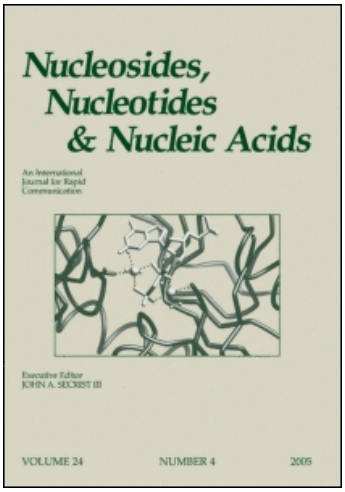

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Synthesis of New Acyclic Nucleoside Vinyl Phosphonates

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SYNTHESIS OF NEW ACYCLIC NUCLEOSIDE VINYL PHOSPHONATES

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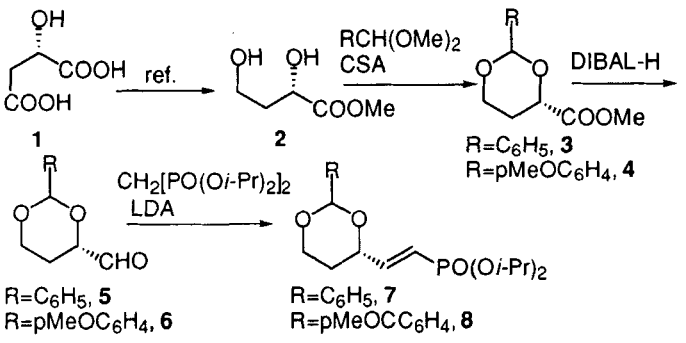
ABSTRACT: Chiral vinyl phosphonates, homomorphous with natural nucleotides, have been prepared starting from (*S*)-malic acid as potential monomers for the synthesis of acyclic polynucleotides.

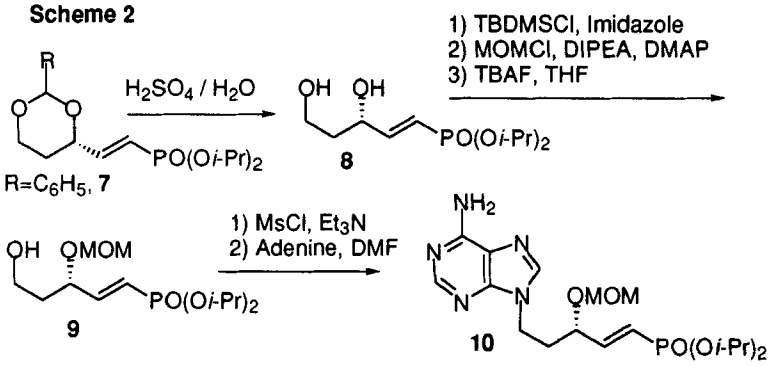
Nucleoside phosphonates have been considered for isosteric alternatives of nucleoside phosphates as antiviral agents.[1] Enantiomerically pure (*S*)-phosphonomethoxypropyl derivatives of purines exhibited a remarkable activity against several DNA and RNA viruses.[2] As a part of our interest in the field of DNA analogues,[3] we decided to prepare simple nucleoside phosphonates homomorphous with natural nucleotides. These new compounds would be acyclic and would contain an element of rigidity as a *trans* double bond. The synthesis started from (S)-malic acid **1** that was transformed into the corresponding diol **2** following standard conditions.[4] Product **2** was further protected as a cyclic acetal using benzaldehyde dimethyl acetal or *p*-metoxybenzaldehyde dimethyl acetal in the presence of canphorsulfonic acid (CSA). Dioxolanes **3** or **4** were reduced to the corresponding aldehydes with DIBAL-H in toluene at -78°C and the aldehydes **5** and **6** underwent Horner-Emmons type reaction with the anion of tetraisopropyl methylene-diphosphonate to give products **7** and **8**.

Scheme 1



We first tryed to selectively deprotect the dioxolane to produce a diol having the secondary OH protected. Unfortunately any attempt to perform this reaction (using DIBAL-H at room temperature or $NaCNBH_3$/ TMSCl)[5] did not give any result. Thus we decided to completely deprotect compound **7** to give diol **9** that was first protected at the primary OH as TBDMS ether (TBDMSCl, DMF, imidazole) then protected at the secondary OH as MOM ether (MOMCl, DIPEA, DMAP) and finally deprotected at the primary OH (TBAF, THF).

Scheme 2



Compound **9** was transformed into the corresponding mesylate (MsCl, Et_3N, CH_2Cl_2) and the reaction with adenine was carried out in DMF at 80°C in the presence of Cs_2CO_3. Product **10** was isolated by crystallisation and resulted a single isomer at ^1H and ^{13}C NMR analysis. Product **10** could be further completely deprotected at the hydroxyl and phosphonate functions to give a nucleoside phosphonate or could be selectively deprotected at one of these two functions for the preparation of modified oligonucleotides.

REFERENCES

1. De Clercq E. *J. Med. Chem.* **1995**, *38*, 2491.

2. Holy, A.; Dvorakova, H.; Jindrich, J.; Masojidkova, M.; Budesinsky, M.; Balzarini, J.; Andrei, G.; De Clercq, E. *J. Med. Chem.* **1996**, *39*, 4073.

3. Ciapetti, P.; Taddei, M. *Tetrahedron* **1998**, *54*, 11305

4 Wünsch, B., Diekmann, H., Höfner, G. *Liebigs Ann. Chem.* **1993**, 1273.

5 Johansson, R., Samuelsson, B. *J. Chem. Soc., Perkin Trans.* I **1984**, 2371.