JOC Article

C4′-Spiroalkylated Nucleosides Having Sulfur Incorporated at the Apex Position

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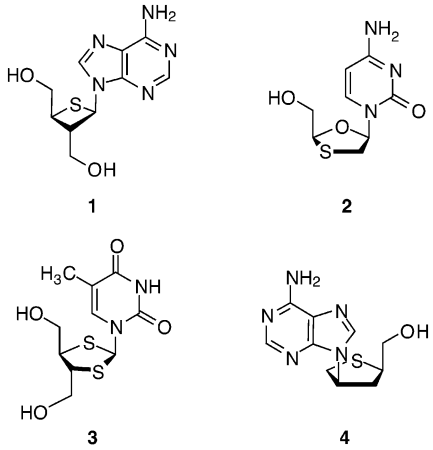
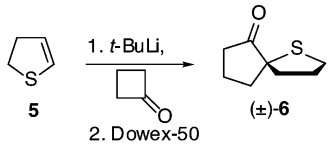
Methodology based on the concept of thionium ion-initiated pinacolic ring expansion has been developed for accessing C4′-spirocyclic thionucleosides. The readily available racemic ketones **6** and **37** are conveniently resolved via their acetals with (*R*)-mandelic acid. Subsequent reactions beginning with utilization of the Pummerer rearrangement lend themselves to functionalization of the spirocyclic core and ultimately incorporation of the nucleosidic bases. Limitations to this strategy are pointed out. Acquisition of the α- and *β*-isomers at C4′ is equally facile. Absolute configurational assignments have been made possible by X-ray crystallography.

Since the earliest pioneering reports of the successful synthesis of thionucleosides,[1] it has come to be recognized that hetero substitution of the furanose ring in this fashion can have a profound effect on biological activity. The rapidity with which 2′,3′-dideoxy-3′-thiacytidine was adopted for clinical use in the treatment of AIDS,[2] and the high-level antiviral and anticancer potency of several sulfur mimics having the heteroatom at the apex position[3,4] has ignited research in this area from several directions. Included among the many modifications are the original 4′-thionucleosides, thiatenose derivatives exemplified by **1**,[5] 1,3-oxathiolane analogues of type **2**,[6] as well as networks such as **3** that incorporate two sulfur atoms.[7] The heightened activity of L-3-TC and L-5-F-ddC against HIV RT[8] has likewise called attention to exciting prospects in the enantiomeric L-series (e.g., **4**).[9] A notable feature of this family of biosteres is their reduced toxicity and improved therapeutic index relative to their D-forms.

Several years ago, we reported the ready conversion of 2,3-dihydrothiophene (**5**) into **6** in a two-step overall yield of 62−93%.[10] In parallel with the 1-oxaspiro[4.4]-nonan-6-ones,[11,12] the ready availability of **6** in this manner was expected to open the door to a wide variety of sulfur-containing spirocyclic nucleosides. Herein, we detail our initial efforts that have culminated in the production of several unique, conformationally restricted nucleosides of the D enantiomeric series.





Results and Discussion

Resolution of Spiroketone 6. The critical role played by the absolute stereochemistry of the projected end products demanded, of course, that proper attention be accorded early to the resolution of **6** and the associated definitive assignment of configuration to its antipodes. The point of departure involved coupling of the enantiopure lithiated *N*,*S*-dimethyl-(*S*)-(+)-phenylsulfoximine **7**[13] to racemic **6** at low temperature[14] (Scheme 1). This choice of chiral auxiliary led to the formation of a 3:1:1

(1) For example: (a) Secrist, J. A., III; Tiwari, K. N.; Riordan, J. M.; Montgomery, J. A. *J. Med. Chem.* **1991**, *34*, 2361. (b) Dyson, M. R.; Coe, P. L.; Walker, R. T. *J. Med. Chem.* **1991**, *34*, 2782. (c) Ewing, D. F.; Mackenzie, G. *Nucleosides Nucleotides* **1996**, *15*, 809. (d) Van Draanen, N. A.; Freeman, G. A.; Short, S. A.; Harvey, R.; Jansen, R.; Szczech, G.; Koszalka, G. W. *J. Med. Chem.* **1996**, *39*, 538. (e) Rahim, S. G.; Trivedi, N.; Bogunovic-Batchelor, M. V.; Hardy, G. W.; Mills, G.; Selway, J. W. T.; Snowden, W.; Littler, E.; Coe, P. L.; Basnak, I.; Whale, R. F.; Walker, R. T. *J. Med. Chem.* **1996**, *39*, 789. (f) Review: Yokoyama, M. *Synthesis* **2000**, 1637.

(2) Chao, Q.; Nair, V. *Tetrahedron* **1997**, *53*, 1957 and relevant references therein.

(3) (a) Dyson, M. R.; Coe, P. L.; Walker, R. T. *J. Chem. Soc., Chem. Commun.* **1991**, 741. (b) Tiwari, K. N.; Secrist, J. A., III; Montgomery, J. A. *Nucleosides Nucleotides* **1994**, *13*, 1819. (c) Young, R. J.; Shaw-Ponter, S.; Thomson, J. B.; Miller, J. A.; Cumming, J. G.; Pugh, A. W.; Rider, P. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2599.

(4) (a) Yoshimura, Y.; Watanabe, M.; Satoh, H.; Ashida, N.; Ijichi, K.; Sakata, S.; Machida, H.; Matsuda, A. *J. Med. Chem.* **1997**, *40*, 2177 (b) Satoh, H.; Yoshimura, Y.; Watanabe, M.; Ashida, N.; Ijichi, K.; Sakata, S.; Machida, H.; Matsuda, A. *Nucleosides Nucleotides* **1998**, *17*, 65.

(5) (a) Nishizono, N.; Koike, N.; Yamagata, Y.; Fujii, S.; Matsuda, A. *Tetrahedron Lett.* **1996**, *37*, 7569. (b) Ichikawa, E.; Yamamura, S.; Kato, K. *Tetrahedron Lett.* **1999**, *40*, 7385.

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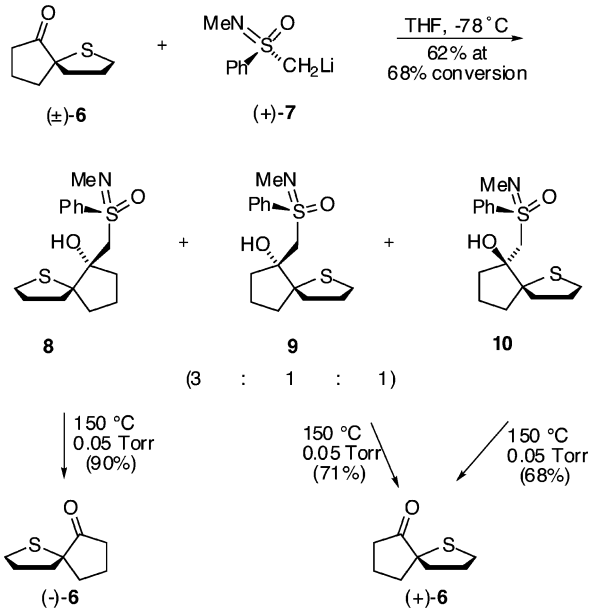
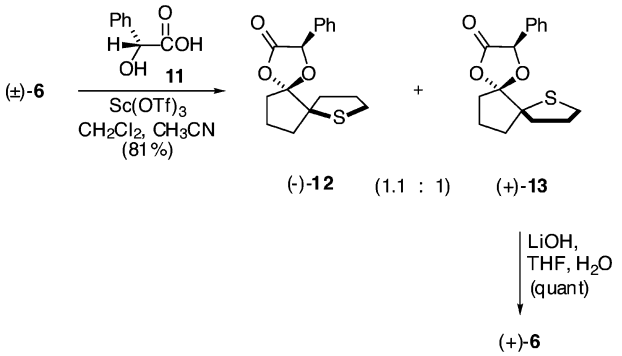
SCHEME 1



mixture of diastereomers in a maximized 62% combined yield at 68% conversion. More advanced consumption of the spiro ketone appeared to be thwarted by competitive enolization, although the co-addition of cerium trichloride was to no avail. The three crystalline adducts **8**, **9**, and **10** proved amenable to chromatographic separation, thus allowing for individual thermal fragmentation to be performed. Heating a neat sample of **8** under vacuum at 150 °C in a Kugelrohr apparatus resulted in the isolation of (−)-**6** in 90% yield alongside recovered sulfoximine. Comparable treatment of **9** and **10** gave rise to (+)-**6** somewhat less efficiently although reproducibly (71% and 68%, respectively).

SCHEME 2



The three-dimensional stereostructure of **8** was deduced by single-crystal X-ray analysis (Figure 1, Supporting Information), thereby confirming the expectation that the absolute configurations and optical rotations of (+)-**6** and (−)-**6** would parallel those established for their oxygen counterparts.[11] These structural elucidations also reveal that **6** displays a kinetic preference for nucleophilic attack anti to the sulfur atom in conformance to the established pattern.[15]

The wide variability in yield with which **8**−**10** could be generated on a useful scale prompted consideration of an alternative resolution strategy. Once again, recourse to acetalization with (*R*)-(−)-mandelic acid (**11**) under catalysis by scandium triflate was found to be particularly advantageous (Scheme 2).[11,16] Significantly, two of the four possible dioxolanones were formed in large excess and chromatographically separated without complication. At this point, the considerable difference in polarity of these compounds was made yet more apparent. Thus, **12** was readily recrystallized from hexanes, whereas for **13** methanol was the solvent of choice.

Acetals **12** and **13** are characterized by the presence of three stereogenic centers. The configuration of the benzylic carbon is defined by the specific enantiomer of mandelic acid in use. The absolute stereochemistry of the spirocyclic carbon in **13** was elucidated following its alkaline hydrolysis to give (+)-**6**. An X-ray determination (Figure 2, Supporting Information) established that the sterically demanding phenyl group occupies the exo position with α-orientation of the lactonic oxygen. The benzylic proton is consequently projected above the carbocyclic chain of the tetrahydrothiophene ring and exhibits an upfield chemical shift (δ 5.68 in $CDCl_3$). For **12**, the same proton is necessarily projected into the deshielding region induced by the sulfur atom and consequently appears at lower field (δ 5.84 in $CDCl_3$).

(6) (a) Beach, J. W.; Jeong, L. S.; Alves, A. J.; Pohl, D.; Kim, H. O.; Chang, C.-N.; Doong, S.-L.; Schinazi, R. F.; Cheng, Y.-C.; Chu, C. K. *J. Org Chem*. **1992**, *57*, 2217. (b) Jeong, L. S.; Schinazi, R. F.; Beach, J. W.; Kim, H. O.; Nampalli, S.; Shanmuganathan, K.; Alves, A. J.; McMillan, A.; Chu, C. K.; Mathis, R. *J. Med. Chem*. **1993**, *36*, 181. (c) Jeong, L. S.; Schinazi, R. F.; Beach, J. W.; Kim, H. O.; Shanmuganathan, K.; Nampalli, S.; Chun, M. W.; Chung, W. K.; Choi, B. G.; Chu, C. K. *J. Med. Chem*. **1993**, *36*, 2627. (d) Jin, H.; Siddiqui, M. A.; Evans, C. A.; Tse, H. L. A.; Mansour, T. S.; Goodyear, M. D.; Ravenscroft, P.; Beels, C. D. *J. Org. Chem*. **1995**, *60*, 2621. (e) Bråvalt, J.; Kvarnström, I.; Classon, B.; Samuelsson, B. *J. Org. Chem*. **1996**, *61*, 3604.

(7) (a) Bråvalt, J.; Kvarnström, I.; Classon, B.; Samuelson, B. *J. Org. Chem*. **1996**, *61*, 3611. (b) Nguyen-Ba, N.; Brown, W. L.; Chan, L.; Lee, N.; Brasili, L.; Lafleur, D.; Zacharie, B. *Chem. Commun*. **1999**, 1245.

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(9) Jung, M. E.; Kretschik, O. *J. Org. Chem*. **1998**, *63*, 2975.

(10) Paquette, L. A.; Dullweber, U.; Branan, B. M. *Heterocycles* **1994**, *37*, 187.

(11) 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.

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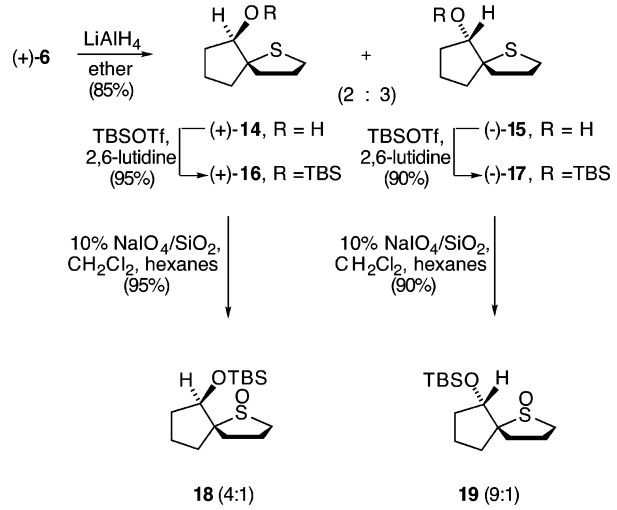
(13) (a) Johnson, C. R. *Aldrichim. Acta* **1985**, *18*, 3. (b) Johnson, C. R.; Zeller, J. R. *J. Am. Chem. Soc*. **1982**, *104*, 4021.

(14) For a preliminary report of the sulfoximine results, consult: Paquette, L. A.; Lanter, J. C.; Owen, D. R.; Fabris, F.; Bibart, R. T.; Alvarez, M. *Heterocycles* **2001**, *54*, 49.

(15) Dimitroff, M.; Fallis, A. G. *Tetrahedron Lett*. **1998**, *39*, 2527.

(16) Ishihara, K.; Karumi, Y.; Kubota, M.; Yamamoto, H. *Synlett* **1996**, 839.

SCHEME 3

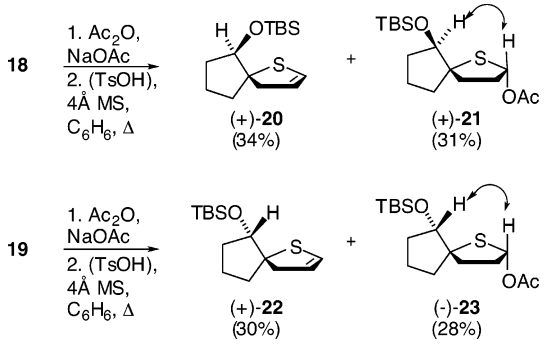


Functionalization of the Spirocyclic Core. Reduction of dextrorotatory **6** of 100% ee with lithium aluminum hydride in ether at 20 °C was met with the formation of alcohols **14** and **15** in significantly less stereoselective fashion than previously reported[15] (Scheme 3). The observed 2:3 partitioning was in fact welcomed since our goal was to access both diastereomeric series. In addition, **14** and **15** differ sufficiently in polarity that their chromatographic separation is routine. The subsequent formation of the *tert*-butyldimethylsilyl ethers **16** and **17** provided substrates ideally suited to examination of the sulfoxidation reaction.

Quite unexpectedly, both tetrahydrothiophenes proved to be unreactive toward *m*-chloroperbenzoic acid in CH_2Cl_2 at room temperature even when three equivalents of the oxidant was present.[17] Sodium periodate in aqueous methanol, a reagent recognized to give very good selectivity in this type of oxidation,[18] proved reasonably effective only in the β series. Where (+)-**16** is concerned, sulfoxide **18** was formed in 86% yield as a 6:1 mixture of isomers alongside 8% of the sulfone. The sluggishness of (−)-**17** under these circumstances can be attributed to the consequences of steric shielding. In light of this ensemble of facts, we were delighted to find that sodium periodate supported on silica gel[19a] was notably effective in oxidizing both (+)-**16** and (−)-**17** to **18** and **19**, respectively, at the 10% level of loading.[20] Longer reaction times were required for the α-siloxy isomer, a kinetic feature that was accompanied by an increase in stereoselectivity from 4:1 to 9:1. The use of ammonium molybdate[19b] provided yet another convenient way to oxidize these sulfides selectively to the sulfoxides (diastereomer ratios of 3:2) without evidence of sulfone production.

The diastereomeric mixtures represented by **18** and **19** were heated in acetic anhydride containing sodium

SCHEME 4



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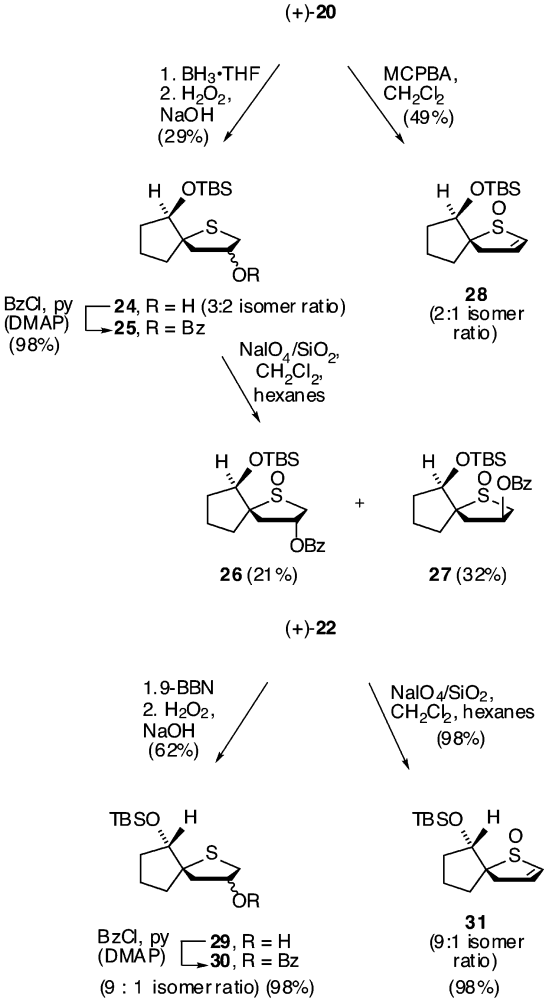


acetate for the purpose of generating their α-acetoxy sulfides by Pummerer rearrangement.[21] In both instances, TLC analysis of the unpurified reaction mixtures showed the presence of several compounds, the separation of which proved difficult. At this point it was observed that standing solutions of these mixtures in $CHCl_3$ underwent convergence largely to two end-products after several hours. These findings prompted the implementation of a second-stage protocol that involved heating in benzene containing *p*-toluenesulfonic acid in the presence of 4 Å molecular sieves.[22] These

(17) (a) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887. (b) Madesclaire, M. *Tetrahedron* **1986**, *42*, 5459.

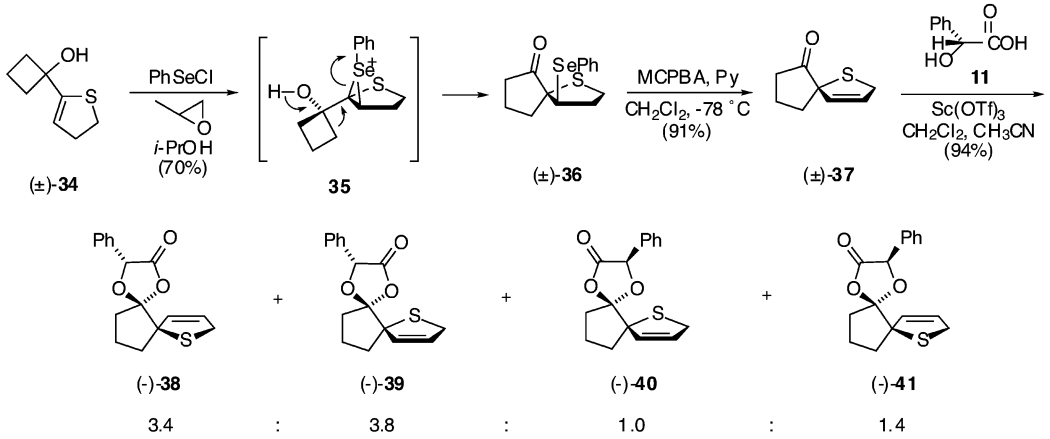
(18) Leonard, N. J.; Johnson, C. R. *J. Org. Chem.* **1962**, *27*, 282.

(19) (a) Gupta, D. N.; Hodge, P.; Davies, J. E. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2970. (b) Bellingham, R.; Jarowicki, K.; Kocienski, P.; Martin, V. *Synthesis* **1996**, 285.

(20) For these experiments, the solid reagents were not completely dried because total dryness gave evidence of prolonging reaction times and lowering reaction efficiency. This phenomenon has been seen in other contexts: Daumas, M.; Vo-Quang, Y.; Vo-Quang, L.; LeGoffic, F. *Synthesis* **1989**, 64.

(21) De Lucchi, O.; Miotti, U.; Modena, G. *Org. React.* **1991**, *40*, 157.

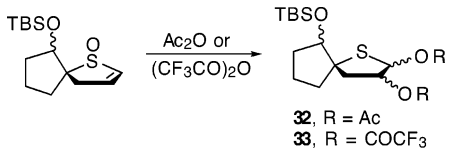
SCHEME 6



conditions were met with generation of the elimination products (+)-**20** and (+)-**22** alongside acetates (+)-**21** and (−)-**23**. Each was formed in a yield approximating 30% (Scheme 4). The stereochemical features of the acetates were elucidated by NOE measurements. The rate of rearrangement of **19** was noted to be somewhat slower than that of **18**.

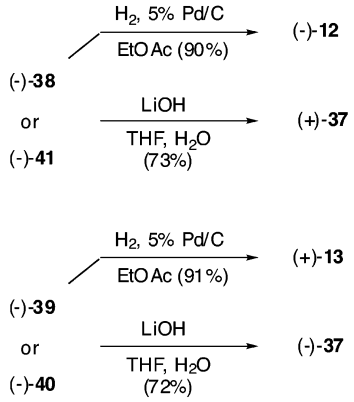
The availability of (+)-**20** and (+)-**22** led us to explore more advanced tetrahydrothiophene ring functionalization from this direction. Although (+)-**20** proved unreactive to 9-BBN and catecholborane, hydroboration did occur in the presence of the borane·THF complex. Although high regioselectivity could be realized in this manner, alcohol **24** was produced in a 3:2 diastereomeric ratio (Scheme 5). The less sterically congested nature of (+)-**22** proved sufficient to allow reaction with 9-BBN to materialize. This more bulky reagent furnished **29** as a 9:1 mixture of epimers. In both cases, separation could be best implemented following conversion to the benzoates. Sulfoxidation as illustrated by the transformation of **25** into **26** and **27** also proved beneficial in this direction.

Sulfides (+)-**20** and (+)-**22** were also converted to their sulfoxide isomer pairs **28** and **31**, respectively, for the purpose of assessing whether their double bond could be migrated into the β,γ-environment.[23,24] This goal was never realized. Nor was allylic oxidation with reagents such as selenium dioxide found to deliver characterizable products. When Pummerer conditions were revisited, its uncommon additive variant[25,26] was found to operate exclusively with formation of **32** and **33**.[27]



An effective means for arriving at this desired structural motif involved phenylselenenyl chloride-initiated ring expansion/rearrangement of carbinol **34** (Scheme 6). When performed in the presence of a large excess of propylene oxide as acid scavenger, the conversion to racemic **36** proceeded cleanly and in a highly selective manner, presumably via the selenonium ion **35**. The chemoselective oxidation of **36** at selenium with concomitant elimination was best effected under basic conditions at high dilution.[28]

SCHEME 7



Spiroketone (±)-**37** was resolved by ketalization with (*R*)-mandelic acid in the manner developed earlier. In the present instance, all four possible dioxolanones were found, with (−)-**38** and (−)-**39** predominating. Although chromatographic separation of these diastereomers was somewhat more involved (the two minor products (−)-**40** and (−)-**41** were isolated by MPLC), the desired (−)-**39** was readily recrystallized from hot methanol. The assignment of absolute configuration in all four diastereomers was then achieved by the controlled catalytic hydrogenation[29] of (−)-**38** and (−)-**39** to (−)-**12** and (+)-**13**, respectively, alongside the four companion hydrolyses summarized in Scheme 7.

Dideoxyspirothionucleoside Synthesis. The ready availability of **18** and **19** led to their selection as ap-

(22) Calinaud, P.; Gelas, J. *Can. J. Chem.* **1983**, *61*, 2103.

(23) (a) O'Connor, D. E.; Broaddus, C. D. *J. Am. Chem. Soc.* **1964**, *86*, 2267. (b) Kimmelma, R. *Acta Chem. Scand.* **1993**, *47*, 706. (c) O'Connor, D. E.; Lyness, W. I. *J. Am. Chem. Soc.* **1964**, *86*, 3840.

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(25) Craig, D.; Daniels, K.; MacKenzie, A. R. *Tetrahedron* **1993**, *48*, 11263.

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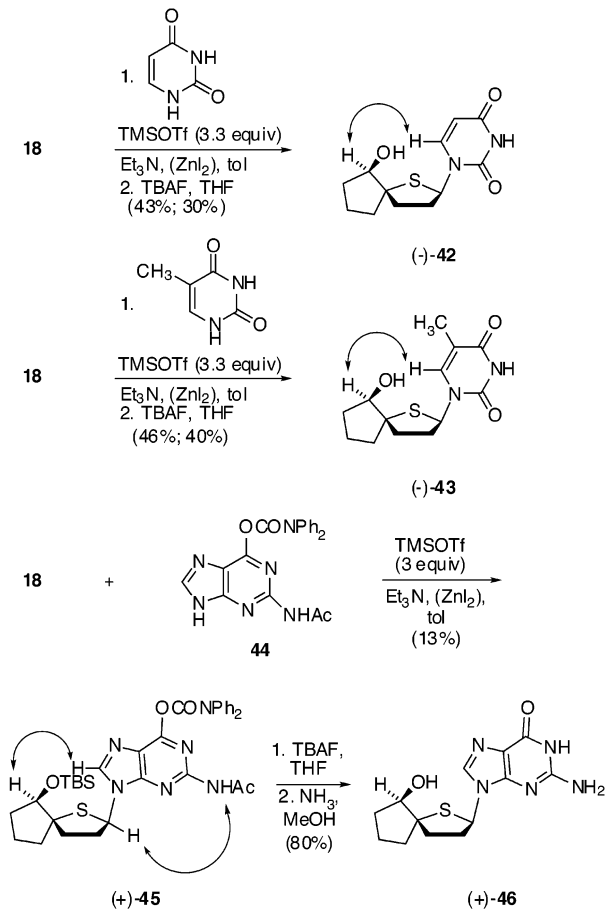
(28) Houllemare, D.; Ponthieux, S.; Outurquin, F.; Paulmier, C. *Synthesis* **1997**, 101.

(29) Mozingo, R.; Harris, S. A.; Wolf, D. E.; Hoffhine, C. E., Jr.; Easton, N. R.; Folkers, K. *J. Am. Chem. Soc.* **1945**, *67*, 2092.

SCHEME 8

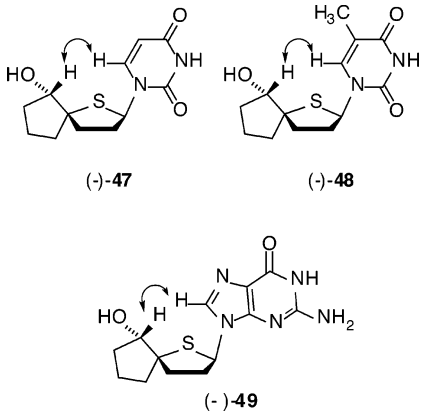


propriate precursors to the dideoxyspirothio-nucleosides of interest. This conclusion was reinforced when, in an attempt to gain a stereoselective advantage and capitalize on the stereochemical configuration already defined at C-1, (+)-**21** was reacted directly with thymine in the presence of hexamethyldisilazane and chlorotrimethylsilane.[1a,30] Complex mixtures resulted. Instead, glycosylation reactions were performed on **18** and **19** by means of silylated bases (generated in situ) and trimethylsilyl triflate, with zinc(II) iodide in catalytic quantities serving as the promoter.[31,32] Of the five examples studied, guanine proved to be the only base that did not result in the formation of dideoxynucleoside epimers (Scheme 8).

In light of the anticipated difficult separation of the resulting pairs of anomers, the silyl groups were removed with TBAF. With the β-hydroxyl group now unmasked, it proved possible to isolate **42** and **43** in pure form and to identify them on the strength of NOE studies. For the cytosine and adenine examples, separation of the anomers was yet not achieved.

The difficulty experienced with the glycosylation of guanine was considered to stem from its well recognized proclivity for the competitive generation of N7 and N9 products. A solution to this problem, which has been developed largely by Robins and co-workers,[33] involves use of the protected derivative **44**. In our hands, this protocol was found to deliver (+)-**45** in modest yield alongside its epimer and other unidentified byproducts. However, the ease with which (+)-**45** could be purified chromatographically made feasible its conversion to the target (+)-**46** under standard conditions.[33]

These accomplishments were matched in the stereoisomeric series defined by an α-hydroxyl on the cyclopentane ring. Sulfoxide **19** proved to be an equally serviceable precursor to **47**−**49** under closely comparable experimental conditions. In the examples defined by this subset of dideoxynucleosides, the glycosylations proceeded smoothly to give anomeric mixtures, the separation of which was accomplished after desilylation (or deacyclation in the case of (−)-**49**). As before, the stereochemical assignments are founded on NOE measurements, in particular those shown on the structural formulas.



The possible synthesis of unsaturated spirocyclic thionucleosides was also briefly explored. As a consequence of difficulties experienced with potential precursors **20**, **22**, **28**, and **31**, attention was turned to the possibilities recognized to be offered by organoselenium chemistry. This option held out the prospect of introducing the double bond at a late stage, while simultaneously providing desirable stereoselectivity during incorporation of the nucleobases.[34] To this end, the Pummerer product (−)-**23** was saponified with lithium hydroxide and subsequently subjected to Swern oxidation under high dilution conditions. This protocol led with good efficiency to **51** via **50** (Scheme 9).

Conversion of **51** to the *O*-silylated thioketene acetal set the stage for α-phenylselenenylation as in **52**. Although a modest 3:1 level of diastereocontrol resulted, it was an easy matter to separate the major α-isomer cleanly by column chromatography. The ensuing tandem Dibal-H reduction/acetylation of **52** gave rise to **53** without complication. Despite existing precedence,[34] attempts to engage **53** in various Vorbrüggen coupling reactions[35] involving silylated uracil and thymine proved unrewarding. Facile cleavage of the OTBS group was

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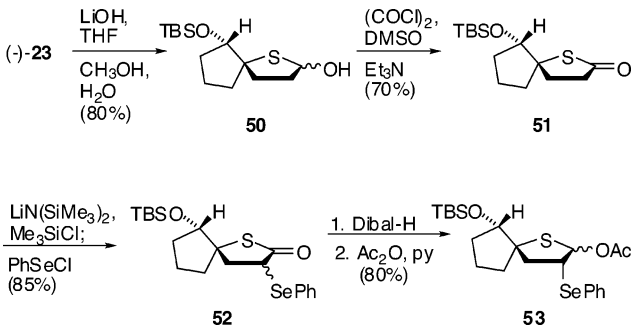
SCHEME 9



particularly vexatious. Recourse to less frangible alcohol-protecting substituents might well rectify this matter, but has not been investigated at this time.

In conclusion, we have developed a convenient strategy for the synthesis of C4′-spiroalkylated thionucleosides. Racemic universal precursors have been resolved and the absolute configuration of their antipodal forms rigorously established by crystallographic means. The corresponding α- and *β*-carbinols are easily generated and separated, thus demonstrating the feasibility of developing both stereoisomeric series. This work represents the first synthesis of these novel ribonucleoside analogues and could ultimately serve to expand the repertoire of modified nucleic acids for use as biochemical probes.

Experimental Section

General Information. Consult ref 11.

Sulfoximine Resolution of 6. A solution of *N*,*S*-dimethyl-(*S*)-(+)-phenylsulfoximine (1.19 g, 7.00 mmol) in dry THF (15 mL) was cooled to 0 °C under N_2 and treated with a solution of *n*-butyllithum in pentane (6.0 mL of 1.9 M, 7.7 mmol), stirred for 20 min at this temperature, cooled to −78 °C, and transferred via cannula to a solution of (±)-**6** (1.0 g, 6.4 mmol) in dry THF (7 mL) at −78 °C. After 2 h, saturated NH_4Cl solution was introduced and the mixture was allowed to warm to 20 °C prior to extraction with ether. The combined organic layers were dried, and the volatile materials were removed to afford an oil that was subjected to flash chromatography on silica gel. Elution with 20% ethyl acetate in hexanes first returned 320 mg (68% conversion) of the sulfoximine. Three adducts were then eluted in the following order:

9: colorless crystals; mp 94−96 °C (300 mg, 15%); IR (film, cm^{-1}) 3200, 1450, 1250, 1150; ^1H NMR (300 MHz, $CDCl_3$) δ 7.94−7.88 (m, 2 H), 7.68−7.56 (m, 3 H), 6.81 (br s, 1 H), 3.76 (d, J = 13.6 Hz, 1 H), 3.40 (d, J = 13.6 Hz, 1 H), 2.92−2.83 (m, 1 H), 2.79−2.69 (m, 1 H), 2.61 (s, 3 H), 2.39−2.14 (series of m, 3 H), 2.10−1.67 (series of m, 7 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 133.1, 129.6, 129.1, 82.7, 72.5, 61.1, 39.8, 36.6, 36.5, 33.5, 30.9, 28.8, 19.7; EI MS *m*/*z* (M^+) calcd 325.1170, obsd 325.1162; $[\alpha]^{22}_D$ −4.9 (*c* 1.0, acetone).

Anal. Calcd for $C_{16}H_{23}NO_2S_2$: C, 59.04; H, 7.12. Found: C, 59.18; H, 7.13.

8: colorless crystals (from ether/hexanes); mp 132−133 °C (728 mg, 35%); IR (film, cm^{-1}) 3200, 1450, 1250, 1150; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90−7.79 (m, 2 H), 7.69−7.57 (m, 3 H), 7.06 (br s, 1 H), 3.78 (d, J = 13.2 Hz, 1 H), 3.00 (d, J = 13.2 Hz, 1 H), 2.84−2.75 (m, 1 H), 2.68−2.57 (m, 1 H), 2.60 (s, 3 H), 2.55−2.45 (m, 1 H), 2.38−2.26 (m, 1 H), 2.13−1.78 (series of m, 5 H), 1.74−1.36 (series of m, 3 H);^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 133.2, 129.6, 129.1, 82.0, 71.6, 60.1, 39.5, 37.5, 35.2, 31.6, 30.5, 28.9, 19.6; EI MS *m*/*z* (M^+) calcd 325.1170, obsd 325.1180; $[\alpha]^{22}_D$ +3.5 (*c* 1.5, acetone).

Anal. Calcd for $C_{16}H_{23}NO_2S_2$: C, 59.04; H, 7.12. Found: C, 59.27; H, 7.13.

This diastereomer was subjected to X-ray crystallographic analysis (Figure 1).

10: colorless crystals (from CH_2Cl_2/hexanes); mp 151−154 °C (250 mg, 12%); IR (film, cm^{-1}) 3420, 1260; ^1H NMR (300 MHz, $CDCl_3$) δ 7.94−7.87 (m, 2 H), 7.68−7.54 (m, 3 H), 5.98 (br s, 1 H), 3.84 (d, J = 14.1 Hz, 1 H), 3.30 (d, J = 14.1 Hz, 1 H), 2.88−2.78 (m, 1 H), 2.76−2.66 (m, 1 H), 2.75 (s, 3 H), 2.32−2.19 (m, 1 H), 2.12−1.89 (m, 3 H), 1.88−1.72 (m, 2 H), 1.60−1.36 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 133.1, 129.4, 129.3, 80.5, 72.3, 61.2, 39.3, 37.3, 35.8, 31.9, 30.7, 29.2, 19.5; EI MS *m*/*z* (M^+) calcd 325.1170, obsd 325.1192; $[\alpha]^{22}_D$ −23.6 (*c* 1.3, acetone).

Anal. Calcd for $C_{16}H_{23}NO_2S_2$: C, 59.04; H, 7.12. Found: C, 59.14; H, 7.12.

Thermolysis of 8. A crystalline sample of **8** (930 mg, 2.86 mmol) was placed in a Kugelrohr apparatus, evacuated to 0.05 Torr, and heated to 150 °C where melting occurred. The distillate accumulated in the collector bulb, which was cooled in dry ice. Final purification of the spiroketone was accomplished by filtration through a pad of silica gel and elution with ether/CH_2Cl_2; colorless oil (400 mg, 95%); $[\alpha]^{22}_D$ −107.9 (*c* 1.5, acetone). Further elution with methanol returned 460 mg (95%) of the sulfoximine.

Comparable handling of **9** and **10** gave the dextrorotatory enantiomer of **6** in yields of 71% and 68%, respectively; $[\alpha]^{22}_D$ +105 (*c* 1.5, acetone).

Formation of Mandelate Acetals 12 and 13. A solution of (±)-**6** (20.0 g, 126 mmol), (*R*)-mandelic acid (24.0 g, 158 mmol), and scandium triflate (1.94 g, 3.94 mmol) in CH_2Cl_2 (500 mL) and acetonitrile (75 mL) was refluxed for 48 h in a Soxhlet apparatus filled with 4 Å molecular sieves. Additional (*R*)-mandelic acid (2.40 g, 15.8 mmol) and scandium triflate (1.30 g, 2.64 mmol) were introduced, and heating was continued for another 24 h. The cooled, dark reaction mixture was poured into saturated $NaHCO_3$ solution (400 mL) and extracted with CH_2Cl_2. The combined extracts were washed with water, dried, and concentrated to leave an oil that was chromatographed on silica gel. Elution with 1:1 CH_2Cl_2/hexanes led to the isolation of two diastereomers in the following order:

12: colorless needles; mp 65−66 °C (from hexanes) (15.8 g, 43%); IR (film, cm^{-1}) 1795; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50−7.33 (m, 5 H), 5.84 (s, 1 H), 2.93−2.83 (m, 2 H), 2.43−1.67 (series of m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 135.4, 128.8, 128.7, 126.3, 118.7, 77.2, 69.4, 38.3, 38.1, 34.0, 32.6, 30.8, 17.7; EI MS *m*/*z* (M^+) calcd 290.0977, obsd 290.0971; $[\alpha]^{22}_D$ −167.4 (*c* 1.7, acetone).

Anal. Calcd for $C_{16}H_{18}O_3S$: C, 66.18; H, 6.25. Found: C, 66.26; H, 6.24.

13: colorless platelets; mp 114−117 °C (from methanol) (14.0 g, 38%); IR (film, cm^{-1}) 1790; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47−7.34 (m, 5 H), 5.68 (s, 1 H), 2.89−2.80 (m, 1 H), 2.33−2.03 (series of m, 6 H), 2.02−1.67 (series of m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 134.7, 128.5, 128.3, 125.8, 118.9, 76.6, 67.5, 38.1, 37.7, 33.4, 32.4, 30.6, 17.4; EI MS *m*/*z* (M^+) calcd 290.0977, obsd 290.0982; $[\alpha]^{22}_D$ +16.8 (*c* 1.4, acetone).

Anal. Calcd for $C_{16}H_{18}O_3S$: C, 66.18; H, 6.25. Found: C, 66.13; H, 6.26.

This diastereomer was subjected to X-ray crystallographic analysis (Figure 2).

Hydrolysis of (+)-13. A homogeneous solution of lithium hydroxide dihydrate (7.0 g, 167 mmol) and (+)-**13** (15.8 g, 54.5 mmol) in a 2:1 mixture of THF and water (1 L) was stirred for 4 h and extracted with ether. The combined organic extracts were washed with water, dried, and concentrated to afford 8.5 g (100%) of (+)-**6** as a colorless oil; $[\alpha]^{22}_D$ +108.4 (*c* 1.4, acetone).

Hydride Reduction of (+)-6. A N_2-blanketed solution of (±)-**6** (8.5 g, 54.4 mmol) in dry ether (50 mL) was transferred via cannula into a solution of lithium aluminum hydride in ether (30 mL of 1 M, 30 mmol). The reaction mixture was stirred for 4 h, treated slowly with 1 M hydrochloric acid (100 mL), and extracted with ether. The combined organic phases

were dried and concentrated to leave an oil that was subjected to flash chromatography on silica gel (elution with 9:1 hexanes/ethyl acetate). There was isolated 2.96 g (34%) of (+)-**14** and 4.39 g (51%) of (−)-**15**, both as colorless oils.

(+)-14: IR (film, cm^{-1}) 3485; ^1H NMR (300 MHz, $CDCl_3$) δ 3.70−3.64 (m, 1 H), 2.95−2.77 (m, 2 H), 2.37 (br s, 1 H), 2.18−1.66 (series of m, 8 H), 1.63−1.45 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 78.2, 70.3, 41.0, 38.0, 32.8, 32.5, 30.5, 20.5; $[\alpha]^{22}_D$ −27.9 (*c* 1.6, acetone). The racemic form of this alcohol has been reported.[15]

(−)-15: IR (film, cm^{-1}) 3445; ^1H NMR (300 MHz, $CDCl_3$) δ 4.06 (t, J = 5.1 Hz, 1 H), 2.89−2.81 (m, 2 H), 2.17−1.93 (m, 5 H), 1.93−1.47 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 79.0, 67.2, 37.9, 35.2, 33.0, 31.3, 30.4, 19.8; $[\alpha]^{22}_D$ −76.6 (*c* 1.1, actone). The racemic form of this alcohol has been reported.[15]

Compound 16. To a cold (0 °C), nitrogen-blanketed solution of (+)-**14** (2.90 g, 18.7 mmol) and 2,6-lutidine (4.40 mL, 37.4 mmol) in dry CH_2Cl_2 (80 mL) was added *tert*-butyldimethylsilyl triflate (6.50 mL, 28.0 mmol). The reaction mixture was allowed to rise slowly to room temperature overnight, filtered through a pad of silica gel (elution with CH_2Cl_2), and evaporated to give 4.8 g (95%) of (+)-**16** as a colorless oil. The analytical sample was obtained by flash chromatography on silica gel (elution with 9:1 hexanes/CH_2Cl_2): IR (film, cm^{-1}) 1115, 1065; ^1H NMR (300 MHz, $CDCl_3$) δ 3.78−3.74 (m, 1 H), 2.89−2.72 (m, 2 H), 2.14−1.92 (m, 3 H), 1.88−1.49 (series of m, 7 H), 0.90 (s, 9 H), 0.11 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 81.1, 68.5, 40.3, 38.4, 33.2, 32.0, 30.3, 25.9, 20.6, 18.2, −4.4, −4.6; EI MS m/z (M^+) calcd 272.1630, obsd 272.1639; $[\alpha]^{22}_D$ +54.0 (*c* 1.5, acetone).

Anal. Calcd for $C_{14}H_{28}OSSi$: C, 61.70; H, 10.36. Found: C, 62.02; H, 10.56.

Compound 17. Entirely comparable silylation of (−)-**15** (4.30 g, 27.1 mmol) furnished 6.6 g (90%) of (−)-**17** as a colorless oil. The analytical sample was comparably prepared: IR (film, cm^{-1}) 1260; ^1H NMR (300 MHz, $CDCl_3$) δ 4.04−3.99 (m, 1 H), 2.96−2.82 (m, 2 H), 2.24−2.13 (m, 1 H), 2.09−1.44 (series of m, 9 H), 0.88 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 80.3, 68.3, 37.8, 36.3, 33.2, 33.1, 30.2, 25.8, 20.6, 18.0, −4.5, −4,8; EI MS m/z (M^+) calcd 272.1630, obsd 272.1653; $[\alpha]^{22}_D$ −15.7 (*c* 1.1, acetone).

Anal. Calcd for $C_{14}H_{28}OSSi$: C, 61.70; H, 10.36. Found: C, 61.46; H, 10.27.

Compound 18. A slurry of (+)-**16** (4.50 g, 16.5 mmol) and 10% sodium periodate on silica gel (38 g) in a 1:1 mixture of CH_2Cl_2 and hexanes (200 mL) was vigorously stirred for 12 h, freed of solvent, and placed atop a short pad of silica gel. Elution with 10% methanol in ether afforded 4.5 g (95%) of **18** as a colorless, oily 4:1 diastereomeric mixture. For the major diastereomer: ^1H NMR (300 MHz, $CDCl_3$) δ 4.08 (t, J = 7.1 Hz, 1 H), 3.09−2.94 (m, 2 H), 2.85−2.72 (m,1 H), 2.62−2.50 (m, 1 H), 2.41−2.26 (m, 1 H), 2.24−1.48 (series of m, 7 H), 0.86 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 81.0, 80.3, 54.2, 36.8, 34.4, 28.1, 25.8, 25.4, 20.1, 17.9, −4.3, −5.0; EI MS m/z (M^+) calcd 288.1578, obsd 288.1588.

Anal. Calcd for $C_{14}H_{28}O_2SSi$: C, 58.28; H, 9.78. Found: C, 58.53; H, 9.77.

Compound 19. Comparable treatment of (−)-**17** (6.0 g, 22.0 mmol), but for a reaction time of 24 h led to the isolation of 5.7 g (90%) of **19** as a colorless, oily 9:1 diastereomeric mixture. For the major diastereomer: ^1H NMR (300 MHz, $CDCl_3$) δ 3.88 (dd, J = 4.6, 4.4 Hz, 1 H), 3.17−3.03 (m, 1 H), 2.82−2.69 (m, 1 H), 2.25−2.24 (m, 2 H), 2.08−1.60 (series of m, 8 H), 0.88 (s, 9 H), 0.06 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.8, 75.2, 53.4, 35.3, 31.5, 28.2, 25.7, 24.3, 21.3, 17.9, −4.3, −5.1; EI MS m/z (M^+) calcd 288.1578, obsd 288.1577.

Anal. Calcd for $C_{14}H_{28}O_2SSi$: C, 58.28; H, 9.78. Found: C, 58.37; H, 9.84.

Pummerer Rearrangement of 18. A magnetically stirred mixture of **18** (310 mg, 1.08 mmol), sodium acetate (290 mg, 3.60 mmol), and acetic anhydride (3 mL) was heated at 110 °C for 3 h. The volatile materials were removed in a vacuum, and the residue was dissolved in dry benzene (50 mL), treated with *p*-toluenesulfonic acid (10 mg), and refluxed over 4 Å molecular sieves for 12 h. After solvent evaporation, the residue was purified by flash chromatography on silica gel (elution with 9:1 hexanes/ether). There was isolated 100 mg (34%) of (+)-**20** and 100 mg (31%) of (+)-**21**.

20: colorless oil; IR (film, cm^{-1}) 1255; ^1H NMR (300 MHz, $CDCl_3$) δ 6.14−6.09 (m, 1 H), 5.42−5.37 (m, 1 H), 3.95−3.90 (m, 1 H), 2.50−2.33 (m, 2 H), 2.16−2.03 (m, 1 H), 1.98−1.55 (series of m, 5 H), 0.89 (s, 9 H), 0.10 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 126.4, 119.5, 80.4, 70.7, 44.8, 37.3, 32.7, 25.8, 19.9, 18.1, −4.5, −4.8; EI MS m/z ($M^+ - CH_3$) calcd 255.1222, obsd 255.1239; $[\alpha]^{22}_D$ +31.1 (*c* 0.4, acetone).

Anal. Calcd for $C_{14}H_{26}OSSi$: C, 62.12; H, 9.69. Found: C, 62.01; H, 9.65.

21: colorless oil; IR (film, cm^{-1}) 1745, 1250; ^1H NMR (300 MHz, $CDCl_3$) δ 5.20−5.13 (m, 1 H), 4.13−4.07 (m, 1 H), 2.96−2.81 (m, 2 H), 2.26−1.84 (series of m, 6 H), 2.04 (s, 3 H), 1.77−1.58 (m, 2 H), 0.90 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 80.4, 79.0, 69.3, 33.5, 31.7, 31.1, 30.8, 28.8, 25.7, 21.1, 18.0, −4.6, −4.9; EI MS m/z (M^+) calcd 330.1685, obsd 330.1639; $[\alpha]^{22}_D$ +29.9 (*c* 1.0, acetone).

Anal. Calcd for $C_{16}H_{30}O_3SSi$: C, 58.14; H, 9.15. Found: C, 58.43; H, 9.17.

Pummerer Rearrangement of 19. Analogous processing of **19** (310 mg, 1.08 mmol) but for 4 h gave 88 mg (30%) of (+)-**22** and 90 mg (28%) of (−)-**23**.

22: colorless oil; IR (film, cm^{-1}) 1260, 1080; ^1H NMR (300 MHz, $CDCl_3$) δ 6.07 (dt, J = 6.1, 2.0 Hz, 1 H), 5.50 (dt, J = 6.1, 6.1 Hz, 1 H), 4.08 (dd, J = 4.9, 2.4 Hz, 1 H), 3.04 (ddd, J = 16.9, 3.0, 2.0 Hz, 1 H), 2.49 (dt, J = 16.9, 2.5 Hz, 1 H), 3.04 (ddd, J = 16.9, 3.0, 2.0 Hz, 1 H), 2.49 (dt, J = 16.9, 2.5 Hz, 1 H), 2.09−1.93 (m, 2 H), 1.91−1.56 (m, 2 H), 0.88 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 124.7, 121.8, 79.4, 70.9, 40.3, 36.7, 33.3, 25.8, 20.9, 18.0, −4.6, −4.9; EI MS m/z (M^+) calcd 270.1474, obsd 270.1476; $[\alpha]^{22}_D$ +40.0 (*c* 0.7, acetone).

Anal. Calcd for $C_{14}H_{26}OSSi$: C, 62.16; H, 9.69. Found: C, 62.29; H, 9.78.

23: colorless oil; IR (film, cm^{-1}) 1740, 1250; ^1H NMR (300 MHz, $CDCl_3$) δ 5.17 (dd, J = 7.3, 4.4 Hz, 1 H), 4.10 (dd, J = 5.7, 4.3 Hz, 1 H), 2.96−2.82 (m, 2 H), 2.26−1.85 (series of m, 6 H), 3.03 (s, 3 H), 1.76−1.57 (m, 2 H), 0.90 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 80.4, 79.0, 69.3, 33.5, 31.7, 31.2, 30.8, 28.8, 25.7, 21.2, 18.0, −4.6, −4.9; EI MS m/z (M^+) calcd 330.1685, obsd 330.1695; $[\alpha]^{22}_D$ −21.0 (*c* 0.5, acetone).

Hydroboration−Oxidation of (+)-20. To a solution of (+)-**20** (230 mg, 0.85 mmol) in dry THF (4 mL) under N_2 was added a solution of the borane•THF complex (1 mL of 1.0 M in THF, 1.0 mmol). The reaction mixture was stirred overnight, at which point ethanol (2 mL), 3 M NaOH solution (2 mL), and 30% hydrogen peroxide (1 mL) were added consecutively at 0 °C. The resulting slurry was stirred in the cold for 3 h and extracted with ether. The combined organic layers were washed with water, dried, and concentrated to leave a residue that was subjected to flash chromatography on silica gel (elution with 25% ethyl acetate in hexanes). There was isolated 70 mg (29%) of **24** (3:2 isomeric ratio) as a colorless oil: IR (film, cm^{-1}) 3400, 1250; ^1H NMR (300 MHz, $CDCl_3$) δ 4.57−4.50 (m, 0.6 H), 4.45−4.41 (m, 0.4 H), 3.94 (dd, J = 7.0, 6.9 Hz, 0.6 H), 3.74 (t, J = 5.2 Hz, 0.4 H), 3.16−2.97 (series of m, 0.6 H), 2.91−2.76 (series of m, 0.4 H), 2.15−1.50 (series of m, 8 H), 0.93 (s, 5.4 H), 0.90 (s, 3.6 H), 0.13 (s, 1.8 H), 0.12 (s, 1.2 H), 0.09 (s, 1.8 H), 0.06 (s, 1.2 H); EI MS m/z (M^+) calcd 288.1579, obsd 288.1602.

Compound 25. A solution of **24** (150 mg, 0.52 mmol) and DMAP (5 mg) in dry pyridine (0.8 mL) was cooled to 0 °C under N_2 and treated dropwise with benzoyl chloride (1.2 mL, 10 mmol). After 4 h of stirring at rt, methanol (1 mL) was introduced and the volatiles were removed under vacuum. The residue was purified by flash chromatography (silica gel, elution with 9:1 hexanes/ethyl acetate) to furnish 200 mg (98%)

of **25** as a 3.2 isomeric mixture: IR (film, cm^{-1}) 1720, 1270; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10−7.95 (m, 2 H), 7.62−7.53 (m, 1 H), 7.50−7.40 (m, 2 H), 5.75−5.67 (m, 0.4 H), 5.56−5.55 (m, 0.6 H), 3.96−3.92 (m, 0.4 H), 3.85 (t, J = 5.3 Hz, 0.6 H), 3.33−3.24 (series of m, 1 H), 3.09 (dd, J = 11.7, 3.9 Hz, 0.4 H), 2.95 (dd, J = 11.0, 6.8 Hz, 0.6 H), 2.26−1.50 (series of m, 8 H), 0.93 (s, 3.6 H), 0.92 (s, 5.4 H), 0.14 (s, 3 H), 0.10 (s, 1.2 H), 0.08 (s, 1.8 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0 (2C), 133.0 (2C), 130.2, 130.0, 129.6 (2C), 128.3 (2C), 80.6, 80.5, 78.0, 76.8, 66.6, 64.3, 44.4, 44.0, 39.0, 38.3, 37.0, 35.1, 32.6, 32.4, 25.8 (2C), 20.4, 20.1, 18.1(2C), −4.3, −4.4, −4.6, −4.7; EI MS m/z (M^+) calcd 392.1841, obsd 392.1868.

Sulfoxidation of 25. A slurry of **25** (140 mg, 0.35 mmol) and 10% sodium periodate adsorbed on silica gel (1 g) in a 1:1 mixture of CH_2Cl_2 and hexanes (20 mL) was vigorously stirred for 48 h. The volatiles were removed, and the dried sample was placed directly atop a column of silica gel. Elution with 8:2 ether/hexanes gave 30 mg (21%) of pure **26** and 45 mg (32%) of pure **27** in addition to a mixture of two lesser sulfoxides. The two diastereomers were not specifically distinguished.

26: pale yellow oil; IR (film, cm^{-1}) 1720, 1270; ^1H NMR (300 MHz, $CDCl_3$) δ 8.09−8.00 (m, 2 H), 7.60−7.52 (m, 1 H), 7.49−7.38 (m, 2 H), 5.85−5.72 (m, 1 H), 4.19 (t, J = 7.4 Hz, 1 H), 3.75 (dd, J = 14.4, 7.6 Hz, 1 H), 2.89 (dd, J = 14.4, 4.4 Hz, 1 H), 2.81−2.58 (series of m, 2 H), 2.45 (dd, J = 13.7, 5.9 Hz, 1 H), 2.16−1.58 (series of m, 5 H), 0.92 (s, 9 H), 0.14 (s, 3 H), 0.11 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 133.2, 129.8, 129.6, 128.4, 80.7, 78.1, 74.7, 58.9, 41.3, 34.0, 27.6, 25.8, 19.8, 17.9, −4.3, −4.9; EI MS m/z (M^+) calcd 408.1790, obsd 408.1801.

Anal. Calcd for $C_{21}H_{32}O_4SSi$: C, 61.73; H, 7.89. Found: C, 61.93; H, 7.97.

27: pale yellow oil; IR (film, cm^{-1}) 1720, 1270; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05−7.97 (m, 2 H), 7.64−7.55 (m, 1 H), 7.51−7.40 (m, 2 H), 5.97−5.85 (m, 1 H), 4.21 (t, J = 6.6 Hz, 1 H), 3.43 (dd, J = 13.5, 6.2 Hz, 1 H), 3.09 (dd, J = 13.5, 8.4 Hz, 1 H), 2.77−2.64 (m, 2 H), 2.22 (dd, J = 13.6, 7.3 Hz, 1 H), 2.10−1.55 (series of m, 5 H), 0.90 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 133.2, 129.8 (2C), 129.6, 128.4 (2C), 80.0, 78.0, 74.9, 55.9, 41.0, 33.7, 28.6, 25.7 (3C), 20.2, 18.0, −4.3, −4.9; EI MS m/z (M^+) calcd 408.1790, obsd 408.1782.

Compound 28. A cold (−78 °C), magnetically stirred solution of (+)-**20** (445 mg, 1.65 mmol) in dry CH_2Cl_2 (10 mL) was blanketed with N_2 and treated slowly with a solution of *m*-chloroperbenzoic acid (285 mg, 1.65 mmol) in dry CH_2Cl_2 (10 mL). The reaction mixture was allowed to warm to rt overnight, poured into saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined organic phases were dried and concentrated prior to flash chromatography on silica gel. Elution with 2% methanol in ether afforded 140 mg (49%) of **28** as a 2:1 mixture of isomers; colorless oil: IR (film, cm^{-1}) 1120, 1000; ^1H NMR (300 MHz, $CDCl_3$) δ 6.84−6.72 (m, 2 H, major), 6.64−6.59 (m, 2 H, minor), 4.43 (d, J = 2.6 Hz, 1 H, major), 4.14 (t, J = 7.0 Hz, 1 H, minor), 3.07−2.95 (m, 1 H from each isomer), 2.73−2.62 (m, 1 H, minor), 2.33−2.23 (m, 1 H, major), 2.22−1.60 (series of m, 6 H), 0.92 (s, 9 H, major), 0.82 (s, 9 H, minor), 0.16 (s, 3 H, major), 0.09 (s, 3 H, major), 0.02 (s, 3 H, minor), −0.01 (s, 3 H, minor); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 142.4, 135.7, 133.4, 104.1, 81.5, 77.4, 76.4, 43.6, 41.5, 33.5, 33.1, 31.6, 27.4, 25.7, 25.6, 21.2, 19.9, 18.0, 15.3, −4.4, −4.5, −5.2 (2C); EI MS m/z (M^+ − H) calcd 285.1344, obsd 285.1310.

Hydroboration−Oxidation of (+)-22. Treatment of (+)-**22** (410 mg, 1.5 mmol) with 9-BBN (4.0 mL of 0.5 M in THF, 2.0 mmol) gave 130 mg (62%) of **29** (9:1 diastereomeric ratio) as a colorless oil: IR (neat, cm^{-1}) 3390, 1460; ^1H NMR (300 MHz, $CDCl_3$) δ 4.18 (dd, J = 4.7, 4.6 Hz, 1 H), 3.03 (dd, J = 12.5, 8.2 Hz, 1 H), 2.48 (dd, J = 12.5, 6.5 Hz, 1 H), 2.22−1.34 (series of m, 9 H), 0.92 (s, 9 H), 0.15 (s, 3 H), 0.10 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 81.1, 66.0, 54.2, 39.3, 37.0, 33.8, 31.2, 25.8, 19.2, 18.1, −4.5, −4.7; EI MS m/z (M^+) calcd 288.1579, obsd 288.1576.

Compound 30. Reaction of **29** (80 mg, 0.30 mmol) with benzoyl chloride (1.2 mL) and DMAP (5 mg) in dry pyridine (0.8 mL) at 0 °C for 4 h as described above, gave 106 mg (98%) of **30** as a 9:1 diastereomeric mixture: IR (film, cm^{-1}) 1720, 1270; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10−8.00 (m, 2 H), 7.62−7.51 (m, 1 H), 7.49−7.39 (m, 2 H), 4.20 (dd, J = 4.4, 4.3 Hz, 1 H), 3.86−3.75 (m, 1 H), 3.17 (dd, J = 12.3, 8.6 Hz, 1 H), 2.44 (dd, J = 12.3, 6.5 Hz, 1 H), 2.17−1.40 (series of m, 8 H), 0.93 (s, 9H), 0.16 (s, 3 H), 0.11 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 133.0, 130.0, 129.6, 128.3, 81.1, 69.9, 54.9, 39.6, 35.0, 32.1, 31.2, 25.8, 19.4, 18.1, −4.5, −4.7; EI MS m/z (M^+) calcd 392.1841, obsd 392.1814.

Compound 31. A mixture of (+)-**22** (200 mg, 0.74 mmol) and 10% sodium periodate adsorbed on silica gel (1.5 g) in 1:1 CH_2Cl_2/hexanes (20 mL) was vigorously stirred for 48 h. Following the removal of volatiles, the residue was placed atop a silica gel column and product was eluted with 5% methanol in ether. There was isolated 120 mg (98%) of **31** as a 9:1 mixture of diastereomers: colorless oil; IR (film, cm^{-1}) 1250, 1040; ^1H NMR (300 MHz, $CDCl_3$) δ 6.75−6.69 (m, 1 H), 6.64−6.59 (m, 1 H), 3.96 (dd, J = 4.5, 4.4 Hz, 1 H), 3.21 (ddd, J = 18.0, 3.2, 1.7 Hz, 1 H), 2.75 (dt, J = 18.0, 2.4 Hz, 1 H), 2.55−1.61 (series of m, 6 H), 0.86 (s, 9 H), 0.03 (s, 3 H), −0.03 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0, 132.5, 77.2, 74.8, 38.3, 35.4, 28.3, 25.7, 21.6, 17.9, −4.6, −5.1; EI MS m/z (M^+) calcd 286.1423, obsd 286.1432.

Compound 36. To a solution of 2,3-dihydrothiophene (2.2 g, 26 mmol) in dry THF (30 mL) cooled to −78 °C under N_2 was added a solution of *tert*-butyllithium in pentane (20 mL of 1.6 M, 32 mmol). The mixture was stirred at this temperature for 30 min, maintained at 0 °C for 30 min, and returned to −78 °C. Cyclobutanone (1.9 mL, 26 mmol) was introduced via syringe and the mixture was allowed to warm to rt overnight. Following the addition of 1 M hydrochloric acid (30 mL), the mixture was extracted with ether, and the combined organic phases were washed with water and brine prior to drying and solvent evaporation. The residue was taken up in isopropyl alcohol (60 mL) and propylene oxide (40 mL), the solution was cooled to −78 °C, and phenylselenenyl chloride (5.0 g, 26 mmol) was added in one portion. The reaction mixture was allowed to warm to rt during 5 h, the volatile materials were removed, and the residue was purified by flash chromatography on silica gel. Elution with 98:2 hexanes/ethyl acetate furnished 5.7 g (70%) of **36** as a yellow oil: IR (film, cm^{-1}) 1730; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60−7.52 (m, 2 H), 7.32−7.24 (m, 3 H), 3.48−3.39 (m, 1 H), 3.07−2.84 (m, 3 H) 2.77−2.68 (m, 1 H), 2.55−2.49 (m, 2 H), 2.26−1.97 (m, 3 H), 1.93−1.75 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.5, 133.8, 131.0, 129.2 (2 C), 127.5 (2 C), 65.2, 50.8, 37.2, 36.3, 34.5, 29.5, 20.6; EI MS m/z calcd 312.0087, obsd 312.0075.

1-Thiaspiro[4.4]non-3-en-6-one (37). To a solution of (±)-**36** (8.8 g, 28.3 mmol) in 450 mL of CH_2Cl_2 was added a solution of *m*-CPBA (4.88 g, 28.3 mmol, 1 eq) in 450 mL of CH_2Cl_2 at −78 °C, and the mixture was stirred at this temperature for 40 min. Pyridine (6.92 mL, 84.9 mmol) was introduced via syringe, and the resulting mixture was stirred at rt for 2 h, washed with 200 mL of water, and quenched with 200 mL of $NaHCO_3$ solution. The separated aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL), and the combined organic extracts were washed with H_2O (50 mL) and brine (50 mL), dried, and concentrated. The residue was purified by flash chromatography on silica gel (gradient elution: 1−5% ethyl acetate in hexanes) to give 3.97 (91%) of (±)-**37** as a faint yellow oil: IR (film, cm^{-1}) 1745, 1150; ^1H NMR (300 MHz, $CDCl_3$) δ 6.10 (dt, J = 6.2, 2.6 Hz, 1 H), 5.52 (dt, J = 6.2, 2.3 Hz, 1 H), 3.92 (dt, J = 14.8, 2.4 Hz, 1 H), 3.82 (dt, J = 14.8, 2.4 Hz, 1 H), 2.56−2.44 (m, 1 H), 2.35−2.14 (series of m, 3 H), 2.12−1.81 (series of m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.7, 131.9, 131.0, 70.8, 39.2, 38.5, 35.2, 20.2; EI MS m/z (M^+) calcd 154.0452, obsd 154.0458.

Formation of Mandelate Acetals 38−41. A solution consisting of (±)-**37** (1.22 g, 7.9 mmol), (*R*)-mandelic acid (24.2 g, 15.9 mmol), and scandium triflate (122 g, 0.24 mmol) in CH_2Cl_2 (33 mL) and CH_3CN (4.1 mL) was refluxed for 2 days over a dropping funnel filled with 4 Å molecular sieves. Additional (*R*)-mandelic acid and $Sc(OTf)_3$ were both added in the process, and fresh sieves were also used. To the resulting dark solution was added saturated $NaHCO_3$ solution (30 mL) and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with H_2O (30 mL) and brine (30 mL), dried, and concentrated to afford an oil that was subjected to flash chromatography on silica gel (gradient elution: 1% to 5% ethyl acetate/hexanes). The overall yield was 94% (2.14 g). Several fractions were further subjected to MPLC on silica gel (5% ethyl acetate in hexanes) to afford the four diastereomers in the following order of elution. **(−)-38:** 33% yield; colorless needles; mp 110 °C (from hexanes); IR (film, cm^{-1}) 1790; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43−7.37 (m, 5 H), 5.96 (dt, J = 8.8, 2.6 Hz, 1 H), 5.77 (dt, J = 6.3, 2.2 Hz, 1 H), 5.68 (s, 1 H), 3.81 (dt, J = 15.0, 2.4 Hz, 1 H), 3.78 (dt, J = 15.2, 2.4 Hz, 1 H), 2.35−2.22 (m, 4 H), 1.93−1.88 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 135.0, 131.5, 130.6, 128.9, 128.7 (2 C), 126.2 (2 C), 119.2, 77.4, 76.1, 38.4, 37.4, 33.9, 18.0; EI MS m/z (M^+ + H) calcd 290.0976, obsd 290.0911; $[\alpha]^{18}_D$ −92.4 (*c* 0.55, acetone).

(−)-39: 37% yield; colorless platelets; mp 119 °C (from methanol); IR (film, cm^{-1}) 1790; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43−7.33 (m, 5 H), 5.97 (dt, J = 6.4, 2.5 Hz, 1 H), 5.77 (dt, J = 6.7, 2.2 Hz, 1 H), 5.56 (s, 1 H), 3.77 (t, J = 2.4 Hz, 2 H), 2.42−2.16 (m, 4 H), 1.96−1.85 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 134.9, 131.9, 130.0, 129.0, 128.7 (2 C), 126.2 (2 C), 118.5, 78.0, 75.5, 38.3, 37.7, 33.7, 18.0; EI MS m/z (M^+ + H) calcd 290.0976, obsd 290.0859; $[\alpha]^{18}_D$ −108 (*c* 1.28, acetone).

(−)-40: 10% yield; colorless oil; IR (film, cm^{-1}) 1798; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53−7.49 (m, 2 H), 7.41−7.34 (m, 3 H), 5.94 (dt, J = 6.4, 2.4 Hz, 1 H), 4.71 (dt, J = 6.3, 2.2 Hz, 1 H), 5.36 (s, 1 H), 3.77 (dd, J = 2.2, 1.1 Hz, 2 H), 2.37−2.11 (m, 4 H), 2.11−1.87 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 133.7, 131.3, 131.2, 129.0, 128.4 (2 C), 127.0 (2 C), 118.7, 76.1, 73.7, 39.0, 37.5, 33.1, 18.1; ES MS m/z ($C_{16}H_{16}O_3SNa^+$) calcd 311.0712, obsd 311.0732; $[\alpha]^{18}_D$ −77.3 (*c* 0.74, acetone).

(−)-41: 14% yield; white solid; 103−104 °C; IR (film, cm^{-1}) 1796; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55−7.52 (m, 2 H), 7.41−7.34 (m, 3 H), 5.92 (dt, J = 6.3, 2.5 Hz, 1 H), 5.74 (dt, J = 6.3, 2.2 Hz, 1 H), 5.40 (s, 1 H), 3.66 (dt, J = 15.0, 2.0 Hz, 1 H), 3.48 (dt, J = 15.0, 2.4 Hz, 1 H), 2.33−2.15 (m, 4 H), 1.93−1.86 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 134.1, 131.4, 130.0, 128.7, 128.3 (2 C), 126.7 (2 C), 117.9, 76.4, 74.1, 38.4, 37.6, 33.0, 17.6; ES MS m/z ($C_{16}H_{16}O_3SNa^+$) calcd 311.0712, obsd 311.0716; $[\alpha]^{18}_D$ −69.8 (*c* 1.25, acetone).

General Procedure for Hydrogenation of 38 and 39. A solution of (−)-**38** (50.0 mg, 0.17 mmol) and 3 mL of ethyl acetate was hydrogenated (1 atm, rt) over 6 mg of 5% palladium on carbon for 48 h, filtered through a short plug of silica gel, and evaporated to afford (−)-**12** (45 mg, 90%).

Hydrogenation of (−)-**39** gave (+)-**13**. Spectral data are identical to those of authentic samples.

General Procedure for Hydrolysis of 38−41. A heterogeneous solution of lithium hydroxide dihydrate (25.5 mg, 0.6 mmol) and (−)-**38** (58.4 mg, 0.2 mmol) in a 2:1 mixture of THF and water (3 mL) was stirred for 4 h and extracted with ether. The combined organic extracts were washed with water and brine, dried, and concentrated to afford 23.1 mg (73%) of (+)-**37** as a colorless oil.

Hydrolysis of (−)-**38** and (−)-**41** gave (+)-**37**: $[\alpha]^{17}_D$ +84.0 (*c* 2.09, acetone).

Hydrolysis of (−)-**39** and (−)-**40** gave (−)-**37**: $[\alpha]^{17}_D$ −76.0 (*c* 1.08, acetone).

General Procedure for Nucleoside Formation. To a nitrogen-blanketed slurry of the purine or pyrimidine base (1.0 mmol) in dry toluene (1 mL) were added in turn triethylamine (0.46 mL or 3.3 mmol for thymine and uracil; 0.61 mL or 4.4 mmol for adenine and cytosine) and trimethylsilyl triflate (0.59 mL or 3.3 mmol for thymine and uracil; 0.79 mL or 4.4 mmol for ademine and cytosine). After the mixture had stirred for 15 min, **18** (0.20 mL, 0.60 mmol) was introduced via syringe and zinc iodide (60 mg, 0.2 mmol) was rapidly added. The resulting bilayer was vigorously stirred at rt for 48 h, at which point saturated $NaHCO_3$ solution was added and the resulting slurry was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried, and concentrated. The residue was purified by flash chromatography on silica gel.

Uridines: elution with ether; 100 mg (43%), 6:4 mixture of epimers.

Thymidines: elution with ether; 110 mg (46%); 6:4 mixture of epimers.

Cytidines: elution with 15% methanol in ether; 110 mg (68%); 1:1 mixture of epimers.

Adenosines: elution with 15% methanol in ether; 110 mg (47%); 6:4 mixture of epimers.

The nucleoside epimers (100 mg, 0.26 mmol) in dry THF (1 mL) were cooled to 0 °C under N_2, treated with TBAF (0.5 mL of 1.0 M in THF, 0.5 mmol), and stirred at rt for 18 h. The volatile materials were carefully removed, and the residue was purified by flash chromatography on silica gel followed by recrystallization.

(−)-42: elution with 10% acetone in ether; 21 mg (30%); colorless needles; mp 180−182 °C (from CH_2Cl_2); IR (film, cm^{-1}) 3400, 1695, 1375; ^1H NMR (300 MHz, $CDCl_3$) δ 9.34 (br s, 1 H), 8.07 (d, J = 8.1 Hz, 1 H), 6.33 (t, J = 6.2 Hz, 1 H), 5.77 (d, J = 8.1 Hz, 1 H), 3.98 (t, J = 6.2 Hz, 1 H), 2.58−1.53 (series of m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 150.7, 141.5, 102.5, 78.7, 71.4, 63.9, 38.4, 37.8, 36.8, 32.9, 19.8; EI MS m/z (M^+) calcd 268.0882, obsd 268.0888; $[\alpha]^{22}_D$ −13.8 (*c* 0.60, acetone).

Anal. Calcd for $C_{12}H_{16}N_2O_3S$: C, 53.71; H, 6.01. Found: C, 53.44; H, 5.95.

(−)-43: elution with ether; 40% yield; colorless solid; mp 92 °C; IR (film, cm^{-1}) 3400, 1675; ^1H NMR (300 MHz, $CDCl_3$) δ 8.75 (br s, 1 H), 7.77 (d, J = 1.2 Hz, 1 H), 6.35 (t, J = 6.5 Hz, 1 H), 3.99 (t, J = 6.3 Hz, 1 H), 2.50−2.37 (m, 1 H), 2.28−1.55 (series of m, 10 H), 1.94 (d, J = 1.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5, 150.7, 136.9, 111.1, 78.7, 71.3, 63.5, 38.6, 37.9, 36.4, 32.9, 19.9, 12.7; EI MS m/z (M^+) calcd 282.1038, obsd 282.1038; $[\alpha]^{22}_D$ −1.6 (*c* 0.60, acetone).

Anal. Calcd for $C_{13}H_{18}N_2O_3S$: C, 55.30; H, 6.43. Found: C, 55.52; H, 6.56.

Compound 45. A solution of **44** (370 mg, 1.0 mmol) in dry toluene (2 mL) under N_2 was treated sequentially and in dropwise fashion with triethylamine (0.46 mL, 3.3 mmol) and trimethylsilyl triflate (0.59 mL, 3.3 mmol). After 20 min of stirring, **18** (0.2 mL, 0.6 mmol) was introduced via syringe followed by zinc iodide (60 mg, 0.2 mmol) under a stream of N_2. The resulting bilayer was vigorously stirred for 48 h, quenched with saturated $NaHCO_3$ solution, and extracted with ethyl acetate. After the combined organic layers were washed with brine, dried, and concentrated, the residue was purified by flash chromatography on silica gel (elution with ethyl acetate) to give 54 mg (13%) of **45**: IR (film, cm^{-1}) 1700, 1490, 1290; ^1H NMR (300 MHz, $CDCl_3$) δ 8.87 (s, 1 H), 8.17 (s, 1 H), 7.47−7.20 (series of m, 10 H), 5.83−5.79 (m, 1 H), 4.00 (t, J = 4.8 Hz, 1 H), 2.62 (s, 3 H), 2.29−1.55 (series of m, 10 H), 0.93 (s, 9 H), 0.17 (s, 3 H), 0.13 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 165.8, 152.1, 151.7, 149.0, 147.8, 141.3, 129.4, 129.1, 127.0, 110.6, 80.1, 71.4, 65.3, 38.4, 37.6, 35.3, 32.9, 25.9, 25.2, 19.7, 18.2, −4.3, −4.4; EI MS m/z (M^+) calcd 307.1102, obsd 307.1111; $[\alpha]^{22}_D$ +8.8 (*c* 0.70, acetone).

Compound 46. A solution of **45** (50 mg, 0.076 mmol) and TBAF (0.5 mL of 1.0 M in THF, 0.5 mmol) in dry THF (1 mL) was prepared at 0 °C, stirred at rt for 24 h, and freed of volatiles. The resulting viscous oil was subjected to flash chromatography on silica gel (elution with 15% methanol in ethyl acetate), and the collected concentrated fractions were

dissolved in methanol saturated with NH_3 at 0 °C and stirred overnight. The resulting solution was concentrated, and CH_2Cl_2 was introduced, causing the precipitation of a powder that was washed with CH_2Cl_2 and dried to give 19 mg (80%) of **46**: mp 295−297 °C dec; IR (film, cm^{-1}) 3320, 1670; ^1H NMR (300 MHz, DMSO-d_6) δ 10.81 (br s, 1 H), 8.42 (s, 1 H), 6.27 (dd, J = 5.1, 2.4 Hz, 1 H), 4.27 (dd, J = 9.3, 5.6 Hz, 1 H), 2.52−2.23 (series of m, 4 H), 2.01−1.40 (series of m, 6 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.5, 159.9, 157.9, 134.1, 132.3, 82.8, 76.0, 69.1, 43.3, 42.5, 41.0, 37.2, 24.6; EI MS m/z (M^+ + H) calcd 307.1102, obsd 307.1099; $[\alpha]^{22}_D$ +10.0 (c 0.20, DMSO).

Synthesis of 47−49. Nucleoside formation in the α-hydroxyl series was performed in an entirely analogous fashion to the β-hydroxyl series.

Uridines: elution with ether; 110 mg (47%); 6:4 mixture of epimers.

Thymidines: elution with ether; 160 mg (66%); 6:4 mixture of epimers.

Cytidines: elution with 15% methanol in ether; 150 mg (54%); 1:1 mixture of epimers.

Adenosines: elution with 15% methanol in ether; 90 mg (38%); 6:4 mixture of epimers.

(−)-47: elution with 10% acetone in ether; 30% yield; colorless needles; mp 187−188 °C; IR (film, cm^{-1}) 3400, 1675; ^1H NMR (300 MHz, $CDCl_3$) δ 8.29 (br s, 2 H), 8.20 (d, J = 8.0 Hz, 1 H), 6.29 (dd, J = 6.1, 3.8 Hz, 1 H), 5.75 (dd, J = 8.0, 2.3 Hz, 1 H), 4.31 (t, J = 6.5 Hz, 1 H), 2.56−1.53 (series of m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8, 150.4, 141.7, 101.9, 78.7, 68.3, 64.6, 37.5, 37.4, 32.4, 32.2, 19.4; EI MS m/z (M^+) calcd 268.0882, obsd 268.0883; $[\alpha]^{22}_D$ −41.8 (c 0.30, acetone).

Anal. Calcd for $C_{12}H_{16}N_2O_3S$: C, 53.71; H, 6.01. Found: C, 53.47; H, 5.96.

(−)-48: elution with ether; 46% yield; colorless solid, mp 146−147 °C; IR (film, cm^{-1}) 3400, 1700, 1250; ^1H NMR (300 MHz, $CDCl_3$) δ 8.92 (br s, 2 H), 7.94 (d, J = 1.0 Hz, 1 H), 6.29 (dd, J = 4.8, 4.7 Hz, 1 H), 4.32 (t, J = 6.2 Hz, 1 H), 2.54−1.54 (series of m, 10 H), 1.94 (d, J = 1.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 150.6, 137.4, 110.5, 78.8, 68.3, 64.2, 37.6, 37.2, 32.6, 32.2, 19.5, 12.6; EI MS m/z (M^+) calcd 282.1038, obsd 282.1045; $[\alpha]^{22}_D$ −13.8 (c 0.60, acetone).

(−)-49: 80% yield; white powder; mp 273−275 °C dec; IR (neat, cm^{-1}) 3340, 1650; ^1H NMR (300 MHz, C_6D_6) δ 11.11 (br s, 1 H), 8.81 (s, 1 H), 6.40 (dd, J = 5.2, 2.3 Hz, 1 H), 4.27 (t, J = 6.8 Hz, 1 H), 2.58−2.16 (series of m, 4 H), 2.06−1.45 (series of m, 6 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.5, 159.8, 157.9, 146.7, 113.1, 82.0, 73.9, 69.5, 42.8, 42.4, 36.8, 36.5, 24.6; EI MS m/z (M^+ + H) calcd 307.1099, obsd 307.1101; $[\alpha]^{22}_D$ −34 (c 0.2, methanol).

Compound 50. To a solution of (−)-**23** (120 mg, 0.36 mmol) in a mixture of THF/methanol/water (3:1:1, 15 mL) was added an excess of lithium hydroxide. The reaction mixture was stirred until the disappearance of starting material (TLC analysis), diluted with water, and extracted with ethyl acetate. The combined organic phases were dried and evaporated to leave a residue that was purified by flash chromatography on silica gel. Gradient elution with 50−5% hexanes in ethyl acetate gave 84 mg (80%) of **50** as a colorless oil: IR (film, cm^{-1}) 3416, 1252; ^1H NMR (300 MHz, $CDCl_3$) δ 4.27 (dd, J = 7.7, 7.7 Hz, 1 H), 3.82 (dd, J = 5.3, 2.1 Hz, 1 H), 2.85−2.70 (m, 2 H), 2.26 (br s, 1 H), 2.21−2.00 (m, 5 H), 1.62−1.36 (m, 3 H), 0.89 (s, 9 H), 0.09 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 78.9, 76.9, 72.2, 32.7, 32.5, 31.2, 30.4, 27.8, 25.8 (3C), 18.1, −4.6, −4.7; $[\alpha]^{22}_D$ −11.3 (c 0.20, $CHCl_3$).

Compound 51. To a solution of oxalyl chloride (0.03 mL, 0.4 mmol) in CH_2Cl_2 (3 mL) was added a solution of DMSO (0.05 mL, 0.9 mmol) in CH_2Cl_2 (3 mL) cooled to −78 °C. This mixture was stirred for 20 min and treated with a solution of **50** (110 mg, 0.35 mmol) in CH_2Cl_2 (10 mL) via syringe at low temperature. After 45 min, triethylamine (0.5 mL, 1.8 mmol) was introduced, and warming to room temperature was allowed to proceed for 30 min prior to quenching with water and extraction with CH_2Cl_2. The combined organic phases were dried and concentrated. Purification of the residue by chromatography on silica gel (elution with 5% ethyl acetate in hexanes) furnished 69 mg (70%) of **51** as a colorless oil; IR (film, cm^{-1}) 1742; ^1H NMR (300 MHz, $CDCl_3$) δ 4.09 (t, J = 4.9 Hz, 1 H), 2.99−2.81 (m, 2 H), 2.62−2.50 (m, 1 H), 2.27−1.71 (m, 1 H), 1.62−1.36 (m, 3 H), 0.89 (s, 9 H), 0.11 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.3, 77.3, 71.4, 33.2, 32.7, 31.2, 30.4, 29.6, 25.7 (3C), 18.0, −4.4, −4.8; ES MS m/z (M + Na)$^+$ calcd 309.1315, obsd 309.1305; $[\alpha]^{22}_D$ −5.8 (c 0.50, $CHCl_3$).

Compound 52. A solution of **51** (280 mg, 0.9 mmol) in dry THF (10 mL) was treated at −78 °C with a solution of lithium hexamethyldisilazide (1.08 mL of 1 M in THF, 1.08 mmol) and stirred in the cold for 1 h prior to the addition of chlorotrimethylsilane (0.18 mL, 1.44 mmol). The reaction mixture was allowed to warm to room temperature during 30 min, returned to −78 °C, and treated dropwise with a solution of phenylselenenyl bromide (335 mg, 1.44 mmol) in THF (5 mL). After 1 h at −78 °C, water was introduced and the product was extracted into ethyl acetate. The combined organic phases were dried and the concentrated filtrate was chromatographed on silica gel (elution with 5% ethyl acetate in hexanes) to give 151 mg of the pure α-isomer. The original α/β ratio was determined to be 3:1 on the basis of the ^1H NMR spectrum of the unpurified product mixture.

For the pure α-isomer: IR (film, cm^{-1}) 1734; ^1H NMR (300 MHz, $CDCl_3$) δ 7.64−7.59 (m, 2 H), 7.36−7.33 (m, 1 H), 7.30−7.27 (m, 2 H), 4.05 (t, J = 8.3 Hz, 1 H), 3.93 (t, J = 4.5 Hz, 1 H), 2.96−2.91 (m, 2 H), 2.85−2.80 (m, 1 H), 2.36−2.30 (m, 1 H), 2.13−2.04 (m, 2 H), 1.94−1.89 (m, 1 H), 1.56−1.46 (m, 2 H), 0.86 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.8, 136.2 (2C), 129.0, 128.7, 127.2, 76.2, 71.2, 42.3, 38.1, 35.9, 32.6, 30.1, 25.6 (3C), 18.0, −4.6, −4.9; ES MS m/z (M + Na)$^+$ calcd 465.0799, obsd 465.0797; $[\alpha]^{22}_D$ −30.6 (c 0.60, $CHCl_3$).

Compound 53. A solution of **52** (145 mg, 0.33 mmol) in toluene (5 mL) at −78 °C was treated with a solution of diisobutylaluminum hydride (0.49 mL of 1 M in toluene, 0.49 mmol), stirred in the cold for 2 h, quenched with methanol, and stirred for another 10 min prior to the introduction of brine. The products were extracted into ethyl acetate, and the combined organic phases were dried and concentrated. Purification by chromatography over silica gel (elution with 5% ethyl acetate in hexanes) afforded 115 mg of the anomeric acetates **53**: IR (film, cm^{-1}) 1741; ^1H NMR (300 MHz, $CDCl_3$) δ 7.62−7.48 (m, 4 H), 7.38−7.32 (m, 2 H), 7.30−7.20 (m, 4 H), 5.54−5.45 (m, 1 H), 5.04 (d, J = 5.1 Hz, 1 H), 4.14−4.11 (m, 1 H), 3.81−3.79 (m, 1 H), 2.67 (dd, J = 5.6, 7.4 Hz, 1 H), 2.26−1.82 (m, 12 H), 1.79−1.77 (m, 1 H), 1.51 (dd, J = 3.0, 5.0 Hz, 1 H), 0.89 (s, 4.5 H), 0.87 (s, 4.5 H), 0.09 (s, 1.5 H), 0.06 (s, 1.5 H), 0.05 (s, 1.5 H), 0.04 (s, 1.5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 170.1, 135.4, 133.3, 131.5, 129.2, 129.1, 128.0, 127.7, 127.2, 84.4, 80.8, 80.6, 72.6, 71.1, 42.7, 41.7, 41.3, 40.4, 39.8, 35.1, 32.9, 32.1, 30.7, 29.8, 25.8, 25.6, 21.1 (3C), 20.9 (3C), 18.1, 18.0, −4.4, −4.5, −4.8, −4.9; ES MS m/z (M + Na)$^+$ calcd 509.1061, obsd 509.1079; $[\alpha]^{22}_D$ −3.0 (c 0.40, $CHCl_3$).

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Supporting Information Available: Copies of high-field ^1H NMR spectra of all compounds, together with tables giving the crystallographic details and structure refinement for **8** and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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