Notes

Stereoselective Synthesis of 2′,3′-Dideoxynucleosides by Addition of Selenium Electrophiles to Glycals. A Formal Synthesis of D4T from 2-Deoxyribose

Yolanda Díaz, Anas El-Laghdach, Mª Isabel Matheu, and Sergio Castillón*

Departament de Química, Universitat Rovira i Virgili, Pça. Imperial Tarraco 1, 43005 Tarragona, Spain

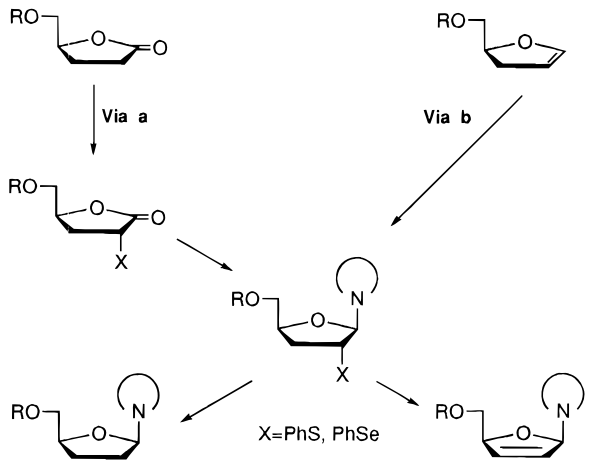
Received August 30, 1996

2′,3′-Dideoxynucleosides are among the most active agents against human immunodeficiency virus (HIV), which is the causative agent for acquired immunodeficiency syndrome (AIDS). In particular, 3′-azido-3′-deoxythymidine (AZT),[1] 2′,3′-dideoxyinosine (ddI),[1] 2′,3′-didehydro-2′-deoxythymidine (D4T),[2ab] and 2′,3′-dideoxycitidine (ddC)[2c,d] have been approved for the treatment of AIDS.

These compounds have been prepared by structural modification of naturally occurring nucleosides or through glycosylation reactions.[3] The main synthetic problem in this latter approach is the control of the stereoselectivity in the absence of substituents at position 2.[4] To overcome this drawback, several reports have described the use of easily removable groups, such as phenylsulfenyl or phenylselenenyl, at position 2 in the furanose ring, which efficiently control the stereoselectivity and enable 2′,3′-dideoxy- and 2′,3′-didehydro-2′,3′-dideoxy nucleosides to be easily obtained. The preparation of the 2′,3′-dideoxy-2′-phenylsulfenyl[5] or 2′,3′-dideoxy-2′-phenylselenenyl[6] nucleosides usually involves four steps, and although good stereoselectivity is obtained in the glycosylation reaction, the validity of the method is limited by the low stereoselectivity in the sulfur or selenium introduction step (Scheme 1, via a).

Better stereoselectivities have been obtained in the synthesis of 2′,3′-dideoxy-2′-iodo-[7,8] and 2′,3′-dideoxy-2′-phenylsulfenyl[9] nucleosides starting from glycals by way of successive NIS,[7] I_2,[8] or PhSCl[9] addition and glycosylation (Scheme 1, via b). To this end the furanoid glycal **6** has usually been prepared from the dihydro-5-(hydroxymethyl)-2(3*H*)-furanone[10,11] or by asymmetric synthesis.[8] Among the groups at position 2 which are able to provide anchimeric assistance, selenium seems to be the best group to choose due to its facile oxidative elimination and reductive removal in mild conditions.[6a] In this report we show that glycal **6** can be synthesized from 2-deoxyribose and stereoselectively converted into **17**, a precursor of D4T, through selenium-mediated glycosylation and selenoxide elimination.

Scheme 1



Thus, 2-deoxyribose was converted into the phenyl 1-seleno-glycoside **4** (mixture α/β = 1.9:1) in four steps involving methyl glycoside synthesis, selective 5-OH protection, Barton deoxygenation, and treatment with PhSeH in the presence of $BF_3{\cdot}OEt_2$. Oxidation of **4** (mixture α/β) gave the glycal **6** with a yield of 52%. We observed that the elimination in the α anomer was faster than in the β. Since glycal **6** turned out to be rather unstable, in order to prevent some glycal decomposition during the reaction, phenyl 1-seleno-glycosides α and β were treated separately and the yield increased to 63% (Scheme 2).[12]

The reaction of glycal **6** with bis(trimethylsilyl)uracil,[13] PhSeCl, and AgOTf at room temperature in ether[14] led to a mixture of 2′-selenenyl nucleosides **8** and **13** in a

(1) (a) Mitsuya, H.; Yarchoan, R.; Broder, S. *Science* **1990**, *249*, 1533. (b) *Design of anti-AIDS Drugs*; DeClercq, E., Ed.; Elsevier: New York, 1990. (c) *AIDS: Modern Concepts and Therapeutic Challenges*; Broder, S., Ed., Marcel Dekker: New York, 1987.

(2) (a) Mansouri, M. M.; Starrett, J. E.; Ghazzouli, I.; Hitchcok, M. J. M.; Sterzycki, R. Z.; Brankovan, V.; Lin, T. S.; August, E. M.; Prussof, W. H.; Sommadossi, J. P.; Martin, J. C. *J. Med. Chem.* **1989**, *32*, 461. (b) Schinazi, R. F.; Mead, J. R.; Feorino, P. M. Insights into HIV Chemotherapy. *AIDS Res. Hum. Retroviruses* **1992**, *8*, 963. (c) Schinazi, R. F. Competitive Inhibitors of Human Inmunodeficiency Virus Reverse Transcriptase. *Perspect. Drug Discovery Des.* **1993**, *1*, 151. (d) Riddler, S. A.; Anderson, R. E.; Mellors, J. W. *Antiviral Res.* **1995**, *27*, 189.

(3) Dueholm, K. L.; Perdersen, E. B. *Synthesis* **1992**, 1.

(4) Mixtures (1:1) of α and β anomers are usually obtained in the absence of stereocontrolling groups. Recently, good stereoselectivity has been obtained starting from phenyl 1-thioglycosides using NBS as activator. See Sujino, K.; Sugimura H. *Synlett* **1992**, 553.

(5) (a) Wilson, L. J.; Liotta, D. C. *Tetrahedron Lett.* **1990**, 31, 1815. (b) Kawakami, K.; Ebata, T.; Koseki, K.; Matsushita, H.; Naoi, Y.; Itoh, K. *Chem. Lett.* **1990**, 1459.

(6) (a) Warren Beach, J. W.; Kim, H. O.; Jeong, L. S.; Nampalli, S.; Islam, Q.; Ahn, S. K.; Babu, J. R.; Chu, C. K. *J. Org. Chem.* **1992**, *57*, 3887. (b) Chu, C. K.; Babu, J. R.; Beach, J. W.; Ahn. S. K.; Huang, H.; Jeong, L. S.; Lee, S. J. *J. Org. Chem.* **1990**, *55*, 1418.

(7) Kim, C. U.; Misco, P. F. *Tetrahedron Lett.* **1992**, *33*, 5733.

(8) McDonald, F. E.; Gleason, M. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 350.

(9) (a) Wang, J.; Wurster, J. A.; Wilson, L. J.; Liotta, D. *Tetrahedron Lett.* **1993**, *34*, 4881. (b) Kawakami, K.; Ebata, T.; Koseki, K.; Matsushita, H.; Naoi, Y.; Itoh, K. *Heterocycles* **1993**, *36*, 665. (c) Kawakami, K.; Ebata, T.; Koseki, K.; Matsushita, H.; Naoi, Y.; Itoh, K. *Heterocycles* **1993**, *36*, 2765.

(10) Takle, A.; Kocienski, P. *Tetrahedron* **1990**, *46*, 4503.

(11) The γ-lactone can be obtained from L-glutamic acid (see Tanaguchi, M.; Koga, K.; Yamada, S. *Tetrahedron* **1974**, *30*, 3547), and from levoglucosenone (see Koseki, K.; Ebata, T.; Kawakami, H.; Matsushita, H.; Itoh, K. *Heterocycles* **1990**, *31*, 423).

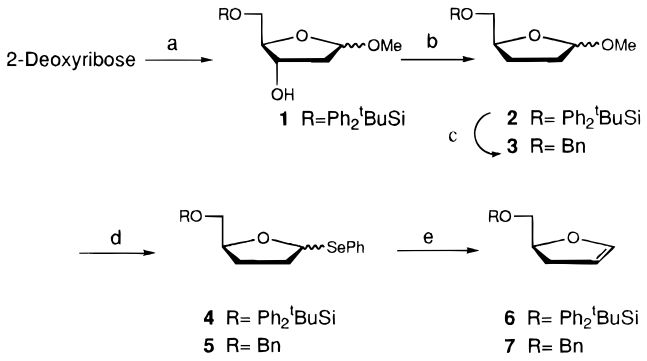
(12) Kassou, M.; Castillón, S. *Tetrahedron Lett.* **1994**, *35*, 5513.

(13) Jorgensen, P. T.; Pedersen, E. B.; Nielsen, C. *Synthesis* **1992**, 1299.

(14) Our research group has recently described the selenium-mediated stereoselective synthesis of nucleosides. (a) (Pyranosyl nucleosides) El-Laghdach, A.; Matheu, M. I.; Castillón, S. *Tetrahedron* **1994**, *50*, 12219. (b) (*threo*-furanosyl nucleosides) El-Laghdach, A.; Díaz, Y.; Castillón, S. *Tetrahedron Lett.* **1993**, *34*, 2821.

S0022-3263(96)01682-9 CCC: $14.00

Scheme 2



a) Ref. 21. b) 1. NaH, CS_2, MeI, THF. 2. Bu_3SnH, AIBN, toluene, reflux. c) 1. Bu_4NF, THF. 2. NaH, BnBr, THF. d) PhSeH, $BF_3.OEt_2$, CH_2Cl_2, -20°C. e) ^tBuOOH, $Ti(O^iPr)_4$, Et^iPr_2N, CH_2Cl_2, r.t.

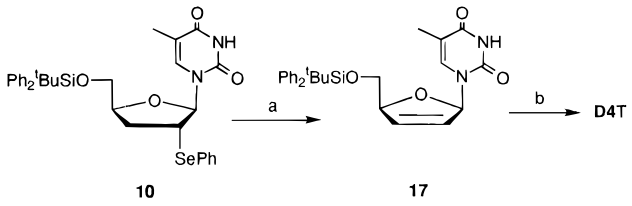
60% yield[15] and with excellent stereoselectivity (99:1) (Table 1, entry 1); however, 25% of a secondary product was also isolated. The product obtained could not be fully characterized, although data from NMR spectra showing (a) a single double bond proton (H-6), (b) 20 aromatic protons, and (c) identical signals for the carbohydrate framework and for compound **8** indicate that the 2′,5-diphenylselenenyl derivative **9** was also obtained. Actually, the formation of 5-(phenylselenenyl)uridine by reaction of uridine with PhSeCl in the presence of silver salts has been reported.[16] In a similar approach, but using $SnCl_4$ as a catalyst, the stereoselectivity was also good although the yield was low (entry 2). On the other hand, no bis-selenenyl derivative was observed, indicating that its formation depends on the catalyst used.[16]

All the 2-PhSe groups of the nucleosides obtained had α-configuration. This can be explained by the easy isomerization of the selenonium cation to give the thermodynamically more stable one, which is particularly favored in ethereal solvents in the presence of Lewis acids.[17]

Using CH_2Cl_2 as a solvent and starting at low temperatures, the yield was improved but the ratio β/α decreased (entry 3). We have shown that, in general, the best stereoselectivities were obtained with ether.[18]

Other catalysts such as TMSOTf were also used, but although yields were improved, (entry 4), the stereoselectivity was not as good as for AgOTf or $SnCl_4$. Thus, we turned our attention to the use of AgOTf as a glycosylation catalyst, and we changed the ratio of reagents to prevent the formation of the 2′,5-bis(phenylselenenyl) derivative. When a small proportion of PhSeCl was used (entry 5), no secondary products were obtained but the expected nucleosides **8** and **13** were isolated in a low yield. Controlling the evolution of the reaction, we observed that nucleosides **8** and **13** were formed first and that extension of the reaction time resulted in the subsequent formation of the bis-selenenylated derivative.

Scheme 3

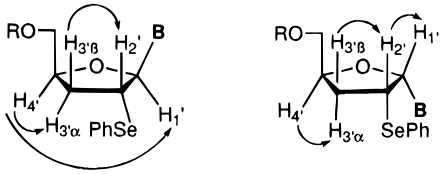


a) ^tBuOOH, $Ti(O^iPr)_4$, Et^iPr_2N, CH_2Cl_2. b) Ref 6b

Hence, we decided to increase the ratio of bis(trimethylsilyl)uracil and to control the evolution of the reaction, obtaining an excellent yield of the expected mixture of nucleosides with good stereoselectivity (entry 6). In the same manner, when the reaction was performed with bis-(trimethylsilyl)thymine, excellent yields of 2′-phenylselenenyl nucleosides were obtained with a ratio of **10**/**14** ~ 90:10 (entries 7 and 8). The different results obtained in entries 1 and 7, which were performed in identical reaction conditions, could be related to the fast isomerization from the α to the β nucleoside due to the selenenylation at position 5 of the uracil derivatives.

To prove the efficiency of this method at synthesizing purine nucleosides we performed the reaction starting from **6** with silylated 6-chloropurine in similar reaction conditions to those used for pyrimidine bases, but a lower stereoselectivity was obtained (ratio **11**/**15** = 3:1) (entry 9).[19] In order to increase the β stereoselectivity of the glycosylation step, we synthesized glycal **7** (with a smaller protecting group at position 2) in a similar way to glycal **6**. In this case a mixture β/α = 89:11 was obtained in a yield of 78% (entry 10).

The structure of isolated nucleosides was attributed taking the following facts into account: (a) the β derivatives, compounds **8**, **10**−**12**, had been previously described,[6a] (b) the relative configurations of all the nucleosides synthesized were determined either by NOESY or ^1H NMR NOE experiments, using the unequivocal configuration of the H_4' proton as reference. Thus, whereas β nucleosides showed NOE correlations between $H_1'-H_4'$, $H_2'-H_{3\beta}'$, and $H_{3\alpha}'-H_4'$, the irradiation of α-nucleosides resulted in NOE effects between $H_1'-H_2'$, $H_2'-H_{3\beta}'$, and $H_{3\alpha}'-H_4'$, (c) N-9 glycosylation for nucleosides **11**, **12** and



15, **16** was confirmed by UV spectroscopy.

The transformation of compounds **8**, **10**, and **11** into the corresponding 2′,3′-dideoxynucleosides has been described.[6a] The oxidative elimination of selenium[20] from compound **10** afforded the corresponding didehydro derivative **17** in 85% yield by using $^tBuOOH/Ti(O^iPr)_4$ as an oxidative system; the deprotection of the $^tBuPh_2Si$ group to give D4T has been reported[6b] (Scheme 3).

In conclusion, nucleophilic (PhSeH) and electrophilic (PhSeCl) selenium reagents can be nicely combined to

(15) Radical side reactions have been invoked to justify the low yields obtained in the selenium-mediated synthesis of nucleosides derived from 2,3-dihydrofuran. See ref 9b.

(16) Silver salts catalyze the selenium substitution at position 5 of nucleosides. (a) Lee, C. H.; Kim, Y. H. *Synlett* **1995**, 349. (b) Lee, C. H.; Kim, Y. H. *Tetrahedron Lett.* **1991**, *32*, 2401.

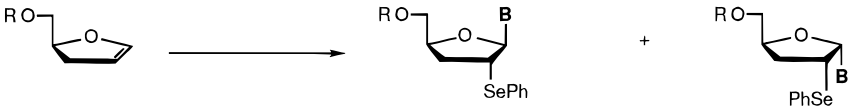
(17) (a) Perez, M.; Beau, J. M. *Tetrahedron Lett.* **1989**, *30*, 75. (b) Kaye, A.; Neidle, S.; Reese, C. B. *Tetrahedron Lett.* **1988**, *29*, 2711. (c) Jaurand, G.; Beau, J. M.; Sinaÿ, P. *J. Chem. Soc., Chem. Commun.* **1981**, 527. d) See ref 14.

(18) For an explanation of the effect of solvent and temperature on the stereoselectivity of reaction, see ref 14a.

(19) For purine type bases, a similar decrease in the stereoselectivity was also observed when sulfenyl reagents were used as catalysts; an inverted β/α ratio is reported in some cases (see ref 9c).

(20) For alternative method of synthesis of D4T based on selenoxide elimination, see: Becouarn, S.; Czernecki, S.; Valéry, J. M. *Nucleosides Nucleotides* **1995**, *14*, 1227, and references cited therein.

Table 1. Reaction of Glycals 6 and 7 with Silylated Uracil, Thymine, and 6-Chloro-purine[a]



6 R = $Ph_2{}^tBuSi$
7 R = Bn

8 B=uracil, R = $Ph_2{}^tBuSi$
9 B=5-PhSe-uracil, R = $Ph_2{}^tBuSi$
10 B=thymine, R = $Ph_2{}^tBuSi$
11 B=6-Cl-purine, R = $Ph_2{}^tBuSi$
12 B=6-Cl-purine, R =Bn

13 B=uracil, R =$Ph_2{}^tBuSi$
14 B=thymine, R =$Ph_2{}^tBuSi$
15 B=6-Cl-purine, R =$Ph_2{}^tBuSi$
16 B=6-Cl-purine, R=Bn

entry	glycal	base	catalyst	reagent ratio glycal/catalyst/ PhSeCl/base	time(h)	yield(%)	products	(β/α)
1	**6**	uracil	AgOTf	1/1.7/1.5/2	1	60	**8:13**	(99:1)[b]
2	**6**	uracil	$SnCl_4$	1/1.7/1.5/2	0.7	52	**8:13**	(98:2)
3	**6**	uracil	$SnCl_4$[c]	1/1.2/1.5/2	1	80	**8:13**	(70:30)
4	**6**	uracil	TMSOTf	1/1.7/1.5/2	2	84	**8:13**	(93:7)
5	**6**	uracil	AgOTf	1/1.3/1.1/1.5	2	54	**8:13**	(91:9)
6	**6**	uracil	AgOTf	1/2/2/2.5	0.25	97	**8:13**	(87:13)
7	**6**	thymine	AgOTf	1/1.7/1.5/2	0.5	76	**10:14**	(84:16)
8	**6**	thymine	AgOTf	1/2/2/2.5	2	95	**10:14**	(91:9)
9	**6**	6-Cl-purine	AgOTf	1/2/1.5/3	5	69	**11:15**	(75:25)
10	**7**	6-Cl-purine	AgOTf	1/2/1.5/3	5	78	**12:16**	(89:11)

[a] Reactions were performed in ether at room temperature. [b] A 25% of compound **9** was also obtained. [c] Solvent CH_2Cl_2, temperature −78 °C − rt.

synthesize D4T from 2-deoxyribose. The oxidative elimination of selenium is the key step in creating the double bond of glycal **6** and D4T. Likewise, the use of electrophilic selenium reagents gives high yields and stereoselectivities in the glycosylation step.

Experimental Section

General Procedures. Melting points are uncorrected. Optical rotations were measured at room temperature in 10 cmcells. ^1H and ^{13}C NMR spectra were recorded in a 300 MHz (300 and 75.4 MHz, respectively) apparatus, with $CDCl_3$ as solvent, unless otherwise specified. Elemental analyses were determined at the Servei de Recursos Cientifics (Universitat Rovira i Virgili). Flash column chromatography was performed using silica gel 60 A CC (230−400 mesh). Radial chromatography was performed on 1, 2, or 4 mm plates of silica gel, depending on the amount of product. Band separation was monitored by UV. TLC plates were prepared by using Kieselgel 60 PF_{254}. Solvents for chromatography were distilled at atmospheric pressure prior to use. Dichloromethane was distilled from P_2O_5. Benzene and toluene were dried by distillation from Na ribbon and stored over 4 Å molecular sieves under argon. Anhydrous ether and THF were obtained by distillation, under nitrogen, from sodium benzophenone ketyl. Other solvents were purified and dried by using standard procedures. All the reactions were carried out in an argon atmosphere using standard syringe techniques. Standard workup means the following: after pouring the reaction mixture into ethyl acetate and saturated $NaHCO_3$ with stirring, the organic layers were separated, washed once with saturated $NaHCO_3$, water, and saturated NaCl solution, dried ($MgSO_4$), filtered, and concentrated.

Methyl 5-*O*-(*tert*-Butyldiphenylsilyl)-α,*β*-D-*glycero*-pentofuranoside (2). A dispersion of NaH (0.58 g, 19.43 mmol) was suspended in anhydrous THF (25 mL), and then a solution of **1**[21] (5 g, 12.45 mmol) in 25 mL of THF was added. The stirring was mantained for 50 min, after which the suspension was cooled to −10 °C and carbon disulfide (1.17 mL, 19.43 mmol) was added dropwise. The reaction mixture was maintained at −10 °C for 10 min and then was allowed to warm to room temperature. When the reaction mixture turned its color into orange, it was cooled to 0 °C, and methyl iodide (0.89 mL, 14.25 mmol) was added. The mixture was allowed to warm to room temperature, and stirring was continued overnight. The reaction was interrupted by removal of the solvent under reduced pressure. The crude thus obtained was dissolved in CH_2Cl_2, and the solids were filtered off. The filtrate was evaporated at low pressure to obtain 6 g (97%) of the xanthate as an anomeric mixture which was used in the next reaction without further purification. To a solution of crude xanthate (6 g, 12.6 mmol) in toluene (80 mL) under argon atmosphere were added tributyltin hydride (13.6 mL, 50.4 mmol) and AIBN (0.160 g). The resulting reaction mixture was heated to reflux for 12 h and then was allowed to cool. The solvent was removed under reduced pressure, and the crude was dissolved in acetonitrile and washed with petroleum ether. Removal of acetonitrile afforded a residue which was purified by flash chromatography, eluting with hexane first and then increasing amounts of ethyl acetate, to give 3.96 g (85%) of compound **2**. **2**α: $[\alpha]^{25}_D$ +52.4° (c =1.16, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.75−7.26 (m, 10H), 5.04 (dd, 1H, J = 1.2, 4.6 Hz), 4.22 (dddd, 1H, J = 4.5, 4.8, 4.8, 7.3 Hz), 3.68 (dd, 1H, J = 10.7 Hz), 3.64 (dd, 1H), 2.11−1.72 (m, 4H), 1.05 (s, 9H);^{13}C NMR ($CDCl_3$) δ 135.6, 133.5, 129.6, 127.6, 105.4, 78.6, 66.1, 54.6, 32.0, 26.8, 25.5, 19.3. Anal. Calcd for $C_{22}H_{30}O_3Si$: C, 71.31: H, 8.16. Found: C, 71.47; H, 8.22. **2***β*: $[\alpha]^{25}_D$ −48.7° (c = 0.97, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.77−7.28 (m, 10H), 4.98 (pseudo t, J = 1.6 and 2.5 Hz), 4.25−4.17 (m, 1H), 3.74 (dd, 1H, J = 5.9, 10.3 Hz), 3.64 (dd, 1H, J = 5.7, 10.3 Hz), 2.08−1.75 (m, 4H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 135.6, 133.7, 129.6, 127.6, 105.1, 80.8, 67.7, 54.3, 32.8, 26.8, 26.1, 19.2. Anal. Calcd for $C_{22}H_{30}O_3Si$: C, 71.31; H, 8.16. Found: C, 71.59; H, 8.26.

Phenyl 5-*O*-(*tert*-Butyldiphenylsilyl)-1-seleno-α,*β*-D-*glycero*-pentofuranoside (4). To a solution of compound **2** (1 g, 2.70 mmol) in anhydrous dichloromethane (8 mL), under argon atmosphere at −20 °C, was added $BF_3{\cdot}OEt_2$ (0.305 mL, 2.43 mmol) dropwise. The resulting mixture was allowed to warm to −10 °C, and stirring was mantained for 10 min. The yellow solution was cooled at −20 °C, and phenylselenol (0.315 mL, 2.97 mmol) was added. The reaction mixture was maintained at this temperature for 45 min. By this time, pyridine (0.25 mL) was added, and the mixture was warmed to room temperature. The solvent was removed at reduced pressure, and the resulting crude was purified by flash chromatography, eluting first with hexane and then hexane/increasing amounts of ethyl acetate, to give 0.87 g (67%) of compound **4** as an anomeric mixture. This α/*β* mixture was separated by radial chromatography using hexane to obtain 0.56 g of α anomer and 0.30 g of *β* anomer as syrups. **4**α: $[\alpha]^{25}_D$ +150.1° (c = 0.66, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.63−7.08 (m, 15H), 5.92 (dd, 1H, J = 3.1, 6.7 Hz), 4.32 (dddd, J = 4.4, 4.6, 6.8, 6.8 Hz), 3.68 (dd, 1H, J = 4.4, 10.8 Hz), 3.64 (dd, 1H, J = 4.6, 10.8 Hz), 2.44−2.30 (m, 1H), 2.10−1.90 (complex multiplet, 2H), 1.84−1.70 (m, 1H), 0.97 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 135.6, 133.7, 129.6, 128.9, 127.6, 129.1, 84.8,

(21) Hansen, P.; Pedersen, E. B. *Acta Chem. Scand.* **1990**, *44*, 522.

79.5, 65.4, 33.7, 26.7, 26.6, 19.2. Anal. Calcd for $C_{27}H_{32}O_3SeSi$: C, 65.43; H, 6.51. Found: C, 65.47; H, 6.53. **4**β: $[\alpha]^{25}_D$ −110.8° (c = 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.66−7.10 (m, 15H), 5.77 (dd, 1H, J = 3.4, 6.5 Hz), 4.18 (dddd, 1H, J = 5.6, 5.7, 7,3, 7.3 Hz), 3.76 (dd, 1H, J = 5.6, 10.5 Hz), 3.62 (dd, 1H, J = 5.7, 10.5 Hz), 2.41−2.22 (m, 1H), 2.18−2.07, 2.03−1.80 (complex multiplets, 3H), 0.99 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 135.6, 134.0, 129.6, 128.9, 127.6, 127.2, 84.0, 82.2, 66.3, 35.0, 27.6, 26.8, 19.2. Anal. Calcd for $C_{27}H_{32}O_3SeSi$: C, 65.43; H, 6.51. Found: C, 65.26; H, 6.48.

(1*S*)-1-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-2,3-dihydrofuran (6). Compound **4** (0.7 g, 1.4 mmol) (mixture α/β) was dissolved in anhydrous dichloromethane (8 mL) under argon atmosphere. The solution was then cooled to 0 °C, and ethyldiisopropylamine (0.41 mL, 2.38 mmol) was added. To this mixture was added *tert*-butyl hydroperoxide (1.07 mL of a 3 M solution in toluene, 3.22 mmol) dropwise over a period of 5 min. Subsequent addition of titanium tetraisopropoxide (0.41 mL, 1.4 mmol) gave a yellowish solution that was allowed to stir at low temperature for 45 min and then warmed to room temperature. The solvent was removed under low pressure, and the crude obtained was purified through a small column of neutral silica gel (hexane/ethyl acetate 150:1) to afford 0.25 g (52%) of glycal **6**, which was immediately used in the synthesis of nucleosides: ^{1}H NMR ($CDCl_3$) δ 7.75−7.40 (m, 10H), 6.27 (q, 1H, J = 2.4 Hz), 4.85 (q, 1H, J = 2.4 Hz), 4.65 (dddd, 1H, J = 4.9, 5.7, 7.4, 10.5 Hz), 3.75 (dd, 1H, J = 5.7, 10.7 Hz), 3.68 (dd, 1H, J = 4.9, 10.7 Hz), 2.64 (qt, 1H, J = 2.4, 2.4, 10.4, 15.2 Hz), 2.46 (qt, 1H, J = 2.4, 2.4, 7.4, 15.2 Hz), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 145.1, 135.6, 129.6, 127.6, 99.0, 81.2, 65.8, 31.2, 26.8, 19.2.

Methyl 5-*O*-Benzyl-α,*β*-D-*glycero*-pentofuranoside (3). A solution of compound **2** (9 g, 24.3 mmol) in dry THF (27 mL) under argon atmosphere was treated with tetrabutylammoniun fluoride (7 g, 26.7 mmol) dissolved in dry THF (27 mL). The resulting reaction mixture was allowed to stir at room temperature for 1 h. The solvent was then removed under low pressure, and the crude obtained was subjected to flash chromatography (hexane/ethyl acetate 3:1) to afford 2.81 g (88%) of the 5-O-deprotected derivative. The alcohol thus obtained was dissolved in dry THF (35 mL), and the resulting solution added to a suspension of NaH (1.26 g, 42.7 mmol) in 35 mL of dry THF. The mixture was stirred for 50 min at room temperature, and then benzyl bromide (2.8 mL, 23.2 mmol) was added. Stirring was maintained overnight, and the reaction was then quenched by the addition of methanol followed by evaporation of the solvent at reduced pressure. The crude was chromatographed over silica gel using hexane first and then increasing amounts of ethyl acetate to afford 2.7 g (56%) of product **3** as an unseparable α/β mixture. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24: H, 8.16. Found: C, 70.45; H, 8.21.

Phenyl 5-*O*-Benzyl-1-seleno-α,*β*-D-*glycero*-pentofuranoside (5). As described for the synthesis of compound **4**, transglycosylation was carried out starting from compound **3** (0.6 g, 2.71 mmol)) by treatment with $BF_3{\cdot}OEt_2$ (0.272 mL, 2.16 mmol) and phenylselenol (0.316 mL, 2.97 mmol) in 8 mL of anhydrous dichloromethane. After 15 min workup provided a reaction crude which was purified by flash chromatography in hexane using polarity gradient with ethyl acetate to give 0.57 g (61%) of the 1-seleno glycoside **5** as an anomeric mixture. This α/β mixture was separated by radial chromatography using ethyl acetate/hexane = 1:60 to give 0.38 g of α anomer and 0.19 g of β anomer as syrups. **5**α: $[\alpha]^{25}_D$ +215.6° (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.68−7.16 (m, 10H), 6.01 (dd, 1H, J = 2.9, 6.7 Hz), 4.56 (s, 2H), 4.51−4.38 (m, 1H), 3.59 (dd, 1H, J = 4.3, 10.4 Hz), 3.55 (dd, 1H, J = 4.9, 10.5 Hz), 2.51−2.37 (m, 1H), 2.17−2.01 (m, 2H), 1.83−1.70 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 138.2, 133.9, 128.9, 128.3, 127.6, 127.2, 84.8, 78.0, 73.3, 71.5, 33.6, 27.0. Anal. Calcd for $C_{18}H_{20}O_2Se$: C, 62.25: H, 5.80. Found: C, 62.47; H, 5.84. **5**β: $[\alpha]^{25}_D$ −117.6° (c = 0.98, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.72−7.16 (m, 10H), 5.86 (dd, 1H, J = 2.9, 6.5 Hz), 4.57 (s, 2H), 4.40−4.27 (m, 1H), 3.67 (dd, 1H, J = 6.4, 10.1 Hz), 3.56 (dd, 1H, J = 4.9, 10.1 Hz), 2.47−2.33, 2.28−2.17, 2.13−2.05, 1.94−1.80 (complex multiplets, 4H); ^{13}C NMR ($CDCl_3$) δ 134.8, 134.1, 129.6, 128.9, 128.3, 127.6, 127.5, 127.3, 84.0, 80.8, 73.4, 73.2, 28.0. Anal. Calcd for $C_{18}H_{20}O_3Se$: C, 62.25: H, 5.80. Found: C, 62.31; H, 5.83.

(1*S*)-1-[(Benzyloxy)methyl]-2,3-dihydrofuran (7). Using a procedure similar to that used for **6**, compound **5** (0.5 g, 1.45 mmol) (mixture α/β) was converted to **7** by reaction with ethyldiisopropylamine (0.43 mL, 2.48 mmol), *tert*-butyl hydroperoxide (1.12 mL of a 3 M solution in toluene, 3.35 mmol), and titanium tetraisopropoxide (0.43 mL, 1.45 mmol). After 40 min, the solvent was removed and the crude purified by filtration through a small column of neutral silica gel (hexane/ethyl acetate 100:1) to afford 0.183 g (67%) of compound **7** which was immediately used in the synthesis of nucleosides. **7**: ^{1}H NMR ($CDCl_3$) δ 7.60−7.20 (m, 5H), 6.30 (q, 1H, J = 2.4 Hz), 4.88 (q, 1H, J = 2.4 Hz), 4.75 (dddd, 1H, J = 4.3, 6.8, 7.7, 10.6 Hz), 4.64 (d, 1H, J = 12.1 Hz), 4.57 (d, 1H, J = 12.1 Hz), 3.59 (dd, 1H, J = 6.8, 10.3 Hz), 3.50 (dd, 1H, J = 4.3, 10.3 Hz), 2.68 (qt, 1H, J = 2.4, 2.4, 10.5, 15.2 Hz), 2.36 (qt, 1H, J = 2.4, 2.4, 7.7, 15.2 Hz); ^{13}C NMR ($CDCl_3$) δ 145.1, 138.0, 128.4, 127.7, 127.6, 99.0, 79.8, 73.3, 72.3, 31.6.

1-[5-*O*-(*tert*-Butyldiphenylsilyl)-3-deoxy-2-*Se*-phenyl-2-seleno-*β*,α-D-*erythro*-pentofuranosyl]uracil (8[6a] and 13) and 1-[5-*O*-(*tert*-Butyldiphenylsilyl)-3-deoxy-2-*Se*-phenyl-2-seleno-*β*,α-D-*erythro*-pentofuranosyl]-5-(phenylselenenyl)uracil (9). Phenylselenenyl chloride (0.036 g, 0.185 mmol) was added to a solution of glycal **6** (0.042 g, 0.125 mmol) in 1 mL of dry ether at room temperature, kept under argon, and protected from light. After 5 min, bis(trimethylsilyl)uracil (0.064 g, 0.25 mmol) was added followed by AgOTf (0.054 g, 0.21 mmol). The reaction was monitored by TLC in ethyl acetate/hexane = 1:10. After 1 h, workup of the reaction afforded a crude which was chromatographed over silica gel, eluting first with hexane and then EtOAc/hexane (up to 1:1) to give 0.023 g (25%) of compound **9** and 0.046 g (60%) of a mixture of **8**/**13**. Radial chromatography using EtOAc/hexane allowed the separation of compound **8** and **13** as hygroscopic foams: **8**: UV (MeOH) λ_{max} 264 nm; ^{1}H NMR ($CDCl_3$) δ 7.9 (bs, 1H), 7.73−7.22 (m, 16H), 6.16 (d, 1H, J = 6.0 Hz), 5.28 (dd, 1H, J = 2.2, 8.1 Hz), 4.34−4.28 (m, 1H), 4.07 (dd, 1H, J = 2.2, 11.7 Hz), 3.76 (td, 1H, J = 6.0, 7.6, 7.6 Hz), 3.68 (dd, 1H, J = 2.3, 11.7 Hz), 2.54 (ddd, 1H, J = 5.7, 7.6, 13.2 Hz), 2.11 (dt, 1H, J =7.6, 7.6, 13.2 Hz), 1.09 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 162.4, 149.8, 139.7, 135.7, 135.6, 135.3, 130.2, 130.1, 129.3, 128.6, 128.0, 102.5, 90.3, 79.4, 65.3, 44.1, 32.6, 26.8, 19.7. **9**: ^{1}H NMR ($CDCl_3$) δ 8.12 (bs, 1H), 7.68−7.22 (m, 21H), 6.10 (d, 1H, J = 7.4 Hz), 4.24−4.16 (m, 1H), 3.83 (dd, 1H, J = 3.1, 11.4 Hz), 3.69 (td, 1H, J = 7.4, 8.2, 8.8 Hz), 3.60 (dd, 1H, J = 3.0, 11.4 Hz), 2.40 (ddd, 1H, J = 4.7, 8.2, 13.0 Hz), 2.11 (dt, 1H, J = 8.8, 8.8, 13.0 Hz), 1.09 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 162.4, 149.9, 143.6, 135.7, 135.6, 135.5, 132.1, 130.1, 130.0, 129.3, 129.2, 128.7, 128.0, 127.9, 127.9, 127.5, 90.4, 78.4, 65.6, 42.6, 33.5, 27.1, 19.6. (**13**)**:** ^{1}H NMR ($CDCl_3$) δ 7.78−7.18 (m, 17H), 6.13 (d, 1H, J = 4.6 Hz), 5.67 (dd, 1H, J = 2.0, 8.1 Hz), 4.55−4.45 (m, 2H), 3.84 (dd, 1H, J = 3.4, 11.2 Hz), 3.65 (dd, 1H, J = 3.7, 11.2 Hz), 2.64 (dt, 1H, J = 7.7, 7.7, 14.0 Hz), 2.23 (ddd, 1H, J =3.5, 6.4, 14.0 Hz), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 162.7, 149.5, 139.9, 135.5, 133.2, 129.9, 129.2, 128.0, 127.9, 127.8, 100.7, 88.0, 79.7, 65.4, 46.1, 33.7, 26.8, 19.2.

1-[5-*O*-(*tert*-Butyldiphenylsilyl)-3-deoxy-2-*Se*-phenyl-2-seleno-*β*-D-*erythro*-pentofuranosyl]thymine (10).[6a] A solution of glycal **6** (0.084 g, 0.25 mmol) in 1 mL of dry ether at room temperature, kept under argon and protected from light, was treated with phenylselenenyl chloride (0.096 g, 0.5 mmol). After 5 min, bis(trimethylsilyl)thymine (0.168 g, 0.62 mmol) and AgOTf (0.128 g, 0.5 mmol) were added. The reaction was monitored by TLC using ethyl acetate/hexane = 1:10. After 2 h, workup of the reaction afforded a crude which was chromatographed over silica gel, eluting first with hexane and then EtOAc/hexane (up to 1:2). The residue obtained (0.153 g, 95%) was further purified by means of radial chromatography using EtOAc/hexane = 1:4 to give compound **10** as a foam: UV (MeOH) λ_{max} 266 nm; ^{1}H NMR ($CDCl_3$) δ 8.28 (bs, 1H), 7.65−7.06 (m, 16H), 6.10 (d, 1H, J = 8.1 Hz), 4.17−4.10 (m, 1H), 3.94 (dd, 1H, J = 2.2, 11.5 Hz), 3.68 (dt, 1H, J = 8.1, 8.1, 10.1 Hz), 3.60 (dd, 1H, J = 2.5, 11.5 Hz), 2.48 (ddd, 1H, J = 3.9, 8.1, 13.0 Hz), 2.09 (ddd, 1H, J = 8.7, 10.1, 13.0 Hz), 1.37 (s, 3H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 163.2, 150.3, 135.9, 135.5, 135.2, 134.8, 133.0, 130.1, 130.0, 129.1, 128.5, 128.0, 127.8, 111.1, 89.6, 77.9, 65.9, 42.5, 32.8, 27.1, 19.5, 11.8.

6-Chloro-9-[5-*O*-(*tert*-butyldiphenylsilyl)-3-deoxy-2-*Se*-phenyl-2-seleno-*β*,α-D-*erythro*-pentofuranosyl]-9*H*-purine (11[6a] and 15). A solution of glycal **6** (0.084 g, 0.25 mmol) in 1 mL of anhydrous ether at room temperature was allowed to react with phenylselenenyl chloride (0.072 g, 0.37 mmol)

under argon atmosphere and protected from light. After 5 min, silylated 6-chloropurine (0.17 g, 0.75 mmol) and AgOTf (0.128 g, 0.5 mmol) were added to the reaction mixture. The reaction was monitored by TLC using ethyl acetate/hexane = 1:6. After 5 h, workup of the reaction afforded a crude that was chromatographed over silica gel, eluting first with hexane and then EtOAc/hexane (up to 1:6). The residue obtained as an α/β mixture (0.162 g, 69%) was submitted to radial chromatography using EtOAc/hexane = 1:10 to afford nucleosides **11** and **15**: (**11**): UV (MeOH) λ_{max} 266 nm; ^{1}H NMR ($CDCl_3$) δ 8.60 (s,1H), 8.19 (s, 1H), 7.67−7.08 (m, 15H), 6.24 (d, 1H, J = 5.8 Hz), 4.46−4.39 (m, 1H), 4.35 (td, 1H, J = 5.9, 7.6, 7.6 Hz), 4.00 (dd, 1H, J = 3.7, 11.3 Hz), 3.76 (dd, 1H, J =3.8, 11.3 Hz), 2.69 (ddd, 1H, J = 5.8, 7.6, 13.3 Hz), 2.20 (ddd, 1H, J = 7.6, 7.6, 13.3 Hz), 1.08 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 151.7, 143.4, 135.6, 135.5, 135.1, 130.0, 129.0, 128.5, 127.9, 127.8, 91.3, 80.2, 65.3, 43.2, 32.9, 26.9, 19.2. (**15**): $[\alpha]^{25}_D$ +100.4° (c = 0.71, $CHCl_3$); UV (MeOH) λ_{max} 266 nm; ^{1}H NMR ($CDCl_3$) δ 8.57 (s,1H), 8.19 (s, 1H), 7.68−7.14 (m, 15H), 6.44 (d, 1H, J = 5.4 Hz), 4.73 (dddd, 1H, J = 3.1, 3.3, 5.3, 7.7 Hz), 4.49 (td, 1H, J = 5.4, 7.7, 7.7 Hz), 3.92 (dd, 1H, J = 3.3, 11.3 Hz), 3.71 (dd, 1H, J =3.1, 11.3 Hz), 2.75 (ddd, 1H, J = 5.3, 7.7, 13.4 Hz), 2.56 (ddd, 1H, J = 7.7, 7.7, 13.4 Hz), 1.08 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 151.5, 143.6, 135.5, 133.5, 129.9, 129.9, 128.9, 127.9, 127.8, 88.5, 80.7, 65.8, 45.9, 33.7, 26.8, 19.2. Anal. Calcd for $C_{32}H_{33}N_4O_2SeClSi$: C, 59.30; H, 5.13; N, 8.64. Found: C, 59.54; H, 5.17; N, 8.57.

6-Chloro-9-[5-*O*-benzyl-3-deoxy-2-*Se*-phenyl-2-seleno-β-D-*erythro*-pentofuranosyl]-9*H*-purine (12). Phenylselenenyl chloride (0.072 g, 0.375 mmol) was added to a solution of glycal **7** (0.047 g, 0.25 mmol) in 1 mL of dry ether at room temperature, kept under argon, and protected from light. After 5 min, silylated 6-chloropurine (0.17 g, 0.75 mmol) was added followed by AgOTf (0.128 g, 0.5 mmol). The reaction was monitored by TLC in ethyl acetate/hexane = 1:4. After 5 h, workup of the reaction afforded a crude that was chromatographed over silica gel, eluting first with hexane and then EtOAc/hexane (up to 1:2). The residue obtained (0.097 g, 78%) was further purified by means of radial chromatography using EtOAc/hexane = 1:5 to give compound **12** as a thick syrup: $[\alpha]^{25}_D$ −39.5° (c = 0.57, $CHCl_3$); UV (MeOH) λ_{max} 266 nm; ^{1}H NMR ($CDCl_3$) δ 8.64 (s,-1H), 8.38 (s, 1H), 7.46−7.12 (m, 10H), 6.29 (d, 1H, J = 5.3 Hz), 4.65 (d, 1H, J =12.0 Hz), 4.57 (d, 1H, J = 12.0 Hz), 4.55−4.48 (m, 1H), 4.32 (td, 1H, J = 5.2, 7.2, 7.2 Hz), 3.82 (dd, 1H, J = 2.9, 10.5 Hz), 3.59 (dd, 1H, J =5.4, 10.5 Hz), 2.66 (ddd, 1H, J = 6.2, 7.2, 13.5 Hz), 2.22 (ddd, 1H, J = 7.2, 7.2, 13.5 Hz); ^{13}C NMR ($CDCl_3$) δ 151.7, 143.7, 135.1, 129.1, 128.6, 128.4, 128.0, 127.8, 91.2, 79.3, 73.6, 71.1, 43.8, 33.1. Anal. Calcd for $C_{23}H_{21}N_4O_2SeCl$: C, 55.30; H, 4.23; N, 11.21. Found: C, 55.33; H, 4.26; N, 11.13.

1-[5-*O*-(*tert*-Butyldiphenylsilyl)-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl]thymine (17).[6a] Compound **10** (0.1 g, 0.18 mmol) was dissolved in 2 mL of dry CH_2Cl_2. The solution was cooled to 0 °C under argon atmosphere, and 0.055 mL (0.32 mmol) of ethyldiisopropylamine was added. To this mixture was added 0.134 mL of 3 M *tert*-butyl hydroperoxide solution in toluene were added dropwise via syringe over a period of 5 min. Subsequent addition of 0.55 mL (0.19 mmol) of titanium tetraisopropoxide turned the solution into a yellowish color, which was allowed to stir at low temperature for 15 min. The reaction was monitored by TLC (CH_2Cl_2/MeOH = 9.5:0.5. Removal of the solvent under reduced pressure afforded a crude that was purified by column chromatography, eluting first with CH_2Cl_2 and then 0.5% MeOH/CH_2Cl_2 to give compound **17** (0.069 g, 85%) as a thick syrup: UV (MeOH) λ_{max} 266 nm; ^{1}H NMR ($CDCl_3$) δ 9.07 (bs, 1H), 7.70−7.31 (m, 10H), 7.15 (s, 1H), 7.01 (ddd, 1H, J = 1.3, 1.7, 3.7 Hz), 6.35 (dt, 1H, J = 1.7, 1.7, 5.9 Hz), 5.87 (ddd, 1H, J = 1.7, 2.0, 5.9 Hz), 4.96−4.90 (m, 1H), 3.93 (dd, 1H, J = 4.1, 11.3 Hz), 3.88 (dd, 1H, J = 4.0, 11.3 Hz), 1.48 (s, 3H), 1.08 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 163.8, 150.8, 135.6, 135.4, 135.3, 134.6, 133.2, 132.7, 130.0, 129.9, 127.8, 126.3, 111.1, 89.7, 86.9, 65.5, 26.9, 19.4, 11.9. Anal. Calcd for $C_{26}H_{30}N_2O_4Si$: C, 67.50; H, 6.54; N, 6.06. Found: C, 67.31; H, 6.60; N, 5.92.

Acknowledgment. Financial support by DGICYT (Ministerio de Educación y Ciencia, Spain), project PB92-0510 is gratefully acknowledged. Y. D. thanks DGU (Generalitat de Catalunya) for a grant.

JO9616825