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Asymmetric synthesis of 2′-phosphonomethyl(3′,4′-dihydroxybutyl)cytosine and -guanine nucleotides

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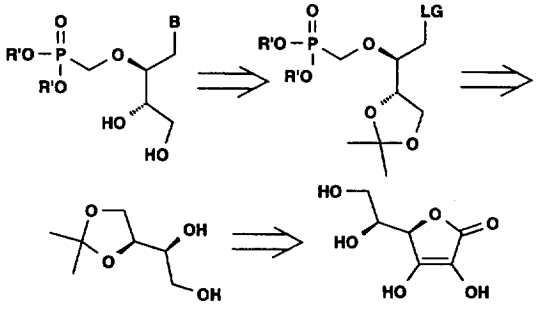
Abstract: The synthesis of 2′-phosphonomethyl(3′,4′-dihydroxylbutyl) nucleotides of cytosine and guanine **13** and **15** possessing the 2′*S*,3′*S* absolute configuration was readily accomplished in eleven and ten steps respectively from L-ascorbic acid via the protected tetrols **9** and **8**. Alcohol **8** undergoes efficiently a regiospecific Mitsunobu coupling with 6-chloro-2-aminopurine to furnish the N-9 isomer which was further transformed to **15**.

The introduction of a hydroxymethyl functionality into the sugar moiety of a nucleoside analogue proved to be a viable strategy for designing potent antiviral agents. Such a strategy, which is particularly successful in the acyclic series,[1] led to the clinical use of Cytovene, Famvir and Cidofovir for the treatment of infections caused by herpes viruses.[2] In keeping with this strategy, the synthesis of novel 2′-phosphonomethyl(3′,4′-dihydroxybutyl) nucleotides attracted our attention.[3] These nucleotides maintain the core phosphonomethoxyethyl (PME) moiety of antiviral analogues (HPMPC, HPMPA, PMPA, FPMPA)[4] and the absolute configuration of C-2′ but carry an additional hydroxymethyl substituent at the terminal 3′ carbon. Accordingly, our retrosynthesis requires an expedient approach to a chiral tetrol synthon which is suitably protected for further elaboration into a phosphomethoxy functionalized derivative (Scheme 1). Herein, we report the asymmetric synthesis of the acyclic nucleotides **13** and **15** from L-ascorbic acid (**1**).



Scheme 1.

Preparation of building block **4** and **5** is outlined in Scheme 2 and follows the elegant strategy of Abushanab *et al.* who established reproducible experimental conditions for the degradation of **1** to **5**.[5–7] In analogy to our previous work,[8,9] the degradative procedure of Abushanab *et al.* is efficiently run on 50 g scale with a minor modification related to the kugelrohr distillations of ester **4** and diol **5**.

Silylation of diol **5** provided alcohol **6**,[6] which was treated with sodium hydride in tetrahydrofuran and then O-alkylated with diethylphosphonomethyltriflate to afford the fully protected tetrol **7** in

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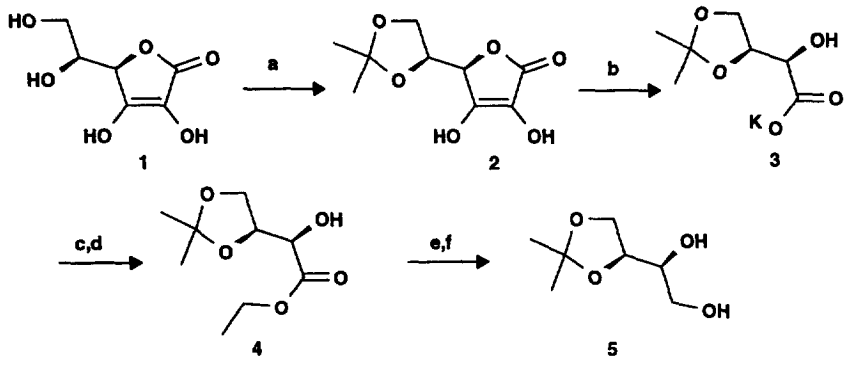
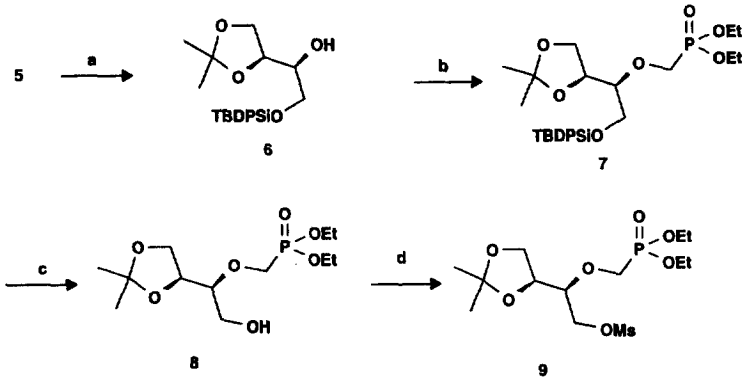


Reagents and conditions: a. acetone, HCl, 2,2-dimethoxypropane, 1h, >99%. b. 30% H_2O_2, K_2CO_3, H_2O, 0 °C for 3 h, rt for 16 h. c. EtI, acetonitrile, reflux 16h. d. Kugelrohr distillation, 87% over b-d. e. LAH, THF, 1h rt, reflux 1h. f. Kugelrohr distillation, 82% over e-f.

Scheme 2.

74% isolated yield.[10] Unmasking the primary alcohol is readily achieved with methanolic ammonium fluoride to provide alcohol **8** in 70% yield. With **8** in hand we next examined its reaction with mesyl chloride to give the requisite mesylate **9** in 74% yield (Scheme 3).

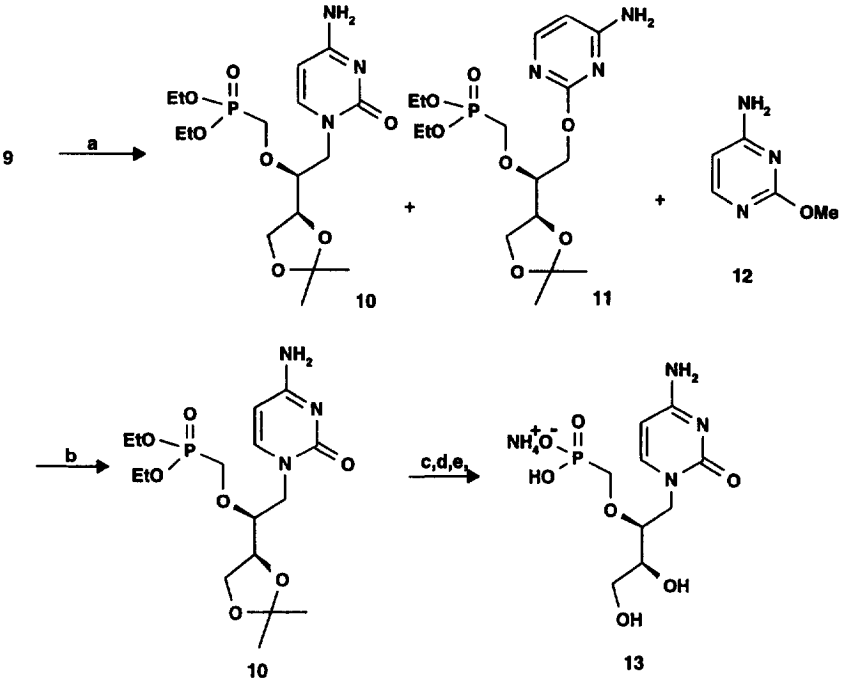


Reagents and conditions: a. TBDPSiCl, triethylamine, CH_2Cl_2, 6h, rt, 95%. b. NaH, THF, $(EtO)_2POCH_2OSO_2CF_3$ 74% c. NH_4F, MeOH, 3h, 60 °C, 70%. d. MsCl, triethylamine, CH_2Cl_2, 0 °C for 1h, rt for 1h, 74%.

Scheme 3.

Alkylation of **9** with cytosine using excess cesium carbonate in dimethylformamide (DMF) afforded a mixture of N- and O-alkylated products **10**:**11** in 4:1 ratio respectively, together with 2-methoxy-4-aminopyrimidine (**12**). Pure **10** was isolated from the mixture by successive chromatographic separation using 10% MeOH/CH_2Cl_2 as eluent. Hydrolysis of **10** with 2 N HCl in methanol removed the isopropylidene group and the resultant diol was purified by chromatography on silica gel (20% MeOH/CH_2Cl_2). Portionwise addition of bromotrimethylsilane in acetonitrile furnished crude **13** which was purified by reverse phase HPLC to give the desired nucleotide **13** (Scheme 4).

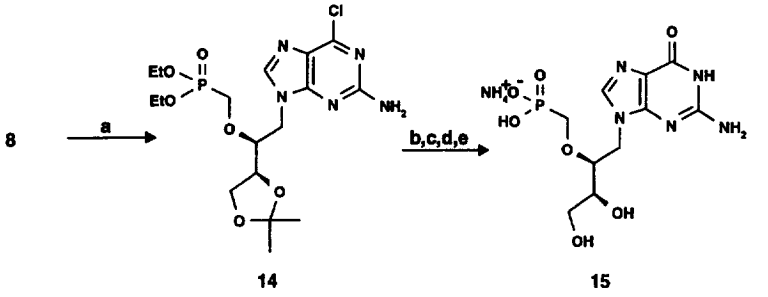
In the preparation of the guanine analogue **15**, the Cs_2CO_3 mediated alkylation procedure of mesylate **9** with 2-amino-6-chloropurine (DMF, 90°C, 4 h) produced the alkylated analogue in low yields (17%). Taking advantage of the solubility of 2-amino-6-chloropurine in DMF, its Mitsunobu coupling with alcohol **8** readily provided, to our satisfaction, the desired N-9 regioisomer **14** in 63% isolated yield.[11] After some experimentation, the order of hydrolysis of **14** to the guanine derivative **15** was established requiring first bromotrimethylsilane mediated hydrolysis of the phosphonate ester,



Reagents and conditions: a. cytosine, Cs_2CO_3, DMF, 90 °C, 3h. b. flash chromatography c. 2N HCl, MeOH, rt, 3h, 52% d. TMSBr, acetonitrile, rt, 16h e. HPLC purification, 40% over d-e.

Scheme 4.

followed by hydrolysis of the 6-chloro moiety simply by stirring in water and finally unmasking the diol with 2 N aqueous HCl under reflux. Final purification was achieved by reverse phase HPLC techniques (Scheme 5).



Reagents and conditions: a. 2-amino-6-chloropurine, DEAD, Ph_3P, DMF, 63% b. TMSBr, acetonitrile c. H_2O d. 2N aq. HCl, reflux 5h e. HPLC purification

Scheme 5.

In summary, we have developed an efficient synthesis of chiral [2′-phosphonomethoxy(3′,4′-dihydroxybutyl)] (PMDHB) nucleotides, having the 2′*S*,3′*S* absolute configuration, from L-ascorbic acid,[12] and demonstrated the high N-9 regioselectivity in the Mitsunobu coupling of 2-amino-6-chloropurine with primary alcohol **8**. Nucleotides **13** and **15** were inactive against HCMV (WF1 strain) in Flow 2002 cells, HSV-1 (KOS strain) and HSV-2 (186 strain) in Vero cells at concentrations up to 100 μg/mL.

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