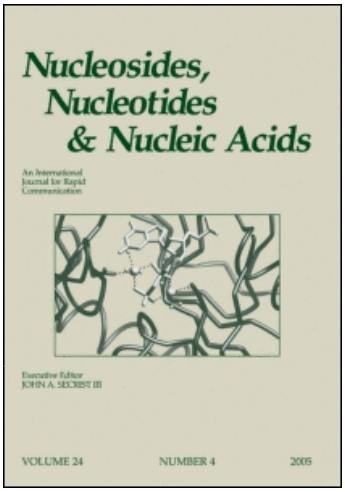

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Diastereo- and Enantioselective Synthesis of 1′-C-Branched *N,O*-Nucleosides

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ABSTRACT

A synthetic approach towards 1′-C-branched N, O-nucleosides is reported, based on 1,3-dipolar cycloaddition of ethoxycarbonylnitrone. The asymmetric version of the process exploits the presence of a chiral auxiliary at the carbon atom of nitrone and leads to β-D and β-L nucleosides in good yields.

Key Words: *C*-Ethoxycarbonyl-*N*-methylnitrone; 1,3-Deoxolanyl-*N*-methylnitrone; *N,O*-Nucleosides.

Modified nucleosides have received great attention over the last decade as antiviral and antitumoral agents.[1] In this contest, great interest has been recently devoted towards the synthesis of compounds in which the furnaose moiety is replaced by alternative carbo- or heterocyclic rings and the design of novel ''ribose'' rings has resulted in the discovery of biologically active agents.[2]

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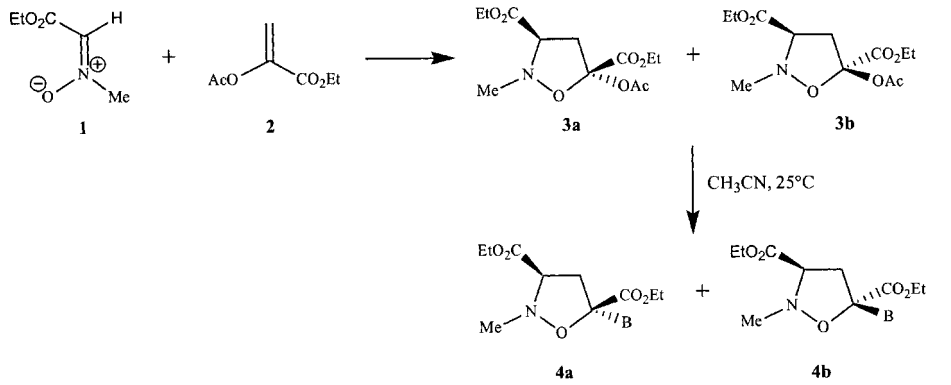

Scheme 1.

Natural psicofuranosyl nuclesoides, carrying a CH_2OH group at the anomeric carbon atom, are endowed with interesting biological activities;[3] on this basis we have designed an easy route towards modified N,O-psiconucleosides, were the sugar unit is replaced by an isoxazolidine ring.

The synthetic approach exploits the potentialities offered by 1,3-dipolar cycloaddition of nitrones. Thus, the 1, 3-dipolar cycloaddition of C-ethoxycarbonyl-N-methyl nitrone 1 with ethyl 2-acetoxyacrylate 2 at room temperature gives epimeric isoxazolidines 3a,b, in a 8.6 : 1 relative ratio (96% combined yields). The major stereoisomer 3a arises from *E* nitrone reacting through an *endo* TS (with respect to CO_2Et group). Coupling reactions with silylated nucleobases afforded α-nucleosides 4a and ß-nucleosides 4b in a nearly equimolar ratio, except for the 5-fluorouracil derivative were the α/ß ratio is 1 : 2.5 (Sch. 1).

An analogous distribution of α- and β-anomers was obtained if nucleosidation is preformed on the separated isoxazolidiners or on the epimeric mixture. Diastereoselectivity and yields are strictly dependent from the experimental conditions: an increase of the temperature to a value of 45°C resulted in a nearly complete diastereoselectivity, with the exclusive formation of ß-anomers for pyrimidine derivatives and α-anomers for purine nucleobases (Table 1). The results suggest that isomerization was occurring during the product formation, with equilibration towards thermodynamically more stable compounds, i.e., β-anomers for pirimidine compounds, α-anomers for purine derivatives.

Table 1. Reactions between isoxazolidines and sylilated nucleobases.

Base	Conditions (°C)	α/β ratio	Yields (%)
Thymine	35	1 : 5	65
Thymine	45	0 : 1	80
Thymine	80	0 : 1	40
N-Acetylcitosine	45	0 : 1	73
5-Fluorouracil	45	0 : 1	70
Adenine	45	1 : 0	50

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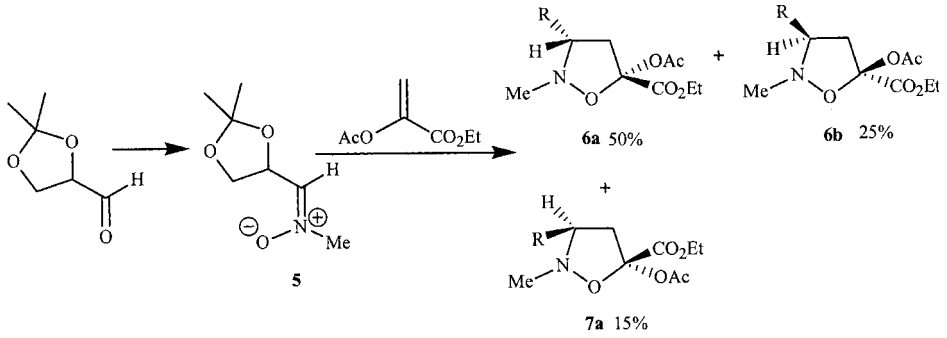
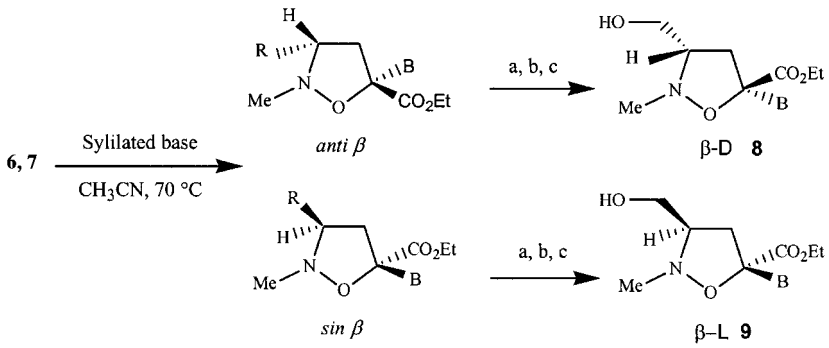


Scheme 2.



B = Thymine, N-acethylcytosine, 5-fluorouracil
a) *p*-TsOH acid; b) $NaIO_4$, CH_2Cl_2; c) $NaBH_4$

Scheme 3.

Enantiomerically pure *N,O*-C-1′-branched nucleosides have been synthesized by asymmetric 1,3-dipolar cycloaddition of nitrone 5 carrying a chiral substituent at the α carbon (Sch. 2).[2]

The cycloaddition reaction proceeds with a good control of *cis*/*trans* diastereoselectivity (5 : 1): cycloadducts 6a,b arise from reaction of Z nitrone through a *endo* TS with respect to CO_2Et group.

Subsequent coupling with silylated thymine, cytosine and uracil, performed at 70 °C, afforded as expected, the exclusive β-anomers which were separated and transformed in the corresponding β-D and β-L nucleosides 8 and 9 (Sch. 3).

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