Synthesis of Fluorinated Carbocyclic Nucleosides: Preparation of (±)-Carbocyclic-FMAU and Some Congeners

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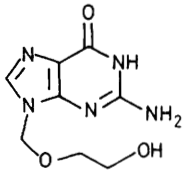
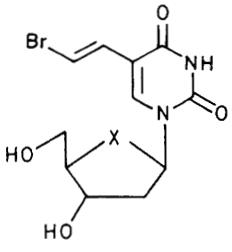
The alcohols (**7**) and (**19**) and the ketone (**28**) were treated with diethylaminosulphur trifluoride (DAST) to give the fluoro-compounds (**8**), (**21**), and (**29**) respectively: compound (**8**) was converted into the potential anti-viral agents carbocyclic-FMAU (**14**) and carbocyclic-FIAU (**16**) while compound (**21**) afforded the 2′-α-fluoro-carbocyclic nucleosides (**24**), (**25**), (**27**), and compound (**29**) gave the difluoro-analogue (**32**) [crystal data were obtained on compounds (**8**) and (**9**)].

One of the major areas of interest in modern-day medicinal chemistry involves the search for anti-viral agents.[1] In particular, the need for novel, orally active agents for the treatment of herpes simplex virus (HSV) infections is of paramount importance.[2] While acyclovir (**1**) is, at present, the compound of choice for use in the clinic against infections caused by HSV-1 and HSV-2,[3] more potent anti-herpes compounds such as 5-(2-bromovinyl)-2′-deoxyuridine (BVDU) (**2**), 1-(2′-deoxy-2′-fluoro-1′-β-D-arabinofuranosyl)-5-methyluracil (FMAU) (**4**), and 1-(2′-deoxy-2′-fluoro-1′-β-D-arabinofuranosyl)-5-iodocytosine (FIAC) (**5**) have attracted considerable attention.[4]

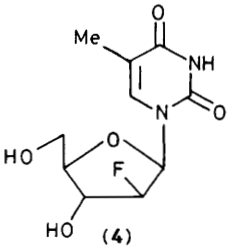
In an effort to improve the pharmacokinetics of the sugar derivative BVDU, the carbocyclic analogue (**3**) was prepared.[5] However both BVDU (**2**) and the carbocyclic analogue (**3**) show only weak activity against HSV-2, so despite the improved bioavailability of the latter compound, it is only poorly effective against HSV-2 infections *in vivo*. With this background knowledge, we took up the challenge to make



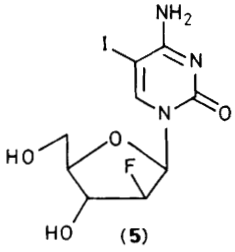
(**1**)



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



(**4**)



(**5**)

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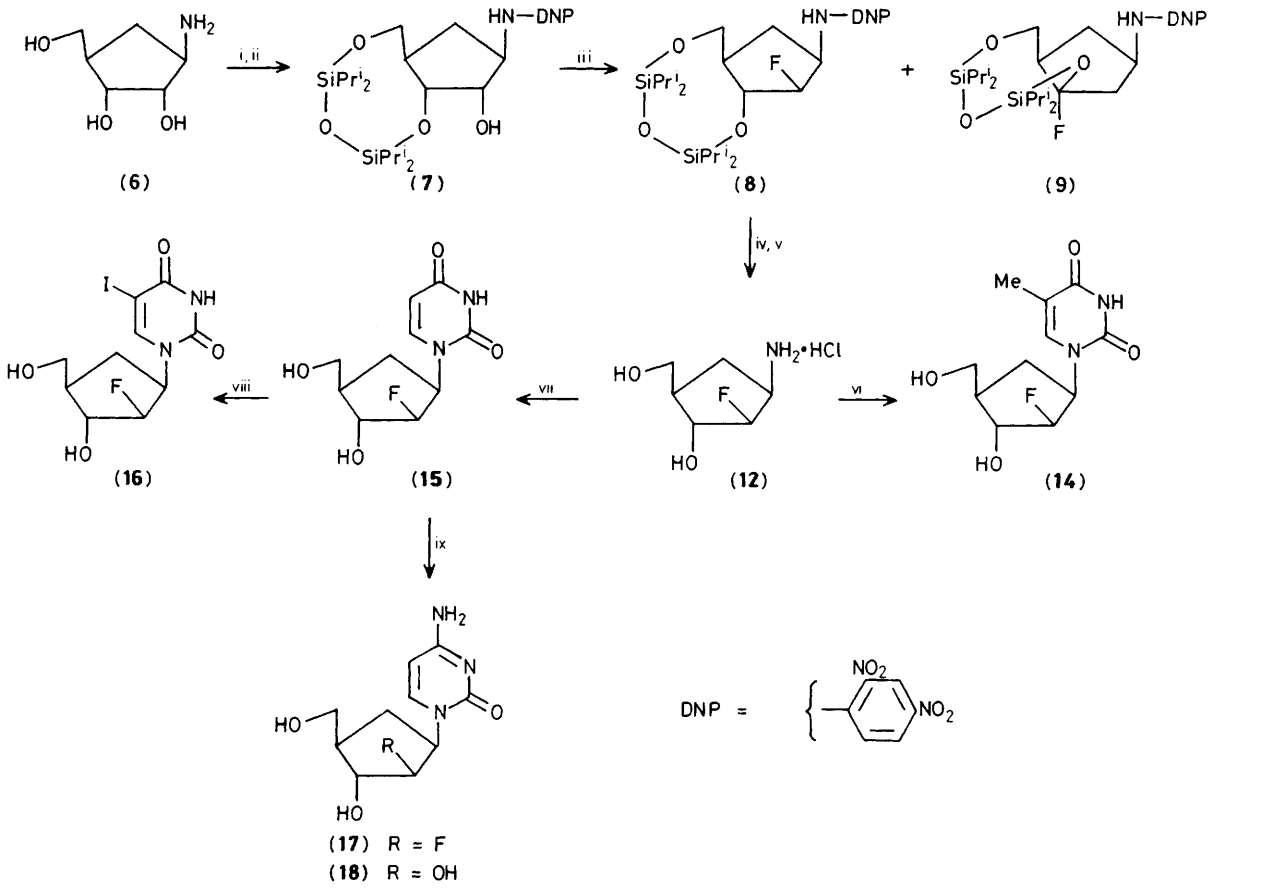
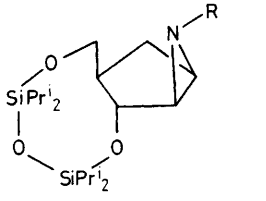
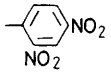


Scheme 1. *Reagents:* i, DNP–F, dimethylformamide (DMF), Na_2CO_3, room temp.; ii, $O(Pr^i_2SiCl)_2$, DMF, imidazole; iii, DAST, CH_2Cl_2, −30 °C; iv, $Bu^n_4N^+F^-$, tetrahydrofuran (THF); v, Amberlite IR 400 (OH^-), H_2O, Me_2CO; vi, EtOCH=C(Me)CONCO (**13**), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), DMF, −20 °C then 2 M-HCl, heat; vii, EtOCH=CHCONCO, DBU, DMF, −20 °C then 2 M-HCl, heat; viii, I_2, HNO_3, $CHCl_3$; ix, Ac_2O, C_5H_5N then *m*-ClC_6H_4–O–P(O)Cl_2, C_5H_5N, triazole then NH_3, MeOH, heat.



(**10**) R = CPh_3

(**11**) R = 

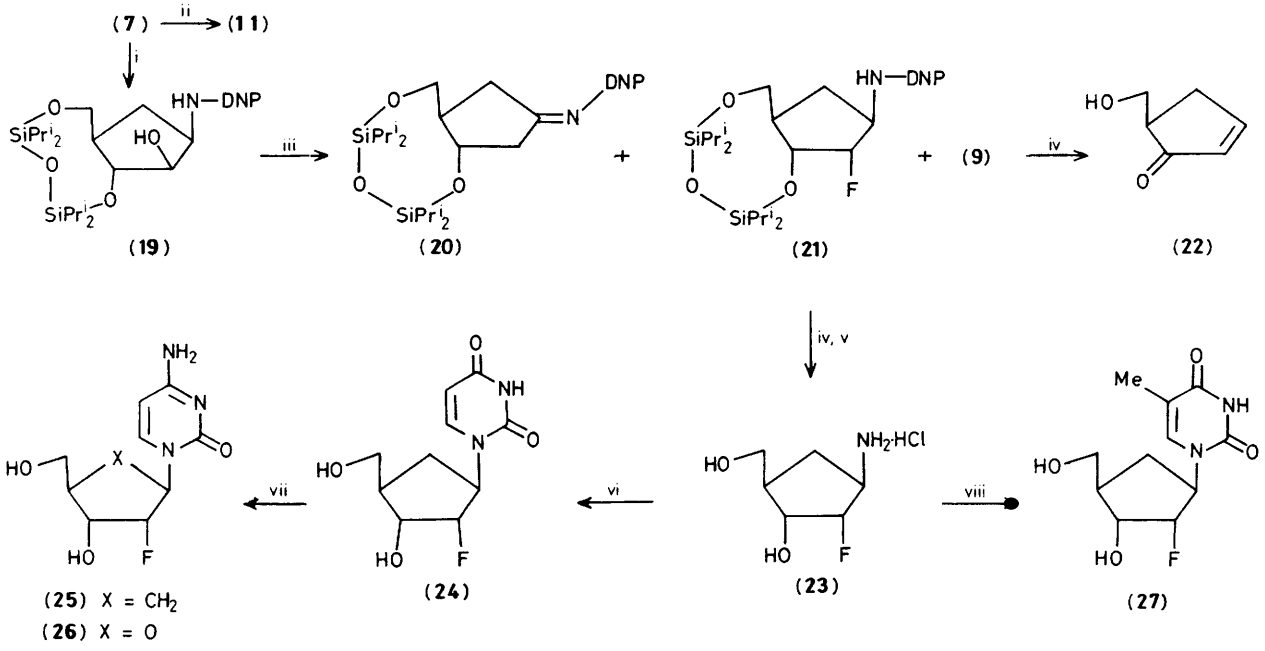
the (±)-carbocyclic counterpart of the broader spectrum anti-viral agent FMAU (**4**) (and some related compounds) and we report the success of this venture in this communication.

The (±)-amino-triol (**6**) is available from cyclopentadiene in seven steps.[6] Protection of the amino-group with the 2,4-dinitrophenyl (DNP) moiety (89%) and formation of the oxybis(di-isopropylsilyl) (TIPS) derivative (79%) gave the key intermediate (**7**) (Scheme 1). Treatment of the alcohol (**7**) with diethylaminosulphur trifluoride (DAST)[7] (2 equiv.) in dichloromethane at −30 °C gave the desired fluoro-compound (**8**) (*ca.* 74%) and a small amount of the protected fluorohydrin (**9**) (*ca.* 18%) (*vide infra*). The configuration of the fluorine atom in (**8**) was confirmed by *X*-ray crystallography (Figure 1).‡ Thus the DAST reaction converts (**7**) into (**8**) with inversion of configuration at C-2′;[8] this conversion is complementary to other work which demonstrated the usefulness of this reagent in the synthesis of fluoro-sugars.[9,10] Two points are worthy of note: first, if an amino-protecting group was employed which did not significantly reduce the electron

‡ *Crystal data:* (±)-(8α,9α)-8-[(2,4-Dinitrophenyl)amino]-9-fluorohexahydro-2,2,4,4-tetrakis(1-methylethyl)cyclopenta[*f*]-1,3,5,2,4-tri-oxadisilocine (**8**), $C_{24}H_{40}FO_7N_3Si_2$, M = 557.8, monoclinic, a = 14.009(3), b = 10.458(3), c = 20.646(4) Å, β = 101.03(2)°, U = 2969 Å^3, space group $P2_1/a$, Z = 4, D_c = 1.25 g cm^{-3}, μ(Cu-K_α) = 15 cm^{-1}. The structure was solved by direct methods and refined anisotropically to give R = 0.085, R_w = 0.063 for 1707 independent observed reflections [$|F_o| > 3\sigma(|F_o|)$, θ ≤ 50°].

(±)(8α,10β)-8-[(2,4-Dinitrophenyl)amino]-10-fluorohexahydro-2,2,4,4-tetrakis(1-methylethyl)-cyclopenta[*f*]-1,3,5,2,4-trioxadisilocine (**9**), $C_{24}H_{40}FO_7N_3Si_2$, M = 557.8, monoclinic, a = 8.870(2), b = 15.129(3), c = 52.150(9) Å, β = 122.03(2)°, U = 5933 Å^3, space group $C2/c$, Z = 8, D_c = 1.25 g cm^{-3}, μ(Cu-K_α) = 15 cm^{-1}. The structure was solved by direct methods and refined anisotropically to give R = 0.046, R_w = 0.047 for 2512 independent observed reflections [$|F_o| > 3\sigma(|F_o|)$, θ ≤ 50°].

In both cases data were measured on a Nicolet R3m diffractometer with Cu-K_α radiation (graphite monochromator) using ω-scans. 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.



Scheme 2. *Reagents:* i, (a) 4-*N*,*N*-dimethylaminopyridine (DMAP), CH_2Cl_2, $MeSO_2Cl$, (b) CsOCOMe, 18-crown-6, toluene, heat, (c) NaOMe, MeOH; ii, Ph_3P, EtO_2C–N=N–CO_2Et, *p*-$MeC_6H_4SO_3Me$, toluene; iii, DAST (1.5 equiv.), CH_2Cl_2, 0 °C; iv, $Bu^n_4N^+F^-$, THF; v, Amberlite IR 400 (OH^-), H_2O, Me_2CO; vi, EtOCH=CHCONCO, DBU, DMF, −20 °C then 2 M-HCl, heat; vii, Ac_2O, C_5H_5N, DMAP then *m*-ClC_6H_4–O–P(O)Cl_2, C_5H_5N, triazole, then NH_4OH; viii, EtOCH=C(Me)CONCO (**13**), DBU, DMF, −20 °C then 2 M-HCl, heat.

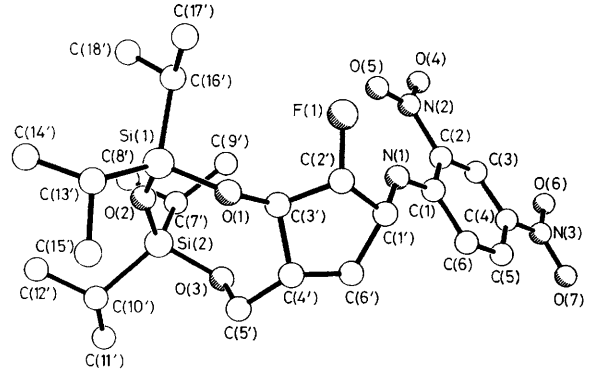


Figure 1. The molecular structure of (**8**). There is an intramolecular hydrogen bond between N(1) and O(5) [N(1) · · · O(5) 2.62, H(1) · · · O(5) 1.90 Å, ∠N(1)H(1)O(5) 130 °].

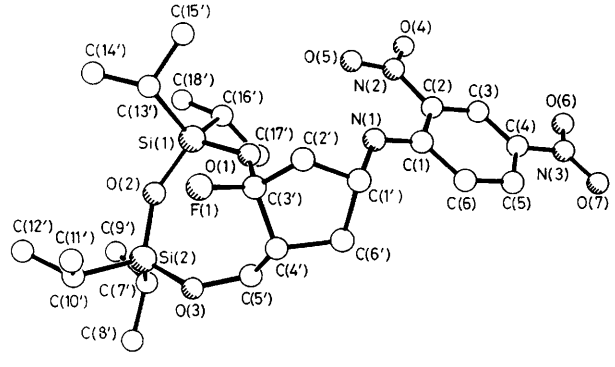


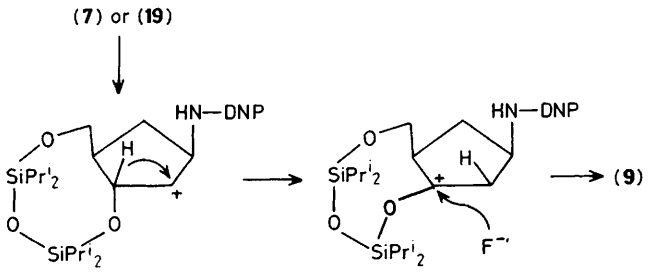
Figure 2. The molecular structure of (**9**). There is an intramolecular hydrogen bond between N(1) and O(5) [N(1) · · · O(5) 2.65, H(1) · · · O(5) 1.94 Å, ∠N(1)H(1)O(5) 129°].

density on the nitrogen atom (*e.g.* trityl), the only product isolable from the DAST reaction was the corresponding aziridine [*e.g.* (**10**)]. Secondly, the TIPS protecting group was stable under the reaction conditions, a fact that was not predictable from earlier reports.[11] The fluoro-compound (**8**) was deprotected to give the aminofluorodiol hydrochloride (**12**) (86%) and this compound was converted into carbocyclic-FMAU (**14**) (21%) using the isocyanate (**13**) followed by treatment with hydrochloric acid in the prescribed fashion (Scheme 1).[11]

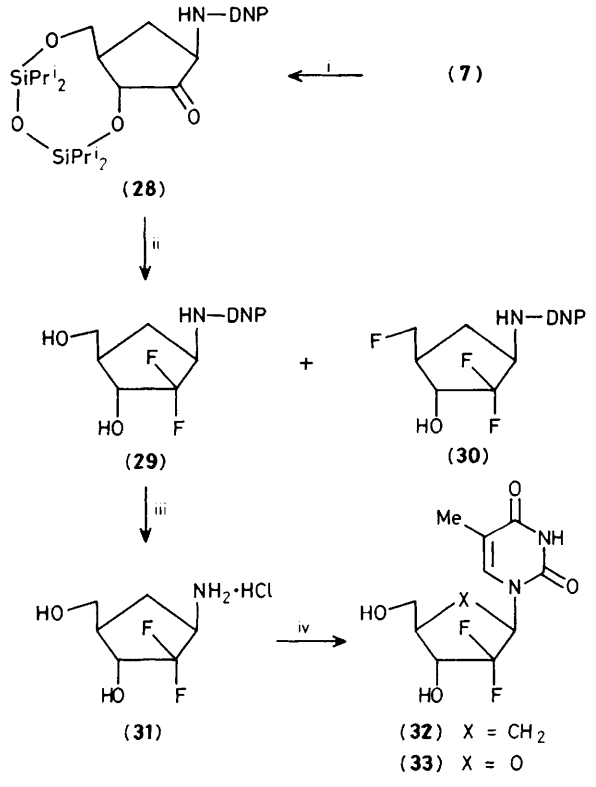
The salt (**12**) was converted into the uracil derivative (**15**) which gave access to the carbocyclic analogue (**16**) [20% from compound (**12**)] of 1-(2′-deoxy-2′-fluoro-1-β-D-arabinofuranosyl)-5-iodouracil (FIAU) and the carbocyclic analogue (**17**) [7.5% from compound (**12**)] of 1-(2′-deoxy-2′-fluoro-1′-β-D-arabinofuranosyl)cytosine. Carbocyclic 1-β-arabinofuranosylcytosine (**18**) has been prepared previously.[12]

Inversion of the free hydroxy group in compound (**7**) was accomplished by methanesulphonylation (72%), displacement of the $MeSO_3$ group by acetate ion (95%), and de-esterification using sodium methoxide (98%) to give the required alcohol (**19**) (Scheme 2). [An attempted Mitsunobu reaction on alcohol (**7**) gave the aziridine (**11**).]

Treatment of the alcohol (**19**) with DAST gave the protected fluorohydrin (**9**), the imine (**20**), and the required fluoro-compound (**21**) (*ca.* 25% yield). The imine (**20**) is presumably formed by dehydration[13] followed by rearrangement of the double bond under the reaction conditions. The structure of compound (**9**) was confirmed by *X*-ray crystallography (Figure 2):‡ one possible mechanism for the formation of (**9**) involves loss of the activated 2′-hydroxy group,[14] and proton shift to give an oxygen-stabilized carbenium ion (Scheme 3) which is attacked by local fluoride ion from the less hindered face. As expected, treatment of (**9**) with tetrabutylammonium fluoride (TBAF) gave 5-hydroxymethylcyclopent-2-enone (**22**). The whole process (**19**) → (**9**) → (**22**) is



Scheme 3



Scheme 4. *Reagents:* i, Me_2SO, $(CF_3CO)_2O$, CH_2Cl_2 −65 °C to room temp. then Pr^i_2NEt; ii, DAST, CH_2Cl_2, room temp., then $Bu^n_4N^+F^-$, THF; iii, Amberlite IR 400 (OH^-), Me_2CO, H_2O then 2 M-HCl; iv, EtOCH=C(Me)CONCO (**13**), DBU, DMF, −20 °C, then 2 M-HCl, heat.

reminiscent of a transformation described by Robins some years ago.[15]

The crude 2′-α-fluoro-compound (**21**) was deprotected in two steps to give the hydrochloride (**23**) [17% from (**19**)] and this compound was converted into the uracil derivative (**24**) [62% yield from (**23**)] and subsequently into the cytosine derivative (**25**) [49% yield from (**24**)], as well as carbocyclic 1-(2′-deoxy-2′-α-fluororibofuranosyl)-5-methyluracil (**27**) [34% yield from (**23**)] (Scheme 2).

The protected aminotriol (**7**) was oxidised under carefully controlled conditions to afford the ketone (**28**) (40%) (Scheme 4). Conversion of simple ketones into the corresponding difluoromethylene compounds using DAST is known to require harsh reaction conditions.[16] Not surprisingly, therefore, the ketone (**28**) was converted into the difluoro-compound (**29**) in variable, at best modest, yield (12—27%) using DAST under the prescribed conditions followed by TBAF to remove the silyl protecting group. A small amount of the trifluoro-compound (**30**) was isolated as a minor product from one of these reactions. Removal of the dinitrophenyl-protecting group from (**29**) gave the salt (**31**) (71%) which was converted into carbocyclic 1-(2′-deoxy-2′,2′-difluororibofuranosyl)-5-methyluracil (**32**) (51%) using the isocyanate (**13**) followed by acid treatment.

Carbocyclic-FMAU (**14**) showed activity in the HSV-1 plaque reduction assay but at a level significantly lower (*ca.* 1000 fold) than that attained by FMAU (**4**). None of the compounds (**24**), (**25**), (**27**), and (**32**) was active against HSV-1 infected cells *in vitro* at a concentration of 300 μg/ml. In contrast the fluoro-sugars (**26**) and (**33**) have been reported to show activity against HSV-infected cells.[17]

We thank Mr. D. J. Knight and Dr. J. A. V. Coates for the biological results; further data will be reported elsewhere.

Received, 7th October 1986; Com. 1416

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