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Synthesis of 2-Deoxy-3,5-di-O-benzoyl-2,2-difluoro-D-ribose from D-Glucose and D-Mannose. A Formal Synthesis of Gemcitabine

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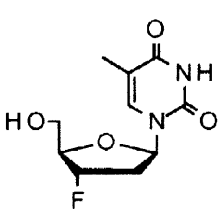
Abstract: The title compound 2-Deoxy-3,5-di-O-benzoyl-2,2-difluoro-D-ribose (**17**), was synthesised from D-glucose and from D-mannose. The key steps of the synthesis from D-glucose are obtaining the 3,3-difluoropyranose **9** by reacting the ulose **7** with DAST, and their conversion into the difluorofuranoside **17** by a degradative reaction of diol **16**. Starting from D-mannose the synthesis obtains the 3,3-difluoroglycal **22** by reaction of the ulose **18** with DAST and oxidation-elimination of selenoglycoside **21**. Ozonolysis of **22** gives the difluorofuranose **17**.

Fluoronucleosides[1] such as FLT[2] (**1**) and 2'-F-dd-ara-A[3] (**2**) are among the more active drugs against different viruses. Interest in *gem*-difluoro nucleosides has increased after the discovery of the antiviral[4] and antitumoral activity[4,5] of gemcitabine (**4**).[4,6] The 3'-deoxy-3',3'-difluoro nucleosides have been much less studied. Concretely, 3'-deoxy-3',3'-difluorothymidine (**3**)[7] has been synthesized in low yield, by treating 3'-ketothymidine with DAST.



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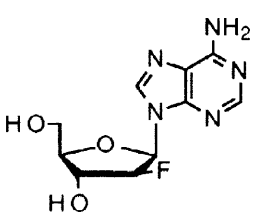

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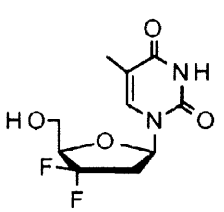

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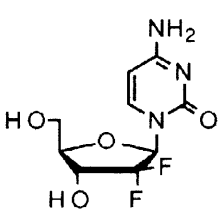

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In general, the synthesis of 2'-deoxy-2',2'-difluoronucleosides depends on the availability of appropriately protected 2-deoxy-2,2-difluororibose (**5**)[6,8,9] (Scheme 1), which is prepared from glyceraldehyde using a Reformatsky reaction with ethyl bromodifluoroacetate as the key step. Further glycosylation with bases such as pyrimidine,[10] purine,[11] pyrido-pyrimidine,[12] etc, gives the corresponding difluoronucleosides.

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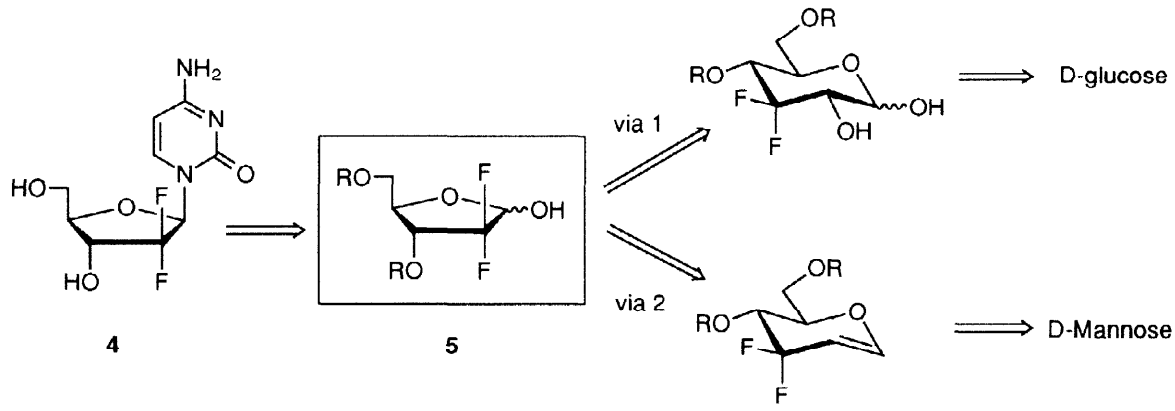


Scheme 1

One of the drawbacks of this method of synthesizing 2-deoxy-2,2-difluororibose (**5**) is the control of the stereoselectivity in the Reformatsky reaction.[13] To counter this, we decided to synthesize it from carbohydrates and perform the *gem*-difluorination by reacting a ulose with DAST.

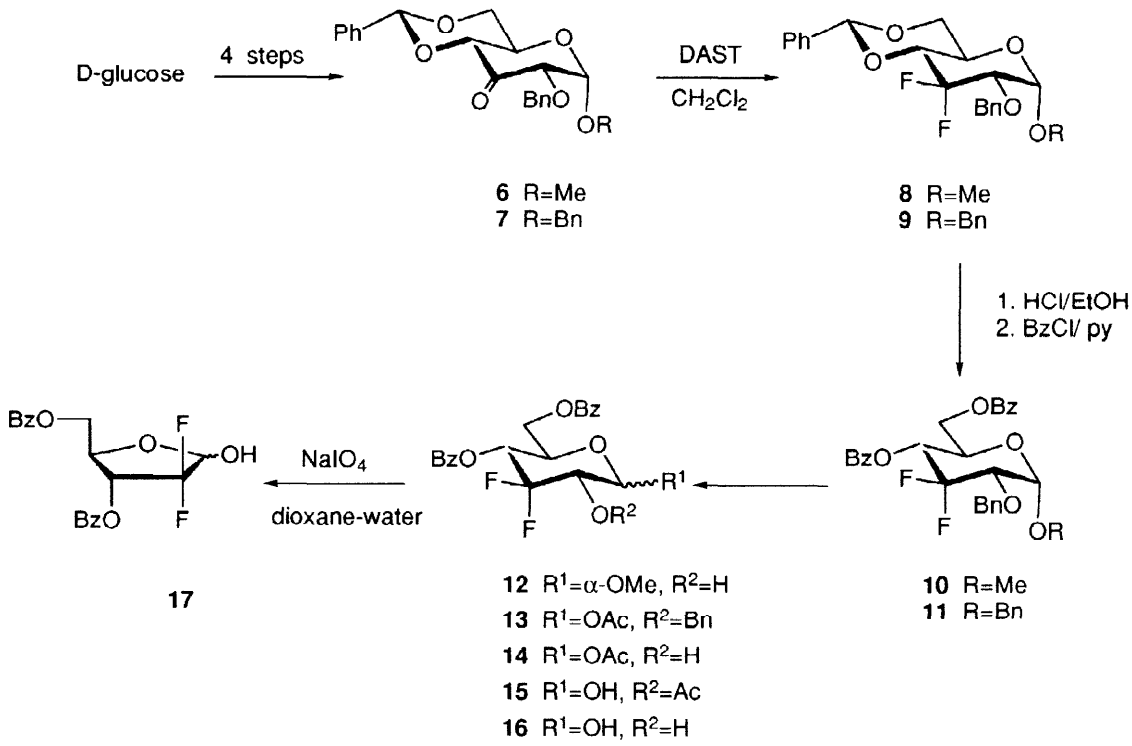
In preliminary experiments we treated differently protected methyl riboside-2-ulose with DAST to give only degradation products. Only small amounts of fluorinated products were recovered. In a previous report we showed that 2- and 3-uloses derived from D-glucose led to difluorinated carbohydrates when treated with DAST,[14] although competitive reactions such as 1,2-rearrangement and fragmentation respectively were observed. Using this methodology, compound **5** can be obtained by degrading a 3,3-difluoropyranose. This degradation can be done by breaking a diol (via 1, Scheme 1) or a double bond (via 2, Scheme 1).

In this work, we show that difluororibose **17** can be obtained from D-glucose and from D-mannose. The degradation process is carried out by oxidative breakdown of the 1,2-diol group,[15] or by synthesizing, and then ozonolyzing, a difluoroglycal, respectively.

Synthesis from D-Glucose

We have previously reported that treatment of ulose **6** with DAST in CH_2Cl_2 gave the difluoro compound **8** in a 40% yield.[14] In order to improve the yield we tried different reaction conditions, and we observed that heating to reflux in benzene and using a tenfold excess of DAST, compound **8** was obtained in a 60% yield. Hydrolysis of the benzylidene group in **8** and successive protection of the free hydroxyl groups by reaction with benzoyl chloride in pyridine gave the difluoro pyranoside **10** in an overall yield of 85% (Scheme 2).

The benzyl group in **10** was cleaved by treating it with cyclohexene and palladium hydroxide, to obtain compound **12** in a 45% yield. When compound **12** was treated with a solution of H_2SO_4 (2%) and H_2O (5%) in dioxane to reflux, no reaction was observed. When the percentage of H_2SO_4 was slightly increased (4%) the starting material progressively degraded. Thus, we decided to hydrolyse the methyl glycoside first. Compound **10** was heated at 45 °C in a 20% solution of trifluoroacetic acid in water, but unexpectedly only compound **12** was recovered from the reaction mixture in a 45% yield. However, the reaction of **10** in a 4% solution of H_2SO_4 in acetic anhydride led principally to compound **13** but the yield was only 40%. The hydrogenolysis of the benzyl group provided a mixture of compounds **14** and **15** where an acetyl group had partially migrated



Scheme 2

from the anomeric position to the hydroxyl at position 2. The subsequent removal of the acetyl groups in the mixture of **14** and **15**, by treatment with a 0.1N methanolic aqueous solution of potassium carbonate led to a complex mixture from which compound **16** could not be isolated.

So, we turned our attention to the difluoro derivative **9** which should allow an easier deprotection of hydroxyl groups at positions 1 and 2. Ulose **7** was obtained in 90% yield by oxidising the corresponding alcohol with PCC, according to a reported procedure.[16] Treatment of **7** with an excess of DAST in CH_2Cl_2 at room temperature gave a mixture of compounds, from which the difluoro derivative **9** was isolated in 60% yield.

The presence of a difluoromethylene group is confirmed by ^{19}F NMR spectroscopy which shows two signals at -116.1 (doublet) and -130.0 (double triplet) with a value of $J_{F,F}$=238 Hz characteristic of a geminal coupling.[17] The ^{13}C NMR spectrum also shows a triplet at 117.2 ppm, with a J=256 Hz typical of a $^1J_{C,F}$.[18] Likewise, the neighbouring carbons C-2 and C-4 appears at 74.8 and 77.9 ppm as triplets with coupling constants of 18.3 Hz and 18.9 Hz, respectively. All other spectroscopic data confirm the existence of the different groups present in the starting material.

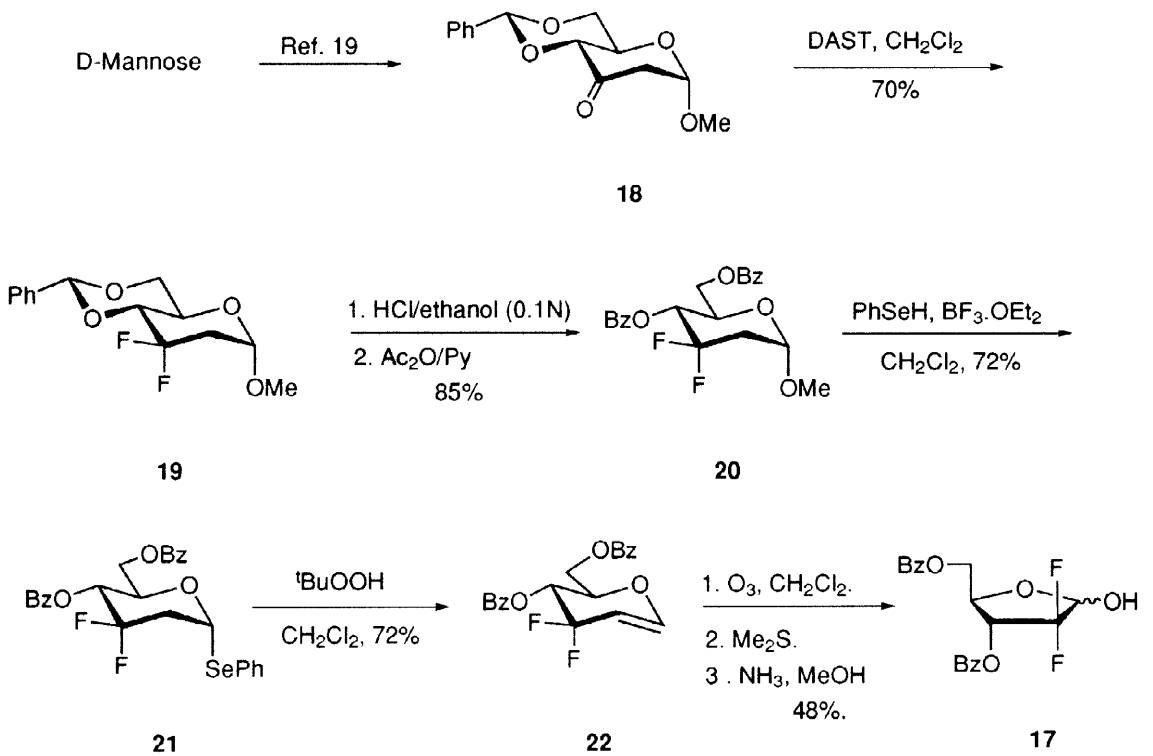
Hydrolysis of the benzylidene group in **9** and the successive protection of the free hydroxyl groups by reaction with benzoyl chloride in pyridine, in the same way as for compound **8**, gave the difluoro pyranoside **11** in an overall yield of 90%. Benzoyl was selected as protecting group for hydroxyl groups because that facilitates the purification of the nucleoside by crystallisation.[6b]

The benzyl groups in **11** were hydrogenolized under hydrogen pressure using palladium on charcoal as a catalyst. The difluoropyranose **16** was obtained as an anomeric mixture in 59% yield. Finally, compound **16** was oxidised by reaction with sodium periodate in dioxane-water to obtain the 4-formyl derivative. The ^1H

NMR spectrum of the crude product also showed the presence of some (25%) difluorofuranose **17**.[6b]

This suggests that formate hydrolysis takes place partially in the reaction medium. Further treatment of the crude product with diluted methanolic ammonia enabled us to complete the reaction obtaining **17** in 43% of overall yield.

Synthesis from D-Mannose



Scheme 3

The ulose **18** was obtained from D-mannose in three steps according to Horton's procedure.[19] Treatment of **18** with DAST gave the difluorosugar **19** in 70 % yield (Scheme 3). The difluoromethylene group formation was established taking into account the following spectroscopic data: a) the presence of two signals in the ^{19}F NMR spectrum at -104.70 and -114.72 ppm showing a $J_{F,F}$= 237 Hz characteristic of a geminal coupling between fluorine atoms;[17] the second signal shows three additional coupling constants of 32.7, 19.5 and 13.2 Hz with H-2ax, H-4 and H-2eq respectively, which shows that the signal corresponds to an axial fluorine. b) In the ^{13}C NMR spectrum, C-3 appears at 117.0 ppm as a triplet ($J_{C,F}$ = 250 Hz) indicating the presence of 2 fluorine atoms bound to C-3.[18]

The 4,6-*O*-benzylidene group was hydrolysed by treating **19** with a 0.1N HCl solution in ethanol. The product obtained was subsequently treated with benzoyl chloride in pyridine to give the protected product **20** in good yield.

We have recently developed a method for the synthesis of furanoid glycals which is based on the oxidative elimination of 1-selenoglycosides.[20] Following this method, compound **20** was converted into the phenyl 1-selenoglycoside **21** by reaction with PhSeH in $BF_3{\cdot}OEt_2$. Compound **21** was oxidised with *tert*-butylhydroperoxide and titanium tetraisopropoxide in the presence of ethyl-diisopropylamine leading to glycal **22** in 72% yield. ^1H, ^{13}C and ^{19}F NMR spectra of compound **22** fully confirm the presence of the double bond and the difluoromethylene group.

Finally, compound **22** was treated with ozone and Me_2S and the resulting formate was hydrolysed with a solution of ammonia in methanol to give, after purification, the difluoro derivative **17**, which was spectroscopically identical to the one reported.[6b]

In conclusion, 3,5-di-*O*-benzoyl-2-deoxy-2,2-difluororibose, which is a precursor in the synthesis of gemcitabine, can be obtained from D-glucose and from D-mannose. The key steps when starting from D-glucose were obtaining the difluoromethylene group by reaction of the ulose **7** with DAST, and degrading the pyranose ring to the furanose by breaking a diol with sodium periodate. On the other hand, starting from D-mannose, the key steps were obtaining the difluoromethylene group by reaction of the ulose **18** with DAST, preparing a 3,3-difluoro-pyranosyl glycal by oxidation-elimination of a phenyl 1-selenoglycoside and degrading the glycal by ozonolysis.

Table 1. Selected ^{13}C NMR data of compounds **19**, **21** and **22** (δ in ppm, J in Hz).

Comp.	C-2	C-3	C-4	$J_{C2,F}$	$J_{C3,F}$	$J_{C4,F}$
19	38.8	117.0	78.7	22.3(t)	250(t)	19.4(t)
21α	41.3	118.8	68.4	20.8(t)	250(t)	19.3(t)
22	98.3	115.0	66.9	26.8(t)	237(t)	18.8(t)

Experimental Section

General Procedures: Melting points are uncorrected. Optical rotations were measured at the indicated temperature in 10 cm cells. ^1H, ^{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 prior to use. Dichloromethane was distilled from P_2O_5 and stored over molecular sieve.

Benzyl 4,6-*O*-benzylidene-2-*O*-benzyl-3-deoxy-3,3-difluoro-α-*D*-*gluco*-pyranoside (9). 0.53 ml (4.0 mmol) of DAST was added to a solution of 300 mg (0.67 mmol) of compound **7** in anhydrous dichloromethane (4 ml). The solution was then stirred at room temperature for 2 hours, and the excess of

DAST was neutralized by careful addition of saturated aqueous $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2, and organic phase was dried and evaporated. The residue was purified by CC (Hexane/ Ethyl acetate 7:1) to afford **9** (189 mg, 60 %). mp 118-119°C, $[\alpha]_D^{23}$ +46.3° (*c* =0.30, $CHCl_3$), ^1H NMR (300 MHz): δ 7.54-7.22 (m, 15H, Ph), 5.51 (s, 1H, H7), 4.86 (d, 1H, J_{gem}=12.6 Hz, CH_2Ph), 4.82 (t, 1H, $J_{H1,H2}$=4.4 Hz, H1), 4.76 (d, 1H, J_{gem}=12.6 Hz, CH_2Ph), 4.65 (d, 1H, J_{gem}=12.6 Hz, CH_2Ph), 4.63 (d, 1H, J_{gem}=12.6 Hz, CH_2Ph), 4.22-4.08 (m, 2H, H5, H6), 3.73-3.58 (m, 3H, H6, H4, H2); ^{13}C NMR (75.4 MHz): δ 129.3-126.3 (Ph), 117.2 (t, $J_{C3,Fa}$=$J_{C3,Fe}$=256.0 Hz, C3), 101.9 (C7), 96.4 (d, $J_{C1,Fa}$= $J_{C1,Fe}$= 9.0 Hz, C1), 77.9 (t, $J_{C4,Fa}$=$J_{C4,Fe}$=18.9 Hz, C4), 74.8 (t, $J_{C2,Fa}$=$J_{C2,Fe}$=18.3 Hz, C2), 73.9 (C6), 69.9 (CH_2Ph), 68.7 (CH_2Ph), 60.6 (C5); ^{19}F NMR (282.3 MHz): δ -116.1 (d, $J_{Fa,Fe}$=237.7 Hz, Fe), -130.0 (dt, $J_{Fa,H2}$=$J_{Fa,H4}$=20.0 Hz, Fa). Anal. Calcd. for $C_{27}H_{26}O_5F_2$: C, 69.23; H, 5.55; Found: C, 69.44; H, 5.64.

Methyl 4,6-di-*O*-benzoyl-2-*O*-benzyl-3-deoxy-3,3-difluoro-α-*D*-*gluco*-hexopyranoside (10). 314 mg (0.80 mmol) of compound **8** was dissolved in a solution of hydrochloric acid in ethanol (100 ml, 0.1 N). After 40 hours, the acid was neutralized by stirring with solid sodium bicarbonate. The solution was filtered and evaporated, and the residue was dissolved in CH_2Cl_2 (10 ml), pyridine (2.5 ml) and benzoyl chloride (2 ml) were added after cooling to 0°C, and stirred for 1.5 hours. The solution was then poured into ice and water (600 ml) containing $NaHCO_3$, extracted with CH_2Cl_2 (3x100 ml), dried ($MgSO_4$) and evaporated to give 348 mg (85%) of **10** as a syrup. $[\alpha]_D^{25}$ +43.6° (*c* 0.93, $CHCl_3$); ^1H NMR (300 MHz): δ 8.15-7.30 (m,15H, Ph), 5.51 (ddd, 1H, $J_{H4,Fa}$= 20.0 Hz, $J_{H4,H5}$= 10.1 Hz, $J_{H4,Fe}$= 4.4 Hz, H4), 4.96 (d, 1H, J_{gem}= 12.6 Hz, CH_2Ph), 4.71 (d, 1H, $J_{H1,H2}$= 4.4 Hz, H1), 4.70 (d, 1H, CH_2Ph), 4.57 (dd, 1H, $J_{H6,H6'}$= 10.8 Hz, $J_{H6,H5}$= 1.4 Hz, H6), 4.44 (m, 1H, H5), 4.40 (dd, 1H, $J_{H6,H5}$= 5.0 Hz, H6), 3.79 (dt, 1H, $J_{H2,Fa}$= 20.0 Hz, $J_{H2,H1}$= $J_{H2,Fe}$= 4.4 Hz, H2), 3.46 (s, 3H, Me); ^{13}C NMR (75.4 MHz): δ 166.0 (CO), 164.8 (CO), 136.7-128.3 (Ph), 118.3 (t, $J_{C3,Fa}$=$J_{C3,Fe}$= 255.3 Hz, C3), 98.1 (d, $J_{C1,F}$= 9.4 Hz, C1), 74.4 (t, $J_{C4,Fa}$=$J_{C4,Fe}$=18.2 Hz, C4), 74.2 (CH_2Ph), 67.6 (t, $J_{C2,Fa}$=$J_{C2,Fe}$= 18.4 Hz, C2), 65.9 (d, $J_{C5,F}$= 6.0 Hz,C5), 62.4 (C6); ^{19}F NMR (282.3 MHz): δ -111.4 (d, $J_{Fa,Fe}$=242.5 Hz, Fe), -126.5 (dt, $J_{Fa,H2}$= $J_{Fa,H4}$= 20.0 Hz, Fa). Anal. Calcd. for $C_{28}H_{26}O_7F_2$: C, 65.61; H, 5.12; Found: C, 65.54; H, 5.19.

Benzyl 4,6-di-*O*-benzoyl-2-*O*-benzyl-3-deoxy-3,3-difluoro-α-*D*-*gluco*-pyranoside (11). Compound **9** (77 mg, 0.16 mmol) was dissolved in a 0.1 N solution of HCl in ethanol and stirred at room temperature for 40 hours. The solution was then neutralized with solid $NaHCO_3$, filtered and evaporated to give an oily product that was dissolved in 2 ml of CH_2Cl_2 and 0.5 ml of pyridine. After cooling to 0°C, 0.40 ml (1.6 mmol) of benzoyl chloride was added and the solution was stirred for 1 hour and poured into ice and water (200 ml) containing $NaHCO_3$, extracted several times with CH_2Cl_2, dried and evaporated to give 86 mg (0.14 mmol, 90 %) of **11**. $[\alpha]_D^{25}$ +76.6° (*c* 0.45, $CHCl_3$); ^1H NMR (300 MHz): δ 8.20-7.23 (m, 20 H, Ph), 5,51 (ddd, 1H, $J_{H4,Fa}$=21.2 Hz, $J_{H4,H5}$=10.2 Hz, $J_{H4,Fe}$= 3.4 Hz, H4), 4.88-4.78 (m, 3H, CH_2Ph, H1), 4.64 (d, 2H, J_{gem}= 12.3 Hz, CH_2Ph), 4.51-4.44 (m, 2H, H6, H5), 4.33 (dd, 1H, $J_{H6,H6'}$=13.1 Hz, $J_{H6,H5}$=4.9 Hz, H6'), 2.05 (dt, 1H, $J_{H2,Fa}$=21.2 Hz, $J_{H2,H1}$=$J_{H2,Fe}$=3.9 Hz, H2); ^{13}C NMR (75.4 MHz): δ 166.0 (CO), 164.9 (CO), 136.8-128.5 (Ph), 118.4 (t, $J_{C3,Fa}$=$J_{C3,Fe}$= 258.0 Hz, C3), 95.4 (C1), 74.6 (t, $J_{C4,Fa}$=$J_{C4,Fe}$=18.3 Hz, C4), 73.9 (CH_2Ph), 69.8 (CH_2Ph), 67.7 (t, $J_{C2,Fa}$=$J_{C2,Fe}$= 19.8 Hz, C2), 66.4 (C6), 62.4 (C5); ^{19}F NMR (282.3 MHz): δ -112.1 (d, $J_{Fa,Fe}$=241.6 Hz, Fe), -126.6 (dt, $J_{Fa,H2}$=$J_{Fa,H4}$=21.2 Hz, Fa). Anal. Calcd. for $C_{34}H_{30}O_7F_2$: C, 69.39; H, 5.10; Found: C, 69.67; H, 5.10.

4,6-di-*O*-benzoyl-3-deoxy-3,3-difluoro-α/β-*D*-*gluco*-pyranose (16). Compound **11** (220 mg, 0.44 mmol) was dissolved in methanol in the presence of 200 mg of palladium on activated charcoal (10% Pd

content). The suspension was stirred at room temperature under hydrogen pressure (10 bar) for 16 hours. The suspension was then filtered through a thin silica gel pad, and evaporated. The residue was purified by CC to give 105 mg (59%) of **16** as an inseparable anomeric mixture (ratio α/β = 5:1).

16α: ^{1}H NMR (300 MHz): δ 8.15-7.33 (m, 10H, Bz), 5.58 (ddt, 1H, $J_{H4,Fa}$=20.3 Hz, $J_{H4,H5}$= 10.3 Hz, $J_{H4,Fe}$=3.0 Hz, H4), 5.47 (t, 1H, $J_{H1,H2}$=$J_{H1,Fa}$= 3.6 Hz, H1), 4.69-4.61 (m, 2H, H5, H6), 4.42-4.34 (m, 1H, H6), 4.20 (s, 1H, OH), 4.00 (d, 1H, $J_{H2,Fa}$= 20.3 Hz, H2), 2.80 (broad s, 1H, OH); ^{13}C NMR (75.4 MHz): δ 166.3 (CO), 164.8 (CO), 135.0-128.3 (Ph), 117.8 (t, $J_{C3,Fa}$=$J_{C3,Fe}$= 250.0 Hz, C3), 91.9 (C1), 69.4 (t, $J_{C2,Fa}$=$J_{C2,Fe}$= 19.8 Hz, C2), 67.3 (t, $J_{C4,Fa}$=$J_{C4,Fe}$= 20.4 Hz, C4), 66.4 (C6), 62.3 (C5); ^{19}F NMR (282.3 MHz): δ -114.1 (d, $J_{Fa,Fe}$= 247.6 Hz, Fe), -128.5 (dt, $J_{Fa,H2}$=$J_{Fa,H4}$= 20.3 Hz, Fa).

16β :^{1}H NMR (300 MHz); 8.15-7.33 (m, 10 H, Bz), 5.58 (ddt, 1H, $J_{H4,Fa}$= 20.0 Hz, $J_{H4,H5}$= 10.3 Hz, $J_{H4,Fe}$= 3.0 Hz, H4), 4.95 (dd, 1H, $J_{H1,H2}$= 7.8 Hz, $J_{H1,Fa}$= 1.6 Hz, H1), 4.69-4.61 (m, 2H, H5, H6), 4.42-4.34 (m, 1H, H6), 3.82 (ddd, 1H, $J_{H2,Fa}$= 20.0 Hz, $J_{H2,Fe}$= 3.9 Hz, H2), 3.60 (broad, 1H, OH-1), 2.80 (broad s, 1 H, OH-2); ^{13}C NMR (75.4 MHz): δ 166.3 (CO), 164.8 (CO), 135.0-128.3 (Ph), 117.8 (t, $J_{C3,Fa}$=$J_{C3,Fe}$= 250.0 Hz, C3), 95.8 (C1), 73.2 (t, $J_{C2,Fa}$=$J_{C2,Fe}$= 19.0 Hz, C2), 67.5 (t, $J_{C4,Fa}$=$J_{C4,Fe}$= 20.1 Hz, C4), 66.3 (C6), 62.6 (C5); ^{19}F NMR (282.3 MHz): δ -117.4 (d, $J_{Fa,Fe}$= 240.0 Hz, Fe), -133.1 (dt, $J_{Fa,H2}$=$J_{Fa,H4}$= 20.0 Hz, Fa).

Synthesis of 3,5-di-*O*-benzoyl-2-deoxy-2,2-difluoro-*D*-ribose (17) from 16. To a solution of 46 mg (0.11 mmol) of **16** in water-dioxane 1:2 (2 ml) was added 120 mg (0.56 mmol) of sodium periodate. Ths resulting solution was stirred at room temperature for 20 hours. Then, more sodium periodate (55 mg, 0.26 mmol) was added and stirring was continued for 6 hours. After that, the solvents were evaporated and the solid was repeatedly extracted with ethyl acetate (total volume 70 ml). The solvent was then evaporated to give a solid that was treated for 15 minutes with a diluted (0.1%) methanolic solution of ammonia. The solution was evaporated and the crude purified by preparative TLC (hexane/ethyl acetate 2:1) to yield 18 mg (0.04 mmol, 43%) of **17**. α-isomer: ^{1}H NMR (300 MHz): δ 5.47 (m,1H, H1), 5.49 (m, 1H, H3), 4.76 (m, 1H, H4), 4.69-4.58 (m, 2H, H5). β-isomer: ^{1}H NMR (300 MHz); 5.73 (1H, H1), 5.35 (dd, 1H, H3), 4.62 (m, 2H, H5), 4.45 (m, 1H, H4).

Methyl 4,6-*O*-benzylidene-2,3-dideoxy-3,3-difluoro-α-*D*-*erythro*-hexopyranoside (19). DAST (0.60 ml, 4.6 mmol) was added to a solution of compound **18**[19] (0.315 g, 1.19 mmol) in dry dichloromethane (10 ml) under argon. The solution was stirred at room temperature for 2.5 hours. The excess of DAST was then neutralized by adding saturated aqueous sodium bicarbonate. The combined layers were extracted (CH_2Cl_2), and the extracts were dried ($MgSO_4$) and evaporated to give a syrup which was purified by column chromatography (hexane/ethyl acetate 2:1), to afford 0.24 g (0.84 mmol, 70%) of compound **19**. Mp 92-94°C; $[\alpha]_D^{23}$ +109.33° (*c* =0.3, $CHCl_3$); ^{1}H NMR (300 MHz): δ 7,60-7.30 (m, 5H, Ph), 5.60 (s, 1H, H7), 4.88 (t, 1H, $J_{H1,H2}$= $J_{H1,H2'}$= 3.8 Hz, H1), 4.34 (dd, 1H, $J_{H6,H6'}$= 10.2, $J_{H6,H5}$ = 4.9 Hz, H6), 4.13 (td, 1H, $J_{H5,H4}$ = $J_{H5,H6}$= 9.8 Hz, $J_{H5,H6'}$= 5 Hz, H5), 3.90-3.72 (m, 2H, H-6, H4), 3.40 (s, 3H, CH_3), 2.47 (td, 1H, $J_{H2,H2'}$= $J_{H2,Fa}$= 14, $J_{H2,Fe}$= 3.7 Hz, H2), 2.21 (ddt, 1H, $J_{H2,H2'}$= 14 Hz, $J_{H2',Fa}$= 32 Hz, $J_{H2',H1}$= 5.7 Hz, H2'); ^{13}C NMR (75.4 MHz): δ 136.5-126.3 (Ph), 117.0 (t, $J_{C3,Fa}$= $J_{C3,Fe}$= 250 Hz, C3), 102.1 (C7), 97.6 (d, $J_{C1,Fa}$= $J_{C1,Fe}$ = 12.7 Hz, C1), 78.7 (t, $J_{C4,Fa}$= $J_{C4,Fe}$= 19.4 Hz, C4), 68.9 (C6), 60.9 (d, $J_{C5,Fa}$= 6.0 Hz, C5), 55.4 (CH_3), 38.8 (t, $J_{C2,Fa}$= $J_{C2,Fe}$= 22.3 Hz, C2). ^{19}F RMN (282.3 MHz): δ -104.70 (d, $J_{Fa,Fe}$ = 237 Hz, Fe), -114.72 (dddd, $J_{Fa,H2'}$= 32.7 Hz, $J_{Fa,H4}$= 19.5 Hz, $J_{Fa,H2}$= 13.2 Hz, Fa). Anal. Calcd for $C_{14}H_{16}O_4F_2$: C, 58.74; H, 5.59. Found: C, 58.53; H, 5.66.

Methyl 4,6-di-*O*-benzoyl-2,3-dideoxy-3,3-difluoro-α-D-*erythro*-hexopyranoside (20). Compound **19** (0.70 g, 2.5 mmol) was dissolved in a 0.1 N ethanolic solution of hydrochloric acid and stirred at room temperature for 1 day. The solution was then neutralized by adding solid sodium bicarbonate. The solids were filtered, the solvent was evaporated to dryness and the residue dissolved in 5 ml of pyridine and 1.5 ml of benzoyl chloride. The solution was stirred for 10 hours, poured into ice-water (300 ml), extracted with dichloromethane (3x100 ml), washed with a saturated solution of sodium bicarbonate, dried ($MgSO_4$) and evaporated, to give 0.86 g (2.1 mmol, 85 %) of **20** as a syrup. $[\alpha]_D^{25}$ +122.8° (*c* = 0.93, $CHCl_3$); ^1H NMR (300 MHz): δ 8.15-7.30 (m,10H, Ph), 5.54 (ddd, 1H, $J_{H4,Fa}$= 18.7 Hz, $J_{H4,H5}$= 10.0 Hz, $J_{H4,Fe}$= 4.5 Hz, H4), 4.99 (t, 1H, $J_{H1,H2}$= $J_{H1,H2'}$= 3.8 Hz, H1), 4.61 (dd, 1H, $J_{H6,H6'}$= 11.7 Hz, $J_{H6,H5}$= 2.4 Hz, H6), 4.50-4.40 (m, 2H, H6, H6'), 3.36 (s, 3H, CH_3), 2.53 (td, 1H, $J_{H2,H2'}$= $J_{H2,Fa}$= 14.1 Hz, $J_{H2,H1}$= 5.0 Hz, H2), 2.33 (ddt, 1H, $J_{H2',Fa}$= 33.5 Hz, $J_{H2',H1}$= 14.8 Hz, $J_{H2',Fe}$= 4.9 Hz, H2'). ^{13}C NMR (75.4 MHz): δ 166.1 (CO), 165.0 (CO), 133.7-128.4 (Ph), 118.4 (t, $J_{C3,Fa}$ = $J_{C3,Fe}$ = 235 Hz, C3), 97.1 (d, $J_{C1,Fa}$= 12.6 Hz, C1), 68.3 (t, $J_{C4,Fa}$= $J_{C4,Fe}$= 21.4 Hz, C4), 66.6 (C6), 62.8 (CH_3), 55.5 (C5), 38.4 (t, $J_{C2,Fa}$= $J_{C2,Fe}$= 22.0 Hz, C2). ^{19}F NMR (282.3 MHz): δ -100.7 (d, $J_{Fa,Fe}$= 238.8 Hz, Fe), -110.5 (dddd, $J_{Fa,H2'}$= 46.6 Hz, $J_{Fa,H4}$= 21.7 Hz, $J_{Fa,H2}$= 13.0 Hz, Fa). Anal. Calcd for $C_{21}H_{20}O_6F_2$: C, 62.07; H, 4.93. Found: C, 62.30; H, 5.03.

Phenyl 4,6-di-*O*-benzoyl-2,3-dideoxy-3,3-difluoro-1-seleno-α/β-D-*erythro*-hexo-pyranoside (21). $BF_3{\cdot}OEt_2$ (0.060 ml, 0.48 mmol as a solution of 48% in BF_3) and phenylselenol (0.064 ml, 0.60 mmol) were added to a stirred solution of compound **20** (100 mg, 0.24 mmol) in anhydrous dichloromethane (2 ml). The solution was heated to reflux for 3 hours, neutralized by dropwise addition of pyridine and evaporated to dryness. The residue was purified by column chromatography (hexane/ethyl acetate 10/1) to afford 92 mg (72%) of **21** as an anomeric mixture which was used directly in the next reaction. A small sample of this mixture was purified by successive migration in TLC using the same mixture of solvents for the elution, and **21**α and **21**β were recovered as pure compounds.

21α: $[\alpha]_D^{25}$ +217.9° (*c* =0.485, $CHCl_3$);^1H NMR (300 MHz): δ 8.20-7.10 (15H, Ph), 5.98 (s, 1H, H1), 5.53 (ddd, 1H, $J_{H4,Fa}$= 19.5 Hz, $J_{H4,H5}$= 10.1 Hz, $J_{H4,Fe}$= 3.1 Hz, H4), 4.97 (m, 1H, H5), 4.67-4.45 (m, 1H, H6'), 4.37 (dd, 1H, $J_{H6,H6'}$= 12.2 Hz, $J_{H6,H5}$= 5.2 Hz, H6), 2.87-2.61 (m, 1H, H2), 2.17-2.40 (m, 1H, H2'). ^{13}C NMR (75.4 MHz): δ 166.1 (CO), 165.0 (CO), 135.2-127.9 (Ph), 118.8 (t, $J_{C3,Fa}$= $J_{C3,Fe}$= 250 Hz, C3), 79.4 (C1), 75.7 (C6), 68.4 (t, $J_{C4,Fa}$= $J_{C4,Fe}$= 19.3 Hz, C4), 62.9 (C5), 41.3 (t, $J_{C2,Fa}$= $J_{C2,Fe}$= 20.8 Hz, C2).^{19}F NMR (282.3 MHz): δ -103.2 (d, $J_{Fa,Fe}$= 242.8 Hz, Fe), -111.3 (ddt, $J_{Fa,H2}$= $J_{Fa,H4}$ = 21.5 Hz, $J_{Fa,H2'}$ = 21.2 Hz, Fa). Anal. Calcd for $C_{26}H_{22}O_5F_2Se$: C, 58.76; H, 4.14. Found: C, 58.64; H, 4.24.

21β: m.p= 100-101 °C. $[\alpha]_D^{25}$ +53.1° (*c* =0.38, $CHCl_3$); ^1H NMR (300 MHz): δ 8.20-7.10 (15H, Ph), 5.43 (ddd, 1H, $J_{H4,Fa}$= 19.8 Hz, $J_{H4,H5}$ = 10.4 Hz, $J_{H4,Fe}$= 3.6 Hz, H4), 5.25 (d, 1H, $J_{H1,H2}$= 12.1 Hz, H1), 4.50 (dd, 1H, $J_{H6,H6'}$= 12.2 Hz, $J_{H6,H5}$= 5.5 Hz, H6), 4.67-4.45 (m, 1H, H6'), 2.87-2.61 (m, 1H, H2), 2.17-2.40 (m, 1H, H2). ^{13}C NMR (75.4 MHz): δ 166.1 (PhCO), 165.0 (PhCO), 135.2-127.9 (Ph), 118.4 (t, $J_{C3,Fa}$= $J_{C3,Fe}$= 250 Hz, C3), 74.9 (C6), 69.4 (C1), 68.2 (t, $J_{C4,Fa}$= $J_{C4,Fe}$=19.3 Hz, C4), 62.8 (C5), 40.3 (t, $J_{C2,Fa}$= $J_{C2,Fe}$= 22.6 Hz, C2). ^{19}F NMR (282.3 MHz): δ -103.6 Hz (d, $J_{Fa,Fe}$= 226.7 Hz, Fe), -111.4 (ddt, $J_{Fa,H2}$ = $J_{Fa,H4}$= 20.0 Hz, $J_{Fa,H2}$= 27.4 Hz, Fa). Anal. Calcd for $C_{26}H_{22}O_5F_2Se$: C, 58.76; H, 4.14. Found: C, 59.00; H, 4.00.

1,5-anhydro-4,6-di-*O*-benzoyl-2,3-dideoxy-3,3-difluoro-D-*erythro*-hex-1-enitol (22). A 3M solution of *t*-butylhydroperoxide in toluene (0.042 ml, 0.12 mmol), titanium tetraisopropoxide (0.008 ml, 0.02 mmol) and ethyl diisopropylamine (0.014 ml, 0.08 mmol) were added to a stirred solution of 40 mg (0.074

mmol) of **21** in 4 ml of anhydrous dichloromethane at room temperature. The reaction was complete within 6 hours, and the solvent was then evaporated to dryness and the residue was quickly purified by preparative TLC to give 20 mg (72%) of **22** as a syrup. $[\alpha]_D^{25}$ +183.7°(*c*=0.49, $CHCl_3$); ^1H NMR (300 MHz): δ 8.15-7.35 (m, 10H, Ph), 6.67 (d, 1H, $J_{H1,H2}$= 6 Hz, H1), 5.86 (td, 1H, $J_{H2,Fa}$= 9.8 Hz, $J_{H1,H2}$= 6.5 Hz, H-2), 5.19 (td, 1H, $J_{H4,Fa}$= $J_{H4,Fe}$= 6.9 Hz, $J_{H4,H5}$= 2.1 Hz, H4), 4.73-4.64 (m, 2H, H5, H6), 4.49 (dd, 1H, $J_{H6',H6}$= 12.6 Hz, $J_{H6',H5}$= 5.1 Hz, H6'). ^{13}C NMR (75.4 MHz): δ 165.9 (CO), 164.7 (CO), 150.1 (C-1), 133.8-128.2 (Ph), 115.0 (t, $J_{C3,Fa}$= $J_{C3,Fe}$= 237.1 Hz, C3), 98.3 (t, $J_{C2,Fa}$= $J_{C2,Fe}$= 26.8 Hz, C2), 74.5 (C4), 66.9 (t, $J_{C4,Fa}$= $J_{C4,Fe}$= 18.8 Hz, C4), 61.6 (C5). ^{19} NMR (282.3 MHz): δ -98.2 (dd, $J_{Fa,Fe}$= 262 Hz, $J_{Fe,H2}$= 12.0 Hz, Fe), -106.2 (dt, $J_{Fa,H2}$= $J_{Fa,H4}$= 7.0 Hz, Fa). Anal. Calcd for $C_{20}H_{16}O_5F_2$: C, 64.17; H, 4.28. Found: C, 64.40; H, 4.35.

Synthesis of 3,5-di-*O*-benzoyl-2-deoxy-2,2-difluoro-*D*-ribose (17) from 22. 44 mg (0.12 mmol) of compound **22** were dissolved in dichloromethane and cooled in an acetone/carbon dioxide bath. Ozone was steadily bubbled through the solution until a light blue colour appeared (*ca* 20 minutes). Then, bubbling oxygen for 10 more minutes, the solution was treated with an excess of dimethyl sulphide and stirred overnight at room temperature, washed with water (3x3ml), dried ($MgSO_4$) and evaporated to dryness to give a residue that was dissolved in methanolic ammonia (0.1% w/w, 1 ml) and stirred at 0°C for 45 minutes. The solvent was then evaporated to dryness and the residue was chromatographed (hexane/ethyl acetate 5:1) to give 14 mg of compound **17** (48%) as a syrup.

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