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Stereochemical Features of Lewis Acid-Promoted Glycosidations Involving 4′-Spiroannulated DNA Building Blocks

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Tin tetrachloride-catalyzed glycosidation of persilylated nucleobases with acetate donor **6** in CH_2Cl_2 solution followed by deprotection gave rise very predominantly to α-spironucleosides. These stereochemical assignments stem from the determination of NOE interactions and an X-ray crystallographic analysis of the latter product. Computational studies revealed that these results are consistent with the fact that the C5′ substituent shields the β-face of the oxonium ion involved in the coupling reaction while the C3′ substituent is projected away from the α-underside. Attack from the more open direction is therefore kinetically favored. Entirely comparable calculations suggested that donor **19** should behave comparably. Experimentation involving this donor gave results consistent with this model although more equitable α/β spironucleoside product ratios were seen when acetonitrile was employed as the reaction medium.

All living species are dependent for survival on the efficient transmission of genetic information from the parental DNA strand to the offspring. The responsible replication machinery consists of the catalysis of DNA synthesis by DNA polymerases.[1] In recent years, the template-directed means by which these enzymes function so as to achieve high fidelity are becoming increasingly known.[2,3] Designed synthetic nucleosides and nucleotides have played a particularly informative role in these studies.[4−6] The distinctively different features capable of being carried within these compounds and their impact on overall enzymatic behavior can shed light on a particular replicative function and contribute to mechanistic understanding at the molecular level. Our own search for antiviral therapeutic agents has involved the synthesis of various classes of spirocyclic nucleosides,[7] ranging from those that carry conventional furanoside features[8] to their thia[9] and carba counterparts.[10] To complement the predescribed approaches to dideoxy and didehydrodideoxy analogues, we have more recently targeted mimics bearing a modified 2′-deoxyribose moiety. The synthetic chemistry surrounding this effort constitutes the subject matter of the present report.

Results and Discussion

The *syn*-C5′ Series. Experimentation was initiated with enantiomerically pure butenolide **1**.[11] From among the several protocols available for the dihydroxylation of this substrate, the method of Shing and co-workers was used.[12] Treatment with catalytic ruthenium tetraoxide in a two-phase solvent system comprised of ethyl acetate, acetonitrile, and water resulted in the rapid (<2 min)

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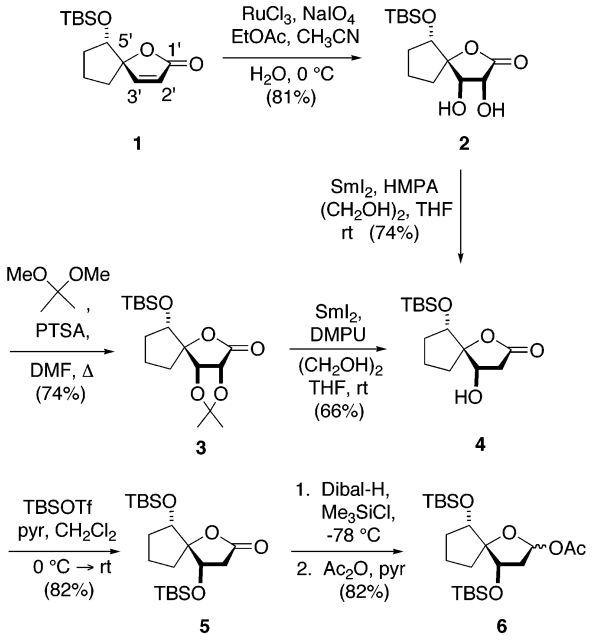
SCHEME 1

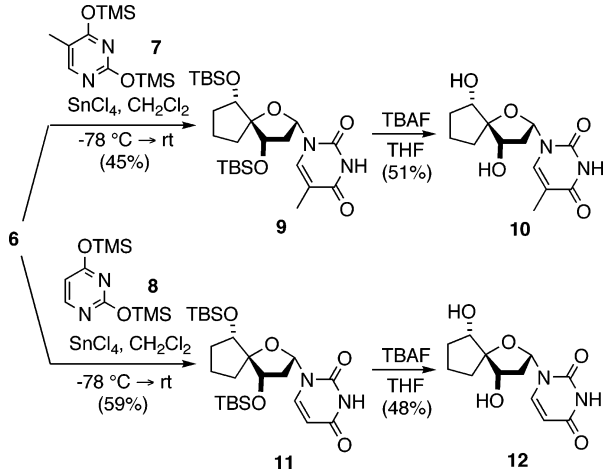


total consumption of **1**, formation of **2** as a single diastereomer, and its isolation in 81% yield (Scheme 1). The stereochemistry of **2** was elucidated by 2D NMR experiments. NOESY correlations were observed between C2′-H and C3′-H and also between C3′-H and C5′-H. This stereoselectivity has also been observed in dihydroxylations of related spirocyclic compounds.[8a,b,9]

In preparation for samarium iodide induced α-deoxygenation, dihydroxy lactone **2** was transformed into acetonide **3**. This transformation proved, however, to be sluggish, with starting material remaining after 7 days at the reflux temperature. The ensuing reaction of **3** with SmI_2 in the presence of DMPU[13−15] produced the 2′-deoxy lactone **4** in satisfactory yield. Despite the success of this sequence, the option of choice for acquiring this intermediate involved direct reduction of diol **2**. In line with the general response of unprotected alcohols to the Sm(II) reductant,[16] no *β*-elimination was encountered.

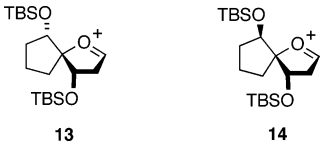
Masking of the 3′-hydroxyl in **4** as the *tert*-butyldimethylsilyl ether was accomplished efficiently despite its hindered nature. Reduction of **5** with diisobutylaluminum hydridefollowed directly by conventional acylation produced the acetate donor **6**. In the absence of a C2′-directing group, glycosylations involving **6** can on the basis of precedent[17] be expected to involve reaction with various nucleobases in a poorly stereoselective manner. However, exposure of CH_2Cl_2 solutions of **6** and the persilylated base **7** with $SnCl_4$ gave rise predominantly to **9** together with 12% (NMR analysis) of its diastereomer. Extension of this methodology to the uracil derivative **8** resulted in the generation of **11** as a single detectable anomer.[18] Desilylation with TBAF made available the anomerically pure spirocyclic α-nucleosides **10** and **12**, respectively (Scheme 2).

SCHEME 2



The absolute configurational assignments depicted for **10** and **12** are derived from several reliable criteria. The strong NOE interactions between H1′ and H3′ with H2′*β* are especially telltale. The stereochemistry of C5′ was defined at the outset, and the NOE between H5′ and H3′ reflect their spatial proximity. In addition, an X-ray crystallographic analysis of **12** was secured.

Computational Studies. The predescribed results point to the fact that nucleophilic attack on oxonium ion intermediate **13** is kinetically preferred from the α surface to a predominant degree. Consequently, **13** and its related diastereomer **14** have been analyzed computationally to determine their most probable ground-state geometry. In so doing, we hoped to determine which face of **13** and **14** is more sterically accessible to an incoming nucleophile.



Since molecular mechanics is incapable of handling molecules containing oxonium cations directly, a feasible assessment of the low-energy geometries of these systems was arrived at in a two-step manner. Initially, Monte Carlo conformational searches were performed on the fully saturated spirotetrahydrofurans in order to obtain an accurate picture of the respective global minima. Once the optimal geometry was defined in each case, a 1′-hydrogen was removed to generate the C−O double bond. The energies of these species were subsequently minimized by the semiempirical AM1 program. The results of this computational optimization are shown in Figure 1 for **13**, **14**, and their dimethoxy congeners (the latter selected to simplify visualization).

On the basis of the depicted geometries, it is clear that the oxonium-containing five-membered rings are essentially flat. In addition, the positions of the OTBS and OCH_3 groups change little in the crossover from molecular mechanics to AM1 output. For all four examples,

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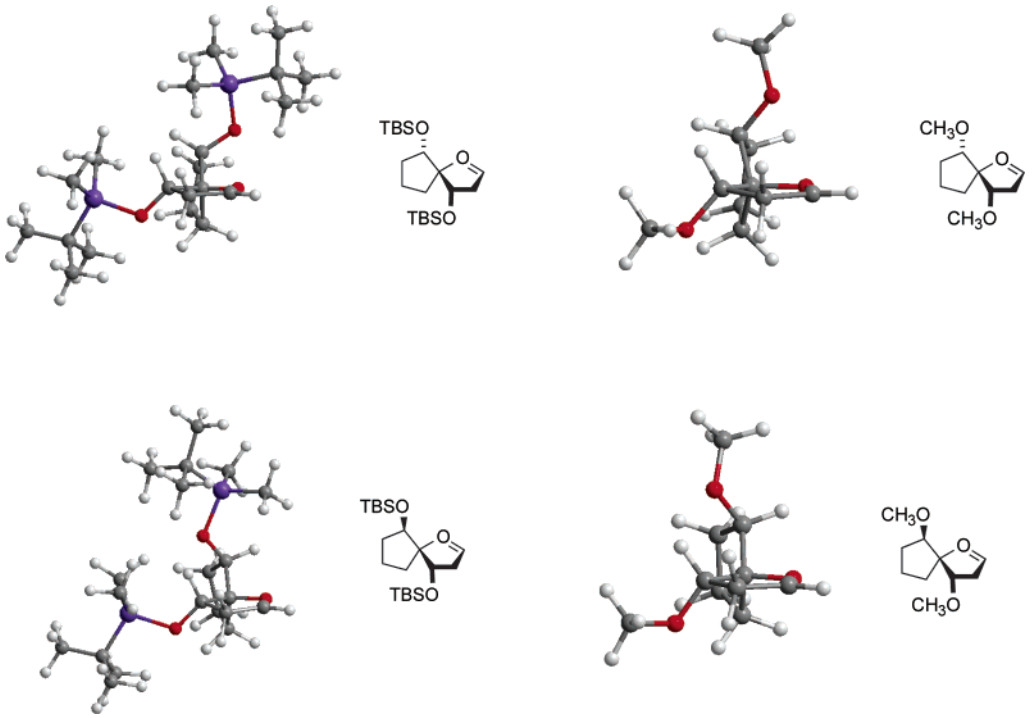
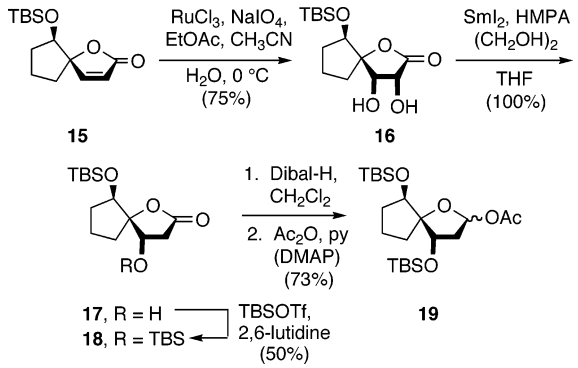


FIGURE 1. Low energy conformations of hypothetical glycosylation intermediates as derived from a combination of molecular mechanics and semiempirical methods. Left: the di-OTBS systems. Right: the di-OCH_3 analogues.

SCHEME 3



the C5′-oxygenated substituent effectively blockades the β face of the oxonium ion. Direct positioning above the double bond may be facilitated as a direct result of the planarity of the heterocyclic ring. In contrast, the 3′α-ether substituents are projected well away from this sector of the nucleosidic intermediates, thereby opening up the bottom surface to a considerable degree. As a consequence, *activated nucleobases can be expected to favor kinetically controlled covalent capture from the sterically less crowded* α*-surface irrespective of the configuration resident at C5′.*

The *anti*-C5′ Series. Although these computational considerations suggested that the stereochemical outcome of those glycosylations involving **14** would also be biased in the α direction, experimental insight was sought. Conversion of **15**[11] to diol **16** was achieved as before with ruthenium tetraoxide. Close monitoring of this oxidation showed the conversion to occur rapidly (Scheme 3). Samarium iodide acted on **16** to furnish the 2′-deoxy lactone **17** quantitatively, thereby allowing for conversion to the key intermediate **19**. We point out that the 3′-hydroxyl group in **17** proved to be less reactive than that in **4**. The maximum yield of **18** realized here was only 50%. Efforts to install an *N*,*N*-diethylthiocarbamate[19,20] or 2-(phenylthio)ethyl ether residue[21−23] at this site in order to gain neighboring group assistance capability and possible blocking of the α-face were to no avail. These developments are, of course, in line with the neopentyl nature of this OH group.

The chemistry of **19** was briefly explored (Scheme 4). Its treatment in CH_2Cl_2 solution with persilylated thymine (**7**)[24] in the presence of $SnCl_4$ resulted in the formation of nucleoside **20** as the sole product. This finding led to a switch in solvent to acetonitrile. This medium is recognized to disrupt σ-complex formation between the tin promoter and the silylated base with resultant lowering of the steric bulk of the nucleophilic agent.[25] Indeed, this modification did result in competitive attack on the β-face of oxonium ion **14**. For example, coupling to silylated cytosine **21** in CH_3CN solution led in 65% yield to an inseparable mixture of 1:1 anomeric nucleosides **22**. Comparable exposure of **19** to bis(trimethylsilyl)adenine[24] was also found to give rise to a 1:1 mixture of anomers. In this instance, however, **24** proved to be chromatographically separable from **25**.

The protected nucleosides **20** and **25** exhibit in common a 1% NOE enhancement between H1′ and H5′. Isomer **24** gives no evidence for such an interaction. The anomeric assignments are tentatively advanced on this basis.

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SCHEME 4

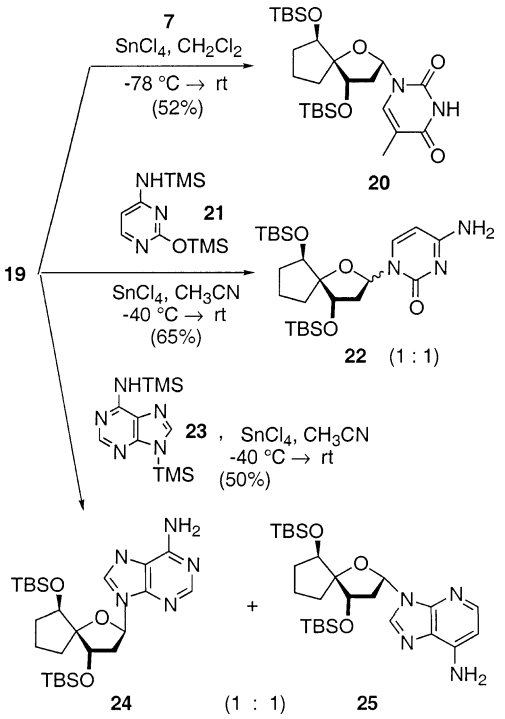

TABLE 1. Comparison of ^{13}C NMR Shifts for Adenosine, 24, and 25

carbon	adenosine[a]	**24**[b]	**25**[b]
C5	119.6	120.5	120.0
C8	140.2	139.8	140.8

[a] Data recorded in DMSO-d_6. [b] Data recorded in $CDCl_3$.

Another criterion developed empirically for this purpose is based on anomeric proton NMR line shapes.[26] Thus, the H1′ proton of β-anomers often appear as an "apparent triplet", in contrast to the doublet of doublets nature of the H1′ exhibited by their α counterparts. Interestingly, those spiro systems such as **9**−**12** that feature an α C−O substituent at C5′ adhere nicely to this qualitative trend.[27] The correlation does not hold for the β C5′ epimers. For example, the H1′ signals in **20**, **24**, and **25** are constituted of a doublet. With regard to the regiochemical issue, reliance has been placed on the chemical shifts of C5 and C8 in the last two examples. Earlier, Kjellberg and Johansson published a detailed spectral study that clearly defines trends for both signals with regard to their N^7 or N^9 isomeric nature.[28] Their data show that C5 in N^7 systems appears approximately 5 ppm upfield from that in N^9 isomers. For C8, the reverse is true in that this signal in N^7 derivatives is positioned 8−10 ppm downfield from that present in N^9 systems. The data provided in Table 1 for **24** and **25** compare closely with adenosine and seemingly discount alternative structural assignments.

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Summary

The previously reported enantiomerically pure butenolides **1** and **15** have been transformed via a four-step route into the acetate donors **6** and **19**, respectively. The utilization of both intermediates as possible precursors to spirocyclic mimics of DNA building blocks was shown to generate appreciable levels of the α-anomers. In select cases where CH_2Cl_2 served as solvent, the proportion of the latter end-products was very predominant. Computational assessment of the probable low-energy conformers of the oxonium ion intermediate reveals that the β-face of these reactive species is sterically shrouded by the C5′ OTBS group irrespective of its configuration. Also, the C3′ substituent is projected in a direction outward from the site of reaction and does not interfere substantially with nucleophile approach from the α direction. Efforts to overcome this kinetic feature by involving special delivery mechanisms are currently under investigation.

Experimental Section

Dihydroxylation of 1. A stock solution of ruthenium tetraoxide sufficient for six reactions was prepared by dissolving $RuCl_3 \cdot xH_2O$ (81 mg, 0.39 mmol) and $NaIO_4$ (823 mg, 3.8 mmol) in H_2O (10.9 mL). Upon dissolution, the black suspension became a dark orange solution having a shelf life of at least 2 h. Butenolide **1** (100 mg, 0.37 mmol) was dissolved in 1:1 (v/v) ethyl acetate−acetonitrile and cooled to 0 °C. The vigorously stirred solution was treated with ruthenium tetraoxide (1.8 mL of stock solution), allowed to react for 2.0 min, quenched by the addition of saturated $Na_2S_2O_3$ solution (2 mL), and transferred to a separatory funnel. This process was repeated until 5.99 g (22.3 mmol) of **1** had been consumed. The aqueous phase was washed with ethyl acetate (5 × 100 mL), and the combined organic phases were dried and concentrated. Purification of the residue by column chromatography on silica gel (eluent 20% ethyl acetate in hexane) returned unreacted **1**(360 mg, 4%) and afforded **2** (5.48 g, 81%) as a white solid: mp 94.0−96.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.72 (d, J = 5.3 Hz, 1 H), 4.24 (d, J = 5.3 Hz, 1 H), 4.00 (dd, J = 7.1, 2.7 Hz, 1 H), 2.10−1.74 (series of m, 6 H), 0.85 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3H) (2 OH not observed); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 95.3, 77.2, 73.4, 70.1, 31.4, 28.8, 25.7 (3 C), 18.1, 17.7, −4.2, −5.0; ES HRMS m/z ($M + Na^+$) calcd 325.1442, obsd 325.1414; $[\alpha]^{20}_D$ +52.0 (c 1.00, $CHCl_3$).

Acetonide 3. A solution of **2** (257 mg, 0.85 mmol) in DMF (1.5 mL) and dimethoxypropane (1.5 mL) was treated with a catalytic amount (∼2 mg) of TsOH, heated to reflux for 7 d, diluted with ether (15 mL), and washed with water (2 × 5 mL). The organic phase was dried (Na_2SO_4), concentrated, and purified by column chromatography (elution with 3% ether in hexane) to yield recovered **2** (51.4 mg, 20%) and **3** (236 mg, 74%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.78 (d, J = 5.4 Hz, 1 H), 4.59 (d, J = 5.4 Hz, 1 H), 3.96 (dd, J = 7.1, 3.0 Hz, 1 H), 2.05−1.59 (series of m, 6 H), 1.45 (s, 3 H), 1.37 (s, 3 H), 0.86 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 112.9, 92.6, 81.0, 77.6, 76.4, 30.5, 28.1, 26.9, 25.9, 25.7 (3 C), 18.6, 17.8, −4.2, −4.9; ES HRMS m/z ($M + Na^+$) calcd 365.1755, obsd 365.1766; $[\alpha]^{20}_D$ +12.4 (c 1.51, $CHCl_3$).

2′-Deoxy Lactone 4. A. From Dihydroxy Lactone 2. A solution of **2** (2.74 g, 9.1 mmol) in THF (90 mL), HMPA (13.5 mL), and ethylene glycol (5.89 mL) was degassed at rt with a flow of argon for 30 min, treated with a solution of samarium iodide in THF (0.1 M, 272 mL), and allowed to react for 3 h. The reaction mixture was diluted with saturated $NaHCO_3$ solution (50 mL), extracted with ether (3 × 100 mL), dried, and concentrated. The residue was chromatographed on silica gel (eluent 20% ethyl acetate in hexane) to give recovered **2** (0.99 g, 37%) and **4** (1.16 g, 46%, 74% brsm) as a colorless solid: mp 64.6−69.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.30 (d,

J = 6.0 Hz, 1 H), 3.96 (dd, J = 7.2, 2.5 Hz, 1 H), 2.99 (dd, J = 11.2, 6.2 Hz, 1 H), 2.40 (br s, 1 H), 2.04−1.60 (series of m, 7 H), 0.87 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 97.8, 77.7, 72.3, 39.7, 31.3, 27.9, 25.7 (3 C), 18.0, 17.8, −4.2, −5.1; ES HRMS m/z (M + Na^+) calcd 309.1493, obsd 309.1491; $[\alpha]^{20}_D$ −16.5 (c 1.02, $CHCl_3$).

B. From Acetonide 3. A solution of **3** (32 mg, 0.09 mmol) in THF (2 mL) containing DMPU (0.18 mL) and ethylene glycol (0.10 mL) was degassed with a flow of argon for 30 min at rt prior to the addition of samarium diiodide (0.1 M solution in THF, 4.7 mL). After 2 h, the reaction mixture was diluted with water (5 mL), extracted with 1:1 ether−hexanes (3 × 15 mL), dried, concentrated, and purified by column chromatography on silica gel (eluent 20% ethyl acetate in hexane) to yield recovered starting material (11 mg, 27%) and **4** (17 mg, 66%) as a white solid spectroscopically identical to that prepared above.

Silylation of 4. A solution of hydroxy lactone **4** (100 mg, 0.35 mmol) in CH_2Cl_2 (1 mL) was treated with pyridine (0.2 mL) and *tert*-butyldimethylsilyl triflate (0.16 mL, 0.7 mmol) at 0 °C and allowed to warm to rt. After 30 min, the reaction mixture was diluted with water (1 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried, concentrated, and purified by column chromatography on silica gel (elution with 5% ether in hexane) to give **5** (115 mg, 82%) as a white solid: mp 117.4−118.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.21 (dd, J = 6.0, 1.5 Hz, 1 H), 3.89 (t, J = 8.5 Hz, 1 H), 2.88 (dd, J = 17.3, 6.0 Hz, 1 H), 2.30 (dd, J = 17.3, 1.5 Hz, 1 H), 1.95−1.82 (m, 5 H), 1.80−1.76 (m, 1 H), 0.86 (s, 9 H), 0.85 (s, 9 H), 0.05 (s, 6 H), 0.04 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 97.3, 77.5, 72.8, 40.0, 31.2, 28.6, 25.7 (3 C), 25.6 (3 C), 18.0, 17.9, 17.8, −4.2, −4.6, −5.0, −5.1; ES HRMS m/z (M + Na^+) calcd 423.2357, obsd 423.2362; $[\alpha]^{20}_D$ −21.2 (c 1.11, $CHCl_3$).

Acetate Donor 6. A solution of **5** (154 mg, 0.38 mmol) and trimethylsilyl chloride (0.29 mL) in dry CH_2Cl_2 (3 mL) was treated with Dibal-H (0.44 mL of 1 M in hexane, 0.44 mmol) at −78 °C. The reaction mixture was held at this temperature for 2 h, quenched with saturated Rochelle's salt solution (2 mL), and stirred overnight. The separated aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were dried and evaporated to provide the crude lactol that was immediately acetylated.

The above material was dissolved in pyridine (3 mL), treated with acetic anhydride (0.5 mL) at rt, stirred overnight, and evaporated to dryness under high vacuum. The residue was dissolved in ethyl acetate (10 mL), washed sequentially with water (5 mL) and brine (5 mL), dried, and concentrated. Purification of the residue by chromatography on silica gel (elution with 95:5 hexanes−ether) gave **6** (146 mg, 86%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) 6.26−6.22 (m, 1 H), 4.26 (dd, J = 8.5, 6.4 Hz, 0.5 H), 4.02 (dd, J = 6.0, 2.3 Hz, 0.5 H), 3.79−3.70 (m, 1 H), 2.48 (ddd, J = 13.8, 5.9, 5.9 Hz, 0.5 H), 2.24−2.16 (m, 0.5 H), 2.01 (s, 3 H), 1.93−1.72 (series of m, 7 H), 0.92 (s, 9 H), 0.89 (s, 9 H), 0.10 (s, 3 H), 0.06 (s, 3 H), 0.05, (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 170.6, 99.2, 96.8, 94.6 (2 C), 77.2, 75.3, 73.8, 71.2, 42.0, 40.8, 31.5, 31.4, 29.3, 28.5, 25.7 (6 C), 25.4 (6 C), 21.6, 21.5, 18.3, 18.2, 18.1 (2 C), 17.9 (2 C), −4.1, −4.2,−4.3, −4.8,−4.9, −5.0 (2 C), −5.1; ES HRMS m/z (M + Na^+) calcd 467.2619, obsd 467.2640; $[\alpha]^{20}_D$ +25.1 (c 0.99, $CHCl_3$) (for the diastereomeric mixture).

Glycosylation of 6 with Persilylated Thymine. A solution of **6** (200 mg, 0.45 mmol) and **7** (243 mg, 0.90 mmol) in CH_2Cl_2 (3 mL) was cooled to −78 °C and treated with neat tin tetrachloride (0.22 mL, 468 mg, 1.8 mmol). The reaction mixture was maintained at −78 °C for 15 min, allowed to warm to rt, quenched with saturated $NaHCO_3$ solution (3 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried and concentrated to leave a residue that was chromatographed on silica gel (elution with 4:1 hexane−ethyl acetate) to give **9** (104 mg, 45%) as a white solid: mp 85.2−88.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63, (br s, 1 H), 7.63 (d, J = 1.1 Hz, 1 H), 6.32 (dd, J = 8.0, 1.7 Hz, 1 H), 4.02 (d, J = 5.3 Hz, 1 H), 3.76 (t, J = 8.0 Hz, 1 H), 2.87−2.77 (m, 1 H), 1.9 (s, 3 H), 1.88−1.59 (m, 7 H), 0.91 (s, 9 H), 0.87 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H), 0.06 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 150.3, 137.2, 109.7, 97.7, 85.5, 78.3, 75.6, 42.7, 32.0, 29.6, 25.7 (3 C), 25.6 (3 C), 18.1, 18.0, 17.9, 12.6, −4.2, −4.7, −4.9, −5.1; ES HRMS m/z (M + Na^+) calcd 533.2837, obsd 533.2856; $[\alpha]^{20}_D$ +23.7 (c 0.49, $CHCl_3$).

Spiro-2′-deoxy-α-nucleoside 10. To a solution of **9** (22.8 mg, 0.045 mmol) in THF (2 mL) was added tetra-*n*-butylammonium fluoride (0.23 mL of 1 M in THF, 0.23 mmol) and allowed to stir for 12 h. The volatiles were removed under reduced pressure, and the residue was purified by chromatography on silica gel (elution with ethyl acetate) to yield **10** (6.1 mg, 52%) as a white solid: mp 78.2−79.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74, (br s, 1 H), 7.56 (s, 1 H), 6.15 (dd, J = 8.2, 2.1 Hz, 1 H), 4.12 (d, J = 6.9 Hz, 1 H), 3.71 (t, J = 5.9 Hz, 1 H), 3.06 (br s, 1 H), 2.85 (ddd, J = 14.5, 8.2, 5.7 Hz, 1 H), 2.27−2.16 (m, 2 H), 2.02−1.51 (series of m, 4 H), 1.88 (s, 3 H) (OH not observed); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 150.6, 137.8, 110.2, 97.4, 86.6, 77.2, 73.7, 40.9, 32.8, 29.0, 19.1, 12.5; ES HRMS m/z (M + Na^+) calcd 305.1108, obsd 305.1100; $[\alpha]^{20}_D$ −1.8 (c 0.11, MeOH).

Glycosylation of 6 with Persilylated Uracil. A solution of **6** (200 mg, 0.45 mmol) and persilylated uracil **8** (189 mg, 0.90 mmol) in CH_2Cl_2 (3 mL) was cooled to −78 °C and treated with neat tin tetrachloride (0.22 mL, 468 mg, 1.8 mmol). The reaction mixture was maintained at −78 °C for 15 min, allowed to warm to rt, quenched with saturated $NaHCO_3$ solution (3 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried and concentrated to leave a residue that was chromatographed on silica gel (elution with 4:1 hexane−ethyl acetate) to give **11** (132 mg, 59%) as a colorless gum: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (br s, 1 H), 7.88 (d, J = 8.2 Hz, 1 H), 6.30 (d, J = 6.7 Hz, 1 H), 5.66 (dd, J = 8.2 Hz, 1 H), 4.01 (d, J = 5.2 Hz, 1 H), 3.76 (t, J = 7.9 Hz, 1 H), 2.83 (ddd, J = 13.9, 8.0, 5.5 Hz, 1 H), 1.96−1.72 (m, 6 H), 1.62 (s, 1 H), 0.91 (s, 9 H), 0.86 (s, 9 H), 0.08 (s, 6 H), 0.07 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 150.1, 141.7, 101.3, 98.0, 85.9, 78.2, 75.5, 42.7, 32.0, 29.7, 25.9 (3 C), 25.7 (3 C), 18.1, 18.0, 17.9, −4.1 (2 C), −5.1 (2 C); ES HRMS m/z (M + Na^+) calcd 519.2681, obsd 519.2663; $[\alpha]^{20}_D$ +16.6 (c 0.91, $CHCl_3$).

Spiro-2′-deoxy-α-nucleoside 12. To a solution of **11** (162 mg, 0.3 mmol) in THF (15 mL) was added tetra-*n*-butylammonium fluoride (2.0 mL of 1 M in THF, 2.0 mmol) and the mixture allowed to stir for 12 h. The volatiles were removed under reduced pressure, and the residue was purified by chromatography on silica gel (elution with 10% methanol in CH_2Cl_2) to yield **12** (42.5 mg, 48%) as a white solid:, mp 203−205 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.92 (s, 1 H), 6.13 (dd, J = 5.8, 1.7 Hz, 1 H), 5.57 (d, J = 8.1 Hz, 1 H), 3.95 (d, J = 5.4 Hz, 1 H), 3.61 (t, J = 7.5 Hz, 1 H), 3.20 (ddd, J = 11.6, 9.9, 8.2 Hz, 1 H), 2.74−2.67 (m, 1 H), 2.09−1.15 (series of m, 6 H) (NH and 2 OH not observed); ^{13}C NMR (75 MHz, CD_3OD) δ 166.6, 152.1, 143.6, 101.7, 97.4, 87.2, 77.7, 74.6, 42.2, 32.9, 29.2, 19.5; ES HRMS m/z (M + Na^+) calcd 291.0951, obsd 291.0953; $[\alpha]^{20}_D$ +14.8 (c 0.19, MeOH).

Dihydroxylation of 15. Lactone **15** (0.20 g, 0.75 mmol) was dissolved in a combination of acetonitrile (4 mL), ethyl acetate (4 mL), and water (1.2 mL). The reaction mixture was cooled to 0 °C and treated with sodium periodate (0.17 g, 0.79 mmol) and 5 min later with $RuCl_3 \cdot H_2O$ (10 mg, 0.047 mmol). After an additional 5 min of stirring, a saturated solution of sodium thiosulfate (25 mL) was introduced and the product was extracted into ethyl acetate (3 × 15 mL). The combined organics were dried and evaporated to leave a residue that was filtered through a silica plug (elution with ether) to give pure **16** (0.17 g, 75%) as a colorless glass: ^{1}H NMR (300 MHz, C_6D_6) δ 4.95 (d, J = 5.1 Hz, 1 H), 4.54 (d, J = 5.1 Hz, 1 H), 3.89 (t, J = 6.3 Hz, 1 H), 2.57−1.95 (m, 1 H), 2.00−1.90 (m, 1 H), 1.78−1.25 (series of m, 4 H), 0.93 (s, 9 H), 0.02 (s, 3 H),

−0.04 (s, 3 H) (OH not observed); ^{13}C NMR (75 MHz, C_6D_6) δ 177.2, 96.6, 78.3, 71.1, 70.1, 32.5, 29.2, 26.0 (3C), 18.6, 18.0, −4.7, −5.0; ES HRMS *m/z* (M + Na)$^+$ calcd 325.1447, obsd 325.1441; $[\alpha]^{18}_D$ −12.0 (*c* 1.0, $CHCl_3$).

2′-Deoxylactone 17. A solution of **16** (0.05 g, 0.17 mmol) in THF (2 mL) was treated with ethylene glycol (0.11 mL, 2.0 mmol) and dry HMPA (0.15 mL). Argon was bubbled through the solution for 10 min prior to the addition of SmI_2 (0.1M in THF, 8.5 mL, 0.85 mmol). The reaction mixture was quenched by the addition of hexane (10 mL), filtered through a plug of silica gel, and evaporated to give **17** (0.05 g, 100%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.58 (dd, J = 4.6, 6.8 Hz, 1 H), 4.04 (t, J = 5.3 Hz, 1 H), 2.88 (dd, J = 6.8, 17.6 Hz, 1 H), 2.52 (dd, J = 4.6, 17.6 Hz, 1 H), 2.33−1.98 (m, 3 H), 1.82−1.72 (m, 2 H), 1.66−1.55 (m, 1 H), 0.88 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H) (OH not observed); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 97.8, 79.0, 69.0, 38.3, 32.7, 28.0, 25.7, 19.6 (3C), 17.8, −4.6, −5.0; ES HRMS *m/z* (M + Na)$^+$ calcd 309.1589, obsd 309.1591.

Silylation of 17. A solution of **17** (0.40 g, 1.4 mmol) was diluted with CH_2Cl_2 (10 mL), treated with 2,6-lutidine (0.50 mL, 4.2 mmol), and cooled to 0 °C. *tert*-Butyldimethylsilyl triflate (0.40 mL, 1.7 mmol) was introduced, and the reaction mixture was quenched with saturated bicarbonate solution (5 mL) after 30 min. The product was extracted into CH_2Cl_2 (2 × 10 mL), and the combined organic layers were dried and evaporated. The residue was purified by column chromatography on silica gel (8:1 hexane/ether) to give **18** (0.28 g, 50%): IR ($CHCl_3$, cm^{-1}) 1771, 1259; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.63 (dd, J = 1.9, 6.0 Hz, 1 H), 4.04 (t, J = 6.3 Hz, 1 H), 2.86 (dd, J = 6.0, 17.5 Hz, 1 H), 2.42 (dd, J = 2.0, 17.4 Hz, 1 H), 2.28−2.23 (m, 1 H), 2.08−2.03 (m, 1 H), 1.91−1.86 (m, 1 H), 1.78−1.71 (m, 2H), 1.64−1.58 (m, 1 H), 0.93 (s, 9 H), 0.92 (s, 9 H), 0.13 (s, 3 H), 0.12 (s, 3 H), 0.11 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8, 99.3, 78.4, 69.4, 40.1, 32.8, 28.8, 26.1 (3C), 26.0 (3C), 19.1, 18.4, 18.3, −4.2 (2C), −4.5, −4.7; ES HRMS *m/z* (M + Na)$^+$ calcd 429.2357, obsd 423.2357; $[\alpha]^{18}_D$ −11.6 (*c* 1.0, $CHCl_3$).

Acetate Donor 19. A solution of **19** (0.28 g, 0.70 mmol) in dry CH_2Cl_2 (20 mL) was treated with Dibal-H (0.9 mL of 1 M in hexane, 0.90 mmol) at −78 °C, stirred at this temperature for 2 h, quenched with saturated Rochelle's salt solution (16 mL), and stirred for 4 h. The separated aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were dried and evaporated to provide the crude lactol that was immediately acetylated.

The above material was dissolved in CH_2Cl_2 (10 mL) and pyridine (1 mL), treated with acetic anhydride (0.13 mL, 1.4 mmol) and DMAP (0.01 g), stirred at rt for 30 min, and evaporated to dryness under high vacuum. The residue was dissolved in ethyl acetate (10 mL), washed sequentially with saturated $CuSO_4$ solution (5 mL), water (5 mL), and brine (5 mL), dried, and concentrated. Purification of the residue by column chromatography on silica gel (9:1 hexane/ether) gave **19** (0.23 g, 73%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.30 (dd, J = 4.0, 5.3 Hz, 0.8 H), 6.19 (dd, J = 1.1, 5.5 Hz, 0.2 H), 4.66 (t, J = 5.1 Hz, 0.8 H), 4.48−4.47 (m, 0.2 H), 4.06 (t, J = 5.7 Hz, 0.8 H), 3.92 (t, J = 5.7 Hz, 0.2 H), 2.46−1.55 (series of m, 11 H), 0.94 (s, 1.8 H), 0.93 (s, 7.2 H), 0.92 (s, 7.2 H), 0.91 (s, 1.8 H), 0.10 (br s, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 170.8, 98.7, 98.6, 98.5, 98.2, 78.6, 78.3, 71.6, 70.4, 42.3, 42.2, 33.7, 32.5, 30.6, 30.0, 26.3 (3C), 26.2 (3C), 26.1 (3C), 26.0 (3C), 21.8 (2C), 19.9, 19.0, 18.4 (2C), 18.3 (2C), −4.1 (2C), −4.2, −4.4 (2C), −4.5 (2C), −4.7; ES HRMS *m/z* (M + Na)$^+$ calcd 467.2619, obsd 467.2634; $[\alpha]^{18}_D$ −20.7 (*c* 0.7, $CHCl_3$).

Glycosidation of 19. A. With Persilylated Thymine. A solution of **7** (0.12 g, 0.44 mmol) and **19** (100 mg, 0.22 mmol) in CH_2Cl_2 (2.5 mL) was cooled to −78 °C and treated with neat tin tetrachloride (0.05 mL, 2 equiv). The reaction mixture was maintained in the cold for 15 min, allowed to warm to rt, quenched with saturated $NaHCO_3$ solution (3 mL), and extracted with CH_2Cl_2. The combined organic layers were dried and concentrated to leave a residue that was chromatographed on silica gel (elution with 3:2 hexane/ether) to give 0.06 g (52%) of **20**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (br s, 1 H), 7.67 (s, 1 H), 6.19 (d, J = 6.6 Hz, 1 H), 4.51 (d, J = 5.2 Hz, 1 H), 3.82 (t, J = 4.3 Hz, 1 H), 2.75−2.69 (m, 1 H), 2.25−2.20 (m, 1 H), 2.08−2.03 (m, 1 H), 1.95 (s, 3 H), 1.91−1.85 (m, 1 H), 1.81−1.74 (m, 2 H), 1.64−1.58 (m, 2 H), 0.94 (s, 9 H), 0.92 (s, 9 H), 0.14 (s, 3 H), 0.11 (s, 3 H), 0.10 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0, 150.7, 137.6, 110.2, 101.0, 85.0, 78.1, 72.0, 42.8, 33.6, 30.3, 30.1, 26.1 (3C), 26.0 (3C), 20.1, 18.4, 18.3, 13.0, −4.0, −4.4, −4.5, −4.6; ES HRMS *m/z* (M + Na)$^+$ calcd 533.2837, obsd 533.2830; $[\alpha]^{18}_D$ −5.5 (*c* 0.2, $CHCl_3$).

B. With Silylated Cytosine. A solution of **21** (0.11 g, 0.44 mmol) and **19** (100 mg, 0.22 mmol) in CH_3CN (2.5 mL) was cooled to −40 °C and treated with neat tin tetrachloride (0.05 mL, 2 equiv). The reaction mixture was maintained at −40 °C for 15 min, allowed to warm to rt, quenched with saturated $NaHCO_3$ solution (3 mL), and extracted with ethyl acetate. The combined organic layers were dried and concentrated to leave a residue that was chromatographed on silica gel (elution with ethyl acetate) to give 0.07 g (60%) of **22**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J = 6.5 Hz, 0.5 H), 7.68 (d, J = 6.5 Hz, 0.5 H), 6.20−5.85 (series of multiplets, 2 H), 4.56 (t, J = 5.7 Hz, 0.5 H), 4.46 (d, J = 4.5 Hz, 0.5 H), 4.11 (t, J = 7.1 Hz, 0.5 H), 3.85−3.80 (m, 0.5 H), 2.72−2.65 (m, 0.5 H), 2.46−2.43 (m, 0.5 H), 2.25−2.14 (m, 1 H), 2.08−1.53 (series of multiplets, 6 H), 0.94 (s, 4.5 H), 0.93 (s, 4.5 H), 0.92 (s, 4.5 H), 0.86 (s, 4.5 H), 0.12 (s, 1.5 H), 0.11 (s, 3 H), 0.10 (s, 3 H), 0.09 (s, 1.5 H), 0.08 (s, 1.5 H), 0.00 (s, 1.5 H) (NH_2 not observed); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9 (2C), 143.0 (2C), 140.9 (2C), 128.7 (2C), 101.4 (2C), 96.6 (2C), 86.3, 85.3, 78.0 (2C), 72.2 (2C), 42.7, 42.0, 33.7, 32.6, 30.5, 29.5, 26.3 (3C), 26.2 (3C), 26.1 (6C), 20.2, 18.9, 18.4 (2C), 18.2 (2C), −3.7, −3.9, −4.0, −4.2, −4.3, −4.5, −4.6, −4.7; ES HRMS *m/z* (M + Na)$^+$ calcd 518.2841, obsd 518.2833; $[\alpha]^{18}_D$ +15.3 (*c* 0.9, $CHCl_3$).

C. With Silylated Adenine. A solution of **23** (1.12 g, 0.44 mmol) and **19** (100 mg, 0.22 mmol) was dissolved in CH_3CN (2.5 mL), cooled to −40 °C, and treated with neat tin tetrachloride (1.9 mL, 2 equiv). The reaction mixture was maintained at −40 °C for 15 min, allowed to warm to rt, quenched with saturated $NaHCO_3$ solution (3 mL), and extracted with ethyl acetate. The combined organic layers were dried and concentrated to leave a residue that was chromatographed on silica gel (elution with 1:2 benzene/ethyl acetate) to give **24** (29 mg, 25%) and **25** (28 mg, 25%).

For **24**: ^{1}H NMR (500 MHz, C_6D_6) δ 8.59 (s, 1 H), 8.40 (s, 1 H), 6.40 (d, J = 6.9 Hz, 1 H), 5.49 (br s, 2 H), 4.51 (d, J = 5.2 Hz, 1 H), 3.67 (t, J = 4.9 Hz, 1 H), 2.57−2.48 (m, 1 H), 2.27−2.17 (m, 2 H), 1.99−1.81 (m, 2 H), 1.67−1.58 (m, 2 H), 1.65−1.51 (m, 1 H), 0.89 (s, 9 H), 0.81 (s, 9 H), −0.02 (s, 3 H), −0.03 (s, 3 H), −0.04 (s, 3 H), −0.15 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 156.2, 153.4, 150.3, 139.8, 120.5, 100.2, 83.8, 78.4, 72.2, 42.6, 33.3, 30.2, 26.0 (3C), 25.9 (3C), 19.8, 18.2, 18.1, −4.5, −4.7, −4.8, −5.1; ES HRMS *m/z* (M + Na)$^+$ calcd 542.2953, obsd 542.2955; $[\alpha]^{18}_D$ −8.2 (*c* 0.6, $CHCl_3$).

For **25**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (s, 2 H), 6.42 (d, J = 7.2 Hz, 1 H), 4.62 (d, J = 5.1 Hz, 1 H), 3.92 (t, J = 5.0 Hz, 1 H), 2.86−2.82 (m, 1 H), 2.37−2.34 (m, 1 H), 2.30−2.25 (m, 1 H), 2.11−2.07 (m, 1 H), 1.93−1.89 (m, 1 H), 1.80−1.74 (m, 2 H), 1.62−1.58 (m, 1 H), 0.95 (s, 9 H), 0.88 (s, 9 H), 0.13 (s, 9 H), 0.01 (s, 3 H) (NH_2 not observed); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 152.6, 149.8, 140.8, 120.0, 101.0, 83.8, 78.6, 72.2, 43.0, 33.5, 30.4, 30.1, 26.3 (3C), 26.2 (3C), 20.0, 18.4, 18.3, −4.0, −4.4, −4.5, −4.7; ES HRMS *m/z* (M + Na)$^+$ calcd 542.2953, obsd 542.2945; $[\alpha]^{18}_D$ +10.3 (*c* 0.4, $CHCl_3$).

It is possible that the structural assignments to **24** and **25** are reversed.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all compounds, as well as the crystallographic details for **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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