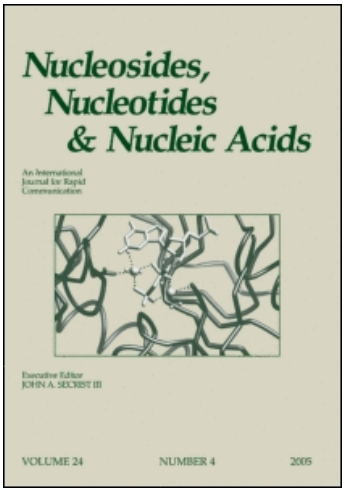

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Facile Synthesis of 3'-C-Branched 1,5-Anhydrohexitol Nucleosides

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FACILE SYNTHESIS OF 3'-C-BRANCHED 1,5-ANHYDROHEXITOL NUCLEOSIDES

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ABSTRACT: The 3'-β-*C*-branched anhydrohexitol nucleosides have been conveniently synthesised starting from commercially available D-ribose following the reaction sequence: (i) conversion of protected pentofuranose sugar to the corresponding hexopyranosyl nitrosugar (ii) addition of the conjugate base of nitrosugar to formaldehyde to obtain *C*-branched nitro sugar (iii) removal of nitro group by n-tributyltin hydride treatment and (iv) Mitsunobu type alkylation to build up the nucleobase.

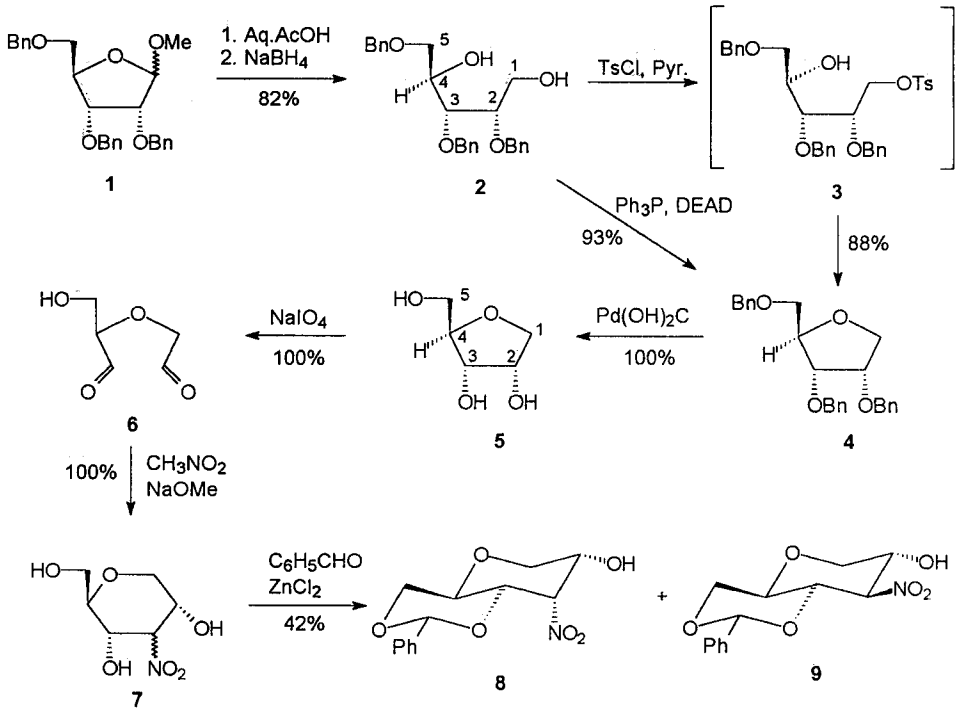
Antiviral activity has been discovered in the past in most series of sugar-modified nucleoside analogues. A lesser developed field is that of nucleosides with a six-membered carbohydrate moiety. Within the limited research efforts on hexopyranosyl nucleosides, a new class of nucleosides[1] with potent inhibitory activity against herpes simplex viruses has been discovered. Recently, we have also shown that even the α-analouge of the corresponding cytosine derivative selectively inhibit the growth of HSV.[2] To further explore the structure-activity relationship of this series of new nucleoside analogues and to analyze the stereochemical and conformational factors which drive the molecule to the antiherpes activity, we synthesized for the first time branched chain anhydrohexitol nucleosides. We devised a synthetic scheme starting from commercially available D-ribose and transformed it first to hexopyranosyl nitro sugar. In the second step, we exploit the unique feature of a nitro group[3] for the *C-C* bond formation at its' α-carbon. Once the *C*-branched hexopyranosyl nitrosugar has been formed, the nitro group can easily be removed by n-tributyltin hydride[4] treatment and it might serve as a common starting material for the synthesis of various modified anhydrohexitol nucleosides. Herein, we

report a facile synthesis of previously unknown 3'-*C*-branched anhydrohexitol nucleosides (Scheme 1, 2 and 3) as potential antiviral agents.

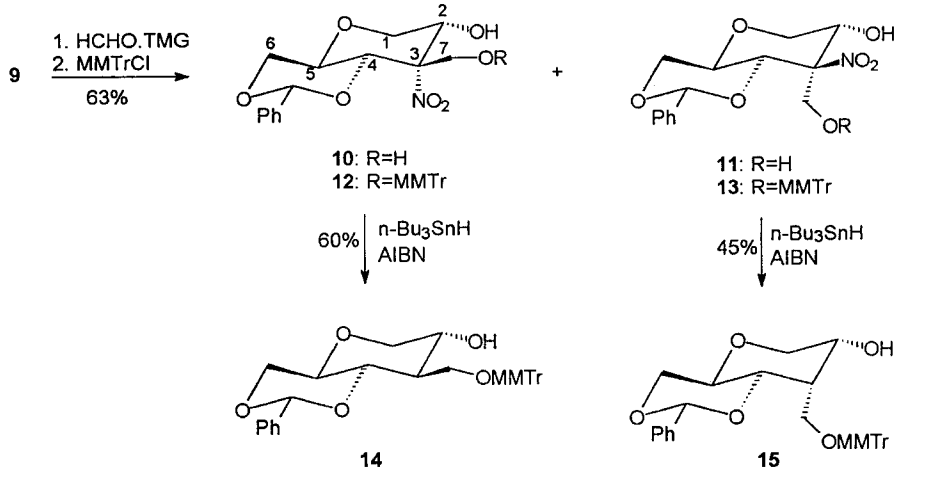
RESULTS AND DISCUSSION

Recently[5], we synthesised 2-deoxyanalouge of **1** starting from 2-deoxy-D-ribose. In a similar manner **1** was synthesised from commercially available D-ribose in 90% yield (from ribose). Compound **1** was treated with 80% acetic acid in water at 90 °C for 9 h. After usual work up the crude reaction mixture was treated with $NaBH_4$ in methanol at 0 °C for 30 min to give **2** in 82% yield (two steps). Treatment of **2** with p-toluenesulfonyl chloride in pyridine at room temperature gave **4** (88%) without isolation of intermediate **3**. In an alternative effort **2** was treated with Ph_3P and diethylazodicarboxylate (DEAD)[6] in dry dioxane at room temperature to give **4** in 93% isolated yield. The reaction was very smooth and isolation of the desired product was extremely easy. On large scale synthesis, however, we prefer to use the tosylation method as the outcome of the Mitsunobu-type condensation is very sensible to reaction circumstances. For further functionalisation the benzyl protecting groups of **4** were removed by catalytic hydrogenation to give **5** in 100% yield.

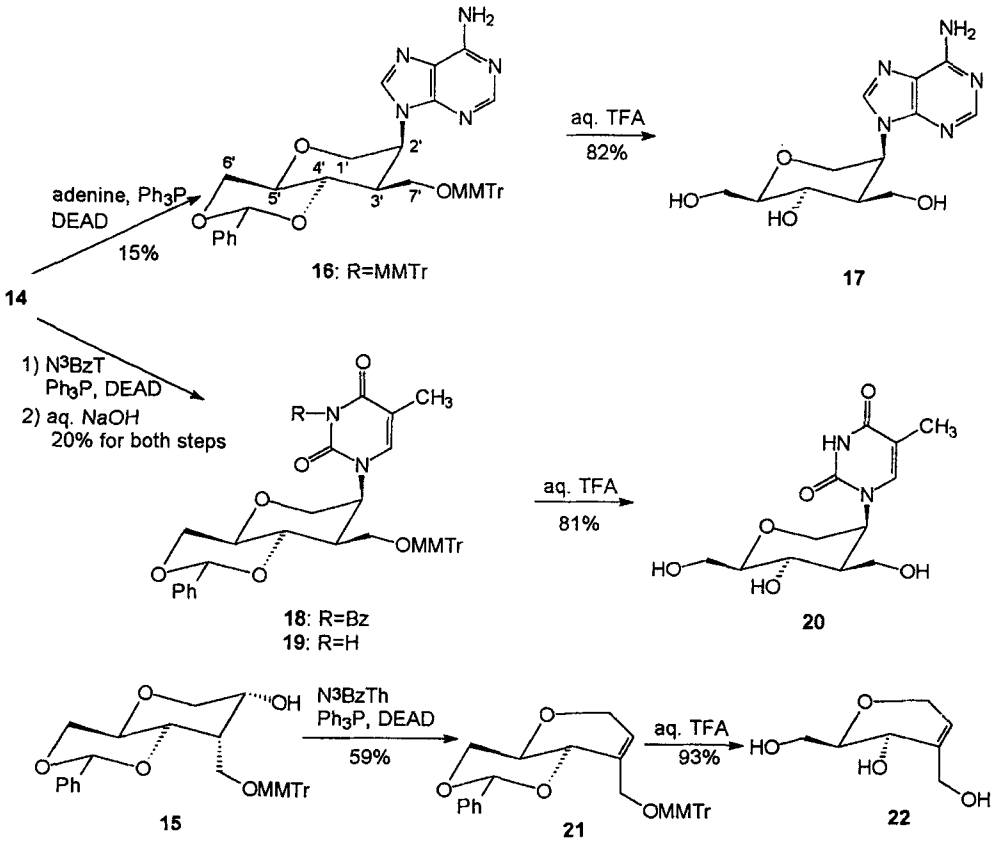
In order to obtain hexopyranosyl sugar, insertion of a methylene unit between C2 and C3 was necessary. Thus, **5** was treated with $NaIO_4$ in methanol and water at 0 °C to give intermediate **6** which, after usual work up, was treated with conjugate base of nitromethane in methanol to afford **7**. After standard work up **7** was treated with benzaldehyde and $ZnCl_2$[8] at room temperature to give **8** (8%) and **9** (34%) in a combined yield of 42%. Compound **8** can easily be isomerised to give **9**. Thus treatment of **8** with Et_3N in methanol at reflux temperature gave **9** (67%) and **8** (20%) after chromatographic *separation*. Treatment of **9** with aqueous formaldehyde in acetonitrile in the presence of catalytic amount of *N,N*-tetramethylguanidine (TMG)[3a,b] for 30 min gave a mixture of *C*-branched sugar **10** and **11** in 63% combined yield. Compounds **10** and **11** were not separated but treated with monomethoxytrityl chloride in pyridine at room temperature to give **12** (33%) and **13** (47%). The substitution of nitro group in branched chain nucleosides by hydrogen using n-tributyltin hydride[9] was described before in nucleoside chemistry[4a,b]. Thus, treatment of **12** with n-tributyltin hydride in the presence of catalytic



Scheme 1



Scheme 2



Scheme 3

amount of AIBN in toluene at 110 °C for 90 min gave **14** in 60% isolated yield. Under identical reaction condition **13** afforded **15** in 45% yield. The denitration of **12** or **13** theoretically should yield two products (*i.e* **14** and **15**). The generated C3 radical of **12** or **13** can abstract a hydrogen atom from tributyltin hydride either at α- or β-face of the sugar moiety. In both cases, only the major isomer was isolated. The other isomer could not be obtained in pure form due to the formation of some by-products.

Normally, denitration of tertiary nitro group by n-tributyltin hydride treatment works well and gives high yields. Often, the secondary nitro group also gives denitrated products in high yield. But it has been found[4a] that when an alkoxy group is attached to the β-position of a secondary nitro group the denitration become more difficult and lower

yields are obtained. In our case despite the fact that **12** and **13** has a tertiary nitro group, the yield of **14** and **15** is moderate due to the presence of a hydroxy group at the β-position of the nitro group. The effect of the presence of an alkoxy or hydroxy group at the β-position of a nitro group to give the corresponding denitrated product upon n-tributyltin hydride treatment need further investigation. Compound **14** and **15** can be used as a starting material for further modifications. Treatment of **14** with Ph_3P, adenine and DEAD in dry dioxane gave **16** in 15% yield. The benzylidene and MMTr protecting groups in **16** were removed by treatment with 80% aqueous CF_3COOH at room temperature to give **17** in 82% isolated yield. Compound **14** was treated with Ph_3P, N^3-benzoylthymine and DEAD in dry dioxane to give **18** which was directly treated with aqueous NaOH (N) in dioxane at room temperature to give **19** in 20% yield (two steps). The coupling yield of both adenine and thymine derivatines (**16** and **18**) is not optimised. Treatment of **19** with aqueous CF_3COOH at room temperature gave **20** in 81% yield. However, treatment of **15** under identical reaction condition as described for the synthesis of **18** forms **14**, **19** gave **21** in 59% isolated yield. Finally, the benzylidene and MMTr protecting groups in **21** were removed by treatment with aqueous CF_3COOH at room temperature to give **22** (93%).

References

1. (a) Verheggen, I.; Van Aerschot, A.; Toppet, S.; Snoeck, R.; Janssen, G.; Balzarini, J.; De Clercq, E.; Herdewijn, P. *J. Med. Chem.* **1993**, *36*, 2033-2040. (b) Verheggen, I.; Van Aerschot, A.; Van Meervelt, L.; Rozenski, J.; Wiebe, L.; Snoeck, R.; Andrei, G.; Balzarini, J.; Claes, P.; De Clercq, E.; Herdewijn, P. *J. Med. Chem.* **1995**, *38*, 826-835. (c) Tino, J. A.; Bisachi, G. S.; Ahmad, S. U.S. patents, 5,314,893 and 5,414,000.
2. Hossain, N.; Rozenski, J.; De Clercq, E.; Herdewijn, P. *J. Org. Chem.* **1997**, *62*, 2442-2447.
3. (a) Hossain, N.; Garg, N.; Chattopadhyaya, J. *Tetrahedron* **1993**, *49*, 100061-10068. (b) Garg, N.; Hossain, N.; Chattopadhyaya, J. *Tetrahedron* **1994**, *50*, 5273-5278.(c) Garg, N.; Plavec, J.; Chattopadhyaya, J. *Tetrahedron* **1993**, *49*, 5189-5202.

4. (a) Hossain, N.; Papchikhin, A.; Garg, N.; Fedorov, I.; Chattopadhyaya, J. *Nucleosides & Nucleotides* **1993**, *12*, 499-528. (b) Hossain, N.; Plavec, J.; Thibaudeau, C.; Chattopadhyaya, J. *Tetrahedron* **1993**, *49*, 9079-9088. (c) Ono, N.; Kamimura, A.; Kaji, A. *Tetrahedron Lett.* **1984**, *25*, 5319-5322.
5. (a) Hossain, N.; Blaton, N.; Peeters, O.; Rozenski, J.; Herdewijn, P. A. *Tetrahedron* **1996**, *52*, 5563-5578. (b) Hossain, N.; Rozenski, J.; De Clercq, E.; Herdewijn, P. *Tetrahedron* **1996**, *52*, 13655-13670.
6. Mitsunobu, O. *Synthesis* **1981**, 1-28.
7. Bear, H. H.; Fischer, H. O. *J. Am. Chem. Soc.* **1959**, *81*, 5184-5189.
8. Richmeyer, N. *In Methods in Carbohydrate Chemistry*, Whistler, R. L.; BeMiller, S. N. Eds.; Academic Press: New York & London, **1972**, Vol. 1, pp 108.
9. Ono. N.; Miyake, H.; Tamura, R.; Kaji, A. *Tetrahedron Lett.* **1981**, *22*, 1705-1708.