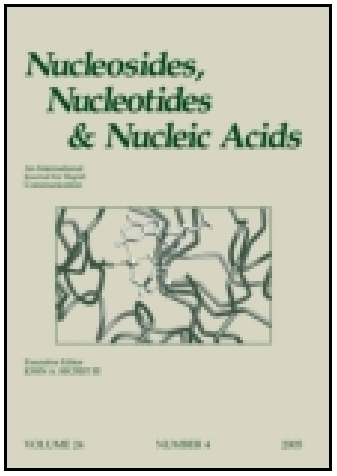

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Synthesis of Some Fully 3′ and 4′-C-Branched-Chain Sugar Nucleoside Analogues

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SYNTHESIS OF SOME FULLY 3' and 4'-C-BRANCHED-CHAIN SUGAR NUCLEOSIDE ANALOGUES.

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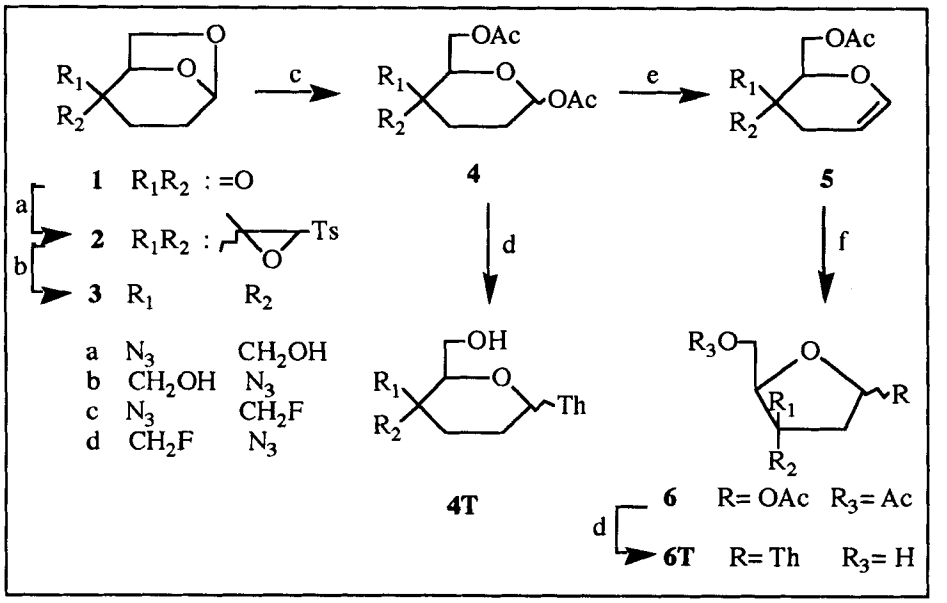
ABSTRACT: The synthesis of some new 3'-azido-3'-C-substituted pyrimidine nucleoside analogues is described. The key step is the geminal disubstitution of an appropriated ketone carbohydrate, via the regioselective ring opening of the corresponding tosyl-epoxide derivative.

As a part of our studies on the stereospecific synthesis of highly functionalized branched-chain sugars[1], two sets of fully 3' and 4'-C-branched-chain sugar nucleoside analogues - 2',3',4'-trideoxypyranosyl and 2',3'-dideoxyfuranosyl - were prepared and evaluated as antiviral agents. These compounds were characterized by the presence of two functional groups (azido and hydroxymethyl or fluoromethyl) on the same carbon of the sugar moiety.

The synthesis of this novel type of nucleoside analogues was based on the formation, from ulose **1**[2], of α,β-epoxy-sulphones **2** followed by regioselective opening of their three-membered ring in the presence of azide ions. The resulting α-azido-aldehyde intermediates were transformed into the α-azido hydroxymethyl derivatives **3(a,b)** and subsequently into the α-azido fluoromethyl derivatives **3(c,d)** by exposure their corresponding triflates to fluoride ions . Acetolysis of **3** and condensation[3] of the resulting branched-chain acetylated sugars **4** with silylated thymine afforded (35-60%) the first set of 2',3',4'-trideoxypyranosylnucleoside analogues **4T**.

The access to the furanosyl series was based on the excision of the anomeric carbon by a two step procedure from the common intermediates **4**. The formation of a double bond **5** (90-95%) and its oxidative cleavage by the catalytic RuO_2-$NaIO_4$ method

resulted in the selective formation of the corresponding lactols (70-75%) which were acetylated to give the desired 2,3-dideoxyfuranosyl derivatives **6**. Condensation of the latter with silylated thymine (90%), deprotection and separation of anomers furnished the dideoxyfuranosylnucleoside analogues **6T** (Scheme 1).



Reagents. (a) $ClCH_2SO_2Tl$, t-BuOH, THF, 85%; (b) (i) NaN_3, MeOH:H_2O, then $NaBH_4$, 85%; (ii) Tf_2O, Py, CH_2Cl_2, then TBAF, THF, 80%; (c) Ac_2O, $BF_3.OEt_2$, 90%; (d) Silylated thymine, IK, 18-crown-6, CH_3CN then NH_3/MeOH; (e) p.TsCl, Py, DMAP, 90-95%; (f) (i) $NaIO_4$, RuO_2, K_2CO_3, CCl_4-H_2O, 70%; (ii) Ac_2O, Py.

Scheme 1

All the compounds synthesized, **4T** and **6T**, were tested for their *in vitro* inhibitory effects on HIV-1 and HBV replication and were found to be inactive.

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