General Syntheses of 2',3'-Dideoxynucleosides and 2',3'-Didehydro-2',3'-dideoxynucleosides

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A general synthetic method for 2',3'-unsaturated nucleosides from the corresponding ribonucleosides is described. The 5'-*O*-silyl protected ribonucleosides were converted to the bisxanthates by reaction with carbon disulfide, followed by alkylation. The bisxanthates on reduction with tri-*n*-butyltin hydride and deprotection of the 5'-*O*-silyl group afforded the unsaturated nucleosides. The desulfurization of cyclic thionocarbonates has also been employed for the preparation of 2',3'-unsaturated nucleosides. 2',3'-Saturated adenosine, guanosine, inosine, and cytidine have been prepared by the catalytic hydrogenation of the corresponding 2',3'-unsaturated nucleosides. Molecular conformations of 2',3'-dideoxy- and 2',3'-didehydro-2',3'-dideoxyadenosine were determined by single-crystal X-ray diffraction studies.

Since 3'-azido-3'-deoxythymidine (1) (AZT, Zidovudine, Retrovir) was identified by Mitsuya et al.[1] as a potent antiviral agent against human immunodeficiency virus type 1 (HIV-1), a number of other nucleosides have been found to inhibit HIV-1 in vitro. Some of the 2',3'-dideoxynucleosides and their 2',3'-unsaturated analogues, which are quite potent as anti-HIV agents, are shown in Figure 1. 2',3'-Dideoxycytidine (d_2C, **4**),[2] 2',3'-dideoxyinosine (d_2I, **11**),[2] and 2',3'-dideoxyadenosine (d_2A, **10**)[2] are currently undergoing clinical trials in patients with acquired immunodeficiency syndrome (AIDS) and AIDS-related complex. 3'-Azido-2',3'-dideoxyuridine (**2**, AzddU, CS-87)[3] and 2',3'-didehydro-3'-deoxythymidine (d_4T, **5**)[4] are undergoing preclinical toxicology for Investigational New Drug application to the Food and Drug Administration.

Several methods have been described for the preparation of 2',3'-unsaturated nucleosides in the literature.[5-19] Among these, the first method, reported by Horwitz and co-workers,[5-8] involved the base-promoted elimination of 3'-*O*-sulfonyl esters of 2'-deoxynucleosides. In recent years, some 2',3'-unsaturated nucleosides have been obtained directly from the corresponding ribonucleosides through their reaction with acetoxyisobutyryl halides, followed by the reductive elimination of the 2'(3')-acetoxy-3'(2')-halogeno derivatives.[11-15] Though this method has been effective for the preparation of 2',3'-didehydro-2',3'-dideoxyadenosine (**7**) and -uridine (**42**), its applicability for the synthesis of other unsaturated nucleosides such as inosine (**8**) and guanosine (**9**) has been very poor.[13] 2',3'-Dideoxynucleosides have been obtained through the Barton deoxygenation of the dithiocarbonates or thionocarbonates of 2'-deoxynucleosides in 40-55% yield.[20-22]

As part of our continuing efforts to study the structure-activity relationships of various nucleosides as anti-HIV agents, we were interested in developing a general synthetic method for 2',3'-unsaturated and 2',3'-saturated nucleosides from the corresponding ribonucleosides.

Results and Discussion

A literature search revealed that Barton et al.[23,24] and Hayashi et al.[25] have reported the synthesis of olefinic carbohydrates and aminoglycosides from the corresponding *vic*-diols through their bisxanthates. It was of interest to explore this procedure as a general synthetic method for the preparation of 2',3'-unsaturated as well as 2',3'-saturated nucleosides from the corresponding ribonucleosides. Another method of simultaneous deoxygenation of ribonucleosides via cyclic thionocarbonates was also explored. The latter method was previously applied[16] to uridine, but the yield was low when Raney nickel was used for the deoxygenation and N^3-methylation was observed when trimethyl phosphite was employed instead of Raney nickel. A similar deoxygenation of the 2',3'-thionocarbonate of

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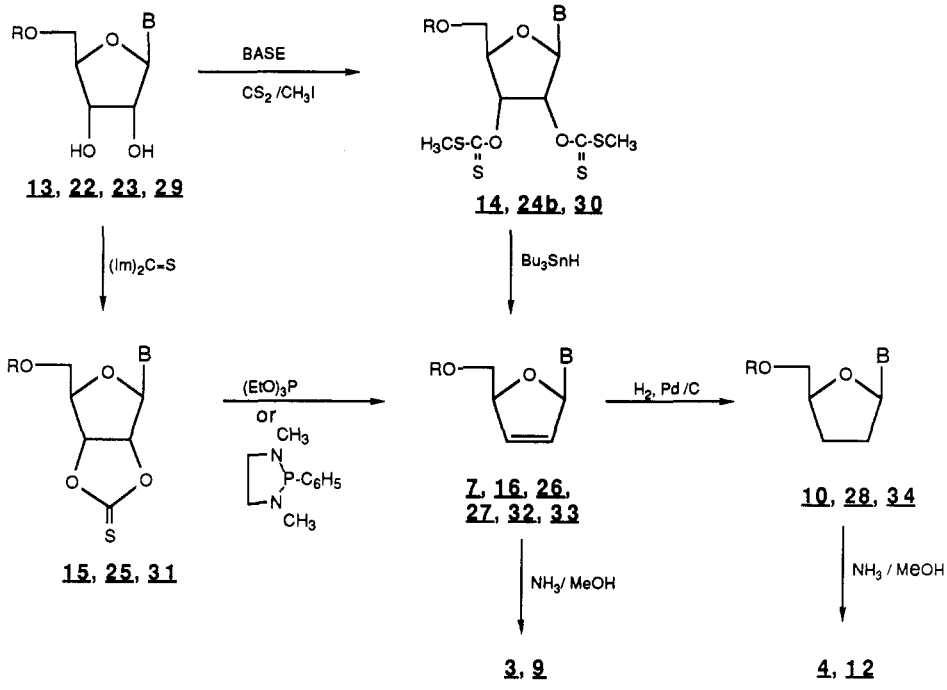
Scheme I



R	B		
H	13	22	29
t-BDMSi	–	23	–
t-BDMSi	14	24b	30
t-BDMSi	15	25	31
t-BDMSi	16	26	32
H	7	27	33
H	10	28	34

adenosine employing Raney nickel failed to yield 2′,3′-didehydro-2′,3′-dideoxyadenosine.[26]

5′-*O*-Silyl protected adenosine was reacted with carbon disulfide in the presence of 5 N sodium hydroxide and alkylated in situ with methyl iodide to give the bisxanthate **14** in moderate yield (70%) (Scheme I). A minor product, 2′,3′-*O*-thionocarbonate **15**, was also obtained (11.7%) in this reaction. Subsequently, **15** was prepared by the reaction of 5′-*O*-silyl protected adenosine with thiocarbonyldiimidazole in 73.5% yield. The bisxanthate **14**, on treatment with tri-*n*-butyltin hydride in refluxing toluene, gave a good yield (93%) of **16** after silica gel column chromatography. Thionocarbonate **15** was also deoxygenated to **16** under mild conditions using 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine.[27] However, this reaction gave a lower yield (51%) of **16** than the bisxanthate method. Attempted reduction of **16** to the corresponding saturated adenosine analogue was not successful, possibly due to the presence of a small amount of residual sulfur byproduct or due to the steric hindrance caused by the bulky 5′-*O*-silyl group as well as the adenine moiety. It is well-known that the catalytic hydrogenation is sensitive to the steric hindrance. Therefore, the unsaturated nucleoside **16** was desilylated to **7** and then reduced to 2′,3′-dideoxyadenosine (**10**).

The preparation of 2′,3′-unsaturated nucleosides via bisxanthates was extended to cytidine to give a fair yield of **32**, which on successive deprotection with tetra-*n*-butylammonium fluoride and methanolic ammonia afforded **3** (Scheme I). However, attempts to obtain **32** via thionocarbonate **31** were not successful due to the instability of **31**.

In an attempt to prepare 2′,3′-unsaturated uridine, 5′-*O*-silylated uridine was reacted with an excess of carbon disulfide and methyl iodide in the presence of aqueous sodium hydroxide and the crude product was treated with tri-*n*-butyltin hydride. The product isolated was found to be the unsaturated N^3-methyluridine **37** (Scheme II).

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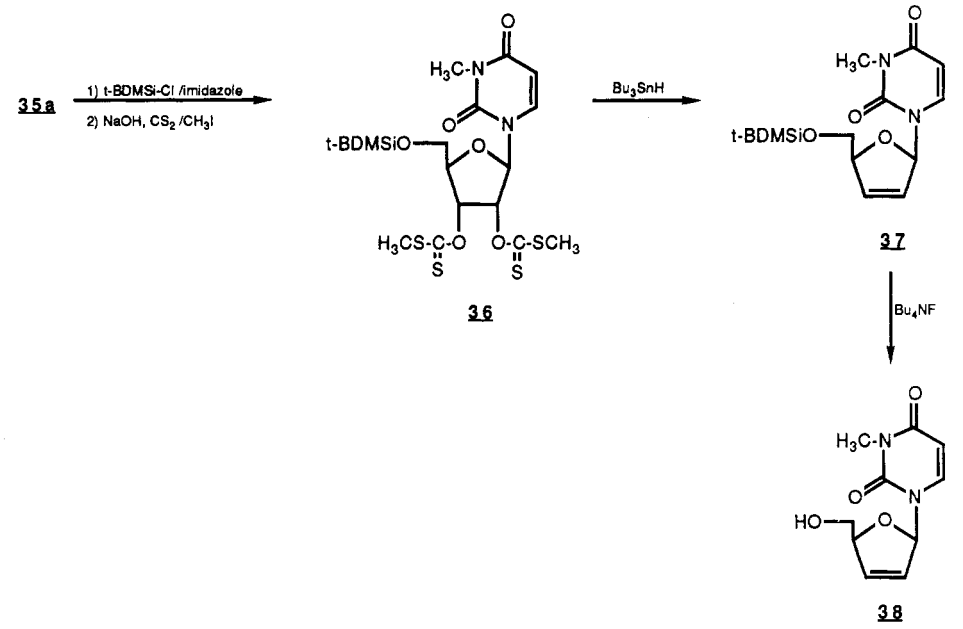
Scheme II



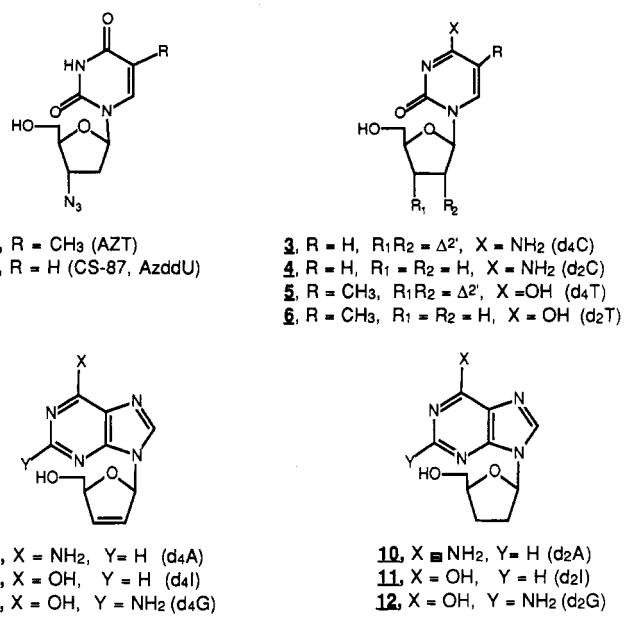


Figure 1.

Cyanoethylation has frequently been employed for the protection of hydroxy and amino groups. It was thought that the use of β-bromopropionitrile as the alkylating agent in this synthesis may lead to the bisxanthate of N^3-cyanoethylated uridine, which can subsequently be converted to the desired 2′,3′-unsaturated uridine. Surprisingly, the reaction of 5′-*O*-silyluridine with carbon disulfide and alkylation with β-bromopropionitrile yielded the bisxanthate **39a** as the only product. The bisxanthate **39a** on sequential treatment with tri-*n*-butyltin hydride and tetra-*n*-butylammonium fluoride gave a good yield of the unsaturated uridine **42** (Scheme III). 2′,3′-Didehydro-3′-deoxythymidine (**5**) was obtained from 1-β-D-ribofuranosylthymine through a similar sequence of reactions. The unsaturated uridine and thymidine derivatives were also obtained from the thionocarbonates **40a** and **40b** by using triethyl phosphite and 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine, respectively, as the desulfurizing agents.

The unsaturated inosine derivative **21** was obtained in 85% yield through the deoxygenation of the bisxanthate **19** prepared by the reaction of 5′-*O*-silylinosine with carbon disulfide followed by alkylation with β-bromopropionitrile. The unsaturated inosine **21** was also obtained, although in lower yield (39%), from the thionocarbonate **20** by deoxygenation with triethyl phosphite. 5′-*O*-Desilylation of **21** to **8** followed by catalytic reduction gave 2′,3′-dideoxyinosine (**11**) (Scheme III). It should be mentioned that the 2′,3′-unsaturated nucleosides, especially the inosine derivative **8**, are unstable to protic solvents, due to deglycosylation.

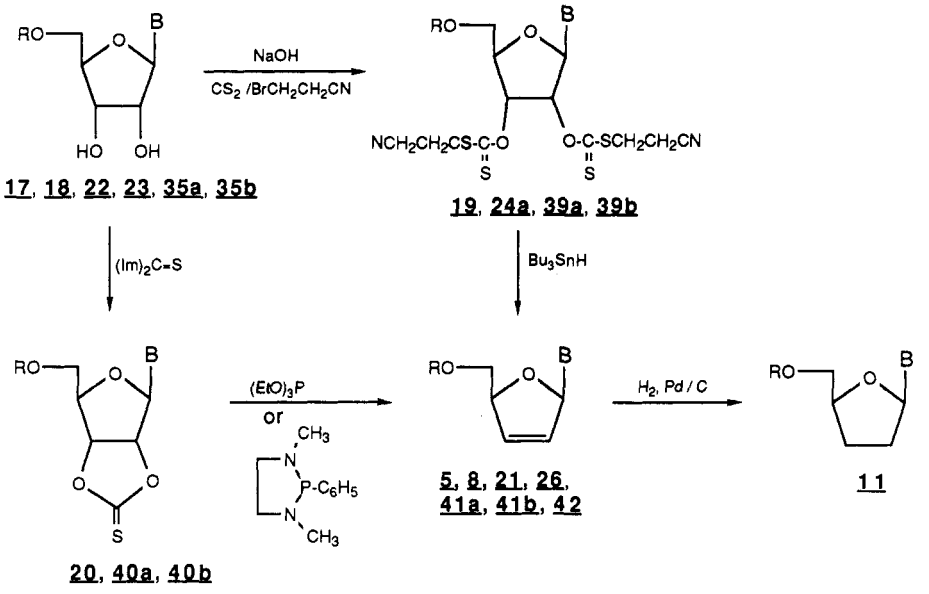
The above methods of deoxygenation were extended to guanosine. Initially, in order to prevent N^1-alkylation, β-bromopropionitrile was used for the preparation of the bisxanthate **24a** (Scheme III). Subsequently, it was found that methyl iodide also did not produce N^1-alkylated product (Scheme I), probably due to the bulky adjacent N^2-isobutyryl group. The bisxanthates **24a** as well as **24b** gave the unsaturated guanosine derivative **26** in about 50–55% yield. Conversion of **25** to **26** in refluxing triethyl phosphite was not successful because of the decomposition of **26** under the reaction conditions. However, the use of 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine, at room temperature, as the deoxygenating agent afforded **26** in 48% yield.

The 2′,3′-Dideoxy- and 2′,3′-didehydro-2′,3′-dideoxynucleosides were characterized by their ^{1}H NMR spectral data. It is noteworthy to mention the ^{1}H NMR assignments of the 2′,3′-unsaturated nucleosides. The olefinic protons of the 2′,3′-unsaturated nucleosides are observed as characteristic broad doublets or doublets of triplets with the low-field signal usually being assigned to the 2′-proton.[9,13,17] In contrast, our assignments are in accordance with a recent report by Robins et al.[15] suggesting the following order of general shift trend for the 2′,3′-unsaturated nucleosides: 1′-H < 3′-H < 2′-H < 4′-H < 5′- and 5″-H, on the basis of their experiments with 3′-deuterio-2′,3′-unsaturated-adenosine.

X-ray Crystallography

In view of the interesting antiviral activity exhibited by 2′,3′-dideoxy- and 2′,3′-didehydro-2′,3′-dideoxynucleosides, it was of interest to study the molecular conformation of these nucleosides by single-crystal X-ray diffraction. As representative compounds, 2′,3′-dideoxyadenosine (**10**) and

Scheme III



R \ B				
H	17	22	35a	35b
t-BDMSi	18	23	–	–
t-BDMSi	19	24a	39a	39b
t-BDMSi	20	26	40a	40b
t-BDMSi	21	-	41a	41b
H	8	-	42	5
H	11	-	–	–

2′,3′-didehydro-2′,3′-dideoxyadenosine (**7**) were chosen for study.

The molecular structure of 2′,3′-dideoxyadenosine (**10**) and the numbering system used are shown in Figure 2. 2′,3′-Dideoxyadenosine (**10**) and its unsaturated analogue **7** are nearly isomorphous. The most important conformational features and intermolecular hydrogen bonding geometries are listed in Table I. The glycosyl link has an anti conformation (torsion angle χ), which limits the steric hindrance between the sugar and the base.[28] The C(5′)–O(5′) group is in the *ap* or gauche–trans conformation [trans to the C(3′)–C(4′) bond], which is one of the three conformations of nearly equal energy that are strongly dependent on the intramolecular hydrogen bonding. The sugar ring of **10** is in an almost undistorted C(3′)-exo envelope conformation. This conformation is an extreme of the commonly observed C(2′)-endo conformation (P = 162°). It is interesting to note that AZT and other active thymidine analogues, CS-85 (3′-azido-5-ethyl-2′,3′-dideoxyuridine) and CS-87 (Azddu), have a similar preference for the C(3′)-exo conformation.[29] The 2′,3′ double

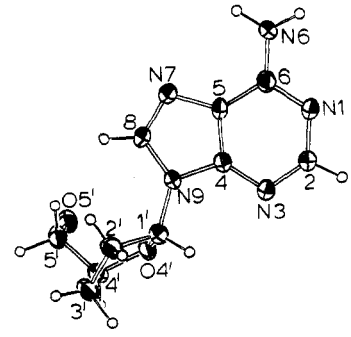


Figure 2. ORTEP diagram showing the molecular structure of 2′,3′-dideoxyadenosine (**10**) with the numbering scheme used in the Table.

bond limits the conformational flexibility of the sugar ring of **7**. The ring is nearly planar with C(4′) above the plane of the other four atoms by 0.09 Å. Comparison with the structures of other adenosine analogues found in the Cambridge Crystallographic Database[30] shows that the observed conformations are not uncommon. 2′,3′-Di-

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Table I. Conformational Parameters of 2′,3′-Dideoxyadenosine (10) and 2′,3′-Didehydro-2′,3′-dideoxyadenosine (7) and Intermolecular Hydrogen Bonding Geometries

parameter	10	7
N(9)–C(1′), Å	1.467 (4)	1.464 (3)
χ C(4′)–N(9)–C(1′)–O(4′), deg	−96.1 (4)	100.2 (3)
γ C(3′)–C(4′)–C(5′)–O(5′), deg	180.0 (3)	179.8 (3)
pseudorotation angle *P*, deg	193	243
maximum torsion angle τ_m, deg	−16.8	−12.1
hydrogen bonding		
N(6)–H(6A)···N(7) (0.5 + *x*, 1.0 − *y*, 1.5 + *z*)		
N(6)···N(7), Å	3.025 (4)	3.081 (3)
N(6)–H(6A), Å	0.94 (4)	0.98 (5)
H(6A)···N(7), Å	2.21 (4)	2.32 (5)
N(6)–H(6A)···N(7), deg	144 (3)	134 (3)
N(6)–H(6B)···O(5′) (1.0 − *x*, 0.5 + *y*, 0.5 − *z*)		
N(6)···O(5′), Å	2.937 (4)	2.883 (3)
N(6)–H(6B), Å	0.96 (4)	0.92 (4)
H(6B)···O(5′), Å	2.03 (4)	2.02 (4)
N(6)–H(6B)···O(5′), deg	155 (3)	155 (3)
O(5′)–H(5′)···N(1) (1.5 − *x*, 1.0 − *y*, −0.5 + *z*)		
O(5′)···N(1), Å	2.758 (4)	2.740 (3)
O(5′)–H(5′), Å		0.83 (5)
H(5′)···N(1), Å		1.92 (5)
O(5′)–H(5′)···N(1), deg		172 (3)

deoxyadenosine (**10**) and 2′,3′-didehydro-2′,3′-dideoxyadenosine (**7**) exhibit similar molecular conformations. The molecules can be superimposed on one another by least-squares fitting of the non-hydrogen atoms of the bases. The largest distance between the equivalent atoms is 0.68 Å for C(3′). The root mean square distance for all atoms is 0.22 Å.

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra were recorded at 90 or 250 MHz. TLC was performed on Uniplates purchased from Analtech Co.

5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-bis-*O*-[(methylthio)thiocarbonyl]adenosine (14) and 5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-*O*-thionocarbonyladenosine (15). To a stirred suspension of adenosine (**13**) (10.0 g, 37.4 mmol) and imidazole (6.12 g, 90 mmol) in DMF (200 mL) was added *tert*-butyldimethylsilyl chloride (6.78 g, 45 mmol). The reaction mixture was stirred with the exclusion of moisture for 20 h. The solvent was removed under vacuum, and the residue was purified by flash vacuum chromatography over silica using $CHCl_3$–MeOH (30:1) as the eluent. Evaporation of the appropriate fractions and trituration of the residue with hexanes yielded 11.66 g (82%) of 5′-*O*-(*tert*-butyldimethylsilyl)adenosine as a colorless solid.

To a solution of 5′-*O*-(*tert*-butyldimethylsilyl)adenosine (3.0 g, 7.87 mmol) and CS_2 (2.0 g, 26.4 mmol) in DMSO (20 mL), maintained at 15 °C, was added dropwise an aqueous 5 N NaOH solution (3.5 mL). The mixture was stirred for 20 min and treated dropwise with CH_3I (2.46 g, 17.3 mmol). The stirring was continued for 1 h, the solvent was removed in vacuo, and the residue was extracted with EtOAc. The organic layer was washed with water, dried ($MgSO_4$), and concentrated. Purification of the oily residue by flash vacuum chromatography on a silica gel column using $CHCl_3$–MeOH (20:1) gave 3.09 g (70%) of **14** and 0.39 g (11.7%) of **15**.

2′,3′-*O*-Bis(dithiocarbonate) **14**: mp 164–165 °C (benzene–hexane); ^{1}H NMR ($CDCl_3$) δ 0.04 (6 H, s, Me_2Si), 0.97 (9 H, s, Me_3CSi), 2.53 (3 H, s, SCH_3), 2.61 (3 H, s, SCH_3), 4.01 (2 H, m, 5′-H), 4.53 (1 H, m, 4′-H), 5.90 (2 H, br s, NH_2), 6.45–6.66 (3 H, m, 1′-, 2′-, and 3′-H), 8.21 (1 H, s, 8-H), 8.38 (1 H, s, 2-H).

Anal. Calcd for $C_{20}H_{31}N_5O_4S_4Si$: C, 42.78; H, 5.53; N, 12.48; S, 22.82. Found: C, 42.77; H, 5.56; N, 12.43; S, 22.74.

Thionocarbonate **15**: mp 198–199 °C ($CHCl_3$); UV (EtOH) λ_{max} (pH 1) 238, 254 (sh), (pH 7) 239, 255 (sh), (pH 12) 229, 258 nm; ^{1}H NMR ($CDCl_3$) δ ~0.0 (6 H, s, Me_2Si), 0.83 (9 H, s, Me_3CSi), 3.70 (2 H, d, *J* = 6 Hz, 5′-H), 4.59 (1 H, dt, *J* = 2.5, 6 Hz, 4′-H), 5.77 (2 H, br s, NH_2), 5.80 (1 H, dd, *J* = 2.5, 7 Hz, 3′-H), 6.30 (1 H, d, *J* = 1.5 Hz, 1′-H), 6.39 (1 H, dd, *J* = 1.5, 7 Hz, 2′-H), 7.92 (1 H, s, 8-H), 8.32 (1 H, s, 2-H).

Anal. Calcd for $C_{17}H_{25}N_5O_4SSi$: C, 48.20; H, 5.95; N, 16.54; S, 7.57. Found: C, 48.25; H, 5.97; N, 16.51; S, 7.63.

5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-*O*-thionocarbonyladenosine (15). To a solution of 5′-*O*-(*tert*-butyldimethylsilyl)adenosine (0.38 g, 1.0 mmol) in DMF (5 mL) was added 1,1′-thiocarbonyldiimidazole (0.2 g, 1.12 mmol), and the mixture was heated at 80 °C for 1 h. The solvent was removed under vacuum, and the residue was triturated with $CHCl_3$ (3 mL). The solid obtained was filtered, dried, and recrystallized from $CHCl_3$ to afford 0.31 g (73.5%) of **15** as white needles: mp 199–200 °C.

5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-didehydro-2′,3′-dideoxyadenosine (16). Method A. From 2′,3′-*O*-Bis(dithiocarbonate) 14. To a solution of **14** (7.23 g, 12.89 mmol) in dry toluene (100 mL), at reflux, was added dropwise a solution of tri-*n*-butyltin hydride (15.0 g, 51.56 mmol) and azobisisobutyronitrile (0.8 g) in dry toluene (100 mL) over 1 h. The solvent was removed under vacuum, and the residue was chromatographed on a silica gel column using 0–3% MeOH in $CHCl_3$. Evapoaration of the appropriate fractions and recrystallization of the residue from benzene yielded 4.18 g (93%) of **16** as a crystalline product: mp 117–121 °C; ^{1}H NMR (DMSO-d_6) δ 0.02 (6 H, s, Me_2Si), 0.85 (9 H, s, Me_3CSi), 3.80 (2 H, d, *J* = 3.96 Hz, 5′-H), 4.80–5.00 (1 H, m, 4′-H), 6.24 (1 H, dt, *J* = 1.6, 6.15 Hz, 2′-H), 6.44 (1 H, dt, *J* = 1.6, 6.15 Hz, 3′-H), 6.97 (1 H, m, 1′-H), 7.27 (2 H, br s, NH_2), 8.12 (1 H, s, 8-H), 8.19 (1 H, s, 2-H).

Anal. Calcd for $C_{16}H_{25}N_5O_2Si$: C, 55.31; H, 7.25; N, 20.15. Found: C, 55.21; H, 7.27; N, 20.07.

Method B. From 2′,3′-*O*-Thionocarbonate 15. To a solution of **15** (0.65 g, 1.5 mmol) in dry THF (5 mL), cooled to 0 °C, was added dropwise 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine (0.9 g, 4.6 mmol). The reaction mixture was stirred under nitrogen at 0 °C for 10 min and then at room temperature for 3 h. The solvent was removed under vacuum, and the oily residue was purified by chromatography on a silica gel column using 4% MeOH in EtOAc. Evaporation of the appropriate fractions and crystallization of the residue from benzene yielded 0.27 g (51%) of **16**.

The use of triethyl phosphite at 150 °C instead of 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine afforded 34% of **16**.

2′,3′-Didehydro-2′,3′-dideoxyadenosine (7). To a solution of **16** (3.79 g, 10.92 mmol) in dry THF (40 mL), cooled in an ice bath, was added a 1 M solution of tetra-*n*-butylammonium fluoride in THF (22 mL, 22.0 mmol). The mixture was stirred for 40 min at room temperature and concentrated. The resulting yellow syrupy residue was purified by chromatography on a silica gel column using a gradient of 3–5% MeOH in $CHCl_3$. Evaporation of the appropriate fractions yielded 2.21 g (86%) of **7**: mp 184–186 °C (MeOH) (lit.[14] mp 185–187 °C); ^{1}H NMR (DMSO-d_6) δ 3.59 (2 H, dd, *J* = 4.1, 5.27 Hz, 5′-H), 4.80–5.10 (2 H, m, 4′-H and OH), 6.14 (1 H, ddd, *J* = 1.46, 1.76, 5.86 Hz, 2′-H), 6.47 (1 H, ddd, *J* = 1.46, 1.76, 5.87 Hz, 3′-H), 6.94 (1 H, m, 1′-H), 7.25 (2 H, br s, NH_2), 8.157 (1 H, s, 8-H), 8.167 (1 H, s, 2-H).

2′,3′-Dideoxyadenosine (10). A solution of **7** (1.27 g) in MeOH (325 mL) was hydrogenated at 15 psi in the presence of 10% Pd/C (0.65 g). The reaction mixture was filtered through Celite, and the filtrate was evaporated. Crystallization of the crude product from MeOH gave 0.57 g of **10**: mp 186–188 °C (lit.[15] mp 185–187 °C).

5′-*O*-(*tert*-Butyldimethylsilyl)inosine (18). Inosine (**17**) (15.0 g, 56 mmol) was converted to **18** according to the procedure described for the preparation of 5′-*O*-(*tert*-butyldimethylsilyl)-adenosine. The crude product was purified chromatograpically by using $CHCl_3$–MeOH (15:2): yield, 16.4 g (76.7%); mp softening at 220 °C, melting at 229–231 °C ($CHCl_3$–Et_2O); ^{1}H NMR (DMSO-d_6) δ ~0.0 (6 H, s, Me_2Si), 0.82 (9 H, s, Me_3CSi), 3.52–4.00 (3 H, m, 4′- and 5′-H), 4.10 [1 H, t, *J* = 4.8 Hz, 2′(3′)-H], 4.41 [1 H, t, *J* = 4.8 Hz, 3′(2′)-H], 5.83 (1 H, d, *J* = 5.3 Hz, 1′-H), 8.00 (1 H, s, 8-H), 8.18 (1 H, s, 2-H).

Anal. Calcd for $C_{16}H_{26}N_4O_5Si$: C, 50.24; H, 6.85; N, 14.65. Found: C, 50.16; H, 6.85; N, 14.63.

5′-O-(*tert*-Butyldimethylsilyl)-2′,3′-bis-O-[[(β-cyanoethyl)thio]thiocarbonyl]inosine (19). Compound **18** (10.0 g, 26 mmol) was reacted with CS_2 (28 mL) in DMSO (75 mL) in the presence of a 5 N aqueous NaOH solution (28 mL) and alkylated with β-bromopropionitrile (73 mL). The crude product was purified by chromatography over silica using $CHCl_3$–MeOH (20:1) to obtain 10.2 g (61%) of **19**: mp 150–155 °C dec ($CHCl_3$–Et_2O); ^1H NMR (DMSO-d_6) δ ~0.0 (6 H, s, Me_2Si), 0.79 (9 H, s, Me_3CSi), 2.69–3.60 (8 H, m, CH_2CH_2CN), 3.91 (2 H, d, J = 2.4 Hz, 5′-H), 4.56 (1 H, m, 4′-H), 6.23–6.71 (3 H, m, 1′-, 2′-, and 3′-H), 7.98 (1 H, s, 8-H), 8.16 (1 H, s, 2-H).

Anal. Calcd for $C_{24}H_{32}N_6O_5S_4Si$: C, 44.98; H, 5.03; N, 13.11. Found: C, 45.05; H, 5.05; N, 13.08.

5′-O-(*tert*-Butyldimethylsilyl)-2′,3′-O-thionocarbonylinosine (20). Compound **18** (4.6 g, 12.04 mmol) was reacted with 1,1′-thiocarbonyldiimidazole (4.2 g, 23.6 mmol) in DMF (50 mL) at room temperature. Workup of the reaction mixture and purification of the crude product by flash chromatography over silica using $CHCl_3$–MeOH (17:1) afforded 2.76 g (54%) of **20**: mp 173–175 °C ($CHCl_3$–Et_2O); UV (MeOH) λ_{max} (pH 3) 272 (sh), 240, (pH 7) 272 (sh), 240, (pH 11) 252, 235 nm (sh); ^1H NMR (DMSO-d_6) δ 0.05 (6 H, s, Me_2Si), 0.84 (9 H, s, Me_3CSi), 3.83 (2 H, d, J = 5.57 Hz, 5′-H), 4.55–4.75 (1 H, m, 4′-H), 5.79 (1 H, dd, J = 2.35, 7.32 Hz, 3′-H), 6.28 (1 H, dd, J = 1.76, 7.32 Hz, 2′-H), 6.59 (1 H, d, J = 1.76 Hz, 1′-H), 8.15 (1 H, s, 8-H), 8.26 (1 H, s, 2-H), 12.50 (1 H, br s, NH, exchangeable).

Anal. Calcd for $C_{17}H_{24}N_4O_5SSi$: C, 48.10; H, 5.70; N, 13.20; S, 7.55. Found: C, 47.98; H, 5.75; N, 13.14; S, 7.48.

5′-O-(*tert*-Butyldimethylsilyl)-2′,3′-didehydro-2′,3′-dideoxyinosine (21). Method A. From 2′,3′-O-Bis(dithiocarbonate) 19. Compound **19** (5.0 g, 7.8 mmol) was converted to **21** by treatment with tri-*n*-butyltin hydride (17.3 g, 59 mmol) and azobisisobutyronitrile (1.5 g) in dry toluene according to the procedure described for the preparation of **16**. Purification of the crude product by flash chromatography on a silica gel column using $CHCl_3$–MeOH (20:1) yielded 2.3 g (85%) of the olefin: mp 178–180 °C (MeOH–acetone); ^1H NMR ($CDCl_3$) δ 0.03 (6 H, s, Me_2Si), 0.85 (9 H, s, Me_3CSi), 3.79, (2 H, d, J = 3.8 Hz, 5′-H), 4.96 (1 H, m, 4′-H), 6.22 (1 H, dt, J = 1.5, 5.86 Hz, 2′-H), 6.52 (1 H, dt, J = 1.5, 5.86 Hz, 3′-H), 6.95 (1 H, m, 1′-H), 8.06 (1 H, s, 8-H), 8.11 (1 H, s, 2-H), 12.30 (1 H, br s, NH, exchangeable).

Anal. Calcd for $C_{16}H_{24}N_4O_3Si$: C, 55.15; H, 6.94; N, 16.08. Found: C, 55.02; H, 6.99; N, 16.03.

Method B. From 2′,3′-O-Thionocarbonate 20. A solution of **20** (1.0 g, 2.4 mmol) in triethyl phosphite (30 mL) was heated to gentle reflux under nitrogen for 30 min. Excess reagent was evaporated under reduced pressure, and the residue was purified by flash chromatography on a silica gel column using $CHCl_3$–MeOH (15:1) to obtain 0.32 g (39%) of **21**.

2′,3′-Didehydro-2′,3′-dideoxyinosine (8). Compound **21** (3.0 g, 8.6 mmol) was deprotected with a 1 M solution of tetra-*n*-butylammonium fluoride in THF (34 mL, 34.0 mmol). Evaporation of the solvent and purification of the residue by chromatography on a silica gel column using $CHCl_3$–MeOH (7:1) yielded 1.36 g (67%) of **8**: mp >310 °C (MeOH) (lit.[13] mp >300 °C); ^1H NMR (DMSO-d_6) δ 3.56 (2 H, d, J = 2.6 Hz, 5′-H), 4.84 (2 H, m, 4′-H and OH, collapses to a multiplet integrating to one proton after D_2O exchange), 6.12 (1 H, br d, J = 5.7 Hz, 2′-H), 6.47 (1 H, br d, J = 5.7 Hz, 3′-H), 6.90 (1 H, m, 1′-H), 8.06 (1 H, s, 8-H), 8.10 (1 H, s, 2-H), 12.40 (1 H, br s, NH).

Anal. Calcd for $C_{10}H_{10}N_4O_3$: C, 51.28; H, 4.30; N, 23.92. Found: C, 51.30; H, 4.32; N, 23.84.

2′,3′-Dideoxyinosine (11). A solution of **8** (0.38 g, 1.6 mmol) in a mixture of EtOH–water (4:1) (70 mL) was hydrogenated in the presence of 10% Pd/C (0.07 g) at 50 psi for 6 h. The mixture was filtered through Celite, and the filtrate was concentrated and cooled. The solid obtained was filtered and dried to yield 0.3 g (78%) of **11**: mp softens at 184–186 °C, but does not melt up to 300 °C (EtOH–H_2O) [lit.[18] mp 160–163 °C (CH_2Cl_2–acetone)];[31] ^1H NMR (DMSO-d_6) δ 1.72–2.48 (4 H, m, 2′- and 3′-H), 3.21–3.67 (2 H, m, 5′-H), 4.17–4.38 (1 H, m, 4′-H), 4.72 (1 H, br s, OH, exchangeable), 6.20 (1 H, dd, J = 3.81, 4.1 Hz, 1′-H), 7.90 (1 H, s, 8-H), 8.15 (1 H, s, 2-H), 12.20 (1 H, br s, NH).

(31) The discrepancy in the melting points may be due to the different solvents used for the crystallization (CH_2Cl_2–acetone vs H_2O–EtOH).

Anal. Calcd for $C_{10}H_{12}N_4O_3$: C, 50.84; H, 5.12; N, 23.72. Found: C, 50.74; H, 5.15; N, 23.66.

5′-O-(*tert*-Butyldimethylsilyl)-N²-isobutyrylguanosine (23). To a suspension of guanosine (20.0 g, 70.67 mmol) in dry DMF (75 mL) was added hexamethyldisilazane (110 mL), and the mixture was stirred for 30 min, during which time all the guanosine went into solution. The mixture was stirred for 12 h, cooled to 10–15 °C, and treated with dry pyridine (100 mL), followed by isobutyric anhydride (180 mL). The reaction mixture was stirred for 24 h, cooled to 0–5 °C, and treated dropwise with MeOH (200 mL). After being stirred for 4 h, the mixture was concentrated to about 100 mL, diluted with a mixture of hexanes and Et_2O (1:1) (500 mL), and left overnight. The gummy product separated was filtered, triturated with Et_2O, and dried to yield 24 g (96%) of N^2-isobutyrylguanosine as a pale yellow solid.

N^2-Isobutyrylguanosine (15.0 g, 42.5 mmol) was converted to **23** according to the procedure described for the preparation of 5′-O-(*tert*-butyldimethylsilyl)adenosine. Workup of the reaction mixture and chromatography of the crude product on a silica gel column using a gradient of 2.5–7.5% MeOH in $CHCl_3$ yielded 14.0 g (70.5%) of the product as a colorless foamy solid: mp 208–210 °C; ^1H NMR (DMSO-d_6) δ 0.05 (6 H, s, Me_2Si), 0.88 (9 H, s, Me_3CSi), 1.12 (6 H, d, J = 6.74 Hz, Me_2C), 2.78 (1 H, septet, J = 6.74 Hz, Me_2CH), 3.60–4.00 (3 H, m, 4′- and 5′-H), 4.15 (1 H, m, 3′-H), 4.40 (1 H, m, 2′-H), 5.30 (1 H, br m, OH), 5.85 (1 H, d, J = 5.28 Hz, 1′-H), 8.15 (1 H, s, 8-H).

Anal. Calcd for $C_{20}H_{33}N_5O_6Si$: C, 51.37; H, 7.11; N, 14.98. Found: C, 51.32; H, 7.14; N, 14.91.

5′-O-(*tert*-Butyldimethylsilyl)-N²-isobutyryl-2′,3′-bis-O-[[(β-cyanoethyl)thio]thiocarbonyl]guanosine (24a). Compound **23** (4.0 g, 8.56 mmol) was reacted with CS_2 (10 mL) in DMSO (20 mL) in the presence of an aqueous NaOH solution (50%) (7 mL, 87.5 mmol) and alkylated with β-bromopropionitrile (10 mL). Chromatography of the crude product over silica using $CHCl_3$–MeOH (100:1) yielded 5.5 g (88.6%) of **24a**: mp 90–92 °C dec; UV (MeOH) λ_{max} (pH 1) 277, 256 (sh), 219 (sh), (pH 7) 277, 256 (sh), 219 (sh), (pH 11) 302 (sh), 276 nm; ^1H NMR (DMSO-d_6) δ 0.10 (6 H, s, Me_2Si), 0.90 (9 H, s, Me_3CSi), 1.13 (6 H, d, J = 6.44 Hz, Me_2C), 2.55–3.10 (5 H, m, CH_2CH_2CN and Me_2CH), 3.10–3.60 (4 H, m, OCH_2), 3.95 (2 H, m, 5′-H), 4.55 (1 H, m, 4′-H), 6.20–6.60 (3 H, m, 1′-, 2′-, and 3′-H), 8.14 (1 H, s, 8-H).

Anal. Calcd for $C_{28}H_{39}N_7O_6S_4Si$: C, 46.32; H, 5.41; N, 13.50; S, 17.66. Found: C, 46.38; H, 5.43; N, 13.48; S, 17.73.

5′-O-(*tert*-Butyldimethylsilyl)-N²-isobutyryl-2′,3′-bis-O-[(methylthio)thiocarbonyl]guanosine (24b). Compound **23** (8.0 g, 17.71 mmol) was reacted with CS_2 (15 mL) in DMSO (20 mL) in the presence of an aqueous NaOH solution (50%) (10 mL, 125 mmol) and alkylated with CH_3I (20 mL). Chromatography of the crude product over silica using $CHCl_3$–MeOH (100:1) yielded 9.5 g (86%) of **24b**: mp 120–122 °C dec; UV (MeOH) λ_{max} (pH 1) 280, 258 (sh), 219 (sh), (pH 7) 279, 258 (sh), 219 (sh), (pH 11) 305 (sh), 278 nm (sh); ^1H NMR (DMSO-d_6) δ 0.01 (6 H, s, Me_2Si), 0.90 (9 H, s, Me_3CSi), 1.13 (6 H, d, J = 6.74 Hz, Me_2C), 2.55 (3 H, s, SCH_3), 2.65–2.80 (4 H, m, SCH_3 and Me_2CH), 3.99 (2 H, m, 5′-H), 4.54 (1 H, m, 4′-H), 6.25–6.65 (3 H, m, 1′-, 2′-, and 3′-H), 8.14 (1 H, s, 8-H).

Anal. Calcd for $C_{24}H_{37}N_5O_6S_4Si$: C, 44.49; H, 5.76; N, 10.81; S, 19.79. Found: C, 44.55; H, 5.77; N, 10.73; S, 19.74.

5′-O-(*tert*-Butyldimethylsilyl)-N²-isobutyryl-2′,3′-O-thionocarbonylguanosine (25). Compound **23** (1.5 g, 3.2 mmol) was reacted with 1,1′-thiocarbonyldiimidazole in DMF at 75–80 °C. Workup of the reaction mixture and purification of the crude product by flash chromatography over silica using $CHCl_3$–MeOH (100:2) afforded 1.5 g (91%) of **25**: mp 150–155 °C; UV (MeOH) λ_{max} (pH 3) 280, 258 (sh), 250 (sh), 243, (pH 7) 283, 258 (sh), 250 (sh), 243, (pH 11) 265, 222 nm; ^1H NMR (DMSO-d_6) δ ~0.0 (6 H, s, Me_2Si), 0.77 (9 H, s, Me_3CSi), 1.14 (6 H, d, J = 6.7 Hz, Me_2C), 2.75 (1 H, septet, J = 6.7 Hz, Me_2CH), 3.72 (2 H, d, J = 5.86 Hz, 5′-H), 4.40–4.60 (1 H, m, 4′-H), 6.00 (1 H, dd, J = 2.6, 7.3 Hz, 3′-H), 6.21 (1 H, dd, J = ~1, 7.3 Hz, 2′-H), 6.46 (1 H, d, J = ~1 Hz, 1′-H), 8.11 (1 H, s, 8-H), 11.70 (1 H, br s, NH, exchangeable).

Anal. Calcd for $C_{21}H_{31}N_5O_6SSi$: C, 49.49; H, 6.13; N, 13.74; S, 6.29. Found: C, 49.49; H, 6.18; N, 13.69; S, 6.20.

5′-O-(*tert*-Butyldimethylsilyl)-N²-isobutyryl-2′,3′-didehydro-2′,3′-dideoxyguanosine (26). Method A. From

2',3'-Bis(dithiocarbonate) 24a. Compound **24a** (4.5 g, 6.2 mmol) was treated with a solution of tri-*n*-butyltin hydride (10.0 g, 34 mmol) and azobisisobutyronitrile (0.45 g) in benzene at 60–65 °C. The solvent was removed under vacuum, and the residue was partitioned between MeOH and hexane. The MeOH layer was separated, washed with hexane, and concentrated. The residue was purified by flash chromatography on a silica gel column using $CHCl_3$–MeOH (100:2) to obtain 1.5 g (55.8%) of the olefin **26** as a foam: mp 113–115 °C; UV (MeOH) λ_{max} (pH 1) 260, (pH 7) 282, 260, (pH 11) 270 nm; ^1H NMR ($CDCl_3$) δ 0.05 (6 H, s, Me_2Si), 0.80 (9 H, s, Me_3CSi), 1.11 (6 H, d, J = 6.75 Hz, Me_2C), 2.77 (1 H, septet, J = 6.75 Hz, Me_2CH), 3.72 (2 H, d, J = 4.1 Hz, 5'-H), 4.89 (1 H, m, 4'-H), 6.20 (1 H, br d, J = 5.86 Hz, 2'-H), 6.49 (1 H, br d, J = 5.86 Hz, 3'-H), 6.76 (1 H, m, 1'-H), 7.90 (1 H, s, 8-H), 11.90 (1 H, br s, NH, exchangeable).

Anal. Calcd for $C_{20}H_{31}N_5O_4Si$: C, 55.40; H, 7.21; N, 16.15. Found: C, 54.90; H, 7.25; N, 15.91.

Under similar conditions, the bisxanthate **24b** yielded 51.3% of **26**.

Method B. From 2',3'-*O*-Thionocarbonate 25. Compound **25** (1.0 g, 1.96 mmol) was stirred with 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine (1.15 g, 5.9 mmol) at room temperature for 3 h. Evaporation of the solvent and chrhomatography of the residue on a silica gel column using $CHCl_3$–MeOH (100:4) yielded 0.41 g (48%) of **26**.

N^2-Isobutyryl-2',3'-didehydro-2',3'-dideoxyguanosine (27). Compound **26** (1.3 g, 3.0 mmol) was deprotected with a 1 M solution of tetra-*n*-butylammonium fluoride in THF (4.3 mL, 4.3 mmol). The solvent was evaporated under reduced pressure, and the residue was purified by chromatography on a silica gel column using a gradient of 5–15% MeOH in $CHCl_3$ to obtain 0.8 g (84%) of **27**: mp >250 °C (benzene–MeOH); ^1H NMR (DMSO-d_6) δ 1.04 (6 H, d, J = 6.74 Hz, Me_2C), 2.75 (1 H, septet, J = 6.74 Hz, Me_2CH), 3.54 (2 H, m, 5'-H), 4.85 (2 H, m, 4'-H and OH, collapses to a multiplet integrating to one proton after D_2O exchange), 6.17 (1 H, dt, J = 1.47, 2.05, 6.0 Hz, 2'-H), 6.47 (1 H, dt, J = 1.47, 1.76, 5.0 Hz, 3'-H), 6.75 (1 H, m, 1'-H), 7.99 (1 H, s, 8-H), 11.90 (1 H, br s, NH).

Anal. Calcd for $C_{14}H_{17}N_5O_4 \cdot H_2O$: C, 49.85; H, 5.68; N, 20.76. Found: C, 50.05; H, 5.71; N, 20.86.

N^2-Isobutyryl-2',3'-dideoxyguanosine (28). Compound **27** (0.3 g, 0.96 mmol) in MeOH (50 mL) was hydrogenated at 30 psi in the presence of 10% Pd/C (150 mg) for 6 h. The catalyst was filtered off, and the solvent was evaporated. Purification of the crude product by column chromatography using $CHCl_3$–MeOH (10:1) yielded 0.2 g (66%) of **28** as a colorless solid: mp 245–247 °C dec (benzene–MeOH); ^1H NMR (DMSO-d_6) δ 1.12 (6 H, d, J = 7.03 Hz, Me_2C), 1.85–2.15 (2 H, m, 3'-H), 2.20–2.52 (2 H, m, 2'-H), 2.77 (1 H, septet, J = 7.03 Hz, Me_2CH), 3.55 (2 H, m, 5'-H), 4.10 (1 H, m, 4'-H), 4.94 (1 H, t, J = 4.7 Hz, OH, exchangeable), 6.08 (1 H, dd, J = 1.46, 4.1 Hz, 1'-H), 8.26 (1 H, s, 8-H), 11.88 (1 H, br s, NH, exchangeable).

Anal. Calcd for $C_{14}H_{19}N_5O_4 \cdot H_iO$: C, 49.55; H, 6.24; N, 20.64. Found: C, 49.63; H, 6.27; N, 20.59.

2',3'-Didehydro-2',3'-dideoxyguanosine (9). A solution of **27** (0.3 g, 0.94 mmol) in MeOH saturated with ammonia (20 mL) was stirred at 50–55 °C for 12 h in a pressure vessel. The reaction mixture was cooled to room temperature, and the solid obtained was filtered, washed with cold 2-propanol, and dried. Crystallization from MeOH afforded 0.2 g (81%) of **9** as an amorphous solid: mp >250 °C; UV (MeOH) λ_{max} (pH 1) 270, 251, (pH 7) 269 (sh), 255, (pH 11) 268 nm; ^1H NMR (DMSO-d_6) δ 3.48–3.59 (2 H, m, 5'-H), 4.70–5.00 (2 H, m, 4'-H and OH), 6.08 (1 H, br d, J = 5.93 Hz, 2'-H), 6.40–6.47 (3 H, m, 3'-H and NH_2), 6.68 (1 H, m, 1'-H), 7.70 (1 H, s, 8-H). The ^1H NMR spectral data were in agreement with the values reported in the literature.[10]

2',3'-Dideoxyguanosine (12). Compound **28** (0.2 g, 0.62 mmol) was treated with methanolic ammonia as described above. The reaction mixture was filtered, and the filtrate was evaporated. Crystallization of the residue from MeOH gave 0.15 g (96%) of **12** as a colorless solid: mp >250 °C (lit.[17] mp >300 °C); ^1H NMR (DMSO-d_6) δ 1.95 (2 H, m, 3'-H), 2.25 (2 H, m, 2'-H), 3.53 (2 H, m, 5'-H), 4.05 (1 H, m, 4'-H), 4.90 (1 H, t, J = 4.7 Hz, OH, exchangeable), 5.98 (1 H, dd, J = 1.76, 4.1 Hz, 1'-H), 6.42 (2 H, s, NH_2), 7.93 (1 H, s, 8-H), 10.55 (1 H, s, NH, exchangeable).

N^4-Acetyl-5'-*O*-(*tert*-butyldimethylsilyl)-2',3'-bis-*O*-[(methylthio)thiocarbonyl]cytidine (30). N^4-Acetylcytidine (8.35 g, 29.3 mmol) was converted to the 5'-*O*-*tert*-butyldimethylsilyl derivative according to the procedure described for the preparation of 5'-*O*-(*tert*-butyldimethylsilyl)adenosine. Workup of the reaction mixture and purification of the crude product by flash vaccuum chromatography on a silica gel column using a gradient of 0–5% MeOH in $CHCl_3$ yielded 8.15 g (70%) of 5'-*O*-silyl protected cytidine as a white foamy solid: mp 159–161 °C; UV (MeOH) λ_{max} (pH 1) 300, 246, (pH 7) 298, 246, (pH 11) 272, 231 nm (sh); ^1H NMR (DMSO-d_6) δ 0.09 (6 H, s, Me_2Si), 0.90 (9 H, s, Me_3CSi), 2.09 (3 H, s, CH_3), 3.70–4.10 (5 H, m, 2'-, 3'-, 4'-, and 5'-H), 5.05 (1 H, br s, OH), 5.55 (1 H, d, J = 4.7 Hz, OH), 5.77 (1 H, m, 1'-H), 7.19 (1 H, d, J = 7.6 Hz, 5-H), 8.31 (1 H, d, J = 7.6 Hz, 6-H), 10.86 (1 H, s, NH).

Anal. Calcd for $C_{17}H_{29}N_3O_6Si$: C, 51.11; H, 7.32; N, 10.52. Found: C, 50.94; H, 7.32; N, 10.46.

A solution of N^4-acetyl-5'-*O*-(*tert*-butyldimethylsilyl)cytidine (8.15 g, 20.4 mmol) prepared as above and imidazole (300 mg) in dry THF (50 mL) was cooled to 5–10 °C and flushed with nitrogen. To the reaction mixture was added portionwise NaH (60% dispersion) (3.3 g, 82.5 mmol) over 5 min. After 1 h of stirring, the mixture was treated with CS_2 (8.4 g, 110.5 mmol) and stirred for an additional 30 min, after which CH_3I (12.0 g, 85 mmol) was added to the reaction mixture and the stirring was continued for an additional 30 min. The reaction mixture was diluted with Et_2O (250 mL), washed with ice-cold water (2 × 50 mL), and dried (Na_2SO_4). The organic layer was concentrated, and the resulting yellow oily residue was purified by flash chromatography over silica using $CHCl_3$–EtOAc (10:1) to yield 6.0 g (51%) of **30**: mp 161–163 °C (benzene–hexane); UV (MeOH λ_{max} (pH 1) 280, 247, (pH 7) 279, 247, (pH 11) 277, 224 nm (sh); ^1H NMR (DMSO-d_6) δ 0.04 (6 H, s, Me_2Si), 0.83 (9 H, s, Me_3CSi), 2.06 (3 H, s, $COCH_3$), 2.53 (3 H, s, SCH_3), 2.56 (3 H, s, SCH_3), 3.91 (2 H, m, 5'-H), 4.50 (1 H, m, 4'-H), 6.10–6.40 (3 H, m, 1'-, 2'-, and 3'-H), 7.19 (1 H, d, J = 7.6 Hz, 5-H), 8.13 (1 H, d, J = 7.6 Hz, 6-H), 10.91 (1 H, s, NH).

Anal. Calcd for $C_{21}H_{33}N_3O_6S_4Si$: C, 43.50; H, 5.74; N, 7.25; S, 22.12. Found: C, 43.60; H, 5.76; N, 7.22; S, 22.20.

N^4-Acetyl-5'-*O*-(*tert*-butyldimethylsilyl)-2',3'-didehydro-2',3'-dideoxycytidine (32). A refluxing solution of **30** (4.0 g, 6.91 mmol) and azobisisobutyronitrile (500 mg) in toluene was treated with a solution of tri-*n*-butyltin hydride (12.0 g, 41 mmol) in toluene. Workup of the reaction mixture and chromatography of the crude product over silica using $CHCl_3$–MeOH (100:2.5) yielded 1.5 g (59%) of **32**: mp 168–170 °C (softens); UV (MeOH) λ_{max} (pH 1) 301, 242, (pH 7) 297, 246, (pH 11) 269 nm; ^1H NMR (DMSO-d_6) δ 0.04 (6 H, s, Me_2Si), 0.85 (9 H, s, Me_3CSi), 2.09 (3 H, s, $COCH_3$), 3.82 (2 H, d, J = 3.22 Hz, 5'-H), 4.90 (1 H, m, 4'-H), 6.03 (1 H, br d, J = 6.15 Hz, 2'-H), 6.38 (1 H, br d, J = 6.15 Hz, 3'-H), 6.88 (1 H, m, 1'-H), 7.17 (1 H, d, J = 7.3 Hz, 5-H), 8.11 (1 H, d, J = 7.3 Hz, 6-H), 10.88 (1 H, s, NH).

Anal. Calcd for $C_{17}H_{27}N_3O_4Si$: C, 55.86; H, 7.45; N, 11.50. Found: C, 55.76; H, 7.50; N, 11.49.

N^4-Acetyl-2',3'-didehydro-2',3'-dideoxycytidine (33). Compound **32** (1.5 g, 4.1 mmol) was deprotected with a 1 M solution of tetra-*n*-butylammonium fluoride in THF (5 mL, 5.0 mmol). Chromatography of the crude product using 5% MeOH in $CHCl_3$ yielded 0.88 g (85%) of **33** as a colorless solid: mp 180–182 °C dec (benzene–MeOH); ^1H NMR (DMSO-d_6) δ 2.09 (3 H, s, $COCH_3$), 3.63 (2 H, m, 5'-H), 4.85 (1 H, m, 4'-H), 4.99 (1 H, t, J = 5.27 Hz, OH), 5.95 (1 H, br d, J = 5.8 Hz, 2'-H), 6.40 (1 H, br d, J = 5.8 Hz, 3'-H), 6.87 (1 H, m, 1'-H), 7.15 (1 H, d, J = 7.3 Hz, 5-H), 8.20 (1 H, d, J = 7.3 Hz, 6-H), 10.86 (1 H, s, NH).

Anal. Calcd for $C_{11}H_{13}N_3O_4$: C, 52.59; H, 5.22; N, 16.72. Found: C, 52.48; H, 5.24; N, 16.68.

2',3'-Didehydro-2',3'-dideoxycytidine (3). Compound **33** (0.26 g, 1.03 mmol) was deacetylated by heating with methanolic ammonia. Evaporation of the solvent and trituration of the residue with 2-propanol yielded 0.15 g (69%) of **3**: mp 167–169 °C (bezene–MeOH) (lit.[7] mp 168–169 °C); ^1H NMR (DMSO-d_6) δ 3.51 (2 H, m, 5'-H), 4.75 (1 H, m, 4'-H), 4.85 (1 H, t, J = 5.5 Hz, OH), 5.68 (1 H, d, J = 7.3 Hz, 5-H), 5.85 (1 H, br d, J = 5.9 Hz, 2'-H), 6.35 (1 H, br d, J = 5.9 Hz, 3'-H), 6.89 (1 H, m, 1'-H), 7.10 (2 H, s, NH_2), 7.67 (1 H, d, J = 7.3 Hz, 6-H).

N^4-Acetyl-2′,3′-dideoxycytidine (34). Compound **33** (0.78 g, 3.1 mmol) in EtOH was hydrogenated to **34** according to the procedure described for **10**. The crude product was chromatographed over silica by using 5% MeOH in $CHCl_3$: yield 0.61 g (77.5%); mp 143–145 °C (benzene–MeOH); ^1H NMR (DMSO-d_6) δ 1.60–2.50 (7 H, m, 2′- and 3′-H and $COCH_3$), 3.40–3.85 (2 H, m, 5′-H), 3.90–4.30 (1 H, m, 4′-H), 5.07 (1 H, t, J = 5.0 Hz, OH), 5.91 (1 H, m, 1′-H), 7.17 (1 H, d, J = 7.6 Hz, 5-H), 8.32 (1 H, d, J = 7.3 Hz, 6-H), 10.80 (1 H, s, NH).

Anal. Calcd for $C_{11}H_{15}N_3O_4$: C, 52.17; H, 5.97; N, 16.59. Found: C, 52.07; H, 6.00; N, 16.53.

2′,3′-Dideoxycytidine (4). Compound **34** (0.6 g, 2.4 mmol) was deacetylated with methanolic ammonia to yield 0.4 g (80%) of **4**: mp 207–209 °C (benzene–EtOH) (lit.[17] mp 209–210 °C); ^1H NMR (DMSO-d_6) δ 1.50–2.50 (4 H, m, 2′- and 3′-H), 3.63 (2 H, m, 5′-H), 4.00 (1 H, m, 4′-H), 4.96 (1 H, t, J = 4.9 Hz, OH), 5.69 (1 H, d, J = 7.25 Hz, 5-H), 5.95 (1 H, m, 1′-H), 7.05 (2 H, s, NH_2), 7.89 (1 H, d, J = 7.3 Hz, 6-H).

5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-didehydro-2′,3′-dideoxy-N^3-methyluridine (37). A solution of 5′-*O*-(*tert*-butyldimethylsilyl)uridine (3.21 g, 8.97 mmol) was reacted with CS_2 (8 mL) in DMSO (12 mL) in the presence of a 5 N aqueous NaOH solution (8 mL) and alkylated with CH_3I (14 mL). A small amount of the product was purified by preparative TLC (hexane–acetone, 3:1): ^1H NMR (DMSO-d_6) δ ~0.0 (6 H, s, Me_2Si), 0.80 (9 H, s, Me_3CSi), 2.47 (3 H, s, SCH_3), 2.52 (3 H, s, SCH_3), 3.05 (3 H, s, NCH_3), 3.82 (2 H, d, J = 2.9 Hz, 5′-H), 4.38 (1 H, m, 4′-H), 5.73 (1 H, d, J = 7.5 Hz, 5-H), 6.12 (3 H, m, 1′-, 2′-, and 3′-H), 7.72 (1 H, d, J = 7.5 Hz, 6-H).

Crude **36** was treated with a solution of tri-*n*-butyltin hydride (11.0 g, 37.9 mmol) and azobisisobutyronitrile (0.68 g, 4.1 mmol) in toluene. Evaporation of the solvent and chromatography of the residue on a silica gel column using benzene–EtOAc (7:1) yielded 1.85 g (63.6%) of the olefin **37**: mp 116–117 °C (Et_2O–hexanes); ^1H NMR (DMSO-d_6) δ ~0.0 (6 H, s, Me_2Si), 0.82 (9 H, s, Me_3CSi), 3.13 (3 H, s, NCH_3), 3.76 (2 H, d, J = 3.2 Hz, 5′-H), 4.80 (1 H, m, 4′-H), 5.62 (1 H, d, J = 7.9 Hz, 5-H), 5.92 (1 H, dt, J = 1.4, 2.1, 6.2 Hz, 2′-H), 6.37 (1 H, dt, J = 6.0, 1.6, and 1.6 Hz, 3′-H), 6.82 (1 H, quintet, J = 1.4, 1.7, 3.2 Hz, 1′-H), 7.65 (1 H, d, J = 7.9 Hz, 6-H).

Anal. Calcd for $C_{16}H_{26}N_2O_4Si$: C, 56.77; H, 7.74; N, 8.27. Found: C, 56.77; H, 7.81; N, 8.22.

2′,3′-Didehydro-2′,3′-dideoxy-N^3-methyluridine (38). Compound **37** (1.8 g, 5.3 mmol) was deprotected with a 1 M solution of tetra-*n*-butylammonium fluoride in THF (6.5 mL, 6.5 mmol). Chromatography of the crude product using $CHCl_3$–MeOH (25:0.5) yielded 1.05 g (88%) of **38**: mp 203–204 °C (MeOH); ^1H NMR (DMSO-d_6) δ 3.15 (3 H, s, NCH_3), 3.58 (2 H, dd, J = 3.5, 5.3 Hz, 5′-H), 4.79 (1 H, m, 4′-H), 4.93 (1 H, t, J = 5.3 Hz, OH), 5.71 (1 H, d, J = 8.3 Hz, 5-H), 5.92 (1 H, dt, J = 1.7, 2.6, 7.3 Hz, 2′-H), 6.37 (1 H, dt, J = 7.1, 2.1, and 2.1 Hz, 3′-H), 6.86 (1 H, quintet, J = 1.8, 1.9, 3.9 Hz, 1′-H), 7.78 (1 H, d, J = 8.1 Hz, 6-H); ^{13}C NMR (DMSO-d_6) δ 161.7 (C-4), 150.8 (C-2), 138.7 (C-6), 134.6, 125.2 (C-2′ and C-3′), 100.1 (C-5), 90.1, 87.1 (C-1′, C-4′), 62.1 (C-5′), 26.6 (CH_3).

Anal. Calcd for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.58; H, 5.39; N, 12.44.

5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-bis-*O*-[[(β-cyanoethyl)thio]thiocarbonyl]uridine (39a). 5′-*O*-(*tert*-Butyldimethylsilyl)uridine (0.5 g, 1.4 mmol) was reacted with CS_2 (1.5 mL) in DMSO (4 mL) in the presence of 5 N aqueous NaOH and alkylated with β-bromopropionitrile (3.9 mL). Purification of the crude product by chromatography using $CHCl_3$–MeOH (60:1) yielded 0.77 g (89.5%) of **39a**. The product could not be analyzed due to its instability: ^1H NMR (DMSO-d_6) δ ~0.0 (6 H, s, Me_2Si), 0.80 (9 H, s, Me_3CSi), 2.67–3.49 (8 H, m, CH_2CH_2CN), 3.82 (2 H, unresolved, 5′-H), 4.44 (1 H, d, J = 2.1 Hz, 4′-H), 5.62 (1 H, dd, J = 1.2, 8.2 Hz, 5-H), 5.93–6.22 (3 H, m, 1′-, 2′-, and 3′-H), 7.64 (1 H, d, J = 8.2 Hz, 6-H), 11.37 (1 H, d, J = 1.2 Hz, NH).

5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-bis-*O*-[[(β-cyanoethyl)thio]thiocarbonyl]-5-methyluridine (39b). 5-Methyluridine (1.42 g, 5.49 mmol) was silylated according to the procedure described for 5′-*O*-(*tert*-butyldimethylsilyl)adenosine. Chromatography of the crude product on a silica gel column using $CHCl_3$–MeOH (30:1) gave 1.49 g (73%) of 5′-*O*-(*tert*-butyldimethylsilyl)-5-methyluridine as a colorless solid: mp 209–211 °C (EtOAc); ^1H NMR (DMSO-d_6) δ ~0.0 (6 H, s, Me_2Si), 0.81 (9 H, s, Me_3CSI), 1.68 (3 H, s, 5-CH_3), 3.60–3.90 (5 H, m, 2′-, 3′-, 4′-, and 5′-H), 4.97 (1 H, d, J = 4.39 Hz, 3′-OH, exchangeable), 5.25 (1 H, d, J = 5.57 Hz, 2′-OH, exchangeable), 5.71 (1 H, d, J = 5.57 Hz, 1′-H), 7.32 (1 H, s, 6-H), 11.21 (1 H, s, NH, exchangeable).

Anal. Calcd for $C_{16}H_{28}N_2O_6Si$: C, 51.58; H, 7.57; N, 7.52. Found: C, 51.61; H, 7.59; N, 7.48.

5′-*O*-(*tert*-Butyldimethylsilyl)-5-methyluridine (0.372 g, 1.0 mmol) was reacted with CS_2 (2.5 g, 33.15 mmol) in the presence of 5 N aqueous NaOH (3.5 mL) in DMSO (3.5 mL) and alkylated with β-bromopropionitrile (4.0 g, 30.35 mmol). Purification by chromatography on a silica gel column using $CHCl_3$–MeOH (50:1) yielded 0.6 g (95%) of **39b** as a pale yellow glassy solid: IR (KBr) 2250 (C≡N), 1760–1650 cm^{-1}; (C=O); ^1H NMR δ 0.18 (6 H, s, Me_2Si), 0.97 (9 H, s, Me_3CSi), 1.94 (3 H, d, J = 1.17 Hz, 5-CH_3), 2.85 (4 H, t, J = 7.0 Hz, 2 × CH_2CN), 3.35 (2 H, t, J = 7.0 Hz, SCH_2), 3.45 (2 H, t, J = 7.0 Hz, SCH_2), 3.98 (2 H, m, 5′-H), 4.43 (1 H, d, J = 1.47 Hz, 4′-H), 5.98 (1 H, dd, J = 5.56, 7.62 Hz, 2′-H), 6.32 (1 H, dd, J = 1.47, 5.56 Hz, 3′-H), 6.52 (1 H, d, J = 7.62 Hz, 1′-H), 7.48 (1 H, d, J = 1.17 Hz, 6-H).

5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-*O*-thionocarbonyluridine (40a). 5′-*O*-(*tert*-Butyldimethylsilyl)uridine (1.59 g, 4.4 mmol) was stirred with 1,1′-thiocarbonyldiimidazole in DMF. Workup of the reaction mixture and chromatography using hexane–acetone (3:1) yielded 0.85 g (48%) of **40a**: mp 172–176 °C; UV (MeOH) λ_{max} (pH 3) 239, (pH 7) 240, (pH 11) 257, 232 nm (sh); ^1H NMR (DMSO-d_6) δ 0.03 (6 H, s, Me_2Si), 0.85 (9 H, s, Me_3CSi), 3.81 (2 H, d, J = 5.86 Hz, 5′-H), 4.30–4.50 (1 H, m, 4′-H), 5.48–5.68 (2 H, m, 2′- and 3′-H), 5.90–6.00 (2 H, m, 1′- and 5-H), 7.72 (1 H, d, J = 7.96 Hz, 6-H), 11.50 (1 H, s, NH).

Anal. Calcd for $C_{16}H_{24}N_2O_6SSi$: C, 47.98; H, 6.04; N, 6.99; S, 8.00. Found: C, 48.08; H, 6.08; N, 6.97; S, 8.04.

5′-*O*-(*tert*-Butyldimethylsilyl)-5-methyl-2′,3′-*O*-thionocarbonyluridine (40b). 5′-*O*-(*tert*-Butyldimethylsilyl)-5-methyluridine (0.372 g, 1.0 mmol) was stirred with 1,1′-thiocarbonyldiimidazole in THF. The solvent was removed under vacuum, and the residue was purified by flash chromatography using $CHCl_3$–MeOH (50:1) as the eluent to obtain 0.28 g (67%) of **40b** as a glassy material: ^1H NMR (DMSO-d_6) δ 0.075 (6 H, s, Me_2Si), 0.89 (9 H, s, Me_3CSi) 1.94 (3 H, s, 5-CH_3), 3.84 (2 H, d, J = 5.57 Hz, 5′-H), 4.40 (1 H, m, 4′-H), 5.50 (1 H, m, 2′-H), 5.70 (2 H, m, 1′- and 3′-H), 7.11 (1 H, s, 6-H), 9.19 (1 H, s, NH exchangeable).

Anal. Calcd for $C_{17}H_{26}N_2O_6SSi$: C, 49.25; H, 6.32; N, 6.75; S, 7.73. Found: C, 49.07; H, 6.37; N, 6.71; S, 7.65.

5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-didehydro-2′,3′-dideoxyuridine (41a). Method A. From 2′,3′-*O*-Bis(dithiocarbonate) 39a. Compound **39a** (0.50 g, 0.81 mmol) was converted to **41a** by treatment with tri-*n*-butyltin hydride and purified by column chromatography using benzene–EtOAc (13:7) to give 0.23 g (87%) of the product: mp 167–168 °C (Et_2O–hexanes); ^1H NMR (DMSO-d_6) δ ~0.0 (6 H, s, Me_2Si), 0.80 (9 H, s, Me_3CSi), 3.75 (2 H, d, J = 3.3 Hz, 5′-H), 4.78 (1 H, m, 4′-H), 5.48 (1 H, d, J = 8.1 Hz, 5-H), 5.90 (1 H, dt, J = 6.0, 1.7 Hz, 2′-H), 6.35 (1 H, dt, J = 5.8, 1.5 Hz, 3′-H), 6.77 (1 H, m, 1′-H), 7.60 (1 H, d, J = 8.1 Hz, 6-H), 11.3 (1 H, br s, NH).

Anal. Calcd for $C_{15}H_{24}N_2O_4Si$: C, 55.53; H, 7.45; N, 8.63. Found: C, 55.63; H, 7.48; N, 8.61.

Method B. From 2′,3′-*O*-Thionocarbonate 40a. Compound **40a** (0.345 g, 0.85 mmol) was converted to **41a** in 62% yield according to the procedure described for **21**.

5′-*O*-(*tert*-Butyldimethylsilyl)-5-methyl-2′,3′-didehydro-2′,3′-dideoxyuridine (41b). Method A. From 2′,3′-*O*-Bis(dithiocarbonate) 39b. Compound **39b** (0.6 g, 0.95 mmol) was treated with tri-*n*-butyltin hydride in the presence of azobisisobutyronitrile in toluene at 90 °C. The solvent was evaporated, and the residue was partitioned between acetonitrile and hexane. Evaporation of acetonitrile and purification of the residue by chromatography using $CHCl_3$–MeOH (30:1) yielded 0.208 g (65%) of **41b** as a colorless powder: mp 169–171 °C; UV (MeOH) λ_{max} 265 nm; ^1H NMR (DMSO-d_6) δ 0.08 (6 H, s, Me_2Si), 0.90 (9 H, s, Me_3CSi), 1.90 (3 H, d, J = 1.17 Hz, 5-CH_3), 3.85 (2 H, d, J = 3.8 Hz, 5′-H), 4.82 (1 H, m, 4′-H), 5.80 (1 H, br d, J = 6.2 Hz, 2′-H), 6.25 (1 H, br d, J = 6.2 H, 3′-H), 6.95 (1 H, m, 1′-H), 7.33 (1 H, d, J = 1.17 Hz, 6-H), 8.53 (1 H, br s, NH, exchangeable).

Anal. Calcd for $C_{16}H_{26}N_2O_4Si$: C, 56.73; H, 7.74; N, 8.27. Found: C, 56.69; H, 7.82; N, 8.23.

Method B. From 2′,3′-*O*-Thionocarbonate 40b. A solution of **40b** (55 mg, 0.15 mmol) and 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine (0.4 mL) in THF (2 mL) was stirred for 24 h. The solvent was removed under reduced pressure, and the residue was purified by chromatography using $CHCl_3$–MeOH (50:1) as the eluent to obtain 24 mg (52%) of **41b**.

2′,3′-Didehydro-2′,3′-dideoxyuridine (42). Compound **41a** (0.38 g, 1.17 mmol) was deprotected with a 1 M solution of tetra-*n*-butylammonium fluoride (1.5 mL, 1.5 mmol). The solvent was evaporated, and the residue was purified by chromatography on a silica gel column using $CHCl_3$–MeOH (20:1) to obtain 0.164 g (67%) of **42**: mp 153–155 °C (MeOH) (lit.[13] mp 155–156 °C); ^{13}C NMR (DMSO-d_6) δ 162.7 (C-4), 150.4 (C-2), 140.3 (C-6), 134.6, 125.2 (C-2′ and C-3′), 101.1 (C-5), 89.1 (C-1′), 87.0 (C-4′), 62.2 (C-5′).

2′,3′-Didehydro-2′,3′-dideoxy-5-methyluridine (5). A solution of **41b** (80 mg, 0.23 mmol) was converted to **5** by the procedure described above and purified by chromatography using $CHCl_3$–MeOH (30:1) as the eluent to obtain 41 mg (80%) of **5** as a colorless solid: mp 164 °C (lit.[6] mp 165–166 °C); ^1H NMR (DMSO-d_6) δ 1.90 (3 H, d, J = 1.17 Hz, 5-CH_3), 3.62 (2 H, dd, J = 3.52, 4.98 Hz, 5′-H), 4.75 (1 H, m, 4′-H), 4.95 (1 H, t, J = 4.98 Hz, 5′-OH, exchangeable), 5.85 (1 H, br d, J = 6.2 Hz, 2′-H), 6.40 (1 H, br d, J = 6.2 Hz, 3′-H), 6.80 (1 H, m, 1′-H), 7.62 (1 H, d, J = 1.17 Hz, 6-H), 11.25 (1 H, s, NH, exchangeable).

X-ray Crystallography. 2′,3′-Dideoxyadenosine (10). Crystals were obtained by slow evaporation of an aqueous acetone solution of 2′,3′-dideoxyadenosine (**10**). A crystal with approximate dimensions of 0.2 × 0.2 × 0.3 mm was used for the data collection on a Nicolet P3 diffractometer using Ni-filtered Cu Kα radiation (λ = 1.5418 Å). The crystal was cooled to 165 (2) K by means of a forced nitrogen stream. The space group is $P2_12_12_1$, and the cell dimensions are a = 9.959 (1) Å, b = 14.028 (1) Å, c = 7.666 (1) Å, V = 1070.95 Å^3, Z = 4, M_r = 235, D_{calcd} = 1.46 g cm^{-1}. Total data (876) with 4° < 2θ < 115° were measured. The structure was determined by direct methods, using the program MULTAN,[32] and refined by full-matrix least squares. All hydrogen atoms except the one bonded to the C-5′ atom were located in difference maps and refined. Final R values are R_w = 0.059, R_{unw} = 0.043 for the 873 observed data [$F > 3\sigma(F)$] and R_{all} = 0.043 for all 876 data. The final difference electron density map showed no features greater than 0.64 e Å^{-3}. Other programs used include data reduction program package DREAM.[33]

2′,3′-Didehydro-2′,3′-dideoxyadenosine (7). Crystals were obtained by slow evaporation of an acetone solution of **7**. The crystal used had approximate dimensions of 0.1 × 0.25 × 0.55 mm. The space group is $P2_12_12_1$, and the cell dimensions are a = 10.035 (2) Å, b = 13.866 (4) Å, c = 7.828 (2) Å, V = 1089.27 Å^3, Z = 4, M_r = 233, D_{calcd} = 1.42 g cm^{-1}. Data were measured at room temperature on an Enraf-Nonius CAD4 diffractometer, using Ni-filtered Cu Kα radiation. Unique data (1322) in the range 3.0° < 2θ < 154° were measured. The structure was determined by direct methods, using the program MULTAN,[32] and refined with full-matrix least squares. All non-hydrogen atoms were refined with anisotropic thermal parameters. All hydrogen atoms were located in difference maps and were refined. Final R values are R_w = 0.057, R_{unw} = 0.043 for the 1305 observed data [$F > 3\sigma(F)$] and R_{all} = 0.043 for all 1322 data. The final difference electron density map showed no features greater than 0.42 e Å^{-3}.

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Supplementary Material Available: Anisotropic thermal parameters, hydrogen atom coordinates, bond lengths, and bond angles for 2′,3′-dideoxy- and 2′,3′-didehydro-2′,3′-dideoxyadenosine and ORTEP stereodiagram showing 2′,3′-dideoxy- and 2′,3′-didehydro-2′,3′-dideoxyadenosine superimposed by least-squares fitting of the atoms of the bases (6 pages). Ordering information is given on any current masthead page.

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Asymmetric Total Synthesis of (+)-Negamycin and (−)-3-Epinegamycin via Enantioselective 1,3-Dipolar Cycloaddition

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Enantioselective total synthesis of (+)-negamycin [(+)-**1**] and (−)-3-epinegamycin [(−)-**2**] has been achieved by the introduction of asymmetry through 1,3-dipolar cycloaddition with chiral nitrones modified with carbohydrates. For the model study, the *trans*-isoxazolidine-3-carboxylate (±)-**6a**, obtained by 1,3-dipolar cycloaddition of the nitrone **4** with *N*-(benzyloxycarbonyl)allylamine (**5**), was converted into the hydrazide (±)-**13** via six steps, catalytic hydrogenation of which resulted in deprotection and N–O bond cleavage at the same time, affording (±)-negamycin [(±)-**1**]. This sequence was next applied to the synthesis of (+)-negamycin. Thus the enantioselective 1,3-dipolar cycloaddition of nitrones modified with carbohydrates, such as D- and L-gulose, D-ribose, and D-mannose derivatives, with **5** was investigated. Among these nitrones the gulosyl series proved to produce the best results. The trans adduct D-**19a** with 94% ee thus obtained by using *N*-D-gulosylnitrone D-**18** was converted into (+)-negamycin [(+)-**1**] by hydrolytic removal of the chiral auxiliary followed by a similar sequence for the synthesis of (±)-**1**. Similarly, the cis adduct D-**19b** with 94% ee obtained by cycloaddition with the D-gulosylnitrone D-**18** was transformed into (−)-**3**-epinegamycin [(−)-**2**]. With synthetic (+)-**1** and (−)-**2** in hand, antibacterial activity was examined.

(+)-Negamycin is a rare and unusual peptidelike antibiotic containing a hydrazide moiety, first isolated in 1970 by Umezawa et al. from *Streptomyces purpeofuscus*[1] and characterized to be [2-[(3*R*,5*R*)-3,6-diamino-5-hydroxyhexanoyl]-1-methylhydrazino]acetic acid [(+)-**1**] in 1971.[2] (+)-Negamycin inhibits growth of Gram-negative and Gram-positive bacteria and is especially notable among antibiotics with regard to low toxicity and its activity

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