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A Practical Synthesis of (S)-HPMPC[1]

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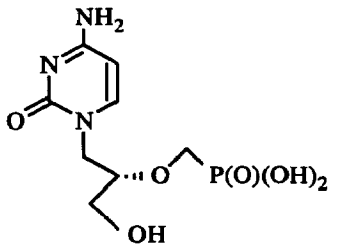
Abstract: Synthesis of the title nucleotide was accomplished in high yield starting from (S)-tritylglycidol (**5**) and N-benzoylcytosine (**9**).

The acyclonucleotide, (S)-1-[3-hydroxy-2-(phosphonylmethoxy)propyl]cytosine (**1**, HPMPC) was found to have potent activity[2] against herpes simplex viruses type 1 and 2 (HSV-1 and HSV-2), vaccinia virus and human cytomegalovirus (HCMV). Its mode of action has been attributed to the diphosphate of **1**, produced by cellular enzymes, which is a selective inhibitor of the viral DNA polymerase[2]. When compared to existing drugs, like acyclovir (**2**) and gancyclovir (**3**), (S)-HPMPC (**1**) has shown better *in vivo* efficacy.[2b]



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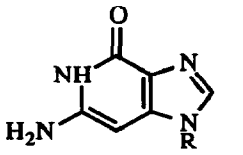

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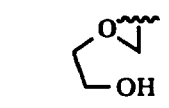

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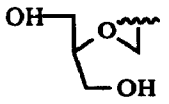

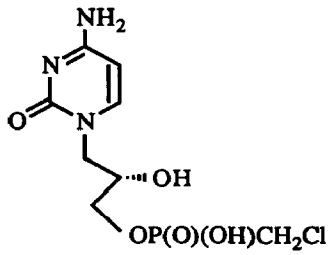

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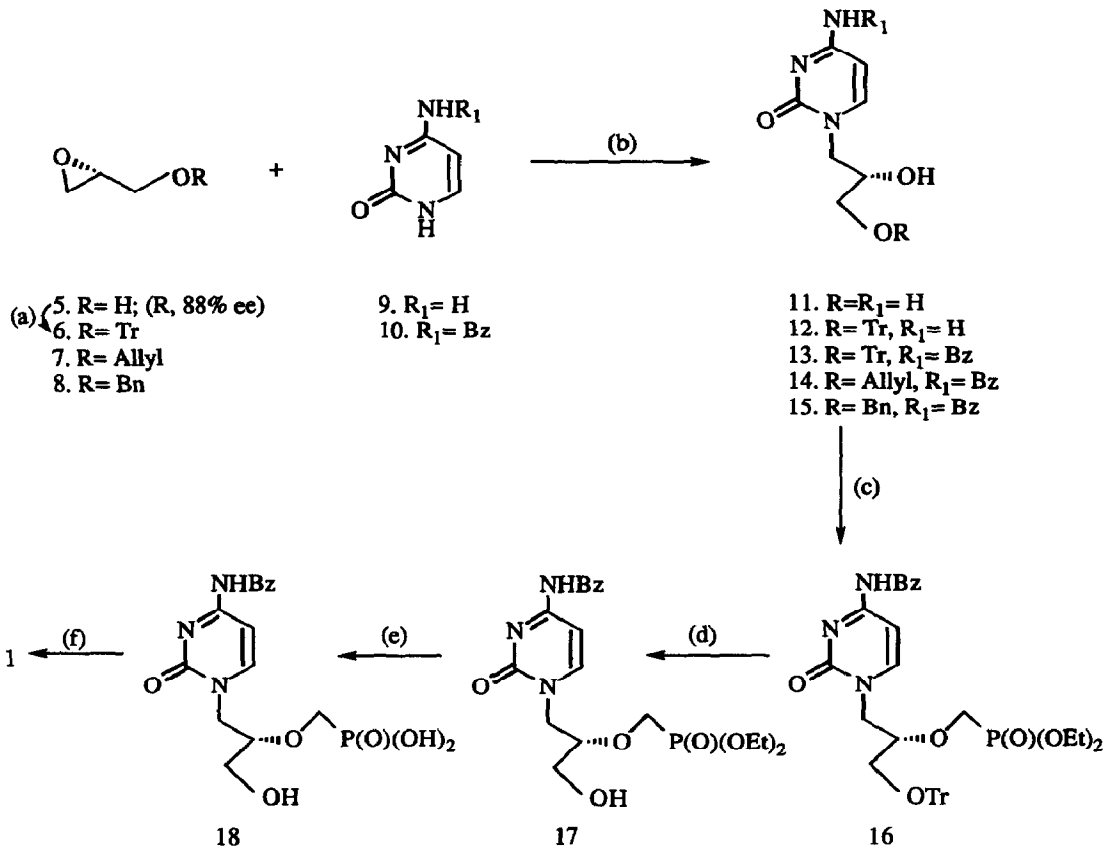
Recently, Bronson and co-workers have reported the synthesis of **1** *via* alkylation of cytosine (**9**) with chiral synthons such as the tosylate (or mesylate) of diethyl (S)-(3-benzyloxy-1-hydroxy-2-propoxy)methylphosphonate[3], or (S)-2,3-O-isopropylidene-1-O-mesylglycerol[4], followed by further

elaboration of the intermediates. Holy *et al.*[5] have made **1** by base catalyzed rearrangement of the chloromethylphosphonate (**4**). Each of these methods involves a multi-step process and requires chromatographic purification of intermediates, which is cumbersome on large scale. In this letter, we wish to present an efficient multi-gram synthesis of (S)-HPMPC (**1**) utilizing a commercially available and inexpensive starting material, (R)-glycidol (**5**). This technology can also be applied to the preparation of analogues, *i.e.*, HPMP-Pyrimidines and HPMP-Purines. [6]

R-Glycidol (**5**, 88% ee)[7] was treated with cytosine (**9**) in the presence of a catalytic amount of potassium carbonate in DMF at 72°C for 5 h to obtain regiospecific opening of the epoxide. The desired nucleoside

Scheme



Reaction Conditions: (a) TrCl, TEA, CH_2Cl_2, rt, 3 h; (b) K_2CO_3, DMF, 72°C, 5 h or NaH (0.22 eq), DMF, 105°C, 5 h; (c) $TsOCH_2P(O)(OEt)_2$, NaH (3 eq), DMF, 0°C, 6 h; (d) HCl_g, CH_2Cl_2, 0-5°C, 10 min.; (e) TMSBr, CH_2Cl_2, rt, 18 h; (f) Conc. NH_4OH, rt, 4 h.

(**11**)[8] was obtained in 43% yield after chromatography. This represents a substantial improvement over the 4% yield from racemic glycidol reported by Ueda and co-workers. [9] However, this yield is still somewhat low due to facile self-polymerization of **5**. The crude reaction product (**11**) was then converted (TrCl, Py, 80°C, 3h) to the (S)-trityl nucleoside (**12**)[10] in 40% yield over the two steps.

In order to improve yield of **12**, the ring opening reaction of glycidyl ethers (**6** - **8**) with cytosine (**9**) or N-benzoylcytosine (**10**) was further investigated. Tritylation[11] of (R)-glycidol (**5**) with trityl chloride (TEA, CH_2Cl_2, rt, 3 h), followed by crystallization of the product, gave the (S)-trityl ether (**6**) in 77% yield. Regiospecific opening of the epoxide (**6**) with **9** in the presence of a catalytic amount of sodium hydride[12] in DMF was sluggish from room temperature to 70°C . However, this reaction at 105°C for 5 h provided **12** in 82% yield. N-Benzoylcytosine (**10**) used in place of cytosine (**9**) resulted in the same good yield of **13**. The chiral (S)-epoxides (**7** and **8**)[13] prepared from (2R)-glycidyl tosylate, were thus reacted with **10** to give **14** in 61% yield and **15** in 65% yield, respectively. Optical purity analyses *via* the Mosher esters[14] utilizing proton and fluorine NMR indicated **14** and **15** were optically pure. The corresponding Mosher esters of **12** and **13** did not form under the usual conditions, perhaps due to the presence of the bulky trityl group.

Further elaboration of **13** to (S)-HPMPC (**1**) was carried out as follows: The *in situ* alkylation of the reaction mixture of **13**, obtained from **6** and **10**, with 1.5 eq of diethyl tosyloxymethylphosphonate[15] in the presence of NaH (80%, 3 eq, 0°C, 6 h) provided the (S)-nucleotide ester (**16**). Acid catalyzed detritylation of **16** in methylene chloride with HClg (0-5°C, 10 min) afforded the corresponding alcohol (**17**) in 55% yield from **6** in three steps. Detritylation with other reagents, such as 80% AcOH, 80% HCOOH, TFA, ZnBr, or Amberlite-15 also gave moderate to good yields. Deprotection[16] of **17** with TMSBr in CH_2Cl_2 at ambient temperature for 18 h gave the crude (S)-N-benzoyl HPMPC (**18**), which on treatment with concentrated ammonium hydroxide (4 h, rt) afforded crystalline (S)-HPMPC (**1**) in 78% yield. Reverse phase HPLC using chiral mobile phase[17] confirmed that the final nucleotide **1** had the same optical purity as (R)-glycidol (**5**, 88 ee%). Two recrystallizations of **1** performed by adjusting an aqueous slurry to pH 6 with 40% NaOH, filtration and reprecipitation with conc. HCl at pH 3 furnished (S)-HPMPC (**1**, 90% recovery) containing 2.4% of its (R)-enantiomer.

In conclusion, we have developed an efficient and scaleable synthesis. The overall yield of (S)-HPMPC (**1**) starting from **6** and **10** amounts to 39% after final crystallization.

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1. This subject is abstracted from patent# WO 92/02511; Dated: 20 February 1992. This work was carried out at Chemical Process Development, Bristol-Myers Squibb Company, R & D, Syracuse, NY.
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17. Chiral HPLC conditions: Column: III Supplies 3 μ, 5 cm x 4 mm I.D. C-18; UV: 280 nm; Flow rate: 0.5 ml/min; Mobile Phase: 4 mM of phenylalanine in 1% $CuSO_4$ solution; Retention times: (S)-HPMPC- 2.2 min, (R)-HPMPC- 2.7 min.

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