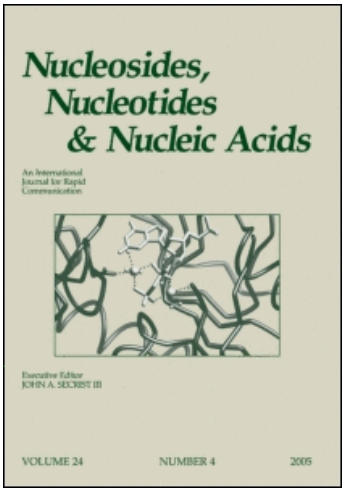

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Synthesis and Testing of New Modified Nucleosides

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SYNTHESIS AND TESTING OF NEW MODIFIED NUCLEOSIDES[1]

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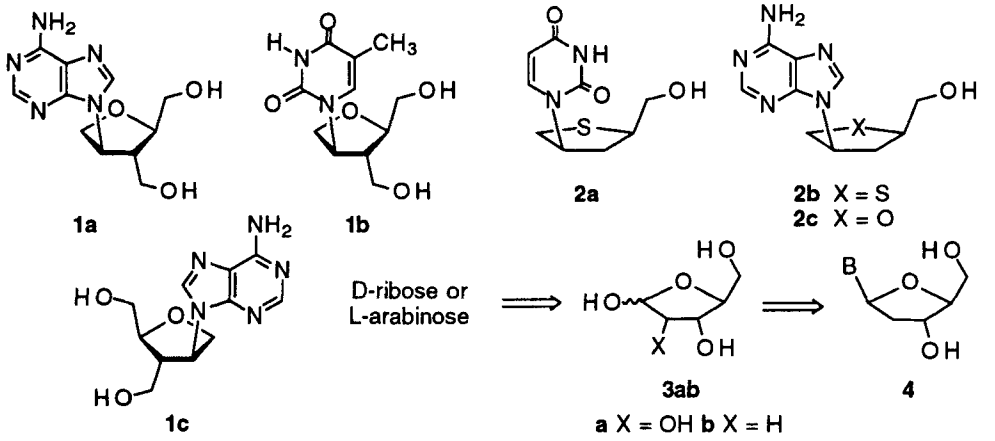
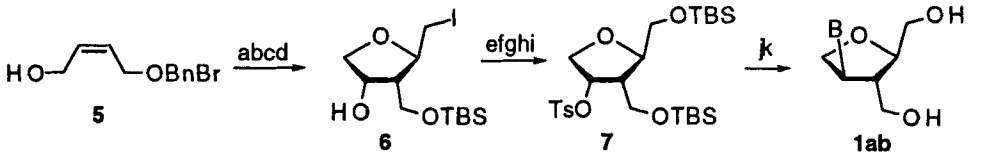
ABSTRACT: New efficient routes for the high-yielding synthesis of several classes of modified nucleosides have been developed. We have prepared both the D- and L-enantiomers of the methylene-expanded oxetanocin isonucleosides **1a-c** and the L-2',3'-dideoxy isonucleosides **2abc** (both the oxa and thia analgoues) as well as new routes for the preparation of L-ribose and 2-deoxy L-ribose **3ab** and their modified nucleosides **4**.

The continuing search for new antiviral compounds has recently led to the synthesis of a variety of nucleoside analogues, including several isonucleosides (nucleosides with the heterocyclic base at a non-anomeric position) and several L-nucleosides, many of which show good activity against a broad spectrum of viruses. In this paper we report new synthetic methods for the preparation of several new classes of modified nucleosides as new potential agents for the treatment of HIV and other viral infections. In particular we have been able to prepare both the D- and L-enantiomers of 'methylene-expanded' oxetanocins, e.g., the compounds **1abc**, by a very novel and efficient route.[4] We have also been able to effect an enantiospecific total synthesis of the L-2',3'-dideoxy isonucleosides **2abc** (both

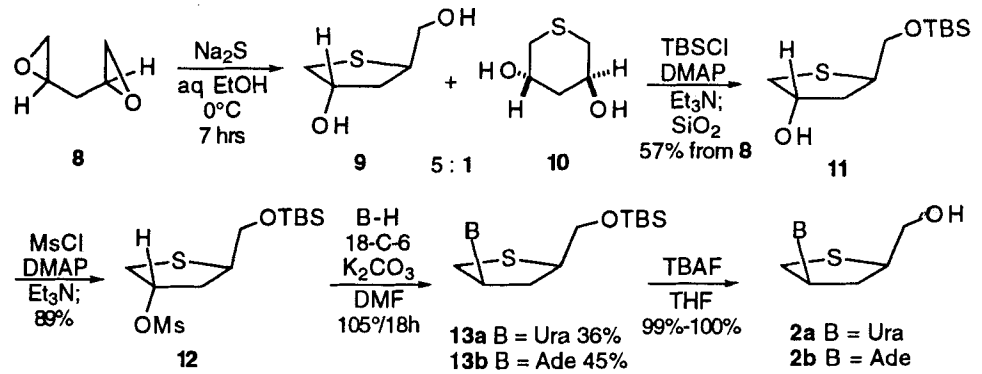


the oxa and thia analogues) via regioselective opening of optically active C_2-symmetric 1,4-pentadiene bis-epoxide.[5] We have developed new methods for the synthesis of L-ribose **3a** and 2-deoxy L-ribose **3b** and their corresponding nucleosides **4** from the inexpensive precursors (L-arabinose and D-glucose).[6]



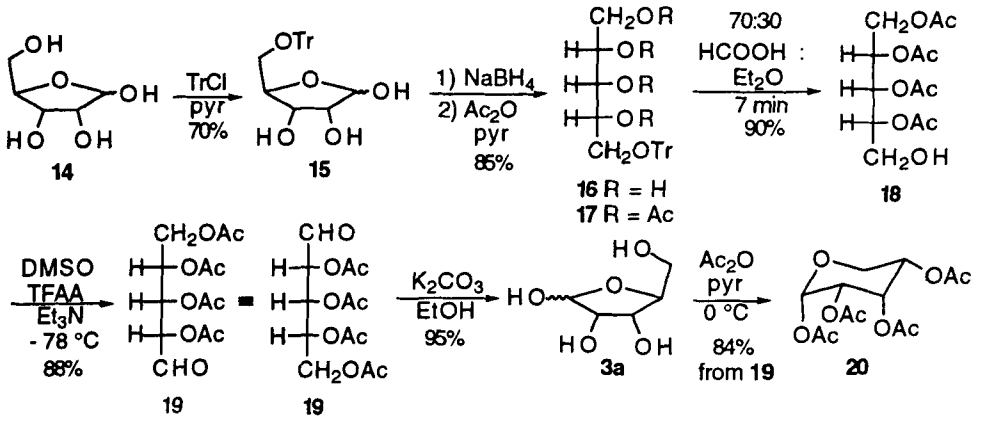
a) L-(+)-DIPT, $Ti(OiPr)_4$, tBuOOH, CH_2Cl_2, mol. sieves, -25 °C, 81%, 96% ee; b) vinylMgBr, CuI, THF, -78 °C → rt, 73%; c) TBSCl, Et_3N, DMAP, CH_2Cl_2, rt, 79%; d) $Ag(coll)_2ClO_4$, I_2,CH_2Cl_2, rt, 52%; e) AcCl, pyr, 0 °C, 81%; f) KOAc (10 eq), DMSO, 87 °C, 41%; g) NH_3, MeOH, 0 °C → rt, 93%; h) TBSCl, Et_3N, DMAP, CH_2Cl_2, 62%; i) TsCl, pyr, 0 °C → rt, 18 h, 68%; j) adenine or thymine, 18-crown-6, K_2CO_3, DMF, 90 °C, 18 h; k) TBAF, THF, rt, 45 min, 35% **1a**, 22% **1b**

The synthesis of the isonucleosides **1ab** involves as the key step an iodo cyclization to give the desired iodomethyl sugar **6**. Thus the monoether of 2-butene-1,4-diol **5** was converted in four steps into the modified carbohydrate **6** which was transformed easily into the tosylate **7**. Addition of the anion of adenine or thymine and deprotection of the silyl groups afforded the desired isonucleosides **1ab**. In an analogous fashion the D-enantiomeric isonucleoside **1c** was also prepared (using the opposite tartrate in the first step). The biological activity of the new compounds L-(+)-**1a** and L-(-)-**1b** against HIV were determined in the anti-HIV drug testing system of the National Cancer Institute. The adenosine analogue L-(+)-**1a** was inactive in this screen while the thymidine analogue L-(-)-**1b** showed moderate anti-HIV activity ($IC_{50} > 2 \times 10^{-4}$ M, $EC_{50} = 8 \times 10^{-7}$ M, TI > 250).[4]



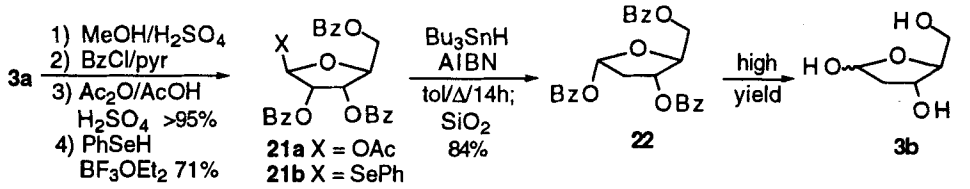
The preparation of the L-enantiomers of the thia isonucleosides **2ab** began with the well-known optically active bis-epoxide **8**.[8] We proposed that treatment of **8** with sodium sulfide would produce the optically active primary, secondary diol **9** via the following process: reaction at the less-hindered primary end of the epoxide to generate the alkoxide, internal proton transfer, and then a final internal opening of the remaining epoxide by the thiol nucleophile to generate the tetrahydrothiophene **9**. In the event, reaction of **8** with sodium sulfide afforded the desired diol **9** along with the isomeric diol **10** in a good yield

as a 5:1 mixture. Silylation of the primary alcohol of **9** allowed for easy separation, giving the desired alcohol **11** in 57% yield from **8**. Mesylation of the secondary alcohol and displacement with the anion of uracil and adenine furnished **13ab** and, after desilylation, the desired thia isonucleosides **2ab**. By using sodium hydroxide in the first step, the corresponding oxa analogues were produced, e.g., **2c**, in comparable yield. These compounds are known to have antiviral properties.[9]

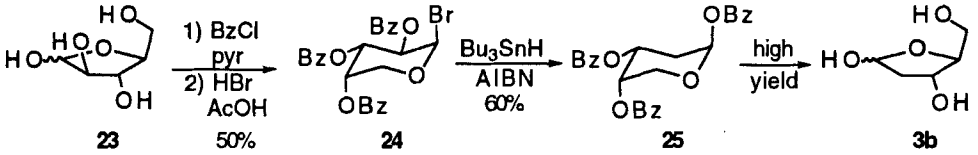


14 **15** **16** R = H, **17** R = Ac **18** **19** **19** **3a** **20**

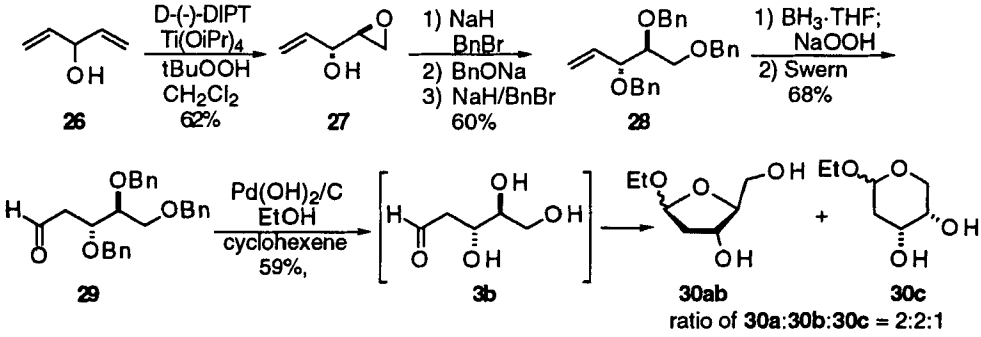
The key observation in our synthetic planning for the preparation of L-ribose and its derivatives was to realize that D-ribose **14** and L-ribose **3a** differ only in the groups at C1 and C5, with C2, C3 and C4 being unchanged. Therefore conversion of **14** into **3a** would require only the interconversion of the two end groups, namely oxidation of the hydroxymethyl to aldehyde and reduction of the aldehyde to a hydroxymethyl group. Selective conversion of D-ribose **14** into 5-*O*-trityl D-ribose **15** in 70% yield was already known.[10] Reduction of the aldehyde with sodium borohydride cleanly furnished the tetrol **16**. We unsuccessfully attempted several direct oxidations of the trityl ether of **16** in the presence of the alcohols, e.g., hydride abstraction with trityl salts.[11] We therefore prepared the tetraacetate **17** by treatment of crude **16** with acetic anhydride and pyridine to give **17** in 85% yield from **15**. Hydrolysis of the trityl ether could be carried out in 90% yield by treatment of **17** with 7:3 formic acid:diethyl ether for 7 min at 25°C. Swern oxidation of the alcohol **18** furnished, after column chromatography, in 88% yield the aldehyde **19**, namely L-ribose 2, 3, 4, 5-tetraacetate. Thus this protected L-ribose derivative is available from D-ribose **14** in only five steps and 47% overall yield. L-Ribose **3a** itself was prepared in 95% yield by basic hydrolysis of **19** using potassium carbonate in ethanol. In order to prove the structure of the L-ribose **1**, we carried out its peracetylation to give the L-ribopyranose tetraacetate **20** in 84% overall yield from the aldehyde **19**. The optical rotation of **20** (+55.2 °) matched that of D-ribopyranose tetraacetate[12] but had the opposite sign, thus proving the structure and chirality of our synthetic material. We have therefore shown that L-ribose **3a** is available from D-ribose **14** in 6 steps in 45% overall yield.



The 2-deoxy L-ribose **3b** could be prepared from L-ribose **3a** by a high-yielding six-step process involving first conversion of **3a** into the acetate **21a** in >95% yield, followed by formation of the selenophenyl compound **21b**. Radical formation and 1,2-acyl shift[13] gave in 84% yield the 2-deoxy sugar **22** which was hydrolyzed to 2-deoxy L-ribose **3b**. Another successful route involved beginning with the inexpensive sugar L-arabinose **23**. Benzoylation and treatment with HBr/AcOH gave the pyranosyl bromide **24** in 50% yield (along with some of the furanosyl bromide). Radical formation and 1,2-acyl migration afforded the desired 2-deoxy sugar **25** which was hydrolyzed to 2-deoxy L-ribose **3b**.



We also examined several other routes to L-ribose **3a** and 2-deoxy L-ribose **3b** that did not begin with carbohydrates, e.g., a *de novo* synthesis from achiral materials. The most successful of these approaches began with divinyl carbinol **26** which was converted into the optically active epoxy alcohol **27** by a Sharpless kinetic resolution-epoxidation.[14] This compound was converted in three steps and 60% yield to the tribenzyl ether **28**[15] which was hydroborated and oxidized to the primary alcohol (along with about 20% of the secondary alcohol) which on Swern oxidation afforded the aldehyde **29** in overall 68% yield. Hydrogenolysis of the benzyl ethers in ethanol gave the desired 2-deoxy L-ribose **3b** which was isolated as the ethyl ribosides **30abc**. Thus 2-deoxy L-ribose **3b** is available from the alcohol **26** in only 7 steps with all of the chirality being introduced in the first step.



Thus we have developed new methods for the synthesis of a wide variety of modified nucleosides and isonucleosides and of L-ribose and 2-deoxy L-ribose derivatives. Further

research in the area of modified nucleoside synthesis is currently underway in our laboratory and will be reported in due course.

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