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SYNTHESIS OF (S)-N^1-(3-HYDROXY-2-PHOSPHONYLMETHOXY)PROPYLCYTOSINE, (S)-HPMPC

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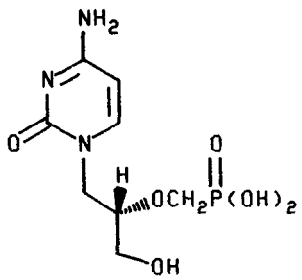
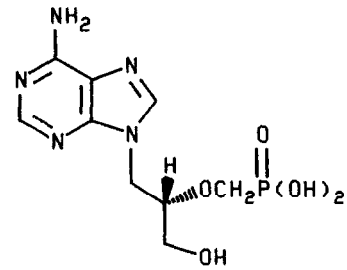
Summary: (S)-HPMPC, (S)-N^1-(3-hydroxy-2-phosphonylmethoxy)propylcytosine 1, a new acyclic nucleotide antiviral, has been synthesized by a route involving direct cesium carbonate promoted alkylation of cytosine with an appropriately constructed glycerol-phosphonate side chain.

(S)-HPMPC, (S)-N^1-(3-hydroxy-2-phosphonylmethoxy)propylcytosine **1** (**Figure 1**), is the cytosine analogue of (S)-HPMPA, (S)-9-(3-hydroxy-2-phosphonylmethoxy)propyl-adenine **2**.[2-4] Both **1** and **2** are new acyclic nucleotide antivirals which have shown **in vitro** efficacy against human cytomegalovirus (CMV).[5]

Figure 1



1

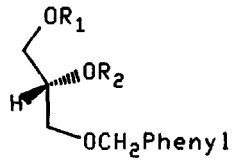


2

(S)-HPMPC **1** has been shown to have a greater therapeutic index of activity against this virus than DHPG, a compound currently under clinical investigation for the treatment of CMV.[5,6] For the comparison of its biological activity with that of (S)-HPMPA **2** and DHPG, we needed an expedient, gram-scale synthesis of **1**.

Our approach to the preparation of **1** involved direct alkylation of cytosine[7] with a pre-assembled glycerol-phosphonate (see Figure 2). This side chain was constructed from isopropylidene-(L)-glycerol[8] through the sequence of benzylation (NaH/DMF/benzylbromide), acetonide removal[9] (pTsOH/MeOH/H_2O/50°C), and monomethoxytritylation (p-anisyldiphenyl-

Figure 2



3 : R_1 = $C(Ph)_2$p-anisyl, R_2 = H

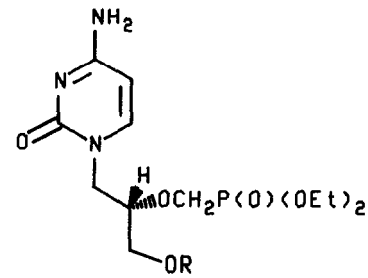
4 : R_1 = $C(Ph)_2$p-anisyl

R_2 = $CH_2P(O)(OEt)_2$

5 : R_1 = H, R_2 = $CH_2P(O)(OEt)_2$

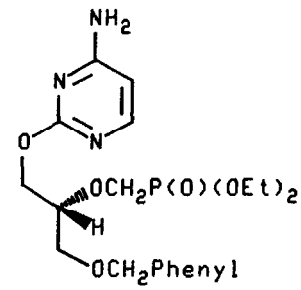
6 : R_1 = SO_2CH_3,

R_2 = $CH_2P(O)(OEt)_2$



7 : R = CH_2Phenyl

9 : R = H



8

chloromethane/pyridine) to give alcohol **3** (59% from glycerol).[10] Alkylation of **3** (NaH in THF) with tosyloxymethyldiethylphosphonate[11] then gave phosphonate **4** (65%). Removal of the monomethoxytrityl protecting group from **4** (80% aqueous acetic acid, 85%) to give alcohol **5** was followed by standard mesylation (methanesulfonylchloride/NEt_3/CH_2Cl_2, 97%) yielding the desired mesylate **6**.[12]

Addition of a mixture of 1 equivalent of dry, solid cytosine and 2 equivalents of cesium carbonate to a solution of mesylate **6** in DMF pre-heated to 90°C (oil bath) effected the desired coupling. The reaction was rapid; after addition of the solid materials, the reaction was judged complete (tlc) in 2 hours. The desired N-alkylated material, adduct **7**, was isolated in 67% yield after chromatography over silica gel.[13] The major by-product was the O-alkylated adduct **8**.[14-16]

To complete the synthesis of (S)-HPMPC, removal of the O-benzyl group from **7** by transfer hydrogenolysis[17] ($Pd(OH)_2$ on carbon/EtOH/cyclohexene/reflux) gave diethyl-(S)-HPMPC **9** in 65% yield. Diethyl ester **9** was subjected to standard ester dealkylation with TMS-bromide[18] and the direct crystallization procedure used previously for (S)-HPMPA[19] to give (S)-HPMPC in 80% yield. The (S)-HPMPC thus obtained was identical (^1H and ^{13}C NMR) with an authentic sample of **1**.

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12. All new compounds gave satisfactory analytical data. Full experimental details and studies on biological activity will be reported elsewhere.
13. Adduct **7** could be easily separated from the less polar adduct **8** by column chromatography over silica gel eluting with 5-10% methanol in methylene chloride.
14. The potassium salt of cytosine (K_2CO_3/DMF/90°C/18h) coupled with mesylate **6** to give a 40% yield of the desired N-alkylated adduct **7**, and a 25% yield of the undesired O-alkylated material **8**. Also obtained were minor quantities of N- and O-ethylated cytosine.
15. The observation of N- and O-alkylation is consistent with the literature, since cytosine is known to behave as an ambident nucleophile in alkylation reactions. See, for example: Ward, A.D.; Baker, B.R. **J. Med. Chem. 1977**, 20(1), 88 and references cited therein.
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