

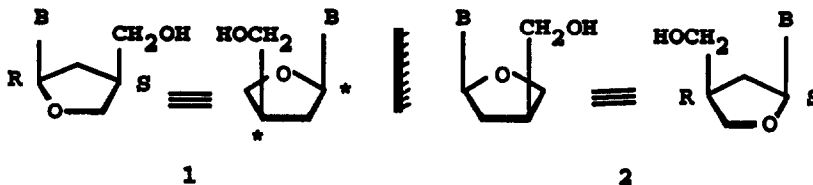
NOVEL ISOMERIC DIDEOXYNUCLEOSIDES OF THE D- AND L-APIOSE FAMILY

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Summary: Short synthetic approaches to optically active, *cis* and *trans* dideoxynucleoside analogs of the D- and L-apiose family have been developed. The chiral precursor for the syntheses was the enzymatically prepared compound, S(-)-2-(2-propenyl)-1,3-propanediol monoacetate (5).

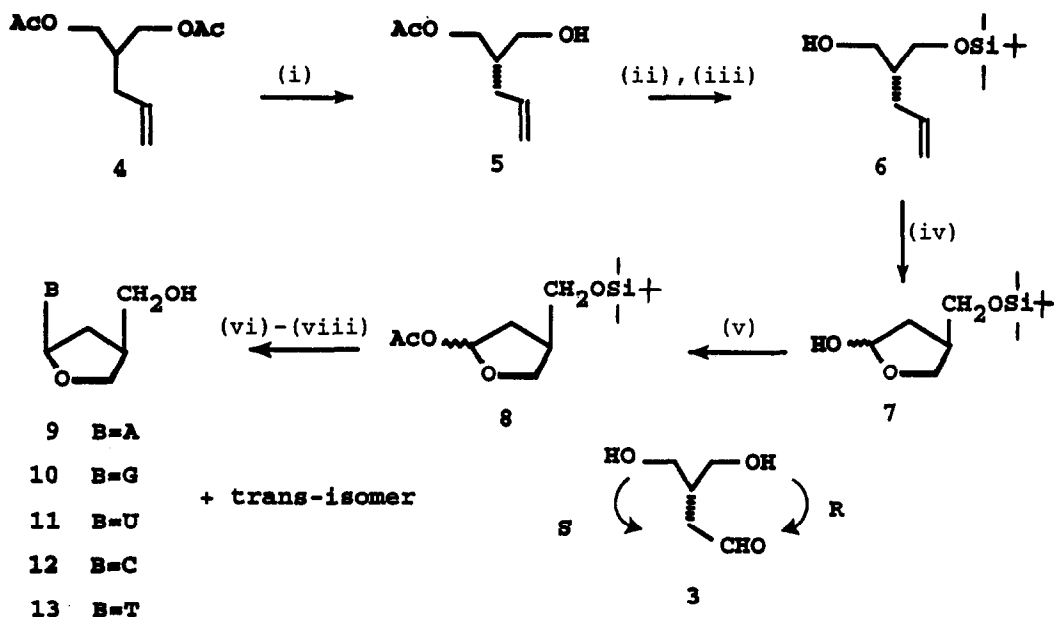
A few dideoxynucleosides, through inhibition of HIV-encoded reverse transcriptase (RT), have proven to be effective pro-drugs for clinical use in the treatment of AIDS.¹ The design and evaluation of additional novel nucleoside-based RT inhibitors are needed in order to develop analogs that exhibit a more favorable toxicity profile and are less susceptible to the development of resistant strains of HIV.² One essential feature in the design of these inhibitors is retention of the 2',3'-dideoxygenation which is necessary for termination of the viral DNA chain elongation. The most common modification of dideoxynucleosides has been strategic substitution on the carbohydrate moiety (i.e. azido and fluoro).^{3,4} A more recent trend in design has been antiviral dideoxynucleosides with no heteroatom or an additional heteroatom within the carbohydrate moiety.⁵⁻¹⁰

An alternative approach involves dideoxygenated nucleosides that contain transposed heteroatoms¹¹⁻¹³ and are regioisomeric with respect to dideoxy analogs of the natural nucleosides. 9-(β-D-Apio-D-furanosyl)adenine, a biologically-active, relatively non-cytotoxic nucleoside¹⁴⁻¹⁷ related to natural D-apiose,¹⁸ is a regioisomer of adenosine through transposition of the C-4' hydroxymethyl to C-3'. We wish to report on the stereoselective synthesis of the complete family of 2',3'-dideoxygenated nucleosides (1 and 2) related to apio nucleosides as potential inhibitors of HIV replication. This study is supported by the observation¹³ that one member of Class 2 has been reported to have anti-HIV activity in MT-4 cells with no apparent toxicity.



The key precursor for the construction of the dideoxyapiose ring was a derivative of the optically pure aldodiol system 3, the cyclization of which in one direction creates the carbon bearing the CH₂OH of R-stereochemistry and in the other direction of S-stereochemistry. This approach allows a shorter synthetic route

than one involving D- or L-apiose and would avoid potential problems such as racemization associated with the deoxygenation of the C-3 tertiary hydroxyl group of apiose. The starting compound for the enantioselective step to the chiral precursor **5**^{19,20} was 2-(2-propenyl)-1,3-propanediol diacetate (**4**), prepared in two steps (reduction followed by acetylation) from diethyl allylmalonate in 80% overall yield (Scheme 1). Stereoselective deacetylation with the lipase from *Candida cylindracea* (Sigma, Type VII) afforded the S-(-)-monoacetate of 2-(2-propenyl)-1,3-propanediol (**5**) ($[\alpha]_D^{20} = -8.0^\circ$, CHCl_3) in a 50% yield (99% ee). Treatment of **5** with *t*-butyldimethylsilyl chloride followed by deesterification gave the R-(+)-**6** ($[\alpha]_D^{20} = +3.7^\circ$, CHCl_3) in 96% overall yield for the two steps. For the key transformation, the formation of the 2,3-dideoxy-D-apiofuranosyl system from **6**, a variety of conditions were examined. The most successful method was the oxidative cleavage of the olefin employing $\text{OsO}_4/\text{NaIO}_4$. Thus, treatment of **6** with OsO_4 and NaIO_4 provided **7** almost quantitatively as an anomeric mixture ($[\alpha]_D^{20} = +24^\circ$, CHCl_3) which, upon acetylation, gave the corresponding 1-O-acetyl-3'-O-(*t*-butyldimethylsilyl)-2,3-dideoxy-D-apiose (**8**) in a 78% yield. Trimethylsilyl triflate promoted condensation²¹



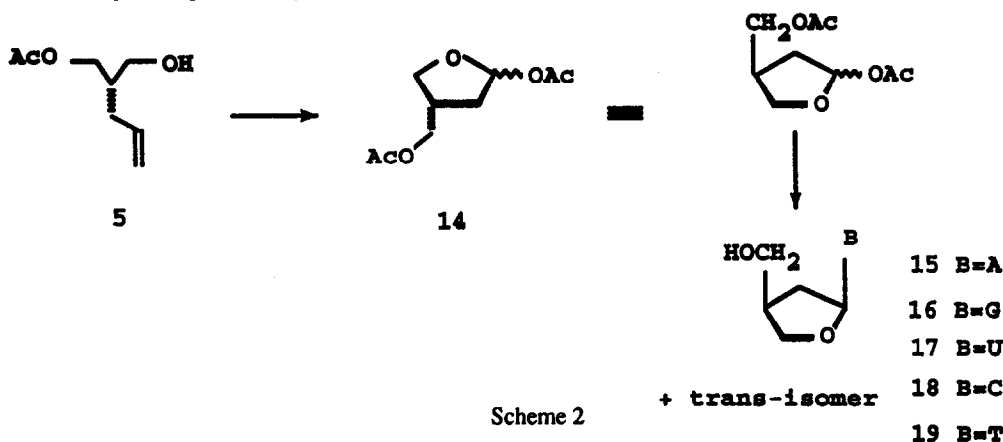
(i) Lipase (0.4 g per mmol **4**), 30% aq. acetone, NaOH (1M, pH 7), 8 h; (ii) TBDMSiCl (1.2 eq), imidazole (1.2 eq), CH_2Cl_2 , 24 h; (iii) NaOMe (1.2 eq), MeOH, 45 min; (iv) OsO_4 (0.05 eq), NaIO_4 (3 eq), $\text{H}_2\text{O}/\text{Et}_2\text{O}$ (50% v/v), 12 h; (v) Ac_2O (1.2 eq), Et_3N (1.4 eq), DMAP (0.1 eq), CH_3CN , 1 h; (vi) purine or pyrimidine base (1.2 eq), bis(trimethylsilyl)acetamide (1.3-2.6 eq), CH_3CN , 82 °C; (vii) TMSOTf (1.1 eq), 0 °C - R.T., 2-5 h; (viii) NH_3/MeOH and/or Et_4NF (2 eq).

Scheme 1

of **8** with silylated N⁶-benzoyladenine, generated *in situ*, gave a 3:2 (α : β) diastereomeric mixture of anomeric adenine isodideoxynucleosides in 43% yield. Separation by preparative layer chromatography and quantitative deprotection of the individual anomers provided 9-(2,3-dideoxy- β -D-apiofuranosyl)adenine (**9**) ($[\alpha]_D = -22.6^\circ$, MeOH) and the corresponding 9-(2,3-dideoxy- α -D-apiofuranosyl)adenine anomer ($[\alpha]_D = +39.8^\circ$, MeOH). Assignments of the anomeric configurations were readily determined through ¹H NMR NOE difference spectroscopy.

Under similar conditions, the persilylated bases of N²-acetyl-O⁶-diphenylcarbamoylguanine, uracil, cytosine, and thymine were coupled with the acetylated dideoxyapiose **8**. Separation of the resulting α and β anomers and deprotection gave the 2',3'-dideoxy- β -D-apiofuranosyl nucleosides **10-13**. In the case of the cytosine and thymine apiosyl nucleosides, the separation is more laborious due to a small difference only in *R_f* values between the anomers.

The nucleosides of the 2,3-dideoxy-L-apiofuranosyl series (Scheme 2) were similarly obtained from the chiral precursor **5**. When **5** was treated with OsO₄/NaIO₄, followed by acetylation, **14** was formed in 63% yield. Glycosylation with the appropriate silylated aglycon, diastereoisomer separation, and deprotection provided the 2',3'-dideoxy- α -L-apiofuranosyl nucleosides **15-19**.



The compounds of these apio dideoxynucleoside families are resistant to enzymatic deamination (e.g. the substrate activity of **9** towards mammalian adenosine deaminase is 0.12% compared to adenosine. Studies of the relative rates of glycosidic bond hydrolysis²² show that these compounds are slightly more stable than 2',3'-dideoxynucleosides (e.g. compound **9** is hydrolyzed at 84% of the rate of 2',3'-dideoxyadenosine at pH 3). Comprehensive antiviral studies are currently in progress and those results will be reported elsewhere.

Acknowledgments. Support of this work by the National Institutes of Health (AI 32851) is gratefully acknowledged. We thank the University of Iowa for a Faculty Scholar Award to V. N.

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