Tetrahedron Letters, Vol.33, No.1, pp 25-28, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press plc

A Novel Synthesis of 1-OXA-HPMPA: A Potent Antiviral Agent Against Herpesviruses

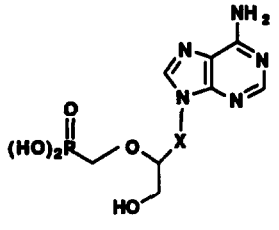
Choung Un Kim*, Bing Y. Luh, and John C. Martin[1]

Bristol-Myers Squibb Company, Pharmaceutical Research Institute
5 Research Parkway, Wallingford, Connecticut 06492-7660

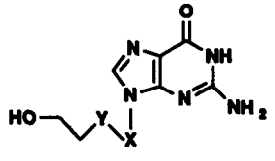
Abstract: A facile synthesis of 1-oxa-HPMPA **2** was achieved via a novel strategy of coupling 9-hydroxyadenine **13** and enol ether phosphonate **11**. The newly synthesized 1-oxa analogue of HPMPA exhibited potent antiherpesvirus activity.

Key Words: HPMPA; 1-oxa-HPMPA; Herpesviruses

Recently, a new acyclic nucleoside phosphonate derivative, (S)-9-(3-hydroxy-2-phosphonomethoxy-propyl)adenine (HPMPA: **1**) has been described as a potent and a selective inhibitor of a broad range of DNA viruses.[2,3] The diphosphorylated derivative of HPMPA, which corresponds to the antivirally active triphosphate of acyclovir (**3**)[4], is a potent inhibitor of herpesvirus DNA polymerase.[3] Previous studies by Beecham group identified 9-(3-hydroxypropoxy)guanine (**4**), an isosteric isomer of acylovir, as a potent antiherpesvirus agent.[5] In continuation of our studies on nucleotide analgoues as antiviral agents,[6,7] we have undertaken the synthesis of 1-oxa-HPMPA (**2**) to investigate structure activity relationships of this class of compounds.



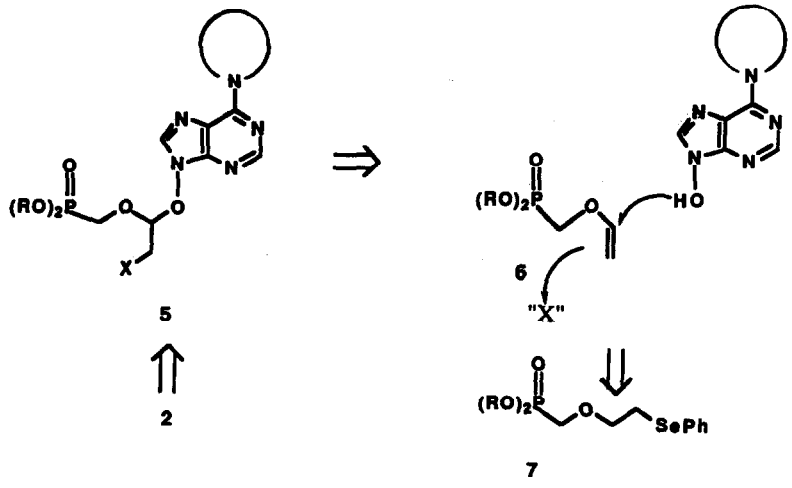
1 X = CH_2 (HPMPA)
2 X = O



3 X = CH_2, Y = O (Acyclovir)
4 X = O, Y = CH_2

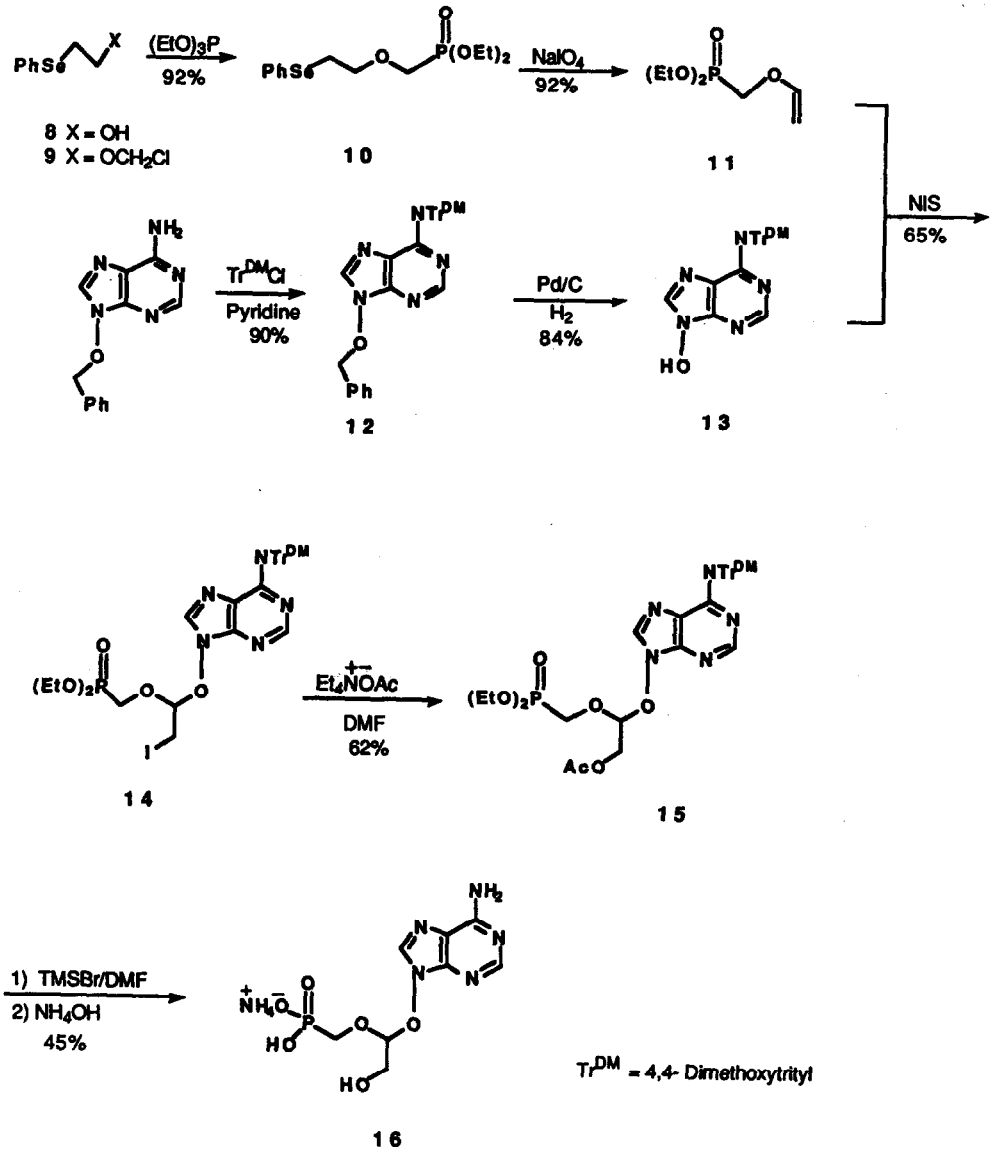
The basic strategy that we selected for the construction of the hydroxymethyl substituted acetal functionality in **2** relies on the regiospecific addition of an appropriately protected 7-hydroxyadenine to enol ether phosphonate **6** under mediation of suitable electrophile (X) (Scheme I). In this sequence, the phenylselenyl derivative **7** would serve as a precursor of enol ether **6**. However, this route requires conversion of the electrophile (X) to the hydroxyl functionality to complete the synthesis of **2**.

SCHEME I



Preparation of requisite enol ether **11** commenced with 2-(phenylselenyl)ethanol (**8**)[8] which was first converted to chloromethyl ether **9** with CH_2O/HCl (in CH_2Cl_2 at 0°C for 2h) (Scheme II). The Arbuzov reaction of **9** with triethyl phosphite (at 120°C for 3 h) gave phosphonate **10** (92% from **8**). Oxidation of **10** with sodium periodate (2 equiv in methanol-water at 23°C for 30 min) followed by thermolysis (benzene reflux for 45 min) of the selenoxide produced enol ether **11** (92%). Next, we prepared N6-amine protected 9-hydroxyadenine. The selection of the N6-amine protecting group was critical for the electrophilic addition of 9-hydroxyadenine to enol ether **11**. Among protecting groups investigated, the dimethoxytrityl group[9] was found to give the most satisfactory result for the addition reaction. This protection also offered advantage of the selective hydrogenolysis of the benzyl group in **12** (84%) which was in turn, readily prepared by tritylation of 9-benzyloxyadenine[10] (90%). With enol ether **11** and N6-trityl-9-hydroxyadenine **13** in hand, we turned our attention to the coupling of these two units. Oxidative coupling of **11** and **13** in the presence of 3-chloroperbenzoic acid gave a complex mixture. It appears that 9-hydroxyadenine is quite sensitive toward oxidation. Attempts to prepare an epoxide of **11** with various peroxides or dimethyldioxirane were not successful. However, when N-iodosuccinimide was added to a mixture of **11** and **13** (1 equiv each) in CH_2Cl_2 at 0°C, iodide **14** was isolated in 65% yield.[11] Conversion of iodide **14** to acetate **15** was achieved in 62% yield by treatment with tetraethylammonium acetate (10 equiv in DMF at 60°C for 4 h). Treatment of **15** with trimethylsilylbromide (9 equiv in DMF at 23°C for 6h) followed by neutralization with ammonium hydroxide gave mono ammonium salt **16** (45%) after reverse-phase column purification. Interestingly, 1-oxa-HPMPA (**16**) thus prepared, was quite acid stable despite the presence of the acetal functionality. A pH 1.5 solution of **16** showed no sign of degradation after 24 h at 23°C as evidenced by NMR and HPLC analysis.

SCHEME II


(EtO)3P
92%
NaIO4
92%
8 X = OH
9 X = OCH2Cl
10
11
NIS
65%
Tr^DM Cl
Pyridine
90%
Pd/C
H2
84%
12
13
Et4NOAc
DMF
62%
14
15
1) TMSBr/DMF
2) NH4OH
45%
16
Tr^DM = 4,4- Dimethoxytrityl

In an antiviral test carried out in Vero (for herpes simplex virus type 2: HSV-2) and MRC-5 (human cytomegalovirus: HCMV) cells, the IC_{50} (50% inhibitory concentration) for inhibition of the replication of HSV-2 and HCMV were 2.6 and 1.0 μg/mL for **16** (cf 40 and 0.5 μg/mL for HPMPA) without any sign of toxicity for the cell monolayer up to 100 μg/mL.

Acknowledgement: The authors wish to thank Dr. M.J.M. Hitchcock and his coworkers for antiviral assays.

References and Notes

1. Present address: Gilead Sciences, 344 Lakeside Drive, Foster City, CA 94404.
2. De Clercq, E.; Holy, A.: Rosenberg, I.; Sakuma, T.; Balzarini, J.; Maudgal, P.C. *Nature*. **1986**, 323, 464.
3. Holy, A.; De Clercq, E.; Votruba, I. ACS Symposium Series No. 401 (J.C. Martin, Ed.), *American Chemical Society*, **1989**, pp. 51-71.
4. Elion, G.B.; Furman, P.A.; Fyfe, J.A.; De Miranda, P.; Beauchamp, L.; Schaeffer, J.J. *Proc. Natl. Acad. Sci.*, USA. **1977**, 74, 5716.
5. Harnden, M.R.; Wyatt, P.G.; Boyd, M.R.; Sutton, D. *J. Med. Chem.* **1990**, 33, 187.
6. Kim, C.U.; Misco, P.F., Luh, B.Y.; Hitchcock, M.J.M.; Ghazzouli, I.; Martin, J.C.*J. Med. Chem.* **1991**, 34, 2286.
7. Kim, C.U.; Luh, B.Y.; Martin, J.C.; *J. Org. Chem.* **1991**, 56, 2642.
8. Rollin, P.; Bencomo, V.V.; Sinay, P. *Synthesis*. **1984**, 134.
9. Kawana, M.; Takeuchi, K.; Ohba, T.; Kuzuhara, H. *Bull. Chem. Soc.* (Japan), **1988**, 61(7), 2437.
10. Watson, A.A. *J. Org. Chem.* **1977**, 42, 1610.
11. For examples of this type of reactions: Friesen, R.W.; Danishefsky, S.J. *J. Am. Chem Soc.* **1989**, 111, 6656, and references cited therein.

(Received in USA 1 October 1991)