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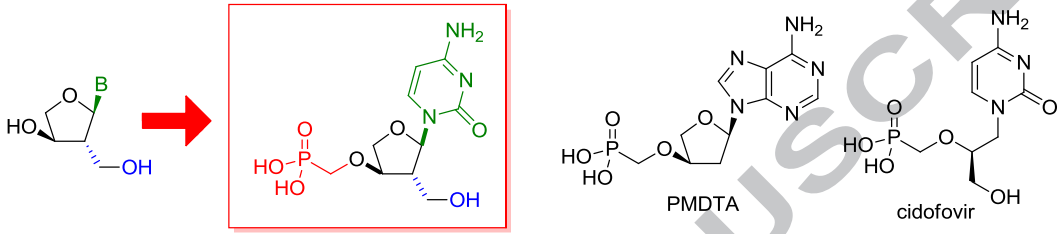

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Design and Synthesis of A Nucleoside and A Phosphonate Analogue Constructed on A Branched-*threo*-tetrofuranose Skeleton

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ABSTRACT

The synthesis of a novel nucleoside phosphonate constructed on a branched-*threo*-tetrofuranose scaffold, as a potential antiviral agent, is described. The pseudosugar moiety served as the nucleoside skeleton was produced starting from 2-butyne-1,4-diol in 10 steps. Glycosylation with the pseudosugar involved stereoselective neighboring group participation of *p*-anisyl group and gave the nucleoside derivative in 94% yield. After manipulating the protecting group and introduction of a methylenephosphate unit, the synthesis of the target novel cytidine phosphonate was achieved. The resulting nucleoside, a synthetic intermediate of the nucleoside phosphonate, would also be expected to serve as a useful building block for the synthesis of novel antisense/antigene derivatives.

Drug development based on nucleosides/nucleotides has resulted in the development of various medicines, the most typical examples of which are antimetabolites for use in combatting cancer and viruses. To date, a wide variety of antitumor, antiherpes and anti-HIV drugs based on nucleoside analogues are approved and used in the clinic.[1] Also drug development focused on antisence, antigene, aptamer and RNAi has long been a subject of interest. These "nucleic acid medicines" are highly attractive since they can directly suppress or block transcription and the action of proteins that cause diseases.[2] However, many problems remain to be solved before the widespread use of nucleic acid medicines is to be achieved. This impedes the development of nucleic acid medicines. As a result, only a few nucleic acid-based drugs have been approved and their uses are limited to topical treatment.[3] One such problem to be overcome is the instability of oligo(deoxy)nucleotides (ONs) in serum due to the nuclease-catalyzed hydrolysis of the phosphodiester linkage. To avoid this problem, ONs containing modified nucleotide units are frequently used.[4] From these points of view, it is obvious that a study of the synthesis of nucleoside derivatives with emphasis on structural novelty would greatly contribute to the development of nucleic acid medicines as well as nucleoside antimetabolites. As part of our ongoing studies related to the synthesis of nucleoside derivatives,[5] we were prompted to consider a nucleoside phosphonate constructed on a novel nucleoside skeleton. Nucleoside phosphonates are promising as antiviral agents. They can bypass the conversion of nucleosides to active triphosphate forms since nucleoside phosphonate derivatives are able to skip the first phosphorylation step. An alkylphosphate unit in their structure mimics a phosphate moiety, which permits them to act as a nucleoside monophosphate.[6] In this study, we report on the synthesis of a nucleoside derivative **1** bearing a branched-*threo*-tetrofuranose scaffold as a pseudosugar moiety and a nucleoside phosphonate derivative **2** obtained from **1**. The nucleoside phosphonate **2** is promising as an anti-HIV agent since it is structurally similar to PMDTA,[7] a known anti-HIV nucleoside phosphonate. In addition, the nucleoside derivative **1** has primary and secondary hydroxyl groups in appropriate positions of

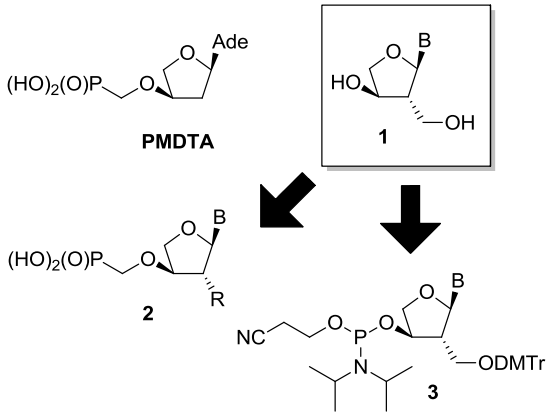

Figure 1: Structures of nucleoside **1** constructed on a branched-*threo*-tetrofuranose scaffold and nucleoside phosphonate **2**.

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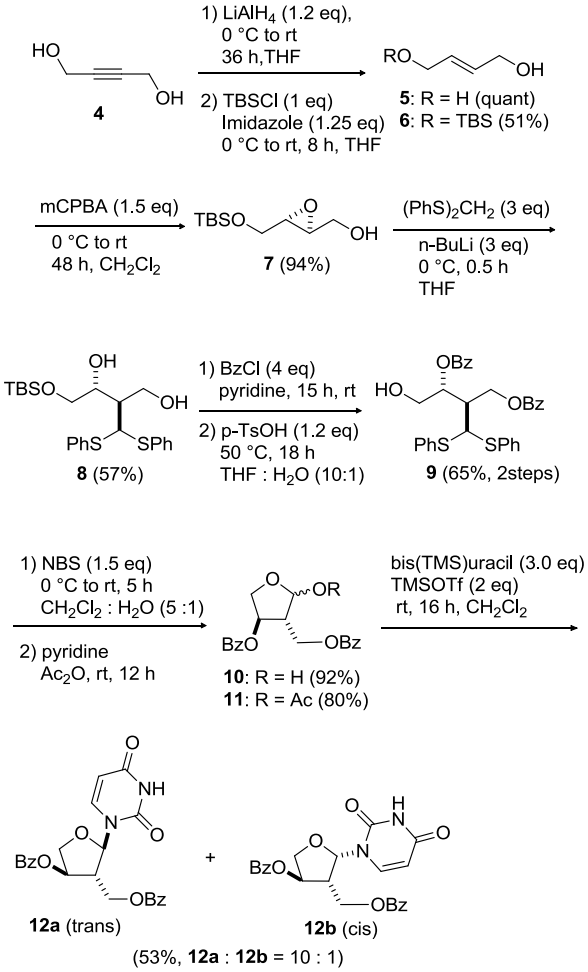
the sugar moiety and might serve as a useful building block, *e.g.* **3**, to create a novel antisense and antigene ONs (Figure 1). This characteristic structure of nucleoside phosphonate **2** is also unique as a mimic of cidofovir, an anti-HCMV drug (vide infra).

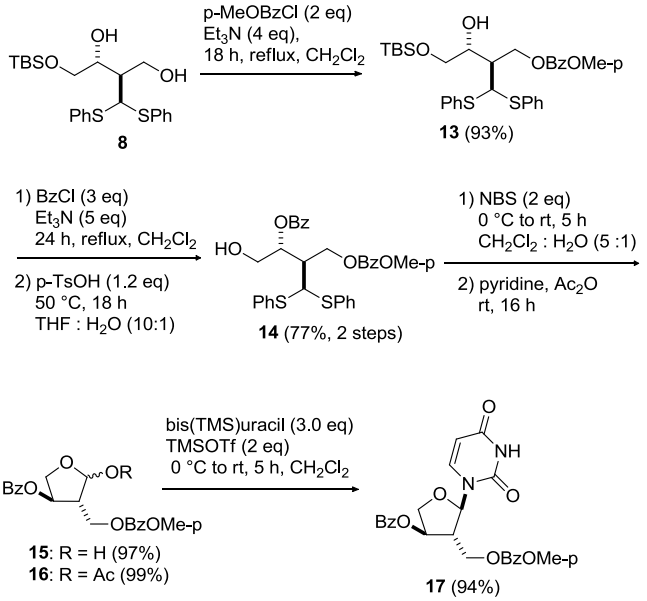
Our first attempt to synthesize a nucleoside derivative **1** having a branched-*threo*-tetrofuranose skeleton started from 2-butyne-1,4-diol (**4**) and was intended to produce **1** as a racemic mixture. The reduction of **4** with lithium aluminum hydride under standard conditions[8] gave the (*E*)-butenediol **5** which was silylated at one primary hydroxyl group to give a mono alcohol **6**. The epoxidation of **6** by treatment with *m*CPBA afforded the epoxide **7** in good yield. To construct the pseudosugar skeleton, it was necessary to introduce a C1 unit equivalent to an aldehyde into **7**. This was achieved by nucleophilic attack of an anion generated from di(thiophenyl)methane. Lithiation of di(thiophenyl)methane by treatment with *n*-butyllithium produced the corresponding anion which, on reaction with **7**, gave the diol derivative **8** in 57%. The nucleophilic attack of the anion occurred selectively from the less hindered side and gave **8** as a single isomer. The diol portion of **8** was protected by introducing a benzoyl group and the resulting crude



Scheme 1: Synthesis of a nucleoside derivative constructed on a branched-*threo*-tetrofuranose scaffold.

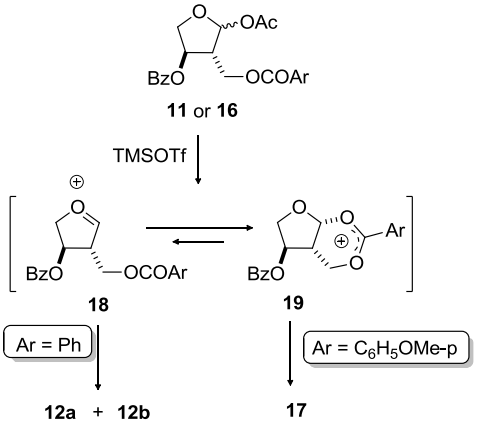
product was subsequently treated with *p*-TsOH to remove the TBS group giving the dibenzoate **9**. Conversion of the di(thiophenyl)methyl unit to an aldehyde was achieved by reacting **9** with NBS[9] to spontaneously form a hemiacetal structure giving **10** in excellent yield. Acetylation of **10** in pyridine gave the pseudosugar donor **11** which was subjected to the glycosylation reaction under Vorbrüggen conditions.[10] Treatment of **11** with bis(trimethylsilyl)uracil in the presence of TMSOTf gave a mixture of **12a** and **12b** in 53% yield as an anomeric mixture in a ratio of 10:1 to **12a** : **12b** (Scheme 1).

The fact that the glycosylation gave a mixture of products in moderate yield prompted us to modify the synthetic route to the target nucleoside in order to find a more efficient glycosylation reaction. To complete this task, we intended to introduce a more electron-donating acyl group at the primary hydroxyl group of the pseudosugar donor, by which the effect of neighboring group participation would be enhanced to stabilize the intermediate for the glycosylation reaction[11] (vide infra). Compound **8** was selectively acylated with a *p*-anisyl group at the primary hydroxyl group to give the *p*-anisyl derivative **13**. Following the synthetic scheme described above, the *p*-anisyl derivative **13** was converted into the pseudosugar donor **16** in 4 steps. The glycosylation of **16** using the Vorbrüggen method[10] gave the nucleoside derivative **17** as a single isomer in 94% yield (Scheme 2).[12] It is noteworthy that yield and selectivity were both improved as we expected.



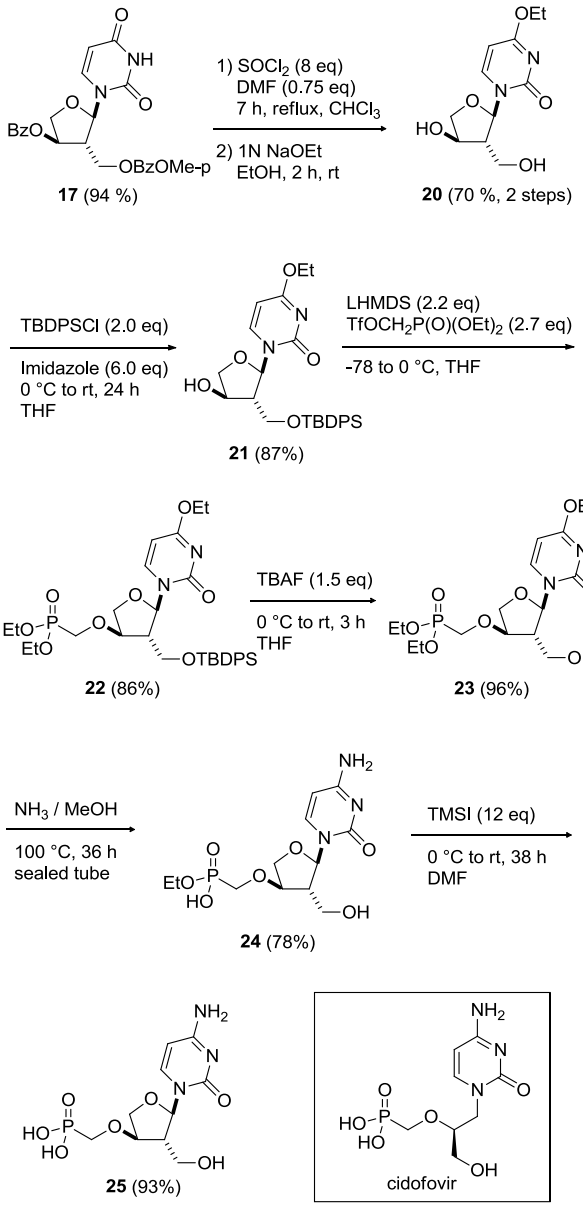
Scheme 2: Modified synthesis of a nucleoside derivative constructed on a branched-*threo*-tetrofuranose scaffold.

From the results mentioned above, a proposed mechanism for the glycosylation reaction is shown in Scheme 3. In both of the reaction from the pseudosugar donors **11** and **16**, the reaction with TMSOTf generates the oxocarbenium ion **18**. In addition, the neighboring



Scheme 3: Postulated reaction mechanism of glycosylation reaction.

group participation of the acyl group would form the cyclic acyloxonium ion **19**. It is clear that **18** and **19** are in equilibrium with each other and that **19** would be the more stabilized form.[11] When silylated uracil only reacts with **18**, the reaction gives a mixture of anomers. On the other hand, the reaction of **19** with silylated uracil would exclusively give one isomer having a 1',2'-trans stereochemistry. In the case of **11**, the reaction predominantly gave **12a** with only minor amounts of **12b** being formed. This result suggests that the oxocarbenium ion **18** partly contributes, although most of the reaction proceeds through **19**. To realize a further shift in the equilibrium toward **19**, the more electron-donating *p*-anisyl group was introduced, as described above. Indeed, the reaction of **16** gave the nucleoside **17** as the sole product, which is consistent with our proposed mechanism (Scheme 3).



Scheme 4: Synthesis of nucleoside phosphonate **25**.

Completion of the synthesis of a nucleoside constructed on a branched-*threo*-tetrofuranose scaffold led us to our second project, i.e., the synthesis of a nucleoside phosphonate derivative. Compound **17** was converted into a 4-ethoxypyrimidone derivative in preparation for its assembly into a nucleoside phosphonate and the conversion of uracil into cytosine, since our final target was the production of a cytidine phosphonate derivative. Treatment of **17** with the Vilsmeyer reagent gave a 4-chloropyrimidone derivative.[13] This unstable intermediate was quickly treated with sodium ethoxide to give the deprotected 4-ethoxypyrimidone derivative **20**. After again protecting the primary hydroxyl group with a TBDPS group, the resulting **21** was assembled by the reaction with diethyl [(trifluoromethanesulfonyl)oxy]methanephosphonate and LHMDS[14] to give the phosphonate **22** in 86% yield. After deprotection of the silyl group, the conversion of **22** to a cytosine derivative via reacting it with methanolic ammonia at 100 °C in a sealed tube gave compound **24**, one ethyl group of which was unexpectedly deprotected. Finally, deprotection of remaining ethyl group by treatment with TMSI gave the desired cytidine phosphonate **25** in good yield (Scheme 4).

In conclusion, we report on the design and synthesis of a novel nucleoside constructed on a branched-*threo*-tetrofuranose skeleton which has the potential to serve as a useful nucleotide building block for synthesizing novel ONs for antisense and antigene applications. As a demonstration of its synthetic usefulness, we also synthesized a new cytidine phosphonate **25** from the obtained nucleoside. It is interesting to note that the cytidine phosphonate **25** has a unique structure that is analogous to cidofovir[15] as well as PMDTA[7] and would be expected to have promise for use as an antiviral agent. Biological evaluations of **25** are currently in progress and the results will be reported elsewhere.

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at.xxxxx.