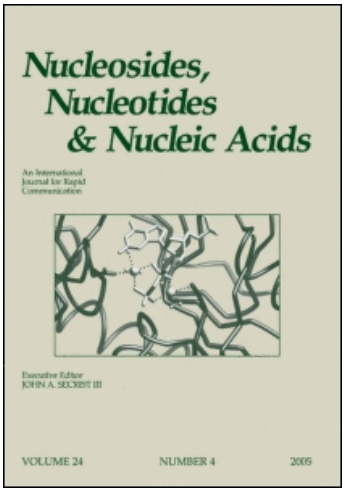

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Phosphonate Isosteres of Acyclovir and Ganciclovir Honophosphates Synthesis and Anti-Herpesvirus Activity

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PHOSPHONATE ISOSTERES OF ACYCLOVIR AND GANCICLOVIR MONOPHOSPHATES: SYNTHESIS AND ANTI-HERPESVIRUS ACTIVITY

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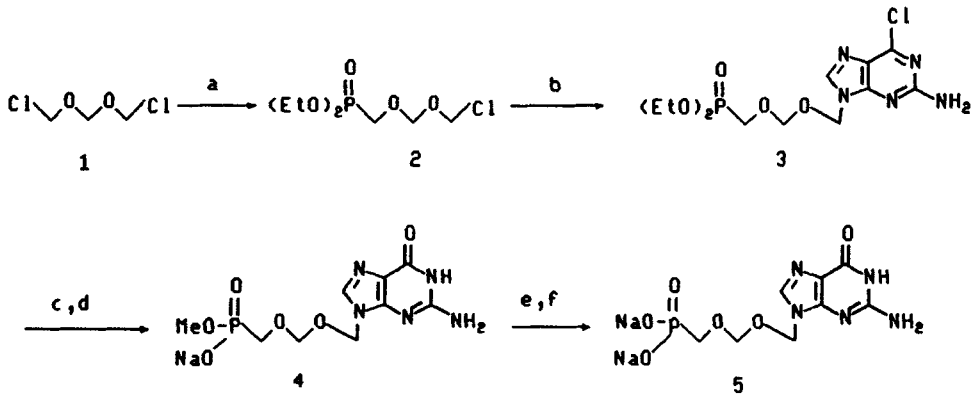
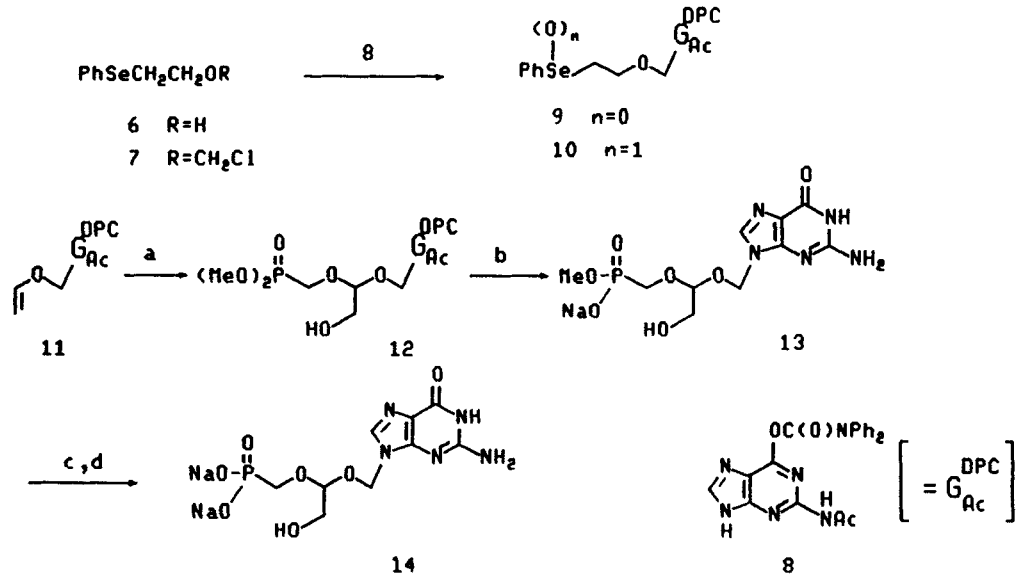
Abstract: Isosteric phosphonate analogues of acyclovir and ganciclovir monophosphates were synthesized. The new phosponates exhibited good anti-herpes activity.

As part of our program on the development of anti-herpes agents, isosteric phosphonate mimics of acyclovir and ganciclovir monophosphates have been synthesized. Metabolically and chemically stable phosphonate analogues, which bypass the initial enzymatic phosphorylation, could potentially be more effective antiviral agents. In the synthesis of the acyclovir monophosphate analogue, a new methodology to assemble the acyclic acetal functionality has been developed as shown in Scheme I. Thus, addition of bischloromethoxymethane (1)[1] to the solution of diethyl phosphite sodium in THF at -70°C produced the chloromethyl ether 2 which was used promptly in the subsequent transformations. Reaction of 2 with 2-amino-6-chloropurine sodium salt in DMF at 25°C to give the acetal 3 (42% from 1), saponification with sodium methoxide followed by sodium hydroxide to form the half ester 4 (85%), and deprotection with trimethylsilylbromide provided the phosphonate 5, an isostere of the acyclovir monophosphate. Next, the ganciclovir monophosphate analogue 14 was prepared as outlined in Scheme II. Thus, treatment of 2-(phenylselenyl)ethanol (6)[2] with 1,3,5-trioxane in the presence of HCl gas (in CH_2Cl_2 at 23° for 2h) resulted in the production of the chloromethyl ether 7, which was used promptly for the next reaction. Addition of 7 to a preheated mixture of the silylated guanine derivative 8[3] and $Hg(CN)_2$ (1.1 equiv) (in benzene at reflux for 3h) provided 9 (67% overall yield). Among many protecting groups used for the protection of the 6-hydroxyl of



(a) $(EtO)_2P(O)Na$; (b) 2-amino-6-chloropurine sodium salt; (c) MeONa; (d) 1 N-NaOH; (e) Me_3SiBr; (f) $NaHCO_3$.

Scheme I



(a) $(MeO)_2P(O)CH_2OH$, MCPBA; (b) 1 N-NaOH; (c) Me_3SiBr/DMF; (d) $NaHCO_3$.

Scheme II

guanine, the diphenylcarbamoyl (DPC)[3] was found to be the most effective for the synthesis of 11. Oxidation of 9 with 1.2 equiv of sodium periodate afforded the selenoxide 10. Thermolysis of 10 was affected by short-time heating (15-20 min) in refluxing benzene in the presence of diisopropylamine (2 equiv) to give the enol ether 11. Addition of m-chloroperbenzoic acid (1.1 equiv) to a solution of 11 and dimethyl hydroxymethylphosphonate[4] (10 equiv) (in CH_2Cl_2 at 23°C for 2h) gave 12 in 42% yield. Saponification of 12 with 1 N-NaOH provided the phosphonate monoester 13 (65%). To complete deprotection, 13 was treated with trimethylsilylbromide followed by neutralization with sodium bicarbonate to give 14. In antiviral tests carried out in Vero cells (for HSV) and MRC-5 cells (for HCMV), the IC_{50}'s (50% inhibitory concentration) for inhibition of the replication of HSV-1 and 2 of HCMV were 2.6, 11 and 5.0 ug/ml for 5 (cf. 0.5, 0.5 and 40 value for acyclovir). The IC_{50} of 14 for HCMV was 0.9 ug/ml (cf. 1.0 ug/ml for ganciclovir) without any sign of toxicity for the cell monolayer up to 100 ug/ml.

In conclusion, the potent anti-herpes activity exhibited by the acyclovir and ganciclovir phosphonate analogues 5 and 14 clearly demonstrates that these phosphonates may act not only as biologically equivalent isolteres of corresponding acyclic nucleoside monophosphates, but also they are taken up enough by cells to exert antiviral activity.

1) P. R. Slapp, J. Org. Chem. 34, 1143 (1969).
2) P. Rollin, V. V. Bencomo, Synthesis 134 (1984).
3) R. Zou, M. J. Robins, Can. J. Chem. 65, 1436 (1987).
4) D. P. Phillion, S. S. Andrews, Tetrahedron Lett. 27, 1477 (1986).