PCH_3), 1.12 (3 H, s, CH_3), 0.89 (9 H, s, $C(CH_3)_3$), 0.11 (6 H, s, $Si(CH_3)_2$); ^{31}P NMR ($(CD_3)_2SO$) 33.11.

Deprotection of the Methylphosphonates. Compounds **15a–17a** or **15b–17b** (50 mg) were dissolved in THF (5 mL). Bu_4NF (5 mL, 1 M in THF) was added, and the solution was stirred (rt, 30 min). Upon evaporation the residue was dissolved in CH_2Cl_2 (20 mL) and extracted with water. The organic layer was dried, the solvent was evaporated, and the residue was dissolved in 80% aqueous AcOH (rt, 10 min). The acid was removed under reduced pressure, and the residue was partitioned between water (25 mL) and CH_2Cl_2 (25 mL). The aqueous phase was evaporated; the residue was dissolved in 25% aqueous NH_3 (40 mL) and stored (3 h; 50 °C water bath). After evaporation compounds **18a–20a** and **18b–20b** were purified on TLC cellulose plates (solvent D). The main zones containing the methylphosphonates were pooled, dissolved in MeOH, and filtered. The filtrate was evaporated affording **18a–20a** and **18b–20b** as glassy solids (40 and 50% yield). Compounds **18a,b**, **19a,b**, and **20a,b** were identified by comparing their ^1H NMR spectra with those already published[3,26,27] and mobilities on HPLC (**20a,b**).[29]

(R_P)-Adenoylyl-(3′→5′)-2′-deoxyadenosine Methylphosphonate (18a):[3,26,27] ^1H NMR (D_2O) δ 8.21, 8.01, 7.97, 7.81 (4 H, 4 s, 8-H and 2-H), 6.26, 6.07 (2 H, 2 pt, 1′-H), 1.67 (3 H, d, J = 17.6 Hz, PCH_3); ^{31}P NMR (D_2O) δ 36.49.

(S_P)-Adenoylyl-(3′→5′)-2′-deoxyadenosine Methylphosphonate (18b):[3,26,27] ^1H NMR (D_2O) δ 8.20, 8.00, 8.95, 7.79 (4 H, 4 s, 8-H and 2-H), 6.25, 6.05 (2 H, 2 pt, 1′-H), 1.64 (3 H, d, J = 17.6 Hz, PCH_3); ^{31}P NMR (D_2O) δ 36.50.

(R_P)-Thymidylyl-(3′→5′)-2′-deoxyadenosine Methylphosphonate (19a):[3,26] ^1H NMR (D_2O) δ 8.28, 8.08 (2 H, 2 s, 8-H and 2-H), 7.30 (1 H, s, 6-H), 6.36, 5.95 (2 H, 2 pt, 1′-H), 1.57 (3 H, d, J = 17.5 Hz, PCH_3).

(S_P)-Thymidylyl-(3′→5′)-2′-deoxyadenosine Methylphosphonate (19b):[3,26] ^1H NMR (D_2O) δ 8.29, 8.08 (2 H, 2 s, 8-H and 2-H), 7.29 (1 H, s, 6-H), 6.35, 5.95 (2 H, 2 pt, 1′-H), 1.58 (2 H, d, J = 17.4 Hz, PCH_3).

General Procedure for Sulfurization of the H-Phosphonates and Deprotection. Method a. The H-phosphonates **7a,b**, **10a,b**, **11a,b** (0.1 mmol, each) were dissolved in dry pyridine (5 mL). *N,O*-Bis(trimethylsilyl)acetamide (1 mL, 5 mmol) and $(Et)_3N$ (0.5 mL) were added, and the solution was stirred at rt for 15 min. Sulfur (200 mg, 6.25 mmol) was added, and the mixture was stirred for another 4 h. Upon filtration the solution was evaporated, and the residue was dissolved in EtOAc and extracted with water. The organic layer was dried and evaporated. FC (silica gel 60 H, solvent E) afforded colorless amorphous **12a,b–14a,b**, which were deprotected as described for the methylphosphonates.

Method b. The H-phosphonates (0.1 mmol) were dissolved in pyridine/CS_2 (1:1, 5 mL). After addition of sulfur (50 mg, 1.5 mmol) the mixture was stirred at rt for 4 h. The solvent was evaporated; the residue was dissolved in EtOAc and extracted with water. The organic phase was dried and deprotected as described for the methylphosphonates. Compounds **27a–29a** and **27b–29b** were identified by their mobilities on HPLC (UV detection at 260 nm).[43] Retention times in solvent system I; t_R(**27b**) = 11.0 min; t_R(**27a**) = 11.7 min; t_R(**28b**) = 12.0 min; t_R(**28a**) = 12.5 min; t_R(**29b**) = 12.4 min; t_R(**29a**) = 13.0 min.

Nuclease P1 Hydrolyses on the Phosphorothioates 21a,-b–23a,b. The deprotected phosphorothioates (25 μmol each) were dissolved in a mixture of NH_4SO_4 (30 mmol, pH 5.3, 0.38 mL) and $ZnSO_4$ (10 mmol, 0.02 mL). Nuclease P1 (100 units) was added. This mixture was stored at 37 °C; samples were taken every 4 h and applied to reversed-phase HPLC (5–25% MeCN, 20 min, 260 nm). Compounds **21b–23b** were resistant to hydrolysis within 40 h. The hydrolyses of **21a–23a** gave two products. **21a**: t_R = 6.7 and 8.5 min. **22a**: t_R = 5.5 and 8.2 min. **23a**: t_R = 4.4 and 6.0 min.

General Procedure for the Oxidation of the H-Phosphonates 7a,b, 10a,b with I_2/[^{18}O]H_2O/Pyridine. The H-phosphonates **7a**, **7b**, **10a**, or **10b** (0.57 mmol) were dried by coevaporation with pyridine and dissolved in pyridine (10 mL). After addition of I_2/[^{18}O]H_2O (215 mg, 0.85 mmol; 1 mL) dissolved in pyridine (5 mL) the mixture was stirred for 15 min at rt. Excess of iodine was reduced by extraction with 1% aqueous Na_2SO_3 solution. The organic phase was extracted with triethylammonium bicarbonate (TBC) buffer (200 mM), washed with water, and dried. The residue was dissolved in CH_2Cl_2 and purified by FC (silica gel 60H, solvent F). ^{18}O Chirally labeled **30a/b** or **31a/b** were deprotected as described for the methylphosphonates. Chromatographical purification was carried out on Sephadex A-25 (aqueous triethylammonium bicarbonate; 0–200 mM) to give the triethylammonium salts of (R_P/S_P)-[^{18}O]-2′-deoxyadenoylyl(3′→5′)-2′-deoxyadenosine (**32a/b**) or (R_P/S_P)-[^{18}O]-2′-deoxythymidylyl(3′→5′)-2′-deoxyadenosine (**33a/b**). For configurational analysis the **32a/b** mixture (10 μmol) was methylated as described for UpA[7] to give the methyl esters as a solution in $(CD_3)_2SO$: ^{31}P NMR ($(CD_3)_2SO$) δ 0.22, 0.20, 0.18, 0.17 ppm. The same reaction was carried out on **33a/b** (10 μmol): ^{31}P NMR ($(CD_3)_2SO$) δ 0.22, 0.20, 0.19, 0.17 ppm.

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Building Blocks for Oligonucleotide Analogues with Dimethylene Sulfide, Sulfoxide, and Sulfone Groups Replacing Phosphodiester Linkages

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Two routes are presented for the synthesis of 3′,5′-bishomodeoxyribonucleosides, building blocks needed to synthesize oligodeoxynucleotide analogues where the OPO_2O groups are replaced by CH_2SCH_2, CH_2SOCH_2, and $CH_2SO_2CH_2$ units. Two of these have been coupled to create an uncharged analogue of a dinucleotide. As isosteric, achiral, and nonionic analogues of natural oligonucleotides stable to both enzymatic and chemical hydrolysis, such molecules have potential application as probes in the laboratory, in studies of the role of individual genes in biological function, and as "antisense" oligonucleotide analogues for the treatment of diseases.

Oligonucleotides with a defined sequence can bind to complementary single-stranded oligonucleotides and disrupt their biological activity.[1] In recent years, it has become widely recognized that this specific interaction

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between "sense" and "antisense" oligonucleotides can be used to probe the role of specific mRNAs in complex biological processes and, more speculatively, to treat diseases involving the unwanted expression of genetic information.[2] As all viral infections, many cancers, most bacterial and parasitic maladies, and many other diseases are of this type, the excitement has been understandable.

However, natural oligonucleotides are easily degraded and cleared in vivo and do not readily pass across biological barriers. Therefore, getting antisense oligonucleotides to their targets (normally, but perhaps not always, intracellular[3]) is difficult. The preferred methods rely on either active or passive transfer of oligonucleotides through the membranes of cells in culture,[4,5] microinjection into single cells,[6] or the synthesis in the target cell of antisense RNA by the transcription of genes introduced by molecular biological methods.[7] While each of these approaches is promising, none has proven to be easily applicable in vivo.

Therefore, analogues of natural oligonucleotides with increased biological stability and membrane permeability have been sought. For example, oligonucleotides containing phosphorothioate groups appear to be more stable to nucleases than their natural counterparts. They display antiviral activity at high concentrations[8] although their mechanism of action remains uncertain.[9] Oligodeoxynucleotide analogues bearing bases in an α-configuration are also apparently more stable to biodegradation.[10]

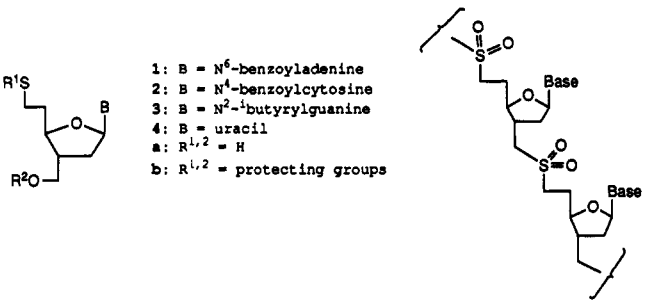

Figure 1. Building blocks for oligonucleotide analogues containing dimethylene sulfone linking groups in place of phosphodiesters found in natural DNA.

To increase membrane permeability, nonionic analogues of natural oligonucleotides have been prepared. These include linear, random polymers of vinyl nucleosides;[11] analogues of oligonucleotides where the phosphate linking group is replaced by carboxyl groups,[12] carbamate groups,[13] and diisopropylsilyl linkages;[14] and a variety of oligonucleotide analogues with modified phosphate linkages,[15] including those where one oxygen of the linking phosphate is replaced by a derivatized nitrogen or a methyl group.[16] The last, "methylphosphonates", show biological properties that may be representative of this group of analogues generally.[17] They appear to cross cell membranes[18] and inhibit the biological action of mRNA, although activity is observed only at concentrations higher than those expected on the basis of their presumed mechanism of action.[19]

This last fact may be understood in terms of the chemistry of these analogues. Methylphosphonates are sensitive to chemical hydrolysis under alkaline conditions, making their synthesis challenging. Further, methylphosphonates (and similar analogues) bear a new chiral center at phosphorus, creating diastereoisomerism that appears to influence the ability of the analogue to bind to natural oligonucleotides.[20] Although considerable effort is being invested in efforts to improve methods for preparing methylphosphonates,[21] there is at present no satisfactory synthetic method to control the chirality at phosphorus, and synthetic oligomethylphosphonates are complex mixtures of diastereomers. The very recent difficulties observed in preparing methylphosphate triester analogues of oligonucleotides may arise from similar chemical problems.[22] Finally, phosphate linkers where both oxygens are

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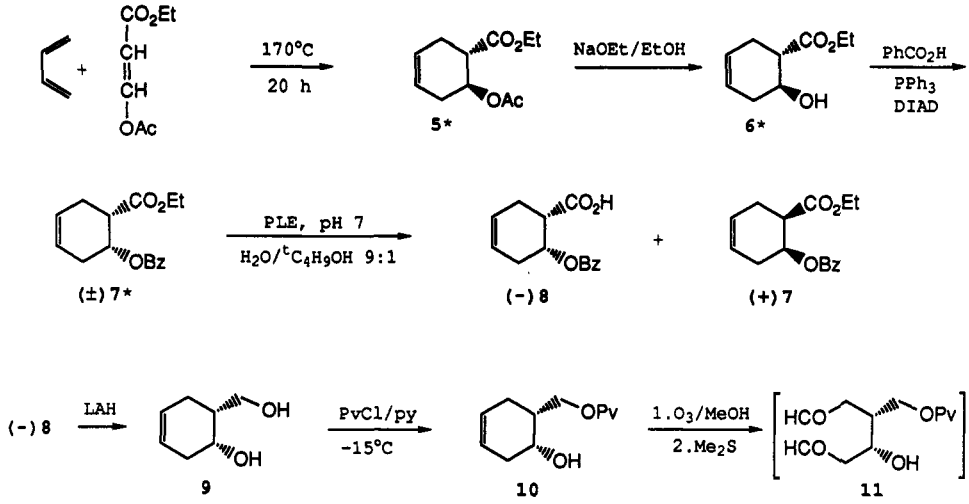
Scheme I[a]



[a] (*) = only one enantiomer shown.

replaced by sulfur (phosphorodithioates) have shown promise as antisense analogues. However, the high reactivity of these molecules is well-known,[23] and it is possible that this reactivity would not confer toxicity on the analogues when placed in a living system.

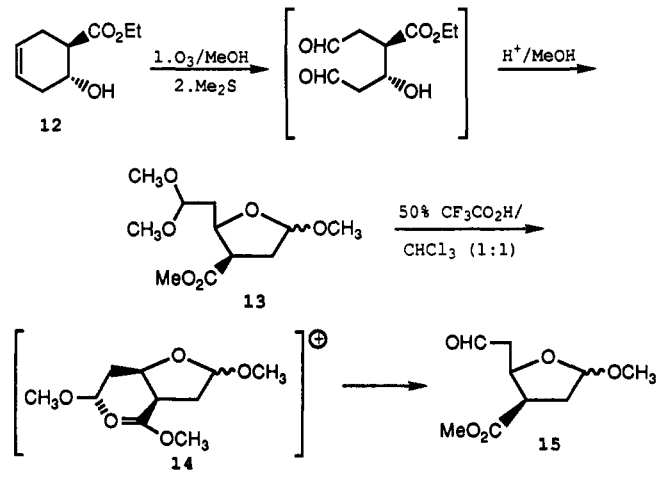
Some time ago we reported that sulfones (such as dimethyl sulfone and sulfolane) as cosolvents can assist the penetration of natural oligonucleotides into cells.[24] This observation suggested to us that incorporating the sulfone moiety directly into an oligonucleotide by replacing the phosphodiester (OPO_2O) groups by sulfone groups ($CH_2SO_2CH_2$) might yield an especially attractive oligonucleotide analogue capable of penetrating cell membranes without cosolvents. Further, sulfones are nonionic, achiral, isosteric analogues of phosphate diesters that are stable to both chemical and biochemical hydrolysis, making them ideal analogues for phosphodiesters on other grounds.

We report here routes for the synthesis of analogues of nucleosides 1–4 (Figure 1), analogues bearing functionalization appropriate for their use as building blocks in the synthesis of oligonucleotide analogues having the phosphodiester groups replaced by sulfide, sulfoxide, or sulfone units (Figure 1). The building blocks are prepared in their protected forms (**1b–4b**), as these derivatives are more stable than the corresponding unprotected ones. Conversion of the protected to unprotected forms immediately prior to coupling is achieved by standard procedures.[25] We also report the synthesis of a dinucleotide analogue from these building blocks. A preliminary report of a part of this work has appeared.[26]

Results

Route 1: Bishomodeoxyribonucleosides. In the first route (Scheme I), the carbon skeleton arises from a Diels–Alder reaction, optical activity is introduced by an enzymatic resolution, and the α- and β-anomers of the nucleoside analogues are separated chromatographically.

Scheme II[a]



[a] Only one enantiomer shown.

Cyclohexene derivative **5**, obtained via a Diels–Alder reaction between ethyl β-acetoxyacrylate and butadiene,[27] was converted to the alcohol **6** with NaOEt in ethanol at room temperature. **6** was then converted to the *cis*-benzoate **7** by using benzoic acid, diisopropyl azodicarboxylate (DIAD), and triphenylphosphine (PPh_3)[28] (45% for two steps).

The product **7** was then resolved by an enzymatic hydrolysis. Pig liver esterase (PLE) hydrolyzes selectively the *pro-R* ester of *meso*-dimethyl tetrahydrophthalate[29] with an enantiomeric excess (ee) of >99%. As the structure of **7** is similar to that of dimethyl tetrahydrophthalate, and as PLE has low substrate specificity,[30] the resolution of the racemic (±)-**7** into its antipodes was attempted by using this enzyme.

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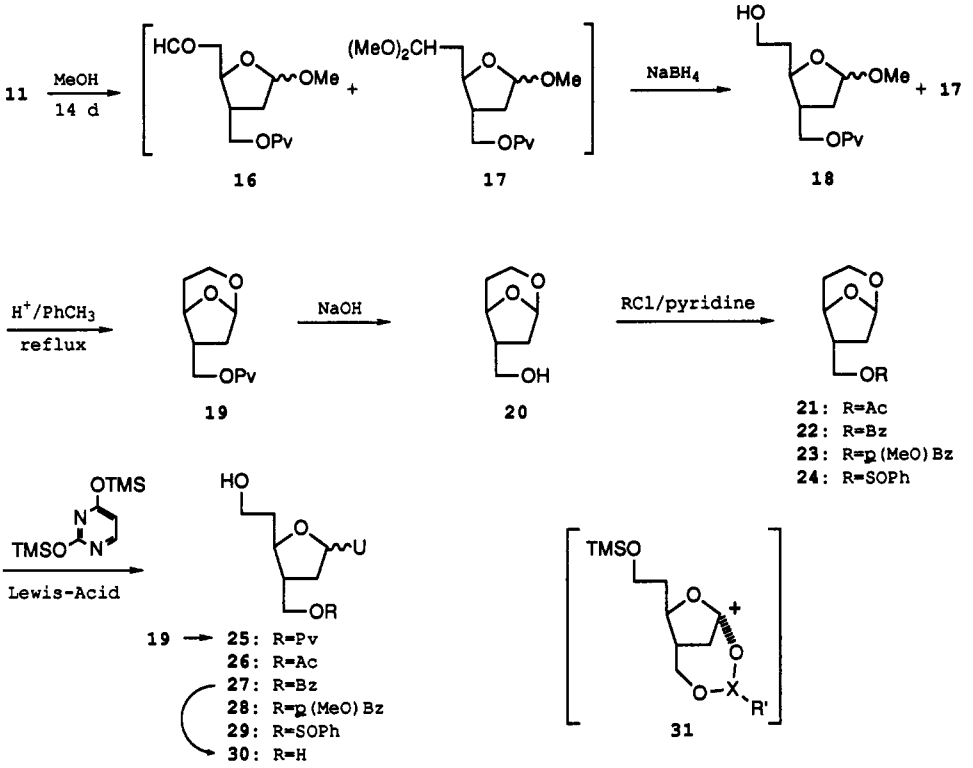
Scheme III



In water at pH 7 (maintained by automatic titration with dilute NaOH), PLE gave (−)-8 with an enantiomeric excess (ee) of 67.5% after 40 mol % of hydroxide had been added. In mixtures of water and *tert*-butyl alcohol (9:1),[31] the acid obtained after addition of 45 mol % sodium hydroxide was enantiomerically pure, as determined by gas chromatographic (GC) analysis of the *l*-isoborneol ester of 8 and by NMR analysis of the methyl ester of 8 (from esterification of 8 with diazomethane) in the presence of the chiral shift reagent Eu(hfc)$_3$ (hfc = [(heptafluoropropyl)hydroxymethylene]-*d*-camphorato). The remaining mixture of (+)-7 and (−)-7 (ca. 10:1, respectively) could then be subjected again to PLE-catalyzed hydrolysis to yield enantiomerically pure (+)-7, as determined by NMR in the presence of Eu(hfc)$_3$. The absolute configuration of (−)-7 was assigned by direct correlation to glucose (vide infra).

(−)-8 was then reduced with $LiAlH_4$ in tetrahydrofuran (THF) to the crystalline diol 9 in 86% yield. 9 was selectively protected with pivaloyl chloride (PvCl) in pyridine at −15 °C to furnish 10 in 96% yield, which was ozonized in methanol at −78 °C, followed by a reductive workup with dimethyl sulfide to yield dialdehyde 11. Compound 11 was not isolated, but was used directly for the next step.

In a model reaction (Scheme II), 12 was ozonized in methanol, treated with dimethylsulfide, and then treated with acidic cation-exchange resin to give 13 in 90% yield. The 6-dimethyl acetal could be selectively deprotected by treatment with 50% trifluoroacetic acid in chloroform to yield the aldehyde 15 in 85% yield.[32] Remarkably, this sequence of reactions applied to 10 failed to yield any of the analogous products (Scheme III). When harsher conditions were applied, several unidentified products were formed. The difference in reactivity of the two isomers presumably arises from participation of the carboxylate group via a six-membered ring (14) during hydrolysis of 13.

Thus, the possibility of selectively protecting one of the aldehyde functionalities in 11 was investigated. After a series of experiments using a variety of acidic catalysts, it was found that diacetal 17 and monoacetal 16 (in an approximately 1:3 ratio) could be obtained from 11 simply by stirring the crude ozonolysis product in methanol in the dark for 14 days. Presumably traces of acid that formed during ozonolysis catalyze this selective acetalization. The crude reaction mixture could be reduced with $NaBH_4$ to furnish 18 in 63% overall yield. To obtain an intermediate suitable for introduction of a base, the 6-hydroxyl group of 18 was internally protected by acid-catalyzed cyclization of 18 to 19 in refluxing toluene (85%). The somewhat strained bicyclic system thus formed is thought to make the introduction of the base more facile, since the formation of the C-1 carbocation[33] should be fast compared with its formation from a methyl furanoside.

Glycosidation reactions to introduce nucleoside bases are generally performed by the Hilbert–Johnson reaction,[34] modified by Wittenberg[35] to use the silyl group and by Vorbrüggen[36] to use Friedel–Crafts catalysts. In the case of peracylated ribose derivatives, it is well-known that the presence of a 2′-acyl group stabilizes the intermediate C-1 carbocation from the α-face, thereby rendering the reaction that attaches the base stereospecific for the β-anomer. We initially hoped that the 3′-pivaloyl group might similarly influence the stereochemical outcome of the reaction in favor of the β-anomer, as the additional carbon atom in

(31) The use of organic solvents and cosolvents with esterases is well documented. See, for example: Cambou, B.; Klibanov, A. M. *J. Am. Chem. Soc.* **1984**, *106*, 2687–2692. Jones, J. B.; Mehes, M. M. *Can. J. Chem.* **1979**, *57*, 2245–2248.

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(35) Wittenburg, E. *Chem. Ber.* **1968**, *101*, 1095–1114.

(36) Niedballa, U.; Vorbrüggen, H. *J. Org. Chem.* **1974**, *39*, 3654–3660. Niedballa, U.; Vorbrüggen, H. *J. Org. Chem.* **1974**, *39*, 3660–3663. Niedballa, U.; Vorbrüggen, H. *J. Org. Chem.* **1976**, *41*, 2084–2086.

the 3′-position could conceivably allow a Lewis basic group attached to the 3′-position to protect the α-face of the intermediate C-1 carbocation (31). Unfortunately, treatment of 19 with bis(trimethylsilyl)uracil with a variety of Lewis acids in dichloroethane or acetonitrile led consistently to a 1:1 mixture of anomers of 25 (Scheme III).

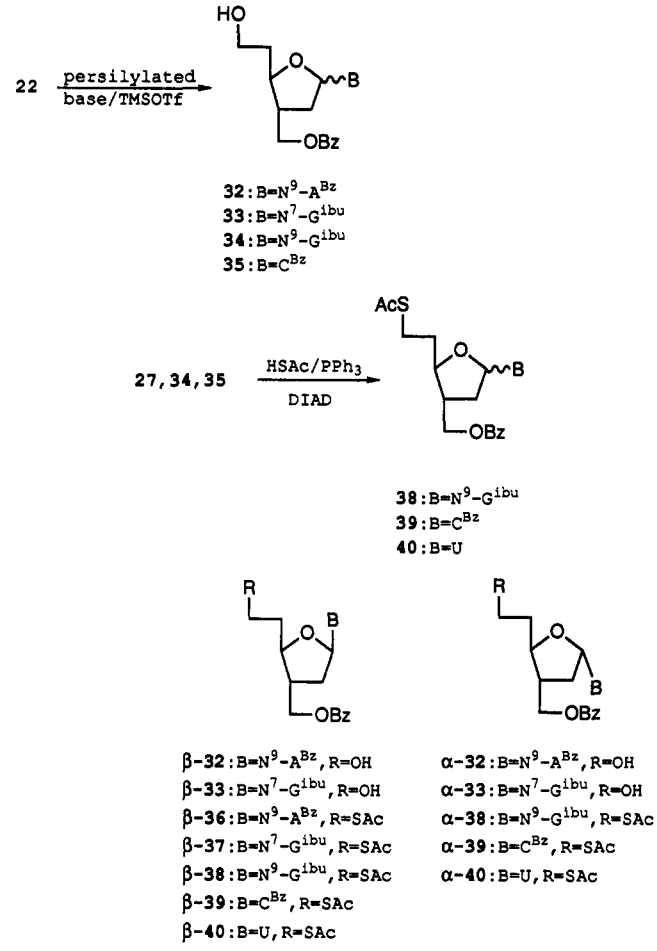
As the steric bulk of the pivaloyl group in 19 might have prevented its participation in the reaction at C-1, derivatives 21–25, listed in the order of increasing basicity, were examined. These were synthesized by reaction of the corresponding acid chlorides with alcohol 20 in pyridine. The stereochemical course of the reaction of these derivatives with bis(trimethylsilyl)uracil was investigated by using both $SnCl_4$ and trimethylsilyl trifluoromethanesulfonate (TMSOTf) as catalysts and both dichloroethane and acetonitrile as solvents. While no stereoselectivity for one of the anomers of 25–28 was observed for reactions with the acyl derivatives 19 and 21–23, sulfinate 24 reacted with silylated uracil in acetonitrile with TMSOTf as catalyst to afforded in moderate yield (45%) a 1.3:1 mixture of anomers of nucleoside 29, analyzed by GC following hydrolysis with sodium hydroxide to the alcohol 30 and pertrimethylsilylation with *N*-methyl-*N*-(trimethylsilyl)-trifluoroacetamide (MSTFA). Although the β-anomer was presumably the predominant product, the moderate stereoselectivity proved on a routine basis to be inadequate to justify the additional synthetic effort.

A final approach toward a stereoselective nucleosidation reaction relied on an S_N2 displacement of a furanosyl derivative possessing an α-leaving group. It has been reported that the chloride in 3′-deoxy chloro ribosides can be stereoselectively displaced by an S_N2 reaction by bis-(trimethylsilyl)uracil.[37] The highest selectivities are obtained when the reaction is carried out in chloroform, since the rate of S_N2 displacement is high relative to the rate of anomerization of the chloride in this solvent. Further, the C-1 acetate groups of ribosides can be displaced by iodine through the action of trimethylsilyl iodide.[38] This suggested that if it were possible to react 22 stereoselectively with trimethylsilyl iodide to give the corresponding α-iodide, and if this compound did not anomerize under the reaction conditions, a second displacement of the iodide should give the β-anomer of uridine analogue 27. Following this scheme, a mixture of 22 and silylated uracil in chloroform was treated at 0 °C with 0.5 equiv of trimethylsilyl iodide. The readily formed uridine analogue again was a 1:1 mixture of anomers of 27.

On the basis of these results, the decision was made to separate the mixture of anomers chromatographically. While a simple silica gel column did not produce base-line separation with a variety of solvent systems for any of the anomeric mixtures examined, saturation of the organic eluants with water made it possible to achieve base-line separation via high-performance liquid chromatography (HPLC) for at least one derivative of each of the analogues, even for relatively large amounts (up to 100 mg/injection on a 30 × 250 mm silica gel column).

Since a specific 3′-acyl derivative was not needed to control anomeric specificity, a 3′ protecting group could be chosen to allow selective deprotection of the 3′-oxygen of the target molecules in the presence of the amide-protected bases. The benzoate 22 is optimal in respect to stability and was therefore used.

Scheme IV



The four bases, N^6-benzoyladenine (A^{Bz}), N^4-benzoylcytosine (C^{Bz}), N^2-isobutyrylguanine (G^{ibu}), and uracil (U) were incorporated into 22 by the silyl–Hilbert–Johnson reaction (Scheme IV). Yields for all four nucleoside analogues were optimized by using dichloroethane and acetonitrile as solvent and varying amounts of $SnCl_4$ and TMSOTf as catalysts at different temperatures. Vorbrüggen recommends that silyl–Hilbert–Johnson reactions involving attachment of adenine or guanine to 2-*O*-benzoylated ribose derivatives be performed at approximately 80 °C. At this temperature, a thermodynamic mixture of N^7- and N^9-substituted purines forms in which the N^9 isomer is strongly favored. Unfortunately, when higher reaction temperatures were used in the reaction between 22 and silylated bases, low yields of products were obtained due to decomposition. Therefore, the ratio of products obtained at lower temperatures under primarily kinetic conditions had to be accepted.

In all cases the nucleosidations were faster and cleaner if acetonitrile, rather than dichloroethane, was used as solvent. In general, higher yields were obtained if TMSOTf was used instead of $SnCl_4$ as the catalyst. In the case of uracil and adenine, catalytic amounts of TMSOTf were sufficient to ensure completion of the reaction within hours, whereas cytosine and guanine required a molar excess of TMSOTf, presumably because the base and the Lewis acid form a complex.[39]

Different methods for the silylation of the bases were also investigated. Best results were obtained if distilled

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Table I. Selected ^1H and ^{13}C NMR Data for Purine Nucleosides[a]

product	C-2	C-4	C-5	C-6	C-8	C-1′	H-1′	H-8
α-38 ($CDCl_3$)	147.5	155.7	122.3	147.7	138.5	85.	46.11	7.73
β-38 ($CDCl_3$)	147.7	155.8	121.8	147.8	137.6	84.7	6.05	7.80
β-37 ($CDCl_3$)	148.1	158.0	111.1	153.1	140.7	87.3	6.53	8.09
41G (DMSO)	153.0	160.7	107.7	154.5	142.5	89.2	5.75	8.06
42G (DMSO)	153.7	151.4	116.7	156.8	135.7	86.4	5.69	7.94
β-36 ($CDCl_3$)	152.5	149.6	123.9	151.2	141.5	85.2		
47 (DMSO)	152.8	160.7	110.2	151.7	144.6	89.4		
42 (DMSO)	152.6	149.2	119.5	156.3	140.2	88.2		

[a] All signals are reported in parts per million relative to tetramethylsilane.

bis(trimethylsilyl)uracil was used; isobutyrylguanine was silylated in situ by using hexamethyldisilazane (HMDS) and trimethylsilyl chloride (TMSCl), and benzoyladenine and benzoylcytosine were silylated in situ by using the strong silylating agents *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide (MSTFA) or *N,O*-bis(trimethylsilyl)-acetamide (BSA). The adenine derivative **32**, which was obtained after treatment of the crude two-phase reaction mixture with excess potassium fluoride and a small amount of 18-crown-6 in 64% yield as a 1:1 mixture of anomers, could be resolved at this stage by silica gel high-performance liquid chromatography (HPLC). The faster moving compound was shown to be the desired β-anomer (vide infra). The isomerically pure β-**32** obtained in this fashion was treated under standard Mitsunobu conditions with HSAc, PPh_3, and diisopropyl azodicarboxylate (DIAD)[40] to furnish the protected nucleoside analogue β-**36** in 69% yield.

The reaction of bis(trimethylsilyl)isobutyrylguanine with **22**, followed by the same workup as for **32**, gave two products, which were separated by chromatography; these were a ca. 1:1 mixture of anomers of the N^7 isomer **33** and a ca. 1:1 mixture of the anomers of the N^9 isomer **34** (vide infra), in a ratio of ca. 1:2 (86% total yield). The anomers of the N^9 isomer could not be separated and were therefore converted to the thioacetate **38** (62%), which was then resolved into its components (α-**38** and β-38) via HPLC on silica gel.

The derivatives bearing benzoylcytosine (**35**) and uracil (**27**) were also both obtained as a mixture of anomers in 64% and 75% yield, respectively. Both compounds were converted to the corresponding thioacetates (**39** and **40**) by Mitsunobu reaction (87% and 78% yield, respectively) and separated by HPLC on silica gel.

Assignment of Structure. Three assignment problems were of concern: (a) the absolute configuration, (b) the configuration at the anomeric center, and (c) the sites of the attachment of the purine ring of guanine and adenine (e.g., N^7 or N^9).

Although the absolute configuration of the analogues could be inferred from assumptions regarding the absolute stereospecificity of the hydrolysis catalyzed by pig liver esterase (vide supra), this inference was not considered to be sufficiently certain, especially for molecules intended to be applied to biochemical and pharmacological problems. Therefore, the absolute configuration of these derivatives was proven by direct correlation with D-glucose via the synthesis of compound **22** from diacetone glucose (vide infra).

The N^7 and N^9 isomers of the purine nucleoside analogues were distinguished by their spectroscopic behaviors. Uniformly, in N-alkylated purines, the H-8 and H-1 proton signals and the C-4, C-8, and C-1′ carbon signals of the N^7 isomers are shifted downfield relative to the corresponding

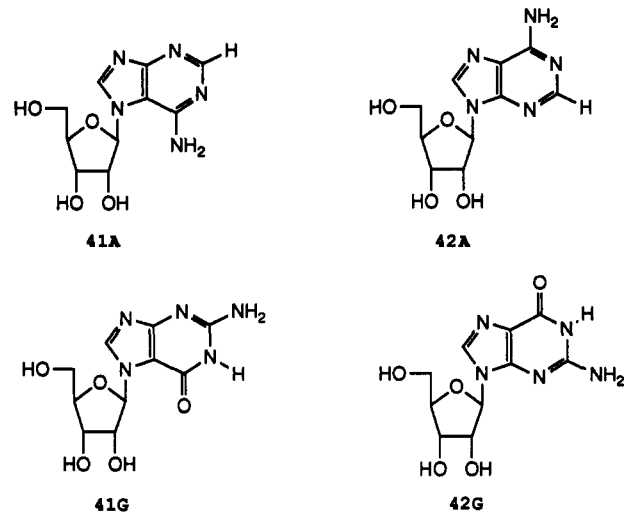

Figure 2. The N^7 and N^9 isomers of adenosine and guanosine.

resonances of the N^9 isomers, while the signal for C-5 of the N^7 isomer is more shielded relative to the signal of the N^9 isomer (Table I and Figure 2).[41-43] In the case of the analogues of guanosine nucleosides prepared here, the N^7 isomers **33** and the N^9 isomers **34** were isolated. To compare the spectra of these isomers in detail, the β-anomer of the N^7 isomer **33** was separated from its α-isomer by crystallization and converted to the thioacetate β-**37**. The H-8 and H-1′ proton signals and the C-4, C-8, and C-1′ carbon signals of the more mobile compound, assigned as the N^7 isomer β-**37**, are downfield, and the C-5 resonance is upfield relative to the corresponding resonances of its isomer β-**38**, assigned as the N^9 isomer.

The point of attachment of the furanose ring in adenosine analogue **32** could not be assigned by comparison of spectra of the N^7 and N^9 isomers, since none of the N^7 isomer was isolated. Instead the ^{13}C NMR spectrum of β-**36** was compared to the spectra of adenosine (**42**) and N^7-ribofuranosyladenine (**41**). The chemical shifts of the purine ^{13}C signals of β-**36** and adenosine are similar, but differ greatly from the chemical shifts reported for N^7-ribofuranosyladenine[44] (Table I). From these data it can be concluded that the adenine analogue prepared is functionalized on N^9.

The anomeric configurations of compounds **32** and **38–40** were assigned by nuclear Overhauser effect (NOE) difference spectroscopy. For the isomer of guanine derivative **38** assigned the β-structure, irradiation at H-1′ gave a significant enhancement of the H-4′ and H-2′α protons as well as the H-8 signal, whereas the isomer of **38** assigned

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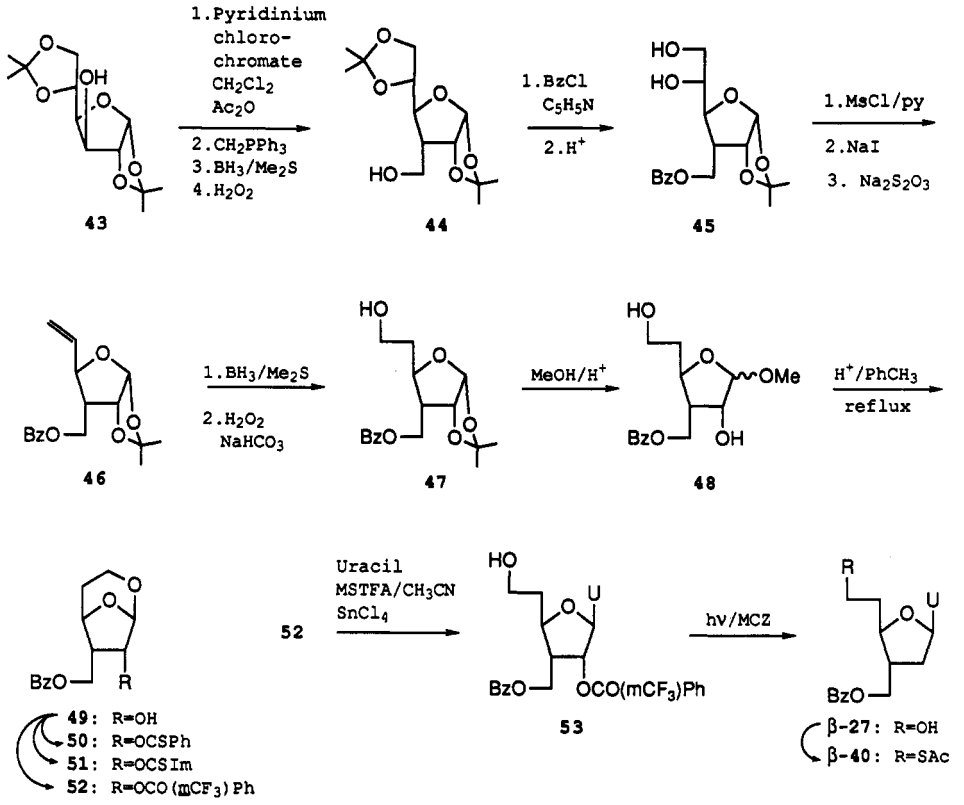
Scheme V



to be the α-anomer showed significant enhancement upon irradiation of H-1′ only at H-2′β and H-8. The anomeric configuration of the N^7 isomer **33** was tentatively assigned to be β according to the chemical shift of the H-4′ signal. It was found that, for all nucleoside analogues synthesized here, the H-4′ signal of the α-anomer is shifted downfield relative to the signal of the β-anomer, presumably because of the anisotropic effect of the bases in the α-position. The adenine analogue β-**32** shows NOE enhancements of the same signals as observed in the guanosine analogue β-**38**, which confirms the β-anomeric configuration.

The anomeric configurations of cytidine and uridine analogues **39** and **40**, respectively, were also assigned by NOE experiments involving irradiation at H-1′. Thus, in both cases the difference spectra of the β-anomers showed signals for H-4′ and H-2′α, whereas the α-anomers only showed signals for H-2′β. In the case of these two analogues, NOE enhancement upon irradiation of H-1′ is also found at H-6, which shows that the N^1 isomers were obtained.

Finally, the uridine analogue prepared by this route could also be correlated with the uridine analogue prepared from diacetone glucose, a route that gives the β-anomer due to neighboring-group participation (vide infra).

Route 2: Bishomoribouracil and Bishomodeoxyribouracil. The second route (Scheme V) begins with D-glucose and leads to bis-homo analogues of ribonucleosides with formation of the β-anomer as the sole product. **44** was synthesized from diacetone glucose (**43**) according to the procedure of Mazur et al.[45] Alcohol **44** was benzoylated with benzoyl chloride in pyridine, and the 5- and 6-oxygens were deprotected by stirring the crude product in a mixture of chloroform, methanol, and 1.6% sulfuric acid (6.3:2.1:1) for 3 days[45] to furnish **45** in 82% yield for the two steps.

To remove the 5-hydroxyl group via the Barton procedure,[46] the 6-hydroxyl group in **45** was initially protected with *tert*-butyldimethylsilyl chloride (TBDMSCl) in dimethylformamide (DMF),[47] the 5-hydroxyl group reacted with thiocarbonyldiimidazole in DMF[48] (85%), and the product reduced in 65% yield with tributyltin hydride and azoisobutyronitrile (AIBN).

The moderate yields and the high cost and toxicity of the reagents made an alternative deoxygenation route preferable for large-scale synthesis. In this alternative procedure, **45** was dimesylated with methanesulfonyl chloride and then, after simple aqueous workup, converted to olefin **46** with sodium iodide in refluxing ethyl methyl ketone.[49] Hydroboration of crude **46** with borane–dimethyl sulfide complex in THF for 24 h furnished **47** in 60% overall yield for the three steps.

Methanolysis of the acetonide group of **47** to form **48** was accomplished in refluxing methanol in the presence of Dowex acidic cation-exchange resin. Intramolecular protection of the 6-hydroxyl group and concomitant activation of the acetal function were achieved as before (vide supra) by ring closure in refluxing toluene in the presence of Dowex acidic cation-exchange resin (69% yield) to furnish **49**.

A substituent at the 2-oxygen was chosen which can direct the base introduction to the β-face of the molecule by neighboring-group participation and will facilitate subsequent 2′-deoxygenation.

Thiocarbonyl derivatives **50** and **51** were synthesized by following reported procedures, with the intention of using

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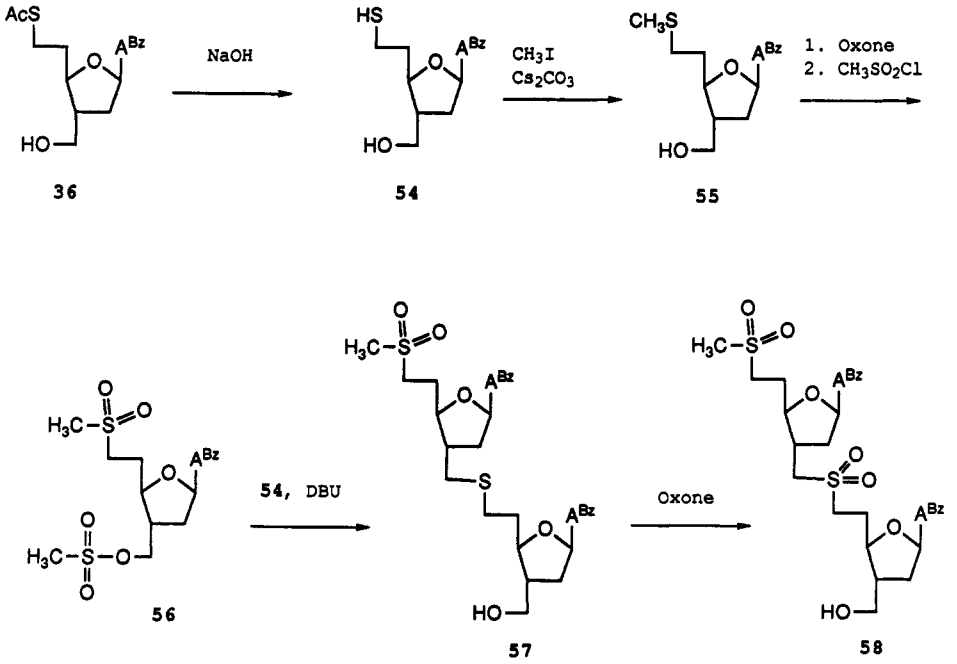
Scheme VI



the Barton reaction for deoxygenation.[50] Unfortunately, the thiocarbonyl group was unstable under the conditions used to introduce the base. Nevertheless, compound **50** was useful for assigning the absolute configuration of **22** synthesized by the first route, as it was readily deoxygenated with tributyltin hydride and AIBN in toluene to afford **22**. Both samples obtained had the same optical activity.

An alternative approach for deoxygenation involves the photochemical removal of a secondary [*m*-(trifluoromethyl)benzoyl]oxy group.[51] Thus, **49** was converted to *m*-(trifluoromethyl)benzoate **52** with *m*-(trifluoromethyl)benzoyl chloride in pyridine in the presence of a catalytic amount of (dimethylamino)pyridine (DMAP) (88% yield). **52** reacted smoothly with silylated uracil and $SnCl_4$ in acetonitrile to furnish nucleoside **53** in 98% yield. NMR analysis revealed that exclusively the β-anomer had formed. Deoxygenation of **53** to **β-27** was achieved in 85% yield by irradiating a 1 mM solution of **53** in a 2-propanol/water mixture (9:1, deoxygenated) with a 400-W high-pressure mercury lamp for 90 min in the presence of *N*-methylcarbazole (MCZ) as photosensitizer. **β-27** was finally converted to the thioacetate **β-40** under standard Mitsunobu conditions. The product of this reaction was identical with **β-40** synthesized from **22** as reported earlier, by NMR, IR, and MS. As the β-anomer is also expected on chemical grounds to be the exclusive product of the reaction, this result establishes the assignment above.

Analogous photochemical deoxygenation of the cytidine derivative proceeded with lower yield. Photochemical deoxygenation of the *N*-benzoyladenine derivative by an analogous route failed, apparently due to intramolecular trapping of the intermediate radical by the purine ring.

Synthesis of a Dimer. The synthesis from the building blocks discussed here of analogues of oligonucleotides where the OPO_2O groups are replaced by CH_2SCH_2, CH_2SOCH_2, and $CH_2SO_2CH_2$ units requires a detailed description elsewhere. However, it is appropriate to report here that coupling of analogues containing both purine and pyrimidine derivatives was facile when using a general procedure illustrated by the example below.

The 5′-thiol of **54** was capped (i.e., derivatized so that it can no longer participate in S_N2 reactions as a nucleophile) and the 3′-hydroxyl group activated for nucleophilic displacement by the thiol group of a second monomer (Scheme VI). Thus, **36** was deprotected to **54** and converted to the methyl sulfide **55** by reaction with methyl iodide (75% yield for two steps). Oxidation of the resulting sulfide with $KHSO_5$ (81% yield) and subsequent mesylation with mesyl chloride in pyridine furnished starting monomer **56** in 77% yield. Coupling of **56** to **54** occurred smoothly in the presence of 2 equiv of diazabicycloundecene (DBU) in dimethylformamide (DMF) to furnish thioether-linked dimer **57**, which could be oxidized in situ to the synthetic target, sulfone-linked dimer **58**, which was isolated in 70% yield.

Discussion

The protected uridine analogue building block **β-40** has been synthesized by two different routes. The second route is well precedented in many of its details and proceeds in higher overall yield, as it begins with optically pure starting material and little material is lost to the undesired β-anomer. However, the first route can be more useful for large-scale (10 g) synthesis of these building blocks, as the starting materials and reagents are inexpensive and the reactions are easier to run.

Analogues of all four deoxynucleoside bases have been prepared by the first route. Further, protected derivatives of analogues of the ribonucleosides of U, T, G, A, and C have been prepared by the second route. However, the photochemical deoxygenation via the route described by Saito et al.[51] of the analogues bearing adenosine, guanosine, and cytosine protected as amides (prepared by the second route) has been problematical in our hands; only photodeoxygenation of the uracil and unprotected adenine derivatives works satisfactorily at present. While efforts continue in this laboratory to develop this method, at present the second route is generally applicable for the preparation of analogues of ribonucleosides.

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Synthesis of building blocks **1b–4b** is the necessary first step for the preparation of analogues of oligonucleotides having CH_2SCH_2, CH_2SOCH_2, and $CH_2SO_2CH_2$ units replacing the OPO_2O groups in natural oligonucleotides. A dimer from these building blocks has been synthesized. Progress in this area, and the chemical properties of oligomers containing these linkages, will be reported separately.

Experimental Section

General Methods. ^{13}C NMR spectra were recorded by using attached proton test (APT) and distortionless enhancement by polarization transfer (DEPT) techniques for determination of carbon substitution; all δ values are in parts per million relative to tetramethylsilane. Preparative HPLC was performed on a Knauer HPLC column (30 × 250 mm, silica gel Nucleosil 7 μ, 10 mL/min flow, 50–55 atm pressure). Reactions were monitored by TLC on Merck 60 F254 precoated plates, and spots were visualized with UV light or by staining with a Ce–Mo staining reagent; for column chromatography Fluka silica gel 60, mesh size 0.040–0.063, was used. All solvents were Fluka p.a. and were used without purification, unless mentioned otherwise. THF and diethyl ether were distilled over sodium/benzophenone, and acetonitrile, dichloroethane, and pyridine were distilled over CaH_2. Reactions with air- or moisture-sensitive compounds were performed under argon atmosphere. The phase "dried and evaporated" indicates drying with magnesium sulfate, followed by evaporation of the solvents under house vacuum.

(±)-*trans*-6-Hydroxy-3-cyclohexene-1-carboxylic Acid Ethyl Ester (6). To a solution of crude 2-acetoxy-1-carbethoxycyclohex-4-ene[27] (**5**) (87.7 g, corresponding to 0.413 mol of pure material) in ethanol (1 L) was added NaH (5.9 g, 55% in oil) in small portions at room temperature. The clear brown reaction mixture was stirred for 30 min at room temperature and was then neutralized with acetic acid. Most of the solvent was evaporated under reduced pressure and the residue partitioned between water (200 mL) and CH_2Cl_2 (200 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL) and the organic phase dried and evaporated. Distillation at 95–100 °C (0.5 Torr) yielded 56.0 g of an oil containing 86% **6** (determined by GC/MS analysis) (0.283 mol, 68% yield). The material could be used for the next step without further purification. The yield of the same reaction carried out on a 1-g scale with pure starting material was 90%; ^1H NMR ($CDCl_3$) δ 1.28 (t, J = 7 Hz, 3 H, CH_3CH_2), 2.14–2.46 (m, 4 H, 5-H, 2-H), 2.57 (m, 1 H, 1-H), 3.03 (s, br, 1 H, OH), 4.08 (m, 1 H, 6-H), 4.19 (q, J = 7 Hz, 2 H, CH_3CH_2), 5.61 (m, 2 H, C=CH); IR (CCl_4) 2582, 2933, 1732, 1182, 1078 cm^{-1}; MS, m/e 170, 152, 125, 95, 88, 79, 67.

***cis*-6-(Benzoyloxy)-3-cyclohexene-1-carboxylic Acid Ethyl Ester [(±)-7].** To a solution of PPh_3 (153 g, 0.566 mol), benzoic acid (72.4 g, 0.593 mol), and **6** (48.1 g, 86% pure, corresponding to 0.283 mol of pure material) in THF (2.5 L) was added, at 0–3 °C, DIAD (110 mL, 0.54 mol) dropwise over a period of 1 h. The reaction mixture was stirred for 1 h at 0 °C and was then poured into saturated Na_2CO_3 (500 mL). After separation of the aqueous phase, the mixture was dried and evaporated to a volume of ca. 700 mL. Ether (1 L) was added, and the $POPh_3$ crystallized at 0 °C overnight and was then removed by filtration. The solvents were evaporated, and the residue was resolved chromatographically (silica gel, hexane/ethyl acetate, 8:2, R_f 0.30). The yield of (±)-**7** as a colorless oil was 50.3 g (0.183 mol, 65% corresponding to pure **6**): ^1H NMR ($CDCl_3$) δ 1.17 (t, J = 7 Hz, 3 H, CH_3CH_2), 2.20–2.70 (m, 5 H, 2-H, 5-H, 1-H), 4.12 (m, 2 H, CH_3CH_2), 5.59–5.80 (m, 2 H, C=CH), 5.77 (m, 1 H, 6-H), 7.80 (m, 3 H, *m,p*-ar-H), 8.17 (m, 2 H, *o*-ar-H); Ir (CCl_4) 3039, 2982, 2881, 1730, 1252 cm^{-1}. Anal. Calcd for $C_{16}H_{18}O_4$ (274.32): C, 70.06; H, 6.61. Found: C, 69.93; H, 6.76.

(1*S*,6*R*)-6-(Benzoyloxy)-3-cyclohexene-1-carboxylic Acid [(−)-8]. A suspension of (±)-**7** (65 g, 0.237 mol) in water *tert*-butyl alcohol 9:1 (4.8 L), at room temperature was hydrolyzed with pig liver esterase (Sigma, 9420 units) at pH 7. The progress of the reaction was monitored by the amount of added 1 N NaOH with an autotitrator. After 45% of the starting material had been hydrolyzed (ca. 16 h), the reaction was stopped by addition of CH_2Cl_2 (40 mL). The reaction mixture was extracted with ether (3 × 300 mL), and the layers were separated by centrifugation. The ether extracts were dried over $MgSO_4$, and the solvent was evaporated to yield 35.5 g of an approximately 10:1 mixture [ratio determined with the chiral shift reagent Eu(hfc)$_3$] (vide infra) of (+)-(1*R*,6*S*)- and (−)-(1*S*,6*R*)-**7**. The aqueous phase was brought to pH 2 and extracted with ether (3 × 200 mL). The ether extracts were dried and evaporated to yield crude (−)-(1*S*,6*R*)-**8** (27 g), which was used for the next reaction without further purification. A small sample was converted to its *l*-isoborneol ester (3 equiv of DMAP, 3 equiv of dicyclohexylcarbodiimide, 3 equiv of triethylamine, CH_2Cl_2) for GC analysis of enantiomeric purity. GC–MS: temperature, 200 °C for 2 min and then 5 deg/min gradient, retention times, isoborneol ester of (1*S*,6*R*)-**8**, 11.57 min (MS, m/e 382, 229, 137, 105, 77); isoborneol ester of (1*R*,6*S*)-**8** not detectable. If the hydrolysis reaction is carried out in pure water, one obtains (1*S*,6*R*)-**8** in 63.5% enantiomeric excess, as determined by GC of the isoborneol ester: isoborneol ester of (1*S*,6*R*)-**8**, 11.57 min, integrated to 81.75%; isoborneol ester of (1*R*,6*S*)-**8**, 11.66 min, integrated to 18.25%; MS, m/e 382, 229, 137, 105, 77. For additional NMR analysis of the enantiomeric purity, an analytical sample was esterified with diazomethane in ether to yield the methyl ester of (−)-**8**: $[\alpha]_D$ −89.5° (*c* 6.35, acetone); ^1H NMR ($CDCl_3$) δ 2.44, 2.68, 2.87 (3 m, 5 H, 1-H, 2-H, 5-H), 3.67 (s, 3 H, CH_3), 5.63, 5.82 (2 m, 2 H, C=CH), 5.75 (m, 1 H, 6-H), 7.55 (m, 3 H, *m,p*-ar-H), 7.98 (dd, 2 H, *o*-ar-H), addition of the chiral shift reagent Eu(hfc)$_3$ (2.5 mol %) in CCl_4/d_6-benzene, 4:1, shifts the signal for 6-H from δ 5.75 to δ 7.86. The 1-H signal of the enantiomer, expected at δ 8.19, is not visible; MS, m/e (relative intensities) 229 (2.5), 138 (34), 105 (100), 79 (98), 77 (99), 51 (21).

(1*R*,6*S*)-*cis*-6-(Benzyloxy)-3-cyclohexene-1-carboxylic Acid Ethyl Ester [(+)-7]. A mixture (ca. 10:1) of (+)-(1*R*,6*S*)- and (−)-(1*S*,6*R*)-**7** (35.5 g, 129.6 mmol) was dissolved in water/*tert*-butyl alcohol, 9:1 (1.35 L), and hydrolyzed with pig liver esterase (Sigma, 4000 units). The reaction was stopped, after 13 mL of 1 N NaOH had been added by an autotitrator (19 h), by addition of CH_2Cl_2 (30 mL). The solution was saturated with NaCl and filtered. The clear solution was extracted with ether (3 × 200 mL), and the organic layers were dried and evaporated to yield (+)-(1*R*,6*S*)-**7** (32.3 g, 117.9 mmol, 91%). The aqueous phase was brought to pH 2 with 1 M HCl and extracted with ether (3 × 200 mL). The combined organic layers were dried and evaporated to yield (−)-(1*S*,6*R*)-**8** (2.93 g, 11.9 mmol, 9%). The enantiomeric excess of (+)-(1*R*,6*S*)-**7** thus obtained was determined by ^1H NMR in the presence of the chiral shift reagent Eu(hfc)$_3$ (2.5 mol %) in CCl_4/d_6-benzene, 4:1, and was >97% (no signal at δ 7.86). For the racemate, the signals for 1-H were shifted from δ 5.65 to δ 7.86 for (−)-(1*S*,6*R*)-**7** and to δ 8.19 for (+)-(1*R*,6*S*)-**7**: $[\alpha]_D$ +105.6° (*c* 3.1, acetone); ^1H NMR ($CDCl_3$) δ 1.02 (t, 3 H, CH_2CH_3), 2.26–2.60 (2 m, 5 H, 1-H, 2-H, 5-H), 3.95 (m, 2 H, CH_2CH_3), 5.44 (m, 1 H, C=CH), 5.65 (m, 2 H, 1 C=CH, 6-H), 7.24 (m, 3 H, *m,p*-ar-H), 7.88 (m, 2 H, *o*-ar-H); IR (CCl_4) 3040, 2985, 2880, 1715, 1250, 1085 cm^{-1}; MS, m/e 51, 77, 79, 105, 123, 152, 229. Anal. Calcd for $C_{16}H_{18}O_4$ (274.32): C, 70.06; H, 6.61. Found: C, 70.19; H, 6.85.

(1*R*,6*R*)-6-(Hydroxymethyl)-3-cyclohexen-1-ol (9). To a suspension of $LiAlH_4$ (1.6 g, 41 mmol) in THF (140 mL) was added a solution of (−)-**8** (3.32 g, 19.5 mmol) in THF (10 mL) at room temperature. The reaction mixture was stirred for 15 min at room temperature, and the reaction was then quenched with ethyl acetate (1 mL) followed by concd HCl (9 mL). The pH was brought to 6 by adding 15% NaOH. After removal of half of the solvent under reduced pressure and sedimentation of the inorganic material, the supernatant was decanted. The residue was continuously extracted with 100 mL of ether for 20 h. The combined organic phases were dried and evaporated, and the residue was chromatographed on silica gel (ethyl acetate, R_f 0.28) to yield **9** (2.155 g, 16.83 mmol, 86%), which crystallized spontaneously. Recrystallization from ethyl acetate/hexane gave analytically pure, colorless crystals, which melted at 65–66 °C: $[\alpha]_D$ +5.6° (*c* 3.7, acetone); ^1H NMR ($CDCl_3$) δ 1.90–2.45 (m, 5 H, 2-H, 5-H, 6-H), 2.74 (s, 2 H, D_2O-exchangeable, OH), 3.80 (m, 2 H, CH_2OH), 4.23 (m, 1 H, 1-H), 5.58–5.73 (m, 2 H, C=CH); IR (CCl_4) 3380, 3032, 2910, 1061 cm^{-1}; MS, m/e (relative intensities) 110 (40), 95 (19), 92 (47), 79 (100), 74 (40), 56 (40), 41 (40). Anal. Calcd for $C_7H_{12}O_2$ (128.17): C, 65.60; H, 9.44. Found: C, 65.54; H, 9.36.

(1*R*,6*R*)-6-[(Pivaloyloxy)methyl]-3-cyclohexen-1-ol (10). To a solution of **9** (2.155 g, 16.83 mmol) in pyridine (30 mL) was added pivaloyl chloride (2.385 mL, 19.36 mmol) dropwise over a period of 1 h at −18 to −15 °C. The reaction mixture was stirred at −18 to −10 °C for 1 h and was then quenched with methanol (4 mL). The solvent was evaporated and the residue purified by chromatography (hexane/ethyl acetate, 7:3, R_f 0.43) to yield **10** (3.40 g, 16.0 mmol, 96%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.21 (s, 9 H, ^{t}Bu), 1.68 (s br, 1 H, D_2O-exchangeable, OH), 2.00–2.42 (m, 5 H, 2-H, 5-H, 6-H), 4.02 (m, 2 H, CH_2O), 4.25 (1 H, 1-H), 5.62–5.73 (m, 2 H, C=CH); IR (CCl_4) 3530, 2980, 2910, 1730, 1160 cm^{-1}; MS, *m/e* 158, 110, 92, 57. Anal. Calcd for $C_{12}H_{20}O_3$ (212.29): C, 67.89; H, 9.50. Found: C, 67.54; H, 9.31.

(2*RS*,4*R*,5*R*)-2-Methoxy-4-[(pivaloyloxy)methyl]-5-(2-hydroxyethyl)tetrahydrofuran (18) and (2*RS*,4*R*,5*R*)-2-Methoxy-4-[(pivaloyloxy)methyl]-5-(2,2-dimethoxyethyl)-tetrahydrofuran (17). A solution of **10** (6.327 g, 29.8 mmol) in methanol (500 mL) was cooled to −78 °C and treated with a stream of ozone until it maintained a blue color (ca. 2 h). After the excess ozone was removed with a stream of dry nitrogen (45 min), dimethyl sulfide (10 mL, 136 mmol) was added and the reaction mixture was slowly warmed to room temperature and stirred for 14 days in the dark. At this point GC analysis showed that a mixture of the 2′-aldehyde **16** (R_f 0.45 hexane/ethyl acetate, 1:1) and the corresponding 2′-dimethyl acetal **17** had formed in a ratio of ca. 3:1. The reaction mixture was cooled to 0 °C, and $NaBH_4$ (2 g, 52.8 mmol) was added in small portions. After 30 min the reaction mixture was brought to pH 6 with 1 M HCl. About half of the solvent was evaporated under reduced pressure, water (100 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried and evaporated, and the residue was chromatographed on silica gel (hexane/ethyl acetate, 1:1) to yield **18** (4.851 g, 62.5%, R_f 0.22) and **17** (1.845 g, 20.3%, R_f 0.36, 0.40, two anomers, hexane/ethyl acetate, 6:4) as colorless oils. The anomers of the latter compound could be separated by silica gel chromatography (hexane/ethyl acetate, 7:3). **18** (1:1 mixture of anomers): ^{1}H NMR ($CDCl_3$) δ 1.20 (1 s, 9 H, ^{t}Bu), 1.59 (s, 1 H, D_2O-exchangeable, OH), 1.65–2.6 (m, 5 H, 3-H, 4-H, $HOCH_2CH_2$), 3.32, 3.35 (2 s, 3 H, α + β OCH_3), 3.82 (m, 2 H, $HOCH_2$), 3.95–4.19 (2 m, 3 H, 5-H, CH_2OPv), 4.98 (dd, *J* = 5 Hz, 0.5 H, 2-H of one anomer), 5.02 (dd, *J* = 1.5, 4 Hz, 0.5 H, 2-H of one anomer); IR (CCl_4) 3560, 2960, 1732, 1155 cm^{-1}; MS, *m/e* (relative intensities) 229 (10), 202 (8), 127 (23), 113 (67), 84 (52), 57 (100). Anal. Calcd for $C_{13}H_{24}O_5$ (260.33): C, 59.98; H, 9.29. Found: C, 59.68; H, 9.55. **17**, first fraction (R_f 0.40): ^{1}H NMR ($CDCl_3$) δ 1.20 (s, 9 H, ^{t}Bu), 1.65–2.29 (3 m, 5 H, 3-H, 4-H, $HOCH_2CH_2$), 3.31, 3.34, 3.36 (3 s, 9 H, OCH_3), 3.92 (m, 1 H, 5-H), 4.12 (m, 2 H, CH_2OPv), 4.61 [dd, *J* = 8, 4 Hz, 1 H, $CH(OCH_3)_2$], 5.01 (dd, *J* = 1.5, 5 Hz, 2-H); ^{13}C NMR δ 27.19 (^{t}Bu CH_3), 35.84 (C-3), 38.33 ($HOCH_2CH_2$), 38.78 (^{t}Bu CCH_3), 42.47 (C-4), 52.96, 53.39, 54.47 (OCH_3), 65.97 (CH_2OPv), 77.03 [$C(OMe)_2$], 102.39, 104.36 (C-2, $HOCH_2$), 178.36 (Me_3CCOO); IR (CCl_4) 2960, 1732, 1285, 1155 cm^{-1}; MS, *m/e* 241, 214, 182, 170, 138, 113, 75, 57. **17**, second fraction (R_f 0.38): ^{1}H NMR ($CDCl_3$) δ 1.20 (s, 9 H, ^{t}Bu), 1.75–2.13 (m, 4 H, 3-H, $HOCH_2CH_2$), 2.49 (m, 1 H, 4-H), 3.33, 3.34, 3.36 (3 s, 9 H, OCH_3), 3.95 (m, 1 H, 5-H), 4.07 (m, 2 H, CH_2OPv), 4.63 [dd, *J* = 8, 3.5 Hz, 1 H, $CH(OCH_3)_2$], 4.96 (dd, *J* = 1.5, 5 Hz, 2-H); ^{13}C NMR ($CDCl_3$) δ 27.18 (^{t}Bu CH_3), 36.71 (C-3), 38.80 (^{t}Bu CCH_3), 40.40 ($HOCH_2CH_2$), 42.11 (C-4), 52.39, 53.50, 54.48 (OCH_3), 65.37 (C-3′), 76.66 [$C(OMe)_2$], 102.45, 104.81 (C-2, $HOCH_2$), 178.32; IR (CCl_4) 2960, 1732, 1285, 1265, 1155 cm^{-1}; MS, *m/e* 241, 214, 182, 170, 138, 113, 75, 57.

(1*R*,5*R*,6*R*)-6-[(Pivaloyloxy)methyl]-2,8-dioxabicyclo-[3.2.1]octane (19). A solution of **18** (1.7 g, 6.538 mmol) in toluene (60 mL) was refluxed in the presence of dry acidic cation-exchange resin (Dowex 50 W8, 400 mg) for 5 h under protection from moisture. The resin was then removed by filtration, the solvent evaporated, and the residue resolved by chromatography (hexane/ethyl acetate, 7:3, R_f 0.28) on silica gel to yield **19** (1.25 g, 5.48 mmol, 84%) as a colorless liquid that solidified when stored at 4 °C: ^{1}H NMR ($CDCl_3$) δ 1.20 (s, 9 H, ^{t}Bu), 1.57–2.38 (m, 4 H, 4-H, 7-H), 2.51 (m, 1 H, 6-H), 3.81–4.08 (m, 4 H, 3-H, CH_2OPv), 4.32 (m, 1 H, 5-H), 5.44 (d, *J* = 5 Hz, 1 H, 1-H); IR (CCl_4) 2978, 2874, 1731, 1480, 1285, 1152 cm^{-1}.

(1*R*,5*R*,6*R*)-6-(Hydroxymethyl)-2,8-dioxabicyclo[3.2.1]-octane (20). A solution of **19** (517 mg, 2.267 mmol) in 10 M NaOH (2.26 mL, 22.6 mmol) was stirred in a mixture of THF, methanol, and H_2O (5:4:1, 5 mL) at room temperature for 2 h. The reaction mixture was brought to pH 6 by adding first pyridinium-Dowex (300 mg) and then 1 M HCl. After filtration of the solution and evaporation of the solvent, the residue was resolved by chromatography (ethyl acetate containing 1% triethylamine, R_f 0.25) to yield **20** (293 mg, 2.034 mmol, 90%) as a viscous, colorless oil, which was used immediately for the next step.

(1*R*,5*R*,6*R*)-6-[(Benzyloxy)methyl]-2,8-dioxabicyclo-[3.2.1]octane (22). From 20. To a solution of **20** (75 mg, 0.521 mmol) in pyridine (1 mL) was added benzoyl chloride (91 mL, 0.782 mmol) dropwise at 0 °C. The reaction mixture was warmed to room temperature and stirred for 30 min. After dilution with ethyl acetate (20 mL), the crude reaction mixture was extracted with saturated $CuSO_4$ (5 mL) followed by saturated NaCl (15 mL). The organic phase was dried and evaporated and the residue chromatographed on silica gel (hexane/ethyl acetate, 7:3) to yield **22** (119 mg, 0.484 mmol, 93%) as a colorless oil, which crystallized upon standing at room temperature. The compound was recrystallized from ethyl acetate/hexane to yield colorless crystals melting at 65–66 °C, $[\alpha]_D$ +5.6° (*c* 1.5, acetone).

From 52. A solution of azoisobutyronitrile (12 mg, 72 μmol), Bu_3SnH (0.550 mmol), and **52** (140 mg, 0.3646 mmol) in toluene (4 mL) was degassed with a stream of argon for 30 min. The mixture was then heated to 75 °C for 1 h. The solvent was removed under reduced pressure and the residue chromatographed on silica gel (hexane/ethyl acetate, 7:3, R_f 0.27). The oil obtained was crystallized from ethyl acetate/hexane to yield 60 mg (66%) of **22**, mp 65–66 °C, $[\alpha]_D$ +4.5° (*c* 1.34, acetone). **22**: ^{1}H NMR ($CDCl_3$) δ 1.32 (2 mc, *J* = 14 Hz, 1 H, 7-H_α), 1.78 (ddd, *J* = 14, 5.5, 4 Hz, 1 H, 7-H_β), 2.35 (m, 2 H, 4-H), 2.66 (m, 1 H, 6-H), 3.91 (m, 2 H, 3-H), 4.23 (m, 2 H, CH_2OBz), 4.44 (m, 1 H, 5-H), 5.49 (dd, *J* = 5.5, 1.5 Hz, 1 H, 1-H), 7.26–8.05 (3 m, 5 H, ar-H); IR ($CHCl_3$) 3100–2900, 2980, 1720, 1600, 1450, 1280, 980, 810 cm^{-1}; MS, *m/e* 248, 230, 219, 204, 189, 176, 148, 143, 126, 123, 105. Anal. Calcd for $C_{14}H_{16}O_4$ (248.28): C, 67.73; H, 6.50. Found: C, 67.83; H, 6.63.

1-[(2*RS*,4*R*,5*R*)-4-[(Pivaloyloxy)methyl]-5-(2-hydroxyethyl)tetrahydrofuran-2-yl]uracil (αβ-25). To a solution of bis(trimethylsilyl)uracil (62 mg, 1.1 equiv) and **19** (50 mg, 0.22 mmol) in dichloroethane (1.0 mL) was added $SnCl_4$ (28 μL, 1.1 equiv, dropwise). The mixture was stirred at room temperature (1 h) and cooled to 0 °C, and saturated $NaHCO_3$ was added. The resulting mixture was filtered through Celite and the Celite washed with ethyl acetate. The mixture was then extracted with CH_2Cl_2 (3×), and the combined organic layers were dried and evaporated to give an oil, which was chromatographed (silica gel, chloroform/methanol, 9:1, R_f 0.31) to yield 36 mg (56%) of **αβ-25**: ^{1}H NMR ($CDCl_3$) δ 1.19 and 1.21 (2 s, 9 H, ^{t}Bu α + β), 1.70–2.52 (m, 5 H, $HOCH_2CH_2$, 3′-H, 4′-H, OH), 2.74 (m, 0.5 H, 3′-H_α), 3.84 (m, 2 H, $HOCH_2$), 3.96–4.28 (m, 3 H, CH_2OPv, 5′-H), 5.77 (2 d, *J* = 8 Hz, 5-H), 6.06 (m, 1 H, 2′-H), 7.43, 7.47 (2 d, *J* = 8 Hz, 6-H). Anal. Calcd for $C_{16}H_{24}N_2O_6$ (340.38): C, 56.46; H, 7.11; N, 8.23. Found: C, 55.97; H, 6.98; N, 8.00.

General Procedure for the Conversion of an Alcohol to a Thioacetate. To a solution of PPh_3 (2.2 equiv) in THF was added at 0 °C diisopropylazodicarboxylate (DIAD) (2.2 equiv). The mixture was stirred for 15 min, by which time a thick precipitate had formed. To this suspension was added dropwise a mixture of the alcohol (1 equiv) and thioacetic acid (2.2 equiv) in THF. Stirring was continued for 1 h at 0 °C, methanol was added, and the solvents were removed under reduced pressure. The residue was then chromatographed.

***N*^{6}-Benzoyl-9-[(2*S*,4*R*,5*R*)-4-[(benzoyloxy)methyl]-5-(2-hydroxyethyl)tetrahydrofuran-2-yl]adenine and the 2*R* Isomer (α-32 and β-32).** To a suspension of *N*^{6}-benzoyladenosine (530 mg, 1.1 equiv) in acetonitrile (7 mL) was added MSTFA (913 μL, 2.2 equiv). The mixture was stirred for 10 min at room temperature, TMSOTf (182 μL, 0.5 equiv) was added, and the mixture was stirred for another 10 min. To the resulting clear solution was added dropwise **22** (500 mg, 2.06 mmol) in acetonitrile (3 mL). The mixture was stirred at 40 °C for 30 min and cooled to 0 °C, and saturated $NaHCO_3$ was added. To the resulting two-phase mixture was added potassium fluoride and a crystal of 18-crown-6, and the reaction mixture was stirred overnight. The reaction mixture was then extracted three times with ethyl

acetate (5 mL), and the combined organic layers were dried and evaporated to give a clear oil, which was chromatographed (silica gel, CH_2Cl_2/methanol, 9:1, R_f 0.23). After evaporation of the solvents under reduced pressure, **32** (346 mg, 64%) was obtained as a tan foam. The anomers of **32** were separated by HPLC chromatography (CH_2Cl_2/THF, 65:35, water saturated). The fraction eluting after 69.4 min contained **β-32**, and the fraction eluting after 76.0 min contained **α-32**, which could be crystallized from CH_2Cl_2/ether/pentane to give white needles melting at 136–137 °C. **α-32**: UV (MeOH) λ_{max} 218 (ε 26 200), 279 (20 800); ^{1}H NMR ($CDCl_3$) δ 1.91 (mc, 1 H, $HOCH_2CH_2$), 2.09 (mc, 1 H, $HOCH_2CH_2$), 2.31 (t, J = 5.5 Hz, 1 H, D_2O-exchangeable, OH), 2.69 (mc, 1 H, 4′-H), 2.89 (m, 2 H, 3′-H), 3.85 (dd, J = 11, 5.5 Hz, 2 H, $HOCH_2$), 4.55 (m, 2 H, CH_2OBz), 4.64 (dt, J = 9 Hz, 1 H, 5′-H), 6.38 (t, J = 6.5 Hz, 1 H, 2′-H), 7.23–7.64 (6 H, *m,p*-ar-H), 8.00–8.05 (m, 4 H, *o*-ar-H), 8.14 (s, 1 H, 8-H), 8.73 (s, 1 H, 2-H), 9.12 (s, 1 H, D_2O-exchangeable, NH); IR (KBr) 3420, 3260, 2930, 1715, 1675, 1575, 1505, 1490, 1270, 1255, 715 cm^{-1}; MS, *m/e* (relative intensities) 487 (<1), 383 (<1), 366 (<1), 353 (<1), 278 (<1), 249 (<1), 239 (6), 162 (9), 108 (21), 105 (100), 77 (67). Anal. Calcd for $C_{26}H_{25}N_5O_5$ (487.52): C, 64.06; H, 5.17; N, 14.37. Found: C, 63.72; H, 5.15; N, 14.26. **β-32**: ^{1}H NMR ($CDCl_3$) δ 1.96–2.20 (m, 3 H, $HOCH_2CH_2$, OH), 2.58 (mc, 1 H, 4′-H), 2.84–3.03 (m, 2 H, 3′-H), 3.88 (t, 2 H, $HOCH_2$), 4.26 (dt, J = 3.5, 8.5 Hz, 1 H, 5′-H), 4.46 (m, 2 H, CH_2OBz), 6.37 (dd, J = 2.5, 7 Hz, 1 H, 2′-H), 7.44–7.64 (m, 6 H, *m,p*-ar-H), 8.03–8.07 (m, 4 H, *o*-ar-H), 8.20 (s, 1 H, 8-H), 8.80 (s, 1 H, 2-H), 9.09 (s, 1 H, NH); IR ($CHCl_3$) 3540, 3405, 3000, 2960, 1720, 1610, 1455, 1275 cm^{-1}; MS, *m/e* (relative intensities) 383 (<1), 366 (<1), 353 (<1), 310 (<1), 278 (<1), 262 (<1), 248 (1.2), 220 (19), 205 (86), 145 (16), 105 (64), 43 (100).

N^6-Benzoyl-9-[(2*R*,4*R*,5*R*)-4-[(benzoyloxy)methyl]-5-[2-(acetylthio)ethyl]tetrahydrofuran-2-yl]adenine (β-36). PPh_3 (960 mg, 2 equiv) and DIAD (740 μL, 2 equiv) in THF (15 mL) were reacted with **β-32** (861 mg, 1.768 mmol) and thioacetic acid (260 μL, 2 equiv) in THF (5 mL). After the reaction was complete (ca. 30 min), chromatographic purification (silica gel, $CHCl_3$/THF, 4:1) yielded **β-36** (660 mg, 69%) as a white foam: UV (MeOH) λ_{max} 218 (ε 32 200), 279 (22 700); ^{1}H NMR ($CDCl_3$) δ 1.98–2.21 (m, 2 H, SCH_2CH_2), 2.32 (s, 3 H, $COCH_3$), 2.57 (ddd, J = 7, 9, 13.5 Hz, 1 H, 3′-H_β), 2.78–2.99 (m, 3 H, 4′-H, SCH_2), 3.18 (ddd, J = 5, 5, 13.5 Hz, 1 H, 3′-H_α), 4.16 (td, J = 3.5, 8.5 Hz, 1 H, 5′-H), 4.47 (m, 2 H, CH_2OBz), 6.37 (dd, J = 3, 7 Hz, 1 H, 2′-H), 7.45–7.65 (m, 6 H, *m,p*-ar-H), 8.04 (m, 4 H, *o*-ar-H), 8.29 (s, 1 H, 8-H), 8.81 (s, 1 H, 2-H), 9.01 (s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 25.9 ($HOCH_2CH_2$), 30.6 (CH_3), 35.3, 35.9 (C-3′, $HOCH_2$), 42.2 (C-4′), 64.4 (CH_2OBz), 82.7 (C-5′), 85.2 (C-2′), 123.9 (C-5), 127.9, 128.6, 128.8, 129.6, 132.7, 133.4, 133.7 (ar-C), 141.5 (C-8), 149.6, 151.2 (C-4, C-6), 152.5 (C-2), 164.8, 166.3, 195.5 (CO); IR (KBr) 3405 (br), 2920, 1720, 1690, 1610, 1580, 1510, 1485, 1450, 1275, 1115 cm^{-1}; MS, *m/e* 545, 517, 502, 470, 440, 398, 366, 352, 307, 239, 239, 141, 105. Anal. Calcd for $C_{28}H_{27}N_5O_5S$: C, 61.64; H, 4.99; N, 12.84. Found: C, 61.61; H, 4.80; N, 12.25.

N^2-Isobutyryl-9-[(2*RS*,4*R*,5*R*)-4-[(benzoyloxy)methyl]-5-(2-hydroxyethyl)tetrahydrofuran-2-yl]guanine (34) and N^2-Isobutyryl-7-[(2*RS*,4*R*,5*R*)-4-[(benzoyloxy)methyl]-5-(2-hydroxyethyl)tetrahydrofuran-2-yl]guanine (33). To a suspension of N^2-isobutyrylguanosine·H_2O (1.590 g, 1.1 equiv) in acetonitrile (20 mL) were added TMSCl (1.70 mL, 2.2 equiv) and HMDS (2.80 mL, 2.2 equiv). The mixture was stirred for 10 min at room temperature, TMSOTf (3.00 mL, 0.5 equiv) was added, and the mixture was stirred for another 10 min. To the resulting clear solution was added **22** (1.50 g, 6.048 mmol) dropwise in acetonitrile (5 mL). The mixture was stirred at 40 °C for 15 min and cooled to 0 °C, and saturated $NaHCO_3$ was added. To the resulting two-phase mixture were added potassium fluoride and a crystal of 18-crown-6, and the mixture was stirred overnight. The mixture was then extracted four times with ethyl acetate (5 mL). The combined organic layers were dried and evaporated to give an oil, which was chromatographed (silica gel, CH_2Cl_2/methanol, 9:1) to give two fractions that contained nucleoside analogues. Evaporation of the solvents under reduced pressure yielded **33** (843 mg, 30%, R_f 0.33) from the first fraction and **34** (1.602 g, 56%, R_f 0.26) from the second fraction, both as white foams which were slightly impure (NMR). From the fraction containing the N^7 isomers (**33**), the β-isomer could be selectively (as a ca. 9:1 mixture of anomers) crystallized from CH_2Cl_2/pentane. **33** (9:1 mixture of anomers, major anomer): ^{1}H NMR ($CDCl_3$) δ 1.24, 1.26 (2 d, 6 H, J = 2.5, 3.5 Hz, ^{i}Bu CH_3), 1.98–2.13 (m, 2 H, $HOCH_2CH_2$), 2.62 (m, 3 H, 3′-H, 4′-H), 2.80 (s br, 1 H, OH), 2.91 (m, 1 H, ^{i}Bu CH), 3.93 (m, 2 H, $HOCH_2$), 4.25 (td, 1 H, J = 9.8, 3 Hz, 5′-H), 4.45 (m, 2 H, CH_2OBz), 6.55 (dd, 1 H, J = 5, 4 Hz, 2′-H), 7.46, 7.58, 8.03 (3 m, 5 H, ar-H), 8.22 (s, 1 H, 8-H), 9.92 (s, 1 H, N^2-H), 12.32 (s, 1 H, 1-NH); IR ($CHCl_3$) 3405, 3200, 3000, 2960, 1690, 1610, 1275 cm^{-1}; MS, *m/e* 425, 407, 357, 329, 281, 248, 189, 151. Anal. Calcd for $C_{23}H_{27}N_5O_6·H_2O$ (487.52): C, 56.67; H, 6.00; N, 14.37. Found: C, 57.55; H, 5.92; N, 13.81. **34** (1:1 mixture of anomers): ^{1}H NMR (d_6-DMSO) δ 1.13, 1.15 (2 s, 6 H, ^{i}Bu CH_3), 1.68–2.00 (m, 2 H, $HOCH_2CH_2$), 2.42–2.86, 3.54 (2 m, 6 H, 3′-H, ^{i}Bu CH, 4′-H, $HOCH_2$, OH, all unresolved), 4.08, 4.34 (2 td, 1 H, 5′-H), 4.50 (m, 2 H, CH_2OBz), 6.07 (dd, 0.5 H, J = 7, 3.5 Hz, 2′-H), 6.07 (t, 0.5 H, J = 6.5 Hz, 2′-H), 7.57, 7.70, 8.01 (3 m, 5 H, ar-H), 8.22, 8.25 (2 s, 1 H, 8-H), 11.66, 12.07 (2 s br, 1 H, 1-NH); IR ($CHCl_3$) 3405, 3200, 3000, 2980, 1690, 1610, 1275 cm^{-1}; MS, *m/e* 374, 248, 221, 204, 189, 151.

N^2-Isobutyryl-9-[(2*S*,4*R*,5*R*)-4-[(benzoyloxy)methyl]-5-[2-(acetylthio)ethyl]tetrahydrofuran-2-yl]guanine and the 2*R* Isomer (α-38 and β-38). PPh_3 (2.170 g, 2.2 equiv) and DIAD (1.670 mL, 2.2 equiv) in THF (40 mL) were reacted with **34** (1.70 g, 3.625 mmol) obtained from the previous reaction and thioacetic acid (590 μL, 2.2 equiv) in THF (10 mL). Chromatography (silica gel, $CHCl_3$/methanol, 95:5) yielded a mixture of **α-38** and **β-38** (1.160 g) as a slightly yellow foam. The anomers were separated by HPLC chromatography ($CHCl_3$/2.5% ethanol, water saturated). The first fraction contained the α-anomer of **38** (retention time 60.5 min), and the second fraction contained the β-anomer of **38** (retention time 64.7 min). Both compounds were recovered as a white foam following evaporation of the solvents. **α-38**: UV (MeOH) λ_{max} 230 (ε 21 300), 257 (18 700), 279 (sh); ^{1}H NMR ($CDCl_3$) δ 1.31, 1.33 (2 d, J = 7 Hz, 6 H, ^{i}Bu), 1.86–1.95 (m, 2 H, SCH_2CH_2), 2.17 (s, 3 H, CH_3), 2.53 (ddd, J = 13.5, 7, 5 Hz, 1 H, 3′-H_β), 2.63–2.96 (m, 4 H, 4′-H, 3′-H_α, CH_2S), 3.03 (dquar = sept, J = 7 Hz, 1 H, ^{i}BuCH), 4.44 (ddd = td, J = 7.5, 4 Hz, 1 H, 5′-H), 4.62 (dd, J = 11.5, 7 Hz, 2 H, CH_2OBz), 6.11 (dd, J = 8, 4.5 Hz, 1 H, 2′-H), 7.48 (mc, 3 H, *m,p*-ar-H), 7.63 (mc, 2 H, *o*-ar-H), 7.73 (s, 1 H, 8-H), 9.57 (s, 1 H, N^2-H), 12.12 (s, 1 H, 1-NH), irradiation at δ 6.11 gives NOE enhancement at δ 7.73 (8-H) and 2.80 (3′-H_α); ^{13}C NMR ($CDCl_3$) δ 19.0, 19.1 (^{i}Bu CH_3), 25.7 (SCH_2CH_2), 30.5 (CH_3CO), 34.7 (C-3′), 35.3 (C-4′), 36.2 (SCH_2), 43.3 (^{i}Bu CH), 64.8 (CH_2OBz), 82.2 (C-5′), 85.4 (C-2′), 122.3 (C-5), 129.3 (ar-C), 128.6, 129.6, 133.7 (ar-CH), 138.5 (C-8), 147.5, 147.7 (C-2, C-6), 155.7 (C-4), 167.0, 179.5, 195.5 (CO); IR (KBr) 3420, (br), 3170 (br), 2970, 2930, 1735, 1685, 1605, 1555, 1275, 1115, 710 cm^{-1}; MS, *m/e* (relative intensities) 221 (83), 151 (18), 141 (9), 108 (47), 77 (20), 43 (100). **β-38**: UV (MeOH) λ_{max} 229 (ε 20 400), 257 (17 900), 279 (sh); ^{1}H NMR ($CDCl_3$) δ 1.27, 1.28 (2 d, J = 8.5 Hz, 6 H, ^{i}Bu), 1.97, 2.12 (2 m, 2 H, SCH_2CH_2), 2.29 (s, 3 H, CH_3), 2.40 (ddd, J = 13.5, 8.5, 7.5 Hz, 1 H, 3′-H_α), 2.72 (m, 2 H, SCH_2), 2.95 (m, 2 H, 4′-H, ^{i}Bu CH), 3.11 (ddd, J = 5, 5, 13.5, 3′-H_β), 4.05 (ddd = td, J = 8, 3.5 Hz, 1 H, 5′-H), 4.39 (mc, 2 H, CH_2OBz), 6.05 (dd, 7.5, 3.5 Hz, 1 H, 2′-H), 7.49 (mc, 3 H, *m,p*-ar-H), 7.60 (mc, 2 H, *o*-ar-H), 7.80 (s, 1 H, 8-H), 8.87 (s, 1 H, N^2-H), 12.08 (s, 1 H, 1-NH), irradiation at δ 6.05 gives NOE enhancement at δ 7.80 (8-H), 4.05 (4′-H), 2.40 (3′-H_α); ^{13}C NMR ($CDCl_3$) δ 19.0, 19.1 (^{i}Bu CH_3), 25.6 (SCH_2CH_2), 30.6 (CH_3CO), 34.7 (C-3′), 35.6 (C-4′), 36.2 (SCH_2), 41.8 (^{i}Bu CH), 64.9 (CH_2OBz), 82.5 (C-5′), 84.7 (C-2′), 121.8 (C-5), 128.5, 129.5, 133.3 (ar-CH), 137.6 (C-8), 147.7, 147.8 (C-2, C-6), 155.8 (C-4), 166.3, 179.5, 196.0 (CO); IR (KBr) see data for α-anomer; MS, *m/e* (relative intensities) 221 (1.5), 151 (4.5), 141 (9), 108 (47), 77 (20), 43 (100). Anal. Calcd for $C_{25}H_{29}N_5O_6S$ (527.60): C, 56.91; H, 5.54; N, 13.27; S, 6.08. Found: C, 56.65; H, 5.47; N, 13.13; S, 6.21.

N^4-Benzoyl-1-[(2*RS*,4*R*,5*R*)-4-[(benzoyloxy)methyl]-5-(2-hydroxyethyl)tetrahydrofuran-2-yl]cytosine (35). To a suspension of N^4-benzoylcytosine (286 mg, 1.1 equiv) in acetonitrile (3 mL) was added MSTFA (550 μL, 2.2 equiv). The mixture was stirred for 10 min at room temperature, TMSOTf (400 μL, 1.8 equiv) was added, and the mixture was stirred for another 10 min. The resulting clear solution was heated to 40 °C, and **22** (300 mg, 1.21 mmol) in acetonitrile (2 mL) was added dropwise. The mixture was stirred at 40 °C for 1 h and cooled to 0 °C, and saturated $NaHCO_3$ was added. The resulting two-phase mixture, which contained a white precipitate, was extracted with ethyl

acetate (3 × 3 mL). The combined organic layers were dried and evaporated to give a clear oil, which was chromatographed (silica gel, CH_2Cl_2/methanol, 9:1, R_f 0.32). After evaporation of the solvents under reduced pressure, α-**35** (346 mg, 64%) was obtained slightly impure (NMR) as a tan foam. A small sample of the mixture of anomers could be separated by fractional crystallization. The first fraction contained α-**35** (90% anomerically pure); the second fraction contained a mixture of α- and β-**35** in a ratio of 1:3. α-**35**: ^{1}H NMR ($CDCl_3$) δ 1.88–2.14 (m, 4 H, 3′-H_α, $HOCH_2CH_2$, OH), 2.63 (mc, 1 H, 4′-H), 3.10 (ddd, J = 6.5, 8, 14 Hz, 1 H, 3′-H_β), 3.91 (br s, 2 H, $HOCH_2$), 4.32–4.44 (m, 3 H, 5′-H, CH_2OBz), 6.11 (t, J = 6 Hz, 1 H, 2′-H), 7.40–7.64 (m, 7 H, m,p-ar-H, 5-H), 7.88–8.03 (m, 5 H, o-ar-H, 6-H), irradiation at δ 6.11 gives NOE enhancement at δ 8.01 (6-H), 3.10 (3′-H_β), 2.63 (4′-H). β-**35**: ^{1}H NMR ($CDCl_3$) δ 1.90–2.14 (m, ~4 H, 3′-H, $HOCH_2CH_2$, OH), 2.41 (m, ~1 H, 3′-H), 2.57 (m, ~1 H, 4′-H), 3.94 (br dd, ~2 H, $HOCH_2$), 4.20 (td, J = 3.5, 9 Hz, ~1 H, 5′-H), 4.40 (m, ~2 H, CH_2OBz), 6.13 (dd, J = 6.5, 2 Hz, ~1 H, 2′-H), 7.40–7.64 (m, 7 H, m,p-ar-H, 5-H), 7.88–8.08 (m, 5 H, o-ar-H, 6-H).

N^4-Benzoyl-1-[(2*S*,4*R*,5*R*)-4-[(benzoyloxy)methyl]-5-[2-(acetylthio)ethyl]tetrahydrofuran-2-yl]cytosine and the 2*R* Isomer (α-39 and β-39). PPh_3 (885 mg, 2 equiv) and DIAD (665 μL, 2 equiv) in THF (20 mL) were reacted with a 1:1 mixture of anomers of **35** (732 mg, 3.625 mmol) and thioacetic acid (238 μL, 2 equiv) in THF (7 mL). Chromatography (silica gel, ethyl acetate) yielded **39** (717 mg, 87%) as a slightly tan oil. The anomers were separated by HPLC chromatography (ethyl acetate/hexane/water, 7:3:0.07). The first fraction contained the β-anomer (retention time 48.3 min), and the second fraction contained the α-anomer (retention time 53.3 min). The β-anomer was crystallized as white needles (mp 138–139 °C) from CH_2Cl_2/ether/pentane at room temperature. The α-anomer could not be crystallized, forming a white foam upon evaporation of the solvents. α-**39**: ^{1}H NMR ($CDCl_3$) δ 1.93–2.14 (m, 2 H, SCH_2CH_2), 2.35 (s, 3 H, $COCH_3$), 2.59 (m, 1 H, 4′-H), 3.11 (m, 2 H, 3′-H), 3.64 (ddd, J = 13.5, 10, 7 Hz, 1 H, SCH_2), 3.88 (ddd, J = 13.5, 10, 7 Hz, 1 H, SCH_2), 4.24 (td, J = 3.5, 8.5 Hz, 1 H, 5′-H), 4.35 (m, 2 H, CH_2OBz), 6.08 (J = 6 Hz, 1 H, 2′-H), 7.42–7.72 (m, 7 H, m,p-ar-H, 5-H), 7.93 (m, 2 H, o-benzamide-H), 7.99 (m, 2 H, o-benzoate-H), 8.03 (d, J = 7.5 Hz, 1 H, 6-H); IR ($CHCl_3$) 3400, 3000, 1740, 1690, 1660, 1480, 1270, 1080 cm^{-1}; MS, m/e (relative intensities) 357 (0.4), 242 (1.1), 215 (5), 186 (7), 153 (5), 141 (30), 108 (79), 105 (100), 95 (45), 77 (98), 43 (86). β-**39**: UV (MeOH) λ_{max} 228 (ε 21 400), 258 (18 700), 303 (8500); ^{1}H NMR ($CDCl_3$) δ 1.97–2.24 (2 m, 2 H, SCH_2CH_2), 2.30–2.50 (s, m, 5 H, CH_3, 4′-H, 3′-H_β), 2.59 (ddd, J = 13.5, 8, 6.5 Hz, 1 H, 3′-H_α), 2.94 (ddd, J = 13.5, 8.5, 7.5, 1 H, SCH_2), 3.29 (ddd, J = 13.5, 9.5, 7 Hz, 1 H, SCH_2), 4.10 (td, J = 10, 7, 3 Hz, 1 H, 5′-H), 4.40 (m, 2 H, CH_2OBz), 6.11 (dd, J = 6.5, 3 Hz, 1 H, 2′-H), 7.44 (m, 7 H, m,p-ar-H, 5-H), 7.91 (d, J = 8 Hz, 2 H, o-benzamide-H), 8.02 (m, 2 H, o-benzoate-H), 8.20 (d, J = 7.5 Hz, 1 H, 6-H), irradiation at δ 6.11 gives NOE enhancement at δ 8.20 (6-H), 4.10 (5′-H), 2.59 (3′-H_α); IR (KBr) 3380, 2950, 1740, 1690, 1660, 1485, 1270, 1095, 710 cm^{-1}; MS, m/e (relative intensities) 280 (0.8), 279 (9), 278 (49), 277 (100), 205 (54), 152 (11), 105 (18), 77 (40), 45 (95). Anal. Calcd for $C_{27}H_{27}N_3O_6S$: C, 62.17; H, 5.22; N, 8.06; S, 6.15. Found: C, 62.48; H, 4.99; N, 7.69; S, 5.98.

1-[(2*RS*,4*R*,5*R*)-4-[(Benzoyloxy)methyl]-5-(2-hydroxyethyl)tetrahydrofuran-2-yl]uracil (27). To a solution of bis(trimethylsilyl)uracil (600 mg, 1.1 equiv) and TMSOTf (125 μL, 0.3 equiv) in acetonitrile (8 mL) was added dropwise a solution of **22** (500 mg, 2.016 mmol) in acetonitrile (2 mL). The mixture was stirred at room temperature for 15 min and cooled to 0 °C, and saturated $NaHCO_3$ was added. The resulting two-phase mixture was extracted three times with ethyl acetate. The combined organic layers were dried and evaporated to give an oil, which was chromatographed (silica gel, CH_2Cl_2/methanol, 9:1). Evaporation of the solvents yielded slightly impure (NMR) **27** (522 mg, 75%) as a tan foam: ^{1}H NMR ($CDCl_3$) δ 1.80–2.20 and 2.20–2.66 (2 m, 5.5 H, 3′-H, 4′-H, $HOCH_2CH_2$, OH), 2.82 (m, 0.5 H, 3′-H), 3.86 (m, 2 H, $HOCH_2$), 4.11 (td, J = 3, 9 Hz, 0.5 H, 5′-H), 4.35 (td, J = 3, 9 Hz, 0.5 H, 5′-H), 4.40 (m, 2 H, CH_2OBz), 5.87, 5.88 (2 d, J = 8 Hz, 1 H, 5-H), 6.09 (t, J = 6.5 Hz, 0.5 H, 2′-H), 6.12 (dd, J = 4, 6.5 Hz, 0.5 H, 2′-H), 7.47 (m, 3 H, m,p-ar-H), 7.60 (m, 2 H, o-ar-H), 8.02 (2 d = t, J = 8 Hz, 1 H, 6-H), 9.60 (s br, 1 H, NH); IR ($CHCl_3$) 3380, 3000, 1720, 1690, 1460, 1450, 1270, 1110 cm^{-1}

1-[(2*S*,4*R*,5*R*)-4-[(Benzoyloxy)methyl]-5-[2-(acetylthio)ethyl]tetrahydrofuran-2-yl]uracil and the 2*R*,4*S*,5*S* Isomer (α-40 and β-40). PPh_3 (2.122 g, 2.2 equiv) and DIAD in THF (40 mL) were reacted with thioacetic acid (570 μL, 2.2 equiv) in THF (10 mL) and **27** (1.347 g, 3.625 mmol). Chromatography (silica gel, ethyl acetate) yielded a mixture of the anomers of **40** (1.273 g, 78%) as a slightly yellow foam. The anomers were separated by HPLC chromatography (ethyl acetate/hexane/water, 7:3:0.07). The first fraction contained the α-anomer (retention time 51.5 min), and the second fraction contained the β-anomer (retention time 56.9 min). The α-anomer was crystallized as white needles (mp 103–104 °C) from CH_2Cl_2/ether/pentane at room temperature. The β-anomer crystallized as a white microcrystalline material (mp 105–106 °C) from ethyl acetate/hexane at room temperature.

α-**40**: ^{1}H NMR ($CDCl_3$) δ 1.88–2.10 (m, 3 H, 3′-H_β, SCH_2CH_2), 2.32 (s, 3 H, $SOCH_3$), 2.55 (mc, 1 H, 4′-H), 2.87 (ddd, J = 13.5, 7, 6.5 Hz, 1 H, 3′-H_α), 2.94–3.14 (m, 2 H, SCH_2), 4.19 (ddd = td, J = 8.5, 8.5, 1.5 Hz, 5′-H), 5.77 (d, J = 8 Hz, 1 H, 5-H), 6.06 (dd = t, J = 6.5, 6.5 Hz, 1 H, 2′-H), 7.46 (m, 3 H, p-ar-H), 7.58 (d, J = 8 Hz, 1 H, 6-H), 7.99 (m, 2 H, o-ar-H), 9.13 (s, 1 H, NH), irradiation at δ 6.06 gives NOE enhancement at δ 7.46 (m-ar-H), 5.77 (5-H), 2.87 (3′-H_α), 2.55 (4′-H); IR (KBr) 3410 (br), 3040, 1740, 1700, 1675, 1460, 1260, 1100 cm^{-1}; MS, m/e (relative intensities) 307 (12), 185 (12), 143 (17), 108 (15), 105 (69), 77 (34), 43 (100). Anal. Calcd for $C_{20}H_{22}N_2O_6S$ (418.47): C, 57.40; H, 5.13; N, 6.69; S, 7.66. Found: C, 57.27; H, 5.17; N, 6.54; S, 7.41. β-**40**: UV (MeOH) λ_{max} 229 (ε 21 400); ^{1}H NMR ($CDCl_3$) δ 1.91–2.17 (2 m, 2 H, SCH_2CH_2), 2.28 (m, 1 H, 3′-H_β), 2.33 (s, 3 H, CH_3), 2.42 (m, 2 H, 3′-H_α, 4′-H), 2.89, 3.18 (2 mc, 2 H, SCH_2), 3.99 (ddd = td, J = 4.5, 4.5, 1.5 Hz, 1 H, 5′-H), 4.38 (mc, 2 H, CH_2OBz), 5.81 (d, J = 8 Hz, 5-H), 6.09 (dd, J = 6.5, 4 Hz, 1 H, 2′-H), 7.26 (m, 2 H, m-ar-H), 7.39 (m, 1 H, p-ar-H), 7.56 (d, J = 8 Hz, 6-H), 8.02 (m, 2 H, o-ar-H), 9.04 (s, 1 H, NH), irradiation at δ 6.09 gives NOE enhancement at δ 8.02 (o-ar-H), 7.56 (6-H), 3.99 (5′-H), 2.42 (3′-H_α); IR ($CHCl_3$) 3390, 3010, 1690, 1715, 1450, 1270, 1115 cm^{-1}; MS, m/e (relative intensities) 307 (16), 185 (22), 143 (23), 108 (55), 95 (32), 77 (53), 43 (100). Anal. Calcd for $C_{20}H_{22}N_2O_6S$ (418.47): C, 57.40; H, 5.13; N, 6.69; S, 7.66. Found: C, 57.27; H, 5.25; N, 6.64; S, 7.75.

N^2-Isobutyryl-7-[(2*R*,4*R*,5*R*)-4-[(benzoyloxy)methyl]-5-[2-(acetylthio)ethyl]tetrahydrofuran-2-yl]guanine (β-37). PPh_3 (116 mg, 2 equiv) and DIAD (84 μL, 2.2 equiv) in THF (1.0 mL) were reacted with β-**33** (100 mg, 0.2130 mmol) and thioacetic acid (31 μL, 2 equiv) in THF (1.2 mL). Chromatography (silica gel, CH_2Cl_2/methanol, 95:5) yielded β-**37** (96 mg, 89%): UV (MeOH) λ_{max} 223 (ε 34 500), 264 (15 600); ^{1}H NMR ($CDCl_3$) δ 1.22 (2 d = t, J = 7 Hz, 6 H, ^{i}Bu CH_3), 1.99–2.17 (m, 2 H, SCH_2CH_2), 2.32 (s, 3 H, CH_3CO), 2.50–2.64 (m, 3 H, 3′-H_β, ^{i}Bu CH, 4′-H), 3.00 (m, 2 H, SCH_2), 3.21 (ddd = sept, J = 5, 8.5, 14 Hz, 1 H, 3′-H_α), 4.12 (dt, J = 3, 9 Hz, 1 H, 5′-H), 4.37, 4.45 (2 dd, J = 5, 11 Hz, 2 H, CH_2OBz), 6.53 (t, J = 5 Hz, 1 H, 2′-H), 7.46 (m, 3 H, m,p-ar-H), 7.59 (m, 2 H, o-ar-H), 8.18 (s, 1 H, 8-H), 10.52 (s, 1 H, N^2-H), 12.39 (s, 1 H, 1-NH); ^{13}C NMR ($CDCl_3$) δ 19.1, 19.2 (^{i}Bu CH_3), 26.1 (SCH_2CH_2), 30.6 (CH_3CO), 35.2 (C-3′), 35.9 (C-4′), 38.3 (SCH_2), 41.6 (^{i}Bu CH), 64.2 (CH_2OBz), 83.0 (C-5′), 84.7 (C-2′), 128.6, 129.6, 133.4 (ar-CH), 140.7 (C-8), 148.1 (C-2), 153.1 (C-6), 158.0 (C-4), 166.3 (NHCO), 180.1 (PhCO), 195.5 (CH_3CO).

3-Deoxy-3-[(benzoyloxy)methyl]-1,2-*O*-isopropylidene-α-D-allofuranose (45). To a solution of **44** (24.1 g, 87.9 mmol) and DMAP (2 mg) in pyridine (50 mL) was added benzoyl chloride (15.0 mL, 1.5 equiv) slowly at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 3 h. Methanol (20 mL) was then added, and the solvents were removed under reduced pressure. The residue was suspended in ethyl acetate and extracted twice with 10% HCl. The organic layer was washed with saturated $NaHCO_3$ and water, dried, and evaporated. The benzoate [3-deoxy-3-[(benzyloxy)methyl]-1:2,5:6-di-*O*-isopropylidene-α-D-allofuranose] obtained was sufficiently pure to be used for the next step. An analytical sample was prepared by TLC (1-mm plate, EtOAc/hexane, 2:8, R_f 0.35): ^{1}H NMR ($CDCl_3$) δ 1.32, 1.33, 1.42, 1.53 (4 s, 12 H, CH_3), 2.43 (dddd = sept, J = 4, 5, 10, 10 Hz, 1 H, 3-H), 3.88 (dd, J = 10, 7 Hz, 1 H, 6-H), 3.96–4.25 (m, 3 H, 4-H, 5-H, 6-H), 4.50 (dd, J = 11, 10 Hz, 1 H, 3′-H), 4.75 (dd, J = 11, 5 Hz, 1 H, 3′-H), 4.82 (t, J = 4 Hz, 1 H, 2-H), 5.82 (d, J = 3.5 Hz, 1 H, 1-H), 7.45 (m,

2 H, *m*-ar-H), 7.58 (m, 1 H, *p*-ar-H), 8.07 (m, 2 H, *o*-ar-H); IR (CCl_4) 2990, 1755, 1385, 1375, 1275 cm^{-1}; MS, *m/e* 363, 305, 277, 219, 181, 155, 105, 77. Anal. Calcd for $C_{20}H_{26}O_7$ (378.42): C, 63.48; H, 6.93. Found: C, 63.50; H, 6.93.

The crude benzoate was dissolved in a mixture of MeOH (630 mL), $CHCl_3$ (210 mL), and 1.6% H_2SO_4 (100 mL) and stirred for 84 h. The reaction mixture was neutralized with saturated $NaHCO_3$, the solvent removed in vacuo, and the residue partitioned between ethyl acetate and water. The water layer was extracted with ethyl acetate, and the combined organic layers were dried and evaporated. The residue was chromatographed on silica gel (ethyl acetate/hexane, 7:3, R_f 0.38) to yield **45** (24.3 g, 82% for two steps) as a clear oil, which solidifies while standing at 4 °C. The waxy material softens at 40 °C and melts at 50–53 °C: ^1H NMR ($CDCl_3$) δ 1.33, 1.52 (2 s, 6 H, CH_3), 1.88 (br, s, 1 H, OH), 2.48 (m, 1 H, 3-H), 3.16 (br s, 1 H, OH), 3.80 (m, 3 H, 6-H, 5-H), 4.00 (dd, *J* = 10, 5.5 Hz, 1 H, 4-H), 4.55 (dd, *J* = 11, 9 Hz, 1 H, 3′-H), 4.70 (dd, *J* = 11, 5 Hz, 1 H, 3-H), 4.80 (dd, *J* = 4, 3.5 Hz, 1 H, 2-H), 5.83 (d, *J* = 3.5 Hz, 1 H, 1-H), 7.45 (m, 2 H, *m*-ar-H), 7.58 (m, 1 H, *p*-ar-H), 8.07 (m, 2 H, *o*-ar-H); IR (CCl_4) 3480 (br), 2990, 1725, 1385, 1375, 1275 cm^{-1}; MS, *m/e* 323, 219, 155, 105, 77. Anal. Calcd for $C_{17}H_{22}O_7$ (338.36): C, 60.35; H, 6.55. Found: C, 60.27; H, 6.53.

3,5,6-Trideoxy-5,6-didehydro-3-[(benzoyloxy)methyl]-1,2-*O*-isopropylidene-α-D-allofuranose (46). To a solution of **45** (24.0 g, 71.0 mmol) in pyridine (100 mL) was added slowly at −10 °C methanesulfonyl chloride (17.0 mL, 3 equiv). The reaction mixture was allowed to warm to room temperature and was stirred for 2 h. Methanol (20 mL) was added and most of the solvent removed under reduced pressure. The residue was partitioned between ethyl acetate and 10% HCl. The aqueous layer was extracted three times with ethyl acetate, and the combined organic layers were washed with saturated $NaHCO_3$ and brine, dried, and evaporated to yield the dimesylate [3-deoxy-3-[(benzoyloxy)-methyl]-5,6-bis-*O*-(methylsulfonyl)-1,2-*O*-isopropylidene-α-D-allofuranose] (29.0 g) as a viscous oil. An analytical sample was prepared by silica gel chromatography (ethyl acetate/hexane, 1:1, R_f 0.40): ^1H NMR ($CDCl_3$) δ 1.33, 1.52 (2 s, 6 H, CCH_3), 2.59 (m, 1 H, 3-H), 3.04, 3.14 (2 s, 6 H, SO_2CH_3), 4.29 (dd, *J* = 10, 5 Hz, 1 H, 6-H), 4.46 (dd, *J* = 12, 6 Hz, 1 H, 3′-H), 4.60 (m, 3 H, 4-H, 3′-H, 6-H), 4.82 (dd, *J* = 4, 3.5 Hz, 1 H, 2-H), 5.02 (m, 1 H, 5-H), 5.85 (d, *J* = 3.5 Hz, 1 H, 1-H), 7.45 (m, 2 H, *m*-ar-H), 7.58 (m, 1 H, *p*-ar-H), 8.07 (m, 2 H, *o*-ar-H); IR (CCl_4) 2990, 1745, 1375, 1270, 1240, 1180 cm^{-1}; MS, *m/e* 479, 219, 155, 123, 105, 77. Anal. Calcd for $C_{19}H_{26}O_{11}S_2$ (494.54): C, 46.15; H, 5.30. Found: C, 46.27; H, 5.22.

To a solution of the crude dimesylate in ethyl methyl ketone (250 mL) was added NaI (30 g), and the mixture was heated at reflux for 15 h. The solvent was then removed in vacuo and the residue partitioned between ethyl acetate and saturated aqueous $Na_2S_2O_3$. The aqueous phase was extracted two times with ethyl acetate, and the combined organic layers were washed with brine. The solvent was dried and evaporated and the residue chromatographed on silica gel (hexane/ethyl acetate, 8:2, R_f 0.36) to yield **46** (20.3 g) as a clear oil, which was ca. 95% pure by NMR (corresponding to an 89% yield after two steps). An analytical sample was prepared by a second chromatographic purification on silica gel: ^1H NMR ($CDCl_3$) δ 1.36, 1.56 (2 s, 6 H, CH_3), 2.30 (m, 1 H, 3-H), 4.38 (dd, *J* = 10, 7 Hz, 1 H, 4-H), 4.43 (dd, *J* = 11, 6 Hz, 1 H, 3′-H), 4.56 (dd, *J* = 11, 8 Hz, 1 H, 3′-H), 4.81 (dd, *J* = 4, 3.5 Hz, 1 H, 2-H), 5.27 (dm, *J* = 11 Hz, 1 H, 6-H_E), 5.41 (dm, *J* = 18 Hz, 1 H, 6-H_Z), 5.83 (dd, *J* = 10, 7 Hz, 1 H, 5-H), 5.91 (d, 1 H, 1-H), 7.45 (m, 2 H, *m*-ar-H), 7.58 (m, 1 H, *p*-ar-H), 8.07 (m, 2 H, *o*-ar-H); IR (CCl_4) 2990, 2960, 2940, 1730, 1450, 1375, 1365, 1270 cm^{-1}; MS, *m/e* 290, 190, 125, 105, 77. Anal. Calcd for $C_{17}H_{20}O_5$ (304.34): C, 67.09; H, 6.62. Found: C, 66.94; H, 6.59.

3,5-Dideoxy-3-[(benzoyloxy)methyl]-1,2-*O*-isopropylidene-α-D-allofuranose (47). The olefin obtained above (20.0 g, 62.5 mmol, calculated on the basis of a content of 95% **46**) was dissolved in THF (200 mL), the solution cooled to 0 °C, and BH_3·Me_2S (15 mL) added. The reaction mixture was stirred for 24 h at 0–4 °C and cooled to −10 °C, and methanol (20 mL) was added carefully. After 1 h at 0 °C, water (100 mL), $NaHCO_3$ (35 g), and then 30% H_2O_2 (60 mL, dropwise) were added while the temperature was maintained at 0 °C. The mixture was allowed to warm to room temperature and was stirred for 2 h. After half of the solvents were removed under reduced pressure, the mixture was extracted three times with ethyl acetate. The organic layer was washed with saturated $Na_2S_2O_3$ and brine, dried, and evaporated. The residue was chromatographed (silica gel, ethyl acetate/hexane, 6:4, R_f 0.40), to yield 13.8 g (68%) of **47** as an oil: ^1H NMR ($CDCl_3$) δ 1.35, 1.54, (2 s, 6 H, CH_3), 1.74–1.86 (m, 1 H, 5-H), 2.04–2.15 (m, 1 H, H-5), 2.06 (s, 1 H, OH), 2.22–2.34 (m, 1 H, 3-H), 3.85 (m, 2 H, 6-H), 4.20 (td, *J* = 11, 3 Hz, 1 H, 4-H), 4.43 (dd, *J* = 11, 7 Hz, 1 H, 3′-H), 4.60 (dd, *J* = 11, 7.5 Hz, 1 H, 3′-H), 4.77 (dd, *J* = 4, 3.5 Hz, 1 H, 2-H), 5.87 (d, *J* = 3.5 Hz, 1 H, 1-H), 7.45 (m, 2 H, *m*-ar-H), 7.58 (m, 1 H, *p*-ar-H), 8.07 (m, 2 H, *o*-ar-H); IR (CCl_4) 3540, 2990, 2960, 2940, 1730, 1450, 1375, 1365, 1275 cm^{-1}; MS, *m/e* 307, 247, 219, 185, 125, 105, 77.

(1*R*,5*R*,6*R*,7*R*)-6-[(Benzoyloxy)methyl]-7-hydroxy-2,8-dioxabicyclo[3.2.1]octane (49). To a solution of **47** (2.246 g, 6.976 mmol) in methanol was added dry acidic cation-exchange resin (Dowex 50 W8, 2.0 g), and the mixture was heated at reflux for 5.5 h. The resin was removed by filtration and the methanol evaporated to leave **48** (2.029 g) as an oil. The oil was dissolved in toluene (25 mL), the solution added to a refluxing suspension of dry cation-exchange resin (Dowex 50 W8, 13 g) in toluene (250 mL), and the mixture refluxed for 15 min. After being filtered, the toluene solution was washed with saturated $NaHCO_3$ and brine, dried, and evaporated. The residue was chromatographed (silica gel, ethyl acetate/hexane, 6:4) to leave **49** (1.250 g, 69%) as a clear oil, which was crystallized from ethyl acetate/hexane (white needles, mp 96–97 °C). **48** (ca. 9:1 mixture of anomers, major anomer): ^1H NMR ($CDCl_3$) δ 1.78–2.04 (m, 2 H, $HOCH_2CH_2$), 2.5 (br, OH), 2.56 (m, 1 H, 3-H), 3.38 (s, 3 H, OCH_3), 3.89 (t, *J* = 7 Hz, 2 H, $HOCH_2$), 4.10–4.28 (m, 3 H, 4-H, 3′-H), 4.80 (dd, *J* = 11, 9.5 Hz, 1 H, 2-H), 4.88 (s, 1 H, 1-H), 7.45 (m, 2 H, *m*-ar-H), 7.58 (m, 1 H, *p*-ar-H), 8.07 (m, 2 H, *o*-ar-H). **49**: ^1H NMR ($CDCl_3$) δ 1.30 (dm, *J* = 13 Hz, 1 H, 4-H), 2.29 (d, *J* = 6.5 Hz, 1 H, OH), 2.38 (m, 1 H, 6-H), 2.73 (m, 1 H, 4-H), 3.82 (td, *J* = 12, 4 Hz, 1 H, 3-H), 3.94 (dd, *J* = 12, 6.5 Hz, 1 H, 3-H), 4.49 (dd, *J* = 11, 4 Hz, 1 H, CH_2OBz), 4.57 (s, 1 H, 5-H), 4.72 (dd, *J* = 11, 7 Hz, 1 H, CH_2OBz), 4.65 (t, *J* = 6.5 Hz, 1 H, 7-H), 5.23 (s, 1 H, 1-H), 7.44 (m, 2 H, *m*-ar-H), 7.60 (m, 1 H, *p*-ar-H), 8.05 (m, 2 H, *o*-ar-H); IR (Kbr) 3470 (br), 2960, 1710, 1290, 1270, 1255, 1140, 1085, 710 cm^{-1}; MS, *m/e* 135, 123, 105, 77. Anal. Calcd for $C_{14}H_{16}O_5$ (264.28): C, 63.63; H, 6.10. Found: C, 63.78; H, 6.19.

(1*R*,5*R*,6*R*,7*R*)-6-[(Benzoyloxy)methyl]-7-[[3-(trifluoromethyl)benzoyl]oxy]-2,8-dioxabicyclo[3.2.1]octane (52). To a solution of **49** (272 mg, 1.030 mmol) and DMAP (5 mg) in pyridine (20 mL) was added at 0 °C *m*-(trifluoromethyl)benzoyl chloride (240 μL, 1.5 equiv). The mixture was warmed to room temperature and stirred for 3 h. Methanol (2 mL) was added, the solvents were removed in vacuo, and the residue was chromatographed (silica gel/hexane/ethyl acetate, 7:3) to yield **52** (396 mg, 88%) as a clear oil: ^1H NMR ($CDCl_3$) δ 1.43 (dm, *J* = 13 Hz, 1 H, 4-H), 2.47 (m, 1 H, 6-H), 3.04 (quar, *J* = 7.5 Hz, 1 H, 4-H), 4.02 (m, 2 H, 3-H), 4.51 (m, 2 H, CH_2OBz), 4.64 (m, 1 H, 5-H), 5.41 (s, 1 H, 1-H), 6.04 (d, *J* = 8 Hz, 1 H, 7-H), 7.34, 7.53, 7.77, 7.86, 8.17, 8.20 (6 m, 9 H, ar-H); IR (CCl_4) 2960, 2870, 1740, 1450, 1335, 1270, 1245 cm^{-1}; MS, *m/e* 436, 364, 275, 263, 173, 145, 105. Anal. Calcd for $C_{22}H_{19}O_6F_3$ (436.38): C, 60.55; H, 4.39. Found: C, 60.59; H, 4.53.

1-[(2*R*,3*R*,4*R*,5*R*)-3-[[3-(Trifluoromethyl)benzoyl]oxy]-4-[(benzoyloxy)methyl]-5-(2-hydroxyethyl)tetrahydrofuran-2-yl]uracil (53). A mixture of **52** (98 mg, 0.211 mmol), uracil (26 mg, 1.1 equiv), and MSTFA in acetonitrile (2.0 mL) was stirred at 80 °C until a clear solution had formed (ca. 30 min). To this solution was added $SnCl_4$ (37 μL) at room temperature, and the solution was stirred for 40 h. The reaction mixture was cooled to 0 °C, and saturated $NaHCO_3$ (1 mL) was added. The mixture was then extracted three times with ethyl acetate. The combined organic layers were dried and evaporated, and the residue was chromatographed (silica gel, ethyl acetate) to yield **53** (110 mg, 95%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.98–2.26 (3 H, $HOCH_2CH_2$, OH), 3.07 (m, 1 H, 4′-H), 3.93 (m, 2 H, $HOCH_2$), 4.45 (td, *J* = 3.5, 9 Hz, 1 H, 5′-H), 4.56 (m, 2 H, CH_2OBz), 5.79 (d, *J* = 8 Hz, 1 H, 5-H), 5.81 (d, *J* = 2 Hz, 1 H, 2′-H), 5.83 (dd, *J* = 6.5, 2 Hz, 3′-H), 7.38, 7.55, 7.83, 7.94, 8.08, 8.24 (6 m, 10 H, 6-H, ar-H), 9.03 (s, 1 H, NH); IR (KBr) 3430, 3120, 3060, 2950, 1720, 1690, 1618, 1600, 1582, 1450, 1250, 1130, 815, 755, 714, 693 cm^{-1}; MS, *m/e* 190, 173, 145, 125, 111, 105, 95, 77.

1-[(2*R*,4*R*,5*R*)-4-[(Benzoyloxy)methyl]-5-(2-hydroxyethyl)tetrahydrofuran-2-yl]uracil (β-27). Benzoate **53** (77 mg, 0.14 mmol) and *N*-methylcarbazole (13 mg, 1.1 equiv) were dissolved in 2-propanol/water (9:1, degassed by saturating with argon for 30 min, 140 mL), and the mixture was irradiated at ca. 10 °C for 90 min with a 400-W high-pressure mercury lamp through a Pyrex filter. The solvents were removed under reduced pressure, and the residue was chromatographed (silica gel/CH_2Cl_2/methanol, 9:1). After evaporation of the solvent, the residue was crystallized from ethyl acetate to give β-**27** (43 mg, 85%) as colorless prisms: mp 157–158 °C; ^1H NMR ($CDCl_3$) δ 1.80–2.58 (5 m, 6 H, 3′-H, 4′-H, $HOCH_2CH_2$, OH), 3.89 (m, 2 H, $HOCH_2$), 4.11 (td, *J* = 9, 3 Hz, 1 H, 5′-H), 4.21 (m, 2 H, CH_2OBz), 5.77 (dd, *J* = 8, 2 Hz, 1 H, 5-H), 6.12 (dd, *J* = 7, 3.5 Hz, 1 H, 2′-H), 7.48 (m, 3 H, *m*-ar-H, 6-H), 7.61 (m, 1 H, *p*-ar-H), 8.02 (m, 3 H, NH, *o*-ar-H); IR (KBr) 3510, 3460, 3110, 3060, 2990, 1727, 1680, 1450, 1220, 1123, 772, 710 cm^{-1}; MS, *m/e* 249, 127, 112, 109, 105, 95, 77. Anal. Calcd for $C_{18}H_{20}N_2O_6$ (360.37): C, 59.99; H, 5.59; N, 7.77. Found: C, 60.03; H, 5.62; N, 7.68.

1-[(2*R*,4*R*,5*R*)-4-[(Benzoyloxy)methyl]-5-[2-(acetylthio)ethyl]tetrahydrofuran-2-yl]uracil (β-40). PPh_3 (39 mg, 2 equiv) and DIAD (30 μL, 2 equiv) in THF (1.5 mL) were reacted with β-**27** (27 mg, 75 μmol) and thioacetic acid (11.5 μL, 2 equiv) in THF (0.75 mL). TLC (1-mm silica gel plate, CH_2Cl_2/methanol, 96:4) yielded β-**40** (21 mg, 67%) as a clear oil (analytical data vide supra).

***N*⁶-Benzoyl-9-[(2*R*,4*R*,5*R*)-4-(hydroxymethyl)-5-(2-mercaptoethyl)tetrahydrofuran-2-yl]adenine (54).** To a solution of **36** (300 mg, 0.550 mmol) in THF/methanol (1:1, 2.0 mL) was added 1 M NaOH (1.7 mL), and the mixture was stirred at 0 °C for 1.5 h. Pyridinium-Dowex was added, the mixture filtered, and the solvent evaporated. The resulting oil was chromatographed (silica gel, CH_2Cl_2/methanol, 9:1) to yield **54** (197 mg, 90%) as a white foam: ^1H NMR ($CDCl_3$) δ 1.98–2.10 and 2.45–2.82 (2 m, 8 H, OH, 3′-H, 4′-H, $HSCH_2CH_2$), 3.82 (m, 2 H, $HOCH_2$), 4.19 (m, 1 H, 5′-H), 6.33 (dd, *J* = 3, 6.5 Hz, 1′-H), 7.50–7.65 (m, 3 H, *m,p*-ar-H), 8.04 (m, 2 H, *o*-ar-H), 8.18 (s, 1 H, 8-H), 8.81 (s, 1 H, 2-H), 9.07 (s br, 1 H, NH); IR (KBr) 3620, 3400, 3000, 2940, 1710, 1610, 1560, 1455.

***N*⁶-Benzoyl-9-[(2*R*,4*R*,5*R*)-4-(hydroxymethyl)-5-[2-(methylthio)ethyl]tetrahydrofuran-2-yl]adenine (55).** To a solution of **54** (30 mg, 75.1 μmol) in DMF (0.2 mL) was added Cs_2CO_3 (25.0 mg, 1.1 equiv), and the mixture was stirred at 0 °C for 2 h. Acetic acid (10 μL) was added and the solvent removed in vacuo. The resulting oil was chromatographed (1-mm silica gel TLC plate, CH_2Cl_2/methanol, 9:1) to yield 25 mg (82%) **55**: ^1H NMR ($CDCl_3$) δ 1.90–2.05 and 2.42–2.80 (2 m, 8 H, OH, 3′-H, 4′-H, $MeSCH_2CH_2$), 2.10 (s, 3 H, CH_3), 3.80 (m, 2 H, $HOCH_2$), 4.14 (m, 1 H, 5′-H), 6.32 (dd, *J* = 3.5, 6.5 Hz, 2′-H), 7.55 (m, 3 H, *m,p*-ar-H), 8.05 (m, 2 H, *o*-ar-H), 8.20 (s, 1 H, 8-H), 8.78 (s, 1 H, 2-H), 9.18 (s br, 1 H, NH); MS, *m/e* 413, 310, 294, 239, 211, 156, 105.

***N*⁶-Benzoyl-9-[(2*R*,4*R*,5*R*)-4-[[(methylsulfonyl)oxy]methyl]-5-[2-(methylsulfonyl)ethyl]tetrahydrofuran-2-yl]adenine (56).** Oxone (400 μL of a 0.625 M solution in 1 M sodoium acetate buffer, pH 4.5) was added at room temperature to a solution of **55** (20 mg, 48 μmol) in methanol (400 μL). The mixture was stirred at room temperature for 30 min. Methanol (1 mL) was added and the mixture filtered. The filtrate was applied to a TLC plate (1 mm), which was eluted three times with CH_2Cl_2/methanol, 9:1. Yield: 25 mg (81%) of the corresponding sulfone. The compound obtained was dissolved in pyridine, the solution was cooled to 0 °C, and MsCl (14 μL, 3.0 equiv) was added. After 1 h at 0 °C the solvent was removed in vacuo and the residue applied to a silica gel TLC plate (0.5 mm), which was eluted with CH_2Cl_2/methanol, 9:1, to furnish **56** (24.5 mg, 77%): ^1H NMR ($CDCl_3$) δ 2.18–2.60 (2 m, 5 H, 3′-H, 4′-H, $SO_2CH_2CH_2$), 2.88 (s, 3 H, O_2SCH_3), 2.90–3.05 (m, 1 H, SO_2CH_2), 3.10 (s, 3 H, O_3SCH_3), 3.15–3.24 (m, 1 H, SO_2CH_2), 4.26 (m, 1 H, 5′-H), 4.38 (m, 2 H, 4″-H), 6.26 (dd, *J* = 3.5, 8 Hz, 2′-H), 7.55 (m, 3 H, *m,p*-ar-H), 8.03 (m, 2 H, *o*-ar-H), 8.12 (s, 1 H, 8-H), 8.77 (s, 1 H, 2-H), 9.13 (s br, 1 H, NH); ^{13}C NMR δ 27.1 (C-5′), 34.5 (C-2′), 37.8, 41.1 (CH_3), 42.6 (C-3′), 51.3 (C-3″), 68.5 (C-6′), 81.4 (C-4′), 128.3, 129.3, 133.3, 133.7 (ar-C), 142.4 (C-8), 150.1, 151.5 (C-4, C-6), 153.2 (C-2), 165.1 (CO); MS, *m/e* 427, 398, 348, 334, 320, 278, 253, 239, 211, 174, 135, 122, 105.

Preparation of 57, the Thioether-Linked Dimer of the Protected Adenosine Analogue. To a solution of **56** (4.7 mg, 8.98 μmol) and **54** (4.3 mg, 1.2 equiv) in DMF (50 μL) was added diazabicycloundecene (DBU, 1.8 μL, 1.3 equiv), and the solution was stirred for 72 h at room temperature. Acetic acid (0.5 μL) was added and the solvent removed in vacuo. The residue was applied to a silica gel TLC plate (0.25 mm) and the plate eluted three times with CH_2Cl_2/methanol, 9:1. Isolation of the product yielded **57** (5.8 mg, 78%): FAB⁺-MS, *m/e* 825 ($M^+ - 1$).

Preparation of 58, the Sulfone-Linked Dimer of the Protected Adenosine Analogue. To a solution of **56** (3.2 mg, 6.13 μmol) and **54** 2.9 mg, 1.2 equiv) in DMF (40 μL) was added DBU (1.2 μL, 1.3 equiv), and the solution was stirred for 96 h at room temperature. Acetic acid (0.5 μL) was added, followed by oxone (30 μL of a 0.625 M solution in 2 M sodium acetate, pH 4.5). The mixture was stirred for 30 min and the solvent removed in vacuo. The residue was applied to a silica gel TLC plate (0.25 mm) and the plate eluted three times with CH_2Cl_2/methanol, 9:1. Isolation of the product afforded **58** (3.5 mg, 70%): ^1H NMR ($CDCl_3$) δ 2.42–2.98 (m, 8 H), 3.09 (s, 3 H, O_2SCH_3), 3.32 (td, 1 H), 3.44–4.03 (m, 10 H), 4.24 (m, 1 H), 4.43 (m, 1 H), 6.56 (dd, *J* = 3.5, 7.5 Hz, 1 H), 6.62 (dd, *J* = 3, 7 Hz, 1 H), 7.24–7.56 (m, 6 H, *m,p*-ar-H), 8.36 (m, 4 H, *o*-ar-H), 8.81, 8.92, 8.94, 9.04 (4 s, 4 H).