Synthesis of Benzodithiol-2-yl-Substituted Nucleoside Derivatives as Lead Compounds Having Anti-Bovine Viral Diarrhea Virus Activity

Kohji Seio,[†,||] Takahide Sasaki,[‡] Koichirou Yanagida,[§] Masanori Baba,[§] and Mitsuo Sekine*[,‡,||]

Frontier Collaborative Research Center and Department of Life Science, Tokyo Institute of Technology, Nagatsuta, Midori-ku, Yokohama 226-8501, Division of Antiviral Chemotherapy, Center for Chronic Viral Diseases, Faculty of Medicine, Kagoshima University, Kagoshima 890-8520, Japan, and CREST, JST (Japan Science and Technology Agency), Nagatsuta-cho, Midori-ku, Yokohama 226-8501, Japan

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Nucleoside derivatives having a benzodithiol-2-yl (BDT) group were synthesized and examined for their anti-bovine viral diarrhea virus (BVDV) activities. Other substituents structurally similar to the BDT group such as 1,3-benzodioxol-2-yl, benzimidazol-2-yl and 1-oxo-benzodithiol-2-yl groups were not effective as the pharmacophore. The anti-BVDV assay revealed that 2′-*O*-BDT-guanosine and 2′-*O*-BDT-inosine had the strongest anti-BVDV activity among the nucleoside derivatives synthesized in this study. Since BVDV has been recognized as a surrogate for human hepatitis C virus (HCV), the BDT-modified nucleosides might become a new class of lead compounds to find nucleoside-type anti-HCV agents such as ribavirin.

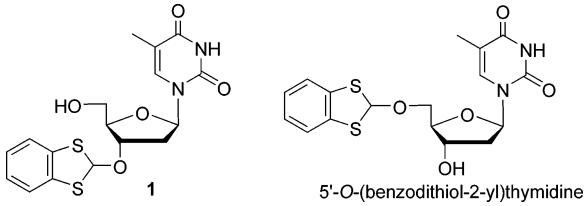
Introduction

Hepatitis C virus is a member of the *Flaviviridae* family.[1] It was estimated that approximately 170 million people are infected by this virus and the infection persisted in more than 80% of the infected population.[2] Moreover, 4−5% of the chronically infected patients will develop liver cirrhosis and hepatocellular carcinoma within 20−30 years after infection.[3] Currently the most effective treatment of HCV infection is the combined use of interferon-α and the antiviral agent ribavirin.[4] However, the treatment is frequently accompanied by severe adverse effects such as fever, depression and atonia, whereas the response is at best around 40%. Therefore, alternative agents for the treatment of HCV have to be discovered.

Although there are a number of molecular targets for the development of anti-HCV drugs,[5] the efficiency of these compounds against the viral replication should be confirmed in cell culture systems. However, the inability to propagate HCV in culture cells apparently hampers the discovery of effective anti-HCV agents. Instead of such cell culture systems, several research groups have developed model systems that can surrogate the cell culture systems of HCV. Among the model systems, bovine viral diarrhea virus (BVDV) is a popular system with which antiviral agents can be evaluated for potential activity against HCV.[6]

BVDV is a *Pestivirus* member which also belongs to the *Flaviviridae* family. The amino acid sequences coded on the BVDV genome have high homology to those of HCV.[1] Since the anti-HCV agent rivabirin showed strong activity against BVDV replication in vitro, it is expected that novel nucleoside-type anti-HCV agents can be discovered through the screening by use of this assay system. In this paper, we report significant anti-BVDV activity of new nucleoside derivatives having a 1,3-benzodithiol-2-yl group introduced into their hydroxyl groups.

Scheme 1. Structure of the Thymidine Derivatives Having a BDT Group



Results and Discussion

Synthesis and Anti-BVDV Activities of BDT-Modified Deoxynucleosides. The lead compound, 3′-*O*-(benzodithiol-2-yl)thymidine (**1**), was first discovered in random screening of our chemical libraries to find first-stage drug candidates that showed inhibitory effects against the BVDV cell culture system described above. The compound was previously reported by Sekine et al. as an intermediate of a synthetic unit for oligodeoxyribonucleotide synthesis.[7] Compound **1** showed weak anti-BVDV activity (EC_{50} = 46 μM) and weaker cytotoxicity (CC_{50} = 72 μM). In the same assay, ribavirin showed much stronger activity (EC_{50} = 1.5 μM) and much weaker cytotoxicity (CC_{50} > 100 μM). Interestingly, a regioisomer of **1**, 5′-*O*-(benzodithiol-2-yl)thymidine[7] (Scheme 1), showed no anti-BVDV activity. Therefore, we focused our interest on nucleoside derivatives modified by benzodithiol-2-yl (BDT) on their 3′-hydroxyl groups to improve the anti-BVDV activity of **1**.

Several 2′-deoxynucleosides having a BDT group (**4a**−**c**) on their 3′-oxygens were synthesized, as shown in Scheme 2. In addition, the ring-opened analogues of **1**, i.e., compounds **6a**−**d** were synthesized by reduction of the intermediates **3a**−**d** with tributyltin hydride followed by the methylation and the deprotection.[8] (Scheme 3)

* To whom correspondence should be addressed. phone: +81-45-924-5706; fax: +81-45-924-5772; e-mail: msekine@bio.titech.ac.jp
† Frontier Collaborative Research Center, Tokyo Institute of Technology.
‡ Department of Life Science, Tokyo Institute of Technology.
§ Kagoshima University.
|| CREST.

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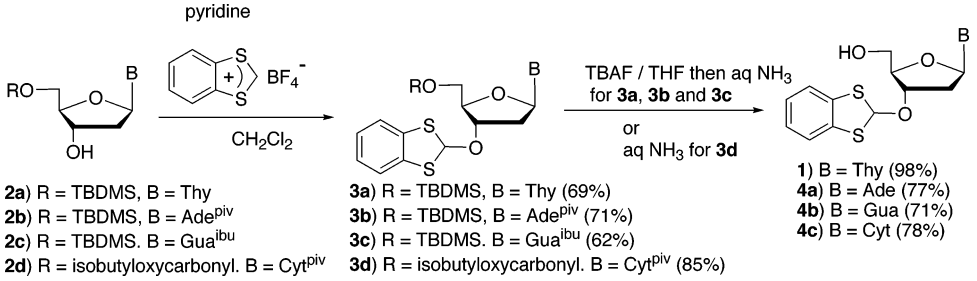
Scheme 2. Synthesis of Deoxynucleoside Derivatives Having a BDT Group



Scheme 3. Synthesis of Deoxynucleoside Derivatives Having a MPTM Group

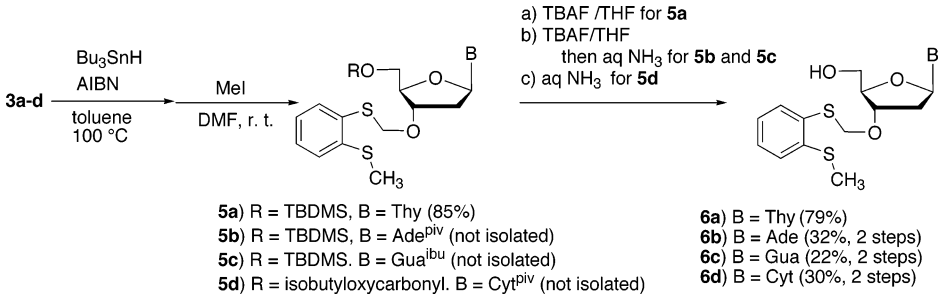
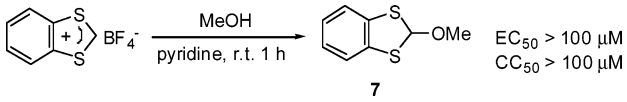


Table 1. Anti-BVDV Activity of Nucleoside Derivatives Having BDT and MPTM Groups[a]

compound	EC_{50} (μM)	EC_{50}^{rel}	CC_{50} (μM)	CC_{50}/EC_{50}
ribavirin	1.5	1	>100	> 67
1	46.8	31.2	72.4	1.5
4a	63.8	42.5	68.4	1.1
4b	79.4	52.9	>100	1.3
4c	69.1	46.1	69.7	1.0
6a	89.6	59.7	>100	> 1.1
6b	>100	-	>100	-
6c	>100	-	>100	-
6d	>100	-	>100	-
16	86.7	57.8	81.3	0.93

[a] $EC_{50}^{rel} = EC_{50(compound)}/EC_{50(ribavirin)}$.

Scheme 4. Synthesis of 2-Methoxybenzodithiol **7**



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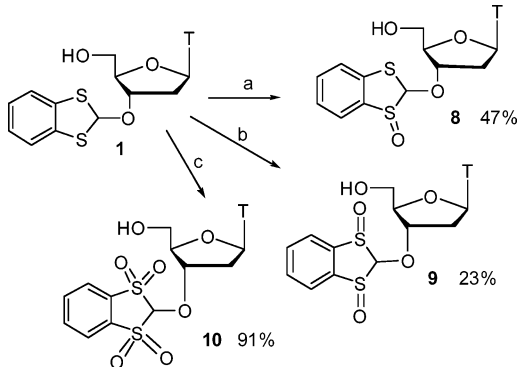
The anti-BVDV activities of **1**, **4a**−**c** and **6a**−**d** thus obtained are listed in Table 1. As shown in Table 1, ribavirin showed potent activity and no cytotoxicity up to 100 μM. The deoxynucleosides modified by the BDT group (**1**, **4a**−**c**) showed weaker but significant activity. In contrast, the deoxynucleosides modified by the MPTM group (**6a**−**d**) showed much weaker or undetectable activity against BVDV replication. From these observations, it was evident that the BDT group was essential for the anti-BVDV activity of the modified deoxynucleosides. Despite the anti-BVDV activity of the BDT-modified deoxynucleosides, they are considered to be inferior to ribavirin in terms of their activity and cycotoxicity. Therefore, further structural modifications were examined to improve these drawbacks.

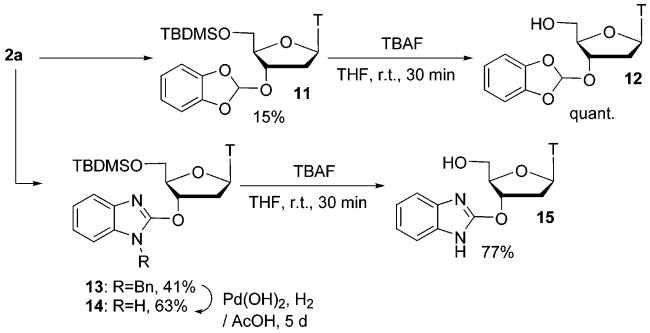
Importance of the Nucleoside Moiety for Anti-BVDV Activity. The importance of the nucleoside moiety was evaluated by testing the anti-BVDV activity of a simple BDT-containing compound **7** (Scheme 4). The anti-BVDV assay revealed that compound **7** had neither anti-BVDV activity nor cytotoxicity. Therefore, it was unambiguously proved that both the nucleoside and BDT moieties were indispensable for the activity of the BDT-modified deoxynucleosides.

Scheme 5. Oxidation of **1**[a]



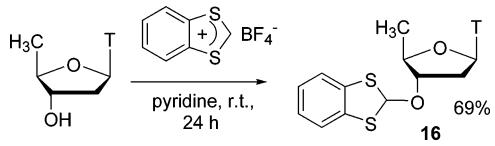
[a] Reagents: (a) mCPBA (1 equiv), $NaHCO_3$ (1 equiv), CH_2Cl_2, r.t., 2 h; (b) mCPBA (2 equiv), $NaHCO_3$ (2 equiv), CH_2Cl_2, r.t., 2 h; (c) mCPBA (4.1 equiv), $NaHCO_3$ (4.1 equiv), CH_2Cl_2, r.t., 90 min.

Scheme 6. Synthesis of Benzodioxole (**12**) and Benzimidazole (**15**) Analogue of **1**



To clarify more detailed structural requirement for the BDT group, several thymidine derivatives were synthesized incorporating other bicyclic substituents which were structurally similar to that of the BDT group. Shown in Schemes 5 and 6 are the synthesis of the sulfoxide and sulfonyl derivatives of **1** prepared by oxidation by use of *m*-CPBA, and 3′-*O*-benzodioxol-2-yl

Scheme 7. Synthesis of 5′-Deoxy Derivative of **1**



(**12**) and 3′-*O*-benzimidazol-2-yl (**15**) derivatives of thymidine. However, all the compounds lacking the BDT moiety showed neither anti-BVDV activity nor cytotoxicity. It should be noted that replacement of the sulfur atoms of **1** to oxygen atoms resulted in loss of the anti-BVDV activity of **12**. Therefore, on the basis of the structure−activity relationship described above, we concluded that the bicyclic structure and the two divalent sulfur atoms were essential for expression of the anti-BVDV activity of the BDT-containing deoxynucleosides.

Modification on the Sugar Moiety. As mentioned above, the BDT group must be left intact to maintain the anti-BVDV activity of modified nucleosides. Therefore, we next tried to modify the structure of the deoxyribose moiety in order to improve the antiviral activity. Initially, we attempted to clarify the importance of the 5′-hydroxyl group using a 5′-deoxythymidine[9] derivative (**16**) (Scheme 7). The anti-BVDV and cytotoxicity of **16** are listed in Table 1. Although the 5′-deoxy derivative **16** still retained weak anti-BVDV activity, the cytotoxicity appeared at the lower concentration range in comparison with the antiviral activity. This result suggested that the intact 5′-hydroxyl group must remain in order to improve the antiviral activity without intensifying the cytotoxicity.

On the other hand, the anti-BVDV activity of **16** provided some implication on the action mechanism of the nucleoside derivatives having a BDT group independent of its 5′-phosphorylation. It is well-known that some nucleoside-type antiviral agents act after their conversion to the corresponding 5′-monophosphate or 5′-triphosphate derivatives in cells. For example, ribavirin elicits its antiviral activity as an inosine 5′-monophosphate (IMP) dehydrogenase inhibitor after its conversion to the corresponding 5′-monophosphate,[10] and AZT and acyclovir act as chain terminators after similar transformation to the 5′-triphosphates.[11]

However, recent studies revealed another type of reaction mechanism of nucleoside derivatives having antiviral activities. Drach and co-workers[12] revealed that the anti-HCMV activity of halogenated β-D-ribosylbenzimidazoles was independent of the phosphorylation of the nucleosides. Moreover, Borowski and coworkers[13] discovered the in vitro inhibitory activity of the same nucleosides against the RNA helicase and NTPase activity of nonstructural protein 3 (NS3) of HCV and related viruses. Considering the importance of the RNA helicase and NTPase activity of NS3 protein in BVDV replication[14] and the anti-BVDV activity of 5′-deoxynucleoside analogue **16**, the BDT-nucleosides described here might have a possibility that they have an anti-NS3 protein activity similar to those of halogenated β-D-ribosylbenzimidazoles.

Table 2. Anti-BVDV Activity of Ribonucleoside Derivatives Having the BDT Group

compound	EC_{50} (μM)	EC_{50}^{rel}	CC_{50} (μM)	CC_{50}/EC_{50}
ribavirin	0.67	1	>100	150<
19	50.6	75.5	73.9	1.46
20	56.7	84.6	67.3	1.19
21	<48.0	<71.69	48.0	<1
23a	28.5	42.5	70.4	2.47
23b	39.2	58.5	74.3	1.89
23c	14.4	21.5	73.2	5.09
26	18.4[a]	15.3[a]	59.2[a]	3.21
30	50.3[b]	82.5[b]	60.1[b]	1.19

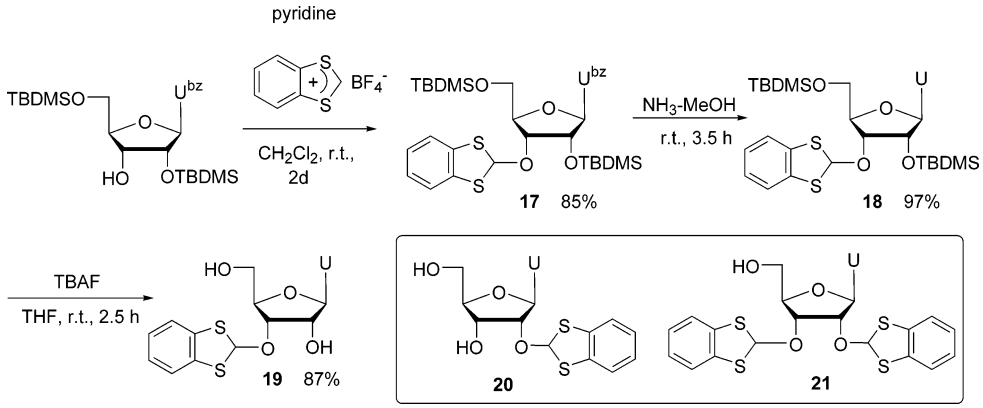
[a] In this case, the EC_{50} and CC_{50} for ribavirin were 1.2 and >100, respectively. [b] In this case, the EC_{50} and CC_{50} for ribavirin were 0.61and 90.2, respectively.

If the 2′-deoxynucleosides derivatives described above act as anti-BVDV agents according to a mechanism similar to that of the halogenated β-D-ribosylbenzimidazoles, ribonucleoside derivatives must be more active than deoxynucleoside derivatives. Therefore, we examined the synthesis of the ribonucleosides modified by BDT groups on their 2′ and 3′ hydroxyl groups. Accordingly, 3′-*O*-BDT-uridine (**19**) was synthesized as shown in Scheme 8, and 2′-*O*-BDT-uridine (**20**) and 2′, 3′-*O*-bis-BDT-uridine (**21**) were synthesized, as reported previously.[15]

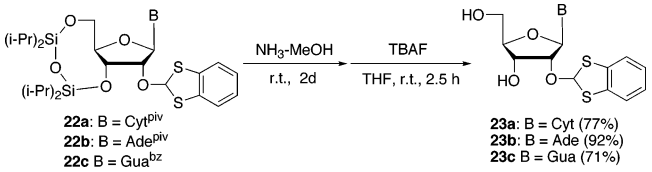
As shown in Table 2, uridine derivatives **19** and **20** having a BDT group showed weaker anti-BVDV activity as compared to the lead compound **1** as judged from their relative EC_{50} values to that of ribavirin, whereas the ratios of CC_{50}/EC_{50} of **19** and **20** were comparable to that of **1**. On the contrary, the uridine derivative **21** bearing two BDT groups showed much higher toxicity.

From these results, it was postulated that a BDT could be introduced either on the 2′ or the 3′ position of ribonucleosides without losing the CC_{50}/EC_{50} ratio and that introduction of two BDT groups in a ribonucleoside could induce severe cytotoxicity.

Scheme 8. Synthesis of Uridine Derivatives Having BDT Groups



Scheme 9. Synthesis of Cytidine, Adenosine and Guanosine Derivatives Having a BDT Group



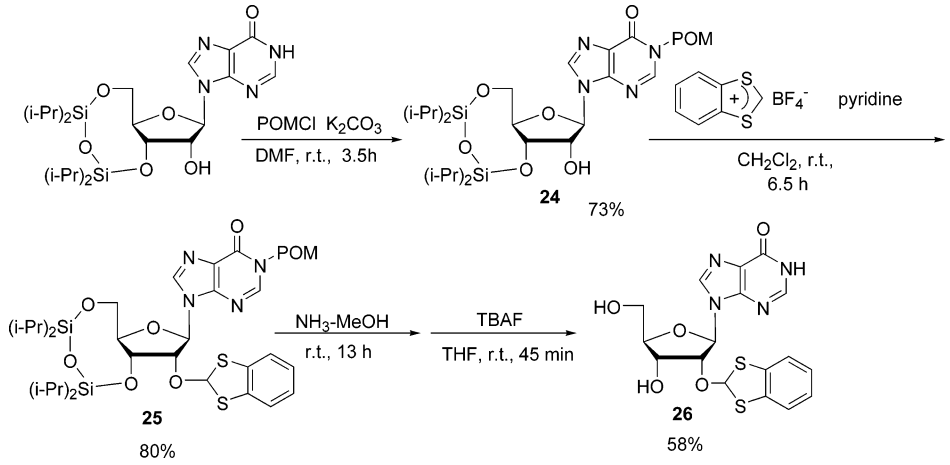
Therefore, we further examined the synthesis of other ribonucleoside derivatives having a BDT group on their 2′ position. The 2′ position was chosen because it can be modified more easily via the selective protection of the 3′- and 5′-hydroxyl groups by the 1,1,3,3-tetraisopropyldisiloxan-1,3-di-yl (TIPDS) group (Scheme 9).

The 2′-BDT derivatives of cytidine, adenosine and guanosine were synthesized starting from the fully protected ribonucleosides, **22a**, **22b** and **22c**, respectively. The 2′-BDT derivatives of inosine **26** and 4-*N*-methoxycarbonyldytidine **30** were synthesized, as shown in Scheme 10 and Scheme 11.

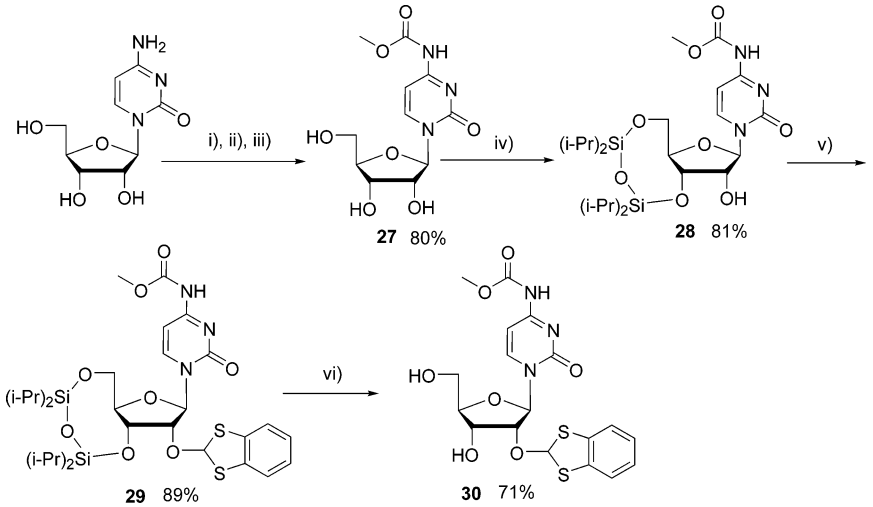
Compound **30** was designed based on our previous finding[16] that 4-*N*-methoxycarbonylcytosine could form a stable base pair with both guanine and adenine. The antiviral agent ribavirin, a positive control used in this study, has been known to form stable base pairs with both the cytosine and uracil bases,[17,18] and this stable mismatch base pair may induce mutation in viral genome. Therefore, a similar effect on viral genome mutation was expected for the mismatch-forming nucleoside **30** if the mechanism of action of BDT-nucleosides is the same as that of ribavirin.

The anti-BVDV activities of the ribonucleoside derivatives are shown in Table 2. As judged from the relative EC_{50} values (EC_{50}^{rel}), the inosine **26** and the guanosine **23c** derivatives showed the best and the second best antiviral activities, respectively. In both cases, the antiviral activities were stronger than that of the lead compound **1** ($EC_{50}^{rel} = 31.2$). On the other hand when the CC_{50}/EC_{50} values were used to evaluate the overall efficacy, the guanosine derivative **23c** was apparently the most preferable among the 2′-deoxyribo- and ribonucleoside derivatives reported in this study. Since the CC_{50}/EC_{50}value of **23c** was significantly smaller than those of **1** and other nucleoside derivatives, the guanosine moiety must play some important role to enhance the antiviral activity without stimulating the cytotoxicity. On the contrary, the mismatch-forming nucleoside **30** showed only weak antiviral activity and rather strong cytotoxicity.

Scheme 10. Synthesis of Inosine Derivative Having a BDT Group



Scheme 11. Synthesis of 4-*N*-Methoxycarbonylcytidine Derivative (**30**)[a]



[a] Reagents: (i) HMDS (3 equiv), TMSCl (cat.), CH_3CN, 60 °C, 1 h; (ii) methyl chloroformate (1.5 equiv), pyridine, r.t., 15 min; (iii) concentrated NH_3-pyridine (1:1, v/v), r.t., 50 min. (iv) 1,3-dichloro-1,1,3,3-tetraisopropyl-1,3-disiloxane (1.2 equiv), pyridine, r.t., 3 h; (v) 1,3-benzodithiolium tetrafluoroborate (1 equiv), pyridine, r.t., 4 h; (vi) tetra-*n*-butylammonium fluoride (2.5 equiv), THF, r.t., 15 min.

Conclusion

In this paper we reported new nucleoside derivatives modified by a BDT group as anti-BVDV agents. Since BVDV is similar to HCV in terms of their genome structure and amino acid sequences, anti-BVDV agents are expected to become good lead compounds for anti-HCV agents. As discussed in the text, some of the 2′-deoxyribo- and ribonucleosides having a BDT group on their hydroxyl functions showed significant anti-BVDV activity. The BDT groups could not be replaced by other heteroaromatic substituents such as benzodioxol-2-yl, benzimidazole-2-yl and the *S*-oxide derivatives of BDT. Therefore, the BDT could be considered as the essential structural component to elicit the anti-BVDV activities. Among all the nucleosides reported newly in this paper, the guanosine derivative **23c** showed the most preferable properties in terms of the high anti-BVDV activity and rather low cytotoxicity. Although the inosine derivative **26** showed much stronger anti-BVDV activity than **23c**, it was not superior to **23c** because of its higher cytotoxicity. The fact that both the guanosine and inosine derivatives showed rather strong anti-BVDV activities while the adenosine derivative **23b** did not exhibit any activity suggested that the carbonyl group and the imino group of the positions 6 and 1 of the purine ring might be important to enhance the anti-BVDV activity.

The detailed mechanism of action of nucleoside derivatives having a BDT group has not been clarified yet. However, the involvement of the mechanism independent of the 5′-phosphorylation was indicated by the anti-BVDV activity of the 5′-deoxy derivative **16**. Such, 5′-phosphorylation independent mechanisms have been recently reported for the activity of halogenated benzimidazole nucleosides on HCV and related viruses.[12,13] Inhibition of the RNA helicase and NTPase activity of NS3 protein is considered important in such a mechanism.[14] Therefore, the new pharmacophore, BDT, found in this study might provide a new drug design strategy to develop nucleoside-type anti-BVDV agents having RNA helicase and/or NTPase activity of NS3 protein. However, further extensive studies are needed to clarify if BDT-modified nucleoside derivatives show the anti-BVDV activity in a similar mode.

Experimental Section

3′-*O*-(1,3-Benzodithiol-2-yl)thymidine (1). Compound **3a** (5.0 g, 9.8 mmol) was dissolved in tetrahydrofuran (100 mL). To this solution was added tetra-*n*-butylammonium fluoride (3.8 g, 14.7 mmol), and the resulting solution was stirred at ambient temperature for 30 min. The solvent was removed under reduced pressure, and the residue was dissolved in $CHCl_3$ (100 mL), washed three times with water (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on a column of silica gel (C200, 150 g) with hexanes−ethyl acetate (35:65, v/v) containing 0.5% triethylamine (v/v) to give **1** (3.8 g, 98%): ^{1}H NMR ($CDCl_3$) δ 1.77 (3H, s), 2.22−2.41 (2H, m), 3.63 (1H, dd, J = 2.7, 12.0 Hz), 3.80 (1H, dd, J = 2.7, 12.3 Hz), 4.01 (1H, m), 4.26−4.31 (1H, m), 6.05 (1H, dd, J = 6.8, 6.8 Hz), 6.69 (1H, s), 7.05−7.35 (5H, m, 6-H); ^{13}C NMR ($CDCl_3$) δ 12.5, 38.2, 61.5, 74.7, 84.8, 86.1, 89.3, 111.0, 121.9, 122.1, 125.6, 135.3, 135.5, 136.5, 150.3, 163.8. MS *m*/*z* calcd for $C_{17}H_{19}N_2O_5S_2^+$: 395.0735, found 395.0738.

3′-*O*-(1,3-Benzodithiol-2-yl)-5′-*O*-(*tert*-butyldimethylsilyl)thymidine (3a). 5′-*O*-(*tert*-Butyldimethylsilyl)thymidine (5.0 g, 14 mmol) was dissolved in anhydrous CH_2Cl_2 (140 mL). To this solution were added 1,3-benzodithiolium tetrafluoroborate (3.7 g, 15.4 mmol) and anhydrous pyridine (2.5 mL, 30.8 mmol). The resulting mixture was stirred at ambient temperature. After 12 h, to this solution was added triethylamine (5.4 mL, 38.5 mmol), and the resulting solution was stirred for an additional 15 min. The reaction mixture was washed three times with water (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was chromatographed on a column of silica gel (120 g) with hexanes−ethyl acetate (85:15, v/v) containing 0.5% pyridine to give **3a** (5.0 g, 69%) as a white foam: ^{1}H NMR ($CDCl_3$) δ −0.10 (3H, s), −0.05 (3H, s), 0.77 (9H, s), 1.80−1.94 (4H, m), 2.38−2.45 (1H, m), 3.52 (1H, dd, J = 1.9 Hz, 11.2 Hz), 3.75 (1H, dd, J = 1.9 Hz, 11.1 Hz), 4.13−4.19 (2H, m), 6.23 (1H, m), 6.89 (1H, s), 7.03−7.32 (5H, m), 9.21 (1H, br); ^{13}C NMR ($CDCl_3$) δ − 5.5, − 5.4, 12.6, 18.2, 25.9, 39.4, 62.8, 75.4, 84.7, 85.5, 88.8, 110.8, 121.8, 121.9, 125.6, 135.0, 135.6, 135.7, 150.2, 163.7. MS *m*/*z* calcd for $C_{23}H_{33}N_2O_5S_2Si^+$: 509.1600, found 509.1594.

3′-*O*-(1,3-Benzodithiol-2-yl)-5′-*O*-(*tert*-butyldimethylsilyl)-6-*N*-pivaloyl-deoxyadenosine (3b). 5′-*O*-(*tert*-Butyldimethylsilyl)-6-*N*-pivaloyl-deoxyadenosine (4.5 g, 10.0 mmol) was dissolved in anhydrous CH_2Cl_2 (100 mL). To this solution were added 1,3-benzodithiolium tetrafluoroborate (3.6 g, 15.0 mmol) and anhydrous pyridine (2.4 mL, 30.0 mmol). The resulting mixture was stirred at ambient tempetarure. After 4.5 h, to this solution was added triethylamine (8.4 mL, 60 mmol), and the resulting solution was stirred for an additional 15 min. The reaction mixture was washed three times with water (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on a column of silica gel (N60, 160 g) with hexanes−ethyl acetate (55:45, v/v) to give **3b** (4.3 g, 71%) as a white foam: ^{1}H NMR ($CDCl_3$) δ −0.06, −0.04 (6H, 2s), 0.79 (9H, s), 1.36 (9H, s), 2.56−2.62 (2H, m), 3.60 (1H, dd, J = 3.0), 3.76 (1H, dd, J = 3.0, 11.1 Hz), 4.20 (1H, m), 4.43 (1H, m), 6.38 (1H, m), 6.78 (1H, s), 7.07−7.34 (4H, m), 8.09 (1H, s), 8.46 (1H, s), 8.65 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.5, −5.4, 18.3, 25.9, 27.5, 39.7, 40.5, 62.7, 75.5, 84.3, 85.8, 89.0, 121.9, 122.0, 122.8, 125.6, 135.4, 135.5, 140.8, 149.2, 151.0, 152.3, 175.3. MS *m*/*z* calcd for $C_{28}H_{40}N_5O_4S_2Si^+$: 602.2291, found 602.2285.

3′-*O*-(1,3-Benzodithiol-2-yl)-5′-*O*-(*tert*-butyldimethylsilyl)-2-*N*-isobutyryl-deoxyguanosine (3c). 5′-*O*-(*tert*-Butyldimethylsilyl)-2-*N*-isobutyryl-deoxyguanosine (3.5 g, 7.8 mmol) was dissolved in anhydrous CH_2Cl_2 (78 mL). To this solution were added 1,3-benzodithiolium tetrafluoroborate (2.8 g, 11.6 mmol) and anhydrous pyridine (1.9 mL, 23.3 mmol). The resulting mixture was stirred at ambient temperature. After 4 h, to this solution was added triethylamine (6.5 mL, 46.5 mmol), and the resulting solution was stirred for an additional 15 min. The reaction mixture was washed three times with water (80 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on a column of silica gel (C300, 180 g) with hexanes−ethyl acetate (50:50, v/v) to give **3c** (2.9 g, 62%) as a white foam: ^{1}H NMR ($CDCl_3$) δ −0.08 (6H, s), 0.77 (9H, s), 1.20 (6H, m), 2.33−2.81 (3H, m), 3.56 (1H, m), 3.68 (1H, dd, J = 2.2, 11.1 Hz), 4.16 (1H, m), 4.33 (1H, m), 6.06 (1H, dd, J = 6.6, 6.6 Hz), 6.77 (1H, s), 7.05−7.33 (4H, m), 7.77 (1H, s), 9.82 (1H, br), 12.19 (1H, br); ^{13}C NMR ($CDCl_3$) δ − 5.6, − 5.4, 18.3, 19.0, 19.1, 25.9, 62.8, 75.5, 83.6, 85.7, 89.0, 120.8, 121.9, 122.0, 125.7, 135.4, 135.5, 136.4, 147.5, 148.0, 155.8, 178.8. MS *m*/*z* calcd for $C_{27}H_{38}N_5O_5S_2Si^+$ 604.2084, found 604.2089.

3′-*O*-(1,3-Benzodithiol-2-yl)-5′-*O*-(isobutyloxycarbonyl)-4-*N*-pivaloyl-deoxycytidine (3d). 5′-*O*-(Isobutyloxycarbonyl)-4-*N*-pivaloyl-deoxycytidine (600 mg, 1.5 mmol) was dissolved in anhydrous CH_2Cl_2 (15 mL). To this solution were added 1,3-benzodithiolium tetrafluoroborate (700 mg, 2.9 mmol) and anhydrous pyridine (0.35 mL, 4.4 mmol). The resulting mixture was stirred at ambient tempetarure. After 7 h, to this solution was added triethylamine (1.2 mL, 8.8 mmol), and the resulting solution was stirred for an additional 15 min. The reaction mixture was washed three times with water (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on a column of silica gel (C200, 20 g) with hexanes−ethyl acetate (60:40, v/v) containing 0.5% pyridine (v/v) to give **3c**

(700 mg, 85%) as a white foam: ^{1}H NMR ($CDCl_3$) δ 0.84 (6H, d, J = 6.9 Hz), 1.17 (9H, s), 1.83−2.68 (3H, m), 3.81 (2H, d, J = 6.8 Hz), 4.05−4.27 (4H, m), 6.06 (1H, dd, J = 5.9, 5.9 Hz), 6.64 (1H, s), 6.97−7.24 (5H, m, 5-H), 7.77 (1H, s, J = 7.6 Hz), 8.09 (1H, s); ^{13}C NMR ($CDCl_3$) δ 18.7, 26.8, 26.9, 27.5, 65.5, 73.7, 74.1, 82.2, 86.6, 86.7, 89.0, 95.7, 121.7, 121.8, 125.3, 134.9, 135.1, 143.4, 154.3, 154.4, 161.7, 177.5. MS *m*/*z* calcd for $C_{26}H_{34}N_3O_7S_2^+$: 564.1838, found 564.1829.

3′-*O*-(1,3-Benzodithiol-2-yl)deoxyadenosine (4a). Compound **3b** (602 mg, 1.0 mmol) was dissolved in 2 M NH_3/CH_3OH (10 mL), and the resulting solution was stirred at ambient temperature for 21 h. The solvent was removed under reduced pressure, and the residue was dissolved in $CHCl_3$ (10 mL). The solution was washed three times with water (10 mL) and the solvent was removed under reduced pressure. The residue was dissolved in tetrahydrofuran (10 mL). To this solution was added tetra-*n*-butylammonium fluoride (392 mg, 1.5 mmol), and the resulting solution was stirred at ambient temperature for 2 h. The solvent was removed under reduced pressure, and the residue was dissolved in $CHCl_3$ (10 mL) and washed three times with water (10 mL). The aqueous layer was extracted with $CHCl_3$ (10 mL), and the all the organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting precipitates were collected by filtration to give **4a** (309 mg, 77%): ^{1}H NMR (DMSO-d_6) δ 2.77−2.87 (2H, m), 3.46−3.61 (2H, m), 4.08 (1H, m), 4.57 (1H, m), 5.41 (1H, t, J = 5.5 Hz), 6.25 (1H, m), 6.99 (1H, s), 7.14−7.19 (2H, m), 7.35 (2H, s), 7.46−7.51 (2H, m), 8.09 (1H, s), 8.26 (1H, s); ^{13}C NMR (DMSO-d_6) δ 36.7, 61.6, 77.8, 84.1, 85.2, 89.1, 119.2, 122.4, 125.5, 135.2, 135.3, 139.5, 148.6, 152.2, 156.0. Anal. Calcd for $C_{17}H_{17}N_5O_3S_2 \cdot 1/10H_2O$: C, 50.38; H, 4.28; N, 17.28; S, 15.82. Found: C, 50.33; H, 4.52; N, 17.09; S, 15.55.

3′-*O*-(1,3-Benzodithiol-2-yl)deoxyguanosine (4b). Compound **3c** (700 mg, 1.16 mmol) was dissolved in 2 M NH_3/CH_3OH (12 mL), and the resulting solution was stirred at ambient temperature for 48 h. The solvent was removed under reduced pressure, and the residue was dissolved in *N*,*N*-dimethylformamide (10 mL)−tetrahydrofuran (10 mL). To this solution was added tetra-*n*-butylammonium fluoride (455 mg, 1.74 mmol), and the resulting solution was stirred at ambient temperature for 3 h. To this solution as added ethyl acetate (10 mL), and the resulting solution was washed twice with water (10 mL). The organic layer was removed and the white precipitation separated from the aqueous layer was collected by filtration to give **4b** (345 mg, 71%): ^{1}H NMR (DMSO-d_6) δ 2.37−2.65 (2H, m), 3.47 (2H, m), 3.99 (1H, m), 4.49 (1H, m), 5.06 (1H, s), 6.00 (1H, m), 6.48 (2H, br), 7.14−7.50 (4H, m), 7.86 (1H, s, 8-H), 10.66 (1H, br, 1-NH); ^{13}C NMR (DMSO-d_6) δ 36.7, 61.3, 77.9, 82.4, 84.7, 89.1, 116.5, 122.5, 125.6, 135.0, 135.2, 150.7, 153.6, 156.6. Anal. Calcd for $C_{17}H_{17}N_5O_4S_2$: C, 48.67; H, 4.08; N, 16.70; S, 15.29. Found: C, 48.37; H, 3.91; N, 16.50; S, 15.29.

3′-*O*-(1,3-Benzodithiol-2-yl)deoxycytidine (4c). Compound **3d** (600 mg, 1.06 mmol) was dissolved in concentrated NH_3/CH_3OH (10 mL), and the resulting solution was stirred at ambient temperature for 11 h. The solvent was removed under reduced pressure and the residue trituated with CH_3OH. The white precipitation was collected by filtration to give **4c** (316 mg, 78%): ^{1}H NMR (DMSO-d_6) δ 1.97−2.07 (1H, m), 2.27−2.49 (1H, m), 3.50 (2H, s), 4.35 (1H, s), 5.06 (1H, t, J = 4.9 Hz), 5.71 (1H, d, J = 7.6 Hz), 6.04−6.09 (1H, m), 6.93 (1H, s), 7.14−7.19 (4H, m), 7.46−7.49 (2H, m), 7.72 (1H, d, J = 7.6 Hz); ^{13}C NMR (DMSO-d_6) δ 37.5, 61.1, 77.4, 84.3, 84.85, 84.93, 89.0, 94.06, 94.15, 122.4, 125.5, 135.20, 135.24, 140.8, 154.8, 165.3. MS *m*/*z* calcd for $C_{16}H_{18}N_3O_4S_2^+$: 380.0739, found 380.0739.

5′-*O*-(*tert*-Butyldimethylsilyl)-3′-*O*-[[2-(methylthio)phenyl]thiomethyl]thymidine (5a). Compound **3a** (1.0 g, 2.0 mmol) was dissolved in toluene (20 mL). To this solution were added tri-*n*-butyltin hydride (1.3 mL, 5.0 mmol) and AIBN (492 mg, 3.0 mmol). The resulting solution was stirred at 100 °C for 90 min. The reaction mixture was cooled to ambient temperature, and the solvent was removed under reduced pressure. To this residue were added anhydrous *N*,*N*-dimethylformamide (20 mL) and methyl iodide (1.3 mL, 20 mmol), and the resulting solution was stirred at ambient temperature for 4 h. The reaction mixture was diluted by adding $CHCl_3$ (50 mL), washed five times with water (50 mL), dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The residue was chromatographed on a column of silica gel (C200, 20 g) with hexanes−ethyl acetate (80:15. v/v) to give **5a** (894 mg, 85%): ^{1}H NMR ($CDCl_3$) δ 0.09 (6H, s), 0.90 (9H, s), 1.89−2.00 (4H, m), 2.33−2.42 (4H, m), 3.75 (1H, dd, J = 2.2, 11.2 Hz), 3.84 (1H, dd, J = 2.2, 11.2 Hz), 4.05 (1H, m), 4.56 (1H, m), 4.93 (1H, d, J = 11.9 Hz), 5.02 (1H, d, J = 11.9 Hz), 6.23−6.28 (1H, m), 7.07−7.50 (5H, m, ArH), 9.46 (1H, br); ^{13}C NMR ($CDCl_3$) δ −5.4, −5.3, 12.6, 15.8, 18.4, 25.9, 37.7, 63.5, 73.6, 77.1, 84.8, 110.8, 125.26, 125.28, 127.9, 131.6, 132.4, 135.1, 140.5, 150.3, 163.8. MS *m*/*z* calcd for $C_{24}H_{37}N_2O_5S_2Si^+$: 525.1913, found 525.1911.

3′-*O*-[[2-(Methylthio)phenyl]thiomethyl]thymidine (6a). Compound **5a** (894 mg, 1.7 mmol) was dissolved in tetrahydrofuran (17 mL). To this solution was added tetra-*n*-butylammonium fluoride (667 mg, 2.55 mmol). The resulting solution was stirred at ambient temperature for 1 h. The solvent was removed under reduced pressure, and the residue was dissolved in $CHCl_3$ (20 mL), washed three times with water (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on a column of silica gel (C200, 30 g) with hexanes−ethyl acetate (55:45, v/v) to give **6a** (550 mg, 79%): ^{1}H NMR ($CDCl_3$) δ 1.86 (3H, s), 2.26−2.32 (2H, m), 2.43 (3H, s), 3.06 (1H, s), 3.70−3.88 (2H, m), 4.02 (1H, m), 4.61−4.65 (1H, m), 4.93 (1H, d, J = 11.7 Hz), 5.06 (1H, d, J = 11.7 Hz), 7.06−7.49 (5H, m, 6-H), 9.47 (1H, s); ^{13}C NMR ($CDCl_3$) δ 12.6, 15.8, 37.0, 62.3, 74.0, 84.7, 86.4, 110.9, 125.2, 125.3, 128.0, 131.7, 132.2, 136.2, 140.5, 150.3, 163.9. MS *m*/*z* calcd for $C_{18}H_{23}N_2O_5S_2^+$: 411.1048, found 411.1049.

3′-*O*-[[2-(Methylthio)phenyl]thiomethyl]deoxyadenosine (6b). Compound **3b** (3.0 g, 5.0 mmol) was dissolved in benzene (50 mL). To this solution were added tri-*n*-butyltin hydride (3.4 mL, 12.5 mmol) and AIBN (1.6 g, 10 mmol). The resulting solution was stirred under reflux for 90 min. The reaction mixture was cooled to ambient temperature and the solvent was removed under reduced pressure. To this residue were added anhydrous *N*,*N*-dimethylformamide (67 mL) and methyl iodide (3.1 mL, 50 mmol), and the resulting solution was stirred at ambient temperature for 2 h. The reaction mixture was diluted by adding $CHCl_3$ (50 mL), washed seven times with water (50 mL), dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The residue was chromatographed on a column of silica gel (C300, 60 g) with hexanes−ethyl acetate (60:40. v/v) to give crude product **5b**. The crude **5b** was dissolved in 2 M NH_3/CH_3OH (23 mL), and the resulting solution was stirred at ambient temperature for 4 days. The solvent was removed under reduced pressure, and the residue was dissolved in tetrahydrofuran (25 mL). To this solution was added tetra-*n*-butylammonium fluoride (890 mg, 3.4 mmol), and the resulting solution was stirred at ambient temperature for 7 h. To this solution was added $CHCl_3$ (30 mL), washed twice with water (30 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The white precipitation separated during the evaporation was collected by filtration to give **6b** (640 mg, 32%): ^{1}H NMR (DMSO-d_6) δ 2.44 (3H, s), 2.49 (1H, m), 2.77−2.87 (1H, m), 3.51−3.70 (2H, m), 4.04 (1H, m), 4.68−4.69 (1H, m), 5.16 (2H, s), 5.45 (1H, m), 6.25−6.30 (1H, m), 7.13−7.57 (6H, m, ArH), 8.14 (1H, s), 8.33 (1H, s); ^{13}C NMR (DMSO-d_6) δ 14.9, 36.3, 38.6, 61.8, 72.6, 77.7, 84.2, 85.2, 119.2, 124.8, 125.0, 127.6, 130.7, 132.0, 139.4, 139.8, 148.6, 152.2, 156.0. Anal. Calcd for $C_{18}H_{21}N_5O_3S_2$: C, 51.53; H, 5.05; N, 16.69; S, 15.29. Found: C, 51.65; H, 5.02; N, 16.56; S, 15.24.

3′-*O*-[[2-(Methylthio)phenyl]thiomethyl]deoxyguanosine (6c). Compound **3c** (1.5 g, 2.4 mmol) was dissolved in benzene (24 mL). To this solution were added tri-*n*-butyltin hydride (2.3 mL, 8.4 mmol) and AIBN (788 g, 4.8 mmol). The resulting solution was stirred under reflux for 2.5 h. The reaction mixture was cooled to ambient temperature, and the solvent was removed under reduced pressure. To this residue

were added anhydrous *N*,*N*-dimethylformamide (24 mL) and methyl iodide (1.5 mL, 24 mmol), and the resulting solution was stirred at ambient temperature for 75 min. The reaction mixture was diluted by adding $CHCl_3$ (50 mL), washed five times with water (50 mL), dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The residue was chromatographed on a column of silica gel (C300, 40 g) with hexanes−ethyl acetate (45:55, v/v) to give crude product **5c**. The crude **5c** was dissolved in 2 M NH_3/CH_3OH (10 mL) and the resulting solution was stirred at ambient temperature for 2 days. The solvent was removed under reduced pressure, and the residue was dissolved in tetrahydrofuran (10 mL). To this solution was added tetra-*n*-butylammonium fluoride (290 mg, 1.1 mmol), and the resulting solution was stirred at ambient temperature for 20 min. To this solution was added $CHCl_3$ (30 mL), and it was washed three times with water (30 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The white precipitation separated during the evaporation was collected by filtration to give **6c** (230 mg, 22%): ^{1}H NMR (DMSO-d_6) δ 2.18−2.66 (5H, m), 3.54 (2H, m), 3.96 (1H, m), 4.60 (1H, m), 5.08−5.14 (3H, m), 6.04 (1H, dd, J = 5.9, 8.1 Hz), 6.48 (2H, br), 7.13−7.55 (4H, m), 7.94 (1H, s), 10.68 (1H, s); ^{13}C NMR (DMSO-d_6) δ 14.9, 36.4, 61.6, 72.5, 77.5, 82.7, 84.8, 116.6, 124.8, 125.0, 127.6, 130.6, 132.0, 135.1, 139.7, 150.7, 153.5, 156.6. MS *m*/*z* calcd for $C_{18}H_{22}N_5O_4S_2^+$: 436.1113, found 436.1125.

3′-*O*-[[2-(Methylthio)phenyl]thiomethyl]-4-*N*-pivaloyldeoxycytidine (6d). Compound **3d** (380 mg, 0.7 mmol) was dissolved in toluene (6.7 mL). To this solution were added tri-*n*-butyltin hydride (0.45 mL, 1.7 mmol) and AIBN (330 g, 2.0 mmol). The resulting solution was stirred at 100 °C for 2 h. The reaction mixture was cooled to ambient temperature, and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (N60, 15 g) with hexanes−ethyl acetate (70:30, v/v) to remove remaining starting material. The fractions containing stanylated intermediated were collected and concentrated under reduced pressure. To this residue were added anhydrous *N*,*N*-dimethylformamide (6.7 mL) and methyl iodide (417 μL, 6.7 mmol), and the resulting solution was stirred at ambient temperature for 24 h. The reaction mixture was diluted by adding $CHCl_3$ (10 mL), washed five times with water (10 mL), dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The residue was chromatographed on a column of silica gel (C200, 15 g) with hexanes−ethyl acetate (60:40. v/v) to give crude product **5d**. The crude **5d** was dissolved in 2 M NH_3/CH_3OH (2 mL), and the resulting solution was stirred at ambient temperature for 22 h. The solvent was removed under reduced pressure, and the residue was dissolved in $CHCl_3$ (10 mL) and washed three times with water (10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on a column of silica gel (C200, 40 g) column with $CHCl_3-CH_3OH$ (96:4. v/v) to give **6d** (75 mg, 30%): ^{1}H NMR ($CDCl_3$) δ 2.42−2.46 (3H, m), 2.95 (1H, br), 3.71−3.93 (2H, m), 4.07 (1H, m), 4.63−4.68 (1H, m), 4.93 (1H, d, J = 11.6 Hz), 5.12 (1H, d, J = 11.6 Hz), 5.35 (2H, 2H, br), 5.68 (1H, d, J = 7.6 Hz), 5.99 (1H, dd, J = 6.5, 6.5 Hz), 7.10−7.53 (4H, m), 7.67 (1H, d, J = 7.6 Hz); ^{13}C NMR (DMSO-d_6) δ 14.9, 37.1, 61.4, 72.5, 77.2, 84.4, 85.0, 94.0, 124.8, 125.0, 127.5, 130.6, 132.0, 139.6, 140.7, 154.8, 165.3. Anal. Calcd for $C_{17}H_{21}N_3O_4S_2 \cdot 3/10H_2O$: C, 50.93; H, 5.43; N, 10.48; S, 16.00. Found: C, 50.99; H, 5.27; N, 10.23; S, 15.96.

2-Methoxybenzodithiol (7). 1,3-Benzodithiolium tetrafluoroborate (9.6 g, 40 mmol) was dissolved in anhydrous pyridine (80 mL). To this solution was added anhydrous methanol (8.1 mL, 200 mmol), and the resulting solution was stirred at ambient temperature for 1 h. Triethylamine (22 mL, 240 mmol) was added, and the mixture was stirred for 15 min. The solvents were removed under reduced pressure, and the residue was dissolved in ethyl acetate (100 mL). The solution was washed three times with water (100 mL). The organic layer was collected and concentrated under reduced pressure. The residue was chromatographed on a column of silica gel (C200, 200 g) with hexane containing 1% triethylamine (v/v) to give **7** (6.3 g, 85%): ^{1}H NMR ($CDCl_3$) δ 3.20 (1H, s), 6.76 (1H, s), 7.07−7.36 (4H, m); ^{13}C NMR ($CDCl_3$) δ 51.2, 90.9, 121.68, 121.71, 125.2, 136.0. MS *m*/*z* calcd for $C_8H_9OS_2^+$: 185.0095, found 185.0026.

3′-*O*-(1-Oxo-1,3-benzodithiol-2-yl)thymidine (8). Compound **1** (394 mg, 1.0 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL). To this solution were added *m*-chlorobenzoic peroxide (240 mg, 1.0 mmol) and $NaHCO_3$ (84 mg, 1.0 mmol). The resulting suspension was stirred vigorously at ambient temperature for 2 h. The reaction mixture was washed three times with saturated aqueous $NaHCO_3$, and the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (C200, 12 g) with $CHCl_3-CH_3OH$ (99:1, v/v) containing 0.5% triethylamine (v/v) to give **8** (191 mg, 47%): ^{1}H NMR (DMSO-d_6) δ 1.76 (3H, s), 2.29 (2H, m), 3.58 (2H, m), 3.92−3.96 (1H, m), 4.68 (1H, m), 5.17 (1H, m), 6.03 (1H, dd, J = 3.0, 3.0 Hz), 6.53 (1H, s), 7.34−8.08 (5H, m, ArH), 11.30 (1H, s); ^{13}C NMR ($CDCl_3$-DMSO-d_6, 9:1, v/v) δ 12.1, 36.9, 37.2, 61.0, 77.2, 102.3, 102.4, 110.1, 110.2, 124.0, 124.1, 125.95, 125.98, 128.3, 128.4, 133.2, 135.1, 135.2, 139.8, 142.1, 149.99, 150.01, 163.6. MS *m*/*z* calcd for $C_{17}H_{19}N_2O_6S_2^+$ 411.0685, found 411.0684. IR (KBr) 1055 cm^{-1} (SO).

3′-*O*-(1,3-Dioxo-1,3-benzodithiol-2-yl)thymidine (9). Compound **1** (394 mg, 1.0 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL). To this solution were added *m*-chlorobenzoic peroxide (480 mg, 2.0 mmol) and $NaHCO_3$ (168 mg, 2.0 mmol). The resulting suspension was stirred vigorously at ambient temperature for 2 h. The reaction mixture was washed three times with saturated aqueous $NaHCO_3$, and the separated white precipitate was collected by filtration to give **9** (100 mg, 23%) as a diastreomeric mixture: ^{1}H NMR (DMSO-d_6) δ 1.77 (3H, s), 2.27−2.44 (2H, m), 3.64 (2H, m), 4.14 (1H, m), 4.80 (1H, m), 5.21 (1H, s), 6.16 (1H, dd, J = 8.6, 8.6 Hz), 6.54 (1H, s), 7.71 (1H, s), 7.85−8.23 (4H, m), 11.33 (1H, s); ^{13}C NMR (DMSO-d_6) δ 12.4, 37.0, 61.3, 83.5, 83.6, 84.4, 85.2, 105.1, 109.5, 109.6, 111.2, 128.4, 129.2, 133.4, 135.8, 135.9, 141.6, 142.97, 143.00, 143.3, 150.27, 150.29, 163.49, 163.51; IR (KBr) 1051 cm^{-1} (SO). MS *m*/*z* calcd for $C_{17}H_{19}N_2O_7S_2^+$ 427.0634, found 427.0638.

3′-*O*-(1,1,3,3-Tetraoxo-1,3-benzodithiol-2-yl)thymidine (10). Compound **1** (394 mg, 1.0 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL). To this solution were added *m*-chlorobenzoic peroxide (983 mg, 4.1 mmol) and $NaHCO_3$ (344 mg, 4.1 mmol). The resulting suspension was stirred vigorously at ambient temperature for 90 m. Ethyl acetate (10 mL) was added, and the reaction mixture was washed three times with water (20 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was trituated with CH_3OH and C_2H_5OH, and the separated white precipitate was collected by filtration to give **10** (418 mg, 91%): ^{1}H NMR (DMSO-d_6) δ 1.77 (3H, s), 2.27−2.48 (2H, m), 3.63 (2H, m), 4.06 (1H, m), 4.23 (1H, m), 6.13 (1H, dd, J = 4.6, 4.6 Hz), 6.11−6.16 (1H, m), 6.95 (1H, s), 7.71 (1H, s), 8.07−8.29 (4H, m), 11.31 (1H, s); ^{13}C NMR (DMSO-d_6) δ 12.4, 37.0, 61.1, 83.5, 84.3, 85.7, 93.9, 109.6, 123.5, 135.7, 136.0, 136.1, 136.4, 150.3, 163.5; IR (KBr) 1178, 1353 cm^{-1} (SO_2). MS *m*/*z* calcd for $C_{17}H_{19}N_2O_9S_2^+$ 459.0532, found 459.0537.

3′-*O*-(1,3-Benzodioxol-2-yl)-5′-*O*-(*tert*-butyldimethylsilyl)thymidine (11). 5′-*O*-(*tert*-Butyldimethylsilyl)thymidine (1.0 g, 2.8 mmol) was dissolved in anhydrous 1,4-dioxane (28 mL). To this solution were added molecular sieves 4A (3.0 g), 2-methoxy-1,3-benzodioxol (4.3 g, 28 mmol) and *p*-toluenesulfonic acid hydrate (1.1 mL, 5.6 mmol). The resulting mixture was stirred under reflux for 29 h. The reaction mixture was cooled to ambient temperature and triethylamine (39 mL, 14 mmol) was added. After 15 min, molecular sieves was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (30 mL), washed three times with water (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue

was chromatographed on a column of silica gel (C200, 40 g) with hexanes−ethyl acetate (70:30, v/v) containing 0.5% pyridine to give **3a** (198 mg, 15%) as a white foam: ^{1}H NMR ($CDCl_3$) δ −0.99, −0.05 (6H, 2s), 0.73 (9H, s), 1.85−2.01 (4H, m), 2.44−2.52 (1H, m), 3.56 (1H, dd, J = 1.9, 11.6 Hz), 3.80 (1H, dd, J = 1.9, 11.6 Hz), 4.19 (1H, m), 4.44 (1H, m), 6.31−6.36 (1H, m), 6.82−6.96 (5H, m), 7.38 (1H, s), 9.50 (1H, br); ^{13}C NMR ($CDCl_3$) δ −5.7, −5.5, 12.5, 18.2, 25.8, 39.2, 62.9, 73.2, 84.5, 85.5, 108.2, 108.3, 110.9, 117.9, 121.9, 122.0, 134.9, 145.3, 145.5, 150.3, 163.8. MS *m*/*z* calcd for $C_{23}H_{33}N_2O_7Si^+$: 477.2057, found 477.2064.

3′-*O*-(1,3-Benzodioxol-2-yl)thymidine (12). Compound **11** (190 mg, 0.4 mmol) was dissolved in tetrahydrofuran (4 mL). To this solution was added tetra-*n*-butylammonium fluoride (157 mg, 0.6 mmol), and the resulting solution was stirred at ambient temperature for 30 min. The solvent was removed under reduced pressure, and the residue was dissolved in $CHCl_3$ (10 mL) and washed three times with water (10 mL). The aqueous layer was extracted twice with $CHCl_3$ (10 mL), and all the organic layer was combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on a column of silica gel (C200, 12 g) with hexanes−ethyl acetate (50:50, v/v) containing 0.5% triethylamine to give **12** in quantitative yield: ^{1}H NMR (DMSO-d_6) δ 1.75 (3H, s), 2.17−2.34 (2H, m), 3.49−3.62 (2H, m), 3.96−3.98 (2H, m), 4.58−4.62 (1H, m), 5.15 (1H, t, J = 4.9 Hz), 6.08−6.13 (1H, m), 6.89−7.05 (4H, m), 7.21 (1H, s), 7.65 (1H, s), 11.3 (1H, s); ^{13}C NMR ($CDCl_3$) δ 12.4, 38.1, 61.7, 73.4, 85.2, 86.4, 108.4, 108.5, 110.9, 118.1, 121.9, 136.8, 145.2, 150.4, 164.0. MS *m*/*z* calcd for $C_{17}H_{19}N_2O_7^+$: 363.1192, found 363.1192.

3′-*O*-(1-Benzylbenzimidazol-2-yl)-5′-*O*-(*tert*-butyldimethylsilyl)thymidine (13). 5′-*O*-(*tert*-Butyldimethylsilyl)thymidine (2.0 g, 5.6 mmol) was dissolved in anhydrous *N*,*N*-dimethylformamide (50 mL). To this solution was added sodium hydride (470 mg, 12 mmol), and the resulting mixture was stirred at ambient temperature for 1 h. 1-Benzylbenzimidazol-2-yl (2.7 g, 11 mmol) was added, and the resulting mixture was stirred for 28 h. The reaction was quenched by adding CH_3OH (10 mL), and the resulting solution was stirred for 15 min. CH_2Cl_2 (50 mL) was added, and the solution was washed four times with water (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on a column of silica gel (C200, 60 g) with hexanes−ethyl acetate (75:25, v/v) to give **13** (1.3 g, 41%) as a white foam: ^{1}H NMR ($CDCl_3$) δ 0.17, 0.18 (6H, 2s), 0.95 (9H, s), 1.94 (3H, s), 2.24−2.70 (2H, m), 3.96 (1H, dd, J = 1.9, 11.5 Hz), 4.11 (1H, dd, J = 1.9, 11.3 Hz), 4.31 (1H, m), 5.17 (1H, s), 6.41 (1H, dd, J = 5.4, 9.2 Hz), 7.12−7.53 (9H, m), 7.59 (1H, s), 9.38 (1H, br); ^{13}C NMR ($CDCl_3$) δ −5.3, −5.2, 12.6, 18.4, 26.0, 38.5, 45.9, 63.7, 80.9, 84.7, 85.3, 108.7, 111.1, 117.9, 121.2, 126.9, 127.8, 128.8, 133.6, 134.9, 135.7, 139.8, 150.4, 155.7, 163.7. MS *m*/*z* calcd for $C_{30}H_{39}N_2O_5Si^+$: 563.2690, found 563.2685.

3′-*O*-(Benzimidazol-2-yl)-5′-*O*-(*tert*-butyldimethylsilyl)thymidine (14). Compound **13** (710 mg, 1.3 mmol) was dissolved in acetic acid (23 mL). To this solution were added palladium hydroxide (1.2 g), and the resulting mixture was stirred under hydrogen atmosphere at ambient temperature for 5 d. The catalyst was removed by filtration using Celite, and the filtrate was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (30 mL), washed three times with water (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on a column of silica gel (C300, 20 g) with hexanes−ethyl acetate (70:30, v/v) to give **14** (375 g, 63%) as a white foam: ^{1}H NMR ($CDCl_3$) δ 0.10 (6H, s), 0.89 (9H, s), 1.92 (3H, s), 2.13−2.59 (2H, m), 3.89−4.05 (2H, m), 4.29 (1H, m), 5.56 (1H, m), 6.35 (1H, dd, J = 4.9, 9.5 Hz), 7.09−7.46 (4H, m), 7.56 (1H, s), 10.03, 10.10 (2H, 2s); ^{13}C NMR ($CDCl_3$) δ −5.42, −5.37, 12.5, 18.3, 25.9, 38.3, 63.7, 80.5, 84.6, 85.0, 110.0, 111.3, 117.2, 121.3, 132.3, 135.0, 140.6, 150.9, 156.6, 164.2. MS *m*/*z* calcd for $C_{23}H_{33}N_4O_5Si^+$: 473.2220, found 473.2227.

3′-*O*-(Benzimidazol-2-yl)thymidine (15). Compound **14** (375 mg, 0.8 mmol) was dissolved in tetrahydrofuran (8 mL). To this solution was added tetra-*n*-butylammonium fluoride (311 mg, 1.2 mmol), and the resulting solution was stirred at ambient temperature for 90 min. The separated precipitate was dissolved by adding $CHCl_3$ and CH_3OH. To this solution was added silica gel (C300, 2.5 g), and the solvent was removed under reduced pressure. The silica gel containing the materials was placed on a column of silica gel (C300, 10 g) and chromatographed with $CHCl_3$−CH_3OH (97.5:2.5, v/v) to give **15** (218 mg, 77%): ^{1}H NMR (DMSO-d_6) δ 1.79 (3H, s), 2.36−2.50 (2H, m), 3.71 (1H, dd, J = 3.2, 11.6 Hz), 3.78 (1H, dd, J = 3.2, 12.0 Hz), 4.20 (1H, m), 5.31 (1H, br), 6.24−6.30 (1H, m), 7.01−7.30 (4H, m), 7.79 (1H, s), 11.38 (1H, s), 11.96 (1H, s); ^{13}C NMR (DMSO-d_6) δ 12.4, 36.9, 61.5, 80.1, 83.7, 84.6, 109.7, 120.7, 135.7, 150.3, 157.0, 163.5. MS *m*/*z* calcd for $C_{17}H_{19}N_4O_5^+$: 359.1355, found 359.1348.

3′-*O*-(1,3-Benzodithiol-2-yl)-5′-deoxythymidine (16). 5′-Deoxythymidine (452 g, 2 mmol) was dissolved in anhydrous pyridine (10 mL). To this solution were added 1,3-benzodithiolium tetrafluoroborate (960 mg, 4.0 mmol), and the resulting mixture was stirred at ambient temperature for 24 h. Triethylamine (1.7 mL, 12 mmol) was added, and the resulting mixture was stirred for 15 min. The solvents were removed under reduced pressure, and the residue was dissolved in $CHCl_3$ (10 mL), washed three times with water (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on a column of silica gel (C200, 20 g) with hexanes−ethyl acetate (65:35, v/v) containing 0.5% pyridine (v/v) to give **16** (520 mg, 69%) as a white foam. ^{1}H NMR ($CDCl_3$) δ 1.25 (3H, d, J = 6.5 Hz), 1.83 (3H, s), 2.00−2.07 (1H, m), 2.42−2.51 (1H, m), 3.74−3.80 (1H, m), 3.99−4.03 (1H, m), 6.05−6.10 (1H, m), 6.74 (1H, s), 6.87−7.31 (5H, m), 9.45 (1H, br); ^{13}C NMR ($CDCl_3$) δ 12.7, 18.5, 38.5, 78.3, 80.0, 84.4, 89.1, 111.0, 121.8, 122.0, 125.6, 134.6, 135.4, 135.7, 150.1, 163.6. MS *m*/*z* calcd for $C_{17}H_{19}N_2O_4S_2^+$: 379.0786, found 379.0784.

3′-*O*-(1,3-Benzodithiol-2-yl)-*N*-3-benzoyl-2′,5′-*O*-bis(*tert*-butyldimethylsilyl)uridine (17). *N*-3-Benzoyl-2′, 5′-*O*-bis(*tert*-butyldimethylsilyl)uridine (1.4 g, 2.4 mmol) was dissolved in anhydrous CH_2Cl_2 (24 mL). To this solution were added 1,3-benzodithiolium tetrafluoroborate (1.3 g, 5.3 mmol) and pyridine (864 mL, 11 mmol), and the resulting mixture was stirred at ambient temperature for 3 days. Triethylamine (1.9 mL, 13 mmol) was added, and the resulting mixture was stirred for 15 min, washed three times with water (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on a column of silica gel (C200, 50 g) with hexanes−ethyl acetate (97:3, v/v) containing 0.5% triethylamine (v/v) to give **17** (1.5 g, 85%) as a white foam: ^{1}H NMR ($CDCl_3$) δ 0.06−0.13 (12H, m), 0.87, 0.92 (18H, 2s), 3.59−3.63 (1H, m), 3.88−3.95 (2H, m), 4.16−4.26 (2H, m), 5.63 (1H, d, J = 8.4 Hz), 5.79 (1H, d, J = 2.7 Hz), 6.80 (1H, s), 7.08−7.92 (9H, m), 7.98 (1H, d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ −5.5, −5.3, −4.7, −4.4, 18.1, 18.5, 25.7, 26.0, 61.4, 72.2, 75.5, 82.6, 89.1, 89.5, 101.6, 121.89, 121.92, 125.7, 126.0, 128.9, 130.4, 131.4, 134.9, 135.3, 135.7, 139.4, 148.8, 162.0, 168.4. MS *m*/*z* calcd for $C_{28}H_{45}N_2O_6S_2Si_2^+$: 625.2258, found 625.2255.

3′-*O*-(1,3-Benzodithiol-2-yl)-2′,5′-*O*-di(*tert*-butyldimethylsilyl)uridine (18). Compound **17** (850 mg, 1.2 mmol) was dissolved in saturated NH_3−MeOH (12 mL). The solution was stirred at ambient temperature for 3.5 h. The solvent was removed under reduced pressure, and the residue was dissolved in $CHCl_3$ (15 mL), washed three times with water (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on a column of silica gel (C200, 15 g) with hexanes−ethyl acetate (85:15, v/v) containing 0.5% triethylamine (v/v) to give **18** (709 g, 97%) as a white foam: ^{1}H NMR ($CDCl_3$) δ 0.03−0.14 (12H, m), 0.882−0.889 (18H, m), 3.56−3.60 (1H, m), 3.85−3.92 (2H, m), 4.11−4.13 (1H, m), 4.22−4.24 (1H, m), 5.54 (1H, d, J = 8.1 Hz), 5.76 (1H, d, J = 3.2 Hz), 6.78 (1H, s), 7.05−7.31 (4H, m), 7.85 (1H, d, J = 7.8 Hz), 9.13 (1H, br); ^{13}C NMR ($CDCl_3$) δ − 5.5, − 5.4, − 4.8, − 4.5, 18.1, 18.5, 25.7, 26.0, 61.3, 72.2, 75.3, 82.4, 88.9, 89.5, 101.7, 121.86, 121.92, 125.7, 135.4, 135.7,

139.6, 149.9, 163.2. MS *m/z* calcd for $C_{28}H_{45}N_2O_6S_2Si_2^+$: 625.2258, found 625.2255.

3′-*O*-(1,3-Benzodithiol-2-yl)uridine (19). Compound **18** (648 mg, 1.0 mmol) was dissolved in tetrahydrofuran (10 mL). To this solution was added tetra-*n*-butylammonium fluoride (678 mg, 2.6 mmol), and the resulting solution was stirred at ambient temperature for 2.5 h. The solvent was removed under reduced pressure and the residue was dissolved in $CHCl_3$ (10 mL), and water (10 mL) was added. The separated precipitate was collected by filtration to give **19** (360 mg, 87%): ^{1}H NMR (DMSO-d_6) δ 3.40−3.57 (2H, m), 3.94 (1H, m), 4.13−4.21 (2H, m), 5.15 (1H, br), 5.60−5.63 (2H, m), 5.71 (1H, d, J = 5.7 Hz), 6.95 (1H, s), 7.12−7.46 (4H, m), 7.78 (1H, d, J = 7.8 Hz), 11.32 (1H, br); ^{13}C NMR (DMSO-d_6) δ 60.5, 67.0, 72.5, 75.7, 82.6, 87.4, 89.9, 101.8, 122.2, 122.4, 125.4, 125.5, 135.0, 135.6, 140.2, 150.6, 162.9. MS *m/z* calcd for $C_{16}H_{17}N_2O_6S_2^+$: 397.0528, found 395.0528.

2′-*O*-(1,3-Benzodithiol-2-yl)cytidine (23a). 2′-*O*-(1,3-Benzodithiol-2-yl)-4-*N*-pivaloyl-3′-5′-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl) cytidine (2.1 g, 2.9 mmol) was dissolved in saturated NH_3−MeOH (30 mL). The solution was stirred at ambient temperateure for 19 h. The solvent was removed under reduced pressure, and to the residue was added $CHCl_3$ (30 mL), washed five times with water (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (30 mL), and to this solution was added tetra-*n*-butylammonium fluoride (1.9 g, 7.3 mmol), and the resulting solution was stirred at ambient temperature for 30 min. The solvent was removed under reduced pressure and the residue was dissolved in $CHCl_3$ (10 mL), and extracted six times with water (10 mL). The aqueous layer was collected and the separated precipitate was collected by filtration to give **23a** (850 mg, 77%): ^{1}H NMR ((DMSO-d_6) δ 3.45−3.64 (2H, m), 3.77 (1H, m), 4.02−4.13 (2H, m), 5.21 (1H, d, J = 5.7 Hz), 5.69 (1H, d, J = 7.3 Hz), 5.86 (1H, d, J = 3.5 Hz), 7.80 (1H, d, J = 7.3 Hz), 7.07−7.44 (7H, m), 7.80 (1H, d, J = 7.3 Hz); ^{13}C NMR (DMSO-d_6) δ 59.9, 67.9, 79.5, 83.9, 87.0, 89.5, 93.9, 122.2, 122.3, 125.25, 125.35, 135.2, 135.4, 140.8, 155.0, 165.5. MS *m/z* calcd for $C_{16}H_{18}N_3O_5S_2^+$ 396.0688, found 396.0687.

2′-*O*-(1,3-Benzodithiol-2-yl)adenosine (23b). 2′-*O*-(1,3-Benzodithiol-2-yl)-6-*N*-pivaloyl-3′-5′-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)adenosine (1.9 g, 2.6 mmol) was dissolved in saturated NH_3−MeOH (25 mL). The solution was stirred at ambient temperateure for 2 days. The solvent was removed under reduced pressure, and the residue was dissolved in tetrahydrofuran (26 mL). To this solution was added tetra-*n*-butylammonium fluoride (1.7 g, 6.4 mmol), and the resulting solution was stirred at ambient temperature for 30 min. The solvent was removed under reduced pressure, the residue was dissolved in $CHCl_3$ (10 mL), and water (10 mL) was added. The separated precipitate was collected by filtration to give **23b** (980 mg, 92%): ^{1}H NMR ((DMSO-d_6) δ 3.41−3.60 (2H, m), 3.94 (1H, m), 4.33 (1H, m), 4.66 (1H, m), 5.38 (1H, d, J = 4.6 Hz), 5.42−5.46 (1H, m), 5.96 (1H, d, J = 6.2 Hz), 7.00−7.38 (6H, m, ArH), 7.96 (1H, s), 8.21 (1H, s); ^{13}C NMR (DMSO-d_6) δ 61.6, 67.0, 77.4, 86.3, 86.5, 89.3, 119.3, 121.5, 122.0, 125.199, 125.240, 134.6, 135.1, 139.9, 148.6, 152.1, 156.0. MS *m/z* calcd for $C_{17}H_{18}N_5O_4S_2^+$: 420.0800, found 420.0796.

2′-*O*-(1,3-Benzodithiol-2-yl)guanosine (23c). 2′-*O*-(1,3-Benzodithiol-2-yl)-2-*N*-benzoyll-3′-5′-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)guanosine (220 mg, 0.28 mmol) was dissolved in saturated NH_3−MeOH (3 mL). The solution was stirred at ambient temperateure for 24 h. The solvent was removed under reduced pressure, and the residue was dissolved in tetrahydrofuran (2 mL) and *N*,*N*-dimethylformamide (1 mL). To this solution was added tetra-*n*-butylammonium fluoride (183 mg, 0.7 mmol), and the resulting solution was stirred at ambient temperature for 30 min. The solvent was removed under reduced pressure, and the residue was dissolved in $CHCl_3$ (10 mL) and washed three times with water (10 mL). The aqueous layer was extracted six times with $CHCl_3$−isopropyl alcohol (7:3, v/v), and all the organic extracts were combined. The solvent was removed under reduced pressure. The residue was trituated with CH_3OH and diethyl ether, and the separated precipitate was collected by filtration to give **23c** (87 mg, 71%): ^{1}H NMR (DMSO-d_6) δ 3.45−3.55 (2H, m), 3.85−3.86 (1H, m), 4.28−4.29 (1H, m), 4.48−4.53 (1H, m), 4.99−5.03 (1H, m), 5.34 (1H, d, J = 4.9 Hz), 5.77 (1H, d, J = 6.8 Hz), 6.35 (2H, s), 6.94 (1H, s), 7.05−7.37 (4H, m), 7.79 (1H, s), 10.62 (1H, s); ^{13}C NMR (DMSO-d_6) δ 61.3, 69.5, 78.2, 84.2, 85.7, 89.4, 116.5, 121.8, 122.1, 125.3, 134.7, 135.2, 153.4, 156.5. MS *m/z* calcd for $C_{17}H_{18}N_5O_5S_2^+$: 436.0749, found 436.0748.

2′-*O*-(1,3-Benzodithiol-2-yl)-1-*N*-pivaloyloxymethyl-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)inosine (25). Compound **24** (1.5 g, 2.4 mmol) was dissolved in anhydrous CH_2Cl_2 (24 mL). To this solution were added 1,3-benzodithiolium tetrafluoroborate (691 g, 2.9 mmol) and pyridine (465 mL, 5.8 mmol), and the resulting mixture was stirred at ambient temperature for 6.5 h. Triethylamine (2.0 mL, 14.4 mmol) was added, and the resulting mixture was stirred for 15 min, washed three times with water (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on a column of silica gel (C200, 40 g) with hexanes−ethyl acetate (75:25, v/v) containing 0.5% triethylamine (v/v) to give **25** (1.5 g, 80%) as a white foam: ^{1}H NMR ($CDCl_3$) δ 0.93−1.24 (37H, m), 3.90−4.07 (3H, m), 4.56 (1H, m), 4.77 (1H, dd, J = 5.9, 9.5 Hz), 5.86−5.97 (3H, m), 6.77−7.20 (5H, m), 7.82, 7.92 (2H, 2s); ^{13}C NMR ($CDCl_3$) δ 12.6, 12.7, 13.0, 13.4, 16.9, 17.1, 17.19, 17.21, 17.27, 17.31, 17.4, 26.9, 38.9, 59.4, 67.5, 68.6, 76.7, 81.2, 89.4, 89.8, 121.5, 121.6, 124.8, 124.9, 125.0, 134.7, 135.5, 139.7, 146.2, 147.4, 155.5, 178.2. MS *m/z* calcd for $C_{35}H_{53}N_4O_8S_2Si_2^+$: 777.2843, found 777.2840.

2′-*O*-(1,3-Benzodithiol-2-yl)inosine (26). Compound **25** (1.5 g, 1.9 mmol) was dissolved in saturated NH_3−MeOH (20 mL). The solution was stirred at ambient temperateure for 13 h. The solvent was removed under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). To this solution was added tetra-*n*-butylammonium fluoride (1.26 g, 4.8 mmol), and the resulting solution was stirred at ambient temperature for 45 min. The solvent was removed under reduced pressure, and the residue was dissolved in $CHCl_3$ (20 mL) and washed three times with water (20 mL). The aqueous layer was extracted seven times with $CHCl_3$−pyridine (7:3, v/v), and all the organic extracts were combined. The solvent was removed under reduced pressure. The residue was trituated with CH_3OH and diethyl ether, and the separated precipitate was collected by filtration to give **26** (470 mg, 58%): ^{1}H NMR (DMSO-d_6) δ 3.33−3.57 (2H, m), 3.90 (1H, m), 4.30 (1H, m), 4.56−4.60 (1H, m), 5.02 (1H, br), 5.39 (1H, br), 5.94 (1H, d, J = 5.9 Hz), 7.00−7.33 (5H, m), 7.89, 8.18 (2H, 2s), 12.35 (1H, br); ^{13}C NMR (DMSO-d_6) δ 61.2, 69.6, 78.1, 85.8, 86.1, 89.4, 121.6, 122.0, 124.5, 125.2, 134.7, 135.2, 138.9, 145.6, 147.8, 156.4. MS *m/z* calcd for $C_{17}H_{17}N_4O_5S_2^+$ 421.0640, found 421.0645.

4-*N*-Methoxycarbonylcytidine (27). Cytidine (2.4 g, 10.0 mmol) was rendered anhydrous by repeated coevaporation with anhydrous pyridine and finally dissolved in anhydrous acetonitrile (100 mL). Hexamethyldisilazane (6.35 mL, 30.0 mmol) and catalytic amount of chlorotrimethylsilane was added, and the resulting solution was stirred at 60 °C for 1 h. The reaction mixture was cooled to ambient temperature, and the solvents were removed under reduced pressure. The residual hexamethyldisilazane was removed by repeated coevaporation with anhydrous pyridine and finally dissolved in anhydrous CH_2Cl_2 (100 mL). To this solution was added anhydrous pyridine (1.45 mL, 18 mmol), and methyl chloroformate (1.2 mL, 15 mmol) was added dropwise at 0 °C. The reaction mixture was warmed to room temperature and stirred for 15 min. The reaction was quenched by adding small amount of water, and the reaction mixture was diluted with $CHCl_3$ (50 mL) and washed twice with saturated aqueous $NaHCO_3$ (50 mL). The aqueous layer was extracted with $CHCl_3$ (50 mL), and all the organic extracts were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. To this residue was added concentrated NH_3−pyridine (1:1, v/v, 100 mL), and the solution was stirred at ambient temperature for 50 min. The solvents were removed under reduced pres-

sure, and the residue was dissolved in water (50 mL). The aqueous solution was washed twice with chloroform (50 mL), and the organic layer was extracted with water (30 mL). All the water extracts were combined and concentrated under reduced pressure. The separated precipitate was collected with filtration to give **27** (2.75 g, 80%): ^{1}H NMR (DMSO-d_6) δ 3.55−3.76 (3H, m), 3.89−3.95 (3H, m), 5.03 (1H, d, J = 5.1 Hz), 5.14 (1H, t, J = 4.9 Hz), 5.47 (1H, d, J = 4.6 Hz), 5.76 (1H, d, J = 2.4 Hz), 7.01 (1H, d, J = 7.6 Hz), 8.39 (1H, d, J = 7.6 Hz), 10.74 (1H, s); ^{13}C NMR (DMSO-d_6) δ 52.5, 60.0, 68.7, 74.4, 84.2, 90.0, 94.0, 144.9, 153.6, 154.3, 162.6. MS *m/z* calcd for $C_{11}H_{16}N_3O_7^+$ 302.0988, found 302.0987.

4-*N*-Methoxycarbonyl-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)cytidine (28). Compound **27** (1.4 g, 4.7 mmol) was rendered anhydrous by repeated coevaporation with anhydrous pyridine and finally dissolved in anhydrous pyridine (45 mL). 1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxan (1.8 mL, 5.6 mmol) was added, and the resulting solution was stirred at ambient temperature for 3 h. Water was added, the reaction mixture was stirred for 15 min, and the solvents were removed under reduced pressure. The residue was dissolved in $CHCl_3$ (50 mL), washed three times with saturated aqueous $NaHCO_3$ (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on a column of silica gel (C200, 50 g) with hexanes−ethyl acetate (45:55, v/v) to give **28** (2.0 g, 81%) as a white foam: ^{1}H NMR ($CDCl_3$) δ 0.95−1.37 (28H, m), 3.11 (1H, br), 3.78 (3H, s), 3.98 (1H, dd, J = 2.2, 13.2 Hz), 4.16−4.30 (4H, m), 5.79 (1H, s), 7.19 (1H, d, J = 7.3 Hz), 7.83 (1H, br), 8.15 (1H, d, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 12.43, 12.92, 12.94, 13.37, 16.82, 16.90, 16.97, 17.28, 17.30, 17.39, 17.47, 53.04, 60.00, 68.45, 74.96, 77.20, 81.85, 91.59, 94.42, 144.05, 152.79, 154.59, 162.48. MS *m/z* calcd for $C_{23}H_{42}N_3O_8Si_2^+$ 544.2510, found 544.2501.

2′-*O*-(1,3-Benzodithiol-2-yl)-4-*N*-methoxycarbonyl-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)cytidine (29). Compound **28** (1.5 g, 2.7 mmol) was dissolved in anhydrous CH_2Cl_2 (27 mL). To this solution were added 1,3-benzodithiolium tetrafluoroborate (994 mg, 2.76 mmol) and pyridine (668 μL, 8.3 mmol), and the resulting mixture was stirred at ambient temperature for 4 h. Triethylamine (2.5 mL, 16.6 mmol) was added, and the resulting mixture was stirred for 15 min, washed three times with water (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on a column of silica gel (C200, 50 g) with hexanes−ethyl acetate (70:30, v/v) containing 0.5% triethylamine (v/v) to give **29** (1.7 g, 89%) as a white foam: ^{1}H NMR ($CDCl_3$) δ 0.87−1.03 (28 H, m), 3.78 (3H, s), 3.86−3.91 (1H, m), 4.11−4.28 (4H, m), 5.80 (1H, s), 7.00−7.35 (5H, m), 8.17 (1H, d, J = 7.6 Hz), 8.72 (1H, br); ^{13}C NMR ($CDCl_3$) δ 12.4, 12.8, 12.9, 13.4, 16.7, 16.8, 17.0, 17.1, 17.3, 17.39, 17.44, 53.1, 59.2, 67.0, 77.2, 79.5, 81.9, 89.4, 90.7, 94.7, 122.3, 122.4, 125.0, 125.1, 134.9, 135.8, 143.5, 152.9, 154.5, 162.8. MS *m/z* calcd for $C_{30}H_{46}N_3O_8S_2Si_2^+$ 696.2265, found 696.2264.

2′-*O*-(1,3-Benzodithiol-2-yl)-4-*N*-methoxycarbonylcytidine (30). Compound **29**(1.6 g, 2.3 mmol) was dissolved in tetrahydrofuran (20 mL). To this solution was added tetra-*n*-butylammonium fluoride (1.5 g, 5.7 mmol), and the resulting solution was stirred at ambient temperature for 15 min. The solvent was removed under reduced pressure, the residue was dissolved in ethyl acetate (10 mL), and water (10 mL) was added. The separated precipitate was collected by filtration to give 38 (730 mg, 71%): ^{1}H NMR (DMSO-d_6) δ 3.50−3.55 (1H, m), 3.69 (4H, m), 3.82−3.85 (1H, m), 4.04−4.11 (1H, m), 4.18−4.21 (1H, m), 5.12 (1H, m), 5.26 (1H, s, J = 5.9 Hz), 5.93 (2H, d, J = 2.7 Hz), 7.02 (1H, d, J = 7.6 Hz), 7.07−7.46 (4H, m), 8.32 (1H, d, J = 7.6 Hz), 10.81 (1H, br); ^{13}C NMR (DMSO-d_6) δ 52.6, 59.4, 67.5, 79.8, 84.1, 87.7, 89.7, 94.3, 122.3, 125.4, 135.1, 135.5, 144.5, 153.7, 154.2, 162.8. Ms *m/z* calcd for $C_{18}H_{20}N_3O_7S_2^+$ 454.0743, found 454.0750.

Anti-BVDV Assay. Madin-Darby bovine kidney (MDBK) cells were grown in Dulbecco's modified Eagle's medium (Gibco/BRL, Gaithersburg, MD) supplemented with 10% heat-inactivated horse serum (Gibco/BRL), 100 U/mL penicillin G, and 100 μg/mL streptomycin (culture medium). MDBK cells (5×10^5 cells/ml) were seeded in a six-well plastic plate and incubated overnight at 37 °C. Then, culture medium was removed, and the cells were infected with approximately 100 focus forming unit of BVDV (nose strain) and incubated in the presence of various concentrations of the test compounds. After a 24-h incubation, the virus inoculum and test compound were removed, and the monolayers were washed with phosphate-buffered saline, overlaid with culture medium containing bactoager, and further incubated. After 24 h, the number of viral foci was counted microscopically.

Cytotoxicity Assay. MDBK cells (2×10^4/well) were seeded in a 96-well plate in the presence of various concentrations of the test compound and incubated at 37 °C. After a 3-day incubation, the number of viable cells was measured in a colorimetric assay using a water-soluble tetrazolium dye.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of all of the newly synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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