Stereoselective Synthesis of Branched and Bicyclo 2′,3′-Dideoxy-*threo*-furanosyl Nucleosides from Pyranoses Using a Ring Contraction Reaction as the Key Step

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Received September 23, 1996 (Revised Manuscript Received March 27, 1997[⊗]*)*

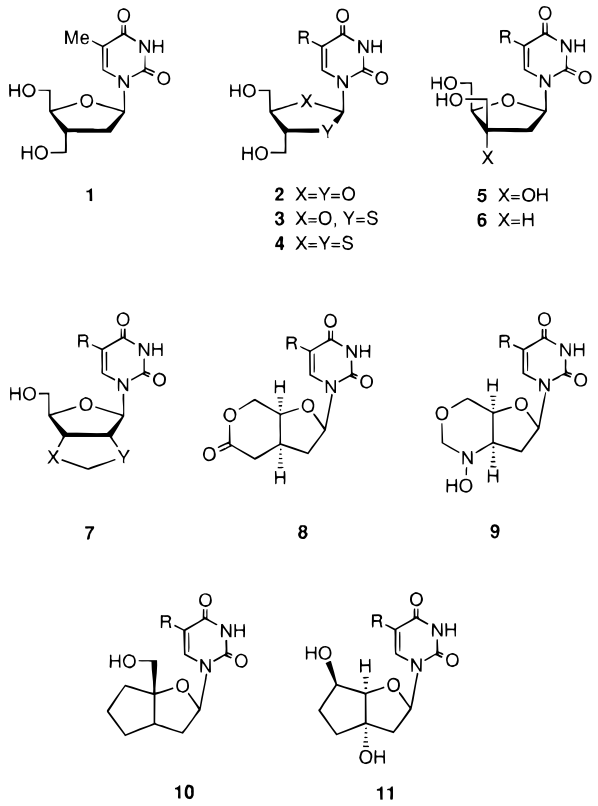
Bicyclo nucleoside **21** and the branched-chain nucleoside **26** have been stereroselectively synthesized (α:β = 1:4) from a common intermediate **14**, which was obtained from methyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-triflyl-α-D-*arabino*-pyranoside (**13**) through a ring contraction reaction. The branched nucleoside **26** was obtained with an α:β selectivity of 1:4 using either electrophilic selenium or sulfur reagents. In contrast the bicyclo nucleoside **21** was only obtained using the phenylthio derivative **20**. The selenium reagents resulted in predominant formation of the α isomer.

Modifying the sugar backbone in a nucleoside or introducing a heteroatom (azide, fluorine, etc.) are useful strategies in the search for biologically active compounds.[1] On the other hand, branched-chain sugar nucleosides are present in a wide range of both naturally occurring and synthetic products, some having antitumor,[2] antiviral,[3] and antibacterial[4] activities. Recently 3′-α-*C*-hydroxymethyl derivatives such as oxetanocin[5] and 3′-deoxy-3′-*C*-(hydroxymethyl)thymidine (**1**)[6] have been shown to have powerful anti-HIV activity *in vitro*. Other derivatives such as 2′,3′-dideoxy-2′-fluoro-3′-(fluoromethyl)-5-iodouridine[6c] also have significant therapeutic value. Very recently, the interesting 4,5-bis(hydroxymethyl) nucleosides[7] incorporating 1,3-dioxolane (**2**),[7a] 1,3-oxathiolane (**3**),[7b] and 1,3-dithiolane (**4**)[7c] have been reported.

The branched-chain nucleosides[8] are usually synthesized by two methods: from γ-(hydroxymethyl)-γ-butyrolactone,[6,9] 3-(hydroxymethyl)furanosides,[10] or from cyclohexenecarboxylic acid derivatives[11] and subsequent glycosylation; and from modified nucleosides, for instance, by addition of a cyanide ion to 3′-ketonucleosides,[12] by opening a 2′,3′-anhydronucleoside,[6c] or from 3′-iodo-[13] or 3′-*O*-[(phenyloxy)thiocarbonyl]nucleoside derivatives by radical coupling.[14]

The corresponding nucleosides with a 3′-β-hydroxymethyl chain have been much less studied. Recently 3′-

Chart 1



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S0022-3263(96)01806-3 CCC: $14.00

β-hydroxymethyl derivatives of thymidine (**5**)[15] and the corresponding 3′-deoxy-*threo* derivative (**6**)[16] have been reported.

Likewise, bicyclo nucleosides have also hardly been studied. Searching for 2′,3′-modified nucleosides, Chattopadhyaya has described different bicyclo nucleosides of general formula **7**[17] and **8**.[18] Bicyclo *threo* nucleosides incorporating a hydroxyamino[19] group (**9**) have shown to be active against the HIV virus. Recently, conformationally restricted bicyclo nucleosides such us **10** and **11** have been synthesized in order to obtain bicyclo-DNA[20] and to look for anti-HIV active compounds, respectively.[21]

In this paper we show that 2′,3′-dideoxy-3′-(hydroxymethyl)-*threo*-furanoses and 2′,3′-dideoxy-bicyclo-*threo*-furanoses can be obtained from pyranoses using a ring contraction reaction as a key step and stereoselectively transformed into the corresponding bicyclo and branched nucleosides, respectively.

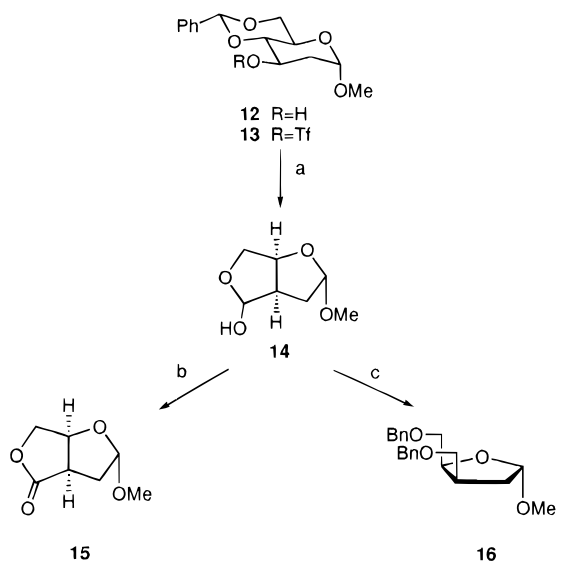
Results and Discussion

Firstly, the 3-*O*-triflyl derivative **13**, obtained from the 2-deoxyglucose derivative **12** by reaction with triflic anhydride, was heated to reflux in 1,1,1,3,3,3-hexafluoro-2-propanol in the presence of pyridine and water to give the ring contraction product **14** in 92% yield.[22]

When compound **14** was treated with PCC in dichlorometane, the bicyclo lactone **15** was obtained in 93% yield (Scheme 1). Bicyclo nucleosides are usually obtained by modifying the carbohydrate framework of nucleosides.[18−20] We envisioned that the bicyclo lactone **15** could be an appropriate starting material in order to obtain bicyclo nucleosides through the glycosylation reaction.

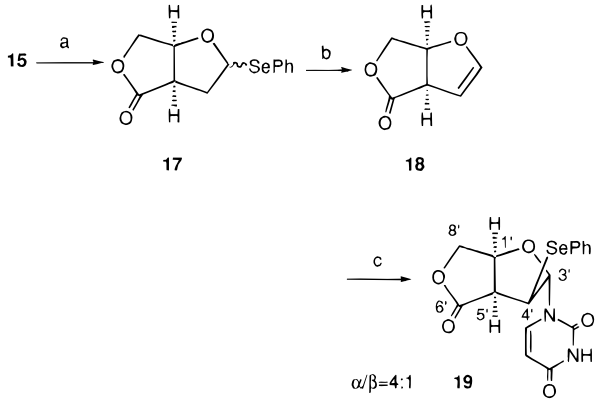
2′-Deoxynucleosides can be stereoselectively obtained[23] starting from glycals and using electrophilic selenium,[24] sulfur,[25] and iodine[26] reagents. So that the selenium methodology could be used in the stereoselective preparation of the bicyclo nucleosides, compound **18** was

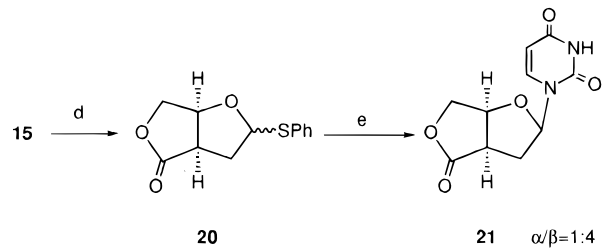
Scheme 1



a)$CF_3CHOHCF_3$, Pyridine, H_2O, reflux, 92%. b) PCC, NaOAc, CH_2Cl_2, rt, 93%. c) 1. $LiAlH_4$, THF. 2. NaH, BnBr, THF, 66%.

Scheme 2





a) PhSeH, $BF_3.OEt_2$, CH_2Cl_2, 77%. b) $^tBuOOH/Ti(O\text{-}^iPr)_4/^iPr_2NEt$, CH_2Cl_2, 68%. c) PhSeCl/uracil(TMS)$_2$/AgOTf, benzene, r.t., 51%. d) PhSH, $BF_3.OEt_2$, CH_2Cl_2, 54%. e) uracil(TMS)$_2$, NBS,CH_2Cl_2, 62%.

obtained by treating **15** with PhSeH in the presence of $BF_3{\cdot}OEt_2$ to give the phenyl 1-seleno-glycoside **17** (Scheme 2). Selenoxide was subsequently formed/eliminated by treatment with the mixture $^tBuOOH/Ti(O^iPr)_4/^iPr_2NEt$,[27] giving an overall yield of 52% for the two steps.

When glycal **18** was treated with PhSeCl/(TMS)$_2$uracil/AgOTf,[24] 2′-deoxy-2′-phenylselenenyl nucleoside **19** was

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Table 1. Selected ^{1}H and ^{13}C NMR Data of Bicyclo Nucleosides 19α and 21β (δ in ppm, *J* in Hz)

compd	$H_{3'}$	$H_{4'a}$	$H_{4'b}$	$J_{3',4'a}$	$J_{3',4'b}$	$C_{3'}$	$C_{4'}$
19α	6.07	4.77	–	4.8	–	88.4	46.0
21β	6.10	2.90	2.46	4.8	7.8	86.7	34.3

Table 2. Selected ^{1}H and ^{13}C NMR Data of Branched Nucleosides 24β and 26β (δ in ppm, *J* in Hz)

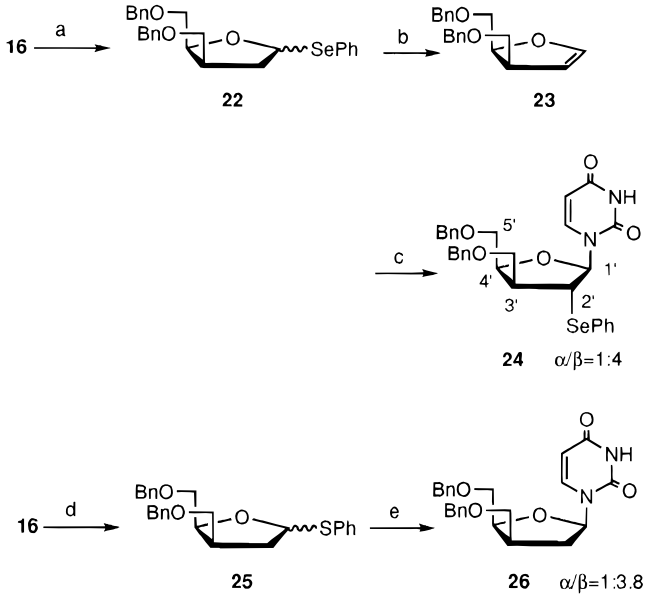
compd	$H_{1'}$	$H_{2'a}$	$H_{2'b}$	$J_{1'2'a}$	$J_{1'2'b}$	$C_{1'}$	$C_{2'}$	$C_{3'}$
24β	6.15	3.30		9.0		88.4	44.4	44.3
26β	6.14	2.34	1.79	8.4	6.0	84.7	35.1	40.5

obtained in 64% yield as an anomeric mixture (ratio α/β = 4:1), from which the isomer **19**α could be isolated in 51% yield. ^{1}H and ^{13}C NMR spectra of compound **19**α clearly show that uracil and phenylselenenyl groups are bonded to the bicyclo framework. Signals were assigned using COSY and HETCOR experiments. Thus, the anomeric proton H-3′ appears at 6.07 ppm (Table 1) and correlates with the carbon at 88.4 ppm, which is characteristic of the anomeric carbon in nucleosides. The stereochemistry of positions 3′ and 4′ was attributed on the basis of a NOE experiment; by irradiation of H-4′, H-1′ and H-5′ increased, but H-3′ did not, which showed that, unexpectedly, the major anomer was α and that the phenylselenenyl group was on the endo face. It has been observed that the chloro-selenenyl derivatives resulting from the addition of PhSeCl to glycals easily isomerize to give the more stable addition products,[28] which are expected to be the compounds with the phenylselenenyl group on the exo face. The behavior observed in this case could be explained by the fact that the stereochemistry of the attack of the electrophilic selenium reagent on the double bond is determined by the presence of the carbonyl group of the lactone. A similar effect has been observed when adding electrophilic reagents (PhSeCl[24b,28a] and iodine[29]) to pyranoid glycals, and electrostatic effects between the polar carbonyl group and the electrophilic reagent have been invoked to explain the selectivity observed.[29]

As the α anomer was the major one obtained, we turned our attention to another glycosylation method. It has been reported that 2′-deoxy-β-nucleosides can be stereoselectively obtained from phenyl 1-thioglycosides when activated with NBS in the presence of bis(trimethylsilyl)uracil.[30] To this end, phenyl 1-thioglycoside **20** (α/β = 6:1) was obtained from **15** in 54% yield, by reaction with PhSH in the presence of $BF_3{\cdot}OEt_2$.

The order of adding the reagents proved to be decisive in the glycosylation reaction leading to the nucleoside. Thus, when NBS was added first, followed by bis(trimethylsilyl)uracil to a solution of **20**, a mixture of compounds was isolated, among which succinimide glycosylation products could be observed. No nucleosides were detected. However, when a mixture of **20** and bis(trimethylsilyl)uracil was stirred for 10 min before adding NBS, the bicyclonucleoside **21** was obtained as an inseparable anomeric mixture in 62% yield (ratio α/β = 1:4).

Scheme 3



a) PhSeH, $BF_3.OEt_2$, CH_2Cl_2, 70%. b) ^{t}BuOOH/Ti(O^iPr)$_4$/^{i}Pr$_2$NEt, CH_2Cl_2, 94%. c) PhSeCl/uracil(TMS)$_2$/AgOTf, benzene, rt, 81%. d) PhSH, $BF_3.OEt_2$, CH_2Cl_2, 66%. e) uracil(TMS)$_2$, NBS, CH_2Cl_2,72%.

In the ^{1}H and ^{13}C spectra the anomeric proton H-3′ of the major isomer appears as a double doublet at 6.10 ppm (Table 1), and C-3′ at 86.7 ppm. Irradiation of H-5′ of the major isomer enabled an NOE effect to be detected in H-3′, indicating that in this case the β anomer was the major one. The attempt to purify the anomeric mixture by column chromatography on silica gel led to isomerization, giving an equimolar mixture of nucleosides.

In order to obtain branched nucleosides, compound **14** was reduced with $LiAlH_4$, and the dihydroxy derivative obtained was treated with NaH/BnBr to give compound **16** in a 66% yield for the two steps (Scheme 1).

For comparative purposes in this case we decided to test the two aforementioned glycosylation procedures. Firstly, compound **16** was treated with PhSeH in the presence of $BF_3{\cdot}OEt_2$ obtaining the phenyl 1-selenoglycoside **22** as an anomeric mixture. Oxidizing selenium with the mixture ^{t}BuOOH/Ti(O^iPr)$_4$/^{i}Pr$_2$NEt and the subsequent elimination of selenoxide gave the glycal **23** in a 94% yield (Scheme 3).

When glycal **23** was treated with PhSeCl/(TMS)$_2$uracil/AgOTf in benzene, the 2′,3′-dideoxy-2′-phenylselenenyl nucleoside **24** was obtained in a 81% yield as an anomeric mixture (ratio α/β = 1:4) from which the β anomer could be isolated. The configuration of the major isomer was determined by irradiation of the anomeric proton H-1′, and an NOE effect was observed in H-3′ and H-4′, but not in the H-2′, indicating a β configuration for this isomer.

In this case, where no carbonyl groups were present the expected β nucleoside resulting from the formation of the selenonium cation on the exo face was the major product.

Likewise, phenyl 1-thio-glycoside **25** was obtained from **16** by reaction with PhSH and catalysis of $BF_3{\cdot}OEt_2$. When the glycosylation of bis(trimethylsilyl)uracil with **25** was performed with NBS activation, taking into account the aforementioned precautions, nucleoside **26**

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was obtained in a 72% yield (ratio α/β = 1:3.8). When the reaction started at −78 °C, no improvement in the stereoselectivity was observed. The ^{1}H NMR spectrum of the major anomer shows a double doublet (J = 8.4; 6.0 Hz) at 6.15 ppm (Table 2) corresponding to the anomeric proton. A NOE experiment performed irradiating H-3′ in the ^{1}H NMR spectrum showed there had been an increase in signals H-4′, H-1′ and in one corresponding to a H-2′ proton, indicating a β configuration for this isomer. The identical anomeric configuration of the major isomers in nucleosides **24** and **26** was proved treating **24**β with Bu_3SnH/AIBN which leads to **26**β. So, both glycosylation methodologies gave similar yields and stereoselectivities in this case.

In conclusion, bicyclo and branched-chain *threo*-furanosyl nucleosides have been stereoselectively obtained from the methyl pyranoside **1** using a ring contraction reaction and glycosylation as key steps. Two different methods of glycosylation have been tested which gave similar β stereoselectivity in the synthesis of the branched nucleosides. A directing effect of the lactone group in **18** has been observed in the phenylselenenyl-induced glycosylation reaction resulting in the preferential formation of the α anomer with the phenylselenenyl group on the endo face of the bicyclic compound. When the phenyl 1-thio-glycoside **25** was the starting material, the β anomer was mainly obtained.

Experimental Section

Melting points were determined in open capillaries and are uncorrected. Optical rotations were determined at 589 nm in $CHCl_3$ solutions at 22 °C. Infrared spectra were recorded in $CHCl_3$ solutions on a FT-spectrometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were determined in $CDCl_3$. Elemental analyses were performed by the "Servei de Recursos Científics, Universitat Rovira i Virgili". Preparative-scale separations were carried out by flash column chromatography using a 2 × 15-cm column of 240−400 mesh silica gel 60 and by TLC on silica gel 60 PF_{254} plates.

[1*S*,3*S*,5*R*]-3-Methoxy-6-oxo-2,7-dioxabicyclo[3.3.0]-octane (15). Pyridinium chlorochromate (666 mg, 3.1 mmol), anhydrous sodium acetate (254 mg, 3.1 mmol), 4 Å molecular sieves (previously activated) (0.773 g), and anhydrous CH_2Cl_2 (4 mL) were placed in a light-protected flask and stirred under argon atmosphere for 10 min. A solution of compound **14** (124 mg, 0.774 mmol) in 1 mL of CH_2Cl_2 was added to the obtained suspension, and the stirring was maintained for 1 h at room temperature. The remaining solution was then diluted with ethyl ether (25 mL), filtered through a silica gel pad, and evaporated to dryness, obtaining compound **15** (114 mg, 93%) as a syrup which crystallized spontaneously: mp 83−84 °C; $[\alpha]^{22}_D$ +37.7 (*c* 1.8, $CHCl_3$); IR ν(CO) 1762 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.13 (dd, 1H, J = 5.5, 1.5 Hz), 4.80 (dd, 1H, J = 6.0, 4.5 Hz), 4.41 (m, 2H), 3.33 (s, 3H, OMe), 3.25 (ddd, 1H, J = 10.2, 6.0, 3.6 Hz), 2.46 (ddd, 1H, J = 13.8, 3.6, 1.5 Hz), 2.29 (ddd, 1H, J = 13.8, 10.2, 5.5 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 178.5, 105.9, 77.5, 71.3, 55.0, 43.4, 36.5. Anal. Calcd for $C_7H_{10}O_4$: C 53.16, H 6.33. Found: C 52.93, H 6.35.

Methyl 5-*O*-Benzyl-3-*C*-[(benzyloxy)methyl]-2,3-dideoxy-α-D-*threo*-pentofuranoside (16). A solution of 36 mg (0.94 mmol) of lithium aluminum hydride in 3 mL of anhydrous THF under argon atmosphere was cooled to 0 °C in an ice bath, and compound **14** (0.1 g, 0.6 mmol) in anhydrous THF (2 mL) was added. After 2.5 h the reaction was finished (TLC control ethyl acetate/hexane 3:2). The reaction mixture was diluted with ethyl acetate and hydrolyzed with water at 0 °C. The organic layer was separated, and the aqueous layer was saturated with sodium chloride and extracted with ethyl acetate 3 × 10 mL. The organic layers were dried over anhydrous $MgSO_4$ and evaporated to dryness obtaining 0.08 g (79%) of the diol, which was dissolved in anhydrous THF (2 mL) and added, under argon atmosphere, to a suspension of 48 mg of NaH in 2 mL of anhydrous THF with stirring. After 30 min, 3 mmol of benzyl bromide were added, and the reaction mixture was left at room temperature with stirring overnight. The resulting mixture was evaporated to dryness and purified by flash chromatography (ethyl acetate/hexane 1:4), obtaining 0.11 g (66%) of compound **16** as a syrup. $[\alpha]^{22}_D$ +51.6 (*c* 0.77, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31−7.27 (m, 10H, Ph), 5.05 (dd, 1H, J = 4.8, 1.8 Hz), 4.50 (d, 2H, J = 12.0 Hz), 4.49 (d, 1H, J = 5.4 Hz), 4.40 (d, 1H, J = 12.0 Hz), 4.33 (ddd, 1H, J = 9.9, 8.7, 4.0 Hz), 3.66−3.38 (m, 4H), 3.35 (s, 3H, OMe), 2.77 (m, 1H), 1.95−1.90 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 139.1, 128.3, 127.6, 127.5, 104.4, 78.1, 73.3, 73.0, 69.9, 69.5, 54.8, 39.1, 36.3. Anal. Calcd for $C_{21}H_{26}O_4$: C 73.66, H 7.65. Found: C 73.55, H 7.87.

[1*S*,3(*S*,*R*),5*R*]-6-Oxo-3-(phenylselenenyl)-2,7-dioxabicyclo[3.3.0]octane (17α and 17β). To solution of compound **15** (296 mg, 1.87 mmol) in 4 mL of CH_2Cl_2, cooled at −10 °C and under argon atmosphere was added $BF_3{\cdot}OEt_2$ (280 μL, 1.57 mmol). After 5 min phenylselenol (220 μL, 2.2 mmol) in 1.5 mL of anhydrous CH_2Cl_2 was added. The reaction mixture was kept at −10−0 °C for 1 h and then was neutralized with a drop of pyridine. After evaporation to dryness the obtained residue was purified by flash chromatography (ethyl acetate/hexane 1:4) to obtain the α-seleno glycoside **17**α (103 mg, 19%) and the β-seleno glycoside **17**β (308 mg, 58%). **17**α: mp 109−110 °C; $[\alpha]^{22}_D$ −148 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.61−7.22 (m, 5H), 6.0 (dd, 1H, J = 7.2, 4.2 Hz), 4.99 (dd, 1H, J = 5.8, 4.0 Hz), 4.48 (d, 1H, J = 11.0 Hz), 4.41 (dd, 1H, J = 11.0, 4.0 Hz), 3.25 (ddd, 1H, J = 9.0, 5.8, 3.0 Hz), 2.86 (ddd, 1H, J = 14.4, 9.0, 7.2 Hz), 2.48 (ddd, 1H, J = 14.4, 4.2, 3.0 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 177.7, 133.9, 129.2, 129.1, 127.8, 83.5, 78.5, 71.1, 44.0, 37.1. Anal. Calcd for $C_{12}H_{12}O_3Se$: C 50.88, H 4.24. Found: C 50.99, H 4.29. **17**β: mp 103−104 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.63−7.19 (m, 5H), 5.88 (dd, 1H, J = 7.2, 2.6 Hz), 4.88 (dd, 1H, J = 6.0, 4.8 Hz), 4.56 (d, 1H, J = 10.8 Hz), 4.47 (dd, 1H, 10.8, 4.8 Hz), 3.25 (ddd, 1H, J = 7.2, 6.0, 1.8 Hz), 2.76 (ddd, 1H, J = 14.0, 7.2, 1.8 Hz), 2.64 (td, 1H, J = 2.7, 9.6); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 177.8, 134.4, 129.1, 129.0, 127.9, 82.4, 80.3, 73.4, 44.5, 37.4. Anal. Calcd for $C_{12}H_{12}O_3Se$: C 50.88, H 4.24. Found: C 51.11, H 4.28.

[1*S*,5*R*]-6-Oxo-2,7-dioxabicyclo[3.3.0]octa-3-ene (18). *Tert*-Butyl peroxide (340 μL of a 3M solution) and diisopropylethylamine (200 μL) were added to a solution of the anomeric mixture **17** (263 mg, 0.93 mmol) in anhydrous CH_2Cl_2. After 5 min under stirring, Ti(O^{i}Pr)$_4$ (45 μL) was also added. After 15 min the reaction mixture was evaporated to dryness, and the residue was purified by flash chromatography (ethyl acetate/hexane 1:9) over neutral silica gel, obtaining 80 mg (68%) of compound **18** as a syrup, which was directly used in the next reaction. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.47 (t, 1H, J = 2.7 Hz), 5.38 (ddd, 1H, J = 9.6, 6.6, 2.7 Hz), 5.14 (t, 1H, J = 2.7 Hz), 4.66 (dd, 1H, J = 10.8, 6.6 Hz), 4.40 (dd, 1H, J = 10.8, 2.7 Hz), 3.84 (td, 1H, J = 2.7, 9.6 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 175.6, 147.4, 97.4, 80.4, 74.6, 47.9. Anal. Calcd for $C_6H_6O_3$: C 57.14, H 4.76. Found: C 57.28, H 4.73.

1-[[1′*S*,3′*S*,4′*S*,5′*R*]-4′-(Phenylselenenyl)-6′-oxo-2′,7′-dioxabicyclo[3.3.0]octan-3′-yl]uracil (19α). To a solution of compound **18** (30 mg, 0.24 mmol) in anhydrous benzene (2 mL), at room temperature and under argon atmosphere, was added PhSeCl (77 mg, 0.36 mmol). The reaction mixture was stirred for 10 min, and then freshly prepared bis(trimethylsilyl)uracil (123 mg, 0.48 mmol) and AgOTf (103 mg, 0.36 mmol) were added. After 40 min the reaction mixture was diluted with ethyl acetate and filtered through a Celite pad. The resulting solution was evaporated to dryness, and the obtained residue was purified by thin layer chromatography (ethyl acetate/hexane 3:2), obtaining nucleoside **19**α (48 mg, 51%). **19**α: mp 136−138 °C; $[\alpha]^{22}_D$ −3.8 (*c* 0.56, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.9 (s, 1H), 7.55 (d, 1H, J = 8.1 Hz), 6.07 (d, 1H, J = 4.8 Hz), 5.72 (d, 1H, J = 8.1 Hz), 5.19 (dd, 1H, J = 5.8, 3.9 Hz), 4.77 (dd, 1H, J = 4.8, 2.4 Hz), 4.56 (d, 1H, J = 11.1 Hz), 4.42 (dd, 1H, J = 11.1, 3.9 Hz), 3.48 (d, 1H, J = 5.8 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 174.0, 162.7,

149.3, 139.3, 136.5, 128.7, 127.0, 122.6, 101.1, 88.4, 78.8, 70.8, 50.6, 46.0. Anal. Calcd for $C_{16}H_{14}O_5N_2Se$: C 48.85, H 3.56, N 7.12. Found: C 49.00, H 3.42, N 6.93.

[[1*S*,3(*S*,*R*),5*R*]-6-Oxo-3-(phenylthio)-2,7-dioxabicyclo-[3.3.0]octane (20α and 20*β*). A solution of compound **15** (250 mg, 1.58 mmol) in CH_2Cl_2 (4 mL) under argon atmosphere was cooled to −10 °C, and $BF_3{\cdot}OEt_2$ (236 μL) was added. The mixture was stirred for 5 min, and then thiophenol (191 mg) was also added. After 2.5 h the crude reaction was purified by flash chromatography (ethyl acetate−hexane 1:4), obtaining compound **20**α (173 mg, 47%) and compound **20***β* (27 mg, 7%). **20**α: mp 109−110 °C; $[\alpha]^{22}_D$ +205.7 (*c* 0.63, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 7.54−7.20 (m, 5H), 5.74 (dd, 1H, *J* = 7.5, 4.5 Hz), 5.01 (dd, 1H, *J* = 6.0, 3.9 Hz), 4.47 (d, 1H, *J* = 13.5 Hz), 4.40 (dd, 1H, *J* = 13.8, 3.9 Hz), 3.28 (ddd, 1H, *J* = 9.6, 6.0, 3.0 Hz), 2.83 (ddd, 1H, *J* = 10.2, 4.5, 3.0 Hz), 2.36 (ddd, 1H, *J* = 10.2, 9.6, 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) *δ* 172.4, 131.4, 129.0, 127.5, 87.8, 78.1, 71.3, 44.2, 36.1; Anal. Calcd for $C_{12}H_{12}O_3S$: C 61.00, H 5.12, S 13.57. Found: C 60.93, H 5.03, S 13.65. **20***β*: mp 109−110 °C; $[\alpha]^{22}_D$ −385.3 (*c* 0.56, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 7.50−7.26 (m, 5H), 5.65 (dd, 1H, *J* = 7.5, 3.0 Hz), 4.88 (t, 1H, *J* = 6.0 Hz), 4.54 (d, 1H, *J* = 10.8 Hz), 4.45 (dd, 1H, *J* = 10.8, 6.0 Hz), 3.25 (ddd, 1H, *J* = 8.7, 6.0, 1.5, Hz), 2.71 (ddd, 1H, *J* = 13.5, 8.7, 7.5 Hz), 2.53 (ddd, 1H, *J* = 13.5, 3.0, 1.5 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) *δ* 177.7, 131.7, 128.9, 127.5, 87.1, 80.0, 73.4, 44.2, 36.3. Anal. Calcd for $C_{12}H_{12}O_3S$: C 61.00, H 5.12, S 13.57; Found: C 60.75, H 5.12, S 13.32.

1-[[1′*S*,3′(*S*,*R*),5′*R*]-6′-Oxo-2′,7′-dioxabicyclo[3.3.0]octan-3′-yl]uracil (21*β*). Freshly prepared bis(trimethylsilyl)uracil (0.8 mmol) was added under argon atmosphere to a solution of the anomeric mixture **20** (100 mg, 0.42 mmol) in anhydrous CH_2Cl_2 (3 mL). The mixture was stirred for 10 min, and then molecular sieves (4 Å) (30 mg) and NBS (98 mg, 1.3 mmol) were added. After 20 min the reaction mixture was diluted with CH_2Cl_2, filtered through a Celite-Silica gel pad, washed with ethyl acetate (20 mL), and evaporated to dryness. Purification by flash chromatography enabled nucleoside **21** (62.5 mg, 62%) to be obtained as an anomeric mixture (α/*β* = 1:4). A small amount of this mixture was purified by radial chromatography using CH_2Cl_2 containing 3% Et_3N. **21***β*: mp: 210−212 °C (dec.); $[\alpha]^{22}_D$ −5.2 (*c* 0.225, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 8.52 (s, 1H), 7.30 (d, 1H, *J* = 7.2 Hz), 6.10 (dd, 1H, *J* = 4.8, 7.8Hz), 5.74 (d, 1H), 4.86 (dd, 1H, *J* = 5.4, 3.6Hz), 4.60 (d, 1H, *J* = 11.5 Hz), 4.47 (dd, 1H, *J* = 11.5 Hz), 3.31 (ddd, 1H, *J* =10.0, 2.1Hz), 2.90 (ddd, 1H, *J* = 14.0 Hz), 2.46 (ddd, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) *δ* 177.9, 163.9, 150.2, 138.8, 102.1, 86.7, 80.14, 71.1, 43.4, 34.3. Anal. Calcd for $C_{10}H_{10}O_5N_2$: C 50.42, H 4.20, N 11.76; Found: C 50.68, H 4.12, N 11.52.

Phenyl 5-*O*-Benzyl-3-*C*-[[benzyloxy)methyl]-2,3-dideoxy-1-seleno-α- and *β*-D-*threo*-pentofuranoside (22α and 22*β*). To a solution of compound **16** (120 mg, 0.35 mmol) in 2.5 mL of CH_2Cl_2, cooled at −10 °C and under argon atmosphere, was added $BF_3{\cdot}OEt_2$ (50 μL, 0.28 mmol). After 5 min phenylselenol (39 μL, 0.39 mmol) in 0.5 mL of anhydrous CH_2Cl_2 was added. The reaction mixture was kept at −10−0 °C for 1 h and then neutralized with a drop of pyridine. After evaporation to dryness the obtained residue was purified by flash chromatography (ethyl acetate/hexane 1:9), obtaining 114 mg (70%) of compound **22** as an anomeric mixture. **22**α: $[\alpha]^{22}_D$ +167.1 (*c* 0.71, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 7.63−7.25 (m, 15H), 6.00 (dd, 1H, *J* = 6.9, 3.4 Hz), 4.48 (m, 3H), 4.41 (s, 2H), 3,70 (dd, 1H, *J* = 10.5, 4.2 Hz), 3.60 (dd, 1H, *J* = 10.5, 5.4 Hz), 3.53 (dd, 1H, *J* = 9.3, 7.2 Hz), 3.38 (dd, 1H, *J* = 9.3, 6.9 Hz), 2.73 (dd, 1H, *J* = 8.1, 6.9 Hz), 2.37 (ddd, 1H, *J* = 13.8, 6.9, 6.9 Hz), 2.23 (ddd, 1H, *J* = 13.8, 8.1, 3.4 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) *δ* 134.1, 128.8, 128.3, 127.6, 127.3, 83.6, 78.8, 73.3−73.1, 69.2, 40.0, 37.6. Anal. Calcd for $C_{26}H_{28}O_3Se$: C 66.80, H 6.04; Found: C 67.04, H 6.17. **22***β*: $[\alpha]^{22}_D$ −71.2 (*c* 0.32, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 7.63−7.24 (m, 15H), 5.69 (t, 1H, *J* = 7.2 Hz), 4.50−4.41 (m, 4H), 4.28 (m, 1H), 3.65−3.42 (m, 4H), 2.71−2.52 (m, 2H), 2.06 (td, 1H, *J* = 7.8, 12.9 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) *δ* 133.7, 128.4, 127.7, 127.2, 82.4, 80.9, 73.4, 73.2, 69.8, 69.2, 41.3, 37.3. Anal. Calcd for $C_{26}H_{28}O_3Se$: C 66.80, H 6.04; Found: C 66.55, H 6.12.

1,4-Anhydro-5-*O*-benzyl-3-*C*-[(benzyloxy)methyl]-2-deoxy-D-*threo*-pent-1-enitol (23). A solution of the anomeric mixture **22** (114 mg, 0.24 mmol) in 3 mL of anhydrous CH_2Cl_2 was cooled at −10 °C, and then *tert*-butyl peroxide (200 μL, 0.6 mmol) in toluene solution and diisopropylethylamine (90 μL, 0.52 mmol) were added. The resulting solution was stirred for 5 min, and then titanium tetraisopropoxide (120 μL) was added. After 15 min the reaction mixture was evaporated to dryness, and the residue was purified by flash chromatography (ethyl acetate/hexane 1:10), obtaining 70 mg (94%) of compound **23** as a syrup, which was directly used in the next reaction. $[\alpha]^{22}_D$ −31.1 (*c* 0.495, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 7.34−7.21 (m, 10H), 6.38 (t, 1H, *J* = 2.4 Hz), 4.88 (t, 1H, *J* = 2.4 Hz), 4.69 (ddd, 1H, *J* = 10.0, 8.4, 3.6 Hz), 4.49 (d, 2H, *J* = 12.3 Hz), 4.41 (d, 2H, *J* = 12.3 Hz), 3.88 (dd, 1H, *J* = 10.5, 3.6 Hz), 3.71 (dd, 1H, *J* = 10.5, 8.1 Hz), 3.43 (dd, 1H, *J* = 10.0, 8.4 Hz), 3.30 (t, 1H, *J* = 10.0 Hz), 3.20 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) *δ* 146.4, 137.9, 128.3, 127.7, 127.6, 101.6, 82.2, 73.4, 73.1 69.4, 69.0, 43.8. Anal. Calcd for $C_{20}H_{22}O_3$: C 77.42, H 7.10. Found: C 77.18, H 7.02.

1-(5′-*O*-benzyl-2′,3′-dideoxy-3′-*C*-[(benzyloxy)methyl]-2′-(phenylselenenyl)-*β*-D-*xylo*-pentofuranosyl)uracil (24). To a solution of compound **23** (70 mg, 0.227 mmol) in anhydrous benzene (2 mL) was added phenylselenenyl chloride (73 mg, 0.34 mmol) at room temperature. After 5 min freshly prepared bis(trimethylsilyl)uracil (115 mg, 0.45 mmol) and finally AgOTf (92 mg, 0.34 mmol) were added. After 20 min the reaction mixture was diluted with ethyl acetate and filtered through a Celite pad. The organic solution was evaporated to dryness to afford a residue which was purified by flash chromatography (ethyl acetate/hexane 2:3), obtaining 105 mg (81%) of the nucleoside **24** as an anomeric mixture. Additional purification by TLC using the same mixture of solvents as eluent led to 68 mg (55%) of the pure *β* anomer being obtained as a syrup. **24**: $[\alpha]^{22}_D$ +61.7 (*c* 0.715, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 8.51 (s, 1H), 7.63 (d, 1H, *J* = 8.1 Hz), 7.50−7.19 (m, 15H), 6.15 (d, 1H, *J* = 9.0 Hz), 5.12 (d, 1H, *J* = 8.1 Hz), 4.58 (d, 1H, *J* = 12.0 Hz), 4.40 (d, 1H, *J* = 12.0 Hz), 4.26 (s, 2H), 3.91 (dd, 1H, *J* = 9.3, 3.9 Hz), 3.73 (m, 4H), 3.30 (dd, 1H, *J* = 12.3, 9.0 Hz), 2.66 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) *δ* 163.21, 150.4, 140.3, 136.4, 129.3, 128.7, 128.3, 128.1, 102.5, 88.4, 78.3, 73.6, 70.5, 67.7, 44.4, 44.3. Anal. Calcd for $C_{30}H_{30}N_2O_5Se$: C 62.39, H 5.19, N 4.85. Found: C 62.63, H 5.29, N 4.76.

Phenyl 5-*O*-Benzyl-3-*C*-[(benzyloxy)methyl]-2,3-dideoxy-1-thio-α,*β*-D-*threo*-pentofuranoside (25). A solution of compound **16** (0.11 g, 0.32 mmol) in CH_2Cl_2 (3 mL), under argon atmosphere, was cooled to −10 °C, and $BF_3{\cdot}OEt_2$ (0.38 mmol) was added. The reaction mixture was stirred for 5 min, and then thiophenol (110 mg, 0.36 mmol) was added. After 20 min the reaction mixture was neutralized with an aqueous saturated solution of $NaHCO_3$, extracted with CH_2Cl_2 (3 × 10 mL), dried over anhydrous $MgSO_4$, and evaporated to dryness. After purification by flash chromatography (ethyl acetate/hexane 5:1), 89 mg (66%) of compound **25** was recovered as an anomeric mixture (α/*β* 3:1). Spectroscopic data of the major isomer obtained from the spectra of the anomeric mixture, **25**α: ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 7.55 −7.29 (m, 15H) 5.72 (dd, 1H, *J* = 7.5, 4.2 Hz), 5.52 (d, 2H, *J* = 12.0 Hz), 4.44 (d, 2H, *J* = 12.0 Hz), 3.76 −3.37 (m, 5H), 2.73 (m, 1H), 2.38 (ddd, 1H, *J* = 13.2, 7.5, 7.2 Hz), 2.12 (dd, 1H, *J* = 13.2, 8.1, 4.2 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) *δ* 138.0, 131.4, 128.7, 128.2, 126.8, 86.5, 78.5, 73.3, 73.1, 69.3, 69.2, 40.1, 36.5.

1-(5′-*O*-Benzyl-3′-*C*-[(benzyloxy)methyl]-2′,3′-dideoxy-α- and *β*-D-*threo*-pentofuranosyl)uracil (26α and 26*β*). To a solution of compound **25** (α,*β* mixture) (60 mg, 0.14 mmol) in 2.5 mL of anhydrous CH_2Cl_2 (2.5 mL) was added NBS (33 mg, 1.3 mmol) under argon atmosphere. The solution was vigorously stirred for 10 min taken an orange color. Then molecular sieves 4 Å (50 mg) and freshly prepared bis-(trismethylsilyl)uracil (73 mg, 0.28 mmol) were also added. After 20 min the reaction mixture was diluted with ethyl acetate (15 mL) and filtered through a Celite−silica gel pad,

and the solvent was evaporated to dryness. Purification by TLC (ethyl acetate/hexane 2:1) of the obtained residue gave compound **26**α (9 mg, 15%) and compound **26***β* (34 mg, 57%). **26***β*: $[\alpha]^{22}_{D}$ +7.27 (*c* 1.1, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 8.79 (s, 1H), 7.84 (d, 1H, *J* = 8.2 Hz), 7.37−7.24 (m, 10H), 6.14 (dd, 1H, *J* = 8.4, 6.0 Hz), 5.30 (d, 1H, *J* = 8.2 Hz), 4.42 (d, 2H, *J* = 11.7 Hz), 4.35 (d, 2H, *J* = 11.7 Hz), 4.27 (td, 1H, *J* = 3.0, 8.1 Hz), 3.75 (dd, 1H, *J* = 10.5, 3.0 Hz), 3.64−3.58 (m, 3H), 2.83 (m, 1H), 2.34 (ddd, 1H, *J* = 12.9, 8.4, 7.5 Hz), 1.79 (ddd, 1H, *J* = 12.9, 8.4, 6.0 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) *δ* 163.2, 150.4, 140.7, 137.6, 129.3, 128.2, 127.8, 101.8, 84.7 (C-1′), 79.2, 73.6, 73.4, 70.3, 70.0, 40.5, 35.1; Anal. Calcd for $C_{24}H_{26}N_2O_5$: C 68.25, H 6.16, N 6.63. Found: C 68.49, H 6.09, N 6.40. **26**α (minor isomer): ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 8.51 (s, 1H), 7.38−7.25 (m, 11H), 6.12 (dd, 1H, *J* = 6.4, 3.0 Hz), 5.69 (d, 1H, *J* = 7.8 Hz), 4.54 (td, 1H, *J* = 7.2, 4.0 Hz), 4.47−4.46 (m, 4H), 3.65−3.50 (m, 4H), 2.66 (m, 1H), 2.43 (ddd, 1H, *J* = 13.2, 6.8. 3.0 Hz), 2.10 (ddd, 1H, *J* = 13.2, 7.5, 6.4 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) *δ* 163.21, 150.4, 139.3, 128.4, 127.8, 127.7, 101.6, 87.3, 81.7, 73.5, 73.4, 69.8, 68.6, 39.6, 36.6.

Acknowledgment. This project was carried out with financial support from DGICYT (Ministerio de Educación y Ciencia, Spain), Project PB95-0521-A. We thank Fernando Bravo for his help during the revison of the manuscript. M.K. thanks DGICYT for a grant. Technical assistance from the "Servei de Recursos Científics" (Universitat Rovira i Virgili) is acknowledged.

JO961806D