

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

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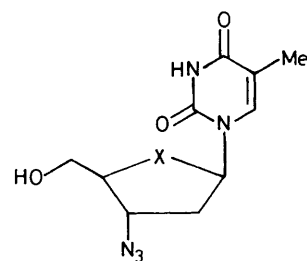
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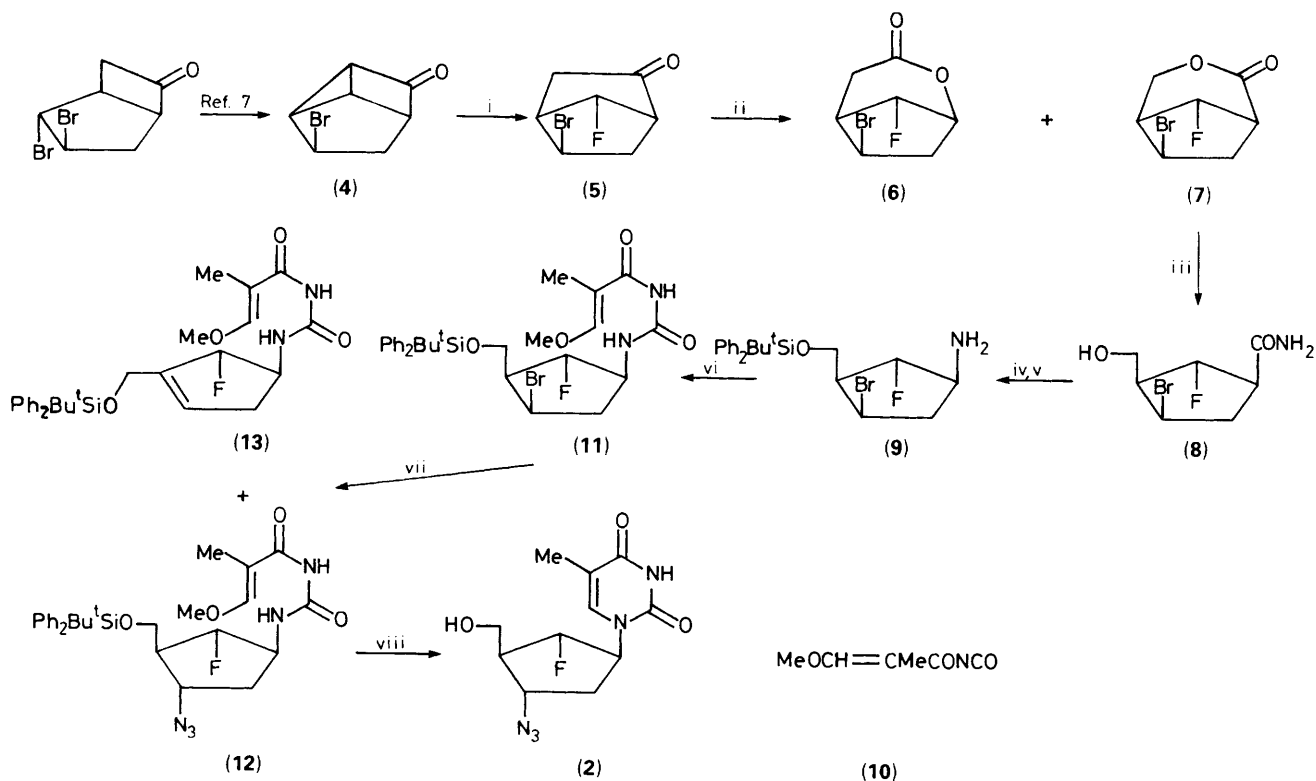
The carbocyclic nucleosides (**2**) and (**3**) have been prepared and tested for anti-HIV activity: AZT-triphosphate (**20**) (AZT = 3'-deoxy-3'-azidothymidine) was synthesized by a new procedure and the same method was used to make the novel triphosphate (**21**).

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. We⁵

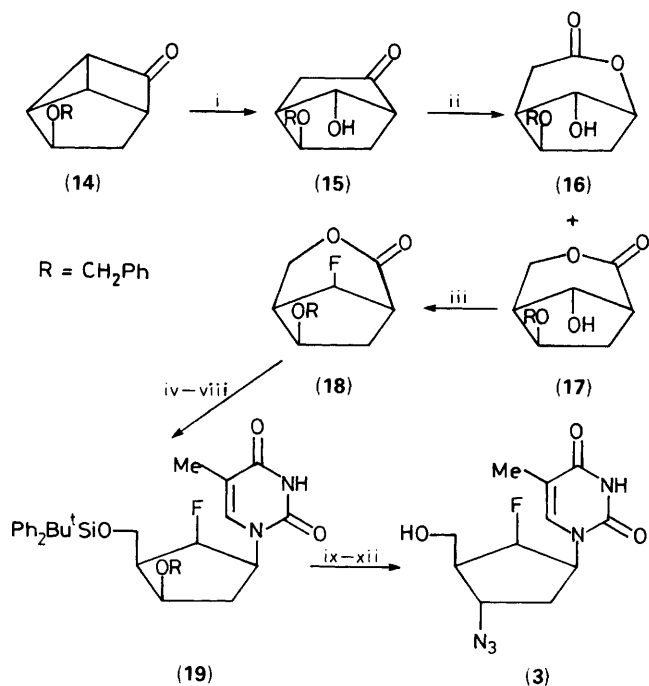
and others⁶ have argued that exchange of the ring oxygen atom in the sugar unit for an isosteric fluoromethylene unit may well lead to retention of a substantial part of the useful biological activity shown by the parent sugar. Considerable



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



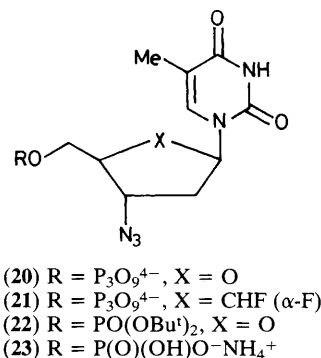
Scheme 1. Reagents, conditions, and yields: i, $\text{NEt}_3 \cdot 3\text{HF}$, CH_2Cl_2 , room temp., 67 h, 55%; ii, MCPBA, NaHCO_3 , CH_2Cl_2 , room temp., 22 h, 57%; iii, NH_3 (liquid), -33°C , 1.5 h, 80%; iv, *t*-butylchlorodiphenylsilane, imidazole, *N,N*-dimethylformamide (DMF), room temp., 29 h; v, $\text{PhI}(\text{OCOCF}_3)_2$, MeCN, H_2O , pyridine, room temp., 6 h, 56% [from (**8**)]; vi, $\text{MeOCH}=\text{C}(\text{Me})\text{CONCO}$, benzene, DMF, $-20^\circ\text{C} \rightarrow$ 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, H₂O/THF, room temp., 39 h, 89%; ii, MCPBA, NaHCO₃, CH₂Cl₂, room temp., 6 h, 100%; iii, DAST, CH₂Cl₂, room temp., 12 h, 28% (18), 55% (16); iv, NH₃ (liquid), -33 °C, 1 h, 83%; v, *t*-butylchlorodiphenylsilane, imidazole, DMF, room temp., 4 h, 97%; vi, PhI(OCOCF₃)₂, MeCN, H₂O, 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, H₂, Pd(OH)₂/C, AcOEt, EtOH, room temp., 24 h, not isolated; x, MeSO₂Cl, pyridine, room temp., 8 h, 78% [from (19)]; xi, NaN₃, 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 trihydrofluoride⁸ 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).



The second target, compound (3), was prepared by a slightly different route (Scheme 2). The tricyclic ketone (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 (ED₅₀ 100 μ g/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*-diethylamino-phosphoramidite¹⁴ 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} (CD₃OD) 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 \times H-5' and H-3'), 3.17 (18H, q, *J* 7 Hz, 9 \times NCH₂), 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 \times Me). The triphosphate (21) was prepared in a similar manner [δ_{H} (CD₃OD) 7.67 (1H, q, *J* 1 Hz, H-6), 5.26 (1H, dt, *J* 5.4, 7 Hz, H-6'), 5.10 (1H, m, H-1'), 4.32–4.21 (3H, m, 2 \times H-5' and H-3'), 3.18 (18H, q, *J* 7 Hz, 9 \times NCH₂), 2.48–2.06 (3H, m, H-4' and 2 \times H-2'), 1.92 (3H, d, *J* 1 Hz, Me-C-5), 1.31 (27H, t, *J* 7 Hz, 9 \times 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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