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Synthesis of Optically Active 2',3'-Dideoxy-3'-oxa-4'-thio-ribonucleoside Analogues by Transposition of a Leaving Group on Chiral Oxathiolanes via a Reductive-oxidative Process

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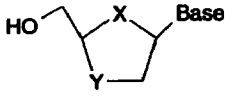
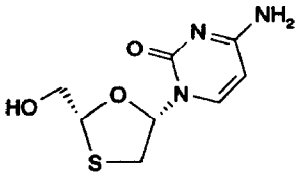
Abstract: The synthesis of chiral nucleoside analogues with a unique structural feature is reported. The strategy is based on a reductive-oxidative process to complete the transposition of the leaving group in chiral oxathiolanes with known configuration.

The antiviral nucleoside analogues containing more than one heteroatoms in the sugar ring (**1**) are a unique class of compounds that were first reported by Belleau et al[1]. An outstanding clinical candidate emerged from these compounds is β-L-(-)-2'-deoxy-3'-thiacytidine (**2**, Lamivudine, 3TC™)[2], which is currently undergoing clinical evaluation for anti-HIV[2a] and HBV activities.[2b] Interestingly, this compound showed much lower cytotoxicity than its antipode the D-enantiomer although both are almost equipotent against the replication of HIV-1 and -2 *in vitro*. In order to clarify the structure-activity relationships in this class of nucleoside analogues, especially in relation to their absolute configurations, a program was initiated to obtain the compounds represented by **1** in enantiomerically pure form.[3] The synthesis of racemates in one particular class of these nucleoside analogues (**1**, X,Y = S, O; base = natural bases) has been reported from this laboratory and the active analogue BCH-371 (base = adenine) has been resolved into its two enantiomers by chiral HPLC,[4] but the tentative assignment of absolute configurations was hypothetically based on enantioselectivity of adenosine deaminase towards one enantiomer. Here, we wish to report convergent asymmetric synthesis of cytosine, 5-fluorocytosine and adenine nucleoside analogues in this series of hetero-substituted nucleoside analogues.



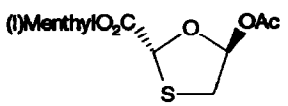
1

X, Y = O, S
= O, O
= S, O



2

The main challenge in this synthesis was the preparation of the chiral 2,4-disubstituted-1,3-oxathiolane sugar surrogate with a proper leaving group at C-4 for further coupling reactions. During the synthetic studies[5] of 3TC™ (**2**), we prepared in good yield the chiral oxathiolanes having an acetoxy group at C-5 (**3** and **4**). The transposition of the leaving group from C-5 to C-4 on the oxathiolane was clearly an attractive approach in view of the fact that the configurations at C-2 were known and those starting material were accessible in pure form.



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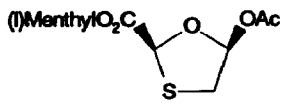


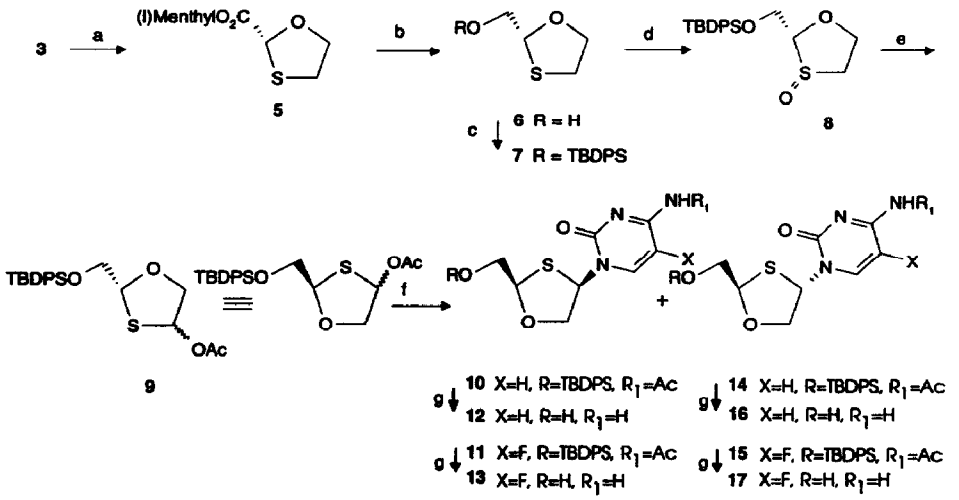
4

There are abundant examples of reductive replacement of an acetoxy group by hydrogen. One such method is the reduction by triethylsilane in the presence of a Lewis acid catalyst.[6] Indeed, we were delighted

to discover that this transformation could be completed smoothly by treating 3 in neat triethylsilane with trimethylsilyl trifluoromethanesulfonate (TMSOTf) at room temperature (scheme 1). It is worth mentioning that the use of dichloromethane as solvent for the reduction resulted in appreciable epimerization at C-2. The oxathiolane 5 was further reduced with sodium borohydride in ethanol to alcohol 6.[7] Protection of hydroxyl group with t-butyldiphenylsilyl chloride and imidazole furnished compound 7 in excellent yield.

The oxathiolane 7 was then subjected to oxidation with m-chloroperoxybenzoic acid (MCPBA) to yield a diastereomeric mixture of sulfoxides 8 which underwent Pummerer rearrangement readily in acetic anhydride in the presence of tetra-n-butylammonium acetate[4] to afford the desired oxathiolane 9 as a mixture of cis and trans isomers.

Scheme 1

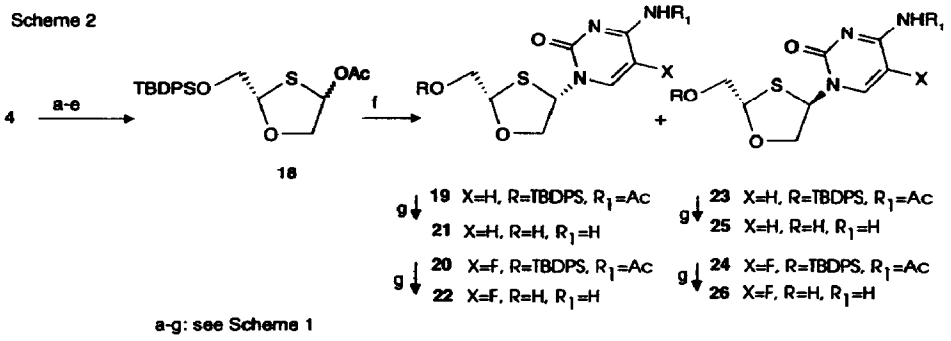


a: Et_3SiH (neat), TMSOTf; 82-86%; b: $NaBH_4$, EtOH, MeOH, 85-91%; c: TBDPSCl, Im, THF, 90-94%; d: MCPBA, CH_2Cl_2, 89-94%; e: $(n\text{-}Bu)_4NOAc$, Ac_2O, 120°C, 51-61%; f: persilylated N-acetylcytosine or persilylated N-acetyl-5-fluorocytosine, TMSOTf, DCE, reflux, 55-78%; g: TBAF,HOAc, THF; K_2CO_3, MeOH, 81-89%.

With the acetoxy group properly transposed to C-4, the stage is set for the coupling with nucleobases (scheme 1). Subjection of acetoxy oxathiolane 9 to the brief reaction with silylated N-acetylcytosine in refluxing 1,2-dichloroethane for 30 min. using TMSOTf as a Lewis acid promoter gave the coupling products 10 and 14 in 65% yield and 1:1.5 ratio respectively as indicated by ^1H NMR.[8] Separation of cis/trans mixture by preparative TLC followed by deprotection gave the final products 12 and 16. The preservation of original chirality at C-2 was confirmed by chiral HPLC analysis.[9] Persilylated N-acetyl-5-fluorocytosine also reacted with acetoxy oxathiolane 9 under the same condition to give a mixture of 11 and 15 (71 %, 1.4:1 ratio as indicated by NMR[7]) which was further converted to nucleoside analogues 13 and 17 after separation and deprotection.

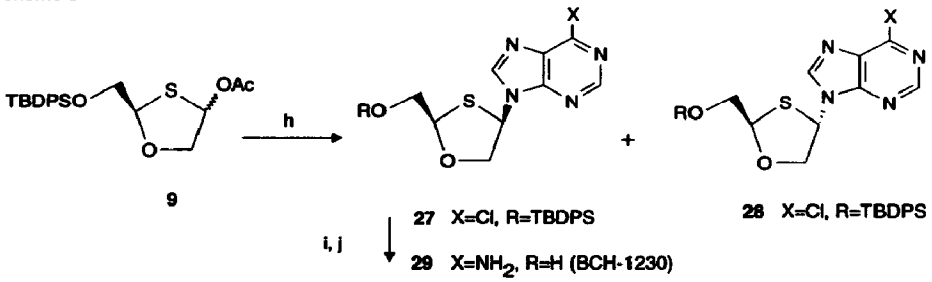
The same reaction sequence was performed to transform the chiral oxathiolane 4 to nucleosides 21, 22, 25, 26 (scheme 2).

Scheme 2



a-g: see Scheme 1

Scheme 3



h: silylated 6-chloropurine, TMSOTf, DCE, reflux, 67%; i: TBAF, HOAc, THF, 91%; j: NH_3, MeOH, 81%

This synthetic method has also been applied to determining unequivocally the absolute configuration of chiral 2',3'-dideoxy-3'-oxa-4'-thio-ribonucleoside analogue **29** (BCH-1230), the enantiomer that has been preferably deaminated by adenosine deaminase from the corresponding racemic mixture.[4] Reaction of acetoxy oxathiolane **9** with silylated 6-chloropurine in the presence of TMSOTf gave a mixture of cis and trans isomer (**27** and **28**) which was subjected to chromatographic seperation. The pure cis compound **27** was desilylated followed by heating with saturated ethanolic ammonia in a sealed vessel to give the adenosine analogue **29**. The correlation of the specific optical rotation between the synthetic product **29** and the sample seperated by chiral HPLC further confirmed the C2 R configuration of BCH-1230 which contains the "natural" D-sugar prototype and has been preferably deaminated by the the adenosine deaminase during the enzyme catalyzed reaction.

In summary, we report the first synthesis of optically active 2',3'-dideoxy-3'-oxa-4'-thio-ribonucleosides starting from sugar precursors with known absolute configuration by transposition of a leaving group via a reductive-oxidative process without serious epimerization. We believe that this synthetic method provides an accessibility to this class of nucleoside analogues in chiral forms for biological evaluation.[10]

Acknowledgement:

We thank Dr. H. L. Allan Tse for the helpful discussion and suggestion, and are indebted to the Glaxo Group Research Ltd., U.K. for providing us with the chiral compounds **3** and **4** and HPLC group of Biochem for chiral HPLC analysis. Drs. John W. Gillard and Gervais Dionne are acknowledged for their encouragement.

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1.a) Belleau, B.; Dixit, D.;Nguyen-Ba, N.; and Kraus, J.-L.; *Abstracts of Papers, Fifth International Conference on AIDS, Montreal, Canada*, **1989**, Abtract No. T.C.01. p.515; b) Mansour, T. S.; Belleau, B.; Bednarski, K.; Breining, T.; Brown, W. L.; Cimpoia, A.; DiMarco, M.; Dixit, D. M.; Evans, C. A.; Jin, J.; Kraus, J.L.; Lafleur, D.; Lee, N.; Nguyen-Ba, N.; Siddiqui, M. A.; Tse, H. L. A.; Zacharie, B. Heteroatom substituted 2',3'-dideoxynucleoside analogues as anti-infective agent; Bentley, P. H. and Ponsfond, R.' eds. Royal Society of Chemistry, Cambridge, Great Britain, :336-347, **1993**.

2. For first report on 3TC™ and anti-HIV activities see a) Coates, J. A. V.; Cammack, N.; Jenkinson, H. J.; Mutton, I. M.; Pearson, B. A.; Storer, R.; Cameron, J. M.; and Penn, C. R. *Antimicrob. Agent Chemother.* **1992**, *36*, 733. For anti-HBV activitites see b) Doong, S.-L.; Tsai, C.-H.; Schinazi, R. F.; Liotta, D. C.; and Cheng, Y.-C. *Proc. Natl. Acad. Sci.* USA **1992**, *88*, 8495.

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4. Belleau, B.; Brasili, L.; Chan, L.; DiMarco, M. P.; Zacharie, B.; Nguyen-Ba, N.; Jenkinson, H. J.; Coates, J. A. V.; and Cameron, J. M. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1723.

5. Mansour, T. S.; Tse, H. L. A.; Jin, H.; Siddiqui, M. A. Patent application. U.S. 07-703,379

6. Bennek, J. A.; and Gray, G. R. *J. Org. Chem.* **1987**, *52*, 892 and the references cited therein.

7. The ^{1}H NMR of Mosher's ester of compound **6** indicated the existantce of about 5-6% 2S enantiomer which was consistant with both the extent of epimerization caused in the reduction of **3** and the chiral HPLC analysis of final product (see note 9). This suggests that step (a) of Scheme 1 was the only step responsible for this partial racemization.

8. The coupling reaction was very sluggish at room temperature. For silicon Lewis acid catalysed glycosylation see: Vorbruggen, H.; Krolikewicz, K.; and Bennua, B. *Chem. Ber.* **1981**, *114*, 1234; For the racemization caused by Ti (IV) and Sn (IV) Lewis acids promoted glycosylation see Jin, H.; Tse, H. L A.; Evans, C. A.; Mansour, T. S.; Beels, C. M.; Ravenscroft, P.; Humber, D. C.; Jones, M. F.; Payne, J. J. and Ransay, M. V. J. *Tetrahedron: Assymetry*, **1993**, *4*, 211 and the references cited.

9. All the final products showed the same spectral data as those of racemate (see reference 4). Some selected chiral HPLC analysis (CYCLOBOND 1 RSP column) and specific optical rotation: **16**: 89% e.e., $[\alpha]_D^{25}$ +190.2° (c 0.62, MeOH); **25**: 93% e.e., $[\alpha]_D^{25}$ -195.4° (c 0.79, MeOH); **21**: 81% e.e., $[\alpha]_D^{25}$ -86.5° (c 0.57, MeOH), the sample for specific rotation was obtained by chiral HPLC seperation (100% by HPLC); the partial racemization at C2 center was caused during reduction (scheme 2, step a) by using CH_2Cl_2 as a co-solvent. **22**: 89% e.e., $[\alpha]_D^{25}$ +75.7° (c 0.56, MeOH); **29**: $[\alpha]_D^{25}$ -49.6° (c 0.25, MeOH) [lit.[4] $[\alpha]_D^{25}$ -51.3° (c 1.0, MeOH)].

10. The preliminary results of anti-HIV tests indicated that analogues **12**, **13**, **21**, **22** showed activities and the detail will be published in due course.

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