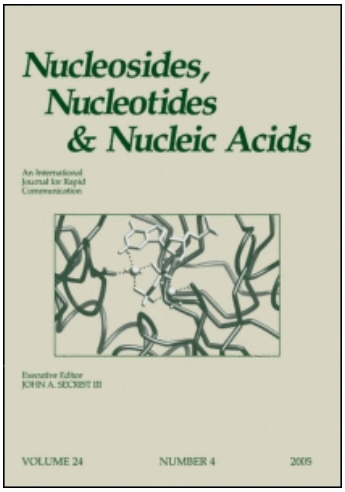

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SYNTHESIS OF NOVEL FLUORO CARBOCYCLIC PURINE NUCLEOSIDE ANALOGUES

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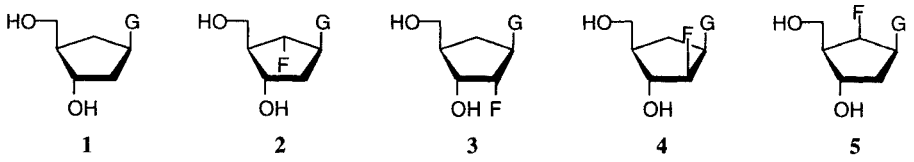
ABSTRACT: *The synthesis of four isomerically pure fluoro-carbocyclic adenosine and guanosine analogues is described.*

In carbocyclic nucleoside analogues the furanose ring oxygen is replaced by a methylene group. This has in several cases resulted in improved anti-viral activities. The fluoro group is a known biomimetic of both hydrogen and of hydroxyl, and notably, replacement of an oxygen ether linkage by a fluoro-methine group has also resulted in a biomimetic transformation. Thus Borthwick *et al.*. has introduced a fluorine atom at various positions of the carbocyclic 2′-deoxyguanosine (**1**), which in itself is active against HSV.[1-3] Significant anti-HSV activity was demonstrated for the fluoro analogues **2** and **4**, where as isomers **3** and **5** were much less active.

2′,3′-Dideoxy-3′-C-hydroxymethyl cytidine (**6**) has been reported to be a potent inhibitor of HIV-1 *in vitro*,[4-6] while its carbocyclic analogues **7** and **8** were found to be devoid of anti-viral activity.[7]

In order to retain some of the electro negativity of the ring oxygen in **6**, fluoro substituents were introduced in the carbocyclic ring, resulting in compounds **9-16**, which have been synthesised and evaluated for their anti-viral activity.

To introduce the fluorine atom in the carbocyclic ring (3*S*,4*S*)-Bis(*t*-butyldiphenylsilyloxymethyl)-cyclopentanone (**17**) was converted to its trimethylsilylenol ether **18** by adding trimethylsilyltriflate to a refluxing mixture of **17** and triethylamine in toluene. The mixture was refluxed for 15 min, worked up, and the crude product was

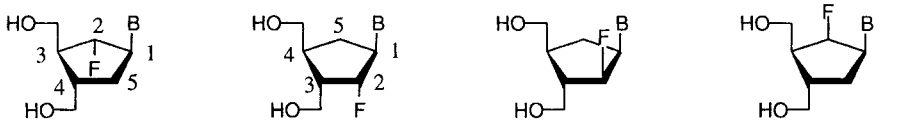


1 **2** **3** **4** **5**

FIG. 1

6 **7:** B=A
8: B=G

FIG. 2



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

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

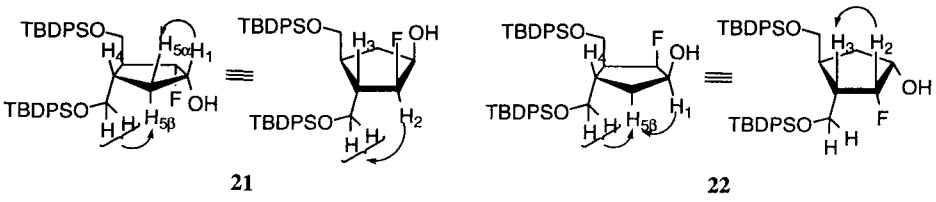
13: B=Adenin-9-yl
14: B=Guanin-9-yl

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

FIG. 3

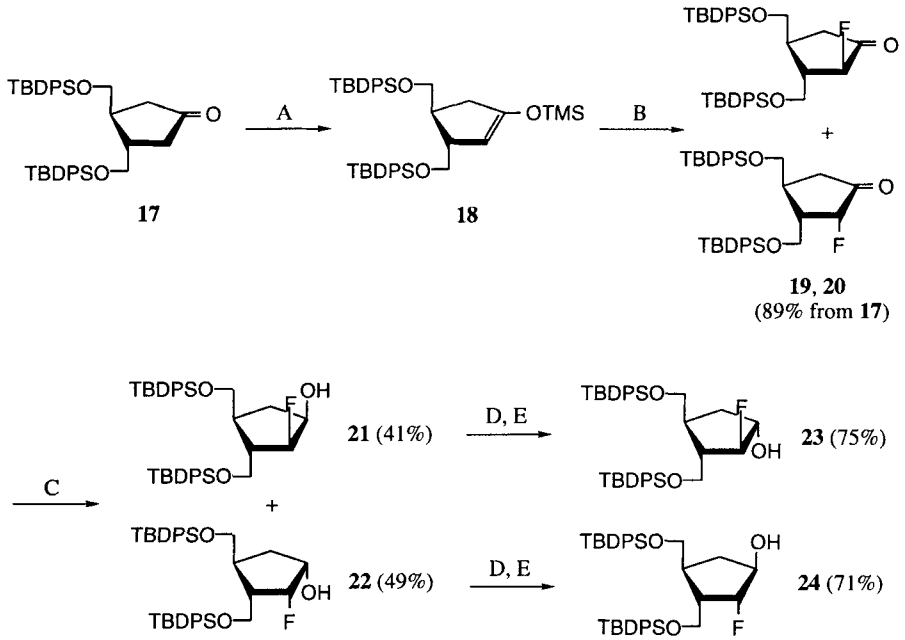
immediately reacted with the electrophilic fluorine reagent F-TEDA-BF_4 (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2] octane bistetrafluoroborate) in dimethylformamide to give an inseparable 1:1 mixture of the fluoroketones **19** and **20** in 89% total yield from **17**.[8]

For stereoselective reduction of the α-haloketones it has been reported that the halogens, including fluorine, directs the incoming nucleophile to the anti-side, giving a cis relationship 1,2-fluoro alcohol product.[9,10] The initial attempt to reduce the mixture of **19** and **20** with sodium borohydride gave approximately 90% cis-products and 10% trans-products. A more stereoselective reduction of the ketones was accomplished in 90% total yield by using LS-selectride in tetrahydrofuran at -78 °C.[11] Within the detection limit no trans-product was observed. The two diastereomeric alcohols could be separated by column chromatography to give **21** and **22** in 41% and 49% yield, respectively.



21 22

FIG. 4

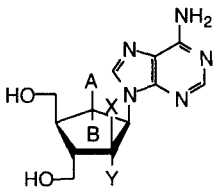


A: TMSOTf, Et_3N, toluene, reflux; B: F-TEDA-BF_4, DMF; C: LS-selectride, THF, -78 °C; D: BzOH, Ph_3P-DIAD, THF; E: NaOMe, MeOH, CH_2Cl_2.

SCHEME 1

COSY experiments were performed to interpret the proton NMR spectra of these compounds. The stereochemistry assignments at C-1 and C-2 in **21** and **22** were based on nOe and NOESY experiments.

The hydroxyls at C-1 in **21** and **22** were separately inverted to their epimers using the Mitsunobu reaction with benzoic acid as the nucleophile,[12] followed by debenzoylation using a catalytic amount of sodium methoxide in methylene chloride-methanol giving **23** and **24** in 75% and 71% yield, respectively.



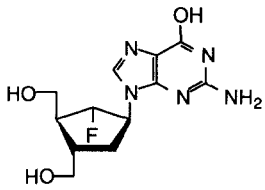
21 $\xrightarrow{A, B, C}$ **9**: B=F; A=X=Y=H (64%)

22 $\xrightarrow{A, B, C}$ **11**: Y=F; A=B=X=H (22%)

23 $\xrightarrow{A, B, C}$ **13**: X=F; A=B=Y=H, (37%)

24 $\xrightarrow{A, B, C}$ **15**: A=F; B=X=Y=H, (20%)

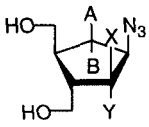
21 $\xrightarrow{D, C, E}$



10 (52%)

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.*

SCHEME 2



22 $\xrightarrow{A, B}$ **25**: Y=F; A=B=X=H (75%) $\xrightarrow{C, D, E, F, G, H}$ **12**: Y=F; A=B=X=H (27%)

23 $\xrightarrow{A, B}$ **26**: X=F; A=B=Y=H (68%) $\xrightarrow{C, D, E, F, G, H}$ **14**: X=F; A=B=Y=H (24%)

24 $\xrightarrow{A, B}$ **27**: A=F; B=X=Y=H (74%) $\xrightarrow{C, D, E, F, G, H}$ **16**: 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-$ClC_6H_4N_2^+Cl^-$, H_2O, AcOH, NaOAc;* ***F:*** *Zn, AcOH, EtOH, reflux;* ***G:*** *$HC(OMe)_3$, HCl, DMF;* ***H:*** *0.6 M HCl, reflux.*

SCHEME 3

For the synthesis of the adenosine derivatives **9**, **11**, **13** and **15**, compounds **21**, **22**, **23** and **24** were first coupled with 6-chloropurine using the Mitsunobu procedure,[12] then reacted with methanolic ammonia in a sealed steel-vessel at 80 °C, followed by deprotection using tetrabutylammonium fluoride in tetrahydrofuran to give compounds **9**, **11**, **13** and **15** in 64%, 22%, 37% and 20% yields, respectively, from the alcohols.[13] It was noted that alcohols **22**, **23** and **24** were less reactive than **22** in the Mitsunobu reaction.

For the synthesis of the corresponding guanosine derivatives **10**, **12**, **14** and **16** compounds **21**, **22**, **23** and **24** were coupled with 2-amino-6-chloropurine under the same conditions (*vide supra*). Notably only alcohol **21** gave the desired product, 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 **10** in 52% yield from **21**.[14]

For the synthesis of the guanosine derivatives **12**, **14** and **16** another strategy was adopted, in which the guanine moiety was synthesised *de novo* from the corresponding cyclopentylamines.[1] Thus alcohols **22**, **23** and **24** were converted to their corresponding azides and desilylated (*vide supra*) to give azides **25**, **26** and **27** in 75%, 68% and 74% yields, respectively. [15]

The azides **25**, **26** and **27** 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 trimethylorthoformate 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 **12**, **14** and **16** in 27%, 24% and 20% yields, respectively, from the azides.

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