87 (s, 1H), 8.61 (s, 1H), 7.38−7.10 (m, 11H), 5.39 (dd, 1H, *J* = 53.8, 4.7), 4.89 (dt, 1H, *J* = 22.7, 2.4, 2.4), 4.58 (ddd, 1H, *J* = 37.8, 7.5, 4.7), 4.59 (d, 1H, *J* = 11.5), 4.54 (d, 1H, *J* = 11.5), 3.76 (d, 2H, *J* = 2.4); ^{13}C NMR *δ* 152.2, 148.3 (d, *J* = 11.4), 133.5, 129.4, 128.7, 128.6, 128.4, 128.2, 127.5, 95.4 (d, *J* = 179.0), 88.5, 84.8 (d, *J* = 23.6), 73.9, 70.1 (d, *J* = 11.0), 50.6 (d, *J* = 19.5); ^{19}F NMR *δ* −173.7 (ddd, *J* = 53.8, 37.8, 22.7). Anal. Calcd for $C_{23}H_{20}N_4O_2SeFCl$: C, 53.35; H, 3.89; N, 10.82. Found: C, 53.46; H, 4.03; N, 10.71.

1-(5-*O*-Benzyl-2,3-dideoxy-3-fluoro-2-phenylselenenyl-α,*β*-D-ribofuranosyl)-*N*^{3}-benzoylthymine (13). Using the general glycosylation procedure starting from 0.078 g (0.21 mmol) of **9** and 0.184 g (0.8 mmol) of *N*^{3}-benzoylthymine,[21] 0.073 g (58%) of **13** was obtained as an α,*β* mixture: R_f 0.47 (C); ^{1}H NMR *δ* 6.74 (d, *J* = 8.1, H-1α), 6.56 (d, *J* = 9.5, H-1*β*); ^{19}F NMR *δ* −173.25 (ddd, *J* = 53.9, 40.3, 22.0, F-3*β*), −179.95 (br m, F-3α).

General Procedure for the Reduction of 2′-Phenylselenenyl Nucleosides. Tributyltin hydride (0.06 mL, 64.9 mg, 0.22 mmol) and AIBN (5 mg, 0.03 mmol) were added to a solution of nucleoside (0.08 mmol) in dry toluene (2 mL) and refluxed for 1 h. After the evaporation the residue was chromatographed using MPLC by elution with a linear gradient of EtOAc in hexane.

9-(5-*O*-Benzyl-2,3-dideoxy-3-fluoro-*β*-D-ribofuranosyl)-6-chloropurine (14). Starting from 86.3 mg (0.167 mmol) of **11***β* the general procedure of reduction was followed [chromatography: linear gradient of EtOAc in hexane (0−70% v/v, V = 0.6 L)] to obtain 55 mg (94%) of **14**: R_f 0.42 (C); $[\alpha]^{21}_D$ −42.1° (*c* = 1.15, $CHCl_3$); ^{1}H NMR *δ* 8.70 (s, 1H), 8.46 (s, 1H), 7.40−7.22 (m, 5H), 6.65 (t, 1H, *J* = 7.5), 5.39 (dt, 1H, *J* = 55, 2.7, 2.7), 4.60 (d, 1H, *J* = 11.7), 4.53 (ddd, 1H, *J* = 26, 3, 3), 4.52 (d, 1H, *J* = 11.7), 3.77 (ddd, 1H, *J* = 10, 3, 1.5), 3.71 (dd, 1H, *J* = 10, 2.7), 2.90−2.65 (m, 2H); ^{13}C NMR *δ* 152.1, 143.6, 136.8, 128.7, 128.3, 128.0, 94.9 (d, *J* = 177.53), 84.8, 84.76 (d, *J* = 25.05), 73.9, 69.6 (d, *J* = 11.4), 39.7 (d, *J* = 21.6); ^{19}F NMR *δ* −176.5 (m). Anal. Calcd for $C_{17}H_{16}N_4O_2FCl$: C, 57.76; H, 4.40; N, 14.76. Found: C, 57.58; H, 4.30; N, 15.00.

1-(5-*O*-Benzyl-2,3-dideoxy-3-fluoro-*β*-D-ribofuranosyl)-thymine (15*β*) and 1-(5-*O*-Benzyl-2,3-dideoxy-3-fluoro-α-D-ribofuranosyl)thymine (15α). Starting from 46.8 mg (0.079 mM) of **13** the general procedure of reduction was used. The reaction crude obtained was treated with a mixture of EtOH−30% NH_4OH (1:1 v/v, 2 mL) for 12 h. Then, the reaction mixture was evaporated to dryness, coevaporated with the mixture of toluene−EtOH (1:1 v/v, 4 × 5 mL), and chromatographed (0−50% v/v, *V* = 0.5 L) to give 7.0 mg (27.5%) of **15***β* and 8.3 mg (32%) of **15**α.

15*β*: R_f 0.23 (C); ^{1}H NMR *δ* 8.38 (br s, 1H), 7.57 (s, 1H, H-6), 7.39−7.23 (m, 5H), 6.49 (dd, 1H, *J* = 9.3, 5.7), 5.29 (dd, 1H, *J* = 53.7, 4.8), 4.60 (s, 2H), 4.41 (bd, 1H, *J* = 27.9), 3.83 (dt, 1H, *J* = 10.8, 1.8, 1.8), 3.73 (dd, 1H, *J* = 10.8, 2.1), 2.58 (ddd, 1H, *J* = 20.4, 14.7, 1.0), 2.19 (m, 1H, *J* = 40.2, 14.7, 9.3, 4.5), 1.63 (s, 3H); ^{13}C NMR *δ* 137.1, 135.6, 128.8, 128.4, 127.6, 94.9 (d, *J* = 177.6), 86.6, 84.0 (d, *J* = 25.1), 73.7, 70.1 (d, *J* = 11.4), 38.6 (d, C-2′, *J* = 20.5), 12.1 (s, Me-5); ^{19}F NMR *δ* −175.5 (ddd, *J* = 54, 41.5, 27, 22).

15α: R_f 0.18 (C); ^{1}H NMR *δ* 8.60 (br s, 1H), 7.39−7.23 (m, 6H), 6.39 (dd, 1H, *J* = 7.8, 1.8), 5.26 (dd, 1H, *J* = 54.0, 4.8), 4.71 (dm, 1H, *J* = 23.4, 4.2, 3.3), 4,58 (d, 1H, *J* = 13.2), 4,50 (d, 1H, *J* = 13.2), 3.59 (dd, 1H, *J* = 10.5, 3.3), 3.53 (ddd, 1H, *J* = 10.5, 4.2, 1.8), 2.82 (dddd, 1H, *J* = 40.8, 15.6, 7.8, 4.8), 2.29 (dd, 1H, *J* = 24.9, 15.6), 1.94 (s, 3H); ^{13}C NMR *δ* 137.3, 135.5, 128.7, 128.1, 127.72, 94.6 (d, *J* = 175.28), 86.6, 86.0 (d, *J* = 22.8), 73.7, 69.8 (d, *J* = 11.4), 39.7 (d, *J* = 20.5), 12.6.

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Supporting Information Available: Experimental description, figures, and tables of data, details of crystal structure determinations, bond lengths and angles, and anisotropic displacement parameters for compounds **11**α and **11***β*. Table containing selected data of ^{1}H, ^{13}C, and ^{19}NMR spectra of compounds **11**α, **11***β*, **12**α, and **12***β* and related comments. This material is available free of charge via the Internet at http://pubs.acs.org.

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