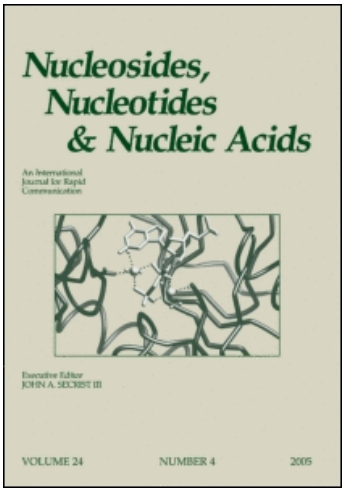

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A GENERAL ROUTE TO D- AND L-SIX-MEMBERED NUCLEOSIDE ANALOGUES

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□ *A simple synthetic route for novel* L- *(as well as* D-*) six-membered nucleosides is described. Particularly, we have provided a general approach to the synthesis of azasugar-based nucleosides, which preparation has been easily achieved starting from the coupling of our three carbon homologating agent* ***1*** *with the well known Garner aldehyde* ***4****. Further suitable and stereocontrolled functionalizations of the intermediate* ***9*** *will provide, after the base insertion, a wide class of six membered modified azanucleosides to be tested as NRTIs.*

Keywords azasugar-based nucleosides; six-membered modified azanucleosides.

In the search for effective, selective and nontoxic antiviral agents, a variety of strategies have been devised to design nucleoside analogues. These strategies have involved several formal modifications of the naturally occurring nucleosides, especially alterations of the carbohydrate moiety.[1] Modifications[2] have concerned, for instance, the inversion of hydroxyl group configurations, their elimination leading to bioactive dideoxy- or didehydro-nucleosides (e.g., ddC and d4T, respectively) or the replacement of the endocyclic oxygen of the sugar moiety with an heteroatom (3TC). In addition, since the discovery of Lamivudine (3TC, β-L-(-)-2-deoxy-3-thiacytidine) as potent inhibitor of reverse transcriptase (NRTI), L-nucleoside enantiomers have been re-evaluated as an emerging class of antiviral agents[3] and a great deal of efforts have been focused towards the synthesis of new L-sugar-based nucleoside analogues as potential NRTIs. As part of our current interest in polyhydroxylated compounds,[4] we designed and set up a new general approach to the synthesis of azasugar based nucleoside analogues, as well as hexopyranosyl nucleosides, belonging to both D- or L-series.

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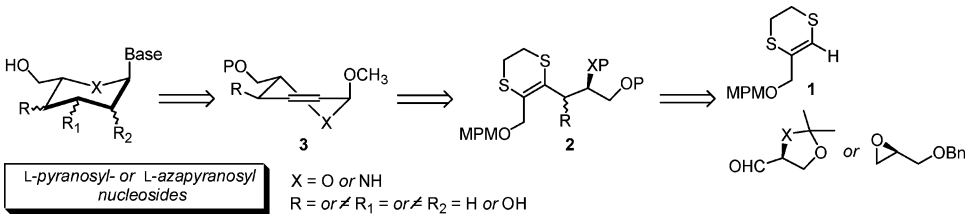


SCHEME 1 Retrosynthetic path for L-six-membered nucleoside analogues.

As depicted in Scheme 1, L-nucleoside analogues easily can be prepared starting from our three-carbon homologating agent **1**[5] and chiral electrophiles such as 2,3-*O*-isopropylidene-L-glyceraldehyde, Garner aldehyde, as well as (*R*)-benzyl glycidyl ether.

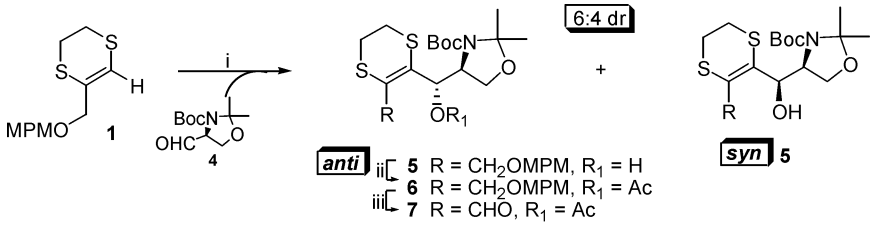
The current strategy comprises the following major steps: (i) preparation of **2** by three-carbon homologation; (ii) synthesis of the 2,3-unsaturated six-membered ring **3** by carbon skeleton cyclization; (iii) suitable double bond functionalization and base insertion.

Obviously, it would be possible to synthesize D-analogues simply by replacing the chiral electrophiles with their enantiomers.

In this preliminary communication, the synthesis of azanucleosides by a noncarbohydrate based route is reported.

The synthesis began with the coupling of **1**, prepared in a few steps from methyl pyruvate,[5] with Garner aldehyde[6] **4** (Scheme 2). Under our conditions, a solution of **4** and a catalytic amount of Ti(*O*-*i*-Pr)$_4$ in THF was added at low temperature to the in situ prepared *C*-3 lithiated carbanion of **1**, providing an *anti/syn* (6:4 dr) diastereomeric mixture of alcohols **5** in 83% yield. After mixture separation by SiO_2 flash chromatography, the more abundant *anti*-**5** diastereoisomer was chosen as a model to test the whole synthetic path. Acetylation of the secondary hydroxyl function, using Ac_2O in Py, afforded **6** in almost quantitative yield.

4-Methoxybenzyl protecting group removal was next attempted (Scheme 2) by treating **6** with DDQ (1.2 eq.) in CH_2Cl_2/H_2O (18:1). As we have previously described[5] with similar substrates, such removal



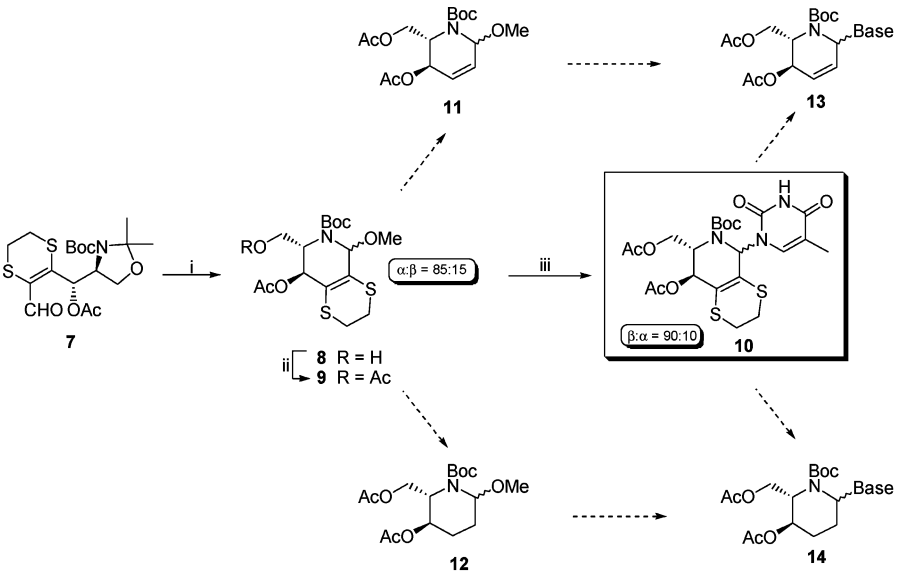
i: BuLi, THF, -78 °C, Ti (O^iPr)$_4$, 83%; ii: Ac_2O, Py, rt, 99%; iii: DDQ, CH_2Cl_2/H_2O, rt, 89%

SCHEME 2 Homologation reaction and MPM group removal.

conditions led quantitatively to the formation of a formyl function rather than the expected primary alcohol. Then, treatment of the aldehyde **7** in the presence of acidic Amberlyst in methanol allowed, in a one-pot simple procedure, the cleavage of the oxazolidine ring and the cyclization to afford the unstable bicyclic compound **8** (Scheme 3). After the acetylation of the crude residue, an α:β diastereomeric mixture of **9** (85:15 dr) was obtained in 97% overall yield. The key intermediate **9** was then coupled with the heterocyclic bases, under standard conditions,[7] to afford nucleoside derivatives **10** (β:α = 90:10). Diastereomeric ratio of the *O*-methyl glycoside **9** and of the nucleoside **10** has been determined by ^{1}HNMR analysis.

As reported in Scheme 3, the versatility of **9** allows the preparation of unsaturated and saturated azanucleosides **13** and **14**. Indeed, compatibly with each substrate, desulfurization will be performed prior or after the base insertion by means of Raney-Ni (1:10 w/w) in THF at 0°C, or using a large excess of Raney-Ni in order to obtain the over-reduction product. Suitable functionalizations at *C*-2/*C*-3 positions, carried out on the compound **13**, will fulfil the wide class of six-membered azanucleosides to be tested as NRTIs.

Works are still in progress concerning the synthesis of L-pyranosyl nucleosides, through the employment of different electrophiles (as shown in the retrosynthetic path), by means of a similar synthetic route to that so far described.



i: Amberlyst 15, MeOH, 0 °C to rt; ii: Ac_2O, Py, rt (97% over two steps); iii: Silylated thymine, $SnCl_4$, DCE, 0 to 20 °C, 72%

SCHEME 3 Carbon skeleton cyclization and base insertion.

In summary, a versatile and profitable approach to the synthesis of L-azapyranosyl nucleosides has been opened up. The versatility of such a method lies in producing intermediates bearing a double bond at *C*-2/*C*-3 positions (like **11**), which can be properly functionalized (or completely reduced) to afford a wide class of target molecules.

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