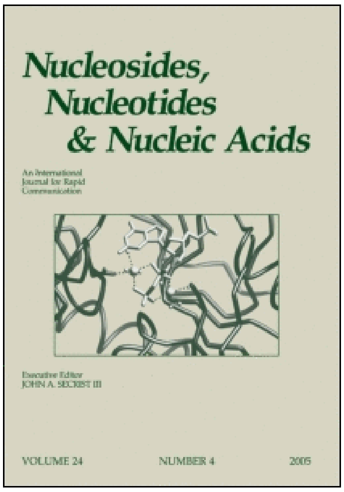

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Synthesis of 1,5-Anhydro-D-Mannitol Nucleosides with a Purine Base Moeety

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SYNTHESIS OF 1,5-ANHYDRO-D-MANNITOL NUCLEOSIDES WITH A PURINE BASE MOIETY

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ABSTRACT: D-Mannitol nucleosides with a purine base moiety have been conveniently synthesized strating from 1,5-anhydro-4,6-O-benzylidene-D-glucitol. The 3-OH function of 1,5-anhydro-4,6-O-benzylidene-D-glucitol was selectively protected with *t*-butyldimethylsilyl group and subsequently converted to the corresponding O-triflate derivative for the introduction of the nucleobase moietes. These nucleoside derivatives were transformed to 1,5-Anhydro-6-O-MMTr-2-(N^6-benzoyladenin-9-yl)-2-deoxy-3-O-TBDMS-D-mannitol and 1,5-Anhydro-6-O-MMTr-2-(N^2-isobutyryl-guanin-9-yl)-2-deoxy-3-O-TBDMS-D-mannitol, useful as the building blocks for oligonucleotide synthesis. Also, the synthesis of the corresponding fully deprotected anhydrohexitol nucleosides were achieved for evaluation of antiviral activity test.

Introduction

The research on modified nucleosides with a six-membered carbohydrate ring has been increased during last years. The interest in six-membered sugar nucleosides is due to the discovery of a new class of biologically active nucleosides.[1] When these nucleosides were incorporated into oligonucleotides[2], the stability of the duplex was increased. Recently, we have shown that even the α-analogue of the corresponding cytosine derivative[3] selectively inhibits the growth of herpes viruses. The pyrimidine series of D-mannitol[4] nucleosides can be synthesized starting from corresponding "ribo"-derivative[4], exploiting neighbouring group (O^2) participation. This unique neighbouring group (O^2) participation reaction can not be exploited for the synthesis of

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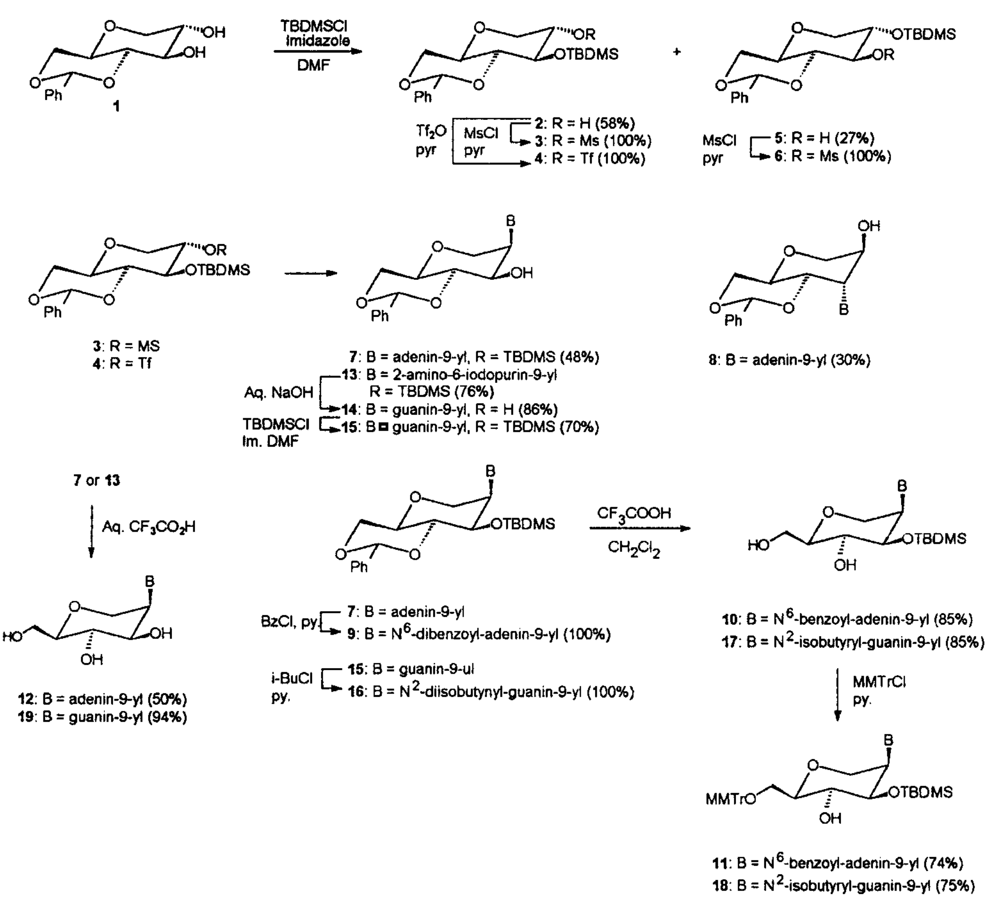
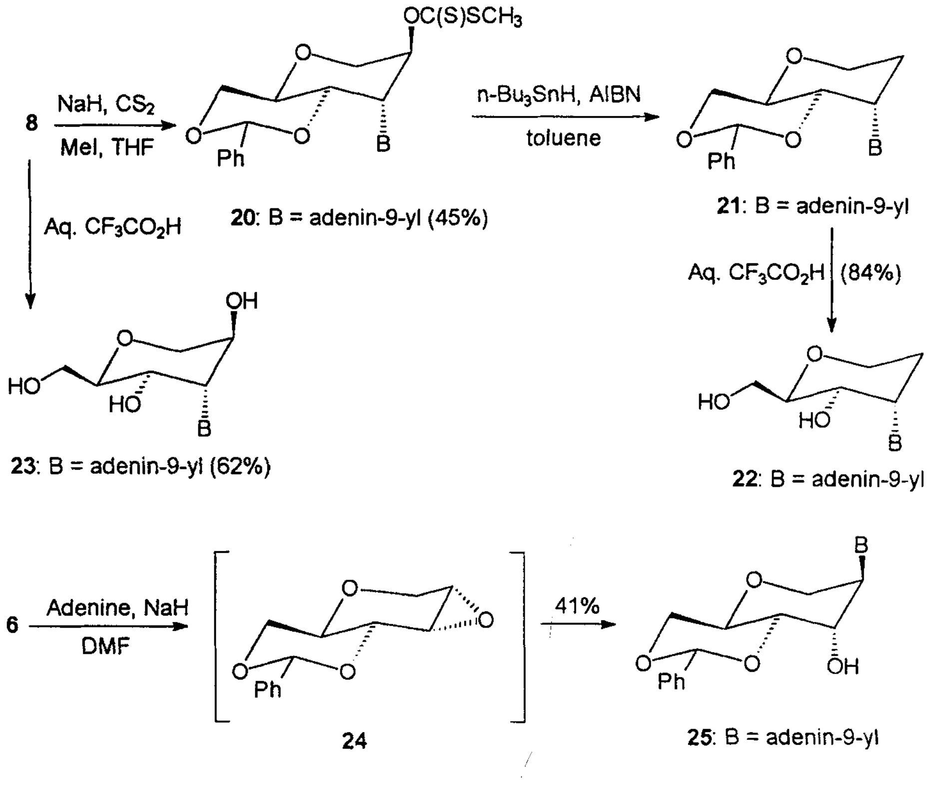


Scheme 1

purine derivatives. Herein, we report a facile synthesis of previously unknown arabinohexitol nucleosides as potential antiviral agents and building blocks for the synthesis of oligonucleotides.

The general starting material, 1,5-anhydro-4,6-O-benzylidene-D-glucitol (**1**), was prepared from commercially available bromo acetyl-α-D-glucose, in three steps. Compound **1** was treated with *t*-butyldimethylsilyl chloride (TBDMSCl) in pyridine at room temperature to give **2** (31%) and **5** (40%). When **1** was treated with TBDMSCl in the presence of imidazole in DMF[5] at room temperature, **2** (58%) was formed as a



Scheme 2

major product along with **5** (27%). Compound **2** was treated with mesyl chloride in pyridine to give **3** which was treated with sodium salt of adenine[6] in DMF at 110 °C to give **7** (20%) and **8** (30%). Compound, **2** was converted to the corresponding triflate[7] derivative **4** upon treatment with trifluoromethanesulfonic anhydride in the presence of pyridine in CH_2Cl_2 at -5 °C. After standard work up, **4** was directly treated with tetrabutylammonium salt of adenine in CH_2Cl_2 to give **7** in 48% yield. Compound **7** was treated with benzoyl chloride in pyridine at room temperature to afford **9** which, after work up, was treated with CF_3COOH in dry CH_2Cl_2 at room temperature to give **10** (85%). Compound **10** was treated with MMTrCl in pyridine to give **11** (74%).

Treatment of **7** with aq. CF_3COOH gives **12** (50%) after crystallisation. Compound **4** was treated with tetrabutylammonium salt of 6-iodo-2-aminopurine in CH_2Cl_2 to give **13** (70%). Compound **13** was treated with aq. NaOH in dioxane at 55 °C to give **14** (96%). In this alkaline reaction condition 3'-TBDMS group was also deblocked. Thus, **14** was reprotected using TBDMSCl in the presence of imidazole in DMF to give **15**. Treatment of **15** with isobutyryl chloride in pyridine gave **16** which was directly treated with CF_3COOH in CH_2Cl_2 to give **17** (80%). Finally, **17** was treated with MMTrCl in pyridine to give **18** (75%). Compound **13** was treated with aq. CF_3COOH[8] to give **19** (94%). In order to determine unambiguously the substitution sites, **8** was converted to **22** and **23**, and **5** to **25**. Compound **8** was treated with CS_2 and MeI in the presence of NaH in THF to give intermediate **20** which was converted to **21** (45%) upon treatment with n-Bu_3SnH in the presence of AIBN in toluene. Finally, **21** was treated with aq. CF_3COOH at room temperature to give **22** (84%). The benzylidene protecting group in **8** was removed upon treatment with aq. CF_3COOH to give **23** (62%). Compound **5** was converted to the corresponding mesyl derivative **6** (100%) which was treated with adenine in the presence of NaH in DMF to give **25** (41%) via the epoxide **24**.

In conclusion, we developed a new synthetic scheme leading to D-anhydromannitol nucleosides with a purine base moiety.

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