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TETRAHEDRON

Synthesis of 2',3'-Dideoxy-3',3'-difluoro and 2',3'-Dideoxy-2',2'-difluoro-pyranosyl Nucleosides Analogues of Gemcitabine

Raul Fernández, Sergio Castillón*

Departament de Química Analítica i Química Orgànica, Universitat Rovira i Virgili,

Pça. Imperial Tarraco 1, 43005 Tarragona, Spain

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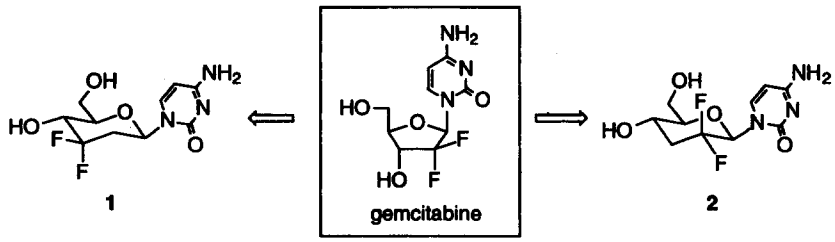
Abstract: The *gem*-difluoronucleosides **1** and **2**, pyranosyl analogues of gemcitabine, have been synthesized from D-mannose and D-glucose respectively. The key steps were the formation of the difluoromethylene group by reaction of the corresponding ulose with DAST, and the glycosylation.

The increasing importance of viral diseases has encouraged interest in nucleoside chemistry, since nucleoside analogues are active antiviral drugs.[1] In particular, pyranosyl nucleosides, as analogues of furanosyl nucleosides, have been used as probes for antiviral activity,[2] and in the synthesis of acyclonucleosides[3] and the preparation of oligopyranosylnucleotides.[4] Introducing fluorine into nucleosides has also proved to be a useful procedure for modifying the biological activity of these compounds. Specially efficient for this purpose is the introduction of fluorine into positions 2'β,[5] 3'α (FLT)[6] and 5 (FTC)[7] of a nucleoside. Gemcitabine, a 2'-deoxy-2',2'-difluoronucleoside (scheme 1), has proved to be highly active against cancer and has recently been approved for treating several types of tumour.[8,9]

In this context, we planned to synthesise 2',3'-dideoxy-3',3'-difluoropyranosyl and 2',3'-dideoxy-2',2'-difluoro nucleosides **1** and **2**, which can be regarded as pyranosyl analogues of gemcitabine.



Scheme 1

Gemcitabine and related 2',2'-difluoronucleosides have been prepared from 2-deoxy-2,2-difluoro-D-ribofuranose, which is obtained from glyceraldehyde through a Reformatsky reaction with ethylbromo-difluoroacetate,[10,11] or from D-mannose and D-glucose by obtaining the 3,3-difluoro-pyranosyl derivative and carrying out a subsequent degradation.[12] In addition, 3',3'-difluoronucleosides have been prepared by reaction of the ketonucleoside with DAST[13] and the same general procedures are also used in the synthesis of difluoropyranoses.[14]

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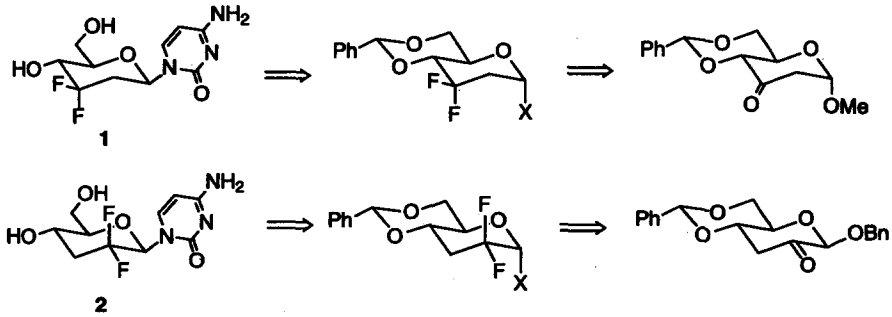
We previously studied the preparation of 2,2-difluoro and 3,3-difluoropyranoses by reacting 2- and 3-uloses with DAST and determining how the configuration of neighbouring groups affected the reaction.[15] Thus, in the case of 2,2-difluoropyranoses, a β-configuration in the anomeric carbon was found to be necessary to prevent the formation of 1,2-difluorocarbohydrates due to a migration process. The reaction of a 3-ulose with DAST gave low yields due to a competitive fragmentation reaction.[15a,16] However, we showed recently that the reaction of 2-deoxy-3-ulose with DAST leads to the 3,3-difluoro carbohydrates in good yields.[12]

Taking these considerations into account, we made a retrosynthetic plan for the synthesis of 1-(2',3'-dideoxy-3',3'-difluoro-ß-D-*eyrthro*-pyranosyl)cytosine (**1**) and 1-(2',3'-dideoxy-2',2'-difluoro-ß-D-*eyrthro*-pyranosyl) cytosine (**2**), which is shown in Scheme 2. In both routes, the key step is the synthesis of a difluorocarbohydrate by reacting a suitable ulose with DAST. In the first route, the 2-deoxy-3,3-difluoropyranose can be readily obtained following a reported procedure,[12] and in the second, a β-ulose which can be obtained through deoxygenation of position 3 of a β-benzylglucoside is needed (Scheme 2).



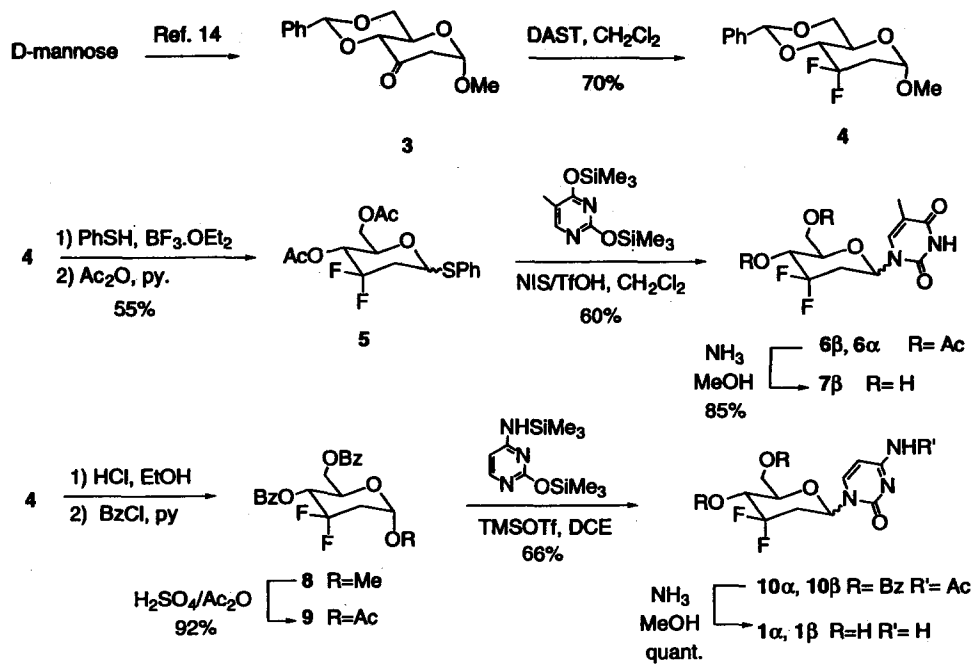
Scheme 2

Synthesis of 1-(2',3'-dideoxy-3',3'-difluoro-α,β-D-*erythro*-hexopyranosyl)-cytosine (1). The 2-deoxy-3-ulose **3**, which can be obtained in three steps from D-Mannose,[17] was treated with DAST in CH_2Cl_2 (Scheme 3), to give the difluoro derivative **4** in 70% yield.[12]

Since thioglycosides are useful glycosyl donors[18] which have been successfully used in the synthesis of disaccharides[19] and nucleosides,[20] we selected the thioglycoside **5** as glycosyl donor. Thus, **4** was treated with PhSH in the presence of $BF_3.OEt_2$ to give the unprotected thioglycoside, which by reaction with acetic anhydride gave compound **5**.

When thioglycoside **5** was reacted with trimethylsilylcytosine in the presence of NBS or NIS/triflic acid in several solvents (CH_2Cl_2, DCE, CH_3CN) at different temperatures, the nucleoside was not formed. An elimination product was detected in some cases. However, reacting **5** with bis-(trimethylsilyl)thymine in the presence of NBS, gave nucleosides **6α** and **6β** in a 50% yield although the stereoselectivity was poor (ratio α/β = 5:4). When NIS and triflic acid were used as promoters, the yield increased to 60% with an α/β ratio of 1:3. Treatment of **6β** with ammonia in methanol led to nucleoside **7β** in 85% yield.

Since all attempts to prepare the cytosine derivative from thioglycoside **5** were unsuccessful, we tried a different glycosylation approach. Thus, the benzylidene group in compound **4** was removed in an acidic medium and the resulting compound was reacted with benzoyl chloride and pyridine to yield the 4,6-di-O-benzoyl derivative **8**.[12] Further treatment of **8** with suphuric acid and acetic anhydride led to the 1-O-acetylpyranose **9**.

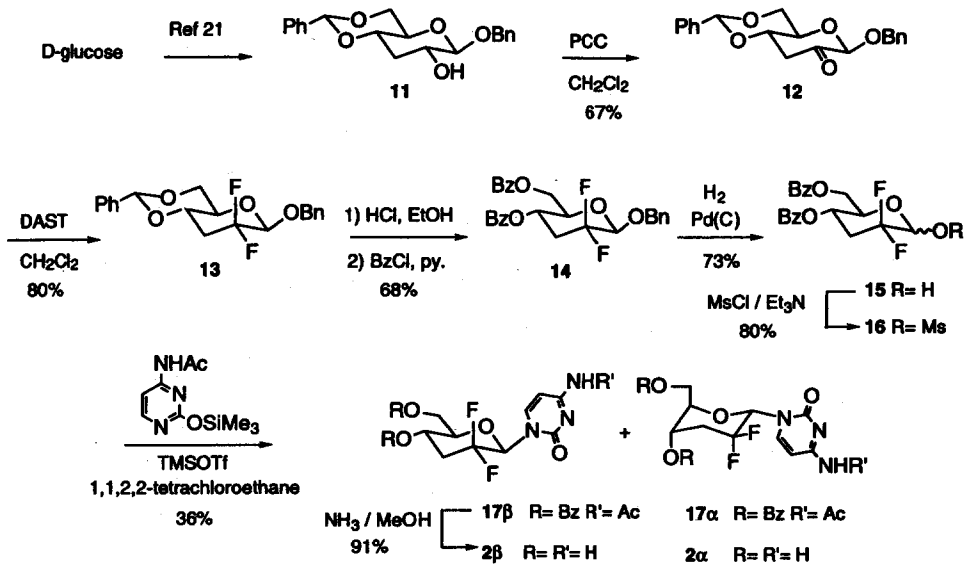


Scheme 3

Compound **9** was readily converted into the mixture of cytosine nucleosides **10α** and **10β** in a 66% yield (α/β = 1:3) by reaction with silyl-protected cytosine in the presence of trimethylsilyl triflate as catalyst. The mixture of protected nucleosides **10** was then treated with saturated ammonia solution to give a quantitative yield of the mixture of cytosine analogues **1α/1β** which were separated by column chromatography.

Synthesis of 1-(2',3'-dideoxy-2',2'-difluoro-α/β-D-*erythro*-hexopyranosyl)-cytosine (2). For the synthesis of the 2',3'-dideoxy-2',2'-difluoropyranosyl analogue of gemcitabine (**2**), a synthetic route starting from D-glucose was devised (Scheme 4). The key compound 3-deoxy-2-ulose **12**, which has the β-configuration necessary for the success of the *gem*-difluorination reaction,[15a] was prepared by oxidation of glycoside **11**.[21] The ulose **12** was then treated with DAST at room temperature to give the *gem*-difluorocompound **13** in good yield; no rearrangement products were detected. Deprotection of the 4,6-benzylidene group and protection of positions 4 and 6 with the benzoyl group afforded compound **14** which was converted into the difluoropyranose **15** by hydrogenolysis of the anomeric benzyl group.

The glycosylation step was carried out following the same procedure described for the synthesis of gemcitabine.[10] Thus, pyranose **15** was converted into the 1-mesyl derivative **16** by treatment with mesyl chloride in pyridine and this compound was then coupled to silylated acetylcytosine using trimethylsilyl triflate as activator. Initially, refluxing dichloroethane was used as solvent, but the reaction proceeded slowly. So, we decided to increase the temperature by using a solvent with a higher boiling point. Thus, when the reaction was carried out in refluxing 1,1,2,2-tetrachloroethane, a mixture of pyranosyl nucleosides **17α/17β** was obtained in a 36% yield and an α/β ratio of 7:4, which, unfortunately, proved to be difficult to separate. However, after



Scheme 4

this mixture had been deprotected by treatment with a methanolic ammonia solution, the mixture of unprotected nucleosides **2α/2β** which was then obtained could be purified by chromatography and characterized.

Structural determination. The presence of the CF_2 group was confirmed by NMR spectroscopy. The ^{19}F NMR spectrum of difluorocompounds shows two signals with a characteristic geminal coupling constant $J_{F,F}$ ~250 Hz. In the ^{13}C NMR spectrum, C-3 for compounds **1α** and **1β** and C-2 for **2α** and **2β** appears as a triplet signal (115-123 ppm, $J_{C,F}$~ 240-250 Hz) which is also characteristic of the CF_2 group.

The NMR data of products **1α**, **1β**, and **2α**, **2β**, confirm the structures of the nucleosides. However, in contrast with the starting glycosides **9** and **16**, the coupling constants $J_{1,2}$ and $J_{1,2''}$ were fairly similar in both anomers (Table 1). Thus, **1β**, as well as **10β**, showed $J_{1,2}$ and $J_{4,5}$ couplings characteristic of protons in a trans-diaxial position, according to a $^4C_1$ chair conformation, having the pyrimidine base equatorially disposed (Figure 1). On the other hand, nucleosides **1α** and **10α** showed a $J_{4,5}$ coupling of an approximate value of 5 Hz, suggesting a *gauche* relationship. These data allowed us to propose a $^1C_4$ inverted chair conformation for **10α** and **1α**. Like nucleosides **10** and **1**, both the anomers in 2,2-difluoronucleosides **17β**, **2β** and **17α**, **2α** had equivalent $J_{1',Fa}$ and $J_{1',Fe}$ values. This was thought to due to an equatorial disposition of the base in both cases. The following data made it possible to assign the anomeric configuration: a) The H-4' signal in **17β** was a complex multiplet in which 10-Hz coupling constants ($J_{4',5'}$, $J_{4',3'}$) could be observed, whereas H-4' in **17α** and **2α** showed virtually no couplings. b) In the ^{19}F-NMR spectrum, there was a signal of axial F with $J_{F,3'}$ and $J_{F,1'}$ couplings of 34 Hz and 19 Hz, confirming an H-F *trans* relationship. These data suggested an inverted chair $^1C_4$ conformation for the nucleosides **17α** and **2α** (Figure 1).

In the ^1H NMR spectra of compounds **2α** and **2β**, a $J_{6,F}$ coupling constant of ~3 Hz is present (Table 2), characteristic of 2'-F-nucleosides —in **17α** and **17β** it is not observed due to the overlapping of signals H5- and H-6--, which agrees with a similar stereochemical relationship between the base and the fluorine atoms in

Table 1. Selected ^{1}H and ^{13}C NMR data for compounds **10α, 10β, 1α, 1β.**

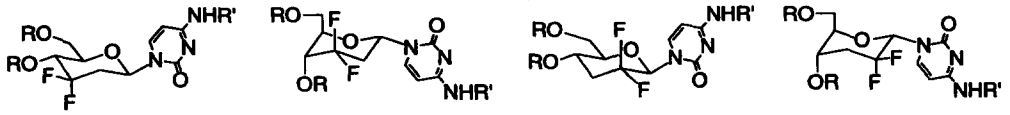
Compound	H-1'	H-4'	$J_{1',2'}$	$J_{1',2''}$	$J_{4',Fa}$	$J_{4',Fe}$	$J_{4',5'}$	C-3'	$J_{C3',F}$
10β	6.14	5.65	11	2	19.4	3.1	10.2	118.1	243
10α	6.30	5.49	10.2	3.1	5.8	0	5.8	118.1	243
1β	5.80	3.51	10.8	2.1	m	m	m	122.1	242
1α	5.81	3.54	7.5	0	11.7	0	5.4	122.1	242

Table 2. Selected ^{1}H and ^{13}C NMR data for compounds **19α, 19β, 2α, 2β.**

Compound	H-6	H-1'	H-4'	$J_{6,F}$	$J_{1',Fa}$	$J_{1',Fe}$	$J_{4',5'}$	C-2'	$J_{C2',F}$
17β	*	6.40	5.40	a	19.2	0	10	115.5	237
17α	*	6.74	5.50	a	19.5	0	0	115.7	237
2β	7.62	6.03	4.01	3.0	20.1	0	*	122.4	270, 244
2α	7.80	6.37	4.10	3.3	19.5	0	<2[b]	119.3	278, 252

[a] Overlapped signals. [b] multiplet

both anomers, as expected for a $^{4}C_1$ conformation in **2β** and a $^{1}C_4$ conformation in **2α** (Figure 1).



1β, 10β ($^{4}C_1$) **1α, 10α** ($^{1}C_4$) **2β, 17β** ($^{4}C_1$) **2α, 17α** ($^{1}C_4$)

Figure 1

In conclusion, compounds **1** and **2**, 2',3'-dideoxy, 3',3'-difluoro– and 2',3'-dideoxy-2',2'-difluoropyranosyl analogues of gemcitabine were synthesized from D-mannose and D-glucose, respectively. In both cases, the key steps are the formation of the difluoromethylene group by reaction of appropriately protected uloses with DAST, and the glycosylation reaction. Compounds **1β**, **2 β** and **7 β** resulted to be inactive against HIV virus and showed no toxicity in MT-4 cells.

EXPERIMENTAL SECTION

General Procedures: Melting points are uncorrected. Optical rotations were measured at the indicated temperature in 10 cm cells. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a 300 MHz (300, 75.4 and 282.3 MHz respectively) apparatus, using $CDCl_3$ as solvent. Elemental analyses were carried out at the Servei de Recursos Cientifics (Universitat Rovira i Virgili). Flash column chromatography was performed using silica gel

60 A CC (230-400 mesh). TLC plates were prepared by using Kieselgel 60 PF_{254}. Solvents for chromatography were distilled at atmospheric pressure before use. Dichloromethane was distilled from P_2O_5 and stored over molecular sieves.

Phenyl 4,6-di-*O*-acetyl-2,3-dideoxy-3,3-difluoro-1-thio-α/β-D-*erythro*-hexopyranoside (5). A 48% solution of boron trifluoride etherate (0.348 ml, 0.26 mmol) and thiophenol (0.135 ml, 1.27 mmol) was added dropwise at 0°C to a solution of compound 4[12] (75 mg, 0.26 mmol) in anhydrous dichloromethane (2 ml). The solution was sttired for 1.5 h to warm to room temperature, diluted with CH_2Cl_2 (3 ml), neutralized by stirring with solid $NaHCO_3$, filtered through a celite pad and evaporated. The residue was then dissolved in pyridine (2 ml) and acetic anhydride (1 ml) and stirred at room temperature for 2 h. The solution was then poured into water (50 ml), extracted with CH_2Cl_2 (3x25 ml), dried ($MgSO_4$) and evaporated. Purification by column chromatography (hexane/ethyl acetate 4:1) afforded 51 mg (55%) of **5** as an α,β mixture (4:11). Major isomer (5β): ^1H NMR (300 MHz); 7.60-7.25 (m, 5H, Ph), 4.93 (d, 1H, $J_{H1,H2}$=12 Hz, H-1), 5.10 (ddd, 1H, $J_{H4,F}$= 22.2 Hz, $J_{H4,H5}$=12 Hz, $J_{H4,F'}$= 4 Hz, H-4), 4.28 (dd, 1H, $J_{H6,H6'}$= 12 Hz, $J_{H6,H5}$= 4.8 Hz, H-6), 4.16 (d, 1H, H-6'), 3.85 (m, 1H, H-5), 2.70-2.50 (m, 2H, H-2, H-2'), 2.17 (s, 3H, Ac), 2.06 (s, 3H, Ac); ^{13}C NMR (75.4 MHz); 170.5 (CO), 169.3 (CO), 132.9-128.2 (Ph), 118.4 (t, $J_{F,C3}$= 255 Hz, C-3), 80.6 (C-1), 74.4 (C-6), 67.1 (d, $J_{F,C4}$=19 Hz, C-4), 62.0 (C-5), 40.1 (t, $J_{F,C2}$= 20 Hz, C-2), 20.7 (Me), 20.5 (Me); ^{19}F NMR (282.3 MHz); -103.9 (d, $J_{F,F'}$=247.0 Hz, Fe), -116.1 (ddd, $J_{F,H2}$= 32.46 Hz, $J_{F,H4}$= 20.9 Hz, $J_{F',H2}$= 11.6 Hz, Fa). Minor isomer (5α): ^1H NMR (300 MHz); 7.60-7.25 (m, 5H, Ph), 5.66 (s, 1H, H-1), 5.20 (ddd, 1H, $J_{H4,F}$=22.2 Hz, $J_{H4,H5}$=12 Hz, $J_{H4,F'}$= 4 Hz, H-4), 4.70 (m, 1H, H-5), 4.41 (dd, 1H, $J_{H6,H6'}$=12 Hz, $J_{H6,H5}$=5.4 Hz, H-6), 4.08 (d, 1H, H6') 2.70-2.50 (m, 2H, H-2, H-2'), 2.14 (s, 3H, Ac), 2.09 (s, 3H, Ac); ^{13}C NMR (75.4 MHz); 17.5 (CO), 169.3 (CO), 132.9-128.2 (Ph), 118.4 (t, $J_{F,C3}$= 255 Hz, C-3), 82.3 (C-1), 74.5 (C-6), 67.6 (d, $J_{C4,F}$= 12 Hz, C-4), 61.7 (C-5), 39.1 (t, $J_{F,C2}$= 21 Hz, C-2), 20.7 (Me), 20.5 (Me); ^{19}F NMR (282.3 Mhz, $CDCl_3$); -102.7 (bd, $J_{F,F'}$= 241.9 Hz, Fe), -110.0 (dddd, $J_{F,H2}$= 47.1 Hz, $J_{F,H4}$= 14.9 Hz,$J_{F,H2'}$= 4.8 Hz, Fa).

1-(4',6'-Di-*O*-acetyl-2',3'-dideoxy-3',3'-difluoro-α,β-D-*erythro*-hexopyranosyl)-thymine (6). 4 Å-Molecular sieve (50 mg), and NIS (225 mg, 1.0 mmol) were added to a solution of **5** (134 mg, 0.41 mmol) in anhydrous CH_2Cl_2 (2ml) kept under argon. After a few minutes silylated thymine (221 mg, 0.82 mmol) and trifluoromethanesulfonic acid (0.044 ml, 0.5 mmol) were added. The suspension was stirred at room temperature for 20 h. An aqueous solution of sodium thiosulfate was then added, while stirring, until the purple color was discharged. After dilution with ethyl acetate (50 ml), the suspension was filtered through a celite-silica pad and the filtrate was dried ($MgSO_4$) and evaporated. Purification of the residue by column chromatography (hexane/ethyl acetate 1:1) gave 110 mg (60%) of **6** as a α,β mixture (α:β= 1:2.7), from which a new purification by preparative tlc (hexane/ethyl acetate 1:1) enabled both isomers to be separated. Major isomer (6β): mp: 168-169°C. $[\alpha]_D^{23}$= +8.05 (c= 0.47, $CHCl_3$). IR: 3191, 306, 2885, 2859, 1706, 1468, 1429, 1230. ^1H NMR (300 MHz): 8.75 (s, 1H, NH), 7.26 (s, 1H, H-6), 6.10 (dd, 1H, $J_{H1',H2'}$= 9.5 Hz, $J_{H1',H2'}$= 4.4 Hz, H-1'), 5.14 (t, 1H, $J_{H4',F}$=$J_{H4',H5'}$= 7.4 Hz, H-4'), 4.57 (dd, 1H, $J_{H6',H6''}$=12.1 Hz, $J_{H6',H5'}$= 8.6 Hz, H-6'), 4.45-4.38 (m, 1H, H-5'), 4.18 (d, 1H, $J_{H6',H5'}$= 12.1 Hz, H-6'), 2.50-2.35 (m, 2H, H-2', H-2''), 2.21 (s, 3H, Ac), 2.10 (s, 3H, Ac), 2.05 (s, 3H, Me). ^{13}C NMR (75.4 MHz); 170.4 ($CH_3\underline{C}O$), 168.9 ($CH_3\underline{C}O$), 163.3 (C-4), 149.6 (C-2), 134.6 (C-6), 118.1 (dd, $J_{C3',F}$=257 Hz, $J_{C3',F'}$= 238.8 Hz, C-3'), 111.9 (C-5),

75.6 (d, $J_{C1',F}$= 4.7 Hz, C-1'), 75.3 (d, $J_{C6',F}$= 11.3 Hz, C-6'), 66.0 (dd, $J_{C4',F}$= 38 Hz, $J_{C4',F'}$= 21.3 Hz, C-4'), 59.5 (d, $J_{C5',F}$= 9.4 Hz, C-5'), 35.0 (t, $J_{C2',F}$= 22.6 Hz, C-2'), 20.7 ($\underline{C}H_3CO$), 20.6 ($\underline{C}H_3CO$), 12.6 (Me). ^{19}F NMR (282.3 MHz, $CDCl_3$); -101.0 (dm, $J_{F,F'}$= 264 Hz, Fe), -103.9 (dm, Fa). IR (cm^{-1}); 3191, 3063, 2885, 2859, 1705, 1468, 1230. Anal. Calcd. for $C_{15}H_{18}O_7N_2F_2$, C 47.88; H 4.82; N 7.44; Found: C 48.05; H 5.02, N 7.51. Minor isomer (**6α**): mp: 120-122°C, $[\alpha]_D^{23}$ = -5.88° (c= 1.03, $CHCl_3$), ^1H NMR (300 MHz); 8.61 (s broad, 1H, NH), 7.18 (s, 1H, H-6), 6.00 (dd, 1H, $J_{H1',H2'}$= 11.2 Hz, $J_{H1',H2''}$= 2.5 Hz, H-1'), 5.22 (ddd, 1H, $J_{H4',F}$= 19.7 Hz, $J_{H4',H5'}$= 10 Hz, $J_{H4',F'}$= 3.5 Hz, H-4'), 4.34 (dd, 1H, $J_{H6',H6''}$= 12.6 Hz, $J_{H6',H5'}$= 4.4 Hz, H-6'), 4.13 (d, 1H, H-6''), 4.03 (d, 1H, H-5'), 2.60 (m, 1H, H-2'), 2.22 (s, 3H, Ac), 2.20 (m, 1H, H-2''), 2.15 (s, 3H, Ac), 2.04 (s, 3H, Me); ^{13}C NMR (75.4 MHz, $CDCl_3$); 170.5 ($CH_3\underline{C}O$), 169.3 ($CH_3\underline{C}O$), 163.2 (C-4), 149.7 (C-2), 134.0 (C-6), 117.9 (dd, $J_{C3',F}$=252.9 Hz, $J_{C3',F'}$= 245.0 Hz, C-3'), 112.4 (C-5'), 78.2 (d, $J_{C6',F}$= 12.3 Hz, C-6'), 73.5 (d, $J_{C1',F}$= 6.6 Hz, C-1'), 66.6 (t, $J_{C4',F}$= 19.4 Hz, C-4'), 61.5 (C-5'), 38.9 (t, $J_{C2',F}$= 21.3 Hz, C-2'), 20.7 (Ac), 20.5 (Ac), 12.6 (Me); ^{19}F NMR (282.3 MHz); -103.3 (d, $J_{F,F'}$= 274 Hz, Fe), -116.1 (dddd, $J_{Fa,H2''}$= 31.3 Hz, $J_{F,H4'}$= 19.8 Hz, $J_{Fa,H2''}$= 10.5 Hz, Fa).

1-(2',3'-Dideoxy-3',3'-difluoro-β-D-*erythro*-hexopyranosyl)-thymine (7β). Compound **6β** (13 mg, 0.03 mmol) was dissolved in a solution of ammonia in methanol (3 ml, 25% saturated) and left in a closed flask for 3 h. Solvents were evaporated and the crude residue was purified by preparative tlc (CH_2Cl_2/MeOH, 20:1) to give **7β** as a white solid (11 mg, 85%). Mp: >220°C (dec). $[\alpha]_D^{25}$ = + 35.4 (c= 0.52, CH_3OH). IR (cm^{-1}): 3448, 2923, 1687, 1462, 1320, 1270, 1191, 1075. ^1H NMR (300 MHz, CD_3OD) 7.52 (s, 1H, H-6), 5.74 (m, 1H, H-1'), 3.87-3.72 (m, 3H,H-6', H-4'), 3.55 (m, 1H, H-5'), 2.44-2.28 (m, 2H, H-2'), 1.82 (s, 3H, CH_3). ^{13}C NMR (75.4 MHz, CD_3OD), 166.5 (C4), 152.2 (C2), 138.0 (C-6), 121.7 (dd, $J_{C3',F}$= 242 Hz, $J_{C3'F}$= 249 Hz, C-3'), 112.3 (C-5), 79.9 (d, $J_{C1',F}$= 12.5 Hz, C-1'), 79.5 (d, $J_{C6',F}$= 6.8 Hz, C6'), 68.5 (t, $J_{C4',F}$= 20.3 Hz, C4'), 61.8 (C5'), 39.2 (t, $J_{C2',F}$= 22.5 Hz, C-2'), 12.4 (CH_3), ^{19}F NMR (282.3 MHz, CD_3OD) -101.5 (d, $J_{F,F}$= 240.5 Hz), -118.2 (dm).

4-N-Acetyl-1-(4',6'-di-O-benzoyl-2',3'-dideoxy-3',3'-difluoro-α,β-D-*erythro*-hexopyranosyl)-cytosine (10). Compound **8** (0.115 g, 0.28 mmol) was dissolved in a solution of sulphuric acid in acetic anhydride (4%, 5 ml). The solution was stirred overnight at room temperature in a closed flask. The liquid was then poured into 100 ml of aqueous $NaHCO_3$ solution, extracted (3 x 50 ml) with CH_2Cl_2, dried ($MgSO_4$) and evaporated to give 0.113 g (92%) of the 1-acetyl derivative **9** which was pure enough to be used in the coupling reaction. Separately, N-acetylcytosine (23 mg, 0.15 mmol) was dissolved in anhydrous 1,2-dichlorothane (2 ml) and bis-trimethylsilylacetamide (6 ml) and the resulting mixture was heated to reflux for 30 min. and evaporated until a syrup of bis-trimethylsilyl-N-acetylcytosine appeared. Then, compound **9** (25 mg, 0.06 mmol) was dissolved in anhydrous 1,2-dichloroethane (1 ml) and added to a solution of bis-trimethylsilyl-N-acetylcytosine in 1,2-dichloroethane (3 ml). Afterwards TMSOTf (0.013 ml) was added and the resulting solution was heated to reflux for 45 minutes. After cooling, the solution was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and evaporated, to give a residue which was purified by flash chromatography (hexane/ethyl acetate 1:1), yielding 21 mg (66%) of **10α/10β** as an inseparable mixture. Major isomer (**10β**): ^1H NMR (300 MHz, $CDCl_3$); 9.10 (bs, 1H, NH), 8.15-7.40 (m, 12 H, Ph, H-5, H-6), 6.14 (dd, 1H, $J_{H1',H2'}$= 11 Hz, $J_{H1',H2''}$= 2 Hz, H-1'), 5.65 (ddd, 1H, $J_{H4',F}$= 19.4 Hz, $J_{H4',H5'}$= 10.2 Hz, $J_{H4',F}$= 3.1 Hz, H-4'), 4.50 (d, 1H, $J_{H6',H6''}$= 11.3 Hz, H-6'), 4.47 (dd, 1H, $J_{H6',H5'}$= 4.7 Hz, H-6'), 4.37 (m, 1H, H-5'), 3.10-2.80 (m, 2H, H-2'), 2.25 (s, 3H, CH_3CO). ^{13}C NMR (75.4 MHz, $CDCl_3$); 170.8 (CH_3CO), 166.1

(PhCO), 165.0 (PhCO), 163.0 (C-4), 154.2 (C-2), 143.5 (C-6), 134.1-128.5 (Ph), 118.1 (t, $J_{C3',F}$= 243 Hz, C-3'), 97.6 (C-5'), 80.2 (d, $J_{C1',F}$= 12.4 Hz, C-1'), 74.1 (C-6'), 67.6 (t, $J_{C4',F}$= 18.4 Hz, C-4'), 62.1 (C-5'), 39.5 (t, $J_{C2',F}$= 20 Hz, C-2'), 24.8 (CH_3CO). ^{19}F NMR (282.3 MHz, $CDCl_3$); -104.3 (d, $J_{F,F'}$= 249 Hz), -117.0 (dddd, $J_{F,H2'}$= 31.6 Hz, $J_{F,H4'}$= 19.4 Hz, $J_{F,H2''}$= 9.6 Hz). Minor isomer (**10α**): ^1H NMR (300 MHz, $CDCl_3$); 9.20 (bs, 1H, NH), 8.15-7.40 (m, 12H, Ph, H-5, H-6), 6.30 (dd, 1H, $J_{H1',H2'}$= 10.2 Hz, $J_{H1',H2''}$= 3.1 Hz, H-1'), 5.49 (t, 1H, $J_{H4',F}$= 5.8 Hz, H-4'), 4.90-4.82 (m, 2H, H-6', H-5'), 4.57 (dd, 1H, $J_{H6',H6''}$= 10 Hz, $J_{H6',H5'}$= 3 Hz, H-6''), 2.25 (s, 3H, CH_3CO), 2.25-2.00 (m, 2H, H-2'). ^{13}C NMR (74.5 MHz, $CDCl_3$); 170.8 (CH_3CO), 166.1 (PhCO), 165 (PhCO), 163.0 (C-4), 154.2 (C-2), 143.8 (C-6), 134.1-128 (Ph), 118.1 (t, $J_{C3',F}$= 243 Hz, C-3'), 97.6 (C-5'), 77.5 (C-1'), 76.0 (C-6'), 66.7 (t, $J_{C4',F}$= 17 Hz, C-4'), 60.1 (C-5'), 35.6 (t, $J_{C2',F}$= 20 Hz, C-2'), 24.8 (CH_3CO). ^{19}F NMR (282.3 MHz, $CDCl_3$); -102.1 (d, $J_{F,F}$= 266 Hz), -104.6 (ddt, $J_{F,H2'}$= 31.6 Hz, $J_{F,H4'}$= $J_{F,H2''}$= 9.9 Hz).

1-(2',3'-Dideoxy-3',3'-difluoro-α,β-D-*erythro*-hexopyranosyl)-cytosine (1). A solution of 0.11g (0.21 mmol) of the mixture **10α/10β** in saturated methanolic ammonia (5 ml) was stirred overnight and evaporated to dryness afterwards to give a residue which was purified by radial tlc (chloroform/methanol from 10:1 to 5:1). **1α** and **1β** were obtained quantitatively. Major isomer (**1β**): mp: >200°C (dec.). $[\alpha]_D^{25}$ = +19.7 (c= 0.69, CH_3OH). IR (cm^{-1}): 3381, 2918, 1673, 1642, 1615, 1491, 1381, 1285, 1189, 1103, 779. ^1H NMR (300 MHz, CD_3OD); 7.70 (d, 1H, $J_{H6,H5}$= 7.5 Hz, H-6), 5.82 (d, 1H, $J_{H5,H6}$= 7.5 Hz, H-5), 5.80 (dd, 1H, $J_{H'1,H2'}$= 10.8 Hz, $J_{H1',H2''}$= 2.1 Hz, H-1'), 3.79-3.65 (m, 3H, H-5', H-6', H-6''), 3.52-3.50 (m, 1H, H-4'), 2.44-2.03 (m, 2H, H-2', H-2''). ^{13}C NMR(75.4 MHz, CD_3OD); 167.7 (C-4), 157.8 (C-2), 142.6 (C-6), 121.5 (t, $J_{F,C3'}$= 242 Hz, C-3'), 96.8 (C-5), 80.9 (d, $J_{C6',F}$= 12.4 Hz, C-6'), 79.4 (d, $J_{C1',F}$= 6.8 Hz, C-1'), 68.5 (t, $J_{C4',F}$= 20.4 Hz, C-4'), 61.7 (C-5'), 39.6 (t, $J_{C2',F}$= 22.6 Hz, C-2'). ^{19}F NMR (282.3 MHz, CD_3OD); -103.2 (d, $J_{F,F'}$= 242 Hz), -119.9 (dddd, $J_{F,H2'}$= 31.6 Hz, $J_{F,H4'}$= 19.5 Hz, $J_{F,H2''}$= 12.1 Hz).. Anal. Calcd. for $C_{10}H_{13}O_4N_3F_2$: C 43.32; H 4.69, N 15.16. Found C 43.42; H 5.05; N 15.10. Minor isomer (**1α**): $[\alpha]_D^{25}$= -11.1° (c= 0.36, CH_3OH). IR (cm^{-1}); 1741, 1661, 1410, 119, 1084. ^1H NMR (300 MHz, CD_3OD); 7.67 (d, 1H, $J_{H6,H5}$= 7.1 Hz, H-6), 5.93 (dd, 1H, $J_{H1',H2'}$= 10.2 Hz, $J_{H1',H2''}$= 3 Hz, H-1'), 5.81 (d, 1H, H-5), 4.06 (m, 1H, H-6'), 3.79-3.68 (m, 2H, H-6'', H-5'), 3.54 (dd, 1H, $J_{H4',F}$= 5.4 Hz, $J_{H4',H5'}$= 11.7 Hz, H-4'), 2.42-2.16 (m, 2H, H-2'). ^{13}C NMR (75.4 MHz, CD_3OD); 167.8 (C-4), 157.9 (C-2), 142.4 (C-6), 122.1 (t, $J_{F,C3'}$= 242 Hz, C-3'), 96.8 (C-5), 82.1 (C-1'), 77.5 (d, $J_{C6',F}$= 10 Hz, C-6'), 67.0 (dd, $J_{C4',F}$= 31.2 Hz, $J_{C4',F}$= 20.4 Hz, C-4'), 59.5 (C-5'), 35.3 (t, $J_{C2',F}$= 22.6 Hz, C-2'). ^{19}F NMR (282.3 MHz, CD_3OD); -101.7 (dt, $J_{F,F'}$= 256 Hz, $J_{F,H}$= 4.8 Hz), -104.3 (ddm, $J_{F,H2'}$= 34.1 Hz, $J_{F,H4'}$= 5 Hz). Anal. Calcd. for $C_{10}H_{13}O_4N_3F_2$: C 43.32; H 4.69, N 15.16. Found: C 43.48; H 4.96; N 15.27.

Benzyl 4,6-benzylidene-3-deoxy-2-oxo-β-D-*erythro*-hexopyranoside (12). Activated 4Å molecular sieve (3 g), pyridinium chlorochromate (3.1 g, 14.4 mmol) and sodium acetate (1.18 g, 14.4 mmol) were added to a solution of compound **11** (1.24 g, 3.6 mmol) in anhydrous dichloromethane (30 ml). The resulting suspension was stirred at room temperature for 3 h protected from light. Then, ethyl ether (300 ml) was added and the solids were removed by filtration through a celite-silica gel pad and the resulting solution was evaporated to give 0.82 g (67%) of compound **12** as a white solid. Mp: 158-160°C, $[\alpha]_D^{25}$ = -47.06 (c=0.085, $CHCl_3$). IR (cm^{-1}): 3066, 2924, 1742, 1458, 1372, 1163, 1112, 1072, 769, 701. ^1H NMR (300 MHz, $CDCl_3$); 7.50-7.30 (m, 10H, Ph), 5.57 (s, 1H, H-7), 4.92 (d, 1H, J_{gem}= 11.7 Hz, $PhCH_2$), 4.85 (s, 1H, H-1), 4.73 (d, 1H, $PhCH_2$), 4.46 (m, 1H, H-5), 4.13-4.06 (m, 1H, H-4), 3.87-3.75 (m, 2H, H-6, H-6'), 3.11

(dd, 1H, $J_{H3,H3'}$= 15.9 Hz, $J_{H3,H4}$= 5.7 Hz, H-3), 3.64 (dd, 1H, $J_{H3',H4}$= 12.3 Hz, H-3'). ^{13}C NMR (75.4 MHz, $CDCl_3$); 198.2 (C-2), 136.8-126.2 (Ph), 101.5 (C-7), 99.3 (C-1), 75.7 (C-4), 70.4 ($PhCH_2$), 69.8 (C-6), 69.1 (C-5), 43.8 (C-3). Anal. Calcd. for $C_{20}H_{20}O_5$: C, 70.59; H, 5.92. Found: C, 70.39; H, 6.22.

Benzyl 4,6-benzylidene-2,3-dideoxy-2,2-difluoro-β-D-*erythro*-hexopyranoside (13). To a solution of compound **12** (0.62 g, 1.81 mmol) in anhydrous dichloromethane (20 ml) kept under argon, DAST (1.19 ml, 9.04 mmol) was added at room temperature. The reaction mixture was stirred for 20 minutes. Then, the excess of reagent was neutralized by carefully adding a saturated aqueous solution of $NaHCO_3$. The organic layer was collected and dried ($MgSO_4$) to give, after evaporation, a residue which was purified by flash column chromatography (linear gradient from hexane to hexane/ethyl acetate 1:1), yielding 0.52 g (80%) of **13** as a white solid. Mp: 146-147°C. $[\alpha]_D^{25}$ = -53.64 (c=0.33, $CHCl_3$). IR (cm^{-1}): 3060, 3045, 2893, 1497, 1452, 1376, 1173, 1126, 1072, 1006, 746, 700. ^1H NMR (300 MHz, $CDCl_3$) 7.50-7.30 (m, 10H, Ph), 5.55 (s, 1H, H-7), 5.00 (d, 1H, J_{gem}=12.3 Hz, $PhCH_2$), 4.74 (d, 1H, $PhCH_2$), 4.64 (d, 1H, $J_{H1,F}$= 15.3 Hz, H-1), 4.39 (dd, 1H, $J_{H6,H6'}$= 10.5 Hz, $J_{H6,H5}$= 4.8 Hz, H-6), 3.94-3.77 (m, 2H, H-6', H-5), 3.50 (td, 1H, $J_{H4,H5}$= $J_{H4,H3}$= 9.9 Hz, $J_{H4,H3'}$= 5.4 Hz, H-4), 2.74-2.63 (m, 1H, H-3), 2.18-1.95 (m, 1H, H-3'). ^{13}C NMR (75.4 MHz, $CDCl_3$); 136.8-126.2 (Ph), 116.5 (t, $J_{C2,F}$= 246 Hz, C-2), 101.8 (C-7), 97.7 (dd, $J_{C1,F}$= 30 Hz, $J_{C1,F'}$=25 Hz, C-1), 74.4 (d, $J_{C4,F}$= 11 Hz, C-4), 71.1 ($PhCH_2$), 70.2 (C-6), 68.6 (C-5), 37.3 (t, $J_{C3,F}$= 25 Hz, C-3). ^{19}F NMR (282.3 MHz, $CDCl_3$); -108.2 (dt, $J_{F,F'}$= 251 Hz, $J_{F,H3}$=$J_{F,H3'}$= 5.3 Hz, Fe), -121.3 (dddd, $J_{F',H3}$= 31.6 Hz, $J_{F',H1'}$= 15.2 Hz, $J_{F',H3}$= 11.8 Hz, Fa). Anal. Calcd. for $C_{20}H_{20}O_4F_2$: C 66.30, H 5.52. Found: C 66.20, H 5.93.

Benzyl 4,6-di-O-benzoyl-2,3-dideoxy-2,2-difluoro-β-D-*erythro*-hexopyranoside (14). Compound **13** (0.68 g, 1.86 mmol) was added to an ethanolic solution of hydrochloric acid 2% (10 ml) and the resulting supension was stirred overnight. It was then neutralized by adding pyridine and the solution was evaporated, giving a solid which was then redissolved in dichloromethane (10 ml), pyridine (10 ml) and benzoyl chloride (5 ml). The solution was stirred at room temperature for 3 h, and was then poured into a 1:1 mixture of water and dichloromethane (overall volume 500 ml) and the layers were vigorously stirred. The organic layer was collected, washed with saturated aqueous $NaHCO_3$ (3x100 ml), dried ($MgSO_4$) and evaporated, to give a residue which was purified by flash chromatography (hexane/ethyl acetate 10:1) yielding 0.618 g (68%) of **14**. Mp: 98-99°C (EtOH). $[\alpha]_D^{25}$ =-48.75 (c= 0.40, $CHCl_3$). IR (cm^{-1}): 3046, 2969, 2877, 1719, 1599, 1455, 1285, 1118, 1074, 714, 680. ^1H NMR (300 MHz, $CDCl_3$) 8.20-7.25 (m, 15H, Ph), 5.42-5.33 (m, 1H, H-4), 4.97 (d, 1H, J_{gem}= 12 Hz, $PhCH_2$), 4.77-4.68 (m, 3H, $PhCH_2$, H-1, H-6), 4.52 (dd, 1H, $J_{H6',H6''}$= 12 Hz, $J_{H6'',H5}$= 5.7 Hz, H-6''), 4.16 (dd, $J_{H5,H6''}$= 5.7 Hz, H-5), 2.95-2.81 (m, 1H, H-3), 2.25-2.06 (m, 1H, H-3'). ^{13}C NMR (75.4 MHz, $CDCl_3$); 166.2 (PhCO), 165.1 (PhCO), 135.8-128.2 (Ph), 115.6 (t, $J_{C2,F}$= 249.9 Hz, C-2), 96.3 (dd, $J_{C1,F}$= 31.6 Hz, $J_{C1,F}$=22.6 Hz, C-1), 74.4 ($PhCH_2$), 70.5 (C-6), 66.5 (d, $J_{C4,F}$= 4.5 Hz, C-4), 63.4 (C-5), 34.5 (t, $J_{C3,F}$= 23.7 Hz, C-3). ^{19}F NMR (282.3 MHz, $CDCl_3$); -108.53 (ddd, $J_{F,F'}$= 252.6 Hz, $J_{F,H1}$= 14.1 Hz, $J_{F,H3}$=7.3 Hz, Fe), -118.9 (ddt, $J_{F,H1}$= 24.3 Hz, $J_{F,H3}$= $J_{F,H3}$= 9.9 Hz, Fa). Anal. Calcd. for $C_{27}H_{24}O_6F_2$: C, 67.22, H, 4.98. Found: C, 67.45; H, 5.13.

4,6-Di-O-benzoyl-2,3-dideoxy-2,2-difluoro-α/β-D-*erythro*-hexopyranose (15). Compound **14** (0.114 g, 0.23 mmol) and palladium on activated charcoal (0.1 g) were suspended in 2 ml of methanol and placed in a hydrogenation autoclave. The autoclave was charged with hydrogen (15 bar) and the suspension was

stirred for 9 h. The catalyst was filtered off and washed with methanol. The collected liquid was then evaporated to obtain 0.066 g (73%) of **15** as a syrup (mixture α:β = 95:5). Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$); 8.20-7.30 (m, 10H, Ph), 5.36 (td, 1H, $J_{H4,H3}$= $J_{H4,H5}$= 11.4 Hz, $J_{H4,H3}$= 5.4 Hz, H-4), 5.16 (s, 1H, H-1), 4.65-4.38 (m, 3H, H-6, H-6', H-5), 2.77 (m, 1H, H-3), 2.41 (m, 1H, H-3'). ^{13}C NMR (75.4 MHz, $CDCl_3$); 166.7 (PhCO), 165.2 (PhCO), 133.7-128.4 (Ph), 117.5 (t, $J_{C2,F}$=246.5 Hz, C-2), 90.3 (t, $J_{C1,F}$= 33.9 Hz, C-1), 67.8 (C-6), 66.0 (C-4), 63.0 (C-5), 32.7 (t, $J_{C3,F}$= 22.6 Hz, C-3). ^{19}F NMR (282.3 MHz, $CDCl_3$); -108.37, (-108.52) (m, Fe, Fa).

4,6-Di-O-benzoyl-2,3-dideoxy-2,2-difluoro-1-methylsulfonyl-α/β-D-*erythro*-hexopyranose (16). Triethylamine (0.13 ml) and methylsulphonyl chloride (0.062 ml) were added to a solution of **15** (0.254 g, 0.64 mmol) in dichloromethane (3 ml) cooled with an ice bath. The solution was stirred while warming to room temperature. After 1 hour, Et_3N (0.060 ml) and MsCl (0.030 ml) were added. Stirring was continued for 3 more hours, and then the solution was washed with diluted aqueous HCl and saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$) and evaporated to give a residue which was purified by flash chromatography (hexane / ethyl acetate 3:1), to yield 0.242 g (80%) of **16** as an α/β mixture (95:5). Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$); 8.20-7.40 (m, 10H, Ph), 5.83 (dd, 1H, $J_{H1,F}$= 5.1 Hz, $J_{H1,F'}$= 1.5 Hz, H-1), 5.39 (td, 1H, $J_{H4,H3}$= $J_{H4,H5}$= 10.2 Hz, $J_{H4,H3'}$= 4.8 Hz, H-4), 4.66 (dd, 1H, $J_{H6,H6'}$= 11.7 Hz, $J_{H6,H5}$= 2.1 Hz, H-6), 4.55-4.46 (m, 1H, H-5), 4.45 (dd, 1H, $J_{H6',H5}$= 6 Hz, H-6'), 3.14 (CH_3), 3.01-2.90 (m, 1H, H-3), 2.46-2.25 (m, 1H, H-3'). ^{13}C NMR (75.4 MHz, $CDCl_3$); 166.1 (PhCO), 164.9 (PhCO), 115.4 (t, $J_{C2,F}$= 253.3 Hz, C-2), 94.5 (dd, $J_{C1,F}$= 41.8 Hz, $J_{C1,F'}$= 31.7 Hz, C-1), 70.6 (C-6), 65.0 (d, $J_{C4,F}$= 9.0 Hz, C-4), 39.7 (CH_3), 32.2 (t, $J_{C3,F}$= 22.6 Hz, C-3). ^{19}F NMR (282.3 MHz, $CDCl_3$); -106.3 (ddm, $J_{F,F'}$= 263 Hz, $J_{F,H3'}$= 34.1 Hz, Fa), -108.7 (d, Fe).

N-Acetyl-1-(2',3'-dideoxy-2',2'-difluoro-4',6'-di-O-benzoyl-α/β-D-*erythro*-hexopyrano-syl) -cytosine (17). N-acetylcytosine (46 mg, 0.3 mmol) was suspended in hexamethyldisilazane (3 ml) under an inert atmosphere. To this suspension 5 mg of ammonium sulfate was added. The suspension was refluxed until a clear solution was obtained (*ca* 1 h). The liquids were evaporated to dryness and the residue was dried under high vacuum before being used. This residue was redissolved in anhydrous 1,1,2,2-tetrachloroethane under argon, and a solution of 50 mg of **16** (0.10 mmol) in the same solvent was added (total volume 4 ml). Then, TMSOTf (0.060 ml) and freshly activated 4Å molecular sieve (50 mg) were added and the mixture was heated to reflux. After 3 h, the solution was diluted in chloroform (50 ml) and filtered. The liquid was then successively washed with saturated aqueous $NaHCO_3$ (20 ml) and brine (20 ml). The organic layer was dried over anhydrous magnesium sulphate and evaporated to give a solid which was purified by flash chromatography (chloroform/methanol 20:1) to yield 19 mg (36%) of **17** as an α/β mixture (58:42). Major isomer (**17**α): ^{1}H NMR (300 MHz, $CDCl_3$); 10.2 (bs, 1H, NH), 8.20-7.40 (m, 12H, PhCO, H-5, H-6), 6.74 (d, 1H, $J_{H1',F}$= 19.5 Hz, H-1'), 5.50 (s, 1H, H-4'), 4.80-4.64 (m, 2H, H-6', H-6''), 4.48 (dd, 1H, $J_{H5',H6'}$= 12.3 Hz, $J_{H5',H6''}$= 5.7 Hz, H-5'), 3.20-2.65 (m, 2H, H-3', H-3''), 2.29 (s, 3H, CH_3CO). ^{13}C NMR (75.4 MHz, $CDCl_3$); 170.9 ($\underline{C}OCH_3$), 166.2, 165.5 ($\underline{C}OPh$), 163.3 (C-4), 155.1 (C-2), 145.9 (d, $J_{C6,F}$= 15.8 Hz, C-6), 133.9-128.7 (Ph), 115.7 (t, $J_{C2',F}$= 237 Hz, C-2'), 97.1 (C-5), 76.7 (dd, $J_{C1',F}$= 52 Hz, $J_{C1',F}$= 21.4 Hz, C-1'), 76.3 (C-6'), 67.2 (d, $J_{C4',F}$= 9 Hz, C-4'), 62.0 (C-5'), 33.6 (t, $J_{C3',F}$= 22.6 Hz, C-3'), 24.9 (CH_3). ^{19}F NMR (282.3 MHz, $CDCl_3$); -106.25 (d, $J_{F,F'}$= 254 Hz, Fe), -115.8 (dm, $J_{F,H3'}$= 34 Hz, $J_{F,H1'}$= 19.4 Hz, Fa). Minor isomer (**17**β): ^{1}H NMR (300 MHz, $CDCl_3$); 10.0 (s, broad, 1H, NH), 8.20-7.40 (m, 12H, Ph, H-5, H-

6), 6.40 (d, 1H, $J_{H1',F}$= 19.2 Hz, H-1'), 5.40 (m, 1H, H-4'), 4.87 (dd, $J_{H6',H6''}$= 10.8 Hz, $J_{H6',H5'}$= 5.7 Hz, H-6'), 4.78-4.64 (m, 1H, H-6''), 4.37 (m, 1H, H-5'), 3.20-2.65 (m, 2H, H-3', H-3''), 2.28 (s, 3H, CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$); 170.9 ($\underline{C}OCH_3$), 166.0 ($\underline{C}OPh$), 164.9 ($\underline{C}OPh$), 163.3 (C-4), 155.1 (C-2), 144.9 (d, $J_{C6,F}$= 15 Hz, C-6), 133.9-128.7 (PhCO), 115.5 (t, $J_{C2',F}$= 237 Hz, C-2'), 97.3 (C-5), 80.2 (dd, $J_{C1',F}$= 29.4 Hz, $J_{C1',F}$= 19.2 Hz, C-1'), 78.1 (C-6'), 65.2 (d, $J_{C4',F}$= 9.0 Hz, C-4'), 62.5 (C-5'), 36.9 (t, $J_{C3',F}$= 22 Hz, C-3'), 25.1 (CH_3CO). ^{19}F NMR (282.3 MHz, $CDCl_3$); -107.9 (d, $J_{F,F'}$= 259 Hz, Fa), -120.0 (dm, Fe).

1-(2',3'-Dideoxy-2',2'-difluoro-α/β-D-*erythro*-hexopyranosyl)-cytosine (2). Compound **17** (22 mg, 0.04 mmol) was dissolved in a methanolic ammonia solution (10 ml) and kept overnight in a closed flask. The soolvent was then evaporated to dryness and the residue was purified by filtration through a thin silica gel pad using chloroform/methanol 10:1 as eluent and increasing the percentage of methanol to yield 10.5 mg (91%) of **2** as an α/β mixture. This mixture was then separated using preparative tlc (chloroform/methanol 10:1). Major isomer (2α): mp: >250°C (dec.). $[\alpha]_D^{25}$ = - 29.7 (c= 0.20, CH_3OH). IR (cm^{-1}): 3330, 3213, 2935, 1641, 1610, 1497, 1107, 1050. ^1H NMR (300 MHz, CD_3OD); 7.62 (dd, 1H, $J_{H6,H5}$= 9 Hz, $J_{H6,F}$= 3 Hz, H-6), 6.03 (d, 1H, $J_{H1',F}$= 20.1 Hz, H-1'), 5.84 (d, 1H, H-5), 4.10 (m, 1H, H-4'), 3.91 (m, 3H, H-6', H-6'', H-5'), 2.66-2.37 (m, 2H, H-3', H-3''). ^{13}C NMR (75.4 MHz, CD_3OD); 167.9 (C-4), 158.2 (C-2), 144.2 (d, $J_{C6,F}$= 6.8 Hz, C-6), 119.3 (dd, $J_{C2',F}$= 278 Hz, $J_{C2',F'}$= 252 Hz, C-2'), 96.3 (C-5), 84.7 (C-6'), 81.6 (dd, $J_{C1',F}$= 30.5 Hz, $J_{C1',F}$= 19.2 Hz, C-1'), 64.2 (d, $J_{C4',F}$= 9.0 Hz, C-4'), 61.9 (C-5'), 40.9 (t, $J_{C3',F}$= 18.1 Hz, C-3'). ^{19}F NMR (282.3 MHz, CD_3OD); -106.1 (dd, $J_{F,F'}$= 250 Hz, $J_{F,H3'}$= 5.1 Hz, Fe), -119.5 (dddd, $J_{F,H3''}$= 31.6 Hz, $J_{F,H1'}$= 18 Hz, $J_{F,H3''}$= 8.4 Hz, Fa). Minor isomer (2β): mp: >160° C (dec.). $[\alpha]_D^{25}$ = + 67.3 (c= 0.05, CH_3OH). IR (cm^{-1}): 3329, 3200, 2933, 1639, 1493, 1185, 1084, ^1H NMR (300 MHz, CD_3OD); 7.80 (dd, 1H, $J_{H6,H5}$= 7.8 Hz, $J_{H6,F}$= 3.3 Hz, H-6), 6.37 (d, 1H, $J_{H1',F}$= 19 Hz, H-1'), 5.91 (d, H-5), 4.10 (m, 3H, H-4', H-6', H-5'), 3.91 (dd, 1H, $J_{H6',H6''}$= 12 Hz, $J_{H6',H5'}$= 6.3 Hz, H-6'), 2.66-2.37 (m, 2H, H-3', H-3''). ^{13}C NMR (75.4 MHz, CD_3OD); 167.9 (C-4), 158.4 (C-2), 144.5 (d, $J_{C6,F}$= 5.6 Hz, C-6), 122.4 (dd, $J_{C2,F}$= 244 Hz, $J_{C2,F'}$= 270 Hz, C-2'), 96.3 (C-5), 83.0 (C-6'), 77.8 (dd, $J_{C1',F}$= 19.2 Hz, $J_{C1',F'}$= 32.8 Hz, C-1'), 66.1 (d, $J_{C4',F}$= 9 Hz, C-4'), 61.6 (C-5'), 37.4 (t, $J_{C3',F}$= 20.3 Hz, C-3'). ^{19}F NMR (282.3 MHz, CD_3OD); -102.9 (d, $J_{F,F'}$= 249.8 Hz, Fa), -111.8 (dddd. $J_{F,H3'}$= $J_{F,H3''}$= $J_{F,H1'}$=16 Hz, Fa). Anal. Calcd. for $C_{10}H_{13}O_4N_3F_2$: C, 43.32, H, 4.69, N, 15.16. Found: C, 43.58, H, 4.78, N, 15.25.

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References and Notes

1. a) Mansour, T.E.; Storer, R. *Current Pharm. Design* **1997**, 3, 227. b) De Clercq, E. *J. Med. Chem.* **1995**, 38, 2491. c) De Cercq, E. *Nucleosides & Nucleotides* **1994**, 13, 1271. d) De Clercq, E. *Med. Res. Rev.* **1993**, 13, 229.
2. a) Verheggen, A.; Van Aerschot, A.; Toppet, S.; Snoeek, R.; Janssen, J.; Balzarini, J.; De Clercq, E.; Herdewijn, P. *J. Med. Chem.* **1993**, 36, 2033. b) Herdewijn, P.; Van Aerschot, A.; Balzarini, J.; De Clercq, E. *Nucleosides & Nucleotides* **1991**, 10, 119. c) Van Aerschot, A.; Kerremans, L.; Balzarini, J.; De Clercq, E.; Herdewijn, P. *Nucleosides & Nucleotides* **1991**, 10, 589. d) Bessodes, M.; Egron, M.J.; Filippi, J.; Antonakis, K. *J. Chem. Soc. Perkins Trans. I*, **1990**, 3035.

3. a) Périgaud, C.; Gosselin, G.; Imbach, J.L. *J. Chem. Soc. Perkins Trans. I* **1992**, 1943. b) Baud, M.V.; Chauvis, C.; Lucas, M.; Imbach, J.L. *Tetrahedron* **1991**, 47, 9993.
4. a) Herdewijn, P.; De Winter, B.; Doboszewski, I.; Verheggen, K.; Augustyns, K.; Hendrix, T.; Saison-Behmoaras, C.; De Ranter, A. Van Aerschot, A.; *Hexopyranosyl-Like Oligonucleotides,* ACS Symp. Ser., Songhavi, I.S. and Dan Cook, P. eds., p 80, **1994**. b) Van Aerschot, A.; Verheggen, K.; Hendrix, T.; Herdewijn, P.; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 1338. c) Augustyns, K.; Rozensky, J.; Van Aerschot, A.; Janssen, G.; Herdewijn, P. *J. Org. Chem.* **1993**, 58, 2977. d) Pitsch, S.; Wenderborn, S.; Jaun, B.; Eschenmoser, A. *Helv. Chim. Acta* **1993**, 76, 2161. e) Hunziker, J.; Roth, H.J., Böhringer, A.; Giger, A.; Schweizer, B.; S.; Jaun, B.; Eschenmoser, A. *Helv. Chim. Acta* **1993**, 76, 2161.
5. a) Wysocki, R.J.; Siddiqui, M.A.; Barchi, J.J.; Driscoll; J.S.; Marquez, V.E. *Synthesis* **1991**, 1005. b) Marquez, V.E.; Tseng, C.K-H.; Mitsuya, H.; Aoki, S.; Kelley, J.A.; Ford, H.; Roth, J.S.; Broder, S.; Johns, D.G., Driscoll, J.S. *J. Med. Chem.* **1990**, 33, 978. c) Fox, J.J.; Watanabe, K.A.; Chou, T.C.; Schinazi, K.F.; Soike, Y.; Fourel, G.; Hantz, G.; Trepo, C. in *Fluorinated Carbohydrates. Chemical and Biochemical Aspects.* ACS Symp. Ser. 374, Taylor, N.F. ed. p 176, **1988**.
6. a) Fleet, G.W.J.; Son, J.C.; Derome, A.E. *Tetrahedron* **1988**, 44, 625. b) Herdewijn, P.; Balzarini, J.; De Clercq, E.; Pauwells, R.; Baba, M.; Broder, S.; Vanderhaeghe, H. *J. Med. Chem.* **1990**, 33, 2150. c) Balzarini, J.; Baba, M.; Pauwells, R.; Herdewijn, P.; De Clercq, E. *Biochem. Pharmacol.* **1988**, 37, 2847.
7. a) Ajmera, S.; Bapat, A.R.; Stephanina, E.; Danenberg, P.V. *J. Med. Chem.* **1988**, 31, 1094. b) Frick, L.W.; St.-John, L.; Taylor, L.C.; Painter, G.R.; Furman, P.A.; Liotta, D.C.; Furfine, E.S.; Nelson, D.J. *Antimicrob. Agents. Chemother.* **1993**, 37, 2285.
8. For reviews about the medicinal behaviour of gemcitabine see: a) Hui, Y.F.; Reitz, J. *Am. J. Health Syst. Pharm.* **1997**, 54, 12. b) Noble, S.; Goa, K.L. *Drugs* **1997**, 54, 447. c) Bunn, P.A.; Kelly, K. *Cancer Res.* **1998**, 4, 1087.
9. Hertel, L.W.; Kroin, J.S.; Grossman, C.S.; Grindey, C.B.; Dorr, A.F.; Storniolo, A.M.V.; Plunkett, W.; Gandhi, V.; Huang, P. in *Biomedical Frontiers of Fluorine Chemistry,* ACS Symp. Ser. 639, Ojima, I., McCarthy, J.R.; Welch, J.T. eds., p 265, **1996**.
10. a) Hertel, L.W.; Kroin, J.S.; Misner, J.W.; Tustin, J.M. *J. Org. Chem.* **1988**, 53, 2406. b) Chou, T.S.; Heath, P.C.; Patterson, L.E.; Poteet, L.M.; Lakin, R.E.; Hunt, A.H. *Synthesis* **1992**, 565. c) Weigel, J.A. *J. Org. Chem.* **1997**, 62, 6108.
11. For a review about methods for the synthesis of *gem*-difluoro-compounds see: Tozer, M.J.; Herpin, T.F. *Tetrahedron* **1996**, 52, 8619.
12. Fernández, R.; Matheu, M.I.; Echarri, R. Castillón, S. *Tetrahedron* **1998**, 54, 3523.
13. Bergstrom, D.; Romo, E.; Shum, P. *Nucleosides & Nucleotides* **1987**, 6, 53.
14. a) Fried, J.; Ann Hallina, E.; Szwedo, M.J. *J. Am. Chem. Soc.* **1984**, 106, 3871. b) Hanzawa, Y.; Izanawa, K. Kon, A.; Aoki, . Kobayashi, I. *Tetrahedron Lett.* **1987**, 28, 659.
15. a) El-Laghdach, A.; Echarri, R.; Matheu, M.I.; Barrena, M.I.; Castillón, S.; García, J. *J. Org. Chem.* **1991**, 56, 4556. b) Barrena, M.I.; Matheu, M.I.; Castillón, S. *J. Org. Chem.* **1998**, 63, 2184.
16. Pyranosides having a good leaving group at position 3β gives easily ring contraction or fragmentation reactions. See for instance: Kassou, M.; Castillón, S. *J. Org. Chem.* **1995**, 60, 4353.
17. Horton, D.; Weckerle, W. *Carbohydr. Res.* **1975**, 44, 227.
18. Norberg, T. in *Mothern Methods in Carbohydrate Synthesis*, Khan, S.H.; and O'Neill, R.A. eds. Harwood Academic Publ., Amsterdam, p. 82, **1996**.
19. See for instance: a) Fukase, K.; Nakai, Y.; Kanoh, T.; Kusumoto, S. *Synlett* **1998**, 84. b) Boons, G-J.; Bowers, S.; Coe, D.M. *Tetrahderon Lett.* **1997**, 38, 3773. c) Whitfield, D.M.; Douglas, S.P.; *Glycoconjugate J.* **1996**, 13, 5. d) Alonso, I.; Khiar, N.; Martín-Lomas, M. *Tetrahedron Lett.* **1996**, 27, 1477. e) Grice, P.; Ley, S.V.; Pietruszka, J.; Priepke, H.W.M.; Walther, E.P.C. *Synlett* **1995**, 781.
20. a) Knapp, S.; Shieh, W. *Tetrahedron Lett.* **1991**, 32, 3627. b) Sujino, K.; Sugimura, H. *Synlett*, **1992**, 553. c) Sugimura, H.; Sujino, K. *Tetrahedron Lett.* **1993**, 33, 2515. d) Sugimura, H., Muramoto, I.; Nakamura, T.; Osumi, K.; *Chem. Lett.*, **1993**, 169. e) Sujino, K.; Sugimura, H. *Tetrahedron Lett.* **1994**, 35, 1883. f) Hartsel, S.A.; Marshall, W.S. *Tetrahedron Lett.* **1998**, 38, 205.
21. Fugedi, P.; Liptak, A.; Nanasi, P.; Szejtli, J.; *Carbohydr. Res.* **1982**, 104, 55.