Synthesis of 2,3,4-Trideoxy-4,4-difluoro-D-*ribo*-hexopyranose Adenosines

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Abstract: A novel synthetic route to 2,3,4-trideoxy-4,4-difluoro-β-D-*ribo*-hexopyranose adenosine and 2,3,4-trideoxy-2,3-didehydro-4,4-difluoro-β-D-*ribo*-hexopyranose adenosine has been developed. The approach highlights the highly regio- and stereoselective palladium-catalyzed glycosylation of Boc-protected pyranose, which was prepared from the oxidation–cyclization of a difluorinated diol. The diol was provided through ozonization and Lindlar reduction of optically pure enynic alcohol.

Key words: nucleosides, fluorinated compounds, palladium-catalyzed glycosylation

The discovery of a large and varied class of natural bioactive hexopyranosyl nucleoside-containing products, such as blasticidin,[1] gougerotin,[2] hikizimycin,[3] and mildiomycin,[4] has inspired many efforts on the synthesis of hexopyranosyl nucleosides as potential anticancer and antiviral agents.[5] Among these hexopyranosyl nucleosides, 2,3-dideoxypyranosyl nucleosides and 2,3-unsaturated hexopyranosyl nucleosides constitute a distinct class of bioactive compounds. They have been demonstrated to show anticancer and antiviral activities. For example, 2,3-dideoxy-β-D-*ribo*-hexopyranose adenosine (**5**) and 2,3-didehydro-β-D-*ribo*-hexopyranose adenosine (**6**) were synthesized as a selective inhibitor of protein synthesis and several transplantable animal tumors[6,7] (Figure 1). Interestingly, the presence of a double bond at C2–C3 of pyranose ring in **6** can make it adopt a twisted half-chair conformation that is similar to the furanose rings of the naturally occurring nucleosides.[6a,8] Based on this fact, many furanose ring mimic nucleosides bearing a 2,3-didehydropyranose ring have been used in various biological systems.[9] Thus, there has been a great demand for efficient synthetic methods to access these valuable compounds. On the other hand, special attention has also been paid to the *gem*-difluoromethylene group (CF_2) because the introduction of this group into organic compounds can bring about remarkable changes in physical, chemical, and biological properties.[10] The well-known example is Gemcitabine,[11] a *gem*-difluoromethylenated nucleoside, which has been used for treatment of lung, ovarian, renal, pancreatic, head, and neck cancers. However, to the best of our knowledge, the *gem*-difluorinated hexopyranosyl nucleosides have never been reported. As part of our continuous study to develop new antiviral and anticancer agents, we designed *gem*-difluorinated hexopyranosyl nucleosides **1** and **3**, in which the hydroxy groups at C4 in **5** and **6** were replaced with a CF_2 group based on the idea that the *gem*-difluoromethylene group (CF_2) is the chemical isostere for hydroxy group.[12] Herein, we describe an efficient synthesis of target molecules **1** and **3** from a fluorinated building block.

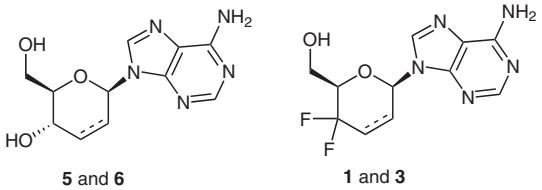

Figure 1 Hexopyranosyl nucleosides **5**, **6** and design of 2,3,4-trideoxy-4,4-difluoro-β-D-*ribo*-hexopyranose adenosines

Very recently, our group has reported the preparation of *gem*-difluorinated 1,2-disubstituted carbocyclic nucleosides via palladium-catalyzed glycosylation. We found that the nitrogen nucleophilic bases can specifically attack the more electrophilic carbon of intermediate **9** resulting only in γ-substituted product **8** (Scheme 1).[13] Interestingly, O'Doherty's group reported that palladium-catalyzed glycosylation of hexopyranosyl substrates with various alcohol nucleophiles proceeded smoothly with excellent stereocontrol and the more electrophilic Pd-π-allyl intermediate **I** (Scheme 1) is essential to the reaction.[14] Employing this strategy, they successfully synthesized hexopyranosyl nucleosides.[7c] Thus, taking all these results together, we planned to install the base moiety of target molecule **1** by palladium-catalyzed N-glycosylation (Scheme 2). We envisaged that the presence of an electron-withdrawing CF_2 group in intermediate **11** would direct bases regioselectively and stereoselectively to attack the carbon far away from the CF_2 group. Therefore, the palladium-catalyzed glycosylation of the difluorinated pyranose **12** with base would give nucleoside **10**, a precursor of **1**. Compound **12** could be prepared from diol **13** by oxidation of the primary hydroxyl to aldehyde followed by the simultaneous cyclization. Diol **13** could be easily obtained via ozonization and Lindlar reduction of our reported optically pure alcohol (*R*)-**14** (Scheme 2).[15]

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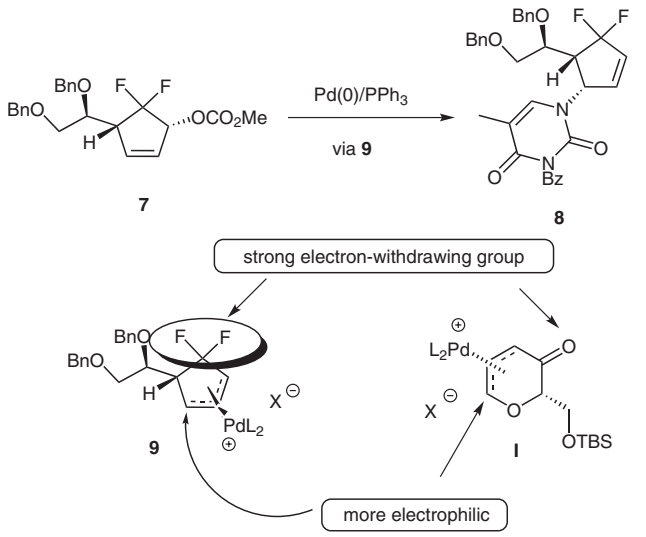
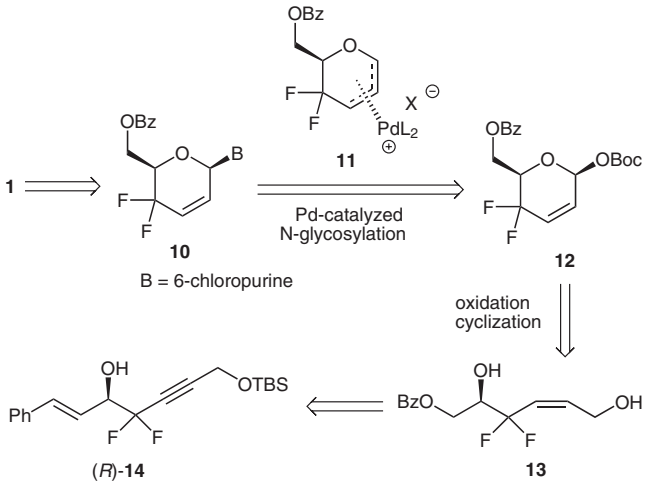


Scheme 1

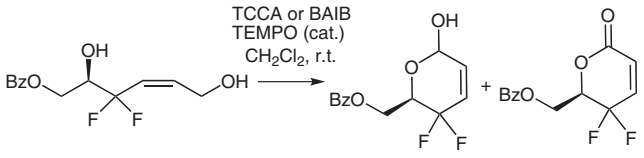


Scheme 2

Thus, the synthesis of the target molecules was started from (*R*)-**14**. Treatment of (*R*)-**14** with O_3 followed by $NaBH_4$-mediated reduction gave diol **15** in 75% yield. Hydrogenation of diol **15** in the presence of Lindlar catalyst gave (*Z*)-diol **16** in 83% yield. Selective benzoylation of the primary hydroxy group of diol **16** and subsequent removal of TBS group with TBAF provided the *gem*-difluorinated alcohol **13** in 70% yield (Scheme 3).

The preparation of lactol **17** was initially carried out by the Giacomelli's procedure for the selective oxidation of primary alcohol to aldehyde in the presence of trichloroisocyanuric acid (TCCA) and catalytic TEMPO (Table 1).[16] However, when diol **13** was treated with 1.0 equivalent of TCCA and catalytic TEMPO at room temperature, only a trace amount of the desired lactol **17** was produced and lactone **18** was formed as the major product (42%) (Table 1, entry 1). The oxidation of diol **13** with bis(acetoxyiodo)benzene (BAIB) afforded the desired lactol **17** in 21% yield (*anti*/*syn* = 4:1), but lactone **18** was still produced in 32% yield (entry 3). To prepare lactol **17** efficiently, the complete conversion of diol **13** to lactone **18** and then reduction of **18** to lactol **17** were investigated. The peroxidation of diol **13** with 3.0 equivalents of TCCA provided lactone **18** in 47% yield (entry 2). We were pleased to find that lactone **18** was isolated in 76% yield when BAIB was used instead of TCCA (entry 4).

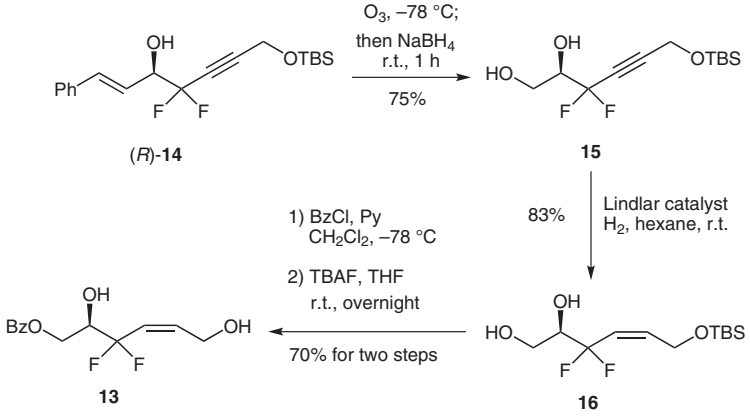
Table 1 Oxidation of Diol **13**



Entry	Oxidant	Equiv	Yield (%) of **17**	Yield (%) of **18**
1	TCCA	1.0	trace	42
2	TCCA	3.0	–	47
3	BAIB	1.0	21[a]	32
4	BAIB	3.0	–	76

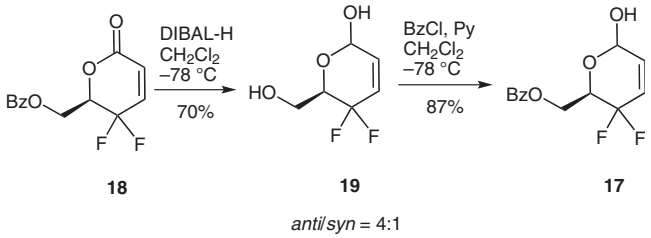
[a] Ratio of *anti*/*syn* = 4:1, determined by ^{19}F NMR spectroscopy.

Reduction of lactone **18** with DIBAL-H afforded diol **19** in 70% yield with *anti*-isomer as the major product (*anti*/



Scheme 3

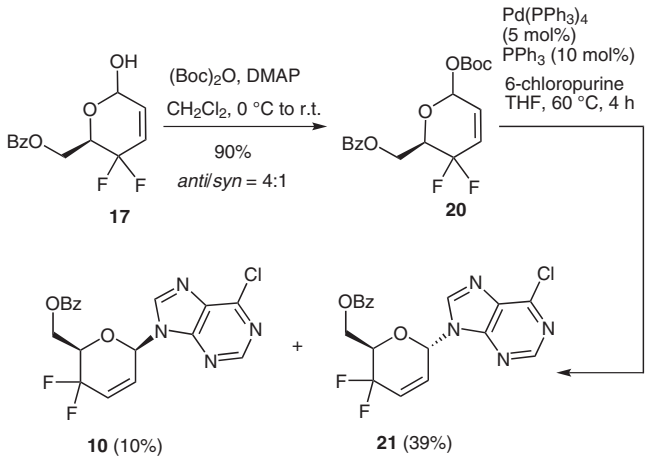
syn = 4:1, determined by ^{19}F NMR spectroscopy). Selective benzoylation of the primary hydroxy group of diol **19** provided lactol **17** in 87% yield (Scheme 4).



Scheme 4

With the key lactol **17** in hand, we then paid our attention to the palladium-catalyzed gylcosylation for the installation of base (Scheme 5). Treatment of **17** with $(Boc)_2O$ gave compound **20**. As we expected, treatment of **20** with 6-chloropurine in the presence of catalytic $Pd(PPh_3)_4$ at 60 °C in THF gave exclusively γ-substituted diastereoisomers **10** and **21**. More gratifyingly, these two diastereoisomers could be readily separated by flash chromatography and their absolute configurations were elucidated from NOESY experiments based on the known configuration at C5 as derived from (*R*)-**14**. It was noteworthy that the ratio of **10**:**21** was the same to that of *syn*/*anti*-**20**. This result showed that this palladium-catalyzed gylcosylation was completely stereocontrolled. That is to say, *syn*-**20** provided only the β-anomer **10** and *anti*-**20** gave only the α-anomer **21**, which is consistent with a π-allylpalladium intermediate.

Exposure of **10** and **21** to saturated methanolic ammonia at 80 °C gave *gem*-difluorinated 2,3-unsaturated hexopyranose adenosines **3** and **4** in 73 and 80% yield, respectively. The structure of compound **4** was further confirmed by X-ray diffraction (Figure 2).[17] Finally, hydrogenation of **3** and **4** in the presence of catalytic Pd/C gave the target molecules 2,3,4-trideoxy-4,4-difluoro-D-*ribo*-hexopyranose adenosines **1** and **2** in 87 and 90% yield, respectively (Scheme 6).



Scheme 5

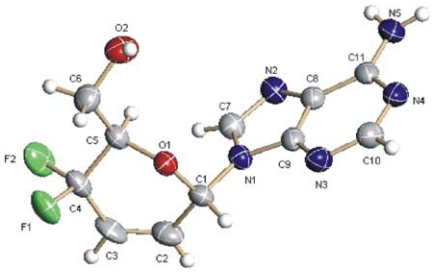
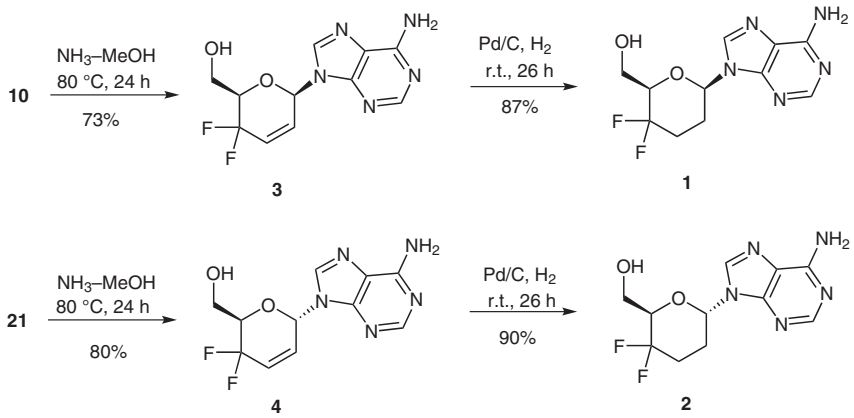


Figure 2 ORTEP drawing of the X-ray crystallographic structure of compound **4**

In conclusion, we have accomplished the synthesis of 2,3,4-trideoxy-4,4-difluoro-β-D-*ribo*-hexopyranose adenosines **1**, **3** and their α-anomers **2**, **4** using palladium-catalyzed glycosylation as a key step. The high regio- and stereoselectivities of such palladium-catalyzed glycosylation could be used as an efficient and practical strategy for the synthesis of other *gem*-difluorinated hexopyranosyl substrates. Antiviral and cytotoxicity evaluations of **1**–**4** are currently in progress and will be reported soon.



Scheme 6

THF and benzene were distilled from sodium metal. CH_2Cl_2 was distilled from CaH_2. Melting points are uncorrected. Petroleum ether (PE) used refers to the fraction boiling in the range 60–90 °C. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM300 spectrometer. ^{19}F NMR spectra were recorded on a Bruker AM300 spectrometer ($CFCl_3$ as external standard and low field is positive). Chemical shifts (δ) are reported in ppm, and coupling constants (*J*) are in Hz.

(*R*)-6-(*tert*-Butyldimethylsilyloxy)-3,3-difluorohex-4-yne-1,2-diol (15)

Ozone was bubbled through a solution of (*R*)-**14** (4.45 g, 12.6 mmol) in MeOH–CH_2Cl_2 (70 mL:70 mL) for 45 min at –78 °C till a blue color persisted. Then, N_2 was bubbled through the solution until the blue color disappeared and $NaBH_4$ (2.35 g, 63.5 mmol) was added. After warming to r.t. and stirring for 1 h, the reaction was quenched with sat. aq NH_4Cl (50 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4) and concentrated under vacuo to give the crude product. Purification by flash silica gel column chromatography (PE–EtOAc, 1:1) yielded **15** (2.66 g, 75%) as a clear oil; $[\alpha]_D^{26}$ +8.9 (*c* 1.03, $CHCl_3$).

IR (film): 3400, 2933, 2861, 1213, 1110, 1074, 838, 781 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.40 (t, *J* = 5.1 Hz, 2 H), 4.02–3.77 (m, 3 H), 2.86 (br, 2 H), 0.90 (s, 9 H), 0.13 (s, 6 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 112.9 (t, *J* = 236.8 Hz), 88.4 (t, *J* = 7.0 Hz), 75.5 (t, *J* = 38.7 Hz), 74.1 (t, *J* = 27.9 Hz), 61.2 (t, *J* = 2.9 Hz), 51.3, 25.7, 18.3, –5.3.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –94.98 to –95.04 (m, 2 F).

MS (MALDI): *m*/*z* = 303.1 $[M + Na]^+$.

HRMS (MALDI): *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{22}F_2O_3Si$ + Na: 303.1199; found: 303.1202.

(*R*,*Z*)-6-(*tert*-Butyldimethylsilyloxy)-3,3-difluorohex-4-ene-1,2-diol (16)

A suspension of Lindlar catalyst (0.44 g) and diol **15** (2.88 g, 10.3 mmol) in hexane (150 mL) was stirred under H_2 for 48 h at r.t. Filtration and removal of the solvent gave the crude product, which was purified by flash silica gel column chromatography (PE–EtOAc, 1:1) to give **16** (2.40 g, 83%) as a clear oil; $[\alpha]_D^{26}$ +4.9 (*c* 0.48, $CHCl_3$).

IR (film): 3400, 2933, 2861, 2257, 1213, 1110, 1074, 838, 781 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.00 (m, 1 H), 5.54 (q, *J* = 13.8 Hz, 1 H), 4.43 (s, 1 H), 3.95–3.80 (m, 3 H), 0.90 (s, 9 H), 0.08 (s, 6 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 140.1 (t, *J* = 5.6 Hz), 120.7 (dd, *J* = 31.9, 25.7 Hz), 117.4 (t, *J* = 140.4 Hz), 73.7 (t, *J* = 29.0 Hz), 61.0 (t, *J* = 4.2 Hz), 59.8 (t, *J* = 4.8 Hz), 25.9, 18.3, –5.3.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –101.76 (dt, *J* = 260.3, 11.8 Hz, 1 F), –105.23 (dt, *J* = 258.6, 13.3 Hz, 1 F).

MS (MALDI): *m*/*z* = 305.1 $[M + Na]^+$.

HRMS (MALDI): *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{24}F_2O_3Si$ + Na: 305.1355; found: 305.1367.

(*R*,*Z*)-3,3-Difluoro-2,6-dihydroxyhex-4-enyl Benzoate (13)

To a solution of *Z*-diol **16** (2.40 g, 8.5 mmol) in anhyd CH_2Cl_2 (100 mL) was slowly added pyridine (14 mL) followed by BzCl (0.85 mL, 0.88 equiv) at –78 °C. The mixture was stirred for 1 h at the same temperature, and then another portion of BzCl (0.23 mL, 0.24 equiv) was added. After stirring the mixture for another 1 h, MeOH (10 mL) was added and the mixture was stirred for 30 min. The mixture was washed sequentially with aq 1 N HCl (50 mL), sat. aq $NaHCO_3$ (30 mL), and brine (30 mL). The organic layer was dried (Na_2SO_4), filtered, and the solvent was removed in vacuo. The residue was purified by flash silica gel column chromatography (PE–EtOAc, 10:1 to 6:1) to give 2.5 g of the product benzoate. The product was dissolved in THF (30 mL) and TBAF (7 mL, 1 M in THF) was added. The mixture was stirred overnight at r.t. After removal of the solvent in vacuo, the residue was purified by flash silica gel column chromatography (PE–EtOAc, 1:1) to give **13** (1.55 g, 70% for two steps); $[\alpha]_D^{26}$ +4.8 (*c* 0.65, $CHCl_3$).

IR (film): 1755, 1726, 1453, 1230, 1070, 711 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 1.5 Hz, 2 H), 7.61 (t, *J* = 1.2 Hz, 1 H), 7.45 (t, *J* = 7.5 Hz, 2 H), 6.15–6.06 (m, 1 H), 5.72–5.56 (m, 1 H), 4.62–4.46 (m, 2 H), 4.43–4.38 (m, 2 H), 4.27–4.17 (m, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 167.0, 139.0 (t, *J* = 3.9 Hz), 133.5, 129.7, 129.3, 128.5, 122.0 (t, *J* = 19.6 Hz), 120.2 (t, *J* = 183.8 Hz), 72.0 (t, *J* = 22.5 Hz), 63.8, 58.7.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –100.83 (dm, *J* = 234.1 Hz, 1 F), –105.00 (ddd, *J* = 228.1, 14.9 Hz, 3.7 Hz, 1 F).

MS (MALDI): *m*/*z* = 273.1 $[M + H]^+$.

HRMS (MALDI): *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{14}F_2O_4$ + Na: 295.0752; found: 295.0758.

(*R*)-(3,3-Difluoro-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)methyl Benzoate (18)

To a solution of benzoate **13** (106 mg, 0.39 mmol) in anhyd CH_2Cl_2 (3 mL) were added BAIB (376 mg, 1.20 mmol) and TEMPO (12 mg, 20 mmol%) at 0 °C. After stirring the mixture for 3 h at r.t., the reaction was quenched with aq $Na_2S_2O_3$ (2 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 2 mL) and the combined organic layers were washed sequentially with sat. aq $NaHCO_3$ (3 mL), NH_4Cl (3 mL), and brine (3 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed in vacuo. The residue was purified by flash silica gel column chromatography (PE–EtOAc, 4:1) to give **18** (79 mg, 76%) as a clear oil; $[\alpha]_D^{26}$ –2.3 (*c* 1.25, $CHCl_3$).

IR (film): 1755, 1726, 1453, 1230, 1070, 711 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 1.5 Hz, 2 H), 7.61 (t, *J* = 1.2 Hz, 1 H), 7.45 (t, *J* = 7.5 Hz, 2 H), 6.89–6.82 (m, 1 H), 6.37 (d, *J* = 10.2 Hz, 1 H), 5.04–4.92 (m, 1 H), 4.82 (dd, *J* = 12.6, 3.6 Hz, 1 H), 4.68 (q, *J* = 6.9 Hz, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 165.8, 159.4, 137.1 (dd, *J* = 26.3, 19.6 Hz), 133.5, 129.7, 129.0, 128.5, 126.7 (t, *J* = 6.7 Hz), 111.9 (t, *J* = 182.0 Hz), 60.4 (t, *J* = 3.9 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –106.82 (dt, *J* = 291.0, 8.2 Hz, 1 F), –108.75 (dd, *J* = 271.3, 19.5 Hz, 1 F).

MS (MALDI): *m*/*z* = 286.0 $[M + NH_4]^+$.

HRMS (MALDI): *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{10}F_2O_4$ + Na: 291.0439; found: 291.0443.

(6*R*)-5,5-Difluoro-6-(hydroxymethyl)-5,6-dihydro-2*H*-pyran-2-ol (19)

To a solution of lactone **18** (122 mg, 0.46 mmol) in anhyd CH_2Cl_2 (5 mL) was added DIBAL-H (2 mL, 1.0 M in toluene) at –78 °C. The mixture was stirred for 1 h at the same temperature, and then MeOH (7 mL) was added. The mixture was warmed to r.t. and filtered. The filtrate was dried (Na_2SO_4), filtered, and the solvent was removed in vacuo. The residue was purified by flash silica gel column chromatography (PE–EtOAc, 1:2) to give **19** (53 mg, 70%) as a white solid.

IR (film): 3204, 1387, 1158, 1103, 1073, 1053, 1025, 937, 868, 789, 754 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 6.17 (dd, *J* = 9.9, 2.7 Hz, 1 H), 5.89 (t, *J* = 9.0 Hz, 1 H), 5.34–5.28 (m, 1 H), 4.21(dq, *J* = 7.2, 3.9 Hz, 1 H), 3.83 (dd, *J* = 12.0, 3.3 Hz, 1 H), 3.70–3.59 (m, 1 H).

^{13}C NMR (75.5 MHz, CD_3OD): δ (major product) = 135.2 (t, *J* = 6.7 Hz), 123.0 (dd, *J* = 23.0, 19.6 Hz), 113.5 (dd, *J* = 182.6, 175.3 Hz), 87.5, 70.5 (dd, *J* = 23.0, 18.6 Hz), 58.4 (d, *J* = 5.1 Hz); δ (minor product) = 138.1 (t, *J* = 7.3 Hz), 123.6 (t, *J* = 21.4 Hz), 113.5 (dd, *J* = 182.6, 175.3 Hz), 91.5, 76.3 (t, *J* = 19.6 Hz), 58.5 (d, *J* = 3.9 Hz).

^{19}F NMR (282 MHz, CD_3OD): δ (major product) = –109.18 (dd, *J* = 278.6, 21.7 Hz, 1 F), –114.02 (ddd, *J* = 279.5, 9.0, 3.1 Hz, 1 F); δ (minor product) = –102.34 (dd, *J* = 274.9, 6.5 Hz, 1 F), –107.60 (ddd, *J* = 274.1, 11.3, 6.8 Hz, 1 F).

MS (MALDI): *m*/*z* = 225.1 $[M + CH_3COO]^-$.

[(2*R*)-3,3-Difluoro-6-hydroxy-3,6-dihydro-2*H*-pyran-2-yl]methyl Benzoate (17)

To a solution of diol **19** (70 mg, 0.42 mmol) in anhyd CH_2Cl_2 (6 mL) was slowly added pyridine (1 mL) followed by BzCl (55 μL) at –78 °C. After stirring the mixture for 1 h at the same temperature, MeOH (2 mL) was added and the mixture was stirred for another 30 min. The mixture was washed sequentially with aq 1 N HCl (5 mL), sat. aq $NaHCO_3$ (3 mL), and brine (3 mL). The resultant organic layer was dried (Na_2SO_4), filtered, and the solvent was removed in vacuo. The residue was purified by flash silica gel column chromatography (PE–EtOAc, 4:1) to give **17** (99 mg, 87%) as a clear oil.

IR (film): 3500, 1725, 1453, 1281, 1103, 1027, 712 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 6.0 Hz, 2 H), 7.60 (t, *J* = 7.2 Hz, 1 H), 7.45 (t, *J* = 7.8 Hz, 2 H), 6.26–6.19 (m, 1 H), 6.05 (t, *J* = 9.9 Hz, 1 H), 5.56 (t, *J* = 3.3 Hz, 0.8 H), 5.49 (t, *J* = 5.7 Hz, 0.2 H), 4.77–4.55 (m, 3 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ (major product) = 166.6, 134.2 (t, *J* = 7.0 Hz), 133.3, 129.4, 128.6, 128.5, 128.4, 124.0 (dd, *J* = 22.9, 19.2 Hz), 88.1, 68.3 (dd, *J* = 23.1, 18.3 Hz), 61.2 (d, *J* = 4.9 Hz); δ (minor product) = 166.6, 136.9 (t, *J* = 7.0 Hz), 133.4, 130.0, 129.9, 129.7, 129.5, 124.4 (t, *J* = 22.0 Hz), 91.8, 73.6 (t, *J* = 42.1 Hz), 61.4 (d, *J* = 3.6 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ (major product) = –109.99 (dd, *J* = 258.9, 20.6 Hz, 1 F), –114.27 (dd, *J* = 269.5, 9.6 Hz, 1 F); δ (minor product) = –105.15 (dm, *J* = 271.8 Hz, 1 F), –106.38 (dm, *J* = 279.2 Hz, 1 F).

MS (MALDI): *m*/*z* = 288.2 $[M + NH_4]^+$.

HRMS (MALDI): *m*/*z* $[M^+]$ calcd for $C_{13}H_{12}F_2O_4$: 270.0704; found: 270.0709.

[(2*R*)-6-(*tert*-Butoxycarbonyloxy)-3,3-difluoro-3,6-dihydro-2*H*-pyran-2-yl]methyl Benzoate (20)

Lactol **17** (100 mg, 0.37 mmol) was dissolved in CH_2Cl_2 (8 mL) and the solution was cooled to 0 °C. A solution of $(Boc)_2O$ (92 mg, 0.42 mmol) and DMAP (20 mg) in CH_2Cl_2 (2 mL) was added to the mixture. The mixture was stirred at r.t. for 4 h. After concentration, the crude product was purified by flash silica gel column chromatography (PE–EtOAc, 10:1) to give **20** (123 mg, 90%) as a clear oil.

IR (film): 2983, 1756, 1729, 1454, 1396, 1372, 1329, 1278, 1257, 1158, 1110, 1068, 953, 849, 712 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 6.0 Hz, 2 H), 7.60 (t, *J* = 7.2 Hz, 1 H), 7.45 (t, *J* = 7.8 Hz, 2 H), 6.26–6.13 (m, 3 H), 4.80–4.48 (m, 3 H), 1.46 (s, 9 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ (major product) = 151.6, 133.1, 131.2 (t, *J* = 7.0 Hz), 128.4, 128.3, 125.8 (dd, *J* = 23.2, 19.0 Hz), 89.0, 83.5, 70.0 (dd, *J* = 23.2, 18.3 Hz), 60.6 (d, *J* = 5.2 Hz); δ (minor product) = 166.0, 133.1, 132.8 (t, *J* = 7.0 Hz), 129.8, 129.7, 129.6, 125.1 (t, *J* = 21.4 Hz), 90.0, 83.6, 73.4 (dd, *J* = 23.2, 19.3 Hz), 61.7 (d, *J* = 5.2 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ (major product) = –109.99 (ddd, *J* = 260.9, 21.6, 2.3 Hz, 1 F), –114.27 (dd, *J* = 273.0, 8.5 Hz, 1 F); δ (minor product) = –98.24 (dm, *J* = 265.9 Hz, 1 F), –109.45 (dm, *J* = 273.8 Hz, 1 F).

MS (MALDI): *m*/*z* = 388.2 $[M + NH_4]^+$.

HRMS (MALDI): *m*/*z* $[M^+]$ calcd For $C_{18}H_{20}F_2O_6$: 370.1228; found: 370.1245.

[(2*R*,6*R*)-6-(6-Chloro-7*H*-purin-7-yl)-3,3-difluoro-3,6-dihydro-2*H*-pyran-2-yl]methyl Benzoate (10) and [(2*R*,6*S*)-6-(6-Chloro-7*H*-purin-7-yl)-3,3-difluoro-3,6-dihydro-2*H*-pyran-2-yl]methyl Benzoate (21)

To a solution of compound **20** (130 mg, 0.35 mmol) and 6-chloropurine (105 mg, 0.68 mmol) in THF (10 mL) was added $Pd(PPh_3)_4$ (20 mg, 5 mmol%) and PPh_3 (9 mg, 10 mmol%). The mixture was stirred at 60 °C for 5 h and then cooled to r.t. After concentration, the crude product was purified by flash silica gel column chromatography (PE–EtOAc, 1:1) to give **21** (55 mg, 39%) and **10** (14 mg, 10%) as foams.

10

$[\alpha]_D^{26}$ +53.7 (*c* 0.65, $CHCl_3$).

IR (film): 3116, 1724, 1590, 1564, 1397, 1337, 1272, 1158, 1093, 1052, 948, 831, 711, 636, 566 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.76 (s, 1 H), 8.24 (s, 1 H), 8.02 (d, *J* = 8.1 Hz, 2 H), 7.57 (t, *J* = 8.1 Hz, 1 H), 7.43 (t, *J* = 7.2 Hz, 2 H), 6.76 (t, *J* = 4.8 Hz, 1 H), 6.45–6.37 (m, 2 H), 4.82–4.79 (m, 1 H), 4.59–4.47 (m, 2 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 171.3, 157.7, 156.6 (d, *J* = 39.9 Hz), 148.0, 138.6, 137.5 (t, *J* = 6.7 Hz), 136.7, 134.9, 134.5, 133.6, 132.8 (dd, *J* = 23.6, 20.2 Hz), 117.2 (dd, *J* = 184.3, 179.2 Hz), 81.9, 80.6 (dd, *J* = 23.6, 19.6 Hz), 65.8 (d, *J* = 4.5 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –106.14 (ddd, *J* = 282.8, 18.0, 7.9 Hz, 1 F), –107.90 (dt, *J* = 283.1, 4.5 Hz, 1 F).

MS (MALDI): *m*/*z* = 407.0 $[M + H]^+$.

HRMS (MALDI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{14}ClF_2N_4O_3$: 407.0717; found: 407.0727.

21

$[\alpha]_D^{26}$ –47.7 (*c* 0.17, MeOH).

IR (film): 2926, 1724, 1591, 1565, 1338, 1276, 1197, 1160, 1096, 1053, 947, 832, 711, 636, 565 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.72 (s, 1 H), 8.21 (s, 1 H), 8.06 (d, *J* = 6.0 Hz, 2 H), 7.60 (t, *J* = 7.2 Hz, 1 H), 7.45 (t, *J* = 7.8 Hz, 2 H), 6.71–6.51 (m, 3 H), 4.70–4.56 (m, 2 H), 4.40–4.30 (m, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 165.7, 152.6, 151.5 (d, *J* = 11.0 Hz), 143.2, 133.3, 131.9, 129.6 (t, *J* = 6.9 Hz), 129.3, 129.0, 128.3, 128.0 (d, *J* = 3.2 Hz), 127.8, 112.0 (dd, *J* = 184.8, 178.1 Hz), 76.0, 70.9 (dd, *J* = 23.5, 18.9 Hz), 60.1 (d, *J* = 4.6 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –109.42 (dd, *J* = 268.7, 16.1 Hz, 1 F), –111.89 (ddd, *J* = 272.7, 7.3, 3.4 Hz, 1 F).

MS (MALDI): *m*/*z* = 407.0 $[M + H]^+$.

HRMS (MALDI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{14}ClF_2N_4O_3$: 407.0717; found: 407.0717.

[(2*R*,6*S*)-6-(6-Amino-7*H*-purin-7-yl)-3,3-difluoro-3,6-dihydro-2*H*-pyran-2-yl]methanol (4)

Methanolic ammonia (20 mL) was added to compound **21** (49 mg, 0.12 mmol) and the mixture was stirred overnight at 80 °C. After evaporation of the solvent, the crude product was purified by flash silica gel column chromatography (MeOH–EtOAc, 1:10) to give **4** (27 mg, 80%) as a white solid; mp 172–174 °C; $[\alpha]_D^{24}$ –88.3 (*c* 0.25, MeOH).

IR (film): 1650, 1601, 1475, 1172, 1151, 1094, 1036, 836 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 8.23 (s, 1 H), 8.20 (s, 1 H), 6.65–6.38 (m, 3 H), 4.19–4.07 (m, 1 H), 3.97–3.68 (m, 2 H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 156.6, 153.5, 149.9, 140.4, 132.8 (t, *J* = 11.6 Hz), 126.0 (t, *J* = 29.4 Hz), 119.4, 114.4, 75.3, 73.7 (t, *J* = 28.4 Hz), 58.1.

^{19}F NMR (282 MHz, CD_3OD): δ = –110.77 (ddd, *J* = 256.6, 19.5, 4.8 Hz, 1 F), –113.95 (ddd, *J* = 268.7, 9.6, 4.5 Hz, 1 F).

MS (MALDI): *m*/*z* = 306.2 $[M + Na]^+$.

HRMS (MALDI): *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{11}F_2N_5O_2$ + Na: 306.0773; found: 306.0774.

Crystal Data[17]

$C_{11}H_{11}F_2N_5O_2$, *M* = 283.25, orthorhombic, space group $P2_12_12_1$, *a* = 6.3537(8) Å, *b* = 12.6258(15) Å, *c* = 15.2441(17) Å, *V* = 1222.9 (3) $Å^3$, *Z* = 4, *Dx* = 1.538 $mg·m^{-3}$, Absorption coefficient 0.131 mm^{-1}, *F*(000) = 584, Crystal size 0.468 × 0.395 × 0.201 mm^3, 6951 reflections collected [*R*(int)] = 0.1288, 1477 unique, *wR*2 = 0.1291, *R* = 0.0561 on *I* values of 1419 diffraction with *I* > 2*s*(*I*); *R* = 0.0577, *wR*2 = 0.1309 for all data and 191 parameters. Unit cell determination and intensity data collection (qmax = 26.49°) were performed on a Bruker SMART APEX2 at 293 (2) K. The structure was solved by direct method and refined by the full-matrix least-squares on F^2.

[(2*R*,6*R*)-6-(6-Amino-7*H*-purin-7-yl)-3,3-difluoro-3,6-dihydro-2*H*-pyran-2-yl]methanol (3)

Using the same conditions as described for compound **4**, compound **3** (7 mg, 73%) was prepared as a white solid from compound **10** (14 mg, 0.03 mmol); mp 109–110 °C; $[\alpha]_D^{24}$ +14.0 (*c* 0.05, MeOH).

IR (film): 1657, 1602, 1575, 1171, 1146, 1087, 1036, 841 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 8.24 (s, 1 H), 8.14 (s, 1 H), 6.66 (t, *J* = 6.0 Hz, 1 H), 6.60 (d, *J* = 22.3 Hz, 1 H), 6.39 (t, *J* = 8.7 Hz, 1 H), 4.28–4.19 (m, 1 H), 3.95 (dd, *J* = 12.0, 2.7 Hz, 1 H), 3.70 (dd, *J* = 12.3, 4.2 Hz, 1 H).

^{19}F NMR (282 MHz, CD_3OD): δ = –107.65 (ddd, *J* = 252.7, 17.2, 8.2 Hz, 1F), –109.1 (dm, *J* = 262.3 Hz, 1 F).

MS (MALDI): *m*/*z* = 284.0 $[M + H]^+$.

HRMS (MALDI): *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{11}F_2N_5O_2$ + Na: 306.0773; found: 306.0778.

[(2*R*,6*S*)-6-(6-Amino-7*H*-purin-7-yl)-3,3-difluorotetrahydro-2*H*-pyran-2-yl]methanol (2)

A suspension of Pd/C (12 mg) and compound **4** (20 mg, 0.07 mmol) in MeOH–EtOAc (5 mL:5 mL) was stirred under H_2 for 26 h at r.t. Filtration and removal of the solvent gave the crude product, which was purified by flash silica gel column chromatography (MeOH–EtOAc = 1:10) to give **2** (18 mg, 90%) as a white solid; mp 234–236 °C; $[\alpha]_D^{24}$ +30.3 (*c* 0.22, MeOH).

IR (film): 2928, 1655, 1474, 1172, 1147, 1036, 840 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 8.24 (s, 1 H), 8.12 (s, 1 H), 6.21 (s, 1 H), 3.94–3.75 (m, 3 H), 2.85–2.76 (m, 1 H), 2.35–2.28 (m, 1 H).

^{13}C NMR (75.5 MHz, CD_3OD): δ = 167.2, 155.4, 152.0, 148.6, 139.1, 118.4 (t, *J* = 178.7 Hz), 77.9, 75.0 (t, *J* = 22.5 Hz), 57.8, 27.9 (t, *J* = 18.6 Hz), 24.7.

^{19}F NMR (282 MHz, CD_3OD): δ = –102.42 (dm, *J* = 210.7 Hz, 1 F), –114.12 (ddd, *J* = 206.1, 27.3, 13.3 Hz, 1 F).

MS (MALDI): *m*/*z* = 286.0 $[M + H]^{+\cdot}$

HRMS (MALDI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{14}F_2N_5O_2$: 286.1110; found: 286.1105.

[(2*R*,6*R*)-6-(6-Amino-7*H*-purin-7-yl)-3,3-difluorotetrahydro-2*H*-pyran-2-yl]methanol (1)

Using the same conditions as described for compound **2**, compound **1** (10 mg, 87%) was prepared as a white solid from compound **3** (11 mg, 0.04 mmol); mp 256–258 °C; $[\alpha]_D^{26}$ –4.4 (*c* 0.05, MeOH).

IR (film): 2920, 1652, 1475, 1170, 1144, 1033, 840 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 8.27 (s, 1 H), 8.14 (s, 1 H), 5.94 (d, *J* = 10.8 Hz, 1 H), 4.10–3.94 (m, 1 H), 3.83 (d, *J* = 12.6 Hz, 1 H), 3.64 (dd, *J* = 12.6, 7.8, 1 H), 2.55 (dd, *J* = 11.7, 5.7 Hz, 1 H), 2.37–2.18 (m, 3 H).

^{19}F NMR (282 MHz, CD_3OD): δ = –110.60 (d, *J* = 246.5 Hz, 1 F), –120.10 (dm, *J* = 174.3 Hz, 1 F).

MS (MALDI): *m*/*z* = 330.0 $[M + HCOO]^-$.

HRMS (MALDI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{14}F_2N_5O_2$: 286.1110; found: 286.1098.

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