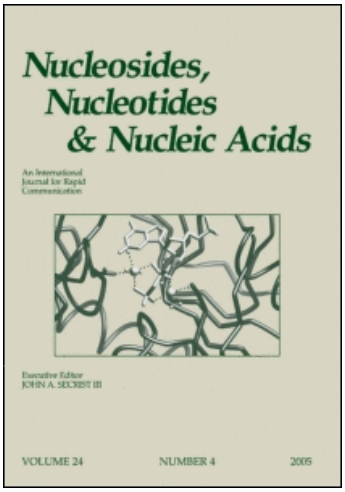

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Novel Bicyclic Nucleoside Analogues Related to Natural Griseolic Acids

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NOVEL BICYCLIC NUCLEOSIDE ANALOGUES RELATED TO NATURAL GRISEOLIC ACIDS

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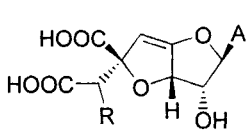
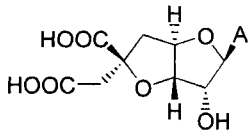
ABSTRACT: Methodologies for the synthesis of novel isomeric nucleosides related to the natural, biologically-active griseolic acids are described. The carbohydrate precursor for the synthesis, 1,4:3,6-dianhydro-D-glucitol, can be prepared easily from D-glucitol.

Naturally occurring hypermodified nucleosides called griseolic acids, **1** and **2**, have been isolated from the cultured broths of *Streptomyces griseoaurantiacus.*[1] They have been shown to have inhibitory activity against cyclic nucleotide phosphodiesterase.[1,2]



R = OH, R = H

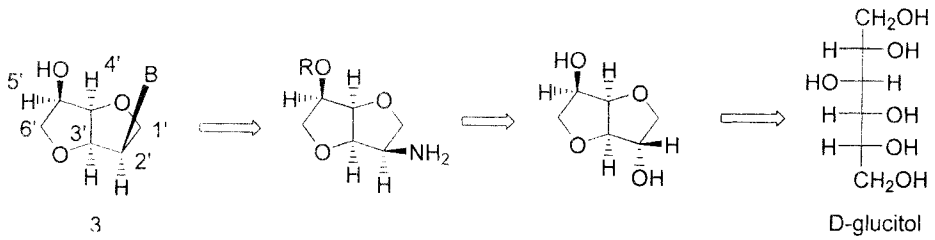
1



2

Our interest in the discovery of unusual nucleoside analogues with the potential for antiviral activity, led to an investigation of the synthesis and antiviral studies of isomeric nucleosides **3** containing the 1,4:3,6-dianhydrohexitol moiety of the natural griseolic acids which is the focus of this report. It should be mentioned that isomeric nucleosides synthesized recently in our laboratory have been found to have antiviral activity.[3-5]

The retrosynthetic plan for these bicyclic isomeric nucleosides is shown in Scheme 1. D-Glucitol is the starting compound and its cyclization would produce the dianhydro intermediate which can be converted stereospecifically to the bicyclic β-amino



3

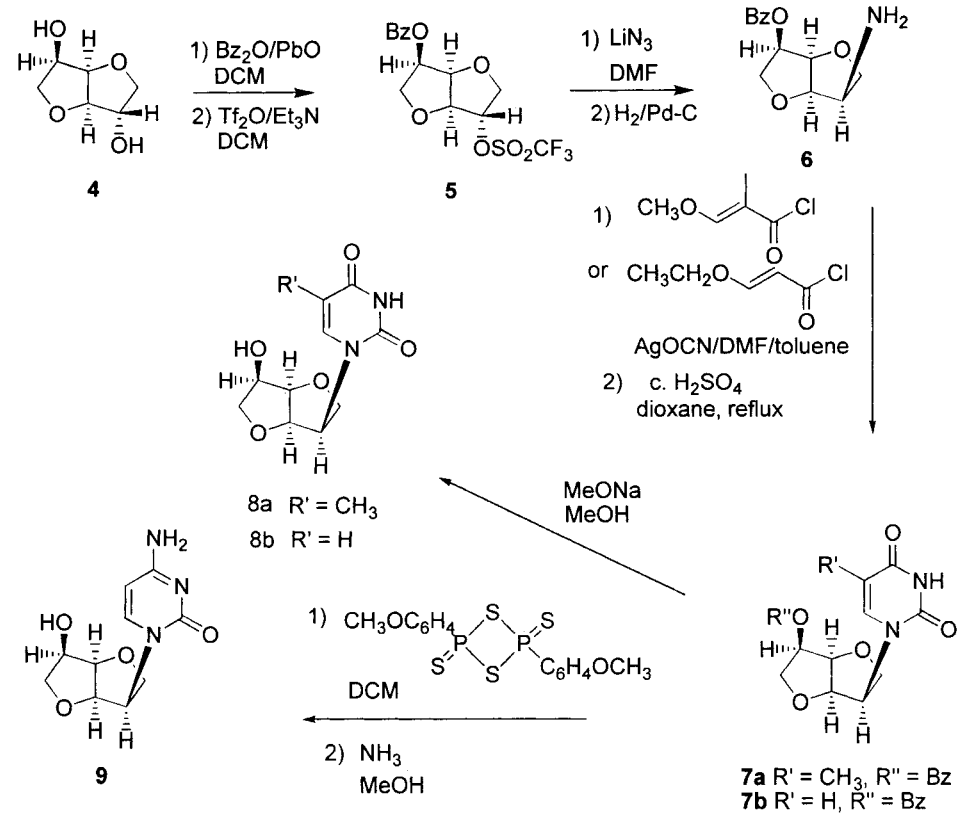
Scheme 1

compound. The nucleobases are constructed on the concave face of the latter intermediate to give the target molecules.

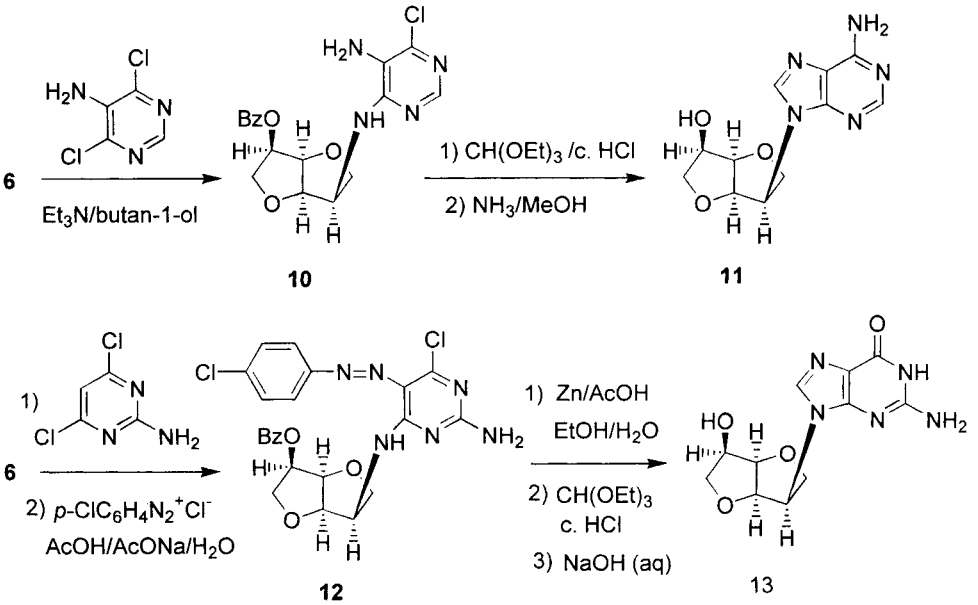
The synthetic details are summarized in Schemes 2 and 3. The precursor **4** was first selectively protected and then converted to its triflate **5** (Scheme 2). Azide displacement of the triflate group was stereospecific and reduction of the resulting azide gave the β-amine **6**. Construction of the pyrimidine bases U and T was carried out by established methods.[6,7] The cytidine analogue **9** was prepared by conversion of **7b** with Lawesson's reagent[8] to its 4-thio derivative and treatment of the latter with methanolic ammonia.

Synthesis of the purine analogues **11** and **13** was also achieved by base construction as summarized in Scheme 3.[9,10]

The structure and stereochemistry of the final products were confirmed by ^{1}H and ^{13}C NMR spectra (including differential NOE spectra and data from decoupling experiments), X-ray crystallography, mass spectrometry, and elemental analysis. In addition to the J values for C-2', C-3', and C-4' protons, differential NOE data also provided support for the stereochemistry of the target compounds. For example, for compound **8b**, NOE values of 6-9% were observed for protons on the *exo* face of the bicyclic system, with an enhancement of 6% between C-6H of the base and the *endo* C-1'H. Further support of the absolute stereochemistry and conformation of the target compounds came from single crystal X-ray data. For example, the ORTEP plot of the bicyclic uridine **8b** showed that the anhydro ring A is in the C-2' envelope conformation (C-2' *exo*) and anhydro ring B is in the C-6' envelope conformation (C-6' *endo*). The concave nature of this carbohydrate



Scheme 2



Scheme 3

moiety is clearly apparent. The base and the C-5' hydroxyl group were found in pseudo-equatorial positions.

Antiviral evaluations of these compounds are being carried out and these results will be reported elsewhere.

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REFERENCES

1. Nakagawa, F.; Okazaki, T.; Naito, A.; Iijima, Y.; Yamazaki, M. *J. Antibiotics* **1985**, *38*, 823-829.
2. Tulshian, D.; Doll, R. J.; Stansberry, M. F. *J. Org. Chem.* **1991**, *56*, 6819-6822.
3. Nair, V.; St. Clair, M.; Reardon, J. E.; Krasny, H. C.; Hazen, R. J.; Paff, M. T.; Boone, L. R.; Tisdale, M.; Najera, I.; Dornsife, R. E.; Everett, D. R.; Borroto-Esoda, K.; Yale, J. L.; Zimmerman, T. P.; Rideout, J. L. *Antimicrob. Agents Chemother.* **1995**, *39*, 1993-1999.
4. Bolon, P. J., Sells, T. , Nuesca, Z. , Purdy, D. F., Nair, V., *Tetrahedron* **1994**, *50*, 7747-7764.
5. Nair, V.; Jahnke, T. S. *Antimicrob. Agents Chemother.* **1995**, *39*, 1017-1029.
6. Shaw, G.; Warrener, R. N. *J. Chem. Soc.* **1958**, 153-156, 157-161.
7. Shealy, Y. F.; O'Dell, C. ; Thorpe, M. *J. Heterocycl. Chem.* **1981**, *18*, 383-389.
8. a. Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061. b. Sharma, R. A.; Bloch, A.; Bobek, M. *J. Heterocyclic Chem.* **1982**, *19*, 1153-1157.
9. a. Kaspersen, F. M.; Pandit U. K. *J. Chem. Soc., Perkin. Trans. 1* **1975**, 1617-1622. b. Shealy, Y. F.; Clayton, J. D. *J. Pharm. Sci.* **1973**, *62*, 1432-1434.