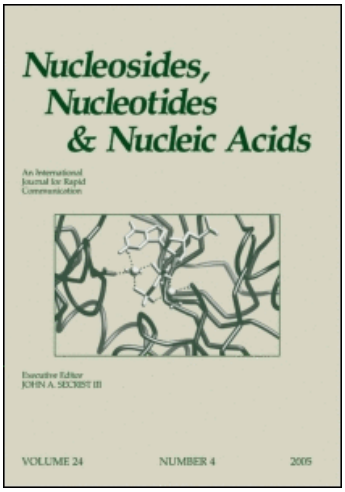

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis of Adenosine, Guanosine and Cytidine Monomer Building Units Bearing the [[2-(Methylthio)-phenyl]thio]methyl (MPTM) Group as The 2'-Hydroxyl Protecting Group

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To cite this Article Sekine, Mitsuo and Nakanishi, Takashi(1992) 'Synthesis of Adenosine, Guanosine and Cytidine Monomer Building Units Bearing the [[2-(Methylthio)-phenyl]thio]methyl (MPTM) Group as The 2'-Hydroxyl Protecting Group', Nucleosides, Nucleotides and Nucleic Acids, 11: 2, 679 — 691
To link to this Article: DOI: 10.1080/07328319208021733
URL: http://dx.doi.org/10.1080/07328319208021733

NUCLEOSIDES & NUCLEOTIDES, 11(2-4), 679-691 (1992)

SYNTHESIS OF ADENOSINE, GUANOSINE AND CYTIDINE MONOMER BUILDING UNITS BEARING THE [[2-(METHYLTHIO)-PHENYL]THIO]METHYL (MPTM) GROUP AS THE 2'-HYDROXYL PROTECTING GROUP

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***ABSTRACT**: A new 2'-hydroxyl protecting group, [[2-(methylthio)phenyl]thio]methyl (MPTM), was introduced into the 2'-position of adenosine, guanosine and cytidine building units required for the synthesis of oligoribonucleotides.*

INTRODUCTION

Oligoribonucleotide synthesis has been extensively studied during the recent 10 years. A number of protecting groups for the 2'-hydroxyl function have been examined and utilized in combination with compatible 5'-hydroxyl protecting groups.[1]

In our previous paper[2], we reported that the [[2-(methylthio)phenyl]thio]methyl (MPTM) group[3] could be used for protection of the 2'-hydroxyl group of uridine and cytidine in oligoribonucleotide synthesis where the MPTM group was introduced to the 2'-hydroxyl group of uridine via a three-step reaction involving tributyltin hydride (TBTH) mediated reduction of the 1,3-benzodithiol-2-yl (BDT) group followed by S-methylation. The cytidine monomer building unit was indirectly prepared from the uridine buildng unit by the use of U-C conversion reported by Reese and his coworkers.[4]

In this paper, we report the synthesis of three ribonucleotide building units bearing the MPTM group at the 2'-position from their parent ribonucleosides.

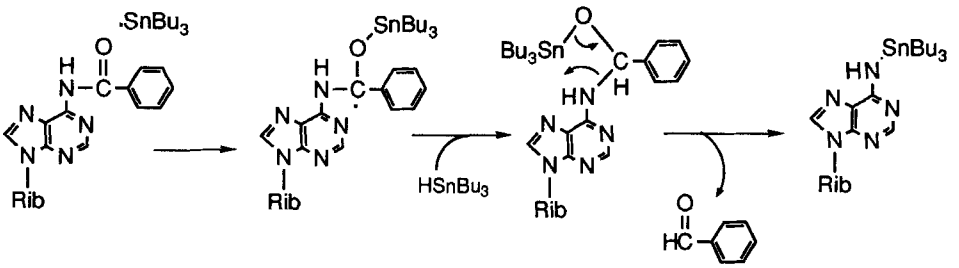
SYNTHESIS OF ADENOSINE AND CYTIDINE BUILDING UNITS (6b and 6j)

The reaction of 6-N-benzoyl-3',5'-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-

§ This paper is dedicated to the memory of Professor Tohru Ueda, Hokkaido University.

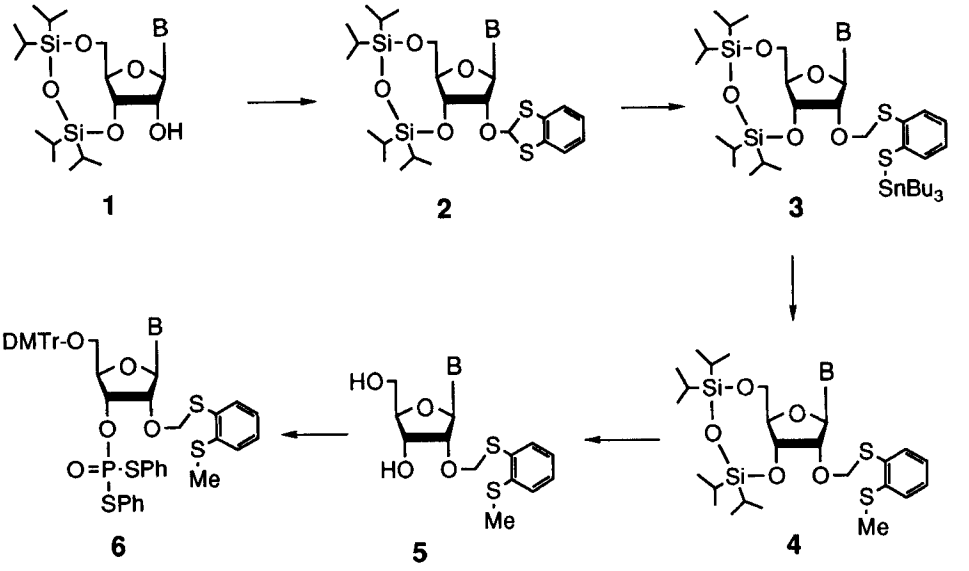
adenosine derivative (**1a**)[5] with 1,3-benzodithiolium tetrafluoroborate (BDTF)[6] in CH_2Cl_2 afforded the 2'-alkylated product (**2a**) in 85% yield. However, reduction of **2a** with 2.5 equiv of TBTH under reflux for 6 h,[2] resulted in a ca. 2:5:3 mixture of unchanged **1a** , the ring-opened compound (**3a**), and the debenzoylated product (**3c**). The incomplete ring opening of **2a** with TBTH might be due to the steric bulk around the 3'-silyl residue. Several attempts to selectively reduce the BDT group of less hindered adenosine derivatives such as the 3',5'-free adenosine derivative (**7**), a 5'-O-monomethoxytritylated adenosine derivative (**8**), and a transiently trimethylsilylated species (**9**) have failed. These reactions also accompanied considerable debenzoylation and consumption of large excess amounts of TBTH for completion of the reduction.

A similar debenzoylation was observed when the reduction of 2'-(1,3-benzo-dithiol-2-yl)-4-N-benzoyl-3',5'-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)cytidine (**2h**) with TBTH was tried. These results strongly suggested that the benzoyl group inhibited smooth cleavage of the C-S bond, trapping the stannyl radical to give a benzyl radical species which abstracted a hydrogen radical from the reagent to give O,N-acetal imtermediate that decomposed to benzaldehyde with elimination of a stannylated 6-amino group. The resulting benzaldehyde consumed considerably the reducing reagent.[7]



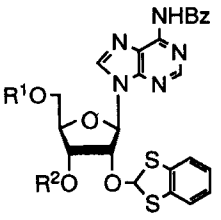
This discussion is somewhat inconsistent with the fact that in most reactions TBTH did not interfer with amides and aldehydes but rather selectively reacted with target functional groups such as halogeno groups.[8-10] Further mechanistic studies might be required.

On the basis of these observations, we decided to use an aliphatic acyl group, as the 6-N-protecting group of adenosine, which should have no ability of trapping radicals. Therefore, we introduced a pivaloyl group to the 6-amino group of a 3',5'-cylclic silyl ether derivative (**1c**) by a transient protection method to give the 6-N-pivaloyladenosine derivative (**1b**) in 63% yield. Reaction of **1b** with BDTF gave the 2'-alkylated product (**2b**) in 96% yield. Now, it was found that reduction of **2b** with TBTH in refluxing benzene proceeded smoothly to give the ring-opened product (**3b**) quantitatively. The subsequent S-methylation of **3b** using methyl iodide gave the 2'-MPTM ether derivative (**4b**) in 73% yield from **2b**. Desilylation of **4b** afforded the 3',5'-free ribonucleoside



a: B = Ad^{Bz} b: B = Ad^{Piv} c: B = Ad d: B = $Gu^{Dpc\cdot Pro}$ e: B = Gu^{Pro} f: B = Gu^{iBu}

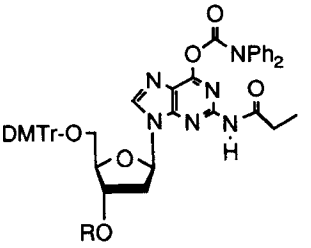
g: B = Gu h: B = Cy^{Bz} i: B = Cy j: B = Cy^{Piv} k: B = Ur^{Bz}



7: $R^1 = R^2 = H$

8: R^1 = MMTr, $R^2 = H$

9: $R^1 = R^2 = SiMe_3$



10: R = H

11: R = BDT

12: R = MPTM

13: R = CH_2S / Bu_3Sn-S

(**5b**) in 98% yield. The usual 5'-dimethoxytritylation of **5b** followed by the 3'-phosphorylation gave the adenosine building unit (**6b**) in 81% yield.

On the basis of the same reason as mentioned above, we synthesized the cytidine building unit (**6j**) using the pivaloyl group as a protecting group of the 4-N amino group as follows. Acylation of 3',5'-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)cytidine (**1i**)[5] with pivaloyl chloride was carried out by the transient protection method using trimethylsilyl chloride to give the 4-N-acyl derivative (**1j**) in 98% yield. Reaction of **1j** with BDTF gave the 2'-O-BDT derivative (**2j**) in 90% yield. The reduction of **2j** with TBTH was readily completed and the successive S-methylation afforded the 2'-MPTM derivative (**4j**) in 52% yield. Desilylation of **4j** gave the 3',5' free diol (**5j**) in 86% yield. The cytidine building unit (**6j**) was synthesized in 83% yield by the two-step reaction from **5j**.

The pivaloyl groups attached to the exo amino groups of cytidine and adenosine could be removed by ammonia under the usual conditions, although longer periods of time were required compared with the benzoyl group. Removal of the pivaloyl group from **5h** required 2 h at 60 °C. At the same temperature, the benzoyl group of 6-N-benzoyladenosine was removed in 40 min.. On the other hand, removal of the pivaloyl group from **5b** required 12 h at 60° C.

SYNTHESIS OF GUANOSINE BUILDING UNIT (6d)

In the case of guanosine, we first examined the two-step conversion of the 3'-O-(1,3-benzodithiol-2-yl)deoxyguanosine derivative (**11**) to the 3'-O-MPTM derivative (**12**) prior to application of the present method to the synthesis of a guanosine building unit (**6d**). Compound **11** was prepared in 96% yield by reaction of 6-O-diphenylcarbamoyl-2-N-propionyl-5'-O-(4,4'-dimethoxytrityl)deoxyguanosine (**1d**)[1b] with BDTF. As a consequence, the first reaction resulted in quantitative formation of the ring- opened intermediate (**13**). However, the second S-methylation was considerably inhibited. The reaction took place only to a degree of ca. 40%. Several attempts to improve the reaction using CsF, KF, or Et_4NF as the Sn-S bond activator[3] were unsuccessful.

Considerable inhibition has been encountered also in the TBTH mediated reduction of the 3'-O-BDT derivative (**2d**) having the diphenylcarbamoyl and propionyl groups at the base part. In this case, significant elimination of the diphenylcarbamoyl group was observed. We felt that the sluggish reaction was markedly inhibited owing to the presence of the diphenylcarbamoyl group and the sterically hindered 2'-O-BDT group. Therefore, reaction of 2-N-propionyl-3',5'-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)guanosine (**1e**), which was not protected at the 6-O position, with BDTF was carried out to give the 2'-O-BDT ether derivative (**2e**) in 88% yield. Expectedly, the reduction of

2e with 3 equiv of TBTH was completed in 2 h to give a single ring-opened product (**3e**), which was methylated with methyl iodide to afford compound **4e** in 53% yield. In a similar manner, N-isobutyrylated guanosine derivative (**4f**) was synthesized via **2f** from **1f**. The relative low yields at the third stage of these reactions using compounds **1e** and **1f** were due mainly to the competitive N^7-methylation. Preliminary experiments showed that compound **2e** was methylated considerably under the same conditions (40 equiv of methyl iodide, DMF, r.t., 2h) as described in the case of methylation of **3e** When methylation of **3e** was prolonged from 2 h to 4 h, a base line material was considerably formed and compound **4e** was obtained in a low yield of 23%. The NMR analysis of the base line material suggested the presence of N-Me.

Finally, the guanosine building unit (**6e**) was synthesized by the following reactions. Compound **4e** was treated with diphenylcarbamoyl chloride in the presence of ethyldiisopropylamine to give the 6-O-protected species (**4d**). The desilylation of this compound gave the 3',5'-free diol (**5d**) in 82% yield. The usual 5'-dimethoxytritylation of **5d** followed by phosphorylation gave the unit **6d** in 94% yield.

DISCUSSION

In this paper, we could develop proper synthetic procedures to prepare three monomer building units **6b**, **6d**, and **6j** required for the oligoribonucleotide synthesis using the MPTM group as the 2'-hydroxyl protecting group. Since we also reported previously the method for the synthesis of the uridine monomer unit **6k**, the routes to all four kinds of units have been established throughout these studies. As the next subject, we are now extending this work to the chemical synthesis of oligoribonucleotides with defined sequence. Introduction of the aliphatic protecting group, pivaloyl, to the base parts of adenosine and cytidine enabled us to reduce successfully the BDT group to the MPTM group. These results suggested that aliphatic protecting groups should be recommended compared with aromatic protecting groups for other types of reactions involving a radical process mediated by TBTH when protecting groups were required at the base residues. However, there have been reported several precedent examples where N-benzoyl protecting groups were employed in similar TBTH mediated reductions of 2',3'-O-isopropylidene-5'-iodo-5'-deoxy-6-N,6-N-dibenzoyladenosine and a carbocyclic 3'-halogeno-6-N-benzoyladenosine derivative to obtain cyclo- and deoxy-adenosine derivatives.[9,10] Therefore, the strong inhibition observed in reduction of compounds **4a** and **4h** having the BDT group was not always associated with only the presence of the benzoyl group. The electronic and steric circumstance around the BDT group should be equally discussed for the present study.

In this paper, we showed a number of reactions of 3',5'-cyclic silylated ribonucleosides with BDTF giving rise to the corresponding 2'-O-BDT derivatives. These reactions of the alkylation type took place rather selectively at the 2'-position without modification of base residues, as demonstrated in the previous papers.[11-13] These results are also interesting since we have recently found a new method for the two-step O-methylation of alcoholic functions via Raney Ni reduction of the resulting O-BDT ether derivatives.[12,13] It would be possible to convert **2** to the 2'-O-methyl ether derivatives.

EXPERIMENTAL

^{1}H NMR spectra were recorded at 60 MHz on a Hitachi 24B spectrometer with Me_4Si as the internal standard. Column chromatography was performed with silica gel C-200 purchased from Waco Co. Ltd., and a minipump for a goldfish bowl was conveniently used to attain sufficient pressure for rapid chromatographic separation.

General Method for Introduction of the BDT Group to the 2'-Hydroxyl Group of 1. An appropriately protected ribonucleoside (1 mmol) was rendered anhydrous by repeated coevaporation with dry pyridine and finally dissolved in dry CH_2Cl_2 (10 ml). To the solution were added successively BDTF (1.5 mmol) and pyridine (3 mmol). The mixture was stirred until the starting material had disappeared on TLC. Then triethylamine (6 mmol) was added and the mixture was stirred for an additional 15 min. Extraction was performed with CH_2Cl_2 and water. The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was chromatographed on a column of silica gel with hexane-CH_2Cl_2-MeOH in the presence of 0.5% pyridine to give the product **2** as listed in Table 1.

General Method for Conversion to the BDT Group to the MPTM Group. To a solution of an appropriate 2'-O-BDT derivative (1 mmol) in benzene (10 ml) was added TBTH (2.5 mmol). The mixture was refluxed and a solution of azobisisobutyronitorile (2 mmol) was dropwise added over the reaction time as listed in Table 2. The mixture was cooled to room temperature and evaporated under reduced pressure. The residue was dissolved in DMF (10 ml) and methyl iodide (10 mmol) was added. The mixture was stirred until the reaction had been finished. Extractive workup using CH_2Cl_2 and water was repeatedly performed to remove DMF. After removal of the solvent, chramatographic separation using silica gel gave the 2'-O-MPTM derivative **4**. The results are summarized in Table 2.

General Procedure for Removal of the 1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl Group from 4. To a solution of an appropriate 3',5'-protected ribonucleoside **3** (1 mmol) in acetonitrile (20 ml)were added KF (6 mmol),

Table 1. Introduction of the BDT Group to Hydroxyl Groups of

compound	equiv of BDTF	time (h)	product	yield (%)
1a	1.5	24	**2a**	88
1b	1.5	36	**2b**	96
1d	1.8	7	**2d**	47
1e	1.5	18	**2e**	88
1f	1.5	23	**2f**	74
1h	1.5	3	**2h**	71
1j	1.5	1.5	**2j**	90
10	1.5	20	**11**	96

Table 2. Conversion of the BDT Group to the MPTM group

Reduction			S-Methylation with MeI		
compound	equiv of	time (h)	time (h)	product	yield (%)
2b	2.5	40 min	1	**4b**	73
2e	2.5	1.5	2	**4e**	53
2f	2.5	2	2	**4f**	61
2j	2.5*	12	4	**4j**	52
11	3.0	1	1	**12**	40

*In this case, 3 equiv of AIBN was used.

Table 3. Desilylation of 4 by Means of KF/Et_4NBr in Wet Acetonitrile

compound	temp (°C)	time (h)	product	yield (%)
2b	60	1	**7**	81
4b	60	1.5	**5b**	98
4d	60	2	**5d**	82
4j	60	1	**5j**	86

Table 4. Synthesis of Ribonucleoside Building Units (6)

Tritylation		Phosphorylation		
compound	time (h)	time (h)	product	yield (%)
5b	7.5	30 min	**6b**	81
5d	6.5	25 min	**6b**	94
5j	7	25 min	**6j**	83

Et_4NBr (6mmol), and water (6 mmol).[15] The mixture was vigorously stirred at 60 °C. After the reaction was completed, the solvent was removed under reduced pressure. The residue was partitioned between CH_2Cl_2 and water. The organic phase was collected and washed with water. The organic layer was dried over Na_2SO_4. Evaporation followed by chromatography on a silica gel column gave the 3',5'-free ribonucleoside derivative **5** as listed in Table 3.

General Procedure for the Synthesis of Ribonucleoside Building Unit 6. An appropriate 3',5'-free ribonucleoside 5 (1 mmol) was coevaporated 3-5 times with dry pyridine and finally dissolved in dry pyridine (10 ml). The solution was treated with 4,4'-dimethoxytrityl chloride (1.05 mmol) at room temperature for the time listed in Table 4. After the tritylation was completed, cyclohexylammonium S,S-diphenyl phosphorodithioate (1.5 mmol), mesitylenedisulfonyl dichloride (2 mmol) and 1-H-tetrazole (4 mmol) were added. After being stirred for the time listed in Table 4, the mixture was quenched by addition of a sodium hydrogencarbonate solution. The mixture was extracted with CH_2Cl_2 and dried over Na_2SO_4. Removal of the solvent under reduced pressure followed by silica gel column chromatography gave the fully protected building unit **6** as summarized in Table 4.

4-N-Pivaloyl-3',5'-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-cytidine (1j). 3',5'-O-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)cytidine (**1i,** 1.46 g, 3 mmol) was rendered anhydrous by repeated coevaporation with dry pyridine (10 ml X 3) and finally dissolved in dry pyridine (30 ml). Trimethylsilyl chloride (1.14 ml, 9 mmol) was added to the solution. After being stirred for 20 min, the mixture was treated with pivaloyl chloride (0.554 ml, 4.5 mmol). The mixture was further stirred for 1.5 h and then quenched by addition of water (3 ml). The resulting solution was kept at room temperature for 20 h to hydrolyze the trimethyl silyl ether bonds. The mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, evaporated under reduced pressure, and the residue chromatographed on a column of silica gel with CH_2Cl_2-MeOH to give **1j** (1.68 g, 98%): ^1H NMR ($CDCl_3$) δ 1.05 (24H, m, iPr_2Si), 1.25 (9H, s, Piv), 4.00-4.40 (5H, m, 2',3',4',5'-H), 5.80 (1H, s, 1'-H), 7.40 (1H, d, J = 6.5 Hz, 5-H), 8.15 (1H, d, J = 6.5 Hz, 6-H), 8.60 (1H, br. s, NH). Anal. Calcd for $C_{26}H_{47}O_7N_3Si_2$: C, 54.80; H, 8.31; N, 7.37. Found: C, 54.42; H. 8.28; N, 7.17.

2'-O-(1,3-Benzodithiol-2-yl)-4-N-pivaloyl-3',5'-O-(1,1,3,3-tetraiso-propyldisiloxane-1,3-diyl)cytidine (2j). ^1H NMR ($CDCl_3$) δ 1.00 (24H, m, iPr_2Si), 1.25 (9H, s, Piv), 3.90-4.40 (5H, m, 2',3',4',5'-H), 5.75 (1H, s, 1'-H), 6.90 (1H, s, SCHS), 7.00-7.30 (4H, m, ArH), 7.30 (1H, d J = 7 Hz, 5-H), 8.10 (1H, d, J = 7 Hz, 5-H). Anal. Calcd for $C_{33}H_{51}O_7N_3S_2Si_2$: C, 54.89; H, 7.12; N, 5.82; S, 8.88. Found: C, 56.67; H. 7.39; N, 5.59; S, 8.35.

2'-O-[[[2-(Methylthio)phenyl]thio]methyl]-4-N-pivaloyl-3',5'-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)cytidine (4j). ^{1}H NMR ($CDCl_3$) δ 1.05 (24H, m, iPr_2Si), 1.30 (9H, s, Piv), 2.50 (3H, s, SCH3), 3.95-4.50 (5H, m, 2',3',4',5'-H), 5.36 and 5.44 (2H, s, CH_2 of MPTM), 5.80 (1H, s, 1'-H), 7.00-7.30 (4H, m, ArH), 7.15 (1H, d J = 7 Hz, 5-H), 8.20 (1H, d, J = 7 Hz, 6-H). Anal. Calcd for $C_{34}H_{55}O_7N_3S_2Si_2$: C, 55.33; H, 7.51; N, 5.69; S, 8.69. Found: C, 55.10; H. 7.49; N, 5.93; S, 8.73.

2'-O-[[[2-(Methylthio)phenyl]thio]methyl]-4-N-pivaloylcytidine (4j). ^{1}H NMR ($CDCl_3$): δ 1.30 (9H, s, Piv), 2.40 (3H, s, SCH3), 3.95 (2H, m, 5'-H), 4.00-4.70 (3H, m, 2',3',4'-H), 5.30 (2H, s, CH_2 of MPTM), 5.80 (1H, s, 1'-H), 7.00-7.50 (4H, m, ArH), 8.20 (1H, d, J = 6 Hz, 6-H), 8.55 (1H, br. s, NH). Anal. Calcd for $C_{22}H_{29}O_6N_3S_2$: C, 53.32; H, 5.90; N, 8.48. Found: C, 54.42; H. 6.09; N, 8.55.

S,S-Diphenyl 5'-O-(4,4'-dimethoxytrityl)-2'-O-[[[2-(methylthio)-phenyl]thio]methyl]-4-N-pivaloylcytidine 3'-Phosphorodithioate (6j). ^{1}H NMR ($CDCl_3$) δ 1.25 (9H, s, Piv), 2.35 (3H, s, SCH3), 3.35 (3H, m, 4',5'-H), 3.70 (6H, s, OCH_3), 4.05 (1H, m, 2'-H), 4.70 (1H, m, 3'-H), 5.00 (2H, s, CH_2 of MPTM), 6.20 (1H, d, J = 5 Hz, 1'-H), 6.60-7.65 (28H, m, ArH), 7.90 (1H, d, J = 7 Hz, 6-H), 8.55 (1H, br. s, NH). Anal. Calcd for $C_{55}H_{56}O_9N_3S_4P$: C, 62.19; H, 5.31; N, 3.96. Found: C, 62.22; H. 5.60; N, 4.02.

2'-O-(1,3-Benzodithiol-2-yl)-6-N-benzoyl-3',5'-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)adenosine (2a). ^{1}H NMR ($CDCl_3$) δ 1.00 (24H, m, iPr_2Si), 3.90 (3H, s, 4',5'-H), 4.75 (2H, m, 2',3'-H), 5.85 (1H, s, 1'-H), 6.60 (1H, s, SCHS), 6.60-7.20 (4H, m, ArH of BDT), 7.40 (3H, m, m,p-ArH of Bz), 7.85 (2H, m, o-ArH of Bz), 8.25 (1H, s, 2-H), 8.85 (1H, s, 8-H). Anal. Calcd for $C_{36}H_{47}O_6N_5S_2Si_2$: C, 56.44; H, 6.18; N, 9.14; S, 8.37. Found: C, 55.91; H. 6.23; N, 8.88; S,8.51.

2'-O-(1,3-Benzodithiol-2-yl)-6-N-benzoyladenosine (7). This compound was obtained as crude material as suggested by the following elemental analysis: Anal. Calcd for $C_{24}H_{21}O_5N_5S_2$: C, 55.06; H, 4.04; N, 13.38; S, 12.25. Found: C, 57.07; H. 4.39 N, 12.96; S,12.22.

6-N-Pivaloyl-3',5'-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-adenosine (1b). ^{1}H NMR ($CDCl_3$) δ 1.10 (24H, m, iPr_2Si), 1.45 (9H, s, Piv), 4.05 (3H, s, 4',5'-H), 4.60 (1H, m, 3'-H), 5.05 (1H, m, 2'-H), 5.90 (1H, s, 1'-H), 8.00 (1H, s, 8-H), 8.40 (1H, br. s, NH), 8.60 (1H, s, 2-H).

2'-O-(1,3-Benzodithiol-2-yl)-6-N-pivaloyl-3',5'-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)adenosine (2b). ^{1}H NMR ($CDCl_3$) δ 1.15 (24H, m, iPr_2Si), 1.45 (9H, s, Piv), 4.00 (3H, s, 4',5'-H), 4.80 (2H, m, 2',3'-H), 5.95 (1H,

s, 1'-H), 6.75 (1H, s, SCHS), 6.65-7.10 (4H, m, ArH), 7.95 (1H, s, 2-H), 8.35 (1H, s, 8-H), 8.45 (1H, br. s, NH). Anal. Calcd for $C_{34}H_{51}O_6N_5S_2Si_2$: C, 54.73; H, 6.89; N, 9.39; S, 8.60. Found: C, 54.30; H. 6.91; N, 9.06; S,8.75.

2'-O-[[[2-(Methylthio)phenyl]thio]methyl]-6-N-pivaloyl-3',5'-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)cytidine (4b). ^1H NMR ($CDCl_3$) δ 1.05 (24H, m, iPr_2Si), 1.40 (9H, s, Piv), 2.30 (3H, s, SCH_3), 4.10 (3H, s, 4',5'-H), 4.80 (2H, m, 2',3'-H), 5.31 and 5.39 (2H, s, CH_2 of MPTM), 5.90 (1H, s, 1'-H), 6.90-7.30 (4H, m, ArH), 8.05 (1H, s, 2-H), 8.50 (1H, br. s, NH), 8.60 (1H, s, 8-H). Anal. Calcd for $C_{35}H_{55}O_6N_5S_2Si_2$: C, 55.16; H, 7.27; N, 9.19; S, 8.41. Found: C, 54.43; H. 7.61; N, 9.03; S,8.42.

2'-O-[[[2-(Methylthio)phenyl]thio]methyl]-6-N-pivaloyladenosine (5b). ^1H NMR ($CDCl_3$) δ 1.40 (9H, s, Piv), 2.30 (3H, s, SCH_3), 3.55-3.90 (3H, s, 4',5'-H), 4.25 (1H, br. s, 3'-H), 4.50 (1H, m, 2'-H), 4.90 (2H, s, CH_2 of MPTM), 5.80 (1H, d, J = 7 Hz, 1'-H), 6.90-7.25 (4H, m, ArH), 7.75 (1H, s, 2-H), 8.40 (1H, br. s, NH), 8.60 (1H, s, 8-H). Anal. Calcd for $C_{23}H_{29}O_5N_5S_2$: C, 53.16; H, 5.63; N, 13.48; S, 12.34. Found: C, 54.02; H. 5.78; N, 13.26; S, 12.23.

S,S-Diphenyl 5'-O-(4,4'-dimethoxytrityl)-2'-O-[[[2-(methylthio)phenyl]thio]methyl]-6-N-pivaloyladenosine 3'-Phosphorodithioate (6b). ^1H NMR ($CDCl_3$) δ 1.45 (9H, s, Piv), 2.30 (3H, s, SCH_3), 3.00-3.50 (3H, s, 4',5'-H), 3.75 (6H, s, OCH_3), 4.10 (1H, br. s, 2'-H), 4.90 (1H, m, 3'-H), 5.00-5.50 (2H, m, CH_2 of MPTM), 6.10 (1H, d, J = 8 Hz, 1'-H), 6.40-7.00 (4H, m, ArH of MPTM), 7.00-7.70 (23H, m, ArH of PSS and DMTr), 8.00 (1H, s, 2-H), 8.50 (1H, br. s, NH), 8.55 (1H, s, 8-H). Anal. Calcd for $C_{56}H_{56}O_8N_5S_4P$: C, 61.92; H, 5.20; N, 6.45; S, 11.81. Found: C, 61.55; H. 5.54; N, 7.16; S, 11.57.

2'-O-(1,3-Benzodithiol-2-yl)-5'-O-(4,4'-dimethoxytrityl)-6-O-diphenylcarbamoyl-2-N-propionyldeoxyguanosine (11). ^1H NMR ($CDCl_3$) δ 1.20 (3H, t, J = 7 Hz, CH_3), 2.63 (4H, m, CH_2), 3.25 (2H, br, 5'-H), 3.70 (6H, s, OCH_3), 4.10 (1H, m, 4'-H), 4.55 (1H, m, 3'-H), 6.40-6.80 (5H, m, CH and ArH of BDT), 6.80-7.60 (23H, m, ArH of PSS and DMTr), 8.50 (1H, br, NH).

2-N-Propionyl-3',5'-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-guanosine (1e). 3',5'-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)guanosine (10.52 g, 20 mmol) was coevaporated four times with dry pyridine and finally dissolved in dry pyridine (100ml). Trimethylsilyl chloride (15.2 ml, 120 mmol) was added. After the mixture was stirred for 30 min, propionic anhydride (3.85 ml, 30 mmol) was added. The solution was stirred for 1.5 h and then water (10 ml) was added to remove the 2'-O-trimethylsilyl group. After being kept at room temperature for 19 h, the mixture was extracted with CH2Cl2. The usual workup followed by silica gel column

chromatography gave the pure material (65%) and crude material (23%) of **1e:** Anal. Calcd for $C_{25}H_{43}O_7N_5Si_2$: C, 51.61; H, 7.45; N, 12.04. Found: C, 51.71; H. 7.68; N, 11.89.

2'-O-(1,3-Benzodithiol-2-yl)-2-N-propionyl-3',5'-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)guanosine (2e). ^1H NMR ($CDCl_3$) δ 1.05 (24H, m, iPr_2Si), 1.20 (3H, t, J = 7 Hz, CH_3), 2.55 (2H, q, J = 7 Hz, CH_2), 3.95 (3H, s, 4',5'-H), 4.35 (2H, m, 2',3'-H), 5.80 (1H, s, 1'-H), 6.80-7.30 (4H, m, ArH), 7.70 (1H, s, 8-H), 8.50 (1H, br, NH), 9.35 (1H, br, NH). Anal. Calcd for $C_{32}H_{47}O_7N_5S_2Si_2$: C, 52.36; H, 6.45; N, 9.54. Found: C, 52.58; H. 6.54; N, 9.40.

2'-O-[[[2-(Methylthio)phenyl]thio]methyl]-2-N-propionyl-3',5'-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)guanosine (4e). ^1H NMR ($CDCl_3$) δ 1.05 (24H, m, iPr_2Si), 1.20 (3H, t, J = 8 Hz, CH3), 2.40 (3H, s, SCH_3), 4.10 (3H, s, 4',5'-H), 4.40 (1H, m, 3'-H), 4.55 (1H, m, 2'-H), 5.30 (2H, s, CH_2 of MPTM), 5.80 (1H, s, 1'-H), 7.10 (4H, m, ArH), 7.85 (1H, s, 8-H), 8.60 (1H, br. s, NH). Anal. Calcd for $C_{33}H_{51}O_7N_5S_2Si_2$: C, 52.84; H, 6.85; N, 9.34; S, 8.55. Found: C, 52.60; H. 7.18; N, 8.94; S, 8.19.

2'-O-(1,3-Benzodithiol-2-yl)-2-N-isobutyryl-3',5'-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)guanosine (2f). Anal. Calcd for $C_{33}H_{49}O_7N_5S_2Si_2$: C, 52.98; H, 6.60; N, 9.36. Found: C, 53.33; H. 6.49; N, 9.28.

2-N-Isobutyryl-2'-O-[[[2-(methylthio)phenyl]thio]methyl]-3',5'-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)guanosine (4f). ^1H NMR ($CDCl_3$) δ 0.70–1.5 (30H, m, iPr_2Si and iBu), 2.40 (3H, s, SCH_3), 4.10 (3H, s, 4',5'-H), 4.40 (1H, m, 3'-H), 4.70 (1H, m, 2'-H), 5.30 (2H, s, CH_2 of MPTM), 5.80 (1H, s, 1'-H), 7.10 (4H, m, ArH), 7.90 (1H, s, 8-H), 8.80 (1H, br. s, NH). Anal. Calcd for $C_{34}H_{53}O_7N_5S_2Si_2$: C, 53.44; H, 6.99; N, 9.17; S, 8.39. Found: C, 52.68; H. 7.36; N, 8.61; S, 8.30.

6-O-Diphenylcarbamoyl-2'-O-[[[2-(methylthio)phenyl]thio]methyl]-2-N-propionyl-3',5'-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)guanosine (4d). Compound **4e** (1.50 g, 2 mmol) was coevaporated several times with dry pyridine and finally dissolved in dry pyridine (20 ml). To the mixture were added diphenylcarbamoyl chloride (0.927 g, 4 mmol) and ethyldiisopropylamine (0.697 ml, 4 mmol). After being stirred for 1 h, the mixture was quenched by addition of water. Extraction with CH_2Cl_2 followed by silica gel column chromatography gave **4d** (1.65 g, 87%): ^1H NMR ($CDCl_3$) δ 1.05 (24H, m, iPr_2Si), 1.15 (3H, t, J = 7 Hz, CH3), 2.30 (3H, s, SCH_3), 2.80 (2H, q, J = 7 Hz, CH2), 4.05 (3H, s, 4',5'-H), 4.60 (2H, m, 2',3'-H), 5.30 (2H, s, CH_2 of MPTM), 5.90 (1H, s, 1'-H), 6.85-7.85 (4H, m, ArH),

8.05 (1H, s, 8-H). Anal. Calcd for $C_{46}H_{60}O_6N_8S_2Si_2$: C, 58.45; H, 6.40; N, 8.89; S, 6.78. Found: C, 58.27; H. 8.75; S, 6.34.

6-O-Diphenylcarbamoyl-2'-O-[[[2-(methylthio)phenyl]thio]methyl]-2-N-propionylguanosine (5d). ^{1}H NMR ($CDCl_3$) δ 1.20 (3H, t, J = 7 Hz, CH_3), 2.25 (3H, s, SCH_3), 2.60 (2H, q, J = 7 Hz, CH_2), 3.30 (2H, m, 5'-H), 3.80 (1H, m, 4'-H), 4.60-5.40 (4H, m, 2',3'-H and CH_2 of MPTM)), 5.95 (1H, s, 1'-H), 6.65-7.15 (4H, m, ArH of MPTM), 7.15-7.55 (10H, m, ArH of Dpc), 8.10 (1H, s, 8-H). Anal. Calcd for $C_{34}H_{34}O_7N_6S_2$: C, 58.11; H, 4.88; N, 11.96; S, 9.12. Found: C, 58.80; H. 4.97; S, 8.49.

S,S-Diphenyl 5'-O-(4,4'-Dimethoxytrityl)-6-O-diphenylcarbamoyl-2'-O-[[[2-(methylthio)phenyl]thio]methyl]-2-N-propionylguanosine 3'-Phosphorodithioate (6b). ^{1}H NMR ($CDCl_3$) δ 1.10 (3H, t, J = 7 Hz, CH_3), 2.20 (3H, s, SCH_3), 2.45 (2H, q, J = 7 Hz, CH_2), 3.30 (3H, m, 4',5'-H), 3.70 (6H, s, OCH3), 4.10 (1H, m, 2'-H), 4.85 (1H, m, 3'-H), 5.35 (2H, br.s, CH2 of MPTM), 5.90 (1H, d, J = 6 Hz, 1'-H), 6.50-6.85 (4H, m, ArH of MPTM), 7.00-7.55 (20H, m, ArH of Dpc and PSS), 7.85 (1H, s, 8-H), 8.45 (1H, br, NH). Anal. Calcd for $C_{67}H_{61}O_{10}N_6S_4P$: C, 63.39; H, 4.84; N, 6.62; S, 10.10 Found: C, 63.30; H. 5.12; N, 7.26; S, 9.52.

ACKNOWLEDGEMENT We express many thanks to the late Professor T. Ueda for his hearty encouragement of our research group. This work was supported by the Grant-in-Aid for Scientific Research on Priority Areas No. 03242104 from the the Ministry of Education, Science and Culture, Japan.

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Received 9/7/91
Accepted 11/15/91