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SYNTHESIS OF A PHOSPHONATE ISOSTERE OF GANCICLOVIR MONOPHOSPHATE: A HIGHLY CYTOMEGALOVIRUS ACTIVE PHOSPHONATE NUCLEOTIDE ANALOGUE

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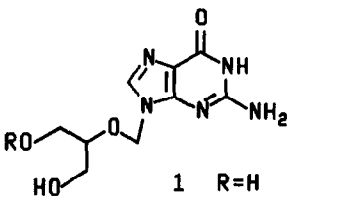
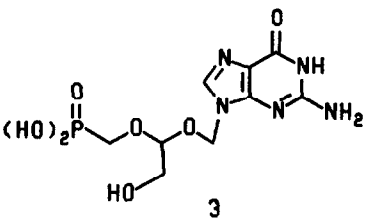
Abstract: A novel synthetic methodology for the hydroxymethyl substituted acyclic acetal functionality was developed. The rationally designed phosphonate analogue 3 of ganciclovir monophosphate was highly active against human cytomegalovirus.

Ganciclovir (1) is an exceptionally potent agent against herpesviruses[1-3] and has been approved for the treatment of cytomegalovirus retinitis. As the essential feature of the biochemical mechanism, ganciclovir is known to be converted to the monophosphate 2 by kinases[2,3] and then further to a triphosphate[2] which acts as an inhibitor of viral DNA polymerase.[4] In continuation of our studies on nucleotide analogues as antiviral agents,[5] we have undertaken the synthesis of compound 3 which is the phosphonate isostere of the ganciclovir monophosphate (2).



1 R=H

2 R=$P(O)(OH)_2$

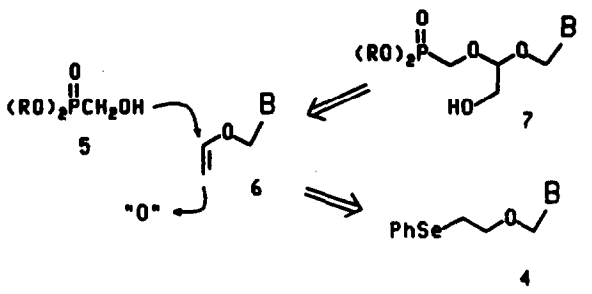


3

The basic strategy envisioned for the assembly of the hydroxymethyl substituted acetal functionality shown in 7 is depicted in Scheme I and relies on the regio-specific addition of diethyl hydroxymethylphosphonate (5) on the enol ether 6 under oxidative conditions. A useful tactic for implementing this conceptual approach would employ the phenylselenyl derivative 4 as a precursor of the enol ether 6.

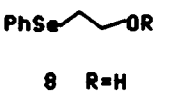
Preparation of the requisite enol ether 13 was readily carried out. Thus, treatment of 2-(phenylselenyl)ethanol (8)[6] with 1,3,5-trioxane (1.1 equiv) in the presence of HCl gas (in CH_2Cl_2 at 23°C for 2h) resulted in the production of the corresponding chloromethyl ether 9, which was used promptly for the next reaction

SCHEME I

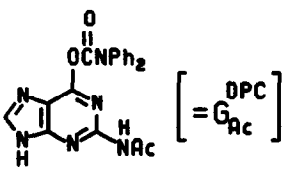


B= protected guanine

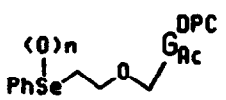
without purification. Addition of 9 to a preheated mixture of the silylated guanine derivative 10[7] and $Hg(CN)_2$[8] (1.05 equiv) (in benzene at reflux for 3h) provided 11 (67% overall yield). Among many protecting groups used for the protection of the 6-hydroxyl of guanine, the diphenylcarbamoyl (DPC) group[7] was found to be the most effective for the synthesis of 13. Oxidation of 11 with 1.2 equiv of sodium periodide (in CH_3OH at 23°C for 45 min) afforded the selenoxide 12 (92%). Thermolysis of 12 was effected by short-time heating (15-20 min) in refluxing benzene in the presence of diisopropylamine (2 equiv) to give the enol ether 13[12] (78%).



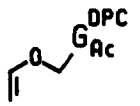
8 R=H
9 R=CH_2Cl



10



11 n=0
12 n=1



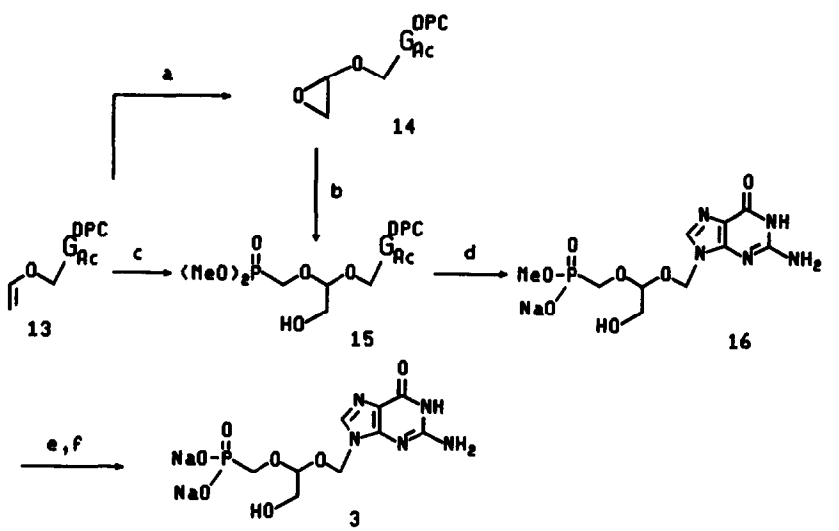
13

With the enol ether 13 in hand, the next objective became the preparation of the epoxide 14. When 13 was treated with di(methyl-d_3)-dioxirane[9] in acetone-d_6 at 0°C, the ^1H nmr spectrum of the reaction solution revealed the immediate formation of the epoxide 14 (epoxide protons at δ 2.59 (t, J=2.9, 6.2 Hz), 2.75 (d, J=2.9 Hz), 4.82

(d, J=2.9 Hz)). However, attempts to obtain pure 14 were not successful due to rapid decomposition while removing solvent. Addition of dimethyl hydroxymethylphosphonate (5, R=CH_3) to the reaction solution of the epoxide 14 resulted in formation of the acetal 15 in low yield (<5%). Considering the similar chemistry reported recently for the synthesis of oligosaccharides via glycal epoxides,[10] the inability to obtain 15 from 14 in reasonable yield remains puzzling. Alternatively, addition of m-chloroperbenzoic acid (1.1 equiv) to a solution of 13 and dimethyl hydroxymethylphosphonate[11] (10 equiv) (in CH_2Cl_2 at 23°C for 2h) afforded 15 in 42% yield. Presumably, the epoxide 14 was formed and reacted in situ with the hydroxy nucleophile. Saponification of 15 with 1N-NaOH (in H_2O-MeOH/1:4 at 23°C for 16h) provided the phosphonate monoester 16 (65%) after C-18 reverse phase column purification. To complete deprotection, the monoester 16 was treated with trimethylsilylbromide (5 equiv) (in DMF at 0°C for 2h) followed by neutralization with sodium bicarbonate to give 3[12] (62%).

In an antiviral test carried out in MRC-5 cells, the IC_{50} (50% inhibitory concentration) of 3 for human cytomegalovirus was 0.9 µg/ml (cf 1.0 µg/ml for gancyclovir) without any sign of toxicity for the cell monolayer up to 100 µg/ml.

SCHEME II



(a) di(methyl-d_3)-dioxirane; CD_3COCO_3; (b) 5(R=CH_3); (c) MCPBA, 5(R=CH_3); (d) 1N-NaOH; (e) TMSBr, DMF; (f) $NaHCO_3$.

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12. The phosphonate **3** was quite acid stable, thus a pH 2 solution of **3** showed no sign of degradation after 24 h at 23°C as evidenced by HPLC and NMR analysis.
13. Selected ^{1}H NMR (300 MHz) data: compound **13** ($CDCl_3$) δ 2.48 (s, 3H), 4.17 (dd, J=2.7, 6.6 Hz, 1H), 4.47 (dd, J=2.7, 14.1 Hz, 1H), 5.70 (s, 2H), 6.39 (dd, J=6.6, 14.1 Hz, 1H), 7-7.5 (m, 10H), 7.96 (s, 1H), 7.99 (s, 1H). Compound **15** ($CDCl_3$) δ 2.38 (s, 3H), 3.58 (dd, J=4.5, 12.5 Hz, 1H), 3.72 (dd, J=4.5, 12.5 Hz, 1H), 3.76 (dd, J=2.9, 10.7 Hz, 6H), 3.79 (dd, J=8.9, 14.0 Hz, 1H), 3.99 (dd, J=8.9, 14.0 Hz, 1H), 4.91 (t, J=4.9 Hz, 1H), 5.65 (d, J=10.8 Hz, 1H), 5.72 (d, J=10.8 Hz, 1H), 7.0-7.4 (m, 10H), 8.03 (s, 1H), 8.16 (s, 1H). Compound **3** (D_2O) δ 3.4-3.5 (m, 2H), 3.60 (dd, J=5.4, 11.6 Hz, 1H), 3.69 (dd, J=9.0, 11.6 Hz, 1H), 4.87 (t, J=4.5 Hz, 1H), 5.66 (d, J=11.3 Hz, 1H), 5.72 (d, J=11.3 Hz, 1H), 7.99 (s, 1H).

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