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Synthesis of *N*-homobicyclic dideoxynucleoside analogues

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ABSTRACT

Syntheses of six *N*-homobicyclic dideoxynucleoside analogues are described. The reaction of mannose diacetonide with trimethylsulfoxonium iodide gave a mixture of diastereomeric hydroxymethyl mannose diacetonides in a ratio of 2:5, which was separated by fractional crystallization. The two stereoisomers were converted to bicyclic furanolactols each of which was coupled with three nucleoside bases. Further debenzylations gave the six target *N*-homobicyclic dideoxynucleosides.

1. Introduction

The synthesis of modified nucleosides has been of interest for over four decades. The finding that 3′-azido-3′-deoxy thymidine (AZT) is a therapeutic agent for the treatment of AIDS[1] triggered explosive new development in this area. Nucleoside modification has been reviewed extensively[2–10] and specialized reviews published on the synthesis of sugar-modified nucleosides such as ketonucleosides,[11] 3-branched nucleoside analogues,[12] AIDS-driven nucleosides chemistry,[13] bicyclic heterocyclic nucleosides,[14] *C*-nucleosides[10,15–19] *C*-branched nucleoside analogues,[20] carbocyclic nuleosides,[21–24] nucleosides with six-membered carbohydrate moieties,[25–27] nucleoside antibiotics,[28,29] azanucleosides,[30] L-nucleosides,[31,32] 2′,3′-dideoxynucleosides,[33,34] 4′,5′-unsaturated nucleosides,[35] *C*-alkenylated pyrimidine nucleosides,[36] anomeric spironucleosides,[37] and isonucleosides.[38] Most of the nucleosides are reverse transcriptase inhibitors like Zidovudine, Zalcitabine, and Stavudine; a few non-nucleosides such as Nevirapine, Delavirdine, and Efavirenzes also inhibit HIV reverse transcriptase. Many 2,3-dideoxyribonucleosides possess significant antiviral activity against HIV and other viruses. It has been suggested that proper puckering of the five-membered monocyclic carbohydrate moiety is required for antiviral activity.[39] However, bicyclic nucleosides from a conformationally different class, such as fused ring cytidine analogues[40–42] and oxytanylthymidine,[43] were recently found to have moderate to significant activity against HIV through the inhibition of HIV reverse transcriptase. These findings led to an investigation of the conformational requirements for dideoxynucleosides as inhibitors of HIV-RT[44] and further studies on bicyclic nucleosides.[45–49] Certain members of the class possess interesting cellular activities, for example, naturally occurring bicyclic nucleosides called griseolic acids, isolated from the cultured broth of *Streptomyces griseoaurantiacus*, show significant inhibitory activity against 3′,5′-cyclic nucleotide phosphodiesterases.[50,51]

Synthetic guanosine analogues of griseolic acids are even more potent against these enzymes[51]; other derivatives are potent antihypertensive agents.[52] Recently, bicyclic nucleosides have also received attention in studies of the stabilities of antisense oligonucleotides.[53–57] Bicyclic nucleosides exhibit increased affinity for complementary RNA or DNA and are also important in the preparation of triple-helix-forming oligonucleotides.[53,56]

Several authors have used similar nucleosides to prepare oligonucleotides.[58–60] As a continuation of our efforts in the discovery of antiviral agents, we chose the synthesis of the bicyclic nucleosides **1**–**6** (Fig. 1).

2. Results and discussion

The synthesis started from mannose diacetonide **7**,[61] readily obtainable from D-mannose in 85% yield (Scheme 1). The reaction of mannose diacetonide **7** with trimethylsulfoxonium iodide and potassium *tert*-butoxide at room temperature for 3 h[62] gave the diastereomeric mixture of key intermediates **8** and **9** in the ratio of 2:5 (by NMR), as a viscous oil in 79% yield.[63] Among the bases (NaH, *n*-BuLi, LiHMDS, NaHMDS, LDA, *t*-BuOK) tried, *t*-BuOK gave the best result for **8**, **9** in terms of yield and separation of the diastereomeric mixture. Here, the lactol moiety reacted with the in situ generated dimethyloxosulfonium methylide to form an epoxide to give hydroxymethyl mannose diacetonide. Fractional crystallization of this mixture (CH_2Cl_2–hexane 1:4) gave **8**, as a

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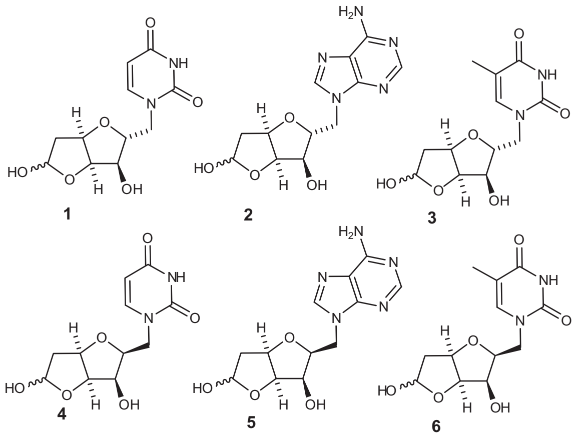
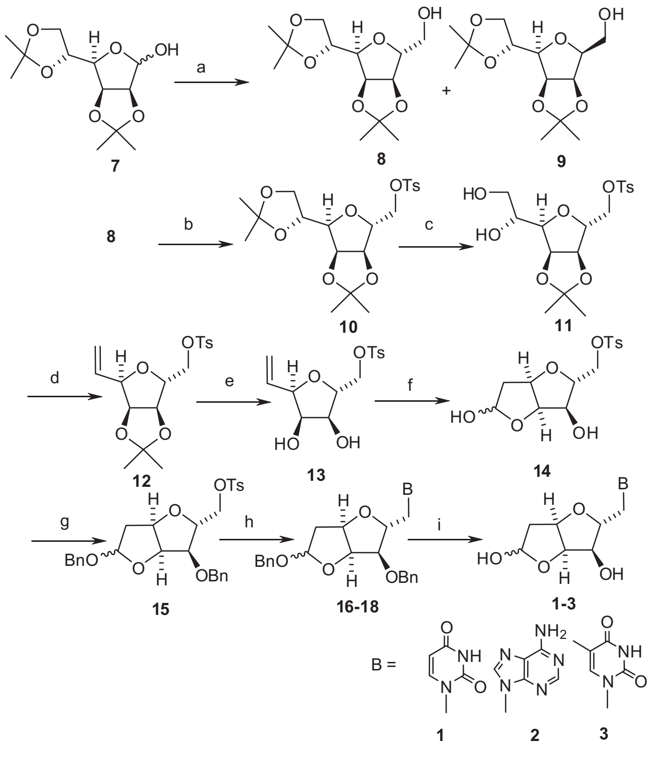
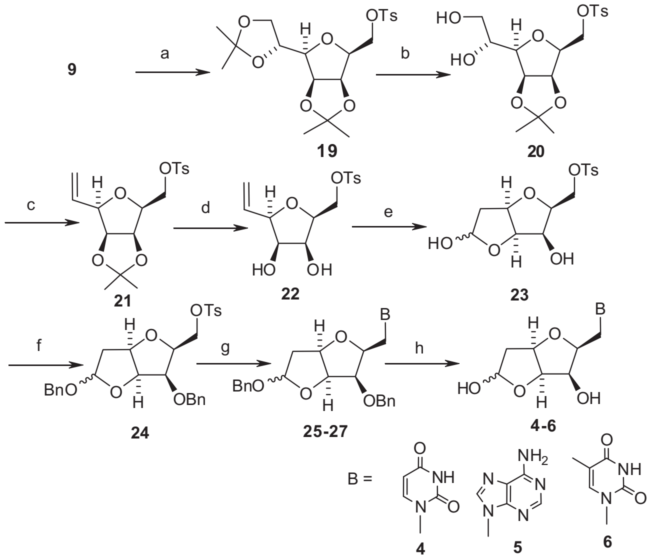


Figure 1. *N*-Homobicyclic dideoxynucleoside analogues.

crystalline compound (30%), mp 83–85 °C and **9** as viscous oil (70%). Tosylation of **8** with *p*-toluenesulfonyl chloride in pyridine to give tosylate **10** in 92% yield. Regioselective hydrolysis of isopropylidene of **10** with $BiCl_3$[64,65] in DCM gave diol **11** in 85% yield. Treatment of diol **11** with triphenylphosphine imidazole and iodine in toluene at 80 °C by reductive elimination gave vinyl furan **12** in 87% yield as viscous oil. Removal of isopropylidene group of vinyl furan **12** with 5% aq H_2SO_4 in 1,4-dioxane gave the desired hydroxy vinyl furan **13**. The crucial step of converting **13** to lactol **14** was achieved in 90% yield using $PdCl_2$, CuCl, DMF, H_2O, and O_2 at room temperature for 4 h.[66,67] Treatment of **14** with NaH, BnBr in DMF gave benzyl derivative **15** in 95% yield. Intermediate **15** was used for the synthesis of bicyclic dideoxynucleosides.



Scheme 1. Synthesis of *N*-homobicyclic-dideoxy nucleosides **1**–**3**. Reagents and conditions: (a) TMSOI, KOBu^t, DMSO (b) TsCl, pyridine, DMAP, (c) $BiCl_3$, DCM, (d) TPP, imidazole, I_2, toluene, 80 °C; (e) 5% aq H_2SO_4, 1,4-dioxane; (f) $PdCl_2$, CuCl, O_2, DMF, H_2O, rt; (g) NaH, BnBr, DMF, rt; (h) NaH, DMF, nucleoside base, 90 °C; (i) $Pd(OH)_2$–H_2.



Scheme 2. Synthesis of *N*-homobicyclic-dideoxy nucleosides **4**–**6**. Reagents and conditions: (a) TsCl, pyridine, DMAP, (b) $BiCl_3$, DCM; (c) TPP, imidazole, I_2, toluene, 80 °C; (d) 5% aq H_2SO_4, 1,4-dioxane; (e) $PdCl_2$, CuCl, O_2, DMF, H_2O; (f) NaH, BnBr, DMF; (g) NaH, DMF, nucleoside base, 90 °C; (h) $Pd(OH)_2$–H_2.

Thus uracil on treatment with NaH in DMF at 90 °C for 15 min followed by addition of tosylate **15** gave *N*-homobicyclic dideoxyuridine nucleoside **16**. Further deprotection of benzyl groups with 20% $Pd(OH)_2$ in methanol under hydrogen atmosphere gave the corresponding *N*-homobicyclic dideoxyuridine nucleoside **1**. Using similar reactions of dibenzyl homobicyclic tosylate **15** with adenine and thymine gave the *N*-homobicyclic dideoxy nucleosides **2** and **3**, respectively. As described in Scheme 2 compound **9** was subjected to similar reactions to obtain *N*-homobicyclo dideoxy nucleosides **4**–**6**.

3. Experimental section

3.1. General methods

Melting points were measured on a Buchi-510 instrument and are uncorrected. Spectra were recorded with the following instruments: IR, Perkin Elmer spectrophotometer; NMR, 200 MHz (Varian) and Unity 300 MHz (Bruker) and mass spectra LC–MS and Micro mass VG 7070H (70 eV). Column chromatography was performed with silica gel (Achme 60–120 mesh or >300 mesh flash chromatography) and TLC with silica gel MERCK GF_{254} (precoated). Visualization of the spots on TLC plates was carried out either in UV light (short wave 250 nm) or by exposing the plates to iodine vapors or spraying with 10% sulfuric acid in CH_3OH and subsequently heating on a hot plate.

3.2. Experimental procedures and spectral data

3.2.1. 2,3;5,6-Di-*O*-isopropylidene–D-mannofuranose (7)

Anhydrous $CuSO_4$ (30 g, 188.6 mmol) was added in one portion to a suspension of D-mannose (20 g, 111.1 mmol) in dry acetone (200 mL); then sulfuric acid (6 drops) was added. The suspension was stirred for 8 h. The solution was filtered under vacuum and then stirred with potassium carbonate (3.4 g) at room temperature until (pH 8). The mixture was filtered through Celite and evaporation of solvent in vacuum gave a white solid, which was dissolved in CH_2Cl_2, and filtered through a bed of silica gel topped with Celite. Evaporation of solvent under reduced pressure gave a white solid. Recrystallisation from diethyl ether–hexane gave **7** as colorless