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Synthesis of Carbocyclic 2′,3′-Dideoxy-2′-fluoro-3′-C-hydroxymethyl Nucleoside Analogues as Potential Inhibitors of HIV and HSV

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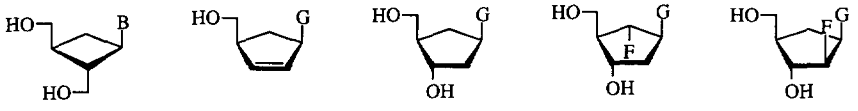
Abstract: The synthesis of four isomerically pure fluoro-carbocyclic adenosine and guanosine analogues is described. The 3*S*,4*S*-bis(*t*-butyldiphenylsilyloxymethyl)-2-fluoropentan-1-ol derivatives **22**, **23**, **24** and **25** synthesised from enantiomerically pure 3*S*,4*S*-bis(*t*-butyldiphenylsilyloxymethyl)-cyclopentanone (**18**), were coupled with chloropurines using the Mitsunobu procedure to give **10**, **11**, **12**, **14** and **16** or converted to their corresponding 1-amino derivatives, from which the fluoro-carbocyclic guanosine analogues **13**, **15** and **17** were prepared. Compounds **10-17** were evaluated as potential anti-viral agents but were found to be inactive.

INTRODUCTION

The design and synthesis of nucleoside analogues as anti-viral agents has over the years provided a number of drugs and drug candidates.[1-4] Among this class of compounds the carbocyclic nucleosides have emerged as particularly promising.[5,6] Compounds such as cyclobut A (**1**), cyclobut G (**2**) and carbovir (**3**) are active against the human immunodeficiency virus (HIV).[7-10] Carbocyclic 2′deoxyguanosine (**4**) and the carbocyclic fluorinated guanosine derivatives (**5**) and (**6**) are active against herpes virus (HSV-1 and HSV-2).[11,12]

Fig.1

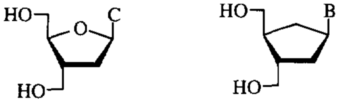


1: B=A **2**: B=G **3** **4** **5** **6**

A special feature of these compounds is the absence of a glycosidic linkage, which increases the metabolic stability against nucleoside phosphorylases and hydrolases, thereby prolonging their half-life *in vivo*.[13] The comparatively higher lipophilicity obtained by replacing the ring oxygen with a methylene group is also potentially beneficial for increased oral bioavailability and cell wall penetration. It has been observed for carbocyclic nucleoside analogues that anti-viral activity is predominantly confined to the purine series.

Previously 2′,3′-dideoxy-3′-C-hydroxymethyl cytidine (**7**) was reported to be a potent inhibitor of HIV-1 *in vitro* and a broad spectrum antiviral agent.[14-16] The carbocyclic analogues of 2′,3′-dideoxy-3′-C-hydroxymethyl cytidine (**7**), *i.e* **8** and **9**, have been synthesised but were found to be devoid of anti-HIV activity.[17]

Fig. 2

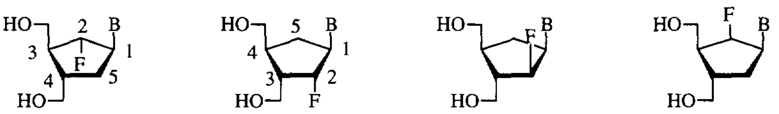


7

8: B=A
9: B=G

In this paper the structure - antiviral activity relationship of compounds **8** and **9** is further explored. In order to retain some of the electro negativity of the ring oxygen in **7**, fluoro substituents were introduced into the carbocyclic ring, resulting in compounds **10-17**, which have been synthesised and evaluated for their antiviral activity.

Fig. 3



10: B=Adenin-9-yl
11: B=Guanin-9-yl

12: B=Adenin-9-yl
13: B=Guanin-9-yl

14: B=Adenin-9-yl
15: B=Guanin-9-yl

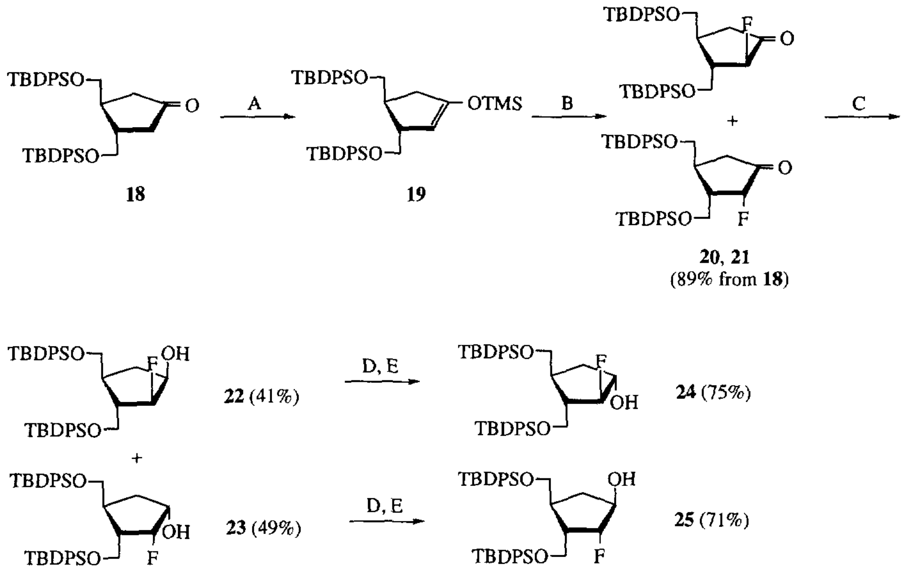
16: B=Adenin-9-yl
17: B=Guanin-9-yl

RESULTS AND DISCUSSION

Chemistry. (3*S*,4*S*)-Bis(*t*-butyldiphenylsilyloxymethyl)-cyclopentanone (**18**)[18,19] was reacted with trimethylsilyl triflate and triethylamine in toluene to give the silylenol ether **19**, which after aqueous workup was reacted with F-TEDA-BF_4 (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)) in dimethylformamide to give an inseparable 1:1 mixture of the fluoroketones **20** and **21** in 89% yield.[20] Stereoselective reduction of the ketones using LS-selectride in tetrahydrofuran at -78 °C gave two diastereomeric alcohols which were separated by column chromatography to give **22** and **23** in 41% and 49% yields, respectively.[21] The hydroxyls at C-1 in **22** and **23** were inverted using the Mitsunobu reaction with benzoic acid as nucleophile, followed by debenzoylation to give **24** and **25** in 75% and 71% yield, respectively.[22]

For the synthesis of the adenosine derivatives **10**, **12**, **14** and **16**, compounds **22**, **23**, **24** and **25** were first coupled with 6-chloropurine using the Mitsunobu procedure,[22] then reacted with methanolic ammonia in a sealed steel-vessel at 80 °C, followed by deprotection using tetrabutylammonium fluoride in tetrahydrofuran to give compounds **10**, **12**, **14** and **16** in 64%, 22%, 37% and 20% yields, respectively, from the alcohols.[23] It was noted that alcohols **23**, **24** and **25** were less reactive than **22** in the Mitsunobu reaction and that most of the material that was not converted to product was recovered as unreacted alcohols.

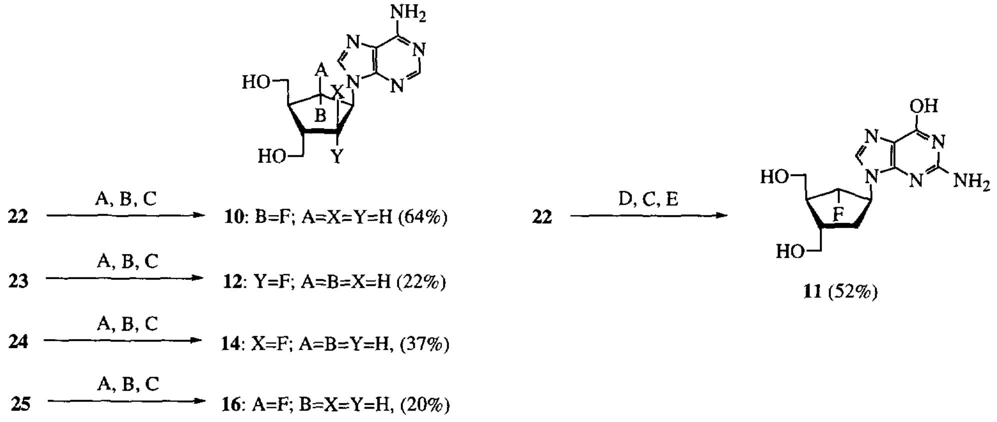
Scheme 1



A: TMSOTf, Et_3N, toluene, reflux; **B**: F-TEDA-BF_4, DMF; **C**: LS-selectride, THF, -78 °C; **D**: BzOH, Ph_3P-DIAD, THF; **E**: NaOMe, MeOH, CH_2Cl_2.

For the synthesis of the corresponding guanosine derivatives **11**, **13**, **15** and **17** couplings of **22**, **23**, **24** and **25** with 2-amino-6-chloropurine under the same conditions (*vide supra*) were examined. In these reactions only alcohol **22** gave the desired product in 67% yield, which was desilylated using tetrabutylammonium fluoride in tetrahydrofuran, and further reacted with 80% formic acid at 80 °C followed by 25% ammonium hydroxide in methanol to give compound **11** in 52% yield from **22**.[24] For the couplings of **23**, **24** and **25** most of the material was recovered as unreacted alcohols.

Scheme 2



A: 6-Chloropurine, Ph_3P-DIAD, THF; **B**: NH_3, MeOH, dioxane, 80 °C; **C**: $Bu_4N^+F^-$, THF; **D**: 2-Amino-6-chloropurine, Ph_3P-DIAD, THF; **E**: HCO_2H, 80 °C then 25% NH_4OH, MeOH.

For the synthesis of the guanosine derivatives **13**, **15** and **17** another strategy was adopted, in which the guanine moiety was synthesised *de novo* from the corresponding cyclopentylamines.[11] Thus alcohols **23**, **24** and **25** were converted to their corresponding azides and desilylated (*vide supra*) to give azides **26**, **27** and **28** in 75%, 68% and 74% yields, respectively.[25]

Scheme 3

$$\mathbf{23} \xrightarrow{\text{A, B}} \mathbf{26}\text{: Y=F; A=B=X=H (75\%)} \xrightarrow{\text{C, D, E, F, G, H}} \mathbf{13}\text{: Y=F; A=B=X=H (27\%)}$$

$$\mathbf{24} \xrightarrow{\text{A, B}} \mathbf{27}\text{: X=F; A=B=Y=H (68\%)} \xrightarrow{\text{C, D, E, F, G, H}} \mathbf{15}\text{: X=F; A=B=Y=H (24\%)}$$

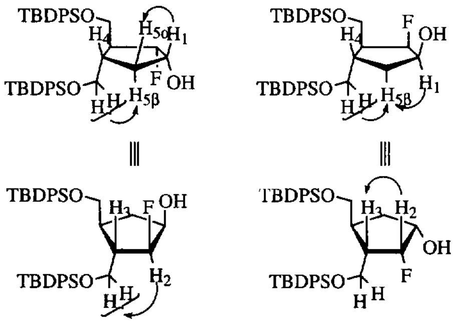
$$\mathbf{25} \xrightarrow{\text{A, B}} \mathbf{28}\text{: A=F; B=X=Y=H (74\%)} \xrightarrow{\text{C, D, E, F, G, H}} \mathbf{17}\text{: A=F; B=X=Y=H (20\%)}$$

A: $(PhO)_2PON_3$, Ph_3P-DIAD, THF; **B**: $Bu_4N^+F^-$, THF; **C**: H_2, Pd-C, EtOH, **D**: 2-amino-4,6-dichloropyrimidine, Et_3N, BuOH, reflux; **E**: $4\text{-ClC}_6H_4N_2^+Cl^-$, H_2O, AcOH, NaOAc; **F**: Zn, AcOH, EtOH, reflux; **G**: $HC(OMe)_3$, HCl, DMF; **H**: 0.6 M HCl, reflux.

The azides **26**, **27** and **28** were reduced by catalytic hydrogenation to the corresponding amines, which were condensed with 2-amino-4,6-dichloropyrimidine in refluxing *n*-butanol in the presence of triethylamine, followed by azo-coupling using (4-chlorophenyl)diazonium chloride and reduction of the resulting diazo compound with zinc and acetic acid in a mixture of ethanol and water. Ring closure with trimethyl orthoformate in dimethylformamide in the presence of a catalytic amount of hydrochloric acid, followed by removal of the N-formates and simultaneous introduction of the 6-hydroxyl group by refluxing in diluted hydrochloric acid, gave the desired target compounds **13**, **15** and **17** in 27%, 24% and 20% yields, respectively, from the azides.

Configuration Assignments. COSY experiments were performed to interpret the proton NMR spectra of **22** and **23**. The stereochemistry assignments at C-1 and C-2 were based on NOE and NOESY experiments. Significant NOE values were found in **22** between the C-4-silyloxymethyl protons and H-5_β and

Fig. 4



22 **23**

between H-1 and H-5$_{\alpha}$, whereas in **23** the NOE values were found between the C-4-silyloxymethyl protons and H-5$_{\beta}$ and between H-1 and H-5$_{\beta}$. This shows that the C-4-silyloxymethyl and C-1-OH have a cis-relationship in **22** and a trans-relationship in **23**. The configuration at C-2 was determined from that only **22** showed NOE between H-2 and C-3-silyloxymethyl protons. Also the NOE between H-2 and H-3 in **22** was very small compared to the same NOE in **23**.

Additional confirmation of the configurations comes from a small fluorine coupling (2.0-2.2 Hz) to H-8 in the purine base, in **14**, **15**, **16** and **17** where the fluorine and base have a cis relationship.[12]

Biological Results. Compounds **10-17** were tested in an XTT assay[26] for anti HIV-1 activity and cytopathic effects and in a similar assay for anti HSV-1 effect [27] but all were found to be inactive in these assays.

EXPERIMENTAL SECTION

General procedures. All solvents were distilled prior to use. Thin layer chromatography was performed using silica gel 60 f-254 (Merck) plates with detection by UV, charring with 8% sulphuric acid, ninhydrin or ammoniummolybdate-cerium(IV)sulfate-10% sulphuric acid (100 g - 2 g - 2 l). Column chromatography was performed on silica gel (Matrix Silica Si 60A, 35-70 m, Amicon). Organic phases were dried over anhydrous sodium sulphate. Concentrations were performed under reduced pressure. Optical rotations were recorded on a Perkin Elmer 241 polarimeter. NMR spectra were recorded on a JEOL GSX-270 instrument, shifts are given in ppm downfield from tetramethylsilane in $CDCl_3$ and CD_3OD, and from acetone (δ_H: 2.23, δ_C: 31.04) in D_2O.

3*S*,4*S*-Bis(*t*-butyldiphenylsilyloxymethyl)-2*S*-fluorocyclopenta-none (20) and 3*S*,4*S*-Bis(*t*-butyldiphenylsilyloxymethyl)-2*R*-fluoro-cyclopentanone (21). To a refluxing solution of *3S,4S-bis(t-butyldiphenyl-silyloxymethyl)cyclopentanone* (**18**) (5.8 g, 9.3 mmol) and triethylamine (44 mL, 316.2 mmol) in toluene (17 mL) under argon, trimethylsilyl triflate (3.4 mL, 18.6 mmol) was added. After 15 min the reaction mixture was cooled to room temperature, diluted with toluene (100 mL) and washed with sat. aqueous $NaHCO_3$ (2 x 30 mL). The organic layer was dried and concentrated to give *3R,4S-bis(t-butyldiphenylsilyloxymethyl)-1-trimethylsilyloxy-1-cyclopentene* (**19**) as a syrup. This product was dissolved in DMF (120 mL) under argon and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (3.3 g, 9.3 mmol) was added. The mixture was stirred at room temperature for 15 min, then diluted with toluene (120 mL) and washed with water (2 x 100 mL). The organic layer was dried, concentrated and purified by column chromatography (toluene) to give the inseparable fluoroketones **20** and **21** as a colorless syrup (5.3 g, 8.3 mmol, 89%). Elemental analysis and NMR were performed on the mixture of **20** and **21**; (Found: C, 73.20; H, 7.35. Calc. for $C_{39}H_{47}O_3Si_2F$: C, 73.31; H, 7.41%); δ_H (270 MHz; $CDCl_3$) 1.00 (18 H, s, 6 CH_3), 2.13-2.60 (4 H, m, H-3, H-4, H-5), 3.46-3.89 (2 H, m, CH_2OSi), 3.64 (2 H, dd, CH_2OSi), 5.00-5.31 (1H, 2 dd, H-2), 7.05-7.75 (20 H, m, 4 Ph); δ_C (67 MHz; $CDCl_3$) 19.2 and 19.3 (2 C-Si), 26.7 and 26.8 (6 CH_3), 32.0 (C-5), 32.1 (C-5), 36.2 (C-4), 36.9 (C-4), 43.4 (C-3, d, $J_{C,F}$=17.1 Hz), 44.5 (C-3, d, $J_{C,F}$=14.7 Hz), 62.1 (CH_2OSi, d, $J_{C,F}$=7.3 Hz), 66.9 (CH_2OSi), 91.5 (C-2, d,

$J_{C,F}$=195.3 Hz), 92.7 (C-2, d, $J_{C,F}$=197.7 Hz), 127.7, 127.8, 129.8, 129.9, 132.6, 132.8, 133.0, 133.1, 135.5 and 135.7 (4 Ph), 210.6 (C-1, d, $J_{C,F}$=14.7 Hz) and 210.8 (C-1, d, $J_{C,F}$=15.6 Hz).

3*S*,4*S*-Bis(*t*-butyldiphenylsilyloxymethyl)-2*S*-fluorocyclopentan-1*R*-ol (22) and 3*S*,4*S*-bis(*t*-butyldiphenylsilyloxymethyl)-2*R*-fluoro-cyclopentan-1*S*-ol (23). The mixture of compounds **20** and **21** (7.3 g, 11.4 mmol) dissolved in THF (70 mL) was added dropwise to a solution of LS-selectride (13.8 mL, 1.0 M) in THF (70 mL) at -78 °C. After 2 h of vigorous stirring at -78 °C, the mixture was allowed to reach room temperature and was subsequently hydrolyzed with water (3 mL) and ethanol (8 mL). The organoborane was then oxidized with 3 M NaOH (10 mL) and 30% H_2O_2 (8 mL) during 2 h. Sat. aqueous NH_4OH (20 mL) was added, and the mixture was extracted with toluene (2 x 30 mL). The organic layer was dried, concentrated and purified by column chromatography (hexane-EtOAc 5:1) to give the two alcohols separated **22**; (3.0 g, 4.7 mmol, 41%) and **23** (3.6 g, 5.6 mmol, 49%). **22**; $[\alpha]_D$ +3.86° (c 1.24, $CHCl_3$); (Found: C, 73.27; H, 7.83. Calc. for $C_{39}H_{49}O_3Si_2F$: C, 73.08; H, 7.71%); δ_H (270 MHz; $CDCl_3$) 1.03 (18 H, s, 6 CH_3), 1.58-1.64 (1 H, m, H-5_β), 2.00-2-11 (2 H, m, H-4 and H-5_α) 2.18-2.32 (1 H, m, H-3), 2.20 (1 H, br, OH), 3.54-3.80 (2 H, m, CH_2OSi), 3.57 (2 H, d, CH_2OSi), 4.05-4.17 (1 H, dddd, H-1, J=4.3, 4.3, 8.6 and 16.0 Hz), 4.93-4.96 (1H, ddd, H-2, J=4.3, 4.3 and 54.0 Hz), 7.25-7.75 (20 H, m, 4 Ph); δ_C (67 MHz; $CDCl_3$) 19.2 and 19.3 (2 C-Si), 26.9 (6 CH_3), 33.7 (C-5), 38.0 (C-4), 47.0 (C-3, d, $J_{C,F}$=18.4 Hz), 63.3 (CH_2OSi, d, $J_{C,F}$=5.5 Hz), 66.7 (CH_2OSi), 72.7 (C-1, d, $J_{C,F}$=18.3 Hz), 96.9 (C-2, d, $J_{C,F}$=181.4 Hz), 127.6, 127.7, 129.6, 129.7, 133.2, 133.3, 133.4 and 135.6 (4 Ph). **23**; $[\alpha]_D$ +18.86° (c 1.25, $CHCl_3$); (Found: C, 73.20; H, 7.76. Calc. for $C_{39}H_{49}O_3Si_2F$: C, 73.08; H, 7.71%); δ_H (270 MHz; $CDCl_3$) 1.00 (18 H, s, 6 CH_3), 1.74-1.86 (1 H, m, H-5_β), 1.90-1.97 (1 H, m, H-5_α), 1.75 (1 H, br, OH), 1.98-2.10 (1 H, m, H-4), 2.13-2.33 (1 H, m, H-3), 3.49 (2 H, d, CH_2OSi), 3.65-3.82 (2 H, m, CH_2OSi), 4.11-4.26 (1 H, dddd, H-1, J=3.1, 8.2, 8.2 and 22.1 Hz) 4.90-5.13 (1H, ddd, H-2, J=3.1, 3.1 and 55.1 Hz), 7.25-7.75 (20 H, m, 4 Ph); δ_C (67 MHz; $CDCl_3$) 19.2 (2 C-Si), 26.8 and 26.9 (6 CH_3), 33.9 (C-5), 39.3 (C-4), 45.7 (C-3, d, $J_{C,F}$=18.4 Hz), 62.0 (CH_2OSi, d, $J_{C,F}$=9.2 Hz), 66.4 (CH_2OSi), 76 (C-1, d, $J_{C,F}$=18.3 Hz), 96.3 (C-2, d, $J_{C,F}$=177.8 Hz), 127.6, 129.7, 133.3, 133.4, 133.5 and 135.6 (4 Ph).

3*S*,4*S*-Bis(*t*-butyldiphenylsilyloxymethyl)-2*S*-fluorocyclopentan-1*S*-ol (24). To a solution of triphenylphosphine (810 mg, 3.0 mmol) in THF (14 mL) under argon at 0 °C, diisopropyl azodicarboxylate (DIAD) (1.0 mL, 3.0 mmol) was added dropwise during 15 min and the mixture was stirred for 30 min to yield a white precipitate of triphenylphosphine-DIAD complex. A solution of benzoic acid (370 mg, 3.0 mmol) and **22** (1.3 g, 2.0 mmol) in THF (11 mL) was added and the mixture was stirred at room temperature for 20 h, concentrated and purified by column chromatography (toluene) to give the *3S,4S-bis(t-butyldiphenylsilyloxymethyl)-1S-O-benzoyl-2S-fluorocyclopentane* (1.4 g, 1.9 mmol, 95%). NaOMe (0.4 mL, 1 M) was added to a solution of this compound in CH_2Cl_2 (8 mL) and MeOH (8 mL). The mixture was stirred at room temperature for 16 h, concentrated and purified by column chromatography (toluene) to give **24** (940 mg, 1.5 mmol, 75% from **22**), $[\alpha]_D$ +5.29° (c 1.40, $CHCl_3$); (Found: C, 72.86; H, 7.82. Calc. for $C_{39}H_{49}O_3Si_2F$: C, 73.08; H, 7.71%); δ_H (270 MHz; $CDCl_3$) 1.00 and 1.05 (18 H, 2 s, 6 CH_3), 1.76-1.94 (2 H, m, H-5), 2.08-2-24 (1 H, m, H-3) 2.28-2.38 (1 H, m, H-4), 2.30 (1 H, br, OH) 3.58 (2 H, d, CH_2OSi), 3.59-3.84 (2 H, m, CH_2OSi), 4.19-4.29 (1 H, dddd, H-1, J=4.2, 4.7, 5.1 and 12.5, Hz) 4.69-4.91 (1H, ddd, H-2, J=3.7, 4.2 and 52.4 Hz), 7.25-7.75 (20 H, m, 4 Ph); δ_C (67 MHz; $CDCl_3$) 19.2 (2 C-Si), 26.9 (6

CH_3), 34.4 (C-5), 38.9 (C-4), 48.4 (C-3, d, $J_{C,F}$=20.2 Hz), 63.8 (CH_2OSi, d, $J_{C,F}$=7.3 Hz), 66.4 (CH_2OSi), 75.4 (C-1, d, $J_{C,F}$= 25.7 Hz), 100.9 (C-2, d, $J_{C,F}$=181.5 Hz), 127.7, 127.8, 129.6, 129.9, 132.8, 132.9, 133.5 and 135.6 (4 Ph).

3*S*,4*S*-Bis(*t*-butyldiphenylsilyloxymethyl)-2*R*-fluorocyclopentan-1*R*-ol (25). Compound **25** was prepared from **23** (1.8 g, 2.8 mmol) via *3S,4S-bis(t-butyldiphenylsilyloxymethyl)-1R-O-benzoyl-2R-fluorocyclopentane* (2.0 g, 2.7 mmol, 96%) in the same manner as described for compound **24** to afford the title compound in 71% yield from **23**. (1.3 g, 2.0 mmol), $[\alpha]_D$ +17.78° (c 0.90, $CHCl_3$); (Found: C, 72.98; H, 7.66. Calc. for $C_{39}H_{49}O_3Si_2F$: C, 73.08; H, 7.71%); δ_H (270 MHz; $CDCl_3$) 1.00 and 1.05 (18 H, 2 s, 6 CH_3), 1.52 (1 H, br, OH), 1.65 (1 H, dd, H-5$_\beta$), 1.97-2.05 (1 H, m, H-4), 2.50-2.67 (1 H, m, H-3), 3.60 (2 H, d, CH_2OSi), 3.65-3.91 (2 H, m, CH_2OSi), 4.18 (1 H, dd, H-1, J=6.0 and 6.0 Hz) 4.86-5.05 (1H, dd, H-2, J=3.7 and 51.7 Hz), 7.25-7.75 (20 H, m, 4 Ph); δ_C (67 MHz; $CDCl_3$) 19.2 (2 C-Si), 26.8 and 26.9 (6 CH_3), 35.1 (C-5), 40.3 (C-4), 45.4 (C-3, d, $J_{C,F}$=18.3 Hz), 62.1 (CH_2OSi, d, $J_{C,F}$=11.0 Hz), 66.4 (CH_2OSi), 74.5 (C-1, d, $J_{C,F}$=27.5 Hz), 99.0 (C-2, d, $J_{C,F}$=179.6 Hz), 127.6, 127.8, 129.6, 129.9, 132.5, 132.6, 133.5, 133.7, 135.5 and 135.6 (4 Ph).

3*S*,4*S*-Bis(hydroxymethyl)-1*R*-azido-2*R*-fluorocyclopentane (26). To a solution of triphenylphosphine (1.1 g, 4.1 mmol) in THF (11 mL) under argon at 0 °C, DIAD (0.81 mL, 4.1 mmol) was added dropwise during 15 min and the mixture was stirred for 30 min at 0 °C to yield a white precipitate of triphenylphosphine-DIAD complex. A solution of **23** (1.3 g, 2.0 mmol) in THF (11 mL) was added and after 10 min diphenylphosphoryl azide (0.88 mL, 4.1 mmol) was added where after the mixture was allowed to reach room temperature and stirred for 20 h, concentrated and purified by column chromatography (hexane-EtOAc 10:1) to give *3S,4S-bis(t-butyldiphenylsilyloxymethyl)-1R-azido-2R-fluorocyclopentane* (1.3 g, 1.9 mmol, 95%). To a stirred solution of this compound in THF (40 mL) a 1.1 M solution of tetrabutylammonium fluoride in THF (3.8 mL) was added and after 3 h at room temperature, water (2 mL) was added, the mixture was concentrated to 2 mL, and passed through a pad of Dowex® 50 WX 8 (Na^+) ion exchange resin and purified by column chromatography ($CHCl_3$-MeOH 9:1) to give **26** (285 mg, 1.5 mmol, 75% from **23**), $[\alpha]_D$ +58.78° (c 0.98, $CHCl_3$); IR ($CHCl_3$) υ_{max} 3650-3200, 3100-2800, 2340, 2100 (N_3), 1220 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.37-1.46 and 2.00-2.42 (4 H, 2 m, H-3, H-4, H-5), 3.42-3.93 (4 H, m, 2 CH_2OH), 3.99-4.11 (1 H, dddd, H-1, J=2.3, 4.6, 6.6, and 17.2, Hz) 4.79-4.99 (1H, dd, H-2, J=2.3 and 52.0 Hz); δ_C (67 MHz; $CDCl_3$) 32.1 (C-5), 42.9 (C-4), 49.3 (C-3, d, $J_{C,F}$=18.3 Hz), 60.9 (CH_2OH, d, $J_{C,F}$=9.1 Hz), 64.7 (C-1, d, $J_{C,F}$=27.5 Hz), 65.5 (CH_2OH), 99.1 (C-2, d, $J_{C,F}$=179.6 Hz).

3*S*,4*S*-Bis(hydroxymethyl)-1*R*-azido-2*S*-fluorocyclopentane (27). Compound **27** was prepared from **24** (375 mg, 0.59 mmol) in the same manner as described for compound **26** via *3S,4S-bis(t-butyldiphenylsilyloxymethyl)-1R-azido-2S-fluorocyclopentane* (325 mg, 0.49 mmol, 83%) to afford the title compound in 68% yield from **24** (75 mg, 0.40 mmol), $[\alpha]_D$ +1.33° (c 1.05, $CHCl_3$); IR ($CHCl_3$) υ_{max} 3650-3200, 3100-2800, 2340, 2100 (N_3), 1220 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.26-1.64 and 1.92-2.32 (4 H, 2 m, H-3, H-4, H-5), 3.51-3.83 (5 H, m, H-1, 2 CH_2OH), 4.64-4.87 (1H, ddd, H-2, J=4.8, 4.8 and 52.6 Hz); δ_C (67 MHz; $CDCl_3$) 29.7 (C-5), 40.8 (C-4), 49.7 (C-3, d, $J_{C,F}$=18.4 Hz), 61.4 (C-1, d, $J_{C,F}$=16.5 Hz), 63.0 (CH_2OH, d, $J_{C,F}$=3.7 Hz), 66.0 (CH_2OH), 96.3 (C-2, d, $J_{C,F}$=188.8 Hz).

3*S*,4*S*-Bis(hydroxymethyl)-1*S*-azido-2*R*-fluorocyclopentane (28).

Compound **28** was prepared from **25** (517 mg, 0.81 mmol) in the same manner as described for compound **26** via *3S,4S-bis(*t*-butyldiphenylsilyloxymethyl)-1S-azido-2R-fluorocyclopentane* (444 mg, 0.67 mmol, 83%) to afford the title compound in 74% yield from **25** (113 mg, 0.60 mmol), $[\alpha]_D$ -1.44° (c 1.25, $CHCl_3$); IR ($CHCl_3$) υ_{max} 3650-3200, 3100-2800, 2340, 2100 (N_3), 1220 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.77-2.35 (4 H, m, H-3, H-4, H-5), 3.38-3.94 (5 H, m, H-1, 2 CH_2OH), 4.93-5.16 (1H, ddd, H-2, J=3.3, 3.3 and 54.6 Hz); δ_C (67 MHz; $CDCl_3$) 29.7 (C-5), 41.6 (C-4), 48.8 (C-3, d, $J_{C,F}$=16.5 Hz), 61.3 (CH_2OH, d, $J_{C,F}$=11.0 Hz), 61.6 (C-1, d, $J_{C,F}$=18.3 Hz), 65.6 (CH_2OH), 97.2 (C-2, d, $J_{C,F}$=183.3 Hz).

6-Amino-9-[3′*S*,4′*S*-bis(hydroxymethyl)-2′*S*-fluorocyclopent-1′*S*-yl]-9*H*-purine (10). To a solution of triphenylphosphine (295 mg, 1.1 mmol) in THF (6 mL) under argon at 0 °C DIAD (221 µL, 1.1 mmol) was added dropwise during 10 min and the mixture was stirred for 30 min at 0 °C to yield a white precipitate of triphenylphosphine-DIAD complex. A suspension of 6-chloropurine (174 mg, 1.1 mmol) and **22** (478 mg, 0.75 mmol) in THF (12 mL) was added, the mixture was allowed to reach room temperature, then stirred for 20 h, concentrated and purified by column chromatography (toluene-EtOAc 3:1) to give *6-chloro-9-[3′S,4′S-bis(*t*-butyldiphenylsilyloxymethyl)-2′S-fluorocyclopent-1′S-yl]-9H-purine* (478 mg, 0.61 mmol, 81%). This compound was dissolved in dioxane (10 mL) and treated with sat. methanolic ammonia (30 mL) in a sealed steel-vessel at 80 °C. After 18 h the mixture was concentrated and purified by column chromatography ($CHCl_3$-MeOH 20:1) to give *6-amino-9-[3′S,4′S-bis(*t*-butyldiphenylsilyloxymethyl)-2′S-fluorocyclopent-1′S-yl]-9H-purine* (434 mg, 0.57 mmol, 93%). This compound was dissolved in THF (15 mL) and a 1.1 M solution of tetrabutylammonium fluoride in THF (1.1 mL) was added. After stirring for 3 h at room temperature, water (5 mL) was added, the mixture concentrated to 5 mL, washed with diethyl ether (2 x 15 mL) and the organic layer was extracted with water (10 mL). The aqueous layer was concentrated to 2 mL, passed through a pad of Dowex® 50 WX 8 (Na^+) ion exchange resin, desalted on a Sephadex® G-10 column and finally purified on a BioGel® P-2 column to give **10** as a white solid (136 mg, 0.48 mmol, 64% from **22**), $[\alpha]_D$ +22.05° (c 1.02, MeOH); (Found: C, 51.07; H, 5.60; N, 24.76. Calc. for $C_{12}H_{16}O_2N_5F$: C, 51.24; H, 5.73; N, 24.90%); δ_H (270 MHz; CD_3OD) 2.14-2.48 (4 H, m, H-3′, H-4′ and H-5′), 3.66 (2 H, dd, CH_2OH), 3.79 (2 H, dd, CH_2OH), 4.97-5.09 (1 H, dddd, H-1′, J=8.1, 8.2, 9.2 and 16.1 Hz) 5.28-5.55 (1 H, ddd, H-2′, J=8.1, 8.1 and 54.8 Hz), 8.22 (2 H, s, H-2 and H-8); δ_C (67 MHz; CD_3OD) 30.7 (C-5′, d, $J_{C,F}$=5.5 Hz), 39.5 (C-4′, d, $J_{C,F}$=5.5 Hz), 48.9 (C-3′, d, $J_{C,F}$=16.5 Hz), 60.8 (C-1′, d, $J_{C,F}$=20.2 Hz), 62.5 (CH_2OH), 65.6 (CH_2OH), 98.2 (C-2′, d, J=188.0 Hz), 120.7 (C-5), 141.6 (C-8), 151.0 (C-4), 153.7 (C-2) and 157.5 (C-6).

2-Amino-9-[3′*S*,4′*S*-bis(hydroxymethyl)-2′*S*-fluorocyclopent-1′*S*-yl]-9*H*-purine-6(1*H*)-one (11). To a solution of triphenylphosphine (249 mg, 0.95 mmol) in THF (5 mL) under argon at 0 °C, DIAD (187 µL, 0.95 mmol) was added dropwise during 10 min and the mixture was stirred for 30 min at 0 °C to yield a white precipitate of triphenylphosphine-DIAD complex. A suspension of 2-amino-6-chloropurine (161 mg, 0.95 mmol) and **22** (403 mg, 0.63 mmol) in THF (12 mL) was added, the mixture was allowed to reach room temperature, then stirred for 20 h, concentrated and purified by column chromatography (toluene-EtOAc 3:1) to give *2-amino-6-chloro-9-[3′S,4′S-bis(*t*-butyldiphenylsilyloxymethyl)-2′S-fluorocyclopent-1′S-*

*yl]-9*H*-purine* (334 mg, 0.42 mmol, 67%). This compound was dissolved in THF (10 mL) and a 1.1 M solution of tetrabutylammonium fluoride in THF (0.8 mL) was added. After stirring for 3 h at room temperature water (5 mL) was added, the mixture concentrated to 5 mL, washed with diethyl ether (2 x 15 mL) and the organic layer was extracted with water (10 mL). The aqueous layer was concentrated to 2 mL, passed through a pad of Dowex® 50 WX 8 (Na^+) ion exchange resin and desalted on a Sephadex® G-10 column to give *2-amino-6-chloro-9-[3′S,4′S-bis(hydroxymethyl)-2′S-fluorocyclopent-1′S-yl]-9*H*-purine* (111 mg, 0.35 mmol, 83%). This compound was dissolved in 80% HCO_2H (6 mL) and stirred at 80 °C for 2 h. The mixture was concentrated and dissolved in MeOH (6 mL) and 25% NH_4OH (0.8 mL). After stirring for 2 h the mixture was concentrated and the residue was dissolved in water (5 mL) and washed with diethylether (5 mL). The aqueous layer was concentrated and purified on a BioGel® P-2 column to give **11** as a white solid (97 mg, 0.33 mmol, 52% from **22**), $[\alpha]_D$ +18.72° (c 0.86, MeOH); (Found: C, 45.80; H, 5.64; N, 22.08. Calc. for $C_{12}H_{16}O_3N_5F$ * 1 H_2O: C, 45.71; H, 5.75; N, 22.03%); δ_H (270 MHz; CD_3OD) 2.12-2.36 (4 H, m, H-3′, H-4′ and H-5′), 3.61 (2 H, d, CH_2OH), 3.75 (2 H, dd, CH_2OH), 4.76-4.90 (1 H, dddd, H-1′, J=8.1, 8.2, 8.6 and 16.7 Hz) 5.23-5.49 (1 H, ddd, H-2, J=8.1, 8.1 and 54.9 Hz), 7.80 (1 H, s, H-8); δ_C (67 MHz; CD_3OD) 30.8 (C-5′, d, $J_{C,F}$=7.3 Hz), 39.5 (C-4′, d, $J_{C,F}$=5.5 Hz), 48.9 (C-3′, d, $J_{C,F}$=22.0 Hz), 60.6 (C-1′, d, $J_{C,F}$=22.0 Hz), 62.4 (CH_2OH), 65.6 (CH_2OH), 98.1 (C-2′, d, J=187.0 Hz), 118.3 (C-5), 138.5 (C-8), 153.0 (C-4), 155.1 (C-2) and 159.5 (C-6).

6-Amino-9-[3′*S*,4′*S*-bis(hydroxymethyl)-2′*R*-fluorocyclopent-1′*R*-yl]-9*H*-purine (12). Compound **12** was prepared from **23** (411 mg, 0.64 mmol) in the same manner as described for compound **10** with the intermediate products *6-chloro-9-[3′S,4′S-bis(*t*-butyldiphenylsilyloxymethyl)-2′R-fluorocyclopent-1′R-yl]-9*H*-purine* (157 mg, 0.20 mmol, 31%) and *6-amino-9-[3′S,4′S-bis(*t*-butyldiphenylsilyloxymethyl)-2′R-fluorocyclopent-1′R-yl]-9*H*-purine* (127 mg, 0.17 mmol, 85%) to afford the title compound in 22% yield from **23** (41 mg, 0.14 mmol), $[\alpha]_D$ +4.55° (c 1.10, MeOH); (Found: C, 51.12; H, 5.74; N, 24.83. Calc. for $C_{12}H_{16}O_2N_5F$: C, 51.24; H, 5.73; N, 24.90%); δ_H (270 MHz; CD_3OD) 2.08-2.57 (4 H, m, H-3′, H-4′ and H-5′), 3.70 (2 H, d, CH_2OH), 3.79 (2 H, dd, CH_2OH), 5.02-5.19 (1 H, dddd, H-1′, J=4.5, 8.8, 17.8 and 22.5 Hz) 5.32-5.57 (1 H, ddd, H-2, J=4.5, 6.6 and 52.9 Hz), 8.19 (1 H, s, H-8), 8.25 (1 H, s, H-2); δ_C (67 MHz; CD_3OD) 33.1 (C-5′, d, $J_{C,F}$=3.7 Hz), 43.0 (C-4′), 49.2 (C-3′, d, $J_{C,F}$=22.0 Hz), 60.8 (CH_2OH, d, $J_{C,F}$=11.0 Hz), 61.9 (C-1′, d, $J_{C,F}$=27.5 Hz), 64.9 (CH_2OH), 99.2 (C-2′, d, J=185.1 Hz), 120.6 (C-5), 141.4 (C-8), 150.8 (C-4), 153.7 (C-2) and 157.4 (C-6).

2-Amino-9-[3′*S*,4′*S*-bis(hydroxymethyl)-2′*R*-fluorocyclopent-1′*R*-yl]-9*H*-purine-6(1*H*)-one (13). A suspension of compound **26** (285 mg, 1.5 mmol) and Pd-C (80 mg) in EtOH (20 mL) was hydrogenated at ambient pressure overnight, filtered and concentrated to give *3′S,4′S-bis(hydroxymethyl)-2′R-fluorocyclopentyl-1′R-amine* (240 mg, 1.45 mmol, 97%). To a solution of this amine in triethylamine (1 mL) and *n*-BuOH (12 mL) was added 2-amino-4,6-dichloropyrimidine (362 mg, 2.2 mmol), the mixture was refluxed under argon for 5 h, concentrated and purified by column chromatography ($CHCl_3$-MeOH 5:1) to give *2,4-diamino-6-chloro-4*N*-[3′S,4′S-bis(hydroxymethyl)-2′R-fluorocyclopent-1′R-yl]-pyrimidine* (248 mg, 0.85 mmol, 59%). To a solution of this compound in water (7.3 mL), acetic acid (7.3 mL) and sodium acetate (1.9 g), a cold solution of 4-chlorobenzendiazonium chloride[28] was added dropwise. The reaction mixture was stirred overnight at room temperature, neutralized with sodium hydroxide (3 M), concentrated and purified by column chromatography ($CHCl_3$-MeOH 9:1) to give *5-[(*p*-chlorophenyl)-azo]-2,4-diamino-6-chloro-4*N*-[3′S,4′S-bis(hydroxymethyl)-2′R-fluorocyclopent-1′R-yl]-pyrimidine* as a yellow solid (282 mg, 0.66 mmol, 78%). A mixture of the 5-[(*p*-chlorophenyl)-azo]-pyrimidine, water (22 mL), EtOH (22 mL), acetic acid (0.45) and zinc dust (0.90 g) was refluxed under argon for 1 h. The mixture was filtered, concentrated and purified by column chromatography ($CHCl_3$-MeOH 5:1) giving *2,4,5-triamino-6-chloro-4*N*-[3′S,4′S-bis(hydroxymethyl)-2′R-fluorocyclopent-1′R-yl]-pyrimidine* (147 mg, 0.48 mmol, 73%). To a solution of the triamine in DMF (0.9 mL) and trimethyl orthoformate (1.8 mL) hydrochloric acid (0.14 mL, conc.) was added and the mixture was stirred at room temperature overnight. The solvent was removed, the crude product was dissolved in hydrochloric acid (2.5 mL 0.6 M) and refluxed for 1 h before pH was adjusted to 7 with sodium hydroxide (3 M). The mixture was concentrated and purified by column chromatography ($CHCl_3$-MeOH 2:1) and on a BioGel® P-2 column to give **13** as a white solid (122 mg, 0.41 mmol, 27% from **26**), $[\alpha]_D$ +7.52° (c 0.75, MeOH); (Found: C, 42.33; H, 5.90; N, 19.98. Calc. for $C_{12}H_{16}O_3N_5F * 2.5\ H_2O$: C, 42.10; H, 6.18; N, 20.46%); δ_H (270 MHz; CD_3OD) 1.98-2.52 (4 H, m, H-3′, H-4′ and H-5′), 3.70 (2 H, d, CH_2OH), 3.80 (2 H, dd, CH_2OH), 4.82-5.04 (1 H, dddd, H-1′, J=4.1, 8.1, 16.5 and 24.5 Hz) 5.28-5.51 (1 H, ddd, H-2, J=4.1, 5.6 and 52.8 Hz), 7.92 (1 H, s, H-8); δ_C (67 MHz; CD_3OD) 33.3 (C-5′, d, $J_{C,F}$=3.7 Hz), 42.9 (C-4′), 47.7 (C-3′, d, $J_{C,F}$=18.3 Hz), 60.6 (CH_2OH, d, $J_{C,F}$=11.0 Hz), 61.6 (C-1′, d, $J_{C,F}$=28.4 Hz), 64.6 (CH_2OH), 99.3 (C-2′, d, J=185.1 Hz), 118.6 (C-5), 138.2 (C-8), 152.8 (C-4), 154.9 (C-2) and 159.8 (C-6).

6-Amino-9-[3′*S*,4′*S*-bis(hydroxymethyl)-2′*S*-fluorocyclopent-1′*R*-yl]-9*H*-purine (14). Compound **14** was prepared from **24** (450 mg, 0.70 mmol) in the same manner as described for compound **10** with the intermediate products *6-chloro-9-[3′S,4′S-bis(*t*-butyldiphenylsilyloxymethyl)-2′S-fluorocyclopent-1′R-yl]-9*H*-purine* (245 mg, 0.32 mmol, 46%) and *6-amino-9-[3′S,4′S-bis(*t*-butyldiphenylsilyloxymethyl)-2′S-fluorocyclopent-1′R-yl]-9*H*-purine* (230 mg, 0.30 mmol, 94%) to afford the title compound in 37% yield from **24** (73 mg, 0.26 mmol), $[\alpha]_D$ +79.04° (c 1.04, MeOH); (Found: C, 48.68; H, 5.59; N, 23.71. Calc. for $C_{12}H_{16}O_2N_5F * 1\ H_2O$: C, 48.16; H, 6.06; N, 23.40%); δ_H (270 MHz; CD_3OD) 2.09-2.48 (4 H, m, H-3′, H-4′ and H-5′), 3.57-3.78 (4 H, m, 2 CH_2OH), 4.86-5.05 (1 H, m, H-1′) 4.99-5.20 (1 H, dd, H-2′, J=3.9 and 53.7 Hz), 8.21 (1 H, d, H-8, $J_{H,F}$=2.0 Hz), 8.23 (1 H, s, H-2); δ_C (67 MHz; CD_3OD) 32.7 (C-5′), 41.6 (C-4′), 51.4 (C-3′, d, $J_{C,F}$=18.3 Hz), 57.7 (C-1′, d, $J_{C,F}$=18.3 Hz), 63.2 (CH_2OH, d, $J_{C,F}$=11.0 Hz), 65.9 (CH_2OH), 97.1 (C-2′, d, J=181.5 Hz), 119.9 (C-5), 141.8 (C-8, d, $J_{C,F}$=3.7 Hz), 150.9 (C-4), 153.8 (C-2) and 157.4 (C-6).

2-Amino-9-[3′*S*,4′*S*-bis(hydroxymethyl)-2′*S*-fluorocyclopent-1′*R*-yl]-9*H*-purine-6(1*H*)-one (15). Compound **15** was prepared from **27** (75 mg, 0.40 mmol) in the same manner as described for compound **13** with the intermediate products *3′S,4′S-bis(hydroxymethyl)-2′S-fluorocyclopentyl-1′R-amine* (51 mg, 0.31 mmol, 78%), *2,4-diamino-6-chloro-4*N*-[3′S,4′S-bis(hydroxymethyl)-2′S-fluorocyclopent-1′R-yl]-pyrimidine* (56 mg, 0.19 mmol, 61%), *5-[(*p*-chlorophenyl)-azo]-2,4-diamino-6-chloro-4*N*-[3′S,4′S-bis(hydroxymethyl)-2′S-fluorocyclopent-1′R-yl]-pyrimidine* (64 mg, 0.15 mmol, 79%) and *2,4,5-triamino-6-chloro-4*N*-[3′S,4′S-bis(hydroxymethyl)-2′S-fluorocyclopent-1′R-yl]-pyrimidine* (35 mg, 0.11 mmol, 73%) to afford the title compound in 24% yield from **27** (29 mg, 0.098 mmol), $[\alpha]_D$ +55.26° (c 0.95, H_2O); (Found: C, 42.13; H, 5.87; N, 20.08. Calc. for $C_{12}H_{16}O_3N_5F * 2.5$

H_2O: C, 42.10; H, 6.18; N, 20.46%); δ_H (270 MHz; D_2O) 1.96-2.42 (4 H, m, H-3′, H-4′ and H-5′), 3.52-3.74 (4 H, m, 2 CH_2OH), 4.61-4.78 (1 H, m, H-1′) 4.95-5.16 (1 H, dd, H-2′, J=3.8 and 53.7 Hz), 7.89 (1 H, d, H-8, $J_{H,F}$=2.0 Hz); δ_C (67 MHz; D_2O) 32.1 (C-5′), 40.5 (C-4′), 50.2 (C-3′, d, $J_{C,F}$=20.1 Hz), 56.9 (C-1′, d, $J_{C,F}$=18.3 Hz), 62.7 (CH_2OH, d, $J_{C,F}$=11.0 Hz), 65.4 (CH_2OH), 97.0 (C-2′, d, J=179.6 Hz), 116.8 (C-5), 140.0 (C-8, d, $J_{C,F}$=3.6 Hz), 152.6 (C-4), 155.1 (C-2) and 160.3 (C-6).

6-Amino-9-[3′*S*,4′*S*-bis(hydroxymethyl)-2′*R*-fluorocyclopent-1′*S*-yl]-9*H*-purine (16). Compound **16** was prepared from **25** (352 mg, 0.55 mmol) in the same manner as described for compound **10** with the intermediate products *6-chloro-9-[3′S,4′S-bis(*t*-butyldiphenylsilyloxymethyl)-2′R-fluorocyclopent-1′S-yl]-9*H*-purine* (113 mg, 0.15 mmol, 27%) and *6-amino-9-[3′S,4′S-bis(*t*-butyldiphenylsilyloxymethyl)-2′R-fluorocyclopent-1′S-yl]-9*H*-purine* (107 mg, 0.14 mmol, 93%) to afford the title compound in 20% yield from **25** (32 mg, 0.11 mmol), $[\alpha]_D$ -24.71° (c 0.70, MeOH); (Found: C, 48.41; H, 5.72; N, 23.48. Calc. for $C_{12}H_{16}O_2N_5F * 1\ H_2O$: C, 48.16; H, 6.06; N, 23.40%); δ_H (270 MHz; CD_3OD) 2.15-2.68 (4 H, m, H-3′, H-4′ and H-5′), 3.57-3.88 (4 H, m, 2 CH_2OH), 4.99-5.22 (1 H, dddd, H-1′, J=2.7, 9.0, 12.1 and 31.2 Hz) 5.14-5.36 (1 H, ddd, H-2′, J=2.7, 2.7 and 55.5 Hz), 8.22 (1 H, s, H-2), 8.24 (1 H, d, H-8, $J_{H,F}$=2.2 Hz); δ_C (67 MHz; CD_3OD) 31.6 (C-5′), 41.3 (C-4′), 48.8 (C-3′, d, $J_{C,F}$=22.0 Hz), 57.7 (C-1′, d, $J_{C,F}$=18.3 Hz), 61.2 (CH_2OH, d, $J_{C,F}$=9.1 Hz), 65.7 (CH_2OH), 96.5 (C-2′, d, J=181.4 Hz), 119.9 (C-5), 141.5 (C-8, d, $J_{C,F}$=5.5 Hz), 151.0 (C-4), 153.8 (C-2) and 157.4 (C-6).

2-Amino-9-[3′*S*,4′*S*-bis(hydroxymethyl)-2′*R*-fluorocyclopent-1′*S*-yl]-9*H*-purine-6(1*H*)-one (17). Compound **17** was prepared from **28** (113 mg, 0.60 mmol) in the same manner as described for compound **13** with the intermediate products *3′S,4′S-bis(hydroxymethyl)-2′R-fluorocyclopentyl-1′S-amine* (77 mg, 0.47 mmol, 78%), *2,4-diamino-6-chloro-4N-[3′S,4′S-bis(hydroxymethyl)-2′R-fluorocyclopent-1′S-yl]-pyrimidine* (55 mg, 0.19 mmol, 40%), *5-[(*p*-chlorophenyl)-azo]-2,4-diamino-6-chloro-4N-[3′S,4′S-bis(hydroxymethyl)-2′R-fluorocyclopent-1′S-yl]-pyrimidine* (61 mg, 0.14 mmol, 74%) and *2,4,5-triamino-6-chloro-4N-[3′S,4′S-bis(hydroxymethyl)-2′R-fluorocyclopent-1′S-yl]-pyrimidine* (41 mg, 0.13 mmol, 93%) to afford the title compound in 20% yield from **28** (36 mg, 0.12 mmol), $[\alpha]_D$ -32.87° (c 0.94, MeOH); (Found: C, 43.57; H, 5.93; N, 21.07. Calc. for $C_{12}H_{16}O_3N_5F * 2\ H_2O$: C, 43.24; H, 6.05; N, 21.01%); δ_H (270 MHz; CD_3OD) 2.16-2.58 (4 H, m, H-3′, H-4′ and H-5′), 3.57-3.87 (4 H, m, 2 CH_2OH), 4.81-4.97 (1 H, dddd, H-1′, J=2.7, 8.5, 12.0 and 30.9 Hz) 5.09-5.31 (1 H, ddd, H-2′, J=2.7, 2.7 and 55.5 Hz), 7.82 (1 H, d, H-8, $J_{H,F}$=2.2 Hz); δ_C (67 MHz; CD_3OD) 31.6 (C-5′), 41.1 (C-4′), 49.2 (C-3′, d, $J_{C,F}$=22.0 Hz), 57.2 (C-1′, d, $J_{C,F}$=16.5 Hz), 61.1 (CH_2OH, d, $J_{C,F}$=9.1 Hz), 65.6 (CH_2OH), 96.4 (C-2′, d, J=183.3 Hz), 117.3 (C-5), 138.2 (C-8, d, $J_{C,F}$=5.3 Hz), 153.1 (C-4), 155.5 (C-2) and 159.7 (C-6).

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28. 4-Chlorobenzendiazonium chloride preparation: To a solution of *p*-chloroaniline (218 mg, 1.7 mmol) in a mixture of water (3 mL) and concentrated hydrochloric acid (1 mL) at 0 °C, a solution of sodium nitrite (130 mg, 1.9 mmol) in water (1.4 mL) was added dropwise during 15 min.

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