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Synthesis of {1-[2',5'-Bis-*O*-(*t*-butyldimethylsilyl)-β-D-xylo- and β-D-ribofuranosyl]Thymine}-3'-spiro-5"-{4"-amino-1",2"-oxathiole-2",2"-dioxide} (TSAO). A Novel Type of Specific Anti-HIV Agents

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Key Words: nucleosides; spiro-substituted nucleosides; aldol-type cyclocondensation; anti-HIV agents; TSAO

Abstract: *Reaction of O-mesylcyanohydrins of furanos-3'-ulosyl thymine with bases afforded β-D-xylo- and ribo-3'-substituted nucleosides. 2'-Deoxygenation of the selectively 5'-O-protected nucleoside gave the ribofuranosyl derivative of thymidine.*

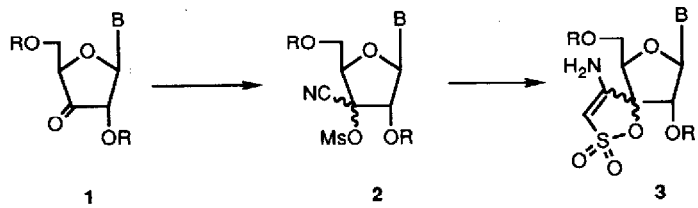
Since the discovery of human immunodeficiency virus (HIV) as the causative agent of the acquired immunodeficiency syndrome (AIDS), several different kinds of nucleosides have proved to be effective anti-HIV agents. Among these, AZT (Azidothymidine) and DDI (Dideoxyinosine) are, so far, the only drugs approved for the clinical treatment of AIDS.[1,2] However, the clinical usefulness of these compounds is counterbalanced by their toxic side effects.[2,3,4] This justifies the search for new compounds with potent and selective anti-HIV activity.

As a part of our studies on the stereospecific synthesis of highly functionalized branched-chain sugars, we found an unexpected behaviour of tertiary cyanomesilates of sugars.[5,6] Under basic conditions, these compounds undergo intramolecular aldol-type cyclocondensation to afford C-branched spiro derivatives.

Our approach[5] involved the reaction of *O*-mesylcyanohydrins of furanos-3-uloses with bases to afford furanose-3-spiro-5'-(4'-amino-1',2'-oxathiole-2',2'-dioxide) derivatives by abstraction of one proton from the mesylate methyl group, followed by nucleophilic attack of the thus formed carbanion at the nitrile carbon atom.

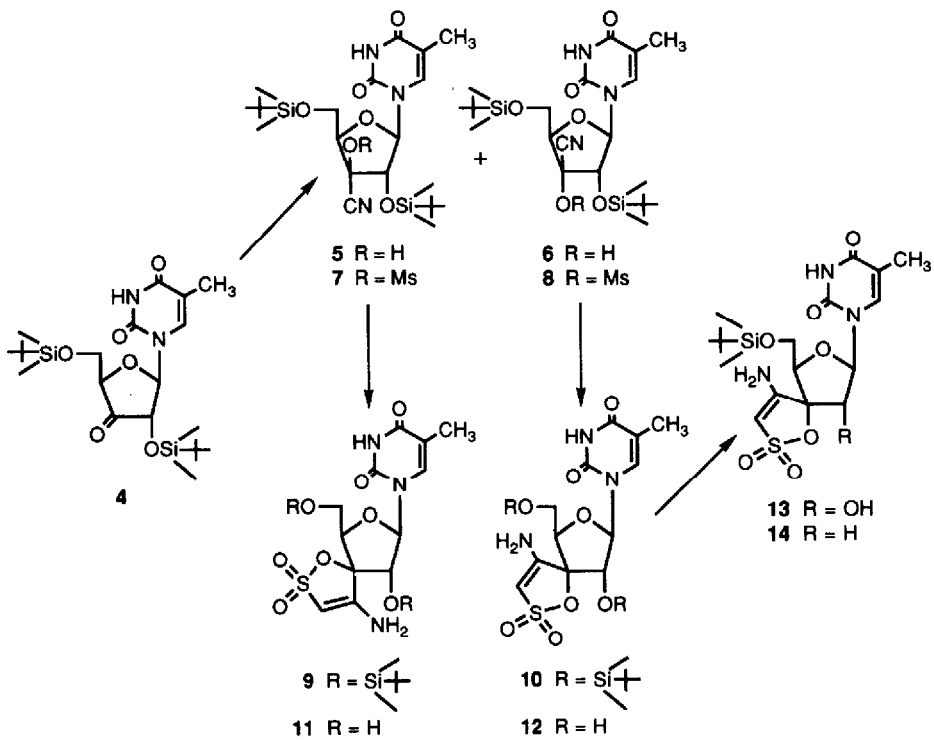
Having this in mind, we decided to extend this method to α-mesyloxynitriles (**2**), prepared from 3'-ketonucleosides (**1**) (Scheme 1). This reaction would lead to a new type of *C*-branched chain nucleosides, having a highly functionalized *C*-branch, the 3'-spiro-5"-(4"-amino-1",2"-oxathiole-2",2"-dioxide) nucleosides[7] (**3**) hitherto unknown in the literature.

Scarce reports on the synthesis of spironucleosides have appeared, the procedures being mainly based on the reactivity of the anomeric position of the sugars.[8,9] In this communication we report on the synthesis of β-D-xylo- and ribofuranosyl-3'-spiro-substituted nucleosides of thymine.



Scheme 1

As shown in Scheme 2, treatment of 1-(β-D-pentofuranos-3'-ulosyl) thymine (**4**)[10] with sodium cyanide and sodium bicarbonate in a stirred mixture of ethyl ether/water (2:1) stereoselectively afforded a (12:1) mixture of the two possible 3'-cyanohydrin epimers **5** and **6**. These compounds, which partially decomposed to ketonucleoside **4** on standing in solution at room temperature, were treated with mesyl chloride in pyridine to give the respective 3'-*C*-cyano-3'-*O*-mesyl-β-D-xylo- and ribofuranosyl thymine nucleosides **7** (53%) and **8** (10%).



Scheme 2

The stereochemistry at C-3' of the α-mesyloxynitriles **7** and **8** was determined by ^{1}H-NMR.[11] Thus, the *xylo* configuration for **7** and *ribo* configuration for **8** was established from the $J_{1',2'}$ coupling constant values observed for **7** ($J_{1',2'}$= 2.0 Hz) and **8** ($J_{1',2'}$= 8.3 Hz), values that are in agreement with those reported for other

β-D-*xylo* and *ribo* C-branched nucleosides described in the literature.[12,13] On the other hand, the observed shielding for H-2 (0.36 ppm) in compound **7** when compared to the same proton in **8** suggested that H-2 and the mesyl group are at the same side of the furanose ring, and, therefore, its conformation is *xylo*. This suggestion was corroborated by a similar shielding for proton H-4 in **8** (0.22 ppm) when compared with the same proton in **7** indicating that the H-4 and the mesyl group in **8** are at the same side of the ring and, thus, its conformation is *ribo*. The stereochemistry at C-3' of the cyanohydrins was inferred from the orientation of the 3'-*C*-cyano group of the α-mesyloxynitriles **7** and **8** obtained from them. The stereochemistry of the resulting cyanohydrin depends on the relative steric hindrance of the upper or lower sides of the furanose ring, which facilitates the approach of the cyanide ion from the less hindered side of the molecule. Thus, a *xylo* configuration for the major cyanohydrin is in agreement with the approach of the cyanide ion from the sterically less hindered α-face of the ulose **4**, opposite to the base.[14]

Reaction of **7** and **8** with Cs_2CO_3, in dry acetonitrile at room temperature, gave {1-[2',5'-bis-*O*-(*t*-butyldimethylsilyl)-β-D-xylo- and ribofuranosyl]thymine}-3'-spiro-5"-{4"-amino-1",2"-oxathiole-2",2"-dioxide} derivatives **9** (87%) and **10** (85%), respectively.[15]

The stereochemistry at C-3' for 3'-spiroderivatives **9** and **10**, and thus, for the β-D-*xylo* (**7**) and β-D-*ribo* (**8**) α-mesyloxynitriles, was unequivocally determined by n.O.e. experiments.[16] Irradiation of the NH_2 group of **9** induced n.O.e. of the signals for H-3", H-4' and H-1'. Irradiation of the NH_2 group of **10** caused n.O.e. of the signals for H-3", H-2' and one of H-5' protons. These results indicated that in nucleoside **9**, protons H-3", H-4', H-1' and NH_2 are all "down" and, hence, its structure is β-D-xylo. Similarly in nucleoside **10**, protons H-3", H-2', H-5'a and NH_2 are "up", thus its structure is β-D-*ribo*.

Deprotection of **9** and **10** with tetrabutylammonium fluoride gave [1-(β-D-xylo- and ribofuranosyl)thymine]-3'-spiro-5"-[4"-amino-1",2"-oxathiole-2",2"-dioxide] **11** (73%) and **12** (60%), respectively.

Reaction of **12** with 1.1 equivalents of *t*-butyldimethylsilyl chloride selectively gave the 5'-*O*-protected 3'-spiroribonucleoside **13** (83%). Treatment of the latter with thiocarbonyldiimidazole in toluene/acetonitrile and then, with tributyltin hydride and α,α'-azobisisobutironitrile in toluene, gave {1-[5'-*O*-(*t*-butyldimethylsilyl)-2'-deoxy-β-D-*erythro*-pentofuranosyl]thymine}-3'-spiro-5"-{4"-amino-1",2"-oxathiole-2",2"-dioxide} (**14**) (50%).

Compounds **9-14** were tested for their *in vitro* inhibitory effects on HIV-1 replication. Compound **10** was found to exhibit a highly specific anti-HIV-1 activity,[17] being inactive against HIV-2 and other (retro)viruses. The peculiar structure of compound **10** as compared to other known anti-HIV agents, together with its high antiviral specificity has led to the discovery of a new family of anti-AIDS drugs.

In conclusion, this communication demonstrates that spiro-substituted nucleosides can be synthesized from the readily available α-mesyloxynitriles of uloses such as **4**. Since our preliminary study indicates that this method is also applicable to the corresponding uridine, cytidine and adenosine derivatives, we believe that the present approach has a considerable scope and should be most valuable in the search for new anti-HIV agents.

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