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cis-Tetrahydrofuran-3,4-diol Structure as a Key Skeleton of New Protecting Groups Removable by Self-Cyclization under Oxidative Conditions

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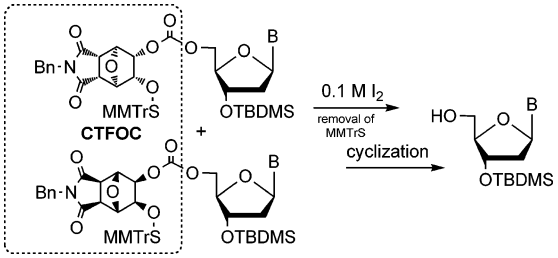
Received May 16, 2006



A variety of carbonate-type acyl groups having a *cis*-tetrahydrofuran-3,4-diol (1,4-anhydroerythritol) backbone structure and a TrS or MMTrS group have been examined as new "protected" protecting groups of the 5′-hydroxyl group of nucleosides. These acyl groups were designed in a manner where they could be deprotected by I_2-promoted removal of the TrS or MMTrS group followed by self-cyclization involving an intramolecular attack of the once-generated neighboring hydroxyl group on the acyl carbon. It turned out that these acyl groups could be introduced into the 5′-hydroxyl group of a 3′-*O*-protected thymidine derivative by use of the corresponding acyl imidazolides or 4-nitrophenyl esters as well as by reaction with carbonyldiimidazole or 4-nitrophenyl chloroformate. Among the acyl groups tested, it was found that the CTFOC group could be easily introduced into the 5′-hydroxyl group of 3′-masked deoxyribonucleoside derivatives and rapidly removed under mild conditions using iodine.

Introduction

In recent years, new oligodeoxynucleotide-synthesis protocols that avoid acid treatment were developed by many groups.[1−13] Some of them have developed oxidatively cleavable protecting groups in place of the acid-labile 4, 4′-dimethoxytrityl (DMTr) group[14] for the 5′-hydroxyl function. These new protocols suppress the unfavorable depurination[15−21] promoted by the acid treatment during the detritylation step in the current DNA synthesis.

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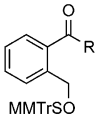
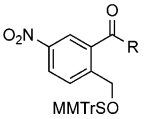
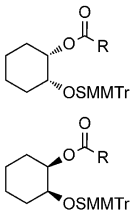
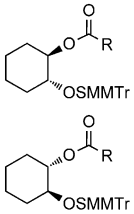
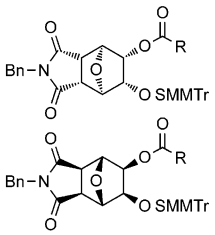
10.1021/jo061006v CCC: $33.50
Published on Web 08/26/2006

TABLE 1. Comparison of Self-Cyclization Kinetics after Treatment with 0.5 M I_2[a]

	MTFOC	MOB				CTFOC
Skeletons of protecting groups						
	9	**19**[3]	**22**	**24**	**26**	**18**
$T_{1/2}$ of cyclization	51 min (44 min, 61 min)	164 h	38 h	no cyclization	no cyclization	6 min (5 min, 7 min)

[a] Compounds **9**, **24**, **26**, and **18** were used as their diastereomeric mixtures. Values in parenthesizes are the $T_{1/2}$ of each diastereoisomers.

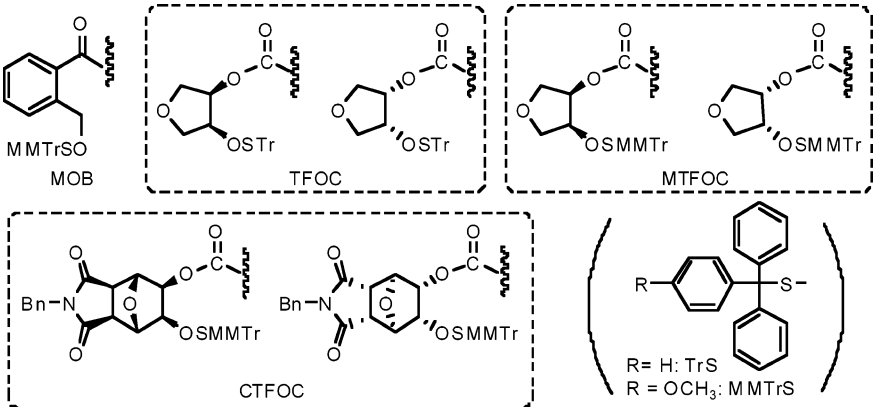


FIGURE 1. Structures of the MOB, TFOC, MTFOC, and CTFOC groups.

We have been interested in the protection of the hydroxyl group as a sulfenic acid ester which can regenerate the original hydroxyl function under nonacidic mild conditions. The first example of sulfenate-type protecting groups in the field of nucleic acid chemistry was shown by Letsinger et al. in 1964.[22] They chose a 2,4-dinitrobenzenesulfenyl group to protect hydroxyl groups and deprotected them by polarizable nucleophiles such as thiosulfate, cyanide and thiolate ions. We reported 4-methoxytritylthio (MMTrS) as a different sulfenate-type protecting group removable under mild oxidative conditions.[2] More recently, we have developed 2-[(4-methoxytritylsulfenyl)-oxymethyl]benzoyl (MOB) as a new acyl-type protecting group having an MMTrS group on the hydroxyl oxygen atom[3] (see Table 1). The MOB group could be readily introduced to the 5′-hydroxyl group of nucleosides and removed in two steps including the oxidative cleavage of the S−O bond by iodine[2−4,23] and the successive base-catalyzed self-cyclization. Oxidatively cleavable protecting groups have been reported by several research groups, and their usefulness in the synthesis of oligodeoxynucleotides has also been demonstrated. For example, Caruthers has reported a new strategy for the synthesis of oligodeoxyribonucleotides by use of 4-chlorophenoxycarbonyl as a new 5′-hydroxyl protecting group that can be removed by treatment with H_2O_2 under slightly basic conditions.[5] On the other hand, Beaucage has reported 2,2,5,5-tetramethylpyrrolidin-3-one-1-sulfinyl as a protecting group that can be removed by a 1 min treatment with 0.02 M I_2 in THF−pyridine−H_2O followed by exposure to a solution of 0.1 M I_2, 0.25 M 3-acetylpyridiine, and 0.125 M trichloroacetic acid in THF−H_2O for 8 min.[6]

In this paper, we report the development of new protected protecting groups such as TFOC, MTFOC and CTFOC (Figure 1) having a TrS or an MMTrS moiety by use of a *cis*-tetrahydrofuran-3,4-diol (1,4-anhydroerythrito) skeleton capable of rapid deprotection by the action of an aqueous I_2 solution in pyridine−H_2O (9:1, v/v) in two steps. The detailed kinetic analyses revealed that the MTFOC and CTFOC groups could be deprotected more rapidly than the previously reported MOB group, in the absence of base catalysts, and could be useful for protection of hydroxyl functions removable under mild conditions.

As described in this paper, the TFOC, MTFOC, and CTFOC groups and nucleoside derivatives incorporating these protecting

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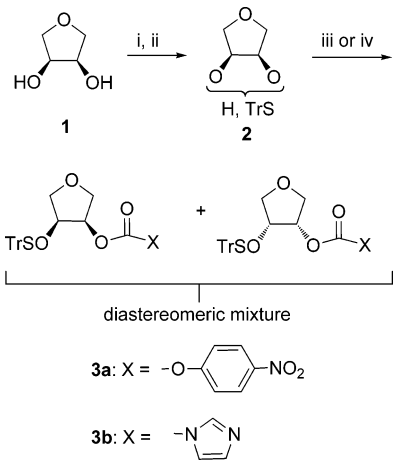
SCHEME 1. Synthesis of Acylating Agents 3a and 3b[a]



[a] Reagents and conditions: (i) NaH, THF; (ii) TrSCl, THF, quant (iii) 4-$NO_2C_6H_4OC(O)Cl$, pyridine, CH_2Cl_2, 77%; (iv) CDI, pyridine, quant.

groups can be used as mixtures of the stereoisomers because of similar physicochemical properties of these isomers. Other previous diastereomeric protecting groups, such as 2,2,5,5-tetramethylpyrrolidin-3-one-1-sulfinyl,[6] tetrahydropyran-2-yl,[24] α-methyl-2-nitropiperonyloxycarbonyl,[25] and *N*-substituted 2-amino-1-phenylethyl-1-yl-oxycarbonyl[26] have been used as diastereoisomeric mixtures without incurring any crucial problems.

Results and Discussion

Introduction of the TFOC and MTFOC Groups into the 5′-Hydroxyl Group. To develop new protecting groups which can be removed more readily than the MOB group in two steps (Scheme 4) under mild conditions, we designed carbonate-type protecting groups, that is, *cis*-[4-(tritylsulfenyloxy)tetrahydrofuran-3-yl]oxycarbonyl (TFOC) and *cis*-[4-[(4-methoxytrityl)-sulfenyloxy]tetrahydrofuran-3-yl]oxycarbonyl (MTFOC), having a *cis*-tetrahydrofuran-3,4-diol backbone structure where one of the hydroxyl functions is masked by a TrS and an MMTrS group, respectively,[3] as shown in Figure 1, Scheme 2 and Scheme 3.

First of all, we studied the introduction of the TFOC group into the 5′-hydroxyl group of nucleosides by use of 3′-*O*-(*tert*-butyldimethylsilyl)thymidine (**4**, Scheme 2) as a model compound. For this purpose, acylating agents **3a** and **3b** were synthesized, as shown in Scheme 1. The reaction of 1,4-anhydroerythritol (**1**) with TrSCl gave the sulfenylated product **2**, which was obtained as a pair of two diastereoisomers, that is, the (3*S*,4*R*)- and (3*R*,4*S*)-isomers. The reaction of **2** with 4-nitrophenyl chloroformate gave the active ester **3a**, whereas the reaction of **2** with carbonyldiimidazole (CDI) gave the urethane **3b**, as shown in Scheme 1. The latter was used without further purification for the next reaction. Both **3a** and **3b** were obtained as diastereomeric mixtures.

Next, we compared the reactivity of **3a** and **3b** to the 5′-hydroxyl group. The reaction of **4** with **3a** for 13 h in the presence of 1.0 equiv of DBU gave a diastereomeric mixture of the 5′-*O*-masked product **5** in 70% yield, as shown in Scheme 2. In contrast, when the imidazolide **3b** was used as the acylating agent, a catalytic amount of DBU[27] (0.15 equiv) was sufficient, and the reaction was completed within 3 h. Thus, compound **5** was obtained in 81% yield. These results clearly suggest that the acylating agent **3b** has higher reactivity than **3a**.

An alternative approach to **5** was also developed, as shown in Scheme 3. In this procedure, the thymidine 5′-*O*-carbonate and carbamate derivatives **6**[28] and **7** were prepared as nucleoside-type acylating agents by the reaction of **4** with 4-nitrophenyl chloroformate and CDI, respectively. The reaction of nucleoside-type acylating agents and the hydroxyl compound **2** successfully gave the desired compound **5**. In agreement with the above-mentioned reactivity of **3a** and **3b**, it was also observed that the reaction of **2** with the imidazolide **7** proceeded much faster (3 h) than that with the 4-nitrophenyl carbonate derivative **6** (6 h). Thus, compound **5** was obtained in 76% yield by use of **6** and in a higher yield of 91% by use of **7**. By comparing the yields of **5** obtained by use of **3a**, **3b**, **6**, and **7**, it was concluded that the use of nucleoside-type acylating agents such as **7** was the best to introduce the TFOC group into the 5′-hydroxyl group of thymidine.

In a similar way, 5′-*O*-MTFOC-3′-*O*-TBDMS-thymidine (**9**) having a more labile MMTrS group in place of the TrS group was also obtained in 93% yield by use of the alcohol **8** which was synthesized in 82% yield from compound **1** and the nucleoside-type acylating agent **7**, as shown in Scheme 3. Both **5** and **9** were obtained as diastereomer mixtures. In both cases, the diastereomer ratios were found to be 1:1 from the NMR spectra.

Unfortunately, the isomers of **5** and **9** could not be separated by silica gel column chromatography. Therefore, they were used as isomeric mixtures in the kinetic studies described below.

Kinetics of Deprotection of the MTFOC Group. To see if the erythritol structure will undergo self-cyclization at the second stage required for removal of the protecting group, **9** was treated with a 0.5 M solution of iodine in pyridine-d_5/D_2O (9:1, v/v) and the reaction was monitored by ^1H NMR (signals of the 1′-H proton were compared, Scheme 4). As expected, the MMTrS group was promptly removed from **9** within 1 min. It turned out that the resulting alcohol intermediate **10** was gradually converted to **4**. The NMR analysis revealed that the half-life of the intermediate **10** was 51 min. Because of the overlap of the two 1′-H protons of the diastereomers of the intermediate **10**, the cyclization kinetic parameter should be considered as an averaged value of the two diastereomers. Such averaged data, however, are sufficient for the practical use of the MTFOC group as a protecting group.

Design of New Protecting Groups by Considering Conformation Energies. We intended to design a new structure which would lead to more rapid deprotection. For this purpose, the conformation properties of *cis*-tetrahydrofuran-3,4-diol (**11**) and *cis*-3,4-oxomethylenedioxy-tetrahydrofuran (**12**), the residue of the MTFOC group generated after the self-cyclization, were analyzed by the ab initio calculations (HF/6-31G*). The results are shown in Figure 2. The lowest energy conformation of the cyclized product **12** was an *O*1-*exo* envelope structure,[29] whereas

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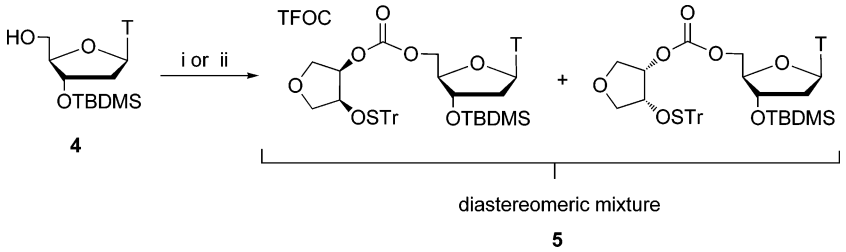
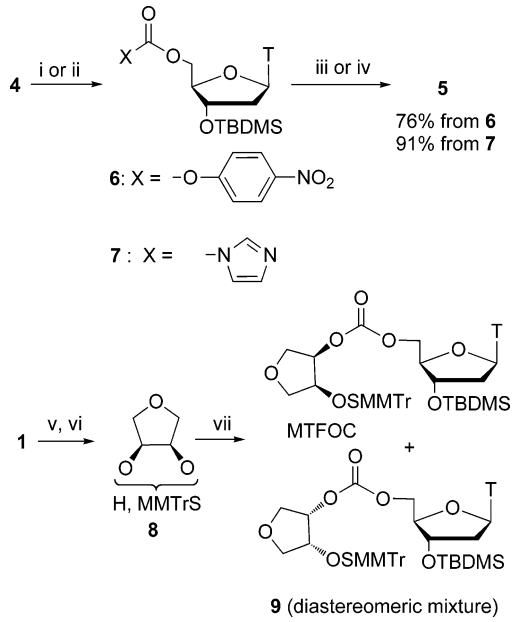
SCHEME 2. Introduction of the TFOC Group by Use of 3a and 3b into the 5′-Hydroxyl Group[a]



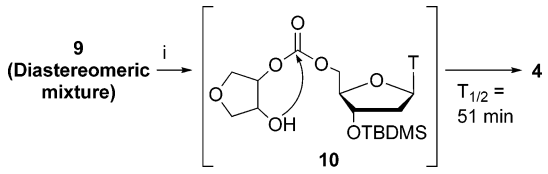
[a] Reagents and conditions: (i) **3a**, DBU, pyridine, 70%; (ii) **3b**, DBU, pyridine, 81%.

SCHEME 3. Alternative Route to 5 and Synthesis of 9[a]



[a] Reagents and conditions: (i) 4-$NO_2C_6H_4OC(O)Cl$, dioxane−pyridine, 82%; (ii) CDI, pyridine; (iii) **6**, **2**, DBU, 76%; (iv) **7**, **2**, DBU, pyridine, 91%; (v) NaH, THF; (vi) MMTrSCl, THF, 82%; (vii) **7**, DBU, 93%.

SCHEME 4. Removal of the MTFOC Group[a]



[a] Reagents and conditions: (i) 0.5 M I_2, pyridine-d_5/D_2O (9:1, v/v).

the lowest energy conformation of **11** was the C3-*endo* or C4-*endo* envelope form. Moreover, it was also proved that the *O*1-exo envelope conformation of **11** (structure not shown in Figure 2) was energetically less favorable by +5.0 kcal/mol than the C3-*endo* or C4-*endo* form. These results indicated that the cyclization of the intermediate **10** needs conformational change of the five-membered ring from the lowest energy C3 (or C4) -*endo* form to the energetically unfavorable *O*1-*exo* form. Therefore, we thought that faster cyclization could be achieved by fixing the five-membered ring of the tetrahydrofuran in *O*1-*exo* conformation by introduction of another ring structure.

(29) In this paper, the C3-*endo*-envelope structure means that C3 is located at the opposite side of the diol function. The *O*1-*exo*-envelope structure means that *O*1 is placed at the same side of the diol function. The conformations of **13** and **14** are named similarly.

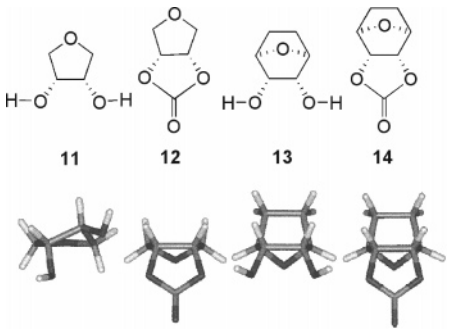


FIGURE 2. Structures (upper row) and the lowest energy conformations (lower row) of *cis*-tetrafuran-3,4-diol derivatives.

To confirm this idea, we designed 2,3-dihydroxy-7-oxabicyclo-[2.2.1]heptane (**13**) and calculated the conformation energies of it and its cyclic carbonate **14**.

As the result, it was found that both of the *cis*-tetrahydrofuran-diol part rings of **13** and **14** were fixed in the *O*7-*exo* form. Therefore, it was expected that there is no necessary conformation change during the cyclization so that the reaction would be accelerated. Such a bicyclic system having a conformationally locked 1,2-diol function has recently been utilized as a base-labile linker, which connects the DNA chain to a polymer support, for the synthesis of oligodeoxynucleotides.[30]

Because **13** was not easily available,[31,32] we designed a new protecting group, CTFOC (Figure 1), which could be introduced to the nucleosides as shown in Scheme 5. Compound **15** was prepared by a Diels−Alder reaction[33] of furan and *N*-benzylmaleimide. The dihydroxylation[34,35] of **15** gave *exo*-*N*-(phenylmethyl)-7-oxabicyclo[2.2.1]heptane-5,6-dihydroxy-2,3-dicarboximide (**16**) as shown in Scheme 5. Compound **16** was converted to the MMTrS derivative **17**, and the reaction of **17** with **7** gave the 5′-*O*-masked product **18** as a diastereomeric mixture in 72% yield according to the almost identical protocols shown in Schemes 1 and 3.

Kinetics of Deprotection of the CTFOC Group. The kinetics of the deprotection of the CTFOC group of **18** by the aqueous iodine treatment was monitored by ^1H NMR (signals of the 1′-H proton were compared, Scheme 4.) As described above, the half-life measured by this method should be regarded

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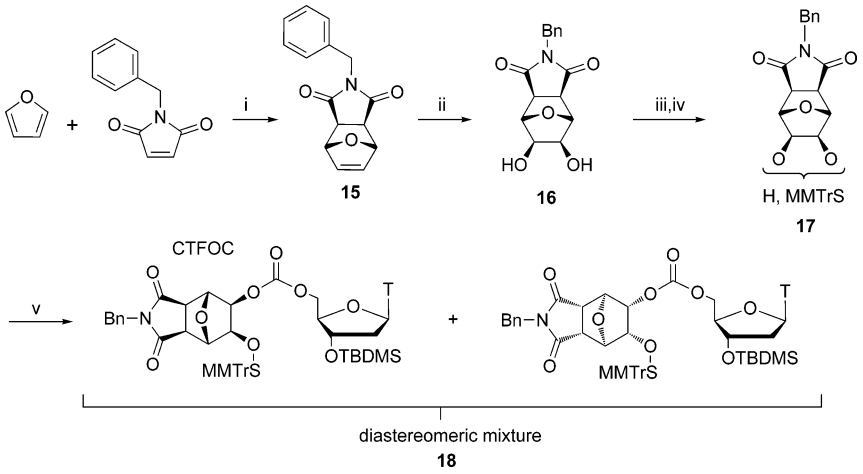
SCHEME 5. Introduction of the CTFOC Group to Compound 7[a]



[a] Reagents and conditions: (i) 1,4-dioxane, 54%; (ii) OsO_4, morpholine-*N*-oxide, acetone−H_2O = 6:1 (v/v), 83%; (iii) NaH, DMF; (iv) MMTrSCl, DMF, 53%; (v) **7**, DBU, pyridine, 72%.

as the averaged values of the diastereomers. In addition to **18**, we studied the deprotection kinetics of the various protecting groups **9**, **19**, **22**, **24**, and **26** (Table 1) to confirm the superiority of the *cis*-tetrahydrofuran-3,4-diol structure of compound **9** and the conformationally locked derivative **18** to other ring structures such as the benzene ring of **19** or **22**, and the cyclohexane ring of **24** or **26**. Compound **19** was synthesized according to the procedure reported previously.[3] The 5-nitrobenzoyl-type[11] derivative **22** was prepared similarly. We also prepared the *cis*-1,2-cyclohexanediol derivative **24** and the *trans*-1,2-cyclohexanediol derivative **26** as regioisomeric mixtures according to the procedure described above (see also Supporting Information).

Apparently, these experiments showed the superiority of **9** ($T_{1/2}$ = 51 min) and **18** ($T_{1/2}$ = 6 min) which have a *cis*-tetrahydrofuran-3,4-diol skeleton to the other substrates (Table 1). Moreover, the CTFOC derivative **18** showed the fastest deprotection rate of all. These results clearly showed the advantage of the conformationally fixed structure as a new protecting group skeleton capable of the rapid removal by its self-cyclization. Neither the *cis*-diol derivative **24** with a six-membered ring nor the *trans*-diol **26** cyclized even after prolonged reaction time. These results indicated that both the *cis*-diol and the five-membered ring were important structural components which enabled the rapid deprotection of the MTFOC and CTFOC groups.

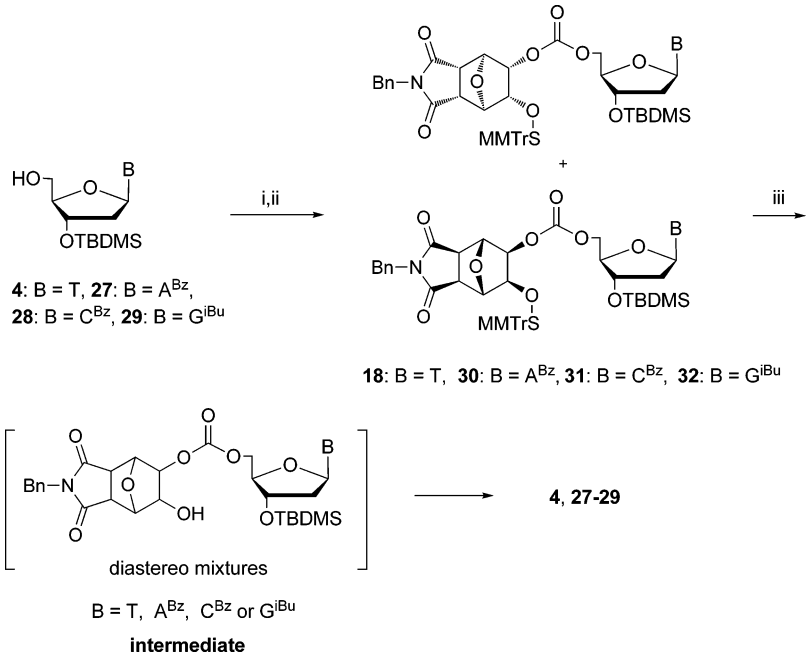
In addition to the analysis of the averaged deprotection kinetics, in the case of compounds **9** and **18**, we could measure deprotection kinetics of each diastereoisomer by monitoring the methyl protons signals of the thymine. The values are shown in Table 1. In the case of compound **9** having the MTFOC group, one of the diastereoisomers cyclized 1.4 times more rapidly with the $T_{1/2}$ value of 44 min than the other with that of 61 min. Similarly, in the case of compound **18** having the CTFOC group, the half-lives of two isomers were 7 and 5 min. These results clearly showed that the cyclization kinetics of the diastereomers were different, but the differences were not so large, at most 1.4 times.

Practical Method for Removal of the CTFOC Group from All Four Canonical Deoxynucleosides. We also examined the protection of the 5′-hydroxyl group of other nucleosides, that is, 6-*N*-benzoyl-5′-*O*-(*tert*-butyldimethylsilyl)deoxyadenosine (**27**), 4-*N*-benzoyl-3′-*O*-(*tert*-butyldimethylsilyl)deoxycytidine (**28**), and 3′-*O*-(*tert*-butyldimethylsilyl)-2-*N*-isobutyryldeoxyguanosine (**29**) with the CTFOC group and the deprotection to clarify the applicability for all four deoxynucleosides. The compounds were synthesized according to the procedure already shown in Scheme 3. When adenosine derivative (**27**) and cytidine derivative (**28**) were treated with 1.5 equiv of CDI, the reactions proceeded smoothly to give the imidazolide intermediates which could be converted to the target material **30** and **31** in 71% and 81% yields, respectively (Scheme 6). In contrast, guanosine derivative **29** required 3 equiv of CDI to complete the formation of the imidazolide. Moreover, the second reaction of the imidazolide of dG^{iBu} with **17** was very slow, 30 h to complete the reaction.

Next, we examined the removal of the CTFOC group of the four deoxynucleosides **18**, **30**, **31**, and **32** and the recovery of the 5′-free nucleosides **4**, **27**, **28**, and **29** by silica gel column chromatography, considering the practical use of the CTFOC group in synthetic chemistry (Scheme 6, step iii). Compound **18** was treated with 0.1 M I_2 in pyridine−H_2O (9:1, v/v), and the reaction was monitored by silica gel TLC. To our surprise, when the reaction mixture was checked after 5 min, the TLC indicated the complete conversion of **18** to the 5′-free nucleoside **4**, not to the intermediates before cyclization, despite the fact that the half-life (= 6 min) of the cyclization in solution was longer (Table 1). These results indicated the acceleration of the cyclization on TLC probably by the catalytic effects of silica gel. On the basis of this observation, we established the following procedure for removal of the CTFOC group.

The protected nucleosides **18**, **30**, **31**, and **32** were treated with 0.1 M I_2 in the pyridine−H_2O for 5 min. After the general workup procedure (see Experimental Section), the solvents were removed under reduced pressure, and the residues were chromatographed on a silica gel column to give the 5′-free nucleosides which were generated by the silica gel catalyzed cyclization on the column. The 5′-free nucleosides **4**, **27**, **28**, and **29** were obtained in quantitative yield, 83%, 95%, and 74% yield, respectively as shown in Scheme 6. These results confirmed the usefulness of the CTFOC group as the protecting group; it could be removed under mild oxidative conditions in combination with general workup procedure and silica gel column chromatography.

SCHEME 6. Introduction of the CTFOC Group and Recovered Yields after the Deprotection[a]



[a] Reagents and conditions: (i) CDI, pyridine; (ii) **17**, DBU, pyridine, 72% for **18**, 71% for **30**, 81% for **31**, 72% for **32**; (iii) 0.1 M I_2, pyridine−H_2O (9:1, v/v), then silica gel column chromatography; quant for **18**, 83% for **30**, 95% for **31**, and 74% for **32**.

Conclusion

In this paper we described new protecting groups, MTFOC and CTFOC, which can be removed in two steps including the cleavage of the MMTrS group under mild oxidative conditions and the self-cyclization. These new protecting groups have the *cis*-tetrahydrofuran-3,4-diol structure in which the two hydroxyl groups are fixed in close proximity by the furan ring. In addition, the five-membered ring of CTFOC group is fixed in *O*7-*exo* conformation to avoid the energetically unfavorable conformation change during the cyclization. We revealed that the conformation-lock of the five-membered ring accelerated the second step self-cyclization 8.5-fold. We also demonstrated that the CTFOC group could be introduced to the 5′-hydroxyl function of all four canonical deoxynucleosides and removed by the combination of the mild oxidation and silica gel assisted cyclization of the resulting intermediates. The CTFOC group is readily removable and can serve as protecting group for the hydroxyl function of various compounds.

Introduction of the MTFOC and CTFOC groups to nucleosides results in the formation of two diastereoisomers because of the presence of a pair of chiral centers. In general, the mixture of diastereomers can be used as described above. However, when the MTFOC and CTFOC groups are applied to molecules containing other diastereomeric protecting groups such as 2,2,5,5-tetramethylpyrrolidin-3-one-1-sulfinyl,[6] tetrahydropyran-2-yl,[24] α-methyl-2-nitropiperonyloxycarbonyl,[25] and N-substituted 2-amino-1-phenylethyl-1-yl-oxycarbonyl[26] groups, the resulting mixtures of isomers would be more complex. Therefore, the MTFOC and CTFOC groups would be the most valuable when applied to the solid-phase synthesis of oligodeoxyribonucleotides. Especially, the most rapidly removable CTFOC group should be useful in the oligonucleotide synthesis without acid treatment as exemplified by precedents using the MMTrS group[3] as well as the aryloxycarbonyl group capable of deprotection by the action of peroxide[5] and 2,2,5,5-tetramethylpyrrolidin-3-one-1-sulfinyl group.[6] In conclusion, we reported the CTFOC group as a new protected protecting group removable under mild oxidative conditions. It should be also emphasized that the CTFOC group is the first example of the carbonate-type protected protecting group utilizing such a *cis*-diol structure.

Experimental Section

(*3S,4R*)- and (*3R,4S*)-4-(Tritylsulfenyloxy)tetrahydrofuran-3-ol (2). To a solution of 1,4-anhydroerythritol (**1**) (0.14 g, 1.3 mmol) in THF (10 mL) was added NaH (64 mg, 1.6 mmol, 60% in oil). The resulting mixture was stirred at room temperature for 40 min, and then tritylsulfenyl chloride (0.50 g, 1.6 mmol) was added. After being stirred at room temperature for 2.5 h, the reaction was quenched by addition of concentrated NH_3 (1 mL). The solution was diluted with ethyl acetate (25 mL) and washed once with water (30 mL) and twice with saturated $NaHCO_3$ (30 mL). The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (20 g) with hexane−ethyl acetate (2:1, v/v) to give **2** (0.51 g, quant): ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.08 (s, 1H), 3.37−3.39 (m, 2H), 3.56 (dd, J = 5.0, 9.5 Hz, 1H), 3.68−3.72 (m, 2H), 3.87 (dd, J = 5.5, 10.0 Hz, 3H) 7.27−7.40 (m, 15H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 70.7, 71.0, 72.5, 87.3, 127.6, 128.2, 129.9, 142.3. ESI-MS: calcd for $C_{23}H_{22}NaO_3S$ $(M + Na)^+$, 401.11819; found, 401.11115.

3′-*O*-*tert*-Butyldimethylsilyl-5′-*O*-[[[(*3S,4R*)- and (*3R,4S*)-4-(tritylsulfenyloxy)tetrahydrofuran-3-yl]oxy]carbonyl]thymidine (5). Method A. Compound **2** (0.38 g, 1.0 mmol) was rendered anhydrous by repeated coevaporation with dry toluene and finally dissolved in dry CH_2Cl_2 (1 mL). To the solution was added dry pyridine (0.19 mL, 2.4 mmol). A solution of 4-nitrophenyl chloroformate (0.24 g, 1.2 mmol) in CH_2Cl_2 (1 mL) was added dropwise over 5 min to the CH_2Cl_2 solution of **2**. After being stirred at room temperature for 70 min, the reaction was quenched by addition of water (1 mL). The solution was diluted with ethyl acetate (30 mL) and washed three times with sat. $NaHCO_3$ (30 mL). The organic layer was collected, dried over $MgSO_4$, filtered, and

concentrated under reduced pressure. The residue was chromatographed twice on a silica gel column (20 g) with hexane−ethyl acetate (100:3, v/v) to give a crude mixture (0.42 g) which contained the target material (**3a**) (90%), the starting material (**2**) (6%), and 4-nitrophenol (4%). Compound **3a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.29−3.36 (m, 2H), 3.81−3.90 (m, 3H), 4.92 (dd, J = 5.13, 10.0 Hz, 1H), 7.22−7.38 (m, 17H), 8.19−8.22 (m, 2H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 68.9, 70.4, 72.4, 76.5, 84.7, 121.8, 125.2, 127.4, 128.0, 129.8, 129.8, 142.1, 145.3, 151.8, 155.2.

A mixture (0.42 g) of the crude product **3a**, which was calculated to contain **3a** (0.40 g, 0.73 mmol), and 3′-*O*-(*tert*-butyldimethylsilyl)thymidine (**4**)[36] (0.26 g, 0.73 mmol) was rendered anhydrous by repeated coevaporation with dry pyridine and finally dissolved in dry pyridine (3 mL). To this solution was added DBU (110 μL, 0.73 mmol). After being stirred at room temperature for 13 h, the solution was diluted with ethyl acetate (30 mL) and washed three times with saturated $NaHCO_3$ (30 mL). The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was chromatographed on an NH-silica gel column with hexane−ethyl acetate (7:13, v/v) to give compound **5** (0.39 g, 70%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.042−0.086 (m, 6H), 0.85−0.93 (m, 9H), 1.92 and 1.95 (2 × s, 3H), 2.12−2.32 (m, 2H), 3.24−3.26 (m, 2H), 3.72−3.84 (m, 3H), 4.06−4.09 (m, 1H), 4.35−4.42 (m, 3H), 4.84−4.89 (m, 1H), 6.33−6.34 (m, 1H), 7.25−7.33 (m, 32H), 7.45 and 7.46 (2 × s, 1H), 9.08 and 9.10 (2 × br, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ −4.9, −4.9, −4.7, 12.6, 12.6, 17.9, 17.9, 25.7, 40.9, 41.0, 67.0, 67.1, 69.3, 69.3, 70.5, 70.7, 71.7, 71.8, 72.4, 75.7, 75.9, 84.5, 84.7, 84.8, 85.0, 85.1, 85.3, 111.3, 127.5, 127.6, 128.1, 130.0, 130.0, 135.3, 135.5, 142.3, 142.3, 150.0, 150.1, 154.1, 163.3. ESI-MS: calcd for $C_{40}H_{48}N_2NaO_9SSi$ $(M + Na)^+$, 783.27420; found, 783.27197.

Method B. Compound **2** (0.19 g, 0.50 mmol) was rendered anhydrous by repeated coevaporation with dry pyridine and finally dissolved in dry pyridine (2 mL). To this solution was added carbonyldiimidazole (0.12 g, 0.75 mmol). After being stirred for 50 min, the solution was diluted with ethyl acetate (20 mL) and washed once with water (20 mL) and twice with brine (20 mL). The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue became an amorphous solid. On the basis of the NMR analysis of this residue, it was confirmed that the starting material was completely changed to 3-[[(1*H*-imidazol-1-yl)carbonyl]oxy]-4-(tritylsulfenyloxy)tetrahydrofuran (**3b**). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.31 (d, J = 5.5 Hz, 1H), 3.70−3.75 (m, 2H), 3.84 (dd, J = 6.0, 10.0 Hz, 1H), 4.92 (dd, J = 5.0, 10.5 Hz, 1H), 7.00−7.37 (m, 17H), 8.10 (s, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 22.8, 69.4, 70.7, 72.5, 75.6, 84.8, 117.2, 127.5, 128.1, 129.9, 130.8, 137.3, 142.2, 148.0.

A mixture of **3b** and **4** (0.12 g, 0.34 mmol) was rendered anhydrous by repeated coevaporation with dry pyridine and finally dissolved in dry pyridine (2 mL). To this mixture was added DBU (7.5 μL, 0.05 mmol). After being stirred at room temperature for 3 h, the solution was diluted with ethyl acetate (20 mL) and washed four times with brine (20 mL). The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with hexane−chloroform (1:1, v/v) to give **5** (0.21 g, 81%).

Method C. Compound **4** (1.8 g, 5.0 mmol) was rendered anhydrous by repeated coevaporation with dry pyridine and finally dissolved in dry pyridine (5 mL). A solution of 4-nitrophenyl chloroformate (1.1 g, 5.0 mmol) in dioxane (5 mL) was added dropwise over 100 min to the pyridine solution of **4**. After being stirred at room temperature for 1.5 h, the solution was diluted with $CHCl_3$ (100 mL) and washed three times with water (100 mL). The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (100 g) with hexane−ethyl acetate (1:4, v/v) to give **6**[28] (2.1 g, 82%).

A mixture of the carbonate intermediate **6** (0.18 g, 0.35 mmol) and **2** (0.13 g, 0.35 mmol) was rendered anhydrous by repeated coevaporation with dry pyridine and finally dissolved in dry pyridine (1 mL). To this mixture was added DBU (52 μL, 0.35 mmol). After being stirred at room temperature for 6 h, the solution was diluted with ethyl acetate (20 mL) and washed once with water (20 mL) and three times with saturated $NaHCO_3$ (20 mL). The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was chromatographed on an NH-silica gel column with hexane−chloroform (1:1, v/v) to give **5** (0.20 g, 76%).

Method D. Compound **4** (1.8 g, 5.0 mmol) was rendered anhydrous by repeated coevaporation with dry pyridine and finally dissolved in dry pyridine (12 mL). To this solution was added carbonyldiimidazole (1.2 g, 7.5 mmol). After being stirred for 1 h, the solution was diluted with ethyl acetate (100 mL) and washed three times with water (100 mL). The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue became an amorphous solid. On the basis of the NMR analysis of this residue, it was confirmed that the starting material was changed to 5′-*O*-[(1*H*-imidazol-1-yl)carbonyl]-3′-*O*-(*tert*-butyldimethylsilyl)thymidine (**7**) completely. A portion of the amorphous solid (0.23 g, 0.50 mmol) was rendered anhydrous by repeated coevaporation with dry pyridine and finally dissolved in dry pyridine (10 mL). Compound **2** (0.19 g, 0.50 mmol) was also rendered anhydrous by repeated coevaporation with dry pyridine. The pyridine solution of **7** was added to this residue. DBU (7.5 μL, 50 μmol) was added. After being stirred at room temperature for 3 h, the solution was diluted with ethyl acetate (20 mL) and washed four times with water (20 mL). The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with hexane−ethyl acetate (3:1, v/v) to give **5** (0.35 g, 91%).

(3*S*,4*R*)- and (3*R*,4*S*)-4-[[(4-Methoxytrityl)sulfenyl]oxy]tetrahydrofuran-3-ol (8). Compound **1** (0.13 g, 1.2 mmol) was dissolved in THF (10 mL). To this solution was added NaH (59 mg, 1.5 mmol), and the resulting mixture was stirred for 40 min. 4-Methoxytritylsulfenyl chloride (0.50 mg, 1.5 mmol) was added. After being stirred at room temperature for 4 h, the mixture was quenched by the addition of concentrated NH_3 (1 mL). The solution was diluted with ethyl acetate (40 mL) and washed once with water (50 mL) and twice with saturated $NaHCO_3$ (50 mL). The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (20 g) with hexane−ethyl acetate (8:2, v/v) to give **8** (0.41 g, 82%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.53 (s, 1H), 3.33−3.39 (m, 2H), 3.50−3.53 (dd, J = 5.1, 9.2 Hz, 1H), 3.65−3.73 (m, 2H), 3.74 (s, 3H), 3.86 (dd, J = 5.3, 10.6 Hz, 1H), 6.80−7.20 (m, 2H), 7.22−7.28 (m, 8H), 7.37−7.38 (m, 4H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 55.0, 70.5, 70.8, 71.8, 72.1, 87.0, 113.2, 127.2, 127.9, 129.7, 129.7, 130.9, 133.6, 142.5, 142.6, 158.6. Anal. Calcd for $C_{24}H_{24}O_4S$: C, 70.56; H, 5.92; S, 7.85. Found: C, 70.37; H, 6.06; S, 7.69.

3′-*O*-*tert*-Butyldimethylsilyl- 5′-*O*-[[(3*S*, 4*R*)- and (3*R*, 4*S*)-4-(4-metoxytrityl)sulfenyl]oxytetrahydrofuran-3-yl]oxycarbonylthymidine (9). The above-mentioned amorphous solid of **7** (0.72 g, 1.6 mmol) was rendered anhydrous by repeated coevaporation with dry pyridine. Compound **8** (0.65 g, 1.6 mmol) was also rendered anhydrous by repeated coevaporation with dry pyridine and finally dissolved in dry pyridine (10 mL). The solution was added to **7**. DBU (24 μL, 0.16 mmol) was added. After being stirred for 2.5 h, the solution was diluted with ethyl acetate (80 mL) and washed three times with burin (80 mL). The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with hexane−ethyl acetate (5:1, v/v) to give **9** (1.2 g, 93%). The ratio of the diastereomers was found to be 1:1 from the NMR spectra. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.046−0.091 (m, 6H),

(36) Ogilvie, K. K. *Can. J. Chem.* **1973**, *51*, 3799−3807.

0.88−0.92 (m, 9H), 1.94 and 1.95 (2 × s, 3H), 2.12−2.32 (m, 2H), 3.26−3.33 (m, 2H), 3.73−3.86 (m, 6H), 4.05−4.10 (m, 1H), 4.35−4.46 (m, 3H), 4.85−5.02 (m, 1H), 6.34−6.37 (m, 1H), 6.80−6.83 (m, 2H), 7.21−7.78 (m, 14H), 9.73 (br, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ −5.0, −5.0, −4.9, −4.8, 12.5, 12.5, 17.7, 17.8, 25.5, 40.7, 40.8, 55.1, 66.8, 66.9, 69.1, 69.2, 70.4, 70.6, 71.5, 71.6, 71.8, 71.8, 75.6, 75.7, 84.2, 84.5, 84.6, 84.8, 84.8, 85.1, 111.2, 111.2, 113.2, 127.3, 127.3, 127.9, 129.8, 129.8, 129.8, 131.0, 131.0, 133.6, 133.6, 135.2, 135.3, 142.5, 142.6, 150.4, 150.5, 154.0, 158.6, 158.7, 163.9, 163.9. ESI-MS calcd for $C_{41}H_{50}N_2NaO_{10}SSi$ $(M + Na)^+$, 813.28476; found, 813.28355.

***exo*-*N*-(Phenylmethyl)-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxiimide (15).** To a solution of *N*-benzylmaleimide (1.87 g, 10 mmol) in dioxane (30 mL) was added furan (2.18 mL, 30 mmol). The reaction apparatus was sealed, heated, and kept at 90 °C for 12 h. After being cooled to the room temperature, the mixture was evaporated under reduced pressure. Addition of ethyl acetate and hexane to the residue gave compound **15** as crystals (1.39 g, 54%). The structure of **15** was confirmed by comparison of its ^{1}H NMR chemical shifts with those reported in the previous paper.[37]

5,6-Dihydroxy-*exo*-*N*-(phenylmethyl)-7-oxabicyclo[2.2.1]-heptane-2,3-dicarboximide (16). Compound **15** (5.7 g, 22 mmol) was dissolved in acetone (180 mL). To this solution were added water (30 mL), OsO_4 (2.5 wt % in 2-methyl-2-propanol, 0.22 mmol, 2.8 mL) and *N*-methylmorpholine *N*-oxide (4.8 M in water, 5.6 mL, 27 mmol). The mixture was stirred in the dark at room temperature for 18 h. From the suspended mixture, acetone was removed by evaporation under reduced pressure. Filtration of the precipitates followed by washing with MeOH gave **16** (5.4 g, 83%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.08 (s, 2H), 3.90 (s, 2H), 4.31 (s, 2H), 4.54 (s, 2H), 4.97 (s, 2H), 7.17−7.32 (m, 5H). ^{13}C NMR (67.8 MHz, DMSO-d_6): δ 41.6, 45.3, 71.8, 83.8, 126.9, 128.5, 135.8, 176.8. Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84. Found: C, 61.90; H, 5.07; N, 4.90. The stereochemistry of this compound was assigned to be *exo*-*cis*-glycol on the basis of the previous papers.[34,35]

6-Hydroxyl-5-[[(4-methoxytrityl)sulfenyl]oxy]-*exo*-*N*-(phenylmethyl)-7-oxabicyclo[2.2.1]heptane-2,3-dicarboximide (17). To a solution of **16** (0.87 g, 3.0 mmol) in DMF (30 mL) was added NaH (0.14 g, 3.6 mmol, 60% in oil). The mixture was stirred at room temperature for 55 min, and then (4-methoxytrityl)sulfenyl chloride (1.2 g, 3.6 mmol) was added. After being stirred for 3 h, the mixture was quenched by the addition of concentrated NH_3 (1 mL). The solution was diluted with ethyl acetate (50 mL) and washed three times with water (50 mL). The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (40 g) with hexane−ethyl acetate (2:1, v/v) to give **17** (0.94 g, 53%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.18 (d, J = 6.8 Hz, 1H), 2.56 (d, J = 7.1 Hz, 1H), 2.62 (d, J = 8.5 Hz, 1H), 3.18 (d, J = 6.1 Hz, 1H), 3.66 (t, J = 7.2 Hz, 1H), 3.82 (s, 3H), 4.16 (d, J = 0.49 Hz, 1H), 4.50 (d, J = 0.73 Hz, 1H), 4.56 (s, 1H), 6.86−6.89 (m, 2H), 7.23−7.41 (m, 17H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 42.7, 44.8, 45.5, 55.3, 72.3, 73.8, 82.3, 84.3, 88.1, 113.5, 127.6, 127.7, 127.9, 128.1, 128.2, 128.3, 128.7, 129.8, 129.9, 131.2, 133.5, 135.1, 142.3, 142.5, 158.9, 174.8, 175.3 ppm. ESI-MS: calcd for $C_{35}H_{31}NNaO_6S$ $(M + Na)^+$, 616.17643; found, 616.17214.

3′-*O*-*tert*-Butyldimethylsilyl-5′-*O*-CTFOC-thymidine (18). Compound **17** (0.30 g, 0.50 mmol) was rendered anhydrous by repeated coevaporation with dry pyridine and finally dissolved in dry pyridine (5 mL). This solution was added to **7** (0.23 g, 0.50 mmol). To the mixture was added 0.1 equiv of DBU (7.5 μL, 0.05 mmol). After being stirred at room temperature for 4 h, the solution was diluted with ethyl acetate (30 mL) and washed four times with burin (30 mL). The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with hexane−ethyl acetate (2:1, v/v) to give **18** (0.35 g, 72%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.03−0.09 (m, 6H), 0.87−0.90 (m, 9H), 1.93 (s, 3H) 2.16−2.29 (m, 1H), 2.67 (t, J = 7.3 Hz, 1H), 3.42 and 3.50 (d, J = 5.9, 6.1 Hz, 1H), 3.79 and 3.80 (2 × s, 3H), 3.97 and 4.03 (2 × s, 1H), 4.07−4.11 (m, 1H), 4.36−4.45 (m, 3H), 4.54 (s, 2H), 4.61 and 4.64 (2 × d, J = 6.1, 5.9 Hz, 1H), 4.67 and 4.70 (2 × s, 1H), 6.37 (t, J = 6.6 Hz, 1H), 6.84−6.87 (m, 2H), 7.21−7.47 (m, 17H), 9.61 (s, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ −5.0, −4.9, −4.9, −4.8, 12.4, 12.5, 17.7, 25.5, 40.6, 40.7, 42.6, 44.8, 45.2, 55.0, 67.2, 67.3, 71.6, 71.6, 72.0, 81.0, 81.1, 82.4, 82.7, 84.2, 84.3, 84.6, 84.8, 88.1, 88.7, 111.2, 111.4, 113.3, 127.5, 127.7, 127.9, 128.0, 128.4, 129.6, 129.8, 131.1, 131.1, 133.3, 133.4, 134.8, 135.2, 135.2, 142.2, 142.5, 142.6, 150.4, 154.0, 158.7, 163.8, 163.9, 174.1, 174.6, 174.6. ESI-MS: calcd for $C_{52}H_{57}N_3O_{12}SSiNa$ $(M + Na)^+$, 998.3324; found, 998.3315.

Tetrabutylammonium 5-Nitro-2-hydroxymethylbenzoate (20). 6-Nitrophthalide (40 g, 0.22 mol) was dissolved in 10% tetrabutylammonium hydroxide in water (560 mL). The solution was heated under reflux for 1 h. The mixture was cooled to room temperature and then concentrated under reduced pressure. The residue was crystallized from ethyl acetate, and the crystals were collected by filtration to give **20** (61 g, 63%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.97 (t, J = 7.3 Hz, 12H), 1.38−1.44 (m, 8H), 1.61−1.68 (m, 8H), 3.28 (t, J = 8.5 Hz, 8H), 4.71 (s, 2H), 7.32−7.35 (m, 1H), 8.03−8.06 (m, 1H), 8.82−8.83 (m, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 129.9, 142.5, 146.8, 147.9, 170.5. Anal. Calcd for $C_{24}H_{42}N_2O_5$: C, 65.72; H, 9.65; N, 6.39. Found: C, 65.42; H, 9.42; N, 6.33.

Triethylammonium 5-Nitro-2-[(4-methoxytritylsulfenyl)oxymethyl]benzoate (21). Compound **20** (4.4 g, 10 mmol) was suspended in THF (50 mL), and the mixture was heated to 47 °C to give a clear solution. NaH (0.60 g, 15 mmol, 60% in oil) was added, and the resulting suspension was stirred at 47 °C for 15 min. The reaction mixture was cooled to room temperature. To this solution was added 4-methoxytritylsulfenyl chloride (5.1 g, 15 mmol). After being stirred for 20 min, the reaction was quenched by the addition of concentrated ammonia (5 mL), and the solution was partitioned between ethyl acetate (300 mL) and saturated $NaHCO_3$ (100 mL). The aqueous layer was removed, and the organic layer was washed twice with saturated $NaHCO_3$ (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The desired product was purified by using a two-layer column of silica gel (100 g, upper layer) and NH silica gel (100 g, lower layer) eluted with $CHCl_3$−MeOH−NEt_3 (100:2:10, v/v/v) to give **21** (3.2 g, 54%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.36 (t, J = 7.5 Hz, 9H), 3.13 (q, J = 7.5 Hz, 6H), 3.76 (s, 3H), 4.92 (s, 2H), 6.78 (d, J = 8.1 Hz, 2H), 7.24−7.44 (m, 13H), 8.11 (d, J = 8.5 Hz, 1H), 8.67 (s, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 8.6, 45.2, 45.4, 45.6, 55.1, 55.3, 72.0, 78.5, 113.2, 113.4, 124.9, 125.1, 127.2, 127.4, 127.9, 128.0, 130.0, 131.2, 131.3, 133.1, 134.1, 143.0, 146.6, 158.7, 169.4. Anal. Calcd for $C_{34}H_{38}N_2O_6S$−NEt_3: C, 67.75; H, 6.35; N, 4.65; S, 5.32. Found: C, 68.17; H, 6.02; N, 4.59; S, 5.20.

3′-*O*-*tert*-Butyldimethylsilyl-5′-*O*-[5-nitro-2-[(4-methoxytritylsulfenyloxy)methyl]benzoyl]thymidine (22). Compound **4** (0.50 g, 1.4 mmol), **21** (0.60 g, 2.1 mmol), and 4-methoxypyridine-1-oxide hydrate (0.13 g, 1.1 mmol) were separately rendered anhydrous by repeated coevaporation with dry pyridine and dissolved in 2 mL, 5 mL, and 5 mL of dry pyridine, respectively. To the solution of **4** were added successively the pyridine solution of triethylammonium 5-nitro-2-[(4-methoxytritylsulfenyl)oxymethyl]-benzoate and the pyridine solution of 4-methoxypyridine-1-oxide, and finally *N*,*N*-bis(2-oxo-3-oxazolidinyl)phosphinic chloride (0.54 g, 2.1 mmol) was added. After being stirred at room temperature for 13 h, the mixture was quenched by the addition of water (5 mL). The solution was diluted with ethyl acetate (200 mL) and washed three times with saturated $NaHCO_3$ (200 mL). The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated

(37) Kwart, H.; Burchuk, I. *J. Am. Chem. Soc.* **1952**, *74*, 3094−3097.

under reduced pressure. The residue was chromatographed on an NH silica gel column with hexane−chloroform (1:1, v/v) to give **22** (1.2 g, 99%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.11 (s, 6H), 0.91 (s, 9H), 1.76 (s, 3H), 2.19−2.24 (m, 1H), 2.33−2.38 (m, 1H), 3.78 (s, 3H), 4.15−4.18 (m, 1H), 4.41−4.43 (m, 1H), 4.44−4.48 (m, 1H), 4.82 (s, 2H), 6.20 (d, J = 6.5 Hz, 1H), 6.80−6.82 (m, 2H), 7.13−7.39 (m, 14H), 8.25−8.27 (m, 2H), 8.66 (s, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ −4.8, −4.7, 12.3, 17.9, 25.6, 40.4, 55.2, 64.5, 71.8, 72.1, 77.6, 84.1, 85.7, 111.2, 113.3, 124.9, 126.8, 127.4, 127.8, 128.1, 128.8, 129.9, 131.2, 133.8, 135.3, 142.8, 142.8, 146.5, 148.0, 149.8, 158.8, 163.2. Anal. Calcd for $C_{44}H_{49}N_3O_{10}SSi$: C, 62.91; H, 5.88; N, 5.00; S, 3.82. Found: C, 63.34; H, 5.77; N, 4.68; S, 3.54.

***cis*-1-[(4-Metoxytrityl)sulfenyl]oxy-cyclohexane-2-ol (23).** *cis*-1,2-Cyclohexanediol (0.23 g, 2.0 mmol) was dissolved in THF (10 mL). To this solution was added lithium bis(trimethylsilyl)amide (1 M solution in THF, 2 mL), and the resulting solution was stirred at room temperature for 30 min. 4-Methoxytritylsulfenyl chloride (0.82 g, 2.4 mmol) was added. After being stirred at room temperature for 4 h, the mixture was quenched by the addition of concentrated NH_3 (1 mL). The solution was diluted with ethyl acetate (80 mL) and washed once with water (80 mL) and twice with burin (80 mL). The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (20 g) with hexane−ethyl acetate (19:1, v/v) to give the crude product of **23** (0.43 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.93−0.97 (m, 1H), 1.12−1.22 (m, 3H), 1.42−1.50 (m, 3H), 1.64−1.68 (m, 1H), 1.78 (br, 1H), 3.08−3.09 (m, 1H), 3.76 (s, 3H), 6.79−6.83 (m, 2H), 7.14−7.40 (m, 12H).

3′-*O*-*tert*-Butyldimethylsilyl-5′-*O*-[(*1R,2S*)- and (*1S,2R*)-[1-(4-methoxytrityl)sulfenyl]oxycyclohexane-2-yl]oxycarbonylthymidine (24). The crude material **23** was rendered anhydrous by repeated coevaporation with dry pyridine and dissolved in pyridine (5 mL). The solution was added to compound **7** (0.45 g, 1.0 mmol). DBU (154 μL, 1.0 mmol) was added. After being stirred at ambient temperature for 4 h, the solution was diluted with ethyl acetate (40 mL) and washed four times with burin (40 mL). The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with hexane−ethyl acetate (4:1, v/v) to give **24** (0.38 g, 46%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.044−0.077 (m, 6H), 0.76−1.00 (m, 10H), 1.11−1.47 (m, 6H), 1.77−2.11 (m, 5H) 2.25−2.30 (m, 1H), 3.16 and 3.22 (2 × br, 1H), 3.79 (s, 3H), 4.03−4.07 (m, 1H), 4.26−4.47 (m, 3H), 4.45−4.47 (m, 1H), 6.29−6.36 (m, 1H), 6.78−6.83 (m, 2H), 7.22−7.50 (m, 14H), 8.89 (s, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ −5.0, −4.9, −4.9, −4.8, −4.7, 12.6, 12.7, 12.7, 17.9, 20.9, 21.5, 22.1, 22.1, 25.6, 25.7, 27.3, 27.7, 28.2, 28.6, 40.7, 40.9, 55.2, 55.2, 66.4, 66.5, 71.5, 71.6, 72.0, 72.1, 84.2, 84.5, 84.7, 84.8, 84.9, 85.2, 111.2, 113.1, 113.2, 127.2, 127.8, 130.0, 131.1, 131.2, 134.4, 134.4, 135.3, 135.7, 143.2, 143.3, 143.4, 150.2, 150.3, 154.2, 154.3, 158.7, 163.7. ESI-MS: calcd for $C_{43}H_{54}N_2O_9SSiNa$ $(M + Na)^+$, 825.32115; found, 825.32612.

***trans*-1-[(4-Metoxytrityl)sulfenyl]oxy-cyclohexane-2-ol (25).** To a solution of *trans*-1,2-cyclohexanediol (0.23 g, 2.0 mmol) in THF (5 mL) was added NaH (0.12 g, 3.0 mmol). The resulting solution was stirred at 44 °C for 20 min, and then the mixture was cooled to room temperature. To this mixture was added (4-methoxytrityl)sulfenyl chloride (0.82 g, 2.4 mmol). After being stirred at room temperature for 4 h, the mixture was quenched by addition of concentrated NH_3 (1 mL). The solution was diluted with ethyl acetate (80 mL) and washed once with water (80 mL) and then twice with burin (80 mL). The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (20 g) with hexane−ethyl acetate (100:7, v/v) to give crude **25** (0.24 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90−1.08 (m, 4H), 1.50−1.52 (br, 2H), 1.60−1.63 (br, 1H), 1.72 (br, 1H), 1.78−1.82 (m, 1H), 2.93−2.97 (m, 1H), 3.77 (s, 3H), 6.81−6.84 (m, 2H), 7.23−7.38 (m, 12H).

3′-*O*-*tert*-Butyldimethylsilyl-5′-*O*-[[(*1S,2S*) and (*1R,2R*)-[1-[(4-methoxytrityl)sulfenyl]oxy]cyclohexane-2-yl]oxy]carbonyl]thymidine (26). The crude material **25** was rendered anhydrous by repeated coevaporation with dry pyridine and finally dissolved in dry pyridine (10 mL). The solution was added to compound **7** (0.26 g, 0.57 mmol). To the mixture was added 1.0 equiv of DBU (85 μL, 0.57 mmol). The resulting mixture was heated to 50 °C and stirred for 3.5 h. Then the solution was diluted with ethyl acetate (40 mL) and washed four times with burin (40 mL). The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with hexane−ethyl acetate (4:1, v/v) to give **26** (70 mg, 15%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.049−0.086 (m, 6H), 0.83−0.88 (m, 10H), 0.96−1.02 (m, 1H), 1.13−1.26 (m, 3H), 1.40−1.45 (m, 1H), 1.52−1.58 (m, 1H), 1.85 and 1.86 (2 × s, 3H), 1.93−2.29 (m, 6H), 3.22−3.33 (m, 1H), 3.79 (s, 3H), 4.02−4.05 (m, 1H), 4.25−4.49 (m, 4H), 6.26 and 6.36 (t, J = 6.6 Hz, 1H), 6.77−6.82 (m, 2H), 6.82−7.47 (m, 14H), 8.88 and 8.97 (2 × s, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ −4.97, −4.88, −4.75, 12.6, 12.7, 17.9, 23.1, 23.3, 23.7, 25.6, 29.6, 30.2, 30.7, 31.1, 41.0, 41.1, 55.2, 66.0, 66.2, 71.4, 71.6, 71.9, 72.1, 80.4, 81.2, 84.5, 84.7, 84.9, 88.3, 89.4, 110.8, 111.0, 113.1, 127.2, 127.3, 127.7, 128.0, 128.2, 129.6, 130.0, 130.1, 130.2, 131.1, 131.2, 133.9, 134.4, 135.3, 135.5, 142.9, 143.1, 143.3, 143.4, 150.3, 154.2, 158.7, 163.6, 163.7. Anal. Calcd for $C_{43}H_{54}N_2O_9SSi$-$^1/_2H_2O$: C, 63.60; H, 6.83; N, 3.45. Found: C, 63.57; H, 6.77; N, 3.54.

6-*N*-Benzoyl-3′-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-5′-*O*-CTFOC-adenosine (30). 6-*N*-Benzoyl-3′-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (**27**)[36] (0.47 g, 1.0 mmol) was rendered anhydrous by repeated coevaporation with dry pyridine and finally dissolved in dry pyridine (7 mL). Carbonyldiimidazole (0.24 g, 1.5 mmol) was added, and the solution was stirred at room temperature for 40 min. The solution was diluted with ethyl acetate (50 mL) and washed three times with water (50 mL). The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue became an amorphous solid. The NMR analysis of this residue suggested that the starting material was changed to the imidazolide intermediate completely. A portion of the amorphous solid, the imidazolide (0.40 g, 0.70 mmol), was rendered anhydrous by repeated coevaporation with dry pyridine. Compound **17** (0.42 g, 0.70 mmol) was also rendered anhydrous by repeated coevaporation with dry pyridine and dissolved in pyridine (2.5 mL). To this solution were added the imidazolide and DBU (11 μL, 0.07 mmol). After being stirred at ambient temperature for 3 h, the solution was diluted with ethyl acetate (20 mL) and washed four times with water (20 mL) and burin (20 mL). The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with hexane−ethyl acetate (1:1, v/v) to give **30** (0.55 g, 71%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.11−0.14 (m, 6H), 0.92−0.93 (m, 9H), 2.15−2.17 (m, 1H), 2.48−2.51 (m, 1H), 2.67−2.71 (m, 1H), 2.82−2.84 (m, 1H), 3.47 and 3.74 (2 × d, J = 4.9, 5.9 Hz, 1H), 3.74 and 3.77 (2 × s, 3H), 3.94 and 4.05 (2 × s, 1H), 4.20−4.56 (m, 5H), 4.66−4.68 (m, 1H), 4.70−4.73 (m, 1H), 6.48−6.51 (m, 1H), 6.81−6.84 (m, 2H), 7.16−7.53 (m, 21H), 7.92 and 7.93 (2 × s, 1H), 7.99 and 8.01 (2 × s, 1H), 8.25 and 8.28 (2 × s, 1H), 8.73 and 8.77 (2 × s, 1H), 9.31 and 9.44 (2 × s, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ −5.0, −4.9, −4.86, 17.7, 25.5, 40.5, 40.6, 42.5, 44.9, 45.2, 55.0, 66.9, 67.5, 71.9, 72.2, 81.0, 82.5, 84.2, 84.7, 84.9, 88.0, 88.6, 113.3, 123.3, 123.4, 127.4, 127.5, 127.7, 127.8, 128.0, 128.4, 128.5, 129.8, 131.1, 132.4, 133.4, 133.6, 141.3, 141.5, 142.3, 142.6, 149.4, 151.2, 151.3, 152.3, 152.4, 154.0, 158.7, 164.5, 164.7, 174.2, 174.6. ESI-MS: calcd for $C_{59}H_{61}N_6O_{11}SSi$ $(M + H)^+$, 1089.3883; found, 1089.3812.

4-*N*-Benzoyl-3′-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-5′-*O*-CTFOC-cytidine (31). 4-*N*-Benzoyl-3′-*O*-(*tert*-butyldimethylsilyl)-2′-

deoxycytidine (**28**)[36] (0.89 g, 2.0 mmol) was rendered anhydrous by repeated coevaporation with dry pyridine and finally dissolved in dry pyridine (15 mL). Carbonyldiimidazole (0.49 g, 3.0 mmol) was added, and the resulting mixture was stirred for 40 min. The solution was diluted with ethyl acetate (40 mL) and washed three times with water (40 mL). The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue became an amorphous solid. The NMR analysis of this residue suggested that the starting material was completely changed to the imidazolide intermediate. The the imidazolide was rendered anhydrous by repeated coevaporation with dry pyridine and finally dissolved in pyridine (4 mL). Compound **17** (1.2 g, 2.0 mmol) was also rendered anhydrous by repeated coevaporation with dry pyridine and dissolved in pyridine (4 mL). To the solution of the imidazolide, **17** and DBU (30 μL, 0.2 mmol) were added. After being stirred at room temperature for 2 h, the mixture was diluted with ethyl acetate (40 mL) and washed four times with burin (40 mL). The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with hexane−ethyl acetate (3:2, v/v) to give **31** (1.7 g, 81%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.04 and 0.08 (2 × s, 6H), 0.84−0.90 (m, 9H), 2.15−2.25 (m, 2H), 2.77−2.82 (m, 1H), 3.41 and 3.49 (2 × d, J = 5.8, 5.8, 1H), 3.76 and 3.77 (2 × s, 3H), 3.98 and 4.18 (2 × s, 1H), 4.14−4.18 (m, 1H), 4.33−4.42 (m, 2H), 4.47−4.59 (m, 3H), 4.66−4.69 (m, 1H), 4.72−4.73 (m, 1H), 6.23−6.29 (m, 1H), 6.81−6.85 (m, 2H), 7.19−7.55 (m, 17H), 7.90−7.91 (m, 2H), 8.07 and 8.12 (2 × d, J = 7.3, 7.6 Hz, 1H), 8.90 (br, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ −5.09, −4.82, 17.7, 17.7, 25.5, 41.7, 41.8, 42.5, 42.6, 44.9, 45.3, 45.4, 55.0, 66.8, 71.0, 71.1, 72.0, 77.8, 77.8, 81.1, 82.5, 82.7, 84.6, 84.8, 86.8, 87.0, 88.1, 88.6, 113.3, 127.4, 127.5, 127.6, 127.8, 128.0, 128.0, 128.4, 128.6, 129.7, 129.8, 131.1, 131.1, 132.8, 133.0, 133.4, 134.9, 142.3, 142.5, 154.0, 154.1, 158.7, 158.7, 162.2, 174.4, 174.7, 174.8. ESI-MS: calcd for $C_{58}H_{61}N_4O_{12}SSi$ $(M + H)^+$, 1065.3785; found, 1065.3771.

3′-*O*-(*tert*-Butyldimethylsilyl)-2′-deoxy-2-*N*-isobutyryl-5′-*O*-CTFOC-guanosine (32). 3′-*O*-(*tert*-Butyldimethylsilyl)-2′-deoxy-2-*N*-isobutyrylguanosine (**29**)[38] (0.41 g, 0.52 mmol) was rendered anhydrous by repeated coevaporation with dry pyridine. The residue was dissolved in dry pyridine (3 mL), and to this solution was added carbonyldiimidazole (0.25 g, 1.6 mmol). After being stirred for 2 h, the solution was diluted with ethyl acetate (20 mL) and washed three times with water (20 mL). The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue became an amorphous solid. The NMR analysis suggested that the starting material was changed to the imidazolide intermediate completely. The imidazolide was rendered anhydrous by repeated coevaporation with dry pyridine and finally dissolved in pyridine (1 mL). Compound **17** (0.31 g, 0.52 mmol) was also rendered anhydrous by repeated coevaporation with dry pyridine and dissolved in pyridine (1.5 mL). To the solution of the imidazolide, **17** and DBU (7.8 μL, 50 μmol) were added. The resulting solution was stirred at room temperature for 30 h. The solution was diluted with ethyl acetate (20 mL) and washed four times with burin (20 mL). The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with hexane−ethyl acetate (1:1, v/v) to give **32** (0.40 g, 72%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.10 and 0.14 (2 × s, 6H), 0.86−0.90 (m, 9H), 1.03−1.26 (m, 6H), 2.17−2.33 (m, 3H), 2.61−2.93 (m, 3H), 3.49 and 3.49 (2 × s, 1H), 3.80 (s, 3H), 3.91 and 3.94 (2 × s, 1H), 4.16−4.26 (m, 1H), 4.30−4.33 (m, 1H), 4.52−4.84 (m, 6H), 6.18−6.22 (m, 1H), 6.84 and 6.85 (2 × s, 3H), 7.23−7.32 (m, 13H), 7.75 and 7.77 (2 × s, 1H), 8.92 and 9.16 (2 × s, 1H), 11.99 and 12.08 (2 × s, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ −4.79, 17.8, 18.7, 18.9, 19.0, 25.6, 36.3, 39.2, 39.8, 42.7, 45.0, 45.4, 55.2, 67.3, 67.4, 72.2, 72.6, 72.9, 81.0, 81.2, 82.8, 84.6, 84.8, 85.6, 88.9, 89.0, 113.5, 121.9, 122.2, 127.2, 128.0, 128.0, 128.2, 128.6, 129.7, 129.9, 131.2, 133.3, 133.5, 135.0, 137.5, 138.0, 142.2, 142.3, 142.6, 147.2, 147.5,148.0, 154.2, 154.6, 155.4, 158.9, 174.3, 174.7, 178.6, 178.8. ESI-MS: calcd for $C_{56}H_{62}N_6O_{12}SSiNa$ $(M + Na)^+$, 1093.38079; found, 1093.3170.

Determination of the Self-Cyclization Rates by ^{1}H NMR. The self-cyclization rate was examined as follows. The starting material (7.1 μmol) was dissolved in a 0.5 M solution of iodine in pyridine-d_5/D_2O (9:1, v/v, 1.0 mL). An aliquot (700 μL) of the solution was taken and placed into an NMR tube. The reaction was monitored by ^{1}H NMR by use of the 1′-H proton signals of the starting material, the intermediate, and the product. The MMTrS groups were removed within 1 min from all of the protecting groups to give the intermediates. See also Supporting Information.

Removal of the CTFOC Group from 5′-*O*-CTFOC-deoxyribonucleoside Derivatives. The typical procedure is as follows: Compound **18** (0.23 g, 0.24 mmol) was suspended in the 0.1 M I_2 solution (pyridine/H_2O = 9:1, v/v, 47 mL) for 5 min. Then the mixture was quenched with saturated $Na_2S_2O_3$ (100 mL). The reaction was extracted with ethyl acetate (100 mL). The organic layer was washed once with water (100 mL) and twice with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The white powder appeared when hexane (2 mL) was added portionwise to give **4** (90 mg, quant).

In a similar manner, **28** (0.53 g, 0.49 mmol), **29** (1.1 g, 1.0 mmol), and **30** (0.40 g, 0.37 mmol) were deprotected to give **22** (0.19 g, 83%), **23** (0.42 g, 95%), and **24** (0.12 g, 74%), respectively.

Acknowledgment. This work was supported by Grant-in-Aid of CREST of JST (Japan Science and Technology) and the Ministry of Education, Science, Sports and Culture, Grant-in-aid for Scientific Research (A). This study was also supported by Industrial Technology Research Grant Program in 2005 from New Energy and Industrial Technology Development Organization (NEDO) of Japan.

Supporting Information Available: List of experimental procedures for the synthesis of the products other than those described in Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

JO061006V

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