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Stereoselective Synthesis of Conformationally Constrained 2′-Deoxy-4′-thia β-Anomeric Spirocyclic Nucleosides Featuring Either Hydroxyl Configuration at C5′

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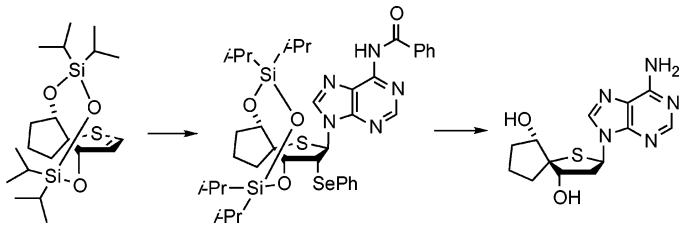
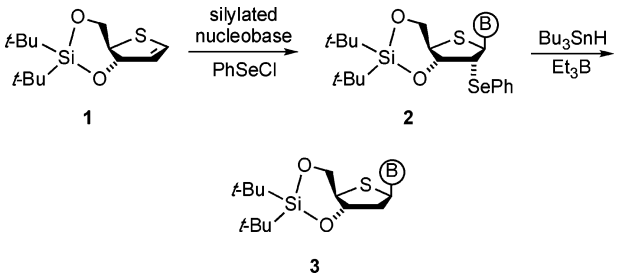


An enantioselective approach to 2′-deoxy-4′-thia spirocyclic nucleosides featuring an α- or β-hydroxyl substituent at C-5′ of the carbocyclic ring is detailed. The starting point is the mandelate acetal **8**. The overall strategy involves the stereocontrolled dihydroxylation of this dihydrothiophene, subsequent generation of the keto acetonide **12** followed by its Meerwein−Ponndorf−Verley reduction and β-elimination, protection of the resulting dihydroxy thiaglycal, electrophilic glycosidation according to the Haraguchi protocol, reductive removal of the phenylseleno group, and end-game global deprotection. Acquisition of the α- and β-5′-isomers is equally facile. Various 1D and 2D NMR techniques are used for assigning configuration.

During the past four decades, 4′-thianucleosides have emerged from the realm of heterocyclic curiosities to become candidate compounds for clinical evaluation. These mimics in which the furanose ring oxygen is replaced by a sulfur atom have come under intense preparative scrutiny.[1,2] This effort has been fueled in large part by the very promising antiviral[3] and anticancer activities[4] of members of this class. The increased stability of the glycosidic bond to nucleases[5] with resultant decreases in the rate of metabolic degradation[6] has also not gone unnoticed. The earliest access route designed to reach 4′-thianucleosides involved Vorbrüggen-type coupling of activated 4-thiapentafuranoses to silylated nucleobases.[7] Early on, such classical glycosylations were recognized to suffer from an inability to deliver predominantly the β-anomer. A notably weak aspect was the lack of dependability even when neighboring C-2 acyloxy participation was available.[8] For this reason, recourse was in turn made to adaptation of the Pummerer rearrangement.[9] However, this approach likewise suffers from coproduction of significant amounts of the α-anomer,[10] especially in the absence of suitable control elements.[11]

These shortcomings in turn prompted the utilization of 4-thiafuranoid glycals as glycosyl donors.[2r,12] The practicalities are such that reaction between a dihydrothiophene typified by **1** and a silylated nucleobase in the presence of phenylselenenyl chloride affords the β-anomer **2**. Subsequent radical-mediated removal of the PhSe substituent gives rise directly to **3**.



More recently, the use of hypervalent iodine compounds for coupling cyclic sulfides with silylated nucleobases has been developed.[2s]

Several years ago, we introduced the concept of spirocyclic restriction in nucleosides.[13] Structural modification in the manner exemplified by **4** allows for proper con-

(1) Review: Yokoyama, M. *Synthesis* **2000**, 1637.

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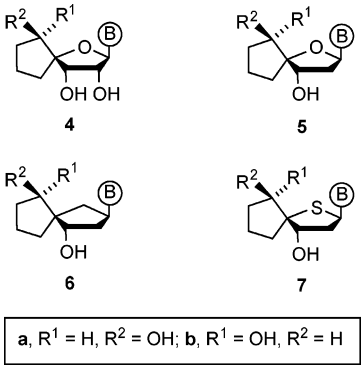
formational biasing and for the purposeful distinction between C5′-stereoisomers (*a* and *b* series).[14] Among the synthetic issues that have since been addressed are those of devising workable approaches to analogues bearing a modified 2′-deoxyribose moiety such as **5**.[15] As matters progressed, a practical route to enantiomerically pure spiro[4.4]nonanes **6** has been realized.[16] We have now focused our attention on extending this investigation to include the sulfur analogues **7a** and **7b**. Our prospects for success were derived in part from methodology developed earlier for incorporating sulfur at the apex position of spirocyclic deoxy congeners.[17]



a, R^1 = H, R^2 = OH; **b**, R^1 = OH, R^2 = H

Results and Discussion

Chemoselective Oxidation Profile. With the ready availability of optically pure **8**,[17] we undertook to explore those features that would result in the selective oxidation of its double bond and not its sulfur atom. The involvement of **8** was founded on the expectation that the significant steric shielding of the mandelate unit might cleanly differentiate the α and β faces of the 2,5-dihydrothiophene ring. For calibration purposes, **8** was initially subjected to the action of sodium periodate supported on silica gel[18] as well as the Davis oxaziridine reagent.[19] In line with expectations,[20] both sets of conditions afforded exclusively one diastereomer of the unsaturated sulfoxide **9**, further treatment of which with *m*-chloroperbenzoic acid gave sulfone **10** (Scheme 1). Other reagents such as peracetic acid[21] and manganese dioxide[22] are recognized for their capability to oxidize sulfides to sulfoxides. All four reagents share the characteristic of engaging very slowly, if at all, in the further oxidation of sulfoxides to sulfones.

In contrast, permanganate ion and osmium tetroxide oxidize sulfoxides rapidly to sulfones, but react slowly

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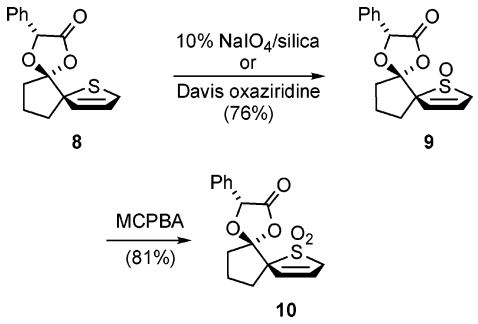
SCHEME 1



with sulfides. In fact, OsO_4 has been reported to be totally inert to reaction with sulfides.[23] However, Kaldor[24] and Priebe[25] have shown that in the presence of tertiary amines, OsO_4 efficiently oxidizes sulfides to sulfones, and furthermore that catalytic quantities of OsO_4 in the presence of stoichiometric amounts of trialkylamine *N*-oxides likewise accomplish this transformation. More relevantly, Hauser used the above reagents to stereospecifically dihydroxylate an olefinic center in an acyclic system that was guided by a sulfoxide group more remote than homoallylic, and furnished diacetoxy sulfones as the final products after acetylation.[26] The use of these oxidant combinations in the present context is consequently precluded.

More recently, Sharpless[27] and Sammakia[28] described the use of AD-mix reagents for the dihydroxylation of olefins in the presence of sulfides, disulfides, and dithianes with potassium ferricyanide serving as the co-oxidant. These researchers also defined the scope of this transformation and illustrated that prevailing steric and electron-withdrawing factors resident in the substrates determined the extent of sulfur over-oxidation. Although a mechanistic rationale of these phenomena remains elusive, synthetic applicability of the AD-mix process for the present purposes demanded exploration.

The choice between AD-mix-α or AD-mix-β[29] happens not to be a critical one because only the α face of the carbon−carbon double bond in **8** is approachable by these sterically demanding reagents. Therefore, selection of the mismatched ligand would only retard the reaction rate and likely lower the yield. Our early experimental probes showed the AD-mix-β yields to be favored over those realized from the AD-mix-α reagent by a factor of 3:1. Consequently, $(DHQD)_2PHAL$ is of the proper chirality to serve as a ligand of choice.

Cyclic cis-disubstituted olefins related to **8** are recognized to be the most difficult type to be oxidized in the AD process, and **8** is no exception. Members of this structural class tend to react slowly and to give rise to low ee values.[30] Ultimately, we found that the chiral ligand $(DHQD)_2PYR$[31] was more suitable than $(DHQD)_2$-PHAL, and that raising the potassium osmate level to 10 mol % with co-addition of 2 equiv of methanesulfonamide rectified the rate problem. An increase in the reaction temperature from room temperature to 40 °C as recommended by others[32] resulted in decomposition and is ill-advised. Under the optimized conditions, **11** was isolated in 66% yield at 84% conversion.

It is well-known that many tertiary amines can dramatically accelerate catalytic osmium-promoted dihydroxylation by enhancing the rate of formation of osmate esters.[32] The possibility of utilizing DABCO presented itself since our concern was not stereoselectivity but chemoselectivity. Indeed, the use of DABCO furnished **11** in 53% yield at 77% conversion. Unfortunately, hydrolysis of the mandelate acetal and oxidation at sulfur were observed to be competing processes. Remarkably, both problems were well resolved when the reaction mixture was buffered with 3 equiv of sodium bicarbonate.[33] These conditions were accompanied by a cleaner, faster reaction, and gave rise to **11** in 77% yield at 77% conversion after overnight stirring (Scheme 2). The stereochemical assignment to **11** was based on a NOESY correlation between the benzylic proton and H-2, reflecting an S-type (2-*endo*/3-*exo*) conformation (Figure 1). The calculations were performed with Monte Carlo simula-

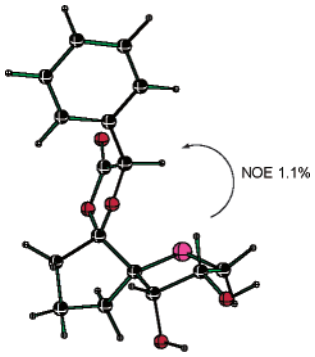
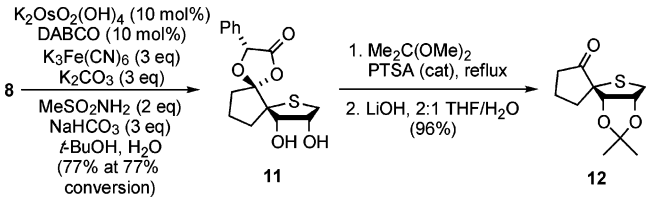


FIGURE 1. Global energy minimum of diol **11**.

SCHEME 2



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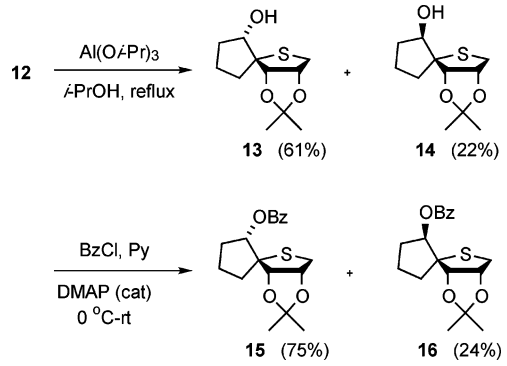
SCHEME 3

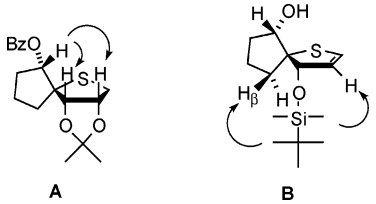


tions (MacroModel version 5.0) of 5000 different conformations in the MM3 force field.

To arrive at **12**, the diol was heated in neat 2,2-dimethoxypropane containing a catalytic quantity of *p*-toluenesulfonic acid,[34] and the resulting acetonide was hydrolyzed with lithium hydroxide in THF and water.[35] The yield of **12** was 96% over two steps.

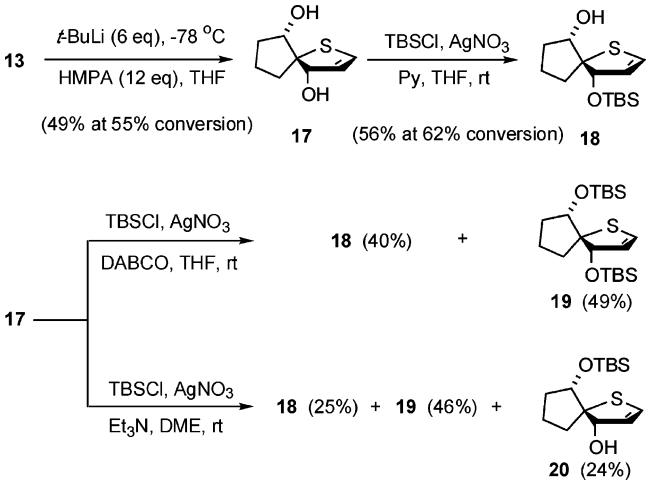
Synthesis of the 4-Thiaglycal. The next interim goal was considered to be a pair of suitably protected 4-thiaglycals otherwise epimeric at C5. It was hoped that conditions would be found to transform **12** into approximately equal amounts of the secondary carbinols. In their study of the parent thiaspiro ketone, Dmitroff and Fallis noted that methyllithium, methylmagnesium bromide, and several hydride reagents exhibited a strong preference for attack anti to the sulfur atom.[36] More balanced product distributions have been noted with zinc borohydride[36] and lithium aluminum hydride.[17] However, exposure of **12** to either of these reagents resulted in highly favored conversion to the syn carbinol **13** (25:1 for $Zn(BH_4)_2$; 15:1 for $LiAlH_4$). When alternative recourse was made to Meerwein-Ponndorf-Verley reduction,[37] **13** and **14** were concomitantly produced in 61% and 22% yield, respectively (Scheme 3). This protocol was equally successful on larger scale, providing that care was taken to use saturated sodium potassium tartrate and sodium hydroxide solutions in the workup. Treatment with the more customary 1 N HCl solution[38] caused destruction of the acetonide unit.

The derived benzoate esters **15** and **16** were easily distinguished on the basis of NOE studies. For example, the *syn* nature of the three carbinol protons in **15** was made evident by the correlations observed between H-5/H-2 and H-5/H-3 as shown in **A**.



At this point, the conversion of **13** into a glycal in preparation for eventual nucleoside formation was targeted for attention. We were mindful that the presence of a sulfide atom exerts an acidifying effect on its α protons as a consequence of electron-withdrawing effects and stabilization of the resulting carbanion by d orbitals.[39] However, such α protons are only very weak acids, and their removal requires a strong base. Often, organolithium reagents are used in conjunction with additives such as hexamethylphosphoramide,[40] tetramethylethylenediamine,[41] and DABCO.[42] In the present case, **13** was treated with *tert*-butyllithium (6 equiv) and HMPA (12 equiv) in THF at −78 °C. These conditions gave rise to diol **17** in 49% yield at 55% conversion (Scheme 4). Recourse to other solvents (e.g., pentane) or alternative ligands (e.g., TMEDA) proved notably less effective, as did prior hydroxyl protection as the TBS ether. Although **17** is sufficiently stable to allow its purification by flash chromatography, storage under nitrogen at −10 °C is mandatory. This sensitive glycal decomposes rapidly in the presence of methanol.

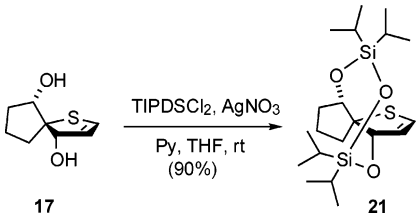
SCHEME 4



The instability of **17** was also apparent during attempts at silylation. Treatment with *tert*-butyldimethylsilyl triflate and 2,6-lutidine at −78 °C[43] led only to decomposition. In the presence of the less reactive silyl chloride, potassium hydride, and 18-crown-6,[44] no reaction was noted. Interesting results were recorded, however, when TBSCl was admixed with silver nitrate in the presence of different base and solvent combinations. Conditions of this type were originally reported by the Ogilvie group for the selective synthesis of either 2′,5′- or 3′,5′-disilylated purine and pyrimidine arabinonucleosides.[45] From among the combinations explored, the addition of TBSCl to a THF solution of **17**, $AgNO_3$, and pyridine furnished **18** (56% at 62% conversion) after overnight stirring. With a switch from pyridine to

(34) Baumgartner, J.; Weber, H. *Chirality* **2001**, *13* 159.
(35) Bigi, F.; Bocelli, G.; Maggi, R.; Sartori, G. *J. Org. Chem.* **1999**, *64*, 5004.
(36) Dimitroff, M.; Fallis, A. G. *Tetrahedron Lett.* **1998**, *39*, 2531.
(37) Paquette, L. A.; Owen, D. R.; Bibart, R. T.; Seekamp, C. K.; Kahane, A. L.; Lanter, J. C.; Corral, M. A. *J. Org. Chem.* **2001**, *66*, 2228.
(38) Schindler, W.; Frey, H.; Reichstein, T. *Helv. Chim. Acta* **1941**, *24*, 360.
(39) (a) von E. Doering, W.; Hoffmann, A. K. *J. Am. Chem. Soc.* **1955**, *77*, 521. (b) von E. Doering, W.; Levy, L. K. *J. Am. Chem. Soc.* **1955**, *77*, 509.
(40) Dolak, T. M.; Bryson, T. A. *Tetrahedron Lett.* **1977**, *23*, 1961.
(41) Peterson, D. *J. Org. Chem.* **1967**, *32*, 1717.
(42) Corey, E. J.; Seebach, D. *J. Org. Chem.* **1966**, *31*, 4097.
(43) (a) Askin, D.; Angst, C.; Danishefsky, S. *J. Org. Chem.* **1987**, *52*, 622. (b) Kocienski, P. J.; Love, C. J.; Whitby, R. J. *Tetrahedron* **1989**, *45*, 3839.
(44) Braish, T. F.; Fuchs, P. L. *Synth. Commun.* **1986**, *16*, 111.

SCHEME 5



DABCO, all of **17** was consumed with generation of both **18** and the bis-silylated derivative **19** (Scheme 4). The most reactive conditions proved to involve 1,2-dimethoxyethane as the solvent and triethylamine as the base. In this instance, the outcome after 3 h was to form all three possible products, including the regioisomer **20** not previously encountered. The two monoprotected spiro thiaglycals were amenable to conversion to **19** simply by extending the reaction time.

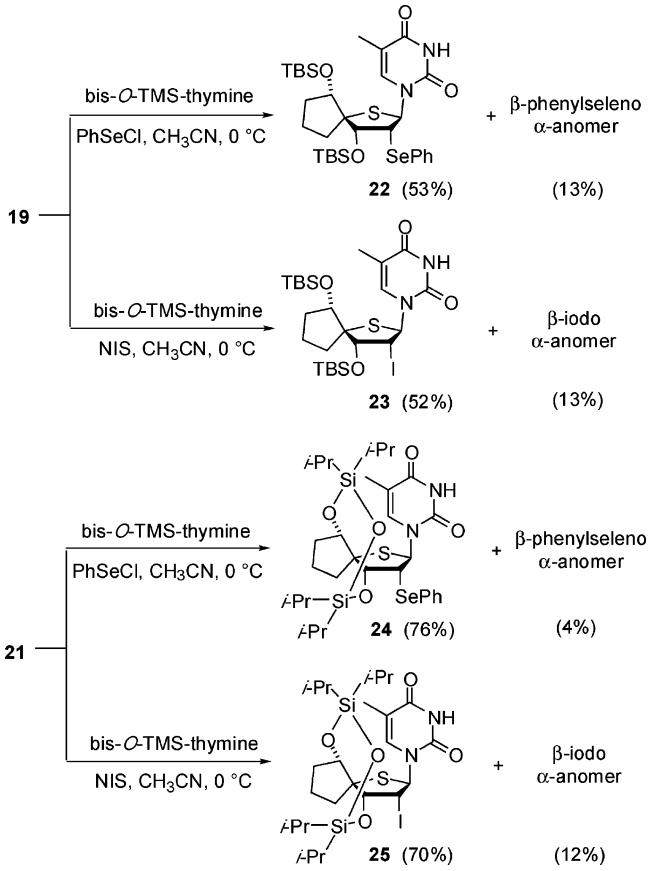
The necessary distinction between **18** and **20** was achieved by application of 2D-NOESY spectroscopy. For **18**, correlations were observed between the silyl methyl protons and H-2, as well as between the silyl *tert*-butyl protons and H-8β (see **B**). These characteristic patterns are not seen in **20**. Added confirmation was derived by subjecting **18** to D_2O exchange. Its free OH peak, observed as a broad doublet, exhibited a COSY correlation with H-5 ($^3J_{5,5-OH}$ = 4.9 Hz), which disappeared when shaken with D_2O. Simultaneously, the H-5 signal became a pseudotriplet, thereby establishing the location of the hydroxyl group.

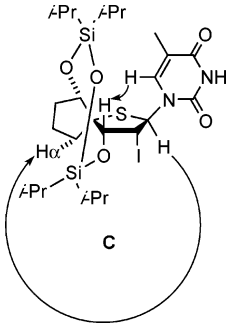
Notwithstanding the success encountered above, the bifunctional 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane reagent ($TIPDSCl_2$)[2r] proved to be superior. Despite the apparently long distance between the two hydroxyl groups in **17**, protection occurs readily at both sites in excellent yield (90%). The advantages offered by **21** (Scheme 5) are made apparent in the sequel. MM3 calculations establish that the belt generated upon introduction of the bifunctional TIPDS protecting group is structured across the β-surface of the spironucleoside core.

Stereoselective Synthesis of Spirocyclic 2′-Deoxy-4′-β-thianucleosides. With spirothiaglycals **19** and **21** in hand, their response to electrophilic glycosidation chemistry was explored. The first demonstration that **19** would react in the manner envisioned came upon reaction with phenylselenenyl chloride and persilylated thymine in CH_3CN at 0 °C. The coupling was complete within 1 h and gave 53% of **22** along with a minor diastereomer (13%, Scheme 6). No difficulties were encountered in substituting *N*-iodosuccinimide as the electrophile. In fact, the distribution of **23** and the α-isomer was essentially identical at 52:13. Improved stereoselectivity was realized with **21** as the glycosidation substrate. More specifically, the isolated yields of **24** and **25** reached 76% and 70%, respectively.

The ^{1}H NMR spectra of **22**−**24** are characterized by extensive overlap of several characteristics signals. However, comprehensive analysis of the relatively less complex spectrum of **25** permitted definition of its stereochemistry. Two key NOESY correlations were observed for H-1′/H-8′α and H-6/H-3′ (see **C**), thereby ruling out the α-configuration. Since the generation of **22**−**24** proceeds via the same mechanistic pathway, these spiro nucleosides should also be β-configured. Indeed, the subsequent transformation products to be defined below provide spectral evidence that confirms this conclusion.

SCHEME 6

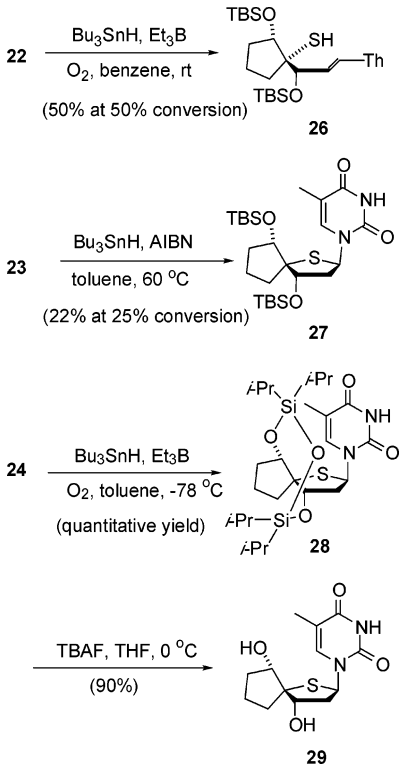




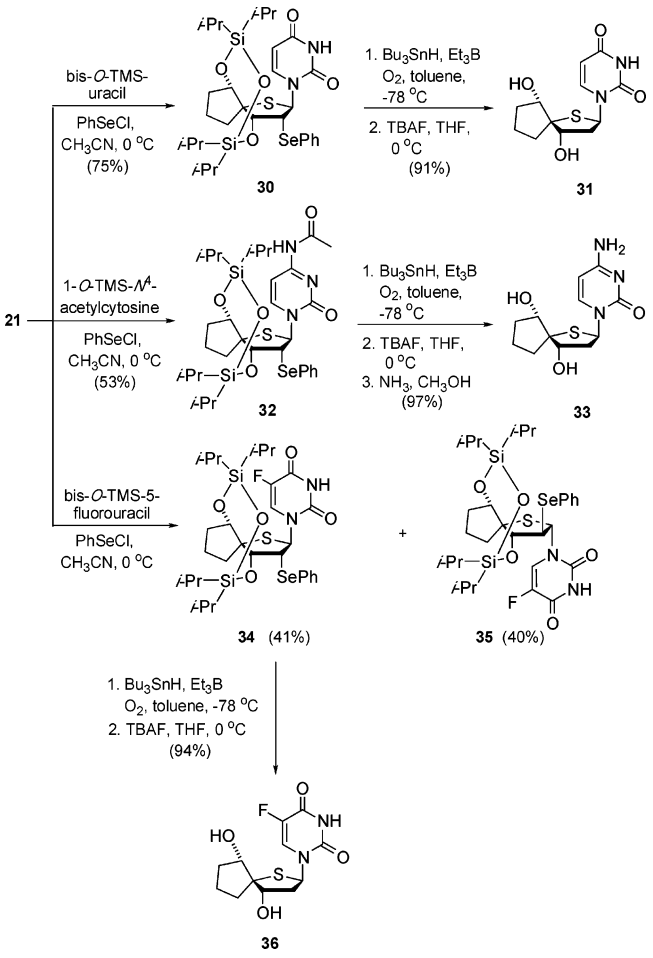
The issue of mechanism has been addressed by Haraguchi et al.[2r] who concluded that these face-selective electrophilic additions are controlled by the silyl protecting groups in use. For example, the TIPDS group was thought to shield the α-face of the thiaglycal double bond less than a 3-*O*-TBS substituent, thus giving rise to preferential α-face attack by the electrophilic agent and increased β/α-anomeric ratios. While this interpretation is a useful conceptual advance, other studies have defined that bulky substituents at the C-3 allylic centers are

(45) (a) Ogilvie, K. K.; McGee, D. P. C.; Boisvert, S. M.; Hakimelahi, G. H.; Proba, Z. A. *Can. J. Chem.* **1983**, *61*, 1204. (b) Ogilvie, K. K.; Hakimelahi, G. H.; Proba, Z. A.; McGee, D. P. C. *Tetrhedron Lett.* **1982**, *23*, 1997. (c) Hakimelahi, G. H.; Proba, Z. A.; Ogilvie, K. K. *Tetrahedron Lett.* **1981**, *22*, 5243.

SCHEME 7



SCHEME 8



necessary for attaining considerable regio- and stereoselectivities in glycosidation chemistry.[46]

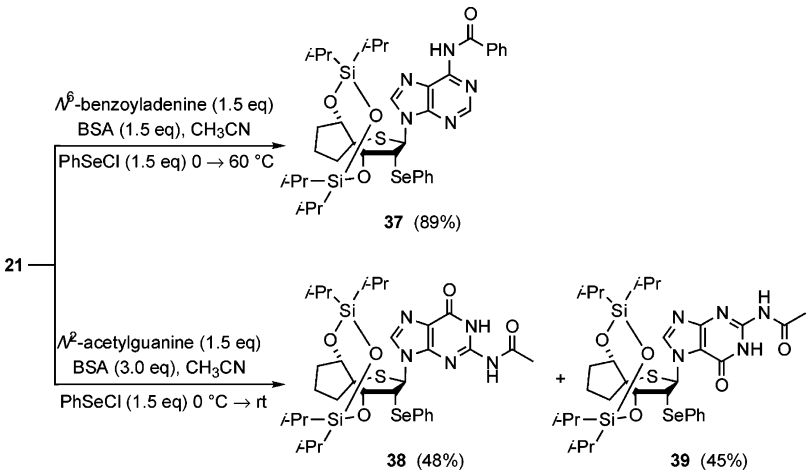
Added insight into these issues is available from the more extensively investigated field of non-sulfur glycal chemistry. According to Castillon,[47] the stereoselectivity of organoselenium addition reactions cannot be accounted for only in terms of the steric hindrance provided by the substituents resident at C-3 and C-5. In the phenylselenonium ion-forming transition state, the aryl group is far removed from substituents on the glycal ring.[48] Furthermore, the initial addition process is reversible and therefore thermodynamically controlled.[49] The possibility remains open that the relative stability of the selenonium cations might be controlled by the steric bulk and/or stereoelectronic stabilizing effect of the C-3/C-5 substituents. In addition, the global conformational characteristics of the glycal may lock the selenonium cation and thereby predetermine the stereoselectivity of nucleophilic attack by the nucleobase.

Studies involving removal of the heteroatom at C-2′ ensued. Unexpectedly, exposure of **22** to the action of tri-*n*-butyltin hydride and triethylborane in benzene at room temperature[2r] afforded only the ring-opened product **26** (Scheme 7). This reaction pathway may be facilitated by the formation of a boron−sulfur complex followed by β-radical elimination with release of ring strain. The complication was skirted to some extent by the reduction of iodide **23** with Bu_3SnH and AIBN in toluene at 60 °C.[50] Although the desired compound was obtained, the extent of conversion was low (25%). As a consequence of the precedent,[50] more elevated temperatures were expected to lead to **26** and were therefore not examined. The combination of relatively low stereoselectivity in the glycosylation step and the poor efficiency of the ensuing radical reduction caused the route involving **19** to be abandoned. It was then found that the conversion of **24** into **28** proceeds quantitatively at −78 °C under a continuous flow of oxygen. Ultimate arrival at **29** was accomplished by routine treatment with TBAF. However, purification of this nucleoside was less than straightforward. When eluted from silica gel with 10% methanol in CH_2Cl_2, **29** was appreciably contaminated with tetra-*n*-butylammonium salts. The R_f of these salts was greatly curtailed with a solvent change to 5% methanol in ethyl acetate, but tailing became an insurmountable problem. After considerable experimentation, 20% ethanol in toluene was found to be ideally suited to our purposes.

Introduction of Other Nucleobases. With the demonstration of a successful synthetic strategy to reach **29**, attention was directed to the introduction of other nucleobases. Three pyrimidine examples are grouped into Scheme 8. The generation of **30** and **32**, as well as their conversion to **31** and **33**, respectively, proceeded rather

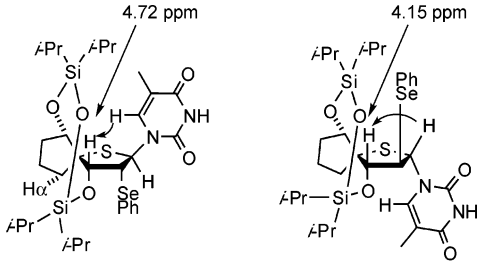
(46) Collins, P. M.; Ferrier, R. J. *Monosaccharides, Their Chemistry and Their Roles in Natural Products*; John Wiley & Sons: Chichester, U.K., 1995; pp 319ff.
(47) Diaz, Y.; El-Laghdach, A.; Castillon, S. *Tetrahedron* **1997**, *53*, 10921.
(48) Wang, J.; Wurster, J. A.; Wilson, L. J.; Liotta, D. *Tetrahedron Lett.* **1993**, *34*, 4881.
(49) Diaz, Y.; El-Laghdach, A.; Matheu, M. I.; Castillon, S. *J. Org. Chem.* **1997**, *62*, 1501.
(50) Miller, J. A.; Pugh, A. W.; Ullah, G. M. *Tetrahedron Lett.* **2000**, *41*, 3265.

SCHEME 9



smoothly. In contrast, treatment of **21** with persilylated 5-fluorouracil resulted in conversion to a 1:1 mixture of anomers **34** and **35**. Chromatographic separation proved feasible, thereby allowing for the ultimate acquisition of pure **36**.

Spectroscopic definition of anomeric configuration in these systems originated with **24** and its diastereomer. For the β-anomer, strong NOESY interaction is seen between H-3′ and H-6 (see **D**); in contrast, H-3′ of the α-anomer correlates with H-1′ (see **E**). Another useful



D **E**

diagnostic is the chemical shift of H-3′. This proton in **D** appears at 4.72 ppm in $CDCl_3$, and is seen to be shifted downfield due to the deshielding effect of the C-2 keto group in the thymine moiety.[51,52] In **E**, H-3′ exhibits a chemical shift of 4.15 ppm. Comparable features are apparent in **34** (4.54 ppm) and **35** (4.13 ppm).

Another empirical criterion based on anomeric proton line shapes has been extended to 4′-thianucleosides.[53] Thus, the H-1′ of β-anomers often appear as an "apparent triplet", in contrast to the doublet of doublets nature of H-1′ exhibited by their α counterparts. All four of the pyrimidine 4′-thiaspironucleosides conform well to this trend.

Last, it has been noted that the splitting patterns of H-1′ in the 2′-deoxy-2′-phenylseleno derivatives doubly protected with a 1,1,3,3-tetraisopropyldisiloxane-1,3-diyl unit at the 3′- and 5′-hydroxyl groups also allow for the assignment of anomeric configuration. For the β isomers, either a slightly broadened singlet or a narrowly coupled doublet (J < 3.2 Hz) is generally observed. On the other hand, the α isomers feature a doublet with J values larger than 9.8 Hz.

In light of the discovery of the significant anti-HIV activity of the purine nucleoside 2′,3′-dideoxyadenosine[54] and its known susceptibility to degradation by the action of adenosine deaminase[54] and purine nucleoside phosphorylase,[55] the pursuit of analogues resistant to forming inactive metabolites in this manner is of timely interest. The spirocyclic architecture and carbon−sulfur glycosidic bond under consideration here hold promise of offering such resistance to nucleoside metabolizing enzymes. With this goal in mind, **21** was brought separately into reaction with N^6-benzoyladenine and N^2-acetylguanine along with an equivalent of *N*,*O*-bis(trimethylsilyl)acetamide for 1 h prior to the addition of phenylselenenyl chloride.[2r] Three separable products were isolated in the adenine example, and two were observed for the guanine base. Interestingly and of great practical value, we found that for the adenine example the two minor products isomerized to the major one in a few days after standing in an NMR tube. Since the *N*-9-β isomers are recognized to be thermodynamically advantaged,[56] it follows that these targeted isomers should be the major products. Consequently, the reaction mixtures were incubated at 60 °C overnight, and **37** was isolated in 89% yield (Scheme 9). However, no significant isomerization was observed for the guanine base, and the extent of silylation affected the regiochemical outcome. Under the above conditions, **39** was isolated in 73% yield along with a small amount of **38**. When bis-silylated nucleobase was employed, **38** and **39** were isolated in 48% and 45% yield, respectively.

In agreement with the tentative assignments as β isomers, the anomeric proton in **37**-**39** appeared as doublets with a small coupling constant (J = 2.2−2.6 Hz). However, NOESY experiments failed to confirm the stereochemical features beyond reasonable doubt. On the

(51) (a) Yoshimura, Y.; Kitano, K.; Satoh, H.; Watanabe, M.; Miura, S.; Sakata, S.; Sasaki, T.; Matsuda, A. *J. Org. Chem.* **1996**, *61*, 822. (b) Yoshimura, Y.; Kitano, K.; Yamada, K.; Satoh, H.; Watanabe, M.; Miura, S.; Sakata, S.; Sasaki, T.; Matsuda, A. *J. Org. Chem.* **1997**, *62*, 3140.

(52) (a) Okabe, M.; Sun, R.-C.; Tam, S. Y.-K.; Todaro, L. J.; Coffen, D. L. *J. Org. Chem.* **1988**, *53*, 4780. (b) Brånalt, J.; Kvarnström, I.; Classon, B.; Samuelsson, B. *J. Org. Chem.* **1996**, *61*, 3604.

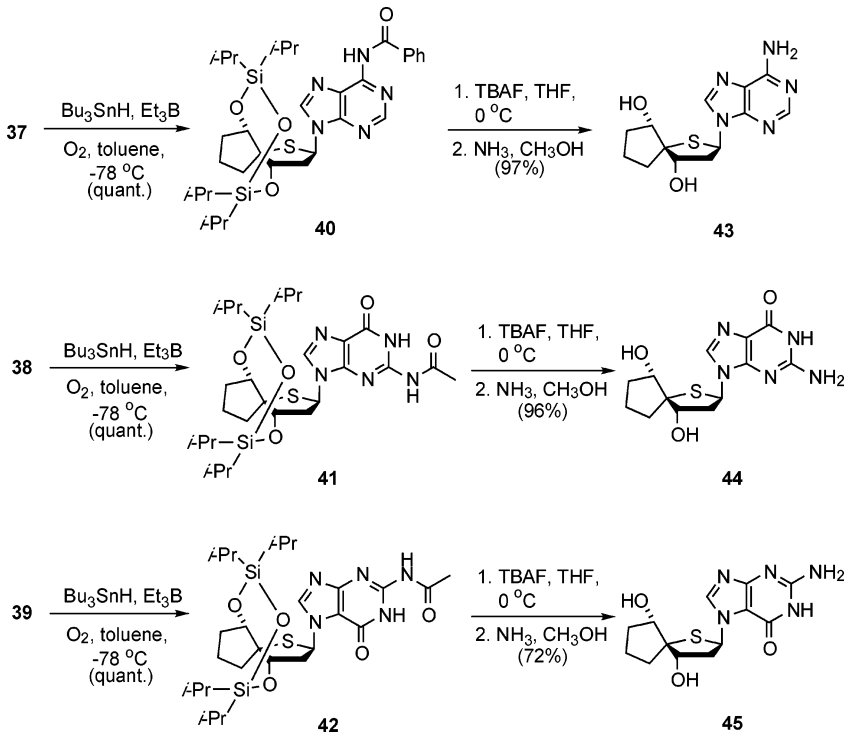
(53) (a) Robins, M. J.; Robins, R. K. *J. Am. Chem. Soc.* **1963**, *87*, 4934. (b) Robins, M. J.; Wood, S. G.; Dalley, N. K.; Herdewijn, P.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1989**, *32*, 1763. (c) Ye, S.; Rezende, M. M.; Deng, W.-P.; Herbert, B.; Daly, J. W.; Johnson, R. A.; Kirk, K. L. *J. Med. Chem.* **2004**, *47*, 1207.

(54) Balzarini, J.; Kang, G.-J.; Dalal, M.; Herdewijn, P.; De Clercq, E.; Broder, S.; Johns, D. B. *Mol. Pharmacol.* **1987**, *32*, 162.

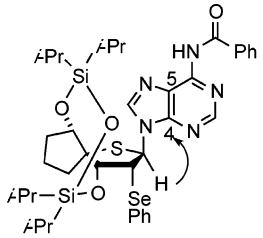
(55) Johnson, M. A.; Ahluwalia, G.; Connelly, M. C.; Cooney, D. A.; Broder, S.; Johns, D. G.; Fridland, A. *J. Biol. Chem.* **1988**, *263*, 15354.

(56) Paquette, L. A.; Kahane, A.; Seekamp, C. K. *J. Org. Chem.* **2004**, *69*, 5555.

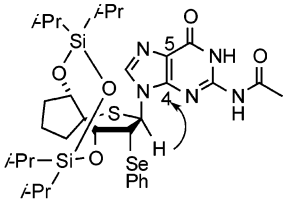
SCHEME 10



other hand, assignment of the site of attachment of the purine base (N-7 or N-9) could be confirmed by heteronuclear long-range bond correlation (HMBC).[53c] As shown in **F** and **G**, a $^3J_{C-H}$ interaction is anticipated between H-1′ and C-4 in the N-9 regioisomer, while the N-7 congeners should be distinguished by $^3J_{C-H}$ coupling between H-1′ and C-5.[57] In actuality, the HMBC spectrum of **37** and **38** conformed to the expectations given by **F** and **G** with no evidence for a correlation involving H-1′ and C-5. Compound **39** was tentatively assigned as the N-7 isomer without the expected H-1′/C-5 correlation observed, and the regiochemistry was confirmed only after the final product was obtained.

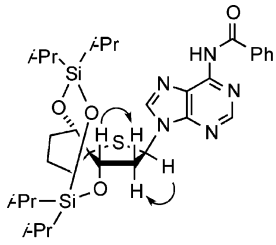


F

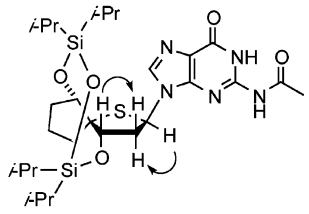


G

With **37**−**39** in hand, the final steps to **43**−**45** were traversed via well-established reactions (Scheme 10). For instance, radical-mediated removal of the phenylseleno groups[2r] served to deliver **40**−**42** in quantitative yield. NOESY experiments involving these intermediates convincingly established the anomeric configuration at C-1′ to be as in **H**−**J** as a consequence of a strong correlation involving H-1′ and H-2′α, and a comparable level of significant interaction involving H-3′ and H-2′β.



H



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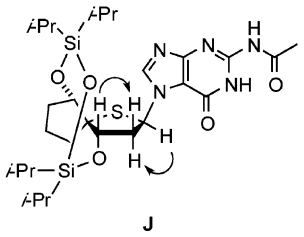


J

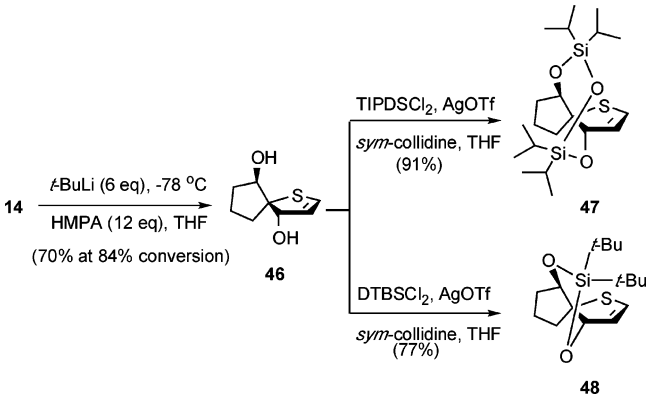
The β-configuration is not perturbed upon desilylation with TBAF and subsequent treatment with methanolic ammonia. UV spectral measurements have indicated that red-shift absorptions are associated with nucleosides where glycosylation has occurred at the 7-position of the purine bases.[58] Actually, **45** displays a UV maximum at 288 nm. In contrast, the UV maxima for **43** and **44** (λ_{max} 262 and 260 in CH_3OH, respectively) suggested the possibility that the N^9-substituted isomer was actually in hand. However, analysis based on the ^{13}C shifts of C-5 and C-8 in the nucleobase is considered to be a more reliable indicator of regiochemistry.[59] The Kjellberg-Johansson analysis rests on the fact that C-5 in N-7 systems appears more than 5 ppm upfield from that in

(57) This analysis was expected to be facilitated by the fact that the ^{13}C chemical shift of C-4 is more than 25 ppm downfield of C-5.
(58) Yoshimura, Y.; Watanabe, M.; Satoh, H.; Ashida, N.; Ijichi, K.; Sakata, S.; Machida, H.; Matsuda, A. *J. Med. Chem.* **1997**, *40*, 2177.
(59) Kjellberg, J.; Johansson, N. G. *Tetrahedron* **1996**, *42*, 6541.

TABLE 1. Comparison of ^{13}C NMR Shifts (ppm) for Adenosine, Guanosine, and 43−45 (DMSO-d_6 Solution)

carbon	adenosine	**43**	guanosine	**44**	**45**
C-5	119.6	119.1	117.5	116.4	108.0
C-8	140.2	140.0	136.9	136.2	142.2

SCHEME 11



N-9 isomers. For C-8, the reverse is true, with the signal in N-7 derivatives being distinguished from that in N-9 isomers by being positioned further than 5 ppm downfield. The data compiled in Table 1 for **43** and **44** are seen to compare very closely with those of adenosine and guanosine, respectively, thereby ruling out alternative structural assignments. The N-7 feature of **45** was confirmed by this comparison, with 9.5 ppm upfield for C-5, and 5.3 ppm downfield for C-8.

Synthetic Studies in the *Anti* Series. To gain broader implementation of the achievements recorded above, we pressed on with transformations involving the *anti*-configured congeners. Treatment of acetonide **14** with *tert*-butyllithium and HMPA supplied the 4-thiaglycal in 70% yield at 84% conversion (Scheme 11). This compound exists as a solid and came qualitatively to be regarded as less prone to degradation than the α-diol **17**. However, adoption of the identical procedure for its protection as the TIPDS derivative gave only 41% of the desired **47** along with 55% of an unidentified product which proved unresponsive to glycosidation. A viable alternative approach involving the use of silver triflate and *sym*-collidine[60] proved to be a key advance in efficiency (91%). These conditions were also suited to the preparation of the highly strained DTBS congener **48**.

For the purpose of assessing relative glycosidation efficiencies, **47** and **48** were treated identically with silylated thymine and uracil in the presence of phenylselenenyl chloride (Scheme 12). Both protected diols reacted readily at 0 °C to give **49**−**52**. In the glycosidation related to **51**, both anomers were formed in a ratio of 14:1. The somewhat lower yields realized for the generation and reactions of **48** conspired to cause us to proceed ahead with **47**.

Once the β-configurational assignment to **49** had been confirmed by 2D NMR techniques, the four additional nucleobases specified in Scheme 13 were incorporated into this *anti*-4-thiaglycal. The mono-*O*-TMS-5-fluorouracil was generated in situ by treatment of 5-fluorouracil

(60) Ziegler, T.; Echkhardt, E.; Neumann, K.; Birault, V. *Synthesis* **1992**, 1013.

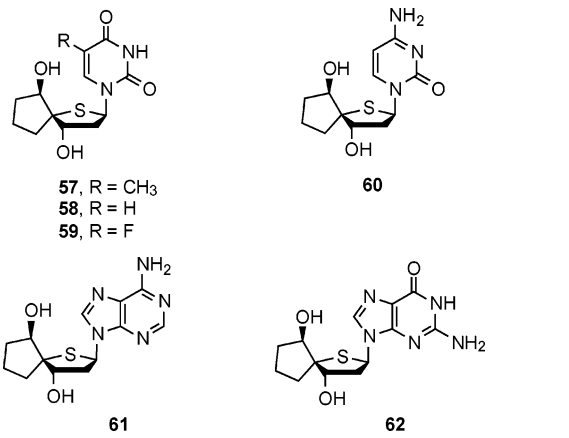
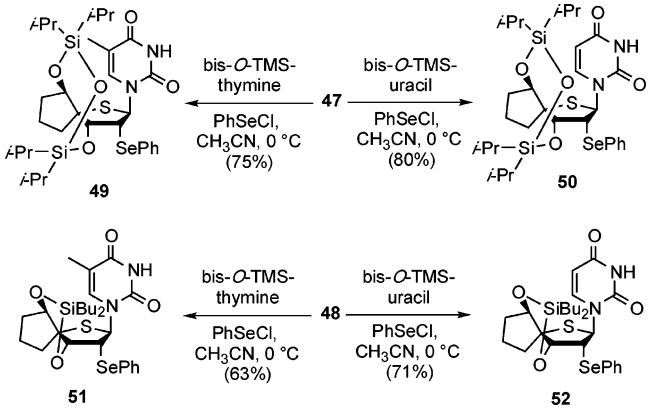


FIGURE 2. End products in the *anti* series.

SCHEME 12

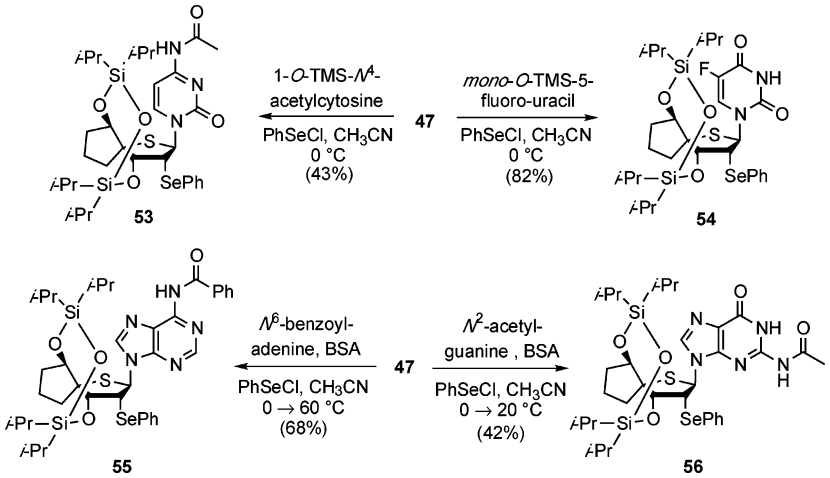


with an equivalent of BSA. A particularly noteworthy finding associated with **54** is the high stereoselectivity of its formation in good yield. This feature contrasts with the poor anomeric distribution realized for the *syn* counterpart when bis-*O*-TMS-5-fluorouracil was used (1:1 ratio of **34** and **35**).

Thereafter, removal of the phenylseleno groups and unmasking of the hydroxyl substituents and nucleobases were accomplished via routine operations to furnish the six spirocyclic 4′-thianucleosides within the *anti* series defined in Figure 2.

Overview. In conclusion, synthetic routes to enantiopure spiroannulated 2′-deoxy-4′-β-thiathymidine, -uridine, -5-fluorouridine, -cytidine, -adenosine, and -guanosine have been developed in both the *syn* and *anti* series. The synthetic pathway is initiated with an enantiomerically pure mandelate ketal, chemo- and stereoselective oxidation of its double bond under modified AD conditions, and β-elimination of the sulfide acetonide. Electrophilic glycosidation reactions mediated by the presence of phenylselenenyl chloride lead to incorporation of the nucleobases. The presence of a siloxane belt across the β-face of the glycal may facilitate installation of the proper anomeric configuration and ultimate arrival at the targeted 2′-deoxy-4′-thiaspironucleosides. Much has been learned about the chemistry of spirocyclic sulfides in the course of this investigation. We are currently developing a program targeting RNA models having analogous structural features. Results of this effort will be disclosed

SCHEME 13



shortly. Biological evaluation of the nucleosides reported herein is presently under investigation.

Experimental Section

Sulfoxide 9. A slurry of **8** (50 mg, 0.17 mmol) and 10% $NaIO_4/SiO_2$ (0.21 mmol/g, 1.66 g, 0.34 mmol) in a 1:1 mixture of CH_2Cl_2 and hexanes (10 mL) was stirred vigorously for 24 h at rt. The reaction mixture was filtered, and the silica was washed with 1% MeOH/Et_2O. The combined fractions were concentrated and subjected to flash chromatography on silica gel (2:1 EtOAc/hexanes) to afford **9** (40.2 mg, 76%) as a white solid: mp 125−126 °C; IR ($CHCl_3$, cm^{-1}) 1802, 1242, 1042; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43−7.35 (m, 5 H), 6.21−6.18 (m, 1 H), 5.86−5.82 (m, 1 H), 5.33 (s, 1 H), 4.15−4.08 (m, 1 H), 3.48−3.41 (m, 1 H), 2.70−2.56 (m, 2 H), 2.39−2.32 (m, 1 H), 2.22−2.14 (m, 1 H), 2.10−2.01 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 133.9, 130.4, 129.3, 129.2 (2 C), 128.9, 126.2 (2 C), 119.5, 88.4, 76.2, 59.0, 35.8, 25.0, 19.2; ES HRMS *m/z* ($M + Na^+$) calcd 327.0661, obsd 327.0666; $[\alpha]^{22}_D$ +248 (*c* 0.45, acetone).

Sulfone 10. To an ice-cold, stirred solution of **9** (35 mg, 0.12 mmol) in CH_2Cl_2 (10 mL) was added a precooled solution of *m*-CPBA (19.9 mg, 0.12 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 6 h at 0 °C, quenched with saturated $NaHCO_3$ solution (10 mL), dried, and concentrated in vacuo to afford an oil that was subjected to flash chromatography on silica gel (2:1 EtOAc/hexanes). Sulfone **10** was obtained as a colorless oil (30 mg, 81%): IR (neat, cm^{-1}) 1807, 1320; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43−7.36 (m, 5 H), 6.31−6.26 (m, 1 H), 6.15−6.11 (m, 1 H), 5.44 (s, 1 H), 3.95−3.88 (m, 1 H), 3.79−3.72 (m, 1 H), 2.77−2.72 (m, 1 H), 2.67−2.59 (m, 1 H), 2.36−2.26 (m, 1 H), 2.11−1.97 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 134.2, 131.3, 129.2, 128.9 (2 C), 126.2 (2 C), 126.0, 118.2, 76.6, 75.7, 55.3, 35.3, 29.7, 29.1, 17.6; ES HRMS *m/z* ($M + Na^+$) calcd 343.0611, obsd 343.0608; $[\alpha]^{20}_D$ −124 (*c* 2.86, acetone).

Dihydroxylation of 8. To a mixture consisting of DABCO (11.2 mg, 0.1 mmol), $K_2OsO_2(OH)_4$ (36.8 mg, 0.1 mmol), $K_3Fe(CN)_6$ (988 mg, 3 mmol), K_2CO_3 (415 mg, 3 mmol), $MeSO_2NH_2$ (190 mg, 2 mmol), $NaHCO_3$ (252 mg, 3 mmol), and 10 mL of *t*-BuOH−H_2O (l: l, 5 mL of each) was added **8** (288 mg, 1 mmol). After vigorous overnight stirring at rt, Na_2SO_3 (1.5 g) was added and stirring was maintained for 60 min. The workup followed the standard Sharpless procedure, except that the combined organic layers were not washed with 2 N KOH to remove $MeSO_2NH_2$, in consideration of the hydrolysis of the mandelate protecting group. The crude product was purified by flash chromatography on silica gel (1:2 EtOAc/hexanes) to afford **11** as a white solid, mp 123−124 °C. The yield was 77% with 23% starting material recovered: IR ($CHCl_3$, cm^{-1}) 3427 (br), 1796, 1323; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46−7.40 (m, 5 H), 5.67 (s, 1 H), 4.58 (dd, J = 10.0, 6.2 Hz, 1 H), 4.28 (d, J = 3.6 Hz, 1 H), 3.00 (dd, J = 11.0, 5.6 Hz, 1 H), 2.93 (dd, J = 11.0, 7.1 Hz, 1 H), 2.86 (br s, 1 H), 2.67 (br s, 1 H), 2.59−2.54 (m, 1 H), 2.41−2.35 (m, 1 H), 2.31−2.25 (m, 1 H), 2.02−1.96 (m, 1 H), 1.93−1.80 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 134.7, 129.2, 128.8 (2 C), 126.1 (2 C), 118.9, 77.9, 76.1, 75.4, 66.7, 34.1, 33.2, 32.4, 18.1; ES HRMS *m/z* ($M + Na^+$) calcd 345.0767, obsd 345.0772; $[\alpha]^{22}_D$ +28.0 (*c* 1.05, acetone).

Acetonide 12. To a stirred solution of **11** (322 mg, 1 mmol) in 2,2-dimethoxypropane (3 mL) was added *p*-toluenesulfonic acid (2 mg). The reaction mixture was refluxed for 3 h, potassium carbonate (5 mg) was introduced, and concentration was effected to afford a dark oil.

The oily residue was placed under high vacuum for 30 min, dissolved in a 2:1 mixture of THF/H_2O (15 mL), and treated with LiOH·H_2O (128 mg, 3 mmol). The heterogeneous solution was vigorously stirred for 4 h and extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine, dried, and concentrated in *vacuo* to afford a yellow oil that was subjected to flash chromatography on silica gel (7% EtOAc/hexanes) to give **12** as a faint yellow oil (219 mg, 96%): IR (neat, cm^{-1}) 1723, 1207, 1050; ^1H NMR (300 MHz, $CDCl_3$) δ 5.00 (t, J = 4.3 Hz, 1 H), 4.49 (d, J = 5.5 Hz, 1 H), 3.04 (dd, J = 13.1, 4.3 Hz, 1 H), 2.82 (d, J = 13.1 Hz, 1 H), 2.65 (dd, J = 20.0, 8.7 Hz, 1 H), 2.22−1.84 (series of m, 5 H), 1.49 (s, 3 H), 1.30 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.8, 110.9, 84.7, 84.6, 67.2, 36.6, 35.2, 31.8, 26.1, 24.5, 20.6; ES HRMS *m/z* ($M + Na^+$) calcd 251.0712, obsd 251.0718; $[\alpha]^{22}_D$ +77.8 (*c* 1.67, acetone).

Meerwein−Ponndorf−Verley Reduction of 12. A solution of **12** (110 mg, 0.5 mmol) in dry isopropyl alcohol (2.5 mL) was treated with aluminum isopropoxide (200 mg, 1.0 mmol), refluxed for 17 h, and distilled slowly at atmospheric pressure until 1.5 mL of distillate had collected. The distillation flask was evaporated to dryness and the residue was dissolved with dry ether (5 mL). The mixture was quenched with saturated Rochelle's salt solution (3 mL), stirred for 30 min, and treated with 1 N NaOH (3 mL). After extraction of the aqueous phase with ether, the combined organic solutions were washed with water, dried, and concentrated in *vacuo* to afford an oil that was subjected to flash chromatography on silica gel (20% EtOAc/hexanes). In total, 91.9 mg of reduction product was obtained as a colorless oil (83% overall yield), which included *syn* isomer **13** (61%) and *anti* isomer **14** (22%) (based on ^1H NMR analysis).

For **13**: IR (neat, cm^{-1}) 3451 (br), 1372, 1209; ^1H NMR (300 MHz, $CDCl_3$) δ 4.89 (dt, J = 5.1, 0.9 Hz, 1 H), 4.19 (d, J = 5.5 Hz, 1 H), 3.59 (br s, 1 H), 2.94 (dd, J = 13.0, 4.7 Hz, 1 H), 2.75 (d, J = 13.0 Hz, 1 H), 2.22−2.16 (m, 1 H), 1.90−1.59 (series of

m, 5 H), 1.51 (s, 3 H), 1.30 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 110.7, 86.6, 83.7, 74.3, 73.3, 36.7, 31.7, 29.3, 26.3, 24.7, 21.0; ES HRMS *m/z* ($M + Na^+$) calcd 253.0869, obsd 253.0877; $[\alpha]^{20}_D$ +139 (*c* 1.68, acetone).

For **14**: white solid; mp 77−79 °C; IR (neat, cm^{-1}) 3453 (br), 1372, 1209; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.93 (dt, J = 5.5, 1.4 Hz, 1 H), 4.84 (d, J = 5.8 Hz, 1 H), 4.10 (t, J = 5.8 Hz, 1 H), 2.84 (d, J = 12.7 Hz, 1 H), 2.35−2.25 (m, 2 H), 1.84−1.58 (series of m, 5 H), 1.52 (s, 3 H), 1.34 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 110.7, 84.0, 80.9, 77.2, 69.1, 37.2, 34.0, 29.7, 26.3, 24.7, 20.4; ES HRMS m/*z* ($M + Na^+$) calcd 253.0869, obsd 253.0880; $[\alpha]^{20}_D$ +177 (*c* 0.32, acetone).

Benzoylation of 13 and 14. Benzoyl chloride (0.51 mL, 4.4 mmol) was added dropwise to a stirred solution of **13** and **14** (both epimers, 252 mg, 1.1 mmol) and a catalytic amount of DMAP in dry pyridine (5 mL) at 0 °C. The mixture was stirred for 24 h at rt, treated with ice-cold saturated $NaHCO_3$ solution (5 mL), and extracted with $CHCl_3$ (3 × 5 mL). The chloroform extracts were washed with water (2 mL) and brine (2 mL), and evaporated in vacuo to afford a syrup. The syrupy residue was evacuated overnight to remove pyridine, and the benzoates were separated and purified by chromatography on silica gel (5% EtOAc/hexanes). The first to elute was **16** (88 mg, 24%), followed by **15** (275 mg, 75% yield), both as colorless oils.

For **15**: IR (neat, cm^{-1}) 1715, 1274; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06−8.03 (m, 2 H), 7.59−7.53 (m, 1 H), 7.47−7.42 (m, 2 H), 5.22 (t, J = 5.0 Hz, 1 H), 4.92 (dt, J = 5.4, 1.3 Hz, 1 H), 4.39 (d, J = 5.8 Hz, 1 H), 3.09 (dd, J = 12.9, 5.0 Hz, 1 H), 2.76 (d, J = 11.7 Hz, 1 H), 2.36−2.16 (m, 2 H), 2.04−1.77 (series of m, 4 H), 1.53 (s, 3 H), 1.33 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 133.5, 130.7, 130.2 (2 C), 128.9 (2 C), 111.6, 87.2, 84.3, 78.7, 70.3, 37.9, 31.3, 30.6, 26.7, 25.2, 21.2; ES HRMS *m/z* ($M + Na^+$) calcd 357.1131, obsd 357.1138; $[\alpha]^{22}_D$ +110 (*c* 2.39, acetone).

For **16**: IR (neat, cm^{-1}) 1715, 1270; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03−8.00 (m, 2 H), 7.69−7.64 (m, 1 H), 7.59−7.43 (m, 2 H), 5.32 (dd, J = 6.0, 2.2 Hz, 1 H), 4.93 (t, J = 4.6 Hz, 1 H), 4.63 (d, J = 5.6 Hz, 1 H), 3.17 (dd, J = 13.2, 4.6 Hz, 1 H), 2.80 (d, J = 13.2 Hz, 1 H), 2.53−2.37 (m, 2 H), 2.01−1.70 (series of m, 4 H), 1.53 (s, 3 H), 1.29 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 134.4, 130.5 (2 C), 130.2, 129.1 (2 C), 110.5, 84.6, 84.0, 81.4, 69.7, 37.6, 31.6, 31.5, 26.1, 24.7, 21.2; ES HRMS *m/z* ($M + Na^+$) calcd 357.1131, obsd 357.1133; $[\alpha]^{20}_D$ +9.3 (*c* 0.91, acetone).

***β*-Elimination of 13.** To a solution of **13** (49.4 mg, 0.21 mmol) and freshly distilled HMPA (0.45 mL, 2.52 mmol) in dry THF (3 mL) was added *t*-BuLi (0.89 mL, 1.4 M in pentane, 1.26 mmol) at −78 °C. An orange color was immediately observed. After being stirred at this temperature for 4 h, the reaction mixture was gradually warmed to 0 °C and maintained at this temperature for 3 h. Ether (2 mL) was added followed by saturated aqueous NH_4Cl (1 mL) and water (1 mL). The aqueous layer was extracted with ether (4 × 2 mL) and the combined organic extracts were washed with brine (2 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was subjected to flash chromatography on silica gel (20% EtOAc/hexanes) to give **17** as a white solid (17 mg, 49% yield at 55% conversion): mp 77−79 °C; IR ($CHCl_3$, cm^{-1}) 3332 (br), 1300, 1022; ^{1}H NMR (300 MHz, d_6-benzene) δ 5.80 (d, J = 6.1 Hz, 1 H), 5.39 (dd, J = 6.1, 2.9 Hz, 1 H), 3.91 (d, J = 2.9 Hz, 1 H), 3.57 (br s, 1 H), 2.30−1.40 (series of m, 6 H); ^{13}C NMR (75 MHz, d_6-benzene) δ 128.3, 127.7, 79.9, 75.7, 45.4, 31.5, 28.2, 21.2; EI HRMS *m/z* (M^+) calcd 172.0553, obsd 172.0542; $[\alpha]^{22}_D$ +351 (*c* 1.01, $CHCl_3$).

Silylation of Glycal 17. Method A. Glycal **17** (8 mg, 0.047 mmol) was dissolved in THF and pyridine (19 μL, 0.24 mmol) was added. Silver nitrate (20 mg, 0.12 mmol) was introduced and stirring was maintained for 1 h at rt prior to the addition of TBSCl (18 mg, 0.12 mmol). The next morning, the cloudy white reaction mixture was filtered into a saturated $NaHCO_3$ aqueous solution. The product was extracted into CH_2Cl_2 and purified by flash chromatography on silica gel (5% EtOAc/hexanes) to furnish **18** (56% yield at 62% conversion) as a colorless oil.

Method B. DABCO (31 mg, 0.28 mmol) was dissolved in dry THF. Silver nitrate (20 mg, 0.12 mmol) was added and the mixture was stirred for 5 min. TBSCl (21 mg, 0.14 mmol) was introduced and, after an additional 5 min, **17** (8 mg, 0.047 mmol) was added and the reaction mixture was stirred at rt overnight. The cloudy white reaction mixture was worked up as above to give **18** (40%) and **19** (49%) after chromatography on silica gel (1% to 5% EtOAc/hexanes).

Method C. This procedure is identical to that described in method A except that DME replaced THF and triethylamine replaced pyridine. After the addition of silver nitrate, the reaction mixture soon turned into black. Quenching the reaction after 3 h afforded three products: **19** (46%), **18** (25%), and **20** (24%). When reaction was allowed to proceed overnight, **19** was the sole product (88%).

For **18**: IR (neat, cm^{-1}) 3486, 1471, 1256; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.32 (d, $J_{1,2}$ = 6.1 Hz, 1 H, H-1), 5.70 (dd, $J_{1,2}$ = 6.1 and $J_{2,3}$ = 2.8 Hz, 1 H, H-2), 4.49 (d, $J_{2,3}$ = 2.8 Hz, 1 H, H-3), 3.82 (br d, $J_{5,5-OH}$ = 4.9 Hz, 1 H, H-5), 2.42−2.37 (m, 1 H, H-8β), 2.29 (br d, $J_{5,5-OH}$ = 4.9 Hz, 1 H, 5-OH), 2.07−1.99 (m, 2 H, H-6β, H-8α), 1.88−1.80 (m, 1 H, H-7α), 1.78−1.64 (m, 2 H, H-6α, H-7β), 0.94 (s, 9 H, *t*-Bu), 0.13 (s, 3 H, CH_3), 0.12 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 128.2, 126.0, 80.6, 76.3, 75.6, 31.6, 28.6, 25.8 (3 C), 20.5, 18.2, −4.0, −4.8; EI HRMS *m/z* (M^+) calcd 286.1417, obsd 286.1419; $[\alpha]^{18}_D$ +182 (*c* 0.43, $CHCl_3$).

For **19**: IR (neat, cm^{-1}) 1463, 1257, 1066; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.28 (dd, J = 6.2, 1.0 Hz, 1 H), 5.47 (dd, J = 6.2, 2.5 Hz, 1 H), 4.51 (br d, J = 1.6 Hz, 1 H), 3.87 (pseudo-t, J = 4.7 Hz, 1 H), 2.42−2.33 (m, 1 H), 1.96−1.55 (series of m, 5 H), 0.86 (s, 9 H), 0.83 (s, 9 H), 0.08 (s, 6 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.3, 123.6, 81.6, 78.1, 74.4, 32.8, 29.5, 25.8 (6 C), 20.6, 18.1, 14.1, −4.5 (2 C), −4.8 (2 C); EI HRMS *m/z* (M^+) calcd 400.2281, obsd 400.2288; $[\alpha]^{18}_D$ +80.0 (*c* 0.97, $CHCl_3$).

For **20**: IR (neat, cm^{-1}) 3389, 1457, 1260; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.41 (d, J = 6.1 Hz, 1 H), 5.69 (dd, J = 6.1, 2.9 Hz, 1 H), 4.22 (br s, 1 H), 3.87 (dd, J = 5.5, 3.9 Hz, 1 H), 2.38−2.27 (m, 1 H), 2.04−1.56 (series of m, 5 H), 0.87 (s, 9 H), 0.07 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.3, 123.2, 84.9, 77.2, 74.6, 32.6, 28.6, 25.8 (3 C), 20.6, 18.3, −4.6, −4.9; EI HRMS *m/z* (M^+) calcd 286.1417, obsd 286.1419; $[\alpha]^{18}_D$ +6.4 (*c* 0.22, $CHCl_3$).

TIPDS Protection of Glycal 17. The process described in method A was adapted. Starting from **17** (50 mg, 0.29 mmol), $TIPDSCl_2$ (0.11 mL, 0.35 mmol), $AgNO_3$ (124 mg, 0.73 mmol), and pyridine (0.12 mL, 1.45 mmol), the usual workup and flash chromatography on silica gel (1% EtOAc/hexanes) afforded **21** (108 mg, 90%) as a white solid: mp 81−82 °C; IR ($CHCl_3$, cm^{-1}) 1465, 1216, 1091; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.17−6.14 (m, 1 H), 5.76 (dd, J = 6.2, 1.7 Hz, 1 H), 5.12 (br s, 1 H), 3.99 (dd, J = 11.1, 7.3 Hz, 1 H), 2.09−1.57 (series of m, 6 H), 1.11−0.83 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 126.6, 123.7, 77.2, 76.1, 71.5, 29.8, 26.9, 17.5 (4 C), 17.3, 17.2, 16.8, 14.5 (4 C), 13.7, 12.9; EI HRMS *m/z* (M^+) calcd 414.2075, obsd 414.2129; $[\alpha]^{18}_D$ −8.7 (*c* 0.82, $CHCl_3$).

Glycosidation Reactions of 19. Method A: PhSeCl as Electrophile. To a stirred CH_3CN solution (1.0 mL) of **19** (10 mg, 0.025 mmol) and bis-*O*-trimethylsilylthymine (10.8 mg, 0.038 mmol) was added a CH_3CN solution (0.5 mL) of PhSeCl (7.7 mg, 0.038 mmol) at 0 °C under N_2. After 1 h, the reaction mixture was partitioned between $CHCl_3$ and saturated $NaHCO_3$ solution. Silica gel chromatography (15% EtOAc/hexanes) of the organic layer gave **22** (53%) as a white foam, as well as a minor isomer (13%, inseparable, based on ^{1}H NMR analysis, 11.3 mg total, 66% overall yield): IR ($CHCl_3$, cm^{-1}) 1681, 1463, 1253; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (s, 1 H), 7.52 (d, J = 7.3 Hz, 2 H), 7.53−7.26 (m, 2 H), 7.20−7.17 (m, 2 H), 6.78 (d, J = 10.7 Hz, 1 H), 4.35 (d, J = 2.9 Hz, 1 H), 4.16−4.06

(m, 1 H), 3.91 (dd, J = 10.7, 2.9 Hz, 1 H), 2.12−1.95 (m, 3 H), 1.69−1.53 (series of m, 6 H), 1.05 (s, 9 H), 0.97 (s, 9 H), 0.35 (s, 3 H), 0.19 (s, 3 H), 0.16 (s, 3 H), 0.12 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0, 150.7, 135.7, 135.2, 129.1 (2 C), 128.2 (2 C), 127.6, 110.7, 82.7, 79.0, 72.9, 63.7, 56.1, 34.4, 31.6, 26.3 (3 C), 26.2 (3 C), 18.6, 18.4, 18.3, 12.2, −2.9, −3.0, −3.8, −4.3; ES HRMS *m/z* ($M + Na^+$) calcd 705.2087, obsd 705.2117; $[\alpha]^{18}_D$ +32.5 (*c* 0.93, $CHCl_3$).

Method B: Using NIS as Electrophile. The reaction was carried out as described above except for the substitution of NIS (8.4 mg, 0.038 mmol) as the electrophile. The usual workup and silica gel chromatography (10% EtOAc/hexanes) gave **23** (52%) as a pale oil and a minor isomer (13%, based on ^{1}H NMR analysis, 10.5 mg total, 65% overall yield): IR ($CHCl_3$, cm^{-1}) 1682, 1471, 1253; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, 1 H), 7.70 (d, J = 1.2 Hz, 1 H), 6.56 (d, J = 10.7 Hz, 1 H), 4.77 (dd, J = 10.7, 2.7 Hz, 1 H), 4.05−4.02 (m, 2 H), 2.09−1.97 (series of m, 6 H), 1.69−1.64 (m, 3 H), 1.04 (s, 9 H), 1.00 (s, 9 H), 0.36 (s, 3 H), 0.21 (s, 3 H), 0.20 (s, 3 H), 0.17 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2, 150.5, 135.7, 111.8, 82.0, 78.8, 72.3, 62.9, 34.6, 32.5, 31.0, 26.3 (3 C), 26.1 (3 C), 18.5, 18.3, 18.2, 12.5, −2.4, −2.8, −4.1, −4.3; ES HRMS *m/z* ($M + Na^+$) calcd 675.1575, obsd 675.1570; $[\alpha]^{18}_D$ +37.9 (*c* 0.97, $CHCl_3$).

Glycosidation Reactions of 21. Method A: PhSeCl as Electrophile. The reaction was carried out according to the procedure described for the preparation of **22** starting with **21** (11.3 mg, 0.027 mmol), bis-*O*-trimethylsilylthymine (11.1 mg, 0.041 mmol), and PhSeCl (7.8 mg, 0.041 mmol). The usual workup and silica gel chromatography (20% EtOAc/hexanes) gave **24** as a white foam (14.4 mg, 76%) and a minor isomer (0.8 mg, 4%).

For **24**: IR ($CHCl_3$, cm^{-1}) 1690, 1464, 1134; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (s, 1 H), 7.64 (d, J = 6.8 Hz, 2 H), 7.31−7.25 (m, 3 H), 7.21 (d, J = 0.8 Hz, 1 H), 6.45 (d, J = 3.2 Hz, 1 H), 4.78 (d, J = 8.3 Hz, 1 H), 4.12−4.07 (m, 2 H), 2.16−2.11 (m, 2 H), 2.06−1.95 (m, 2 H), 1.88 (s, 3 H), 1.86−1.78 (m, 1 H), 1.68−1.56 (m, 1 H), 1.19−1.09 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4, 149.5, 136.3, 135.8, 129.2 (2 C), 128.3 (2 C), 128.1, 111.9, 72.9, 72.8, 71.3, 65.3, 53.5, 29.9, 29.5, 17.6 (2 C), 17.21 (3 C), 17.19, 17.12 (2 C), 17.09, 13.7, 13.6, 12.9, 12.7, 12.6; ES HRMS *m/z* ($M + Na^+$) calcd 719.1880, obsd 719.1924; $[\alpha]^{18}_D$ +39.3 (*c* 0.30, $CHCl_3$).

For the minor isomer: IR ($CHCl_3$, cm^{-1}) 1689, 1465, 1140; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (br s, 1 H), 7.54−7.51 (m, 2 H), 7.26−7.14 (m, 3 H), 6.86 (d, J = 1.1 Hz, 1 H), 6.24 (d, J = 9.9 Hz, 1 H), 4.16−4.05 (m, 2 H), 3.92 (dd, J = 11.8, 9.9 Hz, 1 H), 2.28−2.25 (m, 1 H), 2.05−1.83 (series of m, 4 H), 1.74 (d, J = 1.1 Hz, 3 H), 1.55−1.48 (m, 1 H), 1.17−1.00 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 150.0, 135.7, 134.6, 129.1 (2 C), 128.0 (2 C), 127.3, 111.7, 72.9, 71.8, 67.8, 61.6, 50.8, 29.8, 28.5, 17.7, 17.6, 17.5 (2 C), 17.4, 17.3, 17.2, 17.10, 17.06, 16.4, 14.6, 13.6, 13.1, 12.7; ES HRMS *m/z* ($M + Na^+$) calcd 719.1880, obsd 719.1889; $[\alpha]^{22}_D$ −26.1 (*c* 0.87, $CHCl_3$).

Method B: NIS as Electrophile. The reaction was carried out according to the procedure described for the preparation of **23** starting with **21** (12.8 mg, 0.031 mmol), bis-*O*-trimethylsilylthymine (12.5 mg, 0.047 mmol), and NIS (10.4 mg, 0.047 mmol). The usual workup and silica gel chromatography (15% EtOAc/hexanes) gave **25** as a white solid (14.4 mg, 70%, along with 12% minor isomer, 2.5 mg): mp 164−166 °C; IR ($CHCl_3$, cm^{-1}) 1712, 1464, 1388; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (s, 1H, NH), 7.56 (d, $J_{6,CH3}$ = 1.1 Hz, 1 H, H-6), 6.60 (d, $J_{1′,2′}$ = 2.8 Hz, 1 H, H-1′), 4.56 (dd, $J_{2′,3′}$ = 7.4 and $J_{1′,2′}$ = 2.8 Hz, 1 H, H-2′), 4.06 (dd, $J_{5′,6′\alpha}$ = 11.7 and $J_{5′,6′\beta}$ = 7.2 Hz, 1 H, H-5′), 3.94 (d, $J_{2′,3′}$ = 7.4 Hz, 1 H, H-3′), 2.39−2.34 (m, 1 H, H-8′α), 2.17−2.11 (m, 1 H, H-8′β), 2.05−1.91(m, 5 H, CH_3, H-6′β, H-7′α), 1.83−1.77 (m, 1 H, H-7′β), 1.61−1.52 (m, 1 H, H-6′α), 1.23−1.07 (m, 28 H, TIPDS); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9 (2 C), 135.8, 112.3, 101.4, 73.2, 72.0, 71.4, 65.7, 45.1, 33.0, 29.8, 29.1, 17.5, 17.2 (4 C), 13.6 (4 C), 12.7 (4 C); ES HRMS *m/z* ($M + Na^+$) calcd 689.1368, obsd 689.1429; $[\alpha]^{18}_D$ +1.7 (*c* 0.47, $CHCl_3$).

Ring-Opened Product 26. To a stirred benzene solution (2 mL) of **22** (7.8 mg, 0.011 mmol) were added Bu_3SnH (9.2 μL, 0.033 mmol) and Et_3B (1 M THF solution, 11.4 μL, 0.011 mmol), and the reaction mixture was stirred at rt with O_2 injected via syringe at intervals. After 2 h, the reaction mixture was evaporated and the residue was purified by flash chromatography on silica gel to give **26** as a yellow oil (3.0 mg, 50% at 50% conversion): IR (neat, cm^{-1}) 1650, 1463, 1254; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (br s, 1 H), 7.28 (d, J = 1.1 Hz, 1 H), 7.08 (dd, J = 14.6, 0.7 Hz, 1 H), 5.71 (dd, J = 14.6, 8.0 Hz, 1 H), 4.19 (t, J = 7.5 Hz, 1 H), 4.12 (d, J = 8.2 Hz, 1 H), 2.03−1.85 (series of m, 5 H), 1.68−1.54 (m, 2 H), 1.35−1.26 (m, 2 H), 0.91 (s, 9 H), 0.89 (s, 9 H), 0.11−0.05 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.3, 125.8, 119.0, 112.0, 101.5, 98.6, 75.9, 75.1, 63.6, 32.5, 32.4, 25.9 (6 C), 19.1 (3 C), 12.5, −3.1, −3.5, −4.6, −4.7; ES HRMS *m/z* ($M + Na^+$) calcd 549.2609, obsd 549.2616; $[\alpha]^{18}_D$ +26.2 (*c* 0.21, $CHCl_3$).

Radical Reduction of 23. Iodonucleoside **23** (4.9 mg, 0.0075 mmol) and AIBN (0.4 mg, 0.0026 mmol) were dissolved in dry toluene (0.5 mL) and this solution was added slowly to a solution of Bu_3SnH (6.1 μL, 0.023 mmol) in dry toluene (1.5 mL) being stirred under argon at 45 °C. The temperature was gradually raised to 60 °C and stirring was maintained for 6 h. After being cooled to rt, the reaction mixture was diluted with a saturated solution of NH_4Cl (2 mL) and extracted with ethyl acetate (3 × 2 mL). The combined organic phases were washed with brine, dried, and freed of solvents. The residue was purified by flash chromatography on silica gel (1:4 EtOAc/hexanes) to give **27** as a white foam (0.9 mg, 22% at 25% conversion): IR ($CHCl_3$, cm^{-1}) 1682, 1470, 1257; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (br s, 1 H), 7.92 (s, 1 H), 6.35 (t, J = 7.0 Hz, 1 H), 4.12 (t, J = 4.3 Hz, 1 H), 4.00 (t, J = 7.1 Hz, 1 H), 2.33−2.31 (m, 2 H), 2.21−2.04 (series of m, 4 H), 1.94−1.90 (m, 5 H), 0.93 (s, 9 H), 0.91 (s, 9 H), 0.12−0.07 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5, 150.5, 137.2, 110.7, 84.7, 77.8, 77.3, 59.2, 43.8, 32.7, 32.6, 26.0 (3 C), 25.7 (3 C), 18.8, 18.3, 18.0, 12.6, −4.0, −4.3 (2 C), −4.9; ES HRMS *m/z* ($M + Na^+$) calcd 549.2609, obsd 549.2616; $[\alpha]^{19}_D$ +19.8 (*c* 0.64, $CHCl_3$).

Radical Reduction of 24. A stirred toluene solution (4 mL) of **24** (30 mg, 0.043 mmol) was treated with Bu_3SnH (35 μL, 0.13 mmol) and Et_3B (1 M THF solution, 43 μL, 0.043 mmol) at −78 °C, and the reaction mixture was provided with a continuous O_2 flow. After 1 h, the solvents were evaporated and the residue was purified by flash chromatography on silica gel (20% EtOAc/hexanes) to give **28** (24 mg, quantitative) as a colorless oil: UV (MeOH) λ_{max} 272 nm (ϵ 24 800); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (br s, 1 H), 7.69 (d, J = 1.1 Hz, 1 H), 6.17 (dd, J = 9.4, 1.2 Hz, 1 H), 4.44 (dd, J = 12.6, 6.6 Hz, 1 H), 4.02 (dd, J = 11.5, 7.3 Hz, 1 H), 2.45 (dd, J = 12.6, 9.4 Hz, 1 H), 2.12 (ddd, J = 12.6, 6.6, 1.2 Hz, 1 H), 1.96−1.90 (series of m, 5 H), 1.74−1.58 (m, 3 H), 1.37−1.29 (m, 1 H), 1.20−0.98 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 150.6, 136.5, 111.5, 72.1, 71.2, 70.7, 54.8, 39.0, 30.1, 28.7, 17.7 (2 C), 17.5, 17.33, 17.25 (2 C), 17.22, 17.16, 17.09, 16.7, 13.6, 12.9, 12.7, 12.4; ES HRMS *m/z* ($M + Na^+$) calcd 563.2402, obsd 563.2412; $[\alpha]^{22}_D$ −62.3 (*c* 0.65, CH_3OH).

Completion of Spiro-2′-deoxy-4′-thiathymidine Analogue Synthesis. A stirred THF solution (2 mL) of **28** (20 mg, 0.037 mmol) was treated with tetrabutylammonium fluoride (1 M THF solution, 81 μL, 0.081 mmol) under Ar at 0 °C. After 2 h, the reaction mixture was evaporated and the residue was chromatographed on silica gel (20% EtOH/toluene) to afford **29** (10 mg, 90%) as a white solid: mp 104−105 °C; UV (MeOH) λ_{max} 272 nm (ϵ 8900); ^{1}H NMR (300 MHz, CD_3OD) δ 8.40 (d, J = 1.1 Hz, 1 H), 6.46 (t, J = 7.6 Hz, 1 H), 4.14 (t, J = 3.7 Hz, 1 H), 4.01 (t, J = 7.3 Hz, 1 H), 2.37 (dd, J = 7.6, 3.9 Hz, 2 H), 2.25−2.15 (m, 1 H), 2.08−2.00 (m, 1 H), 1.96−1.87 (series of m, 4 H), 1.68−1.58 (m, 3 H); ^{13}C NMR (75 MHz, CD_3OD) δ 168.9, 155.3, 142.6, 114.2, 81.8, 80.8, 77.8, 64.3, 46.5, 36.1,

35.9, 22.5, 15.1; ES HRMS *m/z* (M + Na^+) calcd 321.0879, obsd 321.0874; $[\alpha]^{19}_D$ −9.4 (*c* 2.25, CH_3OH).

2′-Phenylseleno-4′-thiauridine Analogue 30. The reaction was carried out according to the procedure described for the preparation of **22** starting from **21** (100 mg, 0.24 mmol), bis-*O*-trimethylsilyluracil (93 mg, 0.36 mmol), and PhSeCl (70 mg, 0.36 mmol). The usual workup followed by silica gel chromatography (20% EtOAc/hexanes) of the crude product gave **30** as a white solid (123 mg, 75%): mp 74−75 °C; UV (MeOH) λ_{max} 268 nm (ϵ 12 800); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (br s, 1 H), 7.77 (d, *J* = 8.1 Hz, 1 H), 7.66−7.63 (m, 2 H), 7.29−7.21 (m, 3 H), 6.32 (d, *J* = 2.6 Hz, 1 H), 5.62 (dd, *J* = 8.1, 2.3 Hz, 1 H), 4.55 (d, *J* = 7.3 Hz, 1 H), 4.01, (dd, *J* = 11.8, 6.9 Hz, 1 H), 3.91 (dd, *J* = 7.3, 2.6 Hz, 1 H), 2.15−2.10 (m, 2 H), 1.96−1.88 (m, 2 H), 1.82−1.68 (m, 1 H), 1.59−1.51 (m, 1 H), 1.13−0.88 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 149.4, 141.0, 135.9, 129.2 (2 C), 128.42 (2 C), 128.36, 102.4, 72.9, 72.2, 70.6, 65.9, 54.8, 30.4, 29.2, 17.33, 17.29 (2 C), 17.20 (2 C), 17.15, 17.11, 17.03, 16.97, 13.6, 13.5, 13.3, 12.8; ES HRMS *m/z* (M + Na^+) calcd 705.1723, obsd 705.1759; $[\alpha]^{22}_D$ +65.3 (*c* 1.03, CH_3OH).

2′-Deoxy-4′-thiauridine Analogue 31. Removal of the phenylseleno group followed the procedure for preparing **28** starting from **30** (86 mg, 0.13 mmol), Bu_3SnH (0.10 mL, 0.39 mmol) and Et_3B (1 M THF solution, 0.13 mL, 0.13 mmol) in toluene (12 mL). After purification of the crude product by flash chromatography on silica gel (20% EtOAc/hexanes), the resultant 2′-deoxy derivative was desilylated according to the procedure for preparing **29** by treatment with TBAF (1 M THF solution, 0.28 mL, 0.28 mmol) in THF (3 mL). Finally, chromatography on silica gel (20% EtOH/toluene) furnished **31** (32.5 mg, 91%) as a white solid: mp 166−167 °C; UV (MeOH) λ_{max} 266 nm (ϵ 7500) and 236 nm (ϵ 2300); ^{1}H NMR (300 MHz, CD_3OD) δ 8.56 (d, *J* = 8.1 Hz, 1 H), 6.44 (t, *J* = 7.4 Hz, 1 H), 5.71 (d, *J* = 8.1 Hz, 1 H), 4.13 (t, *J* = 3.7 Hz, 1 H), 3.99 (t, *J* = 7.2 Hz, 1 H), 2.39−2.34 (m, 2 H), 2.25−2.15 (m, 1 H), 2.04−1.87 (m, 2 H), 1.65−1.52 (m, 3 H); ^{13}C NMR (75 MHz, CD_3OD) δ 168.7, 155.1, 146.9, 105.2, 81.8, 80.7, 77.9, 64.6, 46.5, 36.0, 35.9, 22.4; ES HRMS *m/z* (M + Na^+) calcd 307.0723, obsd 307.0729; $[\alpha]^{19}_D$ −5.4 (*c* 1.68, CH_3OH).

2′-Phenylseleno-4′-thiacytidine Analogue 32. The reaction was carried out according to the procedure described for the preparation of **22** starting from **21** (100 mg, 0.24 mmol), 1-*O*-trimethylsilyl-N^4-acetylcytosine (82 mg, 0.36 mmol), and PhSeCl (70 mg, 0.36 mmol). The usual workup followed by silica gel chromatography (50% EtOAc/hexanes) of the crude product gave **32** as a white foam (92 mg, 53%): UV (MeOH) λ_{max} 302 (ϵ 6600) and 250 nm (ϵ 14 100); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.58 (br s, 1 H), 8.44 (d, *J* = 7.5 Hz, 1 H), 7.71−7.68 (m, 2 H), 7.34 (d, *J* = 7.5 Hz, 1 H), 7.23−7.16 (m, 3 H), 6.32 (s, 1 H), 4.41 (d, *J* = 6.2 Hz, 1 H), 3.98 (dd, *J* = 11.5, 7.1 Hz, 1 H), 3.84 (d, *J* = 6.2 Hz, 1 H), 2.21−2.09 (series of m, 5 H), 1.93−1.86 (m, 2 H), 1.80−1.74 (m, 1 H), 1.62−1.52 (m, 1 H), 1.19−0.77 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 162.9, 154.9, 146.2, 135.8 (2 C), 129.5, 129.0 (2 C), 128.2, 96.6, 73.0, 71.6, 70.1, 67.7, 56.0, 31.2, 29.0, 24.8, 17.44, 17.35, 17.29, 17.18 (2 C), 17.14, 17.10, 16.9, 16.8, 13.8, 13.6, 13.3, 12.7; ES HRMS *m/z* (M + Na^+) calcd 746.1989, obsd 746.1990; $[\alpha]^{22}_D$ +20.1 (*c* 0.72, CH_3OH).

2′-Deoxy-4′-thiacytidine Analogue 33. Removal of the phenylseleno group followed the procedure for preparing **28** starting from **32** (92 mg, 0.13 mmol), Bu_3SnH (0.11 mL, 0.39 mmol) and Et_3B (1 M THF solution, 0.13 mL, 0.13 mmol) in toluene (13 mL). After purification by flash chromatography on silica gel (50% EtOAc/hexanes), the resultant 2′-deoxy derivative was desilylated according to the procedure for preparing **29** by treatment with TBAF (1 M THF solution, 0.27 mL, 0.27 mmol) in THF (3 mL). The reaction mixture was stirred for 3 h, evaporated to dryness, and placed under high vacuum for 30 min. Methanolic ammonia (5 mL) was added, and the mixture was kept at rt for 5 h prior to chromatography on silica gel (30% EtOH/toluene) to afford **33** (35 mg, 97%) as a white solid: 223 °C dec; UV (MeOH) λ_{max} 278 nm (ϵ 9500); ^{1}H NMR (300 MHz, CD_3OD) δ 8.55 (d, *J* = 7.4 Hz, 1 H), 6.45 (t, *J* = 6.9 Hz, 1 H), 5.92 (d, *J* = 7.3 Hz, 1 H), 4.12 (t, *J* = 4.1 Hz, 1 H), 3.98 (t, *J* = 7.2 Hz, 1 H), 2.41−2.16 (m, 3 H), 2.05−1.99 (m, 1 H), 1.95−1.86 (m, 1 H), 1.67−1.57 (m, 3 H); ^{13}C NMR (75 MHz, CD_3OD) δ 169.8, 161.3, 147.4, 98.7, 81.3, 80.5, 77.4, 65.3, 46.9, 35.9 (2 C), 22.5; ES HRMS *m/z* (M + Na^+) calcd 306.0883, obsd 306.0898; $[\alpha]^{19}_D$ −12.1 (*c* 0.90, CH_3OH).

2′-Phenylseleno-4′-thia-5-fluorouridine Analogues 34 and 35. The reaction was carried out according to the procedure described for the preparation of **22** starting from **21** (100 mg, 0.24 mmol), bis-*O*-trimethylsilyl-5-fluoro-uracil (100 mg, 0.36 mmol), and PhSeCl (70 mg, 0.36 mmol). The usual workup and silica gel chromatography (10% EtOAc/hexanes) gave β isomer **34** (70 mg, 41%) and α isomer **35** (68 mg, 70%), both as white foams.

For **34**: UV (MeOH) λ_{max} 274 nm (ϵ 10 600); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.36 (br d, *J* = 3.7 Hz, 1 H), 7.83 (d, *J* = 6.1 Hz, 1 H), 7.67−7.64 (m, 2 H), 7.26−7.21 (m, 3 H), 6.35 (s, 1 H), 4.54 (d, *J* = 7.5 Hz, 1 H), 4.07 (dd, *J* = 11.6, 7.0 Hz, 1 H), 3.89 (dd, *J* = 7.5, 2.5 Hz, 1 H), 2.15−2.04 (m, 2 H), 1.97−1.91 (m, 2 H), 1.82−1.72 (m, 1 H), 1.58−1.51 (m, 1 H), 1.15−0.90 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5 (d, *J* = 26.6 Hz, 1 C), 148.4, 140.1 (d, *J* = 239.0 Hz, 1 C), 136.0 (2 C), 129.2 (2 C), 128.5, 128.3, 125.0 (d, *J* = 34.1 Hz, 1 C), 72.8, 72.3, 71.0, 66.2, 54.8, 30.3, 29.3, 17.36, 17.27 (2 C), 17.20, 17.16 (2 C), 17.12, 17.09, 16.98, 13.59, 13.25 (2 C), 12.77; ES HRMS *m/z* (M + Na^+) calcd 723.1629, obsd 723.1628; $[\alpha]^{24}_D$ +69.1 (*c* 1.17, CH_3OH).

For **35**: UV (MeOH) λ_{max} 274 nm (ϵ 10000); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.91 (br s, 1 H), 7.55−7.52 (m, 2 H), 7.28−7.17 (m, 4 H), 6.28 (dd, *J* = 9.8, 1.5 Hz, 1 H), 4.15−4.05 (m, 2 H), 3.82 (dd, *J* = 11.7, 9.8 Hz, 1 H), 2.30−2.26 (m, 1 H), 1.99−1.73 (series of m, 4 H), 1.54−1.47 (m, 1 H), 1.17−0.97 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0 (d, *J* = 26.8 Hz, 1 C), 148.8, 140.4 (d, *J* = 238.8 Hz, 1 C), 134.49, 134.42, 129.29, 129.25, 128.2, 127.1, 124.1 (d, *J* = 33.1 Hz, 1 C), 72.8, 71.8, 68.0, 62.1, 51.0, 30.9, 29.8, 17.7, 17.48, 17.44, 17.33, 17.23, 17.11, 17.06, 16.98, 16.3, 14.6, 13.5, 13.1, 12.7; ES HRMS *m/z* (M + Na^+) calcd 723.1629, obsd 723.1626; $[\alpha]^{24}_D$ −23.2 (*c* 1.30, CH_3OH).

2′-Deoxy-4′-thia-5-fluorouridine Analogue 36. Removal of the phenylseleno group followed the procedure for preparing **28** starting from **34** (70 mg, 0.10 mmol), Bu_3SnH (0.08 mL, 0.30 mmol) and Et_3B (1 M THF solution, 0.10 mL, 0.10 mmol) in toluene (10 mL). After purification by flash chromatography on silica gel (20% EtOAc/hexanes) the resultant 2′-deoxy derivative was desilylated according to the procedure for preparing **29** by treatment with TBAF (1 M THF solution, 0.24 mL, 0.24 mmol) in THF (3 mL). Finally, the reaction mixture was chromatographed on silica gel (15% EtOH/toluene) to afford **36** (28 mg, 94%) as a colorless syrup: UV (MeOH) λ_{max} 274 nm (ϵ 7100); ^{1}H NMR (300 MHz, CD_3OD) δ 8.85 (d, *J* = 7.3 Hz, 1 H), 6.44 (dt, *J* = 7.5, 1.5 Hz, 1 H), 4.13 (t, *J* = 3.6 Hz, 1 H), 4.01 (t, *J* = 7.5 Hz, 1 H), 2.40−2.32 (m, 2 H), 2.25−2.14 (m, 1 H), 2.04−1.87 (m, 2 H), 1.68−1.57 (m, 3 H); ^{13}C NMR (75 MHz, CD_3OD) δ 161.9 (d, *J* = 26.6 Hz, 1 C), 153.8, 144.0 (d, *J* = 231.2 Hz, 1 C), 130.7 (d, *J* = 35.1 Hz, 1 C), 82.1, 80.7, 77.9, 65.2, 46.5, 36.1, 35.9, 22.4; ES HRMS *m/z* (M + Na^+) calcd 325.0629, obsd 325.0631; $[\alpha]^{19}_D$ +3.6 (*c* 1.12, CH_3OH).

Adenosine Analogue 37. The reaction was carried out according to the procedure described for the preparation of **22** starting from **21** (100 mg, 0.24 mmol), monosilylated N^6-benzoyladenine, which was prepared from addition of BSA (89 μL, 0.36 mmol) to N^6-benzoyladenine (87 mg, 0.36 mmol) and stirring for 1 h, and PhSeCl (70 mg, 0.36 mmol). The reaction mixture was kept at 0 °C for 1 h, then incubated at 60 °C overnight. The usual workup and silica gel chromatography (20−40% EtOAc/hexanes) gave **37** as a colorless syrup (173 mg, 89%): UV (MeOH) λ_{max} 266 nm (ϵ 18 500) and 226 nm (ϵ 35 600); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.06 (br s, 1 H),

8.63 (s, 1 H), 8.02 (d, J = 4.4 Hz, 2 H), 7.79 (s, 1 H), 7.62−7.59 (m, 1 H), 7.54−7.51 (m, 4 H), 7.22−7.19 (m, 1 H), 7.13−7.10 (m, 2 H), 6.39 (d, J = 2.6 Hz, 1 H), 5.22 (d, J = 7.7 Hz, 1 H), 4.60 (dd, J = 7.7, 2.6 Hz, 1 H), 4.12 (dd, J = 11.7, 7.3 Hz, 1 H), 2.28−2.18 (m, 2 H), 2.07−1.93 (m, 2 H), 1.86−1.74 (m, 1 H), 1.62−1.52 (m, 1 H), 1.20−0.91 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 152.3, 151.1, 149.4, 141.8, 135.7 (2 C), 133.6, 132.7, 129.2 (2 C), 128.8 (2 C), 128.4, 127.9 (2 C), 127.8, 123.3, 72.9, 72.8, 71.7, 63.6, 52.9, 30.3, 29.5, 17.4, 17.30, 17.25 (3 C), 17.20 (2 C), 17.15, 17.06, 13.5 (2 C), 13.0, 12.8; ES HRMS m/z (M + Na^+) calcd 832.2258, obsd 832.2269; $[\alpha]^{19}_D$ +16.6 (c 0.99, CH_3OH).

Guanosine Analogues 38 and 39. The reaction was carried out according to the procedure described for the preparation of **22** starting from **21** (93 mg, 0.22 mmol), bis-silylated N^2-acetylguanine, which was prepared from addition of BSA (0.18 mL, 0.36 mmol) to N^2-acetylguanine (70 mg, 0.36 mmol) and stirring for 1 h, and PhSeCl (70 mg, 0.36 mmol). The reaction mixture was kept at 0 °C for 1 h, then raised to rt overnight. The usual workup and silica gel chromatography (50% EtOAc/hexanes to 10% CH_3OH/EtOAc) gave **38** (82 mg, 48%) and **39** (77 mg, 45%).

For **38**: colorless syrup; UV (MeOH) λ_{max} 268 (ϵ 22 400); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.85 (br s, 1 H), 8.13 (br s, 1 H), 8.00 (s, 1 H), 7.55−7.52 (m, 2 H), 7.23−7.14 (m, 3 H), 6.06 (d, J = 2.2 Hz, 1 H), 4.76 (d, J = 7.1 Hz, 1 H), 4.16 (dd, J = 7.1, 2.2 Hz, 1 H), 4.04 (dd, J = 11.7, 7.1 Hz, 1 H), 2.28 (s, 3 H), 2.18−1.53 (series of m, 6 H), 1.21−0.90 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 155.6, 146.5 (2 C), 137.8, 135.7, 130.9, 128.9 (2 C), 127.7 (2 C), 121.4, 72.8, 72.1, 70.5, 62.9, 55.3, 30.3, 29.4, 24.5, 17.39, 17.37, 17.28, 17.20, 17.15, 17.11, 17.04, 16.99, 13.6, 13.5, 13.2, 12.7; ES HRMS m/z (M + Na^+) calcd 786.2050, obsd 786.2063; $[\alpha]^{19}_D$ +96.8 (c 0.80, CH_3OH).

For **39**: white solid, mp 230−231 °C dec; UV (MeOH) λ_{max} 270 (ϵ 19 300) and 220 nm (ϵ 32 300); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.19 (br s, 1 H), 11.19 (br s, 1 H), 8.07 (s, 1 H), 7.62−7.60 (m, 2 H), 7.19−7.12 (m, 3 H), 6.71 (d, J = 2.5 Hz, 1 H), 4.92 (d, J = 7.1 Hz, 1 H), 4.24 (dd, J = 7.1, 2.5 Hz, 1 H), 4.08 (dd, J = 11.7, 7.2 Hz, 1 H), 2.38 (s, 3 H), 2.23−2.20 (m, 2 H), 1.99−1.91 (m, 2 H), 1.81−1.73 (m, 1 H), 1.62−1.54 (m, 1 H), 1.19−0.91 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 156.6, 152.4, 148.2, 142.2, 135.8 (2 C), 129.0 (2 C), 128.6, 128.1, 111.7, 73.0, 72.1, 70.6, 65.8, 55.4, 30.3, 29.3, 24.6, 17.38, 17.31 (2 C), 17.25 (2 C), 17.19, 17.15, 17.0, 16.9, 13.6, 13.4, 13.3, 12.8; ES HRMS m/z (M + Na^+) calcd 786.2050, obsd 786.2022; $[\alpha]^{19}_D$ +258 (c 0.06, CH_3OH).

Tin Hydride Reduction of Adenosine Analogue 37. Removal of the phenylseleno group followed the procedure for preparing **28** starting from **37** (46 mg, 0.057 mmol), Bu_3SnH (46 μL, 0.17 mmol) and Et_3B (1 M THF solution, 57 μL, 0.057 mmol) in toluene (6 mL). After purification by flash chromatography on silica gel (50% EtOAc/hexanes), **40** was obtained as a colorless syrup (37 mg, quant): UV (MeOH) λ_{max} 282 (ϵ 20 200) and 234 nm (ϵ 14 300); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.15 (br s, 1 H), 8.81 (s, 1 H), 8.51 (s, 1 H), 8.06 (d, J = 7.4 Hz, 2 H), 7.63 (t, J = 7.4 Hz, 1 H), 7.55 (d, J = 7.4 Hz, 1 H), 6.24 (d, J = 8.2 Hz, 1 H), 4.71 (dd, J = 12.4, 6.1 Hz, 1 H), 4.11 (dd, J = 11.6, 7.3 Hz, 1 H), 2.68−2.60 (m, 1 H), 2.53−2.48 (m, 1 H), 2.11−1.59 (series of m, 6 H), 1.18−0.93 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 152.5, 151.6, 149.5, 142.0, 133.6, 132.8, 128.8 (2 C), 127.9 (2 C), 123.5, 72.0, 70.9, 70.4, 53.3, 39.6, 30.2, 28.8, 17.52, 17.49, 17.33, 17.25 (2 C), 17.21, 17.1 (2 C), 16.7, 13.6, 13.5, 13.1, 12.6; ES HRMS m/z (M + Na^+) calcd 676.2779, obsd 676.2762; $[\alpha]^{19}_D$ −50.2 (c 0.60, CH_3OH).

Tin Hydride Reduction of Guanosine Analogue 38. Removal of the phenylseleno group followed the procedure for preparing **28** starting from **38** (82 mg, 0.11 mmol), Bu_3SnH (0.10 mL, 0.37 mmol) and Et_3B (1 M THF solution, 0.12 mL, 0.12 mmol) in toluene (12 mL). After purification by flash chromatography on silica gel (75% EtOAc/hexanes to 10% CH_3OH/EtOAc), **41** was obtained as a white solid (65 mg, quant): mp 261−263 °C; UV (MeOH) λ_{max} 286 (ϵ 16 500) and 264 nm (ϵ 22 900); ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.16 (br s, 1 H), 9.61 (br s, 1 H), 8.19 (s, 1 H), 5.84 (d, J = 7.8 Hz, 1 H), 4.49 (dd, J = 12.5, 5.7 Hz, 1 H), 4.03 (dd, J = 11.5, 7.3 Hz, 1 H), 2.58−2.49 (m, 1 H), 2.37−2.27 (m, 4 H), 2.01−1.53 (series of m, 6 H), 1.12−0.85 (m, 28 H); ^{13}C NMR (75 MHz, CD_3OD) δ 172.0, 155.9, 148.2, 147.4, 137.8, 121.4, 72.0, 70.5, 70.0, 53.0, 40.0, 30.1, 28.8, 24.5, 17.5, 17.4, 17.3, 17.2, 17.17, 17.14, 17.09, 17.06, 16.7, 13.6, 13.5, 13.2, 12.6; ES HRMS m/z (M + Na^+) calcd 630.2572, obsd 630.2555; $[\alpha]^{19}_D$ −32.5 (c 0.08, CH_3OH).

Tin Hydride Reduction of Guanosine Analogue 39. Removal of the phenylseleno group followed the procedure for preparing **28** starting from **39** (37 mg, 0.048 mmol), Bu_3SnH (39 μL, 0.14 mmol) and Et_3B (1 M THF solution, 48 μL, 0.048 mmol) in toluene (5 mL). After purification by flash chromatography on silica gel (75% EtOAc/hexanes), **42** was obtained as a colorless syrup (27 mg, quant): UV (MeOH) λ_{max} 268 (ϵ 12 200) and 224 nm (ϵ 21 600); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.36 (br s, 1H), 10.94 (br s, 1 H), 8.56 (s, 1 H), 6.39 (d, J = 7.2 Hz, 1 H), 4.37 (dd, J = 12.7, 5.3 Hz, 1 H), 4.06 (dd, J = 11.6, 7.2 Hz, 1 H), 2.67−2.62 (m, 1 H), 2.40−2.36 (m, 4 H), 2.07−1.58 (series of m, 6 H), 1.33−0.88 (m, 28 H); ^{13}C NMR (75 MHz, CD_3OD) δ 173.4, 157.3, 153.2, 148.4, 142.4, 112.1, 72.0, 69.7, 69.6, 56.8, 41.2, 30.0, 28.9, 24.6, 17.44, 17.40, 17.30, 17.25, 17.19, 17.11, 17.02, 16.99, 16.65, 13.6, 13.5, 13.3, 12.5; ES HRMS m/z (M + Na^+) calcd 630.2572, obsd 630.2598; $[\alpha]^{19}_D$ +62.1 (c 0.34, CH_3OH).

Adenosine Analogue 43. A 126 mg (0.19 mmol) sample of **40** was desilylated according to the procedure described for the preparation of **29** by treatment with TBAF (1 M THF solution, 0.42 mL, 0.42 mmol) in THF (4 mL). The reaction mixture was stirred for 4 h, evaporated to dryness, and placed under high vacuum for 30 min. Methanolic ammonia (9 mL) was added to the residue, and the mixture was kept at rt overnight prior to chromatography on silica gel (20% EtOH/toluene) to afford **43** (57 mg, 97%) as a white solid: mp 214 °C dec; UV (MeOH) λ_{max} 262 nm (ϵ 12 900); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1 H), 8.13 (s, 1 H), 7.26 (s, 2 H), 6.25 (t, J = 6.8 Hz, 1 H), 5.31 (d, J = 4.8 Hz, 1 H), 5.29 (d, J = 5.6 Hz, 1 H), 4.13 (br dd, J = 8.6, 4.2 Hz, 1 H), 3.93 (dd, J = 12.4, 6.8 Hz, 1 H), 2.63−2.57 (m, 1 H), 2.46−2.40 (m, 1 H), 2.21−2.14 (m, 1 H), 1.96−1.93 (m, 1 H), 1.79−1.71 (m, 1 H), 1.57−1.43 (m, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.2, 152.4, 149.2, 140.0, 119.1, 76.2, 75.9, 74.1, 57.8, 43.7, 32.6, 31.9, 19.3; ES HRMS m/z (M + Na^+) calcd 330.0995, obsd 330.1002; $[\alpha]^{19}_D$ −18.1 (c 0.16, CH_3OH).

Guanosine Analogue 44. A 51 mg (0.084 mmol) sample of **41** was desilylated according to the procedure described for the preparation of **29** by treatment with TBAF (1 M THF solution, 0.24 mL, 0.24 mmol) in THF (3 mL). The reaction mixture was stirred for 4 h, evaporated to dryness, and placed under high vacuum for 30 min. Methanolic ammonia (7 mL) was added to the residue, and the mixture was kept at rt overnight prior to chromatography on silica gel (30% EtOH/toluene) to afford **44** (26 mg, 96%) as a white solid: mp 245−247 °C; UV (MeOH) λ_{max} 260 nm (ϵ 7300); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.72 (br s, 1 H), 8.16 (s, 1 H), 6.57 (br s, 2 H), 6.00 (t, J = 6.8 Hz, 1 H), 5.31 (br s, 1 H), 5.16 (d, J = 5.2 Hz, 1 H), 4.10 (br s, 1 H), 3.91 (d, J = 5.2 Hz, 1 H), 2.48−2.45 (m, 1 H), 2.38−2.32 (m, 1 H), 2.18−2.11 (m, 1 H), 1.93−1.88 (m, 1 H), 1.78−1.72 (m, 1 H), 1.54−1.50 (m, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.8, 153.8, 150.9, 136.2, 116.4, 76.0, 75.8, 73.7, 56.8, 43.9, 32.4, 31.9, 19.0; ES HRMS m/z (M + Na^+) calcd 346.0944, obsd 346.0951; $[\alpha]^{20}_D$ −3.1 (c 0.13, CH_3OH).

Guanosine Analogue 45. A 18 mg (0.030 mmol) sample of **42** was desilylated according to the procedure described for the preparation of **29** by treatment with TBAF (1 M THF solution, 0.07 mL, 0.07 mmol) in THF (1 mL). The reaction mixture was stirred for 4 h, evaporated to dryness, and placed under high vacuum for 30 min. Methanolic ammonia (2 mL) was added to the residue, and the mixture was kept at rt

overnight prior to chromatography on silica gel (230% EtOH/toluene) to afford **45** (18 mg, 72%) as a white solid: mp 246−247 °C; UV (MeOH) λ_{max} 288 nm (ϵ 5400) and 252 nm (ϵ 5100); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.02 (br s, 1 H), 8.51 (s, 1 H), 6.35 (t, J = 6.2 Hz, 1 H), 6.28 (br s, 2 H), 5.31 (br s, 1 H), 5.13 (d, J = 4.6 Hz, 1 H), 4.06 (br s, 1 H), 3.89 (d, J = 4.6 Hz, 1 H), 2.48−2.37 (m, 2 H), 2.18−2.11 (m, 1 H), 1.94−1.88 (m, 1 H), 1.76−1.69 (m, 1 H), 1.63−1.41 (m, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.1, 154.7, 152.9, 142.2, 108.0, 75.5, 75.0, 73.2, 59.8, 44.6, 32.3, 31.7, 19.1; ES HRMS *m/z* (M + Na$^+$) calcd 346.0944, obsd 346.0955; [α]$^{18}_D$ +42.0 (*c* 0.10, CH_3OH).

***β*-Elimination of 14.** The reaction was carried out according to the procedure described for the preparation of **17** starting from **14** (434 mg, 1.89 mmol), HMPA (3.94 mL, 22.7 mmol) and *t*-BuLi (1.4 M in pentane, 8.0 mL, 11.3 mmol). Comparable workup followed by silica gel chromatography (20% EtOAc/hexanes) afforded **46** as a white solid (226 mg, 70% yield at 84% conversion): mp 97−98 °C; IR ($CHCl_3$, cm^{-1}) 3270 (br), 1453, 1307; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.41 (d, J = 6.1 Hz, 1 H), 5.81 (dd, J = 6.1, 2.9 Hz, 1 H), 4.93 (d, J = 2.9 Hz, 1 H), 4.06 (dd, J = 5.7, 2.7 Hz, 1 H), 2.51−2.43 (m, 1 H), 2.29−2.17 (m, 1 H), 2.01−1.59 (series of m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.1, 125.0, 80.8, 78.1, 73.6, 33.5, 28.9, 21.0; EI HRMS *m/z* (M$^+$) calcd 172.0553, obsd 172.0542; [α]$^{20}_D$ +217 (*c* 1.06, $CHCl_3$).

TIPDS Protection of 46. $TIPDSCl_2$ (0.70 mL, 2.2 mmol) was added at rt to a stirred suspension of **46** (189 mg, 1.1 mmol), AgOTf (1.4 g, 5.5 mmol) and 2,4,6-collidine (0.58 mL, 4.4) in DMF (20 mL), and stirring was continued for 3 h. The yellowish pink reaction mixture was poured into H_2O and extracted with CH_2Cl_2. The combined organic layers were washed with aq. $NaHCO_3$, dried, filtered and concentrated. The residue was chromatographed on silica gel (1% EtOAc/hexanes) to give **47** (411 mg, 91%) as a colorless oil; IR ($CHCl_3$, cm^{-1}) 1464, 1087, 1023; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.11 (dd, J = 5.8, 2.1 Hz, 1 H), 5.52−5.44 (m, 2 H), 4.57 (br s, 1 H), 2.66−2.59 (m, 1 H), 2.04−1.68 (series of m, 5 H), 1.16−0.85 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 127.5, 123.3, 81.5, 80.0, 74.4, 34.6, 29.2, 19.3, 17.8, 17.7, 17.6, 17.5, 17.36, 17.3, 17.2, 17.0, 14.4, 13.6, 13.4, 12.8; ES HRMS *m/z* (M + Na$^+$) calcd 437.1972, obsd 437.2003; [α]$^{19}_D$ +13.3 (*c* 1.47, $CHCl_3$).

DTBS Protection of 46. The reaction was carried out according to the procedure described for the preparation of **47** starting from **46** (37 mg, 0.22 mmol), $DTBSCl_2$ (0.09 mL, 0.44 mmol), AgOTf (276 mg, 1.1 mmol) and 2,4,6-collidine (0.11 mL, 0.88 mmol) in DMF (4 mL). The same workup and flash chromatography on silica gel (1% EtOAc/hexanes) afforded **48** (48.5 mg, 77%) as a colorless oil: IR ($CHCl_3$, cm^{-1}) 1641, 1476, 1120; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.17 (dd, J = 6.1, 3.2 Hz, 1 H), 5.92 (dd, J = 6.1, 1.8 Hz, 1 H), 5.46−5.44 (m, 1 H), 4.80 (d, J = 3.5 Hz, 1 H), 2.79−2.70 (m, 1 H), 1.89−1.74 (series of m, 5 H), 1.12 (s, 9 H), 1.05 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 128.0, 123.4, 82.7, 82.0, 72.0, 34.7, 29.1 (3 C), 28.7, 27.4 (3 C), 23.1, 20.4, 20.1; EI HRMS *m/z* (M$^+$) calcd 312.1574, obsd 312.1595; [α]$^{19}_D$ −13.5 (*c* 0.80, $CHCl_3$).

Glycosidation of 47 To Form 49. The reaction was carried out according to the procedure described for the preparation of **22** starting from **47** (64 mg, 0.15 mmol), bis-*O*-trimethylsilylthymine (62 mg, 0.23 mmol), and PhSeCl (44.8 mg, 0.23 mmol). The usual workup and silica gel chromatography (20% EtOAc/hexanes) gave **49** as a white foam (80 mg, 75%): UV (MeOH) λ_{max} 274 nm (ϵ 12 100); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (br s, 1 H), 7.71−7.68 (m, 2 H), 7.35−7.25 (m, 4 H), 5.86 (d, J = 2.0 Hz, 1 H), 4.88 (d, J = 6.3 Hz, 1 H), 4.46 (br s, 1 H), 4.14 (dd, J = 6.3, 2.0 Hz, 1 H), 2.76−2.68 (m, 1 H), 2.21−2.17 (m, 1 H), 2.01−1.70 (series of m, 7 H), 1.17−0.88 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2, 149.6, 136.7, 129.2 (2 C), 128.5 (2 C), 128.2, 110.2, 83.7, 74.6, 69.5, 66.6, 59.5, 34.4, 31.8, 20.3, 17.64, 17.59, 17.51, 17.3, 17.2, 17.1, 17.0, 16.7, 13.4, 13.13, 13.06, 12.5; ES HRMS *m/z* (M + Na$^+$) calcd 719.1880, obsd 719.1859; [α]$^{19}_D$ +8.9 (*c* 1.24, CH_3OH).

Glycosidation of 47 To Form 50. The reaction was carried out according to the procedure described for the preparation of **22** starting from **47** (80 mg, 0.19 mmol), bis-*O*-trimethylsilyluracil (78 mg, 0.29 mmol), and PhSeCl (56 mg, 0.29 mmol). The usual workup and silica gel chromatography (20% EtOAc/hexanes) gave **50** as a colorless syrup (105 mg, 80%): UV (MeOH) λ_{max} 266 nm (ϵ 25 600); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (br s, 1 H), 7.72−7.69 (m, 2 H), 7.65 (d, J = 8.1 Hz, 1 H), 7.33−7.26 (m, 3 H), 5.87 (d, J = 1.7 Hz, 1 H), 5.60 (dd, J = 8.1, 2.0 Hz, 1 H), 4.86 (d, J = 6.2 Hz, 1 H), 4.46 (br s, 1 H), 4.14 (dd, J = 6.2, 1.7 Hz, 1 H), 2.78−2.70 (m, 1 H), 2.19−2.14 (m, 1 H), 1.96−1.67 (series of m, 4 H), 1.14−0.82 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9, 149.6, 141.1, 136.3 (2 C), 129.2 (2 C), 128.5, 128.1, 101.5, 83.6, 74.4, 69.1, 67.1, 59.2, 34.4, 32.2, 20.4, 17.7, 17.6, 17.5, 17.3, 17.1 (2 C), 17.0, 13.6, 13.4, 13.3, 13.0; ES HRMS *m/z* (M + Na$^+$) calcd 705.1723, obsd 705.1743; [α]$^{19}_D$ +23.1 (*c* 0.59, CH_3OH).

Glycosidation of 48 To Form 51. The reaction was carried out according to the procedure described for the preparation of **22** starting from **48** (20 mg, 0.06 mmol), thymine (12 mg, 0.09 mmol), BSA (50 μL, 0.19 mmol) and PhSeCl (27 mg, 0.13 mmol). The usual workup and silica gel chromatography (20% EtOAc/hexanes) gave **51** (24 mg, 63%) consisting of an anomeric ratio of 14:1.

For β-isomer **51**: white solid, mp 106−107 °C; UV (MeOH) λ_{max} 274 nm (ϵ 11 600); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (br s, 1 H), 7.65−7.62 (m, 2 H), 7.33−7.21 (m, 3 H), 6.89 (d, J = 1.1 Hz, 1 H), 6.15 (d, J = 3.4 Hz, 1 H), 5.34 (d, J = 8.0 Hz, 1 H), 4.63 (d, J = 3.6 Hz, 1 H), 4.26 (dd, J = 8.0, 3.4 Hz, 1 H), 2.88−2.80 (m, 1 H), 2.07−1.94 (m, 3 H), 1.89−1.83 (series of m, 4 H), 1.76−1.68 (m, 1 H), 1.16 (s, 9 H), 1.08 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9, 149.2, 136.9, 135.1, 129.3 (2 C), 129.2 (2 C), 128.6, 111.6, 84.9, 77.2, 67.3, 67.1, 52.4, 34.3, 31.5, 28.8 (3 C), 27.4 (3 C), 23.4, 21.5, 20.7, 12.6; ES HRMS *m/z* (M + Na$^+$) calcd 617.1379, obsd 617.1352; [α]$^{21}_D$ +3.0 (*c* 1.50, CH_3OH).

For the α-isomer: yellow foam; IR ($CHCl_3$, cm^{-1}) 3392, 3190, 1682, 1476; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (br s, 1 H), 7.65−7.62 (m, 2 H), 7.32−7.17 (m, 3 H), 6.97 (d, J = 1.1 Hz, 1 H), 6.34 (d, J = 10.2 Hz, 1 H), 4.58 (d, J = 11.6 Hz, 1 H), 4.49 (d, J = 3.3 Hz, 1 H), 3.63 (dd, J = 11.6, 10.2 Hz, 1 H), 2.88−2.79 (m, 1 H), 2.04−1.62 (series of m, 8 H), 1.18 (s, 9 H), 1.08 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0, 150.6, 135.7, 135.4, 129.3 (2 C), 129.0 (2 C), 126.6, 112.3, 84.9, 77.8, 63.7, 60.7, 50.7, 34.6, 32.6, 28.9 (3 C), 27.3 (3 C), 23.3, 20.7, 20.4, 12.8; ES HRMS *m/z* (M + Na$^+$) calcd 617.1379, obsd 617.1391; [α]$^{19}_D$ +20.1 (*c* 1.99, $CHCl_3$).

Glycosidation of 48 To Form 52. The reaction was carried out according to the procedure described for the preparation of **22** starting from **48** (35.5 mg, 0.11 mmol), bis-*O*-trimethylsilyluracil (44 mg, 0.17 mmol), and PhSeCl (33 mg, 0.17 mmol). The usual workup and silica gel chromatography (25% EtOAc/hexanes) gave **52** as a yellow foam (47 mg, 71%): UV (MeOH) λ_{max} 268 nm (ϵ 8400); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.07 (br s, 1 H), 7.64−7.61 (m, 2 H), 7.26−7.21 (m, 4 H), 6.25 (d, J = 3.4 Hz, 1 H), 5.68 (d, J = 8.0 Hz, 1 H), 5.29 (d, J = 7.9 Hz, 1 H), 4.61 (d, J = 3.4 Hz, 1 H), 4.21 (dd, J = 7.9, 3.4 Hz, 1 H), 2.88−2.80 (m, 1 H), 2.07−1.67 (series of m, 5 H), 1.14 (s, 9 H), 1.08 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 149.3, 141.1, 135.0 (2 C), 129.3 (2 C), 128.5, 128.2, 103.3, 84.8, 77.2, 67.3, 66.8, 52.7, 34.3, 31.5, 28.8 (3 C), 27.4 (3 C), 23.4, 21.4, 20.7; ES HRMS *m/z* (M + Na$^+$) calcd 603.1222, obsd 603.1227; [α]$^{19}_D$ +28.5 (*c* 2.57, CH_3OH).

Protected Spironucleoside 53. The reaction was carried out according to the procedure described for the preparation of **22** starting from **47** (80 mg, 0.19 mmol), 1-*O*-trimethylsilyl-N^4-acetylcytosine (66 mg, 0.29 mmol), and PhSeCl (56 mg, 0.29 mmol). The usual workup and silica gel chromatography (50% EtOAc/hexanes) gave **53** as a white solid (60 mg, 43%): mp 224−226 °C; UV (MeOH) λ_{max} 284 (ϵ 8700) and 248 nm (ϵ 13 400); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.07 (br s, 1 H), 8.10 (d, J = 7.5 Hz, 1 H), 7.79−7.74 (m, 2 H), 7.34 (d, J = 7.5 Hz,

1 H), 7.31−7.21 (m, 3 H), 5.89 (d, J = 1.2 Hz, 1 H), 4.81 (d, J = 5.6 Hz, 1 H), 4.50 (br s, 1 H), 4.16 (dd, J = 5.6, 1.2 Hz, 1 H), 2.81−2.73 (m, 1 H), 2.23−2.16 (m, 4 H), 2.01−1.70 (series of m, 4 H), 1.13−0.71 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 162.8, 154.8, 145.8, 136.1 (2 C), 129.1 (2 C), 129.0, 128.3, 96.0, 84.0, 74.1, 69.2, 69.0, 59.7, 34.3, 32.5, 24.9, 20.4, 17.7, 17.6, 17.5, 17.3, 17.2, 17.02 (2 C), 16.96, 13.5, 13.3, 13.2, 13.0; ES HRMS *m/z* ($M + Na^+$) calcd 746.1989, obsd 746.2003; $[\alpha]^{19}_D$ −28.7 (*c* 1.04, CH_3OH).

Protected Spironucleoside 54. The reaction was carried out according to the procedure described for the preparation of **22** starting from **47** (80 mg, 0.19 mmol), 5-fluorouracil (47 mg, 0.29 mmol), BSA (71 μL, 0.29 mmol) and PhSeCl (56 mg, 0.29 mmol). The usual workup and silica gel chromatography (15% EtOAc/hexanes) gave **54** (114 mg, 82%) as a white foam: UV (MeOH) λ_{max} 274 nm (ϵ 12 400); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.04 (br s, 1 H), 7.81 (d, J = 6.3 Hz, 1 H), 7.74−7.69 (m, 2 H), 7.34−7.25 (m, 3 H), 5.86 (d, J = 2.0 Hz, 1 H), 4.83 (d, J = 6.2 Hz, 1 H), 4.48 (br s, 1 H), 4.11 (dd, J = 6.2, 2.0 Hz, 1 H), 2.80−2.71 (m, 1 H), 2.20−2.14 (m, 1 H), 2.01−1.72 (series of m, 4 H), 1.17−0.83 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5 (d, J = 26.7 Hz, 1 C), 148.3 139.6 (d, J = 236.8 Hz, 1 C), 136.4 (2 C), 129.2 (2 C), 128.6, 127.9, 125.3 (d, J = 34.1 Hz, 1 C), 83.6, 74.3, 69.2, 67.3, 59.2, 34.4, 32.1, 20.4, 17.6, 17.5, 17.4, 17.3, 17.2 (2 C), 17.1, 17.0, 13.6, 13.5, 13.4, 13.1; ES HRMS *m/z* ($M + Na^+$) calcd 723.1629, obsd 723.1642; $[\alpha]^{19}_D$ +34.1 (*c* 0.61, CH_3OH).

Adenosine Analogue 55. The reaction was carried out according to the procedure described for the preparation of **37** starting from **47** (40 mg, 0.10 mmol), N^6-benzoyladenine (35 mg, 0.15 mmol), BSA (36 μL, 0.15 mmol) and PhSeCl (28 mg, 0.15 mmol). The usual workup and silica gel chromatography (20−40% EtOAc/hexanes) gave **55** as a colorless syrup (53 mg, 68%): UV (MeOH) λ_{max} 282 nm (ϵ 21 000); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.08 (br s, 1 H), 8.67 (s, 1 H), 8.00 (d, J = 7.3 Hz, 2 H), 7.64−7.57 (m, 3 H), 7.53−7.48 (m, 3 H), 7.35−7.24 (m, 3 H), 5.86 (d, J = 0.9 Hz, 1 H), 5.81 (d, J = 6.4 Hz, 1 H), 4.65 (dd, J = 6.4, 0.9 Hz, 1 H), 4.61 (br s, 1 H), 2.82−2.74 (m, 1 H), 2.30−2.23 (m, 1 H), 2.04−1.66 (series of m, 4 H), 1.20−0.87 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 152.2, 150.7, 149.6, 142.1, 135.6 (2 C), 133.6, 132.8, 129.5 (2 C), 128.9 (2 C), 128.6, 128.5, 127.8 (2 C), 124.0, 83.4, 75.5, 70.8, 63.2, 58.9, 34.3 (2 C), 31.7, 20.3, 17.69, 17.64, 17.41, 17.33, 17.23, 17.20, 17.07, 13.40, 13.37, 13.09, 12.77; ES HRMS *m/z* ($M + Na^+$) calcd 832.2258, obsd 832.2236; $[\alpha]^{20}_D$ −66.4 (*c* 1.37, CH_3OH).

Guanosine Analogue 56. The reaction was carried out according to the procedure described for the preparation of **38** starting from **47** (80 mg, 0.19 mmol), N^2-acetylguanine (56 mg, 0.29 mmol), BSA (71 μL, 0.29 mmol), and PhSeCl (56 mg, 0.29 mmol). The usual workup and silica gel chromatography (50% EtOAc/hexanes to 10% CH_3OH/EtOAc) gave **56** as a colorless syrup (61 mg, 42%) along with a minor product (27 mg, 18%): UV (MeOH) λ_{max} 264 (ϵ 14 700) and 224 nm (ϵ 25 400); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.77 (br s, 1 H), 7.98 (s, 1 H), 7.77 (s, 1 H), 7.73−7.69 (m, 2 H), 7.40−7.30 (m, 3 H), 5.76 (s, 1 H), 4.89 (d, J = 5.8 Hz, 1 H), 4.50 (br s, 1 H), 4.18 (d, J = 5.8 Hz, 1 H), 2.74−2.70 (m, 1 H), 2.32−2.28 (m, 4 H), 2.13−1.72 (series of m, 4 H), 1.25−0.83 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 155.4, 146.5 (2 C), 137.5, 137.0, 129.6, 129.0 (2 C), 127.6 (2 C), 121.9, 84.1, 74.1, 68.8, 62.6, 60.7, 34.4, 29.7, 24.4, 20.4, 17.8, 17.6, 17.54, 17.46, 17.3, 17.2, 17.1, 17.0, 13.5, 13.3, 13.1, 13.0; ES HRMS *m/z* ($M + Na^+$) calcd 786.2050, obsd 786.2016; $[\alpha]^{19}_D$ −9.1 (*c* 1.56, CH_3OH).

2′-Deoxy-4′-thiathymidine Analogue 57. The phenylseleno group in **49** was removed according to the procedure described for the preparation of **28** starting from **49** (102 mg, 0.15 mmol), Bu_3SnH (0.12 mL, 0.45 mmol) and Et_3B (1 M THF solution, 0.15 mL, 0.15 mmol) in toluene (15 mL). After purification by flash chromatography on silica gel (20% EtOAc/hexanes), the resultant 2′-deoxy derivative was desilylated according to the procedure described for the preparation of **29** by treatment with TBAF (1 M THF solution, 0.32 mL, 0.32 mmol) in THF (3 mL). The residue was chromatographed on silica gel (10% EtOH/toluene) to afford **57** (44 mg, quant) as a white solid: mp 205−206 °C; UV (MeOH) λ_{max} 272 nm (ϵ 7200); ^{1}H NMR (300 MHz, CD_3OD) δ 7.91 (d, J = 1.1 Hz, 1 H), 6.52 (t, J = 7.9 Hz, 1 H), 4.52 (t, J = 3.2 Hz, 1 H), 4.22 (dd, J = 5.8, 4.5 Hz, 1 H), 2.42−2.32 (series of m, 3 H), 2.20−2.07 (m, 1 H), 1.92−1.56 (series of m, 7 H); ^{13}C NMR (75 MHz, CD_3OD) δ 168.2, 155.2, 141.3, 114.7, 84.5, 78.0, 76.4, 64.8, 46.9, 35.9, 35.6, 23.6, 15.1; ES HRMS *m/z* ($M + Na^+$) calcd 321.0879, obsd 321.0876; $[\alpha]^{19}_D$ −58.3 (*c* 0.12, CH_3OH).

2′-Deoxy-4′-thiauridine Analogue 58. The phenylseleno group in **50** was removed according to the procedure described for the preparation of **28** starting from **50** (109 mg, 0.16 mmol), Bu_3SnH (0.13 mL, 0.48 mmol), and Et_3B (1 M THF solution, 0.16 mL, 0.16 mmol) in toluene (16 mL). After purification by flash chromatography on silica gel (20% EtOAc/hexanes), the resultant 2′-deoxy derivative was desilylated according to the procedure described for the preparation of **29** by treatment with TBAF (1 M THF solution, 0.39 mL, 0.39 mmol) in THF (4 mL). The residue was chromatographed on silica gel (10% EtOH/toluene) to afford **58** (44 mg, 98%) as a white solid: mp 203−204 °C; UV (MeOH) λ_{max} 266 nm (ϵ 6700); ^{1}H NMR (300 MHz, CD_3OD) δ 8.11 (d, J = 8.1 Hz, 1 H), 6.52 (t, J = 8.9 Hz, 1 H), 5.76 (d, J = 8.1 Hz, 1 H), 4.53 (t, J = 3.3 Hz, 1 H), 4.21 (dd, J = 5.7, 4.1 Hz, 1 H), 2.44−2.31 (m, 3 H), 2.20−2.09 (m, 1 H), 1.86−1.57 (m, 4 H); ^{13}C NMR (75 MHz, CD_3OD) δ 168.5, 155.1, 145.9, 105.7, 84.4, 78.2, 76.8, 65.1, 47.0, 36.0, 35.6, 23.8; ES HRMS *m/z* ($M + Na^+$) calcd 307.0723, obsd 307.0719; $[\alpha]^{19}_D$ −50.8 (*c* 0.12, CH_3OH).

2′-Deoxy-4′-thia-5-fluorouridine Analogue 59. The phenylseleno group in **54** was removed according to the procedure described for the preparation of **28** starting from **54** (116 mg, 0.17 mmol), Bu_3SnH (0.13 mL, 0.51 mmol) and Et_3B (1 M THF solution, 0.17 mL, 0.17 mmol) in toluene (17 mL). After purification by flash chromatography on silica gel (15% EtOAc/hexanes), the resultant 2′-deoxy derivative was desilylated according to the procedure described for the preparation of **29** by treatment with TBAF (1 M THF solution, 0.38 mL, 0.38 mmol) in THF (4 mL). The residue was chromatographed on silica gel (10% EtOH/toluene) to afford **59** (50 mg, quant) as a white solid: mp 183−184 °C; UV (MeOH) λ_{max} 274 nm (ϵ 5700); ^{1}H NMR (300 MHz, CD_3OD) δ 8.30 (d, J = 6.8 Hz, 1 H), 6.48 (dt, J = 7.6, 1.6 Hz, 1 H), 4.50 (t, J = 3.4 Hz, 1 H), 4.21 (t, J = 5.5 Hz, 1 H), 2.48−2.33 (m, 3 H), 2.20−2.08 (m, 1 H), 1.84−1.58 (m, 4 H); ^{13}C NMR (75 MHz, CD_3OD) δ 161.9 (d, J = 26.1 Hz, 1 C), 153.8, 144.2 (d, J = 232.7 Hz, 1 C), 129.6 (d, J = 35.0 Hz, 1 C), 84.4, 77.9, 76.2, 65.6, 47.1, 35.8, 35.4, 23.5; ES HRMS *m/z* ($M + Na^+$) calcd 325.0629, obsd 325.0632; $[\alpha]^{19}_D$ −50.0 (*c* 0.12, CH_3OH).

2′-Deoxy-4′-thiacytidine Analogue 60. The phenylseleno group in **53** was removed according to the procedure described for the preparation of **28** starting from **53** (64.5 mg, 0.09 mmol), Bu_3SnH (0.07 mL, 0.27 mmol) and Et_3B (1 M THF solution, 0.09 mL, 0.09 mmol) in toluene (9 mL). After purification by flash chromatography on silica gel (50% EtOAc/hexanes), the resultant 2′-deoxy derivative was desilylated according to the procedure described for the preparation of **29** by treatment with TBAF (1 M THF solution, 0.21 mL, 0.21 mmol) in THF (2.5 mL). The reaction mixture was stirred for 1 day, evaporated to dryness, and placed under high vacuum for 30 min. Methanolic ammonia (4 mL) was added to the residue, and the mixture was kept at rt overnight prior to chromatography on silica gel (30% EtOH/toluene) to afford **60** (24 mg, 96%) as a colorless syrup. UV (MeOH) λ_{max} 278 nm (ϵ 5500); ^{1}H NMR (300 MHz, CD_3OD) δ 8.14 (d, J = 7.3 Hz, 1 H), 6.56 (t, J = 7.5 Hz, 1 H), 5.97 (d, J = 6.6 Hz, 1 H), 4.54 (br s, 1 H), 4.20 (t, J = 4.6 Hz, 1 H), 2.49−2.09 (series of m, 4 H), 1.89−1.58 (series of m, 4 H); ^{13}C NMR (75 MHz, CD_3OD) δ 169.8, 161.3, 146.3, 99.3, 84.4, 78.3, 76.4, 65.9, 47.4, 36.0, 35.7, 23.9; ES HRMS *m/z* ($M + Na^+$) calcd 306.0883, obsd 306.0869; $[\alpha]^{19}_D$ −59.5 (*c* 0.21, CH_3OH).

2′-Deoxy-4′-thiaadenosine Analogue 61. The phenylseleno group in **55** was removed according to the procedure described for the preparation of **28** starting from **55** (141 mg, 0.17 mmol), Bu_3SnH (0.14 mL, 0.51 mmol) and Et_3B (1 M THF solution, 0.17 mL, 0.17 mmol) in toluene (17 mL). After purification by flash chromatography on silica gel (20% EtOAc/hexanes), the resultant 2′-deoxy derivative was desilylated according to the procedure described for the preparation of **29** by treatment with TBAF (1 M THF solution, 0.38 mL, 0.38 mmol) in THF (4 mL). The reaction mixture was stirred for 4 h, evaporated to dryness, and placed under high vacuum for 30 min. Methanolic ammonia (9 mL) was added to the residue, and the mixture was kept at rt overnight prior to chromatography on silica gel (20% EtOH/toluene) to afford **61** (53 mg, 98%) as a white solid: mp 202−203 °C; UV (MeOH) λ_{max} 262 nm (ϵ 12 700); ^{1}H NMR (300 MHz, CD_3OD) δ 8.39 (s, 1 H), 8.19 (s, 1 H), 6.42 (t, J = 7.5 Hz, 1 H), 4.63 (br t, J = 3.2 Hz, 1 H), 4.41 (t, J = 5.4 Hz, 1 H), 3.00−2.93 (m, 1 H), 2.69−2.61 (m, 1 H), 2.46−2.36 (m, 1 H), 2.17−2.10 (m, 1 H), 1.90−1.60 (series of m, 6 H); ^{13}C NMR (75 MHz, CD_3OD) δ 157.4, 153.4, 150.2, 141.7, 120.8, 82.1, 75.8, 74.0, 61.5, 45.0, 33.1, 32.8, 21.1; ES HRMS *m/z* ($M + Na^+$) calcd 330.0995, obsd 330.0991; $[\alpha]^{19}_D$ −77.8 (*c* 0.18, CH_3OH).

2′-Deoxy-4′-thiaguanosine Analogue 62. The phenylseleno group in **56** was removed according to the procedure described for the preparation of **28** starting from **56** (33 mg, 0.043 mmol), Bu_3SnH (35 μL, 0.13 mmol) and Et_3B (1 M THF solution, 43 μL, 0.043 mmol) in toluene (5 mL). After purification by flash chromatography on silica gel (50% EtOAc/hexanes) the resultant 2′-deoxy derivative was desilylated according to the procedure described for the preparation of **29** by treatment with TBAF (1 M THF solution, 0.1 mL, 0.1 mmol) in THF (1 mL). The reaction mixture was stirred for 4 h, evaporated to dryness, and placed under high vacuum for 30 min. Methanolic ammonia (2 mL) was added to the residue, and the mixture was kept at rt overnight prior to chromatography on silica gel (30% EtOH/toluene) to afford **62** (12.5 mg, 91%) as a white solid, mp 220−222 °C; UV (MeOH) λ_{max} 260 nm (ϵ 8500); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.81 (br s, 1 H), 8.01 (s, 1 H), 6.61 (br s, 2 H), 6.14 (dd, J = 9.4, 6.2 Hz, 1 H), 5.43 (br s, 1 H), 5.16 (br s, 1 H), 4.51 (s, 1 H), 4.20 (s, 1 H), 2.70−2.63 (m, 1 H), 2.41−2.23 (m, 2 H), 1.97−1.91 (m, 1 H), 1.75−1.20 (series of m, 4 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.7, 153.7, 151.0, 135.5, 113.0, 79.5, 73.8, 73.6., 58.2, 43.7, 32.4, 32.2, 20.4; ES HRMS *m/z* ($M + Na^+$) calcd 346.0944, obsd 346.0942; $[\alpha]^{22}_D$ −15.6 (*c* 0.09, CH_3OH).

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

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