Preparation of Nucleotide Mimics with Potent Inhibitory Activity Against HIV Reverse Transcriptase

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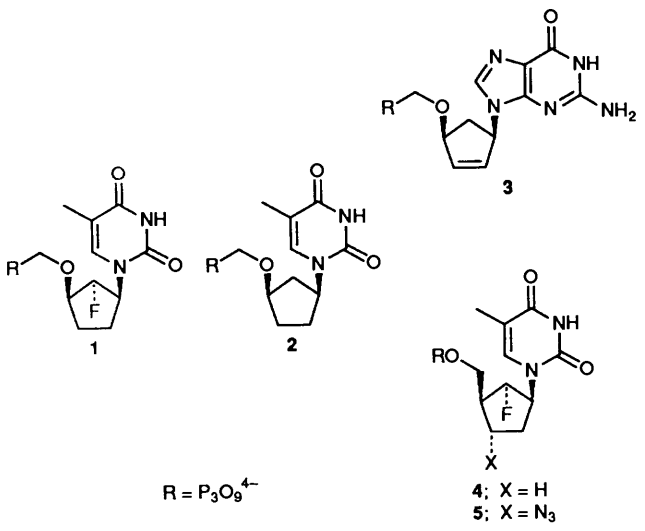
The triphosphate **11** has been synthesised in eight steps from 6-oxabicyclo[3.1.0]hex-2-ene **6** and has been shown to inhibit the enzyme, human immunodeficiency virus reverse transcriptase (HIV-rt).

We have been interested for some time in the synthesis of compounds active against the AIDS virus (HIV).[1,2] Our strategy has involved the preparation of carbocyclic nucleosides and nucleotides designed to inhibit HIV-reverse transcriptase (HIV-rt) and to be relatively stable *in vivo*.[3]

Recently we described the synthesis of the carbocyclic nucleotide **1** and reported that the compound displayed potent inhibition of HIV-rt.[4] The diphosphorylphosphonates **2** and **3** were also prepared from the corresponding phosphonates[4] and show similar, quite spectacular biological activity (Table 1). It is noteworthy that, in comparison, the carbocyclic nucleoside 5′-triphosphates **4**[5] and **5**[1] show a relatively low level of reverse transcriptase inhibitory activity.

To further investigate the potential antiviral activity of unusual nucleotide mimics, the carbocyclic compound **11** has been prepared from 6-oxabicyclo[3.1.0]hex-2-ene **6**[6] by the route described in Scheme 1. Thus the epoxide **6** was treated with tetrakis(triphenylphosphine)palladium(0) and thymine to give the unsaturated alcohol **7** (24% yield). Hydrogenation of **7** gave *N*-cyclopentylthymine, so the hydroxy group was protected from hydrogenolysis by conversion into the *tert*-butyldimethylsilyl derivative. Reduction of **8** (hydrogen and palladium-on-carbon) followed by treatment with fluoride ion gave the required alcohol **9** (63% from **7**). The critical steps involving the conversion of the alcohol **9** into the triphosphate **11** *via* the monophosphate **10** used methodology that we have previously shown to be well suited to the task.[7]

The compound **11** prepared as a racemate, acted as an inhibitor of reverse transcriptase (Table 1) albeit at a level two orders of magnitude weaker than AZT-triphosphate. It is very



Scheme 1 *Reagents and conditions:* i, $(Ph_3P)_4Pd$, thymine, DMF, heat; ii, TBDMSCl, imidazole, DMF, room temp.; iii, H_2, Pd/C, EtOH, room temp.; iv, TBAF, THF, room temp.; v, Di-*tert*-butyl *N*,*N*′-diethylphosphoramidite, 1*H*-tetrazole, THF, room temp., vi, MCPBA, CH_2Cl_2, − 40 °C; vii, CF_3CO_2H, CH_2Cl_2, room temp. then NH_3, EtOH, −2 °C; vii, 1,1′-carbonyldiimidazole, DMF, room temp., then $P_2O_7H_4NBu_3$, DMF, room temp.

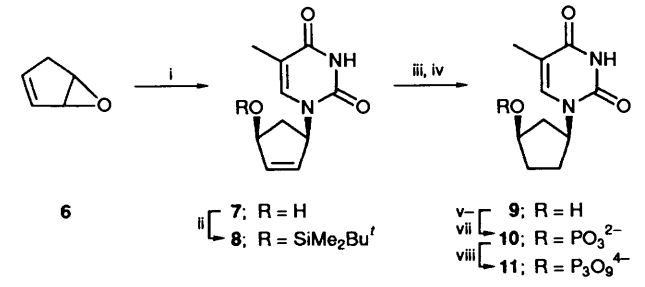


Table 1 Activity of some carbocyclic nucleotides against HIV-rt *

Compound[a]	IC_{50} Against HIV-rt (μmol)
AZT-triphosphate	0.08
Carbovir-triphosphate	0.05
1	0.43
2	0.11
3	0.06
4	16.5
5	13.9
11	7.9

* AZT triphosphate and the thymidine analogues were assayed using (rA)(dT) as the template primer and [^{3}H]dTTP as substrate. In cases of carbovir triphosphate and compound **3**, (rC)(dG) was used as the template primer and [^{3}H]dGTP as substrate.

[a] All compounds **1**–**5**, **11** were prepared in racemic form.

rare to find a triphosphate ester derived from a secondary alcohol with an ability to act as an inhibitor of a virally-coded enzyme. The synthesis of such a simple compound with inhibitory activity against HIV-rt should act as a stimulus to further work in this area.

Experimental

1-[(1′β,4′β)-4′-Hydroxycyclopent-2′-enyl]thymine **7**.— Tetrakis(triphenylphosphine)palladium(0) (0.097 g, 0.08 mmol) was added to a suspension of thymine (1.120 g, 8.88 mmol) in dry DMSO (10 cm^3) under an inert atmosphere in the dark. After being stirred for 2 min at room temp. the reaction mixture was cooled to 0 °C and a solution of 6-oxabicyclo[3.1.0]hex-2-ene **6** (0.649 g, 7.91 mmol) in dry THF (8 cm^3) was added dropwise over 10 min. The yellow solution was allowed to warm to room temperature over 2 h and then stirred overnight. The solvent was evaporated under reduced pressure and the residue dissolved in dichloromethane (20 cm^3), filtered through Celite and evaporated under reduced pressure. The residue was chromatographed using chloroform–ethanol (15:1) to give the title compound **7** (0.0406 g, 1.94 mmol, 24%) as a white crystalline solid, m.p. 196–199 °C (from isopropyl alcohol) (Found: C, 57.55; H, 5.9; N, 13.1. $C_{10}H_{12}N_2O_3$ requires C, 57.69; H, 5.80; N, 13.45%); λ_{max}(pH 6 phosphate buffer)/nm 272.0 (10 050); ν_{max}(KBr)/cm^{-1} 3600–3300s br (NH, OH) and 1688s br (C=O, thymine); δ_H(250 MHz; [$^2H_6$]-DMSO) 11.25 (1 H, s, NH), 7.29 (1 H, s, 6-H), 6.13 (1 H, ddd, *J*† 6, 2, 2, 3′-H), 5.82–5.76 (1 H, m, 2′-H), 5.43–5.33 (1 H, m, 1′-H), 5.23 (1 H, d, *J* 5, OH), 4.68–4.53 (1 H, m, 4′-H), 2.73 (1 H, ddd, *J* 14, 7, 7, α5′-H), 1.76 (3 H, s, Ch_3) and 1.36 (1 H, ddd, *J* 14, 4.5, 4.5, β5′-H); δ_C(62.9 MHz; [$^2H_6$]-DMSO) 163.70, 150.73 (C-2, C-4), 139.88, 137.10, 130.78 (C-6, C-2′, C-3′), 109.24 (C-5), 73.29 (C-4′), 57.75 (C-1′), 40.09 (C-5′) and 12.03 [CH_3C(5)].

† *J*-Values are given in Hz.

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