Development of a Generic Stereocontrolled Pathway to Fully Hydroxylated Spirocarbocyclic Nucleosides as a Prelude to RNA Targeting

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In celebration of a 35-year professional relationship with Steve Ley, during which time he has established for himself a stellar career marked by many significant contributions to organic chemistry.

Abstract: Osmylation of the enantiopure conjugated enones **4** and **15** proceeded predominantly or exclusively from the α-face to give the 2′,3′-diols **6** and **16**. Ensuing conversion into the acetonide allowed for sequential stereocontrolled reduction with L-Selectride, and esterification with triflic anhydride was utilized to form triflates **11** and **19**. The heightened electrophilicity of these intermediates made possible S_N2 displacements with several nucleobases as promoted with potassium hydride in *N*,*N*-dimethylformamide at room temperature. Suitable deprotection measures led to the targeted compounds.

Key words: spirocarbocycles, nucleosides, triflate displacements, osmylation, acetonides

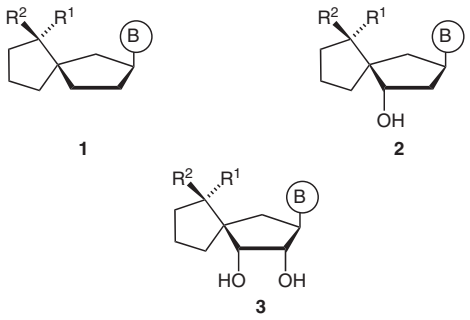

Figure 1

As a direct consequence of the potent antitumor and antiviral properties of select naturally occurring carbocyclic nucleosides,[1] many ingenious inroads have been made into maximizing the structural diversity of synthetic analogues.[2] The innovative modifications have focused on the alteration of anomeric substituents,[3] the desaturation of the cyclopentane pseudosugar, and various means to achieve rigidification of the molecular architecture.[4] Our own efforts in this area have given consideration to spirocyclic restriction.[5] Successful synthetic approaches to the *syn* and *anti* epimers defined by **1**[6] and **2**[7] (Figure 1) have heretofore been reported. As yet unexplored has been a strategy for generating the maximally functionalized members of the class specified by **3**, which is of particular interest because of their structural relationship to aristeromycin.[8] The present report fills this gap by providing the details surrounding a synthetic protocol applicable to the efficient stereocontrolled introduction of both pyrimidine and purine nucleobases to generate the spirocyclic carbanucleosides.

Preliminary Evaluation of S_N2 Reactivity Levels

As depicted in Scheme 1, our initial efforts were focused on the use of readily available cyclopentenone **4**[6,7] as the building block of choice. Typical osmylation conditions resulted in its smooth conversion into the diols **5** and **6**, favoring the latter by a factor of 5. After chromatographic separation, the search for a suitable protecting group was initiated. When two sets of O-allylation conditions were applied to **6** and found to deliver only **7**, it was made clear that β-elimination had to be avoided. Recourse to 2,2-dimethoxypropane and a catalytic quantity of *p*-toluenesulfonic acid positively addressed this issue, giving rise to **8a** in 94% yield. Equivalent success was realized in formation of the benzylidene acetal **8b** (benzaldehyde dimethyl acetal, PTSA; 99% yield), siloxane **8c** [1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane ($TIPDSCl_2$), $AgNO_3$, py, THF; 98% yield],[9] and carbonate **8d** (phosgene, DMAP, CH_2Cl_2; 80% yield). The first three of these protected variants could be successfully reduced with L-Selectride in tetrahydrofuran and efficaciously transformed further into mesylates **9a–c** (R′ = Ms). The reduction of **8d** warrants comment. In contrast to **8a–c**, which were converted exclusively into their α-carbinols **9a–c** (R′ = H), **8d** exhibited reversed stereoselectivity when reduced with sodium borohydride in MeOH and produced a carbinol mixture rich in the β-anomer [(α/β) 1:3]. The significantly reduced levels of steric shielding on the α-face of **8d** are considered responsible for this crossover.

In atypical fashion,[6] mesylates **9a–c** (R′ = Ms) proved totally unreactive to S_N2 displacement involving adenine in *N*,*N*-dimethylformamide at 80 °C as the test conditions. Experiments with carbonate **9d** (R′ = Ms) showed it to be subject to degradation when comparably treated. The approach taken to rectify the obviously low reactivity levels was to involve the triflate derivative instead. Acetonide **11** was accessed without difficulty and its adaptability in the present setting is presented below.

Enabling Technology for the 5′-β Analogs

The direct and selective introduction of several nucleobase units into **11** proceeded slowly without total con-

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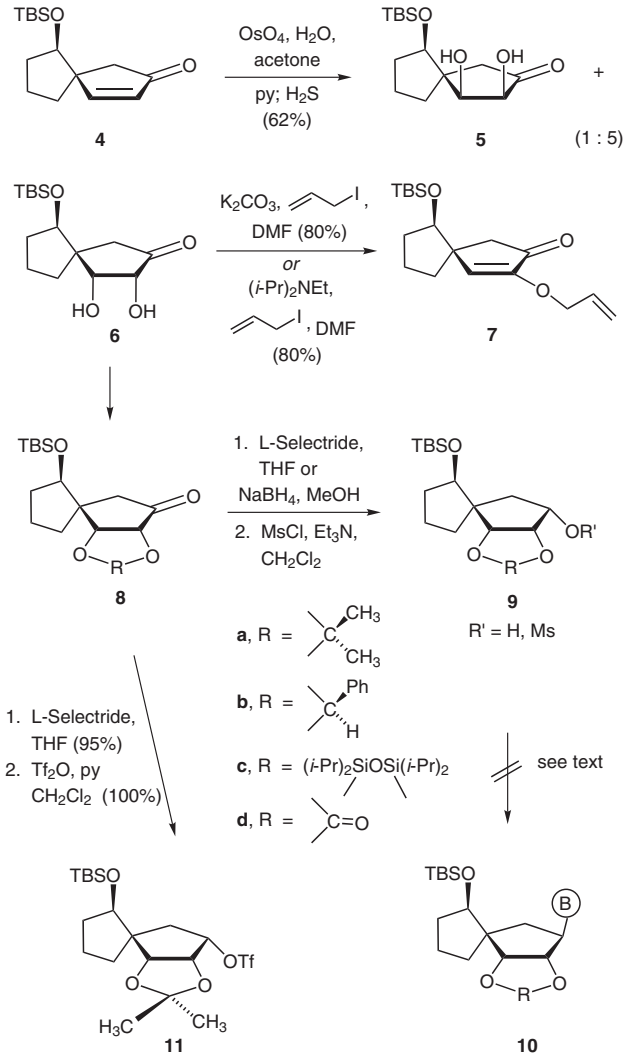
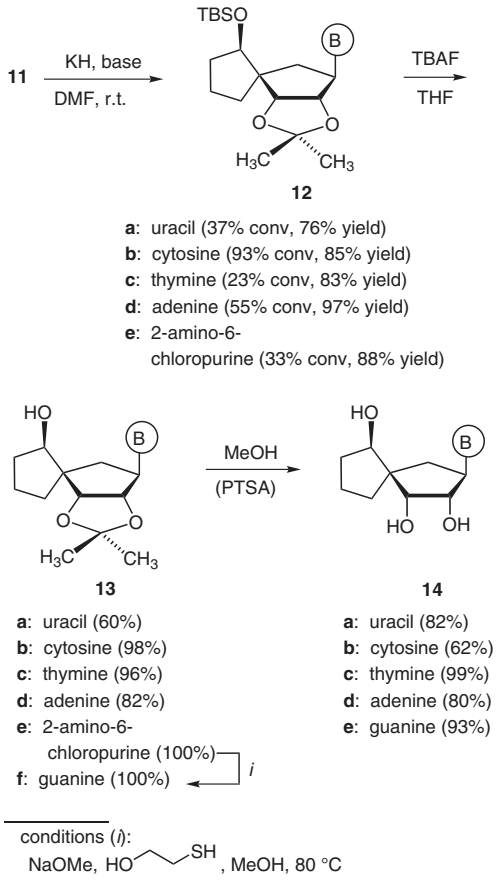


Scheme 1



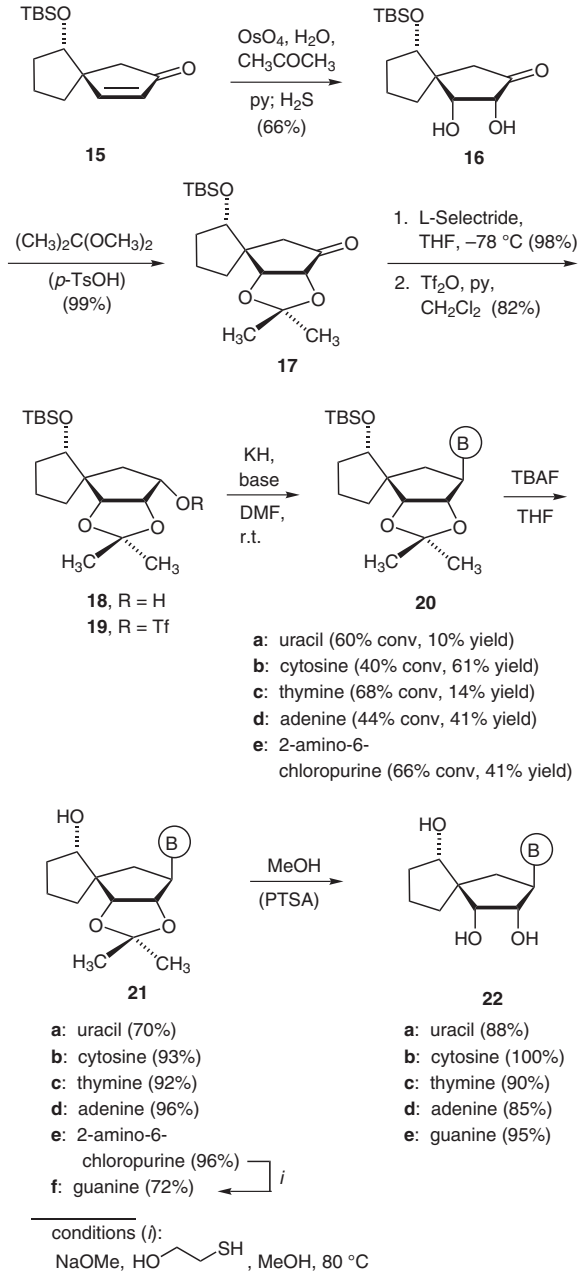
Scheme 2

sumption of the triflate. Notwithstanding, unreacted starting material could be readily separated from the resulting protected nucleosides, such that the adjusted yields were quite acceptable (76–97%, Scheme 2). The level of throughput was highly variable, ranging from a low of 23% conversion for thymine to a high of 93% for cytosine. The guanine subunit was introduced indirectly as has become customary. Thus, initial displacement of the triflate with configurational inversion to give **12e** and desilylation with the generation of **13e** was followed by a hydrolytic removal of the chlorine substituent with 2-sulfanylethanol and sodium methoxide in hot MeOH.[7,10] The final chemoselective hydrolysis of the acetonide functionality in MeOH containing *p*-toluenesulfonic acid needed no optimization.

Synthesis of the 5′-α Nucleoside Diastereomers

Advantage was taken of the lessons derived from the acquisition of **14a–e** for the preparation of those spirocarbocyclic nucleosides epimeric at C-5′ (Scheme 3). Nevertheless, differences in reactivity surfaced immediately. Thus, unlike **4** which experiences attack by osmium tetraoxide from both of its olefinic surfaces, **15** undergoes the analogous reaction in an entirely stereoselective manner to furnish only **16**. The corresponding acetonide **17** was expected as before to be compatible with the reaction conditions that were to follow, and to prove amenable to scale-up should such action become necessary. Under the conditions of L-Selectride reduction, **17** was converted into alcohol **18** from which the triflate **19** was crafted. The reactivity observations made during the course of the S_N2 displacements on **19** by the five nucleobases are in full agreement with the notion that the conformation adopted by the second five-membered ring interferes sterically with the trajectory normally operative in bimolecular displacement processes. In addition, the shelf stability of **19** is significantly less than that of **11**. Utilization of two consecutive deblocking maneuvers then led via **21a–f** to triols **22a–e**.

In summary, an enantioselective synthesis of ten spirocarbocyclic nucleosides was developed, allowing for the two different configurations at C-5′. Unprecedented involvement of triflate intermediates was relied upon to gain sufficient reactivity for effecting installation of the purine or pyrimidine bases with high fidelity at the anomeric center. Evaluation of the biological properties of **14** and **22** is in progress.



Scheme 3

Infrared Spectra were recorded on a Perkin Elmer 1600 Series FT-IR spectrophotometer. ^{1}H NMR spectra were measured on a Bruker DPX-500 in the indicated solvent. Mass spectra were recorded at The Ohio State University Campus Chemical Instrumentation Center or at Chemistry Department Mass Spectrometry Facility. Column chromatographic purifications were performed on silica gel (230–400 mesh). All reactions were performed under N_2 unless otherwise noted.

Keto Diols 5, 6, and 16; General Procedure

α,β-Unsaturated ketone **4** or **15** (0.62 g, 2.3 mmol), H_2O (6.3 mL), acetone (63 mL), py (0.4 mL, 4.7 mmol), and OsO_4 (0.65 g, 2.6 mmol) were combined and stirred for 2 h. H_2S was bubbled through the solution until reduction of the osmate ester was complete by TLC. The solution was filtered through a pad of Celite, and the filtrate was quenched with sat. $NaHCO_3$ soln prior to extraction with Et_2O (3 × 150 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo, and the residue was purified by column chromatography (silica gel, hexanes–EtOAc 5:1).

5

White solid.

Yield: 90 mg (12%).

Mp 105 °C.

$[\alpha]_D^{20}$ +7.7 (*c* 1.0, $CHCl_3$).

IR (CH_2Cl_2): 3555, 1754, 1471 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.33 (d, *J* = 3.8 Hz, 1 H), 4.21–4.18 (m, 1 H), 4.15 (t, *J* = 4.8 Hz, 1 H), 2.36–1.45 (series of m, 8 H), 0.91 (s, 9 H), 0.12 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 215.2, 80.1, 78.2, 75.0, 49.5, 42.4, 33.8, 32.4, 25.6 (3C), 20.2, 17.8, –4.3, –5.1.

ES HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{28}O_4Si$: 323.1649; found: 323.1653.

6

White solid.

Yield: 0.34 g (50%).

Mp 84–85 °C.

$[\alpha]_D^{20}$ –38.5 (*c* 1.1, $CHCl_3$).

IR (CH_2Cl_2): 3557, 1751, 1471 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.49 (dd, *J* = 4.6, 1.6 Hz, 1 H), 4.35 (d, *J* = 4.5 Hz, 1 H), 3.91 (t, *J* = 5.8 Hz, 1 H), 2.32–1.51 (series of m, 8 H), 0.89 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 216.1, 80.7, 78.0, 71.7, 51.1, 43.0, 33.1, 31.2, 25.8 (3C), 19.8, 17.9, –4.3, –4.9.

ES HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{28}O_4Si$: 323.1649; found: 323.1655.

16

White solid.

Yield: 0.10 g (66%).

Mp 102 °C.

$[\alpha]_D^{20}$ +14.7 (*c* 1.6, $CHCl_3$).

IR (CH_2Cl_2): 3552, 1750 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.41 (dd, *J* = 4.5, 1.6 Hz, 1 H), 4.00–3.97 (m, 2 H), 2.74–1.49 (series of m, 8 H), 0.83 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 216.7, 78.3, 77.4, 76.7, 51.0, 39.0, 33.6, 32.1, 25.7 (3C), 19.6, 17.8, –4.0, –5.1.

ES HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{28}O_4Si$: 323.1649; found: 323.1647.

Protocol To Give Acetonides 8a and 17; General Procedure

Keto diols **6** or **16** (32 mg, 0.1 mmol), 2,2-dimethoxypropane (2 mL), and PTSA (2 mg, 0.01 mmol) were combined and heated to 80 °C. The mixture was stirred for 2 h, allowed to cool to r.t., quenched with sat. $NaHCO_3$ soln, and extracted with Et_2O (3 × 30 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo, and the residue was purified by column chromatography (silica gel, hexanes–EtOAc 20:1).

8a

Yield: 34 mg (94%).

$[\alpha]_D^{20}$ –106.5 (*c* 1.0, $CHCl_3$).

IR (neat): 1759, 1472, 1271 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.65 (d, *J* = 5.4 Hz, 1 H), 4.28 (d, *J* = 5.4 Hz, 1 H), 3.85 (t, *J* = 7.8 Hz, 1 H), 2.76–1.54 (series of m, 8 H), 1.44 (s, 3 H), 1.37 (s, 3 H), 0.86 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 212.6, 110.9, 81.4, 79.9, 79.3, 50.4, 43.9, 31.9, 28.5, 26.8, 25.8 (3C), 19.1, 17.9, –4.6, –5.1.

EI HRMS: *m/z* $[M]^+$ calcd for $C_{18}H_{32}O_4Si$: 340.2064; found: 340.2097.

17

Yield: 104 mg (99%).

$[\alpha]_D^{20}$ –77.6 (*c* 1.7, $CHCl_3$).

IR (neat): 1758, 1251, 1086 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.37 (d, *J* = 5.0 Hz, 1 H), 4.27 (d, *J* = 5.0 Hz, 1 H), 3.95 (t, *J* = 8.1 Hz, 1 H), 2.48–1.39 (series of m, 8 H), 1.39 (s, 3 H), 1.33 (s, 3 H), 0.82 (s, 9 H), 0.06 (s, 3 H), 0.02 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 213.3, 111.1, 85.3, 79.6, 79.0, 50.3, 40.7, 32.0, 30.8, 26.9, 25.6 (3C), 25.0, 19.6, 17.8, –4.1, –5.0.

ES HRMS: *m/z* $[M + Na]^+$ calcd for $C_{18}H_{32}O_4Si$: 363.1962; found: 363.1967

Table 1 Characterization of Products

Product	Mp (°C)	$[\alpha]_D^{20}$ (*c*, solvent)	^{1}H NMR (500 MHz), δ	^{13}C NMR (125 MHz), δ	ES or EI HRMS, *m/z*
Acetonides **12a–e** and **20a–e**					
12a	185	–47.8 (*c* 0.7, $CHCl_3$)	($CDCl_3$) 8.46 (s, NH), 7.17 (d, *J* = 8.1 Hz, 1 H), 5.73 (dd, *J* = 8.0, 2.2 Hz, 1 H), 4.77 (d, *J* = 6.7 Hz, 1 H), 4.69–4.65 (m, 2 H), 3.81 (t, *J* = 7.4 Hz, 1 H), 2.30–1.27 (series of m, 8 H), 1.56 (s, 3 H), 1.33 (s, 3 H), 0.94 (s, 9 H), 0.09 (s, 6 H)	($CDCl_3$) 162.7, 150.4, 141.8, 113.5, 102.5, 82.5, 78.7, 78.3, 62.7, 52.9, 39.3, 32.2, 30.4, 26.7, 25.8 (3C), 25.0, 19.4, 18.0, –4.2, –4.9	$[M + Na]^+$ calcd for $C_{22}H_{36}N_2O_5Si$: 459.2285; found: 459.2274
12b		–33.1 (*c* 1.0, $CHCl_3$)	($CDCl_3$) 8.07 (d, *J* = 5.7 Hz, 1 H), 6.09 (d, *J* = 5.7 Hz, 1 H), 5.17–5.15 (m, 1 H), 4.89 (s, NH_2), 4.84 (d, *J* = 6.1 Hz, 1 H), 4.59 (d, *J* = 6.0 Hz, 1 H), 4.23–4.22 (m, 1 H), 2.23–1.43 (series of m, 8 H), 1.51 (s, 3 H), 1.33 (s, 3 H), 0.90 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 3 H)	($CDCl_3$) 164.6, 157.7, 110.3, 99.2, 85.5, 82.6, 81.7, 60.3, 57.6, 39.9, 34.1, 32.0, 26.5, 25.8 (3C), 24.2, 21.0, 20.6, 18.0, –4.3, –4.9	$[M + Na]^+$ calcd for $C_{22}H_{37}N_3O_4Si$: 458.2476; found: 458.2445
12c	205	–36.8 (*c* 0.6, $CHCl_3$)	($CDCl_3$) 8.19 (s, NH), 6.98 (s, 1 H), 4.77 (d, *J* = 6.3 Hz, 1 H), 4.70–4.66 (m, 2 H), 3.80 (t, *J* = 7.6 Hz, 1 H), 2.30–1.27 (series of m, 8 H), 2.06 (s, 3 H), 1.56 (s, 3 H), 1.33 (s, 3 H), 0.95 (s, 9 H), 0.10 (s, 6 H)	($CDCl_3$) 163.2, 150.5, 137.7, 113.4, 111.0, 82.5, 78.7, 78.3, 62.2, 52.8, 39.3, 32.1, 30.4, 26.7, 25.8 (3C), 25.0, 19.4, 18.0, 12.4, –4.1, –4.9	$[M + Na]^+$ calcd for $C_{23}H_{38}N_2O_5Si$: 473.2442; found: 473.2435
12d		–37.3 (*c* 1.1, $CHCl_3$)	($CDCl_3$) 8.31 (s, 1 H), 7.83 (s, 1 H), 5.77 (s, NH_2), 5.00 (dd, *J* = 7.4, 6.1 Hz, 1 H), 4.94 (d, *J* = 7.6 Hz, 1 H), 4.76–4.71 (m, 1 H), 3.85 (t, *J* = 7.8 Hz, 1 H), 2.35–1.33 (series of m, 8 H), 1.57 (s, 3 H), 1.33 (s, 3 H), 0.95 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H)	($CDCl_3$) 155.4, 152.7, 150.2, 139.5, 120.3, 113.5, 83.8, 78.9, 77.9, 60.9, 53.3, 40.6, 32.3, 30.3, 26.7, 25.8 (3C), 24.9, 19.4, 18.0, –4.2, –5.0	$[M + Na]^+$ calcd for $C_{23}H_{37}N_5O_3Si$: 482.2557; found: 482.2576
12e	166	–23.1 (*c* 1.1, $CHCl_3$)	($CDCl_3$) 7.80 (s, 1 H), 5.10 (s, NH_2), 4.98–4.96 (m, 1 H), 4.91 (d, *J* = 7.7 Hz, 1 H), 4.64–4.58 (m, 1 H), 3.84 (t, *J* = 8.2 Hz, 1 H), 2.66 (t, *J* = 12.7 Hz, 1 H), 2.34–2.29 (m, 1 H), 1.93–1.30 (series of m, 6 H), 1.57 (s, 3 H), 1.34 (s, 3 H), 0.97 (s, 9 H), 0.10 (s, 6 H)	($CDCl_3$) 158.6, 153.7, 151.4, 141.6, 126.0, 113.7, 83.2, 78.6, 77.7, 60.9, 53.1, 40.1, 32.2, 30.2, 26.6, 25.9 (3C), 24.9, 19.3, 18.1, –4.1, –4.9	$[M + Na]^+$ calcd for $C_{23}H_{36}ClN_5O_3Si$: 516.2168; found: 516.2157
20a		+3.7 (*c* 0.9, $CHCl_3$)	($CDCl_3$) 8.48 (s, NH), 7.22 (d, *J* = 8.1 Hz, 1 H), 5.73 (dd, *J* = 8.0, 2.4 Hz, 1 H), 4.77–4.67 (m, 2 H), 4.68 (d, *J* = 5.9 Hz, 1 H), 3.95 (t, *J* = 6.9 Hz, 1 H), 1.98–1.26 (series of m, 8 H), 1.55 (s, 3 H), 1.31 (s, 3 H), 0.92 (s, 9 H), 0.10 (s, 3 H), 0.08 (s, 3 H)	($CDCl_3$) 162.7, 150.5, 142.0, 113.6, 102.5, 83.0 (2C), 79.2, 62.4, 53.8, 35.2, 32.2, 29.6, 26.5, 25.8 (3C), 25.0, 19.9, 18.0, –4.2, –4.7	$[M + Na]^+$ calcd for $C_{22}H_{36}N_2O_5Si$: 459.2285; found: 459.2316
20b	143	+29.2 (*c* 1.0, $CHCl_3$)	($CDCl_3$) 8.01 (d, *J* = 5.7 Hz, 1 H), 6.05 (d, *J* = 5.7 Hz, 1 H), 5.27–5.24 (m, 1 H), 4.85 (s, NH_2), 4.65 (d, *J* = 6.4 Hz, 1 H), 4.14 (d, *J* = 6.5 Hz, 1 H), 3.93–3.92 (m, 1 H), 2.24–1.24 (series of m, 8 H), 1.48 (s, 3 H), 1.29 (s, 3 H), 0.79 (s, 9 H), 0.05 (s, 3 H), –0.01 (s, 3 H)	($CDCl_3$) 164.7, 164.6, 157.6, 111.2, 99.1, 85.6, 83.2, 80.0, 78.0, 57.6, 34.7, 33.2, 29.4, 26.3, 25.7 (3C), 24.5, 20.2, 17.9, –4.2, –5.0	$[M + Na]^+$ calcd for $C_{22}H_{37}N_3O_4Si$: 458.2445; found: 458.2442
20c	142	+3.5 (*c* 0.4, $CHCl_3$)	($CDCl_3$) 8.12 (s, NH), 7.01 (d, *J* = 0.9 Hz, 1 H), 4.76–4.68 (m, 2 H), 4.39 (d, *J* = 7.1 Hz, 1 H), 3.96 (t, *J* = 7.1 Hz, 1 H), 2.42–1.23 (series of m, 8 H), 1.94 (s, 3 H), 1.55 (s, 3 H), 1.32 (s, 3 H), 0.93 (s, 9 H), 0.11 (s, 3 H), 0.09 (s, 3 H)	($CDCl_3$) 163.2, 150.5, 137.8, 113.6, 111.0, 82.89, 82.87, 79.1, 61.9, 53.6, 35.0, 32.2, 29.4, 26.5, 25.8 (3C), 25.1, 19.9, 18.0, 12.4, –4.1, –4.8	$[M + Na]^+$ calcd for $C_{23}H_{38}N_2O_5Si$: 473.2442; found: 473.2440

Table 1 Characterization of Products (continued)

Product	Mp (°C)	$[\alpha]_D^{20}$ (*c*, solvent)	^{1}H NMR (500 MHz), δ	^{13}C NMR (125 MHz), δ	ES or EI HRMS, *m/z*
20d	198	+15.5 (*c* 1.7, $CHCl_3$)	($CDCl_3$) 8.32 (s, 1 H), 7.84 (s, 1 H), 5.81 (s, NH_2), 5.02 (dd, *J* = 7.5, 5.5 Hz, 1 H), 4.80–4.75 (m, 1 H), 4.53 (d, *J* = 7.5 Hz, 1 H), 4.00 (t, *J* = 6.7 Hz, 1 H), 2.10–1.41 (series of m, 8 H), 1.55 (s, 3 H), 1.30 (s, 3 H), 0.90 (s, 9 H), 0.09 (s, 3 H), 0.06 (s, 3 H)	($CDCl_3$) 155.5, 152.7, 150.2, 139.5, 120.3, 113.8, 84.1, 82.9, 79.0, 60.4, 54.3, 36.7, 32.5, 29.3, 26.5, 25.7 (3C), 24.9, 20.1, 18.0, –4.1, –4.9	$[M + Na]^+$ calcd for $C_{23}H_{37}N_5O_3Si$: 482.2557; found: 482.2530
20e		–19.5 (*c* 1.2, $CHCl_3$)	($CDCl_3$) 7.80 (s, 1 H), 5.19 (s, NH_2), 4.95–4.92 (m, 1 H), 4.67–4.62 (m, 1 H), 4.49 (d, *J* = 7.5 Hz, 1 H), 3.99–3.97 (m, 1 H), 2.81–1.23 (series of m, 8 H), 1.54 (s, 3 H), 1.30 (s, 3 H), 0.91 (s, 9 H), 0.09 (s, 3 H), 0.06 (s, 3 H)	($CDCl_3$) 158.8, 153.7, 151.3, 141.6, 125.9, 113.9, 83.5, 82.7, 78.8, 60.5, 54.0, 36.0, 32.4, 29.2, 26.5, 25.8 (3C), 24.9, 20.0, 18.0, –4.1, –4.9	$[M + Na]^+$ calcd for $C_{23}H_{36}ClN_5O_3Si$: 516.2168; found: 516.2163
Protected Hydroxy Nucleosides **13a–e** and **21a–e**					
13a	217	–24.3 (*c* 1.0, $CHCl_3$)	($CDCl_3$) 8.87 (s, NH), 7.85 (d, *J* = 8.1 Hz, 1 H), 5.73 (d, *J* = 8.0 Hz, 1 H), 4.86 (d, *J* = 6.7 Hz, 1 H), 4.80–4.72 (m, 2 H), 3.96 (t, *J* = 6.9 Hz, 1 H), 2.47–1.55 (series of m, 8 H), 1.53 (s, 3 H), 1.30 (s, 3 H)	($CDCl_3$) 163.2, 151.0, 143.6, 112.9, 102.4, 83.7, 79.5, 78.7, 62.3, 53.2, 40.0, 32.2, 31.3, 26.9, 25.2, 19.9	$[M + Na]^+$ calcd for $C_{16}H_{22}N_2O_5$: 345.1420; found: 345.1438
13b	149	–11.4 (*c* 0.8, $CHCl_3$)	($CDCl_3$) 8.05 (d, *J* = 5.9 Hz, 1 H), 6.15 (d, *J* = 5.7 Hz, 1 H), 5.22 (d, *J* = 5.6 Hz, 1 H), 5.10 (s, NH_2), 4.70 (d, *J* = 5.3 Hz, 1 H), 4.59 (dd, *J* = 5.5, 1.7 Hz, 1 H), 4.09 (t, *J* = 7.4 Hz, 1 H), 2.32–1.22 (series of m, 8 H), 1.48 (s, 3 H), 1.33 (s, 3 H)	($CDCl_3$) 164.8, 163.7, 157.6, 109.6, 99.9, 81.5, 81.3, 79.7, 55.5, 52.2, 39.9, 33.0, 31.6, 26.4, 25.1, 24.1	$[M + Na]^+$ calcd for $C_{16}H_{23}N_3O_4$: 344.1565; found: 344.1580
13c	256	–34.3 (*c* 1.0, $CHCl_3$)	($CDCl_3$) 8.96 (s, NH), 7.06 (d, *J* = 1.2 Hz, 1 H), 4.90 (dd, *J* = 7.0, 5.4 Hz, 1 H), 4.83 (d, *J* = 7.1 Hz, 1 H), 4.45–4.40 (m, 1 H), 3.94 (t, *J* = 6.1 Hz, 1 H), 2.30–1.39 (series of m, 8 H), 1.93 (dd, *J* = 1.0 Hz, 3 H), 1.56 (s, 3 H), 1.34 (s, 3 H)	($CDCl_3$) 163.7, 150.7, 139.7, 113.2, 111.0, 82.9, 80.0, 79.7, 65.4, 54.2, 39.4, 32.6, 30.7, 26.7, 25.0, 19.9, 12.3	$[M + Na]^+$ calcd for $C_{17}H_{24}N_2O_5$: 359.1577; found: 359.1574
13d	>300	–29.7 (*c* 0.6, $CHCl_3$)	(CD_3OD) 8.26 (s, 1 H), 8.21 (s, 1 H), 5.08 (t, *J* = 7.0 Hz, 1 H), 4.94 (d, *J* = 7.1 Hz, 1 H), 4.93–4.86 (m, 1 H), 3.90 (t, *J* = 6.4 Hz, 1 H), 2.48–1.41 (series of m, 8 H), 1.57 (s, 3 H), 1.34 (s, 3 H)	(CD_3OD) 155.9, 152.1, 149.1, 140.2, 113.1, 84.1, 79.8, 78.1, 60.8, 53.8, 40.5, 31.7, 30.1, 25.7, 23.8, 19.1, 12.4	$[M + H]^+$ calcd for $C_{17}H_{23}N_5O_3$: 346.1873; found: 346.1875
13e	>300	–48.0 (*c* 1.6, py)	(py-d_5) 8.44 (s, 1 H), 5.32–5.29 (m, 2 H), 5.03–4.99 (m, 1 H), 4.06 (t, *J* = 6.2 Hz, 1 H), 2.69–1.44 (series of m, 8 H), 1.59 (s, 3 H), 1.30 (s, 3 H)	(py-d_5) 160.6, 154.6, 151.0, 141.8, 125.4, 112.9, 84.2, 80.1, 77.6, 60.8, 54.1, 40.8, 33.2, 30.8, 26.8, 24.9, 20.0	$[M + Na]^+$ calcd for $C_{17}H_{22}ClN_5O_3$: 402.1303; found: 402.1297
21a		–3.0 (*c* 0.5, $CHCl_3$)	($CDCl_3$) 9.01 (s, NH), 7.36 (d, *J* = 8.1 Hz, 1 H), 5.74 (d, *J* = 7.9 Hz, 1 H), 4.81 (t, *J* = 5.7 Hz, 1 H), 4.61–4.57 (m, 1 H), 4.39 (d, *J* = 6.9 Hz, 1 H), 4.01 (t, *J* = 5.5 Hz, 1 H), 2.50–1.57 (series of m, 8 H), 1.55 (s, 3 H), 1.32 (s, 3 H)	($CDCl_3$) 163.2, 150.7, 143.2, 113.3, 102.4, 83.6, 83.3, 78.77, 64.7, 54.5, 34.9, 32.8, 30.6, 26.7, 25.0, 20.4	$[M + Na]^+$ calcd for $C_{16}H_{22}N_2O_5$: 345.1420; found: 345.1417
21b	273	+13.4 (*c* 1.0, $CHCl_3$)	($CDCl_3$) 8.02 (d, *J* = 5.7 Hz, 1 H), 6.08 (d, *J* = 5.7 Hz, 1 H), 5.39 (s, NH_2), 5.15–5.14 (m, 1 H), 4.58 (d, *J* = 5.6 Hz, 1 H), 4.03 (d, *J* = 5.5 Hz, 1 H), 3.84 (d, *J* = 5.7 Hz, 1 H), 2.11–1.47 (series of m, 8 H), 1.79 (s, 3 H), 1.61 (s, 3 H)	($CDCl_3$) 164.9, 164.1, 157.5, 110.3, 99.8, 85.2, 83.9, 80.7, 76.5, 59.1, 33.9, 33.6, 30.0, 26.3, 24.0, 22.0	$[M + Na]^+$ calcd for $C_{16}H_{23}N_3O_4$: 344.1580; found: 344.1588
21c	248	–5.5 (*c* 0.2, $CHCl_3$)	($CDCl_3$) 8.48 (s, NH), 7.13 (d, *J* = 0.9 Hz, 1 H), 4.83 (dd, *J* = 6.8, 5.4 Hz, 1 H), 4.57–4.53 (m, 1 H), 4.39 (d, *J* = 6.9 Hz, 1 H), 4.02 (t, *J* = 5.8 Hz, 1 H), 2.51–1.19 (series of m, 8 H), 1.94 (d, *J* = 0.8 Hz, 3 H), 1.56 (s, 3 H), 1.32 (s, 3 H)	($CDCl_3$) 163.4, 150.1, 139.1, 113.4, 110.9, 83.6, 83.2, 78.9, 64.5, 54.5, 35.0, 32.9, 30.6, 29.7, 26.7, 25.0, 12.3	$[M + Na]^+$ calcd for $C_{17}H_{24}N_2O_5$: 359.1577; found: 359.1580

Table 1 Characterization of Products (continued)

Product	Mp (°C)	$[\alpha]_D^{20}$ (*c*, solvent)	^{1}H NMR (500 MHz), δ	^{13}C NMR (125 MHz), δ	ES or EI HRMS, *m/z*
21d	>300	–36.2 (*c* 1.0, py)	(py-d_5) 8.63 (s, 1 H), 8.61 (s, 1 H), 8.18 (s, NH_2), 5.33 (1 H not seen), 5.19–5.15 (m, 1 H), 4.72 (d, *J* = 7.1 Hz, 1 H), 4.21 (t, *J* = 4.8 Hz, 1 H), 3.19–1.33 (series of m, 8 H), 1.61 (s, 3 H), 1.33 (s, 3 H)	(py-d_5) 157.1, 153.0, 150.3, 140.1, 120.5, 112.9, 85.0, 84.0, 77.9, 60.9, 55.6, 36.6, 33.3, 30.4, 26.6, 24.8, 20.9	$[M + Na]^+$ calcd for $C_{17}H_{23}N_5O_3$: 368.1693; found: 368.1684
21e		–1.5 (*c* 1.6, py)	(py-d_5) 8.63 (s, 1 H), 7.60 (s, NH_2), 5.22 (dd, *J* = 6.6, 4.5 Hz, 1 H), 5.03–4.99 (m, 1 H), 4.59 (d, *J* = 6.8 Hz, 1 H), 4.11 (s, 1 H), 3.06–3.01 (m, 1 H), 2.38–1.62 (series of m, 7 H), 1.59 (s, 3 H), 1.32 (s, 3 H)	(py-d_5) 160.6, 154.7, 150.8, 141.8, 125.3, 112.6, 85.0, 84.1, 77.4, 60.7, 56.0, 35.9, 33.5, 30.3, 26.7, 24.8, 20.9	$[M + Na]^+$ calcd for $C_{17}H_{22}ClN_5O_3$: 402.1303; found: 402.1280
Spironucleosides **14a–e** and **22a–e**					
14a	>300	–39.6 (*c* 1.4, py)	(py-d_5) 7.95 (d, *J* = 8.0 Hz, 1 H), 5.84 (d, *J* = 7.9 Hz, 1 H), 5.54–5.48 (m, 1 H), 5.10–5.08 (m, 1 H), 4.88 (d, *J* = 4.8 Hz, 1 H), 4.30 (t, *J* = 5.6 Hz, 1 H), 2.73–1.33 (series of m, 8 H)	(py-d_5) 164.6, 152.6, 143.0, 102.0, 79.8, 75.5, 72.9, 62.2, 54.0, 37.7, 33.0, 32.0, 20.2	$[M + Na]^+$ calcd for $C_{13}H_{18}N_2O_5$: 305.1107; found: 305.1115
14b	>300	–20.0 (*c* 0.8, py)	(py-d_5) 8.05 (d, *J* = 3.8 Hz, 1 H), 7.75 (s, NH_2), 6.43–6.41 (m, 1 H), 5.86–5.84 (m, 1 H), 4.98–4.97 (m, 2 H), 4.28 (m, 1 H), 2.69–1.53 (series of m, 8 H)	(py-d_5) 166.1, 154.6, 143.3, 99.8, 82.5, 79.3, 78.4, 74.8, 55.4, 41.2, 33.6, 32.4, 20.8	$[M + Na]^+$ calcd for $C_{13}H_{19}N_3O_4$: 304.1267; found: 304.1256
14c	>300	–36.0 (*c* 0.8, MeOH)	(CD_3OD) 7.47 (s, 1 H), 4.70–4.64 (m, 1 H), 4.40–4.37 (m, 1 H), 4.06 (d, *J* = 5.0 Hz, 1 H), 3.90 (t, *J* = 5.4 Hz, 1 H), 2.18–1.37 (series of m, 8 H), 1.86 (s, 3 H)	(CD_3OD) 163.6, 150.4, 138.0, 108.4, 77.9, 72.7, 70.6, 60.5, 51.9, 34.7, 30.3, 29.5, 17.7, 9.41	$[M + Na]^+$ calcd for $C_{14}H_{20}N_2O_5$: 319.1264; found: 319.1254
14d	>300	–40.0 (*c* 0.7, py)	(py-d_5) 8.55 (s, 1 H), 8.48 (s, 1 H), 8.14 (s, NH_2), 5.75–5.25 (not seen, 1 H), 4.94 (d, *J* = 3.9 Hz, 1 H), 4.49–4.44 (m, 2 H), 2.77–1.61 (series of m, 8 H)	(py-d_5) 157.0, 152.6, 150.0, 140.9, 128.0, 80.0, 76.8, 73.6, 61.3, 54.8, 38.7, 32.8, 32.1, 20.1	$[M + Na]^+$ calcd for $C_{14}H_{19}N_5O_3$: 328.1380; found: 328.1377
14e	>300	–42.2 (*c* 0.5, DMSO)	(DMSO-d_6) 7.78 (s, 1 H), 7.48 (s, NH_2), 4.76–4.75 (m, 1 H), 4.49 (m, 1 H), 3.99–3.96 (m, 1 H), 3.81 (d, *J* = 4.5 Hz, 1 H), 2.09–1.23 (series of m, 8 H)	(DMSO-d_6) 157.3, 153.7, 152.0, 136.1, 114.3, 78.8, 75.8, 72.2, 58.1, 53.6, 32.6, 32.0, 31.4, 19.9	$[M + Na]^+$ calcd for $C_{14}H_{19}N_5O_4$: 344.1329; found: 344.1313
22a	>300	–14.3 (*c* 0.3, DMSO)	(DMSO-d_6) 7.76 (d, *J* = 8.0 Hz, 1 H), 5.62 (d, *J* = 8.0 Hz, 1 H), 4.83–4.76 (m, 2 H), 4.59 (d, *J* = 4.2 Hz, 1 H), 3.49 (t, *J* = 4.3 Hz, 1 H), 1.87–1.36 (series of m, 8 H)	(DMSO-d_6) 163.6, 151.9, 142.7, 101.8, 77.4, 76.8, 74.9, 59.6, 53.3, 33.2, 32.6, 32.1, 19.9	$[M + Na]^+$ calcd for $C_{13}H_{18}N_2O_5$: 305.1107; found: 305.1103
22b	>300	–27.4 (*c* 1.2, py)	(py-d_5) 8.06 (d, *J* = 3.8 Hz, 1 H), 7.68 (s, NH_2), 6.26 (d, *J* = 3.9 Hz, 1 H), 5.91–5.86 (m, 1 H), 4.85 (t, *J* = 5.4 Hz, 1 H), 4.31 (d, *J* = 5.8 Hz, 1 H), 4.24 (t, *J* = 6.2 Hz, 1 H), 2.73–1.53 (series of m, 8 H)	(py-d_5) 166.4, 156.8, 114.3, 99.5, 82.5, 77.6, 77.4, 76.3, 54.9, 34.5, 33.4, 31.4, 20.4	$[M + Na]^+$ calcd for $C_{13}H_{19}N_3O_4$: 304.1267; found: 304.1275
22c	>300	–7.8 (*c* 0.14, MeOH)	(CD_3OD) 7.72 (d, *J* = 1.0 Hz, 1 H), 4.93–4.88 (m, 1 H), 4.34 (dd, *J* = 9.0, 6.9 Hz, 1 H), 3.88 (t, *J* = 7.2 Hz, 1 H), 3.71 (d, *J* = 4.9 Hz, 1 H), 2.06–1.52 (series of m, 8 H), 1.90 (d, *J* = 1.0 Hz, 3 H)	(CD_3OD) 165.0, 152.1, 139.1, 110.0, 77.8, 76.9, 74.9, 60.7, 53.5, 32.4, 31.5, 31.3, 19.2, 11.0	$[M + Na]^+$ calcd for $C_{14}H_{20}N_2O_5$: 319.1264; found: 319.1275
22d	>300	–36.4 (*c* 1.0, py)	(py-d_5) 8.60 (s, 1 H), 8.53 (s, 1 H), 8.17 (s, NH_2), 5.48–5.42 (m, 1 H), 5.22 (dd, *J* = 8.5, 4.3 Hz, 1 H), 4.27 (t, *J* = 6.5 Hz, 1 H), 4.24 (d, *J* = 4.3 Hz, 1 H), 3.96–1.13 (series of m, 8 H)	(py-d_5) 157.3, 152.7, 150.2, 140.7, 121.0, 77.7, 77.6, 75.1, 61.3, 55.1, 45.7, 34.0, 32.4, 20.7	$[M + Na]^+$ calcd for $C_{14}H_{19}N_5O_3$: 328.1380; found: 328.1368
22e	>300	–14.1 (*c* 0.5, DMSO)	(DMSO-d_6) 7.79 (s, 1 H), 6.63 (s, NH_2), 4.93 (d, *J* = 11.1, 5.1 Hz, 1 H), 4.65 (d, *J* = 4.1 Hz, 1 H), 4.33–4.29 (m, 1 H), 3.55 (t, *J* = 4.3 Hz, 1 H), 2.05–1.23 (series of m, 8 H)	(DMSO-d_6) 157.2, 153.9, 152.0, 135.9, 116.9, 77.2, 76.6, 76.3, 58.2, 53.8, 34.7, 33.4, 31.9, 20.2	$[M + Na]^+$ calcd for $C_{14}H_{19}N_5O_4$: 344.1329; found: 344.1323

Reduction of Acetonides 8a and 17; General Procedure

A solution of acetonide **8a** or **17** (34 mg, 0.1 mmol) and THF (1.4 mL) was cooled to –78 °C and L-Selectride (0.11 mL, 0.11 mmol) was added. The mixture was stirred for 20 min, quenched with sat. $NaHCO_3$ soln, transferred to a separatory funnel, and extracted with Et_2O (3 × 30 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo, and the residue was purified by column chromatography (silica gel, hexanes–EtOAc 20:1).

9a (R′ = H)

Yield: 33 mg (95%).

$[\alpha]_D^{20}$ –33.7 (*c* 1.2, $CHCl_3$).

IR (neat): 3543, 1472, 1371 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 4.53 (d, *J* = 5.6 Hz, 1 H), 4.45 (t, *J* = 5.7 Hz, 1 H), 4.21–4.16 (m, 1 H), 3.82 (t, *J* = 7.2 Hz, 1 H), 2.05–1.38 (series of m, 8 H), 1.49 (s, 3 H), 1.38 (s, 3 H), 0.89 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 109.9, 81.3, 80.8, 79.5, 70.4, 52.8, 43.0, 29.9, 26.1, 25.8 (3C), 24.2, 20.2, 17.8, –4.1, –5.0.

ES HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{34}O_4Si$: 365.2118; found: 365.2117.

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Yield: 100 mg (98%).

$[\alpha]_D^{20}$ +29.9 (*c* 1.7, $CHCl_3$).

IR (neat): 3495, 1471, 1372 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 4.46 (t, *J* = 5.7 Hz, 1 H), 4.14–4.11 (m, 1 H), 4.06 (d, *J* = 5.5 Hz, 1 H), 3.64 (t, *J* = 5.7 Hz, 1 H), 2.26–1.34 (series of m, 8 H), 1.49 (s, 3 H), 1.34 (s, 3 H), 0.89 (s, 9 H), 0.04 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 110.4, 85.4, 79.3, 78.0, 70.9, 54.3, 37.8, 33.3, 30.1, 26.0, 25.8 (3C), 24.3, 20.2, 17.9.

ES HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{34}O_4Si$: 365.2118; found: 365.2102.

Mesylation of 9a (R′ = H)

To a solution of **9a** (20 mg, 0.06 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added Et_3N (25 μL, 0.18 mmol) followed by MsCl (14 μL, 0.18 mmol). The mixture was allowed to warm to r.t. over a period of 3 h, and then was quenched with sat. $NaHCO_3$ soln and extracted with Et_2O (3 × 20 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo, and the residue was purified by column chromatography (silica gel, hexanes–EtOAc 10:1).

Yield: 28 mg (100%).

$[\alpha]_D^{20}$ –50.1 (*c* 1.3, $CHCl_3$).

IR (neat): 1457, 1360, 1252 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 5.11–5.07 (m, 1 H), 4.64 (t, *J* = 5.4 Hz, 1 H), 4.51 (d, *J* = 5.4 Hz, 1 H), 3.87 (t, *J* = 7.6 Hz, 1 H), 3.07 (s, 3 H), 2.20 (t, *J* = 11.9 Hz, 1 H), 2.08–1.35 (series of m, 7 H), 1.50 (s, 3 H), 1.36 (s, 3 H), 0.91 (s, 9 H), 0.11 (s, 3 H), 0.07 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 110.7, 81.1, 80.6, 78.5, 78.0, 52.3, 38.9, 38.7, 33.4, 29.3, 26.1, 25.8 (3C), 24.4, 19.8, 17.7, –4.2, –5.0.

ES HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{36}O_6SSi$: 443.1894; found: 443.1897.

Formation of Mesylate 9b (R′ = Ms)

A solution of **6** (40 mg, 0.13 mmol) and PTSA (2.5 mg, 0.01 mmol) in neat $PhCH(OMe)_2$ (0.5 mL) was stirred at 80 °C for 1 h. The mixture was cooled to r.t., quenched with sat. $NaHCO_3$ soln, and extracted with Et_2O (3 × 20 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo, and the residue was purified by column chromatography (silica gel, hexanes–EtOAc 30:1) to give **8b** as a colorless oil.

Yield: 50 mg (99%).

$[\alpha]_D^{20}$ –68.9 (*c* 1.3, $CHCl_3$).

IR (neat): 1737, 1461, 1365 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.47–7.45 (m, 2 H), 7.41–7.37 (m, 3 H), 5.86 (s, 1 H), 4.76 (d, *J* = 5.7 Hz, 1 H), 4.43 (d, *J* = 5.7 Hz, 1 H), 3.90 (t, *J* = 7.9 Hz, 1 H), 2.85 (d, *J* = 18.0 Hz, 1 H), 2.28–1.58 (series of m, 7 H), 0.89 (s, 9 H), 0.07 (s, 3 H), 0.04 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 211.2, 136.1, 129.6, 128.3 (2C), 126.8 (2C), 105.0, 81.5, 81.2, 80.0, 50.7, 44.0, 31.9, 28.4, 25.8 (3C), 19.1, 17.9, –4.5, –5.1.

ES HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{32}O_4Si$: 411.1962; found: 411.1950.

Ketone **8b** (23 mg, 0.06 mmol) and THF (1 mL) were combined and cooled to –78 °C, at which point a 1 M solution of L-Selectride in THF (66 μL, 0.07 mmol) was added. The mixture was stirred for 20 min, quenched with sat. aq $NaHCO_3$, warmed to r.t., transferred to a separatory funnel, and extracted with Et_2O (3 × 15 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to leave a residue that was purified by column chromatography (silica gel, hexanes–EtOAc 10:1) to give **9b** (R′ = H) as a white solid.

Yield: 23 mg (100%).

Mp 66 °C.

$[\alpha]_D^{20}$ –5.8 (*c* 1.0, $CHCl_3$).

IR (neat): 3565, 1460, 1402 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.55–7.53 (m, 2 H), 7.43–7.42 (m, 3 H), 5.82 (s, 1 H), 4.61 (d, *J* = 5.9 Hz, 1 H), 4.55 (t, *J* = 5.9 Hz, 1 H), 4.35–4.30 (m, 1 H), 3.89 (t, *J* = 7.6 Hz, 1 H), 2.19–1.49 (series of m, 8 H), 0.93 (s, 9 H), 0.10 (s, 3 H), 0.08 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 136.5, 129.7, 128.4 (2C), 126.9 (2C), 104.0, 82.7, 81.0, 80.4, 70.8, 53.1, 43.4, 34.0, 30.0, 22.9 (3C), 20.2, 17.8, –4.1, –5.0.

ES HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{34}O_4Si$: 413.2118; found: 413.2117.

A solution of alcohol **9b** (R′ = H) (7.0 mg, 0.02 mmol) in CH_2Cl_2 (1.0 mL) was cooled to 0 °C and treated with Et_3N (15 μL, 0.11 mmol) followed by MsCl (8.4 μL, 0.11 mmol). The mixture was allowed to warm to r.t., stirred for 36 h, quenched with sat. $NaHCO_3$ soln, and extracted with Et_2O (3 × 20 mL). The combined organic phases were dried (Na_2SO_4) and concentrated, and the residue was purified by column chromatography (silica gel, hexanes–EtOAc 3:1) to give **9b** (R′ = Ms) as a colorless oil.

Yield: 8 mg (96%).

$[\alpha]_D^{20}$ –43.3 (*c* 1.0, $CHCl_3$).

IR (neat): 1470, 1360, 1256 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.55 (dd, *J* = 6.7, 3.8 Hz, 2 H), 7.43–7.40 (m, 3 H), 5.80 (s, 1 H), 5.25–5.20 (m, 1 H), 4.73 (t, *J* = 5.7 Hz, 1 H), 4.59 (d, *J* = 5.8 Hz, 1 H), 3.93 (t, *J* = 8.1 Hz, 1 H), 3.02 (s, 3 H), 2.41–1.21 (m, 8 H), 0.94 (s, 9 H), 0.15 (s, 3 H), 0.10 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 136.3, 129.7, 128.3 (2C), 127.1 (2C), 104.6, 82.2, 81.2, 79.0, 78.1, 52.6, 38.7, 33.4, 31.5, 25.8 (3C), 22.6, 19.9, 17.8, –4.1, –5.0.

ES HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{36}O_6SSi$: 491.1894; found: 491.1902.

Formation of Mesylate 9c (R′ = Ms)

A solution of **6** (64 mg, 0.22 mmol), py (140 μL, 1.7 mmol), and $AgNO_3$ (150 mg, 0.86 mmol) in THF (12 mL) was stirred in the dark for 1 h, at which point $TIPDSCl_2$ (137 μL, 0.43 mmol) was added in one portion. The mixture was stirred for 2 h and filtered through a pad of Celite. The filtrate was transferred to a separatory funnel and extracted with Et_2O (3 × 30 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to leave a residue that was purified by column chromatography (silica gel, hexanes–EtOAc 20:1) to give **8c** as a colorless oil.

Yield: 116 mg (98%).

$[\alpha]_D^{20}$ –47.2 (*c* 1.2, $CHCl_3$).

IR (neat): 1765, 1464, 1251 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.68–4.64 (m, 2 H), 3.83 (dd, *J* = 5.5, 4.1 Hz, 1 H), 2.26–1.44 (m, 8 H), 1.12–0.90 (m, 28 H), 0.89 (s, 9 H), 0.07 (s, 3 H), 0.04 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 212.4, 80.8, 79.7, 75.2, 52.0, 43.4, 33.9, 32.5, 25.7 (3C), 19.7, 17.8, 17.4–12.8 (12C), –4.2, –4.9.

ES HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{27}H_{54}O_5Si_3$: 565.3171; found: 565.3191.

Ketone **8c** (116 mg, 0.21 mmol) was dissolved in THF (3 mL), cooled to –78 °C, treated with L-Selectride (235 μL, 0.23 mmol), and stirred for 10 min prior to quenching with sat. $NaHCO_3$ soln and extraction with Et_2O (3 × 30 mL). The combined organic phases were dried (Na_2SO_4) and concentrated, and the residue was purified by column chromatography (silica gel, hexanes–EtOAc 20:1) to give **9c** (R′ = H) as a colorless oil.

Yield: 100 mg (86%).

$[\alpha]_D^{20}$ –0.5 (*c* 1.3, $CHCl_3$).

IR (CH_2Cl_2): 3574, 1464, 1250 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.47 (d, *J* = 4.4 Hz, 1 H), 4.26 (t, *J* = 4.4 Hz, 1 H), 4.03 (dd, *J* = 11.4, 6.0 Hz, 1 H), 3.73 (t, *J* = 7.1 Hz, 1 H), 2.34–1.35 (m, 8 H), 1.12–1.06 (m, 28 H), 0.89 (s, 9 H), 0.05 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 80.8, 77.2, 74.5, 71.2, 54.5, 43.2, 33.8, 32.3, 25.8 (3C), 19.6, 17.9, 17.5–13.0 (12C), –4.3, –4.9.

ES HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{27}H_{56}O_5Si_3$: 567.3327; found: 567.3316.

To a solution of **9c** (R′ = H) (54 mg, 0.1 mmol) in CH_2Cl_2 (3.4 mL) at 0 °C was added Et_3N (42 μL, 0.3 mmol) followed by MsCl (23 μL, 0.3 mmol). The mixture was allowed to warm to r.t., quenched after 6 h with sat. $NaHCO_3$ soln, and extracted with Et_2O (3 × 30 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to leave a residue that was purified by column chromatography (silica gel, hexanes–EtOAc 10:1) to give **9c** (R′ = Ms) as a colorless oil.

Yield: 56 mg (90%).

$[\alpha]_D^{20}$ –4.8 (*c* 1.7, $CHCl_3$).

IR (CH_2Cl_2): 1464, 1360, 1250 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.88 (dd, *J* = 10.8, 6.4 Hz, 1 H), 4.49 (d, *J* = 4.3 Hz, 1 H), 4.35 (t, *J* = 4.4 Hz, 1 H), 3.75 (t, *J* = 7.6 Hz, 1 H), 2.99 (s, 3 H), 2.41–1.20 (series of m, 8 H), 1.12–1.08 (m, 28 H), 0.90 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 80.9, 79.8, 76.3, 73.1, 54.4, 39.6, 38.2, 32.5, 31.2, 25.8 (3C), 19.6, 17.9, 17.5–17.1 (8C), 13.5, 13.4, 13.1, 13.0, –4.3, –4.8.

ES HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{28}H_{58}O_7SSi_3$: 645.3103; found: 645.3121.

Formation of Mesylate 9d (R′ = Ms)

Diol **6** (20 mg, 0.07 mmol) and DMAP (82 mg, 0.7 mmol) were dissolved in CH_2Cl_2 (2 mL), the solution was brought to 0 °C, and a 1-M solution of phosgene in toluene (0.6 mL, 0.6 mmol) was added. The mixture was stirred for 16 h while warming to r.t., quenched carefully with sat. $NaHCO_3$ soln, and extracted with Et_2O (3 × 20 mL). The combined organic phases were dried (Na_2SO_4) and concentrated, and the residue was purified by column chromatography (silica gel, hexanes–EtOAc 10:1) to give **8d** as a colorless oil.

Yield: (17 mg, 80%).

$[\alpha]_D^{20}$ –134.8 (*c* 1.3, $CHCl_3$).

IR (neat): 1825, 1804, 1766, 1471 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 5.15 (d, *J* = 6.7 Hz, 1 H), 4.67 (d, *J* = 6.8 Hz, 1 H), 3.93 (t, *J* = 8.5 Hz, 1 H), 2.78 (d, *J* = 18.3 Hz, 1 H), 2.23 (d, *J* = 18.4 Hz, 1 H), 2.19–1.65 (series of m, 6 H), 0.86 (s, 9 H), 0.05 (s, 3 H), 0.01 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 205.5, 153.8, 81.7, 80.4, 78.1, 52.4, 43.5, 31.5, 27.8, 25.7 (3C), 19.0, 17.8, –4.6, –5.2.

ES HRMS *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{26}O_5Si$: 349.1441; found: 349.1434.

A solution of **8d** (41 mg, 0.13 mmol) in MeOH (4 mL) was cooled to 0 °C and $NaBH_4$ (4.8 mg, 0.13 mmol) was added. The mixture was quenched after 5 min with sat. $NaHCO_3$ soln, transferred to a separatory funnel, and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried (Na_2SO_4) and concentrated, and the residue was purified by column chromatography (silica gel, hexanes–EtOAc 5:1) to give **9d** (R′ = H) and its β-epimer, both as colorless oils.

9d (R′ = H)

Yield: 7 mg (17%).

$[\alpha]_D^{20}$ –35.7 (*c* 1.8, $CHCl_3$).

IR (neat): 3420, 1804, 1471 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 5.00 (d, *J* = 6.6 Hz, 1 H), 4.87 (t, *J* = 6.2 Hz, 1 H), 4.46–4.42 (m, 1 H), 3.89 (t, *J* = 7.7 Hz, 1 H), 2.11–1.50 (series of m, 8 H), 0.90 (s, 9 H), 0.087 (s, 3 H), 0.082 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.8, 82.0, 81.1, 80.8, 71.3, 54.4, 33.8, 31.5, 29.9, 25.8 (3C), 20.2, 17.7, –4.1, –5.0.

ES HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{28}O_5Si$: 351.1598; found: 351.1599.

β-epimer

Yield: 26 mg (63%).

$[\alpha]_D^{20}$ +13.5 (*c* 1.5, $CHCl_3$).

IR (neat): 3512, 1794, 1471 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 5.05–4.99 (m, 1 H), 5.03 (d, *J* = 4.7 Hz, 1 H), 4.20 (d, *J* = 4.8 Hz, 1 H), 3.87 (t, *J* = 5.1 Hz, 1 H), 2.29–1.45 (series of m, 8 H), 0.91 (s, 9 H), 0.107 (s, 3 H), 0.105 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.9, 82.3, 80.3, 78.8, 74.2, 54.5, 40.3, 33.0, 27.8, 25.8 (3C), 21.2, 17.9, –4.3, –4.9.

ES HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{28}O_5Si$: 351.1598; found: 351.1601.

To a solution of **9d** (R′ = H) (26 mg, 0.08 mmol) in CH_2Cl_2 (3.3 mL) at 0 °C was added Et_3N (33 μL, 0.24 mmol) followed by MsCl (19 μL, 0.24 mmol). The mixture was allowed to warm to r.t. over a period of 3 h, quenched with sat. $NaHCO_3$ soln, and extracted with Et_2O (3 × 20 mL). The combined organic phases were dried (Na_2SO_4) and concentrated, and the residue was purified by column chromatography (silica gel, hexanes–EtOAc 3:1) to give **9d** (R′ = Ms) as a colorless oil.

Yield: 28 mg (87%).

$[\alpha]_D^{20}$ –71.4 (*c* 1.4, $CHCl_3$).

IR (neat): 1810, 1471, 1362 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 5.30–5.26 (m, 1 H), 5.07 (t, *J* = 6.0 Hz, 1 H), 4.97 (d, *J* = 6.5 Hz, 1 H), 3.94 (t, *J* = 7.7 Hz, 1 H), 3.12 (s, 3 H), 2.20–1.54 (series of m, 8 H), 0.91 (s, 9 H), 0.13 (s, 3 H), 0.09 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.3, 81.37, 81.32, 78.8, 75.7, 54.2, 38.7, 38.2, 33.2, 29.1, 25.7 (3C), 19.9, 17.7, –4.2, –5.0.

ES HRMS: *m/z* $[M + Na]^+$ calcd for $C_{17}H_{30}O_7SSi$: 429.1373; found: 429.13919.

Synthesis of Triflates 11 and 19

A solution of **9a** (R′ = H) or **18** (259 mg, 0.76 mmol) and CH_2Cl_2 (2.2 mL) was cooled to 0 °C, at which point py (0.12 mL, 1.5 mmol) and Tf_2O (0.15 mL, 0.9 mmol) were added. The mixture was stirred for 40 min, quenched with H_2O, transferred to a separatory funnel, and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried (Na_2SO_4) and concentrated, and the residue was purified by column chromatography (silica gel, hexanes–EtOAc 20:1).

11

White solid (decomposed upon heating).

Yield: 370 mg (100%).

$[\alpha]_D^{20}$ –29.3 (*c* 0.7, $CHCl_3$).

IR (neat): 1415, 1246, 1210 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 5.29–5.25 (m, 1 H), 4.64 (t, *J* = 5.5 Hz, 1 H), 4.49 (d, *J* = 5.3 Hz, 1 H), 3.87 (t, *J* = 8.4 Hz, 1 H), 2.34–1.32 (series of m, 8 H), 1.51 (s, 3 H), 1.38 (s, 3 H), 0.91 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 111.2, 85.2, 81.2, 80.4, 78.4, 52.5, 38.7, 32.9, 28.8, 26.0, 25.7 (3C), 24.4, 19.7, 17.7, –4.1, –5.2.

19

Yield: 97 mg (82%).

$[\alpha]_D^{20}$ –10.3 (*c* 0.7, $CHCl_3$).

IR (neat): 1415, 1246, 1209 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 5.25–5.21 (m, 1 H), 4.61 (t, *J* = 5.5 Hz, 1 H), 4.17 (d, *J* = 5.1 Hz, 1 H), 3.76 (t, *J* = 7.2 Hz, 1 H), 2.40–1.54 (series of m, 8 H), 1.50 (s, 3 H), 1.34 (s, 3 H), 0.89 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 111.8, 86.3, 85.7, 78.8, 78.1, 53.5, 35.0, 32.5, 30.5, 25.9, 25.6 (3C), 24.7, 19.6, 17.8, –4.3, –5.0.

S_N2 Displacement Involving Triflates 11 and 19; General Procedure

To a solution of the nucleobase (0.33 mmol) in DMF (10 mL) at r.t. and under N_2 was added KH (15 mg, 0.36 mmol). The mixture was stirred for 10 min prior to the addition of **11** or **19** (60 mg, 0.12 mmol). The mixture was stirred for 48 h, quenched with H_2O, transferred to a separatory funnel, and extracted with Et_2O (3 × 30 mL). The combined organic phases were dried (Na_2SO_4) and the residue was purified by column chromatography (silica gel, hexanes–EtOAc 2:1).

Desilylation of 12a–e and 20a–e; General Procedure

To a solution of **12a–e** or **20a–e** (0.07 mmol) and THF (1 mL) was added a 1-M solution of TBAF in THF (0.2 mL, 0.21 mmol). The mixture was stirred for 24 h, quenched with brine, transferred to a separatory funnel, and extracted with CH_2Cl_2 (4 × 30 mL). The combined organic phases were dried (Na_2SO_4) and the residue was purified by column chromatography (silica gel, 6% MeOH in CH_2Cl_2).

Guanine-Containing Compounds 13f and 21f; General Procedure

A mixture of **13e** (30 mg, 0.082 mmol), MeOH (10 mL), 2-sulfanylethanol (0.11 mL, 1.64 mmol), and a 5.25 M solution of NaOMe in MeOH (0.33 mL, 1.7 mmol) was stirred at 80 °C for 4 h. The reaction mixture was quenched with sat. $NaHCO_3$ soln, transferred to a separatory funnel, and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried (Na_2SO_4) and the residue was purified by column chromatography (silica gel, 10% MeOH in CH_2Cl_2).

13f

White solid.

Yield: 29 mg (100%).

Mp >300 °C.

$[\alpha]_D^{20}$ –23.5 (*c* 1.5, DMSO).

^1H NMR (500 MHz, DMSO-d_6): δ = 7.86 (s, 1 H), 6.81 (s, NH_2), 4.90–4.80 (m, 3 H), 4.61–4.56 (m, 1 H), 2.79–1.23 (series of m, 8 H), 1.44 (s, 3 H), 1.23 (s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 157.2, 153.9, 151.5, 136.1, 127.8, 112.7, 84.1, 79.5, 77.0, 60.0, 53.8, 41.6, 32.7, 30.5, 27.0, 25.3, 19.8.

EI HRMS: *m/z* $[M + Na]^+$ calcd for $C_{17}H_{23}N_5O_4$: 384.1642; found: 384.1635.

21f

White solid.

Yield: 24 mg (72%).

Mp >300 °C

$[\alpha]_D^{20}$ +2.4 (*c* 1.0, DMSO).

^1H NMR (500 MHz, DMSO-d_6): δ = 7.89 (s, 1 H), 6.48 (s, NH_2), 4.87 (dd, *J* = 7.2, 5.1 Hz, 1 H), 4.72 (d, *J* = 4.4 Hz, 1 H), 4.60–4.56 (m, 1 H), 4.35 (d, *J* = 7.3 Hz, 1 H), 2.95–1.45 (series of m, 8 H), 1.43 (s, 3 H), 1.22 (s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 157.2, 153.9, 151.5, 136.1, 117.2, 112.8, 84.7, 83.4, 77.6, 58.5, 55.1, 38.0, 33.0, 26.8, 25.2, 21.0.

EI HRMS: *m/z* $[M + H]^+$ calcd for $C_{17}H_{23}N_5O_4$: 384.1642; found: 384.1625.

Ultimate Acetonide Hydrolysis To Give Spirocarbocyclic Nucleosides 14 and 22; General Procedure

To a solution of **13a–f** or **21a–f** (20 mg, 0.062 mmol) in MeOH (2.0 mL) was added PTSA (11.8 mg, 0.062 mmol). The mixture was stirred for 24 h, concentrated, and subjected to column chromatography (silica gel, 15% MeOH in CH_2Cl_2).

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