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

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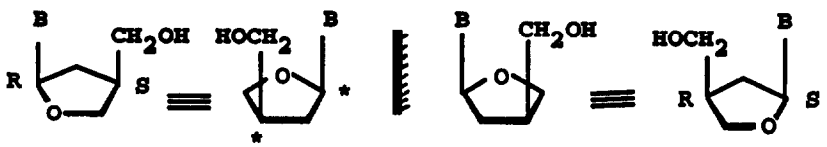
Summary: Short synthetic approaches to optically active, *cis* and *trans* dideoxynucleoside analogs of the D- and L-apiose family have been developed. The chiral precursor for the syntheses was the enzymatically prepared compound, S(-)-2-(2-propenyl)-1,3-propanediol monoacetate (5).

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]

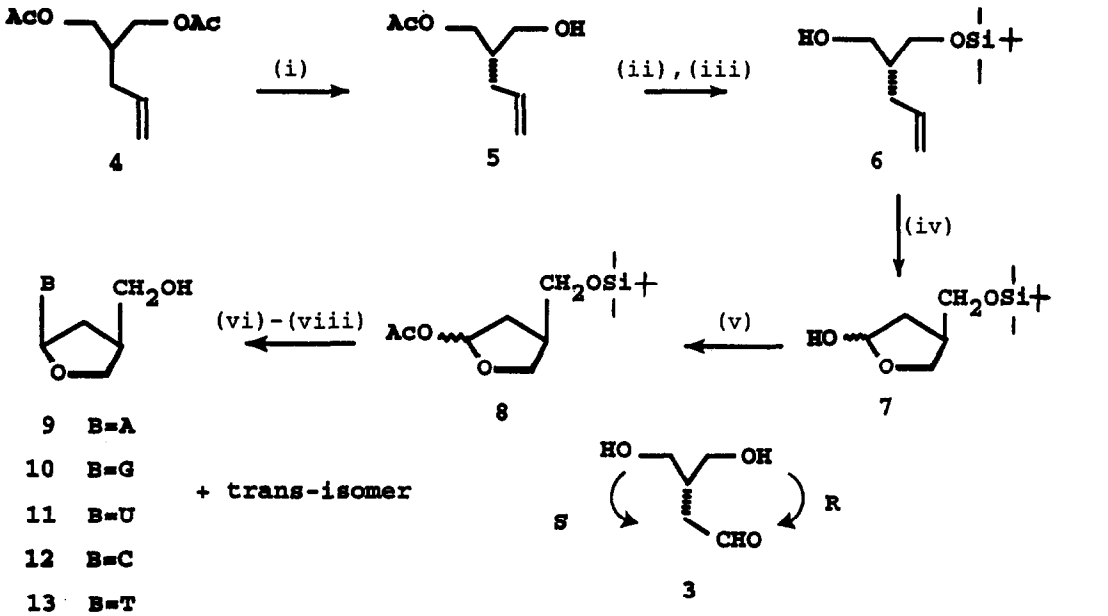
An alternative approach involves dideoxygenated nucleosides that contain transposed heteroatoms[11-13] and are regioisomeric with respect to dideoxy analogs of the natural nucleosides. 9-(β-D-Apio-D-furanosyl)adenine, a biologically-active, relatively non-cytotoxic nucleoside[14-17] related to natural 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 observation[13] that one member of Class **2** has been reported to have anti-HIV activity in MT-4 cells with no apparent toxicity.



1 **2**

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 CH_2OH 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 cylindracia* (Sigma, Type VII) afforded the S-(-)-monoacetate of 2-(2-propenyl)-1,3-propanediol (**5**) ($[\alpha]_D$= -8.0°, $CHCl_3$) in a 50% yield (99% ee). Treatment of **5** with *t*-butyldimethylsilyl chloride followed by deesterification gave the R-(+)-**6** ($[\alpha]_D$= +3.7°, $CHCl_3$) 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 $OsO_4/NaIO_4$. Thus, treatment of **6** with OsO_4 and $NaIO_4$ provided **7** almost quantitatively as an anomeric mixture ($[\alpha]_D$= +24°, $CHCl_3$) 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 condensation[21]



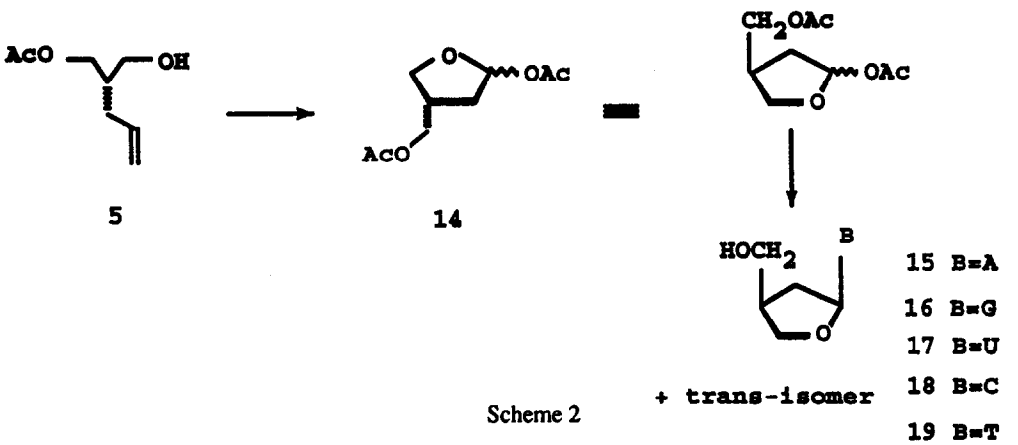
(i) Lipase (0.4 g per mmol **4**), 30% aq. acetone, NaOH (1M, pH 7), 8 h; (ii) TBDMSiCl (1.2 eq), imidazole (1.2 eq), CH_2Cl_2, 24 h; (iii) NaOMe (1.2 eq), MeOH, 45 min; (iv) OsO_4 (0.05 eq), $NaIO_4$ (3 eq), H_2O/Et_2O (50% v/v), 12 h; (v) Ac_2O (1.2 eq), Et_3N (1.4 eq), DMAP (0.1 eq), CH_3CN, 1 h; (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 N^6-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°, MeOH) and the corresponding 9-(2,3-dideoxy-α-D-apiofuranosyl)adenine anomer ($[\alpha]_D$ = +39.8°, MeOH). Assignments of the anomeric configurations were readily determined through ^{1}H NMR NOE difference spectroscopy.

Under similar conditions, the persilylated bases of N^2-acetyl-O^6-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 $OsO_4/NaIO_4$, 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**.



Scheme 2

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 hydrolysis[22] 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.

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