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Stereoselective Synthesis of β-Anomeric 4′-Thiaspirocyclic Ribonucleosides Carrying the Full Complement of RNA-Level Hydroxyl Substitution

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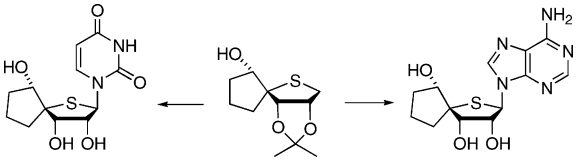
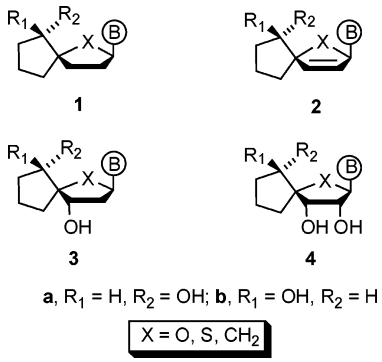


Stereoselective syntheses of a group of 4′-thiaspirocyclic ribonucleosides featuring both pyrimidine and purine classes and both possible configurations at C-5′ are described. Use is made of the Pummerer reaction of substrates carrying an α-oriented 2,4-dimethoxybenzoyloxy substituent at C-2 in order to gain reliable stereocontrol via neighboring group participation. Irrespective of the *S* or *R* configuration of the pivotal sulfoxide intermediates, the nucleobase is captured from the β-face. The competing process is formation of unsaturated sulfoxides, presumably via competing E2-type elimination. Although differences in reactivity between the two stereoisomeric series were noted, the common route has successfully given rise for the first time to desirable β-anomeric sulfur-containing spiroribonucleosides with minimum formation of the α-anomers.

Pyrimidine and purine nucleosides where conformational rotation about the 5′-hydroxymethyl substituent is structurally inhibited by spirocyclic annulation constitute a novel class of mimics.[1] Under such circumstances, the possibility exists to define new stereoisomeric series not otherwise available as a consequence of the necessary presence of two additional stereogenic centers. Beyond that, the broad group of spirocyclic nucleosides may be classified as to the presence of an oxygen, sulfur, or carbon center at the apical position. The extent of hydroxyl functionalization about the nucleobase-substituted ring as in **1**−**4** is an important added consideration.



Synthetic approaches to the syn and anti epimers defined by **1**−**4** have been successfully devised in this laboratory for most members.[2−4] A notable exception is the series represented by **4a**,**b** (X = S),[5] interest in which has remained high because of the obvious relationship to systems based on natural D-ribose and the biological activity/chemotherapeutic value of thianucleosides in general.[6] These considerations have prompted us to develop a convenient synthetic approach to such sulfur-containing spirocyclic agents. The outcome described

(1) Review: Paquette, L. A. *Austr. J. Chem.* **2004**, *57*, 7.

(2) Examples featuring X = O: (a) Paquette, L. A.; Bibart, R. T.; Seekamp, C. K.; Kahane, A. L. *Org. Lett.* **2001**, *3*, 4039. (b) Paquette, L. A. Owen, D. R.; Bibart, R. T.; Seekamp, C. K. *Org. Lett.* **2001**, *3*, 4043. (c) 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*, 2828. (d) Paquette, L. A.; Seekamp, C. K.; Kahane, A. L. *J. Org. Chem.* **2003**, *68*, 8614. (e) Paquette, L. A.; Kahane, A. L.; Seekamp, C. K. *J. Org. Chem.* **2004**, *69*, 5555. (f) Paquette, L. A.; Seekamp, C. K.; Kahane, A. L.; Hilmey, D. G.; Gallucci, J. *J. Org. Chem.* **2004**, *69*, 7442. (g) See also: Wendeborn, S.; Binot, G.; Nina, M.; Winkler, T. *Synlett* **2002**, 1683.

(3) Examples featuring X = S: (a) Paquette, L. A.; Fabris, F.; Gallou, F.; Dong, S. *J. Org. Chem.* **2003**, *68*, 8625. (b) Dong, S.; Paquette, L. A. *J. Org. Chem.* **2005**, *70*, 1580.

(4) Examples featuring X = CH_2: (a) Paquette, L. A.; Hartung, R. E.; France, D. J. *Org. Lett.* **2003**, *5*, 869. (b) Hartung, R. E.; Paquette, L. A. *J. Org. Chem.* **2005**, *70*, 1597. (c) Hartung, R. E.; Paquette, L. A. *Synthesis* **2005**, in press.

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

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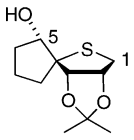
below is a route that proceeds readily with high β-stereoselectivity.

Results and Discussion

Adjacent acyloxy groups at C-2 and C-3 have come to be recognized as reasonably effective neighboring groups in Vorbrüggen-type glycosylation reactions involving a ribofuranose derivative and a nucleobase to deliver β-ribonucleosides.[7] However, unsatisfactory levels of stereocontrol and overall yield are often encountered during the synthesis of 4′-thiaribonucleosides even when a 2-*O*-acetal substituent is present to offer directive assistance.[8] An explanation for this appreciable difference has been advanced on the basis of computational analysis.[9] In essence, α-thiacarbocation intermediates carry less net atom charge at the α-position and consequently are less susceptible to neighboring group effects relative to structurally related oxocarbocations. These unsatisfactory stereochemical features are particularly evident when recourse is made to application of the Pummerer reaction for condensing a nucleobase with a sulfoxide.[10] In the absence of any neighboring group assistance, this process gives rise to the α-anomer as the major product. The presence of a 2-*O*-acyl substituent serves to lead to the β-anomer only in slight excess in many cases.

Several years ago, this problem was addressed systematically by Matsuda and co-workers, and a satisfactory solution was identified in the form of the 2,4-dimethoxybenzoyl group (DMBz).[11] The present investigation details the conversion of the previously described enantiopure acetonides **5** and **6**[3b] to RNA-configured spirocyclic thianucleosides and in so doing explores the extent to which Matsuda activation can be relied upon to guide β-anomer production.



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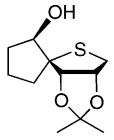

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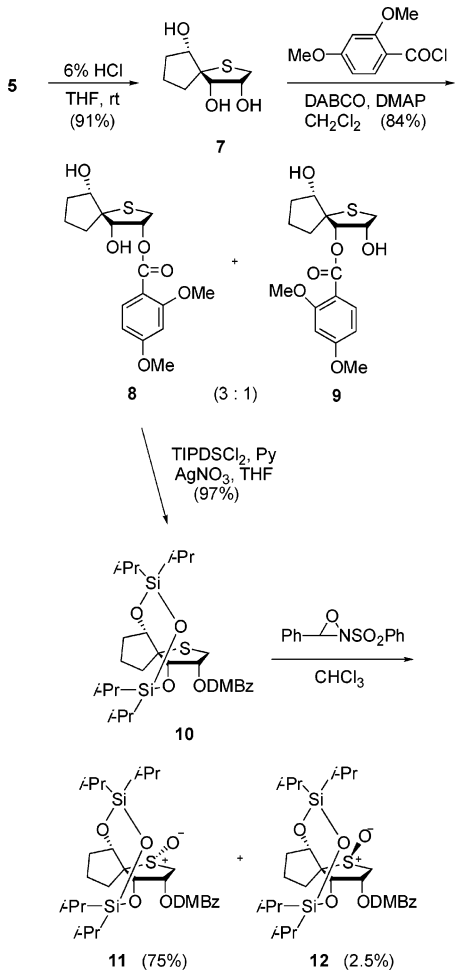
The syn series represented by **5** was first examined. Its hydrolysis with 6% hydrochloric acid in THF[12] gave the polar triol **7** in good yield (Scheme 1). Proper incorporation of the 2,4-DMBz group into the C-2 position now had to be addressed. The situation with the more commonplace 4-thiaribofuranose systems such as 1,4-anhydro-4-thio-D-ribitol is that silylation occurs most readily at 5-OH and 3-OH. For steric reasons, the expectation with spirocyclic analogues such as **7** is that initial reaction should occur regioselectively at the less hindered 2-OH site since the other two hydroxyls are now attached to neopentyl carbon atoms. The merger of these effects was manifested in a slow rate of reaction of **7** with 2,4-dimethoxybenzoyl chloride[13] in CH_2Cl_2 solution. Accompanying quantities of both DABCO[14] and DMAP were required to bring about acylation to the 84% level in 9 h at room temperature.[15] ^{1}H NMR analysis of unpurified reaction mixtures revealed a 4.5:1 ratio of **8** and **9** to be

SCHEME 1



(6) For recent selected reports, consult: (a) Yoshimura, Y.; Watanabe, M.; Satoh, H.; Ashida, N.; Ijichi, K.; Sakata, S.; Machida, H.; Matsuda, A. *J. Med. Chem.* **1997**, *40*, 2177. (b) Haraguchi, K.; Nishikawa, A.; Sasakura, E.; Tanaka, H.; Nakamura, K. T.; Miyasaka, T. *Tetrahedron Lett.* **1998**, *39*, 3713. (c) Yoshimura, Y.; Endo, M.; Miura, S.; Sakata, S. *J. Org. Chem.* **1999**, *64*, 7912. (d) Miller, J. A.; Pugh, A. W.; Ullah, G. M. *Tetrahedron Lett.* **2000**, *41*, 3265. (e) Minakawa, N.; Kaga, D.; Kato, Y.; Endo, K.; Tanaka, M.; Sasaki, T.; Matsuda, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2182. (f) Haraguchi, K.; Takahashi, H.; Tanaka, H. *Tetrahedron Lett.* **2002**, *43*, 5657. (g) Haraguchi, K.; Takahashi, H.; Shiina, N. Horii, C.; Yoshimura, Y.; Nishikawa, A.; Sasakura, E.; Nakamura, K. T.; Tanaka, H. *J. Org. Chem.* **2002**, *67*, 5919. (h) Haraguchi, K.; Shiina, N.; Yoshimura, Y.; Shimada, H.; Hashimoto, K.; Tanaka H. *Org. Lett.* **2004**, *6*, 2645.

(7) Vorbrüggen, H.; Ruh-Pohlenz, C. *Org. React.* **2000**, *55*, 1.

(8) (a) Bobek, M.; Bloch, A.; Parthasarathy, R.; Whistler, R. L. *J. Med. Chem.* **1975**, *18*, 784. (b) Tiwari, K. N.; Secrist, J. A., III; Montgomery, J. A. *Nucleosides Nucleotides* **1994**, *13*, 1819.

(9) Naka, T.; Nishizono, N.; Minakawa, N.; Matsuda, A. *Tetrahedron Lett.* **1999**, *40*, 6297.

(10) (a) O'Neil, I. A.; Hamilton, K. M. *Synlett* **1992**, 791. (b) Yoshimura, Y.; Kitano, K.; Satoh, H.; Watanabe, M.; Miura, S.; Sakata, S.; Sasaki, T.; Matsuda, A. *J. Org. Chem.* **1996**, *61*, 822. (c) Nishizono, N.; Koike, N.; Yamagata, Y.; Matsuda, A. *Tetrahedron Lett.* **1996**, *37*, 7569. (d) Yoshimura, Y.; Kitano, K.; Yamada, K.; Satoh, H.; Watanabe, M.; Miura, S.; Sakata, S.; Sasaki, T.; Matsuda, A. *J. Org. Chem.* **1997**, *62*, 3140. (e) Jeong, L. S.; Moon, H. R.; Choi, Y. J.; Chun, M. W.; Kim. H. O. *J. Org. Chem.* **1998**, *63*, 4821. (f) Lim, M. H.; Kim, H. O.; Moon, H. R.; Chun, M. W.; Jeong, L. S. *Org. Lett.* **2002**, *4*, 529. (g) Zhang, X.; Xia, H.; Dong, X.; Jin, J.; Meng, W.-D.; Qing, F.-L. *J. Org. Chem.* **2003**, *68*, 9026.

(11) Naka, T.; Minakawa, N.; Abe, H.; Kaga, D.; Matsuda, A. *J. Am. Chem. Soc.* **2000**, *122*, 7233.

(12) Varela, O.; Zunszain, P. A. *J. Org. Chem.* **1993**, *58*, 7860.

(13) Meyers, A. I.; Gabel, R.; Mihelich, E. D. *J. Org. Chem.* **1978**, *43*, 1372.

(14) Hartung, J.; Hünig, S.; Kneuer, R.; Schwarz, M.; Wenner, H. *Synthesis* **1997**, 1433.

(15) Triethylamine proved to be a less efficient base than DABCO. Use of pyridine as the base gave rise to only trace amounts of products.

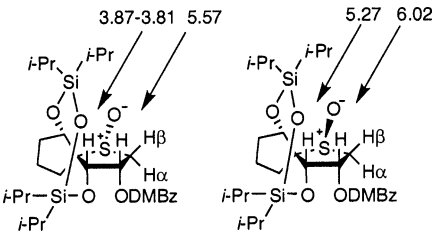
in hand. After chromatographic purification on silica gel, the ratio had changed to 3:1, thereby implicating possible acyl migration. The signals due to H-2 in **8** and H-3 in **9** were used to estimate these ratios. Comparable behavior was noted when crude samples were stored during 2 days or more on the shelf. At first glance, the conversion of **8** into **9** would appear unlikely. However, conformations of the tetrahydrothiophene ring can be adopted that project the 3-carboxylate ester into a quasiequatorial conformation, thereby avoiding nonbonded interaction with the adjacent methylene group.

The position of the ODMBz group in **8** and in **9** is quite apparent by ^{1}H NMR spectroscopy. The 2-derivative displays a characteristic downfield shift for H-2 (5.57−5.51 ppm) relative to the H-3 (4.15 ppm) and H-5 (3.89−3.81 ppm) signals.[16] For **9**, the reverse is true. In this case, H-3 (5.37 ppm) appears downfield of the absorptions attributable to H-2 (4.65−4.58 ppm) and H-5 (3.92−3.85 ppm). Additional evidence was secured on the basis of the 3-OH and 5-OH peaks in **8** whose identity was corroborated by 2D NMR correlations and D_2O exchange experiments.

The critical disilylation of **8** to generate **10** could be performed directly on the **8/9** mixture provided that reaction was performed under dilute conditions (0.02 mol/L). Upon adoption of otherwise standard guidelines, **8** reacts with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane[17] while **9** is inert. The fully protected sulfide **10** produced in this manner was subsequently oxidized with the Davis oxaziridine[18] to furnish the pair of diastereomeric sulfoxides **11** and **12** in isolated yields of 75% and 2.5%, respectively. On the basis of our earlier efforts[3b] and supportive MM3 calculations,[19] it is known that the disiloxane belt is positioned on the β-surface of the spirocyclic core. As a consequence, the α-face of the tetrahydrothiophene ring is left open for delivery of the oxygen atom. On this basis, major product **11** should be the *R*-sulfoxide as shown.

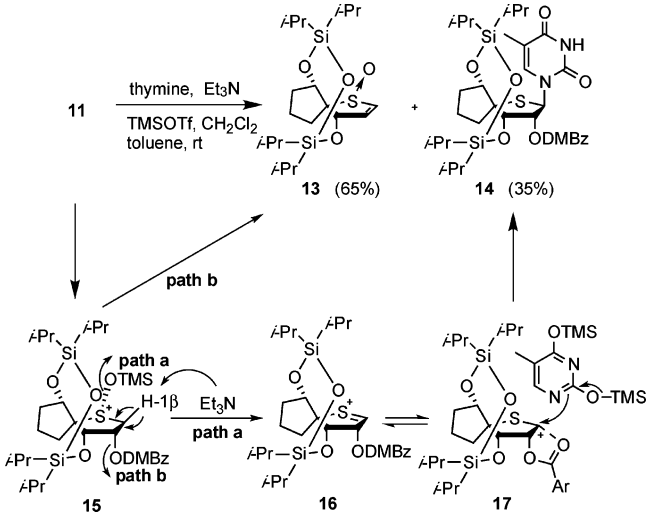
Over the years, several spectroscopic methods have been advanced for establishing proper sulfoxide configurational assignments. Recourse to Eu(dpm)$_3$- and solvent-induced ^{1}H NMR shifts is one of these.[20] The europium reagent coordinates to the sulfinyl oxygen atom, thereby inducing via a pseudo-contact mechanism the downfield shifting of signals stemming from nearby methylene groups. The benzene- or TFA-induced shifts of the resonances of the nonequivalent diastereotopic methylene protons α to the sulfinyl group has been rationalized on the basis of specific interactions of the solvent molecules with the positive end of the S^+-O^- dipole.[21] This diagnostic tool is particularly reliable and convenient when the molecules under consideration are conformationally restricted as in the present setting. As a consequence, by simply going from $CDCl_3$ to C_6D_6 solutions, a greater level of shielding is expected for the proton more remote from the sulfinyl oxygen atom. The relevant data for sulfoxides **11** and **12**, with assignments based on NOESY and COSY data, are listed in Table 1. This analysis conforms fully with the observations made by Rayner who noted that a sulfoxide group has a strong deshielding effect on the 1,3-protons that lie parallel to the S → O bond.[22] When comparison is made between the chemical shifts of H-2 and H-3 in **11** (5.57 and 3.87−3.81 ppm, respectively, in $CDCl_3$) to those of **12** (6.02 and 5.27 ppm, respectively, in the same solvent), it is again evident that the minor sulfoxide must be *S*-configured.

TABLE 1. Spectroscopic Comparison of Sulfoxides 11 and 12



	11			12		
proton	$CDCl_3$	C_6D_6	Δδ	$CDCl_3$	C_6D_6	Δδ
H-1β	3.84	3.14	−0.70	3.28	2.88	−0.40
H-1α	2.61	2.54	−0.07	3.43	2.88	−0.55

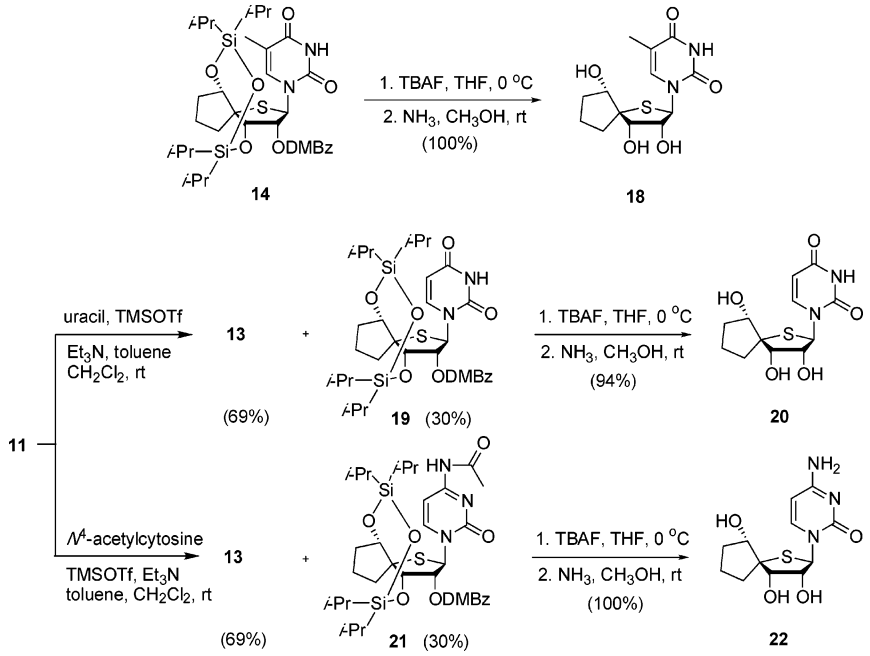
SCHEME 2



The coupling of sulfoxide **11** to silylated thymine was conducted under the optimized Pummerer conditions (such as adding 8 equiv of Et_3N in two portions) described by Matsuda et al.[11] (Scheme 2). Reaction proceeded immediately to deliver the desired thiaspiroribonucleoside **14** in 35% yield, alongside the unsaturated sulfoxide **13** (65%). The β configuration assigned to **14** was suggested by two key NOESY correlations involving H-6/H-2′ and H-6/H-3′. Additional corroboration was gained on the basis of a simple 1D NMR analysis that takes advantage of the fact that ribonucleosides possessing a 1,1,3,3-

(16) Fromageot, H. P. M.; Griffin, B. E.; Reese, C. B.; Sulston, J. E.; Trentham, D. R. *Tetrahedron* **1966**, *22*, 705.
(17) (a) Hutchinson, J. H.; Daynard, T. S.; Gillard, J. W. *Tetrahedron Lett.* **1991**, *32*, 573. (b) Bradford, C. L.; Fleming, S. A.; Ward, S. C. *Tetrahedron Lett.* **1995**, *36*, 4189.
(18) (a) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703. (b) Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919. (c) Davis, F. A.; Jenkins, R., Jr.; Yocklovich, S. G. *Tetrahedron Lett.* **1978**, 5171.
(19) Dong, S. Unpublished results.
(20) (a) Folli, U.; Iarossi, D.; Taddei, F. *J. Chem. Soc., Perkin Trans. 2* **1974**, 933. (b) Fraser, R. R.; Durst, T.; McClory, M. R.; Viau, R.; Wigfield, Y. Y. *Int. J. Sulfur Chem. A* **1971**, *1*, 133. (c) Barbarella, G.; Garbesi, A.; Fava, A. *J. Am. Chem. Soc.* **1975**, *97*, 5883.
(21) Ledaal, T. *Tetrahedron Lett.* **1968**, 1683.
(22) Westwell, A. D.; Thornton-Pett, M.; Rayner, C. M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 847.

SCHEME 3



tetraisopropyldisiloxane-1,3-diyl group to mask their 3′- and 5′-hydroxyl groups are locked into a 2′-*exo*/3′-*endo* conformation. As a direct consequence, H-1′ in the β anomer appears as a doublet with a small J value, while the same proton in the α isomer emerges as a doublet with a large coupling constant.[11] These features are maintained in the spirocyclic analogues, the anomeric proton signal in **14** appearing as a doublet at 6.16 ppm with a J value of 1.2 Hz.

The efficient conversion of **11** to **13** and **14** implicates the competing operation of two reaction pathways. Following initial activation by *O*-silylation with trimethylsilyl triflate, the proton trans to the sulfinyl oxygen atom is presumably rendered more acidic[11] and most prone to abstraction. This would be cause for electron flow to operate in two directions, which are labeled as **path a** and **path b** in Scheme 2. The E2 elimination of Me_3SiOH leads to sulfonium intermediates **16** and **17**, with subsequent nucleophilic attack operating to deliver **14** stereoselectively. With regard to **path b**, the elimination of 2,4-dimethoxybenzoic acid results in dead-end generation of the unsaturated sulfoxide. Attempts to alter the product distribution, such as to involve different silylating agents (e.g., TESCl) of the 3- and 5-hydroxyls, and to use $ZnCl_2$ as the Lewis acid, did not improve matters. When **12** was subjected to comparable Pummerer conditions, the unsaturated (*S*)-sulfoxide was formed exclusively.

Unmasking of the hydroxyl groups in **14** was achieved in a one-flask operation by sequential desilylation and aminolysis to deliver **18** quantitatively (Scheme 3). The two other pyrimidine ribonucleosides **20** and **22** were prepared under similar conditions and in comparable yield.

The introduction of a pair of purine bases was accomplished by coupling **11** to the 6-chloro- and 2-amino-6-chloropurines (Scheme 4). Both reactions were conducted in refluxing dichloroethane-acetonitrile solvent systems and *N*-9-β isomers were generated preferably over the other stereo- and regioisomers by rearrangement. The *N*-9 isomers **24** and **27** were subsequently desilylated with TBAF admixed with equimolar quantities of acetic acid to skirt potential complications arising from displacement of the chlorine substituent by fluoride ion. After this maneuver, **24** and **27** were transformed by conventional means into the spiro 4′-β-thiaadenosine **25** and guanosine **28**.

The anomeric configuration was assigned as β for **24**, **26**, and **27** on the strength of the appearance of the anomeric protons as doublets featuring small J values (0−1.1 Hz). The associated splitting constant in **23** is 5.5 Hz, implicating its α configuration, which was confirmed by NOESY analysis (H-1′/H-3′ correlation observed). Attempts to confirm the regiochemistry of **23** by HMBC analysis gave rise to inconclusive results. Recourse was then made to the reliable 1D NMR analysis of the purine base.[23] According to Kjellberg and Johansson, the most pronounced difference in *N*-9 and *N*-7 isomers resides in the C-5 signal. Thus, the C-5 signal in the *N*-7 system **23** is shifted upfield (122.9 ppm) relative to the corresponding shift (132.7 ppm) in the *N*-9 derivative **24**. Furthermore, all of the carbon signals of the purine skeleton in **24** compare very closely with those of 6-chloropurine riboside, which is most compatible with the *N*-9 feature. The regiochemical assignments to **26** and **27** relied on the characteristic downfield shift displayed by H-8 (8.68 ppm) in the *N*-7 isomer **26** relative to that (8.04 ppm) of *N*-9-substituted molecule **27**. In all cases, the regiochemistry of the final products was further confirmed by comparing the ^{13}C NMR chemical shifts of C-5 and C-8 with those of natural ribopurine nucleosides (Table 2).

As progress was being realized in the syn series, expectations grew that reasonably parallel chemical behavior would be manifested during elaboration of the anti analogues. This was not the case. When acetonide **6**

(23) (a) Kjellberg, J.; Johansson, N. G. *Tetrahedron* **1986**, *42*, 6541. (b) Kjellberg, J.; Johansson, N. G. *Nucleosides Nucleotides* **1989**, *8*, 225. (c) Chenon, M.-T.; Pugmire, R. J.; Grant, D. M.; Panzica, R. P.; Townsend, L. B. *J. Am. Chem. Soc.* **1975**, *97*, 4627. (d) Chenon, M.-T.; Pugmire, R. J.; Grant, D. M.; Panzica, R. P.; Townsend, L. B. *J. Am. Chem. Soc.* **1975**, *97*, 4636.

SCHEME 4

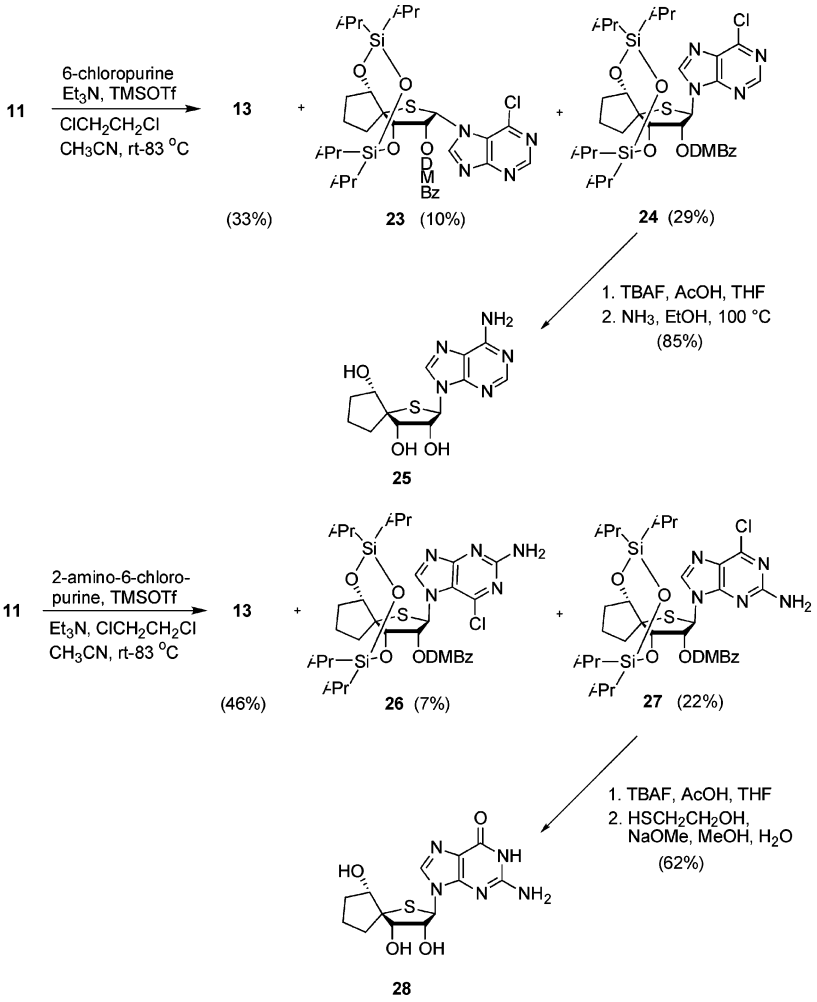
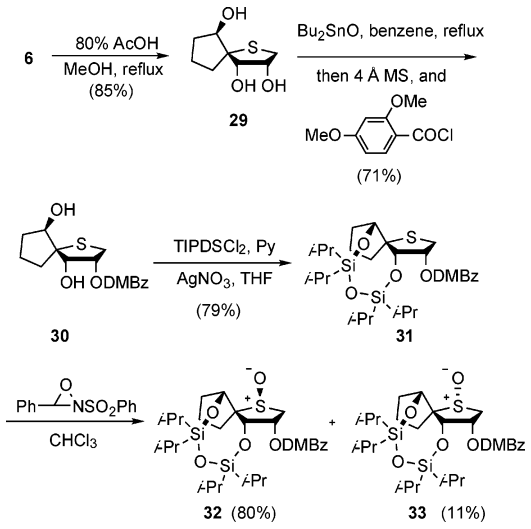


TABLE 2. Comparison of ^{13}C NMR Shifts for Ribopurine Nucleosides (DMSO-d_6)

carbon	adenosine	**25**	guanosine	**28**
C-5	119.6	119.6	117.5	116.3
C-8	140.2	140.7	136.9	136.0

was treated with 6% HCl in THF as before, a large amount of unidentified side product, which proved difficult to separate from desired triol **29** was generated. Alternative recourse to hydrolysis with *p*-toluenesulfonic acid in methanol led to formation of a complex reaction mixture. Ultimately it was discovered that 80% acetic acid in methanol at the reflux temperature[24] was well suited to generating **29** in good yield (Scheme 5). When **29** was subjected to the benzoylating conditions that proved so effective with its diastereomer **7**, complex product mixtures were generated. From among the alternative options that exist, that involving the transient generation of an *O*-stannylene acetal was pursued.[25] Masking of the 1,2-diol functionality in this manner was accomplished by heating **29** with an equivalent of dibutyltin oxide suspended in benzene with removal of water.[26] Subsequent exposure to 2,4-dimethoxybenzoyl

SCHEME 5



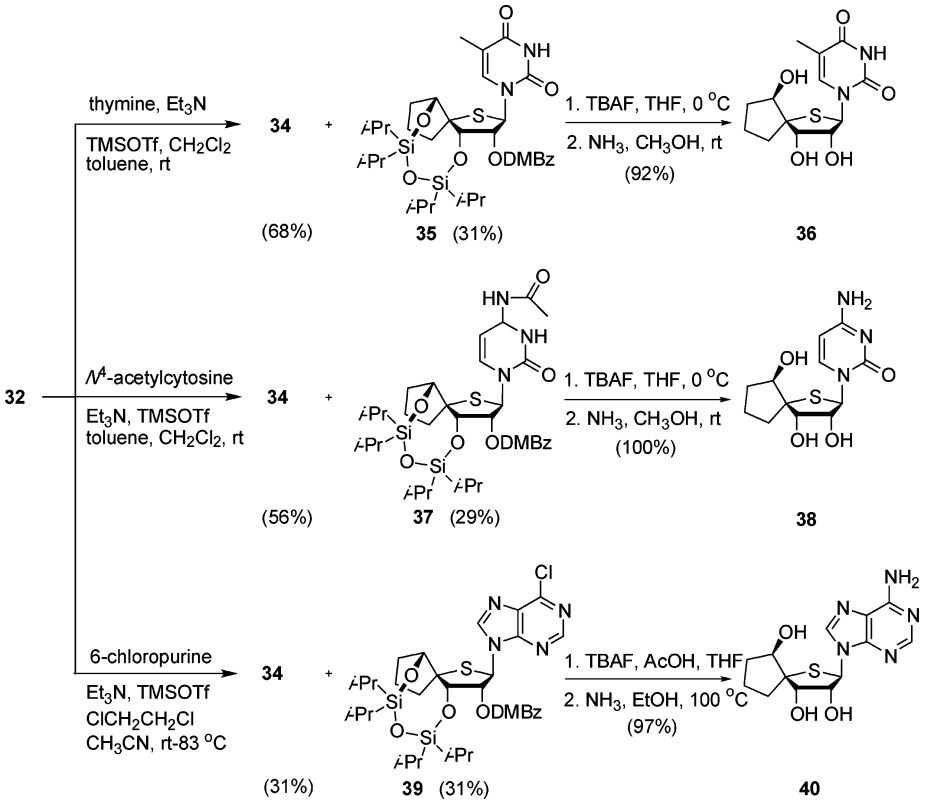
chloride gave the 2-acylated product **30** in 71% yield. As before, the location of the acyl functionality was deduced on the basis of the downfield shift experienced by H-2 (5.61−5.56 ppm) relative to the signals arising from H-3

(24) Nishizono, N.; Baba, R.; Nakamura, C.; Oda, K.; Machida, M. *Org. Biomol. Chem.* **2003**, *1*, 3692.

(25) Wagner, D.; Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1974**, *39*, 24.

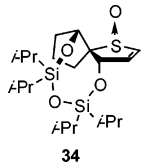
(26) David, S.; Thieffrey, A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1568.

SCHEME 6



(4.56 ppm) and H-5 (4.18 ppm). Also diagnostic was the presence of the 3-OH and 5-OH signals. The ensuing TIPDS protection of **30** as in **31** and oxidation to the sulfoxide level with the Davis sulfonyloxaziridine proceeded uneventfully. The configuration of the major sulfoxide **32** was identified as *S* by virtue of the characteristic downfield shifts of H-2/H-3 (5.96/5.29 ppm) relative to those of minor sulfoxide **33** (5.71/4.45 ppm). Consequently, unlike the effects operating in sulfide **10** which contribute to favored attack from the α-face, the TIPDS protecting group in **31** does not shield the *β*-face in comparable fashion. In actuality, the α-face in **31** is more congested, thus causing sulfoxidation to occur more readily on the *β*-face.

Despite the fact that **11** and **32** are differently configured at sulfur, these two substrates undergo the Pummerer reaction in comparable fashion (Scheme 6). Three examples were studied with incorporation of thymine, N^4-acetylcytosine, and 6-chloropurine; unsaturated sulfoxide **34** was concomitantly formed as a byproduct. In the case of purine base incorporation, it should be noted that the isomeric rearrangement was finished in 9 h (shown by TLC analysis) and *N*-9-*β* isomer **39** was the only stereo- and regioisomer isolated in 31% yield.



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Summary

The stereoselective synthesis of spirocyclic 4′-thia-*β*-ribonucleosides featuring syn or anti stereochemistry at the 5′-position has been realized via a route involving the Pummerer rearrangement as the key step. The successful approach, which began by acidic deprotection of acetonides **5** and **6**, involved subsequent regioselective introduction of a 2,4-dimethoxybenzoyl substituent at C-2 followed by TIPDS protection to arrive at sulfides **10** and **31**. After oxidation of these advanced intermediates to their sulfoxides with the Davis reagent, reaction with several nucleobases was effected with trimethylsilyl triflate and triethylamine. Under these conditions, neighboring group participation was effective in delivering *β*-configured ribonucleosides alongside the corresponding unsaturated sulfoxides. Arrival at the targeted nucleosides was then achieved conventionally. The difference in configuration at C-5 was sufficient to induce reactivity differences in the early phases of the synthetic scheme. Finally, all of the many thiaspirocyclicnucleosides synthesized in the course of this investigation have been submitted to the NIH for evaluation in as many antiviral screens as possible.

Experimental Section

General Procedure. Consult ref 2c.

Triol 7. Acetonide **5** (304 mg, 1.32 mmol) was dissolved in a mixture of THF (8 mL) and 6% aqueous HCl (4 mL), and the solution was stirred for 8 h at rt. Evaporation afforded a dark oil, which was submitted to silica gel chromatography with 85% EtOAc/hexanes as eluent to afford triol **7** (228 mg, 91%) as a colorless syrup: IR (neat, cm^{-1}) 3371 (br), 1447, 1078; ^1H NMR (300 MHz, DMSO-d_6) δ 4.79 (d, J = 6.0 Hz, 1 H), 4.75 (d, J = 5.2 Hz, 1 H), 4.26 (d, J = 6.3 Hz, 1 H), 4.18−4.12 (m, 1 H), 3.61−3.51 (m, 2 H), 2.67 (d, J = 7.0 Hz, 2 H), 2.18−2.09 (m, 1 H), 1.81−1.31 (series of m, 5 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 76.9, 76.1, 74.4, 68.1, 32.8, 32.4, 32.3, 19.4;

EI HRMS *m/z* (M^+) calcd 190.0658, obsd 190.0679; $[\alpha]^{20}_D$ +37.9 (*c* 0.29, $CHCl_3$).

2,4-Dimethoxybenzoylation of Triol 7. A CH_2Cl_2 solution (100 mL) of triol **7** (1.84 mg, 9.66 mmol), DABCO (3.36 g, 30 mmol), and DMAP (1.83 g, 15 mmol) was charged with N_2 and cooled to 0 °C. 2,4-Dimethoxybenzoyl chloride (3.00 g, 15 mmol) was added in small portions, and the mixture was stirred for 9 h at rt, quenched with saturated $NaHCO_3$ solution (50 mL), and washed three times with CH_2Cl_2 (50 mL). The combined organic layers were dried and concentrated in vacuo, and the residue was purified by silica gel chromatography (elution with 40−80% EtOAc/hexanes) to give 2,4-dimethoxybenzoates **8** and **9** as colorless syrups (2.57 g total, 84% yield, 3:1 ratio).

For **8**: IR (neat, cm^{-1}) 3475 (br), 1706, 1609, 1252; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.6 Hz, 1 H), 6.65−6.48 (m, 2 H), 5.57−5.51 (m, 1 H), 4.15 (br s, 1 H), 3.89−3.81 (m, 1 H), 3.89 (s, 3 H), 3.86 (s, 3 H), 3.21 (dd, *J* = 11.2, 6.1 Hz, 1 H), 3.07 (dd, *J* = 11.2, 6.0 Hz, 1 H), 2.94 (br d, *J* = 4.8 Hz, 1 H), 2.44 (br d, *J* = 8.5 Hz, 1 H), 2.34−2.26 (m, 1 H), 2.05−1.94 (m, 2 H), 1.73−1.42 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 164.8, 161.0, 134.4, 111.6, 105.0, 99.0, 77.5, 77.1, 76.3, 69.2, 55.6 (2 C), 32.6, 31.9, 30.9, 19.7; ES HRMS *m/z* ($M + Na^+$) calcd 377.1029, obsd 377.1020; $[\alpha]^{21}_D$ +72.1 (*c* 0.99, $CHCl_3$).

For **9**: IR (neat, cm^{-1}) 3467 (br), 1706, 1609, 1251; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.6 Hz, 1 H), 6.58−6.50 (m, 2 H), 5.37 (d, *J* = 3.6 Hz, 1 H), 4.65−4.58 (m, 1 H), 3.92−3.85 (m, 1 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 3.13−2.95 (series of m, 2 H), 2.22−1.95 (series of m, 3 H), 1.67−1.48 (series of m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 164.7, 160.6, 134.2, 112.0, 105.1, 99.1, 81.1, 76.4, 74.8, 68.6, 56.0, 55.6, 34.1, 33.6, 32.6, 19.6; ES HRMS *m/z* ($M + Na^+$) calcd 377.1029, obsd 377.1020; $[\alpha]^{21}_D$ +48.1 (*c* 0.48, $CHCl_3$).

TIPDS Protection of 8. A solution of **8** (1050 mg, 2.97 mmol) in THF (150 mL) was admixed with pyridine (1.15 mL, 14.24 mmol). Silver nitrate (1.21 g, 7.12 mmol) was introduced, and stirring was maintained for 1 h at rt prior to the addition of $TIPDSCl_2$ (1.14 mL, 3.56 mmol). After vigorous stirring in the dark for 6 h, the cloudy white reaction mixture was filtered into saturated $NaHCO_3$ solution (50 mL). The product was extracted into CH_2Cl_2 (3 × 50 mL) and purified by flash chromatography on silica gel (10% EtOAc/hexanes) to furnish sulfide **10** (1288 mg, 97%) as a colorless oil: IR (neat, cm^{-1}) 1720, 1609, 1465, 1265, 1130; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.7 Hz, 1 H), 6.51−6.48 (m, 2 H), 5.72 (t, *J* = 5.2 Hz, 1 H), 4.26 (d, *J* = 4.7 Hz, 1 H), 3.99 (dd, *J* = 11.4, 7.0 Hz, 1 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 3.28 (dd, *J* = 12.9, 6.5 Hz, 1 H), 2.95 (d, *J* = 12.9 Hz, 1 H), 2.15−2.09 (m, 2 H), 1.92−1.85 (m, 2 H), 1.70−1.50 (m, 2 H), 1.14−0.98 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 164.3, 161.6, 133.7, 112.4, 104.4, 98.9, 73.8, 73.1, 72.6, 67.0, 55.9, 55.5, 31.3, 29.9, 29.7, 17.5 (2 C), 17.4 (2 C), 17.3, 17.2 (2 C), 17.1 (2 C), 13.6, 13.1, 13.0, 12.6; ES HRMS *m/z* ($M + Na^+$) calcd 619.2554, obsd 619.2567; $[\alpha]^{18}_D$ +44.5 (*c* 0.91, $CHCl_3$).

Sulfoxides 11 and 12. To a solution of sulfide **10** (430 mg, 0.72 mmol) in 75 mL of $CHCl_3$ was added the Davis oxaziridine reagent (226 mg, 0.86 mmol). The reaction mixture was stirred at 0 °C for 4 h. The solvent was removed, and the residue was subjected to flash chromatography (25−50% AcOEt/hexanes). Sulfoxides **11** (333 mg, 75%) and **12** (11 mg, 2.5%) are both white foams.

For **11**: IR ($CHCl_3$, cm^{-1}) 1729, 1600, 1249, 1128, 1043; ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.6 Hz, 1 H), 6.53−6.48 (m, 2 H), 5.57 (t, *J* = 5.5 Hz, 1 H), 4.29 (t, *J* = 9.3 Hz, 1 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.87−3.81 (m, 2 H), 2.64−2.48 (m, 2 H), 2.22−1.57 (series of m, 5 H), 1.08−0.90 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 164.3, 161.8, 133.8, 111.6, 104.5, 98.9, 76.2, 73.1, 71.3, 67.0, 55.8, 55.5 (2 C), 29.7, 19.5, 18.2, 17.3, 17.2 (2 C), 17.13 (2 C), 17.10 (2 C), 16.9, 13.5 (2 C), 12.8, 12.6; ES HRMS *m/z* ($M + Na^+$) calcd 635.2501, obsd 635.2505; $[\alpha]^{19}_D$ +3.2 (*c* 0.94, $CHCl_3$).

For **12**: IR ($CHCl_3$, cm^{-1}) 1731, 1608, 1249, 1138, 1037; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 9.3 Hz, 1 H), 6.49−6.45 (m, 2 H), 6.02 (t, *J* = 5.4 Hz, 1 H), 5.27 (d, *J* = 5.4 Hz, 1 H), 4.39 (dd, *J* = 11.7, 7.3 Hz, 1 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 3.42 (dd, *J* = 15.7, 1.6 Hz, 1 H), 3.28 (dd, *J* = 15.7, 7.0 Hz, 1 H), 2.34−1.61 (series of m, 6 H), 1.12−0.97 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 164.2, 161.5, 133.5, 112.0, 104.5, 98.9, 77.2, 74.3, 70.8, 69.9, 57.9, 55.8, 55.5, 30.0, 29.7, 22.7, 17.4, 17.3, 17.28, 17.25, 17.22, 17.1, 17.0, 16.9, 13.4, 13.3, 12.9, 12.5; ES HRMS *m/z* ($M+Na^+$) calcd 635.2501, obsd 635.2505; $[\alpha]^{19}_D$ +59.5 (*c* 1.11, $CHCl_3$).

Pummerer Reaction of Sulfoxide 11 with Thymine. A suspension of thymine (9 mg, 0.071 mmol) in toluene (1 mL) was treated with triethylamine (20 μL, 0.14 mmol) and TMSOTf (50 μL, 0.29 mmol), and the resulting mixture was stirred at rt for 1 h before the addition of dichloromethane (0.5 mL). The clear solution of silylated thymine was added to a solution of **11** (22 mg, 0.036 mmol) in dichloromethane (0.5 mL) slowly over 15 min. An additional amount of triethylamine (20 μL, 0.14 mmol) in toluene (0.5 mL) was added dropwise to the reaction mixture to initiate the Pummerer reaction. After 5 min of stirring at rt, cold water (2 mL) was added, and the aqueous layer was extracted with dichloromethane (3 × 4 mL). The combined organic phases were washed with saturated $NaHCO_3$ solution (4 mL) and brine, dried, and concentrated in a vacuum. The residue was purified by chromatography on silica gel with 25−33% AcOEt/hexanes as eluent to give **13** (10 mg, 65%) and **14** (9 mg, 35%).

For **13**: white solid; mp 83−84 °C; IR ($CHCl_3$, cm^{-1}) 1464, 1131, 1054, 1030; ^1H NMR (300 MHz, $CDCl_3$) δ 6.45 (dd, *J* = 6.5, 1.5 Hz, 1 H), 6.34 (dd, *J* = 6.5, 2.5 Hz, 1 H), 4.73 (br s, 1 H), 4.27 (dd, *J* = 11.4, 7.7 Hz, 1 H), 2.37−2.28 (m, 1 H), 2.08−1.95 (m, 2 H), 1.89−1.83 (m, 1 H), 1.64−1.56 (m, 2 H), 1.09−0.96 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 133.8, 93.5, 72.2, 68.4, 30.1, 18.4, 17.6, 17.3 (2 C), 17.2 (2 C), 17.1 (2 C), 17.0 (2 C), 13.5, 13.4, 12.8, 12.7; ES HRMS *m/z* ($M + Na^+$) calcd 453.1922, obsd 453.1938; $[\alpha]^{19}_D$ −111 (*c* 1.50, $CHCl_3$).

For **14**: colorless oil; UV (MeOH) λ_{max} 286 nm (ε 8900), λ_{max} 262 nm (ε 15 700); ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (br s, 1 H), 7.80 (d, *J* = 8.3 Hz, 1 H), 7.35 (d, *J* = 1.0 Hz, 1 H), 6.50−6.47 (m, 2 H), 6.16 (d, *J* = 1.2 Hz, 1 H), 5.64 (dd, *J* = 5.7, 1.2 Hz, 1 H), 4.56 (d, *J* = 5.7 Hz, 1 H), 4.06 (dd, *J* = 11.5, 7.1 Hz, 1 H), 3.85 (s, 6 H), 2.18−1.52 (series of m, 6 H), 1.91 (d, *J* = 1.0 Hz, 3 H), 1.25−1.01 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 163.8, 161.7, 149.8 (2 C), 136.4, 133.7, 112.3, 111.6, 104.5, 98.9, 76.8, 72.8, 72.6, 70.8, 62.3, 55.8, 55.5, 30.0, 29.8, 29.7, 17.6, 17.24 (2 C), 17.19, 17.13 (2 C), 17.11 (2 C), 17.06, 13.6, 13.5, 13.0, 12.6; ES HRMS *m/z* ($M + Na^+$) calcd 743.2824, obsd 743.2835; $[\alpha]^{19}_D$ −10.2 (*c* 2.19, CH_3OH).

Spirocyclic 4′-β-Thiaribonucleoside 18. A solution of **14** (64 mg, 0.089 mmol) in THF (3 mL) was treated with tetrabutylammonium fluoride (1 M THF solution, 0.20 mL, 0.20 mmol) under Ar at 0 °C. After being stirred for 30 min, the reaction mixture was 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 24 h prior to chromatography on silica gel (10% EtOH/toluene) to afford **18** (28 mg, 100%) as a white solid: mp 134−136 °C; UV (MeOH) λ_{max} 272 nm (ε 8500); ^1H NMR (300 MHz, CD_3OD) δ 8.25 (s, 1 H), 6.19 (d, *J* = 8.0 Hz, 1 H), 4.47 (dd, *J* = 8.0, 3.4 Hz, 1 H), 3.98 (t, *J* = 7.2 Hz, 1 H), 3.88 (d, *J* = 3.4 Hz, 1 H), 2.32−2.18 (m, 1 H), 2.07−1.85 (series of m, 6 H), 1.67−1.60 (m, 2 H); ^{13}C NMR (75 MHz, CD_3OD) δ 166.3, 153.2, 139.6, 112.0, 80.0, 79.2, 78.6, 69.9, 64.4, 34.5, 33.1, 19.6, 12.5; ES HRMS *m/z* ($M + Na^+$) calcd 337.0829, obsd 337.0823; $[\alpha]^{18}_D$ −35.7 (*c* 1.19, CH_3OH).

Pummerer Reaction of 11 with Uracil. The Pummerer reaction was carried out according to the procedure described for the preparation of **14** starting from **11** (120 mg, 0.20 mmol), uracil (44 mg, 0.40 mmol), triethylamine (109 μL, 0.80 mmol, and additional 109 μL, 0.80 mmol), and TMSOTf (0.27 mL, 1.6 mmol). The usual workup followed by silica gel chroma-

tography (50% AcOEt/hexanes) of the crude product gave **13** (53.8 mg, 69%) and **19** (40 mg, 30%).

For **19**: white foam; UV (MeOH) λ_{max} 294 nm (ϵ 5800), λ_{max} 262 nm (ϵ 15 900); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (br s, 1 H), 7.81 (d, J = 8.3 Hz, 1 H), 7.68 (d, J = 8.1 Hz, 1 H), 6.51−6.44 (m, 2 H), 6.09 (d, J = 1.1 Hz, 1 H), 5.74 (dd, J = 8.1, 2.2 Hz, 1 H), 5.64 (dd, J = 5.4, 1.1 Hz, 1 H), 4.48 (d, J = 5.4 Hz, 1 H), 4.09 (dd, J = 15.2, 7.1 Hz, 1 H), 3.85 (s, 6 H), 2.18−1.52 (series of m, 6 H), 1.18−0.95 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 163.7, 162.4, 161.7, 149.7, 140.9, 133.7, 111.6, 104.6, 103.2, 98.9, 76.9, 72.8, 72.2, 70.6, 62.8, 55.8, 55.5, 30.1, 29.6, 17.5, 17. 4, 17.3, 17.2, 17.1, 17.09, 16.9, 13.6, 13.4, 13.1, 12.9; ES HRMS *m/z* (M + Na^+) calcd 729.2668, obsd 729.2698; $[\alpha]^{18}_D$ −0.3 (*c* 1.63, CH_3OH).

Spirocyclic 4′-β-Thiauridine 20. Compound **19** (40 mg, 0.057 mmol) was deprotected in a similar manner as described for **14** by sequential treatment with TBAF (1 M THF solution, 0.12 mL, 0.12 mmol) in THF (3 mL) and methanolic ammonia (5 mL). After purification on silica gel (10% EtOH/toluene), **20** (16 mg, 94%) was obtained as a syrup: UV (MeOH) λ_{max} 266 nm (ϵ 7900); ^{1}H NMR (300 MHz, CD_3OD) δ 8.43 (d, J = 8.1 Hz, 1 H), 6.20 (d, J = 7.9 Hz, 1 H), 5.75 (d, J = 8.1 Hz, 1 H), 4.47 (dd, J = 7.9, 3.3 Hz, 1 H), 3.97 (t, J = 7.2 Hz, 1 H), 3.88 (d, J = 3.3 Hz, 1 H), 2.28−2.17 (m, 1 H), 2.02−1.87 (m, 2 H), 1.64−1.58 (m, 3 H); ^{13}C NMR (75 MHz, CD_3OD) δ 166.1, 153.1, 144.1, 103.2, 80.0, 79.4, 78.5, 70.0, 64.6, 34.4, 33.1, 19.6; ES HRMS *m/z* (M + Na^+) calcd 323.0672, obsd 323.0673; $[\alpha]^{21}_D$ −37.2 (*c* 0.90, CH_3OH).

Pummerer Reaction of 11 with N^4-Acetylcytosine. The Pummerer reaction was carried out according to the procedure described for the preparation of **14** starting from **11** (120 mg, 0.20 mmol), N^4-acetylcytosine (92 mg, 0.60 mmol), triethylamine (82 μL, 0.60 mmol, and additional 136 μL, 1.0 mmol), and TMSOTf (0.27 mL, 1.6 mmol). The usual workup followed by silica gel chromatography (75% AcOEt/hexanes) of the crude product gave **13** (50 mg, 69%) and **21** (40 mg, 30%).

For **21**: white solid, mp 253−254 °C; UV (MeOH) λ_{max} 296 nm (ϵ 15 700), λ_{max} 256 nm (ϵ 30 500); ^{1}H NMR (300 MHz, $CDCl_3$) δ (br s, 1 H), 8.14 (d, J = 7.4 Hz, 1 H), 7.81 (d, J = 8.4 Hz, 1 H), 7.43 (d, J = 7.4 Hz, 1 H), 6.50−6.45 (m, 2 H), 6.24 (s, 1 H), 5.68 (d, J = 5.2 Hz, 1 H), 4.50 (d, J = 5.2 Hz, 1 H), 4.05 (dd, J = 11.7, 7.2 Hz, 1 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 2.27 (s, 3 H), 2.17−2.12 (m, 2 H), 1.98−1.89 (m, 2 H), 1.75−1.53 (m, 2 H), 1.17−0.85 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 164.4, 163.5, 162.4, 161.6, 154.7, 145.9, 133.7, 111.8, 104.5, 98.9, 97.4, 77.0, 72.8, 72.1, 70.5, 64.0, 55.8, 55.5, 30.2, 29.6, 25.0, 17. 4 (2 C), 17.3, 17.23 (2 C), 17.19 (2 C), 17.09 (2 C), 13.6, 13.5, 13.0, 12.9; ES HRMS *m/z* (M + Na^+) calcd 770.2933, obsd 770.2908; $[\alpha]^{20}_D$ −10.0 (*c* 0.29, CH_3OH).

Spirocyclic 4′-β-Thiacytidine 22. Compound **21** (40 mg, 0.053 mmol) was deprotected in a similar manner as described for **14** by sequential treatment with TBAF (1 M THF solution, 0.12 mL, 0.12 mmol) in THF (3 mL) and methanolic ammonia (5 mL). After purification on silica gel (30% EtOH/toluene) **22** (16 mg, 100%) was obtained as a glass: UV (MeOH) λ_{max} 278 nm (ϵ 6400), λ_{max} 226 nm (ϵ 7700); ^{1}H NMR (300 MHz, CD_3OD) δ 8.39 (d, J = 7.3 Hz, 1 H), 6.21 (d, J = 7.3 Hz, 1 H), 5.95 (d, J = 7.3 Hz, 1 H), 4.46 (dd, J = 7.3, 3.1 Hz, 1 H), 3.97 (t, J = 6.9 Hz, 1 H), 3.88 (d, J = 3.1 Hz, 1 H), 2.29−2.19 (m, 1 H), 2.02−1.87 (m, 2 H), 1.66−1.56 (m, 3 H); ^{13}C NMR (75 MHz, CD_3OD) δ 168.2, 160.1, 145.7, 97.8, 80.8, 80.5, 79.3, 70.9, 66.8, 35.4, 34.1, 20.7; ES HRMS *m/z* (M + Na^+) calcd 322.0832, obsd 322.0839; $[\alpha]_D^{21}$ −42.1 (*c* 1.43, CH_3OH).

Pummerer Reaction of Sulfoxide 11 with 6-Chloropurine. A suspension of 6-chloropurine (121 mg, 0.80 mmol) in a mixture of acetonitrile (3.2 mL) and 1,2-dichloroethane (1.6 mL) was treated with triethylamine (109 μL, 0.80 mmol) and TMSOTf (0.27 mL, 1.6 mmol), and the resulting mixture was stirred at rt for 1 h. The clear solution of silylated 6-chloropurine was added to a solution of **11** (120 mg, 0.20 mmol) in 1,2-dichloroethane (1.6 mL) slowly over 15 min. An additional amount of triethylamine (109 μL, 0.80 mmol) in 1,2-dichloroethane (0.8 mL) was added dropwise to the reaction mixture to initiate the Pummerer reaction. After being stirred for 5 min at rt, the reaction mixture was heated at reflux for 24 h. Cold water (5 mL) was added for quenching purposes, and the aqueous layer was extracted with dichloromethane (3 × 5 mL). After being washed with saturated $NaHCO_3$ solution (5 mL) and brine, the combined organic layers were dried and concentrated in a vacuum. The residue was purified by chromatography on silica gel with 25−50% AcOEt/hexanes as eluent to give **13** (24.3 mg, 33%), **23** (13.4 mg, 10%), and **24** (39.3 mg, 29%).

For **23**: white foam; UV (MeOH) λ_{max} 288 nm (ϵ 7000), λ_{max} 262 nm (ϵ 13 400); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (s, 1 H), 8.84 (s, 1 H), 7.49 (d, J = 8.7 Hz, 1 H), 6.88 (d, J = 5.4 Hz, 1 H), 6.41 (dd, J = 8.7, 2.3 Hz, 1 H), 6.35 (d, J = 2.3 Hz, 1 H), 6.16 (dd, J = 5.4, 3.8 Hz, 1 H), 4.48 (d, J = 3.8 Hz, 1 H), 4.05 (dd, J = 11.7, 7.2 Hz, 1 H), 3.81 (s, 3 H), 3.72 (s, 3 H), 2.39−1.52 (series of m, 6 H), 1.29−0.95 (m, 28 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 163.6, 162.2, 161.1, 152.4, 149.4, 142.9, 133.3, 122.9, 110.6, 104.8, 98.8, 73.9, 72.5, 72.1, 70.8, 59.1, 55.7, 55.5, 30.9, 29.7, 29.5, 17.31, 17.26 (2 C), 17.16, 17.14 (2 C), 17.06, 16.9, 13.7, 13.6, 12.9, 12.7; ES HRMS *m/z* (M + Na^+) calcd 771.2441, obsd 771.2464; $[\alpha]^{19}_D$ −48.9 (*c* 0.90, CH_3OH).

For **24**: white foam; UV (MeOH) λ_{max} 292 nm (ϵ 5600), λ_{max} 262 nm (ϵ 17 700); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (s, 1 H), 8.33 (s, 1 H), 7.87 (d, J = 8.6 Hz, 1 H), 6.53−6.48 (m, 2 H), 6.12 (d, J = 1.1 Hz, 1 H), 5.97 (dd, J = 5.4, 1.1 Hz, 1 H), 5.09 (d, J = 5.4 Hz, 1 H), 4.13 (dd, J = 11.6, 7.2 Hz, 1 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 2.29−1.52 (series of m, 6 H), 1.19−0.85 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 163.9, 161.9, 152.0 (2 C), 151.3, 144.3, 133.9, 132.7, 111.2, 104.7, 98.9, 77.2, 72.8, 72.0, 71.2, 61.7, 55.8, 55.6, 30.1, 29.8, 17.8, 17.4, 17.3 (2 C), 17.23, 17.17, 17.14, 17.07, 16.96, 13.6, 13.4, 13.0, 12.9; ES HRMS *m/z* (M + Na^+) calcd 771.2441, obsd 771.2435; $[\alpha]^{18}_D$ −10.8 (*c* 1.32, CH_3OH).

Spirocyclic 4′-β-Thiaadenosine 25. A solution of **24** (33 mg, 0.044 mmol) in THF (3 mL) was treated with AcOH (6.6 μL, 0.11 mmol) and TBAF (1 M THF solution, 0.11 mL, 0.11 mmol). After being stirred at rt for 10 min, the reaction mixture was evaporated to dryness, and the residue was purified by silica gel chromatography (elution with 10% EtOH/toluene). The resulting desilylation product was treated with ethanolic ammonia (5 mL), and the reaction mixture was heated at 100 °C for 24 h in a sealed thick-wall tube. The solvent was removed, and the residue was purified by chromatography on silica gel. Elution with 20% EtOH/toluene gave **25** (12 mg, 85%) as a white solid: mp 134−136 °C; UV (MeOH) λ_{max} 262 nm (ϵ 7100); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (s, 1 H), 8.13 (s, 1 H), 7.30 (br s, 2 H), 5.91 (d, J = 5.7 Hz, 1 H), 5.43 (br s, 3 H), 4.74 (br d, J = 4.2 Hz, 1 H), 3.91 (br s, 1 H), 3.80 (br s, 1 H), 2.24−2.17 (m, 1 H), 1.95−1.91 (m, 1 H), 1.76−1.69 (m, 1 H), 1.49−1.48 (m, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 156.5, 152.7, 150.0, 140.7, 119.6, 78.7, 77.8, 76.7, 69.7, 62.3, 33.4, 32.9, 19.4; ES HRMS *m/z* (M + Na^+) calcd 346.0944, obsd 346.0935; $[\alpha]^{21}_D$ −16.7 (*c* 0.18, CH_3OH).

Pummerer Reaction of 11 with 2-Amino-6-chloropurine. The Pummerer reaction was carried out according to the procedure described for the preparation of **24** starting from **11** (120 mg, 0.20 mmol), 2-amino-6-chloropurine (84 mg, 0.50 mmol), triethylamine (136 μL, 1.0 mmol with an additional 109 μL, 0.80 mmol), and TMSOTf (0.30 mL, 1.8 mmol). The usual workup followed by silica gel chromatography (25−50% AcOEt/hexanes) of the crude product gave **13** (33.8 mg, 46%), **26** (6.2 mg, 7%), and **27** (30.6 mg, 22%).

For **26**: white solid; mp 89−90 °C; UV (MeOH) λ_{max} 326 nm (ϵ 2800), λ_{max} 298 nm (ϵ 5300), λ_{max} 258 nm (ϵ 13 800), λ_{max} 224 nm (ϵ 38 500); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (s, 1 H), 7.80 (d, J = 8.5 Hz, 1 H), 6.54−6.49 (m, 2 H), 6.40 (s, 1 H), 5.78 (d, J = 4.9 Hz, 1 H), 5.27 (br s, 2 H), 4.57 (d, J = 4.9 Hz, 1 H), 4.11−4.04 (m, 1 H), 3.87 (s, 6 H), 2.22−2.17 (m, 2 H), 2.04−1.94 (m, 2 H), 1.79−1.74 (m, 1 H), 1.62−1.55 (m, 1 H), 1.20−0.91 (m, 28 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6,

163.6, 161.5, 159.4, 156.3, 147.0, 143.9, 133.4, 116.4, 111.8, 104.7, 99.0, 77.7, 72.8, 71.6, 70.4, 62.6, 55.8, 55.6, 30.5, 29.6, 17.5, 17.3, 17.2 (2 C), 17.12, 17.08, 16.98 (2 C), 16.91, 13.6, 13.5, 13.2, 12.8; ES HRMS *m/z* ($M + Na^+$) calcd 786.2550, obsd 786.2565; $[\alpha]^{19}_D$ +68.4 (*c* 0.70, CH_3OH).

For **27**: white foam; UV (MeOH) λ_{max} 320 nm (ϵ 5100), λ_{max} 300 nm (ϵ 8800), λ_{max} 256 nm (ϵ 14 100), λ_{max} 222 nm (ϵ 27 800); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (s, 1 H), 7.83 (d, J = 8.4 Hz, 1 H), 6.52−6.48 (m, 2 H), 5.95 (d, J = 1.1 Hz, 1 H), 5.91 (dd, J = 5.3, 1.1 Hz, 1 H), 5.24 (br s, 2 H), 4.79 (d, J = 5.3 Hz, 1 H), 4.09 (dd, J = 11.7, 7.2 Hz, 1 H), 3.86 (s, 6 H), 2.22−1.52 (series of m, 6 H), 1.18−0.85 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 163.6, 161.7, 159.1, 153.3, 151.5, 140.7, 133.7, 125.4, 111.4, 104.7, 98.9, 77.2, 72.8, 72.2, 70.6, 60.4, 55.9, 55.5, 30.2, 29.7, 17.6, 17.4 (2 C), 17.3 (2 C), 17.2 (2 C), 17.1, 17.07, 13.5, 13.2, 13.0, 12.9; ES HRMS *m/z* ($M + Na^+$) calcd 786.2550, obsd 786.2562; $[\alpha]^{18}_D$ +23.2 (*c* 1.71, CH_3OH).

Spirocyclic 4′-β-Thiaguanosine 28. Compound **27** (31 mg, 0.041 mmol) was desilylated in a similar manner as described for **24** by treatment with AcOH (5.1 μL, 0.089 mmol) and TBAF (1 M THF solution, 89 μL, 0.089 mmol) in THF (3 mL) at rt. After purification by silica gel chromatography (10% EtOH/toluene), the resulting product was treated with 2-mercaptoethanol (28 μL, 0.41 mmol) and NaOMe (28% solution, 75 μL, 0.41 mmol) in refluxing methanol (5 mL) for 24 h. After neutralization with 1 N HCl, the solution was concentrated in vacuo. The residue was purified by silica gel chromatography (elution with 30% EtOH/toluene) to give **28** (8 mg, 62%) as a white solid: mp 185−186 °C; UV (MeOH) λ_{max} 276 nm (ϵ 4000), λ_{max} 258 nm (ϵ 5600); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.70 (br s, 1 H), 8.08 (s, 1 H), 6.63 (br s, 2 H), 5.72 (d, J = 5.7 Hz, 1 H), 5.44 (br s, 3 H), 4.61 (br d, J = 4.2 Hz, 1 H), 3.87 (br s, 1 H), 3.78 (br s, 1 H), 2.18−2.14 (m, 1 H), 1.91−1.87 (m, 1 H), 1.73−1.68 (m, 1 H), 1.49−1.46 (m, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 156.7, 153.7, 151.6, 136.0, 116.3, 78.3, 77.3, 76.2, 68.7, 60.4, 32.8, 32.2, 18.7; ES HRMS *m/z* ($M + Na^+$) calcd 362.0893, obsd 362.0895; $[\alpha]^{21}_D$ +7.1 (*c* 0.07, CH_3OH).

Triol 29. To a solution of **6** (460 mg, 2.0 mmol) in methanol (16 mL) was added 80% AcOH (16 mL), and the mixture was refluxed for 8 h. The reaction mixture was quenched with saturated K_2CO_3 solution and filtered. The solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel (elution with 50−90% AcOEt/hexanes) to give **29** (320 mg, 85%) as a colorless syrup: IR (neat, cm^{-1}) 3407 (br), 1638; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.92 (d, J = 4.7 Hz, 1 H), 4.82 (d, J = 6.9 Hz, 1 H), 4.67 (d, J = 4.7 Hz, 1 H), 4.23−4.15 (m, 1 H), 4.02 (t, J = 4.0 Hz, 1 H), 2.80−2.69 (m, 2 H), 2.30−2.20 (m, 1 H), 1.90−1.83 (m, 1 H), 1.68−1.55 (m, 2 H), 1.50−1.37 (m, 2 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 79.7, 74.9, 74.4, 67.7, 33.1, 32.9, 32.5, 19.7; EI HRMS *m/z* (M^+) calcd 213.0556, obsd 213.0567; $[\alpha]^{20}_D$ −4.5 (*c* 0.22, $CHCl_3$).

2,4-Dimethoxybenzoylation of Triol 29. A mixture of triol **29** (301 mg, 1.58 mmol) and dibutyltin oxide (394 mg, 1.58 mmol) in benzene (150 mL) was refluxed overnight with azeotropic removal of water in a Dean−Stark apparatus. After evaporation of excess benzene (120 mL), the mixture was cooled to rt and treated with 4 Å molecular sieves (1.5 g) followed by benzoyl chloride (380 mg, 1.90 mmol). After 5 min, the solution was filtered and evaporated to dryness. The residue was purified by silica gel chromatography (elution with 25−75% AcOEt/hexanes) to give **30** (395 mg, 71%) as a colorless syrup: IR (neat, cm^{-1}) 3481 (br), 1702, 1610, 1254; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.7 Hz, 1 H), 6.54−6.46 (m, 2 H), 5.61−5.56 (m, 1 H), 4.56 (t, J = 4.8 Hz, 1 H), 4.18 (t, J = 3.8 Hz, 1 H), 3.93 (s, 3 H), 3.88 (s, 3 H), 3.32 (dd, J = 11.8, 6.2 Hz, 1 H), 3.23 (d, J = 6.0 Hz, 1 H), 3.08 (dd, J = 11.8, 4.6 Hz, 1 H), 2.56−2.49 (m, 2 H), 2.02−1.64 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 164.8, 161.1, 134.4, 111.6, 105.0, 99.0, 81.8, 77.2, 75.9, 65.4, 55.9, 55.6, 33.3, 32.9, 31.5, 20.5; ES HRMS *m/z* ($M + Na^+$) calcd 377.1029, obsd 377.1039; $[\alpha]^{20}_D$ +28.1 (*c* 0.69, $CHCl_3$).

TIPDS Protection of 30. The conversion was carried out according to the procedure described for the preparation of **10** starting from **30** (178 mg, 0.50 mmol), $TIPDSCl_2$ (0.19 mL, 0.60 mmol), pyridine (0.19 mL, 2.41 mmol), and silver nitrate (205 mg, 1.21 mmol) in THF (25 mL). The predescribed workup followed by silica gel chromatography (5−10% AcOEt/hexanes) of the crude product gave **31** (183 mg, 79%) as a colorless oil: IR (neat, cm^{-1}) 1732, 1608, 1464, 1251; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J = 8.5 Hz, 1 H), 6.53−6.46 (m, 2 H), 5.74 (t, J = 4.0 Hz, 1 H), 4.61 (d, J = 4.0 Hz, 1 H), 4.36 (br s, 1 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.19 (dd, J = 12.5, 4.6 Hz, 1 H), 2.88 (d, J = 12.5 Hz, 1 H), 2.72−2.64 (m, 1 H), 2.09−2.04 (m, 1 H), 1.87−1.58 (m, 4 H), 1.16−0.86 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 164.3, 161.6, 133.8, 112.4, 104.3, 98.9, 84.2, 77.7, 76.3, 66.1, 55.8, 55.5, 34.5, 30.6, 29.7, 20.4, 17.7, 17.6, 17.5, 17.4, 17.3, 17.25, 17.22, 17.0, 13.5, 13.4, 13.1, 12.8; ES HRMS *m/z* ($M + Na^+$) calcd 619.2554, obsd 619.2567; $[\alpha]^{20}_D$ +41.5 (*c* 0.68, $CHCl_3$).

Sulfoxides 32 and 33. The oxidation was effected according to the procedure described for the preparation of **11** and **12** starting from **31** (382 mg, 0.64 mmol) and the Davis oxaziridine reagent (200 mg, 0.77 mmol) in $CHCl_3$ (50 mL). Silica gel chromatography (25−50% AcOEt/hexanes) of the crude product gave **32** (314 mg, 80%) and **33** (43 mg, 11%) as white foams.

For **32**: IR ($CHCl_3$, cm^{-1}) 1731, 1608, 1464, 1249, 1134, 1021; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J = 8.6 Hz, 1 H), 6.51−6.48 (m, 2 H), 5.96 (t, J = 5.0 Hz, 1 H), 5.29 (d, J = 5.0 Hz, 1 H), 5.15 (br s, 1 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 3.61 (d, J = 15.5 Hz, 1 H), 3.10 (dd, J = 15.5, 6.4 Hz, 1 H), 2.62−2.52 (m, 1 H), 2.10−2.00 (m, 2 H), 1.86−1.79 (m, 2 H), 1.51−1.42 (m, 1 H), 1.16−0.86 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 164.0, 161.7, 133.7, 111.6, 104.5, 98.9, 77.5, 76.6, 73.8 (2 C), 56.1, 55.8, 55.5, 35.0, 29.7, 22.1, 17.6, 17.5, 17.46, 17.40 (2 C), 17.3, 17.1, 16.9, 13.8, 13.2, 12.9, 12.6; ES HRMS *m/z* ($M + Na^+$) calcd 635.2501, obsd 635.2500; $[\alpha]^{20}_D$ +68.6 (*c* 0.56, $CHCl_3$).

For **33**: IR ($CHCl_3$, cm^{-1}) 1728, 1608, 1464, 1248, 1136, 1023; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, J = 8.7 Hz, 1 H), 6.54−6.46 (m, 2 H), 5.71 (t, J = 4.0 Hz, 1 H), 4.61 (br s, 1 H), 4.45 (d, J = 4.0 Hz, 1 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 3.33 (dd, J = 15.4, 4.8 Hz, 1 H), 2.83 (d, J = 15.4 Hz, 1 H), 2.54−2.47 (m, 2 H), 2.04−1.64 (m, 4 H), 1.13−0.85 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 164.1, 161.9, 134.2, 111.6, 104.5, 98.9, 81.3, 78.8, 75.4, 72.7, 55.8, 55.5, 52.8, 34.8, 29.7, 22.0, 17.7, 17.6, 17.5, 17.4, 17.3 (2 C), 17.1, 16.9, 13.9, 13.4, 13.0, 12.9; ES HRMS *m/z* ($M + Na^+$) calcd 635.2501, obsd 635.2500; $[\alpha]^{21}_D$ +28.2 (*c* 0.44, $CHCl_3$).

Pummerer Reaction of 32 with Thymine. The Pummerer reaction was carried out according to the procedure described for the preparation of **14** starting from **32** (58 mg, 0.095 mmol), thymine (35.8 mg, 0.28 mmol), triethylamine (79 μL, 0.57 mmol with an additional 26 μL, 0.19 mmol), and TMSOTf (0.14 mL, 0.76 mmol). The usual workup followed by silica gel chromatography (20−30% AcOEt/hexanes) of the crude product gave **34** (25.6 mg, 68%) and **35** (21 mg, 31%).

For **34**: white solid; mp 73−75 °C; IR ($CHCl_3$, cm^{-1}) 1609, 1464, 1116, 1021; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73−6.67 (m, 2 H), 5.91 (br s, 1 H), 4.87 (d, J = 3.1 Hz, 1 H), 2.44−2.36 (m, 1 H), 2.08−1.81 (m, 5 H), 1.34−0.94 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6, 130.9, 77.1, 77.0 (2 C), 34.5, 23.1, 21.1, 17.64, 17.59, 17.44, 17.33 (2 C), 17.27, 17.06, 16.9, 13.7, 13.3, 12.8, 12.7; ES HRMS *m/z* ($M + Na^+$) calcd 453.1922, obsd 453.1902; $[\alpha]^{21}_D$ +61.3 (*c* 0.98, $CHCl_3$).

For **35**: white foam; UV (MeOH) λ_{max} 282 nm (ϵ 10 500), λ_{max} 262 nm (ϵ 18 300), λ_{max} 222 nm (ϵ 21 400); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (s, 1 H), 7.90 (d, J = 8.6 Hz, 1 H), 7.47 (s, 1 H), 6.52−6.48 (m, 2 H), 5.88 (s, 1 H), 5.69 (d, J = 4.6 Hz, 1 H), 4.91 (d, J = 4.6 Hz, 1 H), 4.52 (br s, 1 H), 3.86 (s, 6 H), 2.74−2.69 (m, 1 H), 2.12−1.67 (series of m, 5 H), 1.94 (s, 3 H), 1.18−0.88 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 163.4, 163.1, 161.8, 149.7, 136.6, 133.9, 111.5, 111.3, 104.5, 98.9, 82.8,

80.4, 73.8, 68.8, 63.3, 55.8, 55.5, 34.7, 31.6, 20.4, 17.74, 17.69 (2 C), 17.5, 17.3 (3 C), 17.0, 16.9, 13.7, 13.2, 13.1, 12.5; ES HRMS *m/z* ($M + Na^+$) calcd 743.2824, obsd 743.2820; $[\alpha]^{21}_D$ −11.7 (*c* 0.84, CH_3OH).

Spirocyclic 4′-β-Thiaribonucleoside 36. Compound **35** (44 mg, 0.061 mmol) was deprotected in a manner similar to that described for **14** by sequential treatment with TBAF (1 M THF, 0.13 mL, 0.13 mmol) in THF (3 mL) and methanolic ammonia (5 mL). After purification on silica gel (10% EtOH/toluene) **36** (17.5 mg, 92%) was obtained as a white solid: mp 125−126 °C; UV (MeOH) λ_{max} 272 nm (ϵ 6800); ^{1}H NMR (300 MHz, CD_3OD) δ 7.84 (d, J = 1.0 Hz, 1 H), 6.22 (d, J = 8.8 Hz, 1 H), 4.55 (dd, J = 8.8, 3.6 Hz, 1 H), 4.26−4.22 (m, 2 H), 2.42−2.35 (m, 1 H), 2.13−2.08 (m, 1 H), 1.93 (d, J = 1.0 Hz, 3 H), 1.80−1.55 (m, 4 H); ^{13}C NMR (75 MHz, CD_3OD) δ 166.1, 153.2, 138.6, 112.4, 81.9, 79.4, 75.3, 67.8, 64.5, 33.9, 33.1, 20.3, 12.5; ES HRMS *m/z* ($M + Na^+$) calcd 337.0829, obsd 337.0822; $[\alpha]^{21}_D$ −86.6 (*c* 0.29, CH_3OH).

Pummerer Reaction of 32 with N^4-Acetylcytosine. The Pummerer reaction was carried out according to the procedure described for the preparation of **14** starting from **32** (101 mg, 0.16 mmol), N^4-acetylcytosine (76 mg, 0.49 mmol), triethylamine (69 μL, 0.49 mmol with an additional 115 μL, 0.82 mmol), and TMSOTf (0.24 mL, 1.3 mmol). The usual workup followed by silica gel chromatography (50−75% AcOEt/hexanes) of the crude product gave **34** (36 mg, 56%) and **37** (35.7 mg, 29%).

For **37**: white foam; UV (MeOH) λ_{max} 296 nm (ϵ 6200), λ_{max} 256 nm (ϵ 14 300), λ_{max} 218 nm (ϵ 20 000); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (br s, 1 H), 8.19 (d, J = 7.4 Hz, 1 H), 7.90 (d, J = 8.6 Hz, 1 H), 7.48 (d, J = 7.4 Hz, 1 H), 6.52−6.47 (m, 2 H), 5.95 (s, 1 H), 5.75 (d, J = 4.1 Hz, 1 H), 4.88 (d, J = 4.1 Hz, 1 H), 4.53 (br s, 1 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 2.74−2.68 (m, 1 H), 2.34−1.62 (series of m, 5 H), 2.27 (s, 3 H), 1.16−0.85 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 164.5, 163.4, 162.3, 161.7, 154.7, 145.9, 133.9, 111.7, 104.5, 98.9, 96.9, 83.0, 80.2, 73.3, 68.6, 65.3, 55.8, 55.5, 34.7, 31.8, 25.0, 20.4, 17.72, 17.67, 17.51, 17.37, 17.30, 17.2, 17.1, 16.9, 13.7, 13.3, 13.2, 13.0; ES HRMS *m/z* ($M + Na^+$) calcd 770.2933, obsd 770.2948; $[\alpha]^{21}_D$ −1.6 (*c* 0.37, CH_3OH).

Spirocyclic 4′-β-Thiacytidine 38. Compound **37** (37.5 mg, 0.050 mmol) was deprotected in a manner similar to that described for **14** by sequential treatment with TBAF (1 M THF solution, 0.16 mL, 0.16 mmol) in THF (3 mL) and methanolic ammonia (5 mL). After purification on silica gel (30% EtOH/toluene) **38** (15 mg, 100%) was obtained as a white solid: mp 176−177 °C; UV (MeOH) λ_{max} 278 nm (ϵ 5100), λ_{max} 234 nm (ϵ 5400); ^{1}H NMR (300 MHz, CD_3OD) δ 8.04 (d, J = 7.4 Hz, 1 H), 6.29 (d, J = 8.6 Hz, 1 H), 5.98 (d, J = 7.4 Hz, 1 H), 4.51 (dd, J = 8.6, 3.6 Hz, 1 H), 4.26−4.21 (m, 2 H), 2.42−2.38 (m, 1 H), 2.13−2.07 (m, 1 H), 1.83−1.52 (series of m, 4 H); ^{13}C NMR (75 MHz, CD_3OD) δ 167.2, 159.1, 143.8, 97.0, 81.9, 80.1, 75.7,67.8, 65.6, 33.9, 33.2, 20.4; ES HRMS *m/z* ($M + Na^+$) calcd 322.0832, obsd 322.0830; $[\alpha]^{21}_D$ −82.0 (*c* 0.05, CH_3OH).

Pummerer Reaction of 32 with 6-Chloropurine. The Pummerer reaction was carried out according to the procedure described for the preparation of **24** starting from **32** (100 mg, 0.16 mmol), 6-chloropurine (101 mg, 0.65 mmol), triethylamine (91 μL, 0.65 mmol with an additional 91 μL, 0.65 mmol), and TMSOTf (0.24 mL, 1.3 mmol). The usual workup followed by silica gel chromatography (20−40% AcOEt/hexanes) of the crude product gave **34** (20 mg, 31%) and **39** (38 mg, 31%).

For **39**: white foam; UV (MeOH) λ_{max} 294 nm (ϵ 3200), λ_{max} 262 nm (ϵ 13 500); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (s, 1 H), 8.30 (s, 1 H), 8.00 (d, J = 8.7 Hz, 1 H), 6.56−6.50 (m, 2 H), 5.96 (s, 1 H), 5.87 (d, J = 4.5 Hz, 1 H), 5.72 (d, J = 4.5 Hz, 1 H), 4.63 (br s, 1 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 2.88−2.77 (m, 1 H), 2.21−2.14 (m, 1 H), 1.98−1.71 (series of m, 4 H), 1.20−0.84 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 163.9, 162.0, 151.7, 151.6, 150.9, 144.8, 134.2, 132.7, 111.0, 104.7, 98.9, 82.8, 81.3, 73.7, 69.7, 61.5, 55.9, 55.6, 34.7, 31.4, 20.3, 17.7, 17.6, 17.5, 17.4, 17.3, 17.2, 17.1, 17.0, 13.5, 13.2, 13.0, 12.8; ES HRMS *m/z* ($M + Na^+$) calcd 771.2441, obsd 771.2435; $[\alpha]^{21}_D$ −32.7 (*c* 0.81, CH_3OH).

Spirocyclic 4′-β-Thiaadenosine 40. Compound **39** (36.5 mg, 0.049 mmol) was treated in a similar manner as described for **24** by sequential treatment with AcOH (6.1 μL, 0.11 mmol), TBAF (1 M THF solution, 0.11 mL, 0.11 mmol) in THF (3 mL) at rt, and ethanolic ammonia (5 mL) at 100 °C. After purification on silica gel (30% EtOH/toluene) **40** (15.2 mg, 97%) was obtained as a white solid: mp 134−136 °C; UV (MeOH) λ_{max} 262 nm (ϵ 12100); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 1 H), 8.14 (s, 1 H), 7.26 (s, 2 H), 5.97 (d, J = 8.8 Hz, 1 H), 5.41−5.33 (m, 3 H), 5.07 (br d, J = 6.4 Hz, 1 H), 4.37 (br s, 1 H), 4.22 (br s, 1 H), 2.33−2.28 (m, 1 H), 1.98−1.92 (m, 1 H), 1.69−1.41 (series of m, 4 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.1, 152.3, 149.6, 140.2, 119.3, 79.5, 77.4, 73.9, 67.9, 62.2, 32.8, 32.2, 19.4; ES HRMS *m/z* ($M + Na^+$) calcd 346.0944, obsd 346.0952; $[\alpha]^{21}_D$ −75.0 (*c* 0.16, 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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