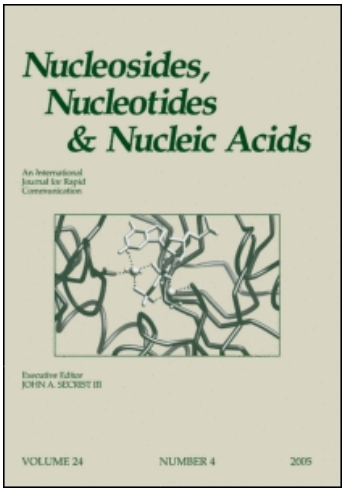

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New Strategies in the Synthesis of 3'-Azido-2',3'-dideoxy-nucleosides with Furanose Configuration

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NEW STRATEGIES IN THE SYNTHESIS OF 3'-AZIDO-2',3'-DIDEOXY-NUCLEOSIDES WITH FURANOSE CONFIGURATION

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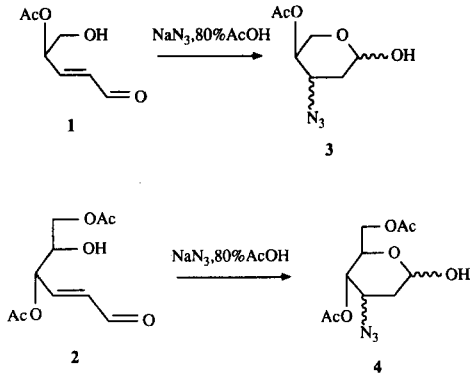
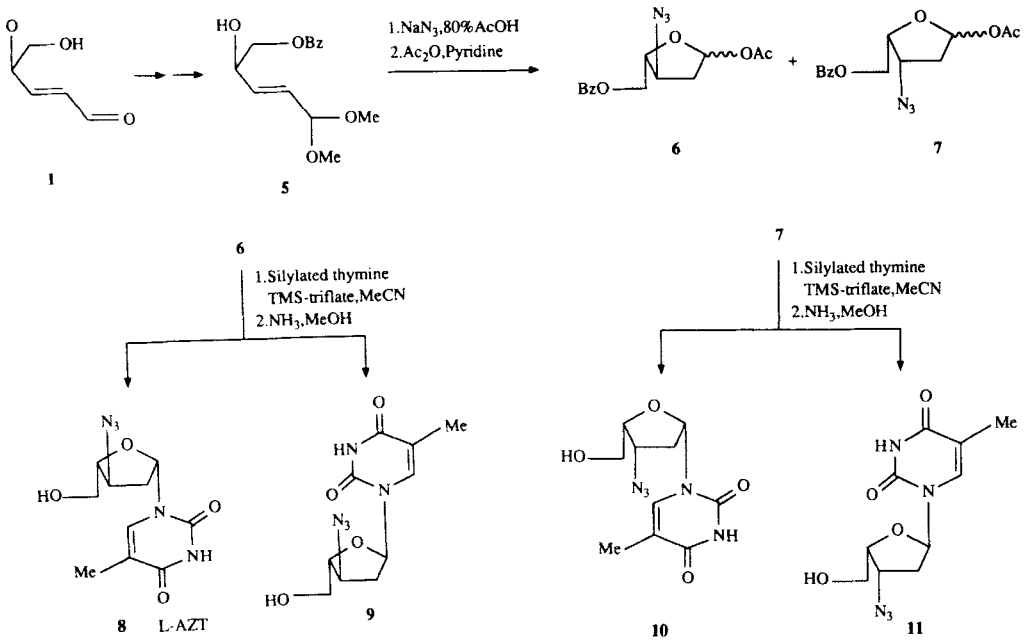
For the synthesis of 3'-substituted 2',3'-dideoxynucleosides we have selected a convergent strategy in which a protected furanose derivative is coupled with a silylated base. This method seems to be the best for synthesizing a large number of nucleosides for the purpose of biological testing.

By Michael type addition of phthalimide to α,β-unsaturated aldehydes and subsequent nucleoside coupling we have prepared 3'-amino-2',3'-dideoxynucleosides[1-3], and we intended to prepare 3'-azido-2',3'-dideoxynucleosides by the same route. Thus, 4-*O*-acetyl-2,3-dideoxy-*aldehydo*-L-*glycero*-*trans*-pent-2-enose **1** and 4,6-di-*O*-acetyl-2,3-dideoxy-*aldehydo*-D-*erythro*-*trans*-hex-2-enose **2** were prepared from 3,4-di-*O*-acetyl-L-arabinal and 3,4,6-tri-*O*-acetyl-D-glucal, respectively, according to standard procedures[4]. Unfortunately, Michael type addition of hydrazoic acid to **1** and **2** gave the undesired 3-azido-2,3-dideoxy-pyranoses **3** and **4** because of lack of acetyl shift from 4–O to 5–O under these acidic conditions.



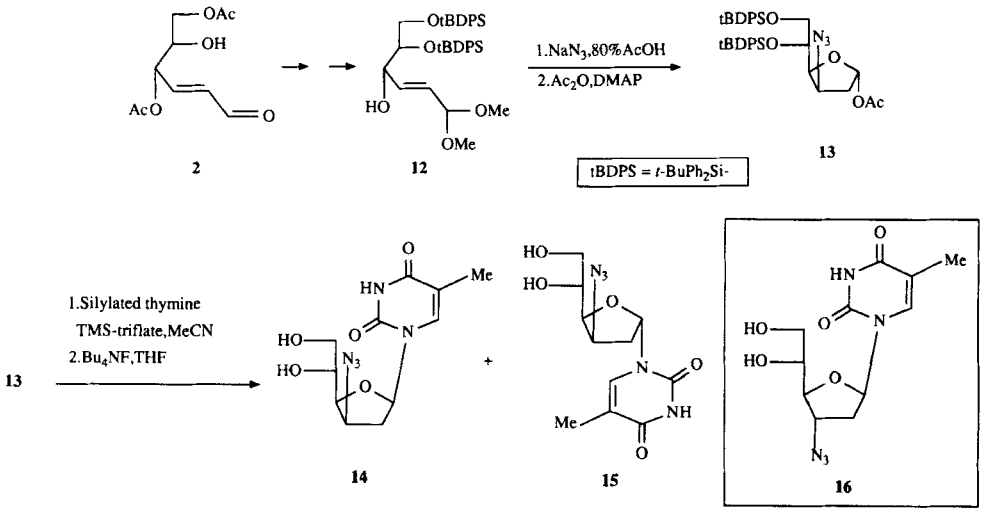
Scheme 1



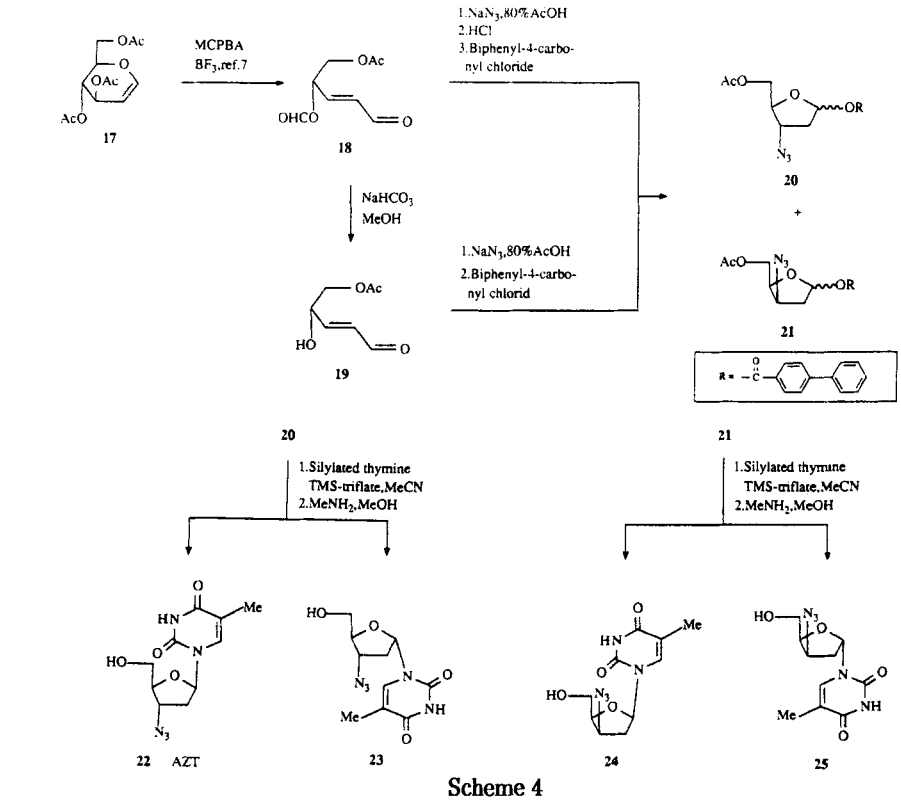
Scheme 2

As the critical problem in the addition of hydrazoic acid to α,β-unsaturated aldehydes is to get an unprotected C–4 hydroxy group, which selectively can react with the aldehyde functionality, we acetalated the α,β-unsaturated aldehyde **1** as the first step in the synthesis of L–AZT **8**. Subsequent deacetylation and selective benzoylation of the primary hydroxy group gave compound **5**. Michael type addition of hydrazoic acid to **5** afforded, after acetylation and separation, anomeric mixtures of 1-*O*-acetyl-5-*O*-benzoyl-3-azido-2,3-dideoxy-L-*erythro*-pentofuranose **6** and 1-*O*-acetyl-5-*O*-benzoyl-3-azido-2,3-dideoxy-L-*threo*-pentofuranose **7**. After coupling of **6** and **7** with silylated thymine using TMS-triflate as the Lewis acid we obtained 1-(3-azido-2,3-dideoxy-L-pentofuranosyl)thymine in all 4 possible configurations **8**–**11**. In experiments testing against AIDS only L–AZT **8** showed anti-HIV activity at 100 μM as virus activity was reduced to 30% of control. The anti-HIV activity of L–AZT is thus approximately 10,000 times lower than that reported for AZT[5,6], and one should notice that it could come from a small amount of D-sugar present in L-arabinose used as starting material or from racemization during the synthesis of L–AZT. Because of the low activity against HIV we conclude that the present synthesis of L–AZT is without any appreciable racemization and that the optical purity of this product is close to 99.99%.

We considered the hexofuranose analogue of AZT **16** as another very interesting molecule. We therefore prepared α,β-unsaturated acetal **12** from α,β-unsaturated aldehyde **2** by acetalation, protection of the C–5 hydroxyl group with *tert*-butyldiphenylsilyl, deacetylation and finally protection of the primary hydroxyl group with *tert*-butyldiphenylsilyl. By Michael type addition of hydrazoic acid to **12** we were only able to isolate the *arabino*



Scheme 3



Scheme 4

isomer **13**. This makes the synthesis of **16** impossible by the present route, and we obtained the β- and α-anomers of 1-(3-azido-2,3-dideoxy-D-*arabino*-hexofuranosyl)thymine **14** and **15** after coupling between the hexofuranose **13** and silylated thymine.

Lichtenthaler *et al.*[7] have recently reported the synthesis of 5-*O*-acetyl-4-*O*-formyl-*aldehydo*-D-*glycero*-*trans*-pent-2-enose **18** in one step from 3,4,6-tri-*O*-acetyl-D-glucal **17** (Scheme 4). Michael type addition of hydrazoic acid to **18** followed by deformylation by adding hydrochloric acid to the reaction mixture gave, after acylation and separation, anomeric mixtures of 5-*O*-acetyl-3-azido-1-*O*-(biphenyl-4-carbonyl)-2,3-dideoxy-D-*erythro*-pentofuranose **20** and the corresponding *threo*-isomer **21**. The present synthesis of **20** and **21** in only 3 steps from commercially available 3,4,6-tri-*O*-acetyl-D-glucal is the shortest route to a protected 3-azido-2,3-dideoxypentofuranose described so far, and it opens up for the synthesis of new AZT analogues by coupling with different nucleobases. We synthesized AZT **22** and its 3 possible D-isomers **23–25** to demonstrate the ability of **20** and **21** to act as synthons for nucleosides. Besides, we wanted to synthesize 1-(3-azido-2,3-dideoxy-α-D-*threo*-pentofuranosyl)thymine **25**, which was the only isomer of 1-(3-azido-2,3-dideoxy-D-pentofuranosyl)thymine never synthesized before.

So far, only 3 of the 8 possible isomers of 1-(3-azido-2,3-dideoxypentofuranosyl)-thymine were known, but after the synthetic work described here all 8 are known.

In our laboratories we have prepared 2',3'-dideoxynucleosides with other 3'-substituents introduced by Michael type addition reactions to α,β-unsaturated aldehydes. This includes 2',3'-dideoxy-3'-piperidino, -3'-pyrrolidino and -3'-(1,2,4-triazol-1-yl) nucleosides, and biological investigation and synthesis of other 3'-substituted 2',3'-dideoxynucleosides are in progress.

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