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Synthesis of a 2,3-dideoxy-2,3-difluorofuranose with the D-*lyxo* configuration. An intramolecular rearrangement of methyl 5-*O*-benzoyl-2,3-dideoxy-2,3-difluoro-D-lyxofuranoside observed during the attempted synthesis of 1-(2,3-dideoxy-2,3-difluoro-β-D-lyxofuranosyl)thymine

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Abstract

A new sugar, methyl 5-*O*-benzoyl-2,3-dideoxy-2,3-difluoro-D-lyxofuranoside (**8**), which features fluorine substituents on adjacent carbon positions above the plane of the tetrahydrofuran ring, was synthesized from 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose in seven steps and 22% overall yield. During the synthesis, introduction of the second fluorine atom required conditions more forceful than those normally used with diethylaminosulfur trifluoride (DAST). An attempt to use **8** in the synthesis of the all-*cis* nucleoside, 1-(2,3-dideoxy-2,3-difluoro-β-D-lyxofuranosyl)thymine, failed to give the desired product, providing instead 1-(3-deoxy-3-fluoro-2-*O*-methyl-β-D-xylofuranosyl)thymine (**11**), the structure of which was confirmed by an independent synthesis. Formation of the rearranged product occurred with the concurrent loss of fluorine and retention of the methoxy group which was transposed from the anomeric to the 2′-position. The present work highlights the reactive nature of this novel dideoxydifluoro sugar precursor.

Key words: 2′,3′-Dideoxy-2′,3′-difluoro nucleoside; Diethylaminosulfur trifluoride; Fluorination; Fluoro sugar; Rearrangement; Synthesis

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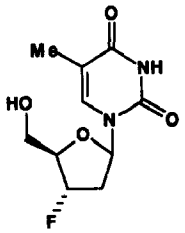
1. Introduction

Glycon fluorine substitution of dideoxynucleosides that operate as reverse transcriptase inhibitors has been studied extensively with the aim of enhancing either potency or stability of the parent, unfluorinated compounds [1]. These investigations have led to the discovery of compounds with potential use for the treatment of AIDS, such as 1-(2,3-dideoxy-3-fluoro-β-D-*erythro*-pentofuranosyl) thymine (1) [2] and 9-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)adenine (2) [3]. The pyrimidine nucleoside 1, known more simply as 3′-deoxy-3′-fluorothymidine or FLT, is able to inhibit HIV replication in cell culture more efficiently than AZT [2], while purine nucleoside 2 is an extremely stable and active analogue of dideoxyadenosine (ddA) [3]. These compounds are currently at various stages of clinical development as anti-HIV agents.



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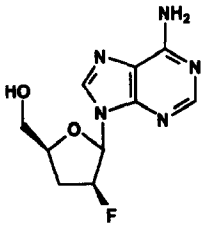

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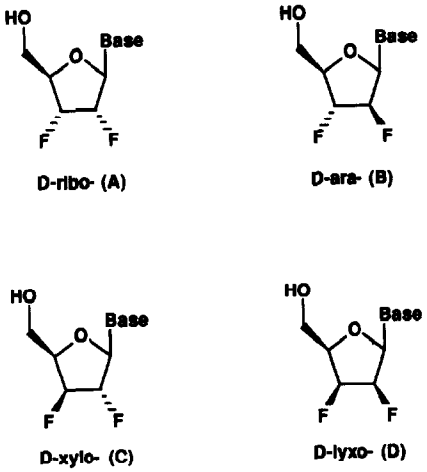
Structure–activity relationship studies on dideoxymonofluoro nucleosides indicate that a fluorine atom at positions 3′-"down" or 2′-"up" produces compounds with fair to excellent anti-HIV activity, while fluorine substitution at the same positions, but with inverted stereochemistry, consistently produces inactive compounds [1b]. An explanation of this phenomenon entreats the possible relationship between a fluorine-induced conformational bias on the otherwise flexible dideoxyribose moiety and a specific conformational preference demanded by a key biological enzyme [1b]. Such conformational changes induced by the fluorine atom are a direct consequence of the socalled *gauche* effect which results from the attractive interaction forces between the very electronegative fluorine and the furanose oxygen [1b,4]. This interaction is maximized when the fluorine atom occupies pseudoaxial positions at 2′ or 3′ [1b].

A comparable correlation for the vicinal dideoxydifluoro nucleosides is expected to be more complicated due to competing *gauche* attractive interactions between fluorine and oxygen, and fluorine and fluorine atoms. However, to date, a complete set of all possible dideoxynucleosides with fluorine atoms replacing both hydroxyl groups of the parent nucleoside has not been available for these studies. Two laboratories have reported syntheses of dideoxydifluoro nucleosides with a D-*ribo*- (**A**) [5] configuration and another laboratory has reported the synthesis of dideoxydifluoro nucleosides with the D-*ara*- (**B**) configuration [6]. We and others have recently completed the synthesis of some dideoxydifluoro nucleosides corresponding to the D-*xylo*- (**C**) configuration [1b,7], and herein we report our attempts

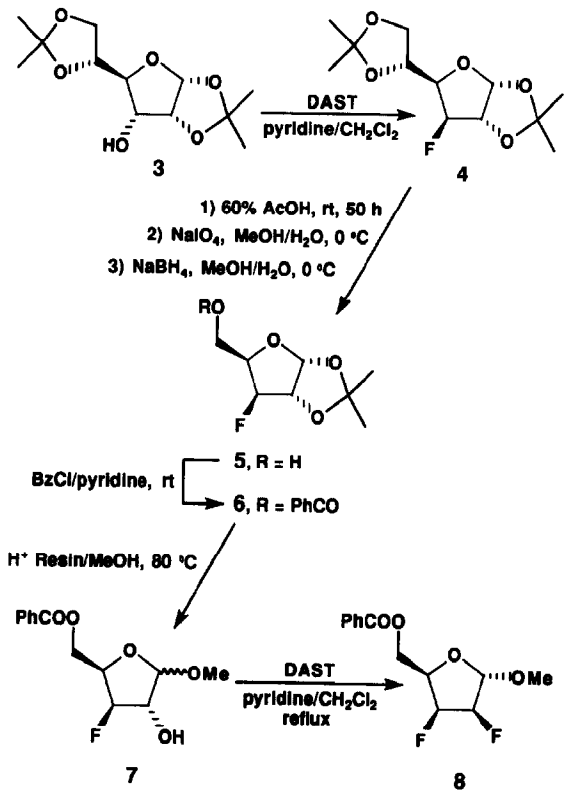


towards the synthesis of the last category of dideoxydifluoro nucleosides which possesses the D-*lyxo*- (**D**) configuration.

Although the present work reports the successful synthesis of the appropriate sugar precursor, methyl 5-*O*-benzoyl-2,3-difluoro-D-lyxofuranoside (**8**), condensation reactions of this intermediate with purine or pyrimidine bases led to the formation of either decomposed or rearranged products that appear to occur with the concurrent loss of fluorine. The characterization of one such rearranged product, which highlights the reactive nature of this novel dideoxydifluoro sugar precursor, is described.

2. Results and discussion

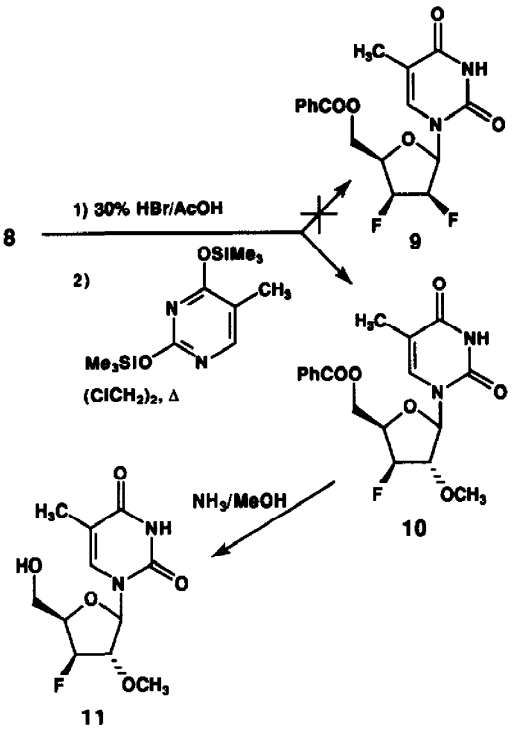
Synthesis of the key difluorodideoxy sugar **8** was performed as shown in Scheme 1. Starting with commercially available 1,2 : 5,6-di-*O*-isopropylidene-α-D-allofuranose, introduction of the fluorine atom with diethylaminosulfur trifluoride (DAST) proceeded with the expected inversion at C-3 to give the known fluoro sugar **4** [3c,8]. Removal of the more labile 5,6-*O*-isopropylidene moiety and cleavage of the resulting vicinal diol with sodium metaperiodate was followed by sodium borohydride reduction of the intermediate aldehyde to afford the corresponding 3-deoxy-3-fluoro-D-xylofuranoside **5**. The 5-hydroxyl group in **5** was subsequently esterified to the benzoate ester **6** [7,9] prior to the acid-catalyzed methanolysis of the 1,2-*O*-isopropylidene moiety to give methyl glycosides **7** as a mixture of anomers. A second DAST fluorination on this intermediate required more forceful conditions than those used to obtain **4**, probably reflecting the existence of repulsive dipole-to-dipole interactions between the fluorine atoms, as well as an increased state of steric congestion that accompanies the formation of the 2,3-dideoxy-2,3-difluoro-D-lyxofuranosides **8**. This contrasts with the milder



Scheme 1.

DAST fluorination conditions, either below 0°C or at room temperature, that were used in the syntheses of 2′,3′-dideoxy-2′,3′-difluoronucleosides with *ribo*- or *ara*-configurations [5,6]. Compound **8** was obtained as a single anomer which displayed only one methyl signal at δ 3.50. The appearance of the anomeric proton as a doublet, which shows only the three-bond coupling constant to the adjacent fluorine at C-2 ($J \sim 14$ Hz), suggested that the anomeric configuration in **8** was α. It is possible that from the 3:2 mixture of anomers in **7** (see Experimental) only the minor α-methoxy anomer gives the expected fluorinated product **8**, while the β-methoxy anomer is converted into other compounds derived from an initial intermediate formed by an intramolecular attack at C-2. No other dideoxydifluoro sugar products could be isolated from this reaction.

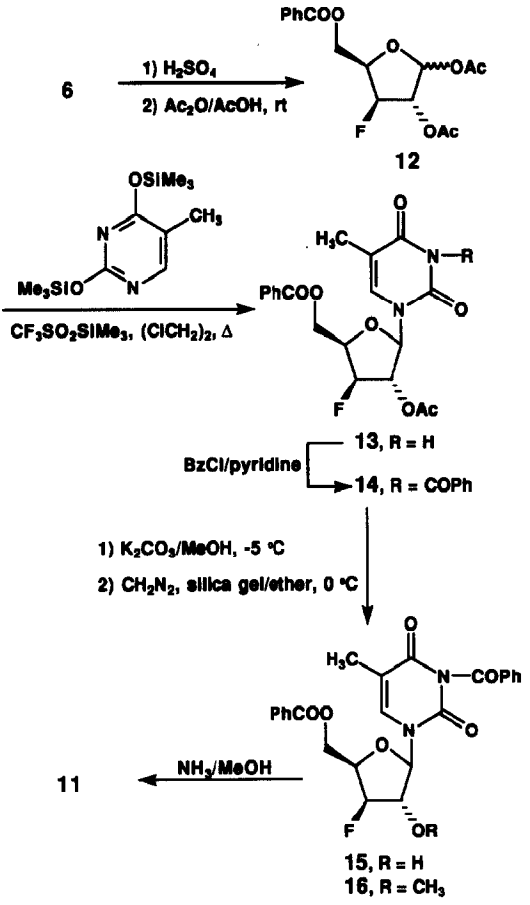
Several attempts to couple **8** with either 6-chloropurine or thymine under a variety of conditions, including the common trimethylsilyltriflate-catalyzed coupling reaction, proceeded with extensive decomposition of the sugar. Mindful of the necessity to direct the attack of the incoming base from an already crowded β side, preparation of a bromo sugar intermediate was sought because of our knowledge that in the case of the analogous 5-*O*-benzoyl-2,3-dideoxy-2-fluoro-D-*threo*-pentofuranosyl bromide [10] and 2-deoxy-2-fluoro-3,5-di-*O*-benzoyl-α-D-



Scheme 2.

arabinofuranosyl bromide [11] the fluorine at C-2 forced the resulting bromo sugar to have the more stable α configuration where the bromine and fluorine atoms are farthest from each other. Therefore, we expected a similar situation to help generate an equivalent α-bromo sugar from compound **8**, which would have insured a selective β-attack from a nucleophilic base. Treatment of a dichloromethane solution of **8** with 30% HBr in acetic acid at 0°C (Scheme 2) showed by TLC disappearance of the starting material, accompanied by the unexpected appearance of a slower moving, more polar material. After removing the excess HBr, the product was extracted and reacted immediately with bis-silylated thymine (Scheme 2). Analysis of the only major product that could be isolated (19% yield) indicated that a thymine nucleoside had indeed been formed. However, the ^{1}H NMR spectrum did not indicate the desired structure (compound **9**). Instead, a thymine nucleoside **10**, in which loss of fluorine had occurred concomitantly with the retention of the methoxy group, was formed. The protected nucleoside **10** was then deblocked to the free nucleoside **11** whose structure was later confirmed by an independent synthesis (vide infra).

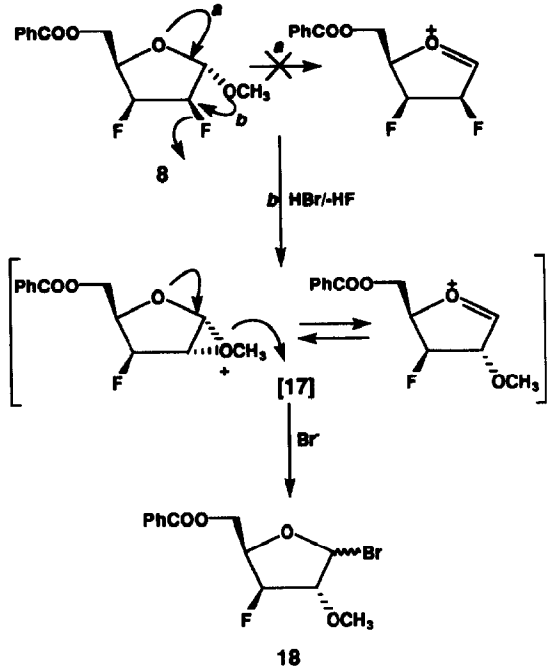
Reaction of *O*-bis-silylated thymine with diacetate **12**, obtained from **6** (Scheme 1), in the presence of trimethylsilyl trifluoromethanesulfonate [12] led to the exclusive formation of the β anomer **13** (Scheme 3). Under these conditions, anchimeric participation of the C-2 acetate during the formation of the intermedi-



Scheme 3.

ate carbocation directed the attack of the base from the β side. Protection of the pyrimidine ring as the N-3 benzoylimide **14** was followed by the selective removal of the C-2′ acetate moiety to give compound **15**. This operation freed the 2′-hydroxyl group, which upon reaction with diazomethane [13], gave the target compound **11**. This compound was identical in every respect to product **11** obtained as described in Scheme 2.

Mechanistically, we have to assume that a glycosyl bromide intermediate was formed. After **8** reacted with HBr, the glycosyl bromide intermediate was extracted into dichloromethane and immediately reacted with bis-silylated thymine (see Experimental). The question is whether loss of fluorine occurred at this stage, or latter during the coupling of the base. We propose that the strong *-I* effect of both fluorine atoms exerts a concerted action to resist formation of a carbocation intermediate at C-1 that would have resulted from the ejection of methanol following protonation. Singly, the stabilizing effect towards cleavage of the glycosylic bond — which proceeds through a cationic transition state — produced by



Scheme 4.

the fluorine atom has been observed in nucleosides having fluorine substitution at either C-2 or C-3 [3a,c,14], and it supports the assumption that with two fluorine substituents the effect should be magnified. This means that the molecule would resist protonation and that under the reaction conditions the only possible path that would lead to a transitional carbocation has to proceed through the ejection of one of the fluorines. This could be envisioned to happen for the C-2 fluorine through the assistance of the α-methoxy group (Scheme 4, path b). The new transitional carbocation **17** could then add Br^- to produce **18**. The stereochemistry at the anomeric carbon in **18** cannot be predicted with certainty on the basis of the stereochemistry of the main isolated product (compound **10**) since it could have arisen from either the α-bromo sugar (direct displacement), or the β-bromo sugar by a double inversion mechanism. Although we were unable to isolate any α nucleoside, we cannot totally rule out its presence in small quantities. It is proposed that the concerted action of the two fluorine atoms is responsible for the unusual behavior of the sugar intermediate **8**.

3. Experimental

General methods.—Silica gel column chromatography was performed on Silica Gel 60 (E. Merck, 230–400 mesh), and analytical TLC was performed on Analtech Uniplates Silica Gel GF with the solvents indicated. Detection of compounds by

TLC was accomplished either by UV light or by 10% MeOH–H_2SO_4 spray, followed by heating on a hot plate. UV spectra were obtained with a Shimadzu scanning UV/Vis spectrophotometer model UV-2101PC, and specific rotations were measured with a Perkin–Elmer Model 241 polarimeter. Proton and ^{13}C NMR spectra were recorded in the solvents indicated at 250 MHz and 62.9 MHz, respectively, on a Bruker AC-250 instrument. Chemical shifts are expressed as δ values with reference to Me_4Si. Positive-ion fast-atom bombardment mass spectra (FABMS) were obtained by using samples dissolved in a glycerol matrix, and ionization was effected by a beam of Xe atoms derived by neutralizing Xe ions accelerated through 8.6 kV. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA, or by Galbraith Laboratories, Inc., Knoxville, TN. All solvents of inclusion as indicated in the elemental analyses were observed by ^1H NMR spectroscopy.

*3-Deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-α-*D*-glucofuranose* (**4**).—To a solution of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**3**) (15 g, 57.6 mmol) in anhyd CH_2Cl_2 (100 mL) was added pyridine (14.9 mL, 184 mmol) followed by the dropwise addition of diethylaminosulfur trifluoride (DAST, 14.9 g, 92 mmol) at 0°C. The mixture was stirred at room temperature for 15 h and then carefully poured onto a satd $NaHCO_3$ solution (100 mL). The organic layer was separated, washed with brine (100 mL), dried ($MgSO_4$), and evaporated. The resulting residue was purified by silica gel column chromatography (5:1 petroleum ether–EtOAc) to give **4** (10.8 g. 71.5%) as a colorless oil whose spectral data were identical to those reported for an authentic sample [8].

*3-Deoxy-3-fluoro-1,2-*O*-isopropylidene-α-*D*-xylofuranose* (**5**).—A solution of **4** (10 g, 38.1 mmol) in aq 60% AcOH (250 mL) was stirred at room temperature for 50 h. The solvents were evaporated under vacuum, and the residue was dissolved in MeOH (300 mL). Solid $NaHCO_3$ (4.8 g, 57.2 mmol) was added to the mixture, followed by the dropwise addition of aq $NaIO_4$ (200 mL; 12.2 g, 57.2 mmol) at 0°C. After the mixture had been stirred at 0°C for 15 min, $NaBH_4$ (2.88 g, 76.2 mmol) was added, and stirring was continued for 15 min at the same temperature. The mixture was filtered, washed with MeOH, and the filtrate was neutralized with glacial AcOH. After reducing the volume under vacuum to one half, the mixture was partitioned between water and EtOAc. The organic layer was separated, washed with satd $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. The resulting residue was purified by silica gel column chromatography (3:1 petroleum ether–EtOAc) to give **5** (6.76 g. 72.2%) as a colorless syrup; ^1H NMR ($CDCl_3$): δ 1.25 (s, 3 H, CH_3), 1.41 (s, 3 H, CH_3), 3.82 (m, 2 H, H-$5_{a,b}$), 4.28 (m, 1 H, H-4), 4.62 (dd, 1 H, $^3J_{2,F}$ 11.1, $J_{2,1}$ 3.8 Hz, H-2), 4.92 (dd, 1 H, $^2J_{3,F}$ 50.4, $J_{3,4}$ 2.3 Hz, H-3), 5.91 (d, 1 H, J 3.8 Hz, H-1). Anal. Calcd for $C_8H_{13}FO_4 \cdot 0.1H_2O$: C, 49.53; H, 6.81; F, 9.79. Found: C, 49.47; H, 7.00; F, 9.23.

*5-*O*-Benzoyl-3-deoxy-3-fluoro-1,2-*O*-isopropylidene-α-*D*-xylofuranose* (**6**).—To a solution of **5** (3 g, 15.6 mmol) in pyridine (10 mL) was added benzoyl chloride (1.99 mL, 17.2 mmol), and the mixture was stirred at room temperature for 2 h. Ice was added to decompose excess benzoyl chloride and the excess pyridine was evaporated. The residue was dissolved in EtOAc (200 mL), and the organic layer was

washed with satd $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. The resulting residue was purified by silica gel column chromatography (5:1 petroleum ether–EtOAc) to give **6** (4.61 g, 99.8%) as a colorless syrup; ^1H NMR ($CDCl_3$): δ 1.29 (s, 3 H, CH_3), 1.48 (s, 3 H, CH_3), 4.52 (m, 3 H, H-4, H-$5_{a,b}$), 4.72 (dd, 1 H, $^3J_{2,F}$ 10.9, $J_{2,1}$ 3.8 Hz, H-2), 5.04 (dd, 1 H, $^2J_{3,F}$ 50.3, $J_{3,4}$ 1.7 Hz, H-3), 6.01 (d, 1 H, J 3.8 Hz, H-1), 7.35–8.10 (m, 5 H, Ph). Anal. Calcd for $C_{15}H_{17}FO_5 \cdot 0.1H_2O$: C, 60.43; H, 5.82; F, 6.37. Found: C, 60.22; H, 6.03; F, 6.23.

*Methyl 5-O-benzoyl-3-deoxy-3-fluoro-*D*-xylofuranoside* (**7**).—A solution of **6** (1.4 g, 4.7 mmol) in MeOH (35 mL) was treated with Dowex 50 × 8–100 [H^+] resin in MeOH (7 mL), and the mixture was heated with stirring at 80°C for 3 h under a blanket of N_2. The mixture was cooled to room temperature, filtered, and the filtrate was evaporated to dryness. The resulting residue was purified by silica gel column chromatography (2:1 petroleum ether–EtOAc) to give **7** (mixture of anomers, 1.16 g, 90.5%) as a colorless syrup; ^1H NMR ($CDCl_3$): δ 2.15 and 2.85 (br s, 1 H, OH), 3.42 and 3.50 (s, 3 H, OMe), 4.31–4.80 (m, 5 H, H-2, H-3, H-4, and H-5), 4.91 (s, 0.6 H, H-1), 5.10 (d, 0.4 H, $J_{1,2}$ 3.9 Hz, H-1), 7.38–8.20 (m, 5 H, Ph). This compound was used in the following step without further purification.

*Methyl 5-O-benzoyl-2,3-dideoxy-2,3-difluoro-*D*-lyxofuranoside* (**8**).—A solution of **7** (1.12 g, 4.1 mmol) and pyridine (1.1 mL, 13.3 mmol) in anhyd CH_2Cl_2 (15 mL) was treated with DAST (0.87 mL, 6.6 mmol), and the mixture was stirred at room temperature for 15 h. Since TLC showed mostly unreacted starting material and a small amount of product, the mixture was heated to reflux until the starting material had disappeared. The mixture was then carefully poured onto cold satd $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2. The combined organic layers were washed with 5% HCl and brine (100 mL), dried ($MgSO_4$), and evaporated. The resulting oil was purified by silica gel column chromatography (4:1 petroleum ether–EtOAc) to give **8** (0.525 g, 44.6%) as a white amorphous solid; ^1H NMR ($CDCl_3$): δ 4.11 (tdd, 1 H, $^3J_{4,F}$ 16.3, $J_{4,3}$ 4.3, J 2.1 Hz, H-4), 4.60 (m, 1 H, H-5_a), 4.70 (d, 1 H, $^3J_{1,F}$ 14.3 Hz, H-1), 4.70 (m, 1 H, H-5_b), 5.25 (ddd, 1 H, $^2J_{3,F}$ 53.2, $J_{3,4}$ 4.3, $J_{3,2}$ 2.8 Hz, H-3), 5.92 (distorted dd, 1 H, $^2J_{2,F}$ 65.7Hz, H-2), 7.40–8.21 (m, 5 H, Ph); high-resolution FABMS: m/z 273.091 (MH^+, calcd 273.094). Anal. Calcd for $C_{13}H_{14}F_2O_4$: C, 57.35; H, 5.18; F, 13.96. Found: C, 57.03; H, 5.32; F, 13.74.

*1-(5-O-Benzoyl-3-deoxy-3-fluoro-2-O-methyl-β-*D*-xylofuranosyl)thymine* (**10**).—To a solution of **8** (100 mg, 0.367 mmol) in anhyd CH_2Cl_2 (5 mL) was added 30% HBr in AcOH (0.18 mL) at 0°C, and the mixture was stirred at room temperature for 2 h. TLC indicated the disappearance of starting material and the appearance of a slower moving spot. Excess HBr and AcOH were evaporated under vacuum, and the residue was dissolved in CH_2Cl_2 (30 mL), washed with satd $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$), and evaporated. The dark-brown residue (90 mg) was dissolved in anhyd $ClCH_2CH_2Cl$ and used immediately for the coupling reaction. This solution of crude glycosyl bromide was added to a solution of silylated thymine in anhyd $ClCH_2CH_2Cl$ (5 mL). The silylated thymine was prepared separately from thymine (0.0695 g, 0.551 mmol), hexamethyldisilazane (HMDS, 15 mL), and catalytic $(NH_4)_2SO_4$. The mixture was refluxed for 2 h, and after reaching room temperature $CHCl_3$ (10 mL) was added. The organic layer was

washed with brine (10 mL), dried ($MgSO_4$), and evaporated to dryness to give an oily residue that was purified by silica gel column chromatography (20:1 $CHCl_3$–MeOH) to give **10** (0.026 g, 19.3% from **8**) as a yellow foam; UV ($CHCl_3$) λ_{max} 265 nm; ^{1}H NMR ($CDCl_3$): δ 1.90 (d, 3 H, J 0.6 Hz, CH_3), 3.53 (s, 3 H, OCH_3), 3.96 (d, 1 H, $^3J_{2',F}$ 15.2 Hz, H-2'), 4.57 (m, 1 H, H-4'), 4.71 (d, 2 H, $J_{4',5'}$ 6.3 Hz, H-5'$_{a,b}$), 5.13 (dd, 1 H, $^2J_{3',F}$ 50.8, $J_{3',4'}$ 2.2 Hz, H-3'), 6.07 (s, 1 H, H-1'), 7.23–8.05 (m, 6 H, H-6 and Ph), 8.61 (br s, 1 H, NH). Anal. Calcd for $C_{18}H_{19}FN_2O_6$: C, 57.14; H, 5.06; N, 7.40. Found: C, 56.86; H, 5.22; N, 7.17.

*1-(3-Deoxy-3-fluoro-2-*O*-methyl-β-*D*-xylofuranosyl)thymine* (**11**).—A solution of **10** (0.02 g, 0.0594 mmol) in methanolic ammonia was stirred at room temperature for 20 h in a sealed vessel. The solvent was evaporated, and the residue was purified by silica gel column chromatography (10:1 $CHCl_3$–MeOH) to give **11** (0.015 g, 92.1%) as a white foam; $[\alpha]_D^{25}$ + 2.62° (c 0.61, MeOH); UV (MeOH) λ_{max} 265 nm; ^{1}H NMR (CD_3OD): δ 1.86 (d, 3 H, J 0.9 Hz, CH_3), 3.51 (s, 3 H, OCH_3), 3.96 (m, 2 H, H-5'$_{a,b}$), 4.06 (d, 1H, $^3J_{2',F}$ 15.1 Hz, H-2'), 4.23 (dm, 1 H, $^3J_{4',F}$ 30.6 Hz, H-4'), 5.15 (dd, 1 H, $^2J_{3'F}$ 50.8, $J_{3'4'}$ 2.4 Hz, H-3'), 5.92 (s, 1 H, H-1'), 7.43 (d, 1 H, J 1.0 Hz, H-6); ^{13}C NMR (CD_3OD): δ 12.60, 58.73, 59.50 (J 9.8 Hz, C-5'), 84.02 (J 19.3 Hz, C-2'), 88.88 (J 27.1 Hz, C-4'), 90.30, 94.45 (J 181.0 Hz, C-3'), 111.46, 137.21, 152.60, 167.20; FABMS m/z (relative intensity) 275 (MH^+, 100), 127 (b + 2 H, 89). Anal. Calcd for $C_{11}H_{15}FN_2O_5$: C. 48.18; H, 5.51; N, 10.21. Found: C, 47.92; H, 5.62; N, 10.03.

*1,2-Di-*O*-acetyl-5-*O*-benzoyl-3-deoxy-3-fluoro-*D*-xylofuranose* (**12**).–A solution of **6** (10 g, 33.8 mmol) in glacial AcOH (170 mL) and Ac_2O (20 mL) was treated with concd H_2SO_4 (1.5 mL) at 0°C, and the resulting solution was stirred at room temperature for 15 h. The solution was carefully poured into 10% aq NaOAc (250 mL), stirred for 30 min at 0°C, and extracted with $CHCl_3$ (3 × 200 mL). The combined organic extract was washed with satd $NaHCO_3$ (200 mL) and brine (200 mL), dried ($MgSO_4$), and evaporated. The residue obtained was purified by silica gel column chromatography (1:1 hexanes–EtOAc) to give **12** (11.0 g. 95.7%) as a colorless syrup; ^{1}H NMR ($CDCl_3$): δ 2.01, 2.03, 2.05, and 2.09 (singlets, 6 H, 2 × $OCOCH_3$), 4.40–4.80 (m, 3 H, H-4 and H-5$_{a,b}$), 5.00–5.50 (m, 2 H, H-2 and H-3), 6.19 (s, 0.4 H, H-1), 6.50 (d, 0.6 H, $J_{1,2}$ 4.6 Hz, H-1), 7.38–8.05 (m, 5 H, Ph). Anal. Calcd for $C_{16}H_{17}FO_7$: C, 56.47; H, 5.04; F, 5.58. Found: C, 56.56; H, 5.40; F, 5.21.

*1-(2-*O*-Acetyl-5-*O*-benzoyl-3-deoxy-3-fluoro-β-*D*-xylofuranosyl)thymine* (**13**).—To a solution of silylated thymine [prepared from thymine (1.12 g, 8.9 mmol), HMDS (30 mL), and catalytic $(NH_4)_2SO_4$] in anhyd $ClCH_2CH_2Cl$ (20 mL) was added compound **12** (2.0 g, 5.9 mol) also dissolved in anhyd $ClCH_2CH_2Cl$ (20 mL). Trimethylsilyl trifluoromethanesulfonate (1.74 mL, 8.9 mmol) was added, and the mixture was refluxed for 2 h. After reaching room temperature, equal portions (100 mL) of $CHCl_3$ and a satd $NaHCO_3$ solution were added, and the mixture was stirred for 30 min. The organic layer was separated, washed with brine (50 mL), dried ($MgSO_4$), and evaporated. The resulting syrup was purified by silica gel column chromatography (20:1 $CHCl_3$–MeOH) to give **13** (1.60 g, 63.0%) as a white foam; UV ($CHCl_3$) λ_{max} 265 nm; ^{1}H NMR ($CDCl_3$): δ 1.91 (s, 3 H, CH_3),

2.13 (s, 3 H, $OCOCH_3$), 4.48 (dm, 1 H, $^3J_{4',F}$ 28.9 Hz, H-4'), 4.73 (m, 2 H, H-$5'_{a,b}$), 5.13 (dd, 1 H, $^2J_{3',F}$ 69.8, $J_{3',4'}$ 2.4 Hz, H-3'), 5.22 (distorted t, 1 H, H-2'), 6.15 (d, 1 H, $J_{1',2'}$ 2.5 Hz, H-1'), 7.19 (s, 1 H, H-6), 7.42–8.09 (m, 5 H,Ph), 8.48 (br s, 1 H, NH). Anal. Calcd for $C_{19}H_{19}FN_2O_7$: C, 56.16; H, 4.71; N, 6.89. Found: C, 56.06; H, 4.89; N, 6.69.

N^3-Benzoyl-1-(2-O-acetyl-5-O-benzoyl-3-deoxy-3-fluoro-β-D-xylofuranosyl)thymine (**14**).—A solution of **13** (0.7 g, 1.72 mmol) in dry pyridine (30 mL) was treated with benzoyl chloride (0.30 mL, 2.58 mmol) at 0°C and stirred at room temperature for 72 h. Pyridine was evaporated, and the residue was dissolved in EtOAc (100 mL). The organic solution was washed with satd $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$), and evaporated. The residue obtained was purified by silica gel column chromatography (1:1 hexanes–EtOAc) to give **14** (0.58 g, 66.0%) as a white foam; UV ($CHCl_3$) λ_{max} 253, 277 (sh) nm; ^1H NMR ($CDCl_3$): δ 1.95 (s, 3 H, CH_3), 2.10 (s, 3 H, $OCOCH_3$), 4.50 (dm, 1 H, $^3J_{4',F}$ 28.6 Hz, H-4'), 4.75 (m, 2 H, H-$5'_{a,b}$), 5.16 (dd, 1 H, $^2J_{3',F}$ 72.3, $J_{3',4'}$ 2.4 Hz, H-3'), 5.28 (distorted t, H-2'), 6.11 (d, 1 H, $J_{1',2'}$ 2.6 Hz, H-1'), 7.30 (s, 1 H, H-6), 7.42–8.11 (m, 10 H, 2 × Ph). Anal. Calcd for $C_{26}H_{23}FN_2O_8$: C, 61.18; H, 4.54; N, 5.49. Found: C, 61.23; H, 4.75; N, 5.32.

N^3-Benzoyl-1-(5-O-benzoyl-3-deoxy-3-fluoro-β-D-xylofuranosyl)thymine (**15**).—To a cold (−5°C) solution of **14** (0.37 g, 0.725 mmol) in MeOH (30 mL) and H_2O (2 drops) was added K_2CO_3 (0.13 g, 0.941 mmol), and the mixture was stirred at −5°C for 15 min. Glacial AcOH was added, and the mixture was partitioned between $CHCl_3$ (100 mL) and H_2O (30 mL). The organic layer was separated, washed with brine (100 mL), dried ($MgSO_4$), and evaporated. The residue obtained was purified by silica gel column chromatography (1:1 hexanes–EtOAc) to give **15** (0.26 g, 76.5%) as a white foam; UV ($CHCl_3$) λ_{max} 253, 276 (sh) nm; ^1H NMR ($CDCl_3$) δ 1.91 (s, 3 H, CH_3), 3.89 (br s, 1 H, 2'-OH), 4.30 (d, 1 H, $^3J_{2',F}$ 15.3 Hz, H-2'), 4.61 (dm, 1 H, $^3J_{4',F}$ 29.5 Hz, H-4'), 4.72 (m, 2 H, H-$5'_{a,b}$), 4.95 (dd, 1 H, $^2J_{3',F}$ 50.5, $J_{3',4'}$ 1.6 Hz, H-3'), 5.79 (d, 1 H, $J_{1',2'}$ 0.8 Hz, H-1'), 7.38 (s, 1 H, H-6), 7.42–8.09 (m, 10 H, 2 × Ph). Anal. Calcd for $C_{24}H_{21}FN_2O_7 \cdot 0.15C_6H_{14}$: C, 62.13; H, 4.83; N, 5.82. Found: C, 62.08; H, 5.05; N, 5.57.

N^3-Benzoyl-1-(5-O-benzoyl-3-deoxy-3-fluoro-2-O-methyl-β-D-xylofuranosyl)thymine (**16**).—A suspension of **15** (0.35 g, 0.686 mmol) and silica gel (30 g, 70–230 mesh) in ether (150 mL) was treated with CH_2N_2 (etherial solution, 300 mL) at 0°C and stirred at that temperature for 2 h. The mixture was filtered and the silica gel cake was washed with ether. The ether was evaporated and the residue was purified by silica gel column chromatography (1:1 hexanes–EtOAc) to give **16** (0.30 g, 83.3%) as a white foam; UV ($CHCl_3$) λ_{max} 253, 277 (sh) nm; ^1H NMR ($CDCl_3$): δ 1.91 (s, 3 H, CH_3), 3.49 (s, 3 H, OCH_3), 4.05 (d, 1 H, $^3J_{2',F}$ 14.1 Hz, H-2'), 4.55 (dm, 1 H, $^3J_{4',F}$ 30.6 Hz, H-4'), 4.72 (m, 2 H, H-$5'_{a,b}$), 5.08 (dd, 1 H, $^2J_{3',F}$ 50.8, $J_{3',4'}$ 1.6 Hz, H-3'), 6.00 (s, 1 H, H-1'), 7.40 (s, 1 H, H-6), 7.50–8.09 (m, 10 H, 2 × Ph). Anal. Calcd for $C_{25}H_{23}FN_2O_7$: C, 62.24; H, 4.80; N, 5.81. Found: C, 62.27; H, 5.14; N, 5.45.

1-(3-Deoxy-3-fluoro-2-O-methyl-β-D-xylofuranosyl)thymine (**11**).—A solution of **16** (0.25 g, 0.477 mmol) and methanolic ammonia (50 mL) was stirred at room

temperature for 20 h. The solvent was evaporated, and the residue was purified by silica gel column chromatography (10:1 $CHCl_3$–MeOH) to give **11** (0.13 g, 65.0%) as a white, amorphous foam. The spectral data were identical with that of compound **11** obtained from the coupling reaction described in Scheme 2.

References

[1] (a) P. Herdewijn., A. Van Aerschot, and L. Kerremans, *Nucleosides Nucleotides,* 8 (1989) 65–96; (b) V.E. Marquez, B.B. Lim, J.J. Barchi, Jr., and M.C. Nicklaus, in C.K. Chu and D.C. Baker (Eds.), *Nucleosides and Nucleotides as Antitumor and Antiviral Agents,* Plenum, New York, 1993, pp 265–284, and references therein.

[2] (a) J. Balzarini, M. Baba, R. Pauwels, and P. Herdewijn, *Biochem. Phamacol.,* 37 (1988) 2847–2856; (b) P. Herdewijn, J. Balzarini, E. De Clercq, R. Pauwels, M. Baba, S. Broder, and H. Vanderhaeghe, *J. Med. Chem.,* 30 (1987) 1270–1278; (c) E. Matthes, C. Lehman, M. Vonjantalipinski, and D. Scholz, *Biochem. Biophys. Res. Commun.*, 165 (1989) 488–495; (d) B. Lundgren, D. Böttiger, L. Ljungdahl-Ståhle, B. Wahren, and B. Öberg, *J. Acquir. Immun. Defic. Syndr.,* 4 (1991) 489–498.

[3] (a) V.E. Marquez, C.K.H. Tseng, J.A. Kelley, H. Mitsuya, S. Broder, J.S. Roth, and J.S. Driscoll, *Biochem. Pharmacol.,* 36 (1987) 2719–2722; (b) P. Herdewijn, R. Pauwels, M. Baba, J. Balzarini, and E. De Clercq, *J. Med. Chem.,* 30 (1987) 2131–2137; (c) V.E. Marquez, C.K.H. Tseng, H. Mitsuya, S. Aoki, J.A. Kelley, H. Ford, Jr., J.S. Roth, S. Broder, D.G. Johns, and J.S. Driscoll, *J. Med. Chem.,* 33 (1990) 978–985.

[4] (a) E.W. Taylor, P. Van Roey, R.F. Schinazi, and C.K. Chu, *Antivir. Chem. Chemother.*, 1 (1990) 163–173; (b) J. Plavec, L.H. Koole, A. Sandström, and J. Chattopadhyaya, *Tetrahedron*, 47 (1991) 7363–7376.

[5] (a) A. Van Aerschot and P. Herdewijn, *Bull. Soc. Chim. Belg.*, 98 (1989) 937–941; (b) P. Herdewijn and A. Van Aerschot, *Bull. Soc. Chim. Belg.*, 98 (1989) 943–947; (c) J.-T. Huang, L.-C. Chen, L. Wang, K.-H. Kim, J.A. Warshaw, D. Armstrong, Q.-Y. Zhu, T.-C. Chou, K.A. Watanabe, J. Matulic-Adamic, T.-L. Su, J.J. Fox, B. Polsky, P.A. Baron, J.W.M. Gold, W.D. Hardy, and E. Zuckerman, *J. Med. Chem.*, 34 (1991) 1640–1646.

[6] J.A. Martin, D.J. Bushnell, I.B. Duncan, S.J. Dunsdon, M.J. Hall, P.J. Machin, J.H. Merrett, K.E.B. Parkes, N.A. Roberts, G.J. Thomas, S.A. Galpin, and D. Kinchington, *J. Med. Chem.*, 33 (1990) 2137–2145.

[7] G. Gosselin, F. Puech, C. Genu-Dellac, and J.-L. Imbach, *Carbohydr. Res.*, 9 (1993) 1–17.

[8] T.J. Tewson and M.J. Welch, *J. Org. Chem.*, 43 (1978) 1090–1092.

[9] F. Puech, G. Gosselin, and J.-L. Imbach, *Tetrahedron Lett.*, 30 (1989) 3171–3174.

[10] R.J. Wysocki, M.A. Siddiqui, J.J. Barchi, Jr., J.S. Driscoll and V.E. Marquez, *Synthesis,* (1991)1005–1008.

[11] C.H. Tann, P.R. Brodfuehrer, S.P. Brundidge, C. Sapino, Jr., and H.G. Howell, *J. Org. Chem.*, 50 (1985) 3644–3647.

[12] H. Vorbrüggen, K. Krolikiewicz, and B. Bennua, *Chem. Ber.*, 114 (1981) 1234–1255.

[13] C. Chavis, F. Dumont, R. Wightman, J.-C. Ziegler, and J.-L. Imbach, in L.B. Townsend and R.S. Tipson (Eds.), *Nucleic Acid Chemistry. Improved and New Synthetic Procedures, Methods, and Techniques*, Part 3, Wiley, New York, 1986, pp 76–80.

[14] P. Oksman, H. Hakala, A. Van Aerschot, and P. Herdewijn, *Phys. Org. Chem.,* 5 (1992) 741–747.