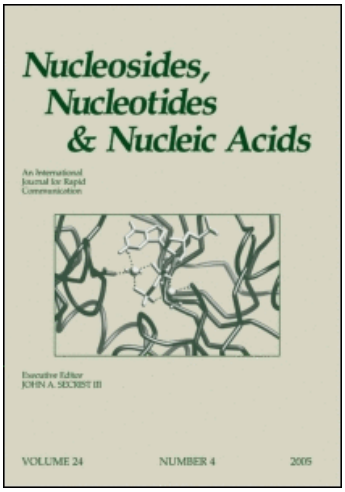

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SYNTHESIS AND ANTI-HIV ACTIVITY OF CARBOCYCLIC RING-ENLARGED 4',1'a-METHANO OXETANOCIN ANALOGUES

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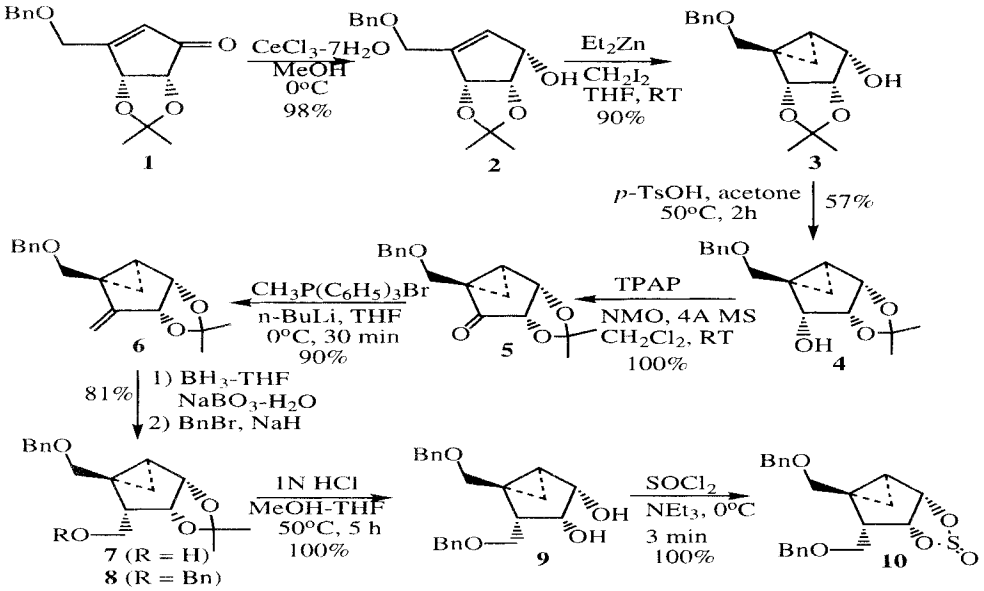
ABSTRACT: Synthesis of carbocyclic ring-enlarged 4',1'a-methano oxetanocin analogues via completely regioselective opening of cyclic sulfites by sodium azide or purine bases is described.

Judging from the X-ray structure of some carbocyclic nucleosides, they appear to crystallize with an unusual sugar ring pucker.[1-3] In comparing the structure of carbathymidine with that of thymidine, which shows a characteristic C3'-exo/C2'-endo pucker ($^2T_3$), the replacement of ring oxygen by CH_2 and the concomminant loss of the gauche effect between the 3'-OH and the sugar oxygen, causes the carbocyclic ring to adopt a rare C1'-exo pucker ($_1E$).[1]

In order to regain the ring pucker that is observed for typical nucleosides, two strategies can be exploited: 1) induction of a conformational change by the interfluorine gauche effect of two adjacent fluorine atoms,[4] or 2) construction of a rigid bicyclo[3.1.0]hexane system with either oxirane or cyclopropane rings fused to the five-membered cyclopentane moiety.

Oxetanocin A[5] exhibited good anti-HIV activity and its ring-expanded analogue showed comparable activity to it.[6] A molecular modeling study revealed that the more stable "northern" conformer of the latter superimposed well on oxetanocin A, and that their hydroxymethyl side chains were almost coincident.[6] However, the ring-expanded

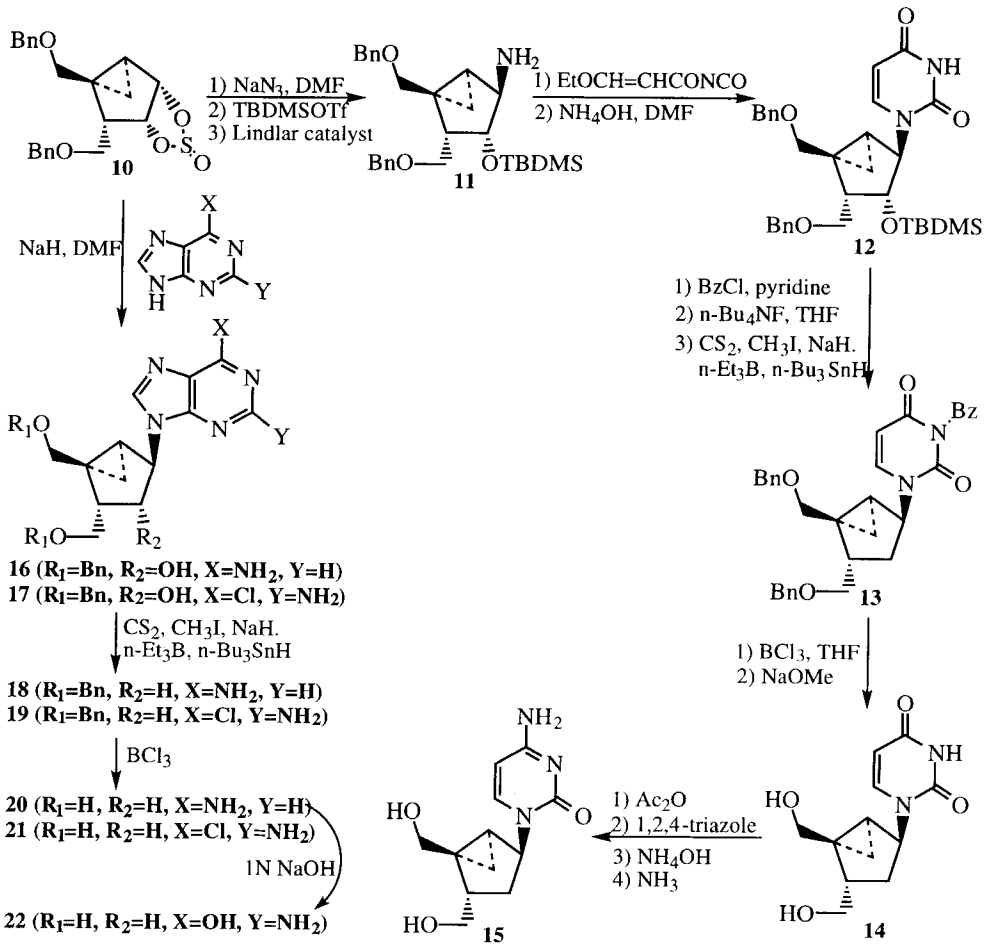


SCHEME 1

carbocyclic version completely lacked anti-HIV activity probably due to the unusual sugar conformation of the carbocyclic ring mentioned above.

Therefore, in view of our continued interest in the effect of sugar ring conformation on the anti-HIV activity of nucleoside analogues, we synthesized carbocyclic, ring-enlarged oxetanocin analogues with a rigid bicyclo[3.1.0]hexane carbasugar which forces a "northern" sugar ring pucker characteristic of the anti-HIV active ring-enlarged oxetanocins. The synthesis of our target nucleosides was accomplished via a completely regioselective opening of cyclic sulfites by sodium azide or purine bases.

The key intermediate, cyclic sulfite **10**, was synthesized starting from cyclopentenone **1** (scheme1). The cyclopentenone **1** was quantitatively reduced to allylic alcohol **2**, which was then treated with Et_2Zn and CH_2I_2 to yield the corresponding bicyclo [3.1.0]hexane intermediate **3**. The acid-catalyzed isomerization of acetonide in **3**, followed by oxidation of the secondary alcohol with tetrapropylammonium perruthenate (VII) (TPAP) gave the ketone **5**, which was converted to olefin **6** by Wittig reaction with methyltriphenyl phosphonium bromide. Hydroboration of **6** proceeded with the desired stereoselectivity to give **7** in 90% isolated yield. Benzyl protection and acid-catalyzed



SCHEME 2

hydrolysis of the acetonide, followed by treatment of the resulting cis-diol **9** with $SOCl_2$ produced the key intermediate **10** in excellent overall yield.

The synthesis of various pyrimidine and purine nucleosides is illustrated in scheme 2. The cyclic sulfite **10** was reacted with NaN_3 in DMF to give the desired product without the formation of the alternative regioisomer. Silyl protection of the newly formed hydroxyl group, followed by reduction of the azide over Lindlar's catalyst produced the amine **11**, which was converted to uracil analogue **12** by the conventional method.[7] Benzoyl protection at N-3 position in uracil **12**, TBDMS removal, and Barton's radical

deoxygenation produced **13**. Debenzylation of **13** with boron trichloride followed by debenzoylation with NaOMe afforded the target bicyclic carbocyclic uracil nucleoside **14**. The uracil nucleoside **14** was converted to the cytosine nucleoside **15** according to the well known procedure of Reese.[8] The cyclic sulfite **10** was also condensed with purine bases such as adenine and 2-amino-6-chloropurine in DMF to give purine nucleosides **16** and **17**. The opening of the cyclic sulfite also proceeded with 100% regioselectivity at the desired position. The secondary hydroxyl groups of **16** and **17** were deoxygenated to give **18** and **19**, respectively. Removal of benzyl protecting groups using boron trichloride afforded the adenine derivative **20**[9] and the 2-amino-6-chloropurine derivative **21**, which was further converted to the guanine analogue **22** with treatment with 1N NaOH.

The synthesized final nucleosides were evaluated for anti-HIV activity, but the preliminary results indicated that none of them showed significant anti-HIV activity in MT-4 cells. The antiviral assay against other viruses is in progress in our laboratory.

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