Design and Synthesis of Isonucleosides Constructed on a 2-Oxa-6-thiabicyclo[3.2.0]heptane Scaffold

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Design and Synthesis of Isonucleosides Constructed on a 2-Oxa-6-thiabicyclo[3.2.0]heptane Scaffold[1]

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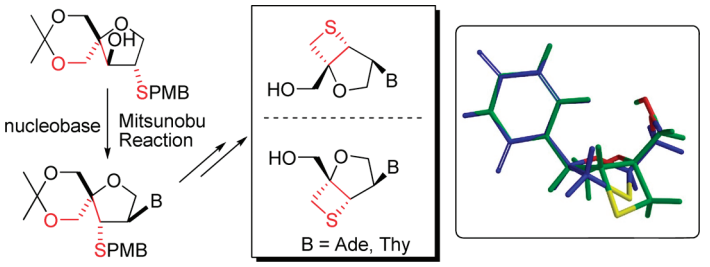

A novel method for the design and synthesis of an isonucleoside containing a 2-oxa-6-thiobicyclo-[3.2.0]heptane skeleton is described. 2,2-Dimethyl-1,3-dioxan-5-one **13** was converted into a dioxabicyclohexane derivative in six steps. After cleavage of the epoxide group with a thiol (thiophenol or PMB mercaptan), the resulting product was subjected to the Mitsunobu reaction in the presence of a nucleobase. The reaction proceeded via the migration of the thiosulfide groups and gave the desired isonucleoside derivatives. In the case of a phenyl sulfide derivative, radical desulfurization followed by deprotection gave 4′-substituted 2′,3′-dideoxyisonucleosides. A PMB sulfide derivative, on the other hand, was converted into the corresponding dimesylate, which was then treated with mercury acetate and trifluoroacetic acid to remove the PMB group. The resulting thiol derivative was treated with DBU to give the desired isonucleoside constructed on a 2-oxa-6-thiobicyclo[3.2.0]heptane scaffold after deprotection. The optimized conformer of the isonucleoside was calculated using DFT at the B3LYP/6-31G** level and was compared with that of lamivudine using model compounds.

Introduction

Since the discovery of 3′-azidothymidine (AZT), the search for more effective chemotherapeutic agents against the human immunodeficiency virus (HIV), a causative agent for AIDS, has continued.[2] To date, more than 20 anti-HIV drugs have now been approved for the treatment of AIDS. The most successful regimen for AIDS, referred to as HAART (highly active anti-retroviral therapy), is the use of a cocktail of anti-HIV drugs, including reverse nucleoside transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs).[3] Although HAART is successful in controlling HIV replication and greatly improves patient lifespan, the virus acquires resistance to the drug under conditions of suboptimal treatment.[4] Therefore, the development of new drugs that are more effective in the treatment of HIV is constantly in demand.

(1) A part of this work has been reported: Yoshimura, Y.; Asami, K.; Matsui, H.; Tanaka, H.; Takahata, H. *Org. Lett.* **2006**, *8*, 6015–6018.

(2) (a) Cihlar, T.; Ray, A. S. *Antiviral Res.* **2010**, *85*, 39–58. and references cited therein. (b) Yamada, K.; Sakata, S.; Yoshimura, Y. *J. Org. Chem.* **1998**, *63*, 6891–6899. (c) Yoshimura, Y.; Yamazaki, Y.; Kawahata, M.; Yamaguchi, K.; Takahata, H. *Tetrahedron Lett.* **2007**, *48*, 4519–4522. (d) Yoshimura, Y.; Ohta, M.; Imahori, T.; Imamichi, T.; Takahata, H. *Org. Lett.* **2008**, *10*, 3449–3452.

(3) Esté, J. A.; Cihlar, T. *Antiviral Res.* **2010**, *85*, 25–33.

(4) (a) Meadows, D. C.; Gervey-Hague, J. *ChemMedChem* **2006**, *1*, 16–29. (b) Imamichi, T. *Curr. Pharm. Des.* **2004**, *10*, 4039–4053.

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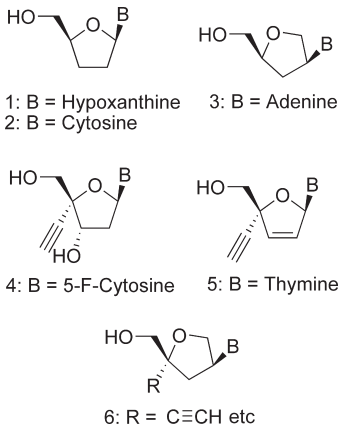


FIGURE 1. Structures of some anti-HIV nucleosides.

One simple and efficient route to obtain novel NRTIs is to design and synthesize nucleoside analogues by structural transformation of known anti-HIV drug based on structure−activity relationship (SAR) studies of NRTIs. For example, dideoxynucleosides, e.g., didanosine (ddI, **1**)[5] and zalcitabine (ddC, **2**),[5] are NRTIs and are critical components of HAART. The transposition of a nucleobase moiety of a dideoxynucleoside from the anomeric to the 2′-position creates isoadenosine **3**, which preserves anti-HIV activity.[6,7] In addition, the transformation could significantly improve the stability of the glycoside bond of dideoxynucleosides, allowing the bond to be resistant to both acidic and enzymatic hydrolysis.[8] Similarly, a report regarding the potent anti-HIV-1 activity of 4′-ethynyl nucleosides such as **4**[9] stimulated the synthesis of the corresponding D4T derivative **5** which proved to have anti-HIV activity.[10] From these results, 4′-substituted 2′,3′-dideoxyisonucleosides **6** are generally considered to be an interesting target as a potential anti-HIV agent (Figure 1).

To our knowledge, attempts to synthesize 4′-substituted 2′,3′-dideoxyisonucleosides have been quite limited, with the exception of a report by Nair et al. concerning the synthesis of the D- and L-enantiomers of 2′,3′-dideoxy-4′-hydroxymethyl derivatives of **6**.[11] However, the synthesis is time-consuming and complex, a fact that discourages further attempts to produce 4′-substituted isonucleoside derivatives. As a result, SARs for the 4′-substituted isonucleosides have not been explored in any detail. To overcome these problems, a more efficient and straightforward methodology for the synthesis of isonucleosides that is applicable to the preparation of the 4′-substituted derivatives would be highly desirable. Therefore, we focused on addressing these problems and developed a strategy for the synthesis of 4′-hydroxymethylisonucleosides which could serve as an intermediate in the synthesis of a variety of 4′-substituted isonucleosides, including a 4′-ethynyl derivative. In addition, using this strategy, we also attempted to synthesize novel isonucleosides **7**, constructed on a 2-oxa-6-thiobicyclo[3.2.0]heptane scaffold. Compound **7** was designed on the basis of lamivudine **8**[12] and the known anti-HIV nucleoside **9**.[13] As can be seen in Figure 2, it is clear that the synthesis and evaluation of the anti-HIV activity of racemic **7** would be efficient because of the structural similarity of the L- and

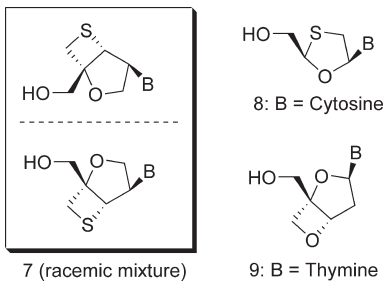
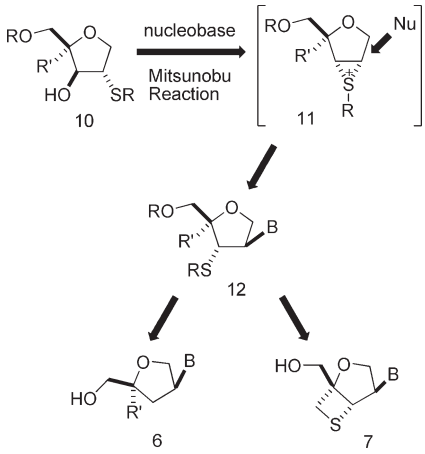


FIGURE 2. Structures of novel isonucleosides built on a 2-oxa-6-thiobicyclo[3.2.0]heptane scaffold.

SCHEME 1. Strategy for the Synthesis of 4′-Substituted Isonucleosides 6 and Bicycloisonucleosides 7



(5) Mitsuya, H.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 1911–1915.

(6) (a) Nair, V.; Nuesca, Z. M. *J. Am. Chem. Soc.* **1992**, *114*, 7951–7953. (b) Huryn, D. M.; Sluboski, B. C.; Tam, S. Y.; Weigele, M.; Sim, I.; Anderson, B. D.; Mitsuya, H.; Border, S. *J. Med. Chem.* **1992**, *35*, 2347–2354. (c) Nair, V. In *Recent Advances in Nucleosides*; Chu, C. K., Eds.; Elsevier Science B.V.: Amsterdam, 2002; pp 149−166 and references cited therein.

(7) Recent reports regarding isonucleosides: (a) Estévez, L.; Besada, P.; Fall, Y.; Teijeira, M.; Terán, C. *Synthesis* **2010**, 425–430. (b) D'Alonzo, D.; Van Aerschot, A.; Guaragna, A.; Palumbo, G.; Schepers, G.; Capone, S.; Rozenski, J.; Herdewijn, P. *Chem.—Eur. J.* **2009**, *15*, 10121–31. (c) Sanki, A. K.; Bhattacharya, R.; Atta, A. K.; Suresh, C. G.; Pathak, T. *Tetrahedron* **2008**, *64*, 10406–10416. (d) Bouisset, T.; Gosselin, G.; Griffe, L.; Meillon, J.-C.; Storer, R. *Tetrahedron* **2008**, *64*, 6657–6661. (e) Nair, V.; Piotrowska, D. G.; Okello, M.; Vadakkan, J. *Nucleosides, Nucleotides Nucleic Acids* **2007**, *26*, 687–690. (f) Jiang, C.; Li, B.; Guan, Z.; Yang, Z.; Zhang, L.; Zhang, L. *Bioorg. Med. Chem.* **2007**, *15*, 3019–3025. (g) Chun, B.-K.; Wang, P.; Hassan, A.; Du, J.; Tharnish, P. M.; Murakami, E.; Stuyver, L.; Otto, M. J.; Schinazi, R. F.; Watanabe, K. A. *Nucleosides, Nucleotides Nucleic Acids* **2007**, *26*, 83–97. (h) Wang, F.; Yang, Z.-J.; Jin, H.-W.; Zhang, L.-R.; Zhang, L.-H. *Tetrahedron: Asymmetry* **2007**, *18*, 2139–2146. (i) Yoo, S. J.; Kim, H. O.; Lim, Y.; Kim, J.; Jeong, L. S. *Bioorg. Med. Chem.* **2002**, *10*, 215–226.

(8) Nair, V.; Jahnke, T. S. *Antimicrob. Agents Chemother.* **1995**, *39*, 1017–1029.

(9) Ohrui, H.; Kohgo, S.; Kitano, K.; Sakata, S.; Kodama, E.; Yoshimura, K.; Matsuoka, M.; Shigeta, S.; Mitsuya, H. *J. Med. Chem.* **2000**, *43*, 4516–4525.

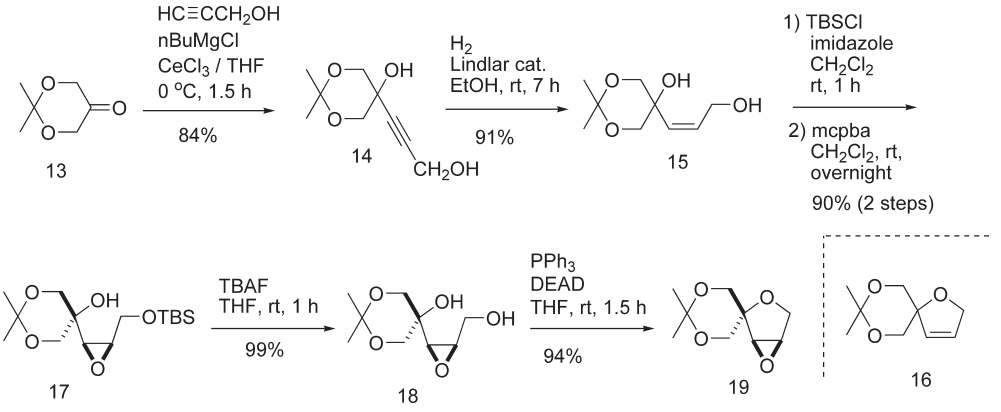
(10) (a) Dutschman, G. E.; Grill, S. P.; Gullen, E. A.; Haraguchi, K.; Takeda, S.; Tanaka, H.; Baba, M.; Cheng, Y.-C. *Antimicrob. Agents Chemother.* **2004**, *48*, 1640–1646. (b) Nitada, T.; Wang, X.; Kumamoto, H.; Haraguchi, K.; Tanaka, H.; Cheng, Y.-C.; Baba, M. *Antimicrob. Agents Chemother.* **2005**, *49*, 3355–3360.

(11) (a) Zintek, L. B.; Jeon, G. S.; Nair, V. *Heterocycles* **1994**, *37*, 1853–1864. (b) Nair, V.; Zintek, L. B.; Jeon, G. S. *Nucleosides Nucleotides* **1995**, *14*, 389–391.

(12) (a) Coates, J. A.; Cammack, N.; Jenkinson, H. J.; Mutton, I. M.; Pearson, B. A.; Storer, R.; Cameron, J. M.; Penn, C. R. *Antimicrob. Agents Chemother.* **1992**, *36*, 202–5. (b) Coates, J. A.; Cammack, N.; Jenkinson, H. J.; Jowett, A. J.; Jowett, M. I.; Pearson, B. A.; Penn, C. R.; Rouse, P. L.; Viner, K. C.; Cameron, J. M. *Antimicrob. Agents Chemother.* **1992**, *36*, 733–9.

(13) O-yang, C.; Kurz, W.; Eugui, E. M.; McRoberts, M. J.; Verheyden, J. P. H.; Kurz., L. J.; Walker, K. A. M. *Tetrahedron Lett.* **1992**, *33*, 41–44.

SCHEME 2. Synthesis of the Dioxabicyclohexane Derivative 19



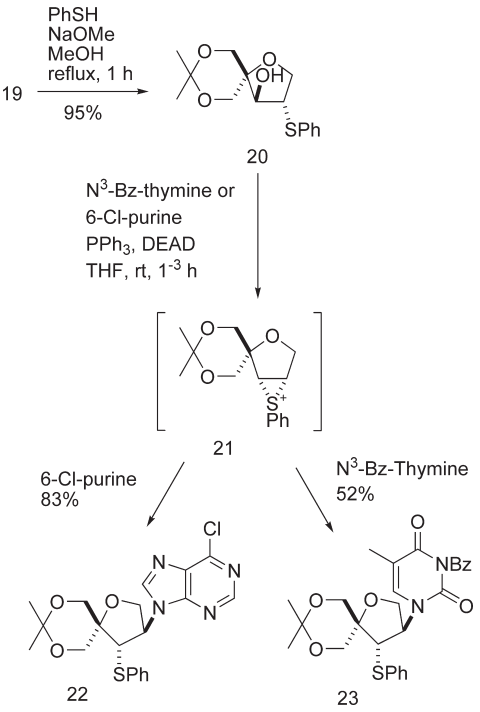
D-enatiomers of **7** with **8** and **9**, respectively. This is also the case for 4′-substituted isonucleosides, since the L-enantiomers of nucleoside derivatives have occasionally been found to have anti-HIV activity with lesser toxicity than the D-isomers.[12,14] In addition, synthesizing new compounds in racemic form would have the advantage that the anitiviral activities of both enatiomers could be assayed in one procedure. To address this issue, we attempted to synthesize racemic mixture of the target compounds **6** and **7** by a method that could potentially be applied to a chiral synthesis.

Following this concept, we attempted to synthesize **6** and **7** from a common intermediate **12**, the desulfurization of which would give the 4′-substituted isonucleoside **6**. The formation of a thietane ring around 3′- and 4′-positions, on the other hand, would afford bicycloisonucleoside **7**. A key to the success of the synthesis is the development of a nucleophilic glycosylation reaction accompanying the sulfide migration, by which the product **10** could serve as an acceptor for a nucleobase to give the desired intermediate **12** (Scheme 1).

Results and Discussion

The known ketone **13**, readily obtained from tris-(trihydroxyethyl)amine hydrochloride as described in the literature,[15] was treated with the lithium or magnesium salt of the propargyl alcohol dianion. The addition of this dianion to **13** gave diol **14** in moderate yields (30−40% yield). The reaction was greatly improved when an organocerium reagent,[16] prepared from the magnesium salt of the dianion of propargyl alcohol and anhydrous cerium chloride, was used and gave the allyl alcohol **14** in 84% yield. The semihydrogenation of **14** in the presence of a Lindlar catalyst gave the (*Z*)-allyl alcohol derivative **15** in 91% yield. We hypothesized that the cyclization of the allyl alcohol to the dihydrofuran derivative **16** and subsequent epoxidation would give the dioxabicyclohexane derivative **18**. However, this procedure failed because of the unexpected instability of the dihydrofuran derivative **16** under the oxidative conditions used in the reaction (data not shown).

SCHEME 3. Synthesis of Isonucleosides Using the Mitsunobu Reaction



Failure to obtain the dioxabicyclohexane derivative prompted us to employ an epoxy alcohol **18** as a precursor in constructing a tetrahydrofuran skeleton. Silylation of the primary alcohol of **14** and subsequent treatment with *m*-chloroperoxybenzoic acid (*m*-CPBA) gave epoxide **17** in good yield. Desilylation of the epoxide **17** by treatment with TBAF gave the epoxy alcohol **18**, which was subjected to intramolecular S_N2 cyclization via Mitsunobu reaction conditions. The intramolecular etherification of **18** was carried out by treatment with PPh_3 and DEAD in THF to give the desired dioxabicyclohexane derivative **19** in excellent yield. It is obvious that the oxirane ring of **18**, which remained intact under the reaction conditions used, could restrict its conformation suitable for cyclization (Scheme 2).

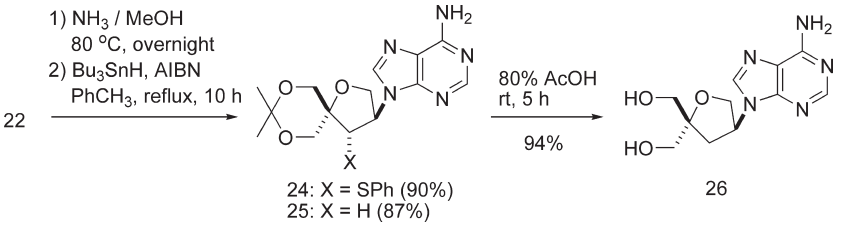
Our next effort was to cleave the oxirane ring of **19** with an appropriate thiol derivative, followed by the introduction of

(14) (a) Lin, T. S.; Luo, M. Z.; Liu, M. C.; Pai, S. B.; Dutschman, G. E.; Cheng, Y. C. *J. Med. Chem.* **1994**, *37*, 798–803. (b) Lin, T. S.; Luo, M. Z.; Liu, M. C.; Zhu, Y. L.; Gullen, E.; Dutschman, G. E.; Cheng, Y. C. *J. Med. Chem.* **1996**, *39*, 1757–9.

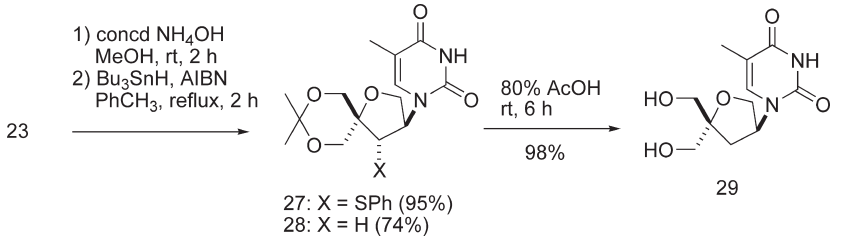
(15) Hoppe, D.; Schmincke, H.; Kleeman, H.-W. *Tetrahedron* **1989**, *45*, 687–694.

(16) Inamoto, T.; Takiyama, N.; Nakamura, K. *Tetrahedron Lett.* **1985**, *26*, 4763–4766.

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



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



the nucleobase moiety. As mentioned above, our strategy assumed that the introduced sulfide group would play the following roles: (1) provide assistance in the next coupling with nucleobases by forming an episulfonium ion, (2) serve as a convertible group to hydrogen for the synthesis of the 4′-substituted isonucleoside, and (3) provide a unit for constructing a thietane ring for a 2-oxa-6-thiobicyclo[3.2.0]heptane skeleton of novel isonucleosides. We initially attempted the reaction of **19** with thiophenol, the product of which was intended for use in examining the nucleophilic glycosylation reaction and conversion to the 4′-substituted isonucleosides. Cleavage of the oxirane moiety of **19** was achieved by treatment with sodium thiophenoxide to give the phenyl sulfide derivative **20** as the sole product in 95% yield. The structure of **20** was confirmed on the basis of ^{1}H NMR spectral data, which showed a triplet signal, corresponding to H-3 at 4.32 ppm, but which collapsed to a doublet on the addition of D_2O. It is clear that the nucleophilic attack of the phenyl sulfide occurred from the less hindered side of **19** as would be expected. With the phenyl sulfide derivative **20** in hand, the nucleophilic glycosylation reaction was next examined. Our first choice for the reaction was the Mitsunobu reaction conditions in the presence of a nucleobase.[17] Fortunately, **19** coupled with 6-chloropurine under Mitsunobu conditions to give the purine isonucleoside derivative **22** in 83% yield. Similarly, the reaction of **19** with N^3-benzoylthymine gave the pyrimidine isonucleoside derivative **23** in 52% yield. In the reaction mixture, an O^2-alkylated thymine derivative was not found. Both reactions proceeded in a regiospecific manner, and no traces of regioisomers were detected in the reaction mixtures. The structures of **22** and **23** were unambiguously determined from spectroscopic data. The ^{1}H NMR spectra of **22** and **23** show the signals corresponding to protons connected to the carbon to which the nucleobase was bound as quartets at 5.06 and 4.88 ppm, respectively. These data provide clear proof that C−N bond formation occurred at the 2-position since it is predictable that the corresponding proton of 3-substituted product would appear as a doublet peak. Therefore, the results strongly suggest that the nucleobases are attacked at the less hindered 2-position, accompanied by the migration of the thiophenol moiety after an intramolecular nucleophilic substitution by the phenyl sulfide group, with the subsequent formation of an episulfonium intermediate **21**, as expected (Scheme 3).

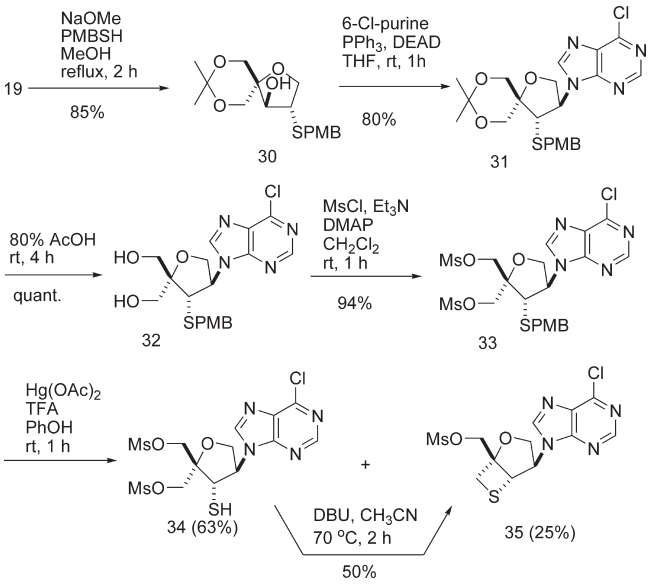
The purine isonucleoside derivative **22** was treated with methanolic ammonia at 100 °C in a sealed tube to give the isoadenosine derivative **24**. Desulfurization of **24** by treatment with tributyltin hydride in the presence of AIBN in refluxing toluene gave **25**, which was deprotected under acidic conditions to give the 2′,3′-dideoxy-4′-hydroxymethylisoadenosine **26** in 94% yield. In the same manner, the pyrimidine derivative **23** was debenzoylated followed by radical desulfurization to give the 3′-deoxy derivative **28**. Finally, deprotection of the acetal group of **28** gave 3′-deoxy-4′-hydroxymethylisothymidine **29** in 98% yield. Spectroscopic data for **26** and **29** were consistent with previously reported data[11] (Schemes 4 and 5).

The success of the sulfur-assisted Mitsunobu reaction for introducing a nucleobase prompted us to start a second project, with the goal of synthesizing isonucleosides constructed on a 2-oxa-6-thiobicyclo[3.2.0]heptane skeleton. As described for the synthesis of **20**, the oxirane ring of **19** was cleaved by treatment with the sodium salt of PMB mercaptan to give the PMB sulfide **30** as the sole product in 85% yield. The sulfur-assisted Mitsunobu reaction of **30** in the presence of 6-chloropurine proceeded efficiently, similar to the case of **20**, to give the purine isonucleoside **31** in 80% yield. On the basis of ^{1}H NMR analyses, there is no doubt that the reaction occurred via the formation of an episulfonium ion followed by migration and substitution at the 2-position (see the Experimental Section). After removal of the acetal group of **31** by acid treatment, the resulting free isonucleoside **32** was converted to dimesylate **33** in good yield. The PMB group of **33** was deprotected by treatment with mercury(II) acetate and phenol in TFA[18] to give a mixture of thiol **34** and thietane **35** in 63 and 25% yields, respectively. The ^{1}H NMR

(17) For example, see: Yoshimura, Y.; Moon, H. R.; Choi, Y.; Marquez, V. E. *J. Org. Chem.* **2002**, *67*, 5938–5945.

(18) Narayan, R. S.; VanNieuwenhze, M. S. *Org. Lett.* **2005**, *7*, 2655–2658.

SCHEME 6. Construction of a 2-Oxa-6-thiobicyclo-[3.2.0]heptane Scaffold



spectrum of **35**, showing loss of one mesylate and a singlet peak corresponding to H-3′ at 3.94 ppm, was consistent with the assigned structure (vide infra). Additionally, the mass spectrum of the compound showed a molecular ion peak (m/z) at 376, thus further supporting the structure assignment. It is interesting to note that thietane **35** was spontaneously formed even under the acidic conditions used for deprotecting the PMB group. The major thiol derivative **34** was also converted to **35** in moderate yield by treatment with DBU in acetonitrile at 70 °C (Scheme 6).

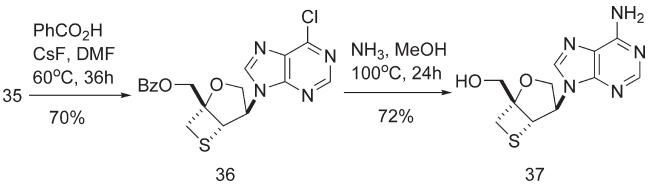
Compound **35** was treated with benzoic acid in the presence of cesium fluoride[19] in an S_N2 reaction to give the 5′-benzoate derivative **36**. Finally, deprotection and conversion to the adenine were achieved by the treatment of **36** with methanolic ammonia in a sealed tube at 100 °C to give desired bicycloisoadenosine **37** in 72% yield (Scheme 7).

The isothymidine analogue of compound **37** was constructed. The common intermediate **30** was subjected to the sulfur-assisted Mitsunobu reaction in the presence of N^3-benzoylthymine to give the isothymidine derivative **38** in 59% yield. After removal of the acetal group followed by mesylation, the PMB group of dimesylate **40** was removed by treatment with mercury(II) acetate and phenol in TFA[19] to give the thiol derivative **41** in quantitative yield. The ^{1}H NMR spectrum of **41** revealed that deprotection of the benzoyl group also occurred under the reaction conditions. In contrast to the results for isoadenosine, a thietane derivative was not formed in this reaction. Thus, the intramolecular nucleophilic substitution of the thiol derivative **41** was achieved by treatment with DBU in acetonitrile to give the thietane **42** in 60% yield. The synthesis of the desired isothymidine **44** was successfully achieved by conversion of the mesylate to a benzoate by an S_N2 reaction of **42**, followed by treatment with aqueous NH_4OH (Scheme 8).

The formation of a thietane ring resulted in a conformational change (sugar puckering) of isonuclceosides, as

(19) Otera, J.; Nakazawa, K.; Sekoguchi, K.; Orita, A. *Tetrahedron* **1997**, *53*, 13633–13640.

SCHEME 7. Synthesis of Isoadenosine Constructed on the 2-Oxa-6-thiobicyclo[3.2.0]heptane Scaffold



evidenced by ^{1}H NMR (vide supra). Similar to the case for **35**, in the ^{1}H NMR spectrum of **42**, the H-3′ proton signal appeared as a singlet at 3.81 ppm. In addition, the H-2′ proton appeared as a doublet at 4.93 ppm due to the loss of coupling with one of the H-1 protons as well as the H-3′ proton. Needless to say, this tendency for coupling constants was maintained in all of the compounds that contain a thietane ring fused at the 3′ and 4′-positions (see the Experimental Section). To determine the preferred conformation of isonucleosides constructed on a 2-oxa-6-thiobicyclo[3.2.0]-heptane skeleton, theoretical calculations using an isodeoxyuridine derivative **45** as a model compound were performed. Possible conformers of **45** were surveyed by molecular mechanics (MM) calculations and were optimized by theoretical calculations using density functional theory (DFT) quantum mechanical calculations at the B3LYP/6-31G** level.[20] The resulting 3D structure of **45** with the lowest energy showed that the dihedral angles between one of the H-1′ and H-2′ and between H-2′ and H-3′ were 93.2 and 99.4°, respectively (Figure 3). The results adequately account for the ^{1}H NMR data reported above and revealed that the simulated structure was in good agreement with the conformation adapted in solution.

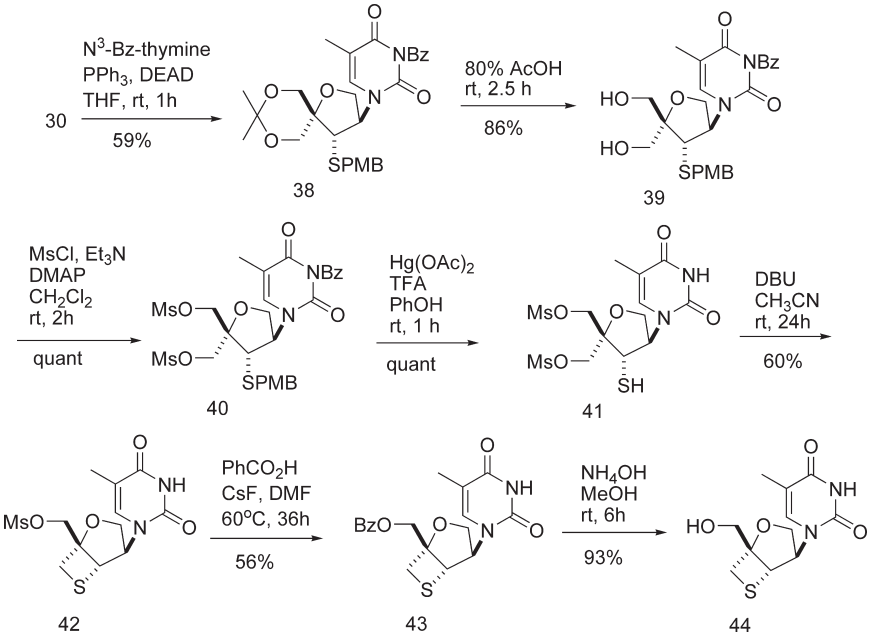
The conformations of nucleosides are defined by the glycosyl torsion angle, the conformation around the C4′−C5′ bond, and sugar puckering.[21] Among these, sugar puckering of nucleosides is important for recognition by enzymes utilizing nucleosides and nucleotides. NRTIs need to be activated by being transformed into their corresponding triphosphate forms which inhibit the reverse transcriptase encoded by HIV. The first step in this transformation is catalyzed by deoxynucleoside kinase, which is reported to preferentially recognize an *S*-form of sugar puckering (C2′-endo).[22] Thus, we calculated the optimized conformer of 3TU **46**, a uracil congener of lamivudine, and compared the findings with the calculated conformer of **45**. Since our compounds, including **45**, are members of a class of isonucleosides in which the base moiety is transposed from the 1′- to the 2′ position, it is difficult to make a direct comparison of sugar puckering. Therefore, we evaluated these structures with a focus on the dispositions of the base, the 5′-hydroxymethyl group, and hetero atoms in a pseudosugar ring. An optimized conformer of **46** was obtained by the same method as described above (DFT calculations using B3LYP/6-31G**). As depicted in

(20) Yoshimura, Y.; Yamazaki, Y.; Saito, Y.; Takahata, H. *Tetrahedron* **2009**, *65*, 9091–9102.

(21) Saenger, W. *Principles in Nucleic Acid Structure*; Springer-Verlag: New York, 1984.

(22) (a) Marquez, V. E.; Ben-Kasus, T.; Barchi, J. J., Jr.; Green, K. M.; Nicklaus, M. C.; Agbaria, R. *J. Am. Chem. Soc.* **2004**, *126*, 543–549. (b) Sabini, E.; Hazra, S.; Konrad, M.; Lavie., A. *J. Med. Chem.* **2007**, *50*, 3004–3014. (c) Russ, P. L.; Gonzalez-Moa, M. J.; Vu, B. C.; Sigano, D. M.; Kelley, J. A.; Lai, C. C.; Deschamps, J. R.; Hughes, S. H.; Marquez, V. E. *ChemMedChem.* **2009**, *4*, 1354–1363.

SCHEME 8. Synthesis of Isothymidine Constructed on the 2-Oxa-6-thiobicyclo[3.2.0]heptane Scaffold



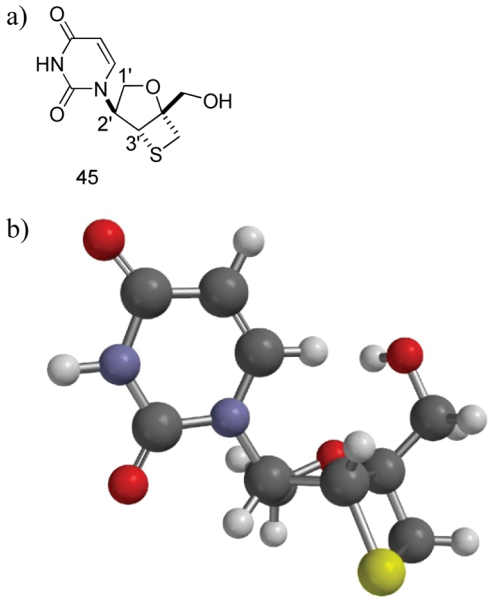


FIGURE 3. Structure of model compound **45**: (a) structural formula of **45**; (b) 3D-structure of optimized **45** shown as a ball-and-stick model.

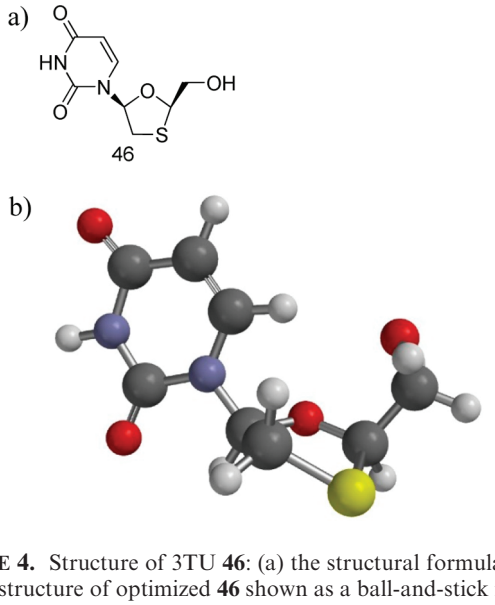


FIGURE 4. Structure of 3TU **46**: (a) the structural formula of **46**; (b) 3D-structure of optimized **46** shown as a ball-and-stick model.

Figure 4, the conformer, the sugar puckering of which had a *C*2′-endo configuration, is consistent with a previous report regarding the calculation results for lamivudine (Figure 4).[23]

With information on the optimized conformer of **46** in hand, the findings were compared with those for **45** described above. To estimate the difference in the positions of functional groups between **45** and **46**, we overlaid the uracil ring of the model compounds, and the results are shown in Figure 5. The positions of oxygen and sulfur atoms in the pseudosugar ring are similar as originally expected. On the other hand, the positions of the hydroxymethyl groups are slightly different. In the case of isonucleoside **45**, the distance between H-6 of the uracil ring and the 5′-oxygen atom is 2.197 Å, while the 5′-oxygen atom of 3TU **46** occupies a position 0.25 Å away from that of **45**. The distance discussed above should be important for considering antiviral activity[24] because the total conformational differences of nucleoside analogues directly influence it. Therefore, even this small difference might make an impact on antiviral activity since enzymes, e.g., deoxynucleoside kinase, recognize their substrate conformations strictly as mentioned above. Indeed, the antiviral evaluation revealed that neither isonucleosides **37**

(23) Yekeler, H. *THEOCHEM* **2004**, *684*, 223–230.

(24) Van Roey, P.; Salerno, J. M.; Chu, C. K.; Schinazi, R. F. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 3929–3933.

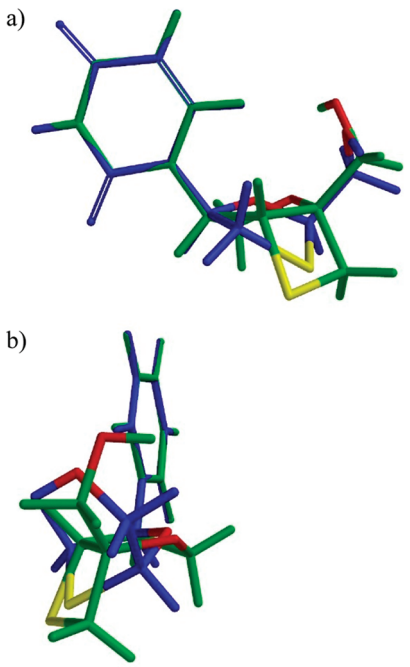


FIGURE 5. Comparison of the optimized conformers of isonucleoside **45** (green) and 3TU **46** (blue). The overlay is based on the atoms in the uracil ring. Oxygen atoms in a sugar portion are shown in red and sulfur atoms in yellow: (a) view from the 2′- and 3′-side; (b) view from the 4′-side.

nor **44** showed antiviral activities against HIV-1 or herpes virus (HSV-1).[25]

In conclusion, we describe a new synthesis of 2′,3′-dideoxy-4′-hydoxymethylisonucleosides, which can serve as intermediates in the synthesis of various 4′-substituted 2′,3′-dideoxyisonucleosides. The synthesis was achieved by using the sulfur-assisted Mitsunobu reaction for introducing a nucleobase onto the sugar portion. In addition, the synthetic intermediates, e.g., **22** and **23**, represent potentially good precursors for preparing isonucleosides containing substituents at the C-3′ as well as the 4′-positions. Thus, by applying the developed method, we synthesized novel isonucleoside analogues constructed on a 2-oxa-6-thiobicyclo[3.2.0]-heptane scaffold. Although the isonucleosides that were designed were inactive against HIV-1 and HSV-1, theoretical calculations using model compounds revealed that the isonucleoside built on the 2-oxa-6-thiobicyclo[3.2.0]heptane scaffold was a good mimic of the *C*2′-endo conformer (*S*-form) of lamivudine. Therefore, such new isonucleosides may be useful as biological tools for investigating steric interactions of enzymes that recognize lamivudine with its analogues as a substrate.

Experimental Section

General Methods. All of the reactions described were performed under argon atmosphere unless other conditions are described. Melting points are uncorrected. NMR spectra were recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C) using $CDCl_3$ or DMSO-d_6 with tetramethylsilane as internal standard. Mass spectra were obtained by EI or FAB mode. Silica gel used for chromatography was Fuji Silysia PSQ 100B. All of the reactions described below were performed under argon atmosphere.

5-(3-Hydroxyprop-1-ynyl)-2,2-dimethyl-1,3-dioxan-5-ol (14). To a solution of *n*-BuMgCl (39.5 mL, 35.4 mmol, 0.90 M THF solution) in THF was slowly added propargyl alcohol (1.03 mL, 17.7 mmol) at 0 °C. After the mixture was stirred at °C for 80 min, the whole mixture was added to an anhydrous suspension of $CeCl_3$ in THF (24 mL), which was prepared from $CeCl_3 \cdot 7H_2O$ (6.70 g, 18.0 mmol) by the reported method. After the mixture was stirred for 1.5 h at 0 °C, a THF solution (6 mL) of 2,2-dimethyl-1,3-dioxan-5-one **13**[14] (1.53 g, 11.8 mmol) was added dropwise at 0 °C by cannula. The mixture was stirred at 0 °C for 1.5 h. After being neutralized with satd NH_4Cl, the mixture was vigorously stirred for 15 min. The resulting gummy residue was removed by decantation and filtration through Celite. The filtrate was concentrated under reduced pressure, and the residual solids were washed and extracted with $CHCl_3$. The combined organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (33−50% AcOEt in hexane) to give **14** (1.86 g, 84%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (3H, s), 1.48 (3H, s), 2.16 (1H, t, J = 6.0 Hz), 3.50 (1H, s), 3.77 (2H, d, J = 11.6 Hz), 4.03 (2H, d, J = 11.6 Hz), 4.30 (2H, d, J = 5.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 27.9, 50.7, 63.2, 68.3, 82.3, 85.5, 98.6; IR (KBr) 3402.4, 1638.0, 1377.5, 1082.8, 1058.8 cm^{-1}; EI-MS (*m*/*z*) 187 ($M^+ + 1$). Anal. Calcd for $C_9H_{14}O_4 \cdot 0.1H_2O$: C, 57.50; H, 7.61. Found: C, 57.58; H, 7.69.

5-((*Z*)-3-*tert*-Butyldimethylsilyloxyprop-1-enyl)-2,2-dimethyl-1,3-dioxan-5-ol (15). A mixture of **14** (2.0 g, 10.8 mmol), Pd−$BaSO_4$ (456 mg), and quinoline (10 drops) was stirred at room temperature for 7 h under H_2 atmosphere. After the catalyst was removed by Celite filtration, the filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (60% AcOEt in hexane) to give **15** (1.84 g, 91%) as a syrup: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (3H, s), 1.48 (3H, s), 3.37 (1H, s), 3.67 (2H, d, J = 12.1 Hz), 3.90 (2H, d, J = 11.6 Hz), 4.30 (2H, s), 5.23 (1H, d, J = 12.6 Hz), 5.89−5.95 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 27.9, 59.1, 68.2, 68.7, 98.2, 127.8, 134.5; IR (neat) 3390.4, 2993.7, 1651.0, 1374.9, 1199.6, 829.9 cm^{-1}; EI-MS (*m*/*z*) 189 ($M^+ + 1$); HRMS calcd for $C_9H_{17}O_4$ 189.1127, found 189.1133.

5-((2*R,3*R**)-3-((*tert*-Butyldimethylsilyloxy)methyloxiran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ol (17).** A mixture of **15** (1.59 g, 8.40 mmol), TBSCl (2.54 g, 16.8 mmol), and imidazole (1.36 g, 20.2 mmol) in CH_2Cl_2 (30 mL) was stirred at room temperature for 1 h. The mixture was diluted with CH_2Cl_2, washed with H_2O and brine, and then dried over Na_2SO_4. After filtration, the solvents were removed under reduced pressure to give crude **15**, which was used for epoxidation without further purification. A solution of *m*-CPBA (6.20 g, 22.2 mmol) in CH_2Cl_2 (50 mL) was added to a solution of crude mixture of TBS ether in CH_2Cl_2 (30 mL) at room temperature. The mixture was stirred at the same temperature overnight. The reaction mixture was washed with satd $NaHCO_3$, 10% $Na_2S_2O_3$, and brine and then dried over Na_2SO_4. After filtration, the solvents were removed under reduced pressure, and the residue was purified by silica gel column chromatography (10% AcOEt in hexane) to give **17** (2.41 g, 90%, two steps) as a syrup: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (6H, d, J = 2.9 Hz), 0.81 (9H, s), 1.35 (3H, s), 1.39 (3H, s), 3.03 (1H, s), 3.12 (1H, dd, J = 9.7, 4.4 Hz), 3.26 (1H, d, J = 4.4 Hz), 3.65−3.73 (3H, m), 3.80 (1H, d, J = 12.1 Hz), 3.92−3.93 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3, 22.5, 24.3, 25.6, 25.7, 25.8, 57.6, 58.1, 61.1, 64.3, 66.7, 67.3, 98.5; IR (neat) 3444.8, 2955.9, 1373.6, 1256.2, 1079.1, 835.4 cm^{-1}; EI-MS (*m*/*z*) 319 ($M^+ + 1$). Anal. Calcd for $C_{15}H_{30}O_5Si$: C, 56.57; H, 9.49. Found: C, 56.39; H, 9.87.

(2*R,3*R**)-5-(3-(Hydroxymethyl)oxiran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ol (18).** To a solution of **17** (2.37 g, 7.40 mmol) in THF

(25) Compounds **37** and **44** did not show any inhibitory activity against HIV-1 at concentrations up to 100 μM. They excibit no inhibitory activity against HSV-1 at concentrations less than 30 μg/mL.

(20 mL) was added a THF solution of TBAF (14.8 mL, 14.8 mmol) at room temperature. The mixture was stirred at the same temperature for 1 h. After the solvents were removed under reduced pressure, the residue was purified by silica gel column chromatography (1% MeOH in $CHCl_3$) to give **18** (1.49 g, 99%) as a white solid: mp 69−70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (3H, d), 1.48 (3H, s), 2.66 (1H, t, J = 6.5 Hz), 3.15 (1H, d, J = 4.4 Hz), 3.28 (1H, q, J = 5.3 Hz), 3.33 (1H, s), 3.71−3.76 (2H, m), 3.86 (1H, dd, J = 12.6, 5.3 Hz), 3.91 (1H, d, J = 11.6 Hz), 3.96 (1H, d, J = 11.6 Hz), 4.06−4.12 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 24.7, 57.4, 57.5, 60.4, 65.1, 67.1, 98.7; IR (KBr) 3449.3, 3276.2, 1372.7, 1202.51, 1074.3, 1018.7, 831.5 cm^{-1}; EI-MS (m/z); 205 ($M^+ + 1$). Anal. Calcd for $C_9H_{16}O_5$: C, 52.93; H, 7.90. Found: C, 52.84; H, 7.95.

(1*R,5*R**)-2,2′-Dimethyl-3,6-dioxaspiro[bicyclo[3.1.0]hexane-2,5′-[1,3]dioxane] (19).** A mixture of PPh_3 (555 mg, 2.22 mmol) and DEAD (2.2 M solution in toluene, 1.01 mL, 2.22 mmol) was stirred for 5 min at room temperature. To this mixture was added a solution of **18** (227 mg, 1.11 mmol) in THF (5 mL), and the mixture was stirred at room temperature for 1.5 h. After the solvents were removed under reduced pressure, the residue was purified by silica gel column chromatography (5% AcOEt in hexane) to give **19** (193 mg, 94%) as a syrup: mp 75−76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (3H, s), 1,48 (3H, s), 3.68 (1H, dd, J = 11.6, 1.9 Hz), 3.69−3.81 (4H, m), 3.91 (1H, dd, J = 11.6, 1.5 Hz), 4.01−4.04 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 27.0, 56.3, 58.5, 62.2, 63.8, 67.0, 75.0, 98.6; IR (KBr) 2875.7, 1374.1, 1202.5, 1079.8, 864.5 cm^{-1}; EI-MS (m/z) 186 (M^+). Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.08; H, 7.65.

(3*S,4*S**)-8,8-Dimethyl-3-(phenylthio)-1,7,9-trioxaspiro[4.5]-decan-4-ol (20).** To a solution of thiophenol (2.3 mL, 21.5 mmol) in dry methanol (10 mL) was added sodium methoxide (620 mg, 10.7 mmol), and the mixture was stirred at room temperature for 20 min. To this mixture was added a solution of **19** (774 mg, 4.15 mmol) in dry methanol (5 mL). After being kept under reflux for 1 h, the mixture was allowed to cool to room temperature. After the solvents were removed under reduced pressure, the residue was purified by silica gel column chromatography (10% AcOEt in hexane) to give **20** (1.09 g, 95%) as a white solid: mp 100−102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (3H, s), 1,48 (3H, s), 2.75 (1H, brs), 3.68−3.76 (3H, m), 3.81 (1H, dd, J = 11.6, 1.9 Hz), 3.87 (1H, d, J = 11.6 Hz), 4.08 (1H, dd, J = 11.6, 1.9 Hz), 4.25 (1H, dd, J = 8.7, 5.8 Hz), 4.32 (1H, d, J = 3.9 Hz), 7.23−7.44 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 26.7, 52.9, 62.7, 66.5, 70.6, 78.1, 80.5, 98.5, 127.1, 129.2, 130.8, 134.3; IR (KBr) 3439.2, 1200.8, 1139.0, 1078.0, 1059.0, cm^{-1}; EI-MS (m/z) 296 (M^+). Anal. Calcd for $C_{15}H_{20}O_4S$: C, 60.79; H, 6.80. Found: C, 60.84; H, 6.74.

6-Chloro-9-[(3*R,4*S**)-8,8-dimethyl-4-(phenylthio)-1,7,9-trioxaspiro[4.5]dec-3-yl]purine (22).** To a solution of **20** (350 mg, 1.18 mmol), PPh_3 (618 mg, 2.36 mmol), and 6-chloropurine (555 mg, 3.54 mmol) in THF (30 mL) was dropwise added DEAD (1.07 mL, 2.36 mmol) at 0 °C. After the mixture was stirred at room temperature for 1 h, the solvents were removed under reduced pressure. The residue was purified by silica gel column chromatography (60% AcOEt in hexane) to give **22** (426 mg, 83%) as a white solid: mp 159−161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (3H, s), 1,49 (3H, s), 3.91 (1H, dd, J = 12.3, 1.7 Hz), 3.99 (1H, dd, J = 12.1, 1.9 Hz), 4.08 (1H, d, J = 12.1 Hz), 4.21 (1H, d, J = 8.7 Hz), 4.25 (1H, d, J = 12.6 Hz), 4.36 (1H, dd, J = 9.2, 7.7 Hz), 4.41 (1H, t, J = 8.9 Hz), 5.06 (1H, q, J = 8.4 Hz), 7.00−7.28 (5H, m), 8.00 (1H, s), 8,26 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 26.3, 55.1, 63.8, 64.0, 65.9, 66.9, 79.2, 98.8, 128,4, 129.0, 131.2, 132.1, 132.6, 144.2, 151.0, 151.3, 151.5; UV (MeOH) λ_{max} 261 nm; IR (KBr) 1596.1, 1560.0, 1340.6, 1201.6, 1062.4, 828.2 cm^{-1}; EI-MS (m/z) 432 (M^+). Anal. Calcd for $C_{20}H_{21}ClN_4O_3S$: C, 55.49; H, 4.89; N, 12.94. Found: C, 55.59; H, 4.81; N, 12.87.

3-Benzoyl-1-[(3*R,4*S**)-8,8-dimethyl-4-(phenylthio)-1,7,9-trioxaspiro[4.5]dec-3-yl]thymine (23).** To a solution of **20** (250 mg, 0.840 mmol), PPh_3 (240 mg, 0.920 mmol), and N^3-benzoylthymine (288 mg, 1.26 mmol) in THF (20 mL) was dropwise added DEAD (417 μL, 1.26 mmol) at 0 °C. After the mixture was stirred at room temperature for 3 h, the solvents were removed under reduced pressure. The residue was purified by silica gel column chromatography (60% AcOEt in hexane) to give **23** (223 mg, 52%) as a white solid: mp 94−96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (1H, s), 1.44 (1H, s), 1.82 (1H, s), 3.71 (1H, d, J = 8.7 Hz), 3.76−3.84 (2H, m), 3.96 (1H, d, J = 12.6 Hz), 4.04 (1H, dd, J = 9.7, 7.2 Hz), 4.17−4.22 (2H, m), 4.88 (1H, q, J = 7.7 Hz), 6.89 (1H, s), 7.30−7.37 (3H, m), 7.46−7.50 (4H, m), 7.63 (1H, m), 7.82−7.85 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5, 20.0, 26.8, 63.2, 65.8, 66.2, 79.4, 98.7, 111.8, 128.6, 129.1, 129.7, 130.4, 131.4, 132.3, 132.9, 135.1, 137.1, 149.4, 162.2, 168.4; UV (MeOH) λ_{max} 254 nm; IR (KBr) 1749.0, 1696.3, 1657.6 cm^{-1}; EI-MS (m/z) 508 (M^+); HRMS calcd for $C_{27}H_{28}N_2O_6S$ 508.1668, found 508.1664

9-[(3*R,4*S**)-8,8-Dimethyl-4-(phenylthio)-1,7,9-trioxaspiro[4.5]dec-3-yl]adenine (24).** A mixture of **22** (350 mg, 0.810 mol) in 8 M ammonia in MeOH (25 mL) was kept at 80 °C overnight in a sealed tube. After the mixture was allowed to cool to room temperature, the solvents were removed under reduced pressure. The residue was purified by silica gel column chromatography (6% MeOH in $CHCl_3$) to give **24** (301 mg, 90%) as a white solid: mp 198−200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (3H, s), 1,47 (3H, s), 3.90 (1H, d, J = 12.6 Hz), 3.99 (2H, s), 4.25 (1H, d, J = 7.3 Hz), 4.28 (1H, d, J = 10.6 Hz), 4.31 (1H, dd, J = 8.7, 7.3 Hz), 4.41 (1H, t, J = 9.2 Hz), 4.94 (1H, q, J = 8.4 Hz), 5.57 (2H, s), 7.06−7.20 (5H, m), 7.67 (1H, s), 8,25 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 26.3, 55.1, 63.8, 64.0, 65.9, 66.9, 79.2, 98.8, 128,4, 129.0, 131.2, 132.1, 132.6, 144.2, 151.0, 151.3, 151.5; UV (MeOH) λ_{max} 259 nm; IR (KBr) 3150.8, 1645.2, 1601.4, 1091.3 cm^{-1}; EI-MS (m/z) 413 (M^+). Anal. Calcd for $C_{20}H_{23}N_5O_3S$: C, 58.09; H, 5.61; N, 16.94. Found: C, 58.28; H, 5.57; N, 16.61.

(*S)-9-[8,8-Dimethyl-1,7,9-trioxaspiro[4.5]dec-3-yl]adenine (25).** To a solution of **24** (250 mg, 0.610 mmol) in toluene (10 mL) were added Bu_3SnH (320 μL, 1.22 mmol) and AIBN (103 mg, 0.610 mmol). The mixture was kept under reflux for 10 h. After the solvents were removed under reduced pressure, the residue was purified by silica gel column chromatography (1% MeOH in $CHCl_3$) to give **25** (162 mg, 87%) as a white solid: mp 252−254 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31 (3H, s), 1.33 (3H, s), 2.17 (1H, dd, J = 13.5, 6.3 Hz), 2.37 (1H, dd, J = 13.5, 7.7 Hz), 3.66−3.78 (4H, m), 4.16 (2H, m), 5.06−5.12 (1H, m), 7.24 (1H, s), 8,13 (1H, s), 8.18 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.3, 24.8, 37.5, 53.5, 65.6, 66.3, 69.4, 77.0, 97.3, 119.0, 139.0, 149.9, 152.4, 156.0; UV (MeOH) λ_{max} 261 nm; IR (KBr) 3388.7, 1664.2, 1599.5, 1081.4 cm^{-1}; EI-MS (m/z) 305 (M^+); HRMS calcd for $C_{14}H_{19}N_5O_3$ 305.1488, found 305.1484.

(*S)-4-[(Adenin-9-yl)-tetrahydrofuran-2,2-diyl]dimethanol ((±)-2′,3′-Dideoxy-4′-hydroxymethylisoadenosine, 26).** A mixture of **25** (50 mg, 0.16 mmol) in 80% aq AcOH was stirred at room temperature for 5 h. After the solvents were removed under reduced pressure, the residual solvents were further removed by repeating coevaporation with EtOH five times. The residue was purified by silica gel column chromatography (5% MeOH in $CHCl_3$) to give **26** (39 mg, 94%) as a white solid: mp 230−232 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.22 (1H, dd, J = 13.0, 6.8 Hz), 2.41 (1H, dd, J = 13.0, 8.2 Hz), 3.37−3.45 (4H, m), 4.05 (1H, dd, J = 9.2, 6.3 Hz), 4.21 (1H, J = 8.7, 6.3 Hz), 4.82−4.86 (2H, m), 5.09−5.16 (1H, m), 7.22 (2H, s), 8.12 (1H, s), 8.26 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 35.2, 54.2, 63.8, 63.9, 86.4, 118.8, 139.0, 149.4, 152.3, 156.0; UV (MeOH) λ_{max} 261 nm; IR (KBr) 3369.5, 3195.1, 1656.2, 1612.1, 1312.9, 1050.7 cm^{-1}; FAB-MS (m/z) 266 ($M^+ + 1$); HRMS calcd for $C_{11}H_{15}N_5O_3$ 266.1253, found 266.1252.

1-[(3*R,4*S**)-8,8-Dimethyl-4-(phenylthio)-1,7,9-trioxaspiro-[4.5]dec-3-yl]thymine (27).** A mixture of **23** (214 mg, 0.420 mol)

in concd aq ammonia (10 mL) and MeOH (10 mL) was stirred at room temperature for 2 h. After the solvents were removed under reduced pressure, the residue was purified by silica gel column chromatography (50% AcOEt in hexane) to give **27** (160 mg, 95%) as a white solid: mp 165−167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (1H, s), 1.45 (1H, s), 1.80 (1H, s), 3.68 (1H, d, J = 8.7 Hz), 3.81−3.87 (2H, m), 3.95−4.01 (2H, m), 4.16−4.23 (2H, m), 4.95 (1H, q, J = 7.9 Hz), 6.83 (1H, s), 7.26−7.29 (3H, m), 7.44−7.46 (2H, m), 9.63 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.3, 19.9, 26.7, 54.8, 63.0, 64.7, 65.8, 66.3, 79.4, 98.6, 111.7, 128.4, 129.3, 132.2, 132.9, 137.0, 150.5, 163.5; UV (MeOH) λ_{max} 261 nm; IR (KBr) 3455.6, 1695.1, 1090.5, 1056.0 cm^{-1}; EI-MS (m/z) 404 (M^+); HRMS calcd for $C_{20}H_{24}N_2O_5S$ 404.1406, found 404.1410.

(*S)-1-[8,8-Dimethyl-1,7,9-trioxaspiro[4.5]dec-3-yl]thymine (28).** To a solution of **27** (154 mg, 0.380 mmol) and Bu_3SnH (298 μL, 1.14 mmol) in toluene (10 mL) was added a solution of AIBN (64 mg, 0.380 mmol) in toluene (5 mL) over 1 h. The mixture was kept under reflux for 2 h. After the solvents were removed under reduced pressure, the residue was purified by silica gel column chromatography (70% AcOEt in hexane) to give **28** (82 mg, 74%) as a white solid: mp 252−253 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (3H, s), 1.32 (3H, s), 1.73 (1H, dd, J = 13.5, 5.8 Hz), 1.78 (1H, s), 2.16 (1H, dd, J = 14.0, 8.7 Hz), 3.62 (2H, s), 3.69 (1H, d, J = 12.1 Hz), 3.79 (1H, d, J = 12.1 Hz), 3.87 (1H, dd, J = 10.1, 5.3 Hz), 3.96 (1H, dd, J = 9.7, 6.8 Hz), 4.91−4.98 (1H, m), 7.47 (1H, s), 11.26 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.2, 22.0, 25.1, 37.0, 54.2, 65.1, 66.3, 68.4, 77.0, 97.2, 109.5, 137.3, 150.9, 163.7; UV (MeOH) λ_{max} 271 nm; IR (KBr) 3175.8, 1689.5, 1672.4, 1282.5, 1089.9, 1050.6 cm^{-1}; EI-MS (m/z) 296 (M^+); HRMS calcd for $C_{14}H_{20}N_2O_5$ 296.1372, found 296.1378

(*S)-4-[(Thymin-1-yl)tetrahydrofuran-2,2-diyl]dimethanol ((±)-3′-Deoxy-4′-hydroxymethylisothymidine, 29).** A mixture of **28** (47 mg, 0.16 mmol) in 80% aq AcOH was stirred at room temperature for 6 h. After the solvents were removed under reduced pressure, the residual solvents were further removed by repeating coevaporation with EtOH 5 times. The residue was purified by silica gel column chromatography (5% MeOH in $CHCl_3$) to give **29** (40 mg, 98%) as a white solid: mp 195−198 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.76 (3H, s), 1.87 (1H, dd, J = 13.5, 6.3 Hz), 2.20 (1H, dd, J = 13.5, 9.2 Hz), 3.24−3.30 (2H, m), 3.38−3.50 (2H, m), 3.78 (1H, dd, J = 9.4, 5.1 Hz), 4.00 (1H, dd, J = 9.7, 7.3 Hz), 4.76 (1H, t, J = 5.8 Hz), 4.89 (1H, t, J = 5.8 Hz), 5.04−5.11 (1H, m), 7.64 (1H, s), 11.22 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.2, 34.3, 54.6, 63.4, 70.1, 86.6, 109.1, 137.7, 150.9, 163.7; UV (MeOH) λ_{max} 271 nm; IR (KBr) 3390.0, 1681.6, 1473.6, 1062.1, 1040.2 cm^{-1}; FAB-MS (m/z) 257 ($M^+ + 1$); HRMS calcd for $C_{11}H_{16}N_2O_5$ 257.1131, found 257.1137.

(3*S,4*S**)-3-(4-Methoxybenzylthio)-8,8-dimethyl-1,7,9-trioxaspiro[4.5]decan-4-ol (30).** To a solution of PMBSH (1.65 mL, 12 mmol) in dry methanol (15 mL) was added sodium methoxide (336 mg, 6.0 mmol), and the mixture was stirred at room temperature for 20 min. To this mixture was added a solution of **19** (559 mg, 3.0 mmol) in dry methanol (20 mL). After being kept under reflux for 2 h, the mixture was allowed to cool to room temperature. After the solvents were removed under reduced pressure, the residue was purified by silica gel column chromatography (20% AcOEt in hexane) to give **30** (867 mg, 85%) as a white solid: mp 108−109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ1.41 (3H, s), 1,47 (3H, s), 2.59 (1H, d, J = 2.9 Hz), 3.13 (1H, td, J = 7.0, 4.8 Hz), 3.53 (1H, dd, J = 9.7, 7.2 Hz), 3.69 (1H, d, J = 12.1 Hz), 3.74−3.85 (7H, m), 3.99−4.01 (1H, m), 4.03 (1H, s), 4.23 (1H, dd, J = 4.6, 2.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 26.5, 35.8, 49.8, 55.3, 62.9, 66.4, 70.7, 77.6, 81.6, 98.5, 114.0, 129.9, 130.0, 158.8; IR (KBr) 3489.5, 1512.5, 1250.5, 1076.8, 1030.2, 830.3 cm^{-1}; EI-MS (m/z) 340 (M^+), Anal. Calcd for $C_{17}H_{24}O_5S$: C, 59.98; H, 7.11. Found: C, 59.92; H, 7.04

6-Chloro-9-((3*R,4*S**)-4-(4-methoxybenzylthio)-8,8-dimethyl-1,7,9-trioxaspiro[4.5]dec-3-yl)-9*H*-purine (31).** To a solution of **30** (170 mg, 0.50 mmol), PPh_3 (196 mg, 0.75 mmol), and 6-chloropurine (117 mg, 0.75 mmol) in THF (30 mL) was dropwise added DEAD (340 μL, 0.75 mmol) at 0 °C. After the mixture was stirred at room temperature for 1 h, the solvents were removed under reduced pressure. The residue was purified by silica gel column chromatography (66% AcOEt in hexane) to give **31** (203 mg, 80%) as a white solid: mp 137−138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ1.49 (3H, s), 1,51 (3H, s), 3.40 (1H, d, J = 8.7 Hz), 3.56 (1H, d, J = 13.5 Hz), 3.66 (1H, d, J = 13.5 Hz), 3.74 (3H, s), 3.84 (1H, d, J = 12.1 Hz), 3.93 (2H, s), 4.20 (1H, dd, J = 9.4, 7.5 Hz), 4.26 (1H, d, J = 12.6 Hz), 4.44 (1H, t, J = 8.9 Hz), 4.70 (1H, q, J = 8.1 Hz), 6.48 (2H, d, J = 8.7 Hz), 6,82 (2H, d, J = 8.7 Hz), 8.00 (1H, s), 8.60 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 24.4, 36.4, 51.0, 55.1, 63.8, 64.3, 66.1, 66.4, 78.6, 98.6, 113.3, 128.1, 129.6, 132.3, 144.6, 150.8, 151.2, 151.4, 158.6; UV (MeOH) λ_{max} 267 nm; IR (KBr) 1594.5, 1561.2, 1513.2, 1250.1, 1191.2, 1084.9, 830.0 cm^{-1}; EI-MS (m/z) 476 (M^+). Anal. Calcd for $C_{22}H_{25}ClN_4O_4S$: C, 55.4; H, 5.28; N, 11.75. Found: C, 55.46; H, 5.14; N, 11.59.

((3*S,4*R**)-4-(6-Chloro-9*H*-purin-9-yl)-3-(4-methoxybenzylthio)-tetrahydrofuran-2,2-diyl)dimethanol (32).** A mixture of **31** (225 mg, 0.47 mmol) in 80% aq AcOH (20 mL) was stirred at room temperature for 4 h. After the solvents were removed under reduced pressure, the residual solvents were further removed by repeating coevaporation with EtOH five times. The residue was purified by silica gel column chromatography (10% MeOH in $CHCl_3$) to give **26** (206 mg, quant) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ1.77 (1H, s), 2.21 (1H, s), 3.43 (1H, d, J = 14.0 Hz), 3.49 (1H, d, J = 14.0 Hz), 3.67 (1H, d, J = 11.6 Hz), 3.78 (1H, d, J = 11.6 Hz), 3.80 (1H, d, J = 11.6 Hz), 3.95 (1H, d, J = 10.1 Hz), 3.99 (1H, d, J = 11.6 Hz), 4.34 (1H, t, J = 8.7 Hz), 4.47 (1H, t, J = 8.2 Hz), 4.99 (1H, dd, J = 17.9, 8.2 Hz), 6.41 (2H, d, J = 8.7 Hz), 6.78 (2H, d, J = 8.7 Hz), 7.94 (1H, s), 8.61 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ36.3, 48.0, 55.0, 63.5, 64.1, 65.1, 68.0, 87.8, 113.1, 128.6, 129.5, 132.4, 145.0, 150.6, 151.1, 151.2, 158.4; UV (MeOH) λ_{max} 268 nm; IR (KBr) 3423.6, 1594.8, 1562.9, 1511.7, 1341.2, 1253.4, 1033.3 cm^{-}1; EI-MS (m/z) 436 (M^+); HRMS calcd for $C_{19}H_{21}ClN_4O_4S$ 436.0972, found 436.0974.

((3*S,4*R**)-4-(6-Chloro-9*H*-purin-9-yl)-3-(4-methoxybenzylthio)-tetrahydrofuran-2,2-diyl)bis(methylene) Dimethanesulfonate (33).** To a solution of **32** (175 mg, 0.4 mmol) in CH_2Cl_2 (10 mL) were added MsCl (104 μL, 1.2 mmol), Et_3N (163 μL, 1.2 mmol), and DMAP (2 mg). After the mixture was stirred at room temperature for 1 h, the mixture was diluted with CH_2Cl_2 and washed with 5% HCl, satd $NaHCO_3$, and brine and then dried over Na_2SO_4. After filtration, the filtrated was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10% MeOH in $CHCl_3$) to give **33** (221 mg, 93%) as a white solid: mp 193−194 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ3.16 (3H, s), 3.21 (3H, s), 3.41 (1H, d, J = 14.0 Hz), 3.50 (1H, d, J = 14.5 Hz), 3.74 (2H, s), 3.97 (1H, d, J = 10.1 Hz), 4.28 (1H, t, J = 8.7 Hz), 4.32 (3H, s), 4.48 (1H, d, J = 11.1 Hz), 4.53 (1H, d, J = 10.6 Hz), 4.57 (1H, t, J = 8.7 Hz), 4.82 (1H, q, J = 9.3 Hz), 6.4 (2H, d, J = 8.2 Hz), 6.76 (2H, d, J = 8.7 Hz), 7.98 (1H, s), 8.57 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ36.3, 37.8, 37.9, 48.7, 55.0, 63.7, 66.9, 68.6, 70.7, 83.7, 113.2, 127.9, 129.4, 132.6, 145.2, 150.4, 151.1, 151.4, 158.6; UV (MeOH) λ_{max} 266 nm; IR (KBr) 1511.8, 1368.6, 1335.2, 1173.3, 962.6, 816.3 cm^{-}1; FAB-MS (m/z) 593 (M^+); HRMS calcd for $C_{21}H_{26}ClN_4O_8S_3$ 593.0606, found 593.0592.

((3*S,4*R**)-4-(6-Chloro-9*H*-purin-9-yl)-3-mercaptotetrahydrofuran-2,2-diyl)bis(methylene) Dimethanesulfonate (34) and ((1*S**,4*R**,5*S**)-4-(6-Chloro-9*H*-purin-9-yl)-2-oxa-6-thiabicyclo[3.2.0]-hept-1-yl)methyl methanesulfonate (35).** To a solution of **33** (90 mg, 0.15 mmol) in TFA (20 mL) were added PhOH (69 mg, 0.75 mmol) and $Hg(OAc)_2$ (113 mg, 0.3 mmol) at room temperature. After the mixture was stirred at room temperature for 1 h,

the solvents were removed under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with 0.1 M potassium thioacetate solution, and then dried over Na_2SO_4. After filtration, the filtrated was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2% MeOH in $CHCl_3$) to give **35** (14 mg, 25%) as a less polar product and **34** (45 mg, 63%).

Data for **34**: mp 155−157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ3.14 (3H, s), 3.17 (3H, s), 4.32 (1H, d, J = 11.6 Hz), 4.38−4.52 (5H, m), 4.62 (1H, d, J = 11.6 Hz), 4.72 (1H, s), 5.04 (1H, q, J = 7.9 Hz), 8.25 (1H, s), 8.67 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ37.9, 38.1, 46.8, 66.3, 68.0, 68.2, 68.9, 84.6, 132.4, 144.5, 151.4, 151.9, 152.1; UV (MeOH) λ_{max} 267 nm; IR (KBr) 3621.0, 1593.8, 1561.1, 1340.1, 1175.4, 964.2 cm^{-1}; FAB-MS (m/z) 471 ($M^+ - 1$); HRMS calcd for $C_{13}H_{16}ClN_4O_7S_3$ 470.9870, found 470.9814.

Data for **35**: mp 167−168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ3.01 (3H, s), 3.24 (1H, d, J = 11.6 Hz), 3.34 (1H, J = 11.1 Hz), 3.94 (1H, s), 4.35 (1H, d, J = 11.1 Hz), 4.54 (1H, d, J = 11.6 Hz), 4.75 (1H, d, J = 11.1 Hz), 5.13 (1H, dd, J = 11.1, 4.4 Hz), 5.37 (1H, d, J = 4.4 Hz), 8.38 (1H, s), 8.75 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ31.6, 37.9, 50.6, 60.7, 66.8, 71.4, 87.9, 131.4, 143.1, 151.1, 151.3, 152.1; UV (MeOH) λ_{max} 265 nm; IR (KBr) 1595.1, 1359.8, 1336.2, 1173.8, 957.0 cm^{-1}; EI-MS (m/z) 376 (M^+); HRMS calcd for $C_{12}H_{13}ClN_4O_4S_2$ 376.0067, found 376.0068.

Conversion of Dimesylate 34 to Thietane 35. To a solution of **34** (56 mg, 0.12 mmol) in CH_3CN (5 mL) was added DBU (45 μL, 0.36 mmol) at room temperature. The mixture was stirred at the same temperature for 6 h. After the solvents were removed under reduced pressure, the residue was dissolved in CH_2Cl_2, washed with satd NH_4Cl and brine, and then dried over Na_2SO_4. After filtration, the filtrated was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5% MeOH in $CHCl_3$) to give **35** (29 mg, 65%) as a white solid.

((1*S,4*R**,5*S**)-4-(6-Chloro-9*H*-purin-9-yl)-2-oxa-6-thiabicyclo-[3.2.0]hept-1-yl)methyl Benzoate (36).** A mixture of CsF (33 mg, 0.22 mmol) and PhCOOH (27 mg, 0.22 mmol) in DMF (4 mL) was stirred at room temperature for 20 min. To this mixture was added a solution of **35** (28 mg, 0.074 mmol) in DMF (2 mL). After being stirred at 60 °C for 36 h, the mixture was partitioned between AcOEt and H_2O. The separated water layer was extracted with AcOEt × 4, and the combined organic layer was washed with satd $NaHCO_3$ and brine and then dried (Na_2SO_4). After filtration, the filtrated was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (50% AcOEt in hexane) to give **36** (21 mg,70%) as a white solid: mp 151−152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.40 (2H, s), 4.03 (1H, s), 4.53 (1H, d, J = 12.1 Hz), 4.60 (1H, d, J = 12.1 Hz), 4.78 (1H, d, J = 11.6 Hz), 5.13 (1H, dd, J = 11.1, 4.4 Hz), 5.33(1H, d, J = 4.4 Hz), 7.41 (2H, t, J = 7.7 Hz), 7.59 (1H, t, J = 7.24 Hz), 7.79 (2H, d, J = 7.24 Hz), 8,32 (1H, s), 8.73 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.5, 51.1, 61.1, 65.0, 71.0, 88.7, 128.5, 128.7, 129.6, 133.7, 151.3, 151.3, 152.1, 166.1; UV (MeOH) λ_{max} 266 nm; IR (KBr) 1717.8, 1593.0, 1268.4, 713.2 cm^{-1}; EI-MS (m/z) 402 (M^+); HRMS calcd for $C_{18}H_{15}ClN_4O_3S$ 402.0553, found 402.0560.

((1*S,4*R**,5*S**)-4-(6-Amino-9*H*-purin-9-yl)-2-oxa-6-thiabicyclo-[3.2.0]hept-1-yl)methanol (37).** A solution of **36** (26 mg, 0.65 mmol) in 8 N NH_3 in MeOH (5 mL) was kept at 100 °C for 24 h in a glass-sealed tube. After the solvents were removed under reduced pressure, the residue was purified by silica gel column chromatography (5% MeOH in $CHCl_3$) to give **37** (13 mg, 72%) as a white solid: mp 223−224 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 3.04 (1H, d, J = 10.6 Hz), 3.15 (1H, d, J = 10.6 Hz), 3.59 (1H, d, J = 12.1 Hz), 3.72 (1H, d, J = 12.1 Hz), 3.80 (1H, s), 4.54 (1H, d, J = 11.1 Hz), 4.93 (1H, dd, J = 11.1, 4.4 Hz), 5.10 (1H, d, 4.4 Hz), 8.10 (1H, s), 8.29 (1H, s); ^{13}C NMR (100 MHz, CD_3OD) δ 32.3, 52.1, 62.5, 64.5, 72.5, 92.1, 119.6, 141.1, 150.3, 152.9, 156.7; UV (MeOH) λ_{max} 260 nm; IR (KBr) 3423.7, 1683.4, 1208.3, 1142.7 cm^{-1}; EI-MS (m/z) 279 (M^+); HRMS calcd for $C_{11}H_{13}N_5O_2S$ 279.0790, found 279.0782.

3-Benzoyl-1-((3*R,4*S**)-4-(4-methoxybenzylthio)-8,8-dimethyl-1,7,9-trioxaspiro[4.5]dec-3-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (38).** To a solution of **30** (340 mg, 1.0 mmol), PPh_3 (392 mg, 1.5 mmol), and N^3-benzoylthymine (251 mg, 1.5 mmol) in THF (30 mL) was dropwise added DEAD (680 μL, 1.5 mmol) at 0 °C. After the mixture was stirred at room temperature for 1 h, the solvents were removed under reduced pressure. The residue was purified by silica gel column chromatography (66% AcOEt in hexane) to give **38** (326 mg, 59%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (6H, s), 1.87 (3H, s), 2.77 (1H, s), 3.63 (1H, dd, J = 12.3, 1.7 Hz), 3.73−3.83 (4H, m), 3.78 (3H, s), 3.97 (1H, dd, J = 10.6, 4.4 Hz), 4.14 (1H, d, J = 13.0 Hz), 4.20 (1H, dd, J = 10.6, 7.2 Hz), 4.94 (1H, s), 6.83 (2H, d, J = 8.7), 6.99 (1H, s), 7.19(2H, d, J = 8.7 Hz), 7.50 (2H, t, J = 7.7 Hz), 7.66 (1H, t, J = 7.5 Hz), 7.92 (2H, d, J = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5, 20.2, 26.7, 36.0, 52.0, 55.2, 62.4, 63.9, 65.9, 67.2, 79.4, 98.5, 112.2, 114.1, 128.4, 129.1, 130.1, 130.4, 131.4, 135.1, 135.6, 149.6, 159.0, 162.3, 168.6; UV (MeOH) λ_{max} 277 nm; IR (KBr) 1748.5, 1698.3, 1655.1, 1252.3 cm^{-1}; EI-MS (m/z) 552 (M^+); HRMS calcd for $C_{29}H_{32}N_2O_7S$ 552.1930, found 552.1931.

3-Benzoyl-1-((3*R,4*S**)-5,5-bis(hydroxymethyl)-4-(4-methoxybenzylthio)tetrahydrofuran-3-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (39).** A mixture of **38** (270 mg, 0.49 mmol) in 80% aq AcOH (30 mL) was stirred at room temperature for 9 h. After the solvents were removed under reduced pressure, the residual solvents were further removed by repeating coevaporation with EtOH five times. The residue was purified by silica gel column chromatography (1% MeOH in $CHCl_3$) to give **39** (216 mg, 86%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79 (1H, s), 2.25 (2H, s), 3.51−3.62 (2H, m), 3.65−3.73 (4H, m), 3.76 (3H, s), 3.81 (1H, d, J = 8.2 Hz), 3.84 (1H, d, J = 6.8 Hz), 4.22 (1H, t, J = 8.7 Hz), 5.06 (1H, q, J = 7.6 Hz), 6.76 (1H, s), 6,84 (2H, d, J = 8.2 Hz), 7.21 (2H, d, J = 8.7 Hz), 7.50 (2H, t, J = 7.7 Hz), 7.65 (1H, t, J = 7.5 Hz), 7.91 (2H, d, J = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5, 36.3, 48.0, 55.1, 63.4, 64.4, 68.3, 77.2, 87.2, 111.7, 114.1, 129.1, 129.5, 130.2, 131.6, 135.1, 136.0, 149.8, 159.0, 162.4, 168.7; UV (MeOH) λ_{max} 279 nm; IR (KBr) 3441.4, 1747.9, 1697.1, 1654.1, 1252.5 cm^{-1}; EI-MS (m/z) 512 (M^+); HRMS calcd for $C_{26}H_{28}N_2O_7S$ 512.1617, found 512.1614.

((3*S,4*R**)-4-(3-Benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-3-(4-methoxybenzylthio)tetrahydrofuran-2,2-diyl)bis(methylene) Dimethanesulfonate (40).** To a solution of **39** (180 mg, 0.35 mmol) in CH_2Cl_2 (10 mL) were added MsCl (91 μL, 1.1 mmol), Et_3N (142 μL, 1.1 mmol), and DMAP (2 mg). After the mixture was stirred at room temperature for 1 h, the mixture was diluted with CH_2Cl_2, washed with 5% HCl, satd $NaHCO_3$, and brine, and then dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2% MeOH in $CHCl_3$) to give **40** (260 mg, quant): ^{1}H NMR (400 MHz, $CDCl_3$) δ1.84 (3H, s), 3.03 (3H, s), 3.09 (3H, s), 3.52 (1H, d, J = 9.2 Hz), 3.68 (2H, s), 3.77 (3H, s), 3.97 (1H, dd, J = 9.4, 7.5 Hz), 4.11 (2H, s), 4.22 (1H, t, J = 9.4 Hz), 4.34 (1H, d, J = 11.1 Hz), 4.41 (1H, d, J = 11.1 Hz), 4.88 (1H, s), 6.84 (2H, d, J = 8.7 Hz), 6.86 (1H, s), 7.19 (2H, d, J = 8.7 Hz), 7.51 (2H, t, J = 7.7 Hz), 7.66 (1H, t, J = 7.5 Hz), 7.91 (2H, d, J = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ12.1, 36.4, 37.5, 37.6, 48.7, 54.9, 63.8, 67.3, 68.8, 69.5, 83.4, 111.7, 114.0, 128.8, 129.1, 130.0, 130.2, 131.3, 135.1, 136.6, 149.5, 158.9, 162.2, 168.7; UV (MeOH) λ_{max} 281 nm; IR (KBr) 1748.2, 1698.4, 1658.2, 1361.7, 1174.8 cm^{-1}; FAB-MS (m/z) 669 ($M^+ + 1$); HRMS calcd for $C_{28}H_{32}N_2O_{11}S_3$ 669.1246, found 669.1252.

((3*S,4*R**)-3-Mercapto-4-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-2,2-diyl)bis(methylene) Dimethanesulfonate (41).** To a solution of **40** (67 mg, 0.1 mmol) in TFA (20 mL) were added PhOH (48 mg, 0.5 mmol) and

$Hg(OAc)_2$ (64 mg, 0.2 mmol) at room temperature. After the mixture was stirred at room temperature for 1 h, the solvents were removed under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with 0.1 M potassium thioacetate solution, and then dried over Na_2SO_4. After filtration, the filtrated was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2% MeOH in $CHCl_3$) to give **41** (46 mg, quant) as a white solid: mp 155−156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76 (1H, s), 3.23 (3H, s), 3.24 (3H, s), 3.83 (1H, m), 4.09 (1H, d, J = 8.2 Hz), 4.14 (1H, dd, J = 10.1, 4.4 Hz), 4.31 (1H, d, J = 11.1 Hz), 4.38 (1H, d, J = 10.6 Hz), 4.39 (1H, d, J = 11.1 Hz), 4.58 (1H, dd, J = 11.1, 3.9 Hz), 4.96 (1H, q, J = 7.7 Hz), 7.50 (1H, s), 11.39 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.2, 36.6, 37.0, 37.1, 50.4, 67.0, 69.2, 69.8, 87.2, 137.0, 150.9, 151.6, 163.6; UV (MeOH) λ_{max} 271 nm; IR (KBr) 3456.2, 1687.9, 1351.5, 1174.0 cm^{-1}; FAB-MS (m/z) 443 ($M^+ - 1$); HRMS calcd for $C_{13}H_{19}N_2O_9S_3$ 443.0253, found 443.0209.

((1*S,4*R**,5*S**)-4-(5-Methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-oxa-6-thiabicyclo[3.2.0]hept-1-yl)methyl Methanesulfonate (42).** To a solution of **41** (30 mg, 0.067 mmol) in CH_3CN (5 mL) was added DBU (26 μL, 0.20 mmol) at room temperature. The mixture was stirred at the same temperature for 24 h. After the solvents were removed under reduced pressure, the residue was dissolved in CH_2Cl_2, washed with satd NH_4Cl and brine, and then dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5% MeOH in $CHCl_3$) to give **42** (14 mg, 60%) as a white solid: mp 239−240 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ1.73 (3H, s), 3.17 (1H, d, J = 11.1 Hz), 3.20 (3H, s), 3.29 (1H, d, J = 6.3 Hz), 3.81 (1H, s), 4.37 (1H, d, J = 11.6 Hz), 4.52 (2H, d, J = 11.1 Hz), 4.74 (1H, dd, J = 11.6, 5.3 Hz), 4.93 (1H, d, J = 5.3 Hz), 7.26 (1H, s), 11.30 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ12.2, 31.0, 36.6, 50.4, 61.9, 69.2, 69.8, 87.2, 108.9, 137.0, 150.9, 163.7; UV (MeOH) λ_{max} 270 nm; IR (KBr) 3664.3, 1687.5, 1348.0, 1172.3 cm^{-1}; EI-MS (m/z) 348 (M^+); HRMS calcd for $C_{12}H_{16}N_2O_6S_2$ 348.0450, found 348.0437.

((1*S,4*R**,5*S**)-4-(5-Methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-oxa-6-thiabicyclo[3.2.0]hept-1-yl)methyl Benzoate (43).** A mixture of CsF (23 mg, 0.16 mmol) and PhCOOH (21 mg, 0.16 mmol) in DMF (4 mL) was stirred at room temperature for 20 min. To this mixture was added a solution of **42** (18 mg, 0.052 mmol) in DMF (2 mL). After being stirred at 60 °C for 36 h, the mixture was partitioned between AcOEt and H_2O. The separated water layer was extracted with AcOEt × 4, and the combined organic layer was washed with satd $NaHCO_3$ and brine and then dried (Na_2SO_4). After filtration, the filtrated was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (50% AcOEt in hexane) to give **36** (8 mg, 40%) as a white solid: mp 181−182 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ1.50 (3H, s), 1.57 (3H, s), 3.28 (1H, d, J = 11.1 Hz), 3.32 (1H, d, J = 11.1 Hz), 3.87 (1H, s), 4.43 (1H, d, J = 11.6 Hz), 4.51 (1H, d, J = 12.1 Hz), 4.66 (1H, d, J = 12.1 Hz), 4.90 (1H, dd, J = 11.6, 5.3 Hz), 5.12 (1H, d, J = 4.8 Hz), 7.42 (2H, t, J = 7.7 Hz), 7.59 (1H, t, J = 7.5 Hz), 7.93 (2H, dd, J = 8.2, 1.5 Hz), 8.14 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 32.1, 51.5, 62.3, 65.0, 69.9, 88.5, 111.6, 128.6, 129.1, 129.6, 133.7, 135.9, 150.7, 163.0, 166.1; UV (MeOH) λ_{max} 272 nm; IR (KBr) 3440.3, 1723.7, 1683.8, 1280.1 cm^{-1}; EI-MS (m/z) 374 (M^+); HRMS calcd for $C_{18}H_{18}N_2O_5S$ 374.0937, found 374.0937.

1-((1*S,4*R**,5*S**)-1-(Hydroxymethyl)-2-oxa-6-thiabicyclo[3.2.0]-hept-4-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (44).** A solution of **43** (3 mg, 0.0080 mmol) in 8 N NH_3 in MeOH (3 mL) was stirred at room temperature for 6 h. After the solvents were removed under reduced pressure, the residue was purified by silica gel column chromatography (9% MeOH in $CHCl_3$) to give **44** (2 mg, 93%) as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 1.75 (3H, s), 2.94 (1H, d, J = 10.6 Hz), 3.11 (1H, d, J = 10.6 Hz), 3.58 (1H, d, J = 12.1 Hz), 3.64 (1H, s), 3.75 (1H, d, J = 12.6 Hz), 4.34 (1H, d, J = 11.6 Hz), 4.73 (1H, d, J = 5.3 Hz), 4.99 (1H, d, J = 5.3 Hz), 7.65 (1H, s); ^{13}C NMR (100 MHz, CD_3OD) δ 12.3, 30.8, 32.1, 52.3, 63.9, 64.4, 71.6, 92.1, 111.0, 139.9, 153.4; UV (MeOH) λ_{max} 271 nm; IR (KBr) 3440.2, 1678.5, 1138.1 cm^{-1}.

Theoretical Calculations. The theoretical calculations were performed by using SPARTAN (Wavefunction, Inc.). Conformers of model compounds were surveyed by molecular mechanics (MM) calculations. The structures of the conformers obtained by MM were further optimized by theoretical calculations using density functional theory (DFT) quantum mechanical calculations at the B3LYP/6-31G** level.[20]

Evaluation for Antiviral Activities. Anti-HIV-1 activities of isonucleosides were assayed by inhibition of HIV replication in peripheral blood mononuclear cells (PBMC). Anti-HIV effect was determined by p24 HIV antigen assay.[26] Anti-HSV-1 activities of isonucleosides were evaluated by a plaque reduction method.[27]

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Supporting Information Available: Data for ^{1}H and ^{13}C NMR of compounds **14**−**44** except **16** and DFT calculation results for compounds **45** and **46**. This material is available free of charge via the Internet at http://pubs.acs.org.

(26) Brann, T. W.; Dewar, R. L.; Jiang, M.-K.; Shah, A.; Nagashima, K.; Metcalf, J. A.; Falloon, J.; Lane, H. C.; Imamichi, T. *J. Virol.* **2006**, *80*, 6136–6145.

(27) Okuda, T.; Kurokawa, K.; Matsuo, K.; Honda, M.; Niimura, M.; Shiraki, K. *J. Med. Virol.* **2004**, *72*, 112–120.