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A NEW AND CONVENIENT APPROACH FOR THE SYNTHESIS OF RIBO- AND 2'-DEOXYRIBO-β-L-FURANONUCLEOSIDES STARTING FROM β-L-XYLOFURANONUCLEOSIDES

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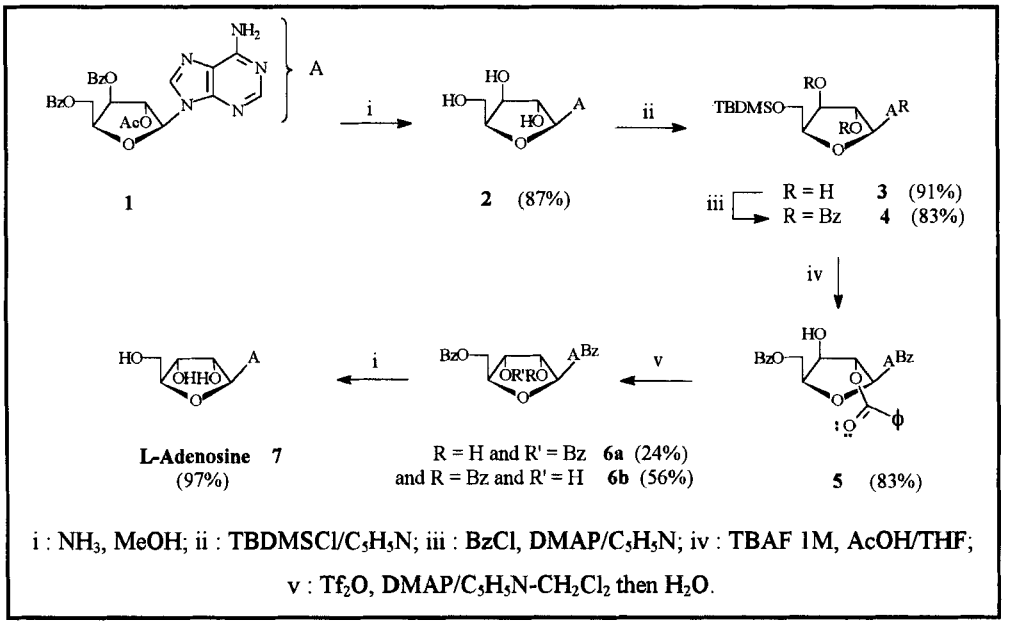
ABSTRACT : Ribo- and 2'-deoxyribo-β-L-furanosyladenine have been synthesized. Although these compounds have been already reported in the literature, it seemed to us that a more convenient approach for their synthesis deserved to be developed. Intramolecular substitution as well as Mitsunobu reaction were used to invert the configuration of carbon 3' of starting β-L-xylofuranosyl intermediates.

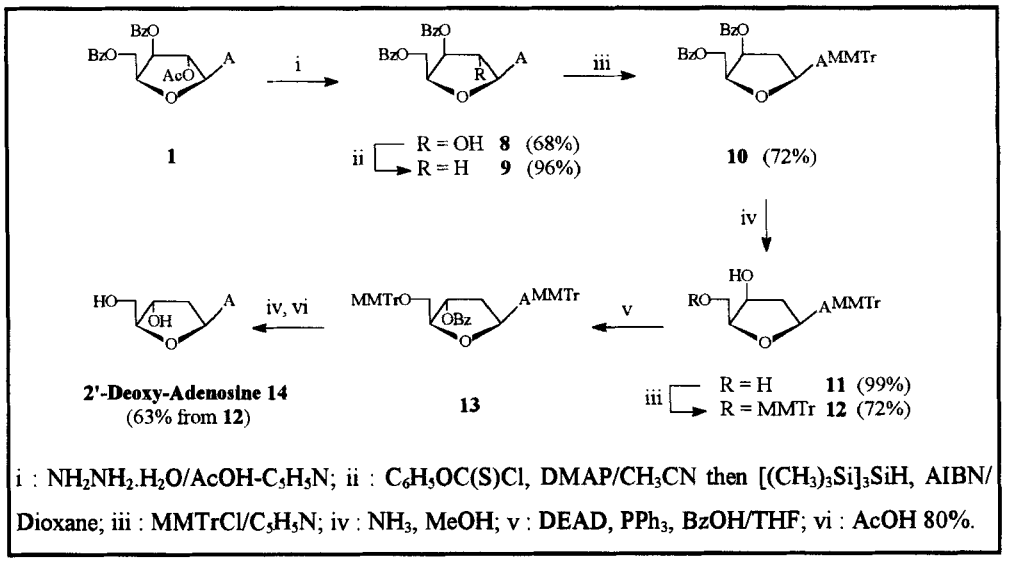
Recently, nucleoside analogues with the unnatural β-L-configuration have emerged as a new class of sugar-modified derivatives with potential antiviral and / or antitumoral activity. For instance, β-L(-)-2',3'-dideoxy-3'-thiacytidine (3TC, Lamivudine) was approved as an anti-immunodeficiency (HIV) agent and β-L-2',3'-dideoxy-5-fluorocytidine has been found to exhibit activity against HIV as well as hepatitis B virus (HBV), both *in vitro* and *in vivo*. Other β-L-dideoxynucleoside enantiomers are currently the subject of intensive research works.[1]

In continuation of our research program on L-sugar modified nucleoside analogues, we now describe the stereospecific synthesis of 9-(β-L-ribofuranosyl)adenine (7) and 9-(2-deoxy-β-L-ribofuranosyl)adenine (14) starting from a suitably protected and easily accessible 9-(β-L-xylofuranosyl)adenine derivative (1).

9-(β-L-Ribofuranosyl)adenine 7 : From a synthetic viewpoint (Scheme 1), the starting compound 1 was obtained according to a method previously described by our group[2] in 44% yield in 6 steps from L-xylose. Then 2' and 5'-OH as well as 6-NH_2



SCHEME 1



SCHEME 2

functions were protected by benzoyl groups (4 steps) to afford the intermediate **5**. The 3'-OH was activated as a triflate ester which was immediately removed under an intramolecular Sn2 mechanism induced by the oxygen doublet of the benzoyl group in position 2'.[3] The reaction led to the formation of an acyloxonium ion between the positions 2' and 3' on the sugar α face. Hydrolysis of this intermediate gave two regioisomers, benzoylated in the 3' position (**6a**) or in the 2' (**6b**). Finally, aminolysis of the benzoyl groups afforded the desired 9-(β-L-ribofuranosyl)adenine **7**.

9-(2-Deoxy-β-L-ribofuranosyl)adenine 14 : (Scheme 2). Selective deacylation of **1** followed by a reductive deoxygenation at C-2' afforded compound **9**. The 6-NH_2 and 5'-OH functions were protected by a monomethoxytrityl group to give compound **12**. A Mitsunobu reaction[4] was carried out in order to invert the configuration of carbon C-3'. The resulting benzoylated compound **13** was successively treated by methanolic ammonia and aqueous acetic acid 80% to give the desired 9-(2-deoxy-β-L-ribofuranosyl)adenine **14**.

Conclusion : During this work we have developed new and convenient approaches for the synthesis of both ribo- and 2'-deoxyribo-β-L-furanonucleosides of adenine. These unnatural L-enantiomers are currently studied for their potential biological activities.

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