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Highly Stereoselective β-Anomeric Glycosidation of a 2′-Deoxy *Syn*-5′-Configured 4′-Spironucleoside

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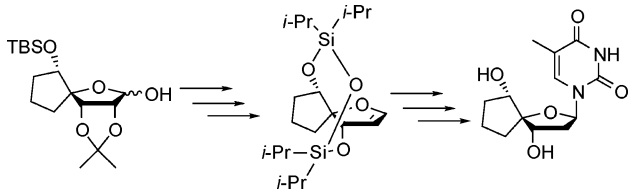
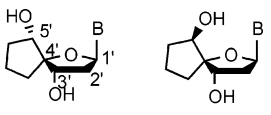


A direct enantioselective pathway that delivers exclusively the β-anomer of a 4′-spironucleoside has been successfully developed. The key starting material is the enantiomerically pure dihydroxy lactone **19**, which has proven amenable to conversion to glycal **22** via the chloro acetonide. This intermediate is then capped as the 3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl) glycal. The latter can enter into *N*-iodosuccinimide-promoted glycosidation with persilylated thymine. Only the β anomer is formed. Ensuing deiodination and desilylation proceed quantitatively to furnish the targeted, previously elusive anomer.

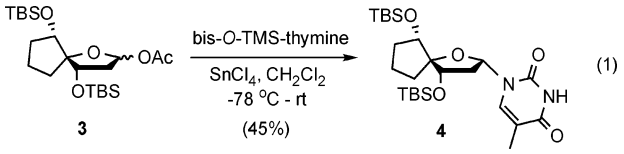
Introduction

During the past several years, we have concerned ourselves with the elaboration of nucleosides where the naturally implanted C-4′ hydroxymethyl group is replaced by a spirocyclopentanol ring.[1] The structural features incorporated in **1** and **2**, for example, were motivated by several factors that have been delineated elsewhere.[2] The most important considerations came from molecular modeling studies that showed **1** likely to adopt an S-type conformation when incorporated into a DNA fragment.[1,3] Under similar conditions, epimer **2** is characterized by a low-energy N-type spatial arrangement. Thus, these different conformational features could prove to be tunable and to provide promising binding properties by purposeful incorporation into nucleotide segments.



1 **2**

In the course of the synthetic studies designed to access **1** and **2**, difficulties in achieving preferential β-incorporation of the nucleobases manifested themselves. For example, when glycosyl donor **3** was engaged in tin tetrachloride-catalyzed coupling to persilylated pyrimidines in CH_2Cl_2 solution, the respective α-4′-spironucleoside **4** was formed predominantly (eq 1).[4] The explanation for this stereochemical outcome was based



3 **4** (1)

on computational considerations that indicated steric shielding by the C-5 substituent to operate on the β-face of the oxonium ion. Concurrently, the silyl ether resident at C-3 is projected out and away from the α-underside. As a consequence, nucleophilic attack from the more open direction is kinetically favored.[4] This stereoselectivity was antithetical to our long-range goals, which necessarily included the design of a convenient protocol for producing the β-anomers exclusively or nearly so. This focused effort constitutes the subject matter of the present report.

Results and Discussion

It is now recognized that select nucleosides can be prepared with high β-selectivity by electrophilic addition of nucleobases

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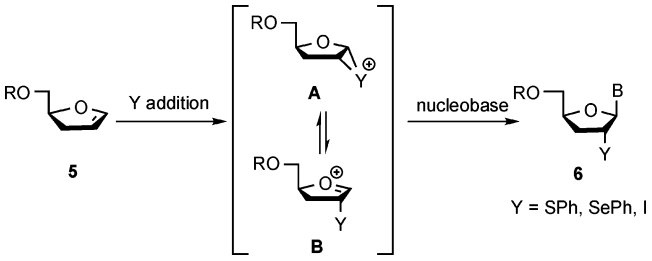
SCHEME 1



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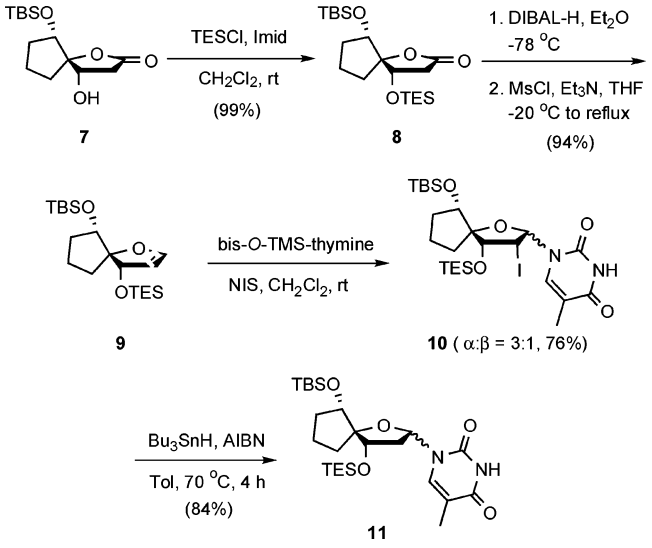
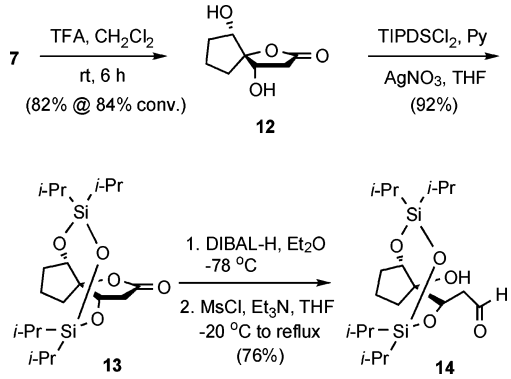


to glycals.[5] The stereoselectivity of the global process is determined by the sequential operation of two distinct steps. The first consists of introducing a group bearing a proper heteroatom by treatment of the furanoid substrate with such electrophiles as NIS, I_2, PhSCl, or PhSeCl. To be favorable for our purposes, the bicyclic cationic intermediate **A** must be generated by endo attack on **5** (Scheme 1). The ring-opened cationic intermediate **B** has also been proposed in support of the stereochemical outcome.[6] In actuality, the relative stabilities of **A** and **B** may vary from system to system.

Our probe of the applicability of this methodology began with the previously described hydroxy lactone **7**,[4] which was protected as the triethylsilyl ether **8** in high yield (Scheme 2). In an adaptation of methodology developed by Townsend,[7] the fully protected lactone **8** was first reduced by DIBAL-H at −78 °C. Without column chromatography, the crude lactol was mesylated at −20 °C in the presence of CH_2Cl_2 and a large excess of triethylamine to avoid dimerization.[8] After the complete consumption of starting material (TLC analysis), the reaction mixture was brought to reflux and elimination was allowed to proceed overnight at this temperature.[7] The sensitive **9** so produced was purified on silica gel which had been pretreated with ether−petroleum ether containing 3% of triethylamine. Subsequently, it was discovered that THF is a preferred solvent relative to CH_2Cl_2 for this conversion (94% versus 80% yield). This solvent change permitted reaction times as short as 2 h to be employed.[9]

SCHEME 3



The PhSeCl-mediated electrophilic glycosidation of **9** with silver triflate serving as promoter[10] gave a disappointingly low yield (<30%) of desired product. When this condensation with persilylated thymine was initiated instead with *N*-iodosuccinimide,[11] no catalyst was necessary, and the reaction proceeded rapidly to generate 2′-iodo-4′-spironucleoside **10** in 76% yield. Unexpectedly, the α/β ratio was biased in the wrong direction (3:1). NOESY studies of the major anomer revealed it to be α-configured on the basis of a characteristic H-1′/H-3′ correlation. This assignment was further substantiated by direct comparison of the high-field ^{1}H NMR spectrum of deiodinated product **11** with that of the closely related **4**.

In view of these unfavorable developments, attention was redirected to the possibilities offered by 3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl) (TIPDS) protection. Masking of thiafuranoid glycals in this manner has recently been shown to be remarkably effective in delivering the corresponding β-anomeric thianucleosides.[12,13] Our analysis of the serviceability of TIPDS protection in the present context began with the desilylation of **7** under acidic conditions (Scheme 3). When recourse was made to formic acid in aqueous THF for this purpose,[14] hydrolysis of the hindered TBS ether required one week to proceed to completion. By comparison, exposure of **7** to trifluoroacetic acid in CH_2Cl_2[15] gave rise to diol **12** in 82% yield at 84% conversion in only 6 h. The treatment of **12** with $TIPDSCl_2$, pyridine, and silver nitrate proceeded smoothly and efficiently as expected to deliver **13**. When the reduction−mesylation−elimination protocol employed so successfully above was applied to this intermediate, the targeted TIPDS-protected glycal was not

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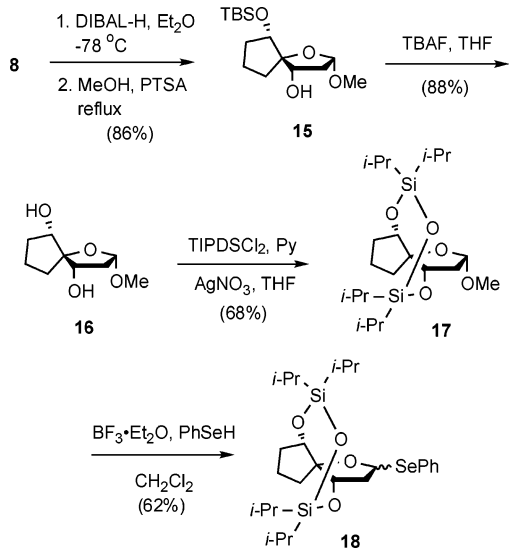
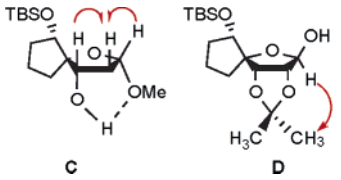
SCHEME 4



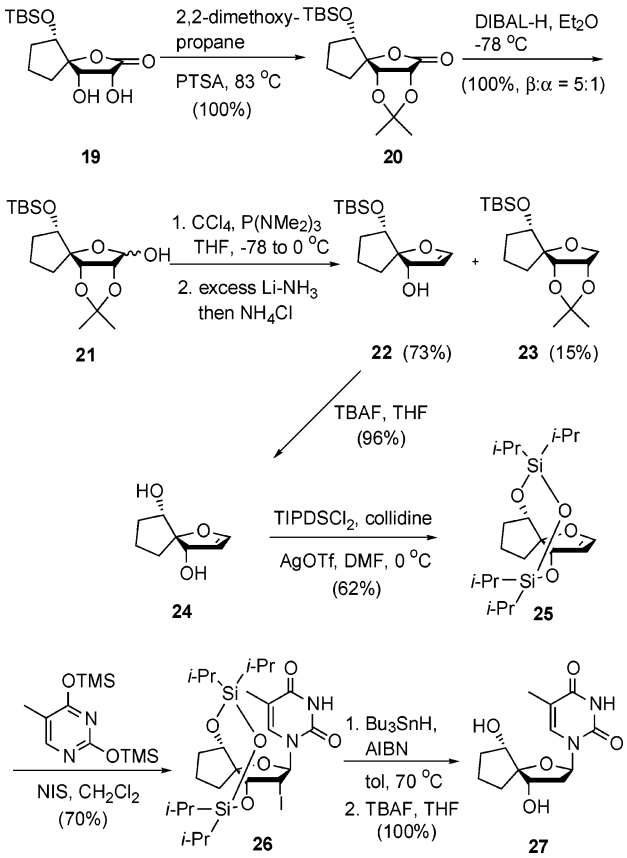
observed. Instead, formation of aldehyde **14** took place. In this example, the strain energy residing in the disiloxane ring causes ring opening to be kinetically favored.

To skirt this state of affairs, it seemed reasonable to defer TIPDS protection until after the reduction step. To test this proposition, lactone **8** was reduced with DIBAL-H and exposed directly to a solution of *p*-toluenesulfonic acid in distilled methanol (Scheme 4).[16] This one-pot operation provided a 2.4:1 mixture of the two methyl acetals, both of which had undergone hydrolytic loss of the TES group. Rapid equilibration was observed between these anomers in $CDCl_3$ solution. Ultimately, **15** was isolated in 86% yield. The stereochemical assignment to **15** is based on the results of NOESY measurements which showed both H-1 and H-3 to correlate with H-2β (see **C**). The desilylation of **15** with TBAF made available the diol **16** whose conversion to **17** was accomplished efficiently in the predescribed manner. Notwithstanding the success of this step, the subsequent conversion to selenoacetal **18** was soon uncovered to not be well suited for consideration as a preparatively utilitarian step. For this reason, this route was not further developed and the pathway summarized in Scheme 5 was accorded attention.



All relevant stumbling blocks were effectively dismissed when the known dihydroxy lactone **19**[4,17] served as the starting point. With minor modifications, the formation of acetonide **20** was accomplished quantitatively. This rather sluggish reaction could be driven to completion simply by refluxing **19** in neat 2,2-dimethoxypropane containing a catalytic quantity of *p*-toluenesulfonic acid. The conversion to **20** was complete in 30 min. Subsequent DIBAL-H reduction resulted in quantitative conversion to lactol **21** as a mixture of two anomers (β/α =

SCHEME 5



5:1). NOESY studies indicated the β-isomer to be major. The diagnostic correlation involved H-1 and the endo methyl group of the acetonide as in **D**. The endo CH_3 substituent is positioned in the deshielding region induced by the THF oxygen atom and is consequently shifted downfield relative to its exo counterpart (1.46 versus 1.31 ppm). The observed isomer distribution indicates that the OTBS functionality shields the β-face more than the acetonide subunit does the α-face.

With lactol **21** in hand, the applicability of Ireland's method[18] for generating ribofuranoid glycals was explored. Thus, the intermediate chloride was generated in situ by admixture with tris(dimethylamino)phosphine and carbon tetrachloride at −78 to 0 °C. When the resulting mixture was added to a solution of excess lithium in liquid ammonia, the reduction products **22** and **23** could be isolated in 73% and 15% yield, respectively. The formation of **23** is the likely result of protonation of the intermediate carbanion. The desilylation of **22** with TBAF to provide **24** required several days to proceed to completion, thereby setting the stage for the acquisition of the targeted TIPDS glycal **25**. Submission of **25** to NIS-initiated glycosidation with persilylated thymine resulted in the formation of a single isomer in very respectable yield (70%). The identification of **26** as the β-isomer is based reliably on the coupling constant of 1.9 Hz observed for the signal attributable to H-1′ [13] in tandem with the observed NOESY correlation involving H-6 and H-3′. The targeted nucleoside was obtained quantitatively following sequential deiodination and desilylation. The configurational assignment was further reinforced by the pseudo-triplet splitting pattern exhibited by H-1′ (centered at 6.23 ppm).[19]

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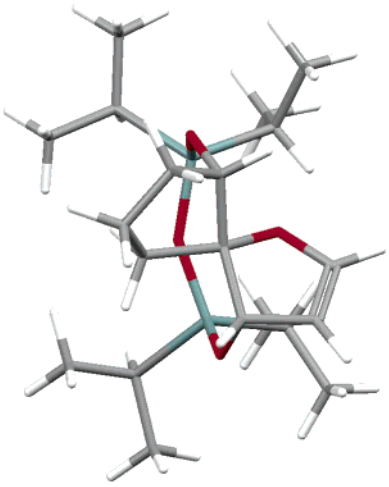
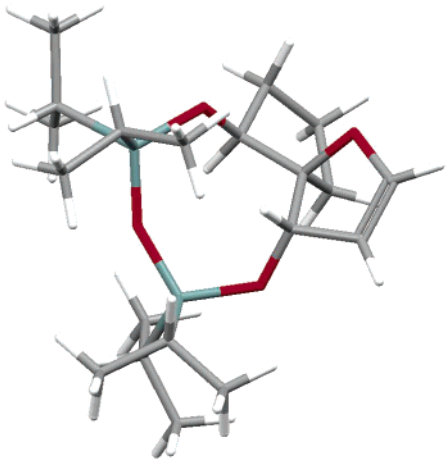
Computational Studies and Conformational Issues of 25

The readiness with which glycal **24** undergoes conversion to its TIPDS-protected derivative **25** brings into question the actual placement of the disiloxane belt in the global molecular context. Does this belt pass across the β-face of the spirocyclic unit or is the α-surface experiencing steric screening? MMFFs calculations were performed and 5000 different spatial arrangements were defined by Monte Carlo simulation with MacroModel 8.6. The possible conformations of **25** were optimized in analogous fashion. The global energy minima **E** (belt covering the α-face) and **F** (belt passing over the β-surface) are shown below. Of these, **E** is disfavored by steric strain in excess of 122 kcal/mol (E_S for **E** = 147.9 kcal/mol; E_S for **F** = 25.7 kcal/mol). A major cause of this divergence in energy is the need to strain both five-membered rings so that the steric bulk delivered by the triad of methylene groups could be avoided in **E**. Additional evidence was derived from the observed NOESY correlation between H-2′, H-3′, and the TIPDS protons in **26**.



E



F

Conclusions

An effective solution has been found for steering the essentially complete β-glycosidation of a 2′-deoxy *syn*-5′ configured 4′-spironucleoside. The key step involves the initial formation of a TIPDS-protected glycal, whose reaction with *N*-iodosuccinimide delivers the α-iodonium ion to the virtual exclusion of the other stereochemical alternative. An additional practical attraction of the method is its exceptional efficiency in the final stages.

Experimental Section

Silylation of 7. A solution of **7** (100 mg, 0.35 mmol) in CH_2Cl_2 (0.8 mL) was treated with imidazole (71.3 mg, 1.05 mmol) and triethylsilyl chloride (57.9 mg, 0.39 mmol). After 15 min, the reaction mixture was diluted with water (1 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried and concentrated, and the residue was chromatographed on silica gel (5% ether in hexanes) to give **8** (138 mg, 99%) as a white solid: mp 79.2−81.0 °C; IR ($CHCl_3$, cm^{-1}) 1774, 1170; ^1H NMR (300 MHz, $CDCl_3$) δ 4.23 (dd, J = 6.0, 1.5 Hz, 1 H), 3.89 (dd, J = 9.5, 7.4 Hz, 1 H), 2.88 (dd, J = 17.3, 6.1 Hz, 1 H), 2.30 (dd, J = 17.3, 1.5 Hz, 1 H), 1.93−1.72 (m, 5 H), 1.66−1.55 (m, 1 H), 0.93 (t, J = 7.8 Hz, 9 H), 0.84 (s, 9 H), 0.57 (q, J = 7.8 Hz, 6 H), 0.03 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 97.3, 77.6, 72.6, 40.2, 31.2, 28.4, 25.7 (3 C), 18.0, 17.8, 6.7, (3 C), 4.7 (3 C), −4.2, −5.0; ES HRMS m/z ($M + Na^+$) calcd 423.2357, obsd 423.2384; $[\alpha]^{20}_D$ −18.9 (c 1.09, $CHCl_3$).

Glycal 9. To a stirred ethereal solution (20 mL) of **8** (110.6 mg, 0.28 mmol) was added DIBAL-H (1 M toluene solution, 0.41 mL, 0.41 mmol) dropwise under argon at −78 °C. After 1 h, the reaction mixture was quenched by the addition of saturated Rochelle's salt solution (5 mL) and stirred for 5 h while warming to rt. The separated aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were dried and evaporated to provide the crude lactol that was used without further purification.

The above material was dissolved in THF (3 mL) and cooled to −20 °C. To this solution was added triethylamine (1.2 mL, 8.30 mmol) followed by methanesulfonyl chloride (0.13 mL, 1.66 mmol). Stirring was continued for 2 h when starting material was fully consumed as determined by TLC. The reaction mixture was warmed to rt, heated at reflux for 2 h, returned to rt, and filtered. The filtrate was evaporated to afford a crude oil that was subjected to silica gel chromatography (pretreated with drops of triethylamine, 2%−5% ether in petroleum ether) to afford **9** (100 mg, 94%) as a colorless oil: IR (neat, cm^{-1}) 1250, 1158, 1079; ^1H NMR (300 MHz, C_6D_6) δ 6.38 (dd, J = 2.6, 0.7 Hz, 1 H), 4.91 (t, J = 2.6 Hz, 1 H), 4.62 (dd, J = 2.6, 0.7 Hz, 1 H), 3.78 (t, J = 6.1 Hz, 1 H), 2.39−1.46 (series of m, 6 H), 1.05−0.96 (m, 18 H), 0.64−0.56 (m, 6 H), 0.10 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 149.4, 103.0, 96.8, 78.3, 77.6, 31.7, 27.0, 25.8 (3 C), 19.0 (2 C), 6.9 (3 C), 5.3 (3 C), −4.7, −4.9; ES HRMS m/z ($M + Na^+$) calcd 407.2408, obsd 407.2409; $[\alpha]^{20}_D$ +140 (c 0.72, C_6H_6).

Glycosidation of 9. To a stirred CH_2Cl_2 solution (1.0 mL) of **9** (23 mg, 0.060 mmol) and bis-*O*-trimethylsilylthymine (26 mg, 0.096 mmol) was added *N*-iodosuccinimide (22 mg, 0.096 mmol) at rt under N_2. After 1 h, the reaction mixture was partitioned between $CHCl_3$ and saturated $NaHCO_3$ solution. Silica gel chromatography (15% EtOAc/hexanes) of the organic residue gave **10** (28.9 mg, 76%, α/β = 3:1, inseparable) as a colorless syrup.

For the major isomer **10**α: IR ($CHCl_3$, cm^{-1}) 1695, 1470, 1279, 1127; ^1H NMR (300 MHz, $CDCl_3$) δ 8.50 (br s, 1 H), 7.07 (d, J = 0.9 Hz, 1 H), 6.38 (d, J = 8.7 Hz, 1 H), 4.50 (d, J = 7.0 Hz, 1 H), 3.93−3.88 (m, 2 H), 2.07−1.52 (series of m, 9 H), 1.02−0.94 (m, 18 H), 0.74−0.65 (m, 6 H), 0.13 (s, 3 H), 0.10 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4, 150.1, 134.5, 111.6, 93.9, 88.2, 81.4, 78.0, 76.3, 30.8, 28.9, 25.9 (3 C), 18.5, 18.2, 12.7, 6.9 (3 C), 5.2 (3 C), −4.0, −4.7; ES HRMS m/z ($M + Na^+$) calcd 659.1804, obsd 659.1780.

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Deiodination of 10. Iodonucleoside **10** (32 mg, 0.050 mmol) and AIBN (4 mg, 0.025 mmol) were dissolved in dry toluene (2 mL), and Bu_3SnH (16 μL, 0.060 mmol) was added dropwise. The reaction mixture was stirred at 70 °C for 4 h, cooled to rt, diluted with saturated NH_4Cl solution (2 mL), and extracted with ethyl acetate (3 × 2 mL). The combined organic phases were washed with brine, dried, and freed of solvents. The residue was purified by flash chromatography on silica gel (1:4 EtOAc/hexanes) to give **11** as a white foam (21.4 mg, 84%).

For the major isomer **11**α: IR ($CHCl_3$, cm^{-1}) 1688, 1469, 1272; ^1H NMR (300 MHz, $CDCl_3$) δ 8.36 (br s, 1 H), 7.71 (d, J = 1.2 Hz, 1 H), 6.37 (dd, J = 8.1, 1.8 Hz, 1 H), 4.05 (d, J = 5.2 Hz, 1 H), 3.75 (t, J = 8.0 Hz, 1 H), 2.87−2.78 (m, 1 H), 2.06−1.25 (series of m, 10 H), 0.99−0.89 (m, 18 H), 0.64−0.56 (m, 6 H), 0.09 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 150.3, 137.5, 109.7, 97.6, 85.3, 78.4, 75.4, 42.8, 32.0, 29.5, 25.8 (3 C), 18.0, 17.9, 12.5, 6.8 (3 C), 4.7 (3 C), −4.2, −4.9; ES HRMS m/z ($M + Na^+$) calcd 533.2843, obsd 533.2827.

Desilylation of 7. To a stirred solution of **7** (11 mg, 0.035 mmol) in CH_2Cl_2 (0.22 mL) at rt was added trifluoroacetic acid (0.2 mL). After 6 h, the mixture was concentrated in vacuo, and the residue was purified by chromatography on silica gel, eluting with 20−50−80% EtOAc/hexanes to return starting material **7** (1.7 mg, 16%) and provide **12** (5.4 mg, 82%) as a syrup: IR ($CHCl_3$, cm^{-1}) 3285, 1757, 1088; ^1H NMR (300 MHz, $CDCl_3$) δ 4.43 (br d, J = 4.1 Hz, 1 H), 3.95 (br t, J = 8.2 Hz, 1 H), 3.06 (dd, J = 17.7, 6.3 Hz, 1 H), 2.50 (dd, J = 17.7, 2.8 Hz, 1 H), 2.18−1.64 (series of m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 96.0, 76.9, 71.7, 39.0, 32.1, 28.4, 18.2; HRMS: molecular ion too fleeting for accurate mass measurement; $[\alpha]^{20}_D$ +7.9 (c 0.14, $CHCl_3$).

TIPDS Protection of 12. A solution of **12** (16 mg, 0.093 mmol) in THF (3 mL) was admixed with pyridine (38 μL, 0.47 mmol). Silver nitrate (40 g, 0.23 mmol) was introduced, and stirring was maintained for 1 h at rt prior to the addition of $TIPDSCl_2$ (36 μL, 0.11 mmol). After vigorous stirring in the dark for 6 h, the cloudy white reaction mixture was filtered into saturated $NaHCO_3$ solution (5 mL). The product was extracted into CH_2Cl_2 (3 × 5 mL) and purified by flash chromatography on silica gel (5% EtOAc/hexanes) to furnish **13** (35.5 mg, 92%) as a white solid: mp 67−68 C; IR ($CHCl_3$, cm^{-1}) 1789, 1464; ^1H NMR (400 MHz, $CDCl_3$) δ 4.44 (dd, J = 12.0, 8.0 Hz, 1 H), 4.01 (t, J = 9.4 Hz, 1 H), 2.74−2.64 (m, 2 H), 1.98−1.87 (m, 4 H), 1.76−1.71 (m, 1 H), 1.61−1.58 (m, 1 H), 1.08−1.03 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 93.4, 70.5, 66.0, 36.1, 27.0, 24.7, 17.3, 17.2, 17.1, 17.06, 17.02, 17.00, 16.9 (2 C), 16.5, 13.5, 13.4, 12.8, 12.7; ES HRMS m/z ($M + Na^+$) calcd 437.2150, obsd 437.2144; $[\alpha]^{21}_D$ +3.4 (c 0.53, $CHCl_3$).

Reductive Ring Opening of 13. The reaction was carried out according to the procedure described for the preparation of glycal **9** starting with **13** (36 mg, 0.087 mmol), DIBAL-H (1 M toluene solution, 0.13 mL, 0.13 mmol), triethylamine (0.18 mL, 2.60 mmol), and methanesulfonyl chloride (20 μL, 0.52 mmol). The usual workup and silica gel chromatography (10% EtOAc/hexanes) gave **14** as a colorless oil (27 mg, 76%): IR (neat, cm^{-1}) 1728, 1465, 1091; ^1H NMR (300 MHz, $CDCl_3$) δ 9.81 (t, J = 2.5 Hz, 1 H), 4.25 (t, J = 8.7 Hz, 1 H), 4.13 (dd, J = 6.9, 5.3 Hz, 1 H), 2.86−2.75 (m, 1 H), 2.63−2.52 (m, 1 H), 1.87−1.54 (series of m, 6 H), 1.11−0.85 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0, 82.0, 72.8, 68.1, 47.7, 28.7, 26.5, 17.44, 17.40, 17.33 (2 C), 17.30, 17.15 (2 C), 17.12, 17.06, 13.5, 13.4, 12.6, 12.5; ES HRMS m/z ($M + Na^+$) calcd 439.2312, obsd 439.2347; $[\alpha]^{19}_D$ −5.5 (c 0.77, $CHCl_3$).

Methyl Acetal 15. Lactone **8** (34 mg, 0.085 mmol) was dissolved in dry ether (2 mL), and the solution was cooled to −78 °C. DIBAL-H (2 M hexanes solution, 0.085 mL, 0.17 mmol) was added dropwise. After 1 h of stirring, dry MeOH (2 mL) and PTSA (65 mg, 0.34 mmol) were introduced, and the mixture was warmed slowly to rt, refluxed overnight, freed of solvent, diluted with saturated Rochelle's salt solution (10 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried, and evaporated to give an oil. Chromatographic separation (20% EtOAc/hexanes) afforded a mixture of two isomers, the isomerization of which occurred in $CDCl_3$. Acetal **15** (22 mg, 86%) was obtained as a colorless oil: IR ($CHCl_3$, cm^{-1}) 1472, 1144, 1089; ^1H NMR (300 MHz, $CDCl_3$) δ 5.08 (d, J = 4.7 Hz, 1 H), 3.87 (d, J = 5.3 Hz, 1 H), 3.78 (dd, J = 8.9, 6.9 Hz, 1 H), 3.37 (s, 3 H), 2.35−1.52 (series of m, 8 H), 0.87 (s, 9 H), 0.33 (s, 3 H), 0.30 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 128.0, 96.1, 77.6, 75.8, 54.6, 41.4, 31.9, 30.2, 25.9 (3 C), 18.4, 18.0, −4.3, −4.9; ES HRMS m/z ($M + Na^+$) calcd 325.1806, obsd 325.1810; $[\alpha]^{18}_D$ +84.8 (c 0.21, $CHCl_3$).

Desilylation of 15. A THF solution (3 mL) of 15 (27 mg, 0.089 mmol) was treated with TBAF (1 M THF solution, 0.18 mL, 0.18 mmol). After being stirred at rt for 16 h, the reaction mixture was purified on silica gel (eluting with 50% EtOAc/hexanes) to give **16** (14.8 mg, 88%) as a colorless oil: IR ($CHCl_3$, cm^{-1}) 3409 (br), 1441; ^1H NMR (300 MHz, $CDCl_3$) δ 5.07 (d, J = 4.5 Hz, 1 H), 3.83 (dd, J = 5.2, 0.8 Hz, 1 H), 3.60 (t, J = 5.7 Hz, 1 H), 3.38 (s, 3 H), 2.33−1.52 (series of m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.8, 96.0, 76.3, 75.0, 55.0, 41.1, 32.8, 30.5, 19.8; HRMS molecular ion too fleeting for accurate mass measurement; $[\alpha]^{18}_D$ +77.6 (c 0.33, $CHCl_3$).

TIPDS Protection of 16. The reaction was carried out according to the procedure described for the protection of diol **12** starting with **16** (4.2 mg, 0.022 mmol), pyridine (14 μL, 0.18 mmol), $AgNO_3$ (15 mg, 0.089 mmol), and $TIPDSCl_2$ (14 μL, 0.045 mmol). The usual workup and silica gel chromatography (5% EtOAc/hexanes) gave **17** as a colorless oil (6.5 mg, 68%): IR ($CHCl_3$, cm^{-1}) 1465, 1102; ^1H NMR (300 MHz, $CDCl_3$) δ 5.01 (t, J = 5.8 Hz, 1 H), 4.08 (dd, J = 11.9, 7.3 Hz, 1 H), 3.84 (t, J = 9.7 Hz, 1 H), 3.39 (s, 3 H), 2.46−2.35 (m, 1 H), 1.98−1.84 (m, 4 H), 1.65−1.60 (m, 3 H), 1.08−0.95 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 125.9, 88.4, 71.3, 67.8, 55.6, 37.4, 27.7, 25.2, 17.4 (2 C), 17.22, 17.18 (2 C), 17.12 (2 C), 17.09, 17.06, 13.7, 13.5, 12.8, 12.5; ES HRMS m/z ($M + Na^+$) calcd 453.2463, obsd 453.2452; $[\alpha]^{19}_D$ +1.8 (c 0.57, $CHCl_3$).

Spirocyclic Selenoacetal 18. To a solution of acetal **17** (7.5 mg, 0.017 mmol) in anhydrous dichloromethane (0.5 mL) under argon at −20 °C was added boron trifluoride etherate (2.6 μL, 0.021 mmol) dropwise, The resulting mixture was allowed to warm to −10 °C where stirring was maintained for 10 min. The yellow solution was cooled at −20 °C, and phenylselenol (2.2 μL, 0.021 mmol) was added. The reaction mixture was maintained at this temperature for 45 min. By this time, a few drops of pyridine were added, and the mixture was warmed to rt. The solvent was removed under reduced pressure, and the resulting crude product was purified by flash chromatography, eluting with 5% EtOAc/hexanes to give **18** (6 mg, 62%) as an anomeric mixture.

For the major anomer: ^1H NMR (300 MHz, $CDCl_3$) δ 7.67−7.63 (m, 2 H), 7.33−7.28 (m, 3 H), 5.96 (t, J = 6.8 Hz, 1 H), 4.35−4.30 (m, 1 H), 3.74−3.70 (m, 1 H), 2.54−1.59 (series of m, 8 H), 1.12−0.92 (m, 28 H); HRMS molecular ion too fleeting for accurate mass measurement.

Acetonide 20. To a stirred solution of **19** (63.2 mg, 0.21 mmol) in 2,2-dimethoxypropane (4 mL) was added *p*-toluenesulfonic acid (2 mg). The reaction mixture was refluxed for 30 min, and potassium carbonate (5 mg) was introduced. Concentration was effected to afford a dark oil that was subjected to flash chromatography on silica gel (10% EtOAc/hexanes) to give **20** as a faint yellow oil (71.5 mg, 100%). Spectroscopic data are identical to those reported.[4]

Lactol 21. A solution of **20** (21.1 mg, 0.062 mmol) in dry ether (4 mL) was cooled to −78 °C, treated dropwise with DIBAL-H (2 M hexanes solution, 0.06 mL, 0.12 mmol), stirred for 1 h, quenched with saturated Rochelle's salt solution (5 mL), and stirred for 5 h while warming to rt. The separated aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were dried and evaporated to provide a crude oil that was subjected to

flash chromatography on silica gel (10% EtOAc/hexanes) to give **21** as a pale oil (21.2 mg, 100%, α/β = 1:5).

For the major isomer **21**β: IR (neat, cm^{-1}) 3386, 1255, 1099; ^1H NMR (300 MHz, $CDCl_3$) δ 5.22 (d, J = 11.5 Hz, 1 H), 5.07 (d, J = 11.5 Hz, 1 H), 4.59−4.48 (m, 2 H), 3.93−3.87 (m, 1 H), 1.92−1.59 (series of m, 6 H), 1.46 (s, 3 H), 1.31 (s, 3 H), 0.92 (s, 9 H), 0.15 (s, 3 H), 0.14 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 112.0, 102.5, 95.9, 88.3, 83.7, 78.4, 30.0, 26.4, 25.8 (3 C), 25.1, 18.3, 17.9 (2 C), −4.5, −4.9; ES HRMS *m*/*z* ($M + Na^+$) calcd 367.1917, obsd 367.1918.

Glycal 22. To a stirred solution of **21** (66 mg, 0.19 mmol) and carbon tetrachloride (28 μL, 0.29 mmol) in dry THF (0.5 mL) at −78 °C under an argon atmosphere was added tris(dimethylamino)-phosphine (38 μL, 0.21 mmol). After 30 min, the mixture was warmed in an ice−water bath, and after 3 min at 0 °C, the entire reaction mixture was taken up in an argon-flushed syringe and added rapidly to a cold (−78 °C) stirred solution of lithium (10 mg) in anhydrous liquid ammonia (5 mL). The reaction mixture was warmed and ammonia was allowed to reflux. Anhydrous ammonium chloride (77 mg, 1.44 mmol) was added to the blue reaction mixture. The resulting colorless mixture was diluted with ether (5 mL), and anhydrous sodium sulfate was added. The ethereal suspension was filtered, and the solids were washed with ether. The combined filtrates were concentrated and the crude was subjected to column chromatography on silica gel (triethylamine pretreated, 10−50% ether/petroleum ether) to afford **22** (37 mg, 73%) and **23** (9.7 mg, 15%).

For **22**: IR (neat, cm^{-1}) 3398, 1252, 1154; ^1H NMR (300 MHz, C_6D_6) δ 6.30 (dd, J = 2.7, 0.7 Hz, 1 H), 4.83 (t, J = 2.7 Hz, 1 H), 4.26 (d, J = 2.1 Hz, 1 H), 3.62 (t, J = 6.1 Hz, 1 H), 2.16−2.08 (m, 1 H), 1.91−1.66 (m, 5 H), 1.47−1.39 (m, 1 H), 0.97 (s, 9 H), 0.028 (s, 3 H), 0.001 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 150.3, 103.3, 96.9, 78.3, 77.3, 32.0, 26.8, 26.1 (3 C), 19.2, 18.4, −4.4, −4.7; ES HRMS *m*/*z* ($M + Na^+$) calcd 293.1549, obsd 293.1547; $[\alpha]^{19}_D$ +178 (*c* 0.22, C_6H_6).

For **23**: IR (neat, cm^{-1}) 1253, 1142, 1104; ^1H NMR (300 MHz, $CDCl_3$) δ 4.78 (dd, J = 5.8, 5.0 Hz, 1 H), 4.39 (d, J = 6.2 Hz, 1 H), 4.20 (dd, J = 9.7, 4.6 Hz, 1 H), 4.05 (d, J = 9.4 Hz, 1 H), 3.63 (dd, J = 8.5, 6.7 Hz, 1 H), 2.07−2.01 (m, 2 H), 1.92−1.77 (m, 2 H), 1.66−1.57 (m, 1 H), 1.55 (s, 3 H), 1.38−1.34 (m, 1 H), 1.32 (s, 3 H), 0.89 (s, 9 H), −0.04 (s, 3 H), −0.07 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 111.9, 92.8, 84.9, 82.3, 79.8, 73.6, 31.1, 29.1, 26.5, 25.8 (3 C), 25.2, 18.4, 17.9, −4.3, −5.1; ES HRMS *m*/*z* ($M + Na^+$) calcd 351.1968, obsd 351.1979; $[\alpha]^{20}_D$ +42.8 (*c* 0.50, $CHCl_3$).

Desilylation of 22. A THF solution (0.5 mL) of **22** (16 mg, 0.060 mmol) was treated with TBAF (1 M THF solution, 0.12 mL, 0.12 mmol). After the solution was stirred at rt overnight, another portion of TBAF (1 M THF solution, 0.12 mL, 0.12 mmol) was added, and stirring was continued for an additional 2 days. The reaction mixture was purified on silica gel eluting with 20−100% ether/petroleum ether (pretreated with triethylamine) to give **24** (8.9 mg, 96%) as a colorless oi: IR (neat, cm^{-1}) 3336, 1147, 1035; ^1H NMR (300 MHz, C_6D_6) δ 6.05 (dd, J = 2.7, 0.9 Hz, 1 H), 4.78 (t, J = 2.7 Hz, 1 H), 4.08 (br s, 1 H), 3.54 (m, 1 H), 2.19−2.10 (m, 1 H), 1.92−1.61 (m, 5 H), 1.41−1.34 (m, 2 H); ^{13}C NMR (75 MHz, C_6D_6) δ 149.0, 128.4, 104.7, 97.5, 76.5, 76.4, 31.3, 26.5, 19.8; HRMS molecular ion too fleeting for accurate mass measurement; $[\alpha]^{21}_D$ +132 (*c* 0.12, C_6H_6).

TIPDS Protection of 24. A sample of **24** (11.2 mg, 0.072 mmol) was treated with collidine (25 μL, 0.19 mmol), AgOTf (44 mg, 0.17 mmol), and $TIPDSCl_2$ (28 μL, 0.086 mmol) in 1 mL of dry DMF at 0 C. After 1 h, the reaction mixture was purified on silica gel chromatography (0−10% ether/petroleum ether, pretreated with triethylamine) to give **25** as a colorless oil (17.7 mg, 62%): IR (neat, cm^{-1}) 1161, 1142, 1113; ^1H NMR (300 MHz, C_6D_6) δ 6.07 (t, J = 2.7 Hz, 1 H), 5.60 (br s, 1 H), 5.20 (dd, J = 2.9, 1.6 Hz, 1 H), 4.07 (dd, J = 12.4, 7.4 Hz, 1 H), 2.32−2.24 (m, 1 H), 1.96−1.81 (m, 4 H), 1.58−1.47 (m, 1 H), 1.17−0.90 (m, 28 H); ^{13}C NMR (75 MHz, C_6D_6) δ 145.6, 107.2, 96.6, 72.5, 71.5, 27.6, 24.8, 17.7, 17.57, 17.51 (2 C), 17.47, 17.39, 17.36 (2 C), 17.32, 14.1, 13.9, 13.6, 13.4; ES HRMS *m*/*z* ($M + Na^+$) calcd 421.2206, obsd 421.2215; $[\alpha]^{23}_D$ +7.8 (*c* 0.45, C_6H_6).

Glycosidation of 25. The reaction was carried out according to the procedure described for the reaction of glycal **9** starting with **25** (16 mg, 0.040 mmol), bis-*O*-TMS-thymine (13.6 mg, 0.060 mmol), and NIS (16.3 mg, 0.060 mmol). The usual workup and silica gel chromatography (10−25% ethyl acetate/hexanes) gave **26** as a white foam (18 mg, 70%): IR ($CHCl_3$, cm^{-1}) 1696, 1465; ^1H NMR (500 MHz, $CDCl_3$) δ 8.34 (br s, 1 H), 7.47 (d, J = 0.9 Hz, 1 H), 6.31 (d, J = 1.9 Hz, 1 H), 4.36 (dd, J = 7.5, 1.9 Hz, 1 H), 3.88 (t, J = 9.5 Hz, 1 H), 3.80 (d, J = 7.5 Hz, 1 H), 2.05−2.01 (m, 1 H), 1.90 (d, J = 0.9 Hz, 3 H), 1.87−1.79 (m, 4 H), 1.72−1.65 (m, 1 H), 1.11−0.85 (m, 28 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4, 149.8, 134.7, 111.0, 99.9, 92.0, 91.5, 72.2, 67.2, 30.6, 26.6, 25.4, 17.44, 17.39 (2 C), 17.37, 17.14, 17.07, 17.02, 16.97, 16.93, 13.6, 13.3, 12.7, 12.5; ES HRMS *m*/*z* ($M + Na^+$) calcd 673.1602, obsd 673.1609; $[\alpha]^{20}_D$ −9.6 (*c* 0.57, $CHCl_3$).

Nucleoside 27. The deiodination reaction was carried out according to the procedure described for the reaction of **10** starting with **26** (15 mg, 0.023 mmol), Bu_3SnH (8 μL, 0.028 mmol), and AIBN (2 mg, 0.012 mmol). The usual workup and silica gel chromatography (10−25% ethyl acetate/hexanes) gave deiodonation product as a white foam. This product was then treated with TBAF (1 M solution in THF, 50 μL, 0.050 mmol) in 1 mL THF. After purification on silica gel chromatography (10−20% EtOH/toluene) the final product **27** was obtained as a white solid (6.5 mg, 100%): UV (MeOH) λ_{max} 268 nm (ϵ 6600); ^1H NMR (500 MHz, CD_3OD) δ 8.19 (d, J = 1.1 Hz, 1 H), 6.23 (t, J = 6.4 Hz, 1 H), 4.24 (t, J = 5.2 Hz, 1 H), 3.91 (t, J = 7.7 Hz, 1 H), 2.32−2.26 (m, 2 H), 2.05−1.95 (m, 2 H), 1.87 (d, J = 1.1 Hz, 3 H), 1.79−1.71 (m, 3 H), 1.58−1.54 (m, 1 H); ^{13}C NMR (75 MHz, CD_3OD) δ 166.5, 152.4, 139.0, 111.0, 96.0, 85.5, 76.6, 736., 41.1, 32.5, 29.8, 19.2, 12.5; ES HRMS *m*/*z* ($M + Na^+$) calcd 305.1113, obsd 305.1116; $[\alpha]^{20}_D$ +45.0 (*c* 0.10, CH_3OH).

Supporting Information Available: High-field ^1H NMR spectra for all compounds described herein and NOESY spectra for compounds **10**, **15**, **21**, and **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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