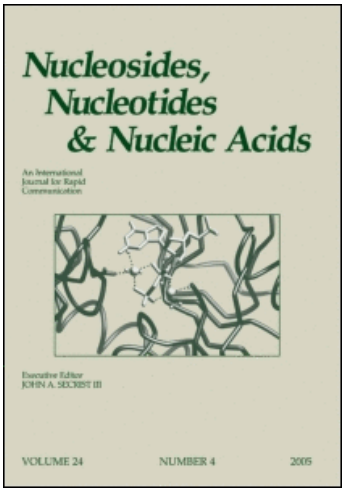

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SOME NOVEL AMINOPROPYL NUCLEOSIDE PHOSPHONATES

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□ *The aminopropyl nucleoside phosphonates **1–3** have an amino function within either the acyclic chain (series **2** and **3**) or as substituent (series **1**) of HPMPC (Cidofovir). Both purine and pyrimidine nucleoside anologs have been synthesized. In contrast to HPMPC, only a weak antiherpes virus activity could be demonstrated for **2b** and **2c**.*

Keywords acyclic nucleotides; aminopropyl phosphonic acids; antiviral activity

INTRODUCTION

2-(Phosphonomethoxy)alkyl derivatives of purine and pyrimidine bases—acyclic nucleoside phosphonates (ANPs)—possess significant antiviral and cytostatic activity. These nucleotide analogs contain an isopolar phosphonomethyl ether moiety instead of the nucleotide phosphate ester group, which prohibits their enzymatic degradation and/or eliminates problems associated with the intracellular phosphorylation necessary for nucleoside activation.[1,2]

One of the antivirally most active compounds to date is 9-(S)-[3-hydroxy-2-(phosphonomethoxy)propyl]adenine [(S)-HPMPA],[3] followed by 1-(S)-[3-hydroxy-2-(phosphonomethoxy)propyl]cytosine [(S)-HPMPC; cidofovir, Vistide]. Cidofovir, which is on the market for the treatment of human cytomegalovirus retinitis in immunocompromized patients, is potentially a good candidate for the treatment of a poxvirus outbreak, in the absence of any vaccination.[4]

In our efforts to further delineate the biological properties of acyclic nucleotide analogs, compounds **1–3** (Figure 1) were envisaged, bearing in the acyclic chain as well as an amino group as hydroxyl functionality. Compounds **1a–d** are (phosphonomethoxy)propyl analogs with an amino substituent in the 2'-position. Compounds **2a–d** are the (phospho-

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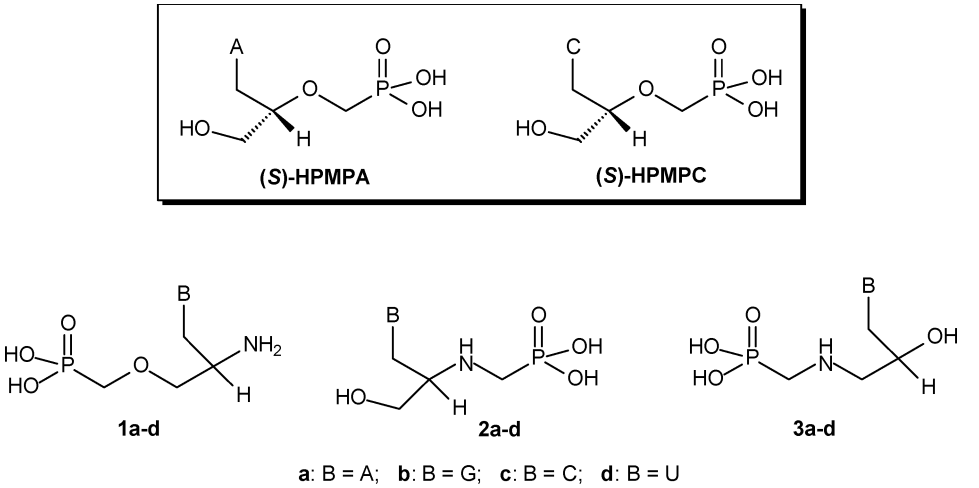


FIGURE 1 Overview of the different envisaged structures and analogy with the known antivirals HPMPA and HPMPC.

nomethyl)amino congeners of HPMPA and HPMPC. The third series, **3a–d**, have inverse functionality compared with the first series, **1a–d**, and a secondary amino group instead of a primary amino function. These compounds could be expected to have potential for being effective antiviral agents.

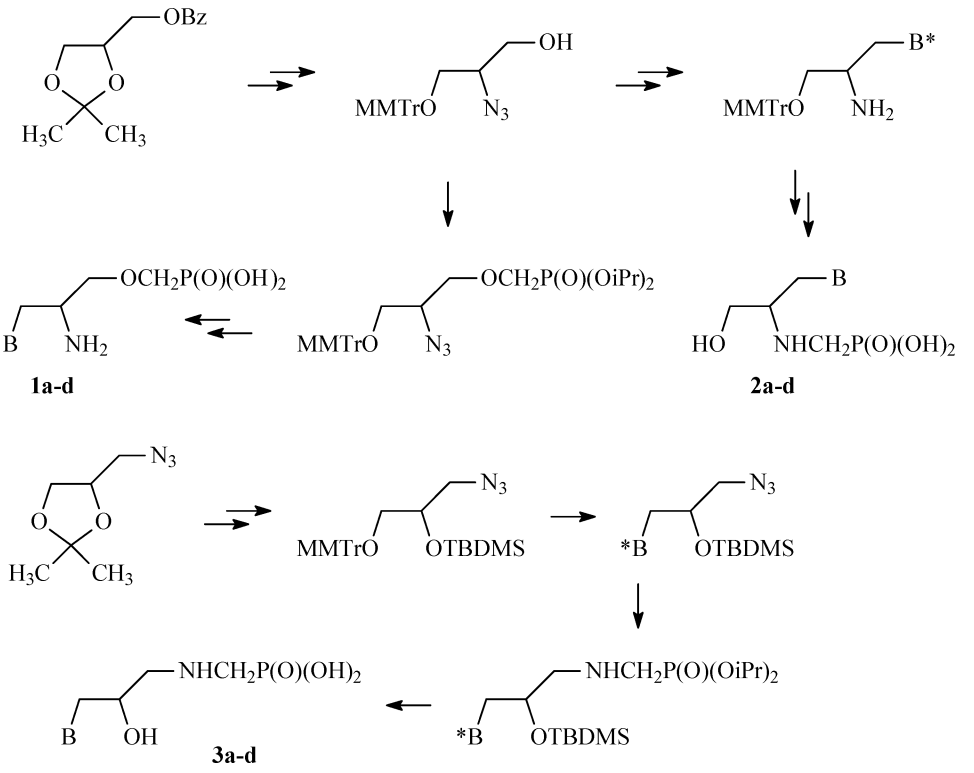
RESULTS AND DISCUSSION

Two different strategies starting from racemic 1,2-*O*-isopropylideneglycerol can be envisaged to attain the desired aminopropyl phosphonate nucleosides. Either phosphonoylation of the preformed acyclic nucleosides is carried out, as exemplified for aminopropyl phosphonic acids of types **2** and **3**, or alternatively, the aglycon is introduced following the phosphonoylation reaction, as shown for aminopropyl phosphonate nucleosides of type **1**.[5,6] The synthetic pathways are briefly outlined in Schemes 1 and 2.

Following silica gel chromatography, all phosphonates **1a–d**, **2a–d**, **3a–d** were further purified by ion exchange chromatography (Sephadex-DEAE A-25 resin). The obtained triethylammonium salts were passed through a column of Dowex 50WX8 (Na^+) resin and eluted with water to afford the sodium salts as white solids.

Biological Results

All acyclic nucleoside phosphonates **1–3**, were evaluated *in vitro* for cytotoxicity and for their activity against a variety of viruses including HIV-1,



SCHEME 1 Concise synthetic outline in obtaining the respective phosphonates **1a–d**, **2a–d,** and **3a–d**, with B being respectively the A, G, C, or U heterocyclic base, and *B a protected base (A^{bz}, 2-amino-6-chloropurine, C^{bz}, or U).

HIV-2, HSV-1, HSV-2, thymidine kinase (TK)-deficient HSV-1/TK^- and vaccinia virus (VV), varicella-zoster virus (VZV TK^- and TK^+), and cytomegalovirus (CMV) replication in HEL cells. Compounds **1-3** did not display cytotoxicity and proved inactive against HIV-1 and HIV-2. The best, but still marginal, biological activity was observed for **2b** with a minimum inhibitory concentration to inhibit virus replication with 50% (MIC_{50}) of 48 μg/mL versus HSV-1 and HSV-2, and of 45 μg/mL versus CMV.

CONCLUSIONS

The synthesis of aminopropyl phosphonate nucleosides **1–3** has been described. Compounds of types **2** and **3** are obtained by phosphonoylation of the preformed acyclic nucleosides, while for series **1** the order is reversed with prior formation of the phosphonomethyl ether followed by introduction of the aglycon. Compounds **2a–d** are the (phosphonomethyl)amino congeners of HPMPA and HPMPC. Only in this series marginal activity against HSV and CMV could be demonstrated.

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