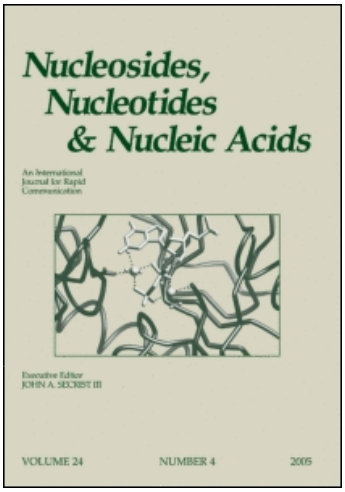

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Asymmetric Synthesis of Cyclopropyl Carbocyclic Nucleosides

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ASYMMETRIC SYNTHESIS OF CYCLOPROPYL CARBOCYCLIC NUCLEOSIDES

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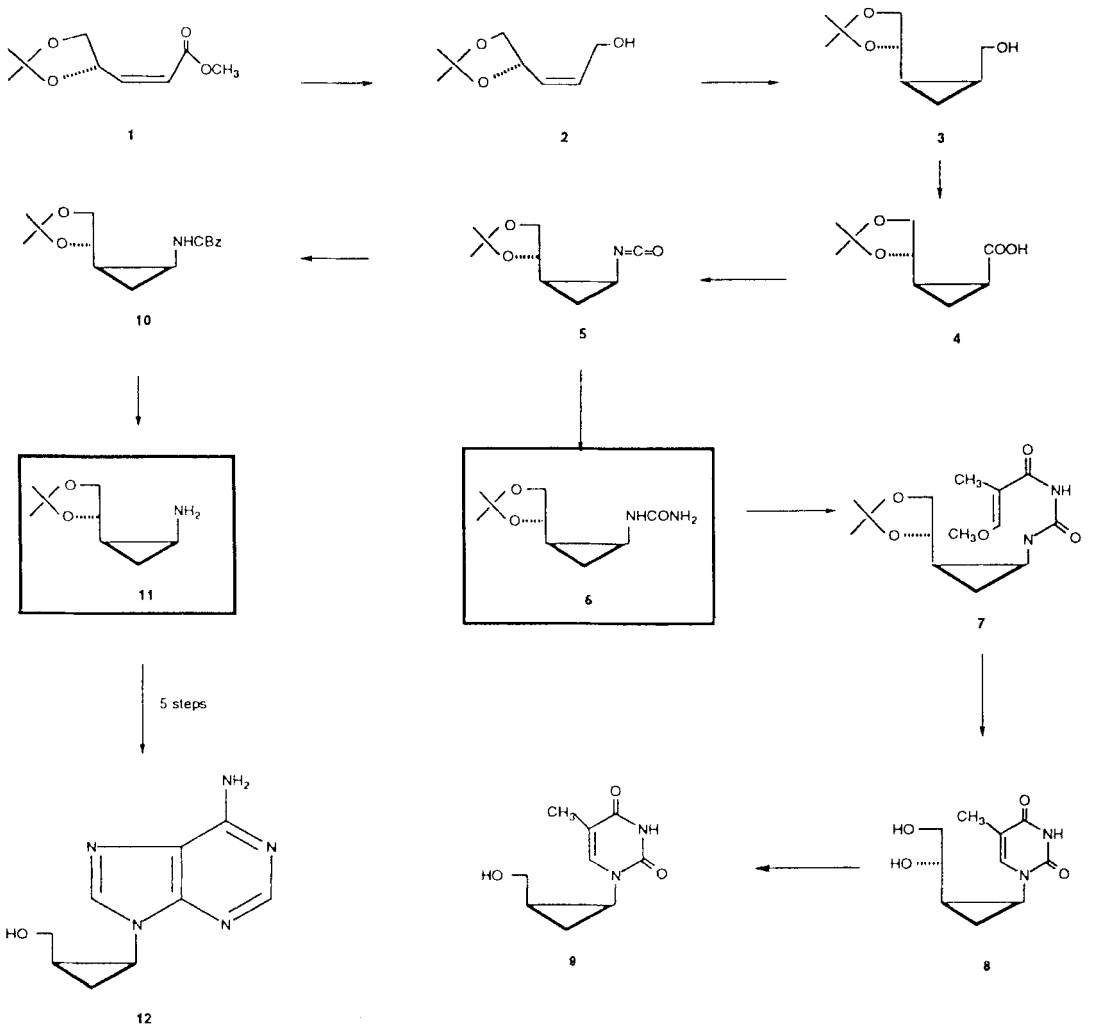
A number of nucleosides have been synthesized as potential antiviral and antitumor agents.[1] More recently , various dideoxynucleosides have been synthesized and found to be potent anti-HIV agents.[2] As a part of our drug discovery program for the treatment of HIV and HBV, we have initiated to synthesize cyclopropyl carbocyclic nucleosides as potential antiviral agents. Several papers regarding the synthesis of cyclopropyl carbocyclic nucleosides have appeared in the literature.[3-5] However, they are all reported as racemic mixtures. In this abstract, we wish to report the asymmetric synthesis of cylopropyl carbocyclic nucleosides from optically active common intermediates, **6** and **11**.

Our synthesis utilized z-olefin **1** as a starting material which was readily prepared from Wittig reaction of D-glyceraldehyde and phosphorane. Since attempts of cyclopropylation of **1** were unsuccessful, the ester **1** was reduced to allyl alcohol **2** by DIBALH, which was subjected to cyclopropylation to **3** by $Zn(Et)_2$ and ICH_2Cl. The cyclopropyl derivative **3** was then oxidized to acid **4** with $RUO_2/NaIO_4$ followed by chlorination with chloroformate, NaN_3 treatment and then the hydrazide was heated to give isocyanate **5**. The isocyanate was converted to urea derivative **6** by ammonia, which was treated with ß-methoxyacryloyl chloride followed by a reaction with NH_4OH and then acid treatment to give the thymine derivative **8**. The reaction of **8** with $NaIO_4/NaBH_4$ afforded the desired nucleoside **9**. The adenine derivative **12** was also synthesized from the isocynate **5**, which was converted to **10** followed by reduction to give the amino derivative **11**, which subsequently led to the synthesis of adenine derivative **12**.



SCHEME 1

In summary, the above described stereoselective synthesis of cyclopropyl nucleosides can be extended to other pyrimidine and purine derivatives. Furthermore, this method can also be applied for the synthesis of other enantiomers, which is in progress in our laboratories.

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