Synthesis of Fluorinated Carbocyclic Nucleosides: Preparation of Carbocyclic 1-(2'-Deoxy-6'-fluororibofuranosyl)-5-iodouracils

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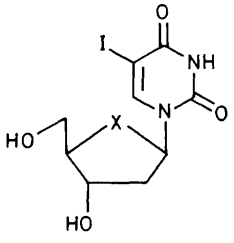
The epoxide (**4**) was opened regioselectively using azide ion and fluoride ion to give the alcohols (**5**) and (**13**) respectively as the major products; azido alcohol (**5**) was converted into the anti-viral carbocyclic 2'-deoxy-6'-fluorouridines (**11**) and (**16**) [crystal data were obtained on compound (**15**)].

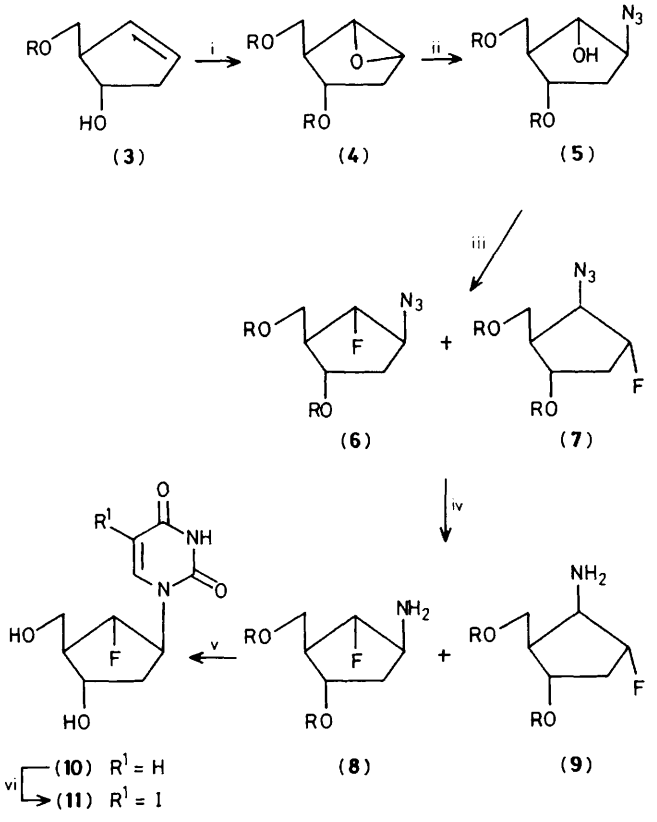
There has been considerable interest in modified nucleosides such as 5-iodo-2'-deoxyuridine (IDU) (**1**) and the corresponding carbocyclic compounds, for example carbocyclic-IDU (**2**).[1] Compounds from both series exhibit interesting and useful anti-viral properties.[1,2] The replacement of the heterocyclic oxygen atom of the sugar by a methylene group is a drastic change in terms of the stereoelectronic effect on the rest of the molecule. A more subtle change involves replacement of the oxygen atom by a fluoromethylene group; the isosteric relationship of an oxygen atom and a fluoromethylene group has been noted previously.[3] We describe herein the preparation and anti-herpes activity of two carbocyclic 2'-deoxy-6'-fluorouridines.[4]

Conversion of cyclopentadiene into the optically active alcohol (**3**) (enantiomeric excess, e.e., >98%) was accomplished in 38% yield using an asymmetric hydroboration procedure.[5] Oxidation of the cyclopentene derivative (**3**) under Sharpless' conditions followed by protection of the hydroxy group gave the oxirane (**4**) (Scheme 1). Reaction of (**4**) with azide ion gave the required azido alcohol (**5**) in 85% yield. Treatment of the alcohol (**5**) with diethylaminosulphur trifluoride (DAST) gave a mixture of the fluoro-compounds (**6**) and (**7**) in the ratio 2:3. Participation of a neighbouring azido group in a reaction employing DAST (resulting in replacement of the hydroxy group by a fluorine atom with retention of configuration and partial or total migration of the azido-group) has been reported previously.[6] Reduction of the mixture of (**6**) and (**7**) gave the amines (**8**) and (**9**) which were separated by chromatography. The amine (**8**) was readily converted into the uracil derivative (**10**) in three steps (overall yield 60%). Carbocyclic 1-(2'-deoxy-6'-α-fluororibofuranosyl)-5-iodouracil (**11**), $[\alpha]_D^{22}$ 37° (*c* 0.5, Me_2SO), was obtained from (**10**) in 51% yield.

Not surprisingly, opening of the epoxide in compound (**4**) by potassium hydrogen difluoride was highly regioselective in the wrong sense (in terms of providing a route to the second



(**1**) X = O
(**2**) X = CH_2



R = $PhCH_2$

Scheme 1. *Reagents:* i, Bu^tOOH, vanadyl acetylacetonate, then NaH, $PhCH_2Br$, $Bu_4N^+I^-$(cat.); ii, NaN_3, NH_4Cl, aq. EtOH, heat; iii, DAST, CH_2Cl_2; iv, H_2, Lindlar cat.; v, EtOCH=CHCONCO, C_6H_6, 5 °C, then 0.5 M-H_2SO_4, aq. dioxane, heat, then H_2, Pd/C, aq. EtOH, H^+ (cat.); vi, I_2, HNO_3, $CHCl_3$, heat.

objective) affording the required alcohol (**12**) (7%) and the isomeric fluorohydrin (**13**) (61%) (Scheme 2). The alcohol (**12**) was transformed into the azide (**14**) in two steps.‡ A far better route to the azide (**14**) involved activation of the hydroxy group in compound (**5**) by formation of the trifluoromethanesulphonate derivative and displacement of the latter moiety by fluoride ion.[7] The azide (**14**) was converted into the uracil derivative (**15**) (52%) and the configuration of the fluorine atom in this compound was confirmed by *X*-ray

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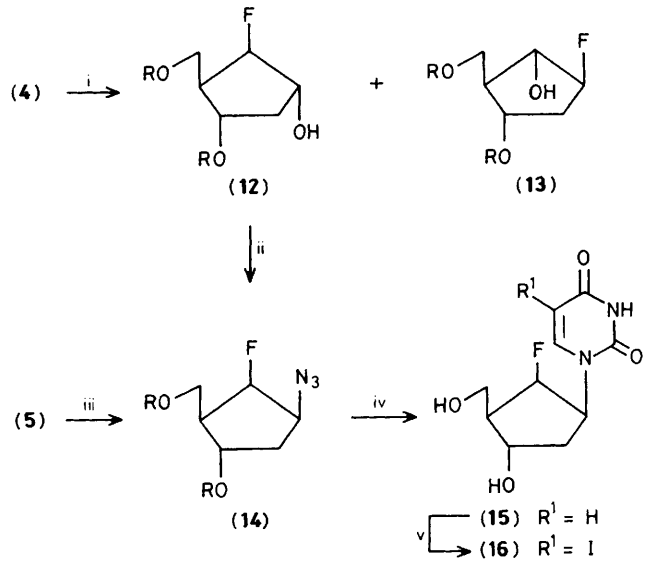
‡ A small quantity of 3-fluoro-4-benzyloxymethylcyclopent-1-ene was obtained as a side-product in this conversion.



R = $PhCH_2$

Scheme 2. *Reagents:* i, KHF_2, $MeO[CH_2]_2OH$, heat; ii, *p*-$MeC_6H_4SO_2Cl$, 4-*N*,*N*-dimethylaminopyridine (DMAP), NEt_3, CH_2Cl_2 then NaN_3, dimethylformamide (DMF), heat; iii; CF_3SO_2Cl, DMAP, NEt_3, CH_2Cl_2 then BuN_4F, tetrahydrofuran (THF); iv, H_2, Lindlar cat., then EtOCH=CHCONCO, C_6H_6, 5 °C then 0.5 M-H_2SO_4, aq. dioxane, heat, then H_2, Pd/C, aq. EtOH, H^+ (cat.); v, I_2, HNO_3, $CHCl_3$, heat.

crystallography (Figure 1).§ The required carbocyclic 1-(2′-deoxy-6′-β-fluororibofuranosyl)-5-iodouracil (**16**) (49%) was produced from (**15**) in the usual manner.

Interestingly, the 6′-α-fluoro-compound (**11**) was highly active against herpes simplex virus type 1 (HSV-1) infected cells in the microtitre assay (*ca.* one half the activity of acyclovir) while the 6′-β-fluoro-compound (**16**) was at least two orders of magnitude less active.

§ *Crystal data:* 1-(*c*-2-fluoro-*t*-4-hydroxy-*c*-3-hydroxymethyl-*r*-1-cyclopentyl)uracil (**15**), $C_{10}H_{13}FO_4N_2$, M = 244.2, monoclinic, a = 9.670(5), b = 10.685(4), c = 10.696(7) Å, β = 98.85(5)°, U = 1092 Å^3, space-group $P2_1$, Z = 4 (2 crystallographically independent molecules), D_c = 1.48 g cm^{-3}, μ(Cu-K_α) = 10 cm^{-1}. Data were measured on a Nicolet R3m diffractometer with Cu-K_α radiation (graphite monochromator) using ω-scans. The structure was solved by direct methods and refined anisotropically to give R = 0.055, R_w = 0.054 for 1501 independent observed reflections [$|F_o|>3\sigma(|F_o|)$, θ <58°). Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

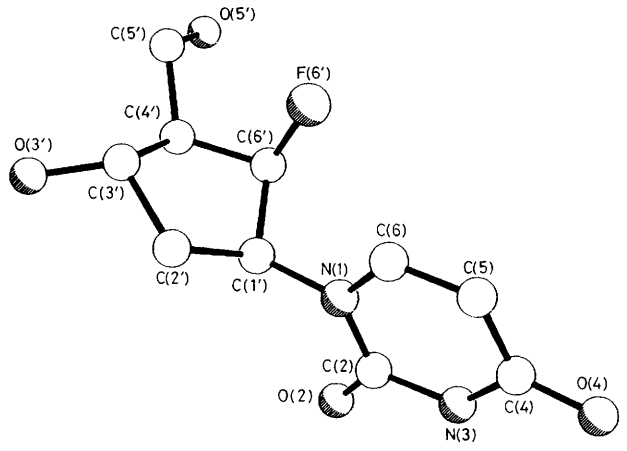


Figure 1. The molecular structure of (**15**) (there are no major differences between the conformations of the two independent molecules). In both molecules, A and B, the hydroxy groups are involved in intermolecular hydrogen bonds; molecule A: O(3′) · · · O(5′) 2.88, H · · · O(5′) 1.91 Å, angle at H 172°; O(5′) · · · O(4) 2.78, H · · · O(4) 1.80 Å, angle at H 175°; molecule B: O(3*′) · · · O(5*′) 2.86, H · · · O(5*′) 1.95 Å, angle at H 153°; O(5*′) · · · O(4*) 2.76, H · · · O(4*) 1.79 Å, angle at H 174°. There are no hydrogen-bonding interactions between molecules A and B.

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