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New Synthesis of (±)-Isonucleosides

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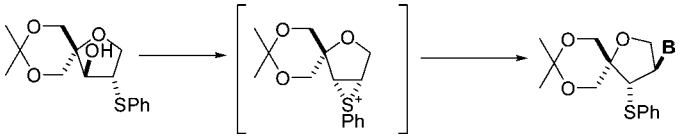
ABSTRACT



A novel method for synthesizing isonucleosides, a new class of anti-HIV nucleosides, is described. 2,2-Dimethyl-1,3-dioxan-5-one was converted into a dioxabicyclohexane derivative in six steps. After cleaving the epoxide group with thiophenol, the resulting product was subjected to the Mitsunobu reaction in the presence of a nucleobase to give the desired isonucleoside derivative via migration of the thiophenyl group. Removal of the thiophenyl group under radical conditions followed by deprotection led to the 4′-substituted 2′,3′-dideoxyisonucleosides as a racemic mixture.

Nucleoside reverse transcriptase inhibitors (NRTIs) play a critical role in the treatment of AIDS and are referred to as HAART (highly active antiretroviral therapy). Even though HAART can efficiently suppress human immunodeficiency virus (HIV) loading and greatly improves patient lifespan, the emergence of drug-resistant strains of the virus is still a serious problem.[1] Thus, the development of new drugs effective for HIV is constantly in demand. In searching for novel NRTIs, we focused on isonucleosides,[2] nucleoside derivatives transposing a nucleobase moiety from the 1′- to the 2′-position.[3] This novel category is represented by isodideoxyadenosine[3] (isoddA, **1**, Figure 1) which has potent anti-HIV-1 activity with superior acid tolerance, in comparison with dideoxynucleoside analogues, didanosine[4] (ddI, **2**) and zaclcitabine[4] (ddC, **3**), which are currently in clinical use. IsoddA **1** is so attractive that it is also resistant to enzymatic hydrolysis by nucleoside phosphorylase.[3c] Recent reports regarding the potent anti-HIV-1 activity of 4′-

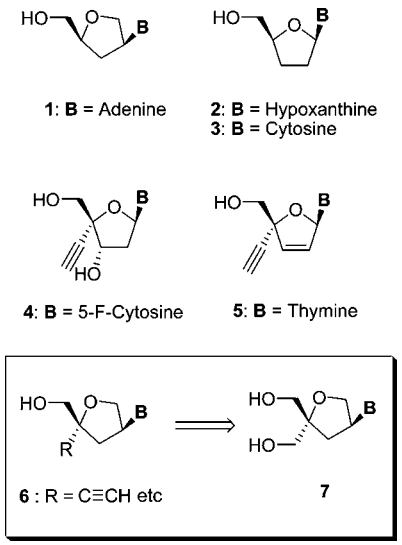


Figure 1. Structures of anti-HIV nucleosides.

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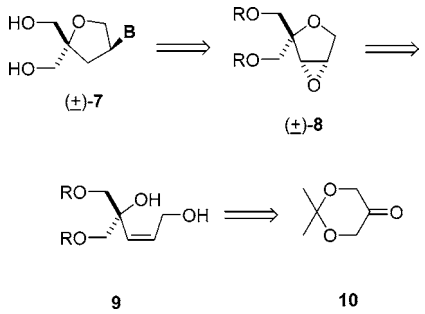
substituted nucleosides **4**[5] including a D4T derivative **5**[6] prompted us to investigate the preparation of 4′-substituted 2′,3′-dideoxyisonucleosides **6** as a potential anti-HIV agent.

To our knowledge, the synthesis of 4′-substituted 2′,3′-dideoxyisonucleosides **6** is quite limited, and a report by Nair et al. concerning the synthesis of D- and L-enantiomers of 2′,3′-dideoxy-4′-hydroxymethylisonucleosides **7** was particularly interesting.[7] Although the compounds themselves were inactive against HIV, they represent a key intermediate in the synthesis of various 4′-substituted 2′,3′-dideoxyisonucleosides **6**. In this report, we describe a novel and convenient synthesis of 4′-hydroxymethylisonucleosides **7**.

Synthesizing new compounds in racemic form would have the advantage that the antiviral activities of both enantiomers can be assayed in one procedure. Therefore, we decided to synthesize a racemic mixture of 4′-substituted nucleosides **6** by a method that can potentially be applied to a chiral synthesis. Following this concept, we attempted to synthesize (±)-**7**, the key intermediate for synthesizing **6**, from achiral 2,2-dimethyl-1,3-dioxan-5-one **10** by the method shown in Scheme 1.

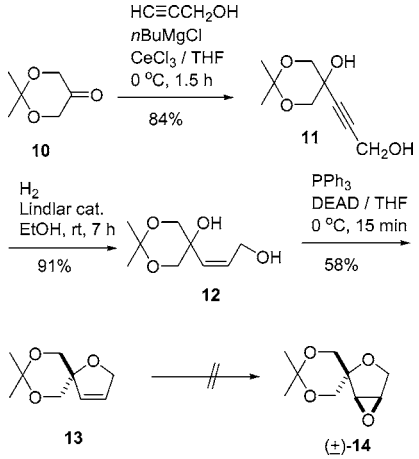
Scheme 1. Retro Synthesis of 4′-Substituted Isonucleosides



A key intermediate of this synthesis should be the dioxabicyclohexane derivative **8** which can serve as an acceptor for a nucleobase to construct an isonucleoside skeleton. The dioxabicyclohexane derivative **8** can be obtained from allyl alcohol **9** which can be prepared from 2,2-dimethyl-1,3-dioxan-5-one **10**. Therefore, we first investigated the addition reaction of a dianion of propargyl alcohol to **10**.

The starting material **10** was readily obtained from tris(trihydroxyethyl)amine hydrochloride as described in the literature.[8] After a lithium or magnesium salt of a propargyl alcohol dianion was prepared by the reaction with *n*-butyllithium or *n*-butylmagnesium chloride, the addition of these dianions to **10** gave diol **11** in moderate yields (30−40% yields). The use of an organocerium reagent,[9] prepared from the magnesium salt of the dianion and anhydrous cerium chloride, greatly improved the yield of **11** (84%). The semi-hydrogenation of **11** in the presence of a Lindlar catalyst gave a (*Z*)-allyl alcohol derivative **12** in 91% yield. Cyclization of the allyl alcohol derivative **12** to a dihydrofuran derivative **13** was achieved by the Mistunobu reaction in 58% yield. However, the epoxidation of the dihydrofuran **13** to give dioxabicyclohexane **14** gave a complex and troublesome mixture (Scheme 2).

Scheme 2. Synthesis of the Dihydrofuran Derivative **13**



Failure to obtain the dioxabicyclohexane derivative led us to synthesize an epoxy alcohol derivative **17** which should be a precursor to **14**. The allyl alcohol derivative **12** was silylated at the primary hydroxyl group to give **15**. Compound **15** was treated with *m*-chloroperoxybenzoic acid (mcpba) to give the epoxide **16** which was desilylated to afford the epoxy alcohol **17**. As in the case of the synthesis of the dihydrofuran derivative **13**, the epoxy alcohol **17** was subjected to intramolecular S_N2 cyclization via the Mitsunobu reaction. Thus, treatment of the epoxy alcohol **17** with PPh_3 and DEAD in THF gave the desired dioxabicyclohexane derivative **14** in excellent yield. It is noteworthy that the oxirane ring of **14** remained intact under the reaction conditions employed. We next attempted the direct introduction of a nucleobase unit into **14** via the nucleophilic opening of the oxirane ring.

When **14** was treated with 6-chloropurine and potassium carbonate in DMF, the reaction was too sluggish. Even under harsh conditions (heating at reflux), the same reaction gave none of the desired isonucleosides (data not shown). It is likely that the weak nucleophilicity of the purine base resulted in the unsuccessful reaction.

To circumvent this difficulty, we attempted to cleave the oxirane ring of **14** by an appropriate thiol derivative which is more nucleophilic. The tactics also include the possibility

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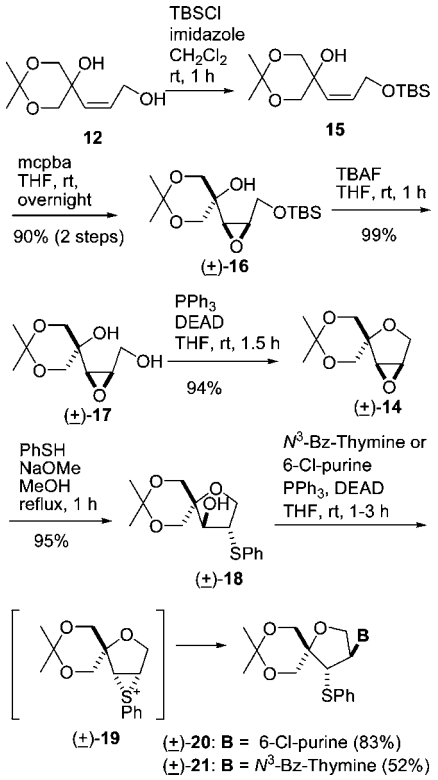
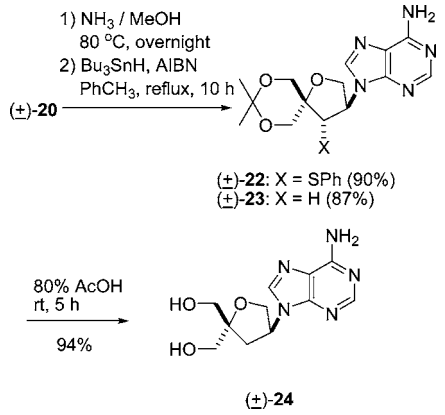
that the introduced sulfide group would assist in the next coupling with nucleobases by forming an episulfonium ion[10] (vide infra). Cleavage of the oxirane moiety of **14** was achieved by treatment with thiophenol and sodium methoxide. The reaction gave **18** as the sole product in 95% yield. The ^{1}H NMR of **18** shows a signal at 4.32 ppm, appearing as a triplet but turned to a doublet by the addition of D_2O. This strongly supports the structure of **18** shown in Scheme 3. This also suggests that the nucleophilic attack of the

Scheme 3. Synthesis of Isonucleosides



phenylsulfide occurred from the less-hindered side of **14**. This fact prompted us to synthesize isonucleosides by the direct Mitsunobu coupling of **14** with a nucleobase because a second nucleophilic substitution would be expected to occur at the less-hindered side of an episulfonium intermediate formed in the first intramolecular S_N2 reaction. The coupling of **18** with 6-chloropurine under Mitsunobu conditions gave the purine isonucleoside derivative **20** in 83% yield. A similar reaction of **18** with N^3-benzoylthymine gave a pyrimidine isonucleoside derivative **21** in 52% yield. The structures of **20** and **21** were confirmed from spectroscopic data, and no traces of regioisomers were observed in the reaction mixtures. The ^{1}H NMR spectra of **20** and **21** show the signals corresponding to protons connected to a carbon at which the nucleobase was bound as quartets at 5.06 and 4.88 ppm, respectively. The ^{1}H NMR data demonstrate that the nucleobases attacked at the less-hindered 2-position and strongly suggest that the coupling reaction proceeds via an episulfonium intermediate **19** which reacts with nucleobases accompanied by the migration of the thiophenol moiety, as expected

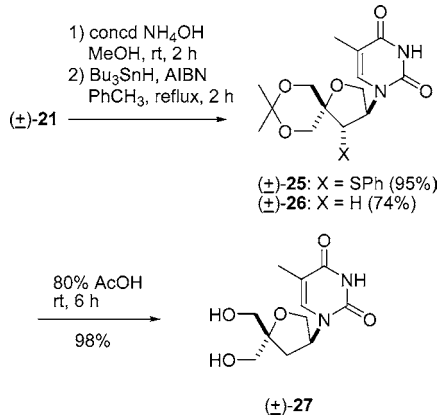
Scheme 4. Synthesis of 2′,3′-Dideoxy-4′-hydroxymethylisoadenosine



(Scheme 3). In the above Mitsunobu reaction, the thiophenyl group functions as a guide for the introduction of the nucleobases into **18**. The reductive removal of the thiophenyl group of **20** and **21** gives the desired 4′-hydroxymethylisonucleosides directly (vide infra). On the other hand, the thiophenyl group could be used to introduce some functional groups by applying the Pummerer reaction.[11] Thus, compounds **20** and **21** should be good intermediates for preparing isonucleoside derivatives having a diversity of substituents.

The purine isonucleoside derivative **20** was treated with methanolic ammonia at 100 °C in a sealed tube to give the isoadenosine derivative **22**. Treatment of **22** with tributyltin hydride in the presence of AIBN in refluxing toluene gave **23** which was deprotected under acidic conditions to give 2′,3′-dideoxy-4′-hydroxymethylisoadenosine **24** in 94% yield. Similarly, the pyrimidine derivative **21** was converted to 3′-deoxy-4′-hydroxymethylisothymidine in three steps: (1) debenzoylation, (2) radical desulfurization, and (3) acetal deprotection. The spectroscopic data of **24** and **27** were in agreement with previously reported data (Schemes 4 and 5).[7]

Scheme 5. Synthesis of 3′-Deoxy-4′-hydroxymethylisothymidine



In conclusion, we describe a novel synthesis of 2′,3′-dideoxy-4′-hydroxymethylisonucleosides which can serve as

an intermediate in the synthesis of various 4′-substituted 2′,3′-dideoxyisonucleosides. Compared with previous reports,[7] the total yield of the products has been improved substantially: 2′,3′-dideoxy-4′-hydroxymethylisoadenosine and 3′-deoxyisothymidine were synthesized in 11 steps in total yields of 37% and 22% from **10**, respectively. In addition, the synthetic intermediates, e.g., **20** and **21**, should be good precursors for preparing isonucleosides containing substituents at the C-3′ as well as the 4′-position. The synthesis of other novel 4′-substituted 2′,3′-dideoxyisonucleoside derivatives is currently in progress and will be reported in the future.

Acknowledgment. This work was supported in part by a Grant-in-Aid for Scientific Research (No. 18590103), JSPS (Y.Y.), and by the High Technology Research Program from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Supporting Information Available: Experimental procedures and characterization data for compounds **11**−**27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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