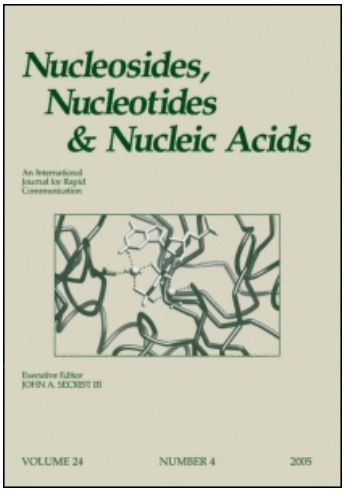

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STEREOSELECTIVE SYNTHESIS OF CARBOCYCLIC α-L-HOMONUCLEOSIDES

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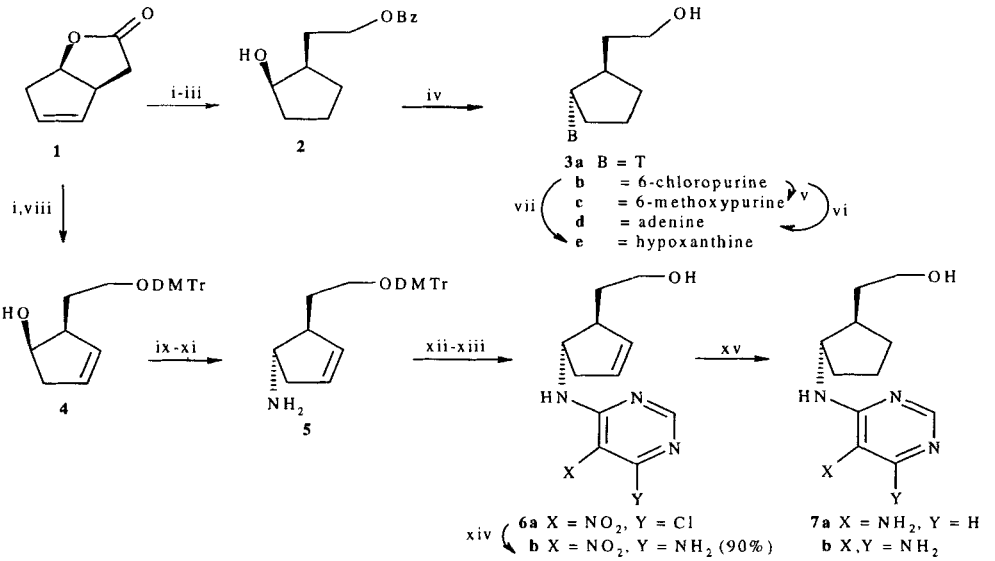
ABSTRACT : The synthesis of several optically pure carbocyclic α-L-isomeric homonucleosides [**3a-e**, **6a,b**, **7a,b**, **10a-d**] is reported. The (*1R,5S*)-2-oxabicyclo[3.3.0]oct-6-en-3-one **1** was used as a chiral starting material.

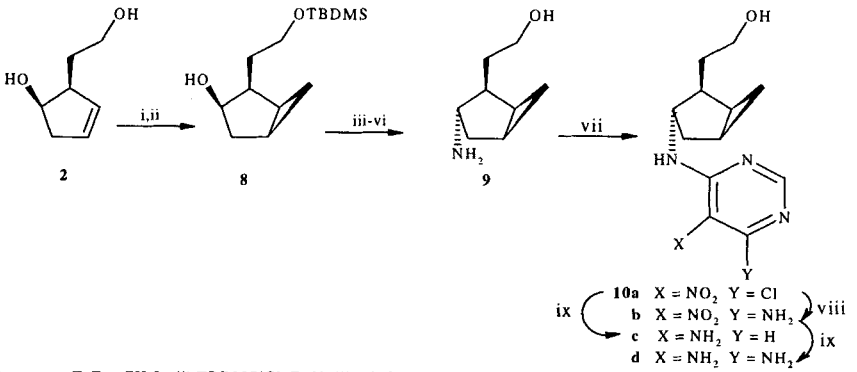
The pharmaceutical importance of carbocyclic nucleoside analogues[1] has prompted the design and synthesis of many new examples of these compounds. As part of our research program, we wish to report the synthesis of several optically pure carbocyclic α-L-isomeric homonucleosides. Our synthetic strategy utilized the known compound, (*1R,5S*)-2-oxabicyclo[3.3.0]oct-6-en-3-one **1** as a chiral starting material (Scheme 1). After several well known steps, the N-alkylation of thymine or 6-chloropurine with the cyclopentanol **2** was achieved under Mitsunobu conditions and afforded after deprotection and/or different modifications of the purine the desired carbocyclic nucleosides **3a-e**. The carbocyclic cyclopentenyl-α-L-homonucleosides **6a,b** and their cyclopentyl analogues **7a,b** were obtained by a linear approach. The desired stereochemistry of cyclopentenylamine **5** was achieved by mesylation of **4**, nucleophilic substitution by an azido group and reduction. The amine **5** was coupled with 4,6-dichloro-5-nitropyrimidine and afforded after deprotection and amonolysis first the carbocyclic analogues **6a,b** respectively, then by hydrogenation the carbocyclic nucleosides**7a** and **7b** respectively.[2] Finally, the recent interest in the influence of sugar conformation on biological activity in which small rings are fused onto the sugar,[3,4] prompts us to report preliminary results of the synthesis of bicarbocyclic nucleosides (Scheme 2). The key step of this approach was the diastereoselective cyclopropanation

of **2** by the Simmons-Smith modified reaction to the bicyclo[3.1.0]hexane template **8**. The carbocyclic analogues **10a-d** were obtained following the same approach than depicted into scheme 1, through the bicycloamine **9**.



Reagents: i) DIBAL-H; ii) BzCl, Et_3N; iii) H_2, 10% Pd/C; iv) Thymine, Ph_3P, DEAD then MeONa/MeOH to **3a** or 6-chloropurine, Ph_3P, DEAD to **3b**; v) MeONa/MeOH; vi) NH_3/MeOH; vii) 0.5N NaOH/H_2O; viii) DMTrCl, Et_3N; ix) MsCl, Et_3N; x) NaN_3, DMF; xi) PPh_3, THF then H_2O; xii) 4,6-dichloro-5-nitropyrimidine, Et_3N; xiii) 2% TFA in CH_2Cl_2; xiv) MeOH/NH_3; xv) H_2, Pd/C 10%.

Scheme 1



Reagents : $ZnEt_2$, CH_2I_2; ii) TBDMSiCl, Et_3N; iii) MsCl, pyridine; iv) NaN_3; v) nBu_4NF/THF; vi) H_2, Pd/C; vii) 4,6-dichloro-5-nitropyrimidine, Et_3N; viii) MeOH/NH_3; ix) H_2, Pd/C, MeOH.

Scheme 2

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5. All obtained compounds were fully characterized by NMR, $[\alpha]_D$, MS and elemental analysis.