Synthesis of Compounds active against HIV. Part 2. Preparation of some 2′,3′-Dideoxy-6′-fluorocarbocyclic Nucleosides

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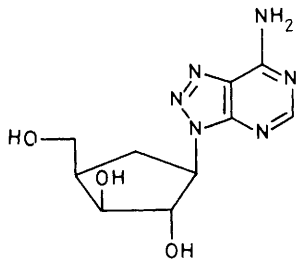
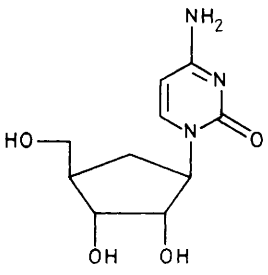
A series of 2′,3′-dideoxy-6′-fluorocarbocyclic nucleosides have been prepared and tested for activity against HIV: compound (**20**) showed weak antiviral activity.

The importance of carbocyclic nucleosides in some areas of medicinal chemistry is well established.[1] Thus the carbocyclic nucleoside (**1**) exhibits antitumour activity,[2] while carbodine (**2**) selectivity inhibits the replication of influenza virus in kidney cells.[3] Cycloaradine (**3**),[4] the fluoro-compound (**4**),[5] and the 2′-deoxy-carbocyclic nucleosides (**5**)[6] and (**6**)[7] show significant activity against herpes simplex virus. More recently it has been demonstrated that carbovir (**7**) displays potent and selective activity against HIV.[8]

We have been interested in replacing the ring oxygen atom of (deoxy)ribofuranoses by the CHF-moiety[9] and have shown that, with this iso-steric change, interesting biological activity can be retained.[10] Since 2′,3′-dideoxynucleosides are known to inhibit the cytopathic effect of HIV,[11] the synthesis of the 6′-fluorocarbocyclic counterparts was undertaken.



(**1**)



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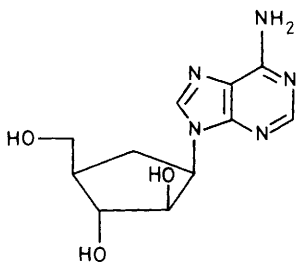
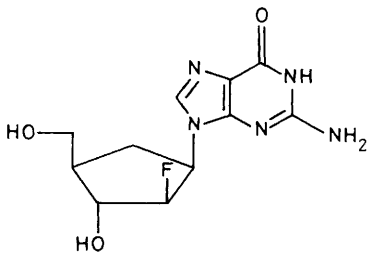
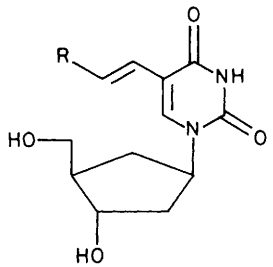


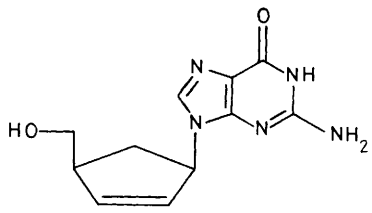
(**3**)



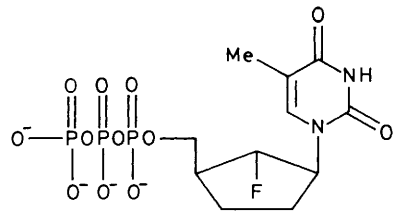
(**4**)



(**5**) R = Me
(**6**) R = Br



(**7**)

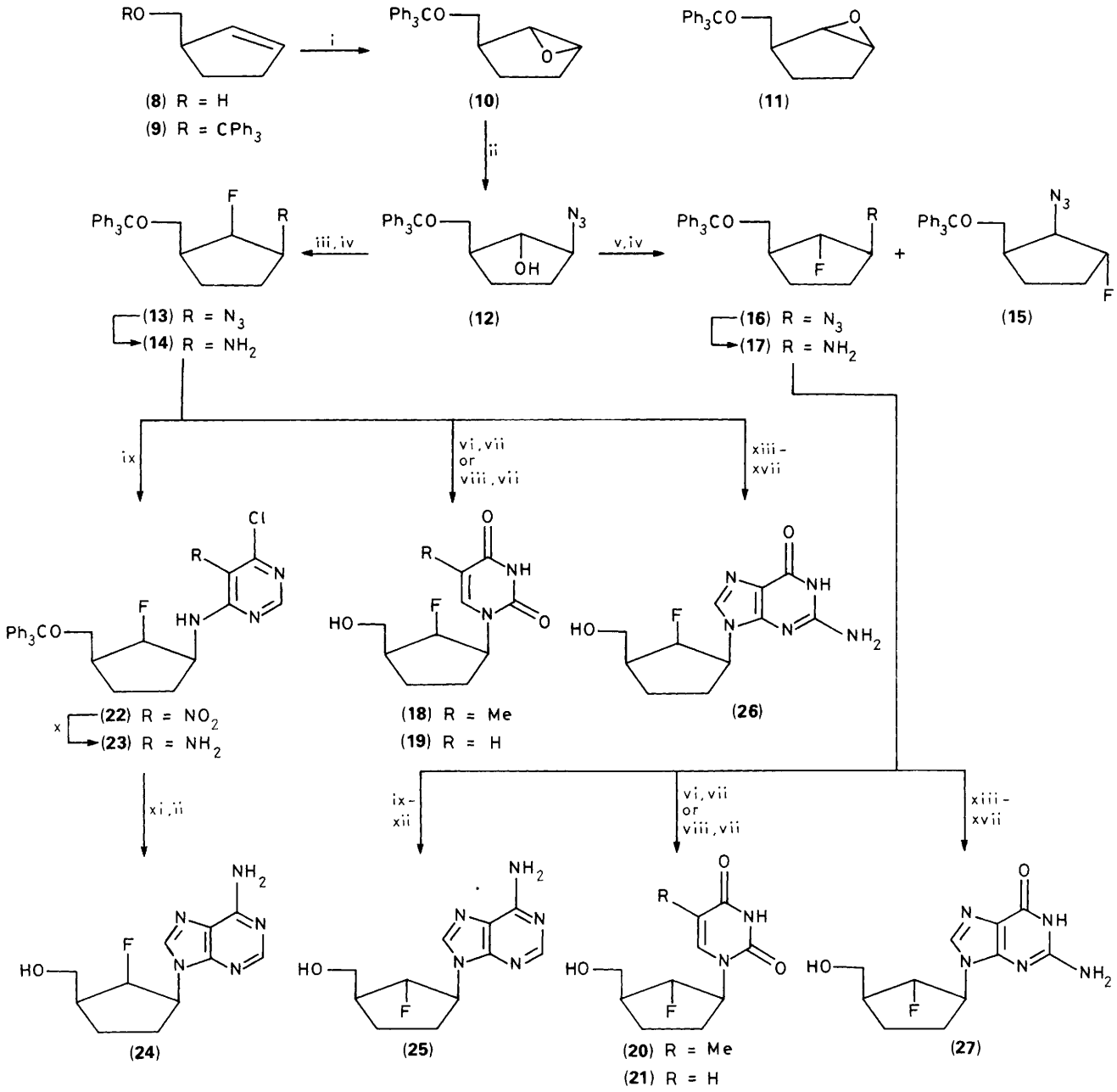


(**28**)

Racemic cyclopent-2-enylmethanol (**8**)[12] was tritylated (98%) and the trityl derivative (**9**) was converted into the epoxide (**10**) using a two-step procedure (87%) (Scheme 1). [Oxidation of the trityl ether (**9**) with *m*-chloroperbenzoic acid gave mainly the isomeric epoxide (**11**).] Azide ion attacked the oxirane ring in compound (**10**) with very high selectivity to give the alcohol (**12**) (84%). Formation of the trifluoromethanesulphonate derivative of the azido-alcohol (**12**) and displacement of the triflate group with fluoride ion gave the β-fluoro compound (**13**) (44% yield overall). Reduction of the azide (**13**) with hydrogen and Lindlar catalyst gave a quantitative yield of the amine (**14**).

Treatment of the azido-alcohol (**12**) with diethylaminosulphur trifluoride (DAST) gave a mixture of the fluoroazides (**15**) and (**16**) (2.7:1; 75%); the latter compound was reduced with Lindlar catalyst to give the amine (**17**).

The amine (**14**) was converted into the uracil derivatives (**18**) (m.p. 193—194 °C) (33%) and (**19**) (m.p. 214—216 °C) (32%) using standard procedures (Scheme 1). Likewise the isomeric amine (**17**) was transformed into the nucleoside analogues (**20**) (m.p. 188—190 °C) (77.5%) and (**21**) (m.p. 87 °C) (45.5%). The β-fluorocompound (**14**) was inert towards 5-amino-4,6-dichloropyrimidine but reacted with 4,6-dichloro-5-nitropyrimidine to give the amine (**22**) (41%). Raney



Scheme 1. *Reagents and conditions*; i, dimethyldibromohydantoin, H_2O, acetone, 0 °C; then K_2CO_3 in MeOH; ii, NaN_3, NH_4Cl, EtOH, H_2O, 90 °C; iii, $(CF_3SO_2)_2O$, pyridine then $Bu_4N^+F^-$, tetrahydrofuran (THF); iv, H_2, EtOH, Lindlar catalyst; v, Et_2NSF_3, CH_2Cl_2, 0 °C; vi, MeOCH=C(Me)CONCO, C_6H_6, dimethylformamide (DMF), −15 °C to room temp., 18 h; vii, toluene-*p*-sulphonic acid, MeOH, CH_2Cl_2 then HCl, heat, 30 min; viii, EtOCH=CHCONCO, C_6H_6, DMF, 15 °C to room temp., 18 h; ix, 4,6-dichloro-5-nitropyrimidine, CH_2Cl_2, Et_3N, room temp.; x, H_2, dioxan, Raney Ni; xi, $(EtO)_3CH$, H^+; xii, NH_3(l), room temp., 18 h; then HCl (aq.), 5 min; xiii, 2-amino-4,6-dichloropyrimidine, DMF, Et_3N, 80 °C; xiv, *p*-chlorophenyldiazonium chloride, $MeCO_2H$, H_2O, $MeCO_2Na$; xv, Zn, $MeCO_2H$, EtOH, H_2O, 70 °C; xvi, $(EtO)_3CH$, H^+, DMF; xvii, HCl, heat, 5 h.

nickel catalysed hydrogenation of the nitro group gave the amine (**23**) (77%) and the latter compound was converted into the 9-substituted adenine (**24**) (m.p. 210 °C) (68%). The α-fluoroamine (**17**) provided access to the isomeric purine (**25**) (m.p. 155 °C) (13% overall yield). A five step sequence of reactions converted the fluoroamine (**14**) into the guanosine analogue (**26**) (m.p. 220 °C) (20% overall yield); similarly the fluoroamine (**17**) furnished the carbocyclic nucleoside (**27**) (m.p. 210 °C) (20% overall yield).

The purines (**24**)—(**27**) showed no activity against HIV infected cells: the pyrimidines (**18**), (**19**), and (**21**) were also inactive. However the thymidine analogue (**20**) showed weak anti-HIV activity (ED_{50} 100 μg ml^{-1}). The triphosphate (**28**) was prepared and was, as expected from the whole cell experiments, an inhibitor of HIV reverse transcriptase albeit at a level *ca.* 100 times lower than that observed for azidothymidine (AZT) triphosphate.

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