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Stereoselective Synthesis of Carbocyclic α -L-Homonucleosides

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STEREOSELECTIVE SYNTHESIS OF CARBOCYCLIC α -L-HOMONUCLEOSIDES

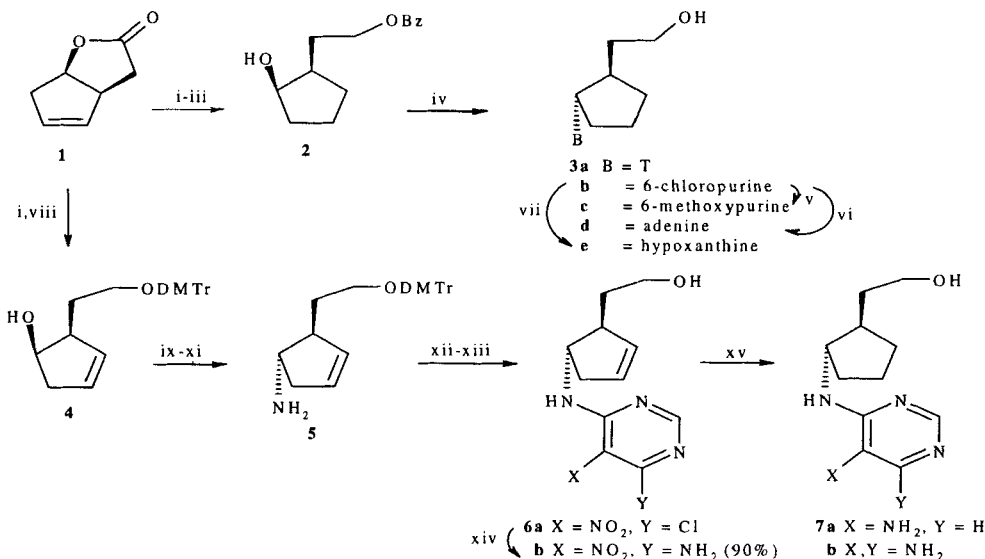
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ABSTRACT : The synthesis of several optically pure carbocyclic α -L-isomeric homonucleosides [**3a-e**, **6a,b**, **7a,b**, **10a-d**] is reported. The (*1R,5S*)-2-oxabicyclo[3.3.0]oct-6-en-3-one **1** was used as a chiral starting material.

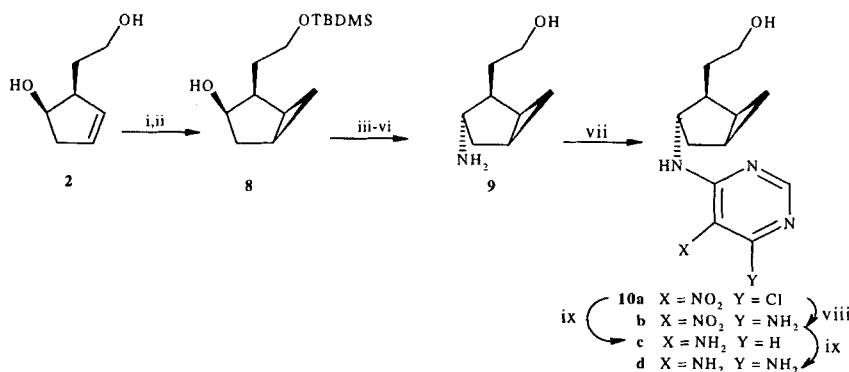
The pharmaceutical importance of carbocyclic nucleoside analogues¹ has prompted the design and synthesis of many new examples of these compounds. As part of our research program, we wish to report the synthesis of several optically pure carbocyclic α -L-isomeric homonucleosides. Our synthetic strategy 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 amination 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, Et₃N; iii) H₂, 10% Pd/C; iv) Thymine, Ph₃P, DEAD then MeONa/MeOH to **3a** or 6-chloropurine, Ph₃P, DEAD to **3b**; v) MeONa/MeOH; vi) NH₃/MeOH; vii) 0.5N NaOH/H₂O; viii) DMTrCl, Et₃N; ix) MsCl, Et₃N; x) NaN₃, DMF; xi) PPh₃, THF then H₂O; xii) 4,6-dichloro-5-nitropyrimidine, Et₃N; xiii) 2% TFA in CH₂Cl₂; xiv) MeOH/NH₃; xv) H₂, Pd/C 10%.

Scheme 1



Reagents: i) ZnEt₂, CH₂I₂; ii) TBDMSiCl, Et₃N; iii) MsCl, pyridine; iv) NaN₃; v) nBu₄NF/THF; vi) H₂, Pd/C; vii) 4,6-dichloro-5-nitropyrimidine, Et₃N; viii) MeOH/NH₃; ix) H₂, Pd/C, MeOH.

Scheme 2

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