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TETRAHYDROTHIOPHENE NUCLEOSIDES AS POTENTIAL ANTI-HIV AGENTS[1]

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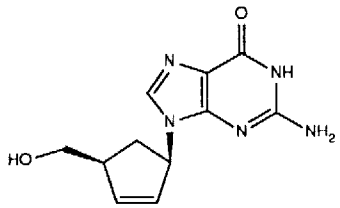
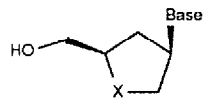
Summary : A series of novel tetrahydrothiophene nucleosides have been prepared in homochiral form from D-glucose and assessed as anti-HIV agents in whole cell assay.

The potential offered by carbocyclic nucleosides as anti-HIV agents has been demonstrated by Carbovir (1)[2,3]. An advantageous feature of members of this class is their increased stability to enzymic and acid hydrolysis, which is conferred by the replacement of the furanose oxygen by a methylene group in this series of nucleoside analogues. Recent reports by workers at Hoffmann-La Roche[4,5] and by Orgel[6] describe 3′-oxa (2) and 3′-aza (3) variants, some of which display marked anti-HIV activity. Modification of the 3′ position of carbocyclic nucleosides is, therefore, clearly an area which merits further investigation. For our part, we have described[1] an alternative route to iso-ddA ((2), Base = Adenine) and confirmed the significant anti-HIV activity of this compound. The corresponding tetrahydrothiophenes (4) presented themselves as prime targets and we now report an enantiospecific route to this novel class of nucleoside analogues.



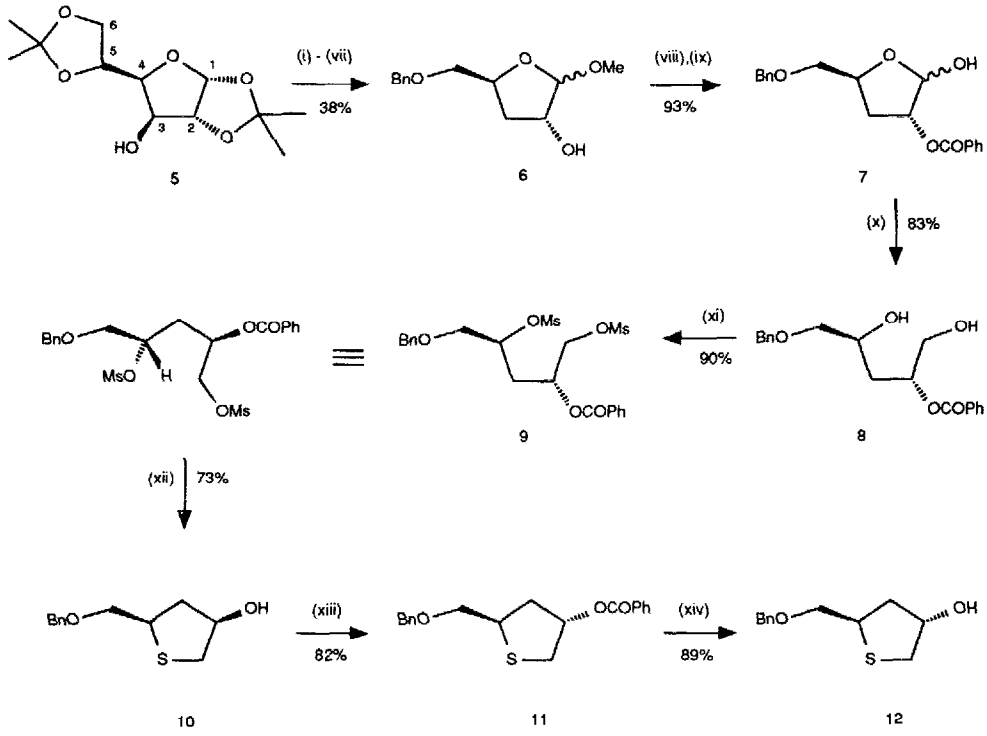
1 Carbovir



Base = Guanine, Adenine, Thymine, Cytosine, Uracil

2 X = O; 3 X = NH; 4 X = S.

Benzyl ether (6) (Scheme 1) was obtained from diacetone-D-glucose (5) in 38% overall yield, as a 4:1 β/α anomeric mixture, by a series of straightforward transformations well known in the carbohydrate literature[7]. The initial part of the sequence followed generally that described by Masamune[8] with the exception that the radical deoxygenation of the 3-position was carried out *via* the xanthate rather than the phenyl thiocarbonate derivative. The synthesis then called for protection of the C-2 hydroxyl, followed by acetal hydrolysis and reductive ring opening to an acyclic diol (8). The benzoate ester derived from (6) underwent acid mediated acetal hydrolysis to afford the lactol (7). Sodium triacetoxyborohydride proved to be

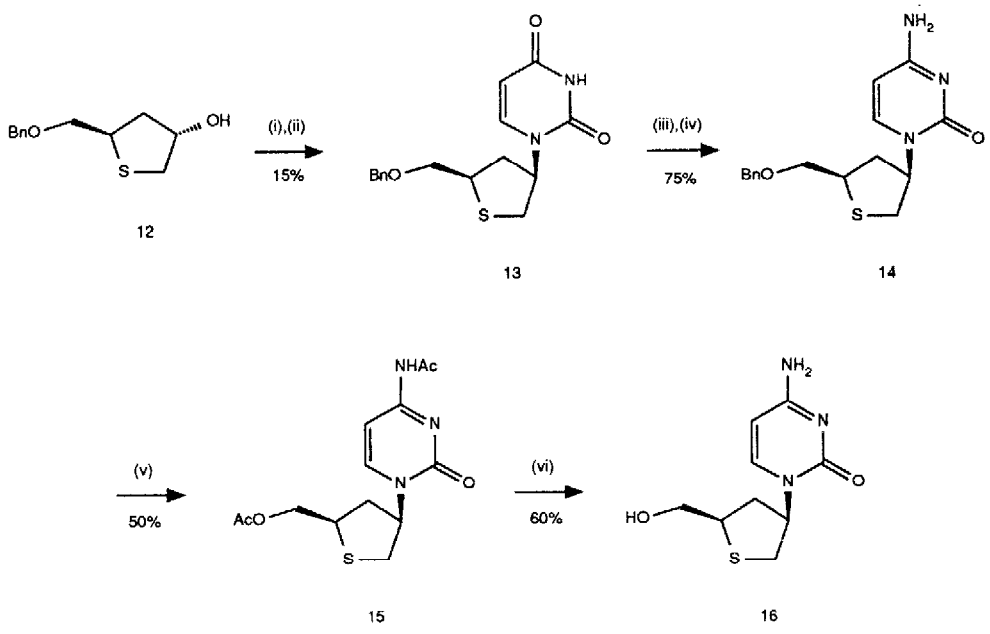


(i) NaH, CS_2, THF; MeI. (ii) nBu_3SnH, AIBN, PhMe, Δ. (iii) HCl, H_2O, MeOH. (iv) $NaIO_4$, MeOH, H_2O. (v) $NaBH_4$, MeOH. (vi) NaH, BnBr, nBu_4NI, THF. (vii) MeOH, Dowex 50W-X8(H), Δ. (viii) PhCOCl, DMAP, CH_2Cl_2. (ix) TFA, H_2O, THF. (x) $NaBH(OAc)_3$, PhMe, Δ. (xi) MsCl, pyr, CH_2Cl_2. (xii) Na_2S, DMF, Δ. (xiii) Ph_3P, DEAD, $PhCO_2H$, THF. (xiv) K_2CO_3, MeOH.

Scheme 1

the reducing agent of choice, providing the diol (8) in excellent yield. Ring closure of the bis-mesylate (9) was effected smoothly upon exposure to anhydrous sodium sulphide in DMF at 100°C [9]. Concomitant loss of the benzoate ester occurred, furnishing the tetrahydrothiophene (10) in good yield. Epimerisation of the secondary hydroxyl was achieved by Mitsunobu esterification[10] followed by deprotection to afford (12).

Elaboration of (12) to compounds of interest was *via* mesylate activation followed by S_N2 displacement by a range of nucleoside heterocyclic bases, employing the method of Johnson and co-workers[11]. The purines, adenine and 2-amino-6-chloropurine, reacted to afford predominantly the N-9 alkylated products in 40% and 38% yield respectively. Displacement by pyrimidine bases was less efficient and the low yield reported for the uracil alkylation to afford (13) was typical.



(i) MsCl, DMAP, CH_2Cl_2. (ii) Uracil, K_2CO_3, DMSO, Δ. (iii) 1,2,4-Triazole, Et_3N, $POCl_3$, CH_3CN. (iv) NH_3, Dioxan, H_2O. (v) $BF_3.Et_2O$, Ac_2O. (vi) NH_3, MeOH.

Scheme 2

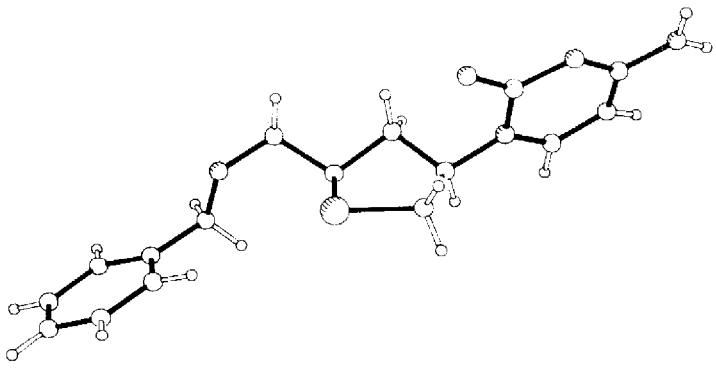


Figure 1

The conclusion of the route is exemplified by the preparation of the cytidine analogue (16) (Scheme 2). Conversion of the heterocyclic base from uracil to cytosine followed established procedures[12] to afford (14), whose structure was unambiguously established by single crystal X-ray diffraction analysis (Figure 1). A two step deprotection procedure was adopted for the removal of the benzyl protecting group. Boron trifluoride acetolysis followed by treatment with ammonia furnished the target molecule (16) in good yield.

Debenzylation of the adenine, uracil, thymine and 9-(2-amino-6-chloropurine) variants of (14) was achieved by exposure to boron tribromide at low temperature (-78°C). Final conversion to the guanine target was accomplished by hydrolysis of the 2-amino-6-chloropurine variant with hot hydrochloric acid.

None of the target compounds showed anti-HIV activity in whole cell assay (MT-4 cells, RF strain of HIV-1) at concentrations below 100μg/ml[13]. This is in sharp contrast to iso-ddA and iso-ddG which demonstrated significant activity in parallel assay. A possible reason for this is that the tetrahydrothiophene nucleosides are not recognised by the cellular kinases which are responsible for the activation of anti-HIV nucleoside agents to the corresponding triphosphates.

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