Synthesis of Some Mimics of Nucleoside Triphosphates

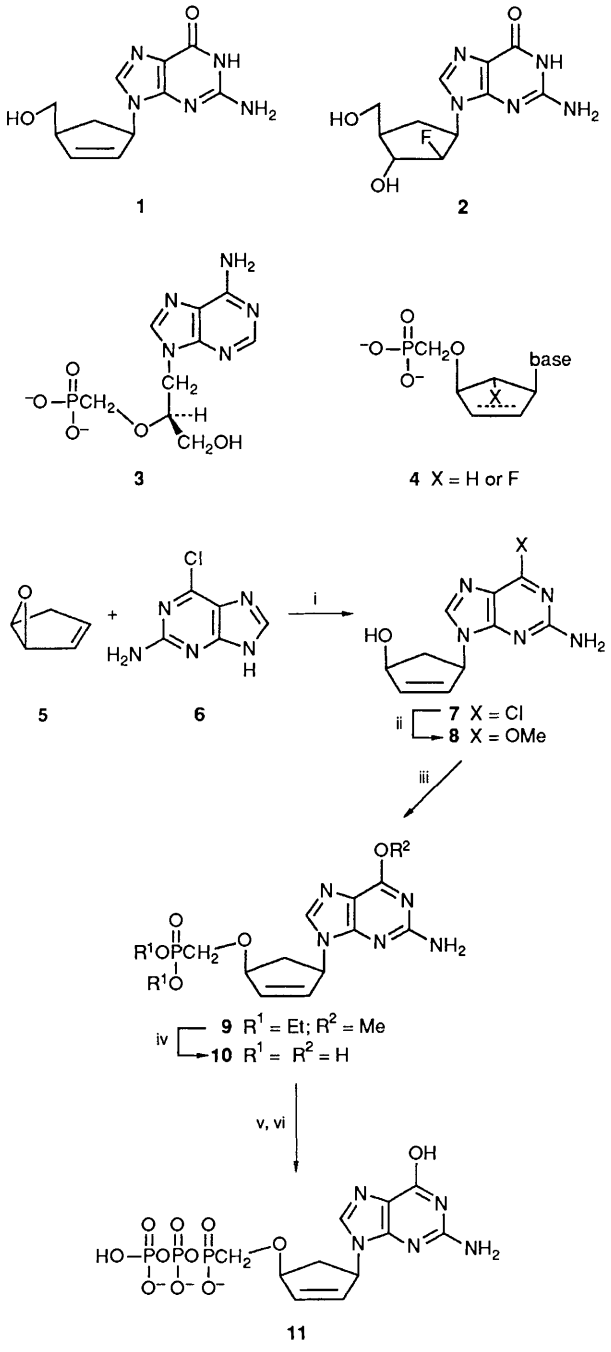
Diane M. Coe,[a] Hans Hilpert,[a] Stewart A. Noble,[b] Michael R. Peel,[c] Stanley M. Roberts[a] and Richard Storer[b]

[a] *Department of Chemistry, Exeter University, Stocker Road, Exeter, Devon EX4 4QD, UK*
[b] *Department of Medicinal Chemistry, Glaxo Group Research, Greenford, Middlesex UB6 0HE, UK*
[c] *Department of Chemistry, Glaxo Inc., North Carolina, USA*

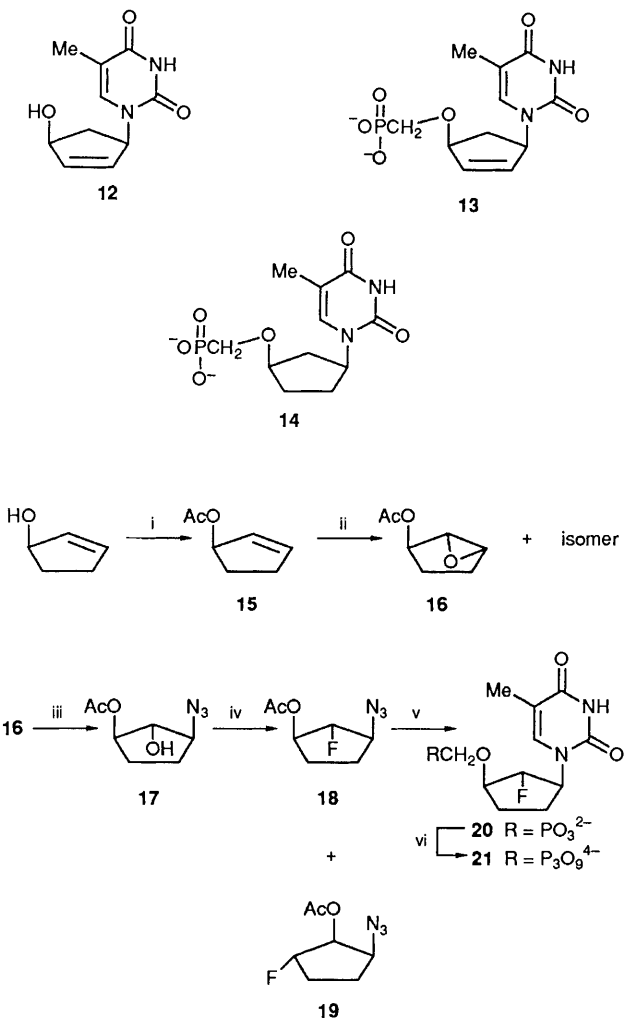
The nucleotide analogues **10**, **13**, **14** and **20** have been synthesised; the latter phosphonate was converted into the diphosphoryl-phosphonate **21** and this compound was shown to be a potent inhibitor of HIV-coded reverse transcriptase.

There is considerable current interest in the synthesis of carbocyclic nucleosides (for example carbovir **1**[1] and carbocyclic-AFG **2**[2]) and selected phosphonates [*e.g.* (*S*)-HPMPA **3**[3]] as antiviral agents. As a result of hybridizing these two strategies, which are both aimed at the design of metabolically stable, biologically active nucleoside analogues, we set ourselves the target of preparing phosphonates of the type **4**.

The epoxide **5** is readily available.[4] Reaction of this compound with the purine **6** using a Pd^0 catalyst[5] gave the cyclopentene derivative **7** (Scheme 1) as a white crystalline



Scheme 1 *Reagents*: i, $(Ph_3P)_4Pd$, dimethyl sulphoxide (DMSO), tetrahydrofuran (THF), 18 h, 0–20 °C (57%); ii, K_2CO_3, MeOH, 45 min, reflux (86%); iii, NaH, THF then $(EtO)_2P(O)CH_2O$-$SO_2C_6H_4Me$-*p* (25%); iv,Me_3SiI, dimethylformamide (DMF), 18 h, room temp. (25%); v; *N,N'*-dicyclohexylcarbodiimide, morpholine, Bu^tOH, H_2O, reflux 4.5 h; vi, tributylammonium pyrophosphate, DMSO, room temp., 108 h

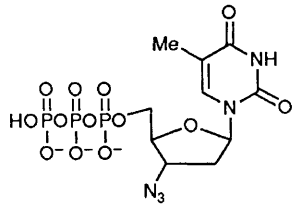


Scheme 2 *Reagents*: i, Ac_2O, pyridine (90%); ii, *m*-chloroperoxybenzoic acid; iii, NaN_3, NH_4Cl, EtOH, H_2O, (83%); iv, $(CF_3SO_2)_2O$, pyridine then H_2O; work-up then DAST, CH_2Cl_2, room temp.; v, NH_3–MeOH, room temp., 14 h then NaH, dry THF then $(EtO)_2$-$P(O)CH_2OSO_2C_6H_4Me$-*p*, then H_2, MeOH, Lindlar cat., then β-methoxy-α-methylacryloyl isocyanate, C_6H_6, DMF, room temp., 12 h, then 2 mol dm^{-3} H_2SO_4, 100 °C 1 h, then Me_3SiI, DMF, room temp., 12 h then 0.2 mol dm^{-3} $Et_3NH_2CO_3$, room temp., 3 h (18% overall); vi, 1,1'-carbonyldiimizadole, DMF, room temp., 6.5 h then $Bu^n_3NH_4P_2O_7$, DMF, room temp. (53%)

solid, m.p. 156–158 °C. Nucleophilic substitution of the chlorine atom for a methoxy group furnished the purine **8**, m.p. 152–153 °C and reaction of the methoxy compound with sodium hydride and diethyl *p*-tolylsulphonyloxymethanephosphonate[6] gave the phosphonate **9**. Treatment of the latter compound with trimethylsilyl iodide led to removal of the ethyl and methyl protecting groups; the crude product was purified by chromatography over Sephadex LH-20 [eluent methanol–aqueous formic acid (0.1 mol dm^{-3}), ratio 1 : 1] followed by HPLC over Microsorb C18 [eluent 10% methanol in water] to give the guanine derivative **10**. The phosphonate **10** was transformed into the corresponding morpholidate and treated with tributylammonium pyrophosphate[7] to afford the diphosphorylphosphonate **11**. Pure material was obtained (as the trisammonium salt) by chromatography over Sephadex DEAE-A25 using water and ammonium hydrogen carbonate (0.4 mol dm^{-3}) as eluent (30% yield). The spectral characteristics of compound **11** were as follows: λ_{max}/nm (pH 7.5 buffer) 256 and 276; ν_{max}/cm^{-1} 3600–2600, 1691, 1614 and 1240; ^1H NMR δ (250 MHz, D_2O), *inter alia* 7.97 (s, 1H, 8-H), 6.53 (1H, d, J 6 Hz, 3'-H), 6.24 (1H, dm, *J* 6 Hz, 2'-H), 5.48 (1H, m, 1'-H), 4.02 (2H, d, *J* 9 Hz, PCH_2O), 3.15 (1H, ddd, *J* 15, 8 and 8 Hz, 5'-H), 2.05 (1H, ddd, *J* 15, 4 and 4 Hz, 5'-H); ^{31}P NMR δ (162 MHz, D_2O), 9.6 (1-P), −7.7 (3-P) and −21.6 (2-P).

5-Methylpyrimidine-2,4-dione reacted with the epoxide **5** to give the alcohol **12**. This compound was transformed into the nucleoside analogues **13** and **14** using similar methods to those described above for the key step, namely phosphonate formation.

The synthesis of an analogue of a 6'-fluorocarbocyclic nucleoside required a different strategy (Scheme 2). Thus cyclopent-2-en-l-ol[8] was converted into the acetate **15**. Treat-



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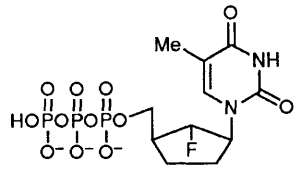

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ment of this alkene with peracid gave two epoxides (ratio 5:4); the major product **16** (52%) was isolated by chromatography. Epoxide ring opening by azide ion was regiospecific furnishing the alcohol **17** (83%). Inversion of the hydroxy group (using trifluoromethanesulphonic anhydride in pyridine followed by water) and then treatment with diethylaminosulphur trifluoride (DAST) gave the required fluoro-azide **18** (38%) and a small amount of the isomer **19** (14%). The azide **18** was converted into the nucleoside analogue **20** (18% overall yield; isolated as the triethylammonium salt) and the latter compound was transformed into the triphosphate analogue **21** (53%) *via* the appropriate imidazolidate. The spectral data for compound **21** are as follows: λ_{max} 270 nm; ν_{max}/cm^{-1} (KBr) 1695 and 1240; ^1H NMR δ (250 MHz, CD_3OD), *inter alia* 7.59 (1H, br s, 6-H), 5.16 (1H, ddd, *J* 52, 5, 3 Hz, 5′-H), 4.95 (1H, dm, *J* 20 Hz, 1′-H), 4.13 (1H, dm, *J* 14 Hz, 4′-H), 3.88 (2H, d, *J* 10 Hz, PCH_2O), 2.22–1.95 (4H, m, 2 × 2′-H and 2 × 3′-H) and 1.92 (3H, br s, Me); ^{31}P NMR δ (162 MHz, CD_3OD), 9.5 (1P, d, *J* 26 Hz, 1-P), −7.7 (1P, d, *J* 20 Hz, 3-P) and −20.8 (1P, dd, *J* 26 and 20 Hz, 2-P).

Some of these novel compounds that are reported above proved to have extremely interesting biological properties. For example the diphosphorylphosphonate **21** was shown to be a potent inhibitor of HIV-coded reverse transcriptase. The IC_{50} (0.01 μ mol dm^{-3}) was of the same order of magnitude as that observed for AZT-triphosphate **22**. Equally interesting and thought-provoking was the observation that the carbocylic nucleoside triphosphate **23**[9] was a much less effective inhibitor of the reverse transcriptase (IC_{50} 200 μ mol dm^{-3}). A full discussion of these and other biological results will be published elsewhere.

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