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Diastereoselective Synthesis of L-(+)-Homolamivudine

Noshena Khan, Shyamal R. Bastola, Kevin G. Witter and Peter Scheiner*

Department of Natural Science, York College, City University of New York
Jamaica, New York 11451 USA

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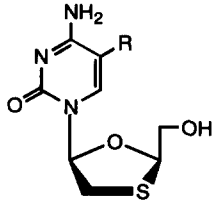
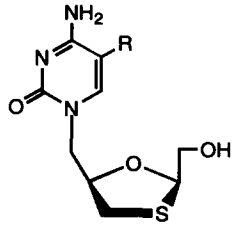
Abstract: L-homolamivudine (**2a**, (2R,5R)-(+)-*cis*-5-(1-cytosinylmethyl)-2-hydroxymethyl-1,3-oxathiolane) and its 5-fluoro congener (**2b**, L-homoFTC) have been prepared from (R)-glycidol by diastereoselective synthesis. Enantioselectivity resulted from stereoselective cyclothioacetalization that preferentially gave the (2R,5R)-*cis*-2,5-disubstituted-1,3-oxathiolane (**5**), *cis/trans* = 5.7.

Lamivudine (**1a**, (2R,5S)-(-)-*cis*-5-cytosinyl-2-hydroxymethyl-1,3-oxathiolane, 3TC), the first approved nucleoside analogue possessing the 'unnatural' L configuration, is widely employed in combination therapies for the treatment of AIDS.[1] Although both **1a** and its D-enantiomer are potent HIV reverse transcriptase and HBV DNA polymerase inhibitors,[2] only the L form (lamivudine) is essentially free of cytotoxic side reactions, due in part to lack of recognition by mammalian mitochondrial DNA polymerases.[3] Similar antiviral properties have been reported for the L-5-fluorocytosinyl derivative (**1b**, FTC),[4] positional isomers of **1a**[5] and several other L-nucleosides.[6] Recently, L-1,3-dioxolanyl uracils have been found effective against Epstein Barr virus,[7] further indicating the growing therapeutic importance of L-nucleoside analogues.



1a R = H (Lamivudine)
1b R = F (FTC)



2a R = H (L-Homolamivudine)
2b R = F (L-HomoFTC)

Synthesis of chiral **1** was first reported using a stereoselective (*cis* > *trans)* glycosylation catalyzed by $SnCl_4$, followed by enzymatic resolution.[8] A multistep asymmetric synthesis starting from

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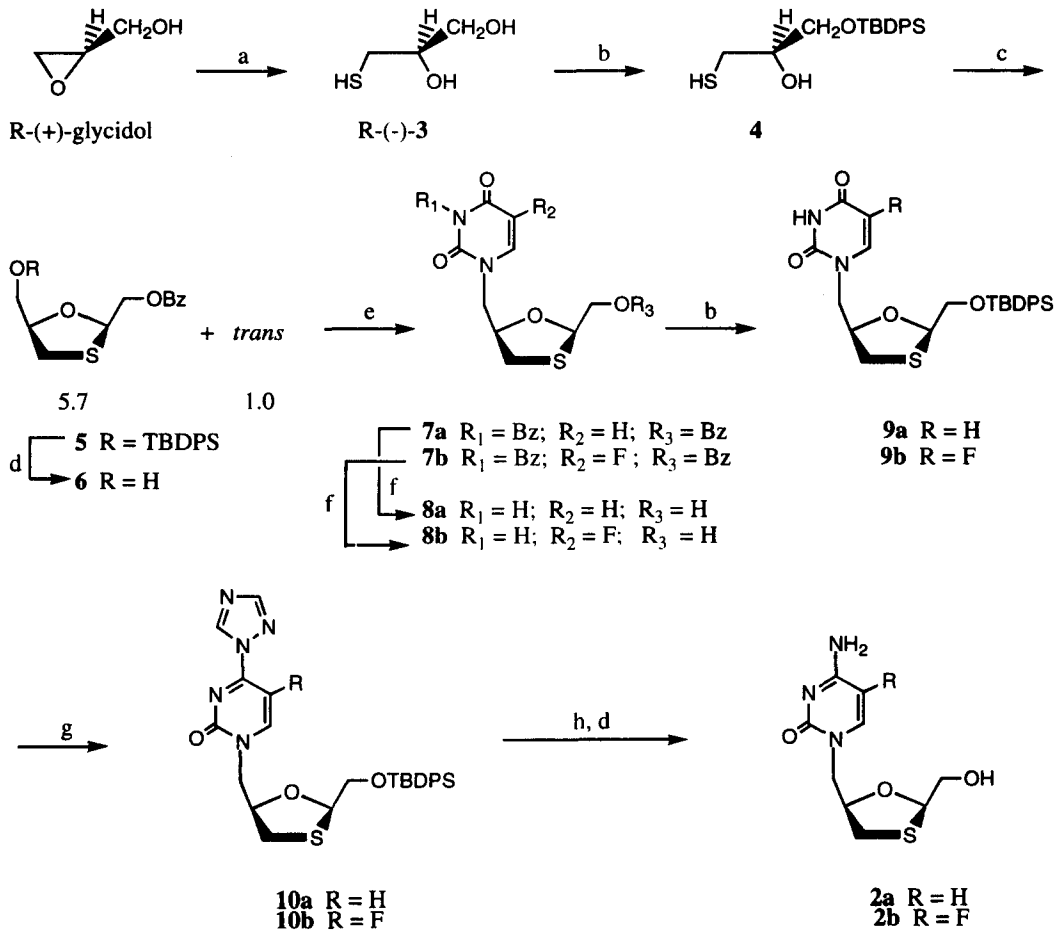
L-β,γ-6,3-gulonolactone has also been described.[2b] Prompted by the desirability of additional structure-activity information in the L-nucleoside series, and by the inefficiency and consequent cost of the reported syntheses, we have investigated the asymmetric preparation of a simple modification of **1**, L-homolamivudine (**2a**) and its 5-fluoro congener (**2b**). The outlined diastereoselective synthesis (**Scheme 1**) afforded the desired 2R,5R (L) products in satisfactory overall yield. The enantiomeric D-nucleosides could be obtained *via* **Scheme 1,** starting from S-(-)-glycidol.

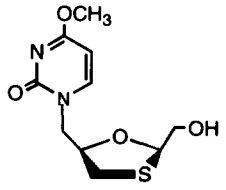
Scheme 1



a. H_2S, $Ca(OH)_2$, MeOH. b. TBDPSCl, DMAP, THF. c. $BzOCH_2CHO$, TsOH, 80° C, 1-2 mm Hg. d. TBAF, THF. e. Ph_3P, DEAD, (**a**) 3-benzoyluracil or (**b**) 3-benzoyl-5-fluorouracil. f. NH_3, MeOH. g. p-$ClC_6H_4OPO(Cl)_2$, 1,2,4-triazole, pyr. h. NH_4OH, p-dioxane.

Addition of hydrogen sulfide to (R)-glycidol produced (R)-(-)-3-mercapto-1,2-propanediol (**3**)[9] more efficiently than the previously described 4-step procedure.[10] After selective protection of the primary hydroxyl group with *tert*-butylchlorodiphenylsilane (TBDPSCl), acid-catalyzed cyclothioacetalization of **4** with benzoyloxyacetaldehyde occurred in high yield with notable stereoselectivity.[11] The desired *cis*-(2R,5R)-2,5-disubstituted-1,3-oxathiolane (**5**) predominated, along with small amounts of the *trans*-(2S,5R)-diastereomer. In agreement with previous results,[11] *cis*:*trans* ratios greater than 5.0 were observed (NMR). The *cis* stereochemistry of the major product (**5**) was later confirmed by NMR comparison of the homonucleoside products with related 1,3-oxathiolanes, as discussed below. A similar though somewhat less selective cycloacetalization of this aldehyde has been described in the 1,3-dioxanyl nucleoside series.[12] Deprotection of **5** with tetrabutylammonium fluoride gave alcohol **6**; overall yield (**3-6**), 69%.

Mitsunobu condensation of **6** with 3-benzoyluracil or 3-benzoyl-5-fluorouracil gave, after complete debenzoylation of **7**, the corresponding L-uracil homonucleosides **8a** (61%) and **8b** (45%). Following protection of the hydroxyl groups (TBDPSCl), these compounds were converted to cytosines **2a** and **2b** *via* their 1,2,4-triazole derivatives (**10a,b**)[13] in yields of 28% and 36%, respectively. An attempt to aminate and deprotect triazole **10a** in a single step with methanolic NH_3 afforded **11** as the major product.



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The *cis* (β) stereochemistry of the homonucleosides was verified by comparison of the relative chemical shift positions of corresponding protons in the major (*cis)* products and their minor (*trans*) isomers. In **2a,b**, **8a,b,** and all intermediates shown in **Scheme 1**, the H-2 and H-5 signals were upfield from those of the *trans* isomers. On the other hand, the $\underline{CH_2}OH$ signals of the major products appeared downfield from the minor isomers. These correlations (*cis* H-2, H-5 upfield from *trans*; *cis* $\underline{CH_2}OH$ downfield from *trans*) have been firmly established and used to assign stereochemistry (and absolute configuration) in the 1,3-oxathiolane nucleoside series.[14] They reflect the relative proximity of protons in the *cis* and *trans* isomers to the heterocyclic base, relationships that also appear applicable to the homonucleosides.

Diastereoselective cyclization afforded **5** with the (*cis*) 2R,5R configuration. Subsequent reactions, remote from the stereogenic centers, did not alter the configurations at these positions. Thus the derived (2R,5R)-homonucleosides possess the carbohydrate L-configuration, as indicated in **Scheme 1**.[15]

Structures in **Scheme 1** are in agreement with their ^{1}H and ^{13}C NMR spectra. Satisfactory elemental analyses (**2a,b, 8a,b**) and molecular weights by high resolution mass spectrometry (**6, 7a,b, 9a,b, 11**) were also obtained.[16] Biological results and full experimental details will be reported elsewhere.

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14. Jeong, L.S.; Schinazi, R.F.; Beach, J.W.; et al. *J. Med. Chem.* **1993**, *36*, 181-195.
15. The homonucleoside 2R,5R configurations differ from lamivudine (2R,5S) due to insertion of the lower priority CH_2 group. Nevertheless, both are L-family nucleosides.
16. **2a**: $[\alpha]_{589}^{20} = +77.6^{o}$. **2b**: $[\alpha]_{589}^{20} = +76.2^{o}$.