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# Design and synthesis of a novel ring-expanded 4′-thio-*apio*-nucleoside derivatives

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**Abstract**—The synthesis of a ring-expanded 4′-thio-*apio*-nucleoside derivative **4**, designed to serve as a potential anti-HIV agent, is described. The epoxy alcohol derivative **10**, prepared from 2-butene-1,4-diol, was converted to an allylsulfide derivative **13** in 3 steps. Ring-closing-metathesis of **13** gave the dihydrothiopyran derivative **20**, which was further converted into sulphoxide **24**. A Pummerer-type thioglycosylation reaction of **24** with a persilylated uracil derivative, followed by conversion to a cytosine derivative and deprotection, gave a racemic mixture of the ring-expanded 4′-thio-*apio*-nucleoside derivative **4** in good yield.


In recent AIDS treatment, referred to as HAART (highly active anti-retroviral therapy), nucleoside reverse transcriptase inhibitors (NRTIs) play a critical role.[1] Nucleoside derivatives containing a sulfur atom in a sugar or a pseudosugar skeleton, for example, 4′-thionucleosides, are of particular interest: Lamivudine[2] (3TC, **1**, Chart 1), an NRTI used in the clinical treatment of AIDS, may formally belong to a category of D-*iso*-4′-thionucleosides.

In addition, it was recently reported that L-2′,3′-dideoxydidehydrocytidine (L-D4C, **2**) has anti-HIV-1 activity.[3] We previously reported on the design and synthesis of *iso*-4′-thiocytidine **3**, but, no activity against HIV was observed.[4] In our continuous attempts to design and synthesize novel nucleoside derivatives,[4,5] we designed a dihydrothiopyranylcytosine derivative **4** as a potential anti-HIV agent. Compound **4** can be considered to be a ring-expanded 4′-thio-*apio*-nucleoside derivative designed from L-D4C. The *apio*-nucleoside is another novel class of nucleoside derivatives,[6] some of which are known to have anti-HCMV activity and cytotoxicity.[6b,c] To the best of our knowledge, dihydrothiopyranylcytosine derivatives similar to **4** as well as its 4′-oxy congener **5** have not been reported. From the standpoint of nucleosides built on a cyclohexene scaffold, the ring-expanded 4′-thio-*apio*-nucleoside derivative **4** is unique. The synthesis of cyclohexenyl nucleosides **6** and **7** were recently reported[7] and the latter was proven to have anti-herpes virus activity.[7b,c] Herein, we report on the racemic synthesis of **4** starting from 2-butene-1,4-diol (Chart 1).

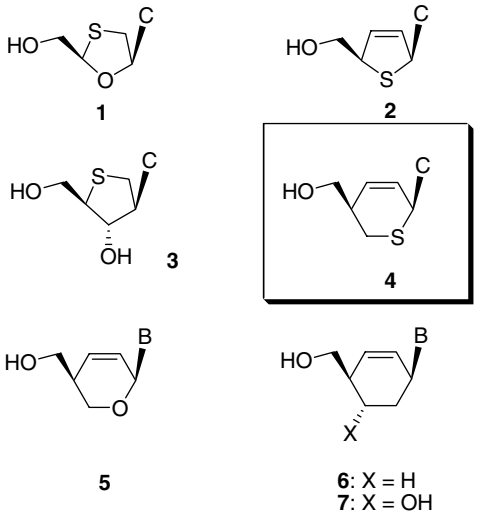


**Chart 1.**

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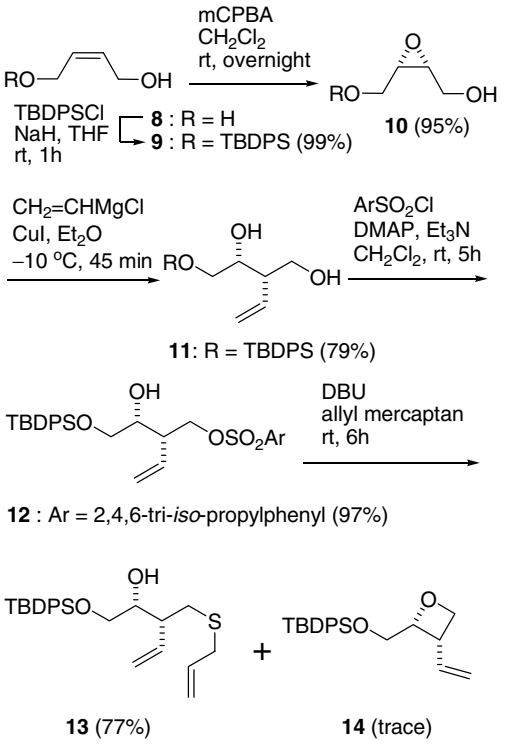
The monosilylation of 2-butene-1,4-diol by a known method[8a,c] gave an allyl alcohol **9** in 99% yield. It has already been reported that the Sharpless asymmetric epoxidation of **9** gives the corresponding epoxy alcohol with high enatiomeric excess.[8b,c] However, we did not attempt to synthesize the target compound in an enatiomerically pure form, because the antiviral evaluation of the racemic target compounds would give results regarding both enatiomers in one procedure. We intended to synthesize a racemic mixture of **4** and treated allyl alcohol **9** with mCPBA in $CH_2Cl_2$ to give (±)-**10** in 95% yield. Cleavage of the epoxy ring of **10** was achieved by a known method[8b,c,9] with minor modifications to give the vinyl diol **11** in good yield. Selective monotosylation at the primary hydroxyl group of **11** was attempted. However, all efforts were unsuccessful: the typical reaction for tosylation (TsCl, $Et_3N$, DMAP, $CH_2Cl_2$) gave a ditosylated derivative as the major product (data not shown).[10] Instead of the tosyl group, a more bulky 2,4,6-triisopropylbenzenesulfonyl (TPS) group was next employed. The reaction of **11** with TPSCl, triethylamine, and DMAP in $CH_2Cl_2$ gave the desired mono-TPS derivative **12** in 97% yield. It is noteworthy that no di-TPS derivative was detected in the reaction mixture. A nucleophilic substitution reaction of **12** with allyl mercaptan (10 equiv) and DBU (2 equiv) in $Et_2O$ gave an allyl sulfide and oxetane derivatives in 51% and 16%, respectively, after acetylation (see supporting information). To suppress the formation of the oxetane derivative which was formed via an intramolecular $S_N2$ reaction, the substitution reaction was performed using allyl mercaptan as the solvent.[11] As a result, the allyl sulfide **13** was obtained in 77% yield with only trace amounts of the oxetane derivative **14**. The fact that the reaction of **14** with allyl mercaptan and DBU did not proceed at all, suggests that the substitution of the TPS group occurs via a direct $S_N2$ reaction (Scheme 1).



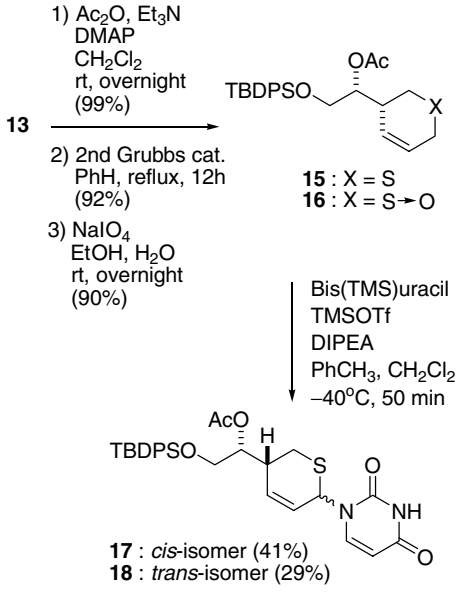

**Scheme 1.** Synthesis of ally sulfide derivative **13**.

In order to construct a dihydrothiopyran skeleton, RCM reaction of **13** was attempted. The reaction of **13** with 1st Grubbs catalyst, after the acetylation of the hydroxyl group, gave dihydrothiopyran **15** in poor yield (data not shown). In contrast, the use of the 2nd Grubbs catalyst in refluxing benzene[11] resulted in a more efficient reaction, giving the desired **15** in 92% yield.

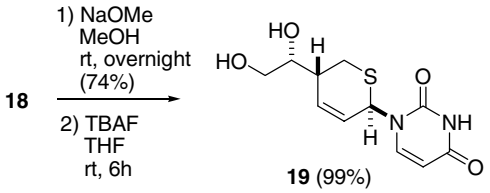
To achieve the synthesis of a thionucleoside, the formation of a thioglycosyl bond is a key reaction. The Pummerer-type thioglycosylation reaction, developed by us,[12] appeared to be the most suitable for the synthesis of our target compound. Prior to the synthesis of the ring-expanded 4′-thio-*apio*-D4C **4**, the Pummerer-type thioglycosylation reaction of **16** derived from **15** was examined as a model reaction. Upon treatment with $NaIO_4$ in EtOH/$H_2O$ overnight, compound **15** was oxidized to give a diastereomeric mixture of the corresponding sulphoxide **16** in 90% yield.

We found that the Pummerer-type thioglycosylation of the sulphoxide **16** by treatment with bis(trimethylsilyl)uracil, TMSOTf, and DIPEA in toluene and $CH_2Cl_2$ (1:1, v/v) at −40 °C gave the dihydorothiopyranyluracil derivatives **17** and **18** in 41% and 29% yields, respectively (Scheme 2). It is noteworthy that the adducts reacted at the 3′-position, formed via the γ-alkylation of an allylic sulfonium intermediate, were not observed.

The stereochemistry of the dihydorothiopyranyluracil derivative **17** was elucidated by NOE experiments and




**Scheme 2.** Synthesis of dihydrothiopyran derivative **16** and its Pummerer-type thioglycosylation.




**Scheme 3.** Synthesis of dihydrothiopyranyluracils **19**.

was determined to be the *cis*-isomer (data not shown). On the other hand, compound **18**, after deprotection with sodium methoxide and subsequent treatment with TBAF, gave dihydrothiopyranyluracil **19** (Scheme 3).

Based on the X-ray crystallographic analysis of **19** as depicted in Figure 1, its relative stereochemistry could be unambiguously confirmed as 'trans'.

We next attempted the synthesis of the ring-expanded 4′-thio-*apio*-nucleoside **4**. As in the case of the acetylated derivative mentioned above, the RCM-reaction of **13**, without protection of the secondary hydroxyl group, catalyzed by 2nd Grubbs catalyst effectively gave rise to the dihydrothiopyran derivative **20** in 85% yield. The oxidative cleavage of the side-chain of **20** appeared problematic since the reaction needed to proceed without oxidation of the sulfur in the dihydrothiopyran ring. Fortunately, the conversion of **15** to the sulphoxide **16** required long periods of time for completion (vide supra). This suggests that oxidative cleavage could be carried out selectively if the cleavage were sufficiently fast that the sulfur atom would not be oxidized. Therefore, after deprotection of the TBDPS group by treatment with TBAF, compound **21** thus obtained was treated with $NaIO_4$ followed by sodium borohydride. The reaction gave 3-hydroxymethyl-3,6-dihydrothiopyran **22** in moderate yield, as expected. Compound **22** was protected by introducing a TBDPS group at the primary hydroxyl group, then, oxidized with $NaIO_4$ to give the sulphoxide **24** in good yield (Scheme 4).

Using conditions similar to those described above, the Pummerer-type thioglycosylation reaction of **24** with bis(trimethylsilyl)uracil gave the desired ring-expanded

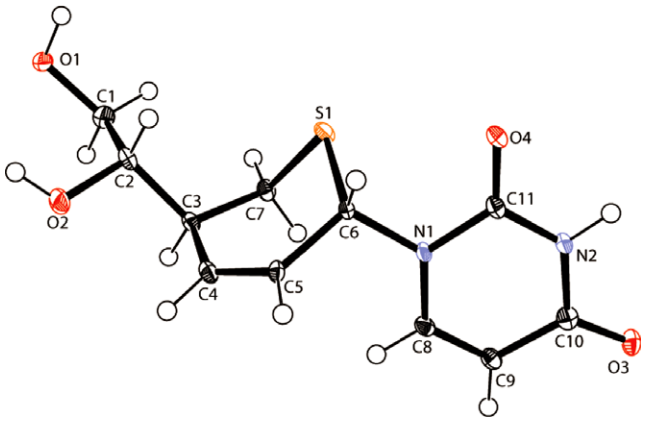
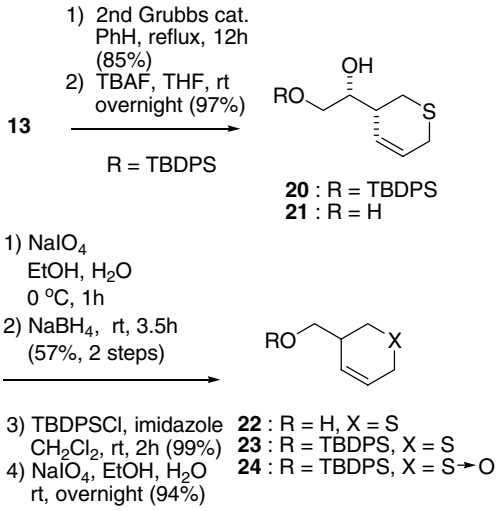
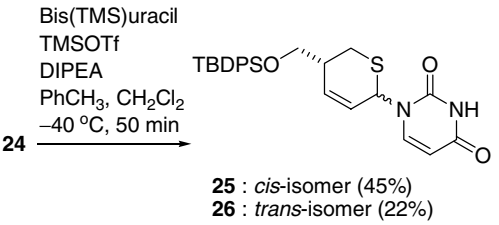



**Figure 1.** ORTEP diagram of compound **19**.




**Scheme 4.** Synthesis of dihydrothiopyran derivative **24**.



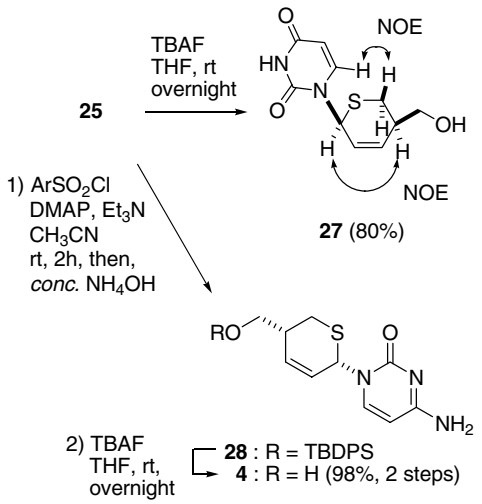

**Scheme 5.** Pummerer-type thioglycosylation of **24**.

4′-thio-*apio*-nucleoside derivatives **25** and **26** in 45% and 22% yields, respectively (Scheme 5).

NOE experiments of a ring-expanded 4′-thio-D4U **27** obtained by the deprotection of **25** showed that the major procuct **25** was the cis-isomer. It is interesting to note that the Pummerer-type thioglycosylation of **24** as well as **16** both gave cis-isomers as major products. However, the reason for the predominant formation of these cis-isomers is not clear at present.

Finally, the conversion of the uracil moiety of **25** to cytosine was achieved by treatment with TPSCl and DMAP followed by *conc*. $NH_4OH$[13] to give **28**, which was further treated with TBAF to give the desired ring-expanded 4′-thio-D4C **4** in 98% yield (Scheme 6).

In summary, we report on the design of a novel ring-expanded 4′-thio-*apio*-D4C derivative **4** as a potential antiviral agent including anti-HIV. The synthesis of 3-hydroxymethyl-3,6-dihydrothiopyran, the sugar portion of the target compound, started from 2-butene-1,4-diol and was achieved by the RCM-reaction after the introduction of vinyl and allyl sulfide moieties. The dihydrothiopyran **23** was converted to the corresponding sulphoxide, the Pummerer-type thioglycosylation of which gave the desired 4′-thio-*apio*-D4C derivative. The evaluation of anti-HIV activity of **4** is currently in progress and will be reported elsewhere.




**Scheme 6.** Synthesis of ring-expanded 4′-thio-*apio*-D4C **4**.

## Acknowledgments

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## Supplementary data

Experimental procedures and characterization data for compounds **9**–**27**, and **4**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.04.139.

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