Synthesis of Compounds Active Against HIV: Preparation of 6′-Fluorocarbocyclic AZT (AZT =3′-deoxy-3′-azidothymidine)

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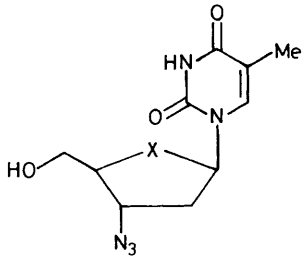
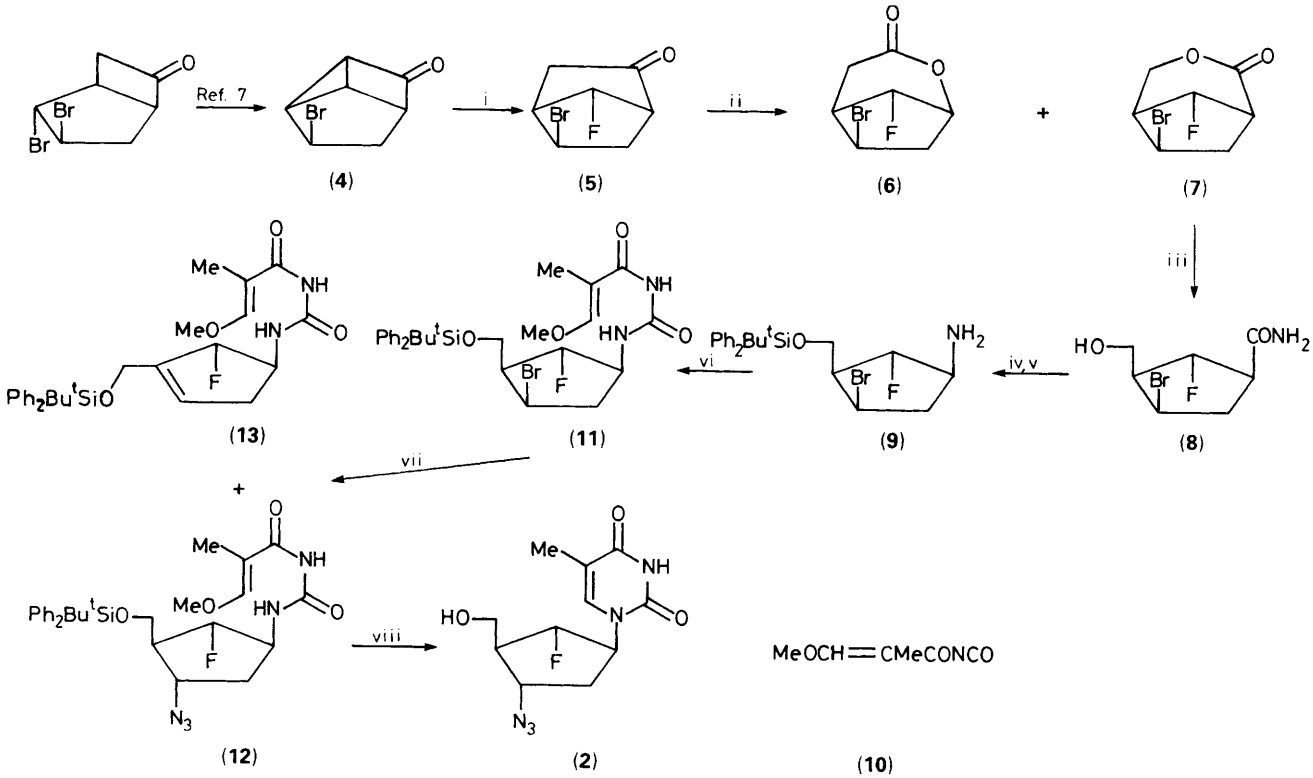
The carbocyclic nucleosides (**2**) and (**3**) have been prepared and tested for anti-HIV activity: AZT-triphosphate (**20**) (AZT = 3′-deoxy-3′-azidothymidine) was synthesized by a new procedure and the same method was used to make the novel triphosphate (**21**).

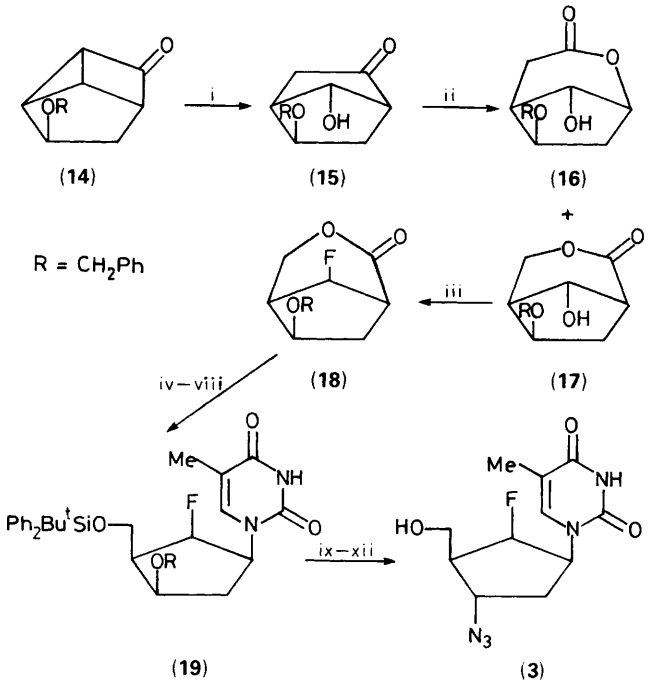
Since the discovery of the 'Acquired Immune Deficiency Syndrome' (AIDS)[1] much research has been aimed at controlling the responsible virus, now called the human immunodeficiency virus (HIV). Two approaches have been explored. First the search for a suitable vaccine has been undertaken;[2] secondly a chemotherapeutic agent has been sought.[3] In the latter area of endeavour a number of interesting leads have been generated.[4] However, at the present time the only compound available in the clinic for the treatment of AIDS patients is 3′-deoxy-3′-azidothymidine (AZT) (**1**). While this compound is effective in prolonging the life of persons suffering from AIDS, the side effects caused by the drug are quite severe.[4] Part of the problem is that AZT is metabolised quite rapidly in the body and high doses of the compound need to be administered. We reasoned that a metabolically more stable compound that exhibited the same inhibitory effect against HIV reverse transcriptase (a key enzyme coded by the virus) would be a desirable target. We[5] and others[6] have argued that exchange of the ring oxygen atom in the sugar unit for an isosteric fluoromethylene unit may well lead to retention of a substantial part of the useful biological activity shown by the parent sugar. Considerable



(**1**) X = O
(**2**) X = CHF (α-F)
(**3**) X = CHF (β-F)



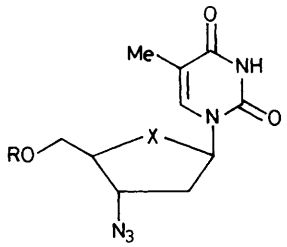
Scheme 1. *Reagents, conditions, and yields:* i, $NEt_3 \cdot 3HF$, CH_2Cl_2, room temp., 67 h, 55%; ii, MCPBA, $NaHCO_3$, CH_2Cl_2, room temp., 22 h, 57%; iii, NH_3 (liquid), −33 °C, 1.5 h, 80%; iv, t-butylchlorodiphenylsilane, imidazole, *N,N*-dimethylformamide (DMF), room temp., 29 h; v, $PhI(OCOCF_3)_2$, MeCN, H_2O, pyridine, room temp., 6 h, 56% [from (**8**)]; vi, MeOCH=C(Me)CONCO, benzene, DMF, −20 °C → room temp., over 1 h, then room temp., 15 h, 80%; vii, NaN_3, dimethyl sulphoxide (DMSO), 55 °C, 0.75 h, 74%; viii, 2 M aqueous HCl/dioxane (1 : 1), 80 °C, 0.5 h, 44%.



Scheme 2. *Reagents, conditions, and yields:* i, H_2O/THF, room temp., 39 h, 89%; ii, MCPBA, $NaHCO_3$, CH_2Cl_2, room temp., 6 h, 100%; iii, DAST, CH_2Cl_2, room temp., 12 h, 28% (**18**), 55% (**16**); iv, NH_3 (liquid), −33 °C, 1 h, 83%; v, t-butylchlorodiphenylsilane, imidazole, DMF, room temp., 4 h, 97%; vi, $PhI(OCOCF_3)_2$, MeCN, H_2O, pyridine, room temp., 6.5 h, 75%; vii, MeOCH=C(Me)CONCO, benzene, DMF, −20 °C, room temp. over 1 h, then room temp. 15 h, 75%; viii, 2 M aqueous HCl/dioxane (1 : 1), reflux, 1.5 h, evaporated, then t-butylchlorodiphenylsilane, imidazole, DMF, room temp., 1 h, 70%; ix, H_2, $Pd(OH)_2$/C, AcOEt, EtOH, room temp., 24 h, not isolated; x, $MeSO_2Cl$, pyridine, room temp., 8 h, 78% [from (**19**)]; xi, NaN_3, DMSO, 55 °C, 2 h, 54%; xii, tetrabutylammonium fluoride (TBAF), THF, room temp., 4 h, 100%.

advantage can be gained from the enhanced stability of the carbocyclic nucleosides which are, for example, not degraded by phosphorylases *in vivo*. Thus, in terms of searching for a potentially superior compound for the treatment of AIDS, the nucleoside analogues (**2**) and (**3**) represented interesting target compounds.

The sugar mimic (**2**) was synthesized by the method shown in Scheme 1. The strained tricyclic ketone (**4**)[7] was opened by triethylamine trihydrofluoride[8] in methylene chloride to give the dihaloketone (**5**). Other sources of fluoride anion were much less satisfactory for this type of ring opening reaction. Baeyer–Villiger reaction of compound (**5**) gave, as expected,[9] the isomeric δ-lactones (**6**) and (**7**) in the ratio 1 : 4. The mixture does not have to be separated since the major product (**7**) was converted into the polar amide (**8**) using liquid ammonia while the minor component (**6**) was recovered unchanged:[10] the amide (**8**) was purified by chromatography over silica and transformed into the required amine (**9**) in two steps using [bis(trifluoroacetoxy)iodo]benzene as the reagent of choice for the Hofmann reaction.[11] Reaction of the isocyanate (**10**) with the amine (**9**) gave the compound (**11**). Nucleophilic displacement of the bromine atom by an azide ion proceeded satisfactorily to afford the required derivative of urea (**12**) [as well as a small amount of the product (**13**) resulting from an elimination process] and compound (**12**) was cyclized using mineral acid to give the required carbocyclic nucleoside (**2**) (m.p. 178—179 °C).



(**20**) R = $P_3O_9^{4-}$, X = O
(**21**) R = $P_3O_9^{4-}$, X = CHF (α-F)
(**22**) R = $PO(OBu^t)_2$, X = O
(**23**) R = $P(O)(OH)O^-NH_4^+$

The second target, compound (**3**), was prepared by a slightly different route (Scheme 2). The tricycle (**14**)[12] reacted with aqueous tetrahydrofuran (THF) to give the alcohol (**15**). Baeyer–Villiger oxidation of the hydroxyketone (**15**) gave a mixture of lactones (**16**) and (**17**) in the ratio 62 : 38. This mixture was treated with diethylaminosulphur trifluoride (DAST) to furnish the required fluorolactone (**18**) (28%) and unreacted hydroxylactone (**16**) (55%). The halolactone (**18**) was converted into the nucleoside analogue (**19**) in five steps. Debenzylation, formation of the methane sulphonate derivative, displacement of the mesylate moiety with an azide ion, and desilylation completed the synthesis of the required compound (**3**) (m.p. 176—177 °C).

The biological activity of compounds (**2**) and (**3**) was interesting in that compound (**2**) showed activity (ED_{50} 100 μg/ml) against HIV infected cells whereas the isomer (**3**) was less active. In order to compare the ability of AZT (**1**) and 6′-fluorocarbocyclic AZT (**2**)[13] to inhibit HIV-coded reverse transcriptase the corresponding triphosphates, (**20**) and (**21**), were prepared by a method involving a new strategy for the preparation of the requisite monophosphate intermediates. Thus AZT was reacted with di-t-butyl *N*,*N*-diethylaminophosphoramidite[14] to give the trialkyl phosphite which, without isolation, was oxidised using *m*-chloroperoxybenzoic acid (MCPBA) in methylene chloride at −40 °C for five minutes to provide the phosphate ester (**22**). Removal of the t-butyl groups, using trifluoroacetic acid in methylene chloride at room temperature for one hour, gave the corresponding nucleoside monophosphate which was treated with ammonia to give the ammonium salt (**23**). The ammonium phosphate ester (**23**) was transformed into the triphosphate (**20**) by formation of the corresponding imidazolidate and reaction with tributylammonium pyrophosphate.[15] The product was purified on a Sephadex DEAE A-25 anion exchange column and eluted using a linear gradient of water and triethylammonium hydrogen carbonate (0—0.4 M) to yield the triphosphate (**20**) (86% yield), isolated as the tris-triethylammonium salt: δ_H (CD_3OD) 7.81 (1H, q, *J* 1 Hz, H-6),6.24 (1H, dd, *J* 8, 6 Hz, H-1′), 4.62 (1H, m, H-4′), 4.32—4.08 (3H, m, 2 × H-5′ and H-3′), 3.17 (18H, q, *J* 7 Hz, 9 × NCH_2), 2.49 (1H, ddd, *J* 14, 8, 6.5 Hz, H-2′), 2.32 (1H, ddd, *J* 14, 6, 3 Hz, H-2′), 1.93 (3H, d, *J* 1 Hz, Me–C-5), 1.30 (27H, t, *J* 7 Hz, 9 × Me). The triphosphate (**21**) was prepared in a similar manner [δ_H (CD_3OD) 7.67 (1H, q, *J* 1 Hz, H-6), 5.26 (1H, dt, *J* 54, 7 Hz, H-6′), 5.10 (1H, m, H-1′), 4.32—4.21 (3H, m, 2 × H-5′ and H-3′), 3.18 (18H, q, *J* 7 Hz, 9 × NCH_2), 2.48—2.06 (3H, m, H-4′ and 2 × H-2′), 1.92 (3H, d, *J* 1 Hz, Me–C-5), 1.31 (27H, t, *J* 7 Hz, 9 × Me)].

AZT-triphosphate (**20**) proved to be a better inhibitor of HIV reverse transcriptase than the analogue (**21**) by two orders of magnitude.

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References

1 M. S. Gottlieb, R. Schroff, H. M. Schanker, J. D. Weisman, P. T. Fan, R. A. Wolf, and A. Saxon, *New Engl. J. Med.*, 1981, **305**, 1425; 1431; and 1439.
2 H. Mitsuya and S. Broder, *Nature*, 1987, **325**, 773.
3 E. De Clercq, *TIPS Reviews*, 1987, **8**, 339.
4 H. Mitsuya, K. J. Weinhold, P. A. Furman, M. H. St. Clair, S. Nusinoff-Lehrman, R. C. Gallo, D. Bolognesi, D. W. Barry, and S. Broder, *Proc. Natl. Acad. Sci. U.S.A.*, 1985, **82**, 7096; H. Mitsuya and S. Broder, *ibid.*, 1986, **83**, 1911; T. S. Lin, M. S. Chen, C. McLaren, Y.-S. Gao, I. Ghazzanli, and W. H. Prusoff, *J. Med. Chem.*, 1987, **30**, 440; E. Matthes, Ch. Lehmann, D. Scholz, H. A. Rosenthal, and P. Langen, *Biochem. Biophys. Res. Commun.*, 1988, **153**, 825; P. Scheiner, A. Geer, A.-M. Bucknor, J.-L. Imbach, and R. F. Schinazi, *J. Med. Chem.*, 1989, **32**, 73.
5 K. Biggadike, A. D. Borthwick, A. M. Exall, B. E. Kirk, S. M. Roberts, P. Youds, A. M. Z. Slawin, and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1987, 255.
6 G. M. Blackburn and D. E. Kent, *J. Chem. Soc., Perkin Trans. 1*, 1986, 913.
7 J. C. Gilbert, T. Luo, and R. E. Davis, *Tetrahedron Lett.*, 1975, 2545; Z. Grudzinski and S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1767.
8 R. Franz, *J. Fluorine Chem.*, 1980, **15**, 423.
9 Z. Grudzinski, S. M. Roberts, C. Howard, and R. F. Newton, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1182.
10 *Cf.* R. F. Newton, D. P. Reynolds, C. F. Webb, S. N. Young, Z. Grudzinski, and S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2789.
11 M. R. Almond, J. B. Shimmel, A. E. Thompson, and G. H. Loudon, *Org. Synth.*, 1987, **66**, 132.
12 T. V. Lee, S. M. Roberts, and R. F. Newton, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1179.
13 G. V. Madhavan and J. C. Martin, *J. Org. Chem.*, 1986, **51**, 1287.
14 J. W. Perich and R. B. Johns, *Synthesis*, 1988, 142.
15 D. E. Hoard and D. G. Ott, *J. Am. Chem. Soc.*, 1965, **87**, 1785.