Synthesis of the first homo-3′,5′-cyclic nucleotide

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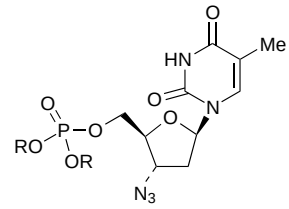
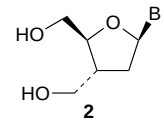
Syntheses of 2′,3′-dideoxy-3′-hydroxymethylcytidine-6′-diphenylphosphate and the corresponding 5′,6′-cyclicphenylphosphate from 5(*S*)-*tert*-butyldimethylsilyloxymethylfuran-2(5*H*)-one are achieved.

In the search for drugs with activity against HIV reverse transcriptase, novel analogues of the natural nucleosides have always been the most popular targets for synthesis. Recent discoveries include biologically potent l-series nucleosides[1] and variously protected phosphates like **1**, which are prodrugs of AZT.[2] Our synthesis of 2′,3′-dideoxy-3′-hydroxymethyl nucleosides of general structure **2** demonstrated that the cytidine derivative (B = cytosine) and 5-fluorocytidine derivative (B = 5-fluorocytosine) had particularly potent activity against a range of viruses,[3] and this encouraged us to try to prepare the monophosphate and cyclic phosphate derivatives for biological evaluation. Here we describe the successful attainment of these goals.

We have previously described the photoinduced addition of methanol to 5(*S*)-*tert*-butyldimethylsilyloxymethylfuran-2(5*H*)-one **3** to produce adduct **4**,[4] but for the present work this reaction was carried out on the 30 g scale with yields in the range 45–50%. Protection of the free hydroxy as its benzoate ester **5a** allowed selective reduction of the lactone (disiamyl borane in THF) and derivatisation of the resultant lactols to yield the anomeric acetates **6a** (overall yield 52%). These were reacted with bis-trimethysilylcytosine in the presence of tin(iv) chloride to yield the protected nucleoside analogue **7a** as a *ca.* 1 : 1 anomeric mixture, which could not be separated by flash chromatography. Selective removal of the benzoate was



1 R = subst. aryl or $RCOSCH_2CH_2$



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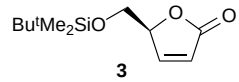

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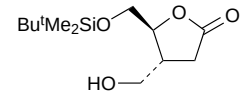

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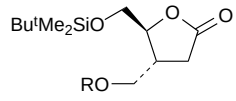
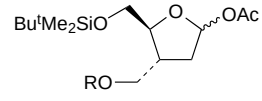
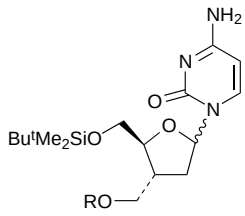


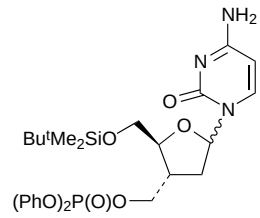
5a R = Bz
b R = Bu^tMe_2Si



6a R = Bz
b R = Bu^tMe_2Si



7a,**b**



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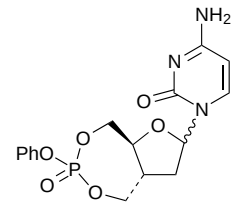

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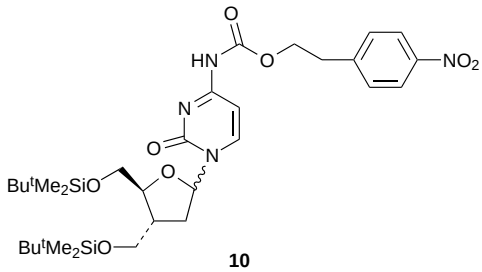

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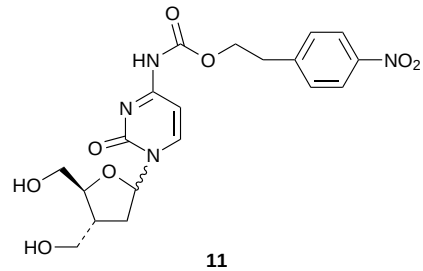

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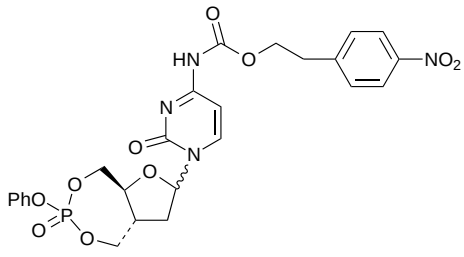

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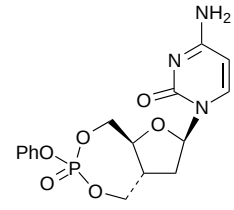

13

possible using base (1% NaOH in MeOH) and the free hydroxy was selectively phosphorylated using a modification of the method of Uchiyama *et al*.[5] This involved reaction of the nucleoside with 1 equiv. of *tert*-butylmagnesium chloride in the presence of diphenylphosphorochloridate to produce the desired 6′-diphenylphosphate **8** (63% yield). We had hoped to convert this compound into the cyclic phosphate **9**, but despite considerable efforts, this goal eluded us.

We thus turned our attention to the bis-silylated adduct **5b** which was reduced (DIBAL-H) and derivatised to provide lactol esters **6b** and thence the protected nucleoside anomers **7b** (52% overall). Protection of the free amino group of the cytosine as its 2-(*p*-nitrophenyl)ethyl carbamate[6] yielded the fully-protected nucleoside anomers **10**, and to our delight the anomers could now be separated (with relative ease) by flash chromatography. (Indeed we have used this protecting group to facilitate separation of anomeric mixtures of several substituted cytidines.) The silyl ether groups of these individual anomers were now removed (toluene-*p*-sulfonic acid in MeOH) and the resultant diols **11** were reacted in pyridine with bis(benzotriazolyl)phenyl phosphate[7] (from 2 equiv. of 1-hydroxybenzotriazole and phenylphosphodichloridate in the presence of triethylamine), to produce the desired cyclic phosphates **12** (35% α and 31% β after chromatography.† The α-anomer was more easily recrystallised than the β-anomer, and an X-ray crystallographic study confirmed the structure of this compound.‡ Finally, the carbamate group was removed from the β-anomer using triethylamine to yield the novel homo-cyclic nucleotide **13**,§ which was submitted for biological evaluation. We had hoped that the compound would act as a prodrug from compound **2** (B = cytosine), a compound with good activity against several viruses.[3] It did in fact show modest activity against HIV-1 (EC_{50} 350 μmolar) and is presently being evaluated in other systems.

All of the reactions as far as compound **11** have been carried out routinely on the half-gram scale (though the cyclic phosphate formation has only been accomplished thus far on the 100 mg scale). One obvious extension of this work is to replace the phenyl group with other aryl groups or by *S*-acyl-2-thioethyl groups as in prodrugs like **1**, in an attempt to improve the bioavailability of the compounds. However, given the pivotal importance of cyclic-3′,5′-AMP and -GMP in biological processes, a more urgent task is to extend this methodology to the purine series in order to make homologues of these very important compounds.

J. G. thanks the MRC for a studentship under the AIDS Initiative Programme and we thank Dr Naheed Mahmood (MRC) for the (ongoing) biological evaluation. We are also very grateful for the advice given by Professor Colin Reese and for the numerous FAB mass spectra provided by the EPSRC Mass Spectrometry Centre at the University of Swansea.

Footnotes

† *Selected spectroscopic data* for the α-anomer of **12**: δ_H (400 MHz, $CDCl_3$ and CD_3OD), integration values for the discrete diastereoisomers have not been given but were in the approximate ratio of 2 : 1 with respect to the signals for the discrete diastereoisomers, 1.75–1.84 (m, 2 × 2′-H), 2.45–2.51 (m, 2′-H), 2.80–2.87 (m, 2 × 3′-H), 2.93–2.99 (m, 2′-H), 3.14 (t, *J* 6.6 Hz, CH_2-npeoc), 3.51 (dd, J_{gem} 11.0, $J_{6',3'}$ 6.6 Hz, 6′-H), 3.59 (dd, J_{gem} 11.0, $J_{6',3'}$ 5.1 Hz, 6′-H), 3.76 (dd, J_{gem} 11.0, $J_{6',3'}$ 4.4 Hz, 6′-H), 3.82 (dd, J_{gem} 11.0, $J_{6',3'}$] 4.0 Hz, 6′-H), 4.12–4.25 (m, 5′-H, 2 × 4′-H), 4.40 (ddd, $J_{5',P}$ 24.9, J_{gem} 11.7, $J_{5',3'}$ 3.7 Hz, 5′-H), 4.47 (t, *J* 6.6 Hz, 2 × CH_2-npeoc), 4.50–4.55 (m, 5′-H), 4.59 (ddd, $J_{5',P}$ 19.2, J_{gem} 10.3, $J_{5',4'}$ 4.2 Hz, 5′-H), 6.02 (t, $J_{1',2'}$ 5.9 Hz, 1′-H), 6.09 (t, $J_{1',2'}$ 6.6 Hz, 1′-H), 7.20–7.27 (m, 2 × 5-H, 4 × Ar), 7.38 (t, *J* 7.7 Hz, 6 × Ar), 7.46 (d, *J* 8.8 Hz, 4 × Ar npeoc), 7.95 (d, $J_{6,5}$ 7.7 Hz, 6-H), 7.99 (d, $J_{6,5}$ 7.3 Hz, 6-H) and 8.19 (d, *J* 8.8 Hz, 4 × Ar npeoc); δ_C (100.4 MHz, $CDCl_3$ and CD_3OD) 34.8 (CH_2-npeoc), 35.7 (C-2′), 36.6 (C-2′), 42.7 (C-3′), 42.8 (C-3′), 62.4 (C-6′), 65.0 (C-6′), 65.4 (CH_2-npeoc), 67.2 (C-5′), 68.4 (C-5′), 81.5 (C-4′), 84.4 (C-4′), 88.3 (C-1′), 88.7 (C-1′), 119.7 (2 × C-5), 123.6 (Ar), 123.8 (Ar), 125.7 (Ar), 129.8 (Ar), 142.8 (Ar), 142.9 (Ar), 143.3 (C-6), 143.4 (C-6), 145.2 (C–NO_2), 146.9 (C-quart), 150.0 (C-quart), 152.8 (2 × C-4), 155.6 (2 × C=O, npeoc) and 163.2 (2 × C-2).

For the β-anomer of **12**: δ_H (400 MHz, $CDCl_3$), integration values for the discrete diastereoisomers have not been given but were in the approximate ratio of 5 : 1 with respect to the signals for the discrete diastereoisomers, 2.29–2.43 (m, 4 × 2-H′), 2.56–2.64 (m, 2 × 3-H′), 3.11 (t, *J* 6.6 Hz, 2 × CH_2-npeoc), 4.09 (dd, J_{gem} 12.8, $J_{6',3'}$ 10.3 Hz, 6′-H), 4.14–4.24 (m, 3 × 6′-H), 4.32 (dd, J_{gem} 11.7, $J_{5',4'}$ 3.7 Hz, 5′-H), 4.34–4.42 (m, 2 × 4′-H, 5′-H), 4.45 (t, *J* 6.6 Hz, 2 × CH_2-npeoc), 4.49–4.58 (m, 5′-H), 4.67 (ddd, $J_{5',P}$ 18.3, J_{gem} 10.6, $J_{5',4'}$ 4.4 Hz, 5′-H), 6.05 (dd, $J_{1',2'}$ 6.8, $J_{1',2'}$ 1.6 Hz, 1′-H), 6.12 (d, $J_{1',2'}$ 7.0 Hz, 1′-H), 7.22 (d, *J* 7.7 Hz, 4 × Ar), 7.32–7.38 (m, 2 × 5-H, 6 × Ar), 7.41 (d, *J* 8.4 Hz, 4 × Ar npeoc), 7.76 (d, $J_{6,5}$ 7.3 Hz, 6-H), 7.89 (d, $J_{6,5}$ 6.6 Hz, 6-H) and 8.17 (d, *J* 8.4 Hz, 4 × Ar npeoc); δ_P (81 MHz, $CDCl_3$) −5.2 and −5.7; *m/z* 572.1294 (M^+) ($C_{25}H_{25}N_4O_{10}P$ requires 572.1308).

‡ We thank A. Jahans and Dr M. G. B. Drew for the X-ray structure determination, which will be described in detail elsewhere. Suffice to say, the compound crystallised in an extended conformation.

§ *Selected spectroscopic data* for **13**: δ_H (400 MHz, CD_3OD), integration values for the discrete diastereoisomers have not been given but were in the approximate ratio of 2 : 1 with respect to the signals for the discrete diastereoisomers, 2.16–2.21 (m, 4 × 2-H′), 2.71–2.78 (m, 2 × 3-H′), 4.0 (dd, $J_{5',P}$ 20.9, J_{gem} 11.0 Hz, 5′-H), 4.05–4.17 (m, 2 × 4′-H, 2 × 5′-H), 4.23 (ddd, $J_{6',P}$ 22.3, J_{gem} 10.3, $J_{6',3'}$ 8.2 Hz, 6′-H), 4.32–4.44 (m, 3 × 6′-H), 4.49 (ddd, $J_{5',P}$ 20.0, J_{gem} 10.3, $J_{5',4'}$ 3.9 Hz, 5′-H), 5.81 (d, $J_{5,6}$ 7.7 Hz, 5-H), 5.83 (d, $J_{5,6}$ 7.7 Hz, 5-H), 5.99 (dd, $J_{1',2'}$ 6.6, $J_{1',2'}$ 3.7 Hz, 1′-H), 6.03 (dd, $J_{1',2'}$ 6.9, $J_{1',2'}$ 2.9 Hz, 1′-H), 7.15 (t, *J* 7.9 Hz, 6 × Ar), 7.30 (t, *J* 7.9 Hz, 4 × Ar), 7.57 (d, *J* 7.7 Hz, 6-H) and 7.59 (d, *J* 7.7 Hz, 6-H); *m/z* 380.1011 [$(M + H)^+$] ($C_{16}H_{19}N_3O_6P$ requires 380.1011).

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