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A Stereoselective Approach to β-L-Arabino Nucleoside Analogues: Synthesis and Cyclization of Acyclic 1′,2′-*syn* *N*,*O*-Acetals

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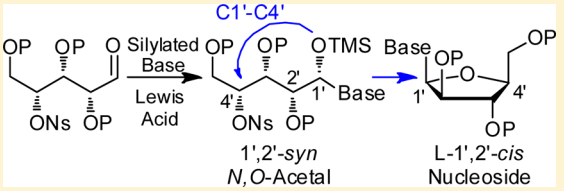
Supporting Information

ABSTRACT: Reported herein is a novel and versatile strategy for the stereoselective synthesis of unnatural β-L-arabinofuranosyl nucleoside analogues from acyclic *N*,*OTMS*-acetals bearing pyrimidine and purine bases. These unusual acetals undergo a C1′ to C4′ cyclization where the OTMS of the acetal serves as the nucleophile to generate 2′-oxynucleosides with complete retention of configuration at the C1′ acetal center. *N*,*OTMS*-acetals are obtained diastereoselectively from additions of silylated nucleobases onto acyclic polyalkoxyaldehydes in the presence of $MgBr_2 \cdot OEt_2$. The strategy reported is addressing important synthetic challenges by providing stereoselective access to unnatural L-nucleosides starting from easily accessible pools of D-sugars and, as importantly, by allowing the formation of the sterically challenging 1′,2′-*cis* nucleosides. A wide variety of nucleoside analogues were synthesized in 7−8 steps from easily accessible D-xylose.



INTRODUCTION

Many therapeutically relevant nucleoside analogues that have been used for the treatment of leukemia display arabino scaffolds with 1′,2′-*cis* arrangements between the nucleobase attached at the anomeric center and the electron withdrawing group attached at C2′ (Figure 1).[1] This particular stereochemical arrangement was demonstrated to increase the rate of monophosphorylation by dCK (deoxycytidine kinase), a critical step for the pharmacological activity of numerous nucleoside analogues.[2] The 1′,2′-*cis* relationship represents an important synthetic challenge since it cannot be obtained by anchimeric assistance of a neighboring group.[3] The nucleobase must be delivered from the most hindered face of the sugar moiety.[4,5] Since the discovery of L-3TC,[6] the interest of the medicinal chemistry community for the L-series has grown exponentially, as demonstrated by the number of compounds and clinical uses investigated (cancer, HBV, HIV).[7] L-Analogues have been shown to have increased antiviral activity with reduced cytotoxicity as compared to their D-enantiomers.[8] A single versatile method addressing these two synthetic challenges would be a useful tool for medicinal chemists in order to investigate new and improved biologically active nucleoside analogues as exemplified by the HBV antiviral agent Clevudine (Figure 1).[9]

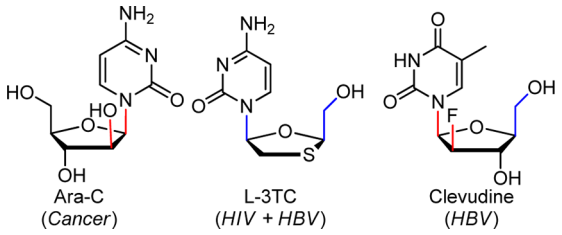
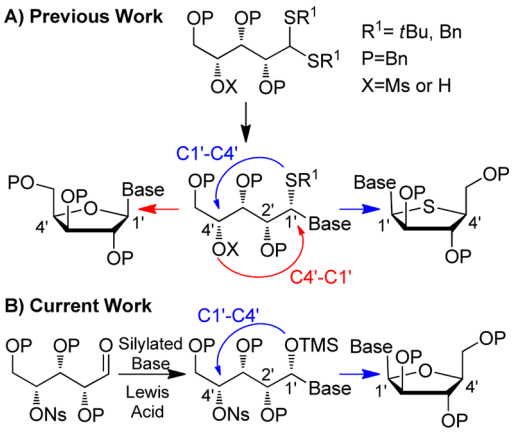


Figure 1. Anticancer and antiviral agents with a 1′,2′-*cis* relative stereochemistry and/or in the L-series.

We previously developed an approach to generate two series of nucleoside analogues from a common acyclic thioaminal (Scheme 1A).[10] These acyclic intermediates can undergo two distinct intramolecular cyclization processes. A first mode of

Scheme 1



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cyclization leads to D-1′,2′-*trans* nucleoside analogues (C4′ → C1′ cyclization). The second mode of cyclization yields L-1′,2′-*cis*-4′-thionucleosides (C1′ → C4′ cyclization). In both cyclization processes, the stereochemistry of the nucleoside obtained is provided by the acyclic thioaminal precursor. This is in contrast with other acyclic approaches where the stereochemistry of the anomeric center is determined during the cyclization step.[11] The efficiency and versatility of this approach convinced us to investigate the cyclization of 1′,2′-*syn* acyclic *N,O*-acetals allowing access to L-1′,2′-*cis* nucleoside analogues starting from common D-sugars (Scheme 1B). Herein, we report a cyclization protocol for acyclic *N,OTMS*-acetals, which are accessed with high 1′,2′-*syn* diastereoselectivity by addition of silylated nucleobases to aldehydes with $MgBr_2{\cdot}OEt_2$, a bidentate Lewis acid. In the cyclization reaction, the OTMS of the acetal serves as the putative nucleophile involved in the displacement of the leaving group at the C4′ position with inversion of configuration.

RESULTS AND DISCUSSION

At the onset of our study to synthesize L-nucleoside analogues from acyclic precursors, we realized that the simple extension of our previous work to selectively prepare the targeted *N,O*-acyclic acetals was unsuccessful. Indeed, using the acetal as opposed to the thioacetal (Scheme 1) led to poor diastereoselectivity in the addition step.[10,12] A different scenario was therefore considered: the addition of silylated nucleobases onto aldehydes derived from D-sugars, followed by intramolecular displacement of a leaving group. Two major hurdles were identified and had to be circumvented to render this strategy efficient. The acyclic *N,OTMS*-acetals had to be generated with high *syn* diastereoselectivity and the chemical stability of these intermediates had to be sufficient to withstand a cyclization protocol.[13] Although silyloxy ethers have been suggested to be involved in intramolecular reactions,[14] we anticipated a reduced nucleophilicity of the oxygen in the *N,OTMS*-acetal that could compromise the planned cyclization. This cyclization, which had not been previously reported in the literature, was evaluated experimentally.

Diastereoselective Synthesis of *N,OTMS*-Acetals. In order to investigate the nucleobase coupling onto an acyclic aldehyde, we elected to synthesize two aldehydes bearing either a mesylate or a nosylate at C4, the latter being a better leaving group. Aldehyde **2** was prepared by oxidation of the mesylate protected dithioacetal **S1** (Scheme 2).[15] A similar approach with the corresponding nosylate dithioacetal led to a mixture of products, including cyclic thiofuranosides. An alternate strategy to access the requisite aldehyde **4** was therefore developed (Scheme 2). The partially protected sugar derived from D-xylose was subjected to a Wittig reaction to give acyclic alkene **3**.[16] The resulting secondary alcohol was successfully protected with a nosyl group, and subsequent ozonolysis provided the C4-nosylate protected aldehyde **4** in high yield.

The coupling step was then examined with these aldehydes bearing a leaving group at C4 (Table 1). Interestingly, the 1′,2′-

Scheme 2. Formation of Aldehydes 2 and 4

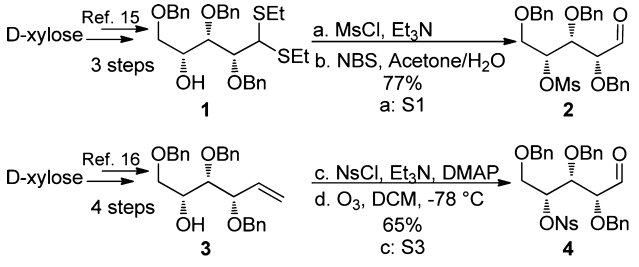
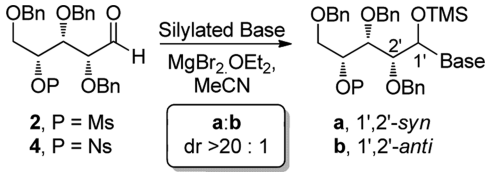


Table 1. *N,OTMS*-Acetal Formation



entry	nucleobase	P	yield (%)[a,b]
1	Thymine	Ms (**5a**)	74
2	"	Ns (**6a**)	62
3	Uracil	Ms (**7a**)	61
4	"	Ns (**8a**)	63
5	Adenine	Ms (**9a**)	66
6	"	Ns (**10a**)	54
7	5F-Uracil	Ms (**11a**)	57
8	"	Ns (**12a**)	58
9	Cytosine	Ms (**13a**)	71
10	"	Ns (**14a**)	65
11	N^4–AcCytosine	Ms (**15a**)	49

[a]All *N,OTMS*-acetals were formed with >20:1 diastereoselectivity for the 1′,2′-*syn* isomer. [b]Silylated base (2.0–4.0 equiv), $MgBr_2{\cdot}OEt_2$ (1.5–2.0 equiv), −40 °C.

syn N,OTMS-acetals **5a** (P = Ms) and **6a** (P = Ns) were obtained with high diastereoselectivity (>20:1)[17] when silylated thymine in the presence of 2.0 equiv of $MgBr_2{\cdot}OEt_2$ were reacted in acetonitrile with aldehydes **2** or **4** (entries 1 and 2). Contrary to our initial apprehensions, we were able to isolate these *N,OTMS*-acetals **5a** and **6a** in 74 and 62% yields, respectively, with standard aqueous workup and flash chromatography. Persilylated uracil provided the *N,OTMS*-acetals **7a** and **8a** in high diastereoselectivity as well (Table 1, entries 3 and 4). Although introduction of purine bases is known to be challenging, we were pleased that the adenosine *N,OTMS*-acetals **9a** and **10a** could be synthesized with high regio-(N9) and diastereoselectivity (Table 1, entries 5 and 6). Couplings of silylated 5F-uracil and cytosine proved to be as effective (entries 7–10). A slightly lower yield was noticed with N^4–AcCytosine **15a** (entry 11). Formation of N9-guanosine *N,OTMS*-acetals was unsuccessful, possibly due to competing N3 and N7 nucleophilic sites.

The desired 1′,2′-*syn* diastereoselectivity could result from the addition of persilylated nucleobase (Nu) on the opposite side of the C2 substituent of five-membered ring magnesium chelate **A** (Scheme 3). The generated alkoxyde intermediate **B** would then be either silylated intramolecularly or intermolecularly by a second persilylated nucleobase. Five-membered magnesium chelates have previously been shown to form preferentially over six-membered chelates, which could be generated by chelation of the C3 alkoxy group.[18]

Cyclization of *N,OTMS*-Acetals. We then sought to find conditions allowing C1′ → C4′cyclization without epimerization of the stereogenic center at C1′. The cyclization of *N,OTMS*-acetals bearing a mesylate at C4′ did not occur directly after coupling in the presence of $MgBr_2{\cdot}OEt_2$ at low temperatures, and warming the reaction mixtures only provided

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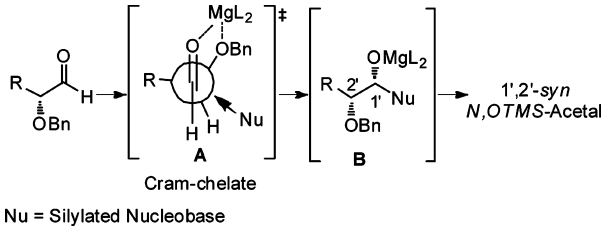
Scheme 3. Bidentate pathway leading to 1′,2′-*syn* *N,O*-Acetals



the corresponding aldehyde **2**. Alternative conditions were therefore examined to cyclize the mesylate series.[19] When **5a** was heated at 140 °C for 3 h in DMSO, only trace amounts of the cyclized product were observed (Table 2, entry 1).[20]

Table 2. S_N2-Like Cyclization of C4′-Mesylate *N,OTMS*-Acetals[a]

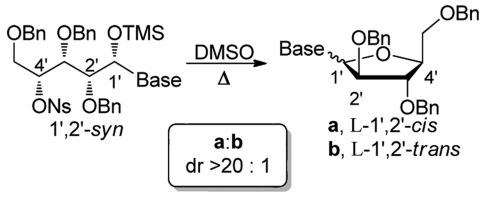
entry	*N,OTMS*-acetal	product	conditions	yield (%)
1	**5a** (Thymine)	**16a**	A	traces
2	"	"	B	34
3	"	"	C	52
4	**7a** (Uracil)	**17a**	B	49
5	"	"	C	57
6	**9a** (Adenine)	**18a**	B	40
7	"	"	C	38

[a]Conditions A: 140 °C, 3 h. Conditions B: 140 °C, 3 h, $Al(OiPr)_3$ (3.0 equiv). Conditions C: 180 °C, MW, 10 min, $Al(OiPr)_3$ (0.6 equiv).

Addition of Lewis acids such as $Al(OiPr)_3$ have been shown to facilitate cyclization reactions proceeding via the displacement of mesylate to form oxetane rings.[21] We were pleased to note that upon addition of $Al(OiPr)_3$, the desired L-1′,2′-*cis* nucleoside analogue **16a** could be isolated in 34% yield (Table 2, entry 2) with a >20:1 diastereoselectivity consistent with an S_N2-like intramolecular cyclization. The C1′ → C4′ cyclization was further investigated using microwave heating. Optimization of the cyclization conditions (180 °C for 10 min using 0.6 equiv of $Al(OiPr)_3$) resulted in improved yields for the thymine and uracil 1′,2′-*cis* nucleoside analogues **16a** and **17a** (Table 2, entries 3 and 5). The same conditions resulted in a 40% yield of the adenosine nucleoside analogue **18a** using conventional heating (entry 6) and a 38% yield with microwave heating (entry 7). The main advantages of using microwave conditions are a much faster reaction time (180 °C for 10 min vs 140 °C for 3 h) with a lower amount of aluminum Lewis acid (0.6 equiv vs 3.0 equiv). In all the above cyclizations, residual starting material was not detected in the crude reaction mixtures. The low yields obtained were therefore attributed to decomposition of the starting *N,OTMS*-acetals at these high cyclization temperatures. We thus turned our attention to the nosylate series bearing a better leaving group at C4′.[22]

When heated at only 90 °C, *N,OTMS*-acetal **6a** bearing a nosylate group cyclized in good yields (Table 3, entry 1) to provide L-1′,2′-*cis* nucleoside analogue **16a** (77% yield).

Table 3. S_N2-Like Cyclization of C4′-Nosylate *N,OTMS*-Acetals[a]



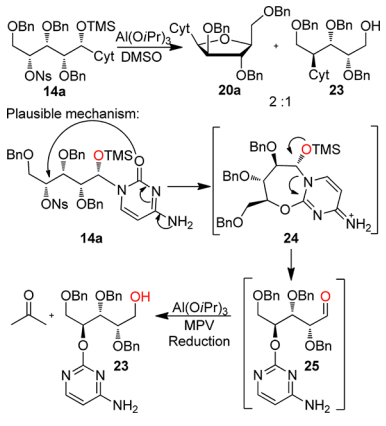
entry	*N,OTMS*-acetal	product	conditions	yield (%)
1	**6a** (Thymine)	**16a**	D	77
2	"	"	E	63
3	**8a** (Uracil)	**17a**	D	74
4	"	"	E	61
5	**10a** (Adenine)	**18a**	D	17
6	"	"	E	60
7	**12a** (5F-Uracil)	**19a**	D	63
8	"	"	E	45
9	**14a** (Cytosine)	**20a**	D	28
10	"	"	E	46
11[b]	**21a** (N^4–AcCyt)	**22a**	D	8
12	"	"	E	52

[a]Conditions D: 90 °C, 3 h. Conditions E: 90 °C, 3 h, $Al(OiPr)_3$ (3.0 equiv). [b]*N,OTMS*-N^4–AcCytosine acetal **21a** was synthesized through acetylation of the 1′,2′-*syn* cytosine acetal **14a**.

Satisfying results were also achieved with uracil and 5F-uracil using this simple procedure (entries 3 and 7). Low yields were noted, however, for *N,OTMS*-acetals bearing adenine, cytosine and N^4–AcCytosine nucleobases (Table 3, entries 5, 9, and 11). The addition of $Al(OiPr)_3$ was thus considered. Whereas no improvements were noted for the thymine, uracil and 5F-uracil cases (entries 2, 4 and 8), significantly higher yields were noted with adenine (entry 6, 60% yield), along with cytosine and its derivative (entries 10 and 12). The role of the Lewis acid in these reactions has yet to be elucidated, but its acidic character could allow for complexation to the sulfonate oxygens of the C4′ protecting group, enhancing its leaving group ability.[23]

In the course of the synthesis of 1′,2′-*cis* analogue **20a** bearing cytosine as the nucleobase (Table 3, entry 10), we observed the formation of primary alcohol **23** in a 1:2 ratio with the cyclized nucleoside **20a** (Scheme 4). This side product could form through an intramolecular or an intermolecular S_N2 displacement of the C4′-Ns by the carbonyl group of the

Scheme 4. Formation of Side-Product 23



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cytosine moiety. The formation of only one regioisomer suggests that the intramolecular displacement prevails. The resulting cyclic intermediate **24** would collapse to the corresponding aldehyde **25** with rearomatization of the cytosine. In the presence of $Al(OiPr)_3$, the aldehyde would then undergo a Meerwein-Ponndorf-Verley (MPV) reduction[24] to furnish primary alcohol **23**. This side product was formed in various amounts with the other nucleobases in the presence of $Al(OiPr)_3$. It is noteworthy that adenine precursors did not lead to this side product.

In all the nucleobase coupling reactions, the *N,OTMS*-acetals were purified prior to cyclization. Since some acetal cleavage was suspected on silica gel, cyclization of the crude acetals was tested. The L-1′,2′-*cis* nucleoside analogues were formed over two steps using the crude 1′,2′-*syn N,OTMS*-acetal product for the C1′ → C4′ cyclization. It was observed that the yields of L-1′,2′-*cis* analogues obtained from cyclization of crude *N,OTMS*-acetals were consistent with those obtained from the purified acetals. This indicates that there is no need to purify the 1′,2′-*syn N,OTMS*-acetals prior to C1′ → C4′ cyclization, rendering the process even simpler.

Mechanistic Insights for the C1′ → C4′ Cyclization. Different scenarios were considered for the mechanism of C1′ → C4′ cyclization. It was first hypothesized that the oxygen of the *N,OTMS*-acyclic acetal could serve as the nucleophile displacing the leaving group at C4′ to form the L-nucleosides (Figure 2, Path A). Alternatively, the reacting intermediate in the cyclization could involve a hexacoordinate silicon complex[25] in the presence of DMSO that would increase the nucleophilicity of the oxygen. ^{1}H NMR spectroscopic analysis of the C1′ → C4′ cyclizations of nosylated acetals in DMSO-d_6 unveiled yet another possibility (Figure 2). This experiment indicates that cyclization of **6a** proceeds within 47 h at room temperature with the formation of an intermediate species that completely converts to product. Despite the fact that we could not isolate this intermediate, observed ^{1}H NMR characteristics are in good agreement with a hemiaminal arising from in situ deprotection of the OTMS acetal. As seen in Figure 2, NMR chemical shifts that may correspond to H1′ and H4′ of the intermediate are very similar to those of the starting material, suggesting that the acetal center and nosylate protecting group are still present. It is also interesting to note that there are no NMR signals corresponding to an additional silyl protecting group, which further indicates that **6a** has indeed been deprotected to the corresponding hemiaminal **26**.[26] The cyclization could therefore occur through the hemiaminal generated after in situ deprotection of the *N,OTMS*-acetal with retention of configuration at C1′ (Figure 2, Path B). In the course of these NMR experiments, the hemiaminal **26** did not decompose to aldehyde **4** with loss of the thymine nucleobase.

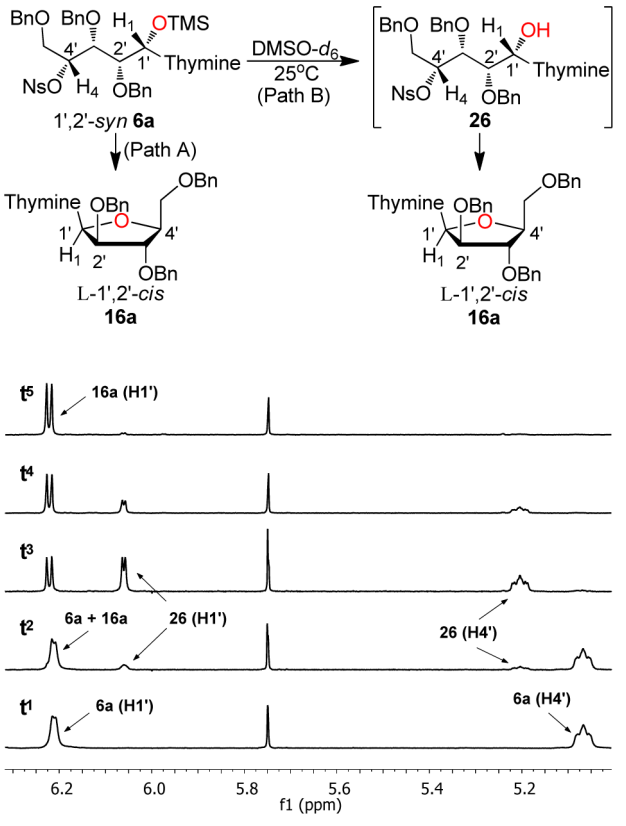
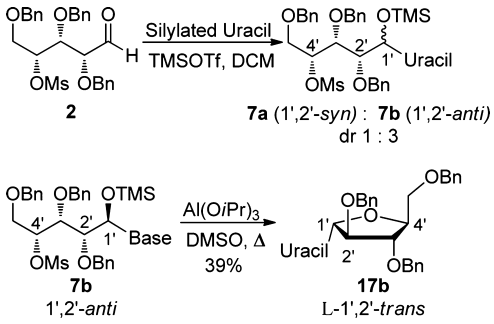


Figure 2. ^{1}H NMR spectra during cyclization of 1′,2′-*syn N,OTMS*-acetal **6a** at 25 °C where t^1 = 0 h, t^2 = 7 h, t^3 = 14 h, t^4 = 21 h, t^5 = 47 h.

In order to confirm that the C1′ → C4′ cyclization proceeds with retention of configuration at C1′, a 1′,2′-*anti N,OTMS*-acetal was synthesized and cyclized (Scheme 5). This opposite

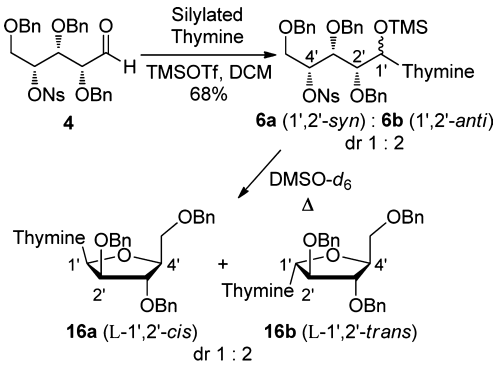
Scheme 5. Synthesis and Cyclization of 1′,2′-*anti* *N,OTMS*-Acetal 7b



1′,2′-*anti* configuration was generated with poor selectivity (1′,2′-*syn*:1′,2′-*anti*; 1:3) in presence of TMSOTf, but a pure fraction of the 1′,2′-*anti* product could be separated by flash chromatography. Cyclization of **7b** provided only the L-1′,2′-*trans* nucleoside analogue **17b** (>20:1), as determined by the ^{1}H NMR of the crude reaction mixture.

The retention of configuration at C1′ for the C1′ → C4′ cyclization was also further examined in the nosylate series (Scheme 6). A 1:2 mixture of **6a**:**6b** was prepared by coupling

Scheme 6. Synthesis and Cyclization of a Mixture of *N,OTMS*-Acetals 6a and 6b



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aldehyde **4** with silylated thymine in presence of TMSOTf (Scheme 6). The 1′,2′-*syn* and *anti N,OTMS*-acetals could not be separated and were therefore cyclized as a mixture in DMSO-d_6. The corresponding 1:2 mixture of the L-1′,2′-*cis* and *trans* nucleoside analogues **16a** and **16b** was obtained cleanly as expected.

CONCLUSIONS

We have reported a novel strategy for the synthesis of valuable L-1′,2′-*cis* nucleoside analogues from unusual 1′,2′-*syn N,OTMS*-acetals bearing pyrimidine as well as purine bases. In order to diastereoselectively generate these acyclic precursors, we have developed a methodology that involves addition of silylated nucleobases onto polyalkoxyaldehydes in the presence of $MgBr_2{\cdot}OEt_2$ through a suggested Cram-chelate transition state. These *N,OTMS*-acetals can undergo unprecedented C1′ → C4′ cyclization with complete retention of configuration at C1′. NMR studies of the reaction may have unveiled a possible mechanism involving an in situ deprotection of the *N,OTMS*-acetals. This strategy provides a stereoselective access to unnatural L-nucleosides starting from easily accessible pools of D-sugars. As importantly, this methodology addresses the challenging synthesis of 1′,2′-*cis* nucleosides. Finally, this sequence has proven to be reliable and versatile for a variety of nucleobases.

EXPERIMENTAL SECTION

General Comments. All reactions requiring anhydrous conditions were carried out under an atmosphere of nitrogen or argon in flame-dried glassware using standard syringe techniques. Dichloromethane, acetonitrile, toluene and dimethylsulfoxide were dried with 4 Å molecular sieves prior to use. The 4 Å molecular sieves (1−2 mm beads) were activated by heating at 180 °C for 48 h under a vacuum prior to adding to new bottles of solvent purged with argon. Commercially available reagents were used as received unless otherwise noted. Silylated bases were prepared by known methods.[27] Ambersep 900 OH basic resin obtained from commercial sources was rinsed thoroughly with methanol and acetone, kept under a vacuum for 16 h and stored at 25 °C. Flash chromatography was performed on silica gel 60 (0.040−0.063 mm) using forced flow flash chromatography or an automated flash purification system. Analytical thin-layer chromatography (TLC) was carried out on precoated (0.25 mm) silica gel aluminum plates. Visualization was performed with UV short wavelength and/or revealed with ammonium molybdate or potassium permanganate solutions. ^{1}H NMR spectra were recorded at room temperature on 400 and 500 MHz NMR spectrometers as indicated. The data are reported as follows: chemical shift in ppm referenced to residual solvent ($CDCl_3$ δ 7.26 ppm), multiplicity (s = singlet, apps = apparent singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, appdd = apparent doublet of doublets, t = triplet, appt = apparent triplet, m = multiplet), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded at room temperature using 100 or 125 MHz as indicated. The data are reported as follows: chemical shift in ppm referenced to residual solvent ($CDCl_3$ δ 77.16 ppm). Infrared spectra were recorded using a FTIR spectrophotometer on a NaCl support, and signals are reported in cm^{-1}. Mass spectra were recorded either through electrospray ionization (ESI) or electron impact (EI) on an instrument operating at 70 eV. An Orbitrap mass analyzer was used for HRMS measurements. Optical rotations were measured at room temperature from the sodium D line (589 nm) using CH_2Cl_2 as solvent unless otherwise noted and calculated using the formula $\alpha_D = (100)\alpha_{obs}/(l \cdot (c))$, where c = (g of substrate/100 mL of solvent) and l = 1 dm.

(−)-(2*R*,3*S*,4*R*)-1,3,4-tris(Benzyloxy)-5,5-bis(ethylthio)-pentan-2-ol (1). To a solution of methyl 2,3,5-tri-*O*-benzy-D-*xylo*-furanoside[15] (9.85 g, 23 mmol) in EtSH (9.8 mL, 131.5 mmol, 5.8 equiv) was added concentrated HCl (13.6 mL, 7.5 equiv). The reaction mixture was maintained for 16 h at 25 °C and diluted with distilled water (50 mL). The aqueous layer was extracted with ether (3 × 50 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 80:20) provided **1** (9.15 g, 77%) as a yellow solid: R_f = 0.2 (hexanes/EtOAc, 80:20); $[\alpha]^{25}_D$ −11.0 (c 1.00, CH_2Cl_2); mp 55−57 °C; Formula $C_{30}H_{38}O_4S_2$; MW 526.7503 g/mol; IR (neat) ν_{max} 3450, 2925, 1452 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.21 (m, 15H), 4.91 (d, J = 11.1 Hz, 1H), 4.81 (d, J = 2.1 Hz, 1H), 4.78 (d, J = 2.1 Hz, 1H), 4.56−4.43 (m, 3H), 4.12 (dd, J = 7.4, 3.0 Hz, 1H), 4.03 (d, J = 3.0 Hz, 1H), 3.99−3.94 (m, 2H), 3.54 (dd, J = 9.5, 6.7 Hz, 1H), 3.43 (dd, J = 9.5, 5.5 Hz, 1H), 2.81−2.61 (m, 4H), 2.50 (s, 1H), 1.26 (t, J = 4.7 Hz, 3H), 1.23 (t, J = 4.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 138.1, 137.8, 128.31, 128.30, 128.23, 128.16, 127.73, 127.69, 127.67, 127.63, 127.4, 83.2, 79.8, 75.3, 75.0, 73.2, 71.3, 69.8, 53.2, 25.9, 25.2, 14.5, 14.4 ppm; HRMS calcd for $C_{30}H_{38}O_4NaS_2$ [M + Na$^+$] 549.2104, found 549.2105 (−0.8 ppm).

(−)-(2*R*,3*R*,4*R*)-1,3,4-tris(Benzyloxy)-5,5-bis(ethylthio)-pentan-2-yl methanesulfonate (S1). To a 0.2 M solution of dithioacetal **1** (3.99 g, 7.57 mmol) in CH_2Cl_2 (38 mL) at −40 °C were added Et_3N (1.6 mL, 11.35 mmol, 1.5 equiv) and MsCl (0.77 mL, 9.84 mmol, 1.3 equiv). The reaction was maintained for 30 min at −40 °C and 2 h at 0 °C. 1 N HCl (5 mL) was then added to the reaction mixture. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL), dried over $MgSO_4$ and concentrated in vacuo. **S1** was obtained as a colorless oil and used as a crude mixture for the next reaction. Purification by flash chromatography (hexanes/EtOAc, 80:20) of an aliquot of the reaction mixture allowed for characterization of **S1**: R_f = 0.43 (hexanes/EtOAc, 80:20); $[\alpha]^{25}_D$ −8.70 (c 1.00, CH_2Cl_2); Formula $C_{31}H_{40}O_6S_3$; MW 604.8407 g/mol; IR (neat) ν_{max} 3030, 2926, 1357, 1173 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.25 (m, 15H), 4.96−4.90 (m, 2H), 4.81 (d, J = 11.4 Hz, 1H), 4.72 (d, J = 10.9 Hz, 1H), 4.63 (d, J = 11.4 Hz, 1H), 4.44 (dd, J = 28.8, 11.7 Hz, 2H), 4.23 (dd, J = 6.1, 4.4 Hz, 1H), 4.18 (d, J = 4.5 Hz, 1H), 4.00 (dd, J = 6.1, 4.5 Hz, 1H), 3.72 (dd, J = 11.2, 7.1 Hz, 1H), 3.57 (dd, J = 11.3, 3.1 Hz, 1H), 3.00 (s, 3H), 2.86−2.60 (m, 4H), 1.29−1.26 (m, 3H), 1.25−1.23 (m, 3H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.2, 137.8, 137.3, 128.53, 128.47, 128.43, 128.34, 128.0, 127.99, 127.93, 127.91, 127.7, 81.7, 81.4, 78.7, 75.4, 75.1, 73.3, 69.7, 52.7, 38.7, 25.5, 25.2, 14.6, 14.7 ppm; HRMS calcd for $C_{31}H_{40}O_6NaS_3$ [M + Na$^+$] 627.1879, found 627.1902 (2.8 ppm).

(−)-(2*R*,3*R*,4*R*)-1,3,4-tris(Benzyloxy)-5-oxopentan-2-yl methanesulfonate (2). To a 0.1 M solution of **S1** (4.58 g, 7.57 mmol) in a 3:1 mixture of acetone (90 mL):H_2O (30 mL) at 0 °C were added 2,6-lutidine (7.0 mL, 60.5 mmol, 8.0 equiv) and NBS (11.0 g, 60.5 mmol, 8.0 equiv). After the reaction was maintained for 15 min at 0 °C, a 15% solution of $Na_2S_2O_3$ (100 mL) was added. The aqueous layer was extracted with ether (3 × 100 mL), and the combined organic layers were washed with 1 N HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 80:20) provided aldehyde **2** (2.89 g, 77%) as a yellowish oil: R_f = 0.13 (hexanes/EtOAc, 80:20); $[\alpha]^{25}_D$ −26.4 (c 1.00, CH_2Cl_2); Formula $C_{27}H_{30}O_7S$; MW 498.5879 g/mol; IR (neat) ν_{max} 3031, 1732, 1357, 1175 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (d, J = 0.8 Hz, 1H), 7.39−7.24 (m, 15H), 4.95−4.89 (m, 1H), 4.70 (d, J = 11.7 Hz, 1H), 4.63 (d, J = 11.3 Hz, 1H), 4.54 (d, J = 11.3 Hz, 1H), 4.48 (d, J = 11.8 Hz, 1H), 4.43 (d, J = 11.6 Hz, 1H), 4.38 (d, J = 11.8 Hz, 1H), 4.19 (dd, J = 6.0, 3.9 Hz, 1H), 3.91 (dd, J = 3.9, 0.8 Hz, 1H), 3.75 (dd, J = 11.1, 3.7 Hz, 1H), 3.56 (dd, J = 11.1, 5.7 Hz, 1H), 2.94 (s, 3H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 201.8, 137.3, 136.8, 136.4, 128.7, 128.58, 128.57, 128.56, 128.45, 128.42, 128.3, 128.1, 128.0, 81.4, 80.3, 77.3, 74.7, 73.39, 73.37, 68.4, 38.2 ppm; HRMS calcd for $C_{27}H_{30}O_7NaS$ [M + Na$^+$] 521.1604, found 521.1589 (−2.1 ppm).

(2*R*,3*S*,4*S*)-1,3,4-tris(Benzyloxy)hex-5-en-2-ol (3). The reported procedure for the formation of **3** was slightly modified.[16a] *n*-Butyllithium (2.5 M in hexane, 2.86 mL, 7.15 mmol, 3.0 equiv) was

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added dropwise to a stirred suspension of methyltriphenylphosphonium bromide (2.5 g, 7.15 mmol, 3.0 equiv previously dried with benzene) in dry THF (0.55 M,13 mL) at 0 °C. The resulting yellowish mixture was maintained for 2 h at 25 °C. The reaction mixture was cooled to 0 °C before dropwise addition of 2,3,5-*O*-tribenzyl-D-*xylo*furanose[16b,c] (1.0 g, 2.4 mmol) in dry THF (0.3 M, 8 mL). A cream-colored precipitate appeared, and the reaction mixture was refluxed for 2 h at 100 °C. After cooling to 25 °C, silica gel (1.5 g) was added to the reaction mixture, and the solvent was removed in vacuo. The resulting crude mixture was dissolved in ether (100 mL) and passed through a silica gel pad. The mixture was again concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 70:30) provided **3** (0.70 g, 70%) as a yellow oil. ^{1}H NMR spectroscopic data correlate with the previously reported data for the enantiomer of **3**:[28] Formula $C_{27}H_{30}O_4$; MW 418.5247 g/mol; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.25 (m, 15H), 5.87 (ddd, J = 17.9, 10.4, 7.8 Hz, 1H), 5.36 (d, J = 25.0 Hz, 1H), 5.36 (s, 1H), 4.86 (d, J = 11.2 Hz, 1H), 4.63 (d, J = 11.8 Hz, 1H), 4.56 (d, J = 11.2 Hz, 1H), 4.47 (d, J = 11.9 Hz, 1H), 4.43 (d, J = 11.9 Hz, 1H), 4.39 (d, J = 11.8 Hz, 1H), 4.13−4.08 (m, 1H), 3.95−3.91 (m, 1H), 3.62 (dd, J = 6.5, 2.6 Hz, 1H), 3.45 (dd, J = 9.5, 6.1 Hz, 1H), 3.42 (dd, J = 9.5, 6.3 Hz, 1H), 2.43 (s, 1H).

(+)-(2*R*,3*R*,4*S*)-1,3,4-tris(Benzyloxy)hex-5-en-2-yl 4-nitrobenzenesulfonate (S3). To a 0.2 M solution of **3** (2 g, 4.8 mmol) in CH_2Cl_2 (24 mL) at 0 °C was added NsCl (2.12 g, 9.6 mmol, 2.0 equiv). A 0.4 M solution of DMAP (0.47 g, 3.83 mmol, 0.8 equiv) and Et_3N (2.4 mL, 17.2 mmol, 3.6 equiv) in CH_2Cl_2 (10 mL) was then added dropwise. The reaction mixture was refluxed for 16 h at 50 °C, and 1 N HCl (5 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 85:15) provided **S3** (2.25 g, 78%) as a yellow oil: R_f = 0.26 (hexanes/EtOAc, 85:15); $[\alpha]^{25}_D$ +0.950 (*c* 1.26, CH_2Cl_2); Formula $C_{33}H_{33}NO_8S$; MW 603.6820 g/mol; IR (neat) ν_{max} 2869, 1531, 1349, 1185 cm^{-1}; ^{1}H NMR 8.00−7.88 (m, 4H), 7.38−7.24 (m, 11H), 7.18 (dd, J = 6.8, 2.4 Hz, 2H), 7.14 (dd, J = 6.8, 2.4 Hz, 2H), 5.89 (ddd, J = 17.6, 10.0, 7.5 Hz, 1H), 5.38 (d, J = 5.1 Hz, 1H), 5.35 (s, 1H), 4.96 (ddd, J = 6.5, 5.8, 2.7 Hz, 1H), 4.62 (d, J = 11.5 Hz, 1H), 4.58 (d, J = 11.8 Hz, 1H), 4.46 (d, J = 11.5 Hz, 1H), 4.31 (d, J = 11.7 Hz, 1H), 4.24 (d, J = 11.8 Hz, 1H), 4.15 (d, J = 11.7 Hz, 1H), 3.95 (dd, J = 7.4, 4.0 Hz, 1H), 3.76 (dd, J = 6.6, 4.0 Hz, 1H), 3.66 (dd, J = 11.5, 2.7 Hz, 1H), 3.45 (dd, J = 11.5, 5.6 Hz, 1H). ^{13}C NMR (125 MHz, CD_3Cl) δ 150.2, 142.9, 137.8, 137.7, 137.4, 134.4, 129.1, 128.55, 128.51, 128.4, 128.3, 128.1, 127.98, 127.96, 127.91, 127.8, 123.9, 120.1, 83.9, 79.8, 79.2, 74.9, 73.3, 70.5, 68.9 ppm; HRMS calcd for $C_{33}H_{34}NO_8S$ [M + H$^+$] 604.2000, found 604.2018 (2.9 ppm).

(+)-(2*R*,3*R*,4*R*)-1,3,4-tris(Benzyloxy)-5-oxopentan-2-yl 4-nitrobenzenesulfonate (4). A 0.025 M solution of **S3** (1.27 g, 2.1 mmol) in CH_2Cl_2 (84 mL) was cooled to −78 °C and bubbled with O_3 in O_2 atmosphere for 40 min. TLC indicated the disappearance of the starting material. The system was purged with N_2 to remove the unreacted O_3. Et_3N (0.60 mL, 4.19 mmol, 2.0 equiv) was added to the reaction mixture, which was warmed to 25 °C for 30 min, followed by the addition of 1 N HCl (2 mL). The aqueous layer was extracted with ether (3 × 50 mL), and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 70:30) provided **4** (1.07 g, 84%) as a brown oil: R_f = 0.37 (hexanes/EtOAc, 70:30); $[\alpha]^{25}_D$ +14.5 (*c* 2.37, CH_2Cl_2); Formula $C_{32}H_{31}NO_9S$; MW 605.6548 g/mol; IR (neat) ν_{max} 2870, 1535, 1369, 1186 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.61 (s, 1H), 8.03−8.00 (m, 2H), 7.93−7.89 (m, 2H), 7.39−7.34 (m, 3H), 7.34−7.25 (m, 8H), 7.18−7.12 (m, 4H), 4.96 (ddd, J = 6.2, 5.7, 3.0 Hz, 1H), 4.69 (d, J = 11.7 Hz, 1H), 4.47 (d, J = 1.2 Hz, 2H), 4.43 (d, J = 11.7 Hz, 1H), 4.31 (d, J = 11.6 Hz, 1H), 4.21−4.17 (m, 2H), 3.90 (d, J = 3.6 Hz, 1H), 3.69 (dd, J = 11.5, 3.0 Hz, 1H), 3.45 (dd, J = 11.5, 5.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.9, 150.4, 142.2, 137.1, 136.9, 136.4, 129.3, 128.8, 128.72, 128.69, 128.59, 128.47, 128.36, 128.29, 128.04, 128.03, 124.0, 82.4, 81.7, 77.4, 74.8, 73.54, 73.45, 68.4 ppm; HRMS calcd for $C_{32}H_{35}N_2O_9S$ [M + NH_4^+] 623.2058, found 623.2047 (−1.7 ppm).

General Procedure A: Preparation of *N,OTMS*-Acetals. To a solution of aldehyde **2** or **4** in MeCN (0.1 M) at −40 °C were successively added silylated base (2.0−4.0 equiv of a 0.6 M solution in CH_2Cl_2) and $MgBr_2{\cdot}OEt_2$ (2.0 equiv). The reaction mixture was maintained for 4 h at −40 °C, followed by addition of saturated aqueous $NaHCO_3$ (2 mL). The aqueous layer was extracted with ethyl acetate (3 × 5 mL), and the combined organic layers were washed with brine (5 mL), dried over $MgSO_4$ and concentrated in vacuo.

(−)-(2*R*,3*R*,4*R*,5*S*)-1,3,4-tris(Benzyloxy)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-5-((trimethylsilyl)oxy)-pentan-2-yl methanesulfonate (5a). Following general procedure A, silylated thymine (0.56 mL of a 0.64 M solution in CH_2Cl_2, 0.36 mmol, 2.0 equiv) and $MgBr_2{\cdot}OEt_2$ (92 mg, 0.36 mmol, 2.0 equiv) were added to a solution of aldehyde **2** (89 mg, 0.18 mmol) in MeCN (1.8 mL). ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (hexanes/EtOAc, 70:30) provided **5a** (92 mg, 74%) as a white foam: R_f = 0.13 (hexanes/EtOAc, 70:30); $[\alpha]^{25}_D$ −52.9 (*c* 1.16, $CDCl_3$); Formula $C_{35}H_{44}N_2O_9SiS$; MW 696.8824 g/mol; IR (neat) ν_{max} 3191, 1691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.19 (m, 14H), 7.08 (dd, J = 6.5, 2.9 Hz, 2H), 6.18 (d, J = 2.3 Hz, 1H), 4.99−4.93 (m, 1H), 4.81 (d, J = 11.1 Hz, 1H), 4.68 (d, J = 3.1 Hz, 1H), 4.65 (d, J = 3.1 Hz, 1H), 4.53 (d, J = 11.7 Hz, 1H), 4.47 (d, J = 11.7 Hz, 1H), 4.29 (d, J = 11.1 Hz, 1H), 4.03 (dd, J = 6.7, 5.1 Hz, 1H), 3.89 (dd, J = 10.0, 5.7 Hz, 1H), 3.84 (dd, J = 10.1, 5.8 Hz, 1H), 3.80 (dd, J = 6.6, 2.3 Hz, 1H), 3.11 (s, 3H), 1.83 (s, 3H), 0.15 (s, 9H) ppm; *NH signal missing possibly due to exchange in CDCl$_3$*; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.4, 150.2, 137.6, 137.48, 136.52, 128.6, 128.45, 128.41, 128.34, 128.25, 128.18, L-127.9, 127.7, 127.6, 109.4, 79.6, 79.3, 77.5, 76.8, 75.3, 75.2, 73.3, 68.2, 38.7, 12.3, −0.40 ppm; HRMS calcd for $C_{35}H_{45}N_2O_9SiS$ [M + H$^+$] 697.2610, found 697.2619 (0.6 ppm).

(−)-(2*R*,3*R*,4*R*,5*S*)-1,3,4-tris(Benzyloxy)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-5-((trimethylsilyl)oxy)-pentan-2-yl 4-nitrobenzenesulfonate (6a). Following general procedure A, silylated thymine (1.4 mL of a 0.62 M solution in CH_2Cl_2, 0.84 mmol, 2.0 equiv) and $MgBr_2{\cdot}OEt_2$ (218 mg, 0.84 mmol, 2.0 equiv) were added to a solution of aldehyde **4** (255 mg, 0.42 mmol) in MeCN (4.2 mL). ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (hexanes/EtOAc, 70:30) provided **6a** (209 mg, 62%) as a white foam: R_f = 0.19 (hexanes/EtOAc, 70:30); $[\alpha]^{25}_D$ −33.3 (*c* 0.840, CH_2Cl_2); Formula $C_{40}H_{45}N_3O_{11}SiS$; MW 803.9493 g/mol; IR (neat) ν_{max} 3032, 1690, 1531 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.06−7.94 (m, 4H), 7.39−7.20 (m, 12H), 7.14 (dd, J = 6.5, 2.9 Hz, 2H), 7.06 (dd, J = 7.2, 2.0 Hz, 2H), 6.29 (d, J = 3.1 Hz, 1H), 5.07 (ddd, J = 6.8, 6.3, 3.5 Hz, 1H), 4.66 (d, J = 11.4 Hz, 1H), 4.55 (dd, J = 12.6, 11.5 Hz, 2H), 4.33 (d, J = 11.5 Hz, 1H), 4.30 (d, J = 2.8 Hz, 1H), 4.28 (d, J = 2.4 Hz, 1H), 3.95 (dd, J = 6.7, 5.8 Hz, 1H), 3.84 (dd, J = 10.9, 3.4 Hz, 1H), 3.72−3.65 (m, 2H), 1.84 (s, 3H), 0.18 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7, 150.3, 149.7, 142.8, 137.5, 137.4, 137.3, 136.5, 129.3, 128.68, 128.62, 128.59, 128.53, 128.48, 128.28, 128.24, 128.1, 127.8, 123.9, 109.8, 83.7, 78.7, 77.4, 75.8, 74.79, 74.77, 73.5, 68.7, 12.5, −0.24 ppm; HRMS calcd for $C_{40}H_{46}O_{11}N_3SiS$ [M + H$^+$] 804.2617, found 804.2635 (2.3 ppm).

(2*R*,3*R*,4*R*)-1,3,4-tris(Benzyloxy)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-5-((trimethylsilyl)oxy)pentan-2-yl 4-nitrobenzenesulfonate (6a and 6b). To a solution of aldehyde **4** (96 mg, 0.16 mmol) in CH_2Cl_2 (0.1 M, 1.6 mL) at 0 °C were successively added silylated thymine (0.87 mL of a 0.64 M solution in CH_2Cl_2, 0.55 mmol, 3.5 equiv) and TMSOTf (57 μL, 0.32 mmol, 2.0 equiv). The reaction mixture was maintained at 0 °C for 5 h, followed by addition of saturated aqueous $NaHCO_3$ (2 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were washed with brine (5 mL), dried over $MgSO_4$ and concentrated in vacuo. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a 1:2 mixture of 1′,2′-*syn* and *anti* diastereomers. Purification by flash chromatography (hexanes/EtOAc, 70:30) did not allow for separation of the

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diastereomers and provided a mixture of **6a** and **6b** (87 mg, 68%) as a white foam: R_f = 0.19 (hexanes/EtOAc, 70:30); Representative NMR resonances, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (s, 1H, isomer a), 8.51 (s, 1H, isomer b), 8.07−7.95 (m, 8H, isomer a and b), 7.35−7.24 (m, 24H, isomer a and b), 7.22 (dd, J = 7.3, 2.0 Hz, 2H, isomer b), 7.14 (dd, J = 6.5, 2.9 Hz, 2H, isomer a), 7.06 (dd, J = 7.2, 2.1 Hz, 2H, isomer a), 7.01 (dd, J = 6.9, 2.4 Hz, 2H, isomer b), 6.29 (d, J = 3.1 Hz, 1H, isomer a), 6.21 (d, J = 5.2 Hz, 1H, isomer b), 5.26−5.20 (m, 1H, isomer b), 5.07 (ddd, J = 6.9, 6.4, 3.5 Hz, 1H, isomer a), 4.81 (dd, J = 21.4, 11.5 Hz, 2H, isomer b), 4.67 (d, J = 11.7 Hz, 1H, isomer a), 4.55 (appt, J = 11.7 Hz, 2H, isomer a), 4.34 (d, J = 11.5 Hz, 1H, isomer a), 4.30 (d, J = 5.2 Hz, 1H, isomer a), 4.28 (d, J = 4.9 Hz, 1H, isomer a), 4.20 (d, J = 11.6 Hz, 2H, isomer b), 4.05−3.98 (m, 2H, isomer b), 3.97−3.93 (m, 1H, isomer a), 3.85 (dd, J = 10.9, 3.4 Hz, 1H, isomer a), 3.73−3.68 (m, 2H, isomer b), 3.66 (dd, J = 7.4, 3.1 Hz, 2H, isomer a), 3.41−3.32 (m, 2H, isomer b), 1.84 (s, 3H, isomer a), 1.79 (d, J = 0.7 Hz, 3H, isomer b), 0.18 (s, 9H, isomer a), 0.14 (s, 9H, isomer b) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7 (isomer a), 163.6 (isomer b), 150.6 (isomer b), 150.4 (isomer b), 150.3 (isomer a), 149.7 (isomer a), 142.8 (isomer a), 142.5 (isomer b), 137.5 (isomer a), 137.41 (isomer a), 137.38 (isomer b), 137.34, 137.1 (isomer b), 136.8 (isomer b), 136.5 (isomer a), 129.30 (isomer b), 129.25(isomer a), 128.68, 128.62 (isomer a), 128.58, 128.52 (isomer a), 128.49 (isomer a), 128.47 (isomer b), 128.44 (isomer b), 128.38 (isomer b), 128.28 (isomer a), 128.23 (isomer a), 128.20 (isomer b), 128.18 (isomer b), 128.07 (isomer a), 127.81 (isomer a, 127.79 (isomer b), 123.96 (isomer b), 123.94 (isomer a), 110.6 (isomer b), 109.8 (isomer a), 83.7 (isomer a), 82.9 (isomer b), 79.3 (isomer b), 78.7 (isomer a), 77.4 (isomer a), 76.9 (isomer b), 75.8 (isomer a), 75.5 (isomer b), 75.06 (isomer b), 74.77 (isomer a), 73.5 (isomer a), 73.1 (isomer b), 68.9 (isomer b), 68.6 (isomer a), 12.6 (isomer b), 12.5 (isomer a), −0.25 (isomer a), −0.29 (isomer b) ppm.

(−)-(2*R*,3*R*,4*R*,5*S*)-1,3,4-tris(Benzyloxy)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-5-((trimethylsilyl)oxy)pentan-2-yl methanesulfonate (7a). Following general procedure A, silylated uracil (0.45 mL of a 0.69 M solution in CH_2Cl_2, 0.312 mmol, 2.0 equiv) and $MgBr_2{\cdot}OEt_2$ (81 mg, 0.312 mmol, 2.0 equiv) were added to a solution of aldehyde **2** (78 mg, 0.16 mmol) in MeCN (1.6 mL). ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (hexanes/EtOAc, 50:50) provided **7a** (64 mg, 61%) as a white foam: R_f = 0.31 (hexanes/EtOAc, 50:50); $[\alpha]^{25}_D$ −58.6 (c 0.910, CH_2Cl_2); Formula $C_{34}H_{42}N_2O_9SiS$; MW 682.8558 g/mol; IR (neat) ν_{max} 3190, 2955, 1687 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.36−7.25 (m, 13H), 7.10 (dd, J = 7.0, 2.1 Hz, 2H), 6.18 (d, J = 2.6 Hz, 1H), 5.59 (dd, J = 8.1, 2.0 Hz, 1H), 4.98−4.95 (m, 1H), 4.77 (d, J = 11.1 Hz, 1H), 4.66 (d, J = 11.1 Hz, 1H), 4.62 (d, J = 11.2 Hz, 1H), 4.52 (d, J = 11.7 Hz, 1H), 4.47 (d, J = 11.7 Hz, 1H), 4.32 (d, J = 11.2 Hz, 1H), 4.02−3.98 (m, 1H), 3.88 (dd, J = 10.2, 5.2 Hz, 1H), 3.82 (dd, J = 10.2, 5.8 Hz, 1H), 3.76 (dd, J = 6.6, 2.7 Hz, 1H), 3.07 (s, 3H), 0.16 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2, 149.7, 141.8, 137.6, 137.5, 136.5, 128.9, 128.68, 128.66, 128.56, 128.54, 128.4, 128.2, 127.99, 127.87, 101.3, 80.4, 78.6, 77.9, 76.6, 75.3, 75.1, 73.6, 68.6, 38.8, −0.26 ppm; HRMS calcd for $C_{34}H_{43}N_2O_9SiS$ [M + H$^+$] 683.2453, found 683.2456 (0.5 ppm).

(+)-(2*R*,3*R*,4*R*,5*R*)-1,3,4-tris(Benzyloxy)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-5-((trimethylsilyl)oxy)pentan-2-yl methanesulfonate (7b). To a solution of aldehyde **2** (54 mg, 0.11 mmol) in CH_2Cl_2 (0.1 M, 1.1 mL) at 0 °C were successively added silylated uracil (0.77 mL of a 0.5 M solution in CH_2Cl_2, 0.38 mmol, 3.5 equiv) and TMSOTf (30 μL, 0.16 mmol, 1.5 equiv). The reaction mixture was maintained at 0 °C for 16 h, followed by addition of saturated aqueous $NaHCO_3$ (2 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were washed with brine (5 mL), dried over $MgSO_4$ and concentrated in vacuo. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a 1:3 mixture of 1′,2′-*syn* and *anti* diastereomers. Purification by flash chromatography (hexanes/EtOAc, 50:50) provided **7b** as a white foam. A total of 33 mg (45%) of pure 1′,2′-*anti* diastereomer 7b and a mixture of 1′,2′-*syn* and *anti* diastereomers was obtained. **7b**: R_f = 0.49 (hexanes/EtOAc, 50:50); $[\alpha]^{25}_D$ +24.6 (c 1.15, $CDCl_3$); Formula $C_{34}H_{42}N_2O_9SiS$; MW 682.8558 g/mol; IR (neat) ν_{max} 3188, 2955, 1685 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.43 (d, J = 8.2 Hz, 1H), 7.35−7.31 (m, 15H), 6.14 (d, J = 5.0 Hz, 1H), 5.53 (dd, J = 8.1, 2.1 Hz, 1H), 5.18−5.13 (m, 1H), 4.82 (d, J = 11.4 Hz, 1H), 4.78 (d, J = 11.6 Hz, 1H), 4.64 (d, J = 11.5 Hz, 1H), 4.55 (d, J = 11.4 Hz, 1H), 4.45 (d, J = 11.7 Hz, 1H), 4.39 (d, J = 11.7 Hz, 1H), 3.97 (dd, J = 7.4, 5.2 Hz, 1H), 3.71 (dd, J = 10.8, 7.8 Hz, 1H), 3.56 (dd, J = 7.5, 2.6 Hz, 1H), 3.40 (dd, J = 10.8, 3.5 Hz, 1H), 3.05 (s, 3H), 0.11 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.7, 150.4, 141.2, 137.4, 137.34, 137.32, 128.8, 128.63, 128.62, 128.59, 128.34, 128.27, 128.18, 128.13, 128.0, 102.2, 80.9, 79.9, 78.7, 76.8, 75.5, 75.4, 73.3, 69.6, 38.8, −0.33 ppm; HRMS calcd for $C_{34}H_{43}N_2O_9SiS$ [M + H$^+$] 683.2453, found 683.2459 (0.8 ppm).

(−)-(2*R*,3*R*,4*R*,5*S*)-1,3,4-tris(Benzyloxy)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-5-((trimethylsilyl)oxy)pentan-2-yl 4-nitrobenzenesulfonate (8a). Following general procedure A, silylated uracil (0.70 mL of a 0.74 M solution in CH_2Cl_2, 0.51 mmol, 2.0 equiv) and $MgBr_2{\cdot}OEt_2$ (132 mg, 0.51 mmol, 2.0 equiv) were added to a solution of aldehyde **4** (154 mg, 0.26 mmol) in MeCN (2.6 mL). ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (hexanes/EtOAc, 50:50) provided **8a** (127 mg, 63%) as a white foam: R_f = 0.53 (hexanes/EtOAc, 50:50); $[\alpha]^{25}_D$ −34.0 (c 1.32, CH_2Cl_2); Formula $C_{39}H_{43}N_3O_{11}SiS$; MW 789.9227 g/mol; IR (neat) ν_{max} 3167, 2873, 1687, 1532 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.03−7.96 (m, 4H), 7.49 (d, J = 8.1 Hz, 1H), 7.35−7.25 (m, 11H), 7.15 (dd, J = 6.5, 2.9 Hz, 2H), 7.08 (dd, J = 7.4, 1.7 Hz, 2H), 6.31 (d, J = 2.9 Hz, 1H), 5.62 (dd, J = 8.1, 2.1 Hz, 1H), 5.11 (ddd, J = 6.7, 6.0, 3.4 Hz, 1H), 4.65 (d, J = 11.4 Hz, 1H), 4.54 (d, J = 4.6 Hz, 1H), 4.52 (d, J = 4.5 Hz, 1H), 4.37−4.27 (m, 3H), 3.94 (dd, J = 7.1, 5.7 Hz, 1H), 3.86 (dd, J = 10.9, 3.3 Hz, 1H), 3.72−3.66 (m, 2H), 0.20 (s, 9H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.47, 150.29, 149.75, 142.90, 141.73, 137.38, 137.27, 136.33, 129.19, 128.78, 128.68, 128.58, 128.55, 128.46, 128.29, 128.21, 128.06, 127.83, 123.91, 101.45, 83.94, 78.18, 77.52, 75.65, 74.71, 74.59, 73.49, 68.66, −0.30 ppm; HRMS calcd for $C_{39}H_{44}O_{11}N_3SiS$ [M + H$^+$] 790.2460, found 790.2461 (0.12 ppm).

(−)-(2*R*,3*R*,4*R*,5*S*)-5-(6-Amino-9*H*-purin-9-yl)-1,3,4-tris(benzyloxy)-5-(trimethylsilyl)oxy)pentan-2-yl methanesulfonate (9a). Following general procedure A, silylated adenine (0.60 mL of a 0.71 M solution in CH_2Cl_2, 0.43 mmol, 4.0 equiv) and $MgBr_2{\cdot}OEt_2$ (28 mg, 0.11 mmol, 1.0 equiv) were added to a solution of aldehyde **2** (53 mg, 0.11 mmol) in MeCN (1.1 mL) and maintained at −20 °C for 16 h. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (hexanes/EtOAc, 0:100) provided **9a** (50 mg, 66%) as a white foam: R_f =0.40 (hexanes/EtOAc, 0:100); $[\alpha]^{25}_D$ −14.2 (c 1.00, CH_2Cl_2); Formula $C_{35}H_{43}N_5O_7SiS$; MW 705.8957 g/mol; IR (neat) ν_{max} 3299, 3135, 1680, 1605 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.96 (s, 1H), 7.37−7.20 (m, 13H), 7.08 (dd, J = 6.4, 2.8 Hz, 2H), 6.42 (d, J = 4.0 Hz, 1H), 5.80 (s, 2H), 5.02 (appdd, J = 10.3, 5.7 Hz, 1H), 4.64 (s, 2H), 4.54 (d, J = 11.1 Hz, 1H), 4.47 (s, 2H), 4.31 (d, J = 11.1 Hz, 1H), 4.00−3.95 (m, 1H), 3.90 (dd, J = 6.0, 5.5 Hz, 1H), 3.85 (dd, J = 10.6, 4.3 Hz, 1H), 3.74 (dd, J = 10.6, 5.9 Hz, 1H), 3.10 (s, 3H), 0.07 (s, 9H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.4, 153.0, 148.9, 139.9, 137.64, 137.61, 136.8, 128.62, 128.60, 128.55, 128.458, 128.457, 128.16, 128.15, 127.95, 127.85, 119.4, 81.0, 79.1, 77.9, 76.5, 75.1, 74.9, 73.5, 68.8, 38.7, −0.29 ppm; HRMS calcd for $C_{35}H_{44}N_5O_7SiS$ [M + H$^+$] 706.2725, found 706.2724 (−0.2 ppm).

(−)-(2*R*,3*R*,4*R*,5*S*)-5-(6-Amino-9*H*-purin-9-yl)-1,3,4-tris(benzyloxy)-5-((trimethylsilyl)oxy)pentan-2-yl 4-nitrobenzenesulfonate (10a). Following general procedure A, silylated adenine (1.5 mL of a 0.69 M solution in CH_2Cl_2, 0.99 mmol, 4.5 equiv) and $MgBr_2{\cdot}OEt_2$ (58 mg, 0.22 mmol, 1.0 equiv) were added to a solution of aldehyde **4** (135 mg, 0.22 mmol) in MeCN (2.2 mL) and maintained at −40 °C for 6 h. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer

(>20:1). Purification by flash chromatography (hexanes/EtOAc, 50:50) provided **10a** (98 mg, 54%) as a white foam: R_f = 0.21 (hexanes/EtOAc, 50:50); $[\alpha]^{25}_D$ −6.0 (*c* 1.0, CH_2Cl_2); Formula $C_{40}H_{44}N_6O_9SiS$; MW 812.9627 g/mol; IR (neat) ν_{max} 3333, 3129, 1644, 1531 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.01−7.93 (m, 4H), 7.91 (s, 1H), 7.31−7.22 (m, 11H), 7.10 (dd, *J* = 6.5, 2.9 Hz, 2H), 7.08 (dd, *J* = 6.4, 2.8 Hz, 2H), 6.44 (d, *J* = 4.5 Hz, 1H), 5.66 (s, 2H), 5.11−5.06 (m, 1H), 4.49 (d, *J* = 13.1 Hz, 3H), 4.41 (d, *J* = 11.3 Hz, 1H), 4.26 (dd, *J* = 27.3, 11.6 Hz, 2H), 3.93 (appt, *J* = 4.4 Hz, 1H), 3.82−3.78 (m, 2H), 3.59 (dd, *J* = 11.2, 6.0 Hz, 1H), 0.06 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 153.1, 150.3, 149.1, 142.8, 139.9, 137.44, 137.38, 136.8, 129.2, 128.58, 128.54, 128.50, 128.49, 128.25, 128.24, 128.23, 128.1, 127.9, 123.9, 119.4, 83.9, 78.9, 77.7, 75.9, 74.7, 74.6, 73.4, 68.7, −0.30 ppm; HRMS calcd for $C_{40}H_{45}N_6O_9SiS$ $[M + H^+]$ 813.2733, found 813.2756 (2.9 ppm).

(−)-(2*R*,3*R*,4*R*,5*S*)-1,3,4-tris(Benzyloxy)-5-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-5-((trimethylsilyl)oxy)-pentan-2-yl methanesulfonate (11a). Following general procedure A, silylated 5F-uracil (1.0 mL of a 0.63 M solution in CH_2Cl_2, 0.62 mmol, 3.5 equiv) and $MgBr_2{\cdot}OEt_2$ (92 mg, 0.355 mmol, 2.0 equiv) were added to a solution of aldehyde **2** (89 mg, 0.18 mmol) in MeCN (1.8 mL) and maintained at −20 °C for 16 h. ^1H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (hexanes/EtOAc, 50:50) provided **11a** (71 mg, 57%) as a white foam: R_f = 0.49 (hexanes/EtOAc, 50:50); $[\alpha]^{25}_D$ −28.5 (*c* 2.27, CH_2Cl_2); Formula $C_{34}H_{41}FN_2O_9SiS$; MW 700.8462 g/mol; IR (neat) ν_{max} 3185, 2955, 1707 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.04 (d, *J* = 4.6 Hz, 1H), 7.48 (d, *J* = 6.2 Hz, 1H), 7.38−7.26 (m, 13H), 7.08 (dd, *J* = 6.4, 2.9 Hz, 2H), 6.13 (s, 1H), 4.98−4.95 (m, 1H), 4.79 (d, *J* = 11.2 Hz, 1H), 4.69 (d, *J* = 11.2 Hz, 1H), 4.65 (d, *J* = 11.4 Hz, 1H), 4.54 (d, *J* = 11.7 Hz, 1H), 4.49 (d, *J* = 11.7 Hz, 1H), 4.29 (d, *J* = 11.4 Hz, 1H), 4.01 (dd, *J* = 6.6, 5.6 Hz, 1H), 3.89 (dd, *J* = 10.2, 5.2 Hz, 1H), 3.83 (dd, *J* = 10.2, 5.8 Hz, 1H), 3.76 (dd, *J* = 6.8, 2.5 Hz, 1H), 3.09 (s, 3H), 0.16 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.8 (d, *J* = 26.6 Hz), 148.2, 140.6, 138.7, 137.5 (d, *J* = 9.6 Hz), 136.3, 129.090, 129.089, 128.75, 128.69, 128.56, 128.49, 128.3, 128.0, 127.9, 126.1 (d, *J* = 34.2 Hz), 80.3, 78.5, 78.1, 76.5, 75.4, 75.1, 73.6, 68.5, 38.9, −0.30 ppm; HRMS calcd for $C_{34}H_{42}FN_2O_9SiS$ $[M + H^+]$ 701.2359, found 701.2364 (0.7 ppm).

(−)-(2*R*,3*R*,4*R*,5*S*)-1,3,4-tris(Benzyloxy)-5-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-5-((trimethylsilyl)oxy)-pentan-2-yl 4-nitrobenzenesulfonate (12a). Following general procedure A, silylated 5F-uracil (1.3 mL of a 0.69 M solution in CH_2Cl_2, 0.89 mmol, 3.5 equiv) and $MgBr_2{\cdot}OEt_2$ (132 mg, 0.51 mmol, 2.0 equiv) were added to a solution of aldehyde **4** (155 mg, 0.26 mmol) in MeCN (2.6 mL) and maintained at −20 °C for 16 h. ^1H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (hexanes/EtOAc, 70:30) provided **12a** (121 mg, 58%) as a white foam: R_f = 0.24 (hexanes/EtOAc, 70:30); $[\alpha]^{25}_D$ −37.2 (*c* 0.990, $CDCl_3$); Formula $C_{39}H_{42}FN_3O_{11}SiS$; MW 807.9132 g/mol; IR (neat) ν_{max} 3181, 2872, 1706, 1532 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.04−7.97 (m, 4H), 7.45 (d, *J* = 6.2 Hz, 1H), 7.36−7.25 (m, 11H), 7.14 (dd, *J* = 6.4, 2.9 Hz, 2H), 7.01 (dd, *J* = 7.6, 1.5 Hz, 2H), 6.22 (s, 1H), 5.11 (ddd, *J* = 7.0, 6.4, 3.4 Hz, 1H), 4.65 (d, *J* = 11.5 Hz, 1H), 4.59 (d, *J* = 11.4 Hz, 1H), 4.54 (d, *J* = 11.5 Hz, 1H), 4.35 (d, *J* = 11.5 Hz, 1H), 4.29 (d, *J* = 11.5 Hz, 1H), 4.20 (d, *J* = 11.5 Hz, 1H), 3.94 (dd, *J* = 7.0, 6.0 Hz, 1H), 3.82 (dd, *J* = 10.9, 3.4 Hz, 1H), 3.70−3.61 (m, 2H), 0.20 (s, 9H) ppm; *NH signal missing possibly due to exchange in CDCl*$_3$*; ∼10% aldehyde remaining in product*; ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.4 (d, *J* = 26.9 Hz), 150.4, 147.8, 143.0, 140.6, 138.7, 137.3 (d, *J* = 12.3 Hz), 135.9, 129.2, 129.1, 128.9, 128.8, 128.7, 128.54, 128.46, 128.38, 128.1, 127.9, 126.1 (d, *J* = 34.1 Hz), 123.9, 83.9, 78.0, 77.7, 75.5, 74.9, 74.5, 73.6, 68.6, −0.27 ppm; HRMS calcd for $C_{39}H_{43}O_{11}FN_3SiS$ $[M + H^+]$ 808.2366, found 808.2360 (−0.72 ppm).

(−)-(2*R*,3*R*,4*R*,5*S*)-5-(4-Amino-2-oxopyrimidin-1(2*H*)-yl)-1,3,4-tris(benzyloxy)-5-((trimethylsilyl)oxy)pentan-2-yl methanesulfonate (13a). Following general procedure A, silylated cytosine (1.3 mL of a 0.71 M solution in CH_2Cl_2, 0.92 mmol, 3.5 equiv) and $MgBr_2{\cdot}OEt_2$ (102 mg, 0.39 mmol, 1.5 equiv) were added to a solution of aldehyde **2** (131 mg, 0.26 mmol) in MeCN (2.6 mL) and maintained at −20 °C for 16 h. ^1H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (acetone/DCM, 50:50) provided **13a** (128 mg, 71%) as a white foam: R_f = 0.19 (acetone/DCM, 50:50); $[\alpha]^{25}_D$ −85.9 (*c*1.02, CH_2Cl_2); Formula $C_{34}H_{43}N_3O_8SSi$; MW 681.8710 g/mol; IR (neat) ν_{max} 3333, 2955, 1645, 1494 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.4 Hz, 1H), 7.34−7.24 (m, 13H), 7.13 (dd, *J* = 6.6, 2.8 Hz, 2H), 6.31 (d, *J* = 1.9 Hz, 1H), 5.71 (d, *J* = 7.4 Hz, 1H), 4.98 (appdd, *J* = 10.4, 5.7 Hz, 1H), 4.83 (d, *J* = 11.1 Hz, 1H), 4.59 (appt, *J* = 10.8 Hz, 2H), 4.51 (d, *J* = 11.7 Hz, 1H), 4.45 (d, *J* = 11.7 Hz, 1H), 4.26 (d, *J* = 10.9 Hz, 1H), 4.01 (dd, *J* = 7.1, 4.5 Hz, 1H), 3.92−3.83 (m, 3H), 3.15 (s, 3H), 0.14 (s, 9H) ppm; *NH*$_2$ *signal missing possibly due to exchange in CDCl*$_3$; ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 155.5, 142.7, 137.9, 137.7, 137.3, 128.531, 128.529, 128.5, 128.4, 128.3, 128.1, 127.9, 127.85, 127.81, 93.9, 79.9, 79.6, 78.3, 77.2, 75.6, 75.3, 73.5, 68.5, 38.8, −0.15 ppm; HRMS calcd for $C_{34}H_{44}N_3O_8SiS$ $[M + H^+]$ 682.2613, found 682.2626 (1.9 ppm).

(−)-(2*R*,3*R*,4*R*,5*S*)-5-(4-Amino-2-oxopyrimidin-1(2*H*)-yl)-1,3,4-tris(benzyloxy)-5-((trimethylsilyl)oxy)pentan-2-yl 4-nitrobenzenesulfonate (14a). Following general procedure A, silylated cytosine (1.1 mL of a 0.59 M solution in CH_2Cl_2, 0.66 mmol, 3.5 equiv) and $MgBr_2{\cdot}OEt_2$ (73 mg, 0.28 mmol, 1.5 equiv) were added to a solution of aldehyde **4** (114 mg, 0.19 mmol) in MeCN (1.9 mL) and maintained at −40 °C for 6 h. ^1H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (hexanes/EtOAc, 0:100) provided **14a** (96 mg, 65%) as a white foam: R_f = 0.41 (hexanes/EtOAc, 0:100); $[\alpha]^{25}_D$ −56.9 (*c* 2.07, CH_2Cl_2); Formula $C_{39}H_{44}N_4O_{10}SiS$; MW 788.9380 g/mol; IR (neat) ν_{max} 3331, 2956, 1658, 1529, 1486, 1185 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.99 (apps, 4H), 7.52 (d, *J* = 7.4 Hz, 1H), 7.30−7.22 (m, 11H), 7.17−7.13 (m, 2H), 7.09−7.06 (m, 2H), 6.42 (d, *J* = 2.8 Hz, 1H), 5.64 (d, *J* = 7.3 Hz, 1H), 5.12−5.08 (m, 1H), 4.66 (d, *J* = 11.3 Hz, 1H), 4.43 (dd, *J* = 11.2, 2.6 Hz, 2H), 4.36−4.25 (m, 3H), 3.89 (dd, *J* = 11.8, 5.4 Hz, 2H), 3.74 (dd, *J* = 10.8, 5.9 Hz, 2H), 0.16 (s, 9H) ppm; *NH*$_2$ *signal missing possibly due to exchange in CDCl*$_3$; ^{13}C NMR (125 MHz, $CDCl_3$) δ165.7, 155.4, 150.4, 143.0, 142.9, 137.70, 137.69, 137.2, 129.5, 128.7, 128.55, 128.54, 128.51, 128.294, 128.292, 128.09, 128.06, 127.9, 124.0, 93.8, 83.9, 78.8, 78.1, 76.3, 75.1, 74.6, 73.6, 68.9, −0.06 ppm; HRMS calcd for $C_{39}H_{45}N_4O_{10}SiS$ $[M + H^+]$ 789.2620, found 789.2629 (1.1 ppm).

(−)-(2*R*,3*R*,4*R*,5*S*)-5-(4-Acetamido-2-oxopyrimidin-1(2*H*)-yl)-1,3,4-tris(benzyloxy)-5-((trimethylsilyl)oxy)pentan-2-yl methanesulfonate (15a). Following general procedure A, silylated N^4−AcCytosine (1.3 mL of a 0.60 M solution in CH_2Cl_2, 0.75 mmol, 2.0 equiv) and $MgBr_2{\cdot}OEt_2$ (193 mg, 0.75 mmol, 2.0 equiv) were added to a solution of aldehyde **2** (186 mg, 0.37 mmol) in MeCN (3.7 mL) and maintained at 0 °C for 16 h. ^1H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (hexanes/EtOAc, 50:50) provided **15a** (133 mg, 49%) as a white foam: R_f = 0.12 (hexanes/EtOAc, 50:50); $[\alpha]^{25}_D$ −92.4 (*c* 1.41, CH_2Cl_2); Formula $C_{36}H_{45}N_3O_9SiS$; MW 723.9077 g/mol; IR (neat) ν_{max} 3030, 2956, 1719, 1669, 1496 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.63 (s, 1H), 7.90 (d, *J* = 7.5 Hz, 1H), 7.36−7.23 (m, 14H), 7.06 (dd, *J* = 6.8, 2.4 Hz, 2H), 6.32 (d, *J* = 1.8 Hz, 1H), 5.02−4.98 (m, 1H), 4.82 (d, *J* = 11.0 Hz, 1H), 4.65 (d, *J* = 11.0 Hz, 1H), 4.58 (d, *J* = 11.1 Hz, 1H), 4.54 (d, *J* = 11.7 Hz, 1H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.16 (d, *J* = 11.1 Hz, 1H), 4.06 (dd, *J* = 7.2, 4.7 Hz, 1H), 3.96−3.88 (m, 3H), 3.18 (s, 3H), 2.27 (s, 3H), 0.14 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 162.8, 154.7, 146.4, 137.70, 137.66, 136.8, 128.7, 128.66, 128.59, 128.51, 128.311, 128.309, 128.1, 127.9, 127.8, 95.9, 79.7, 79.1, 78.6, 77.0, 75.6, 75.4, 73.6, 68.3, 38.8, 25.0, −0.20 ppm; HRMS calcd for $C_{36}H_{46}N_3O_9SiS$ $[M + H^+]$ 724.2719, found 724.2739 (2.8 ppm).

(−)-(2*R*,3*R*,4*R*,5*S*)-5-(4-Acetamido-2-oxopyrimidin-1(2*H*)-yl)-1,3,4-tris(benzyloxy)-5-((trimethylsilyl)oxy)pentan-2-yl 4-nitro-

benzenesulfonate (21a). To a 0.3 M solution of **14a** (0.33 g, 0.42 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C were added Ac_2O (80 μL, 0.85 mmol, 2.0 equiv) and pyridine (0.14 mL, 1.69 mmol, 4.0 equiv). The reaction was maintained for 2 h at 25 °C and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 50:50) provided **21a** (271 mg, 77%) as a white form: R_f = 0.35 (hexanes/EtOAc, 50:50); $[\alpha]^{25}_D$ −63.2 (*c* 1.43, CH_2Cl_2); Formula $C_{41}H_{46}N_4O_{11}SSi$; MW 830.9746 g/mol; IR (neat) ν_{max} 3031, 2956, 1662, 1529, 1492 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.02 (apps, 4H), 7.84 (d, *J* = 7.5 Hz, 1H), 7.32−7.25 (m, 10H), 7.24−7.21 (m, 2H), 7.18−7.15 (m, 2H), 7.00 (d, *J* = 6.5 Hz, 2H), 6.42 (d, *J* = 2.3 Hz, 1H), 5.15−5.11 (m, 1H), 4.67 (d, *J* = 11.2 Hz, 1H), 4.49 (d, *J* = 11.2 Hz, 1H), 4.44 (d, *J* = 11.3 Hz, 1H), 4.37 (d, *J* = 11.4 Hz, 1H), 4.33 (d, *J* = 11.7 Hz, 1H), 4.15 (d, *J* = 11.3 Hz, 1H), 3.95 (appt, *J* = 6.6 Hz, 1H), 3.92 (dd, *J* = 10.8, 3.7 Hz, 1H), 3.79 (dd, *J* = 10.8, 5.9 Hz, 1H), 3.75 (dd, *J* = 6.0, 2.5 Hz, 1H), 2.26 (s, 3H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 162.4, 154.5, 150.3, 146.5, 142.8, 137.5, 137.4, 136.5, 129.4, 128.70, 128.67, 128.51, 128.47, 128.41, 128.35, 128.1, 128.0, 127.9, 123.9, 95.7, 83.8, 78.8, 77.8, 75.9, 74.9, 74.7, 73.5, 68.6, 25.1, −0.20 ppm; HRMS calcd for $C_{41}H_{47}N_4O_{11}SiS$ [M + H^+] 831.2726, found 831.2734 (0.95 ppm).

General Procedure B: C1′ → C4′ Cyclization of *N,OTMS*-Acetals with C4′-Ms Using Conventional Heating. L-Nucleoside analogues **16a**, **17a**, and **18a** were first cyclized from their respective *N,OTMS*-acetals **5a**, **7a**, and **9a** with a C4′-Ms using conventional heating. A 0.06 M solution of *N,OTMS*-acetal in anhydrous DMSO was added to a 15 mL thick-walled glass test tube and heated with $Al(OiPr)_3$ (3.0 equiv). The test tube was sealed with a Teflon cap, and the reaction mixture was maintained for 3 h in a 140 °C sand bath. The reaction mixture was cooled to 25 °C followed by addition of brine (2 mL) and 1 M NaOH (1 mL, to break emulsion formation). The aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were then dried over $MgSO_4$ and concentrated in vacuo.

General Procedure C: C1′ → C4′ Cyclization of *N,OTMS*-Acetals with C4′-Ms Using Microwave Heating. L-Nucleoside analogues **16a**, **17a**, and **18a** were cyclized from their respective *N,OTMS*-acetals **5a**, **7a**, and **9a** with a C4′-Ms using microwave heating. A 0.06 M solution of *N,OTMS*-acetal in anhydrous DMSO was added to a glass test tube fitted for microwave conditions and heated with $Al(OiPr)_3$ (0.6 equiv). The test tube was sealed, and the reaction mixture was maintained for 10 min at 180 °C in the microwave. The reaction mixture was cooled to 25 °C followed by addition of brine (2 mL) and 1 M NaOH (1 mL, to break emulsion formation). The aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were then dried over $MgSO_4$ and concentrated in vacuo.

General Procedures D and E: C1′ → C4′ Cyclization of *N,OTMS*-Acetals with C4′-Ns Using Conventional Heating. A 0.06 M solution of *N,OTMS*-acetal in anhydrous DMSO was added to a 15 mL thick-walled glass test tube and heated with $Al(OiPr)_3$ [0 equiv (procedure D) or 3.0 equiv (procedure E)]. The test tube was sealed with a Teflon cap, and the reaction mixture was maintained for 3 h in a 90 °C sand bath. The reaction mixture was cooled to 25 °C followed by addition of brine (2 mL) and 1 M NaOH (1 mL, to break emulsion formation). The aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were then dried over $MgSO_4$ and concentrated in vacuo.

(−)-1-((2*S*,3*R*,4*S*,5*S*)-3,4-bis(Benzyloxy)-5-((benzyloxy)-methyl)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (16a). Following general procedure D, a solution of *N,OTMS*-acetal **6a** (100 mg, 0.12 mmol) was heated in DMSO (2.1 mL). ^1H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (hexanes/EtOAc, 50:50) provided **16a** (50 mg, 77%) as a colorless gum. ^1H NMR spectroscopic data correlate with the previously reported data for the enantiomer of **16a**:[10] R_f = 0.26 (hexanes/EtOAc, 50:50); $[\alpha]^{25}_D$ −53.3 (*c* 0.940, $CDCl_3$); Formula $C_{31}H_{32}N_2O_6$; MW 528.5956 g/mol; ^1H NMR (500 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.44 (d, *J* = 1.1 Hz, 1H), 7.38−7.25 (m, 13H), 7.15 (dd, *J* = 7.2, 2.0 Hz, 2H), 6.31 (d, *J* = 5.2 Hz, 1H), 4.59 (d, *J* = 11.9 Hz, 1H), 4.57−4.50 (m, 3H), 4.43 (d, *J* = 11.7 Hz, 1H), 4.40 (d, *J* = 11.6 Hz, 1H), 4.24 (dd, *J* = 5.0, 4.2 Hz, 1H), 4.13 (dd, *J* = 5.5, 4.1 Hz, 1H), 4.08−4.05 (m, 1H), 3.72 (dd, *J* = 10.5, 4.0 Hz, 1H), 3.66 (dd, *J* = 10.5, 4.3 Hz, 1H), 1.68 (d, *J* = 0.7 Hz, 3H) ppm; HRMS calcd for $C_{31}H_{33}N_2O_6$ [M + H^+] 529.2333, found 529.2342 (1.7 ppm).

(−)-1-((2*S*,3*R*,4*S*,5*S*)-3,4-bis(Benzyloxy)-5-((benzyloxy)-methyl)tetrahydrofuran-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (17a). Following general procedure D, a solution of *N,OTMS*-acetal **8a** (151 mg, 0.19 mmol) was heated in DMSO (3.2 mL). ^1H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (hexanes/EtOAc, 50:50) provided **17a** (73 mg, 74%) as a colorless gum: R_f = 0.38 (hexanes/EtOAc, 50:50); $[\alpha]^{25}_D$ −71.2 (*c* 1.50, $CDCl_3$); Formula $C_{30}H_{30}N_2O_6$; MW 514.5690 g/mol; IR (neat) ν_{max} 3190, 2919, 1690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.15 (s, 1H), 7.62 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.37−7.24 (m, 13H), 7.14 (d, *J* = 7.5 Hz, 2H), 6.30 (d, *J* = 4.9 Hz, 1H), 5.47 (d, *J* = 8.1 Hz, 1H), 4.58 (d, *J* = 11.9 Hz, 1H), 4.54−4.46 (m, 3H), 4.43 (d, *J* = 11.6 Hz, 1H), 4.39 (d, *J* = 11.6 Hz, 1H), 4.26−4.22 (m, 1H), 4.10−4.08 (m, 2H), 3.69 (dd, *J* = 10.3, 2.1 Hz, 1H), 3.64 (dd, *J* = 10.3, 2.4 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7, 150.6, 142.1, 137.6, 137.4, 136.7, 128.6, 128.57, 128.55, 128.2, 128.1, 128.04, 127.89, 127.869, 127.867, 101.2, 84.4, 81.9, 80.9, 80.5, 73.5, 73.2, 72.2, 68.7 ppm; HRMS calcd for $C_{30}H_{31}N_2O_6$ [M + H^+] 515.2177, found 515.2159 (−3.4 ppm).

(+)-1-((2*R*,3*R*,4*S*,5*S*)-3,4-bis(Benzyloxy)-5-((benzyloxy)-methyl)tetrahydrofuran-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (17b). Following general procedure B, a solution of *N,OTMS*-acetal **7b** (70 mg, 0.10 mmol) and $Al(OiPr)_3$ (63 mg, 0.31 mmol, 3.0 equiv) was heated in DMSO (1.7 mL). ^1H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (hexanes/EtOAc, 50:50) provided **17b** (21 mg, 39%) as a colorless gum: R_f = 0.31 (hexanes/EtOAc, 50:50); $[\alpha]^{25}_D$ +32.1 (*c* 0.860, $CDCl_3$); Formula $C_{30}H_{30}N_2O_6$; MW 514.5690 g/mol; IR (neat) ν_{max} 3171, 2923, 1686 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.42 (d, *J* = 8.2 Hz, 1H), 7.37−7.25 (m, 13H), 7.13 (dd, *J* = 6.6, 2.8 Hz, 2H), 6.07 (s, 1H), 5.60 (dd, *J* = 8.2, 2.3 Hz, 1H), 4.76 (d, *J* = 12.1 Hz, 1H), 4.64−4.57 (m, 3H), 4.52 (d, *J* = 12.1 Hz, 1H), 4.45 (d, *J* = 11.8 Hz, 1H), 4.37 (d, *J* = 11.8 Hz, 1H), 4.11 (s, 1H), 3.99 (s, 1H), 3.65 (dd, *J* = 9.8, 6.7 Hz, 1H), 3.57 (dd, *J* = 9.8, 6.8 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2, 150.1, 140.6, 137.9, 137.3, 136.8, 128.72, 128.67, 128.60, 128.3, 128.2, 127.98, 127.935, 127.932, 127.90, 101.4, 91.2, 86.5, 85.6, 82.9, 73.6, 72.3, 72.0, 69.8 ppm; HRMS calcd for $C_{30}H_{31}N_2O_6$ [M + H^+] 515.2177, found 515.2177 (0.07 ppm).

(−)-9-((2*S*,3*R*,4*S*,5*S*)-3,4-bis(Benzyloxy)-5-((benzyloxy)-methyl)tetrahydrofuran-2-yl)-9*H*-purin-6-amine (18a). Following general procedure E, a solution of *N,OTMS*-acetal **10a** (205 mg, 0.25 mmol) and $Al(OiPr)_3$ (155 mg, 0.76 mmol, 3.0 equiv) was heated in DMSO (4.2 mL). ^1H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (hexanes/EtOAc, 0:100) provided **18a** (81 mg, 60%) as a colorless gum. ^1H NMR spectroscopic data correlate with the commercially available enantiomer of **18a**:[29] R_f = 0.37 (hexanes/EtOAc, 0:100); $[\alpha]^{25}_D$ −9.50 (*c* 1.18, $CDCl_3$); Formula $C_{31}H_{31}N_5O_4$; MW 537.5089 g/mol; IR (neat) ν_{max} 3318, 3156, 2914, 1653, 1599 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.18 (s, 1H), 7.37−7.25 (m, 10H), 7.22−7.17 (m, 3H), 6.92 (dd, *J* = 7.3, 1.7 Hz, 2H), 6.51 (d, *J* = 4.3 Hz, 1H), 5.73 (s, 2H), 4.61 (d, *J* = 11.9 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 3H), 4.27 (dd, *J* = 5.1, 2.3 Hz, 2H), 4.26 (s, 1H), 4.22 (s, 1H), 4.21−4.18 (m, 1H), 3.69 (d, *J* = 4.9 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 153.0, 149.9, 141.1, 137.8, 137.5, 136. 6, 128.65, 128.62, 128.55, 128.2, 128.1, 128.0, 127.93, 127.92, 127.89, 119.2, 83.4, 81.9, 81.5, 80.9, 73.5, 72.9, 72.3, 69.2 ppm; HRMS calcd for $C_{31}H_{32}N_5O_4$ [M + H^+] 538.2449, found 538.2443 (−1.0 ppm).

(−)-1-((2*S*,3*R*,4*S*,5*S*)-3,4-bis(Benzyloxy)-5-((benzyloxy)-methyl)tetrahydrofuran-2-yl)-5-fluoropyrimidine-2,4(1*H*,3*H*)-dione (19a). Following general procedure D, a solution of *N,OTMS*-

acetal **12a** (119 mg, 0.15 mmol) was heated in DMSO (2.5 mL). ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (hexanes/EtOAc, 50:50) provided **19a** (50 mg, 63%) as a colorless gum: R_f = 0.36 (hexanes/EtOAc, 50:50); $[\alpha]^{25}_D$ −35.8 (*c* 0.760, $CDCl_3$); Formula $C_{30}H_{29}FN_2O_6$; MW 532.5595 g/mol; IR (neat) ν_{max} 3186, 2922, 1717 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.31 (d, *J* = 4.2 Hz, 1H), 7.85 (d, *J* = 6.4 Hz, 1H), 7.40−7.25 (m, 13H), 7.16 (d, *J* = 7.4 Hz, 2H), 6.28 (d, *J* = 5.0 Hz, 1H), 4.58 (dd, *J* = 11.8, 4.6 Hz, 2H), 4.55−4.49 (m, 2H), 4.45 (s, 2H), 4.26 (appt, *J* = 4.2 Hz, 1H), 4.14−4.08 (m, 2H), 3.70 (dd, *J* = 10.3, 3.6 Hz, 1H), 3.63 (dd, *J* = 10.4, 3.8 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9 (d, *J* = 26.5 Hz), 149.1, 139.9 (d, *J* = 235.8 Hz), 137.40, 137.36, 136.7, 128.7, 128.671, 128.666, 128.4, 128.2, 128.1, 128.0, 127.93, 127.88, 126.4 (d, *J* = 34.8 Hz), 84.6, 82.1, 80.8, 80.7, 73.6, 73.4, 72.4, 68.5 ppm; HRMS calcd for $C_{30}H_{30}FN_2O_6$ [M + H$^+$] 533.2082, found 533.2074 (−1.5 ppm).

(−)-4-Amino-1-((2*S*,3*R*,4*S*,5*S*)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-yl)pyrimidin-2(1*H*)-one (20a) and (+)-(2S,3R,4S)-4-((4-Aminopyrimidin-2-yl)oxy)-2,3,5-tris(benzyloxy)pentan-1-ol (23). Following general procedure E, a solution of *N*,*OTMS*-acetal 14a (95 mg, 0.12 mmol) and Al(O*i*Pr)$_3$ (74 mg, 0.36 mmol, 3.0 equiv) was heated in DMSO (2.0 mL). ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1), however, with a 2:1 mixture of nucleoside analogue **20a** and primary alcohol **23**. Purification by flash chromatography (hexanes/EtOAc, 0:100) provided **20a** (28 mg, 46%) and **23** (11 mg, 18%) as colorless gums.

20a: R_f = 0.06 (hexanes/EtOAc, 0:100); $[\alpha]^{25}_D$ −109 (*c* 0.900, $CDCl_3$); Formula $C_{30}H_{31}N_3O_5$; MW 513.5842 g/mol; IR (neat) ν_{max} 3347, 2925, 1626, 1481 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.4 Hz, 1H), 7.37−7.22 (m, 13H), 7.16−7.12 (m, 2H), 6.38 (d, *J* = 4.6 Hz, 1H), 5.57 (d, *J* = 7.4 Hz, 1H), 4.57−4.49 (m, 3H), 4.46−4.39 (m, 2H), 4.35−4.29 (m, 2H), 4.14−4.11 (m, 1H), 4.01 (dd, *J* = 4.5, 3.0 Hz, 1H), 3.65 (d, *J* = 4.9 Hz, 2H) ppm; *NH_2 signal missing possibly due to exchange in $CDCl_3$*; ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 155.6, 143.8, 137.9, 137.5, 137.3, 128.60, 128.58, 128.55, 128.07, 128.06, 127.96, 127.90, 127.892, 127.890, 93.2, 85.9, 82.1, 81.4, 80.8, 73.5, 73.2, 72.1, 69.2 ppm; HRMS calcd for $C_{30}H_{32}N_3O_5$ [M + H$^+$] 514.2336, found 514.2346 (1.9 ppm).

The N1 regiochemistry and 1′,2′-*cis* configuration of **20a** was confirmed by comparison of the ^{13}C NMR spectrum of the debenzylated nucleoside with its commercially available enantiomer:[30] ^{13}C NMR (125 MHz, DMSO) δ 165.6, 155.2, 142.9, 92.4, 85.7, 84.8, 76.3, 74.8, 61.1 ppm.

23: R_f = 0.31 (hexanes/EtOAc, 0:100); $[\alpha]^{25}_D$ +3.5 (*c* 0.71, DCM); Formula $C_{30}H_{33}N_3O_5$; MW 515.6001 g/mol; IR (neat) ν_{max} 3340, 3207, 2923, 1626, 1595 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 5.8 Hz, 1H), 7.34−7.24 (m, 15H), 6.08 (d, *J* = 5.7 Hz, 1H), 5.37−5.33 (m, 1H), 4.95 (s, 2H), 4.82 (d, *J* = 11.2 Hz, 1H), 4.70 (d, *J* = 11.2 Hz, 1H), 4.63 (d, *J* = 1.2 Hz, 2H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.17 (dd, *J* = 7.0, 2.8 Hz, 1H), 4.00 (dd, *J* = 10.7, 4.0 Hz, 1H), 3.94 (dd, *J* = 10.7, 6.1 Hz, 1H), 3.86 (d, *J* = 3.1 Hz, 2H), 3.73−3.69 (m, 1H) ppm; *OH signal missing possibly due to exchange in $CDCl_3$*; ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 164.5, 157.2, 138.6, 138.5, 138.3, 128.5, 128.42, 128.38, 128.273, 128.271, 128.1, 127.8, 127.70, 127.69, 99.8, 80.4, 80.3, 76.4, 75.1, 73.7, 73.1, 68.9, 62.5 ppm; HRMS calcd for $C_{30}H_{34}N_3O_5$ [M + H$^+$] 516.2493, found 516.2498 (0.9 ppm).

(−)-*N*-(1-((2*S*,3*R*,4*S*,5*S*)-3,4-bis(Benzyloxy)-5-((benzyloxy)-methyl)tetrahydrofuran-2-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)acetamide (22a). Following general procedure E, a solution of *N*,*OTMS*-acetal **21a** (55 mg, 0.07 mmol) and Al(O*i*Pr)$_3$ (40 mg, 0.20 mmol, 3.0 equiv) was heated in DMSO (1.1 mL). ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (hexanes/EtOAc, 0:100) provided **22a** (19 mg, 52%) as a colorless gum: R_f = 0.26 (hexanes/EtOAc, 0:100); $[\alpha]^{25}_D$ −104 (*c* 1.10, $CDCl_3$); Formula $C_{32}H_{33}N_3O_6$; MW 555.6209 g/mol; IR (neat) ν_{max} 3030, 2924, 1665, 1495 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.02 (d, *J* = 7.5 Hz, 1H), 7.38−7.22 (m, 14H), 7.08 (dd, *J* = 6.9, 2.4 Hz, 2H), 6.37 (d, *J* = 4.5 Hz, 1H), 4.55 (d, *J* = 11.6 Hz, 1H), 4.50 (d, *J* = 11.6 Hz, 2H), 4.43 (d, *J* = 8.5 Hz, 1H), 4.40 (d, *J* = 8.2 Hz, 1H), 4.37 (dd, *J* = 4.5, 2.9 Hz, 1H), 4.31 (d, *J* = 11.7 Hz, 1H), 4.21−4.17 (m, 1H), 4.01 (dd, *J* = 4.1, 3.0 Hz, 1H), 3.65 (d, *J* = 5.2 Hz, 2H), 2.23 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 162.5, 155.2, 146.7, 137.7, 137.4, 137.1, 128.7, 128.63, 128.59, 128.15, 128.13, 127.97, 127.94, 127.93, 127.91, 95.8, 86.7, 81.7, 81.5, 81.2, 73.5, 73.3, 72.1, 69.0, 25.1 ppm; HRMS calcd for $C_{32}H_{34}N_3O_6$ [M + H$^+$] 556.2442, found 556.2446 (0.7 ppm).

Preparation of L-Nucleoside Analogues Using DMSO-d_6. 1-((2*S*,3*R*,4*S*,5*S*)-3,4-bis(Benzyloxy)-5-((benzyloxy)methyl)-tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (16a and 16b). A 1:2 mixture of *N*,*OTMS*-acetals **6a** and **6b** (25 mg, 0.031 mmol) in DMSO-d_6 (0.06 M, 0.52 mL) was placed in an NMR tube. The reaction mixture was maintained at 90 °C for 3 h in a sand bath and then cooled to 25 °C. Nucleoside analogue **16a** was formed in 33% and analogue **16b** in 54% on the basis of comparison of the area of the residual DMSO-d_6 solvent peak at 2.50 ppm (d_1 relaxation time was set to 10 s) with the area of the acetal center peak of the starting material taken before heating the reaction mixture. Brine (0.2 mL) and 1 M NaOH (0.2 mL, to break emulsion formation) were added to the reaction mixture. The aqueous layer was extracted with ethyl acetate (3 × 0.5 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The expected corresponding 1:2 mixture of L-1′,2′-*cis* and *trans* nucleoside analogues **16a** and **16b** was obtained. ^{1}H NMR spectroscopic data of the crude reaction mixture in $CDCl_3$ correlate with the enantiomers of **16a** and **16b** that have previously been reported in the literature.[10]

■ ASSOCIATED CONTENT

Supporting Information

Stereochemical proofs and ^{1}H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(30) Cytosine β-D-arabinofuranoside (CAS: 147−94−4).